# Synthetic method development of drug-like heterocycles and medicinal chemistry optimization of anti-infective and anti-cancer compounds

By

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# Abstract

The Golden research group is interested in synthesizing and developing useful small molecules for drug discovery. In this dissertation, two novel synthetic methodologies for building drug-like heterocycles were developed. Additionally, hit identification and optimization of anti-infective or anti-cancer agents were achieved to improve their potency or physical chemical properties. Specifically, two unprecedented ring-fused pyridopyrimidinediones were assembled from the vinylogous amides or ureas through a palladium catalyzed carbonylation reactions. In addition, a highly efficient 2-chloroquinazolin-4(3*H*)-one rearrangement was developed that generated either twisted-cyclic or ring-fused guanidines. Moreover, this research identified, validated and optimized three different scaffolds against glucose uptake of the parasites *Trypanosoma brucei* and *Leishmania. donovani*. Furthermore, structure modification of sulfonamidebenzamides and benzamidines were performed as anticancer and antiviral agents, respectively.

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# Chapter 1. Introduction and Research Summary

The Golden research group is interested in synthesizing and developing useful small molecules for drug discovery. We develop synthetic methodologies to generate novel chemical scaffolds and explore their associated pharmacological activities. This dissertation focused on the synthetic methodology development of drug-like heterocycles and the medicinal chemistry optimization of anti-infective and anti-cancer compounds.

## ***Synthetic methodology development of drug-like heterocycles***

Heterocycles are important building blocks in bioactive molecules and marketed drugs. However, the assembly of known and novel heterocyclic scaffolds is still a challenging task and there are unmet needs of new synthetic methods based on their relevance on natural products, materials and bioactive molecules.[1-16] In this dissertation, two novel synthetic methodologies were developed for the synthesis of drug-like heterocycles (**Chapter 2** and **Chapter 3**).

**Chapter 2** describes a palladium-catalyzed cyclocarbonylation reaction for the assembly of novel ring-fused pyridopyrimidinediones. Two novel scaffolds were generated via a palladium catalyzed, pyridine directed, C-H activation/carbonylation procedure. The reactions proceed successfully under mild conditions to afford over 30 products in up to 90% yield. Optimization studies, the scope of the reaction and mechanistic studies were discussed in this chapter.

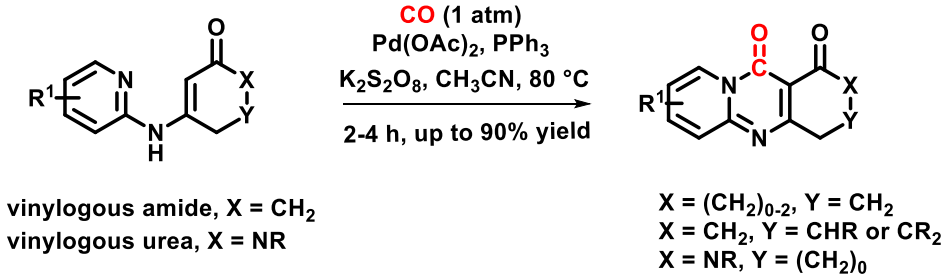



**Figure 1-1.** Palladium-catalyzed cyclocarbonylation reaction for the synthesis of ring-fused pyridopyrimidinediones

**Chapter 3** shows highly efficient 2-chloroquinazolin-4(3*H*)-one rearrangement reactions for the generation of either twisted-cyclic or ring-fused guanidines. This transformation generated 55 guanidines and delivered twisted-cyclic guanidines with robust plasma stability and an abbreviated total synthesis of an antitumor ring-fused guanidine (4 steps, 55% yield). Optimization studies, the scope of the reaction and the applications of these guanidines were discussed in this chapter.

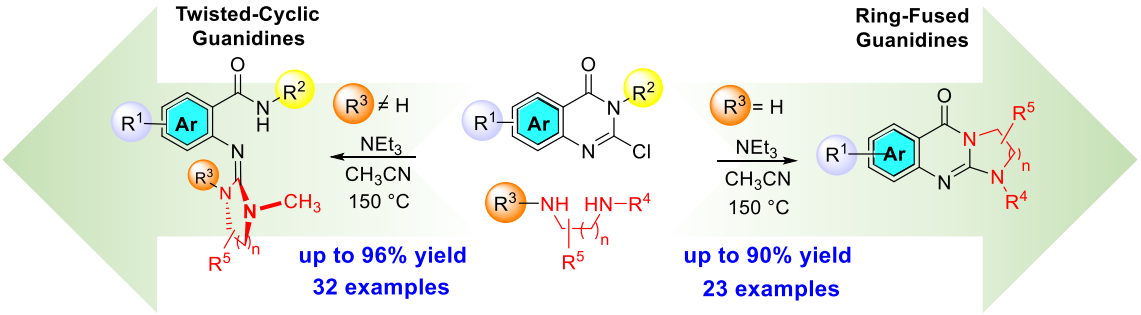



**Figure 1-2.** Rearrangement of 2-chloroquinazolin-4(3*H*)-one for the generation of twisted-cyclic or ring-fused guanidines

## ***Medicinal chemistry optimization of anti-infective and anti-cancer compounds***

The Golden group is interested in developing antiparasitic, antiviral and anticancer agents. In this dissertation, a few projects focusing on developing small molecules against parasites (including *T. brucei* and *Leishmania*), encephalitic alphaviruses and cancer will be discussed.

**Chapter 4** reports the identification, validation and preliminary structure-activity relationship (SAR) studies of parasite glucose uptake inhibitors. The identification of parasite glucose uptake inhibitors was achieved via a high-throughput screening method. The resulting hits were resynthesized to validate their glucose uptake inhibition and growth inhibition of the parasites. Preliminary structure-activity relationship (SAR) was investigated. The results showed that two scaffolds were validated that can block the glucose transport of procyclic form *T. brucei* parasites and growth inhibition of bloodstream form *T. brucei* parasites with micromolar to submicromolar activity. In addition, another scaffold is active against both *T. brucei* and *L. donovani*. Screening, synthesis and the preliminary SAR studies were discussed in this chapter.

**Chapter 5** describes the structure optimization of CHOP activator sulfonamidebenzamides as anticancer agents to improve their physical chemical properties. The Golden group discovered that sulfonamidebenzamide compounds, such as **ML291**, exhibited good potency on activation of CHOP pathway, which is a promising target for the treatment of cancer. However, these compounds exhibited poor microsomal stabilities. In this chapter, a scaffold hopping of **ML291** led to the discovery of **BDGR-6029**, a new scaffold that displayed good activity on CHOP activation and a 2100-fold improvement of microsomal stability.

**Chapter 6** reports the structure optimization of antiparasitic agents sulfonamidebenzamides. The Golden group discovered sulfonamidebenzamide scaffold showing potent anti-*T. brucei* activity. However, these compounds exhibited poor microsomal stabilities and solubilities. In this chapter, the structure optimization was performed to optimize physical chemical properties of these molecules while retaining the antiparasitic activity. A scaffold hopping led to the discovery of **BDGR-6029**, a new scaffold that showed potent antiparasitic

activities with minimum toxicity and good microsomal stability. Synthesis, structure optimization, SAR and structure property relationship (SPR) will be discussed in this chapter.

**Chapter 7** shows the preliminary results of the development of bicyclic/tricyclic benzamidines as antiviral compounds. Encephalitic alphaviruses, including Venezuelan/Western/Eastern Equine Encephalitis Virus (V/W/EEEV), are endemic in American continent and can be developed as bioweapons. However, there are no FDA approved human vaccines or drugs available. Therefore, novel agents for the treatment of encephalitic alphaviruses are in high demand. The Golden group discovered and developed the benzamidine series, as exemplified by **BDGR-4**, which showed good potency against VEEV and WEEV. However, the SAR of the bicyclic/tricyclic benzamidines has not been investigated yet. In this chapter, a series of compounds bearing bicyclic or tricyclic benzamidines were designed and synthesized in order to increase the activity and physical chemical properties of **BDGR-4**. The associated antiviral activities were evaluated against VEEV and WEEV. Synthesis and the preliminary SAR will be discussed.

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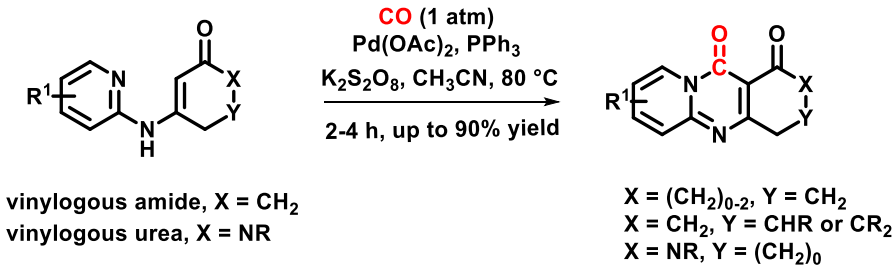
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# Chapter 2. Palladium-Catalyzed Cyclocarbonylation of Pyridinylated Vinylogous Amides and Ureas to Generate Novel Ring Fused Pyridopyrimidinones

## 2.1 Abstract

Aiming to generate novel heterocyclic compound libraries for medicinal chemistry exploration, a new method is described for the assembly of novel ring-fused pyridopyrimidinediones, a scaffold expected to demonstrate valuable, yet unknown, bioactivity based on diverse therapeutic relevance reported for related structures. Specifically, a series of 11*H*-pyrido[2,1-*b*]quinazoline-1,11(2*H*)-diones and 2,3-dihydropyrido[1,2-a]pyrrolo[3,4-d]pyrimidine -1,10-diones were generated via a palladium catalyzed, pyridine directed, C-H activation/carbonylation of 2-pyridyl-linked vinylogous amides and ureas. The reactions proceed successfully under mild conditions to afford over 30 products in up to 90% yield. Optimization studies, the scope of the reaction and mechanistic studies were discussed.




Adapted from **Gang Yan**, Jennifer E Golden. Palladium-Catalyzed Cyclocarbonylation of Pyridinylated Vinylogous Amides and Ureas to Generate Ring-Fused Pyridopyrimidinones. *Organic Letters* **2018**, *20* (15), 4393-4396.

## 2.2 Introduction

The pyridopyrimidinedione core (**Figure 2-1**, red highlight) is a well-recognized, privileged scaffold[1-2] in medicinal chemistry, meaning that the core motif is imbedded within a variety of more structurally complex molecules that display distinct biological activity depending on the functional groups attached to this core. A few examples are depicted in **Figure 2-1** including allergy drug, Barmastine **2-1**[3] and Pemirolast **2-2**[4-5], the antidepressant drug Lusaperidone **2-3**[6], the antihypertensive drug Seganserin **2-4**[7], anti-HIV compound **2-5**[8], anti-ulcer agent **2-6**[9], and antiproliferative agent **7**[10]. Given the lack of structural examples containing lactam-fused and other cycloalkanone-fused pyridopyrimidinonecompounds, scaffolds **2-8** and **2-9** were designed for medicinal chemistry exploration of unknown bioactivity. As such, we sought an efficient strategy to construct and diversify these scaffolds.

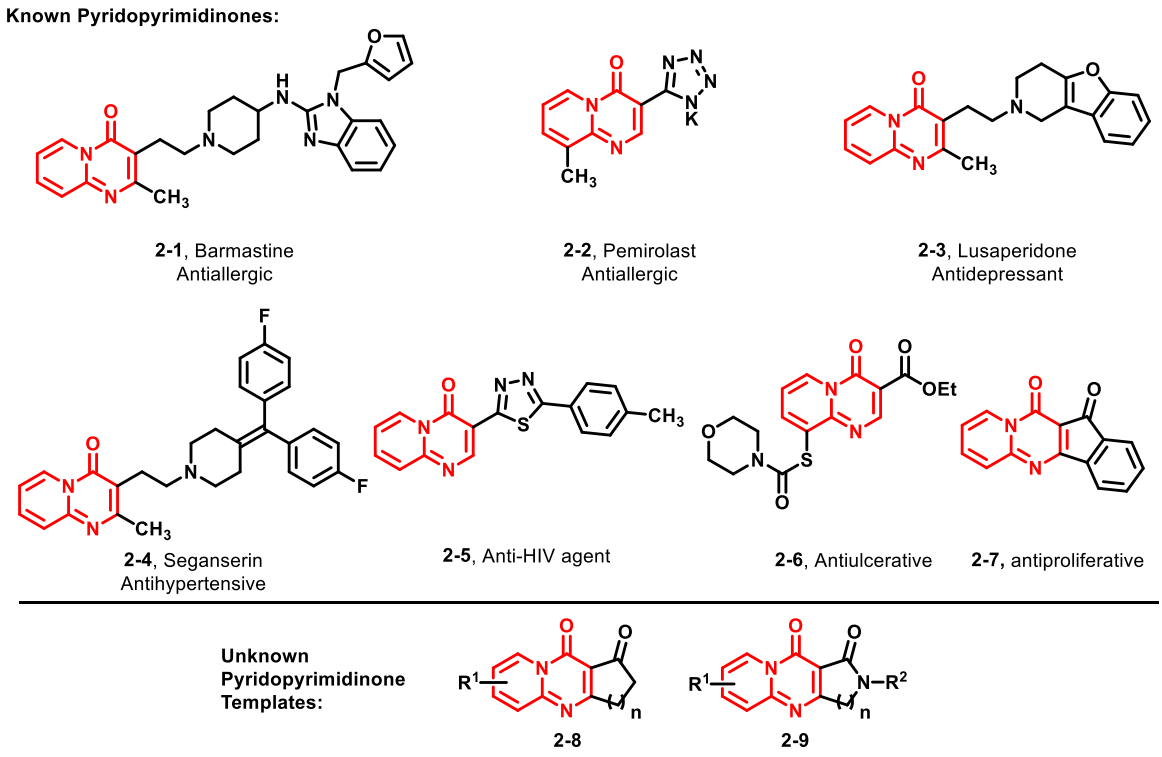
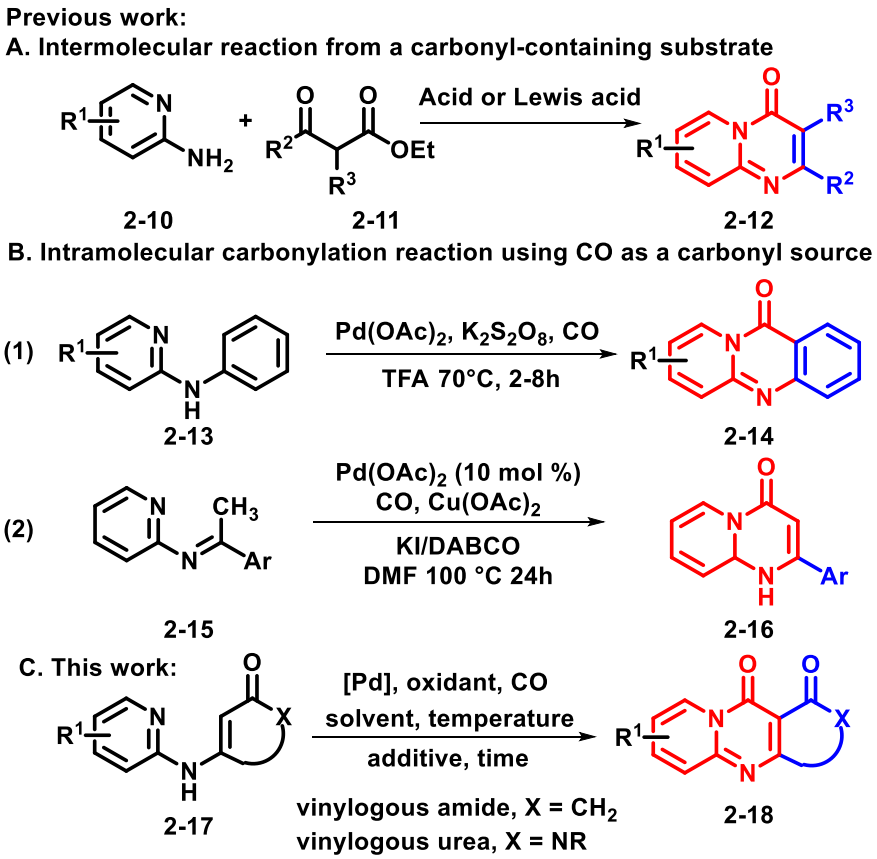



**Figure 2-1.** Pharmacological and structural diversity of derivatized pyridopyrimidinones and prospective template opportunities

The previous methods for making pyridopyrimidinones are listed in **Scheme 2-1**. Traditionally, these scaffolds were assembled by condensation of 2-aminopyridines with other carbonyl-containing partners (**Scheme 2-1A**).[6, 11-14] For instance, Marini and co-workers reported the synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones by intermolecular coupling of 2-aminopyridine (**2-10**) and β-keto esters (**2-11**) under acidic conditions.[14] Jaenicke and co-workers also reported the similar transformation by a solvent free reaction using Lewis acid as catalysts.[12] More recently, the development of transition metal-catalyzed carbonylation chemistry has been developed using carbon monoxide (CO) as a carbonyl source for building different scaffolds,[15-18] including the related phenyl ring-fused pyridopyrimidinones (**Scheme 2-1B**). For examples, Zhu and co-workers reported a palladium-catalyzed C-H activation/carbonylation reaction of *N*-phenylpyridin-2-amine (**2-13**) by using $K_2S_2O_8$ as oxidants in TFA to afford the 11*H*-pyrido[2,1-*b*]quinazolin-11-ones (**2-14**, **Scheme 2-1B-(1)**).[19] Zeng and co-workers developed Pd-catalyzed carbonylation of ketoimines (**2-15**) for the synthesis of pyrido[1,2-*a*]pyrimidin-4-ones (**2-16, Scheme 2-1B-(2)**).[20] These methods suggested the possibility of developing a cyclocarbonylation reaction for making scaffold **2-8** and **2-9** in **Figure 2-1**.

Here, the first synthesis of novel pyridopyrimidinediones (**2-18**) was achieved using a pyridine-directed, palladium-catalyzed C-H activation/carbonylation reaction to bridge an attached vinylogous amide or urea (**2-17**). (**Scheme 2-1C**)

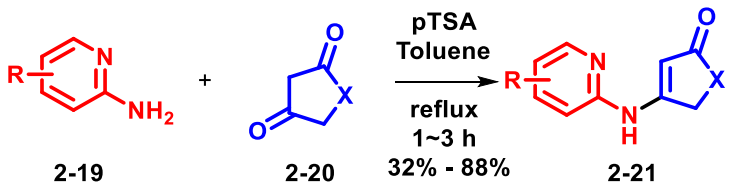



**Scheme 2-1.** General approaches for the synthesis of pyridopyrimidinones

## 2.3 Results and discussion

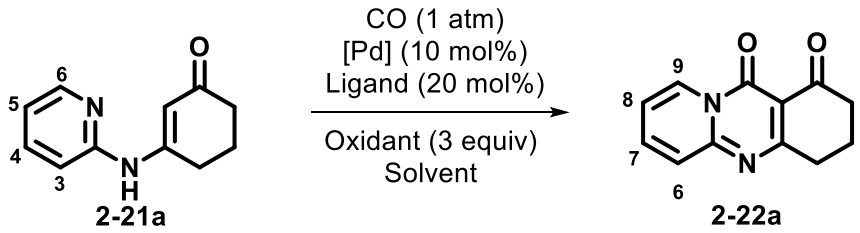
### ***Optimization of reaction conditions***

To initiate this study, vinylogous substrates (**2-21**) were prepared by coupling 2-aminopyridines (**2-19**) with 1,3-cyclic diones (**2-20**) under acid catalyzed conditions (**Scheme 2-2**).[21] With substrates in hand, different reaction conditions were screened to facilitate the cyclocarbonylation (**Table 2-1**).




**Scheme 2-2.** Synthesis of vinylogous amides/ureas

**Table 2-1.** Optimization of reaction conditions[a]




| entry | catalyst (10 mol %) | ligand (20 mol %) | oxidant (3 equiv) | solvent | yield (%)[b] | entry | catalyst (10 mol %) | ligand (20 mol %) | oxidant (3 equiv) | solvent | yield (%)[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[c] | $Pd(OAc)_2$ | - | $K_2S_2O_8$ | TFA | 0 | 9 | $Pd(OAc)_2$ | $CH_3PPh_2$ | $K_2S_2O_8$ | dioxane | trace |
| 2 | $Pd(OAc)_2$ | - | $K_2S_2O_8$ | dioxane | 10 | 10 | $Pd(OAc)_2$ | $PPh_3$ | $Cu(OAc)_2$ | dioxane | 12 |
| 3 | $Pd(OAc)_2$ | $PPh_3$ | $K_2S_2O_8$ | dioxane | 48 | 11 | $Pd(OAc)_2$ | $PPh_3$ | Air[g] | dioxane | 41 |
| 4 | $PdCl_2(PPh_3)_2$ | $PPh_3$ | $K_2S_2O_8$ | dioxane | 0 | 12 | $Pd(OAc)_2$ | $PPh_3$ | $K_2S_2O_8$ | toluene | 11 |
| 5 | $PdCl_2(PhCN)_2$ | $PPh_3$ | $K_2S_2O_8$ | dioxane | trace | 13 | $Pd(OAc)_2$ | $PPh_3$ | $K_2S_2O_8$ | DMF | 24 |
| 6 | $Pd(OAc)_2$ | dppp[d] | $K_2S_2O_8$ | dioxane | 14 | 14[h] | $Pd(OAc)_2$ | $PPh_3$ | $K_2S_2O_8$ | $CH_3CN$ | 75 |
| 7 | $Pd(OAc)_2$ | tdmpp[e] | $K_2S_2O_8$ | dioxane | 36 | **15[i]** | **$Pd(OAc)_2$** | **$PPh_3$** | **$K_2S_2O_8$** | **$CH_3CN$** | **90 (68)[i]** |
| 8 | $Pd(OAc)_2$ | tbtfmpp[f] | $K_2S_2O_8$ | dioxane | 22 | | | | | | |

[a]Reaction conditions: **2-20a** (0.3 mmol), Pd catalyst (10 mol %), ligand (20 mol %), oxidant (3 equiv), CO balloon (1 atm), solvent (2 mL), 100 °C, 15 h; [b]Isolated yield of **2-21a**; [c]70 °C, 3 h; [d]dppp: 1,3-bis(diphenylphosphino)propane; [e]tdmpp: tris(2,6-dimethoxyphenyl)phosphine; [f]tbtfmpp = tris[3,5-bis(trifluoromethyl)phenyl]phosphine; [g]Air:CO = 1:1; [h]80 °C; [i]80 °C, 3h, $CH_3CN$ (1 mL). [i]The reaction was performed in 10 mmol scale.

A pilot reaction using vinylogous amide **2-21a** was originally screened using the condition reported by Zhu[19] using trifluoroacetic acid (TFA) as solvent; however, product **2-22a** was not obtained, presumably due to the instability of **2-21a** in the harsh acidic environment based on the TLC (entry 1). Encouragingly, when **2-21a** was treated with a non-acidic solvent 1,4-dioxane at 100 °C, the desired pyridopyrimidinone **2-22a** was obtained in 10% yield with a large amount of remaining starting material **2-21a** (entry 2). As solvents and catalyst loading were screened, the effect of adding $PPh_3$ as a potential ligand was examined. To our delight, a 48% yield of **2-21a** was obtained when 20 mol % $PPh_3$ was employed as a ligand (entry 3). Other palladium catalysts, ligands and oxidants were also screened. However, exchange of $Pd(OAc)_2$ for other palladium catalyst (entries 4-5), switching $PPh_3$ to other phosphine ligands bearing either electron-donating

or electron-withdrawing substituents (entries 6-9), or different oxidants (entries 10-11 and experimental section **Table 2-4**) failed to increase the yield. Solvents were also screened. While toluene and DMF were less effective than the use of 1,4-dioxane, switching to acetonitrile afforded a yield of 75% after 15 h at a lower temperature (80 °C) and with full consumption of **2-21a** based on TLC (entry 14). By further monitoring the reactions by TLC, a full conversion to product occurred after only 3 h, affording **2-22a** in 90% isolated yield of (entry 15). A scale up reaction was also performed using 10 mmol (1.88 g) **2-21a**, affording **2-22a** in 68% yield after 4 h. With the optimized conditions in hand, the scope of the reactions was explored (**Table 2-2**). Reactions were worked up after full consumption of the starting material based on TLC.

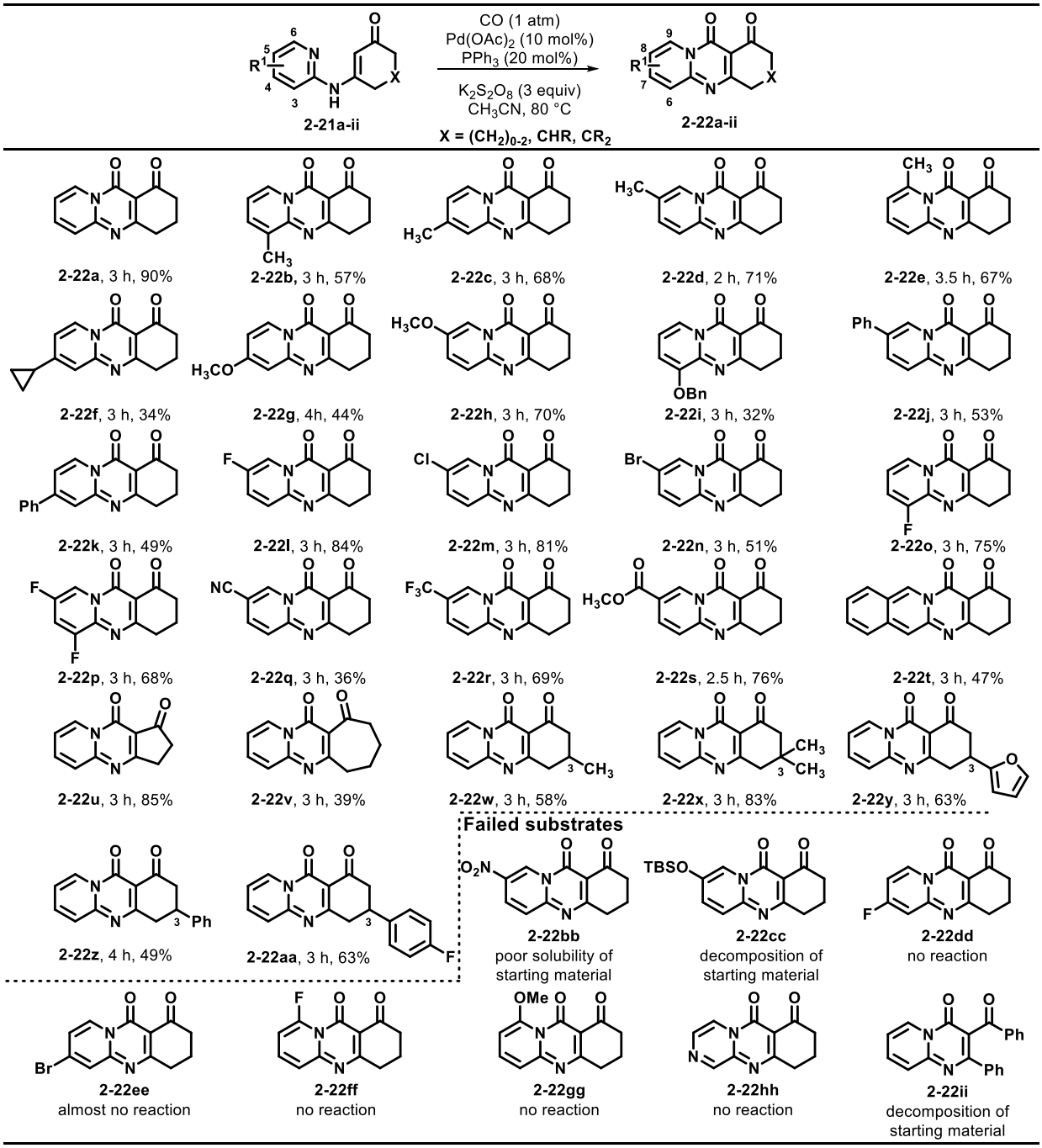
***Substrate scope of the reaction***

We first assessed substrates bearing different substitutions on the pyridyl ring (**Table 2-2**, **2-22a-t**). Unsubstituted pyridyl substrates (**2-21a**) or substrates bearing a methyl group at any of one of the C3-C6 positions of the pyridyl ring (**2-21b-e**) afforded moderate to good yields of corresponding pyridopyrimidinone products (**2-22a-e**). Substrates bearing different C5 substitution were well tolerated in this reaction. For example, pyridyl substrates with C5-methyl (**2-21d**), C5-methoxy (**2-21h**), C5-phenyl (**2-21j**), C5-halides (**2-21l-n**), C5-CN group (**2-21q**), C5-$CF_3$ group (**2-21r**) and a C5-ester group (**2-21s**) were successfully converted to the desired C8-substituted products in 36%–84% yield. In addition, a reasonable tolerance for C4/C5-disubstitution was observed with the formation of ring-fused pyridoisoquinolinone **2-22t** (47%). However, substrates bearing C5-$NO_2$ (**2-21bb**) or C5-OTBS (**2-21cc**) group failed to generate the desired products (**2-22bb-cc**) due to the solubility or stability of the substrates. Substrates bearing C3 substitution were synthetically more challenging to obtain; however, a few examples bearing electron rich and poor pyridyl ring were explored. Pyridopyrimidinones with methyl (**2-22b**),

benzyloxy (**2-22i**), and fluorine (**2-22o**) substituents were obtained in yields of 32-75%, and a 3,5-difluorinated substrate was also cyclocarbonylated in good yield (**2-22p**, 68%).

Comparatively, the C4 and C6 positions were more sensitive to the electronic character of the substituent. For C4-substitution of the pyridyl ring, substrates bearing C4-methyl (**2-21c**), C4-cyclopropyl (**2-21f**), C4-methoxy (**2-21g**) and C4-phenyl (**2-21k**) were successfully transformed to the corresponding C7-substituted products in yields of 34-68%. However, substrates with deactivating groups such as C4-F (**2-21dd**) or C4-Br (**2-21ee**) were unreactive under the same conditions to generate **2-22dd** and **2-22ee**. For C6-substituted pyridyl ring, while the C6-methyl substrate performed well to afford **2-22e** in 67% yield, substrates with a C6-F (**2-21ff**) or C6-$OCH_3$ (**2-21gg**) group failed to generate the corresponding products (**2-22ff** and **2-22gg**) under these conditions. It is reasoned that the electron withdrawing -F/-Br atom at C4/6 position reduces the coordination of the pyridine nitrogen with the Pd-catalysts. While the C6-$OCH_3$ substituent has opposing inductive and resonance effects, it appears that the inductive effect of the ortho-methoxy group prevails at the C6 position. The coordination of the pyridine nitrogen is very important in this reaction, which is supported by the failure of reactions using pyrazines in place of the pyridyl group (**2-22hh**), as the additional ring nitrogen inductively pulls the electron density away from the coordinating nitrogen.

**Table 2-2.** Substrate Scope of Substituted 2-Aminopyridyl Substrates with an Appended *NH*-Cycloalkenone[a,b]




[a]Reaction conditions: **2-21a-ii** (0.3 mmol), $Pd(OAc)_2$ (10 mol %), $PPh_3$ (20 mol %), $K_2S_2O_8$ (3 equiv), CO balloon (1 atm), $CH_3CN$ (2 mL), 80 °C and appropriate time listed under the structure. [b]Each yield is averaged from n $\geq$ 2 reactions.

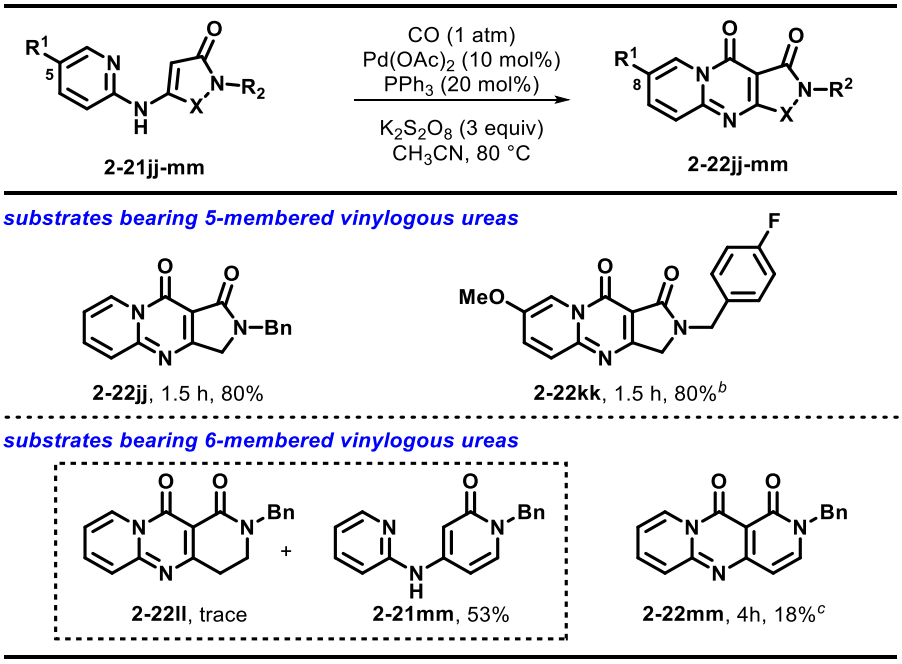
Substrate scope of the unsaturated carbonyl partner appended to the 2-aminopyridyl directing group was also investigated (**Table 2-2**, **2-22a** and **2-22u-aa**). The reactions tolerated a 6- or 5-membered ring cycloalkenone (**2-21a** and **2-21u**) to afford desired 6- or 5-membered ring-fused pyridopyrimidinones (**2-22a** and **2-22u**) in good yield. However, a 7-membered ring-fused analog (**2-22v**) was generated with a diminished yield (39%), presumably due to increased steric effect of the C-H activation step. Several substrates with *NH*-appended C3-substituted cyclohexenones, including alkyl group (**2-21w-x**) and aryl group (**2-21y-aa**), were transformed to the corresponding products (**2-22w-aa**) in 49-83% yield. Substrate bearing a ring-opened unsaturated carbonyl partner appended to the 2-aminopyridyl group has also been investigated (**2-21ii**), however, the desired product (**2-22ii**) was not obtained due to the decomposition of starting material under the same reaction conditions.

Given the tolerance of the reaction for a variety of vinylogous amide substrates, substrates bearing vinylogous ureas were also examined (**Table 2-3**). A reported procedure[22-23] was adapted to prepare the 5-membered vinylogous ureas **2-21jj** and **2-21kk**. (See experimental section) Submission of each to the optimized conditions afforded the corresponding pyrrolidinone-fused pyridopyrimidinones **2-22jj** and **2-22kk** in 80% and 58%, respectively.

While the 5-membered vinylogous ureas **2-21jj-kk** were successfully transformed to desired products, 6-membered substrates did not perform well. The 6-membered vinylogous urea **2-21ll** was prepared by a 5-step protocol[24] (See experimental section) and then submitted to the standard reaction conditions. After 30 min of reaction time, the starting material was consumed, however, only trace amounts of desired product **2-22ll** could be detected by $^{1}$H NMR, and the oxidized vinylogous urea **2-21mm** was isolated in 53% yield. Interestingly, the cyclocarbonylated product **2-22mm**, expected from **2-21mm,** was not detected even after prolonging the reaction for

5 h. Isolated **2-21mm** was resubmitted to the standard reaction conditions resulted in isolation of **2-22mm** in 18% yield after 4h. Prolonging the reaction time and/or adding additional catalyst and/or oxidant did not increase the yield.

**Table 2-3.** Substrate scope of *NH*-Pyridyl Vinylogous Ureas[a]



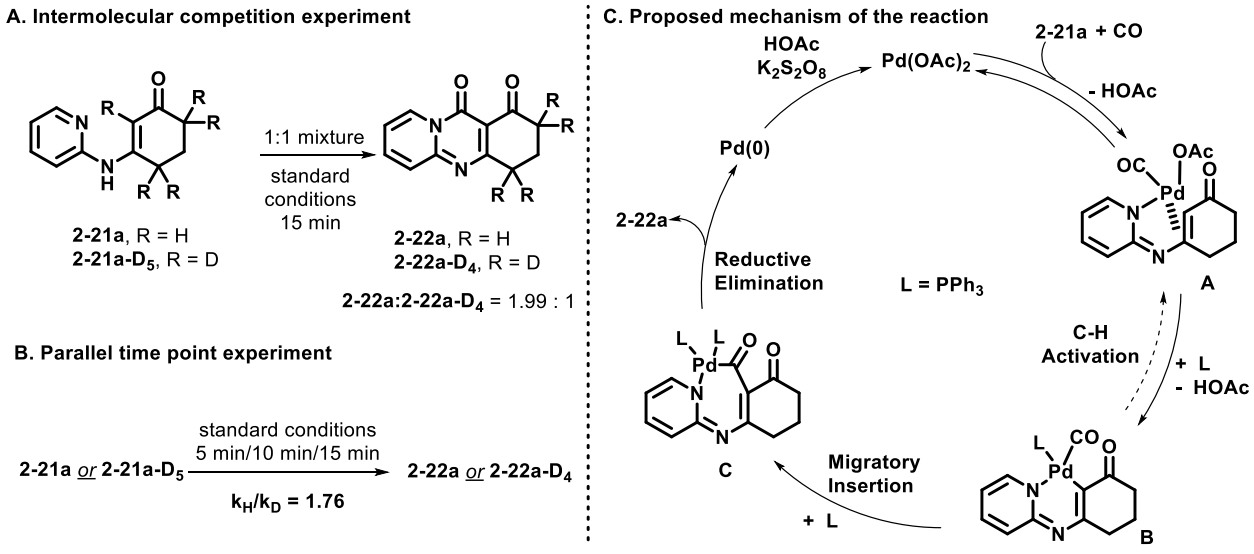

[a]Reaction conditions: **2-21jj-mm** (0.3 mmol), $Pd(OAc)_2$ (10 mol %), $PPh_3$ (20 mol %), $K_2S_2O_8$ (3 equiv), CO balloon (1 atm), $CH_3CN$ (2 mL), 80 °C and appropriate time listed under the structure. [b]The reaction was performed in 0.1 mmol scale. [c]The reaction was performed in 0.2 mmol scale.

## ***Mechanistic Studies***

In order to understand the mechanism of the reactions, deuterium-labeled 3-(pyridin-2-ylamino)cyclohex-2-enone **2-21a-D$_5$** was synthesized to investigate the kinetic isotope effect (**KIE**) of this process.[25] An intermolecular competition experiment was done in which a 1:1 mixture of non-isotopically labeled **2-21a** and deuterated **2-21a-D$_5$** were submitted to the standard reaction conditions. After 15 min, examination by $^1$H NMR showed a 1.99:1 ratio of **2-22a** to **2-22a-D$_4$** (**Scheme 2-3A**). Parallel experiments were also performed in which **2-21a** or **2-21a-D$_5$** was

subjected to the optimized conditions individually, and NMR yields were determined at three time points (5, 10 and 15 min) to calculate a $k_H/k_D$ value of 1.76 (**Scheme 2-3B**). These combined results indicated that the C-H bond activation step might be the turnover-determine step, or C-H activation might be a reversible step that occurs before the turnover-determine step.[25]

A possible mechanism is shown that takes into account the observations from the KIE studies (**Scheme 2-3C**). It is reasoned that the pyridyl nitrogen of **2-21a** coordinates to Pd(II), and subsequent ligand exchange of acetate with CO forms complex **A**. the C($sp^2$)-H activation step with the loss of acetic acid leads to intermediate **B** formation. After migratory insertion of CO to form intermediate **C**, reductive elimination affords product **2-22a** along with Pd(0), which is oxidized by $K_2S_2O_8$ to regenerate the Pd (II) catalyst. It is notable that other palladium catalysts that lacked the acetate ligand were not functional in promoting the reaction (**Table 2-1**, entry 4-5) , which may implicate a Concerted Metallation Deprotonation Pathway (CMD) pathway[26-27] of the C-H activation (not pictured).




**Scheme 2-3.** Evaluation of Kinetic Isotope Effects (A and B) and proposed mechanism (C)

## 2.4 Conclusion

The efficient synthesis of ring-fused pyridopyrimidinediones was demonstrated. Electronic and steric effects, as well as functional group tolerance, was assessed and shown to work for an array of substitution patterns. Aspects of the mechanism leading to these products was explored, revealing that the C-H bond activation step might be the turnover-determine step. The transformation uses pyridyl group to direct the palladium-mediated cyclocarbonylation of vinylogous amides and ureas which are bidirectionally diversified. Notably, the transformation was carried out in a few hours with catalytic quantities of palladium acetate and with atmospheric CO pressure. Over 25 substrates were exemplified under these conditions in yields up to 90%. As the pyridopyrimidine substructure is a well-recognized privileged motif and diverse therapeutic relevance has been reported for related structures,[3-10] we expect to find hits in broad biological screening of these new compounds .

## 2.5 Perspective and future directions

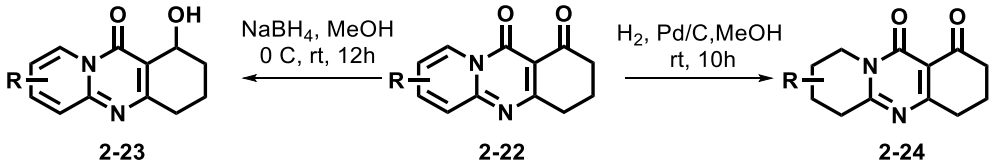
***Limitation of this methodology***

In this methodology, there are some problems that need to be resolved in the future. For example, substrates bearing electron deficient substitution at C4/6 position or bearing heterocycles other than pyridine ring are unreactive under the standard conditions. In addition, the 6-membered vinylogous amides and the ring-opened vinylogous amides are unstable under these conditions. Therefore, the screening of other conditions is needed to facilitate the assembly of these products.

***Follow-up of this work***

After developing this method, a postdoc Dr. Satish C. Philkhana in Golden group made more analogues of these pyridopyrimidinediones using this method. Most of these compounds

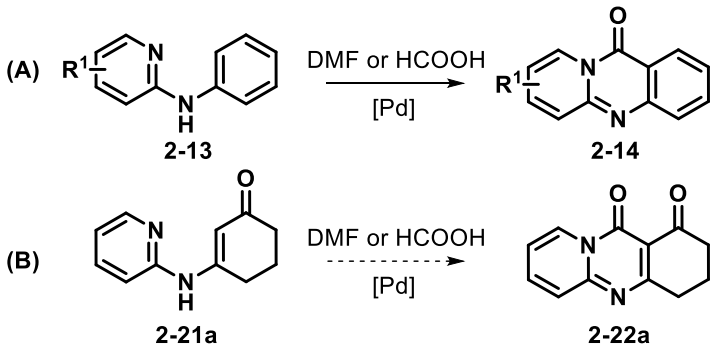
were further derivatized including reduction of the ketones and dearomatized reduction of the pyridyl ring to afford product **2-23** and **2-24**, respectively. These derivatized products, along with the pyridopyrimidinones, have been collectively submitted to a broad-spectrum screening effort that will survey the library for valuable biological activity that can be optimized as part of a traditional medicinal chemistry program. The associated medicinal chemistry investigation will be published in the future. (**Scheme 2-4**)




**Scheme 2-4.** Derivatization of the pyridopyrimidinones

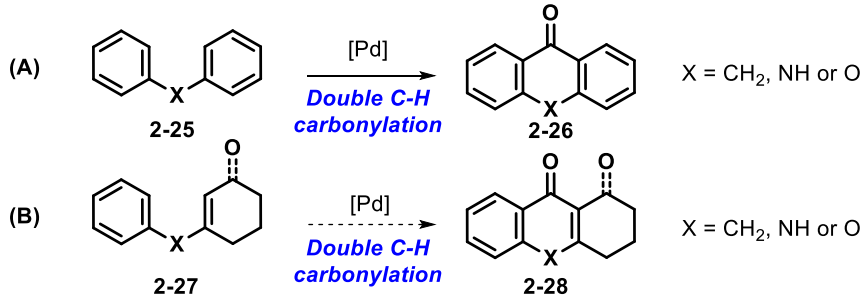
## ***Future directions***

***CO-Free carbonylation reactions*** There is no doubt that CO is a great carbonyl source for the carbonylation reactions, however, it also has its limitations including toxicity, flammability, and complicated gas handling procedures. Therefore, efforts have been spent on alternative CO sources such as DMF, formic acid, etc.[28-31] In recent years, researchers have developed methods using DMF or HCOOH as CO source for the synthesis of pyridopyrimidinones (**Scheme 2-5A**).[32-33] With these successful examples, it is reasonable to expect that we can develop methods to make our pyridopyrimidinediones to replace the use of flammable and toxic CO (**Scheme 2-5B**).




**Scheme 2-5.** (A) Synthesis of pyridopyrimidinones using DMF or HCOOH as CO source; (B) Proposed future directions

***Double C-H activation/carbonylation reactions*** Furthermore, oxidative C–H/C–H carbonylation reactions have been developed in recent years.[34] Selected works in **Scheme 2-6A** show the synthesis of the tricyclic ketone structure (**2-26**) using the oxidative C–H/C–H carbonylation strategy.[35-36] We propose that similar reaction could be achieved through a double C-H carbonylation reaction for making novel scaffolds (**2-28**), which is similar to the pyridopyrimidinediones made in this method.




**Scheme 2-6.** (A) Synthesis of tricyclic ketone motif using double C-H carbonylation reactions; (B) Proposed future directions for making novel scaffolds

## 2.6 Acknowledgement

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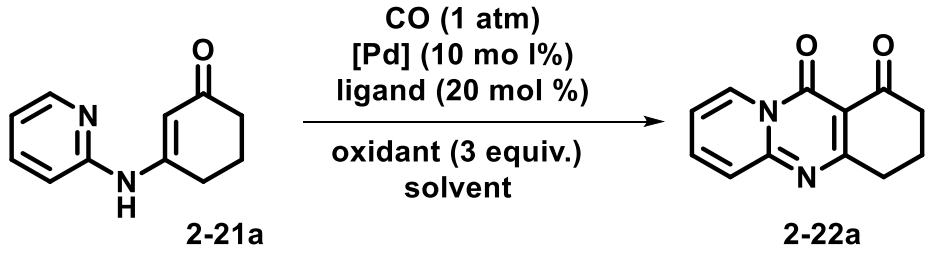
## 2.8 Experimental section

### *2.8.1. General information*

Commercial reagents and solvents were used as received from Sigma Aldrich, Fischer Scientific, Acros Organics, TCI America, Oakwood Products Inc, VWR International, etc. All thin layer chromatography was performed using precoated silica gel plates. Flash chromatography separations were carried out using a Teledyne Isco CombiFlash Rf 200 purification system with silica gel columns. Melting points were measured on OptiMelt MPA100 Automated Melting Point System. $^{1}H$ and $^{13}C$ nuclear magnetic resonance (NMR) spectra were obtained on a Varian Unity-Inova 400 MHz or 500 MHz, or Bruker Ascend 400 MHz in $CDCl_3$ or DMSO-$d_6$. The chemical shifts (δ) reported are given in parts per million (ppm). The Signal splitting patterns were described as s = singlet, d = doublet, t = triplet, q = quartet, p = pentuplet, dd = doublet of doublet, dt = doublet of triplet, td = triplet of doublet, tt = triplet of triplet, ddd = doublet of doublet of doublet, and m = multiplet, with coupling constants (*J*) in hertz (Hz). High resolution mass spectra (HRMS) were performed by Analytical Instrument Center at the School of Pharmacy on an Electron Spray Injection (ESI) mass spectrometer. All final compounds were determined to be of ≥ 95% purity by UV-LCMS at 254 nm.

### *2.8.2. List of screening reaction conditions for optimization*

**Table 2-4.** List of screening reaction conditions for optimization



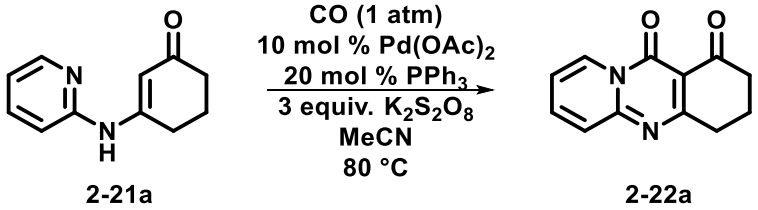
| Entry | [Pd] catalyst (10 mol %) | ligand (20 mol % | oxidant (3 equiv.) | additive (2 equiv.) | solvent (2 mL) | T/°C | time | yield (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | - | $K_2S_2O_8$ | - | TFA | 100 | 3 h | 0 |
| 2 | $Pd(OAc)_2$ | - | $K_2S_2O_8$ | - | Dioxane | 100 | 15 h | 10 |
| 3 | $Pd(OAc)_2$ | - | $K_2S_2O_8$ | TFA | Dioxane | 100 | 12 h | 10 |
| 4 | $Pd(OAc)_2$ | - | $K_2S_2O_8$ | - | Toluene | 100 | 15 h | 9 |
| 5 | 20% $Pd(OAc)_2$ | - | $K_2S_2O_8$ | - | Dioxane | 100 | 15 h | 26 |
| 6 | 1 equiv. $Pd(OAc)_2$ | - | $K_2S_2O_8$ | - | Dioxane | 100 | 15 h | 37 |
| 7 | $PdCl_2(PPh_3)_2$ | - | $K_2S_2O_8$ | - | Dioxane | 100 | 15 h | trace |
| 8 | $Pd(OAc)_2$ | - | $K_2S_2O_8$ | - | Dioxane | 80 | 15 h | trace |
| 9 | $Pd(OAc)_2$ | $PPh_3$ | $K_2S_2O_8$ | - | Dioxane | 100 | 15 h | 48 |
| 10 | $Pd(OAc)_2$ | $PPh_3$ | $K_2S_2O_8$ | - | Dioxane | 80 | 19 h | 25 |
| 11 | $Pd(OAc)_2$ | $PPh_3$ | $K_2S_2O_8$ | - | Dioxane | 100 | 19 h | 25 |
| 12 | $Pd(OAc)_2$ | dppp | $K_2S_2O_8$ | - | Dioxane | 100 | 19 h | 15 |
| 13 | $Pd(OAc)_2$ | $PPh_3$ | $K_2S_2O_8$ | - | Dioxane | 100 | 15 h | 37 |
| 14 | $Pd(OAc)_2$ | $PPh_3$ | $K_2S_2O_8$ | - | Dioxane | 100 | 15 h | 55 |
| 15 | $Pd(OAc)_2$ | dppp | $K_2S_2O_8$ | - | Dioxane | 100 | 15 h | 14 |
| 16 | $Pd(OAc)_2$ | dppp | $K_2S_2O_8$ | - | Dioxane | 100 | 15 h | 13 |
| 17 | $Pd(OAc)_2$ | $PPh_3$ | $K_2S_2O_8$ | - | Dioxane | 100 | 15 h | 45 |
| 18 | $Pd(OAc)_2$ | dppm | $K_2S_2O_8$ | - | Dioxane | 100 | 15 h | 0 |
| 19 | $Pd(OAc)_2$ | dppe | $K_2S_2O_8$ | - | Dioxane | 100 | 15 h | trace |
| 20 | $Pd(OAc)_2$ | dppb | $K_2S_2O_8$ | - | Dioxane | 100 | 15 h | 16 |
| 21 | $PdCl_2(PPh_3)_2$ | $PPh_3$ | $K_2S_2O_8$ | - | Dioxane | 100 | 15 h | 0 |
| 22 | $Pd(OAc)_2$ | $PPh_3$ | $K_2S_2O_8$ | - | Toluene | 100 | 15 h | 11 |
| 23 | $Pd(OAc)_2$ | $PPh_3$ | $K_2S_2O_8$ | - | DMF | 100 | 15 h | 24 |
| 24 | $Pd(OAc)_2$ | $PPh_3$ | $K_2S_2O_8$ | pTSA | Dioxane | 100 | 15 h | 14 |
| 25 | $Pd(OAc)_2$ | $PPh_3$ | $K_2S_2O_8$ | $Cs_2CO_3$ | Dioxane | 100 | 15 h | trace |
| 26 | $Pd(OAc)_2$ | $P(C_6F_5)_3$ | $K_2S_2O_8$ | - | Dioxane | 100 | 15 h | 9 |
| 27 | $Pd(OAc)_2$ | tdmpp | $K_2S_2O_8$ | - | Dioxane | 100 | 15 h | 36 |
| 28 | $Pd(OAc)_2$ | $MePPh_2$ | $K_2S_2O_8$ | - | Dioxane | 100 | 15 h | trace |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 29 | $Pd(OAc)_2$ | dpmpp | $K_2S_2O_8$ | - | Dioxane | 100 | 15 h | 20 |
| 30 | $Pd(OAc)_2$ | tbtfmpp | $K_2S_2O_8$ | - | Dioxane | 100 | 15 h | 22 |
| 31 | $Pd(OAc)_2$ | $PPh_3$ | $Cu(OAc)_2$ | - | Dioxane | 100 | 15 h | 12 |
| 32 | $Pd(OAc)_2$ | tdmpp | $K_2S_2O_8$ | - | Dioxane | 100 | 15 h | 33 |
| 33 | $PdCl_2(PhCN)_2$ | - | $K_2S_2O_8$ | - | Dioxane | 100 | 15 h | 20 |
| 34 | $PdCl_2(PhCN)_2$ | $PPh_3$ | $K_2S_2O_8$ | - | Dioxane | 100 | 15 h | trace |
| 35 | 20% $Pd(OAc)_2$ | 40%$PPh_3$ | $K_2S_2O_8$ | - | Dioxane | 100 | 15 h | 70 |
| 36 | $Pd(OAc)_2$ | $PPh_3$ | Air | - | Dioxane | 100 | 15 h | 41 |
| 37 | $Pd(OAc)_2$ | $PPh_3$ | $K_2S_2O_8$ | - | MeCN | 80 | 15 h | 75 |
| 38 | $Pd(OAc)_2$ | $PPh_3$ | $K_2S_2O_8$ | - | MeCN | 80 | 7 h | 80 |
| 39 | $Pd(OAc)_2$ | - | $K_2S_2O_8$ | - | MeCN | 80 | 7 h | 35 |
| 40 | $Pd(OAc)_2$ | $PPh_3$ | Air | - | MeCN | 80 | 23 h | 25 |
| 41 | $Pd(OAc)_2$ | $PPh_3$ | $K_2S_2O_8$ | - | MeCN | 80 | 3 h | 90 |
| Entry | [Pd] catalyst (10 mol %) | ligand (20 mol % | oxidant (3 equiv.) | additive (2 equiv.) | solvent (2 mL) | T/°C | time | yield (%) |
| 42 | $Pd(OAc)_2$ | $PPh_3$ | $K_2S_2O_8$ | - | MeCN | 60 | 6 h | 72 |
| 43 | 5% $Pd(OAc)_2$ | 10%$PPh_3$ | $K_2S_2O_8$ | - | MeCN | 80 | 3.5 h | 66 |
| 44 | $Pd(OAc)_2$ | $O=PPh_3$ | $K_2S_2O_8$ | - | MeCN | 80 | 3 h | 14 |
| **45** | $Pd(OAc)_2$ | - | $O=PPh_3$ | - | MeCN | 80 | 3 h | trace |
| **46** | **$Pd(OAc)_2$** | **$PPh_3$** | **$K_2S_2O_8$** | **-** | **MeCN 1 mL** | **80** | **3 h** | **91** |
| 47 | **$Pd(OAc)_2$** | **$PPh_3$** | **$K_2S_2O_8$** | **-** | **MeCN 1 mL** | **80** | **3 h** | **89** |
| 48 | $Pd(OAc)_2$ | $PPh_3$ | 2 equiv. $K_2S_2O_8$ | - | MeCN 1 mL | 80 | 3 h | 65 |
| 49 | $Pd(OAc)_2$ | $PPh_3$ | 1 equiv. $K_2S_2O_8$ | - | MeCN 1 mL | 80 | 3 h | 31 |
| 50 | $Pd(OAc)_2$ | $PPh_3$ | $O=PPh_3$ | - | MeCN 1 mL | 80 | 3 h | trace |
| 51 | $Pd(OAc)_2$ | $PPh_3$ | $O_2$:CO = 1:1 | - | MeCN 1 mL | 80 | 8 h | 55 |
| 52 | $Pd(OAc)_2$ | $PPh_3$ | $O_2$:CO = 1:1 | - | MeCN 1 mL | 80 | 8 h | 59 |
| 53 | $Pd(OAc)_2$ | $PPh_3$ | $O_2$:CO = 2:1 | TFA | MeCN 1 mL | 80 | 8 h | 26 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 54 | $Pd(OAc)_2$ | $PPh_3$ | $O_2$:CO = 1:2 | - | MeCN 1 mL | 80 | 3 h | 52 |
| 55 | $Pd(OAc)_2$ | $PPh_3$ | $O_2$:CO = 1:4 | - | MeCN 1 mL | 80 | 3 h | 51 |
| 56 | $PdCl_2(PPh_3)_2$ | - | $K_2S_2O_8$ | - | MeCN 1 mL | 80 | 3 h | 0 |
| 57 | $PdCl_2(PPh_3)_2$ | - | $K_2S_2O_8$ | HOAc (20 mol %) | MeCN 1 mL | 80 | 3 h | 0 |
| 58 | $PdCl_2(PPh_3)_2$ | - | $K_2S_2O_8$ | NaOAc (20 mol %) | MeCN 1 mL | 80 | 3 h | 16 |

Reaction conditions: **2-21a** (0.3 mmol); dppm: 1,3-Bis(diphenylphosphino)methane; dppe: 1,3-Bis(diphenylphosphino)ethane; dppp: 1,3-Bis(diphenylphosphino)propane; dppb: 1,3-Bis(diphenylphosphino)butane; tdmpp: Tris(2,6-dimethoxyphenyl) phosphine; dpmpp: Diphenyl(2-methoxyphenyl)phosphine; tbtfmpp: Tris[3,5-bis(trifluoromethyl)phenyl]phosphine

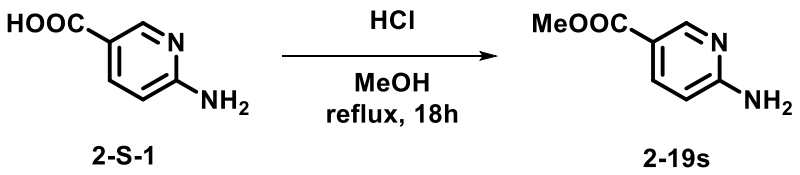
### *2.8.3. Representative Example of Procedure*




**10 mmol scale.** To an oven-dried Schlenk-flask was added **2-21a** (1.88g, 10 mmol), $Pd(OAc)_2$ (225 mg, 1 mmol), $PPh_3$ (525 mg, 2 mmol) and $K_2S_2O_8$ (8.11 g, 30 mmol). A balloon filled with CO was connected to the flask. Then, the flask was evacuated and backfilled with CO. Then MeCN (35 mL) was added into the flask and the mixture was stirred at 80 °C for 4 h. After the completion of the reaction, the mixture was cooled to room temperature and quenched with saturated $NaHCO_3$ (100 mL), and then extracted with DCM (3 × 100 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$ and purified by column chromatography with 5%~15% EtOAc/MeOH, 1.46 g yellowish solid, yield: 68%.

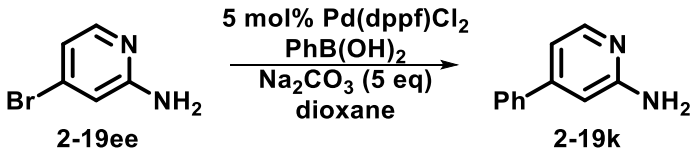
### *2.8.4. Experimental Procedures and Product Characterization*

#### 2.8.4.1 Methods for the preparation of the 2-aminopyridines




2-S-1 2-19s

**Methyl 6-aminonicotinate**. (**2-19a**) To a round bottom flask was added 6-aminonicotinic acid (**2-S-1**, 2.76 g, 20 mmol) and 3 M HCl in MeOH (70 mL), the mixture was refluxed for 18 hours. After the reaction, the solvent was removed under vacuum, the residue was dissolved in ethyl acetate (200 mL) and washed with saturated $Na_2CO_3$ solution and brine, dried over $Na_2SO_4$. The product was used in the next step without further purification; yield: 2.98 g, 98%, white solid; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, *J* = 2.4 Hz, 1H), 8.01 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.47 (d, *J* = 8.6 Hz, 1H), 5.10 (s, 2H), 3.88 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 166.3, 161.2, 151.5, 139.0, 116.5, 107.5, 51.8. Data is consistent with reported data[1].

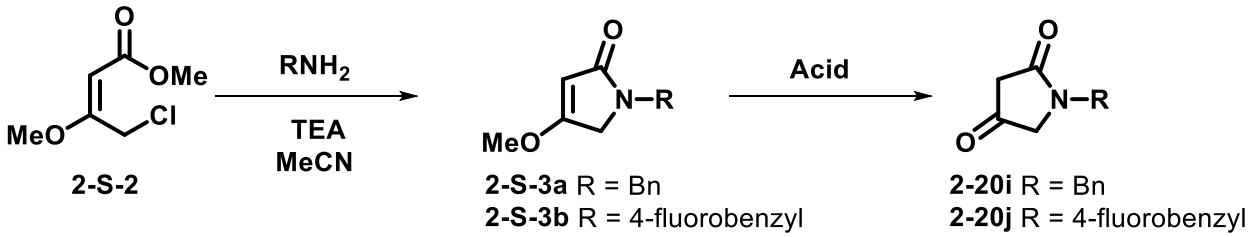



2-19ee 2-19k

**4-phenylpyridin-2-amine**. (**2-19k**) To a Schlenk-flask was added 4-bromopyridine (**2-19ee**, 692 mg, 4 mmol), Phenylboronic acid (586 mg, 4.8 mmol), $Pd(dppf)Cl_2$ (160 mg, 0.2 mmol) and $Na_2CO_3$ (2120 mg, 20 mmol). Then, the flask was evacuated and backfilled with $N_2$. Dioxane (20 mL) was added into the flask and stirred at 80 °C for 6 hours. After the reaction, the mixture was diluted with brine and extracted with DCM for 3 times. The combined organic layer was dried over $Na_2SO_4$ and purified by flash column chromatography. Eluent: EtOAc/Hexane 50%~90%. Yield: 283 mg, 42%, orange solid. Used in the next step directly.

**2.8.4.2 Methods for the preparation of the *N*-substituted tetramic acids and 2,4-piperidine dione:**

**Preparation of tetramic acids:**

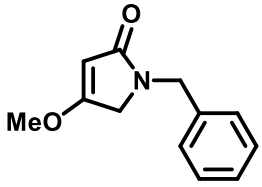



**2-S-2**

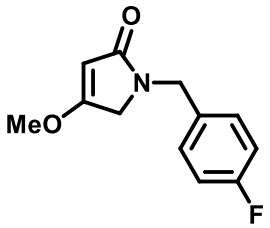
**2-S-3a** R = Bn
**2-S-3b** R = 4-fluorobenzyl

**2-20i** R = Bn
**2-20j** R = 4-fluorobenzyl

**Step 1:** To a refluxing solution of the amine (13 mmol) in MeCN (5 mL) were added dropwise methyl (*E*)-4-chloro-3-methoxy-2-butenoate (**2-S-2**, 1.4 mL, 10 mmol) in MeCN (10 mL) and a solution of $Et_3N$ (1.8 mL, 13 mmol) in MeCN (10 mL) in parallel. After the addition, the reaction was refluxed (set up temperature was 90 °C) for 4 hours. After the reaction, the mixture was cooled to room temperature. The precipitated solid was removed by filtration. The solution was concentrated and purified by flash column chromatography.

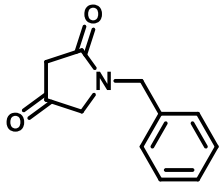



**1-benzyl-4-methoxy-1,5-dihydro-2*H*-pyrrol-2-one**. (**2-S-3a**) Eluent: MeOH/DCM 0.2%~1%; yield: 1.61g, 79%, yellow oil at first and then turned into yellow solid after overnight at RT. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.35 - 7.20 (m, 5H), 5.10 (t, *J* = 0.7 Hz, 1H), 4.56 (s, 2H), 3.76 (s, 3H), 3.72 (d, *J* = 0.6 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 173.5, 172.1, 137.4, 128.7, 127.9, 127.5, 94.2, 58.1, 49.9, 45.3. Data is consistent with the reference[2].

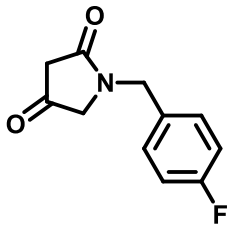



**1-(4-fluorobenzyl)-4-methoxy-1,5-dihydro-2*H*-pyrrol-2-one**. (**2-S-3b**) 20 mmol scale; Eluent: MeOH/DCM 0.2%~2%; yield: 2.7 g, 61%, yellow oil. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.17 (m, 2H), 7.05 – 6.96 (m, 2H), 5.09 (s, 1H), 4.53 (s, 2H), 3.78 (s, 3H), 3.71 (s, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 173.5, 172.1, 162.2 (d, *J* = 245.6 Hz), 133.3 (d, *J* = 3.0 Hz), 129.6 (d, *J* = 8.2 Hz), 115.6 (d, *J* = 21.6 Hz), 94.2, 58.2, 49.9, 44.7. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -115.10. HRMS (ESI) m/z for $C_{12}H_{12}FNO_2$ (M+H), 222.0925 (Calc.), found 222.0924.

**Step 2:**



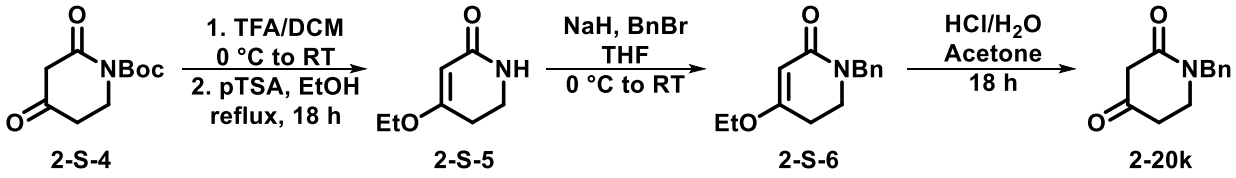

**1-benzylpyrrolidine-2,4-dione**. (**2-20i**) To a vial was added 1-benzyl-4-methoxy-1,5-dihydro-2H-pyrrol-2-one (**S-3**, 1.02 g, 5 mmol) and 9 M sulfuric acid solution (50 mL). The mixture was stirred at room temperature for 3 hours. After the reaction, the mixture was extracted with DCM for 4 times, the combined organic layer was dried over $Na_2SO_4$ and purified by flash column chromatography. Eluent: EtOAc/Hexane 40%~50%; yield: 589 mg, 62%, yellow oil. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.16 (m, 5H), 4.64 (t, *J* = 0.6 Hz, 2H), 3.74 (t, *J* = 1.3 Hz, 2H), 3.11 (tt, *J* = 1.3, 0.6 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 203.2, 168.8, 135.0, 129.0, 128.4, 128.2, 56.8, 46.1, 41.7. Data is consistent with the reference[3].



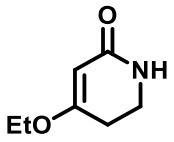
**1-(4-fluorobenzyl)pyrrolidine-2,4-dione**. (**2-20j**) To a vial was added 1-(4-fluorobenzyl)-4-methoxy-1,5-dihydro-2H-pyrrol-2-one (**S-4**, 2.21 g, 10 mmol) and conc. HCl solution (50 mL). The mixture was stirred at room temperature for 6 hours. After the reaction, the mixture was extracted with DCM for 4 times, the combined organic layer was dried over $Na_2SO_4$ and purified by flash column chromatography. Eluent: EtOAc/Hexane 40%~50%; yield: 1.18 mg, 57%, yellow solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 2H), 7.10 – 7.01 (m, 2H), 4.61 (s, 2H), 3.74 (s, 2H), 3.11 (s, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 203.0, 168.8, 162.6 (d, *J* = 247.2 Hz), 131.0 (d, *J* = 3.3 Hz), 130.3 (d, *J* = 8.3 Hz), 116.0 (d, *J* = 21.6 Hz), 56.7, 45.4, 41.7. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -113.65. HRMS (ESI) m/z for $C_{11}H_{10}FNO_2$ (M+H), 208.0768 (Calc.), found 208.0769.

**Preparation of 2,4-piperidinedione:**

We first tried literature method[4] described by Ward et al. to synthesize 2,4-piperidinedione. However, we were not able to isolate the pure intermediate. So we tried a similar method[5] listed here.

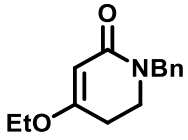



**Step 1.**




**4-ethoxy-5,6-dihydropyridin-2(1*H*)-one**. (**2-S-5**)[5] To a round bottom flask was added tert-butyl 2,4-dioxopiperidine-1-carboxylate (**2-S-4**, 2.13g, 10 mmol), 20 mL DCM and 10 mL trifluoroacetic acid (TFA). The mixture was stirred at room temperature for 1 h. After the reaction, the solvent was removed under reduced pressure. The remaining oil was solved in EtOH (80 mL), *p*-toluenesulfonic acid (190 mg) was added into the mixture. Then the mixture was refluxed under $N_2$ for 18 h. After the completion of the reaction, EtOH was removed and the residue was partitioned between EtOAc and water. The organic layer was separated and the water layer was extracted with EtOAc for 2 times. The combined organic layer was washed with brine, dried and purified by column. Eluent: MeOH/DCM 1%~3%; yield: 1.03 g, 73%, white solid. The product was used in the next step directly.

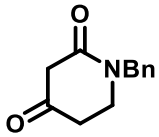
**Step 2.**




**1-benzyl-4-ethoxy-5,6-dihydropyridin-2(*1H*)-one**. (**2-S-6**) To a suspension of NaH (220 mg, 5.5 mmol) in THF (5 mL) was added **4-ethoxy-5,6-dihydropyridin-2(1*H*)-one** (**2-S-5**, 705 mg, 5 mmol) in THF (8 mL) at 0 °C under $N_2$. The resulting mixture was stirred at RT for 15 min and then cooled to 0 °C. To this solution was added a solution of BnBr (0.65 mL, 5.5 mmol) in THF (2 mL) dropwise. The resulting mixture was stirred at RT for 2.5 h. After the completion of the reaction, the mixture was poured into crush ice and extracted with DCM for 3 times. The organic

layer was combined, dried and purified by column. Eluent: EtOAc/Hexane 50%; yield: 1.01 g, 87%, colorless oil. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.20 (m, 5H), 5.14 (s, 1H), 4.61 (s, 2H), 3.89 (q, *J* = 7.1 Hz, 2H), 3.29 (t, *J* = 7.1 Hz, 2H), 2.40 (t, *J* = 7.2 Hz, 2H), 1.35 (t, *J* = 7.0 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 167.7, 167.3, 137.9, 128.6, 128.0, 127.3, 94.7, 64.2, 49.4, 43.7, 28.11, 14.3. The NMR showed minor impurities with the same polarities as the compound **S-6**. It has been used in the next step without further purification.

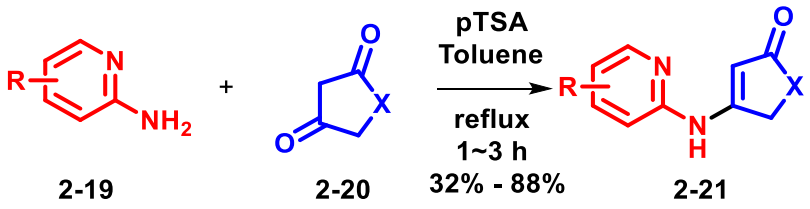
**Step 3.**



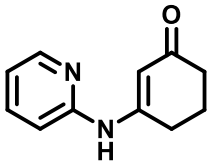

**1-benzylpiperidine-2,4-dione**. (**2-20k**) To a solution of **1-benzyl-4-ethoxy-5,6-dihydropyridin-2(*1H*)-one** (**2-S-6**, 1.01 g, 4.35 mmol) in acetone (20 mL) was added 10% HCl aq. solution (10 mL). The mixture was stirred at RT for 18 h. After the completion of the reaction, the excess of acetone was removed and the residue was extracted with DCM for 3 times. The organic layer was combined, dried and purified by column. Eluent: EtOAc/Hexane 50%~80%; yield: 732 mg, 83%, white solid. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.20 (m, 5H), 4.64 (s, 2H), 3.42 (t, *J* = 6.2 Hz, 2H), 3.37 (s, 2H), 2.48 (t, *J* = 6.2 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 203.4, 166.3, 136.3, 128.9, 128.2, 127.9, 50.1, 48.9, 42.3, 38.7. Data is consistent with the reference[4].

**2.8.4.3 Methods for the preparation of the vinylogous amides and vinylogous urea:**

Unless otherwise noted, the substrates were prepared by the following methods:

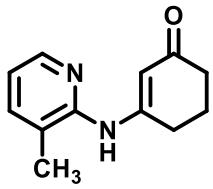



**Procedure:** To an oven-dried flask connected to a Dean-Stark trap was added aminopyridine (**2-19**, 10 mmol), 1,3-dicarbonyl compound (**2-20**, 12.5 mmol) and 1 mmol pTSA·$H_2O$. The mixture was refluxed under $N_2$ until the 2-aminopyrimidine was gone as monitored by TLC. After cooling to room temperature, the reaction mixture was treated with cold 5% $NaHCO_3$ (40 mL) and extracted with DCM (40 mL × 5). The combined organic layer was dried over anhydrous $Na_2SO_4$, concentrated, and then purified through flash column chromatography.

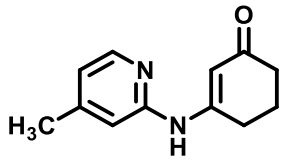



**3-(Pyridin-2-ylamino)cyclohex-2-en-1-one. (2-21a)** 5 h; Eluent: MeOH/DCM 0.2%~5% followed by recrystallization using DCM-MeOH/Hexane; yield: 583 mg, 31%; orange solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.23 (s, 1H), 8.28 (ddd, $J$ = 5.0, 2.0, 0.8 Hz, 1H), 7.68 (ddd, $J$ = 8.3, 7.2, 1.9 Hz, 1H), 7.02 (dt, $J$ = 8.4, 1.0 Hz, 1H), 6.95 (ddd, $J$ = 7.2, 5.0, 1.0 Hz, 1H), 6.84 (s, 1H), 2.54 (t, $J$ = 6.1 Hz, 2H), 2.19 (t, $J$ = 6.5 Hz, 2H), 1.90 (p, $J$ = 6.5 Hz, 2H). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.31 (ddd, $J$ = 4.9, 1.9, 0.9 Hz, 1H), 7.64 (ddd, $J$ = 8.3, 7.3, 1.9 Hz, 1H), 7.10 (dt, $J$ = 8.4, 1.0 Hz, 1H), 6.97 (ddd, $J$ = 7.4, 4.9, 0.9 Hz, 1H), 6.70 (s, 1H), 6.29 (s, 1H), 2.56 (t, $J$ = 6.1 Hz, 2H), 2.41 (t, $J$ = 6.5 Hz, 2H), 2.07 (p, $J$ = 6.3 Hz, 2H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ

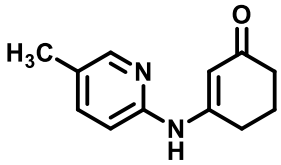
197.9, 158.5, 154.7, 147.9, 138.1, 117.7, 114.2, 105.3, 36.9, 29.2, 22.1. $^{1}$H NMR in $CDCl_3$ is consistent with the reference[6].



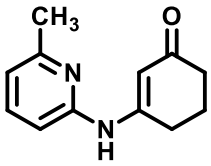

**3-((3-methylpyridin-2-yl)amino)cyclohex-2-en-1-one. (2-21b)** 4 h; Eluent: EtOAc/Hexane 70%~100; yield: 563 mg, 28%; yellow oil. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, *J* = 4.4 Hz, 1H), 7.47 (d, *J* = 7.4 Hz, 1H), 6.95 (dd, *J* = 7.5, 4.8 Hz, 1H), 6.45 – 6.26 (m, 2H), 2.60 (t, *J* = 6.2 Hz, 2H), 2.39 (t, *J* = 6.5 Hz, 2H), 2.26 (s, 3H), 2.07 (p, *J* = 6.3 Hz, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 199.2, 158.6, 151.3, 146.1, 139.1, 123.0, 119.5, 105.4, 36.7, 30.1, 22.0, 17.4. Data is consistent with the reference[6].



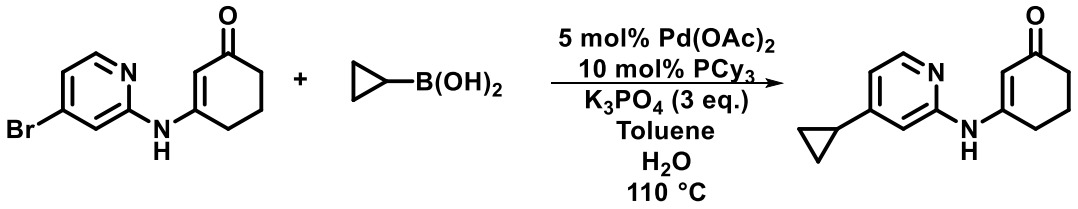

**3-((4-methylpyridin-2-yl)amino)cyclohex-2-en-1-one. (2-21c)** 2 h; Eluent: MeOH/DCM 0.3%~5% followed by recrystallization using DCM/Hexane; yield: 345 mg, 17%; orange solid. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 5.1, 0.7 Hz, 1H), 7.85 (s, 1H), 6.94 (dd, *J* = 1.5, 0.8 Hz, 1H), 6.77 (ddd, *J* = 5.2, 1.5, 0.7 Hz, 1H), 6.29 (s, 1H), 2.55 (t, *J* = 6.1 Hz, 2H), 2.41 - 2.33 (m, 2H), 2.29 (s, 3H), 2.08 - 1.96 (m, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.3, 159.0, 152.8, 149.6, 147.9, 120.1, 114.8, 103.6, 36.6, 30.0, 21.8, 21.2. Data is consistent with the reference[6].



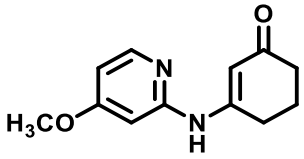
**3-((5-methylpyridin-2-yl)amino)cyclohex-2-en-1-one. (2-21d)** 3 h; Eluent: MeOH/DCM 0.3%~5% followed by recrystallization using DCM/Hexane; yield: 650 mg, 32%; orange solid. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.11 - 8.04 (m, 1H), 7.87 (s, 1H), 7.40 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.27 (s, 1H), 2.54 (t, *J* = 6.1 Hz, 2H), 2.36 (t, *J* = 6.5 Hz, 2H), 2.25 (s, 3H), 2.01 (p, *J* = 6.5 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.2, 159.3, 150.5, 148.2, 138.7, 128.2, 114.2, 103.2, 36.6, 29.9, 21.8, 17.8. Data is consistent with the reference[6].



**3-((6-methylpyridin-2-yl)amino)cyclohex-2-en-1-one. (2-21e)** 1 h; Eluent: MeOH/DCM 0.3%~5% followed by recrystallization using DCM/Hexane; yield: 643 mg, 32%; orange solid. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.49 (t, *J* = 7.8 Hz, 1H), 7.15 (s, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.80 (d, *J* = 7.4 Hz, 1H), 6.34 (s, 1H), 2.53 (t, *J* = 6.2 Hz, 2H), 2.43 (s, 3H), 2.40 - 2.34 (m, 2H), 2.03 (p, *J* = 6.5 Hz, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 199.3, 158.7, 157.8, 151.9, 138.3, 118.2, 111.1, 104.0, 36.7, 30.3, 24.3, 21.8. Data is consistent with the reference[6].

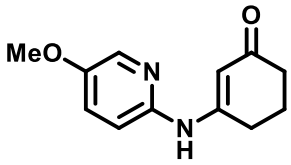



**3-((4-cyclopropylpyridin-2-yl)amino)cyclohex-2-en-1-one. (2-21f)** To a schlenk-flask was added **1o** (534 mg, 2 mmol), cyclopropylboronic acid (224 mg, 2.6 mmol), $Pd(OAc)_2$ (22.4 mg, 0.1 mmol) and $K_3PO_4$ (1272 mg, 6 mmol). Then, the flask was evacuated and backfilled with $N_2$. Toluene (20 mL) and $H_2O$ (2 mL) were added into the flask and stirred at 110 °C for 7 hours. After the reaction, the mixture was diluted with DCM and washed with brine. The organic layer was dried over $Na_2SO_4$ and purified by column. Eluent: Eluent: EtOAc/Hexane 50%~80%; yield: 325 mg, 71%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 5.3 Hz, 1H), 7.28 (s, 1H), 6.86 (d, *J* = 1.4 Hz, 1H), 6.58 (dd, *J* = 5.3, 1.5 Hz, 1H), 6.24 (s, 1H), 2.55 (t, *J* = 6.2 Hz, 2H), 2.40 (t, *J* = 6.5 Hz, 2H), 2.06 (p, *J* = 6.4 Hz, 2H), 1.89 - 1.78 (m, 1H), 1.15 - 1.03 (m, 2H), 0.85 - 0.70 (m, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.07, 158.60, 156.43, 152.40, 148.10, 115.56, 111.61, 103.72, 36.61, 30.18, 21.74, 15.31, 10.63.

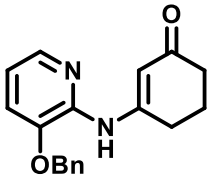



**3-((4-methoxypyridin-2-yl)amino)cyclohex-2-en-1-one. (2-21g)** 3.5 h; Eluent: MeOH/DCM 0.2%~5%, followed by recrystallization using DCM-MeOH/Hexane; yield: 669 mg, 31%; yellow solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 5.8 Hz, 1H), 7.49 (s, 1H), 6.63 (d, *J* = 2.2 Hz, 1H), 6.54 (dd, *J* = 5.8, 2.2 Hz, 1H), 6.26 (s, 1H), 3.83 (s, 3H), 2.56 (t, *J* = 6.2 Hz, 2H), 2.44 - 2.36

(m, 2H), 2.05 (p, *J* = 6.4 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.1, 167.3, 158.6, 154.0, 149.4, 106.0, 104.1, 99.5, 55.4, 36.6, 30.1, 21.7. HRMS (ESI) m/z for $C_{12}H_{14}N_2O_2$ (M+H), 219.1128 (Calc.), found 219.1125.

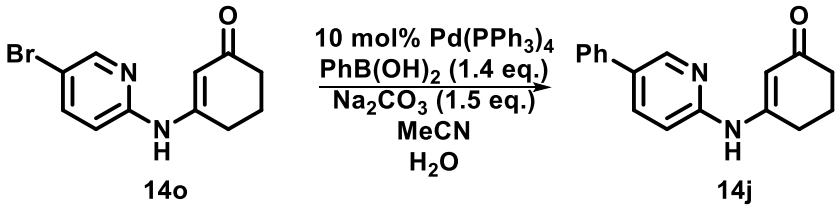



**3-((5-methoxypyridin-2-yl)amino)cyclohex-2-en-1-one. (2-21h)** 4 h; Eluent: MeOH/DCM 1%~5%; yield: 1600 mg, 76%; orange solid. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 3.1, 0.7 Hz, 1H), 7.28 (s, 1H), 7.19 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.07 (dd, *J* = 8.9, 0.7 Hz, 1H), 6.12 (s, 1H), 3.82 (s, 3H), 2.53 (t, *J* = 6.2 Hz, 2H), 2.37 (t, *J* = 6.3 Hz, 2H), 2.03 (p, *J* = 6.4 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.0, 159.4, 152.4, 145.8, 134.8, 123.7, 115.6, 102.2, 56.0, 36.6, 30.0, 21.8. HRMS (ESI) m/z for $C_{12}H_{14}N_2O_2$ (M+H), 219.1128 (Calc.), found 219.1130.

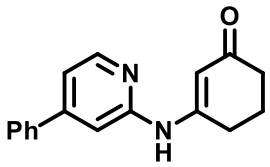



**3-((3-(benzyloxy)pyridin-2-yl)amino)cyclohex-2-en-1-one. (2-21i)** 5 h; Eluent: EtOAc/Hexane 50%~80%, followed by recrystallization using DCM/Hexane; yield: 783 mg, 27%; yellow solid. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 4.9 Hz, 1H), 7.49 - 7.34 (m, 5H), 7.22 (s, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 6.98 (s, 1H), 6.83 (dd, *J* = 8.0, 5.0 Hz, 1H), 5.13 (s, 2H), 2.56 (t, *J* = 6.2 Hz, 2H), 2.39 (t, *J* = 6.6 Hz, 2H), 2.06 (p, *J* = 6.4 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.67, 156.5,

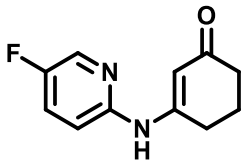
144.4, 142.6, 139.1, 135.5, 128.9, 128.7, 127.6, 117.6, 117.3, 107.1, 70.9, 36.7, 30.4, 21.9. HRMS (ESI) m/z for $C_{18}H_{18}N_2O_2$ (M+H), 295.1441 (Calc.), found 295.1439.



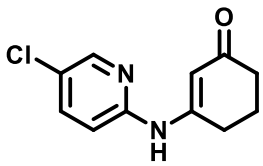

**3-((5-phenylpyridin-2-yl)amino)cyclohex-2-en-1-one. (2-21j)** To a Schlenk-flask was added **2-21o** (534 mg, 2 mmol), Phenylboronic acid (342 mg, 2.8 mmol), $Pd(PPh_3)_4$ (231 mg, 0.2 mmol) and $Na_2CO_3$ (318 mg, 3 mmol). Then, the flask was evacuated and backfilled with $N_2$. MeCN (15 mL) and $H_2O$ (5 mL) were added into the flask and stirred at 90 °C for 17 hours. After the reaction, the mixture was diluted with EtOAc and washed with brine for 2 times. The organic layer was dried over $Na_2SO_4$ and purified by column. Eluent: Eluent: EtOAc/Hexane 50%~70%; yield: 487 mg, 92%; yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 2.4 Hz, 1H), 7.84 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.57 - 7.51 (m, 2H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.40 - 7.36 (m, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 7.16 (s, 1H), 6.38 (s, 1H), 2.59 (t, *J* = 6.1 Hz, 2H), 2.43 (t, *J* = 6.3 Hz, 2H), 2.08 (p, *J* = 6.3 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.1, 158.1, 151.6, 146.7, 137.2, 136.5, 131.8, 129.1, 127.9, 126.7, 113.7, 104.4, 36.6, 30.2, 21.8. HRMS (ESI) m/z for $C_{17}H_{16}N_2O$ (M+H), 265.1335 (Calc.), found 265.1332.



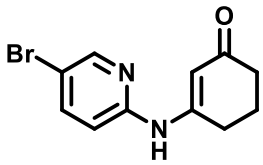
**3-((4-phenylpyridin-2-yl)amino)cyclohex-2-en-1-one. (2-21k)** 2 mmol scale, 3 h; Eluent: EtOAc/Hexane 50%~70%; yield: 324 mg, 62%; yellow solid. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 5.2 Hz, 1H), 7.64 - 7.55 (m, 2H), 7.52 - 7.41 (m, 3H), 7.29 (d, *J* = 1.5 Hz, 1H), 7.19 (dd, *J* = 5.2, 1.5 Hz, 1H), 7.01 (s, 1H), 6.36 (s, 1H), 2.60 (t, *J* = 6.1 Hz, 2H), 2.42 (t, *J* = 6.5 Hz, 2H), 2.09 (p, *J* = 6.4 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.1, 158.1, 153.0, 151.0, 148.9, 137.8, 129.4, 129.2, 127.1, 117.2, 111.7, 104.3, 36.6, 30.4, 21.8. HRMS (ESI) m/z for $C_{17}H_{16}N_2O$ (M+H), 265.1335 (Calc.), found 265.1331.



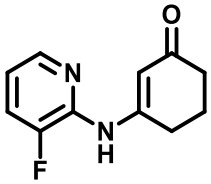

**3-((5-fluoropyridin-2-yl)amino)cyclohex-2-en-1-one. (2-21l)** 3 h; Eluent: MeOH/DCM 1%~5%; yield: 1680 mg, 81%; yellowish solid. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.08 (d, *J* = 3.0 Hz, 1H), 7.31 (ddd, *J* = 8.9, 7.6, 3.0 Hz, 1H), 7.04 (dd, *J* = 9.0, 3.7 Hz, 1H), 6.57 (s, 1H), 2.57 (t, *J* = 6.1 Hz, 2H), 2.36 (t, *J* = 6.4 Hz, 2H), 2.01 (p, *J* = 6.6 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.9, 159.7, 155.7 (d, *J* = 251.1 Hz), 149.5 (d, *J* = 2.3 Hz), 135.3 (d, *J* = 25.0 Hz), 125.3 (d, *J* = 20.3 Hz), 115.3 (d, *J* = 4.4 Hz), 103.7, 36.6, 29.7, 21.8. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -133.57. HRMS (ESI) m/z for $C_{11}H_{11}FN_2O$ (M+H), 207.0928 (Calc.), found 207.0918.



**3-((5-chloropyridin-2-yl)amino)cyclohex-2-en-1-one. (2-21m)** 3 h; Eluent: MeOH/DCM 1%~5%; yield: 1920 mg, 86%; yellowish solid. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 2.6 Hz, 1H), 7.55 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.44 (s, 1H), 7.01 (d, *J* = 8.8 Hz, 1H), 6.44 (s, 1H), 2.57 (t, *J* = 6.1 Hz, 2H), 2.39 (t, *J* = 6.3 Hz, 2H), 2.05 (p, *J* = 6.5 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.5, 158.3, 151.2, 146.9, 137.7, 125.7, 114.6, 104.9, 36.6, 30.0, 21.8. Data is consistent with the reference[6].

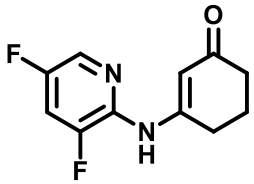



**3-((5-bromopyridin-2-yl)amino)cyclohex-2-en-1-one. (2-21n)** 3 h; Eluent: MeOH/DCM 1%~5%; yield: 2200 mg, 82%; yellowish solid. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 2.4, 0.7 Hz, 1H), 7.68 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.42 (s, 1H), 6.96 (d, *J* = 8.7 Hz, 1H), 6.44 (s, 1H), 2.57 (t, *J* = 6.1 Hz, 2H), 2.39 (t, *J* = 6.3 Hz, 2H), 2.05 (p, *J* = 6.4 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.5, 158.2, 151.5, 149.1, 140.4, 115.0, 113.5, 105.1, 36.6, 30.1, 21.7. Data is consistent with the reference[6].

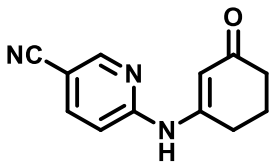



**3-((3-fluoropyridin-2-yl)amino)cyclohex-2-en-1-one. (2-21o)** 3 h; Eluent: MeOH/DCM 0.2%~2%; yield: 1329 mg, 64%; yellow solid.$^{1}$H NMR (500 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 5.0, 1.4

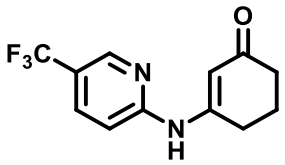
Hz, 1H), 7.35 (ddd, *J* = 10.8, 8.1, 1.5 Hz, 1H), 7.10 (s, 1H), 6.92 (ddd, *J* = 8.2, 4.9, 3.6 Hz, 1H), 6.67 (s, 1H), 2.62 (t, *J* = 6.2 Hz, 2H), 2.41 (t, *J* = 6.6 Hz, 2H), 2.10 (p, *J* = 6.4 Hz, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 199.7, 156.3, 148.1 (d, *J* = 257.1 Hz), 143.1 (d, *J* = 6.3 Hz), 143.1 (d, *J* = 10.2 Hz), 122.1 (d, *J* = 16.2 Hz), 118.0 (d, *J* = 2.4 Hz), 107.7, 36.7, 30.2, 21.9. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -136.58. HRMS (ESI) m/z for $C_{11}H_{11}FN_2O$ (M+H), 207.0928 (Calc.), found 207.0925.



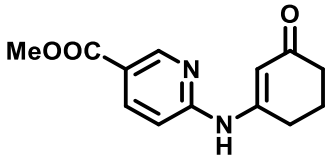

**3-((3,5-difluoropyridin-2-yl)amino)cyclohex-2-en-1-one. (2-21p)** 10 mmol scale, 4 h; Eluent: EtOAc/Hexane 60%~100%; yield: 1230 mg, 55%; yellow solid.$^{1}$H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 2.6 Hz, 1H), 7.23 (ddd, *J* = 10.3, 7.5, 2.7 Hz, 1H), 6.96 (s, 1H), 6.56 (s, 1H), 2.60 (t, *J* = 6.2 Hz, 2H), 2.41 (t, *J* = 6.6 Hz, 2H), 2.10 (p, *J* = 6.3 Hz, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 199.8, 157.4, 154.5 (dd, *J* = 256.2, 3.5 Hz), 147.6 (dd, *J* = 264.3, 5.9 Hz), 139.4 (dd, *J* = 9.5, 2.3 Hz), 130.0 (dd, *J* = 24.0, 5.5 Hz), 111.9 (dd, *J* = 23.4, 19.3 Hz), 106.4, 36.6, 29.8, 21.9. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -131.30 (d, *J* = 2.7 Hz), -131.50 (d, *J* = 2.7 Hz). HRMS (ESI) m/z for $C_{11}H_{10}F_2N_2O$ (M+H), 225.0834 (Calc.), found 225.0831.



**6-((3-oxocyclohex-1-en-1-yl)amino)nicotinonitrile. (2-21q)** 4h, after the reaction, the mixture was dilute with DCM, the solid was filtered out and washed with DCM and water, dried to get the clean product; yield: 1.57 g, 74%; yellow solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 9.71 (s, 1H), 8.74 (d, $J$ = 2.3 Hz, 1H), 8.06 (dd, $J$ = 8.7, 2.3 Hz, 1H), 7.10 (d, $J$ = 8.7 Hz, 1H), 6.92 (s, 1H), 2.57 (t, $J$ = 6.1 Hz, 2H), 2.23 (t, $J$ = 6.5 Hz, 2H), 1.94 (p, $J$ = 6.3 Hz, 2H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 198.48, 157.27, 157.06, 152.66, 140.64, 118.18, 113.79, 108.54, 101.18, 36.87, 29.11, 21.93.

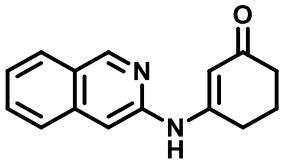



**3-((5-(trifluoromethyl)pyridin-2-yl)amino)cyclohex-2-en-1-one. (2-21r)** 3 h; Eluent: MeOH/DCM 0.2%~5%; yield: 1960 mg, 77%; yellow solid. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, $J$ = 2.4 Hz, 1H), 7.87 (s, 1H), 7.78 (dd, $J$ = 8.7, 2.4 Hz, 1H), 7.10 (d, $J$ = 8.7 Hz, 1H), 6.72 (s, 1H), 2.64 (t, $J$ = 6.1 Hz, 2H), 2.42 (t, $J$ = 6.5 Hz, 2H), 2.09 (p, $J$ = 6.3 Hz, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 200.0, 158.0, 155.8, 145.8 (q, $J$ = 4.3 Hz), 135.0 (q, $J$ = 3.3 Hz), 123.7 (q, $J$ = 271.4 Hz), 120.7 (q, $J$ = 33.4 Hz), 112.8, 107.0, 36.7, 30.0, 21.8. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -61.85. HRMS (ESI) m/z for $C_{12}H_{11}F_3N_2O$ (M+H), 257.0896 (Calc.), found 257.0894.

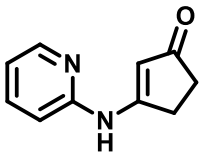



**Methyl 6-((3-oxocyclohex-1-en-1-yl)amino)nicotinate. (2-21s)** 10 mmol scale, 3 h; Eluent: EtOAc/Hexane 50%~100%; yield: 1341 mg, 88%; yellow solid. $^{1}$H NMR (500 MHz, $CDCl_3$) δ

8.89 (d, *J* = 2.2 Hz, 1H), 8.17 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.66 (s, 1H), 7.06 (d, *J* = 8.7 Hz, 1H), 6.63 (s, 1H), 3.92 (s, 3H), 2.63 (t, *J* = 6.1 Hz, 2H), 2.43 (t, *J* = 6.5 Hz, 2H), 2.09 (p, *J* = 6.4 Hz, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 199.7, 165.5, 157.6, 156.1, 150.7, 139.0, 120.3, 112.3, 107.1, 52.3, 36.7, 30.1, 21.8. HRMS (ESI) m/z for $C_{13}H_{14}N_2O_3$ (M+H), 247.1077 (Calc.), found 247.1072.

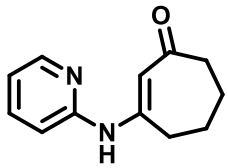



**3-(isoquinolin-3-ylamino)cyclohex-2-en-1-one. (2-21t)** 4 h; Eluent: MeOH/DCM 1%~5%; yield: 2060 mg, 87%; light brown solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 1H), 7.66 - 7.58 (m, 1H), 7.56 - 7.39 (m, 3H), 6.22 (s, 1H), 2.61 (t, *J* = 6.1 Hz, 2H), 2.43 (t, *J* = 6.3 Hz, 2H), 2.08 (p, *J* = 6.4 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.1, 158.8, 151.8, 147.2, 137.7, 131.2, 127.6, 126.2, 126.1, 125.9, 108.3, 102.7, 36.6, 30.3, 21.8. HRMS (ESI) m/z for $C_{15}H_{14}N_2O$ (M+H), 239.1179 (Calc.), found 239.1179.

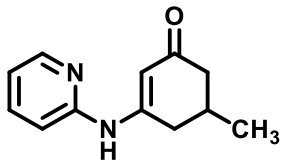



**3-(pyridin-2-ylamino)cyclopent-2-en-1-one. (2-21u)** 5 h; Eluent: MeOH/DCM 0.3%~5% followed by recrystallization using DCM/Hexane; yield: 615 mg, 35%; yellow solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.06 (s, 1H), 8.30 (ddd, *J* = 5.0, 1.9, 0.9 Hz, 1H), 7.71 (ddd, *J* = 8.3, 7.3, 1.9 Hz, 1H), 7.02 (dt, *J* = 8.3, 1.0 Hz, 1H), 6.98 (ddd, *J* = 7.2, 5.0, 1.0 Hz, 1H), 6.35 (s, 1H), 2.82 - 2.71 (m, 2H), 2.24 - 2.14 (m, 2H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 205.9, 169.6, 154.1, 148.3,

138.4, 118.0, 113.1, 107.7, 32.8, 29.3. HRMS (ESI) m/z for $C_{10}H_{10}N_2O$ (M+H), 175.0866 (Calc.), found 175.0867.

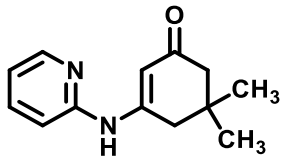


**3-(pyridin-2-ylamino)cyclohept-2-en-1-one. (2-21v)** 3 mmol scale, 3 h; Eluent: EtOAc/Hexane 50%~100% followed by recrystallization using DCM/Hexane; yield: 296 mg, 49%; yellow solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 5.0, 1.8 Hz, 1H), 7.61 (td, *J* = 7.6, 1.9 Hz, 1H), 7.19 (s, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 6.94 (dd, *J* = 7.3, 5.0 Hz, 1H), 6.33 (s, 1H), 2.71 – 2.59 (m, 4H), 1.93 (p, *J* = 6.7, 6.3 Hz, 2H), 1.90 – 1.81 (m, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 203.0, 157.4, 153.0, 148.6, 138.0, 118.5, 114.3, 107.3, 41.2, 34.0, 24.0, 21.4. HRMS (ESI) m/z for $C_{12}H_{14}N_2O$ (M+H), 203.1179 (Calc.), found 203.1177.

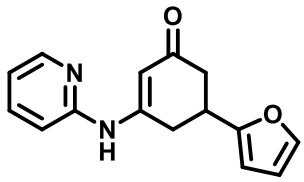


**5-methyl-3-(pyridin-2-ylamino)cyclohex-2-en-1-one. (2-21w)** 3 h; Eluent: EtOAc/Hexane 40%~70%; yield: 860 mg, 43%; light orange solid$^1$H NMR (500 MHz, $CDCl_3$) δ 8.30 (ddd, *J* = 5.0, 1.9, 0.9 Hz, 1H), 7.62 (ddd, *J* = 8.3, 7.3, 1.9 Hz, 1H), 7.59 (s, 1H), 7.09 (dt, *J* = 8.3, 1.0 Hz, 1H), 6.96 (ddd, *J* = 7.3, 4.9, 0.9 Hz, 1H), 6.42 (s, 1H), 2.55 – 2.43 (m, 2H), 2.41 – 2.24 (m, 2H), 2.15 – 2.06 (m, 1H), 1.15 – 1.05 (m, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 199.5, 158.1, 152.9,

148.4, 138.0, 118.6, 114.2, 103.8, 45.0, 38.3, 29.3, 21.1. HRMS (ESI) m/z for $C_{12}H_{14}N_2O$ (M+H), 203.1179 (Calc.), found 203.1176.

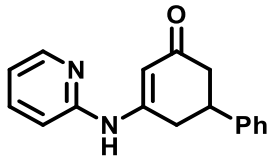


**5,5-dimethyl-3-(pyridin-2-ylamino)cyclohex-2-en-1-one. (2-21x)** 5 mmol scale, 3 h. Eluent: EtOAc/Hexane 40%~60% followed by recrystallization using DCM-MeOH/Hexane; yield: 489 mg, 37%; yellow solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.30 (ddd, *J* = 5.0, 1.9, 0.9 Hz, 1H), 7.62 (ddd, *J* = 8.3, 7.3, 1.9 Hz, 1H), 7.37 (s, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 6.96 (ddd, *J* = 7.4, 4.9, 0.9 Hz, 1H), 6.45 (s, 1H), 2.42 (s, 2H), 2.27 (s, 2H), 1.11 (s, 6H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 199.2, 156.7, 152.9, 148.5, 138.0, 118.6, 114.1, 103.1, 50.5, 44.0, 32.8, 28.4. HRMS (ESI) m/z for $C_{13}H_{16}N_2O$ (M+H), 217.1335 (Calc.), found 217.1333.

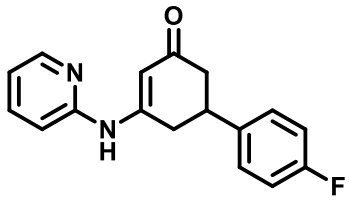


**5-(furan-2-yl)-3-(pyridin-2-ylamino)cyclohex-2-en-1-one. (2-21y)** 10 mmol scale, 3 h; Eluent: EtOAc/Hexane 30%~60%, followed by recrystallization using DCM-MeOH/Hexane; yield: 823 mg, 32%; red solid.$^1$H NMR (500 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 5.0, 1.8 Hz, 1H), 7.63 (td, *J* = 7.8, 1.9 Hz, 1H), 7.41 (s, 1H), 7.34 (d, *J* = 1.7 Hz, 1H), 7.09 (d, *J* = 8.2 Hz, 1H), 6.97 (dd, *J* = 7.3, 4.9 Hz, 1H), 6.45 (s, 1H), 6.31 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.09 (d, *J* = 3.2 Hz, 1H), 3.58 - 3.48 (m, 1H),

2.92 - 2.81 (m, 2H), 2.79 - 2.71 (m, 1H), 2.66 - 2.56 (m, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 197.7, 157.0, 156.1, 152.7, 148.5, 141.6, 138.1, 118.8, 114.2, 110.3, 104.8, 104.1, 40.9, 34.8, 33.3. HRMS (ESI) m/z for $C_{15}H_{14}N_2O_2$ (M+H), 255.1128 (Calc.), found 255.1124.

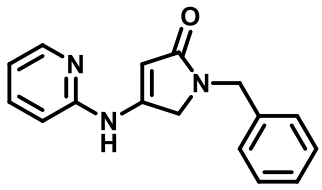



**5-(pyridin-2-ylamino)-1,6-dihydro-[1,1'-biphenyl]-3(*2H*)-one. (2-21z)** 3 h. Eluent: EtOAc/Hexane 30%~60%; yield: 669 mg, 31%; yellowish solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 5.1, 1.8 Hz, 1H), 7.62 (td, *J* = 7.8, 2.0 Hz, 1H), 7.44 (s, 1H), 7.38 - 7.30 (m, 2H), 7.30 - 7.21 (m, 3H), 7.10 (d, *J* = 8.3 Hz, 1H), 6.96 (ddd, *J* = 7.4, 5.0, 0.9 Hz, 1H), 6.49 (d, *J* = 1.4 Hz, 1H), 3.47 - 3.35 (m, 1H), 2.94 - 2.83 (m, 1H), 2.74 - 2.57 (m, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 198.5, 157.6, 152.7, 148.6, 142.9, 138.1, 128.9, 127.1, 126.8, 118.8, 114.2, 104.1, 43.7, 39.9, 37.7. HRMS (ESI) m/z for $C_{17}H_{16}N_2O$ (M+H), 265.1335 (Calc.), found 265.1330.

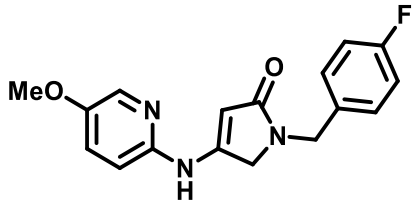



**4'-fluoro-5-(pyridin-2-ylamino)-1,6-dihydro-[1,1'-biphenyl]-3(2*H*)-one. (2-21aa)** 4 mmol scale, 3.5 h; Eluent: EtOAc/Hexane 30%~65%, followed by recrystallization using DCM-MeOH/Hexane; yield: 406 mg, 36%; red solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 5.0, 1.8 Hz, 1H), 7.64 (td, *J* = 7.8, 1.9 Hz, 1H), 7.28 (s, 1H), 7.22 (dd, *J* = 8.5, 5.4 Hz, 2H), 7.09 (d, *J*

= 8.3 Hz, 1H), 7.03 (t, *J* = 8.6 Hz, 2H), 6.97 (dd, *J* = 7.3, 4.9 Hz, 1H), 6.47 (s, 1H), 3.45 - 3.36 (m, 1H), 2.89 - 2.81 (m, 1H), 2.72 - 2.55 (m, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 198.2, 161.8 (d, *J* = 245.5 Hz), 157.3, 152.6, 148.6, 138.6 (d, *J* = 3.3 Hz), 138.1, 128.3 (d, *J* = 7.9 Hz), 118.9, 115.7 (d, *J* = 21.3 Hz), 114.1, 104.1, 43.8, 39.2, 37.9. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -115.57. HRMS (ESI) m/z for $C_{17}H_{15}FN_2O$ (M+H), 283.1241 (Calc.), found 283.1239.

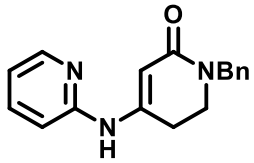



**1-benzyl-4-(pyridin-2-ylamino)-1,5-dihydro-2*H*-pyrrol-2-one. (2-21jj)** 4.7 mmol scale, 1.5 h. Eluent: EtOAc/Hexane 50%~100%; yield: 401 mg, 32%; brown solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.20 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 1H), 7.94 (s, 1H), 7.54 (ddd, *J* = 8.0, 7.4, 1.9 Hz, 1H), 7.34 - 7.28 (m, 2H), 7.26 - 7.21 (m, 3H), 6.87 - 6.80 (m, 2H), 5.72 (s, 1H), 4.62 (s, 2H), 4.26 (s, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 173.4, 154.0, 153.3, 148.1, 137.9, 137.8, 128.7, 127.7, 127.4, 117.0, 111.0, 97.4, 52.1, 45.6. HRMS (ESI) m/z for $C_{16}H_{15}N_3O$ (M+H), 266.1288 (Calc.), found 266.1289.

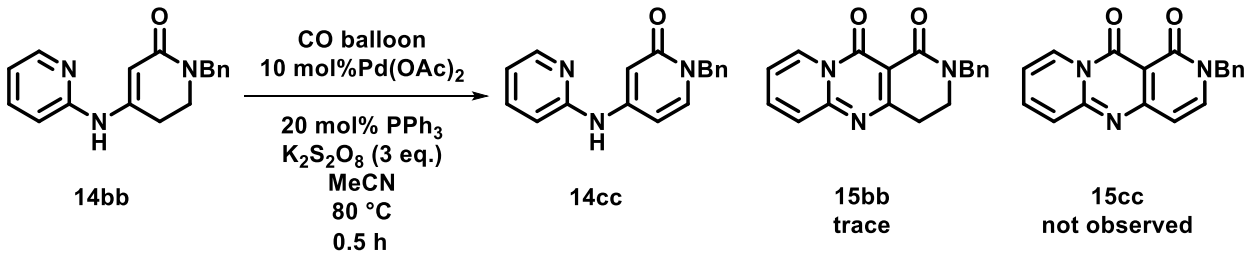



**1-(4-fluorobenzyl)-4-((5-methoxypyridin-2-yl)amino)-1,5-dihydro-2*H*-pyrrol-2-one. (2-21kk)** 1 mmol scale, 3 h. Eluent: MeOH/DCM 0.2%~1%; yield: 48 mg, 15%; yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 3.0 Hz, 1H), 7.75 (s, 1H), 7.25 - 7.12 (m, 3H), 6.98 (t, *J* = 8.4

Hz, 2H), 6.80 (d, *J* = 8.9 Hz, 1H), 5.63 (s, 1H), 4.57 (s, 2H), 4.17 (s, 2H), 3.81 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 173.6, 162.1 (d, *J* = 245.4 Hz), 154.3, 151.3, 147.2, 133.7, 133.6 (d, *J* = 3.1 Hz), 129.4 (d, *J* = 8.0 Hz), 124.7, 115.5 (d, *J* = 21.5 Hz), 111.7, 95.6, 56.1, 51.7, 44.8. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -115.35. HRMS (ESI) m/z for $C_{17}H_{16}FN_3O$ (M+H), 314.1299 (Calc.), found 314.1298.

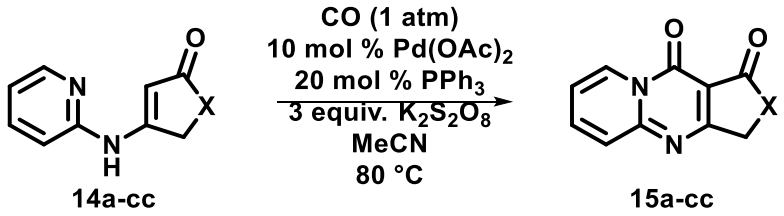



**1-benzyl-4-(pyridin-2-ylamino)-5,6-dihydropyridin-2(1*H*)-one. (2-21ll)** 2 mmol scale, 3 h. After the reaction, the mixture was cooled to RT, the solid were filtered out and washed with DCM (2 mL) and hexane (5 mL). Yield: 389 mg, 70%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 4.9 Hz, 1H), 7.59 (t, *J* = 7.9 Hz, 1H), 7.34 – 7.26 (m, 5H), 7.06 (d, *J* = 8.3 Hz, 1H), 6.90 (t, *J* = 6.2 Hz, 1H), 6.71 (s, 1H), 6.17 (s, 1H), 4.65 (s, 2H), 3.35 (t, *J* = 7.0 Hz, 2H), 2.56 (t, *J* = 7.0 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 167.6, 153.2, 148.4, 148.1, 138.0, 137.9, 128.5, 128.0, 127.2, 117.7, 112.7, 97.1, 49.4, 43.7, 29.3. HRMS (ESI) m/z for $C_{17}H_{17}N_3O$ (M+H), 280.1444 (Calc.), found 280.1438.



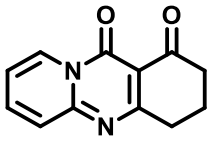
**1-benzyl-4-(pyridin-2-ylamino)pyridin-2(1*H*)-one. (2-21mm)** Following the general procedure described in **3.4**. 0.5 mmol scale, 0.5 h. Eluent: MeOH/EtOAc 0%~1%; yield: 74 mg, 53%; yellow solid. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 5.2, 1.8 Hz, 1H), 7.59 (ddd, *J* = 8.7, 7.3, 1.9 Hz, 1H), 7.41 – 7.27 (m, 5H), 7.13 (d, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 1H), 6.90 (dd, *J* = 7.3, 5.0 Hz, 1H), 6.82 (s, 1H), 6.64 (d, *J* = 2.5 Hz, 1H), 6.29 (dd, *J* = 7.5, 2.5 Hz, 1H), 5.11 (s, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 163.7, 153.9, 150.8, 147.9, 137.7, 137.0, 136.9, 128.8, 127.9, 127.7, 117.2, 112.5, 101.4, 100.1, 51.2. HRMS (ESI) m/z for $C_{17}H_{15}N_3O$ (M+H), 278.1288 (Calc.), found 278.1284.Trace amount of **2-22bb** were also detected by NMR, but **2-22cc** was not observed even if it was stirred for longer time (5 h) or using 5 equiv. oxidants.

## 2.8.4.4 Methods for the Palladium-Catalyzed Cyclocarbonylation

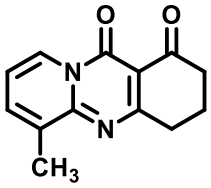



To an oven-dried Schlenk-flask was added the vinylogous amides/urea (**2-21**, 0.3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), $PPh_3$ (16 mg, 0.06 mmol) and $K_2S_2O_8$ (243 mg, 0.9 mmol). A balloon filled with CO was connected to the flask. Then, the flask was evacuated and backfilled with CO. MeCN (1 mL) was added into the flask and stirred at 80 °C. When the reaction was completed (detected by TLC), the mixture was cooled to room temperature. The reaction was quenched with saturated $NaHCO_3$ (15 mL) and extracted with DCM (3 × 15 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$ and purified by column chromatography with

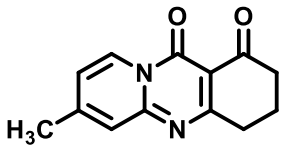
EtOAc/MeOH or DCM/MeOH as the eluent. (Note: the starting material and the product may have the same RF when using DCM/MeOH as eluent.)



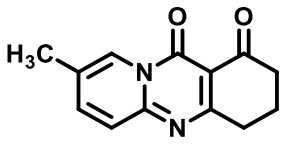
**3,4-dihydro-*1H*-pyrido[2,1-*b*]quinazoline-1,11(2*H*)-dione**. **(2-22a)** 3 h; Eluent: MeOH/EtOAc 5%~15%; yield: 57 mg, 89% and 59 mg, 91%, respectively; yellowish solid; mp 226−227 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 9.08 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.87 (ddd, *J* = 8.6, 6.8, 1.7 Hz, 1H), 7.53 (dt, *J* = 8.8, 1.0 Hz, 1H), 7.21 (td, *J* = 6.9, 1.4 Hz, 1H), 2.90 (t, *J* = 6.2 Hz, 2H), 2.54 (t, *J* = 6.2 Hz, 2H), 2.03 (p, *J* = 6.4 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 195.0, 172.7, 153.8, 151.6, 139.7, 128.9, 125.9, 116.7, 108.5, 39.4, 33.9, 20.9. HRMS (ESI) m/z for $C_{12}H_{10}N_2O_2$ (M+H), 215.0815 (Calc.), found 215.0811.



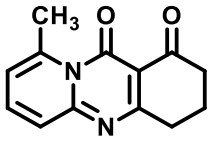
**6-methyl-3,4-dihydro-1*H*-pyrido[2,1-*b*]quinazoline-1,11(2*H*)-dione**. **(2-22b)** 3 h; Eluent: MeOH/DCM 1%~2%; yield: 38 mg, 56% and 40 mg, 58%, respectively; yellowish solid; mp 181−182 °C. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 9.11 (d, *J* = 7.0 Hz, 1H), 7.76 (d, *J* = 6.9 Hz, 1H), 7.15 (t, *J* = 7.0 Hz, 1H), 3.04 (t, *J* = 6.2 Hz, 2H), 2.67 (t, *J* = 6.5 Hz, 2H), 2.61 (s, 3H), 2.15 (p, *J* = 6.4 Hz, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 195.4, 172.0, 154.5, 151.1, 138.4, 135.0, 127.0, 116.0, 108.5, 39.6, 34.3, 21.2, 18.0. HRMS (ESI) m/z for $C_{13}H_{12}N_2O_2$ (M+H), 229.0972 (Calc.), found 229.0973.



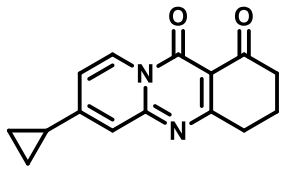
**7-methyl-3,4-dihydro-1*H*-pyrido[2,1-*b*]quinazoline-1,11(2*H*)-dione**. **(2-22c)** 3 h; Eluent: MeOH/EtOAc 3%~10%; yield: 47 mg, 69% and 46 mg, 67%, respectively; yellowish solid; mp 206−207 °C. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 9.10 (d, *J* = 7.2 Hz, 1H), 7.42 (d, *J* = 2.1 Hz, 1H), 7.07 (dd, *J* = 7.2, 1.9 Hz, 1H), 2.99 (t, *J* = 6.2 Hz, 2H), 2.65 (t, *J* = 6.4 Hz, 2H), 2.53 (s, 3H), 2.13 (p, *J* = 6.5 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 195.1, 173.0, 154.0, 152.6, 151.5, 128.3, 124.3, 119.1, 108.2, 39.4, 34.0, 21.7, 21.0. HRMS (ESI) m/z for $C_{13}H_{12}N_2O_2$ (M+H), 229.0972 (Calc.), found 229.0966.



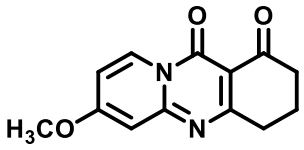
**8-methyl-3,4-dihydro-1*H*-pyrido[2,1-*b*]quinazoline-1,11(2*H*)-dione**. **(2-22d)** 2 h; Eluent: MeOH/EtOAc 3%~15%; yield: 47 mg, 69% and 50 mg, 73%, respectively; yellow solid; mp 231−233 °C. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 9.01 (d, *J* = 2.2 Hz, 1H), 7.76 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.57 (d, *J* = 8.9 Hz, 1H), 3.00 (t, *J* = 6.2 Hz, 2H), 2.66 (d, *J* = 6.3 Hz, 2H), 2.47 (s, 3H), 2.14 (p, *J* = 6.5 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 195.3, 172.1, 154.0, 150.4, 142.4, 127.2, 126.7, 125.4, 108.4, 39.5, 34.0, 21.0, 18.4. HRMS (ESI) m/z for $C_{13}H_{12}N_2O_2$ (M+H), 229.0972 (Calc.), found 229.0968.



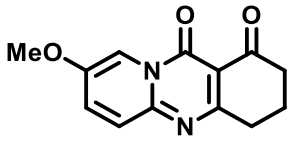
**9-methyl-3,4-dihydro-1*H*-pyrido[2,1-*b*]quinazoline-1,11(2*H*)-dione**. **(2-22e)** 3.5 h; Eluent: MeOH/EtOAc 3%~15%; yield: 45 mg, 66% and 47 mg, 69%, respectively; yellow solid; mp 204−205 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 8.8, 7.0 Hz, 1H), 7.40 (dd, *J* = 8.8, 1.5 Hz, 1H), 6.83 (dt, *J* = 7.0, 1.3 Hz, 1H), 3.05 (s, 3H), 2.92 (t, *J* = 6.3 Hz, 2H), 2.62 (t, *J* = 6.3 Hz, 2H), 2.11 (p, *J* = 6.5 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 194.9, 171.7, 157.9, 154.2, 146.4, 138.6, 124.6, 119.8, 110.2, 39.4, 33.4, 24.6, 21.0. HRMS (ESI) m/z for $C_{13}H_{12}N_2O_2$ (M+H), 229.0972 (Calc.), found 229.0967.



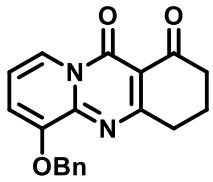
**7-cyclopropyl-3,4-dihydro-1*H*-pyrido[2,1-*b*]quinazoline-1,11(2*H*)-dione**. **(2-22f)** 3 h; Eluent: MeOH/EtOAc 0.2%~5%; yield: 26 mg, 34% and 25 mg, 33%, respectively; yellow solid. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 9.06 (d, *J* = 7.3 Hz, 1H), 7.24 (d, *J* = 2.0 Hz, 1H), 6.90 (dd, *J* = 7.4, 2.0 Hz, 1H), 2.96 (t, *J* = 6.2 Hz, 2H), 2.64 (t, *J* = 6.5 Hz, 2H), 2.12 (p, *J* = 6.4 Hz, 2H), 2.08 - 1.99 (m, 1H), 1.39 - 1.25 (m, 2H), 1.05 - 0.96 (m, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 195.21, 173.10, 159.90, 154.17, 151.56, 128.67, 119.93, 115.39, 108.03, 39.54, 34.22, 21.17, 16.18, 12.47. HRMS (ESI) m/z for $C_{15}H_{14}N_2O_2$ (M+H), 255.11280 (Calc.), found 255.11268.



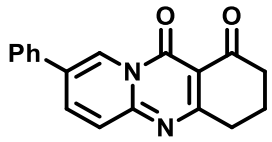
**7-methoxy-3,4-dihydro-1*H*-pyrido[2,1-*b*]quinazoline-1,11(2*H*)-dione**. **(2-22g)** 4 h; Eluent: MeOH/EtOAc 3%~10%; yield: 33 mg, 45% and 31 mg, 42%, respectively; brown solid; mp 166−168 °C. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 9.07 (d, *J* = 7.7 Hz, 1H), 6.88 (d, *J* = 2.6 Hz, 1H), 6.86 (dd, *J* = 7.7, 2.7 Hz, 1H), 4.01 (s, 3H), 2.95 (t, *J* = 6.2 Hz, 2H), 2.63 (t, *J* = 6.5 Hz, 2H), 2.12 (p, *J* = 6.4 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 195.3, 173.4, 168.0, 154.3, 153.8, 130.5, 110.8, 107.5, 102.6, 56.8, 39.3, 34.1, 21.0. HRMS (ESI) m/z for $C_{13}H_{12}N_2O_3$ (M+H), 245.0921 (Calc.), found 245.0910.



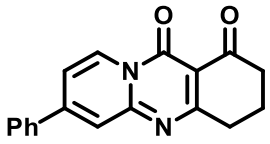
**8-methoxy-3,4-dihydro-1*H*-pyrido[2,1-*b*]quinazoline-1,11(2*H*)-dione**. **(2-22h)** 3 h; Eluent: MeOH/EtOAc 5%~15%; yield: 52 mg, 71% and 50 mg, 68%, respectively; yellow solid; mp 230−231 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 2.9 Hz, 1H), 7.68 (dd, *J* = 9.5, 2.8 Hz, 1H), 7.60 (d, *J* = 9.5 Hz, 1H), 3.97 (s, 3H), 3.01 (t, *J* = 6.1 Hz, 2H), 2.67 (t, *J* = 6.4 Hz, 2H), 2.15 (p, *J* = 6.4 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 195.2, 171.0, 153.5, 151.5, 148.4, 134.0, 126.7, 108.8, 107.9, 56.7, 39.5, 33.8, 21.1. HRMS (ESI) m/z for $C_{13}H_{12}N_2O_3$ (M+H), 245.0921 (Calc.), found 245.0919.



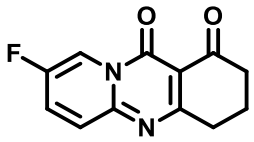

**6-(benzyloxy)-3,4-dihydro-1*H*-pyrido[2,1-*b*]quinazoline-1,11(2*H*)-dione**. **(2-22i)** 3 h; Eluent: MeOH/EtOAc 0.2%~5%; yield: 29 mg, 30% and 32 mg, 33%, respectively; yellow solid; mp 220−221 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.82 (dd, *J* = 7.1, 1.3 Hz, 1H), 7.48 - 7.44 (m, 2H), 7.42 - 7.33 (m, 3H), 7.17 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.05 (t, *J* = 7.4 Hz, 1H), 5.41 (s, 2H), 3.12 (t, *J* = 6.2 Hz, 2H), 2.67 (t, *J* = 6.5 Hz, 2H), 2.15 (p, *J* = 6.4 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 195.4, 172.0, 154.1, 150.9, 145.9, 135.0, 128.9, 128.5, 127.0, 120.9, 117.5, 115.4, 109.2, 71.9, 39.5, 34.3, 21.1. HRMS (ESI) m/z for $C_{19}H_{16}N_2O_3$ (M+Na), 343.1053 (Calc.), found 343.1051.



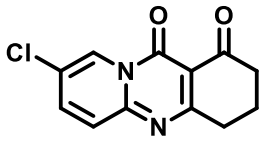

**8-phenyl-3,4-dihydro-1*H*-pyrido[2,1-*b*]quinazoline-1,11(2*H*)-dione**. **(2-22j)** 3 h; Eluent: 100% EtOAc; yield: 48 mg, 55% and 44 mg, 51%, respectively; yellow solid; mp 260−262 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 9.40 (d, *J* = 2.2 Hz, 1H), 8.19 (dd, *J* = 9.1, 2.2 Hz, 1H), 7.73 (d, *J* = 9.0 Hz, 1H), 7.70 - 7.60 (m, 2H), 7.60 - 7.44 (m, 3H), 3.05 (t, *J* = 6.2 Hz, 2H), 2.69 (t, *J* = 6.5 Hz, 2H), 2.17 (p, *J* = 6.4 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 195.0, 172.4, 153.9, 150.7, 139.3, 134.9, 130.6, 129.6, 129.3, 127.0, 126.1, 125.9, 108.7, 39.5, 34.0, 21.1. HRMS (ESI) m/z for $C_{18}H_{14}N_2O_2$ (M+Na), 313.0948 (Calc.), found 313.0935.



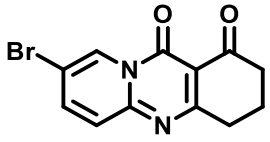

**7-phenyl-3,4-dihydro-1*H*-pyrido[2,1-*b*]quinazoline-1,11(2*H*)-dione**. **(2-22k)** 3 h; Eluent: 100% EtOAc; yield: 43 mg, 49% and 42 mg, 48%, respectively; yellow solid; mp 251−252 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 9.25 (d, *J* = 7.4 Hz, 1H), 7.85 (d, *J* = 1.9 Hz, 1H), 7.81 - 7.73 (m, 2H), 7.61 - 7.54 (m, 3H), 7.52 (dd, *J* = 7.4, 2.0 Hz, 1H), 3.04 (t, *J* = 6.2 Hz, 2H), 2.68 (t, *J* = 6.5 Hz, 2H), 2.17 (p, *J* = 6.4 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 195.0, 173.0, 153.9, 151.9, 151.8, 135.5, 131.0, 129.6, 129.3, 127.3, 121.8, 115.6, 108.5, 39.4, 34.1, 21.0. HRMS (ESI) m/z for $C_{18}H_{14}N_2O_2$ (M+Na), 313.0948 (Calc.), found 313.0933.



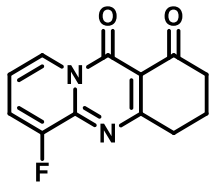

**8-fluoro-3,4-dihydro-1*H*-pyrido[2,1-*b*]quinazoline-1,11(2*H*)-dione**. **(2-22l)** 3 h; Eluent: MeOH/EtOAc 1%~10%; yield: 59 mg, 85% and 57 mg, 82%, respectively; yellow solid; mp 230−232 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 9.10 (dd, *J* = 4.2, 2.8 Hz, 1H), 7.87 (ddd, *J* = 9.4, 6.4, 2.8 Hz, 1H), 7.71 (dd, *J* = 9.6, 5.0 Hz, 1H), 3.03 (t, *J* = 6.2 Hz, 2H), 2.67 (t, *J* = 6.5 Hz, 2H), 2.17 (p, *J* = 6.4 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 194.9, 172.3, 154.5 (d, *J* = 248.0 Hz), 153.3 (d, *J* = 1.5 Hz), 149.6, 131.5 (d, *J* = 24.5 Hz), 128.0 (d, *J* = 7.1 Hz), 115.3 (d, *J* = 40.7 Hz), 108.1, 39.4, 33.9, 20.9. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -130.73. HRMS (ESI) m/z for $C_{12}H_9FN_2O_2$ (M+H), 233.0721 (Calc.), found 233.0721.



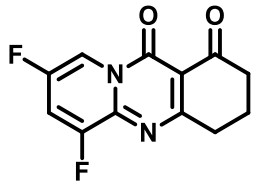
**8-chloro-3,4-dihydro-1*H*-pyrido[2,1-*b*]quinazoline-1,11(2*H*)-dione**. **(2-22m)** 3 h; Eluent: MeOH/EtOAc 1%~10%; yield: 56 mg, 80% and 57 mg, 81%, respectively; yellow solid; mp 222−224 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 9.19 (dd, *J* = 2.4, 0.7 Hz, 1H), 7.85 (dd, *J* = 9.4, 2.4 Hz, 1H), 7.61 (dd, *J* = 9.3, 0.7 Hz, 1H), 3.03 (t, *J* = 6.2 Hz, 2H), 2.68 (t, *J* = 6.4 Hz, 2H), 2.16 (p, *J* = 6.6 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 194.8, 172.7, 152.9, 150.2, 140.5, 127.1, 126.7, 125.2, 108.9, 39.4, 33.9, 20.9. HRMS (ESI) m/z for $C_{12}H_9ClN_2O_2$ (M+H), 249.0425 (Calc.), found 249.0425.



**8-bromo-3,4-dihydro-1*H*-pyrido[2,1-*b*]quinazoline-1,11(2*H*)-dione**. **(2-22n)** 3 h; Eluent: MeOH/EtOAc 0%~5%; yield: 45 mg, 52% and 44 mg, 50%, respectively; yellow solid; mp 218−219 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 9.28 (d, *J* = 2.2 Hz, 1H), 7.94 (dd, *J* = 9.3, 2.2 Hz, 1H), 7.54 (d, *J* = 9.3 Hz, 1H), 3.02 (t, *J* = 6.2 Hz, 2H), 2.67 (t, *J* = 6.4 Hz, 2H), 2.16 (p, *J* = 6.4 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 194.7, 172.8, 152.8, 150.3, 142.6, 129.1, 127.1, 111.8, 109.08, 39.4, 34.0, 20.9. HRMS (ESI) m/z for $C_{12}H_9BrN_2O_2$ (M+H), 292.9920 (Calc.), found 292.9917.

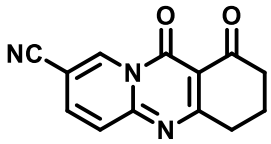


**6-fluoro-3,4-dihydro-1*H*-pyrido[2,1-*b*]quinazoline-1,11(2*H*)-dione**. **(2-22o)** 3 h; Eluent: MeOH/EtOAc 0%~3%; yield: 54 mg, 78% and 50 mg, 72%, respectively; yellow solid; mp 254−255 °C. $^{1}$H NMR (500 MHz, $CDCl_3$) 9.02 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.71 – 7.62 (m, 1H), 7.21 (td, *J* = 7.4, 4.5 Hz, 1H), 3.10 (t, *J* = 6.2 Hz, 2H), 2.69 (t, *J* = 6.2 Hz, 2H), 2.17 (p, *J* = 6.4 Hz, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 194.9, 172.7, 153.9 (d, *J* = 259.2 Hz), 153.2, 144.7 (d, *J* = 19.4 Hz), 125.0 (d, *J* = 5.4 Hz), 121.8 (d, *J* = 17.9 Hz), 114.7 (d, *J* = 6.8 Hz), 109.6, 39.4, 34.2, 21.0. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -122.94. HRMS (ESI) m/z for $C_{12}H_9FN_2O_2$ (M+Na), 255.0540 (Calc.), found 255.0534.

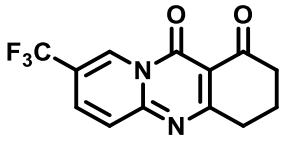


**6,8-difluoro-3,4-dihydro-1*H*-pyrido[2,1-*b*]quinazoline-1,11(2*H*)-dione**. **(2-22p)** 3 h; Eluent: EtOAc/Hexane 80%~90%; yield: 51 mg, 68% and 50 mg, 67%, respectively; yellow solid; mp 257−259 °C. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 9.05 – 8.89 (m, 1H), 7.70 – 7.57 (m, 1H), 3.10 (t, *J* = 6.2 Hz, 2H), 2.69 (t, *J* = 6.6 Hz, 2H), 2.18 (p, *J* = 6.4 Hz, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 194.7, 172.2, 154.0 (dd, *J* = 264.3, 10.9 Hz), 152.7 (dd, *J* = 248.2, 10.2 Hz), 152.6, 142.9 (dd, *J* = 18.9, 1.1 Hz), 115.1 (dd, *J* = 28.0, 20.9 Hz), 111.6 (dd, *J* = 40.3, 6.2 Hz), 109.3, 39.4, 34.0, 20.9.

$^{19}$F NMR (376 MHz, $CDCl_3$) δ -117.33 (d, *J* = 6.1 Hz), -128.95 (d, *J* = 6.1 Hz). HRMS (ESI) m/z for $C_{12}H_8F_2N_2O_2$ (M+Na), 273.0446 (Calc.), found 273.0446.

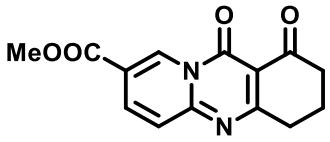



**1,11-dioxo-2,3,4,11-tetrahydro-1*H*-pyrido[2,1-*b*]quinazoline-8-carbonitrile**. **(2-22q)** 4 h; Eluent: EtOAc/Hexane 80%; yield: 26 mg, 36% and 25 mg, 35%, respectively; yellow solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 9.50 (d, *J* = 2.0 Hz, 1H), 7.89 (dd, *J* = 9.2, 2.0 Hz, 1H), 7.67 (d, *J* = 9.2 Hz, 1H), 3.06 (t, *J* = 6.2 Hz, 2H), 2.69 (t, *J* = 6.5 Hz, 2H), 2.18 (p, *J* = 6.4 Hz, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 194.59, 174.38, 152.68, 151.13, 137.69, 135.28, 127.45, 114.63, 110.28, 102.71, 39.25, 34.08, 20.80. HRMS (ESI) m/z for $C_{13}H_9N_3O_2$ (M+Na), 262.05870 (Calc.), found 262.05856.

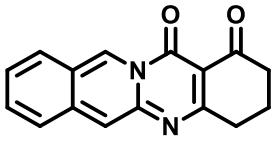



**8-(trifluoromethyl)-3,4-dihydro-1*H*-pyrido[2,1-*b*]quinazoline-1,11(2*H*)-dione**. **(2-22r)** 3 h; Eluent: EtOAc/Hexane 70%~80%; yield: 60 mg, 71% and 56 mg, 66%, respectively; yellowish solid; mp 217−219 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.46 (d, *J* = 2.9 Hz, 1H), 7.99 (dd, *J* = 9.2, 2.2 Hz, 1H), 7.74 (d, *J* = 9.3 Hz, 1H), 3.06 (t, *J* = 6.2 Hz, 2H), 2.68 (t, *J* = 6.8 Hz, 2H), 2.18 (p, *J* = 6.4 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 194.5, 174.0, 153.2, 151.8, 134.4 (q, *J* = 2.4 Hz), 127.9 (q, *J* = 5.5 Hz), 127.4, 122.3 (q, *J* = 272.0 Hz), 120.1 (q, *J* = 35.7 Hz), 109.8, 39.3, 34.0,

20.8. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -63.10. HRMS (ESI) m/z for $C_{13}H_{19}F_3N_2O_2$ (M+Na), 305.0508 (Calc.), found 305.0495.

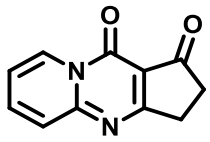



**methyl 1,11-dioxo-2,3,4,11-tetrahydro-1*H*-pyrido[2,1-*b*]quinazoline-8-carboxylate**. **(2-22s)** 2.5 h; Eluent: MeOH/EtOAc 2%; yield: 63 mg, 77% and 60 mg, 74%, respectively; yellow solid; mp 207−208 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 9.78 (d, *J* = 1.9 Hz, 1H), 8.36 (dd, *J* = 9.2, 2.0 Hz, 1H), 7.64 (d, *J* = 9.2 Hz, 1H), 4.02 (s, 3H), 3.05 (t, *J* = 6.2 Hz, 2H), 2.68 (t, *J* = 6.6 Hz, 2H), 2.17 (p, *J* = 6.4 Hz, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 194.7, 173.9, 163.6, 153.5, 152.3, 138.1, 132.6, 126.0, 119.9, 109.6, 53.2, 39.4, 34.1, 20.9. HRMS (ESI) m/z for $C_{14}H_{12}N_2O_4$ (M+H), 273.0870 (Calc.), found 273.0869.

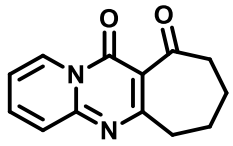



**3,4-dihydro-1*H*-isoquinolino[3,2-*b*]quinazoline-1,13(2*H*)-dione**. **(2-22t)** 3 h; Eluent: MeOH/EtOAc 0%~5%; yield: 36 mg, 45% and 38 mg, 48%, respectively; yellow solid; mp 312−313 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 10.18 (s, 1H), 8.17 (s, 1H), 8.14 (d, *J* = 8.6 Hz, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.78 (t, *J* = 7.6 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 3.07 (t, *J* = 6.2 Hz, 2H), 2.71 (t, *J* = 6.4 Hz, 2H), 2.18 (p, *J* = 6.4 Hz, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 195.3, 171.3,

153.6, 147.5, 140.2, 134.3, 132.9, 129.2, 128.4, 126.4, 123.5, 121.4, 104.6, 39.7, 34.6, 21.2. HRMS (ESI) m/z for $C_{16}H_{12}N_2O_2$ (M+H), 265.0972 (Calc.), found 265.0970.

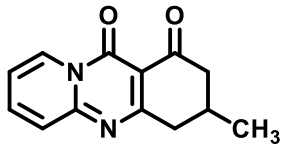


**2,3-dihydrocyclopenta[*d*]pyrido[1,2-*a*]pyrimidine-1,10-dione**. **(2-22u)** 3 h; Eluent: MeOH/EtOAc 5%~15%; yield: 52 mg, 86% and 51 mg, 84%, respectively; yellow solid; mp 279−280 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.25 (ddd, *J* = 7.0, 1.7, 0.8 Hz, 1H), 7.99 (ddd, *J* = 8.6, 6.8, 1.6 Hz, 1H), 7.75 (dt, *J* = 8.8, 1.0 Hz, 1H), 7.32 (td, *J* = 6.9, 1.4 Hz, 1H), 3.16 - 3.08 (m, 2H), 2.76 - 2.67 (m, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 201.2, 183.1, 153.9, 152.4, 140.2, 129.6, 126.3, 116.8, 110.2, 35.0, 29.1. HRMS (ESI) m/z for $C_{11}H_8N_2O_2$ (M+H), 201.0659 (Calc.), found 201.0649.

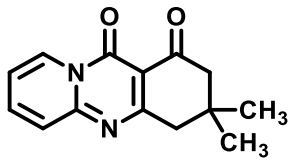


**6,7,8,9-tetrahydrocyclohepta[*d*]pyrido[1,2-*a*]pyrimidine-10,11-dione**. **(2-22v)** 3 h; Eluent: MeOH/EtOAc 1%~10%; yield: 41 mg, 41% and 25 mg, 37%, respectively; yellow solid; mp 154−156 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 9.17 (dd, *J* = 7.1, 1.5 Hz, 1H), 7.87 (ddd, *J* = 8.6, 6.7, 1.6 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.24 (td, *J* = 7.0, 1.4 Hz, 1H), 2.99 (t, *J* = 6.4 Hz, 2H), 2.81 - 2.69 (m, 2H), 2.07 - 1.95 (m, 2H), 1.95 - 1.83 (m, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 202.6,

167.3, 154.7, 151.0, 138.2, 128.7, 126.3, 116.3, 113.7, 42.0, 36.1, 23.4, 21.7. HRMS (ESI) m/z for $C_{13}H_{12}N_2O_2$ (M+H), 229.0972 (Calc.), found 229.0972.

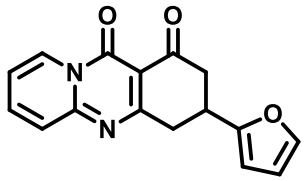


**3-methyl-3,4-dihydro-1*H*-pyrido[2,1-*b*]quinazoline-1,11(2*H*)-dione**. **(2-22w)** 3 h; Eluent: MeOH/EtOAc 2%~10%; yield: 38 mg, 56% and 41 mg, 60%, respectively; yellow to orange solid; mp 185−187 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 9.23 (d, *J* = 7.0 Hz, 1H), 7.93 (ddd, *J* = 8.5, 6.6, 1.6 Hz, 1H), 7.66 (d, *J* = 8.7 Hz, 1H), 7.27 (t, *J* = 6.0 Hz, 1H), 3.13 - 2.99 (m, 1H), 2.82 - 2.65 (m, 2H), 2.44 - 2.28 (m, 2H), 1.16 (d, *J* = 5.9 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 195.4, 172.3, 154.0, 151.8, 139.6, 129.2, 126.1, 116.6, 108.3, 47.6, 42.1, 28.3, 21.1. HRMS (ESI) m/z for $C_{13}H_{12}N_2O_2$ (M+Na), 251.0791 (Calc.), found 251.0789.

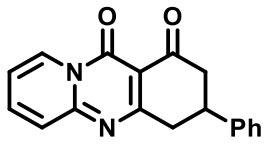


**3,3-dimethyl-3,4-dihydro-1*H*-pyrido[2,1-*b*]quinazoline-1,11(2*H*)-dione**. **(2-22x)** 3 h; Eluent: MeOH/EtOAc 3%~10%; yield: 59 mg, 81% and 61 mg, 84%, respectively; yellow solid; mp 172−173 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 9.28 - 9.20 (m, 1H), 7.96 (ddd, *J* = 8.7, 6.8, 1.7 Hz, 1H), 7.68 (dt, *J* = 8.8, 1.0 Hz, 1H), 7.30 (td, *J* = 6.9, 1.4 Hz, 1H), 2.91 (s, 2H), 2.53 (s, 2H), 1.14 (s, 6H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 195.1, 171.5, 153.8, 152.0, 139.6, 129.1, 126.1, 116.7,

107.7, 53.0, 47.7, 32.1, 28.3. HRMS (ESI) m/z for $C_{14}H_{14}N_2O_2$ (M+H), 243.1128 (Calc.), found 243.1126.

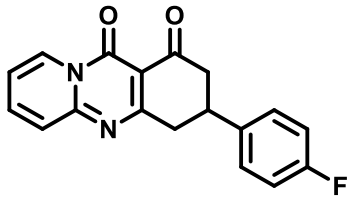


**3-(furan-2-yl)-3,4-dihydro-1*H*-pyrido[2,1-*b*]quinazoline-1,11(2*H*)-dione**. **(2-22y)** 3 h; Eluent: MeOH/EtOAc 0%~1%; yield: 51 mg, 61% and 54 mg, 64%, respectively; yellow solid; mp 188−189 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 9.23 (dd, *J* = 7.1, 1.6 Hz, 1H), 7.95 (ddd, *J* = 8.6, 6.8, 1.7 Hz, 1H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.35 (d, *J* = 1.8 Hz, 1H), 7.30 (td, *J* = 7.2, 1.6 Hz, 1H), 6.30 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.11 (d, *J* = 3.2 Hz, 1H), 3.68 - 3.58 (m, 1H), 3.44 - 3.35 (m, 1H), 3.31 - 3.21 (m, 1H), 3.10 - 3.00 (m, 1H), 2.92 - 2.82 (m, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 193.4, 171.0, 155.6, 153.7, 152.0, 141.9, 139.8, 129.2, 126.2, 116.8, 110.3, 108.4, 105.2, 43.4, 38.4, 32.3. HRMS (ESI) m/z for $C_{16}H_{12}N_2O_3$ (M+Na), 303.0740 (Calc.), found 303.0735.

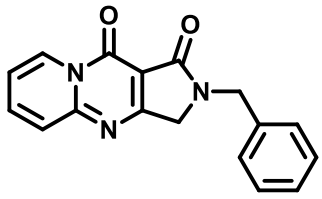


**3-phenyl-3,4-dihydro-1*H*-pyrido[2,1-*b*]quinazoline-1,11(2*H*)-dione**. **(2-22z)** 4 h; Eluent: MeOH/EtOAc 0%~10%; yield: 43 mg, 50% and 42 mg, 48%, respectively; brown solid; mp 225−227 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 9.25 (d, *J* = 7.0 Hz, 1H), 7.94 (t, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.39 - 7.26 (m, 5H), 3.59 - 3.46 (m, 1H), 3.34 - 3.20 (m, 2H), 3.04 - 2.80 (m, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 194.5, 171.8, 153.9, 152.0, 142.5, 139.8, 129.2, 128.9, 127.2,

126.7, 126.2, 116.8, 108.3, 46.4, 41.4, 38.6. HRMS (ESI) m/z for $C_{18}H_{14}N_2O_2$ (M+H), 291.1128 (Calc.), found 291.1124.

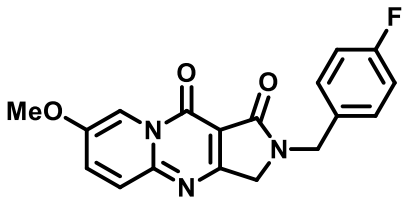


**3-(4-fluorophenyl)-3,4-dihydro-1*H*-pyrido[2,1-*b*]quinazoline-1,11(2*H*)-dione**. **(2-22aa)** 3 h; Eluent: MeOH/EtOAc 0%~3%; yield: 59 mg, 64% and 56 mg, 61%, respectively; light brown solid; mp 227−229 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 9.24 (d, *J* = 7.0 Hz, 1H), 7.96 (t, *J* = 7.9 Hz, 1H), 7.67 (d, *J* = 8.7 Hz, 1H), 7.31 (t, *J* = 6.9 Hz, 1H), 7.29 - 7.20 (m, 2H), 7.05 (t, *J* = 8.5 Hz, 2H), 3.57 - 3.45 (m, 1H), 3.32 - 3.24 (m, 1H), 3.24 - 3.14 (m, 1H), 3.02 - 2.91 (m, 1H), 2.88 - 2.76 (m, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 194.1, 171.5, 161.8 (d, *J* = 245.5 Hz), 153.9, 152.0, 139.9, 138.2 (d, *J* = 3.1 Hz), 129.2, 128.2 (d, *J* = 8.0 Hz), 126.2, 116.9, 115.8 (d, *J* = 21.2 Hz), 108.3, 46.5, 41.5, 37.9. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -115.62. HRMS (ESI) m/z for $C_{18}H_{13}FN_2O_2$ (M+Na), 331.0853 (Calc.), found 331.0838.

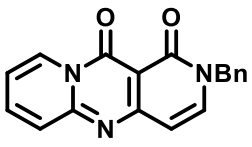


**2-benzyl-2,3-dihydropyrido[1,2-*a*]pyrrolo[3,4-*d*]pyrimidine-1,10-dione**. **(2-22jj)** 1.5 h; Eluent: MeOH/EtOAc 5%~15%; yield: 70 mg, 80% and 69 mg, 91%, respectively; yellowish solid; mp 167−168 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.21 (ddd, *J* = 7.1, 1.6, 0.8 Hz, 1H), 7.86 (ddd, *J* =

8.6, 6.7, 1.6 Hz, 1H), 7.63 (ddd, *J* = 8.8, 1.4, 0.8 Hz, 1H), 7.29 - 7.17 (m, 6H), 4.70 (s, 2H), 4.14 (s, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 170.6, 166.1, 153.5, 152.4, 138.9, 136.9, 129.0, 128.8, 128.2, 127.7, 126.3, 116.5, 104.6, 50.6, 45.9. HRMS (ESI) m/z for $C_{17}H_{13}N_3O_2$ (M+Na), 314.0900 (Calc.), found 314.0885.




**2-(4-fluorobenzyl)-7-methoxy-2,3-dihydropyrido[1,2-*a*]pyrrolo[3,4-*d*]pyrimidine-1,10-dione**. **(2-22kk)** 0.1 mmol scale, 1.5 h; Eluent: MeOH/DCM 0.2%~1%; yield: 19.5 mg, 58%; brown solid; mp 219−220 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, *J* = 2.6 Hz, 1H), 7.76 - 7.61 (m, 2H), 7.37 - 7.27 (m, 2H), 7.09 - 6.95 (m, 2H), 4.74 (s, 2H), 4.18 (s, 2H), 3.99 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 168.9, 166.3, 162.3 (d, *J* = 246.1 Hz), 152.3, 151.5, 150.1, 133.5, 132.8 (d, *J* = 3.2 Hz), 130.0 (d, *J* = 8.1 Hz), 126.9, 115.7 (d, *J* = 21.4 Hz), 108.9, 103.7, 56.8, 50.3, 45.2. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -114.66. HRMS (ESI) m/z for $C_{18}H_{14}FN_3O_3$ (M+Na), 362.0911 (Calc.), found 362.0903.

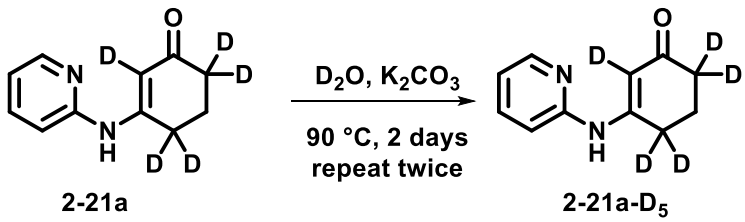



**2-benzyl-1*H*-dipyrido[1,2-*a*:4',3'-*d*]pyrimidine-1,11(2*H*)-dione. (2-22mm)** 0.2 mmol scale, 4 h; Eluent: MeOH/EtOAc 0.2%~15%; yield: 11 mg, 18%; yellow solid; mp 246−247 °C. $^1$H NMR

(500 MHz, $CDCl_3$) δ 9.13 (dd, *J* = 7.3, 1.5 Hz, 1H), 7.77 (ddd, *J* = 8.6, 6.6, 1.6 Hz, 1H), 7.53 (d, *J* = 8.9 Hz, 1H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.43 – 7.27 (m, 5H), 7.08 (td, *J* = 6.9, 1.4 Hz, 1H), 6.35 (d, *J* = 7.5 Hz, 1H), 5.18 (s, 2H). $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 160.6, 159.8, 155.6, 152.3, 140.9, 138.3, 136.5, 129.0, 128.6, 128.5, 128.2, 125.8, 114.5, 105.5, 103.7, 51.6. HRMS (ESI) m/z for $C_{18}H_{13}N_3O_2$ (M+Na), 326.0900 (Calc.), found 326.0896.

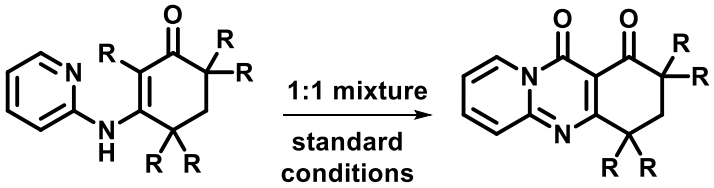
## ***2.8.5. Mechanistic studies***

### **2.8.5.1 Synthesis and characterization of deuterated substrate 2-21a-$D_5$**




**3-(Pyridin-2-ylamino)cyclohex-2-en-1-one-2,4,4,6,6-*d*$_5$. (2-21a-$D_5$)** To a round-bottom flask was added **2-21a** (564 mg, 3 mmol), $K_2CO_3$ (828 mg, 6 mmol) and $D_2O$ (15 mL). The mixture was stirred at 90 °C for 2 days. Then the solvent was removed under reduced pressure, another 15 mL $D_2O$ was added to the mixture. The mixture was stirred at 90 °C for another 2 days. After the reaction, the mixture was cooled to room temperature and diluted with DCM (20 mL) and brine (5 mL), and washed with DCM for 3 times. The combined organic layer was dried over $Na_2SO_4$ and purified by column. Eluent: EtOAc/Hexane 60%~90%; yield: 209 mg, 36%; white solid. $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 5.0, 1.8 Hz, 1H), 7.63 (td, *J* = 7.8, 1.9 Hz, 1H), 7.23 – 7.10 (m, 1H), 7.09 (s, 1H), 6.97 (dd, *J* = 7.3, 5.0 Hz, 1H), 2.04 (s, 2H). HRMS (ESI) m/z for $C_{11}H_7D_5N_2O$ (M+H), 194.1336 (Calc.), found 194.1327.

**2.8.5.2 Intermolecular competition reaction**



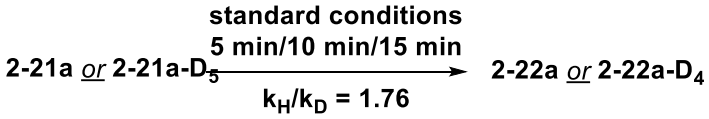

**2-21a**, R = H
**2-21a-D$_5$**, R = D

**2-22a**, R = H
**2-22a-D$_4$**, R = D

**2-22a:2-22a-D$_4$** = 1.99 : 1

To an oven-dried Schlenk-flask was added the **2-21a** (28.2 mg, 0.15 mmol), **2-21a-D$_5$** (29.0 mg, 0.15 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), $PPh_3$ (16 mg, 0.06 mmol) and $K_2S_2O_8$ (243 mg, 0.9 mmol). A balloon filled with CO was connected to the flask. Then, the flask was evacuated and backfilled with CO. MeCN (1 mL) was added into the flask and the mixture was stirred at 80 °C for 15 min. Then the reaction was quenched with saturated $NaHCO_3$ (15 mL) and extracted with DCM (3 × 15 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$ and purified by column chromatography to give a total yield of **2-22a** and **2-22a-D$_4$** in total yield of 15% (with some impurities). The ratio of **2-22a**:**2-22a-D$_4$** is 1.99:1 as determined by $^1$H-NMR.

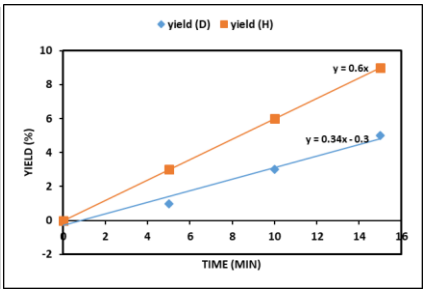
**2.8.5.3 Parallel time point reactions**




Three identical reactions were set up at the same time. Each reaction tube was charged with **2-21a** (18.8 mg, 0.1 mmol), $Pd(OAc)_2$ ( 2.2 mg, 0.01 mmol), $PPh_3$ (5.4 mg, 0.02 mmol) and $K_2S_2O_8$ (81 mg, 0.3 mmol). A balloon filled with CO was connected to the flask. Then, the flask was evacuated and backfilled with CO. MeCN (0.33 mL) was added into the flask and the mixture was stirred at 80 °C. The reaction was stopped in 5, 10, 15 min, respectively. In the parallel experiments, the

same 3 reactions were performed using **2-21a-D$_5$** (19.3 mg, 0.1 mmol) as substrate instead of **2-21a**. After the reaction, 1,3,5-trimethoxybenzene (5.6 mg, 0.033 mmol) was added to the mixture as internal standard. The work up procedure was performed as mentioned above. The crude $^1$H NMR was analyzed to determine the NMR yield of each reactions. The yields of **2-22a** or **2-22a-D$_4$** of the 6 reactions were plotted against time. The KIE ($k_H/k_D$) was determined by comparing the slopes.

| time (min) | yield (D) | yield (H) | |
|---|---|---|---|
| 0 | 0 | 0 | |
| 5 | 1 | 3 | |
| 10 | 3 | 6 | |
| 15 | 5 | 9 | |
| | slope (D) | slope (H) | KIE |
| | 0.34 | 0.6 | 1.76 |




## ***2.8.6. References***

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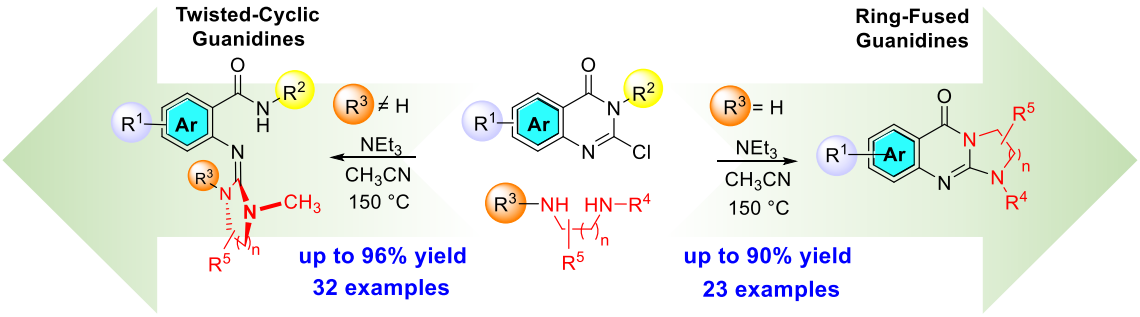
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# Chapter 3. Twisted-Cyclic or Ring-Fused Guanidines via Rearrangement of 2-Chloroquinazolin-4(3*H*)-ones with Diamines

## 3.1 Abstract

A highly efficient 2-chloroquinazolin-4(3*H*)-one rearrangement was developed that generates either twisted-cyclic or ring-fused guanidines in a single operation, depending on the presence of a primary versus secondary amine in the accompanying diamine reagent. Exclusive formation of twisted-cyclic guanidines results from pairing 2-chloroquinazolinones with secondary diamines. Use of primary amine-containing diamines permits a domino quinazolinone rearrangement/intramolecular cyclization, gated through (*E*)-twisted-cyclic guanidines, to afford ring-fused *N*-acylguanidines. This scalable, structurally tolerant transformation generated 55 guanidines and delivered twisted-cyclic guanidines with robust plasma stability and an abbreviated total synthesis of an antitumor ring-fused guanidine (4 steps, 55% yield).




Adapted from **Gang Yan**, Bereket L. Zekarias, Xiaoyu Li, Victor A. Jaffett, Ilia Guzei, and Jennifer E. Golden. Divergent 2-Chloroquinazolin-4(3*H*)-one Rearrangement: Twisted-Cyclic Guanidine Formation or Ring-Fused *N*-Acylguanidines via a Domino Process. *Chem. Euro. J.* **2020**, *accepted.*

## 3.2 Introduction

Guanidines are broadly used across multiple industries as agrochemicals, artificial sweeteners, catalysts, organic superbases and curing agents. (**Figure 3-1**)[1-12] Guanidine derivatives can be widely found in many marketed drugs and bioactive molecules with a broad spectrum of bioactivities.[13-15] Notable monosubstituted guanidines include the orally bioavailable antiviral zanamivir (Relenza®) **3-5**[16-17] and anti-ulcer drug, famotidine (Pepcid®) **3-6**[18]; however, cyclic variants are also abundant (**Figure 3-1**).

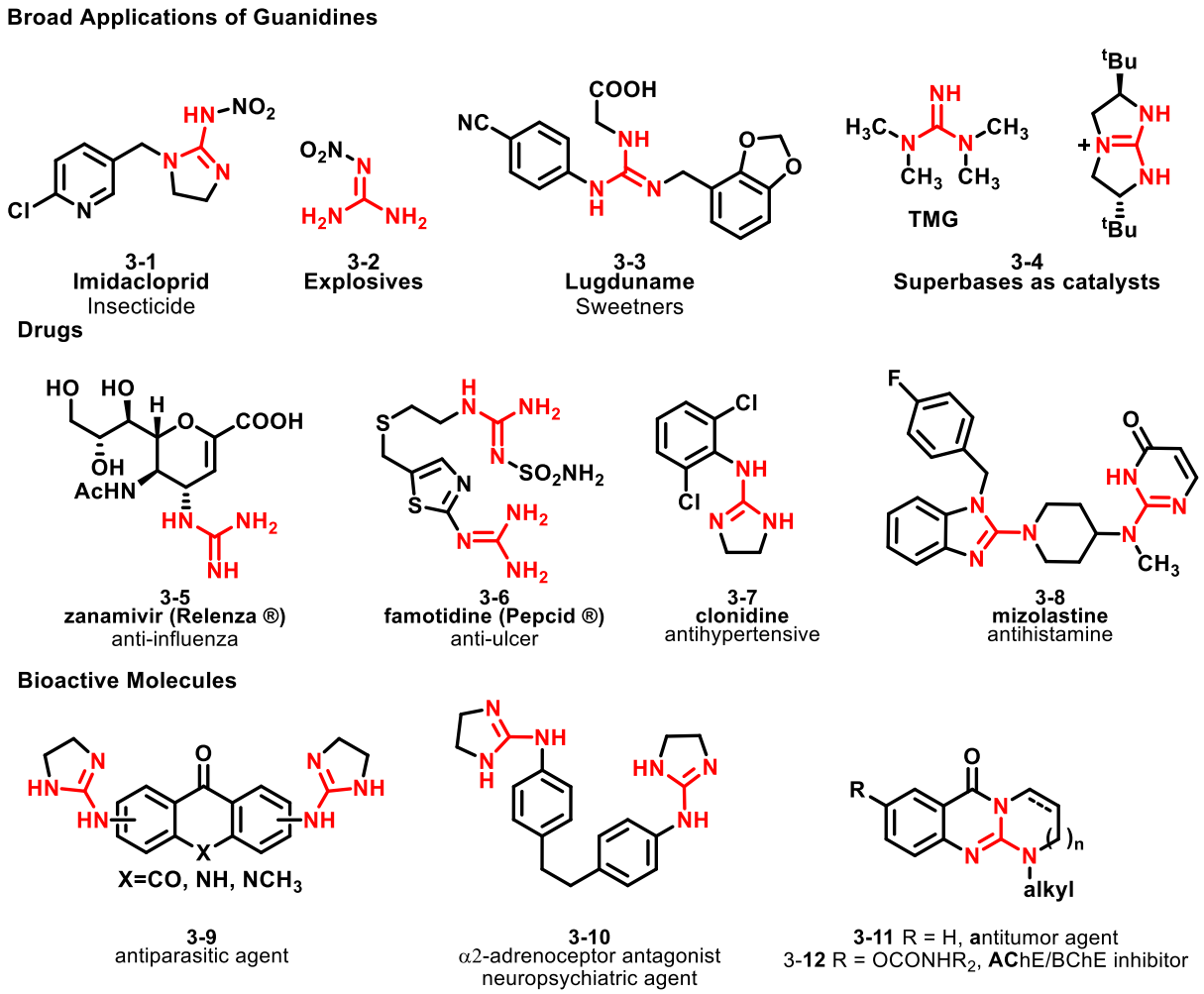


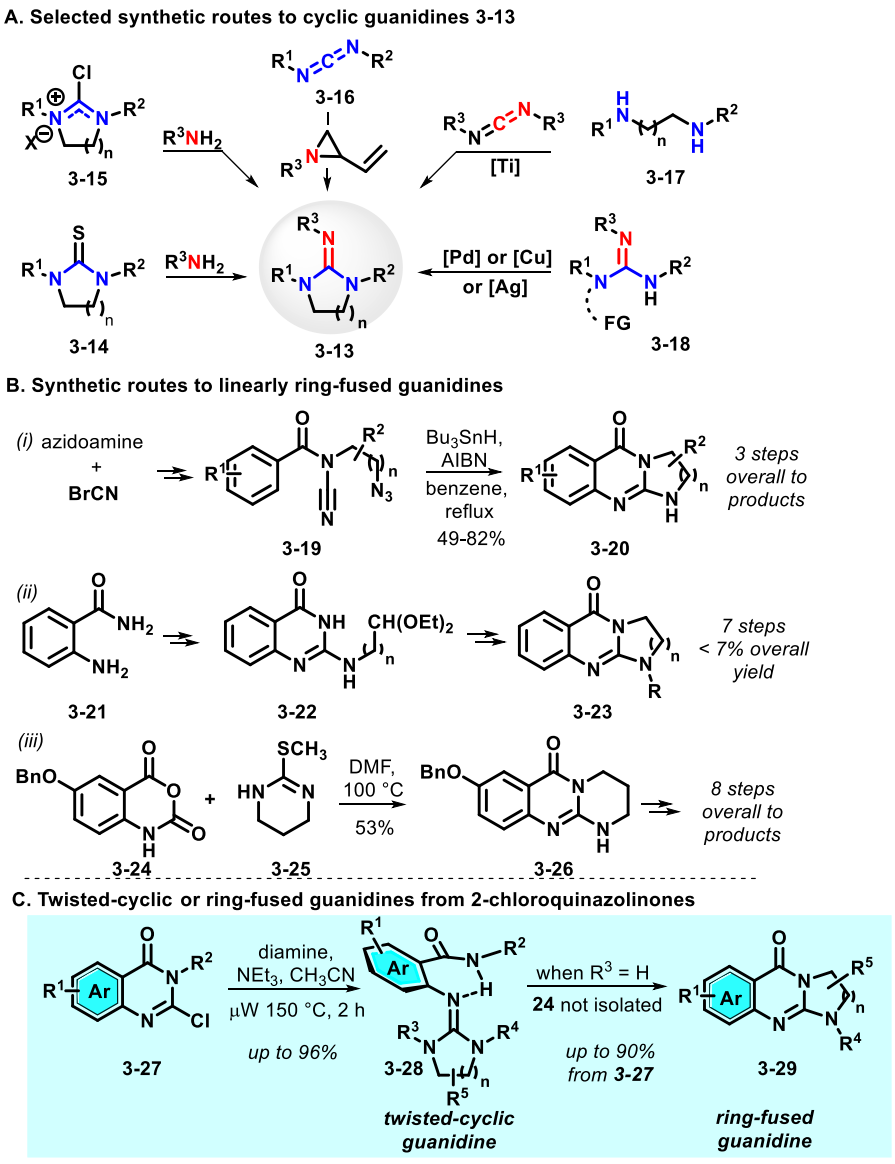

**Figure 3-1.** Drugs and bioactive molecules containing a guanidine motif (red).

A few cyclic examples include the antihypertensive drug, clonidine **3-7**[19], as well as the antihistamine, mizolastine **3-8**[20]. Many development compounds have been reported, such as antiparasitic compound **3-9**[21] and the α2-adrenoceptor antagonist **3-10**[22] as a neuropsychiatric agent, while fully substituted, tricyclic guanidines **3-11** and **3-12** exhibit *in vivo* efficacy as an antitumor agent[23] and an inhibitor of acetyl- and butyrylcholinesterases (AChE/BChE)[24], respectively. Therefore, it is very important for constructing novel guanidine-containing frameworks efficiently.

Over the past decades, many methods have been developed for the assembly of cyclic guanidines **3-13** (**Scheme 3-1A**). Popular approaches include treating thioureas[21-22, 25] **3-14** or Vilsmeier-like precursors **3-15**[26-30] with amines. Carbodiimides (**3-16**)[31-34] are also important reagent for making cyclic guanidines. For instance, the Alper group reported Pd-catalyzed cyclization reactions from carbodiimides and vinylaziridines.[31-32] Xie group[35] and Ruijter group[36] developed Ti- or Pd-catalyzed intermolecular cyclization reactions of carbodiimides with diamines (**3-17**). Metal-catalyzed intramolecular ring-closing reactions between a guanidine and an appended alkene or alkyne (**3-18**) have also been described.[37-41]

Fewer methods have focused on the synthetically more challenging ring-fused guanidines (**Scheme 3-1B**). For examples, Fensterbank group reported a radical cascade cyclization reaction using azido-*N*-cyanobenzamides (**3-19**) for the synthesis of $N^1$-H tricyclic guanidines (**3-20**).[42] Lebegue and coworkers reported a seven-step synthesis of a series of $N^1$-substituted guanidines (**3-23)** with potent *in vivo* antitumor activity from anthranilamide (**3-21)**.[23] In a separate study, Decker group used isatoic anhydrides (**3-24**) and cyclic isothiourea (**3-25**) to afford $N^1$-H tricyclic guanidines (**3-26**), which were used for the synthesis of AChE/BChE inhibitors over 8 total steps.[24] Collectively, these pioneering methods generated novel guanidines of diverse utility;

however, all offer access to only one of the two classes of guanidines discussed here, and most still suffer from one or more challenges associated with availability of starting materials, reagent toxicity, limited substrate scope or poor overall yield. Therefore, new synthetic approaches to novel cyclic guanidines continue to be in high demand. We now report an unprecedented, one-step rearrangement of 2-chloroquinazolinones **3-27** to either structurally unique, bioactive twisted-cyclic guanidines **3-28** or ring-fused guanidines **3-29** in high yield (**Scheme 3-1C**, *blue box*).

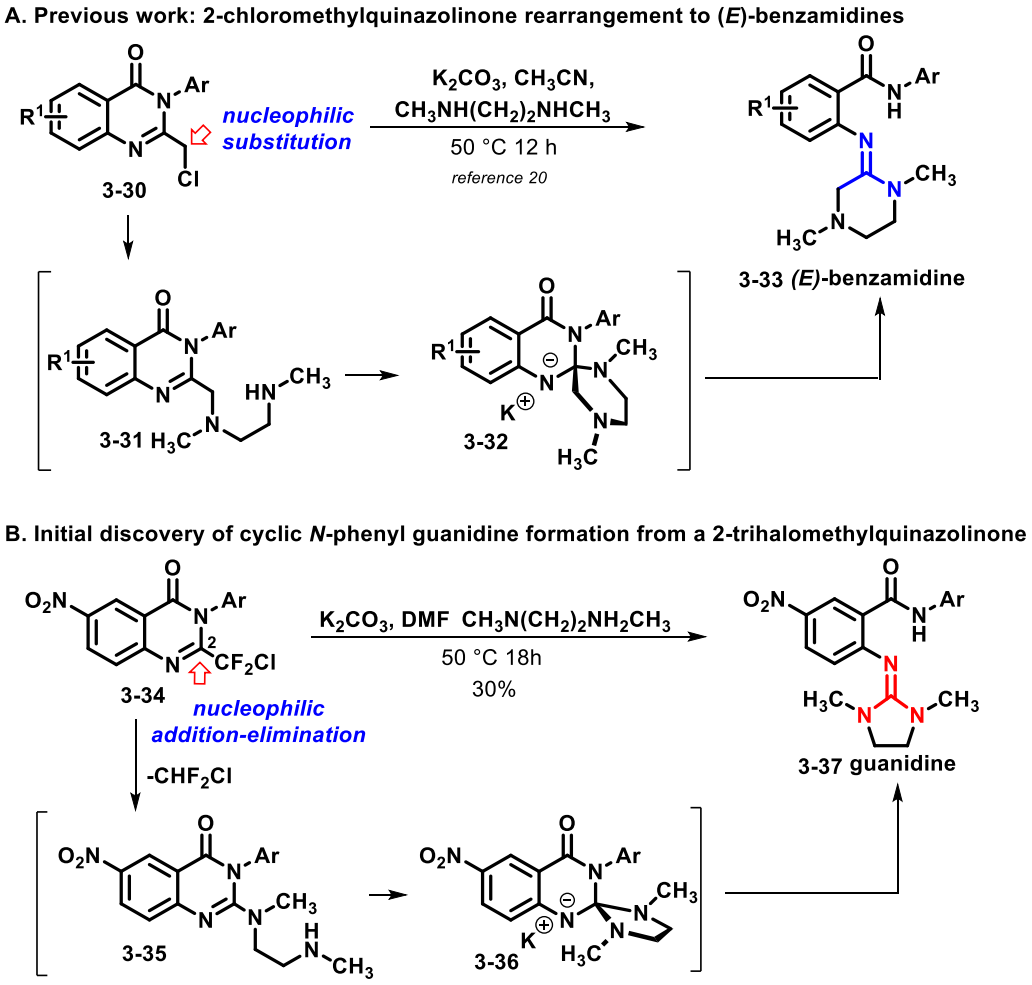



**Scheme 3-1.** Synthetic approaches to cyclic and linearly ring-fused guanidines.

## 3.3 Results and discussion

***Discovery of the novel rearrangement to afford cyclic guanidines***

As part of a medicinal chemistry driven antiviral program, we previously showed that 2-chloromethylquinazolinones **3-30** undergo a rearrangement reaction[43-45] to exclusively form (*E*)-benzamidines **3-33** when treated with $N^1$,$N^2$-dialkyldiamines (**Scheme 3-2A**).




**Scheme 3-2.** Quinazolinone rearrangements leading to (*E*)-benzamidines and novel cyclic guanidines

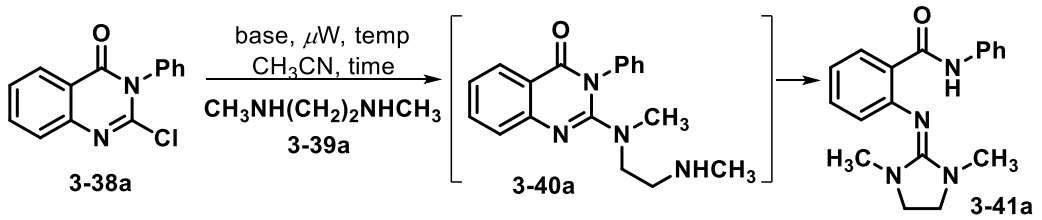
In the pursuit of structure-property relationships associated with the benzamidines, we explored alternatives to the 2-chloromethylquinazolinone starting material, such as 2-

difluorochloromethylquinazolinone **3-34** (**Scheme 3-2B**). Similar reaction conditions used for benzamidine generation were examined by graduate student Mr. Victor Jaffett, though the solvent was switched to DMF to solubilize **3-35**. Interestingly, a novel cyclic guanidine **3-37** was obtained in 30% yield. Mechanistically, the guanidine product might result from a nucleophilic addition-elimination reaction at C2 position (**Scheme 3-2B**, red arrow) to form intermediate **3-35**. Cyclization to form spirocycle **3-36**, followed by ring opening, would afford the cyclic guanidine **3-37**.

***Optimization of the substrates and reaction conditions***

Preparation of quinazolinone **3-34** was challenging due to the volatility and expense of difluorochloroacetyl chloride and the marginal yield of product obtained from **3-34** and other trihalomethylquinazolinones. Given these issues and the prospect that the product likely resulted from a nucleophilic addition-elimination reaction by loss of haloform. Another graduate student, Ms. Bereket Zekarias, explored the use of 2-chloroquinazolin-4(3*H*)-one **3-38a** as substrate in the reaction. Notably, this material contained a better leaving group (-Cl) and was easily prepared in 85% yield over two steps from anthranilic acid and phenyl isothiocyanate.[46] By collaborating with graduate student Ms. Bereket Zekarias, pilot reactions using **3-38a** with $N^1$,$N^2$-dimethyl-1,2-ethanediamine **3-39a** were explored to identify ideal conditions for this transformation (**Table 3-1**).

**Table 3-1.** Quinazolinone to cyclic guanidine reaction optimization [a]




| entry | base | equiv. base | solvent | T/°C | time (h) | $^1$H NMR[b] conversion | yield[c] **3-41a** |
|---|---|---|---|---|---|---|---|
| 1[d] | $K_2CO_3$ | 2 | DMF | 50 | 4 | > 85% | 66% |
| 2[d] | $K_2CO_3$ | 2 | $CH_3CN$ | 50 | 4 | 47% | 45% |
| 3[e] | $K_2CO_3$ | 3 | $CH_3CN$ | 100 | 4 | 58% | 53% |
| 4 | $K_2CO_3$ | 3 | $CH_3CN$ | 100 | 1 | 78% | 61% |
| 5 | $K_2CO_3$ | 3 | $CH_3CN$ | 150 | 1 | > 99% | 71% |
| 6 | $NEt_3$ | 3 | $CH_3CN$ | 100 | 1 | 80% | 79% |
| 7 | $NEt_3$ | 3 | $CH_3CN$ | 100 | 2 | 82% | 81% |
| **8** | **$NEt_3$** | **3** | **$CH_3CN$** | **150** | **2** | **> 99%** | **93% (92%) (85%)[f]** |

[a] Conditions: **3-38a** (0.2 mmol), **3-39a** (0.26 mmol), base, and solvent (2 mL) under microwave irradiation unless otherwise noted. [b] Calculated based on the consumption of **3-38a**. [c] NMR yield with 1,3,5-trimethoxybenzene as internal standard. Parenthetical value is isolated yield. [d] Thermal heating. [e] Sealed tube experiment. [f] 2 mmol scale reaction yield.

Under the conditions initially identified with quinazolinone **3-34**, when 2-chloroquinazolin-4(3*H*)-one (**3-38a**) was treated with dimethylethylenediamine **3-39a**, the starting material was consumed in less than 4 h, as determined by TLC, and guanidine **3-41a** was observed in 66% yield with greater than 85% conversion by $^1$H NMR (entry 1). Considering the complicated work up of DMF, acetonitrile was assessed, though comparatively this resulted in ~ 20% diminished yield and reduced conversion (entry 2). By increasing the equivalency of base (3 equiv.), switching to microwave irradiation, elevating the temperature to 150 °C and reducing the reaction time to 1 h (entries 3-5), conversion was improved to >99% while the yield was 71%, which we thought might be due to decomposition of the starting material or side reactions under

this condition (entry 5). To our delight, replacing the $K_2CO_3$ with triethylamine at 100 °C for 1 or 2 hours gave slightly increased yields (79% and 81%) and comparative conversion (80% and 82%) (entry 6-7). Finally, increasing temperature to 150 °C using trimethylamine as base resulted in full conversion and an isolated yield of 92% of **3-41a** (entry 8). On a 2 mmol scale, **3-41a** was obtained in 85% yield (> 500 mg).

***Crystal structure of twisted cyclic guanidine 3-41a***

Visualization of the cyclic guanidine geometry was facilitated with the X-ray crystal structure of **3-41a** (**Figure 3-2A**). An intramolecular hydrogen bond is formed between the nearby amide -$N^1$H- and the imine-like nitrogen ($N^2$) of the guanidine (distance = 1.96 Å), thereby restricting the scaffold conformation. (**Figure 3-2B**) The dimethylethylguanidine (DMEG) moiety was twisted and bent relative to the core phenyl ring. The dihedral angle in **3-41a** between the guanidine plane (pink plane) and the phenyl ring core plane (gray plane) was 54.41° (**Figure 3-2C**). The reason for the twisted guanidine conformation is possibly due to the steric interactions between the core phenyl ring and the methyl -$C^{17}H_3$, which would contribute to the selectivity of the (*E*)-guanidine product when asymmetrical diamines were used in this reaction (See *substrate scope* section). The distance from the amide -$N^1H$- hydrogen to the methyl –$C^{18}H_3$ hydrogen (2.87 Å) is closer than to the methyl -$C^{17}H_3$ hydrogen (4.10 Å). The associated nuclear overhauser effect (NOE) was used to determine the Z/E-configuration of the guanidines, which will be discussed in later section (**Table 3-3**).

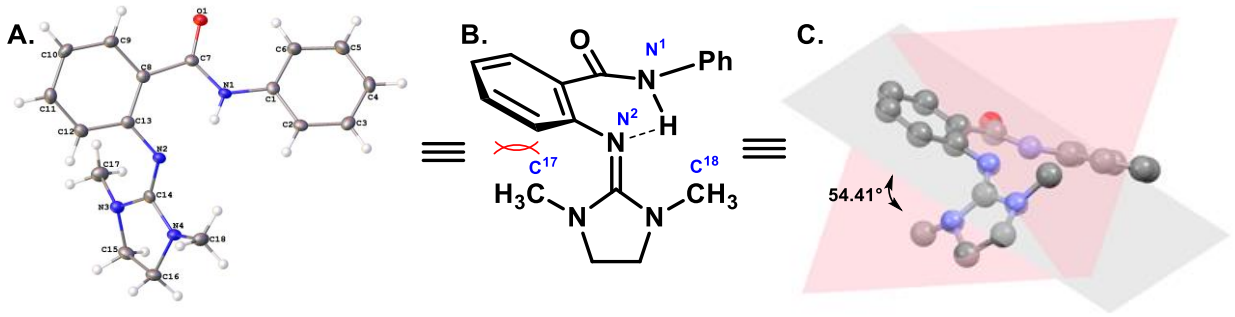



**Figure 3-2.** Crystal structure of **3-41a**. A. Molecular drawing of **3-41a** shown with 50% probability ellipsoids. B. Chemdraw view of **3-41a**. C. Alternate view of X-ray representation of **3-41a** without hydrogens for clarity and showing dihedral angle between the guanidine plane (pink plane) and core phenyl ring (gray plane). (planes were generated in Mercury 4.1.3)

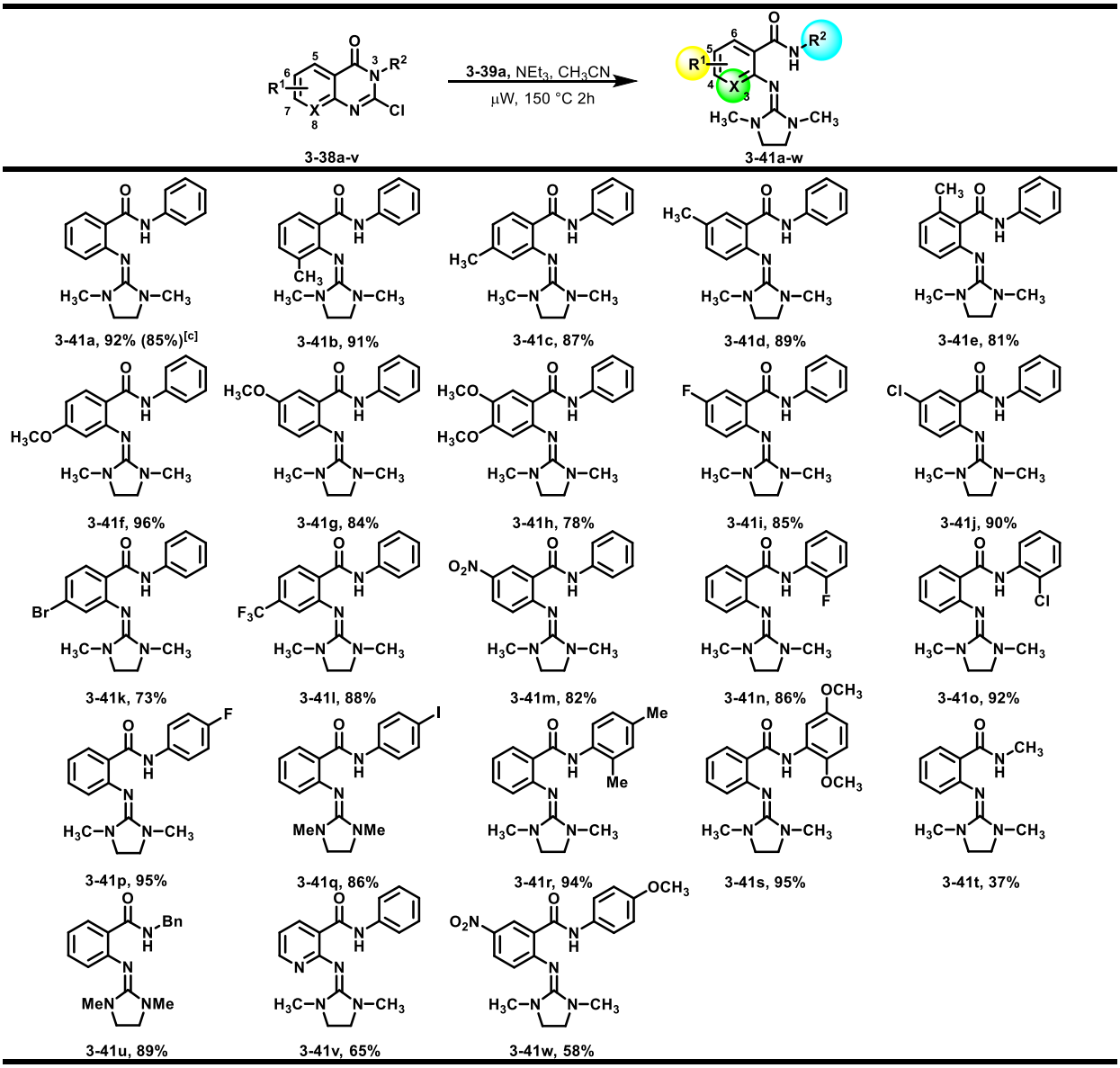
***Substrate scope for the synthesis of twisted-cyclic guanidines***

The optimized conditions were then applied to substrates bearing substituted 2-choroquinazolinones and diamines to evaluate the sensitivity of the method to electronic and steric factors. We first examined effects of heteroatom incorporation or substituents on the quinazolinone core, along with *NH*-amide substituent changes, using different 2-chloroquinazolinones **3-38a-v** (**Table 3-2**).

The transformation was extraordinarily tolerant of substitutions on the phenyl ring core of the quinazolinone structure. A methyl group at any of one of the C8 – C5 positions of the quinazolinone core afforded the corresponding guanidine products **3-41b-e** in good yield (81–91%). Installation of an electron donating methoxy group at C7 and/or C6 position of the substrate core rearranged successfully, affording the desired products **3-41f-h** in 78% – 96% yield. Substrates bearing electron withdrawing substituents also fared well, showing exceptional tolerance at the C4 or C5 product position for a range of halogens, trifluoromethyl or nitro group substituents (**3-41i-m**, 73%–90%). Quinazolinones with amide substituted $N^3$-phenyl rings

afforded corresponding guanidines in high yield (**3-41n-s**). While the $N^3$-methyl amide substrate only gave 37% of guanidine **3-41t**, rearrangments leading to the *N*-benzyl **3-41u** (89%) and pyridyl derivatives **3-41v** (65%) were more productive.

**Table 3-2.** Effect of 2-chloroquinazolinone modification on guanidine formation[a][b]




[a] Conditions: **3-38** (0.2 mmol), **3-39a** (0.26 mmol), $NEt_3$ (0.6 mmol) and $CH_3CN$ (2 mL). [b] Isolated yields, averaged from two independent experiments. [c] 2 mmol scale.

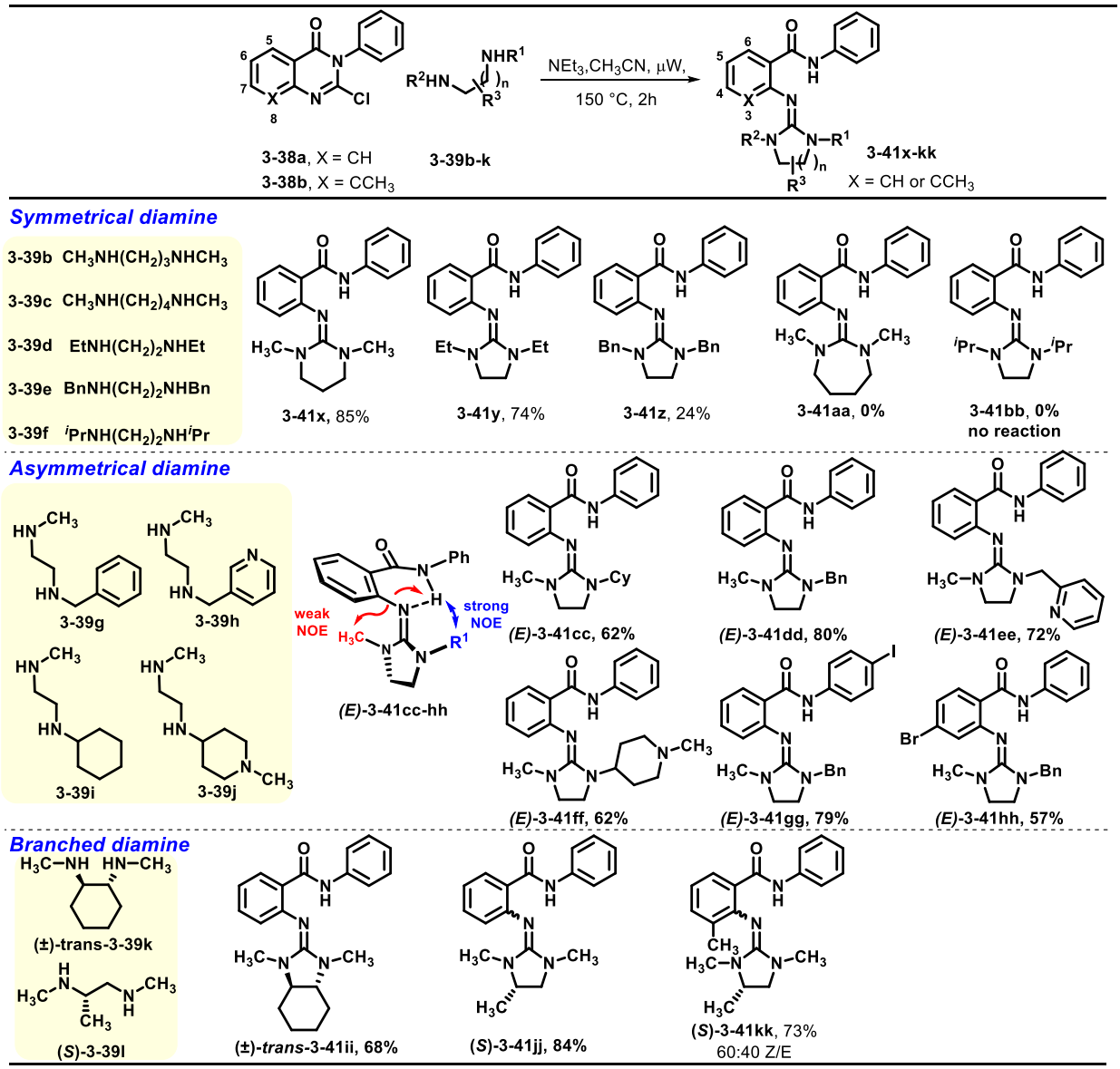
Attention was then shifted to assessing changes in the diamine moiety (**Table 3-3**). diamines **3-39a** and **3-39b** afforded 5- or 6-membered cyclic guanidines **3-41a** and **3-41x**, respectively, in high yield (85-92%). Seven-membered cyclic guanidines (**3-41aa**) could not be obtained when using *N*$^{1}$,*N*$^{2}$-dimethyl-1,4-butanediamine (**3-39c**), presumably due to energetically unfavorable formation of a 7-membered intermediate. Steric effects of diamines with different $R^1$ and $R^2$ substitution were determined to be important. Increasing steric bulk on the diamine by using *N*,*N*'-diethyl (**3-39d**) or *N*,*N*'-dibenzylethylenediamine (**3-39e**) lowered the yield of the products **3-41y** and **3-41z** in 74% and 24% yield, respectively. Further increase of steric bulk by using *N*,*N*'-diisopropylethylenediamine (**3-39f**) in the reaction failed to form any desired product (**3-41bb**).

A series of asymmetrically substituted *N*$^{1}$-methyl-*N*$^{2}$-alkyl-1,2-ethanediamines **3-39g-j** were also evaluated in the reaction, revealing the formation of (*E*)-guanidines **3-41cc-hh** in good yield (57-80%). Each product showed a strong NOE between the larger $R^2$ group and the *NH*-amide compared to a weaker NOE between the guanidine *N*-methyl substituent and the *NH*-amide proton. The excellent (*E*)-selectivity was attributed to reduced steric interactions when the larger *N*-substituent occupied a region of space away from the core phenyl ring, accommodated by the (*E*)-configuration. The observed NOE data was consistent with relative distances observed between the *N*-guanidine substituents and the amide-*NH* in the X-ray structure of **3-41a** (**Figure 3-2**).

Branched diamines were also successfully incorporated. Reaction of **3-38a** with (±)-*trans*-*N*$^{1}$,*N*$^{2}$-dimethylcyclohexane-1,2-diamine **3-39k** afforded (±)-*trans*-**3-41ii** in 68% yield, while *(S)*-*N*$^{1}$,*N*$^{2}$-dimethylpropane-1,2-diamine **3-39l** gave (*S*)-**3-41jj** as a mixture of *E* and *Z* isomers in 84%

yield. The installation of a C8-methyl substituent on the quinazolinone core led to a 73% yield of (*S*)-**3-41kk** in a 60:40 ratio of *Z*/*E* isomers.

**Table 3-3.** Effects of altering diamine structure on cyclic guanidine formation[a][b]

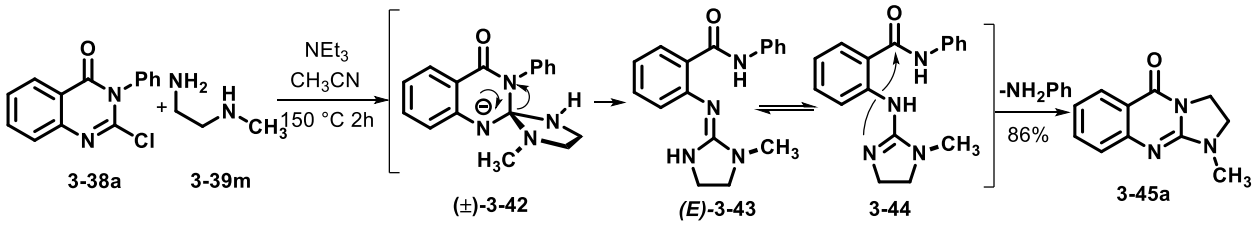



[a] Reaction conditions: **3-38a** or **3-38b** (0.2 mmol), **3-39** (0.26 mmol), $NEt_3$ (0.6 mmol) and $CH_3CN$ (2 mL). [b] Isolated yields, averaged from two independent experiments. [c] Used di-HCl salt form of diamine **3-39** and $NEt_3$ (1 mmol). [d] Used tri-HCl salt form of the diamine **20** and $NEt_3$ (1.2 mmol).

Generally, these reactions were high yielding for a variety of regional structural changes and electronic influences, and exclusive cyclic (*E*)-guanidines formation occurred when a disparity in diamine *N*-substituent size was introduced.

***Substrate scope for the synthesis of ring-fused guanidines***

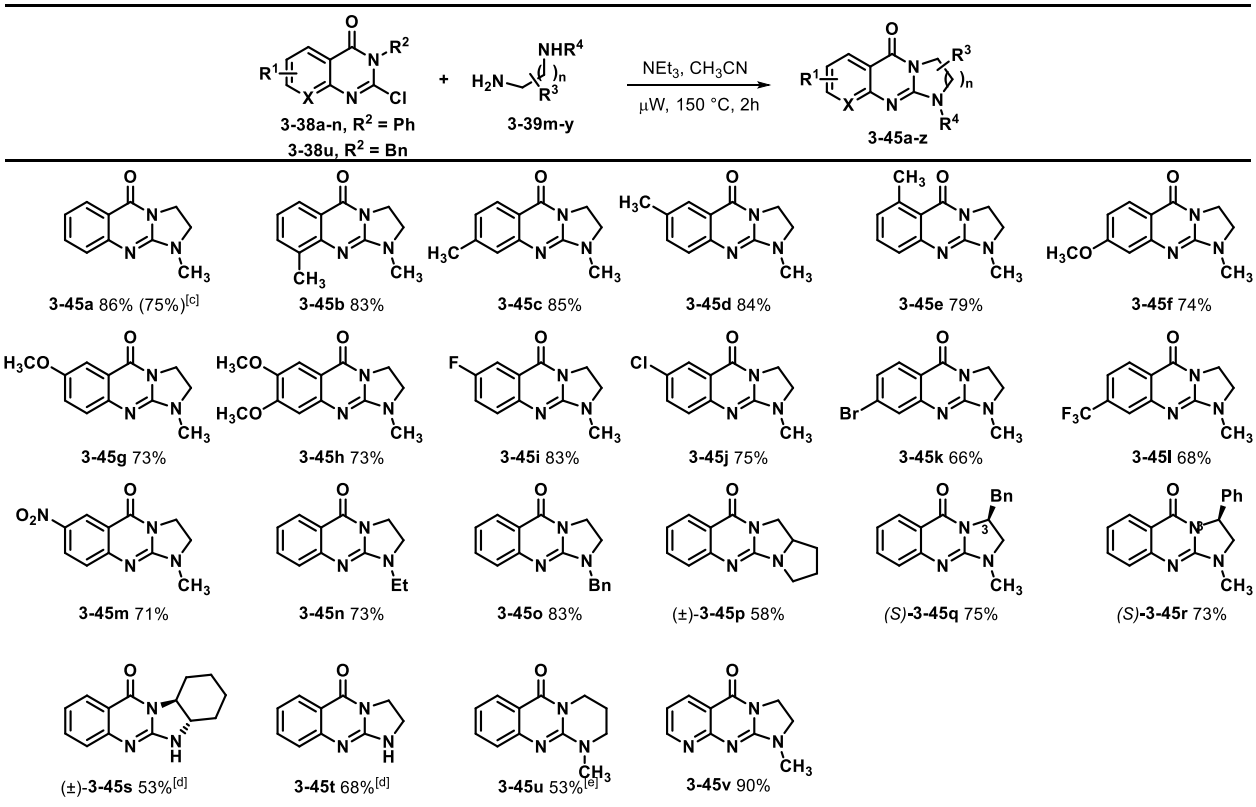
As part of our reaction assessment, we also evaluated diamines containing at least one primary amine. Notably, we did not observe expected *NH*-guanidine analogs, but rather discovered that *ring-fused* guanidines were formed in high yield under the optimized conditions. For example, treatment of **3-38a** with diamine **3-39m** afforded 86% yield of ring-fused guanidine **3-45a** (**Scheme 3-3**).




**Scheme 3-3.** Proposed mechanism for the novel formation of ring-fused *N*-acylguanidines from primary amines and 2-chloroquinazolinones

Mechanistically, we propose that the diamine attacks 2-chloroquinazolinone **3-38a** to form a spirocycle **(±)-3-42**, followed by ring-opening to form cyclic guanidine **3-43**. As we have shown, the (*E*)-configuration is favored when the guanidine nitrogen atoms bear substituents of unequal size, and this configuration is necessary for intramolecular *N*-acylation of guanidine, which affords a ring-fused *N*-acylguanidine **3-45a**. The scope of this transformation was investigated, revealing successful reactions for a spectrum of quinazolinone core substitutions and diamines (**Scheme 3-4**).

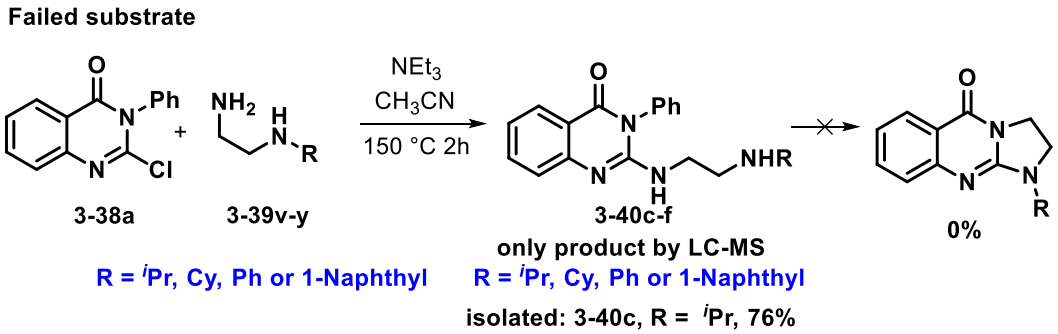
**Scheme 3-4.** Yield and scope of rearrangement affording ring-fused guanidines[a][b]




[a] Conditions unless otherwise noted: **3-38** ($R^2$ = Ph, 0.2 mmol), **3-39** (0.26 mmol), $NEt_3$ (0.6 mmol) and $CH_3CN$ (2 mL). [b] Isolated yields, averaged from two independent experiments. [c] 2 mmol scale. [d] Used 3.0 equiv. of diamine (0.6 mmol). [e] Used **3-38t** ($R^2$ = Bn).

Ring-fused guanidines **3-45a**–**m**, derived from *N*-methylethane-1,2-diamine **3-39m** and variously substituted 2-chloroquinazolinones (**3-38a-m**), were obtained in 66–86% yield. (**Scheme 3-4**) Ring-fused guanidines with $N^1$-Et (**3-45n**), $N^1$-Bn (**3-45o**) and tetracyclic guanidine (±)-**3-45p** were obtained in good yield when differentially substituted diamines were employed. Incorporation of chiral diamines gave the corresponding C3-substituted products **3-45q** (75%) and **3-45r** (73%) with stereoretention. Ring-fused guanidines bearing $N^1$-H were also generated when diprimary amines were used. Specifically, $N^1$-H tricyclic guanidine **3-45s** and tetracyclic guanidine **3-45t** were obtained in 53% and 68% yield, respectively, when three equivalents of the diamine

was used. Synthesis of the 6.6.6-tricylic system of **3-45u** was initially achieved in 23% yield from *N*-methyl-1,3-propanediamine and **3-38a**; however, when *N*-phenyl quinazolinone **3-38a** was replaced in the reaction with *N*-benzyl derivative **3-38u**, a 30% improvement in yield was observed for making **3-45u**. Diamines bearing bulkier *N*-substituents or less nuclophilic diamines, such as *N*-isopropylethane-1,2-diamine **3-39v,** *N*-cyclohexylethane-1,2-diamine **3-39w** or *N*-arylethane diamines (**3-39x** (R = Ph) and **3-39y** (R = 1-naphthyl)), did not afford twisted cyclic or ring-fused guanidines. In fact, these reactions revealed elusive the intermediates **3-40c-f**, of which the R = isopropyl intermediate (**3-40c**) was isolated in 76% yield. (**Scheme 3-5**)




**Scheme 3-5.** Diamines bearing bulkier *N*-substituents or less nuclophilic *N*-aryldiamines affording intermediate **3-40c-f** only

## ***Applications of the guanidine derivatives***

Finally, we were excited to apply this method to the generation of useful guanidines.

Venezuelan equine encephalitis virus (VEEV) is one of the new world alphaviruses transmitted by the bite of infected mosquitoes. Alphaviruses, including VEEV, have been developed as bioweapons, and unfortunately, there are no FDA approved vaccines or drugs available for the treatment of VEEV. The Golden group discovered and developed the benzamidine compound series (**ML-336** and **BDGR-4**, **Figure 3-3**)[43] that showed good potency and *in vivo* efficacy against VEEV. However, these compounds also generally show some liability

in mouse plasma stability assay which was attributed to potential enzymatic hydrolysis of the amidine functionality. As the twisted-cyclic guanidines described herein are structural isosteres of our lead benzamidines and are less prone to hydrolysis, we tested the stability of select guanidine analogs. The selected guanidine analogs **3-41m** and **3-41w** showed increased plasma stability (100% and 78%, respectively) while retaining potency against VEEV. Considering that these compounds have not been optimized for VEEV inhibition, we were excited to see reasonable activity for some of these analogs and a marked improvement in plasma stability compared to the their amidine predecessors. The guanidine compounds are considered new hit compounds that are now part of an anti-VEEV project which will be part of a future publication.

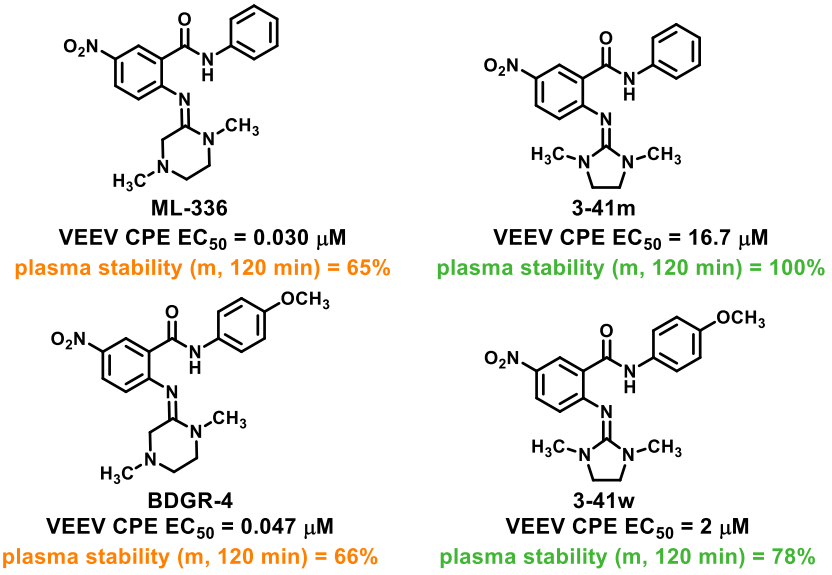
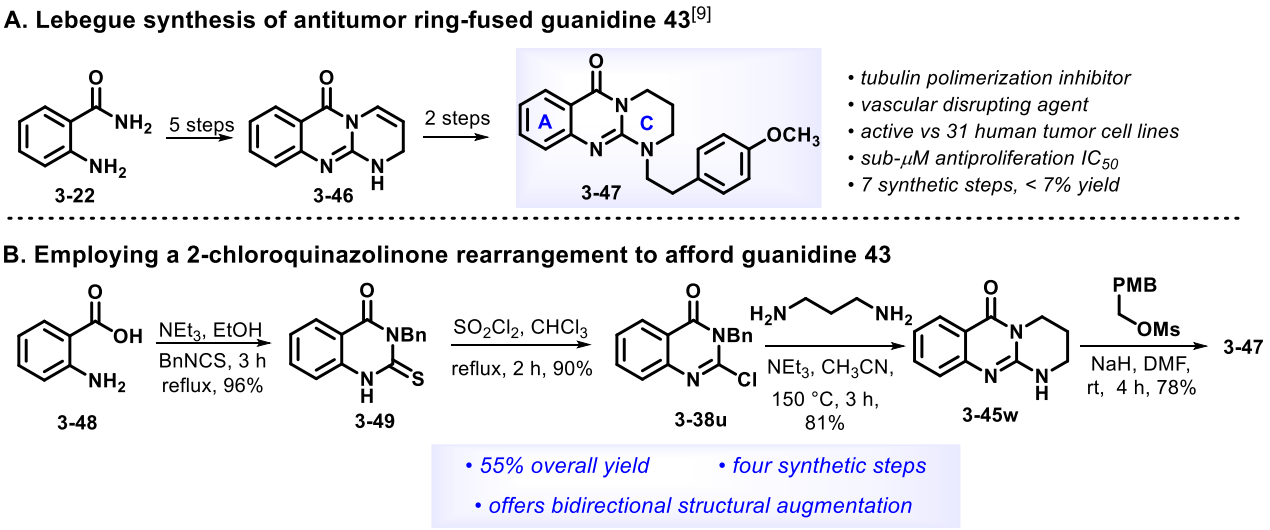



**Figure 3-3.** Improved plasma stability for the guanidine derivatives

While the twisted guanidines are valuable to the alphavirus project, the domino transformation advantageously generated a separate class of bioactive, ring-fused *N*-acylguanidines. For instance, compound **3-47** is a tubulin polymerization inhibitor, vascular disrupting agent, and inhibited growth of 31 human cancer cell lines representing nine cancer cell types (**Scheme 3-6A**).[23] We speculate that the synthesis of **3-47**, accomplished in < 7% overall

yield and requiring 7 steps from anthranilamide **3-22**, has possibly impeded structure-activity relationship (SAR) exploration.




**Scheme 3-6.** Reported synthesis (A) of an antitumor ring-fused *N*-acyl guanidine and (B) a high-yielding, analog-enabling total synthesis of **3-47** using a 2-choroquinazolinone rearrangement

We recognized that **3-47** might be more efficiently prepared and analogs thereof may be more expediently explored using our 2-chloroquinazolinone rearrangement. To assess this approach, the requisite *N*-benzyl-2-chloroquinazolinone **3-38u** was generated from anthranilic acid **3-48** in 86% yield over 2 steps (**Scheme 3-6B**). In the key rearrangement step, **3-38u** was treated with 1,3-diaminopropane (10 equiv.) to afford $N^1$-H tricyclic guanidine **3-45w** in 81% yield after microwave irradiation at 150 °C for 3 hours. Subsequent *N*-alkylation of **3-45w** with 4-methoxyphenethyl methanesulfonate afforded the desired guanidine **3-47** in 78% yield. Thus, guanidine **3-47** was obtained in four steps and 55% overall yield. Based on the previous substrate scope investigation in **Table 3-2**, we anticipate this method permits extensive SAR investigation of the terminal rings (rings A and C) of this guanidine scaffold, possibly revealing new development opportunities. Furthermore, all of the compounds between the two guanidine classes

prepared by this method have been submitted for extensive screening to elucidate additional activity of interest.

## 3.4 Conclusion

A unique and highly efficient rearrangement of 2-chloroquinazolin-4(3*H*)-ones that predictable and selectively generated either twisted-cyclic or ring-fused *N*-acylguanidines in a single operation was developed. The reaction pathway was controlled by the presence of a primary versus secondary amine in the diamine reagent. Use of secondary diamines afforded exclusively twisted-cyclic guanidines, while diamines bearing at least one primary amine generated twisted-cyclic guanidines *in situ* that subsequently underwent intramolecular ring closure to afford ring-fused *N*-acylguanidines. Both reaction pathways showed broad structural substrate tolerance, generating 32 novel twisted-cyclic guanidines in up to 96% yield and 23 ring-fused *N*-acylguanidines in up to 90% yield. Twisted-cyclic guanidines have found utility in our antiviral program, offering increased plasma stability compared to our related benzamidine scaffold. The method was also deployed in the total synthesis of a known antitumor agent containing the ring-fused *N*-acylguanidine scaffold. Hence, the desired ring-fused guanidine **3-47** was synthesized in only four steps and in 55% yield, which is three steps shorter and with an 8-fold increase in yield compared to the published report.[23] The divergent yet tractable nature of this transformation to generate two distinct classes of bioactive guanidines with high efficiency is expected to facilitate the development of new guanidine-containing frameworks.

## 3.5 Perspective and future directions

As mentioned in the previous section, the twisted-cyclic guanidine analogs showed increased plasma stability (100% and 78%, respectively) while retaining weak potency against VEEV and WEEV. Moreover, these compounds have also shown potent activity against EEEV

(data not shown here). Therefore, these compounds are now being investigated as an anti-viral project and will be part of a future publication.

## 3.6 Acknowledgement

The authors acknowledge funding from the National Institutes of Health (1R01AI118814-01). This work made use of instrumentation at the UW−Madison Medicinal Chemistry Center and Analytical Instrumentation Center, funded by the UW School of Pharmacy. Gang Yan are thankful to the co-authors and collaborators Mr. Victor Jaffett for the discovery of this novel rearrangement, Ms. Bereket Zekarias for optimizing the reaction conditions, Dr. Ilia Guzei for getting the crystal structure of compound **3-41a** and Dr. Donghoon Chung's laboratory from University of Louisville for measuring the antiviral activity against VEEV.

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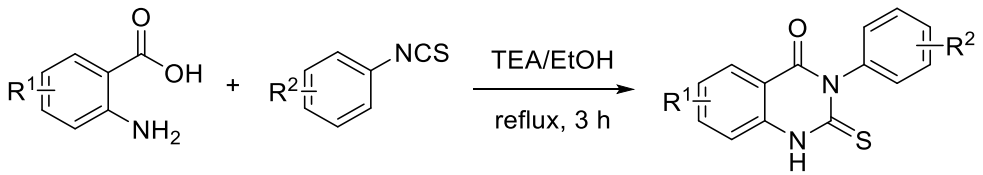
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## 3.8 Experimental section

### *3.8.1. General Information*

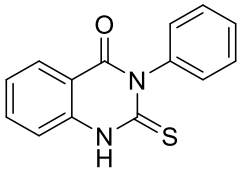
Commercial reagents and solvents were used as received from Sigma Aldrich, Fischer Scientific, Acros Organics, TCI America, Oakwood Products Inc, VWR International, etc. All thin layer chromatography was performed using precoated silica gel plates. Microwave irradiated (MWI) reactions were carried out using an Anton Paar Monowave 300 Microwave Synthesis Reactor. Flash chromatography separations were carried out using a Teledyne Isco CombiFlash Rf 200 purification system with silica gel columns. $^{1}H$ and $^{13}C$ nuclear magnetic resonance (NMR) spectra were obtained on a Varian Unity-Inova 500 MHz, or Bruker Ascend 400 MHz in $CDCl_3$, $D_2O$ or DMSO-$d_6$. The chemical shifts (δ) reported are given in parts per million (ppm). The Signal splitting patterns were described as s = singlet, d = doublet, t = triplet, q = quartet, p = pentuplet, dd = doublet of doublet, dt = doublet of triplet, td = triplet of doublet, tt = triplet of triplet, ddd = doublet of doublet of doublet, and m = multiplet, with coupling constants (*J*) in hertz (Hz). High resolution mass spectra (HRMS) were performed by Analytical Instrument Center at the School of Pharmacy on an Electron Spray Injection (ESI) mass spectrometer. Optical rotations were measured on a Perkin Elmer Polarimeter-241. All final compounds were determined to be of > 95% purity by UV-LC-MS at 254 nm.

### *3.8.2. Synthesis of 3-substituted-2-thioxo-2,3-dihydroquinazolin-4(1H)-one*

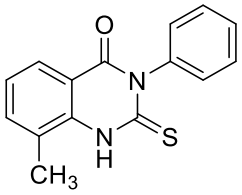



**3-S-1a~l** **3-S-2a~i** **3-S-3a~l, 3-S-3n~u**

**General procedure:** To a round-bottom flask was added anthranilic acid (**3-S-1**, 10 mmol, 1 equiv.), isothiocyanate (**3-S-2**, 11 mmol, 1.1 equiv.), triethylamine ($NEt_3$, 11 mmol, 1.1 equiv.) and EtOH (30 mL). The reaction mixture was stirred under reflux condition for 3 hours. After the completion of the reaction, the mixture was cooled to room temperature. The precipitates were filtered out and washed with hexane to get the pure products.

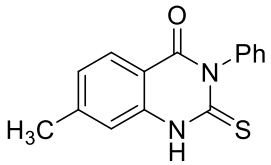



**3-phenyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3-S-3a)** The reaction was performed with anthranilic acid (**41**, 1.37 g, 10 mmol), phenyl isothiocyanate (**3-S-2a**, 1.3 mL, 11 mmol), $NEt_3$ (1.53 mL, 11 mmol) and EtOH (30 mL); yield: 2.41 g, 96%; white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 13.03 (s, 1H), 7.95 (dd, $J$ = 8.0, 1.4 Hz, 1H), 7.82 – 7.74 (m, 1H), 7.52 – 7.43 (m, 3H), 7.43 – 7.37 (m, 1H), 7.35 (t, $J$ = 7.6 Hz, 1H), 7.31 – 7.24 (m, 2H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 176.0, 159.8, 139.6, 139.3, 135.6, 129.0, 128.9, 128.1, 127.4, 124.3, 116.2, 115.7. Data is consistent with reference[1].

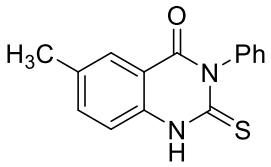



**8-methyl-3-phenyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3-S-3b)** The reaction was performed with 3-methyl anthranilic acid (**3-S-1b**, 750 mg, 5 mmol), phenyl isothiocyanate (**3-S-**

**2a**, 0.65 mL, 5.5 mmol), $NEt_3$ (0.77 mL, 5.5 mmol) and EtOH (15 mL); yield: 1.20 g, 90%; white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.82 (s, 1H), 7.83 (dd, $J$ = 8.0, 1.4 Hz, 1H), 7.62 (d, $J$ = 7.7 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.44 – 7.38 (m, 1H), 7.31 – 7.22 (m, 3H), 2.52 (s, 3H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 176.4, 159.8, 139.5, 138.0, 136.8, 128.9, 128.9, 128.0, 125.3, 124.5, 124.2, 116.5, 17.4. Data is consistent with reference[1].

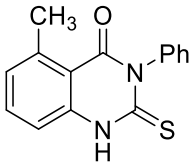



**7-methyl-3-phenyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3-S-3c)** The reaction was performed with 4-methyl anthranilic acid (**3-S-1c**, 1.51 g, 10 mmol), phenyl isothiocyanate (**3-S-2a**, 1.3 mL, 11 mmol), $NEt_3$ (1.53 mL, 11 mmol) and EtOH (30 mL); yield: 2.6 g, 97%; white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.97 (s, 1H), 7.84 (d, $J$ = 8.1 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.43 – 7.36 (m, 1H), 7.33 – 7.20 (m, 3H), 7.17 (d, $J$ = 8.2 Hz, 1H), 2.42 (s, 3H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 176.1, 159.6, 146.4, 139.6, 139.3, 129.0, 128.9, 128.0, 127.3, 125.7, 115.3, 113.9, 21.6. HRMS (ESI) m/z for $C_{15}H_{13}N_2OS^+$ $(M+H)^+$, 269.0743 (Calc.), found 269.0737.

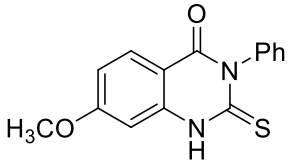



**6-methyl-3-phenyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3-S-3d)** The reaction was performed with 5-methyl anthranilic acid (**3-S-1d**, 1.51 g, 10 mmol), phenyl isothiocyanate (**3-S-2a**, 1.3 mL, 11 mmol), $NEt_3$ (1.53 mL, 11 mmol) and EtOH (30 mL); yield: 2.56 g, 96%; white

solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 12.98 (s, 1H), 7.75 (d, *J* = 1.9 Hz, 1H), 7.61 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.44 – 7.37 (m, 1H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.30 – 7.22 (m, 2H), 2.37 (s, 3H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 175.5, 159.8, 139.4, 137.6, 136.6, 133.9, 129.0, 128.9, 128.0, 126.7, 116.0, 115.7, 20.4. Data is consistent with reference[2].

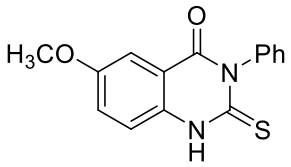



**5-methyl-3-phenyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3-S-3e)** The reaction was performed with 6-methyl anthranilic acid (**3-S-1e**, 1.51 g, 10 mmol), phenyl isothiocyanate (**3-S-2a**, 1.3 mL, 11 mmol), $NEt_3$ (1.53 mL, 11 mmol) and EtOH (30 mL); yield: 2.07 g, 77%; white solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 12.88 (s, 1H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.51 – 7.43 (m, 2H), 7.42 – 7.36 (m, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.28 – 7.22 (m, 2H), 7.12 (dt, *J* = 7.4, 1.1 Hz, 1H), 2.63 (s, 3H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 175.5, 160.2, 141.3, 140.8, 139.6, 134.6, 129.1, 128.8, 127.9, 126.9, 114.4, 113.9, 22.1. HRMS (ESI) m/z for $C_{15}H_{13}N_2OS^+$ $(M+H)^+$, 269.0743 (Calc.), found 269.0750.

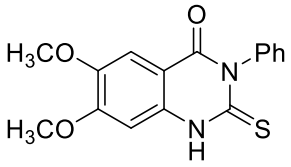



**7-methoxy-3-phenyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3-S-3f)** The reaction was performed with 4-methoxy anthranilic acid (**3-S-1f**, 1.67 g, 10 mmol), phenyl isothiocyanate (**3-S-2a**, 1.3 mL, 11 mmol), $NEt_3$ (1.53 mL, 11 mmol) and EtOH (30 mL); yield: 2.46 g, 87%; white

solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 12.87 (s, 1H), 7.87 (d, $J$ = 8.5 Hz, 1H), 7.52 – 7.34 (m, 3H), 7.25 (dd, $J$ = 7.2, 2.0 Hz, 2H), 6.93 (d, $J$ = 8.5 Hz, 2H), 3.87 (s, 3H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 176.3, 164.7, 159.3, 141.4, 139.3, 129.4, 129.0, 128.8, 128.0, 112.6, 109.5, 98.5, 55.8. Data is consistent with reference[2].

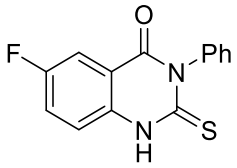



**6-methoxy-3-phenyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3-S-3g)** The reaction was performed with 5-methoxy anthranilic acid (**3-S-1g**, 1.67 g, 10 mmol), phenyl isothiocyanate (**3-S-2a**, 1.3 mL, 11 mmol), $NEt_3$ (1.53 mL, 11 mmol) and EtOH (30 mL); yield: 2.61 g, 92%; white solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 12.99 (s, 1H), 7.52 – 7.37 (m, 5H), 7.37 – 7.32 (m, 1H), 7.30 – 7.22 (m, 2H), 3.82 (s, 3H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 174.6, 159.7, 155.9, 139.4, 134.1, 129.0, 128.9, 128.1, 124.6, 117.6, 117.0, 107.9, 55.7. Data is consistent with reference[2].

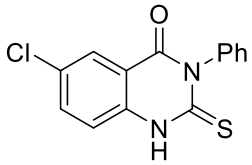



**6,7-dimethoxy-3-phenyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3-S-3h)** The reaction was performed with 4, 5-dimethoxy anthranilic acid (**3-S-1h**, 1.97 g, 10 mmol), phenyl isothiocyanate (**3-S-2a**, 1.3 mL, 11 mmol), $NEt_3$ (1.53 mL, 11 mmol) and EtOH (30 mL); yield: 2.80 g, 89%; white solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 12.84 (s, 1H), 7.50 – 7.44 (m, 2H), 7.43 – 7.38 (m, 1H), 7.28 – 7.22 (m, 3H), 6.98 (s, 1H), 3.87 (s, 3H), 3.81 (s, 3H). $^{13}$C NMR (101 MHz, DMSO-$d_6$)

δ 174.9, 159.3, 155.3, 146.5, 139.5, 135.5, 129.0, 128.8, 128.0, 108.6, 106.9, 97.9, 56.0, 55.8. Data is consistent with reference[3].

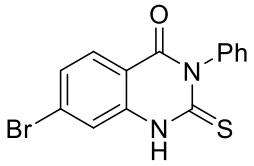



**6-fluoro-3-phenyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3-S-3i)** The reaction was performed with 5-fluoro anthranilic acid (**3-S-1i**, 1.55 g, 10 mmol), phenyl isothiocyanate (**3-S-2a**, 1.3 mL, 11 mmol), $NEt_3$ (1.53 mL, 11 mmol) and EtOH (30 mL); yield: 2.55 g, 94%; white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 13.10 (s, 1H), 7.74 – 7.61 (m, 2H), 7.54 – 7.45 (m, 3H), 7.44 – 7.37 (m, 1H), 7.33 – 7.21 (m, 2H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 175.6, 159.2, 159.1, 158.2 (d, $J$ = 242.7 Hz), 139.1, 136.5 (d, $J$ = 1.3 Hz), 128.9, 128.2, 123.7 (d, $J$ = 24.4 Hz), 118.3 (d, $J$ = 7.9 Hz), 117.5 (d, $J$ = 8.1 Hz), 112.4 (d, $J$ = 24.2 Hz). $^{19}$F NMR (376 MHz, DMSO-$d_6$) δ -117.37. Data is consistent with reference[3].

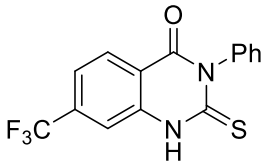



**6-chloro-3-phenyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3-S-3j)** The reaction was performed with 5-chloro anthranilic acid (**3-S-1j**, 1.71 g, 10 mmol), phenyl isothiocyanate (**3-S-2a**, 1.3 mL, 11 mmol), $NEt_3$ (1.53 mL, 11 mmol) and EtOH (30 mL); yield: 2.72 g, 94%; white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 13.15 (s, 1H), 7.88 (d, $J$ = 2.5 Hz, 1H), 7.84 (dd, $J$ = 8.8, 2.5 Hz, 1H), 7.51 – 7.39 (m, 4H), 7.32 – 7.24 (m, 2H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 176.0,

158.8, 139.1, 138.4, 135.5, 128.9, 128.9, 128.2, 128.1, 126.3, 117.9, 117.7. Data is consistent with reference[4].

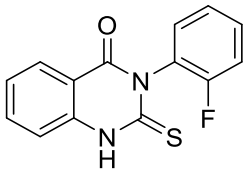



**7-bromo-3-phenyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3-S-3k)** The reaction was performed with 4-bromo anthranilic acid (**3-S-1k**, 2.16 g, 10 mmol), phenyl isothiocyanate (**3-S-2a**, 1.3 mL, 11 mmol), $NEt_3$ (1.53 mL, 11 mmol) and EtOH (30 mL); yield: 2.65 g, 80%; white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 13.05 (s, 1H), 7.85 (d, $J$ = 8.4 Hz, 1H), 7.61 (d, $J$ = 1.8 Hz, 1H), 7.55 – 7.44 (m, 3H), 7.44 – 7.37 (m, 1H), 7.34 – 7.21 (m, 2H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 176.4, 159.3, 140.5, 139.1, 129.5, 128.9, 128.9, 128.2, 127.1, 118.0, 115.5. HRMS (ESI) m/z for $C_{14}H_{10}BrN_2OS^+$ $(M+H)^+$, 332.9692 (Calc.), found 332.9675.

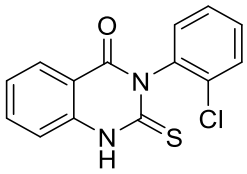



**3-phenyl-2-thioxo-7-(trifluoromethyl)-2,3-dihydroquinazolin-4(1*H*)-one (3-S-3l)** The reaction was performed with 4-trifluoromethyl anthranilic acid (**3-S-1l**, 2.05 g, 10 mmol), phenyl isothiocyanate (**3-S-2a**, 1.3 mL, 11 mmol), $NEt_3$ (1.53 mL, 11 mmol) and EtOH (30 mL); yield: 2.56 g, 80%; white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 13.21 (s, 1H), 8.14 (d, $J$ = 8.2 Hz, 1H), 7.75 (d, $J$ = 1.6 Hz, 1H), 7.63 (dd, $J$ = 8.3, 1.6 Hz, 1H), 7.55 – 7.45 (m, 2H), 7.45 – 7.37 (m, 1H), 7.34 – 7.26 (m, 2H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 176.6, 159.0, 139.8, 139.0, 134.6 (q, $J$ =

32.3 Hz), 129.2, 129.0, 128.8, 128.3, 123.2 (q, *J* = 273.2 Hz), 120.0 (q, *J* = 3.4 Hz), 119.3, 112.7 (q, *J* = 3.9 Hz). $^{19}$F NMR (376 MHz, DMSO-$d_6$) δ -62.70. HRMS (ESI) m/z for $C_{15}H_{10}F_3N_2OS^+$ $(M+H)^+$, 323.0460 (Calc.), found 323.0466.

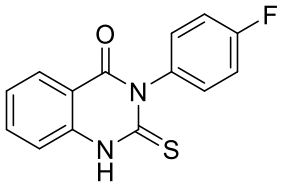



**3-(2-fluorophenyl)-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3-S-3n)** The reaction was performed with anthranilic acid (**41**, 1.37 g, 10 mmol), 2-fluorophenyl isothiocyanate (**3-S-2b**, 1.35 mL, 11 mmol), $NEt_3$ (1.53 mL, 11 mmol) and EtOH (30 mL); yield: 2.51 g, 92%; white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 13.22 (s, 1H), 7.98 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.82 (ddd, *J* = 8.6, 7.3, 1.5 Hz, 1H), 7.55 – 7.43 (m, 3H), 7.42 – 7.27 (m, 3H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 175.5, 159.2, 157.2 (d, *J* = 247.6 Hz), 139.6, 136.0, 131.3, 130.7 (d, *J* = 7.9 Hz), 127.5, 126.4 (d, *J* = 13.2 Hz), 124.9 (d, *J* = 3.5 Hz), 124.7, 116.1, 115.9, 115.5. $^{19}$F NMR (376 MHz, DMSO-$d_6$) δ -123.44. HRMS (ESI) m/z for $C_{14}H_{10}FN_2OS^+$ $(M+H)^+$, 273.0492 (Calc.), found 273.0499.

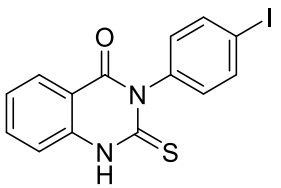



**3-(2-chlorophenyl)-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3-S-3o)** The reaction was performed with anthranilic acid (**41**, 1.37 g, 10 mmol), 2-chlorophenyl isothiocyanate (**3-S-2c**, 1.44 mL, 11 mmol), $NEt_3$ (1.53 mL, 11 mmol) and EtOH (30 mL); yield: 2.50 g, 87%; white solid.

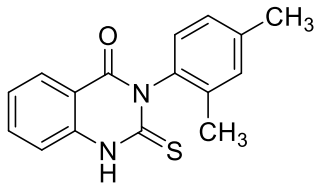
$^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 13.19 (s, 1H), 7.98 (dd, $J$ = 8.1, 1.4 Hz, 1H), 7.82 (td, $J$ = 7.9, 7.2, 1.5 Hz, 1H), 7.68 – 7.57 (m, 1H), 7.55 – 7.42 (m, 4H), 7.37 (t, $J$ = 7.6 Hz, 1H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 175.1, 159.0, 139.7, 136.5, 136.0, 131.5, 131.2, 130.2, 129.6, 128.0, 127.5, 124.6, 115.9, 115.6. HRMS (ESI) m/z for $C_{14}H_{10}ClN_2OS^+$ $(M+H)^+$, 289.0197 (Calc.), found 289.0203.



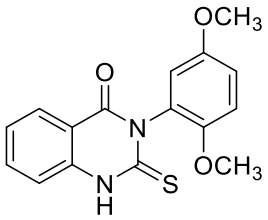

**3-(4-fluorophenyl)-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3-S-3p)** The reaction was performed with anthranilic acid (**41**, 1.37 g, 10 mmol), 4-fluorophenyl isothiocyanate (**3-S-2d**, 1.68 g, 11 mmol), $NEt_3$ (1.53 mL, 11 mmol) and EtOH (30 mL); yield: 2.64 g, 97%; white solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 13.05 (s, 1H), 7.95 (dd, $J$ = 8.0, 1.4 Hz, 1H), 7.78 (ddd, $J$ = 8.6, 7.3, 1.5 Hz, 1H), 7.45 (d, $J$ = 8.2 Hz, 1H), 7.40 – 7.21 (m, 5H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 176.1, 161.5 (d, $J$ = 244.4 Hz), 159.9, 139.6, 135.6, 135.5 (d, $J$ = 3.2 Hz), 131.2 (d, $J$ = 8.8 Hz), 127.4, 124.3, 116.2, 115.9, 115.7 (d, $J$ = 7.2 Hz). $^{19}$F NMR (376 MHz, DMSO-$d_6$) δ -114.70. Data is consistent with reference[5].



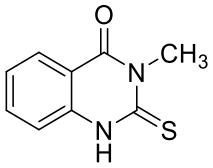
**3-(4-iodophenyl)-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3-S-3q)** The reaction was performed with anthranilic acid (**41**, 1.37 g, 10 mmol), 4-iodophenyl isothiocyanate (**3-S-2e**, 2.6 g, 10 mmol), $NEt_3$ (1.53 mL, 11 mmol) and EtOH (30 mL); yield: 3.45g, 91%; white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 13.06 (s, 1H), 7.95 (d, $J$ = 8.0 Hz, 1H), 7.90 – 7.81 (m, 2H), 7.78 (t, $J$ = 7.9 Hz, 1H), 7.44 (d, $J$ = 8.3 Hz, 1H), 7.34 (t, $J$ = 7.7 Hz, 1H), 7.20 – 7.06 (m, 2H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 175.8, 159.7, 139.6, 139.2, 137.8, 135.6, 131.5, 127.4, 124.4, 116.2, 115.7, 94.4. HRMS (ESI) m/z for $C_{14}H_{10}IN_2OS^+$ $(M+H)^+$, 380.9553 (Calc.), found 380.9566.




**3-(2,4-dimethylphenyl)-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3-S-3r)** The reaction was performed with anthranilic acid (**41**, 1.37 g, 10 mmol), 2,4-dimethylphenyl isothiocyanate (**3-S-2f**, 1.79 g, 11 mmol), $NEt_3$ (1.53 mL, 11 mmol) and EtOH (30 mL); yield: 2.51 g, 89%; white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 13.07 (s, 1H), 7.96 (dd, $J$ = 8.0, 1.4 Hz, 1H), 7.82 – 7.74 (m, 1H), 7.46 (d, $J$ = 8.2 Hz, 1H), 7.35 (t, $J$ = 7.6 Hz, 1H), 7.14 (s, 1H), 7.09 (dd, $J$ = 8.0, 1.8 Hz, 1H), 7.05 (d, $J$ = 7.9 Hz, 1H), 2.33 (s, 3H), 1.99 (s, 3H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 175.4, 159.4, 139.7, 137.6, 135.7, 134.8, 131.1, 128.5, 127.5, 127.4, 124.4, 115.8, 115.7, 20.7, 16.9. Data is consistent with reference[6].

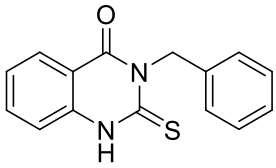


**3-(2,5-dimethoxyphenyl)-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3-S-3s)** The reaction was performed with anthranilic acid (**41**, 1.37 g, 10 mmol), 2-isothiocyanato-1,4-dimethoxybenzene (**3-S-2g**, 2.15 g, 11 mmol), $NEt_3$ (1.53 mL, 11 mmol) and EtOH (30 mL); yield: 2.91 g, 93%; white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 13.03 (s, 1H), 7.95 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.79 (ddd, *J* = 8.5, 7.3, 1.5 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.39 – 7.29 (m, 1H), 7.07 (d, *J* = 9.0 Hz, 1H), 6.97 (dd, *J* = 9.0, 3.1 Hz, 1H), 6.89 (d, *J* = 3.1 Hz, 1H), 3.72 (s, 3H), 3.66 (s, 3H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 175.8, 159.1, 153.2, 148.6, 139.6, 135.7, 128.1, 127.4, 124.4, 116.1, 115.7, 115.7, 114.3, 113.0, 56.1, 55.5. HRMS (ESI) m/z for $C_{16}H_{15}N_2O_3S^+$ $(M+H)^+$, 315.0798 (Calc.), found 315.0805.



**3-methyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3-S-3t)** The reaction was performed with anthranilic acid (**41**, 1.37 g, 10 mmol), methyl isothiocyanate (**3-S-2i**, 0.684 mL, 10 mmol), $NEt_3$ (1.53 mL, 11 mmol) and EtOH (30 mL); yield: 1.62 g, 84%; white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.93 (s, 1H), 7.94 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.72 (ddd, *J* = 8.5, 7.2, 1.5 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.35 – 7.28 (m, 1H), 3.65 (s, 3H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ

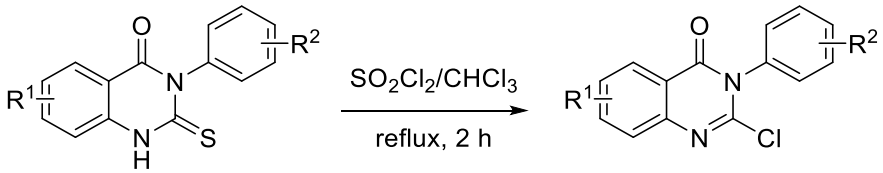
175.3, 159.6, 139.0, 135.3, 127.2, 124.3, 115.5, 115.2, 33.3. HRMS (ESI) m/z for $C_9H_9N_2OS^+$ $(M+H)^+$, 193.0430 (Calc.), found 193.0436.



**3-benzyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3-S-3u** or **49)** The reaction was performed with anthranilic acid (**3-S-1a** (i.e. **48**), 1.37 g, 10 mmol), benzyl isothiocyanate (**3-S-2h**, 1.33 mL, 10 mmol), $NEt_3$ (1.53 mL, 11 mmol) and EtOH (30 mL); yield: 2.58 g, 96%; white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 13.06 (s, 1H), 7.95 (d, $J$ = 7.9 Hz, 1H), 7.75 (t, $J$ = 7.8 Hz, 1H), 7.42 (d, $J$ = 8.1 Hz, 1H), 7.38 – 7.26 (m, 5H), 7.26 – 7.18 (m, 1H), 5.67 (s, 2H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 175.5, 159.4, 139.1, 136.6, 135.6, 128.2, 127.3, 127.1, 126.9, 124.6, 115.7, 115.4, 48.7. Data is consistent with reference[1].

## *3.8.3. Synthesis of 2-chloro-3-substitutedquinazolin-4(3H)-one*

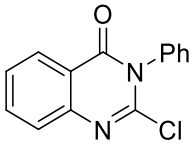
### 3.8.3.1. Method 1:



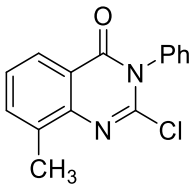

**S-3a-l, S-3n-u** **31a-l, 31n-u**

**General procedure:** To a suspension of 3-substituted-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (**3-S-3**, 5 mmol, 1 equiv.) in $CHCl_3$ (25 mL) was added $SO_2Cl_2$ (5 mmol, 1 equiv). The reaction

mixture was stirred under reflux condition for 2 hours. After the completion of the reaction, the mixture was cooled to room temperature and diluted with $CH_2Cl_2$ (30 mL). The organic mixture was washed with brine, dried with $MgSO_4$ and purified by flash column.

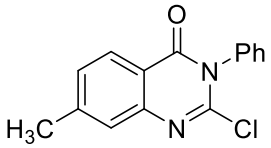



**2-chloro-3-phenylquinazolin-4(3*H*)-one (3-38a)** The reaction was performed with **3-S-3a** (5.08 g, 20 mmol), $SO_2Cl_2$ (1.62 mL, 20 mmol) and $CHCl_3$ (100 mL). Eluent: 70% $CH_2Cl_2$/Hexane; yield: 4.5 g, 87%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.0 Hz, 1H), 7.81 (t, *J* = 7.7 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.64 – 7.47 (m, 4H), 7.39 – 7.27 (m, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 162.2, 146.9, 144.3, 137.4, 135.4, 129.9, 129.8, 128.5, 127.8, 127.7, 127.1, 120.8. HRMS (ESI) m/z for $C_{14}H_{10}ClN_2O^+$ $(M+H)^+$, 257.0476 (Calc.), found 257.0469.

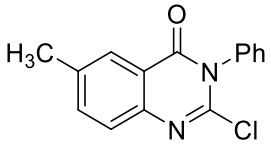



**2-chloro-8-methyl-3-phenylquinazolin-4(3*H*)-one (3-38b)** The reaction was performed with **3-S-3b** (536 mg, 2 mmol), $SO_2Cl_2$ (0.162 mL, 2 mmol) and $CHCl_3$ (10 mL), the reaction mixture was refluxed for 18 h; Eluent: 3% Ethyl acetate/Hexane; yield: 230 mg, 43%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.11 (ddd, *J* = 8.0, 1.5, 0.7 Hz, 1H), 7.65 (ddd, *J* = 7.3, 1.7, 0.9 Hz, 1H), 7.59 – 7.49 (m, 3H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.33 – 7.27 (m, 2H), 2.63 (s, 3H). $^{13}$C NMR (101 MHz,

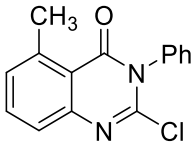
$CDCl_3$) δ 162.7, 145.6, 143.0, 137.6, 136.0, 135.8, 129.8, 129.7, 128.5, 127.4, 125.4, 120.8, 17.4. HRMS (ESI) m/z for $C_{15}H_{12}ClN_2O^+$ $(M+H)^+$, 271.0633 (Calc.), found 271.0643.



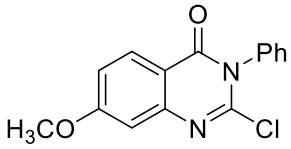

**2-chloro-7-methyl-3-phenylquinazolin-4(3*H*)-one (3-38c)** The reaction was performed with **3-S-3c** (1.34 g, 5 mmol), $SO_2Cl_2$ (0.405 mL, 5 mmol) and $CHCl_3$ (25 mL), the reaction mixture was refluxed for 18 h; Eluent: 3% Ethyl acetate/Hexane; yield: 450 mg, 33%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.59 – 7.51 (m, 3H), 7.49 (s, 1H), 7.38 – 7.32 (m, 1H), 7.32 – 7.25 (m, 2H), 2.53 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 162.1, 147.0, 146.7, 144.3, 137.5, 129.8, 129.7, 129.3, 128.5, 127.5, 126.9, 118.3, 22.1. HRMS (ESI) m/z for $C_{15}H_{12}ClN_2O^+$ $(M+H)^+$, 271.0633 (Calc.), found 271.0639.



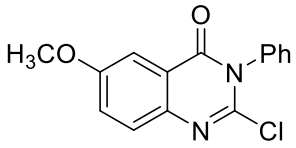

**2-chloro-6-methyl-3-phenylquinazolin-4(3*H*)-one (3-38d)** The reaction was performed with **3-S-3d** (1.34 g, 5 mmol), $SO_2Cl_2$ (0.405 mL, 5 mmol) and $CHCl_3$ (25 mL). Eluent: 3% Ethyl acetate/Hexane; yield: 890 mg, 66%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.66 – 7.49 (m, 5H), 7.37 – 7.27 (m, 2H), 2.49 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 162.2, 144.8, 143.4, 138.2, 137.5, 136.8, 129.8, 129.7, 128.5, 127.1, 126.9, 120.5, 21.5. HRMS (ESI) m/z for $C_{15}H_{12}ClN_2O^+$ $(M+H)^+$, 271.0633 (Calc.), found 271.0640.



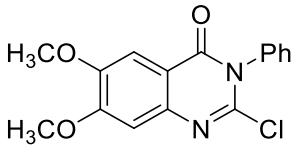

**2-chloro-5-methyl-3-phenylquinazolin-4(3*H*)-one (3-38e)** The reaction was performed with **3-S-3e** (1.34 g, 5 mmol), $SO_2Cl_2$ (0.405 mL, 5 mmol) and $CHCl_3$ (25 mL). Eluent: 3% Ethyl acetate/Hexane; yield: 882 mg, 65%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.63 (t, *J* = 7.8 Hz, 1H), 7.60 – 7.47 (m, 4H), 7.35 – 7.24 (m, 3H), 2.81 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 162.7, 148.3, 143.9, 142.3, 137.6, 134.4, 130.5, 129.9, 129.7, 128.5, 125.3, 119.1, 22.9. HRMS (ESI) m/z for $C_{15}H_{12}ClN_2O^+$ $(M+H)^+$, 271.0633 (Calc.), found 271.0641.



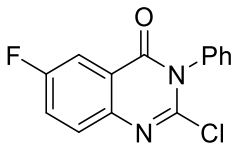

**2-chloro-7-methoxy-3-phenylquinazolin-4(3*H*)-one (3-38f)** The reaction was performed with **3-S-3f** (852 mg, 3 mmol), $SO_2Cl_2$ (0.243 mL, 3 mmol) and $CHCl_3$ (15 mL). Eluent: 50% -70% $CH_2Cl_2$/Hexane; yield: 570 mg, 66%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 9.5 Hz, 1H), 7.59 – 7.50 (m, 3H), 7.34 – 7.27 (m, 2H), 7.13 – 7.04 (m, 2H), 3.93 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.4, 161.7, 149.0, 145.0, 137.5, 129.8, 129.7, 129.2, 128.5, 117.5, 114.0, 108.2, 55.9. HRMS (ESI) m/z for $C_{15}H_{12}ClN_2O_2^+$ $(M+H)^+$, 287.0582 (Calc.), found 287.0589.



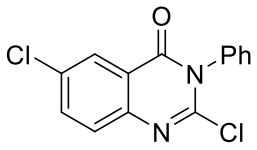
**2-chloro-6-methoxy-3-phenylquinazolin-4(3*H*)-one (3-38g)** The reaction was performed with **3-S-3g** (852 mg, 3 mmol), $SO_2Cl_2$ (0.243 mL, 3 mmol) and $CHCl_3$ (15 mL). Eluent: 50% -70% $CH_2Cl_2$/Hexane; yield: 570 mg, 66%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.49 (m, 5H), 7.38 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.35 – 7.26 (m, 2H), 3.91 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 162.1, 159.1, 141.9, 141.4, 137.6, 129.8, 129.7, 128.6, 128.5, 125.3, 121.7, 107.3, 56.0. HRMS (ESI) m/z for $C_{15}H_{12}ClN_2O_2^+$ $(M+H)^+$, 287.0582 (Calc.), found 287.0588.



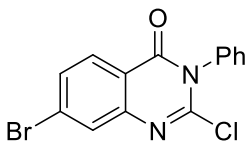
**2-chloro-6,7-dimethoxy-3-phenylquinazolin-4(3*H*)-one (3-38h)** The reaction was performed with **3-S-3h** (942 mg, 3 mmol), $SO_2Cl_2$ (0.243 mL, 3 mmol) and $CHCl_3$ (15 mL). Eluent: 100% $CH_2Cl_2$; yield: 590 mg, 62%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.48 (m, 4H), 7.38 – 7.28 (m, 2H), 7.09 (s, 1H), 4.01 (s, 3H), 3.98 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 161.6, 155.6, 149.6, 143.1, 142.8, 137.6, 129.8, 129.7, 128.5, 114.0, 107.6, 106.4, 56.5, 56.5. HRMS (ESI) m/z for $C_{16}H_{14}ClN_2O_3^+$ $(M+H)^+$, 317.0687 (Calc.), found 317.0696.



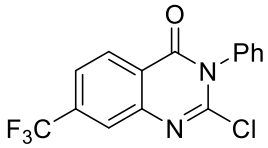
**2-chloro-6-fluoro-3-phenylquinazolin-4(3*H*)-one (3-38i)** The reaction was performed with **3-S-3i** (1.36 g, 5 mmol), $SO_2Cl_2$ (0.405 mL, 5 mmol) and $CHCl_3$ (25 mL). Eluent: 3% - 10% Ethyl acetate/Hexane; yield: 1120 mg, 82%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 8.2, 3.0 Hz, 1H), 7.71 (dd, *J* = 8.9, 4.8 Hz, 1H), 7.65 – 7.45 (m, 4H), 7.41 – 7.26 (m, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 161.4 (d, *J* = 3.4 Hz), 161.4 (d, *J* = 250.1 Hz), 143.8 (d, *J* = 2.5 Hz), 143.4 (d, *J* = 2.2 Hz), 137.2, 129.9, 129.9, 129.5 (d, *J* = 8.1 Hz), 128.3, 123.8 (d, *J* = 24.2 Hz), 122.2 (d, *J* = 8.8 Hz), 112.7 (d, *J* = 24.1 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$) δ -111.0. HRMS (ESI) m/z for $C_{14}H_9ClFN_2O^+$ $(M+H)^+$, 275.0382 (Calc.), found 275.0390.



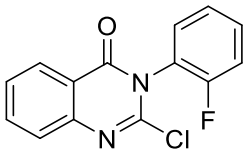

**2,6-dichloro-3-phenylquinazolin-4(3*H*)-one (3-38j)** The reaction was performed with **3-S-3j** (1.44 g, 5 mmol), $SO_2Cl_2$ (0.405 mL, 5 mmol) and $CHCl_3$ (25 mL). Eluent: 5% - 10% Ethyl acetate/Hexane; yield: 892 mg, 61%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 2.4 Hz, 1H), 7.74 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.65 (d, *J* = 8.7 Hz, 1H), 7.60 – 7.51 (m, 3H), 7.35 – 7.26 (m, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 161.1, 145.3, 144.7, 137.1, 135.8, 133.7, 130.0, 130.0, 128.7, 128.3, 127.0, 121.9. HRMS (ESI) m/z for $C_{14}H_9Cl_2N_2O^+$ $(M+H)^+$, 291.0086 (Calc.), found 291.0094.



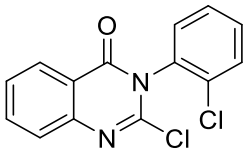
**7-bromo-2-chloro-3-phenylquinazolin-4(3*H*)-one (3-38k)** The reaction was performed with **3-S-3k** (999 mg, 3 mmol), $SO_2Cl_2$ (0.243 mL, 3 mmol) and $CHCl_3$ (15 mL). Eluent: 40% $CH_2Cl_2$/Hexane; yield: 316 mg, 31%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 1.9 Hz, 1H), 7.63 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.60 – 7.50 (m, 3H), 7.34 – 7.26 (m, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 161.6, 147.7, 145.7, 137.1, 131.2, 130.2, 130.0, 129.9, 129.9, 129.1, 128.3, 119.6. HRMS (ESI) m/z for $C_{14}H_9BrClN_2O^+$ $(M+H)^+$, 336.9560 (Calc.), found 336.9565.



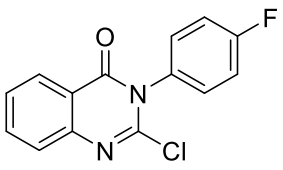

**2-chloro-3-phenyl-7-(trifluoromethyl)quinazolin-4(3*H*)-one (3-38l)** The reaction was performed with **3-S-3l** (1288 mg, 4 mmol), $SO_2Cl_2$ (0.324 mL, 4 mmol) and $CHCl_3$ (20 mL). Eluent: 50% $CH_2Cl_2$/Hexane; yield: 988 mg, 76%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.37 (dd, *J* = 8.4, 3.1 Hz, 1H), 7.98 (d, *J* = 3.3 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.64 – 7.49 (m, 3H), 7.34 – 7.24 (m, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 161.3, 146.8, 146.1, 137.0, 136.9 (q, *J* = 33.2 Hz), 130.1, 130.0, 128.9, 128.3, 124.6 (q, *J* = 4.1 Hz), 123.9 (q, *J* = 3.0 Hz), 123.2, 122.8 (q, *J* = 272.1 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$) δ -63.35. HRMS (ESI) m/z for $C_{15}H_9ClF_3N_2O^+$ $(M+H)^+$, 325.0350 (Calc.), found 325.0360.



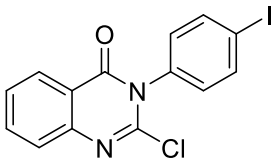
**2-chloro-3-(2-fluorophenyl)quinazolin-4(3*H*)-one (3-38n)** The reaction was performed with **3-S-3n** (817 mg, 3 mmol), $SO_2Cl_2$ (0.243 mL, 3 mmol) and $CHCl_3$ (15 mL). Eluent: 50% $CH_2Cl_2$/Hexane; yield: 670 mg, 81%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.82 (ddd, *J* = 8.6, 7.3, 1.7 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.62 – 7.50 (m, 2H), 7.42 – 7.28 (m, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 161.5, 157.9 (d, *J* = 252.1 Hz), 146.8, 143.9, 135.6, 132.0 (d, *J* = 7.8 Hz), 130.3, 128.0, 127.8, 127.2, 125.1 (d, *J* = 4.0 Hz), 125.0 (d, *J* = 13.8 Hz), 120.5, 117.0 (d, *J* = 19.5 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$) δ -120.67. HRMS (ESI) m/z for $C_{14}H_9ClFN_2O^+$ $(M+H)^+$, 275.0382 (Calc.), found 275.0391.



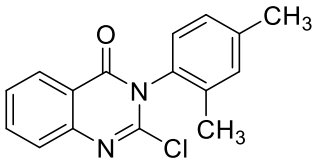

**2-chloro-3-(2-chlorophenyl)quinazolin-4(3*H*)-one (3-38o)** The reaction was performed with **3-S-3o** (873 mg, 3 mmol), $SO_2Cl_2$ (0.243 mL, 3 mmol) and $CHCl_3$ (15 mL). Eluent: 50% $CH_2Cl_2$/Hexane; yield: 675 mg, 77%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.0 Hz, 1H), 7.83 (t, *J* = 7.7 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.67 – 7.58 (m, 1H), 7.58 – 7.43 (m, 3H), 7.43 – 7.33 (m, 1H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 161.4, 146.9, 143.7, 135.6, 135.1, 133.0, 131.3, 130.7, 130.3, 128.3, 127.9, 127.8, 127.2, 120.6. HRMS (ESI) m/z for $C_{14}H_9Cl_2N_2O^+$ $(M+H)^+$, 291.0086 (Calc.), found 291.0094.



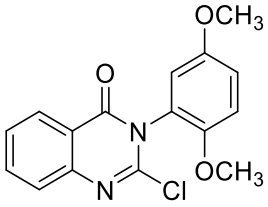
**2-chloro-3-(4-fluorophenyl)quinazolin-4(3*H*)-one (3-38p)** The reaction was performed with **3-S-3p** (817 mg, 3 mmol), $SO_2Cl_2$ (0.243 mL, 3 mmol) and $CHCl_3$ (15 mL). Eluent: 50% $CH_2Cl_2$/Hexane; yield: 640 mg, 78%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.25 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.86 – 7.76 (m, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.35 – 7.17 (m, 4H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 163.1 (d, *J* = 250.2 Hz), 162.2, 146.7, 144.1, 135.5, 133.2 (d, *J* = 3.5 Hz), 130.4 (d, *J* = 9.0 Hz), 128.0, 127.7, 127.1, 120.6, 117.0 (d, *J* = 23.3 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$) δ -110.84. HRMS (ESI) m/z for $C_{14}H_9ClFN_2O^+$ $(M+H)^+$, 275.0382 (Calc.), found 275.0389.



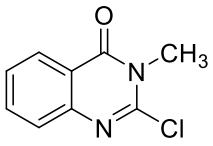

**2-chloro-3-(4-iodophenyl)quinazolin-4(3*H*)-one (3-38q)** The reaction was performed with **3-S-3q** (1900 mg, 5 mmol), $SO_2Cl_2$ (0.405 mL, 5 mmol) and $CHCl_3$ (25 mL). Eluent: 55% $CH_2Cl_2$/Hexane; yield: 1.63 g, 85%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.0 Hz, 1H), 7.98 – 7.85 (m, 2H), 7.81 (t, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.12 – 7.01 (m, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 161.9, 146.7, 143.6, 139.1, 137.0, 135.6, 130.3, 128.0, 127.7, 127.2, 120.6, 95.8. HRMS (ESI) m/z for $C_{14}H_9ClIN_2O^+$ $(M+H)^+$, 382.9443 (Calc.), found 382.9457.



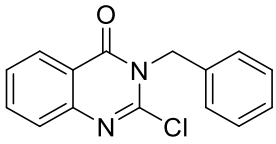
**2-chloro-3-(2,4-dimethylphenyl)quinazolin-4(3*H*)-one (3-38r)** The reaction was performed with **3-S-3r** (846 mg, 3 mmol), $SO_2Cl_2$ (0.243 mL, 3 mmol) and $CHCl_3$ (15 mL). Eluent: 80% $CH_2Cl_2$/Hexane; yield: 205 mg, 24%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.0 Hz, 1H), 7.81 (t, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.23 – 7.13 (m, 2H), 7.06 (d, *J* = 7.9 Hz, 1H), 2.41 (s, 3H), 2.13 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 161.8, 147.0, 144.9, 140.2, 135.4, 135.3, 134.1, 132.2, 128.2, 128.0, 127.8, 127.7, 127.1, 120.8, 21.4, 17.5. HRMS (ESI) m/z for $C_{16}H_{14}ClN_2O^+$ $(M+H)^+$, 285.0789 (Calc.), found 285.0799.




**2-chloro-3-(2,5-dimethoxyphenyl)quinazolin-4(3*H*)-one (3-38s)** The reaction was performed with **3-S-3s** (942 mg, 3 mmol), $SO_2Cl_2$ (0.243 mL, 3 mmol) and $CHCl_3$ (15 mL). Eluent: 80% $CH_2Cl_2$/Hexane; yield: 666 mg, 70%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.80 (ddd, *J* = 8.6, 7.1, 1.6 Hz, 1H), 7.70 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.51 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.04 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.00 (d, *J* = 9.0 Hz, 1H), 6.83 (d, *J* = 2.7 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 161.8, 153.9, 149.1, 147.0, 145.1, 135.2, 127.8, 127.6, 127.0, 126.4, 120.8, 116.5, 115.2, 113.1, 56.4, 56.0. HRMS (ESI) m/z for $C_{16}H_{14}ClN_2O_3^+$ $(M+H)^+$, 317.0687 (Calc.), found 317.0699.

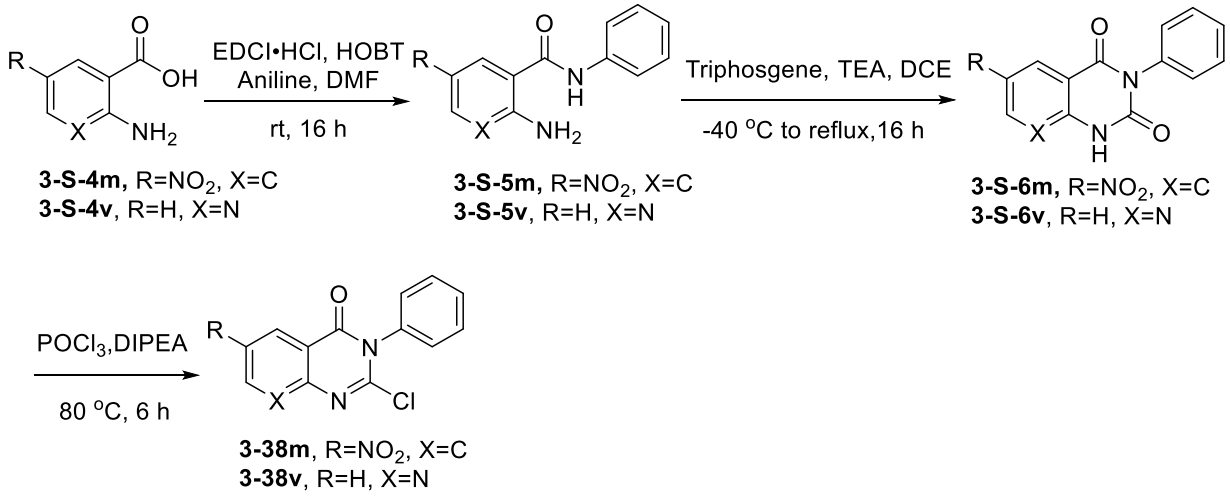


**2-chloro-3-(4-iodophenyl)quinazolin-4(3*H*)-one (3-38t)** The reaction was performed with **3-S-3u** (960 mg, 5 mmol), $SO_2Cl_2$ (0.405 mL, 5 mmol) and $CHCl_3$ (25 mL). Eluent: 10% Ethyl acetate/Hexane; yield: 671 mg, 69%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.68 – 7.58 (m, 1H), 7.55 – 7.44 (m, 1H), 3.76 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 162.2, 146.6, 145.2, 135.0, 127.6, 127.4, 126.8, 120.2, 33.5. HRMS (ESI) m/z for $C_9H_8ClN_2O^+$ $(M+H)^+$, 195.0320 (Calc.), found 195.0326.

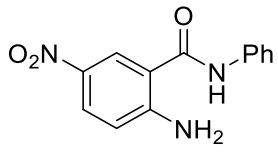



**3-benzyl-2-chloroquinazolin-4(3*H*)-one (3-38u)** The reaction was performed with **49** (1340 mg, 5 mmol), $SO_2Cl_2$ (0.405 mL, 5 mmol) and $CHCl_3$ (25 mL). Eluent: 5%-10% Ethyl acetate/Hexane; yield: 1.22 g, 90%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.77 (td, *J* = 7.7, 7.1, 1.5 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.56 – 7.47 (m, 1H), 7.43 – 7.26 (m, 5H), 5.52 (s, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 162.3, 146.7, 144.9, 135.5, 135.2, 128.9, 128.1, 127.8, 127.7, 127.7, 127.0, 120.5, 49.7. HRMS (ESI) m/z for $C_{15}H_{12}ClN_2O^+$ $(M+H)^+$, 271.0633 (Calc.), found 271.0636.

**3.8.3.2. Method 2:**

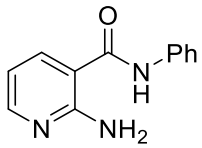



**Step 1 Procedure:** To a suspension of **3-S-4m** or **3-S-4v** (11.00 mmol, 1 equiv.) in anhydrous DMF (50 mL) was added EDCI·HCl (13.20 mmol, 1.2 equiv.) and HOBT (12.10 mmol, W% = 84%, 1.1 equiv.). The reaction mixture was stirred at room temperature for 0.5 hour. Then, aniline (11.00 mmol, 1 equiv.) was added into the reaction mixture, and stirred at room temperature for another 16 hours. After the completion of the reaction, the mixture was quenched by water (100 mL). The aqueous layer was extracted with EtOAc (80 mL × 3). The combined organic layers were washed with saturated aqueous $Na_2CO_3$, water and brine in turn, dried with $MgSO_4$, and concentrated to obtain the product.



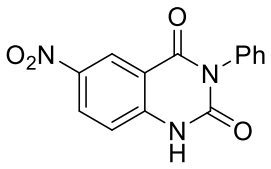
**2-amino-5-nitro-*N*-phenylbenzamide (3-S-5m)** The reaction was performed with **3-S-4m** (2.00 g, 11.00 mmol), EDCI·HCl (2.53 g, 13.20 mmol), HOBT (1.63 g, 12.10 mmol) and DMF (50 mL). Yield: 2.30 g, 81%; yellow solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.49 (s, 1H), 8.67 (d, $J$ = 2.5

Hz, 1H), 8.14 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.77 – 7.75 (m, 2H), 7.70 (s, 2H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.20 – 7.16 (m, 1H), 6.93 – 6.91 (m, 1H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 166.5, 155.6, 139.1, 135.4, 129.0, 128.1, 126.9, 124.4, 121.3, 116.4, 114.0. HRMS (ESI) m/z for $C_{13}H_{12}N_3O_3^+$ $(M+H)^+$, 258.0873 (Calc.), found 258.0884.

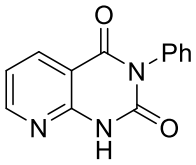



**2-amino-*N*-phenylnicotinamide (3-S-5v)** The reaction was performed with **3-S-4v** (1.00 g, 7.24 mmol), EDCI·HCl (1.66 g, 8.67 mmol), HOBT (1.28 g, 7.97 mmol) and DMF (20 mL). Yield: 1.30 g, 84%; pale yellow solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.13 (s, 1H), 8.16 – 8.08 (m, 1H), 8.08 – 7.96 (m, 1H), 7.72 – 7.63 (m, 2H), 7.38 – 7.27 (m, 2H), 7.15 – 7.04 (m, 1H), 6.94 (s, 2H), 6.68 – 6.59 (m, 1H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 166.6, 158.8, 151.6, 138.9, 137.2, 128.6, 123.7, 120.7, 111.4, 110.2. HRMS (ESI) m/z for $C_{12}H_{12}N_3O^+$ $(M+H)^+$, 214.0975 (Calc.), found 214.0977.

**Step 2 Procedure:** To a suspension of **3-S-5m or 3-S-5v** (8.95 mmol, 1 equiv.) in anhydrous DCE (50 mL) cooled to -40 °C under $N_2$ was added $NEt_3$ (13.42 mmol, 1.5 equiv.) and triphosgene (3.58 mmol, 0.4 equiv.) in several portions. The reaction mixture was stirred at room temperature for 0.5 hour. Then, it was heated to reflux for another 16 hours. After the completion of the reaction, the reaction mixture was concentrated, and purified by flash column.

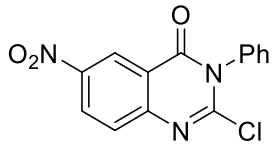


**6-nitro-3-phenylquinazoline-2,4(1*H*,3*H*)-dione (3-S-6m)** The reaction was performed with 3-S-5m (2.30 g, 8.95 mmol), $NEt_3$ (1.86 mL, 13.42 mmol), triphosgene (1.06 g, 3.58 mmol) and anhydrous DCE (50 mL). Eluent: 0-3% MeOH/$CH_2Cl_2$; yield: 2.10 g, 82%; yellow solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.17 (s, 1H), 8.63 (d, $J$ = 2.7 Hz, 1H), 8.51 (dd, $J$ = 9.0, 2.7 Hz, 1H), 7.56 – 7.30 (m, 6H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 161.6, 150.4, 145.1, 142.4, 135.6, 130.3, 129.4, 129.3, 128.9, 124.1, 117.1, 115.1. HRMS (ESI) m/z for $C_{14}H_{10}N_3O_4^+$ $(M+H)^+$, 284.0666 (Calc.), found 284.0678.

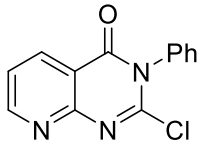


**3-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (3-S-6v)** The reaction was performed with 3-S-5v (500 mg, 2.35 mmol), $NEt_3$ (0.49 mL, 3.52 mmol), triphosgene (418 mg, 1.41 mmol) and anhydrous DCE (10 mL). Eluent: 10-40% ($CH_2Cl_2$:EtOAc=1:10)/hexane; yield: 300 mg, 53%; yellow solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.06 (s, 1H), 8.67 (d, $J$ = 4.8 Hz, 1H), 8.32 (d, $J$ = 7.7 Hz, 1H), 7.54 – 7.41 (m, 3H), 7.37 – 7.28 (m, 3H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 162.4, 155.2, 151.8, 150.9, 137.4, 136.0, 129.5, 129.3, 128.7, 119.5, 110.5. HRMS (ESI) m/z for $C_{13}H_{10}N_3O_2^+$ $(M+H)^+$, 240.0768 (Calc.), found 240.0779.

Step 3 Procedure: To a suspension of 3-S-6m or 3-S-6v (1.77 mmol, 1 equiv.) in $POCl_3$ (10 mL) was added DIPEA (7.07 mmol, 4 equiv.). The reaction mixture was heated to reflux for 6 hours. Then, it was heated to reflux for another 16 hours. After the completion of the reaction, the reaction mixture was concentrated, quenched by ice, and adjusted to pH = 9 - 10 using saturated aqueous $Na_2CO_3$. The aqueous layer was extracted with $CH_2Cl_2$ (50 mL × 3). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated to obtain the product.

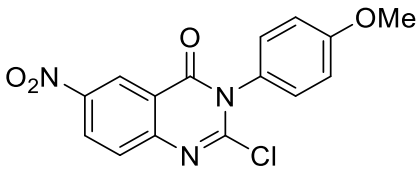



**2-chloro-6-nitro-3-phenylquinazolin-4(3*H*)-one (3-38m)** The reaction was performed with 3-S-6v (500 mg, 1.77 mmol), DIPEA (1.25 mL, 7.07 mmol) and $POCl_3$ (10 mL). Yield: 430 mg, 81%; brown solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.10 (d, *J* = 2.6 Hz, 1H), 8.59 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.84 (d, *J* = 8.9 Hz, 1H), 7.63 – 7.53 (m, 3H), 7.34 – 7.27 (m, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 160.7, 150.5, 148.2, 146.2, 136.5, 130.2, 130.0, 129.4, 128.6, 128.0, 124.1, 121.1. HRMS (ESI) m/z for $C_{14}H_9ClN_3O_3^+$ $(M+H)^+$, 302.0327 (Calc.), found 302.0339.




**2-chloro-3-phenylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one (3-38v)** The reaction was performed with 3-S-6v (500 mg, 1.77 mmol), DIPEA (1.25 mL, 7.07 mmol) and $POCl_3$ (10 mL). Yield: 430 mg, 81%; brown solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.02 (dd, *J* = 4.6, 2.0 Hz, 1H), 8.60 (dd, *J* = 7.9,

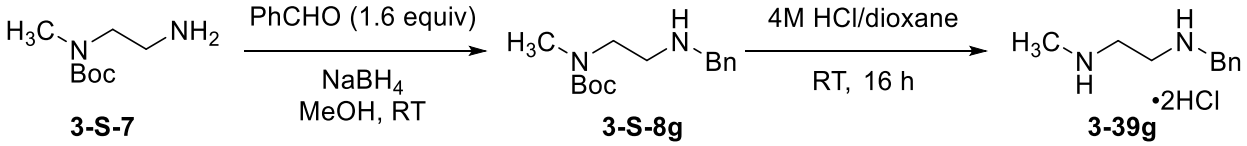
2.0 Hz, 1H), 7.63 – 7.53 (m, 3H), 7.50 (dd, *J* = 7.9, 4.6 Hz, 1H), 7.33 – 7.27 (m, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 162.2, 156.8, 156.7, 148.4, 137.2, 136.8, 130.0, 129.9, 128.1, 123.1, 116.2. HRMS (ESI) m/z for $C_{13}H_9ClN_3O^+$ $(M+H)^+$, 258.0429 (Calc.), found 258.0435.




**2-chloro-3-(4-methoxyphenyl)-6-nitroquinazolin-4(3*H*)-one (3-38w)** The reaction was performed in 1.5 mmol scale in one pot without the isolation of the intermediate. Yield: 198 mg, 40%, white solid. $^1$H NMR (400 MHz, Chloroform-*d*) δ 9.11 (d, *J* = 2.6 Hz, 1H), 8.59 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.83 (d, *J* = 8.9 Hz, 1H), 7.24 – 7.17 (m, 2H), 7.11 – 7.02 (m, 2H), 3.89 (s, 3H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 161.1, 160.8, 150.7, 149.0, 146.3, 129.5, 129.2, 129.2, 128.7, 124.3, 121.2, 115.3, 55.8.

## ***3.8.4. Synthesis of the diamines***

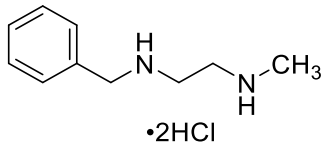
### **3.8.4.1. Method 1:**




**Step 1**: To a round-bottom flask was added *N*-Boc-*N*-methylethylenediamine (**3-S-7**, 0.9 mL, 5 mmol), benzaldehyde (0.813 mL, 8 mmol) and MeOH (10 mL). The mixture was stirred at room temperature for 5 hours. Then, $NaBH_4$ (1140 mg, 30 mmol) tablet was added to the mixture at

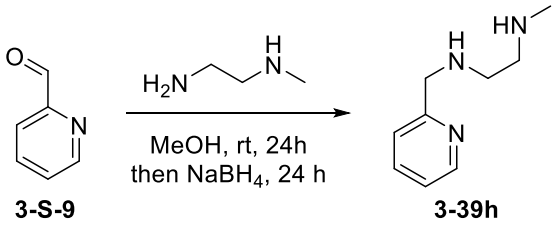
0 °C. The mixture was allowed to warm to room temperature and stirred for 16 hours. After the completion of the reaction, the mixture was quenched with saturated water (10 mL) and ethyl acetate (20 mL), then extracted with 0.5 M HCl (50 mL × 3). The combined aqueous layer was basified with $NH_4OH$ and extracted with $CHCl_3$ (50 mL × 3). The combined organic layer was dried with $MgSO_4$, filtered and concentrated to give the 3-S-8e, which was used in the next step without further purification.

**Step 2**: To a vial was added **3-S-8g** (2 mmol) and 4 M HCl/dioxane (6 mL). The mixture was stirred overnight at room temperature. After the completion of the reaction, the precipitated HCl salts were filtered out, washed with hexane and dried under vacuum to give pure diamine HCl salts.



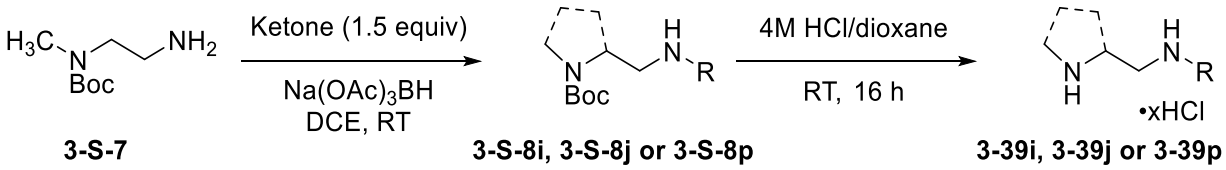

***N*$^1$-benzyl-*N*$^2$-methylethane-1,2-diamine dihydrochloride (3-39g)** Yield: 414 mg, 87%; white solid. $^1$H NMR (400 MHz, Deuterium Oxide) δ 7.61 – 7.47 (m, 5H), 4.36 (d, *J* = 1.6 Hz, 2H), 3.58 – 3.43 (m, 4H), 2.82 (d, *J* = 1.6 Hz, 3H). $^{13}$C NMR (101 MHz, Deuterium Oxide) δ 130.1, 130.0, 129.9, 129.4, 51.7, 44.4, 42.4, 33.3. HRMS (ESI) m/z for $C_{10}H_{17}N_2^+$ $(M+H)^+$, 165.1386 (Calc.), found 165.1388.

**3.8.4.2. Method 2:**




***N*$^1$-methyl-*N*$^2$-(pyridin-2-ylmethyl)ethane-1,2-diamine (3-39h)** To a suspension of **3-S-9** (700 mg, 6.54 mmol) in MeOH (10 mL) was added *N*$^1$-methylethane-1,2-diamine (**3-39m**, 484 mg, 6.54 mmol). The reaction mixture was stirred at room temperature for 24 hours. Then, $NaBH_4$ (370 mg, 9.80 mmol) was added into the reaction mixture, and stirred at room temperature for another 24 hours. After the completion of the reaction, the mixture was concentrated, and diluted with water (20 mL). The aqueous layer was extracted with $CH_2Cl_2$ (20 mL × 6). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated to obtain the product. Yield: 300 mg, 30%; yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.7 Hz, 1H), 7.63 (td, *J* = 7.7, 1.8 Hz, 1H), 7.30 (d, *J* = 7.7 Hz, 1H), 7.17 – 7.13 (m, 1H), 3.92 (s, 2H), 2.82 - 2.79 (m, 2H), 2.74 - 2.72 (m, 2H), 2.44 (s, 3H). Data is consistent with reference[7].

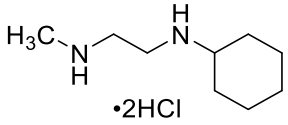
**3.8.4.3. Method 3:**



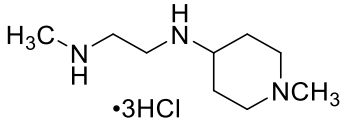

**Step 1**: To a round-bottom flask was added *N*-Boc-*N*-methylethylenediamine (**3-S-7**, 696 mg, 4 mmol), ketone (6 mmol) and DCE (20 mL). Then, $Na(OAc)_3BH$ (1696 mg, 8 mmol) was added to the mixture. The mixture was stirred at room temperature for 16 hours. After the completion of the reaction, the mixture was quenched with saturated $NaHCO_3$ solution (40 mL). The aqueous layer was extracted with $CH_2Cl_2$ (50 mL×2). The combined organic layer was dried with $MgSO_4$,

filtered and concentrated to give the intermediates **3-S-8i** or **3-S-8j**, which were used in the next step without further purification. **3-S-8p** is commercial available.

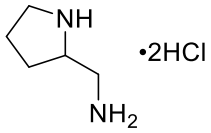
**Step 2**: To a vial was added intermediate **3-S-8i**, **3-S-8j** or **3-S-8p** (1 mmol) and 4 M HCl/dioxane. The mixture was stirred overnight at room temperature. After the completion of the reaction, the precipitated HCl salts were filtered out, washed with Hexane and dried under vacuum to give pure diamine HCl salts.




***N*$^1$-cyclohexyl-*N*$^2$-methylethane-1,2-diamine dihydrochloride (3-39i)** Step 1: The reaction was performed with **3-S-7** (696 mg, 4 mmol), cyclohexanone (0.62 mL, 6 mmol), $Na(OAc)_3BH$ (1696 mg, 8 mmol) and DCE (20 mL); yield: 1.01 g, 99%; colorless oil. Step 2: The reaction was performed with **3-S-8i** (256 mg, 1 mmol) and 3 mL 4 M HCl/dioxane; yield: 225 mg, 98%; white solid. $^1$H NMR (400 MHz, $D_2O$) δ 3.52 – 3.41 (m, 4H), 3.28 – 3.17 (m, 1H), 2.83 (s, 3H), 2.15 – 2.04 (m, 2H), 1.91 – 1.81 (m, 2H), 1.73 – 1.66 (m, 1H), 1.44 – 1.28 (m, 4H), 1.25 – 1.15 (m, 1H). $^{13}$C NMR (101 MHz, $D_2O$) δ 58.1, 44.6, 39.8, 33.3, 28.8, 24.4, 23.9. HRMS (ESI) m/z for $C_9H_{21}N_2^+$ $(M+H)^+$, 157.1699 (Calc.), found 157.1704.

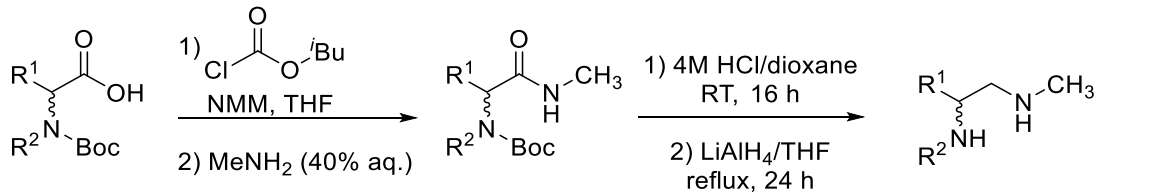


***N*$^1$-methyl-*N*$^2$-(1-methylpiperidin-4-yl)ethane-1,2-diamine trihydrochloride (3-39j)** Step 1: The reaction was performed with **3-S-7** (696 mg, 4 mmol), cyclohexanone (0.74 mL, 6 mmol), $Na(OAc)_3BH$ (1696 mg, 8 mmol) and DCE (20 mL); yield: 594 mg, 55%; colorless oil. Step 2: The reaction was performed with **3-S-8j** (271 mg, 1 mmol) and 3 mL 4 M HCl/dioxane; yield: 271 mg, 96%; white solid. $^1$H NMR (400 MHz, $D_2O$) δ 3.76 – 3.68 (m, 2H), 3.68 – 3.60 (m, 1H), 3.58 – 3.52 (m, 2H), 3.52 – 3.45 (m, 2H), 3.24 – 3.13 (m, 2H), 2.93 (s, 3H), 2.84 (s, 3H), 2.55 – 2.40 (m, 2H), 2.06 – 1.92 (m, 2H). $^{13}$C NMR (101 MHz, $D_2O$) δ 52.5, 52.3, 44.4, 43.1, 40.5, 33.4, 26.0. HRMS (ESI) m/z for $C_9H_{22}N_3^+$ $(M+H)^+$, 172.1808 (Calc.), found 172.1809.



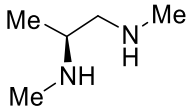

**Pyrrolidin-2-ylmethanamine dihydrochloride (3-39p)** Step 2: The reaction was performed with commercial available *tert*-butyl 2-(aminomethyl)pyrrolidine-1-carboxylate (**3-S-8p**, 0.198 mL, 1 mmol) and 2 mL 4 M HCl/dioxane; yield: 158 mg, 91%; white solid. $^1$H NMR (400 MHz, Deuterium Oxide) δ 4.0 – 3.9 (m, 1H), 3.6 – 3.4 (m, 4H), 2.4 – 2.3 (m, 1H), 2.2 – 2.0 (m, 2H), 1.9 – 1.8 (m, 1H). $^{13}$C NMR (101 MHz, Deuterium Oxide) δ 57.2, 46.1, 39.9, 28.3, 22.9. HRMS (ESI) m/z for $C_5H_{13}N_2^+$ $(M+H)^+$, 101.1073 (Calc.), found 101.1078.

**<u>3.8.4.4. Method 4:</u>**



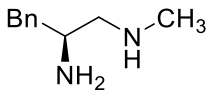
**Step 1**: To a solution of Boc-amino acid **(3-S-10l, 3-S-10q** or **3-S-10r**, 5 mmol) in THF (10 mL) at –20 °C was added *N*-Methyl morpholine (0.55 mL, 5 mmol) and isobutyl chloroformate (0.65 mL, 5 mmol) successively. The mixture was stirred at –20 °C for 5 min, then 40 % aqueous methylamine (2.5 mL, 30 mmol) was added to above solution, and the resulting solution was stirred for 2 h at –20 °C followed by the addition of 5 % NaHCO3 (20 mL). After 30 min at room temperature, the aqueous phase was extracted with $CH_2Cl_2$ (50 mL × 3). The combined organic layer was washed with 5 % $NaHCO_3$ (20 mL × 2), dried with $MgSO_4$, filtered, concentrated and used in the next step without further purification.

**Step 2**: 1) Boc-deprotection: To a vial was added **3-S-11l, 3-S-11q** or **3-S-11r** (4 mmol) and 4 M HCl/dioxane (10 mL). The mixture was stirred overnight at room temperature. After the completion of the reaction, the precipitated HCl salts were filtered out, washed with hexane and dried under vacuum to give pure HCl salts. 2) Reduction: To a solution of above HCl salts in dry THF (15 mL) was added $LiAlH_4$ (608 mg, 16 mmol) portionwise under ice bath. The mixture was refluxed for 24 h. The reaction mixture was cooled to 0 °C and diluted with $Et_2O$ (15 mL) followed by addition of water (1 mL), quenched with 20% NaOH (1 mL) and stirred for 30 min at room temperature. The precipitate was filtered off and washed with ether. The combined organic solution were dried over $MgSO_4$, concentrated. The product was used in the next step directly or purified by distillation.

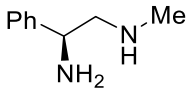



**(*S*)-*N*$^1$,*N*$^2$-dimethylpropane-1,2-diamine ((*S*)-3-39l)** The reaction was performed in 5 mmol scale for step 2. Yield: 272 mg, 53%; colorless oil; bp 58-59 °C (0.3 bar). $^1$H NMR (400 MHz,

$CDCl_3$) δ 2.66 – 2.52 (m, 2H), 2.51 – 2.45 (m, 1H), 2.43 (s, 3H), 2.41 (s, 3H), 1.40 (s, 2H), 1.03 (d, *J* = 6.2 Hz, 3H). $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 58.1, 54.5, 36.8, 34.2, 18.3. Data is consistent with reference[8].

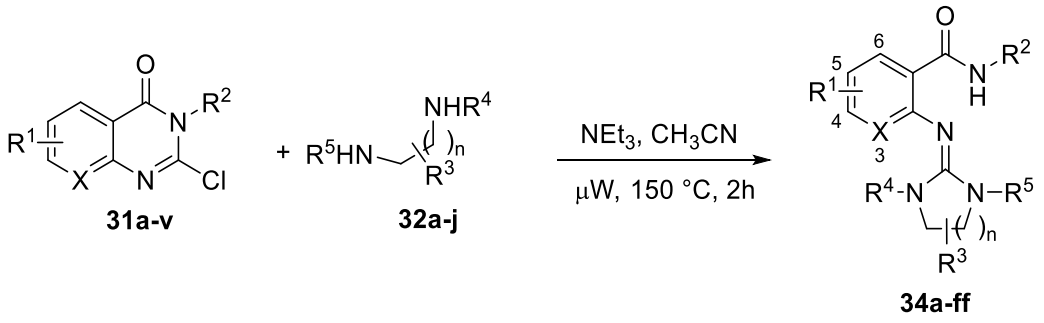



**(*S*)-*N*$^1$-methyl-3-phenylpropane-1,2-diamine ((*S*)-3-39q)** The reaction was performed in 4 mmol scale step 2. Yield: 651 mg, 99%; colorless oil. $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H), 7.25 – 7.16 (m, 3H), 3.18 – 3.05 (m, 1H), 2.83 – 2.76 (m, 1H), 2.66 (dd, *J* = 11.7, 4.0 Hz, 1H), 2.55 – 2.45 (m, 2H), 2.44 (s, 3H), 1.45 (s, 3H). Data is consistent with reference[9].



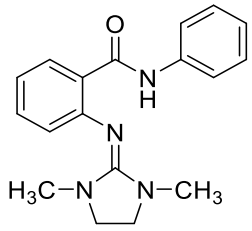

**(*S*)-*N*$^1$-methyl-2-phenylethane-1,2-diamine ((*S*)-3-39r)** The reaction was performed in 5 mmol scale for step 2. Yield: 511 mg, 68%; colorless oil; bp: 135-136 °C (1 mmHg). $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 4H), 7.29 – 7.23 (m, 1H), 4.05 (dd, *J* = 7.8, 5.3 Hz, 1H), 2.81 – 2.69 (m, 2H), 2.44 (s, 3H), 1.55 (s, 3H). Data is consistent with reference[10].

### ***3.8.5. Synthesis of the N-Aryl Cyclic Guanidines***



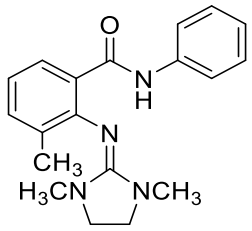

**31a-v** **32a-j** **34a-ff**

**General Procedure**: To a microwave vial was added substituted 2-chloroquinazolin-4(3*H*)-one (**3-38a-v**, 0.2 mmol), *N,N'*-disubstituted diamine (**3-39a-j**, 0.26 mmol), $NEt_3$ (0.6 mmol) and $CH_3CN$ (2 mL). After heating the mixture under microwave irradiation at 150 °C for 2 h, the cooled mixture was diluted with $CH_2Cl_2$ (20 mL) and washed with saturated $NaHCO_3$ solution (15 mL). The aqueous layer was then washed with $CH_2Cl_2$ (20 mL). The combined organic layer was dried with $MgSO_4$, filtered and purified by flash column.

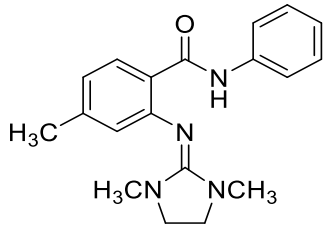


**2-((1,3-dimethylimidazolidin-2-ylidene)amino)-*N*-phenylbenzamide (3-41a)** The reaction was performed with **3-38a** (51 mg, 0.2 mmol), *N*,*N*′-dimethylethylenediamine (**3-39a**, 0.03 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 40% - 60% Ethyl acetate/Hexane; yield: 57 mg and 57 mg, 92% and 92%; white solid, m.p. 165-167 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 12.33 (s, 1H), 8.27 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.78 – 7.67 (m, 2H), 7.33 (t, *J* = 7.9 Hz, 2H), 7.30 – 7.23 (m, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 7.01 – 6.92 (m, 1H), 6.83 (dd, *J* = 8.2, 2.1 Hz, 1H), 3.41 (s, 4H), 2.75 (s, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.4, 157.4, 148.3, 139.6, 131.5, 131.1,

129.0, 124.1, 123.3, 122.9, 120.5, 120.1, 48.5, 35.3. HRMS (ESI) m/z for $C_{18}H_{21}N_4O^+$ $(M+H)^+$, 309.1710 (Calc.), found 309.1713.

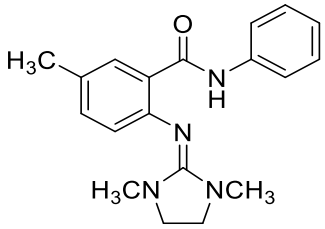


**2-((1,3-dimethylimidazolidin-2-ylidene)amino)-3-methyl-*N*-phenylbenzamide (3-41b)** The reaction was performed with **3-38b** (54 mg, 0.2 mmol), *N*,*N*′-dimethylethylenediamine (**3-39a**, 0.03 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 30% Ethyl acetate/Hexane; yield: 60 mg and 58 mg, 93% and 90%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 11.75 (s, 1H), 8.11 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.74 – 7.68 (m, 2H), 7.37 – 7.31 (m, 2H), 7.25 – 7.20 (m, 1H), 7.07 (tt, *J* = 7.3, 1.2 Hz, 1H), 6.96 (t, *J* = 7.6 Hz, 1H), 3.39 – 3.29 (m, 4H), 2.65 (s, 6H), 2.12 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.7, 154.8, 147.0, 139.5, 133.2, 130.6, 129.0, 129.0, 125.4, 123.3, 121.3, 120.0, 48.4, 34.6, 18.8. HRMS (ESI) m/z for $C_{19}H_{23}N_4O^+$ $(M+H)^+$, 323.1866 (Calc.), found 323.1880.

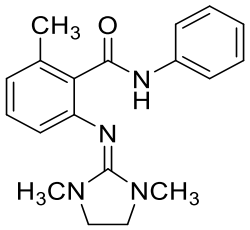


**2-((1,3-dimethylimidazolidin-2-ylidene)amino)-4-methyl-*N*-phenylbenzamide (3-41c)** The reaction was performed with **3-38c** (54 mg, 0.2 mmol), *N*,*N*′-dimethylethylenediamine (**3-39a**,

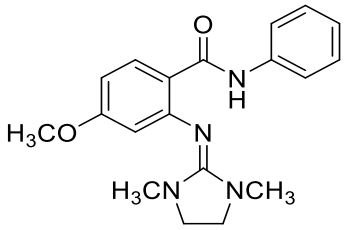
0.03 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 40% Ethyl acetate/Hexane; yield: 58 mg and 55 mg, 90% and 85%; white solid. $^1H$ NMR (400 MHz, $CDCl_3$) δ 12.21 (s, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 7.76 – 7.64 (m, 2H), 7.37 – 7.27 (m, 2H), 7.05 (t, *J* = 7.3 Hz, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 6.68 – 6.59 (m, 1H), 3.41 (s, 4H), 2.81 – 2.70 (m, 6H), 2.31 (s, 3H). $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 165.5, 157.2, 148.2, 141.8, 139.7, 131.1, 129.0, 123.2, 123.1, 121.8, 121.6, 120.0, 48.5, 35.3, 21.5. HRMS (ESI) m/z for $C_{19}H_{23}N_4O^+$ $(M+H)^+$, 323.1866 (Calc.), found 323.1876.




**2-((1,3-dimethylimidazolidin-2-ylidene)amino)-5-methyl-*N*-phenylbenzamide (3-41d)** The reaction was performed with **3-38d** (54 mg, 0.2 mmol), *N*,*N*′-dimethylethylenediamine (**3-39a**, 0.03 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 40% Ethyl acetate/Hexane; yield: 59 mg and 56 mg, 92% and 87%; white solid. $^1H$ NMR (400 MHz, $CDCl_3$) δ 12.31 (s, 1H), 8.07 (s, 1H), 7.78 – 7.66 (m, 2H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.13 – 7.00 (m, 2H), 6.75 (d, *J* = 8.1 Hz, 1H), 3.39 (s, 4H), 2.74 (s, 6H), 2.32 (s, 3H). $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 165.5, 157.2, 145.7, 139.7, 132.4, 131.2, 129.9, 129.0, 123.8, 123.2, 122.9, 120.0, 48.5, 35.3, 20.8. HRMS (ESI) m/z for $C_{19}H_{23}N_4O^+$ $(M+H)^+$, 323.1866 (Calc.), found 323.1878.

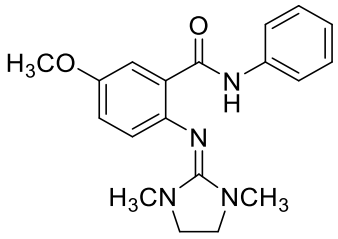


**2-((1,3-dimethylimidazolidin-2-ylidene)amino)-6-methyl-*N*-phenylbenzamide (3-41e)** The reaction was performed with **3-38e** (54 mg, 0.2 mmol), *N*,*N*′-dimethylethylenediamine (**3-39a**, 0.03 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 60% Ethyl acetate/Hexane; yield: 52 mg and 53 mg, 81% and 82%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.70 – 7.57 (m, 2H), 7.37 – 7.28 (m, 2H), 7.14 – 7.04 (m, 2H), 6.78 (d, *J* = 7.4 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 3.22 (s, 4H), 2.63 (s, 6H), 2.52 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 167.5, 155.4, 147.9, 139.3, 139.2, 129.6, 129.0, 127.8, 123.9, 123.5, 121.1, 119.6, 48.4, 35.1, 21.6. HRMS (ESI) m/z for $C_{19}H_{23}N_4O^+$ $(M+H)^+$, 323.1866 (Calc.), found 323.1879.

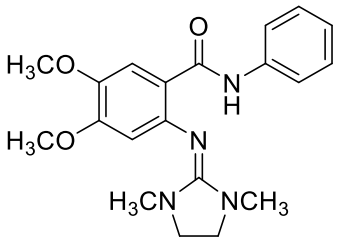


**2-((1,3-dimethylimidazolidin-2-ylidene)amino)-4-methoxy-*N*-phenylbenzamide (3-41f)** The reaction was performed with **3-38f** (57 mg, 0.2 mmol), *N*,*N*′-dimethylethylenediamine (**3-39a**, 0.03 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 40% Ethyl acetate/Hexane; yield: 64 mg and 66 mg, 95% and 97%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 12.10 (s, 1H), 8.22 (d, *J* = 8.8 Hz, 1H), 7.73 – 7.65 (m, 2H), 7.36 – 7.28 (m, 2H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.55 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.33 (d, *J* = 2.0 Hz, 1H), 3.81 (s, 3H), 3.42 (s, 4H), 2.78

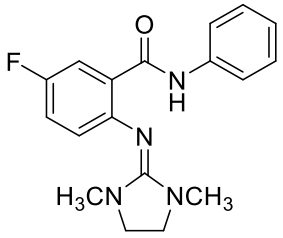
(s, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.3, 162.3, 157.4, 149.9, 139.8, 132.8, 129.0, 123.1, 119.9, 117.8, 107.3, 106.8, 55.4, 48.5, 35.3. HRMS (ESI) m/z for $C_{19}H_{23}N_4O_2^+$ $(M+H)^+$, 339.1816 (Calc.), found 339.1825.



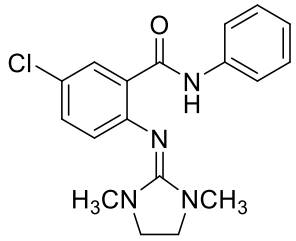
**2-((1,3-dimethylimidazolidin-2-ylidene)amino)-5-methoxy-*N*-phenylbenzamide (3-41g)** The reaction was performed with **3-38g** (57 mg, 0.2 mmol), *N*,*N*′-dimethylethylenediamine (**3-39a**, 0.03 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 40% Ethyl acetate/Hexane; yield: 56 mg and 58 mg, 83% and 86%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 12.39 (s, 1H), 7.83 (d, *J* = 3.1 Hz, 1H), 7.75 – 7.68 (m, 2H), 7.39 – 7.30 (m, 2H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.91 (dd, *J* = 8.7, 3.1 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 3.84 (s, 3H), 3.38 (s, 4H), 2.74 (s, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.1, 157.3, 153.9, 141.9, 139.5, 129.0, 124.5, 124.3, 123.4, 120.0, 119.8, 113.1, 55.7, 48.6, 35.3. HRMS (ESI) m/z for $C_{19}H_{23}N_4O_2^+$ $(M+H)^+$, 339.1816 (Calc.), found 339.1829.



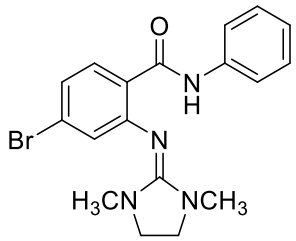
**2-((1,3-dimethylimidazolidin-2-ylidene)amino)-4,5-dimethoxy-*N*-phenylbenzamide (3-41h)** The reaction was performed with **3-38h** (64 mg, 0.2 mmol), *N*,*N*′-dimethylethylenediamine (**3-39a**, 0.03 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 50% Ethyl acetate/Hexane; yield: 56 mg and 60 mg, 76% and 81%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 12.09 (s, 1H), 7.80 (s, 1H), 7.75 – 7.66 (m, 2H), 7.37 – 7.30 (m, 2H), 7.08 – 7.02 (m, 1H), 6.39 (s, 1H), 3.93 (s, 3H), 3.88 (s, 3H), 3.41 (s, 4H), 2.77 (s, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.2, 157.0, 151.7, 143.6, 142.8, 139.7, 129.0, 123.1, 119.9, 116.5, 112.5, 105.9, 56.1, 48.6, 35.3. HRMS (ESI) m/z for $C_{20}H_{25}N_4O_3^+$ $(M+H)^+$, 369.1921 (Calc.), found 369.1932.




**2-((1,3-dimethylimidazolidin-2-ylidene)amino)-5-fluoro-*N*-phenylbenzamide (3-41i)** The reaction was performed with **3-38i** (55 mg, 0.2 mmol), *N*,*N*′-dimethylethylenediamine (**3-39a**, 0.03 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 30% Ethyl acetate/Hexane; yield: 54 mg and 57 mg, 83% and 87%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 12.36 (s, 1H), 7.97 (dd, *J* = 10.2, 3.2 Hz, 1H), 7.74 – 7.65 (m, 2H), 7.38 – 7.29 (m, 2H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.00 (ddd, *J* = 8.7, 7.5, 3.2 Hz, 1H), 6.80 (dd, *J* = 8.8, 5.0 Hz, 1H), 3.42 (s, 4H), 2.75 (s, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 164.2, 157.6, 157.3 (d, *J* = 238.7 Hz), 144.5, 139.3, 129.0, 125.2 (d, *J* = 6.4 Hz), 124.0 (d, *J* = 6.9 Hz), 123.6, 120.1, 118.6 (d, *J* = 22.8 Hz), 116.7 (d, *J* = 23.6 Hz), 48.5, 35.3. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -123.37. HRMS (ESI) m/z for $C_{18}H_{20}FN_4O^+$ $(M+H)^+$, 327.1616 (Calc.), found 327.1629.

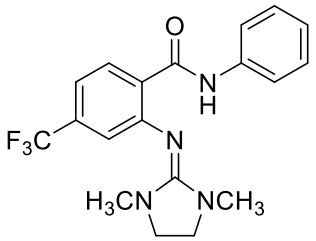


**5-chloro-2-((1,3-dimethylimidazolidin-2-ylidene)amino)-*N*-phenylbenzamide (3-41j)** The reaction was performed with **3-38j** (58 mg, 0.2 mmol), *N*,*N*′-dimethylethylenediamine (**3-39a**, 0.03 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 30% Ethyl acetate/Hexane; yield: 64 mg and 60 mg, 93% and 88%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 12.32 (s, 1H), 8.25 (d, *J* = 2.7 Hz, 1H), 7.74 – 7.64 (m, 2H), 7.39 – 7.30 (m, 2H), 7.21 (dd, *J* = 8.6, 2.7 Hz, 1H), 7.11 – 7.04 (m, 1H), 6.76 (d, *J* = 8.6 Hz, 1H), 3.44 (s, 4H), 2.76 (s, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 164.1, 157.8, 146.9, 139.3, 131.3, 130.7, 129.1, 125.5, 125.2, 124.1, 123.6, 120.1, 48.5, 35.3. HRMS (ESI) m/z for $C_{18}H_{20}ClN_4O^+$ $(M+H)^+$, 343.1320 (Calc.), found 343.1331.

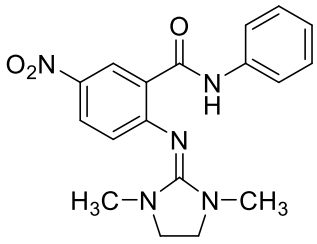


**4-bromo-2-((1,3-dimethylimidazolidin-2-ylidene)amino)-*N*-phenylbenzamide (3-41k)** The reaction was performed with **3-38k** (67 mg, 0.2 mmol), *N*,*N*′-dimethylethylenediamine (**3-39a**, 0.03 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 20% Ethyl acetate/Hexane; yield: 58 mg and 56 mg, 75% and 72%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 12.23 (s, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 7.75 – 7.65 (m, 2H), 7.39 – 7.30 (m, 2H), 7.11 – 7.03 (m,

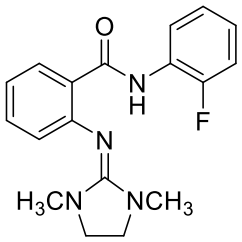
2H), 6.97 (d, *J* = 1.9 Hz, 1H), 3.46 (s, 4H), 2.79 (s, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 164.7, 158.0, 149.4, 139.4, 132.6, 129.0, 125.7, 125.0, 123.5, 123.3, 122.8, 120.1, 48.4, 35.3. HRMS (ESI) m/z for $C_{18}H_{20}BrN_4O^+$ $(M+H)^+$, 387.0815 (Calc.), found 387.0827.



**2-((1,3-dimethylimidazolidin-2-ylidene)amino)-*N*-phenyl-4-(trifluoromethyl)benzamide phenylbenzamide (3-41l)** The reaction was performed with **3-38l** (65 mg, 0.2 mmol), *N*,*N*′-dimethylethylenediamine (**3-39a**, 0.03 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 15% - 20% Ethyl acetate/Hexane; yield: 66 mg and 66 mg, 88% and 88%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 12.42 (s, 1H), 8.38 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.78 – 7.64 (m, 2H), 7.38 – 7.29 (m, 2H), 7.16 (d, *J* = 8.1 Hz, 1H), 7.12 – 7.01 (m, 2H), 3.49 (s, 4H), 2.78 (s, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 164.3, 158.1, 148.6, 139.2, 133.0 (q, *J* = 32.0 Hz), 132.0, 129.1, 126.5, 124.1 (q, *J* = 273.7 Hz), 123.7, 120.2, 119.3 (q, *J* = 3.6 Hz), 116.1 (q, *J* = 3.7 Hz), 48.4, 35.2. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -63.05. HRMS (ESI) m/z for $C_{19}H_{19}F_3N_4O^+$ $(M+H)^+$, 377.1584 (Calc.), found 377.1595.

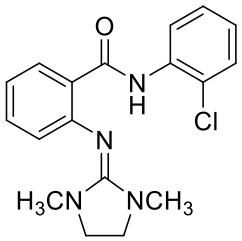


**2-((1,3-dimethylimidazolidin-2-ylidene)amino)-5-nitro-*N*-phenylbenzamide (3-41m)** The reaction was performed with **3-38m** (60 mg, 0.2 mmol), *N*,*N*′-dimethylethylenediamine (**3-39a**, 0.03 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 0% - 15% ($CH_2Cl_2$ : EtOAc = 1 : 1)/Hexane; yield: 56 mg and 60 mg, 79% and 85%; yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 12.24 (s, 1H), 9.21 (d, *J* = 2.9 Hz, 1H), 8.10 (dd, *J* = 9.0, 2.9 Hz, 1H), 7.75 – 7.62 (m, 2H), 7.42 – 7.31 (m, 2H), 7.16 – 7.00 (m, 1H), 6.75 (d, *J* = 9.0 Hz, 1H), 3.60 (s, 4H), 2.85 (s, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 163.2, 159.3, 154.5, 139.8, 138.9, 129.0, 128.2, 126.2, 123.8, 122.8, 121.4, 120.1, 48.1, 34.9. HRMS (ESI) m/z for $C_{18}H_{20}N_5O_3^+$ $(M+H)^+$, 354.1561 (Calc.), found 354.1560.

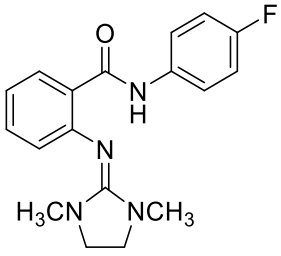



**2-((1,3-dimethylimidazolidin-2-ylidene)amino)-*N*-(2-fluorophenyl)benzamide (3-41n)** The reaction was performed with **3-38n** (55 mg, 0.2 mmol), *N*,*N*′-dimethylethylenediamine (**3-39a**, 0.03 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 15% Ethyl acetate/Hexane; yield: 58 mg and 55 mg, 89% and 84%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 12.49 (s, 1H), 8.70 (t, *J* = 8.2 Hz, 1H), 8.27 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.33 – 7.26 (m, 1H), 7.14 (t, *J* = 7.8 Hz, 1H), 7.11 – 7.03 (m, 1H), 7.03 – 6.91 (m, 2H), 6.83 (d, *J* = 8.1 Hz, 1H), 3.42 (s, 4H), 2.74 (s, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.8, 158.1, 152.9 (d, *J* = 243.7 Hz), 149.0, 131.8, 131.2, 128.2 (d, *J* = 10.5 Hz), 124.5 (d, *J* = 3.3 Hz), 123.6, 123.1 (d, *J* = 7.5 Hz), 122.8, 122.2 (d,

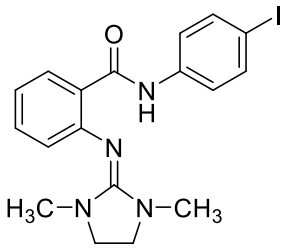
*J* = 2.1 Hz), 120.1, 114.6 (d, *J* = 19.3 Hz), 48.5, 35.2, 35.1. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -128.53. HRMS (ESI) m/z for $C_{18}H_{20}FN_4O^+$ $(M+H)^+$, 327.1616 (Calc.), found 327.1622.



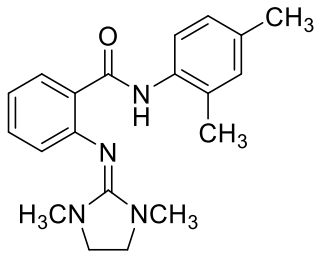

**2-((1,3-dimethylimidazolidin-2-ylidene)amino)-*N*-(2-chlorophenyl)benzamide (3-41o)** The reaction was performed with **3-38o** (58 mg, 0.2 mmol), *N*,*N*′-dimethylethylenediamine (**3-39a**, 0.03 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 15% Ethyl acetate/Hexane; yield: 65 mg and 60 mg, 95% and 89%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 12.19 (s, 1H), 8.58 (dd, *J* = 8.3, 1.5 Hz, 1H), 8.30 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.36 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.31 – 7.25 (m, 2H), 7.00 (td, *J* = 7.8, 1.5 Hz, 1H), 6.94 (td, *J* = 7.6, 1.2 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 3.42 (s, 4H), 2.73 (s, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.8, 158.8, 149.5, 136.9, 132.0, 131.4, 129.1, 127.4, 124.0, 123.9, 123.6, 123.4, 122.8, 120.1, 48.5, 35.3. HRMS (ESI) m/z for $C_{18}H_{20}ClN_4O^+$ $(M+H)^+$, 343.1320 (Calc.), found 343.1325.



**2-((1,3-dimethylimidazolidin-2-ylidene)amino)-*N*-(4-fluorophenyl)benzamide (3-41p)** The reaction was performed with **3-38p** (55 mg, 0.2 mmol), *N*,*N*′-dimethylethylenediamine (**3-39a**, 0.03 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 30% Ethyl acetate/Hexane; yield: 62 mg and 62 mg, 95% and 95%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 12.36 (s, 1H), 8.26 (d, *J* = 8.1 Hz, 1H), 7.74 – 7.60 (m, 2H), 7.32 – 7.26 (m, 1H), 7.07 – 6.91 (m, 3H), 6.83 (d, *J* = 8.1 Hz, 1H), 3.43 (s, 4H), 2.75 (s, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.4, 158.8 (d, *J* = 241.8 Hz), 157.5, 148.3, 135.7 (d, *J* = 2.7 Hz), 131.6, 131.1, 123.8, 122.8, 121.4 (d, *J* = 7.6 Hz), 120.5, 115.5 (d, *J* = 22.2 Hz), 48.5, 35.3. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -119.78. HRMS (ESI) m/z for $C_{18}H_{20}FN_4O^+$ $(M+H)^+$, 327.1616 (Calc.), found 327.1624.

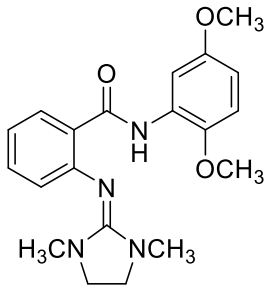



**2-((1,3-dimethylimidazolidin-2-ylidene)amino)-*N*-(4-iodophenyl)benzamide (3-41q)** The reaction was performed with **3-38q** (77 mg, 0.2 mmol), *N*,*N*′-dimethylethylenediamine (**3-39a**, 0.03 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 25% Ethyl acetate/Hexane; yield: 77 mg and 73 mg, 89% and 84%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 12.44 (s, 1H), 8.24 (d, *J* = 8.0 Hz, 1H), 7.67 – 7.58 (m, 2H), 7.55 – 7.46 (m, 2H), 7.32 – 7.26 (m, 1H), 6.96 (t, *J* = 7.7 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 3.44 (s, 4H), 2.75 (s, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.6, 157.6, 148.3, 139.4, 137.9, 131.7, 131.1, 123.8, 122.9, 122.0, 120.6, 86.0, 48.5, 35.3. HRMS (ESI) m/z for $C_{18}H_{20}IN_4O^+$ $(M+H)^+$, 435.0676 (Calc.), found 435.0694.



**2-((1,3-dimethylimidazolidin-2-ylidene)amino)-*N*-(2,4-dimethylphenyl)benzamide (3-41r)**

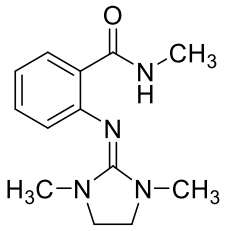
The reaction was performed with **3-38r** (57 mg, 0.2 mmol), *N*,*N*′-dimethylethylenediamine (**3-39a**, 0.03 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 30% Ethyl acetate/Hexane; yield: 63 mg and 64%, 94% and 95%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 11.45 (s, 1H), 8.38 – 8.26 (m, 1H), 8.05 (d, *J* = 8.1 Hz, 1H), 7.31 – 7.25 (m, 1H), 7.07 – 6.93 (m, 3H), 6.80 (d, *J* = 8.0 Hz, 1H), 3.39 (s, 4H), 2.69 (s, 6H), 2.30 (s, 3H), 2.28 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.4, 158.5, 149.0, 135.0, 133.5, 131.5, 131.4, 130.8, 128.8, 127.1, 124.1, 123.4, 122.9, 120.4, 48.5, 35.4, 21.0, 18.7. HRMS (ESI) m/z for $C_{20}H_{25}N_4O^+$ $(M+H)^+$, 337.2023 (Calc.), found 337.2032.



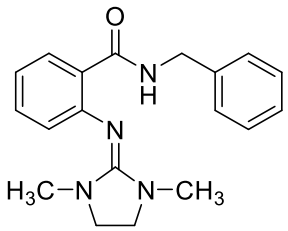
***N*-(2,5-dimethoxyphenyl)-2-((1,3-dimethylimidazolidin-2-ylidene)amino)benzamide (3-41s)**

The reaction was performed with **3-38s** (64 mg, 0.2 mmol), *N*,*N*′-dimethylethylenediamine (**3-39a**, 0.03 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 30% - 40% Ethyl acetate/Hexane; yield: 71 mg and 69 mg, 96% and 94%; white solid. $^1$H NMR (400 MHz, $CDCl_3$)

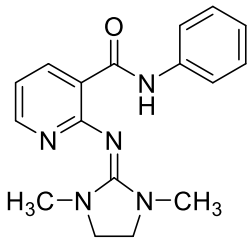
δ 11.97 (s, 1H), 8.43 (d, *J* = 3.0 Hz, 1H), 8.31 – 8.24 (m, 1H), 7.29 – 7.24 (m, 1H), 6.94 (t, *J* = 7.6 Hz, 1H), 6.85 – 6.77 (m, 2H), 6.57 (dd, *J* = 8.9, 2.9 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.41 (s, 4H), 2.73 (s, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.7, 158.2, 154.1, 149.0, 143.5, 131.6, 131.2, 130.0, 124.3, 122.9, 120.2, 111.5, 108.8, 107.1, 56.4, 56.0, 48.6, 35.3. HRMS (ESI) m/z for $C_{20}H_{25}N_4O_3^+$ $(M+H)^+$, 369.1921 (Calc.), found 369.1930.



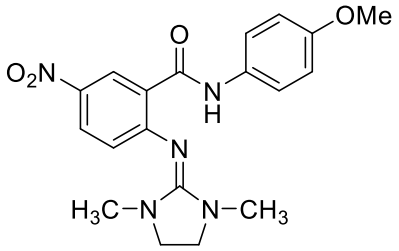
**2-((1,3-dimethylimidazolidin-2-ylidene)amino)-*N*-methylbenzamide (3-41t)** The reaction was performed with **3-38t** (39 mg, 0.2 mmol), *N*,*N*′-dimethylethylenediamine (**3-39a**, 0.03 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 1% MeOH/$CH_2Cl_2$; yield: 18 mg and 18 mg, 37% and 37%; colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, *J* = 4.7 Hz, 1H), 8.20 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.22 (ddd, *J* = 8.0, 7.1, 1.7 Hz, 1H), 6.91 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 6.78 (dd, *J* = 8.0, 1.2 Hz, 1H), 3.39 (s, 4H), 2.97 (d, *J* = 4.8 Hz, 3H), 2.67 (s, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 168.2, 157.0, 148.3, 130.9, 130.9, 124.0, 122.8, 120.3, 48.5, 35.2, 26.1. HRMS (ESI) m/z for $C_{13}H_{19}N_4O^+$ $(M+H)^+$, 247.1553 (Calc.), found 247.1560.



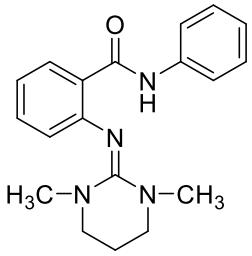
***N*-benzyl-2-((1,3-dimethylimidazolidin-2-ylidene)amino)benzamide (3-41u)** The reaction was performed with **3-38u** (54 mg, 0.2 mmol), *N*,*N*′-dimethylethylenediamine (**3-39a**, 0.03 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 40% Ethyl acetate/Hexane; yield: 57 mg and 57 mg, 89% and 89%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 10.25 (t, *J* = 4.8 Hz, 1H), 8.23 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.40 – 7.33 (m, 2H), 7.33 – 7.27 (m, 2H), 7.27 – 7.21 (m, 2H), 6.94 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H), 6.78 (dd, *J* = 8.0, 1.2 Hz, 1H), 4.66 (d, *J* = 5.2 Hz, 2H), 3.30 (s, 4H), 2.50 (s, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 167.4, 156.5, 148.5, 139.5, 131.1, 131.0, 128.5, 127.9, 127.0, 124.0, 123.0, 120.4, 48.4, 43.9, 34.9. HRMS (ESI) m/z for $C_{19}H_{23}N_4O^+$ $(M+H)^+$, 323.1866 (Calc.), found 323.1876.




**2-((1,3-dimethylimidazolidin-2-ylidene)amino)-*N*-phenylnicotinamide (3-41v)** The reaction was performed with **3-38v** (52 mg, 0.2 mmol), *N*,*N*′-dimethylethylenediamine (**3-39a**, 0.03 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 10% - 30% ($CH_2Cl_2$: MeOH : $NEt_3$ = 100 : 2 : 1)/Hexane; yield: 40 mg and 40 mg, 65% and 65%; %; yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 12.69 (s, 1H), 8.56 (dd, *J* = 7.7, 2.1 Hz, 1H), 8.32 (dd, *J* = 4.8, 2.1 Hz, 1H), 7.78 – 7.66 (m, 2H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.09 (t, *J* = 7.4 Hz, 1H), 6.85 (dd, *J* = 7.7, 4.8 Hz, 1H), 3.58 (s, 4H), 2.85 (s, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 164.2, 159.4, 158.4, 150.6, 140.0, 139.2, 128.9, 123.5, 120.0, 118.7, 115.2, 48.1, 34.8. HRMS (ESI) m/z for $C_{17}H_{20}N_5O^+$ $(M+H)^+$, 310.1662 (Calc.), found 310.1670.

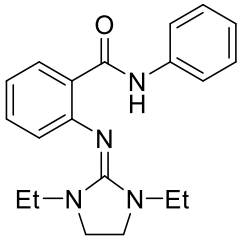


**2-((1,3-dimethylimidazolidin-2-ylidene)amino)-*N*-(4-methoxyphenyl)-5-nitrobenzamide (3-41w)** The reaction was performed with **3-38m** (60 mg, 0.2 mmol), *N*,*N*′-dimethylethylenediamine (**3-39a**, 0.03 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 0% - 15% ($CH_2Cl_2$ : EtOAc = 1 : 1)/Hexane; yield: 44 mg and 45 mg, 57% and 59%; yellow solid. $^1$H NMR (400 MHz, Chloroform-*d*) δ 12.14 (s, 1H), 9.20 (d, *J* = 2.9 Hz, 1H), 8.07 (dd, *J* = 9.0, 2.9 Hz, 1H), 7.68 – 7.57 (m, 2H), 6.95 – 6.85 (m, 2H), 6.73 (d, *J* = 9.0 Hz, 1H), 3.81 (s, 3H), 3.60 (s, 4H), 2.84 (s, 6H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 163.0, 159.3, 156.1, 154.5, 140.0, 132.3, 128.2, 126.2, 123.1, 121.5, 121.5, 114.3, 55.7, 48.3, 35.0. HRMS (ESI) m/z for $C_{19}H_{22}N_5O_4^+$ $(M+H)^+$, 384.1666 (Calc.), found 384.1673.

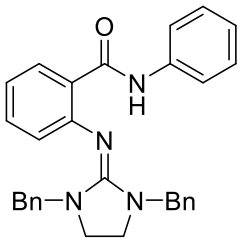


**2-((1,3-dimethyltetrahydropyrimidin-2(1*H*)-ylidene)amino)-*N*-phenylbenzamide (3-41x)** The reaction was performed with **3-38a** (51 mg, 0.2 mmol), *N*,*N*′-dimethyl-1,3-propanediamine (**3-39b**, 0.033 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 50% -

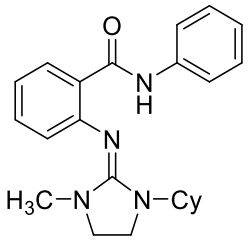
80% Ethyl acetate/Hexane; yield: 55 mg and 56 mg, 85% and 86%; white solid. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 13.02 (s, 1H), 8.27 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.77 – 7.67 (m, 2H), 7.37 – 7.28 (m, 2H), 7.22 (ddd, *J* = 8.4, 7.1, 1.8 Hz, 1H), 7.09 – 7.00 (m, 1H), 6.83 (ddd, *J* = 8.0, 7.0, 1.2 Hz, 1H), 6.64 – 6.56 (m, 1H), 3.31 (t, *J* = 6.1 Hz, 4H), 2.89 (s, 6H), 2.03 (p, *J* = 6.1 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.9, 155.4, 150.6, 140.0, 131.7, 131.3, 128.9, 123.1, 122.4, 120.6, 120.2, 118.4, 48.7, 39.6, 22.8. HRMS (ESI) m/z for $C_{19}H_{23}N_4O^+$ $(M+H)^+$, 323.1866 (Calc.), found 323.1875.




**2-((1,3-diethylimidazolidin-2-ylidene)amino)-*N*-phenylbenzamide (3-41y)** The reaction was performed with **3-38a** (51 mg, 0.2 mmol), *N*,*N*′-diethylethylenediamine (**3-39d**, 0.038 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 20% Ethyl acetate/Hexane; yield: 51 mg and 48 mg, 76% and 72%; white solid. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 12.24 (s, 1H), 8.28 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.75 – 7.66 (m, 2H), 7.39 – 7.30 (m, 2H), 7.29 – 7.23 (m, 1H), 7.09 – 7.03 (m, 1H), 6.96 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 6.86 (dd, *J* = 8.1, 1.2 Hz, 1H), 3.42 (s, 4H), 3.18 (q, *J* = 7.2 Hz, 4H), 1.05 (t, *J* = 7.2 Hz, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.4, 156.5, 148.7, 139.5, 131.5, 131.2, 129.0, 123.5, 123.3, 122.5, 120.4, 120.2, 45.1, 41.9, 12.0. HRMS (ESI) m/z for $C_{20}H_{25}N_4O^+$ $(M+H)^+$, 337.2023 (Calc.), found 337.2033.

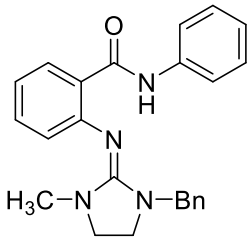


**2-((1,3-dibenzylimidazolidin-2-ylidene)amino)-N-phenylbenzamide (3-41z)** The reaction was performed with **3-38a** (51 mg, 0.2 mmol), *N*,*N*′-dibenzylethylenediamine (**3-39e**, 63 mg, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 15% - 20% Ethyl acetate/Hexane; yield: 23 mg and 22 mg, 25% and 24%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 12.01 (s, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 7.62 – 7.52 (m, 2H), 7.29 – 7.17 (m, 13H), 7.08 – 6.92 (m, 3H), 4.39 (s, 4H), 3.34 (s, 4H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.2, 156.6, 148.0, 139.3, 136.3, 131.8, 131.5, 128.9, 128.9, 127.9, 127.8, 123.9, 123.4, 122.6, 121.0, 120.3, 51.2, 45.5. HRMS (ESI) m/z for $C_{30}H_{29}N_4O^+$ $(M+H)^+$, 461.2336 (Calc.), found 461.2349.



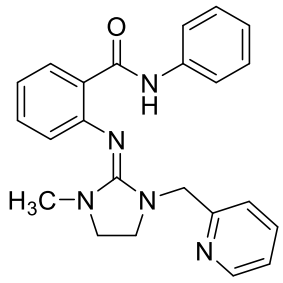
**(*E*)-2-((1-cyclohexyl-3-methylimidazolidin-2-ylidene)amino)-*N*-phenylbenzamide (*(E)*-3-41cc)**The reaction was performed with **3-38a** (51 mg, 0.2 mmol), **3-39i** (60 mg, 0.26 mmol), $NEt_3$ (0.14 mL, 1 mmol) and $CH_3CN$ (2 mL). Eluent: 20% Ethyl acetate/Hexane; yield: 48 mg and 45 mg, 64% and 60%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 12.31 (s, 1H), 8.27 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.73 – 7.66 (m, 2H), 7.36 – 7.29 (m, 2H), 7.28 – 7.24 (m, 1H), 7.06 (tt, *J* = 7.4, 1.2 Hz, 1H), 6.99 – 6.92 (m, 1H), 6.82 (dd, *J* = 8.0, 1.2 Hz, 1H), 3.82 (tt, *J* = 11.8, 3.5 Hz, 1H), 3.58 – 3.21

(m, 4H), 2.60 (s, 3H), 1.85 – 1.70 (m, 4H), 1.67 – 1.58 (m, 1H), 1.46 – 1.33 (m, 2H), 1.28 – 1.20 (m, 2H), 1.12 – 1.00 (m, 1H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.5, 156.6, 148.8, 139.6, 131.5, 131.2, 129.0, 123.7, 123.3, 122.6, 120.3, 120.1, 53.9, 49.4, 40.1, 36.1, 29.8, 25.7, 25.6. HRMS (ESI) m/z for $C_{23}H_{29}N_4O^+$ $(M+H)^+$, 377.2336 (Calc.), found 377.2345.

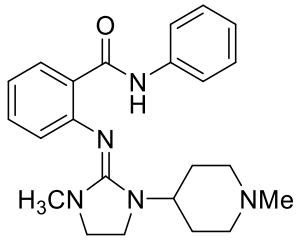



**(*E*)-2-((1-benzyl-3-methylimidazolidin-2-ylidene)amino)-*N*-phenylbenzamide (*(E)*-3-41dd)**

The reaction was performed with **3-38a** (51 mg, 0.2 mmol), **3-39g** (62 mg, 0.26 mmol), $NEt_3$ (0.14 mL, 1 mmol) and $CH_3CN$ (2 mL). Eluent: 20% Ethyl Acetate/Hexane; yield: 61 mg and 62 mg, 79% and 81%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 12.14 (s, 1H), 8.28 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.65 – 7.58 (m, 2H), 7.31 – 7.23 (m, 8H), 7.07 – 7.01 (m, 1H), 7.00 – 6.94 (m, 1H), 6.90 (dd, *J* = 8.1, 1.2 Hz, 1H), 4.50 (s, 2H), 3.51 – 3.26 (m, 4H), 2.67 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.3, 157.1, 148.2, 139.4, 136.6, 131.6, 131.3, 128.9, 128.9, 127.8, 127.8, 124.1, 123.3, 122.8, 120.7, 120.2, 51.0, 49.0, 45.1, 35.8. HRMS (ESI) m/z for $C_{24}H_{25}N_4O^+$ $(M+H)^+$, 385.2023 (Calc.), found 385.2035.

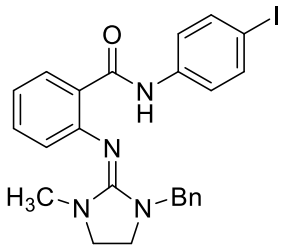


**(*E*)-2-((1-methyl-3-(pyridin-2-ylmethyl)imidazolidin-2-ylidene)amino)-*N*-phenylbenzamide (*(E)*-3-41ee)** The reaction was performed with **3-38a** (51 mg, 0.2 mmol), **3-39h** (43 mg, 0.26 mmol), $NEt_3$ (0.085 mL, 1 mmol) and $CH_3CN$ (2 mL). Eluent: 60% Ethyl Acetate/Hexane; yield: 57 mg and 54 mg, 74% and 70%; white solid. $^1H$ NMR (400 MHz, $CDCl_3$) δ 12.02 (s, 1H), 8.48 (d, *J* = 4.8 Hz, 1H), 8.24 (d, *J* = 7.9 Hz, 1H), 7.65 – 7.56 (m, 2H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.33 – 7.23 (m, 3H), 7.15 – 7.00 (m, 3H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 4.54 (s, 2H), 3.67 – 3.43 (m, 4H), 2.73 (s, 3H). $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 165.2, 157.1, 156.8, 149.6, 148.2, 139.4, 136.8, 131.5, 131.2, 128.9, 124.1, 123.2, 122.9, 122.6, 121.9, 120.7, 120.2, 52.5, 48.9, 46.4, 35.5. HRMS (ESI) m/z for $C_{23}H_{24}N_5O^+$ $(M+H)^+$, 386.1975 (Calc.), found 386.1983.

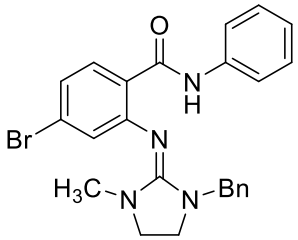


**(*E*)-2-((1-methyl-3-(1-methylpiperidin-4-yl)imidazolidin-2-ylidene)amino)-*N*-phenylbenzamide (*(E)*-3-41ff)** The reaction was performed with **3-38a** (51 mg, 0.2 mmol), **3-39j** (73 mg, 0.26 mmol), $NEt_3$ (0.17 mL, 1.2 mmol) and $CH_3CN$ (2 mL). Eluent: 1% - 3% MeOH/$CH_2Cl_2$; yield: 49 mg and 48 mg, 63% and 61%; white solid. $^1H$ NMR (400 MHz, $CDCl_3$)

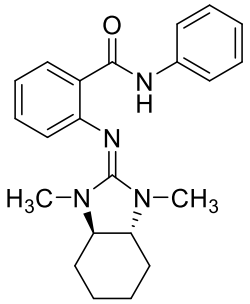
δ 12.09 (s, 1H), 8.27 (d, *J* = 7.9 Hz, 1H), 7.72 – 7.60 (m, 2H), 7.37 – 7.26 (m, 3H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 3.87 (t, *J* = 12.3 Hz, 1H), 3.43 (s, 4H), 3.11 – 3.02 (m, 2H), 2.63 (s, 3H), 2.39 (s, 3H), 2.17 (t, *J* = 12.2 Hz, 2H), 2.10 – 1.95 (m, 2H), 1.80 – 1.70 (m, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.3, 156.4, 148.3, 139.4, 131.6, 131.2, 129.0, 123.9, 123.5, 122.6, 120.7, 120.1, 54.8, 51.2, 49.1, 45.9, 45.2, 40.3, 35.7. HRMS (ESI) m/z for $C_{23}H_{30}N_5O^+$ $(M+H)^+$, 392.2445 (Calc.), found 392.2450.




**(*E*)-2-((1-benzyl-3-methylimidazolidin-2-ylidene)amino)-*N*-(4-iodophenyl)benzamide (*(E)*-3-41gg)** The reaction was performed with **3-38q** (191 mg, 0.5 mmol), **3-39g** (154 mg, 0.65 mmol), $NEt_3$ (0.35 mL, 2.5 mmol) and $CH_3CN$ (5 mL). Eluent: 15% Ethyl acetate/Hexane; yield: 201 mg, 79%; white solid. $^1$H NMR (400 MHz, Chloroform-*d*) δ 12.23 (s, 1H), 8.24 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.39 – 7.33 (m, 2H), 7.33 – 7.27 (m, 4H), 7.25 – 7.20 (m, 2H), 6.96 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H), 6.89 (dd, *J* = 8.1, 1.2 Hz, 1H), 4.49 (s, 2H), 3.53 – 3.33 (m, 4H), 2.67 (s, 3H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 165.5, 157.4, 148.2, 139.2, 137.8, 136.6, 131.8, 131.3, 129.0, 127.8, 127.6, 123.7, 122.7, 122.1, 120.7, 86.0, 50.9, 49.0, 45.3, 35.9.

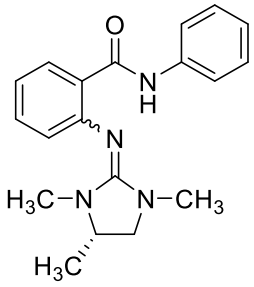


**(*E*)-2-((1-benzyl-3-methylimidazolidin-2-ylidene)amino)-4-bromo-*N*-phenylbenzamide ((*E*)-3-41hh)** The reaction was performed with **3-38k** (134 mg, 0.4 mmol), **3-39g** (123 mg, 0.52 mmol), $NEt_3$ (0.3 mL, 2 mmol) and $CH_3CN$ (4 mL). Eluent: 10% ~ 15% Ethyl acetate/Hexane; yield: 105 mg, 57%; white solid. $^1$H NMR (400 MHz, Chloroform-*d*) δ 12.03 (s, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 7.64 – 7.53 (m, 2H), 7.34 – 7.22 (m, 7H), 7.12 – 7.00 (m, 3H), 4.49 (s, 2H), 3.63 – 3.33 (m, 4H), 2.73 (s, 3H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 164.6, 157.8, 149.3, 139.2, 136.2, 132.8, 129.0, 129.0, 127.9, 127.8, 125.9, 124.9, 123.5, 123.5, 122.8, 120.2, 51.1, 48.8, 45.3, 35.8.

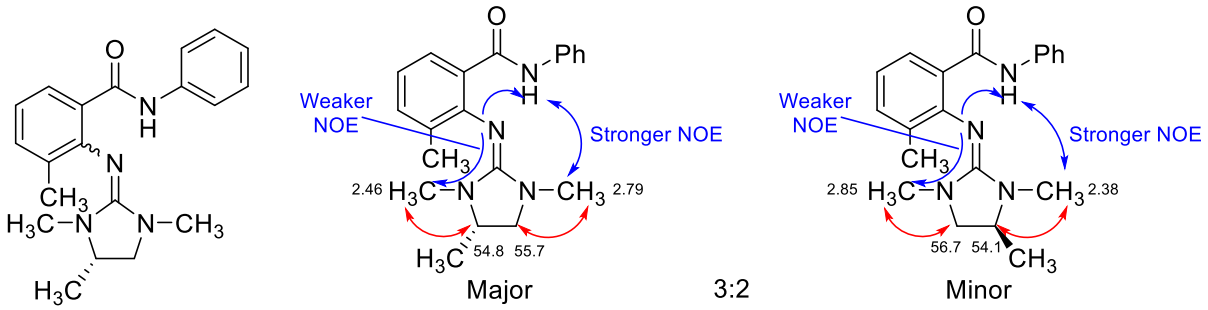



(±)-trans

**(±)-2-(((3a*R*,7a*R*)-1,3-dimethyloctahydro-2*H*-benzo[*d*]imidazol-2-ylidene)amino)-*N*-phenylbenzamide ((±)-*trans*-3-41ii)** The reaction was performed with **3-38a** (51 mg, 0.2 mmol), *trans*-*N*,*N*′-Dimethylcyclohexane-1,2-diamine (**3-39k**, 0.041 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 0.5% - 1% Ethyl acetate/$CH_2Cl_2$; yield: 51 mg and 48 mg, 70% and 66%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 12.14 (s, 1H), 8.27 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.76 – 7.69 (m, 2H), 7.38 – 7.31 (m, 2H), 7.31 – 7.26 (m, 1H), 7.10 – 7.04 (m, 1H), 7.03 – 6.95 (m, 1H), 6.89 (dd, *J* = 8.1, 1.1 Hz, 1H), 2.90 (s, 3H), 2.73 – 2.61 (m, 2H), 2.41 (s, 3H), 2.22 – 1.97 (m, 2H), 1.97 – 1.83 (m, 2H), 1.47 – 1.30 (m, 4H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.2, 160.0, 147.8, 139.4, 131.4, 131.0, 128.9, 124.1, 123.2, 123.0, 120.8, 120.0, 67.5, 64.9, 34.3, 32.2, 28.5, 28.3, 24.2. HRMS (ESI) m/z for $C_{22}H_{27}N_4O^+$ $(M+H)^+$, 363.2179 (Calc.), found 363.2189.



**(*S*)-*N*-phenyl-2-((1,3,4-trimethylimidazolidin-2-ylidene)amino)benzamide ((*S*)-3-41jj)** The reaction was performed with **3-38a** (51 mg, 0.2 mmol), **(*S*)-3-39l** (27 mg, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 20% Ethyl acetate/Hexane; yield: 56 mg and 53 mg, 87% and 82%; white solid. $^1H$ NMR (400 MHz, $CDCl_3$) δ 12.35 (s, 1H), 8.27 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.79 – 7.68 (m, 2H), 7.38 – 7.30 (m, 2H), 7.30 – 7.26 (m, 1H), 7.06 (t, *J* = 7.3 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 3.65 – 3.48 (m, 2H), 3.07 – 2.38 (m, 7H), 1.31 (d, *J* = 5.9 Hz, 3H). $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 165.5, 157.3, 148.3, 139.6, 131.5, 131.1, 129.0, 124.1, 123.3, 122.9, 120.5, 120.1, 55.4, 34.5, 18.5. HRMS (ESI) m/z for $C_{19}H_{23}N_4O^+$ $(M+H)^+$, 323.1866 (Calc.), found 323.1877. (NMR data at 25 °C is not clear, however, at -15 °C, it showed clearly that this compound is a mixture of (*Z*)- and (*E*)-isomers, Z/E = 3:2)

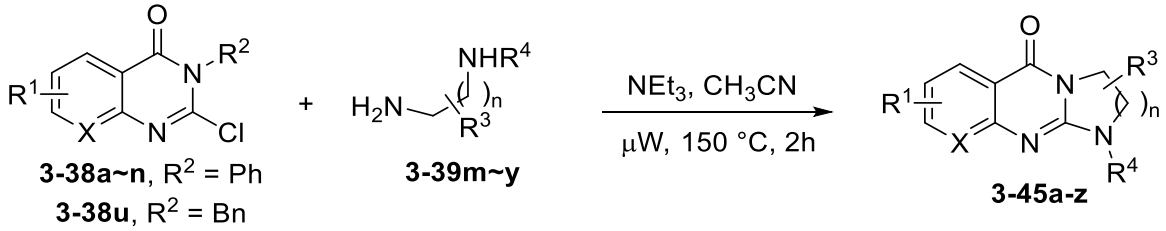


**(*S*)-3-methyl-*N*-phenyl-2-((1,3,4-trimethylimidazolidin-2-ylidene)amino)benzamide ((*S*)-3-41kk)** The reaction was performed with **3-38b** (54 mg, 0.2 mmol), **(*S*)-3-39l** (27 mg, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 20% Ethyl acetate/Hexane; yield: 48 mg and 51 mg, 71% and 76%; white solid. A mixture of *Z*-/*E*-isomer, Z/E = 3:2.

For **(*Z*)-isomer**: $^1$H NMR (400 MHz, $CDCl_3$) δ 11.87 (s, 1H), 8.15 – 8.09 (m, 1H), 7.75 – 7.66 (m, 2H), 7.38 – 7.30 (m, 2H), 7.25 – 7.19 (m, 1H), 7.09 – 7.04 (m, 1H), 6.99 – 6.93 (m, 1H), 3.55 – 3.42 (m, 2H), 2.95 – 2.89 (m, 1H), 2.79 (s, 3H), 2.46 (s, 3H), 2.11 (s, 3H), 1.26 (d, *J* = 5.6 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.8, 154.7, 147.1, 139.5, 133.3, 130.5, 129.0, 129.0, 125.3, 123.3, 121.2, 120.0, 55.7, 54.8, 34.2, 32.1, 18.8, 18.6.

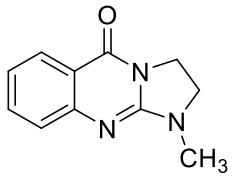
For **(*E*)-isomer**: $^1$H NMR (400 MHz, $CDCl_3$) δ 11.70 (s, 1H), 8.15 – 8.09 (m, 1H), 7.75 – 7.66 (m, 2H), 7.38 – 7.30 (m, 2H), 7.25 – 7.19 (m, 1H), 7.09 – 7.04 (m, 1H), 6.99 – 6.93 (m, 1H), 3.55 – 3.42 (m, 2H), 2.85 (s, 1H), 2.81 – 2.79 (m, 1H), 2.38 (s, 1H), 2.11 (s, 3H), 1.26 (d, *J* = 5.6 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.8, 154.9, 147.1, 139.5, 133.1, 130.6, 129.0, 129.0, 125.4, 123.3, 121.3, 119.9, 56.7, 54.1, 34.7, 31.9, 18.8, 18.1.

## ***3.8.6. Synthesis of the Ring-Fused Guanidines***

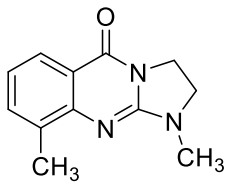



**General Procedure**: To a microwave vial was added substituted 2-chloroquinazolin-4(3*H*)-one (**3-38a~n or 3-38u**, 0.2 mmol), *N,N'*-disubstituted diamine (**3-39m-y**, 0.26 mmol; 0.6 mmol for

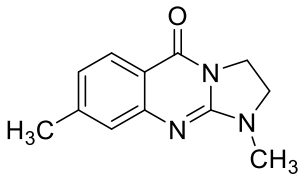
making **3-45s** and **3-45t**), $NEt_3$ (0.6 mmol) and $CH_3CN$ (2 mL). After heating the mixture under microwave irradiation at 150 °C for 2 h, the cooled mixture was diluted with $CH_2Cl_2$ (20 mL) and washed with saturated $NaHCO_3$ solution (15 mL). The aqueous layer was then washed with $CH_2Cl_2$ (20 mL). The combined organic layer was dried with $MgSO_4$, filtered and purified by flash column.



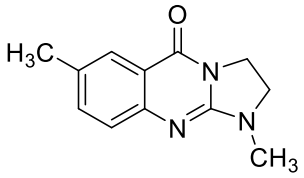
**1-methyl-2,3-dihydroimidazo[2,1-*b*]quinazolin-5(1*H*)-one (3-45a)** The reaction was performed with **3-38a** (51 mg, 0.2 mmol), *N*-methylethylenediamine (**3-39m**, 0.023 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 50% - 95% Ethyl acetate/Hexane; yield: 35 mg and 34 mg, 87% and 85%; white solid, m.p. 177-178 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.56 (ddd, *J* = 8.5, 7.0, 1.6 Hz, 1H), 7.39 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.16 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 4.21 – 4.11 (m, 2H), 3.70 – 3.61 (m, 2H), 3.07 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 161.3, 153.1, 151.0, 134.4, 126.6, 124.9, 122.7, 117.8, 47.1, 40.5, 31.9. HRMS (ESI) m/z for $C_{11}H_{12}N_3O^+$ $(M+H)^+$, 202.0975 (Calc.), found 202.0977.



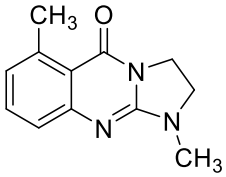
**1,9-dimethyl-2,3-dihydroimidazo[2,1-*b*]quinazolin-5(1*H*)-one (3-45b)** The reaction was performed with **3-38b** (54 mg, 0.2 mmol), *N*-methylethylenediamine (**3-39m**, 0.023 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 50% - 95% Ethyl acetate/Hexane; yield: 36 mg and 35 mg, 84% and 82%; white solid. $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 7.2 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 4.15 (t, *J* = 8.3 Hz, 2H), 3.63 (t, *J* = 8.3 Hz, 2H), 3.15 – 3.03 (m, 3H), 2.48 (s, 3H). $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 161.8, 152.2, 149.6, 134.8, 133.2, 124.2, 122.0, 117.5, 47.1, 40.4, 31.8, 17.6. HRMS (ESI) m/z for $C_{12}H_{14}N_3O^+$ $(M+H)^+$, 216.1131 (Calc.), found 216.1136.



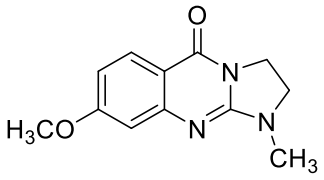

**1,8-dimethyl-2,3-dihydroimidazo[2,1-*b*]quinazolin-5(1*H*)-one (3-45c)** The reaction was performed with **3-38c** (54 mg, 0.2 mmol), *N*-methylethylenediamine (**3-39m**, 0.023 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 50% - 60% Ethyl acetate/Hexane; yield: 36 mg and 37 mg, 84% and 86%; white solid. $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 1.6 Hz, 1H), 6.99 (dd, *J* = 8.0, 1.6 Hz, 1H), 4.20 – 4.12 (m, 2H), 3.69 – 3.61 (m, 2H), 3.07 (s, 3H), 2.41 (s, 3H). $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 161.3, 153.3, 151.1, 145.2, 126.4, 124.9, 124.3, 115.4, 47.2, 40.4, 31.9, 22.0. HRMS (ESI) m/z for $C_{12}H_{14}N_3O^+$ $(M+H)^+$, 216.1131 (Calc.), found 216.1137.



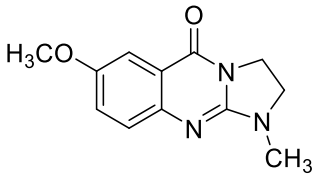
**1,7-dimethyl-2,3-dihydroimidazo[2,1-*b*]quinazolin-5(1*H*)-one (3-45d)** The reaction was performed with **3-38d** (54 mg, 0.2 mmol), *N*-methylethylenediamine (**3-39m**, 0.023 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 50% - 95% Ethyl acetate/Hexane; yield: 37 mg and 35 mg, 86% and 82%; white solid. $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 2.8 Hz, 1H), 7.39 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 1H), 4.20 – 4.11 (m, 2H), 3.69 – 3.60 (m, 2H), 3.06 (s, 3H), 2.39 (s, 3H). $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 161.4, 152.7, 148.8, 135.8, 132.4, 126.1, 124.8, 117.5, 47.2, 40.5, 31.9, 21.0. HRMS (ESI) m/z for $C_{12}H_{14}N_3O^+$ $(M+H)^+$, 216.1131 (Calc.), found 216.1137.



**1,6-dimethyl-2,3-dihydroimidazo[2,1-*b*]quinazolin-5(1*H*)-one (3-45e)** The reaction was performed with **3-38e** (54 mg, 0.2 mmol), *N*-methylethylenediamine (**3-39m**, 0.023 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 50% - 80% Ethyl acetate/Hexane; yield: 35 mg and 33 mg, 81% and 77%; white solid. $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.39 (t, *J* = 7.9 Hz, 1H), 7.25 (d, *J* = 9.2 Hz, 1H), 6.91 (d, *J* = 7.3 Hz, 1H), 4.12 (t, *J* = 8.1 Hz, 2H), 3.63 (t, *J* = 8.5 Hz, 2H), 3.05 (s, 3H), 2.80 (s, 3H). $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 162.1, 152.8, 152.7, 141.1, 133.4, 125.7, 123.3, 116.3, 47.1, 40.5, 31.9, 23.0. HRMS (ESI) m/z for $C_{12}H_{14}N_3O^+$ $(M+H)^+$, 216.1131 (Calc.), found 216.1139.

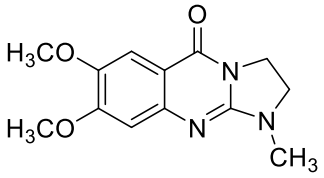


**8-methoxy-1-methyl-2,3-dihydroimidazo[2,1-*b*]quinazolin-5(1*H*)-one (3-45f)** The reaction was performed with **3-38f** (57 mg, 0.2 mmol), *N*-methylethylenediamine (**3-39m**, 0.023 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 50% - 80% Ethyl acetate/Hexane; yield: 35 mg and 33 mg, 76% and 72%; white solid. $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.9 Hz, 1H), 6.81 (d, *J* = 2.4 Hz, 1H), 6.74 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.15 (t, *J* = 8.2 Hz, 2H), 3.87 (s, 3H), 3.66 (t, *J* = 8.2 Hz, 2H), 3.07 (s, 3H). $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 164.8, 161.0, 153.7, 153.3, 128.1, 112.5, 111.3, 106.2, 55.6, 47.2, 40.4, 31.9. HRMS (ESI) m/z for $C_{12}H_{14}N_3O_2^+$ $(M+H)^+$, 232.1081 (Calc.), found 232.1089.

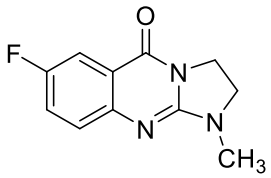


**7-methoxy-1-methyl-2,3-dihydroimidazo[2,1-*b*]quinazolin-5(1*H*)-one (3-45g)** The reaction was performed with **3-38g** (57 mg, 0.2 mmol), *N*-methylethylenediamine (**3-39m**, 0.023 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 50% - 80% Ethyl acetate/Hexane; yield: 34 mg and 33 mg, 74% and 72%; white solid. $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 3.0 Hz, 1H), 7.34 (d, *J* = 8.9 Hz, 1H), 7.20 (dd, *J* = 8.9, 3.0 Hz, 1H), 4.17 (t, *J* = 8.2 Hz, 2H), 3.86 (s, 3H), 3.65 (t, *J* = 8.2 Hz, 2H), 3.05 (s, 3H). $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 161.2, 155.6, 152.2,

145.4, 126.4, 124.3, 118.1, 106.6, 55.9, 47.3, 40.6, 32.0. HRMS (ESI) m/z for $C_{12}H_{14}N_3O_2^+$ $(M+H)^+$, 232.1081 (Calc.), found 232.1087.

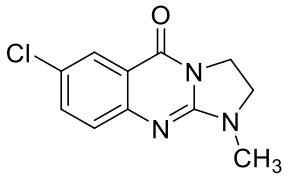


**7,8-dimethoxy-1-methyl-2,3-dihydroimidazo[2,1-*b*]quinazolin-5(1*H*)-one (3-45h)** The reaction was performed with **3-38h** (64 mg, 0.2 mmol), *N*-methylethylenediamine (**3-39m**, 0.023 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 50% - 100% Ethyl acetate/Hexane; yield: 39 mg and 37 mg, 75% and 71%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 6.86 (s, 1H), 4.20 – 4.13 (m, 2H), 3.96 (s, 3H), 3.95 (s, 3H), 3.69 – 3.61 (m, 2H), 3.06 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 160.8, 155.0, 152.9, 147.2, 146.1, 110.3, 106.2, 106.1, 56.3, 56.3, 47.4, 40.6, 32.0. HRMS (ESI) m/z for $C_{13}H_{16}N_3O_3^+$ $(M+H)^+$, 262.1186 (Calc.), found 262.1192.

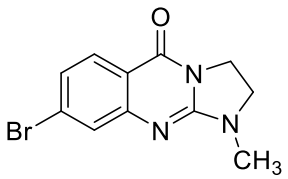


**7-fluoro-1-methyl-2,3-dihydroimidazo[2,1-*b*]quinazolin-5(1*H*)-one (3-45i)** The reaction was performed with **3-38i** (55 mg, 0.2 mmol), *N*-methylethylenediamine (**3-39m**, 0.023 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 50% - 80% Ethyl acetate/Hexane; yield: 37 mg and 36 mg, 84% and 82%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.72 (m,

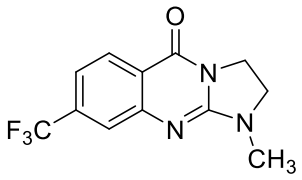
1H), 7.40 – 7.33 (m, 1H), 7.33 – 7.27 (m, 1H), 4.22 – 4.13 (m, 2H), 3.72 – 3.64 (m, 2H), 3.06 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 160.6 (d, *J* = 3.4 Hz), 158.5 (d, *J* = 242.4 Hz), 152.8, 147.6 (d, *J* = 1.7 Hz), 126.8 (d, *J* = 7.7 Hz), 122.6 (d, *J* = 23.8 Hz), 118.5 (d, *J* = 8.2 Hz), 111.5 (d, *J* = 23.5 Hz), 47.2, 40.5, 31.9. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -119.67. HRMS (ESI) m/z for $C_{11}H_{11}FN_3O^+$ $(M+H)^+$, 220.0881 (Calc.), found 220.0887.



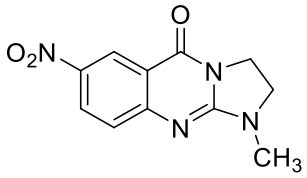

**7-chloro-1-methyl-2,3-dihydroimidazo[2,1-*b*]quinazolin-5(1*H*)-one (3-45j)** The reaction was performed with **3-38j** (58 mg, 0.2 mmol), *N*-methylethylenediamine (**3-39m**, 0.023 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 50% - 80% Ethyl acetate/Hexane; yield: 36 mg and 35 mg, 76% and 74%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 2.5 Hz, 1H), 7.48 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.31 (d, *J* = 8.7 Hz, 1H), 4.22 – 4.12 (m, 2H), 3.73 – 3.64 (m, 2H), 3.07 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 160.3, 153.1, 149.7, 134.6, 128.0, 126.5, 125.9, 118.8, 47.1, 40.5, 31.8. HRMS (ESI) m/z for $C_{11}H_{11}ClN_3O^+$ $(M+H)^+$, 236.0585 (Calc.), found 236.0591.



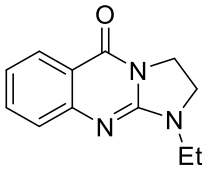
**8-bromo-1-methyl-2,3-dihydroimidazo[2,1-*b*]quinazolin-5(1*H*)-one (3-45k)** The reaction was performed with **3-38k** (58 mg, 0.2 mmol), *N*-methylethylenediamine (**3-39m**, 0.023 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 50% - 80% Ethyl acetate/Hexane; yield: 38 mg and 36 mg, 68% and 64%; white solid. $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.5 Hz, 1H), 7.56 (d, *J* = 1.8 Hz, 1H), 7.25 (dd, *J* = 8.5, 1.9 Hz, 1H), 4.21 – 4.11 (m, 2H), 3.74 – 3.64 (m, 2H), 3.07 (s, 3H). $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 160.9, 153.6, 152.3, 129.1, 128.0, 127.7, 125.9, 116.7, 47.1, 40.5, 31.7. HRMS (ESI) m/z for $C_{11}H_{11}BrN_3O^+$ $(M+H)^+$, 280.0080 (Calc.), found 280.0087.



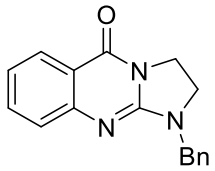

**1-methyl-8-(trifluoromethyl)-2,3-dihydroimidazo[2,1-*b*]quinazolin-5(1*H*)-one (3-45l)** The reaction was performed with **3-38l** (65 mg, 0.2 mmol), *N*-methylethylenediamine (**3-39m**, 0.023 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 50% - 60% Ethyl acetate/Hexane; yield: 38 mg and 35 mg, 71% and 65%; white solid. $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.2 Hz, 1H), 7.65 (d, *J* = 1.9 Hz, 1H), 7.34 (dd, *J* = 8.2, 1.7 Hz, 1H), 4.24 – 4.16 (m, 2H), 3.76 – 3.68 (m, 2H), 3.09 (s, 3H). $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 160.5, 153.6, 151.2, 135.8 (q, *J* = 32.4 Hz), 127.6, 123.8 (q, *J* = 273.0 Hz), 122.4 (q, *J* = 4.1 Hz), 120.1, 118.5 (q, *J* = 3.6 Hz), 47.0, 40.6, 31.7. $^{19}F$ NMR (376 MHz, $CDCl_3$) δ -63.34. HRMS (ESI) m/z for $C_{12}H_{11}F_3N_3O^+$ $(M+H)^+$, 270.0849 (Calc.), found 270.0857.



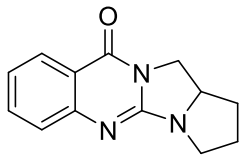
**1-methyl-7-nitro-2,3-dihydroimidazo[2,1-*b*]quinazolin-5(1*H*)-one (3-45m)** The reaction was performed with **3-38m** (60 mg, 0.2 mmol), *N*-methylethylenediamine (**3-39m**, 0.023 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 0% - 60% ($CH_2Cl_2$: EtOAc = 1 : 1)/Hexane; yield: 33 mg and 37 mg, 67% and 75%; yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.96 (d, *J* = 2.7 Hz, 1H), 8.34 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.39 (d, *J* = 9.0 Hz, 1H), 4.23 (t, *J* = 8.6 Hz, 2H), 3.79 (t, *J* = 8.6 Hz, 2H), 3.14 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 159.9, 156.0, 154.5, 142.4, 128.6, 125.7, 123.6, 117.2, 46.9, 40.4, 31.5. HRMS (ESI) m/z for $C_{11}H_{11}N_4O_3^+$ $(M+H)^+$, 247.0826 (Calc.), found 247.0830.



**1-ethyl-2,3-dihydroimidazo[2,1-*b*]quinazolin-5(1*H*)-one (3-45n)** The reaction was performed with **3-38a** (51 mg, 0.2 mmol), *N*-ethylethylenediamine (**3-39n**, 0.028 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 50% Ethyl acetate/Hexane; yield: 33 mg and 30 mg, 77% and 70%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.62 – 7.52 (m, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 4.17 (t, *J* = 8.3 Hz, 2H), 3.67 (t, *J* = 8.4 Hz, 2H), 3.56 (q, *J* = 7.4 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 161.5, 152.5, 151.1, 134.3, 126.6, 125.0, 122.5, 117.9, 44.0, 40.5, 39.4, 12.3. HRMS (ESI) m/z for $C_{12}H_{14}N_3O^+$ $(M+H)^+$, 216.1131 (Calc.), found 216.1135.

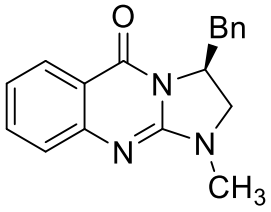


**1-benzyl-2,3-dihydroimidazo[2,1-*b*]quinazolin-5(1*H*)-one (3-45o)** The reaction was performed with **3-38a** (51 mg, 0.2 mmol), *N*-benzylethylenediamine (**3-39o**, 0.039 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 30% Ethyl acetate/Hexane; yield: 46 mg and 46 mg, 83% and 83%; white solid. 1H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, J = 7.9, 1.6 Hz, 1H), 7.59 (ddd, J = 8.6, 7.1, 1.6 Hz, 1H), 7.42 (dd, J = 8.3, 1.1 Hz, 1H), 7.40 – 7.28 (m, 5H), 7.18 (ddd, J = 8.0, 7.1, 1.2 Hz, 1H), 4.69 (s, 2H), 4.19 – 4.09 (m, 2H), 3.58 – 3.48 (m, 2H). $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 161.5, 152.7, 151.1, 136.0, 134.4, 129.0, 128.5, 128.1, 126.6, 125.1, 122.7, 118.1, 48.7, 44.1, 40.5. HRMS (ESI) m/z for $C_{17}H_{16}N_3O^+$ $(M+H)^+$, 278.1288 (Calc.), found 278.1295.

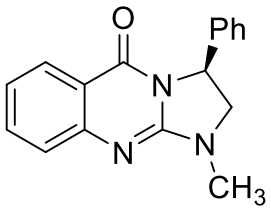


**(±)-2,3,12,12a-tetrahydro-1*H*,10*H*-pyrrolo[1',2':3,4]imidazo[2,1-*b*]quinazolin-10-one (±)-3-45p**) The reaction was performed with **3-38a** (51 mg, 0.2 mmol), **3-39p** (45 mg, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 50% Ethyl acetate/Hexane; yield: 27 mg and 26 mg, 59% and 57%; yellowish solid. $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.60 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H), 7.45 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.21 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 4.23 (dd, *J* = 12.1, 8.6 Hz, 1H), 4.16 (dd, *J* = 12.1, 3.2 Hz, 1H), 4.09 – 3.99 (m, 1H), 3.86 (dt, *J* = 11.2, 8.1 Hz, 1H), 3.44 (ddd, *J* = 11.3, 9.1, 3.7 Hz, 1H), 2.21 – 2.05 (m, 2H), 2.05 –

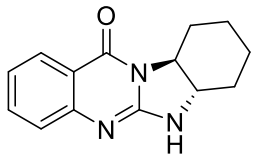
1.93 (m, 1H), 1.50 – 1.37 (m, 1H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 161.5, 155.7, 150.7, 134.4, 126.6, 125.3, 123.3, 118.5, 59.3, 47.6, 46.0, 31.3, 25.6. HRMS (ESI) m/z for $C_{13}H_{14}N_3O^+$ $(M+H)^+$, 228.1131 (Calc.), found 228.1137.




**(*S*)-3-benzyl-1-methyl-2,3-dihydroimidazo[2,1-*b*]quinazolin-5(1*H*)-one** (**(*S*)-3-45-q**) The reaction was performed with **3-38a** (51 mg, 0.2 mmol), **3-39q** (43 mg, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 30% Ethyl acetate/Hexane; yield: 43 mg and 45 mg, 74% and 77%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.9 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 1H), 7.34 – 7.22 (m, 5H), 7.18 (t, *J* = 7.6 Hz, 1H), 4.93 – 4.83 (m, 1H), 3.57 (dd, *J* = 13.6, 3.3 Hz, 1H), 3.49 (t, *J* = 9.1 Hz, 1H), 3.41 (dd, *J* = 9.4, 3.0 Hz, 1H), 2.96 (s, 3H), 2.89 (dd, *J* = 13.4, 9.5 Hz, 1H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 161.3, 152.8, 151.0, 136.2, 134.4, 129.6, 128.9, 127.2, 126.7, 124.9, 122.6, 118.0, 54.1, 51.3, 37.5, 31.7. HRMS (ESI) m/z for $C_{18}H_{18}N_3O^+$ $(M+H)^+$, 292.1444 (Calc.), found 292.1453; $[\alpha]_D^{25}$ = + 40.4° (c = 1.0, $CHCl_3$).

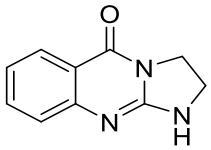


**(*S*)-3-benzyl-1-methyl-2,3-dihydroimidazo[2,1-*b*]quinazolin-5(1*H*)-one** (**(*S*)-3-45-r**) The reaction was performed with **3-38a** (51 mg, 0.2 mmol), **3-39r** (39 mg, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 20% - 40% Ethyl acetate/Hexane; yield: 43 mg and 45 mg, 74% and 77%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.61 – 7.54 (m, 1H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.39 – 7.28 (m, 5H), 7.14 (t, *J* = 7.5 Hz, 1H), 5.60 (dd, *J* = 9.5, 3.1 Hz, 1H), 4.02 (t, *J* = 9.3 Hz, 1H), 3.58 (dd, *J* = 9.2, 3.1 Hz, 1H), 3.13 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 160.7, 153.1, 151.0, 139.4, 134.5, 129.2, 128.6, 126.9, 126.2, 124.9, 122.8, 118.2, 56.2, 56.1, 31.9. HRMS (ESI) m/z for $C_{17}H_{16}N_3O^+$ $(M+H)^+$, 278.1288 (Calc.), found 278.1297; $[\alpha]_D^{25}$ = + 72.9° (c = 1.0, $CHCl_3$).

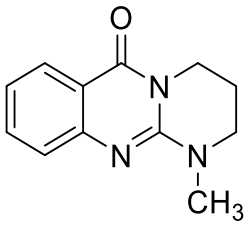


(±)-trans

**(±)-(6a*S*,10a*S*)-6a,7,8,9,10,10a-hexahydrobenzo[4,5]imidazo[2,1-*b*]quinazolin-12(6*H*)-one** (**(±)-3-45-s**) The reaction was performed with **3-38a** (51 mg, 0.2 mmol), (±)-*trans*-1,2-Diaminocyclohexane (**3-39s**, 0.074 mL, 0.6 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 30% - 100% Ethyl acetate/Hexane; yield: 26 mg and 25 mg, 54% and 52%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 8.3 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 6.80 (s, 1H), 3.77 – 3.67 (m, 1H), 3.45 – 3.34 (m, 1H), 3.27 – 3.18 (m, 1H), 2.27 – 2.16 (m, 1H), 2.03 – 1.87 (m, 2H), 1.82 – 1.60 (m, 2H), 1.59 – 1.38 (m, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 162.6, 155.8, 149.9, 134.4, 126.9, 124.3, 123.3, 119.3, 64.6, 61.5, 29.8, 29.2, 24.5, 23.9. HRMS (ESI) m/z for $C_{14}H_{15}N_3O^+$ $(M+H)^+$, 242.1288 (Calc.), found 242.1293. Data is consistent with reference[11].



**2,3-dihydroimidazo[2,1-*b*]quinazolin-5(1*H*)-one** (**3-45-t**) The reaction was performed with **3-38a** (51 mg, 0.2 mmol), ethylenediamine (**3-39t**, 0.042 mL, 0.6 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 50% - 100% Ethyl acetate/$CH_2Cl_2$; yield: 26 mg and 25 mg, 70% and 67%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.58 (ddd, *J* = 8.5, 7.2, 1.6 Hz, 1H), 7.28 – 7.23 (m, 1H), 7.19 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 6.90 (s, 1H), 4.36 – 4.26 (m, 2H), 3.90 – 3.80 (m, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 161.2, 154.7, 150.4, 134.5, 126.9, 124.3, 123.1, 118.0, 42.8, 40.2. HRMS (ESI) m/z for $C_{10}H_9N_3O^+$ $(M+H)^+$, 188.0818 (Calc.), found 188.0823. Data is consistent with reference[12].



**1-methyl-1,2,3,4-tetrahydro-6*H*-pyrimido[2,1-*b*]quinazolin-6-one** (**3-45-u**) The reaction was performed with **3-38u** (54 mg, 0.2 mmol), *N*-methyl-1,3-diaminopropane (**3-39u**, 0.027 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: 30% Ethyl acetate/Hexane; yield: 23 mg and 23 mg, 53% and 53%; white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.0 Hz, 1H), 7.59 – 7.50 (m, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 4.11 (t, *J* = 6.0 Hz, 2H), 3.45 (t, *J* = 6.1 Hz, 2H), 3.25 (s, 3H), 2.10 (p, *J* = 6.1 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$)

δ 162.6, 149.6, 149.4, 134.3, 127.0, 124.7, 122.0, 116.5, 48.0, 39.9, 37.7, 20.9. HRMS (ESI) m/z for $C_{12}H_{14}N_3O^+$ $(M+H)^+$, 216.1131 (Calc.), found 216.1135.

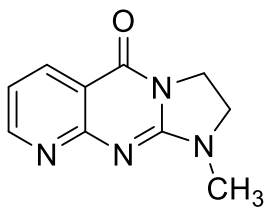
**Optimization of the reaction conditions for the synthesis of compound 3-45u**

The synthesis of **3-45-u** was first performed at standard condition using **3-38a** as starting material. However, only 23% of product was isolated. By switching the starting material to **3-38u** and **3-38v**, yields were increased to 53% and 42%.

**Table 2-5.** Optimization of the reaction condition for the synthesis of 6,6,6-tricyclic guanidine.

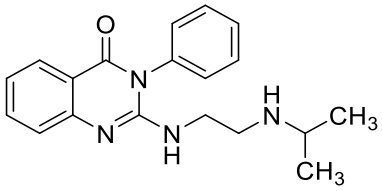
| entry | Starting material | yield |
|---|---|---|
| 1 | **3-38a** | 23% |
| 2 | **3-38u** | 53% |
| 3 | **3-38t** | 42% |

[a] all reactions were carried out with **3-38a** or **3-38t** or **3-38u** (0.2 mmol), *N*-methyl-1,3-diaminopropane (0.26 mmol), $NEt_3$ (0.6 mmol) and $CH_3CN$ (2 mL) under microwave irradiation at 150 °C for 2 hours, yields are reported as isolated yields.



**1-methyl-2,3-dihydroimidazo[1,2-*a*]pyrido[2,3-*d*]pyrimidin-5(1*H*)-one** (**3-45-v**) The reaction was performed with **3-38v** (52 mg, 0.2 mmol), *N*-methylethylenediamine (**3-39m**, 0.023 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: Eluent: 0 - 40% ($CH_2Cl_2$: MeOH : $NEt_3$ = 100 : 2 : 1)/Hexane; yield: 36 mg and 37 mg, 89% and 91%, yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.71 (dd, J = 4.6, 2.1 Hz, 1H), 8.39 (dd, J = 7.8, 2.1 Hz, 1H), 7.10 (dd, J = 7.8, 4.6 Hz, 1H), 4.20 (t, J = 8.5 Hz, 2H), 3.75 (t, J = 8.5 Hz, 2H), 3.16 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 161.1, 161.0, 155.5, 154.7, 135.9, 118.2, 112.4, 46.8, 40.3, 31.6. HRMS (ESI) m/z for $C_{10}H_{11}N_4O^+$ $(M+H)^+$, 203.0927 (Calc.), found 203.0934.

**Unsuccessful substrate**




**2-((2-(isopropylamino)ethyl)amino)-3-phenylquinazolin-4(3*H*)-one** (**3-40c**) The reaction was performed with **3-38a** (51 mg, 0.2 mmol), *N*-isopropylethylenediamine (**3-39v**, 0.033 mL, 0.26 mmol), $NEt_3$ (0.085 mL, 0.6 mmol) and $CH_3CN$ (2 mL). Eluent: Eluent: 5% $CH_2Cl_2$: MeOH; yield: 49 mg, 76%, white solid. $^1$H NMR (400 MHz, Chloroform-*d*) δ 9.4 (s, 1H), 8.1 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.7 – 7.5 (m, 4H), 7.4 (d, *J* = 8.2 Hz, 1H), 7.3 – 7.3 (m, 2H), 7.2 (t, *J* = 7.5 Hz, 1H), 5.2 (s, 1H), 3.8 (t, *J* = 5.2 Hz, 2H), 3.3 – 3.1 (m, 3H), 1.4 (d, *J* = 6.5 Hz, 6H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 162.4, 150.2, 148.4, 135.0, 134.2, 130.8, 130.2, 129.0, 127.6, 124.5, 123.4, 117.9, 50.7, 45.3, 39.4, 19.4. MS (ESI) m/z for $C_{19}H_{23}N_4O^+$ $(M+H)^+$, 323.2 (Calc.), found 323.1.

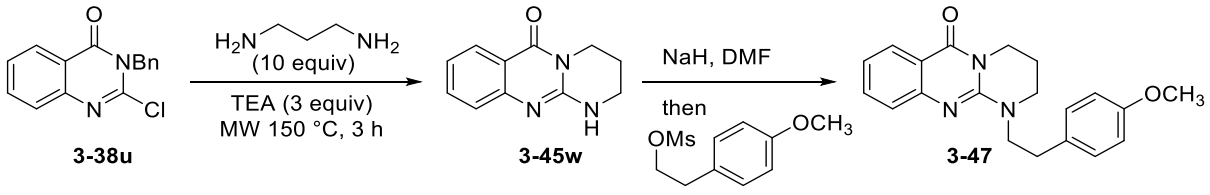
### *3.8.7. Procedures of the scale up reactions of compound 3-41a and 3-45a*

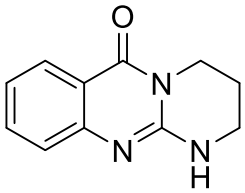
**General procedure:** To a microwave vial was added substituted 2-chloroquinazolin-4(3*H*)-one (**3-38a**, 512mg, 2 mmol), *N*,*N*′-dimethylethylenediamine (**3-39a**, 0.28 mL, 2.6 mmol) for making **3-41a** or *N*-methylethylenediamine (**3-39m**, 0.23 mL, 2.6 mmol) for making **3-45a**, $NEt_3$ (0.85 mL, 6 mmol) and $CH_3CN$ (15 mL). The mixture was heated under microwave condition at 150 °C for 2 hours. After the completion of the reaction, the mixture was diluted with $CH_2Cl_2$ (100 mL) and washed with saturated $NaHCO_3$ solution (50 mL). The aqueous layer was then washed with $CH_2Cl_2$ (50 mL). The combined organic layer was dried with $MgSO_4$, filtered and purified by flash column.

**2-((1,3-dimethylimidazolidin-2-ylidene)amino)-*N*-phenylbenzamide (3-41a)** Yield: 523 mg, 85%; white solids.

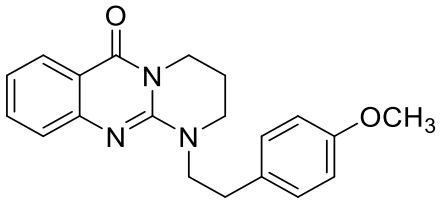
**1-methyl-2,3-dihydroimidazo[2,1-*b*]quinazolin-5(1*H*)-one (3-45a)** Yield: 301 mg, 75%; white solids.

### *3.8.8. Synthesis of antitumor compound 3-47*





**1,2,3,4-tetrahydro-6*H*-pyrimido[2,1-*b*]quinazolin-6-one** (**38w**) To a microwave vial was added **3-38t** (540 mg, 2 mmol), 1,3-diaminopropane (1.67 mL, 20 mmol), $NEt_3$ (0.85 mL, 6 mmol) and $CH_3CN$ (15 mL). The mixture was heated under microwave condition at 150 °C for 3 hours. After the completion of the reaction, the solvent was removed and the crude product was diluted with $CH_2Cl_2$ (60 mL) and washed with brine (40 mL). The aqueous layer was then washed with $CH_2Cl_2$ (40 mL). The combined organic layer was dried with $MgSO_4$, filtered and purified by flash column. Eluent 70% - 90% Ethyl acetate/Hexane; yield: 324 mg, 81%; white solids. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.87 (dd, $J$ = 7.9, 1.6 Hz, 1H), 7.70 (s, 1H), 7.51 (ddd, $J$ = 8.4, 7.0, 1.7 Hz, 1H), 7.12 (d, $J$ = 8.2 Hz, 1H), 7.02 (ddd, $J$ = 8.0, 7.0, 1.1 Hz, 1H), 3.99 – 3.88 (m, 2H), 3.29 (t, $J$ = 5.8 Hz, 2H), 1.95 (p, $J$ = 5.8 Hz, 2H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 161.4, 150.2, 149.9, 134.0, 126.3, 123.4, 120.6, 115.9, 39.6, 38.4, 19.9. HRMS (ESI) m/z for $C_{11}H_{12}N_3O^+$ $(M+H)^+$, 202.0975 (Calc.), found 202.0977. Data is consistent with reference[11].



**1-(4-methoxyphenethyl)-1,2,3,4-tetrahydro-6*H*-pyrimido[2,1-*b*]quinazolin-6-one** (**40**) To a round-bottom flask was added NaH (4.8 mg, 0.12 mmol) and DMF (1 mL). The air was removed from the flask and the flask was back filled with $N_2$ (3X). Then a solution of **38v** in DMF (1 mL)

was added into the flask and the mixture was stirred for 30 minutes, followed by the addition of 4-methoxyphenethyl methanesulfonate in DMF (1 mL). The mixture was further stirred at room temperature for 4 hours. After the completion of the reaction, the reaction was quenched with water (15 mL), extracted with ethyl acetate (15 mL × 3). The combined organic phace were washed with saturated NaHCO3 aqueous solution (30 mL × 2) and brine (30 mL × 3). The organic phase was dried with $Na_2SO_4$, filtered and purified by flash column. Eluent 25% Ethyl acetate/Hexane; yield: 26 mg, 78%; white solids. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.55 (ddd, *J* = 8.4, 7.0, 1.5 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.23 – 7.13 (m, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.90 – 6.81 (m, 2H), 4.09 – 4.00 (m, 2H), 3.85 (t, *J* = 7.3 Hz, 2H), 3.79 (s, 3H), 3.24 (t, *J* = 5.9 Hz, 2H), 2.99 (t, *J* = 7.2 Hz, 2H), 1.96 (p, *J* = 5.9 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 162.8, 158.3, 149.8, 148.5, 134.2, 131.6, 130.0, 126.9, 124.9, 121.8, 116.5, 114.1, 55.4, 52.3, 47.1, 40.2, 32.6, 20.9. Data is consistent with reference[13].

### ***3.8.9. Crystallographic Structural Report for 34a***

#### **3.8.9.1 Data Collection**

A colorless crystal with approximate dimensions 0.35 x 0.28 x 0.23 mm3 was selected under oil under ambient conditions and attached to the tip of a MiTeGen MicroMount©. The crystal was mounted in a stream of cold nitrogen at 100(1) K and centered in the X-ray beam by using a video camera.

The crystal evaluation and data collection were performed on a Bruker SMART APEXII diffractometer with Cu Kα (λ = 1.54178 Å) radiation and the diffractometer to crystal distance of 4.03 cm [14].

The initial cell constants were obtained from three series of ω scans at different starting angles. Each series consisted of 25 frames collected at intervals of 1.0º in a 25º range about ω with the exposure time of 2 seconds per frame. The reflections were successfully indexed by an automated indexing routine built in the APEX3 program. The final cell constants were calculated from a set of 9021 strong reflections from the actual data collection.

The data were collected by using the full sphere data collection routine to survey the reciprocal space to the extent of a full sphere to a resolution of 0.80 Å. A total of 22130 data were harvested by collecting 21 sets of frames with 1.0º scans in ω and φ with an exposure time 10 sec per frame. These highly redundant datasets were corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements[15].

**3.8.9.2 Structure Solution and Refinement**

The systematic absences in the diffraction data were consistent for the space groups $P2_1$ and $P2_1/m$. The *E*-statistics strongly suggested the non-centrosymmetric space group $P2_1$ that yielded chemically reasonable and computationally stable results of refinement [16-21]

A successful solution by the direct methods provided most non-hydrogen atoms from the *E*-map. The remaining non-hydrogen atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms (except the hydrogen bound to N1) were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients.

The absolute structure was unequivocally established by anomalous dispersion effects.

The final least-squares refinement of 213 parameters against 3072 data resulted in residuals *R* (based on $F^2$ for $I \geq 2\sigma$) and *wR* (based on $F^2$ for all data) of 0.0272 and 0.0709, respectively. The final difference Fourier map was featureless.

### ***3.8.9.3 Summary***

**Crystal Data** for $C_{18}H_{20}N_4O$ (*M* =308.38 g/mol): monoclinic, space group $P2_1$ (no. 4), *a* = 8.5544(4) Å, *b* = 9.2284(7) Å, *c* = 10.4804(5) Å, *β* = 108.240(3)°, *V* = 785.79(8) $Å^3$, *Z* = 2, *T* = 99.99 K, μ(Cu Kα) = 0.669 $mm^{-1}$, *Dcalc* = 1.303 $g/cm^3$, 20522 reflections measured (8.884° ≤ 2Θ ≤ 146.746°), 3072 unique ($R_{int}$ = 0.0227, $R_{sigma}$ = 0.0128) which were used in all calculations. The final $R_1$ was 0.0272 (I > 2σ(I)) and $wR_2$ was 0.0709 (all data).

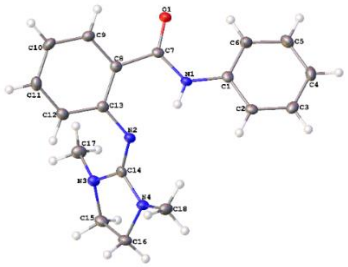


**Figure 2-2.** A molecular drawing of Golden04 shown with 50% probability ellipsoids.

**Table 2-6.** Crystal data and structure refinement for Golden04.

| | |
|---|---|
| Identification code | Golden04 |
| Empirical formula | $C_{18}H_{20}N_4O$ |
| Formula weight | 308.38 |
| Temperature/K | 99.99 |
| Crystal system | monoclinic |
| Space group | $P2_1$ |
| a/Å | 8.5544(4) |
| b/Å | 9.2284(7) |

| | |
|---|---|
| c/Å | 10.4804(5) |
| α/° | 90 |
| β/° | 108.240(3) |
| γ/° | 90 |
| Volume/Å$^3$ | 785.79(8) |
| Z | 2 |
| $\rho_{calc}$g/cm$^3$ | 1.303 |
| μ/mm$^{-1}$ | 0.669 |
| F(000) | 328.0 |
| Crystal size/mm$^3$ | 0.35 × 0.28 × 0.23 |
| Radiation | Cu Kα (λ = 1.54178) |
| 2Θ range for data collection/° | 8.884 to 146.746 |
| Index ranges | -10 ≤ h ≤ 10, -11 ≤ k ≤ 11, -13 ≤ l ≤ 13 |
| Reflections collected | 20522 |
| Independent reflections | 3072 [$R_{int}$ = 0.0227, $R_{sigma}$ = 0.0128] |
| Data/restraints/parameters | 3072/1/213 |
| Goodness-of-fit on F$^2$ | 1.065 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0272, $wR_2$ = 0.0708 |
| Final R indexes [all data] | $R_1$ = 0.0273, $wR_2$ = 0.0709 |
| Largest diff. peak/hole / e Å$^{-3}$ | 0.14/-0.20 |
| Flack parameter | 0.05(4) |

**Table 2-7.** Fractional Atomic Coordinates (×10$^4$) and Equivalent Isotropic Displacement Parameters (Å$^2$×10$^3$) for Golden04. $U_{eq}$ is defined as 1/3 of of the trace of the orthogonalised $U_{IJ}$ tensor.

| **Atom** | ***x*** | ***y*** | ***z*** | **U(eq)** |
|---|---|---|---|---|
| O1 | 5204.5(14) | 5529.5(15) | 9034.7(11) | 23.1(3) |

| | | | | |
|---|---|---|---|---|
| N1 | 6772.8(16) | 5297.4(15) | 7641.5(13) | 15.5(3) |
| N2 | 5313.0(16) | 4095.5(17) | 5229.0(13) | 16.5(3) |
| N3 | 3714.6(17) | 4786.6(16) | 2952.3(13) | 17.5(3) |
| N4 | 6360.5(17) | 4231.2(17) | 3443.4(13) | 17.9(3) |
| C1 | 8185.2(19) | 6092.2(18) | 8341.9(15) | 15.0(3) |
| C2 | 9573(2) | 5936.7(18) | 7921.3(16) | 16.2(3) |
| C3 | 11003(2) | 6704(2) | 8543.2(17) | 18.8(3) |
| C4 | 11066(2) | 7664(2) | 9581.4(17) | 21.7(4) |
| C5 | 9687(2) | 7808(2) | 10002.7(19) | 23.3(4) |
| C6 | 8256(2) | 7030.0(19) | 9408.4(16) | 19.2(3) |
| C7 | 5396.2(19) | 5052.4(18) | 8001.1(15) | 15.2(3) |
| C8 | 4126.1(19) | 4091.6(19) | 7067.5(16) | 14.9(3) |
| C9 | 2928(2) | 3544.2(19) | 7602.6(17) | 17.4(3) |
| C10 | 1700(2) | 2619.9(19) | 6885.1(18) | 20.0(3) |
| C11 | 1644(2) | 2222.8(19) | 5587.7(18) | 20.3(3) |
| C12 | 2793(2) | 2752.9(19) | 5032.7(17) | 18.8(3) |
| C13 | 4065.6(19) | 3691.7(17) | 5744.8(16) | 15.4(3) |
| C14 | 5095(2) | 4344.5(17) | 3954.0(16) | 15.9(3) |
| C15 | 4185(2) | 5203(2) | 1767.2(16) | 20.1(4) |
| C16 | 5787(2) | 4377(2) | 1980.1(16) | 20.3(4) |
| C17 | 2406(2) | 5637(2) | 3199.5(18) | 24.1(4) |
| C18 | 7822(2) | 3396(2) | 4096.7(17) | 22.4(4) |

**Table 2-8.** Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for Golden04. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|---|---|---|---|---|---|---|
| O1 | 22.6(6) | 32.7(7) | 16.5(6) | -7.9(5) | 9.7(4) | -6.4(5) |
| N1 | 17.1(6) | 19.0(7) | 11.3(6) | -3.0(5) | 5.8(5) | -1.0(5) |

| | | | | | | |
|---|---|---|---|---|---|---|
| N2 | 16.5(6) | 21.3(7) | 12.5(6) | -2.9(5) | 5.4(5) | -1.2(6) |
| N3 | 17.0(7) | 20.9(7) | 14.7(6) | -1.1(5) | 5.1(5) | 1.7(5) |
| N4 | 18.3(6) | 23.5(7) | 12.9(6) | -0.8(5) | 6.2(5) | 0.0(6) |
| C1 | 16.3(7) | 14.6(7) | 12.8(7) | 3.5(6) | 2.6(6) | 1.6(6) |
| C2 | 20.3(7) | 16.7(8) | 12.2(7) | 1.6(6) | 5.9(6) | 1.1(6) |
| C3 | 17.0(7) | 22.1(8) | 17.8(8) | 5.4(6) | 6.0(6) | 0.4(6) |
| C4 | 19.1(8) | 23.4(9) | 19.4(8) | 0.4(7) | 1.4(6) | -6.7(7) |
| C5 | 27.3(10) | 22.8(9) | 19.7(8) | -6.8(7) | 7.1(7) | -3.8(7) |
| C6 | 18.2(7) | 22.6(9) | 17.6(8) | -2.7(7) | 7.0(6) | 0.5(7) |
| C7 | 17.0(8) | 17.2(8) | 11.2(7) | 2.2(6) | 4.1(6) | 2.1(6) |
| C8 | 14.5(7) | 15.0(7) | 14.7(7) | 1.8(6) | 3.8(6) | 3.2(6) |
| C9 | 17.2(7) | 20.1(8) | 16.6(7) | 0.5(6) | 7.6(6) | 2.6(6) |
| C10 | 17.1(8) | 21.4(8) | 24.7(9) | 2.0(7) | 11.2(6) | -0.3(7) |
| C11 | 15.9(7) | 19.1(8) | 24.2(9) | -3.5(7) | 3.7(6) | -1.4(6) |
| C12 | 19.1(8) | 20.5(8) | 16.1(8) | -2.6(7) | 4.6(6) | 1.3(7) |
| C13 | 15.3(7) | 15.3(8) | 15.2(7) | 0.3(6) | 4.3(6) | 3.1(6) |
| C14 | 16.7(7) | 14.5(8) | 16.2(8) | -5.1(6) | 4.9(6) | -2.9(6) |
| C15 | 24.9(8) | 21.2(9) | 13.5(7) | 0.9(6) | 5.0(6) | 1.2(7) |
| C16 | 23.6(8) | 24.7(9) | 13.9(8) | -1.0(7) | 7.9(7) | 0.1(7) |
| C17 | 23.0(8) | 26.6(9) | 23.8(9) | 0.7(7) | 8.7(7) | 6.7(7) |
| C18 | 19.2(8) | 30.3(10) | 18.9(8) | 0.3(7) | 7.8(7) | 4.3(7) |

**Table 2-9.** Bond Lengths for Golden04.

| Atom | Atom | Length/Å | Atom | Atom | Length/Å |
|---|---|---|---|---|---|
| O1 | C7 | 1.227(2) | C2 | C3 | 1.386(2) |
| N1 | C1 | 1.408(2) | C3 | C4 | 1.391(3) |
| N1 | C7 | 1.363(2) | C4 | C5 | 1.389(3) |

| | | | | | |
|---|---|---|---|---|---|
| N2 | C13 | 1.390(2) | C5 | C6 | 1.387(2) |
| N2 | C14 | 1.310(2) | C7 | C8 | 1.503(2) |
| N3 | C14 | 1.374(2) | C8 | C9 | 1.407(2) |
| N3 | C15 | 1.471(2) | C8 | C13 | 1.420(2) |
| N3 | C17 | 1.455(2) | C9 | C10 | 1.379(2) |
| N4 | C14 | 1.353(2) | C10 | C11 | 1.394(3) |
| N4 | C16 | 1.463(2) | C11 | C12 | 1.379(2) |
| N4 | C18 | 1.446(2) | C12 | C13 | 1.409(2) |
| C1 | C2 | 1.397(2) | C15 | C16 | 1.523(2) |
| C1 | C6 | 1.400(2) | | | |

**Table 2-10.** Bond Angles for Golden04.

| **Atom** | **Atom** | **Atom** | **Angle/˚** | **Atom** | **Atom** | **Atom** | **Angle/˚** |
|---|---|---|---|---|---|---|---|
| C7 | N1 | C1 | 128.10(14) | O1 | C7 | C8 | 121.16(15) |
| C14 | N2 | C13 | 124.23(14) | N1 | C7 | C8 | 115.40(14) |
| C14 | N3 | C15 | 109.02(13) | C9 | C8 | C7 | 114.87(14) |
| C14 | N3 | C17 | 123.32(13) | C9 | C8 | C13 | 119.17(15) |
| C17 | N3 | C15 | 115.98(14) | C13 | C8 | C7 | 125.95(14) |
| C14 | N4 | C16 | 111.11(13) | C10 | C9 | C8 | 122.01(15) |
| C14 | N4 | C18 | 122.28(14) | C9 | C10 | C11 | 118.85(15) |
| C18 | N4 | C16 | 120.14(13) | C12 | C11 | C10 | 120.41(16) |
| C2 | C1 | N1 | 117.22(14) | C11 | C12 | C13 | 121.97(15) |
| C2 | C1 | C6 | 119.12(14) | N2 | C13 | C8 | 120.83(14) |
| C6 | C1 | N1 | 123.65(14) | N2 | C13 | C12 | 121.27(14) |
| C3 | C2 | C1 | 120.72(15) | C12 | C13 | C8 | 117.59(14) |
| C2 | C3 | C4 | 120.36(15) | N2 | C14 | N3 | 130.16(15) |
| C5 | C4 | C3 | 118.73(16) | N2 | C14 | N4 | 120.92(15) |
| C6 | C5 | C4 | 121.69(16) | N4 | C14 | N3 | 108.88(14) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| C5 | C6 | C1 | 119.34(15) | N3 | C15 | C16 | 102.52(13) |
| O1 | C7 | N1 | 123.40(15) | N4 | C16 | C15 | 101.00(12) |

**Table 2-11.** Hydrogen Bonds for Golden04.

| D | H | A | d(D-H)/Å | d(H-A)/Å | d(D-A)/Å | D-H-A/° |
|---|---|---|---|---|---|---|
| N1 | H1 | N2 | 0.83(2) | 1.96(2) | 2.6844(19) | 145(2) |

**Table 2-12.** Torsion Angles for Golden04.

| A | B | C | D | Angle/° | A | B | C | D | Angle/° |
|---|---|---|---|---|---|---|---|---|---|
| O1 | C7 | C8 | C9 | -13.1(2) | C9 | C8 | C13 | C12 | -0.1(2) |
| O1 | C7 | C8 | C13 | 167.95(17) | C9 | C10 | C11 | C12 | -0.3(3) |
| N1 | C1 | C2 | C3 | 178.78(15) | C10 | C11 | C12 | C13 | 0.7(3) |
| N1 | C1 | C6 | C5 | -177.57(16) | C11 | C12 | C13 | N2 | 173.16(16) |
| N1 | C7 | C8 | C9 | 164.43(14) | C11 | C12 | C13 | C8 | -0.4(2) |
| N1 | C7 | C8 | C13 | -14.5(2) | C13 | N2 | C14 | N3 | 26.2(3) |
| N3 | C15 | C16 | N4 | -26.19(16) | C13 | N2 | C14 | N4 | -156.55(16) |
| C1 | N1 | C7 | O1 | 0.5(3) | C13 | C8 | C9 | C10 | 0.5(2) |
| C1 | N1 | C7 | C8 | -177.03(15) | C14 | N2 | C13 | C8 | -149.54(16) |
| C1 | C2 | C3 | C4 | -1.3(3) | C14 | N2 | C13 | C12 | 37.1(2) |
| C2 | C1 | C6 | C5 | 1.5(2) | C14 | N3 | C15 | C16 | 22.83(18) |
| C2 | C3 | C4 | C5 | 1.7(3) | C14 | N4 | C16 | C15 | 22.79(18) |
| C3 | C4 | C5 | C6 | -0.5(3) | C15 | N3 | C14 | N2 | 168.23(17) |
| C4 | C5 | C6 | C1 | -1.1(3) | C15 | N3 | C14 | N4 | -9.30(19) |
| C6 | C1 | C2 | C3 | -0.3(2) | C16 | N4 | C14 | N2 | 172.84(15) |
| C7 | N1 | C1 | C2 | 166.70(15) | C16 | N4 | C14 | N3 | -9.36(19) |
| C7 | N1 | C1 | C6 | -14.2(3) | C17 | N3 | C14 | N2 | 26.9(3) |
| C7 | C8 | C9 | C10 | -178.47(15) | C17 | N3 | C14 | N4 | -150.66(16) |
| C7 | C8 | C13 | N2 | 5.1(2) | C17 | N3 | C15 | C16 | 167.35(14) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| C7 | C8 | C13 | C12 | 178.71(15) | C18 | N4 | C14 | N2 | 21.1(3) |
| C8 | C9 | C10 | C11 | -0.3(3) | C18 | N4 | C14 | N3 | -161.06(16) |
| C9 | C8 | C13 | N2 | -173.78(15) | C18 | N4 | C16 | C15 | 175.19(15) |

**Table 2-13.** Hydrogen Atom Coordinates ($Å \times 10^4$) and Isotropic Displacement Parameters ($Å^2 \times 10^3$) for Golden04.

| **Atom** | ***x*** | ***y*** | ***z*** | **U(eq)** |
|---|---|---|---|---|
| H1 | 6740(30) | 4950(20) | 6900(20) | 19 |
| H2 | 9537.09 | 5298.49 | 7201.41 | 19 |
| H3 | 11944.33 | 6572.73 | 8258.76 | 23 |
| H4 | 12033.39 | 8210.49 | 9994.39 | 26 |
| H5 | 9724.95 | 8456.44 | 10716.01 | 28 |
| H6 | 7333.35 | 7132.47 | 9722.22 | 23 |
| H9 | 2966.02 | 3819.92 | 8485.17 | 21 |
| H10 | 906.96 | 2259.9 | 7268.04 | 24 |
| H11 | 808.04 | 1583.12 | 5082.9 | 24 |
| H12 | 2724.25 | 2476.59 | 4143.57 | 23 |
| H15A | 4357.91 | 6261.93 | 1742.48 | 24 |
| H15B | 3339.11 | 4900.83 | 925.08 | 24 |
| H16A | 5593.07 | 3419.98 | 1531.06 | 24 |
| H16B | 6575.07 | 4935.59 | 1654.99 | 24 |
| H17A | 2225.65 | 5304.91 | 4030.28 | 36 |
| H17B | 1390.79 | 5517.68 | 2446.7 | 36 |
| H17C | 2721.8 | 6662.26 | 3288 | 36 |
| H18A | 8162.61 | 3575.22 | 5066.74 | 34 |
| H18B | 8709.22 | 3684.07 | 3742.52 | 34 |
| H18C | 7585.84 | 2362.53 | 3923.65 | 34 |

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# Chapter 4. Identification, validation and preliminary SAR studies of parasite glucose uptake inhibitors

## 4.1 Abstract

*T. brucei* and *Leishmania* spp, are kinetoplastid parasites responsible for the widespread tropical diseases human African trypanosomiasis and leishmaniasis, respectively, which afflict millions of people living in tropical areas. Unfortunately, current drugs are limited by toxicity, side effects, difficulty of administration and increasing drug resistance. These parasites rely on the metabolism of glucose in glycosomes, a unique organelle for kinetoplastids, into which glucose must be actively transported.[1-2] Thus, selectively targeting glucose transport, and thereby metabolism, in these parasites may offer a promising therapeutic strategy. The identification of parasite glucose uptake inhibitors was achieved via a high-throughput screening method. The resulting hits were resynthesized to validate their glucose uptake inhibition and growth inhibition of the parasite. Preliminary structure-activity relationship (SAR) was investigated. The results showed that two scaffolds were validated that show blockage of glucose transport of procyclic form *T. brucei* parasites and growth inhibition of bloodstream form *T. brucei* parasites with micromolar to submicromolar activity. In addition, one scaffold is active against both *T. brucei* and *L. donovani*.

Adapted from **Gang Yan,** Charles Voyton, Daniel Call, Jacob Vance, Jillian E. Milanes, Neil P. Monaghan, Kelsey Bryant, Kenneth A. Christensen, James C. Morris, Karl A. Werbovetz and Jennifer E. Golden*. Identification, validation and preliminary SAR studies of parasite glucose uptake inhibitors. (*Manuscript in preparation*)

## 4.2 Introduction

Protozoan kinetoplastid parasites, including *Trypanosoma* and *Leishmania*, afflict millions of people living in tropical areas and place a tremendous burden on human health.[3] Human African trypanosomiasis (HAT), also called African sleeping sickness, is caused by two subspecies *T. brucei. gambiense* and *T. brucei. rhodesiense*, both of which are transmitted by the bite of infected tsetse flies.[3] The diseases occur in two stages: in the first stage (hemolymphatic stage) the parasite will spread to the blood and lymphatic system; in the second stage (encephalitic stage), the parasite will cross the blood-brain barrier and enter the brain.[3] Patients have high risk of death without treatment. There are only a few drugs (**Figure 4-1**) available today.[3-4] Pentamidine (**4-1**)[5] and suramin (**4-2**)[6] are available only for the first stage of the disease.[4] Melarsoprol (**4-4**)[7], eflornithine (**4-5**)[8] and its combination therapy nifurtimox (**4-6**)[9-11] are available for the second stage.[4] Fexinidazole (**4-3**)[12-13] was approved in 2018 for the treatment of first stage and the non-severe stage 2 of *T. b. gambiense* infection. However, these drugs are limited by the efficacy, toxicity and side effects, difficulties of administration, poor pharmacokinetics (PK) profiles and the growing prevalence of parasite resistance. (**Figure 4-1**)[3-4] Therefore, it is urgent to develop new therapeutics for the treatment of HAT.

*Leishmania* spps are another genus of protozoan kinetoplastid parasites including more than 20 species that can infect humans and cause Leishmaniasis.[14] Different from *T. brucei*, which is completely an extracellular parasite, *Leishmania* can also enter into human macrophage cells. This disease is endemic in over 90 countries and leads to thousands of deaths each year.[14] However, the current treatment is limited, which requires the human immune system because the current drugs cannot entirely remove the parasites.[14] Therefore, it is critical to develop new drugs for the treatment of leishmaniasis.

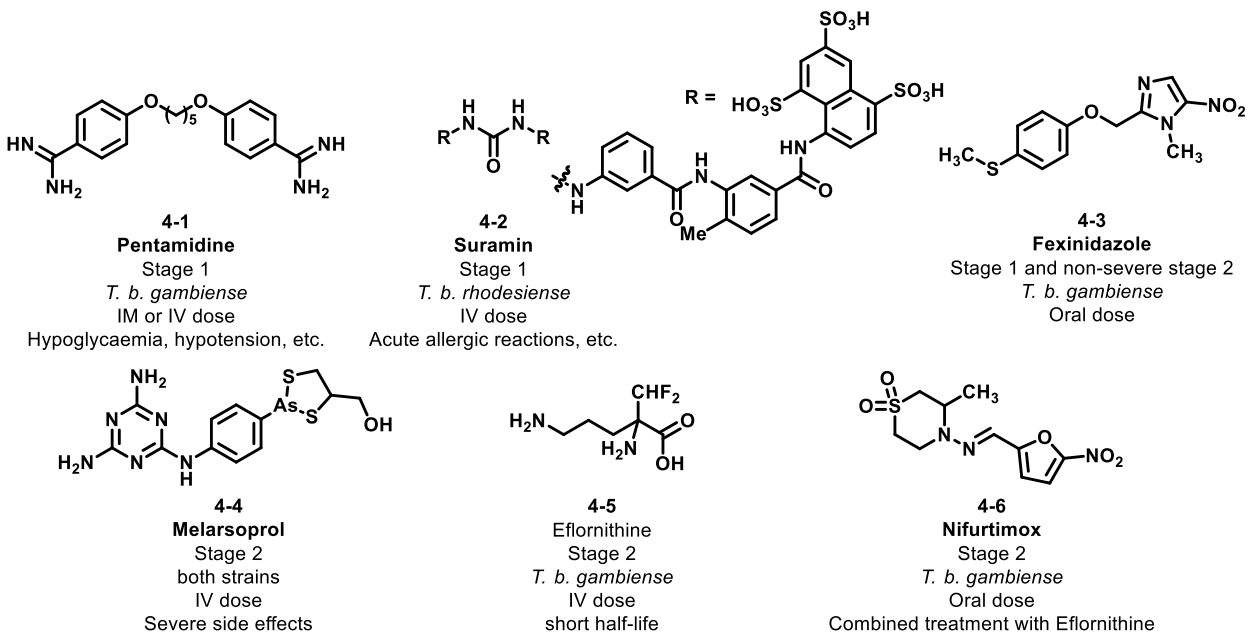



**Figure 4-1.** Current marketed drugs for the treatment of different stages of HAT and their limitations

The energy metabolism of kinetoplastids is different from mammalian cells. Glucose is the only energy source for the bloodstream form (BSF) *T. brucei* in human hosts, and the parasites die rapidly without glucose.[1] The glucose metabolism for ATP production is compartmentally localized in the glycosome, a unique organelle in kinetoplastids which does not exist in mammalian cells.[2] Glucose enters the cytosol of the *T. brucei* cell through the trypanosome hexose transporter (THT) THT1 and THT2,[15-16] both of which are different from human glucose transporter in terms of the affinity to glucose and the types of sugar transported.[17-18] Then the glucose in the cytosol will be transported into the glycosome. Although the mechanism of glycosomal glucose transportation is not well understood,[2, 19-20] targeting glucose uptake of the parasites is a promising strategy for the treatment of HAT with minimal toxicity to the host.[21]

Prof. Christensen and Prof. Morris groups have developed a method that can monitor the glucose concentration in the cytosol and glycosomes of the living procyclic form (PCF) *T. brucei*

using a fluorescent protein biosensor expressed.[22-23] (**Figure 4-2**) The protein sensor can bind with glucose and lead to a conformational change of the sensor, which cause a quantifiable fluorescence change to determine the glucose concentration in the living cell. This method has been further optimized into a high-throughput assay for identifying the parasites glucose uptake inhibitors in cytosol or glycosomes.

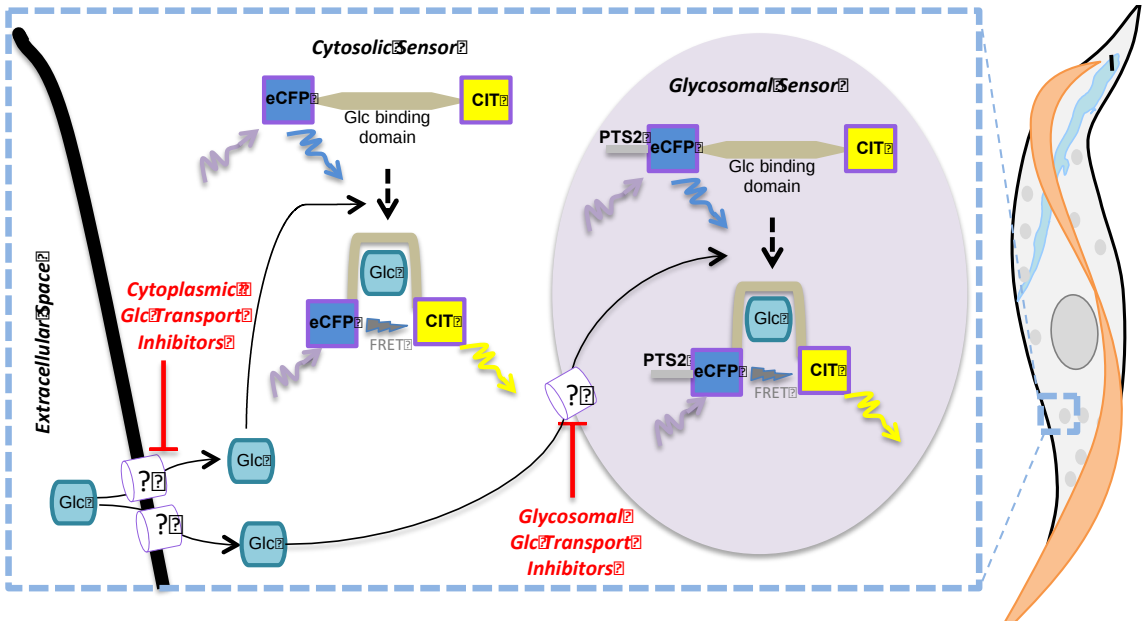



**Figure 4-2.** Method for monitoring cytosolic and glycosomal glucose in living procyclic form (PCF) parasites

In this work, the identification of parasite glucose uptake inhibitors was achieved via a high-throughput screening method. The resulting hits were resynthesized to validate their glucose uptake inhibition and growth inhibition of the parasites. Preliminary structure-activity relationships (SAR) were investigated.

## 4.3 Results and discussion

### ***Screening and Hit Identification***

The high-throughput screening (HTS) was performed by Prof. Christensen group and Prof. Morris group, and the flow chart was shown in **Figure 4-3**. A total number of 25,000 compounds was evaluated in both the PCF cytosol and glycosome assays at a single concentration of 10 $\mu$M. Compounds with signal greater than a 3-fold standard deviation (SD) below the high glucose control were defined as hits. The select hits were assessed in mammalian HEK293 cytotoxicity assay. As a result, 385 compounds were identified as hit compounds in either of cytosol or glycosome glucose uptake assay with low mammalian toxicity ($CC_{50}$ > 10 $\mu$M).

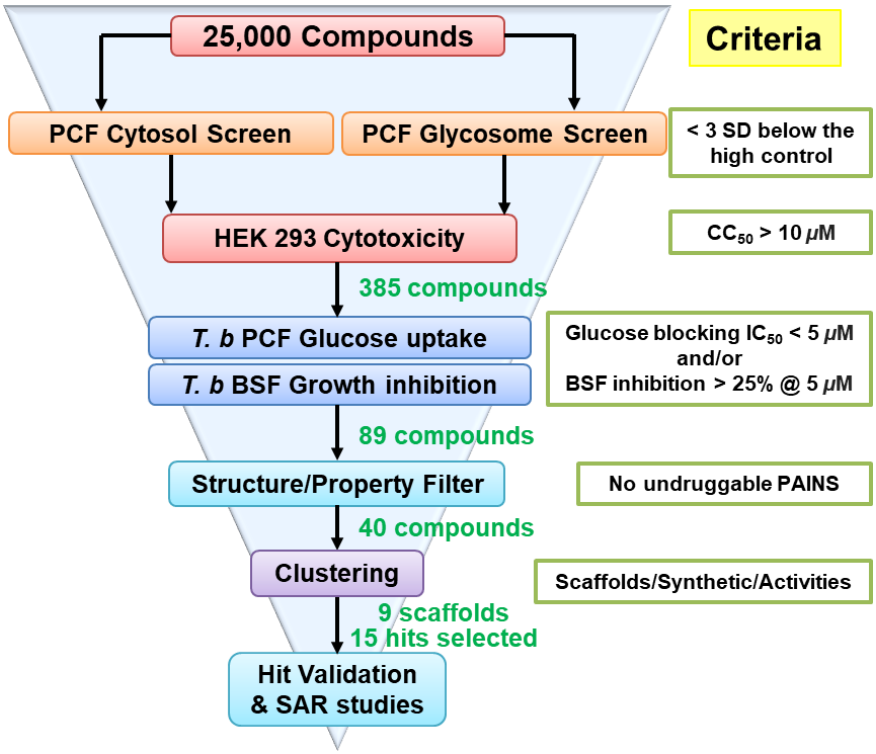



**Figure 4-3.** Flow chart of the high through put screening of the *T. brucei* glucose uptake inhibitors

Compounds were then assessed in the glucose uptake assays in dose response format with a maximum concentration of 5 $\mu$M due to the limitation of compound quantities. At the same time, compounds were evaluated for growth inhibition of BSF *T. brucei*. 89 compounds were identified as hit compounds with PCF glucose uptake $EC_{50}$ < 5 $\mu$M and/or BSF inhibition >25% at 5 $\mu$M. From this step, the undruggable pan-assay interference compounds (PAINS) were removed

because these compounds tend to hit numerous targets. At this point, 40 compounds that can block the glucose uptake of the PCF *T. brucei*, and/or inhibit the BSF parasite growth with no toxicity at 10 $\mu$M in HEK293 cells were selected. These compounds were clustered to 9 scaffolds by structure similarities. Considering the preliminary activity and synthetic feasibility, 15 compounds were selected for hit validation. (**Figure 4-4**) These compounds were resynthesized or purchased and purified, certified of > 95% purity on LC-MS and resubmitted to the glucose uptake assay and antiparasitic assay to validate the activities.

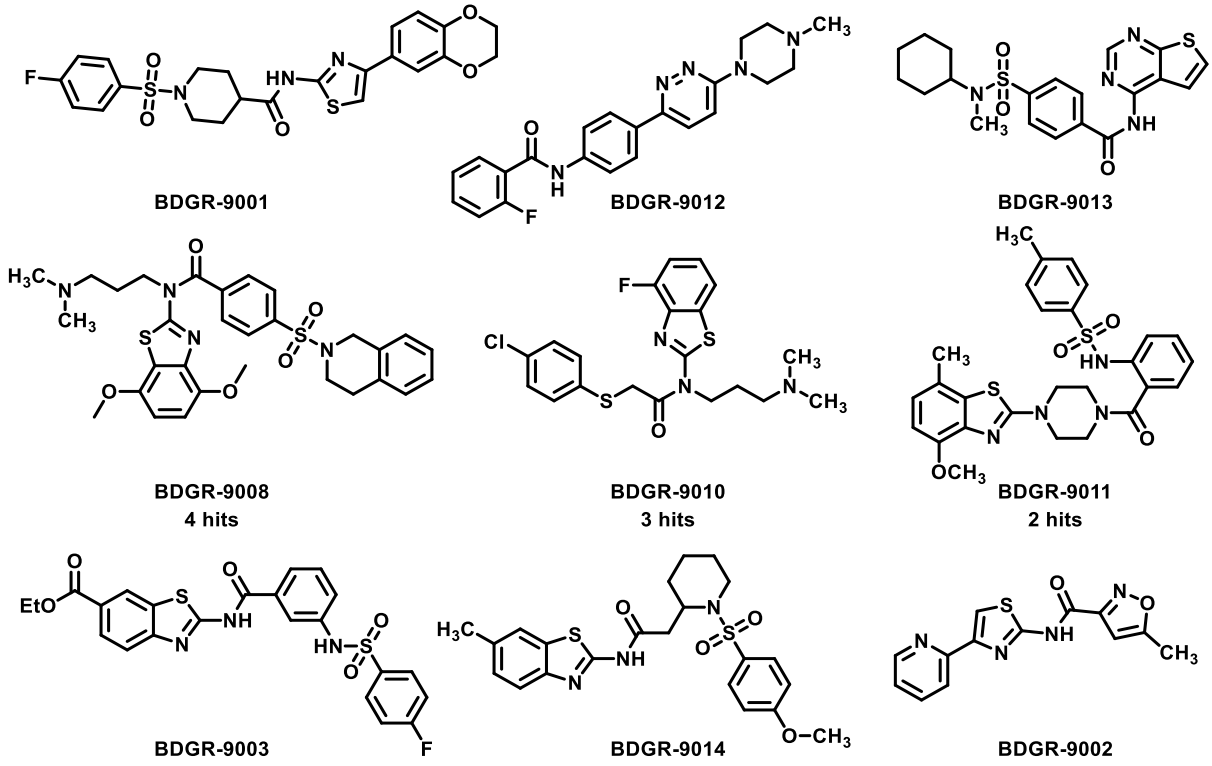


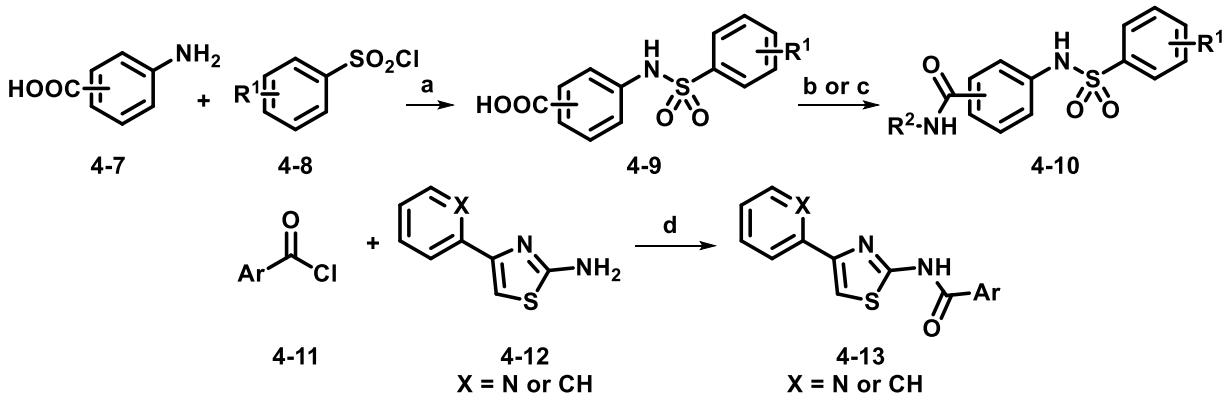

**Figure 4-4.** 9 scaffolds of the selected hit compounds.

## ***Chemistry***

The synthesis of the hit compounds and their derivatives is shown in **Scheme 4-1** ~ **4-3**.

The preparation of **BDGR-9002** and **BDGR-9003** series is shown in **Scheme 4-1**. The sulfonylation reactions between the corresponding aminobenzoic acid (**4-7**) and substituted

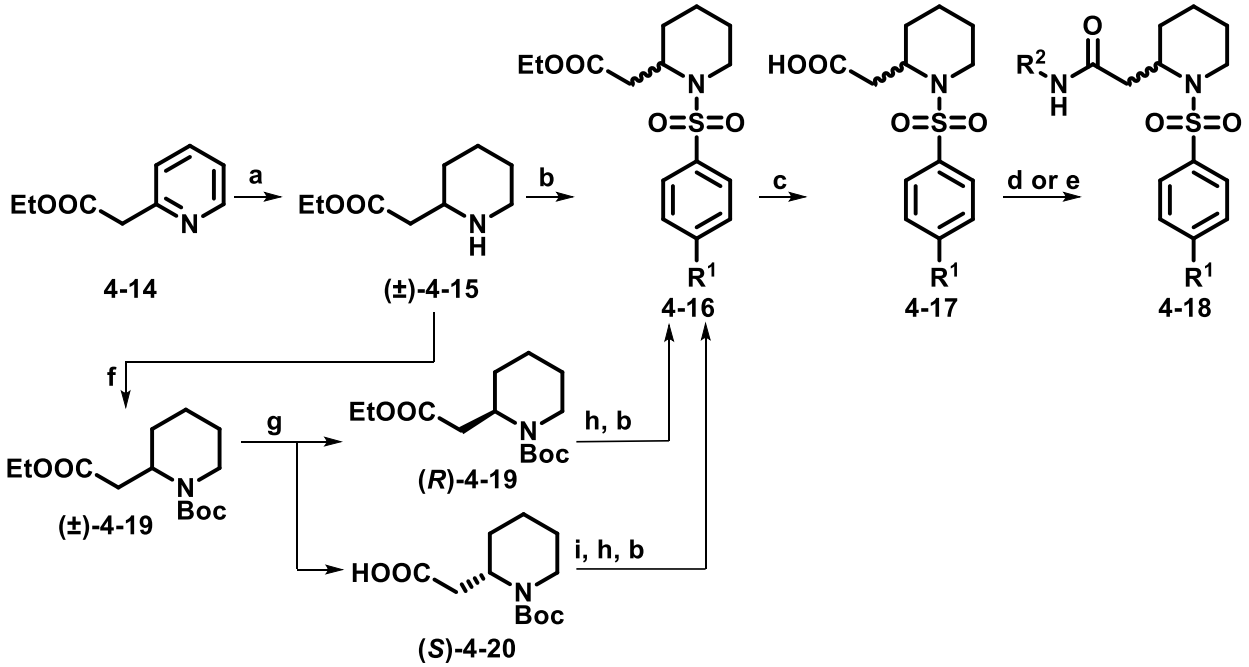
benzenesulfonylchloride (**4-8**) led to the formation of intermediate **4-9**, which was transformed to the final compounds (**4-10**) through peptide coupling reactions. Some of the **BDGR-9002** derivatives (**4-13**) were synthesized through a one-step acylation reaction between aryl acid chloride (**4-11**) and the 4-arylthiazol-2-amine (**4-12**) under basic conditions.




**Scheme 4-1.** Synthesis of **BDGR-9002** and **BDGR-9003** series: (a) $Na_2CO_3$, $H_2O$, rt, 24 h, 63% ~ 93%; (b) $R^2NH_2$, HOBt, EDCI, TEA, DCM, rt, overnight, 16% ~ 50%; (c) $(COCl)_2$, DCM, 0 ºC, 1h, then $R_2NH_2$, TEA or pyridine, DCM, rt, overnight, 23% ~ 58%; (d) TEA or pyridine, DCM, rt, overnight, 43% ~ 96%.

The synthesis of **BDGR-9014** series is described in **Scheme 4-2**. The hydrogenation reaction of compound **4-14** gave the racemic ethyl 2-(piperidine-2-yl)acetate (**(±)-4-15**), which was treated with substituted benzenesulfonyl chloride to afford compound **4-16**. The ester group of **4-16** was hydrolyzed under basic conditions, followed by the peptide coupling reaction to form final compound **4-18**. Notably, the final compound in this series has a stereocenter. In order to figure out whether one enantiomer is more active than the other, an enzymatic kinetic resolution method was used to synthesize the enantiopure compounds.[24] Specifically, the -NH- of the racemic compound **(±)-4-15** was protected by Boc-group to generate compound **(±)-4-19**. Then the lipase from *Burkholderia cepacian* was used to selectively hydrolyzed the ester group of the

**(*S*)-4-19** to afford **(*S*)-4-20**, while the **(*R*)-4-19** was retained. The acid **(*S*)-4-20** was transformed to the ester using DCC as a dehydrating agent. Then each enantiomer underwent Boc-deprotection and sulfonylation reaction to form enantiopure compounds **4-16**, which were converted to the final compounds in two steps with ee% value over 90%.

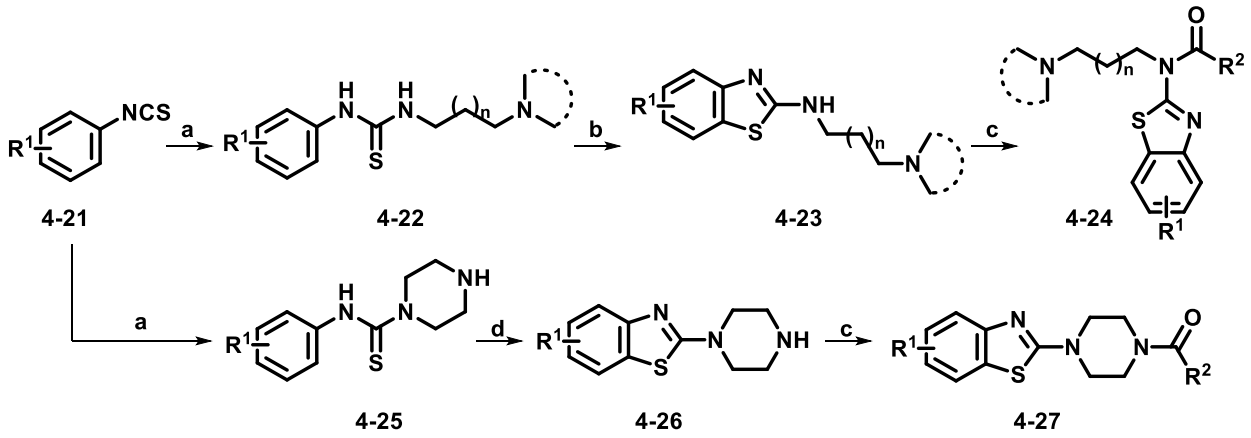



**Scheme 4-2.** Synthesis of **BDGR-9014** series: (a) $PtO_2$, $H_2$ (1 atm), HCl, EtOH, rt, 24h, 70%; (b) $R^1$-Ph-$SO_2Cl$, pyridine or TEA, DCM, rt, overnight, 42% ~ 51%; (c) NaOH, $H_2O$, 1,4-dioxane, 89% ~ 99%; (d) $R^2NH_2$, HOBt, EDCI, TEA, DCM, rt, overnight, 26% ~ 60%; (e) $(COCl)_2$, DCM, 0 ºC, 1 h, then $R_2NH_2$, TEA or pyridine, DCM, rt, overnight, 19% ~ 59%; (f) $Boc_2O$, DCM, 0 ºC – rt, overnight, 98%; (g) Lipase from *Burkholderia cepacia*, PBS, $H_2O$, THF, 35 ºC, 39 h, 49% for **(*S*)-4-20** and 45% for **(*R*)**-4-19; (h) TFA, DCM, rt, 1 h, 100%; (i) DCC, DMAP, EtOH, MeCN, rt, 2h, 96%

The preparation of **BDGR-9008**, **BDGR-9010** and **BDGR-9011** series is shown in **Scheme 4-3**. The synthesis began with the nucleophilic addition reaction of isothiocyanate (**4-21**) with appropriate amines or piperazine to give the thiourea intermediate (**4-22** or **4-25**), which was

cyclized to form benzothiazole intermediate (**4-23** or **4-26**) using $Br_2$ or $BnN(CH_3)_3Br_3$. The final compounds (**4-24** or **4-27**) were obtained by a peptide coupling reaction between intermediate **4-23** or **4-26** with appropriate carboxylic acid.

A total number of 66 compounds were synthesized. All final compounds were confirmed by $^1H$ and $^{13}C$ NMR, and purity was validated to be > 95% by UV/LCMS.




**Scheme 4-3.** Synthesis of **BDGR-9008**, **BDGR-9010** and **BDGR-9011** series: (a) diamines or piperazine, toluene, rt, 2 h, 89% ~ quantitative; (b) $Br_2$, AcOH, rt, 2 h, 25% ~ 80%; (c) $R^2COOH$, HOBt, EDCI, TEA, DCM, rt, overnight, 16% ~ 87%; (d) $BnN(CH_3)_3Br_3$, THF, rt, overnight, 67%.

***Biological assays***

All compounds were evaluated in PCF *T. brucei* glucose uptake assays in cytosol or glycosome, BSF *T. brucei* growth inhibition assay and HEK293 cell toxicity. The growth inhibition against *Leishimania donovani* has also been evaluated towards the extracellular parasite (*L. donovani* axenic amastigotes assay). For compounds with promising activity against the extracellular *L. donovani*, the growth inhibition of the intracellular parasite (*L. donovani* intracellular assay) were tested as well. In addition, kinetic solubility, which is another key physical chemical property, has also been evaluated for selected compounds.

At the hit validation stage, the screening concentrations were increased (up to 50 $\mu$M) relative to the initial screening (5 or 10 $\mu$M). As a result, although control experiments remained identical to the previous results, the irregular sensor responses were observed for some compounds and gave the false negative results at higher compound concentration, possibly due to interaction between the compound and FRET sensor (which contains a glucose binding domain). Therefore, similar to the reported method[25], we developed and validated an orthogonal secondary screening assay using the fluorescent glucose analog 2-NBD-Glucose (2-NBDG) in a glucose uptake assay. To validate this assay, we demonstrated that compounds that initially yielded a dose-response using the FRET sensor assays also showed substantial dose-response in the 2-NBDG uptake assay. The SAR exploration of validated hits relies on this orthogonal assay.

***Preliminary SAR***

As mentioned in the previous section, 15 compounds across 9 scaffolds (**Figure 4-5**) were selected for hit validation. These compounds were resynthesized or purchased and purified, certified of > 95% purity on LC-MS and resubmitted to the glucose uptake assay and antiparasitic assay to validate the activities.

A total number of 66 compounds were synthesized to validate the activity and investigate the SAR (**Figure 4-5**). Three scaffolds (**BDGR-9001**, **BDGR-9012**, **BDGR-9013**, red) did not show promising results upon resynthesis and testing. Three scaffolds (**BDGR-9008**, **BDGR-9010**, **BDGR-9011**, blue) including 9 hits have micromolar activity in the *T. brucei* BSF growth inhibition assay. However, because of the relative weak activity and the off-target properties (i.e not active against glucose uptake) of these scaffolds, the SAR is not discussed in this chapter. Two scaffolds (**BDGR-9003**, **BDGR-9014**, green) were confirmed to be true hit compounds in the *T. brucei* PCF glucose uptake assay and BSF growth inhibition assay. One scaffold (**BDGR-9002**,

pink), although was not active against the parasite glucose uptake, showed promising activities against the growth inhibition of both parasites (*T. brucei* BSF and *L. donovani*).

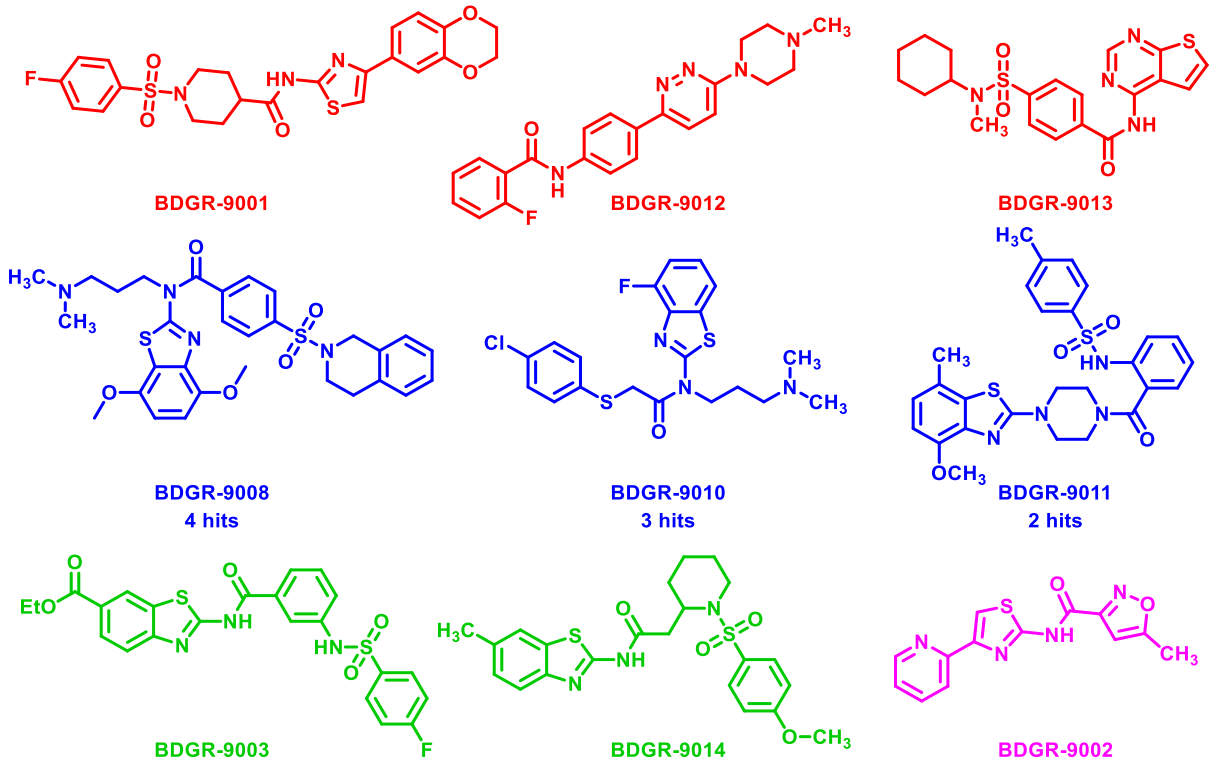



**Figure 4-5.** 9 scaffolds of the selected hit compounds. Red: inactive compounds upon resynthesis/testing; Blue: confirmed activity against *T. brucei* BSF growth inhibition only; Green: confirmed activity against *T. brucei* PCF glucose uptake and BSF growth inhibition; Pink: confirmed activity against *T. brucei* BSF and *L. donovani axenic amastigote* growth inhibition

**2-Benzamidobenzothiazole-6-carboxylate series**

The first series of compounds was optimized based on the hit compound **BDGR-9003**, which displayed $EC_{50}$ values of 0.9 $\mu$M and 1.1 $\mu$M for *T. brucei* PCF cytosolic and glycosomal glucose uptake inhibition, respectively. (**Figure 4-6**) It also exhibited comparable activity ($EC_{50}$ = 1.9 $\mu$M) in the 2-NBDG uptake assay. Although **BDGR-9003** was not active against *L. donovani*,

it showed 2.5 $\mu$M activity against the growth inhibiton of the BSF *T. brucei* with no cytotoxicity against HEK293 cell line in up to 50 $\mu$M.

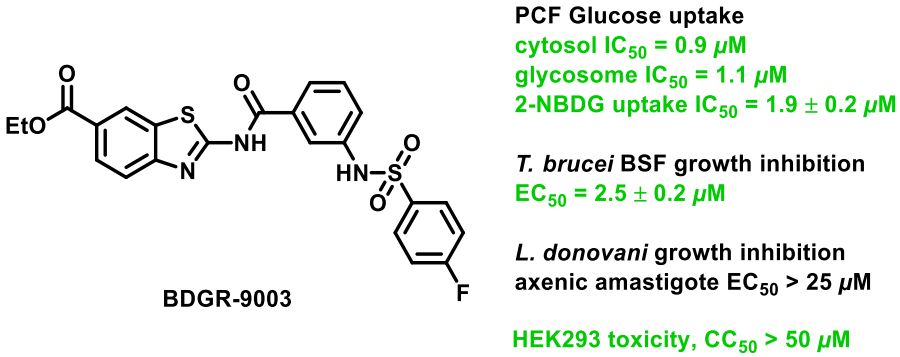
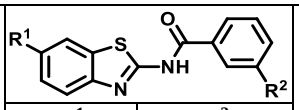
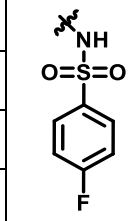



**Figure 4-6.** Activity profile of hit compound **BDGR-9003**

Although **BDGR-9003** displays promising activities as a hit compound against the PCF glucose uptake and BSF growth inhibition, structure modifications are still needed to increase the activity and address other physical chemical properties. (**Table 4-1**) The ester group in **BDGR-9003** is essential for both glucose uptake and growth inhibition activities. Removal of the $R^1$ ester group (**BDGR-9024**) or replacement of the ester with a more metabolic stable *N*,*N*-dimethyl amide (**BDGR-9030**) diminished the activities in all assays. The replacement of ethyl ester with a stable *t*-butyl ester yielded **BDGR-9032** which showed a 7-fold improvement in 2-NBDG uptake inhibition compared to **BDGR-9003** while retaining similar growth inhibition of *T. brucei* BSF parasites with $EC_{50}$ = 4.0 $\mu$M and non-toxic profile towards HEK293 cell line ($CC_{50}$ > 50 $\mu$M).

The other modification to **BDGR-9003** included truncating the structure by removing the $R^2$ 4-fluoroarylsulfonamide moiety (**BDGR-9021**), but all activity was lost. However, by looking at this structure, this compound showed some structure similarities with the hit compound **BDGR-9002** (**Figure 4-5**), which was active against both *T. brucei* and *L. donovani* parasites. The scaffold hybridization of these two series of compounds will be discussed in the next section.

**Table 4-1.** SAR of 2-Benzamidobenzothiazole-6-carboxylates series

| Cmpd. ID |  | | *T. brucei* PCF 2-NBDG uptake inhibition, $IC_{50}$ ($\mu$M) | *T. brucei* BSF growth inhibition, $EC_{50}$ ($\mu$M) | *L. donovani* axenic amastigote growth inhibition, $EC_{50}$ ($\mu$M) | HEK293 cell toxicity, $CC_{50}$ ($\mu$M) |
|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | | | | |
| **BDGR-9003** | $CO_2Et$ |  | 1.9 ± 0.2 | 2.5 ± 0.2 | > 25 | > 50 |
| **BDGR-9024** | H | | > 50 | > 10 | > 25 | > 50 |
| **BDGR-9030** | $CONMe_2$ | | > 50 | > 10 | > 25 | 17 |
| **BDGR-9032** | $CO_2tBu$ | | 0.28 ± 0.04 | 4.0 ± 2.3 | > 12.5 | > 50 |
| **BDGR-9021** | $CO_2Et$ | H | > 50 | > 10 | > 25 | > 50 |

In summary, the preliminary SAR of **BDGR-9003** series has been investigated (**Figure 4-7**). A better compound **BDGR-9032** showed a 7-fold improvement of 2-NBDG uptake activity and retained the antiparasitic activity. Although the SAR is at the initial stages, the solubility (pH = 7.4) of **BDGR-9032** was relatively low (2.4 $\mu$M). More in-depth structure modifications will be undertaken to improve the activity and properties in the future.

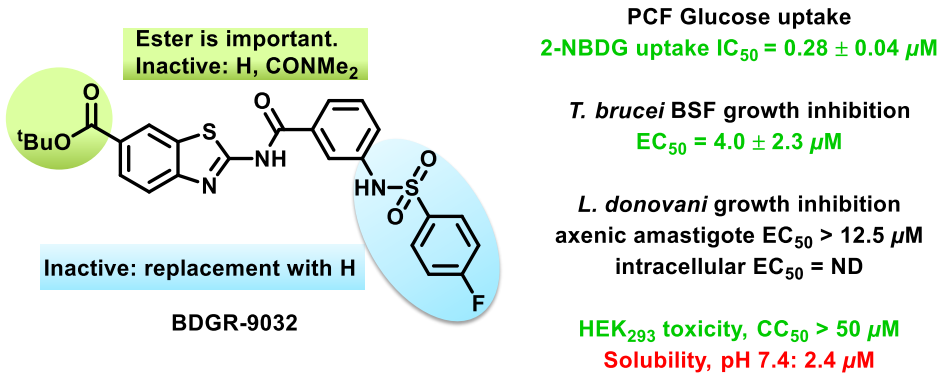



**Figure 4-7.** SAR Summary of 2-benzamidobenzothiazole-6-carboxylates series and the activity profile of **BDGR-9032**

***N*-(4-(pyridin-2-yl)thiazol-2-yl)arylamide series**

The second hit compound **BDGR-9002** did not inhibit the glucose or 2-NBDG uptake at up to 50 $\mu$M, but it inhibited the growth of both BSF *T. brucei* and *L. donovani* axenic amastigotes

with $EC_{50}$ values of 2.8 $\mu$M and 3.1 $\mu$M, respectively. (**Figure 4-8**) The initial modification on **BDGR-9002** (**Figure 4-8** and **Table 4-2**) showed that the pyridyl N atom was critical to the activity, since the phenyl substituted compound (**BDGR-9020**, **Table 4-2**) was inactive against both *T. brucei* at 10 $\mu$M and *L. donovani* at 25 $\mu$M. Replacement of isooxazole ring of **BDGR-9002** with a phenyl ring gave compound **BDGR-9027**, which showed ~ 4-fold improvement of the antiparasitic activities on both parasites.

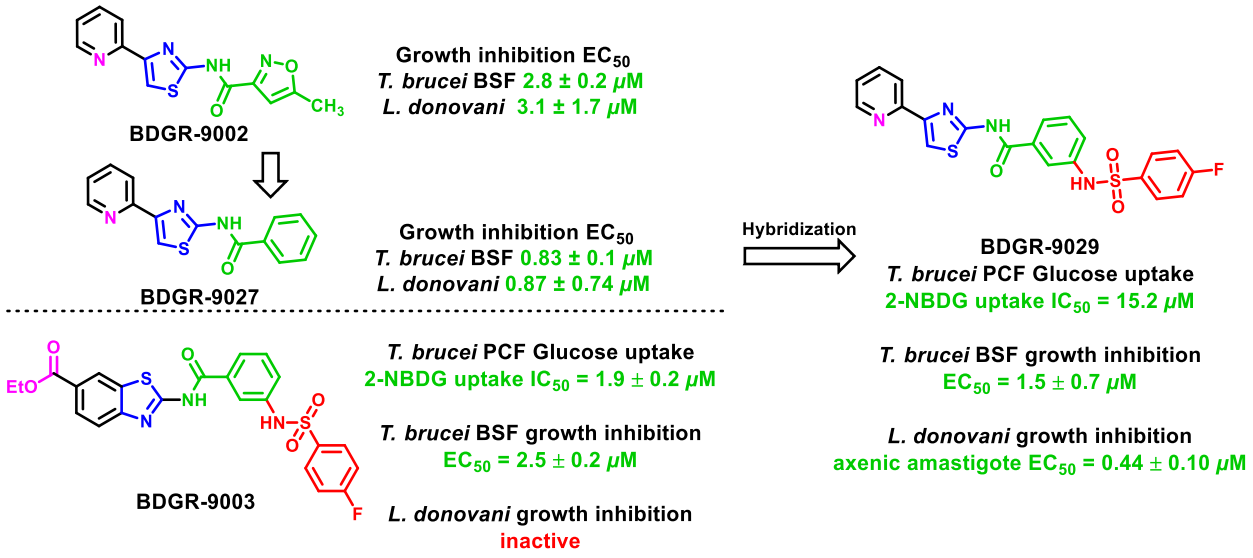



**Figure 4-8.** Hybridization of **BDGR-9003** and **BDGR-9002** series leads to compound **BDGR-9029**

By looking at the structures of **BDGR-9002** and **BDGR-9027**, they showed some structure similarities with compounds **BDGR-9003**, which is not active against *L. donovani*. (**Figure 4-8**) Both series of molecules contain a critical hydrogen bond acceptor, either the pyridyl N atom or an ester group (pink), a thiazole-containing heterocycle (blue) and an aryl amide motif (green). These structural similarities led to the generation of the hybridized compound **BDGR-9029**, which the benzothiazole carboxylate group of **BDGR-9003** was replaced with the 4-(pyridin-2-yl)thiazol-2-yl group. This compound showed modest activity ($IC_{50}$ = 15.2 $\mu$M) for blocking the

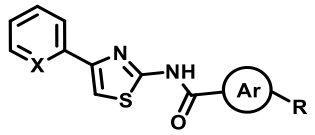
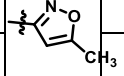
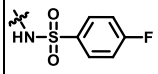
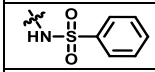
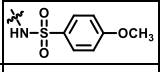
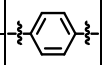
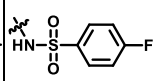
2-NBDG uptake in PCF *T. brucei* and good antiparasitic activity against both BSF *T. brucei* and *L. donovani* axenic amastigotes ($EC_{50}$ = 1.5 $\mu$M and 0.44 $\mu$M, respectively).

A series of analogues have been investigated to understand the SAR of **BDGR-9029**. (**Table 4-2**) As described before, the pyridyl N atom, which might serve as a key hydrogen bond acceptor, was very important to the activity. Compounds bearing a phenyl group (**BDGR-9031** vs **BDGR-9029**) lost all the activities at the maximum testing concentration. Other modification has been made at the terminal R group and the linker Ar group. These compounds, although was not active on 2-NBDG uptake ($EC_{50}$ > 50 $\mu$M), showed great antiparasitic activities. Compounds bearing different terminal R group (**BDGR-9056** and **BDGR-9047**) exhibited comparative sub-$\mu$M antiparasitic activities to **BDGR-9029**. Replacement of the linker Ar group (1,3-substituted phenyl) with a 1,4-substituted phenyl linker gave compound **BDGR-9052**, which gave increased antiparasitic activities ($EC_{50}$ = 0.46 $\mu$M and 0.10 $\mu$M for BSF *T. brucei* and *L. donovani* axenic amastigotes, respectively). The HCl salt of **BDGR-9029** and **BDGR-9052** has also been synthesized in order to facilitate the solubility. Both compounds (**BDGR-9044** and **BDGR-9055)** showed similar activities to the parent compounds. The cytotoxicity against HEK293 cell line has also been evaluated. Although weak toxicity has been seen in some compounds, these compounds displayed great selectivity index ($CC_{50}/EC_{50}$). For example, **BDGR-9055** exhibited selectivity indexes of 55 and 278 for BSF *T. brucei* and *L. donovani* axenic amastigotes, respectively.

Due to the complexity of the *Leishmania*-infected macrophage assay, the *L. donovani* intracellular activities has only been tested for selected compounds. The hit compound **BDGR-9002** displayed 7.8 $\mu$M inhibition against the intracellular *Leishmania*. The hybridized compound **BDGR-9029**, although exhibited great activity against the axenic amastigotes, showed modest

intracellular activity ($EC_{50}$ = 2.9 $\mu$M), possibly due to the low permeability or low solubility. Notably, **BDGR-9027** shows excellent activity ($EC_{50}$ = 0.75 $\mu$M) against intracellular *L. donovani*.

**Table 4-2.** SAR of *N*-(4-(pyridin-2-yl)thiazol-2-yl)arylamide series

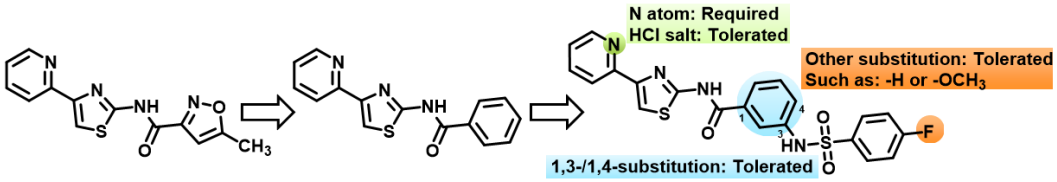
| Cmpd. ID |  | | | *T. brucei* PCF 2-NBDG uptake inhibition, $IC_{50}$ ($\mu$M) | *T. brucei* BSF growth inhibition, $EC_{50}$ ($\mu$M) | *L. donovani* growth inhibition, $EC_{50}$ ($\mu$M) | | HEK293 cell toxicity, $CC_{50}$ ($\mu$M) |
|---|---|---|---|---|---|---|---|---|
| | X | Ar | R | | | axenic amastigote | intracellular | |
| **BDGR-9002** | N |  | H | > 50 | 2.8 ± 0.2 | 3.1 ± 1.7 | 7.8 | > 50 |
| **BDGR-9020** | CH | | H | > 50 | > 10 | > 25 | ND | > 50 |
| **BDGR-9027** | N |  | H | > 50 | 0.83 ± 0.10 | 0.87 ± 0.74 | 0.75 | > 50 |
| **BDGR-9029** | N |  |  | 15.2 | 1.5 ± 0.7 | 0.44 ± 0.10 | 2.9 | 25 |
| **BDGR-9044** | N•HCl | | | 13.3 | 0.45 ± 0.29 | 0.48 ± 0.10 | ND | 17 |
| BDGR-9031 | CH | | | > 50 | > 10 | > 25 | ND | > 50 |
| **BDGR-9056** | N | |  | > 50 | 0.69 ± 0.22 | 0.61 ± 0.25 | ND | > 50 |
| **BDGR-9047** | N | |  | > 50 | 0.60 ± 0.68 | 0.71 ± 0.06 | ND | 10 |
| **BDGR-9052** | N |  |  | > 50 | 0.46 ± 0.04 | 0.10 ± 0.01 | ND | 19.2 |
| **BDGR-9055** | N•HCl | | | > 50 | 0.91 ± 0.07 | 0.18 ± 0.09 | ND | > 50 |

ND = not determined

In summary for this series (**Table 4-3**), the structure of hit compound **BDGR-9002** has been modified to afford **BDGR-9027** with increased antiparasitic activities against both parasites. Further optimization enabled the generation of a hybridized compound **BDGR-9029**, which showed good potency against both parasites and modest 2-NBDG uptake activity of PCF *T. brucei*. However, this compound displayed poor solubility (2 $\mu$M) and weak toxicity ($CC_{50}$ = 25 $\mu$M), which needs to be improved in the future. The preliminary SAR of **BDGR-9029** has been investigated, most derivatives showed comparable antiparasitic activities, but most of them exhibited no activity against 2-NBDG uptake of PCF *T. brucei* at 50 $\mu$M. These data suggested that the mechanism of the growth inhibition of these parasites was not by the inhibition of the

glucose uptake. Considering all the properties, **BDGR-9027** displayed great antiparasitic activities (especially for the great intracellular *L. donovani* activity), low toxicity and great ligand efficiency (LE = 1.4(-*log*$EC_{50}$)/Number of heavy atom, LE = 0.42~0.43 for **BDGR-9027** vs 0.25~0.29 for **BDGR-9029**), which make it to be a better compound for a more in-depth SAR modification in the future.

**Table 4-3.** Summary of **BDGR-9002** series

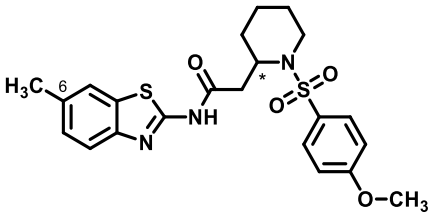



| | BDGR-9002 | BDGR-9027 | BDGR-9044 |
|---|---|---|---|
| *T. brucei* (PCF), 2-NBDG uptake $IC_{50}$ | > 50 μM | > 50 μM | 15.2 μM |
| *T. brucei* (BSF), $EC_{50}$ | 2.8 ± 0.2 μM | 0.83 ± 0.10 μM (LE = 0.43) | 1.5 ± 0.7 μM (LE = 0.26) |
| *L. donovani* (axenic amastigote), $EC_{50}$ | 3.1 ± 1.7 μM | 0.87 ± 0.74 μM (LE = 0.42) | 0.44 ± 0.10 μM (LE = 0.29) |
| *L. donovani* (intracellular), $EC_{50}$ | ND | 0.75 μM (LE = 0.43) | 2.9 μM (LE = 0.25) |
| HEK293 toxicity, $CC_{50}$ | > 50 μM | > 50 μM | 25 μM |
| | | | Solubility, pH 7.4: 2 μM |

**Sulfonylpiperidin-2-yl-*N*-arylacetamide series**

The third series of compounds was optimized based on the hit compound **BDGR-9014** (**Figure 4-9**), which displayed $EC_{50}$ values of 1.6 μM and 1.5 μM for *T. brucei* PCF cytosolic and glycosomal glucose uptake inhibition, respectively. It also displayed comparable activity ($EC_{50}$ = 0.51 μM) in the 2-NBDG uptake assay. Although no significant activity was detected against *L. donovani* axenic amastigotes (> 25 μM), **BDGR-9014** exhibited 4.9 μM activity against the growth inhibiton of the BSF *T. brucei* with no cytotoxicity against HEK293 cell line in up to 50 μM.

**BDGR-9014** shows good potency and toxicity profile, but it showed poor kinetic solubility (2.6 $\mu$M).




BDGR-9014

PCF Glucose uptake
cytosol $IC_{50}$ = 1.6 $\mu$M
glycosome $IC_{50}$ = 1.5 $\mu$M
2-NBDG uptake $IC_{50}$ = 0.51 ± 0.17 $\mu$M

*T. brucei* BSF growth inhibition
$EC_{50}$ = 4.9 ± 0.5 $\mu$M

*L. donovani* growth inhibition
axenic amastigote $EC_{50}$ > 25 $\mu$M

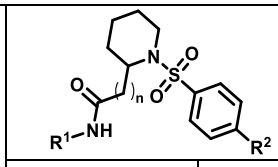
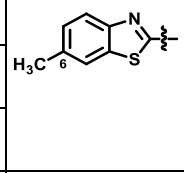
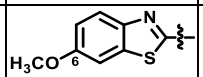
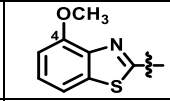
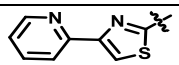
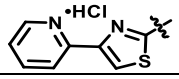
HEK293 toxicity, $CC_{50}$ > 50 $\mu$M
Solubility, pH 7.4: 2.6 µM

**Figure 4-9.** Activity profile of hit compound **BDGR-9014**

Structure modifications were made on this scaffold for investigating the SAR to improve the potency and solubility of **BDGR-9014**. (**Table 4-4**) The length of the piperidine linker appeared to be crucial for the activity. Compounds bearing a shorter linker (**BDGR-9034**) lost the activity against the PCF 2-NBDG uptake and BSF growth inhibition at the maximum tested concentration. To investigate the SAR of the right-hand side $R^2$ group, compounds bearing methyl group (**BDGR-9050**) or F atom (**BDGR-9051**) on the $R^2$ group were synthesized. However, both compounds were 10-fold less potent in the 2-NBDG uptake assay of PCF *T. brucei* and, to some extent, displayed weaker growth inhibition against BSF *T. brucei*. Compounds bearing more polar 4- or 6-$OCH_3$ substituted benzothiazole at $R^1$ position were synthesized in order to explore the SAR of $R^1$ and facilitate the solubility of **BDGR-9014**. Compound bearing a 6-$OCH_3$ group (**BDGR-9048**) retained the 2-NBDG uptake assay with an $EC_{50}$ value of 0.67 $\mu$M, while the 4-$OCH_3$ substitution (**BDGR-9049**) was 2~3 fold less effective. However, both compounds lost the activities against the growth inhibition of BSF *T. brucei*. As the SAR discussion in the previous section, 4-pyridylthiazole might be a good replacement of the benzothiazole group, analogue **BDGR-9046** was synthesized, which not only displayed a retained 2-NBDG uptake inhibition

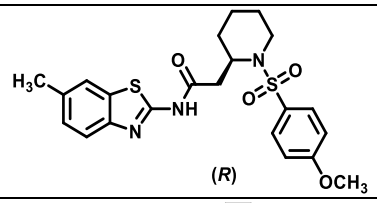
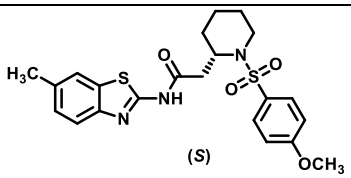
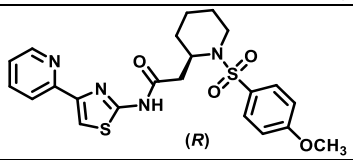
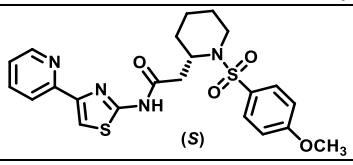
($IC_{50}$ = 0.45 $\mu$M) and *T. brucei* growth inhibition ($EC_{50}$ = 7.6 $\mu$M), but also gained activity against *L. donovani* axenic amastigotes ($EC_{50}$ = 8.3 $\mu$M). The HCl salt form **BDGR-9054** has been made which showed similar activity profile to the parent compound **BDGR-9049**. More importantly, compound **BDGR-9054** showed a great improvement in solubility (16.9 $\mu$M, **Figure 4-10**) vs the hit compound **BDGR-9014**. To some extent, **BDGR-9049** and **BDGR-9054** showed some toxicity ($CC_{50}$ = 18 $\mu$M and 22 $\mu$M). But we are in the early stage of the optimization, this problem can be fixed in the future based on the non-toxic profile of the other molecules.

**Table 4-4.** SAR of sulfonylpiperidin-2-yl-*N*-arylacetamide series

| Cmpd. ID |  | | | *T. brucei* PCF 2-NBDG uptake inhibition, $IC_{50}$ ($\mu$M) | *T. brucei* BSF growth inhibition, $EC_{50}$ ($\mu$M) | *L. donovani* axenic amastigote growth inhibition, $EC_{50}$ ($\mu$M) | HEK293 cell toxicity, $CC_{50}$ ($\mu$M) |
|---|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | n | | | | |
| **BDGR-9014** |  | $OCH_3$ | 1 | 0.51 ± 0.17 | 4.9 ± 0.5 | > 25 | > 50 |
| **BDGR-9034** | | $OCH_3$ | 0 | > 50 | > 10 | > 25 | > 50 |
| **BDGR-9050** | | $CH_3$ | 1 | 5.5 ± 1.2 | > 10 | > 25 | > 50 |
| **BDGR-9051** | | F | 1 | 3.7 ± 0.8 | 6.1 ± 0.7 | ND | > 50 |
| **BDGR-9048** |  | $OCH_3$ | 1 | 0.67 ± 0.06 | > 10 | > 12.5 | > 50 |
| **BDGR-9049** |  | $OCH_3$ | 1 | 1.5 ± 0.2 | > 10 | > 25 | > 50 |
| **BDGR-9046** |  | $OCH_3$ | 1 | 0.45 ± 0.05 | 7.6 ± 2.3 | 8.3 ± 2.8 | 18 |
| **BDGR-9054** |  | $OCH_3$ | 1 | 0.84 ± 0.03 | 8.5 ± 0.9 | 8.2 ± 0.5 | 22 |

Since the compounds in this series are racemic, an enzymatic kinetic resolution method[24] (described in the previous section, **Scheme 4-2**) was used for the synthesis of each enantiomers of **BDGR-9014** and **BDGR-9054,** for the purpose of figuring out if one enantiomer would be more active than the other. The activity data has been shown in **Table 4-5**.

**Table 4-5.** Data for the Enantiomers of **BDGR-9014** and **BDGR-9054**

| Cmpd. ID | Structure | *T. brucei* PCF 2-NBDG uptake inhibition, $IC_{50}$ ($\mu$M) | *T. brucei* BSF growth inhibition, $EC_{50}$ ($\mu$M) | *L. donovani* axenic amastigote growth inhibition, $EC_{50}$ ($\mu$M) |
|---|---|---|---|---|
| **BDGR-9063** |  | 3.2 ± 0.8 | 9.8 ± 1.4 | > 25 |
| **BDGR-9065** |  | 0.97 ± 0.29 | > 10 (44% @ 10 $\mu$M) | > 25 |
| **BDGR-9062** |  | 2.1 ± 0.6 | 9.4 ± 2.9 | 10 |
| **BDGR-9064** |  | 0.56 ± 0.09 | 6.2 ± 0.3 | 10 |

Although both of the (*S*)-enantiomers (**BDGR-9064** and **BDGR-9065**) showed slightly better (3~4-fold) activity than the (*R*)-enantiomers (**BDGR-9062** and **BDGR-9063)** against the 2-NBDG uptake activity, the overall differences of antiparasitic profiles between the (*R*)- and (*S*)-enantiomers are limited. For enantiomers of **BDGR-9014**, the (*S*)-enantiomer **BDGR-9065** was the more active configuration to inhibit the 2-NBDG uptake of the PCF *T. brucei* ($IC_{50}$ = 0.97 $\mu$M) than the (*R*)-configuration (**BDGR-9063**, $IC_{50}$ = 3.2 $\mu$M). The (*R*)-enantiomer displayed an $EC_{50}$ value of 9.8 $\mu$M against the growth inhibition of BSF *T. brucei*. The corresponding (*S*)-enantiomer (**BDGR-9065**) showed 44% inhibition rate at 10 $\mu$M, indicating the $EC_{50}$ values would be slightly over 10 $\mu$M, which was similar to the (*R*)-enantiomer. The enantiomers of **BDGR-9054** has the similar trend. The (*S*)-enantiomer **BDGR-9064** was slightly more active against the 2-NBDG uptake of the PCF *T. brucei* ($IC_{50}$ = 0.56 $\mu$M) than the (*R*)-enantiomer. However, both enantiomers

exhibited similar antiparasitic activities against BSF *T. brucei* ($EC_{50}$ = 6 ~ 9 $\mu$M) and *L. donovani* axenic amastigote ($EC_{50}$ = 10 $\mu$M).

In summary, the preliminary SAR of **BDGR-9014** series has been investigated (**Figure 4-10**). Finally, the optimized compound **BDGR-9054** not only retained the glucose uptake inhibition and *T. brucei* growth inhibition, but also gained some activity against *L. donovani* axenic amastigotes and improvement in solubility.

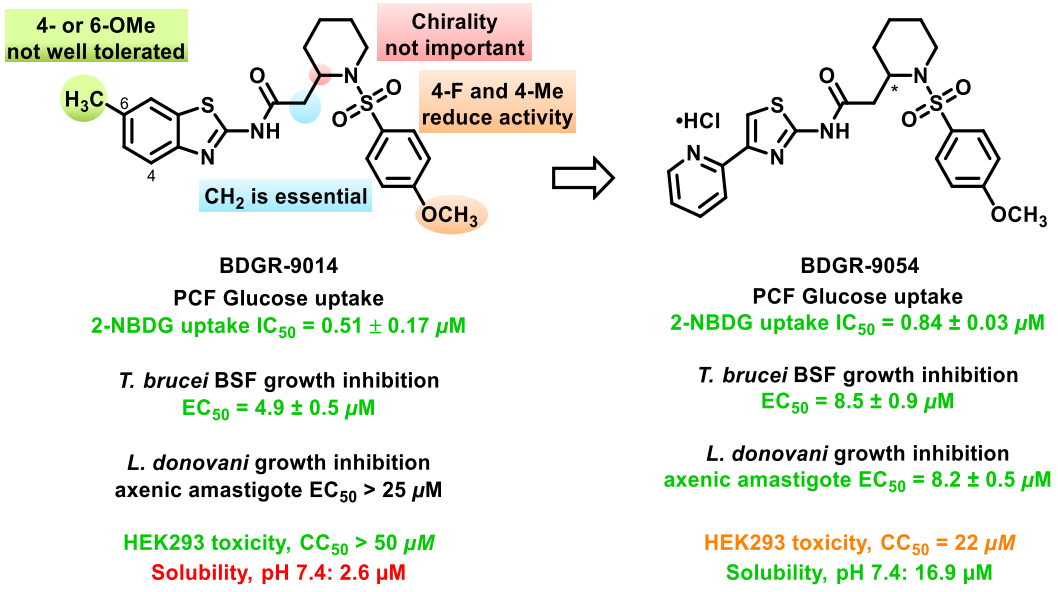



**Figure 4-10.** Summary of **BDGR-9014** series

## ***Specificity against T. brucei versus human cells***

The specificity of the above compounds for blocking the kinetoplastid glucose transport versus human glucose transporters (hGLUTs) is a very important parameters for the understanding of the potential toxicity profiles, although the $CC_{50}$ of these compounds against HEK293 cell line are at least 3-fold greater than the potency ($IC_{50}$ or $EC_{50}$), and the known mammalian glucose transport inhibitors phloretin and cytochalasin B, which showed great specificity to hGLUTs vs *T.*

*brucei*,[26] are structurally significantly different from the compounds for the screening and SAR studies.

In order to get some insight into the specificity, we assessed the activity of these compounds on glucose uptake in HEK293 cells, which are known to express hGLUT1. This approach in HEK293 cells was similar to the 2-NBDG uptake assay[25] performed in the PCF *T. brucei*. As a result, most compounds showed no measurable inhibition (< 25%) on glucose uptake of HEK293 cells at 50 $\mu$M. These data indicated that all of the compounds exhibited great specificity for blocking the parasite glucose transport versus human glucose transporters.

## 4.4 Conclusions

The identification of parasite glucose uptake inhibitors was achieved via a high-throughput screening method. A total number of 15 initial hit compounds and more than 50 derivatives were synthesized to validate their glucose uptake inhibition and growth inhibition of the parasite. Preliminary structure-activity relationship was investigated. As a result, two scaffolds were validated to block the glucose transport of PCF *T. brucei* parasites and growth inhibition of BSF *T. brucei* parasites with micromolar to submicromolar activity. In addition, one scaffold was active against both BSF *T. brucei* and *L. donovani* with submicromolar activity. These hits have also showed great specificity for blocking the parasite, rather than human, glucose uptake.

## 4.5 Perspective and future directions

### ***SAR and SPR Studies of the Hit compounds***

These compounds displayed good potency against the glucose uptake of PCF *T. brucei* and the growth inhibition of the parasites as hit compounds. However, they are not perfect molecules

and still have some problems that are needed to be optimized in the next hit to lead optimization stage in terms of potency and other properties.

**Potency**

Compounds **BDGR-9032** and **BDGR-9054** exhibits good, although improvable, potency ($IC_{50}$ = 0.28 $\mu$M and 0.84 $\mu$M, respectively) against glucose uptake of PCF *T. brucei*. However, the antiparasitic activity is modest, only in the micromolar range. At the same time, only limited compounds have been synthesized, which only covers a small portion of the chemical space. Therefore, further SAR studies are needed to improve the potency against the glucose uptake and the antiparasitic activities in the future.

**Solubility**

Solubility is a critical property for a drug-like molecule. Compounds **BDGR-9032** and **BDGR-9029** showed poor solubilities (2.4 $\mu$M and 2 $\mu$M at pH = 7.4, respectively). From the structure of these two scaffolds, both scaffolds are highly aromatic/planar molecules. It is known that breaking the planarity and aromaticity of the molecules will reduce the crystal packing and increase the solubility.[27] Therefore, switching the aromatic rings to sp3-richer ring will be a strategy for improving the solubility of the molecules.

**Toxicity**

From the data above, some molecules showed some toxicity with a $CC_{50}$ about ~20 $\mu$M against HEK293 cell. The selectivity index is still acceptable at this stage. However, the potential toxicity issue is still a property that needed to be focused in the future.

In summary, a more in-depth structure modifications will be performed to investigate more chemical space of each scaffold and to tune the activity and other properties.

## 4.6 Acknowledgement

The authors acknowledge funding from the National Institutes of Health (1R21AI127575-01). This work made use of instrumentation at the UW−Madison Medicinal Chemistry Center and Analytical Instrumentation Center, funded by the UW School of Pharmacy. Gang Yan are thankful to the collaborators Dr. Kenneth A. Christensen's laboratory from Brigham Young University for measuring the glucose uptake inhibition of PCF *T. brucei*, Dr. James Morris's laboratory from Clemson University for measuring the growth inhibition against BSF *T. brucei* and Dr. Karl Werbovetz's laboratory from the Ohio State University for measuring the growth inhibition against *L. donovani*.

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## 4.8 Experimental section

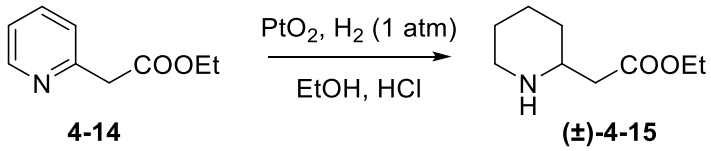
### *4.8.1. General information*

Commercial reagents and solvents were used as received from Sigma Aldrich, Fischer Scientific, Acros Organics, TCI America, Oakwood Products Inc, VWR International, etc. All thin layer chromatography was performed using precoated silica gel plates. Flash chromatography separations were carried out using a Teledyne Isco CombiFlash Rf 200 purification system with silica gel columns. Melting points were measured on OptiMelt MPA100 Automated Melting Point System. $^{1}H$ and $^{13}C$ nuclear magnetic resonance (NMR) spectra were obtained on a Varian Unity-Inova 400 MHz or 500 MHz, or Bruker Ascend 400 MHz in $CDCl_3$ or DMSO-$d_6$. The chemical shifts (δ) reported are given in parts per million (ppm). The Signal splitting patterns were described as s = singlet, d = doublet, t = triplet, q = quartet, p = pentuplet, dd = doublet of doublet, dt = doublet of triplet, td = triplet of doublet, tt = triplet of triplet, ddd = doublet of doublet of doublet, and m = multiplet, with coupling constants (*J*) in hertz (Hz). The chemical shifts of $^{19}F$ NMR was referenced by "Absolute Reference" of MestReNova. High resolution mass spectra (HRMS) were performed by Analytical Instrument Center at the School of Pharmacy on an Electron Spray Injection (ESI) mass spectrometer. All final compounds were determined to be of $\geq$ 95% purity by UV-LCMS at 254 nm.

### *4.8.2. Experimental Procedures and Product Characterization*

#### 4.8.2.1 Synthesis of intermediates

**4.8.2.1.1 Synthesis of ethyl 2-(piperidin-2-yl)acetate and each enantiomers through a kinetic resolution method**




**4-14** **(±)-4-15**

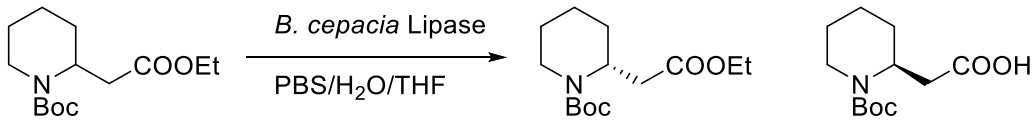
***(rac)*-Ethyl 2-(piperidin-2-yl)acetate** (**(±)-4-15** or **4-115-1-GY**) To a stirred solution of ethyl-2-pyridyl acetate (**4-14**, 3.3 g, 20 mmol) in EtOH (40 mL) and 6 M HCl(aq) (8 mL) was added $PtO_2$ (56 mg, 0.24 mmol). The reaction flask evacuated under reduced pressure and back filled with $N_2$ three times. After a final evacuation, a balloon of hydrogen was added and the reaction mixture was stirred vigorously at room temperature for 24 h. The mixture was filtered through Celite and washed with EtOH (50 mL) and the filtrate was evaporated under reduced pressure. Then, the residue was dissolved in 2 M $NH_4OH$(aq) (50 mL) and the aqueous layer was extracted with DCM (5 × 30 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and evaporated under reduced pressure to give the product. Yield: 2.4 g, 70%; colorless oil, which is used in the next step without further purification.




**(±)-4-15** **(±)-4-19**

***Tert*-Butyl 2-(2-ethoxy-2-oxoethyl)piperidine-1-carboxylate (**(±)-4-19** or **4-176-1-GY)** A solution of di-*tert*-butyl dicarbonate (**(±)-4-15,** 1.962 g, 9 mmol) in $CH_2Cl_2$ (5 mL) was added dropwise a stirred solution of ethyl 2-(piperidin-2-yl)acetate (1.539 g, 9 mmol) in $CH_2Cl_2$ (25 mL) at 0 °C. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. Then, 1 M HCl(aq) was added, the mixture was extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and evaporated under reduced pressure to give the product.

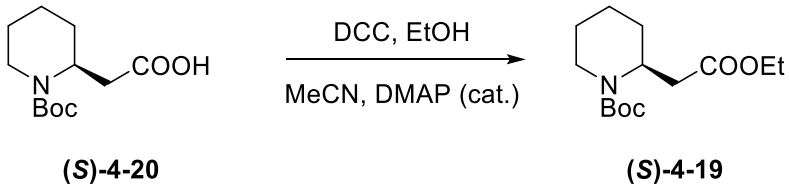
Yield: 2.39 g, 98%; colorless oil. $^{1}$H NMR (500 MHz, Chloroform-*d*) δ 4.70 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.99 (d, *J* = 13.4 Hz, 1H), 2.78 (t, *J* = 13.1 Hz, 1H), 2.61 – 2.46 (m, 2H), 1.70 – 1.57 (m, 4H), 1.56 – 1.33 (m, 11H), 1.25 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 171.5, 154.8, 79.6, 60.6, 48.0, 39.4, 35.5, 28.5, 28.3, 25.4, 19.0, 14.3.




**(±)-4-19** **(*R*)-4-19** **45%** **>99:1 e.r.** **(*S*)-4-20** 49%

Following the same procedure as the reference[1]: A solution of *tert*-Butyl 2-(2-ethoxy-2-oxoethyl)piperidine-1-carboxylate (**(±)-4-19**, 1.355 g, 5 mmol) in THF (2 mL) was added in one portion to a gently stirred 1:1 mixture of 0.1 M phosphate buffer (pH 7.0) and $H_2O$ (20 mL). Lipase from *Burkholderia cepacia* (1.355 g) was added in one portion and the reaction was stirred at 35 °C for 39 h. The reaction mixture was cooled to rt, filtered through Celite® and washed with $H_2O$ (10 mL) and $Et_2O$ (10 mL). saturated $Na_2CO_3$(aq) (20 mL) was added to the filtrate. The mixture was extracted with $Et_2O$ (3 × 30 mL) and the combined organic layers were dried with $Na_2SO_4$, filtered and evaporated under reduced pressure to give ***tert*-butyl (*R*)-2-(2-ethoxy-2-oxoethyl)piperidine-1-carboxylate** (**(*R*)-4-19** or **(*R*)-4-178-2-GY**) (Yield: 610 mg, 49%; colorless oil; e.r. (*S/R*) = 99:1. CSP-HPLC: Chiralcel AD-H (95:5 hexane:i-PrOH, 1.0 mL/min) **(*R*)-enantiomer** 5.4 min, **(*S*)-enantiomer** was not observed). The aqueous layer was acidified with 1 M HCl (aq) and extracted with $Et_2O$ (3 × 30 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and evaporated under reduced pressure to give acid **(*S*)-2-(1-(*tert*-butoxycarbonyl)piperidin-2-**

**yl)acetic acid** (**(*S*)-4-20** or **(*S*)-4-178-1-GY** (Yield: 595 mg, 45%; colorless oil). Both product was used in the next step without further purification.




**(*S*)-4-20** **(*S*)-4-19**

**(*R*)-2-(2-ethoxy-2-oxoethyl)piperidine-1-carboxylate ((*S*)-4-19, 4-184-1-GY)** To a mixture of (*S*)-2-(1-(*tert*-butoxycarbonyl) piperidin-2-yl)acetic acid (**(*S*)-4-20**, 729 mg, 3 mmol), DMAP (37 mg, 0.3 mmol), EtOH (0.6 mL, 10 mmol) in MeCN (20 mL) was added DCC (681 mg, 3.3 mmol) at room temperature. The mixture was stirred at room temperature for 2 hours. After the completion of the reaction, the precipitated solids was removed by filtration and washed with MeCN (2 mL). The filtrate was concentrated under reduced pressure. Then 1 M HCl (20 mL) and $Et_2O$ (20 mL) was added into the mixture. The aqueous layer was extracted with $Et_2O$ (3 ×20 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and evaporated under reduced pressure to give the product, which was used in the next step without further purification. Yield: 780 mg, 96%; colorless oil, e.r. (*S/R*) = 99:1. CSP-HPLC: Chiralcel AD-H (95:5 hexane:i-PrOH, 1.0 mL/min) **(*R*)-enantiomer** 5.4 min (< 1%), **(*S*)-enantiomer** 6.0 min (> 99%)

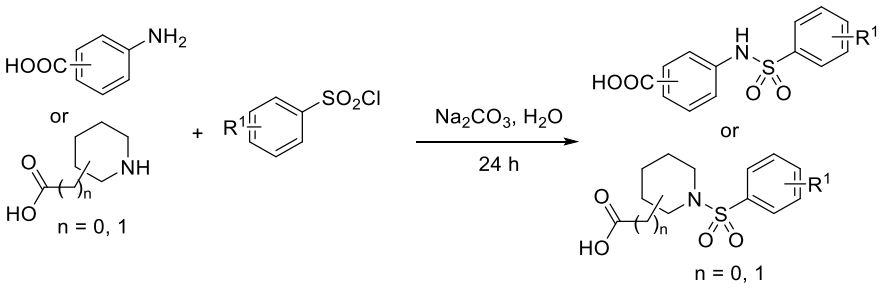



***(R)* or *(S)*-Ethyl 2-(piperidin-2-yl)acetate** Boc-deprotection of the chiral intermediates: To a solution of the give chiral *tert*-butyl 2-(2-ethoxy-2-oxoethyl)piperidine-1-carboxylate (542 mg, 2

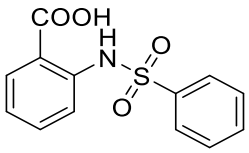
mmol) in DCM (4 mL) was added 2 mL TFA. The mixture was stirred at room temperature for 1 hour. After the completion of the reaction, the solvent was removed to give the product in quantitative yield, which is used in the next step without further purification.

#### 4.8.2.1.2 Synthesis of substituted phenylsulfonamido acid

**Method 1:**

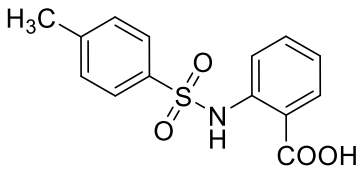



**General procedure**: To a suspension of appropriate amino acid or substituted amino benzoic acid (10 mmol) and substituted benzenesulfonyl chloride (10 mmol) in water (50 mL) was added saturated $Na_2CO_3$ solution in water (30 mL). The reaction mixture was stirred at room temperature for 24 hours. After the completion of the reactions, the mixture was acidified with 6N HCl to adjust pH = 3. The precipitated solids were filtered out, washed with water and dried under vacuum to give the pure product.

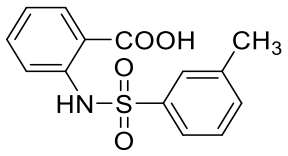



**2-(phenylsulfonamido)benzoic acid (4-72-1-GY)** The reaction was performed with anthranilic acid (2.74g, 20 mmol), benzenesulfonyl chloride (2.03 mL, 20 mmol), saturated aq. $Na_2CO_3$ (60

mL) and water (100 mL). Yield: 4.37 g, 79%; white solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 11.15 (s, 1H), 7.89 (dd, $J$ = 7.8, 1.5 Hz, 1H), 7.86 – 7.76 (m, 2H), 7.67 – 7.61 (m, 1H), 7.61 – 7.48 (m, 4H), 7.18 – 7.07 (m, 1H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.8, 139.7, 138.5, 134.5, 133.6, 131.5, 129.5, 126.8, 123.4, 118.5, 116.8.

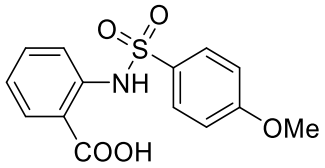



**2-((4-methylphenyl)sulfonamido)benzoic acid (3-207-1-GY)** The reaction was performed with anthranilic acid (1.37g, 10 mmol), 4-methylbenzenesulfonyl chloride (1.91 g, 10 mmol), saturated aq. $Na_2CO_3$ (30 mL) and water (50 mL). Yield: 2720 mg, 93%; white solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 11.12 (s, 1H), 7.90 (dd, $J$ = 7.9, 1.5 Hz, 1H), 7.71 (d, $J$ = 8.3 Hz, 2H), 7.62 – 7.47 (m, 2H), 7.36 (d, $J$ = 8.0 Hz, 2H), 7.12 (ddd, $J$ = 8.2, 6.8, 1.7 Hz, 1H), 2.34 (s, 3H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.8, 144.1, 139.9, 135.7, 134.5, 131.5, 130.0, 126.9, 123.2, 118.3, 116.5, 21.0.

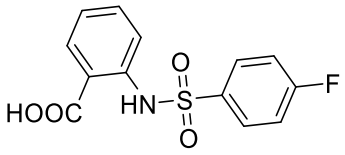



**2-((3-methylphenyl)sulfonamido)benzoic acid (4-102-1-GY)** The reaction was performed with anthranilic acid (1.37g, 10 mmol), 3-methylbenzenesulfonyl chloride (1.91 g, 10 mmol), saturated aq. $Na_2CO_3$ (30 mL) and water (50 mL). Yield: 2.31 g, 79%; white solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 11.11 (s, 1H), 7.89 (dd, $J$ = 7.9, 1.5 Hz, 1H), 7.69 – 7.63 (m, 1H), 7.63 – 7.58 (m,

1H), 7.58 – 7.48 (m, 2H), 7.48 – 7.40 (m, 2H), 7.12 (ddd, *J* = 8.2, 7.0, 1.5 Hz, 1H), 2.33 (s, 3H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.8, 139.8, 139.4, 138.6, 134.5, 134.2, 131.5, 129.3, 127.0, 124.0, 123.3, 118.4, 116.7, 20.7.

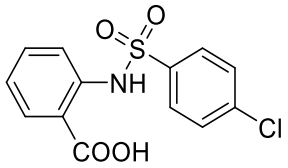



**2-((4-methoxyphenyl)sulfonamido)benzoic acid (4-74-1-GY)** The reaction was performed with anthranilic acid (2.74g, 20 mmol), 4-methoxybenzenesulfonyl chloride (4.01 g, 20 mmol), saturated aq. $Na_2CO_3$ (60 mL) and water (100 mL). Yield: 4.89 g, 80%; white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.05 (s, 1H), 7.90 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.80 – 7.73 (m, 2H), 7.60 – 7.49 (m, 2H), 7.12 (ddd, *J* = 8.2, 6.8, 1.8 Hz, 1H), 7.09 – 7.01 (m, 2H), 3.80 (s, 3H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.8, 162.9, 140.0, 134.6, 131.6, 130.0, 129.2, 123.2, 118.2, 116.5, 114.7, 55.7.

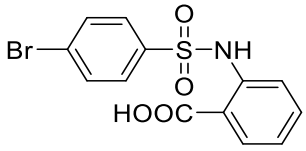



**2-((4-fluorophenyl)sulfonamido)benzoic acid (4-44-1-GY)** The reaction was performed with anthranilic acid (1.37g, 10 mmol), 4-fluorobenzenesulfonyl chloride (1.95 g, 10 mmol), saturated aq. $Na_2CO_3$ (30 mL) and water (50 mL). Yield: 2090 mg, 71%; white solid. $^1$H NMR (500 MHz, Chloroform-*d*) δ 10.41 (s, 1H), 8.05 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.94 – 7.86 (m, 2H), 7.69 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.54 (ddd, *J* = 8.6, 7.3, 1.6 Hz, 1H), 7.19 – 7.05 (m, 3H). $^{13}$C NMR (126 MHz,

Chloroform-*d*) δ 172.5, 165.5 (d, *J* = 255.9 Hz), 140.9, 135.9, 135.3 (d, *J* = 3.3 Hz), 132.6, 130.2 (d, *J* = 9.5 Hz), 123.6, 119.1, 116.6 (d, *J* = 22.7 Hz), 114.9. $^{19}$F NMR (470 MHz, Chloroform-*d*) δ -103.90.

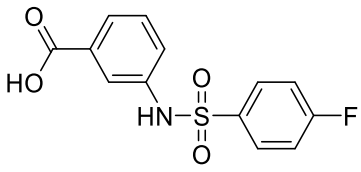



**2-((4-chlorophenyl)sulfonamido)benzoic acid (4-73-1-GY)** The reaction was performed with anthranilic acid (2.74g, 20 mmol), 4-chlorobenzenesulfonyl chloride (4.22 g, 20 mmol), saturated aq. $Na_2CO_3$ (60 mL) and water (100 mL). Yield: 3.92 g, 63%; white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.10 (s, 1H), 7.90 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.87 – 7.77 (m, 2H), 7.68 – 7.60 (m, 2H), 7.56 (ddd, *J* = 8.7, 7.2, 1.7 Hz, 1H), 7.49 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.15 (td, *J* = 7.6, 1.3 Hz, 1H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.6, 139.3, 138.5, 137.4, 134.6, 131.6, 129.7, 128.8, 123.8, 118.8, 117.2.

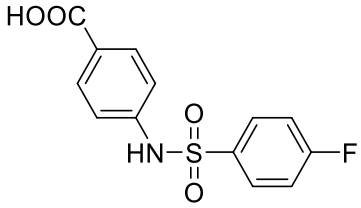



**2-((4-bromophenyl)sulfonamido)benzoic acid (4-103-1-GY)** The reaction was performed with anthranilic acid (2.74g, 20 mmol), 4-bromobenzenesulfonyl chloride (5.11 g, 20 mmol), saturated aq. $Na_2CO_3$ (60 mL) and water (100 mL). Yield: 5.03 g, 71%; white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.74 (s, 1H), 7.90 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.83 – 7.68 (m, 4H), 7.53 (ddd, *J* = 8.7,

7.2, 1.7 Hz, 1H), 7.46 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.17 – 7.08 (m, 1H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 169.6, 139.8, 138.2, 134.3, 132.6, 131.5, 128.8, 127.3, 123.4, 118.7, 117.6.

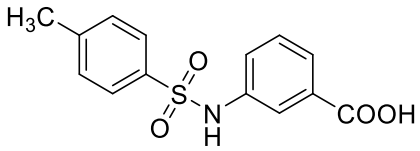


**3-((4-fluorophenyl)sulfonamido)benzoic acid (4-51-1-GY)** The reaction was performed with 3-aminobenzoic acid (2.74g, 20 mmol), 4-fluorobenzenesulfonyl chloride (3.9 g, 20 mmol), saturated aq. $Na_2CO_3$ (60 mL) and water (100 mL). Yield: 4.74 g, 80%; white solid. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 13.05 (s, 1H), 10.53 (s, 1H), 7.84 – 7.78 (m, 2H), 7.68 (t, *J* = 1.9 Hz, 1H), 7.61 (dt, *J* = 7.4, 1.5 Hz, 1H), 7.43 – 7.32 (m, 4H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 166.7, 164.4 (d, *J* = 251.8 Hz), 137.8, 135.6 (d, *J* = 3.0 Hz), 131.8, 129.7 (d, *J* = 9.7 Hz), 129.6, 125.1, 124.3, 120.8, 116.6 (d, *J* = 22.8 Hz). $^{19}$F NMR (470 MHz, DMSO-$d_6$) δ -106.23.

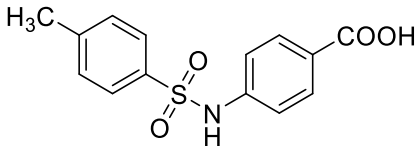


**4-((4-fluorophenyl)sulfonamido)benzoic acid (4-50-1-GY)** The reaction was performed with 4-aminobenzoic acid (2.74g, 20 mmol), 4-fluorobenzenesulfonyl chloride (3.90 g, 20 mmol), saturated aq. $Na_2CO_3$ (60 mL) and water (100 mL). Yield: 4.75 g, 81%; white solid. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 12.75 (s, 1H), 10.84 (s, 1H), 7.92 – 7.85 (m, 2H), 7.84 – 7.78 (m, 2H), 7.45 – 7.37 (m, 2H), 7.23 – 7.17 (m, 2H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 166.7, 164.5 (d, *J* = 252.2

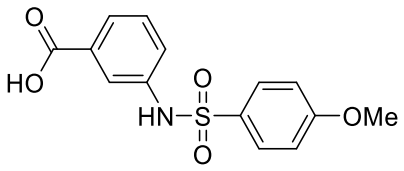
Hz), 141.7, 135.6 (d, *J* = 3.1 Hz), 130.8, 129.8 (d, *J* = 9.7 Hz), 125.9, 118.4, 116.7 (d, *J* = 22.9 Hz). $^{19}$F NMR (470 MHz, DMSO-$d_6$) δ -106.00.



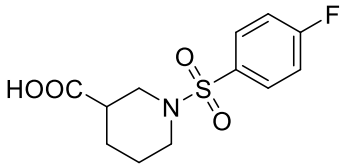

**3-((4-methylphenyl)sulfonamido)benzoic acid (4-66-1-GY)** The reaction was performed with 3-aminobenzoic acid (2.74g, 20 mmol), 4-methylbenzenesulfonyl chloride (3.81 g, 20 mmol), saturated aq. $Na_2CO_3$ (60 mL) and water (100 mL). Yield: 4.96 g, 85%; white solid. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 13.03 (s, 1H), 10.45 (s, 1H), 7.69 (t, *J* = 2.1 Hz, 1H), 7.66 – 7.62 (m, 2H), 7.58 (dt, *J* = 6.9, 1.8 Hz, 1H), 7.38 – 7.30 (m, 4H), 2.32 (s, 3H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 166.7, 143.5, 138.2, 136.4, 131.7, 129.8, 129.5, 126.7, 124.7, 123.8, 120.3, 21.0.



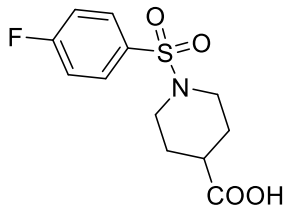

**3-((4-methylphenyl)sulfonamido)benzoic acid (4-67-1-GY)** The reaction was performed with 4-aminobenzoic acid (2.74g, 20 mmol), 4-methylbenzenesulfonyl chloride (3.81 g, 20 mmol), saturated aq. $Na_2CO_3$ (60 mL) and water (100 mL). Yield: 4.12 g, 71%; white solid. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 12.73 (s, 1H), 10.74 (s, 1H), 7.83 – 7.77 (m, 2H), 7.74 – 7.68 (m, 2H), 7.38 – 7.33 (m, 2H), 7.22 – 7.16 (m, 2H), 2.32 (s, 3H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 166.8, 143.7, 142.1, 136.4, 130.7, 129.9, 126.8, 125.5, 118.0, 21.0.



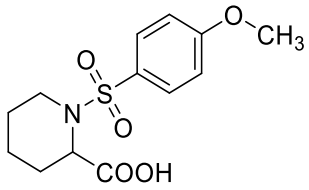
**3-((4-methoxyphenyl)sulfonamido)benzoic acid (4-118-1-GY)** The reaction was performed with 3-aminobenzoic acid (1.37g, 10 mmol), 4-methoxybenzenesulfonyl chloride (2.02 g, 10 mmol), saturated aq. $Na_2CO_3$ (30 mL) and water (50 mL). Yield: 2.66 g, 87%; white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 13.02 (s, 1H), 10.37 (s, 1H), 7.73 – 7.65 (m, 3H), 7.61 – 7.54 (m, 1H), 7.39 – 7.31 (m, 2H), 7.10 – 7.02 (m, 2H), 3.78 (s, 3H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 166.8, 162.5, 138.3, 131.7, 130.8, 129.5, 128.9, 124.7, 123.8, 120.3, 114.5, 55.6.



**1-((4-fluorophenyl)sulfonyl)piperidine-3-carboxylic acid (4-127-1-GY)** The reaction was performed with piperidine-3-carboxylic acid (2.58g, 20 mmol), 4-fluorobenzenesulfonyl chloride (3.90 g, 20 mmol), saturated aq. $Na_2CO_3$ (60 mL) and water (100 mL). Yield: 5.05 g, 88%; white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.52 (s, 1H), 7.88 – 7.76 (m, 2H), 7.54 – 7.43 (m, 2H), 3.60 – 3.47 (m, 1H), 3.32 – 3.25 (m, 1H), 2.59 – 2.51 (m, 2H), 2.42 (td, $J$ = 10.9, 3.0 Hz, 1H), 1.86 – 1.65 (m, 2H), 1.57 – 1.29 (m, 2H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 173.7, 164.6 (d, $J$ = 251.7 Hz), 131.8 (d, $J$ = 3.0 Hz), 130.5 (d, $J$ = 9.6 Hz), 116.7 (d, $J$ = 22.7 Hz), 47.4, 46.0, 25.5, 23.4. $^{19}$F NMR (376 MHz, DMSO-$d_6$) δ -106.46.

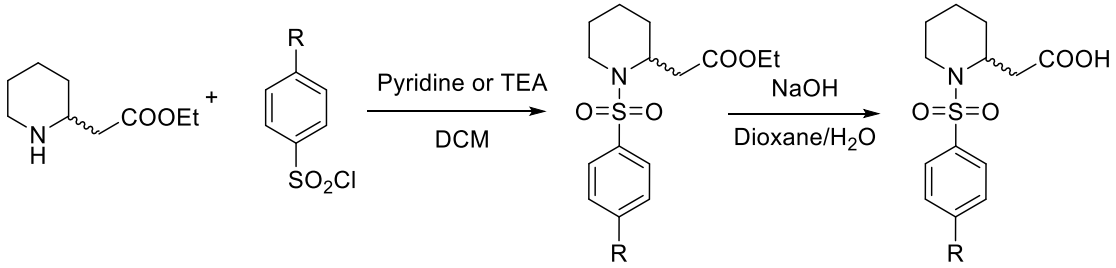



**1-((4-fluorophenyl)sulfonyl)piperidine-4-carboxylic acid (3-199-1-GY)** The reaction was performed with piperidine-4-carboxylic acid (516 mg, 4 mmol), 4-fluorobenzenesulfonyl chloride (973 mg, 5 mmol), saturated aq. $Na_2CO_3$ (30 mL) and water (50 mL). Yield: 976 mg, 68%; white solid. $^1$H NMR (400 MHz, Chloroform-*d*) δ 11.11 (s, 1H), 7.78 (dd, *J* = 8.7, 5.1 Hz, 2H), 7.22 (t, *J* = 8.5 Hz, 2H), 3.64 (dt, *J* = 12.0, 4.2 Hz, 2H), 2.51 (td, *J* = 11.4, 2.9 Hz, 2H), 2.32 (tt, *J* = 10.5, 4.0 Hz, 1H), 2.09 – 1.93 (m, 2H), 1.93 – 1.72 (m, 2H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 179.8, 165.2 (d, *J* = 255.1 Hz), 132.3 (d, *J* = 3.3 Hz), 130.3 (d, *J* = 9.3 Hz), 116.4 (d, *J* = 22.5 Hz), 45.3, 39.7, 27.1.

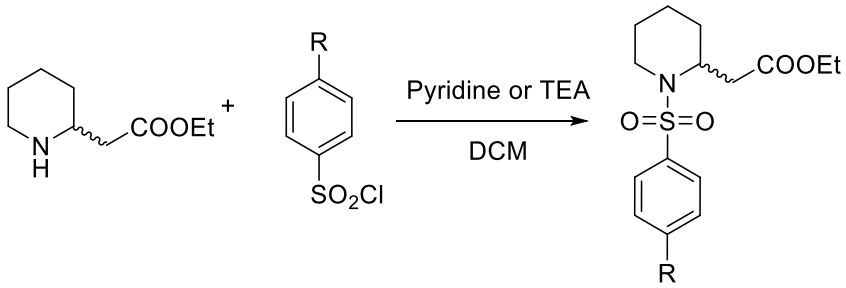



**1-((4-methoxyphenyl)sulfonyl)piperidine-2-carboxylic acid (4-76-1-GY)** The reaction was performed with piperidine-2-carboxylic acid (2.58g, 20 mmol), 4-methoxybenzenesulfonyl chloride (4.01 g, 20 mmol), saturated aq. $Na_2CO_3$ (60 mL) and water (100 mL). Yield: 3.86g, 65%; white solid. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 12.83 (s, 1H), 7.74 – 7.68 (m, 2H), 7.11 – 7.04 (m, 2H), 4.56 – 4.48 (m, 1H), 3.83 (s, 3H), 3.64 – 3.54 (m, 1H), 3.20 – 3.13 (m, 1H), 2.01 – 1.94 (m, 1H), 1.59 – 1.47 (m, 3H), 1.24 – 1.14 (m, 2H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 171.9, 162.3, 131.9, 128.9, 114.3, 55.6, 54.5, 42.1, 27.1, 24.0, 19.7.

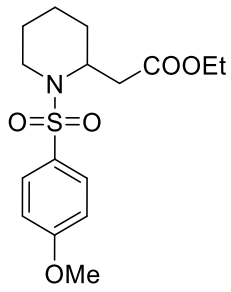
**Method 2:**



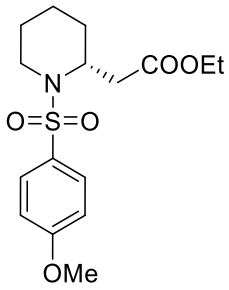

**Step 1:**




**Procedure:** A mixture of ethyl 2-(piperidin-2-yl)acetate or the amines (5 mmol, 1 equiv), substituted benzenesulfonyl chloride or methyl 4-(chlorosulfonyl)benzoate (5 mmol, 1 equiv), pyridine or TEA (10 mmol, 2 equiv) and DCM (20 mL) was stirred at room temperature overnight. After the completion of the reaction, the mixture was dilute with DCM (30 mL), extracted with aq. citric acid, aq. $NaHCO_3$ and brine. The organic layer was dried with $Na_2SO_4$, filtered and purified by flash column.

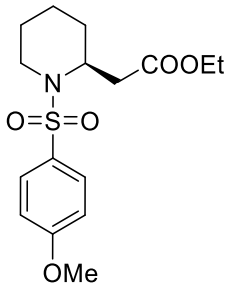


**(*rac*)-Ethyl 2-(1-((4-methoxyphenyl)sulfonyl)piperidin-2-yl)acetate (4-120-1-GY)** The reaction was performed with ethyl 2-(piperidin-2-yl)acetate (855 mg, 5 mmol), 4-methoxybenzenesulfonyl chloride (1008 mg, 5 mmol), pyridine (0.8 mL, 10 mmol) and DCM (20 mL) using the above method. Eluent: 15% - 25% Ethyl acetate/Hexane; yield: 708 mg, 42%; clear oil. $^{1}$H NMR (500 MHz, Chloroform-*d*) δ 7.80 – 7.72 (m, 2H), 7.00 – 6.91 (m, 2H), 4.56 – 4.50 (m, 1H), 4.16 – 4.05 (m, 2H), 3.87 (s, 3H), 3.81 – 3.74 (m, 1H), 2.98 – 2.90 (m, 1H), 2.62 (dd, *J* = 14.9, 9.3 Hz, 1H), 2.49 (dd, *J* = 14.9, 5.6 Hz, 1H), 1.60 – 1.45 (m, 5H), 1.39 – 1.31 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 170.9, 162.7, 132.9, 129.2, 114.3, 60.8, 55.6, 49.7, 41.0, 35.1, 27.7, 24.7, 18.4, 14.2.

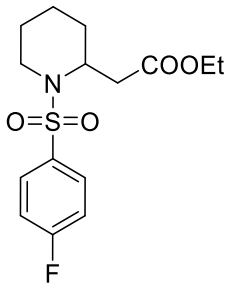



**Ethyl (*R*)-2-(1-((4-methoxyphenyl)sulfonyl)piperidin-2-yl)acetate (4-179-1-GY)** The reaction was performed with ethyl **(*R*)-**2-(piperidin-2-yl)acetate (342 mg, 2 mmol), 4-methoxybenzenesulfonyl chloride (455 mg, 2.2 mmol), TEA (1 mL, 7.7 mmol, to neutralized the TFA) and DCM (10 mL) using the above method. Eluent: 15% - 25% Ethyl acetate/Hexane; yield: 708 mg, 42%; clear oil; e. r. (*S*/*R*) = 3:97. CSP-HPLC: Chiralcel AD-H (90:10 hexane:i-PrOH, 1.0 mL/min) (*R*)-enantiomer 24.4 min (97%), (*S*)-enantiomer 20.9 min (3%).$^{1}$H NMR (500 MHz, Chloroform-*d*) δ 7.81 – 7.72 (m, 2H), 6.99 – 6.91 (m, 2H), 4.51 (d, *J* = 7.1 Hz, 1H), 4.11 (qd, *J* = 7.2, 4.5 Hz, 2H), 3.87 (s, 3H), 3.81 – 3.74 (m, 1H), 2.97 – 2.90 (m, 1H), 2.62 (dd, *J* = 14.9, 9.4 Hz,

1H), 2.49 (dd, *J* = 14.9, 5.6 Hz, 1H), 1.60 – 1.45 (m, 5H), 1.34 (qd, *J* = 13.1, 5.5 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H). Data is consistant with the racemic product.

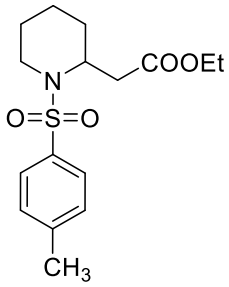



**Ethyl (*S*)-2-(1-((4-methoxyphenyl)sulfonyl)piperidin-2-yl)acetate (4-185-1-GY)** The reaction was performed with ethyl **(*R*)-**2-(piperidin-2-yl)acetate (342 mg, 2 mmol), 4-methoxybenzenesulfonyl chloride (455 mg, 2.2 mmol), TEA (1 mL, 7.7 mmol, to neutralized the TFA) and DCM (10 mL) using the above method. Eluent: 15% - 25% Ethyl acetate/Hexane; yield: 708 mg, 42%; clear oil; e. r. (*S*/*R*) > 99:1. CSP-HPLC: Chiralcel AD-H (90:10 hexane:i-PrOH, 1.0 mL/min) (*R*)-enantiomer 24.4 min (< 0.2%), (*S*)-enantiomer 20.9 min (> 99.8%). Data is consistant with the racemic product.



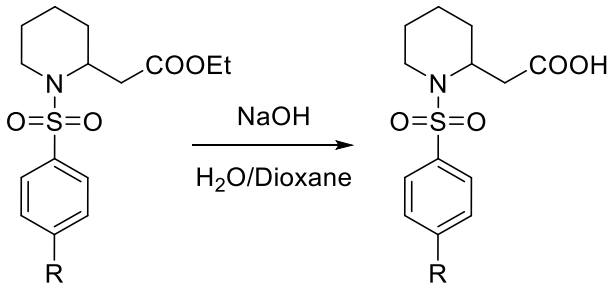

**(*rac*)-Ethyl 2-(1-((4-fluorophenyl)sulfonyl)piperidin-2-yl)acetate (4-125-1-GY)** The reaction was performed with ethyl 2-(piperidin-2-yl)acetate (342 mg, 2 mmol), 4-fluorobenzenesulfonyl

chloride (429 mg, 2.2 mmol), pyridine (0.24 mL, 3 mmol) and DCM (10 mL) using the above method. Eluent: 5% - 15% Ethyl acetate/Hexane; yield: 307 mg, 47%; clear oil. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 7.91 – 7.79 (m, 2H), 7.23 – 7.11 (m, 2H), 4.59 – 4.48 (m, 1H), 4.18 – 4.04 (m, 2H), 3.84 – 3.73 (m, 1H), 3.03 – 2.90 (m, 1H), 2.63 (dd, *J* = 14.9, 9.0 Hz, 1H), 2.50 (dd, *J* = 14.9, 5.9 Hz, 1H), 1.64 – 1.53 (m, 5H), 1.41 – 1.28 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 170.8, 165.0 (d, *J* = 254.3 Hz), 137.4 (d, *J* = 3.3 Hz), 129.8 (d, *J* = 9.2 Hz), 116.4 (d, *J* = 22.5 Hz), 60.9, 49.9, 41.2, 35.3, 27.9, 24.8, 18.4, 14.3. $^{19}$F NMR (376 MHz, Chloroform-*d*) δ -105.88.

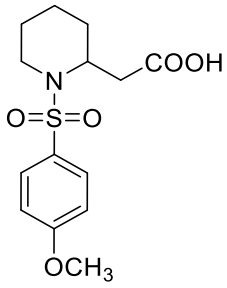



**(*rac*)-Ethyl 2-(1-((4-methylphenyl)sulfonyl)piperidin-2-yl)acetate (4-126-1-GY)** The reaction was performed with ethyl 2-(piperidin-2-yl)acetate (342 mg, 2 mmol), 4-methylbenzenesulfonyl chloride (420 mg, 2.2 mmol), pyridine (0.24 mL, 3 mmol) and DCM (10 mL) using the above method. Eluent: 15% - 25% Ethyl acetate/Hexane; yield: 333 mg, 51%; clear oil. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 7.76 – 7.68 (m, 2H), 7.33 – 7.27 (m, 2H), 4.59 – 4.48 (m, 1H), 4.18 – 4.03 (m, 2H), 3.86 – 3.75 (m, 1H), 3.02 – 2.88 (m, 1H), 2.62 (dd, *J* = 14.9, 9.3 Hz, 1H), 2.48 (dd, *J* = 14.9, 5.7 Hz, 1H), 2.42 (s, 3H), 1.59 – 1.49 (m, 5H), 1.40 – 1.31 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 171.0, 143.2, 138.3, 129.8, 127.1, 60.8, 49.8, 41.1, 35.2, 27.8, 24.7, 21.6, 18.4, 14.3.

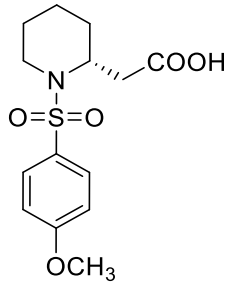
**Step 2:**



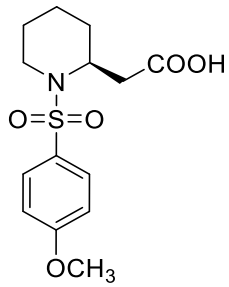

**Procedure**: A mixture of the above ester (2 mmol), 1N NaOH aq. (15 mL) and dioxane (20 mL) was stirred at room temperature for 3 hours. After the completion of the reaction, the organic solvent was removed under reduced pressure. The aqueous phase was acidified by 6 N HCl to pH = 3 and extracted with DCM (20 mL × 3). The combined organic layer was dried with $Na_2SO_4$, filtered and concentrated to give the product, which was used in the next step without further purification.



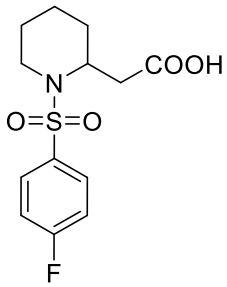

**(*rac*)-2-(1-((4-Methoxyphenyl)sulfonyl)piperidin-2-yl)acetic acid (4-121-1-GY)** The reaction was performed with ethyl 2-(1-((4-methoxyphenyl)sulfonyl)piperidin-2-yl)acetate (682 mg, 2 mmol) 1N NaOH aq. (15 mL) and dioxane (20 mL) using the above method. Yield: 556 mg, 89%; clear oil. The product was used in the next step without further purification.



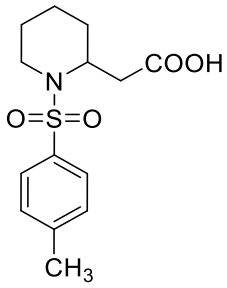

**(*S*)-2-(1-((4-Methoxyphenyl)sulfonyl)piperidin-2-yl)acetic acid (4-183-1-GY)** The reaction was performed with ethyl 2-(1-((4-methoxyphenyl)sulfonyl)piperidin-2-yl)acetate (470 mg, 1.4 mmol) 1N NaOH aq. (10 mL) and dioxane (15 mL) using the above method. Yield: 405 mg, 92%; clear oil. The product was used in the next step without further purification.




**(*R*)-2-(1-((4-Methoxyphenyl)sulfonyl)piperidin-2-yl)acetic acid (4-186-1-GY)** The reaction was performed with ethyl 2-(1-((4-methoxyphenyl)sulfonyl)piperidin-2-yl)acetate (470 mg, 1.4 mmol) 1N NaOH aq. (10 mL) and dioxane (15 mL) using the above method. Yield: 432 mg, 98%; clear oil. The product was used in the next step without further purification.

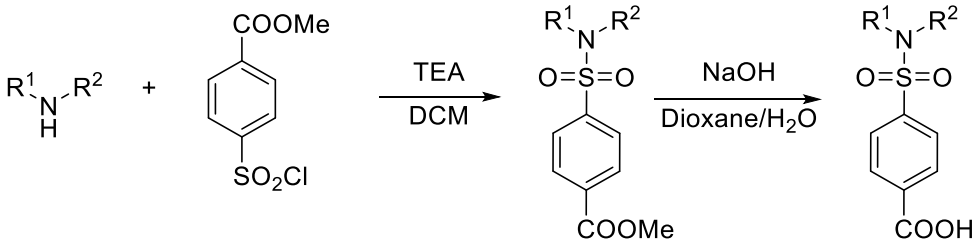



**(*rac*)-2-(1-((4-Fluorophenyl)sulfonyl)piperidin-2-yl)acetic acid (4-121-1-GY)** The reaction was performed with ethyl 2-(1-((4-fluorophenyl)sulfonyl)piperidin-2-yl)acetate (300 mg, 0.9 mmol) 1N NaOH aq. (8 mL) and dioxane (10 mL) using the above method. Yield: 269 mg, 99%; clear oil. The product was used in the next step without further purification.

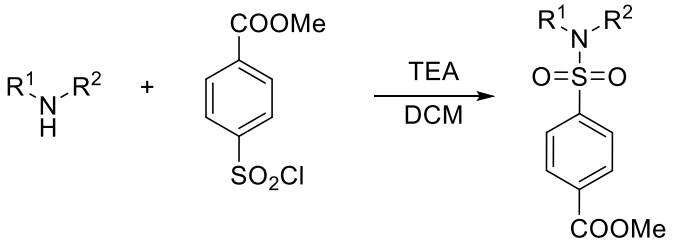



**(*rac*)-2-(1-((4-Methoxyphenyl)sulfonyl)piperidin-2-yl)acetic acid (4-121-1-GY)** The reaction was performed with ethyl 2-(1-((4-methylphenyl)sulfonyl)piperidin-2-yl)acetate (300 mg, 0.9 mmol) 1N NaOH aq. (8 mL) and dioxane (10 mL) using the above method. Yield: 267 mg, 99%; clear oil. The product was used in the next step without further purification.

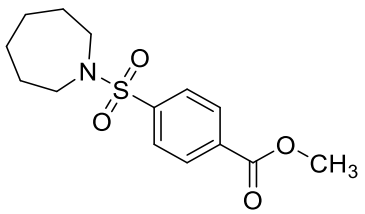
#### 4.8.2.1.3. Synthesis of 4-(*N*,*N*-disubstituted sulfamoyl)benzoic acid




**Step 1:**

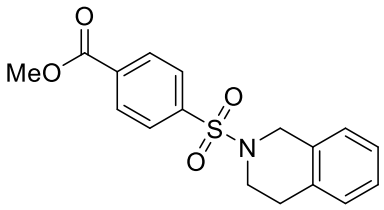



**Procedure:** A mixture of the above amines (3.6 mmol, 1.2 equiv), methyl 4-(chlorosulfonyl)benzoate (3 mmol, 1 equiv), pyridine or TEA (6 mmol, 2 equiv) and DCM (15 mL) was stirred at room temperature overnight. After the completion of the reaction, the mixture was dilute with DCM (30 mL), extracted with aq. citric acid, aq. $NaHCO_3$ and brine. The organic layer was dried with $Na_2SO_4$, filtered and purified by flash column.

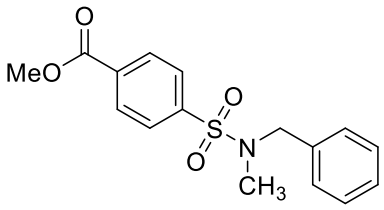



**Methyl 4-(azepan-1-ylsulfonyl)benzoate (3-210-1-GY)** The reaction was performed with azepane (0.41 mL, 3.6 mmol), methyl 4-(chlorosulfonyl)benzoate (704 mg, 3 mmol), TEA (0.96 mL, 6 mmol) and DCM (15 mL) using the above method. Eluent: 15% - 25% Ethyl acetate/Hexane; yield: 861 mg, 97%; white solid. $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.25 – 8.11 (m, 2H), 7.93

– 7.80 (m, 2H), 3.96 (s, 3H), 3.34 – 3.23 (m, 4H), 1.79 – 1.66 (m, 4H), 1.65 – 1.53 (m, 4H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 165.9, 143.7, 133.5, 130.4, 127.0, 52.7, 48.4, 29.3, 27.0.



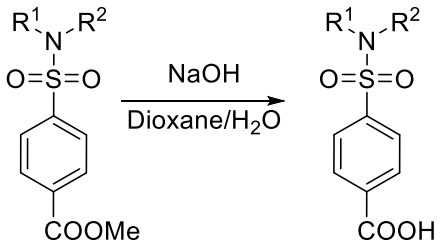

**Methyl 4-((3,4-dihydroisoquinolin-2(1*H*)-yl)sulfonyl)benzoate (3-213-1-GY)** The reaction was performed with 1,2,3,4-tetrahydroisoquinoline (0.45 mL, 3.6 mmol), methyl 4-(chlorosulfonyl)benzoate (704 mg, 3 mmol), TEA (0.96 mL, 6 mmol) and DCM (15 mL) using the above method. Eluent: 20% - 50% Ethyl acetate/Hexane; yield: 931 mg, 94%; white solid. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 8.18 (d, *J* = 8.1 Hz, 2H), 7.91 (d, *J* = 8.1 Hz, 2H), 7.20 – 7.11 (m, 2H), 7.11 – 6.99 (m, 2H), 4.31 (s, 2H), 3.95 (s, 3H), 3.42 (t, *J* = 5.9 Hz, 2H), 2.92 (t, *J* = 5.9 Hz, 2H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 165.7, 140.8, 134.1, 133.0, 131.4, 130.4, 129.0, 127.7, 127.0, 126.6, 126.4, 52.8, 47.6, 43.8, 28.9.



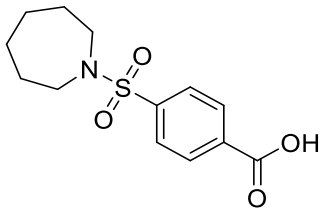

**Methyl 4-(N-benzyl-*N*-methylsulfamoyl)benzoate (3-214-1-GY)** The reaction was performed with *N*-methyl-1-phenylmethanamine (0.47 mL, 3.6 mmol), methyl 4-(chlorosulfonyl)benzoate (704 mg, 3 mmol), TEA (0.96 mL, 6 mmol) and DCM (15 mL) using the above method. Eluent:

20% - 50% Ethyl acetate/Hexane; yield: 865 mg, 90%; white solid. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 8.22 (d, *J* = 8.2 Hz, 2H), 7.91 (d, *J* = 8.2 Hz, 2H), 7.41 – 7.27 (m, 5H), 4.17 (s, 2H), 3.98 (s, 3H), 2.63 (s, 3H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 165.8, 141.6, 135.3, 134.0, 130.5, 128.9, 128.5, 128.2, 127.5, 54.3, 52.8, 34.5.

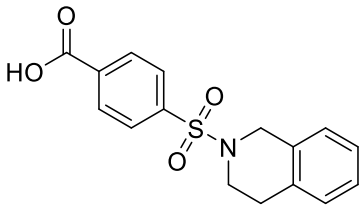
**Step 2:**



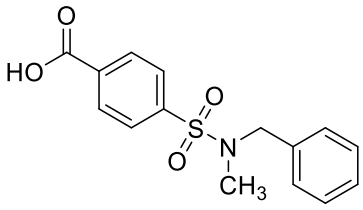

**Procedure**: A mixture of the above ester (2 mmol), 1N NaOH aq. (15 mL) and dioxane (20 mL) was stirred at room temperature for 3 hours. After the completion of the reaction, the organic solvent was removed under reduced pressure. The aqueous phase was acidified by 6 N HCl to pH = 3 and extracted with DCM (20 mL × 3). The combined organic layer was dried with $Na_2SO_4$, filtered and concentrated to give the product, which was used in the next step without further purification.



**4-(azepan-1-ylsulfonyl)benzoic acid (3-222-1-GY)** The reaction was performed with the acid (800 mg, 2.7 mmol) 1N NaOH aq. (15 mL) and dioxane (20 mL) using the above method. Yield: 712 mg, 93%; white solid. The product was used in the next step without further purification.



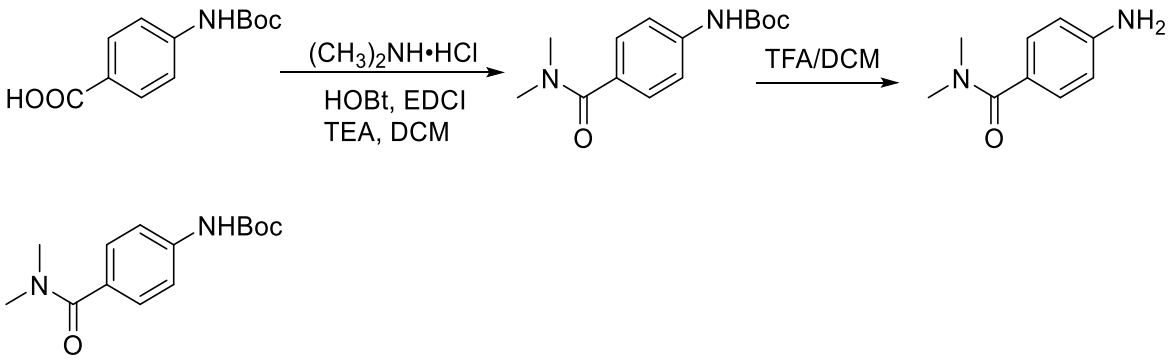
**4-((3,4-dihydroisoquinolin-2(1*H*)-yl)sulfonyl)benzoic acid (3-231-1-GY)** The reaction was performed with the acid (900 mg, 2.7 mmol) 1N NaOH aq. (15 mL) and dioxane (20 mL) using the above method. Yield: 820 mg, 95%; white solid. The product was used in the next step without further purification.



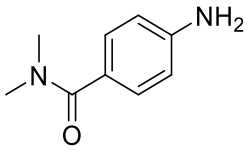
**4-(*N*-benzyl-*N*-methylsulfamoyl)benzoic acid (3-221-1-GY)** The reaction was performed with the acid (800 mg, 2.5 mmol) 1N NaOH aq. (15 mL) and dioxane (20 mL) using the above method. Yield: 718 mg, 94%; white solid. The product was used in the next step without further purification.

#### 4.8.2.1.4. Synthesis of 2-aminobenzothiazole derivatives

##### 4.8.2.1.4.1. Synthesis of 4-aminobenzamide or 4-aminobenzoate

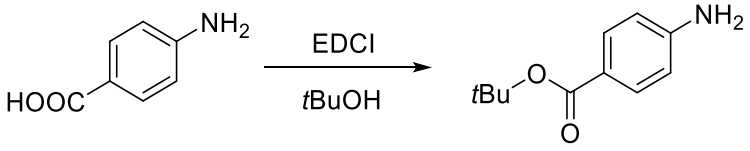



***Tert*-butyl (4-(dimethylcarbamoyl)phenyl)carbamate (4-19-1-GY)** To a solution of the 4-((tert-butoxycarbonyl)amino)benzoic acid (2.37 g, 10 mmol), EDCI·HCl (2.1g, 11 mmol) in DCM (50 mL) was added HOBt·$H_2O$ (1.7 g, 11 mmol). The mixture was stirred for 15 minutes, then the Dimethylamine hydrochloride (1.64 g, 20 mmol) and TEA (7 mL, 50 mmol) were added into the mixture. The mixture was stirred at room temperature overnight. After the completion of the reaction, the mixture was diluted with DCM (15 mL), extracted with saturated aq. $NaHCO_3$ (15 mL) and brine (15 mL × 2), the organic phase was dried with $Na_2SO_4$ and purified by flash column. Eluent: 50% - 70% Ethyl acetate/Hexane; yield: 2.33 g, 84%; white solid. $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.43 – 7.34 (m, 4H), 6.82 (s, 1H), 3.08 (s, 3H), 3.01 (s, 3H), 1.52 (s, 9H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 171.4, 152.7, 139.9, 130.5, 128.5, 117.9, 80.9, 39.8, 35.6, 28.4.

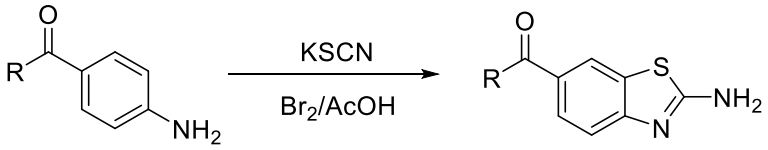



**4-Amino-*N*,*N*-dimethylbenzamide (4-21-1-GY)** To a solution of tert-butyl (4-(dimethylcarbamoyl)phenyl) carbamate (1.32 g, 5 mmol) in DCM (25 mL) was added TFA (7 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 4 hours. After the completion of the reaction, the solvent was removed under vacuum, then dilute with water (5 mL)

and bacified with aq. $NaHCO_3$. The mixture was extracted with DCM (15 mL × 3), dried with $Na_2SO_4$ and purified by flash column. Eluent: 50% - 80% Ethyl acetate/Hexane; yield: 746 mg, 91%; white solid. $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.31 – 7.25 (m, 2H), 6.68 – 6.61 (m, 2H), 3.87 (s, 2H), 3.05 (s, 6H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 172.0, 148.0, 129.4, 125.8, 114.1.



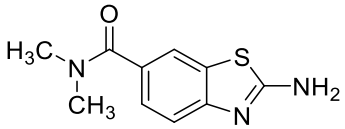

***Tert*-butyl 4-aminobenzoate (4-24-1-GY)** To a solution of 4-aminobenzoic acid (1.37 g, 10 mmol) in *t*BuOH (30 mL) was added a solution of EDCI (2.1 g, 11 mmol) in *t*BuOH (30 mL). The mixture was heated to refluxed for 18 hours. Afterh the completion of the reaction, the mixture was cooled to 0 °C and water (50 mL) was added. Then the mixture was extracted with DCM (100 mL). The organic phase was dried with $Na_2SO_4$ and purified by flash column. Eluent: 30% - 40% Ethyl acetate/Hexane; yield: 1.16 g, 60%; white solid. $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.83 – 7.77 (m, 2H), 6.64 – 6.59 (m, 2H), 4.00 (s, 2H), 1.56 (s, 9H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 166.0, 150.4, 131.4, 121.8, 113.8, 80.1, 28.4.



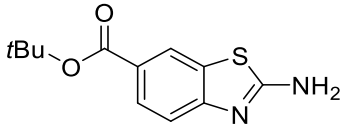

A mixture of appropriate aniline (1 mmol), KSCN (388 mg, 4 mmol) and HOAc (3 mL) were stirred at room temperature for 30 minutes. Then the mixture was cooled to 0 °C and $Br_2$ (52 µL, 1 mmol) in HOAc (2 mL) was added to the mixture. The mixture was allowed to warm to room

temperature and stirred overnight. After the reaction, the acetic acid was removed and the mixture was basified with ammonium hydroxide (15 mL), extracted with DCM (20 mL × 3). The organic phase was dried with $Na_2SO_4$ and purified by flash column.

#### 4.8.2.1.4.2 Synthesis of 2-aminobenzothiazole



**2-Amino-N,N-dimethylbenzo[d]thiazole-6-carboxamide (4-25-1-GY)** The reaction was performed with 4-amino-*N*,*N*-dimethylbenzamide (**4-21-1-GY**, 164 mg, 1 mmol) using the above method. Eluent: 0.5% - 3% MeOH/DCM; yield: 158 mg, 71%; yellowish solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.75 (d, *J* = 1.7 Hz, 1H), 7.65 (s, 2H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.27 (dd, *J* = 8.2, 1.7 Hz, 1H), 2.97 (s, 6H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 170.6, 168.3, 154.2, 131.1, 129.0, 125.5, 120.8, 117.3, 35.7.

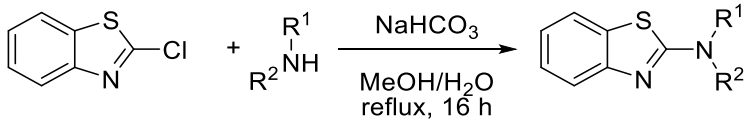


***Tert*-butyl 2-aminobenzo[*d*]thiazole-6-carboxylate (4-26-1-GY)** The reaction was performed with *tert*-butyl 4-aminobenzoate (**4-24-1-GY**, 193 mg, 1 mmol) using the above method. Eluent: 0.2% - 1% MeOH/DCM; yield: 195 mg, 78%; white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.21 (d, *J* = 1.8 Hz, 1H), 7.86 (s, 2H), 7.76 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 1.54 (s,

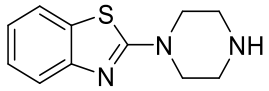
9H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 170.0, 165.4, 157.0, 131.4, 127.4, 124.0, 122.8, 117.4, 80.6, 28.4.

#### 4.8.2.1.4.3 Synthesis of 2-*N*-substituted benzothiazole

**Method 1:**

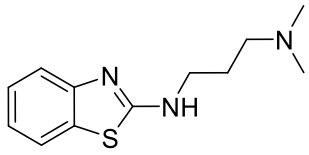



**Procedure**: To a solution of amines or piperazines (10 mmol) in MeOH (16 mL) and water (4 mL) was added $NaHCO_3$ (1680 mg, 20 mmol) and 2-chlorobenzo[*d*]thiazole (0.65 mL, 5 mmol). The mixture was refluxed for 16 hours. After the completion of the reaction, water (15 mL) was added into the mixture and the mixture was extracted with ethyl acetate (30 mL). The organic layer was dried over $Na_2SO_4$ and purified by flash column.

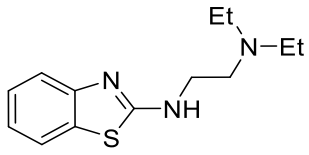



**2-(Piperazin-1-yl)benzo[*d*]thiazole (BDGR-9000, 3-197-1-GY)** The reaction was performed with piperazine (861 mg, 10 mmol), MeOH (16 mL), water (4 mL), $NaHCO_3$ (1680 mg, 20 mmol) and 2-chlorobenzo[*d*]thiazole (0.65 mL, 5 mmol) using the above method. Eluent: 5% - 10% MeOH/DCM; yield: 1060 mg, 97%; yellowish oil and was solidified at room temperature overnight. $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.60 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.55 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.29 (td, *J* = 7.7, 1.3 Hz, 1H), 7.07 (td, *J* = 7.6, 1.2 Hz, 1H), 3.69 – 3.53 (m, 4H), 3.08 – 2.93 (m, 4H), 1.69 (s, 1H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 169.1, 152.7, 130.6, 126.0,

121.4, 120.7, 119.1, 49.5, 45.5. HRMS (ESI) m/z for $C_{11}H_{14}N_3S^+$ $(M+H)^+$, 220.0903 (Calc.), found 220.0905.



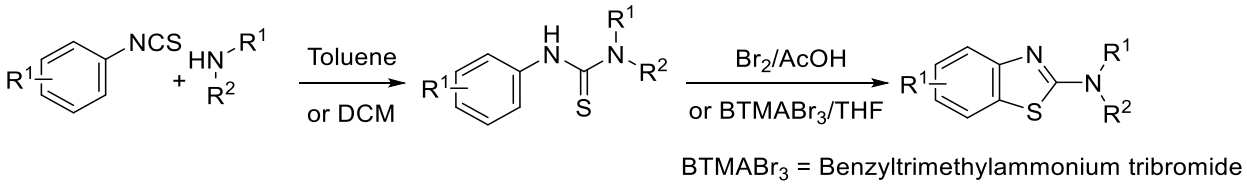

***N*¹-(benzo[*d*]thiazol-2-yl)-*N*³,*N*³-dimethylpropane-1,3-diamine (BDGR-9005, 3-198-1-GY)** The reaction was performed with $N^1$,$N^1$-dimethylpropane-1,3-diamine (1.26 mL, 10 mmol), MeOH (16 mL), water (4 mL), $NaHCO_3$ (1680 mg, 20 mmol) and 2-chlorobenzo[*d*]thiazole (0.65 mL, 5 mmol) using the above method. Eluent: 5% - 15% MeOH/DCM; yield: 954 mg, 81%; yellowish oil and was solidified at room temperature overnight. $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.57 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.53 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.31 – 7.24 (m, 1H), 7.13 – 6.97 (m, 2H), 3.53 (t, *J* = 6.2 Hz, 2H), 2.49 (t, *J* = 6.1 Hz, 2H), 2.28 (s, 6H), 1.84 (p, *J* = 6.1 Hz, 2H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 167.6, 152.8, 130.6, 125.8, 121.2, 120.7, 118.7, 58.7, 45.5, 45.4, 25.8. HRMS (ESI) m/z for $C_{12}H_{18}N_3S^+$ $(M+H)^+$, 236.1216 (Calc.), found 236.1217.




***N*¹-(benzo[*d*]thiazol-2-yl)-*N*²,*N*²-diethylethane-1,2-diamine (3-282-1-GY)** The reaction was performed with $N^1$,$N^1$- diethylethane-1,2-diamine (2.8 mL, 20 mmol), MeOH (32 mL), water (8 mL), $NaHCO_3$ (3360 mg, 40 mmol) and 2-chlorobenzo[*d*]thiazole (1.3 mL, 10 mmol) using the

above method. Eluent: 5% - 15% MeOH/DCM; yield: 1.9 g, 77%; colorless oil. The product was used in the next step.

**Method 2:**

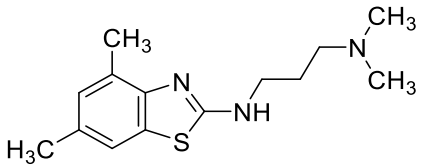



$BTMABr_3$ = Benzyltrimethylammonium tribromide

Unless otherwise stated, the product was synthesized by the following methods.

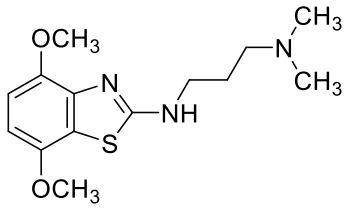
**Procedure: Step 1:** To a solution of isothiocyanate (5 mmol) in Toluene (5 mL) was added amine (5 mmol). The mixture was stirred at room temperature for 2 hours. After the completion of the reactions, the solvent was removed under reduced pressure to give the pure thiourea product, which is used in the next step without further purification.

**Step 2: Method 1:** To a solution of the above urea (5 mmol) in acetic acid (10 mL) was added bromine (5 mmol). The mixture was stirred at room temperature for 2 hours. After the completion of the reaction, the mixture was quenched by 10% aq. $Na_2S_2O_3$ (10 mL), diluted with DCM (20 mL) and basified with $Na_2CO_3$. The mixture was extracted with DCM (3 × 30 mL); the combined organic phase was dried with $Na_2SO_4$ and purified by flash column.



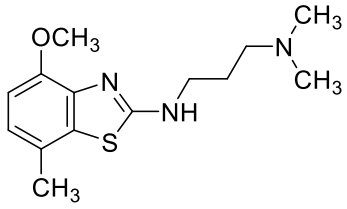
**$N^1$-(4,6-dimethylbenzo[*d*]thiazol-2-yl)-$N^3$,$N^3$-dimethylpropane-1,3-diamine (3-220-1-GY)**

Step 1: The reaction was performed with 1-isothiocyanato-2,4-dimethylbenzene (815 mg, 5 mmol), $N^1$,$N^1$-dimethylpropane-1,3-diamine (0.63 mL, 5 mmol), toluene (5 mL). Step 2: The reaction was performed with 0.5 mmol of the urea product from step 1, bromine (0.052 mL, 1 mmol) and acetic acid (1 mL). Eluent: 2% - 15% MeOH/DCM; yield: 106 mg, 80%; colorless oil. $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.23 (s, 1H), 6.92 (s, 1H), 6.39 (s, 1H), 3.49 (t, *J* = 7.7 Hz, 2H), 2.59 – 2.45 (m, 5H), 2.35 (s, 3H), 2.30 (s, 6H), 1.94 – 1.78 (m, 2H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 166.2, 149.5, 130.8, 130.3, 128.0, 127.9, 118.2, 58.1, 45.3, 44.9, 26.2, 21.2, 18.4.

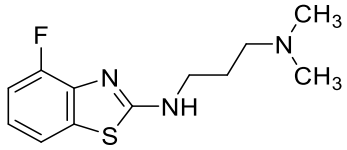



**$N^1$-(4,7-dimethoxybenzo[*d*]thiazol-2-yl)-$N^3$,$N^3$-dimethylpropane-1,3-diamine (3-228-1-GY)**

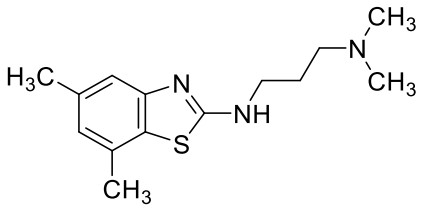
Step 1: The reaction was performed with 1-isothiocyanato-2,5-dimethoxybenzene (997 mg, 5 mmol), $N^1$,$N^1$-dimethylpropane-1,3-diamine (0.63 mL, 5 mmol), toluene (5 mL). Step 2: The reaction was performed with 2 mmol of the urea product from step 1, bromine (0.21 mL, 4 mmol) and acetic acid (3 mL). Eluent: 2% - 15% MeOH/DCM; yield: 375 mg, 63%; brown oil. The product contains minor impurities, but it's fine to be directly used in the next step



**$N^1$-(4-methoxy-7-methylbenzo[*d*]thiazol-2-yl)-$N^3$,$N^3$-dimethylpropane-1,3-diamine (3-229-1-GY)** Step 1: The reaction was performed with 1-isothiocyanato-2-methoxy-5-methylbenzene (0.78 mL, 5 mmol), $N^1$,$N^1$-dimethylpropane-1,3-diamine (0.63 mL, 5 mmol), toluene (5 mL). Step 2: The reaction was performed with 2 mmol of the urea product from step 1, bromine (0.21 mL, 4 mmol) and acetic acid (3 mL). Eluent: 2% - 15% MeOH/DCM; yield: 300 mg, 54%; brown oil. The product contains minor impurities, but it's fine to be directly used in the next step.

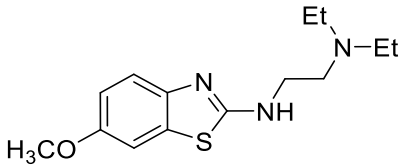



**$N^1$-(4-fluorobenzo[*d*]thiazol-2-yl)-$N^3$,$N^3$-dimethylpropane-1,3-diamine (3-232-1-GY)** Step 1: The reaction was performed with 1-isothiocyanato-2-fluorobenzene (0.62 mL, 5 mmol), $N^1$,$N^1$-dimethylpropane-1,3-diamine (0.63 mL, 5 mmol), toluene (5 mL). Step 2: The reaction was performed with 3 mmol of the urea product from step 1, bromine (0.17 mL, 3 mmol) and acetic acid (6 mL). Eluent: 2% - 15% MeOH/DCM; yield: 460 mg, 61%; brownish oil. $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.68 (s, 1H), 7.33 (dt, *J* = 7.5, 1.4 Hz, 1H), 7.05 – 6.93 (m, 2H), 3.52 (t, *J* = 6.3 Hz, 2H), 2.47 (t, *J* = 6.2 Hz, 2H), 2.26 (s, 6H), 1.84 (p, *J* = 6.2 Hz, 2H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 168.16, 153.13 (d, *J* = 249.4 Hz), 141.13 (d, *J* = 13.0 Hz), 132.95 (d, *J* = 4.8 Hz), 121.31 (d, *J* = 6.9 Hz), 116.48 (d, *J* = 3.7 Hz), 112.00 (d, *J* = 18.4 Hz), 58.7, 45.9, 45.5, 25.9.

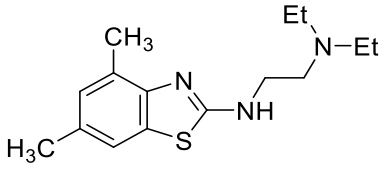



**$N^1$-(5,7-dimethylbenzo[*d*]thiazol-2-yl)-$N^3$,$N^3$-dimethylpropane-1,3-diamine (3-271-1-GY)**

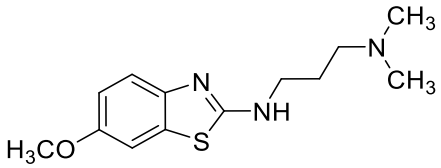
Step 1: The reaction was performed with 1-isothiocyanato-5,7-dimethoxybenzene (1.63 g, 10 mmol), $N^1$,$N^1$-dimethylpropane-1,3-diamine (1.4 mL, 11 mmol), toluene (10 mL). Step 2: The reaction was performed with 4 mmol of the urea product from step 1, bromine (0.246 mL, 4.8 mmol) and acetic acid (8 mL). Eluent: 2% - 15% MeOH/DCM; yield: 363 mg, 35%; yellowish oil. $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.20 (s, 1H), 7.01 (s, 1H), 6.71 (s, 1H), 3.50 (t, *J* = 6.3 Hz, 2H), 2.48 – 2.45 (m, 2H), 2.38 (s, 3H), 2.37 (s, 3H), 2.26 (s, 6H), 1.82 (p, *J* = 6.2 Hz, 2H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 167.6, 152.8, 135.8, 130.2, 127.5, 123.2, 116.7, 58.7, 45.5, 45.5, 26.0, 21.5, 21.3.



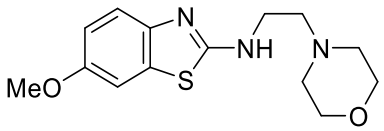

**$N^1$-(6-methoxybenzo[*d*]thiazol-2-yl)-$N^2$,$N^2$-diethylethane-1,2-diamine (3-286-1-GY)** Step 1: The reaction was performed with 1-isothiocyanato-4-methoxybenzene (1.65 g, 10 mmol), $N^1$,$N^1$-diethylethane-1,2-diamine (1.4 mL, 10 mmol), toluene (10 mL). Step 2: The reaction was performed with 10 mmol of the urea product from step 1, bromine (0.62 mL, 12 mmol) and acetic acid (20 mL). Eluent: 2% - 10% MeOH/DCM. The isolated product was impure and was used in the next step.



**$N^1$-(4,6-dimethylbenzo[*d*]thiazol-2-yl)-$N^2$,$N^2$- diethylethane-1,2-diamine (3-295-1-GY)** Step 1: The reaction was performed with 1-isothiocyanato-2,4-dimethylbenzene (815 mg, 5 mmol), $N^1$,$N^1$-diethylethane-1,2-diamine (0.7 mL, 5 mmol), toluene (5 mL). Step 2: The reaction was performed with 3 mmol of the urea product from step 1, bromine (0.21 mL, 4 mmol) and acetic acid (8 mL). Eluent: 0.5% - 3% MeOH/DCM; yield: 609 mg, 73%; yellowish oil. $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.23 (s, 1H), 6.92 (s, 1H), 5.89 (t, *J* = 5.3 Hz, 1H), 3.39 (q, *J* = 5.7 Hz, 2H), 2.69 (t, *J* = 6.0 Hz, 2H), 2.56 (q, *J* = 7.1 Hz, 7H), 2.52 (s, 4H), 2.35 (s, 3H), 1.02 (t, *J* = 7.1 Hz, 6H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 166.2, 149.6, 130.8, 130.4, 128.2, 128.1, 118.3, 51.4, 46.6, 42.8, 21.2, 18.5, 11.7.

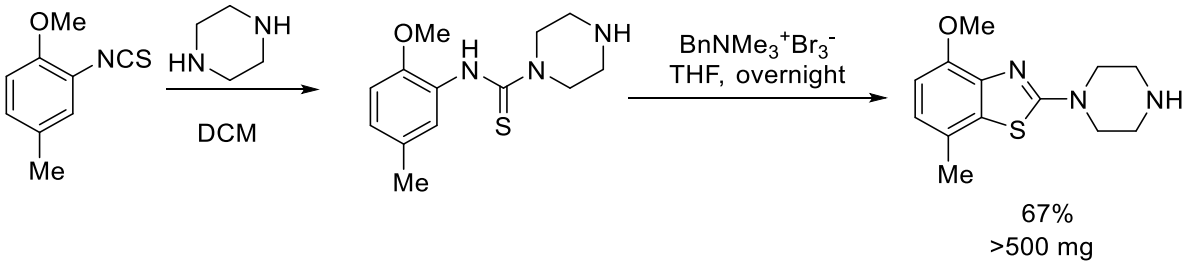


**$N^1$-(6-methoxybenzo[*d*]thiazol-2-yl)-$N^3$,$N^3$-dimethylpropane-1,3-diamine (3-297-1-GY)** Step 1: The reaction was performed with 1-isothiocyanato-4-methoxybenzene (1.65 g, 10 mmol), $N^1$,$N^1$-dimethylpropane-1,3-diamine (1.4 mL, 11 mmol), toluene (10 mL). Step 2: The reaction was performed with 10 mmol of the urea product from step 1, bromine (0.57 mL, 11 mmol) and acetic acid (20 mL). Eluent: 5% MeOH/DCM; yield: 670 mg, 25%; brown oil. The product contains minor impurities, but it's fine to be directly used in the next step.




**6-methoxy-*N*-(2-morpholinoethyl)benzo[*d*]thiazol-2-amine (4-5-1-GY)** Step 1: The reaction was performed with 1-isothiocyanato-4-methoxybenzene (1.65 g, 10 mmol), 2-morpholinoethan-1-amine (1.3 mL, 10 mmol), toluene (10 mL). Step 2: The reaction was performed with 3 mmol of the urea product from step 1, bromine (0.19 mL, 3.6 mmol) and acetic acid (10 mL). Eluent: 0.5% - 2% MeOH/DCM; yield: 256 mg, 29%; brown oil. $^{1}$H NMR (500 MHz, Chloroform-*d*) δ 7.44 (d, *J* = 8.8 Hz, 1H), 7.13 (d, *J* = 2.6 Hz, 1H), 6.89 (dd, *J* = 8.8, 2.7 Hz, 1H), 5.76 (s, 1H), 3.82 (s, 3H), 3.72 (t, *J* = 4.7 Hz, 4H), 3.49 (t, *J* = 5.8 Hz, 2H), 2.64 (t, *J* = 5.9 Hz, 2H), 2.49 (t, *J* = 4.8 Hz, 4H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 165.5, 155.2, 146.8, 131.6, 119.3, 113.5, 105.5, 67.0, 56.8, 56.0, 53.3, 41.1.

**Method 3:**



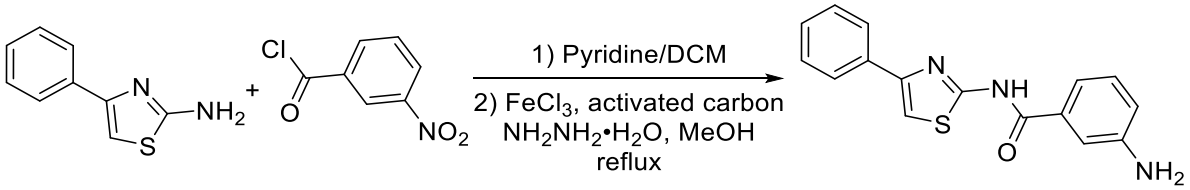

**4-methoxy-7-methyl-2-(piperazin-1-yl)benzo[*d*]thiazole (4-87-1-GY)**

**Step 1:** To a solution of 2-isothiocyanato-1-methoxy-4-methylbenzene (5 mmol) in DCM (25 mL) was added a solution of piperazine (15 mmol) in DCM (10 mL) dropwise. The mixture was stirred at room temperature for 1 hours. After the completion of the reactions, the solvent was removed under reduced pressure. The crude product was diluted with 40 mL water. The insoluble solid was

filtered out. The mother liquor was extracted with DCM (3 × 30 mL); the combined organic phase was dried with $Na_2SO_4$ and purified by flash column. Eluent: 4% MeOH/DCM; yield: 1175 mg, 89%; white solid.

**Step 2:** To a solution of the above urea product (705 mg, 4 mmol) in THF (20 mL) was added $BTMABr_3$ (1560 mg, 4 mmol). The mixture was stirred at room temperature overnight. After the completion of the reaction, the mixture basified with $NaHCO_3$ (30 mL). The mixture was extracted with DCM (40 mL); the organic phase was dried with $Na_2SO_4$ and purified by flash column. Eluent: 3% MeOH/DCM; yield: 705 mg, 67%; yellowish solid. $^1$H NMR (400 MHz, Chloroform-*d*) δ 6.83 (d, *J* = 8.1 Hz, 1H), 6.74 (d, *J* = 8.1 Hz, 1H), 3.95 (s, 3H), 3.69 – 3.58 (m, 4H), 3.06 – 2.96 (m, 4H), 2.38 (s, 3H), 1.72 (s, 1H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 168.4, 148.8, 141.6, 131.9, 122.8, 122.1, 107.4, 56.0, 49.7, 45.7, 20.6.

#### 4.8.2.1.5 Synthesis of 3-amino-*N*-(4-phenylthiazol-2-yl)benzamide



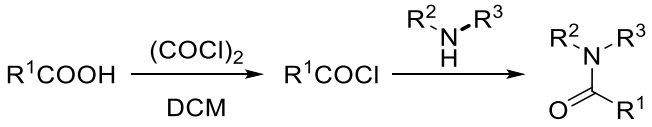

**3-amino-*N*-(4-phenylthiazol-2-yl)benzamide (4-37-1-GY)** A mixture of the 4-phenylthiazol-2-amine (880 mg, 5 mmol), 3-nitrobenzoyl chloride (1.48 g, 8 mmol), pyridine (0.8 mL, 10 mmol) and DCM (20 mL) was stirred at room temperature overnight. After the completion of the reaction, the precipitated solids were filtered out to give the intermediates. To a solution of this intermediates (975 mg, 3 mmol) in MeOH (50 mL) was added $FeCl_3$•$H_2O$ (52 mg, 0.2 mmol) and activated charcoal (118 mg, 10 mmol). The mixture was heated to reflux, then the hydrazine hydrate (1.2

mL, 16 mmol) was added to the mixture. The mixture was refluxed for 5 hours. After the completion of the reaction, the mixture was filtered through celite and washed with MeOH. The mixture was concentrated under reduced pressure and then dilute with DCM. The organic phase was washed with aq. $NH_4OH$, dried and purified by column. Eluent: 20% - 40% Ethyl acetate/Hexane; yield: 602 mg, 68% over two steps; white solid. $^1$H NMR (500 MHz, Chloroform-*d*) δ 10.08 (s, 1H), 7.84 – 7.77 (m, 2H), 7.43 – 7.36 (m, 2H), 7.33 – 7.28 (m, 1H), 7.25 – 7.13 (m, 4H), 6.86 – 6.82 (m, 1H), 3.83 (s, 2H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 165.1, 158.5, 150.3, 147.2, 134.4, 133.1, 130.0, 128.9, 128.2, 126.1, 119.4, 117.0, 113.9, 108.1.

**4.8.2.2 Synthesis of final products**

Except compound **BDGR-9031**, the rest of the compounds were made by one of the following methods.

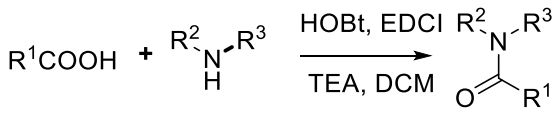
**Method A:**




**Step 1**: To a suspension of the appropriate carboxylic acid (1 mmol) in DCM (1 mL) and 2.0 M $(COCl)_2$ in DCM (1 mL) under ice bath, then a drop of DMF was added into the mixture. The mixture was stirred under ice bath for 1 hour. After the completion of the reaction, the solvent was removed under reduced pressure to give the crude carbonyl chloride. **Step 2**: To this above crude carbonyl chloride or commercial available carbonyl chloride was added the appropriate amines/anilines (0.8 mmol), TEA (0.28 mL, 2 mmol) or pyridine (0.16 mL, 2 mmol) and DCM (5 mL). The mixture was stirred at room temperature overnight. After the completion of the reaction,

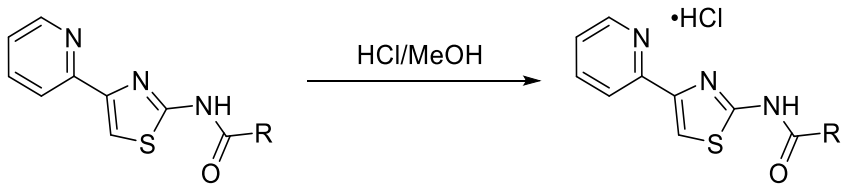
the mixture was diluted with DCM (15 mL), extracted with saturated aq. $NaHCO_3$ (15 mL) and brine (15 mL × 2), the organic phase was dried with $Na_2SO_4$ and purified by flash column.

**Method B:**

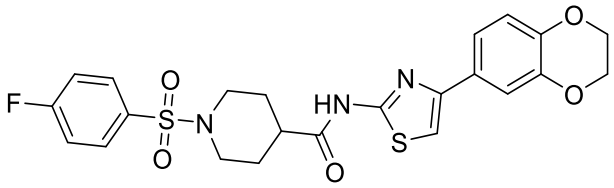



To a solution of the appropriate carboxylic acid (1 equiv), EDCI·HCl (1.1 equiv) in DCM was added HOBt·$H_2O$ (1.1 equiv). The mixture was stirred for 15 minutes, then the amines (1 equiv) and TEA (3 equiv) were added into the mixture. The mixture was stirred at room temperature overnight. After the completion of the reaction, the mixture was diluted with DCM (15 mL), extracted with saturated aq. $NaHCO_3$ (15 mL) and brine (15 mL × 2), the organic phase was dried with $Na_2SO_4$ and purified by flash column.

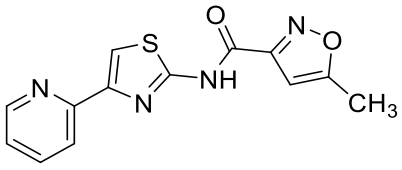
**Method C:**




To a mixture of the pyridyl parent compound (0.05 mmol) in MeOH (1 mL) was added a solution of 3M HCl in MeOH (0.2 mL). The mixture was stirred at room temperature overnight. After the completion of the reaction, the solvent was removed to give pure product.

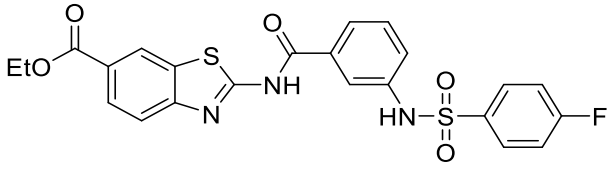


***N*-(4-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)thiazol-2-yl)-1-((4-fluorophenyl)sulfonyl)piperidine-4-carboxamide (BDGR-9001, 3-201-1-GY)** The reaction was performed with acid (287 mg, 1 mmol), 2M $(COCl)_2$/DCM (1 mL, 2 mmol), 1 drop of DMF and DCM (1 mL) followed by 4-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)thiazol-2-amine (187 mg, 0.8 mmol), TEA (0.28 mL, 2 mmol) and DCM (5 mL) using method A. Eluent: 0% - 0.2% MeOH/DCM; yield: 259 mg, 64%; white solid. $^1$H NMR (400 MHz, Chloroform-*d*) δ 11.53 (s, 1H), 7.73 (dd, *J* = 8.7, 5.2 Hz, 2H), 7.30 – 7.25 (m, 2H), 7.20 (d, *J* = 2.0 Hz, 1H), 7.09 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.96 (s, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 4.25 (s, 4H), 3.59 (dt, *J* = 11.6, 3.4 Hz, 2H), 1.91 – 1.64 (m, 6H), 1.53 (dd, *J* = 12.7, 3.3 Hz, 2H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 172.4, 165.2 (d, *J* = 255.0 Hz), 159.8, 148.7, 144.0, 143.8, 132.4 (d, *J* = 3.2 Hz), 130.3 (d, *J* = 9.2 Hz), 127.7, 119.3, 117.8, 116.4 (d, *J* = 22.4 Hz), 115.0, 107.1, 64.5, 64.4, 45.0, 41.4, 27.7. HRMS (ESI) m/z for $C_{23}H_{23}FN_3O_5S_2^+$ $(M+H)^+$, 504.1058 (Calc.), found 504.1066.

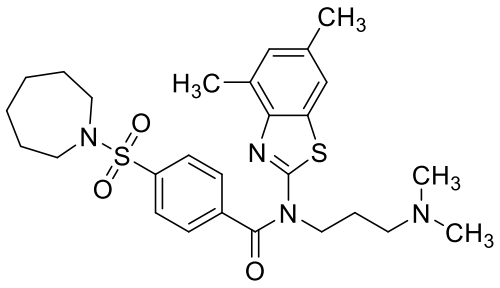


**5-methyl-*N*-(4-(pyridin-2-yl)thiazol-2-yl)isoxazole-3-carboxamide (BDGR-9002, 3-208-1-GY)** The reaction was performed with 4-(pyridin-2-yl)thiazol-2-amine (89 mg, 0.5 mmol), 5-methylisoxazole-3-carbonyl chloride (87 mg, 0.6 mmol), TEA (0.15 mL, 1.1 mmol) and DCM (2 mL) using step 2 of method A. Eluent: 0% - 0.2% MeOH/DCM; yield: 90 mg, 63%; yellowish

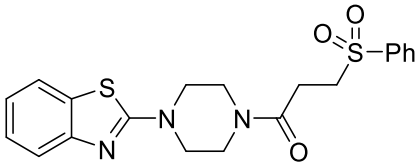
solid. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 10.05 (s, 1H), 8.63 (d, *J* = 5.2 Hz, 1H), 7.97 (d, *J* = 7.9 Hz, 1H), 7.84 – 7.67 (m, 2H), 7.23 (dd, *J* = 7.5, 4.9 Hz, 1H), 6.58 (s, 1H), 2.54 (s, 3H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 172.3, 157.2, 156.6, 156.3, 152.2, 150.3, 149.6, 136.9, 122.8, 120.7, 112.3, 101.5, 12.5. HRMS (ESI) m/z for $C_{13}H_{11}N_4O_2S^+$ $(M+H)^+$, 287.0597 (Calc.), found 287.0611.




**Ethyl 2-(3-((4-fluorophenyl)sulfonamido)benzamido)benzo[*d*]thiazole-6-carboxylate (BDGR-9003, 3-219-1-GY)** The reaction was performed with ethyl 2-aminobenzo[*d*]thiazole-6-carboxylate (61 mg, 0.27 mmol), 3-((4-fluorophenyl)sulfonamido) (xx, 74 mg, 0.25 mmol), HOBt·$H_2O$ (42 mg, 0.27 mmol), EDCI·HCl (53 mg, 0.25 mmol), TEA (0.07 mL, 0.5 mmol) and DCM (2 mL) using method B. Eluent: 20% - 25% Ethyl acetate/Hexane; yield: 20 mg, 16%; white solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 13.13 (s, 1H), 10.65 (s, 1H), 8.69 (s, 1H), 8.05 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.95 – 7.75 (m, 5H), 7.51 – 7.31 (m, 4H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 166.1, 166.0, 164.9 (d, *J* = 251.9 Hz), 138.6, 136.1 (d, *J* = 3.0 Hz), 133.2, 132.4, 130.3 (d, *J* = 9.6 Hz), 130.2, 127.7, 127.6, 125.5, 124.8, 124.5, 124.4, 123.0, 120.7, 117.1 (d, *J* = 22.9 Hz), 61.3, 14.8. HRMS (ESI) m/z for $C_{23}H_{19}FN_3O_5S_2^+$ $(M+H)^+$, 500.0745 (Calc.), found 500.0760.

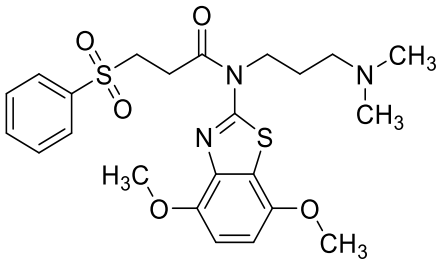


**4-(azepan-1-ylsulfonyl)-*N*-(3-(dimethylamino)propyl)-*N*-(4,6-dimethylbenzo[*d*]thiazol-2-yl)benzamide (BDGR-9004)** The reaction was performed with amine (80 mg, 0.3 mmol), acid (xx, 85 mg, 0.3 mmol), HOBt·$H_2O$ (46 mg, 0.3 mmol), EDCI·HCl (63 mg, 0.3 mmol), TEA (0.14 mL, 3 mmol) and DCM (5 mL) using method B. Eluent: 0.2% - 1% MeOH/DCM; yield: 96 mg, 61%; white solid. $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 8.1 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.44 (s, 1H), 7.08 (s, 1H), 4.28 – 4.15 (m, 2H), 3.29 (t, *J* = 5.9 Hz, 4H), 2.60 (s, 3H), 2.44 (s, 3H), 2.22 (t, *J* = 6.8 Hz, 2H), 2.12 (s, 6H), 1.96 (p, *J* = 6.9 Hz, 2H), 1.81 – 1.67 (m, 4H), 1.62 – 1.59 (m, 4H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 169.8, 145.7, 141.5, 139.0, 134.4, 133.3, 131.2, 128.4, 127.8, 127.3, 118.3, 56.7, 48.8, 48.4, 45.3, 29.2, 27.0, 26.3, 21.6, 18.0. HRMS (ESI) m/z for $C_{27}H_{37}N_4O_3S_2^+$ $(M+H)^+$, 529.2302 (Calc.), found 529.2308.

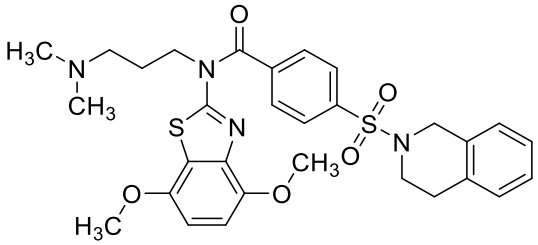


**1-(4-(benzo[*d*]thiazol-2-yl)piperazin-1-yl)-3-(phenylsulfonyl)propan-1-one (BDGR-9006)** The reaction was performed with acid (107 mg, 0.5 mmol), 2M $(COCl)_2$/DCM (1 mL, 2 mmol), 1 drop of DMF and DCM (1 mL), followed by the addition of **BDGR-9000** (88 mg, 0.4 mmol), TEA (0.14 mL, 1 mmol) and DCM (3 mL) using method A. Eluent: 0.2% - 1% MeOH/DCM; yield: 96

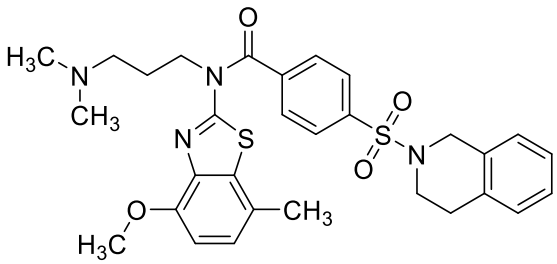
mg, 57%; white solid. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 8.00 – 7.87 (m, 2H), 7.73 – 7.54 (m, 5H), 7.38 – 7.29 (m, 1H), 7.12 (td, *J* = 7.7, 1.2 Hz, 1H), 3.80 – 3.67 (m, 4H), 3.67 – 3.55 (m, 4H), 3.55 – 3.44 (m, 2H), 2.97 – 2.84 (m, 2H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 168.3, 167.5, 152.4, 139.1, 134.0, 130.8, 129.4, 128.0, 126.2, 122.0, 120.9, 119.5, 51.9, 48.2, 48.0, 44.8, 41.3, 26.0. HRMS (ESI) m/z for $C_{20}H_{22}N_3O_3S_2^+$ $(M+H)^+$, 416.1097 (Calc.), found 416.1107.



***N*-(4,7-dimethoxybenzo[*d*]thiazol-2-yl)-*N*-(3-(dimethylamino)propyl)-3-(phenylsulfonyl)propanamide (BDGR-9007)** The reaction was performed with amine (148 mg, 0.5 mmol), acid (107 mg, 0.5 mmol), HOBt·$H_2O$ (77 mg, 0.5 mmol), EDCI·HCl (105 mg, 0.55 mmol), TEA (0.14 mL, 3 mmol) and DCM (10 mL) using method B. Eluent: 0.2% - 4% MeOH/DCM; yield: 46 mg, 19%; white solid. $^{1}$H NMR (500 MHz, Chloroform-*d*) δ 8.02 – 7.88 (m, 2H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.62 – 7.52 (m, 2H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.67 (d, *J* = 8.7 Hz, 1H), 4.51 – 4.26 (m, 2H), 3.98 (s, 3H), 3.92 (s, 3H), 3.59 (t, *J* = 7.6 Hz, 2H), 3.40 – 3.22 (m, 2H), 2.33 (t, *J* = 6.4 Hz, 2H), 2.20 (s, 6H), 2.06 – 1.89 (m, 2H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 169.7, 158.2, 148.4, 147.2, 139.6, 139.1, 134.1, 129.5, 128.2, 123.6, 108.0, 104.5, 56.9, 56.4, 56.2, 51.8, 45.4, 29.8, 25.9. HRMS (ESI) m/z for $C_{23}H_{30}N_3O_5S_2^+$ $(M+H)^+$, 492.1621 (Calc.), found 492.1632.

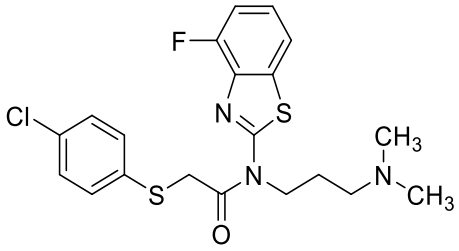


**4-((3,4-dihydroisoquinolin-2(1*H*)-yl)sulfonyl)-*N*-(4,7-dimethoxybenzo[*d*]thiazol-2-yl)-*N*-(3-(dimethylamino)propyl)benzamide (BDGR-9008)** The reaction was performed with amine (148 mg, 0.5 mmol), acid (159 mg, 0.5 mmol), HOBt·$H_2O$ (77 mg, 0.5 mmol), EDCI·HCl (105 mg, 0.55 mmol), TEA (0.14 mL, 1 mmol) and DCM (10 mL) using method B. Eluent: 0.2% - 3% MeOH/DCM; yield: 92 mg, 31%; white solid. $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.91 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.20 – 7.13 (m, 2H), 7.11 – 7.07 (m, 1H), 7.05 – 7.00 (m, 1H), 6.79 (d, *J* = 8.6 Hz, 1H), 6.69 (d, *J* = 8.6 Hz, 1H), 4.28 (s, 2H), 4.27 – 4.20 (m, 2H), 3.91 (s, 6H), 3.39 (t, *J* = 5.9 Hz, 2H), 2.93 (t, *J* = 5.9 Hz, 2H), 2.20 (t, *J* = 6.7 Hz, 2H), 2.06 (s, 6H), 1.93 (p, *J* = 6.9 Hz, 2H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 169.6, 148.3, 147.3, 139.9, 139.5, 138.6, 133.0, 131.4, 129.0, 128.3, 127.9, 127.1, 126.6, 126.5, 123.8, 108.0, 104.9, 56.8, 56.5, 56.2, 48.9, 47.6, 45.3, 43.9, 28.9, 26.0.

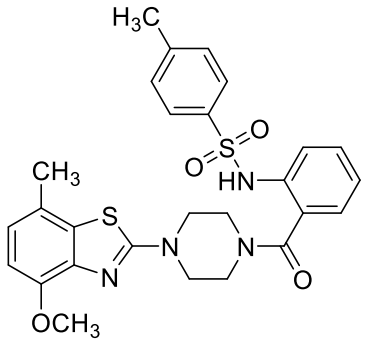


**4-((3,4-dihydroisoquinolin-2(1*H*)-yl)sulfonyl)-*N*-(3-(dimethylamino)propyl)-*N*-(4-methoxy-7-methylbenzo[*d*]thiazol-2-yl)benzamide (BDGR-9009)** The reaction was performed with amine (140 mg, 0.5 mmol), acid (159 mg, 0.5 mmol), HOBt·$H_2O$ (77 mg, 0.5 mmol), EDCI·HCl

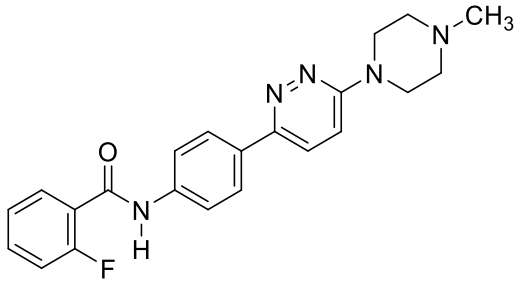
(105 mg, 0.55 mmol), TEA (0.14 mL, 1 mmol) and DCM (10 mL) using method B. Eluent: 0.2% - 3% MeOH/DCM; yield: 169 mg, 58%; white solid. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 7.91 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.23 – 7.13 (m, 2H), 7.12 – 6.95 (m, 3H), 6.80 (d, *J* = 8.1 Hz, 1H), 4.35 – 4.19 (m, 4H), 3.92 (s, 3H), 3.40 (t, *J* = 6.0 Hz, 2H), 2.93 (t, *J* = 5.9 Hz, 2H), 2.46 (s, 3H), 2.20 (t, *J* = 6.8 Hz, 2H), 2.06 (s, 6H), 1.93 (p, *J* = 6.9 Hz, 2H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 169.7, 150.9, 139.5, 138.5, 138.1, 135.2, 133.0, 131.4, 129.0, 128.2, 127.9, 127.1, 126.6, 126.5, 125.4, 123.3, 107.7, 56.5, 56.3, 48.9, 47.6, 45.3, 43.9, 28.9, 26.1, 20.1.




**2-((4-chlorophenyl)thio)-*N*-(3-(dimethylamino)propyl)-*N*-(4-fluorobenzo[*d*]thiazol-2-yl)acetamide (BDGR-9010)** The reaction was performed with amine (127 mg, 0.5 mmol), acid (102 mg, 0.5 mmol), HOBt·$H_2O$ (77 mg, 0.5 mmol), EDCI·HCl (105 mg, 0.55 mmol), TEA (0.14 mL, 1 mmol) and DCM (10 mL) using method B. Eluent: 60% - 70% Ethyl acetate/Hexane; yield: 90 mg, 41%; yellowish solid. $^{1}$H NMR (500 MHz, Chloroform-*d*) δ 7.56 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.43 – 7.36 (m, 2H), 7.31 – 7.24 (m, 3H), 7.24 (dd, *J* = 8.0, 4.5 Hz, 2H), 7.13 (ddd, *J* = 10.5, 8.0, 1.0 Hz, 1H), 4.44 – 4.33 (m, 2H), 4.27 (s, 2H), 2.32 (t, *J* = 6.3 Hz, 2H), 2.21 (s, 6H), 2.06 (q, *J* = 7.0, 6.3 Hz, 2H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 169.4, 155.1 (d, *J* = 254.6 Hz), 136.4 (d, *J* = 3.4 Hz), 133.9, 132.6, 129.5, 128.7, 124.7 (d, *J* = 5.6 Hz), 116.8 (d, *J* = 4.2 Hz), 111.8 (d, *J* = 18.0 Hz), 56.0, 46.7, 45.3, 38.4, 26.1. $^{19}$F NMR (376 MHz, Chloroform-*d*) δ -125.25.

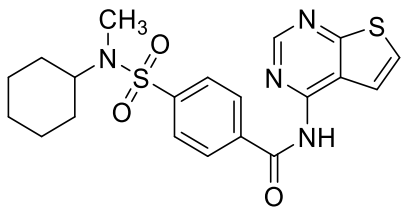


***N*-(2-(4-(4-methoxy-7-methylbenzo[*d*]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-4-methylbenzenesulfonamide (BDGR-9011)** The reaction was performed with amine (53 mg, 0.2 mmol), acid (87 mg, 0.3 mmol), HOBt·$H_2O$ (46 mg, 0.3 mmol), EDCI·HCl (63 mg, 0.33 mmol), TEA (0.14 mL, 1 mmol) and DCM (5 mL) using method B. Eluent: 30% - 40% Ethyl acetate/Hexane; yield: 56 mg, 52%; white solid. $^1$H NMR (500 MHz, Chloroform-*d*) δ 8.47 (s, 1H), 7.72 – 7.63 (m, 3H), 7.41 (ddd, *J* = 8.6, 5.4, 3.6 Hz, 1H), 7.19 (d, *J* = 8.1 Hz, 2H), 7.16 – 7.11 (m, 2H), 6.89 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 3.96 (s, 3H), 3.77 – 3.30 (m, 8H), 2.40 (s, 3H), 2.28 (s, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 168.9, 167.4, 149.1, 144.1, 141.3, 137.2, 136.6, 132.2, 131.6, 129.8, 127.8, 127.4, 125.0, 124.3, 124.3, 123.0, 122.8, 107.8, 56.1, 48.3, 21.5, 20.6. HRMS (ESI) m/z for $C_{27}H_{29}N_4O_4S_2^+$ $(M+H)^+$, 537.1625 (Calc.), found 537.1634.

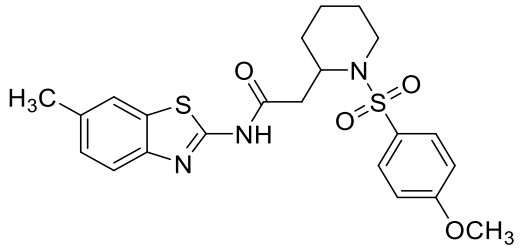


**2-fluoro-*N*-(4-(6-(4-methylpiperazin-1-yl)pyridazin-3-yl)phenyl)benzamide (BDGR-9012)** This compound was purchased and purified by flash column. Eluent: 2% - 10% MeOH/DCM;

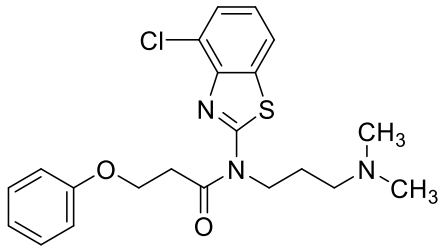
white solid. $^{1}$H NMR (500 MHz, Chloroform-*d*) δ 8.56 (d, *J* = 15.8 Hz, 1H), 8.18 (td, *J* = 8.0, 1.9 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 9.6 Hz, 1H), 7.52 (tdd, *J* = 7.6, 5.2, 1.9 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.18 (dd, *J* = 12.3, 8.2 Hz, 1H), 6.97 (d, *J* = 9.6 Hz, 1H), 3.73 (t, *J* = 5.0 Hz, 4H), 2.56 (t, *J* = 5.0 Hz, 4H), 2.36 (s, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 161.4 (d, *J* = 3.3 Hz), 160.5 (d, *J* = 246.4 Hz), 158.9, 150.6, 138.4, 134.0 (d, *J* = 9.5 Hz), 133.2, 132.4 (d, *J* = 1.7 Hz), 126.7, 125.3 (d, *J* = 3.2 Hz), 125.0, 121.4 (d, *J* = 11.1 Hz), 120.7, 116.3 (d, *J* = 25.1 Hz), 113.1, 54.8, 46.3, 45.1. $^{19}$F NMR (470 MHz, Chloroform-*d*) δ -113.11 (dddd, *J* = 16.9, 12.9, 8.1, 5.3 Hz). HRMS (ESI) m/z for $C_{22}H_{23}FN_5O^+$ $(M+H)^+$, 392.1881 (Calc.), found 392.1886.




**4-(*N*-cyclohexyl-*N*-methylsulfamoyl)-*N*-(thieno[2,3-*d*]pyrimidin-4-yl)benzamide (BDGR-9013)** This compound was purchased and purified by flash column. Eluent: 0.2% - 1% MeOH/DCM; white solid. $^{1}$H NMR (500 MHz, Chloroform-*d*) δ 8.90 (s, 1H), 8.82 (s, 1H), 8.11 (d, *J* = 8.0 Hz, 2H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 6.0 Hz, 1H), 7.54 (d, *J* = 6.1 Hz, 1H), 3.86 – 3.74 (m, 1H), 2.79 (s, 3H), 1.81 – 1.72 (m, 2H), 1.66 – 1.59 (m, 1H), 1.54 – 1.44 (m, 2H), 1.39 – 1.25 (m, 4H), 1.07 – 0.95 (m, 1H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 171.4, 164.6, 152.6, 151.8, 144.8, 136.5, 128.7, 127.5, 125.5, 122.7, 121.3, 57.3, 30.5, 28.9, 25.9, 25.4. HRMS (ESI) m/z for $C_{20}H_{23}N_4O_3S_2^+$ $(M+H)^+$, 431.1206 (Calc.), found 431.1215.

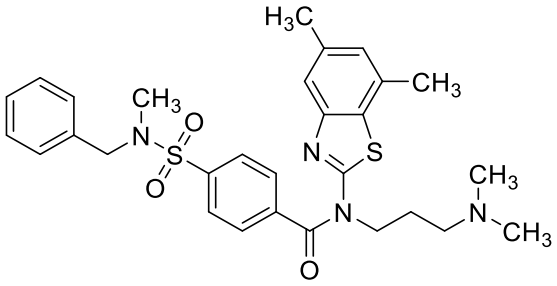


**(*rac*)-2-(1-((4-methoxyphenyl)sulfonyl)piperidin-2-yl)-*N*-(6-methylbenzo[*d*]thiazol-2-yl)acetamide (BDGR-9014, 3-251-1-GY)** This compound was purchased and purified by flash column. Eluent: 0.2% ~ 0.5% MeOH/DCM; white solid. $^{1}$H NMR (500 MHz, Chloroform-*d*) δ 11.37 (s, 1H), 7.78 – 7.66 (m, 2H), 7.66 – 7.54 (m, 2H), 7.31 – 7.21 (m, 1H), 6.93 – 6.81 (m, 2H), 4.51 – 4.42 (m, 1H), 3.78 (s, 3H), 3.69 – 3.59 (m, 1H), 2.76 (dd, *J* = 14.9, 6.6 Hz, 1H), 2.68 (dd, *J* = 15.0, 8.0 Hz, 1H), 2.63 – 2.55 (m, 1H), 2.48 (s, 3H), 1.39 – 1.13 (m, 6H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 169.0, 162.8, 158.8, 145.8, 134.2, 132.5, 132.2, 129.1, 127.9, 121.5, 120.1, 114.3, 55.6, 49.8, 40.8, 38.0, 27.7, 24.4, 21.5, 18.3. HRMS (ESI) m/z for $C_{22}H_{26}N_3O_4S_2^+$ $(M+H)^+$, 460.1359 (Calc.), found 460.1372.

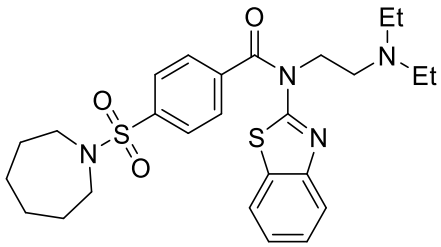


***N*-(4-chlorobenzo[*d*]thiazol-2-yl)-*N*-(3-(dimethylamino)propyl)-3-phenoxypropanamide (BDGR-9015)** This compound was purchased and purified by flash column. Eluent: 5% MeOH/DCM; white solid. $^{1}$H NMR (500 MHz, Chloroform-*d*) δ 7.72 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.46 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.31 – 7.24 (m, 3H), 6.99 – 6.94 (m, 1H), 6.94 – 6.89 (m, 2H), 4.55 (t, *J* = 7.2 Hz, 2H), 4.44 (t, *J* = 6.0 Hz, 2H), 3.34 (t, *J* = 7.5 Hz, 2H), 3.24 (t, *J* = 6.0 Hz, 2H), 2.89

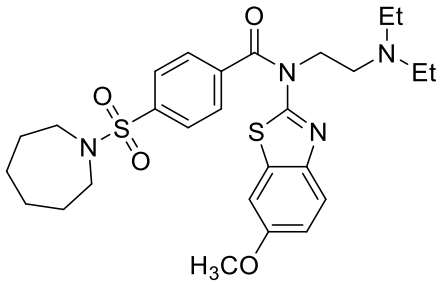
(s, 6H), 2.53 (p, *J* = 7.3 Hz, 2H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 171.0, 159.8, 158.4, 145.0, 134.9, 129.7, 126.5, 126.2, 124.9, 121.5, 120.1, 114.8, 63.5, 56.0, 45.8, 43.2, 34.8, 24.5. HRMS (ESI) m/z for $C_{21}H_{25}ClN_3O_2S^+$ $(M+H)^+$, 418.1351 (Calc.), found 418.1359.




**4-(*N*-benzyl-*N*-methylsulfamoyl)-*N*-(3-(dimethylamino)propyl)-*N*-(5,7-dimethylbenzo[*d*]thiazol-2-yl)benzamide (BDGR-9017)** The reaction was performed with amine (132 mg, 0.5 mmol), acid (183 mg, 0.6 mmol), HOBt·$H_2O$ (92 mg, 0.6 mmol), EDCI·HCl (124 mg, 0.66 mmol), TEA (0.14 mL, 1 mmol) and DCM (5 mL) using method B. Eluent: 0.2% - 4% MeOH/DCM; yield: 76 mg, 28%; white solid. $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.51 (s, 1H), 7.39 – 7.32 (m, 3H), 7.31 (tt, *J* = 5.9, 1.6 Hz, 4H), 7.00 (s, 1H), 4.28 – 4.21 (m, 2H), 4.18 (s, 2H), 2.64 (s, 3H), 2.54 (s, 3H), 2.46 (s, 3H), 2.22 (t, *J* = 6.7 Hz, 2H), 2.10 (s, 6H), 1.99 – 1.90 (m, 2H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 169.8, 159.0, 148.8, 139.5, 139.5, 136.4, 135.3, 131.1, 130.6, 128.9, 128.5, 128.2, 128.1, 127.8, 126.6, 119.6, 56.6, 54.3, 48.9, 45.3, 34.5, 26.2, 21.6, 20.9.

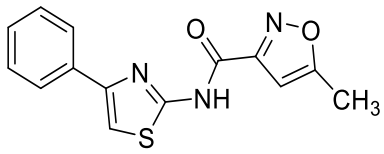


**4-(Azepan-1-ylsulfonyl)-*N*-(benzo[*d*]thiazol-2-yl)-*N*-(2-(diethylamino)ethyl)benzamide (BDGR-9018)** The reaction was performed with amine (149 mg, 0.6 mmol), acid (142 mg, 0.5 mmol), HOBt·$H_2O$ (92 mg, 0.6 mmol), EDCI·HCl (124 mg, 0.66 mmol), TEA (0.14 mL, 1 mmol) and DCM (5 mL) using method B. Eluent: 30% Ethyl acetate/Hexane; yield: 157 mg, 61%; white solid. $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.94 – 7.87 (m, 2H), 7.87 – 7.82 (m, 2H), 7.74 – 7.67 (m, 2H), 7.48 – 7.44 (m, 1H), 7.37 – 7.33 (m, 1H), 4.30 (t, *J* = 6.3 Hz, 2H), 3.35 – 3.23 (m, 4H), 2.73 (t, *J* = 6.3 Hz, 2H), 2.32 (q, *J* = 7.1 Hz, 4H), 1.79 – 1.70 (m, 4H), 1.65 – 1.56 (m, 4H), 0.81 (t, *J* = 7.1 Hz, 6H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 170.4, 159.5, 148.5, 141.5, 138.9, 133.4, 128.4, 127.2, 126.2, 124.4, 121.8, 121.3, 50.5, 48.9, 48.4, 47.8, 29.3, 27.0, 11.8.

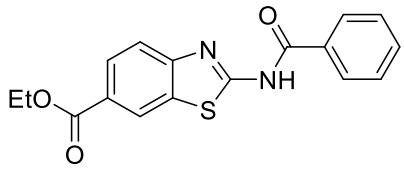


**4-(azepan-1-ylsulfonyl)-*N*-(2-(diethylamino)ethyl)-*N*-(6-methoxybenzo[*d*]thiazol-2-yl)benzamide (BDGR-9019)** The reaction was performed with amine (168 mg, 0.6 mmol), acid (142 mg, 0.5 mmol), HOBt·$H_2O$ (92 mg, 0.6 mmol), EDCI·HCl (124 mg, 0.66 mmol), TEA (0.14 mL, 1 mmol) and DCM (5 mL) using method B. Eluent: 25% - 50% Ethyl acetate/Hexane; yield:

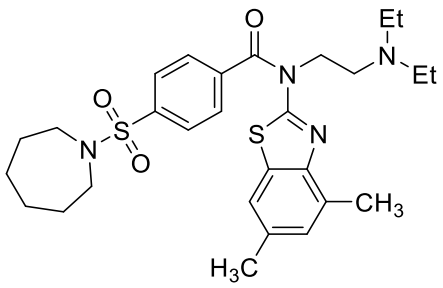
42 mg, 16%; white solid. $^{1}$H NMR (500 MHz, Chloroform-*d*) δ 7.95 – 7.85 (m, 2H), 7.73 (d, *J* = 8.9 Hz, 1H), 7.71 – 7.59 (m, 2H), 7.29 (d, *J* = 2.6 Hz, 1H), 7.05 (dd, *J* = 8.9, 2.6 Hz, 1H), 4.25 (t, *J* = 6.4 Hz, 2H), 3.87 (s, 3H), 3.27 (t, *J* = 5.9 Hz, 4H), 2.71 (t, *J* = 6.4 Hz, 2H), 2.32 (q, *J* = 7.1 Hz, 4H), 1.79 – 1.65 (m, 4H), 1.65 – 1.53 (m, 4H), 0.81 (t, *J* = 7.1 Hz, 6H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 170.1, 157.2, 142.7, 141.4, 139.0, 134.7, 128.4, 127.2, 122.5, 115.4, 103.8, 55.9, 50.4, 48.8, 48.4, 47.7, 29.3, 27.0, 11.8.




**5-Methyl-*N*-(4-phenylthiazol-2-yl)isoxazole-3-carboxamide (BDGR-9020, 3-290-1-GY)** The reaction was performed with 4-phenylthiazol-2-amine (88 mg, 0.5 mmol), 5-methylisoxazole-3-carbonyl chloride (87 mg, 0.6 mmol), pyridine (0.1 mL, 1.2 mmol) and DCM (5 mL) using step 2 of method A. Eluent: 20% Ethyl acetate/Hexane; yield: 96 mg, 67%; white solid. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 10.08 (s, 1H), 7.89 – 7.80 (m, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.37 – 7.29 (m, 1H), 7.21 (s, 1H), 6.57 (s, 1H), 2.53 (s, 3H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 172.3, 157.2, 156.5, 156.2, 150.5, 134.1, 128.8, 128.2, 126.1, 108.2, 101.5, 12.4. HRMS (ESI) m/z for $C_{14}H_{12}N_3O_2S^+$ $(M+H)^+$, 286.0645 (Calc.), found 286.0658.

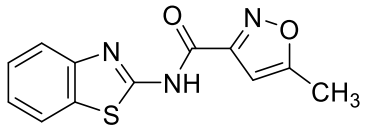


**Ethyl 2-benzamidobenzo[*d*]thiazole-6-carboxylate (BDGR-9021, 3-291-1-GY)** The reaction was performed with ethyl 2-aminobenzo[*d*]thiazole-6-carboxylate (111 mg, 0.5 mmol), benzoyl chloride (0.12 mL, 1 mmol), pyridine (0.1 mL, 1.2 mmol) and DCM (5 mL) using step 2 of method A. Eluent: 20% - 50% Ethyl acetate/Hexane; yield: 70 mg, 43%; white solid. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 11.94 (s, 1H), 8.57 (d, *J* = 1.7 Hz, 1H), 8.08 – 7.99 (m, 2H), 7.96 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.29 (s, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 166.2, 166.0, 162.5, 151.0, 133.4, 131.8, 131.7, 129.1, 128.0, 127.6, 126.2, 123.6, 120.1, 61.2, 14.4. HRMS (ESI) m/z for $C_{17}H_{15}N_2O_3S^+$ $(M+H)^+$, 327.0798 (Calc.), found 327.0804.

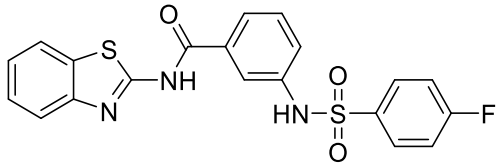



**4-(azepan-1-ylsulfonyl)-*N*-(2-(diethylamino)ethyl)-*N*-(4,6-dimethylbenzo[*d*]thiazol-2-yl)benzamide (BDGR-9022)** The reaction was performed with amine (139 mg, 0.5 mmol), acid (142 mg, 0.5 mmol), HOBt·$H_2O$ (92 mg, 0.6 mmol), EDCI·HCl (124 mg, 0.66 mmol), TEA (0.14 mL, 1 mmol) and DCM (5 mL) using method B. Eluent: 25% - 50% Ethyl acetate/Hexane; yield: 135 mg, 50%; white solid. $^{1}$H NMR (500 MHz, Chloroform-*d*) δ 7.92 – 7.86 (m, 2H), 7.71 – 7.65 (m, 2H), 7.45 (s, 1H), 7.09 (s, 1H), 4.28 (t, *J* = 6.9 Hz, 2H), 3.28 (t, *J* = 6.0 Hz, 4H), 2.74 (t, *J* = 6.9 Hz, 2H), 2.60 (s, 3H), 2.44 (s, 3H), 2.38 (q, *J* = 7.1 Hz, 4H), 1.79 – 1.69 (m, 4H), 1.66 – 1.54 (m, 4H), 0.86 (t, *J* = 7.1 Hz, 6H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 170.0, 157.6, 145.6, 141.4,

139.1, 134.4, 133.4, 131.2, 128.4, 128.2, 127.3, 118.4, 50.4, 48.6, 48.4, 47.9, 29.3, 27.0, 21.6, 18.0, 12.1.

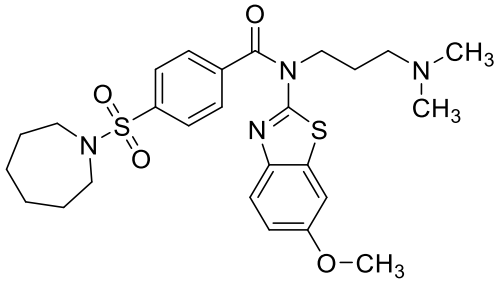


***N*-(benzo[*d*]thiazol-2-yl)-5-methylisoxazole-3-carboxamide (BDGR-9023, 4-6-1-GY)** The reaction was performed with 2-aminobenzothiazole (150 mg, 1 mmol), 5-methylisoxazole-3-carbonyl chloride (218 mg, 1.5 mmol), pyridine (0.2 mL, 2.4 mmol) and DCM (5 mL) using step 2 of method A. Eluent: 15% - 25% Ethyl acetate/Hexane; yield: 248 mg, 96%; white solid. $^{1}$H NMR (500 MHz, Chloroform-*d*) δ 10.31 (s, 1H), 7.85 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.81 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.46 (ddd, *J* = 8.2, 7.2, 1.3 Hz, 1H), 7.34 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H), 6.59 (q, *J* = 0.9 Hz, 1H), 2.53 (d, *J* = 0.9 Hz, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 172.5, 157.2, 157.2, 156.5, 148.6, 132.4, 126.5, 124.4, 121.5, 121.5, 101.6, 12.5. HRMS (ESI) m/z for $C_{12}H_{10}N_3O_2S^+$ $(M+H)^+$, 260.0488 (Calc.), found 260.0494.

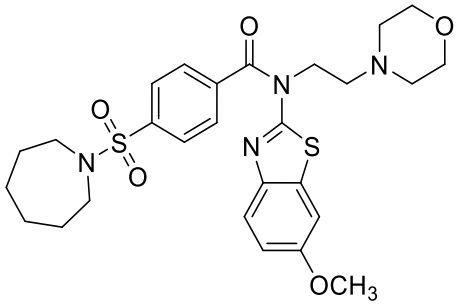


***N*-(benzo[*d*]thiazol-2-yl)-3-((4-fluorophenyl)sulfonamido)benzamide (BDGR-9024, 4-7-1-GY)** The reaction was performed with 2-aminobenzothiazole (150 mg, 1 mmol), 3-((4-fluorophenyl)sulfonamido)benzoic acid (xx, 148 mg, 0.5 mmol), HOBt·$H_2O$ (92 mg, 0.6 mmol),

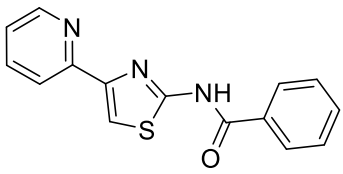
EDCI·HCl (115 mg, 0.6 mmol), TEA (0.21 mL, 1.5 mmol) and DCM (5 mL) using method B. Eluent: 20% Ethyl acetate/Hexane; yield: 106 mg, 50%; white solid. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 12.93 (s, 1H), 10.63 (s, 1H), 8.03 (d, *J* = 7.9 Hz, 1H), 7.93 – 7.81 (m, 4H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.52 – 7.32 (m, 6H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 165.4, 163.4, 138.0, 135.6 (d, *J* = 3.0 Hz), 129.8 (d, *J* = 9.8 Hz), 129.6, 126.2, 124.2, 123.9, 123.75, 121.8, 120.2, 116.6 (d, *J* = 22.9 Hz). $^{19}$F NMR (470 MHz, DMSO-$d_6$) δ -106.19 (tt, *J* = 9.2, 5.2 Hz). HRMS (ESI) m/z for $C_{20}H_{15}FN_3O_3S_2^+$ $(M+H)^+$, 428.0533 (Calc.), found 428.0536.



**4-(azepan-1-ylsulfonyl)-*N*-(3-(dimethylamino)propyl)-*N*-(6-methoxybenzo[*d*]thiazol-2-yl)benzamide (BDGR-9025)** The reaction was performed with amine (161 mg, 0.6 mmol), acid (142 mg, 0.5 mmol), HOBt·$H_2O$ (92 mg, 0.6 mmol), EDCI·HCl (124 mg, 0.66 mmol), TEA (0.14 mL, 1 mmol) and DCM (5 mL) using method B. Eluent: 0.5% - 1% MeOH/Ethyl acetate; yield: 52 mg, 20%; white solid. $^{1}$H NMR (500 MHz, Chloroform-*d*) δ 7.92 – 7.86 (m, 2H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.69 – 7.64 (m, 2H), 7.29 (d, *J* = 2.6 Hz, 1H), 7.06 (dd, *J* = 8.9, 2.6 Hz, 1H), 4.26 – 4.17 (m, 2H), 3.88 (s, 3H), 3.35 – 3.24 (m, 4H), 2.21 (t, *J* = 6.8 Hz, 2H), 2.08 (s, 6H), 1.97 – 1.90 (m, 2H), 1.78 – 1.68 (m, 4H), 1.66 – 1.55 (m, 4H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 169.8, 157.3, 142.9, 141.6, 138.9, 134.7, 127.9, 127.3, 122.6, 115.4, 103.9, 56.6, 56.0, 48.8, 48.5, 45.3, 29.3, 27.0, 26.3. HRMS (ESI) m/z for $C_{26}H_{35}N_4O_4S_2^+$ $(M+H)^+$, 531.2094 (Calc.), found 531.2093.

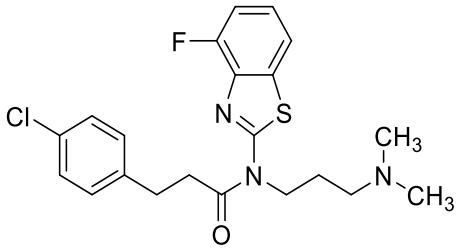


**4-(azepan-1-ylsulfonyl)-*N*-(6-methoxybenzo[*d*]thiazol-2-yl)-*N*-(2-morpholinoethyl)benzamide (BDGR-9026)** The reaction was performed with amine (117 mg, 0.4 mmol), acid (142 mg, 0.5 mmol), HOBt·$H_2O$ (92 mg, 0.6 mmol), EDCI·HCl (124 mg, 0.66 mmol), TEA (0.14 mL, 1 mmol) and DCM (5 mL) using method B. Eluent: 30% - 40% Ethyl acetate/Hexane; yield: 53 mg, 24%; white solid. $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.90 – 7.85 (m, 2H), 7.75 – 7.69 (m, 3H), 7.28 (d, *J* = 2.6 Hz, 1H), 7.06 (dd, *J* = 8.9, 2.6 Hz, 1H), 4.33 (t, *J* = 6.1 Hz, 2H), 3.88 (s, 3H), 3.54 (t, *J* = 4.6 Hz, 4H), 3.28 (t, *J* = 6.0 Hz, 4H), 2.68 (t, *J* = 6.1 Hz, 2H), 2.29 (t, *J* = 4.5 Hz, 4H), 1.72 (d, *J* = 120.6 Hz, 4H), 1.62 – 1.55 (m, 4H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 169.9, 157.4, 142.8, 141.8, 138.7, 134.9, 128.6, 127.3, 122.6, 115.5, 103.9, 67.0, 56.9, 56.0, 54.0, 48.5, 47.3, 29.3, 27.0. HRMS (ESI) m/z for $C_{27}H_{35}N_4O_5S_2^+$ $(M+H)^+$, 559.2043 (Calc.), found 559.2041.

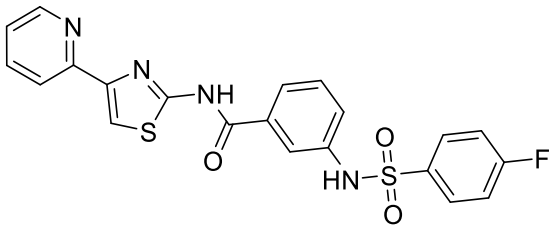


***N*-(4-(pyridin-2-yl)thiazol-2-yl)benzamide (BDGR-9027, 4-11-1-GY)** The reaction was performed with 4-(pyridin-2-yl)thiazol-2-amine (89 mg, 0.5 mmol), benzoyl chloride (0.12 mL, 1

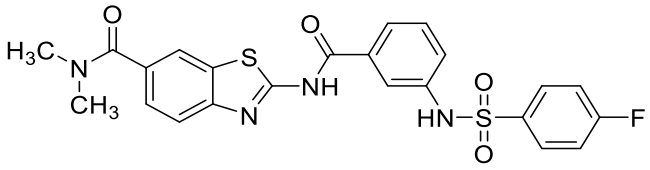
mmol), pyridine (0.1 mL, 1.2 mmol) and DCM (5 mL) using step 2 of method A. Eluent: 0% - 0.2% MeOH/DCM; yield: 110 mg, 78%; yellowish solid. $^{1}$H NMR (500 MHz, Chloroform-*d*) δ 8.66 – 8.59 (m, 1H), 8.02 – 7.94 (m, 2H), 7.86 (d, *J* = 7.9 Hz, 1H), 7.78 – 7.67 (m, 2H), 7.59 – 7.53 (m, 1H), 7.52 – 7.45 (m, 2H), 7.20 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 165.1, 159.2, 152.2, 149.7, 137.0, 133.1, 132.0, 130.2, 129.1, 128.5, 127.7, 122.9, 120.7, 112.4. HRMS (ESI) m/z for $C_{15}H_{12}N_3OS^+$ $(M+H)^+$, 282.0696 (Calc.), found 282.0704.




**3-(4-chlorophenyl)-*N*-(3-(dimethylamino)propyl)-*N*-(4-fluorobenzo[*d*]thiazol-2-yl)propanamide (BDGR-9028)** The reaction was performed with amine (65 mg, 0.25 mmol), acid (95 mg, 0.5 mmol), HOBt·$H_2O$ (92 mg, 0.6 mmol), EDCI·HCl (124 mg, 0.66 mmol), TEA (0.14 mL, 1 mmol) and DCM (5 mL) using method B. Eluent: 60% - 80% Ethyl acetate/Hexane; 60 mg, 57%; white solid. $^{1}$H NMR (500 MHz, Chloroform-*d*) δ 7.57 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.31 – 7.17 (m, 5H), 7.12 (ddd, *J* = 10.6, 8.0, 1.0 Hz, 1H), 4.32 (t, *J* = 7.5 Hz, 2H), 3.15 – 3.00 (m, 4H), 2.35 (t, *J* = 6.6 Hz, 2H), 2.22 (s, 6H), 2.01 – 1.94 (m, 2H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 172.5, 159.2, 155.1 (d, *J* = 254.3 Hz), 139.1, 136.3 (d, *J* = 3.4 Hz), 132.4, 130.0, 128.9, 124.5 (d, *J* = 6.7 Hz), 116.8 (d, *J* = 4.2 Hz), 111.8 (d, *J* = 18.1 Hz), 56.5, 46.3, 45.5, 36.4, 30.2, 26.3. $^{19}$F NMR (470 MHz, Chloroform-*d*) δ -125.33. HRMS (ESI) m/z for $C_{21}H_{23}ClFN_3OS^+$ $(M+H)^+$, 420.1307 (Calc.), found 420.1311.

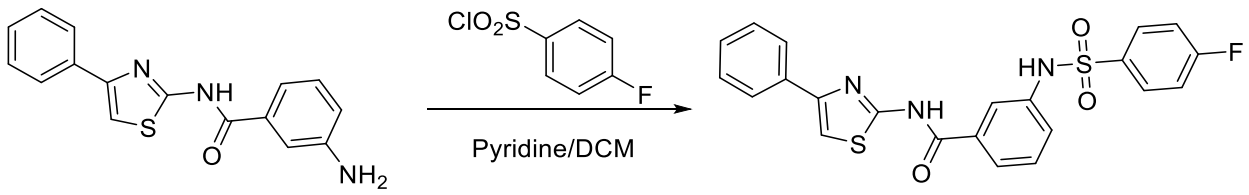


**3-((4-Fluorophenyl)sulfonamido)-*N*-(4-(pyridin-2-yl)thiazol-2-yl)benzamide (BDGR-9029, 4-16-1-GY)** The reaction was performed with acid (295 mg, 1 mmol), 2M $(COCl)_2$/DCM (1 mL, 2 mmol), 1 drop of DMF and DCM (1 mL), followed by the addition of 4-(pyridin-2-yl)thiazol-2-amine (142 mg, 0.8 mmol), pyridine (0.2 mL, 2.4 mmol) and DCM (5 mL) using method A. Eluent: 0.2% - 1% MeOH/DCM, then recrystalized with Ethyl acetate/Hexane; yield: 211 mg, 58%; white/yellowish solid. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 12.89 (s, 1H), 10.67 (s, 1H), 8.67 (ddd, $J$ = 4.8, 1.7, 0.9 Hz, 1H), 8.07 (dt, $J$ = 8.0, 1.1 Hz, 1H), 7.98 – 7.88 (m, 5H), 7.87 (t, $J$ = 1.9 Hz, 1H), 7.51 – 7.44 (m, 3H), 7.42 – 7.38 (m, 2H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 165.3, 164.9 (d, $J$ = 251.7 Hz), 159.2, 152.5, 150.1, 149.9, 138.5, 137.8, 136.1 (d, $J$ = 3.0 Hz), 133.6, 130.3, 130.2, 130.1, 124.5, 124.2, 123.4, 120.6 (d, $J$ = 1.5 Hz), 117.1 (d, $J$ = 22.8 Hz), 112.8. $^{19}$F NMR (470 MHz, DMSO-$d_6$) δ -106.16 (tt, $J$ = 9.0, 5.1 Hz). HRMS (ESI) m/z for $C_{21}H_{16}FN_4O_3S_2^+$ $(M+H)^+$, 455.0642 (Calc.), found 455.0650.



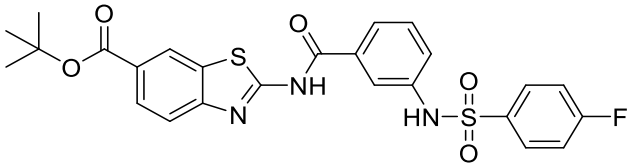
**2-(3-((4-Fluorophenyl)sulfonamido)benzamido)-*N*,*N*-dimethylbenzo[*d*]thiazole-6-carboxamide (BDGR-9030, 4-28-1-GY)** The reaction was performed with acid (148 mg, 0.5 mmol), 2M $(COCl)_2$/DCM (1 mL, 2 mmol), 1 drop of DMF and DCM (1 mL), followed by the

addition of 2-Amino-*N*,*N*-dimethylbenzo[*d*]thiazole-6-carboxamide (**4-25-1-GY**, 66.3 mg, 0.3 mmol), pyridine (0.05 mL, 0.6 mmol) and DCM (2 mL) using method A. Eluent: 0.2% - 2% MeOH/DCM; yield: 35 mg, 23%; white solid. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 13.01 (s, 1H), 10.63 (s, 1H), 8.12 (d, *J* = 1.6 Hz, 1H), 7.91 – 7.76 (m, 5H), 7.50 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.46 – 7.35 (m, 4H), 2.99 (s, 6H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 169.8, 165.3, 163.3, 138.0, 135.5 (d, *J* = 3.0 Hz), 131.6, 129.7 (d, *J* = 9.8 Hz), 129.6, 125.4, 124.2, 123.8, 121.0, 120.1, 116.5 (d, *J* = 22.9 Hz), 34.9. $^{19}$F NMR (470 MHz, DMSO-$d_6$) δ -106.18. HRMS (ESI) m/z for $C_{23}H_{20}FN_4O_4S_2^+$ $(M+H)^+$, 499.0905 (Calc.), found 499.0909.

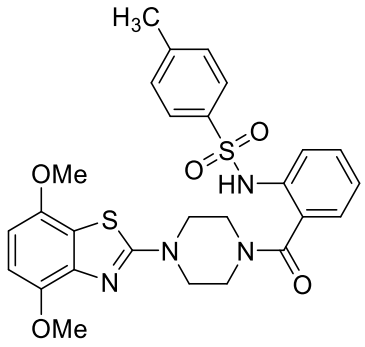



**3-((4-Fluorophenyl)sulfonamido)-*N*-(4-phenylthiazol-2-yl)benzamide (BDGR-9031)** A mixture of the above amines (148 mg, 0.5 mmol), 4-fluorobenzenesulfonyl chloride (195 mg, 1 mmol), pyridine (0.08 mL, 1 mmol) and DCM (5 mL) was stirred at room temperature overnight. After the completion of the reaction, the mixture was dilute with DCM (10 mL), extracted with aq. citric acid (20 mL), aq. $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried with $Na_2SO_4$, filtered and purified by flash column. Eluent: 30% Ethyl acetate/Hexane; yield: 211 mg, 93%; white solid. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 12.79 (s, 1H), 10.61 (s, 1H), 7.97 – 7.92 (m, 2H), 7.90 – 7.82 (m, 3H), 7.81 (t, *J* = 2.0 Hz, 1H), 7.70 (s, 1H), 7.49 – 7.38 (m, 5H), 7.37 – 7.31 (m, 2H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 164.7, 164.4 (d, *J* = 251.9 Hz), 158.4, 149.2, 138.0, 135.6 (d, *J* = 3.1 Hz), 134.3, 133.1, 129.7 (d, *J* = 9.7 Hz), 129.5, 128.7, 127.8, 125.8, 123.9, 123.7,

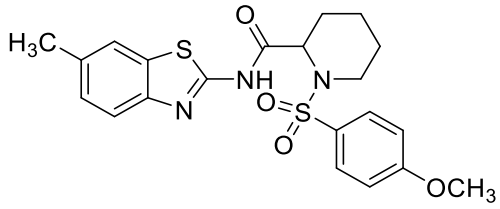
120.1, 116.6 (d, $J$ = 22.8 Hz), 108.7. $^{19}$F NMR (376 MHz, DMSO-$d_6$) δ -106.21. HRMS (ESI) m/z for $C_{22}H_{17}FN_3O_3S_2^+$ $(M+H)^+$, 454.0690 (Calc.), found 454.0696.



***Tert*-butyl 2-(3-((4-fluorophenyl)sulfonamido)benzamido)benzo[*d*]thiazole-6-carboxylate (BDGR-9032, 4-40-1-GY)** The reaction was performed with *tert*-butyl 2-aminobenzo[*d*]thiazole-6-carboxylate (**4-25-1-GY**, 75 mg, 0.3 mmol), 3-((4-fluorophenyl)sulfonamido) benzoic acid (xx, 118 mg, 0.4 mmol), HOBt·$H_2O$ (67 mg, 0.44 mmol), EDCI·HCl (84 mg, 0.44 mmol), TEA (0.12 mL, 0.9 mmol) and DCM (2 mL) using method B. Eluent: 25% Ethyl acetate/Hexane; yield: 40 mg, 25%; white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 13.10 (s, 1H), 10.64 (s, 1H), 8.60 (s, 1H), 7.98 (dd, $J$ = 8.5, 1.8 Hz, 1H), 7.91 – 7.78 (m, 5H), 7.47 – 7.35 (m, 4H), 1.58 (s, 9H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 164.7, 164.4 (d, $J$ = 251.9 Hz), 161.9, 138.1, 135.6 (d, $J$ = 3.0 Hz), 132.9, 131.6, 129.8 (d, $J$ = 9.7 Hz), 129.7, 128.7, 127.1, 126.5, 125.8, 124.3, 124.0, 123.7, 120.2, 116.6 (d, $J$ = 22.8 Hz), 80.8, 27.9. $^{19}$F NMR (376 MHz, DMSO-$d_6$) δ -106.18. HRMS (ESI) m/z for $C_{25}H_{23}FN_3O_5S_2^+$ $(M+H)^+$, 528.1058 (Calc.), found 528.1065.

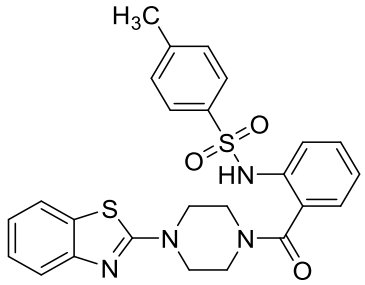


***N*-(2-(4-(4,7-dimethoxybenzo[*d*]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-4-methylbenzenesulfonamide (BDGR-9033)** The reaction was performed with amine (84 mg, 0.3 mmol), acid (175 mg, 0.6 mmol), HOBt·$H_2O$ (110 mg, 0.72 mmol), EDCI·HCl (138 mg, 0.72 mmol), TEA (0.21 mL, 1.5 mmol) and DCM (5 mL) using method B. Eluent: 5% - 15% Ethyl acetate/DCM; yield: 92 mg, 55%; white solid. $^1$H NMR (500 MHz, Chloroform-*d*) δ 8.47 (s, 1H), 7.73 – 7.70 (m, 1H), 7.69 – 7.64 (m, 2H), 7.41 (dt, *J* = 8.2, 4.5 Hz, 1H), 7.23 – 7.17 (m, 2H), 7.16 – 7.10 (m, 2H), 6.77 (d, *J* = 8.7 Hz, 1H), 6.56 (d, *J* = 8.7 Hz, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.74 – 3.26 (m, 8H), 2.27 (s, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 168.9, 168.4, 148.0, 145.8, 144.1, 143.0, 137.2, 136.6, 131.6, 129.8, 127.8, 127.4, 125.0, 124.4, 124.3, 120.0, 107.8, 102.8, 56.4, 56.1, 21.5. HRMS (ESI) m/z for $C_{27}H_{29}N_4O_5S_2^+$ $(M+H)^+$, 553.1574 (Calc.), found 553.1580.



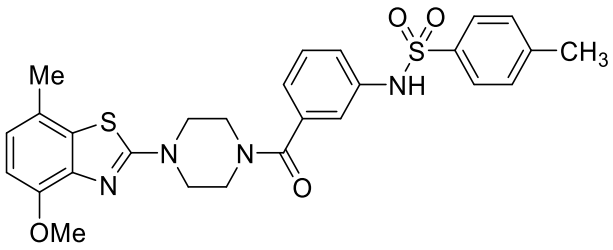
**1-((4-methoxyphenyl)sulfonyl)-*N*-(6-methylbenzo[*d*]thiazol-2-yl)piperidine-2-carboxamide (BDGR-9034)** The reaction was performed with amine (164 mg, 1 mmol), acid (299 mg, 1 mmol), HOBt·$H_2O$ (168 mg, 1.1 mmol), EDCI·HCl (211 mg, 1.1 mmol), TEA (0.42 mL, 3 mmol) and

DCM (5 mL) using method B. Eluent: 15% - 20% Ethyl acetate/Hexane; yield: 132 mg, 30%; white solid. $^{1}$H NMR (500 MHz, Chloroform-*d*) δ 9.95 (s, 1H), 7.86 – 7.80 (m, 2H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.61 (d, *J* = 1.7 Hz, 1H), 7.26 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.05 – 6.97 (m, 2H), 4.74 – 4.69 (m, 1H), 4.07 – 3.98 (m, 1H), 3.87 (s, 3H), 3.16 – 3.07 (m, 1H), 2.48 (s, 3H), 2.34 – 2.26 (m, 1H), 1.60 – 1.53 (m, 1H), 1.50 – 1.38 (m, 2H), 1.29 – 1.16 (m, 2H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 168.9, 163.5, 156.4, 146.5, 134.3, 132.5, 131.2, 129.6, 127.9, 121.2, 121.0, 114.8, 56.5, 55.8, 44.1, 23.8, 23.3, 21.6, 20.0. HRMS (ESI) m/z for $C_{21}H_{24}N_3O_4S_2^+$ $(M+H)^+$, 446.1203 (Calc.), found 446.1211.

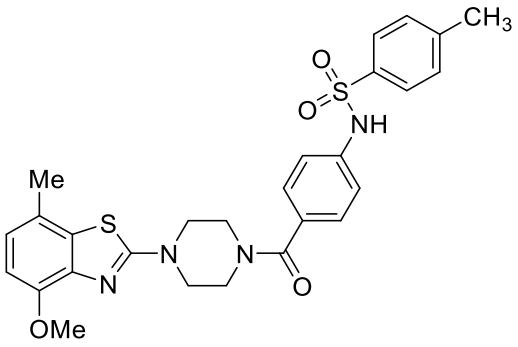



***N*-(2-(4-(benzo[*d*]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-4-methylbenzenesulfonamide (BDGR-9035)** The reaction was performed with amine (219 mg, 1 mmol), acid (320 mg, 1 mmol), HOBt·$H_2O$ (183 mg, 1.1 mmol), EDCI·HCl (230 mg, 1.2 mmol), TEA (0.42 mL, 3 mmol) and DCM (10 mL) using method B. Eluent: 35% - 40% Ethyl acetate/Hexane; yield: 428 mg, 87%; white solid. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 8.48 (s, 1H), 7.76 – 7.66 (m, 3H), 7.64 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.45 – 7.38 (m, 1H), 7.37 – 7.30 (m, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.17 – 7.07 (m, 3H), 3.85 – 3.14 (m, 8H), 2.25 (s, 3H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 168.9, 168.3, 152.5, 144.1, 137.2, 136.6, 131.6, 130.9, 129.8, 127.8, 127.4, 126.4,

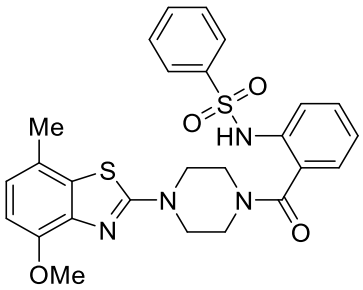
125.1, 124.4, 124.3, 122.2, 121.0, 119.6, 48.2, 21.5. HRMS (ESI) m/z for $C_{25}H_{25}N_4O_3S_2^+$ $(M+H)^+$, 493.1363 (Calc.), found 493.1369.




***N*-(3-(4-(4-methoxy-7-methylbenzo[*d*]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-4-methylbenzenesulfonamide (BDGR-9036)** The reaction was performed with amine (53 mg, 0.2 mmol), acid (87 mg, 0.3 mmol), HOBt·$H_2O$ (51 mg, 0.33 mmol), EDCI·HCl (69 mg, 0.33 mmol), TEA (0.14 mL, 1 mmol) and DCM (5 mL) using method B. Eluent: 50% - 60% Ethyl acetate/Hexane; yield: 90 mg, 84%; white solid. $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.74 (s, 1H), 7.70 – 7.61 (m, 2H), 7.32 – 7.27 (m, 1H), 7.27 – 7.24 (m, 1H), 7.24 – 7.19 (m, 2H), 7.18 – 7.12 (m, 2H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 3.94 (s, 3H), 3.93 – 3.32 (m, 8H), 2.38 (s, 3H), 2.38 (s, 3H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 169.9, 167.6, 149.0, 144.2, 141.3, 137.6, 136.3, 136.1, 132.2, 129.9, 129.9, 127.3, 123.5, 123.0, 122.7, 122.4, 119.7, 107.7, 56.1, 48.5, 21.7, 20.6. HRMS (ESI) m/z for $C_{27}H_{29}N_4O_4S_2^+$ $(M+H)^+$, 537.1625 (Calc.), found 537.1628.

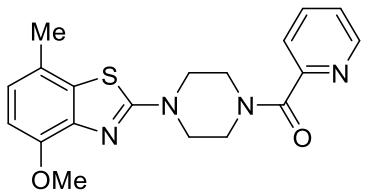



***N*-(4-(4-(4-methoxy-7-methylbenzo[*d*]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-4-methylbenzenesulfonamide (BDGR-9037)** The reaction was performed with amine (53 mg, 0.2 mmol), acid (87 mg, 0.3 mmol), HOBt·$H_2O$ (51 mg, 0.33 mmol), EDCI·HCl (69 mg, 0.33 mmol), TEA (0.14 mL, 1 mmol) and DCM (5 mL) using method B. Eluent: 45% - 60% Ethyl acetate/Hexane; yield: 87 mg, 81%; white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.56 (s, 1H), 7.75 – 7.65 (m, 2H), 7.35 (t, *J* = 8.7 Hz, 4H), 7.19 – 7.12 (m, 2H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 3.82 (s, 3H), 3.72 – 3.48 (m, 8H), 2.34 (s, 3H), 2.31 (s, 3H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 168.8, 166.5, 148.7, 143.6, 141.1, 139.3, 136.6, 131.6, 130.4, 129.9, 128.6, 126.7, 122.3, 122.2, 118.7, 108.6, 55.7, 48.0, 48.0, 21.0, 20.2. HRMS (ESI) m/z for $C_{27}H_{29}N_4O_4S_2^+$ $(M+H)^+$, 537.1625 (Calc.), found 537.1627.

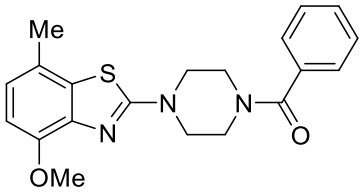



***N*-(2-(4-(4-methoxy-7-methylbenzo[*d*]thiazol-2-yl)piperazine-1-carbonyl)phenyl)benzenesulfonamide (BDGR-9038)** The reaction was performed with amine

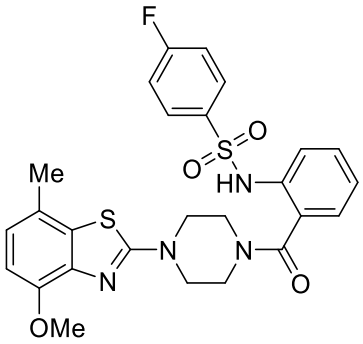
(53 mg, 0.2 mmol), acid (83 mg, 0.3 mmol), HOBt·$H_2O$ (51 mg, 0.33 mmol), EDCI·HCl (69 mg, 0.33 mmol), TEA (0.14 mL, 1 mmol) and DCM (5 mL) using method B. Eluent: 35% - 45% Ethyl acetate/Hexane; yield: 62 mg, 59%; white solid. $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.52 (s, 1H), 7.84 – 7.76 (m, 2H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.52 – 7.36 (m, 4H), 7.19 – 7.10 (m, 2H), 6.89 (d, *J* = 8.1 Hz, 1H), 6.78 (d, *J* = 8.1 Hz, 1H), 3.97 (s, 3H), 3.83 – 3.11 (m, 8H), 2.40 (s, 3H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 168.9, 167.4, 149.1, 141.2, 140.1, 136.4, 133.2, 132.2, 131.6, 129.2, 127.8, 127.3, 125.2, 124.5, 124.5, 123.0, 122.8, 107.7, 56.1, 48.2, 20.6. HRMS (ESI) m/z for $C_{26}H_{27}N_4O_4S_2^+$ $(M+H)^+$, 523.1468 (Calc.), found 523.1474.




**(4-(4-methoxy-7-methylbenzo[*d*]thiazol-2-yl)piperazin-1-yl)(pyridin-2-yl)methanone (BDGR-9039)** The reaction was performed with amine (79 mg, 0.3 mmol), acid (62 mg, 0.5 mmol), HOBt·$H_2O$ (93 mg, 0.6 mmol), EDCI·HCl (125 mg, 0.65 mmol), TEA (0.14 mL, 1 mmol) and DCM (5 mL) using method B. Eluent: 75% - 80% Ethyl acetate/Hexane; yield: 94 mg, 85%; white solid. $^1$H NMR (500 MHz, Chloroform-*d*) δ 8.61 (dt, *J* = 4.7, 1.4 Hz, 1H), 7.83 (td, *J* = 7.7, 1.8 Hz, 1H), 7.73 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.38 (ddd, *J* = 7.6, 4.9, 1.3 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 3.98 (d, *J* = 5.3 Hz, 2H), 3.96 (s, 3H), 3.86 – 3.70 (m, 6H), 2.39 (s, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 167.7, 167.7, 153.6, 149.0, 148.4, 141.4, 137.3, 132.2, 125.0, 124.4, 122.9, 122.5, 107.6, 56.1, 48.8, 46.8, 20.6. HRMS (ESI) m/z for $C_{19}H_{21}N_4O_2S^+$ $(M+H)^+$, 369.1380 (Calc.), found 369.1390.

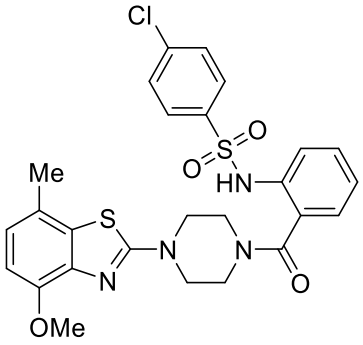



**(4-(4-methoxy-7-methylbenzo[*d*]thiazol-2-yl)piperazin-1-yl)(phenyl)methanone (BDGR-9040)** The reaction was performed with amine (79 mg, 0.3 mmol), acid (62 mg, 0.5 mmol), HOBt·$H_2O$ (93 mg, 0.6 mmol), EDCI·HCl (125 mg, 0.65 mmol), TEA (0.14 mL, 1 mmol) and DCM (5 mL) using method B. Eluent: 30% - 35% Ethyl acetate/Hexane; yield: 89 mg, 81%; white solid. $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.50 – 7.38 (m, 5H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 3.96 (s, 3H), 3.91 – 3.45 (m, 8H), 2.38 (s, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 170.8, 167.7, 149.0, 141.3, 135.3, 132.2, 130.2, 128.8, 127.2, 122.9, 122.7, 107.7, 56.1, 48.6, 20.6. HRMS (ESI) m/z for $C_{20}H_{22}N_3O_2S^+$ $(M+H)^+$, 368.1427 (Calc.), found 368.1441.

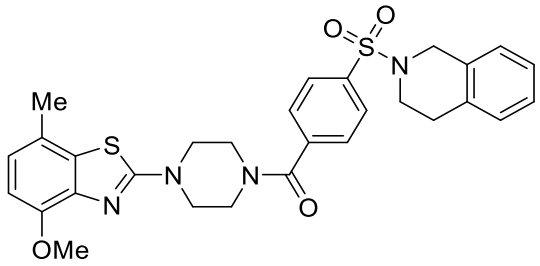



**4-fluoro-*N*-(2-(4-(4-methoxy-7-methylbenzo[*d*]thiazol-2-yl)piperazine-1-carbonyl)phenyl)benzenesulfonamide (BDGR-9041)** The reaction was performed with amine (53 mg, 0.2 mmol), acid (89 mg, 0.3 mmol), HOBt·$H_2O$ (51 mg, 0.33 mmol), EDCI·HCl (69 mg, 0.33 mmol), TEA (0.14 mL, 1 mmol) and DCM (5 mL) using method B. Eluent: 30% - 40% Ethyl acetate/Hexane; yield: 99 mg, 91%; white solid. $^1$H NMR (500 MHz, Chloroform-*d*) δ 8.51 (s, 1H),

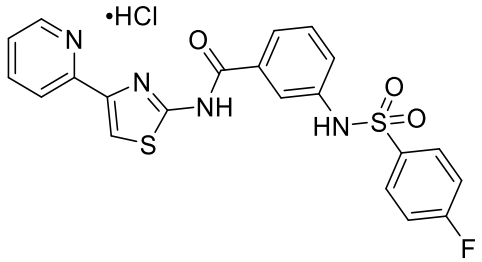
7.91 – 7.81 (m, 2H), 7.61 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.40 (ddd, *J* = 8.5, 7.1, 1.8 Hz, 1H), 7.23 – 7.04 (m, 4H), 6.89 (d, *J* = 8.1 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 3.97 (s, 3H), 3.85 – 3.36 (m, 8H), 2.39 (s, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 168.9, 167.5, 165.3 (d, *J* = 256.1 Hz), 149.1, 141.3, 136.5, 136.0 (d, *J* = 3.3 Hz), 132.3, 131.7, 130.2 (d, *J* = 9.3 Hz), 128.0, 124.8, 124.4, 123.3, 123.0, 122.8, 116.4 (d, *J* = 22.6 Hz), 107.7, 56.1, 48.3, 20.6. $^{19}$F NMR (470 MHz, Chloroform-*d*) δ -104.00. HRMS (ESI) m/z for $C_{26}H_{26}FN_4O_4S_2^+$ $(M+H)^+$, 541.1374 (Calc.), found 541.1379.



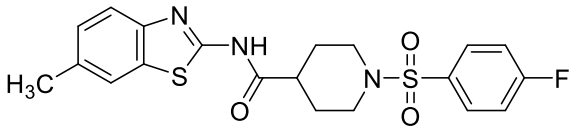

**4-chloro-*N*-(2-(4-(4-methoxy-7-methylbenzo[*d*]thiazol-2-yl)piperazine-1-carbonyl)phenyl)benzenesulfonamide (BDGR-9042)** The reaction was performed with amine (53 mg, 0.2 mmol), acid (94 mg, 0.3 mmol), HOBt·$H_2O$ (51 mg, 0.33 mmol), EDCI·HCl (69 mg, 0.33 mmol), TEA (0.14 mL, 1 mmol) and DCM (5 mL) using method B. Eluent: 30% - 40% Ethyl acetate/Hexane; yield: 94 mg, 84%; white solid. $^1$H NMR (500 MHz, Chloroform-*d*) δ 8.56 (s, 1H), 7.82 – 7.72 (m, 2H), 7.62 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.47 – 7.35 (m, 3H), 7.20 – 7.12 (m, 2H), 6.89 (d, *J* = 8.1 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 3.97 (s, 3H), 3.81 – 3.38 (m, 8H), 2.39 (s, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 168.8, 167.5, 149.2, 141.3, 139.7, 138.4, 136.4, 132.3, 131.7, 129.5, 128.9, 128.0, 124.9, 124.5, 123.7, 123.0, 122.8, 107.7, 56.1, 48.4, 20.6. HRMS (ESI) m/z for $C_{26}H_{26}ClN_4O_4S_2^+$ $(M+H)^+$, 557.1079 (Calc.), found 557.1080.



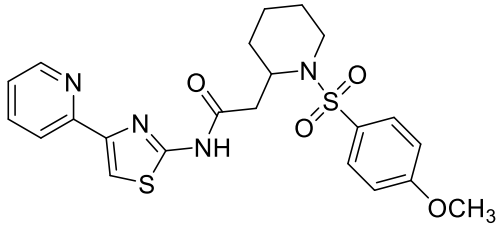

**(4-((3,4-dihydroisoquinolin-2(1*H*)-yl)sulfonyl)phenyl)(4-(4-methoxy-7-methylbenzo[*d*]thiazol-2-yl)piperazin-1-yl)methanone (BDGR-9043)** The reaction was performed with amine (53 mg, 0.2 mmol), acid (95 mg, 0.3 mmol), HOBt·$H_2O$ (51 mg, 0.33 mmol), EDCI·HCl (69 mg, 0.33 mmol), TEA (0.14 mL, 1 mmol) and DCM (5 mL) using method B. Eluent: 35% - 50% Ethyl acetate/Hexane; yield: 92 mg, 82%; white solid. $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.97 – 7.87 (m, 2H), 7.62 – 7.52 (m, 2H), 7.21 – 7.12 (m, 2H), 7.11 – 7.06 (m, 1H), 7.06 – 7.01 (m, 1H), 6.88 (d, *J* = 8.1 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 4.32 (s, 2H), 3.96 (s, 3H), 3.94 – 3.46 (m, 8H), 3.44 (t, *J* = 5.9 Hz, 2H), 2.93 (t, *J* = 5.9 Hz, 2H), 2.39 (s, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 168.9, 167.5, 149.1, 141.2, 139.6, 138.5, 133.0, 132.2, 131.4, 129.0, 128.2, 127.9, 127.0, 126.6, 126.4, 122.9, 122.8, 107.7, 56.1, 48.5, 47.6, 43.8, 28.8, 20.6. HRMS (ESI) m/z for $C_{29}H_{31}N_4O_4S_2^+$ $(M+H)^+$, 563.1781 (Calc.), found 563.1783.



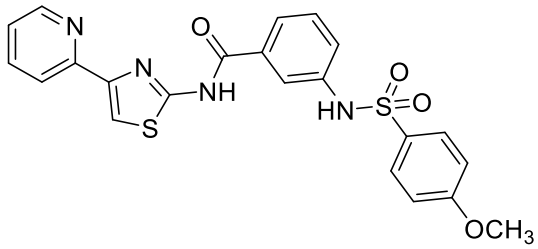
**3-((4-Fluorophenyl)sulfonamido)-*N*-(4-(pyridin-2-yl)thiazol-2-yl)benzamide hydrochloride (BDGR-9044)** The reaction was performed with **BDGR-9029** (23 mg, 0.05 mmol), 3M HCl/MeOH (0.2 mL) and MeOH (1 mL) using method C. Yield: 25 mg, 100%; white solid. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 12.99 (s, 1H), 10.74 (s, 1H), 8.78 – 8.75 (m, 1H), 8.33 (s, 1H), 8.32 – 8.25 (m, 2H), 7.97 – 7.89 (m, 3H), 7.87 (t, 1H), 7.71 – 7.65 (m, 1H), 7.53 – 7.38 (m, 4H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 165.0, 164.4 (d, $J$ = 251.8 Hz), 159.2, 149.0, 146.3, 145.6, 141.4, 138.0, 135.6 (d, $J$ = 3.0 Hz), 132.9, 129.8 (d, $J$ = 9.7 Hz), 129.6, 124.2, 124.0, 123.8, 121.8, 120.1, 116.6 (d, $J$ = 22.9 Hz), 115.4. $^{19}$F NMR (470 MHz, DMSO-$d_6$) δ -105.62 (tt, $J$ = 9.0, 5.1 Hz).




**1-((4-Fluorophenyl)sulfonyl)-*N*-(6-methylbenzo[*d*]thiazol-2-yl)piperidine-4-carboxamide (BDGR-9045, 4-119-1-GY)** The reaction was performed with 6-methylbenzo[d]thiazol-2-amine (164 mg, 1 mmol), 1-((4-fluorophenyl)sulfonyl)piperidine-4-carboxylic acid (xx, 287 mg, 1 mmol), HOBt·$H_2O$ (168 mg, 1.1 mmol), EDCI·HCl (211 mg, 1.1 mmol), TEA (0.42 mL, 3 mmol) and DCM (5 mL) using method B. Eluent: 30% - 70% Ethyl acetate/Hexane; yield: 172 mg, 40%; white solid. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 12.27 (s, 1H), 7.89 – 7.81 (m, 2H), 7.73 (d, $J$ = 1.6 Hz, 1H), 7.59 (d, $J$ = 8.3 Hz, 1H), 7.55 – 7.46 (m, 2H), 7.23 (dd, $J$ = 8.4, 1.7 Hz, 1H), 3.67 (dt, $J$ = 12.0, 3.8 Hz, 2H), 2.39 (s, 3H), 2.34 (td, $J$ = 11.9, 2.7 Hz, 2H), 1.98 – 1.90 (m, 2H), 1.72 – 1.60 (m, 2H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 173.3, 164.6 (d, $J$ = 251.9 Hz), 157.0, 146.4, 133.0, 131.9 (d, $J$ = 2.9 Hz), 131.6, 130.6 (d, $J$ = 9.6 Hz), 127.4, 121.3, 120.1, 116.7 (d, $J$ = 22.6 Hz), 69.9, 45.2, 27.2, 21.0. $^{19}$F NMR (470 MHz, DMSO-$d_6$) δ -105.76 (tt, $J$ = 9.1, 5.0 Hz). HRMS (ESI) m/z for $C_{20}H_{21}FN_3O_3S_2^+$ $(M+H)^+$, 434.1003 (Calc.), found 434.1008.

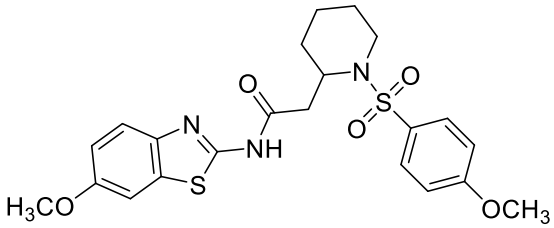


**(*rac*)-2-(1-((4-methoxyphenyl)sulfonyl)piperidin-2-yl)-*N*-(4-(pyridin-2-yl)thiazol-2-yl)acetamide (BDGR-9046, 4-187-1-GY)** The reaction was performed with acid (157 mg, 0.5 mmol), 2M $(COCl)_2$/DCM (1 mL, 2 mmol), 1 drop of DMF and DCM (1 mL), followed by the addition of 4-(pyridin-2-yl)thiazol-2-amine (88 mg, 0.5 mmol), pyridine (0.08 mL, 1 mmol) and DCM (2 mL) using method A. Eluent: 1% - 2% MeOH/DCM; yield: 44 mg, 19%; white solid. $^1$H NMR (400 MHz, Chloroform-*d*) δ 10.52 (s, 1H), 8.61 (d, *J* = 4.8 Hz, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.84 – 7.66 (m, 4H), 7.26 – 7.18 (m, 1H), 6.96 – 6.85 (m, 2H), 4.55 – 4.41 (m, 1H), 3.81 (s, 3H), 3.76 – 3.65 (m, 1H), 2.86 – 2.75 (m, 1H), 2.73 – 2.56 (m, 2H), 1.51 – 1.38 (m, 4H), 1.35 – 1.24 (m, 2H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 168.6, 162.9, 158.6, 152.3, 149.7, 149.5, 137.2, 132.4, 129.3, 123.0, 120.8, 114.4, 112.1, 55.7, 49.9, 41.1, 37.4, 27.9, 24.5, 18.4. HRMS (ESI) m/z for $C_{22}H_{25}N_4O_4S_2^+$ $(M+H)^+$, 473.1312 (Calc.), found 473.1317.



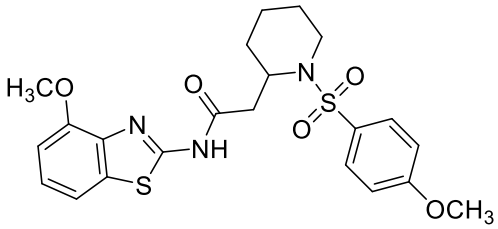
**3-((4-methoxyphenyl)sulfonamido)-*N*-(4-(pyridin-2-yl)thiazol-2-yl)benzamide (BDGR-9047, 4-123-1-GY)** The reaction was performed with acid (307 mg, 1 mmol), 2M $(COCl)_2$/DCM (2 mL,

2 mmol), 1 drop of DMF and DCM (1 mL), followed by the addition of 4-(pyridin-2-yl)thiazol-2-amine (89 mg, 0.5 mmol), pyridine (0.08 mL, 1 mmol) and DCM (2 mL) using method A. Eluent: 1% - 5% MeOH/DCM; yield: 121 mg, 52%; white solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 12.96 (s, 1H), 10.53 (s, 1H), 8.74 (d, $J$ = 5.1 Hz, 1H), 8.44 (s, 1H), 8.39 – 8.24 (m, 2H), 7.91 – 7.79 (m, 2H), 7.78 – 7.65 (m, 3H), 7.48 – 7.32 (m, 2H), 7.06 (d, $J$ = 8.5 Hz, 2H), 3.78 (s, 3H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 165.2, 162.5, 159.4, 148.0, 145.2, 144.4, 142.8, 138.5, 132.7, 130.9, 129.5, 128.9, 124.4, 123.7, 123.3, 122.4, 119.6, 116.5, 114.5, 55.7. HRMS (ESI) m/z for $C_{22}H_{19}N_4O_4S_2^+$ $(M+H)^+$, 467.0842 (Calc.), found 467.0849.

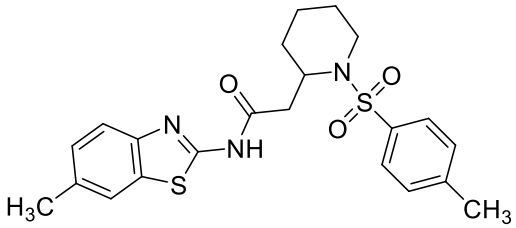



***N*-(6-methoxybenzo[*d*]thiazol-2-yl)-2-(1-((4-methoxyphenyl)sulfonyl)piperidin-2-yl)acetamide (BDGR-9048, 4-124-1-GY)** The reaction was performed with 6-methoxybenzo[*d*]thiazol-2-amine (90 mg, 0.5 mmol), acid (xx, 157 mg, 0.5 mmol), HOBt·$H_2O$ (85 mg, 0.55 mmol), EDCI·HCl (115 mg, 0.6 mmol), TEA (0.21 mL, 3 mmol) and DCM (5 mL) using method B. Eluent: 15% Ethyl acetate/Hexane; yield: 98 mg, 41%; white solid. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 11.18 (s, 1H), 7.74 – 7.68 (m, 2H), 7.66 (d, $J$ = 8.8 Hz, 1H), 7.31 (d, $J$ = 2.5 Hz, 1H), 7.04 (dd, $J$ = 8.8, 2.5 Hz, 1H), 6.92 – 6.85 (m, 2H), 4.54 – 4.44 (m, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 3.71 – 3.62 (m, 1H), 2.85 – 2.60 (m, 3H), 1.46 – 1.17 (m, 6H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 169.0, 162.8, 157.5, 157.0, 142.2, 133.4, 132.5, 129.2, 121.3, 115.5, 114.4, 104.6,

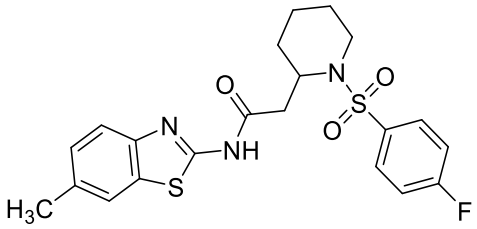
56.0, 55.7, 49.9, 41.0, 37.5, 27.8, 24.4, 18.4. HRMS (ESI) m/z for $C_{22}H_{26}N_3O_5S_2^+$ $(M+H)^+$, 476.1308 (Calc.), found 476.1314.




***N*-(4-methoxybenzo[*d*]thiazol-2-yl)-2-(1-((4-methoxyphenyl)sulfonyl)piperidin-2-yl)acetamide (BDGR-9049, 4-130-1-GY)** The reaction was performed with 4-methoxybenzo[*d*]thiazol-2-amine (90 mg, 0.5 mmol), acid (xx, 157 mg, 0.5 mmol), HOBt·$H_2O$ (85 mg, 0.55 mmol), EDCI·HCl (115 mg, 0.6 mmol), TEA (0.21 mL, 3 mmol) and DCM (5 mL) using method B. Eluent: 30% Ethyl acetate/Hexane; yield: 143 mg, 60%; white solid. $^1$H NMR (500 MHz, Chloroform-*d*) δ 11.21 (s, 1H), 7.70 – 7.62 (m, 2H), 7.43 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.28 (t, *J* = 8.0, 7.4 Hz, 1H), 6.91 (dd, *J* = 8.0, 0.9 Hz, 1H), 6.89 – 6.82 (m, 2H), 4.41 (q, *J* = 7.0, 6.4 Hz, 1H), 3.97 (s, 3H), 3.79 (s, 3H), 3.63 – 3.57 (m, 1H), 2.81 – 2.67 (m, 2H), 2.59 – 2.50 (m, 1H), 1.40 – 1.23 (m, 4H), 1.18 – 1.04 (m, 2H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 169.5, 162.8, 158.3, 151.9, 138.0, 133.6, 132.7, 129.1, 125.1, 114.3, 113.8, 107.2, 56.0, 55.6, 50.0, 40.8, 37.0, 27.6, 24.5, 18.2. HRMS (ESI) m/z for $C_{22}H_{26}N_3O_5S_2^+$ $(M+H)^+$, 476.1308 (Calc.), found 476.1316.

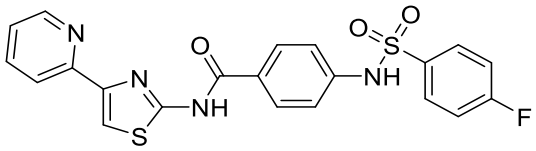


***N*-(6-methylbenzo[*d*]thiazol-2-yl)-2-(1-tosylpiperidin-2-yl)acetamide (BDGR-9050, 4-131-1-GY**) The reaction was performed with 6-methylbenzo[*d*]thiazol-2-amine (82 mg, 0.5 mmol), acid (xx, 149 mg, 0.5 mmol), HOBt·$H_2O$ (85 mg, 0.55 mmol), EDCI·HCl (115 mg, 0.6 mmol), TEA (0.21 mL, 3 mmol) and DCM (5 mL) using method B. Eluent: 15% - 20% Ethyl acetate/Hexane; yield: 58 mg, 26%; white solid. $^1$H NMR (500 MHz, Chloroform-*d*) δ 11.35 (s, 1H), 7.70 – 7.59 (m, 4H), 7.26 – 7.23 (m, 1H), 7.23 – 7.17 (m, 2H), 4.47 (q, *J* = 6.6 Hz, 1H), 3.70 – 3.63 (m, 1H), 2.80 – 2.67 (m, 2H), 2.66 – 2.57 (m, 1H), 2.48 (s, 3H), 2.35 (s, 3H), 1.40 – 1.26 (m, 4H), 1.18 – 1.10 (m, 2H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 169.0, 158.8, 145.9, 143.4, 138.0, 134.3, 132.3, 129.8, 128.0, 127.1, 121.5, 120.2, 49.9, 41.0, 37.5, 27.6, 24.4, 21.6, 18.3. HRMS (ESI) m/z for $C_{22}H_{26}N_3O_3S_2^+$ $(M+H)^+$, 466.1230 (Calc.), found 466.1224.

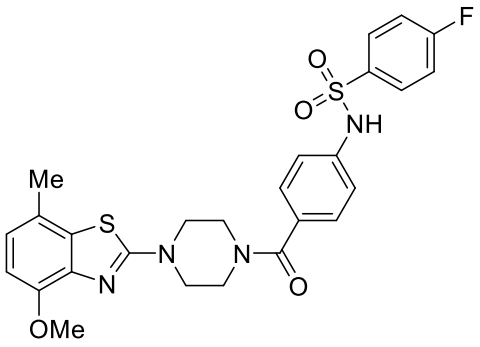



**2-(1-((4-fluorophenyl)sulfonyl)piperidin-2-yl)-*N*-(6-methylbenzo[*d*]thiazol-2-yl)acetamide (BDGR-9051, 4-132-1-GY)** The reaction was performed with 6-methylbenzo[*d*]thiazol-2-amine (82 mg, 0.5 mmol), acid (xx, 150 mg, 0.5 mmol), HOBt·$H_2O$ (85 mg, 0.55 mmol), EDCI·HCl (115 mg, 0.6 mmol), TEA (0.21 mL, 3 mmol) and DCM (5 mL) using method B. Eluent: 15% - 20% Ethyl acetate/Hexane; yield: 89 mg, 40%; white solid. $^1$H NMR (500 MHz, Chloroform-*d*) δ 11.56 (s, 1H), 7.79 – 7.73 (m, 2H), 7.69 – 7.62 (m, 2H), 7.27 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.12 – 7.04 (m, 2H), 4.46 (q, *J* = 6.8 Hz, 1H), 3.67 – 3.58 (m, 1H), 2.83 – 2.66 (m, 2H), 2.65 – 2.57 (m, 1H), 2.48 (s, 3H), 1.42 – 1.26 (m, 4H), 1.18 – 1.09 (m, 2H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 167.0,

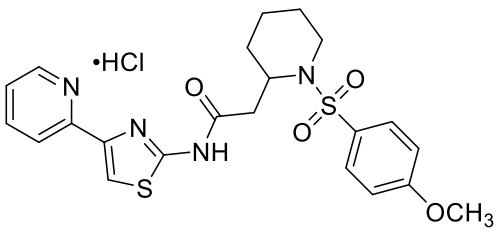
165.0 (d, *J* = 254.5 Hz), 159.0, 145.7, 137.1 (d, *J* = 3.3 Hz), 134.4, 132.2, 129.7 (d, *J* = 9.1 Hz), 128.1, 121.6, 120.1, 116.4 (d, *J* = 22.5 Hz), 50.0, 41.0, 37.5, 27.8, 24.4, 21.6, 18.2. $^{19}$F NMR (470 MHz, Chloroform-*d*) δ -105.52. HRMS (ESI) m/z for $C_{21}H_{23}FN_3O_3S_2^+$ $(M+H)^+$, 448.1159 (Calc.), found 448.1171.



**4-((4-fluorophenyl)sulfonamido)-*N*-(4-(pyridin-2-yl)thiazol-2-yl)benzamide (BDGR-9052, 4-134-1-GY)** The reaction was performed with acid (295 mg, 1 mmol), 2M $(COCl)_2$/DCM (2 mL, 2 mmol), 1 drop of DMF and DCM (1 mL), followed by the addition of 4-(pyridin-2-yl)thiazol-2-amine (89 mg, 0.5 mmol), pyridine (0.08 mL, 1 mmol) and DCM (2 mL) using method A. Eluent: 0.2% - 1% MeOH/DCM; yield: 68 mg, 30%; white solid. $^1$H NMR (400 MHz, Methanol-$d_4$) δ 8.54 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 8.08 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.97 – 7.88 (m, 4H), 7.86 (td, *J* = 7.8, 1.8 Hz, 1H), 7.76 (s, 1H), 7.38 – 7.20 (m, 5H). $^{13}$C NMR (101 MHz, Methanol-$d_4$) δ 166.7, 166.7 (d, *J* = 253.5 Hz), 160.2, 153.7, 150.5, 150.0, 143.4, 138.9, 137.2 (d, *J* = 3.2 Hz), 131.2 (d, *J* = 9.5 Hz), 130.4, 128.9, 124.1, 122.5, 120.2, 117.3 (d, *J* = 23.0 Hz), 113.3. $^{19}$F NMR (376 MHz, Methanol-$d_4$) δ -107.93. HRMS (ESI) m/z for $C_{21}H_{16}FN_4O_3S_2^+$ $(M+H)^+$, 455.0642 (Calc.), found 455.0650.

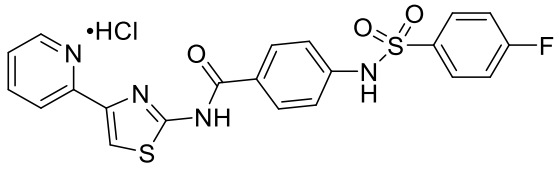



**4-fluoro-*N*-(4-(4-(4-methoxy-7-methylbenzo[*d*]thiazol-2-yl)piperazine-1-carbonyl)phenyl)benzenesulfonamide (BDGR-9053)** The reaction was performed with amine (53 mg, 0.2 mmol), acid (89 mg, 0.3 mmol), HOBt·$H_2O$ (51 mg, 0.33 mmol), EDCI·HCl (69 mg, 0.33 mmol), TEA (0.14 mL, 1 mmol) and DCM (5 mL) using method B. Eluent: 35% - 50% Ethyl acetate/Hexane; yield: 92 mg, 85%; white solid. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 7.86 – 7.78 (m, 2H), 7.48 (s, 1H), 7.38 – 7.30 (m, 2H), 7.19 – 7.07 (m, 4H), 6.88 (d, *J* = 8.1 Hz, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 3.93 (s, 3H), 3.89 – 3.41 (m, 8H), 2.39 (s, 3H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 170.2, 167.9, 165.6 (d, *J* = 256.2 Hz), 149.2, 141.4, 138.6, 135.3 (d, *J* = 3.3 Hz), 132.4, 131.8, 130.2 (d, *J* = 9.4 Hz), 129.0, 123.1, 122.9, 120.6, 116.8 (d, *J* = 22.7 Hz), 107.8, 56.2, 48.7, 20.8. $^{19}$F NMR (376 MHz, Chloroform-*d*) δ -103.80. HRMS (ESI) m/z for $C_{26}H_{26}FN_4O_4S_2^+$ $(M+H)^+$, 541.1374 (Calc.), found 541.1384.

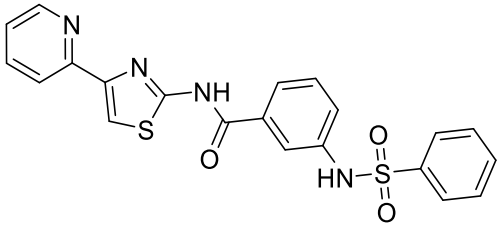



**2-(1-((4-methoxyphenyl)sulfonyl)piperidin-2-yl)-*N*-(4-(pyridin-2-yl)thiazol-2-yl)acetamide hydrochloride (BDGR-9054)** The reaction was performed with **BDGR-9046** (25 mg, 0.05 mmol),

3M HCl/MeOH (0.2 mL) and MeOH (1 mL) using method C. Yield: 19 mg, 70%; white solid. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 12.39 (s, 1H), 8.73 – 8.68 (m, 1H), 8.28 – 8.20 (m, 2H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.72 – 7.66 (m, 2H), 7.66 – 7.59 (m, 1H), 7.02 – 6.95 (m, 2H), 4.57 – 4.50 (m, 1H), 3.74 (s, 3H), 3.66 – 3.62 (m, 1H), 3.08 – 3.02 (m, 1H), 2.82 – 2.71 (m, 2H), 1.59 – 1.38 (m, 5H), 1.23 – 1.16 (m, 1H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 169.8, 162.7, 159.0, 149.3, 146.6, 145.5, 142.2, 132.8, 129.3, 124.6, 122.3, 115.6, 114.9, 56.0, 50.3, 49.1, 36.4, 28.3, 24.6, 18.5. HRMS (ESI) m/z for $C_{22}H_{25}N_4O_4S_2^+$ $(M+H)^+$, 473.1312 (Calc.), found 473.1296.

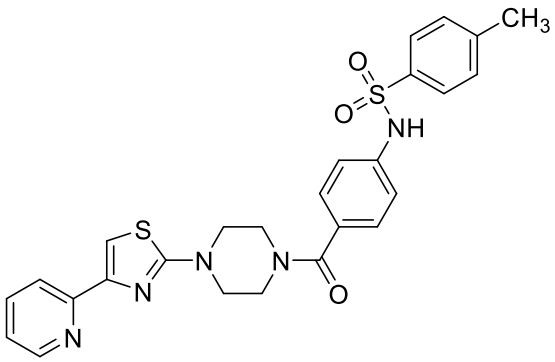



**4-((4-Fluorophenyl)sulfonamido)-*N*-(4-(pyridin-2-yl)thiazol-2-yl)benzamide hydrochloride (BDGR-9055)** The reaction was performed with **BDGR-9052** (30 mg, 0.066 mmol), 3M HCl/MeOH (0.25 mL) and MeOH (2 mL) using method C. Yield: 30 mg, 93%; white solid. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 12.79 (s, 1H), 11.03 (s, 1H), 8.75 – 8.69 (m, 1H), 8.38 – 8.19 (m, 3H), 8.09 – 7.98 (m, 2H), 7.97 – 7.86 (m, 2H), 7.67 (t, *J* = 6.8 Hz, 1H), 7.49 – 7.38 (m, 2H), 7.32 – 7.19 (m, 2H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 164.8, 164.5 (d, *J* = 252.2 Hz), 159.5, 148.4, 145.6, 144.7, 142.3, 141.8, 135.7 (d, *J* = 3.1 Hz), 129.9, 129.8, 126.6, 124.2, 122.2, 118.3, 116.7 (d, *J* = 22.9 Hz), 115.9. HRMS (ESI) m/z for $C_{21}H_{16}FN_4O_3S_2^+$ $(M+H)^+$, 455.0642 (Calc.), found 455.0636.



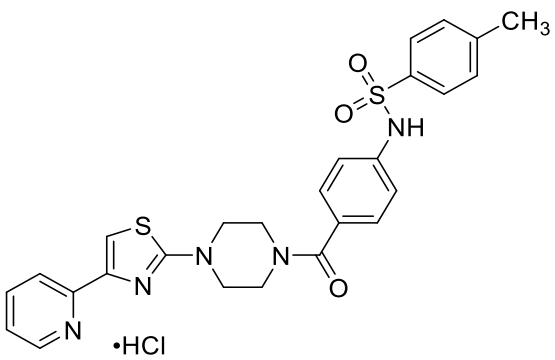
**3-(phenylsulfonamido)-*N*-(4-(pyridin-2-yl)thiazol-2-yl)benzamide (BDGR-9056, 4-143-1-GY)**

The reaction was performed with acid (277 mg, 1 mmol), 2M $(COCl)_2$/DCM (2 mL, 2 mmol), 1 drop of DMF and DCM (1 mL), followed by the addition of 4-(pyridin-2-yl)thiazol-2-amine (89 mg, 0.5 mmol), pyridine (0.08 mL, 1 mmol) and DCM (2 mL) using method A. Eluent: 0.2% - 1% MeOH/DCM; yield: 74 mg, 34%; white solid. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 12.82 (s, 1H), 10.61 (s, 1H), 8.61 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 8.01 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.92 – 7.87 (m, 2H), 7.85 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.82 – 7.78 (m, 3H), 7.63 – 7.59 (m, 1H), 7.58 – 7.53 (m, 2H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.37 – 7.32 (m, 2H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 164.8, 158.7, 152.0, 149.6, 149.4, 139.3, 138.2, 137.3, 133.1, 133.1, 129.5, 129.4, 126.7, 123.8, 123.5, 122.9, 120.1, 119.9, 112.3. HRMS (ESI) m/z for $C_{21}H_{17}N_4O_3S_2^+$ $(M+H)^+$, 437.0737 (Calc.), found 437.0744.



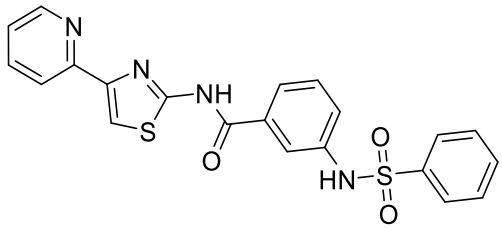
**4-methyl-*N*-(4-(4-(4-(pyridin-2-yl)thiazol-2-yl)piperazine-1-carbonyl)phenyl)benzenesulfonamide (BDGR-9057)** The reaction was performed with amine

(74 mg, 0.3 mmol), acid (146 mg, 0.5 mmol), HOBt·$H_2O$ (93 mg, 0.6 mmol), EDCI·HCl (125 mg, 0.65 mmol), TEA (0.14 mL, 1 mmol) and DCM (5 mL) using method B. Eluent: 0.2% - 0.5% MeOH/DCM; yield: 115 mg, 74%; white solid. $^1$H NMR (500 MHz, Chloroform-*d*) δ 8.58 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.96 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.76 – 7.68 (m, 3H), 7.63 (s, 1H), 7.41 (s, 1H), 7.35 – 7.29 (m, 2H), 7.26 – 7.22 (m, 2H), 7.18 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 7.16 – 7.12 (m, 2H), 3.92 – 3.52 (m, 8H), 2.39 (s, 3H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 170.9, 170.2, 152.9, 151.8, 149.5, 144.4, 138.9, 137.0, 136.2, 131.2, 130.0, 128.8, 127.4, 122.6, 121.1, 120.1, 106.8, 48.6, 21.7. HRMS (ESI) m/z for $C_{26}H_{26}FN_4O_4S_2^+$ $(M+H)^+$, 520.1472 (Calc.), found 520.1481.

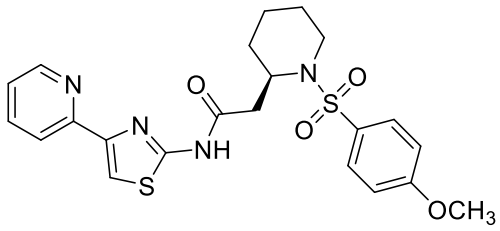



**4-methyl-*N*-(4-(4-(4-(pyridin-2-yl)thiazol-2-yl)piperazine-1-carbonyl)phenyl)benzenesulfonamide hydrochloride (BDGR-9058)**. The reaction was performed with **BDGR-9057** (30 mg, 0.058 mmol), 3M HCl/MeOH (0.25 mL) and MeOH (2 mL) using method C. Yield: 30 mg, 94%; yellow solid. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.63 (s, 1H), 8.74 – 8.68 (m, 1H), 8.43 – 8.35 (m, 2H), 8.17 (s, 1H), 7.77 (t, *J* = 6.3 Hz, 1H), 7.73 – 7.66 (m, 2H), 7.42 – 7.30 (m, 4H), 7.20 – 7.14 (m, 2H), 3.61 (s, 8H), 2.34 (s, 3H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 170.7, 170.6, 168.8, 144.1, 143.5, 139.4, 136.6, 136.5, 130.3, 129.8, 128.5, 126.7,

124.9 – 124.2 (m), 123.5 – 122.7 (m), 118.7, 47.9, 21.0. HRMS (ESI) m/z for $C_{26}H_{26}FN_4O_4S_2^+$ $(M+H)^+$, 520.1472 (Calc.), found 520.1484.

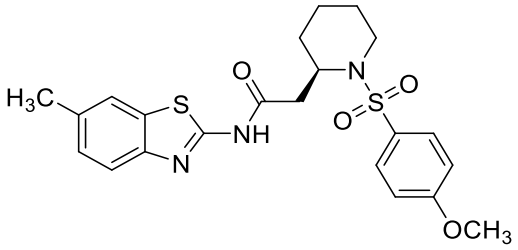


**3-(phenylsulfonamido)-*N*-(4-(pyridin-2-yl)thiazol-2-yl)benzamide (BDGR-9059, 4-143-1-GY) )**. The reaction was performed with **BDGR-9056** (25 mg, 0.05 mmol), 3M HCl/MeOH (0.25 mL) and MeOH (2 mL) using method C. Yield: 25 mg, 92%; white solid. HRMS (ESI) m/z for $C_{21}H_{17}N_4O_3S_2^+$ $(M+H)^+$, 437.0737 (Calc.), found 437.0744.

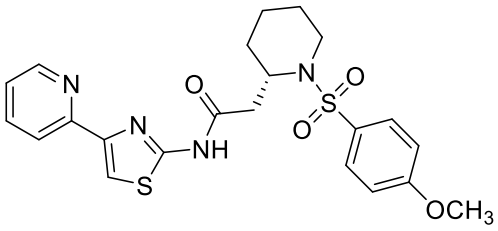


**(*R*)-2-(1-((4-methoxyphenyl)sulfonyl)piperidin-2-yl)-*N*-(4-(pyridin-2-yl)thiazol-2-yl)acetamide (BDGR-9062, 4-187-1-GY)** The reaction was performed with acid (157 mg, 0.5 mmol), 2M $(COCl)_2$/DCM (1 mL, 2 mmol), 1 drop of DMF and DCM (1 mL), followed by the addition of 4-(pyridin-2-yl)thiazol-2-amine (88 mg, 0.5 mmol), pyridine (0.08 mL, 1 mmol) and DCM (2 mL) using method A. Eluent: 1% - 2% MeOH/DCM; yield: 135 mg, 57%; white solid; e. r. (*S*/*R*) = 3.1:96.9. CSP-HPLC: Chiralcel AD-H (50:50 hexane:i-PrOH, 0.5 mL/min) (*R*)-

enantiomer 13.9 min 96.9%), (*S*)-enantiomer 11.6 min (3.1%). Data is consistant with racemic compound **BDGR-9046.**

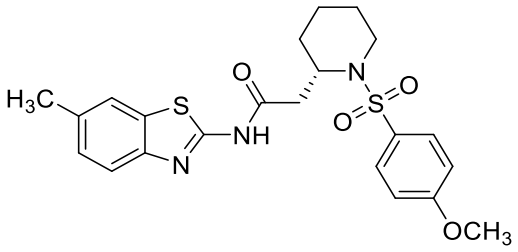



**(*R*)-2-(1-((4-methoxyphenyl)sulfonyl)piperidin-2-yl)-*N*-(6-methylbenzo[d]thiazol-2-yl)acetamide (BDGR-9063, 4-188-1-GY)** The reaction was performed with 6-methylbenzo[*d*]thiazol-2-amine (82 mg, 0.5 mmol), acid (xx, 157 mg, 0.5 mmol), HOBt·$H_2O$ (85 mg, 0.55 mmol), EDCI·HCl (115 mg, 0.6 mmol), TEA (0.21 mL, 3 mmol) and DCM (5 mL) using method B. Eluent: 0.2% ~ 0.5% MeOH/DCM; yield: 91 mg, 40%; white solid; e. r. (*S/R*) = 5:95. CSP-HPLC: Chiralcel AD-H (50:50 hexane:i-PrOH, 0.7 mL/min) (*R*)-enantiomer 22.9 min (95.4%), (*S*)-enantiomer 17.1 min (4.6%). Data is consistant with racemic compound **BDGR-9014.**




**(*S*)-2-(1-((4-methoxyphenyl)sulfonyl)piperidin-2-yl)-*N*-(4-(pyridin-2-yl)thiazol-2-yl)acetamide (BDGR-9064, 4-189-1-GY)** The reaction was performed with acid (157 mg, 0.5 mmol), 2M $(COCl)_2$/DCM (1 mL, 2 mmol), 1 drop of DMF and DCM (1 mL), followed by the addition of 4-(pyridin-2-yl)thiazol-2-amine (88 mg, 0.5 mmol), pyridine (0.08 mL, 1 mmol) and

DCM (2 mL) using method A. Eluent: 1% - 2% MeOH/DCM; yield: 140 mg, 59%; white solid; e. r. (*S/R*) > 99:1. CSP-HPLC: Chiralcel AD-H (50:50 hexane:i-PrOH, 0.5 mL/min) (*R*)-enantiomer was not observed), (*S*)-enantiomer 11.3 min (3.1%). Data is consistant with racemic compound **BDGR-9046.**




**(*S*)-2-(1-((4-methoxyphenyl)sulfonyl)piperidin-2-yl)-*N*-(6-methylbenzo[d]thiazol-2-yl)acetamide (BDGR-9065, 4-190-1-GY)** The reaction was performed with 6-methylbenzo[*d*]thiazol-2-amine (123 mg, 0.75 mmol), acid (xx, 157 mg, 0.5 mmol), HOBt·$H_2O$ (85 mg, 0.55 mmol), EDCI·HCl (115 mg, 0.6 mmol), TEA (0.21 mL, 3 mmol) and DCM (5 mL) using method B. Eluent: 0.2% ~ 0.5% MeOH/DCM; yield: 120 mg, 52%; white solid; e. r. (*S/R*) = 98.9:1.1. CSP-HPLC: Chiralcel AD-H (50:50 hexane:i-PrOH, 0.7 mL/min); (*R*)-enantiomer 22.9 min (1.1%), (*S*)-enantiomer 17.1 min (98.9%). Data is consistant with racemic compound **BDGR-9014.**

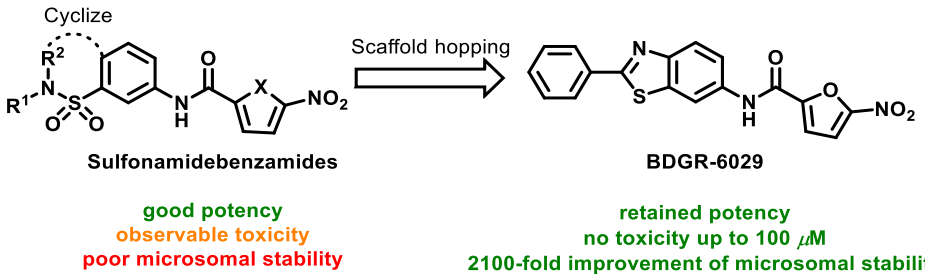
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# Chapter 5. Synthesis and Optimization of CHOP activators as anticancer agents

## 5.1 Abstract

Accumulation of misfolded proteins in the endoplasmic reticulum (ER) will trigger a cellular response known as the unfolded protein response (UPR). The cell will first try to restore the homeostasis of ER, but will initiate cell apoptosis by activating a CHOP pathway if it fails to clear the accumulated proteins and restore homeostasis. Therefore, activating the CHOP pathway to induce cell apoptosis is a promising strategy for the treatment of cancer if suitable selectivity can be achieved between healthy cells that are experiencing less metabolic stress compared to cancerous cells. The Golden group discovered that sulfonamidebenzamide compounds, such as **ML291**, exhibited good potency on activation of CHOP. However, these compounds exhibited poor microsomal stability. In this chapter, a scaffold hopping from **ML291** led to the discovery of **BDGR-6029**, a new scaffold that displayed good activity on CHOP activation and a 2100-fold improvement of microsomal stability.




Adapted from **Gang Yan,** Alok Nerurkar, Bereket L. Zekarias, Andrew Fribley* and Jennifer E. Golden*. Hit to lead optimization of apoptotic CHOP pathway activators of the unfolded protein response. (*Manuscript in preparation*)

## 5.2 Introduction

Endoplasmic reticulum (ER) is responsible for multiple cellular functions including protein folding and post-translational modification of the secreted proteins and cell membrane proteins.[1] The homeostasis in the ER lumen is critical to the normal function of the cell. When too many unfolded or misfolded proteins accumulate in the ER, it will trigger unfolded protein response (UPR).[2-3] The UPR is initially an adaptive response trying to reestablish the normal function of ER by enhancement of the protein folding, degradation or removal of the misfolded protein, and inhibition of protein translation process.[4-5] However, if these actions fail to restore the homeostasis of ER, it will lead to the accumulation of activating transcription factor 4 (ATF4) and CCAAT/enhancer-binding protein (C/EBP) homologous protein (CHOP), which will lead to cell apoptosis.[6-10] Healthy cells are experiencing less metabolic stress than the cancer cells. Therefore, activating CHOP to induce cell apoptosis is a potential strategy for the treatment of cancer if suitable selectivity can be achieved between healthy cells and cancerous cells.[11]

A high throughput screening of 331,676 compounds was performed by Dr. Andrew Fribley and Dr. Randall Kaufmann lab in Chinese hamster ovary (CHO) K1 cells containing luciferase reporter gene on *Chop* activation. Hit compound **5-1** bearing a sulfonamidebenzamide scaffold was identified to activate CHOP with an $AC_{50}$ value of 1.9 $\mu$M.[12] The Golden group pursued a traditional medicinal chemistry optimization of compound **5-1**, affording compound **ML291** with CHOP $AC_{50}$ = 0.8 $\mu$M. (**Figure 5-1**)[12]

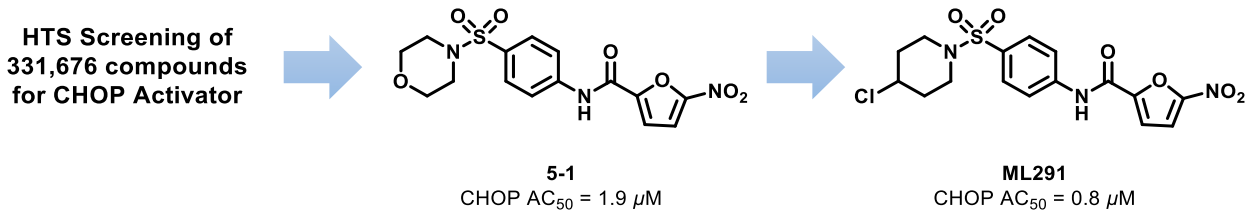



**Figure 5-1.** HTS and hit optimization of CHOP activators leading to compound **ML291**

Since **ML291** displayed promising CHOP-luciferase activation, other assays were performed to investigate other properties.[12] **ML291** displayed the activation of the CHOP gene transcriptions in different oral squamous cancer cell (OSCC) lines including UMSCC23, A253 and HN12 OSCC cell lines (data not shown). The antiproliferation activities of **ML291** were also assessed against six OSCCs. The results showed that **ML291** had single-digit micromolar potency against UMSCC-23, HN12, and HN30 cell lines (data not shown). An *in vivo* study was also performed using the oral tongue xenograft (OTX) mice model. **ML291** treated mice (100 mg/kg, IP, QD) had an 80% survival rate (n = 5) for over 200 days, while all of the vehicle mice were dead (n = 6). Although **ML291** displayed great *in vitro* and *in vivo* activities, metabolic studies showed it had poor microsomal stability (0.02% remaining after 1 hour) in mouse microsomes.

In this chapter, a scaffold hopping of **ML291** led to the discovery of **BDGR-6029**, a new scaffold that showed good activity on CHOP activation with minimum toxicity and acceptable microsomal stability.

## 5.3 Results and discussion

In collaboration with Dr. Alok Nerurkar, over 80 compounds bearing sulfonamidebenzamide scaffold were synthesized. All final compounds were tested the CHOP activation activity at a translational level using a luciferase reporter gene assay.[12] The toxicity of these compounds was also assessed. Since these compounds were CHOP activators, immortalized cell lines, which is commonly used to assess the mammalian toxicity, are not the best choice for toxicity measurement due to their high sensitivity to cell apoptosis modulators. As such, non-immortalized human foreskin fibroblast (HFF) cell line were used to measure the mammalian cytotoxicity. For selected compound, microsomal stability was tested to monitor the parent compound remaining after 1 hour in mouse microsomes.

However, in most cases, compounds were less active than **ML291** and the microsomal stability was not improved (i.e. compounds displayed < 10% parent drug remaining in mouse microsomes). Some compounds also showed toxicity against HFF cell line and poor solubility. (data not shown in this chapter)

A scaffold hopping strategy was performed affording a new chemotype **BDGR-6029**. (**Figure 5-2**) A benzothiazole middle core was incorporated for the replacement of phenylsulfonamide core of the sulfonamidebenzamide series. Fortunately, **BDGR-6029** not only retained the potency against CHOP activation, but also displayed an excellent toxicity profile with $CC_{50}$ > 100 $\mu$M. In addition, as a hit compound, **BDGR-6029** showed good solubility (12 $\mu$M) and microsomal stability (42% remaining after 1 hour).

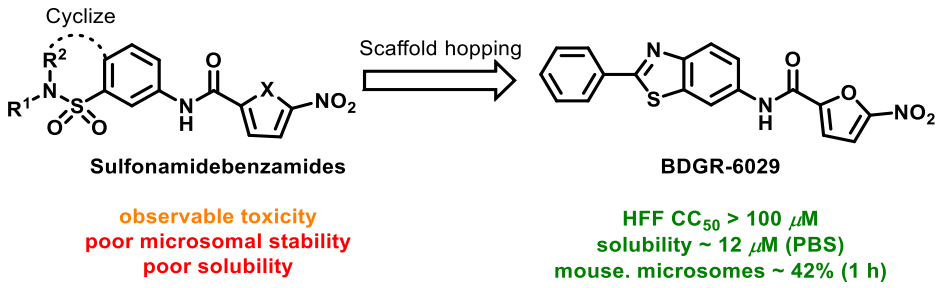
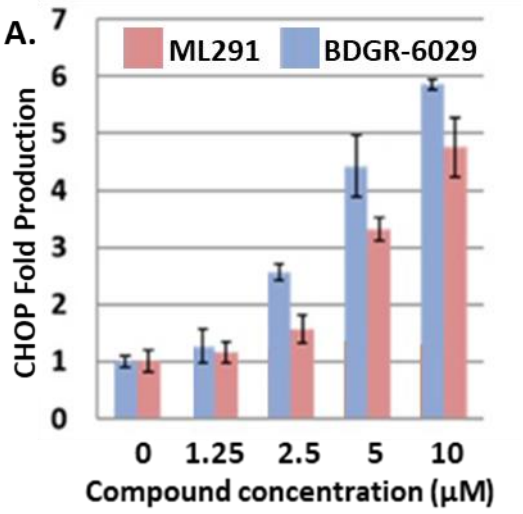


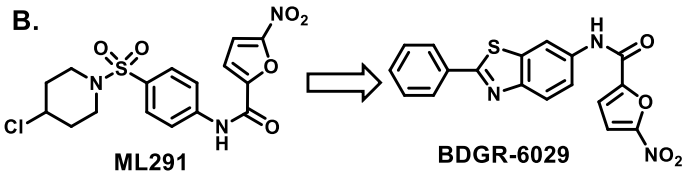

**Figure 5-2.** Scaffold hopping to afford new chemotype **BDGR-6029**

CHOP fold production in cells treated with **BDGR-6029** and **ML291** at different concentration was evaluated. (**Figure 5-3A**) **BDGR-6029** was able to activate CHOP in a dose response manner with about 6-fold activation of CHOP at 10 $\mu$M. The antiproliferation activity of **BDGR-6029** was also evaluated against oral squamous cell carcinoma (OSCC) cells, since they are more sensitive to UPR-inducers.[12] (**Figure 5-3B**) **BDGR-6029** displayed $EC_{50}$ = 10.2 $\mu$M against WT SCC23 cell line, while CHOP KO SCC23 cell line was less sensitive to **BDGR-6029** ($EC_{50}$ = 35.3 $\mu$M). Both **ML291** and **BDGR-6029** displayed similar antiproliferation activity, low toxicity and moderate solubility. However, **BDGR-6029** shows a 2100-fold improvement of

microsomal stability, makes it a better compound for further optimization. A graduate student Ms. Bereket Zekarias explored the preliminary SAR of **BDGR-6029**, however, none of these new analogues showed better results (data not shown).




B.




| | ML291 | BDGR-6029 |
|---|---|---|
| Antiproliferation *(24 h)* | | |
| SCC23 (WT), $EC_{50}$ | 10.4 $\mu$M | 10.2 $\mu$M |
| SCC23 (KO), $EC_{50}$ | 25.3 $\mu$M | 35.3 $\mu$M |
| Cytotoxicity, $CC_{50}$ | > 25 $\mu$M [1] | > 100 $\mu$M [2] |
| PBS solubility[3] | 9.4 $\mu$M | 12 $\mu$M |
| Microsomal stability[4] | 0.02% | 42.3% |

[1]IMR90 cells; [2]HFF cells; [3]pH 7.4, [4]mouse, 1h, % parent remaining

**Figure 5-3.** CHOP activation (**A**), antiproliferation activities and physical chemical profiles (**B**) of **ML291** and **BDGR-6029**

## 5.4 Conclusions

A scaffold hopping of sulfonamidebenzamides led to the discovery of **BDGR-6029**, a new chemotype that showed good activity on CHOP activation and antiproliferation activity ($EC_{50}$ = 10.2 $\mu$M) against SCC23 cell line with minimum toxicity ($CC_{50}$ > 100 $\mu$M). Notably, **BDGR-6029** showed a 2100-fold improvement of microsomal stability (42.3% parent drug remaining at 1 hour in mouse microsomes), and was selected for further structure modification.

## 5.5 Acknowledgement

This work made use of instrumentation at the UW−Madison Medicinal Chemistry Center and Analytical Instrumentation Center, funded by the UW School of Pharmacy. Gang Yan are

thankful to the collaborators Dr. Andrew Fribley's laboratory from Wayne State University for measuring activation against CHOP.

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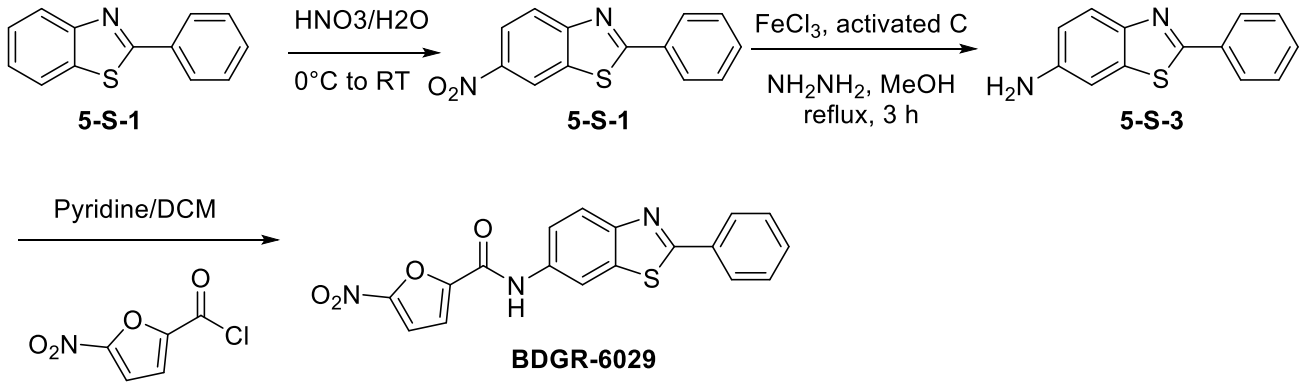
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## 5.6 Experimental section

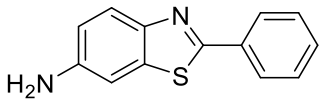
### *5.6.1. Synthesis of BDGR-6029*




**Procedure:**

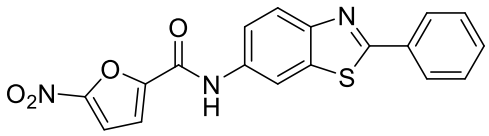
**Step 1:** To a vial was added **5-S-1** (1055 mg, 5 mmol) and conc. $HNO_3$ (> 90%, 20 mL) at 0 ºC. The mixture was stirred at room temperature overnight. After the completion of the reaction, the mixture was quenched with crush ice and basified with 30% aq. NaOH. The precipitates was filtered out, washed with water and dried under vaccum. Yield: 1.25 g, 98%, yellowish solid. The solid was used in the next step without further purification.

**Step 2:** To a vial was added the starting material **5-S-1** (512 mg, 2 mmol), $FeCl_3$•$6H_2O$ (36 mg, 0.132 mmol), activated charcoal (640 mg, 6.6 mmol) and MeOH (50 mL). The mixture was heated to reflux for 10 min, followed by the addition of 65% $NH_2NH_2$•$xH_2O$ (640 mg, 8 mmol). The mixture was refluxed for 3 hours. After the completion of the reaction, the mixture was filtered through celite, concentrated under reduced pressure and purified by flash column. Eluent: 0% ~ 1% Ethyl acetate/DCM. Yield: 272 mg, 60%, yellowish solid.



**2-phenylbenzo[*d*]thiazol-6-amine (5-S-2)** $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 8.01 – 7.91 (m, 2H), 7.70 (d, *J* = 8.7 Hz, 1H), 7.54 – 7.44 (m, 3H), 7.10 (d, *J* = 2.2 Hz, 1H), 6.81 (dd, *J* = 8.7, 2.2 Hz, 1H), 5.50 (s, 2H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 160.45, 147.53, 145.18, 136.34, 133.50, 130.19, 129.22, 126.42, 123.24, 115.17, 103.73.

**Step 3:** To a solution of **5-S-2** (68 mg, 0.3 mmol) and pyridine (0.08 mL, 1 mmol) in DCM (5 mL) was added 5-nitrofuran-2-carbonyl chloride (88 mg, 0.5 mmol). The mixture was stirred at room temperature overnight. After the completion of the reaction, the mixture was diluted with DCM (10 mL) and extracted with 10% aq. Citric acid (15 mL), aq. $NaHCO_3$ (15 mL) and brine (15 mL). The organic phase was dried with $Na_2SO_4$ and purified by column. Eluent: 0.2% ~ 1% MeOH/DCM. Yield: 72 mg, 65%, orange solid.



**5-nitro-*N*-(2-phenylbenzo[*d*]thiazol-6-yl)furan-2-carboxamide (BDGR-6029)** $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 10.89 (s, 1H), 8.59 (d, *J* = 2.1 Hz, 1H), 8.10 – 8.03 (m, 3H), 7.84 – 7.79 (m, 2H), 7.67 (d, *J* = 3.9 Hz, 1H), 7.60 – 7.53 (m, 3H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 166.76, 154.71, 151.83, 150.46, 147.77, 135.50, 135.06, 132.85, 131.32, 129.41, 127.07, 122.95, 120.41, 116.79, 113.49, 113.43.

# Chapter 6. Synthesis and Optimization of Sulfonamidebenzamides Targeting the *Trypanosoma brucei*

## 6.1 Abstract

*T. brucei* parasites are responsible for the widespread tropical disease human African trypanosomiasis, which afflict millions of people living in tropical areas. Unfortunately, current drugs are limited by toxicity, side effects, difficulty of administration and increasing drug resistance. The Golden group discovered sulfonamidebenzamide scaffold showing potent anti-*T. brucei* activity. However, these compounds exhibited poor microsomal stabilities and solubilities. In this chapter, the structure optimization was performed to optimize physical chemical properties of these molecules while retaining the antiparasitic activity. A scaffold hopping led to the discovery of **BDGR-6029**, a new scaffold that showed potent antiparasitic activities with minimum toxicity and good microsomal stability.

Adapted from **Gang Yan,** Alok Nerurkar, Bereket L. Zekarias, James Morris* and Jennifer E. Golden*. Synthesis and Optimization of Sulfonamidebenzamides Targeting the *Trypanosoma brucei* (*Manuscript in preparation*)

## 6.2 Introduction

As mentioned in **Chapter 4**, *T. brucei* parasites are responsible for the widespread tropical disease human African trypanosomiasis (HAT). Unfortunately, current drugs are limited by toxicity, side effects, difficulty of administration and increasing drug resistance.[1] It is urgent to develop new therapeutics for the treatment of HAT.

The Golden group developed sulfonamidebenzamides, as exemplified by compound **5-1** (**Figure 6-1**), which exhibited good potency on activation of CHOP pathway (See **Chapter 5**). At the same time, we noted that these compounds such as hit compound **5-1** shared similar structural features with **Nifurtimox** (**6-1**)[2-4], an orally bioavailable anti-*T. brucei* drug. (**Figure 6-1**) Both compounds contain a 5-nitrofuran group in conjugation with a $sp^2$ hybridized carbon system (orange region), a nitrogen containing linker (blue region) and a -$SO_2$- containing group (sulfone or sulfonamide, red region). Given the visual similarities of these molecules with **Nifurtimox**, we decided to assess the antiparasitic activity against *T. brucei*.

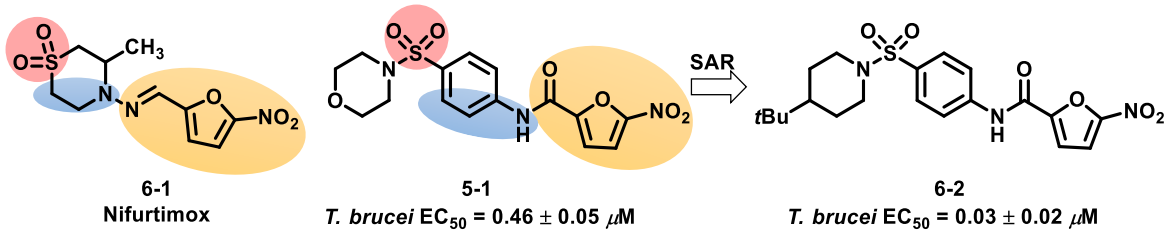



**Figure 6-1.** Similar structural motifs between Nifurtimox and hit compound **5-1**, and the SAR studies affording compound **6-2**

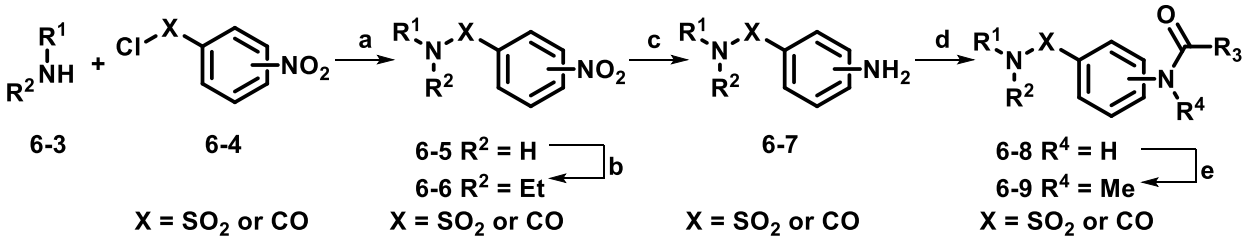
To our delight, compound **5-1** showed an $EC_{50}$ value of 0.46 $\mu$M against BSF *T. brucei*. SAR studies were performed by the Golden group affording compound **6-2** with $EC_{50}$ = 0.03 $\mu$M against BSF *T. brucei* (**Figure 6-1**).[5] In addition, the SAR showed a different trend from the CHOP SAR, which suggested a different mechanism rather than CHOP activation of *T. brucei*.

The preliminary mechanistic studies suggested that these compounds triggered programmed cell death (PCD)-like responses in the parasite.[5]

In this chapter, the SAR optimization was performed to optimize toxicity and the microsomal stability of these molecules while retaining the antiparasitic activity. A scaffold hopping of sulfonamidebenzamides led to the discovery of **BDGR-6029**, a new scaffold that showed potent antiparasitic activities with minimum toxicity and improved microsomal stability.

## 6.3 Chemistry

The syntheses of these compounds are described in **Scheme 6-1**. In this route, substituted amines (**6-3**) were coupled with nitrobenzenesulfonyl/carbonyl chloride (**6-4**) to afford intermediates **6-5**, some of which was transformed to the *N*-Et product **6-6** using EtI under basic condition. Then the nitro group was reduced to amino group affording intermediate **6-7,** followed by another amide coupling reaction to form the final compounds (**6-8**). The *N*-$CH_3$ product (**6-9**) was obtained by *N*-methylation reaction of **6-8** with MeI under basic conditions.




**Scheme 6-1.** Synthesis of sulfonamidebenzamides. Reagent and conditions: (a) pyridine, DCM, RT, overnight, 36% ~ 91%; (b) EtI, $K_2CO_3$, MeCN, 65 °C, 48h, 75% ~ 76%; (c) 6.5 mol% $FeCl_3 \cdot H_2O$, activated charcoal, $NH_2NH_2 \cdot H_2O$, MeOH, reflux, 1~2h, quantitative; (d) $R^3COCl$, pyridine, DCM, overnight, 38% ~ 90%; (e) MeI, $K_2CO_3$, MeCN, 40 °C, 24h, 72% ~ 75%.

By collaborating with Dr. Alok Nerurkar, over 80 compounds were synthesized. All final compounds were confirmed by $^{1}H$ and $^{13}C$ NMR, and purity was validated to be > 95% by UV/HPLC.

## 6.4 Results and discussion

Compounds were optimized through iterative analog synthesis and testing. All final compounds were assessed in the growth inhibition assay against BSF *T. brucei*. The toxicity of these compounds was also assessed. Since these compounds were originally CHOP activators, immortalized cell lines, which is commonly used to assess the mammalian toxicity, are not the best choice for toxicity measurement due to their high sensitivity to cell apoptosis modulators. As such, non-immortalized human foreskin fibroblast (HFF) cell line were used to measure the mammalian cytotoxicity. For selected compound, microsomal stability was tested to monitor the parent compound remaining after 1 hour in mouse microsomes.

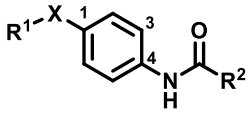
The antiparasitic activities, toxicities and selectivity index (SI = $EC_{50}/CC_{50}$) of compounds bearing a 1,4-substituted middle phenyl ring are shown in **Table 6-1**. The tolerance of linker X was investigated. Compounds bearing a sulfonyl group (**6-10**, **6-12**, **6-15**) as linker displayed similar or slightly better growth inhibition activity against BSF *T. brucei* than compounds bearing a carbonyl linker (**6-11**, **6-13**, **6-16**), while the -$SO_2$- containing compounds showed better toxicity profile with selectivity up to 1040 (**6-15**). A survey of different $R^1$ groups were also explored. Compounds bearing 4-substituted piperidyl group, such as 4-(*tert*-butyl)piperidin-1-yl (**6-10**, $EC_{50}$ = 30 nM) or 3-azaspiro[5.5]undecan-3-yl group (**6-14**, $EC_{50}$ = 30 nM), are 8 times more potent than 1-(pyridin-3-ylmethyl)amino group (**6-12**, $EC_{50}$ = 230 nM**)** against BSF *T. brucei*. However, the toxicity displayed the opposite way. Compound **6-12** showed a SI value of 250, while significant cytotoxicities were observed in compounds **6-10** and **6-14**, showing SI values of 21 or

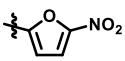
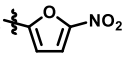
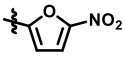
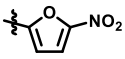
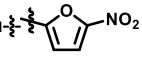
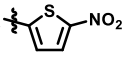
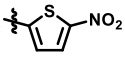
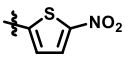
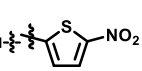
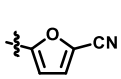
18, respectively. A broader investigation of $R^2$ group was also pursued. Compounds with 5-nitrofuran-2-yl (**6-10**) or 5-nitrothiophen-2-yl (**6-15**) moiety have significantly better activity than other substitution. Incorporating other substituents for $R^2$ group (compound **6-19 ~ 6-27**), however, showed significant loss of potency against parasite growth inhibition. Although both 5-nitrofuran-2-yl and 5-nitrothiophen-2-yl substitution displayed similar good potency, the 5-nitrothiophen-2-yl substitution displayed lower toxicity than 5-nitrofuran-2-yl compounds (**6-10** vs **6-15**, **6-14** vs **6-18**). Other modifications on this scaffold were also performed. The hydrogen atom of the amide -*NH*- of **6-10**or **6-15** were replaced with methyl group, affording compound **6-28** and **6-29**, both of which were about 30 times less potent than the original -*NH*- compound, suggesting that the amide -*NH*- might be a critical hydrogen bond donor to the target. Replacement of phenyl ring of **6-10** with benzothiazole ring (**6-30**) showed 24 times less potent antiparasitic activity. In all of this series of compounds, compound **6-15** displayed best overall profile with good activity (0.03 $\mu$M) against the growth inhibition of BSF *T. brucei* and relatively low toxicity (31.2 $\mu$M) with the SI value for over 1000.

Compounds bearing a 1,3-disubstituted phenyl core were also explored. (**Table 6-2**) The SAR trend is comparable to compounds bearing 1,4-disubstituted phenyl core. The -$NO_2$ group was critical to the activity. Compounds bearing a -CN substituted furan or thiophene ring (**6-43**, **6-44**) almost lost the activity. The $R^2$ group bearing 5-nitrothiophen-2-yl substitution (**6-32**, **6-34, 6-35 ~ 6-38**) showed similar or better activity than the corresponding 5-nitrofuran-2-yl compounds (**6-31**, **6-33, 6-39 ~ 6-42**). All of the compounds with a 5-nitrofuran-2-yl group (**6-31**, **6-33, 6-39 ~ 6-42**) displayed significant cytotoxicity to the HFF cell line with $CC_{50}$ value of 0.037 - 0.84 $\mu$M and SI value of <20, even though some of them showed very potent antiparasitic activity (such as **6-41**, $EC_{50}$ = 2 nM). However, compounds bearing a 5-nitrothiophen-2-yl group (**6-32**, **6-34, 6-35**

**~ 6-38**) exhibited better toxicity profiles with SI values of up to 556. The tolerance of different $R^1$ substitution was also explored. Compounds bearing $R^1$ as *cis* or *trans* 4-*t*-butylcyclohexylamino group and $R^2$ as 5-nitrothiophen-2-yl group (**6-35 ~ 6-38**) showed single digit nanomolar activity (8 ~ 9 nM) against *T. brucei* and tolerate toxicity with 100 ~ 500-fold SI.

**Table 6-1.** Anti-*T brucei* activities and toxicities of the 1,4-disubstituted sulfonamidebenzamides



| Cmpd No. | X | $R_1$ | $R_2$ | *T. brucei* BSF $EC_{50}$ ($\mu$M) | HFF $CC_{50}$ ($\mu$M) | SI |
|---|---|---|---|---|---|---|
| 6-10 |  |  |  | 0.03±0.02 | 0.675 | 21 |
| 6-11 |  |  |  | 0.09 ± 0.02 | <1 | < 11 |
| 6-12 |  |  |  | 0.20±0.01 | > 50 | 250 |
| 6-13 |  |  |  | 0.23±0.01 | <10 | 43 |
| 6-14 |  |  |  | 0.03 ± 0.00 | 0.548 | 18 |
| 6-15 |  |  |  | 0.03 ± 0.00 | 31.2 | 1040 |
| 6-16 |  |  |  | 0.09 ± 0.05 | 0.054 | 0.6 |
| 6-17 |  |  |  | 0.14 ± 0.01 | 49.3 | 352 |
| 6-18 |  |  |  | 0.03 ± 0.01 | > 5 | >167 |
| 6-19 |  |  |  | >10 | ND | ND |
| 6-20 |  |  |  | 6.3 ± 1.1 | 49.8 | 8 |

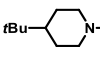
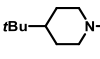
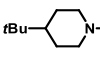
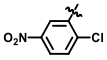
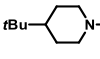
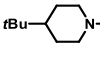
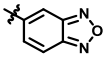
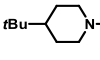
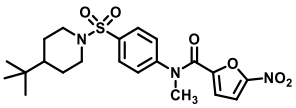
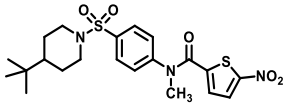
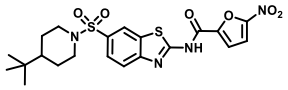
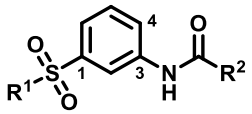
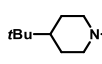
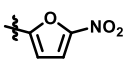
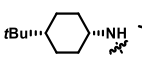
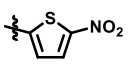
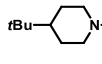
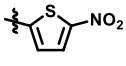
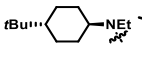
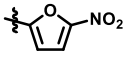
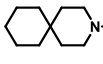
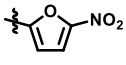
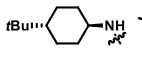
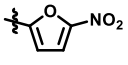
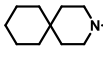
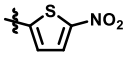
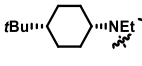
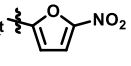
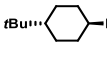
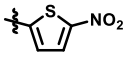
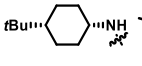
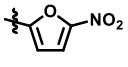
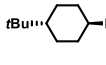
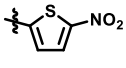
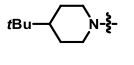
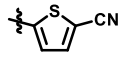
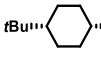
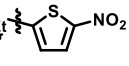
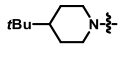
| Cmpd No. | X | $R_1$ | $R_2$ | *T. brucei* BSF $EC_{50}$ ($\mu$M) | HFF $CC_{50}$ ($\mu$M) | SI |
|---|---|---|---|---|---|---|
| 6-21 |  |  |  | 8.9 ± 2.1 | 5~10 | ~1 |
| 6-22 |  |  |  | 0.21 ± 0.04 | > 5 | > 24 |
| 6-23 |  |  |  | > 10 | > 5 | ND |
| 6-24 |  |  |  | 5.76 ± 0.46 | 47.9 | 8 |
| 6-25 |  |  |  | > 10 | 12.1 | <1 |
| 6-26 |  |  |  | 4.5 ± 0.1 | 14.9 | 3 |
| 6-27 |  |  |  | 6.5 ± 1.0 | >50 | > 8 |
| 6-28 |  | | | 1.3 ± 0.2 | > 50 | 40 |
| 6-29 |  | | | 0.96 ± 0.19 | 39.5 | 41 |
| 6-30 |  | | | 0.72 ± 0.19 | 0.68 | 1 |

**Table 6-2.** Anti-*T brucei* activities and toxicities of the 1,3-disubstituted sulfonamidebenzamides



| Cmpd No. | $R_1$ | $R_2$ | *T. brucei* BSF $EC_{50}$ ($\mu$M) | HFF CC50 ($\mu$M) | SI | Cmpd No. | $R_1$ | $R_2$ | *T. brucei* BSF $EC_{50}$ ($\mu$M) | HFF CC50 ($\mu$M) | SI |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 6-31 12a |  |  | 0.50 ± 0.03 | 0.36 | 0.7 | 6-38 12h |  |  | 0.046 ± 0.006 | > 5 | >108 |
| 6-32 12b |  |  | 0.009 ± 0.006 | > 5 | > 556 | 6-39 12i |  |  | 0.092 ± 0.015 | 0.18 | 2 |
| 6-33 12c |  |  | 0.20 ± 0.01 | 0.84 | 4 | 6-40 12j |  |  | 0.026 ± 0.003 | 0.11 | 4 |
| 6-34 12d |  |  | 0.13 ± 0.01 | > 5 | > 38 | 6-41 12k |  |  | 0.002 ± 0.001 | 0.037 | 16 |
| 6-35 12e |  |  | 0.009 ± 0.003 | 4.2 | 485 | 6-42 12l |  |  | 0.361 ± 0.056 | 0.36 | 1 |
| 6-36 12f |  |  | 0.008 ± 0.002 | 0.83 | 107 | 6-43 12m |  |  | >10 | >100 | ND |
| 6-37 12g |  |  | 0.008 ± 0.001 | 2.3 | 283 | 6-44 12n |  |  | >10 | > 50 | ND |

The microsomal stabilities and solubilities were evaluated for selected compounds. (**Figure 6-2**) Some compounds exhibited good potency against growth inhibition of BSF *T. brucei* and acceptable cytotoxicity, however, similar to **ML291** (0% remaining in mouse microsomes), they showed poor microsomal stabilities. For example, compounds **6-32**, **6-35** and **6-37** displayed 8 ~ 9 nM antiparasitic activity, however, the parent drug remaining in mouse microsomes were 0%, 7.7% and 0.5%, respectively. The solubilities for both **6-32** and **6-37** were also very low with values of 0.47 $\mu$M and 0.041 $\mu$M, respectively.

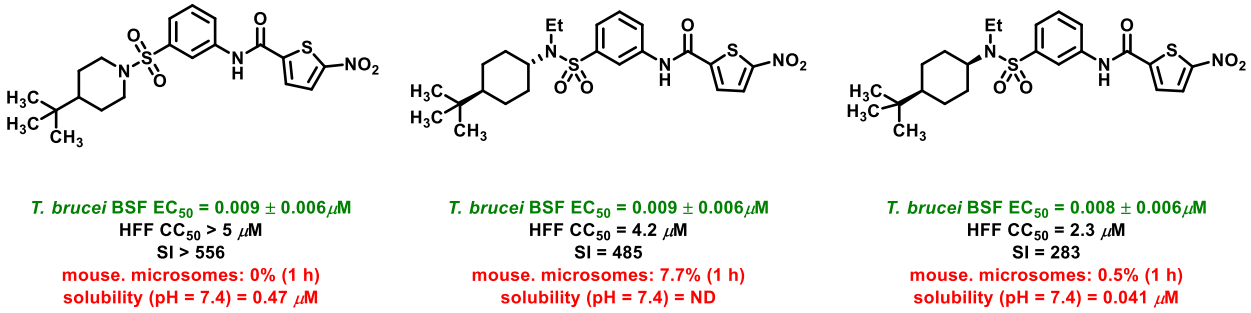



**Figure 6-2.** Activity and property profiles for selected compounds

As described in **Chapter 5**, a scaffold hopping strategy was performed affording a new chemotype **BDGR-6029**. (**Figure 6-3**) A benzothiazole middle core was incorporated for the replacement of phenylsulfonamide core of the sulfonamidebenzamide series. Fortunately, **BDGR-6029** not only retained the potency against BSF *T. brucei* with an $EC_{50}$ value of 0.29 $\mu$M, but also displayed excellent toxicity profile with $CC_{50}$ > 100 $\mu$M and SI > 345. In addition, as a hit compound, **BDGR-6029** showed good solubility (12 $\mu$M) and microsomal stability (42% remaining after 1 hour).

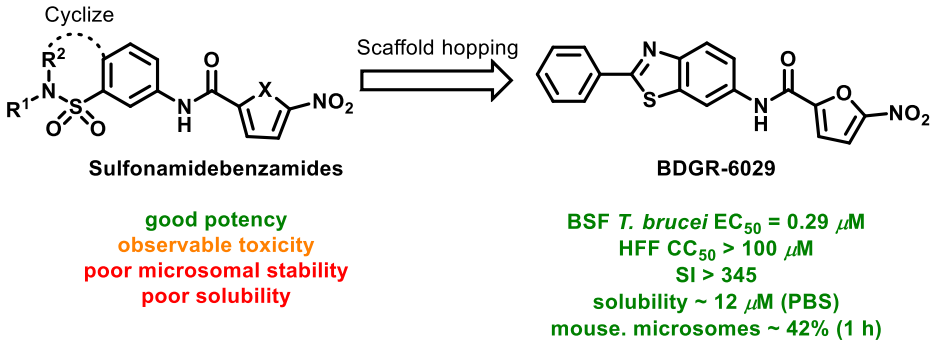



**Figure 6-3.** Scaffold hopping to afford new chemotype **BDGR-6029**

## 6.5 Conclusion

The SAR optimization of sulfonamidebenzamides was performed to optimize the physical chemical properties while retaining the antiparasitic activity. As a result, although some compounds displayed single digit nanomolar activity against BSF *T. brucei*, they still showed

observable toxicity and poor physical chemical properties. A scaffold hopping led to the discovery of **BDGR-6029**, a new chemotype that showed potent antiparasitic activities ($EC_{50}$ = 0.29 $\mu$M against BSF *T. brucei*) with minimum toxicity ($CC_{50}$ > 100 $\mu$M). Notably, **BDGR-6029** showed a great improvement of microsomal stability (42.3% parent drug remaining at 1 hour in mouse microsomes), and was selected for further structure modification.

## 6.6 Acknowledgement

This work made use of instrumentation at the UW−Madison Medicinal Chemistry Center and Analytical Instrumentation Center, funded by the UW School of Pharmacy. Gang Yan are thankful to the collaborators Dr. James Morris's laboratory from Clemson University for measuring the growth inhibition against BSF *T. brucei*.

## 6.7 References

[1] *WHO Trypanosomiasis, human African (sleeping sickness) Fact sheet* **October 2019**, https://www.who.int/en/news-room/fact-sheets/detail/trypanosomiasis-human-african-(sleeping-sickness).

[2] G. Priotto, S. Kasparian, W. Mutombo, D. Ngouama, S. Ghorashian, U. Arnold, S. Ghabri, E. Baudin, V. Buard, S. Kazadi-Kyanza, M. Ilunga, W. Mutangala, G. Pohlig, C. Schmid, U. Karunakara, E. Torreele, V. Kande, *The Lancet* **2009**, *374*, 56-64.

[3] G. Priotto, S. Kasparian, D. Ngouama, S. Ghorashian, U. Arnold, S. Ghabri, U. Karunakara, *Clinical Infectious Diseases* **2007**, *45*, 1435-1442.

[4] F. Checchi, P. Piola, H. Ayikoru, F. Thomas, D. Legros, G. Priotto, *PLOS Neglected Tropical Diseases* **2007**, *1*, e64.

[5] A. Hackler, S. L. Patrick, E. W. Kahney, D. P. Flaherty, E. R. Sharlow, J. C. Morris, J. E. Golden, *Bioorganic & Medicinal Chemistry Letters* **2017**, *27*, 755-758.

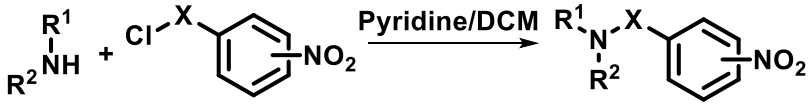
## 6.8 Experimental section

### *6.8.1. General information*

Commercial reagents and solvents were used as received from Sigma Aldrich, Fischer Scientific, Acros Organics, TCI America, Oakwood Products Inc, VWR International, etc. All thin layer chromatography was performed using precoated silica gel plates. Flash chromatography separations were carried out using a Teledyne Isco CombiFlash Rf 200 purification system with silica gel columns. Melting points were measured on OptiMelt MPA100 Automated Melting Point System. $^{1}H$ and $^{13}C$ nuclear magnetic resonance (NMR) spectra were obtained on a Varian Unity-Inova 400 MHz or 500 MHz, or Bruker Ascend 400 MHz in $CDCl_3$ or DMSO-$d_6$. The chemical shifts (δ) reported are given in parts per million (ppm). The Signal splitting patterns were described as s = singlet, d = doublet, t = triplet, q = quartet, p = pentuplet, dd = doublet of doublet, dt = doublet of triplet, td = triplet of doublet, tt = triplet of triplet, ddd = doublet of doublet of doublet, and m = multiplet, with coupling constants (*J*) in hertz (Hz). The chemical shifts of $^{19}F$ NMR was referenced by "Absolute Reference" of MestReNova. All final compounds were determined to be of ≥ 95% purity by UV-HPLC at 254 nm.

### *6.8.2. Experimental Procedures and Product Characterization*

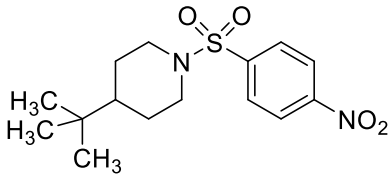
#### 6.8.2.1 Synthesis of intermediate 6-5



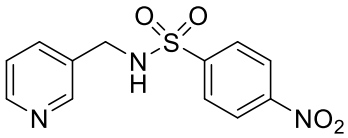

X = $SO_2$ or CO  X = $SO_2$ or CO

**General procedure**: To a solution of amine/piperidine (1 mmol) and pyridine (0.18 mL, 2.2 mmol) in DCM (5 mL) was added appropriate sulfonyl chloride or acyl chloride (1 mmol). The mixture

was stirred at room temperature overnight. After the completion of the reaction, the mixture was diluted with DCM (10 mL) and extracted with 10% aq. Citric acid (15 mL), aq. $NaHCO_3$ (15 mL) and brine (15 mL). The organic phase was dried with $Na_2SO_4$ and purified by column or recrystallized with DCM/Hexane.

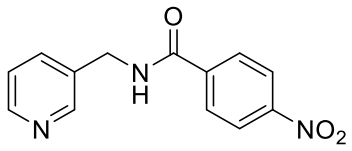



**4-(*tert*-butyl)-1-((4-nitrophenyl)sulfonyl)piperidine (1-5-1-GY)** The reaction was performed with 4-(*tert*-butyl)piperidine (155 mg, 1.1 mmol), pyridine (0.18 mL, 2.2 mmol), 4-nitrobenzenesulfonyl chloride (221 mg, 1 mmol) and DCM (5 mL) using the above method. Recrystallized with DCM/Hexane. Yield: 205 mg, 63%; yellowish solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.53 – 8.33 (m, 2H), 8.10 – 7.92 (m, 2H), 3.76 (d, $J$ = 11.4 Hz, 2H), 2.22 (t, $J$ = 12.0 Hz, 2H), 1.68 (d, $J$ = 12.9 Hz, 2H), 1.25 – 1.13 (m, 2H), 0.93 (t, $J$ = 12.1 Hz, 1H), 0.77 (s, 9H).

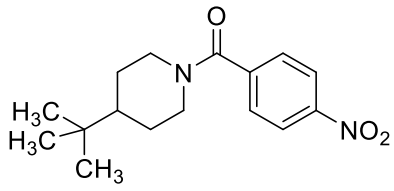



**4-nitro-*N*-(pyridin-3-ylmethyl)benzenesulfonamide (1-7-1-GY)** The reaction was performed with pyridin-3-ylmethanamine (119 mg, 1.1 mmol), pyridine (0.18 mL, 2.2 mmol), 4-nitrobenzenesulfonyl chloride (221 mg, 1 mmol) and DCM (5 mL) using the above method. Recrystallized with DCM/Hexane. Yield: 249 mg, 84%; yellowish solid. $^1$H NMR (500 MHz,

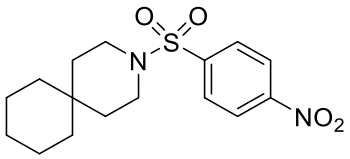
DMSO-$d_6$) δ 8.65 (t, *J* = 6.2 Hz, 1H), 8.49 – 8.39 (m, 2H), 8.39 – 8.28 (m, 2H), 8.09 – 7.96 (m, 2H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 6.3 Hz, 1H), 4.13 (d, *J* = 6.1 Hz, 2H).



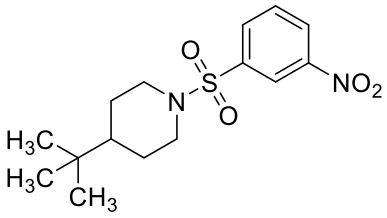

**4-nitro-*N*-(pyridin-3-ylmethyl)benzamide (1-9-1-GY)** The reaction was performed with pyridin-3-ylmethanamine (119 mg, 1.1 mmol), pyridine (0.18 mL, 2.2 mmol), 4-nitrobenzoyl chloride (186 mg, 1 mmol) and DCM (5 mL) using the above method. The product was crush out from the reaction mixture, the solids were filtered out and washed with hexane (10 mL × 3). Yield: 226 mg, 88%; yellowish solid. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 9.41 (t, *J* = 5.9 Hz, 1H), 8.57 (d, *J* = 2.2 Hz, 1H), 8.47 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.33 (d, *J* = 8.8 Hz, 2H), 8.11 (d, *J* = 8.9 Hz, 2H), 7.75 (dt, *J* = 7.8, 2.0 Hz, 1H), 7.37 (dd, *J* = 7.8, 4.8 Hz, 1H), 4.53 (d, *J* = 5.8 Hz, 2H).



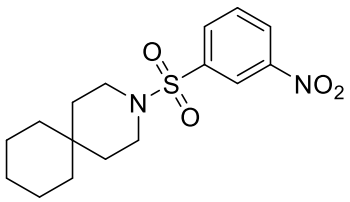

**(4-(*tert*-butyl)piperidin-1-yl)(4-nitrophenyl)methanone (1-29-1-GY)** The reaction was performed with 4-(*tert*-butyl)piperidine (141 mg, 1 mmol), pyridine (0.18 mL, 2.2 mmol), 4-nitrobenzoyl chloride (203 mg, 1.1 mmol) and DCM (5 mL) using the above method. Eluent: 20% Ethyl acetate/Hexane. Yield: 204 mg, 70%; white solid. $^1$H NMR (500 MHz, Chloroform-*d*) δ 8.32 – 8.23 (m, 2H), 7.62 – 7.52 (m, 2H), 4.81 (d, *J* = 13.2 Hz, 2H), 3.63 (d, *J* = 13.4 Hz, 2H), 2.99 (t, *J* = 13.1 Hz, 2H), 2.70 (t, *J* = 11.5 Hz, 2H), 1.67 (d, *J* = 13.0 Hz, 1H), 0.88 (s, 9H).



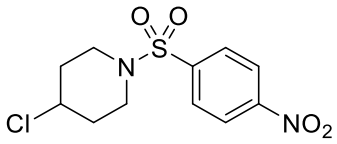
**3-((4-nitrophenyl)sulfonyl)-3-azaspiro[5.5]undecane (1-43-1-GY)** The reaction was performed with 3-azaspiro[5.5]undecane (168 mg, 1.1 mmol), pyridine (0.18 mL, 2.2 mmol), 4-nitrobenzenesulfonyl chloride (221 mg, 1 mmol) and DCM (5 mL) using the above method. Eluent: 10% Ethyl acetate/Hexane. Yield: 220 mg, 65%; white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.49 – 8.37 (m, 2H), 8.04 – 7.95 (m, 2H), 2.96 (t, $J$ = 5.7 Hz, 4H), 1.44 (t, $J$ = 5.7 Hz, 4H), 1.30 (s, 6H), 1.17 (s, 4H).



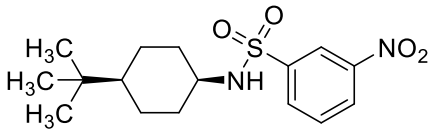
**4-(*tert*-butyl)-1-((3-nitrophenyl)sulfonyl)piperidine (1-57-1-GY)** The reaction was performed with 4-(*tert*-butyl)piperidine (155 mg, 1.1 mmol), pyridine (0.18 mL, 2.2 mmol), 3-nitrobenzenesulfonyl chloride (221 mg, 1 mmol) and DCM (5 mL) using the above method. Eluent: 20% Ethyl acetate/Hexane.Yield: 254 mg, 78%; white solid. $^1$H NMR (400 MHz, Chloroform-$d$) δ 8.60 (s, 1H), 8.45 (d, $J$ = 8.1 Hz, 1H), 8.09 (d, $J$ = 7.8 Hz, 1H), 7.76 (t, $J$ = 8.0 Hz, 1H), 3.93 (d, $J$ = 11.3 Hz, 2H), 2.24 (t, $J$ = 11.8 Hz, 2H), 1.76 (d, $J$ = 13.2 Hz, 2H), 1.39 (qd, $J$ = 12.6, 4.1 Hz, 2H), 0.96 – 0.89 (m, 1H), 0.83 (s, 9H).



**3-((3-nitrophenyl)sulfonyl)-3-azaspiro[5.5]undecane (1-43-1-GY)** The reaction was performed with 3-azaspiro[5.5]undecane (168 mg, 1.1 mmol), pyridine (0.18 mL, 2.2 mmol), 3-nitrobenzenesulfonyl chloride (221 mg, 1 mmol) and DCM (5 mL) using the above method. Eluent: 10% Ethyl acetate/Hexane. Yield: 219 mg, 66%; white solid. $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.60 (t, *J* = 2.0 Hz, 1H), 8.45 (ddd, *J* = 1.1, 2.2, 8.2 Hz, 1H), 8.09 (ddd, *J* = 1.1, 1.7, 7.8 Hz, 1H), 7.77 (t, *J* = 8.0 Hz, 1H), 3.15 – 2.96 (m, 4H), 1.60 – 1.49 (m, 4H), 1.45 – 1.29 (m, 6H), 1.23 (t, *J* = 4.8 Hz, 4H).

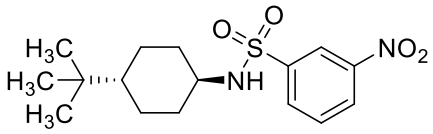



**4-chloro-1-((4-nitrophenyl)sulfonyl)piperidine (1-105-1-GY)** The reaction was performed with 4-chloropiperidine (119 mg, 1.5 mmol), pyridine (0.18 mL, 2.2 mmol), 4-nitrobenzenesulfonyl chloride (332 mg, 1.5 mmol) and DCM (5 mL) using the above method. Eluent: 20% Ethyl acetate/Hexane. Yield: 258 mg, 85%; white solid. $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.41 (d, *J* = 8.7 Hz, 2H), 7.96 (d, *J* = 8.7 Hz, 2H), 4.26 – 4.18 (m, 1H), 3.36 – 3.24 (m, 2H), 3.24 – 3.13 (m, 2H), 2.23 – 2.11 (m, 2H), 2.03 – 1.92 (m, 2H).

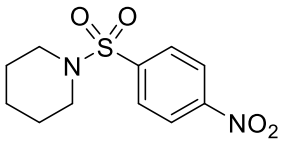



***N*-((1*s*,4*s*)-4-(*tert*-butyl)cyclohexyl)-3-nitrobenzenesulfonamide (1-155-1-GY)** The reaction was performed with a mixture of cis/trans 4-(*tert*-butyl)cyclohexan-1-amine (775 mg, 5 mmol), pyridine (0.9 mL, 11 mmol), 3-nitrobenzenesulfonyl chloride (1655 mg, 7.5 mmol) and DCM (15 mL) using the above method. Eluent: 5% Ethyl acetate/Hexane. Yield: *cis* product: 606 mg, 36%; white solid. $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.76 (s, 1H), 8.43 (d, *J* = 8.2 Hz, 1H), 8.25 (d, *J* = 7.9 Hz, 1H), 7.76 (t, *J* = 8.1 Hz,

1H), 5.38 (d, *J* = 7.3 Hz, 1H), 3.66 – 3.52 (m, 1H), 1.78 – 1.67 (m, 2H), 1.65 – 1.53 (m, 2H), 1.45 (t, *J* = 14.0 Hz, 2H), 1.19 – 1.04 (m, 2H), 0.99 – 0.91 (m, 1H), 0.81 (s, 9H).

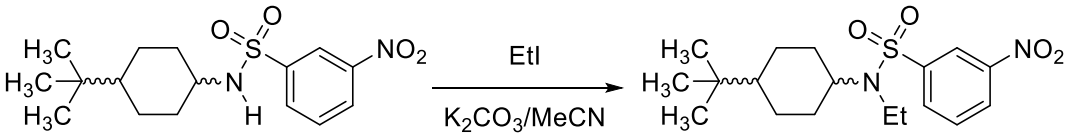


***N*-((1*r*,4*r*)-4-(*tert*-butyl)cyclohexyl)-3-nitrobenzenesulfonamide (1-155-2-GY)** The same batch from the above reaction. The reaction was performed with a mixture of cis/trans 4-(*tert*-butyl)cyclohexan-1-amine (775 mg, 5 mmol), pyridine (0.9 mL, 11 mmol), 3-nitrobenzenesulfonyl chloride (1655 mg, 7.5 mmol) and DCM (15 mL) using the above method. Eluent: 5% Ethyl acetate/Hexane. Yield: *trans* product: 620 mg, 37%; white solid. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 8.73 (t, *J* = 2.1 Hz, 1H), 8.42 (dt, *J* = 8.0, 1.8 Hz, 1H), 8.22 (d, *J* = 7.5 Hz, 1H), 7.74 (t, *J* = 8.0 Hz, 1H), 4.73 (d, *J* = 7.8 Hz, 1H), 3.12 (tdt, *J* = 11.8, 8.1, 4.1 Hz, 1H), 1.89 (d, *J* = 9.7 Hz, 2H), 1.73 (d, *J* = 11.5 Hz, 2H), 1.20 – 1.09 (m, 2H), 1.05 – 0.94 (m, 2H), 0.93 – 0.86 (m, 1H), 0.80 (s, 9H).

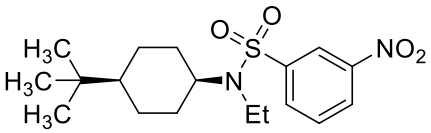


**1-((4-nitrophenyl)sulfonyl)piperidine (1-293-1-GY)** The reaction was performed with a mixture of cis/trans piperidine (0.98 mL, 10 mmol), pyridine (1.8 mL, 22 mmol), 4-nitrobenzenesulfonyl chloride (3.32 g, 15 mmol) and DCM (20 mL) using the above method. Eluent: 40% ~ 100% DCM/Hexane. Yield: 2459 mg, 91%; yellowish solid. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 8.37 (d, *J* = 8.9 Hz, 2H), 7.93 (d, *J* = 8.9 Hz, 2H), 3.04 (t, *J* = 4.4 Hz, 4H), 1.65 (p, *J* = 5.8 Hz, 4H), 1.49 – 1.39 (m, 2H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 150.2, 142.7, 128.8, 124.4, 47.0, 25.2, 23.5.

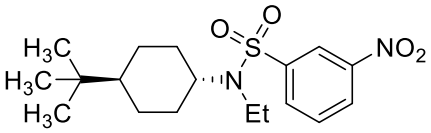
## 6.8.2.2 Synthesis of intermediate 6-6




**General procedure:** To a sealed tube was added the *N*-(4-(*tert*-butyl)cyclohexyl)-3-nitrobenzenesulfonamide (340 mg, 1 mmol), $K_2CO_3$ (274 mg, 2 mmol), EtI (1550 mg, 10 mmol) and MeCN (2 mL). The mixture was stirred at 60 ºC for 48 hours. After the completion of the reaction, the solvent was removed under reduced pressure. The crude product was purified by flash column.



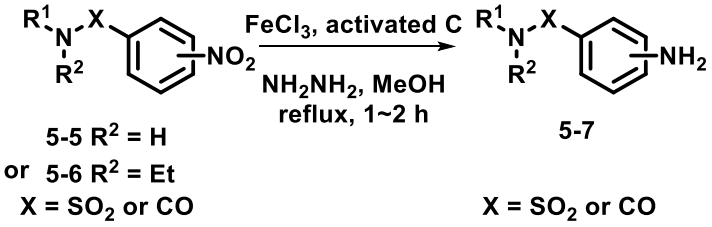

***N*-((1*s*,4*s*)-4-(*tert*-butyl)cyclohexyl)-*N*-ethyl-3-nitrobenzenesulfonamide (1-157-1-GY)** The reaction was performed as the method described above. Eluent: 3% Ethyl acetate/Hexane. Yield: 276 mg, 75%; white solid. $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.66 (ddd, *J* = 2.2, 1.7, 0.5 Hz, 1H), 8.39 (ddd, *J* = 8.2, 2.2, 1.1 Hz, 1H), 8.16 (ddd, *J* = 7.8, 1.8, 1.1 Hz, 1H), 7.71 (ddd, *J* = 8.3, 7.8, 0.5 Hz, 1H), 3.89 (tt, *J* = 8.3, 5.1 Hz, 1H), 3.32 (q, *J* = 7.0 Hz, 2H), 1.74 – 1.67 (m, 2H), 1.57 – 1.49 (m, 4H), 1.47 – 1.38 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.22 – 1.15 (m, 1H), 0.84 (s, 9H).




***N*-((1*r*,4*r*)-4-(*tert*-butyl)cyclohexyl)-*N*-ethyl-3-nitrobenzenesulfonamide (1-159-1-GY)** The reaction was performed as the method described above. Eluent: 3% Ethyl acetate/Hexane. Yield: 280 mg, 76%; white solid. $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.67 (ddd, *J* = 2.2, 1.7, 0.4 Hz, 1H), 8.39 (ddd, *J* = 8.2,

2.2, 1.1 Hz, 1H), 8.16 (ddd, *J* = 7.8, 1.7, 1.0 Hz, 1H), 7.71 (td, *J* = 8.0, 0.5 Hz, 1H), 3.65 (tt, *J* = 12.1, 3.8 Hz, 1H), 3.27 (q, *J* = 7.1 Hz, 2H), 1.84 – 1.75 (m, 2H), 1.71 – 1.63 (m, 2H), 1.48 – 1.36 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.12 – 1.02 (m, 2H), 0.94 – 0.87 (m, 1H), 0.82 (s, 9H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 148.4, 144.3, 132.5, 130.5, 126.7, 122.1, 58.7, 47.2, 39.0, 32.4, 31.9, 27.7, 26.9, 17.7.

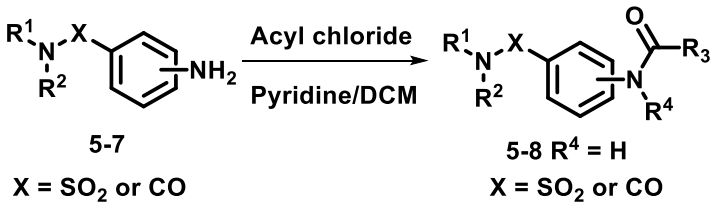
### 6.8.2.3. Synthesis of intermediates 6-7



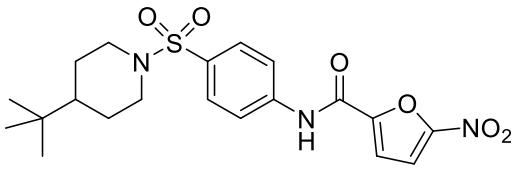

**General procedure:** To a vial was added the starting material **6-5** or **6-6** (1 mmol), $FeCl_3$•$6H_2O$ (18 mg, 0.0065 mmol), activated charcoal (40 mg, 3.3 mmol) and MeOH (10 mL). The mixture was heated to reflux for 10 min, followed by the addition of 65% $NH_2NH_2$•$xH_2O$ (320 mg, 4 mmol). The mixture was refluxed for 1 ~ 2 hours. After the completion of the reaction, the mixture was filtered through celite, concentrated under reduced pressure and dried under vacuum. The crude product was used in the next step without further purification.

### 6.8.2.4. Synthesis of the final products

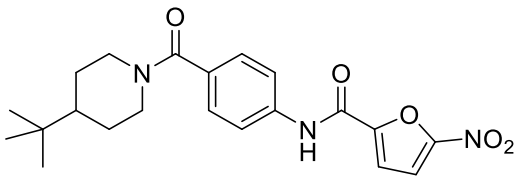
**Method 1:**



**General procedure**: To a solution of **6-7** (0.2 mmol) and pyridine (0.04 mL, 0.4 mmol) in DCM (2 mL) was added appropriate acyl chloride (0.3 mmol). The mixture was stirred at room temperature overnight. After the completion of the reaction, the mixture was diluted with DCM (10 mL) and extracted with 10% aq. Citric acid (15 mL), aq. $NaHCO_3$ (15 mL) and brine (15 mL). The organic phase was dried with $Na_2SO_4$ and purified by column.

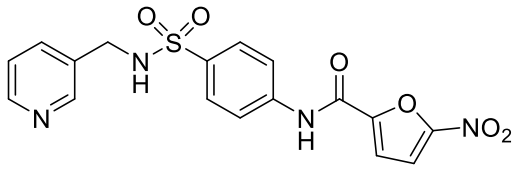


***N*-(4-((4-(*tert*-butyl)piperidin-1-yl)sulfonyl)phenyl)-5-nitrofuran-2-carboxamide (6-10 or 1-21-1-GY)** The reaction was performed with 4-((4-(*tert*-butyl)piperidin-1-yl)sulfonyl)aniline (**1-20-1-GY**, 30 mg, 0.1 mmol), pyridine (0.02 mL, 0.22 mmol), 5-nitrofuran-2-carbonyl chloride (20 mg, 0.11 mmol) and DCM (1 mL) using the above method. Eluent: 20% Ethyl acetate/Hexane. Yield: 26 mg, 60%; yellowish solid. $^1$H NMR (500 MHz, Chloroform-*d*) δ 8.42 (s, 1H), 7.87 (d, *J* = 8.8 Hz, 2H), 7.79 (d, *J* = 8.8 Hz, 2H), 7.47 – 7.40 (m, 2H), 3.90 – 3.84 (m, 2H), 2.19 (td, *J* = 2.4, 12.0 Hz, 2H), 1.73 (d, *J* = 13.5 Hz, 2H), 1.43 – 1.32 (m, 2H), 0.97 – 0.88 (m, 2H), 0.82 (s, 9H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 154.3, 147.2, 140.3, 132.7, 129.3, 120.2, 117.7, 112.8, 47.3, 46.0, 32.3, 27.3, 26.4.

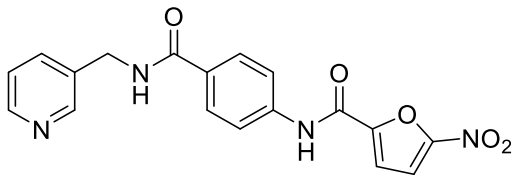


***N*-(4-(4-(*tert*-butyl)piperidine-1-carbonyl)phenyl)-5-nitrofuran-2-carboxamide (6-11 or 1-33-1-GY)** The reaction was performed with (4-aminophenyl)(4-(*tert*-butyl)piperidin-1-

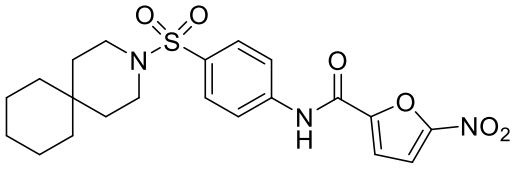
yl)methanone (**1-31-1-GY**, 26 mg, 0.1 mmol), pyridine (0.02 mL, 0.22 mmol), 5-nitrofuran-2-carbonyl chloride (35 mg, 0.2 mmol) and DCM (1 mL) using the above method. Eluent: 20% Ethyl acetate/Hexane. Yield: 17 mg, 43%; yellowish solid. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 8.54 (s, 1H), 7.69 – 7.67 (m, 1H), 7.46 – 7.38 (m, 3H), 4.80 (s, 2H), 3.85 (s, 2H), 2.95 (s, 2H), 2.69 (s, 2H), 1.81 (s, 1H), 0.88 (s, 9H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 169.6, 154.3, 147.8, 137.6, 133.4, 128.3, 120.5, 117.1, 112.8, 47.0, 32.4, 27.4.



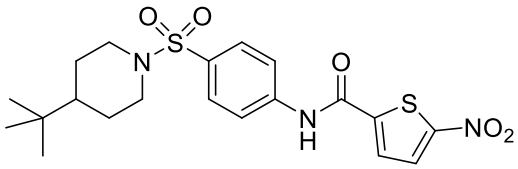
**5-nitro-*N*-(4-(*N*-(pyridin-3-ylmethyl)sulfamoyl)phenyl)furan-2-carboxamide (6-12 or 1-17-1-GY)** The reaction was performed with 4-amino-*N*-(pyridin-3-ylmethyl)benzenesulfonamide (**1-15-1-GY**, 26 mg, 0.1 mmol), pyridine (0.02 mL, 0.22 mmol), 5-nitrofuran-2-carbonyl chloride (20 mg, 0.11 mmol) and DCM (1 mL) using the above method. Product was filtered out from the reaction solution and washed with Hexane. Yield: 16 mg, 40%; yellowish solid. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 10.95 (s, 1H), 8.52 – 8.35 (m, 2H), 8.20 (t, *J* = 6.3 Hz, 1H), 7.95 (d, *J* = 8.8 Hz, 2H), 7.85 (d, *J* = 4.0 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.71 (d, *J* = 4.0 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.32 (dd, *J* = 7.8, 4.8 Hz, 1H), 4.06 (d, *J* = 6.2 Hz, 2H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 154.9, 151.9, 148.9, 148.4, 147.4, 141.4, 135.7, 135.4, 133.3, 127.6, 123.3, 120.4, 117.2, 113.4, 43.7.



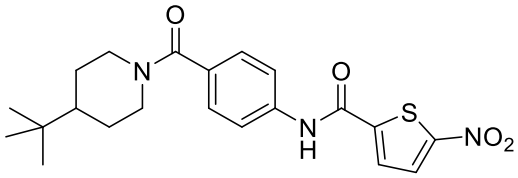
**5-nitro-*N*-(4-((pyridin-3-ylmethyl)carbamoyl)phenyl)furan-2-carboxamide (6-13 or 1-39-1-GY)** The reaction was performed with 4-amino-*N*-(pyridin-3-ylmethyl)benzamide (**1-37-1-GY**, 45 mg, 0.2 mmol), pyridine (0.04 mL, 0.4 mmol), 5-nitrofuran-2-carbonyl chloride (70 mg, 0.4 mmol) and DCM (2 mL) using the above method. Product was filtered out from the reaction solution and washed with DCM and Hexane. Yield: 65 mg, 89%; yellow solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 11.11 (s, 1H), 9.35 (t, *J* = 5.8 Hz, 1H), 8.85 (s, 1H), 8.76 (dd, *J* = 1.4, 5.6 Hz, 1H), 8.44 (dt, *J* = 1.7, 8.2 Hz, 1H), 8.00 – 7.86 (m, 6H), 7.79 (d, *J* = 3.9 Hz, 1H), 4.61 (d, *J* = 5.8 Hz, 2H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 166.0, 154.8, 151.9, 147.6, 143.9, 141.3, 141.0, 139.3, 129.2, 128.2, 126.6, 119.9, 117.2, 113.4, 40.0.



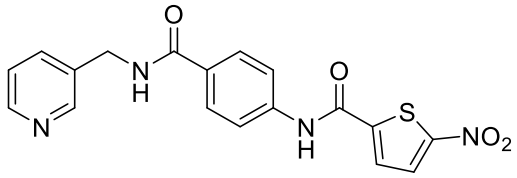
***N*-(4-((3-azaspiro[5.5]undecan-3-yl)sulfonyl)phenyl)-5-nitrofuran-2-carboxamide (6-14 or 1-47-1-GY)** The reaction was performed with 4-((3-azaspiro[5.5]undecan-3-yl)sulfonyl)aniline (**1-45-1-GY**, 60 mg, 0.2 mmol), pyridine (0.04 mL, 0.4 mmol), 5-nitrofuran-2-carbonyl chloride (70 mg, 0.4 mmol) and DCM (2 mL) using the above method. . Eluent: 0.2% MeOH/DCM. Yield: 46 mg, 52%; white solid. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 11.28 (s, 1H), 8.10 (d, *J* = 8.8 Hz, 2H), 7.96 (d, *J* = 3.9 Hz, 1H), 7.85 (d, *J* = 4.0 Hz, 1H), 7.77 (d, *J* = 8.6 Hz, 2H), 2.89 (t, *J* = 5.6 Hz, 4H), 1.45 (t, *J* = 5.7 Hz, 4H), 1.31 (s, 6H), 1.17 (s, 4H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 155.0, 152.0, 147.3, 142.1, 130.5, 128.5, 120.4, 117.4, 113.3, 41.6, 35.2, 34.7, 30.0, 26.1, 20.7.



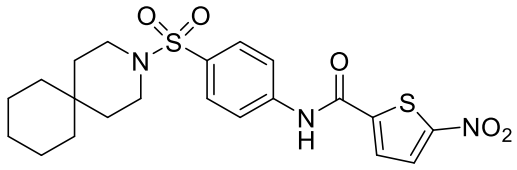
***N*-(4-((4-(*tert*-butyl)piperidin-1-yl)sulfonyl)phenyl)-5-nitrothiophene-2-carboxamide (6-15 or 1-25-1-GY)** The reaction was performed with 4-((4-(*tert*-butyl)piperidin-1-yl)sulfonyl)aniline (**1-20-1-GY**, 15 mg, 0.05 mmol), pyridine (0.01 mL, 0.11 mmol), 5-nitrothiophene-2-carbonyl chloride (11 mg, 0.055 mmol) and DCM (1 mL) using the above method. Eluent: 20% Ethyl acetate/Hexane. Yield: 15 mg, 60%; yellowish solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 11.03 (s, 1H), 8.19 (d, *J* = 4.4 Hz, 1H), 8.13 (d, *J* = 4.5 Hz, 1H), 7.98 (d, *J* = 8.9 Hz, 2H), 7.72 (d, *J* = 8.8 Hz, 2H), 3.67 (d, *J* = 11.2 Hz, 2H), 2.12 – 2.04 (m, 2H), 1.63 (d, *J* = 12.8 Hz, 2H), 1.20 – 1.10 (m, 2H), 0.90 – 0.83 (m, 1H), 0.74 (s, 9H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 158.8, 153.7, 145.4, 142.1, 130.5, 130.1, 129.2, 128.6, 120.3, 46.7, 44.8, 31.8, 27.0, 25.7.



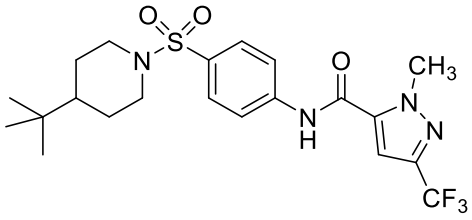

***N*-(4-(4-(*tert*-butyl)piperidine-1-carbonyl)phenyl)-5-nitrothiophene-2-carboxamide (6-16 or 1-35-1-GY)** The reaction was performed with (4-aminophenyl)(4-(*tert*-butyl)piperidin-1-yl)methanone (**1-31-1-GY**, 52 mg, 0.2 mmol), pyridine (0.04 mL, 0.4 mmol), 5-nitrothiophene-2-carbonyl chloride (58 mg, 0.3 mmol) and DCM (2 mL) using the above method. Eluent: 25% Ethyl acetate/Hexane. Yield: 49 mg, 59%; yellow solid. $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 10.79 (s, 1H), 8.24 (d, *J* = 4.4 Hz, 1H), 8.10 (d, *J* = 4.4 Hz, 1H), 7.81 (d, *J* = 8.6 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 4.56 (s, 2H), 3.73 (s, 2H), 2.97 (s, 2H), 2.65 (s, 2H), 1.67 (s, 1H), 0.86 (s, 9H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 168.3, 158.4, 153.5, 146.0, 138.8, 132.2, 130.1, 128.6, 127.8, 120.1, 46.0, 32.0, 27.1.



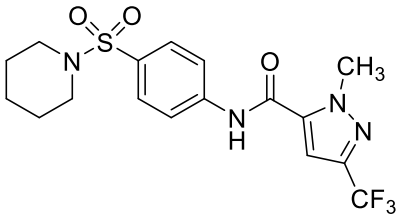
**5-nitro-*N*-(4-((pyridin-3-ylmethyl)carbamoyl)phenyl)thiophene-2-carboxamide (6-17 or 1-39-1-GY)** The reaction was performed with 4-amino-*N*-(pyridin-3-ylmethyl)benzamide (**1-37-1-GY**, 45 mg, 0.2 mmol), pyridine (0.04 mL, 0.4 mmol), 5-nitrothiophene-2-carbonyl chloride (76 mg, 0.4 mmol) and DCM (2 mL) using the above method. Product was filtered out from the reaction solution and washed with DCM and Hexane. Yield: 65 mg, 85%; yellow solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 11.14 (s, 1H), 9.29 (t, $J$ = 5.8 Hz, 1H), 8.81 (s, 1H), 8.73 (d, $J$ = 5.4 Hz, 1H), 8.36 (d, $J$ = 7.9 Hz, 1H), 8.31 (d, $J$ = 4.4 Hz, 1H), 8.17 (d, $J$ = 4.4 Hz, 1H), 7.97 – 7.82 (m, 4H), 4.59 (d, $J$ = 5.7 Hz, 2H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 166.0, 158.6, 153.5, 146.0, 143.0, 142.1, 141.0, 138.9, 130.1, 129.3, 129.1, 128.2, 126.3, 119.9.



***N*-(4-((3-azaspiro[5.5]undecan-3-yl)sulfonyl)phenyl)-5-nitrothiophene-2-carboxamide (6-18 or 1-49-1-GY)** The reaction was performed with 4-((3-azaspiro[5.5]undecan-3-yl)sulfonyl)aniline (**1-45-1-GY**, 60 mg, 0.2 mmol), pyridine (0.04 mL, 0.4 mmol), 5-nitrothiophene-2-carbonyl chloride (76 mg, 0.4 mmol) and DCM (2 mL) using the above method. . Eluent: 0.2% MeOH/DCM. Yield: 35 mg, 38%; white solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 11.25 (s, 1H), 8.28 (d, $J$ = 4.4 Hz, 1H), 8.19 (d, $J$ = 4.4 Hz, 1H), 8.04 (d, $J$ = 8.8 Hz, 2H), 7.71 (d, $J$ = 8.8 Hz, 2H), 2.83 (t, $J$ = 5.6 Hz, 4H), 1.39 (t, $J$ = 5.7 Hz, 4H), 1.26 (s, 6H), 1.11 (s, 4H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 158.9, 153.7, 145.6, 142.2, 130.5, 130.1, 129.4, 128.5, 120.4, 41.6, 35.2, 34.7, 30.0, 26.1, 20.7.

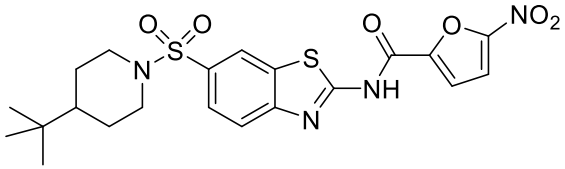


***N*-(4-((4-(tert-butyl)piperidin-1-yl)sulfonyl)phenyl)-1-methyl-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide (6-20 or 1-299-1-GY)** The reaction was performed with 4-((4-(*tert*-butyl)piperidin-1-yl)sulfonyl)aniline (**1-20-1-GY**, 90 mg, 0.3 mmol), pyridine (0.06 mL, 0.66 mmol), 1-methyl-3-(trifluoromethyl)-1*H*-pyrazole-5-carbonyl chloride (127 mg, 0.6 mmol) and DCM (3 mL) using the above method. Eluent: 10% Ethyl acetate/Hexane. Yield: 73 mg, 52%; yellowish solid. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 8.43 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 2H), 7.69 (d, *J* = 8.8 Hz, 2H), 7.14 (s, 1H), 4.27 (s, 3H), 3.82 (dt, *J* = 11.3, 2.5 Hz, 2H), 2.18 (td, *J* = 12.0, 2.4 Hz, 2H), 1.72 (d, *J* = 13.2 Hz, 2H), 1.34 (qd, *J* = 12.6, 4.1 Hz, 2H), 0.88 (tt, *J* = 12.1, 3.2 Hz, 1H), 0.82 (s, 9H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 157.3, 141.3, 140.9 (q, *J* = 39.0 Hz), 136.2, 131.7, 129.0, 120.8 (q, *J* = 268.7, 268.7, 268.3 Hz), 120.4, 105.8, 47.3, 45.9, 40.6 (q, *J* = 1.7 Hz), 32.2, 27.3, 26.3.

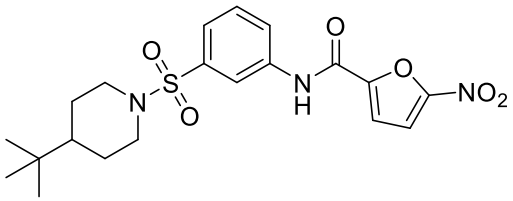


**1-methyl-*N*-(4-(piperidin-1-ylsulfonyl)phenyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide (6-21 or 2-5-1-GY)** The reaction was performed with 4-(piperidin-1-

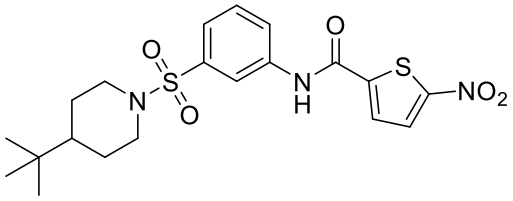
ylsulfonyl)aniline (**1-295-1-GY**, 120 mg, 0.5 mmol), pyridine (0.1 mL, 1.2 mmol), 1-methyl-3-(trifluoromethyl)-1*H*-pyrazole-5-carbonyl chloride (127 mg, 0.6 mmol) and DCM (3 mL) using the above method. Eluent: 20% Ethyl acetate/Hexane. Yield: 136 mg, 65%; white solid. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 8.48 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.14 (s, 1H), 4.26 (s, 3H), 2.98 (t, *J* = 5.4 Hz, 4H), 1.63 (p, *J* = 5.6 Hz, 4H), 1.42 (p, *J* = 5.9 Hz, 2H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 157.3, 141.3, 140.9 (q, *J* = 39.4 Hz), 136.3, 131.9, 128.9, 120.8 (q, *J* = 268.7 Hz), 120.4, 105.8, 47.1, 40.5, 25.2, 23.5.




***N*-(6-((4-(*tert*-butyl)piperidin-1-yl)sulfonyl)benzo[*d*]thiazol-2-yl)-5-nitrofuran-2-carboxamide (6-30** or **1-121-1-GY)** The reaction was performed with 6-((4-(tert-butyl)piperidin-1-yl)sulfonyl)benzo[*d*] thiazol-2-amine (70 mg, 0.2 mmol), pyridine (0.04 mL, 0.44 mmol), 5-nitrofuran-2-carbonyl chloride (70 mg, 0.4 mmol) and DCM (2 mL) using the above method. Eluent: 30% Ethyl acetate/Hexane. Yield: 69 mg, 71%; yellow solid, very poor solubility in DMSO. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 10.67 (s, 1H), 8.32 (d, *J* = 1.6 Hz, 1H), 7.87 (d, *J* = 8.5 Hz, 1H), 7.82 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.57 (d, *J* = 3.8 Hz, 1H), 7.46 (d, *J* = 3.8 Hz, 1H), 3.92 (d, *J* = 11.1 Hz, 2H), 2.20 (t, *J* = 12.0 Hz, 2H), 1.74 (d, *J* = 13.2 Hz, 2H), 1.45 – 1.34 (m, 2H), 0.94 – 0.87 (m, 1H), 0.82 (s, 9H).

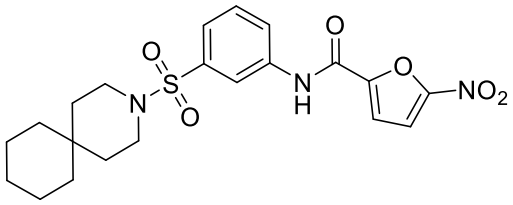


***N*-(3-((4-(*tert*-butyl)piperidin-1-yl)sulfonyl)phenyl)-5-nitrofuran-2-carboxamide (6-31 or 1-63-1-GY)** The reaction was performed with 3-((4-(*tert*-butyl)piperidin-1-yl)sulfonyl)aniline (**1-61-1-GY**, 30 mg, 0.1 mmol), pyridine (0.02 mL, 0.22 mmol), 5-nitrofuran-2-carbonyl chloride (35 mg, 0.2 mmol) and DCM (1 mL) using the above method. Eluent: 20% Ethyl acetate/Hexane. Yield: 36 mg, 84%; white solid. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 8.49 (s, 1H), 8.05 (s, 1H), 7.98 (d, *J* = 7.4 Hz, 1H), 7.63 – 7.51 (m, 2H), 7.43 (q, *J* = 3.8 Hz, 2H), 3.90 (d, *J* = 11.3 Hz, 2H), 2.24 (t, *J* = 11.8 Hz, 2H), 1.74 (d, *J* = 13.0 Hz, 2H), 1.45 – 1.32 (m, 2H), 0.91 (t, *J* = 12.3 Hz, 1H), 0.82 (s, 9H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 154.9, 151.8, 147.4, 138.7, 136.0, 129.9, 124.4, 123.1, 119.0, 117.1, 113.4, 46.7, 44.8, 31.7, 26.9, 25.6.

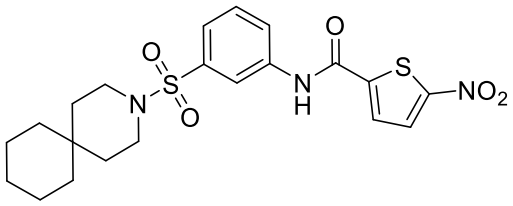


***N*-(3-((4-(*tert*-butyl)piperidin-1-yl)sulfonyl)phenyl)-5-nitrothiophene-2-carboxamide (6-32 or 1-65-1-GY)** The reaction was performed with 3-((4-(*tert*-butyl)piperidin-1-yl)sulfonyl)aniline (**1-61-1-GY**, 30 mg, 0.1 mmol), pyridine (0.02 mL, 0.22 mmol), 5-nitrothiophene-2-carbonyl chloride (38 mg, 0.2 mmol) and DCM (1 mL) using the above method. Eluent: 20% Ethyl acetate/Hexane. Yield: 36 mg, 80%; yellow solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 10.90 (s, 1H), 8.19 (d, *J* = 4.3 Hz, 1H), 8.12 (s, 1H), 8.04 (s, 2H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 7.8 Hz,

1H), 3.68 (d, *J* = 11.3 Hz, 2H), 2.13 (t, *J* = 12.2 Hz, 2H), 1.64 (d, *J* = 12.8 Hz, 2H), 1.23 – 1.08 (m, 2H), 0.93 – 0.84 (m, 1H), 0.73 (s, 9H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 158.6, 153.6, 145.5, 138.8, 136.0, 130.1, 130.0, 128.8, 124.3, 123.1, 118.9, 46.7, 44.8, 31.7, 26.9, 25.6.

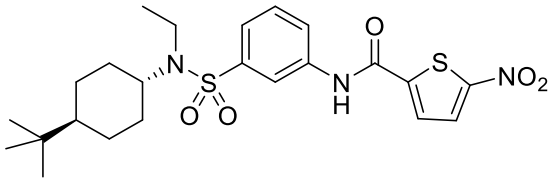


***N*-(3-((3-azaspiro[5.5]undecan-3-yl)sulfonyl)phenyl)-5-nitrofuran-2-carboxamide (6-33 or 1-75-1-GY)** The reaction was performed with 4-((3-azaspiro[5.5]undecan-3-yl)sulfonyl)aniline (**1-73-1-GY**, 62 mg, 0.2 mmol), pyridine (0.04 mL, 0.4 mmol), 5-nitrofuran-2-carbonyl chloride (70 mg, 0.4 mmol) and DCM (2 mL) using the above method. Eluent: 10% Ethyl acetate/Hexane. Yield: 54 mg, 61%; white solid. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 8.58 (s, 1H), 8.09 – 8.00 (m, 2H), 7.61 – 7.54 (m, 2H), 7.44 (d, *J* = 3.8 Hz, 1H), 7.42 (d, *J* = 3.8 Hz, 1H), 3.04 (t, *J* = 5.7 Hz, 4H), 1.53 (t, *J* = 5.7 Hz, 4H), 1.36 (s, 6H), 1.22 (s, 4H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 154.5, 151.6, 147.4, 137.6, 137.5, 130.2, 124.4, 124.3, 119.4, 117.4, 112.7, 42.1, 35.9, 35.5, 30.6, 26.7, 21.4.

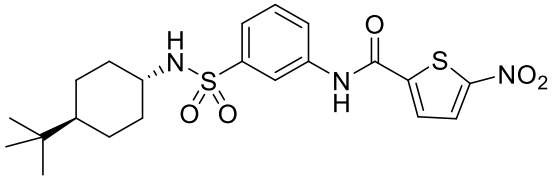


***N*-(3-((3-azaspiro[5.5]undecan-3-yl)sulfonyl)phenyl)-5-nitrothiophene-2-carboxamide (6-34 or 1-77-1-GY)** The reaction was performed with 4-((3-azaspiro[5.5]undecan-3-yl)sulfonyl)aniline

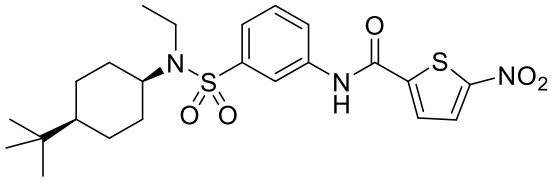
(**1-73-1-GY**, 31 mg, 0.1 mmol), pyridine (0.02 mL, 0.2 mmol), 5-nitrothiophene-2-carbonyl chloride (35 mg, 0.2 mmol) and DCM (1 mL) using the above method. Eluent: 10% Ethyl acetate/Hexane. Yield: 30 mg, 74%; yellow solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 10.90 (s, 1H), 8.20 (d, $J$ = 4.4 Hz, 1H), 8.12 (s, 1H), 8.09 – 7.94 (m, 2H), 7.63 (t, $J$ = 8.2 Hz, 1H), 7.47 (d, $J$ = 7.8 Hz, 1H), 2.88 (t, $J$ = 5.3 Hz, 4H), 1.42 (t, $J$ = 4.7 Hz, 4H), 1.27 (s, 6H), 1.12 (s, 4H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 158.6, 153.6, 145.5, 138.7, 136.1, 130.1, 130.0, 128.8, 124.3, 123.0, 118.8, 41.6, 35.2, 34.7, 30.0, 26.1, 20.7.




***N*-(3-(*N*-((1*r*,4*r*)-4-(*tert*-butyl)cyclohexyl)-*N*-ethylsulfamoyl)phenyl)-5-nitrothiophene-2-carboxamide (6-35 or 1-171-1-GY)** The reaction was performed with 3-amino-*N*-((1*r*,4*r*)-4-(*tert*-butyl)cyclohexyl)-*N*-ethylbenzenesulfonamide (**1-165-1-GY**, 68 mg, 0.2 mmol), pyridine (0.04 mL, 0.4 mmol), 5-nitrothiophene-2-carbonyl chloride (76 mg, 0.4 mmol) and DCM (2 mL) using the above method. Eluent: 50% Ethyl acetate/Hexane. Yield: 88 mg, 90%; orange solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 10.89 (s, 1H), 8.28 – 8.24 (m, 1H), 8.22 (d, $J$ = 4.4 Hz, 1H), 8.08 (d, $J$ = 4.4 Hz, 1H), 8.04 – 7.97 (m, 1H), 7.63 – 7.54 (m, 2H), 3.54 (tt, $J$ = 11.9, 3.9 Hz, 1H), 3.19 (q, $J$ = 6.9 Hz, 2H), 1.70 (d, $J$ = 12.2 Hz, 2H), 1.55 – 1.45 (m, 2H), 1.45 – 1.33 (m, 2H), 1.15 (t, $J$ = 7.0 Hz, 3H), 1.07 – 0.96 (m, 2H), 0.94 – 0.86 (m, 1H), 0.79 (s, 9H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 158.6, 153.6, 145.6, 141.8, 138.7, 130.1, 130.0, 128.8, 123.7, 122.1, 118.0, 57.7, 46.2, 38.0, 32.0, 30.8, 27.4, 26.3, 17.6.

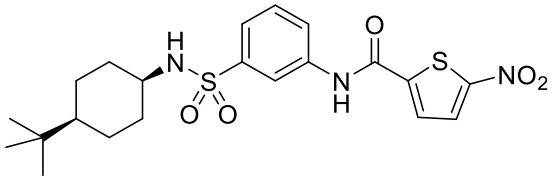


***N*-(3-(*N*-((1*r*,4*r*)-4-(*tert*-butyl)cyclohexyl)sulfamoyl)phenyl)-5-nitrothiophene-2-carboxamide (6-36 or 1-177-1-GY)** The reaction was performed with 3-amino-*N*-((1*r*,4*r*)-4-(*tert*-butyl)cyclohexyl) benzenesulfonamide (**1-169-1-GY**, 62 mg, 0.2 mmol), pyridine (0.04 mL, 0.4 mmol), 5-nitrothiophene-2-carbonyl chloride (76 mg, 0.4 mmol) and DCM (2 mL) using the above method. Eluent: 50% Ethyl acetate/Hexane. Yield: 72 mg, 77%; yellow solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 10.90 (s, 1H), 8.25 (q, *J* = 1.4 Hz, 1H), 8.22 (d, *J* = 4.4 Hz, 1H), 8.09 (d, *J* = 4.4 Hz, 1H), 8.01 – 7.93 (m, 1H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.64 – 7.53 (m, 2H), 2.86 (tdt, *J* = 15.9, 8.2, 4.1 Hz, 1H), 1.74 – 1.55 (m, 4H), 1.10 (q, *J* = 11.8 Hz, 2H), 0.95 – 0.81 (m, 3H), 0.76 (s, 9H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 158.6, 153.6, 145.7, 142.9, 138.4, 130.1, 129.8, 128.7, 123.6, 122.1, 118.1, 52.7, 46.4, 33.6, 31.9, 27.3, 25.8.

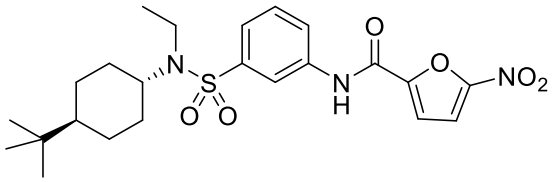


***N*-(3-(*N*-((1*s*,4*s*)-4-(*tert*-butyl)cyclohexyl)-*N*-ethylsulfamoyl)phenyl)-5-nitrothiophene-2-carboxamide (6-37 or 1-179-1-GY)** The reaction was performed with 3-amino-*N*-((1*s*,4*s*)-4-(*tert*-butyl)cyclohexyl)-*N*-ethylbenzenesulfonamide (**1-167-1-GY**, 68 mg, 0.2 mmol), pyridine (0.04 mL, 0.4 mmol), 5-nitrothiophene-2-carbonyl chloride (76 mg, 0.4 mmol) and DCM (2 mL) using the above method. Eluent: 50% Ethyl acetate/Hexane. Yield: 70 mg, 71%; yellow solid. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 9.10 (s, 1H), 8.39 (ddd, *J* = 8.1, 2.1, 1.2 Hz, 1H), 7.99 (t, *J* = 1.9 Hz,

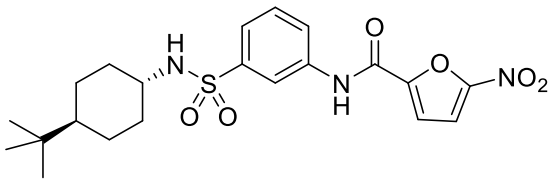
1H), 7.93 (d, *J* = 4.3 Hz, 1H), 7.82 (d, *J* = 4.4 Hz, 1H), 7.60 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 3.88 – 3.78 (m, 1H), 3.26 (q, *J* = 7.0 Hz, 2H), 1.66 – 1.55 (m, 2H), 1.51 – 1.29 (m, 6H), 1.22 (t, *J* = 7.0 Hz, 3H), 1.11 – 1.03 (m, 1H), 0.80 (s, 9H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 158.9, 155.1, 145.2, 141.4, 138.6, 130.5, 128.4, 127.3, 124.5, 122.8, 118.4, 54.6, 42.5, 39.9, 33.2, 28.4, 28.0, 23.2, 17.6.




***N*-(3-(*N*-((1*s*,4*s*)-4-(*tert*-butyl)cyclohexyl)sulfamoyl)phenyl)-5-nitrothiophene-2-carboxamide (6-38 or 1-185-1-GY)** The reaction was performed with 3-amino-*N*-((1*s*,4*s*)-4-(*tert*-butyl)cyclohexyl) benzenesulfonamide (**1-183-1-GY**, 62 mg, 0.2 mmol), pyridine (0.04 mL, 0.4 mmol), 5-nitrothiophene-2-carbonyl chloride (76 mg, 0.4 mmol) and DCM (2 mL) using the above method. Eluent: 50% Ethyl acetate/Hexane. Yield: 64 mg, 69%; yellow solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 10.89 (s, 1H), 8.25 (s, 1H), 8.20 (d, *J* = 4.4 Hz, 1H), 8.07 (d, *J* = 4.4 Hz, 1H), 7.95 (dt, *J* = 6.4, 2.4 Hz, 1H), 7.67 (d, *J* = 6.0 Hz, 1H), 7.62 – 7.55 (m, 2H), 3.26 – 3.18 (m, 1H), 1.63 – 1.51 (m, 2H), 1.41 – 1.32 (m, 2H), 1.32 – 1.17 (m, 4H), 0.90 – 0.82 (m, 1H), 0.79 (s, 9H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 158.5, 153.6, 145.7, 142.0, 138.4, 130.1, 129.8, 128.7, 123.6, 122.2, 118.4, 48.2, 47.0, 32.3, 31.0, 27.4, 20.8.

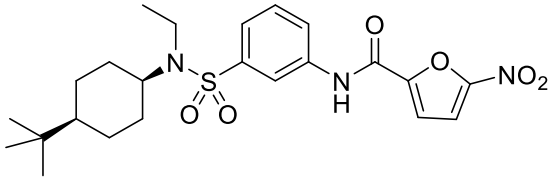


***N*-(3-(*N*-((1*r*,4*r*)-4-(*tert*-butyl)cyclohexyl)-*N*-ethylsulfamoyl)phenyl)-5-nitrofuran-2-carboxamide (6-39 or 1-173-1-GY)** The reaction was performed with 3-amino-*N*-((1*r*,4*r*)-4-(*tert*-butyl)cyclohexyl)-*N*-ethylbenzenesulfonamide (**1-165-1-GY**, 68 mg, 0.2 mmol), pyridine (0.04 mL, 0.4 mmol), 5-nitrofuran-2-carbonyl chloride (70 mg, 0.4 mmol) and DCM (2 mL) using the above method. Eluent: 50% Ethyl acetate/Hexane. Yield: 86 mg, 90%; white solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 10.90 (s, 1H), 8.27 (q, *J* = 1.4 Hz, 1H), 8.06 – 8.00 (m, 1H), 7.83 (d, *J* = 3.9 Hz, 1H), 7.67 (d, *J* = 3.9 Hz, 1H), 7.64 – 7.53 (m, 2H), 3.54 (tt, *J* = 11.9, 3.8 Hz, 1H), 3.20 (q, *J* = 7.0 Hz, 2H), 1.71 (d, *J* = 12.3 Hz, 2H), 1.52 (d, *J* = 11.0 Hz, 2H), 1.46 – 1.33 (m, 2H), 1.16 (t, *J* = 7.0 Hz, 3H), 1.07 – 0.94 (m, 2H), 0.94 – 0.85 (m, 1H), 0.79 (s, 9H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 154.9, 151.8, 147.4, 141.8, 138.6, 130.0, 123.8, 122.1, 118.1, 117.0, 113.4, 57.7, 46.2, 38.0, 32.0, 30.8, 27.4, 26.3, 17.6.

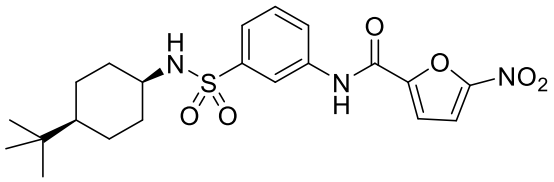


***N*-(3-(*N*-((1*r*,4*r*)-4-(*tert*-butyl)cyclohexyl)sulfamoyl)phenyl)-5-nitrofuran-2-carboxamide (6-40 or 1-175-1-GY)** The reaction was performed with 3-amino-*N*-((1*r*,4*r*)-4-(*tert*-butyl)cyclohexyl) benzenesulfonamide (**1-169-1-GY**, 62 mg, 0.2 mmol), pyridine (0.04 mL, 0.4 mmol), 5-nitrofuran-2-carbonyl chloride (70 mg, 0.4 mmol) and DCM (2 mL) using the above method. Eluent: 50% Ethyl acetate/Hexane. Yield: 77 mg, 86%; yellow solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 10.91

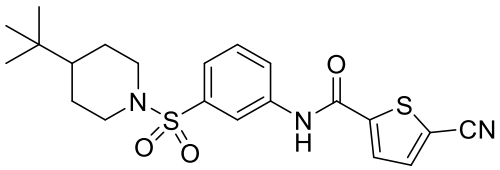
(s, 1H), 8.29 – 8.22 (m, 1H), 8.04 – 7.95 (m, 1H), 7.83 (d, *J* = 3.9 Hz, 1H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.68 (d, *J* = 4.0 Hz, 1H), 7.65 – 7.55 (m, 2H), 2.86 (tdt, *J* = 11.6, 7.8, 3.9 Hz, 1H), 1.69 (d, *J* = 11.6 Hz, 2H), 1.62 (d, *J* = 9.6 Hz, 2H), 1.11 (q, *J* = 11.2, 10.4 Hz, 2H), 0.95 – 0.82 (m, 3H), 0.76 (s, 9H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 154.8, 151.8, 147.5, 142.9, 138.4, 129.8, 123.7, 122.0, 118.2, 116.9, 113.4, 52.7, 46.4, 33.6, 31.9, 27.3, 25.8.




***N*-(3-(*N*-((1*s*,4*s*)-4-(*tert*-butyl)cyclohexyl)-*N*-ethylsulfamoyl)phenyl)-5-nitrofuran-2-carboxamide (6-41 or 1-181-1-GY)** The reaction was performed with 3-amino-*N*-((1*s*,4*s*)-4-(*tert*-butyl)cyclohexyl)-*N*-ethylbenzenesulfonamide (**1-167-1-GY**, 68 mg, 0.2 mmol), pyridine (0.04 mL, 0.4 mmol), 5-nitrofuran-2-carbonyl chloride (70 mg, 0.4 mmol) and DCM (2 mL) using the above method. Eluent: 50% Ethyl acetate/Hexane. Yield: 69 mg, 72%; yellow solid. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 8.65 (s, 1H), 8.16 (s, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.46 – 7.36 (m, 2H), 3.92 – 3.81 (m, 1H), 3.32 (q, *J* = 7.2 Hz, 2H), 1.77 – 1.63 (m, 2H), 1.61 – 1.36 (m, 6H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.20 – 1.13 (m, 1H), 0.84 (s, 9H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 154.4, 151.5, 147.5, 142.7, 137.3, 130.0, 123.8, 123.6, 118.8, 117.2, 112.7, 54.2, 42.7, 39.8, 33.2, 28.5, 28.1, 23.3, 17.5.

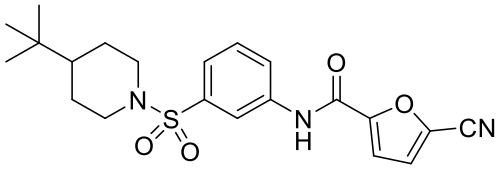


***N*-(3-(*N*-((1*s*,4*s*)-4-(*tert*-butyl)cyclohexyl)sulfamoyl)phenyl)-5-nitrofuran-2-carboxamide (6-42 or 1-187-1-GY)** The reaction was performed with 3-amino-*N*-((1*s*,4*s*)-4-(*tert*-butyl)cyclohexyl) benzenesulfonamide (**1-183-1-GY**, 62 mg, 0.2 mmol), pyridine (0.04 mL, 0.4 mmol), 5-nitrofuran-2-carbonyl chloride (70 mg, 0.4 mmol) and DCM (2 mL) using the above method. Eluent: 50% Ethyl acetate/Hexane. Yield: 62 mg, 67%; yellow solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 10.91 (s, 1H), 8.26 (s, 1H), 8.03 – 7.95 (m, 1H), 7.83 (d, *J* = 4.0 Hz, 1H), 7.72 – 7.64 (m, 2H), 7.64 – 7.55 (m, 2H), 3.29 – 3.20 (m, 1H), 1.65 – 1.50 (m, 2H), 1.45 – 1.33 (m, 2H), 1.33 – 1.17 (m, 4H), 0.92 – 0.84 (m, 1H), 0.81 (s, 9H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 154.8, 151.8, 147.5, 142.0, 138.3, 129.8, 123.7, 122.2, 118.5, 116.9, 113.4, 48.2, 47.0, 32.3, 31.0, 27.4, 20.8.



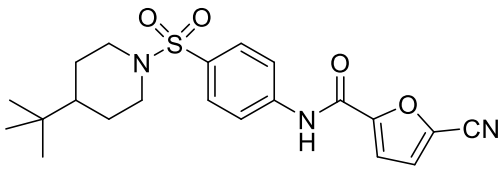
***N*-(3-((4-(*tert*-butyl)piperidin-1-yl)sulfonyl)phenyl)-5-cyanothiophene-2-carboxamide (6-43 or 1-199-1-GY)** The reaction was performed with 3-((4-(*tert*-butyl)piperidin-1-yl)sulfonyl)aniline (**1-61-1-GY**, 30 mg, 0.1 mmol), pyridine (0.02 mL, 0.22 mmol), 5-cyanothiophene-2-carbonyl chloride (35 mg, 0.2 mmol) and DCM (2 mL) using the above method. Eluent: 0% ~ 1% MeOH/DCM. Yield: 30 mg, 69%; yellowish solid. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 8.93 (s, 1H), 8.42 (ddd, *J* = 8.1, 2.2, 1.2 Hz, 1H), 7.88 (t, *J* = 1.9 Hz, 1H), 7.84 (d, *J* = 4.1 Hz, 1H), 7.67 (d, *J* = 4.0 Hz, 1H), 7.59 (t, *J* = 7.9 Hz, 1H), 7.53 (dt, *J* = 7.9, 1.4 Hz, 1H), 3.80 (d, *J* = 11.2 Hz, 2H), 2.26 – 2.17 (m, 2H), 1.71 (d, *J* = 13.0 Hz, 2H), 1.30 – 1.23 (m, 2H), 0.93 – 0.87 (m, 1H), 0.79

(s, 9H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 158.9, 145.9, 138.8, 137.9, 136.0, 130.4, 128.4, 125.0, 123.5, 118.9, 114.7, 113.5, 47.4, 45.7, 32.2, 27.2, 26.3.



***N*-(3-((4-(*tert*-butyl)piperidin-1-yl)sulfonyl)phenyl)-5-cyanofuran-2-carboxamide (6-44** or **1-205-1-GY)** The reaction was performed with 3-((4-(*tert*-butyl)piperidin-1-yl)sulfonyl)aniline (**1-61-1-GY**, 60 mg, 0.2 mmol), pyridine (0.02 mL, 0.22 mmol), 5-cyanofuran-2-carbonyl chloride (31 mg, 0.2 mmol) and DCM (2 mL) using the above method. Eluent: 20% Ethyl acetate/Hexane. Yield: 40 mg, 49%; white solid. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 8.77 (s, 1H), 8.11 (dt, *J* = 5.7, 2.6 Hz, 1H), 8.05 (s, 1H), 7.62 – 7.48 (m, 2H), 7.35 (d, *J* = 3.8 Hz, 1H), 7.25 (d, *J* = 3.7 Hz, 1H), 3.88 (d, *J* = 11.2 Hz, 2H), 2.31 – 2.16 (m, 2H), 1.72 (d, *J* = 13.7 Hz, 2H), 1.35 (qd, *J* = 12.8, 12.3, 3.8 Hz, 2H), 0.94 – 0.86 (m, 1H), 0.81 (s, 9H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 154.7, 150.8, 137.8, 137.0, 130.1, 127.3, 124.4, 124.1, 123.8, 119.3, 116.1, 110.5, 47.4, 45.9, 32.2, 27.3, 26.3.

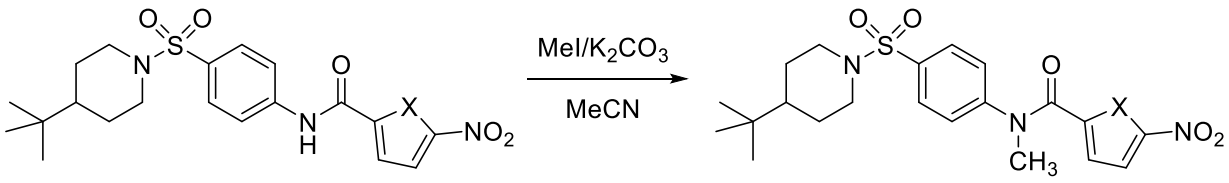
**Method 2:**



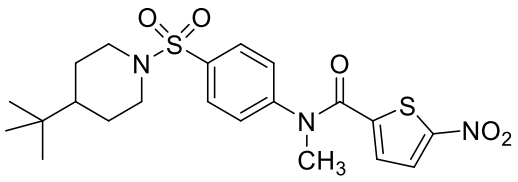
***N*-(4-((4-(*tert*-butyl)piperidin-1-yl)sulfonyl)phenyl)-5-cyanofuran-2-carboxamide (6-19 or 1-91-1-GY)** To a vial was added 4-((4-(*tert*-butyl)piperidin-1-yl)sulfonyl)aniline (**1-20-1-GY**, 30 mg, 0.1 mmol), NaH (6 mg, 0.15 mmol), THF (1 mL) under ice bath. The mixture was stirred

under ice bath for 30 min, then 5-cyanofuran-2-carbonyl chloride (17 mg, 0.11 mmol) in THF (1 mL) was added dropwise. The mixture was warmed to room temperature and stirred for 2 hours. After the completion of the reaction, the mixture was quenched with aq. $NH_4Cl$ and extracted with DCM for 3 times. The combined organic layer was dried with $Na_2SO_4$ and purified by column. Eluent: 20% Ethyl acetate/Hexane. Yield: 10 mg, 25%; white solid. $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.33 (s, 1H), 7.85 (d, *J* = 8.8 Hz, 2H), 7.79 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 3.8 Hz, 1H), 7.26 (d, *J* = 3.6 Hz, 1H), 3.91 – 3.83 (m, 2H), 2.19 (td, *J* = 2.5, 12.0 Hz, 2H), 1.73 (d, *J* = 13.1 Hz, 2H), 1.42 – 1.33 (m, 2H), 0.93 – 0.87 (m, 1H), 0.82 (s, 9H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 154.3, 150.6, 140.6, 132.5, 129.3, 127.3, 123.8, 120.0, 116.5, 110.4, 47.3, 46.0, 32.3, 27.3, 26.4.

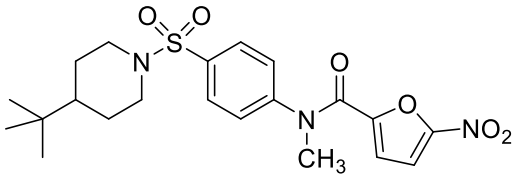
**Method 3**




**General procedure:** To a sealed tube was added the starting material (0.1 mmol), $K_2CO_3$ (28 mg, 0.2 mmol), MeI (0.06 mL, 1 mmol) and MeCN (1 mL). The mixture was stirred at 40 ºC for 24 hours followed by the addition of another 0.06 mL of MeI (1 mmol). The mixture was stirred at 40 ºC for another 24 hours. After the completion of the reaction, the solvent was removed under reduced pressure. The crude product was purified by flash column.



***N*-(4-((4-(*tert*-butyl)piperidin-1-yl)sulfonyl)phenyl)-*N*-methyl-5-nitrothiophene-2-carboxamide (6-28 or 1-151-1-GY)** The reaction was performed with **6-15** (45 mg, 0.1 mmol), $K_2CO_3$ (28 mg, 0.2 mmol), MeI (0.06 mL + 0.06 mL, 1 mmol + 1 mmol) and MeCN (1 mL). using the above method. Eluent: 20% Ethyl acetate/Hexane. Yield: 33 mg, 72%; white solid. $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.83 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 4.2 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.02 (d, *J* = 4.4 Hz, 1H), 3.92 – 3.83 (m, 2H), 3.51 (s, 3H), 2.20 – 2.12 (m, 2H), 1.81 – 1.72 (m, 2H), 1.45 – 1.34 (m, 2H), 1.00 – 0.92 (m, 1H), 0.85 (s, 9H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 160.6, 154.7, 146.6, 141.8, 136.5, 131.7, 129.8, 128.7, 127.2, 47.5, 45.8, 39.1, 32.2, 27.3, 26.4.



***N*-(4-((4-(*tert*-butyl)piperidin-1-yl)sulfonyl)phenyl)-*N*-methyl-5-nitrothiophene-2-carboxamide (6-29 or 1-151-1-GY)** The reaction was performed with **6-10** (44 mg, 0.1 mmol), $K_2CO_3$ (28 mg, 0.2 mmol), MeI (0.06 mL + 0.06 mL, 1 mmol + 1 mmol) and MeCN (1 mL). using the above method. Eluent: 20% Ethyl acetate/Hexane. Yield: 33 mg, 75%; white solid. $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.20 (d, *J* = 3.8 Hz, 1H), 7.06 (d, *J* = 3.8 Hz, 1H), 3.84 (dt, *J* = 11.1, 2.6 Hz, 2H), 3.51 (s, 3H), 2.24 – 2.12 (m, 2H), 1.75 (d, *J* = 12.2 Hz, 2H), 1.39 (qd, *J* = 12.6, 4.1 Hz, 2H), 1.01 (tt, *J* = 11.9, 3.3 Hz, 1H), 0.85 (s, 9H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 157.2, 151.4, 147.9, 146.6, 135.6, 129.5, 127.2, 118.8, 111.4, 47.2, 45.4, 38.8, 32.2, 27.3, 26.4.

# Chapter 7. Development of Bicyclic/Tricyclic Benzamidines with Cellular Potency Against Venezuelan Equine Encephalitis Virus (VEEV) and Western Equine Encephalitis Virus (WEEV)

## 7.1 Abstract

Encephalitic alphaviruses, including Venezuelan/Western/Eastern Equine Encephalitis Virus (V/W/EEEV), are endemic in American continent and can be developed as bioweapons. However, there are no FDA approved human vaccines or drugs available. Therefore, novel agents for the treatment of encephalitic alphaviruses are in high demand. The Golden group discovered and developed the benzamidine series, as exemplified by **BDGR-4**, which displayed good potency against VEEV and WEEV. However, it showed moderate plasma stability and microsomal stability. We noted that the SAR of the bicyclic/tricyclic benzamidines has not been investigated yet, which may lead to the discovery of compounds with more potent antiviral activity or physical chemical properties. In this chapter, a series of compounds bearing bicyclic or tricyclic benzamidines were designed and synthesized. The associated antiviral activities were evaluated against VEEV and WEEV. The preliminary SAR will be discussed.

## 7.2 Introduction

The *Alphavirus* genius of the *Togaviridae* family are ssRNA(+) group virus that are broadly distributed in the world. Most of their members are transmitted by the bite of infected mosquitoes. Based on their geographic origin, alphavirus can be classified as "Old World" alphavirus or "New World" alphavirus.[1] The Old World alphaviruses, such as Chikungunya virus (CHIKV), Semliki Forest virus (SFV), Ross River virus (RRV), O'Nyong–Nyong virus (ONNV), and Sindbis virus (SINV), can cause fever, rash and arthralgia syndrome, while the New World alphaviruses, including Venezuelan equine encephalitis virus (VEEV), Western equine encephalitis virus (WEEV) and Eastern equine encephalitis virus (EEEV), can cause a flu-like symptom and finally progress to encephalitis.[1-2] Encephalitic alphaviruses are endemic in American continent and can be developed as bioweapons[3-4], thus have brought great attention in recent years. However, there are no FDA approved human vaccines or drugs available[5]. Therefore, novel agents for the treatment of encephalitic alphaviruses are in high demand.

The Golden group discovered and developed the benzamidine series, as exemplified by **ML-336** (**Figure 7-1**), which showed good potency in VEEV-induced cytopathic effect (CPE) assay ($EC_{50}$ = 0.032 $\mu$M) and viral titer reduction assay (VEEV titer (log) = 7 at 5 $\mu$M).[6] Further optimization led to the identification of **BDGR-4** ($EC_{50}$ = 0.047 $\mu$M aganist VEEV), which also displayed potent activity against WEEV ($EC_{50}$ = 0.10 $\mu$M) and EEEV ($EC_{50}$ = 0.15 $\mu$M)[7]. (**Figure 7-1**) The SAR of the amidine series[6-7] (**Figure 7-1**, colored highlight) reveals that the -$NO_2$ group (green highlight) of the core phenyl ring is critical to the antiviral activity. *N*-phenyl or *N*-(4-methoxyphenyl) group of the amide (blue highlight) are tolerated for activity. Installation of methyl group at 3-position of the piperazine ring (purple highlight) can reduce the microsomal

stabilities. However, the SAR of the 5- or 6-position of the piperazine ring (red highlight) and other substitution at 3-position have not been investigated yet.

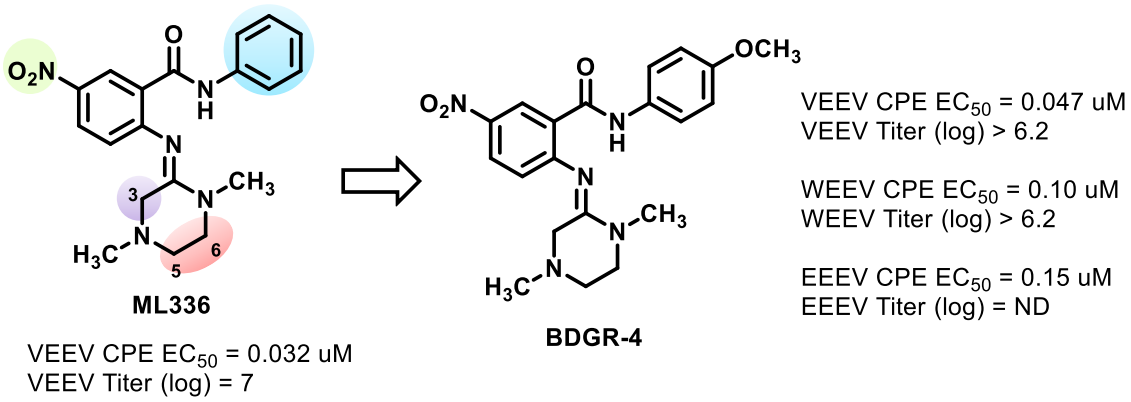


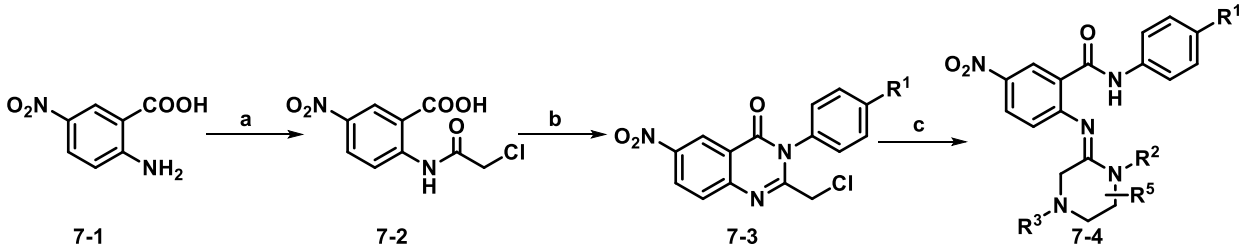

**Figure 7-1.** SAR of benzamidines and activity profiles of **ML336** and **BDGR-4**

In this chapter, a series of compounds bearing bicyclic or tricyclic benzamidines were designed and synthesized in order to investigate the SAR and SPR of these compounds. The associated antiviral activities were evaluated against VEEV and WEEV.

## 7.3 Chemistry

All compounds were synthesized based on the similar method[6] published by Golden group by collaborating with Dr. Xufeng Cao.

Generally, the final compounds were prepared by a three-step synthesis procedure. (**Scheme 7-1**) The amide bond formation by treating 2-amino-5-nitrobenzoic acid (**7-1**) with chloroacetyl chloride under basic condition afforded 2-(2-chloroacetamido)-5-nitrobenzoic acid (**7-2**) in high yield. Cyclization of intermediate **7-2** with aniline or *p*-anisidine in the presence of $POCl_3$ gave the chloromethyl quinazolinone intermediate **7-3** under microwave irradiation at 150 °C**.** The final compounds (**7-4**) was generated by a rearrangement reaction of **7-3** with diamines.[6, 8-9]




**Scheme 7-1.** Synthesis of bicyclic or tricyclic benzamidines. Reagents: (a) $ClCOCH_2Cl$, $NEt_3$, $CH_2Cl_2$, 0 °C to rt, overnight, 95%; (b) substituted aniline, $POCl_3$, acetonitrile, MWI, 150 °C, 15 min, 68% ~ 72%; (c) substituted diamines, $K_2CO_3$, MeCN, 50 °C, 2 h, 51% ~ 59%.

## 7.4 Results and discussion

A total number of 13 compounds bearing different ring-fused piperazine rings were synthesized by collaborating with Dr. Xufeng Cao. All final compounds were purified after synthesis, characterized by $^1H$ and $^{13}C$ NMR, and analyzed for purity by UV-LCMS (> 95%). Compounds were evaluated for CPE-based dose response assay and titer reduction assay in VEEV (strain TC-83, an attenuated strain of VEEV) and WEEV (strain California). (**Table 7-1**)

In general, compounds bearing pyrrolidino-fused piperazine ring displayed lower antiviral potency against WEEV and VEEV than **BDGR-4** in both CPE assay and viral titer reduction assay. (**Table 7-1**) Compound **7-5**, which had a pyrrolidino-fused piperazine at 1,6-position, was 12-fold and 40-fold less potent than **BDGR-4** against WEEV and VEEV, respectively. Racemic compound **7-7** bearing ring-fusion at 3,4-position exhibited slightly better antiviral activity when $R^1$ is methoxy group. Replacement of methoxy group of **7-7** with a hydrogen atom (**7-6**) showed a 2-fold improvement in the CPE assay with $EC_{50}$ values of 0.55 $\mu$M and 1.04 $\mu$M against WEEV and VEEV, respectively. In order to figure out which enantiomer is more active, the two enantiomers of **7-6** were synthesized, which reveals that the (*S*)-enantiomer (**7-9**) was 6-fold more active against both WEEV and VEEV than the (*R*)-enantiomer. In addition, **7-9** displayed good titer reduction

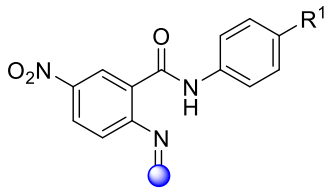
against VEEV (titer (log) = 6.89), while other bicyclic compounds displayed titer reduction (log) in a range of 4 ~ 6. Bicyclic compound bearing ring-fusion at 4,5-position (**BDGR-25** and **BDGR-26**) were not very stable The dipyrrolidino-fused compounds (**7-14 ~ 7-17**) did not show anti-WEEV activities at 1.25 $\mu$M, and only displayed micromolar activity in the VEEV CPE assay.

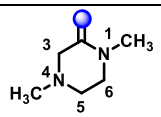
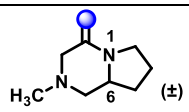
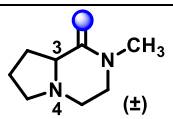
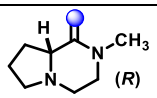
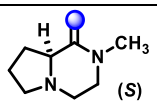
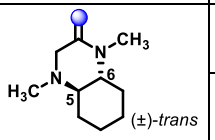
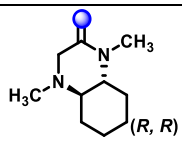
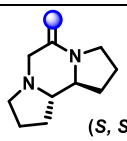
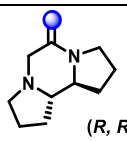
Compounds bearing a fused cyclohexane ring at 5,6-position (**7-11** and **7-10**) were also synthesized using (±)-*trans*-$N^1$,$N^2$-dimethylcyclohexane-1,2-diamine. To our delight, these compounds exhibited potent activity against both WEEV and VEEV. Compounds bearing a (*R*, *R*)-configuration were also synthesized affording **7-13** and **7-12**, both of which showed good potency against WEEV and VEEV in the CPE assay. The synthesis of (*S*, *S*)-enantiomers is in progress. The most promising compounds, **7-13**, exhibited 0.11 $\mu$M and 0.035 $\mu$M $EC_{50}$ against WEEV and VEEV. The viral titer reduction of these compounds is being tested.

## 7.5 Conclusions

A total number of 13 bicyclic/tricyclic benzamidines were synthesized and evaluated for antiviral activity. The preliminary results showed that compounds bearing pyrrolidino-fused piperazine ring at different positions were less potent than **BDGR-4**. However, compounds bearing a fused cyclohexane ring at 5,6-position of the piperazine displayed promising antiviral activity. These preliminary results, combining with the previous SAR studies of the benzamidine series, indicated that the 5- and 6-position of the piperazine ring might be able to tolerate different substitution for the further investigation of SAR and SPR in the future.

**Table 7-1.** Antiviral SAR exploration of the bicyclic or tricyclic benzamidines



| Cmpd. No. | Structure | | WEEV[a] | | VEEV[b] | |
|---|---|---|---|---|---|---|
| | $R^1$ | X | $EC_{50}$ $\mu$M[c,d] | titer log[e] | $EC_{50}$ $\mu$M[c,d] | titer log[e] |
| **BDGR-4** | $OCH_3$ |  | 0.10 | > 6.2 | 0.047 | > 6.2 |
| **7-5** | $OCH_3$ |  | 1.20 | 3.59 | 1.87 | 4.96 |
| **7-6** | H |  | 0.55 | 3.38 | 1.04 | 5.18 |
| **7-7** | $OCH_3$ | | 0.95 | 4.78 | 1.42 | 5.30 |
| **7-8** | H |  | 2.50 | 3.41 | 2.20 | 4.63 |
| **7-9** | H |  | 0.40 | 4.45 | 0.41 | 6.89 |
| **7-10** | H |  | 0.19 | ND | 0.049 | ND |
| **7-11** | $OCH_3$ | | 0.20 | ND | 0.054 | ND |
| **7-12** | H |  | 0.37 | ND | 0.099 | ND |
| **7-13** | $OCH_3$ | | 0.11 | ND | 0.035 | ND |
| **7-14** | H |  | > 1.25 | ND | 1.65 | ND |
| **7-15** | $OCH_3$ | | > 1.25 | ND | 0.89 | ND |
| **7-16** | H |  | > 1.25 | ND | 2.32 | ND |
| **7-17** | $OCH_3$ | | > 1.25 | ND | 1.11 | ND |

[a]WEEV strain California; [b]VEEV strain TC83; [c]cytopathic effect (CPE) data; [d]average of at least three replicates; [e]plaque assay.at 5 $\mu$M

## 7.6 Acknowledgement

The authors acknowledge funding from the National Institutes of Health (1R01AI118814-01). This work made use of instrumentation at the UW−Madison Medicinal Chemistry Center and Analytical Instrumentation Center, funded by the UW School of Pharmacy. Gang Yan are thankful to the collaborators Dr. Donghoon Chung's laboratory from University of Louisville for measuring the antiviral activity against VEEV and WEEV.

## 7.7 References

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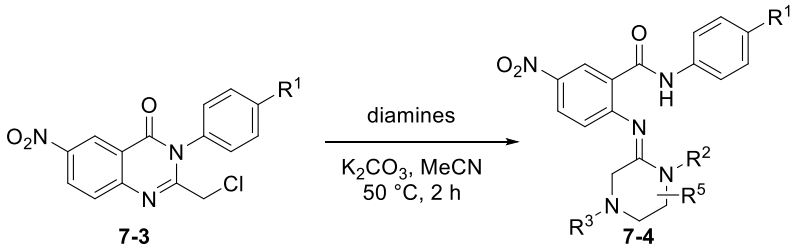
## 7.8 Experimental section

### *7.8.1. General information*

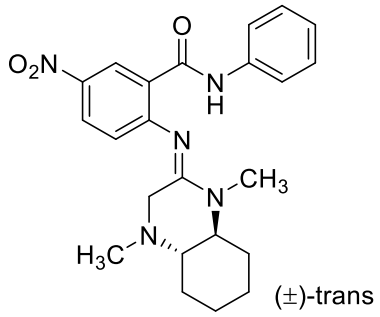
Commercial reagents and solvents were used as received from Sigma Aldrich, Fischer Scientific, Acros Organics, TCI America, Oakwood Products Inc, VWR International, etc. All thin layer chromatography was performed using precoated silica gel plates. Flash chromatography separations were carried out using a Teledyne Isco CombiFlash Rf 200 purification system with silica gel columns. Melting points were measured on OptiMelt MPA100 Automated Melting Point System. $^{1}H$ and $^{13}C$ nuclear magnetic resonance (NMR) spectra were obtained on a Varian Unity-Inova 400 MHz or 500 MHz, or Bruker Ascend 400 MHz in $CDCl_3$ or DMSO-$d_6$. The chemical shifts (δ) reported are given in parts per million (ppm). The Signal splitting patterns were described as s = singlet, d = doublet, t = triplet, q = quartet, p = pentuplet, dd = doublet of doublet, dt = doublet of triplet, td = triplet of doublet, tt = triplet of triplet, ddd = doublet of doublet of doublet, and m = multiplet, with coupling constants (*J*) in hertz (Hz). The chemical shifts of $^{19}F$ NMR was referenced by "Absolute Reference" of MestReNova. All final compounds were determined to be of $\geq$ 95% purity by UV-LCMS at 254 nm.

### *7.8.2. Experimental Procedures and Product Characterization*

The synthesis and characterization of compound **7-3** are the same as references. The synthesis of compounds **7-5** ~ **7-9**, which is made by Dr. Xufeng Cao, are not included in this thesis

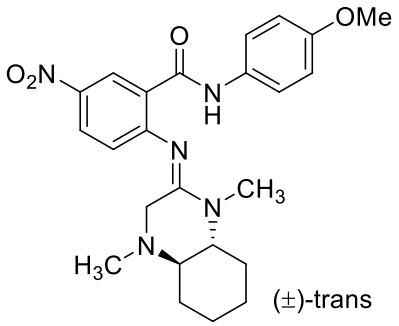



**General Procedure**: A mixture of **7-3** (0.5 mmol), diamines (1 mmol), $K_2CO_3$ (138 mg, 1 mmol) and MeCN (2 mL) was attired at 50 ºC for 2 hours. After the completion of the reaction, the mixture was concentrated and purified by column.

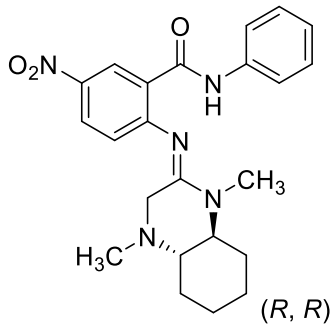



**(±)-2-(((4a*R*,8a*R*,*E*)-1,4-dimethyloctahydroquinoxalin-2(1*H*)-ylidene)amino)-5-nitro-*N*-phenylbenzamide (7-10** or **6-118-1-GY)** The reaction was performed with 2-(chloromethyl)-6-nitro-3-phenylquinazolin-4(3*H*)-one (158 mg, 0.5 mmol), (±)-*trans*-$N^1$,$N^2$-dimethylcyclohexane-1,2-diamine (0.16 mL, 1 mmol), $K_2CO_3$ (138 mg, 1 mmol) and MeCN (2 mL) using above method. Eluent: DCM/Ethyl acetate/Hexane/TEA = 10/40/50/0.5. Yield: 125 mg, 59%; orange solid. $^1$H NMR (400 MHz, Chloroform-*d*) δ 10.84 (s, 1H), 9.15 (d, *J* = 2.8 Hz, 1H), 8.17 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.64 – 7.59 (m, 2H), 7.38 – 7.33 (m, 2H), 7.15 – 7.09 (m, 1H), 6.81 (d, *J* = 8.8 Hz, 1H), 3.54 (d, *J* = 16.1 Hz, 1H), 3.26 (s, 3H), 3.15 – 3.05 (m, 1H), 2.93 (d, *J* = 16.2 Hz, 1H), 2.41 – 2.32 (m, 1H), 2.16 (s, 3H), 2.12 – 2.05 (m, 1H), 2.03 – 1.95 (m, 1H), 1.94 – 1.81 (m, 2H), 1.40 – 1.20

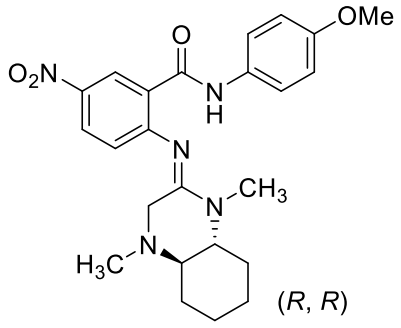
(m, 4H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 162.8, 157.5, 154.5, 143.0, 138.4, 129.2, 127.9, 126.6, 126.1, 124.3, 123.8, 120.2, 66.1, 63.4, 56.6, 40.2, 32.6, 30.1, 28.9, 24.6.



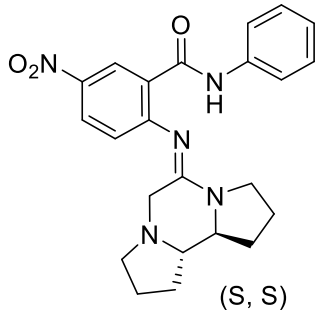

**(±)-2-(((4a*R*,8a*R*,*E*)-1,4-dimethyloctahydroquinoxalin-2(1*H*)-ylidene)amino)-*N*-(4-methoxyphenyl)-5-nitrobenzamide (7-11** or **6-116-1-GY)** The reaction was performed with 2-(chloromethyl)-3-(4-methoxy phenyl)-6-nitroquinazolin-4(3*H*)-one (173 mg, 0.5 mmol), (±)-*trans*-$N^1$,$N^2$-dimethylcyclohexane-1,2-diamine (0.16 mL, 1 mmol), $K_2CO_3$ (138 mg, 1 mmol) and MeCN (2 mL) using above method. Eluent: DCM/Ethyl acetate/Hexane/TEA = 10/40/50/0.5. Yield: 129 mg, 57%; orange solid. $^1$H NMR (400 MHz, Chloroform-*d*) δ 10.74 (s, 1H), 9.13 (d, *J* = 2.9 Hz, 1H), 8.14 (dd, *J* = 8.8, 2.9 Hz, 1H), 7.62 – 7.47 (m, 2H), 6.94 – 6.85 (m, 2H), 6.79 (d, *J* = 8.8 Hz, 1H), 3.80 (s, 3H), 3.52 (d, *J* = 16.0 Hz, 1H), 3.23 (s, 3H), 3.15 – 3.04 (m, 1H), 2.94 (d, *J* = 16.1 Hz, 1H), 2.41 – 2.30 (m, 1H), 2.15 (s, 3H), 2.09 (d, *J* = 12.5 Hz, 1H), 1.99 (t, *J* = 10.3 Hz, 1H), 1.92 – 1.82 (m, 2H), 1.40 – 1.17 (m, 4H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 162.5, 157.4, 156.4, 154.4, 142.9, 131.6, 127.7, 126.5, 126.2, 123.7, 121.6, 114.4, 66.1, 63.3, 56.6, 55.6, 40.1, 32.6, 30.1, 28.9, 24.6.



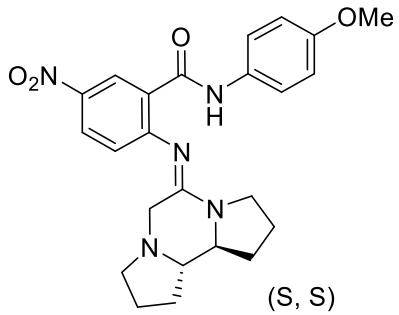

**(±)-2-(((4a*R*,8a*R*,*E*)-1,4-dimethyloctahydroquinoxalin-2(1*H*)-ylidene)amino)-5-nitro-*N*-phenylbenzamide (7-12** or **6-133-1-GY)** The reaction was performed with 2-(chloromethyl)-6-nitro-3-phenylquinazolin-4(3*H*)-one (158 mg, 0.5 mmol), (±)-*trans*-$N^1$,$N^2$-dimethylcyclohexane-1,2-diamine (0.16 mL, 1 mmol), $K_2CO_3$ (138 mg, 1 mmol) and MeCN (2 mL) using above method. Eluent: DCM/Ethyl acetate/Hexane/TEA = 10/40/50/0.5. Yield: 122 mg, 58%; orange solid. Data is consistent with the racemic compound.



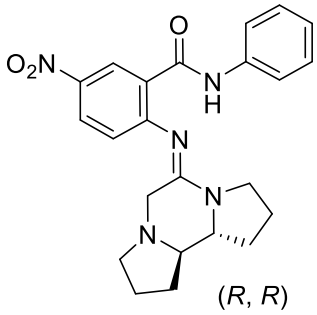

**(±)-2-(((4a*R*,8a*R*,*E*)-1,4-dimethyloctahydroquinoxalin-2(1*H*)-ylidene)amino)-*N*-(4-methoxyphenyl)-5-nitrobenzamide (7-13** or **6-134-1-GY)** The reaction was performed with 2-(chloromethyl)-3-(4-methoxy phenyl)-6-nitroquinazolin-4(3*H*)-one (173 mg, 0.5 mmol), (±)-*trans*-$N^1$,$N^2$-dimethylcyclohexane-1,2-diamine (0.16 mL, 1 mmol), $K_2CO_3$ (138 mg, 1 mmol) and MeCN (2 mL) using above method. Eluent: DCM/Ethyl acetate/Hexane/TEA = 10/40/50/0.5. Yield: 131 mg, 58%; orange solid. Data is consistent with the racemic compound.




**5-nitro-2-(((10a*S*,10b*S*,*E*)-octahydrodipyrrolo[1,2-*a*:2',1'-*c*]pyrazin-5(6*H*)-ylidene)amino)-*N*-phenylbenzamide (7-14** or **6-119-1-GY)** The reaction was performed with 2-(chloromethyl)-6-nitro-3-phenylquinazolin-4(3*H*)-one (158 mg, 0.5 mmol), (2*S*,2'*S*)-2,2'-bipyrrolidine (140 mg, 1 mmol), $K_2CO_3$ (138 mg, 1 mmol) and MeCN (2 mL) using above method. The product was recrystalized from Ethyl acetate/Hexane Yield: 111 mg, 53%; yellow solid. $^1$H NMR (400 MHz, Chloroform-*d*) δ 11.11 (s, 1H), 9.16 (d, *J* = 2.8 Hz, 1H), 8.16 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.66 – 7.56 (m, 2H), 7.42 – 7.31 (m, 2H), 7.17 – 7.08 (m, 1H), 6.89 (d, *J* = 8.8 Hz, 1H), 3.89 – 3.71 (m, 2H), 3.68 (d, *J* = 15.9 Hz, 1H), 3.35 (ddd, *J* = 11.1, 8.8, 5.0 Hz, 1H), 3.08 (d, *J* = 15.9 Hz, 1H), 3.02 (td, *J* = 8.4, 3.1 Hz, 1H), 2.23 – 1.94 (m, 6H), 1.93 – 1.79 (m, 2H), 1.61 – 1.50 (m, 2H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 162.9, 155.4, 154.7, 143.0, 138.4, 129.2, 127.8, 126.5, 126.4, 124.3, 124.1, 120.4, 65.5, 64.2, 54.1, 52.3, 47.2, 30.1, 27.6, 22.9, 22.3.

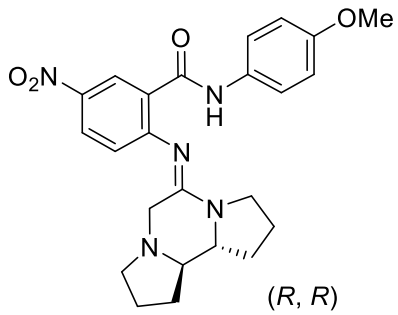


***N*-(4-methoxyphenyl)-5-nitro-2-(((10a*S*,10b*S*,*E*)-octahydrodipyrrolo[1,2-*a*:2',1'-*c*]pyrazin-5(6*H*)-ylidene)amino)benzamide (7-15** or **6-120-1-GY)** The reaction was performed with 2-(chloromethyl)-3-(4-methoxy phenyl)-6-nitroquinazolin-4(3*H*)-one (173 mg, 0.5 mmol), (2*S*,2'*S*)-2,2'-bipyrrolidine (140 mg, 1 mmol), $K_2CO_3$ (138 mg, 1 mmol) and MeCN (2 mL) using above method. The product was recrystalized from Ethyl acetate/Hexane Yield: 118 mg, 53%; yellow solid. $^1$H NMR (400 MHz, Chloroform-*d*) δ 11.03 (s, 1H), 9.15 (d, *J* = 2.8 Hz, 1H), 8.15 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.57 – 7.47 (m, 2H), 6.92 – 6.85 (m, 3H), 3.81 (s, 3H), 3.80 – 3.63 (m, 3H), 3.34 (ddd, *J* = 11.2, 8.7, 4.9 Hz, 1H), 3.08 (d, *J* = 15.8 Hz, 1H), 3.02 (td, *J* = 8.4, 3.0 Hz, 1H), 2.21 – 2.07 (m, 4H), 2.00 (dddd, *J* = 19.5, 9.7, 7.9, 3.5 Hz, 2H), 1.86 (dtd, *J* = 15.5, 12.3, 8.8 Hz, 2H), 1.56 (tdd, *J* = 14.8, 6.5, 3.6 Hz, 2H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 162.6, 156.4, 155.3, 154.6, 142.9, 131.5, 127.7, 126.5, 126.3, 124.0, 121.9, 114.4, 65.4, 64.2, 55.6, 54.1, 52.3, 47.1, 30.1, 27.6, 22.9, 22.3.




**5-nitro-2-(((10a*S*,10b*S*,*E*)-octahydrodipyrrolo[1,2-*a*:2',1'-*c*]pyrazin-5(6*H*)-ylidene)amino)-*N*-phenylbenzamide (7-16** or **6-121-1-GY)** The reaction was performed with 2-(chloromethyl)-6-nitro-3-phenylquinazolin-4(3*H*)-one (158 mg, 0.5 mmol), (2*R*,2'*R*)-2,2'-bipyrrolidine (140 mg, 1 mmol), $K_2CO_3$ (138 mg, 1 mmol) and MeCN (2 mL) using above method. The product was

recrystalized from Ethyl acetate/Hexane Yield: 121 mg, 57%; yellow solid. Data is consistent with the (*S*, *S*)-enantiomer.




***N*-(4-methoxyphenyl)-5-nitro-2-(((10a*S*,10b*S*,*E*)-octahydrodipyrrolo[1,2-*a*:2',1'-*c*]pyrazin-5(6*H*)-ylidene)amino)benzamide (7-17** or **6-122-1-GY)** The reaction was performed with 2-(chloromethyl)-3-(4-methoxy phenyl)-6-nitroquinazolin-4(3*H*)-one (173 mg, 0.5 mmol), (2*R*,2'*R*)-2,2'-bipyrrolidine (140 mg, 1 mmol), $K_2CO_3$ (138 mg, 1 mmol) and MeCN (2 mL) using above method. The product was recrystalized from Ethyl acetate/Hexane Yield: 115 mg, 51%; yellow solid. Data is consistent with the (*S*, *S*)-enantiomer.

# Appendix I Publications and Presentations

## Publications

1. **Gang Yan**, Bereket L. Zekarias, Xiaoyu Li, Victor A. Jaffett, Jennifer E. Golden*. Divergent 2-Chloroquinazolin-4(3*H*)-one Rearrangement: Twisted-Cyclic Guanidine Formation or Ring-Fused *N*-Acylguanidines via a Domino Process. *Chem. Eur. J.* 2020, accepted.

2. **Gang Yan**, Jennifer E. Golden*. Palladium-Catalyzed Cyclocarbonylation of Pyridinylated Vinylogous Amides and Ureas to Generate Ring-Fused Pyridopyrimidinones. *Org. Lett.*, **2018**, *20* (15), 4393–4396

3. **Gang Yan,** Alok Nerurkar, Bereket L. Zekarias, Andrew Fribley* and Jennifer E. Golden*. Hit to lead optimization of apoptotic CHOP pathway activators of the unfolded protein response. (*Manuscript in preparation*)

4. **Gang Yan,** Jillian E. Milanes, Neil P. Monaghan, Kelsey Bryant, Charles Voyton, Daniel Call, Jacob Vance, Kenneth A. Christensen, James C. Morris, Karl A. Werbovetz and Jennifer E. Golden*. Discovery and SAR studies of small molecule inhibitors against kinetoplastids including *Trypanosoma* and *Leishmania*. (*Manuscript in preparation*)

5. **Gang Yan,** Charles Voyton, Daniel Call, Jacob Vance, Jillian E. Milanes, Neil P. Monaghan, Kelsey Bryant, Kenneth A. Christensen, James C. Morris, Karl A. Werbovetz and Jennifer E. Golden*. Identification, validation and preliminary SAR studies of parasite glucose uptake inhibitors. (*Manuscript in preparation*)

6. **Gang Yan**[#], Lina Hao[#], Yan Niu*, Wenjie Huang, Wei Wang, Fengrong Xu, Lei Liang, Chao Wang, Hongwei Jin, Ping Xu*. 2-Substituted-thio-*N*-(4-substituted-thiazol/1*H*-imidazol-2-yl)

acetamides as BACE1 inhibitors: Synthesis, biological evaluation and docking studies. *Eur. J. Med. Chem*., **2017**, 137, 462-475 ([#] Equal Contribution)

7. **Patent:** Xu, Ping.; Niu, Yan.; **Yan, Gang**.; Xu, Fengrong. *Compound capable of inhibiting beta-secretase, and preparation method and application thereof.* CN104860937A, 2015.; CN104860937B, 2018.

8. Qi Sun, Bo Xu, Yan Niu*, Fengrong Xu, Lei Liang, Chao Wang, Jiapei Yu, **Gang Yan**, Wei Wang, Hongwei Jin*, Ping Xu*. Synthesis, Bioactivity, Docking and Molecular Dynamics Studies of Furan-Based Peptides as 20S Proteasome Inhibitors. *ChemMedChem*, **2015**, 10, 498-510

9. Peng Liu, Yan Niu*, Chao Wang, Qi Sun, Yaya Zhai, Jiapei Yu, Jing Sun, Fengrong Xu, **Gang Yan**, Wenjie Huang, Lei Liang, Ping Xu*. 4-oxo-1,4-dihydro-quinoline-3-carboxamides as BACE-1 inhibitors: Synthesis, biological evaluation and docking studies. *Eur. J. Med. Chem*., **2014**, 79, 413-421.

10. Yaya Zhai, **Gang Yan**, Wenjie Huang, Yan Niu*, Fengrong Xu, Lei Liang, Chao Wang, Ping Xu*. Synthetic strategies for piperazine derivatives. *J. Chin. Pharm. Sci*., **2014**, 23(8), 572-577.

## Presentations

1. "Identification, validation and preliminary SAR studies of parasite glucose uptake inhibitors" **Yan, G.**; Voyton, C.; Call, D.; Vance, J.; Milanes, J.E.; Monaghan, N.P.; Bryant, K.; Christensen, K.A.; Morris, J.C.; Werbovetz, K. and Golden, J.E. The Gordon Research Seminar on Medicinal Chemistry, Colby-Sawyer College, New London, NH, USA, August 3-4, 2019. (**poster**, **YAN -** presented)

2. "Rearrangement of 2-Chloroquinazolin-4(3*H*)-ones to Afford Novel Cyclic (*E*)-Arylguanidines" **Yan, G.**; Zekarias, B.; Jaffett, V.; Li, X.; Golden, J.E. The 46th National Organic Chemistry Symposium, Indiana University, Bloomington, IN, USA, June 23-27, 2019. (**poster**, **YAN** - presented)

3. "Rearrangement of 2-Chloroquinazolin-4(3*H*)-ones to Afford Novel Cyclic (*E*)-Arylguanidines" **Yan, G.**; Zekarias, B.; Jaffett, V.; Li, X.; Golden, J.E. The 51th Annual Pharmaceutics Graduate Students Research Meeting (PGSRM), The University of Wisconsin-Madison, Madison, WI, USA, June 13-15, 2019. (**poster and oral presentation**, **YAN** - presented)

4. "Rearrangement of 2-Chloroquinazolin-4(3*H*)-ones to Afford Cyclic Guanidines with Potential Axial Chirality." **Yan, G.**; Zekarias, B.; Jaffett, V.; Li, X.; Golden, J.E. The 57th Annual MIKIW Medicinal Chemistry Meeting-in-Miniature, The University of Kansas, Lawrence, KS, USA, April 12-14, 2019. (**poster**, **YAN** - presented)

5. "Palladium-Catalyzed Carbonylation of Pyridinylated Vinylogous Amides and Ureas to Generate Privileged Pyridopyrimidinediones." **Yan, G.**; Golden, J.E. The 50th Annual Pharmaceutics Graduate Students Research Meeting (PGSRM), University of Minnesota Twin Cities, Minneapolis, MN, USA, June 7-9, 2018. (**poster**, **YAN** - presented)

6. "Palladium-Catalyzed Carbonylation of Pyridine-Directing Vinylogous Amides to Generate Privileged Pyridopyrimidinediones." **Yan, G.**; Golden, J.E. The 56th Annual MIKI Medicinal Chemistry Meeting-in-Miniature, University of Illinois at Chicago, Chicago, Illinois, USA, April 6-8, 2018. (**poster**, **YAN** - presented)

7. “Design and synthesis of thio-*N*-(thiazol-2-yl)acetamides as BACE-1 inhibitors.”**Yan, G**.; Niu, Y.; and Xu, P. 2013 Chinese Medicinal Chemistry Symposium & 4th CPA-RSC Symposium on Medicinal Chemistry, Shandong University, Jinan, November 2-3, 2013. (**poster**, **YAN** - presented)

# Appendix II NMR Spectra of Compounds

**Chapter 2: Page 341 ~ 420**

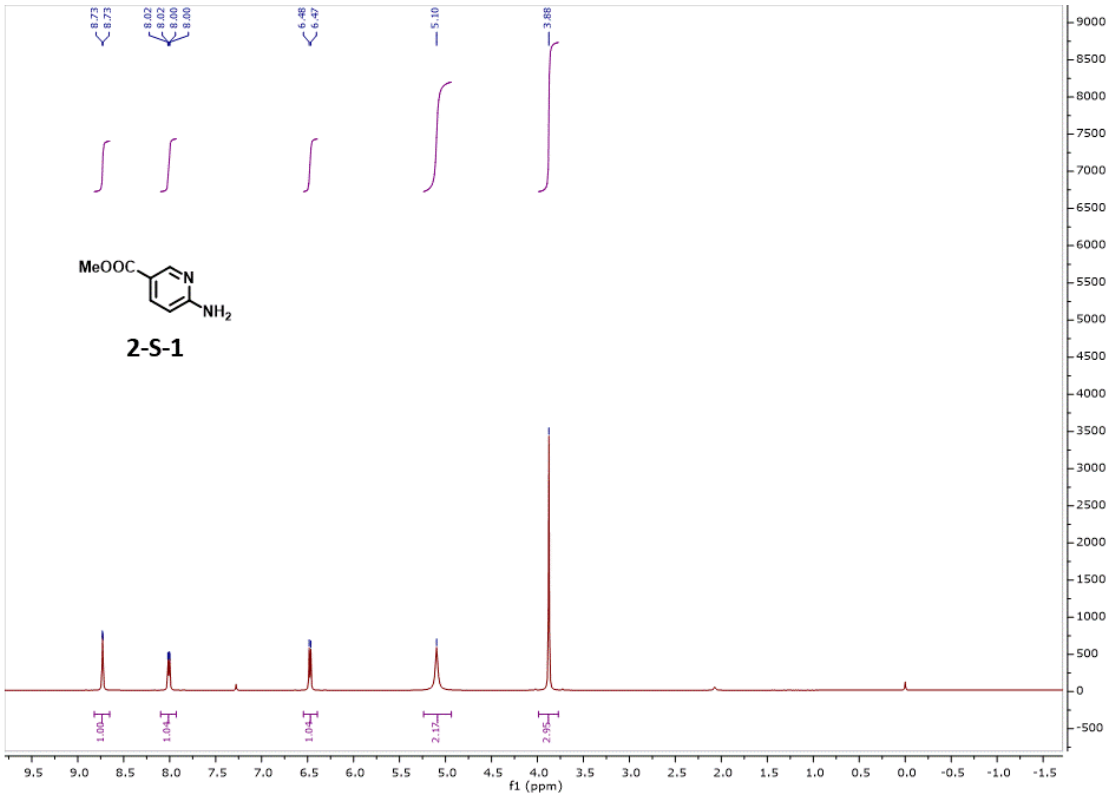
**Chapter 3: Page 420 ~ 549**

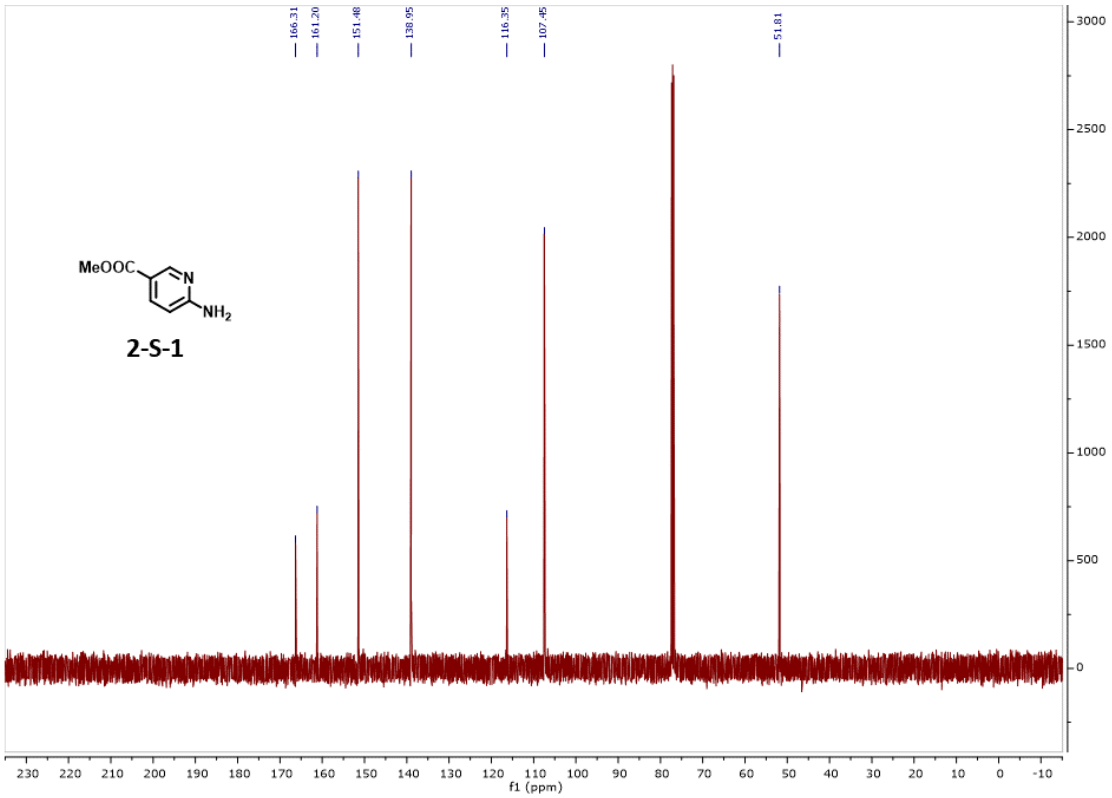
**Chapter 4: Page 549 ~ 656**

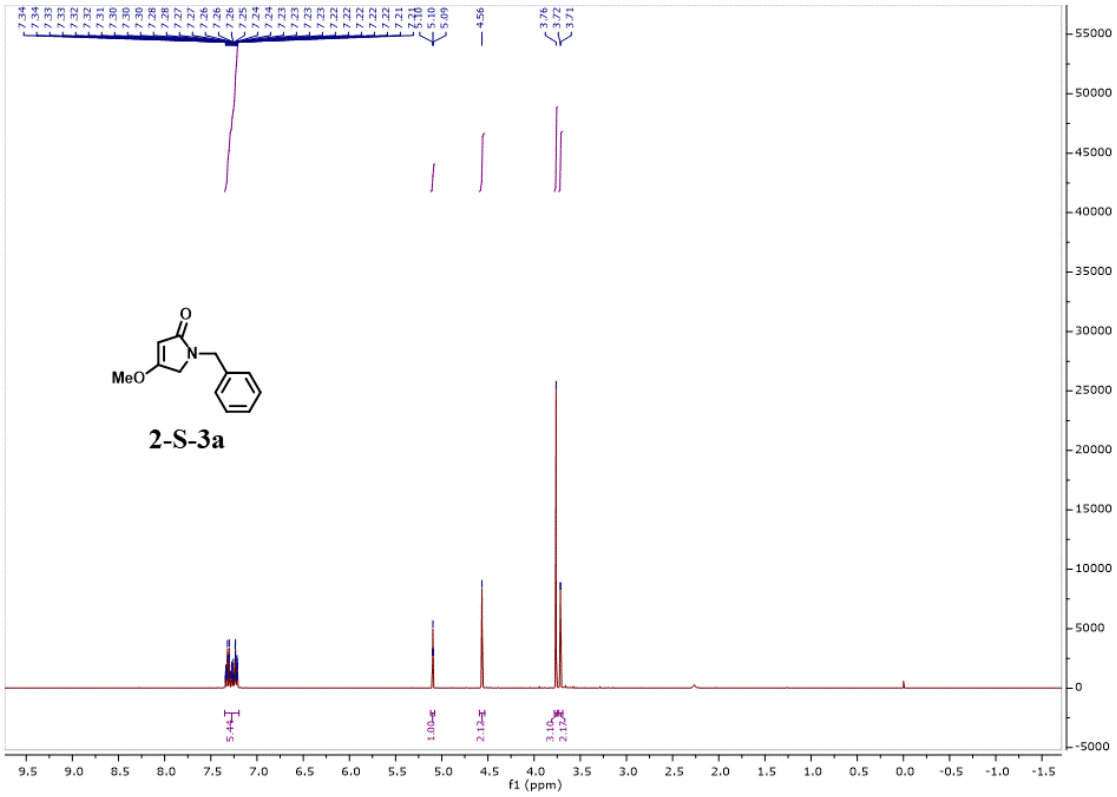
**Chapter 5: Page 657 ~ 658**

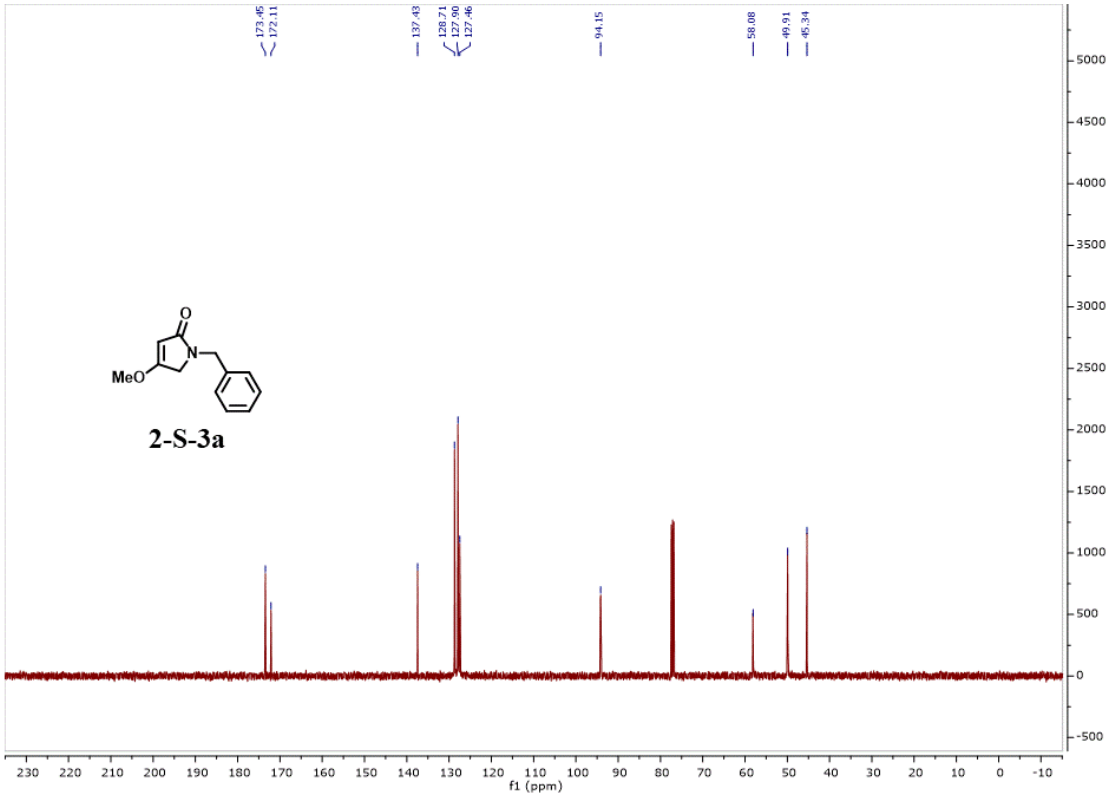
**Chapter 6: Page 659 ~ 694**

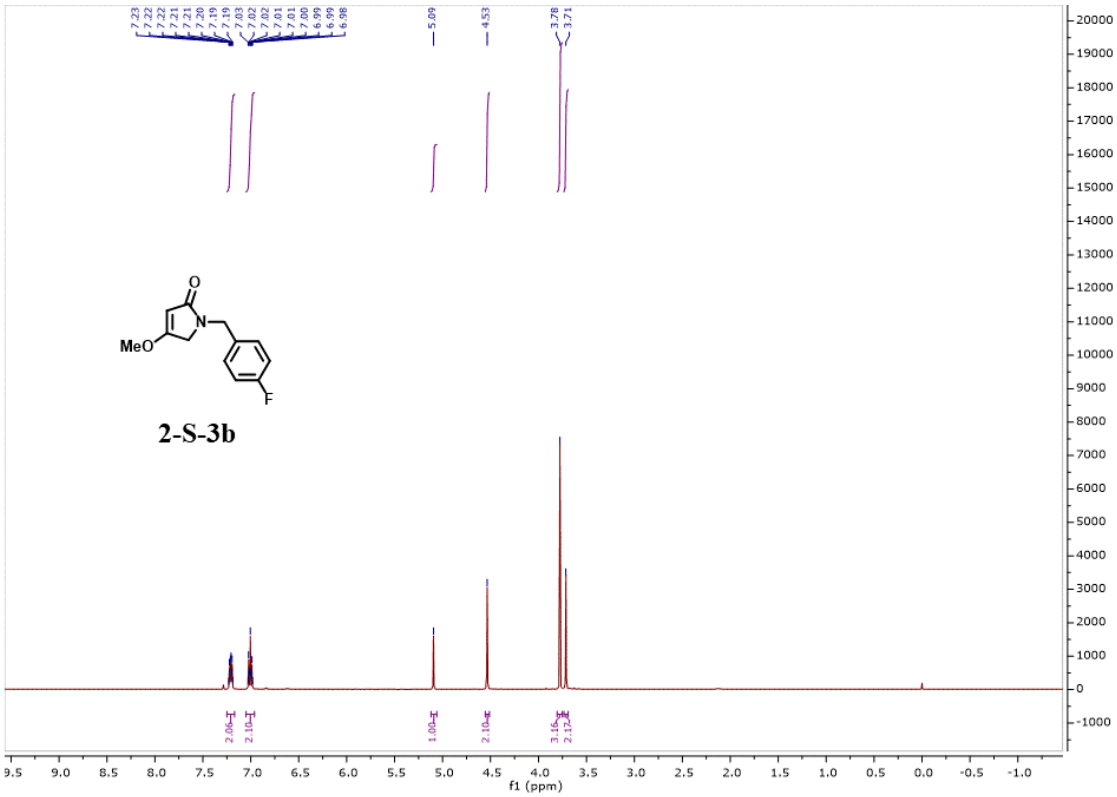
**Chapter 7: Page 695 ~ 702**

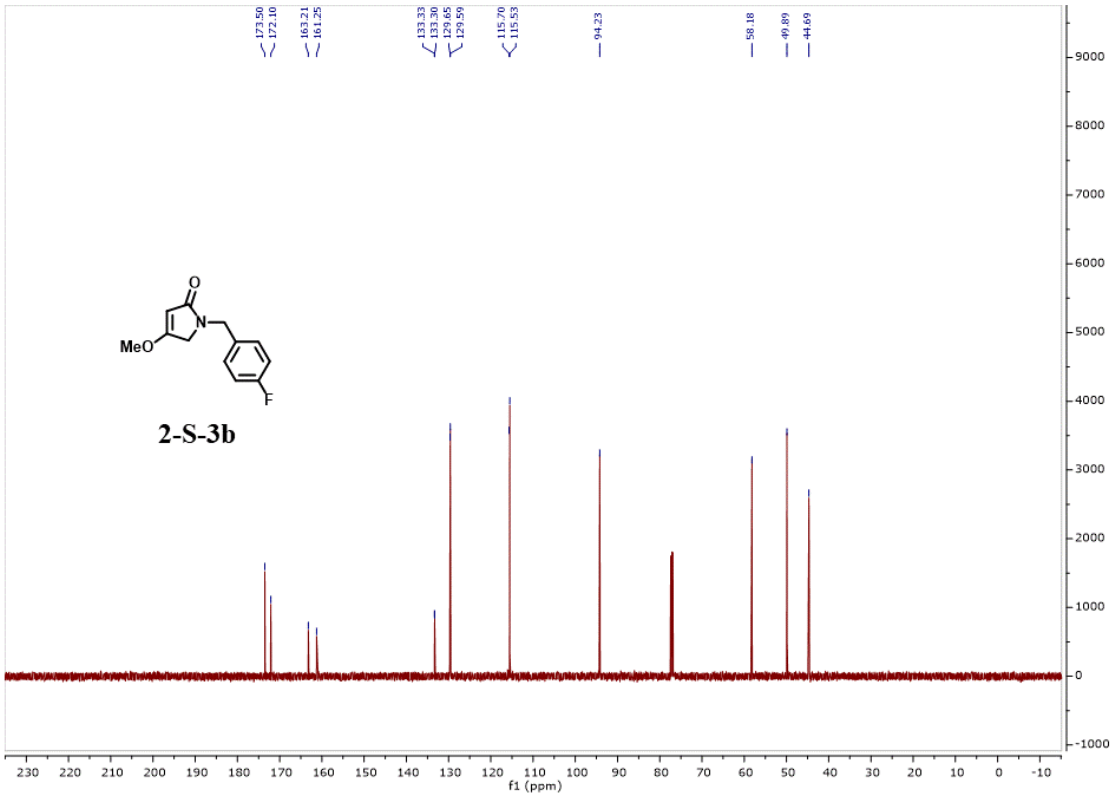

8.73
8.73
8.02
8.02
8.00
8.00
6.48
6.47
5.10
3.88
MeOOC
N
NH2
2-S-1
1.00
1.04
1.04
2.17
2.95
f1 (ppm)

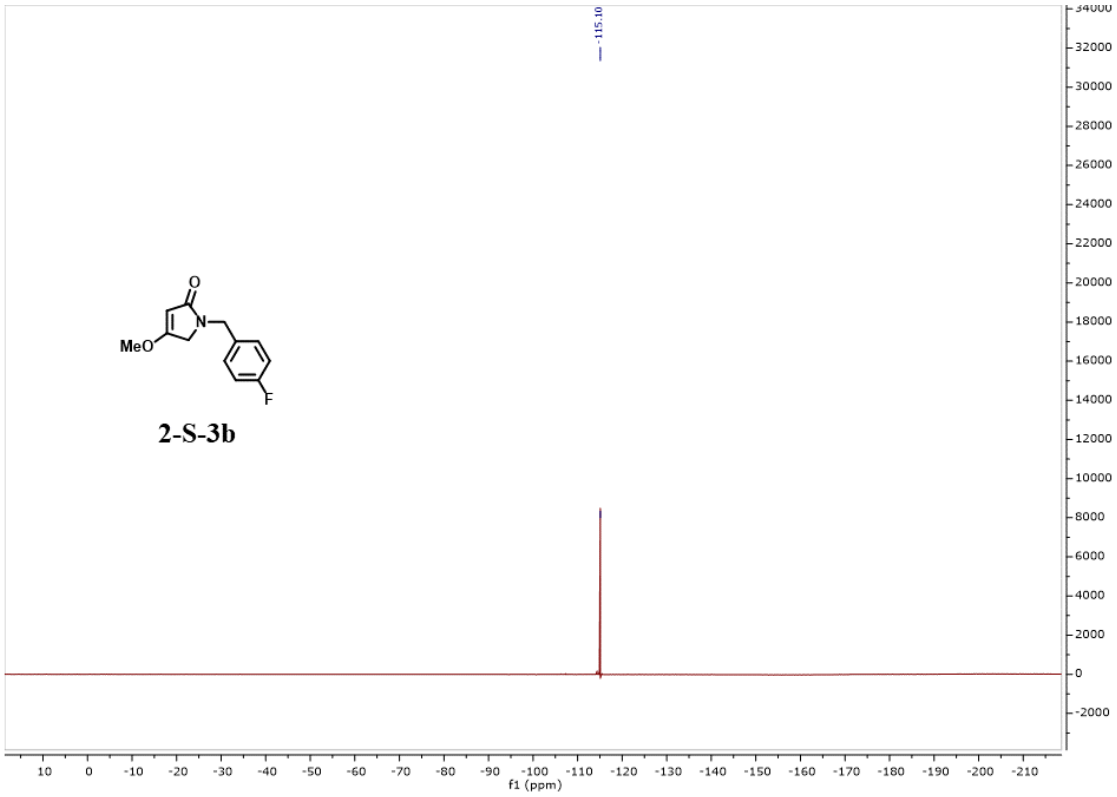

166.31
161.20
151.48
138.95
116.35
107.45
51.81
MeOOC
N
NH2
2-S-1
f1 (ppm)

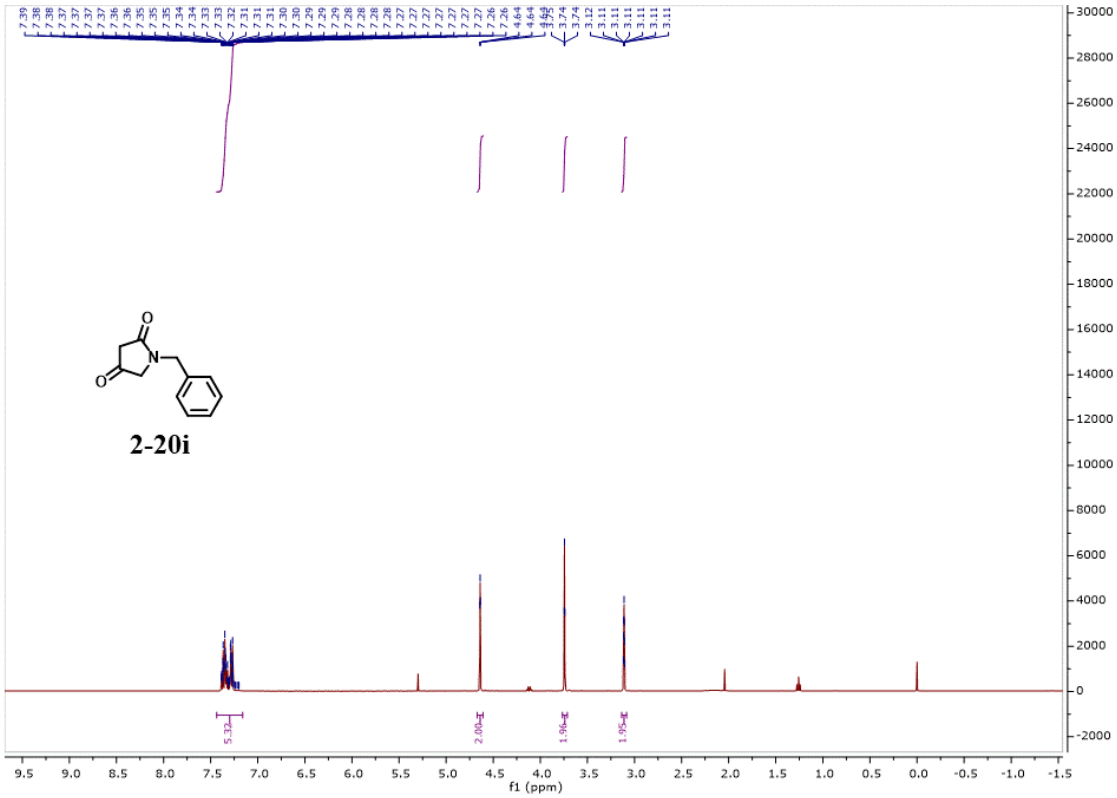

MeO
O
N
2-S-3a
f1 (ppm)

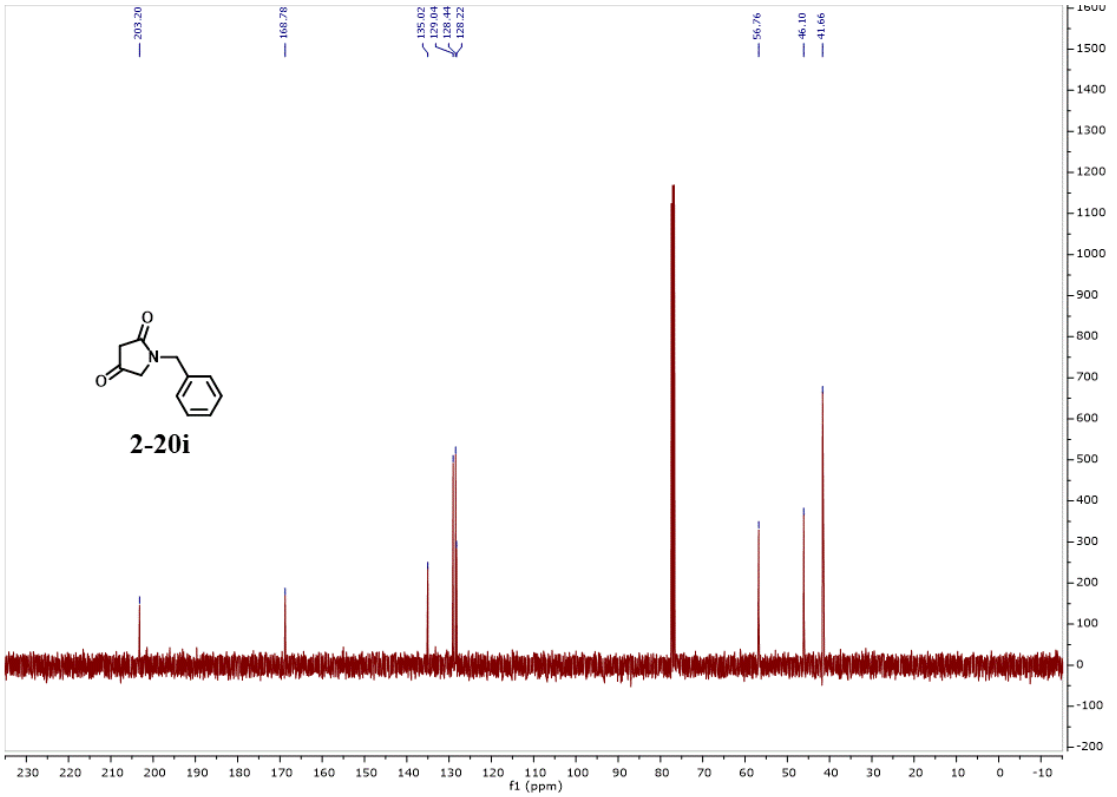

MeO
O
N
2-S-3a
f1 (ppm)


7.23
7.22
7.22
7.21
7.21
7.20
7.19
7.19
7.03
7.02
7.02
7.01
7.01
7.00
6.99
6.99
6.98
5.09
4.53
3.78
3.71
MeO
O
N
F
2-S-3b
2.06
2.10
1.00
2.10
3.15
2.12
f1 (ppm)

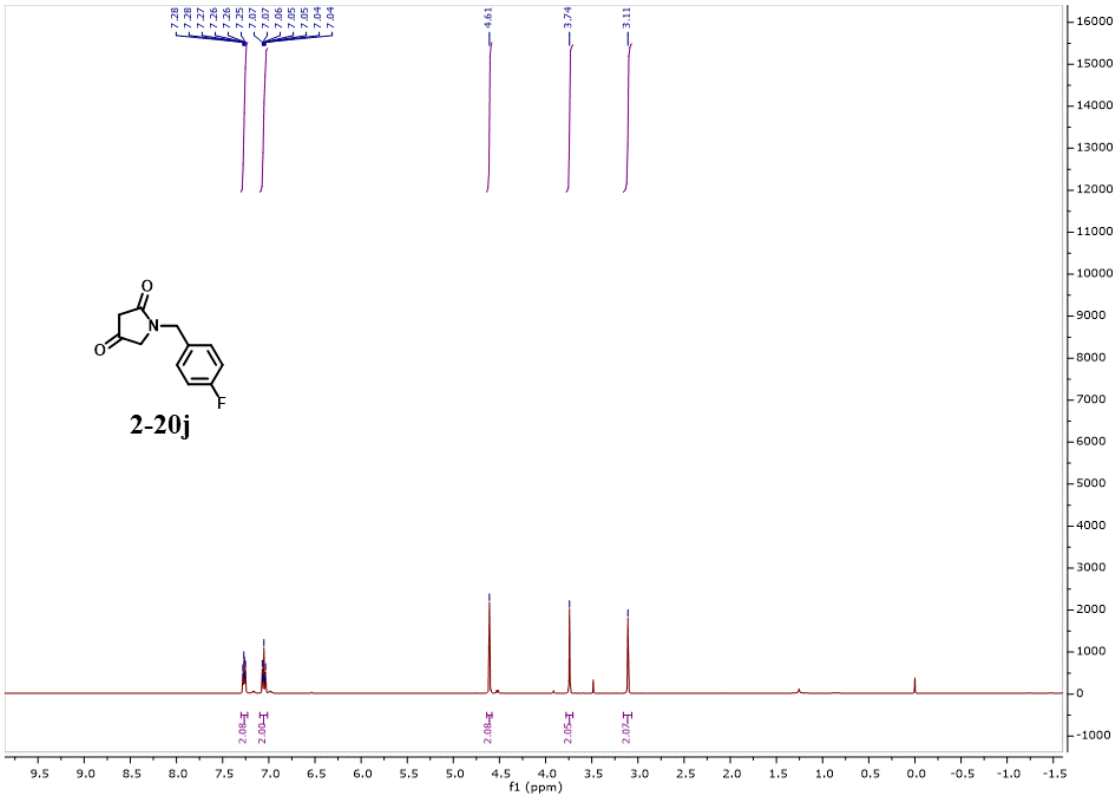

173.50
172.10
163.21
161.25
133.33
133.30
129.65
129.59
115.70
115.53
94.23
58.18
49.89
44.69
MeO
O
N
F
2-S-3b
f1 (ppm)


-115.10
MeO
F
2-S-3b
f1 (ppm)

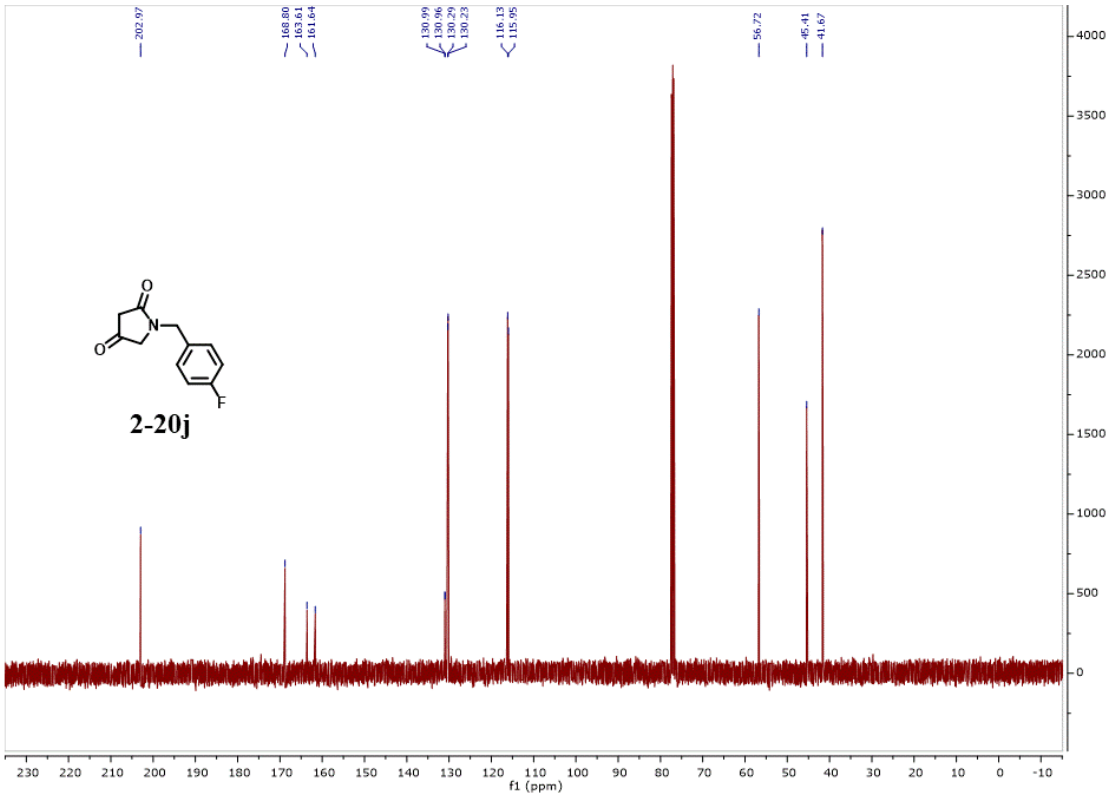

2-20i
f1 (ppm)

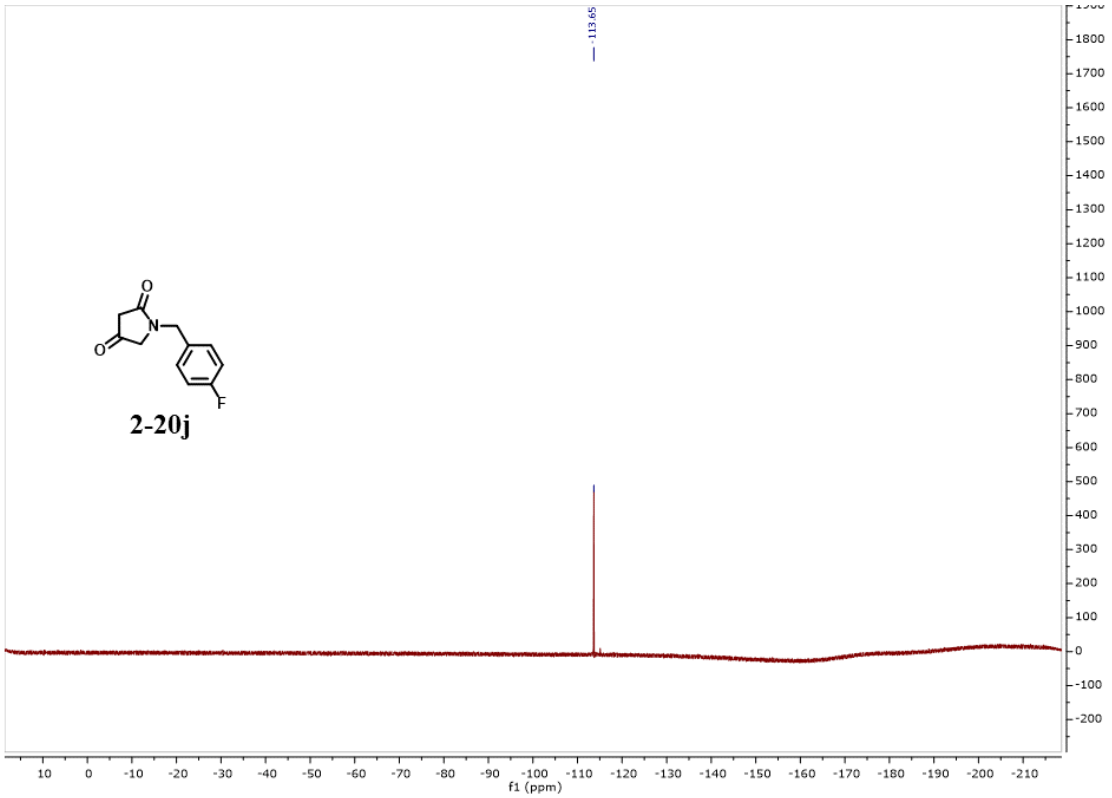

203.20
168.78
135.02
129.04
128.44
128.22
56.76
46.10
41.66
f1 (ppm)

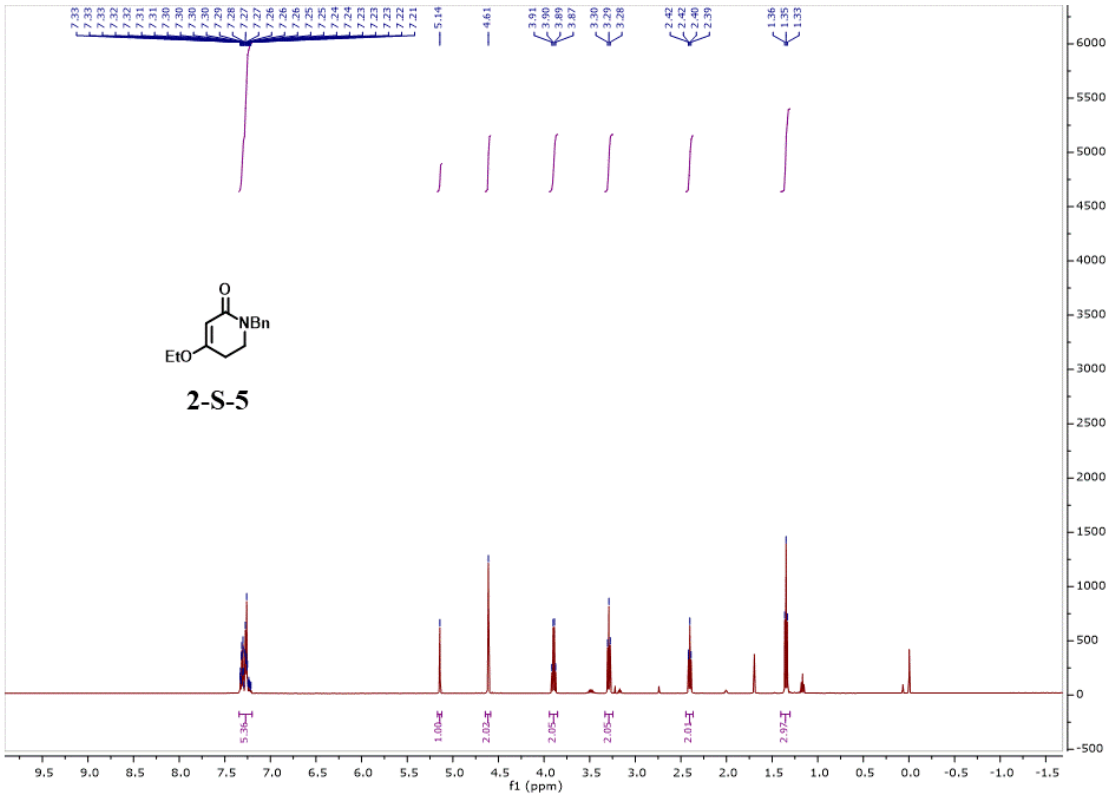
**2-20i**

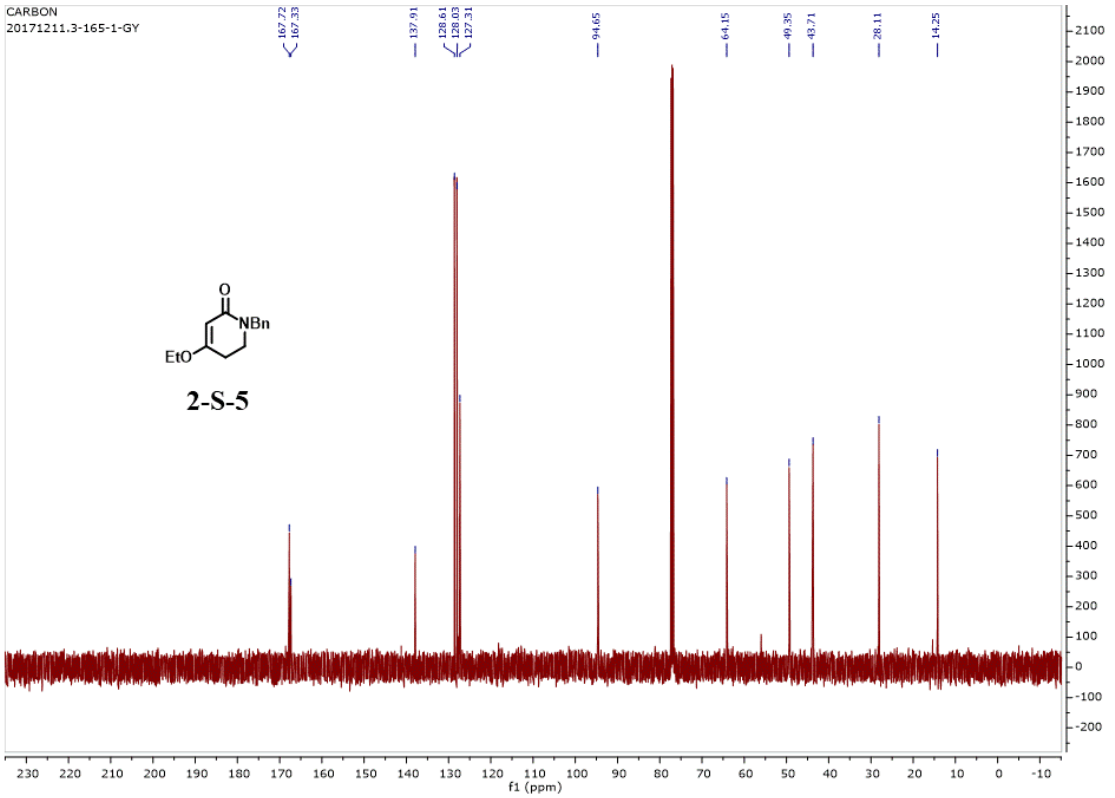

7.28
7.28
7.27
7.26
7.25
7.07
7.07
7.06
7.05
7.05
7.04
7.04
4.61
3.74
3.11
2.08
2.00
2.08
2.05
2.07
f1 (ppm)

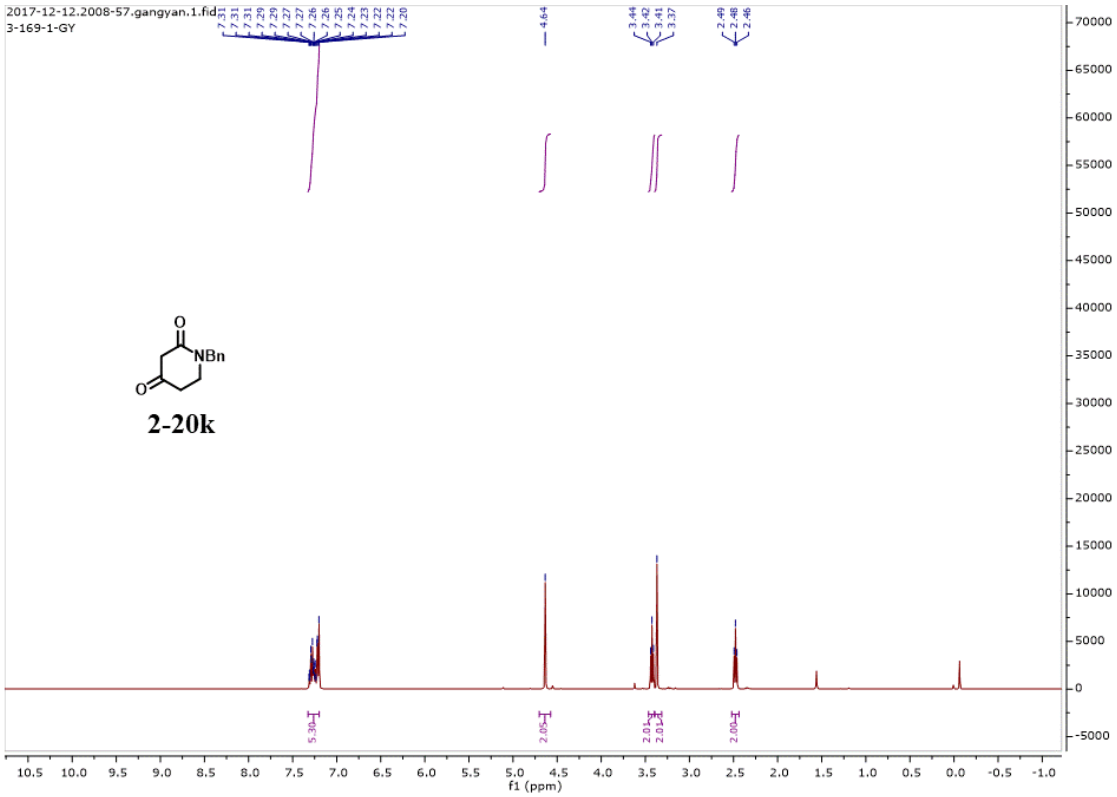
**2-20j**

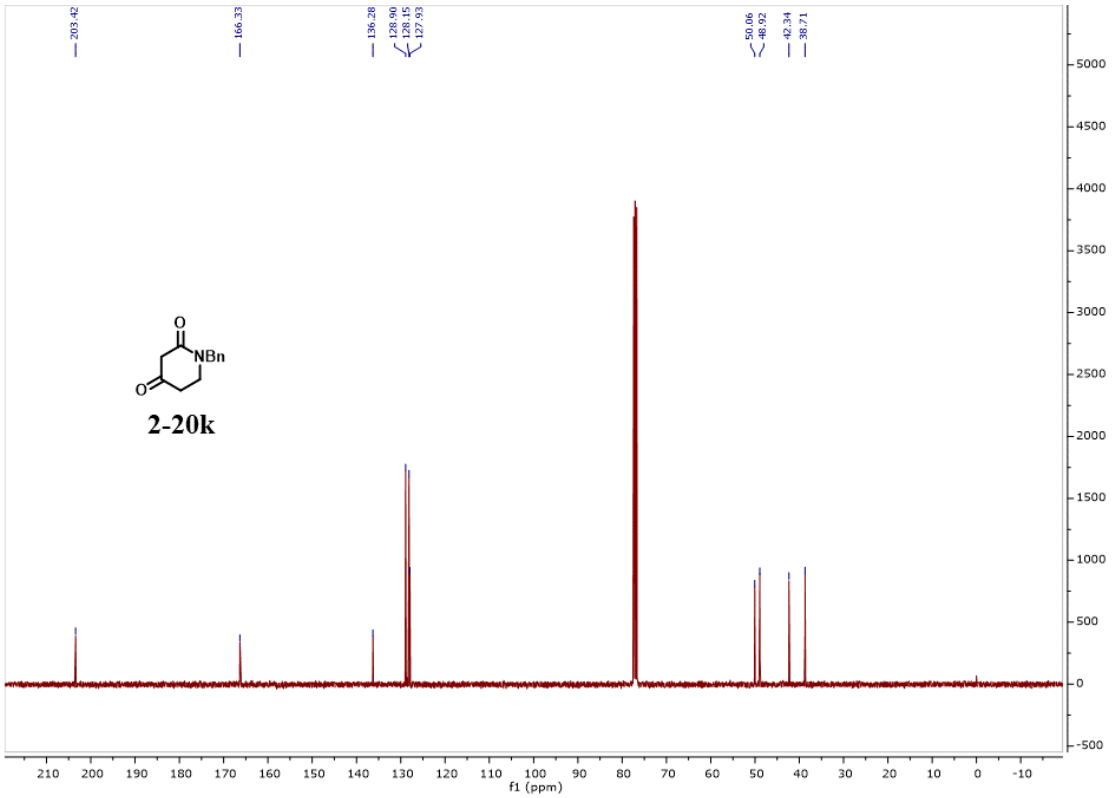

202.97
168.80
163.61
161.64
130.99
130.96
130.29
130.23
116.13
115.95
56.72
45.41
41.67
2-20j
f1 (ppm)

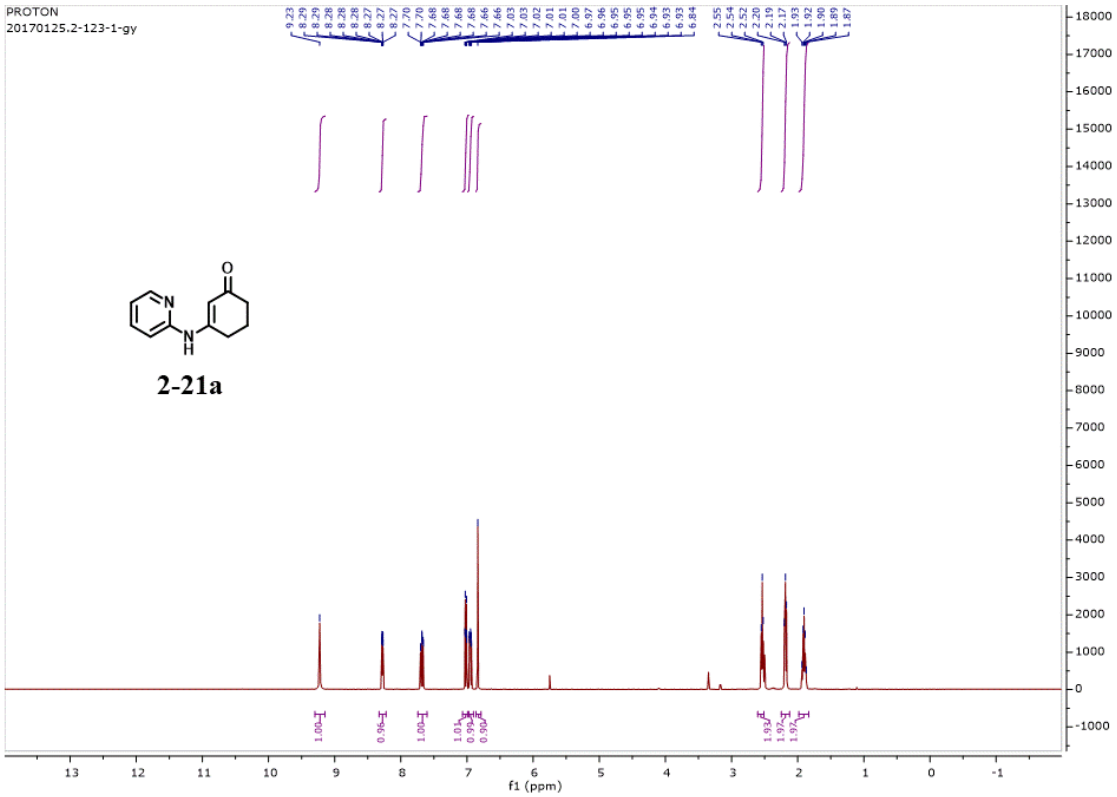

113.65
2-20j
f1 (ppm)

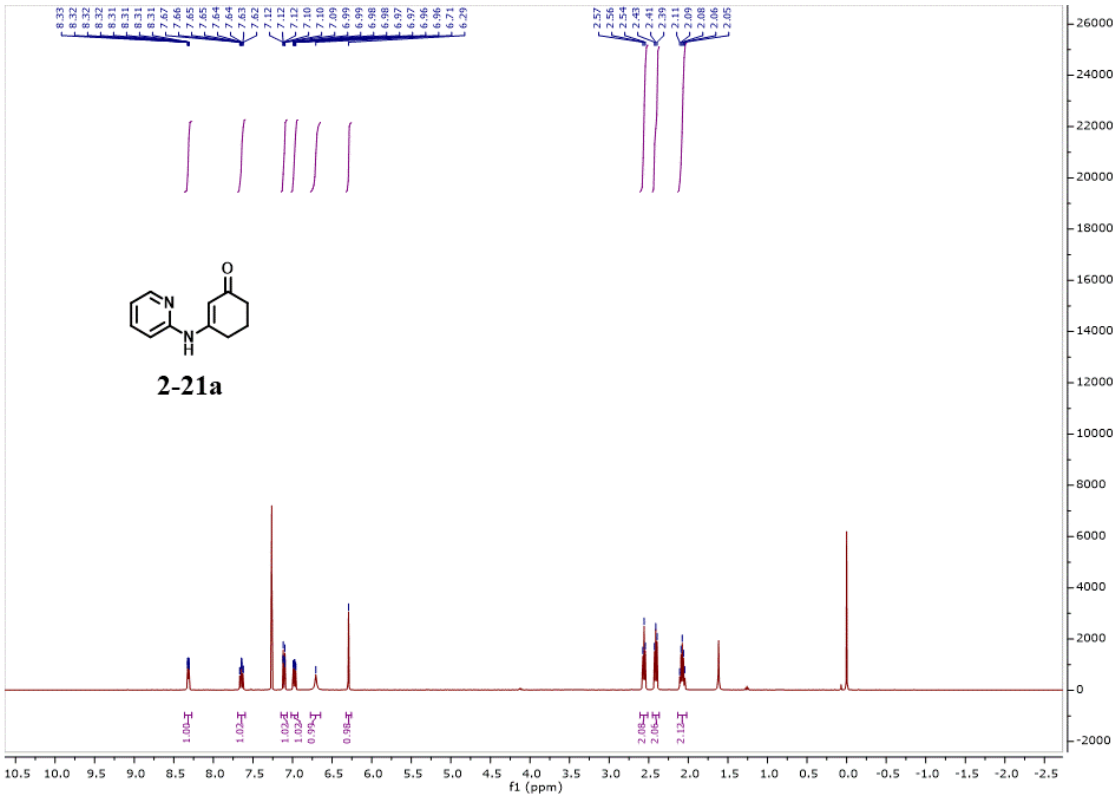

NBn
EtO
2-S-5
f1 (ppm)

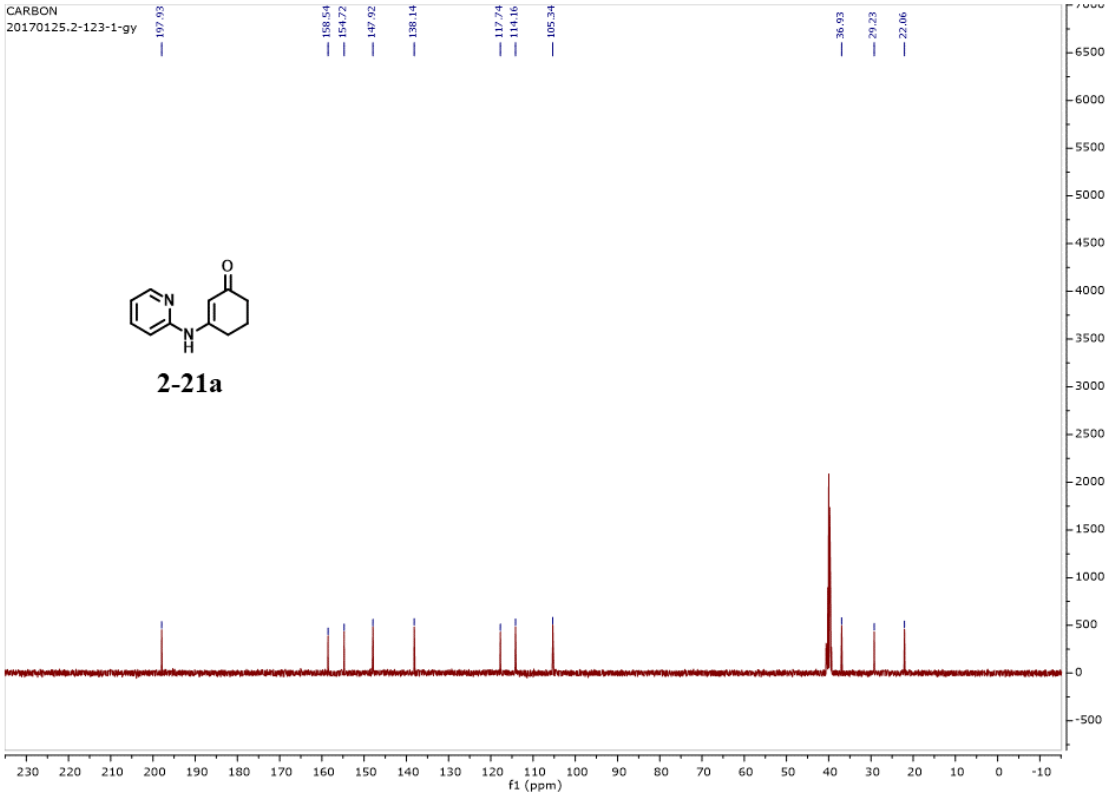

CARBON
20171211.3-165-1-GY
NBn
EtO
2-S-5
f1 (ppm)


2017-12-12.2008-57.gangyan.1.fid
3-169-1-GY
NBn
2-20k
f1 (ppm)

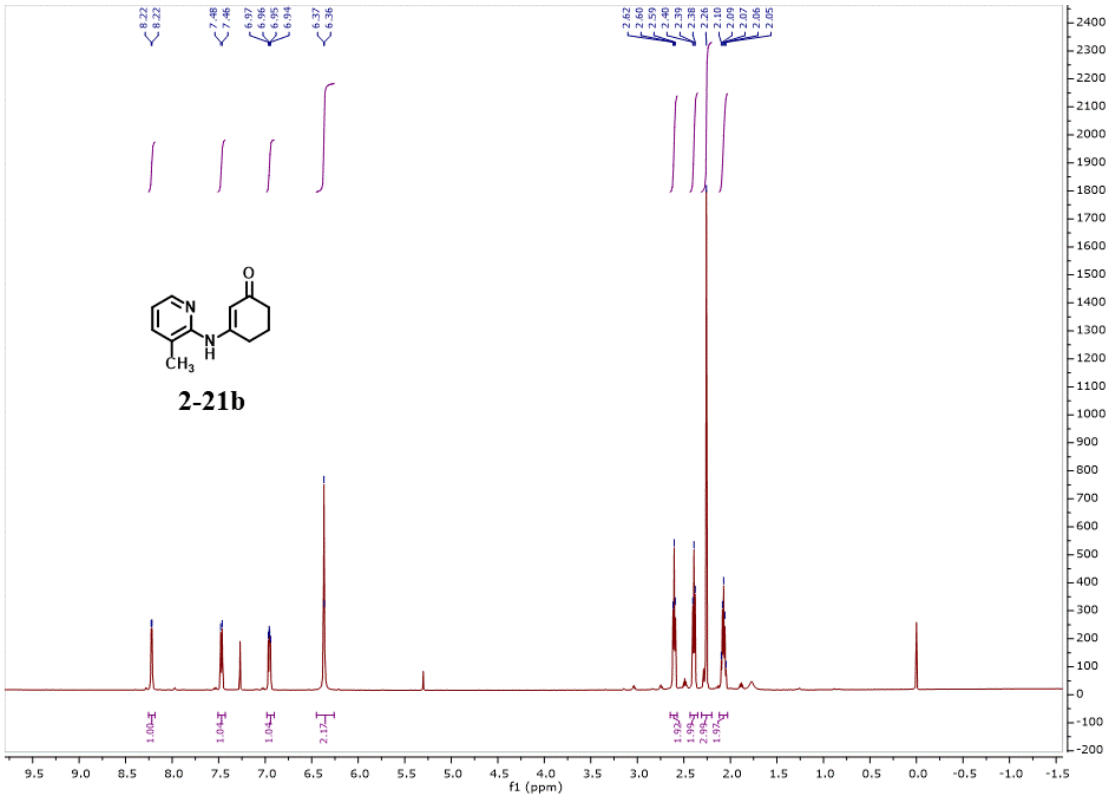

NBn
2-20k
f1 (ppm)


PROTON
20170125.2-123-1-gy
2-21a
f1 (ppm)

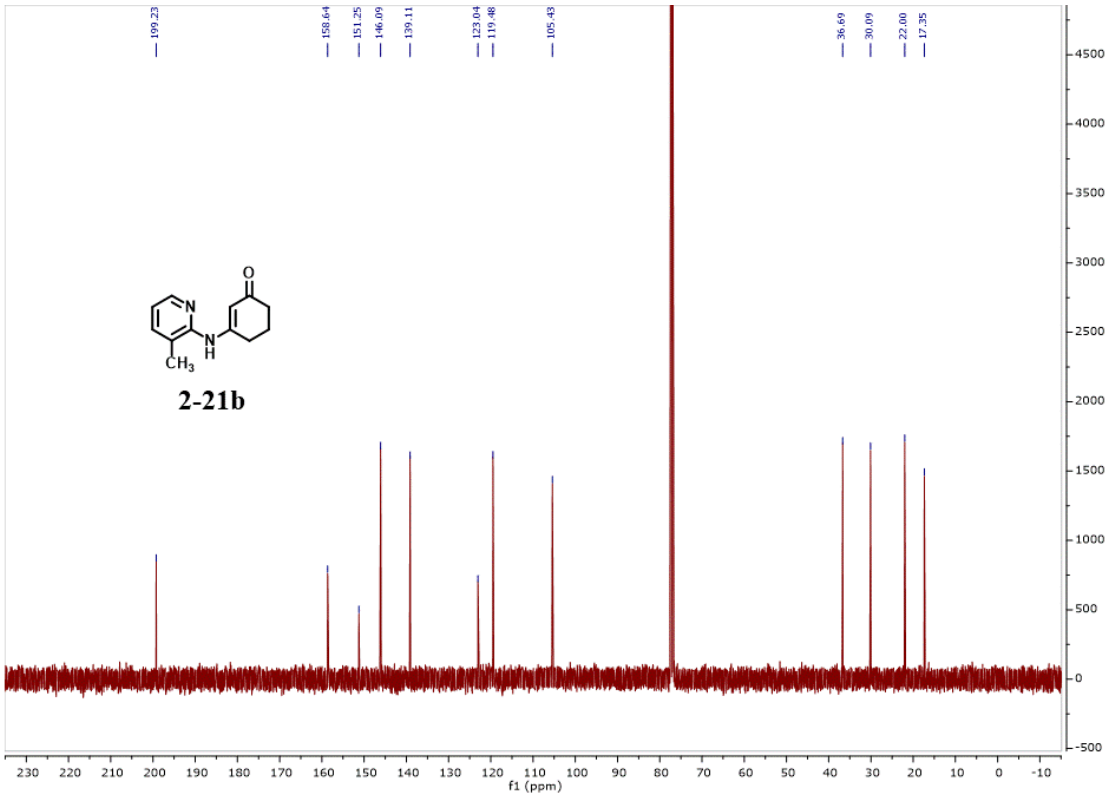

2-21a
f1 (ppm)

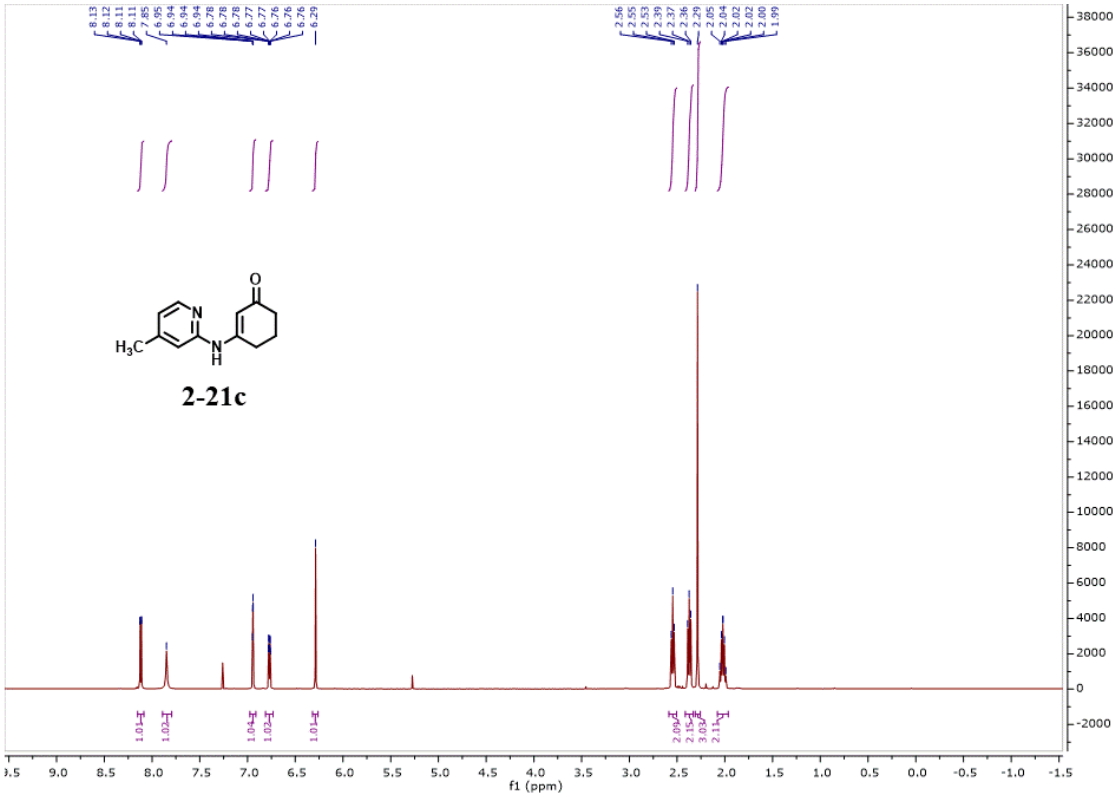

CARBON
20170125.2-123-1-gy
197.93
158.54
154.72
147.92
138.14
117.74
114.16
105.34
36.93
29.23
22.06
f1 (ppm)

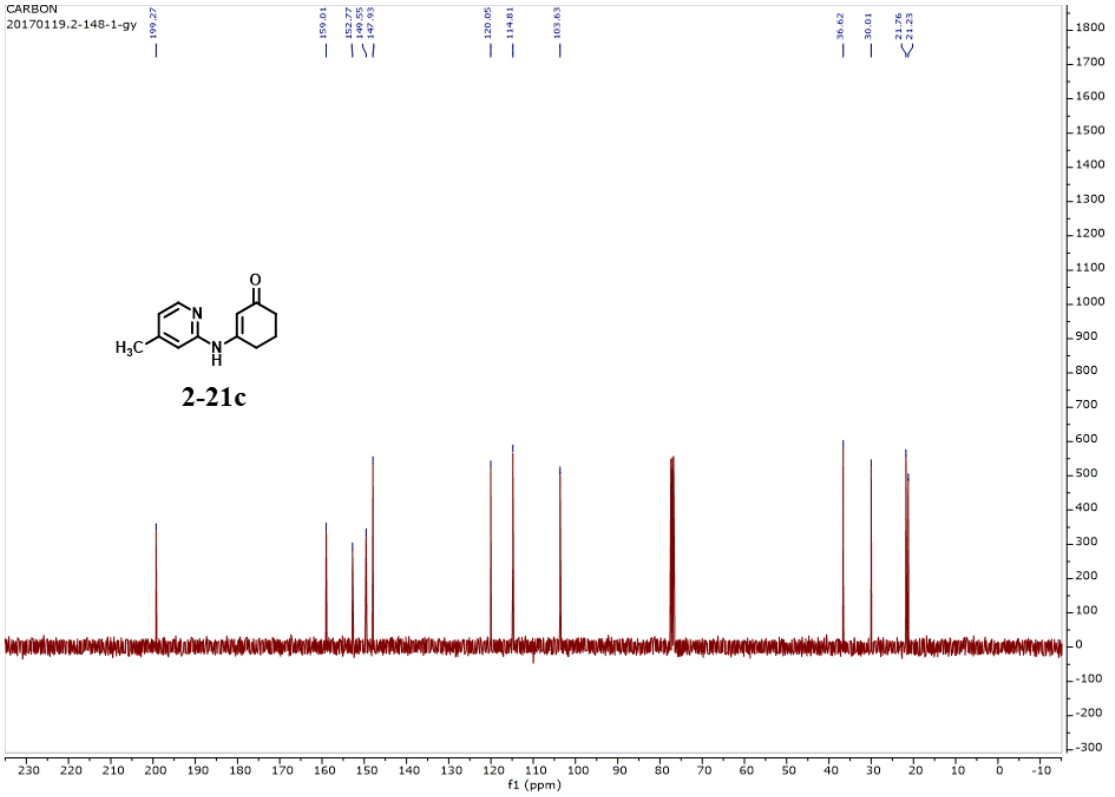
**2-21a**


8.22
8.22
7.48
7.46
6.97
6.96
6.95
6.94
6.37
6.36
2.62
2.60
2.55
2.40
2.39
2.38
2.26
2.10
2.09
2.07
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1.99
2.99
1.97
f1 (ppm)

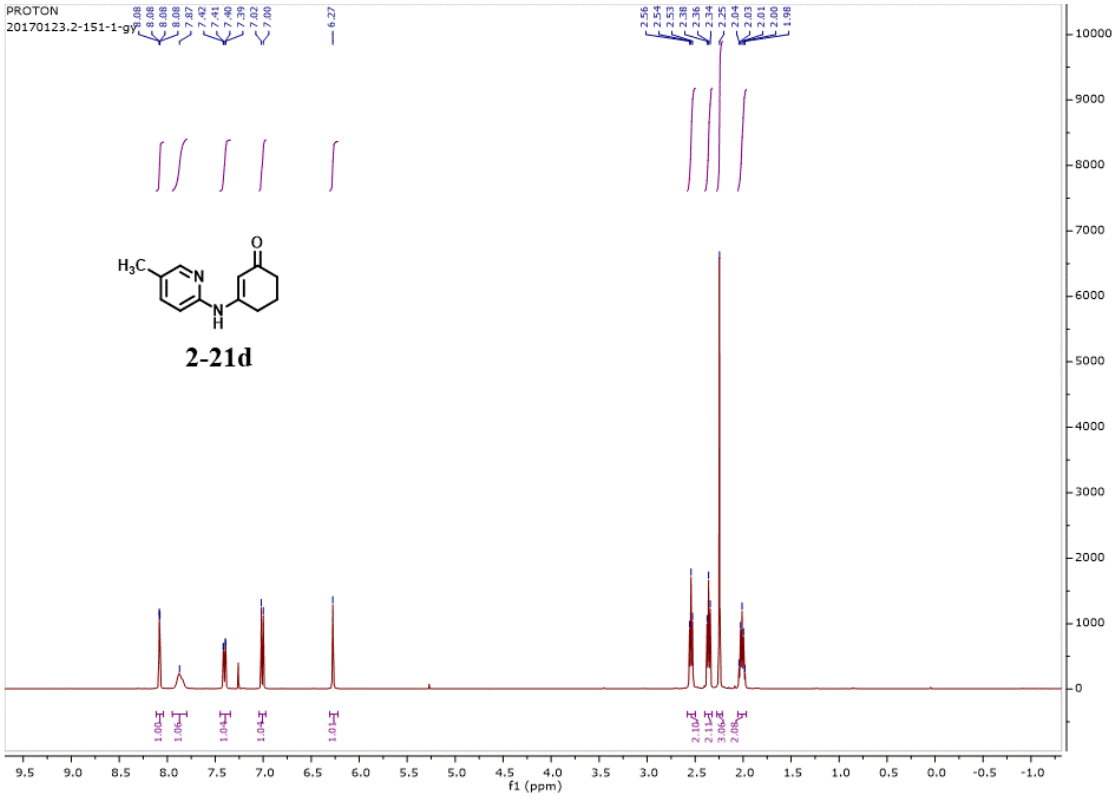
**2-21b**


199.23
158.64
151.25
146.09
139.11
123.04
119.48
105.43
36.69
30.09
22.00
17.35
2-21b
f1 (ppm)

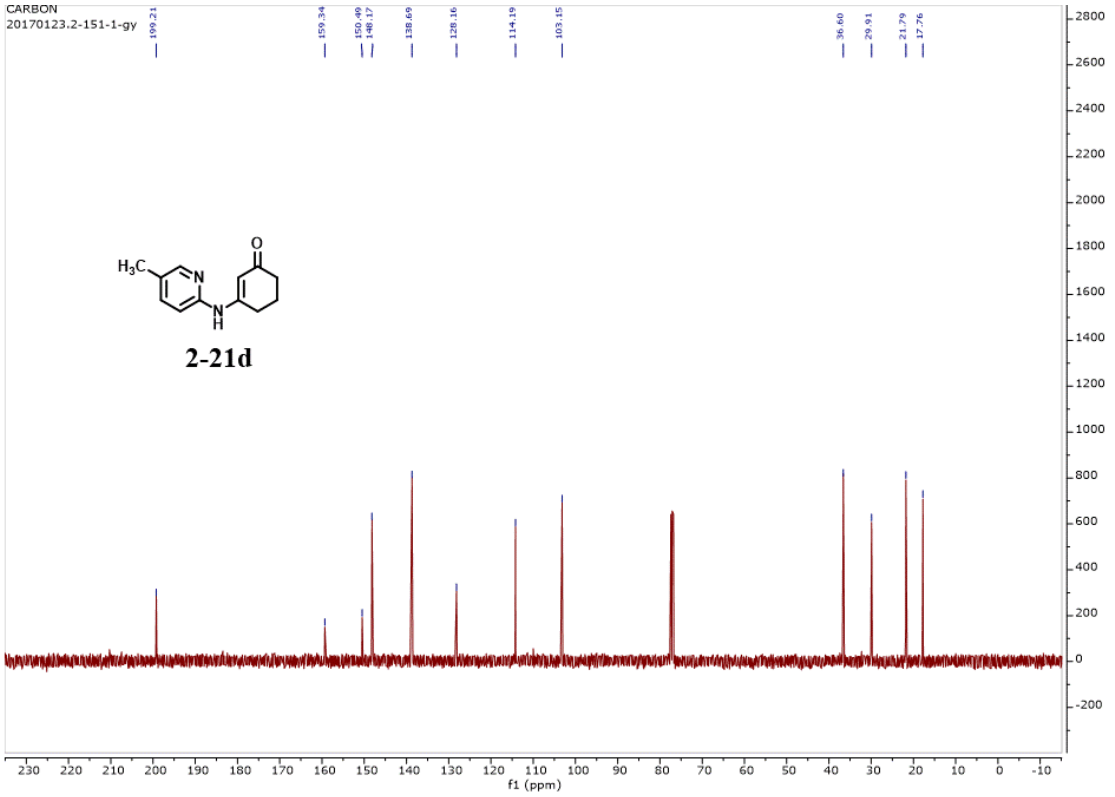

2-21c
f1 (ppm)


CARBON
20170119.2-148-1-gy
199.27
159.01
152.77
149.55
147.93
120.05
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103.63
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30.01
21.76
21.23
f1 (ppm)

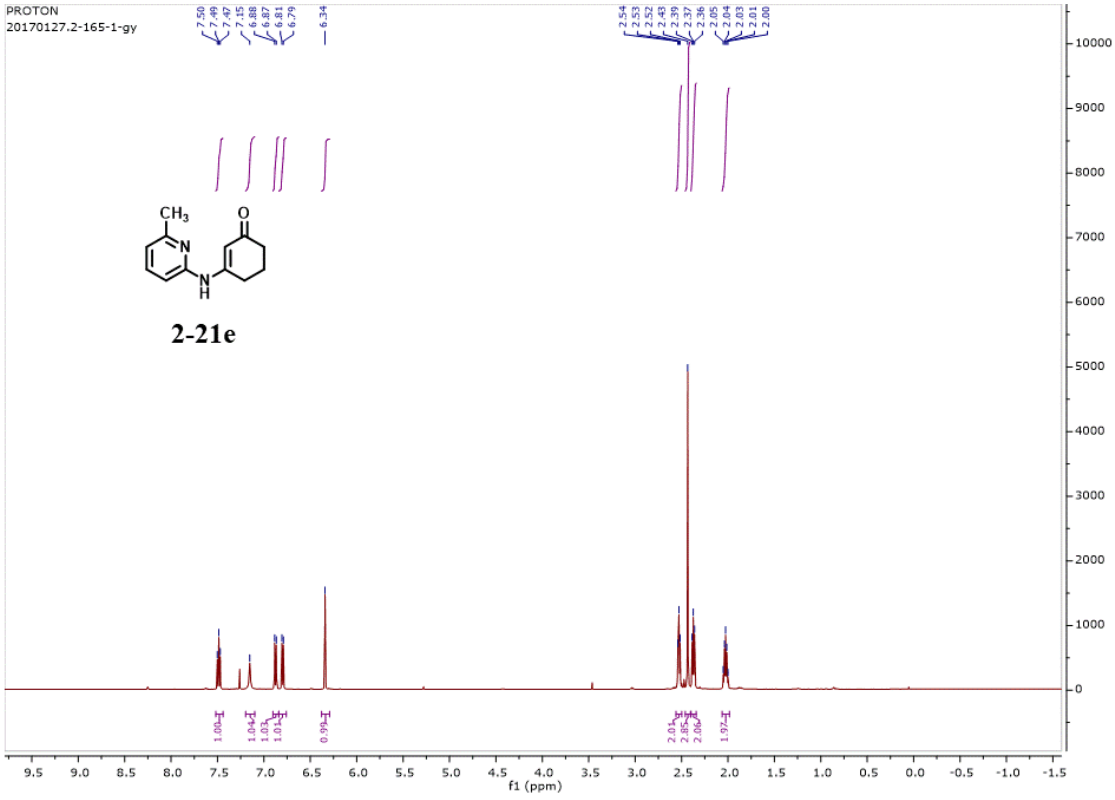
**2-21c**


PROTON
20170123.2-151-1-gy
8.08
8.08
8.08
8.08
7.97
7.42
7.41
7.40
7.39
7.02
7.00
6.27
2.56
2.54
2.53
2.38
2.36
2.34
2.25
2.04
2.03
2.01
2.00
1.98
1.00
1.06
1.04
1.04
1.01
2.10
2.11
3.06
2.08
f1 (ppm)

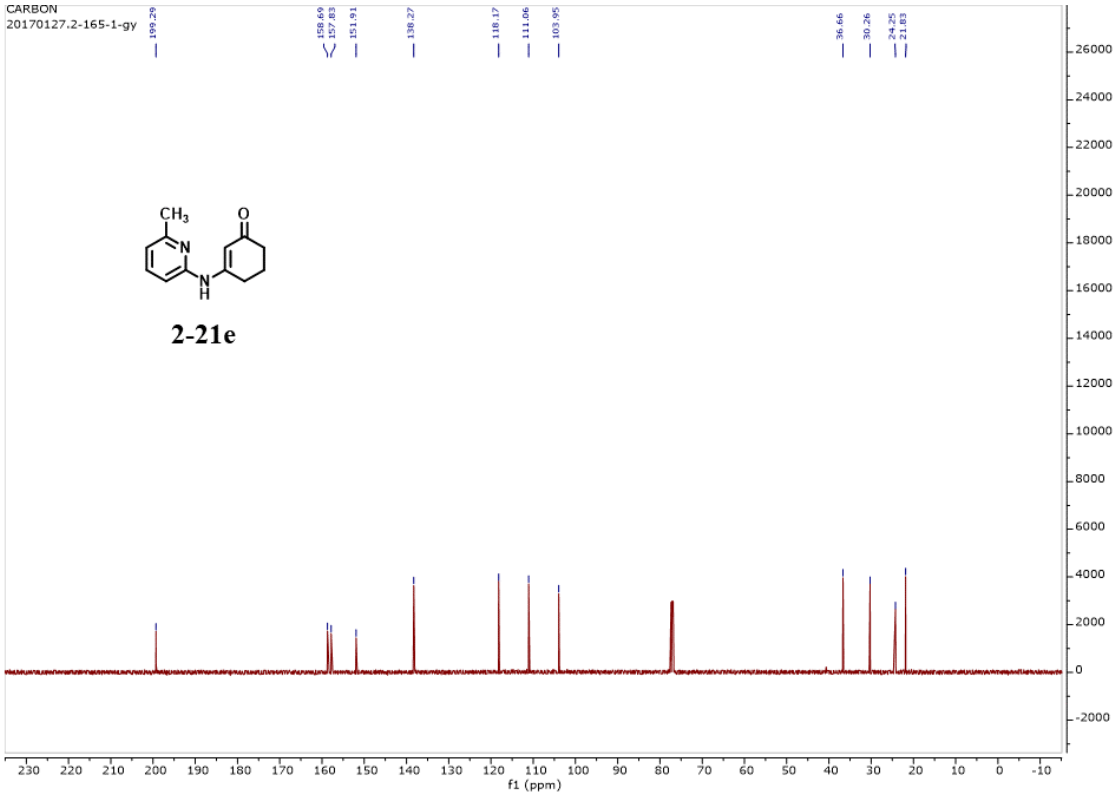
**2-21d**


CARBON
20170123.2-151-1-gy
199.21
159.34
150.49
146.17
138.69
128.16
114.19
103.15
36.60
29.91
21.79
17.76
f1 (ppm)

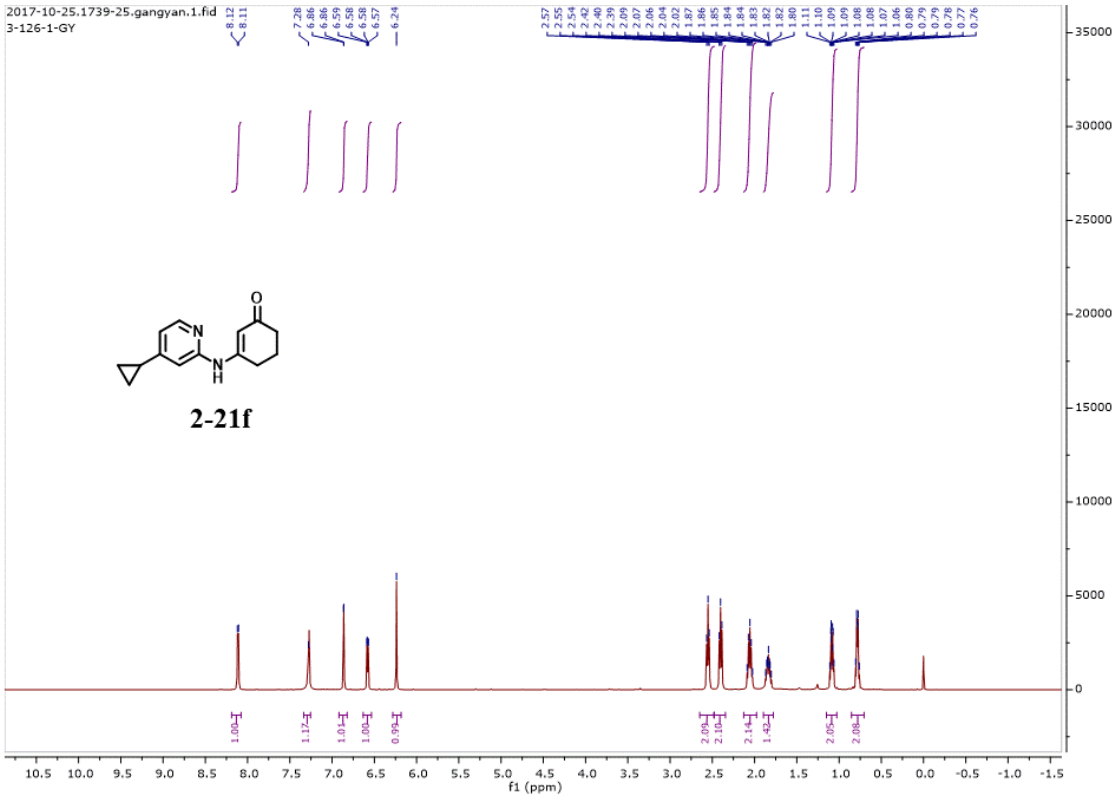
**2-21d**


PROTON
20170127.2-165-1-gy
7.50
7.49
7.47
7.15
6.88
6.87
6.81
6.79
6.34
2.54
2.53
2.52
2.43
2.39
2.37
2.36
2.05
2.04
2.03
2.01
2.00
1.00
1.04
1.03
1.01
0.99
2.01
2.85
2.06
1.97
f1 (ppm)

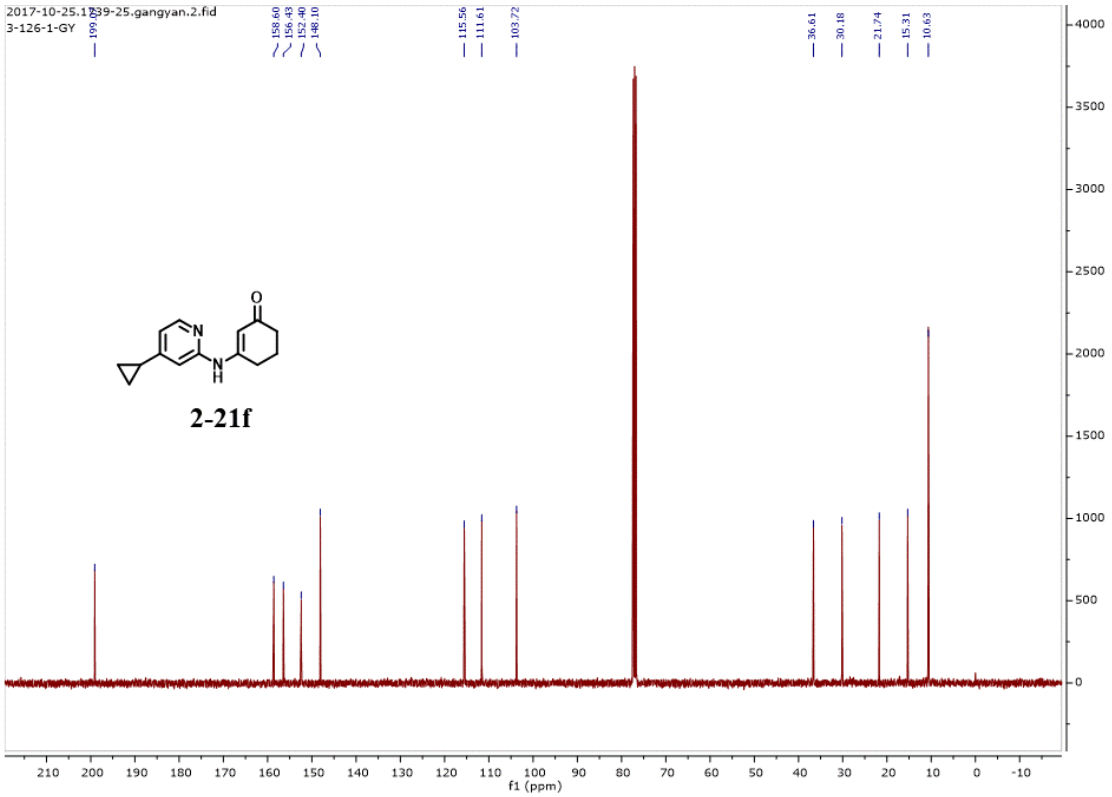
**2-21e**


CARBON
20170127.2-165-1-gy
199.29
158.69
157.83
151.91
138.27
118.17
111.06
103.95
36.66
30.26
24.25
21.83
f1 (ppm)

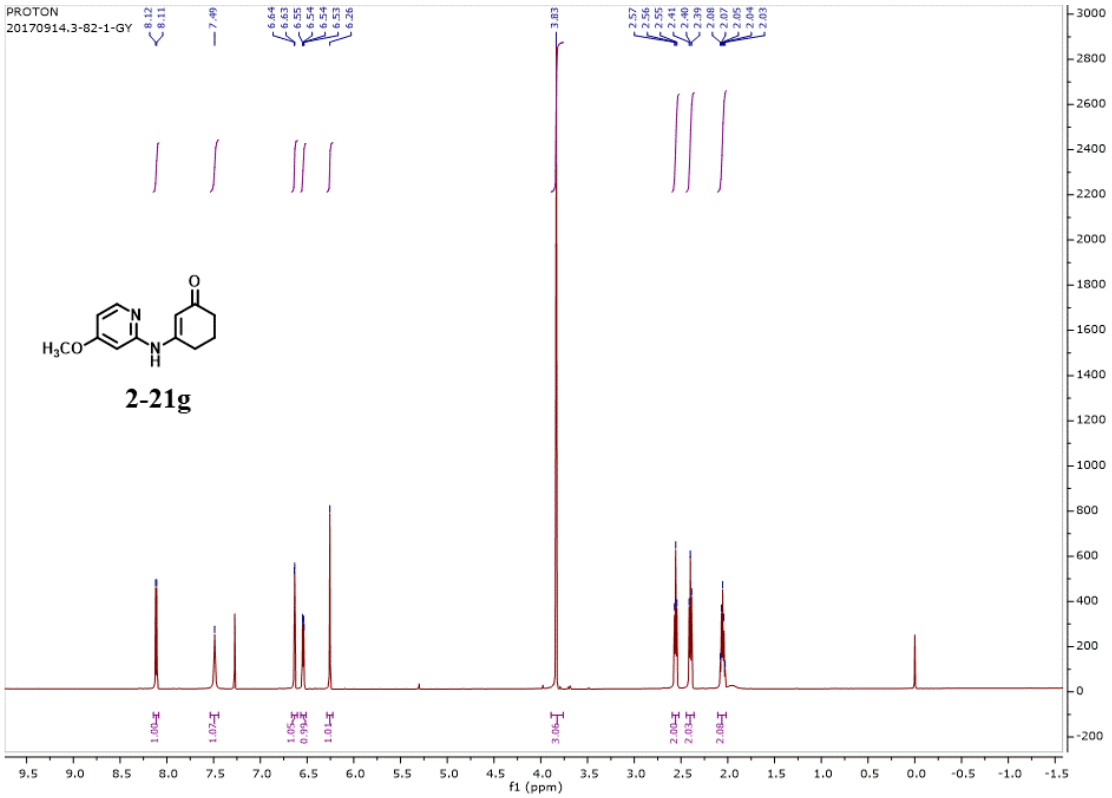
**2-21e**


2017-10-25.1739-25.gangyan.1.fid
3-126-1-GY
f1 (ppm)

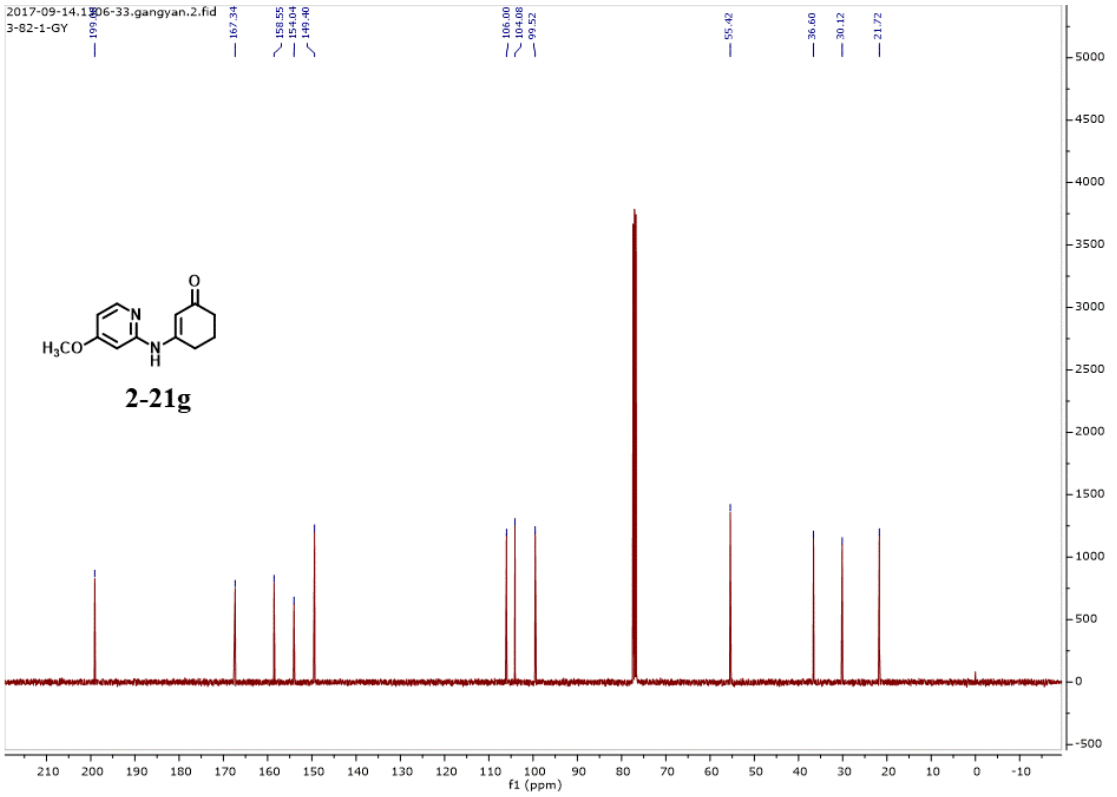
**2-21f**

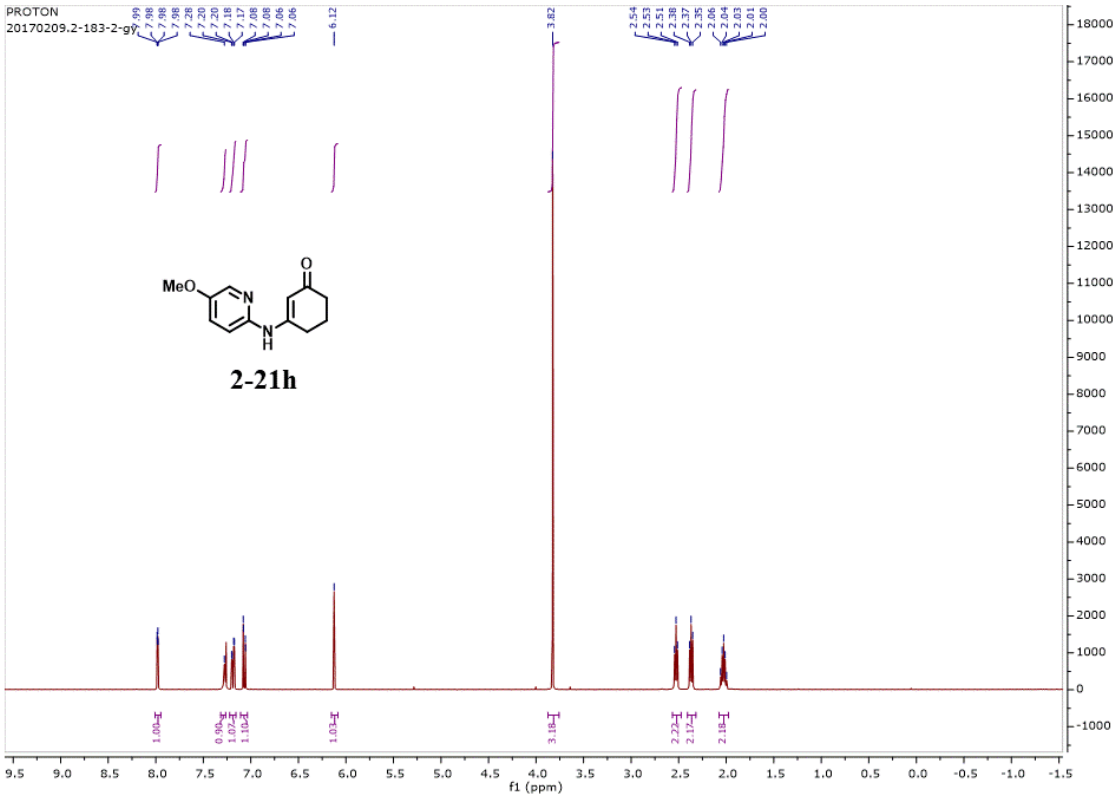

2017-10-25.1[illegible]39-25.gangyan.2.fid
3-126-1-GY
199.03
158.60
156.45
152.40
148.10
115.56
111.61
103.72
36.61
30.18
21.74
15.31
10.63
f1 (ppm)

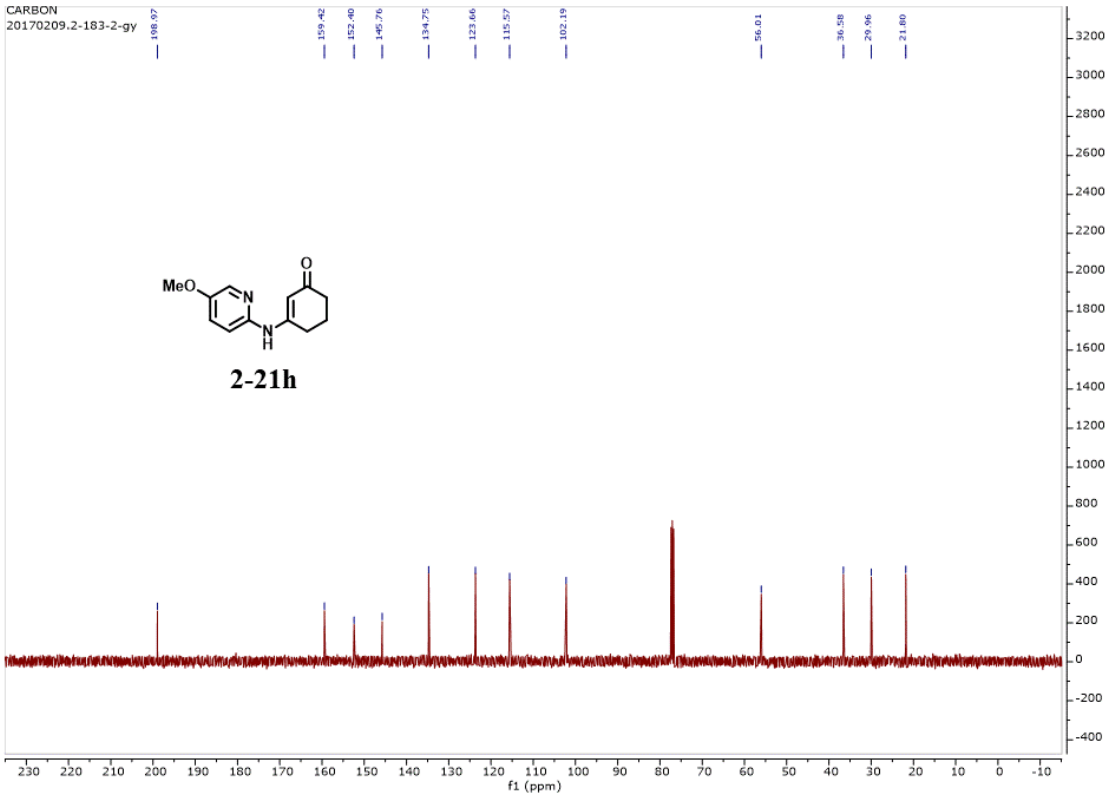
**2-21f**


PROTON
20170914.3-82-1-GY
8.12
8.11
7.49
6.64
6.63
6.55
6.54
6.54
6.53
6.26
3.83
2.57
2.56
2.55
2.41
2.40
2.39
2.08
2.07
2.05
2.04
2.03
1.00
1.07
1.05
0.99
1.01
3.06
2.04
2.03
2.08
f1 (ppm)

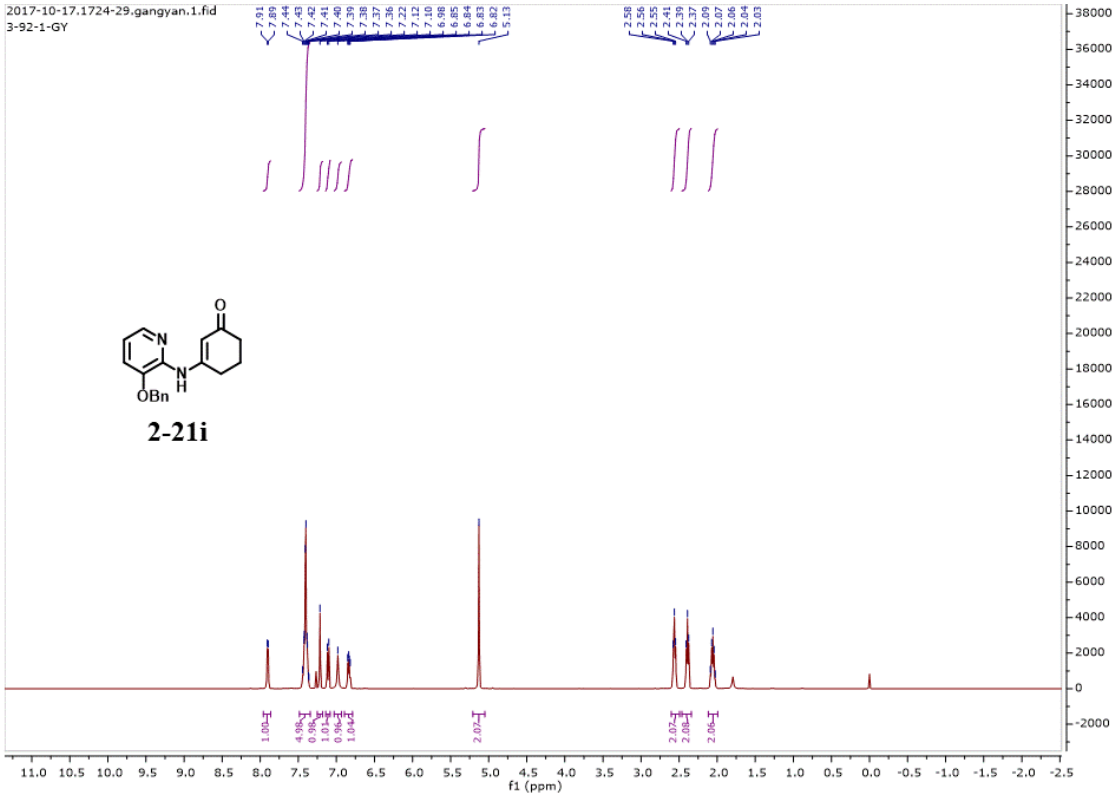
**2-21g**


2017-09-14.1206-33.gangyan.2.fid
3-82-1-GY
199.00
167.34
158.55
154.04
149.40
106.00
104.08
99.52
55.42
36.60
30.12
21.72
H3CO
N
H
O
2-21g
f1 (ppm)

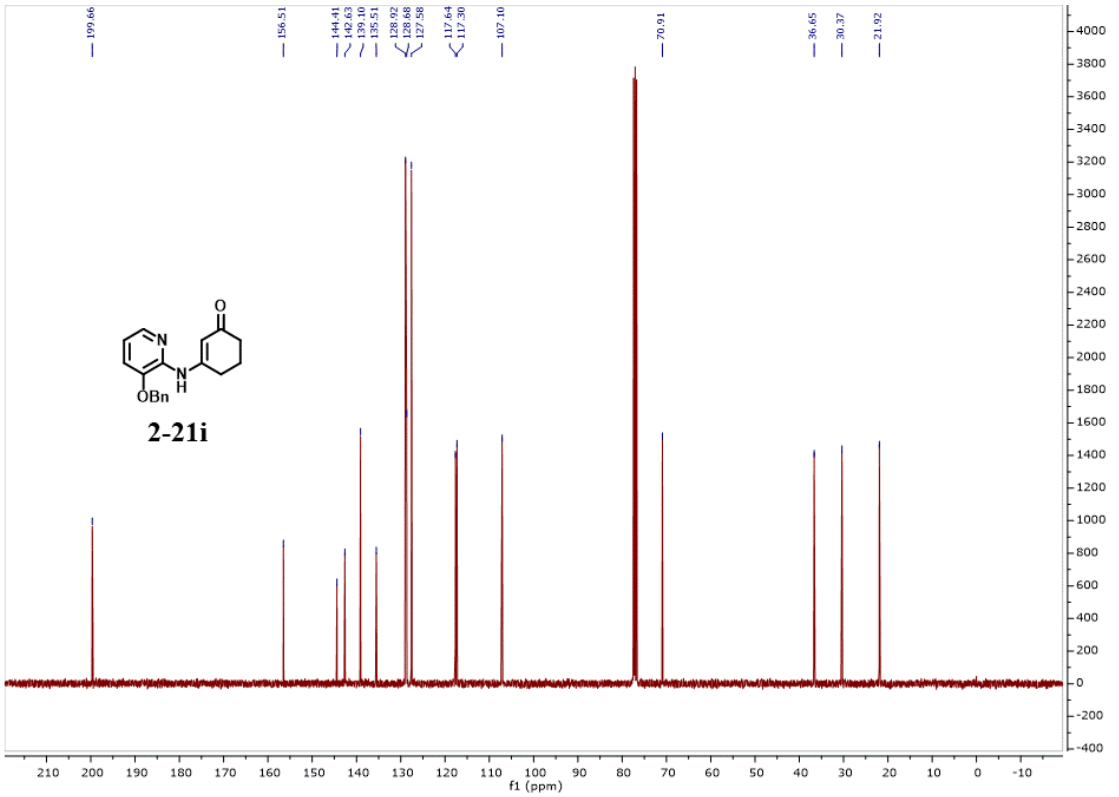

PROTON
20170209.2-183-2-gy
7.99
7.98
7.98
7.98
7.96
7.28
7.20
7.18
7.17
7.08
7.08
7.06
7.06
6.12
3.82
2.54
2.53
2.51
2.38
2.37
2.35
2.06
2.04
2.03
2.01
2.00
MeO
N
H
O
2-21h
1.00
0.90
1.02
1.10
1.03
3.18
2.22
2.17
2.18
f1 (ppm)

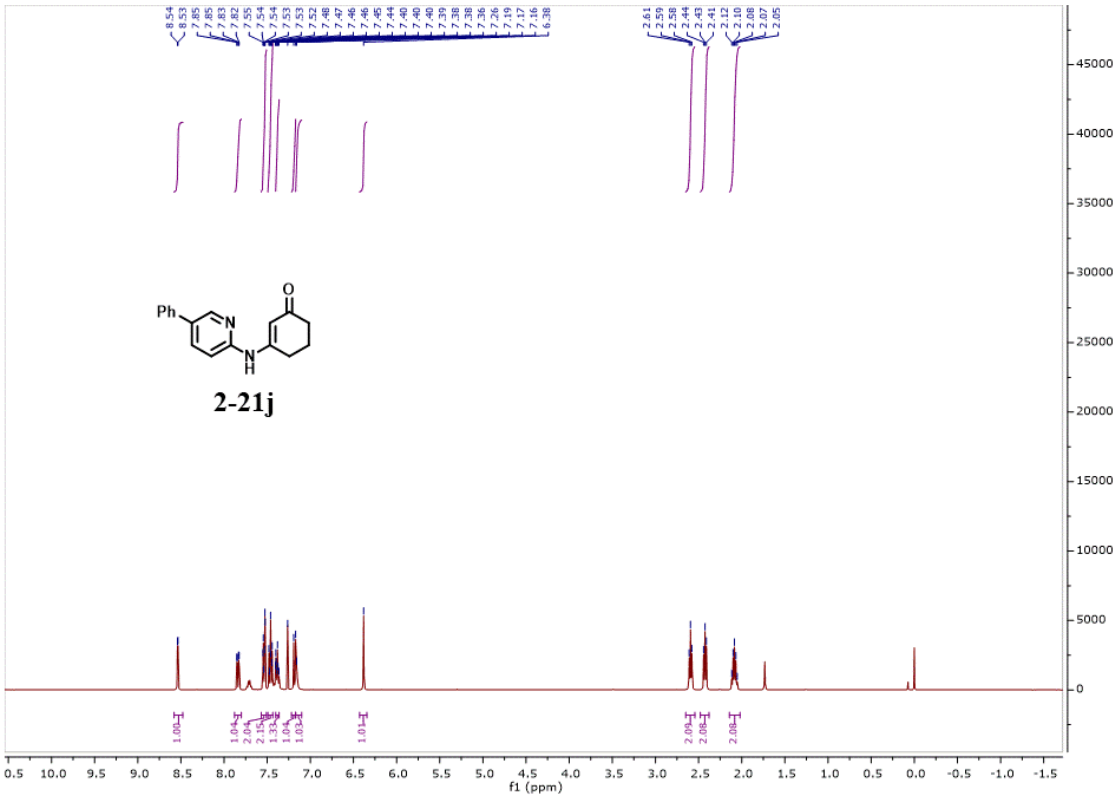

CARBON
20170209.2-183-2-gy
198.97
159.42
152.40
145.76
134.75
123.66
115.57
102.19
56.01
36.58
29.96
21.60
MeO
N
H
O
f1 (ppm)

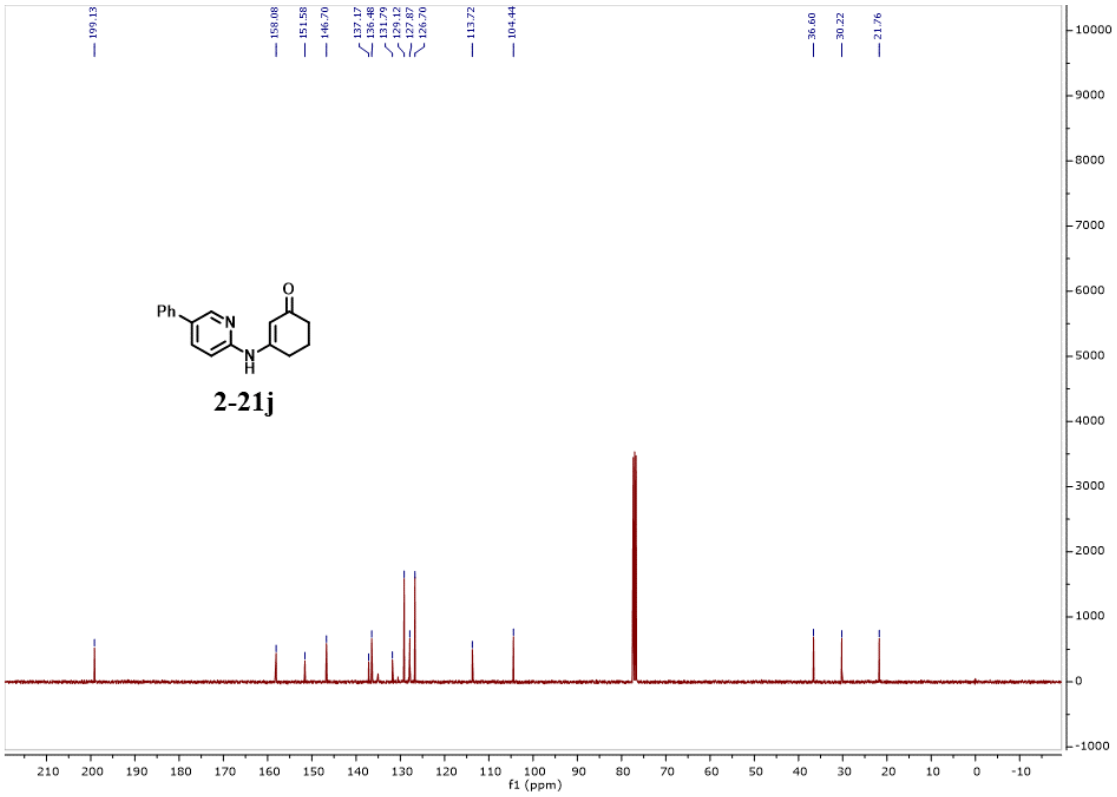
**2-21h**


2017-10-17.1724-29.gangyan.1.fid
3-92-1-GY
7.91
7.89
7.44
7.43
7.42
7.41
7.40
7.39
7.38
7.37
7.36
7.22
7.12
7.10
7.08
6.85
6.84
6.83
6.82
5.13
2.58
2.56
2.55
2.41
2.39
2.37
2.09
2.07
2.06
2.04
2.03
1.00
4.98
0.98
1.01
1.01
0.96
1.04
2.07
2.07
2.08
2.06
N
H
O
OBn
f1 (ppm)

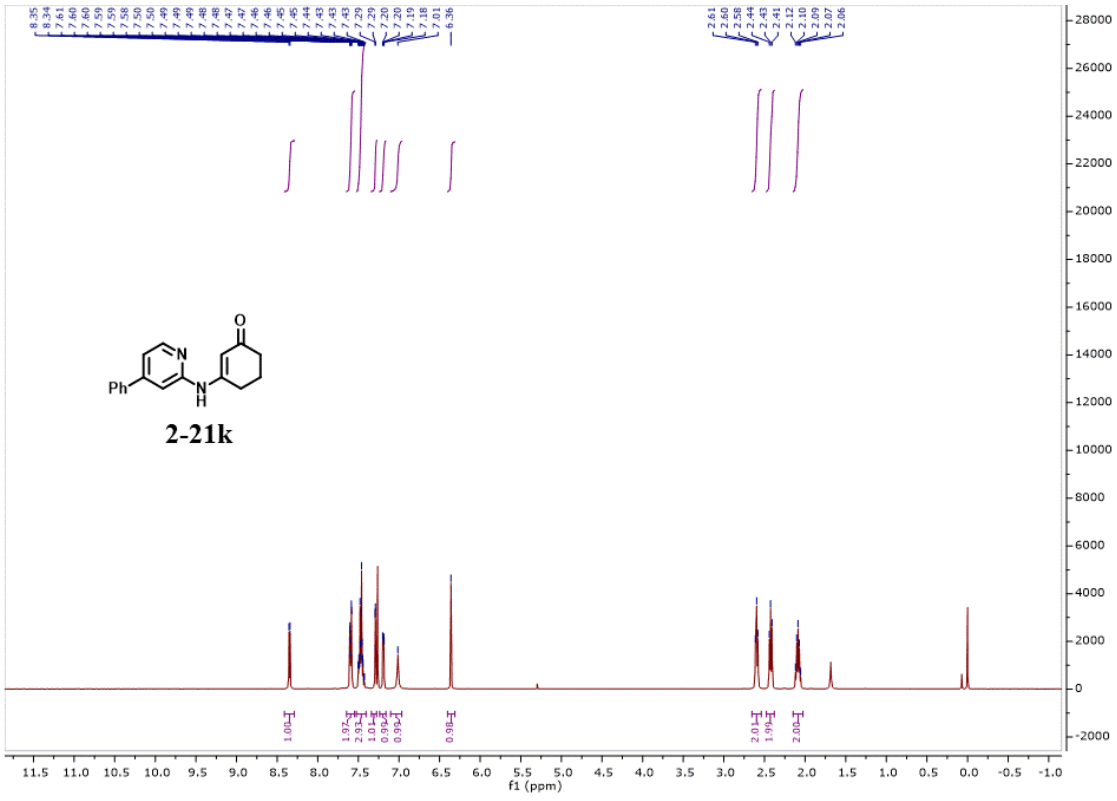
**2-21i**


199.66
156.51
144.41
142.63
139.10
135.51
128.92
128.68
127.58
117.64
117.30
107.10
70.91
36.65
30.37
21.92
OBn
2-21i
f1 (ppm)

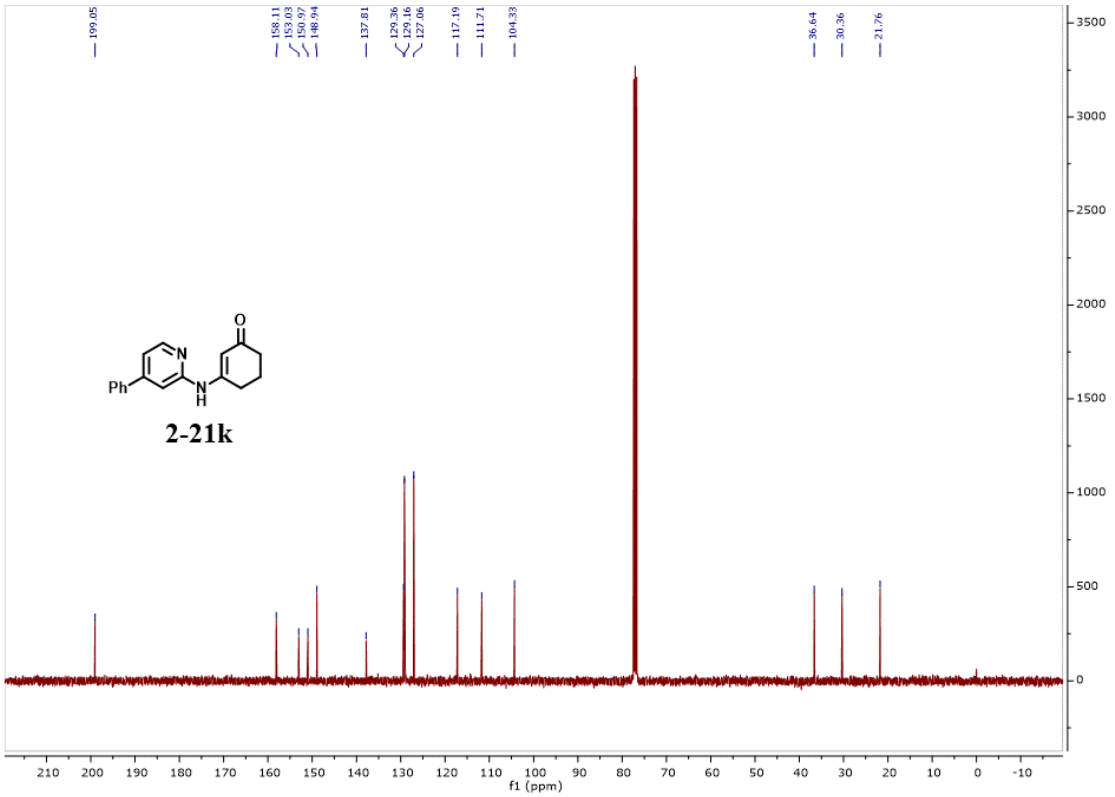

Ph
2-21j
f1 (ppm)


199.13
158.08
151.58
146.70
137.17
136.48
131.79
129.12
127.87
126.70
113.72
104.44
36.60
30.22
21.76
Ph
N
H
O
f1 (ppm)

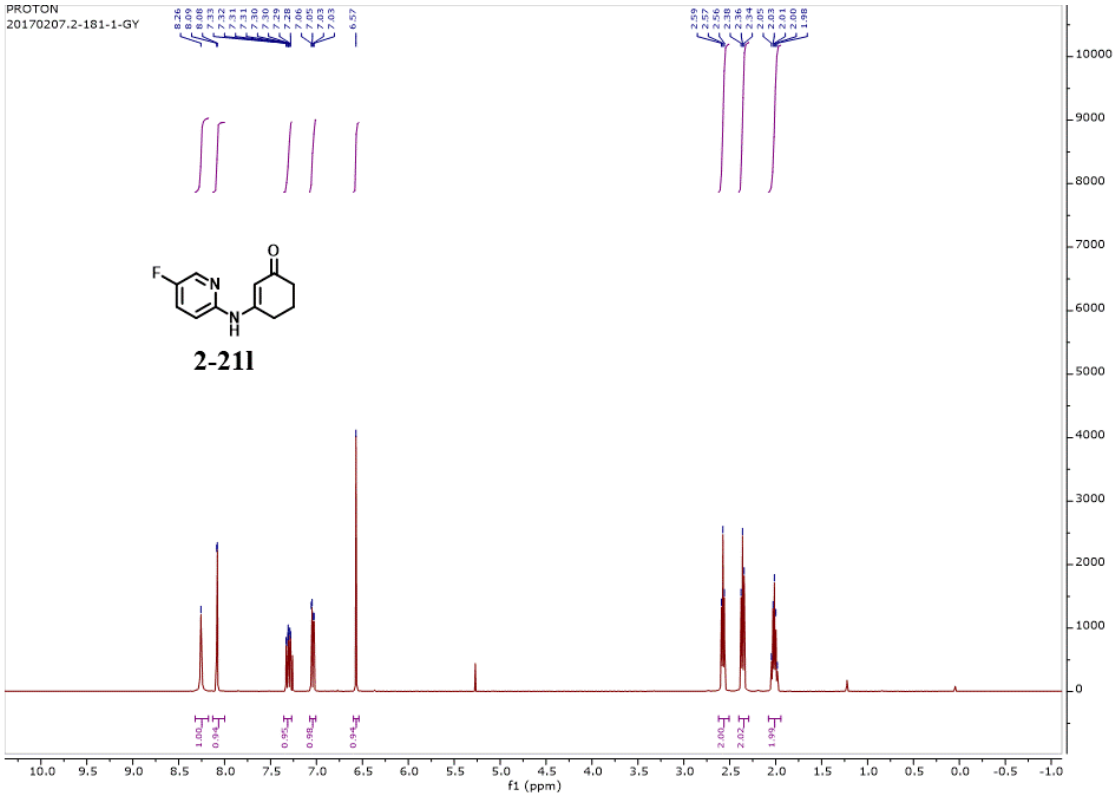
**2-21j**


8.35
8.34
7.61
7.60
7.60
7.59
7.59
7.58
7.50
7.50
7.49
7.49
7.48
7.48
7.48
7.47
7.47
7.46
7.46
7.45
7.45
7.44
7.43
7.43
7.43
7.29
7.29
7.20
7.20
7.19
7.18
7.01
6.36
2.61
2.60
2.58
2.44
2.43
2.41
2.12
2.10
2.09
2.07
2.06
1.00
1.92
2.93
1.01
0.99
0.99
0.98
2.01
1.99
2.00
Ph
N
H
O
f1 (ppm)

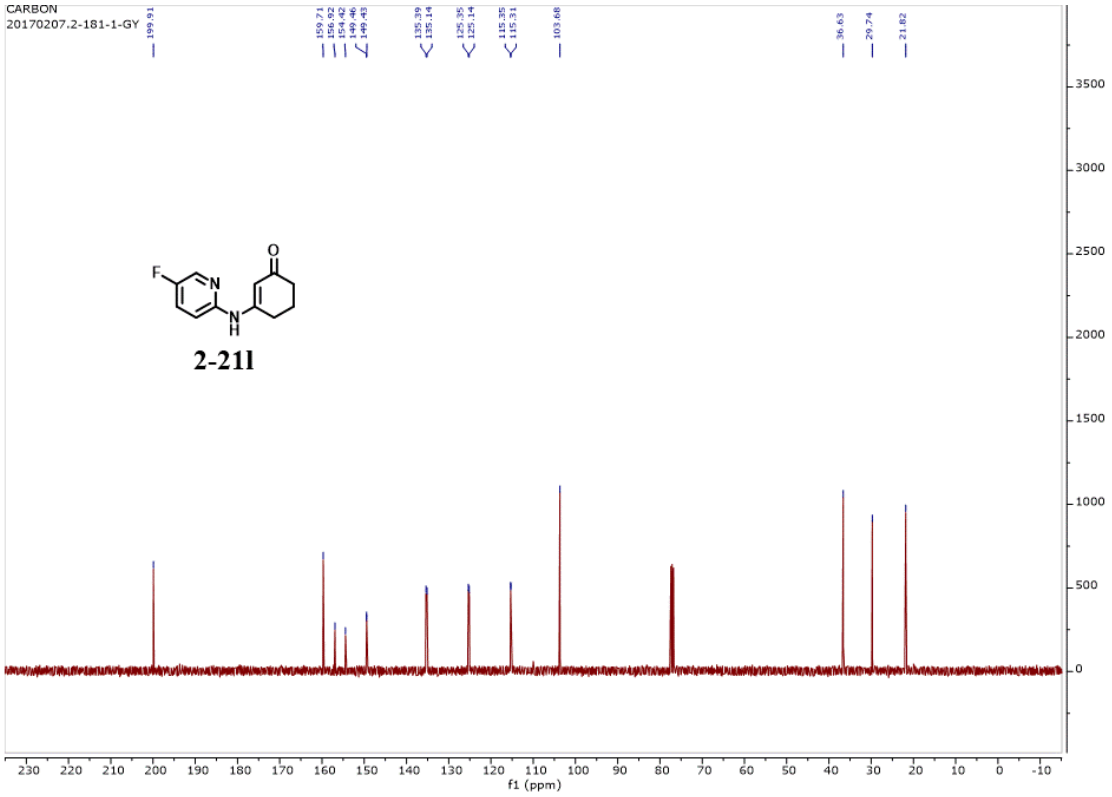
**2-21k**

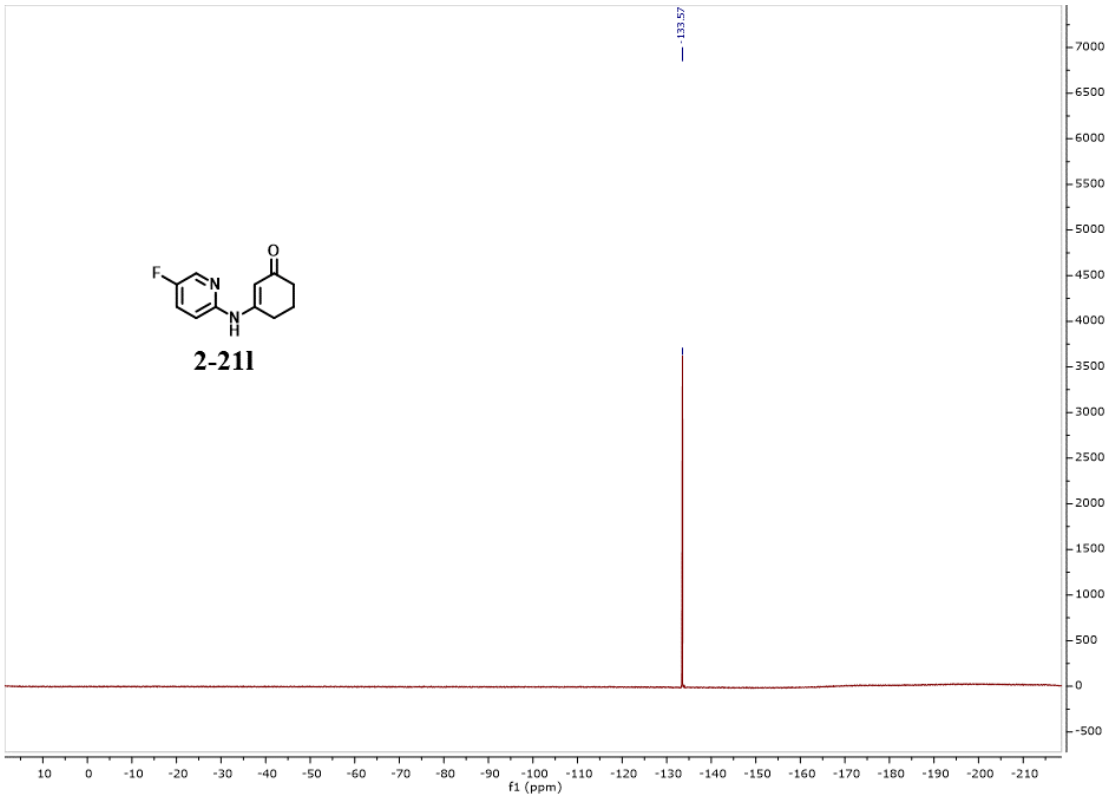

199.05
158.11
153.03
150.97
148.94
137.81
129.36
129.16
127.06
117.19
111.71
104.33
36.64
30.36
21.76
Ph
N
H
O
f1 (ppm)

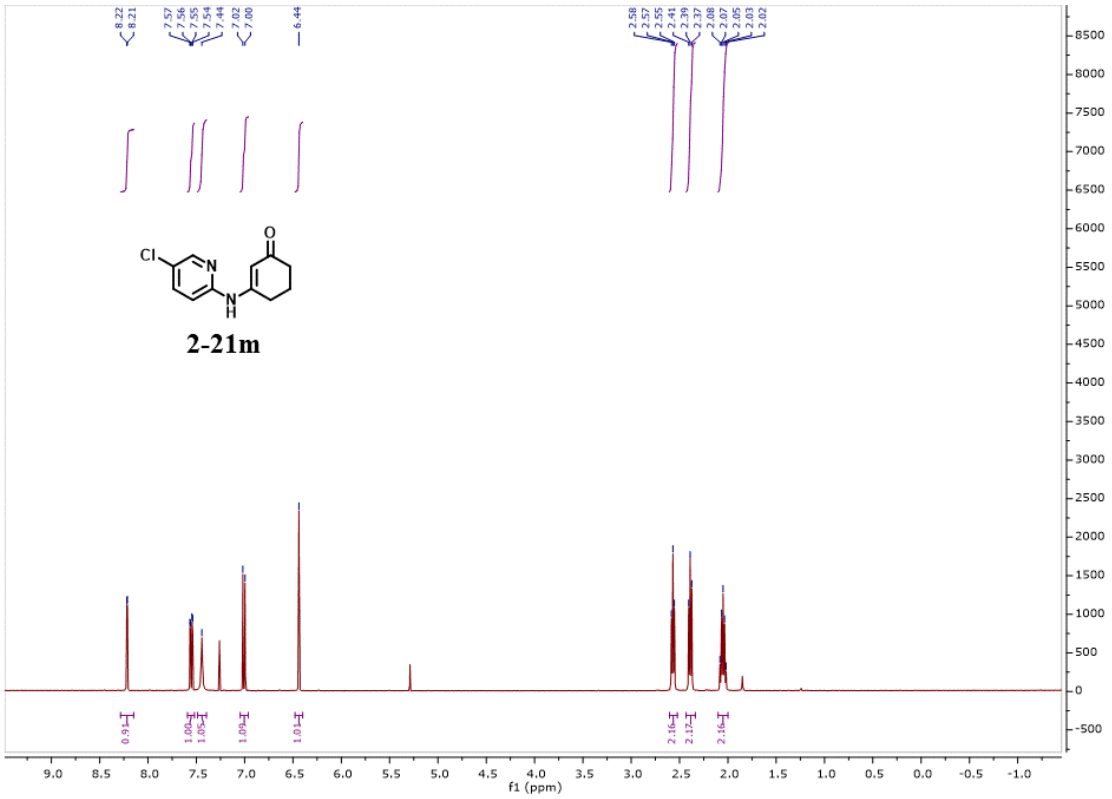
**2-21k**

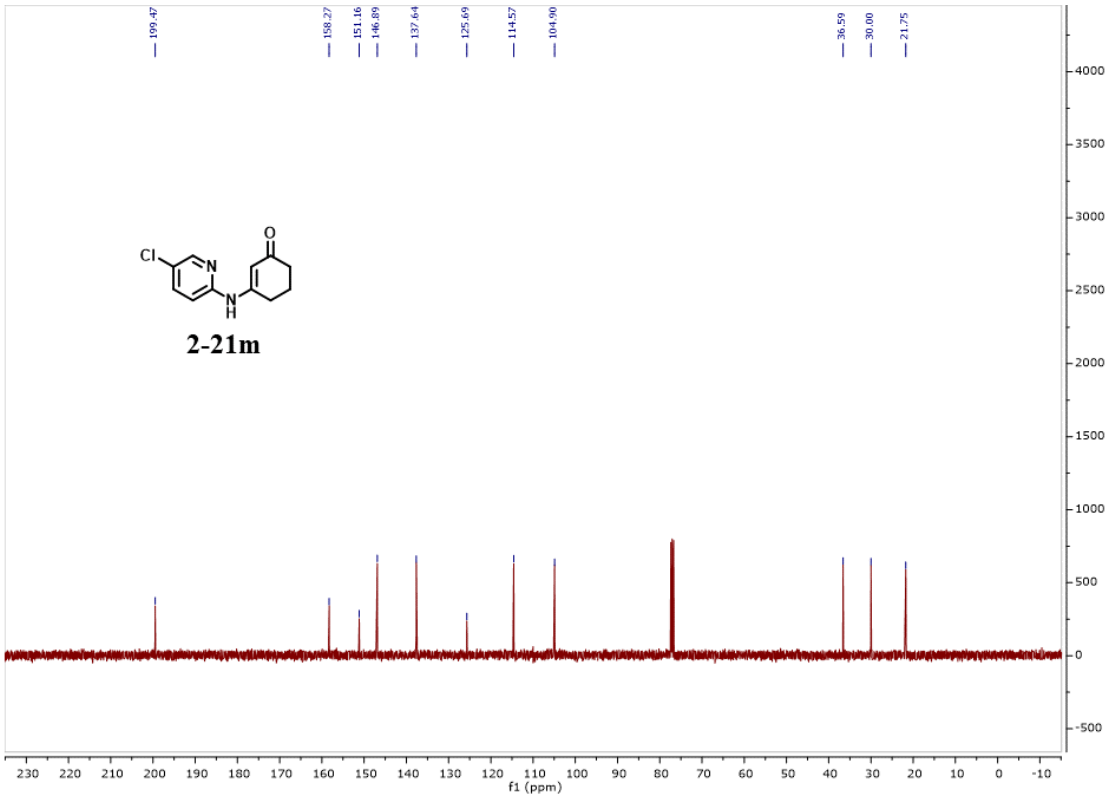

PROTON
20170207.2-181-1-GY
F
N
H
O
f1 (ppm)

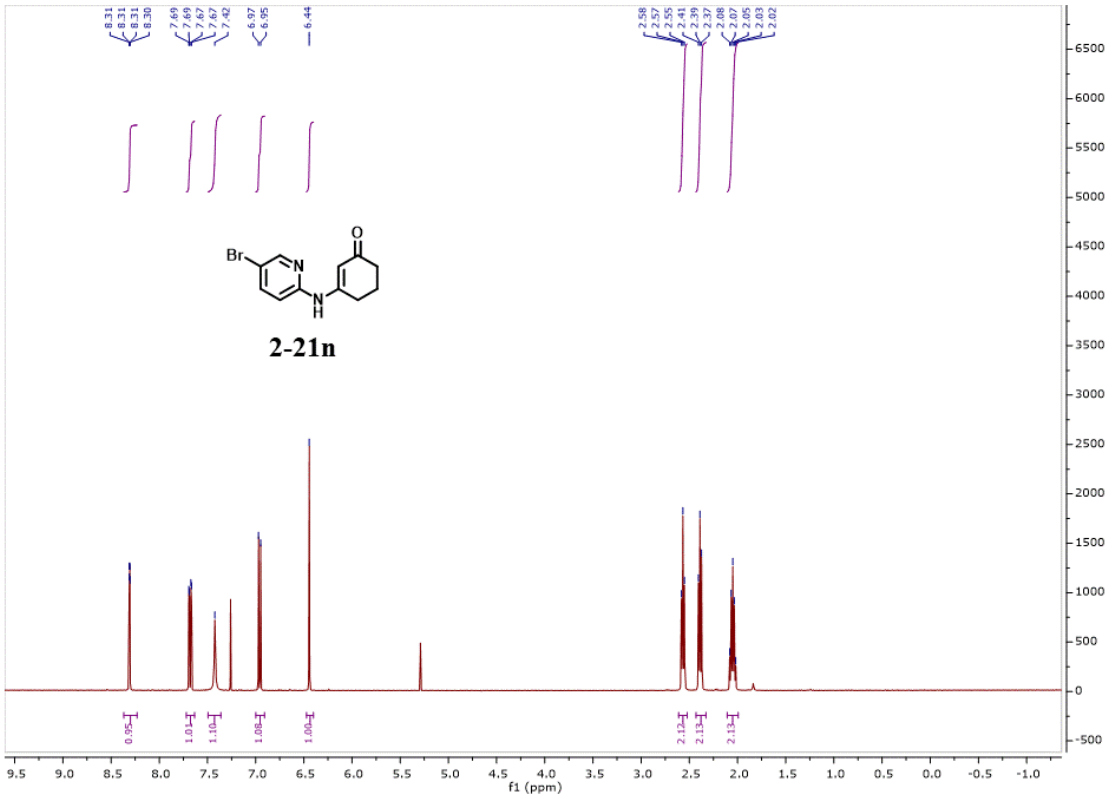
**2-21l**

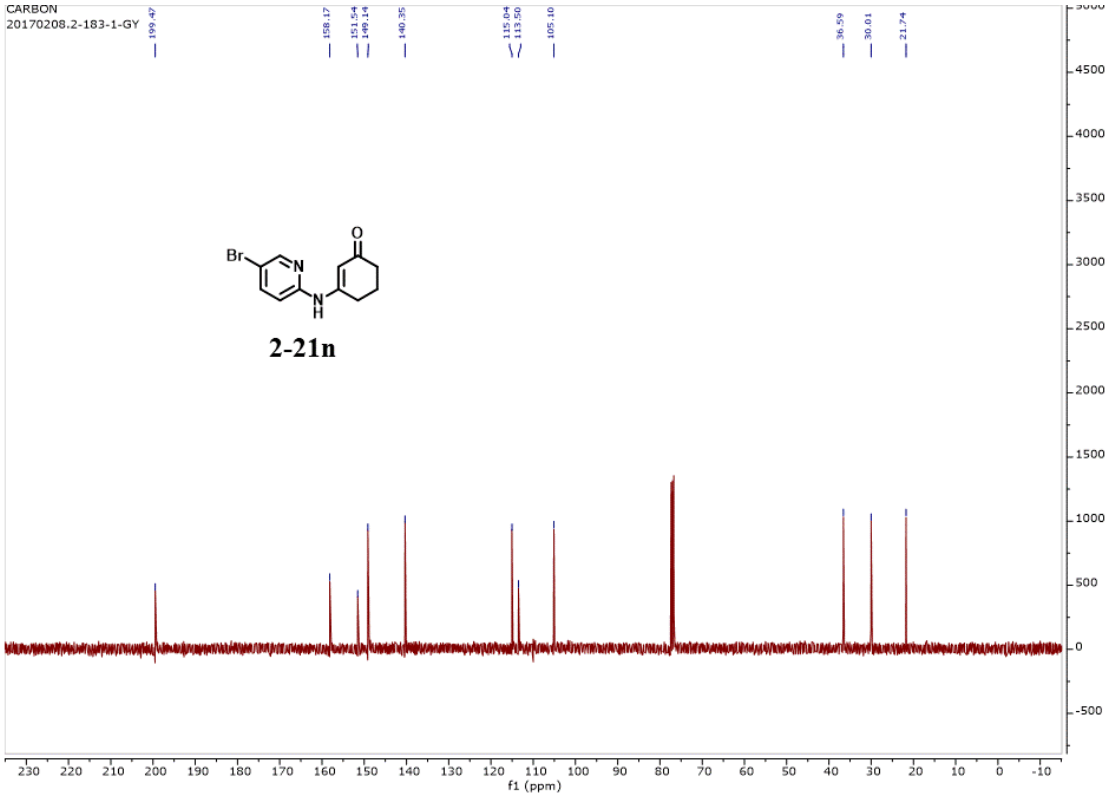

CARBON
20170207.2-181-1-GY
199.91
159.71
156.92
154.46
149.46
149.43
135.39
135.14
125.35
125.14
115.35
115.31
103.68
36.63
29.74
21.82
F
N
H
O
2-21l
f1 (ppm)

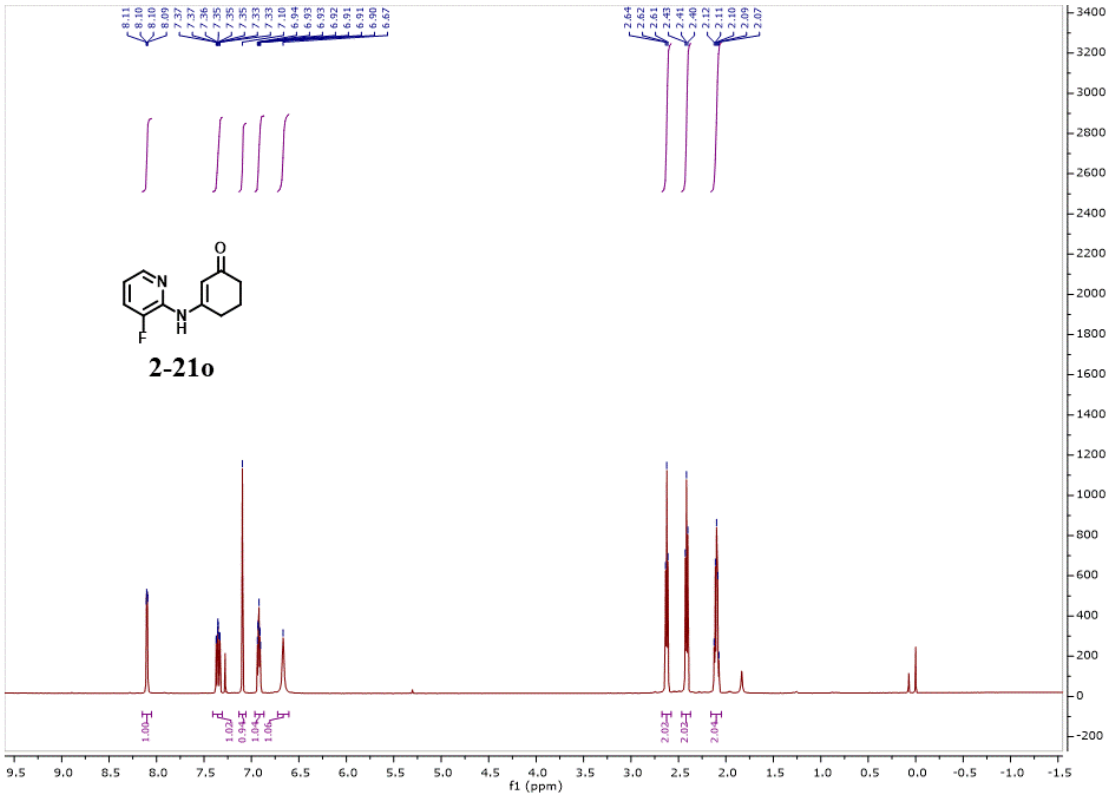

-133.57
F
N
H
O
2-21l
f1 (ppm)

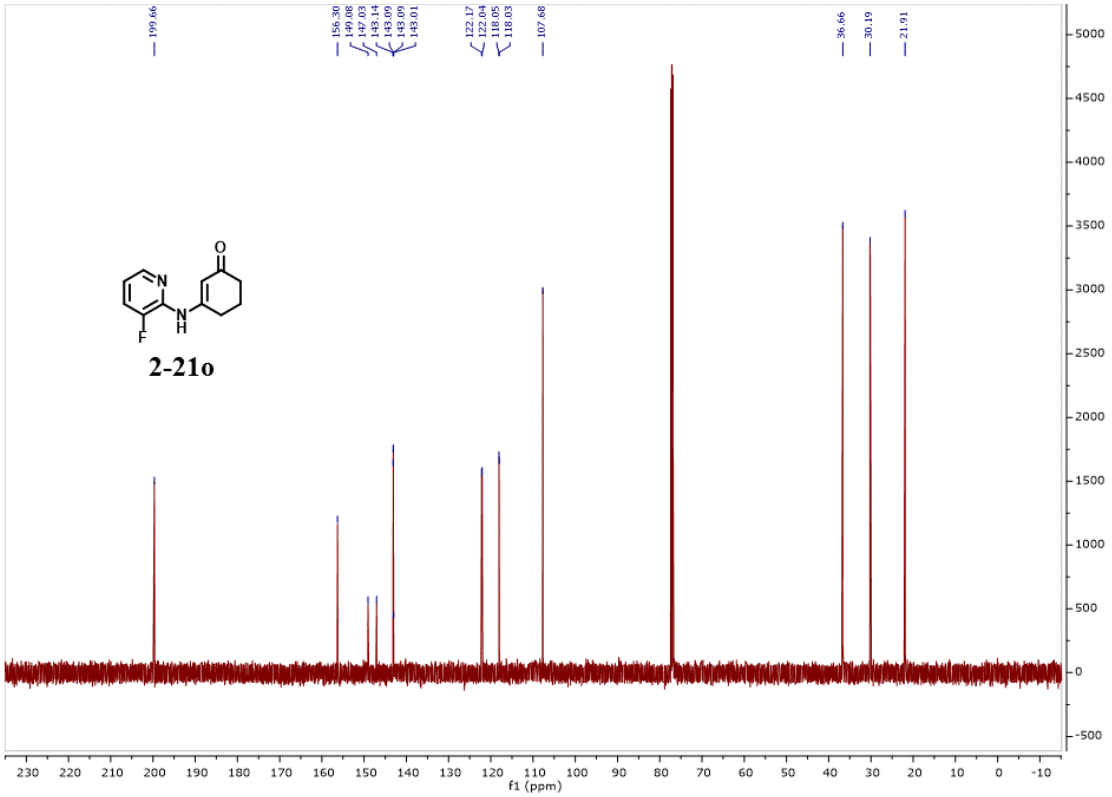

8.22
8.21
7.57
7.56
7.55
7.54
7.44
7.02
7.00
6.44
2.58
2.57
2.55
2.41
2.39
2.37
2.08
2.07
2.05
2.03
2.02
Cl
N
N
H
O
2-21m
0.91
1.00
1.05
1.09
1.01
2.16
2.17
2.16
f1 (ppm)

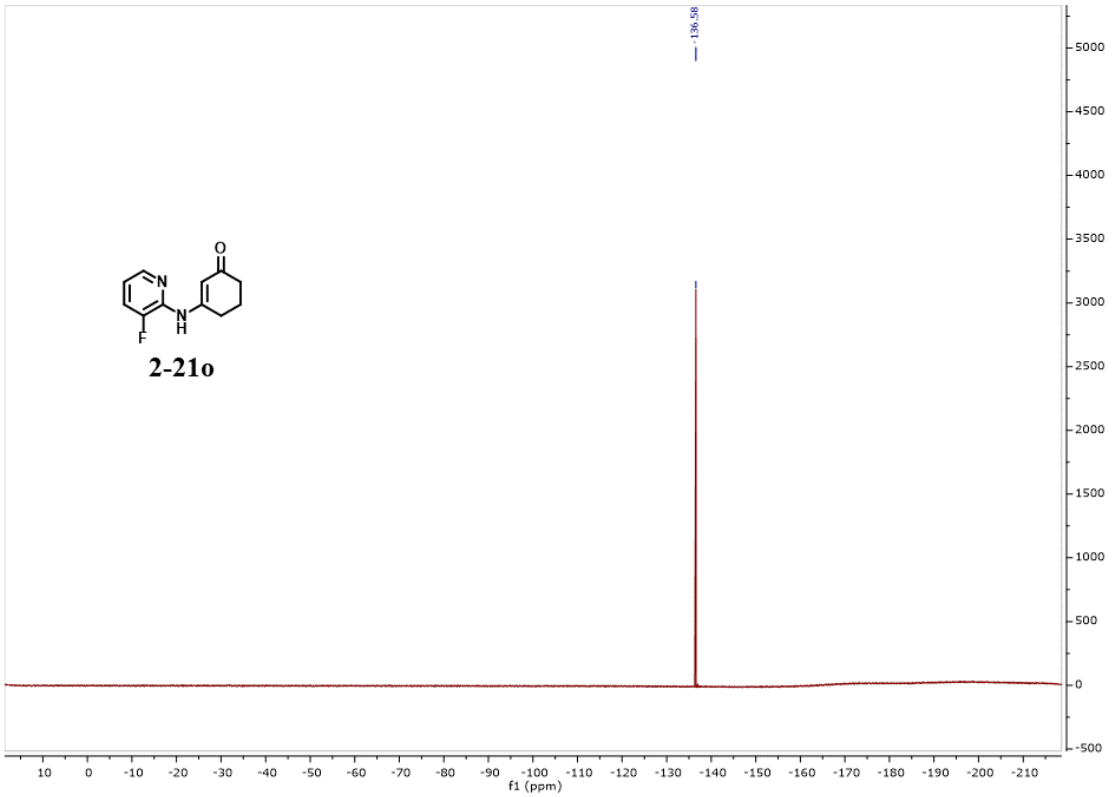

199.47
158.27
151.16
146.89
137.64
125.69
114.57
104.90
36.59
30.00
21.75
Cl
N
N
H
O
2-21m
f1 (ppm)


8.31
8.31
8.31
8.30
7.69
7.69
7.67
7.67
7.42
6.97
6.95
6.44
2.58
2.57
2.55
2.41
2.39
2.37
2.08
2.07
2.05
2.03
2.02
Br
N
N
H
O
2-21n
0.95
1.01
1.10
1.08
1.00
2.12
2.13
2.13
f1 (ppm)

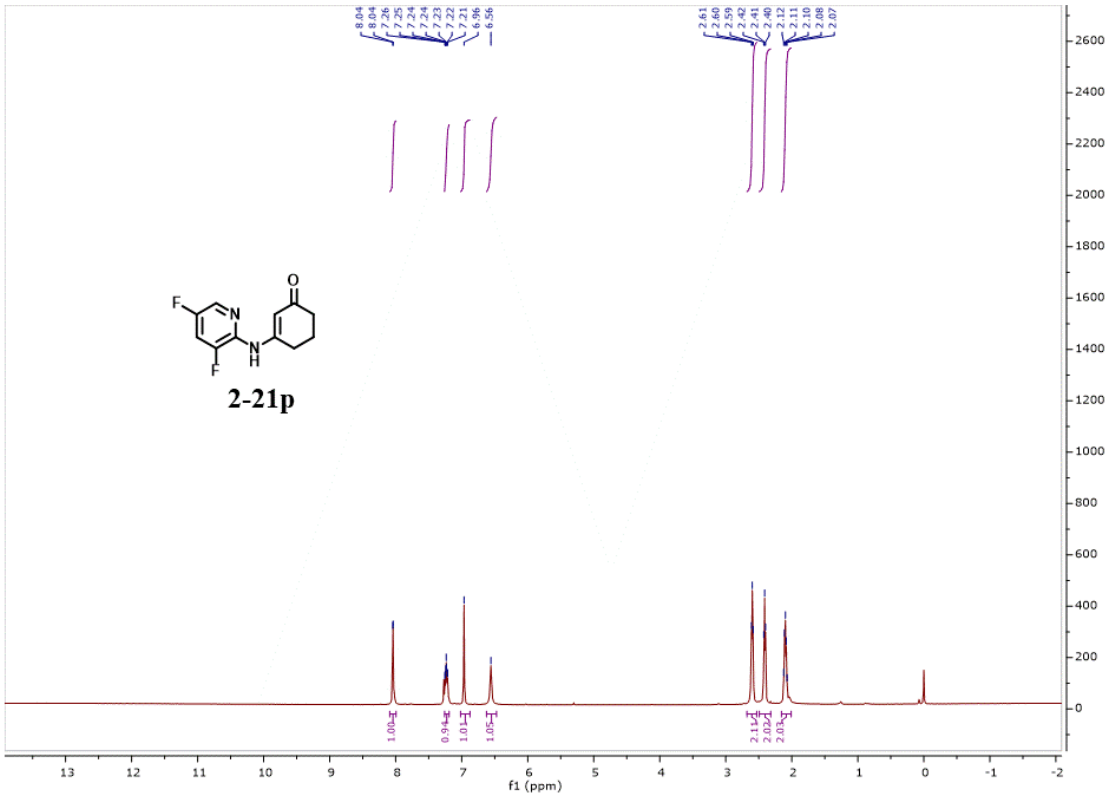

CARBON
20170208.2-183-1-GY
199.47
158.17
151.54
149.14
140.35
115.04
113.50
105.10
36.59
30.01
21.74
Br
N
N
H
O
2-21n
f1 (ppm)


8.11
8.10
8.10
8.09
7.37
7.37
7.36
7.35
7.35
7.33
7.33
7.10
6.94
6.93
6.93
6.92
6.91
6.91
6.90
6.87
2.64
2.62
2.61
2.45
2.44
2.40
2.12
2.11
2.10
2.09
2.07
O
N
N
H
F
2-21o
1.00
1.02
0.94
1.04
1.06
2.02
2.02
2.04
f1 (ppm)

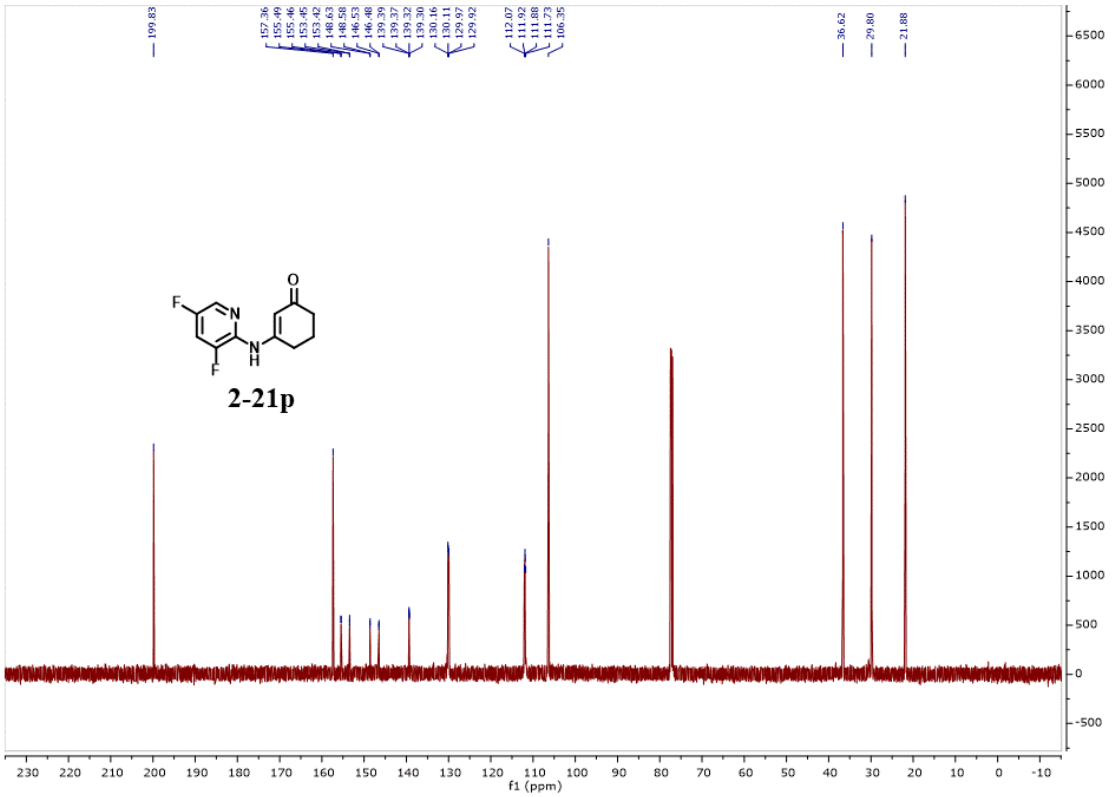

199.66
156.30
149.08
147.03
143.14
143.09
143.09
143.01
122.17
122.04
118.05
118.03
107.68
36.66
30.19
21.91
O
N
N
H
F
2-21o
f1 (ppm)

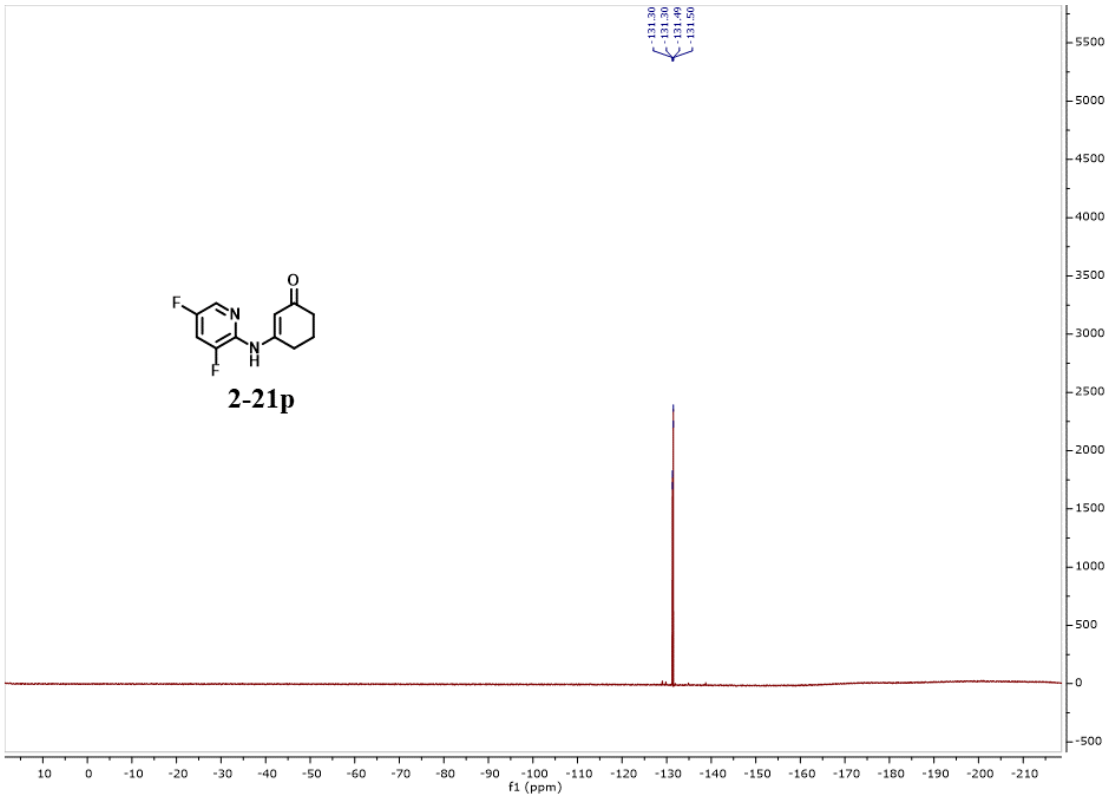

-136.58
f1 (ppm)

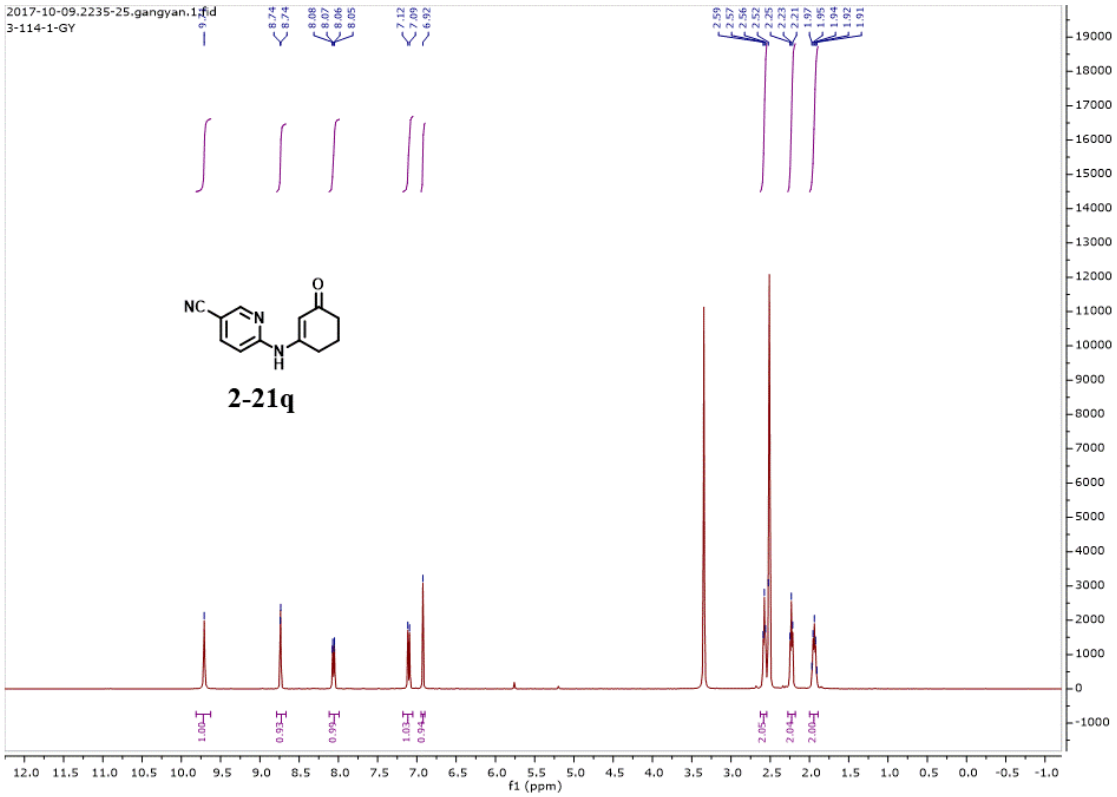
**2-21o**

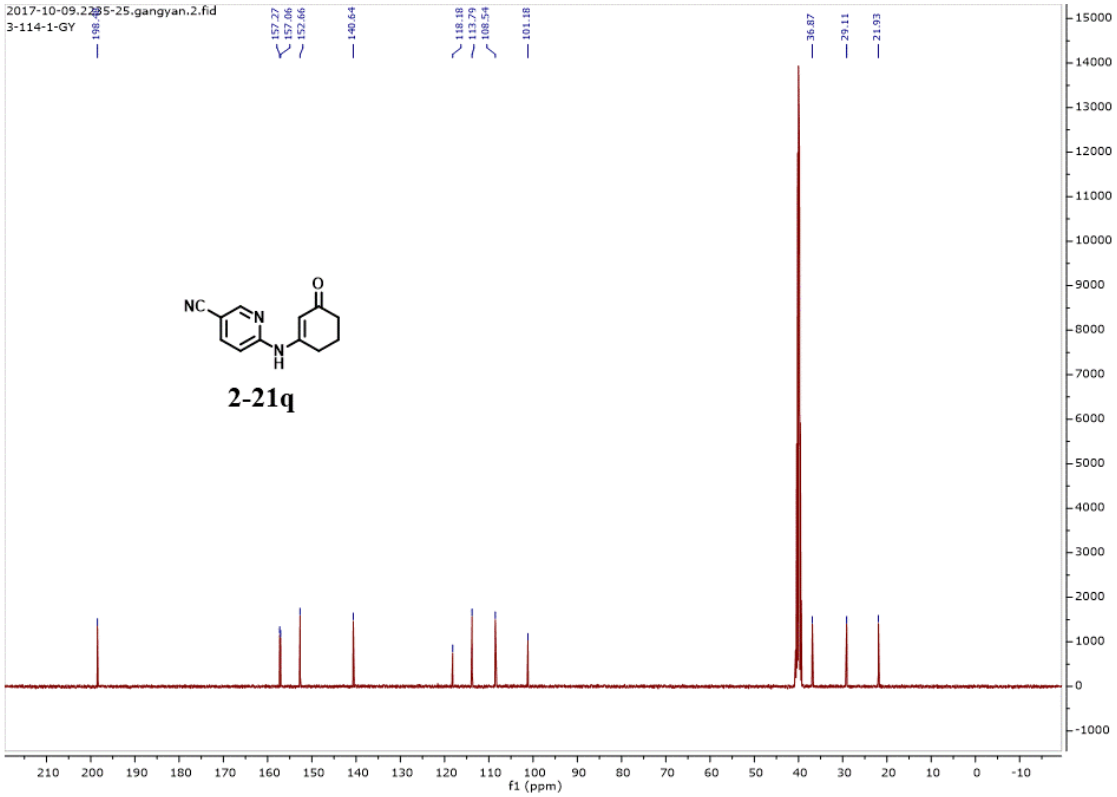

8.04
8.04
7.26
7.25
7.24
7.24
7.23
7.22
7.21
6.96
6.56
2.61
2.60
2.59
2.42
2.41
2.40
2.12
2.11
2.10
2.08
2.07
1.00
0.94
1.01
1.05
2.11
2.02
2.03
f1 (ppm)

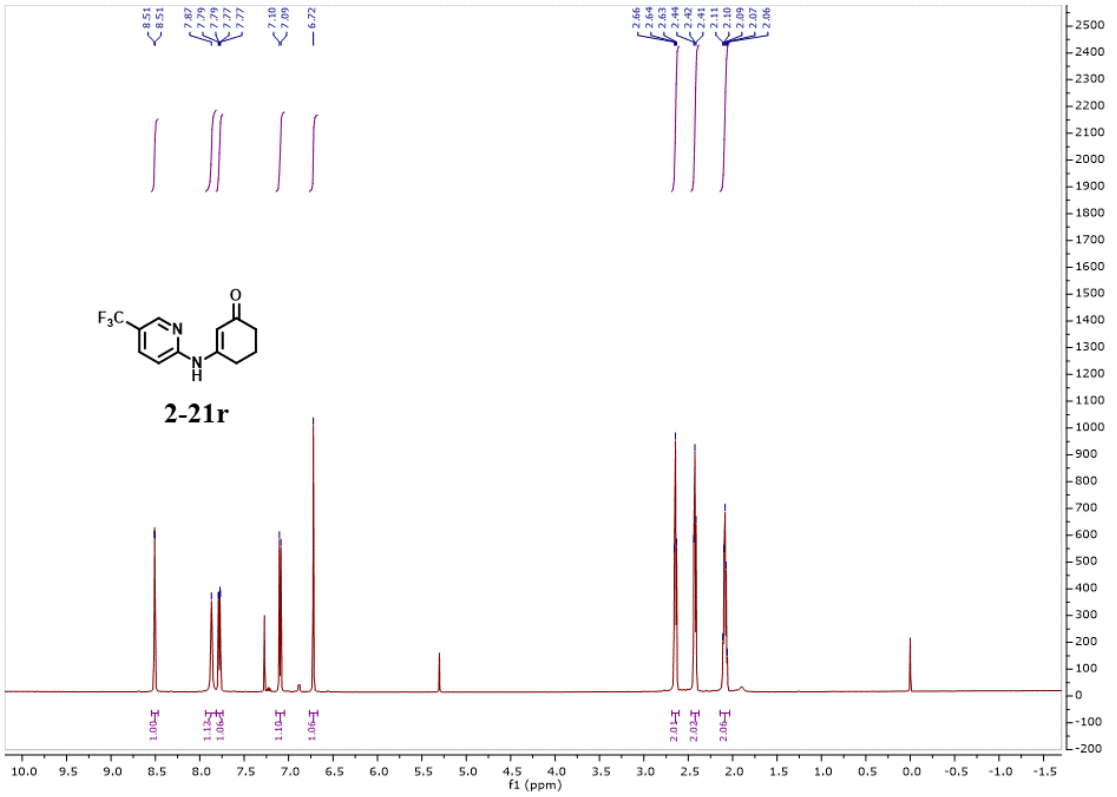
**2-21p**

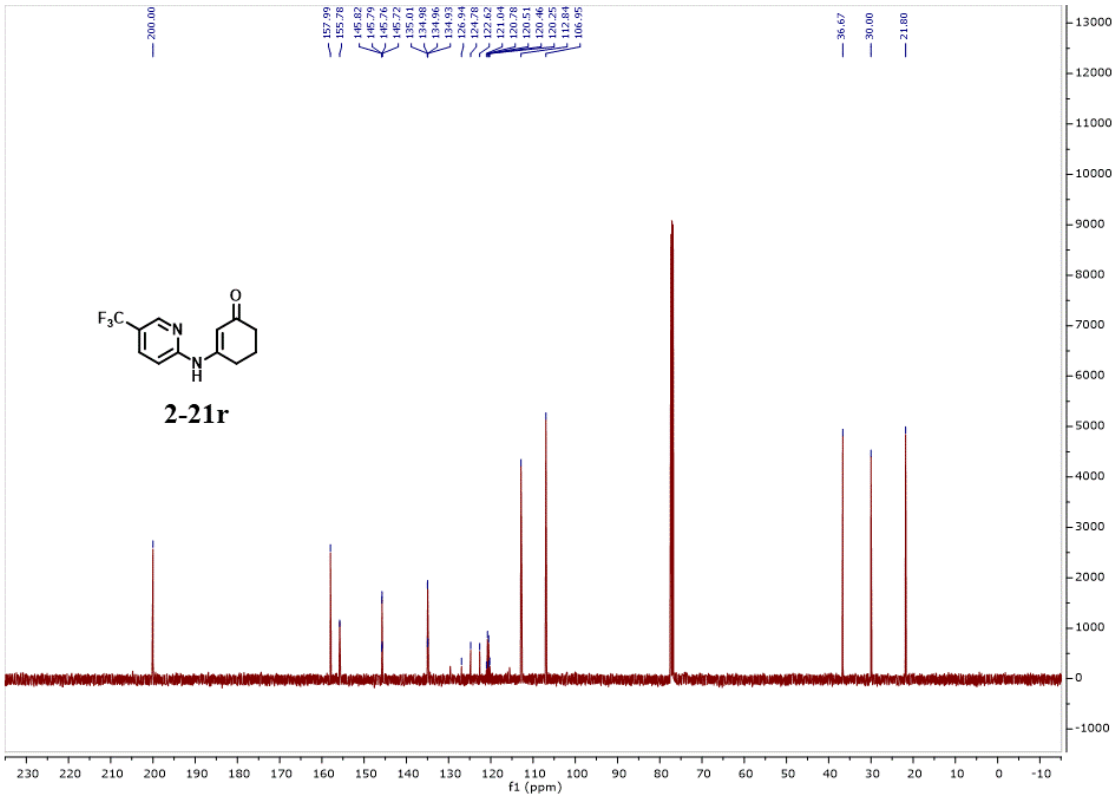

199.83
157.36
155.49
155.46
153.45
153.42
148.63
148.58
146.53
146.48
139.39
139.37
139.32
139.30
130.16
130.11
129.97
129.92
112.07
111.92
111.88
111.73
106.35
36.62
29.80
21.88
F
N
O
N
H
F
2-21p
f1 (ppm)

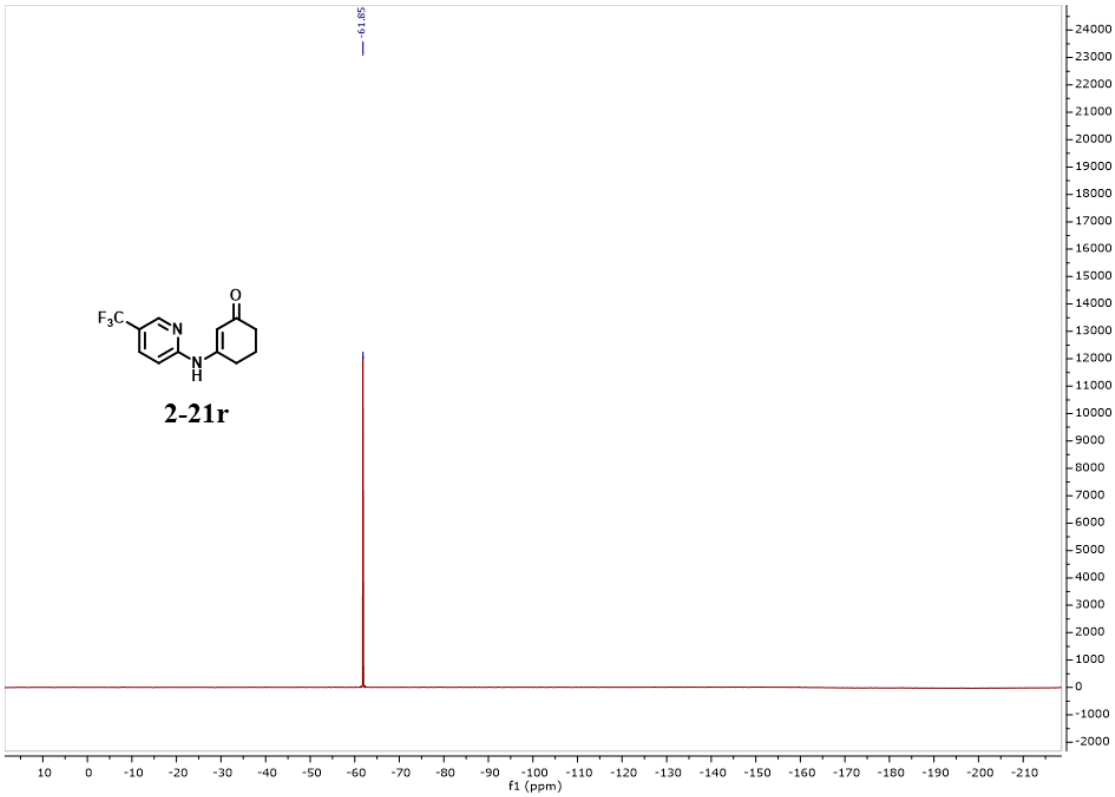

131.30
131.30
131.49
131.50
F
N
O
N
H
F
2-21p
f1 (ppm)

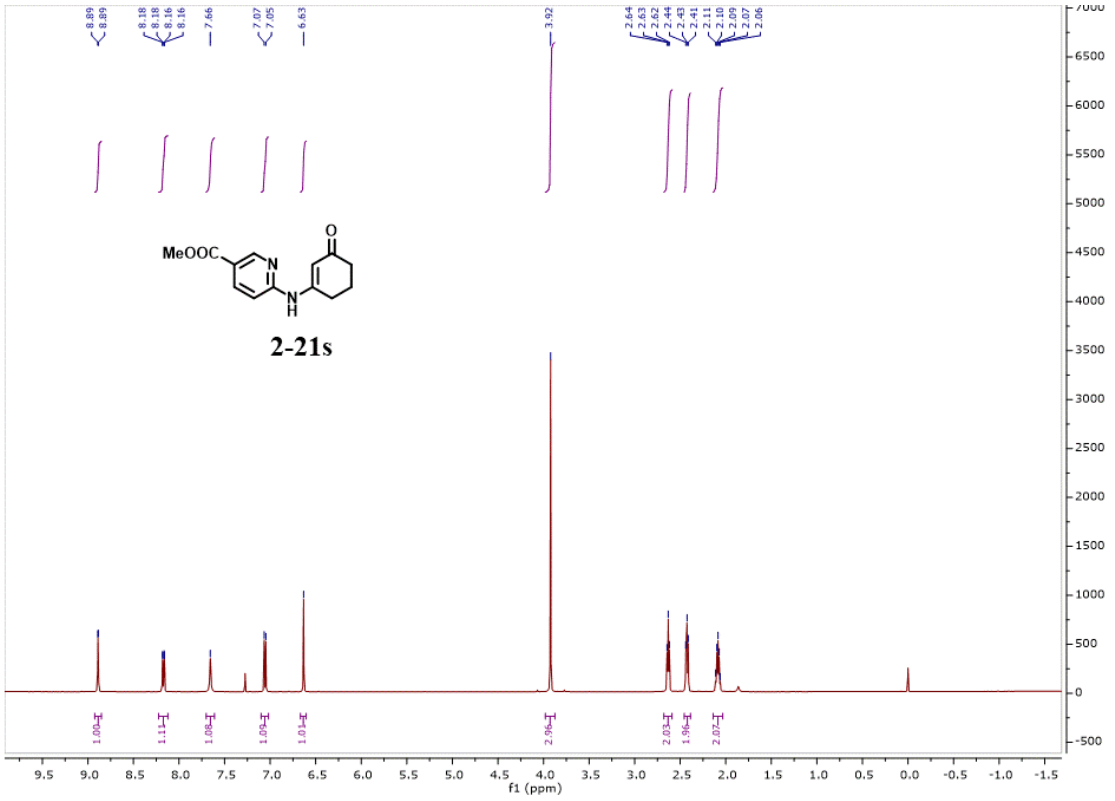

2017-10-09.2235-25.gangyan.1.fid
3-114-1-GY
9.21
8.74
8.74
8.08
8.07
8.06
8.05
7.12
7.09
6.92
2.59
2.57
2.56
2.52
2.25
2.23
2.21
1.97
1.95
1.94
1.92
1.91
NC
N
H
O
2-21q
1.00
0.93
0.99
1.03
0.94
2.05
2.04
2.00
f1 (ppm)

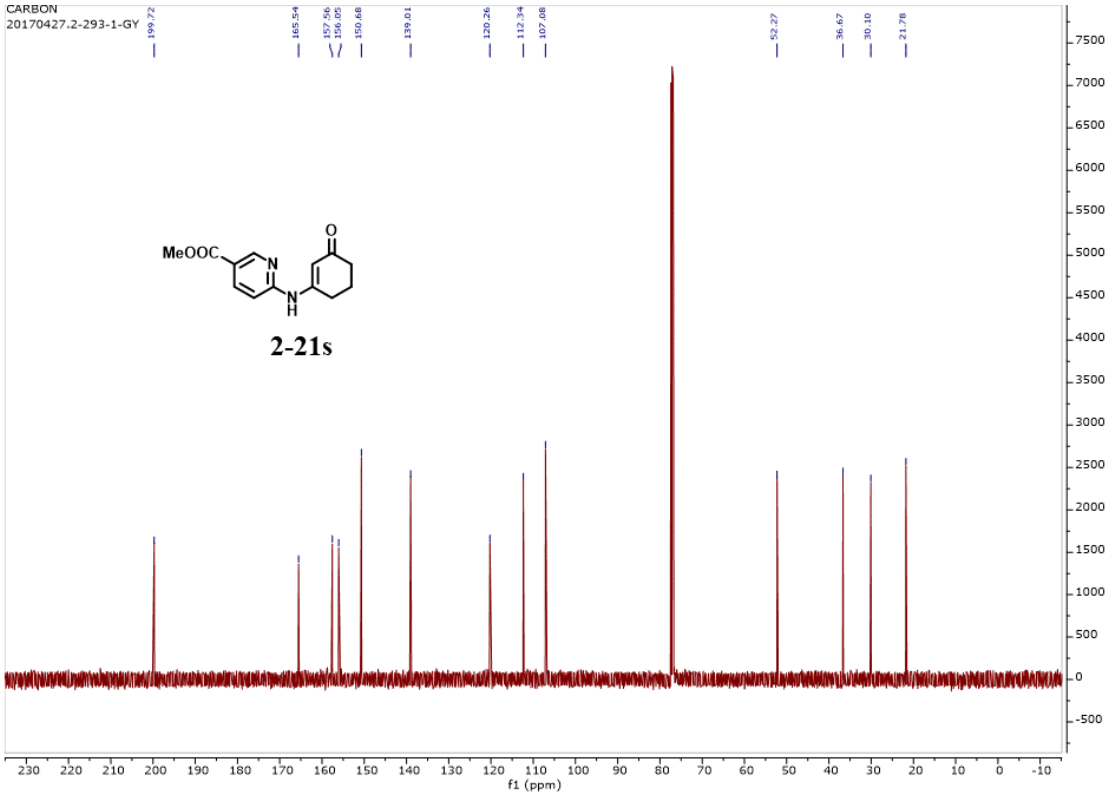

2017-10-09.2235-25.gangyan.2.fid
3-114-1-GY
198.88
157.27
157.06
152.66
140.64
118.18
113.79
108.54
101.18
36.87
29.11
21.93
NC
N
H
O
2-21q
f1 (ppm)


8.51
8.51
7.87
7.79
7.79
7.77
7.77
7.77
7.10
7.09
6.72
2.66
2.64
2.63
2.44
2.42
2.41
2.11
2.10
2.09
2.07
2.06
F3C
N
H
O
2-21r
1.00
1.12
1.06
1.01
1.06
2.01
2.02
2.06
f1 (ppm)

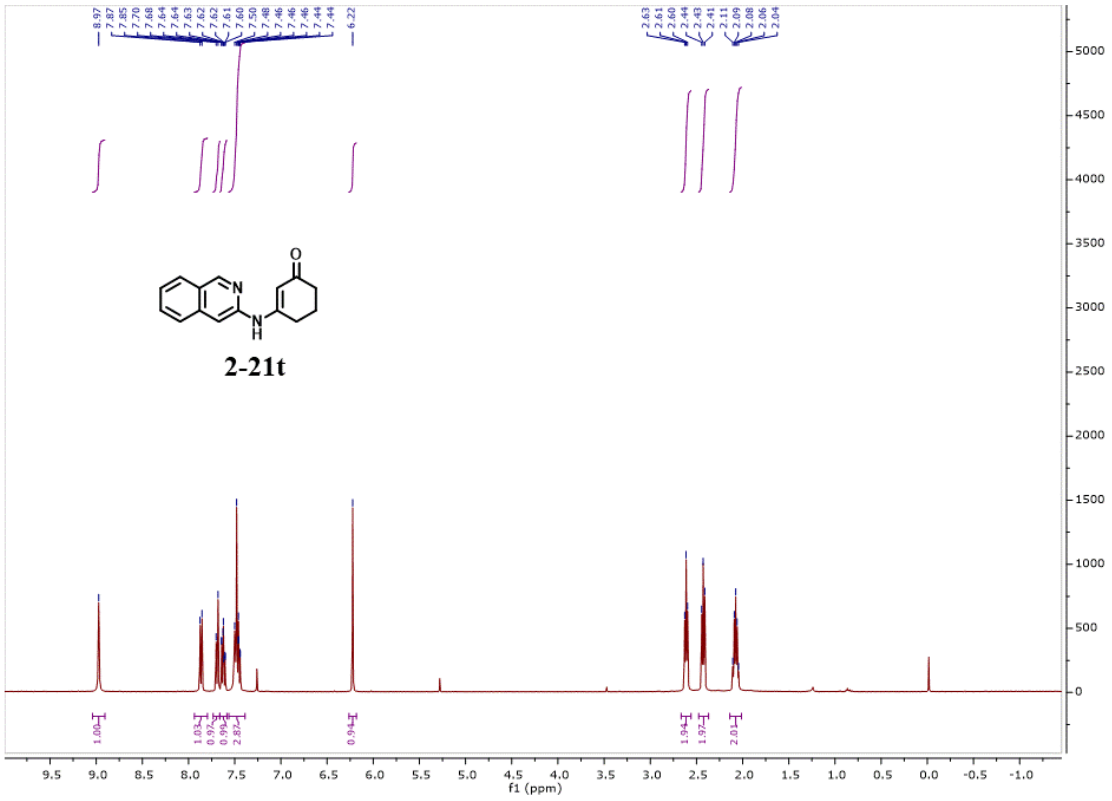

200.00
157.99
155.78
146.82
146.79
146.76
146.72
135.01
134.98
134.96
134.93
126.94
124.78
122.62
121.04
120.78
120.51
120.46
120.25
112.84
106.95
36.67
30.00
21.80
F3C
N
H
O
2-21r
f1 (ppm)


-61.85
F3C
N
H
O
2-21r
f1 (ppm)

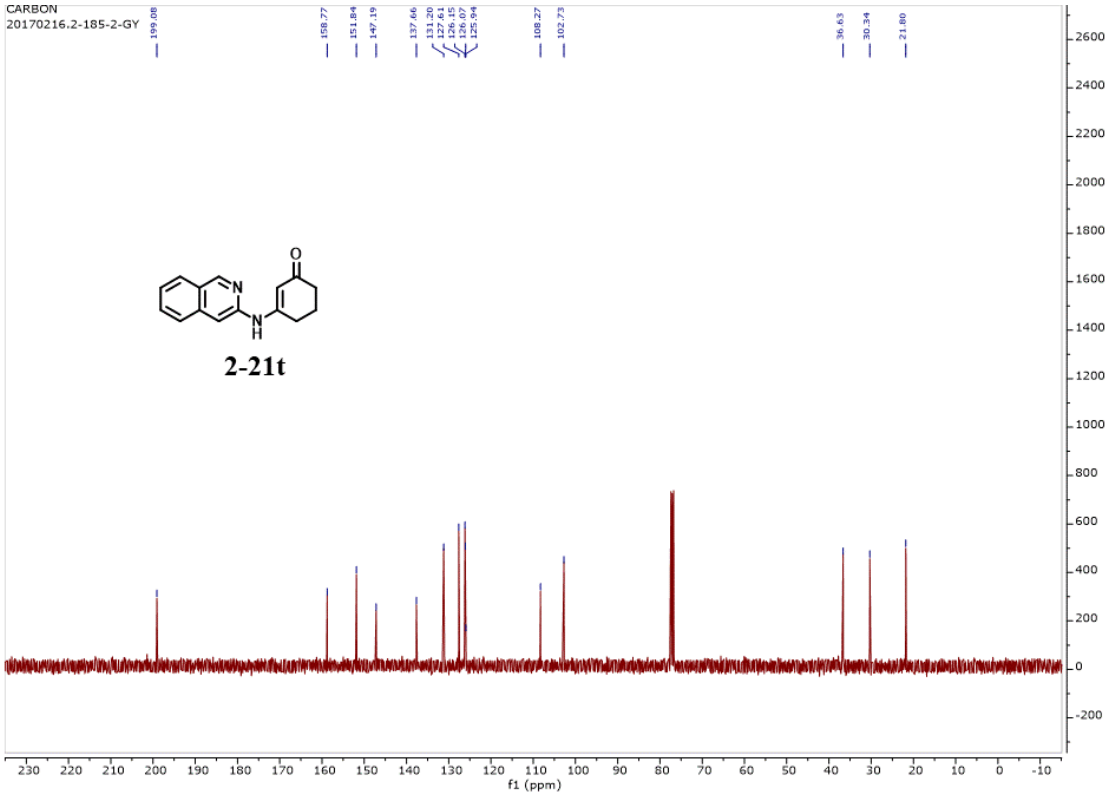

8.89
8.89
8.18
8.18
8.16
8.16
7.66
7.07
7.05
6.63
3.92
2.64
2.63
2.62
2.44
2.43
2.41
2.11
2.10
2.09
2.07
2.06
MeOOC
N
H
O
2-21s
1.00
1.11
1.08
1.09
1.01
2.96
2.03
1.96
2.07
f1 (ppm)


CARBON
20170427.2-293-1-GY
199.72
165.54
157.56
156.05
150.68
139.01
120.26
112.34
107.08
52.27
36.67
30.10
21.78
MeOOC
N
H
O
f1 (ppm)

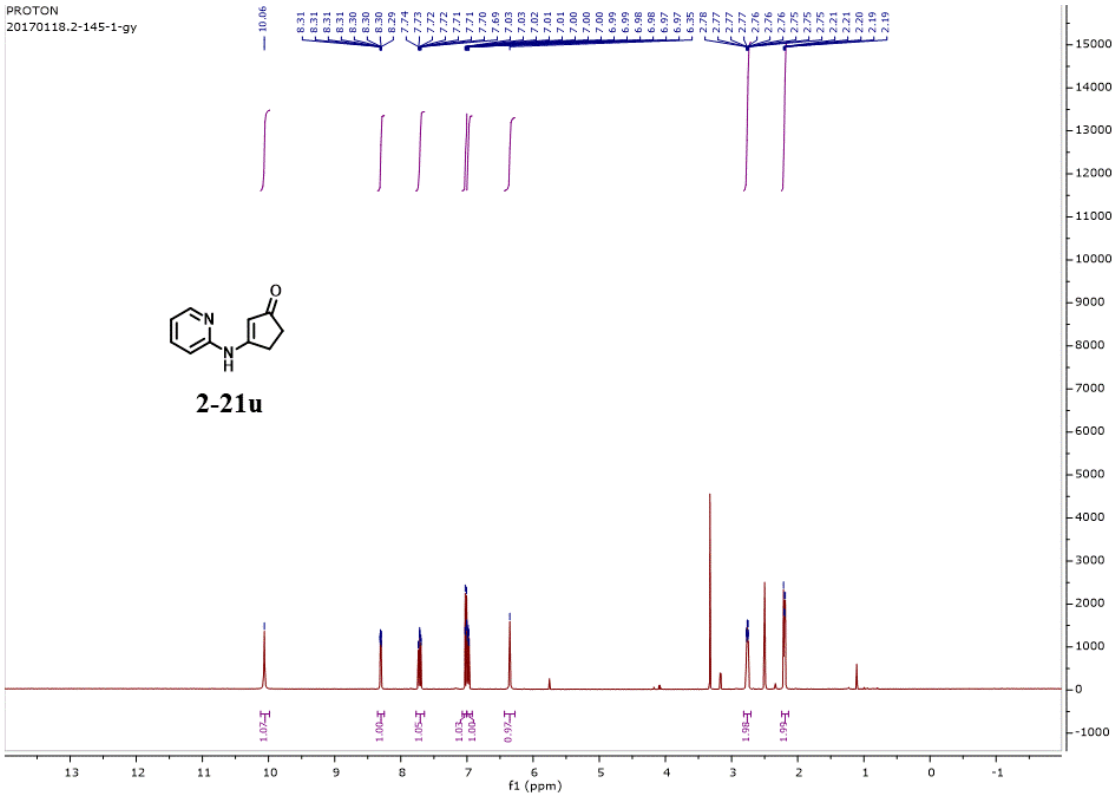
**2-21s**


8.97
7.87
7.85
7.70
7.68
7.64
7.64
7.63
7.62
7.62
7.61
7.60
7.50
7.48
7.46
7.46
7.46
7.44
7.44
6.22
2.63
2.61
2.60
2.44
2.43
2.41
2.11
2.09
2.08
2.06
2.04
1.00
1.03
0.97
0.99
2.87
0.94
1.94
1.97
2.01
N
H
O
f1 (ppm)

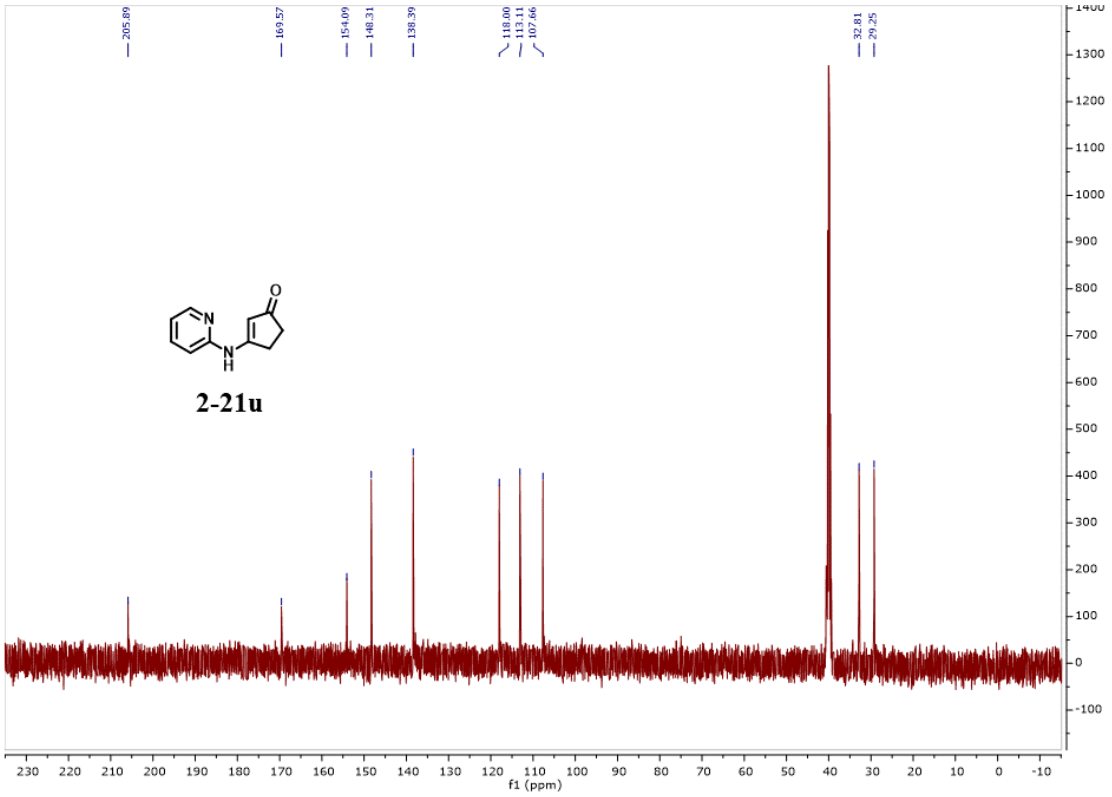
**2-21t**


CARBON
20170216.2-185-2-GY
199.08
158.77
151.84
147.19
137.66
131.20
127.61
126.15
126.07
125.94
108.27
102.73
36.63
30.34
21.80
f1 (ppm)

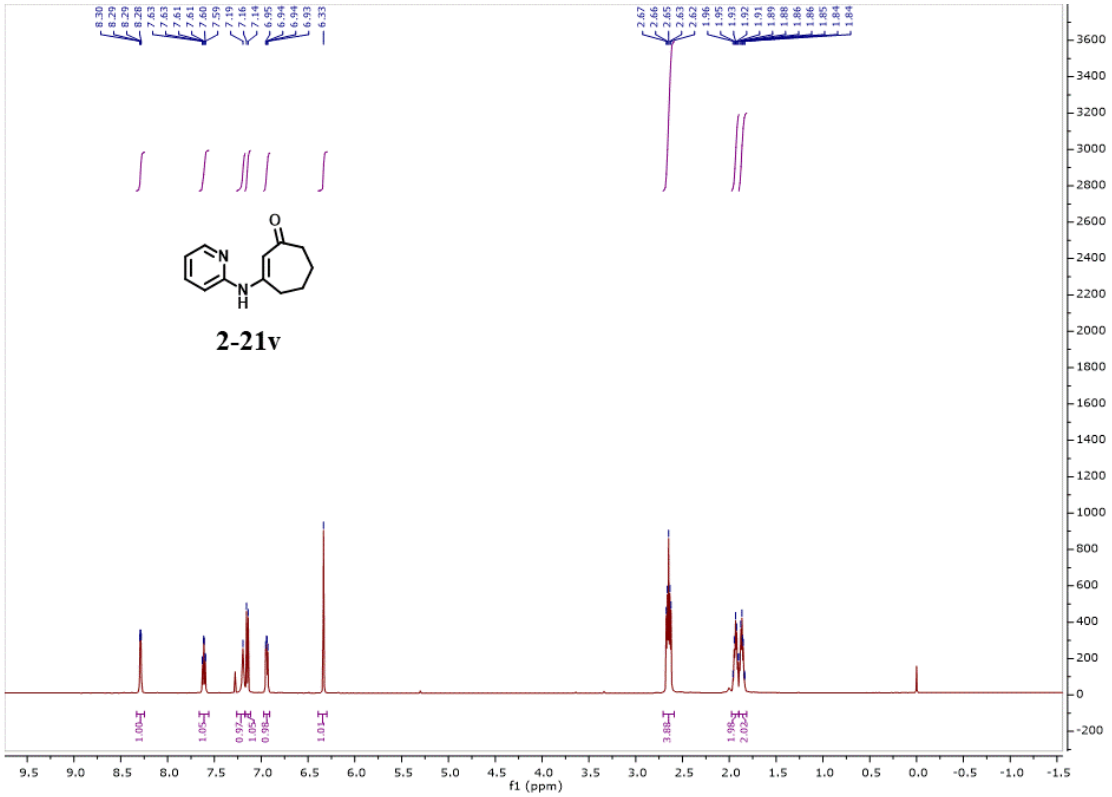
**2-21t**


PROTON
20170118.2-145-1-gy
10.06
f1 (ppm)

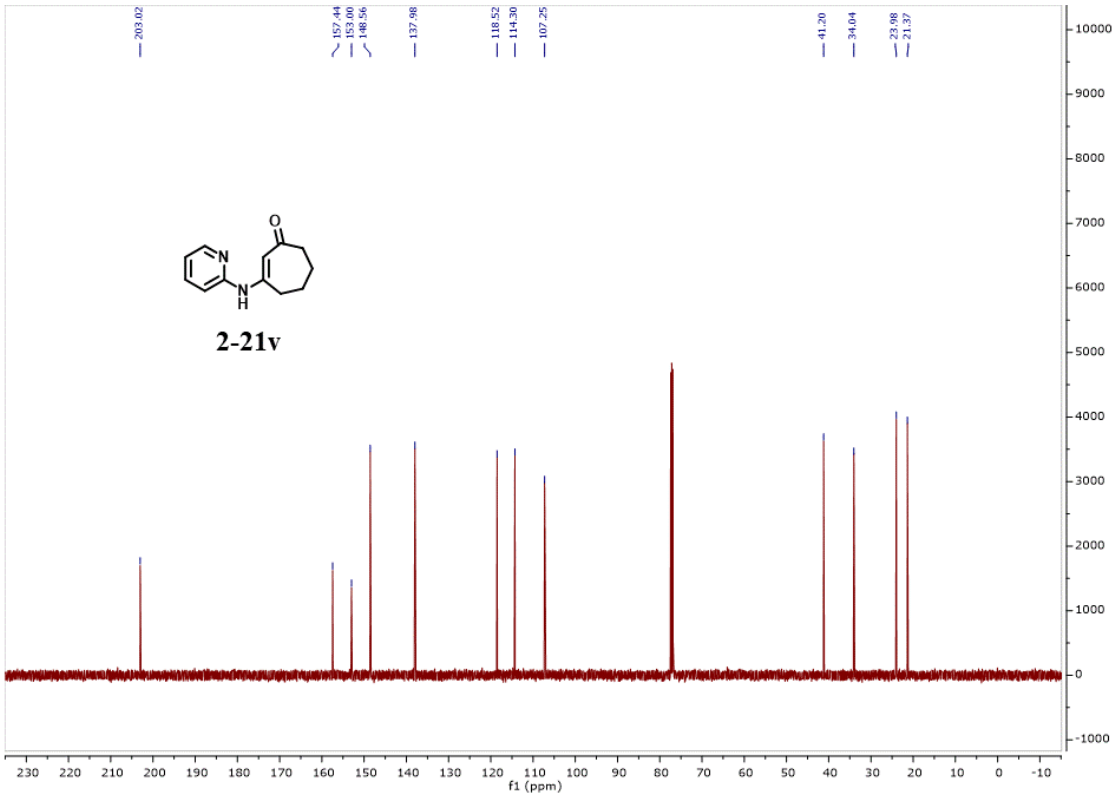
**2-21u**

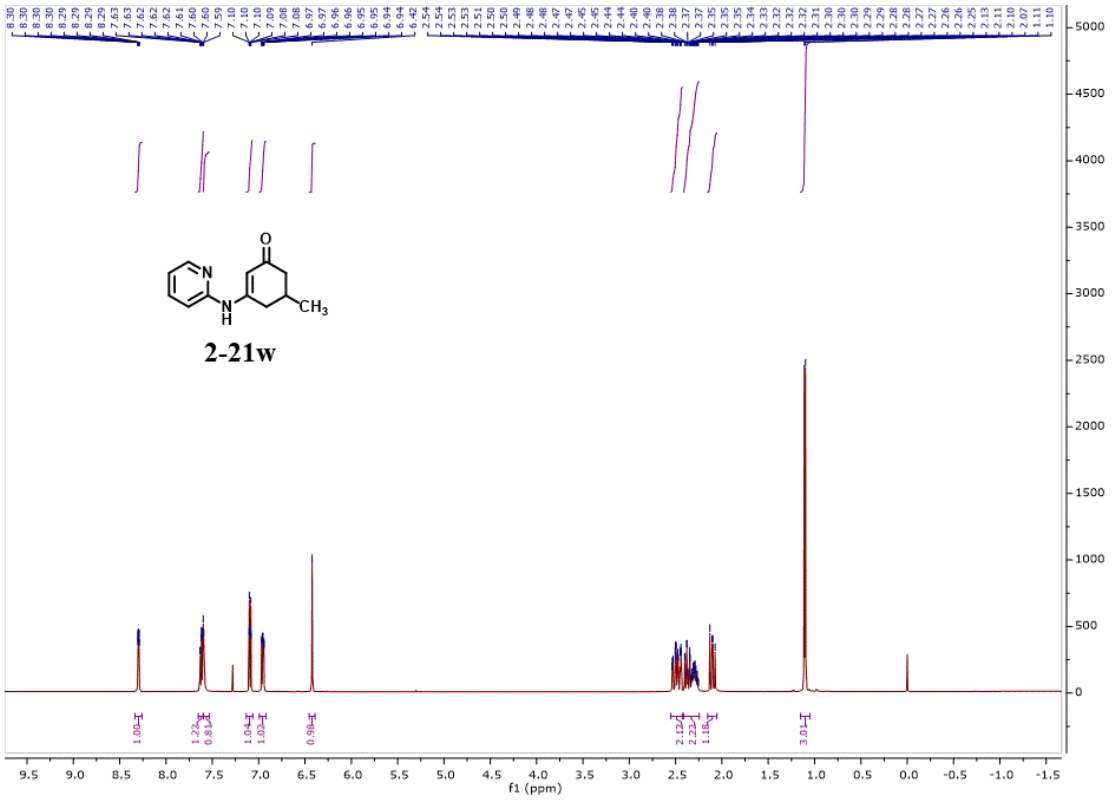

205.89
169.57
154.09
148.31
138.39
118.00
113.11
107.66
32.81
29.25
f1 (ppm)

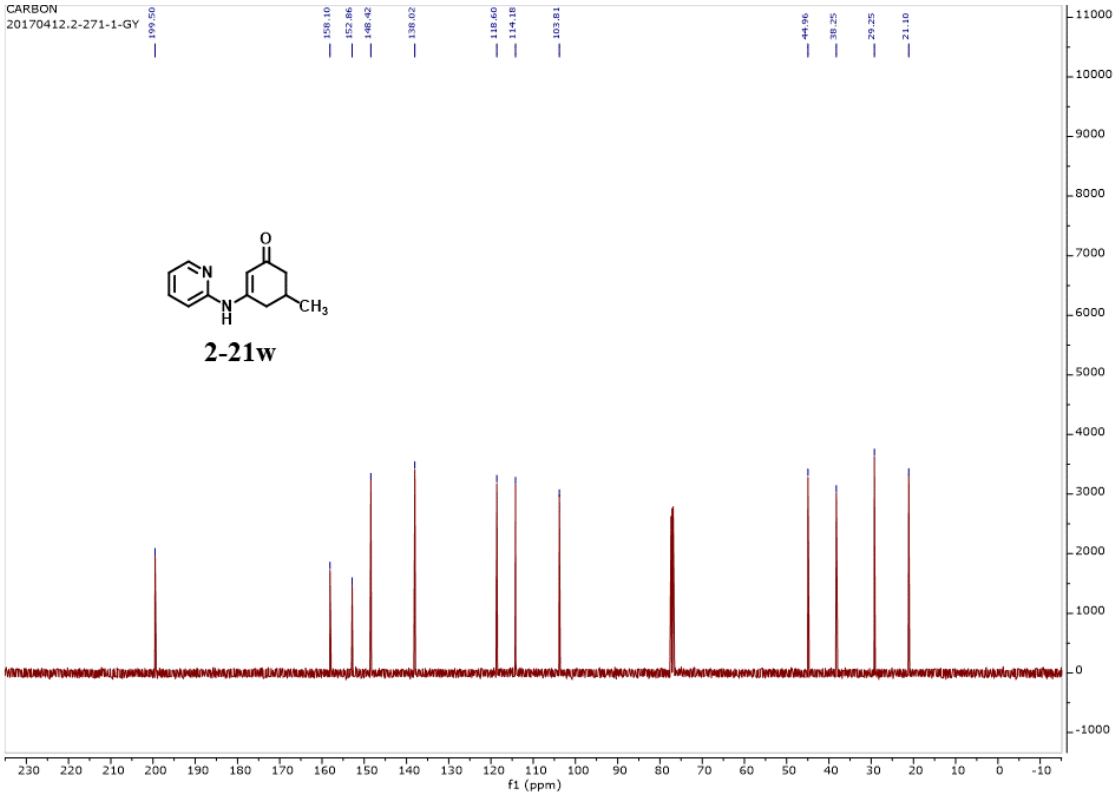
**2-21u**


8.30
8.29
8.29
8.28
7.63
7.63
7.61
7.61
7.60
7.59
7.19
7.16
7.14
6.95
6.94
6.94
6.93
6.33
2.67
2.66
2.65
2.63
2.62
1.96
1.95
1.93
1.92
1.91
1.89
1.88
1.86
1.86
1.85
1.84
1.84
1.00
1.05
0.97
1.05
0.98
1.01
3.88
1.98
2.02
f1 (ppm)

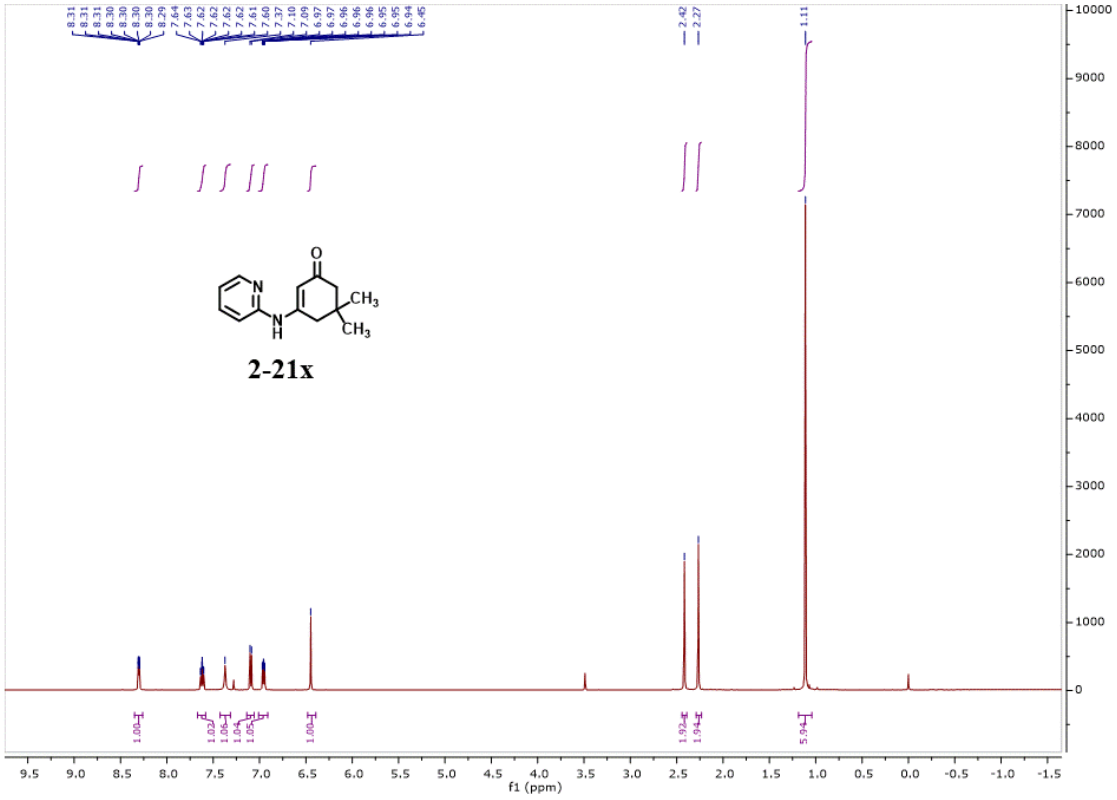
**2-21v**


203.02
157.44
153.00
148.56
137.98
118.52
114.30
107.25
41.20
34.04
23.98
21.37
2-21v
f1 (ppm)

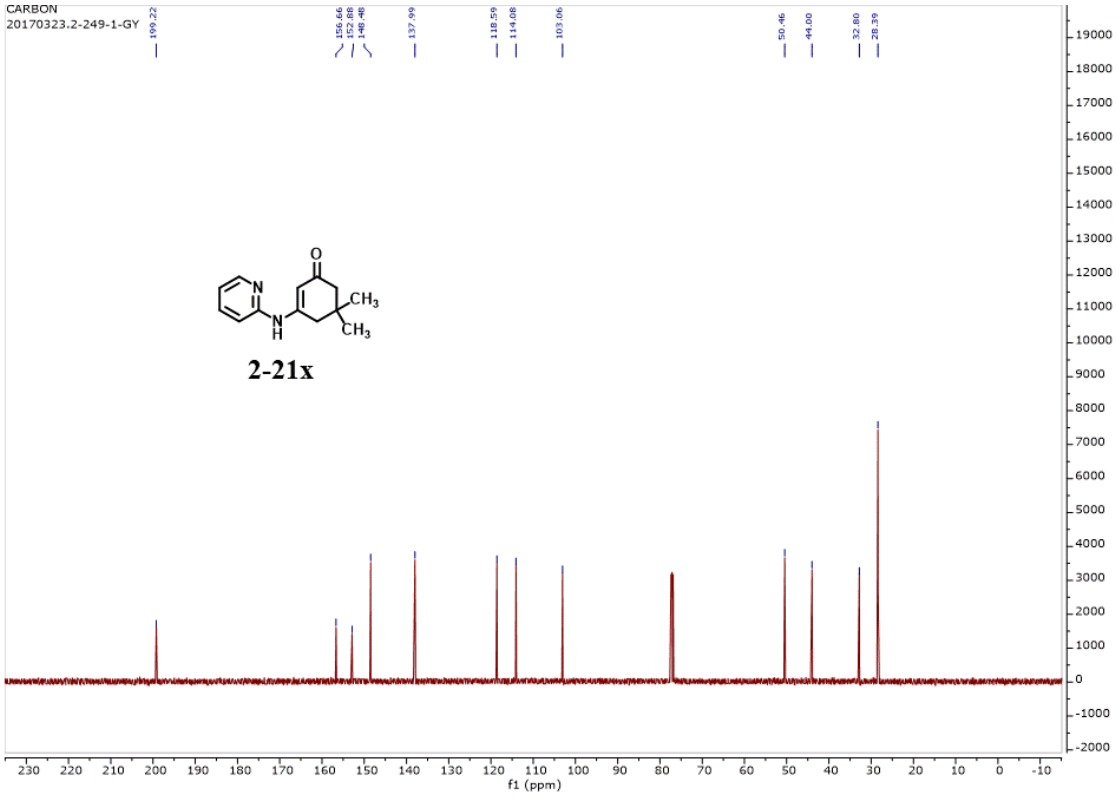

2-21w
f1 (ppm)


CARBON
20170412.2-271-1-GY
199.50
158.10
152.86
148.42
136.02
118.60
114.18
103.81
44.96
38.25
29.25
21.10
f1 (ppm)

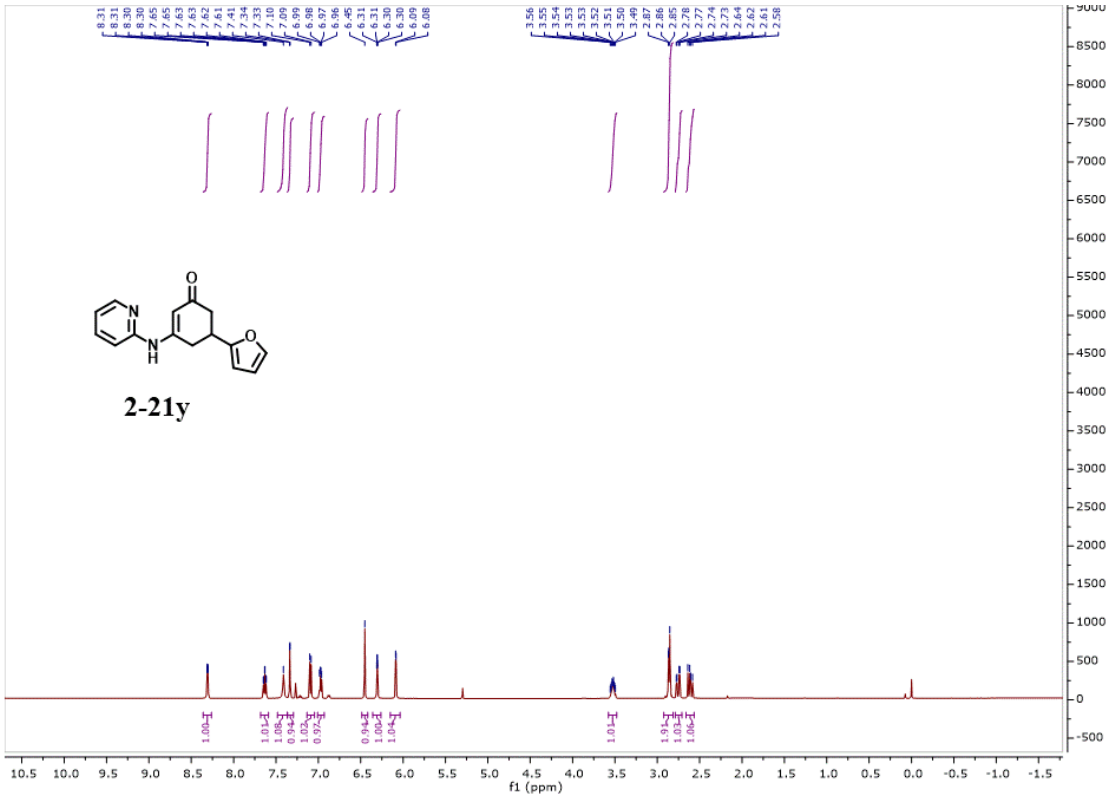
**2-21w**


8.31
8.30
7.64
7.63
7.62
7.61
7.60
7.37
7.10
7.09
6.97
6.96
6.95
6.94
6.45
2.42
2.27
1.11
1.00
1.02
1.06
1.04
1.05
1.00
1.92
1.94
5.94
f1 (ppm)

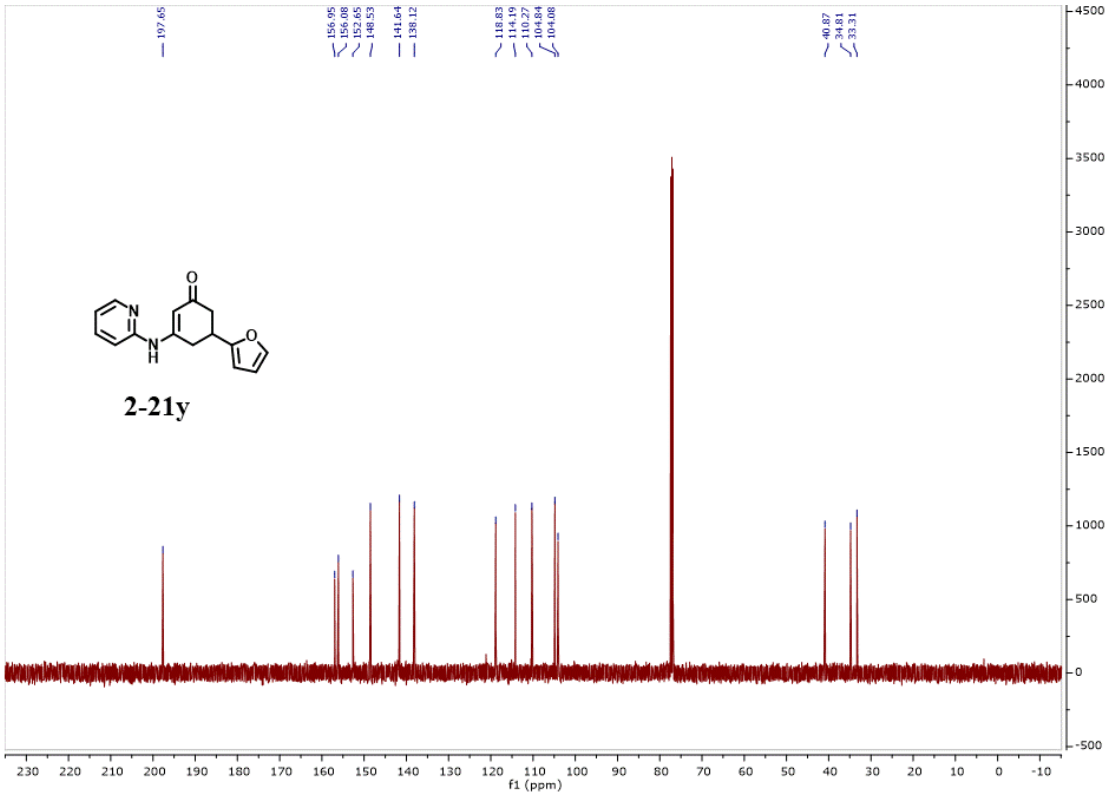
**2-21x**

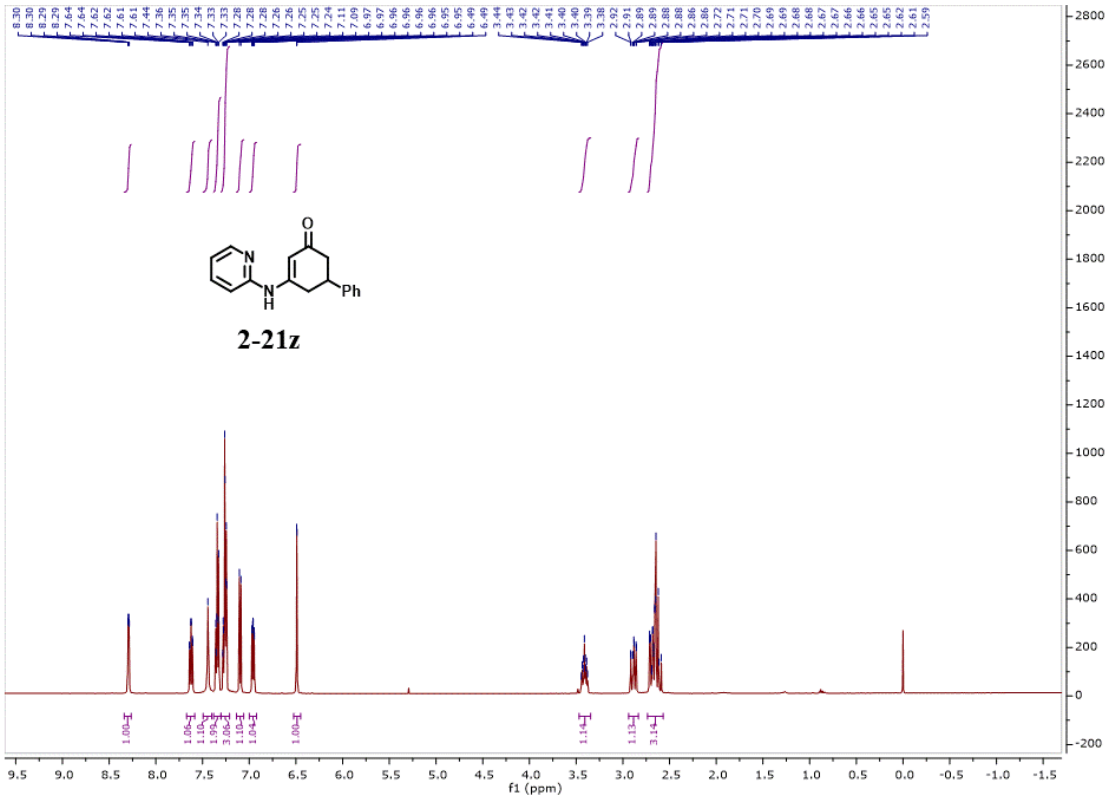

CARBON
20170323.2-249-1-GY
199.22
156.66
152.88
148.48
137.99
118.59
114.08
103.06
50.46
44.00
32.80
28.39
f1 (ppm)

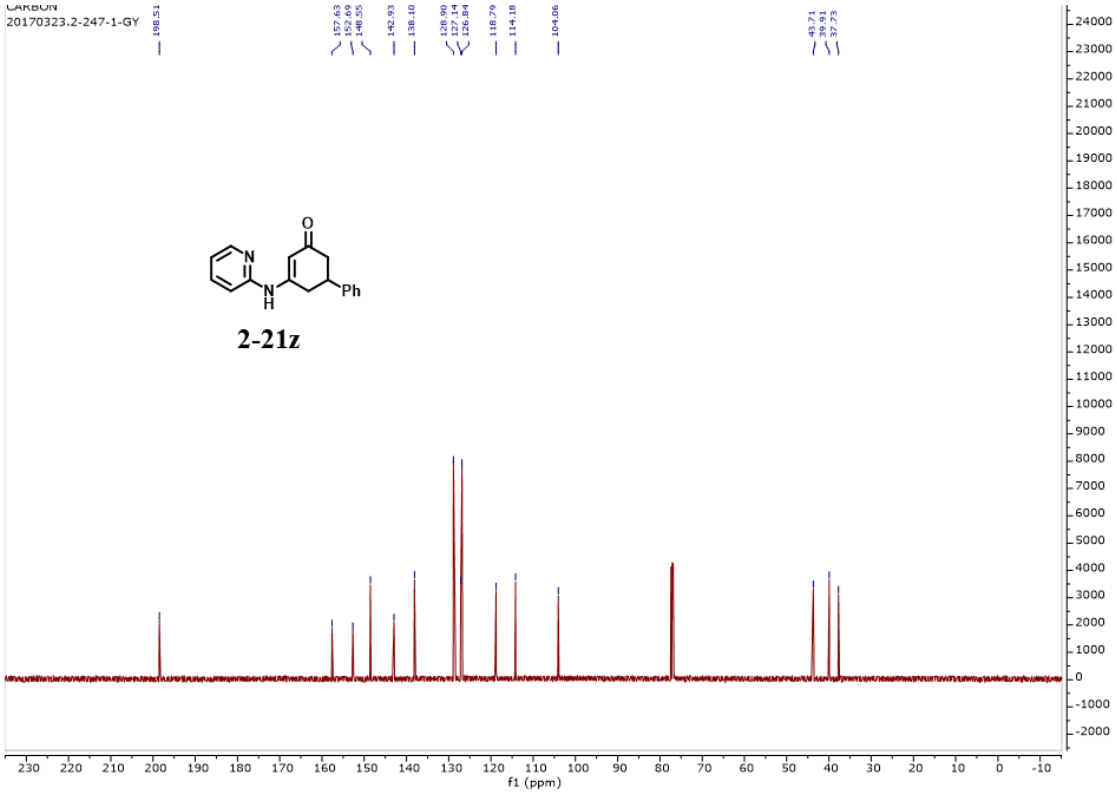
**2-21x**


f1 (ppm)

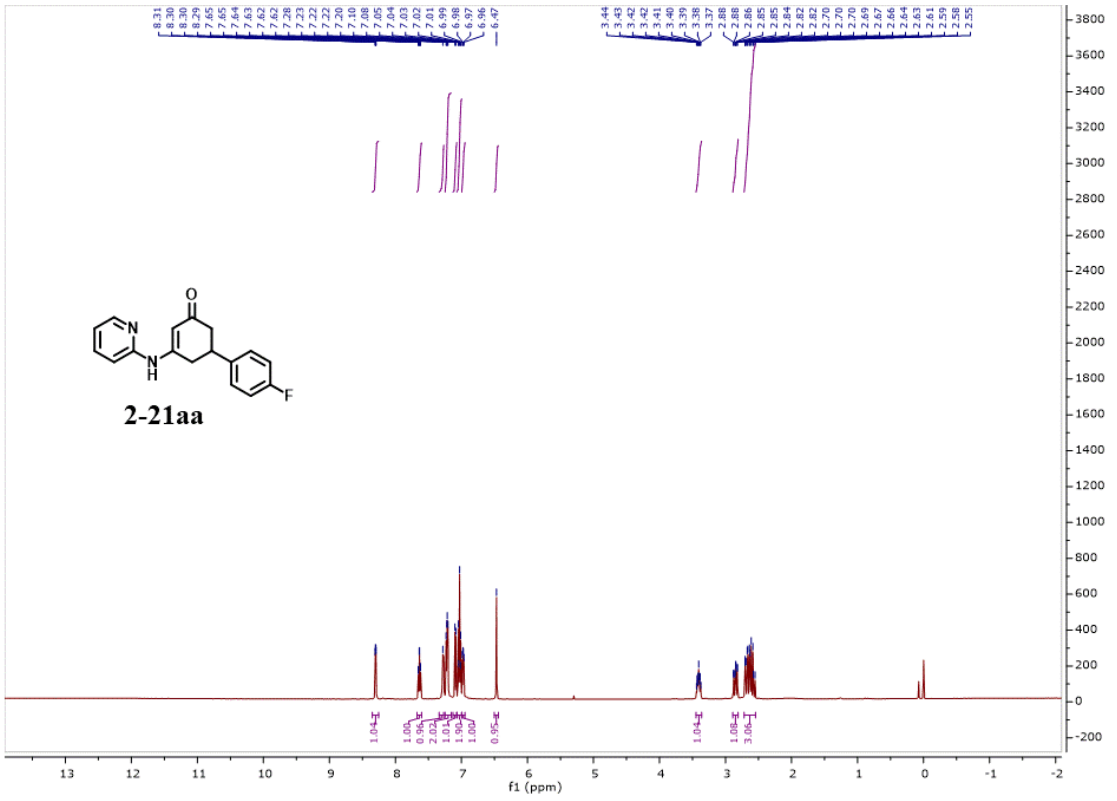
**2-21y**


197.65
156.95
155.08
152.65
148.53
141.64
138.12
118.83
114.19
110.27
104.84
104.08
40.87
34.81
33.31
2-21y
f1 (ppm)

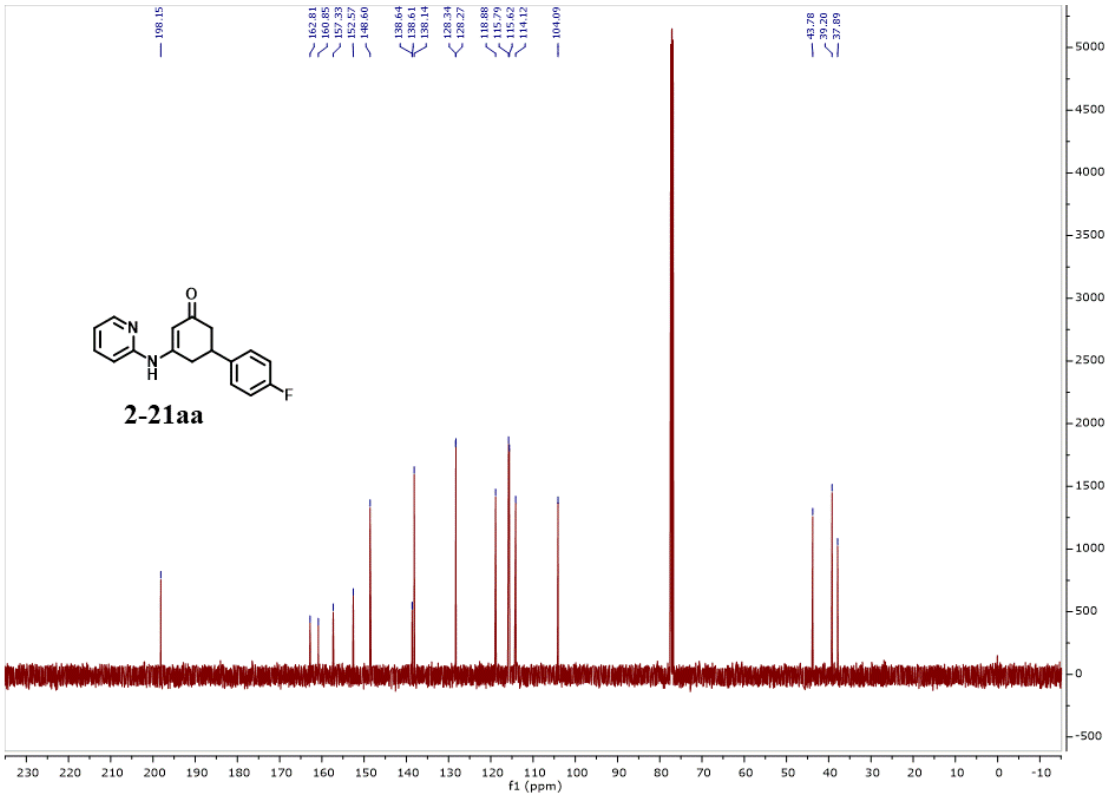

2-21z
f1 (ppm)

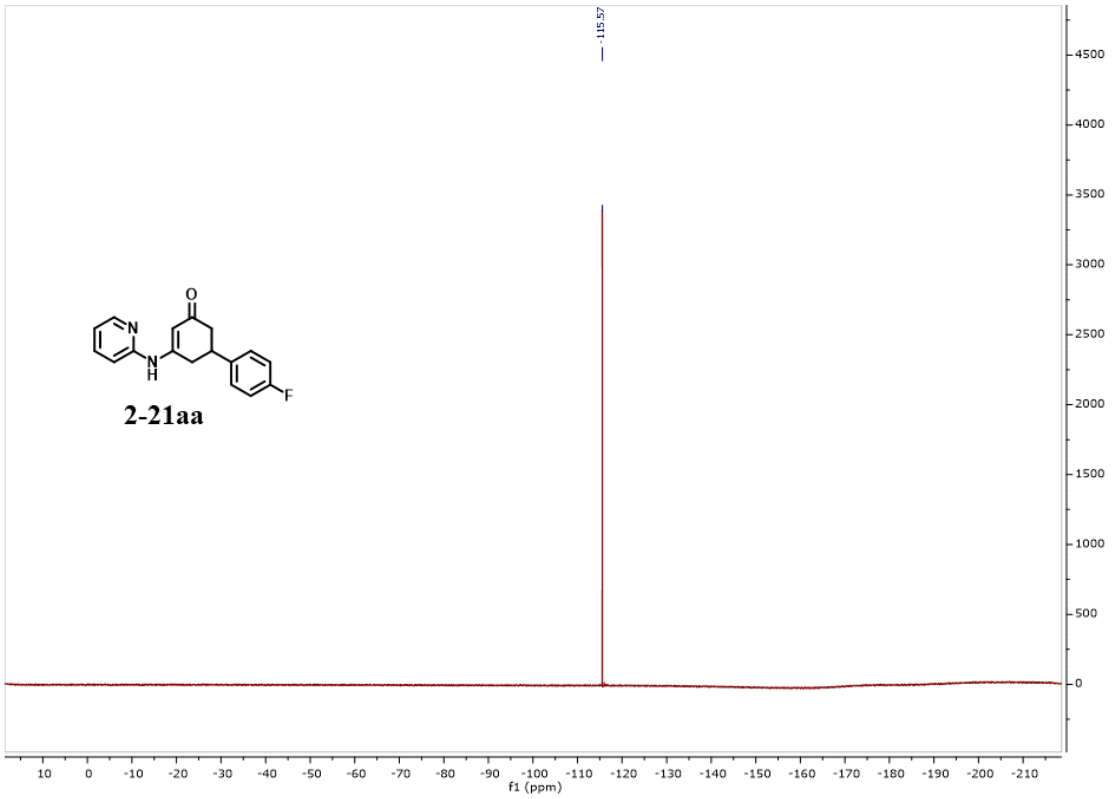

CARBON
20170323.2-247-1-GY
198.51
157.63
152.69
146.55
142.93
138.10
129.90
127.14
126.84
118.79
114.18
104.06
43.71
39.91
37.73
Ph
f1 (ppm)

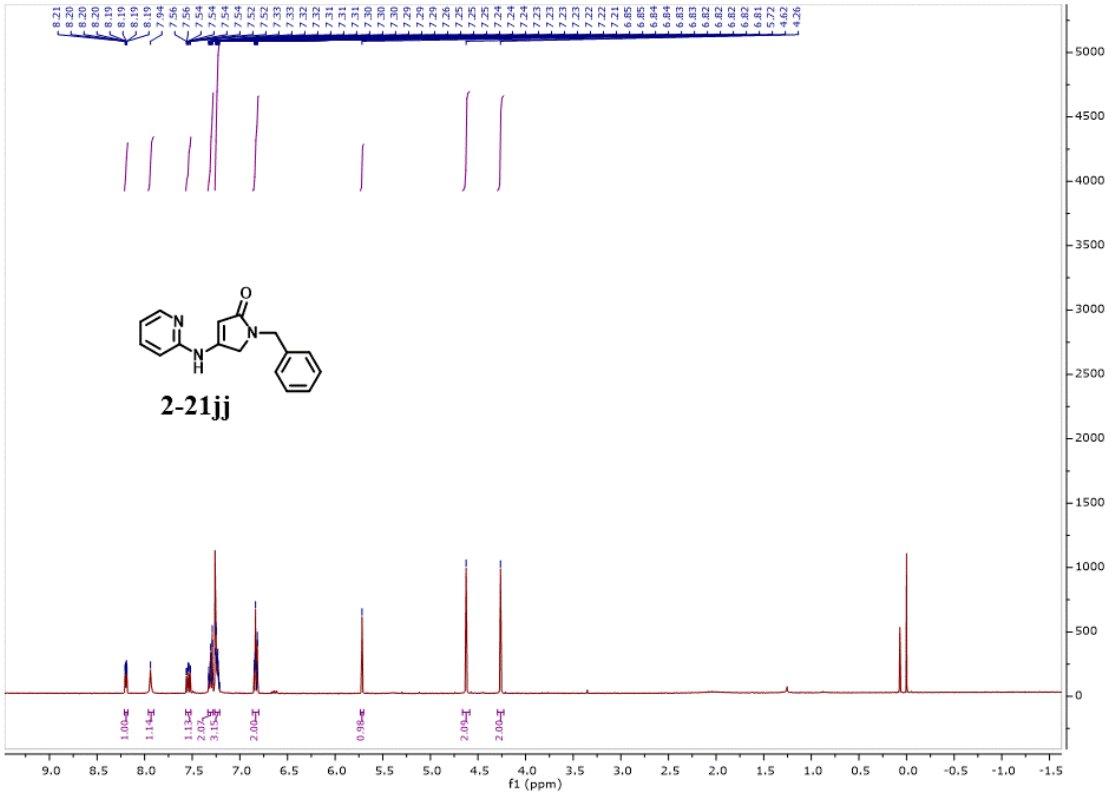
2-21z

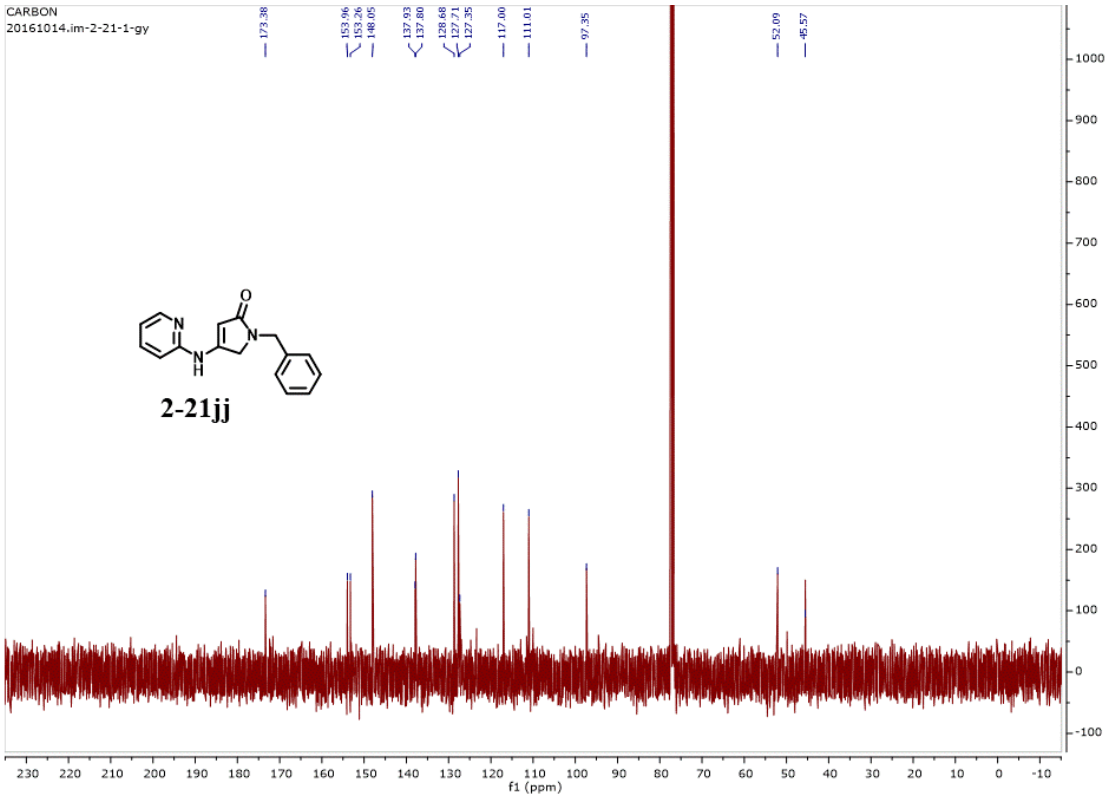

8.31
8.30
8.30
8.29
7.65
7.65
7.64
7.63
7.62
7.62
7.28
7.23
7.22
7.22
7.20
7.10
7.08
7.05
7.04
7.03
7.02
7.01
6.99
6.98
6.97
6.96
6.47
3.44
3.43
3.42
3.42
3.41
3.40
3.39
3.38
3.37
2.88
2.88
2.86
2.85
2.85
2.84
2.82
2.82
2.70
2.70
2.70
2.69
2.67
2.66
2.64
2.63
2.61
2.59
2.58
2.55
F
f1 (ppm)

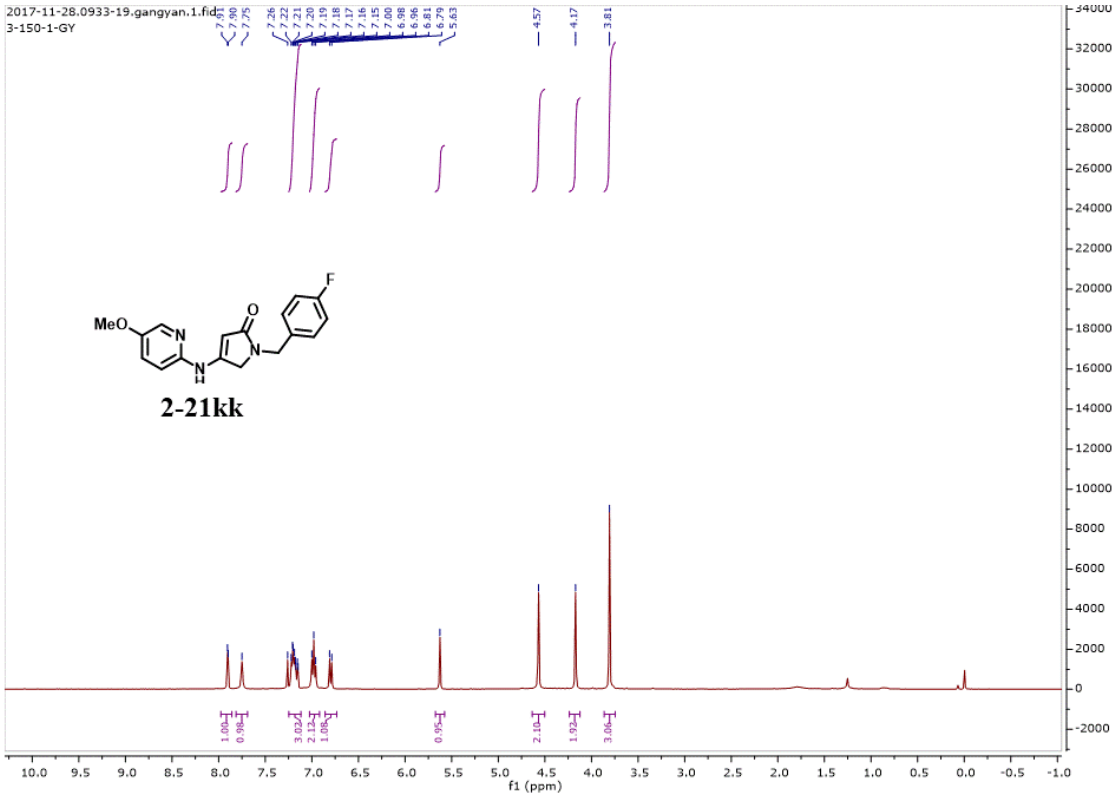
2-21aa

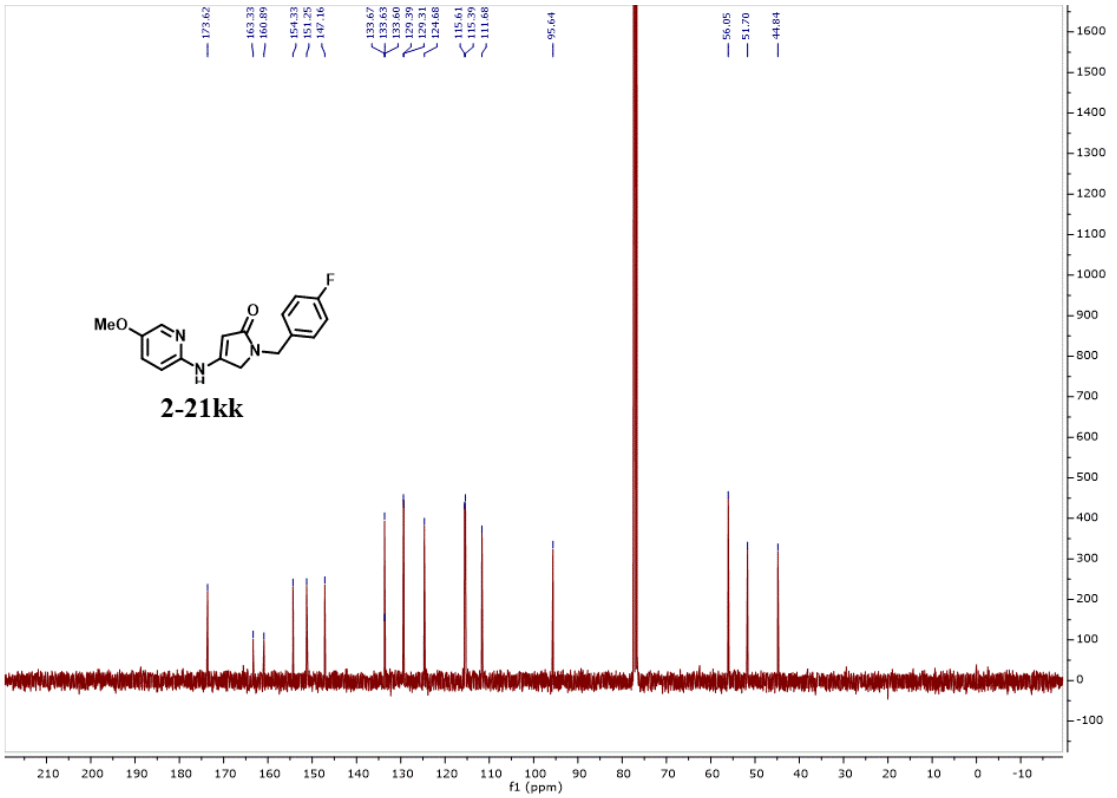

198.15
162.81
160.85
157.33
152.57
148.60
138.64
138.61
138.14
128.34
128.27
118.88
115.79
115.62
114.12
104.09
43.78
39.20
37.89
2-21aa
f1 (ppm)

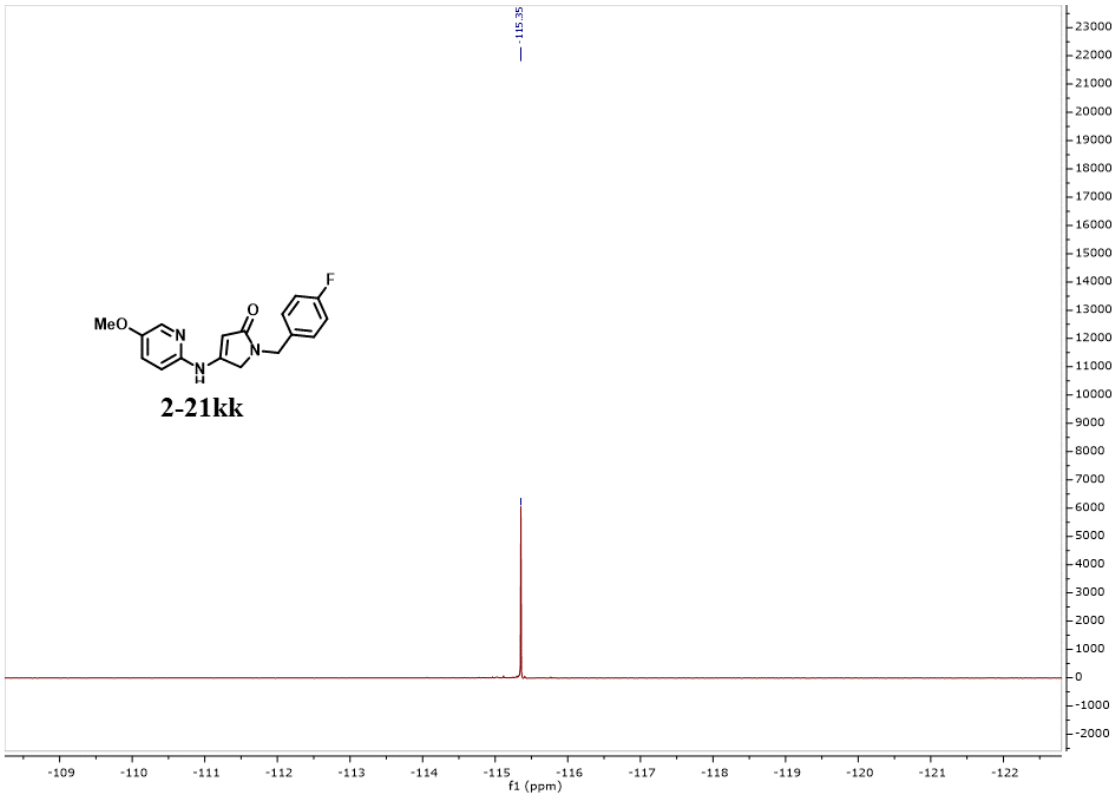

115.57
2-21aa
f1 (ppm)

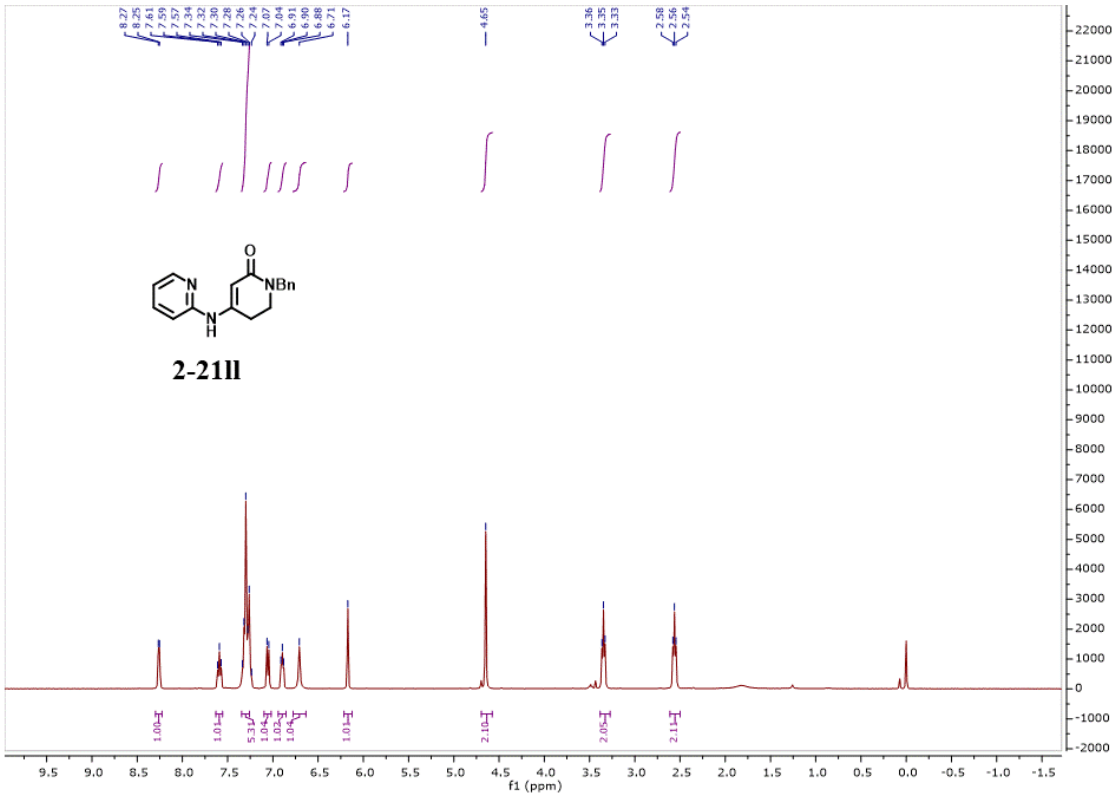

2-21jj
f1 (ppm)

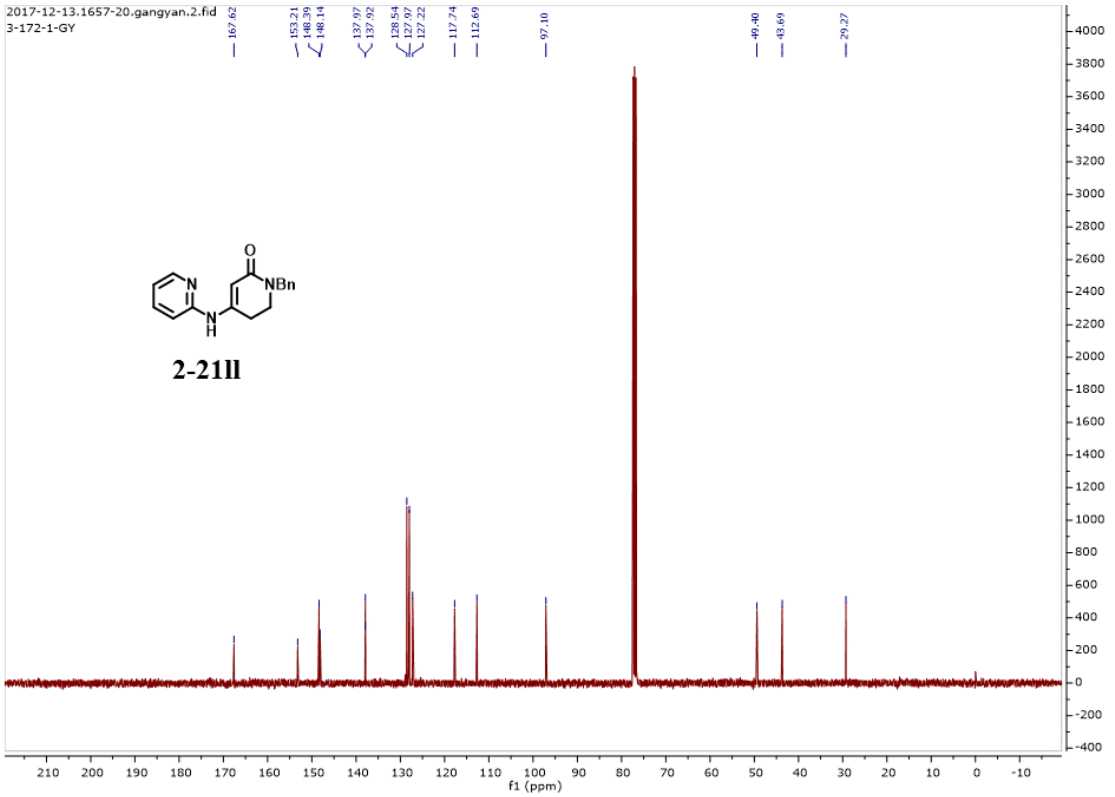

CARBON
20161014.im-2-21-1-gy
2-21jj
f1 (ppm)

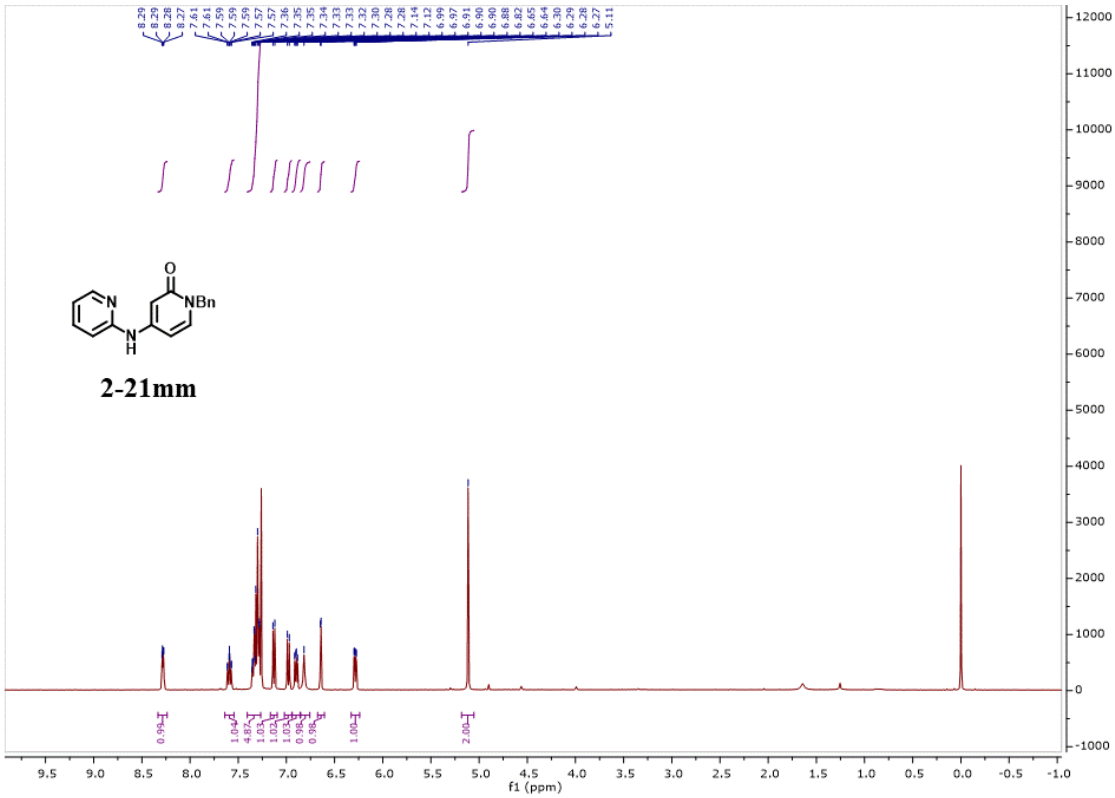

2017-11-28.0933-19.gangyan.1.fid
3-150-1-GY
MeO
F
O
N
H
2-21kk
f1 (ppm)

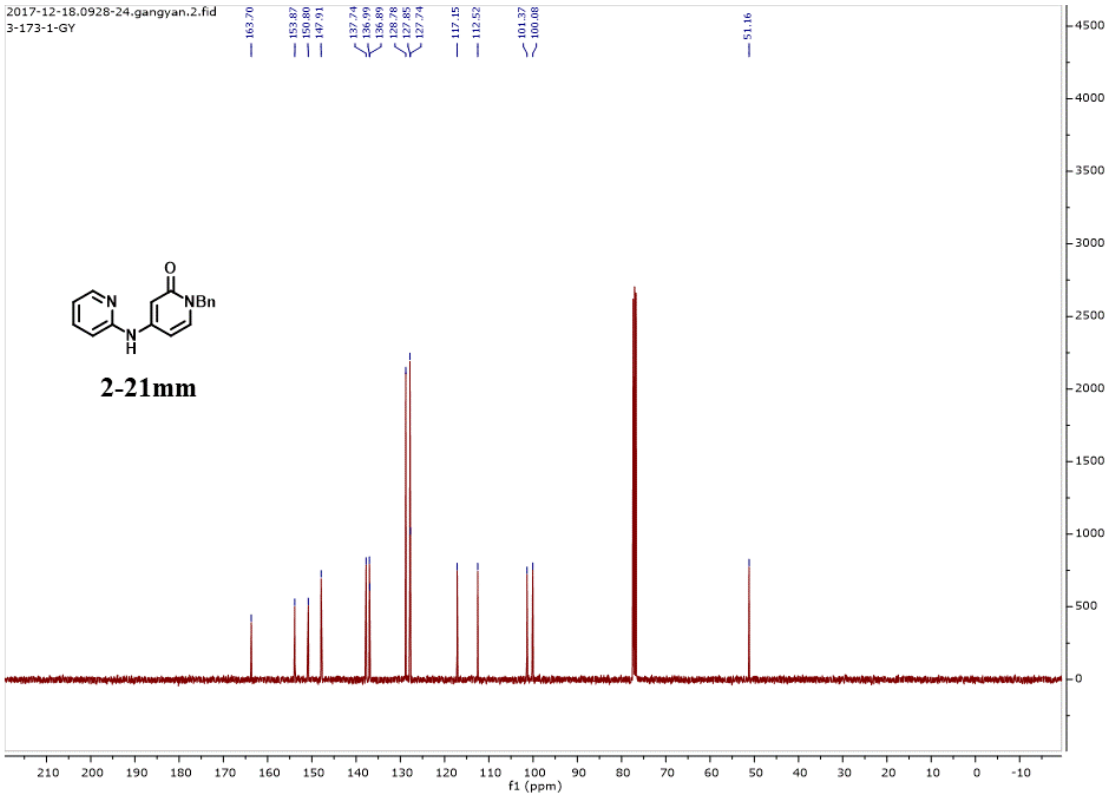

MeO
F
O
N
H
2-21kk
f1 (ppm)

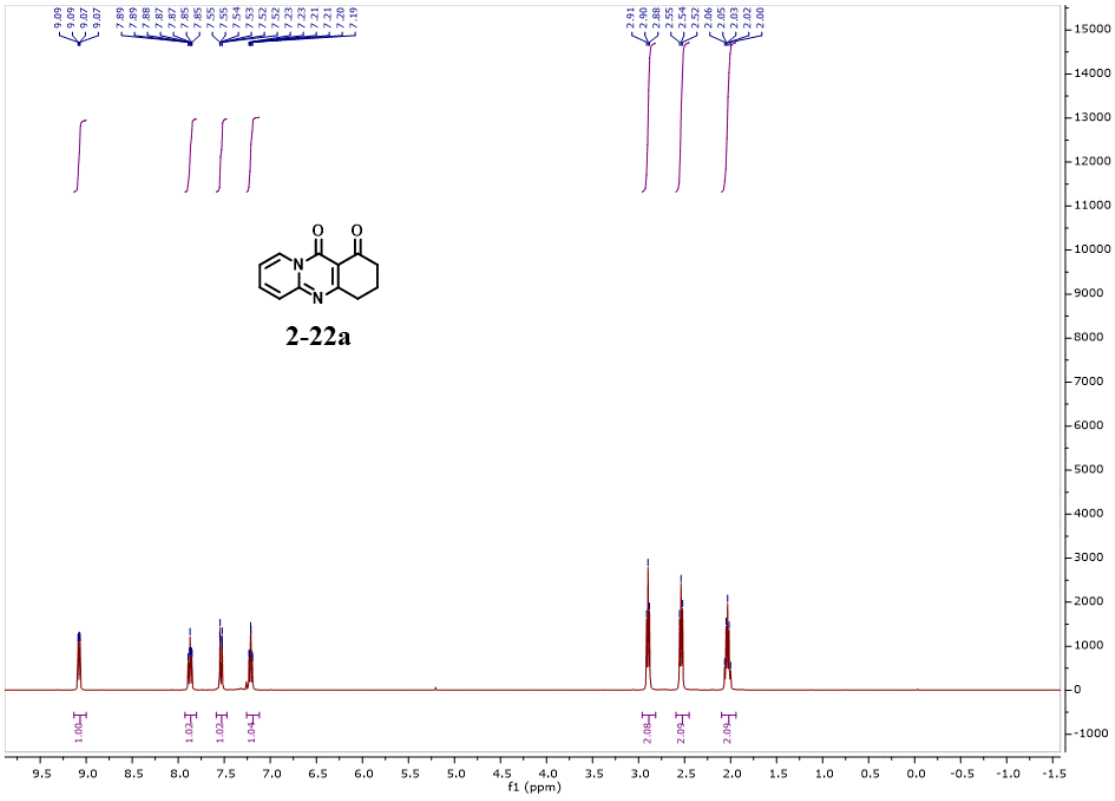

-115.35
MeO
N
O
F
N
H
N
2-21kk
f1 (ppm)

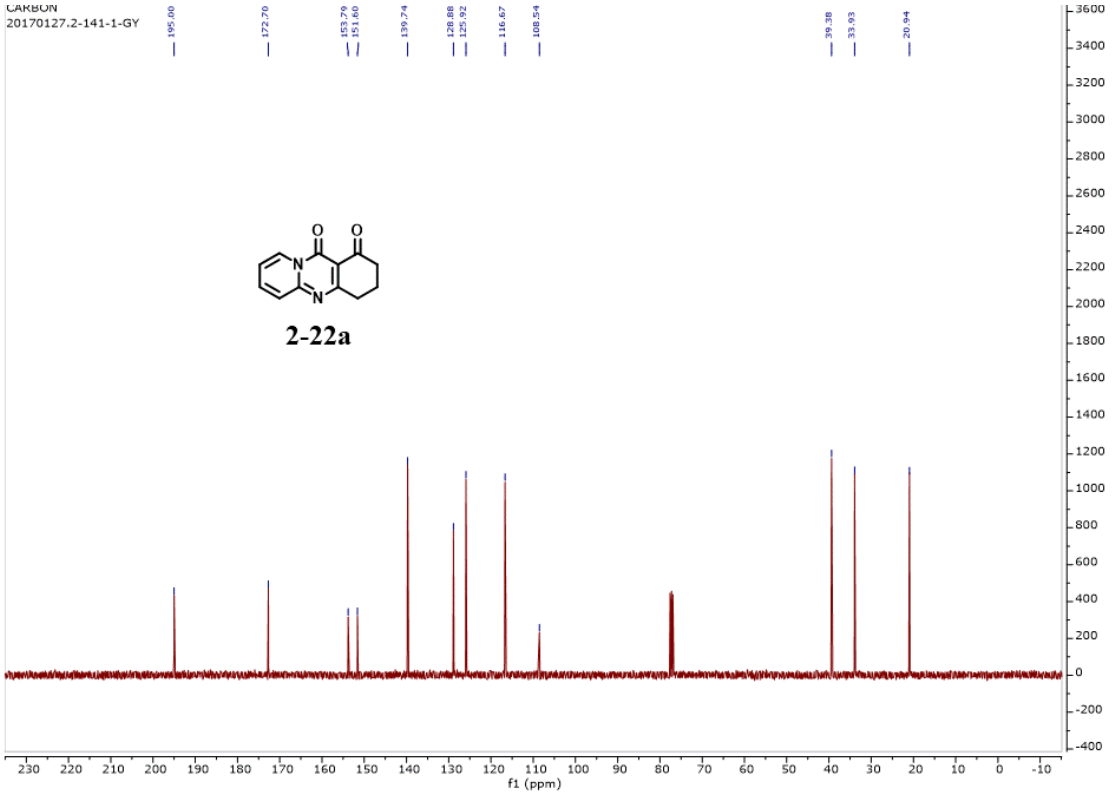

8.27
8.25
7.61
7.59
7.57
7.34
7.32
7.30
7.28
7.26
7.24
7.07
7.04
6.91
6.90
6.88
6.71
6.17
4.65
3.36
3.35
3.33
2.58
2.56
2.54
O
N
NBn
N
H
2-21ll
1.00
1.01
5.31
1.04
1.02
1.04
1.01
2.01
2.05
2.11
f1 (ppm)


2017-12-13.1657-20.gangyan.2.fid
3-172-1-GY
167.62
153.21
148.39
148.14
137.97
137.92
128.54
127.97
127.22
117.74
112.69
97.10
49.40
43.69
29.27
NBn
2-21ll
f1 (ppm)

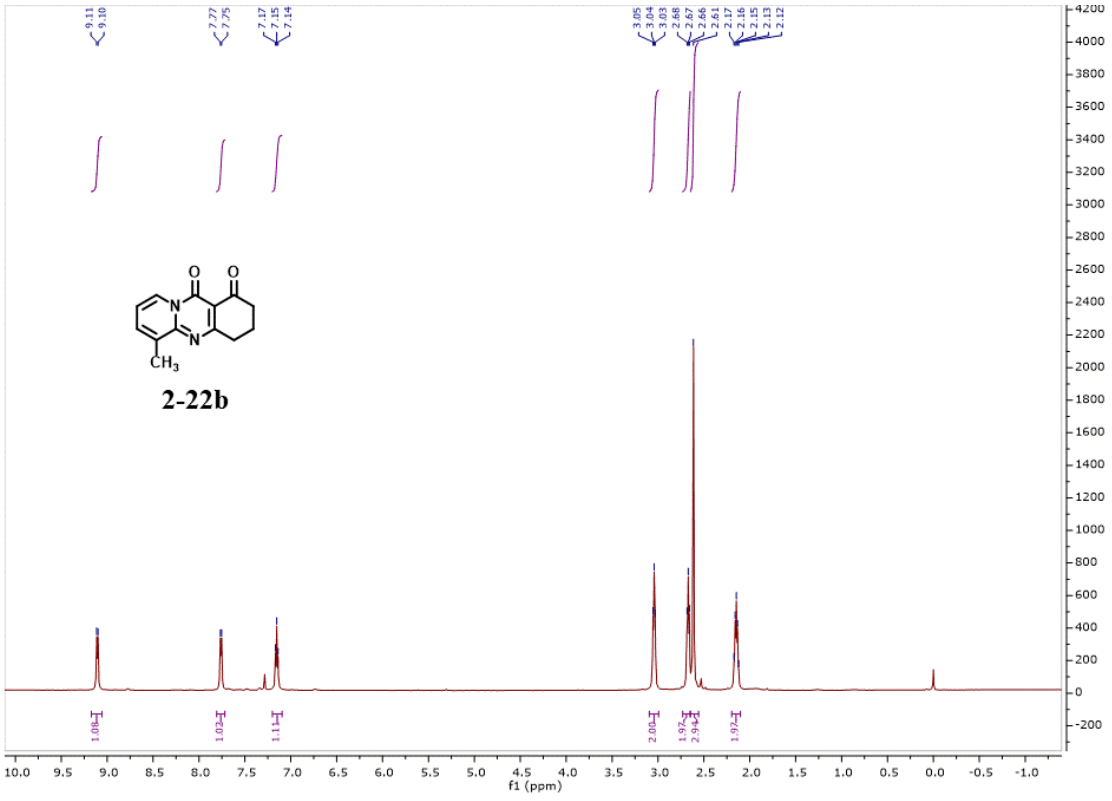

NBn
2-21mm
f1 (ppm)


2017-12-18.0928-24.gangyan.2.fid
3-173-1-GY
163.70
153.87
150.80
147.91
137.74
136.99
136.89
128.78
127.85
127.74
117.15
112.52
101.37
100.08
51.16
O
NBn
N
H
2-21mm
f1 (ppm)

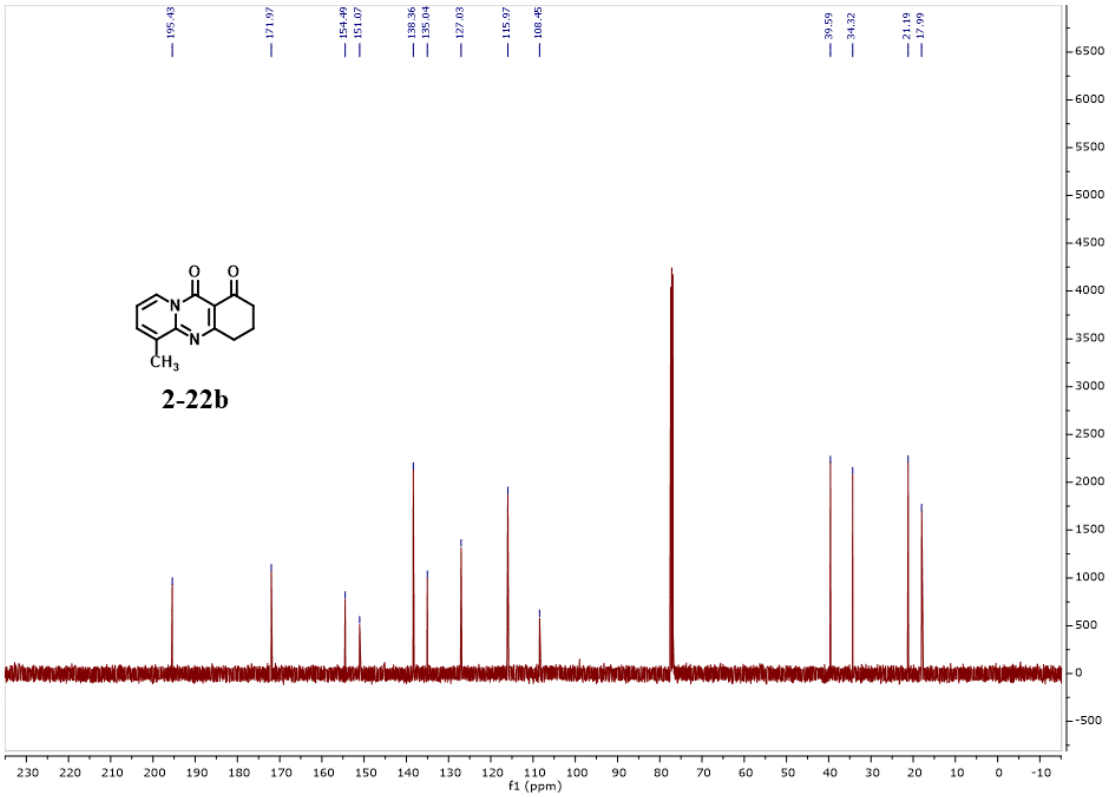

9.09
9.09
9.07
9.07
7.89
7.89
7.88
7.87
7.87
7.85
7.85
7.55
7.55
7.54
7.53
7.52
7.52
7.23
7.23
7.21
7.21
7.20
7.19
2.91
2.90
2.88
2.55
2.54
2.52
2.06
2.05
2.03
2.02
2.00
O
O
N
N
2-22a
1.00
1.02
1.02
1.04
2.08
2.09
2.09
f1 (ppm)


CARBON
20170127.2-141-1-GY
195.00
172.70
153.79
151.60
139.74
128.88
125.92
116.67
108.54
39.38
33.93
20.94
f1 (ppm)

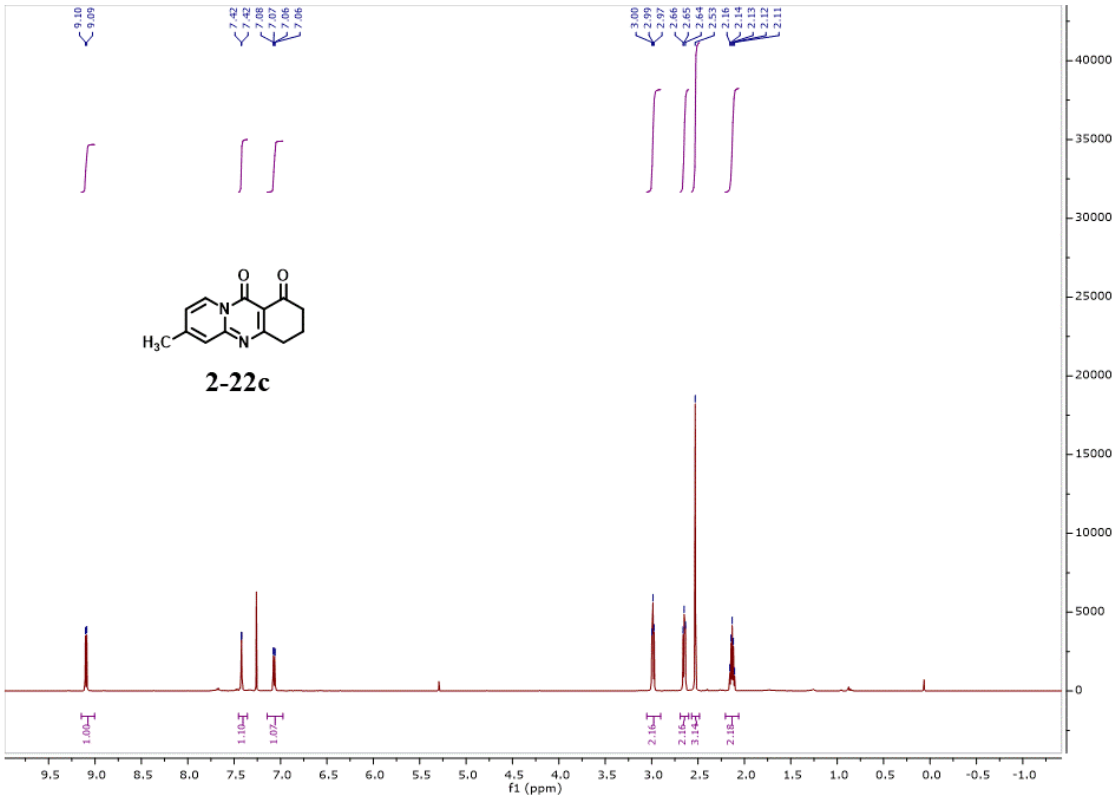
2-22a


9.11
9.10
7.77
7.75
7.17
7.15
7.14
3.05
3.04
3.03
2.68
2.67
2.66
2.61
2.17
2.16
2.15
2.13
2.12
1.08
1.02
1.11
2.00
1.97
2.94
1.97
f1 (ppm)

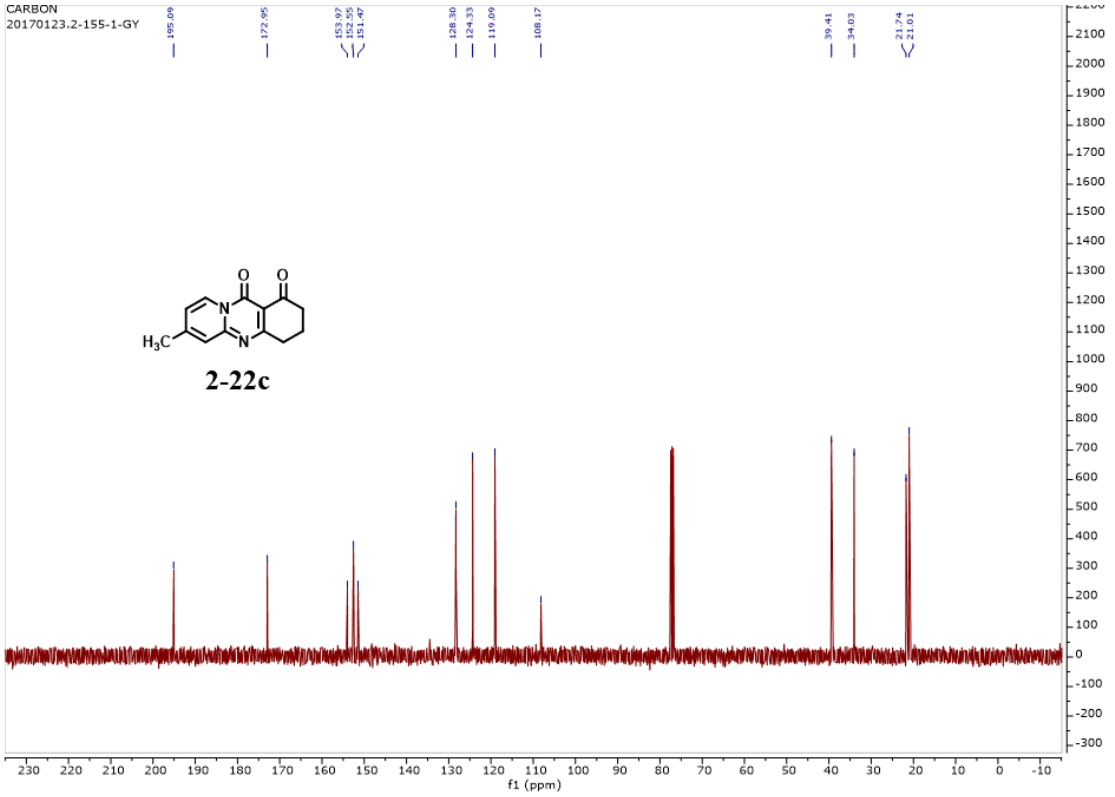
2-22b


195.43
171.97
154.49
151.07
138.36
135.04
127.03
115.97
108.45
39.59
34.32
21.19
17.99
f1 (ppm)

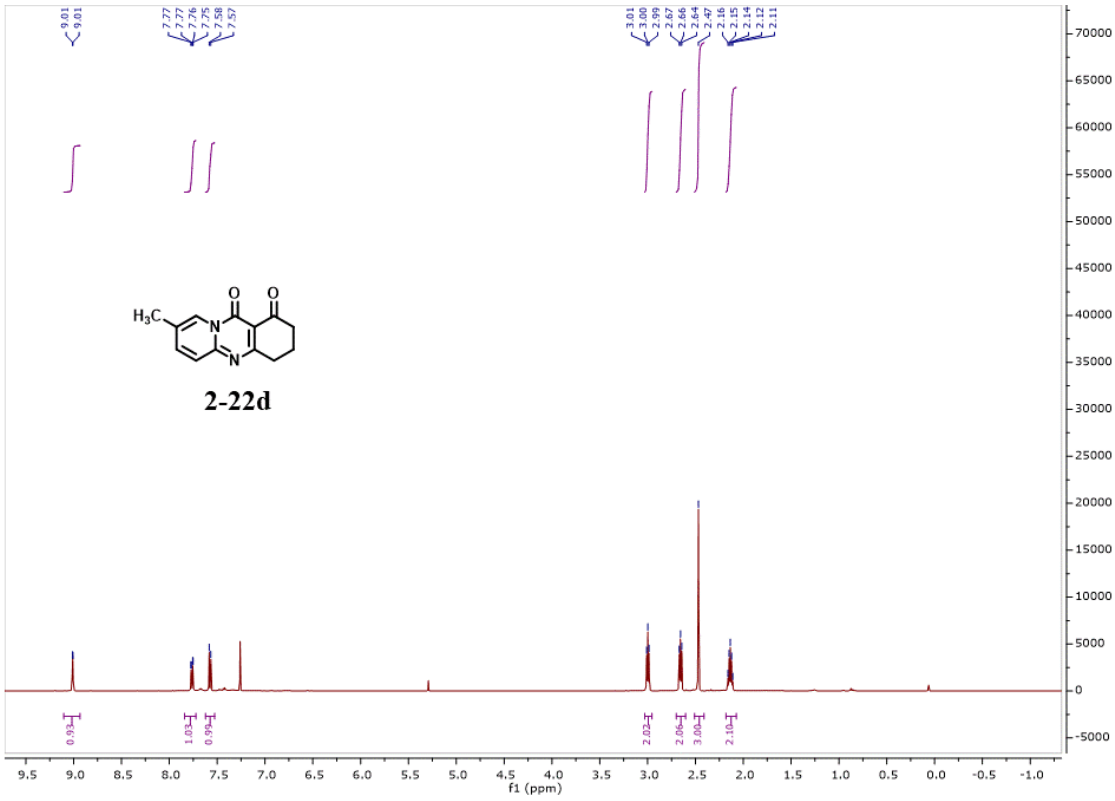
**2-22b**


9.10
9.09
7.42
7.42
7.08
7.07
7.06
7.06
3.00
2.99
2.97
2.66
2.65
2.64
2.53
2.16
2.14
2.13
2.12
2.11
1.00
1.10
1.07
2.16
2.16
3.14
2.18
f1 (ppm)

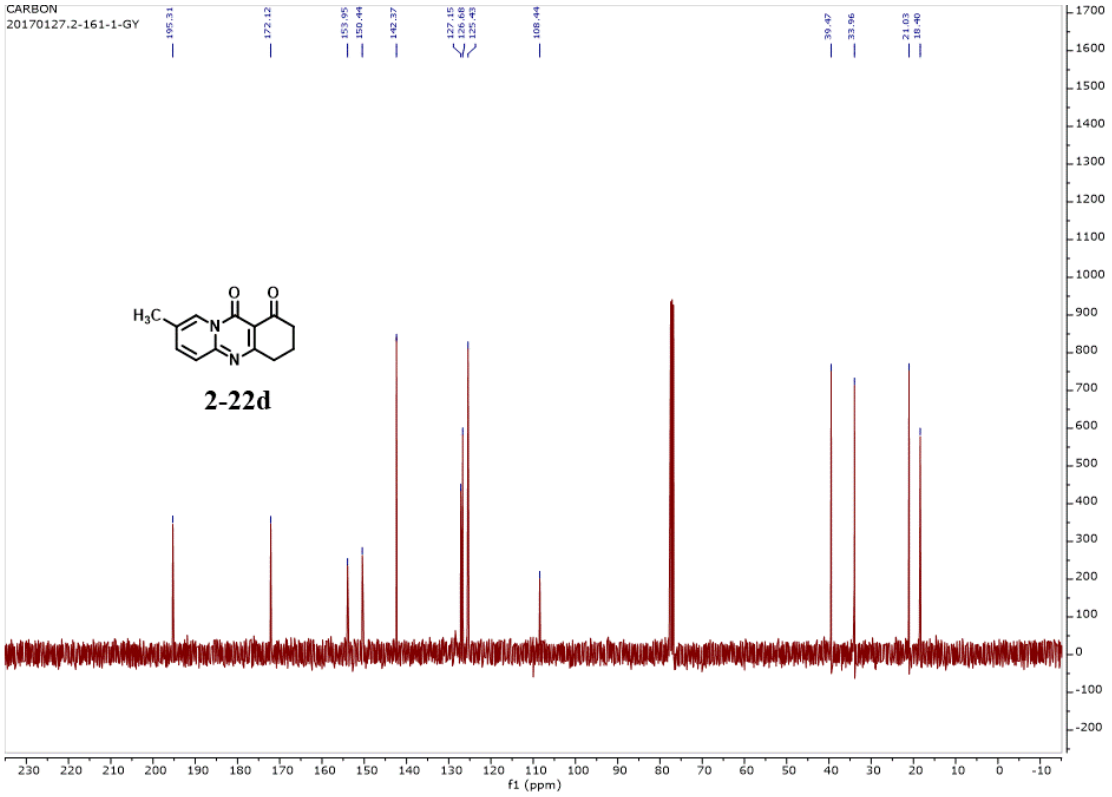
**2-22c**

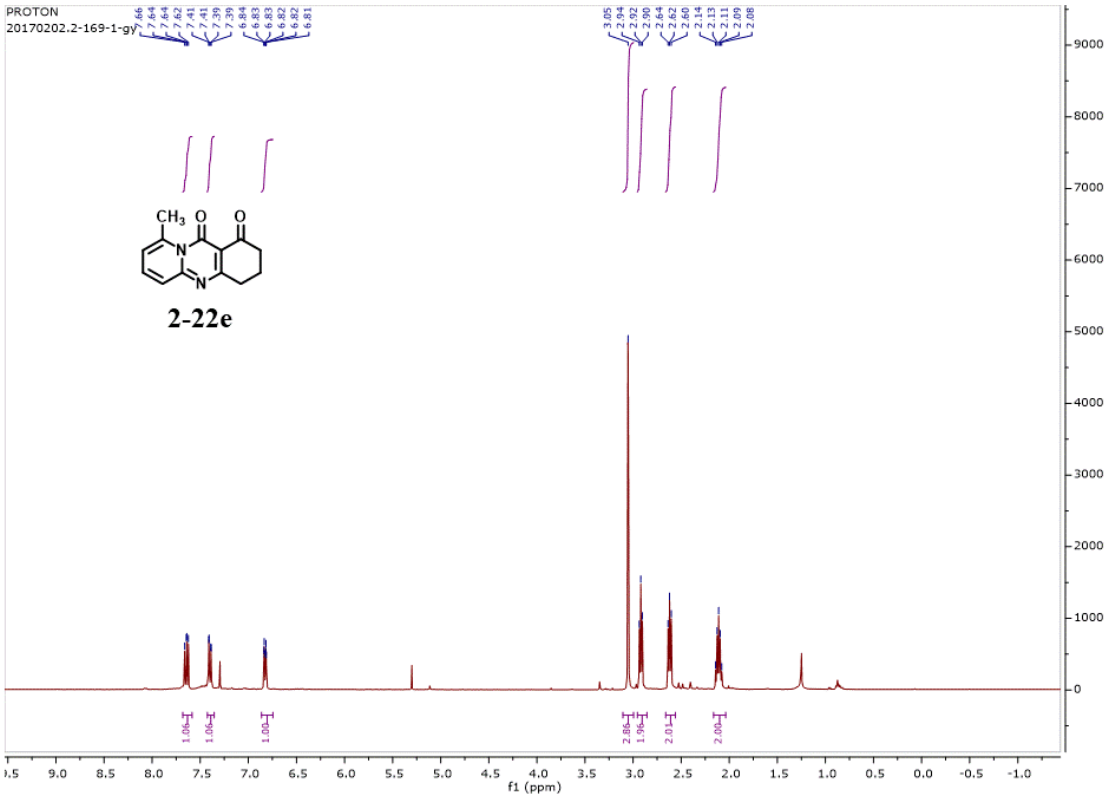

CARBON
20170123.2-155-1-GY
195.09
172.95
153.97
152.55
151.47
128.30
124.33
119.09
108.17
39.41
34.03
21.74
21.01
f1 (ppm)

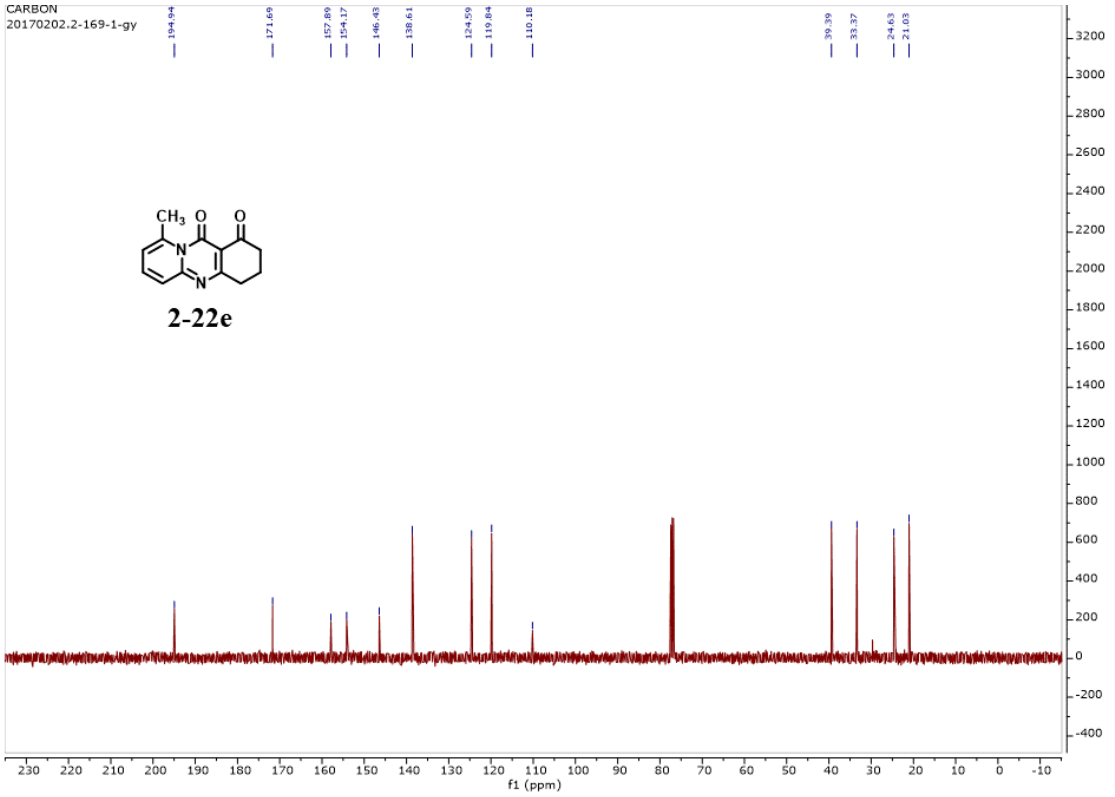
**2-22c**


9.01
9.01
7.77
7.77
7.76
7.75
7.58
7.57
3.01
3.00
2.99
2.67
2.66
2.64
2.47
2.16
2.15
2.14
2.12
2.11
0.93
1.03
0.99
2.02
2.06
3.00
2.10
f1 (ppm)

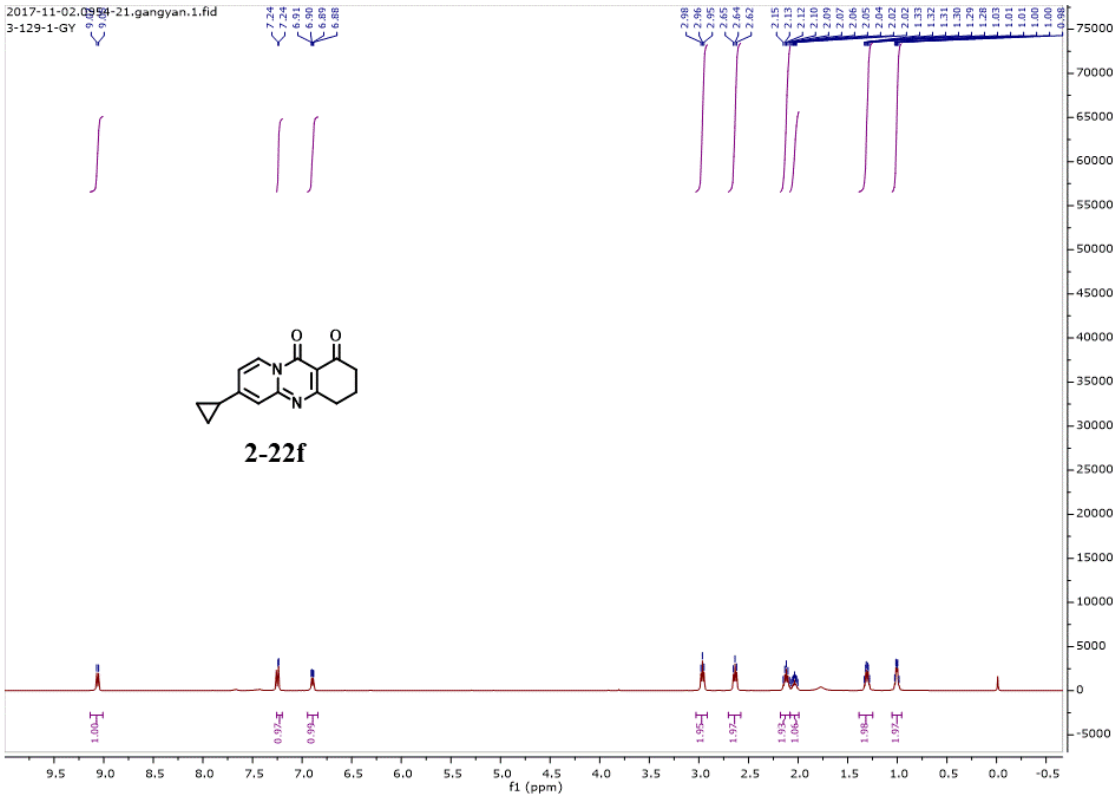
**2-22d**


CARBON
20170127.2-161-1-GY
195.31
172.12
153.95
150.44
142.37
127.15
126.68
125.43
108.44
39.47
33.96
21.63
18.40
2-22d
f1 (ppm)

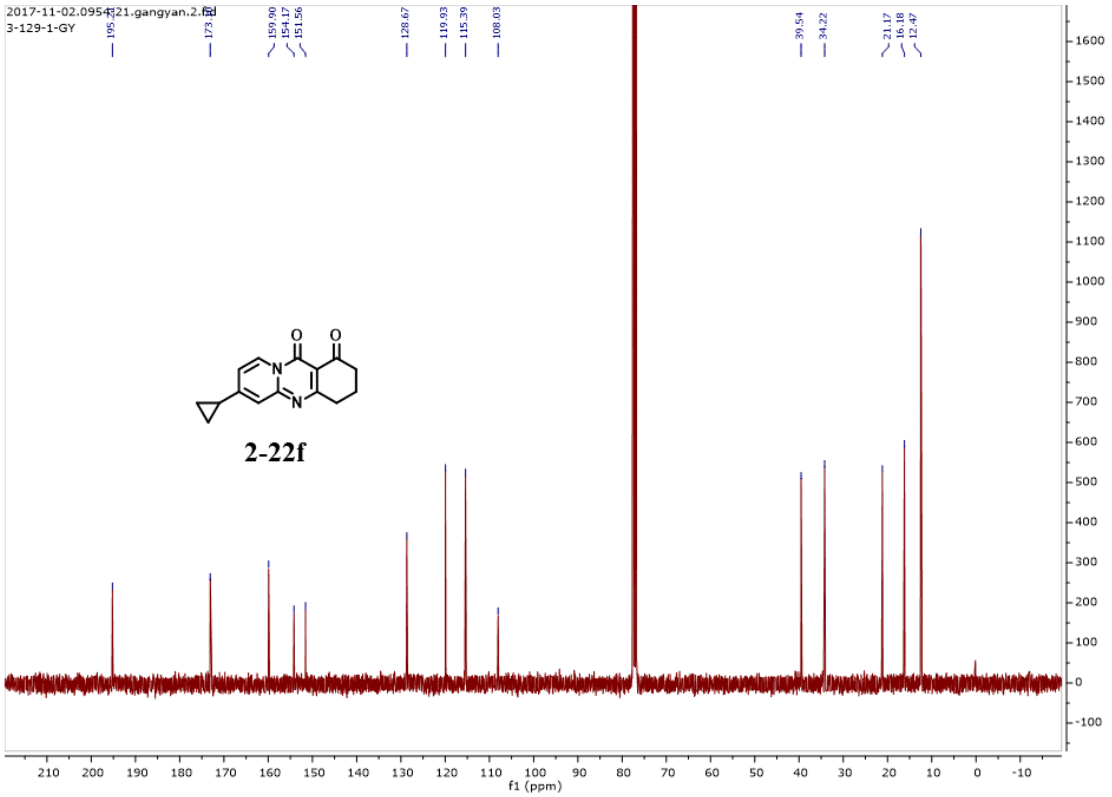

PROTON
20170202.2-169-1-gy
7.66
7.64
7.64
7.62
7.41
7.41
7.39
7.39
6.84
6.83
6.83
6.82
6.82
6.81
3.05
2.94
2.92
2.90
2.64
2.62
2.60
2.14
2.13
2.11
2.09
2.08
2-22e
1.00
1.06
1.00
2.86
1.96
2.01
2.00
f1 (ppm)

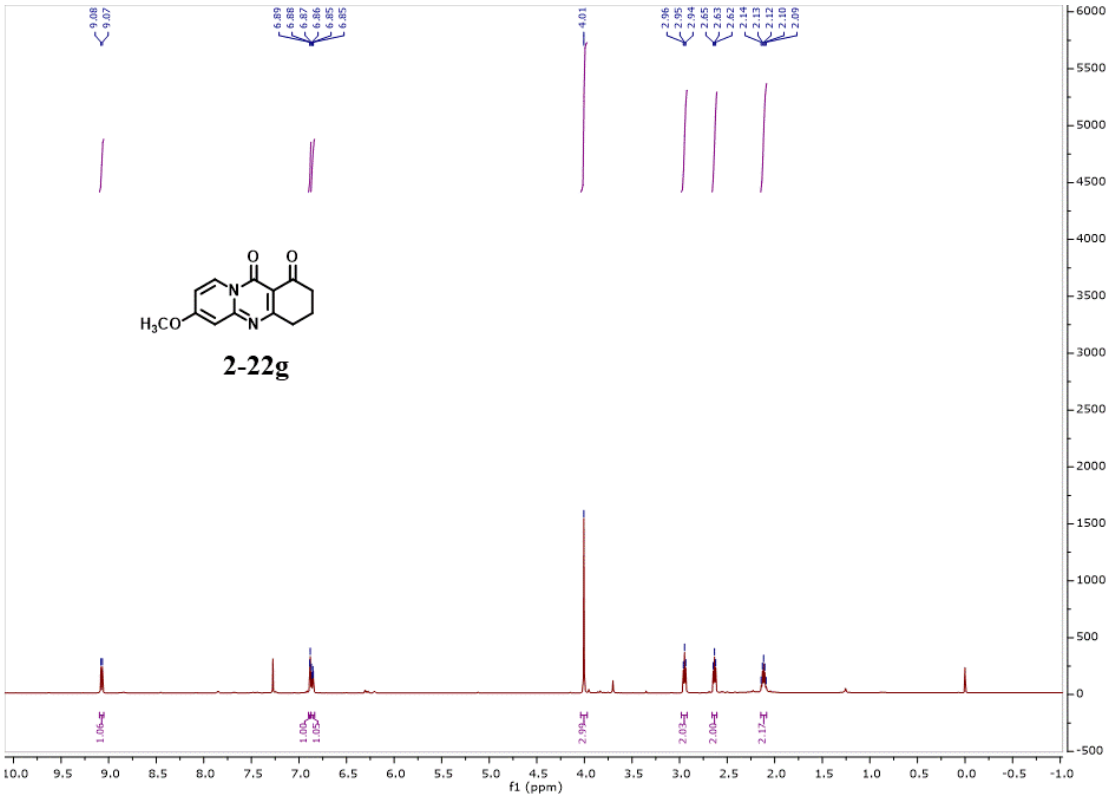

CARBON
20170202.2-169-1-gy
194.94
171.69
157.89
154.17
146.43
138.61
124.59
119.84
110.18
39.39
33.37
24.63
21.03
CH3
O
O
N
N
f1 (ppm)

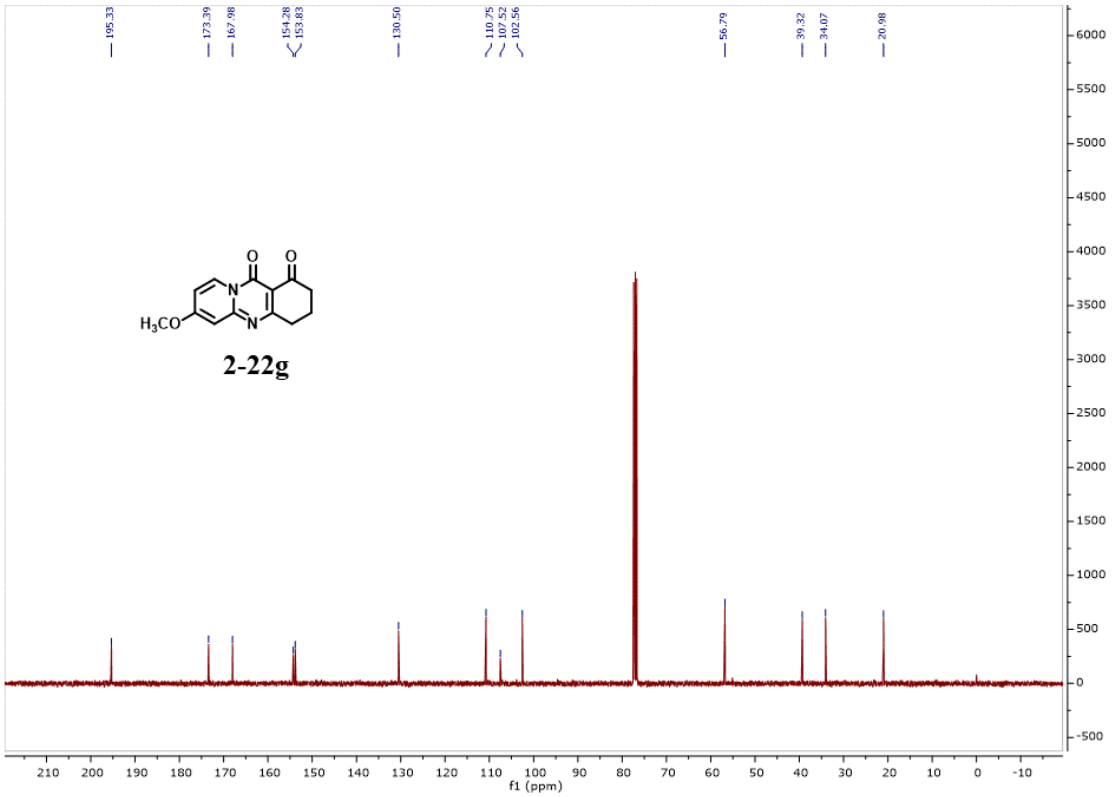
**2-22e**

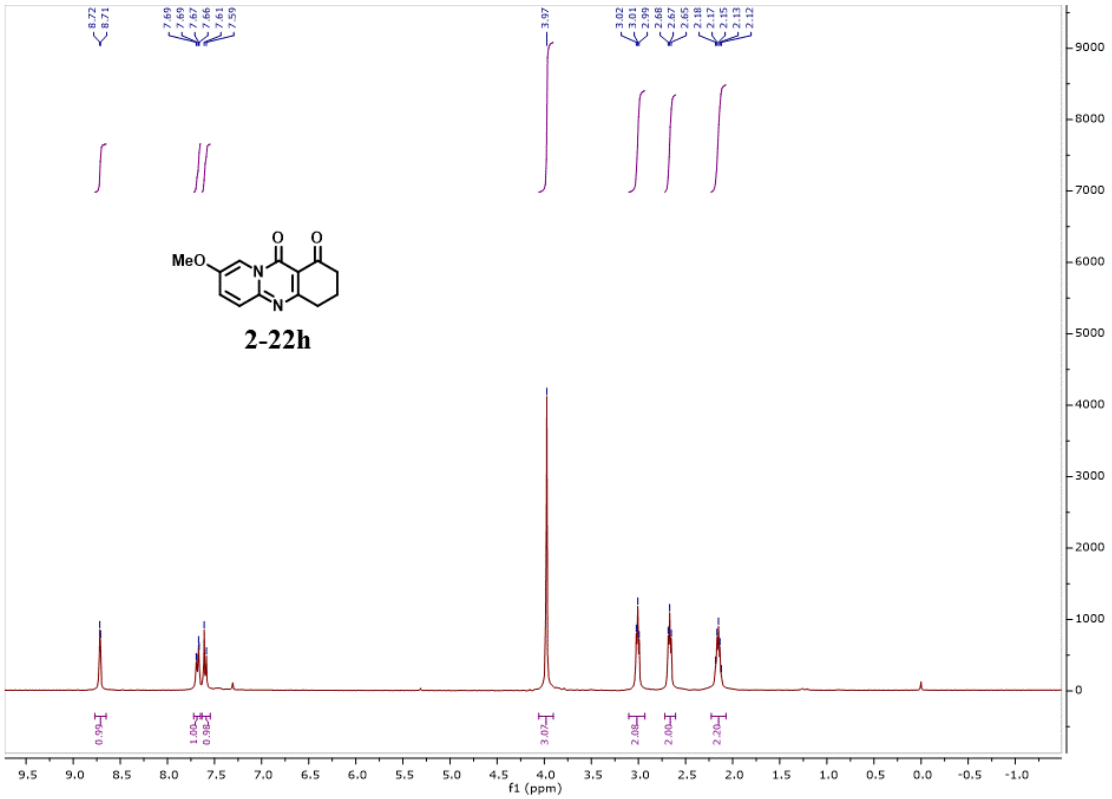

2017-11-02_0954-21.gangyan.1.fid
3-129-1-GY
9.04
9.03
7.24
7.24
6.91
6.90
6.89
6.88
2.98
2.96
2.95
2.65
2.64
2.62
2.15
2.13
2.12
2.10
2.09
2.07
2.06
2.05
2.04
2.02
2.02
1.33
1.32
1.31
1.30
1.29
1.28
1.03
1.01
1.01
1.00
1.00
0.98
1.00
0.97
0.99
1.95
1.97
1.93
1.06
1.98
1.97
O
O
N
N
f1 (ppm)

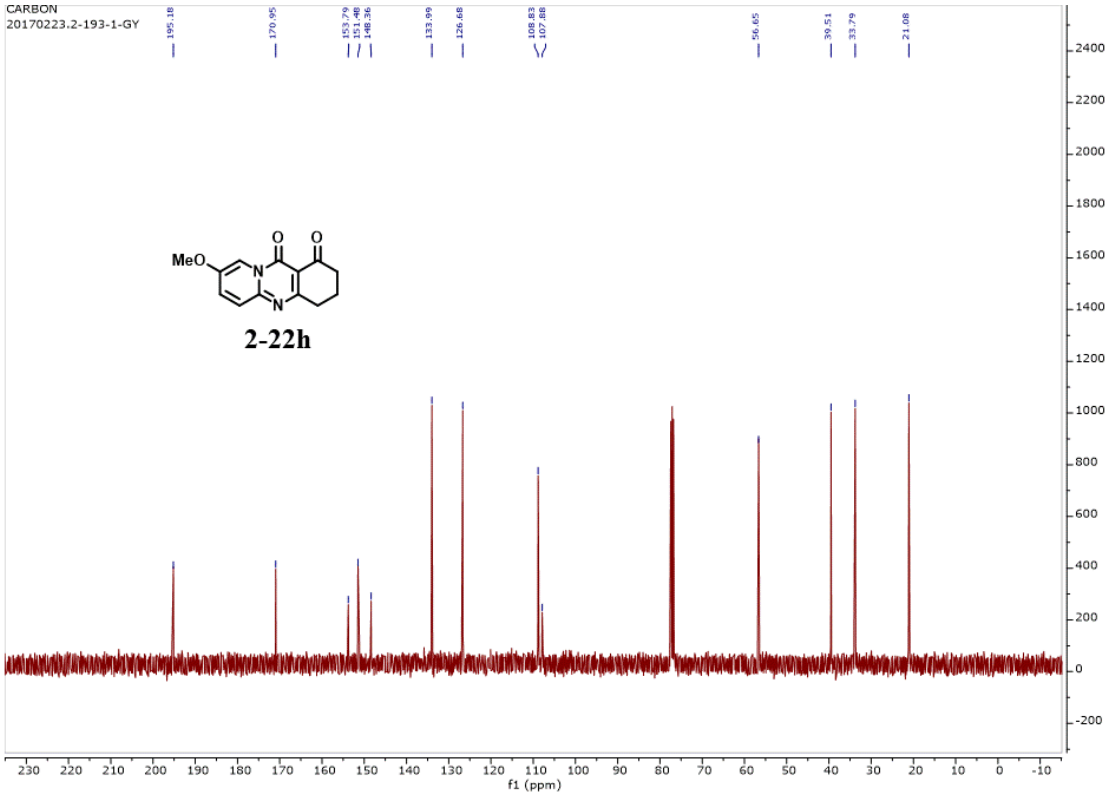
**2-22f**

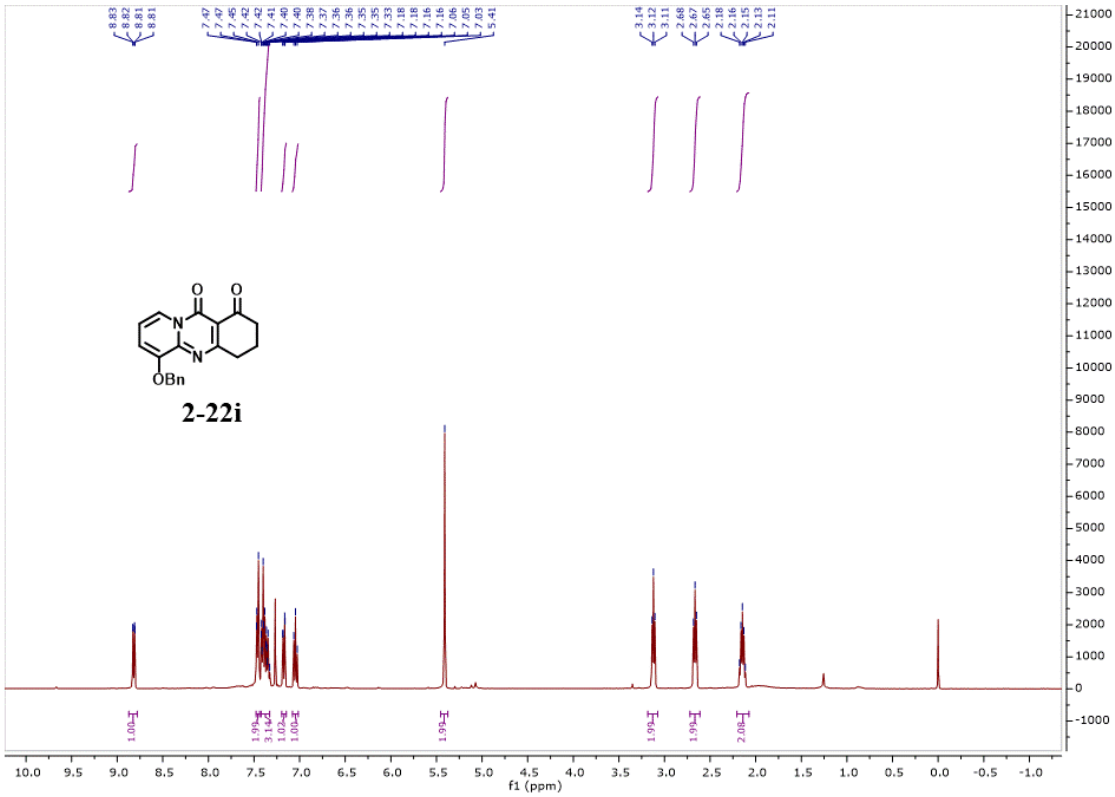

2017-11-02.0954.121.gangyan.2.1d
3-129-1-GY
195.24
173.62
159.90
154.17
151.56
128.67
119.93
115.39
108.03
39.54
34.22
21.17
16.18
12.47
2-22f
f1 (ppm)

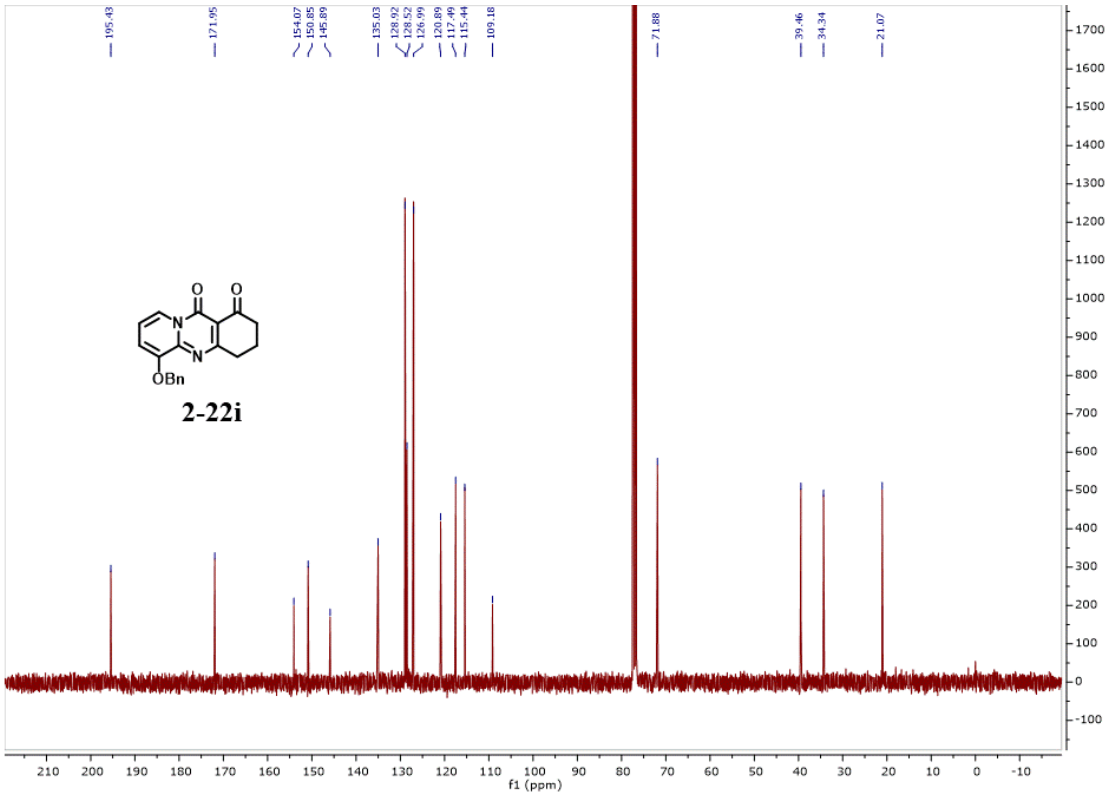

9.08
9.07
6.89
6.88
6.87
6.86
6.85
6.85
4.01
2.96
2.95
2.94
2.65
2.63
2.62
2.14
2.13
2.12
2.10
2.09
H3CO
2-22g
1.06
1.00
1.05
2.94
2.03
2.00
2.17
f1 (ppm)


195.33
173.39
167.98
154.28
153.83
130.50
110.75
107.52
102.56
56.79
39.32
34.07
20.98
H3CO
2-22g
f1 (ppm)

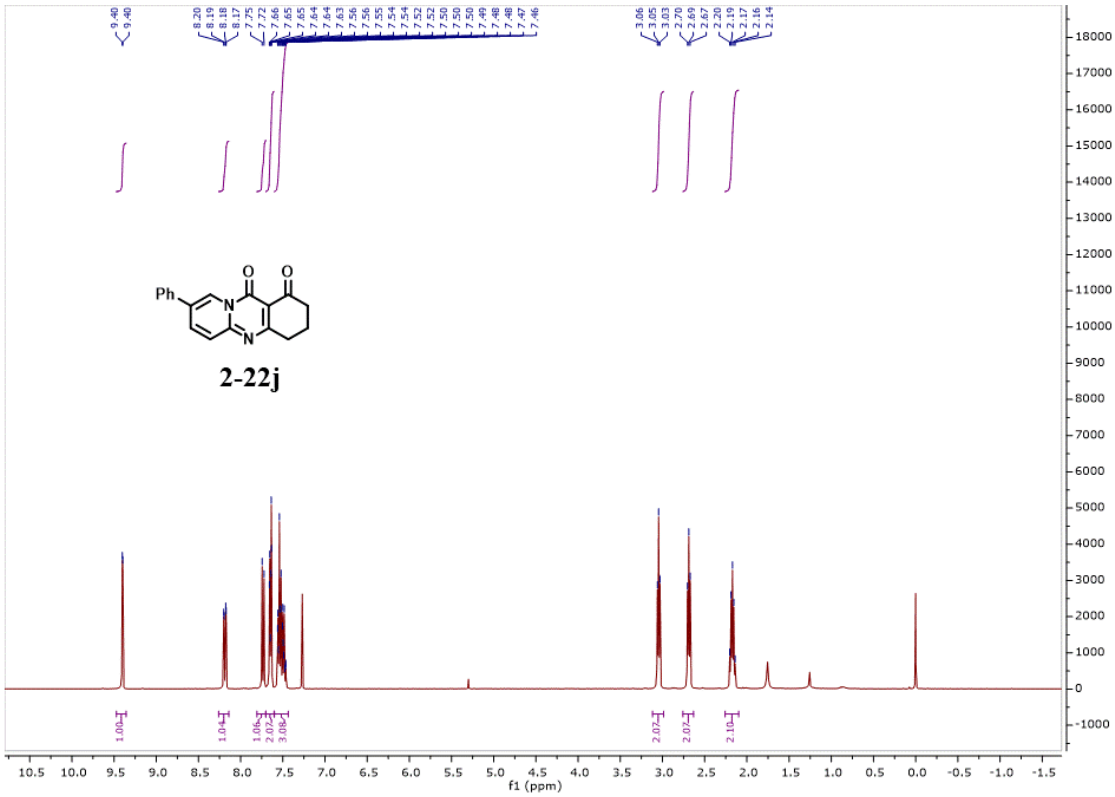

8.72
8.71
7.69
7.69
7.67
7.66
7.61
7.59
3.97
3.02
3.01
2.99
2.68
2.67
2.65
2.18
2.17
2.15
2.13
2.12
MeO
2-22h
0.99
1.00
0.98
3.07
2.08
2.00
2.20
f1 (ppm)


CARBON
20170223.2-193-1-GY
195.18
170.95
153.79
151.48
148.36
133.99
126.68
108.83
107.88
56.65
39.51
33.79
21.08
MeO
O
O
N
N
2-22h
f1 (ppm)

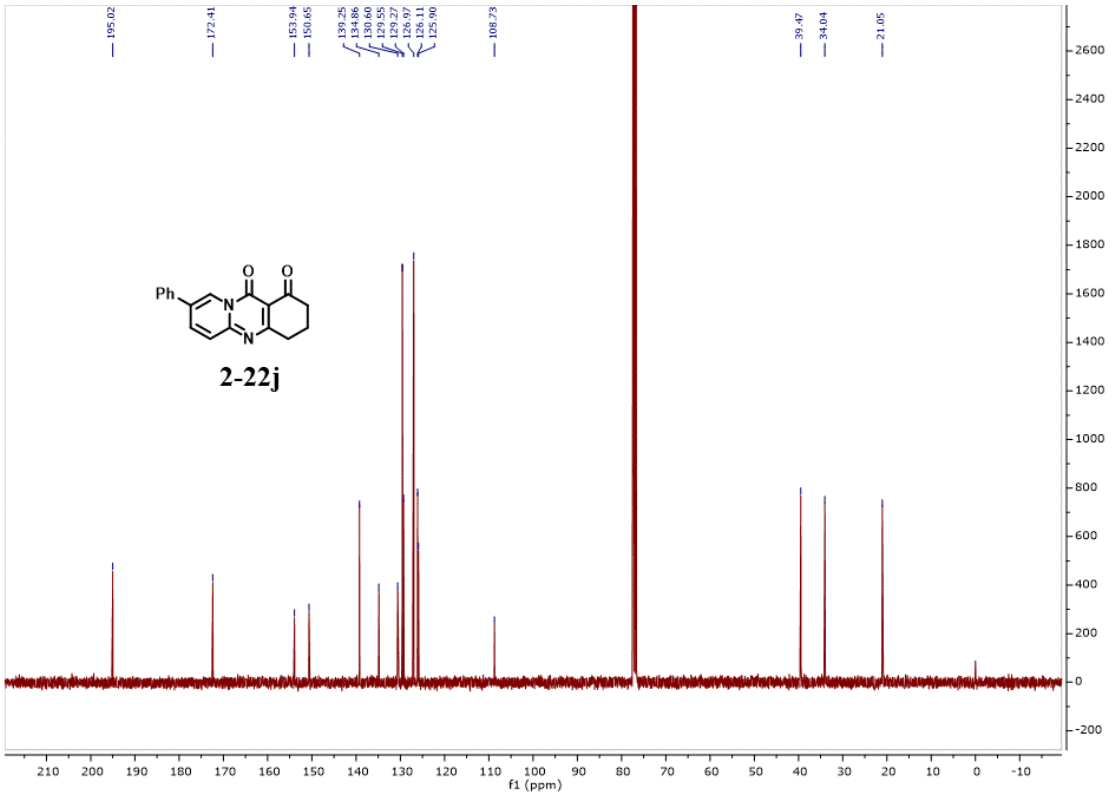

8.83
8.82
8.81
8.81
7.47
7.47
7.45
7.42
7.41
7.40
7.38
7.37
7.36
7.36
7.35
7.33
7.18
7.18
7.16
7.16
7.06
7.05
7.03
5.41
3.14
3.12
3.11
2.68
2.67
2.65
2.18
2.16
2.15
2.13
2.11
1.00
1.94
3.14
1.02
1.00
1.94
1.94
1.94
2.08
O
O
N
N
OBn
2-22i
f1 (ppm)


195.43
171.95
154.07
150.85
145.89
135.03
128.92
128.52
126.99
120.89
117.49
115.44
109.18
71.88
39.46
34.34
21.07
OBn
f1 (ppm)

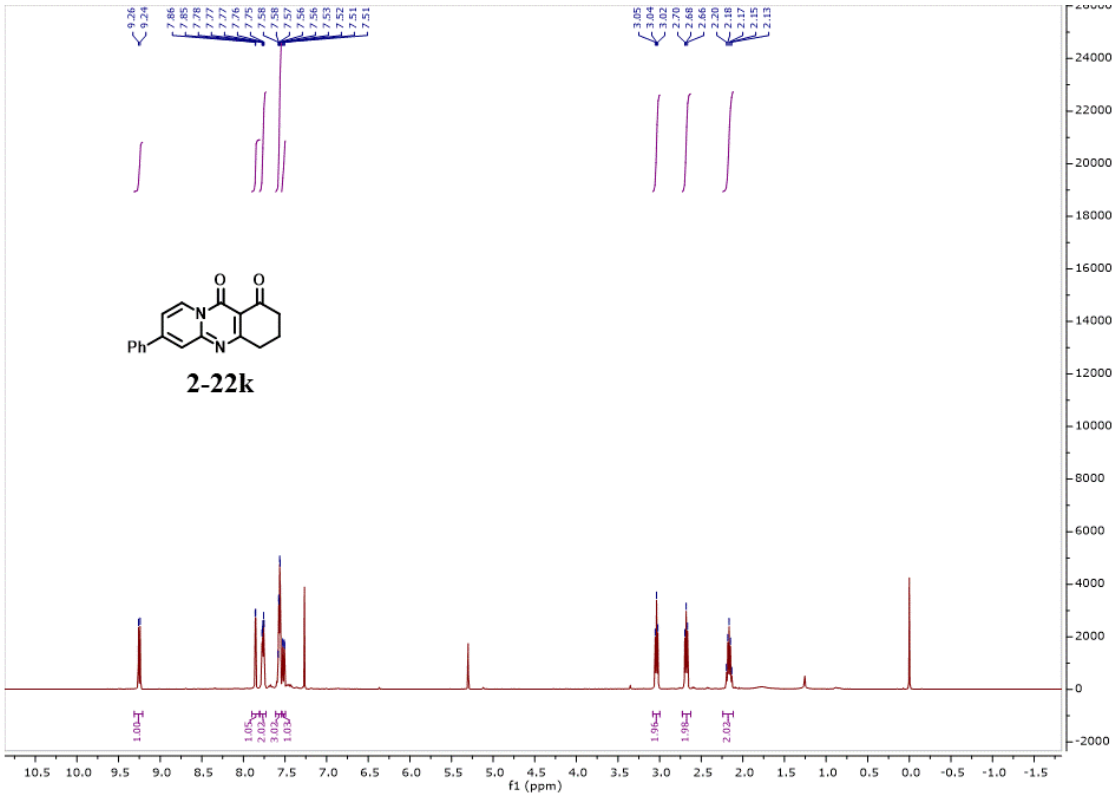
**2-22i**


9.40
8.20
8.19
8.18
8.17
7.75
7.72
7.66
7.65
7.64
7.63
7.56
7.55
7.54
7.52
7.50
7.49
7.48
7.47
7.46
3.06
3.05
3.03
2.70
2.69
2.67
2.20
2.19
2.17
2.16
2.14
Ph
1.00
1.04
1.06
2.02
3.08
2.07
2.07
2.10
f1 (ppm)

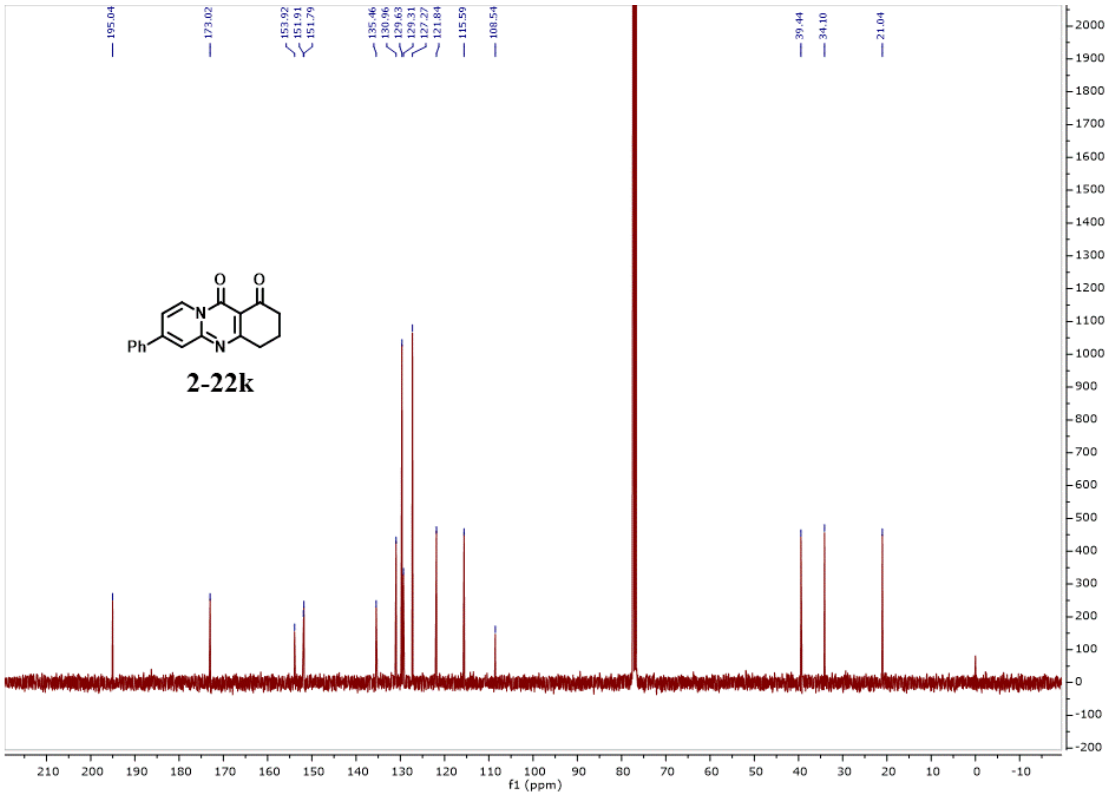
**2-22j**


195.02
172.41
153.94
150.65
139.25
134.86
130.60
129.55
129.27
126.97
126.11
125.90
108.73
39.47
34.04
21.05
Ph
O
O
N
N
f1 (ppm)

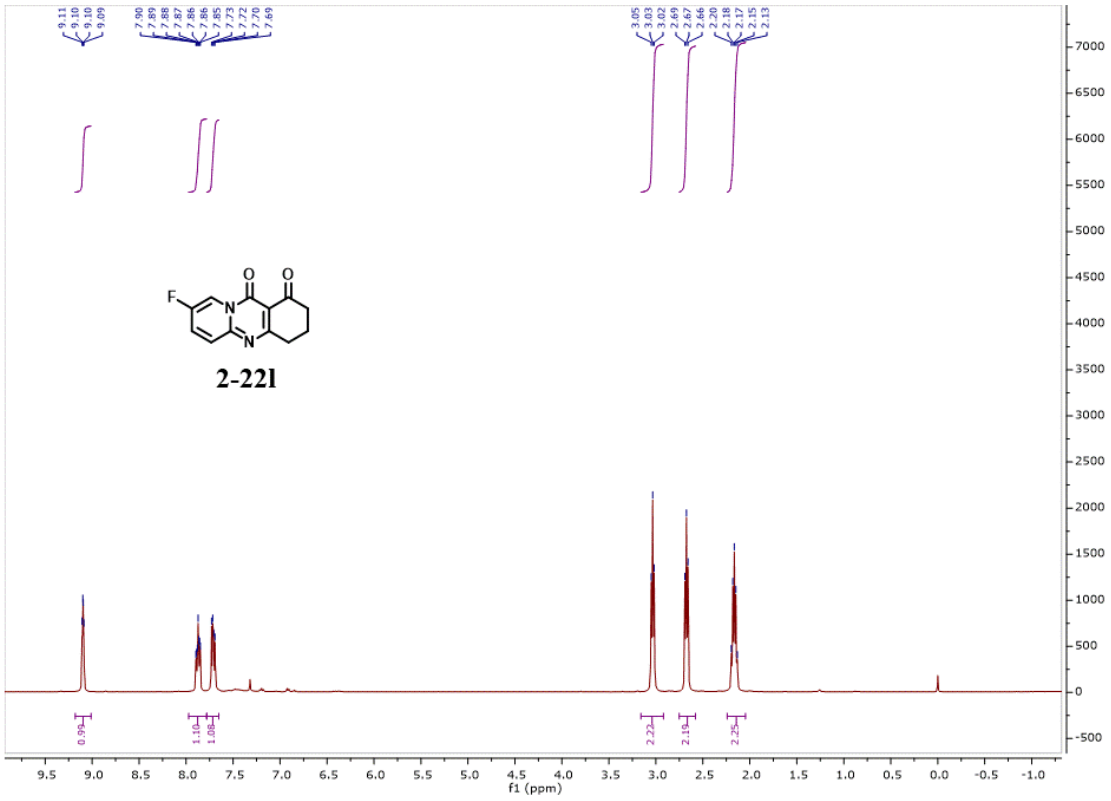
**2-22j**


9.26
9.24
7.86
7.85
7.78
7.77
7.77
7.76
7.75
7.58
7.57
7.56
7.53
7.52
7.51
7.51
3.05
3.04
3.02
2.70
2.68
2.66
2.20
2.18
2.17
2.15
2.13
1.00
1.05
2.02
3.02
1.03
1.96
1.98
2.02
Ph
O
O
N
N
f1 (ppm)

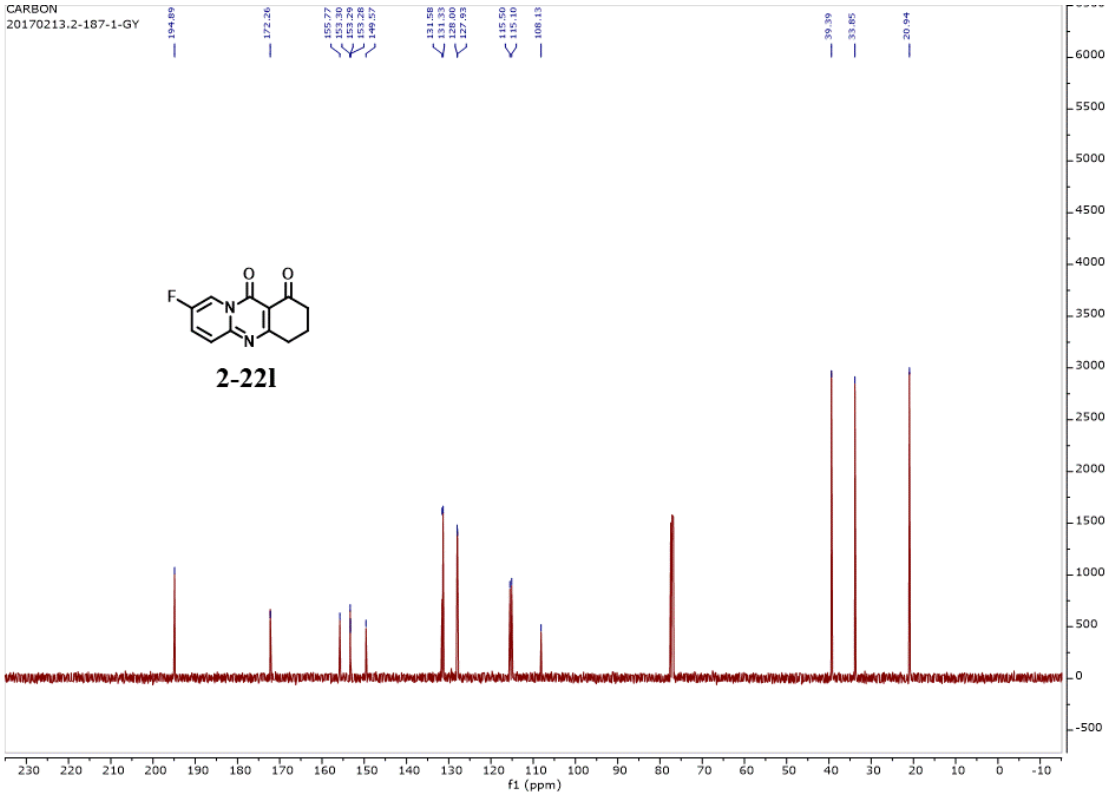
**2-22k**

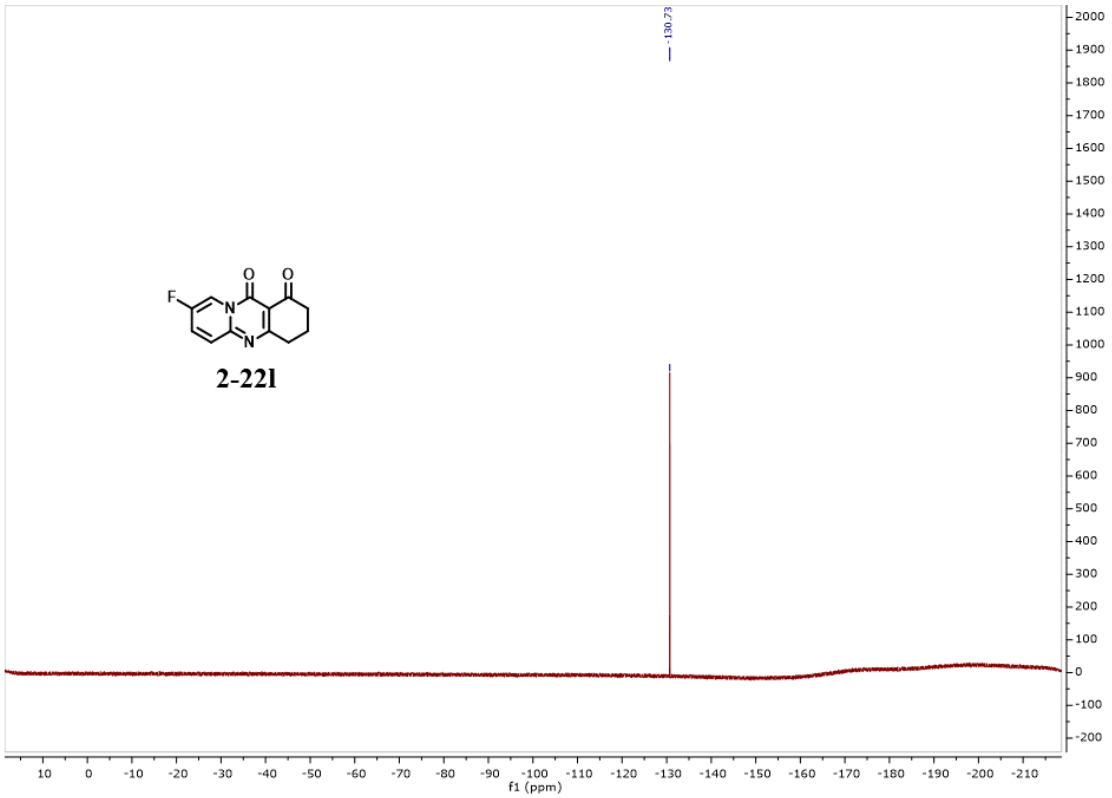

195.04
173.02
153.92
151.91
151.79
135.46
130.96
129.65
129.31
127.27
121.84
115.59
108.54
39.44
34.10
21.04
Ph
f1 (ppm)

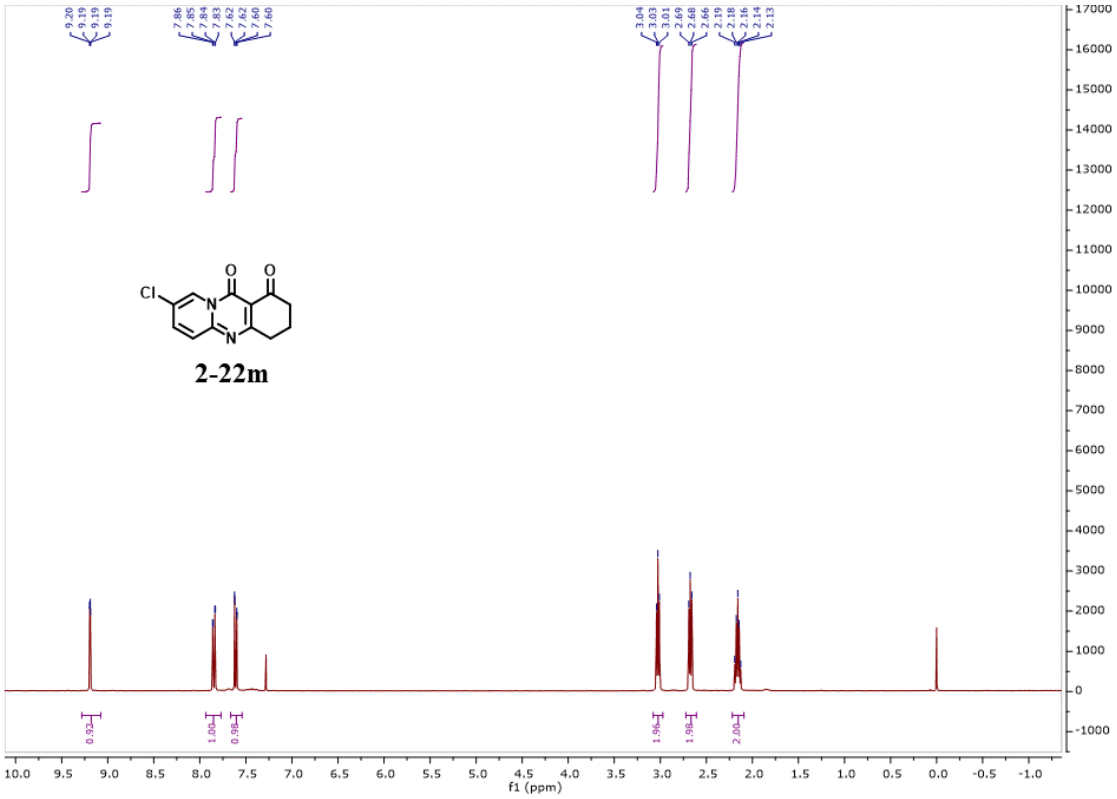
**2-22k**

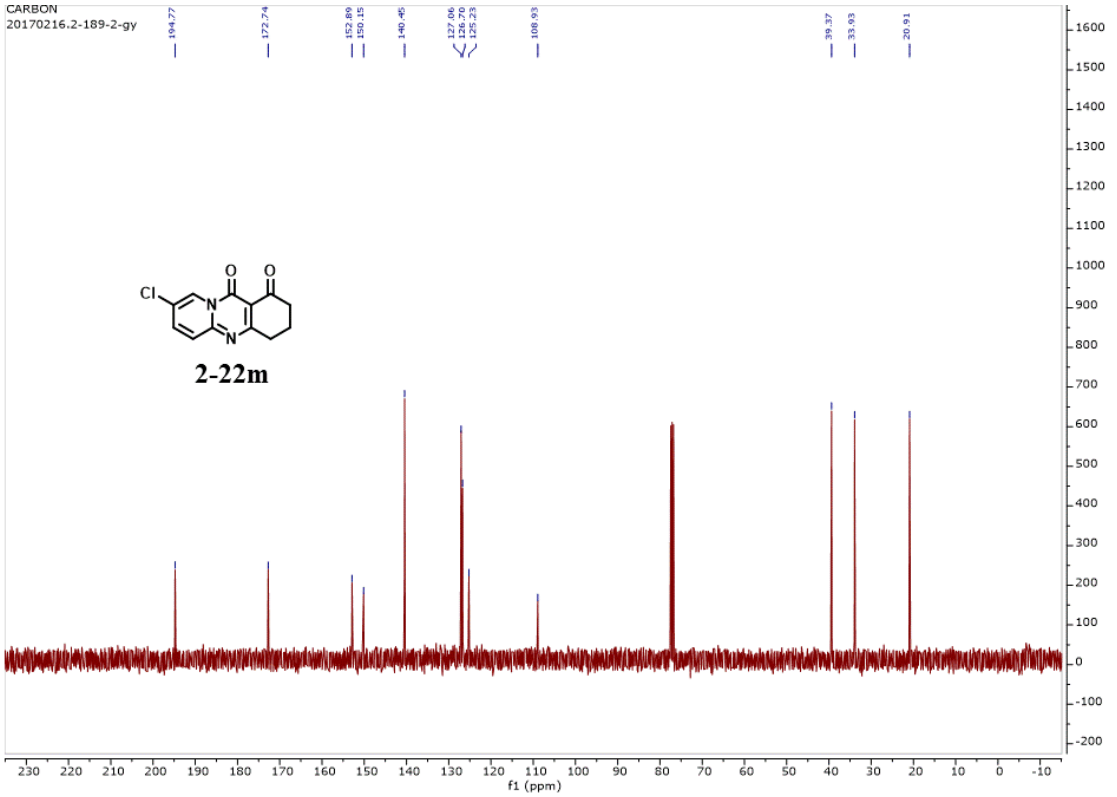

9.11
9.10
9.10
9.09
7.90
7.89
7.88
7.87
7.86
7.86
7.85
7.73
7.72
7.70
7.69
3.05
3.03
3.02
2.69
2.67
2.66
2.20
2.18
2.17
2.15
2.13
F
0.99
1.10
1.08
2.22
2.19
2.25
f1 (ppm)

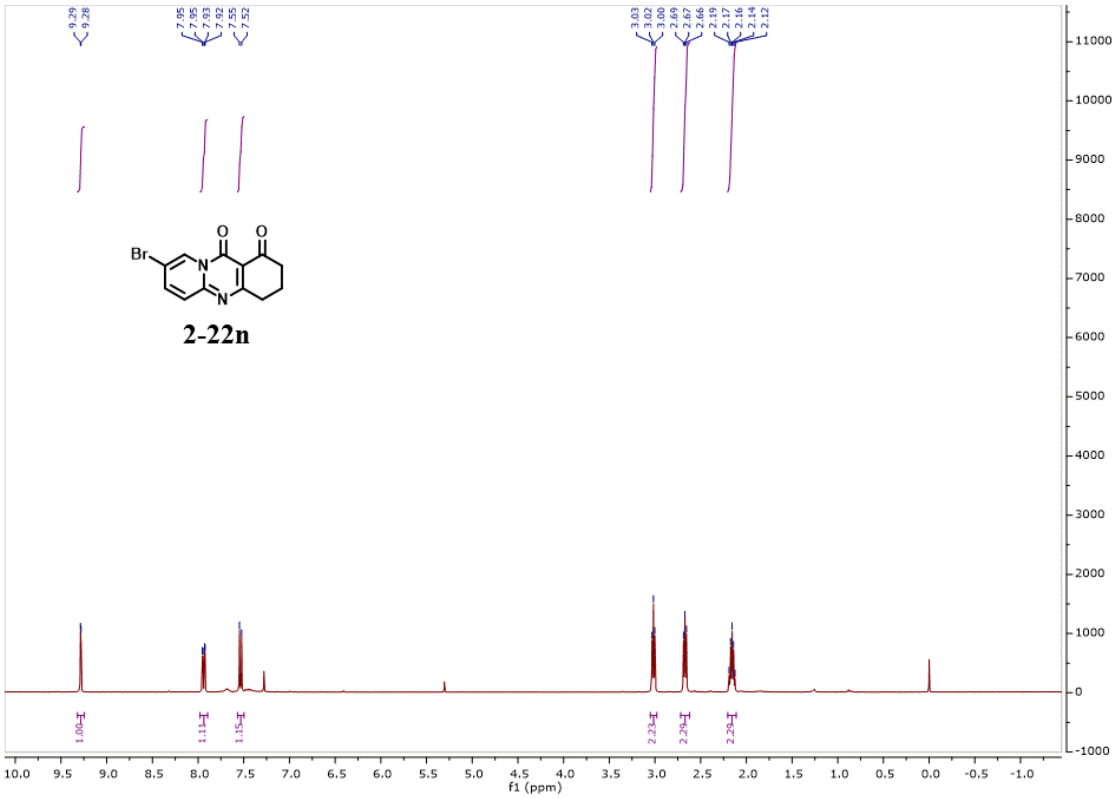
**2-22l**

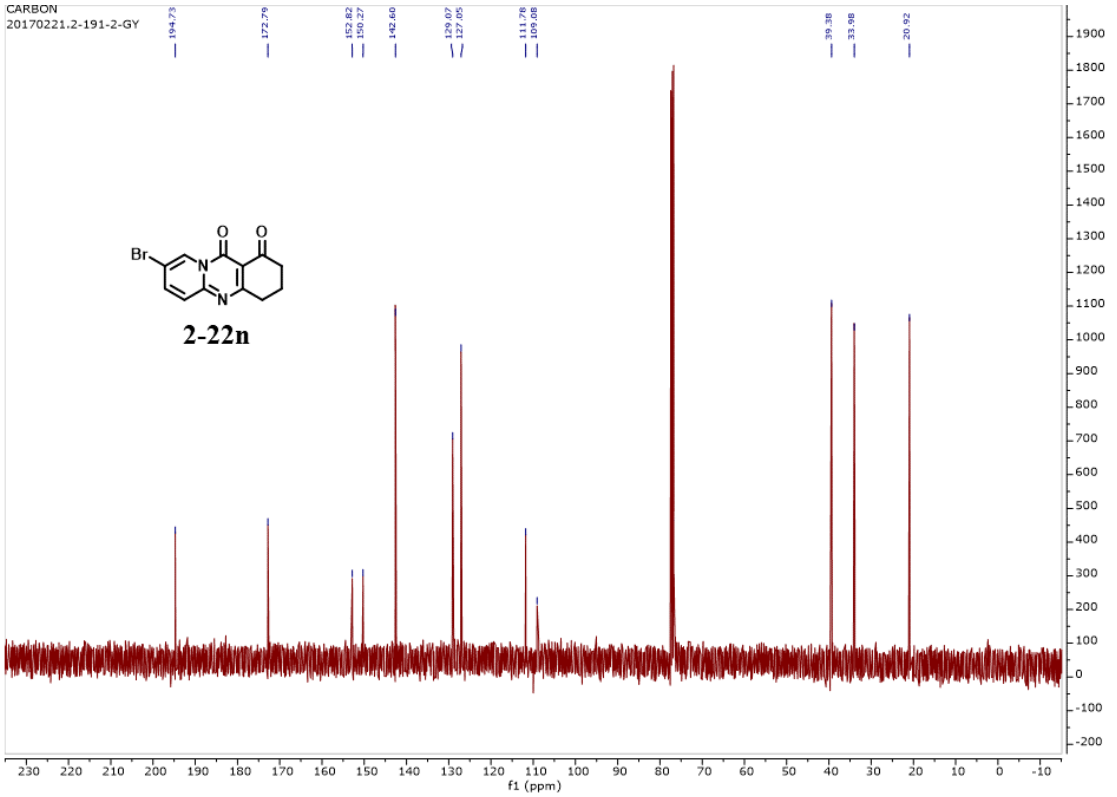

CARBON
20170213.2-187-1-GY
194.89
172.26
155.77
153.30
153.29
153.28
149.57
131.58
131.35
128.00
127.93
115.50
115.10
108.13
39.39
33.85
20.94
F
O
O
N
N
2-22l
f1 (ppm)

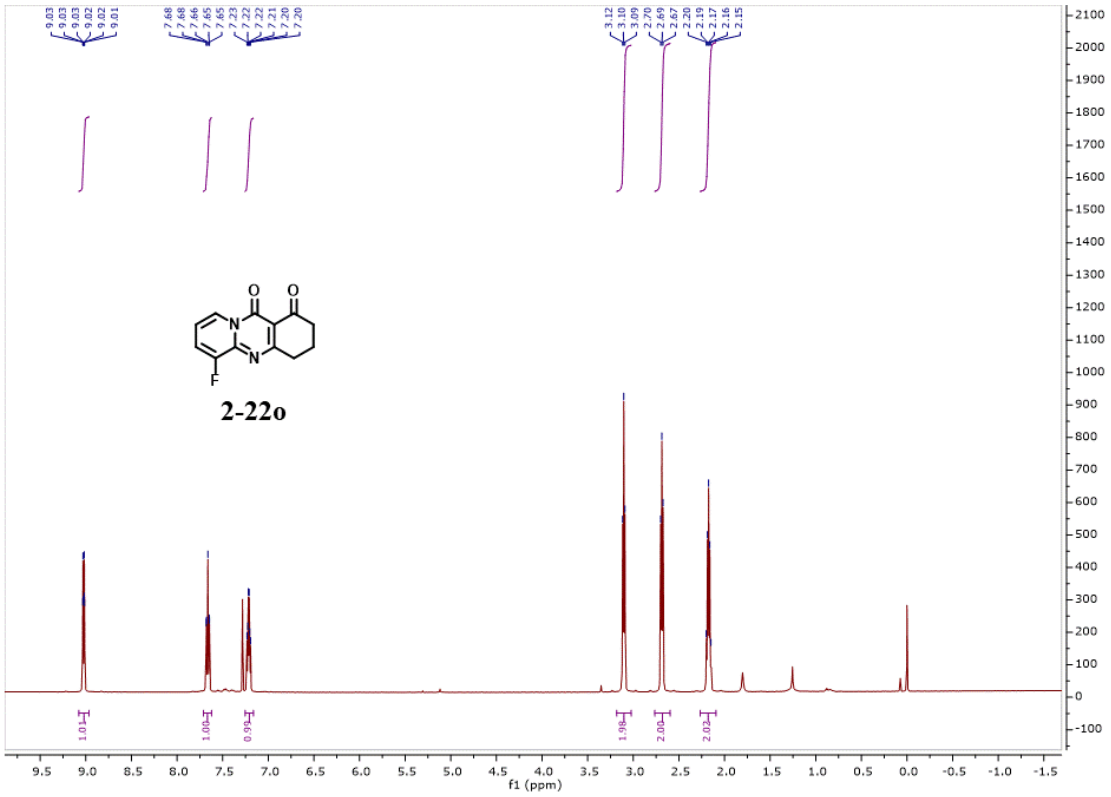

-130.73
F
O
O
N
N
2-22l
f1 (ppm)

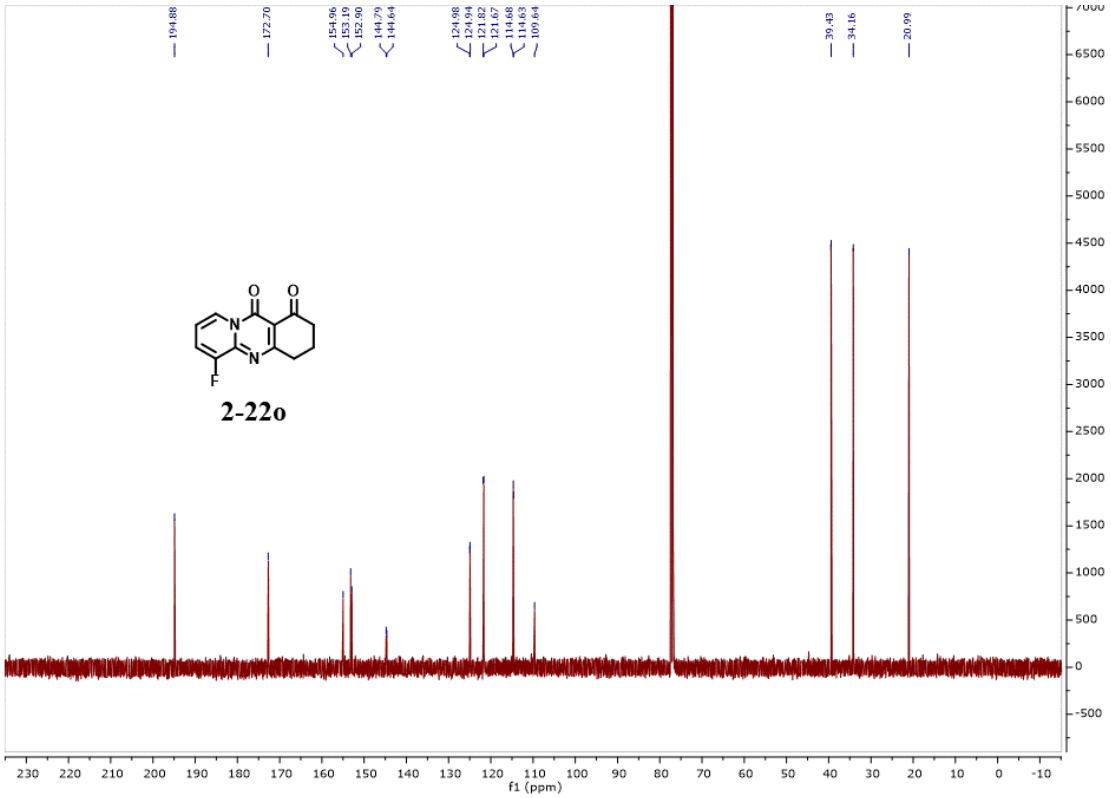

9.20
9.19
9.19
9.19
7.86
7.85
7.84
7.83
7.62
7.62
7.60
7.60
3.04
3.03
3.01
2.69
2.68
2.66
2.19
2.18
2.16
2.14
2.13
Cl
O
O
N
N
2-22m
0.92
1.00
0.98
1.96
1.98
2.00
f1 (ppm)

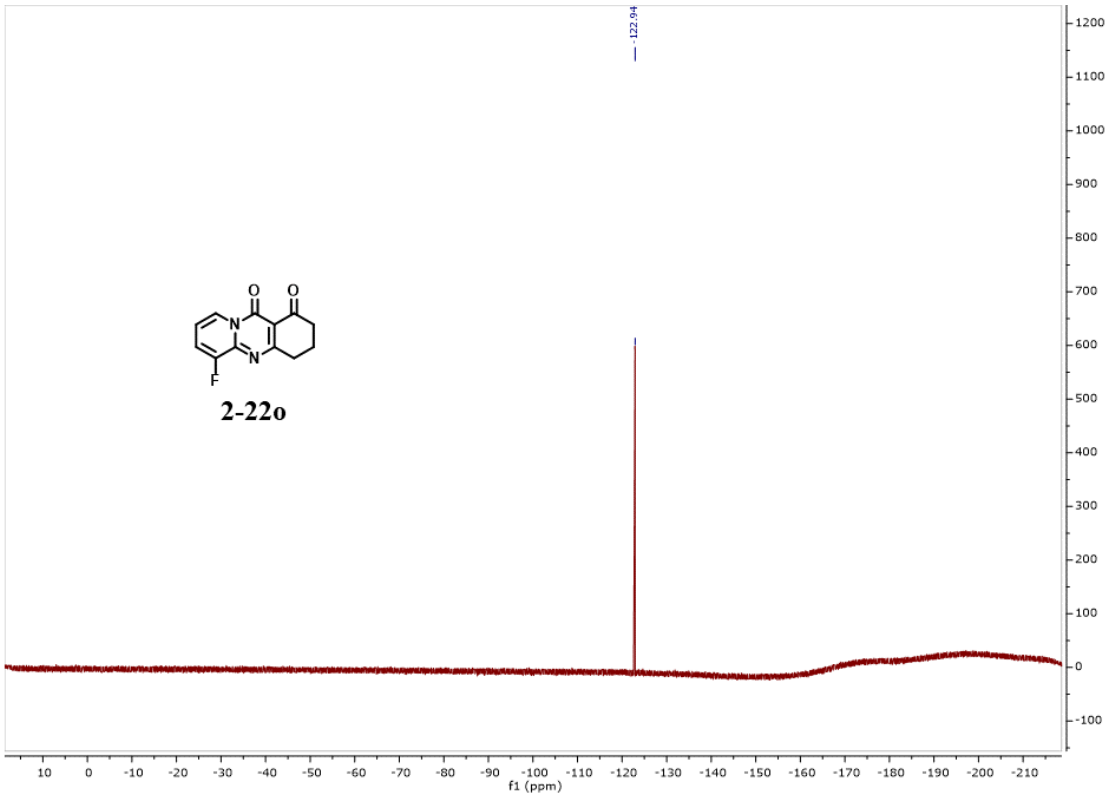

CARBON
20170216.2-189-2-gy
194.77
172.74
152.89
150.15
140.45
127.06
126.70
125.23
108.93
39.37
33.93
20.91
Cl
O
O
N
N
2-22m
f1 (ppm)


9.29
9.28
7.95
7.95
7.93
7.92
7.55
7.52
3.03
3.02
3.00
2.69
2.67
2.66
2.19
2.17
2.16
2.14
2.12
Br
O
O
N
N
2-22n
1.00
1.11
1.15
2.23
2.29
2.29
f1 (ppm)

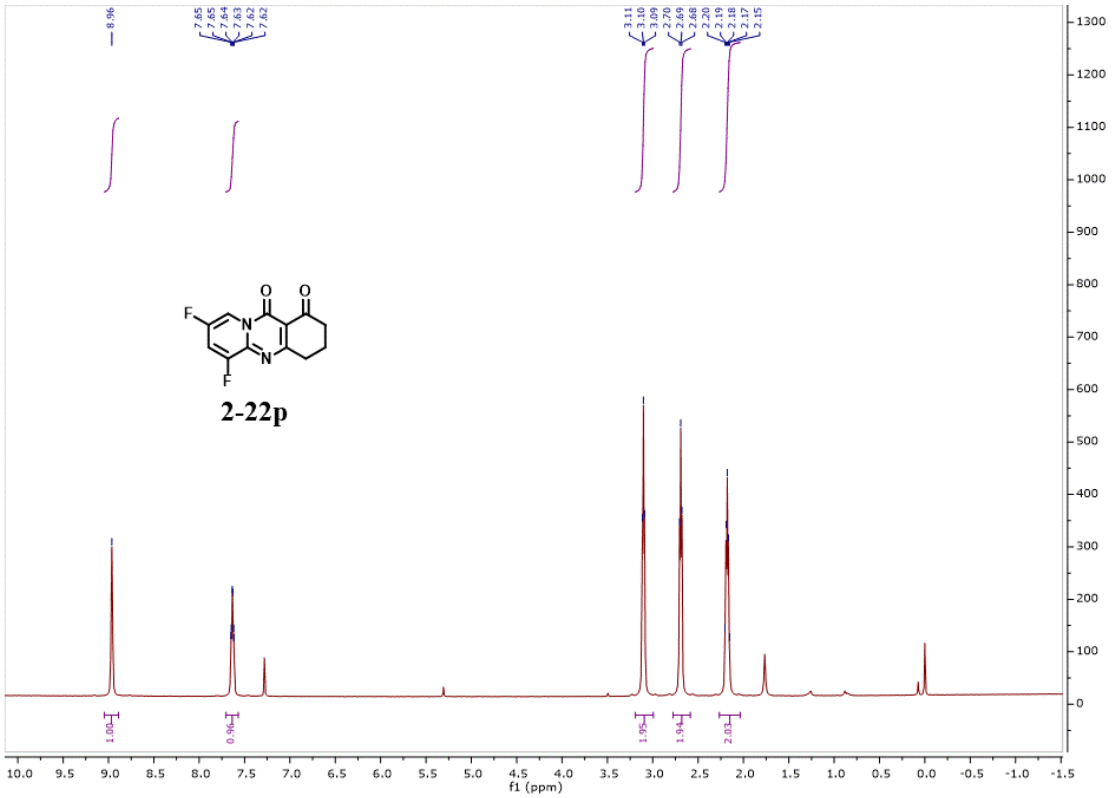

CARBON
20170221.2-191-2-GY
194.73
172.79
152.82
150.27
142.60
129.07
127.05
111.76
109.08
39.38
33.98
20.92
Br
O
O
N
N
2-22n
f1 (ppm)


9.03
9.03
9.03
9.02
9.02
9.01
7.68
7.68
7.66
7.65
7.65
7.23
7.22
7.22
7.21
7.20
7.20
3.12
3.10
3.09
2.70
2.69
2.67
2.20
2.19
2.17
2.16
2.15
O
O
N
N
F
2-22o
1.01
1.00
0.99
1.98
2.00
2.02
f1 (ppm)

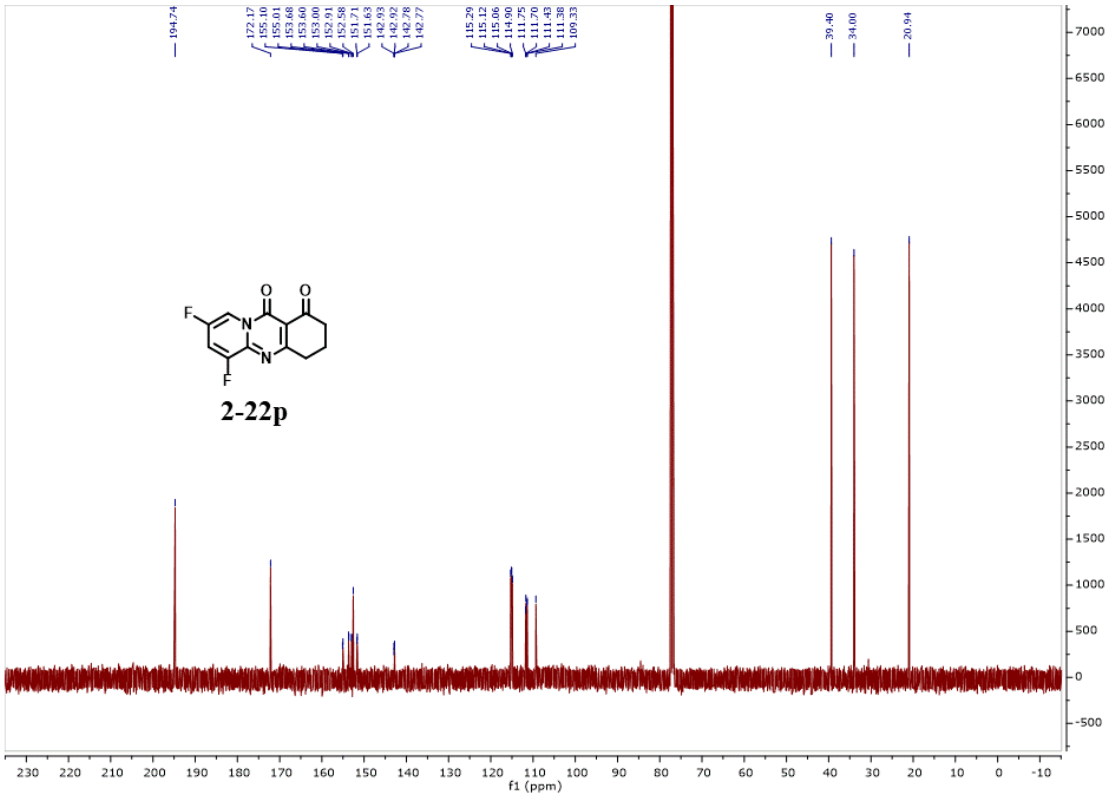

194.88
172.70
154.96
153.19
152.90
144.79
144.64
124.98
124.94
121.82
121.67
114.68
114.63
109.64
39.43
34.16
20.99
O
O
N
N
F
2-22o
f1 (ppm)

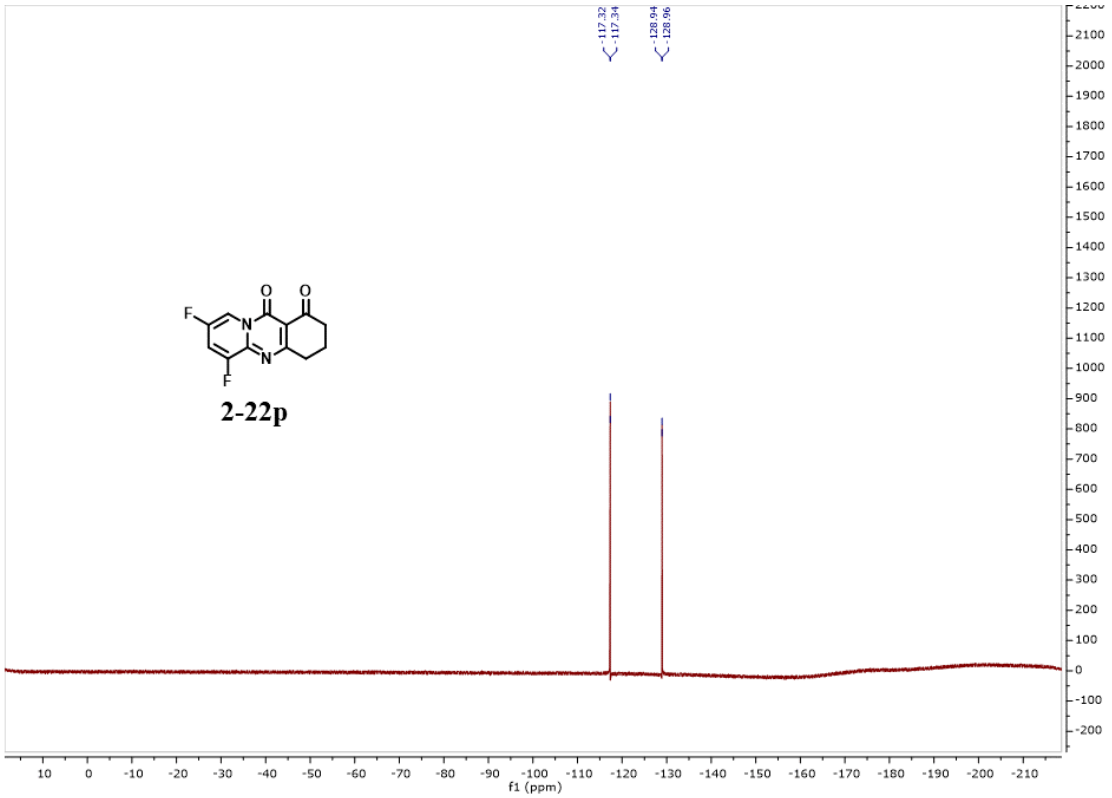

-122.94
f1 (ppm)

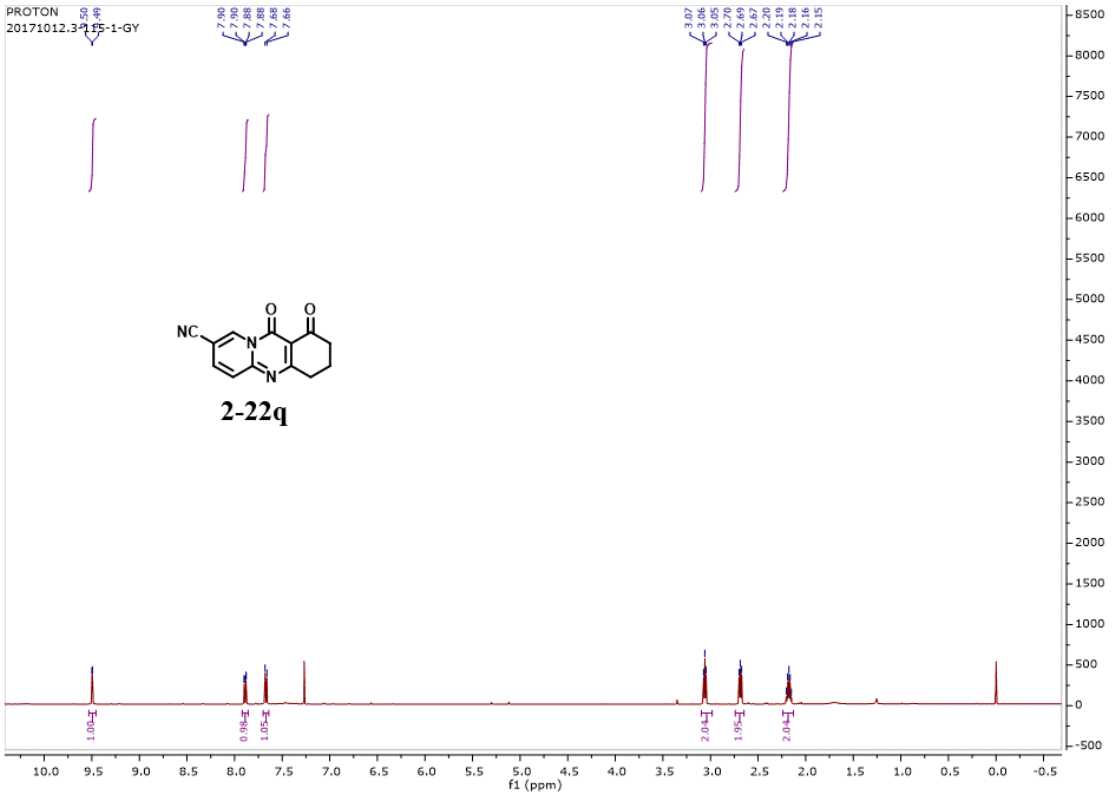
2-22o

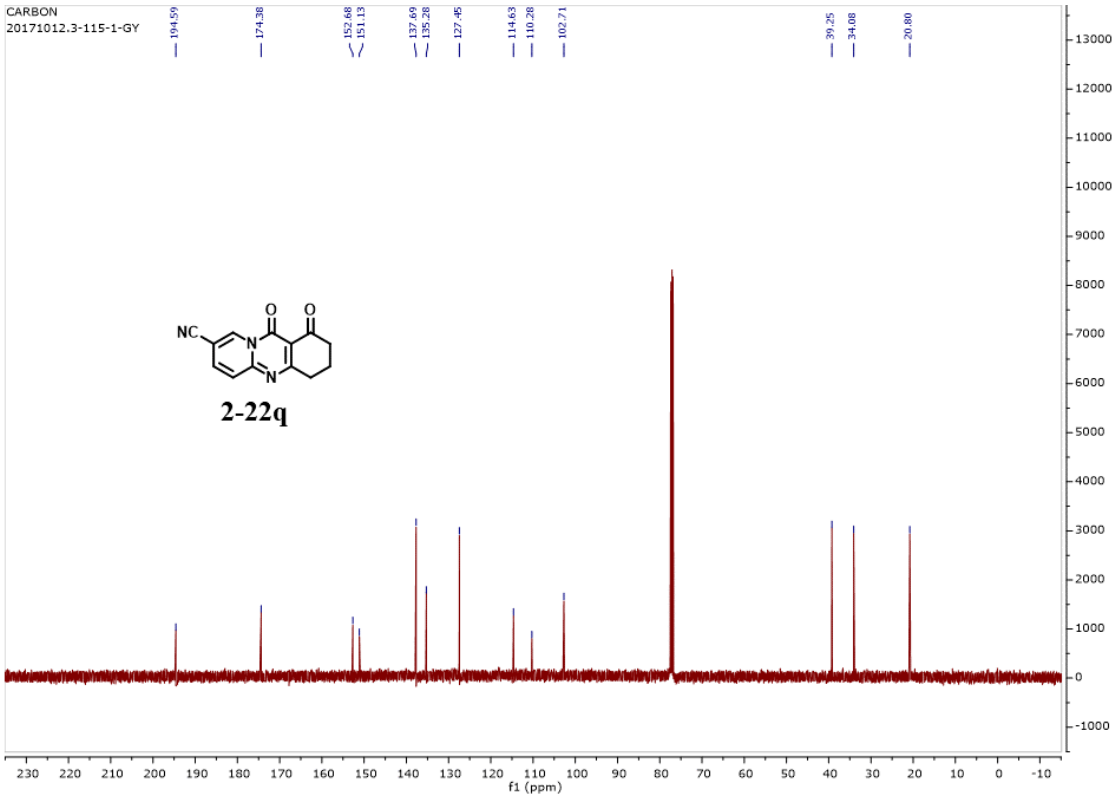

8.96
7.65
7.65
7.64
7.63
7.62
7.62
3.11
3.10
3.09
2.70
2.69
2.68
2.20
2.19
2.18
2.17
2.15
1.00
0.96
1.95
1.94
2.03
f1 (ppm)

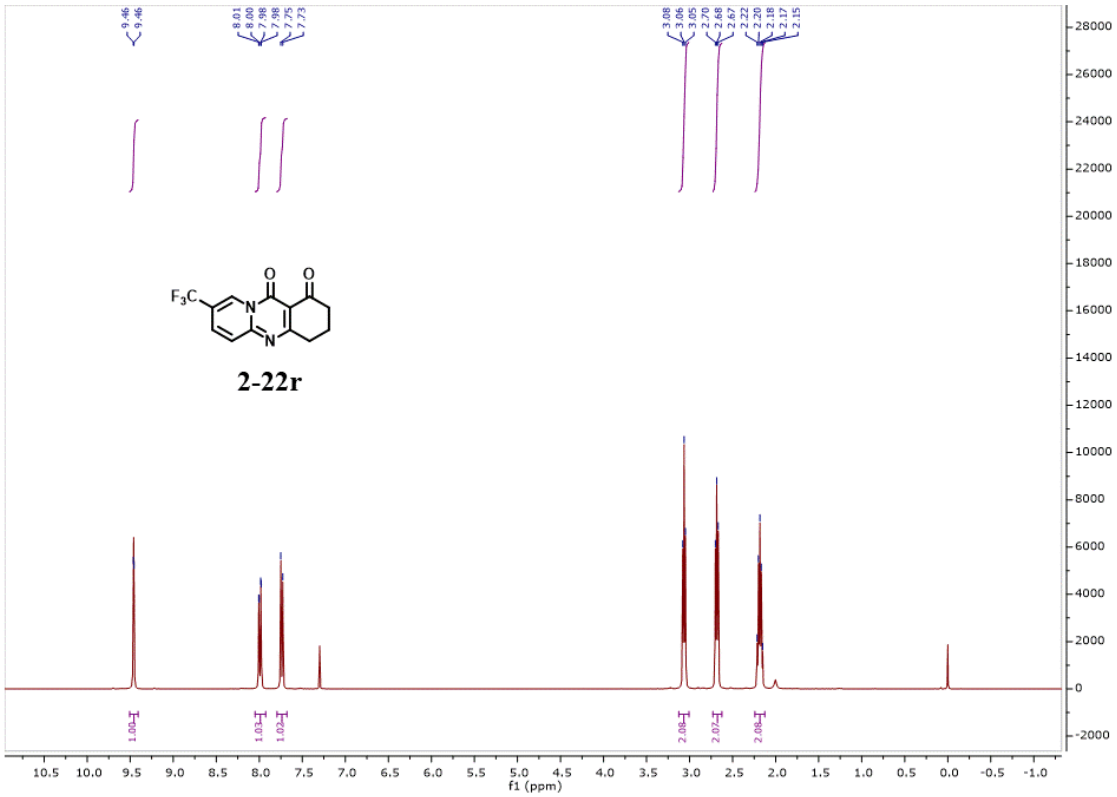
2-22p

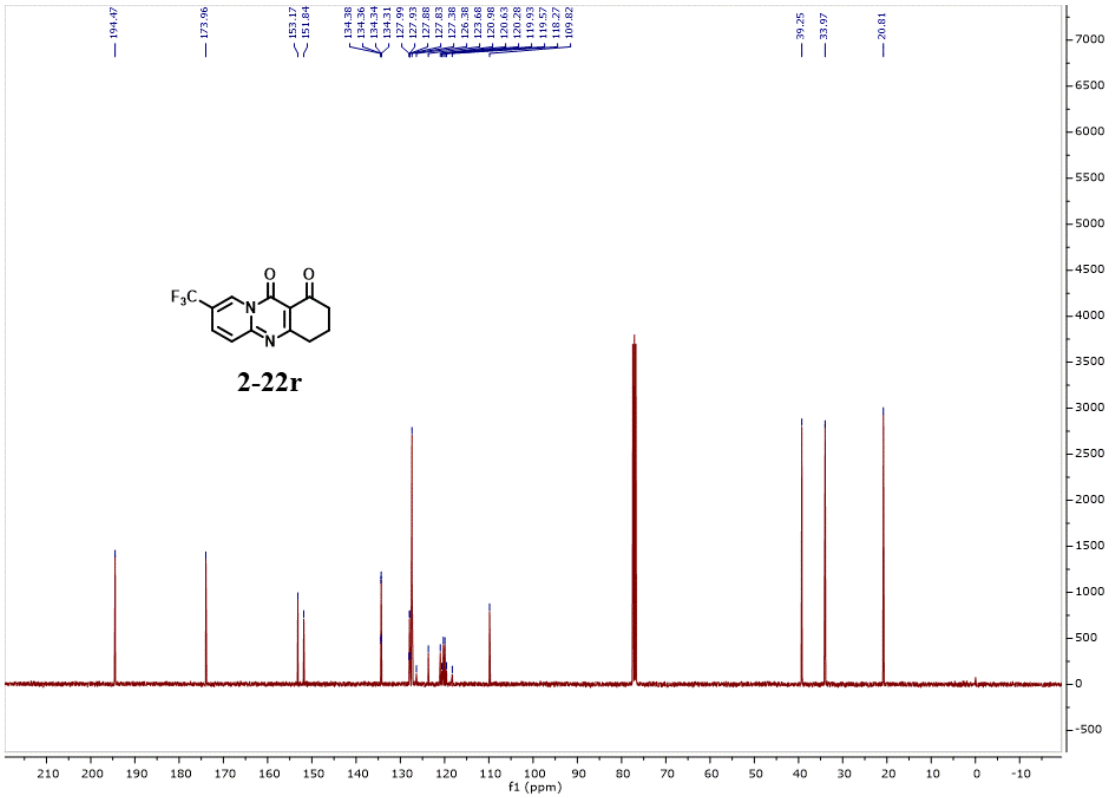

194.74
172.17
155.10
155.01
153.68
153.60
153.00
152.91
152.58
151.71
151.63
142.93
142.92
142.78
142.77
115.29
115.12
115.06
114.90
111.75
111.70
111.43
111.38
109.33
39.40
34.00
20.94
F
O
O
N
N
F
2-22p
f1 (ppm)

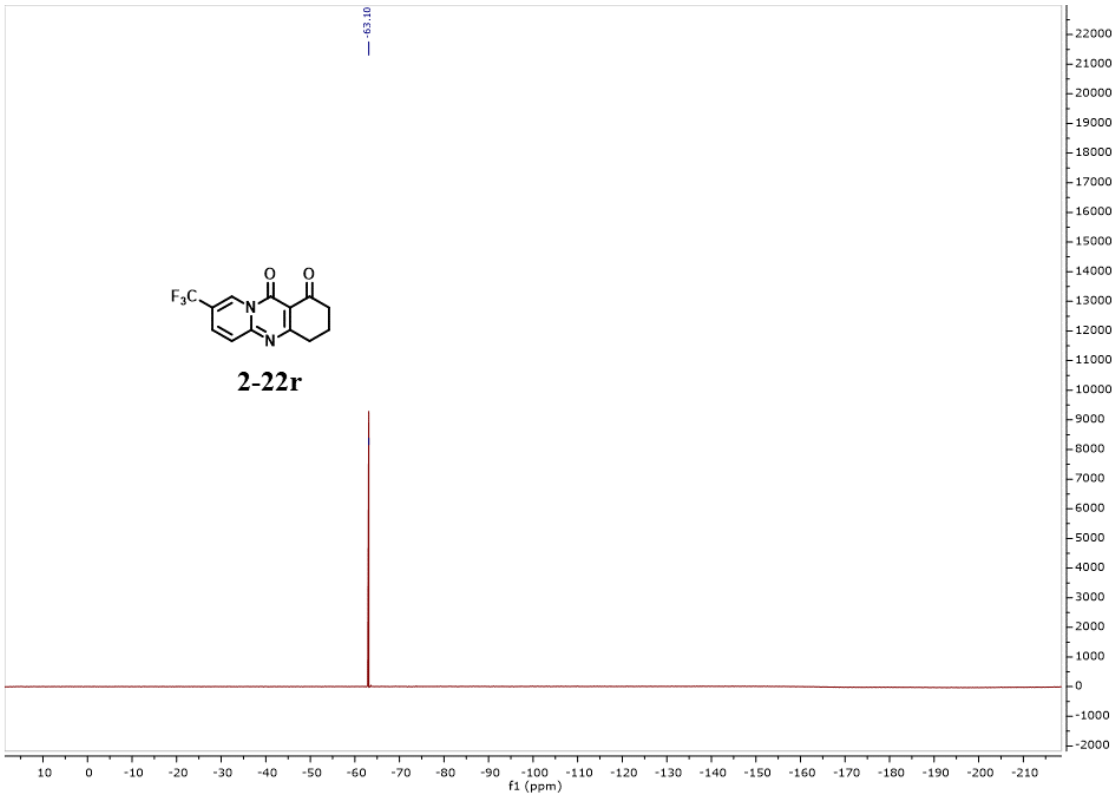

-117.32
-117.34
-128.94
-128.96
F
O
O
N
N
F
2-22p
f1 (ppm)

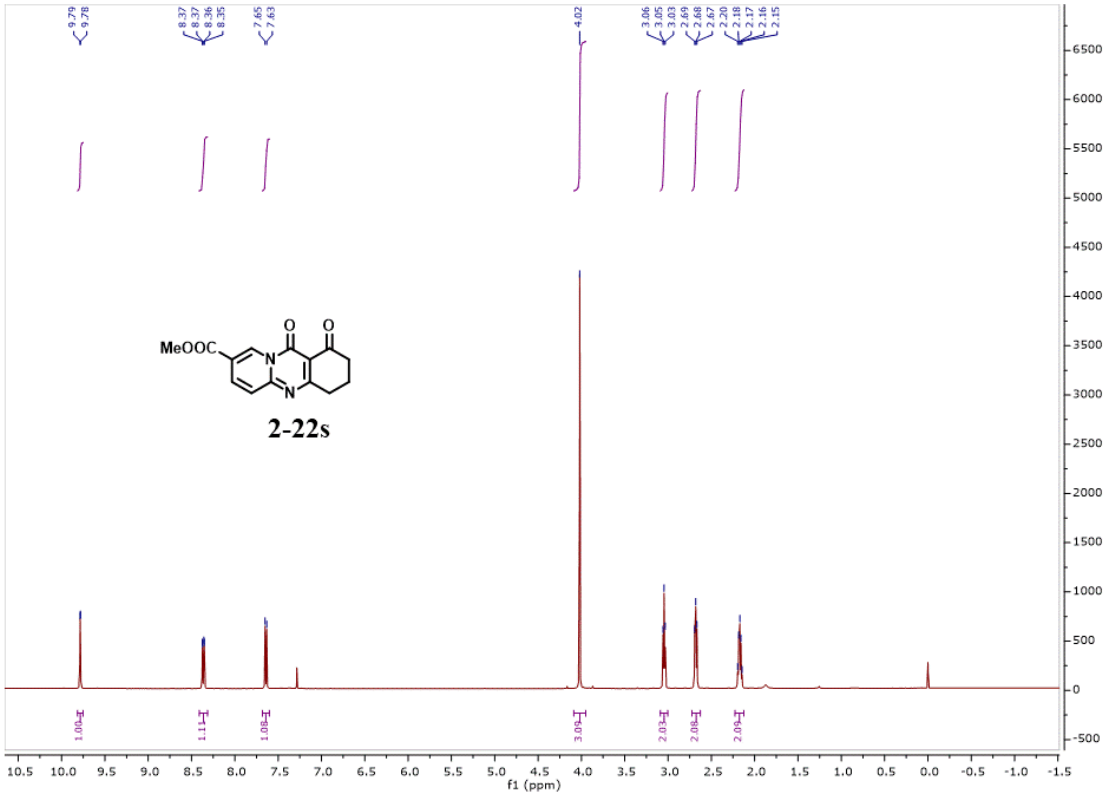

PROTON
20171012.3-115-1-GY
7.90
7.90
7.88
7.88
7.86
7.86
3.07
3.06
3.05
2.70
2.69
2.67
2.20
2.19
2.18
2.16
2.15
NC
O
O
N
N
2-22q
1.00
0.98
1.05
2.04
1.95
2.04
f1 (ppm)

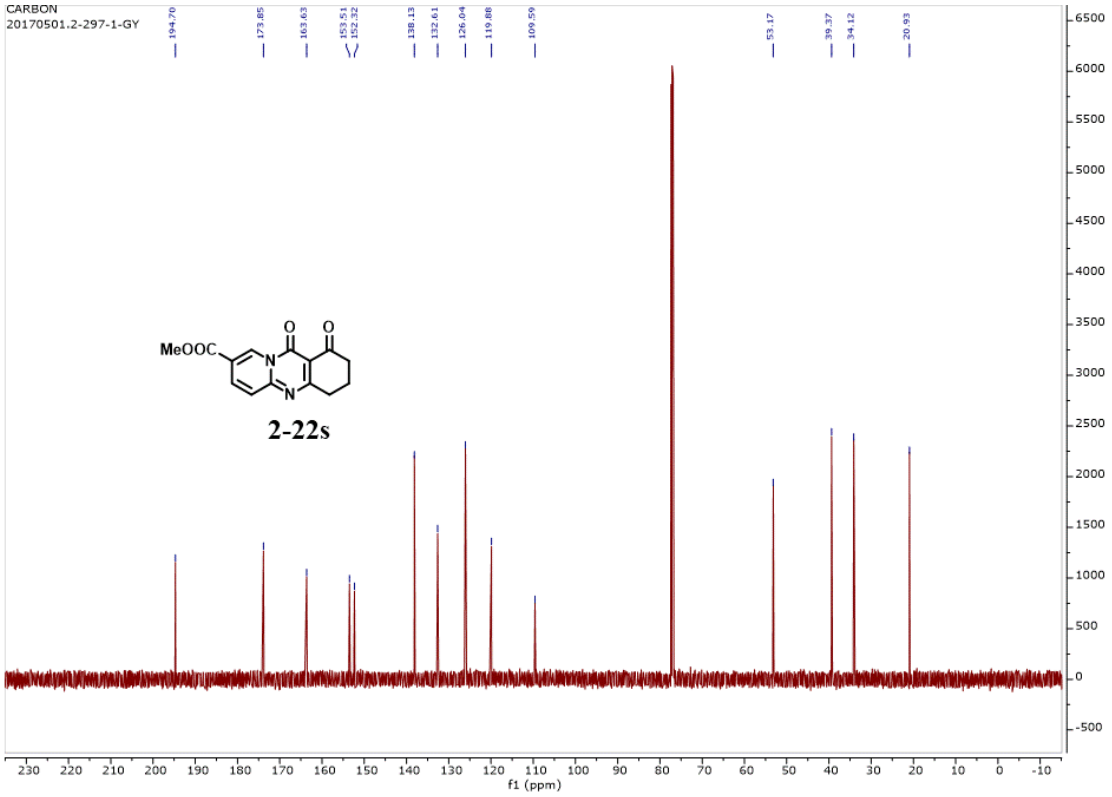

CARBON
20171012.3-115-1-GY
194.59
174.38
152.68
151.13
137.69
135.28
127.45
114.63
110.28
102.71
39.25
34.08
20.80
NC
O
O
N
N
2-22q
f1 (ppm)


9.46
9.46
8.01
8.00
7.98
7.98
7.75
7.73
3.08
3.06
3.06
3.05
2.70
2.68
2.67
2.22
2.20
2.18
2.17
2.15
F3C
O
O
N
N
2-22r
1.00
1.03
1.02
2.08
2.07
2.08
f1 (ppm)

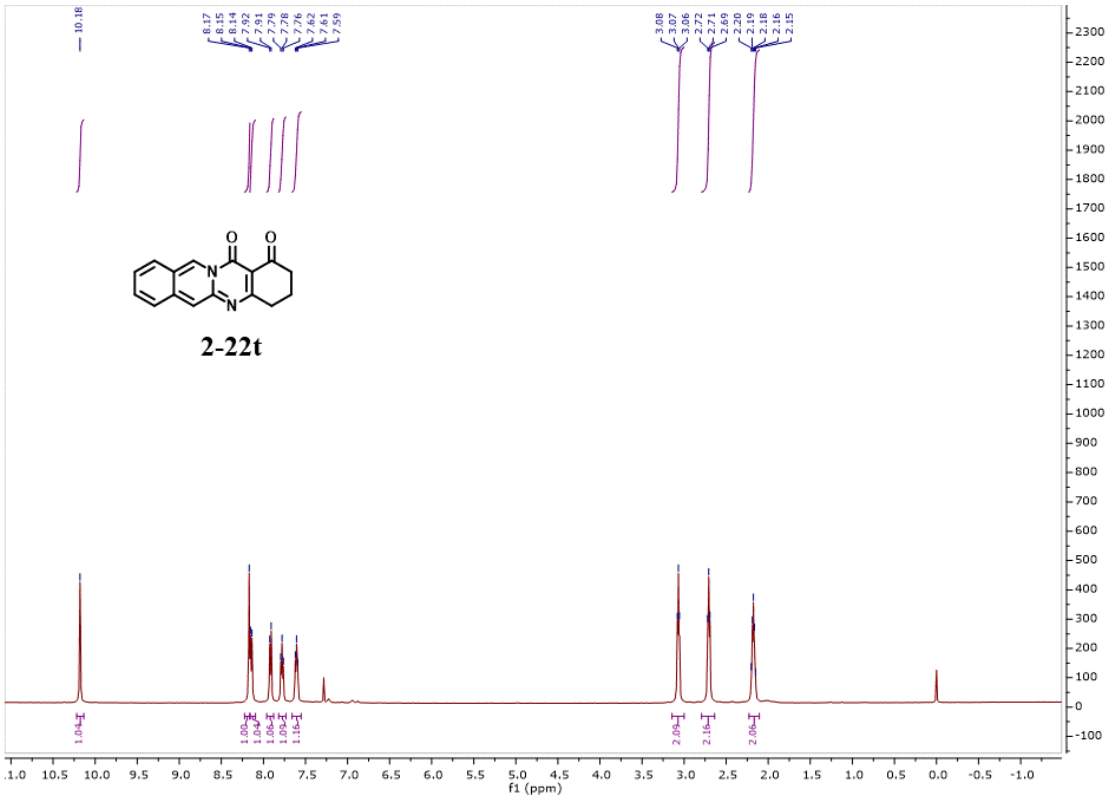

194.47
173.96
153.17
151.84
134.38
134.36
134.34
134.31
127.99
127.93
127.88
127.83
127.38
126.38
123.68
120.98
120.63
120.28
119.93
119.57
118.27
109.82
39.25
33.97
20.81
F3C
O
O
N
N
2-22r
f1 (ppm)


-63.10
F3C
O
O
N
N
2-22r
f1 (ppm)

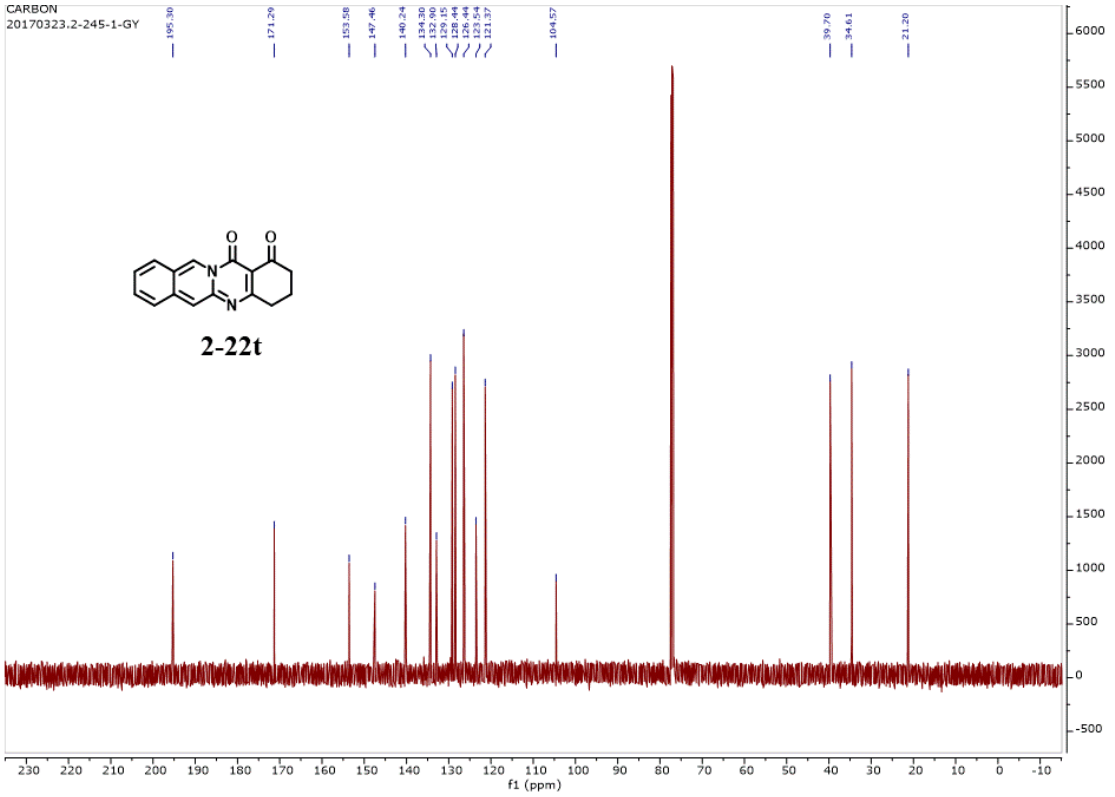

9.79
9.78
8.37
8.37
8.36
8.35
7.65
7.63
4.02
3.06
3.05
3.03
2.69
2.68
2.67
2.20
2.18
2.17
2.16
2.15
MeOOC
O
O
N
N
2-22s
1.00
1.11
1.08
3.09
2.03
2.08
2.09
f1 (ppm)


CARBON
20170501.2-297-1-GY
194.70
173.85
163.63
153.51
152.32
138.13
132.61
126.04
119.88
109.59
53.17
39.37
34.12
20.93
MeOOC
O
O
N
N
f1 (ppm)

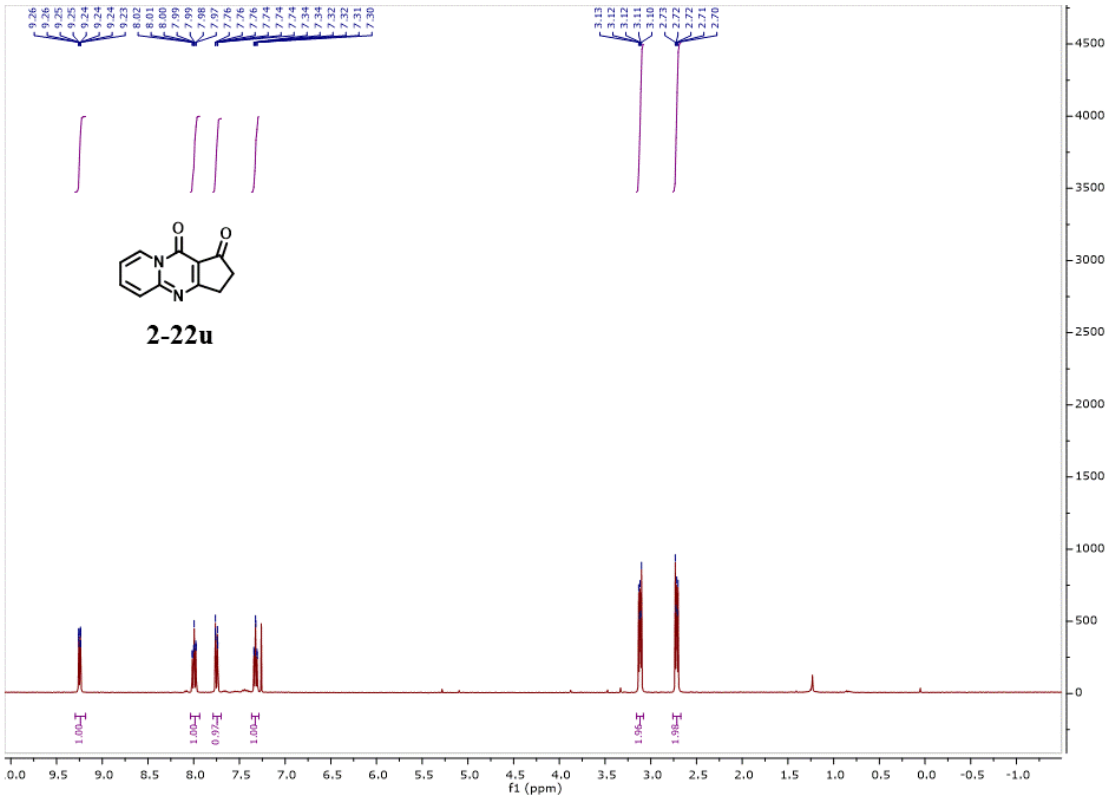
2-22s


10.18
8.17
8.15
8.14
7.92
7.91
7.79
7.78
7.76
7.62
7.61
7.59
3.08
3.07
3.06
2.72
2.71
2.69
2.20
2.19
2.18
2.16
2.15
1.04
1.05
1.04
1.06
1.09
1.16
2.09
2.16
2.06
O
O
N
N
f1 (ppm)

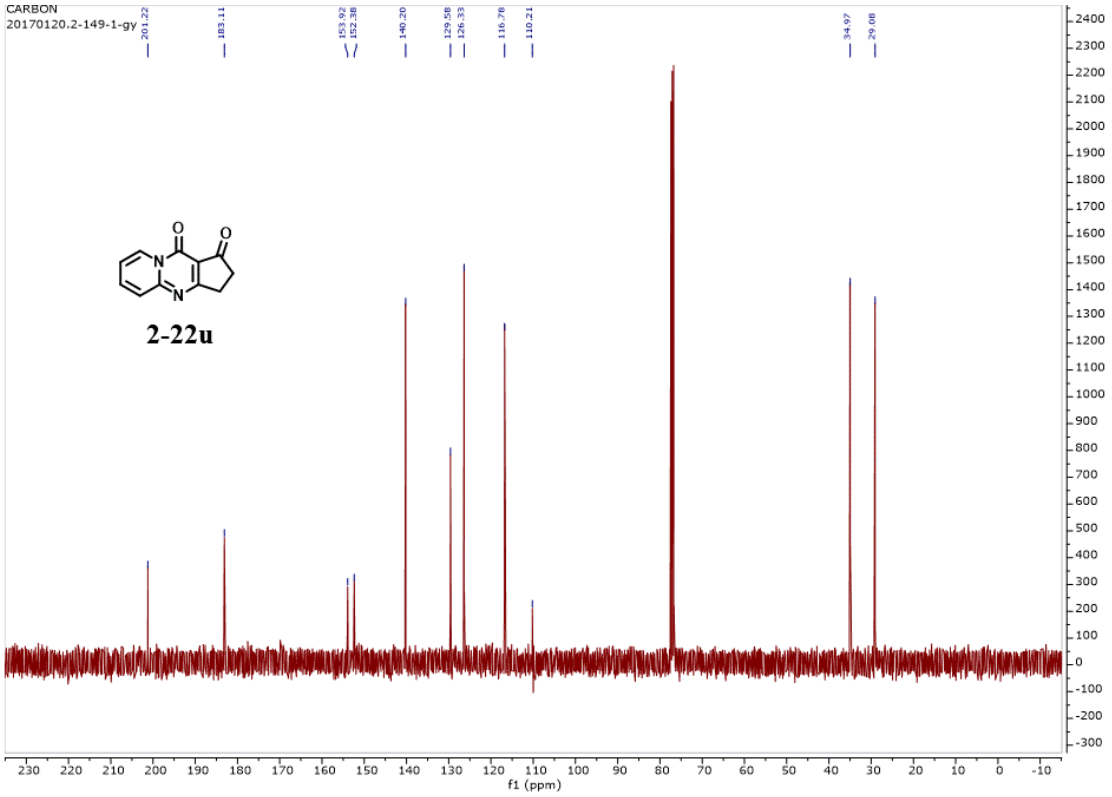
2-22t


CARBON
20170323.2-245-1-GY
195.30
171.29
153.58
147.46
140.24
134.30
132.90
129.15
128.44
126.44
123.54
121.37
104.57
39.70
34.61
21.20
f1 (ppm)

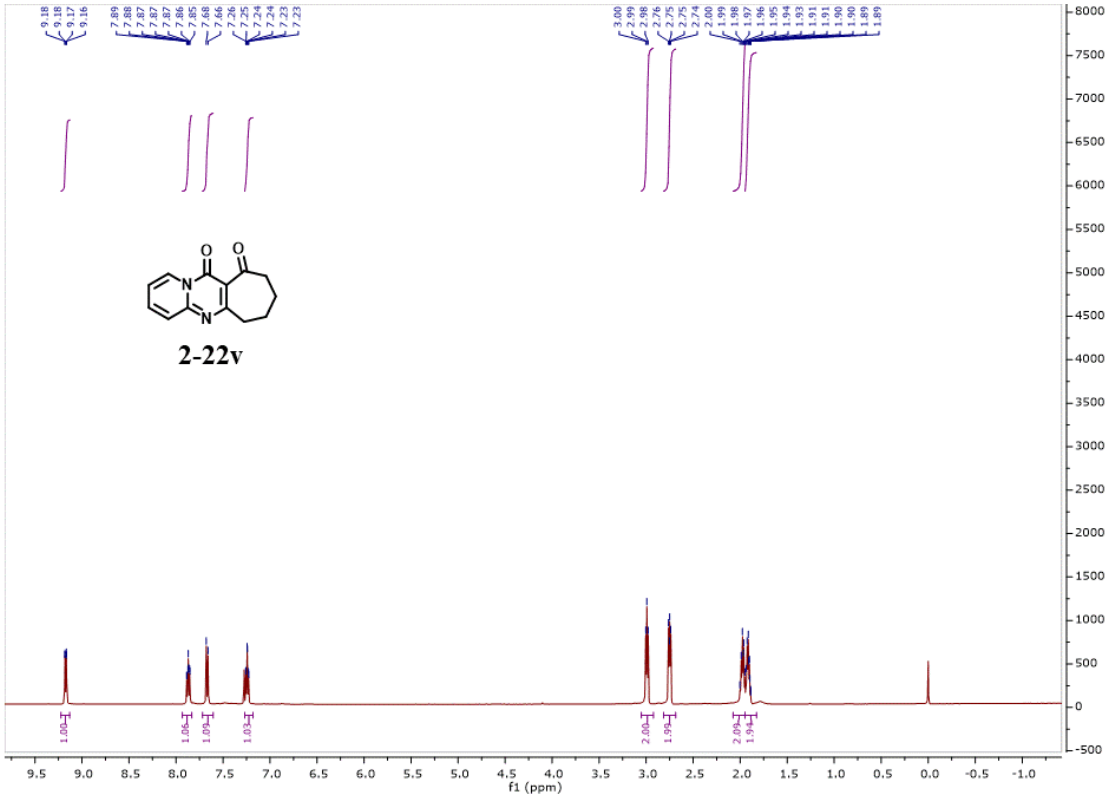
2-22t


9.26
9.26
9.25
9.25
9.24
9.24
9.24
9.23
8.02
8.01
8.00
7.99
7.99
7.98
7.97
7.76
7.76
7.76
7.74
7.74
7.74
7.34
7.34
7.32
7.32
7.31
7.30
3.13
3.12
3.12
3.11
3.11
3.10
2.73
2.72
2.72
2.71
2.70
1.00
1.00
0.97
1.00
1.96
1.98
f1 (ppm)

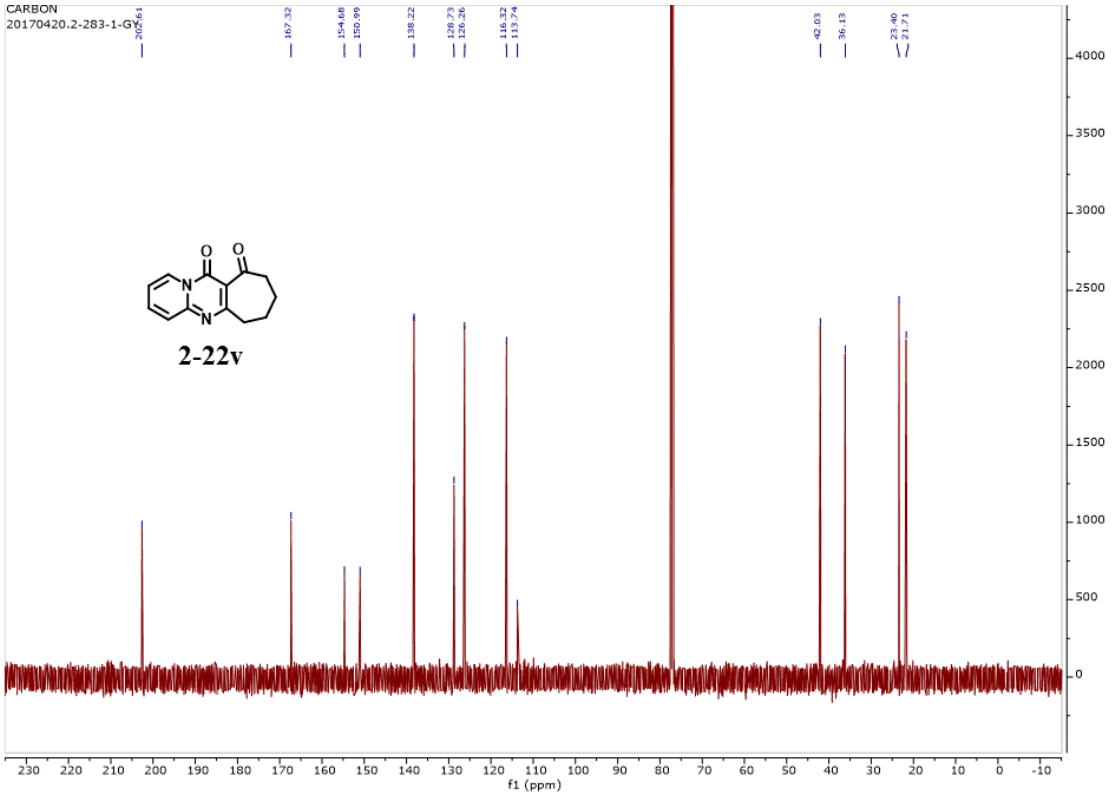
2-22u

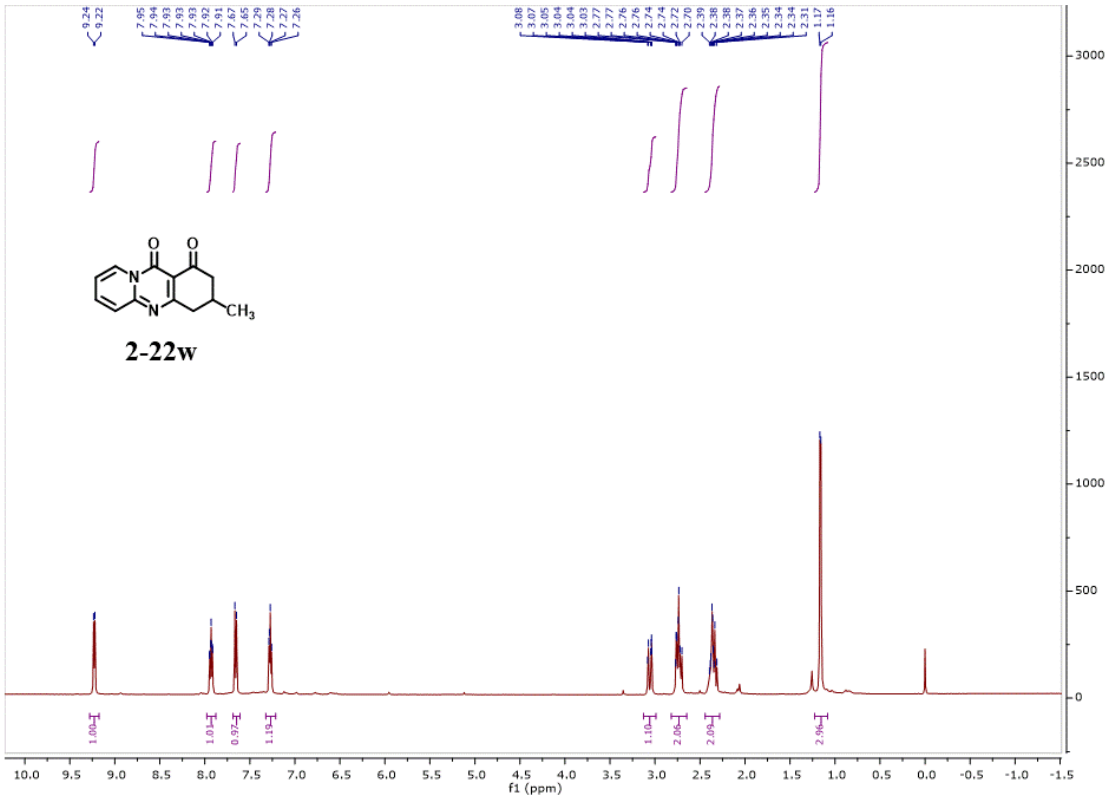

CARBON
20170120.2-149-1-gy
201.22
183.11
153.92
152.38
140.20
129.58
126.33
116.76
110.21
34.97
29.08
f1 (ppm)

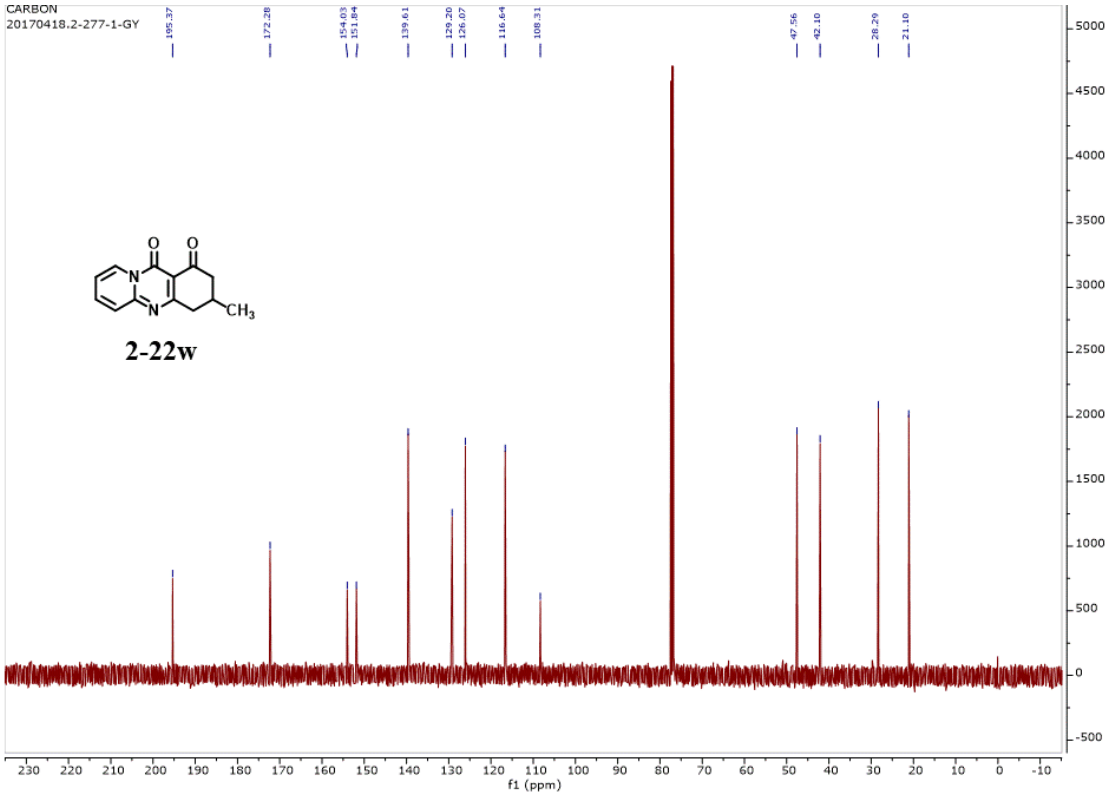
2-22u


9.18
9.18
9.17
9.16
7.89
7.88
7.87
7.87
7.87
7.86
7.85
7.68
7.66
7.36
7.35
7.24
7.24
7.23
7.23
3.00
2.99
2.98
2.76
2.75
2.75
2.74
2.00
1.99
1.98
1.97
1.96
1.95
1.94
1.93
1.91
1.91
1.90
1.90
1.89
1.89
1.00
1.06
1.09
1.03
2.00
1.94
2.09
1.94
f1 (ppm)

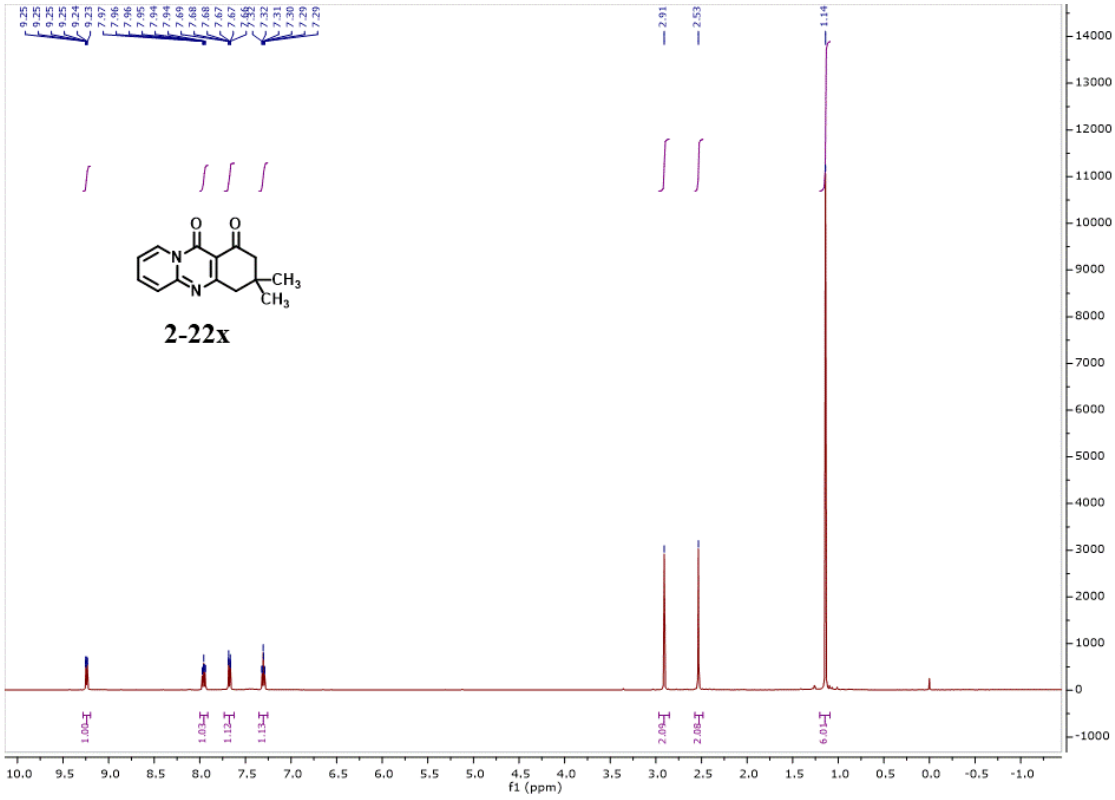
2-22v


CARBON
20170420.2-283-1-GY
202.61
167.32
154.68
150.99
138.22
128.73
126.26
116.32
113.74
42.03
36.13
23.40
21.71
2-22v
f1 (ppm)

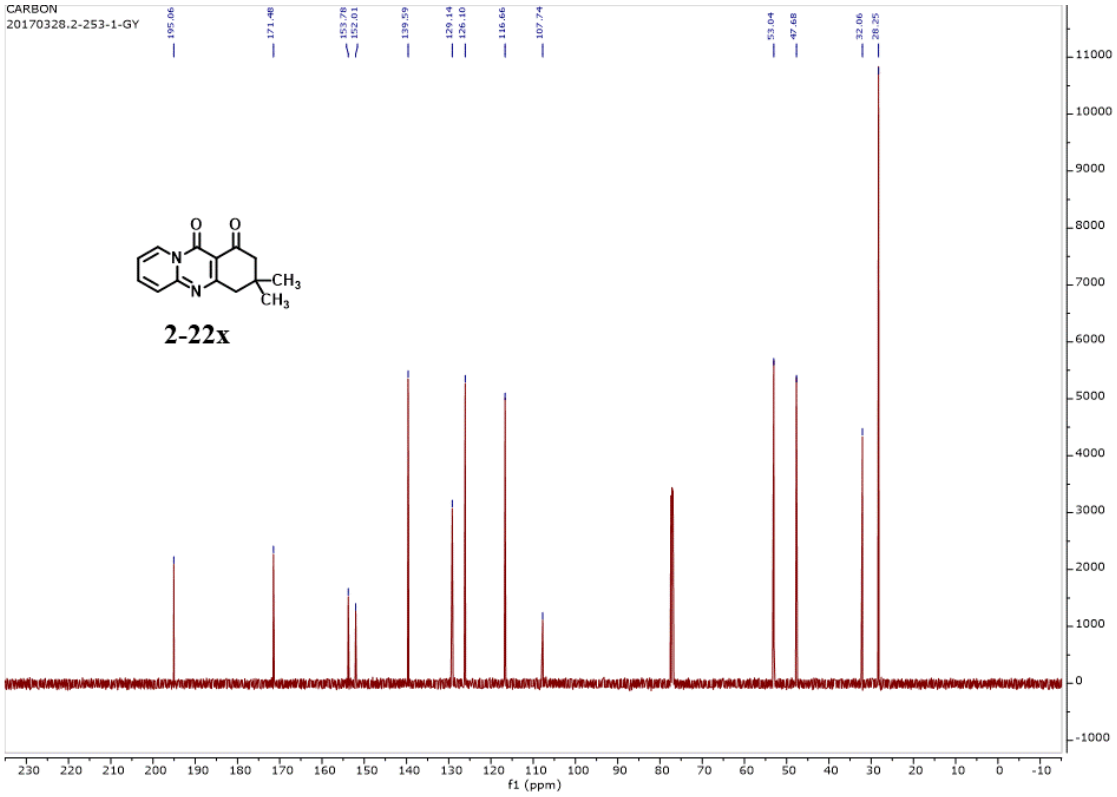

9.24
9.22
7.95
7.94
7.93
7.93
7.93
7.92
7.91
7.67
7.65
7.29
7.28
7.27
7.26
3.08
3.07
3.05
3.04
3.04
3.03
2.77
2.77
2.76
2.76
2.74
2.74
2.72
2.70
2.39
2.38
2.38
2.37
2.36
2.35
2.34
2.34
2.31
1.17
1.16
1.00
1.01
0.97
1.19
1.10
2.05
2.09
2.96
2-22w
f1 (ppm)

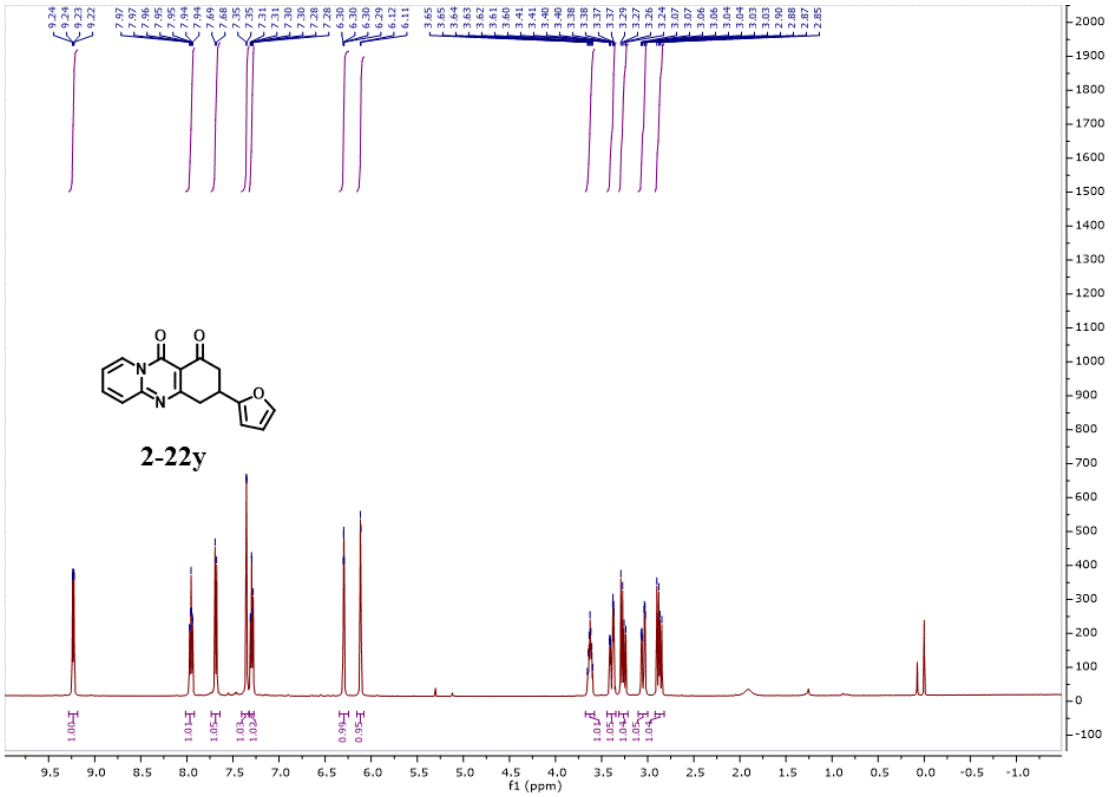

CARBON
20170418.2-277-1-GY
195.37
172.28
154.03
151.84
139.61
129.20
126.07
116.64
108.31
47.56
42.10
28.29
21.10
f1 (ppm)

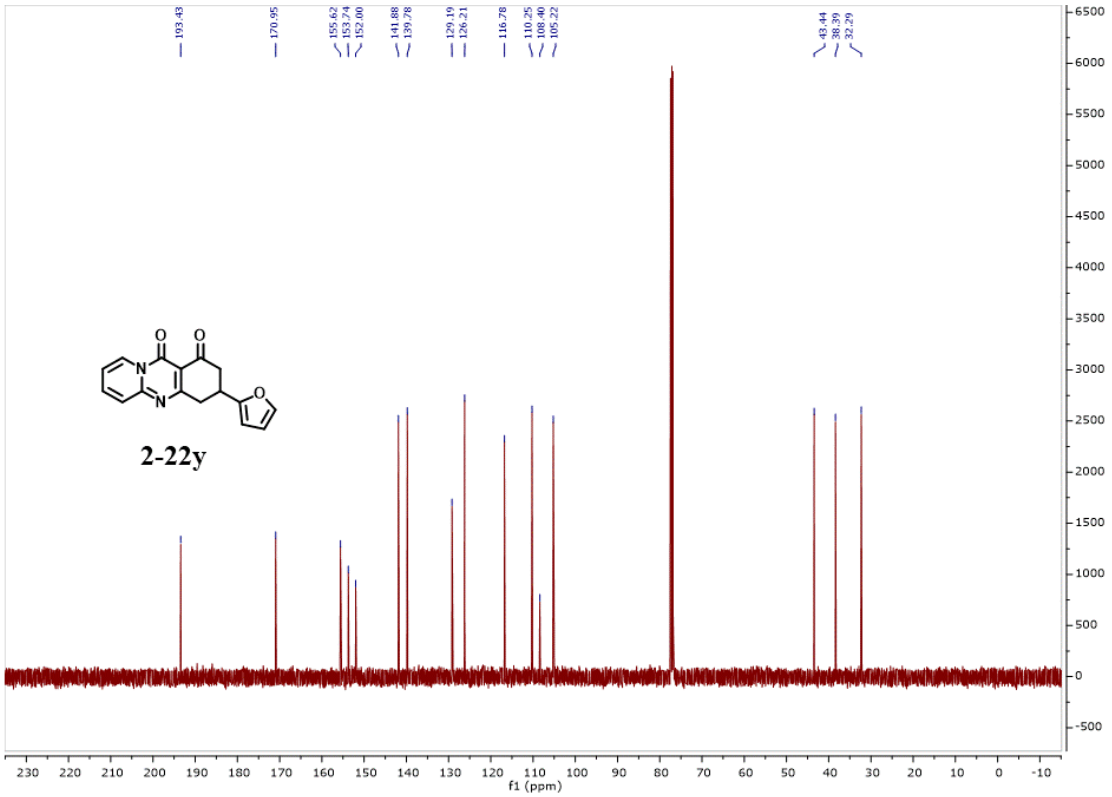
**2-22w**


9.25
9.25
9.25
9.25
9.24
9.23
7.97
7.96
7.96
7.95
7.94
7.94
7.69
7.68
7.68
7.67
7.67
7.32
7.31
7.30
7.29
7.29
2.91
2.53
1.14
1.00
1.03
1.12
1.13
2.09
2.08
6.01
f1 (ppm)

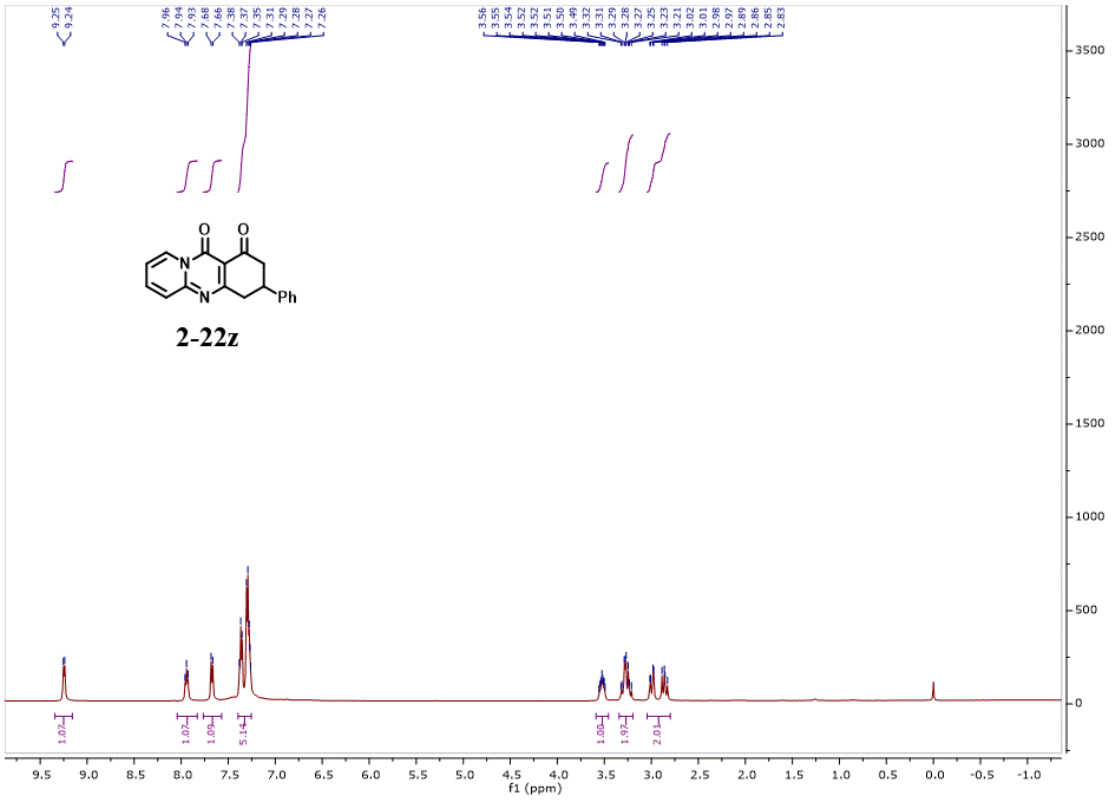
**2-22x**


CARBON
20170328.2-253-1-GY
195.06
171.48
153.78
152.01
139.59
129.14
126.10
116.66
107.74
53.04
47.68
32.06
28.25
2-22x
f1 (ppm)

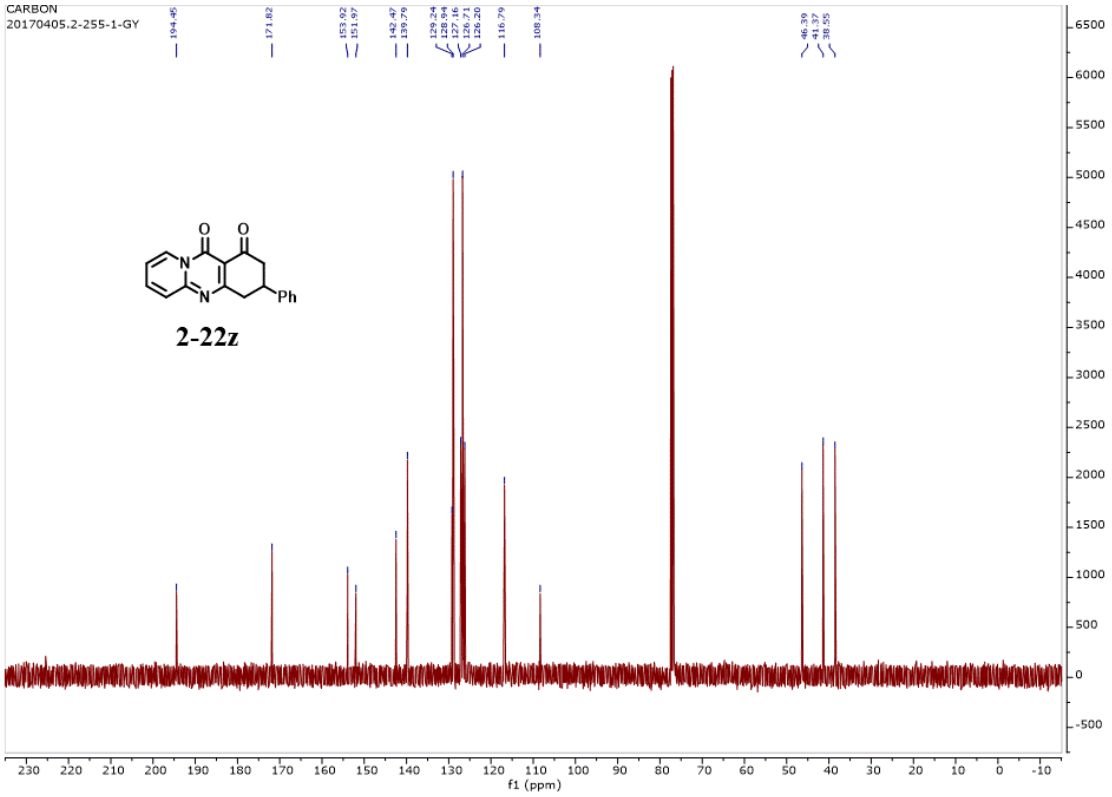

2-22y
f1 (ppm)

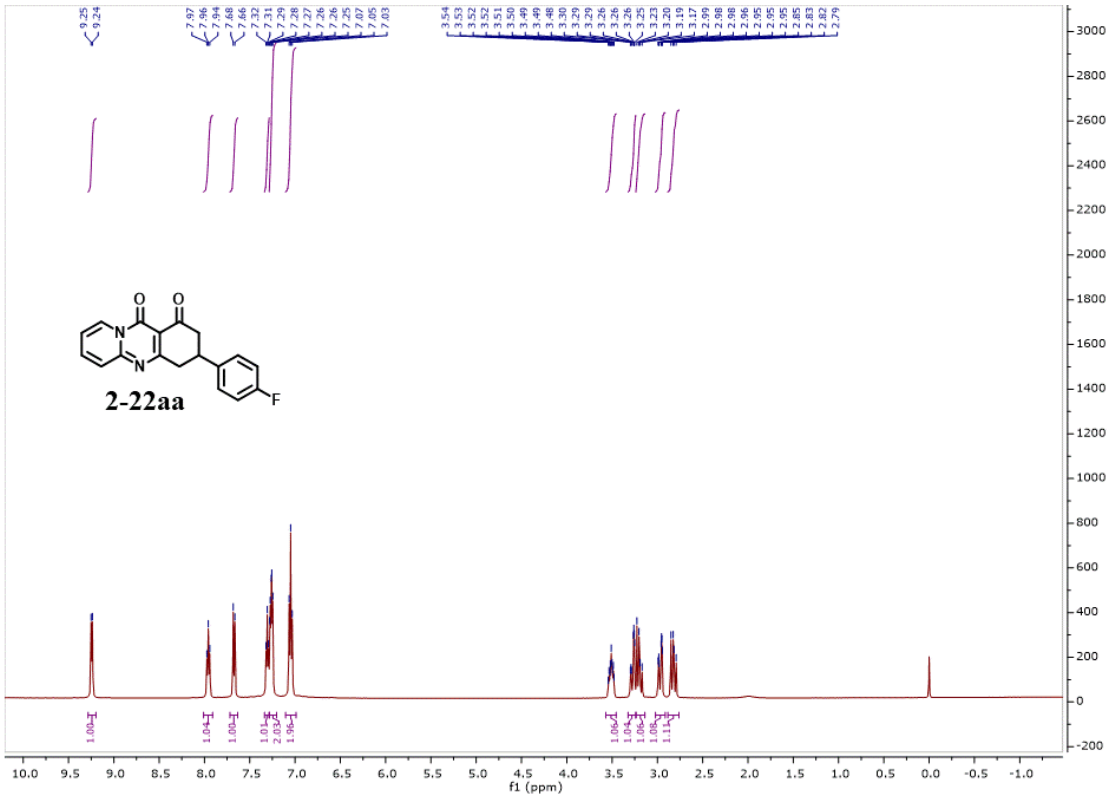

193.43
170.95
155.62
153.74
152.00
141.88
139.78
129.19
126.21
116.78
110.25
108.46
105.22
43.44
38.39
32.29
f1 (ppm)

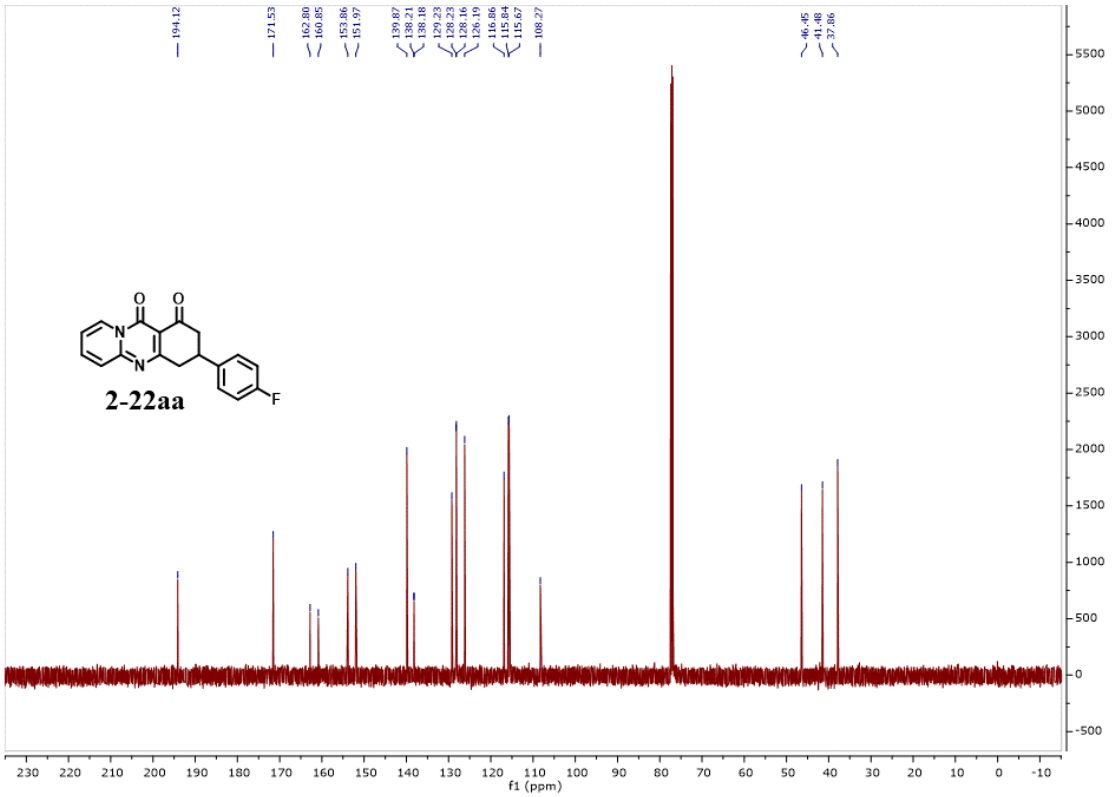
**2-22y**

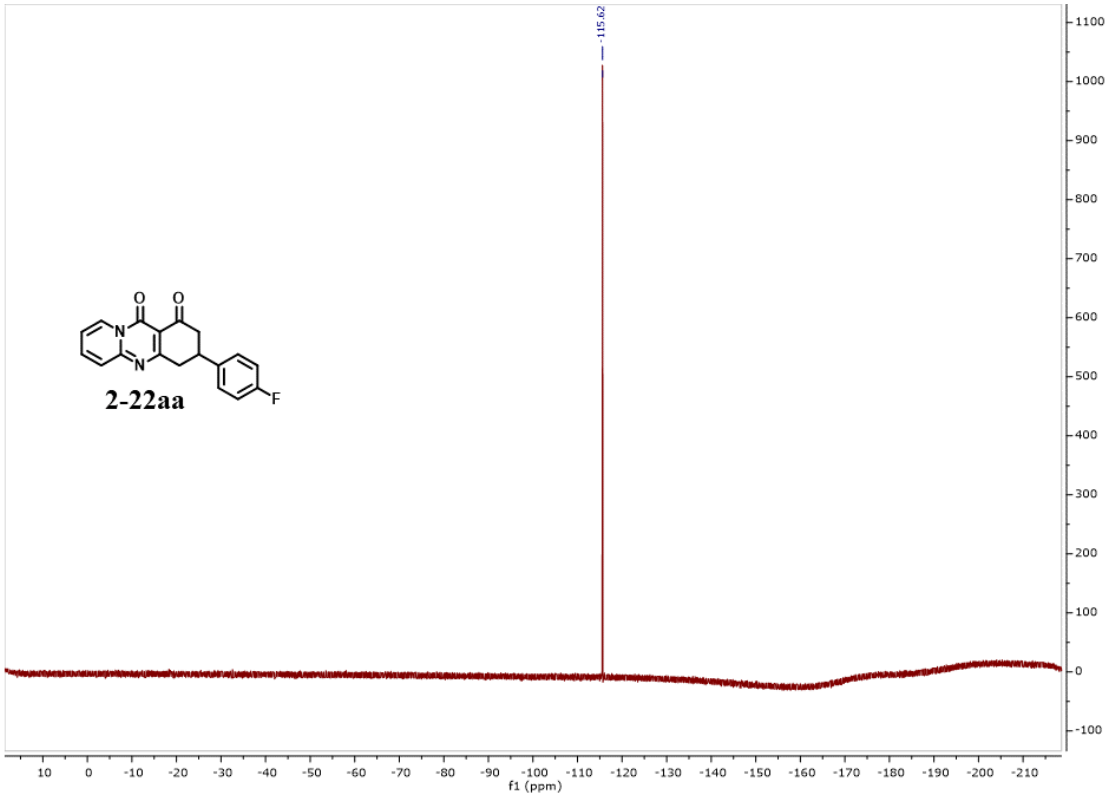

9.25
9.24
7.96
7.94
7.93
7.68
7.66
7.38
7.37
7.35
7.31
7.29
7.28
7.27
7.26
3.56
3.55
3.54
3.52
3.52
3.51
3.50
3.49
3.32
3.31
3.29
3.28
3.27
3.25
3.23
3.21
3.02
3.01
2.98
2.97
2.89
2.86
2.85
2.83
1.07
1.07
1.09
5.14
1.00
1.97
2.01
f1 (ppm)

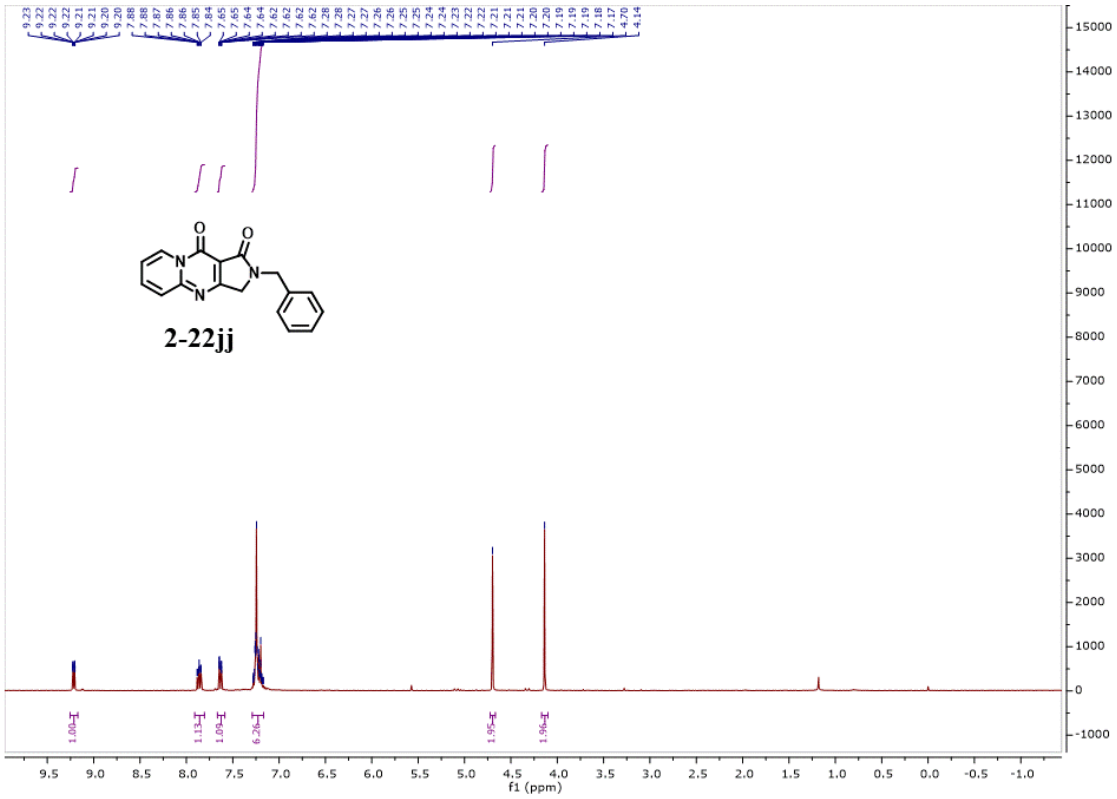
**2-22z**

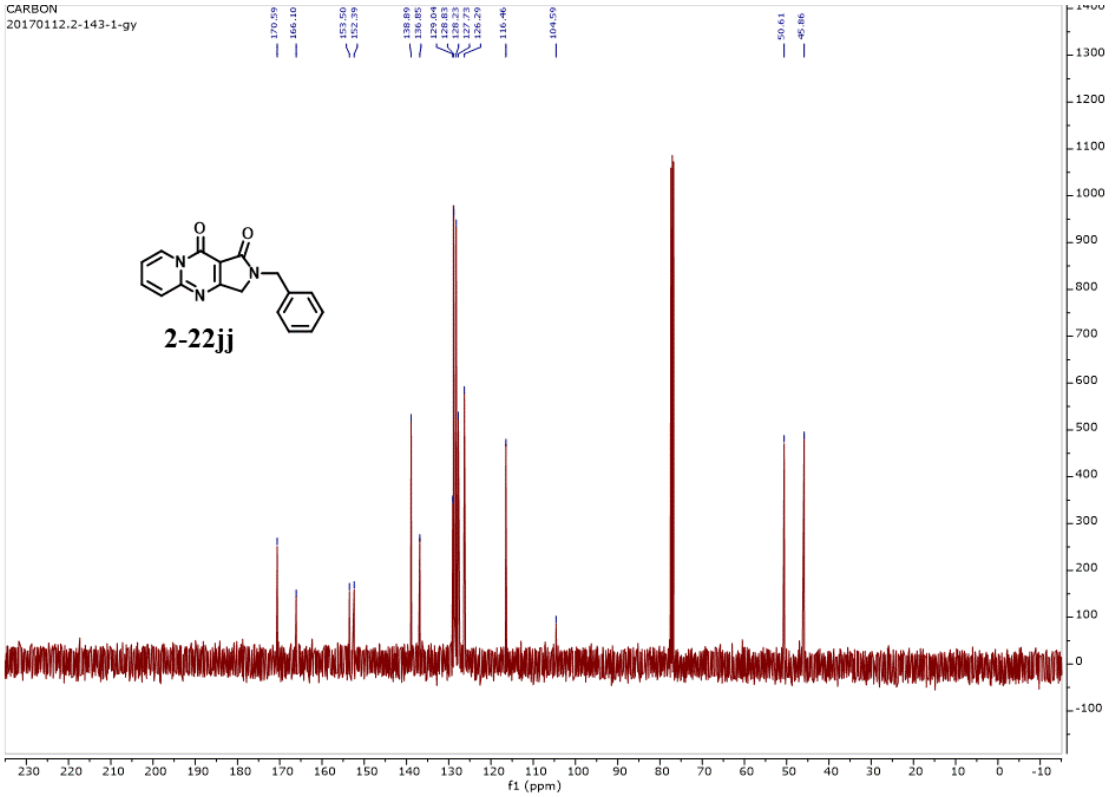

CARBON
20170405.2-255-1-GY
194.95
171.82
153.92
151.97
142.47
139.79
129.24
128.94
127.46
126.71
126.20
116.79
108.34
46.39
41.37
38.55
Ph
2-22z
f1 (ppm)

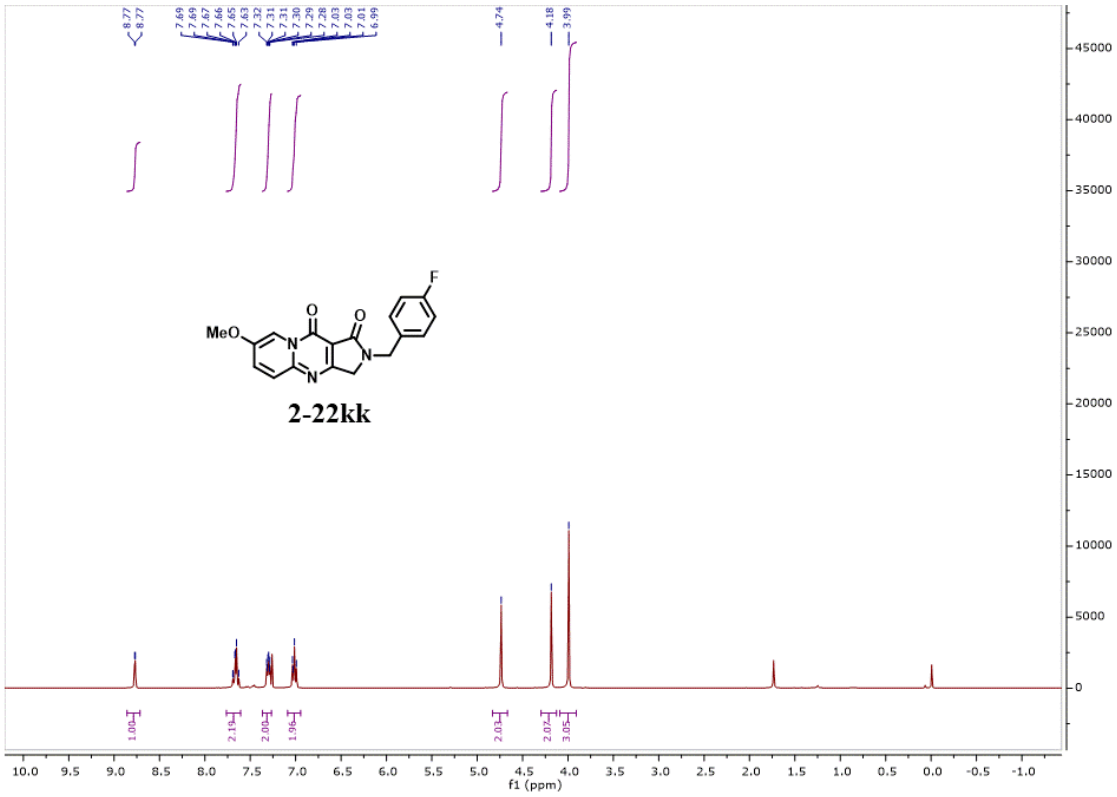

9.25
9.24
7.97
7.96
7.94
7.68
7.66
7.32
7.31
7.29
7.28
7.27
7.26
7.25
7.07
7.05
7.03
3.54
3.53
3.52
3.51
3.50
3.49
3.48
3.30
3.29
3.29
3.26
3.26
3.25
3.23
3.20
3.19
3.17
2.99
2.98
2.98
2.96
2.95
2.95
2.95
2.85
2.83
2.82
2.79
1.00
1.04
1.00
1.01
2.03
1.96
1.06
1.04
1.06
1.08
1.14
F
2-22aa
f1 (ppm)

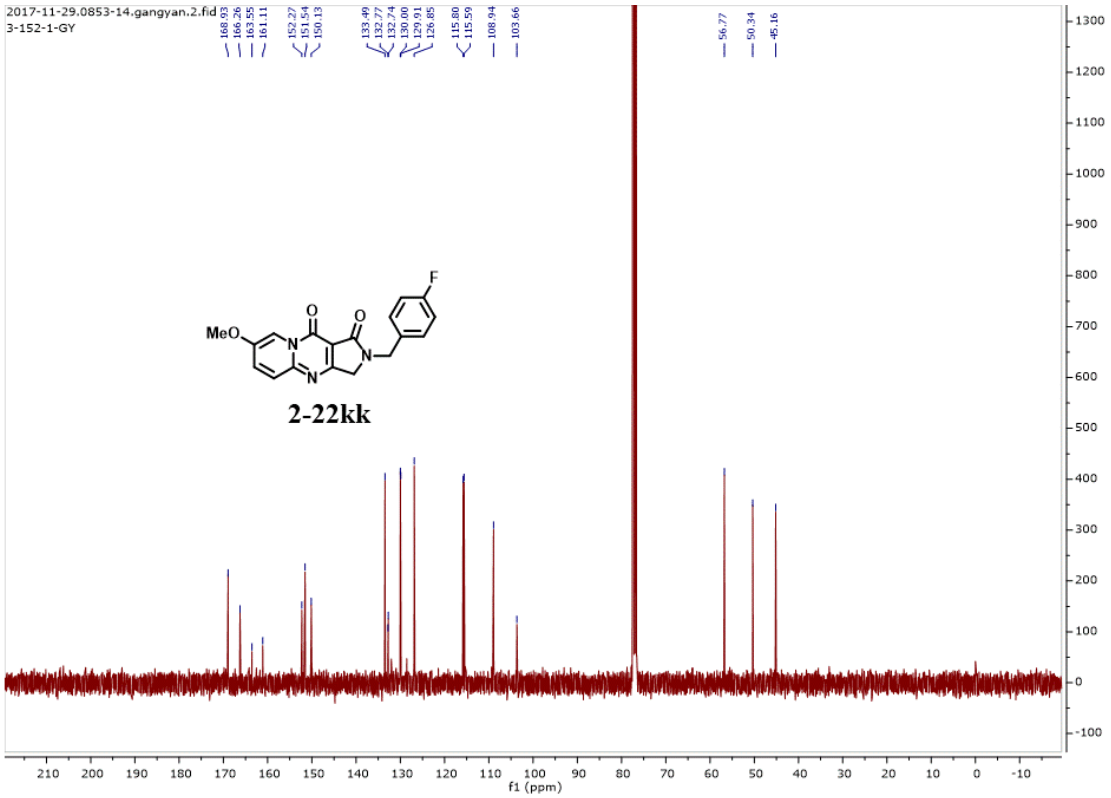

194.12
171.53
162.80
160.85
153.86
151.97
139.87
138.21
138.18
129.23
128.23
128.16
126.19
116.86
115.84
115.67
108.27
46.45
41.48
37.86
2-22aa
F
f1 (ppm)

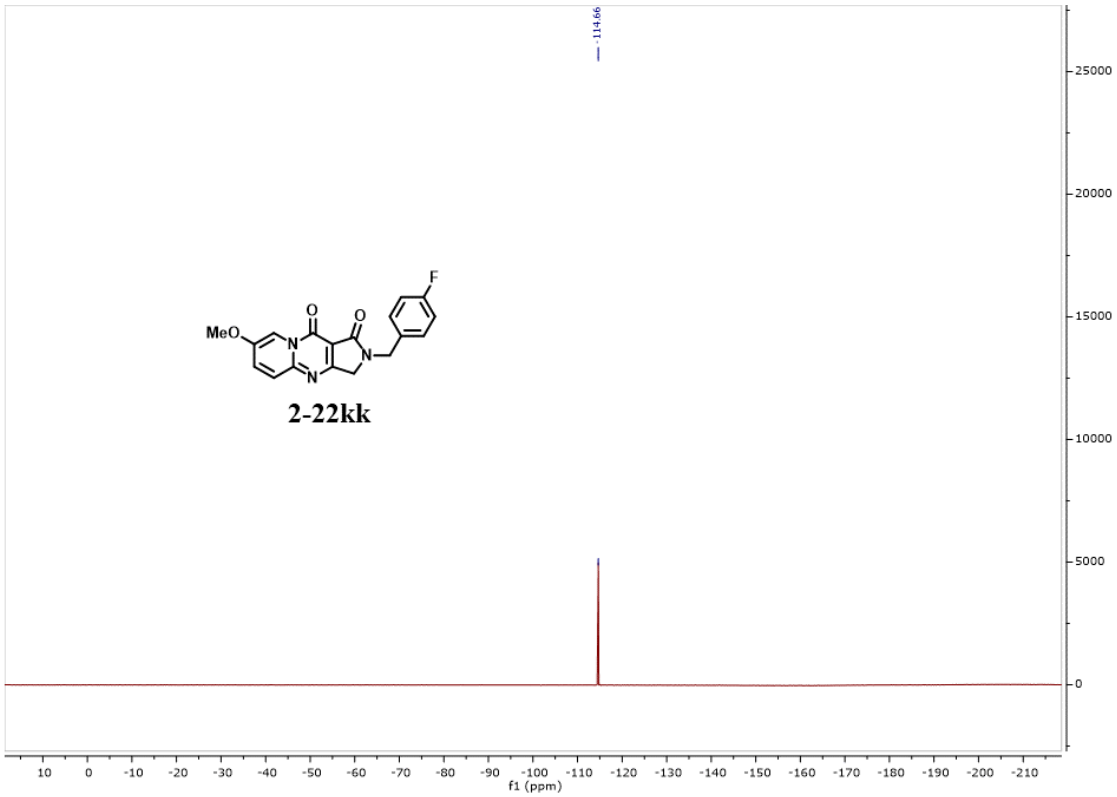

-115.62
2-22aa
F
f1 (ppm)

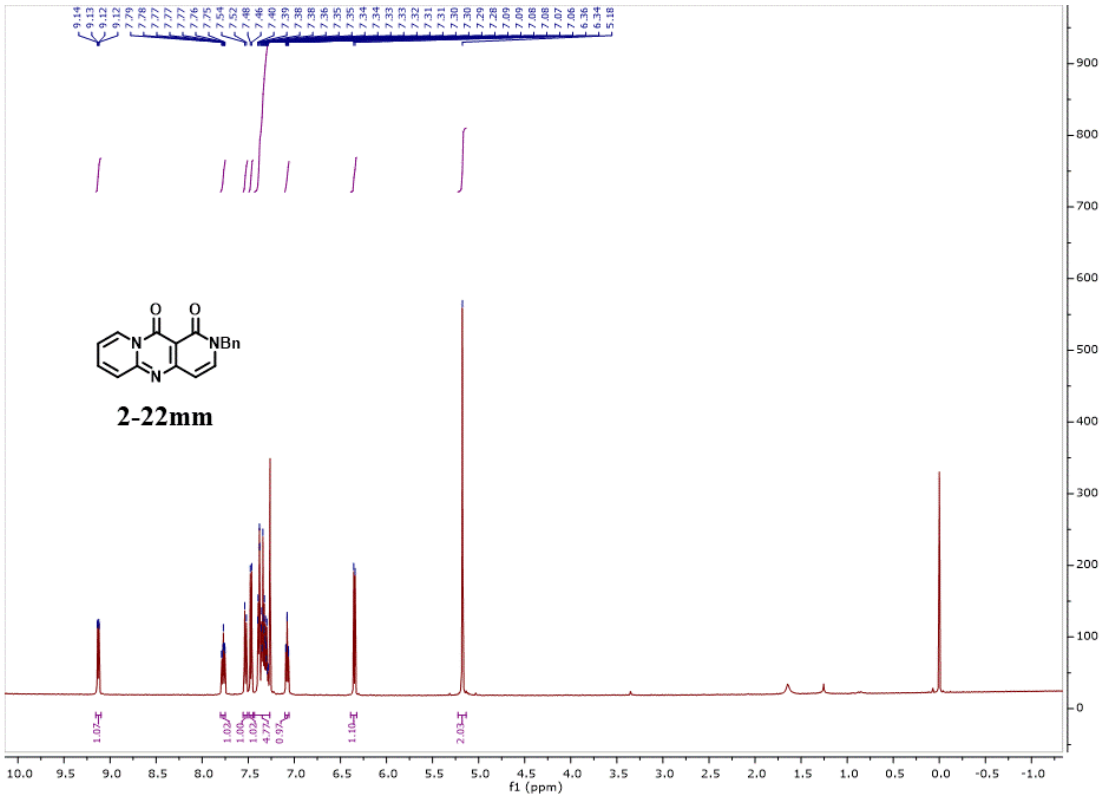

2-22jj
f1 (ppm)

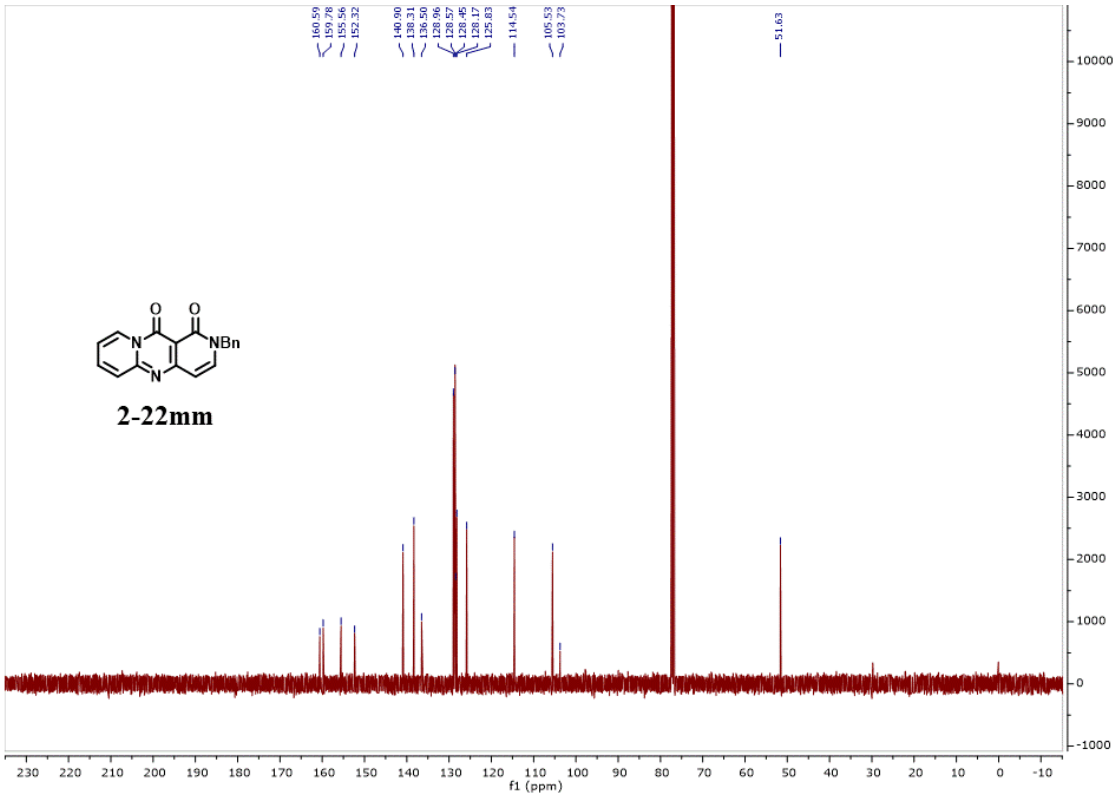

CARBON
20170112.2-143-1-gy
2-22jj
f1 (ppm)

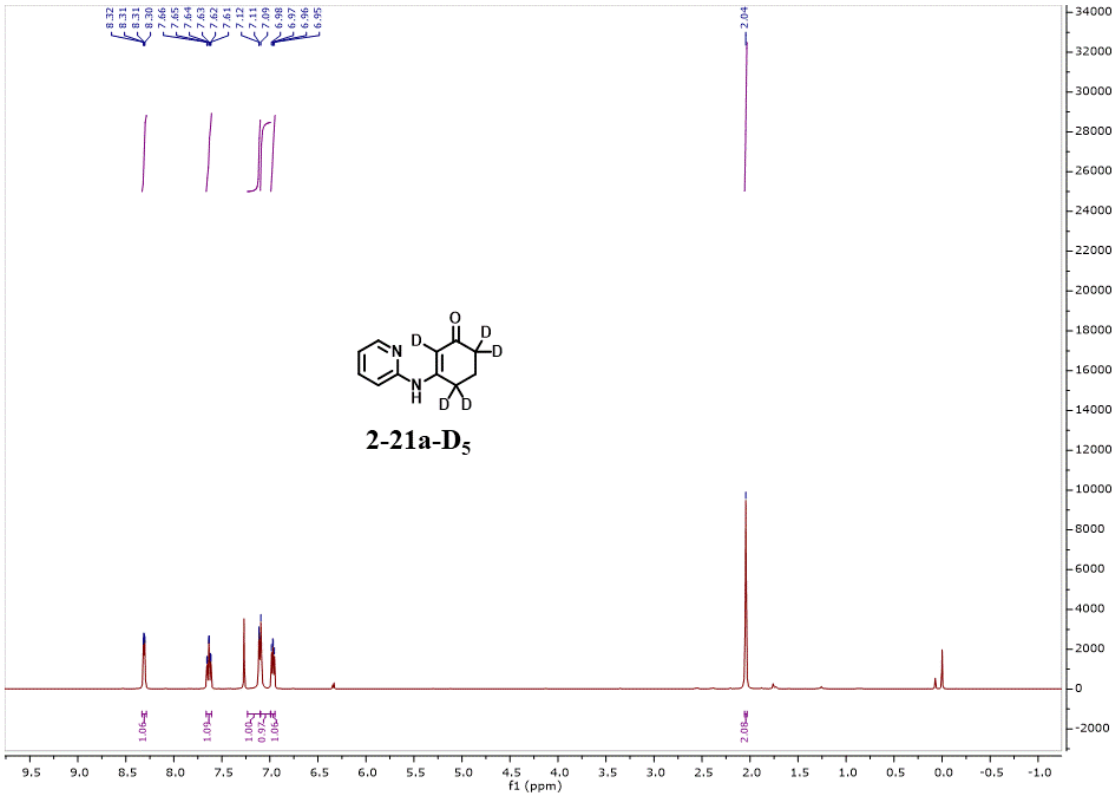

8.77
8.77
7.69
7.69
7.67
7.66
7.65
7.63
7.32
7.31
7.31
7.30
7.29
7.28
7.03
7.03
7.01
6.99
4.74
4.18
3.99
F
O
O
MeO
N
N
N
2-22kk
1.00
2.19
2.00
1.96
2.03
2.07
3.05
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


2017-11-29.0853-14.gangyan.2.fid
3-152-1-GY
168.93
166.26
163.55
161.11
152.27
151.54
150.13
133.49
132.77
132.74
130.00
129.91
126.85
115.80
115.59
108.94
103.66
56.77
50.34
45.16
F
O
O
MeO
N
N
N
2-22kk
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


-114.66
MeO
O
O
N
N
N
F
2-22kk
f1 (ppm)

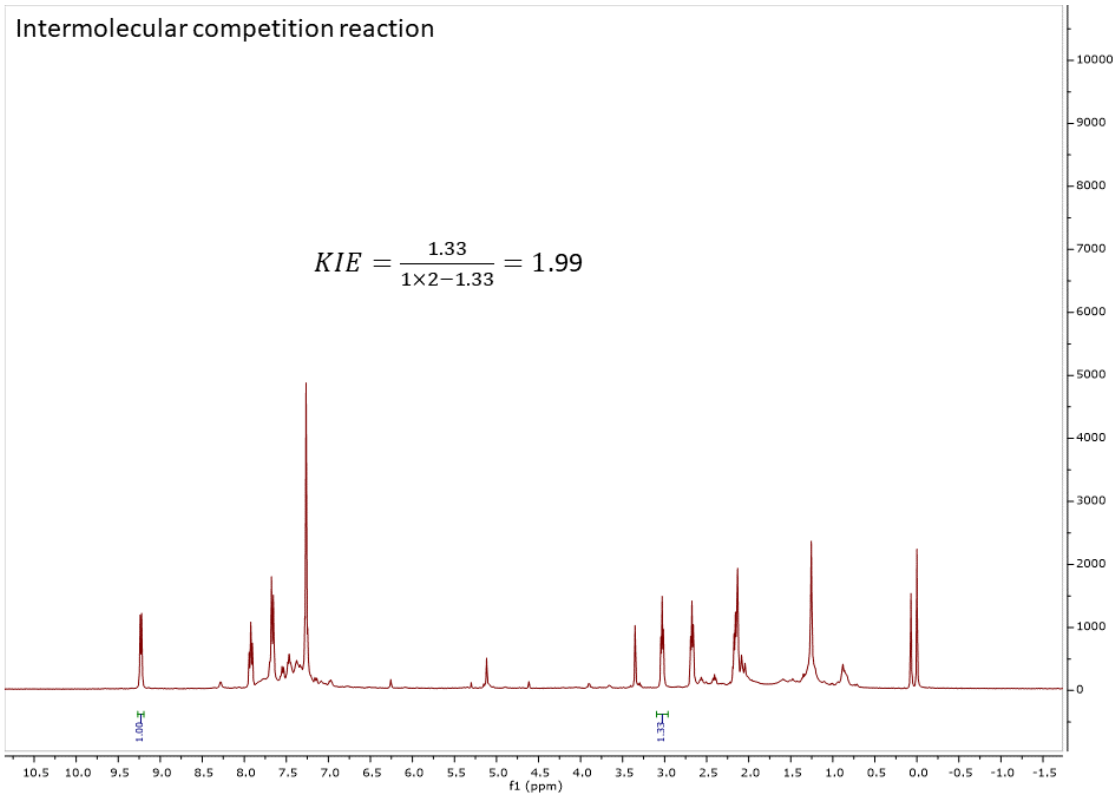

O
O
N
N
NBn
2-22mm
f1 (ppm)


160.59
159.78
155.56
152.32
140.90
138.31
136.50
128.96
128.57
128.45
128.17
125.83
114.54
105.53
103.73
51.63
NBn
2-22mm
f1 (ppm)


8.32
8.31
8.31
8.30
7.66
7.65
7.64
7.63
7.62
7.61
7.12
7.11
7.09
6.98
6.97
6.96
6.95
2.04
D
D
D
D
D
N
H
O
2-21a-D5
1.06
1.04
1.05
0.97
1.06
2.08
f1 (ppm)

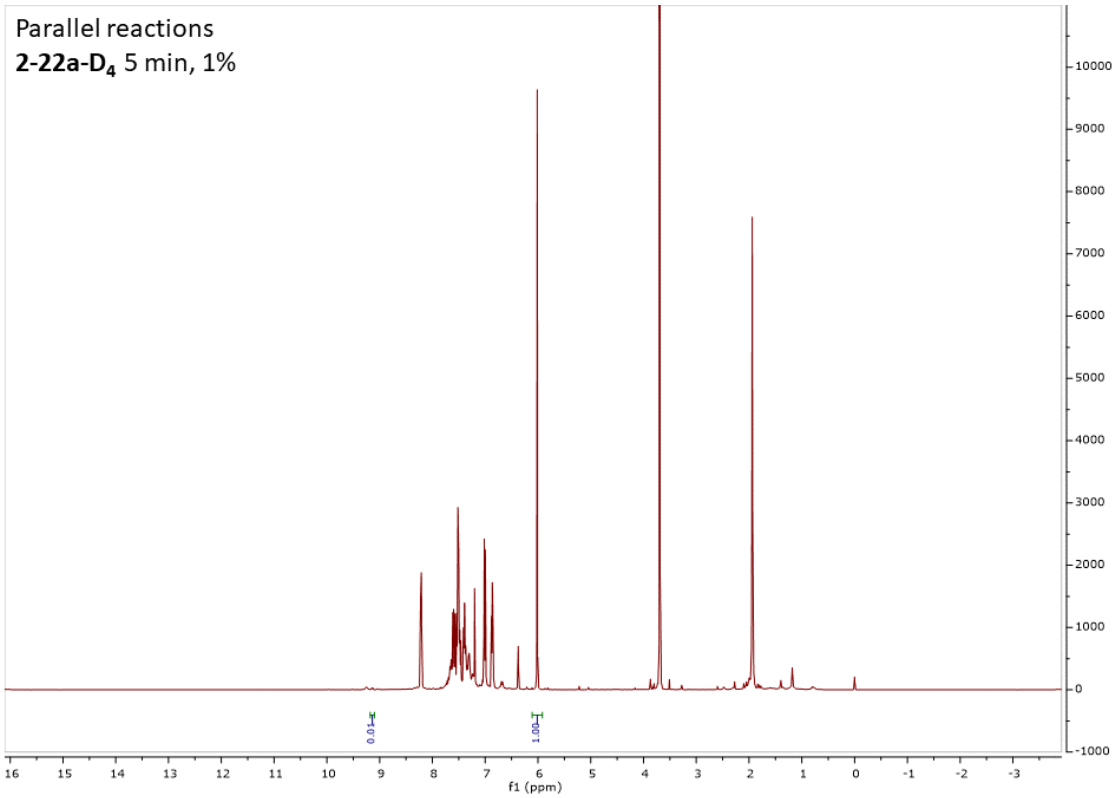
Intermolecular competition reaction

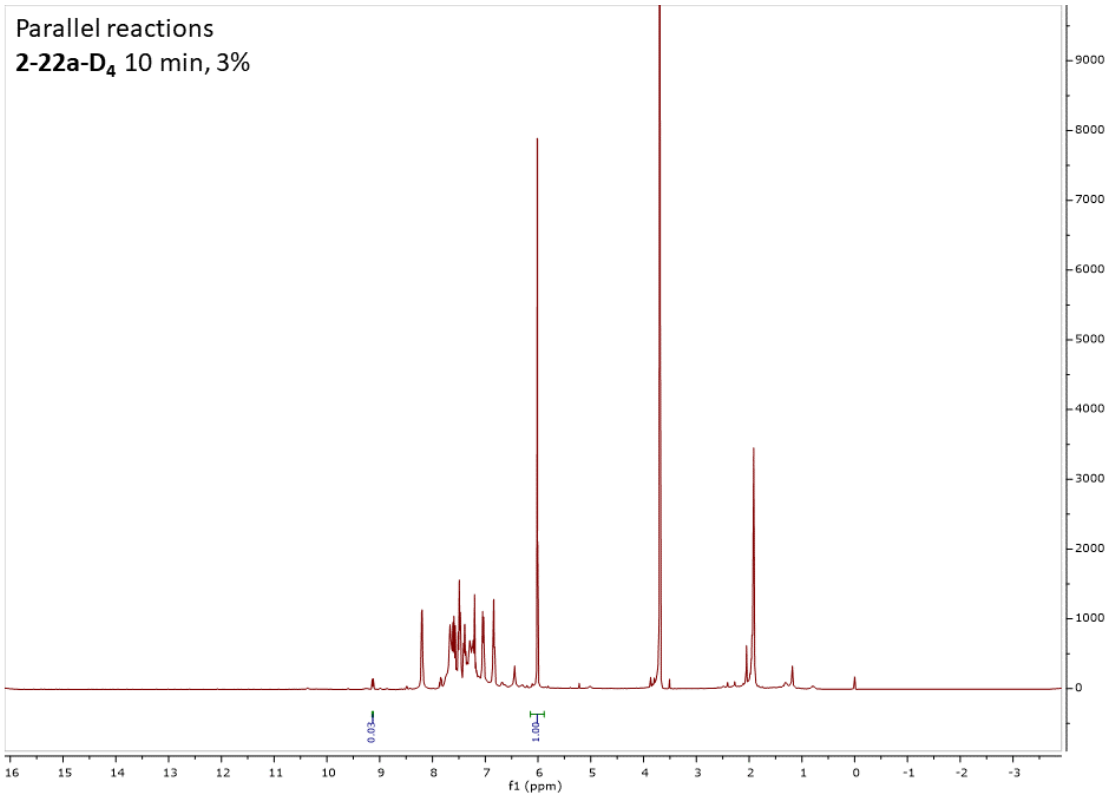
$$KIE = \frac{1.33}{1\times2-1.33} = 1.99$$

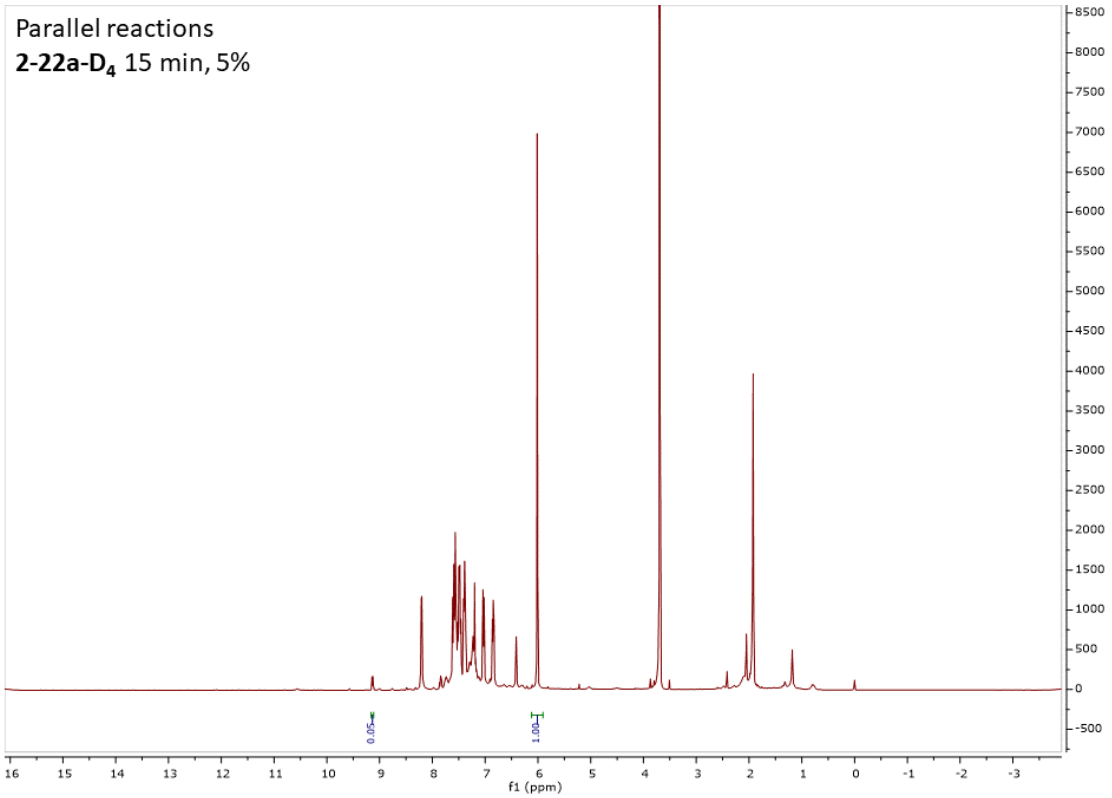


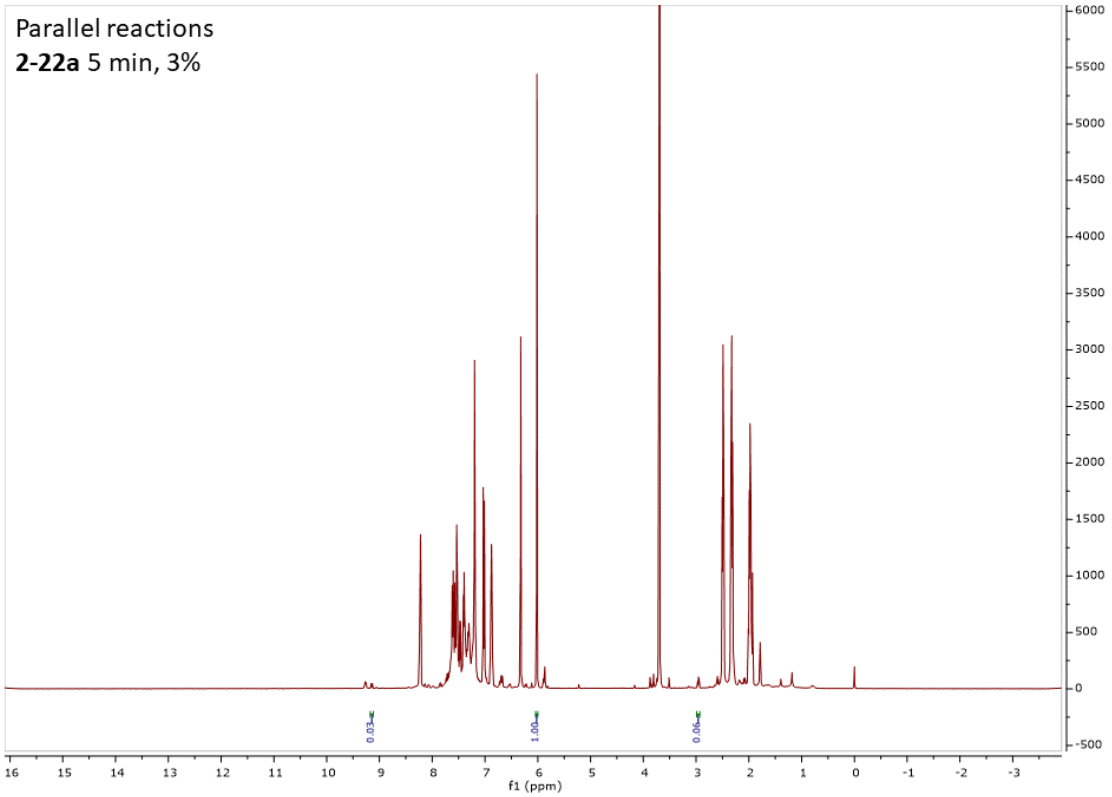

Parallel reactions

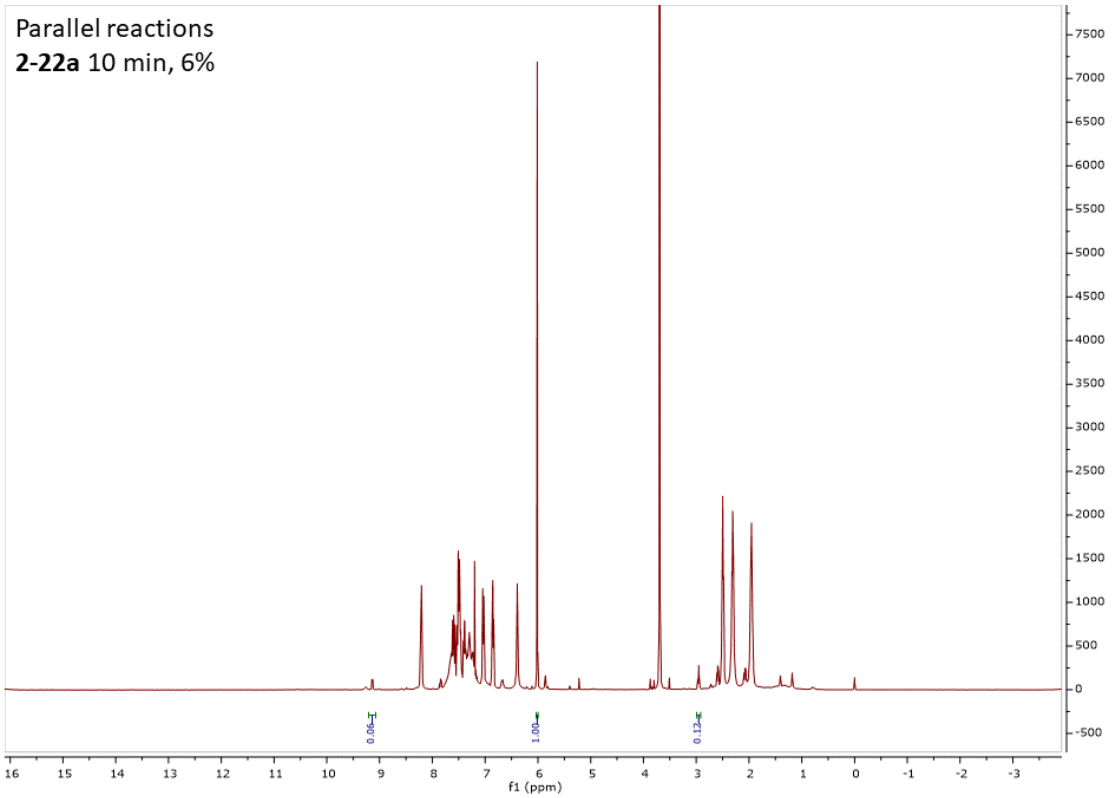
**2-22a-$D_4$** 5 min, 1%

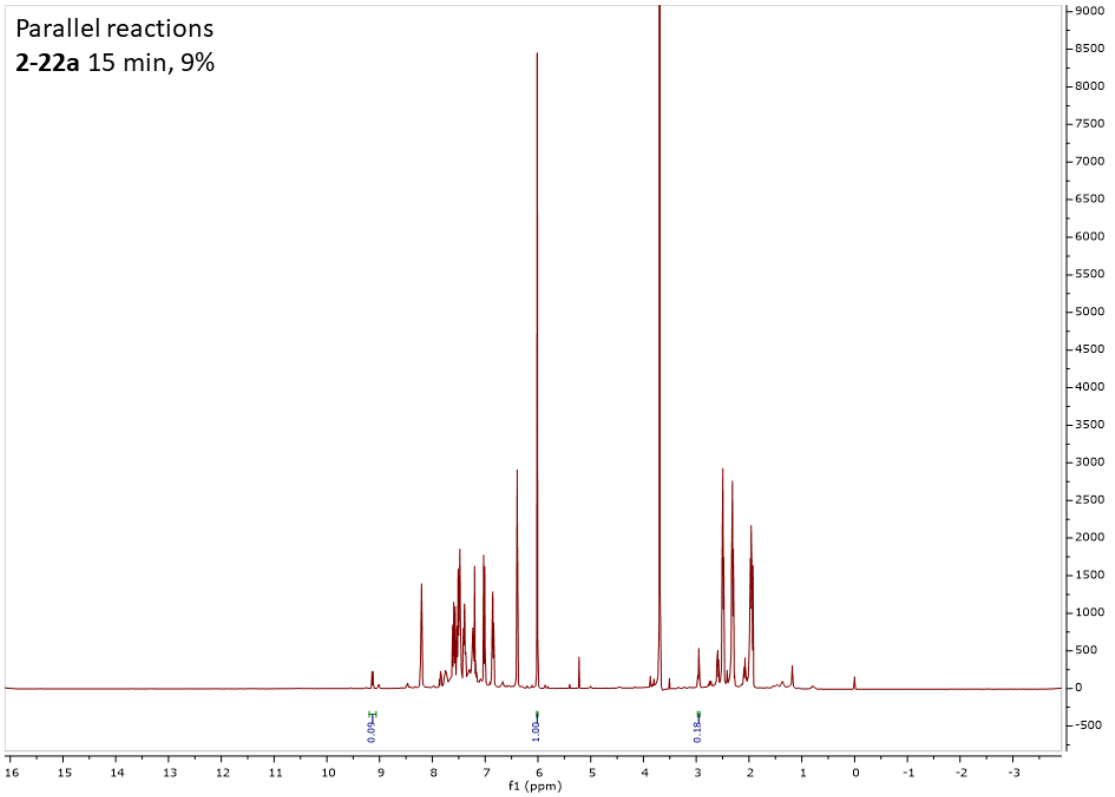


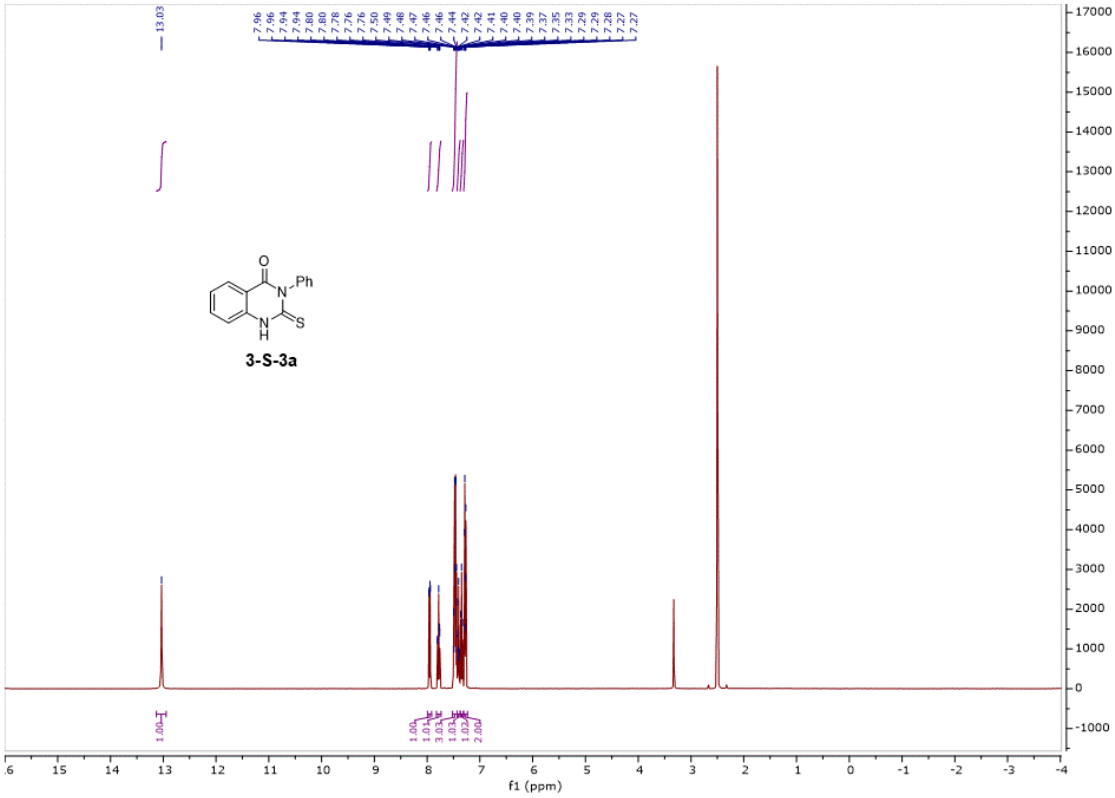

Parallel reactions
2-22a-D4 10 min, 3%
f1 (ppm)

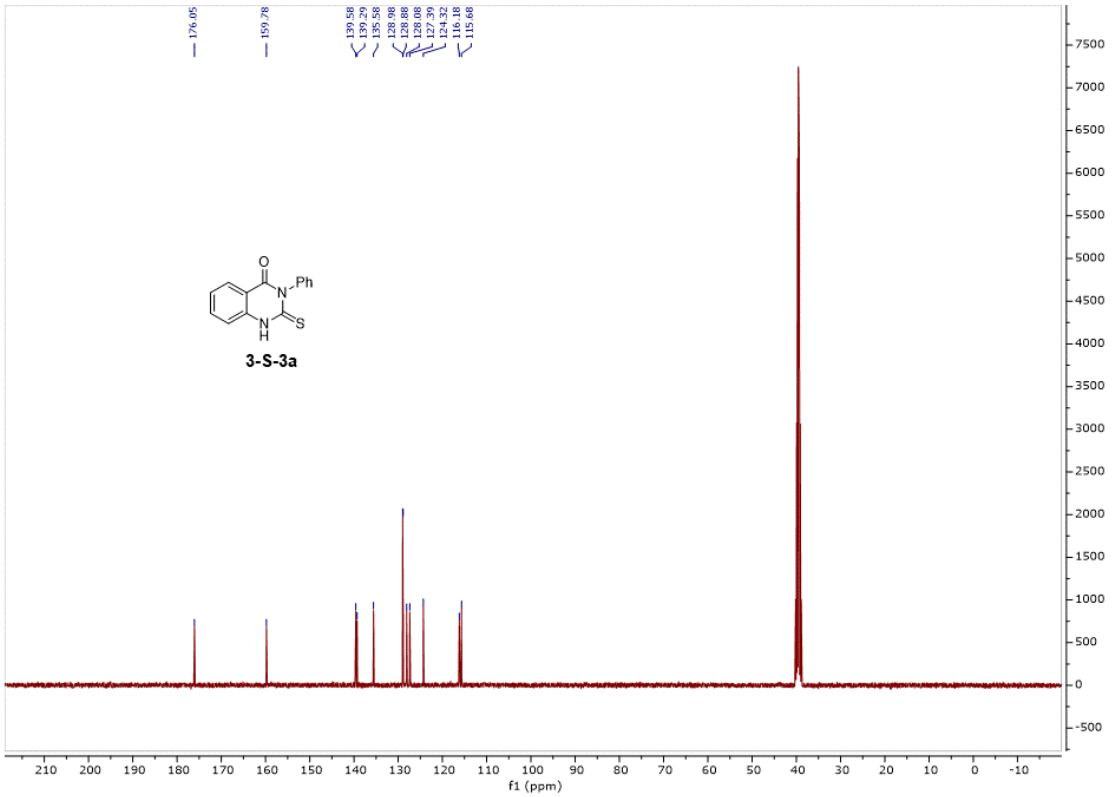

Parallel reactions
2-22a-D4 15 min, 5%
f1 (ppm)

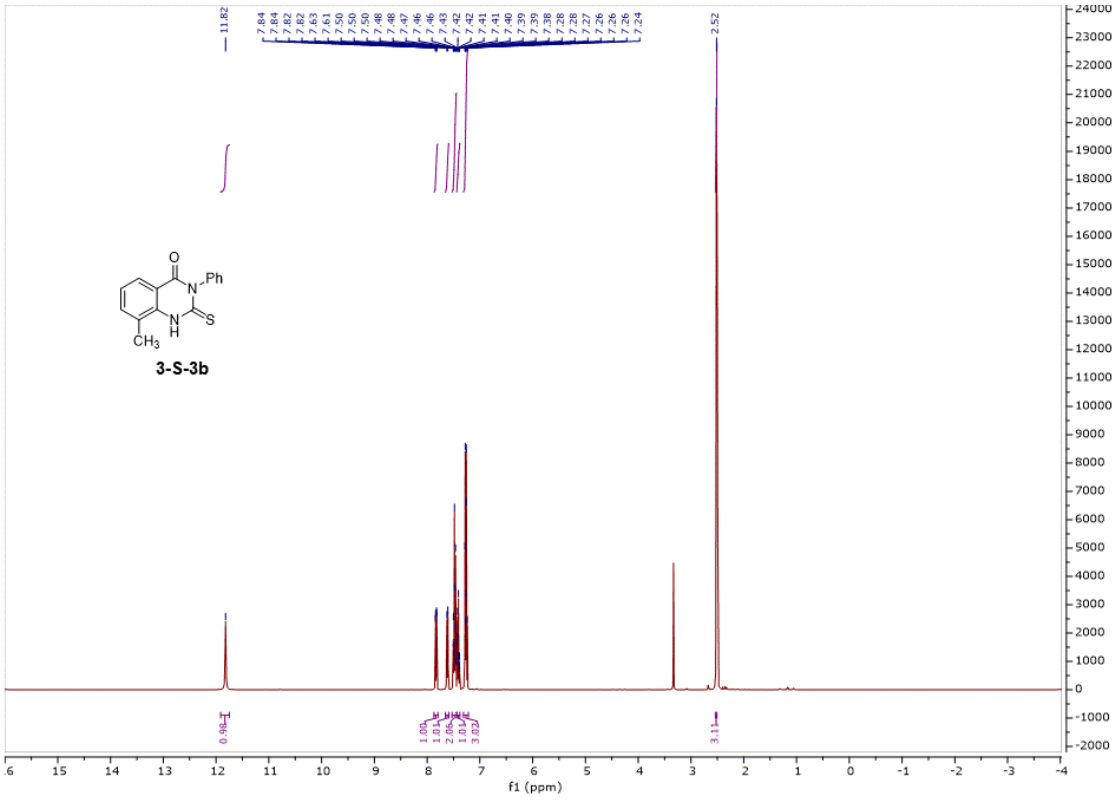

Parallel reactions
**2-22a** 5 min, 3%
f1 (ppm)

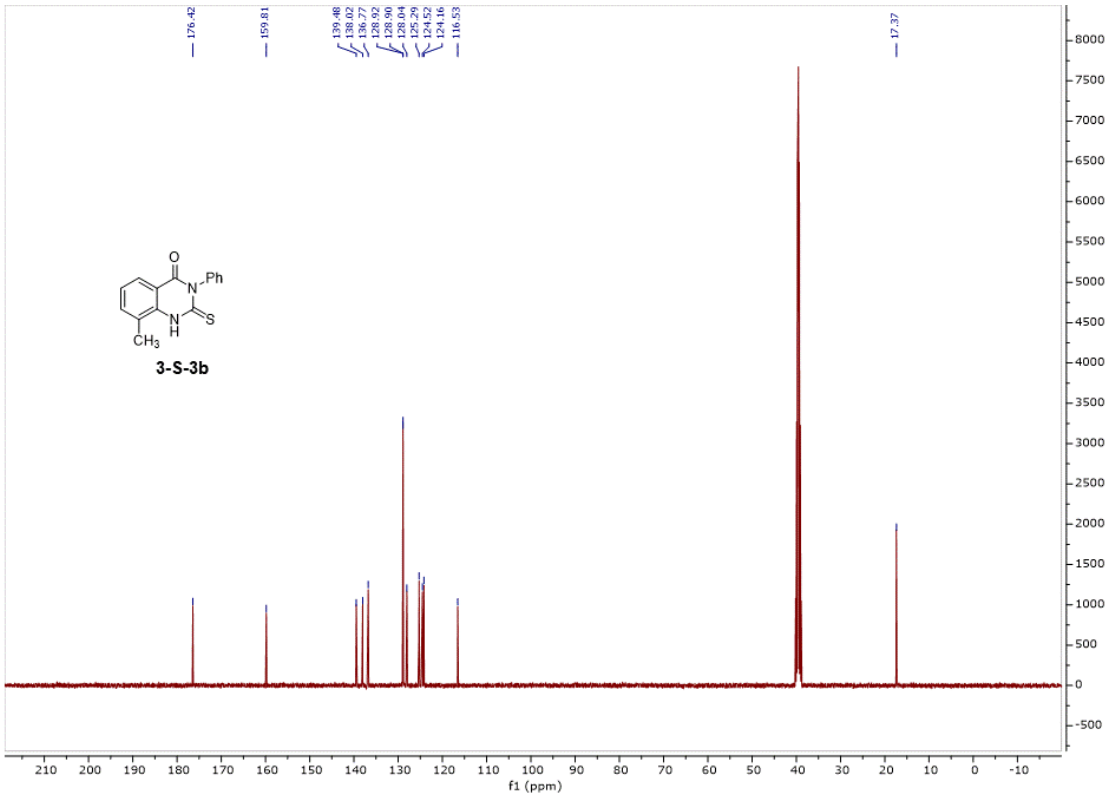

Parallel reactions
**2-22a** 10 min, 6%
f1 (ppm)

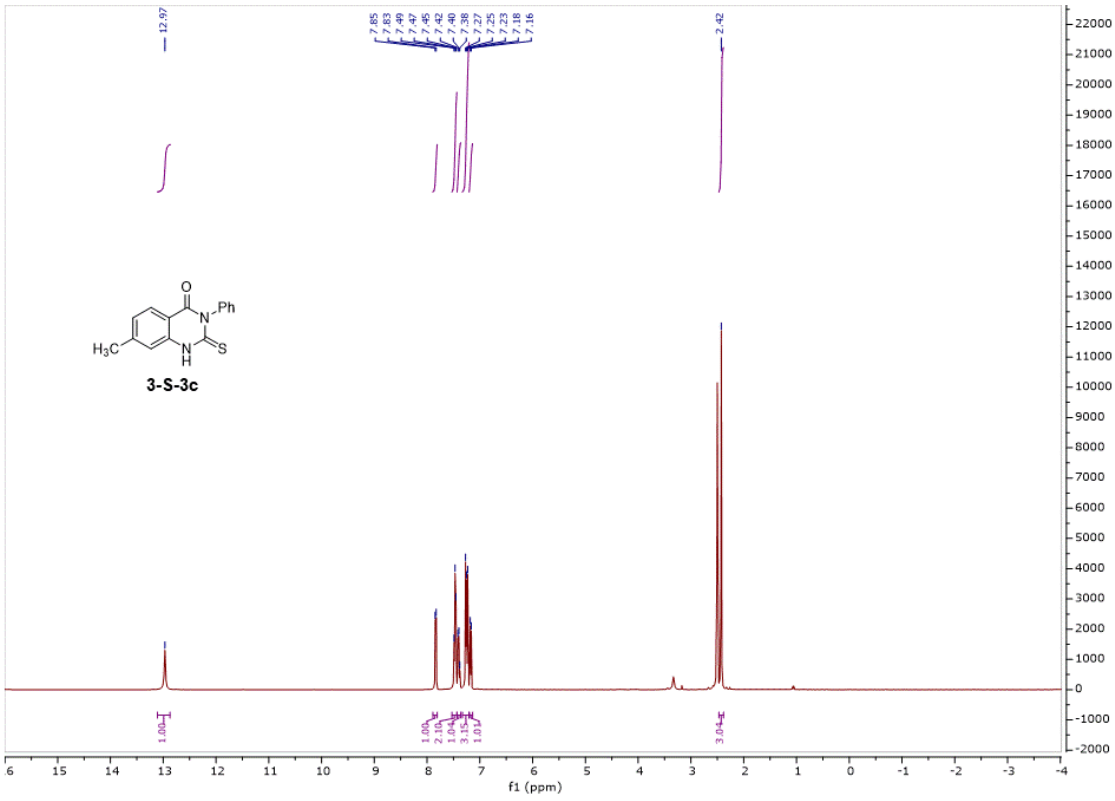

Parallel reactions
**2-22a** 15 min, 9%
f1 (ppm)

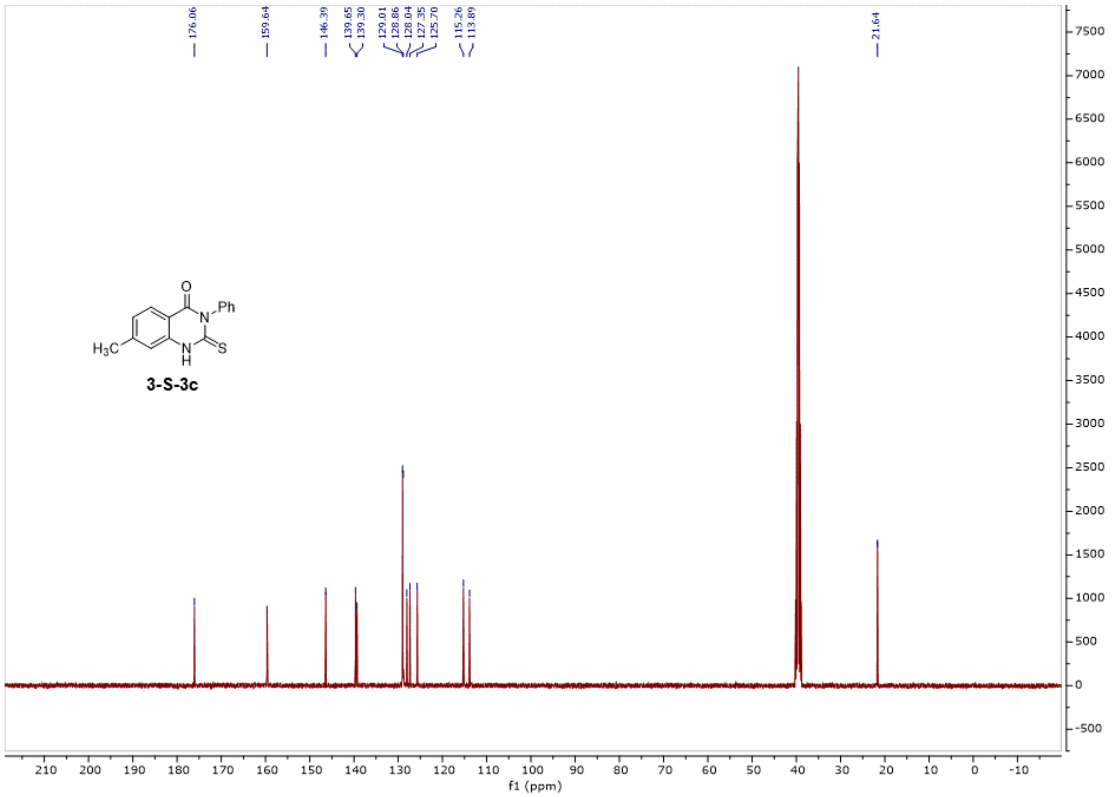

3-S-3a
f1 (ppm)

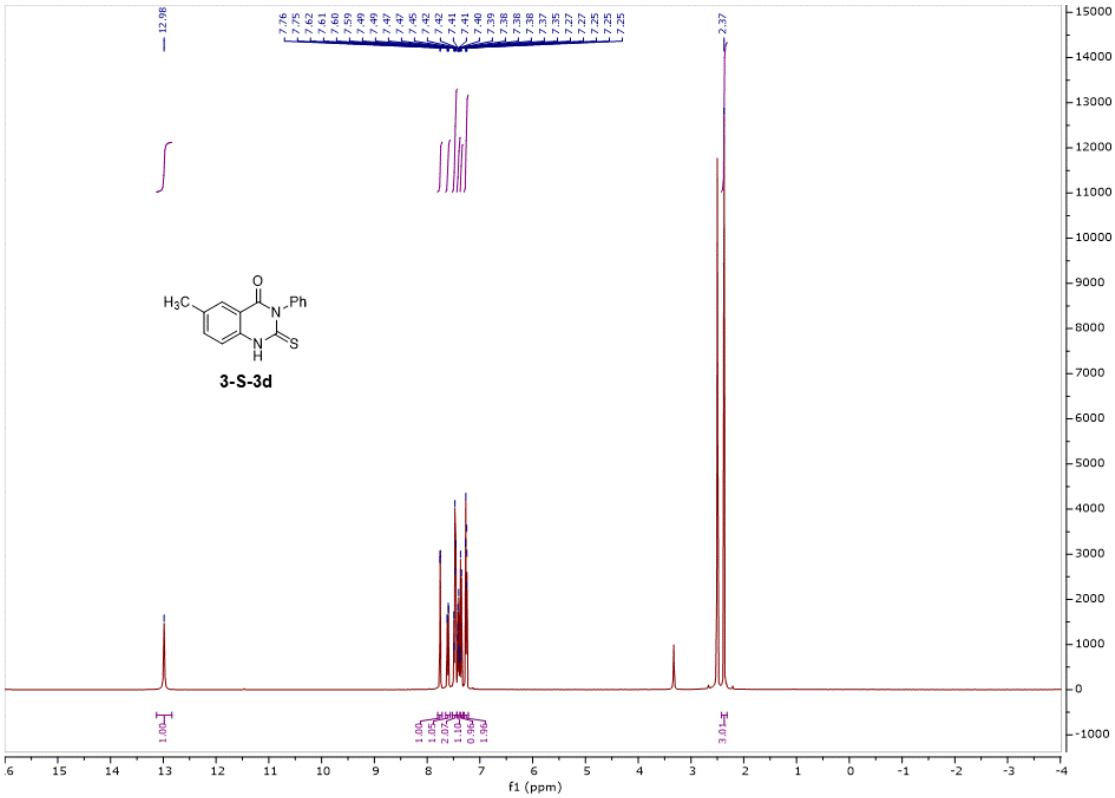

176.05
159.78
139.58
139.29
135.58
128.98
128.88
128.08
127.39
124.32
116.18
115.68
O
N
Ph
N
H
S
3-S-3a
f1 (ppm)

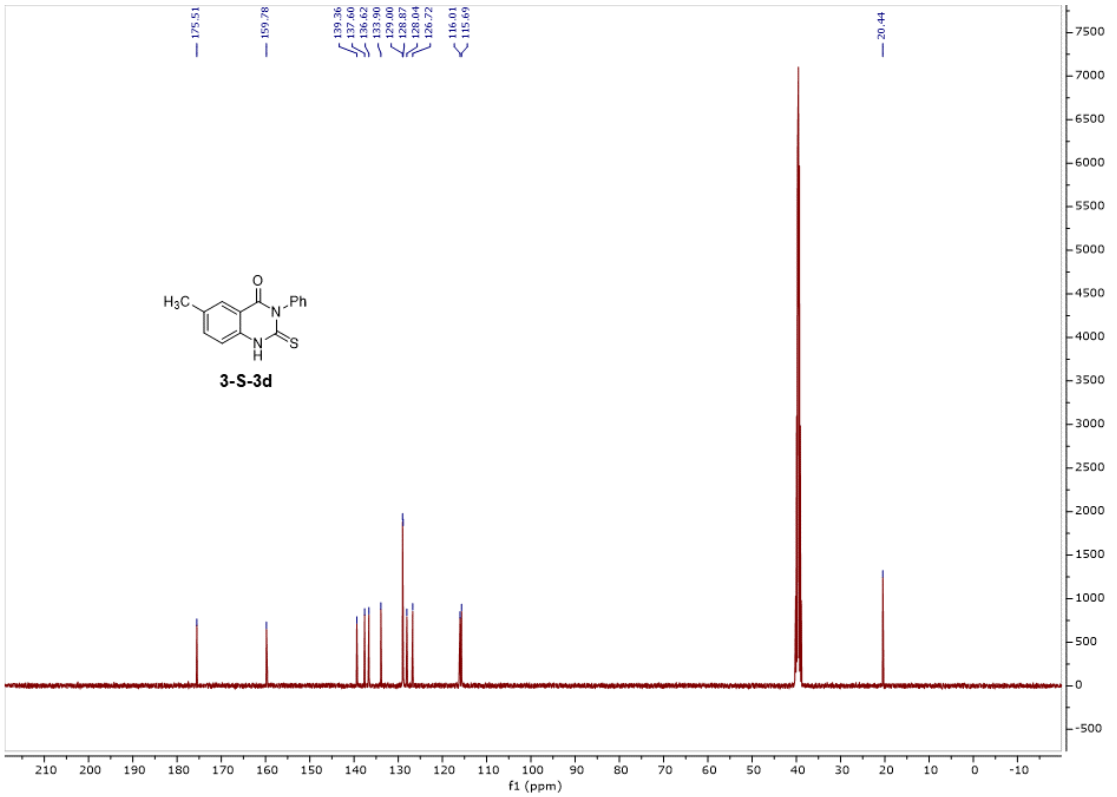

11.82
7.84
7.84
7.82
7.82
7.63
7.61
7.50
7.50
7.50
7.48
7.48
7.47
7.46
7.46
7.43
7.42
7.42
7.41
7.41
7.40
7.39
7.39
7.38
7.28
7.28
7.27
7.26
7.26
7.26
7.24
2.52
O
N
Ph
N
H
S
CH3
3-S-3b
f1 (ppm)

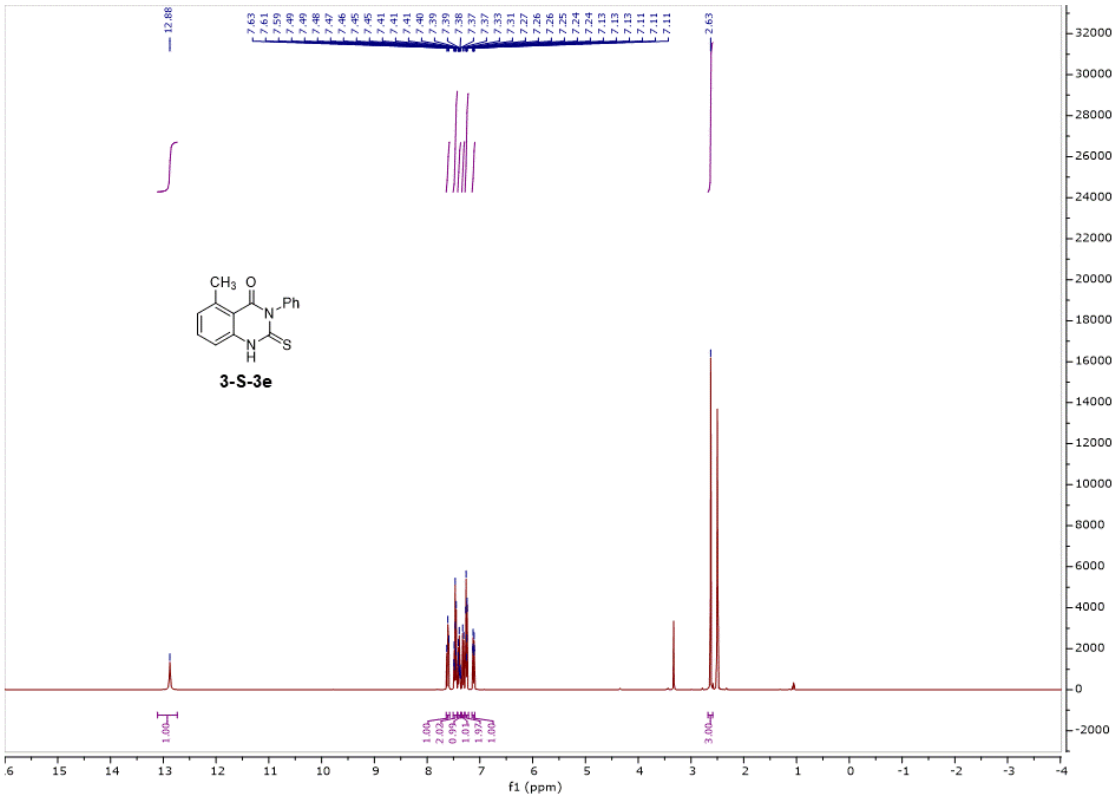

176.42
159.81
139.48
138.02
136.77
128.92
128.90
128.04
125.29
124.52
124.16
116.53
17.37
O
N
Ph
N
H
S
CH3
3-S-3b
f1 (ppm)

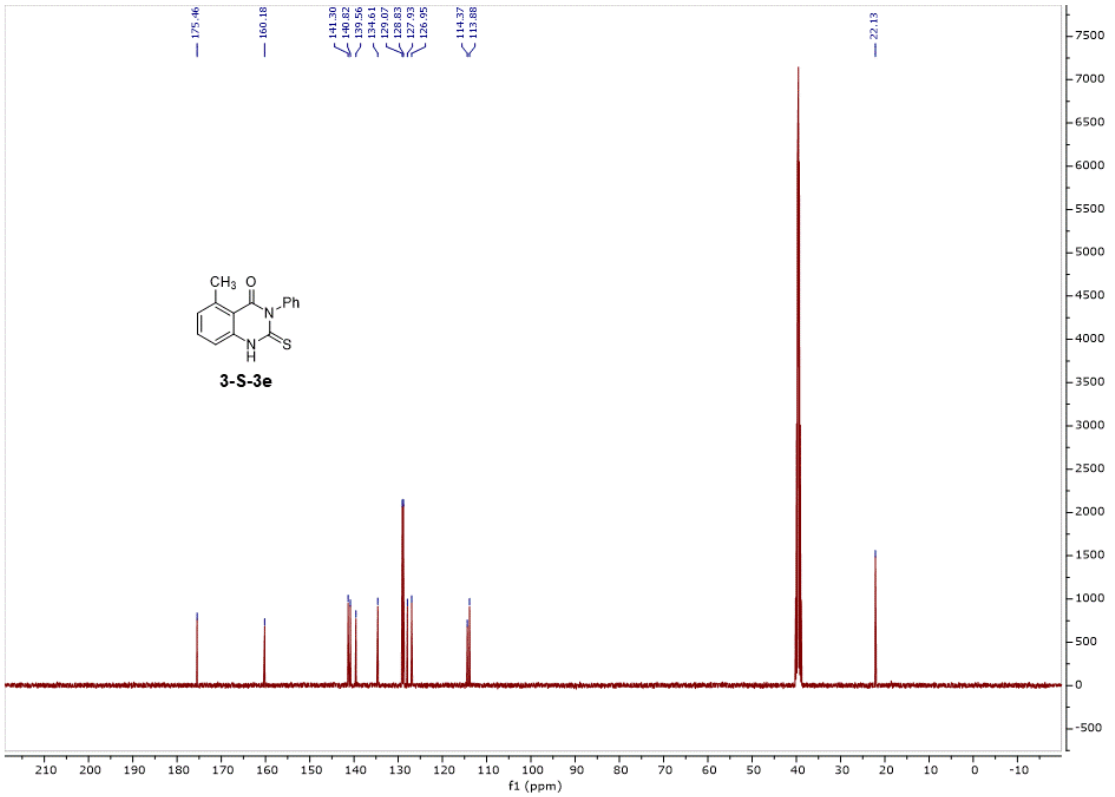

12.97
7.85
7.83
7.49
7.47
7.45
7.42
7.40
7.38
7.27
7.25
7.23
7.18
7.16
2.42
O
N
Ph
H3C
N
H
S
3-S-3c
1.00
1.03
2.10
1.04
3.15
1.01
3.04
f1 (ppm)

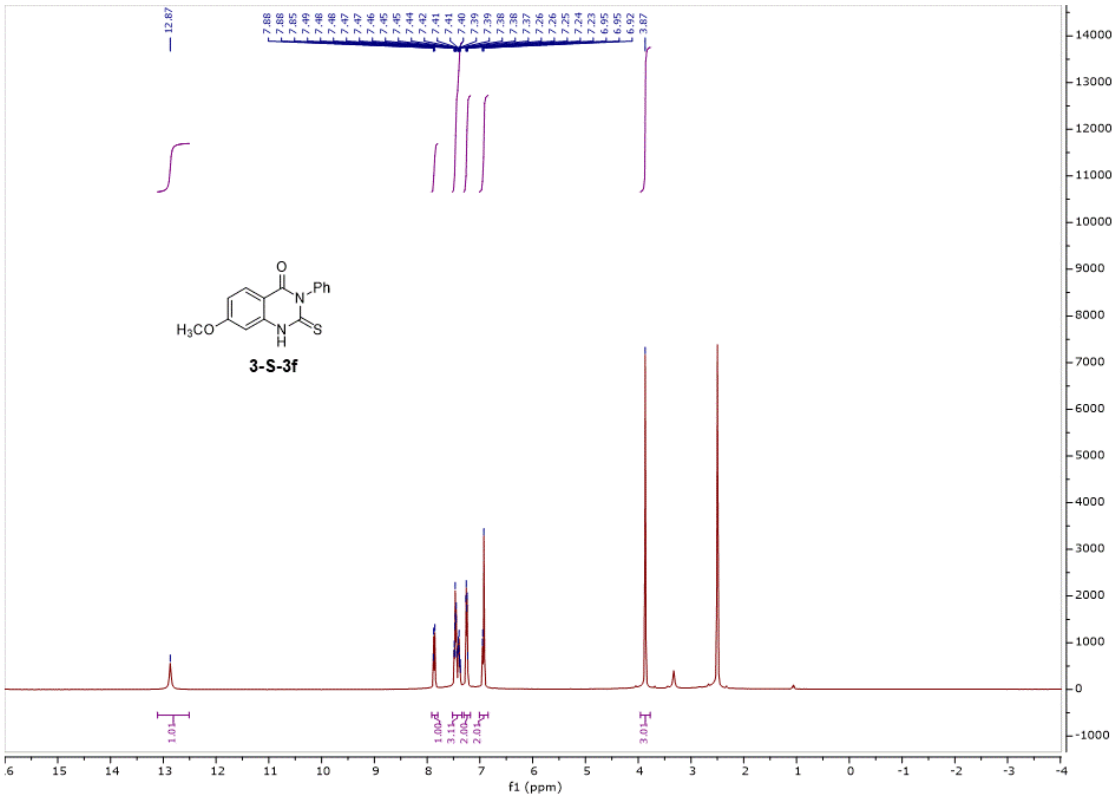

176.06
159.64
146.39
139.65
139.30
129.01
128.86
128.04
127.35
125.70
115.26
113.89
21.64
3-S-3c
f1 (ppm)

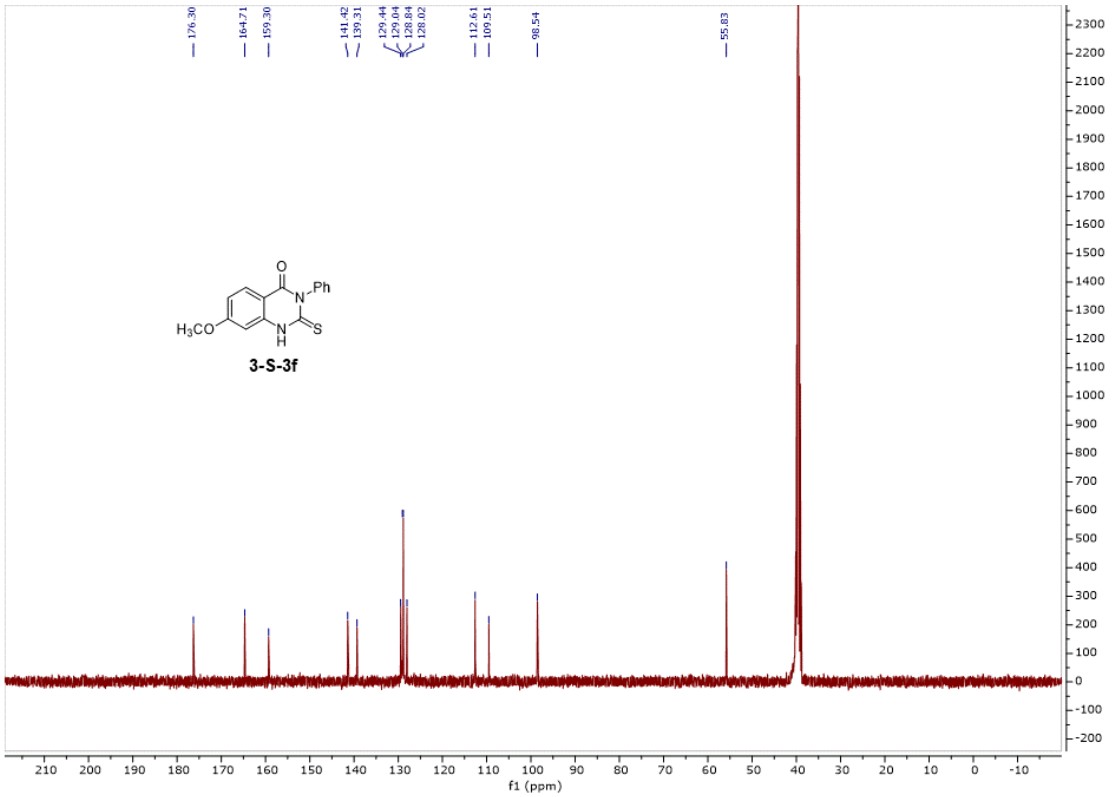

12.98
7.76
7.75
7.62
7.61
7.60
7.59
7.49
7.49
7.47
7.47
7.46
7.42
7.41
7.41
7.40
7.39
7.38
7.38
7.38
7.37
7.35
7.27
7.27
7.25
7.25
7.25
2.37
1.00
1.00
1.05
2.07
1.10
0.96
1.96
3.01
3-S-3d
f1 (ppm)

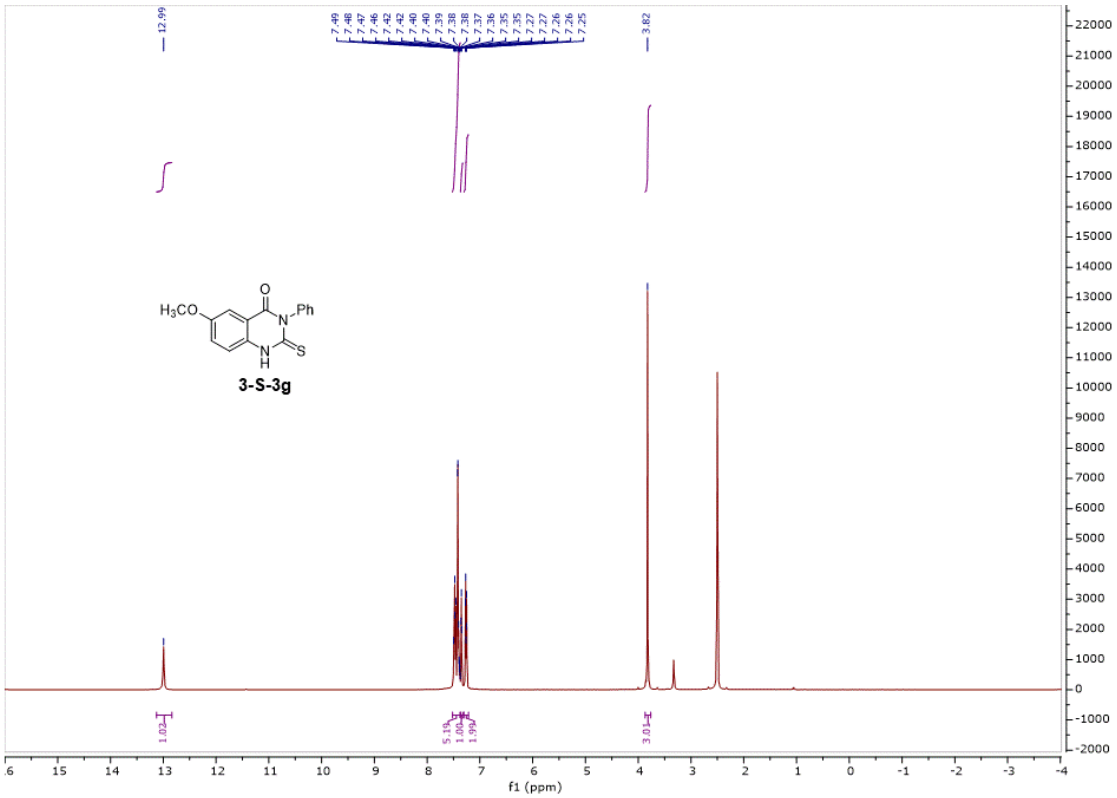

175.51
159.78
139.36
137.60
136.62
133.90
129.00
128.87
128.04
126.72
116.01
115.69
20.44
H3C
O
N
Ph
N
H
S
3-S-3d
f1 (ppm)

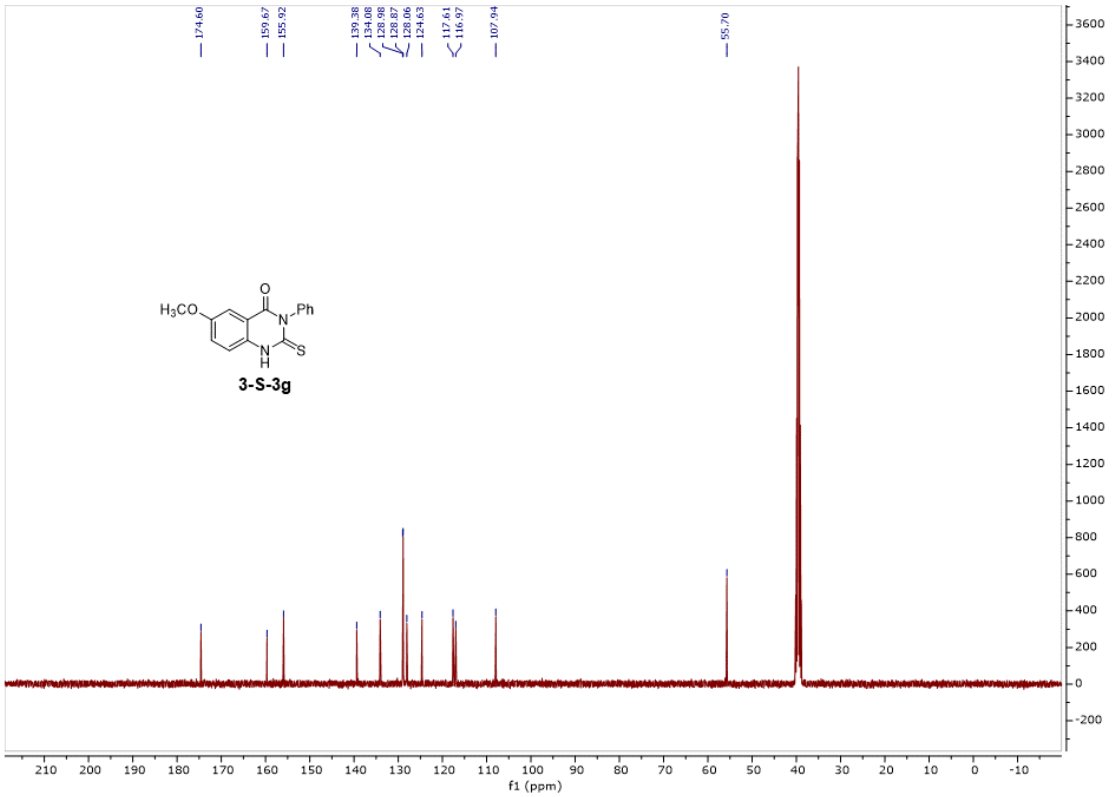

12.88
7.63
7.61
7.59
7.49
7.49
7.48
7.47
7.46
7.45
7.45
7.41
7.41
7.41
7.40
7.39
7.39
7.38
7.37
7.37
7.37
7.33
7.31
7.27
7.26
7.26
7.25
7.24
7.24
7.13
7.13
7.11
7.11
7.11
7.11
2.63
CH3
O
N
Ph
N
H
S
3-S-3e
1.00
1.00
2.02
0.99
1.01
1.92
1.00
3.00
f1 (ppm)


175.46
160.18
141.30
140.82
139.56
134.61
129.07
128.83
127.93
126.95
114.37
113.88
22.13
CH3
O
N
Ph
N
H
S
3-S-3e
f1 (ppm)

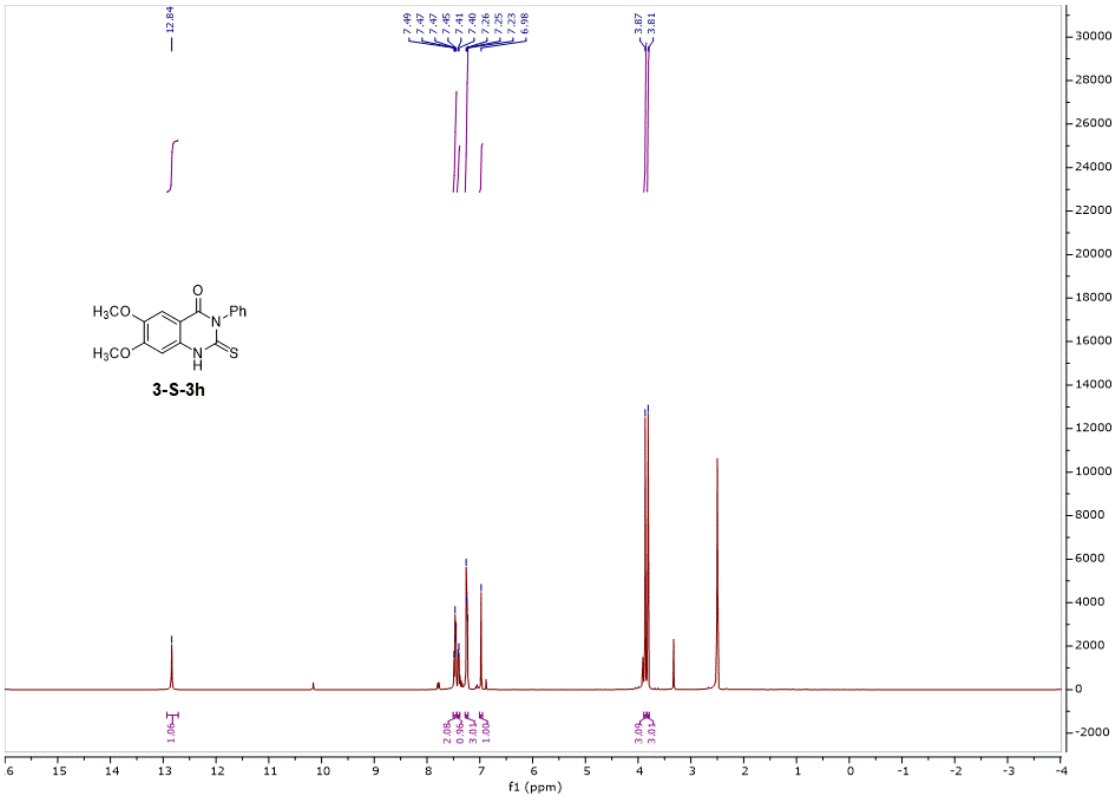

12.87
7.88
7.88
7.85
7.49
7.48
7.48
7.47
7.47
7.46
7.45
7.45
7.44
7.42
7.41
7.41
7.40
7.39
7.39
7.38
7.38
7.37
7.26
7.26
7.25
7.24
7.23
6.95
6.95
6.92
3.87
O
N
Ph
H3CO
N
H
S
3-S-3f
1.01
1.00
3.11
2.00
2.01
3.01
f1 (ppm)


176.30
164.71
159.30
141.42
139.31
129.44
129.04
128.84
128.02
112.61
109.51
98.54
55.83
O
N
Ph
H3CO
N
H
S
3-S-3f
f1 (ppm)

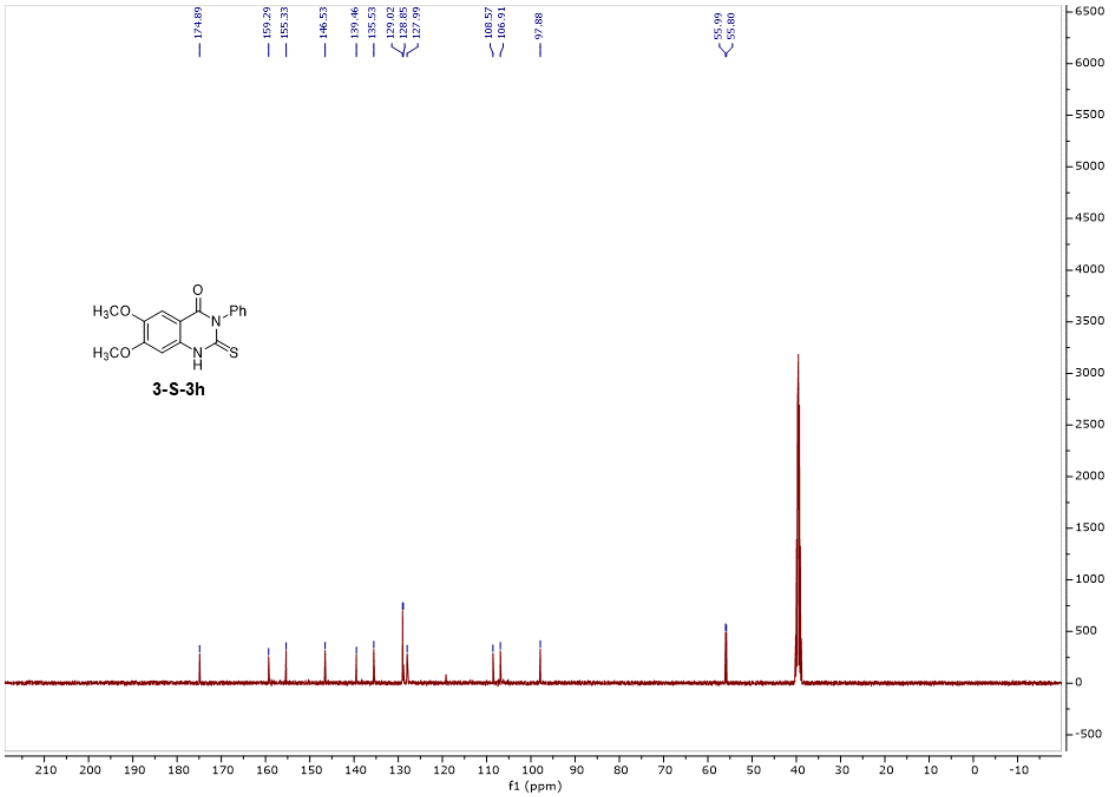

12.99
7.49
7.48
7.47
7.46
7.42
7.42
7.40
7.39
7.38
7.38
7.37
7.36
7.35
7.35
7.27
7.27
7.26
7.26
7.25
3.82
1.02
5.13
1.00
1.99
3.01
H3CO
O
N
Ph
N
H
S
3-S-3g
f1 (ppm)

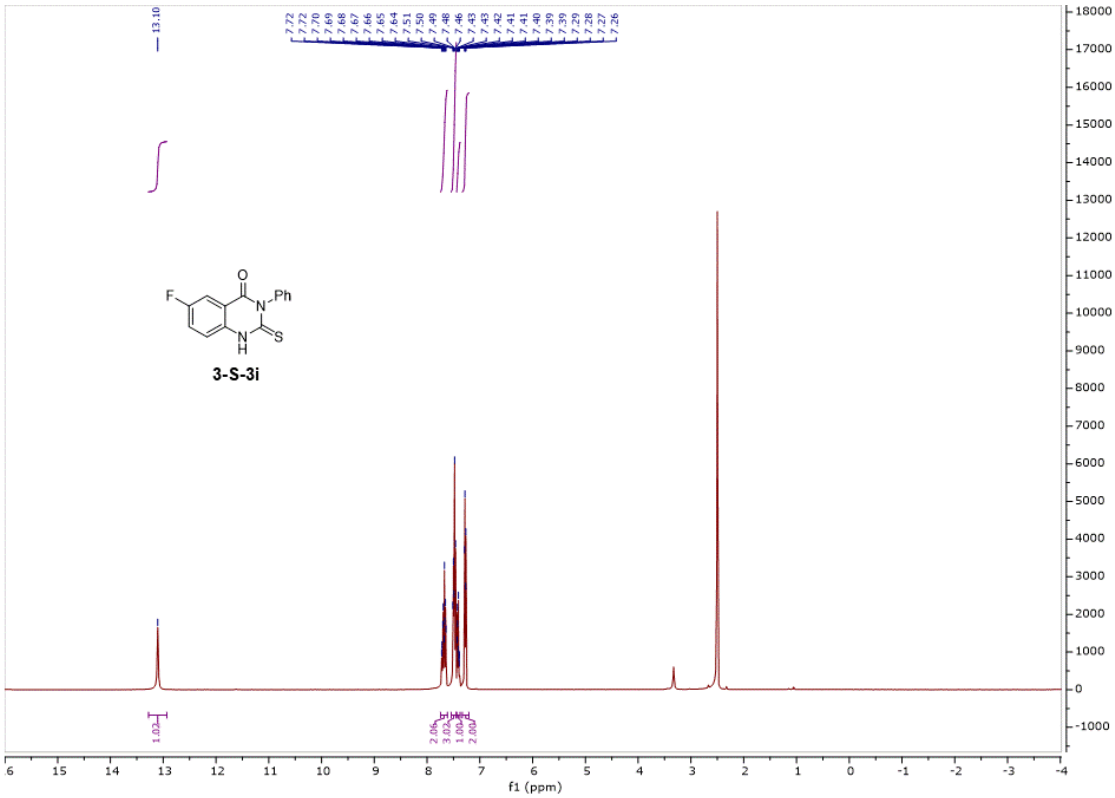

174.60
159.67
155.92
139.38
134.08
128.98
128.87
128.06
124.63
117.61
116.97
107.94
55.70
H3CO
O
N
Ph
N
H
S
f1 (ppm)

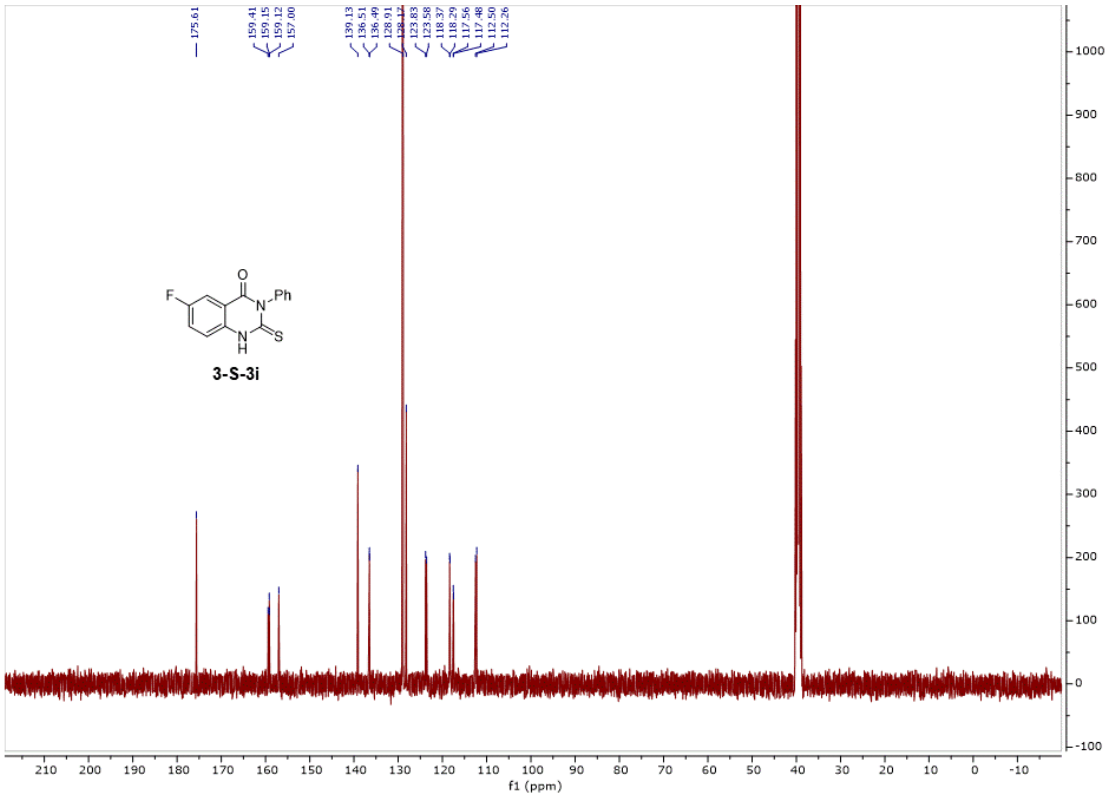
3-S-3g

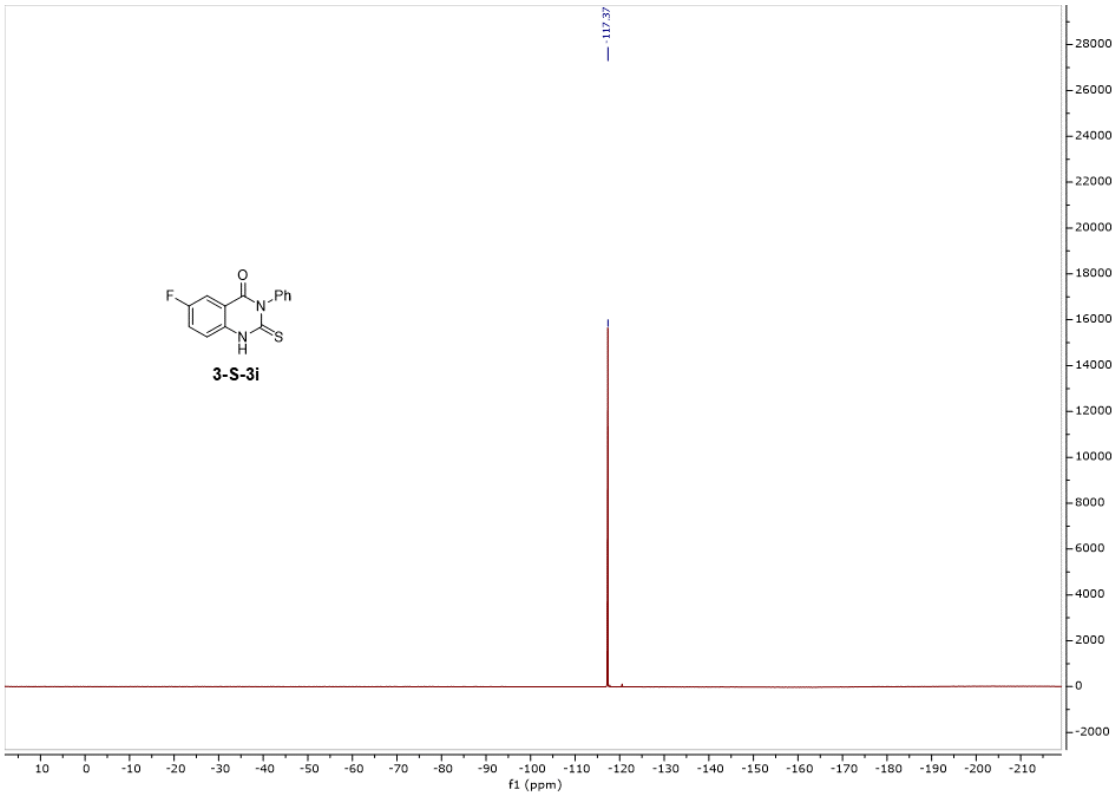

12.84
7.49
7.47
7.47
7.45
7.41
7.40
7.26
7.25
7.23
6.98
3.87
3.81
H3CO
H3CO
O
N
Ph
N
H
S
1.06
2.08
0.96
3.91
1.00
3.09
3.91
f1 (ppm)

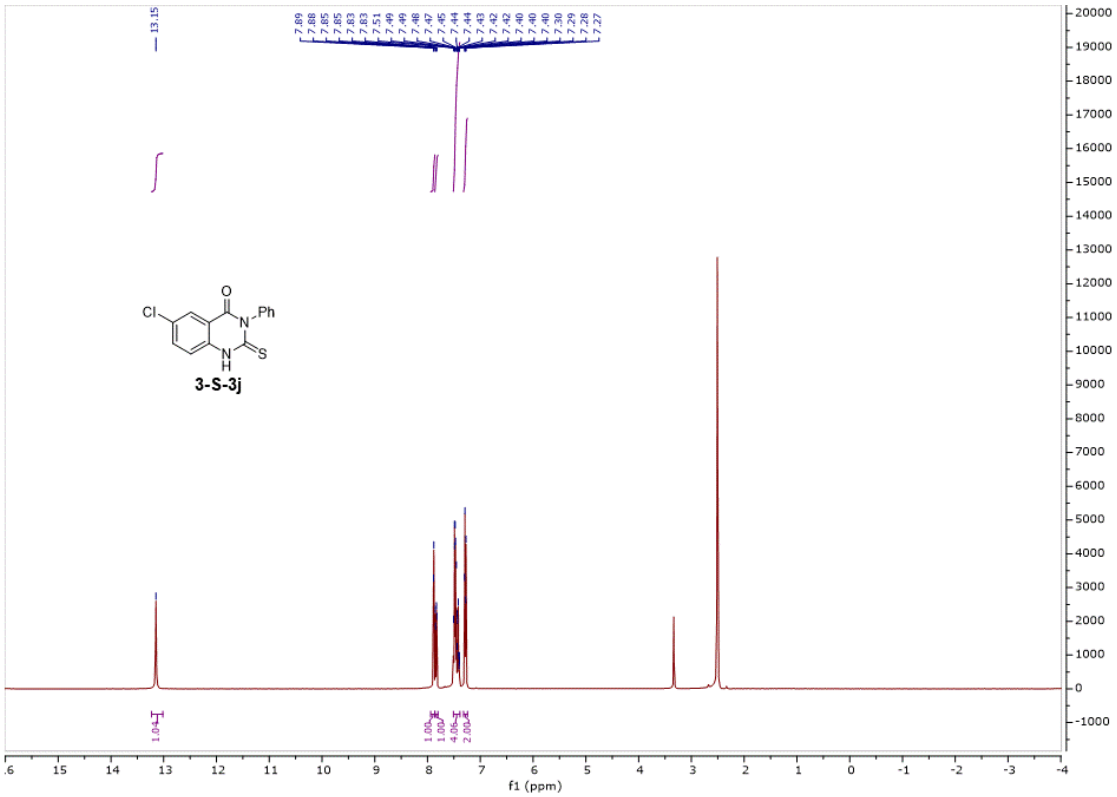
3-S-3h

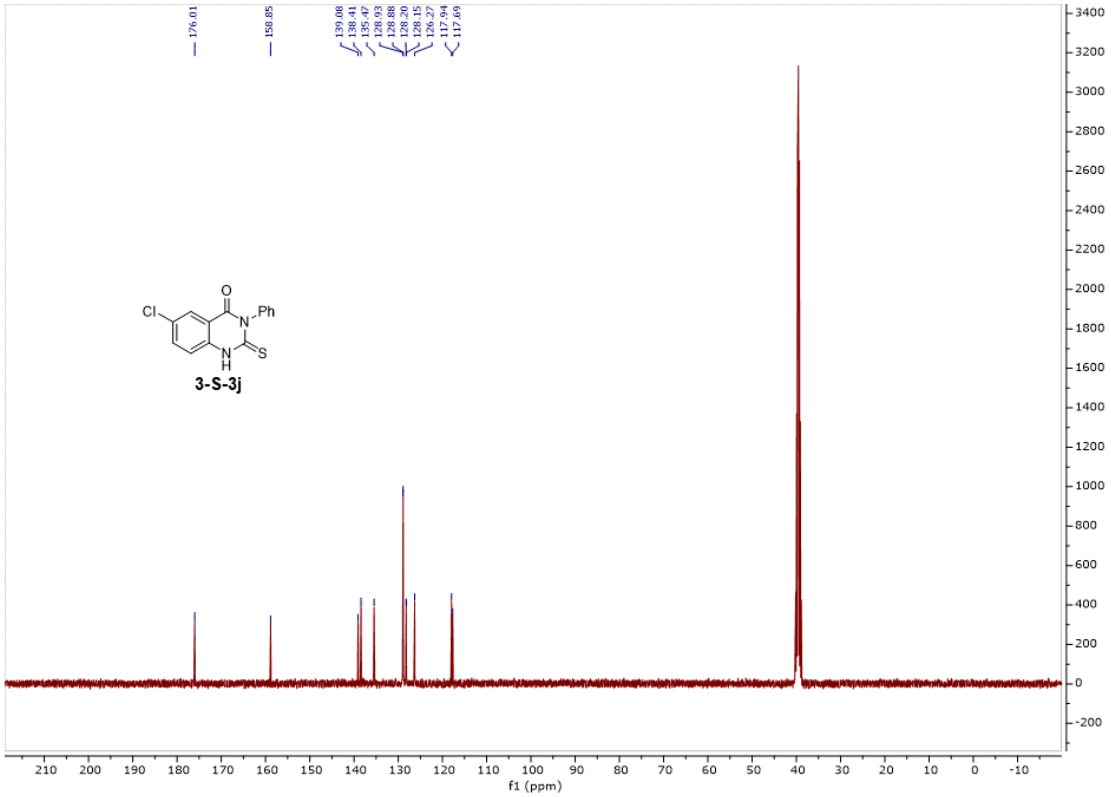

174.89
159.29
155.33
146.53
139.46
135.53
129.02
128.85
127.99
108.57
106.91
97.88
55.99
55.80
H3CO
H3CO
O
N
Ph
S
H
3-S-3h
f1 (ppm)

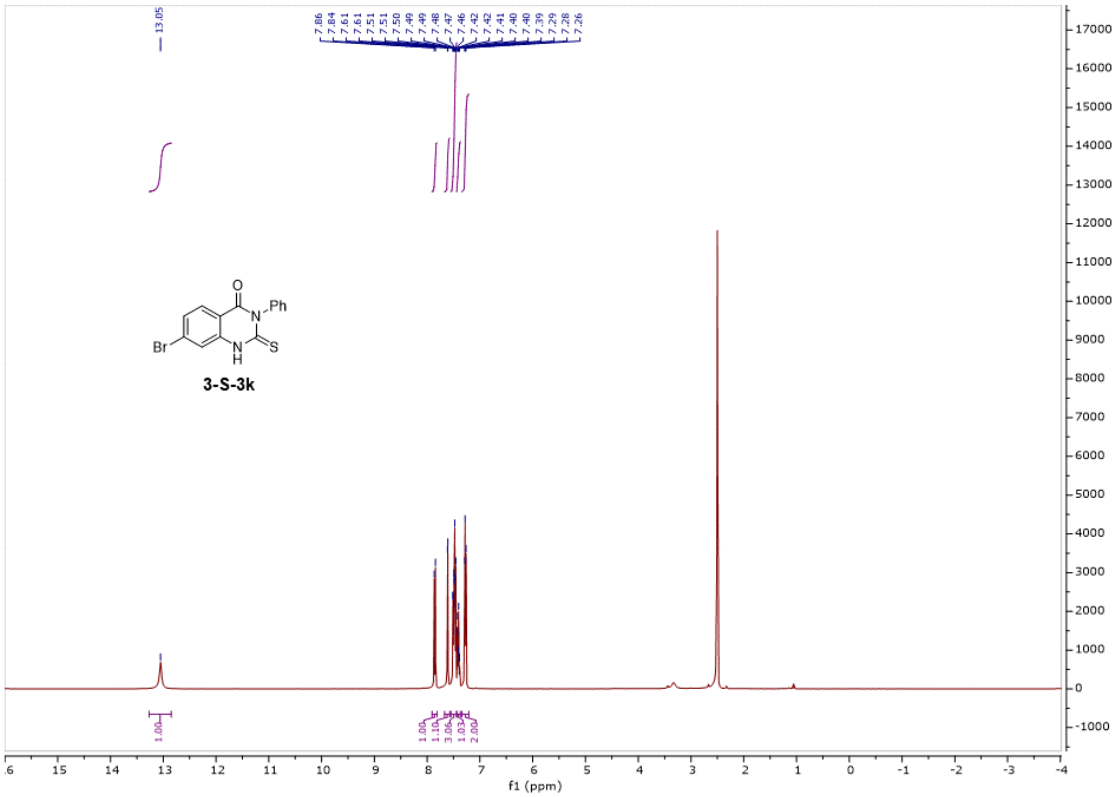

13.10
7.72
7.72
7.70
7.69
7.68
7.67
7.66
7.65
7.64
7.51
7.50
7.49
7.48
7.46
7.43
7.43
7.42
7.41
7.40
7.39
7.39
7.29
7.28
7.27
7.26
F
O
N
Ph
S
H
3-S-3i
f1 (ppm)

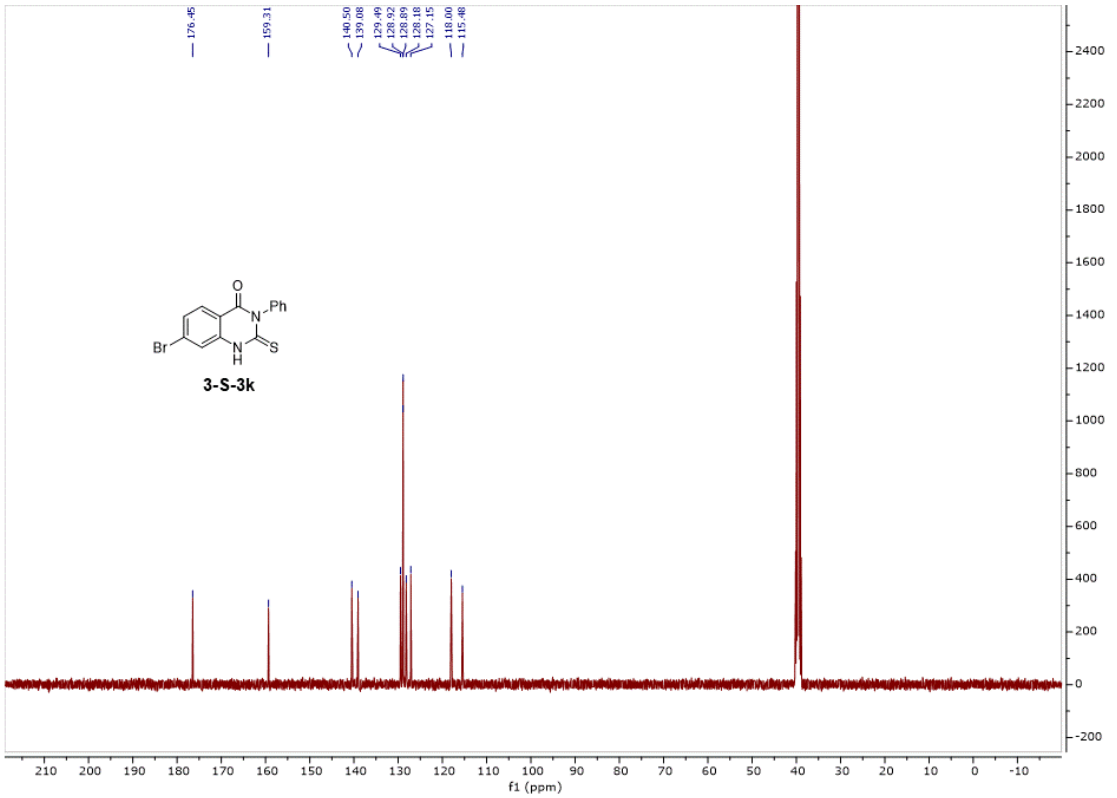

175.61
159.41
159.15
159.12
157.00
139.13
136.51
136.49
128.91
128.14
123.83
123.58
118.37
118.29
117.56
117.48
112.50
112.26
F
O
N
Ph
N
H
S
3-S-3i
f1 (ppm)

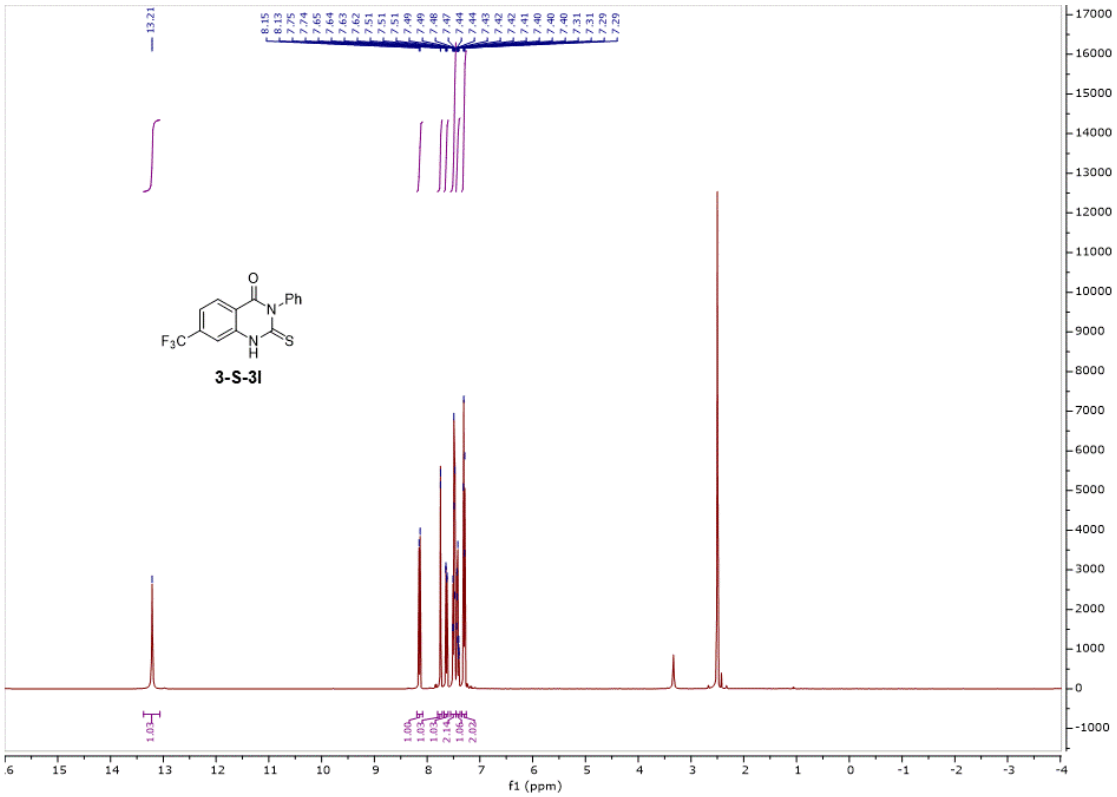

117.37
F
O
N
Ph
N
H
S
3-S-3i
f1 (ppm)

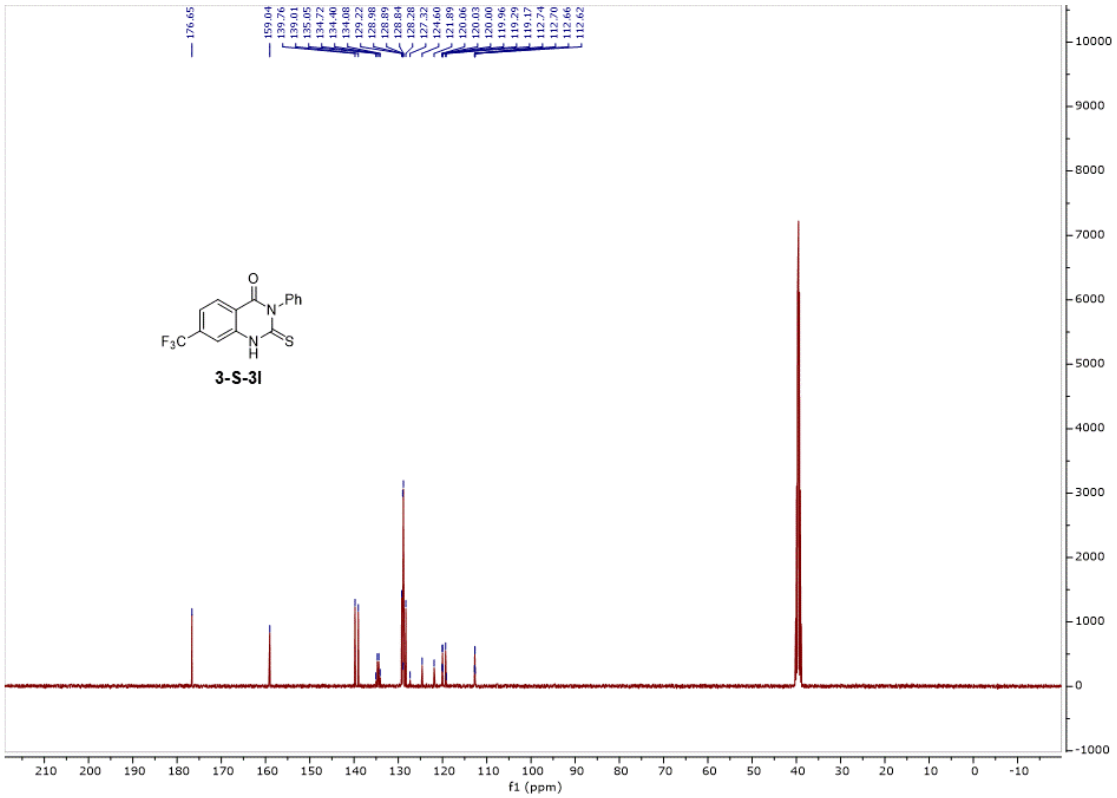

13.15
7.89
7.88
7.85
7.85
7.83
7.83
7.51
7.49
7.49
7.48
7.47
7.45
7.44
7.44
7.43
7.42
7.42
7.40
7.40
7.40
7.30
7.29
7.28
7.27
Cl
O
N
Ph
N
H
S
3-S-3j
1.04
1.00
1.00
4.06
2.04
f1 (ppm)

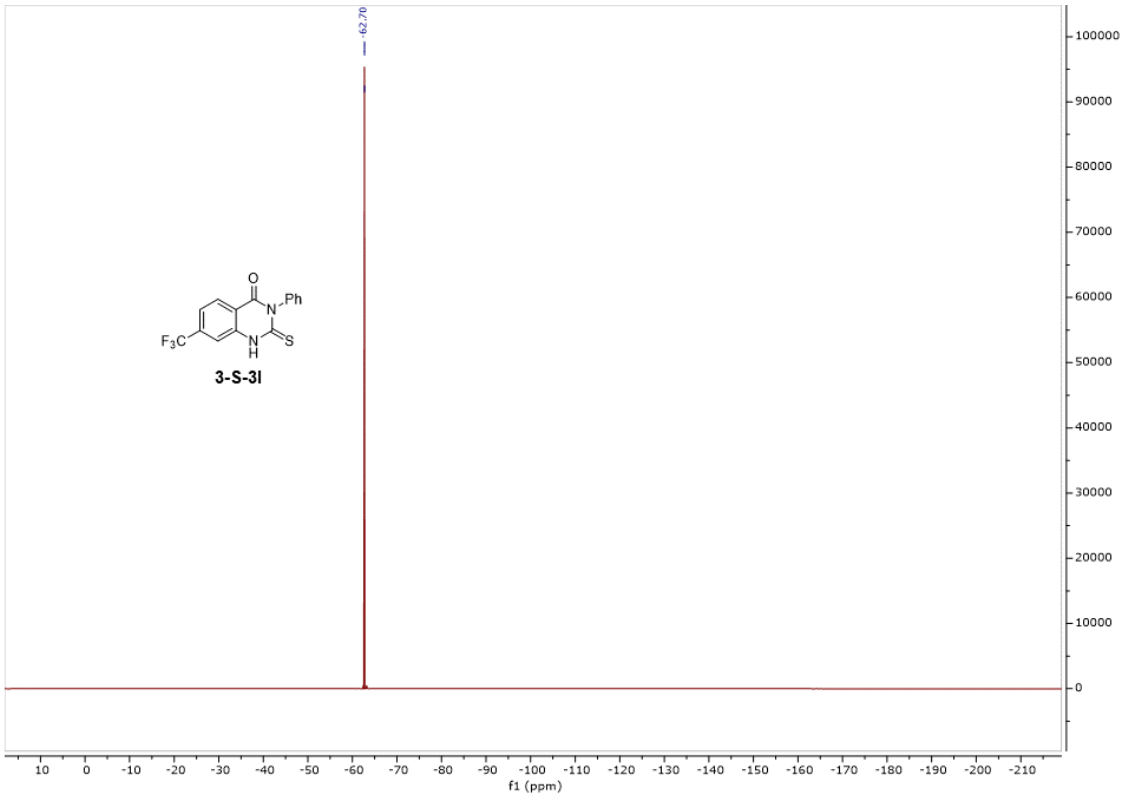

176.01
158.85
139.08
138.41
135.47
128.93
128.88
128.20
128.15
126.27
117.94
117.69
Cl
O
N
Ph
N
H
S
3-S-3j
f1 (ppm)

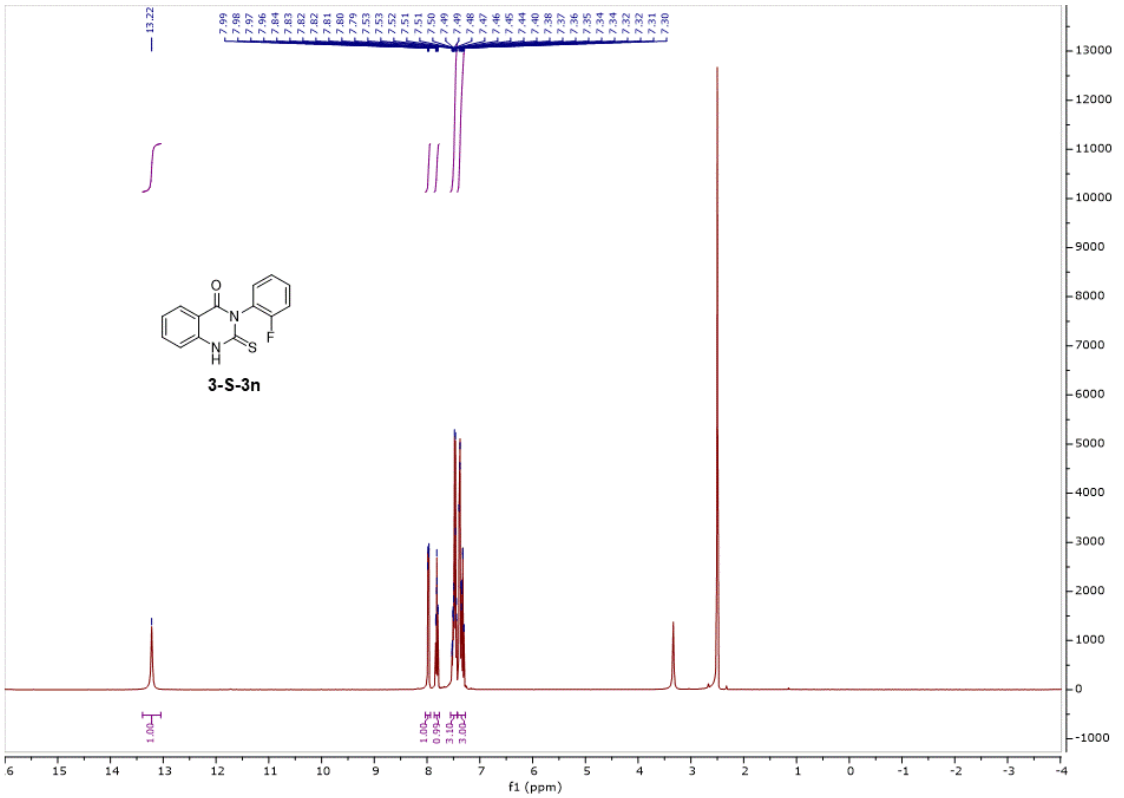

13.05
7.86
7.84
7.61
7.61
7.51
7.51
7.50
7.49
7.49
7.48
7.47
7.46
7.42
7.42
7.41
7.40
7.40
7.39
7.39
7.29
7.28
7.26
Ph
O
N
Br
N
H
S
3-S-3k
f1 (ppm)

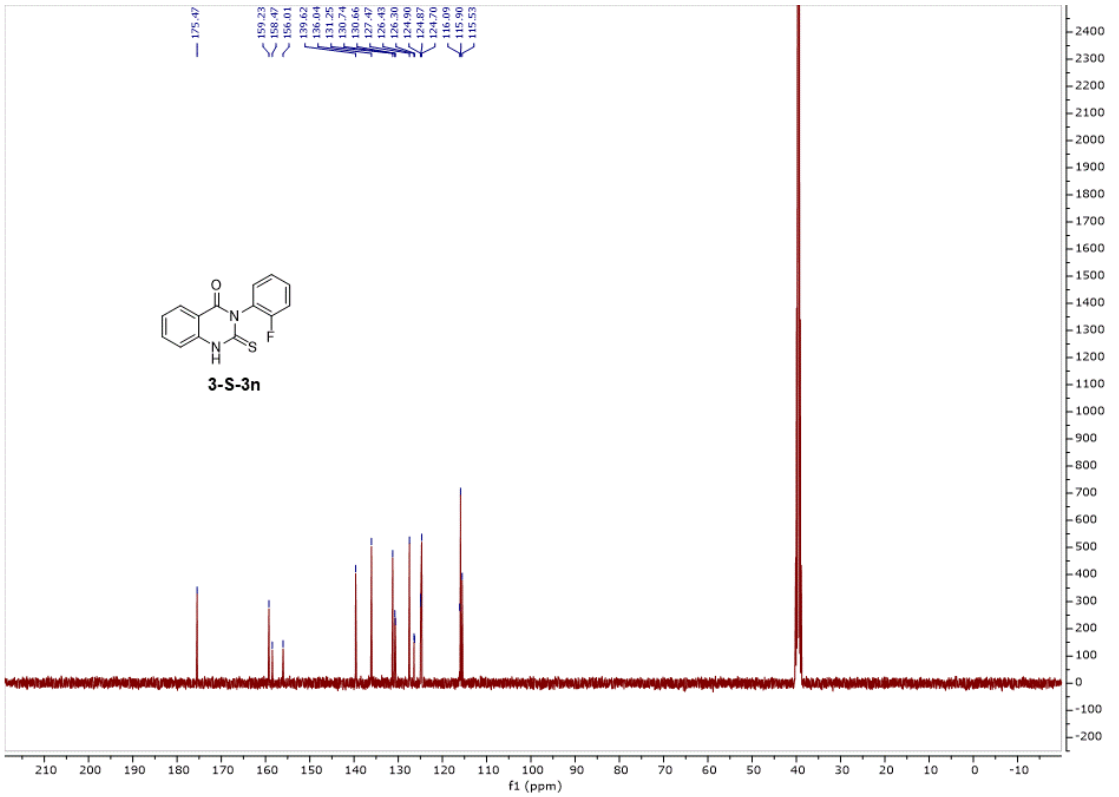

176.45
159.31
140.50
139.08
129.49
128.92
128.89
128.18
127.15
118.00
115.48
Ph
O
N
Br
N
H
S
3-S-3k
f1 (ppm)

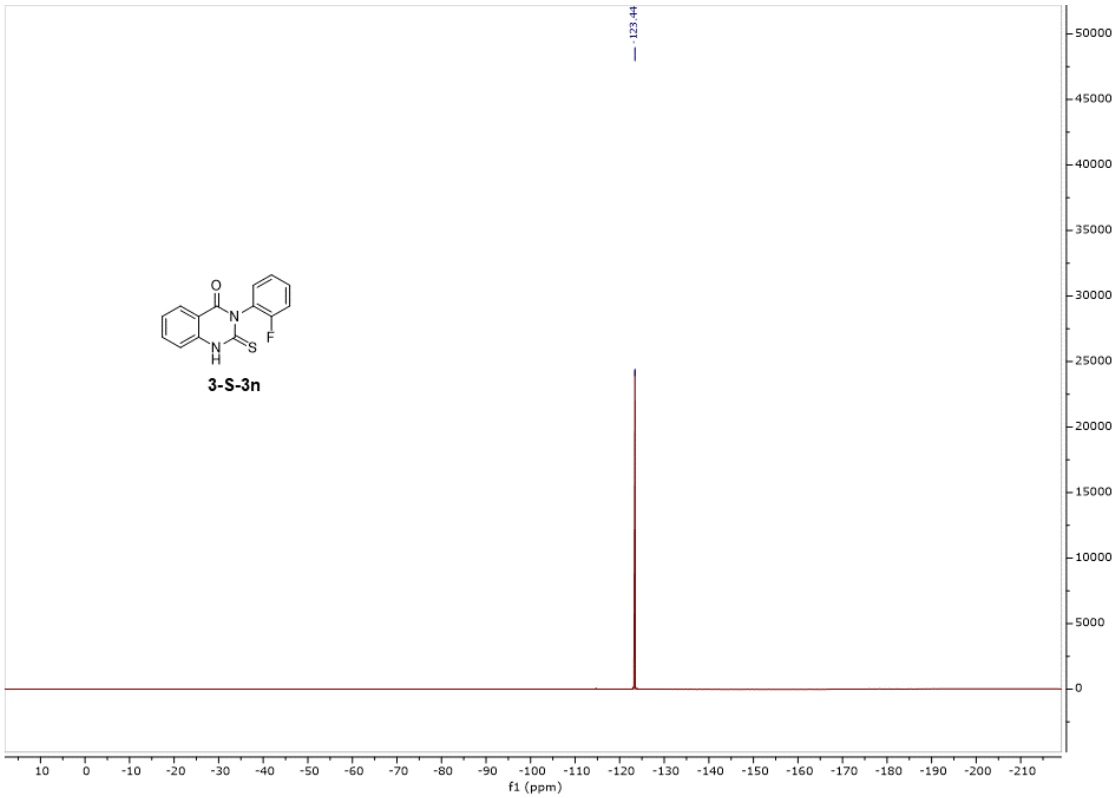

13.21
8.15
8.13
7.75
7.74
7.65
7.64
7.63
7.62
7.51
7.51
7.51
7.49
7.49
7.48
7.47
7.44
7.44
7.43
7.42
7.42
7.41
7.40
7.40
7.40
7.31
7.31
7.29
7.29
O
N
Ph
F3C
N
H
S
3-S-3l
1.03
1.00
1.03
1.03
2.14
1.06
2.02
f1 (ppm)

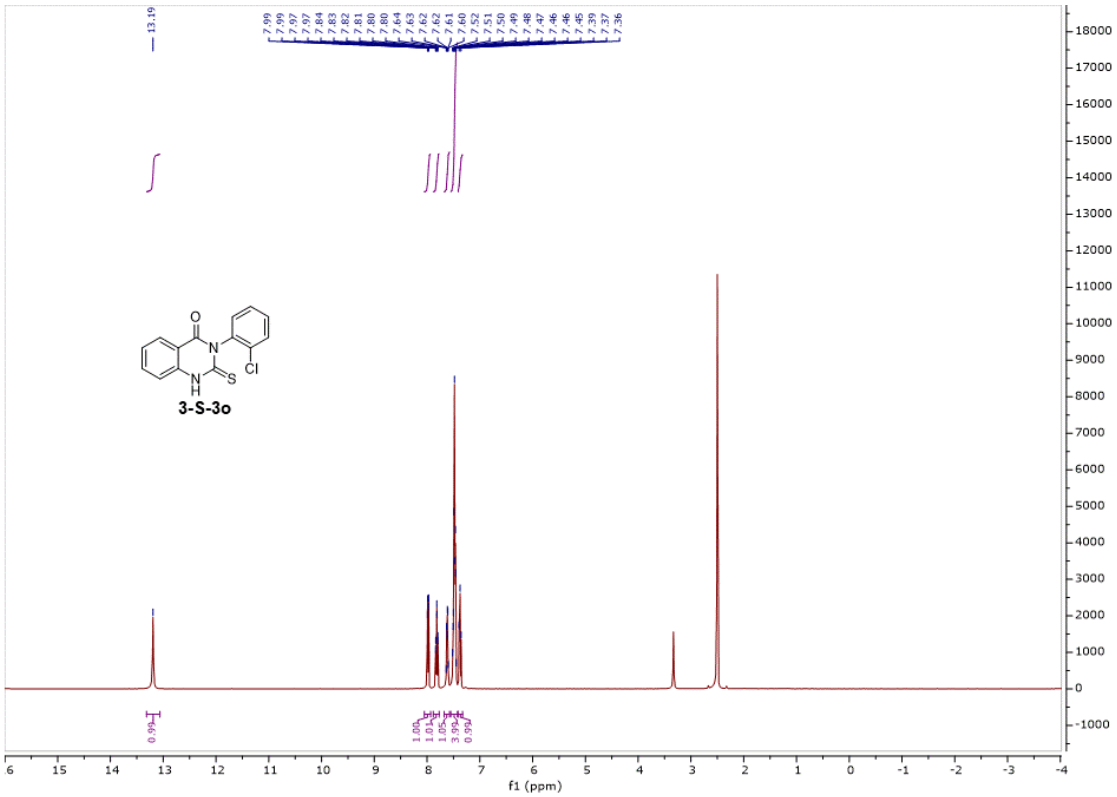

176.65
159.04
139.76
139.01
135.05
134.72
134.40
134.08
129.22
128.98
128.89
128.84
128.28
127.32
124.60
121.89
120.06
120.03
120.00
119.96
119.29
119.17
112.74
112.70
112.66
112.62
O
N
Ph
F3C
N
H
S
3-S-3l
f1 (ppm)

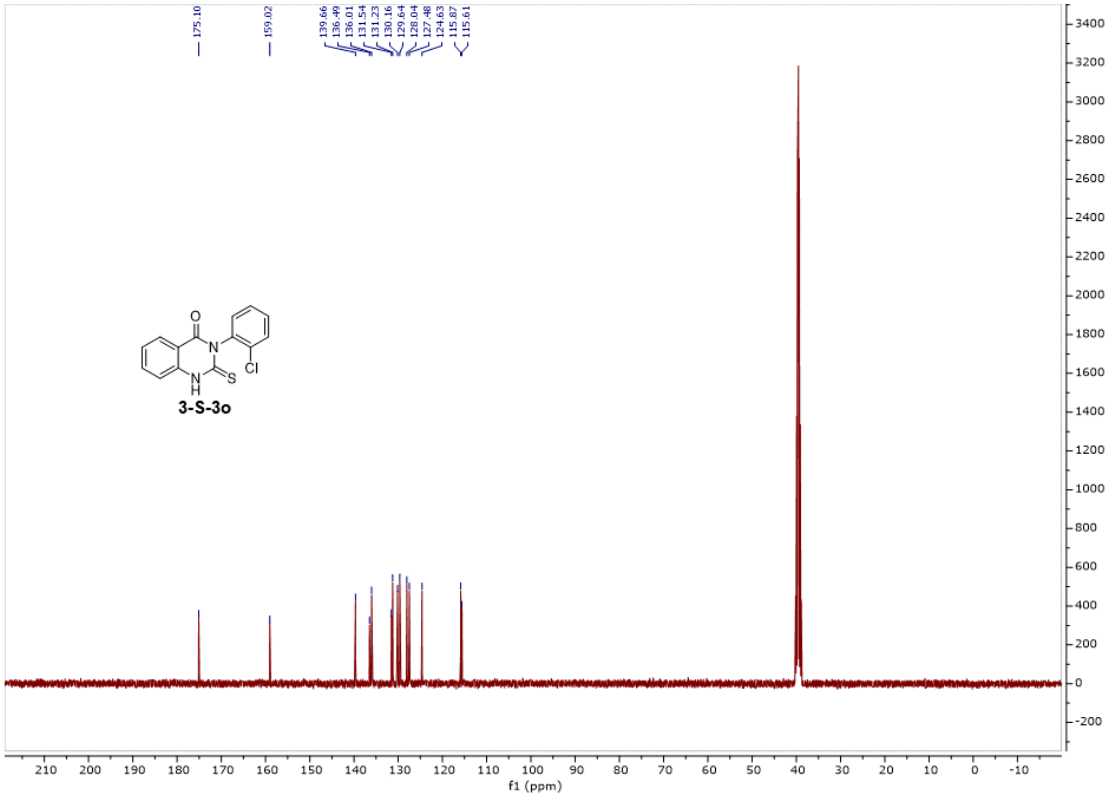

62.70
3-S-3l
f1 (ppm)

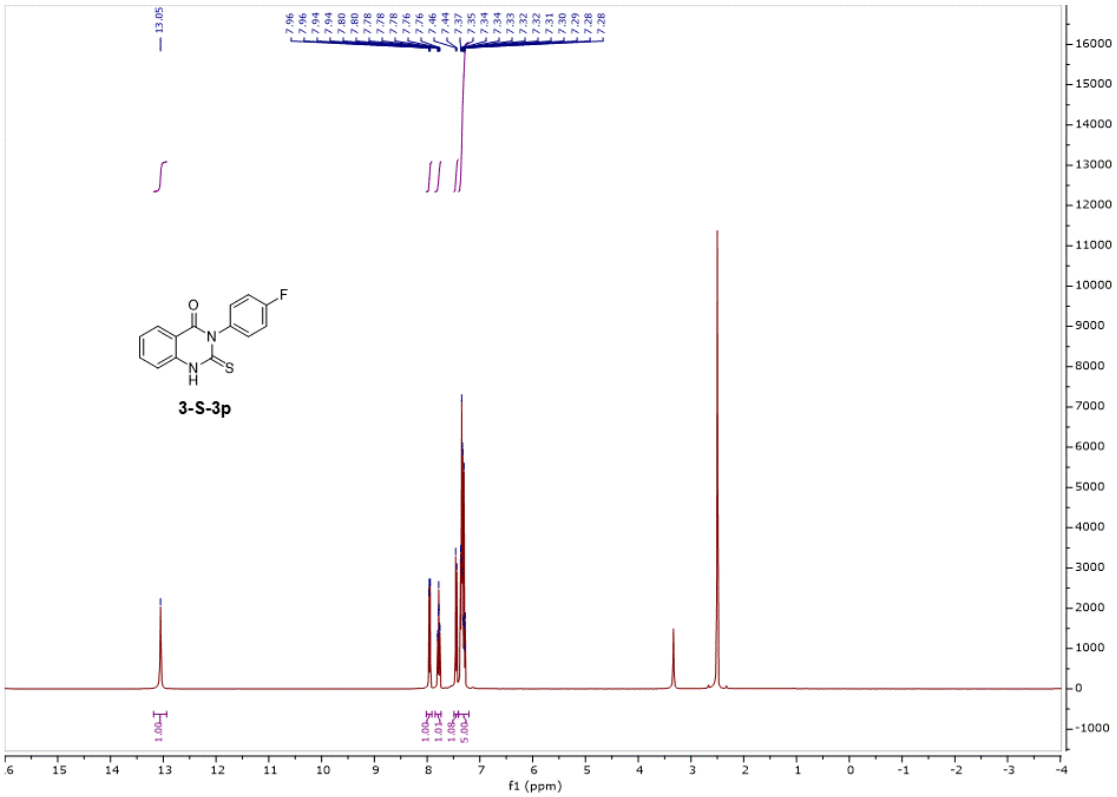

13.22
7.99
7.98
7.97
7.96
7.84
7.83
7.82
7.82
7.81
7.80
7.79
7.53
7.53
7.52
7.51
7.51
7.50
7.49
7.49
7.48
7.47
7.46
7.45
7.44
7.40
7.38
7.37
7.36
7.35
7.34
7.34
7.32
7.32
7.31
7.30
3-S-3n
1.00
1.00
0.99
3.10
3.00
f1 (ppm)

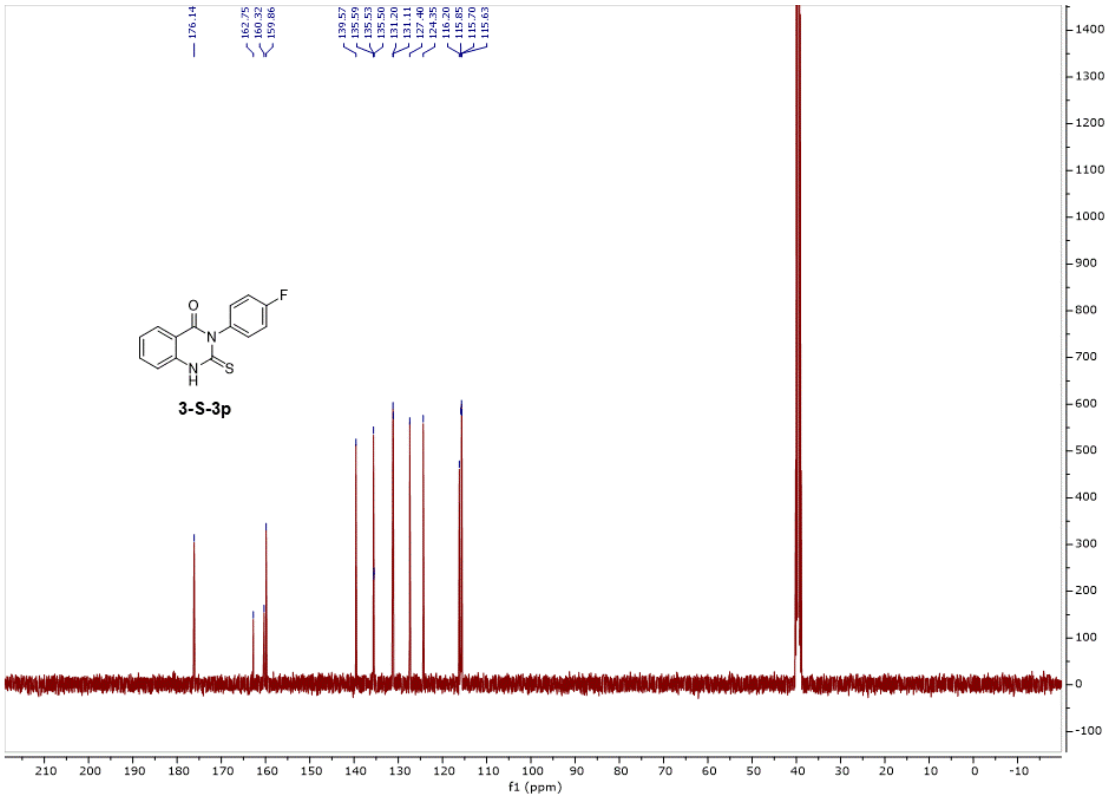

175.47
159.23
158.97
156.01
139.62
136.04
131.25
130.74
130.66
127.47
126.43
126.30
124.90
124.87
124.70
116.09
115.90
115.53
3-S-3n
f1 (ppm)

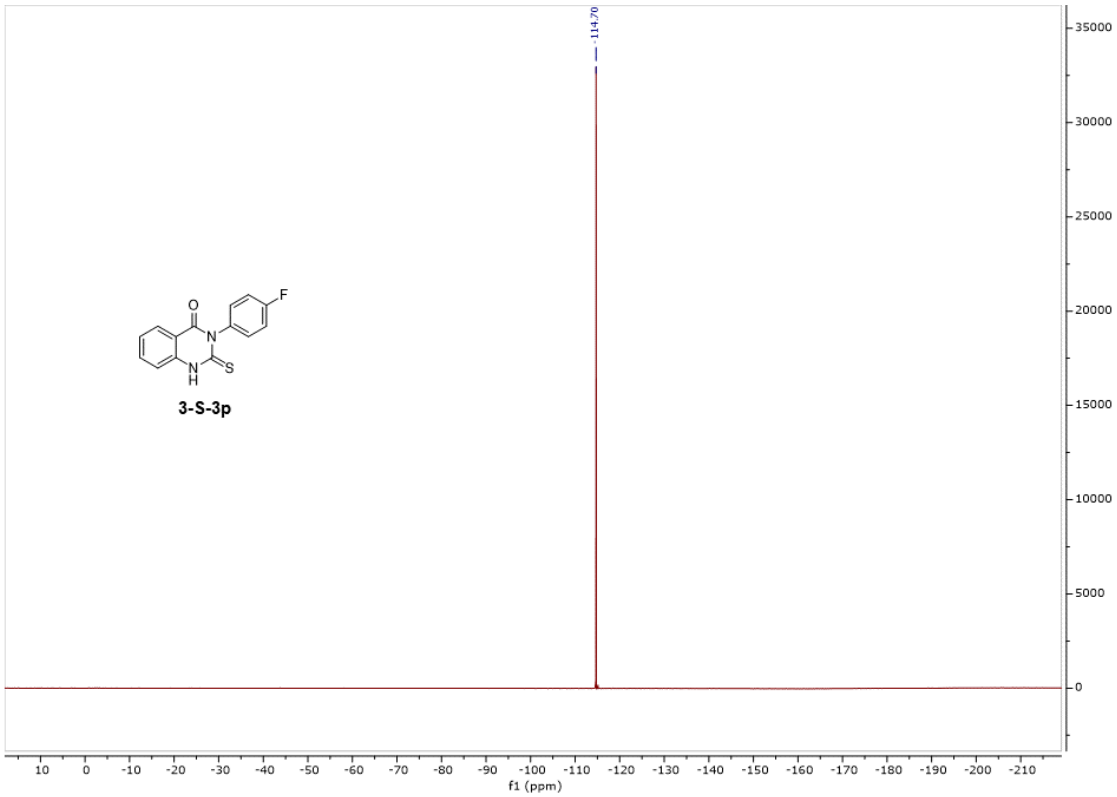

123.44
3-S-3n
f1 (ppm)

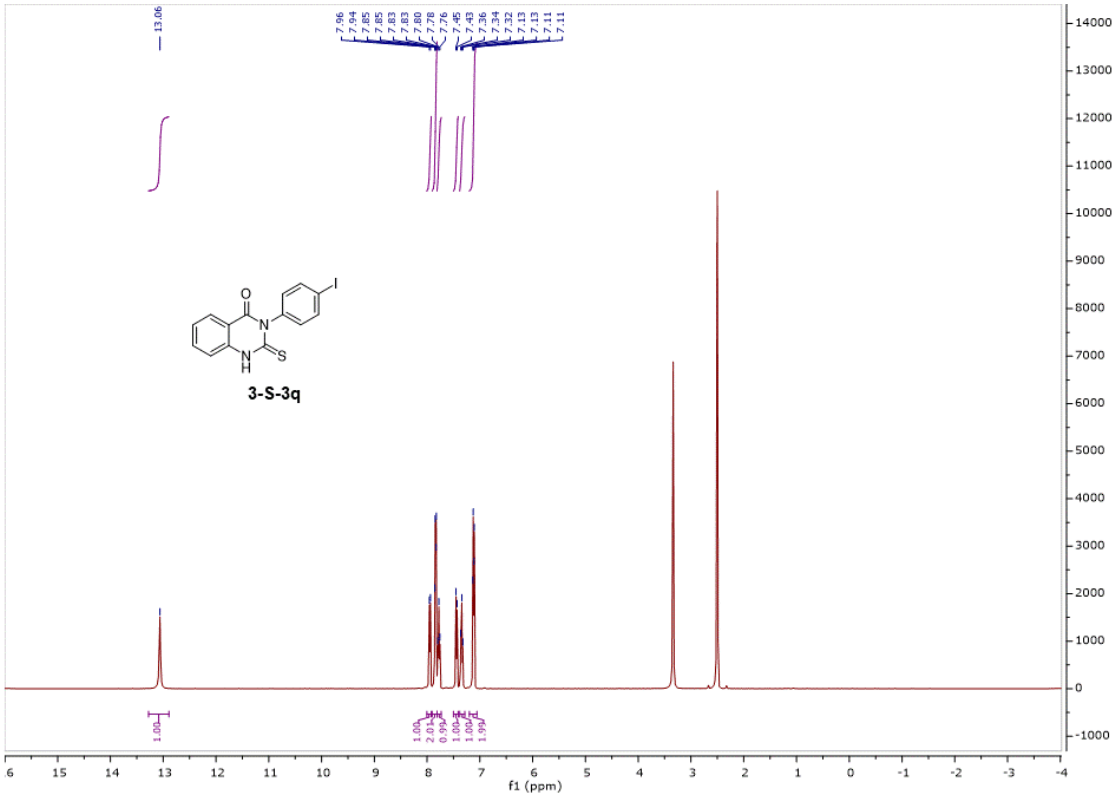

13.19
7.99
7.99
7.97
7.97
7.84
7.83
7.82
7.81
7.80
7.80
7.64
7.63
7.62
7.62
7.61
7.60
7.52
7.51
7.50
7.49
7.48
7.47
7.46
7.46
7.45
7.39
7.37
7.36
O
N
Cl
N
H
S
3-S-3o
0.99
1.00
1.01
1.05
3.00
0.99
f1 (ppm)

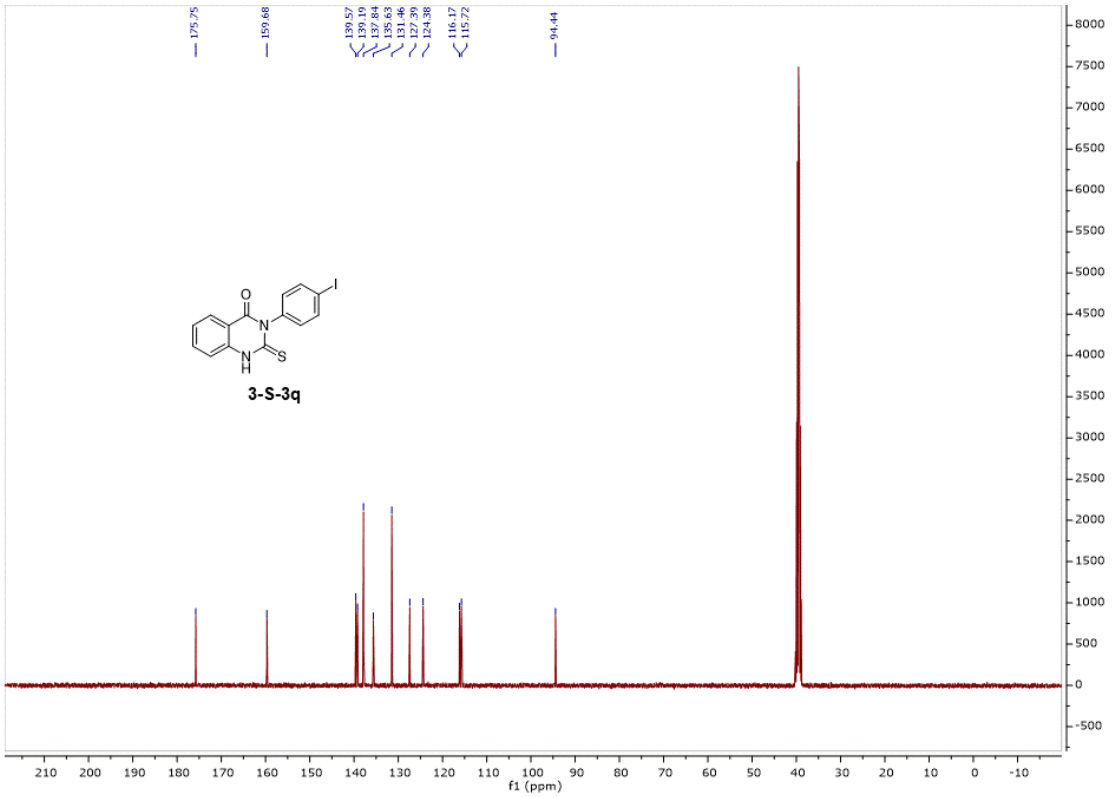

175.10
159.02
139.66
136.49
136.01
131.54
131.23
130.16
129.64
129.04
127.48
124.63
115.87
115.61
O
N
Cl
N
H
S
3-S-3o
f1 (ppm)

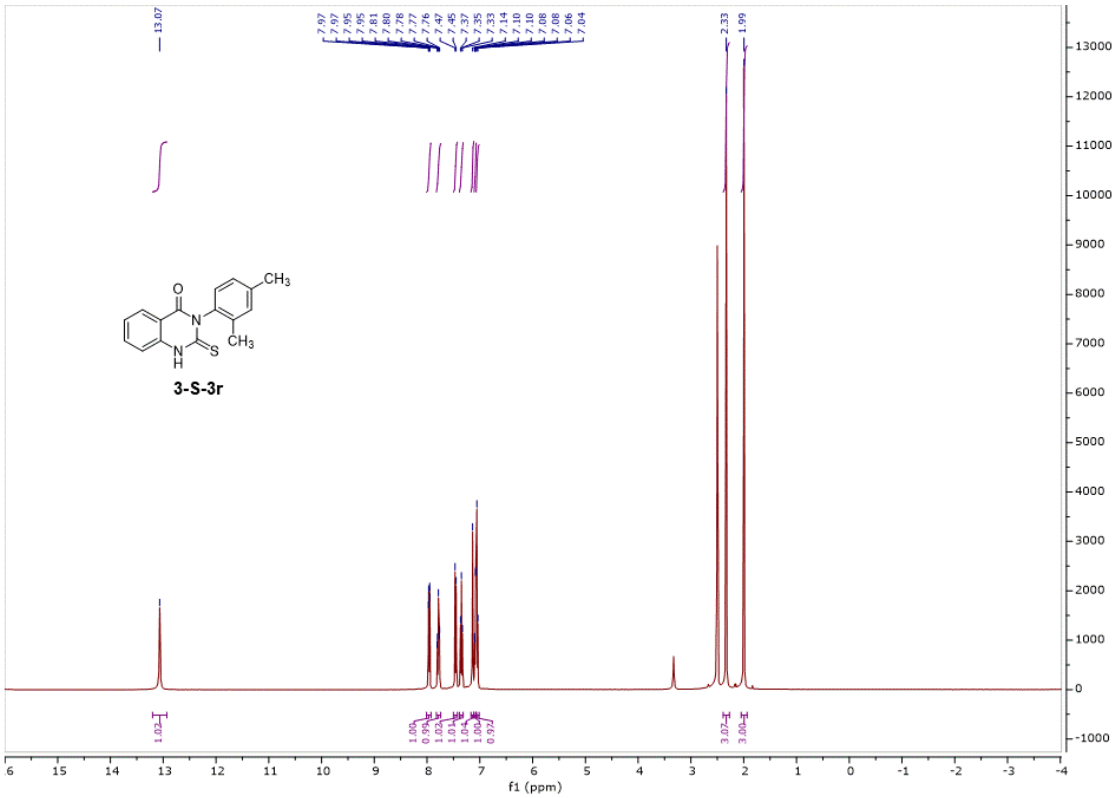

13.05
7.96
7.96
7.94
7.94
7.80
7.78
7.78
7.78
7.76
7.76
7.46
7.44
7.37
7.35
7.34
7.34
7.33
7.32
7.32
7.31
7.30
7.29
7.28
7.28
F
O
N
N
H
S
3-S-3p
1.00
1.00
1.01
1.08
5.00
f1 (ppm)

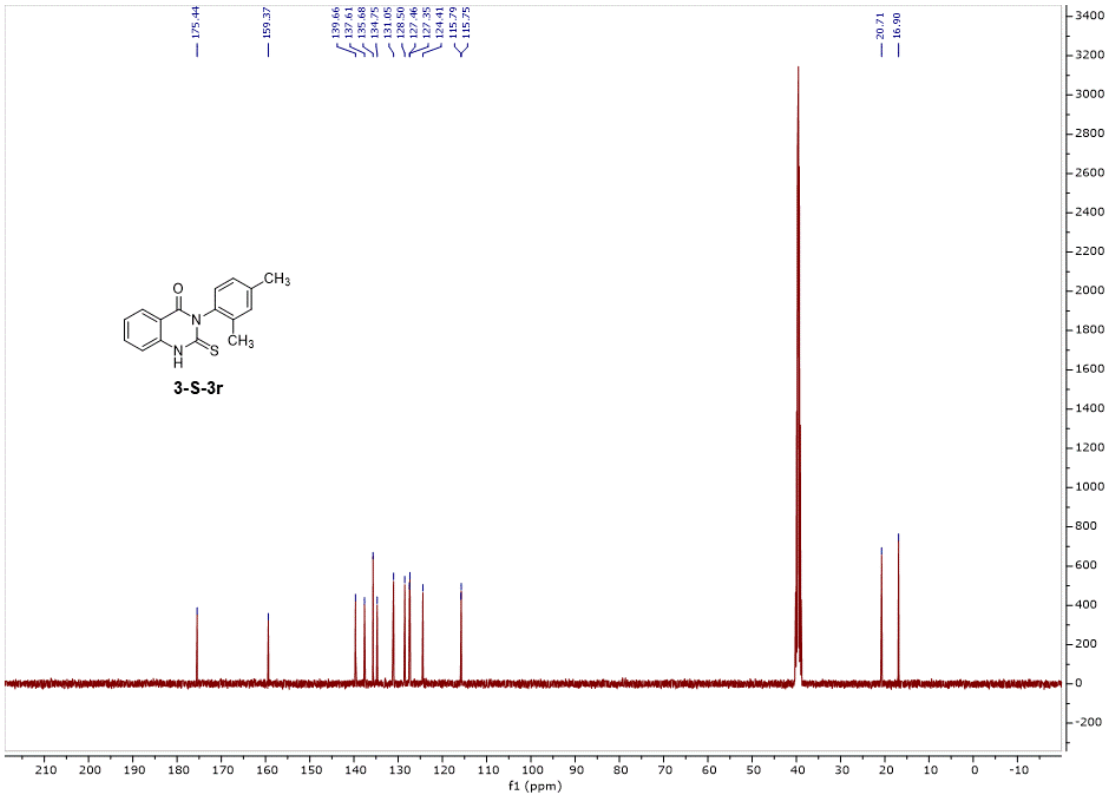

176.14
162.75
160.32
159.86
139.57
135.59
135.53
135.50
131.20
131.11
127.40
124.35
116.20
115.85
115.70
115.63
F
O
N
N
H
S
3-S-3p
f1 (ppm)

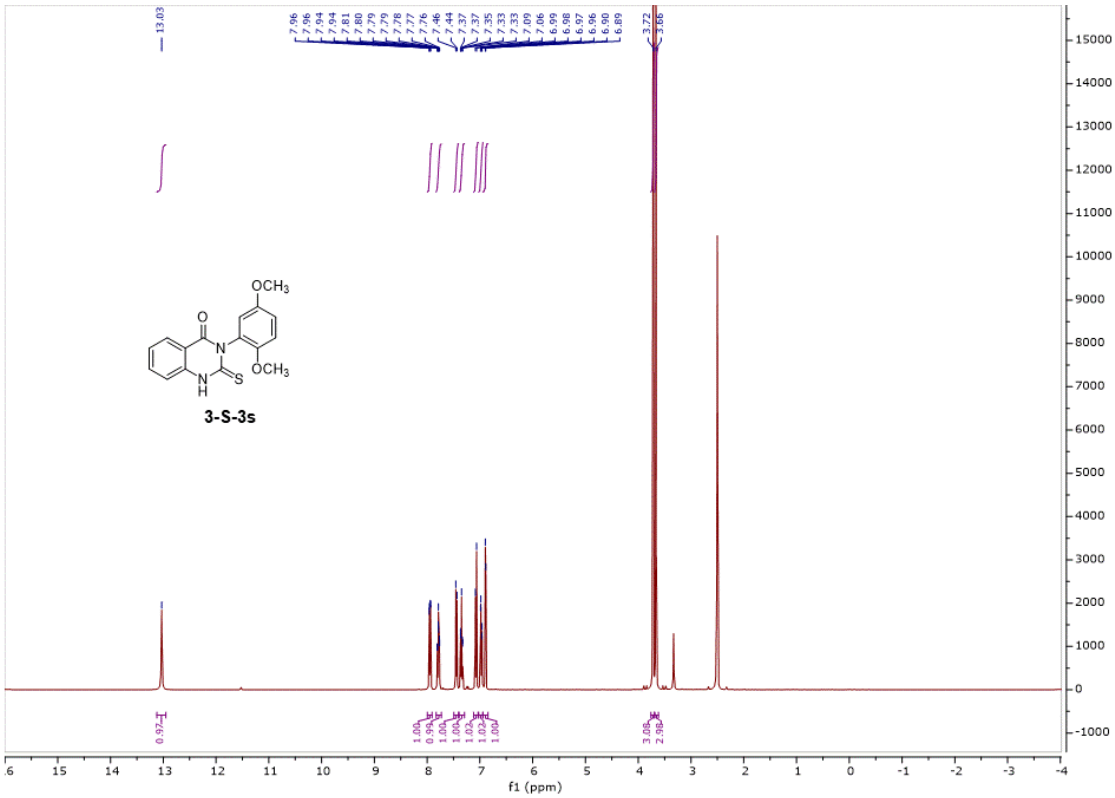

114.70
F
O
N
N
H
S
3-S-3p
f1 (ppm)

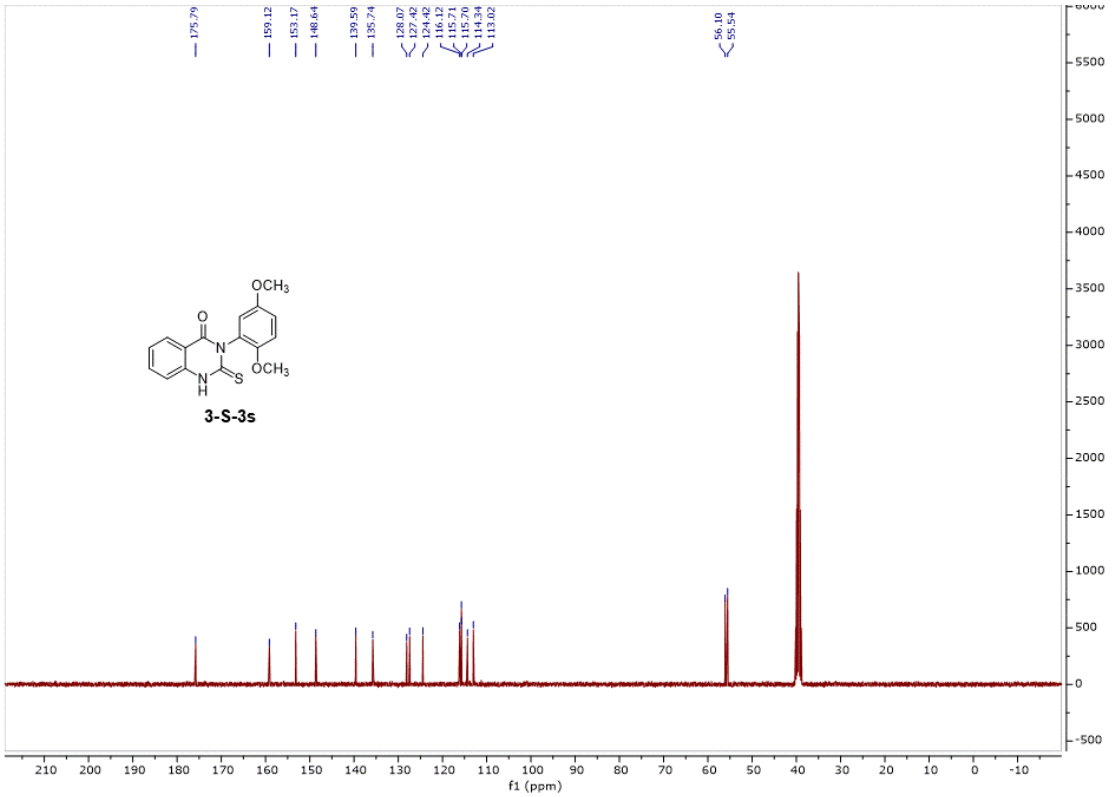

13.06
7.96
7.94
7.85
7.85
7.83
7.80
7.78
7.76
7.45
7.43
7.36
7.34
7.32
7.13
7.13
7.11
7.11
I
O
N
N
H
S
3-S-3q
1.00
1.00
2.01
0.99
1.00
1.00
1.99
f1 (ppm)

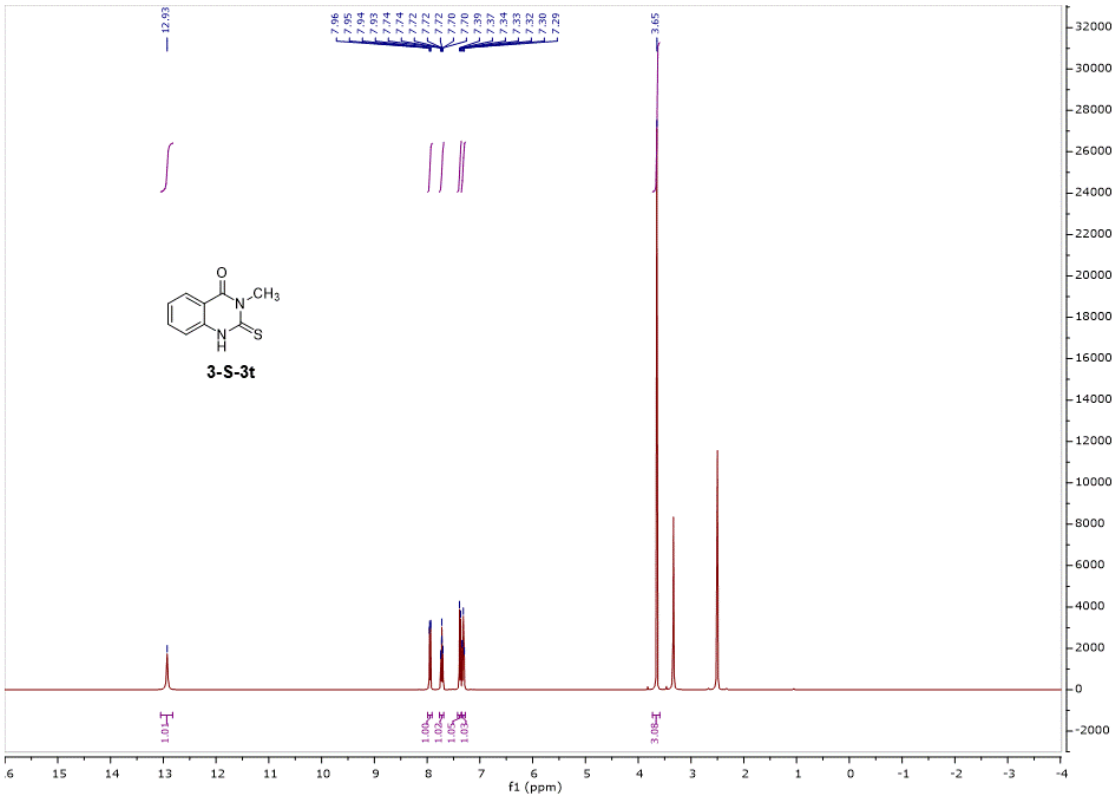

175.75
159.68
139.57
139.19
137.84
135.63
131.46
127.39
124.38
116.17
115.72
94.44
3-S-3q
f1 (ppm)

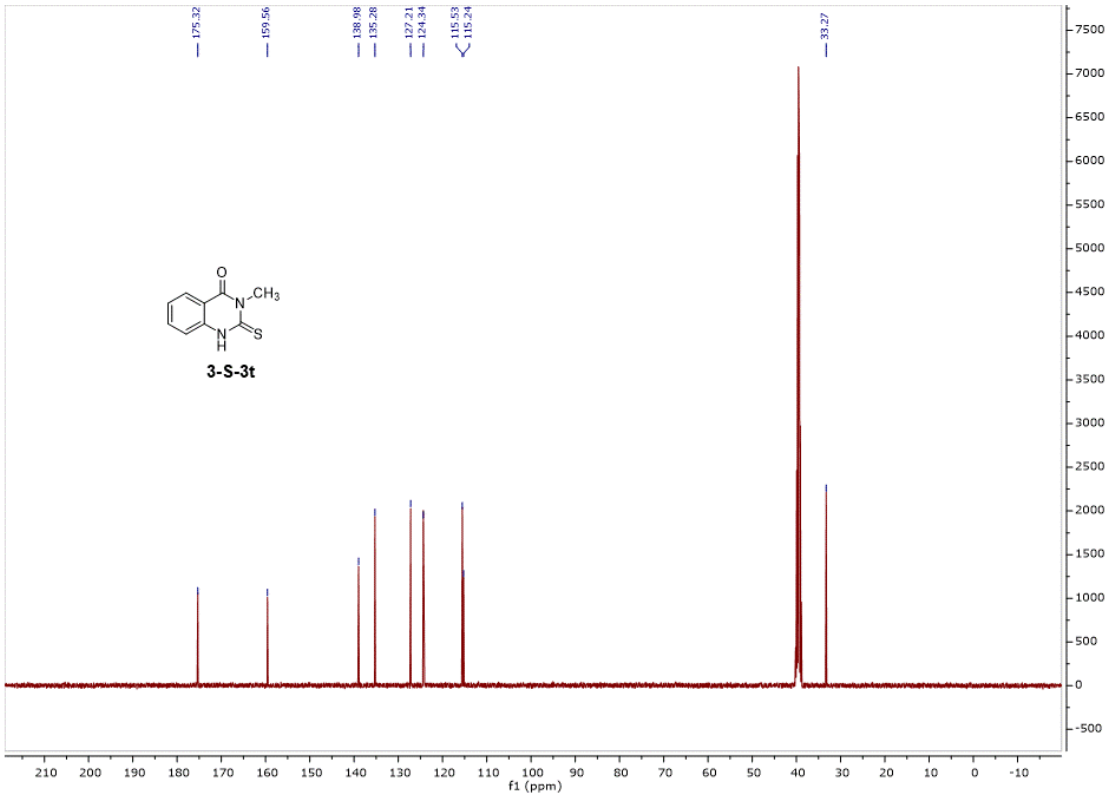

13.07
7.97
7.97
7.95
7.95
7.81
7.80
7.78
7.77
7.76
7.47
7.45
7.37
7.35
7.33
7.14
7.10
7.10
7.08
7.08
7.06
7.04
2.33
1.99
3-S-3r
f1 (ppm)

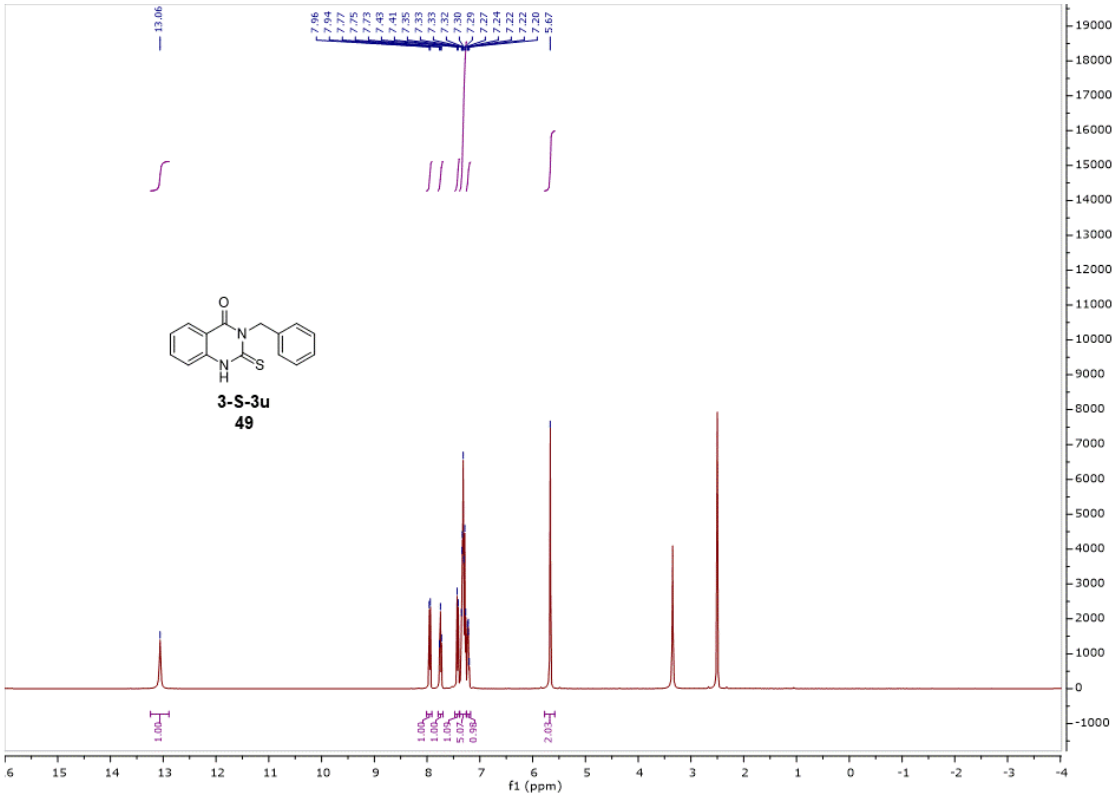

175.44
159.37
139.66
137.61
135.68
134.75
131.05
128.50
127.46
127.35
124.41
115.79
115.75
20.71
16.90
CH3
CH3
O
N
S
H
3-S-3r
f1 (ppm)

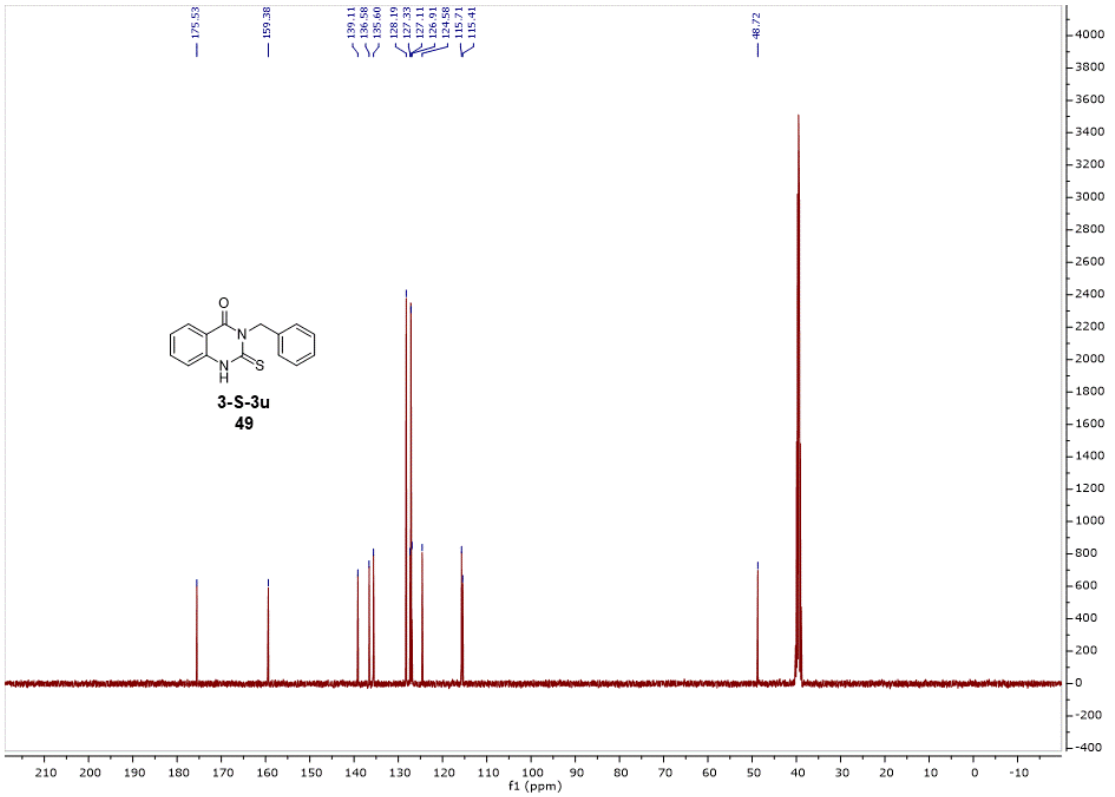

13.03
7.96
7.96
7.94
7.94
7.81
7.80
7.79
7.79
7.78
7.77
7.76
7.46
7.44
7.37
7.37
7.35
7.33
7.33
7.09
7.06
6.99
6.98
6.97
6.96
6.90
6.89
3.72
3.66
OCH3
OCH3
O
N
S
H
3-S-3s
0.97
1.00
0.94
1.00
1.00
1.00
1.02
1.00
3.08
2.96
f1 (ppm)

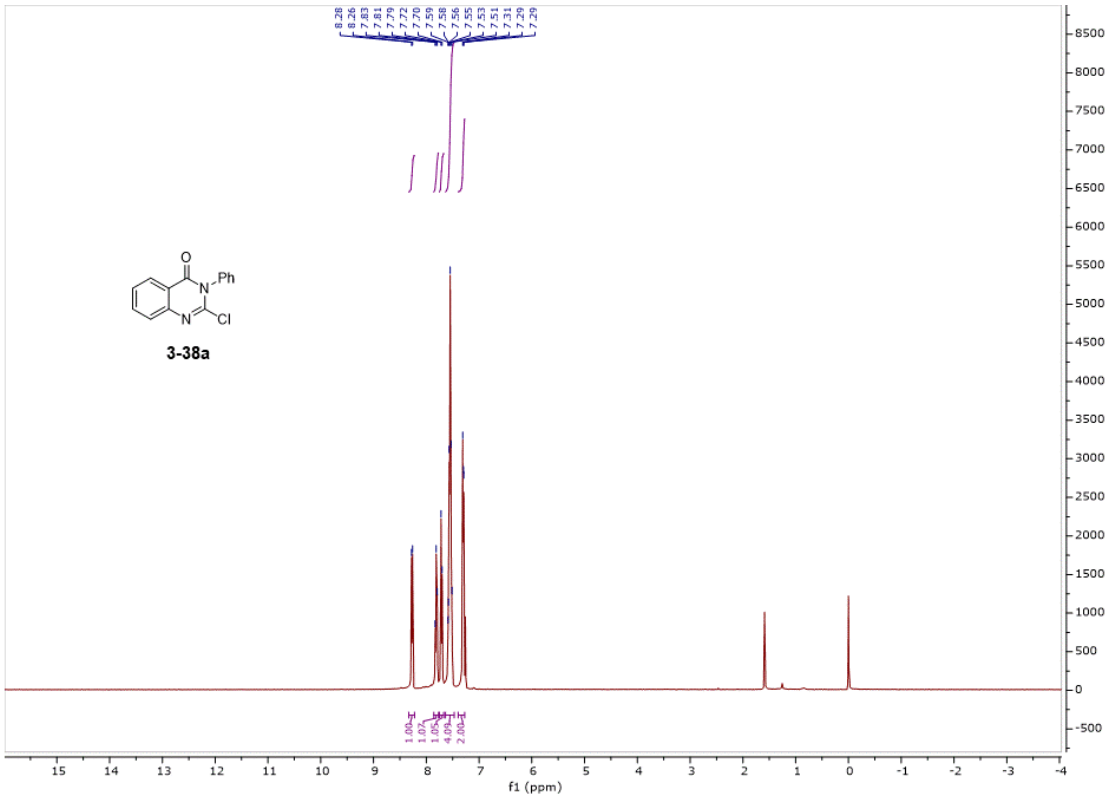

175.79
159.12
153.17
148.64
139.59
135.74
128.07
127.42
124.42
116.12
115.71
115.70
114.34
113.02
56.10
55.54
OCH3
OCH3
O
N
S
H
3-S-3s
f1 (ppm)

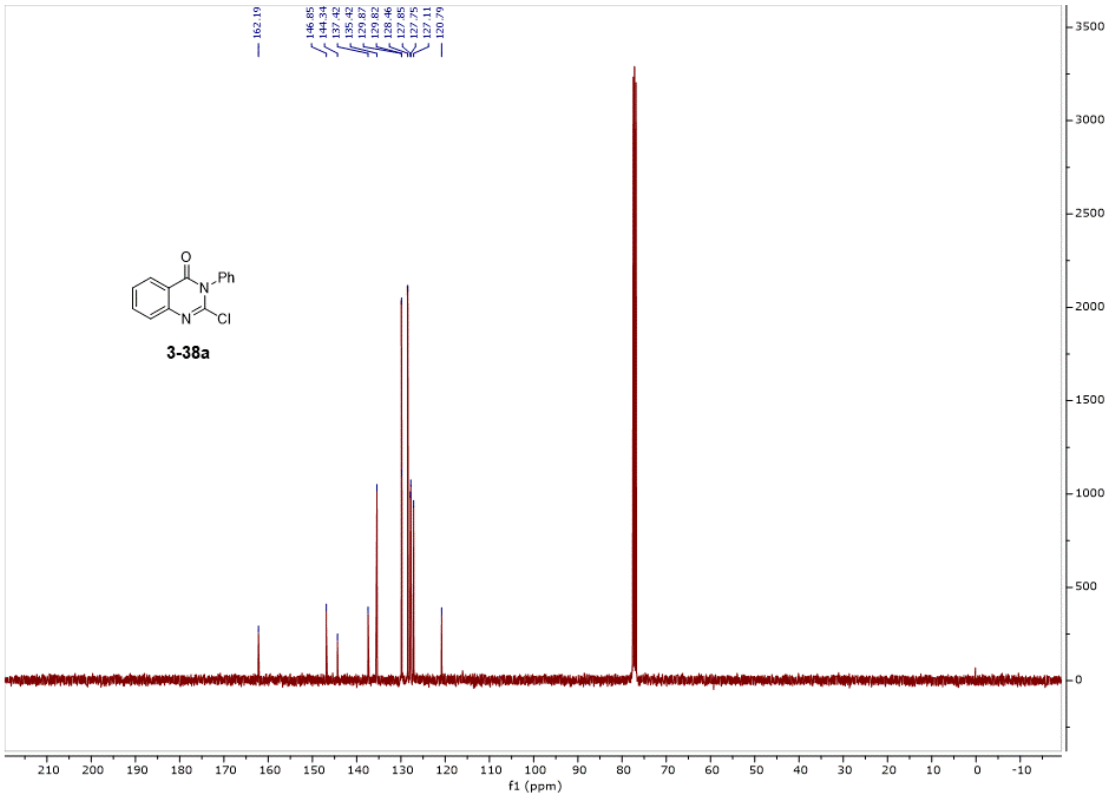

12.93
7.96
7.95
7.94
7.93
7.74
7.74
7.72
7.72
7.72
7.70
7.70
7.39
7.37
7.34
7.33
7.32
7.30
7.29
3.65
CH3
O
N
S
H
3-S-3t
1.01
1.02
1.05
1.03
3.08
f1 (ppm)

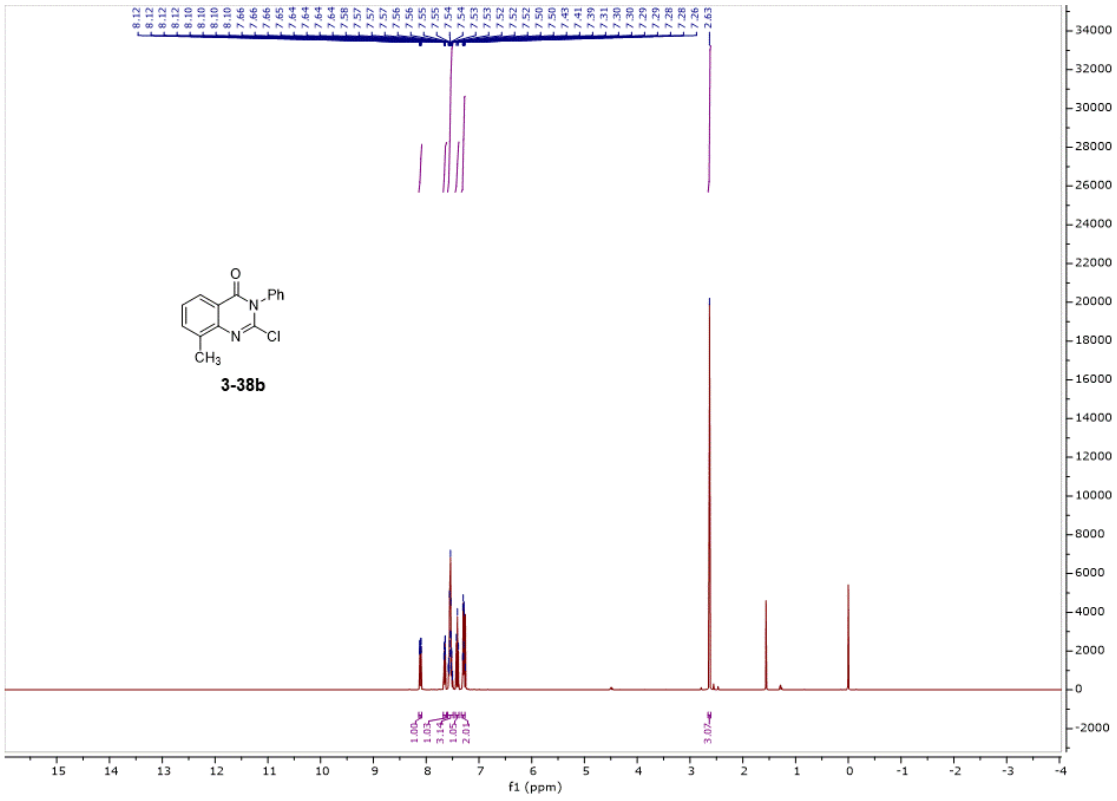

175.32
159.56
138.98
135.28
127.21
124.34
115.53
115.24
33.27
3-S-3t
f1 (ppm)

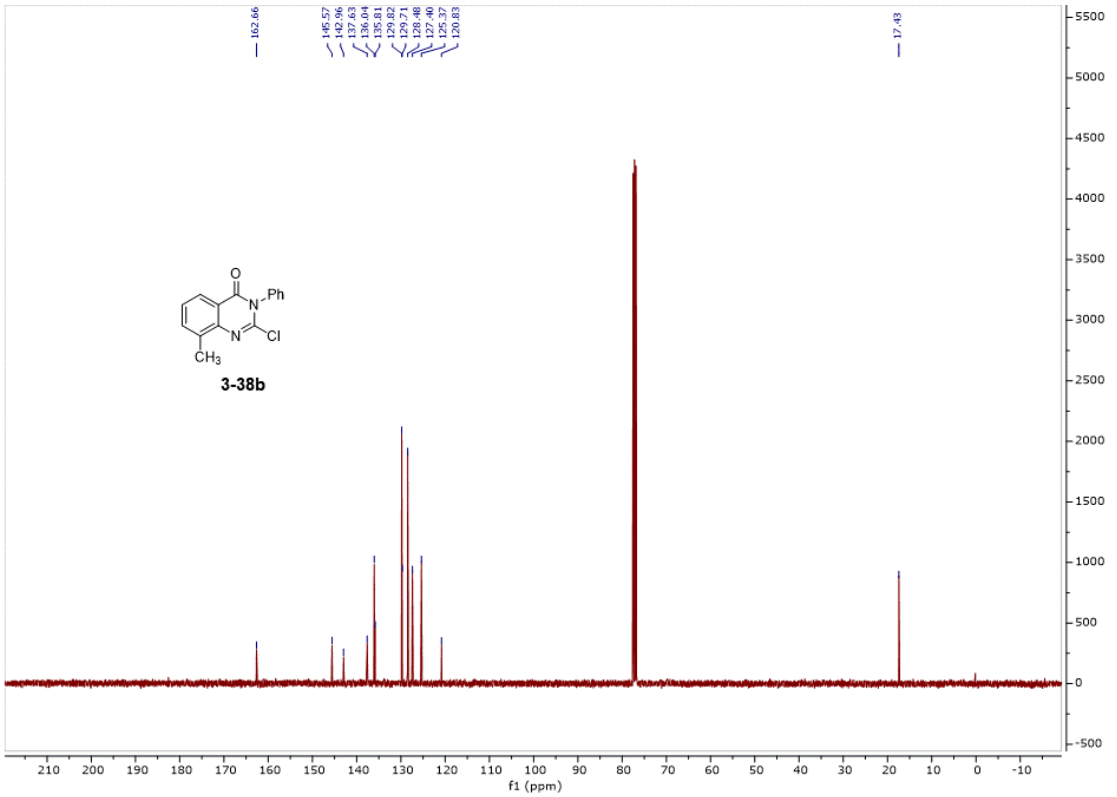

13.06
7.96
7.94
7.77
7.75
7.73
7.43
7.41
7.35
7.33
7.33
7.32
7.30
7.29
7.27
7.24
7.22
7.22
7.20
5.67
3-S-3u
49
f1 (ppm)

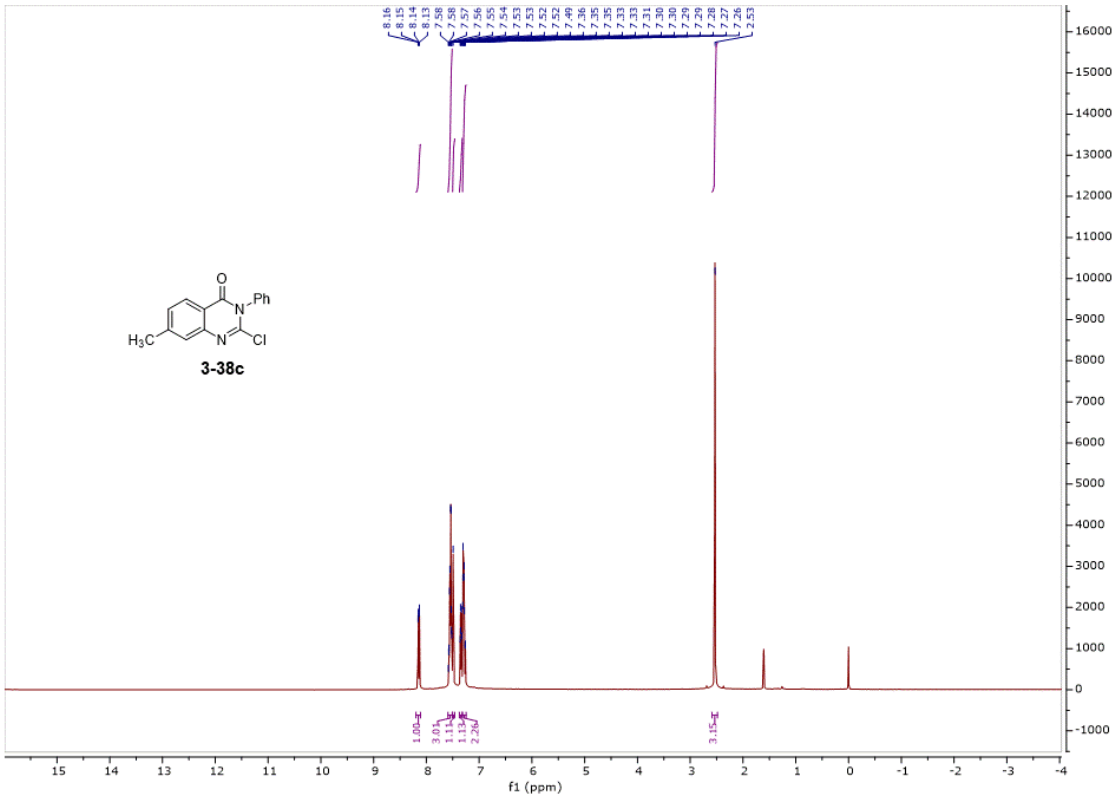

175.53
159.38
139.11
136.58
135.60
128.19
127.33
127.11
126.91
124.58
115.71
115.41
48.72
3-S-3u
49
f1 (ppm)

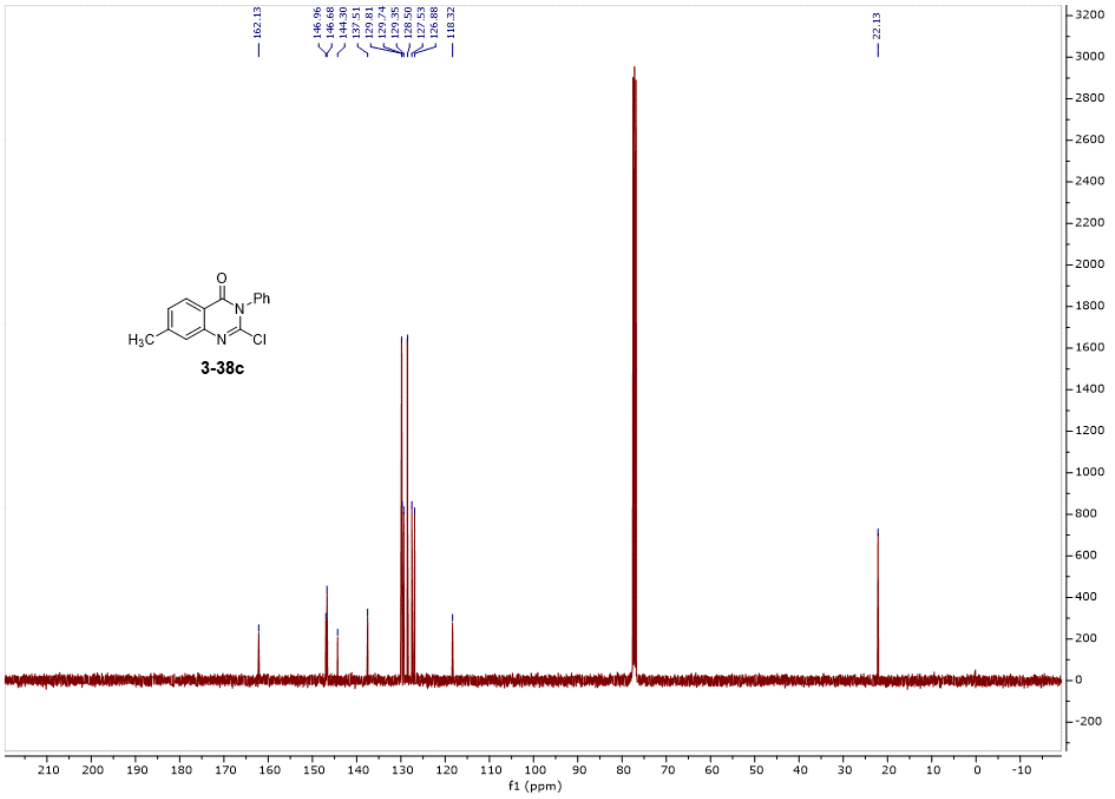

8.28
8.26
7.83
7.81
7.79
7.72
7.70
7.59
7.58
7.56
7.55
7.53
7.51
7.31
7.29
7.29
1.00
1.07
1.05
4.09
2.00
3-38a
f1 (ppm)

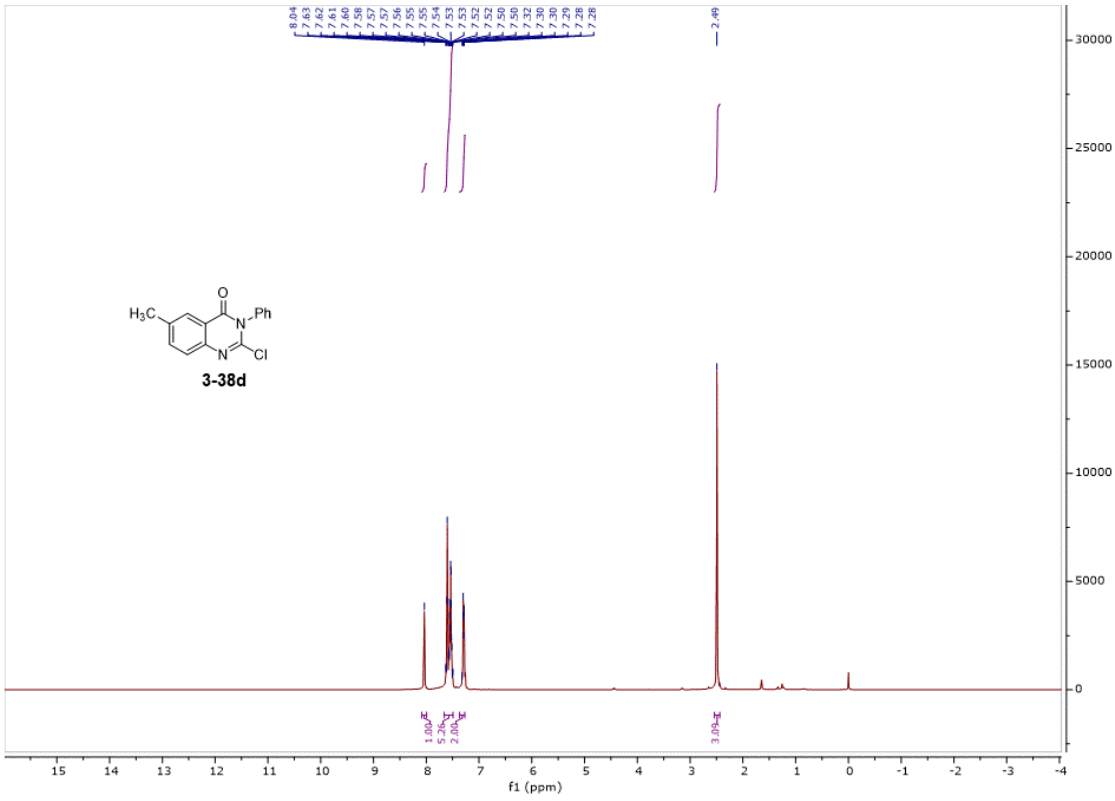

162.19
146.85
144.34
137.42
135.42
129.87
129.82
128.46
127.85
127.75
127.11
120.79
O
N
Ph
N
Cl
3-38a
f1 (ppm)

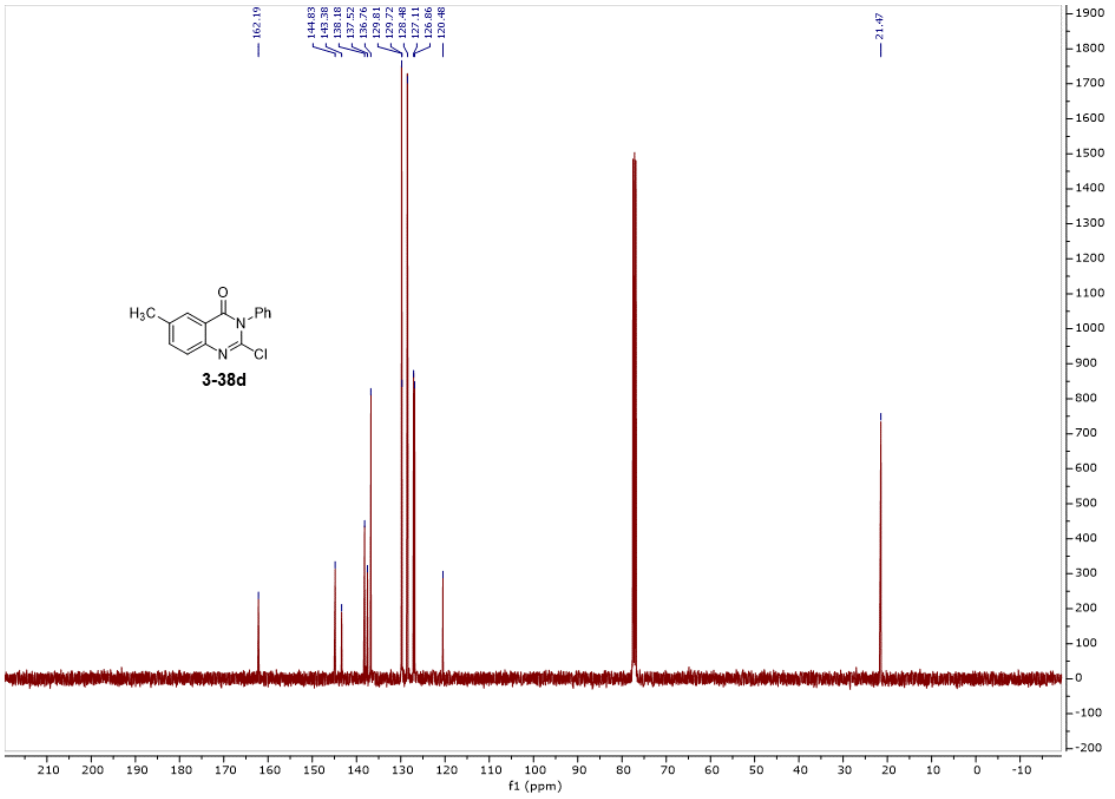

O
N
Ph
N
Cl
CH3
3-38b
f1 (ppm)

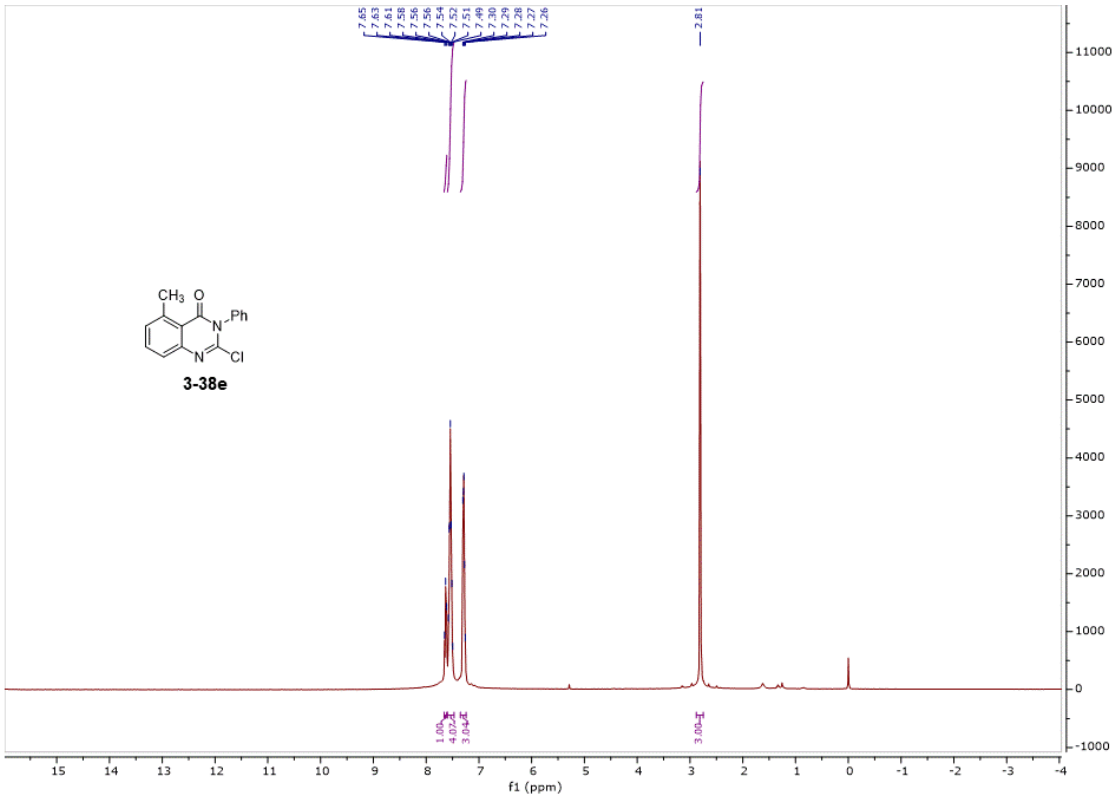

162.66
145.57
142.96
137.63
136.04
135.81
129.82
129.71
128.48
127.40
125.37
120.83
17.43
O
N
Ph
N
Cl
CH3
3-38b
f1 (ppm)

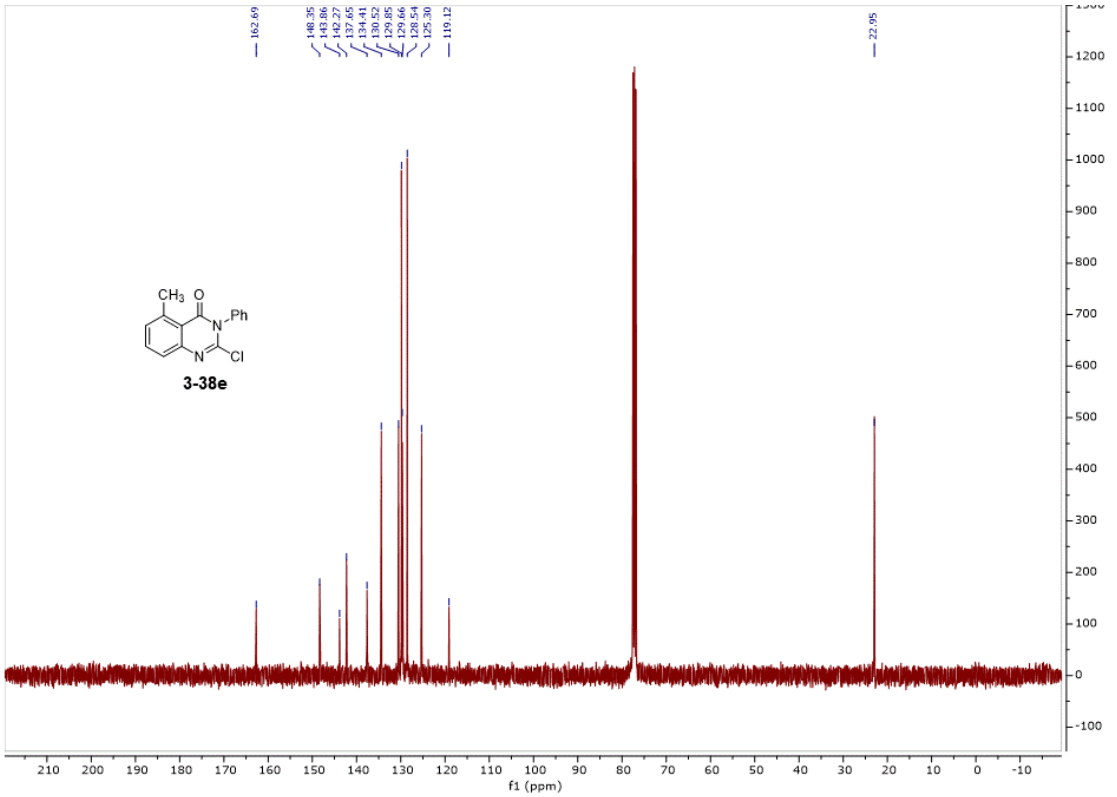

8.16
8.15
8.14
8.13
7.58
7.57
7.56
7.55
7.54
7.53
7.53
7.52
7.52
7.49
7.36
7.35
7.35
7.33
7.31
7.30
7.30
7.29
7.29
7.28
7.27
7.26
2.53
1.00
3.01
1.11
1.13
2.26
3.15
O
N
Ph
N
Cl
H3C
3-38c
f1 (ppm)

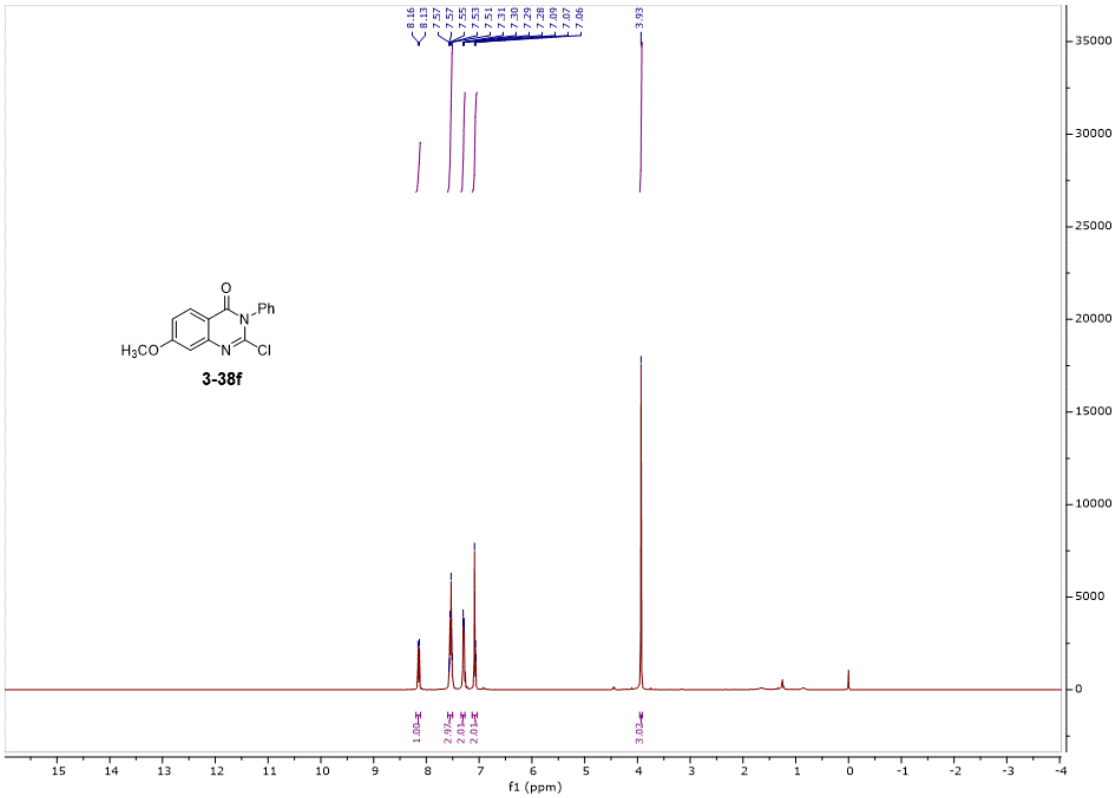

162.13
146.96
146.66
144.30
137.51
129.81
129.74
129.35
128.50
127.53
126.88
118.32
22.13
Ph
N
O
Cl
N
H3C
3-38c
f1 (ppm)

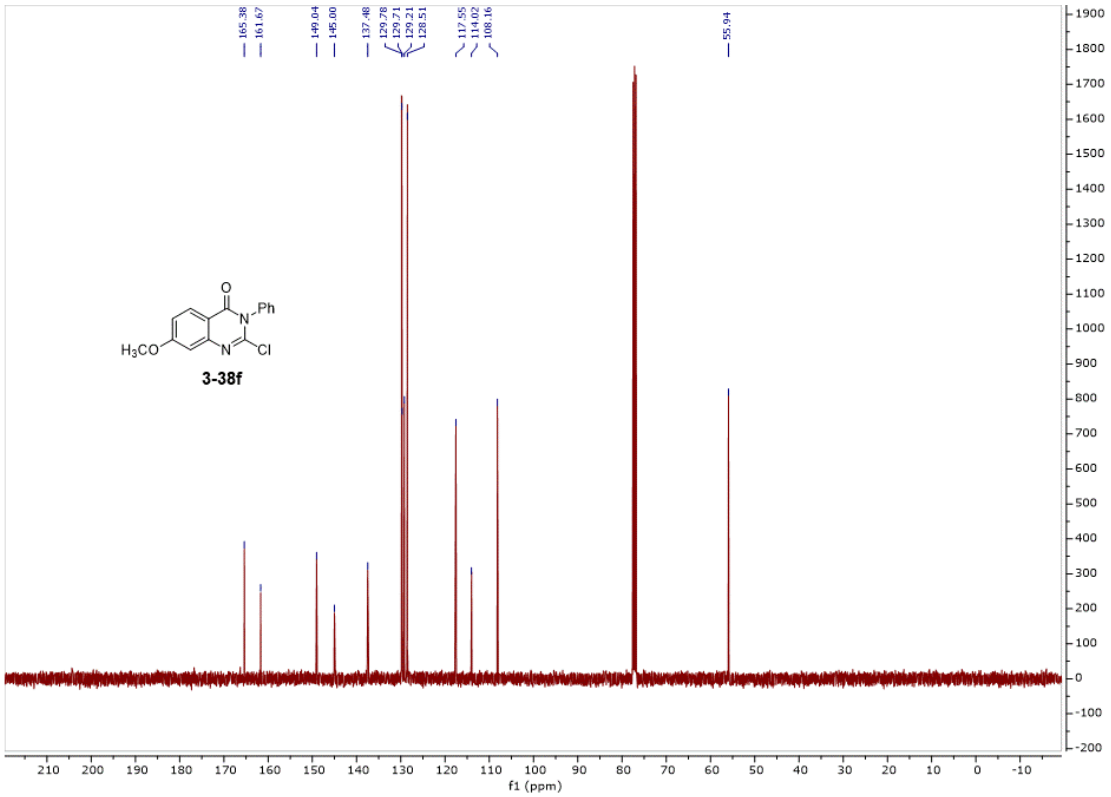

8.04
7.63
7.62
7.61
7.60
7.58
7.57
7.57
7.56
7.55
7.55
7.54
7.53
7.53
7.52
7.52
7.50
7.50
7.32
7.30
7.30
7.29
7.28
7.28
2.49
1.00
1.30
2.00
3.09
Ph
N
O
Cl
N
H3C
3-38d
f1 (ppm)

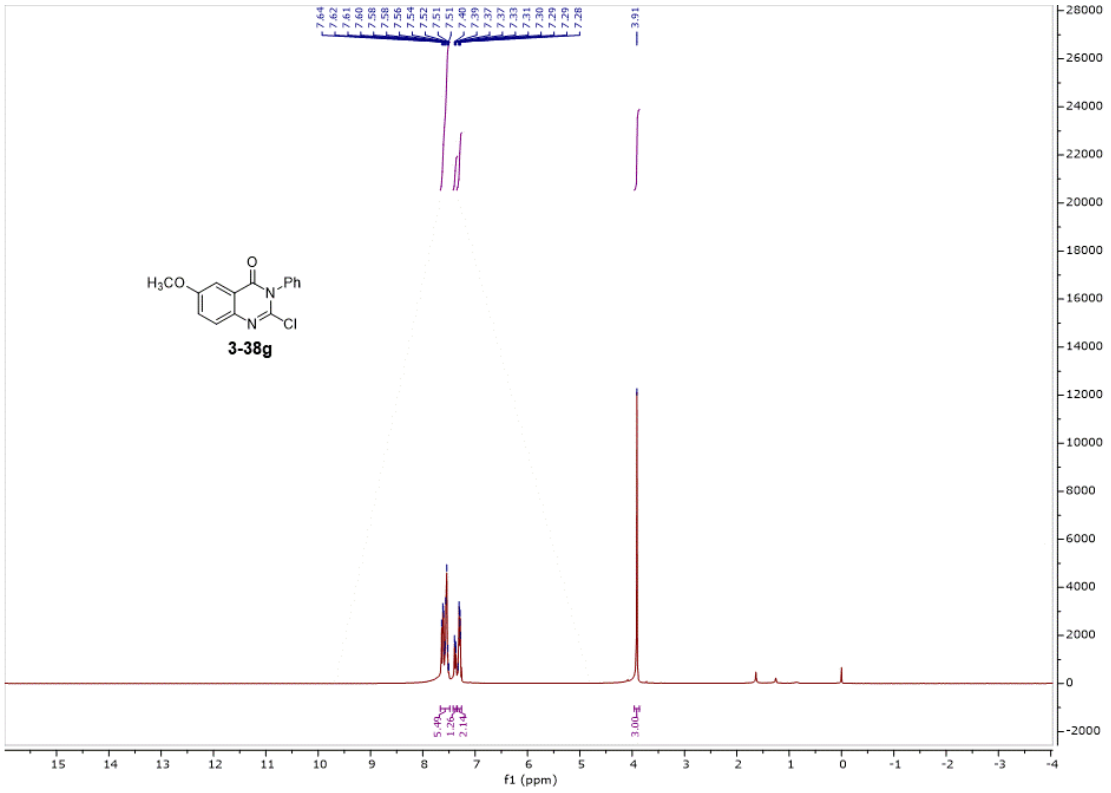

162.19
144.83
143.38
138.18
137.52
136.76
129.81
129.72
128.48
127.11
126.86
120.48
21.47
H3C
O
N
Ph
N
Cl
3-38d
f1 (ppm)

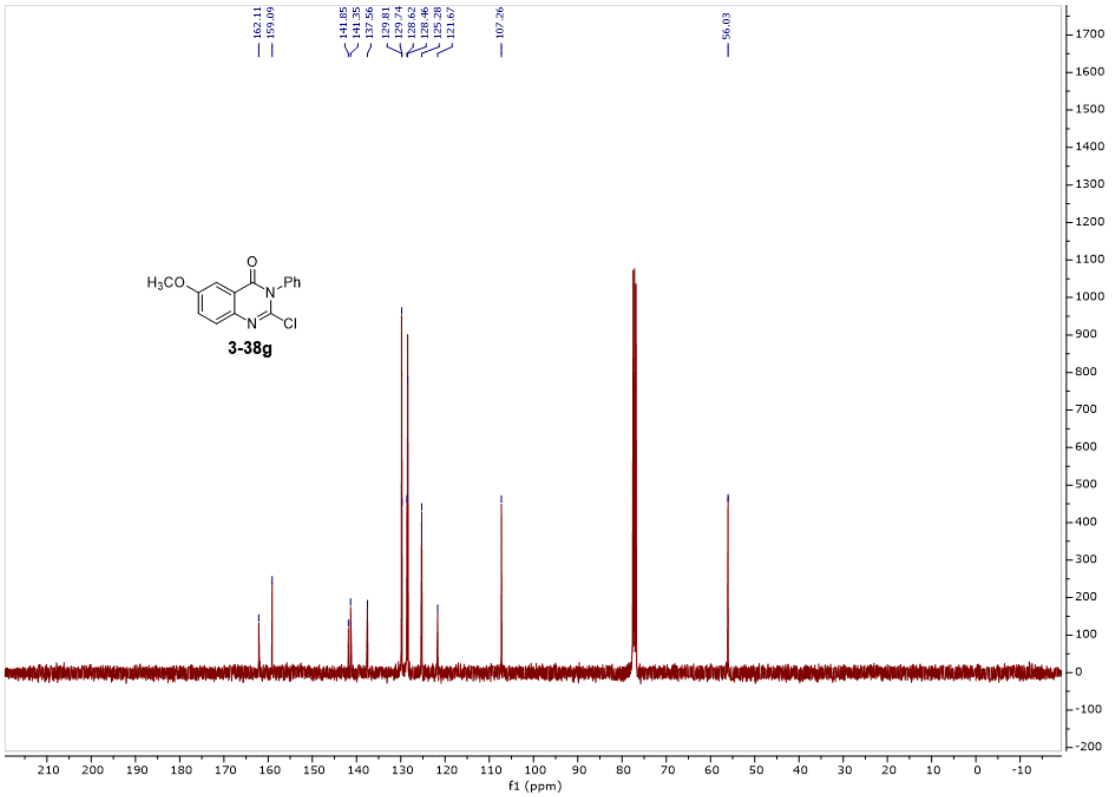

7.65
7.63
7.61
7.58
7.56
7.55
7.54
7.52
7.51
7.49
7.30
7.29
7.28
7.27
7.26
2.81
CH3
O
N
Ph
N
Cl
3-38e
1.00
4.02
3.04
3.00
f1 (ppm)

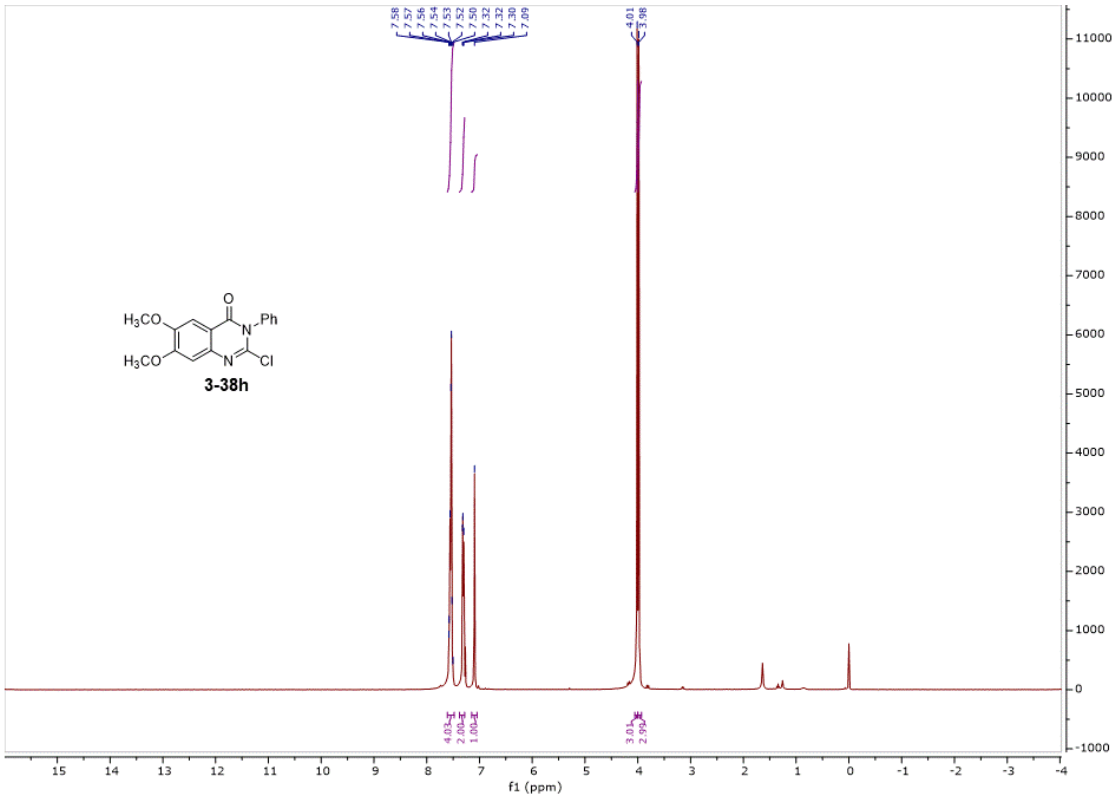

162.69
148.35
143.86
142.27
137.65
134.41
130.52
129.85
129.66
128.54
125.30
119.12
22.95
CH3
O
N
Ph
N
Cl
3-38e
f1 (ppm)

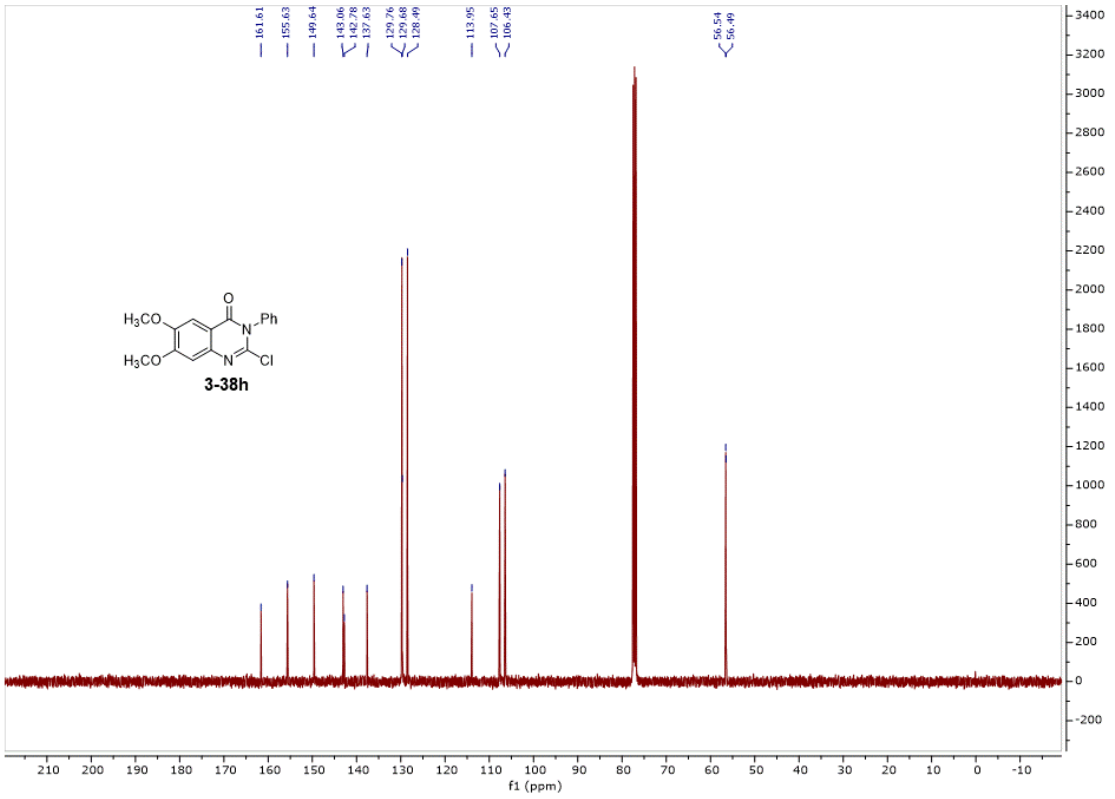

8.16
8.13
7.57
7.57
7.55
7.53
7.51
7.31
7.30
7.29
7.28
7.09
7.07
7.06
3.93
O
N
Ph
H3CO
N
Cl
3-38f
1.00
2.97
2.01
2.01
3.02
f1 (ppm)

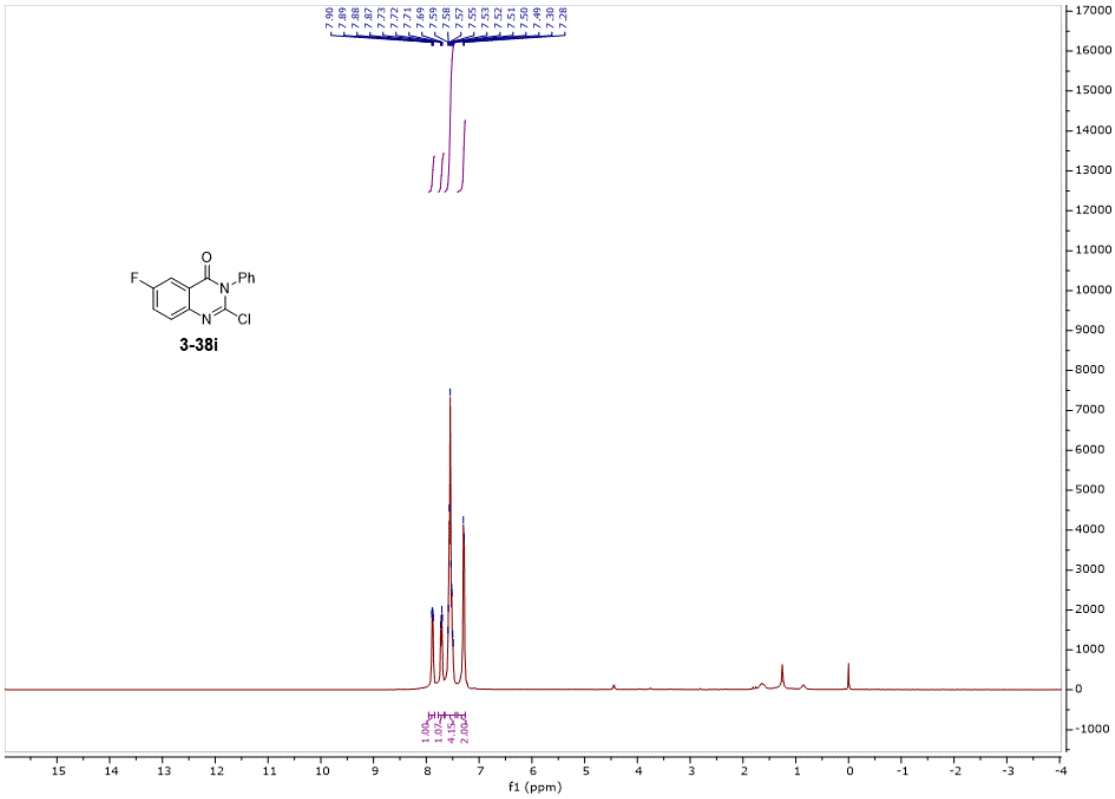

165.38
161.67
149.04
145.00
137.48
129.78
129.71
129.21
128.51
117.55
114.02
108.16
55.94
O
N
Ph
H3CO
N
Cl
3-38f
f1 (ppm)

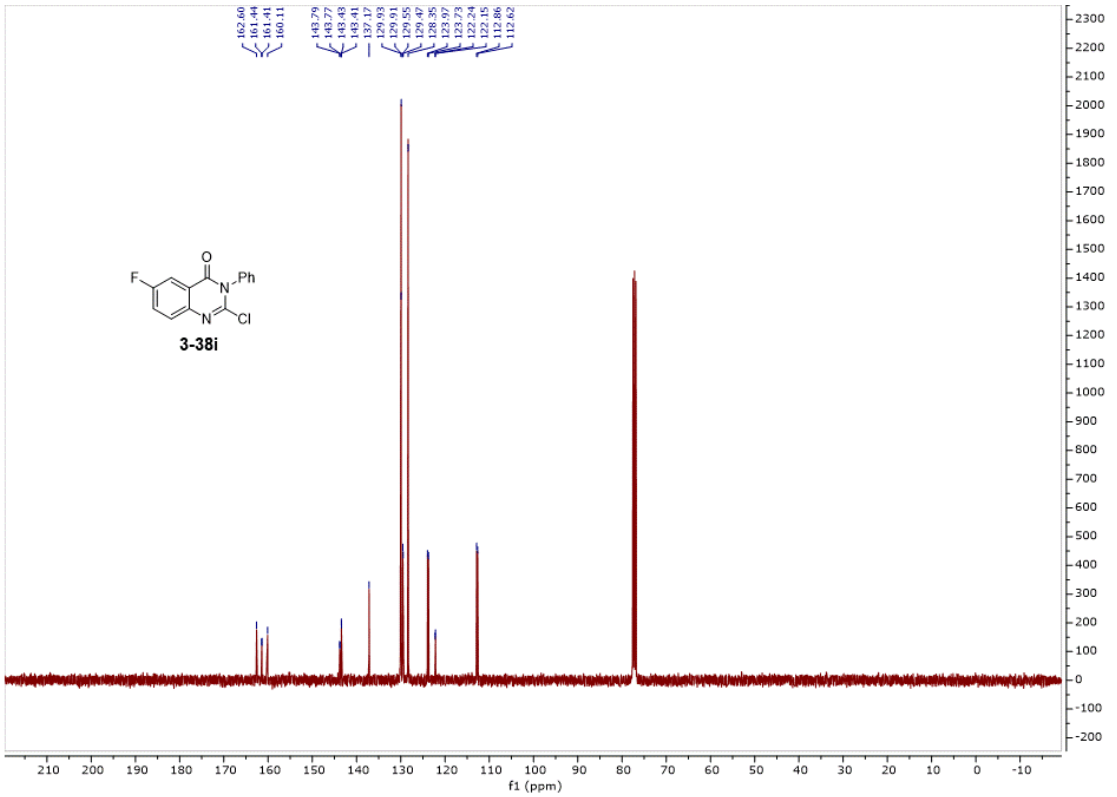

7.64
7.62
7.61
7.60
7.58
7.56
7.54
7.52
7.51
7.51
7.40
7.39
7.37
7.37
7.33
7.31
7.30
7.29
7.29
7.28
3.91
5.49
1.24
2.14
3.00
O
N
Ph
H3CO
N
Cl
3-38g
f1 (ppm)

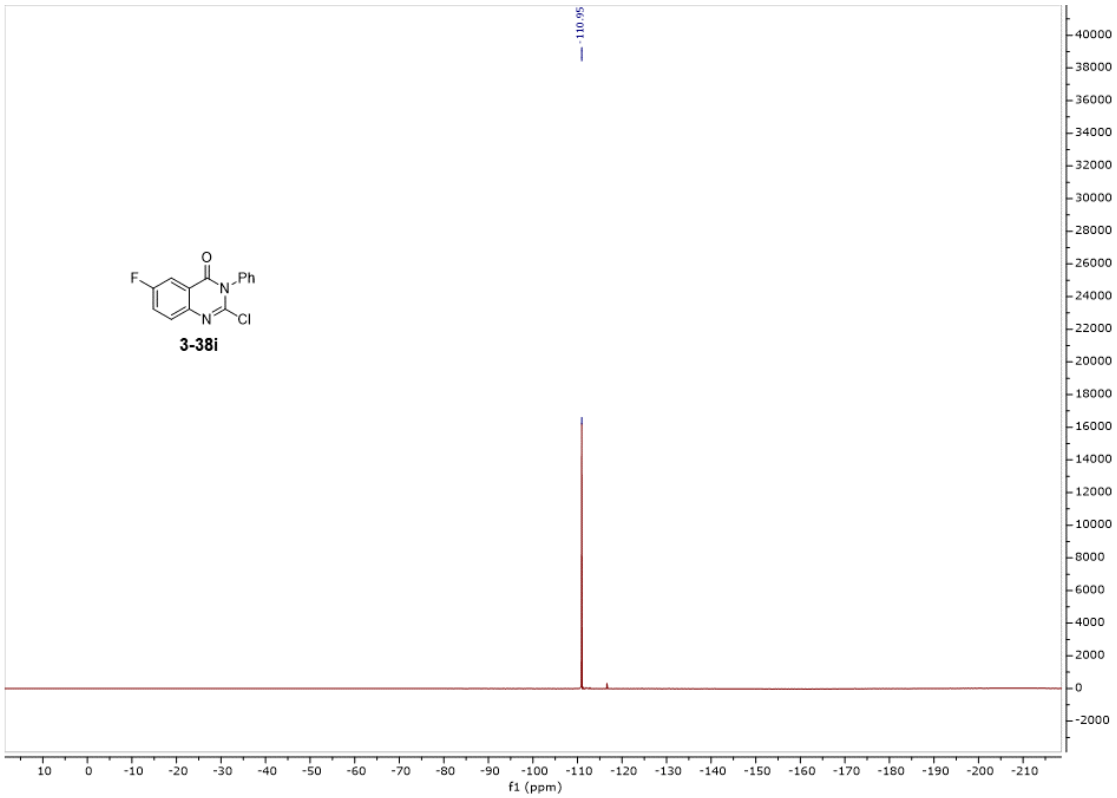

162.11
159.09
141.85
141.35
137.56
129.81
129.74
128.62
128.46
125.28
121.67
107.26
56.03
H3CO
O
N
Ph
N
Cl
3-38g
f1 (ppm)

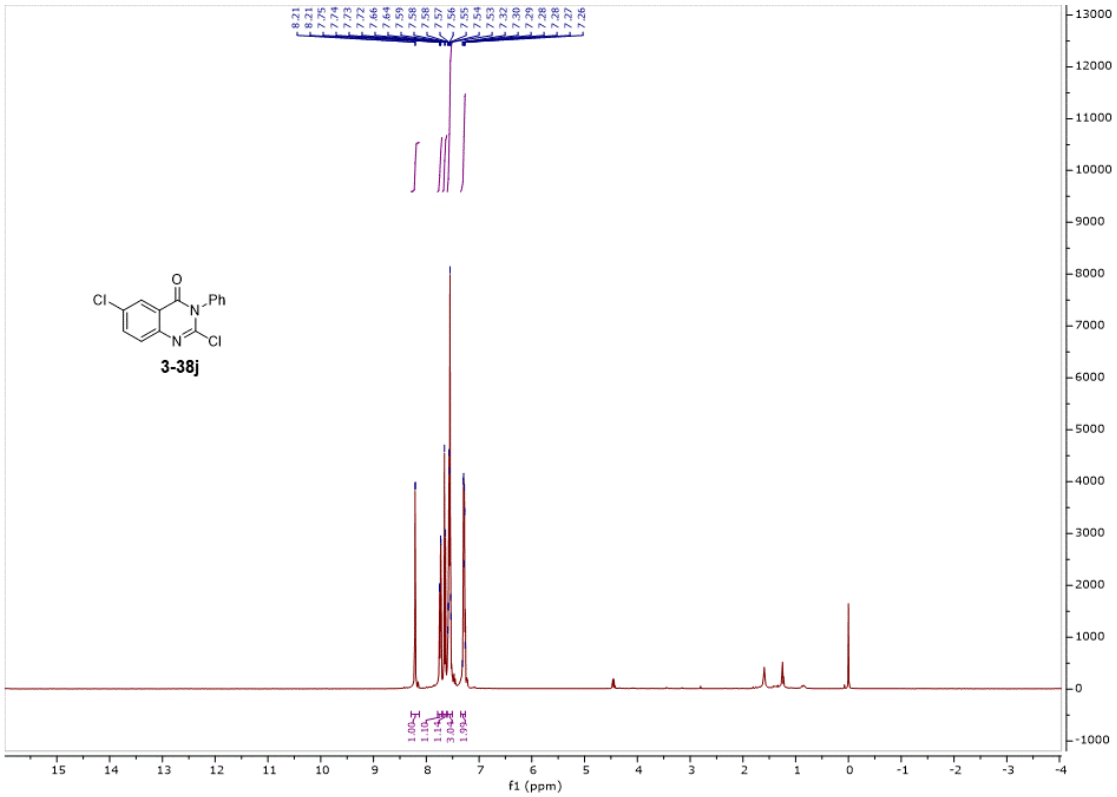

7.58
7.57
7.56
7.54
7.53
7.52
7.50
7.32
7.30
7.09
4.01
3.98
H3CO
H3CO
O
N
Ph
N
Cl
3-38h
4.03
2.00
1.00
3.01
2.99
f1 (ppm)

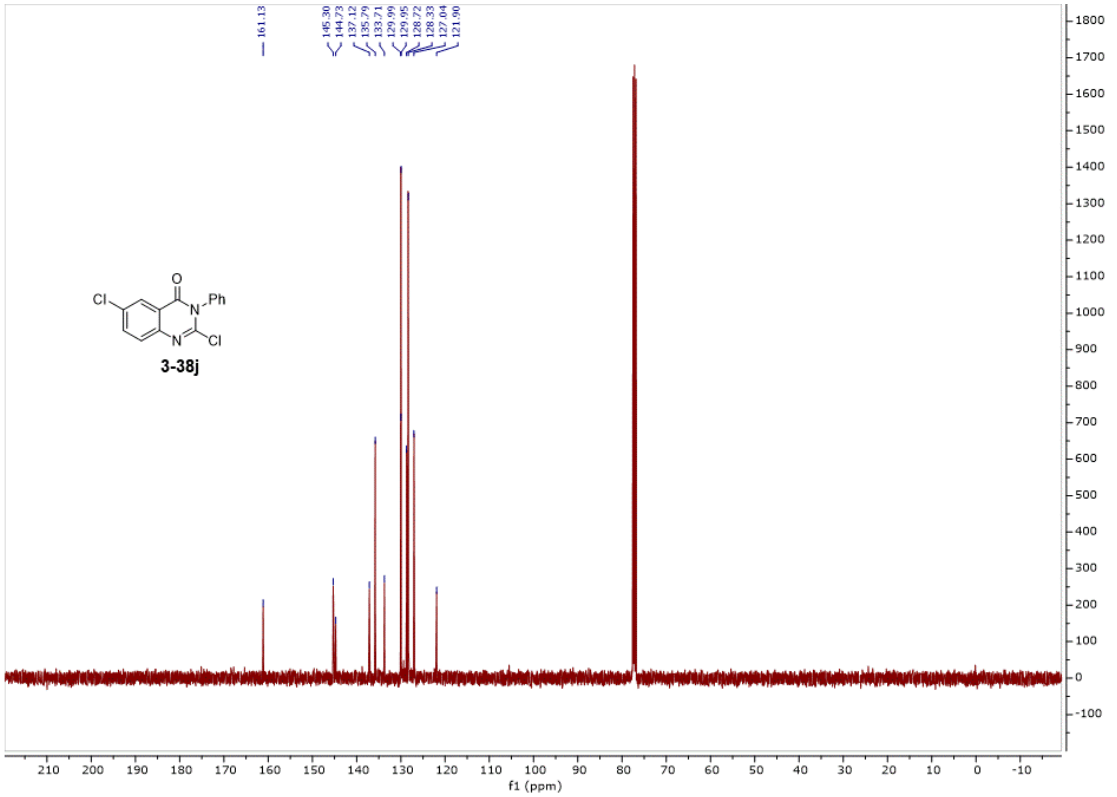

161.61
155.63
149.64
143.06
142.78
137.63
129.76
129.68
128.49
113.95
107.65
106.43
56.54
56.49
H3CO
H3CO
O
N
Ph
N
Cl
3-38h
f1 (ppm)

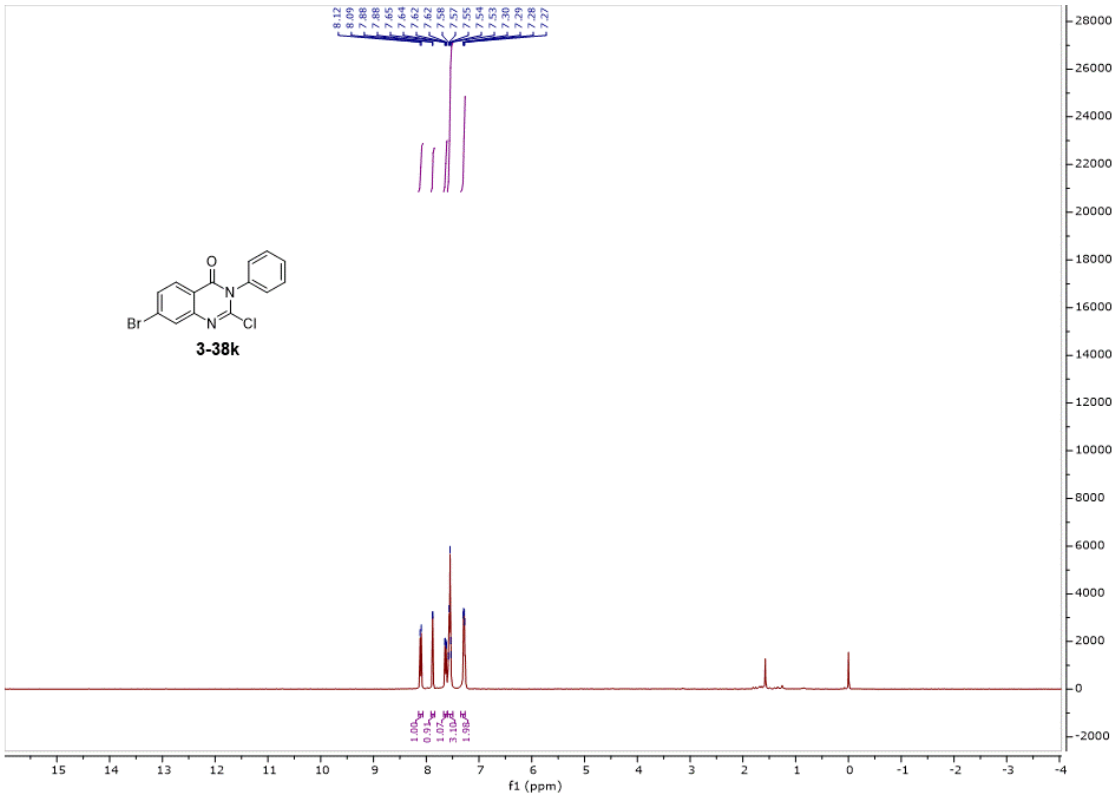

7.90
7.89
7.88
7.87
7.73
7.72
7.71
7.69
7.59
7.58
7.57
7.55
7.53
7.52
7.51
7.50
7.49
7.30
7.28
F
O
N
Ph
N
Cl
3-38i
1.00
1.07
4.15
2.00
f1 (ppm)

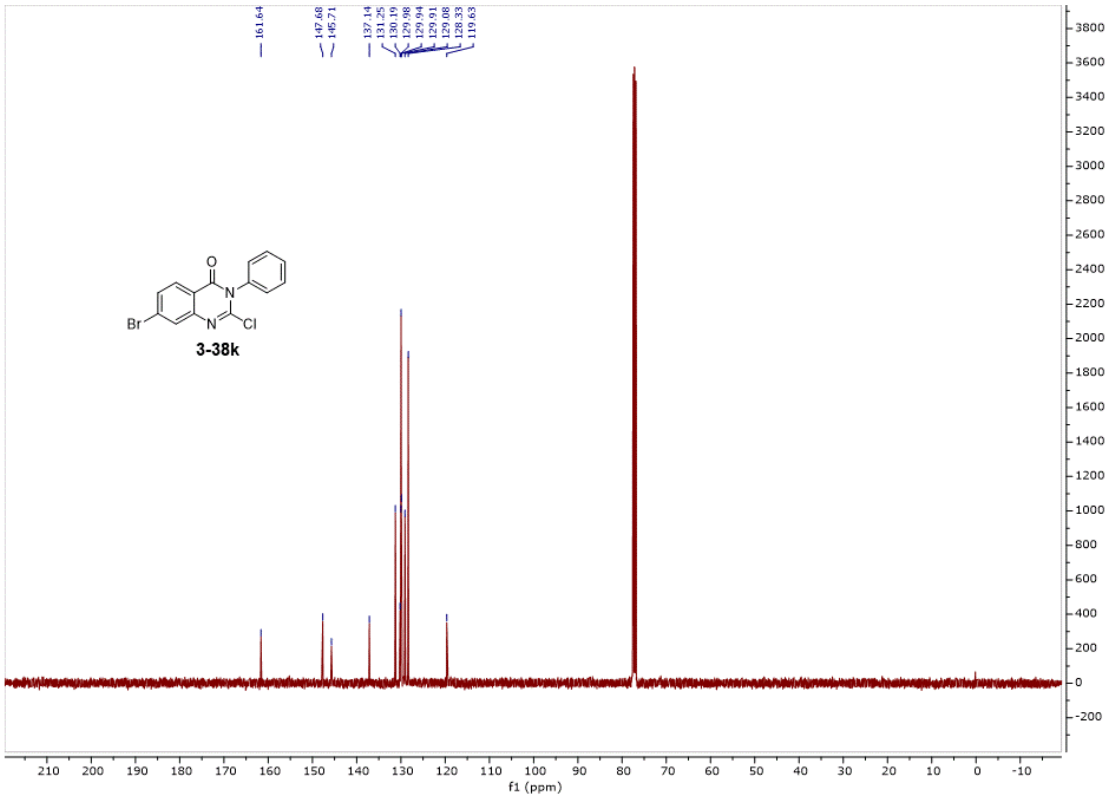

162.60
161.44
161.41
160.11
143.79
143.77
143.43
143.41
137.17
129.93
129.91
129.55
129.47
128.35
123.97
123.73
122.24
122.15
117.86
112.62
O
F
N
Ph
N
Cl
3-38i
f1 (ppm)

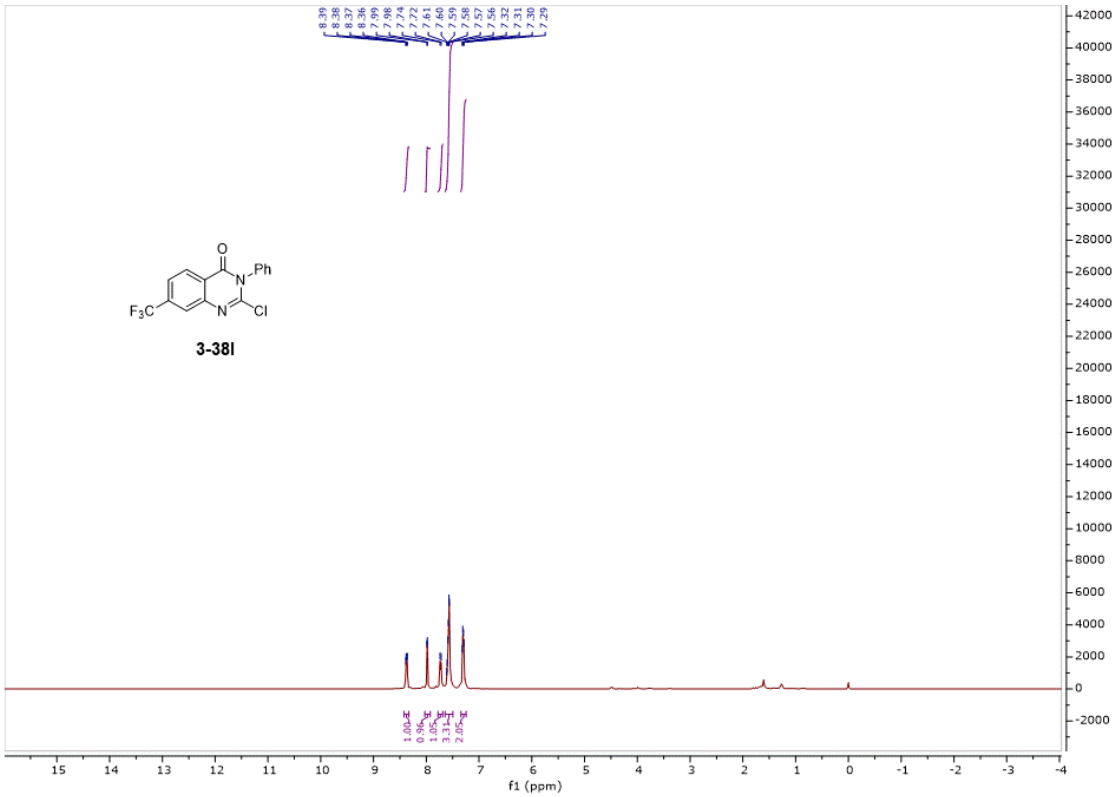

110.95
O
F
N
Ph
N
Cl
3-38i
f1 (ppm)

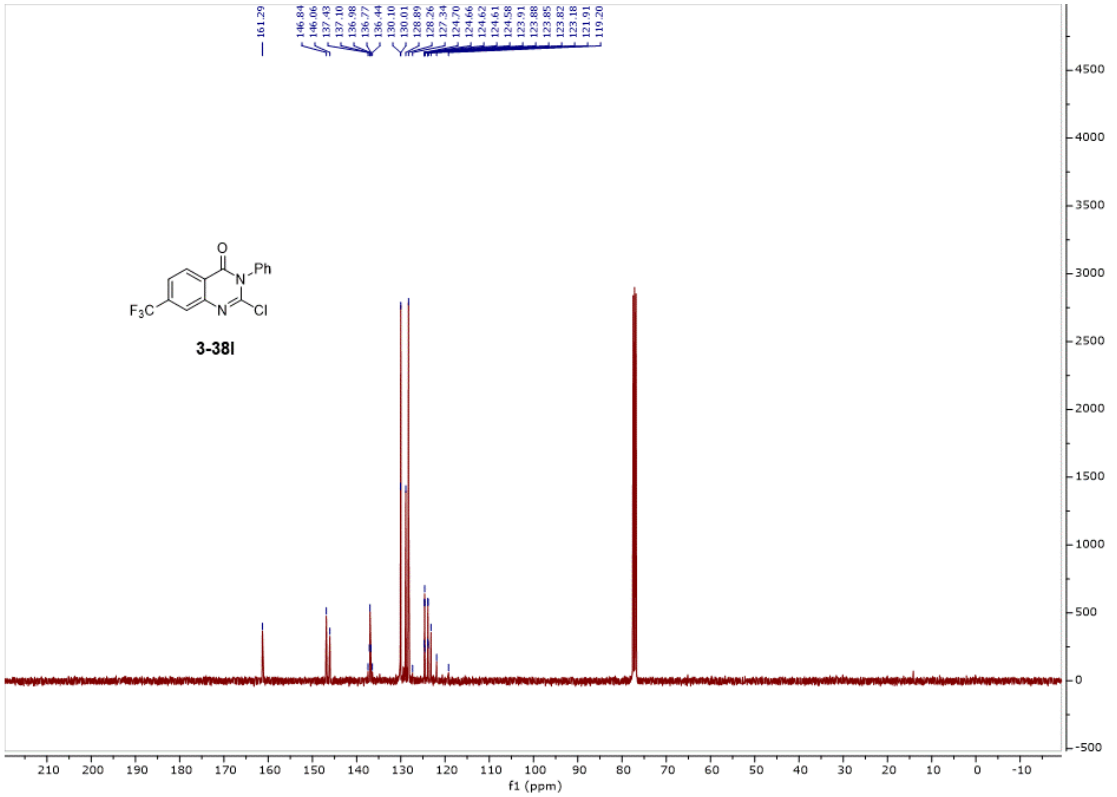

8.21
8.21
7.75
7.74
7.73
7.72
7.66
7.64
7.59
7.58
7.58
7.57
7.56
7.55
7.54
7.53
7.32
7.30
7.29
7.28
7.28
7.27
7.26
Cl
O
N
Ph
N
Cl
3-38j
1.00
1.05
1.14
3.04
1.99
f1 (ppm)

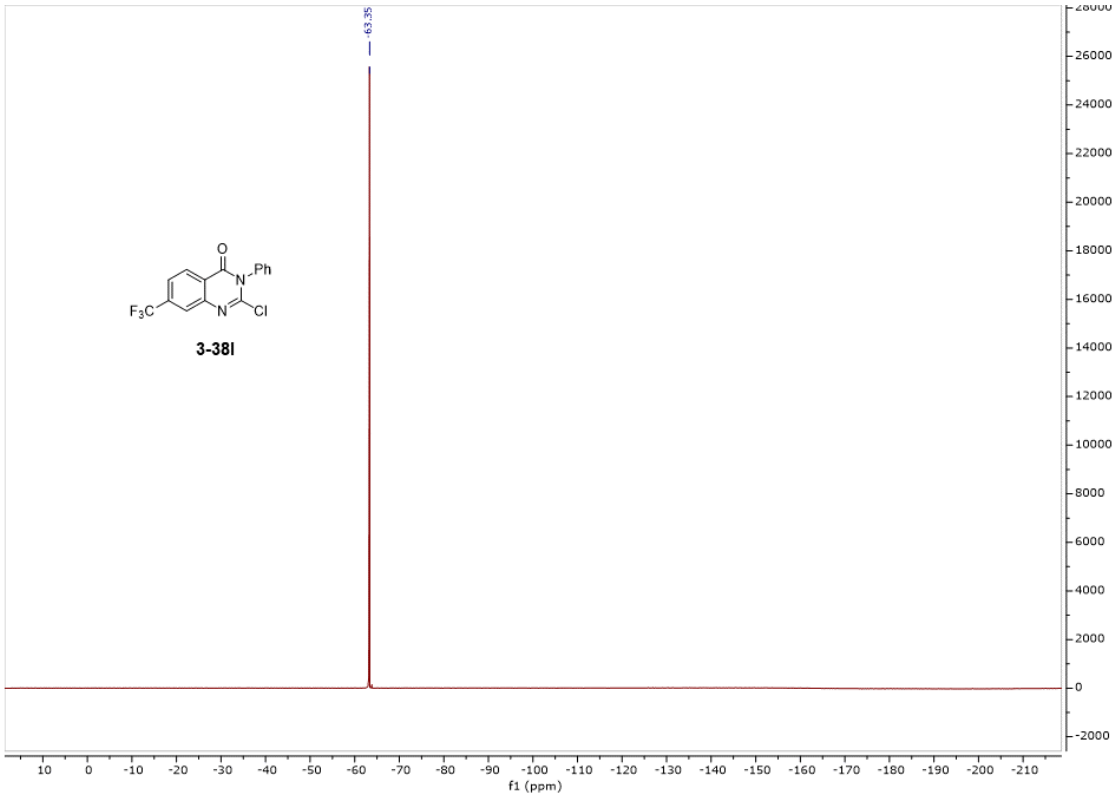

161.13
145.30
144.73
137.12
135.79
133.71
129.99
129.95
128.72
128.33
127.04
121.90
Cl
O
N
Ph
N
Cl
3-38j
f1 (ppm)

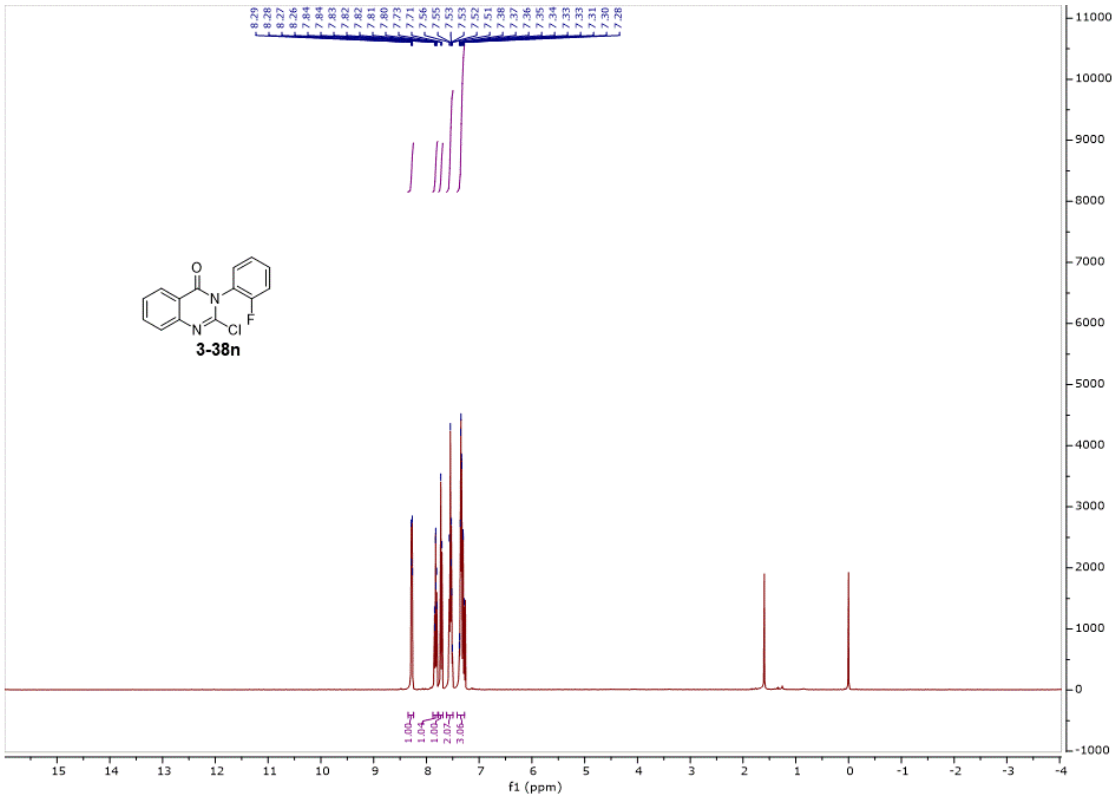

8.12
8.09
7.88
7.88
7.65
7.64
7.62
7.62
7.58
7.57
7.55
7.54
7.53
7.30
7.29
7.28
7.27
Br
N
O
N
Cl
3-38k
1.00
0.91
1.07
3.10
1.98
f1 (ppm)

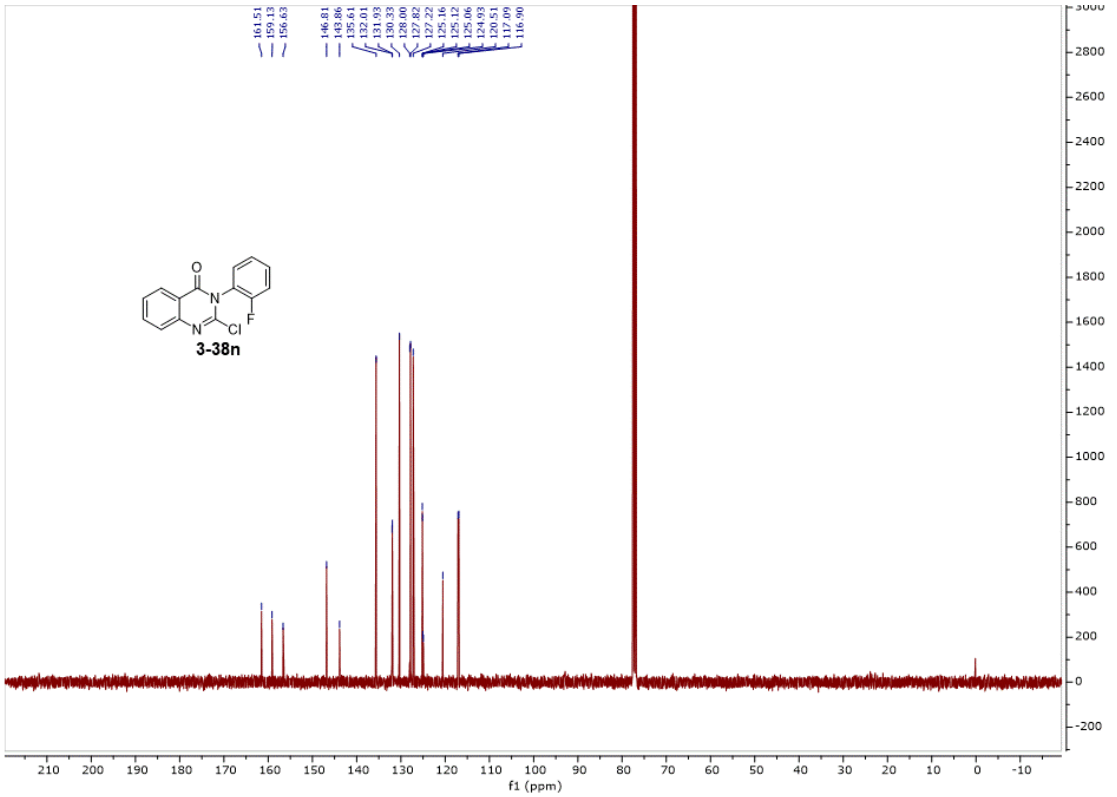

161.64
147.68
145.71
137.14
131.25
130.19
129.98
129.94
129.91
129.08
128.33
119.63
Br
N
O
N
Cl
3-38k
f1 (ppm)

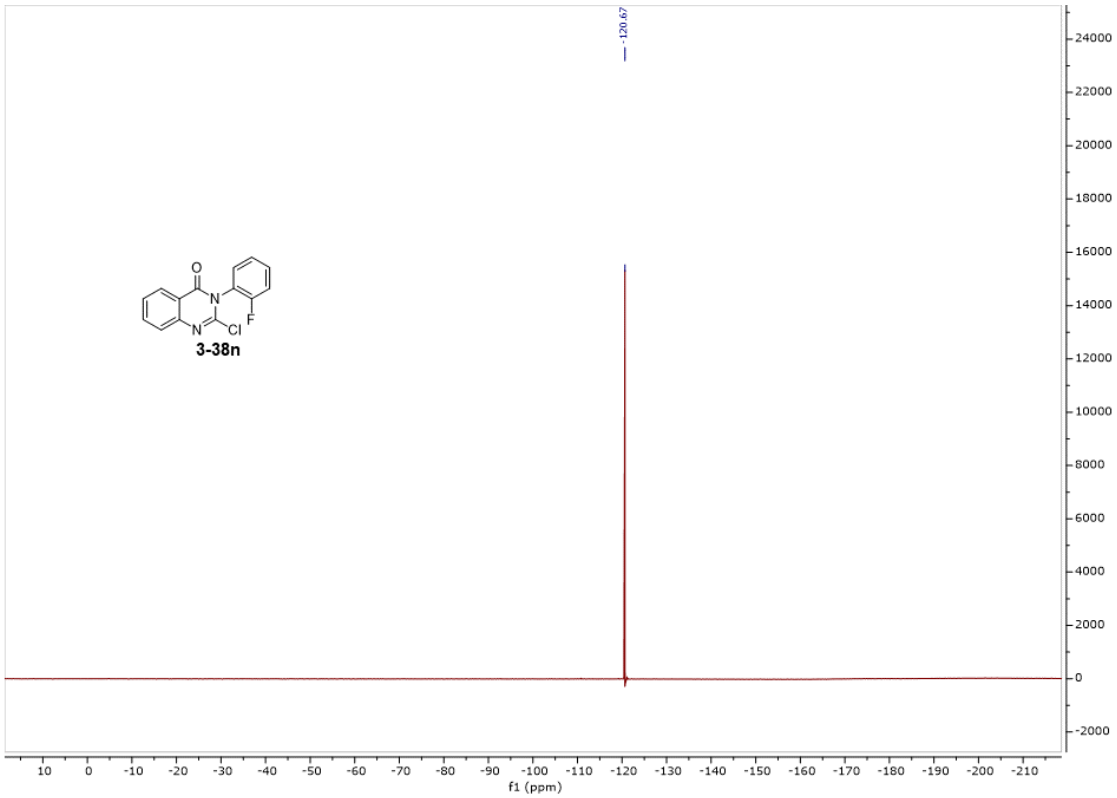

8.39
8.38
8.37
8.36
7.99
7.98
7.74
7.72
7.61
7.60
7.59
7.58
7.57
7.56
7.32
7.31
7.30
7.29
O
N
Ph
F3C
N
Cl
3-38l
1.00
0.96
1.05
3.31
2.05
f1 (ppm)

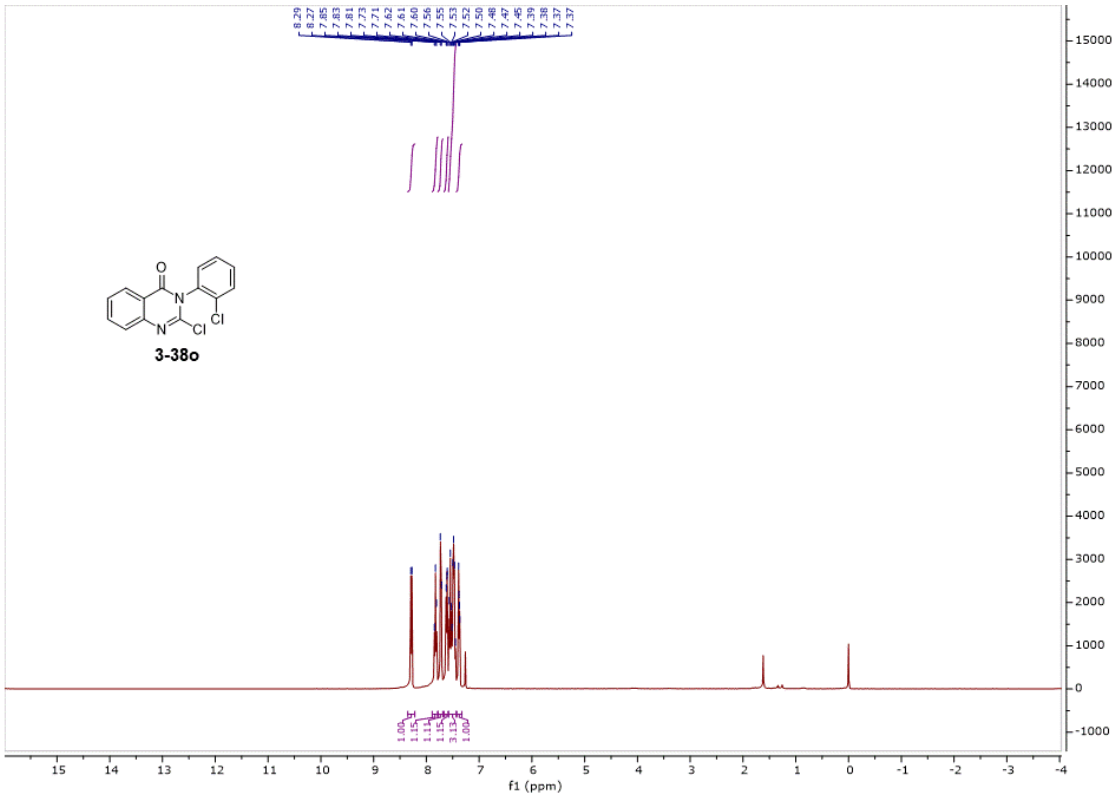

161.29
146.84
146.06
137.43
137.10
136.98
136.77
136.44
130.10
130.01
128.89
128.26
127.34
124.70
124.66
124.62
124.61
124.58
123.91
123.88
123.85
123.82
123.18
121.91
119.20
O
N
Ph
F3C
N
Cl
3-38l
f1 (ppm)

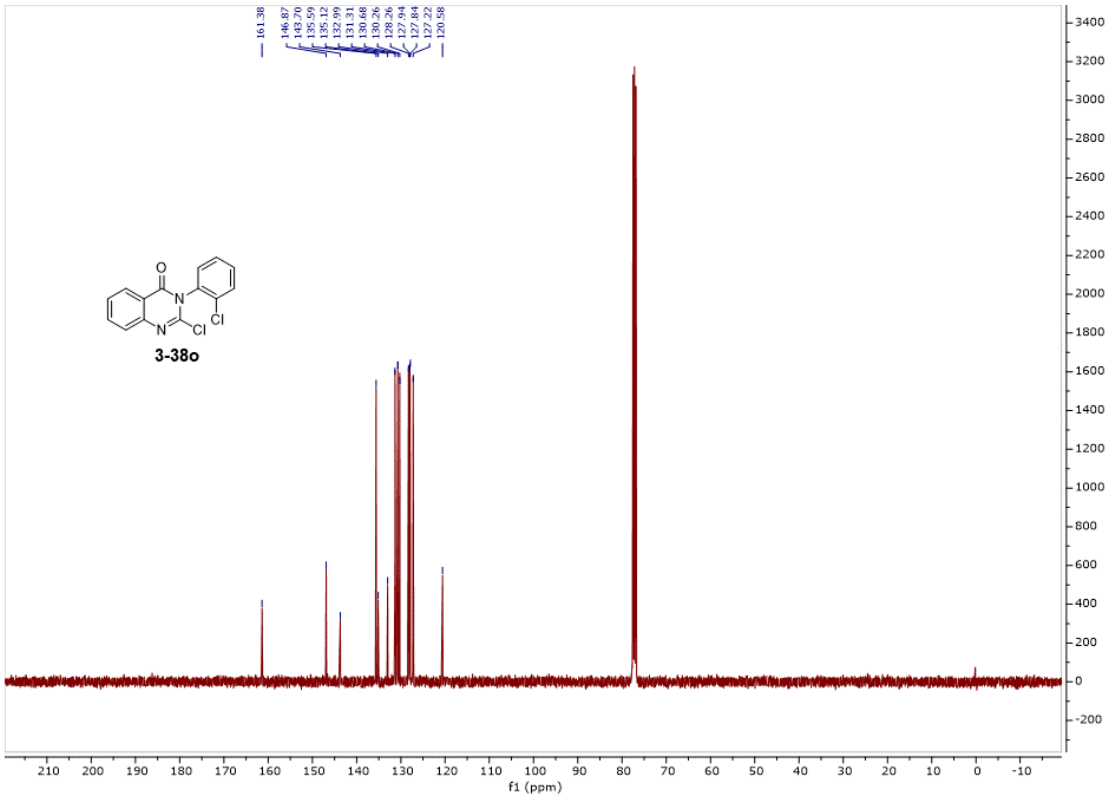

63.35
3-38l
f1 (ppm)

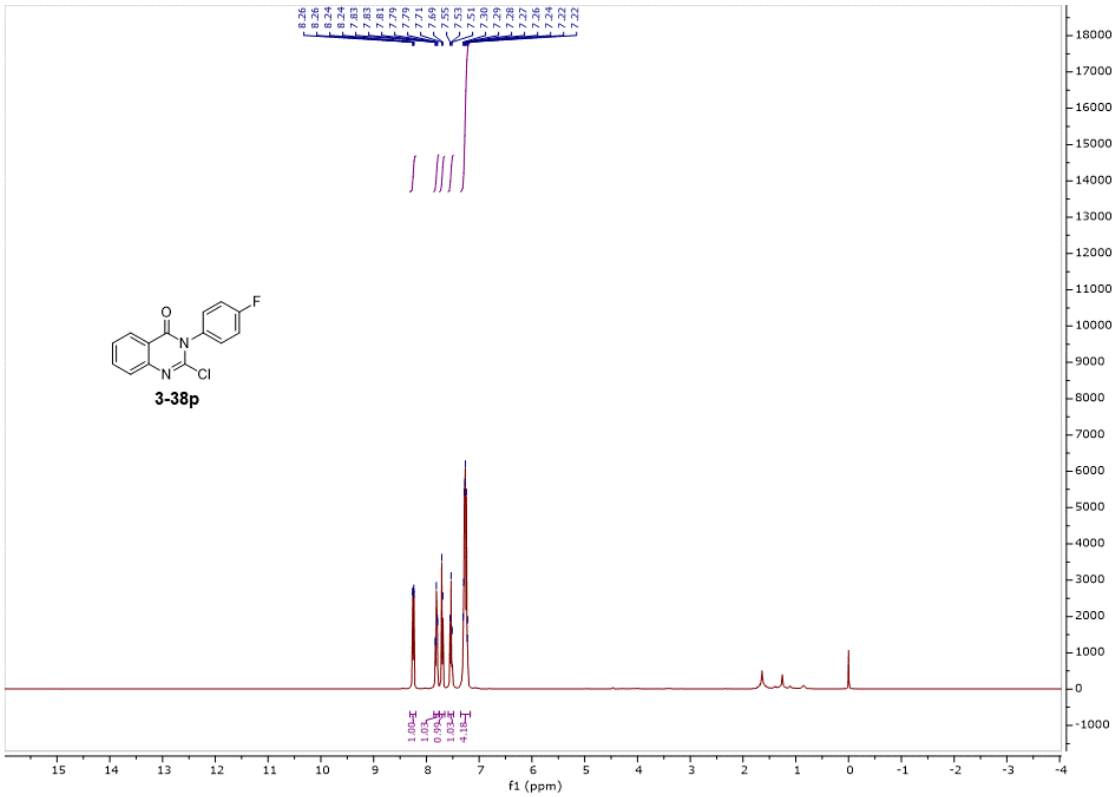

3-38n
f1 (ppm)

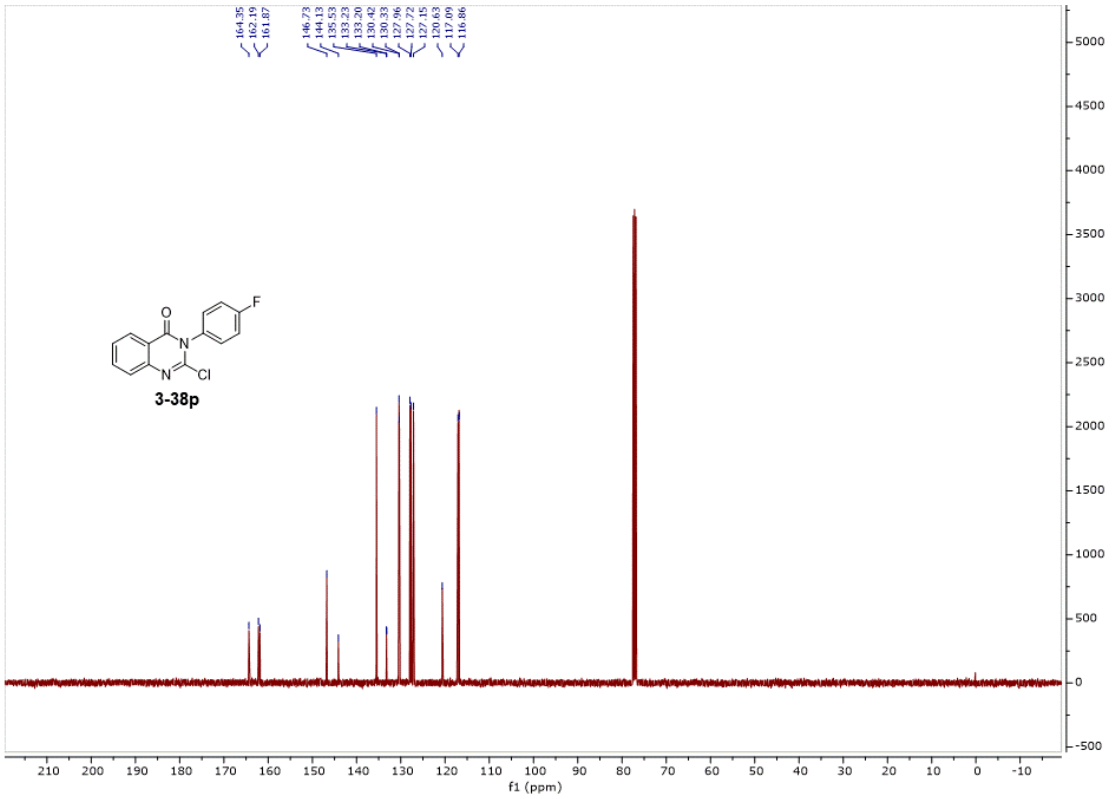

161.51
159.13
156.63
146.81
143.86
135.61
132.01
131.93
130.33
128.00
127.82
127.22
125.16
125.12
125.06
124.93
120.51
117.09
116.90
3-38n
f1 (ppm)

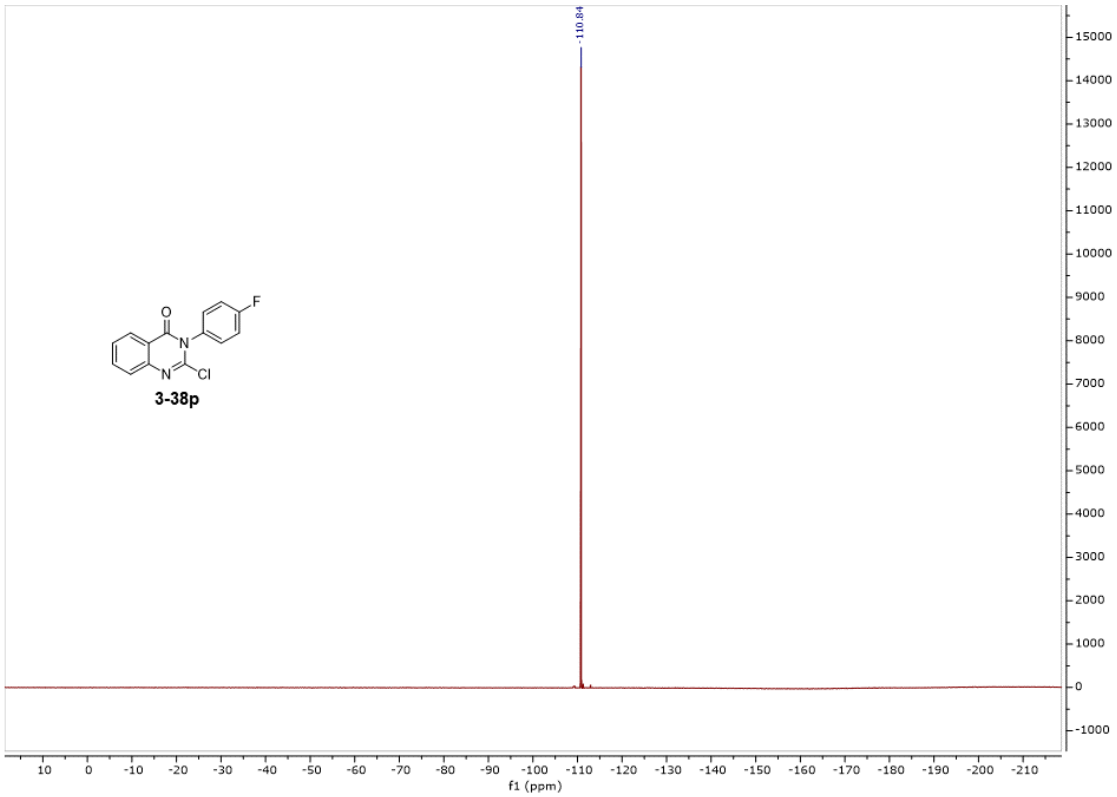

-120.67
3-38n
f1 (ppm)

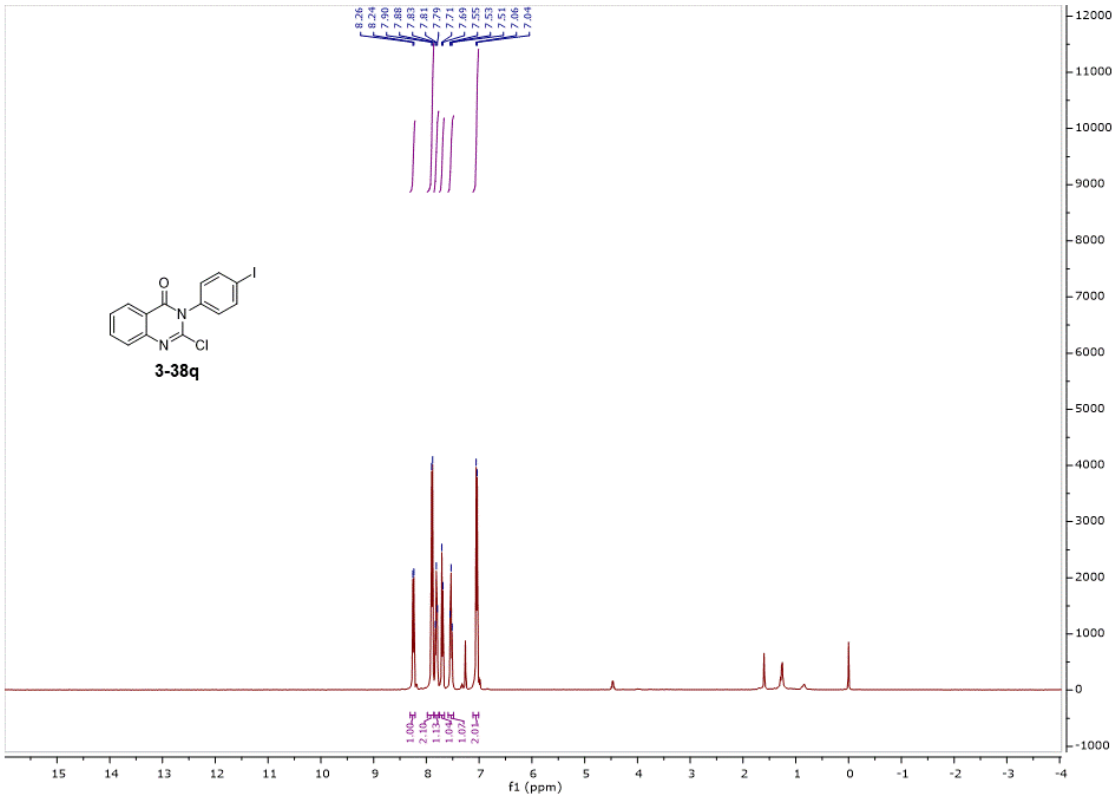

8.29
8.27
7.85
7.83
7.81
7.73
7.71
7.62
7.61
7.60
7.56
7.55
7.53
7.52
7.50
7.48
7.47
7.45
7.39
7.38
7.37
7.37
O
N
N
Cl
Cl
3-38o
1.05
1.15
1.11
1.15
3.13
1.00
f1 (ppm)

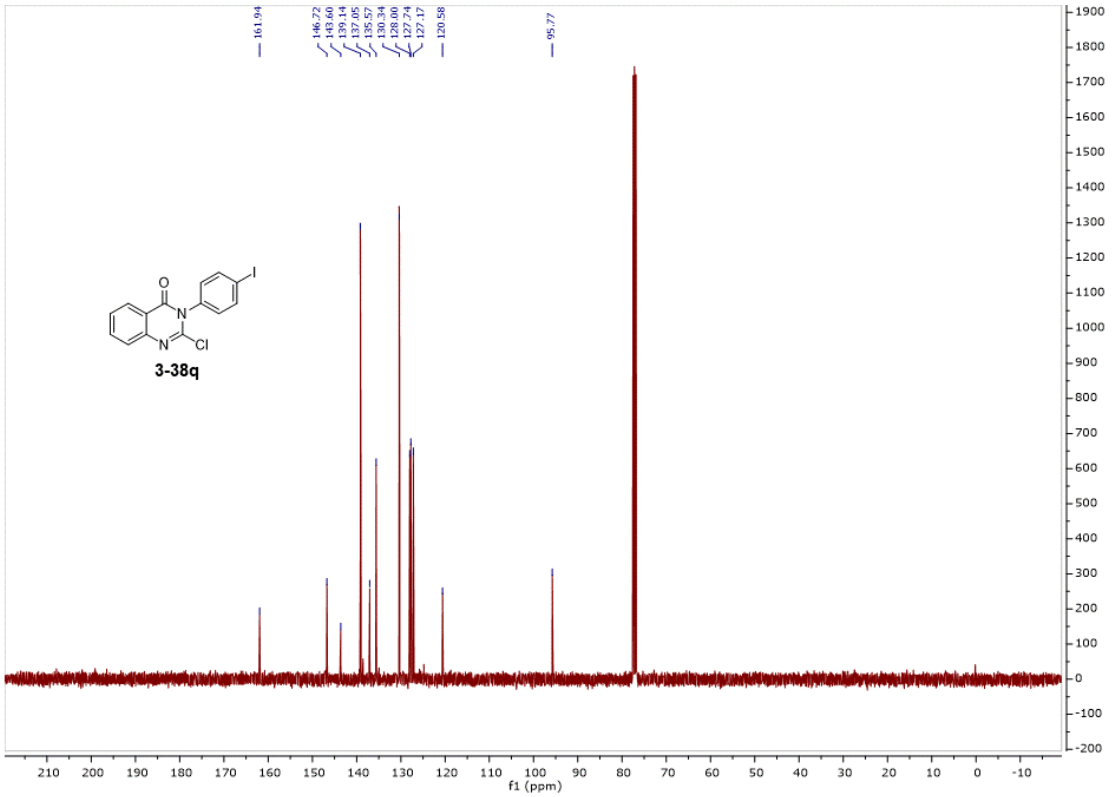

161.38
146.87
143.70
135.59
135.12
132.99
131.31
130.68
130.26
128.26
127.94
127.84
127.22
120.58
O
N
N
Cl
Cl
3-38o
f1 (ppm)

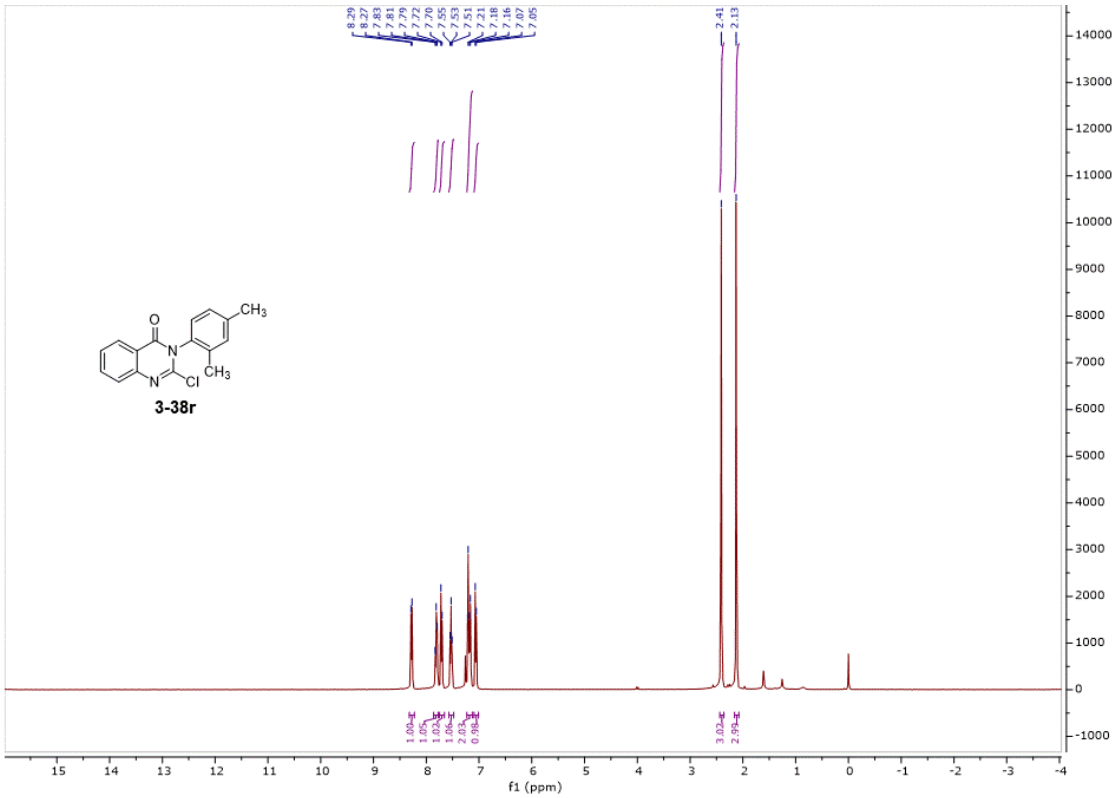

8.26
8.26
8.24
8.24
8.24
7.83
7.83
7.81
7.79
7.79
7.71
7.69
7.55
7.53
7.51
7.30
7.29
7.28
7.27
7.26
7.24
7.22
7.22
O
N
F
N
Cl
3-38p
1.00
1.03
0.99
1.03
4.18
f1 (ppm)

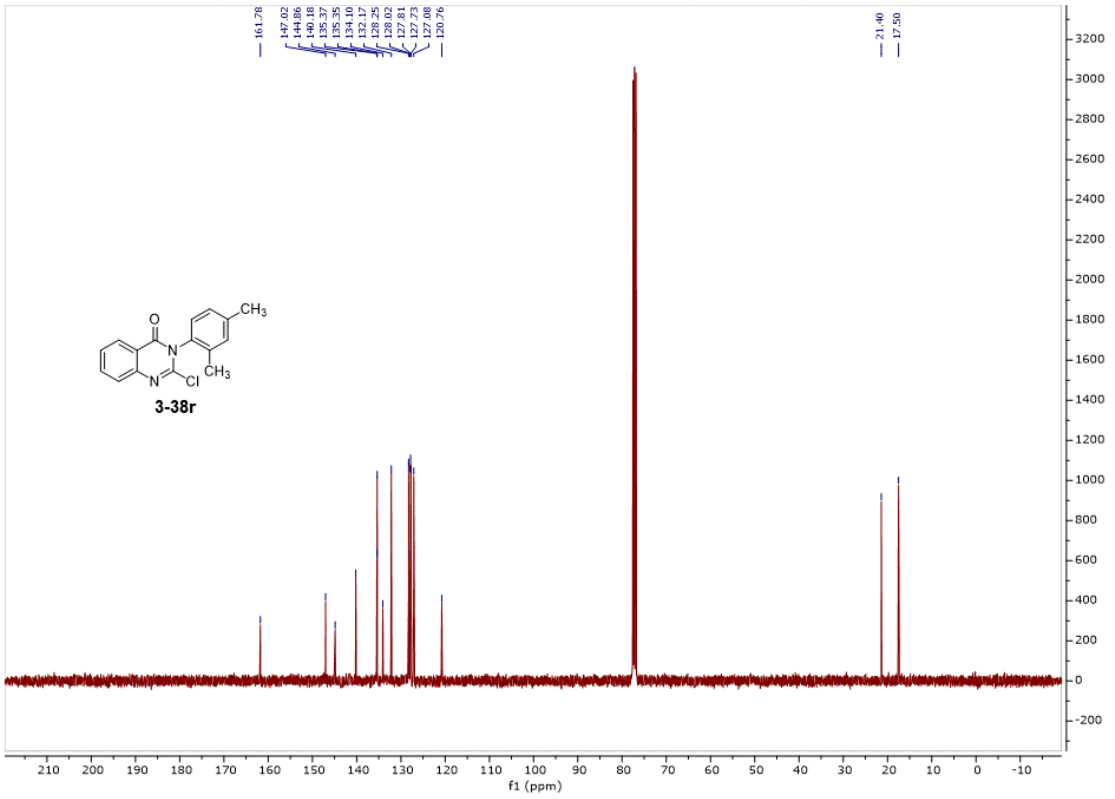

164.35
162.19
161.87
146.73
144.13
135.53
133.23
133.20
130.42
130.33
127.96
127.72
127.15
120.63
117.09
116.86
O
N
F
N
Cl
3-38p
f1 (ppm)

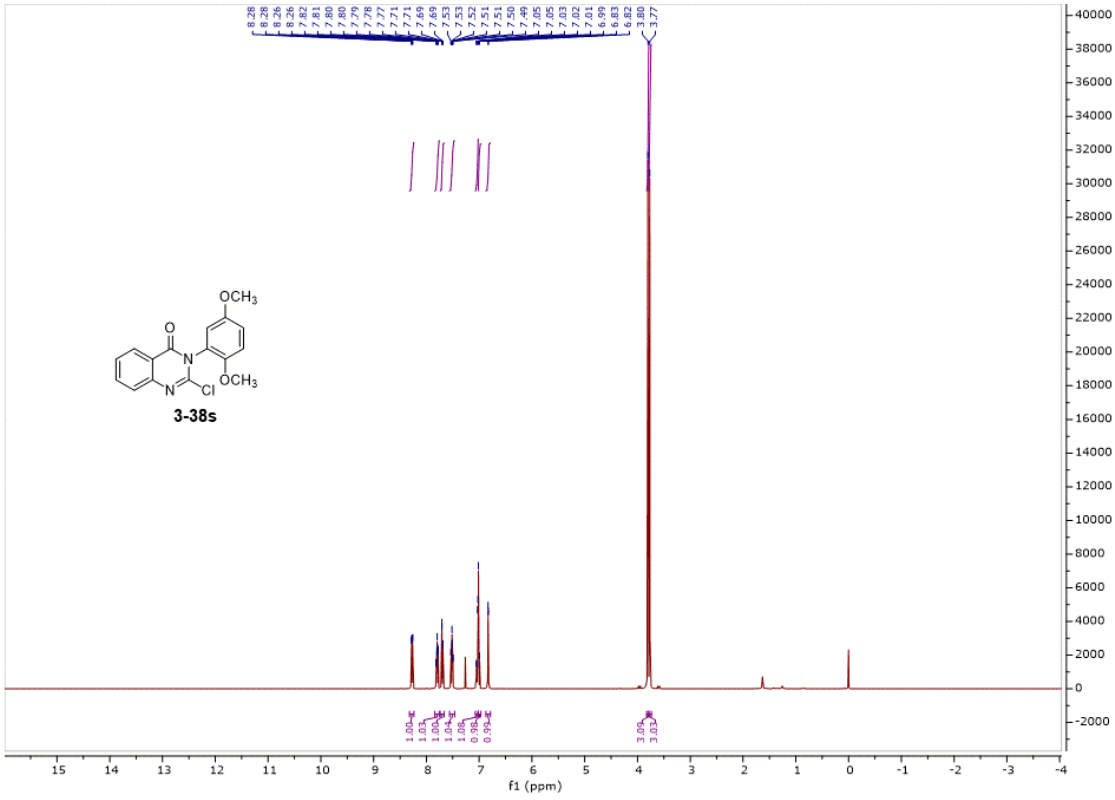

-110.84
F
O
N
N
Cl
3-38p
f1 (ppm)

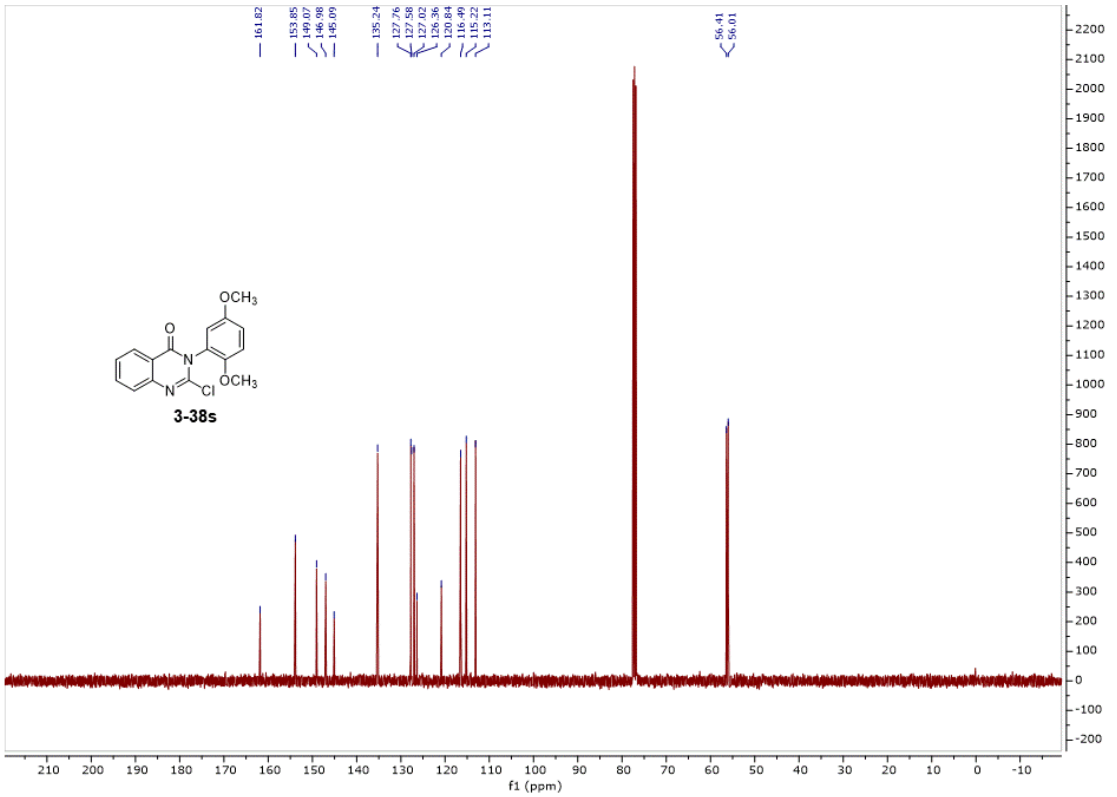

8.26
8.24
8.00
7.88
7.83
7.81
7.79
7.71
7.69
7.55
7.53
7.51
7.06
7.04
I
O
N
N
Cl
3-38q
1.00
2.10
1.13
1.04
1.02
2.01
f1 (ppm)

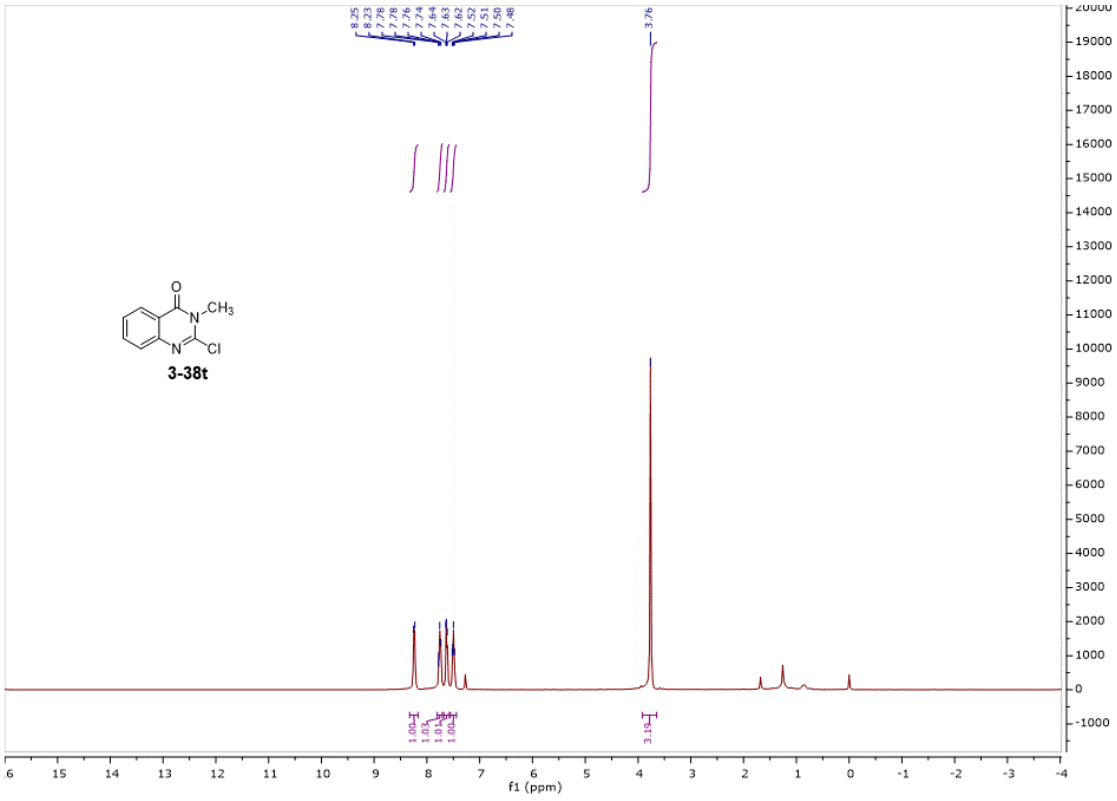

161.94
146.72
140.60
139.14
137.05
135.57
130.34
128.00
127.74
127.17
120.58
95.77
O
N
N
Cl
I
3-38q
f1 (ppm)

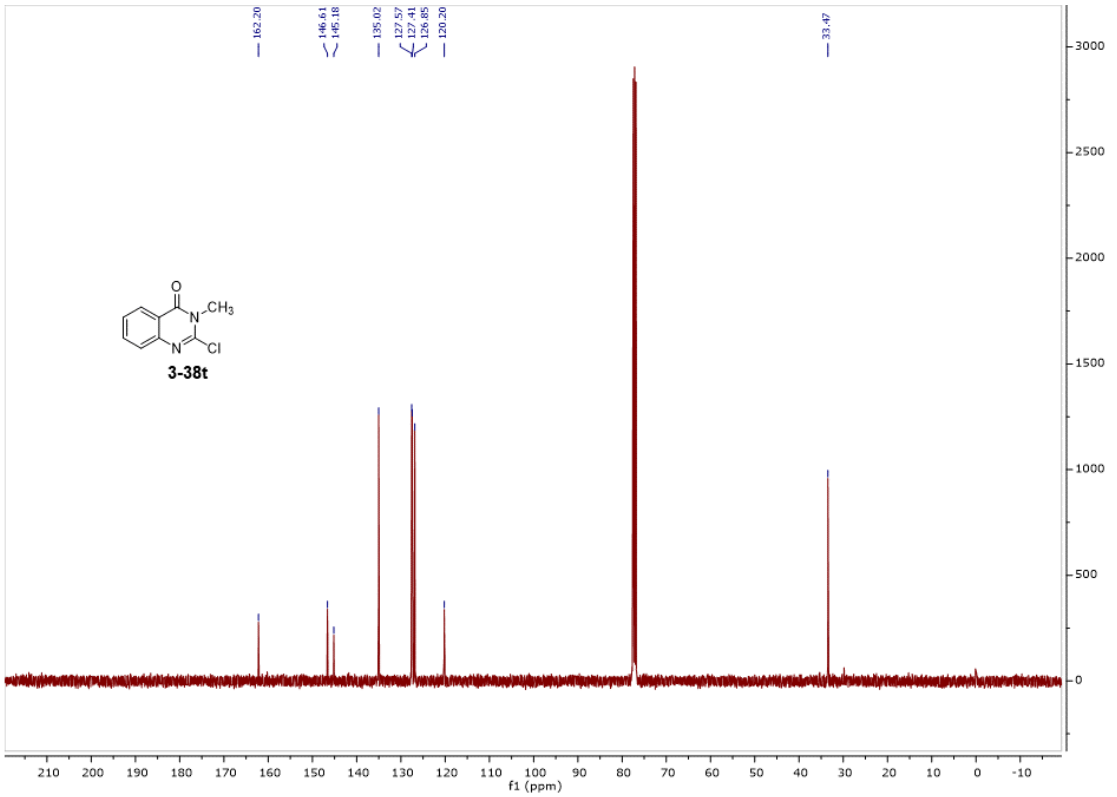

8.29
8.27
7.83
7.81
7.79
7.72
7.70
7.55
7.53
7.51
7.21
7.18
7.16
7.07
7.05
2.41
2.13
1.00
1.05
1.02
1.06
2.03
0.98
3.02
2.99
O
N
N
Cl
CH3
CH3
3-38r
f1 (ppm)

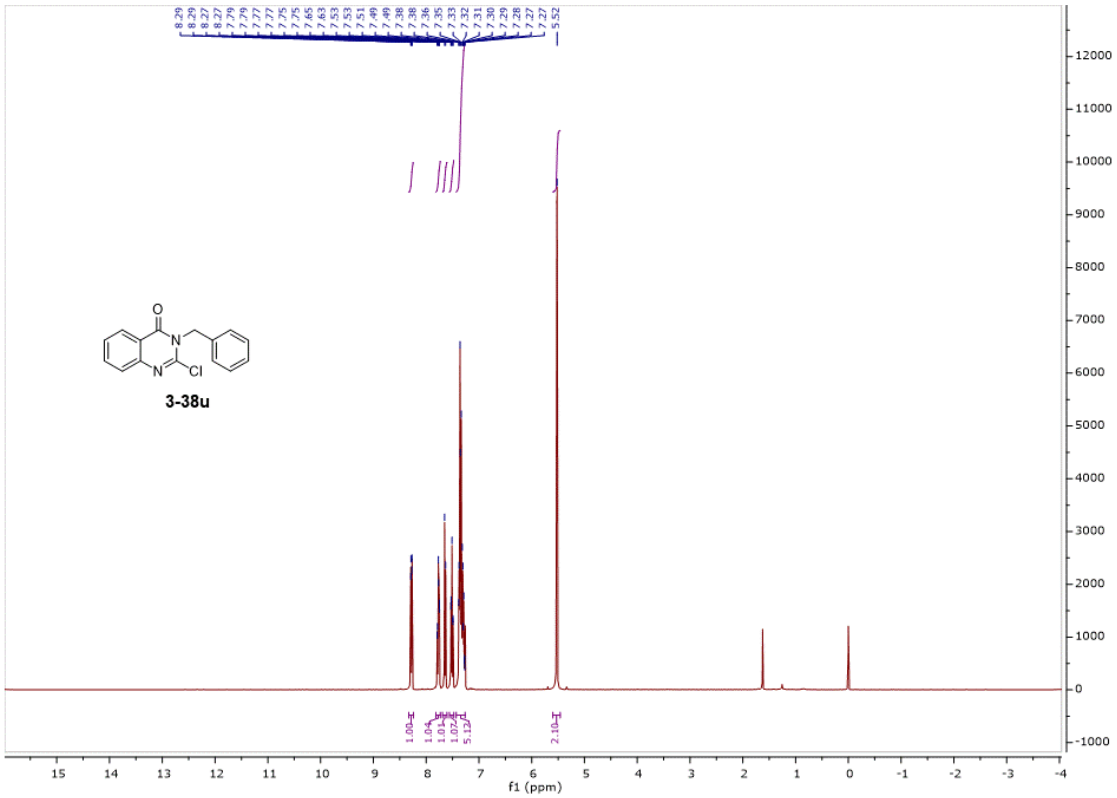

161.78
147.02
144.86
140.18
135.37
135.35
134.10
132.17
128.25
128.02
127.81
127.73
127.08
120.76
21.40
17.50
CH3
CH3
O
N
N
Cl
3-38r
f1 (ppm)

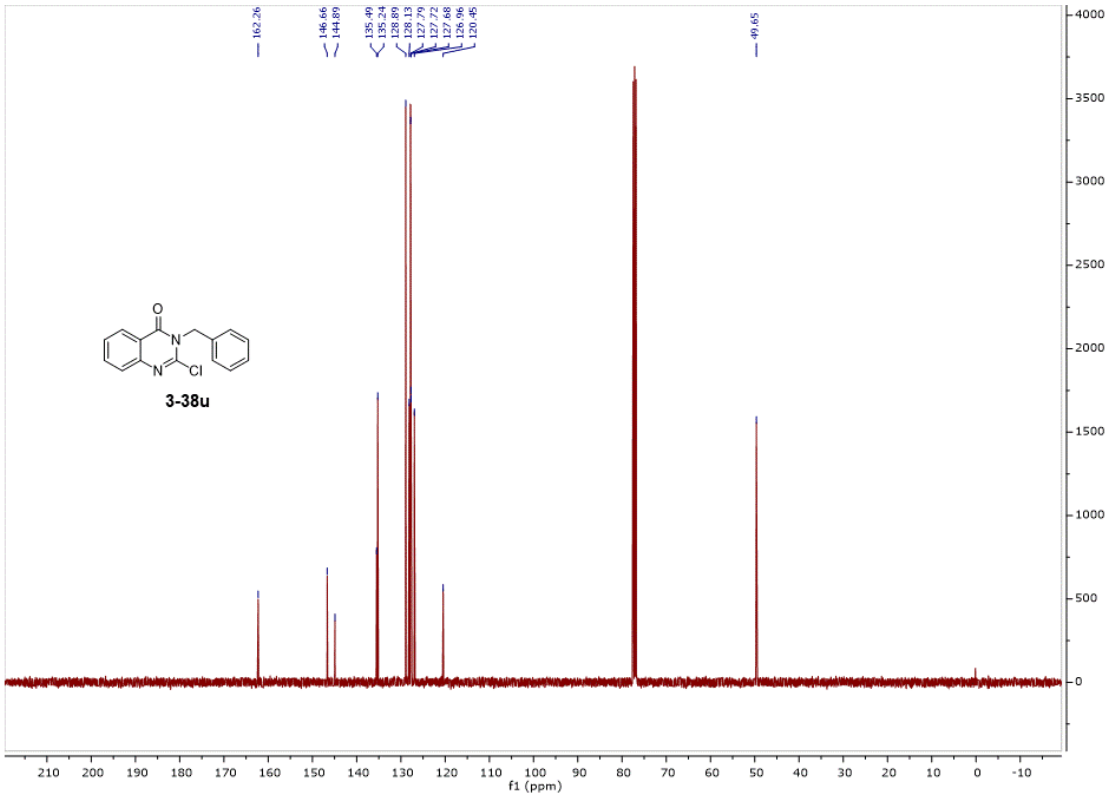

8.28
8.28
8.26
8.26
7.82
7.81
7.80
7.80
7.79
7.78
7.77
7.71
7.71
7.69
7.69
7.53
7.52
7.51
7.51
7.50
7.49
7.05
7.05
7.03
7.02
7.01
6.99
6.83
6.82
3.80
3.77
OCH3
OCH3
O
N
N
Cl
3-38s
1.00
1.03
1.04
1.04
1.08
0.98
0.99
3.05
3.03
f1 (ppm)

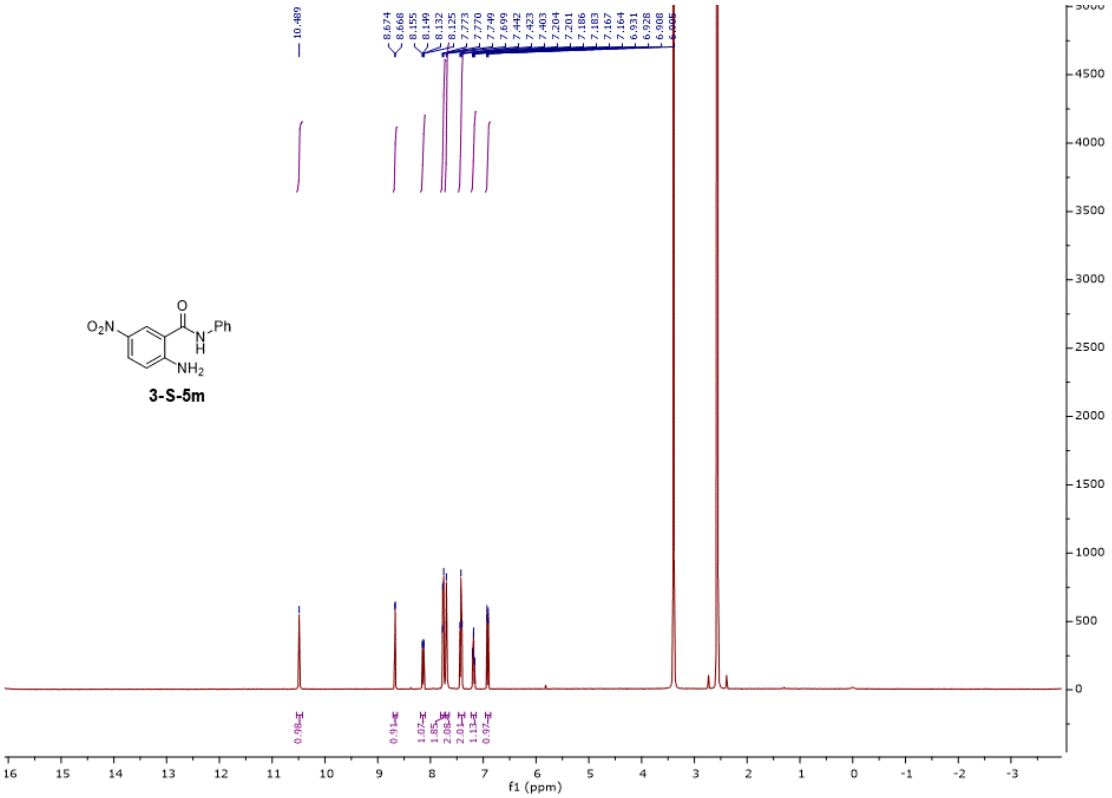

161.82
153.85
149.07
146.98
145.09
135.24
127.76
127.58
127.02
126.36
120.84
116.49
115.22
113.11
56.41
56.01
OCH3
OCH3
Cl
3-38s
f1 (ppm)

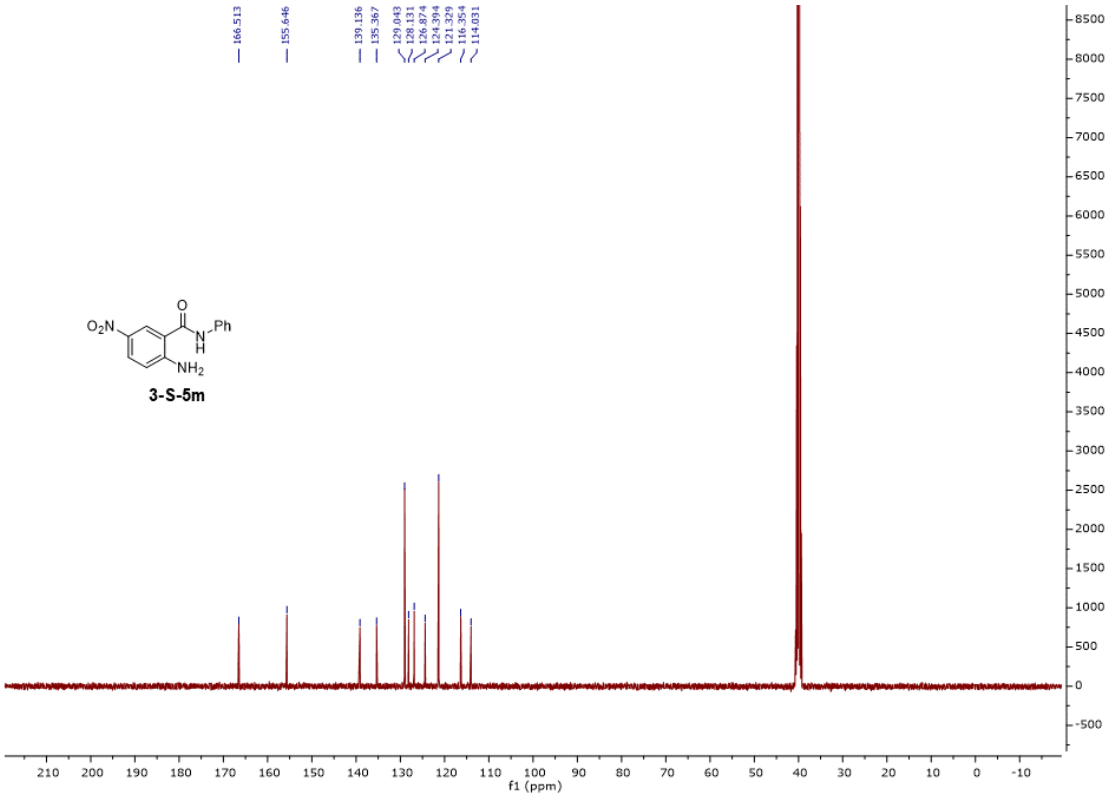

8.25
8.23
7.78
7.78
7.76
7.74
7.64
7.63
7.62
7.52
7.51
7.50
7.48
3.76
CH3
Cl
3-38t
1.00
1.03
1.01
1.00
3.19
f1 (ppm)

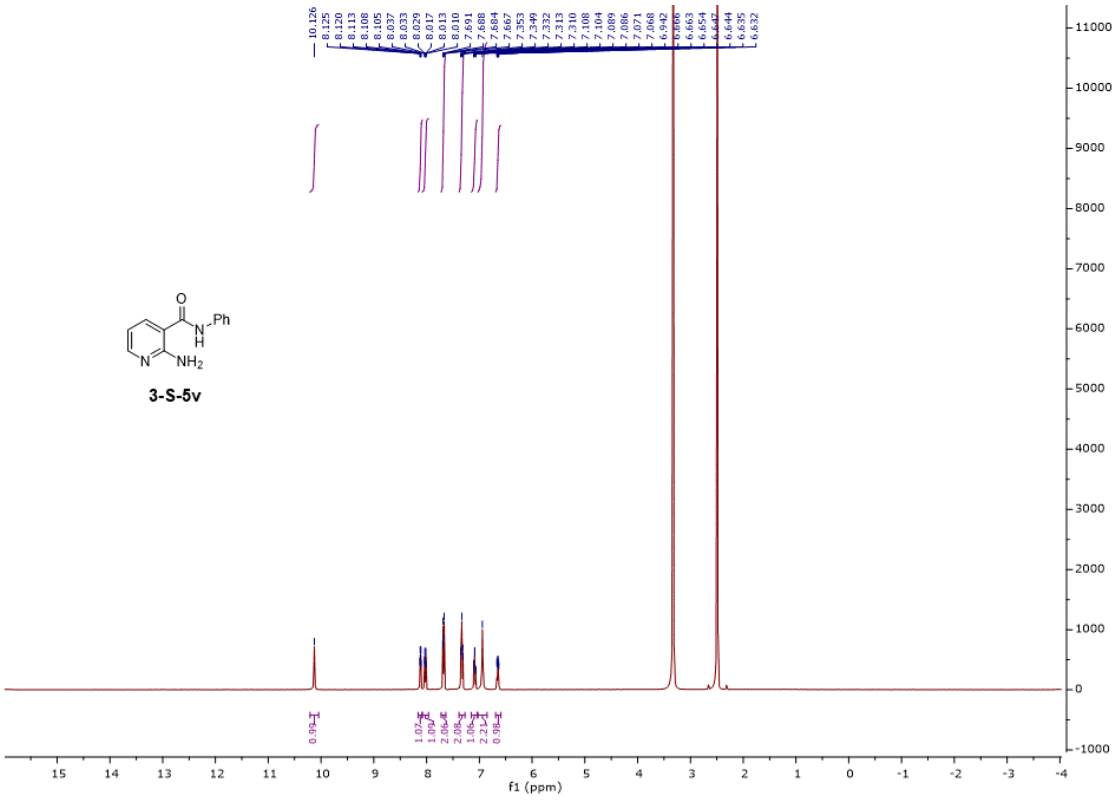

162.20
146.61
145.18
135.02
127.57
127.41
126.85
120.20
33.47
3-38t
f1 (ppm)

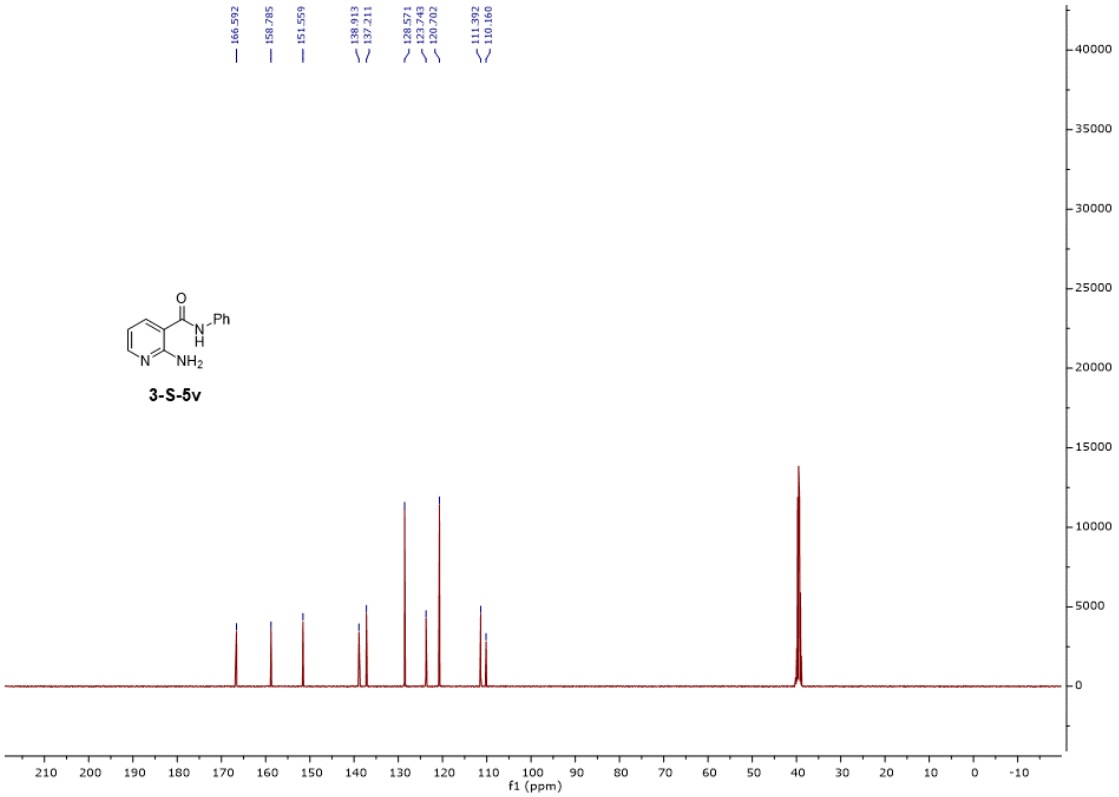

3-38u
f1 (ppm)

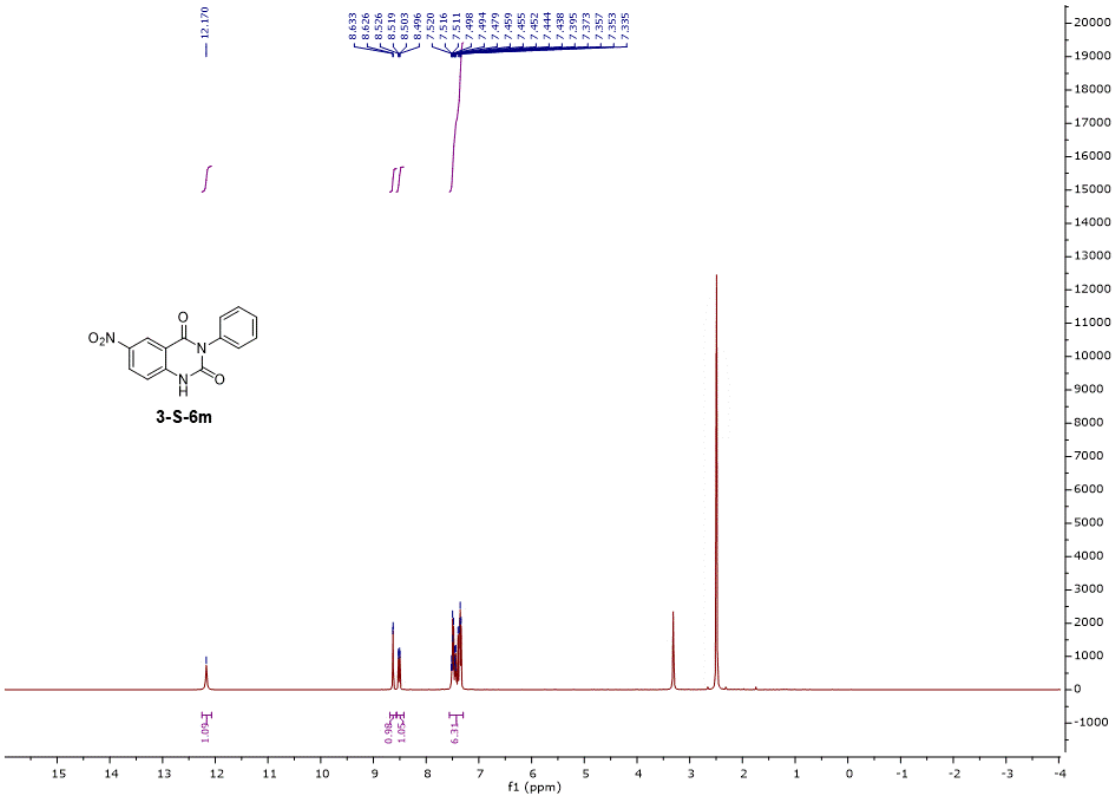

162.26
146.66
144.89
135.49
135.24
128.89
128.13
127.79
127.72
127.68
126.96
120.45
49.65
3-38u
f1 (ppm)

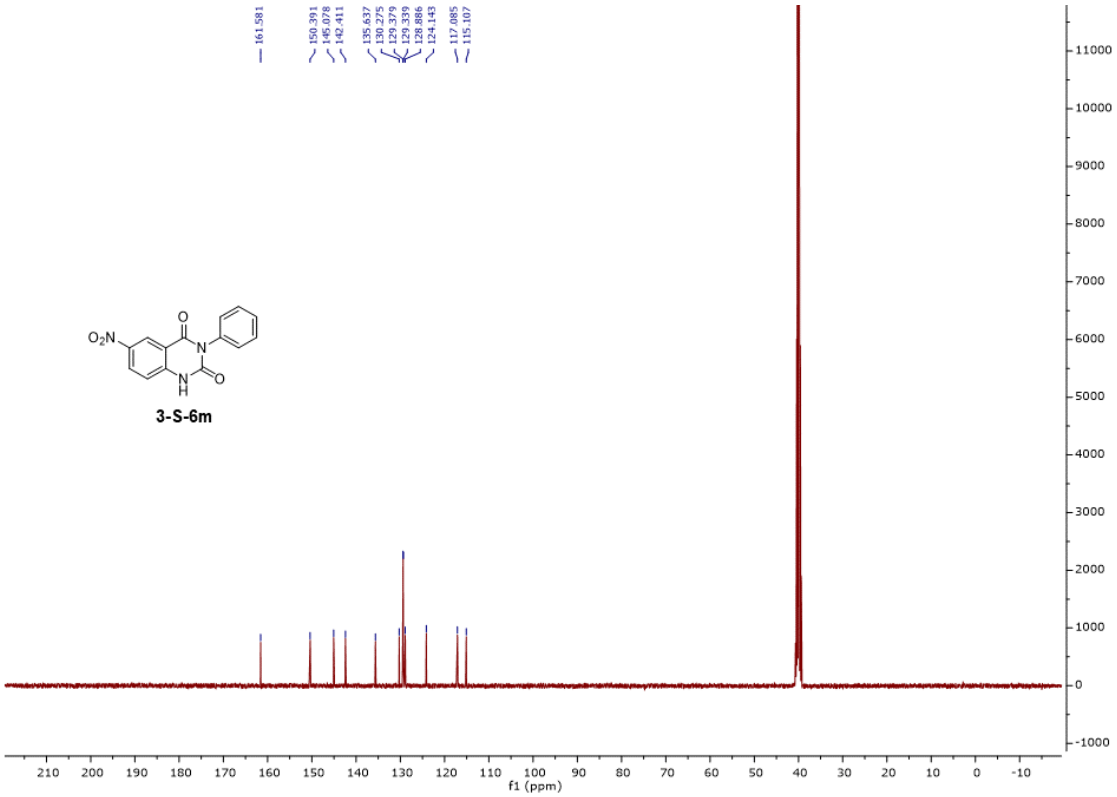

10.489
8.674
8.668
8.155
8.149
8.132
8.125
7.773
7.770
7.749
7.699
7.442
7.423
7.403
7.204
7.201
7.186
7.183
7.167
7.164
6.931
6.928
6.908
6.905
0.98
0.91
1.07
1.85
2.08
2.01
1.13
0.97
3-S-5m
f1 (ppm)

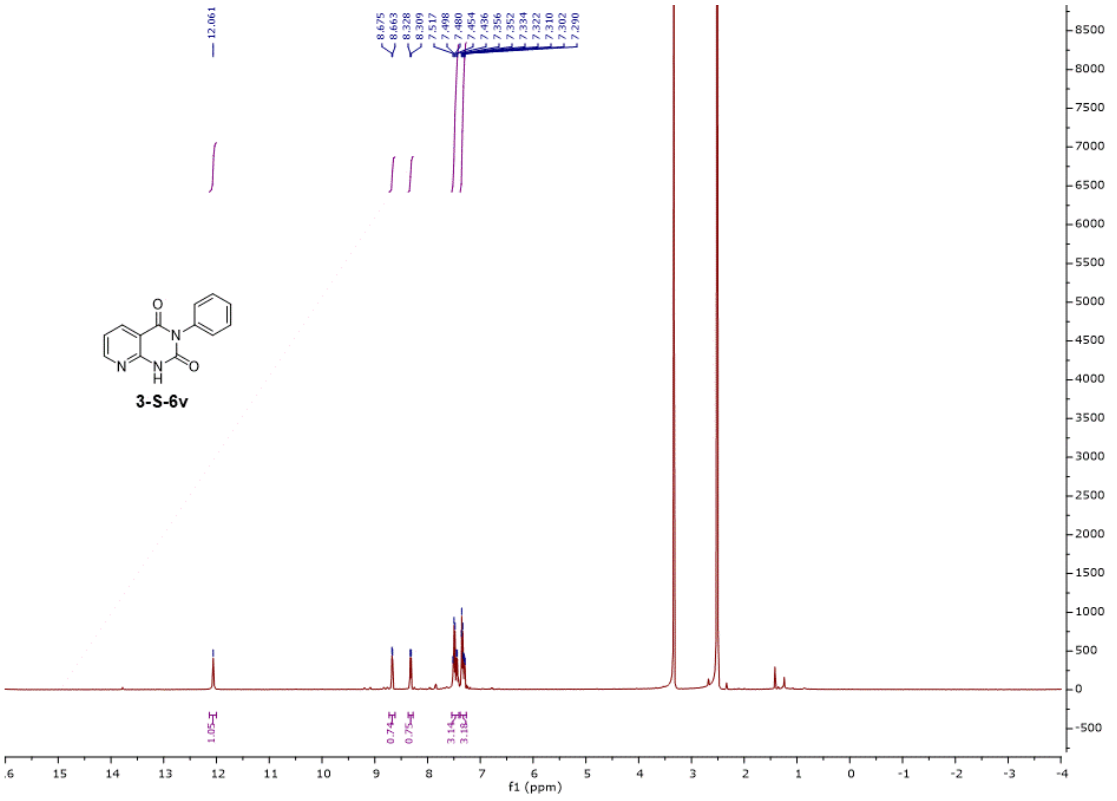

166.513
155.646
139.136
135.367
129.043
128.131
126.874
124.394
121.329
116.354
114.031
O2N
O
N
H
Ph
NH2
3-S-5m
f1 (ppm)

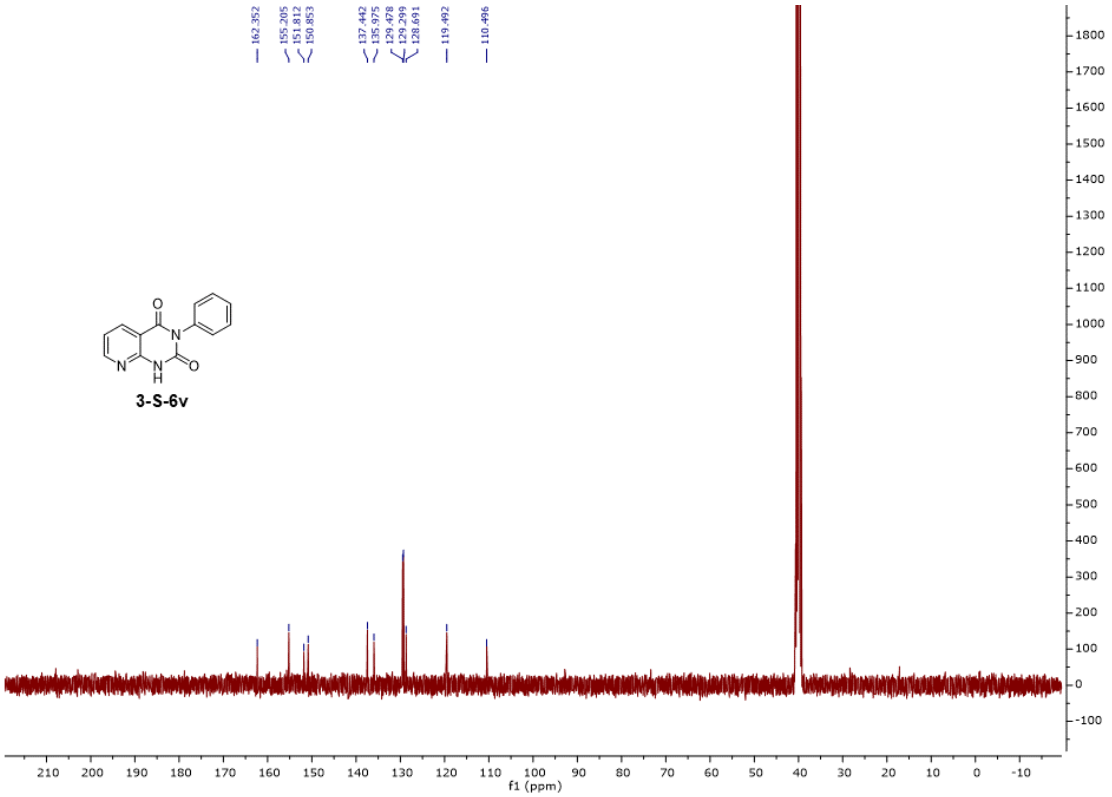

10.126
8.125
8.120
8.113
8.108
8.105
8.037
8.033
8.029
8.017
8.013
8.010
7.691
7.688
7.684
7.667
7.353
7.349
7.332
7.313
7.310
7.108
7.104
7.089
7.086
7.071
7.068
6.942
6.866
6.663
6.654
6.647
6.644
6.635
6.632
O
N
H
Ph
N
NH2
3-S-5v
f1 (ppm)

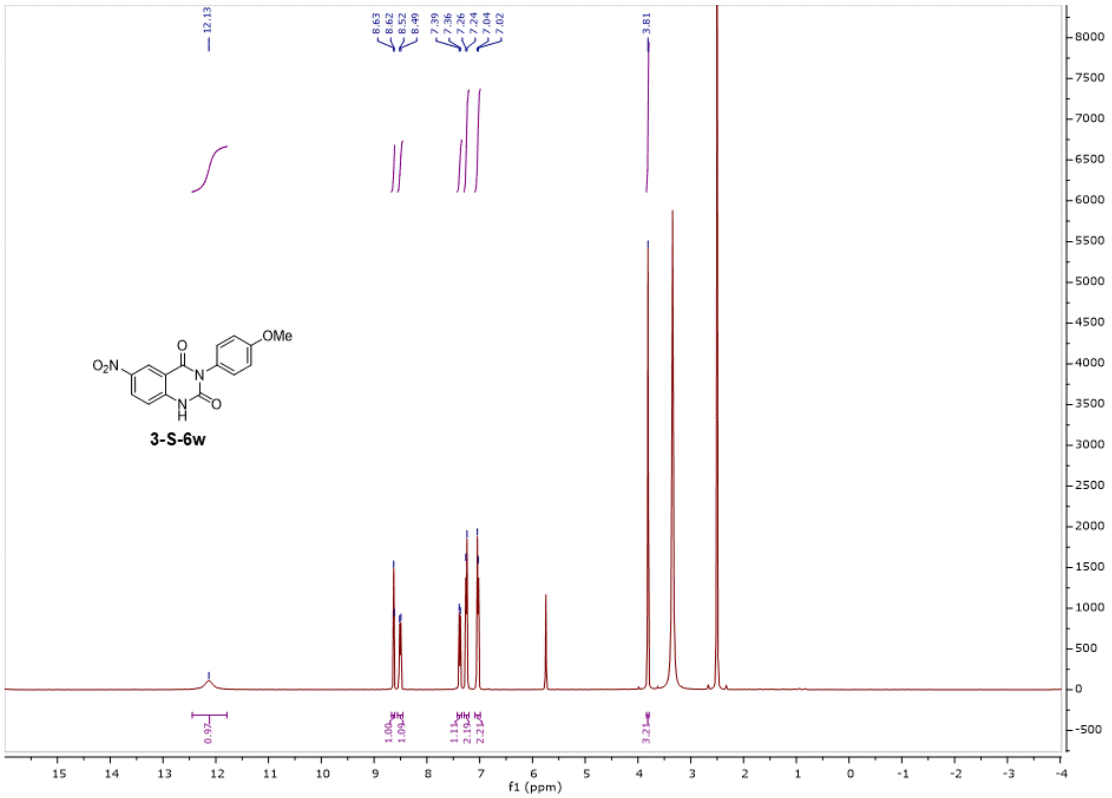

166.592
158.785
151.559
138.913
137.211
128.571
123.743
120.702
111.392
110.160
3-S-5v
f1 (ppm)

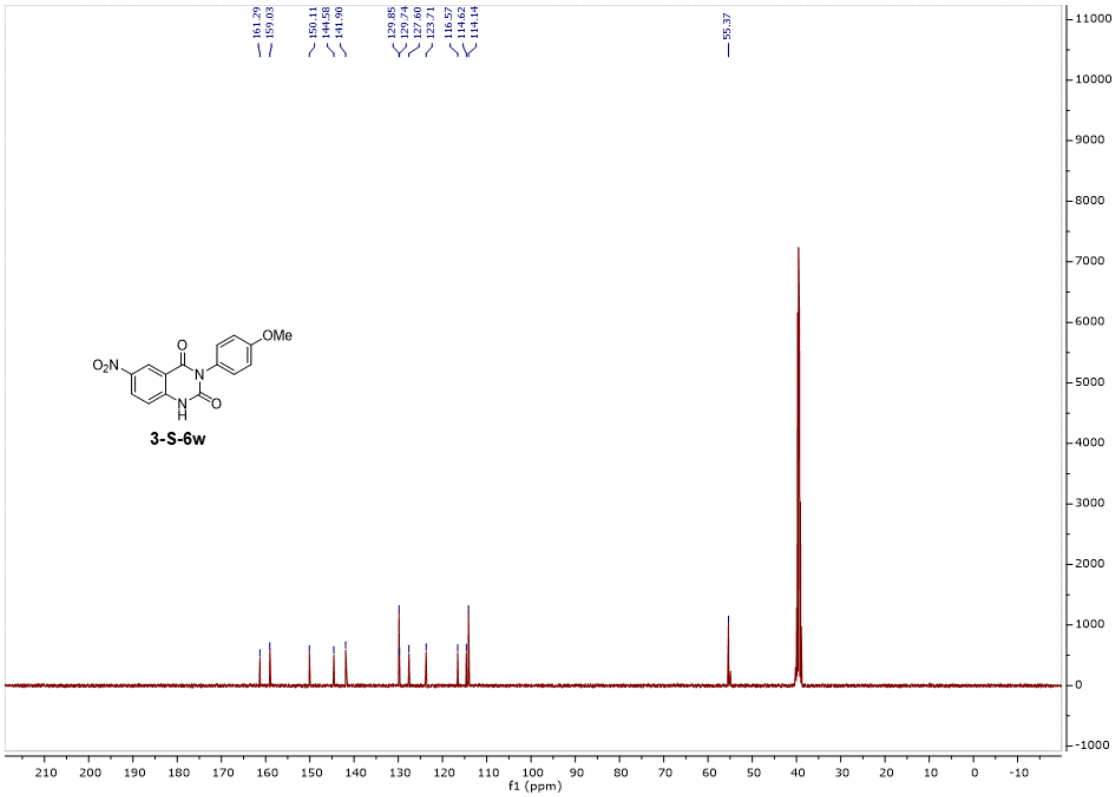

12.170
8.633
8.626
8.526
8.519
8.503
8.496
7.520
7.516
7.511
7.498
7.494
7.479
7.459
7.455
7.452
7.444
7.438
7.395
7.373
7.357
7.353
7.335
1.09
0.98
1.05
6.31
3-S-6m
f1 (ppm)

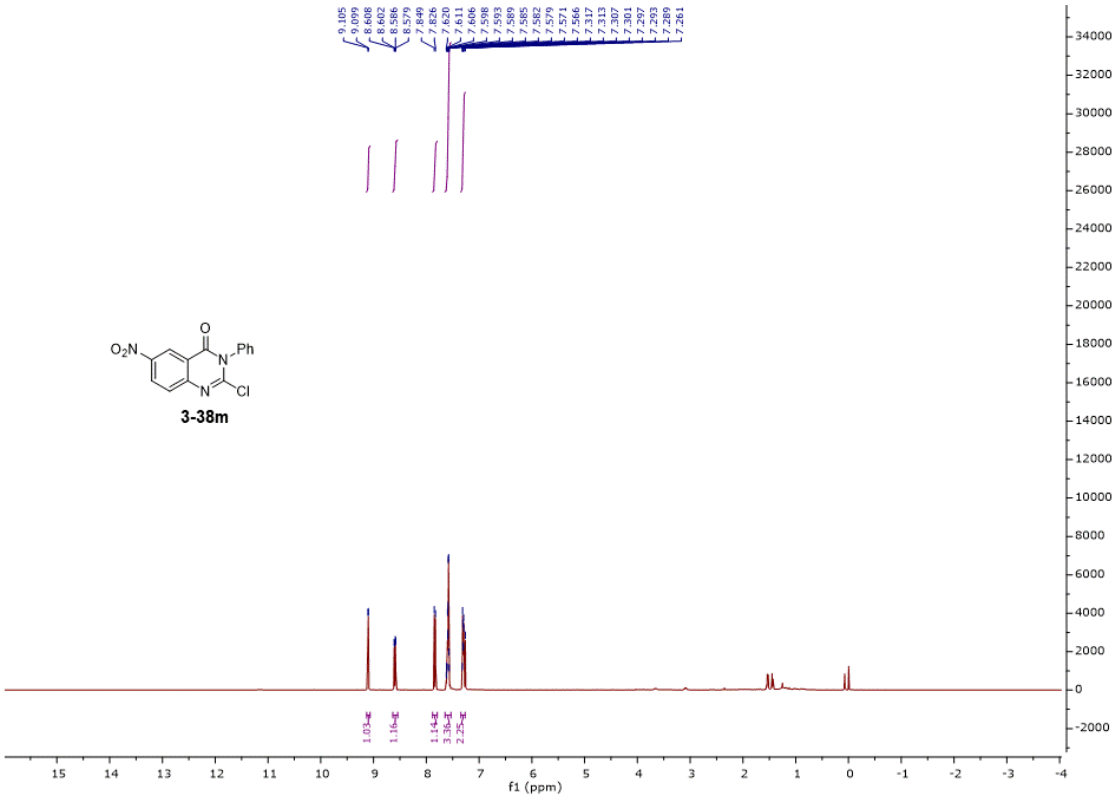

161.581
150.391
145.078
142.411
135.637
130.275
129.379
129.339
128.886
124.143
117.085
115.107
O2N
O
N
H
N
O
3-S-6m
f1 (ppm)

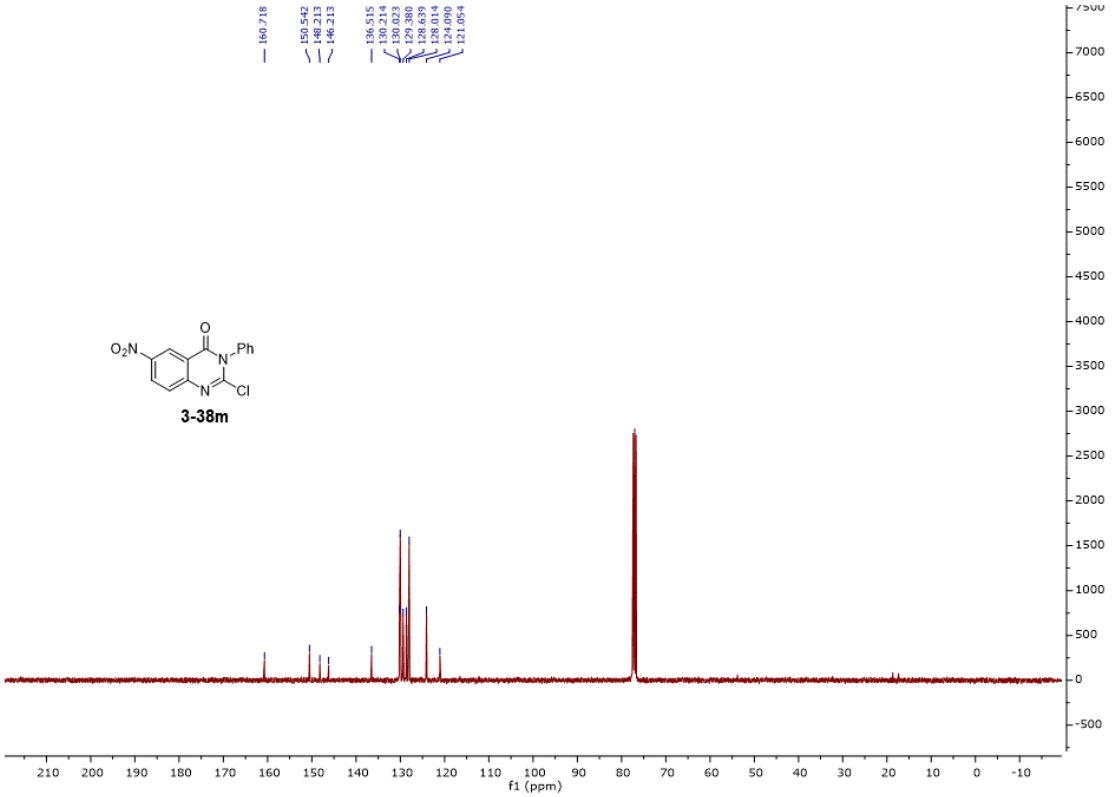

12.061
8.675
8.663
8.328
8.309
7.517
7.498
7.480
7.454
7.436
7.356
7.352
7.334
7.322
7.310
7.302
7.290
1.05
0.74
0.75
3.14
3.18
O
N
H
N
O
3-S-6v
f1 (ppm)

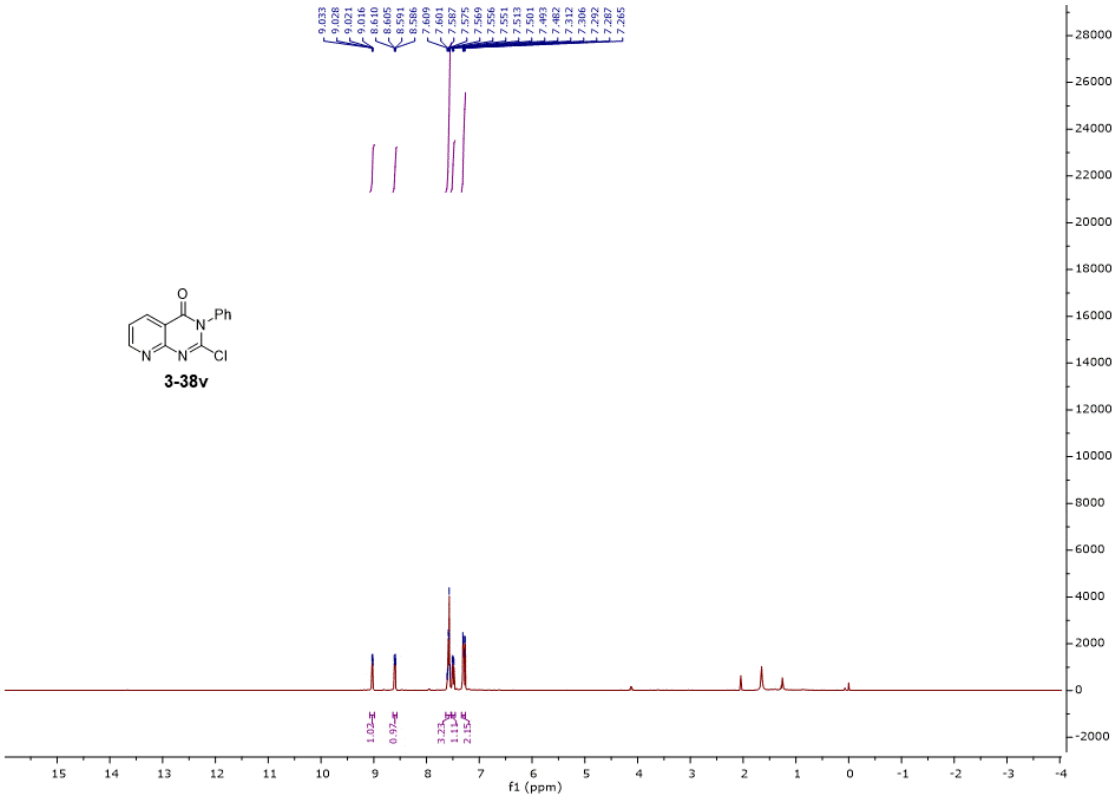

162.352
155.205
151.812
150.853
137.442
135.975
129.478
129.299
128.691
119.492
110.496
3-S-6v
f1 (ppm)

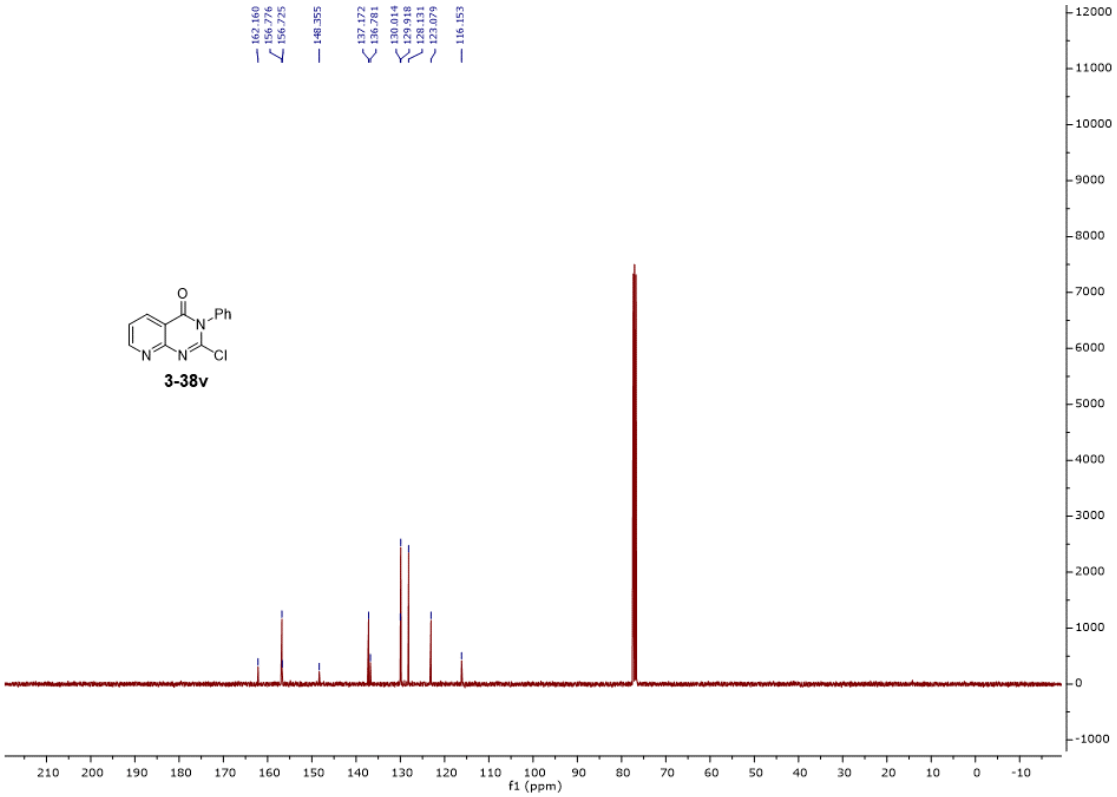

12.13
8.63
8.62
8.52
8.49
7.39
7.36
7.26
7.24
7.04
7.02
3.81
OMe
3-S-6w
f1 (ppm)

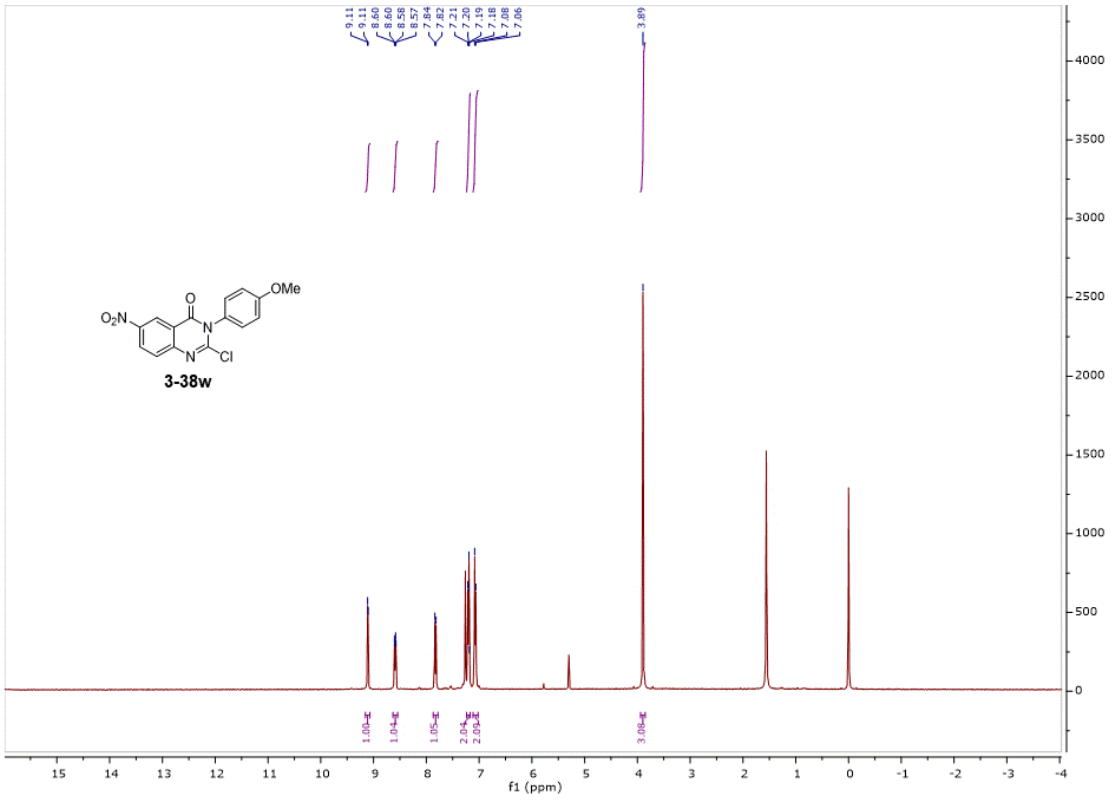

161.29
159.03
150.11
144.58
141.90
129.85
129.74
127.60
123.71
116.57
114.62
114.14
55.37
OMe
O2N
O
N
H
3-S-6w
f1 (ppm)

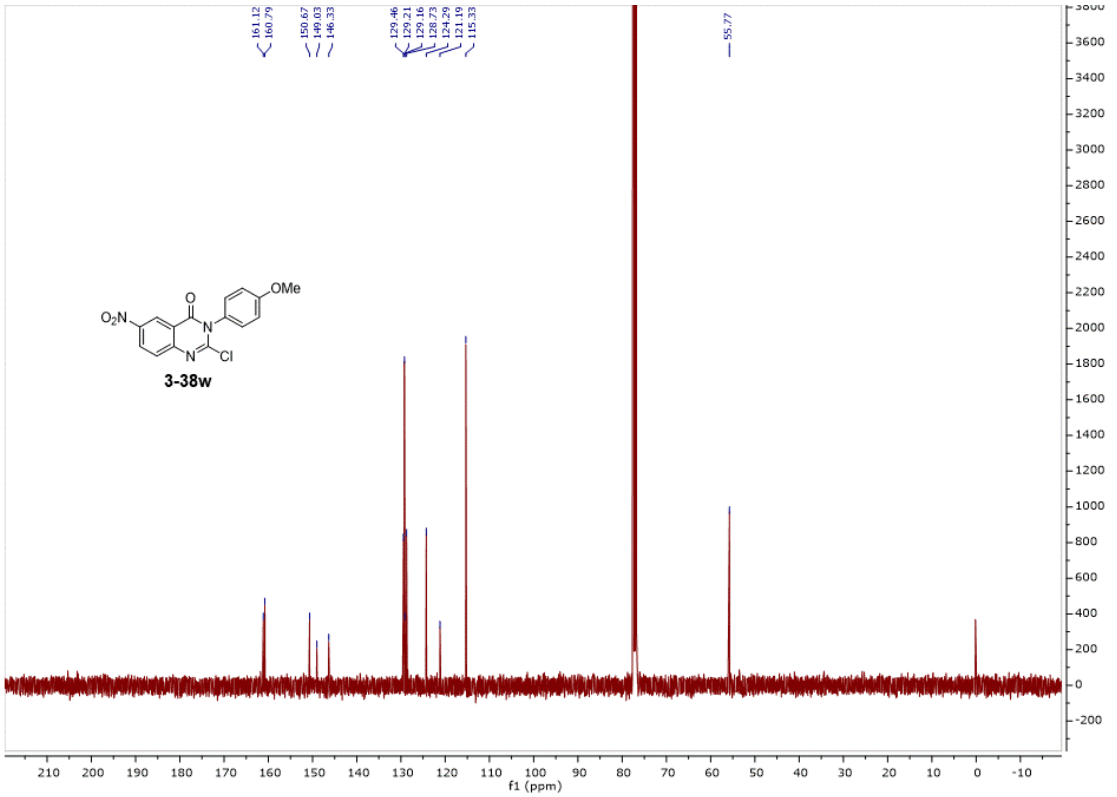

9.105
9.099
8.608
8.602
8.586
8.579
7.849
7.826
7.620
7.611
7.606
7.598
7.595
7.589
7.585
7.582
7.579
7.571
7.566
7.317
7.313
7.307
7.301
7.297
7.293
7.289
7.261
O2N
Ph
Cl
3-38m
1.03
1.16
1.14
3.36
2.25
f1 (ppm)

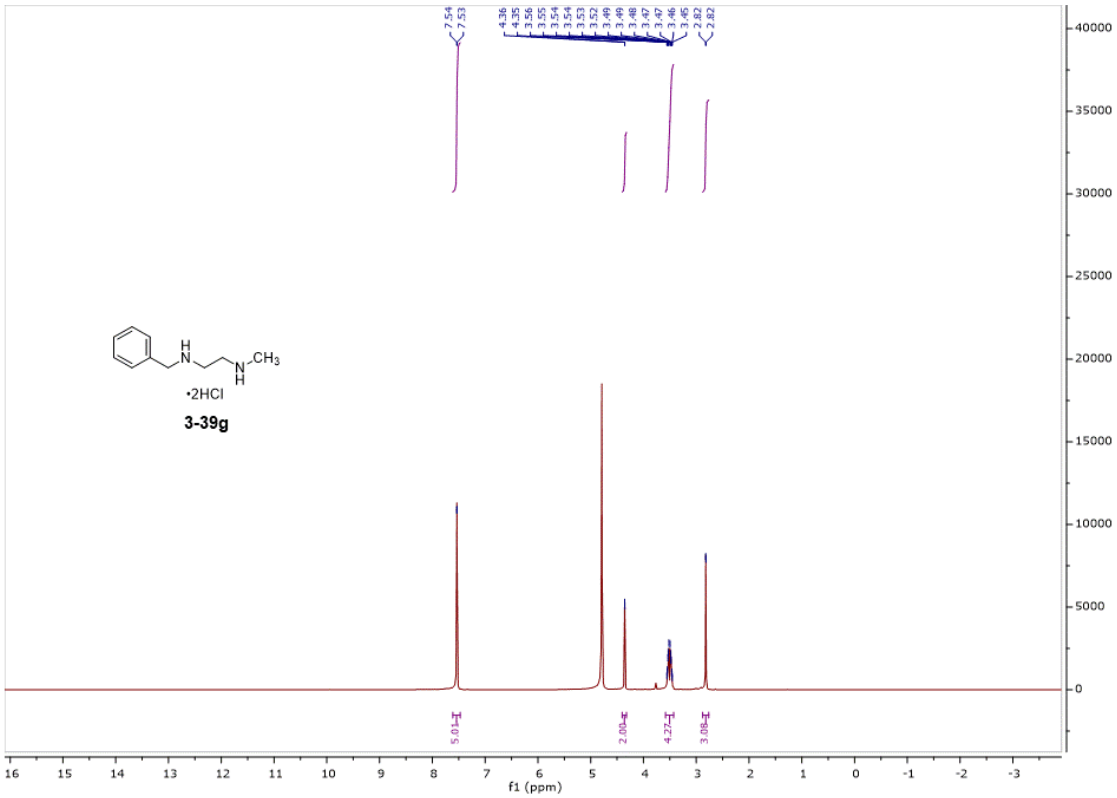

160.718
150.542
148.213
146.213
136.515
130.214
130.023
129.380
128.639
128.014
124.090
121.054
O2N
O
N
Ph
N
Cl
3-38m
f1 (ppm)

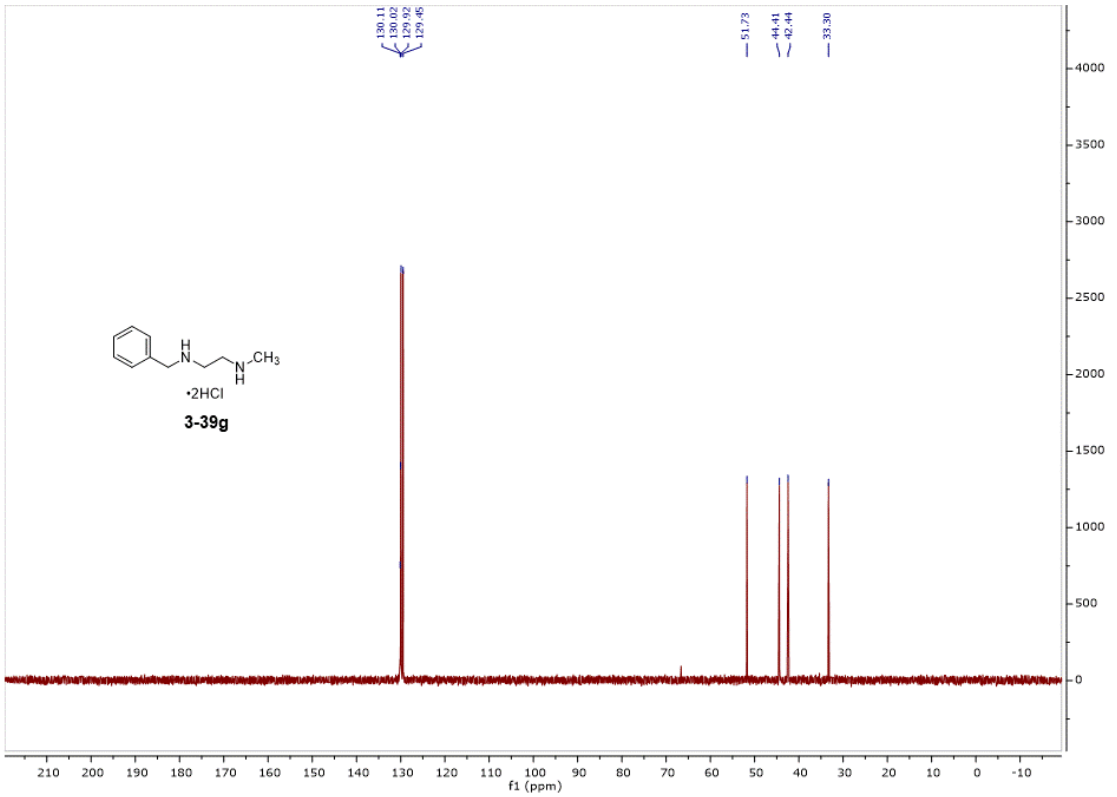

9.033
9.028
9.021
9.016
8.610
8.605
8.591
8.586
7.609
7.601
7.587
7.575
7.569
7.556
7.551
7.513
7.501
7.493
7.482
7.312
7.306
7.292
7.287
7.265
O
N
Ph
N
N
Cl
3-38v
1.03
0.97
3.23
1.11
2.15
f1 (ppm)


162.160
156.776
156.725
148.355
137.172
136.781
130.014
129.918
128.131
123.079
116.153
O
N
Ph
N
Cl
3-38v
f1 (ppm)

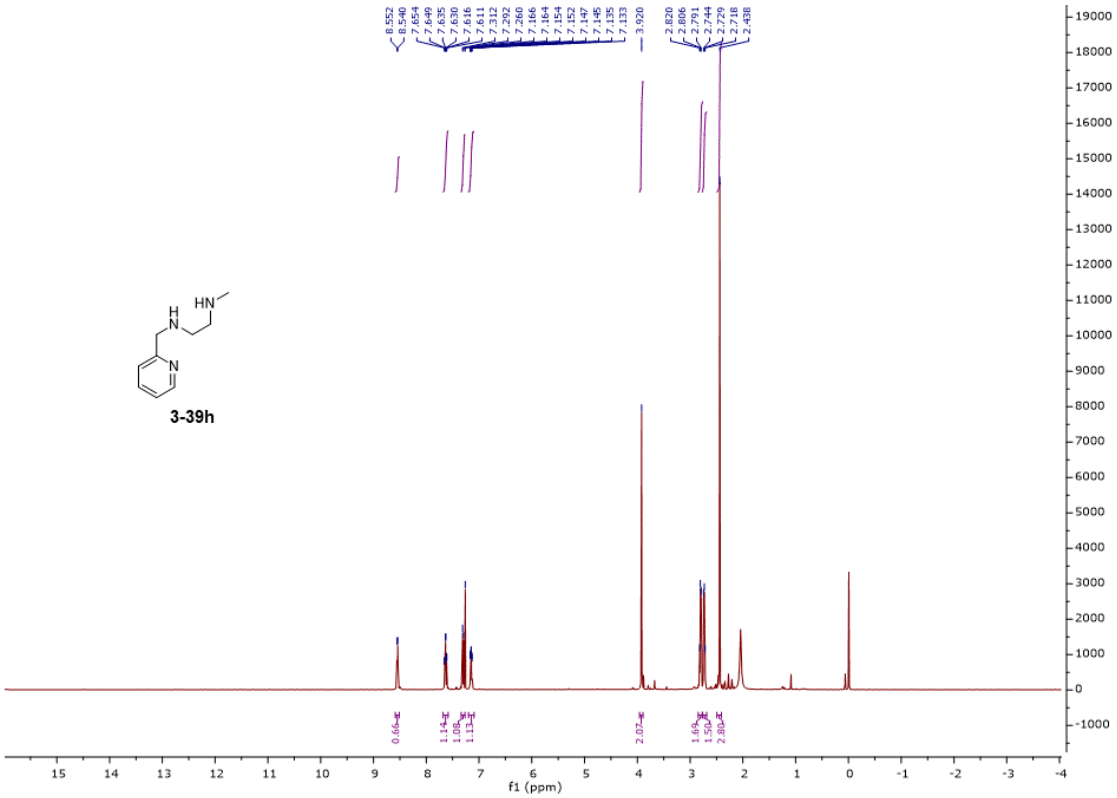

9.11
9.11
8.60
8.60
8.58
8.57
7.84
7.82
7.21
7.20
7.19
7.18
7.08
7.06
3.89
O
N
OMe
O2N
N
Cl
3-38w
1.00
1.04
1.05
2.04
2.05
3.08
f1 (ppm)


161.12
160.79
150.67
149.03
146.33
129.46
129.21
129.16
128.73
124.29
121.19
115.33
55.77
O2N
OMe
O
N
N
Cl
3-38w
f1 (ppm)

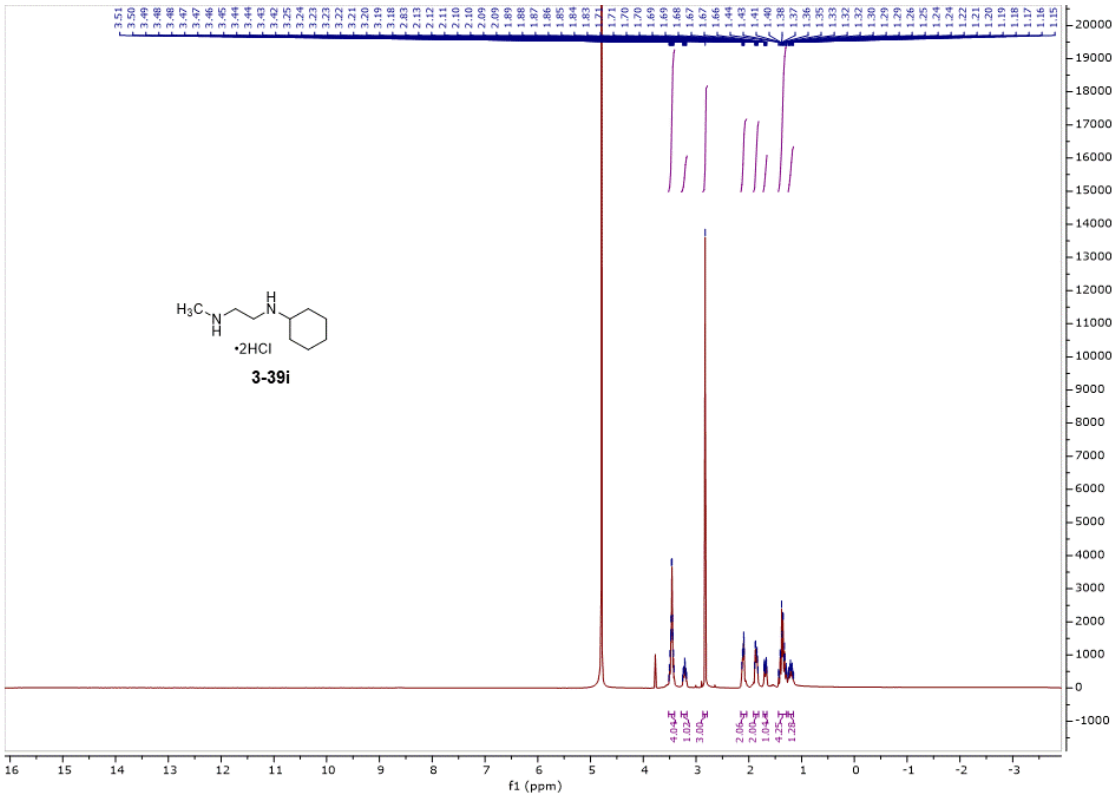

7.54
7.53
4.36
4.35
3.56
3.55
3.54
3.54
3.53
3.52
3.49
3.49
3.48
3.47
3.47
3.46
3.45
2.82
2.82
H
N
N
CH3
H
•2HCl
3-39g
5.01
2.00
4.27
3.08
f1 (ppm)

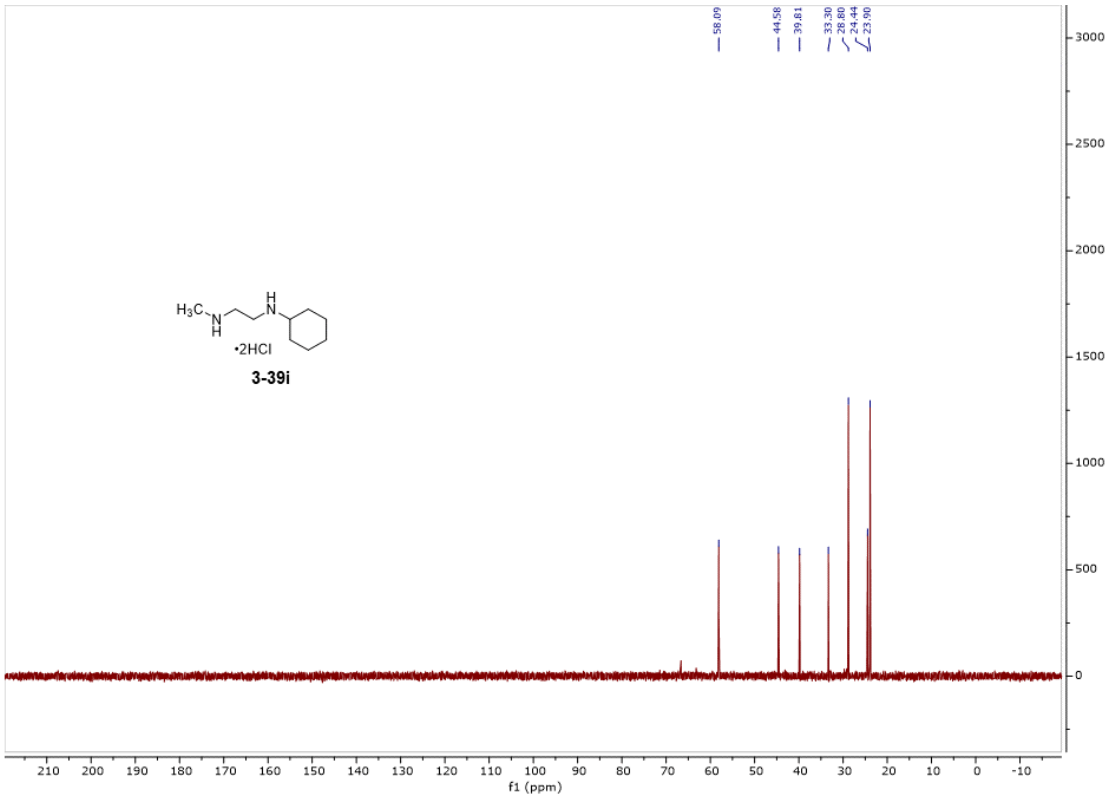

130.11
130.02
129.92
129.45
51.73
44.41
42.44
33.30
•2HCl
f1 (ppm)

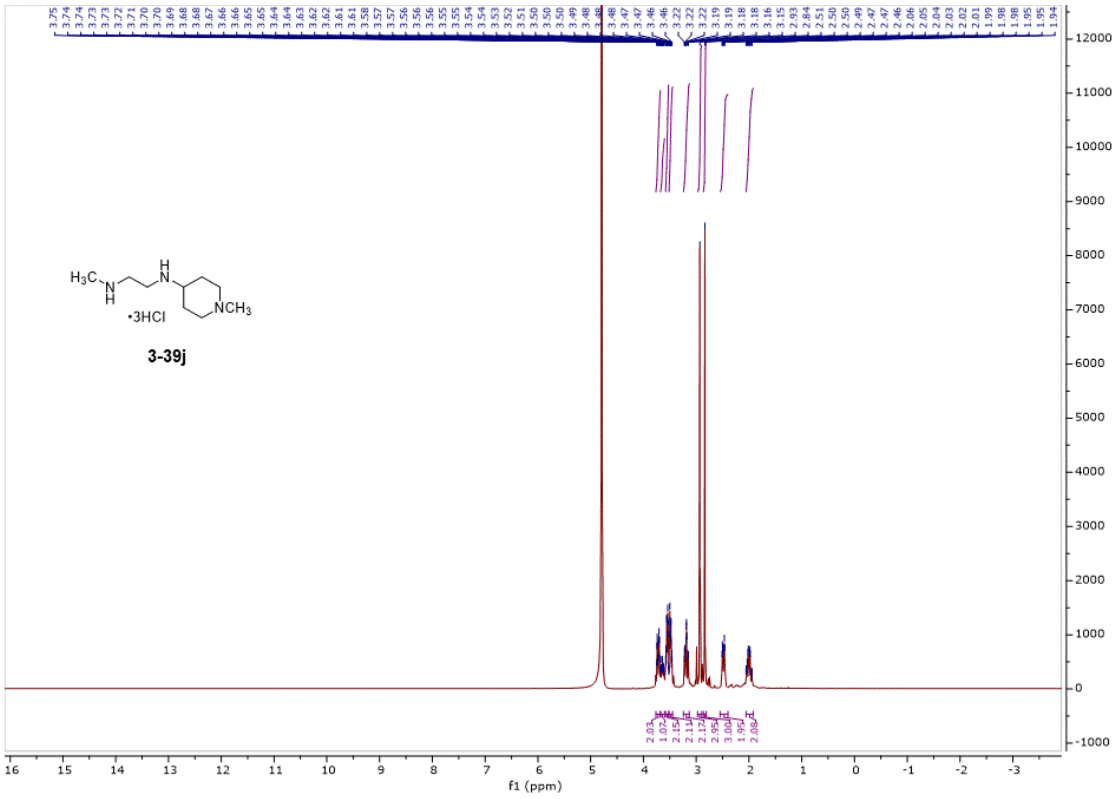
3-39g

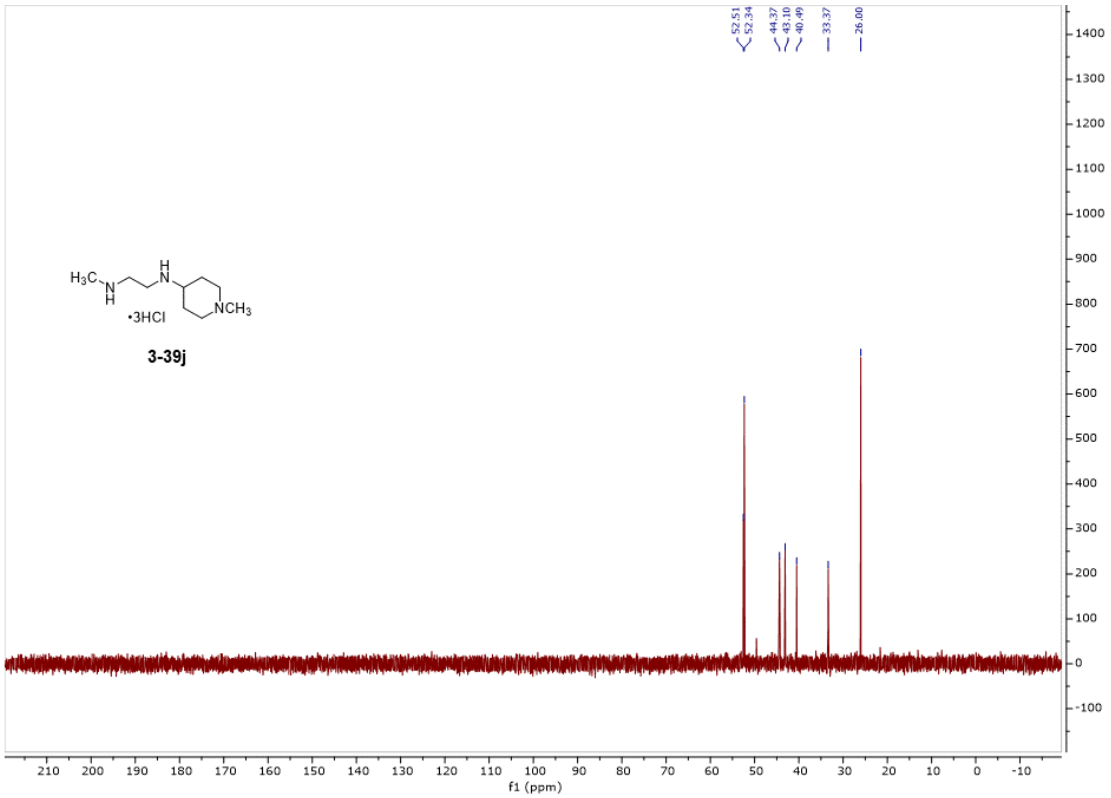

8.552
8.540
7.654
7.649
7.635
7.630
7.616
7.611
7.312
7.292
7.286
7.166
7.164
7.154
7.152
7.147
7.145
7.135
7.133
3.920
2.820
2.806
2.791
2.744
2.729
2.716
2.438
f1 (ppm)

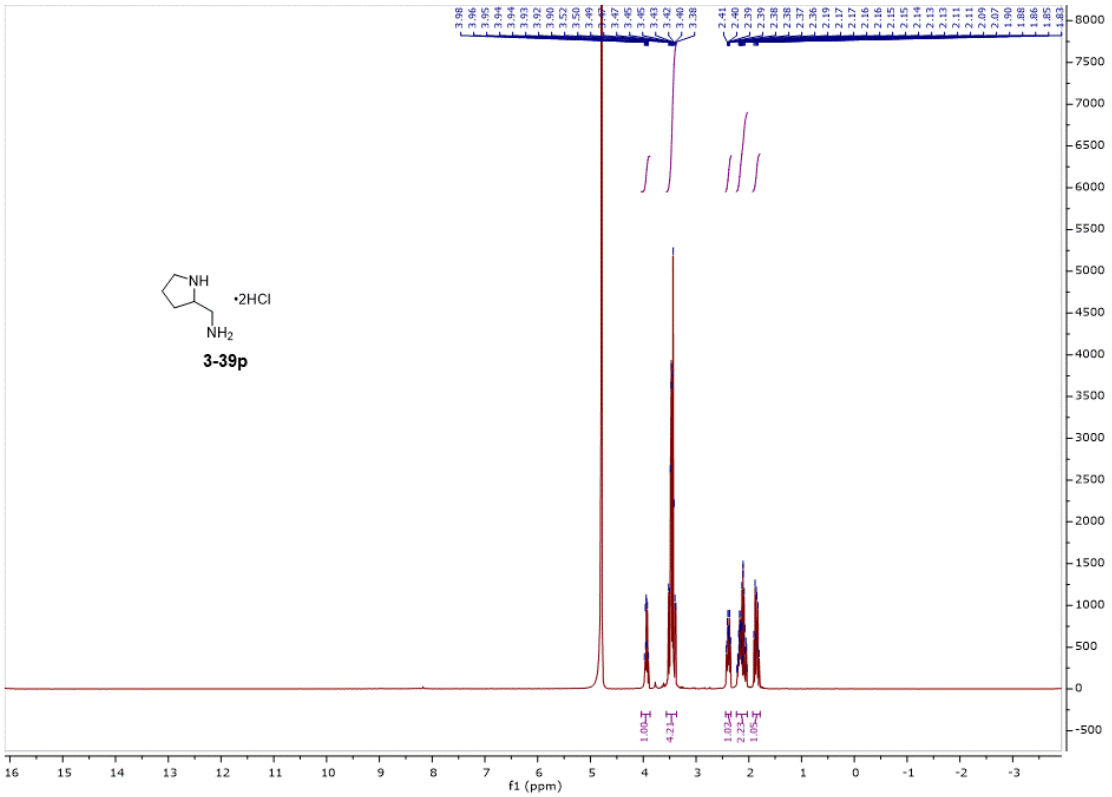
3-39h

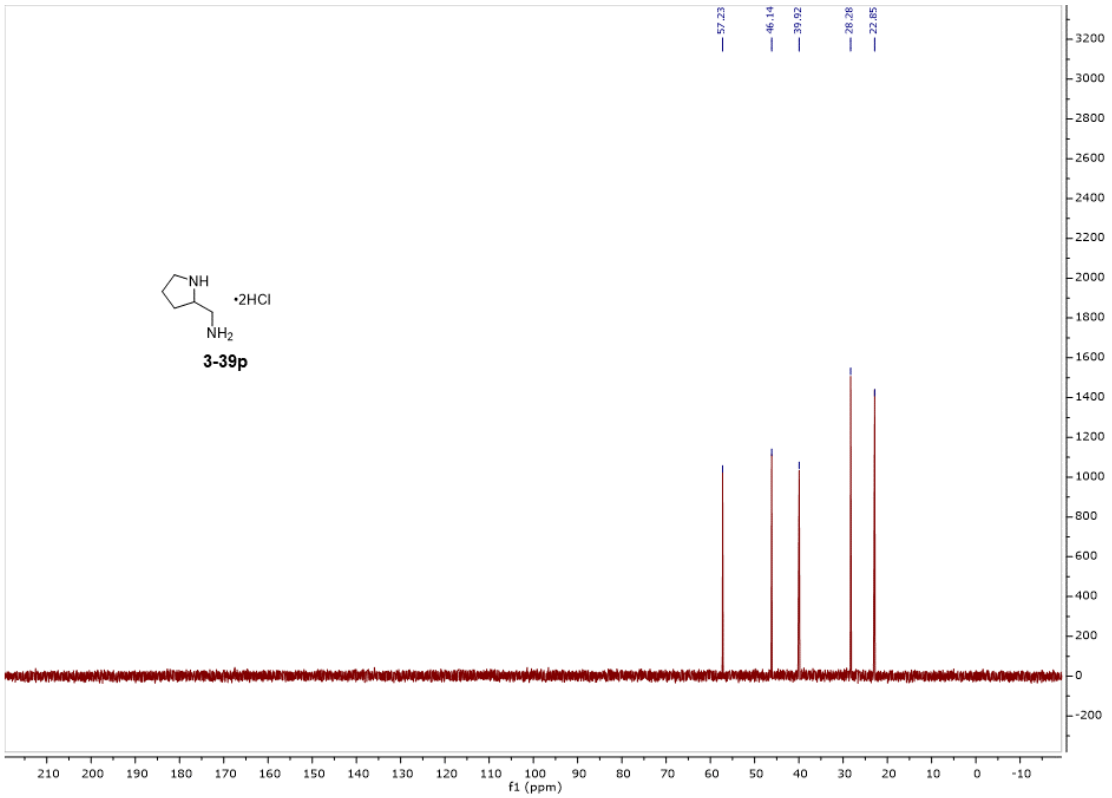

•2HCl
3-39i
f1 (ppm)

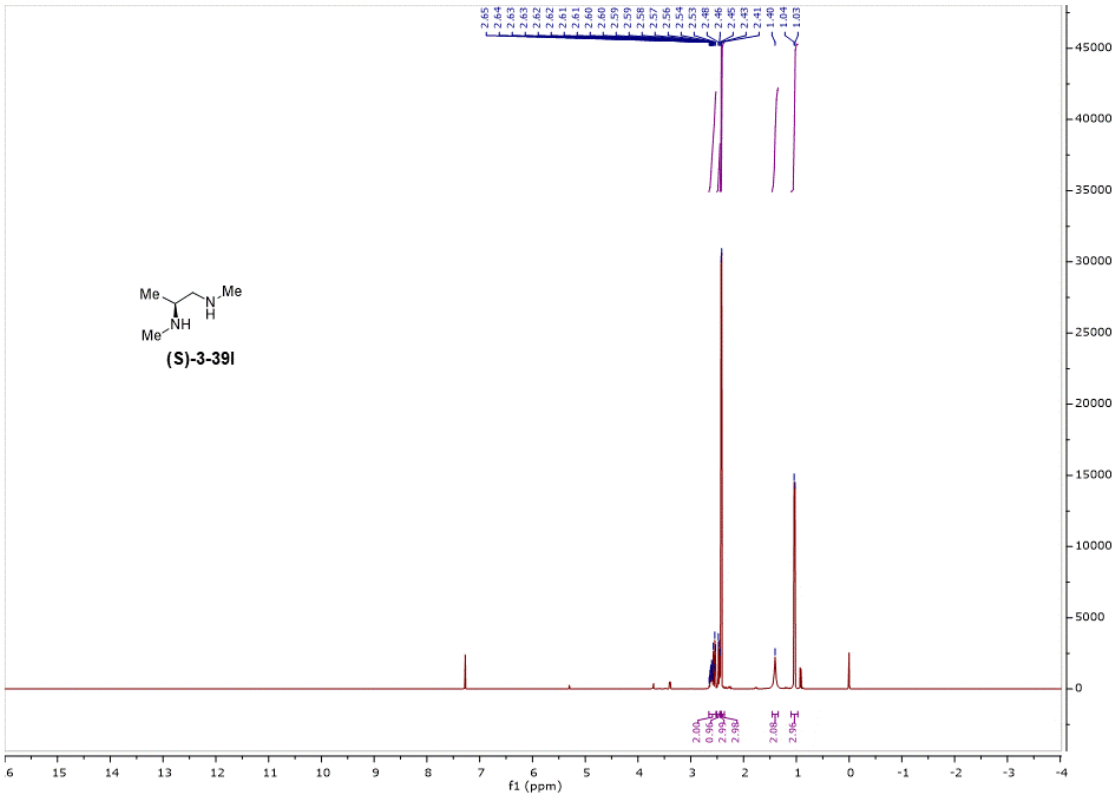

58.09
44.58
39.81
33.30
28.80
24.44
23.90
•2HCl
3-39i
f1 (ppm)

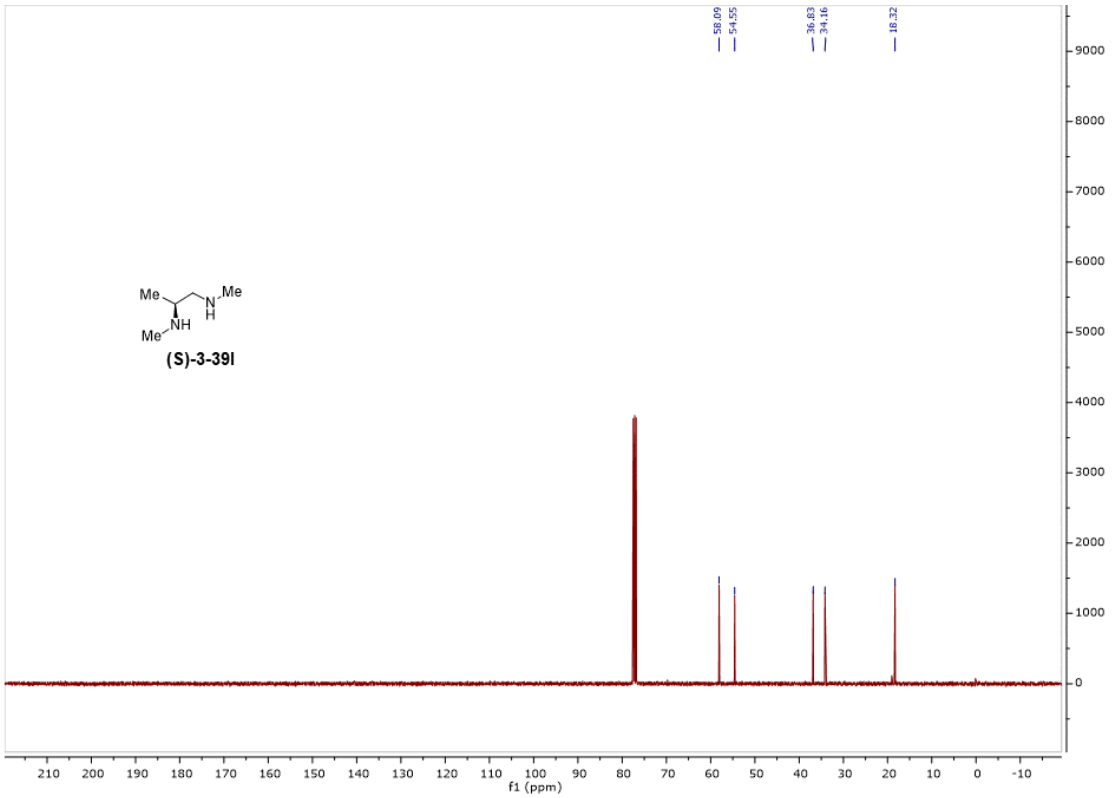

•3HCl
3-39j
f1 (ppm)

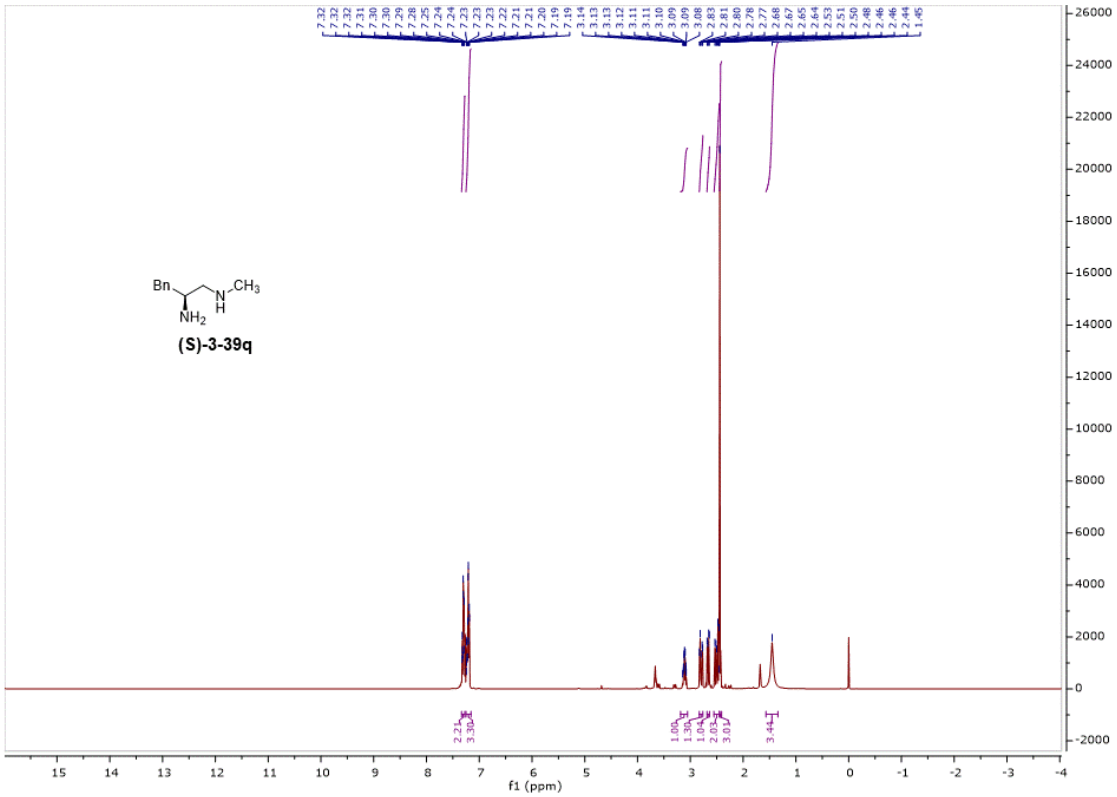

•3HCl
3-39j
f1 (ppm)

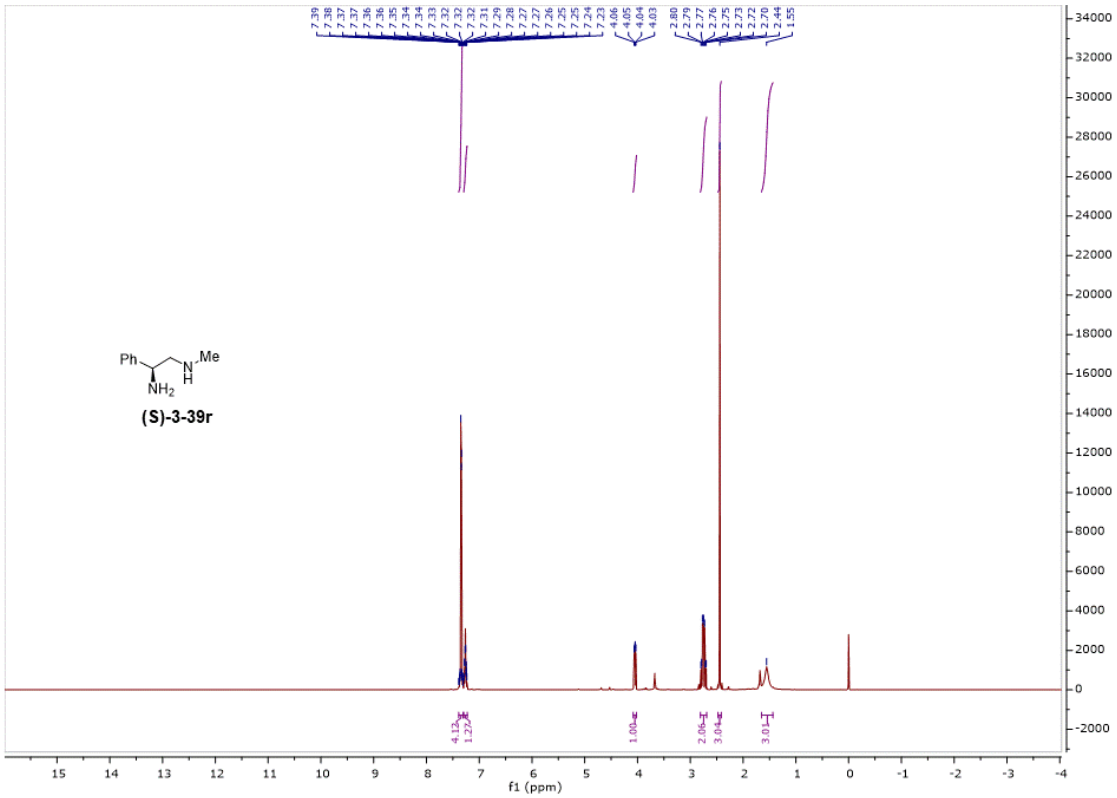

NH
•2HCl
NH2
3-39p
f1 (ppm)

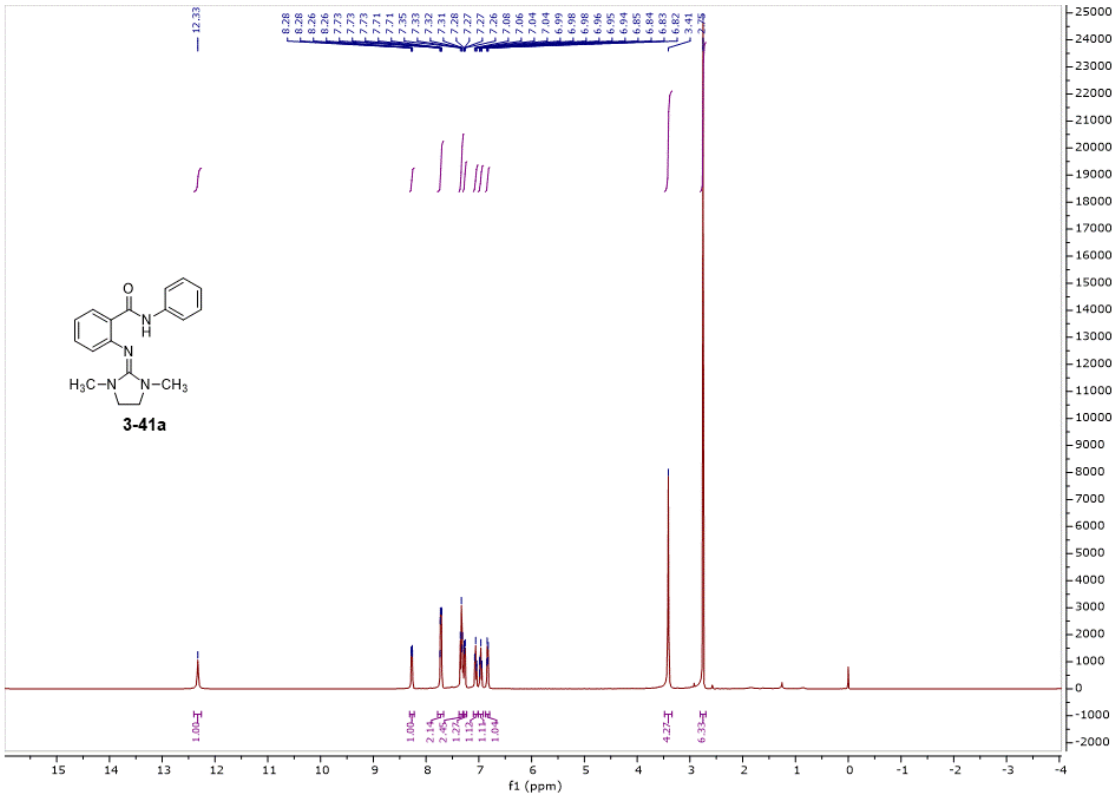

57.23
46.14
39.92
28.28
22.85
NH
•2HCl
NH2
3-39p
f1 (ppm)

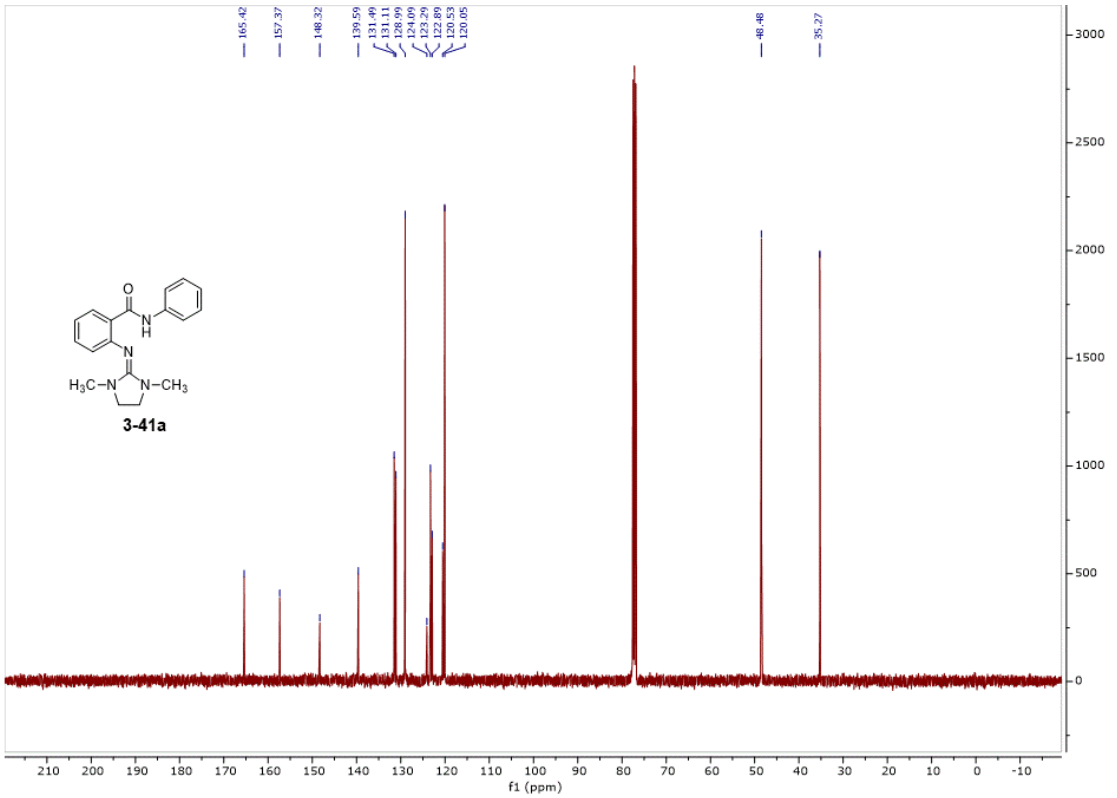

Me
N
H
Me
NH
Me
(S)-3-39l
f1 (ppm)

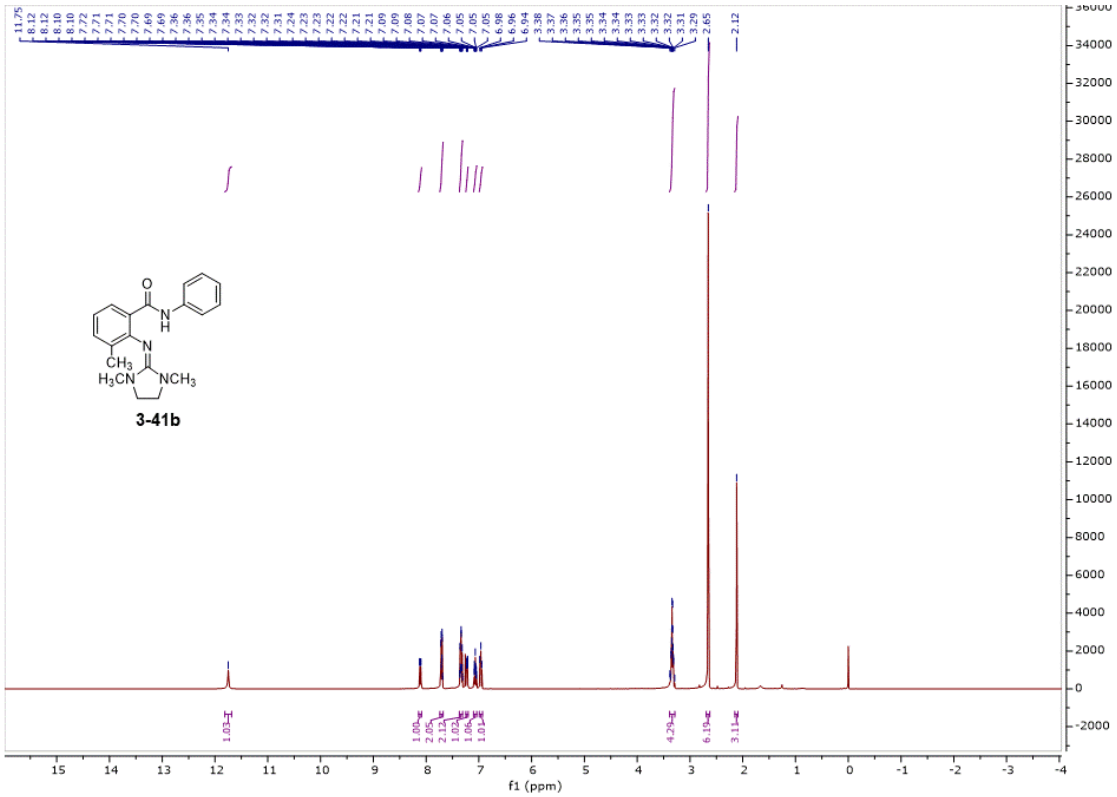

Me
N
H
Me
NH
Me
(S)-3-39l
f1 (ppm)

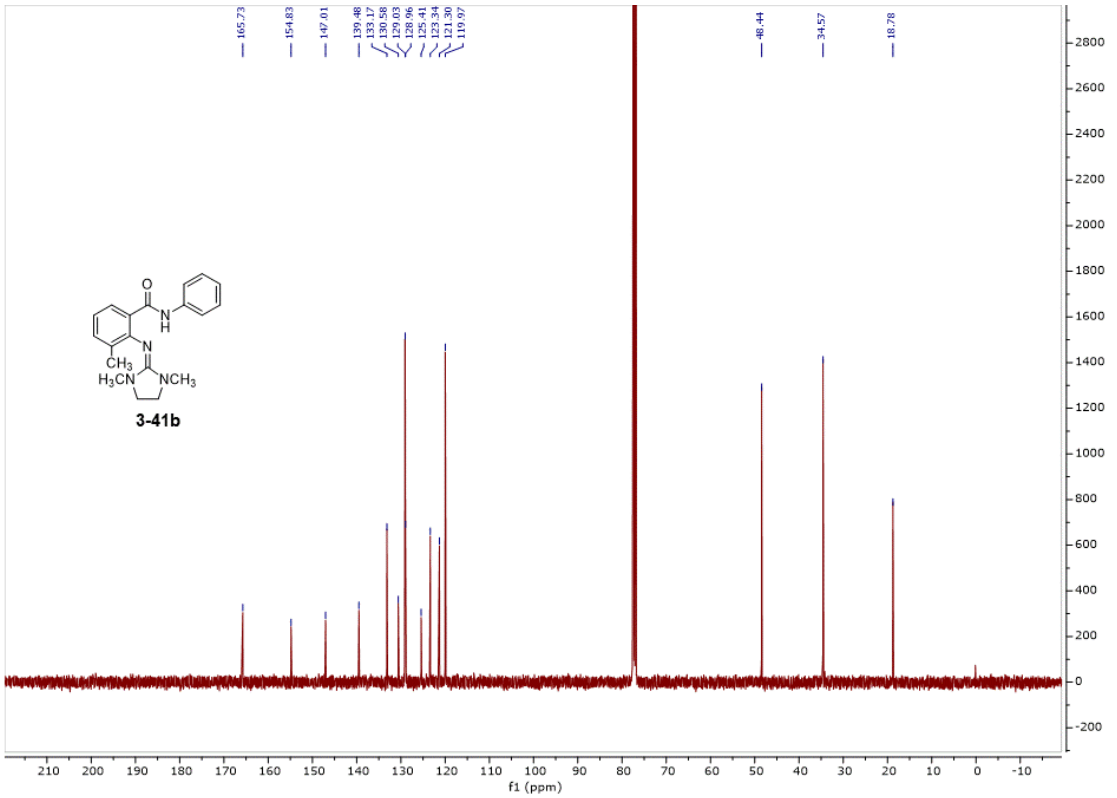

Bn
N
H
CH3
NH2
(S)-3-39q
f1 (ppm)

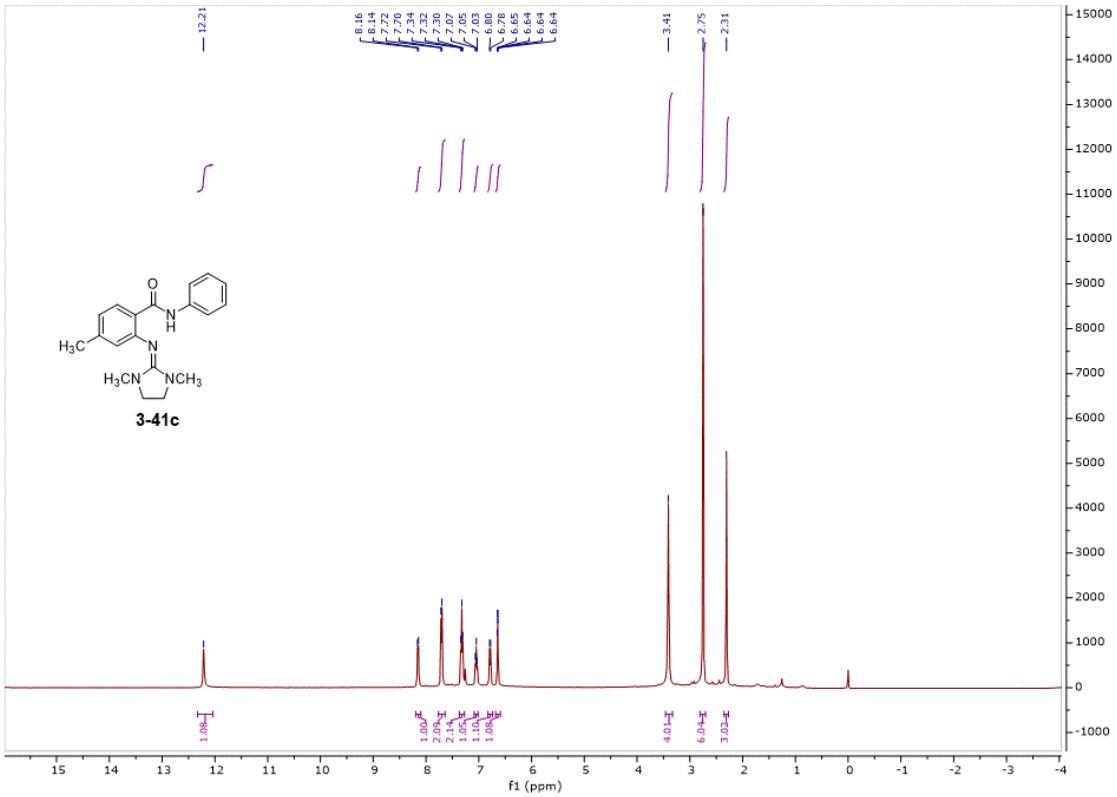

Ph
N
H
Me
NH2
(S)-3-39r
f1 (ppm)

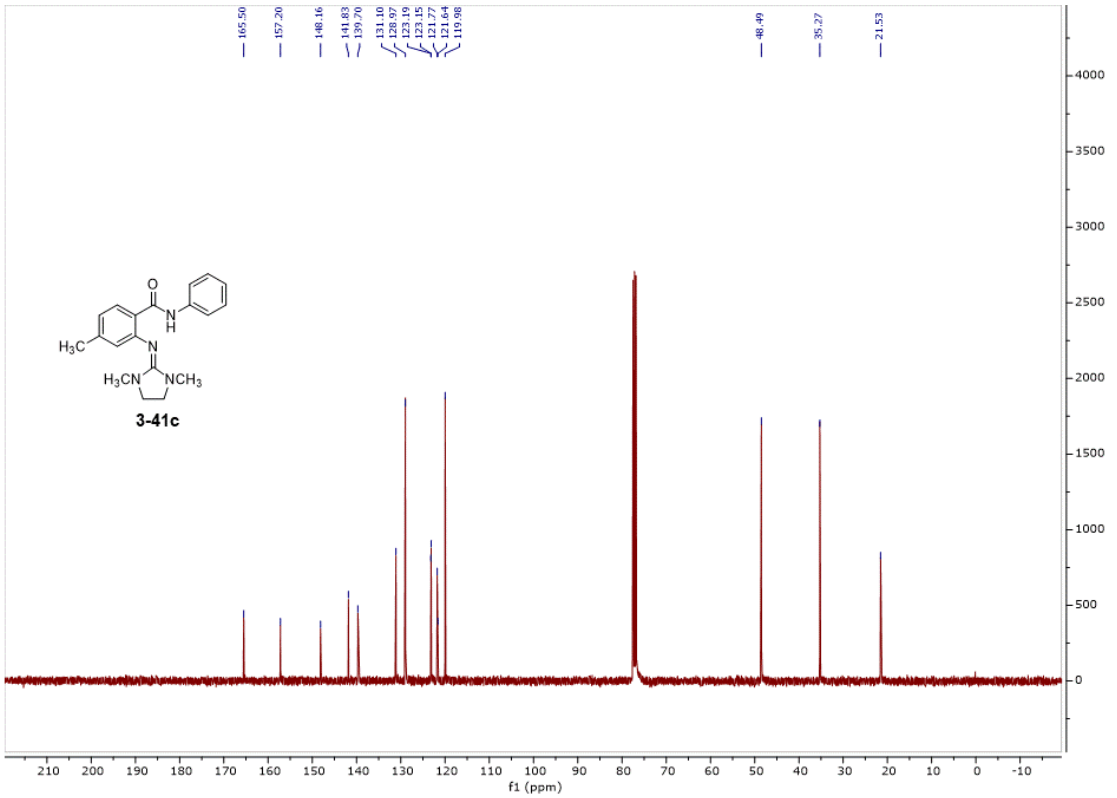

12.33
8.28
8.28
8.26
8.26
7.73
7.73
7.71
7.71
7.35
7.33
7.32
7.31
7.28
7.27
7.27
7.26
7.08
7.06
7.04
7.04
6.99
6.98
6.98
6.96
6.95
6.84
6.85
6.84
6.83
6.82
3.41
2.25
1.00
1.00
2.14
2.45
1.23
1.13
1.13
1.04
4.27
6.33
f1 (ppm)
3-41a

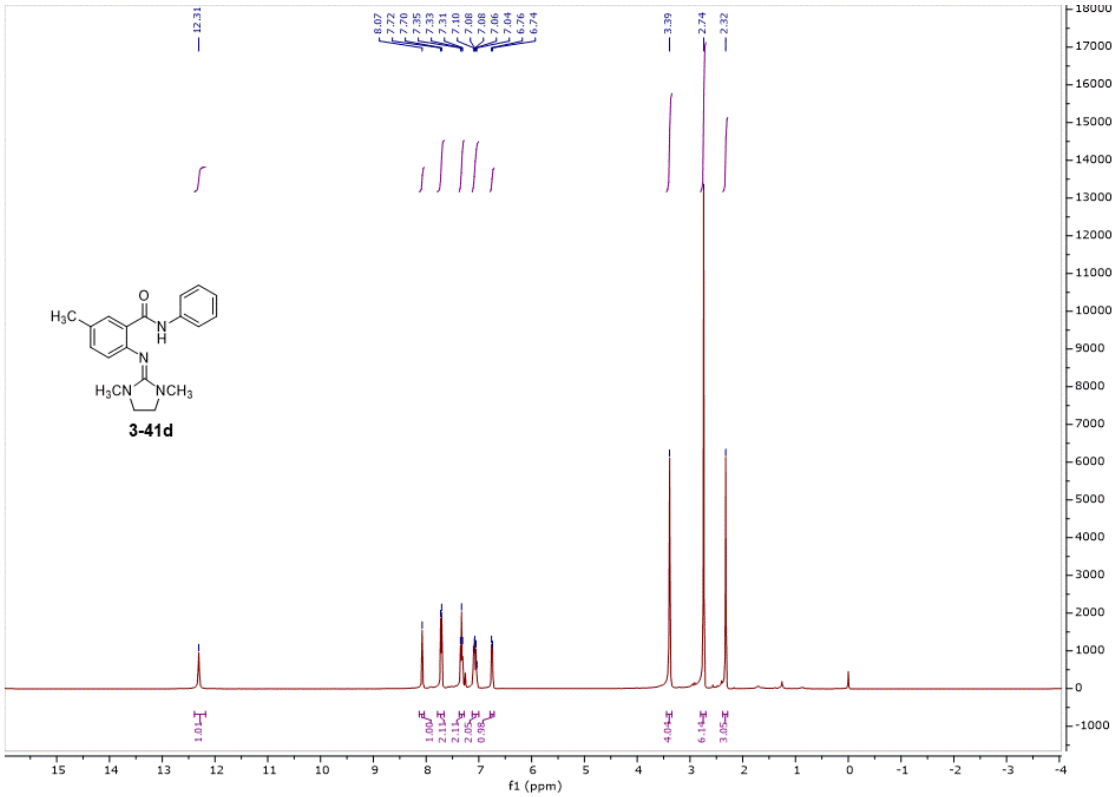

165.42
157.37
148.32
139.59
131.49
131.11
128.99
124.09
123.29
122.89
120.53
120.05
48.48
35.27
f1 (ppm)
3-41a

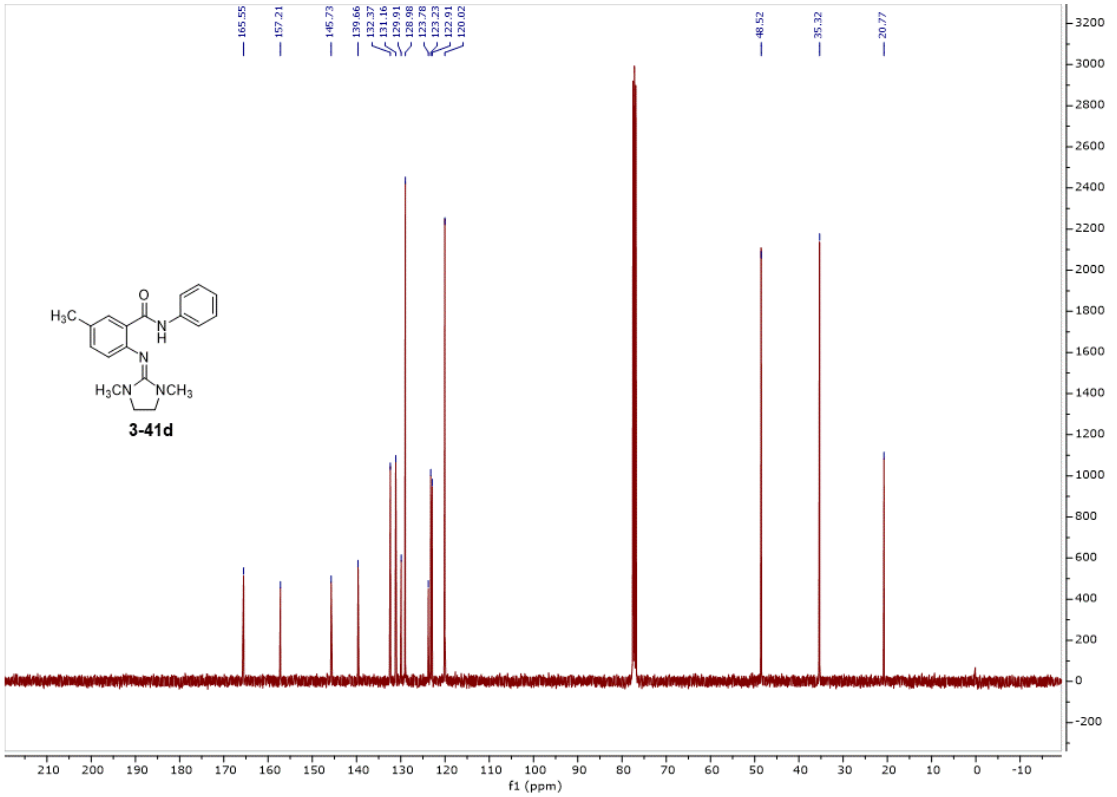

11.75
8.12
8.12
8.10
8.10
7.72
7.71
7.71
7.70
7.70
7.69
7.69
7.36
7.36
7.35
7.34
7.34
7.33
7.32
7.32
7.31
7.24
7.23
7.23
7.22
7.22
7.21
7.21
7.09
7.09
7.08
7.07
7.07
7.06
7.05
7.05
7.05
6.98
6.96
6.94
3.38
3.37
3.36
3.35
3.35
3.34
3.34
3.33
3.33
3.32
3.32
3.31
3.30
2.65
2.12
O
N
H
N
CH3
H3CN
NCH3
3-41b
1.03
1.06
2.05
2.13
2.02
1.06
1.01
4.29
6.19
3.11
f1 (ppm)

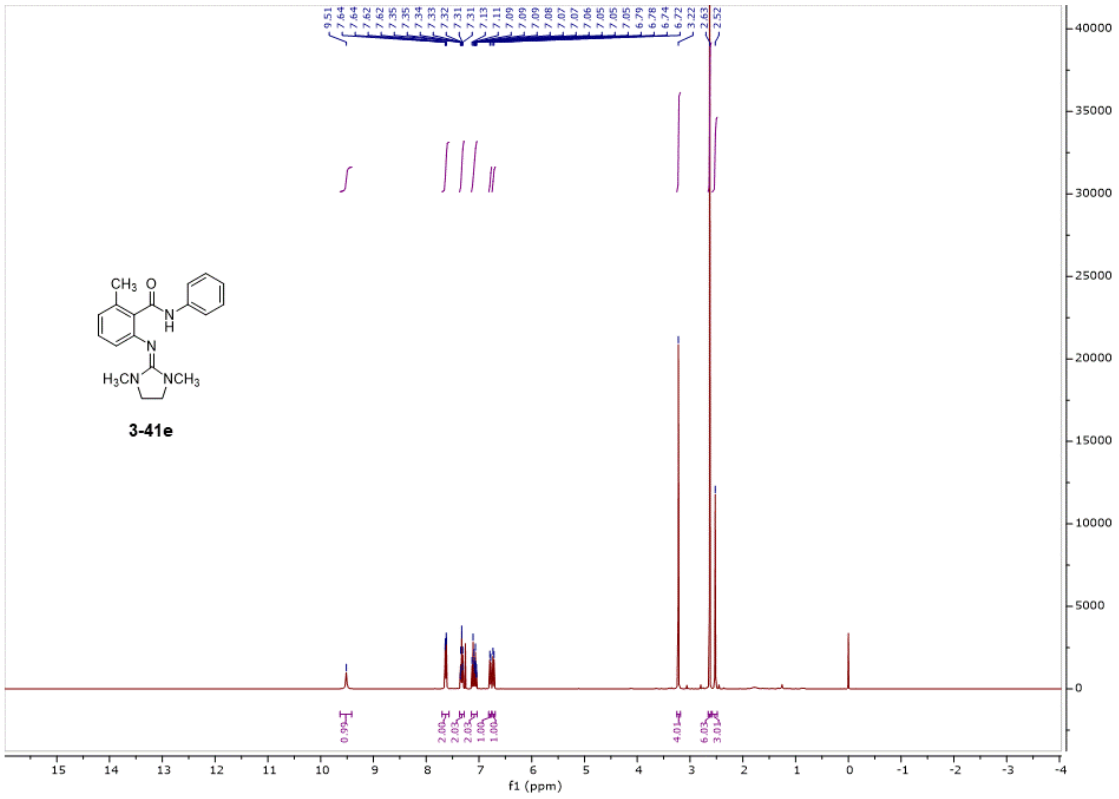

165.73
154.83
147.01
139.48
133.17
130.58
129.03
128.96
125.41
123.34
121.30
119.97
48.44
34.57
18.78
O
N
H
N
CH3
H3CN
NCH3
3-41b
f1 (ppm)


12.21
8.16
8.14
7.72
7.70
7.34
7.32
7.30
7.07
7.05
7.03
6.80
6.78
6.65
6.64
6.64
6.64
3.41
2.75
2.31
1.08
1.00
2.04
2.14
1.05
1.10
1.08
4.01
6.04
3.02
f1 (ppm)
3-41c


165.50
157.20
148.16
141.83
139.70
131.10
128.97
123.19
123.15
121.77
121.64
119.98
48.49
35.27
21.53
f1 (ppm)
3-41c

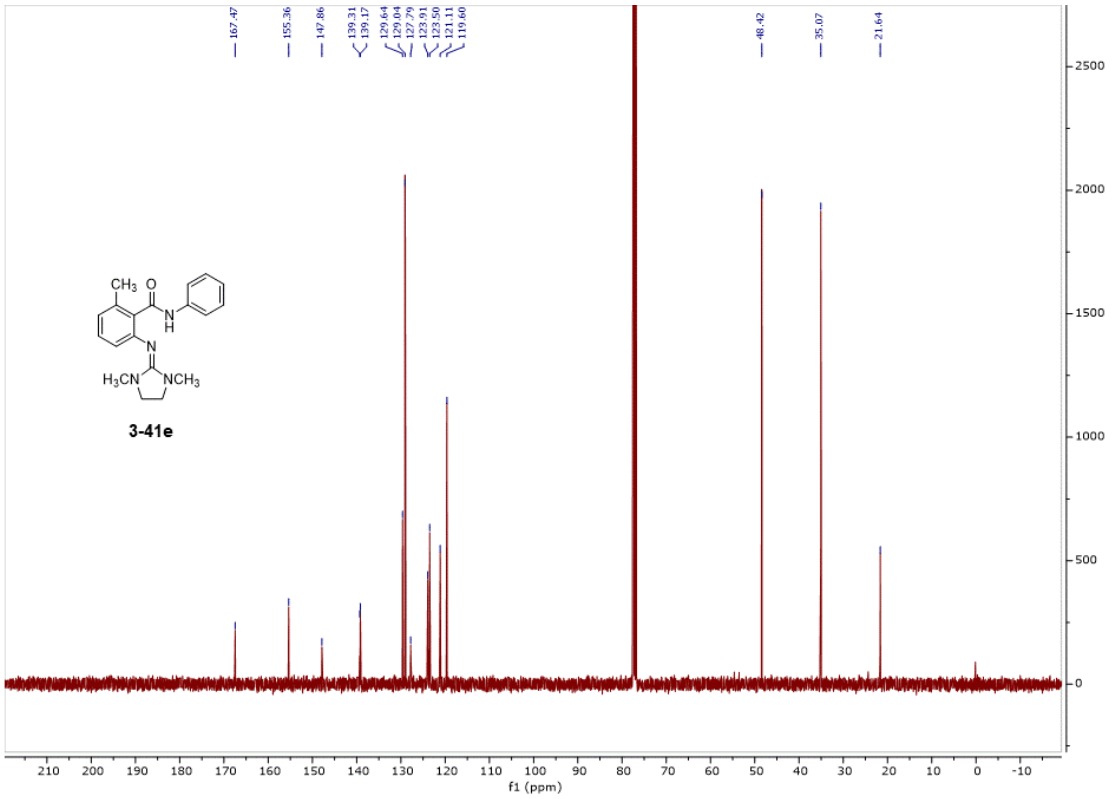

12.31
8.07
7.72
7.70
7.35
7.33
7.31
7.10
7.08
7.08
7.06
7.04
6.76
6.74
3.39
2.74
2.32
1.01
1.00
2.11
2.05
2.05
0.98
4.04
6.14
3.05
f1 (ppm)
3-41d


165.55
157.21
145.73
139.66
132.37
131.16
129.91
128.98
123.78
123.23
122.91
120.02
48.52
35.32
20.77
f1 (ppm)
3-41d


9.51
7.64
7.62
7.35
7.34
7.33
7.32
7.31
7.13
7.11
7.09
7.08
7.07
7.06
7.05
6.79
6.78
6.74
6.72
3.22
2.63
2.52
0.99
2.00
2.03
2.03
1.00
1.00
4.01
6.03
3.01
f1 (ppm)

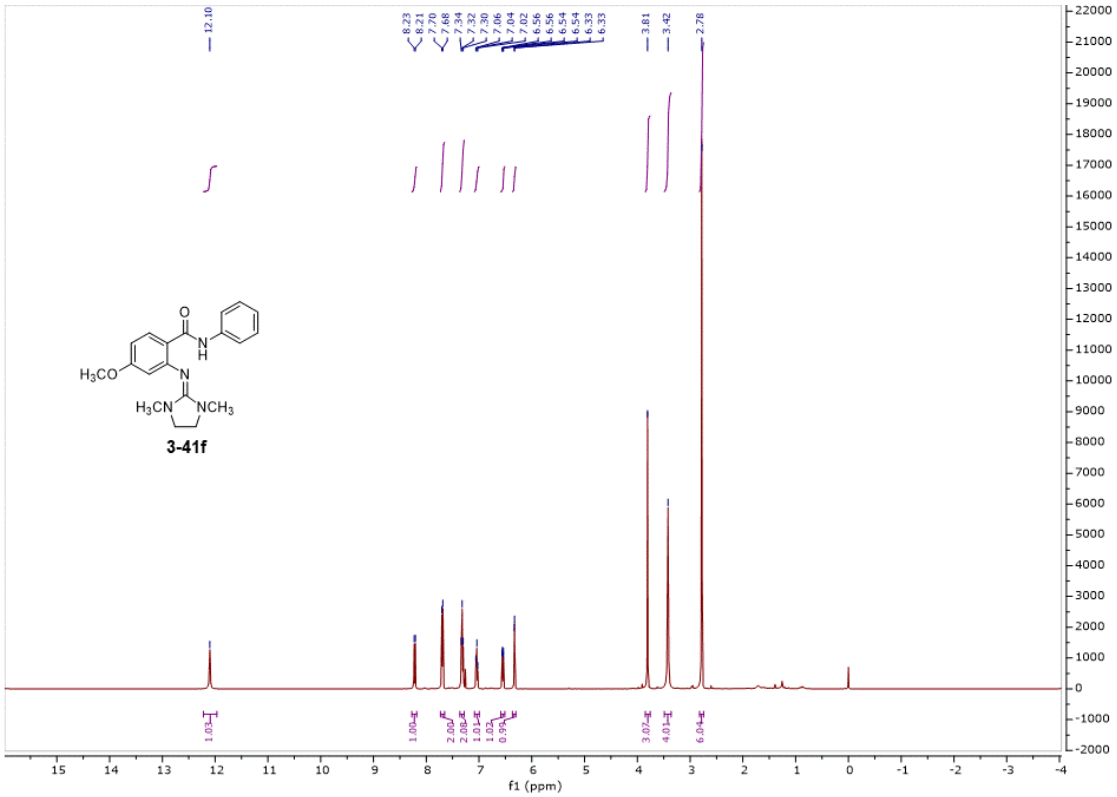

CH3
O
N
H
N
H3CN
NCH3

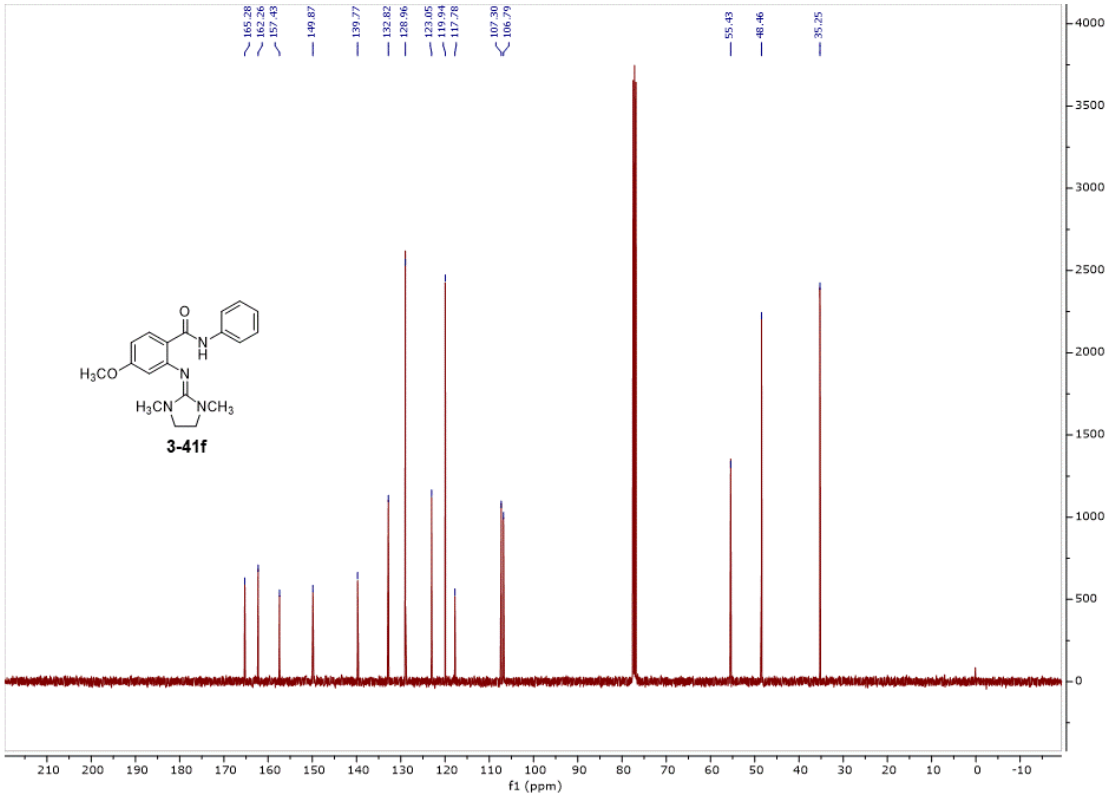
**3-41e**

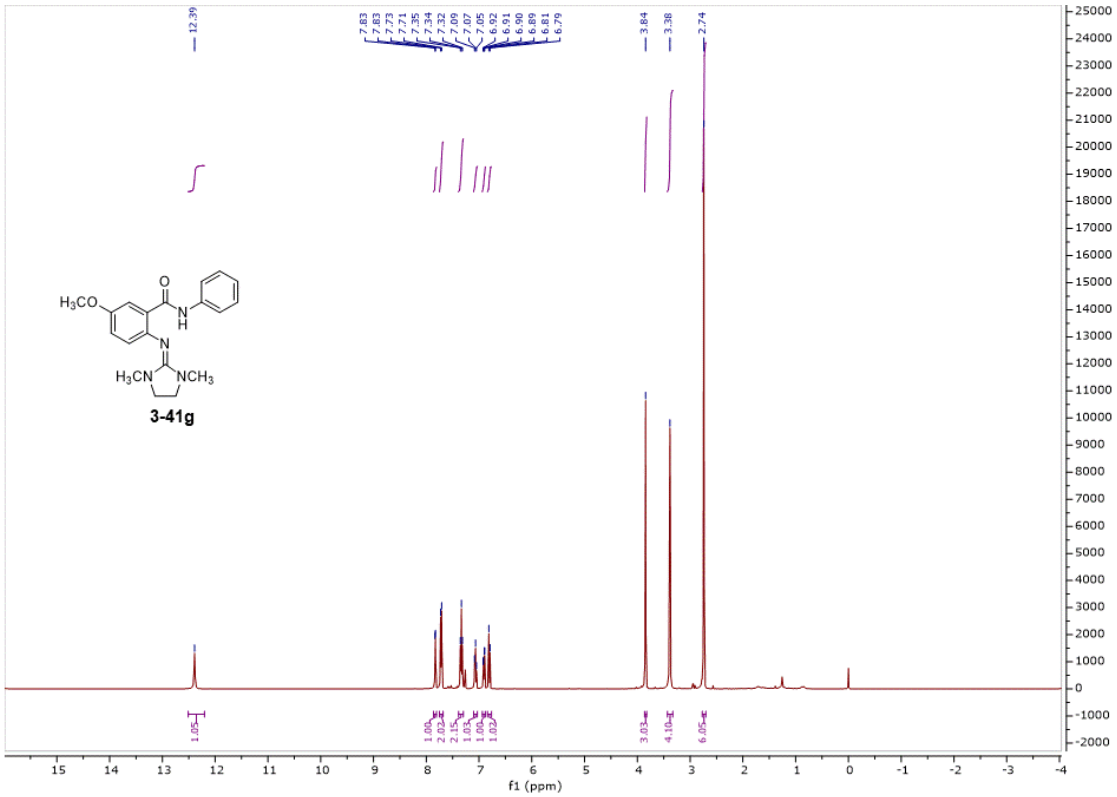

167.47
155.36
147.86
139.31
139.17
129.64
129.04
127.79
123.91
123.50
121.11
119.60
48.42
35.07
21.64
f1 (ppm)

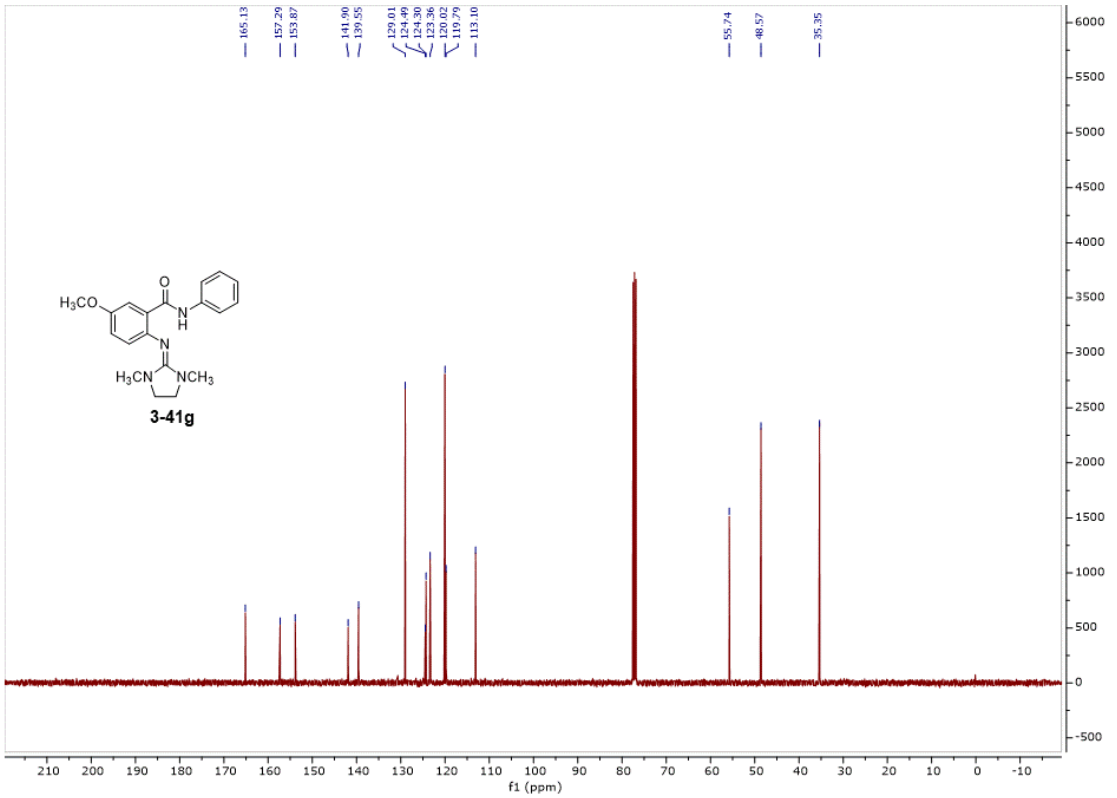

CH3
O
N
H
N
H3CN
NCH3

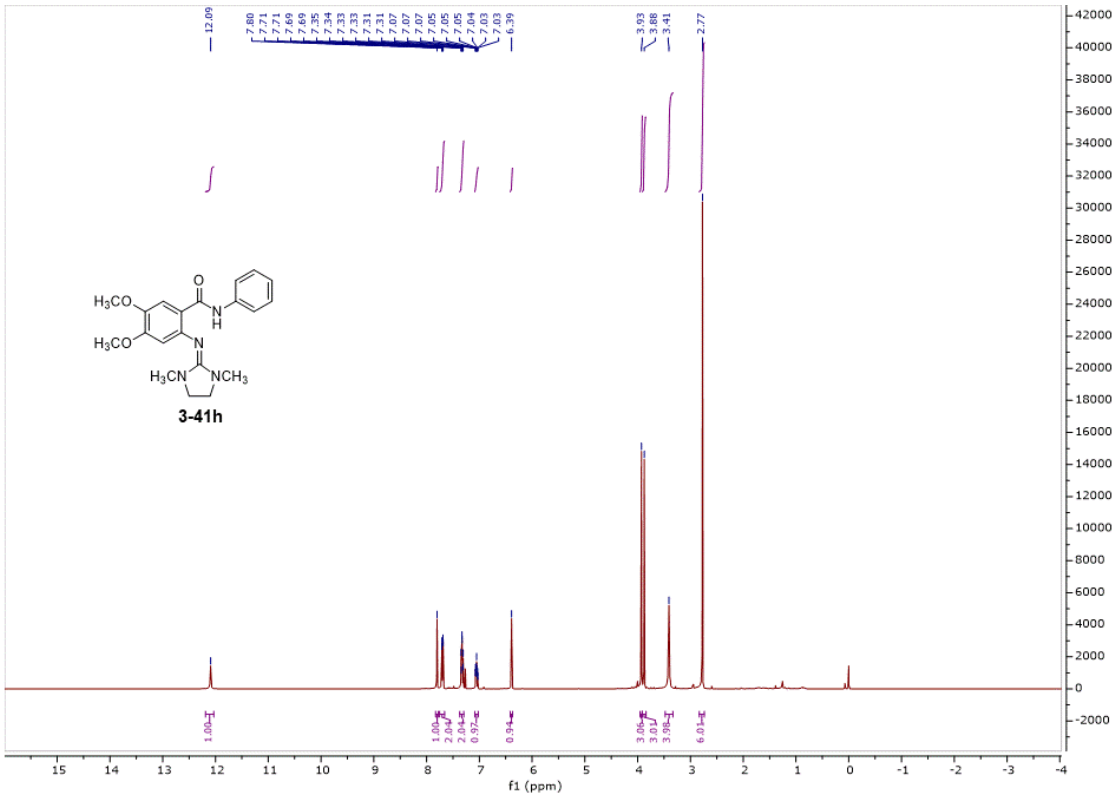
**3-41e**

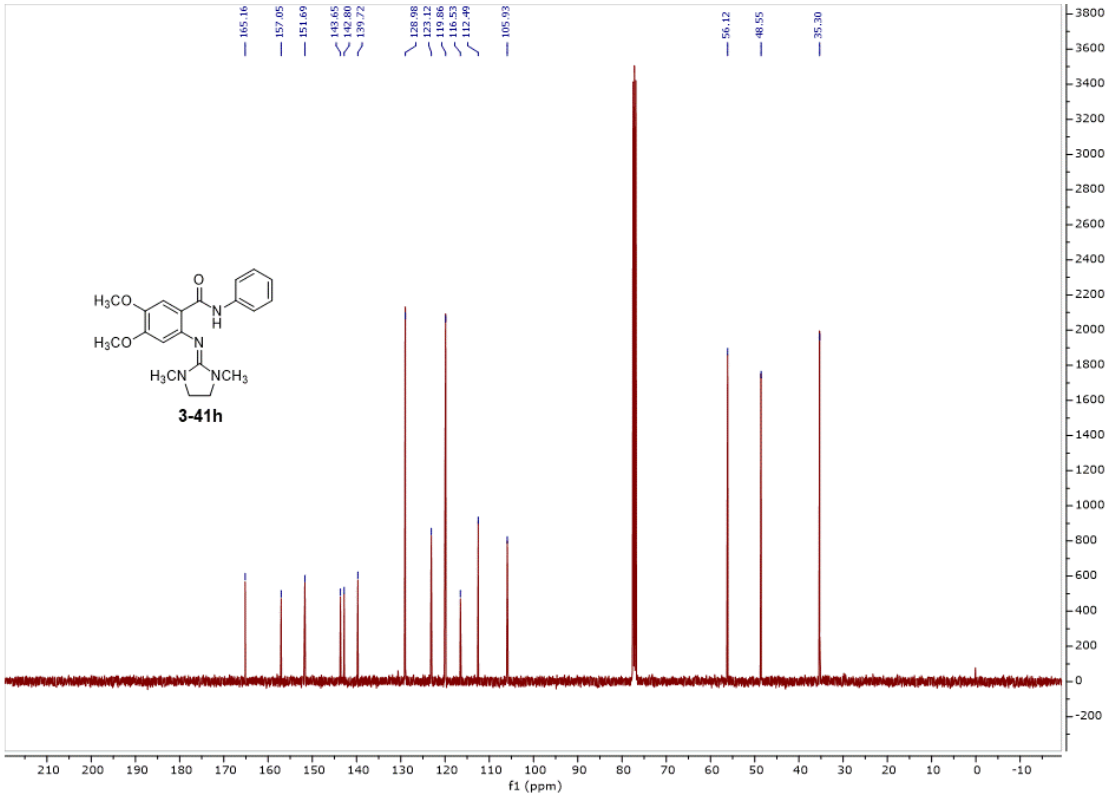

12.10
8.23
8.21
7.70
7.68
7.34
7.32
7.30
7.06
7.04
7.02
6.56
6.54
6.54
6.33
6.33
3.81
3.42
2.78
1.03
1.00
2.00
2.08
1.01
1.02
0.99
3.07
4.01
6.04
f1 (ppm)
3-41f

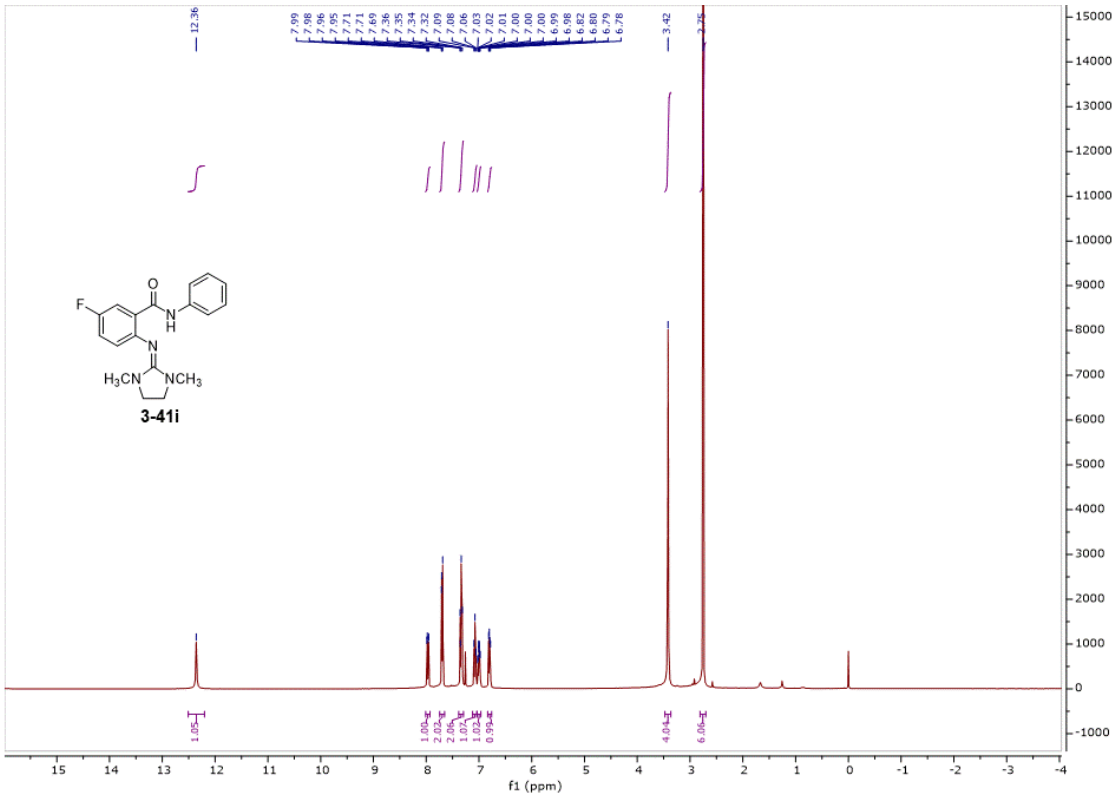

165.28
162.26
157.43
149.87
139.77
132.82
128.96
123.05
119.94
117.78
107.30
106.79
55.43
48.46
35.25
f1 (ppm)
3-41f

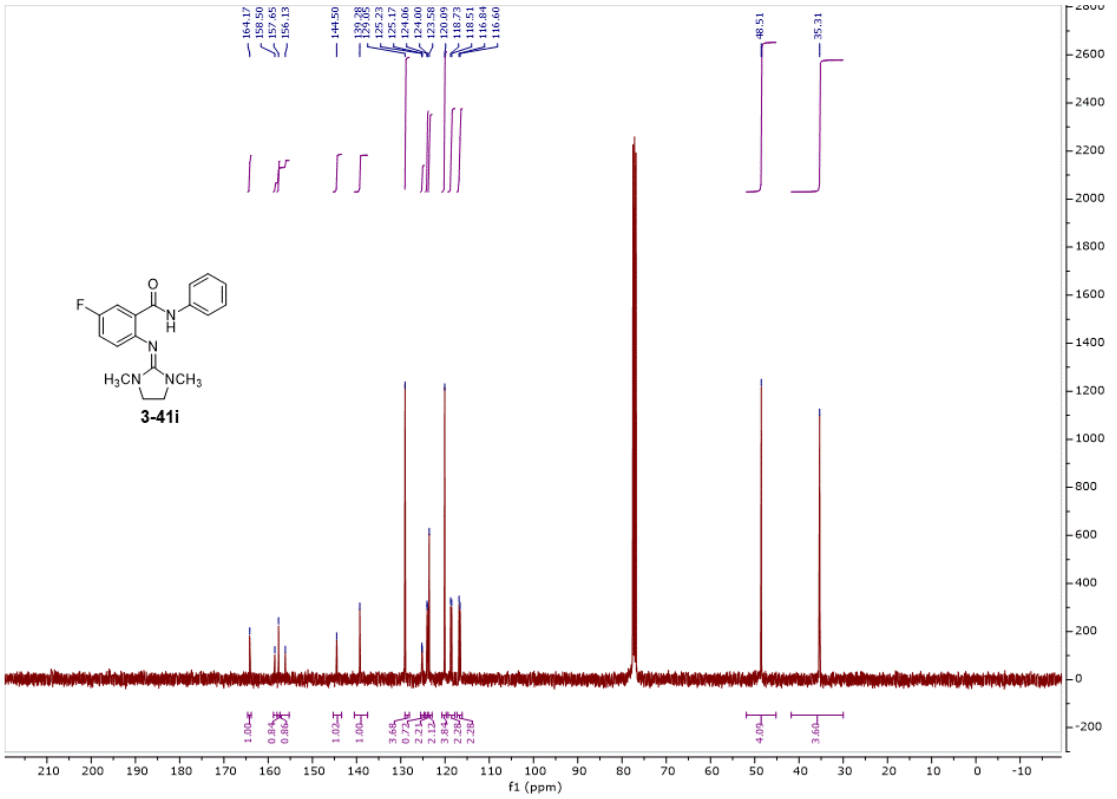

12.39
7.83
7.83
7.73
7.71
7.35
7.34
7.22
7.09
7.07
7.05
6.92
6.91
6.90
6.89
6.81
6.79
3.84
3.38
2.74
H3CO
O
N
H
N
H3CN
NCH3
3-41g
1.05
1.00
2.02
2.15
1.03
1.05
1.02
3.03
4.10
6.05
f1 (ppm)

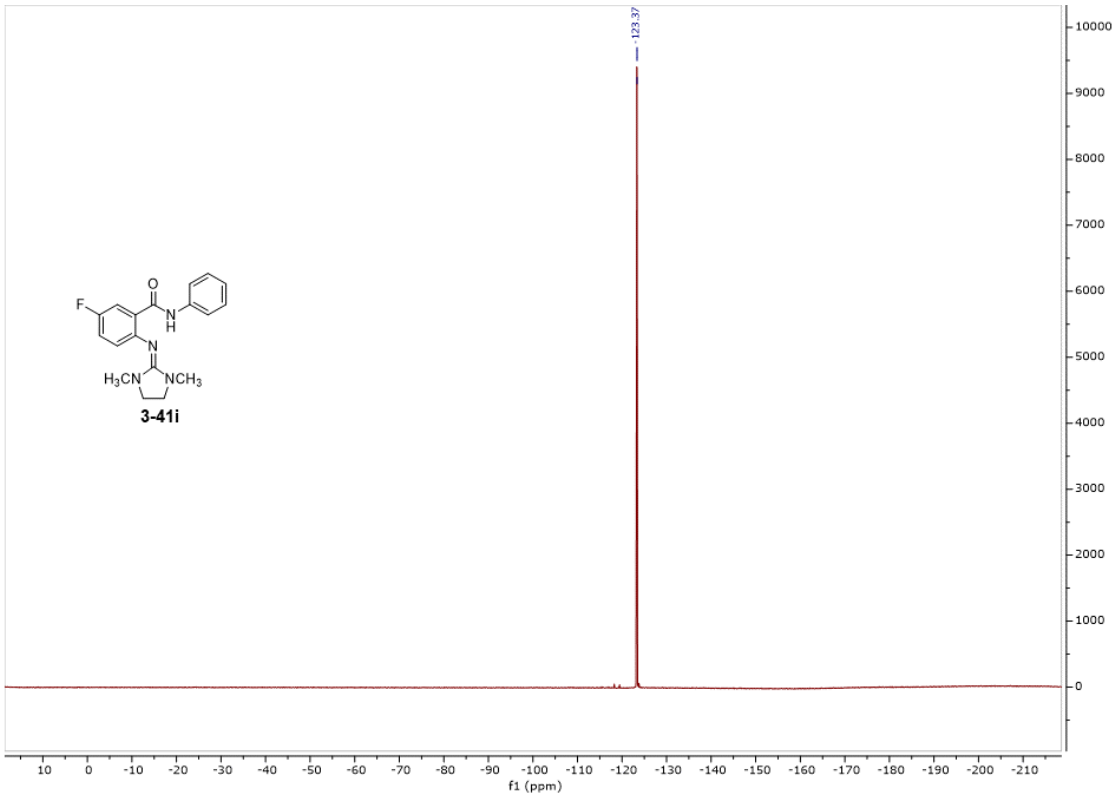

165.13
157.29
153.87
141.90
139.55
129.01
124.49
124.30
123.36
120.02
119.79
113.10
55.74
48.57
35.35
H3CO
O
N
H
N
H3CN
NCH3
3-41g
f1 (ppm)

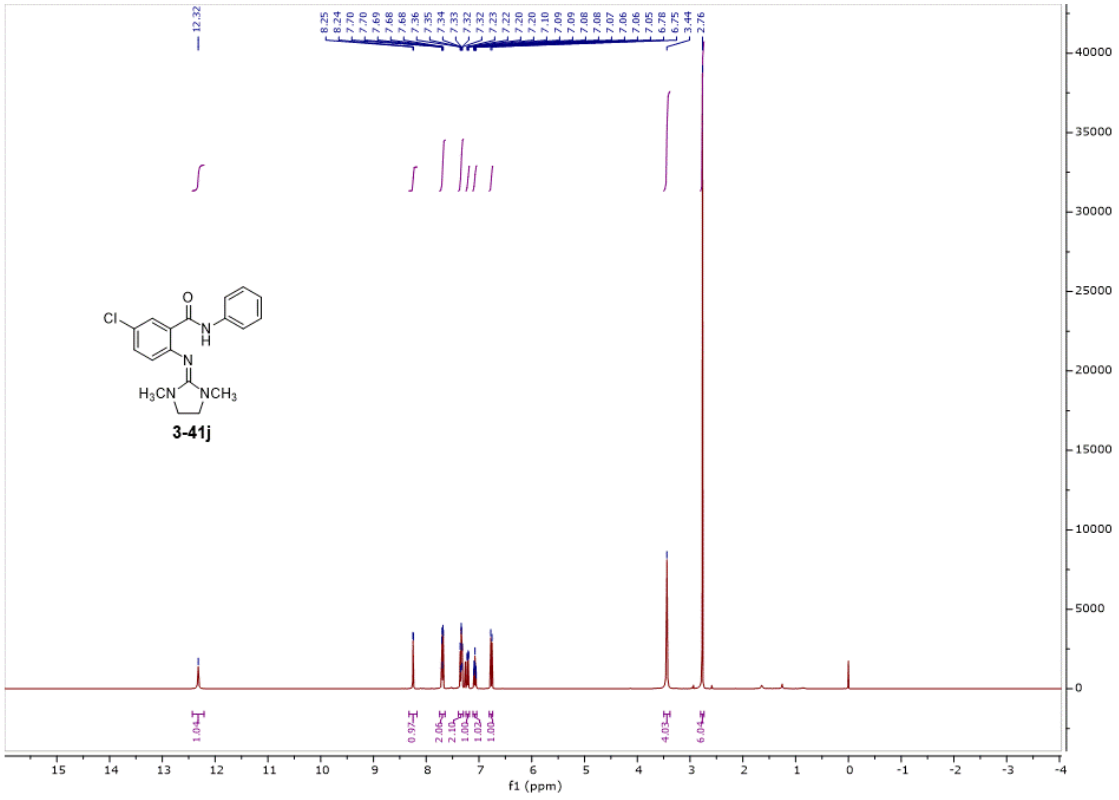

12.09
7.80
7.71
7.71
7.69
7.66
7.35
7.34
7.33
7.33
7.31
7.31
7.07
7.07
7.07
7.05
7.05
7.05
7.04
7.03
7.03
6.39
3.93
3.88
3.41
2.77
1.00
1.00
2.04
2.04
0.92
0.94
3.06
3.01
3.98
6.01
f1 (ppm)
3-41h

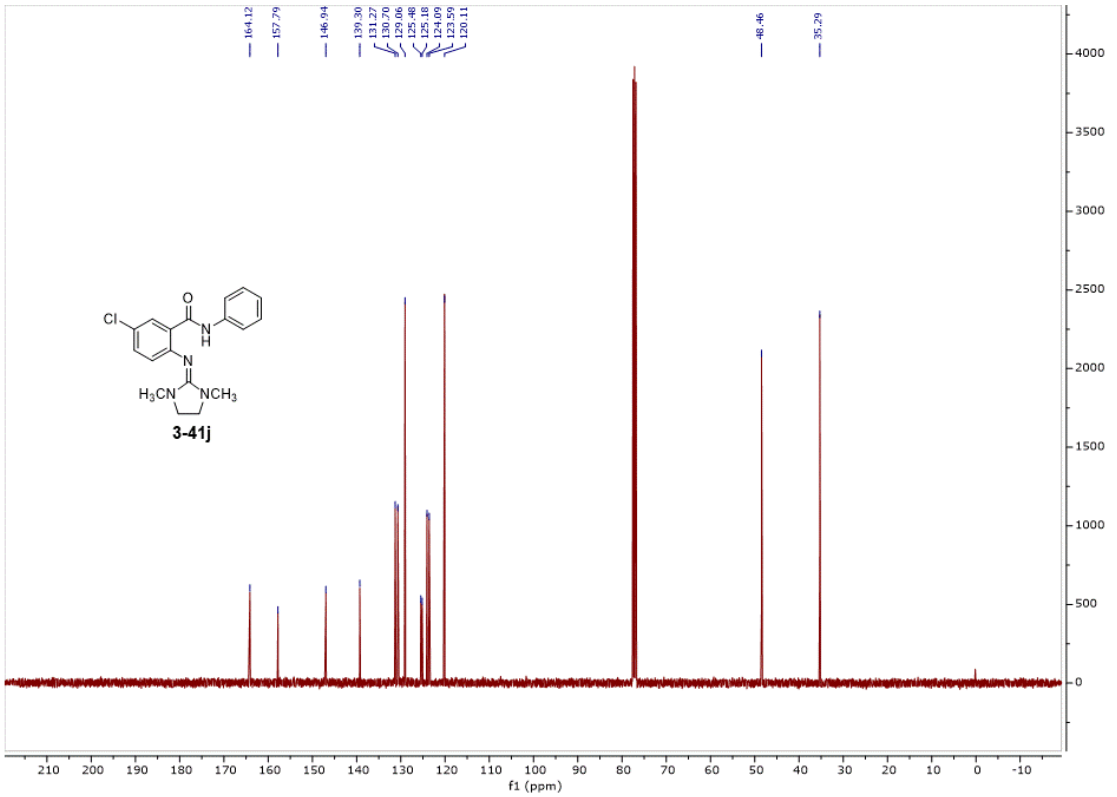

165.16
157.05
151.69
143.65
142.80
139.72
128.98
123.12
119.86
116.53
112.49
105.93
56.12
48.55
35.30
f1 (ppm)
3-41h

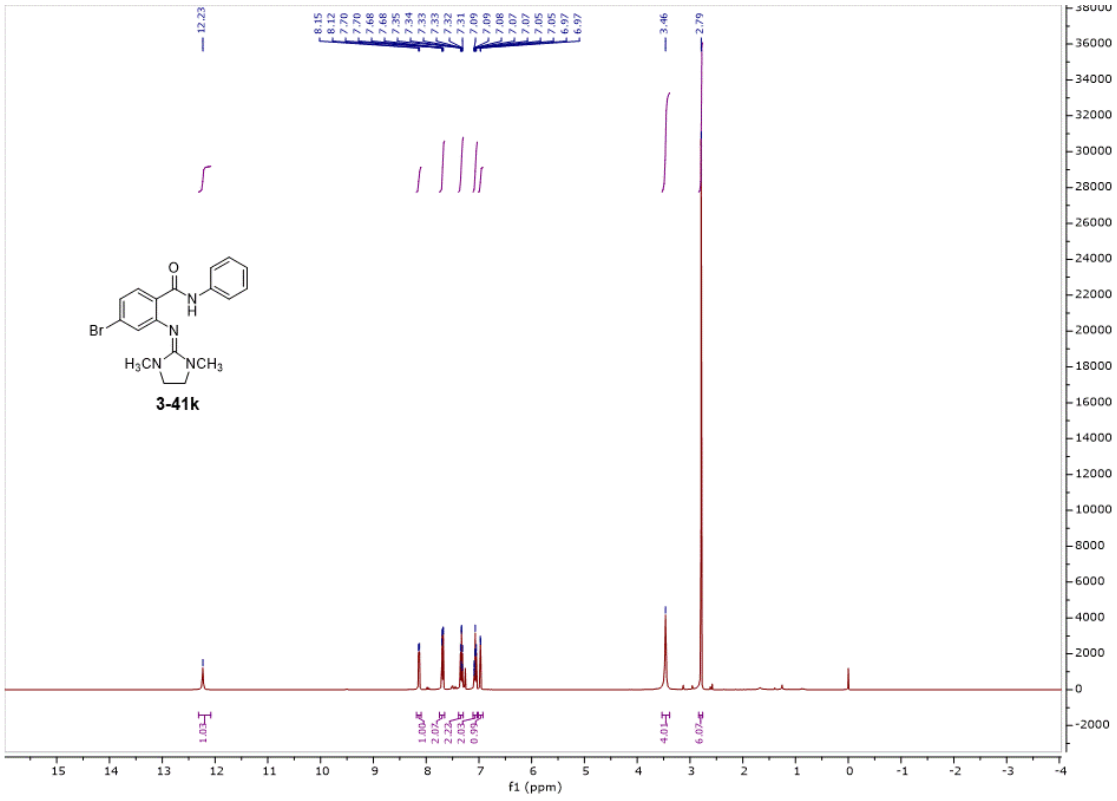

12.36
7.99
7.98
7.96
7.95
7.71
7.71
7.69
7.36
7.35
7.34
7.32
7.09
7.08
7.06
7.03
7.02
7.01
7.00
7.00
7.00
6.99
6.98
6.82
6.80
6.79
6.78
3.42
2.75
F
O
N
H
N
H3CN
NCH3
3-41i
1.05
1.00
2.02
2.04
1.07
1.02
0.99
4.04
6.06
f1 (ppm)

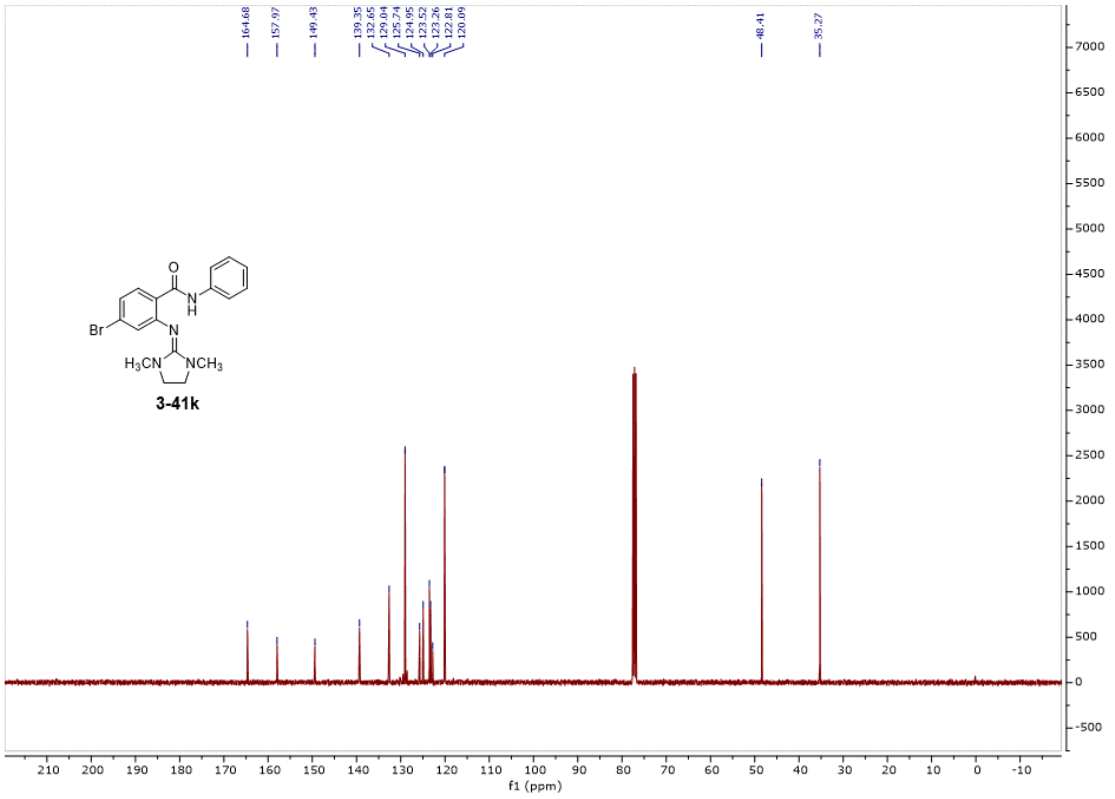

164.17
158.50
157.65
156.13
144.50
130.28
129.85
125.23
125.17
124.06
124.00
123.58
120.09
118.73
118.51
116.84
116.60
48.51
35.31
F
O
N
H
N
H3CN
NCH3
3-41i
1.00
0.84
0.86
1.02
1.00
3.68
0.72
2.21
2.12
3.84
2.28
2.28
4.09
3.60
f1 (ppm)

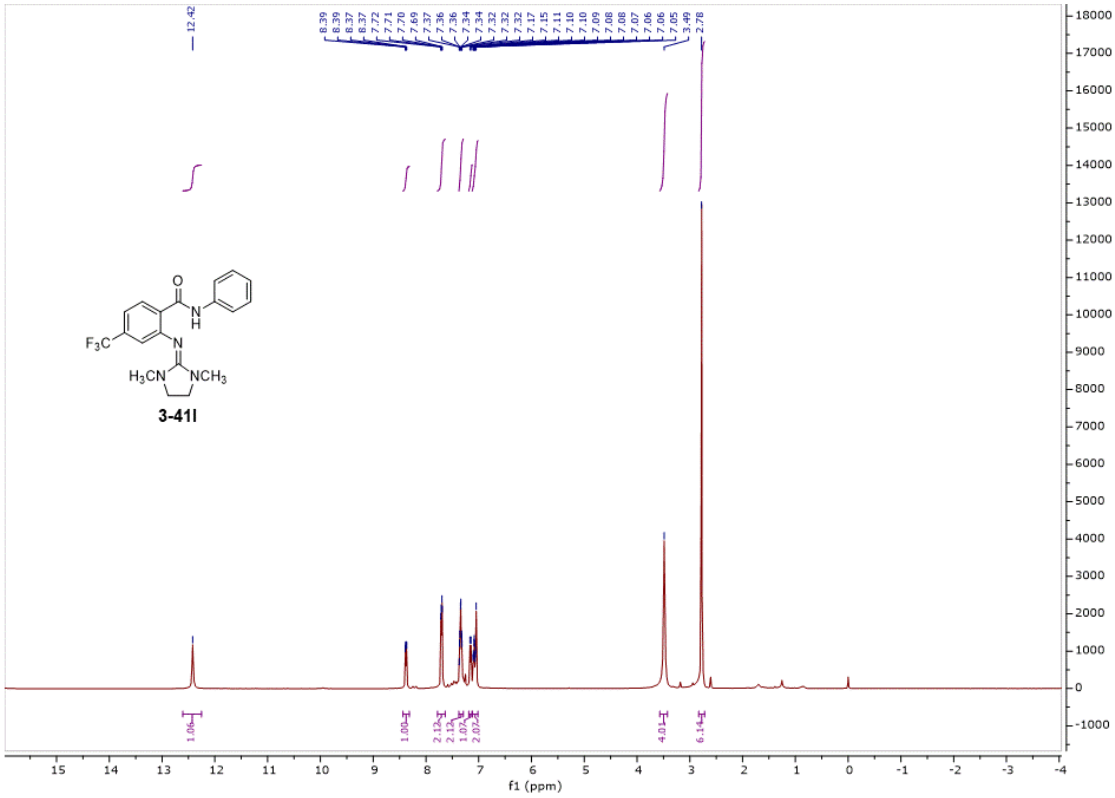

-123.37
F
O
N
H
N
H3CN
NCH3
3-41i
f1 (ppm)

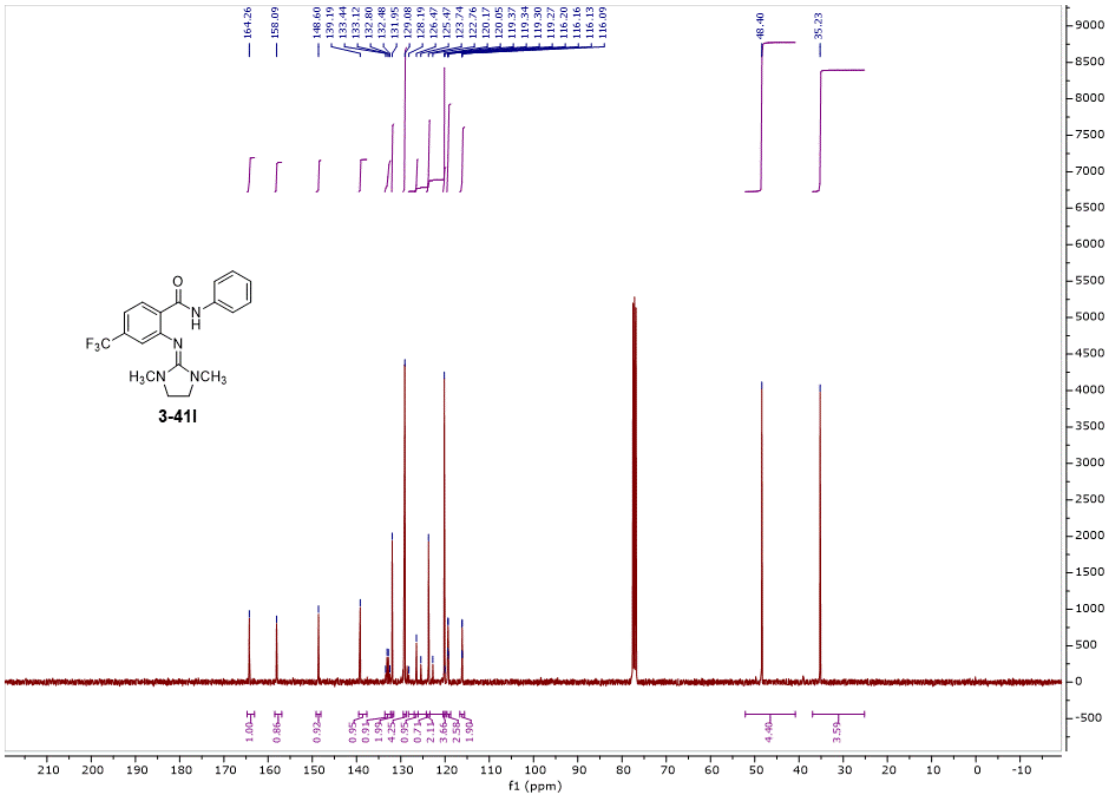

12.32
8.25
8.24
7.70
7.70
7.70
7.69
7.68
7.68
7.36
7.35
7.34
7.33
7.32
7.32
7.32
7.23
7.22
7.20
7.20
7.10
7.09
7.09
7.08
7.08
7.07
7.06
7.06
7.05
6.78
6.75
3.44
2.76
Cl
O
N
H
N
H3CN
NCH3
3-41j
1.04
0.97
2.06
2.10
1.04
1.02
1.00
4.03
6.04
f1 (ppm)

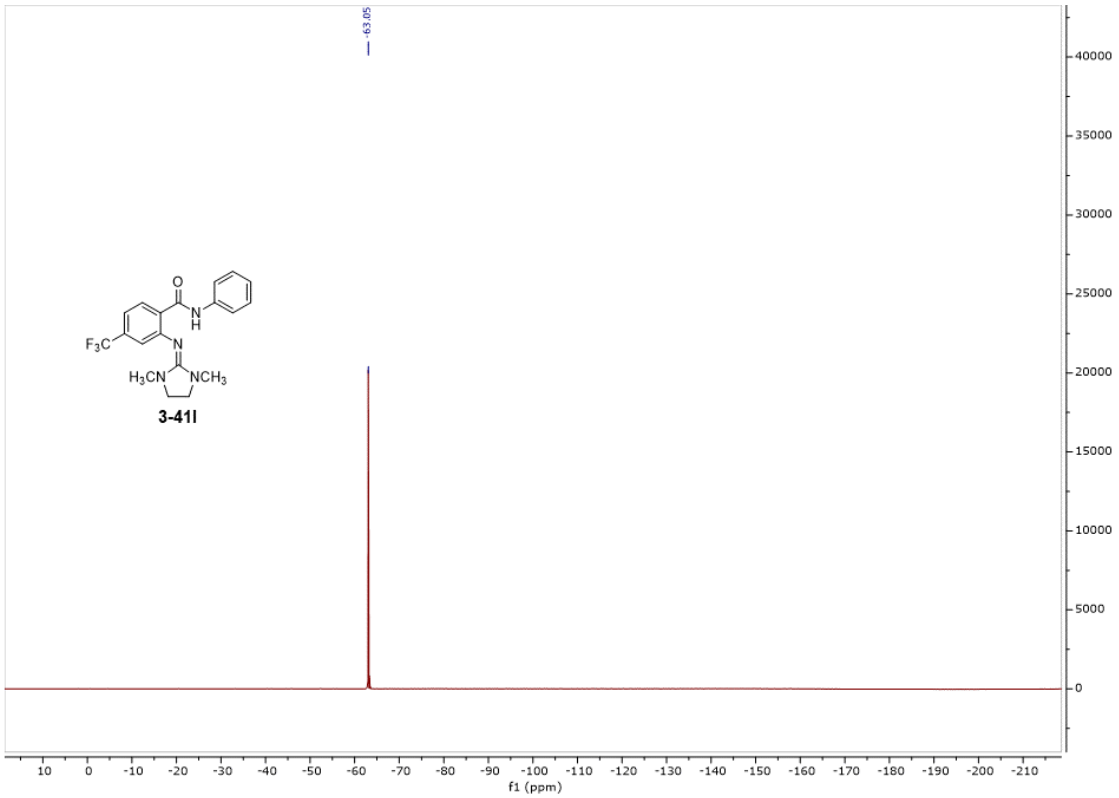

164.12
157.79
146.94
139.30
131.27
130.70
129.06
125.46
125.18
124.09
123.59
120.11
48.46
35.29
Cl
O
N
H
N
H3CN
NCH3
3-41j
f1 (ppm)

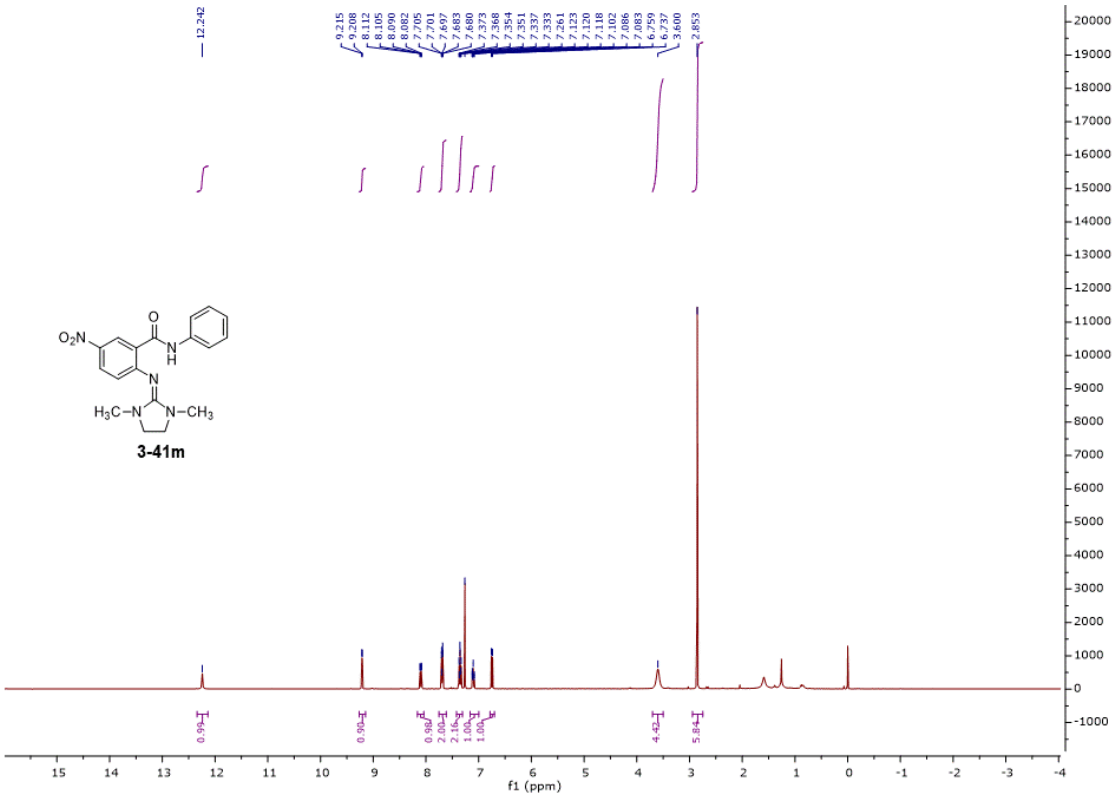

12.23
8.15
8.12
7.70
7.68
7.35
7.34
7.33
7.32
7.31
7.09
7.08
7.07
7.05
6.97
3.46
2.79
1.03
1.00
2.07
2.22
2.03
0.99
4.01
6.07
Br
O
N
H
N
H3CN
NCH3
3-41k
f1 (ppm)


164.68
157.97
149.43
139.35
132.65
129.04
125.74
124.95
123.52
123.26
122.81
120.09
48.41
35.27
Br
N
H
O
N
H3CN
NCH3
3-41k
f1 (ppm)


12.42
8.39
8.39
8.37
8.37
7.72
7.71
7.70
7.69
7.37
7.36
7.36
7.34
7.34
7.32
7.32
7.32
7.17
7.15
7.11
7.10
7.10
7.09
7.08
7.08
7.07
7.06
7.06
7.05
3.49
2.78
F3C
N
H
O
N
H3CN
NCH3
3-41l
1.06
1.00
2.12
2.12
1.07
2.07
4.01
6.14
f1 (ppm)

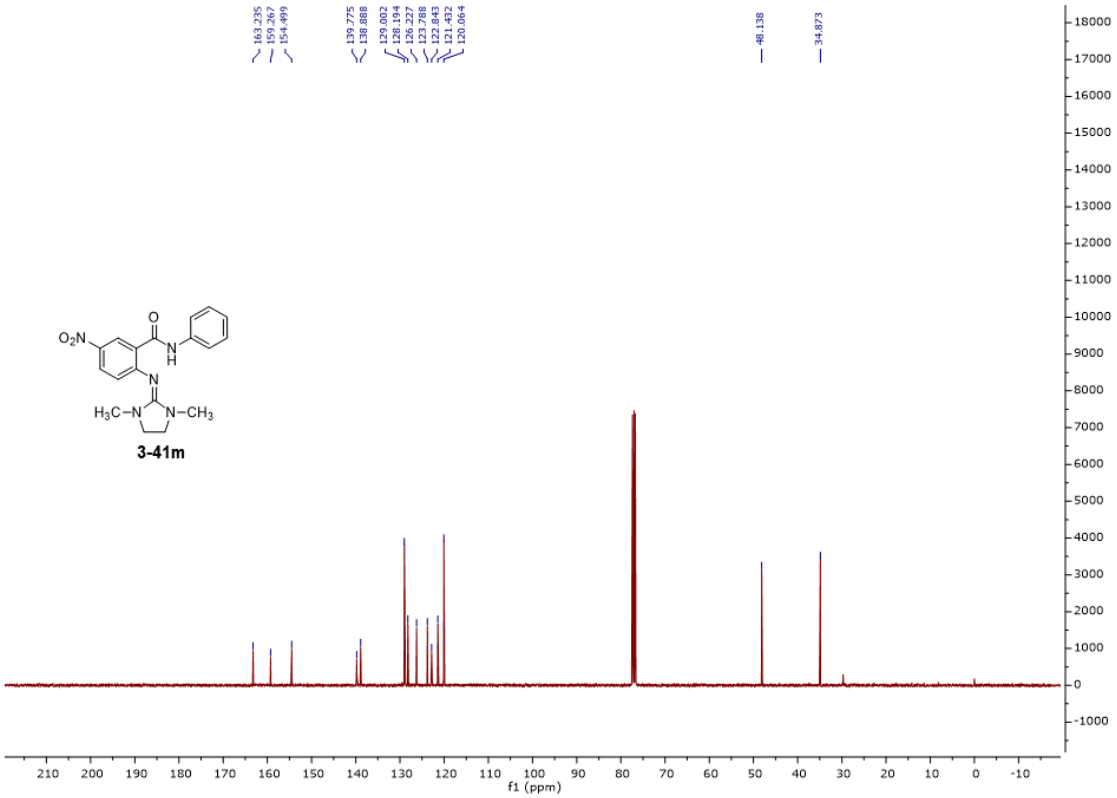

164.26
158.09
140.60
139.19
133.44
133.12
132.80
132.48
131.95
129.08
128.19
126.47
125.47
123.74
122.76
120.17
120.05
119.37
119.34
119.30
119.27
116.20
116.16
116.13
116.09
48.40
35.23
O
N
H
F3C
N
H3CN
NCH3
3-41l
f1 (ppm)


-63.05
O
N
H
F3C
N
H3CN
NCH3
3-41l
f1 (ppm)


12.242
9.215
9.208
8.112
8.105
8.090
8.082
7.705
7.701
7.697
7.683
7.680
7.373
7.368
7.354
7.351
7.337
7.333
7.261
7.123
7.120
7.118
7.102
7.086
7.083
6.739
6.737
3.600
2.853
0.94
0.90
0.98
2.00
2.16
1.00
1.00
4.42
5.84
f1 (ppm)

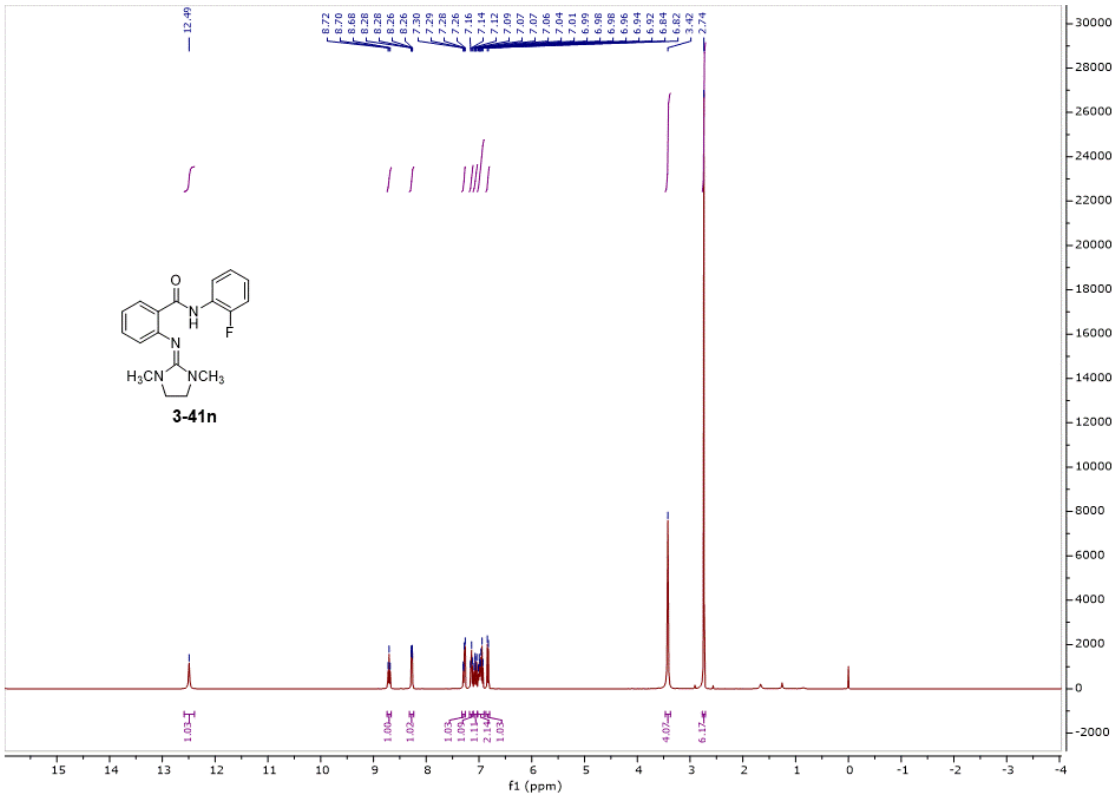


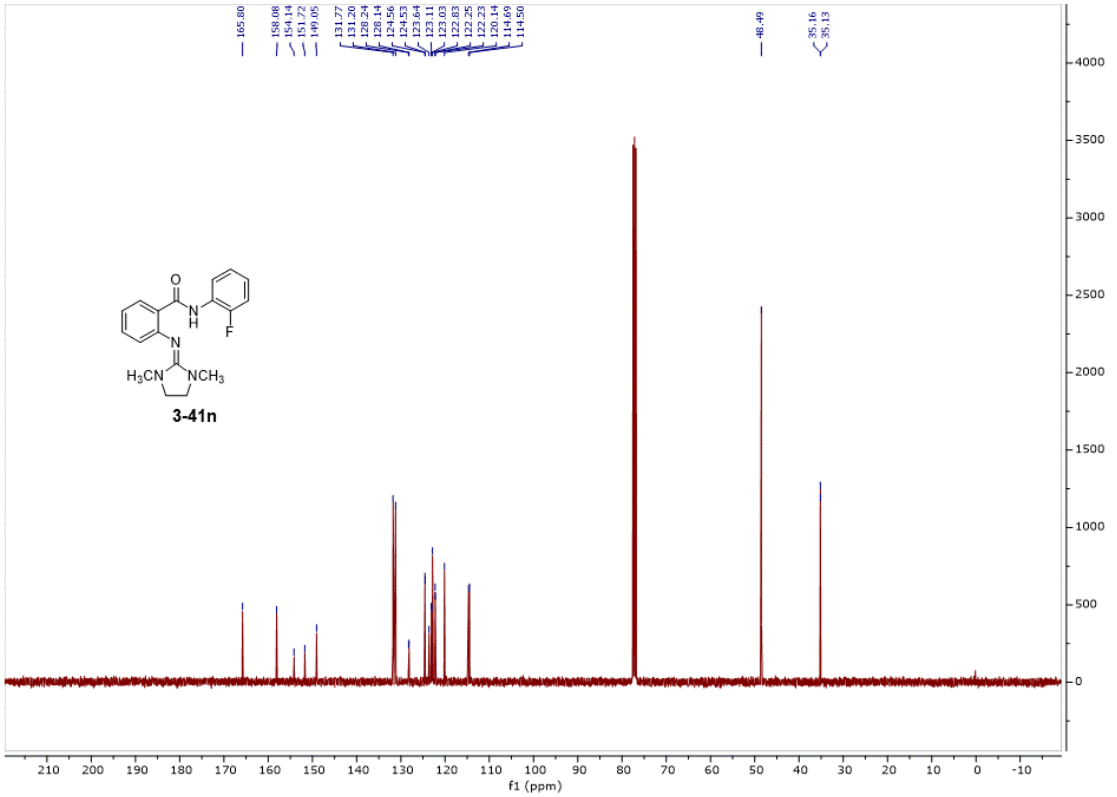
3-41m

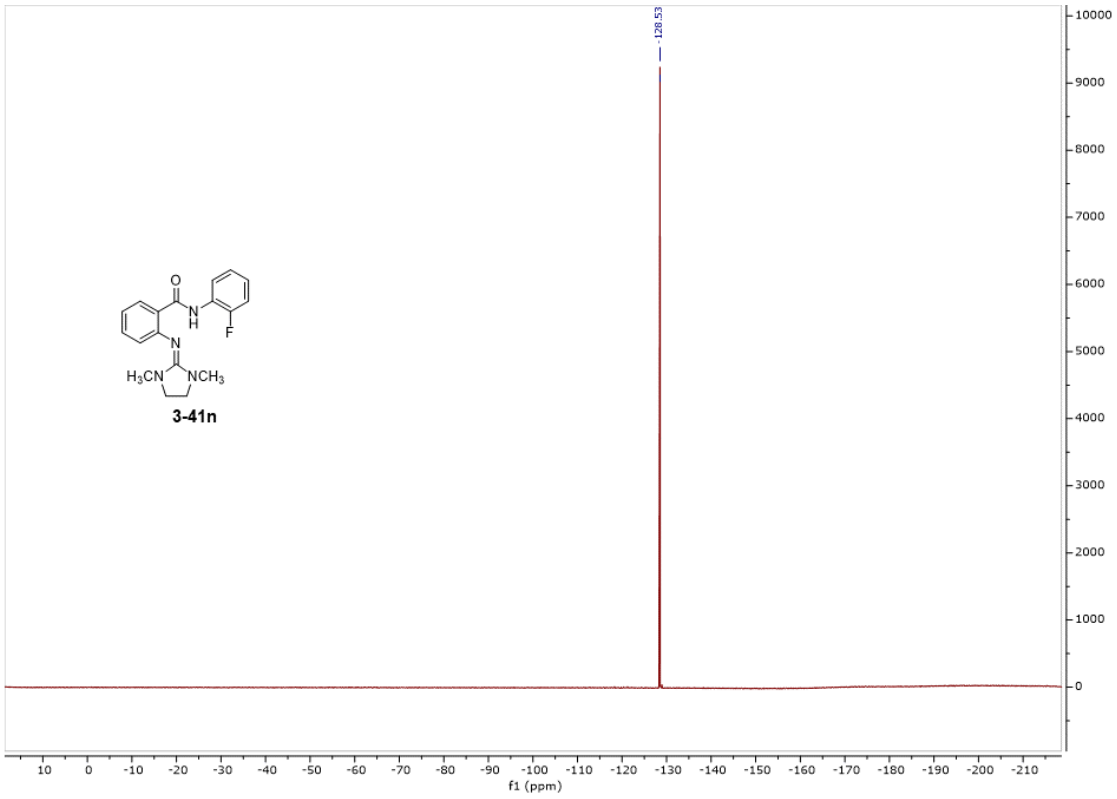

163.235
159.267
154.499
139.775
138.888
129.002
128.194
126.227
123.788
122.843
121.432
120.064
48.138
34.873
f1 (ppm)



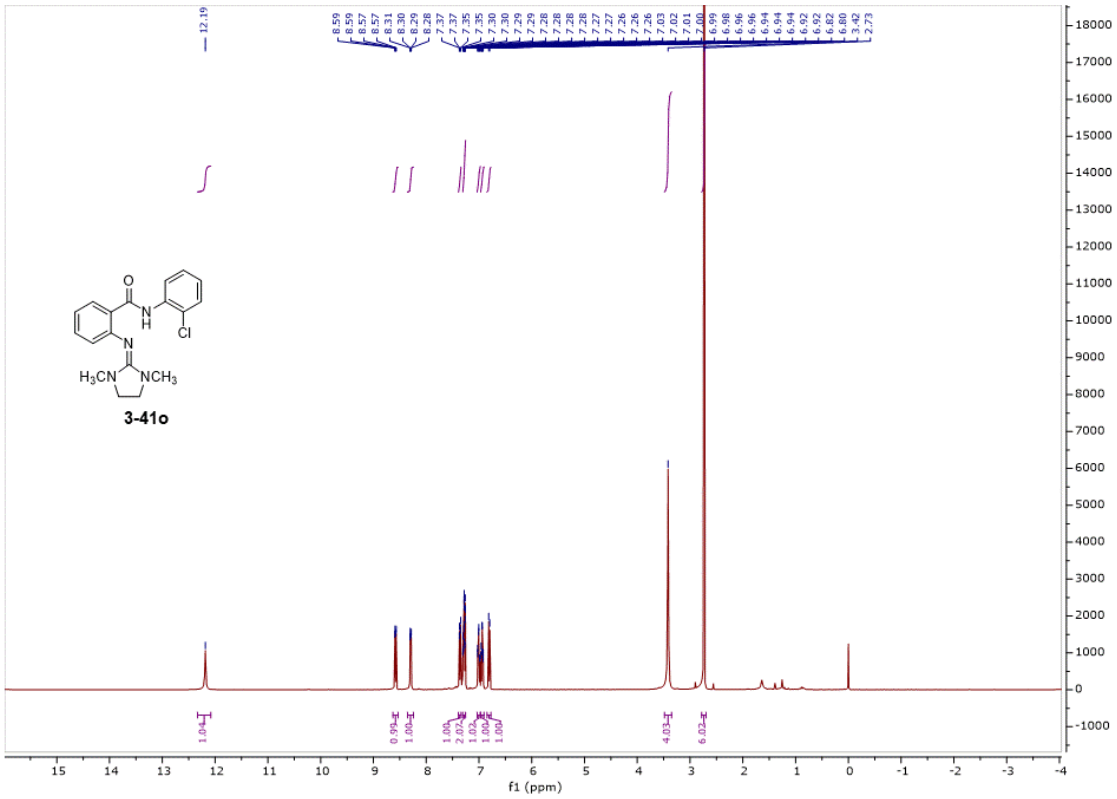
3-41m


12.49
8.72
8.70
8.68
8.28
8.26
8.26
7.30
7.29
7.28
7.26
7.16
7.14
7.12
7.09
7.07
7.07
7.06
7.04
7.01
6.99
6.98
6.98
6.96
6.94
6.92
6.84
6.82
3.42
2.74
1.03
1.00
1.02
1.03
1.09
1.11
2.14
1.03
4.07
6.17
f1 (ppm)
3-41n

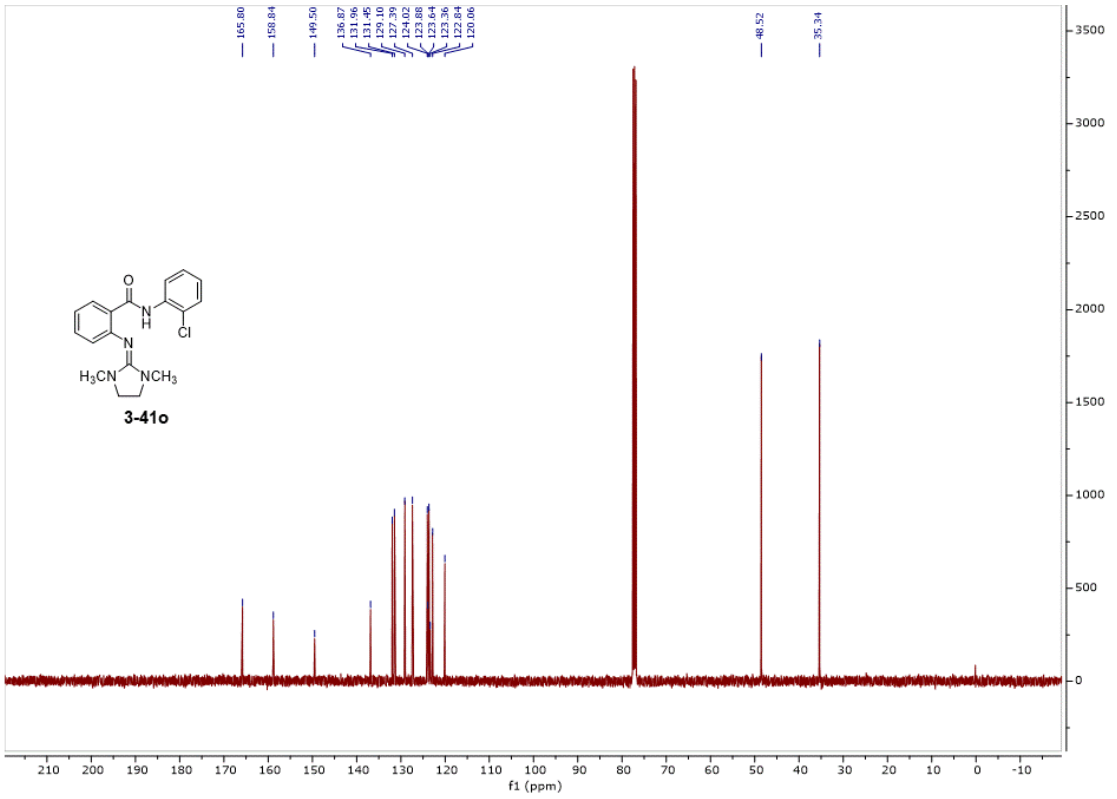

165.80
158.08
154.14
151.72
149.05
131.77
131.20
128.24
128.14
124.56
124.53
123.64
123.11
123.03
122.83
122.25
122.23
120.14
114.69
114.50
48.49
35.16
35.13
f1 (ppm)
3-41n

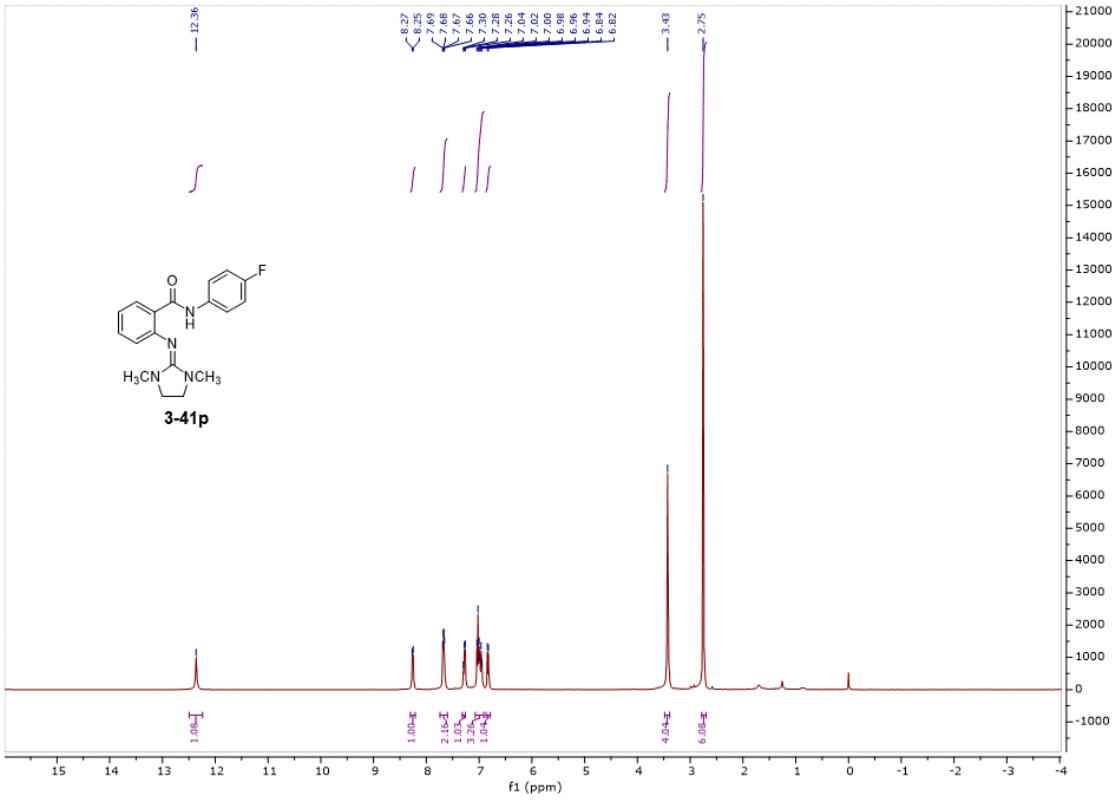


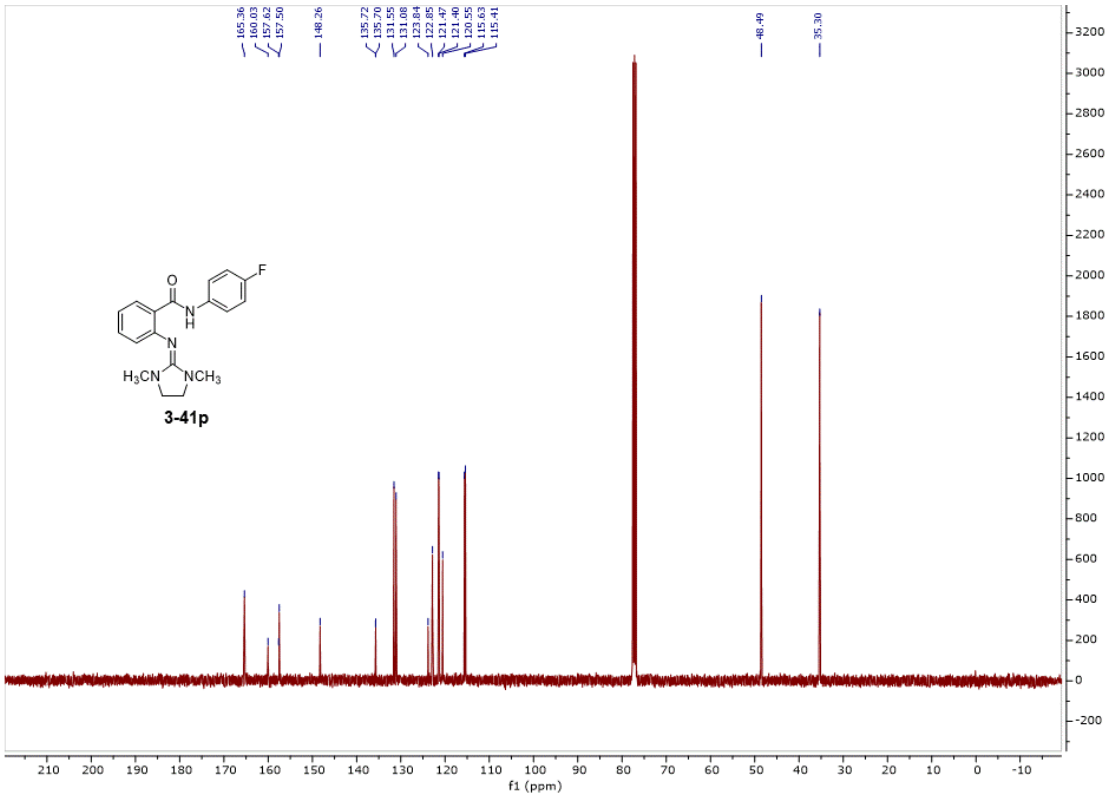

3-41n

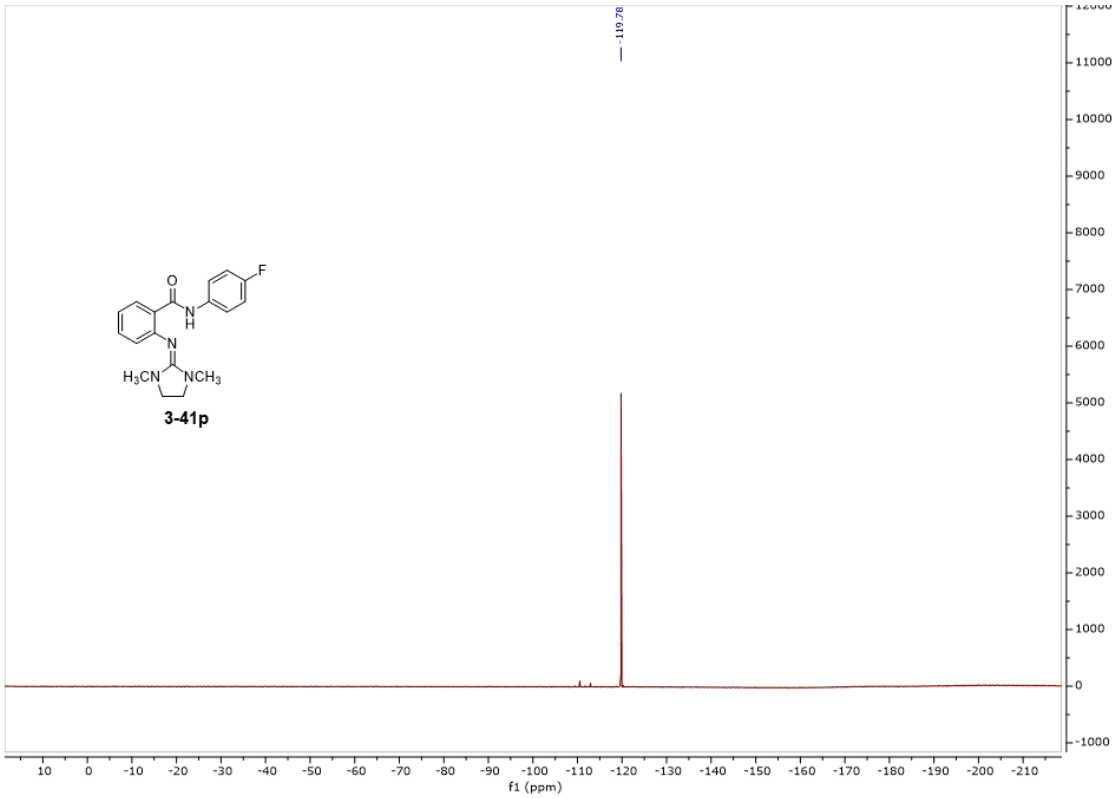


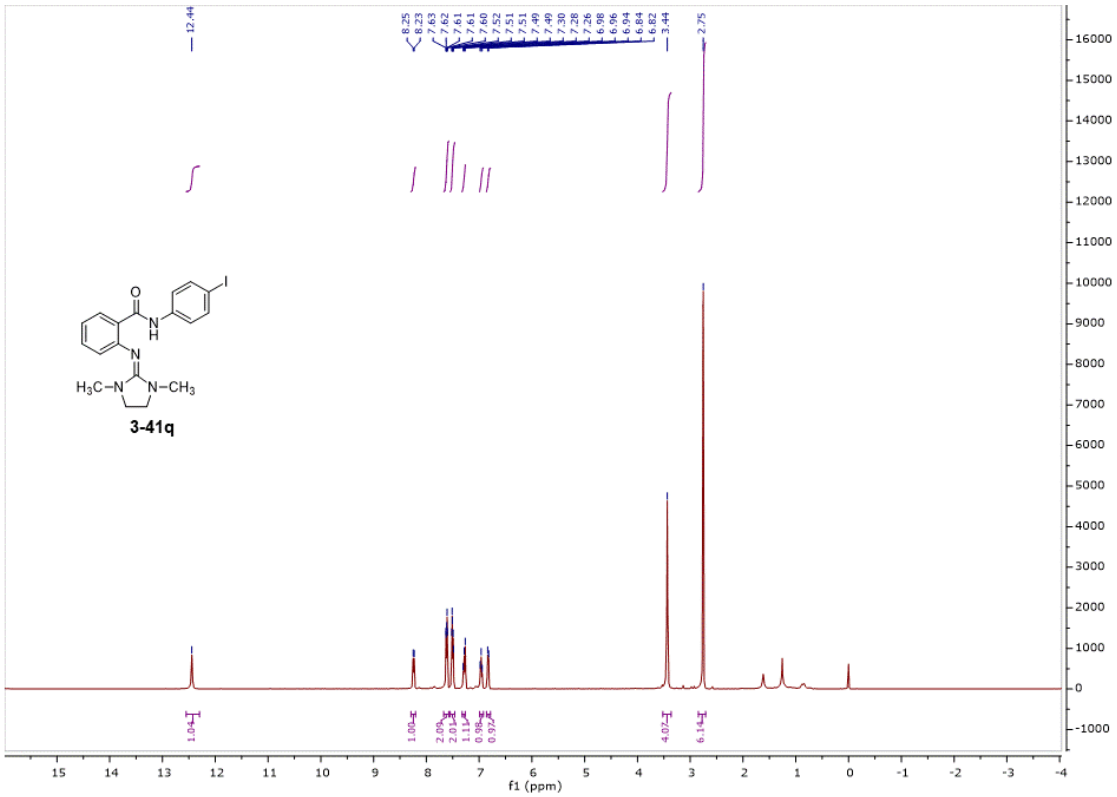

3-41o

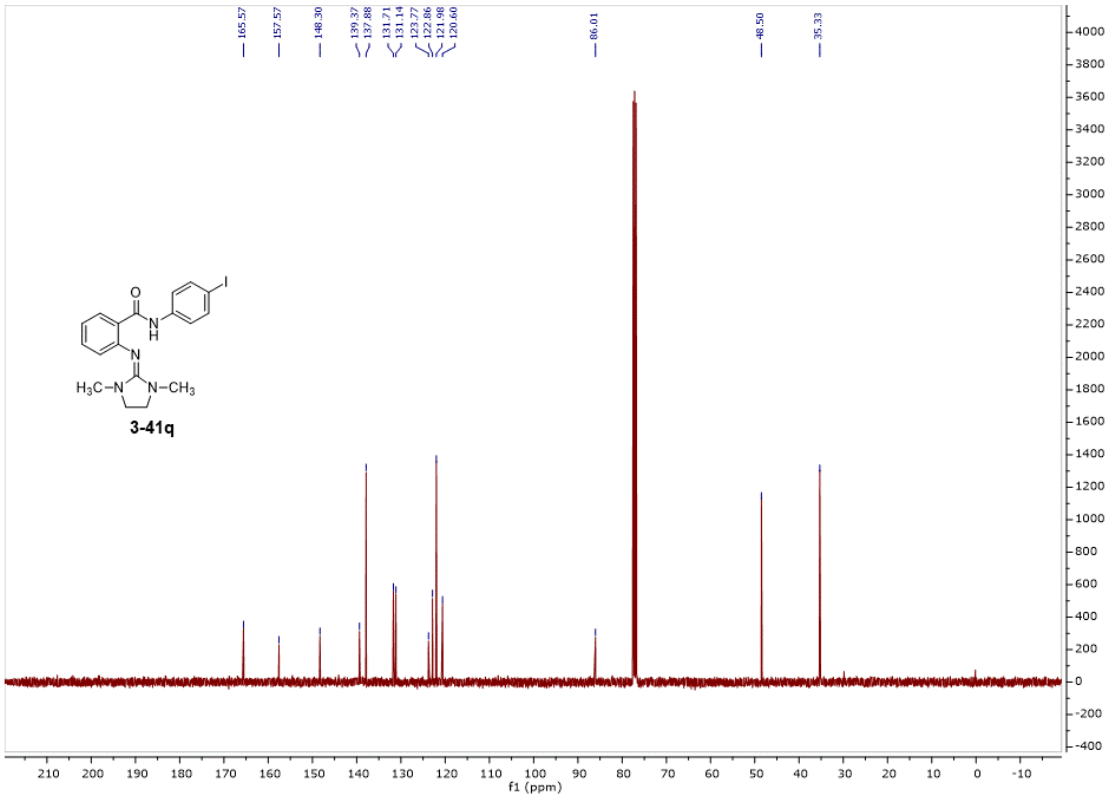

165.80
158.84
149.50
136.87
131.96
131.45
129.10
127.39
124.02
123.88
123.64
123.36
122.84
120.06
48.52
35.34
3-41o
f1 (ppm)

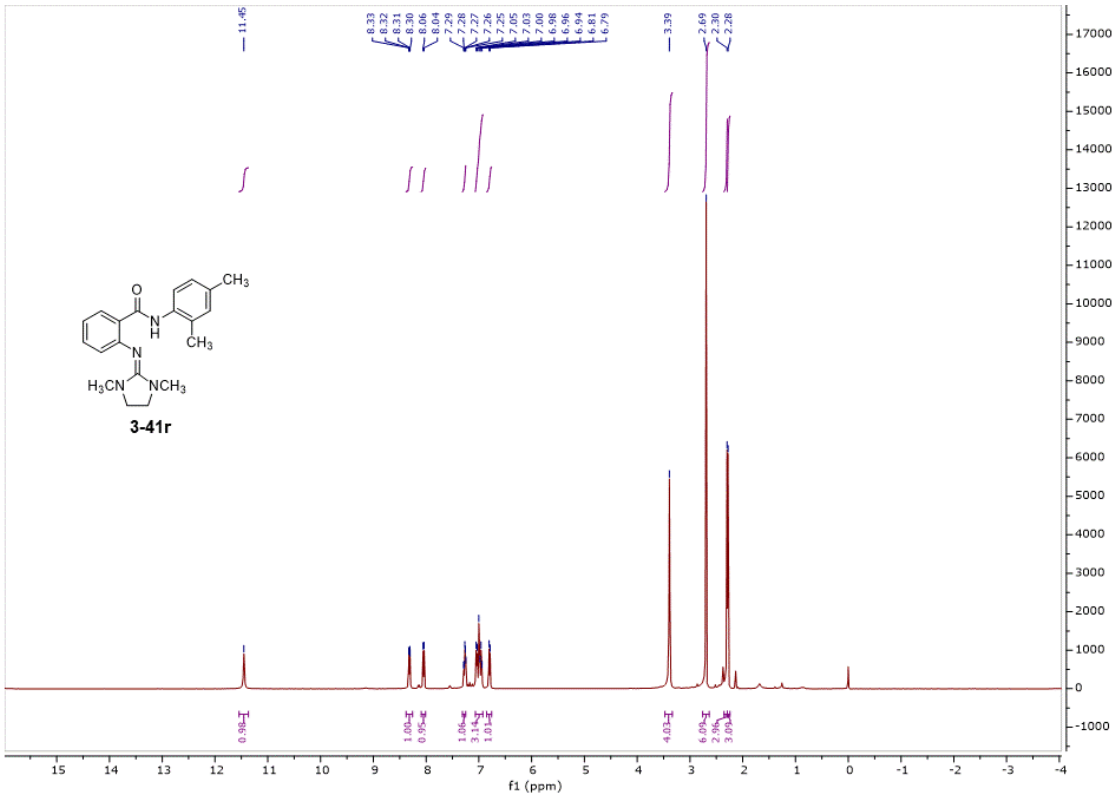

12.36
8.27
8.25
7.69
7.68
7.67
7.66
7.30
7.28
7.26
7.04
7.02
7.00
6.98
6.96
6.94
6.84
6.82
3.43
2.75
3-41p
f1 (ppm)

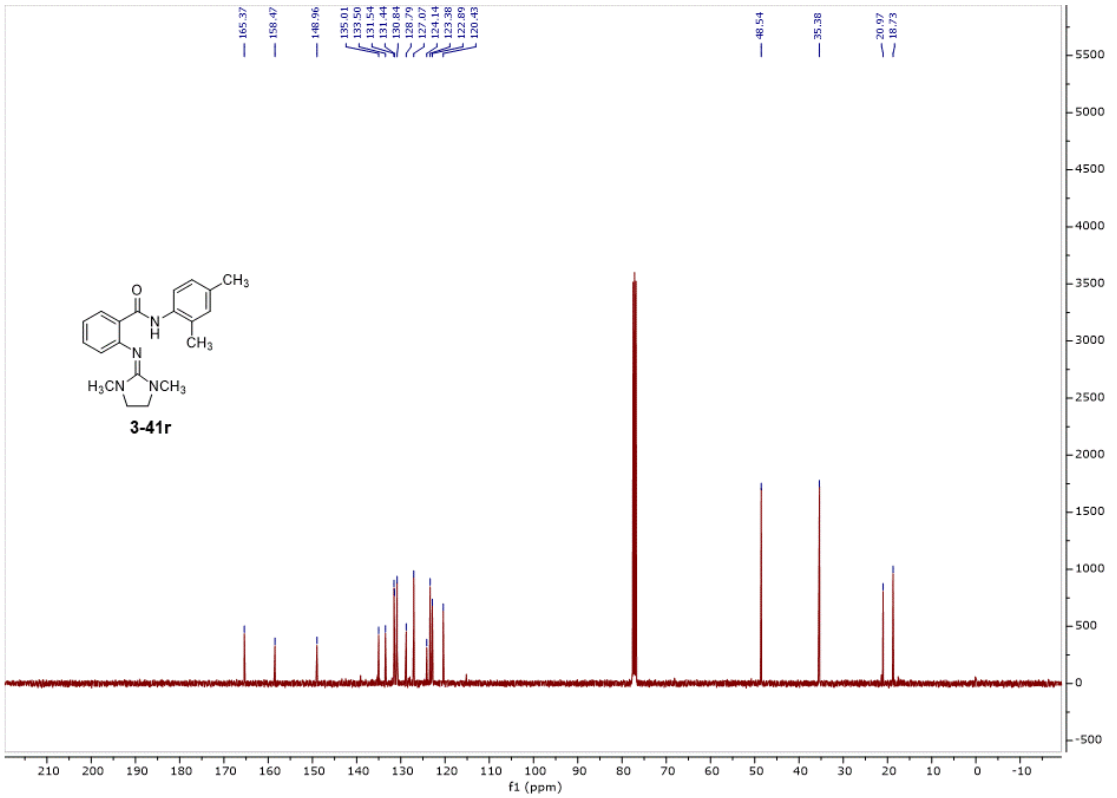

165.36
160.03
157.62
157.50
148.26
135.72
135.70
131.55
131.08
123.84
122.85
121.47
121.40
120.55
115.63
115.41
48.49
35.30
3-41p
f1 (ppm)

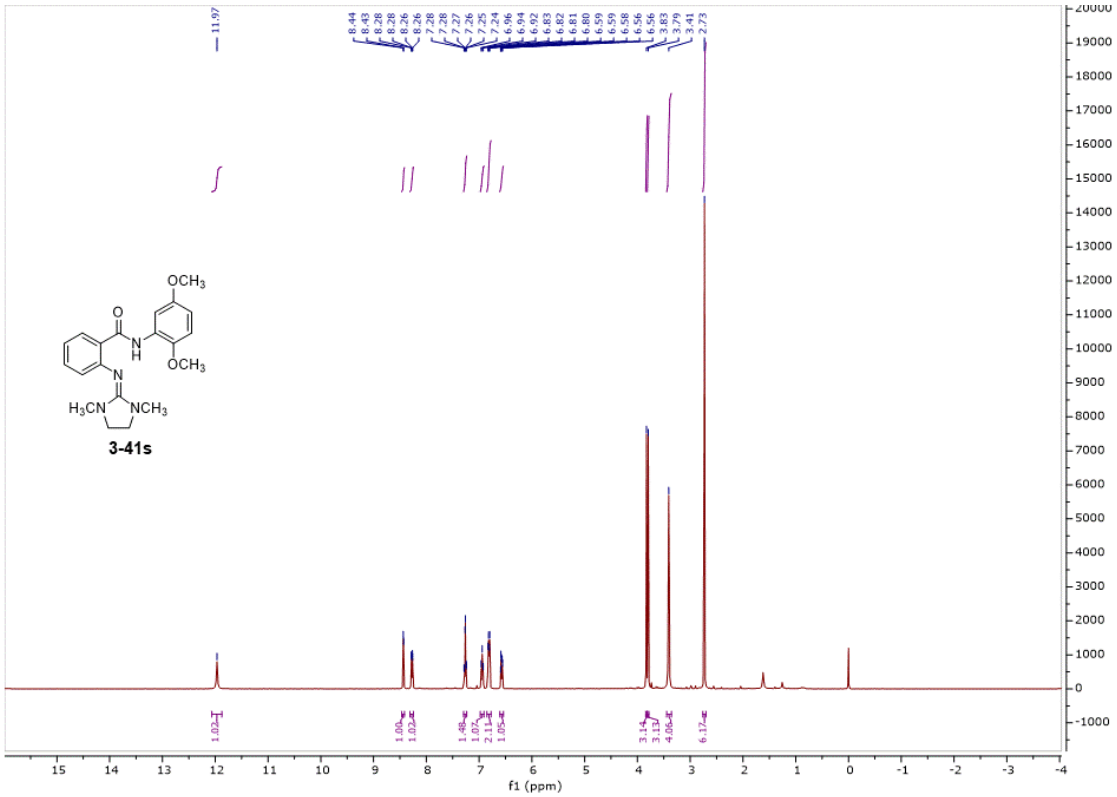

-119.78
3-41p
f1 (ppm)

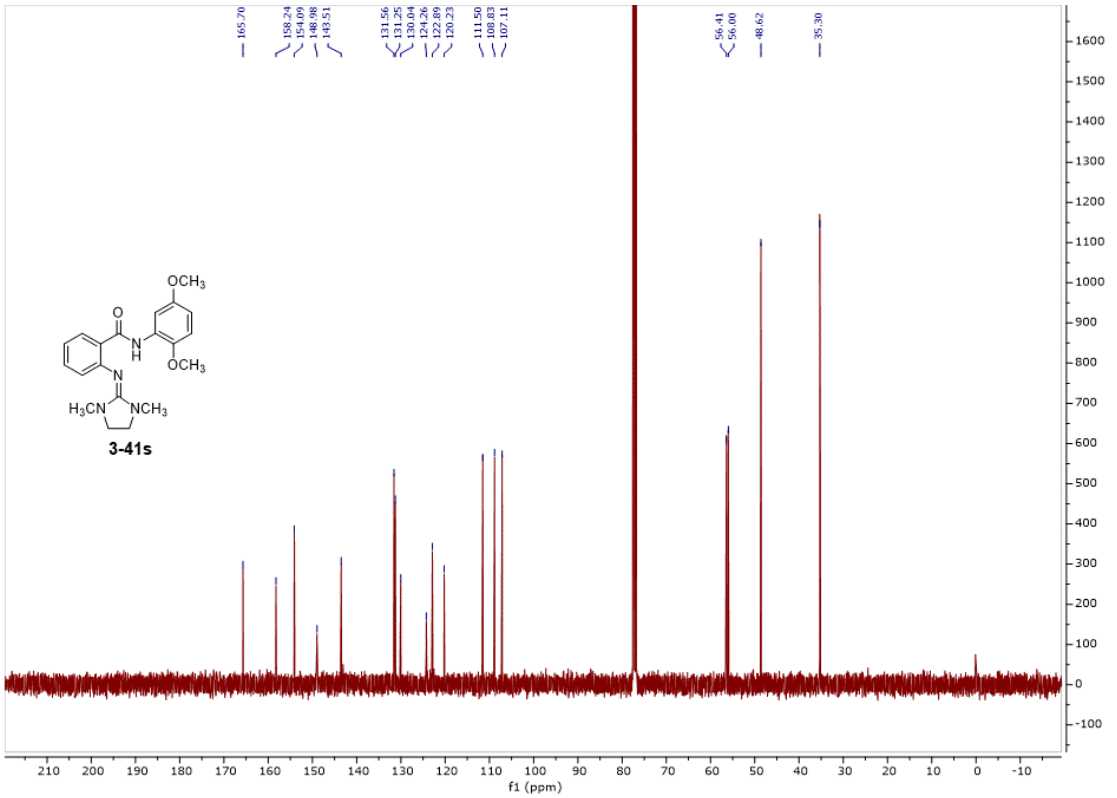

12.44
8.25
8.23
7.63
7.62
7.61
7.61
7.60
7.52
7.51
7.51
7.49
7.49
7.30
7.28
7.26
6.98
6.96
6.94
6.84
6.82
3.44
2.75
1.04
1.00
2.09
2.01
1.11
0.98
0.97
4.07
6.14
f1 (ppm)
3-41q

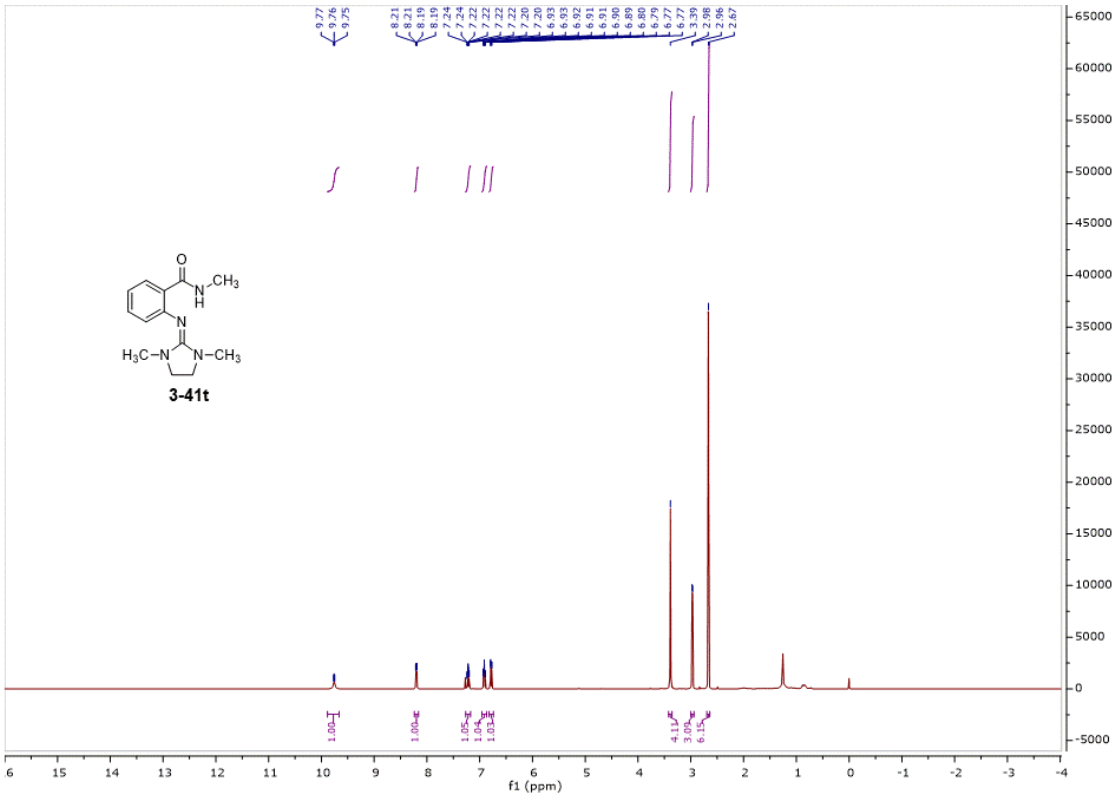

165.57
157.57
148.30
139.37
137.88
131.71
131.14
123.77
122.06
121.98
120.60
86.01
48.50
35.33
f1 (ppm)
3-41q

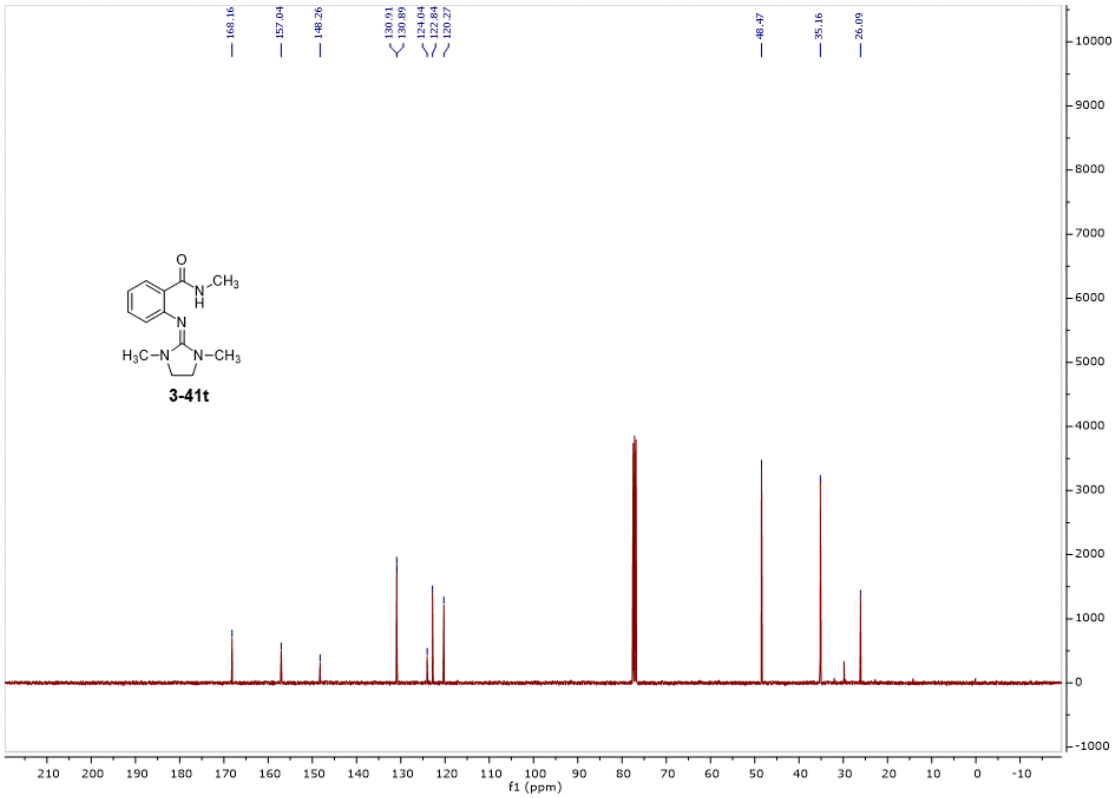

11.45
8.33
8.32
8.31
8.30
8.06
8.04
7.29
7.28
7.27
7.26
7.25
7.05
7.03
7.00
6.98
6.96
6.94
6.81
6.79
3.39
2.69
2.30
2.28
0.98
1.05
0.95
1.06
3.14
1.01
4.03
6.09
2.96
3.09
f1 (ppm)
3-41r


165.37
158.47
140.96
135.01
133.50
131.54
131.44
130.84
128.79
127.07
124.14
123.38
122.89
120.43
48.54
35.38
20.97
18.73
f1 (ppm)
3-41r

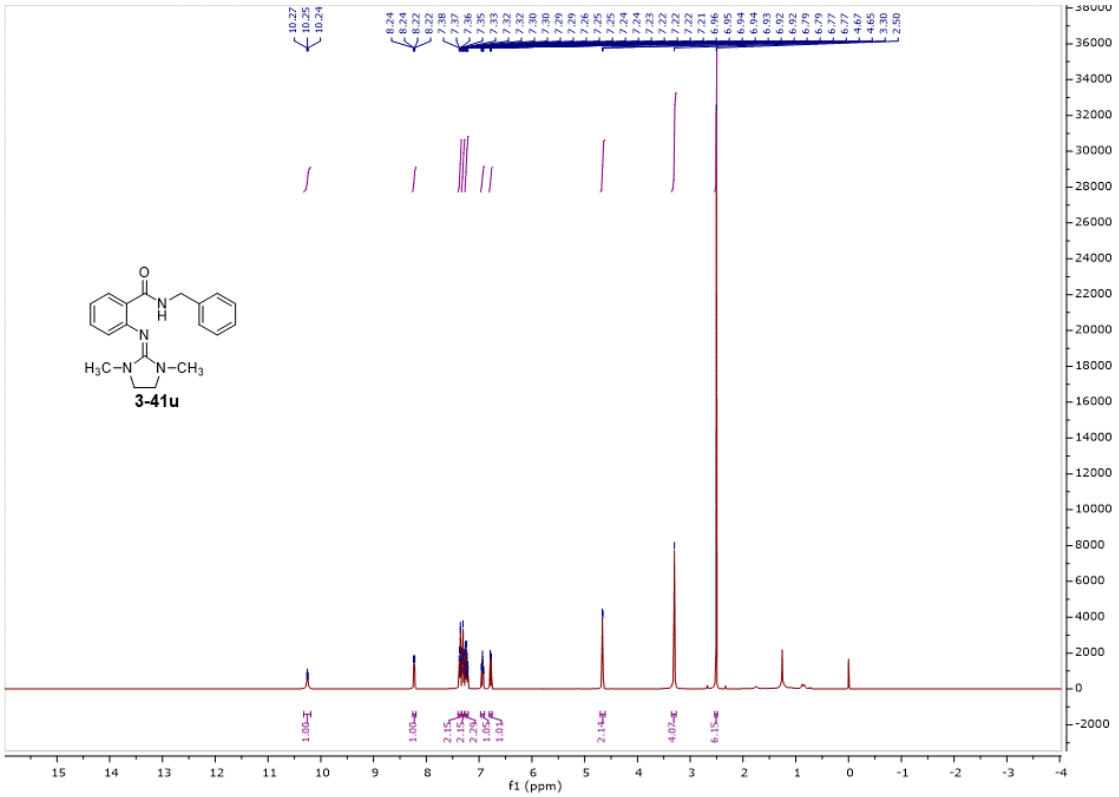

11.97
8.44
8.43
8.28
8.26
7.28
7.27
7.26
7.25
7.24
6.96
6.94
6.92
6.83
6.82
6.81
6.80
6.59
6.58
6.56
6.56
3.83
3.79
3.41
2.73
OCH3
O
N
H
N
OCH3
H3CN
NCH3
3-41s
1.02
1.00
1.02
1.48
1.07
2.11
1.05
3.14
3.13
4.06
6.17
f1 (ppm)

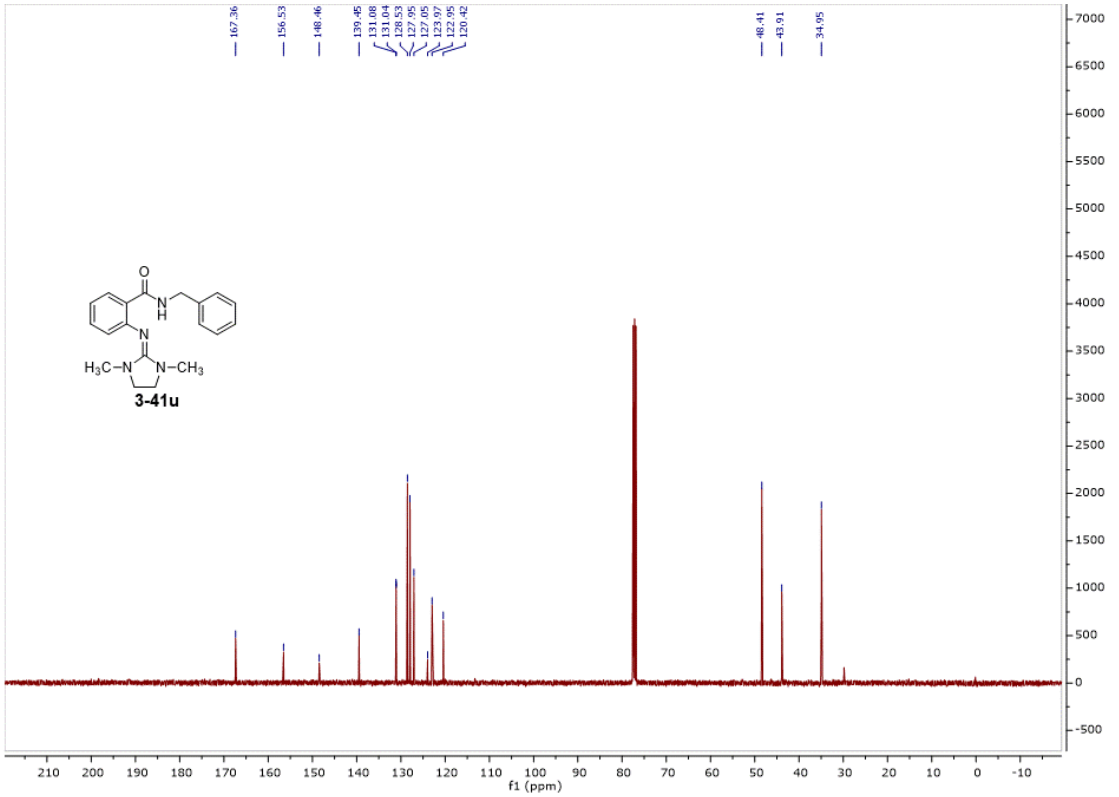

165.70
158.24
154.09
148.98
143.51
131.56
131.25
130.04
124.26
122.89
120.23
111.50
108.83
107.11
56.41
56.00
48.62
35.30
OCH3
O
N
H
N
OCH3
H3CN
NCH3
3-41s
f1 (ppm)

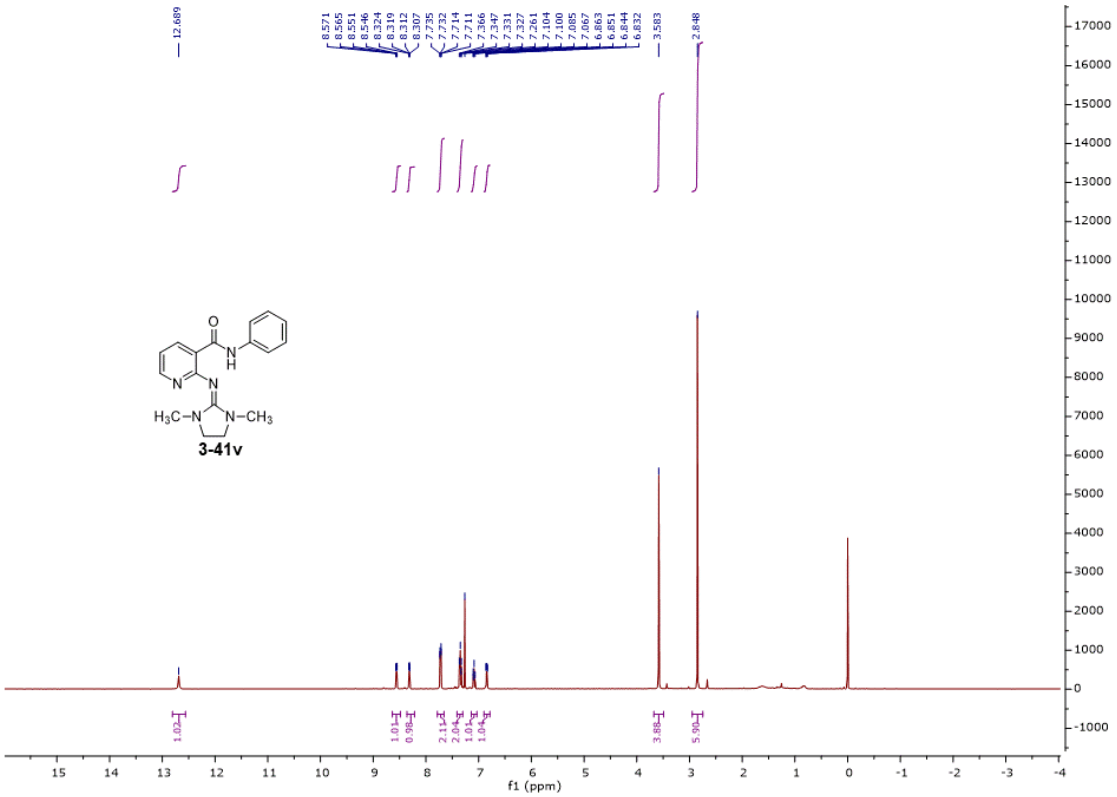

9.77
9.76
9.75
8.21
8.21
8.19
8.19
7.24
7.24
7.22
7.22
7.22
7.22
7.20
7.20
6.93
6.93
6.92
6.91
6.91
6.90
6.89
6.80
6.79
6.77
6.77
3.39
2.98
2.96
2.67
1.00
1.00
1.05
1.04
1.03
4.11
3.09
6.15
f1 (ppm)

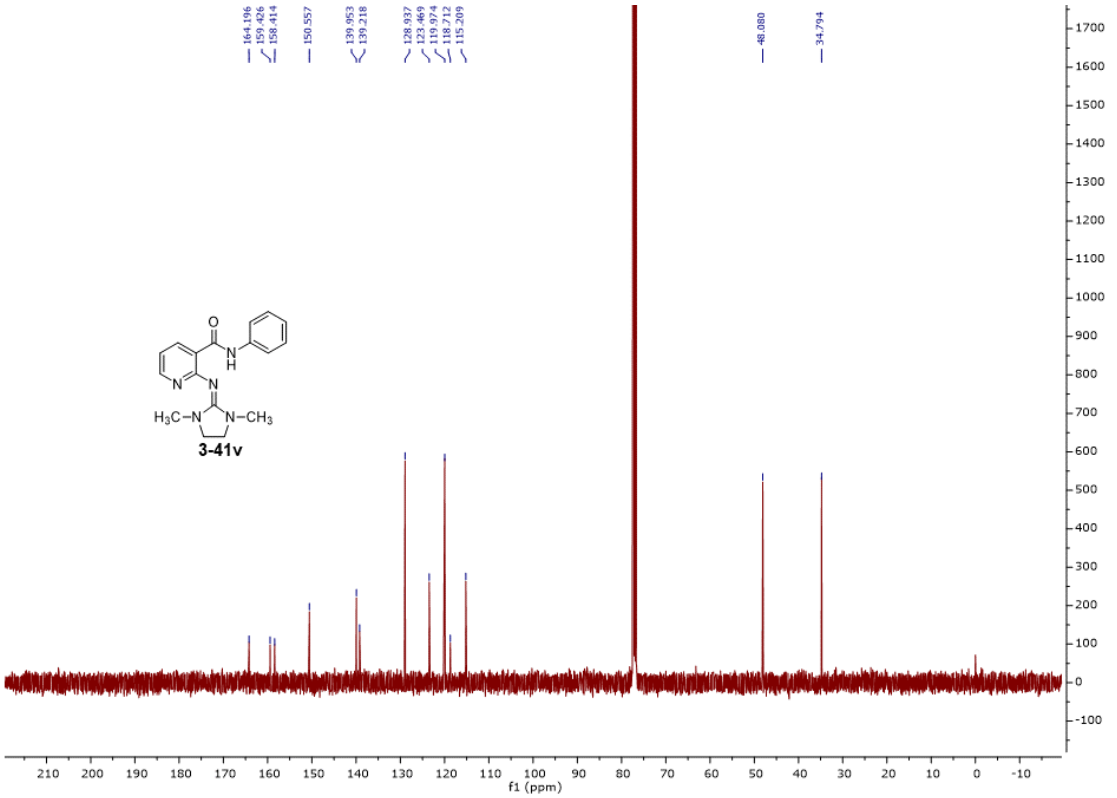

168.16
157.04
148.26
130.91
130.89
124.04
122.84
120.27
48.47
35.16
26.09
f1 (ppm)

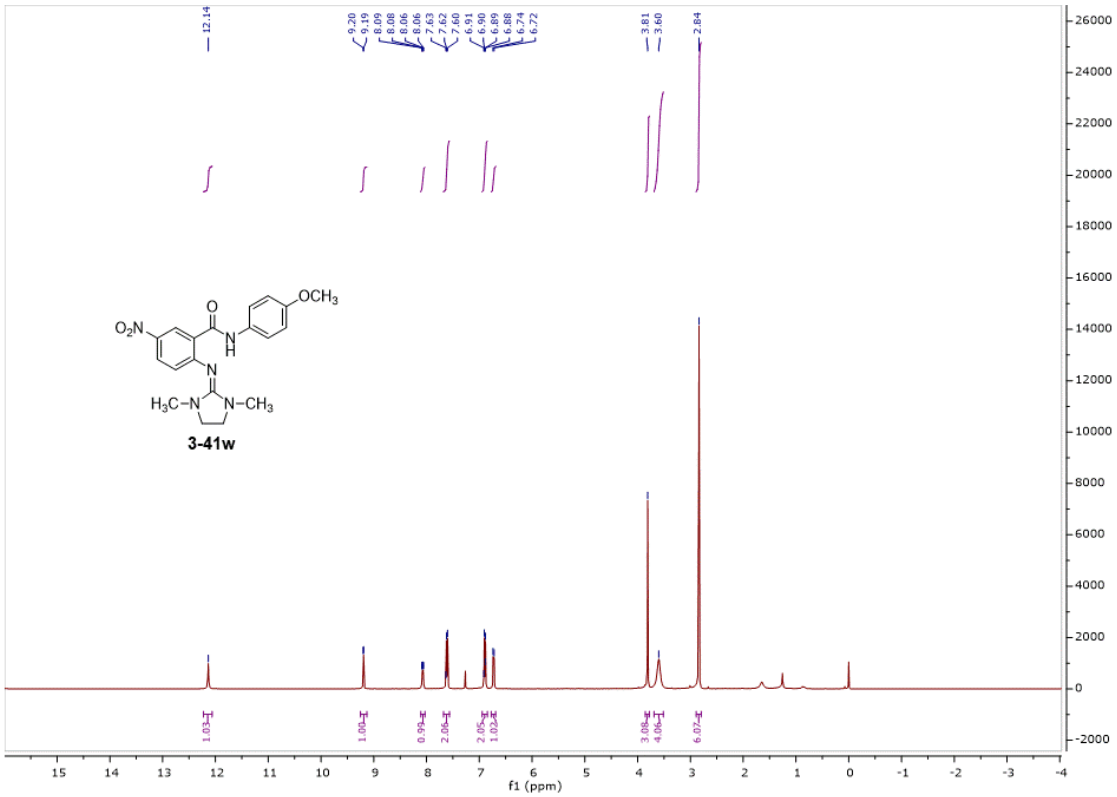
3-41t

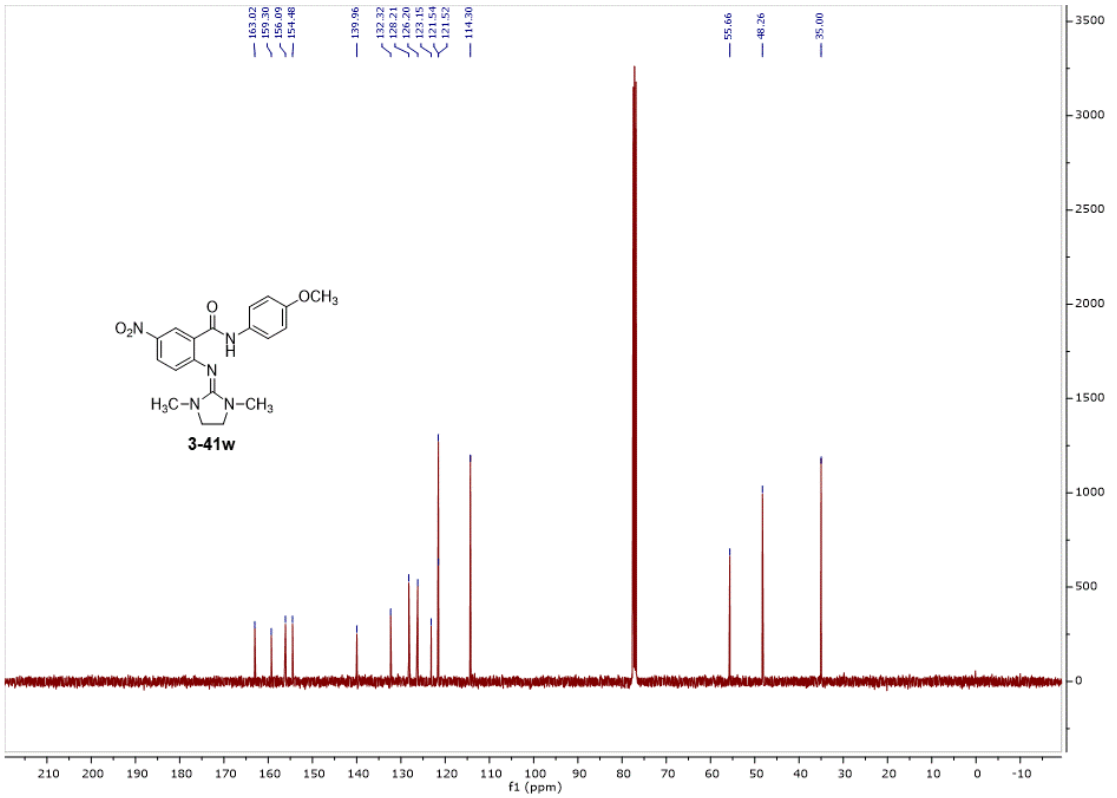

3-41u
f1 (ppm)

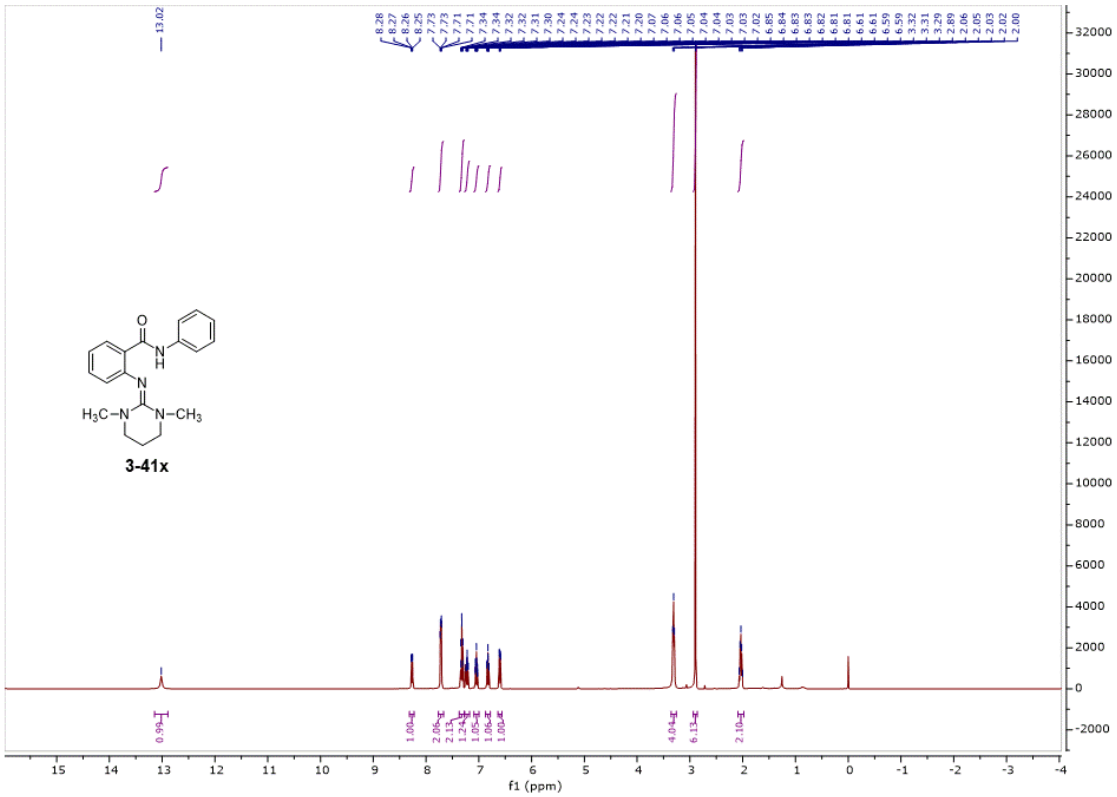

3-41u
f1 (ppm)


12.689
8.571
8.565
8.551
8.546
8.324
8.319
8.312
8.307
7.735
7.732
7.714
7.711
7.366
7.347
7.331
7.327
7.261
7.104
7.100
7.085
7.067
6.863
6.851
6.844
6.832
3.583
2.848
3-41v
f1 (ppm)

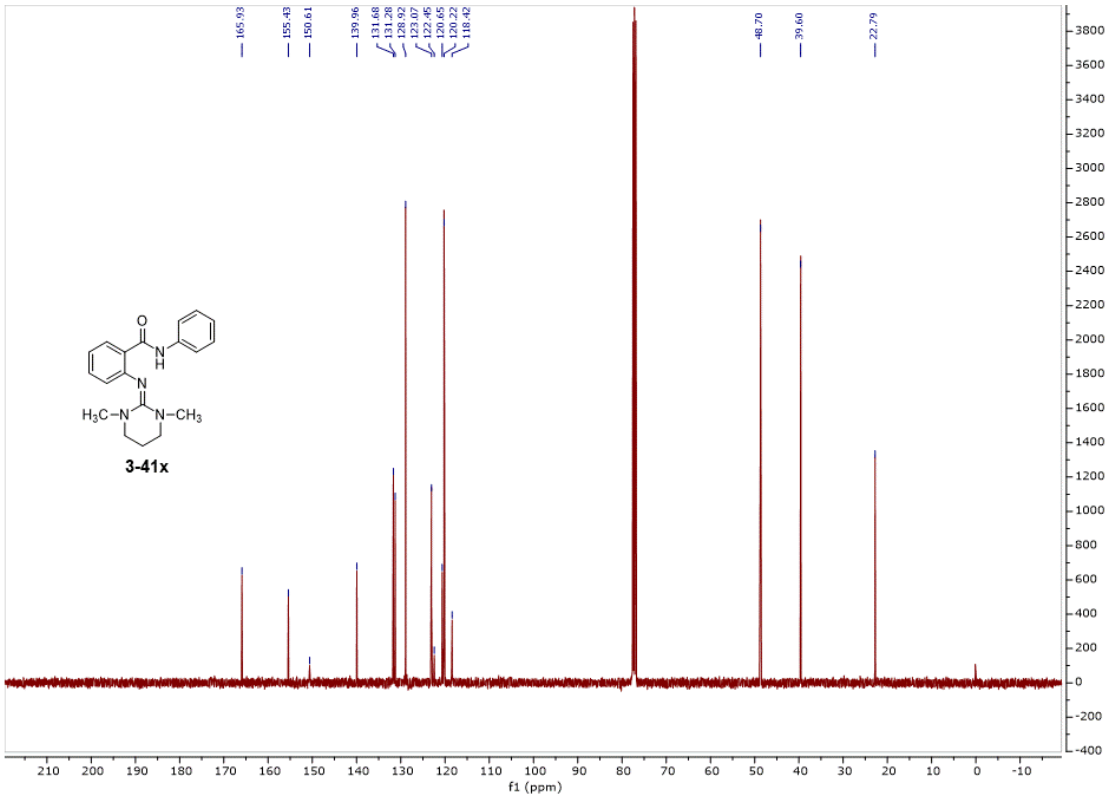

164.196
159.426
158.414
150.557
139.953
139.218
128.937
123.469
119.974
118.712
115.209
48.080
34.794
3-41v
f1 (ppm)


12.14
9.20
9.19
8.09
8.08
8.06
8.06
7.63
7.62
7.60
6.91
6.90
6.89
6.88
6.74
6.72
3.81
3.60
2.84
O2N
OCH3
O
N
H
N
H3C–N
N–CH3
3-41w
1.03
1.00
0.93
2.06
2.05
1.02
3.08
4.06
6.07
f1 (ppm)

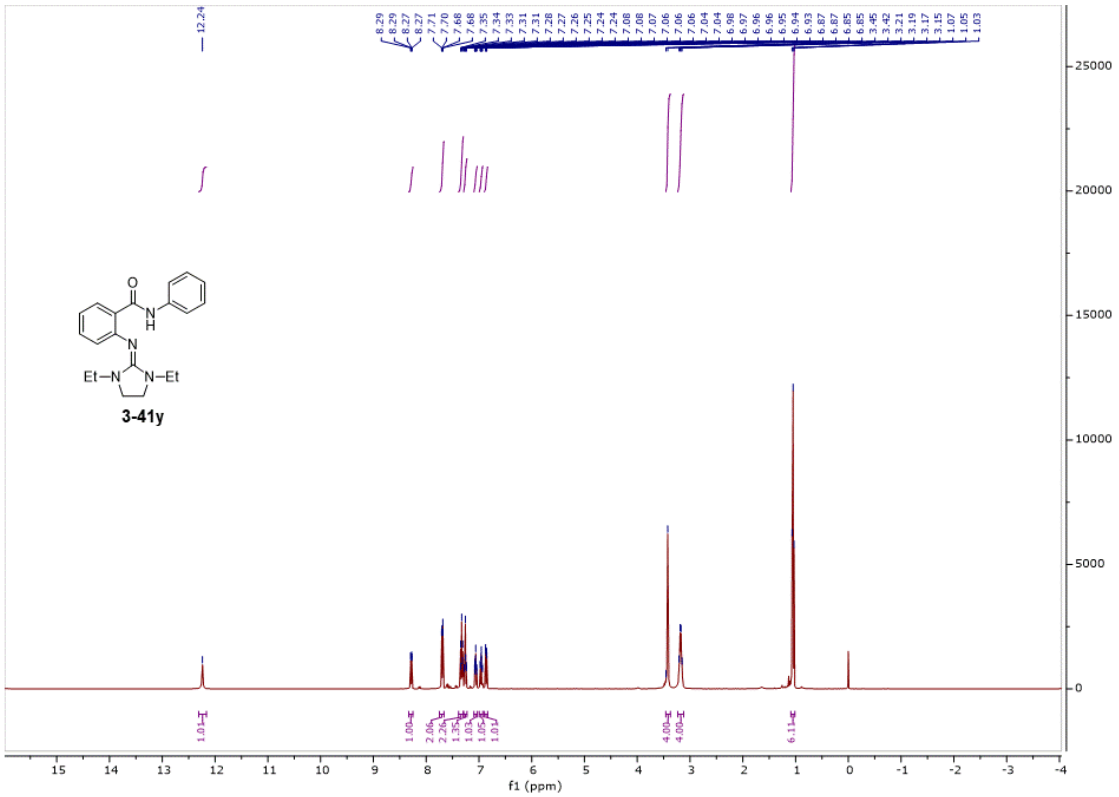

163.02
159.30
156.09
154.48
139.96
132.32
128.21
126.20
123.15
121.54
121.52
114.30
55.66
48.26
35.00
O2N
OCH3
O
N
H
N
H3C–N
N–CH3
3-41w
f1 (ppm)

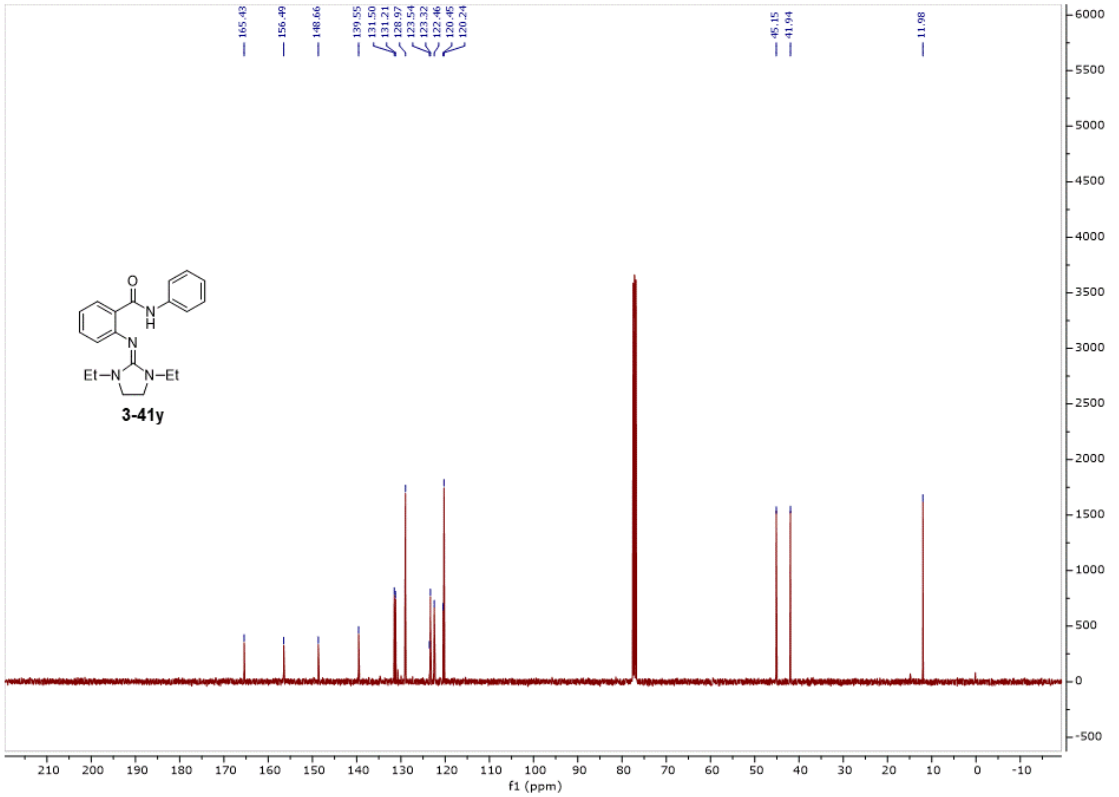

13.02
8.28
8.27
8.26
8.25
7.73
7.73
7.71
7.71
7.34
7.34
7.32
7.32
7.31
7.30
7.24
7.24
7.23
7.22
7.22
7.21
7.20
7.07
7.06
7.06
7.05
7.04
7.04
7.03
7.03
7.02
6.85
6.84
6.83
6.83
6.62
6.61
6.61
6.61
6.61
6.59
6.59
3.32
3.31
3.29
2.89
2.06
2.05
2.03
2.02
2.00
0.94
1.03
2.06
2.13
1.24
1.05
1.06
1.00
4.04
6.13
2.10
f1 (ppm)

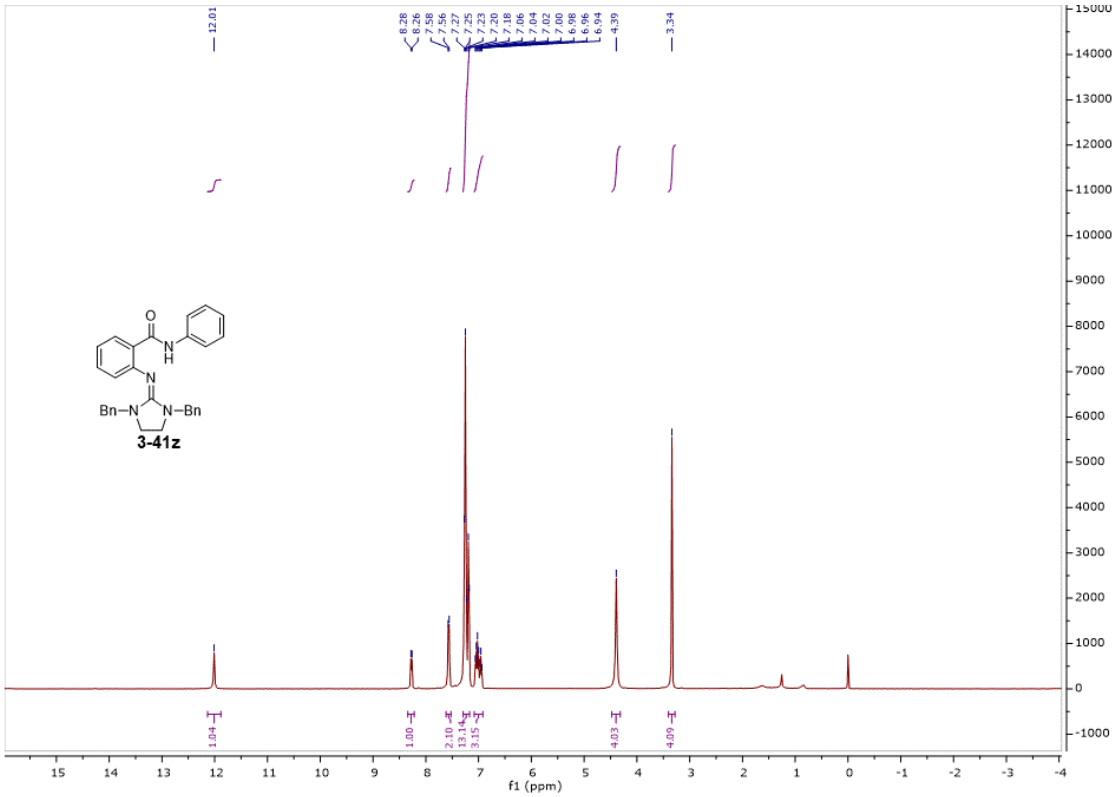
3-41x

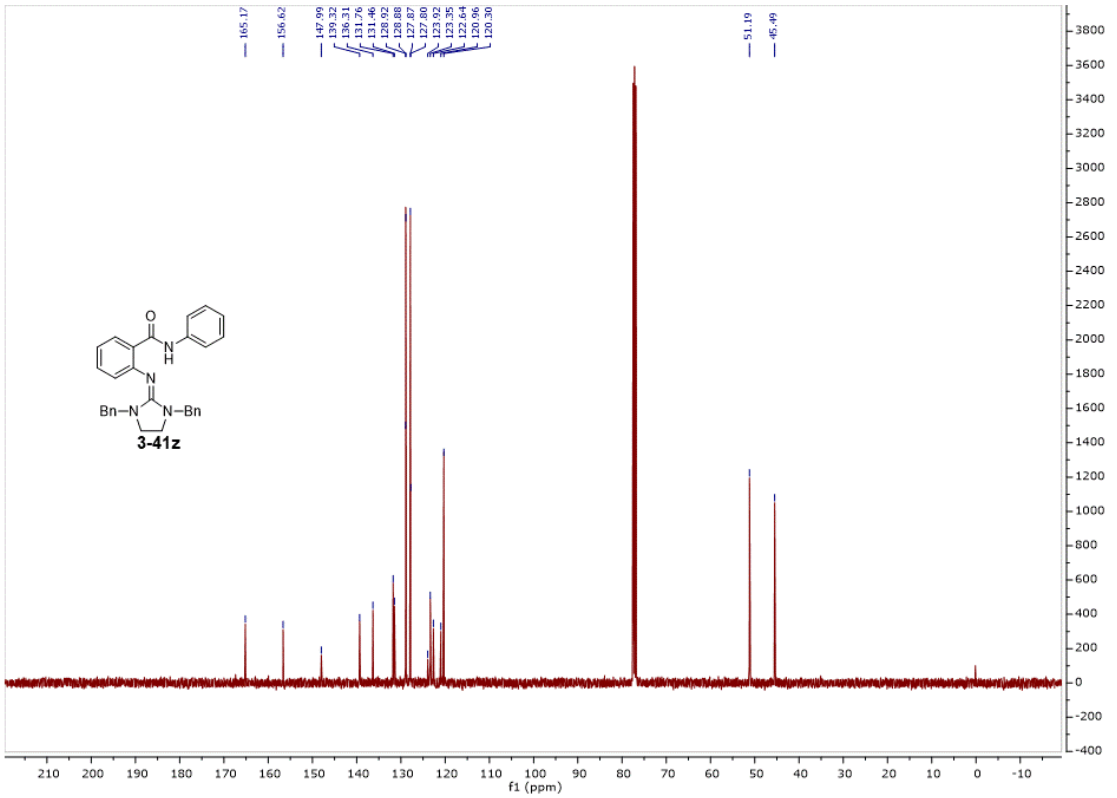

165.93
155.43
150.61
139.96
131.68
131.28
128.92
123.07
122.45
120.65
120.22
118.42
48.70
39.60
22.79
f1 (ppm)

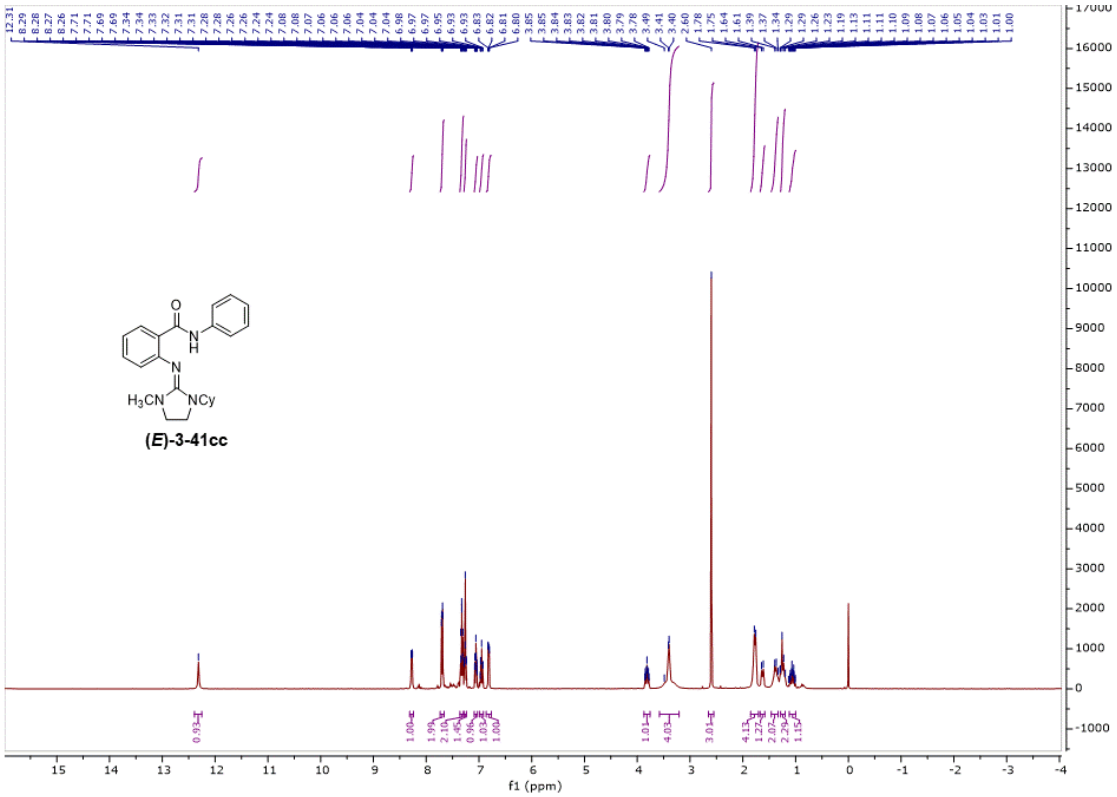
3-41x

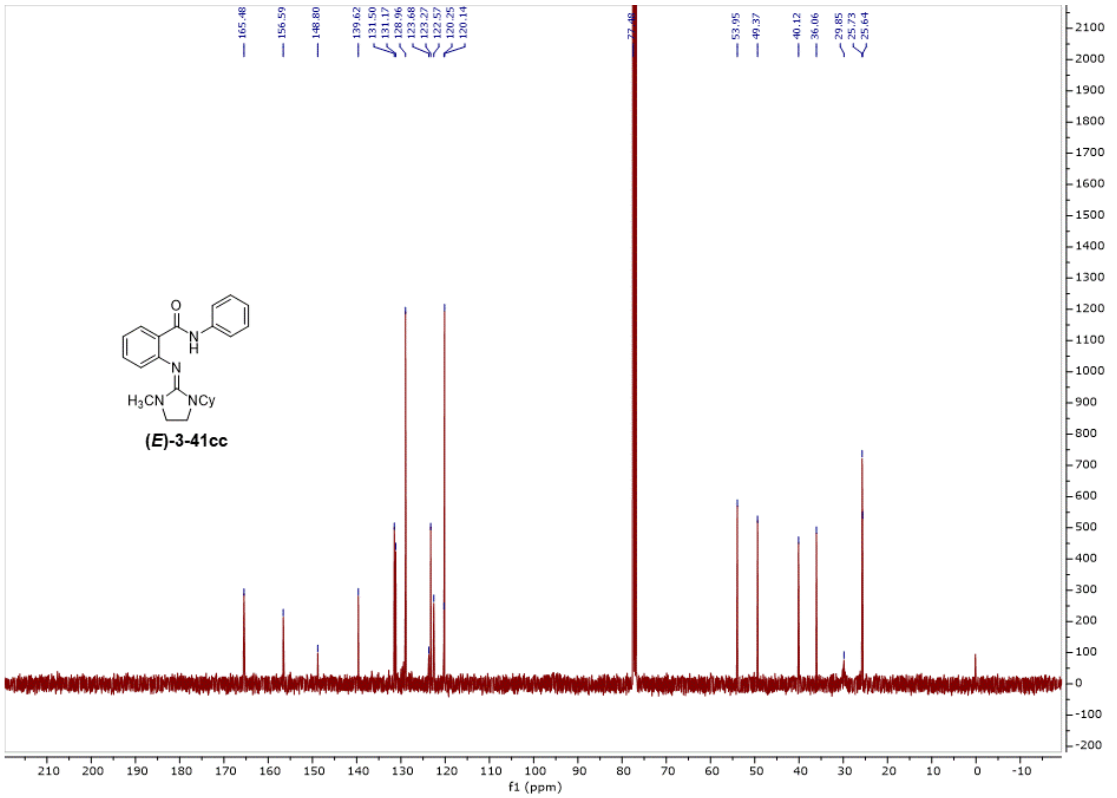

3-41y
f1 (ppm)

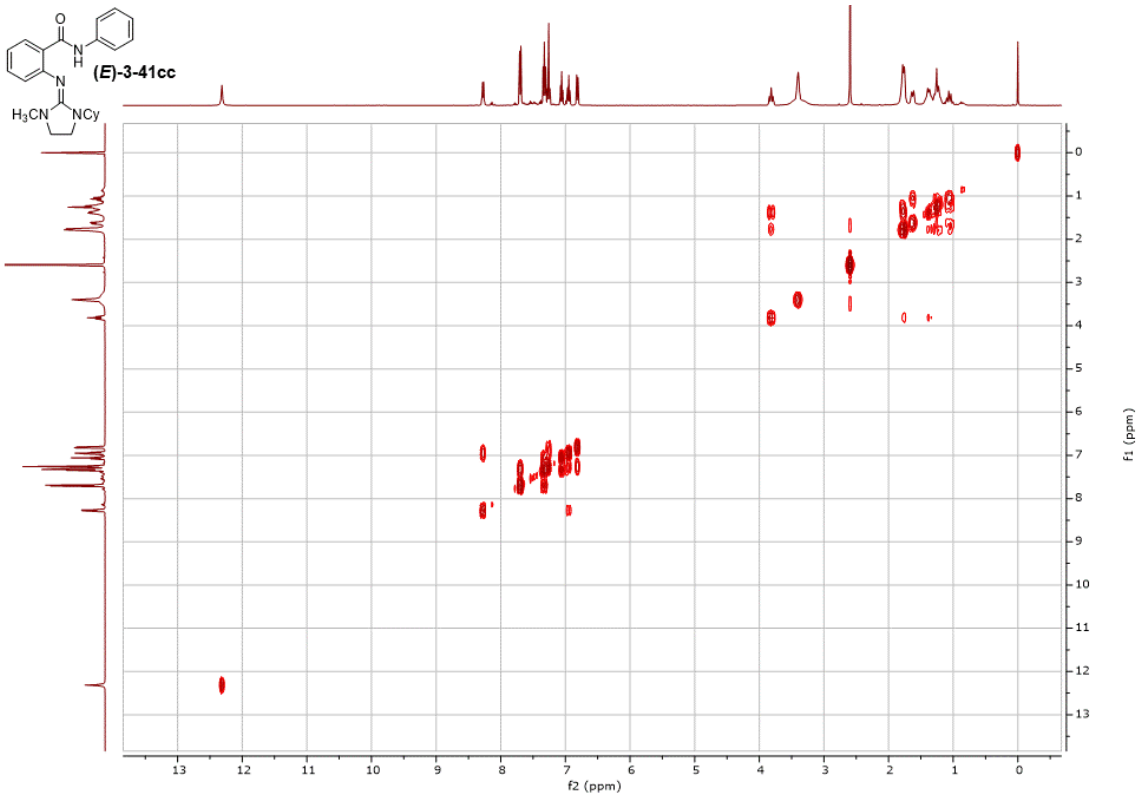

3-41y
f1 (ppm)

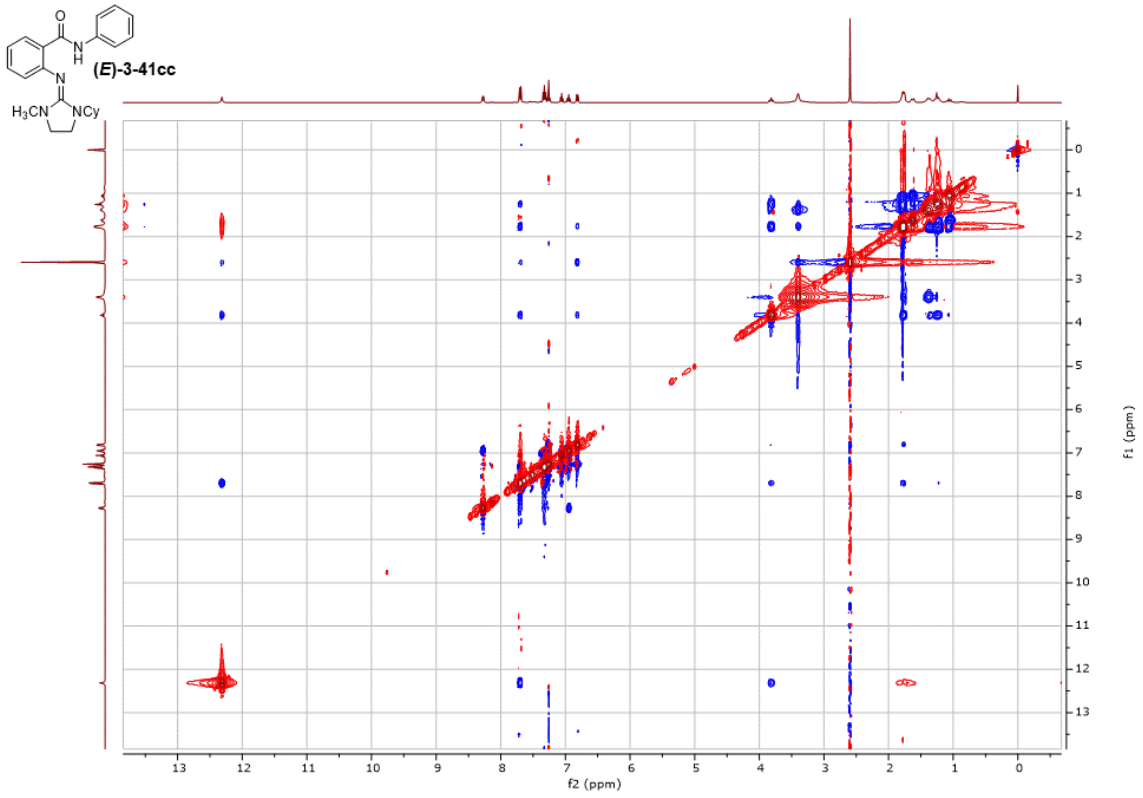

12.01
8.28
8.26
7.58
7.56
7.27
7.25
7.23
7.20
7.18
7.06
7.04
7.02
7.00
6.98
6.96
6.94
4.39
3.34
1.04
1.00
2.10
13.14
3.15
4.03
4.09
f1 (ppm)
3-41z

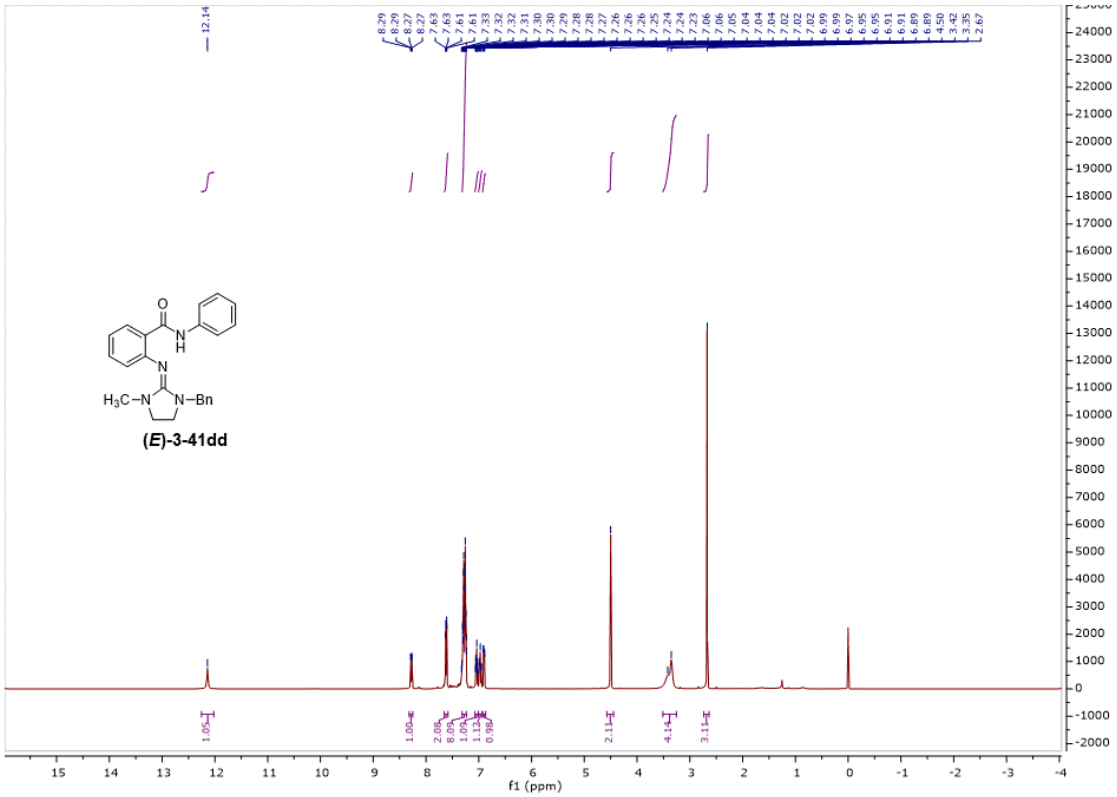

165.17
156.62
147.99
139.32
136.31
131.76
131.46
128.92
128.88
127.87
127.80
123.92
123.35
122.64
120.96
120.30
51.19
46.49
f1 (ppm)
3-41z

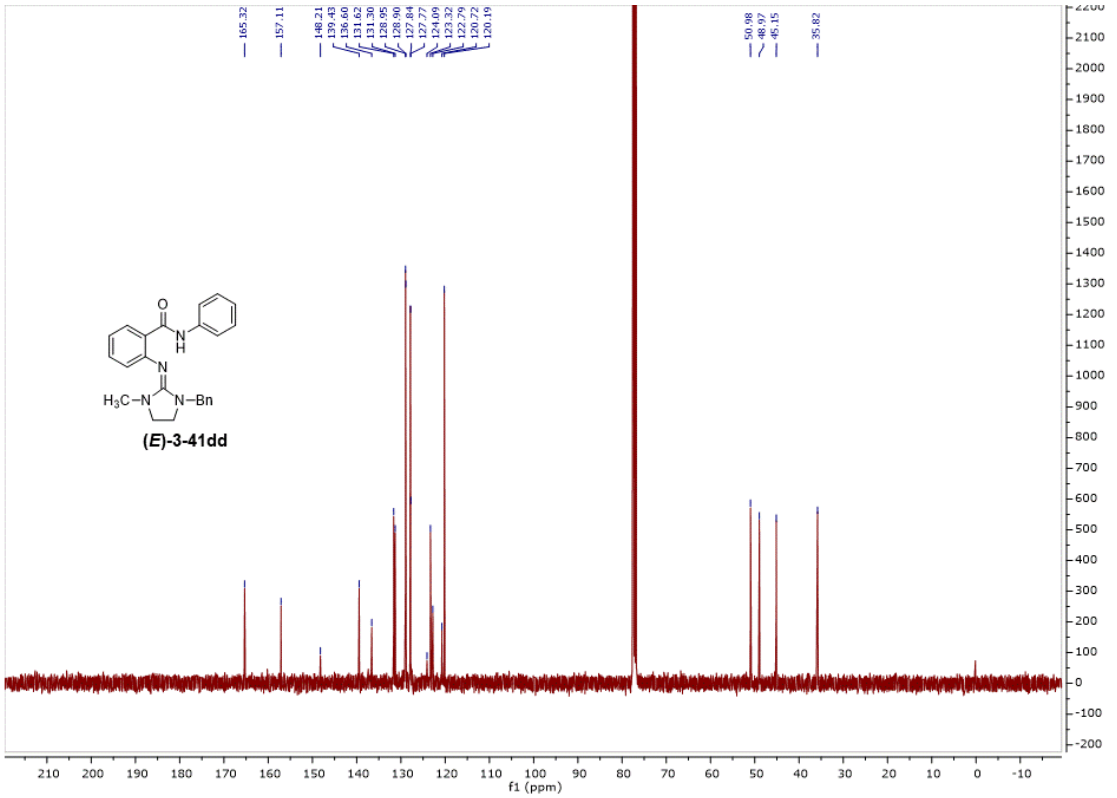

(E)-3-41cc
f1 (ppm)

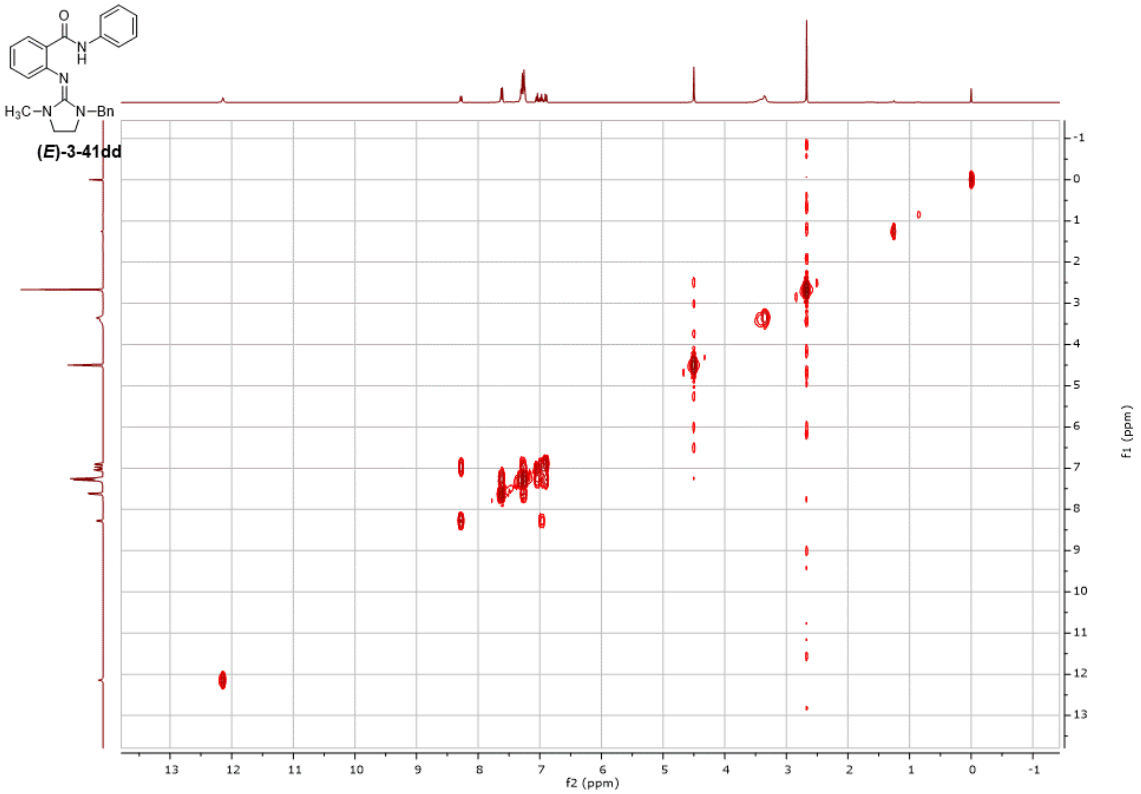

(E)-3-41cc
f1 (ppm)

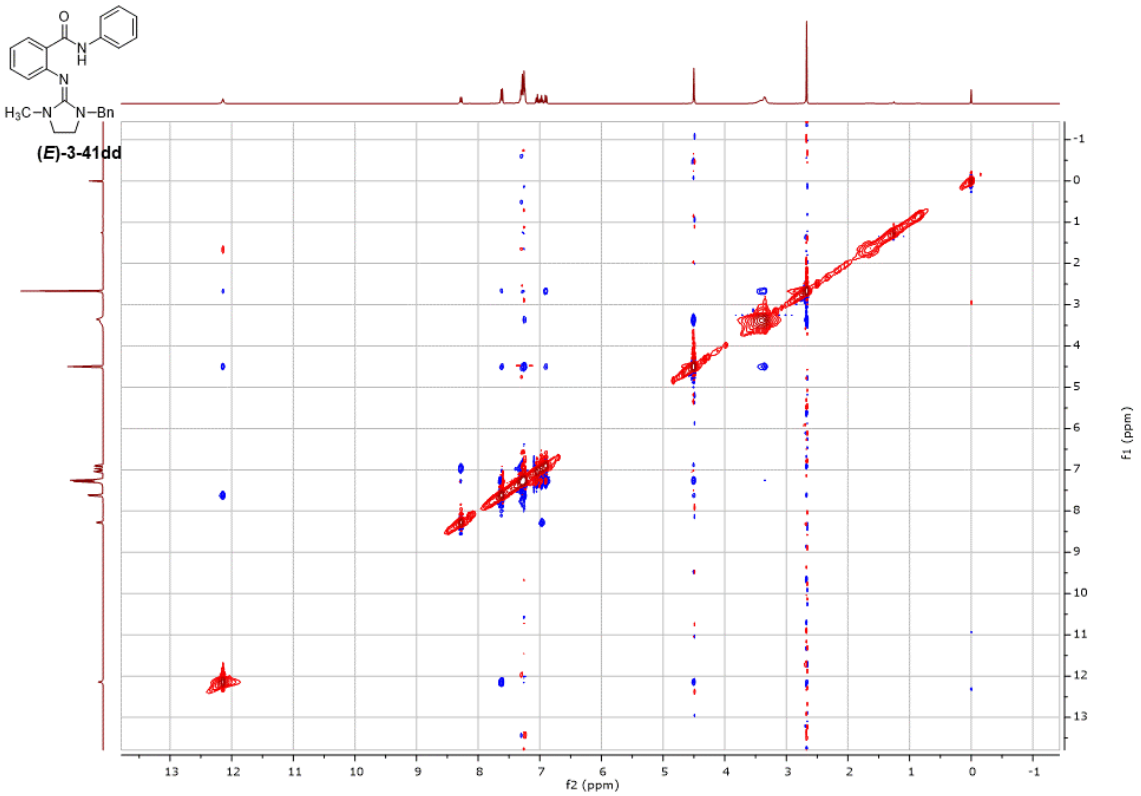

(E)-3-41cc
H3CN
NCy
f2 (ppm)
f1 (ppm)

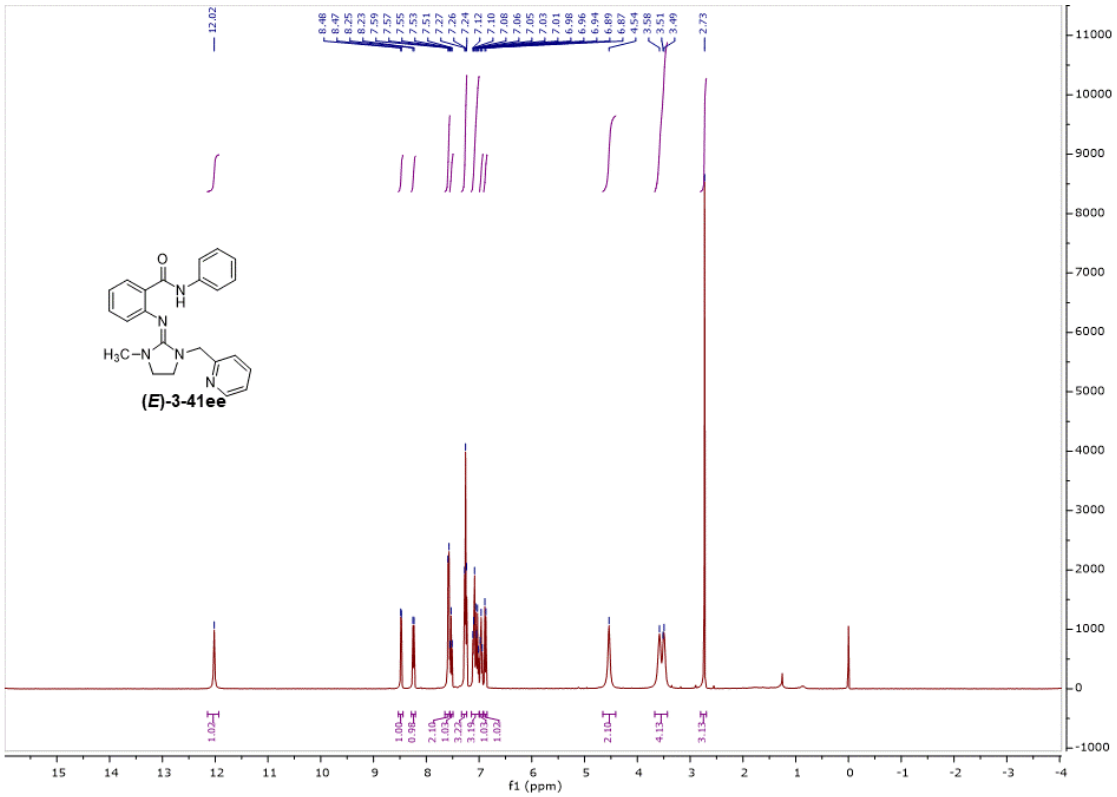

(E)-3-41cc
H3CN
NCy
f2 (ppm)
f1 (ppm)

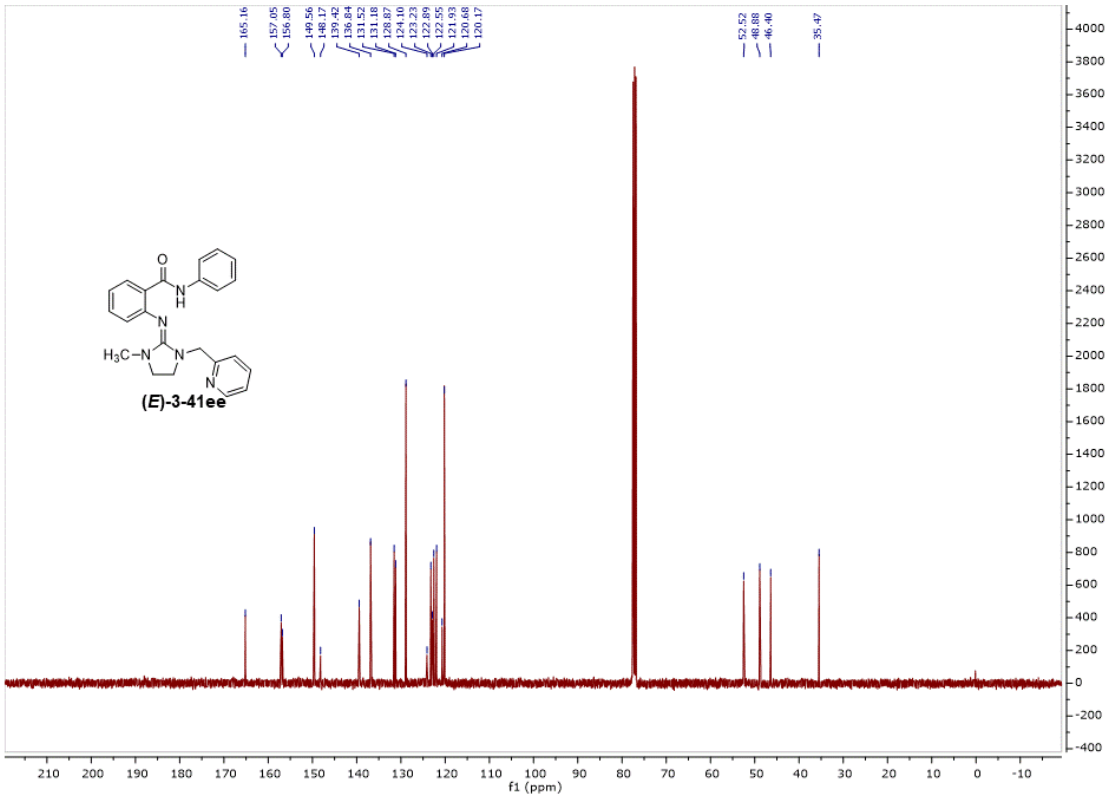

(E)-3-41dd
f1 (ppm)

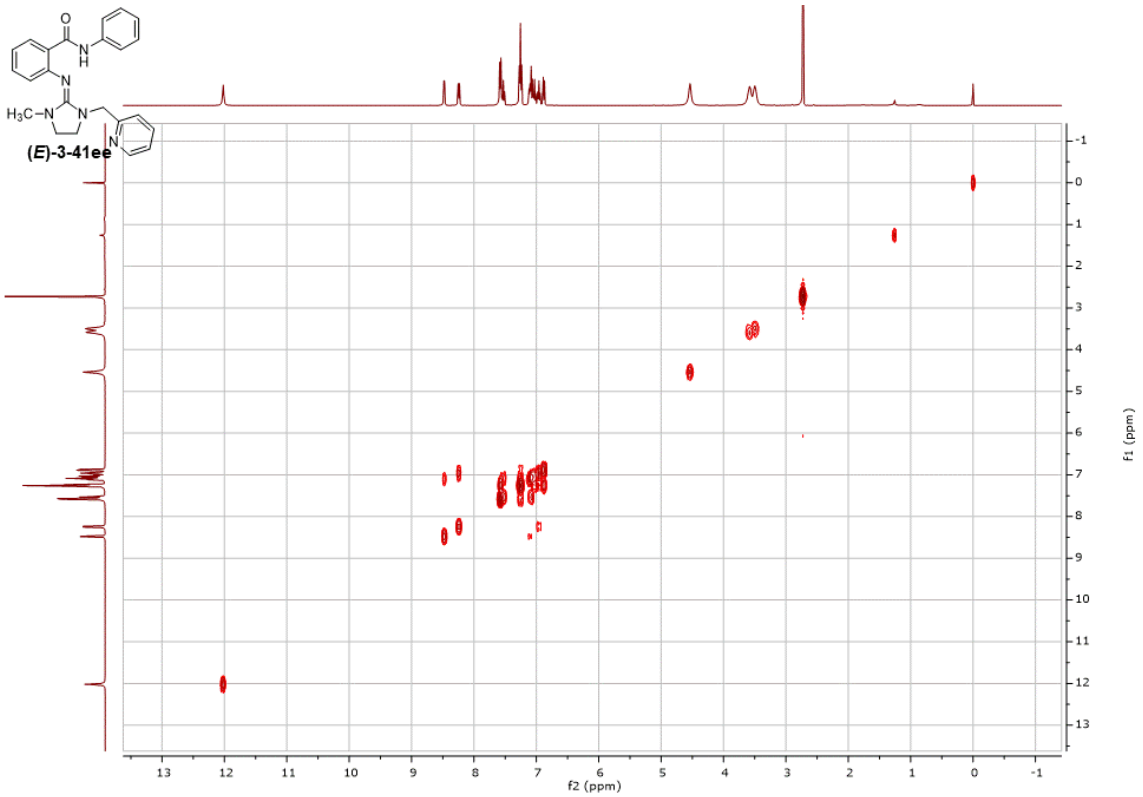

(E)-3-41dd
f1 (ppm)

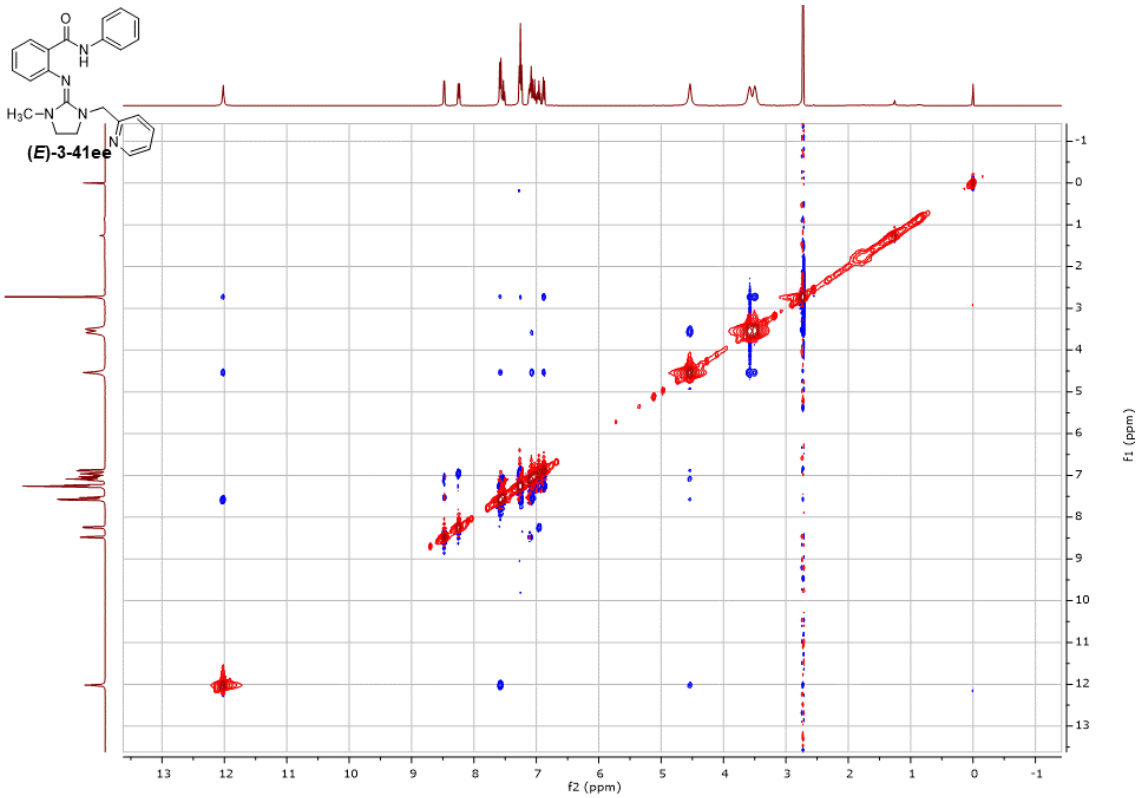

(E)-3-41dd
f2 (ppm)
f1 (ppm)

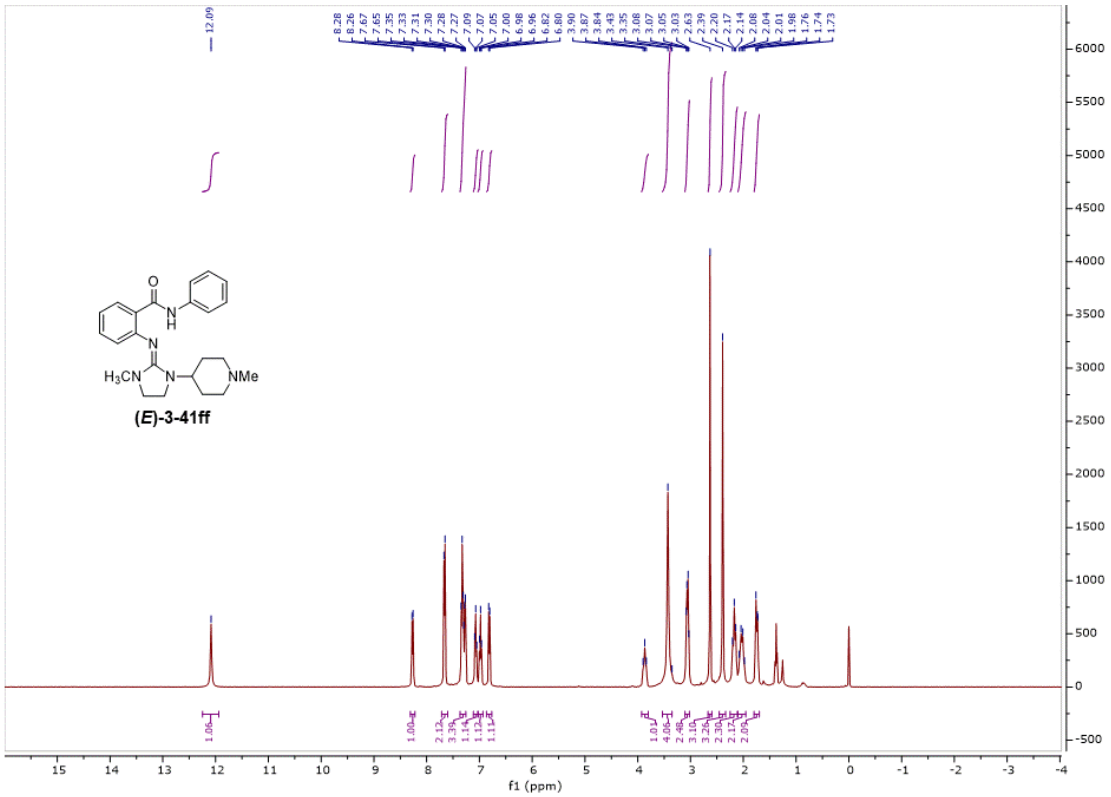

(E)-3-41dd
f2 (ppm)
f1 (ppm)

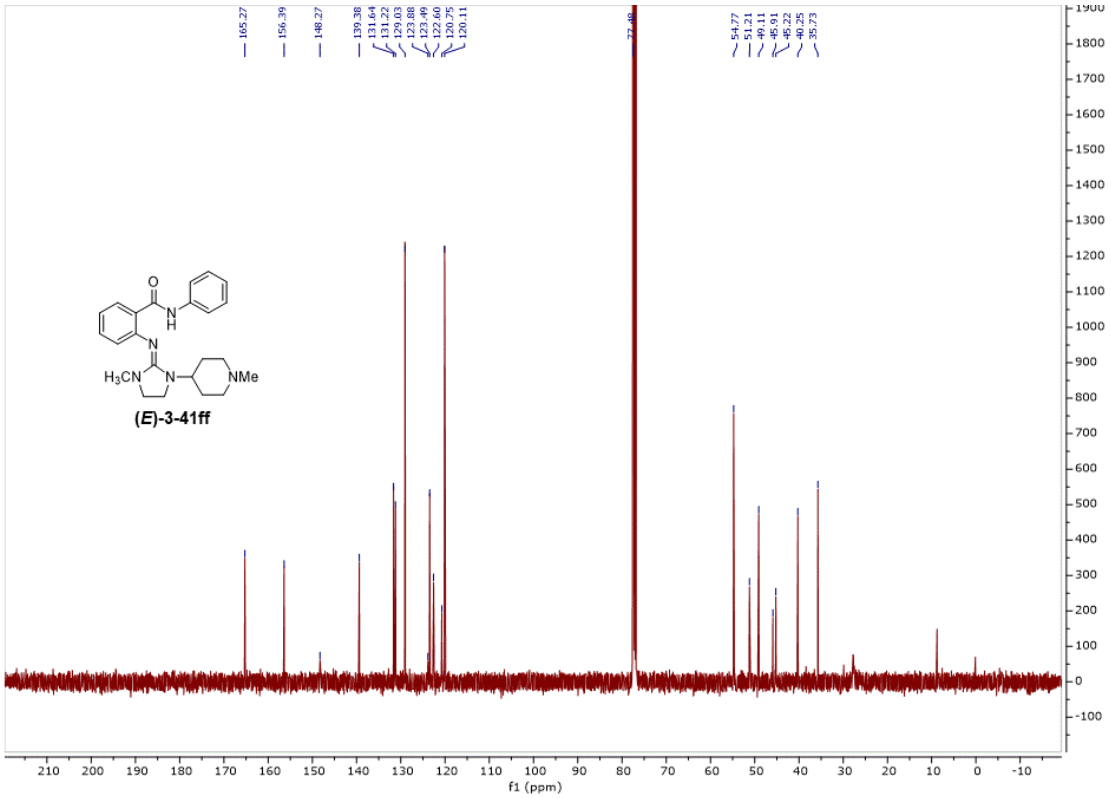

12.02
8.48
8.47
8.25
8.23
7.59
7.57
7.55
7.53
7.51
7.27
7.26
7.24
7.12
7.10
7.08
7.06
7.05
7.03
7.01
6.98
6.96
6.94
6.89
6.87
4.54
3.58
3.51
3.49
2.73
(E)-3-41ee
f1 (ppm)

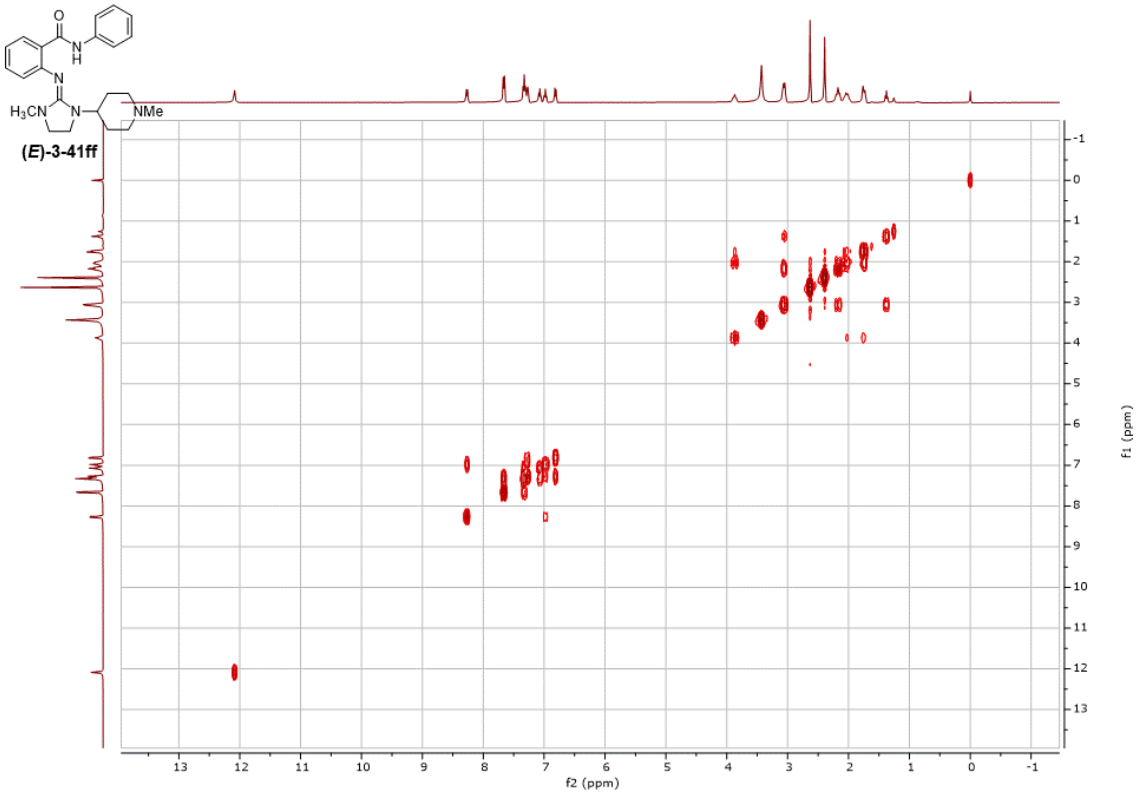

165.16
157.05
156.80
149.56
148.17
139.42
136.84
131.52
131.18
128.87
124.10
123.23
122.89
122.55
121.93
120.68
120.17
52.52
48.88
46.40
35.47
(E)-3-41ee
f1 (ppm)

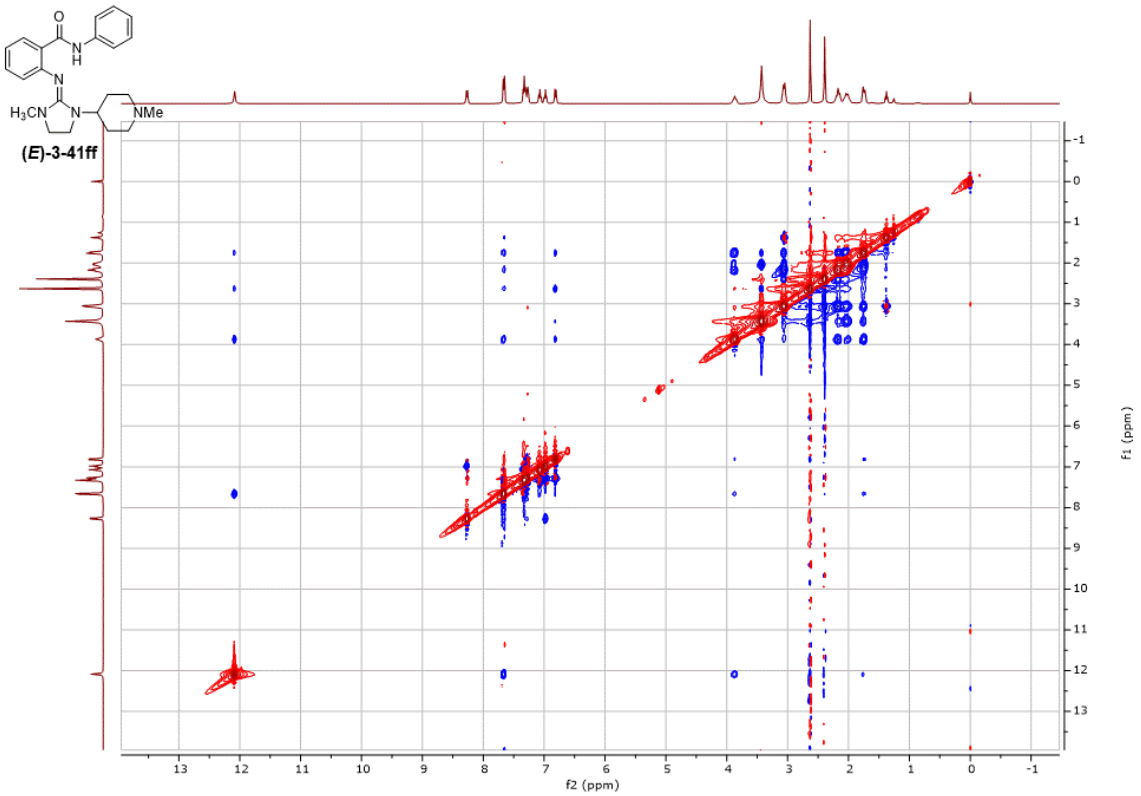

(E)-3-41ee
f2 (ppm)
f1 (ppm)

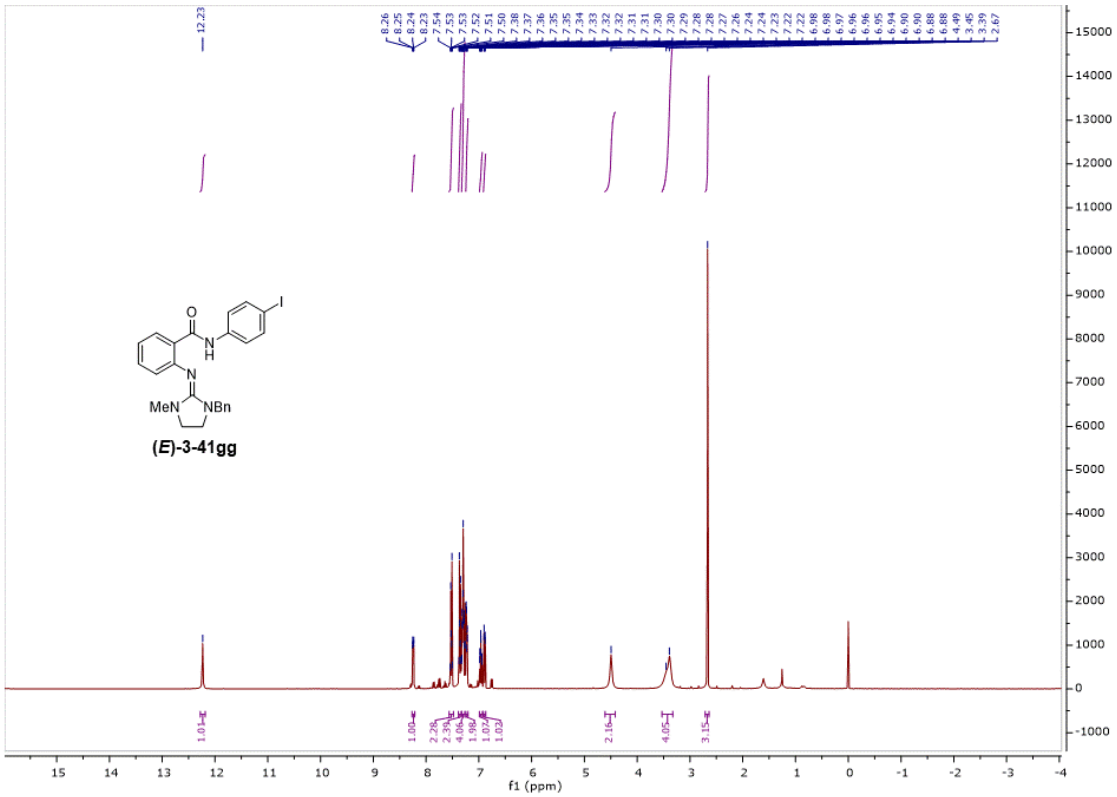

(E)-3-41ee
f2 (ppm)
f1 (ppm)

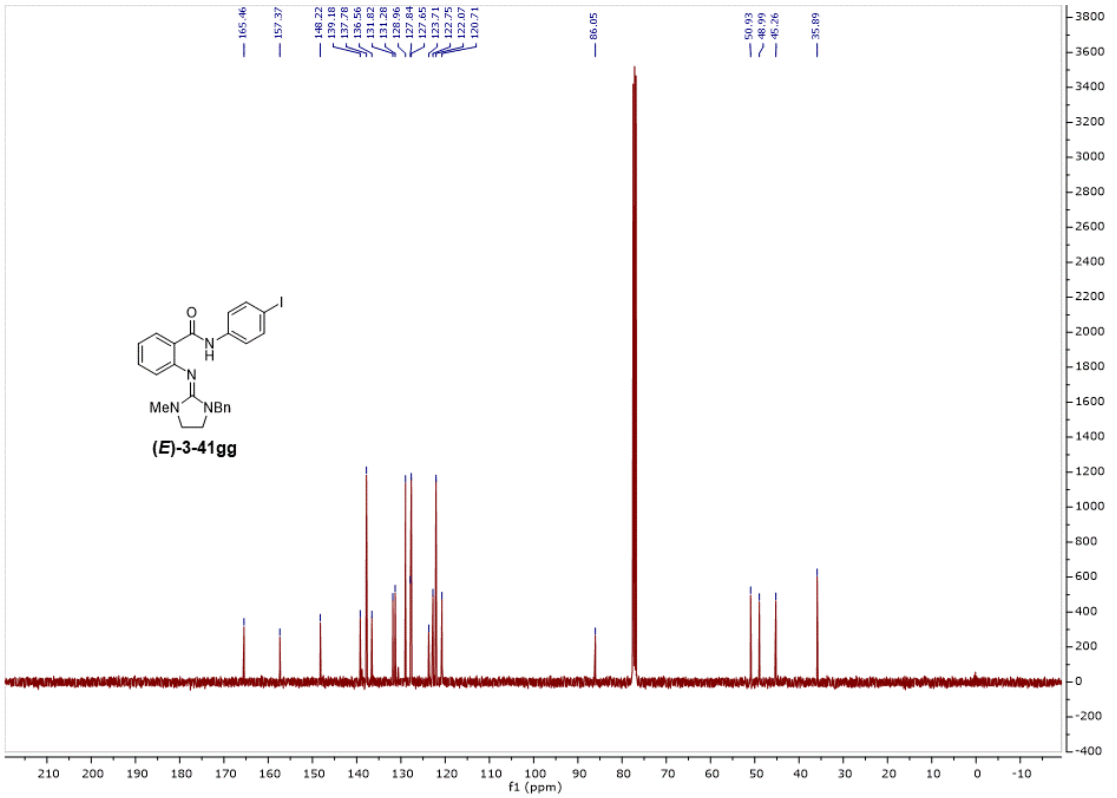

12.09
8.28
8.26
7.67
7.65
7.35
7.33
7.31
7.30
7.28
7.27
7.09
7.07
7.05
7.00
6.98
6.96
6.82
6.80
3.90
3.87
3.84
3.43
3.35
3.08
3.07
3.05
3.03
2.63
2.39
2.20
2.17
2.14
2.08
2.04
2.01
1.98
1.76
1.74
1.73
1.06
1.00
2.12
3.39
1.14
1.12
1.11
1.01
4.06
4.48
2.10
3.26
2.30
2.12
2.04
H3CN
NMe
(E)-3-41ff
f1 (ppm)

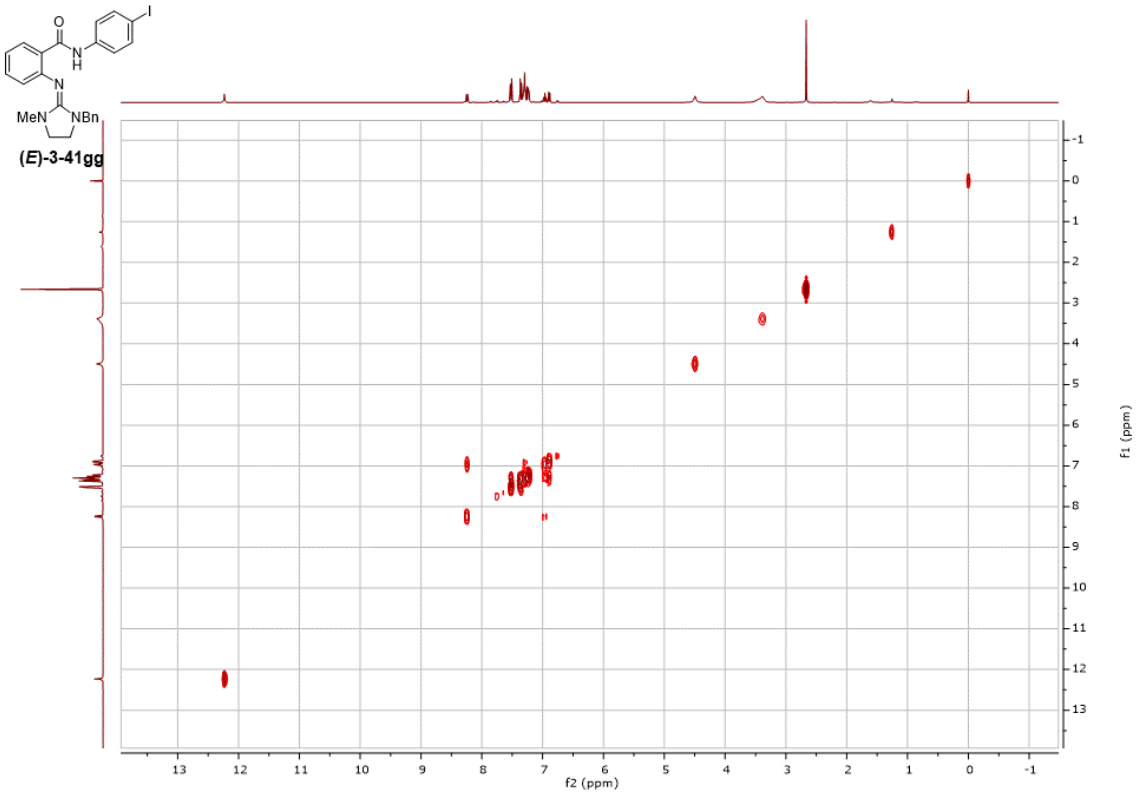

165.27
156.39
148.27
139.38
131.64
131.22
129.03
123.88
123.49
122.60
120.75
120.11
77.48
54.77
51.21
49.11
45.91
45.22
40.25
35.73
H3CN
NMe
(E)-3-41ff
f1 (ppm)

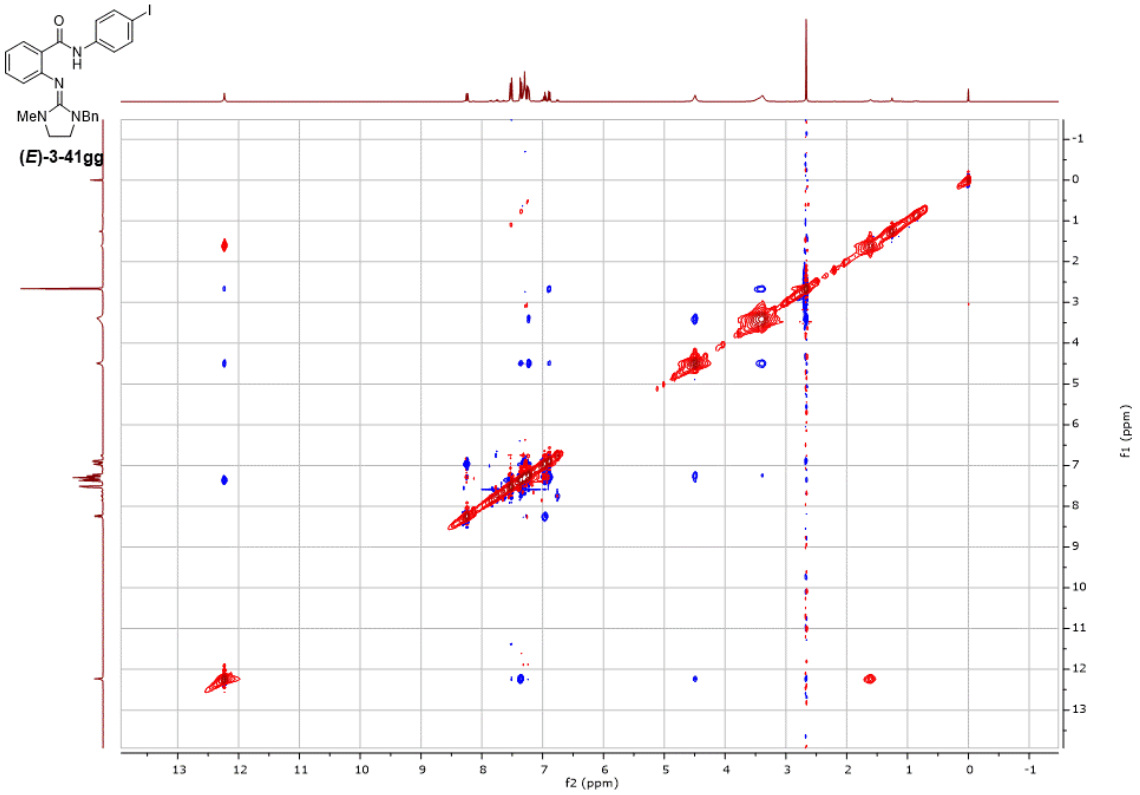

(E)-3-41ff
NMe
f2 (ppm)
f1 (ppm)

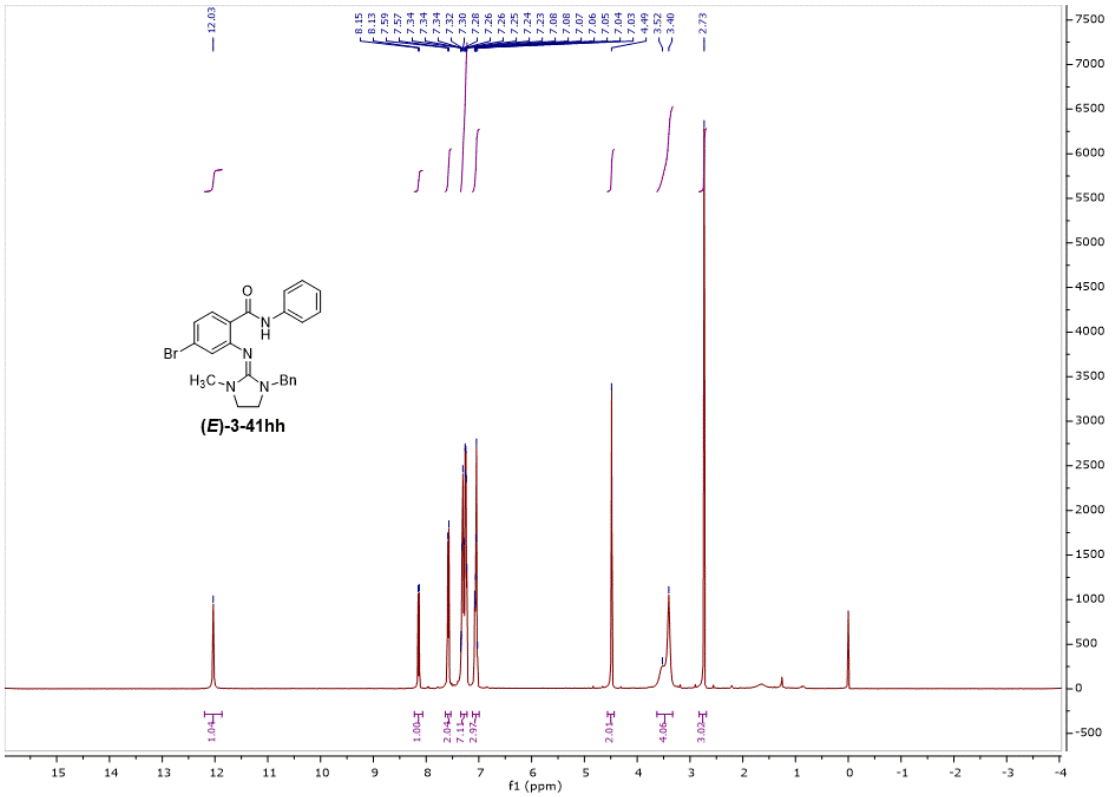

(E)-3-41ff
NMe
f2 (ppm)
f1 (ppm)

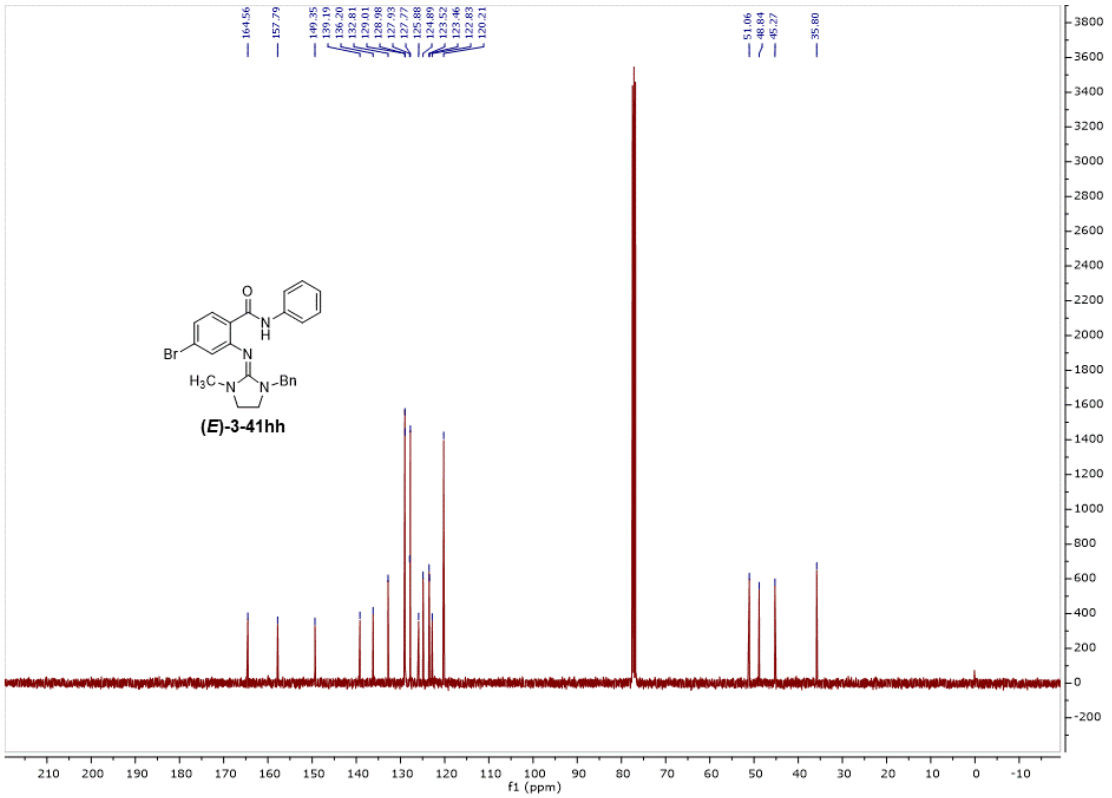

12.23
8.26
8.25
8.24
8.23
7.54
7.53
7.52
7.51
7.50
7.38
7.37
7.36
7.35
7.34
7.33
7.32
7.31
7.30
7.29
7.28
7.27
7.25
7.24
7.23
7.22
6.98
6.97
6.96
6.95
6.94
6.90
6.89
6.88
4.49
3.45
3.39
2.67
1.01
1.00
2.28
2.39
4.06
1.98
1.07
1.02
2.16
4.05
3.15
O
N
H
I
N
MeN
NBn
(E)-3-41gg
f1 (ppm)

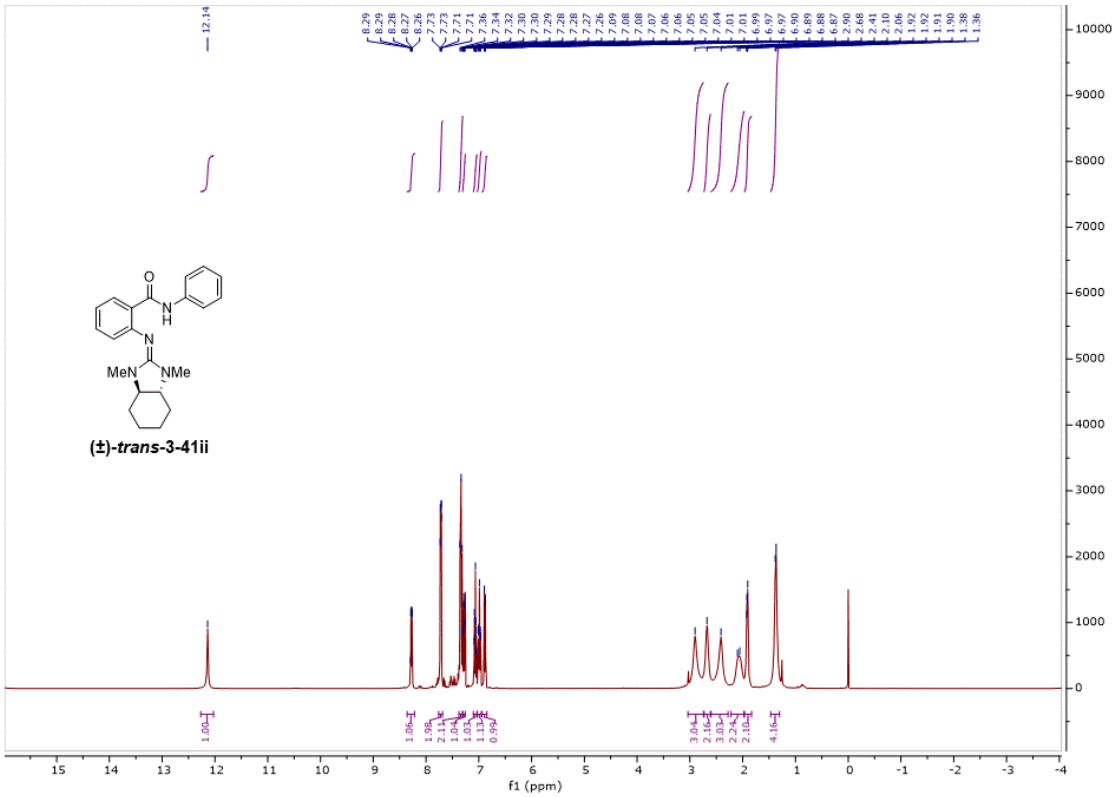

165.46
157.37
140.22
139.18
137.78
136.56
131.82
131.28
128.96
127.84
127.65
123.71
122.75
122.07
120.71
86.05
50.93
48.99
45.26
35.89
O
N
H
I
N
MeN
NBn
(E)-3-41gg
f1 (ppm)

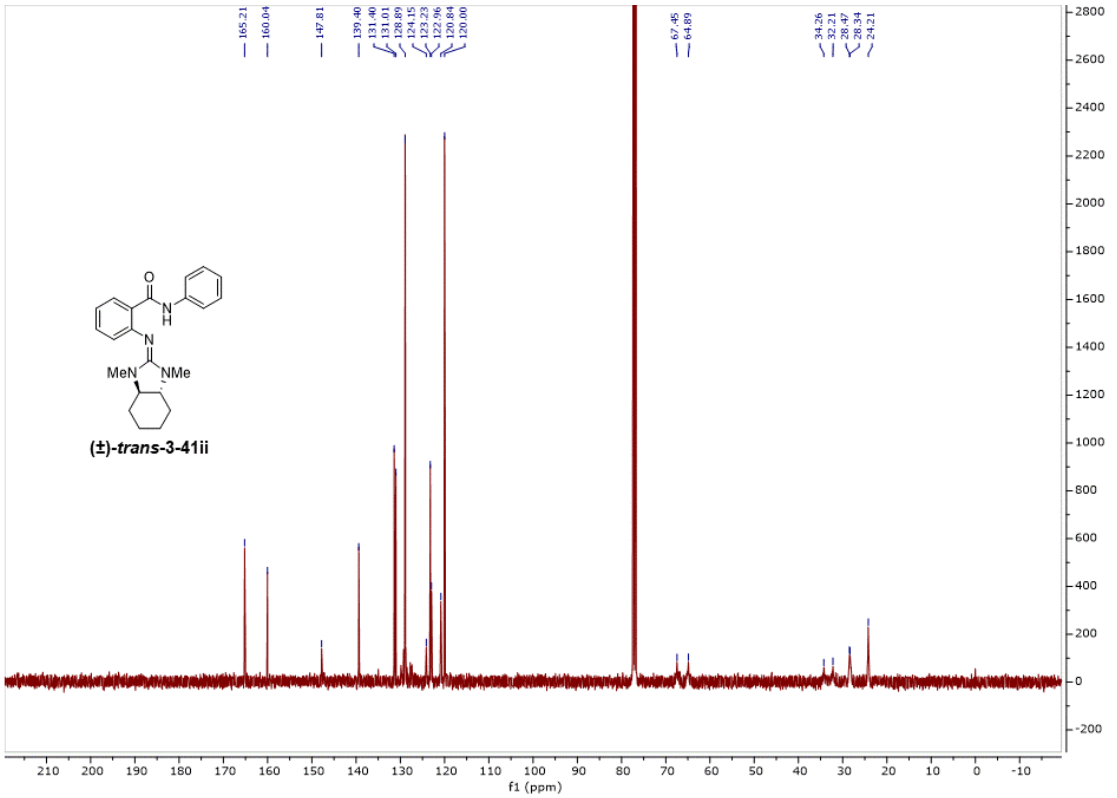

(E)-3-41gg
f2 (ppm)
f1 (ppm)

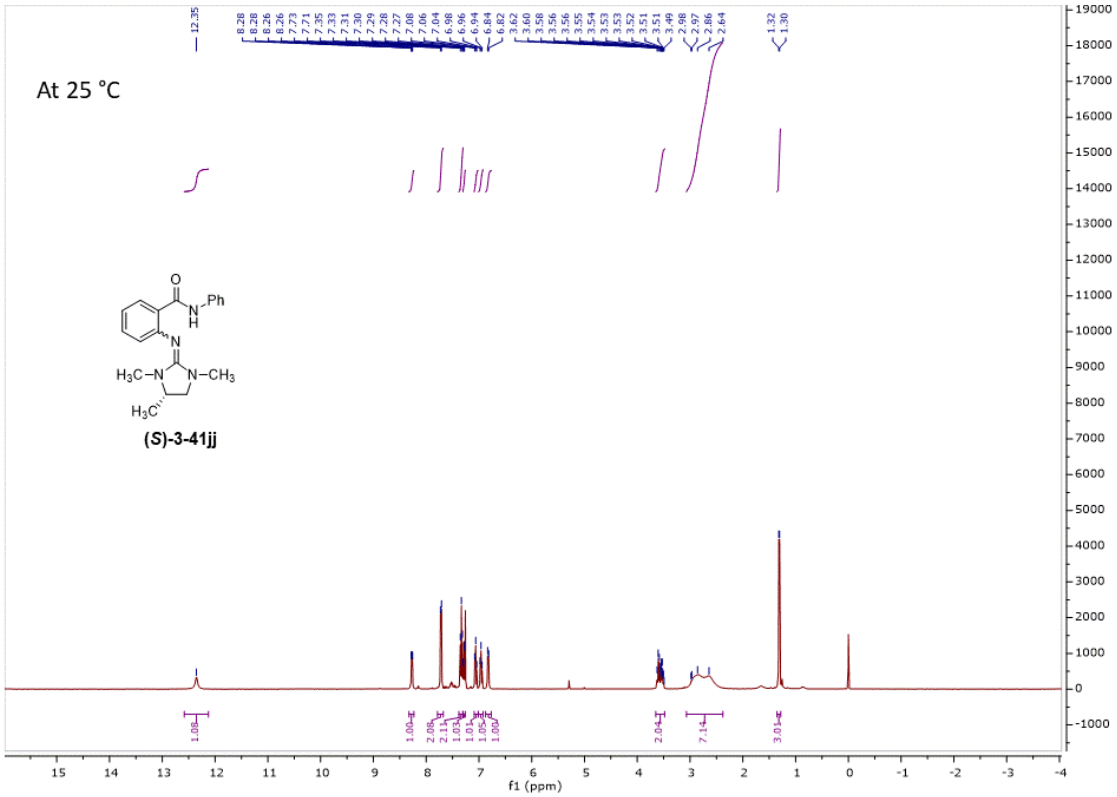

(E)-3-41gg
f2 (ppm)
f1 (ppm)

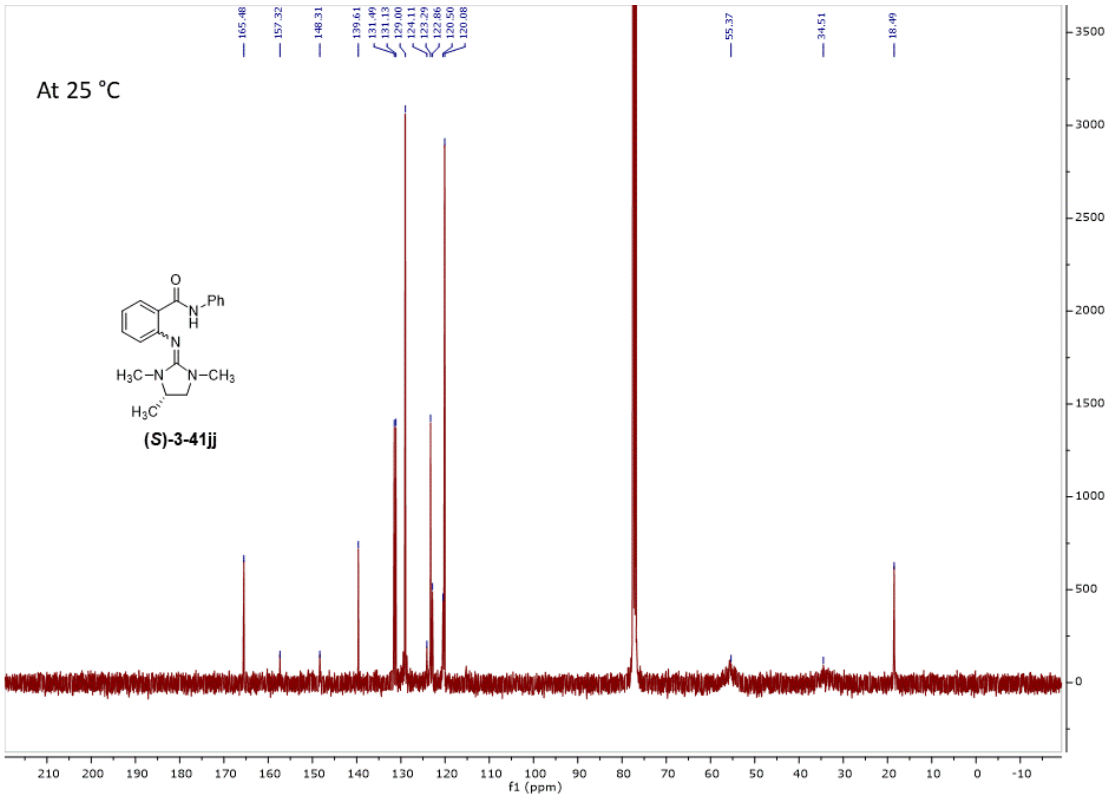

12.03
8.15
8.13
7.59
7.57
7.34
7.34
7.34
7.32
7.30
7.28
7.26
7.26
7.25
7.24
7.23
7.08
7.07
7.06
7.05
7.04
7.03
4.49
3.52
3.40
2.73
1.04
1.00
2.04
7.11
2.97
2.01
4.06
3.02
f1 (ppm)
(E)-3-41hh

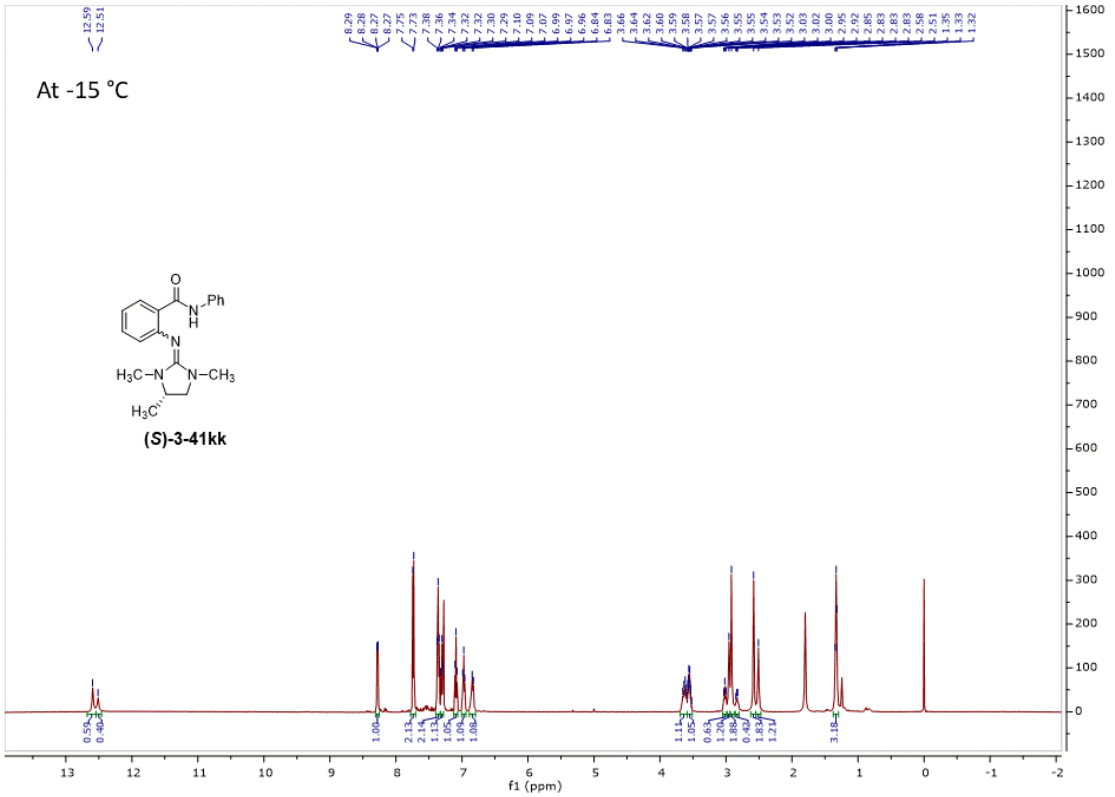

164.56
157.79
149.35
139.19
136.20
132.81
129.01
128.98
127.93
127.77
125.88
124.89
123.52
123.46
122.83
120.21
51.06
48.84
45.27
35.80
f1 (ppm)
(E)-3-41hh

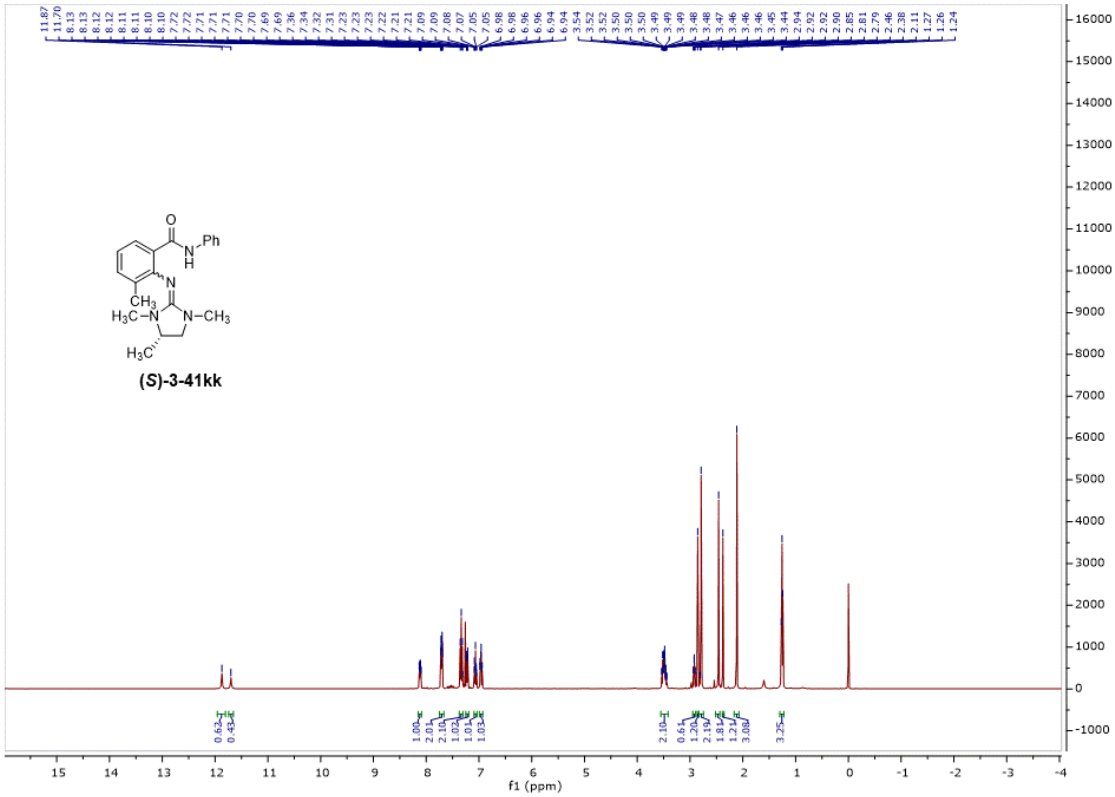

(±)-*trans*-3-41ii
f1 (ppm)

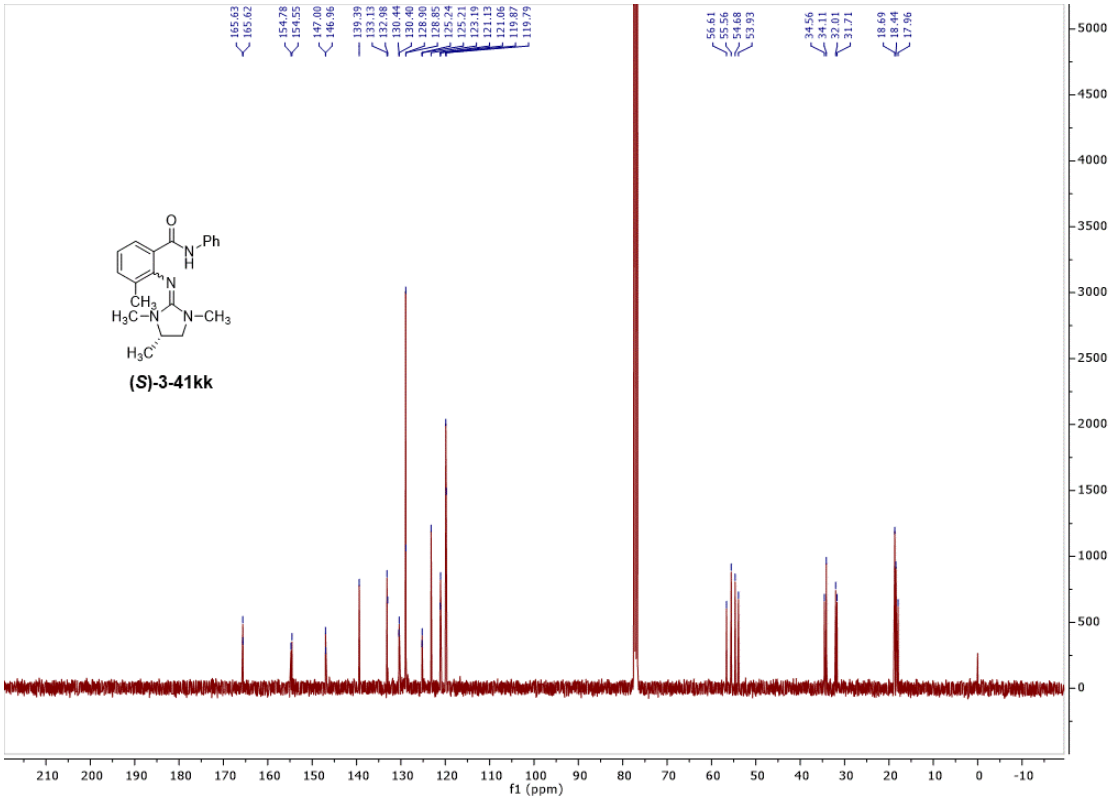

(±)-*trans*-3-41ii
f1 (ppm)

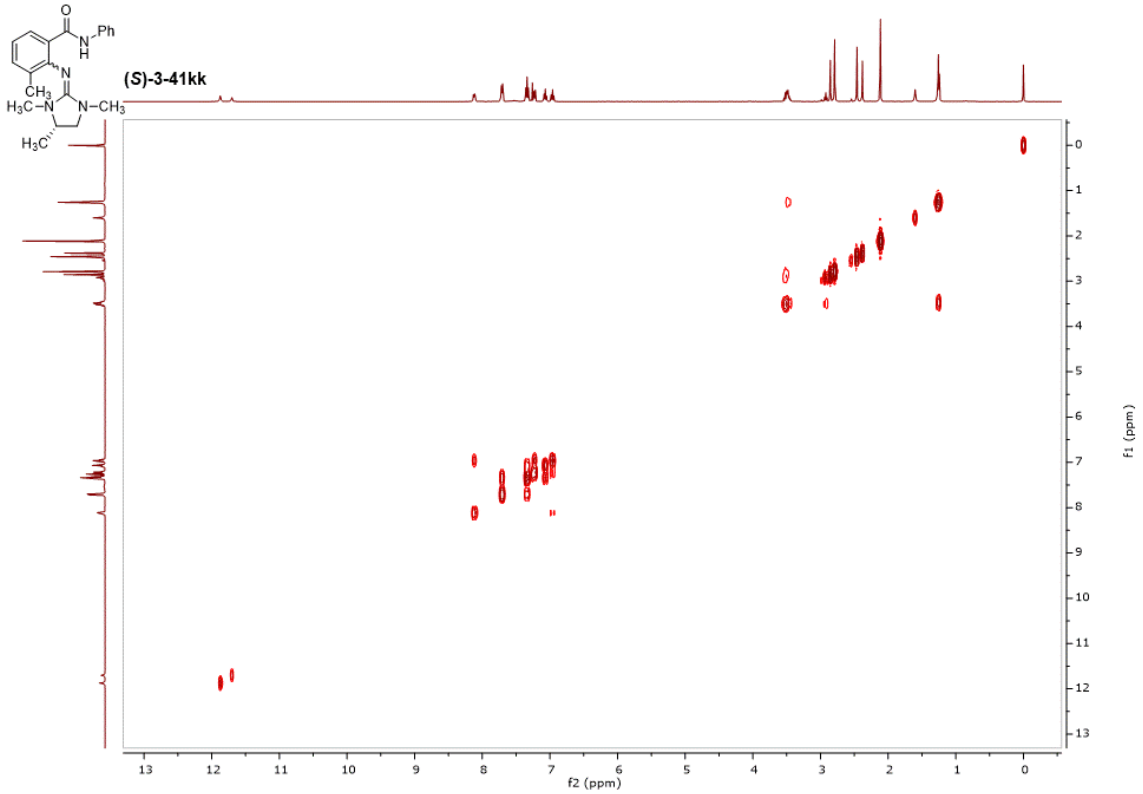

At 25 °C
(S)-3-41jj
f1 (ppm)

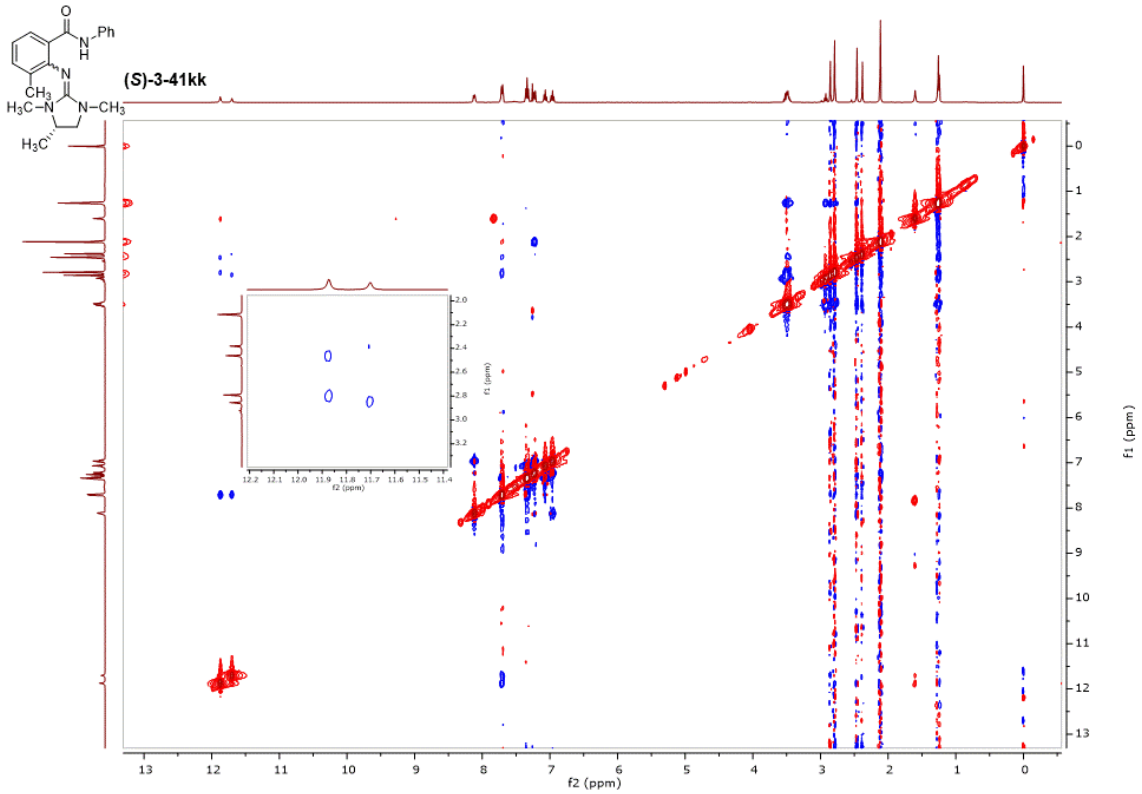

At 25 °C
(S)-3-41jj
f1 (ppm)

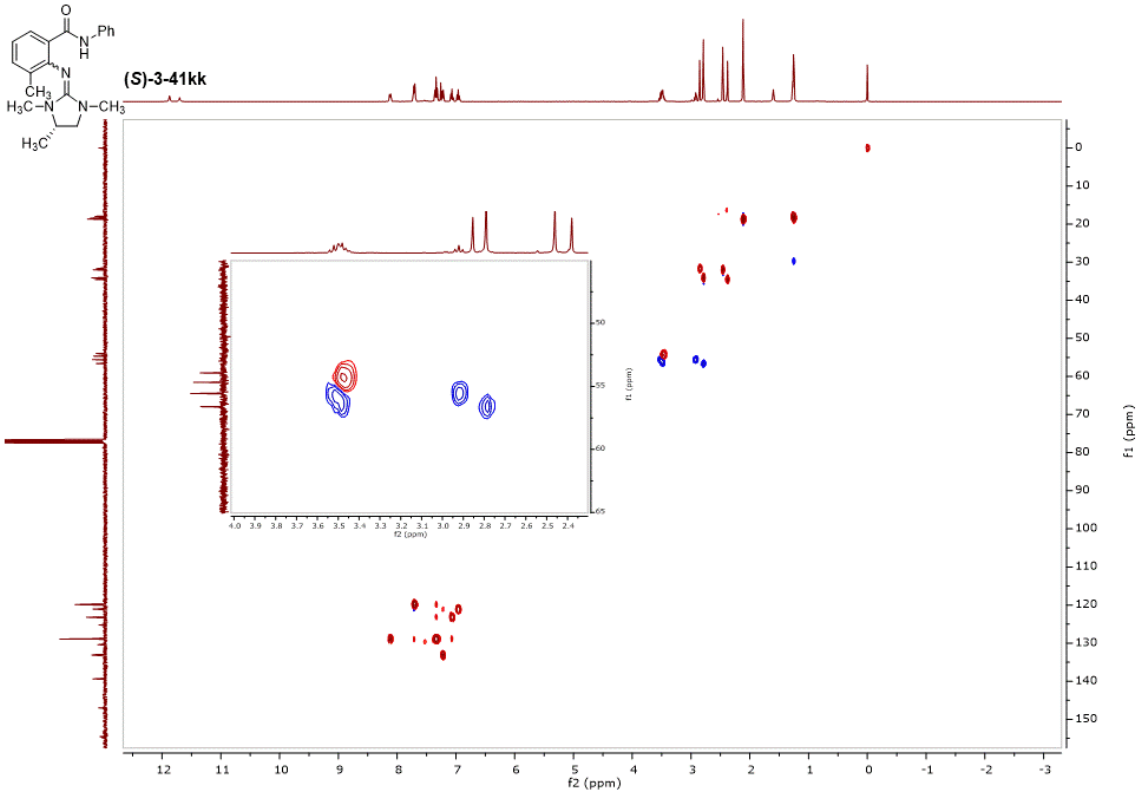

At -15 °C
(S)-3-41kk
f1 (ppm)

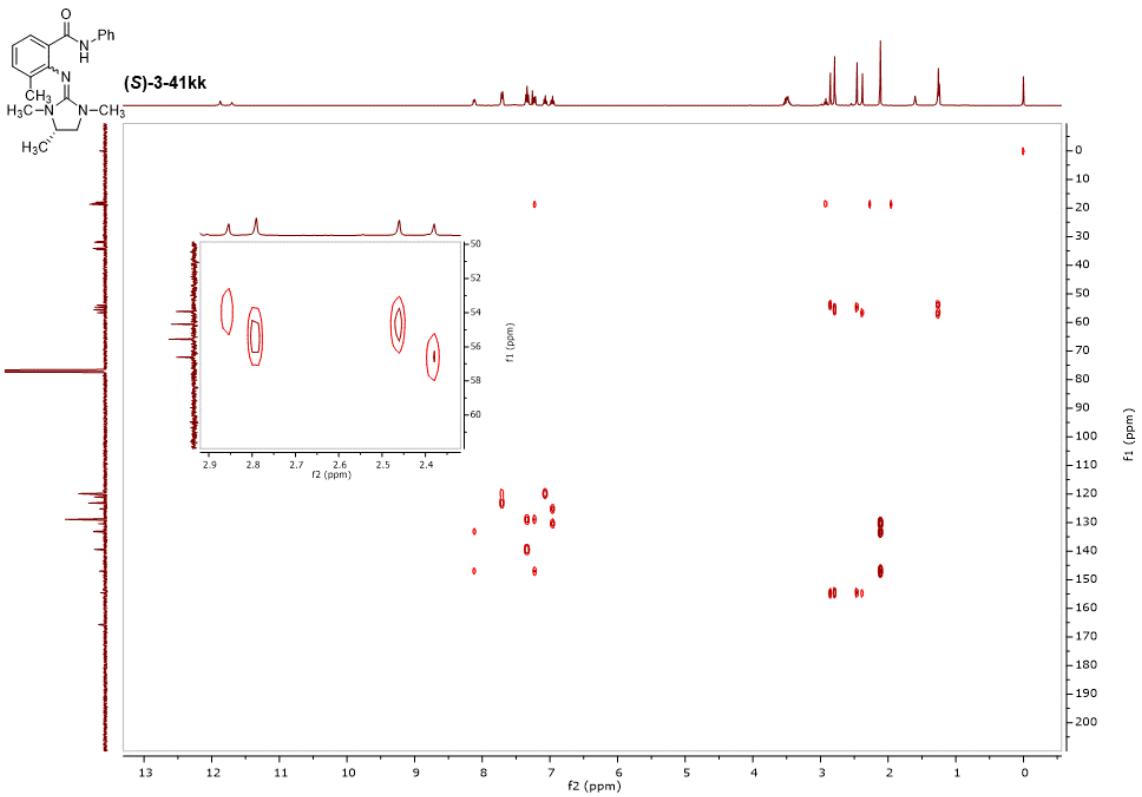

(S)-3-41kk
f1 (ppm)

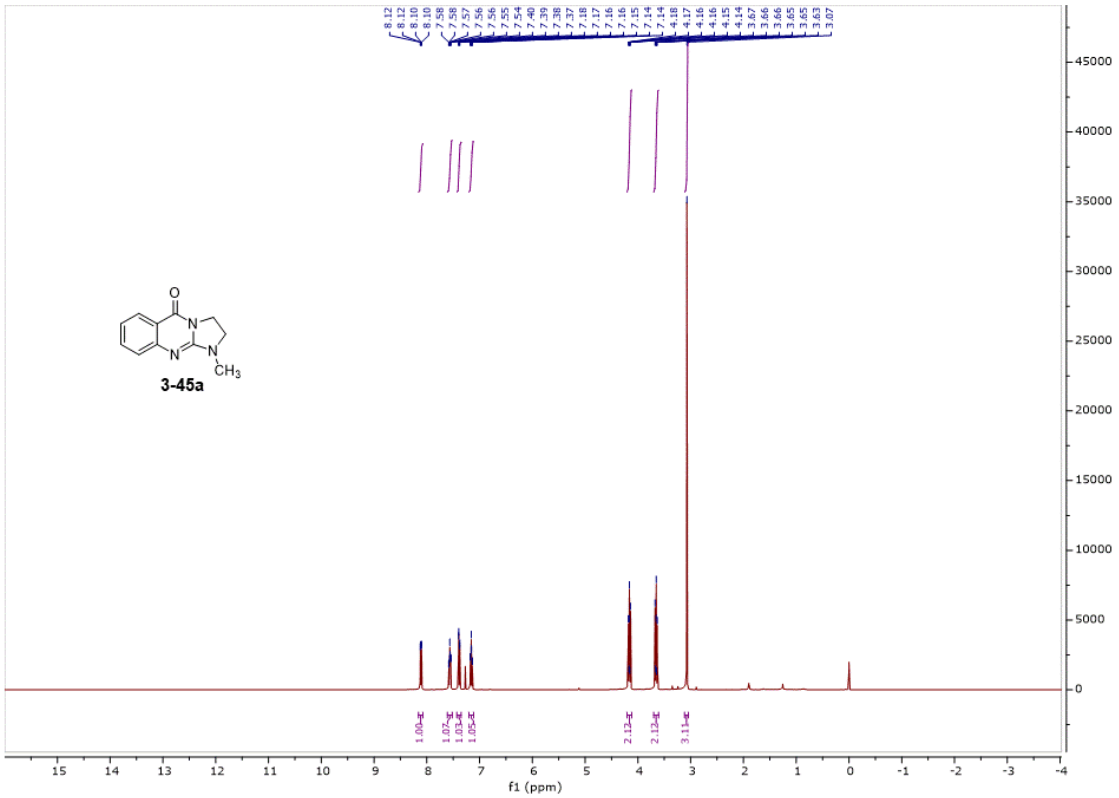

(S)-3-41kk
f1 (ppm)

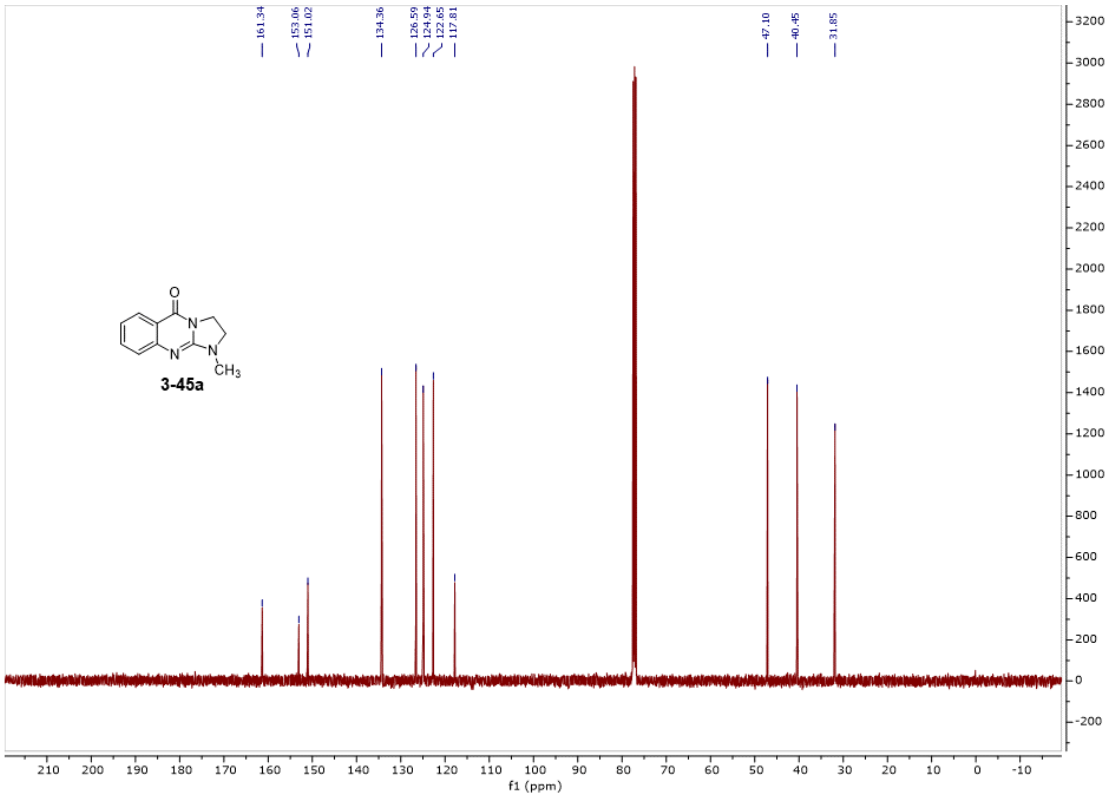

(S)-3-41kk
f2 (ppm)
f1 (ppm)

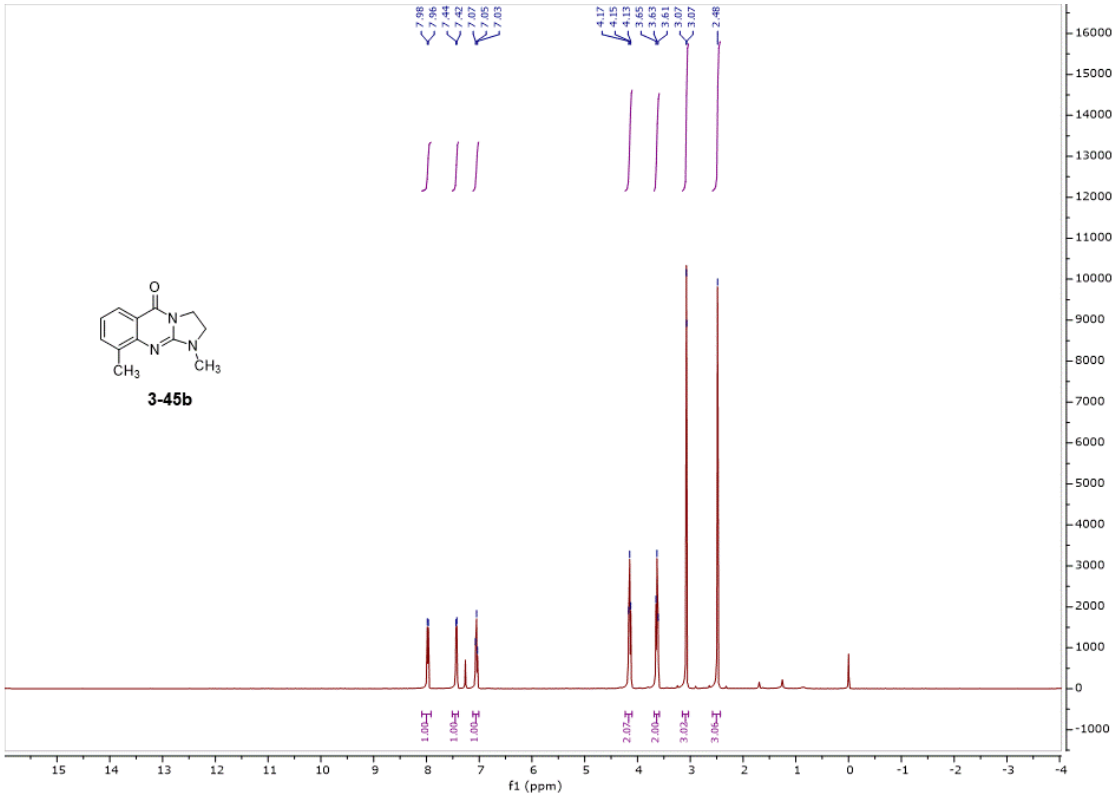

(S)-3-41kk
f2 (ppm)
f1 (ppm)

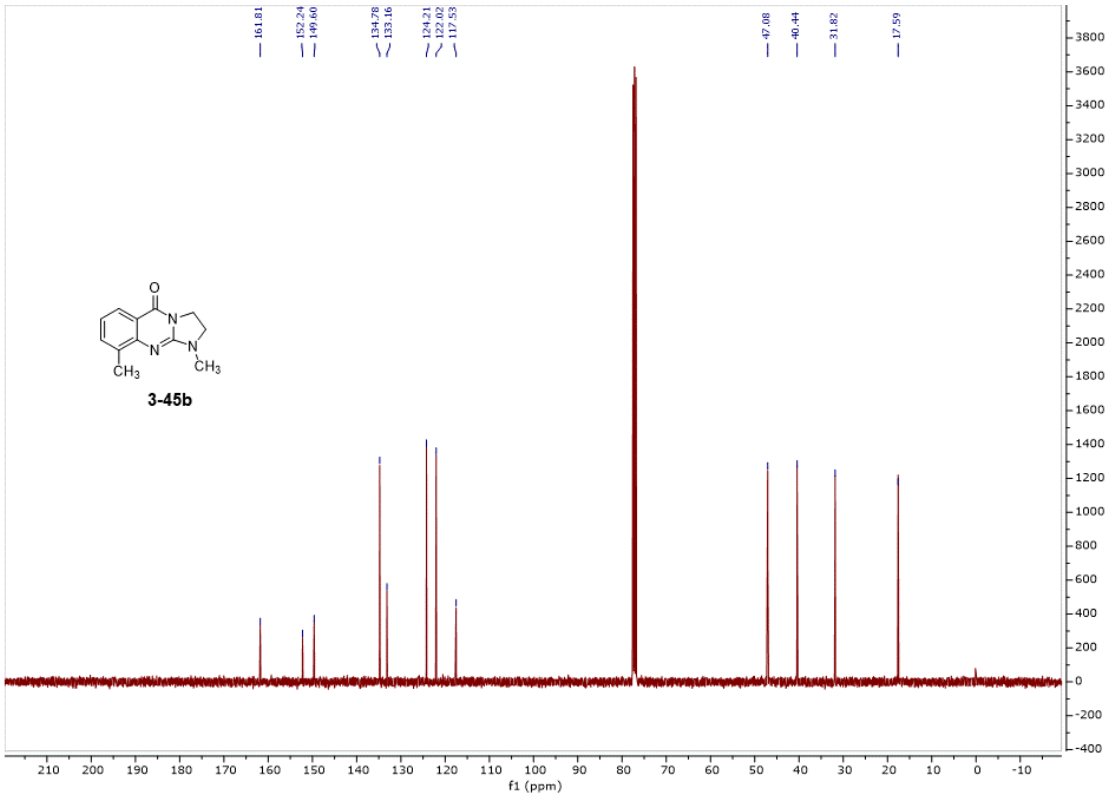

(S)-3-41kk
f2 (ppm)
f1 (ppm)


(S)-3-41kk
f2 (ppm)
f1 (ppm)

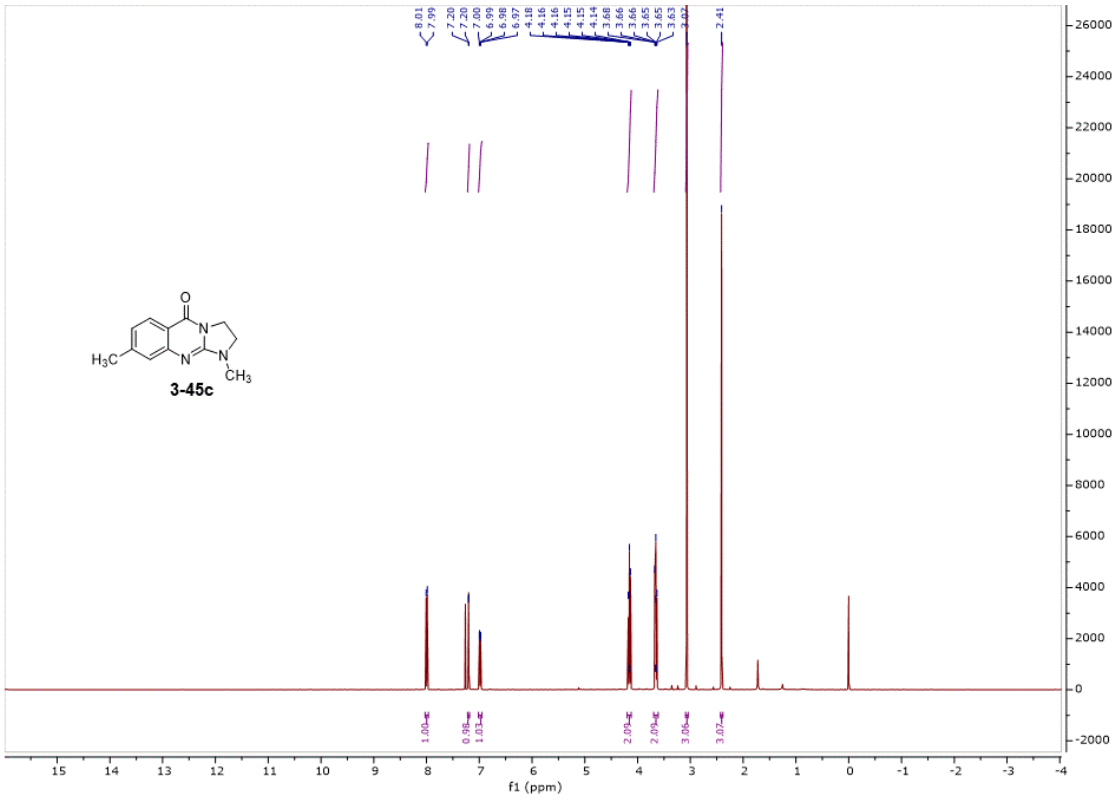

3-45a
f1 (ppm)


161.34
153.06
151.02
134.36
126.59
124.94
122.65
117.81
47.10
40.45
31.85
3-45a
f1 (ppm)

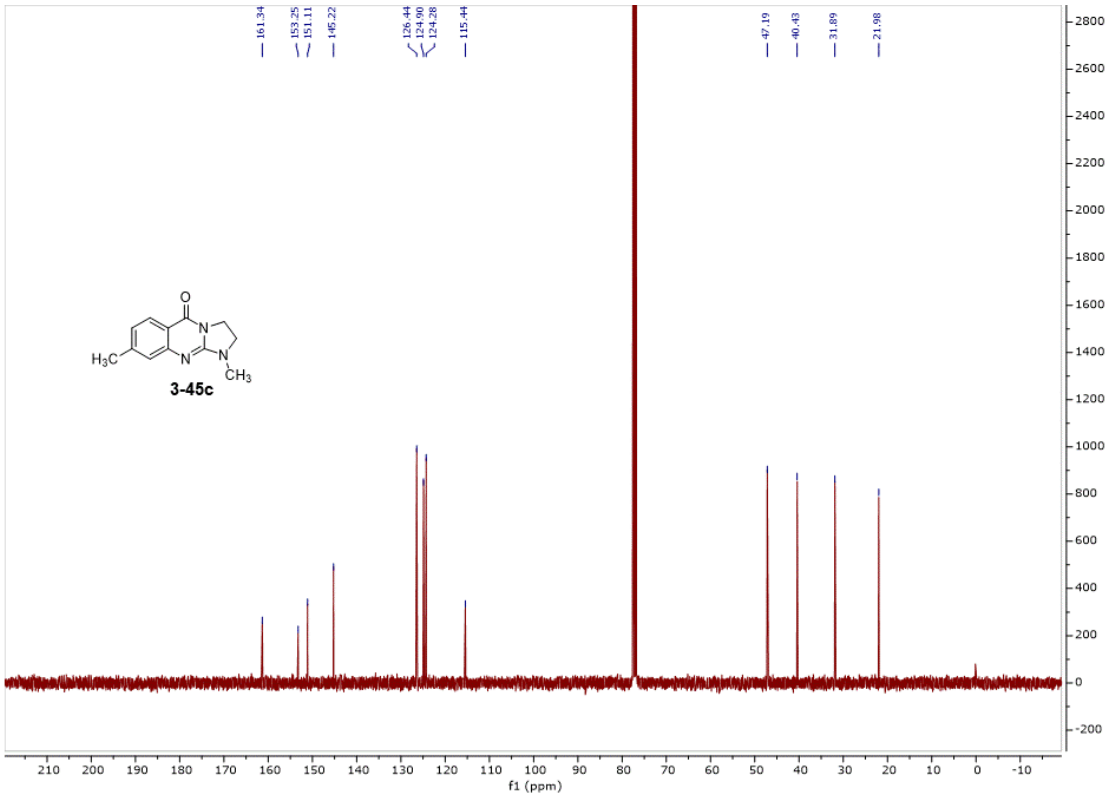

7.98
7.96
7.44
7.42
7.07
7.05
7.03
4.17
4.15
4.13
3.65
3.63
3.61
3.07
3.07
2.48
1.00
1.03
1.00
2.07
2.00
3.02
3.06
3-45b
f1 (ppm)

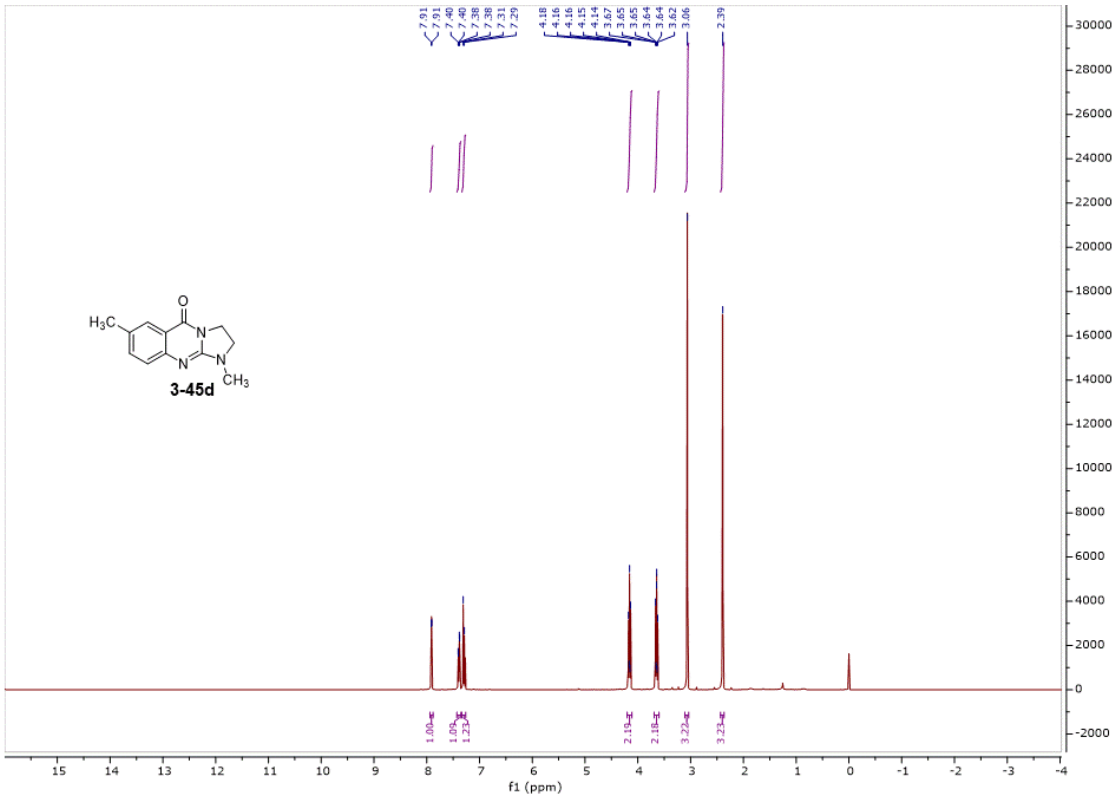

161.81
152.24
149.60
134.78
133.16
124.21
122.02
117.53
47.08
40.44
31.82
17.59
f1 (ppm)

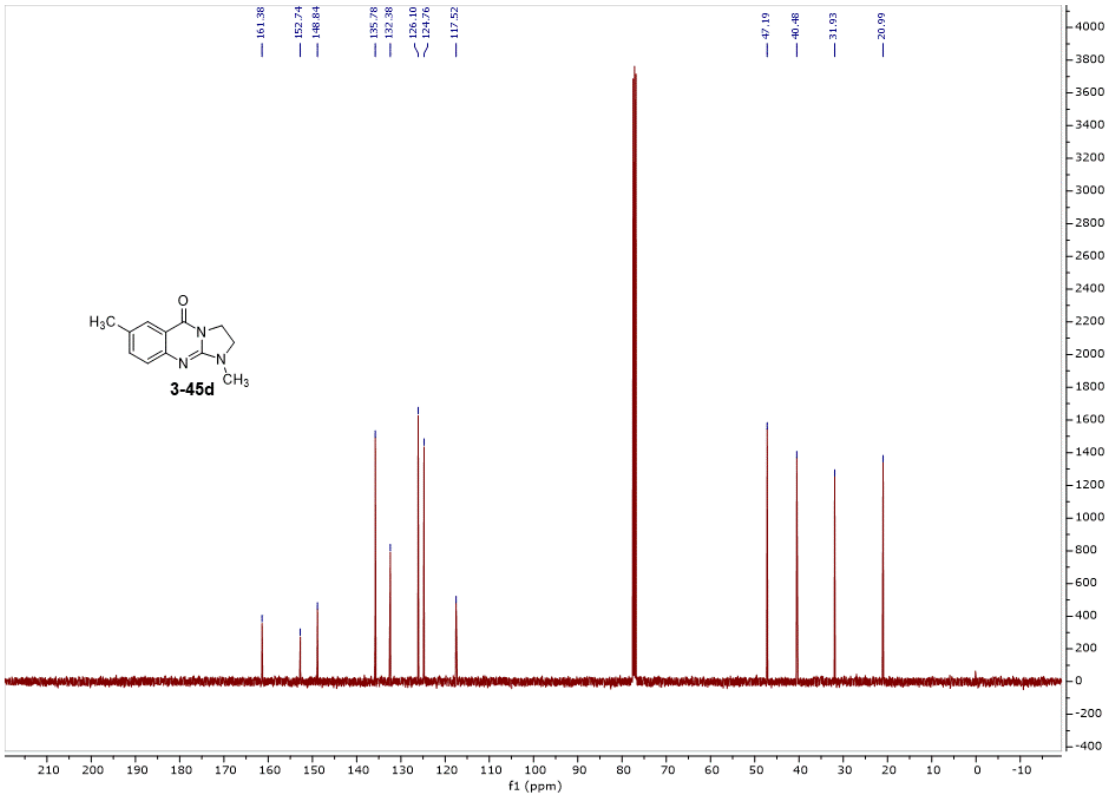
3-45b

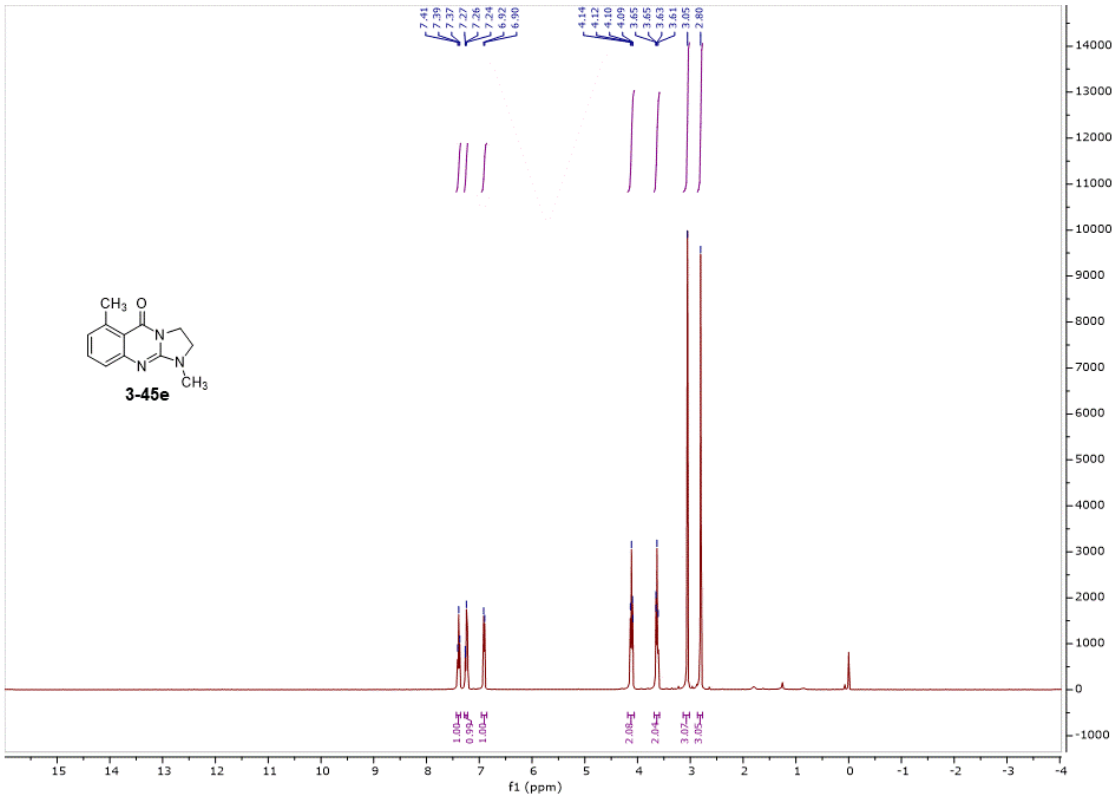

8.01
7.99
7.20
7.20
7.00
6.99
6.98
6.97
4.18
4.16
4.16
4.15
4.15
4.14
3.68
3.66
3.66
3.65
3.65
3.63
3.62
2.41
1.00
0.98
1.03
2.09
2.09
3.06
3.07
f1 (ppm)

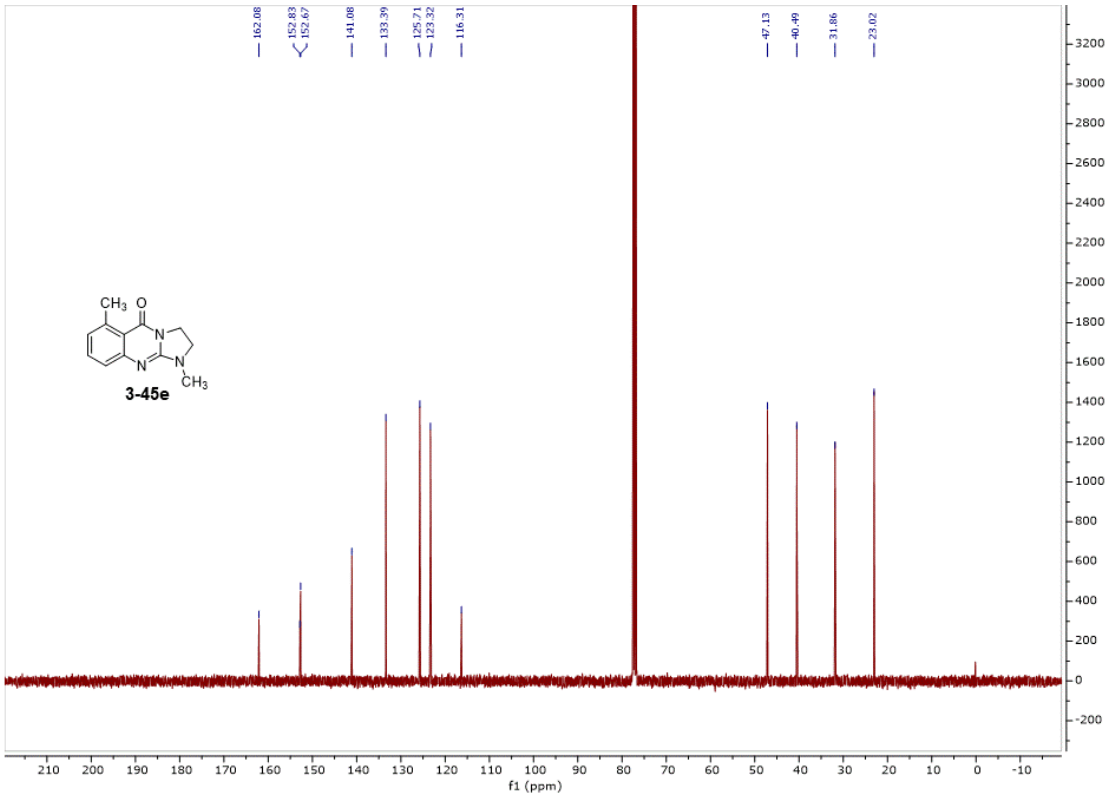
3-45c

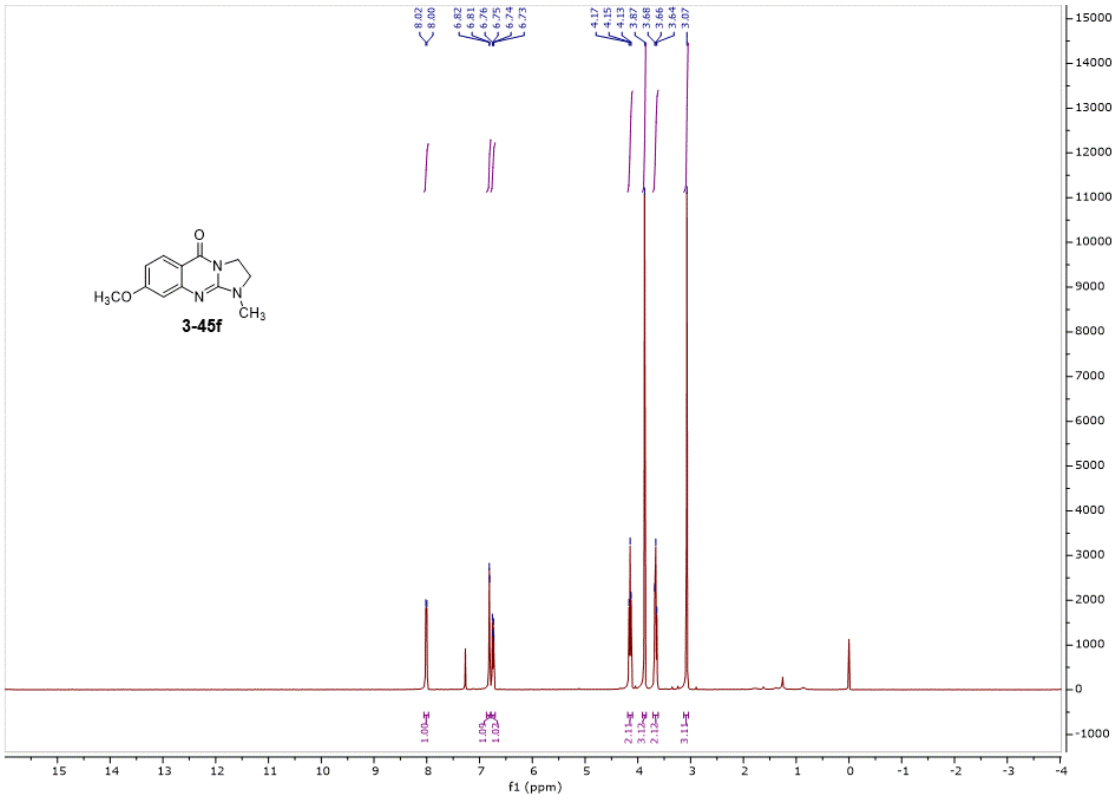

161.34
153.25
151.11
145.22
126.44
124.90
124.28
115.44
47.19
40.43
31.89
21.98
3-45c
f1 (ppm)

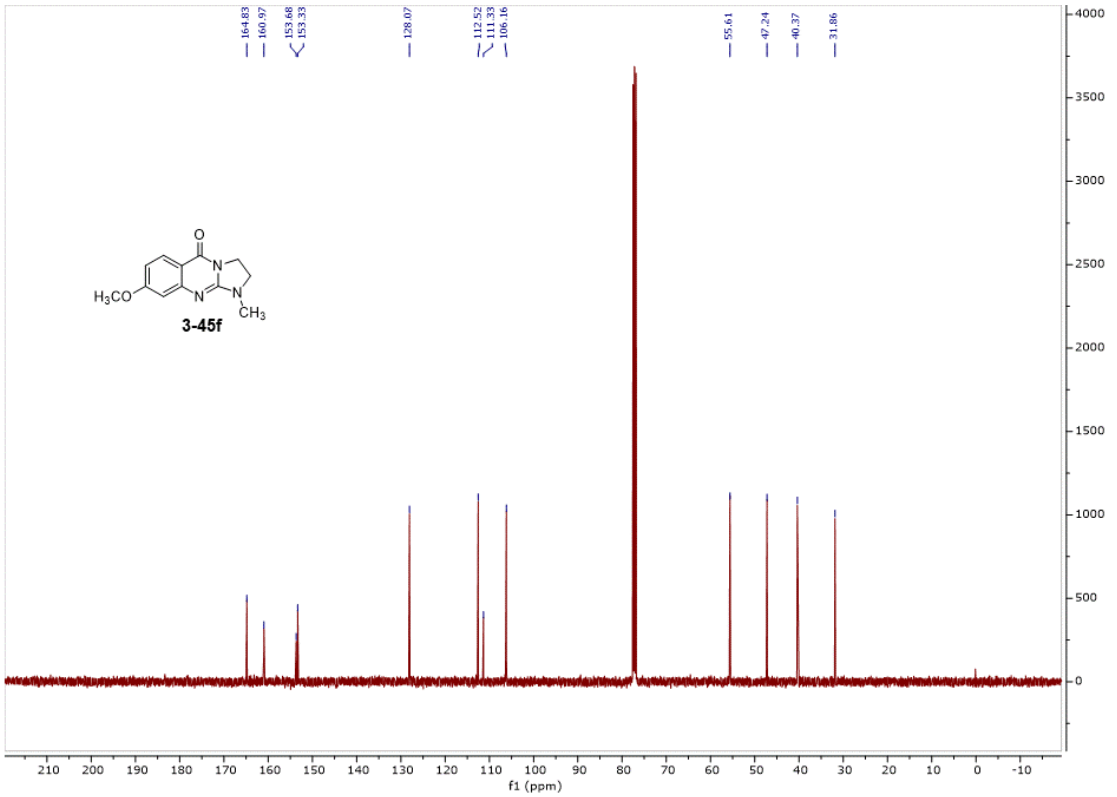

7.91
7.91
7.40
7.40
7.38
7.38
7.31
7.29
4.18
4.16
4.16
4.15
4.14
3.67
3.65
3.65
3.64
3.64
3.62
3.06
2.39
1.00
1.09
1.23
2.19
2.18
3.22
3.23
3-45d
f1 (ppm)

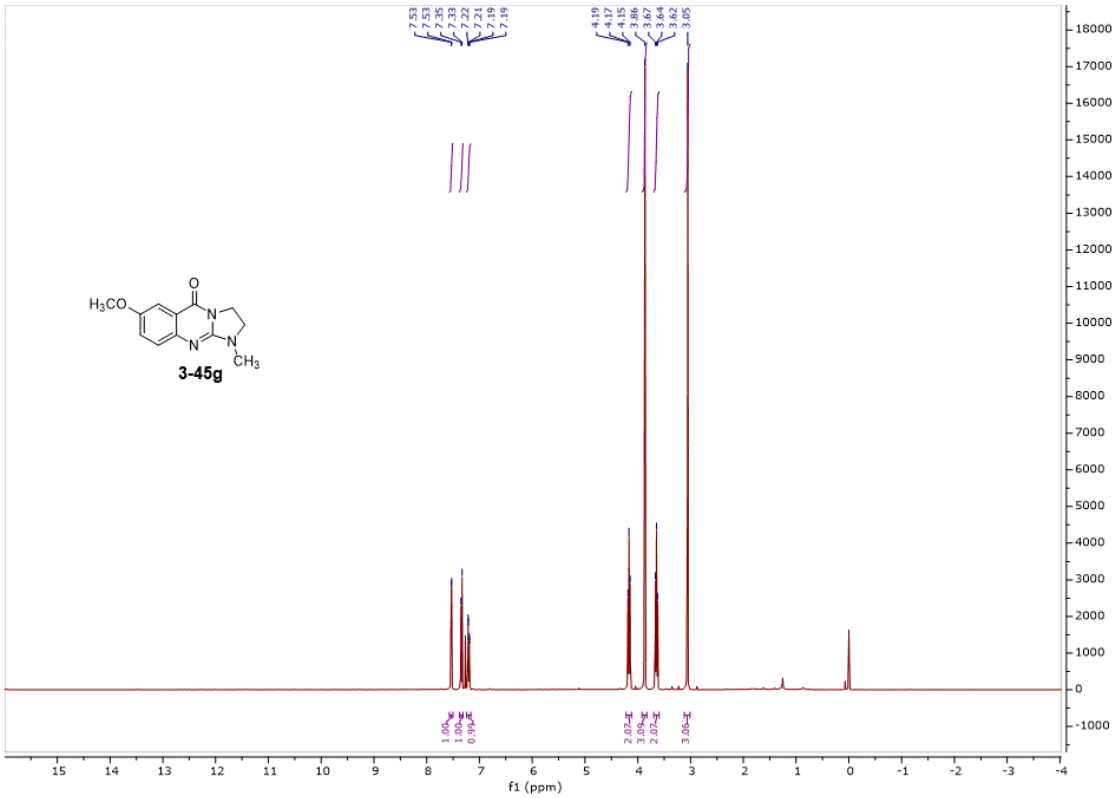

161.38
152.74
148.84
135.78
132.38
126.10
124.76
117.52
47.19
40.48
31.93
20.99
3-45d
f1 (ppm)

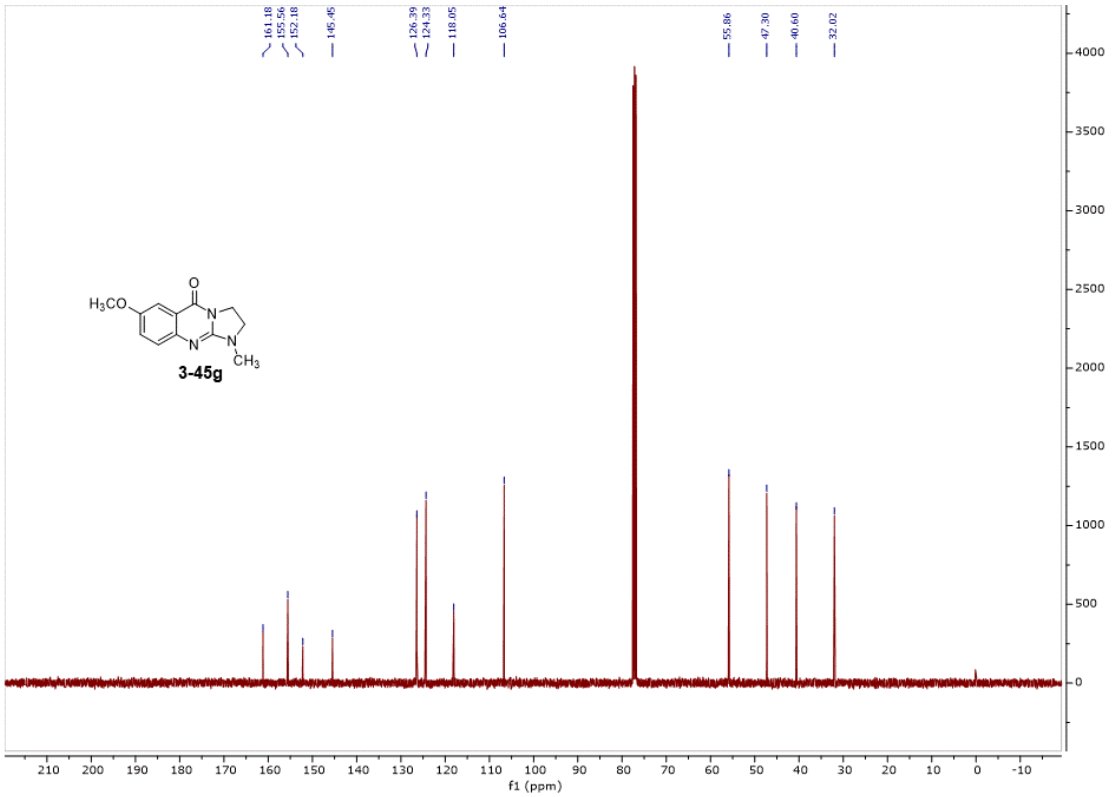

7.41
7.39
7.37
7.27
7.26
7.24
6.92
6.90
4.14
4.12
4.10
4.09
3.65
3.63
3.61
3.05
2.80
3-45e
f1 (ppm)

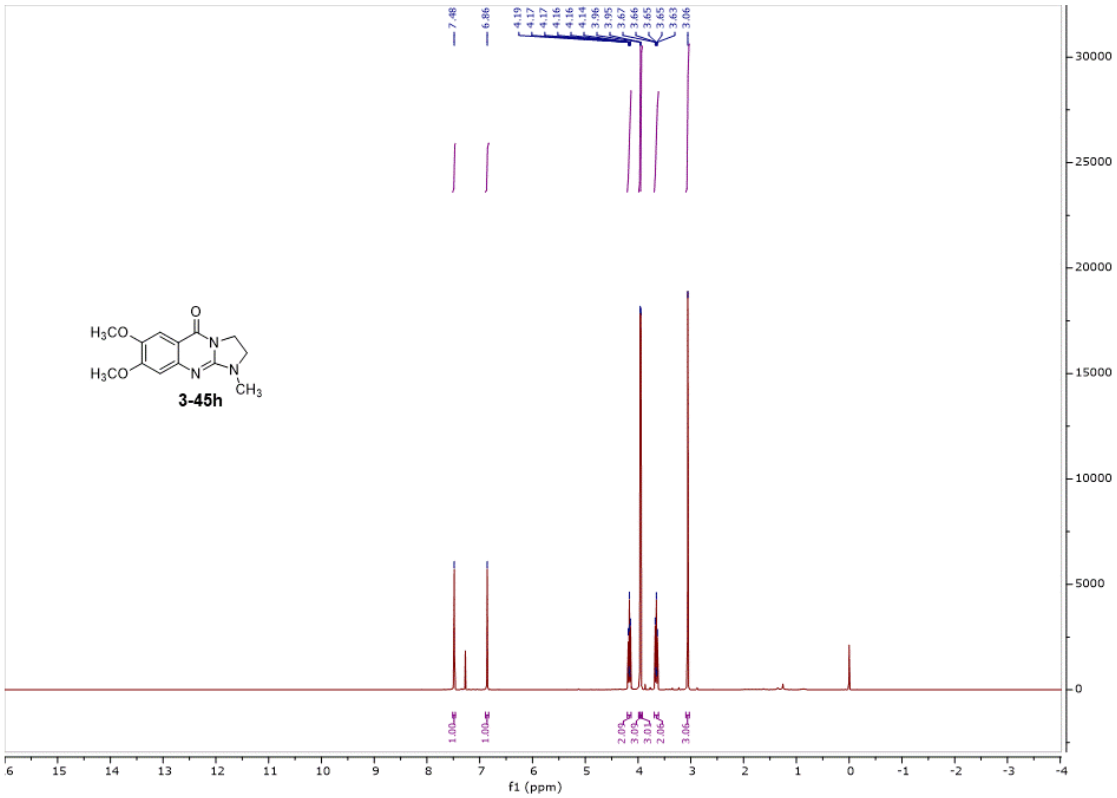

162.08
152.83
152.67
141.08
133.39
125.71
123.32
116.31
47.13
40.49
31.86
23.02
CH3
O
N
N
CH3
3-45e
f1 (ppm)

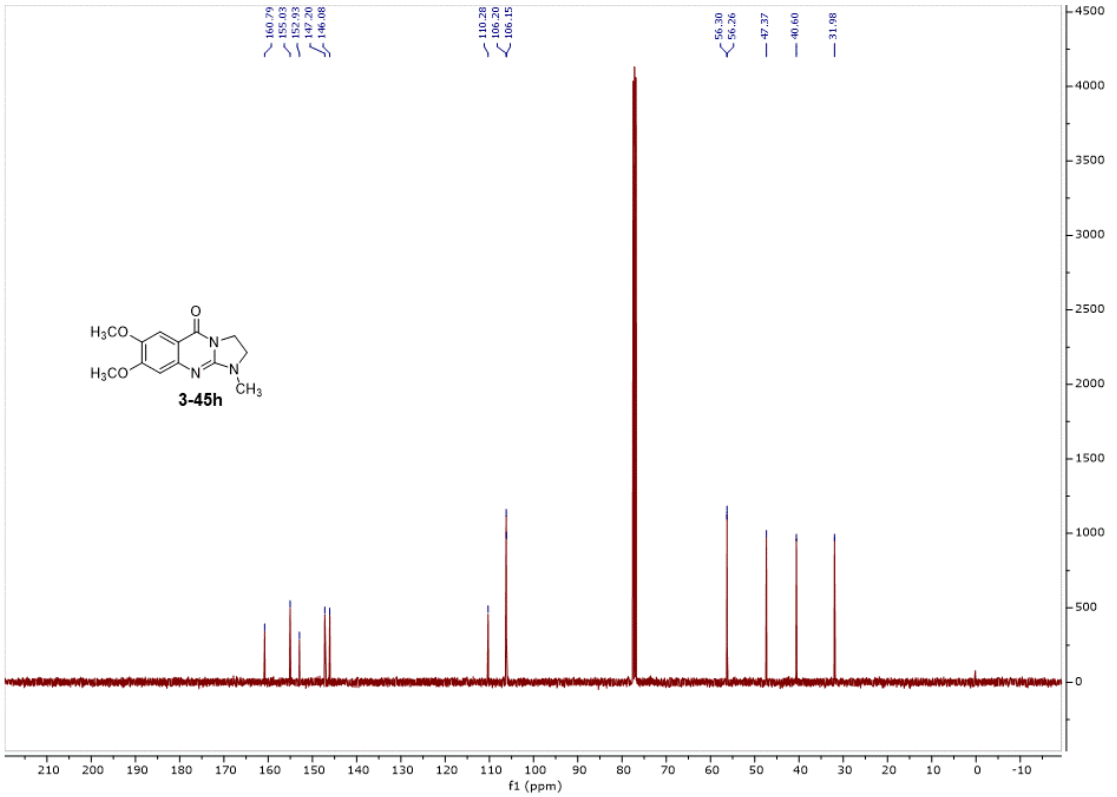

8.02
8.00
6.82
6.81
6.76
6.75
6.74
6.73
4.17
4.15
4.13
3.87
3.68
3.66
3.64
3.07
1.00
1.05
1.02
2.11
3.12
2.12
3.11
H3CO
O
N
N
CH3
3-45f
f1 (ppm)

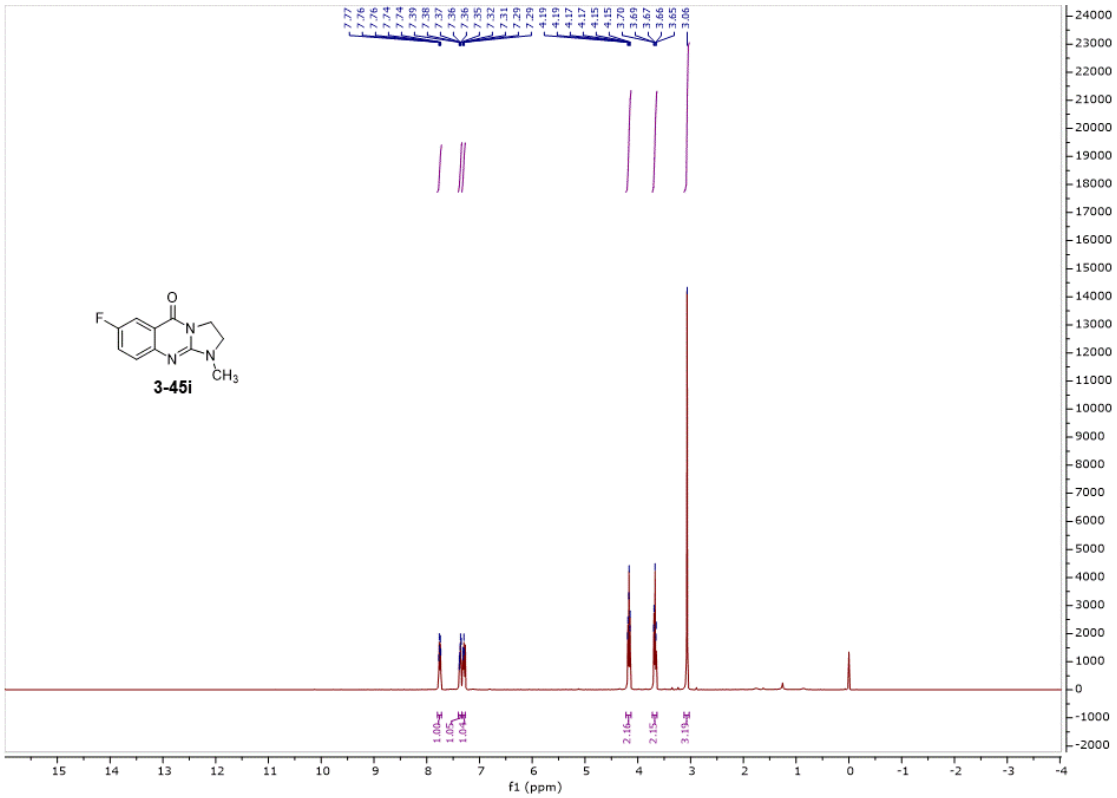

164.83
160.97
153.68
153.33
128.07
112.52
111.33
106.16
55.61
47.24
40.37
31.86
H3CO
N
N
CH3
O
3-45f
f1 (ppm)

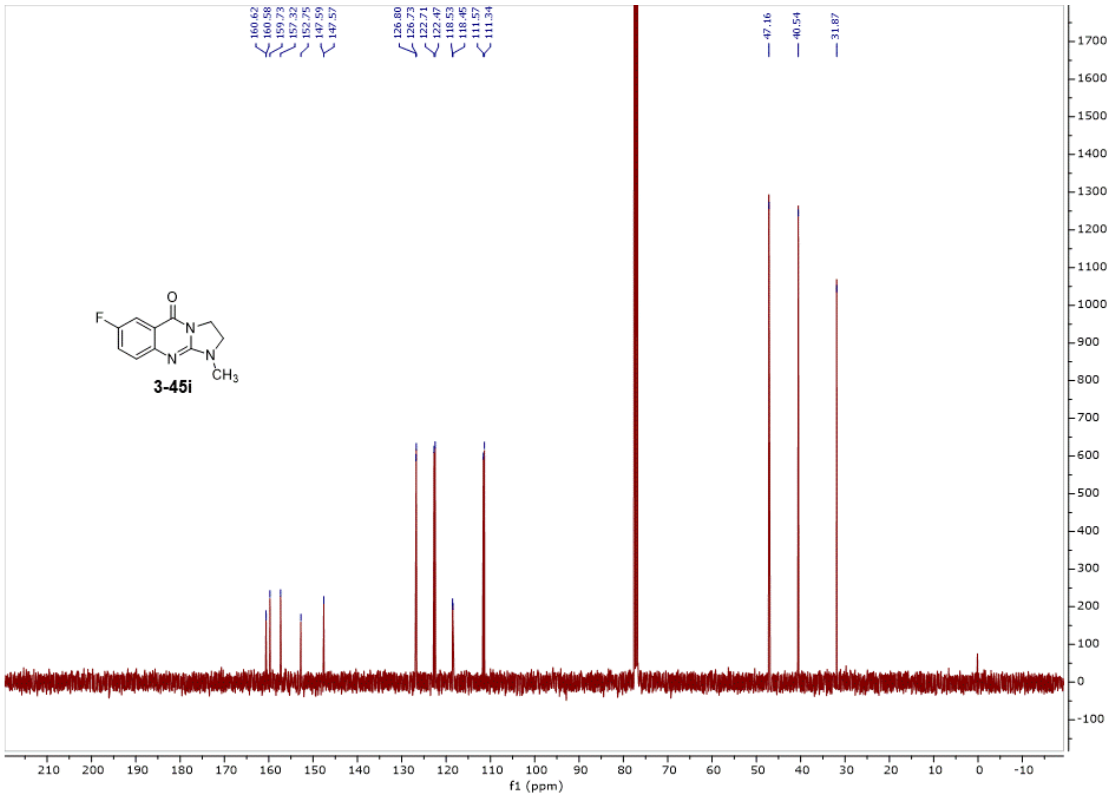

7.53
7.53
7.35
7.33
7.22
7.21
7.19
7.19
4.19
4.17
4.15
3.86
3.67
3.64
3.62
3.05
1.00
1.00
0.99
2.07
3.09
2.07
3.06
H3CO
N
N
CH3
O
3-45g
f1 (ppm)

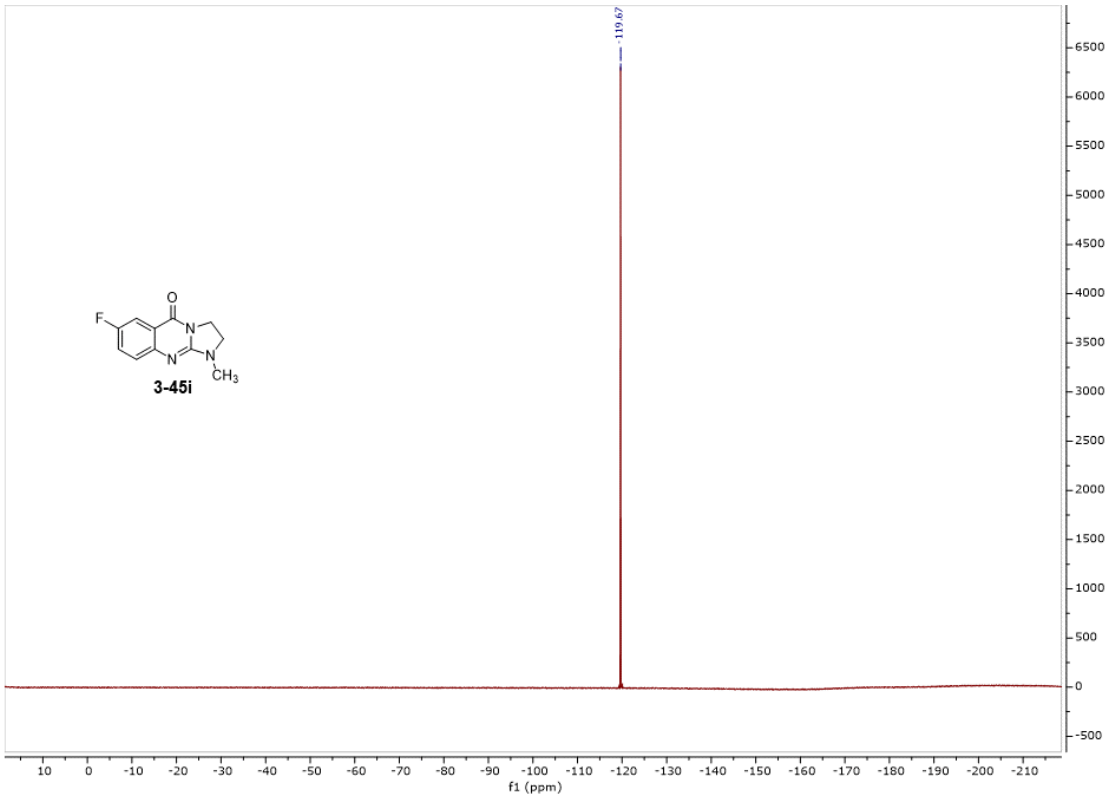

161.18
155.56
152.18
145.45
126.39
124.33
118.05
106.64
55.86
47.30
40.60
32.02
H3CO
CH3
3-45g
f1 (ppm)

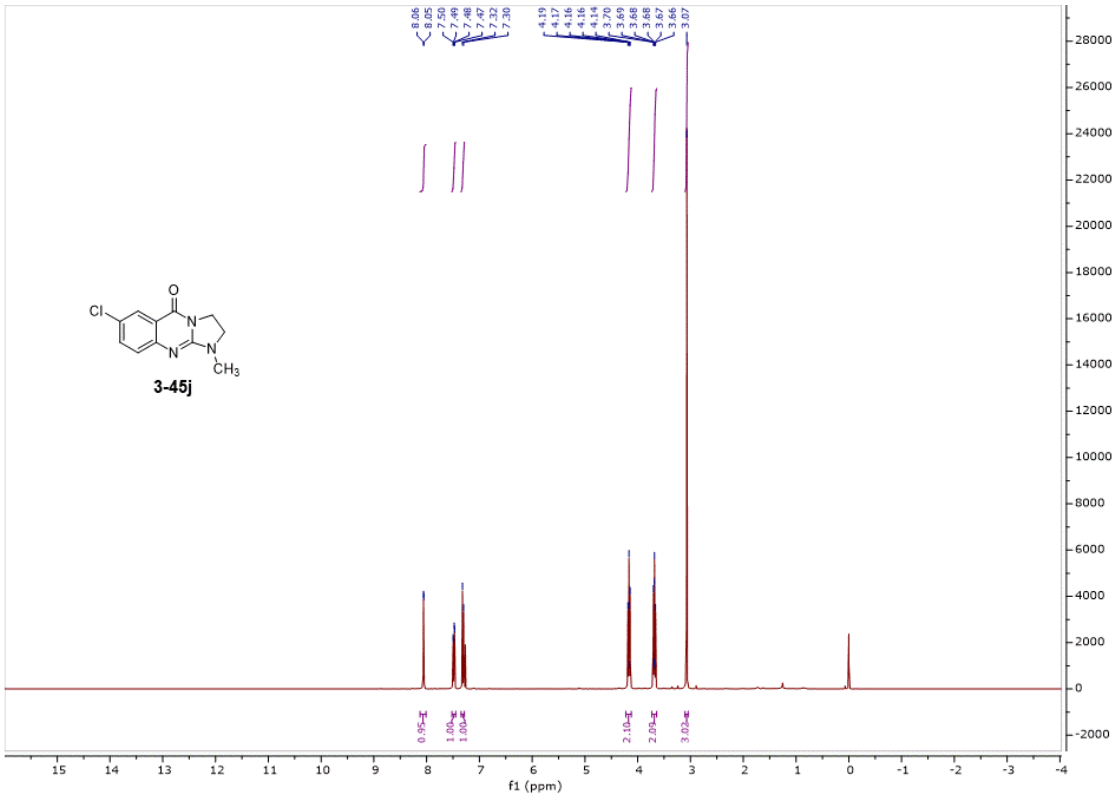

7.48
6.86
4.19
4.17
4.17
4.16
4.16
4.14
3.96
3.95
3.67
3.66
3.65
3.65
3.63
3.06
1.00
1.00
2.03
3.03
3.01
2.06
3.06
H3CO
H3CO
CH3
3-45h
f1 (ppm)

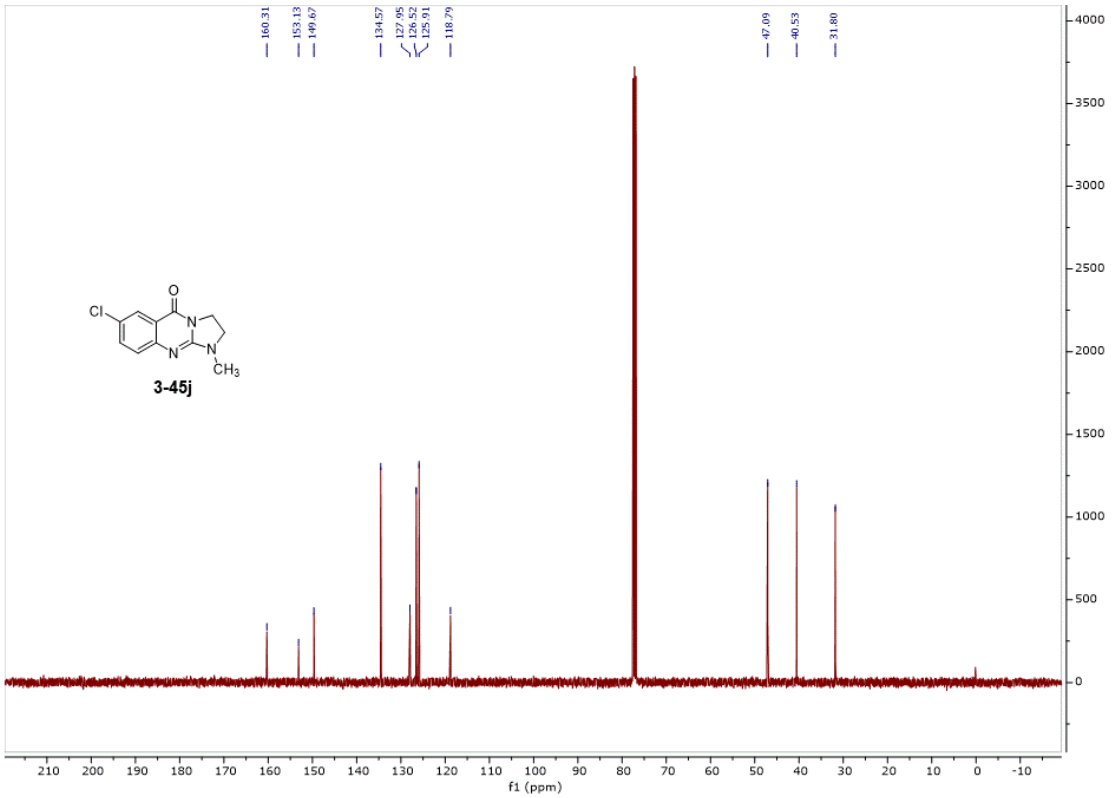

160.79
155.03
152.93
147.20
146.08
110.28
106.20
106.15
56.30
56.26
47.37
40.60
31.98
H3CO
H3CO
O
N
N
CH3
3-45h
f1 (ppm)

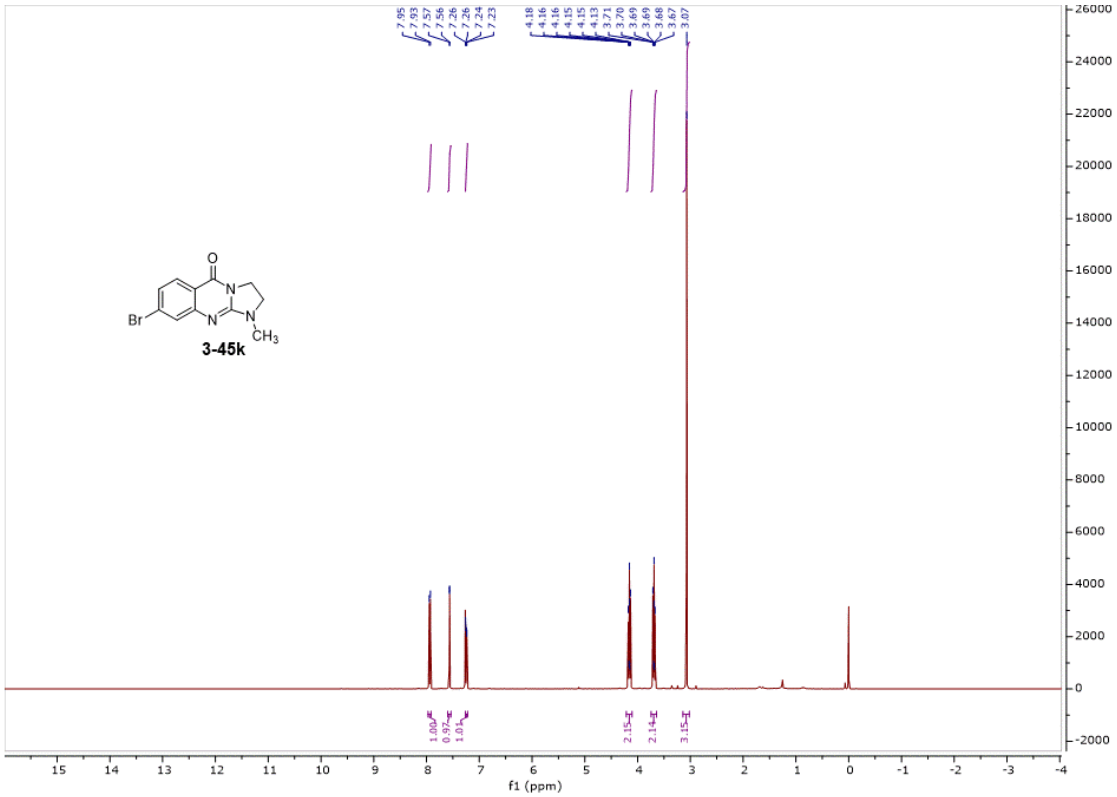

7.77
7.76
7.76
7.74
7.74
7.39
7.38
7.37
7.36
7.36
7.35
7.32
7.31
7.29
7.29
4.19
4.19
4.17
4.17
4.15
4.15
3.70
3.69
3.67
3.66
3.65
3.06
F
O
N
N
CH3
3-45i
1.00
1.05
1.04
2.16
2.15
3.19
f1 (ppm)

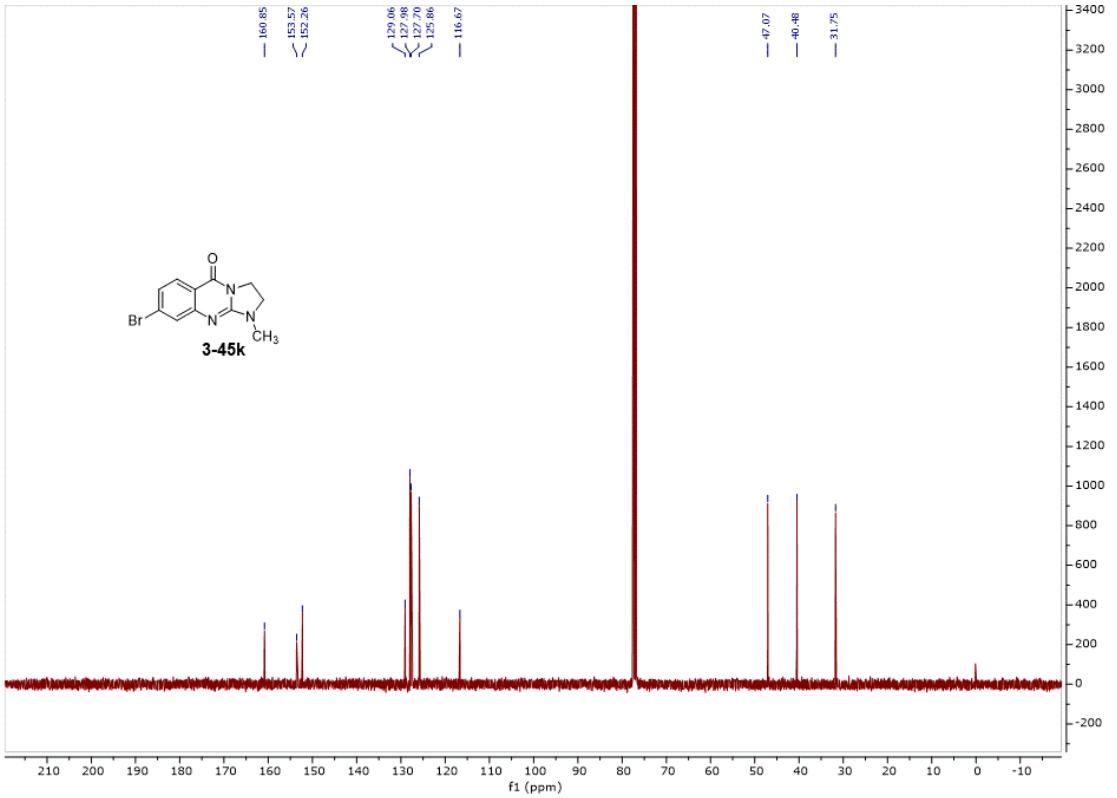

160.62
160.58
159.73
157.32
152.75
147.59
147.57
126.80
126.73
122.71
122.47
118.53
118.45
111.57
111.34
47.16
40.54
31.67
F
O
N
N
N
CH3
3-45i
f1 (ppm)

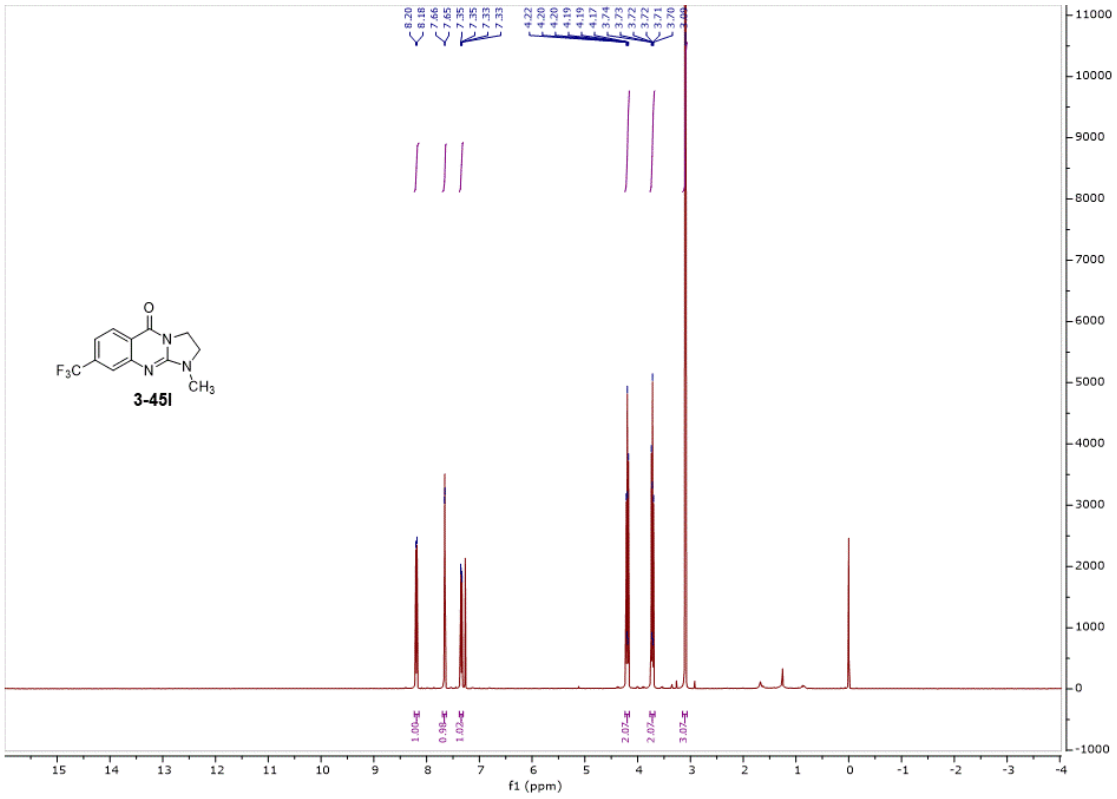

119.67
F
O
N
N
N
CH3
3-45i
f1 (ppm)

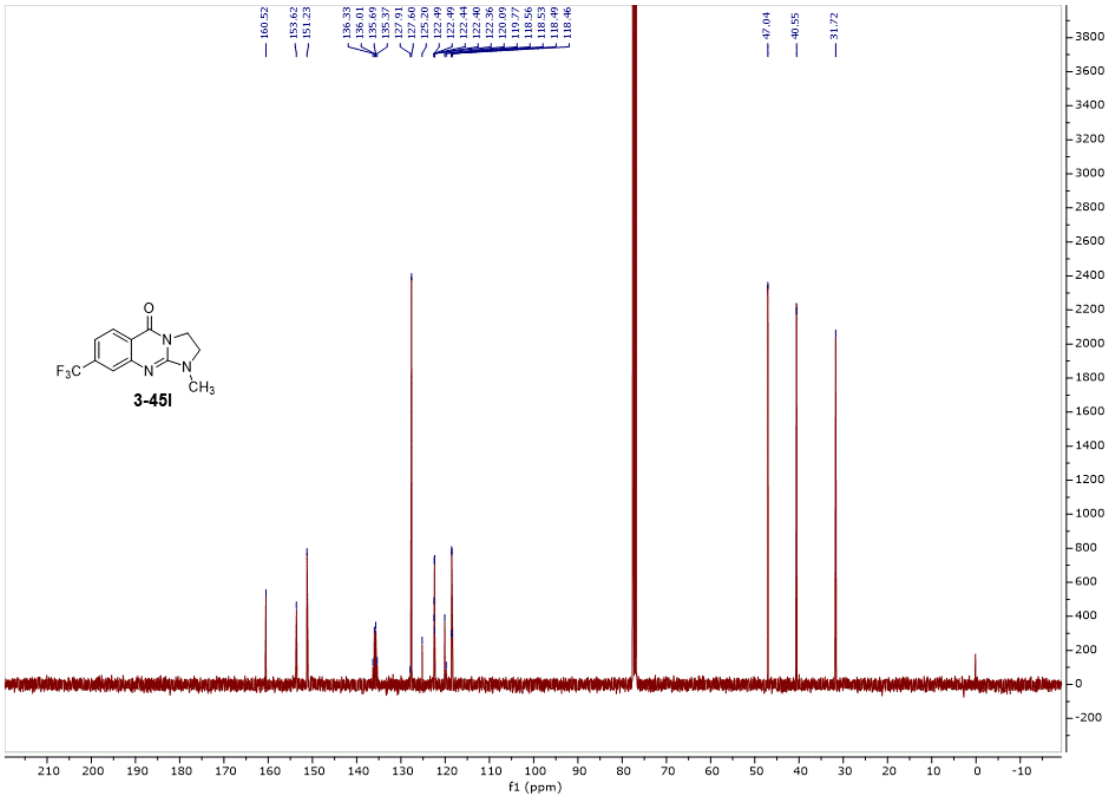

8.06
8.05
8.03
7.49
7.48
7.47
7.32
7.30
4.19
4.17
4.16
4.16
4.14
4.14
3.70
3.69
3.68
3.68
3.67
3.66
3.07
0.95
1.00
1.00
2.10
2.09
3.02
f1 (ppm)
Cl
O
N
N
CH3
3-45j

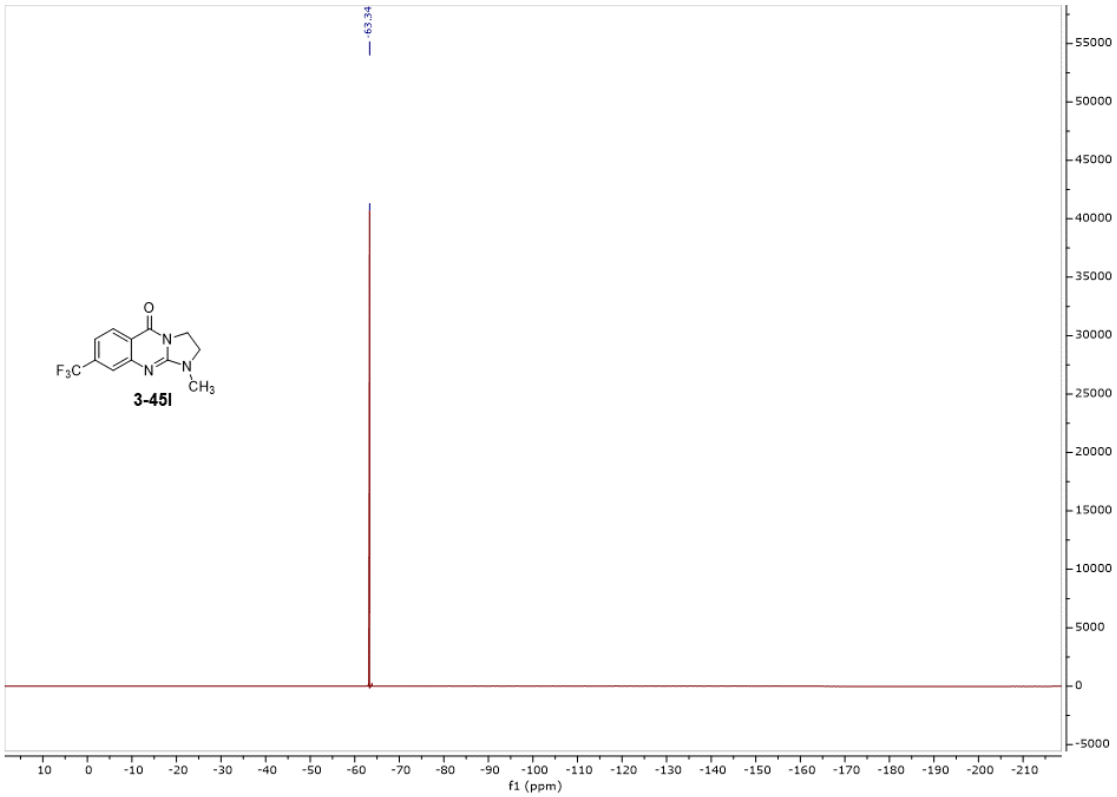

160.31
153.13
149.67
134.57
127.95
126.52
125.91
118.79
47.09
40.53
31.80
f1 (ppm)
Cl
O
N
N
CH3
3-45j

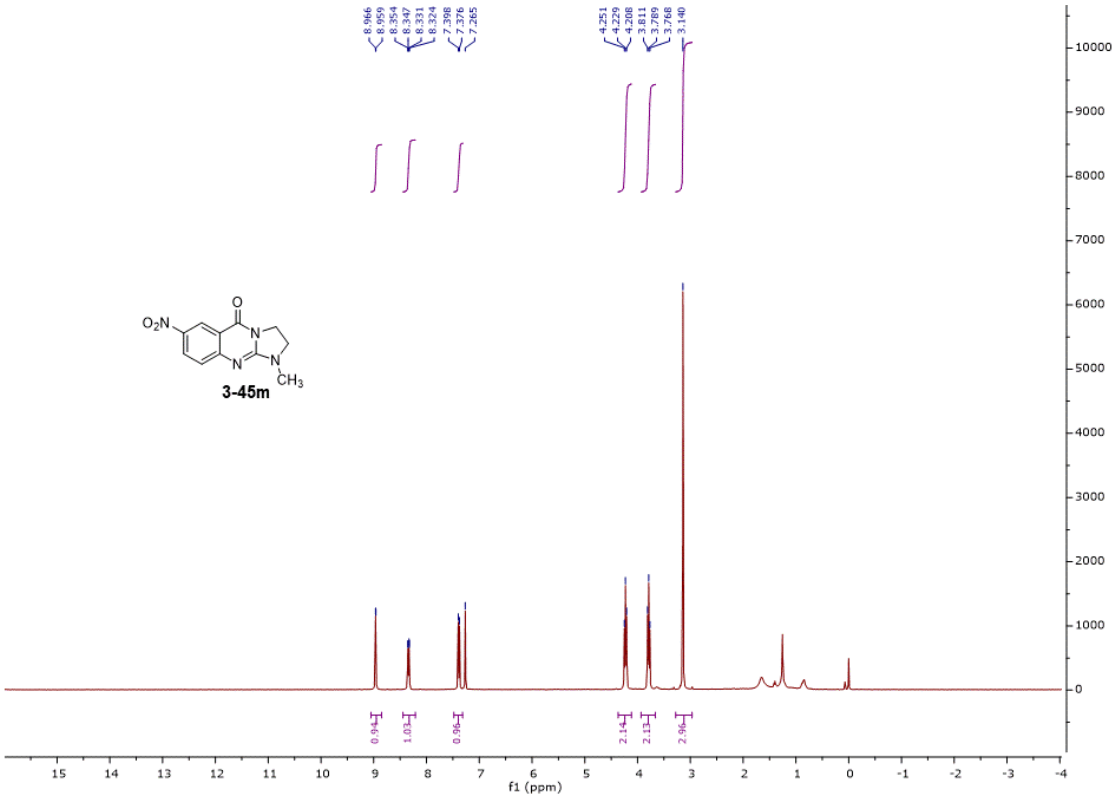

7.95
7.93
7.57
7.56
7.26
7.26
7.24
7.23
4.18
4.16
4.16
4.15
4.15
4.13
3.71
3.70
3.69
3.69
3.68
3.67
3.07
Br
N
N
O
CH3
3-45k
1.00
0.92
1.01
2.15
2.14
3.15
f1 (ppm)

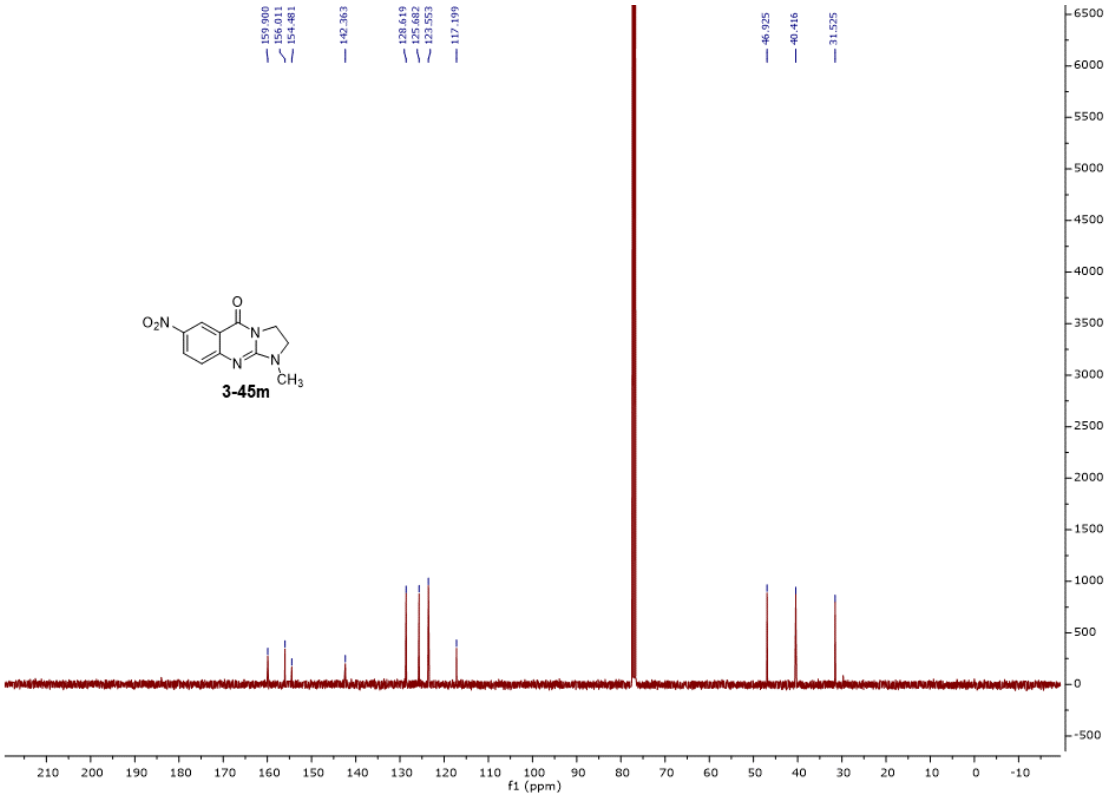

160.85
153.57
152.26
129.06
127.98
127.70
125.86
116.67
47.07
40.48
31.75
Br
N
N
O
CH3
3-45k
f1 (ppm)

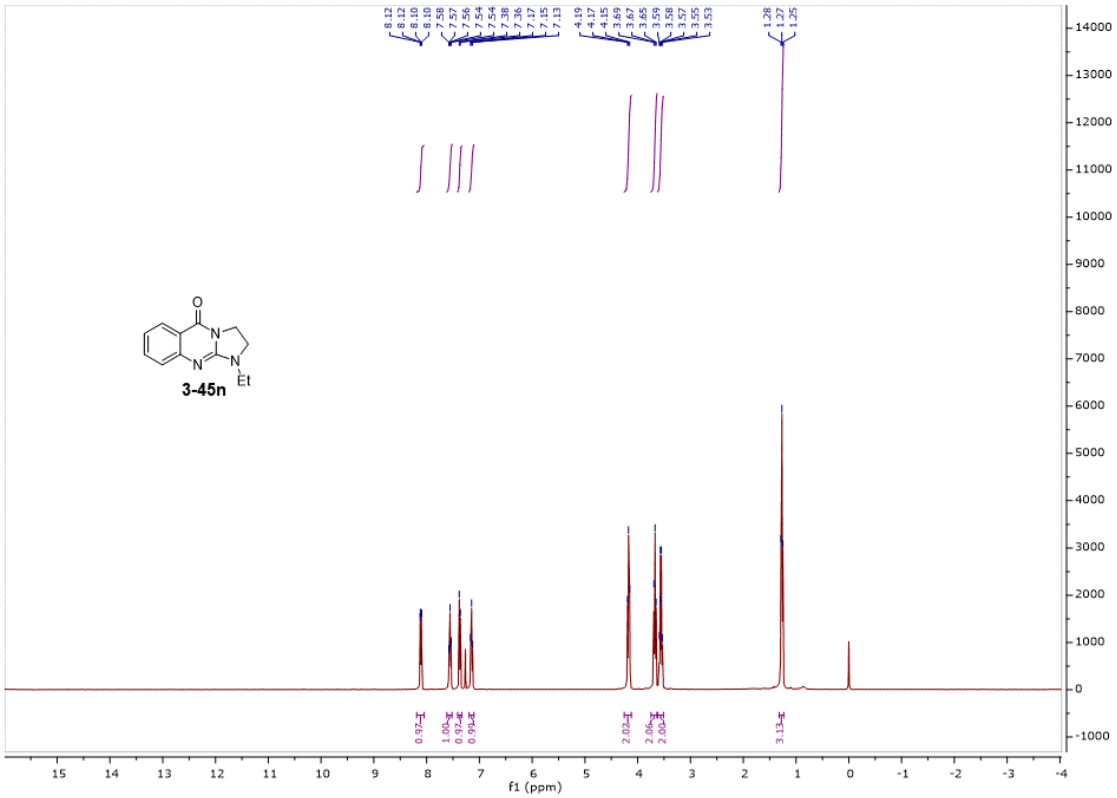

8.20
8.18
7.66
7.65
7.35
7.35
7.33
7.33
4.22
4.20
4.20
4.19
4.19
4.17
3.74
3.73
3.72
3.72
3.71
3.70
2.66
1.00
0.98
1.02
2.07
2.07
3.07
f1 (ppm)
3-45l

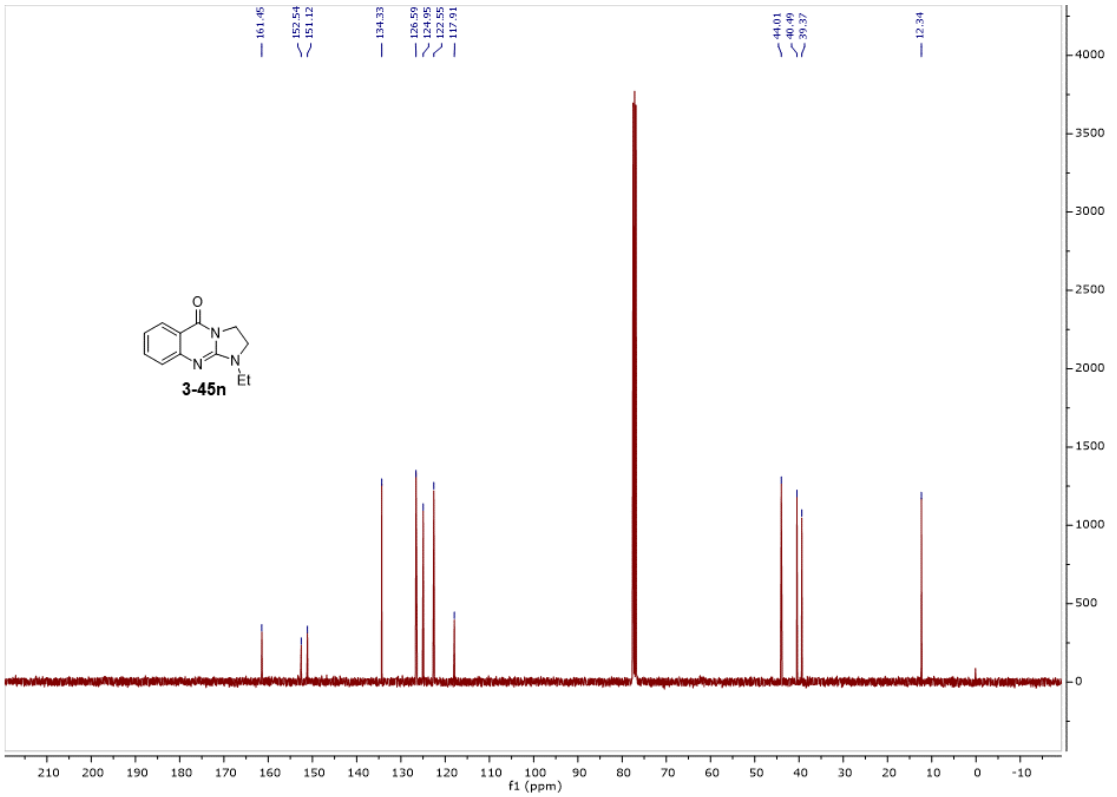

160.52
153.62
151.23
136.33
136.01
135.69
135.37
127.91
127.60
125.20
122.49
122.49
122.44
122.40
122.36
120.09
119.77
118.56
118.53
118.49
118.46
47.04
40.55
31.72
f1 (ppm)
3-45l

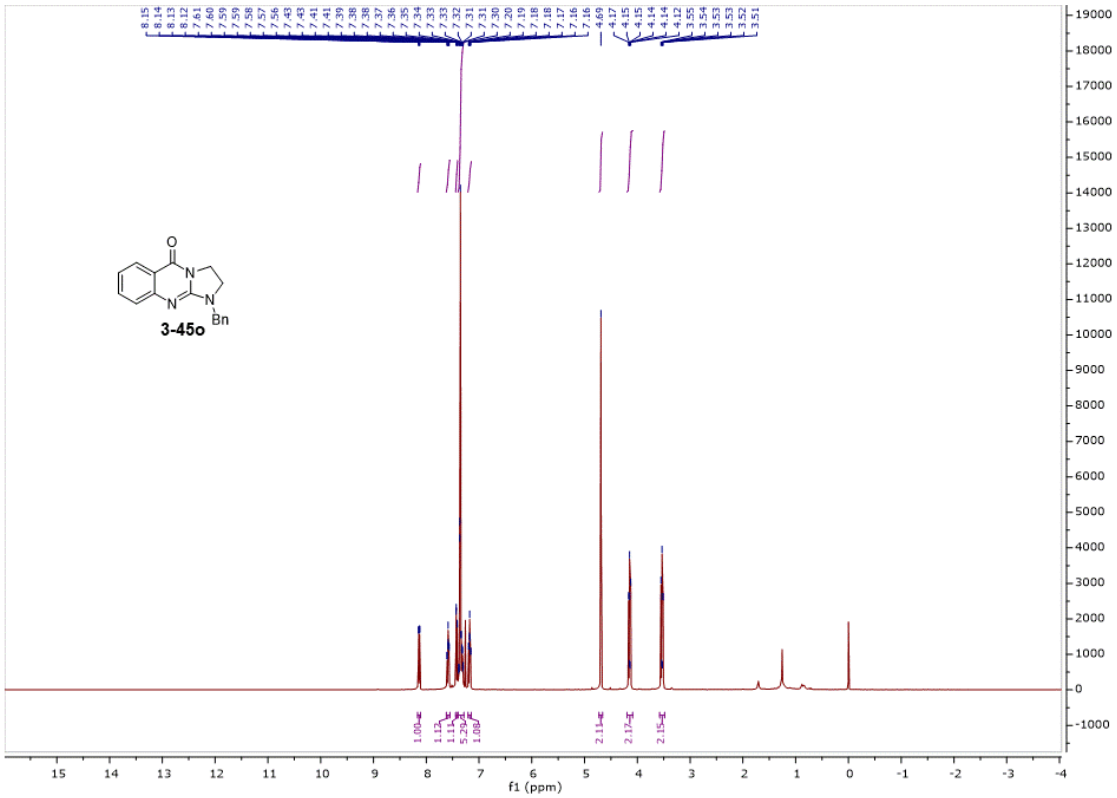

63.34
3-45l
f1 (ppm)

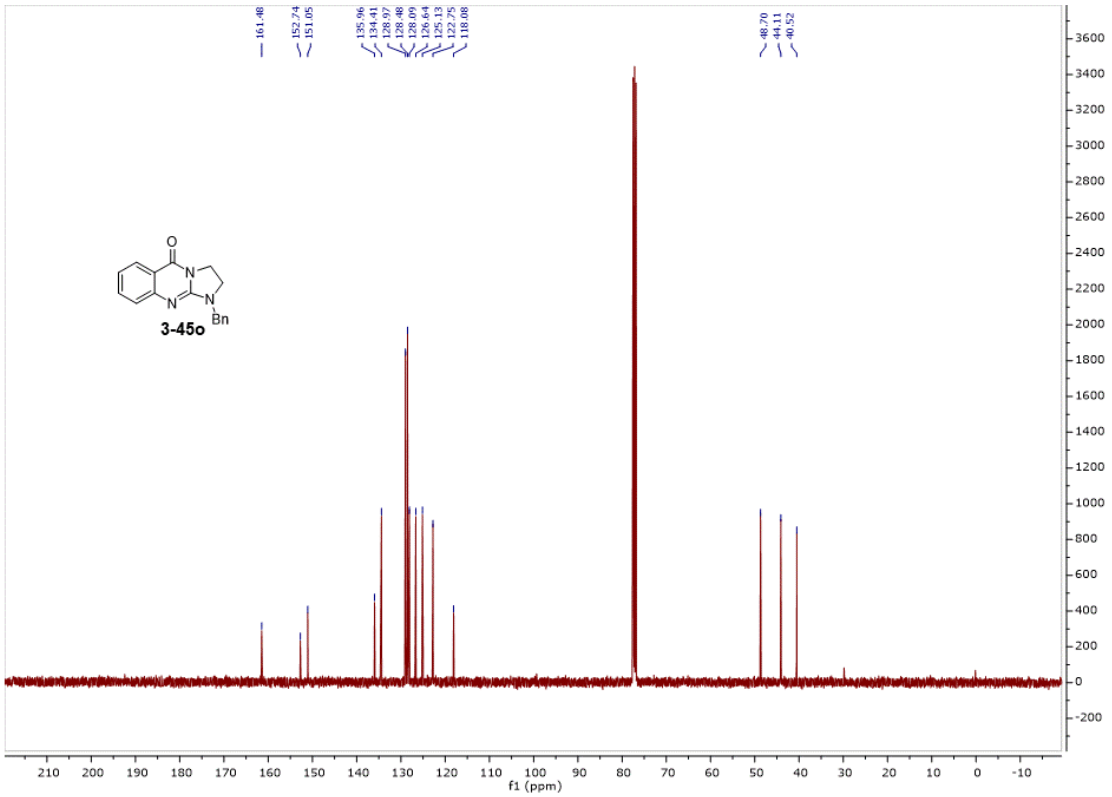

8.966
8.959
8.354
8.347
8.331
8.324
7.398
7.376
7.265
4.251
4.229
4.208
3.811
3.789
3.768
3.140
0.94
1.03
0.96
2.14
2.13
2.96
3-45m
f1 (ppm)

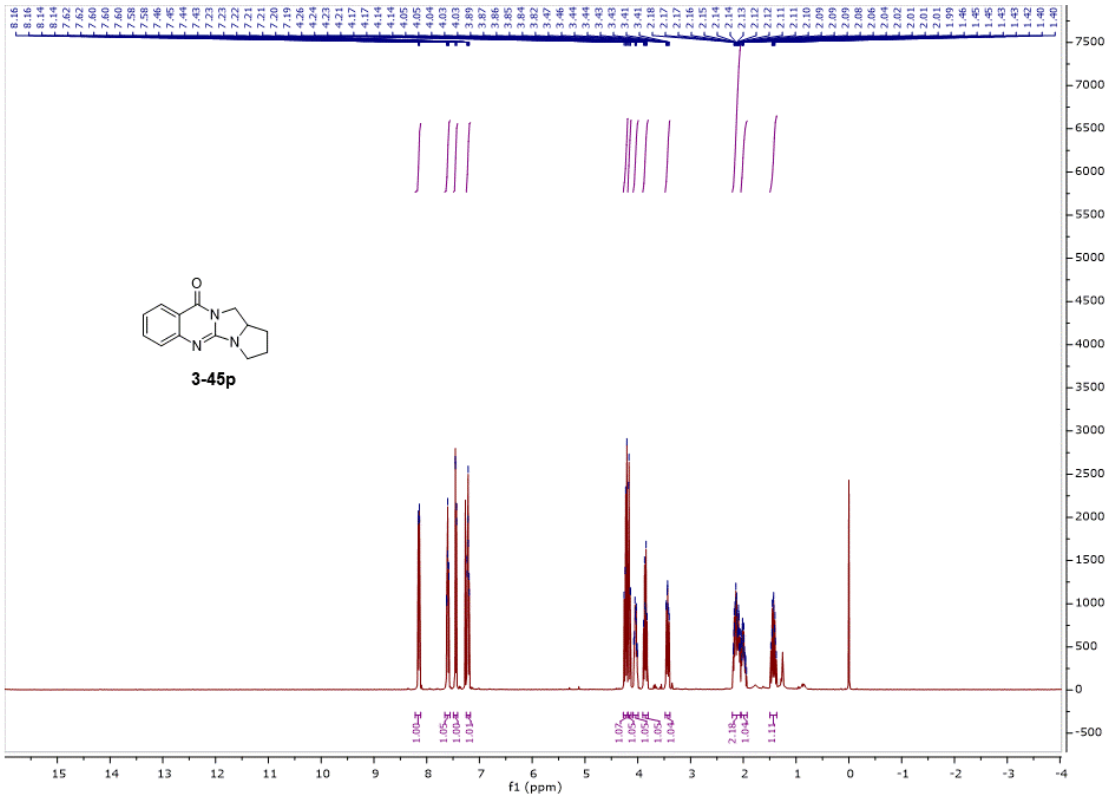

159.900
156.011
154.481
142.363
128.619
125.682
123.553
117.199
46.925
40.416
31.525
O2N
O
N
N
N
CH3
3-45m
f1 (ppm)

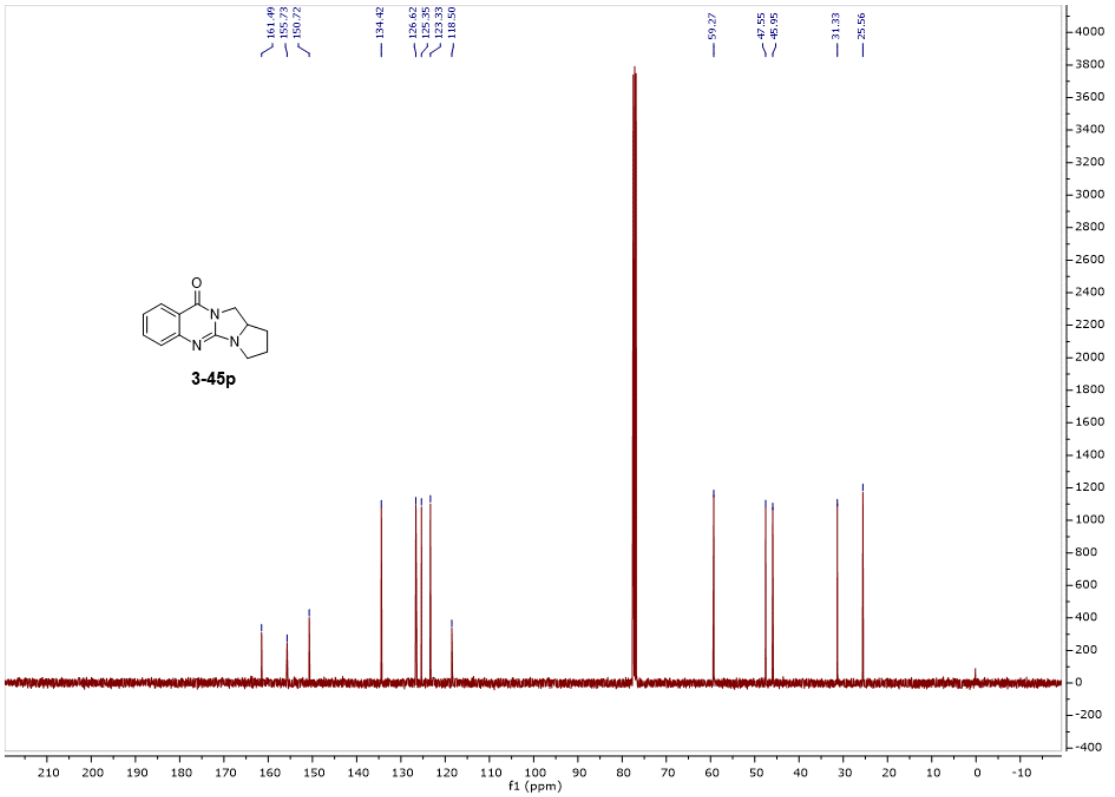

8.12
8.12
8.10
8.10
7.58
7.57
7.56
7.54
7.54
7.38
7.36
7.17
7.15
7.13
4.19
4.17
4.15
3.69
3.67
3.65
3.59
3.58
3.57
3.55
3.53
1.28
1.27
1.25
O
N
N
N
Et
3-45n
0.97
1.00
0.97
0.99
2.02
2.06
2.00
3.13
f1 (ppm)

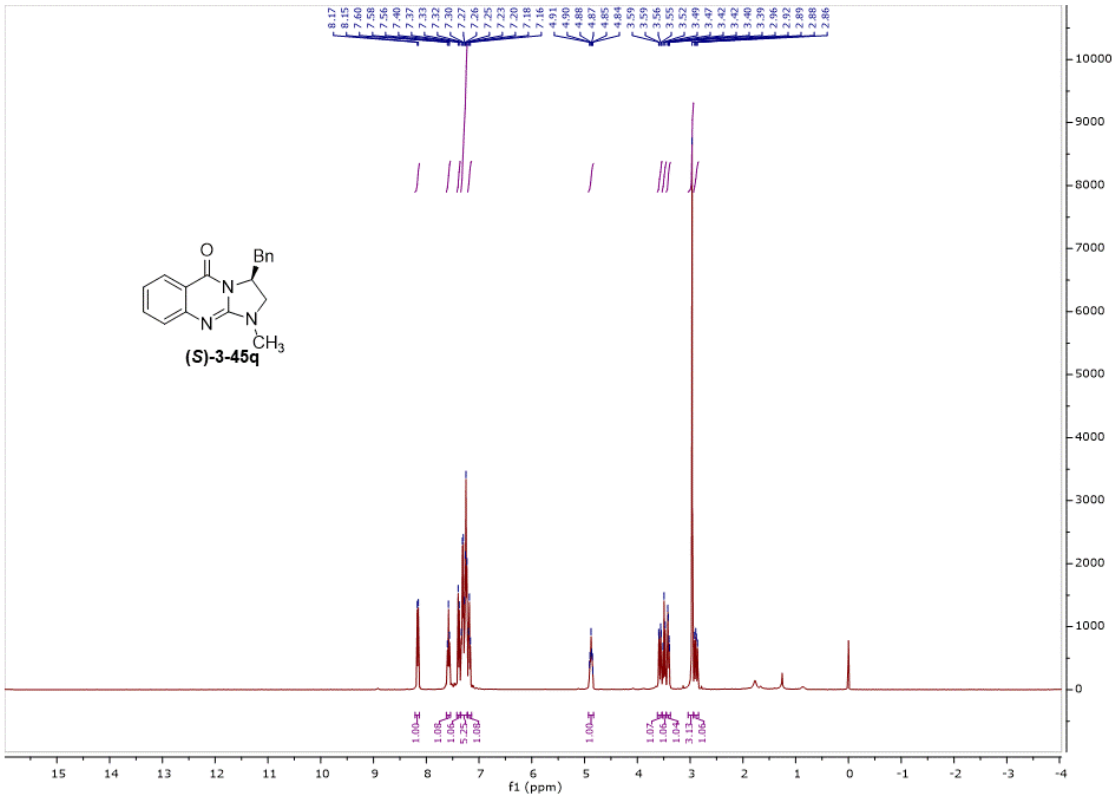

161.45
152.54
151.12
134.33
126.59
124.95
122.55
117.91
44.01
40.49
39.37
12.34
3-45n
Et
f1 (ppm)

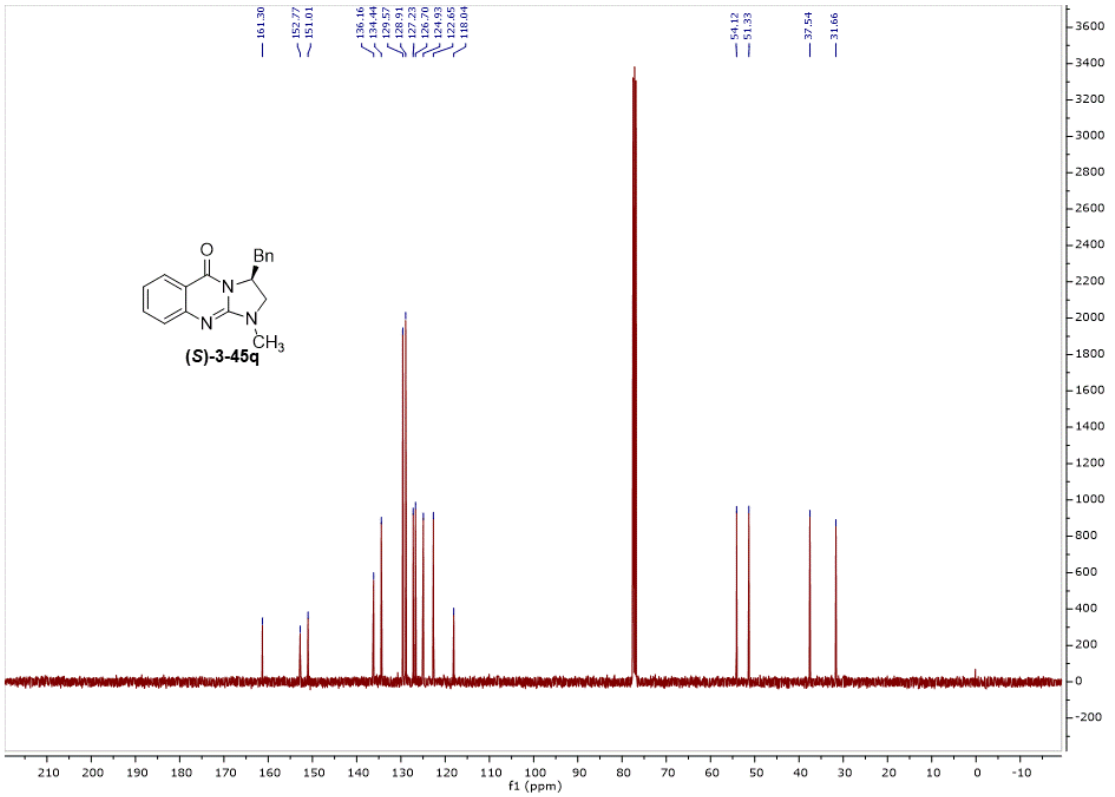

3-45o
Bn
f1 (ppm)

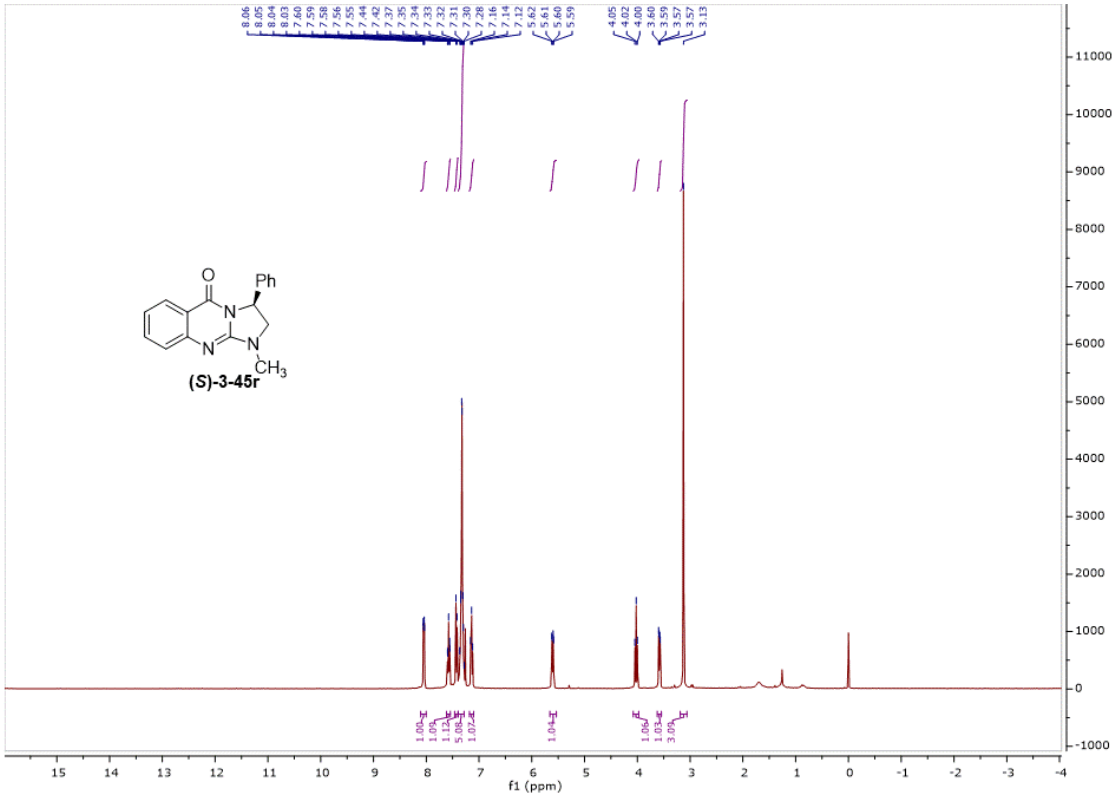

161.48
152.74
151.05
135.96
134.41
128.97
128.40
128.09
126.64
125.13
122.75
118.08
48.70
44.11
40.52
3-45o
Bn
f1 (ppm)

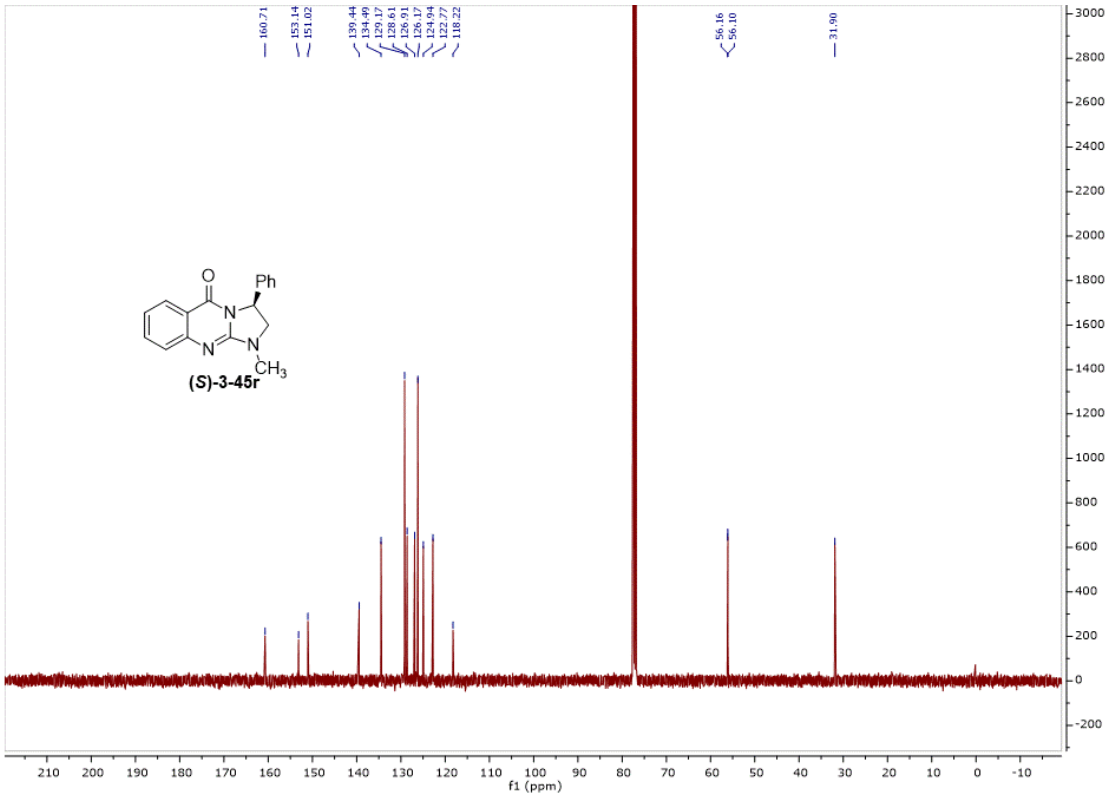

3-45p
f1 (ppm)

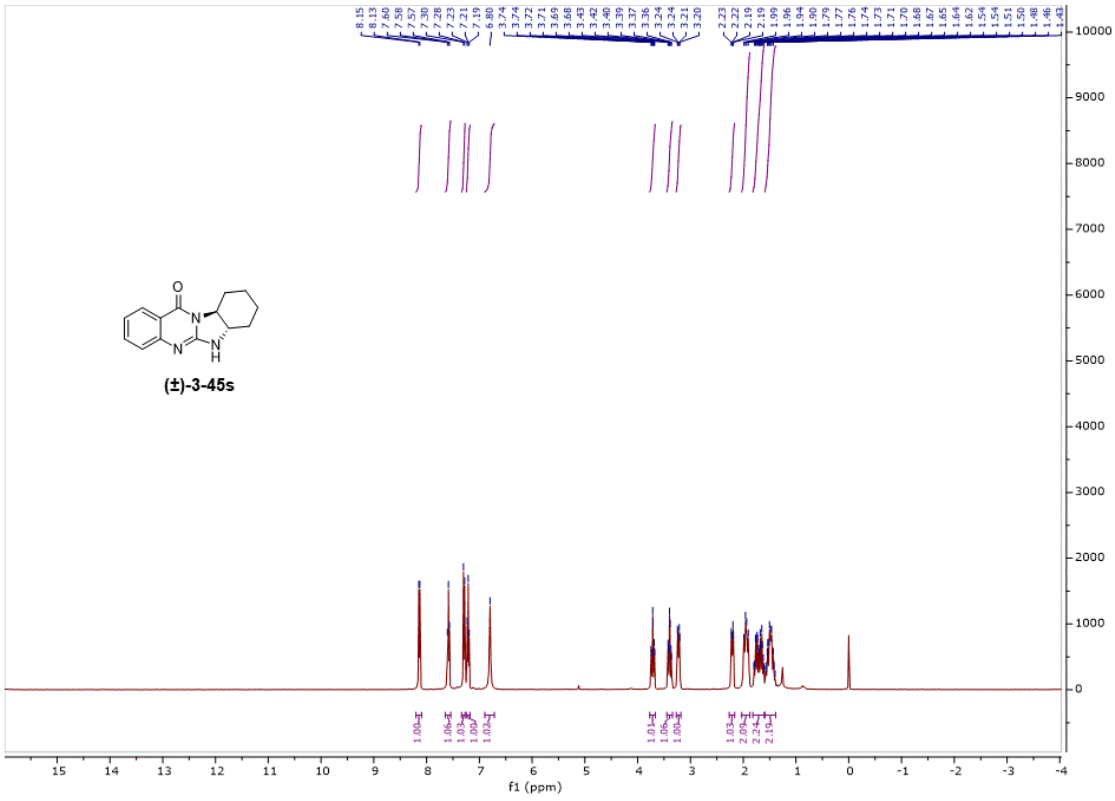

161.49
155.73
150.72
134.42
126.62
125.35
123.33
118.50
59.27
47.55
45.95
31.33
25.56
3-45p
f1 (ppm)

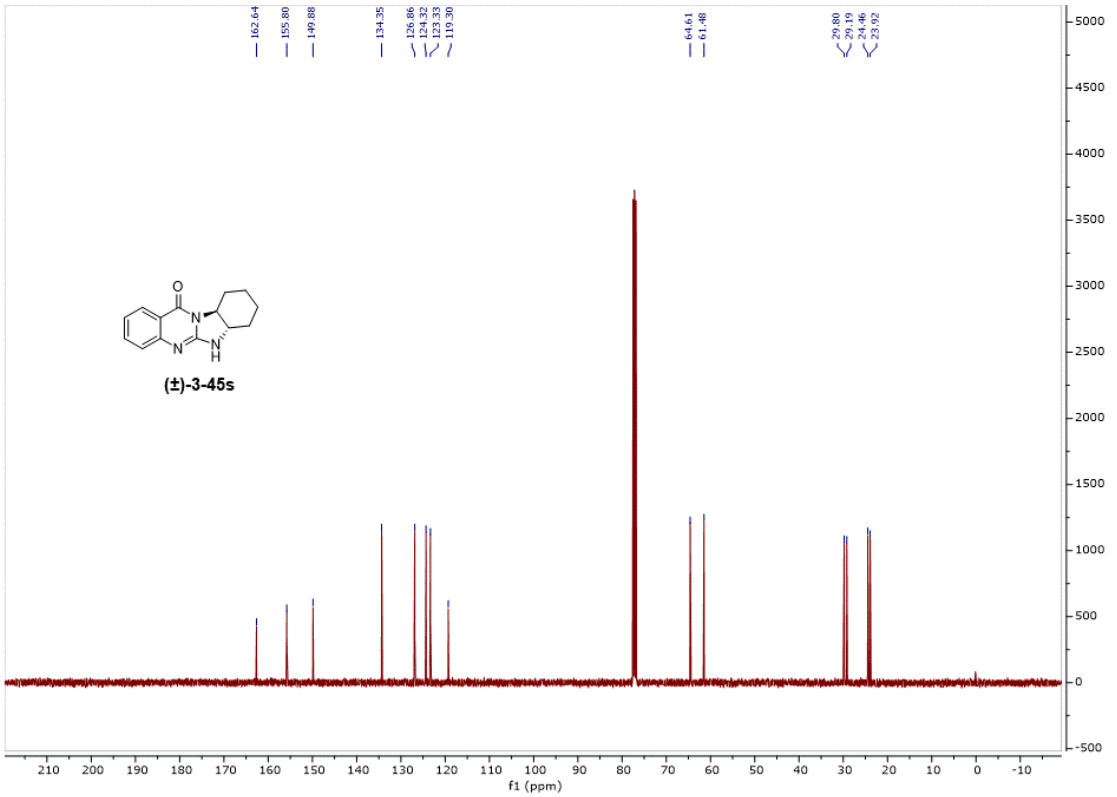

Bn
CH3
(S)-3-45q
f1 (ppm)

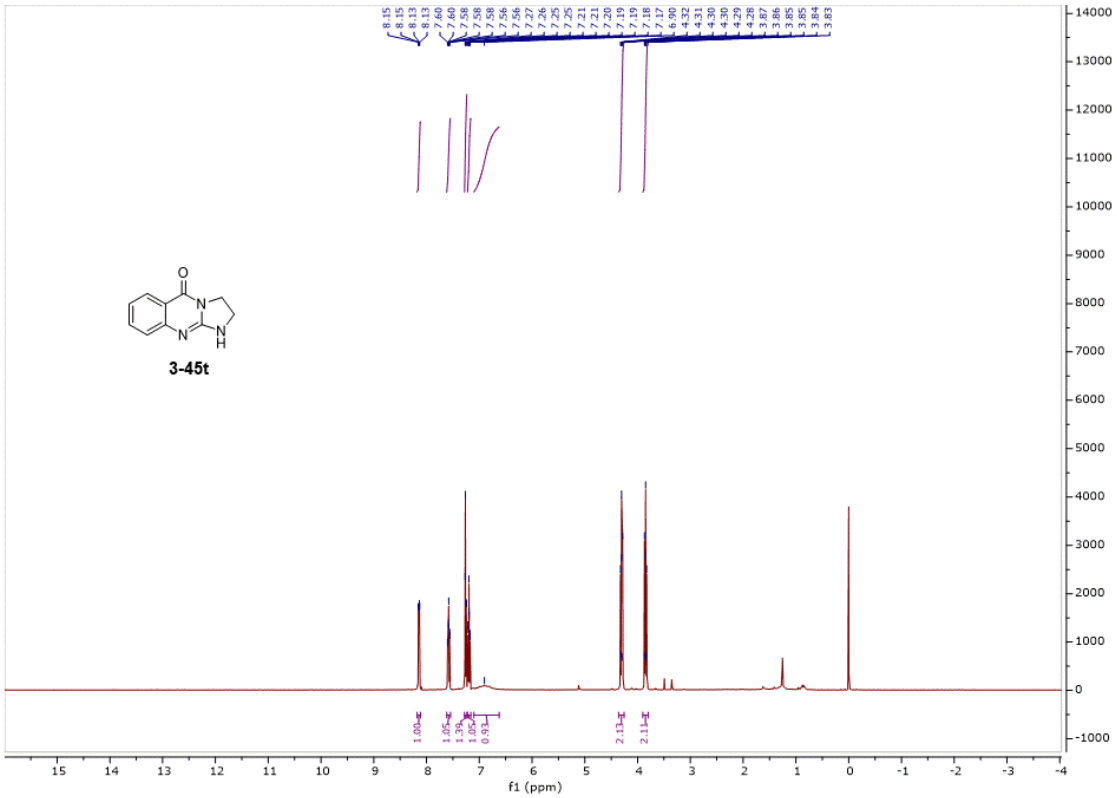

161.30
152.77
151.01
136.16
134.44
129.57
129.31
127.23
126.70
124.93
122.65
118.04
54.12
51.33
37.54
31.66
Bn
CH3
(S)-3-45q
f1 (ppm)

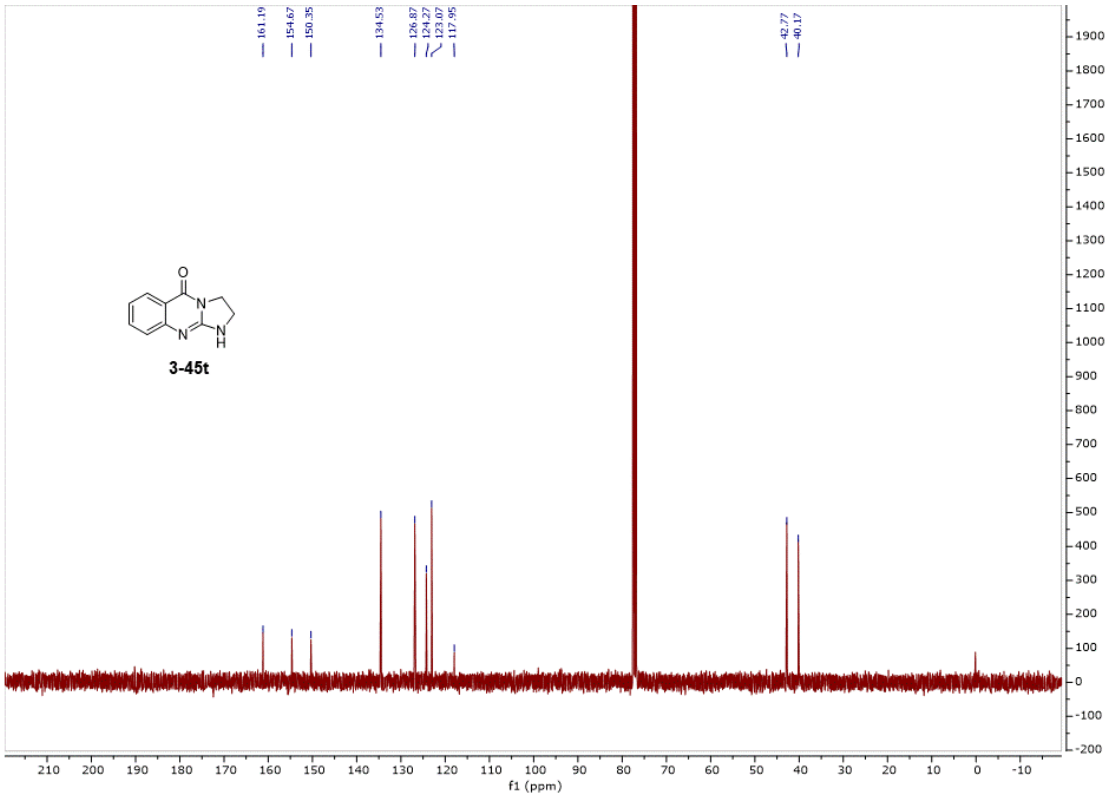

8.06
8.05
8.04
8.03
7.60
7.59
7.58
7.56
7.55
7.44
7.42
7.37
7.35
7.34
7.33
7.32
7.31
7.30
7.28
7.16
7.14
7.12
5.62
5.61
5.60
5.59
4.05
4.02
4.00
3.60
3.59
3.57
3.57
3.13
1.00
1.04
1.12
5.08
1.07
1.04
1.06
1.03
3.09
Ph
CH3
(S)-3-45r
f1 (ppm)

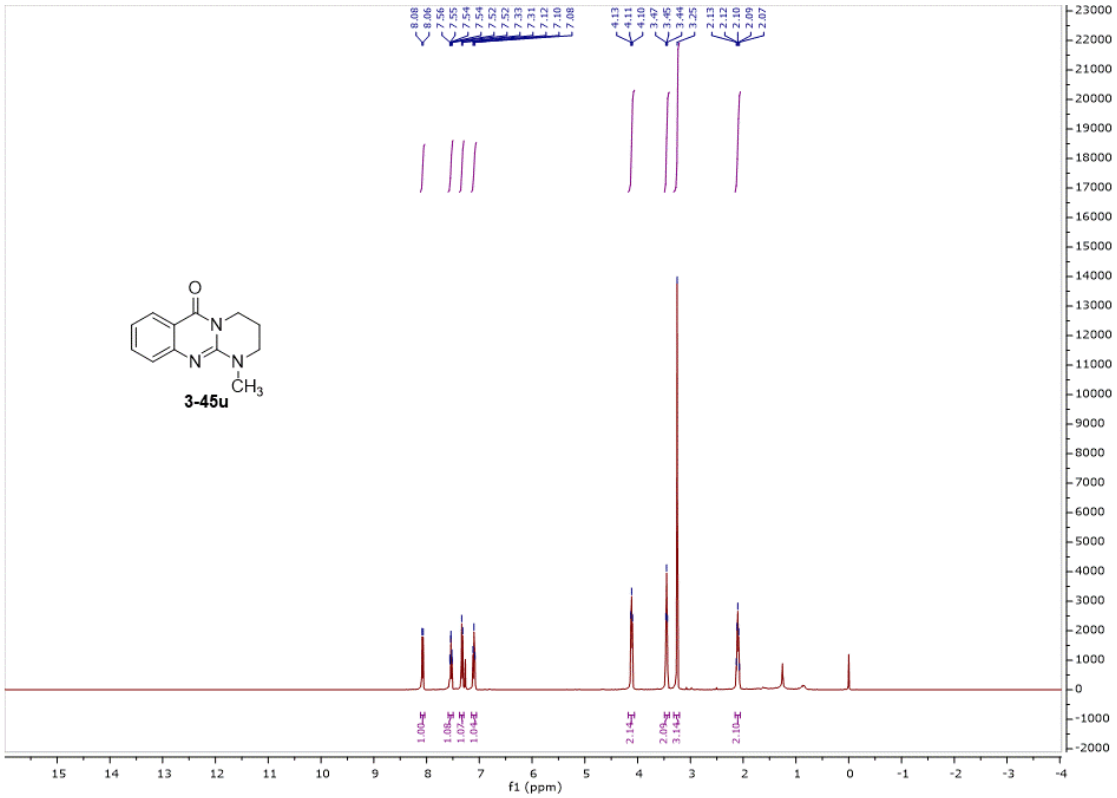

160.71
153.14
151.02
139.44
134.49
129.17
128.61
126.91
126.17
124.94
122.77
118.22
56.16
56.10
31.90
Ph
CH3
(S)-3-45r
f1 (ppm)

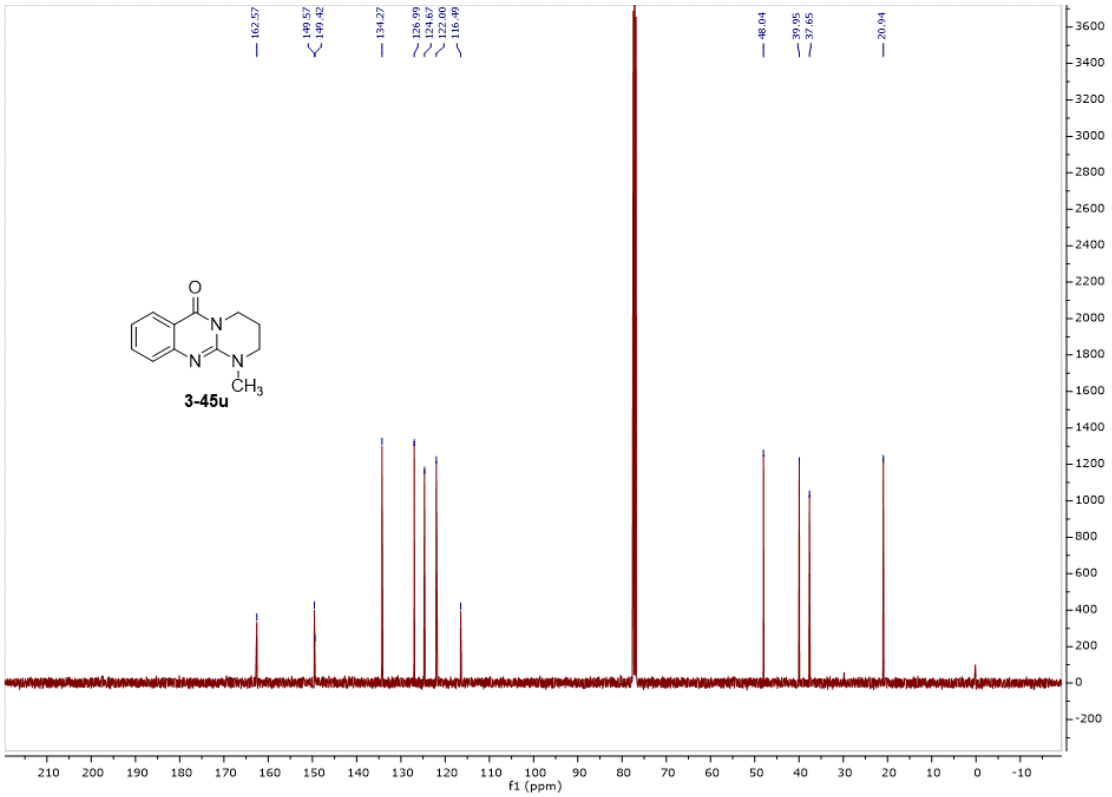

(±)-3-45s
f1 (ppm)

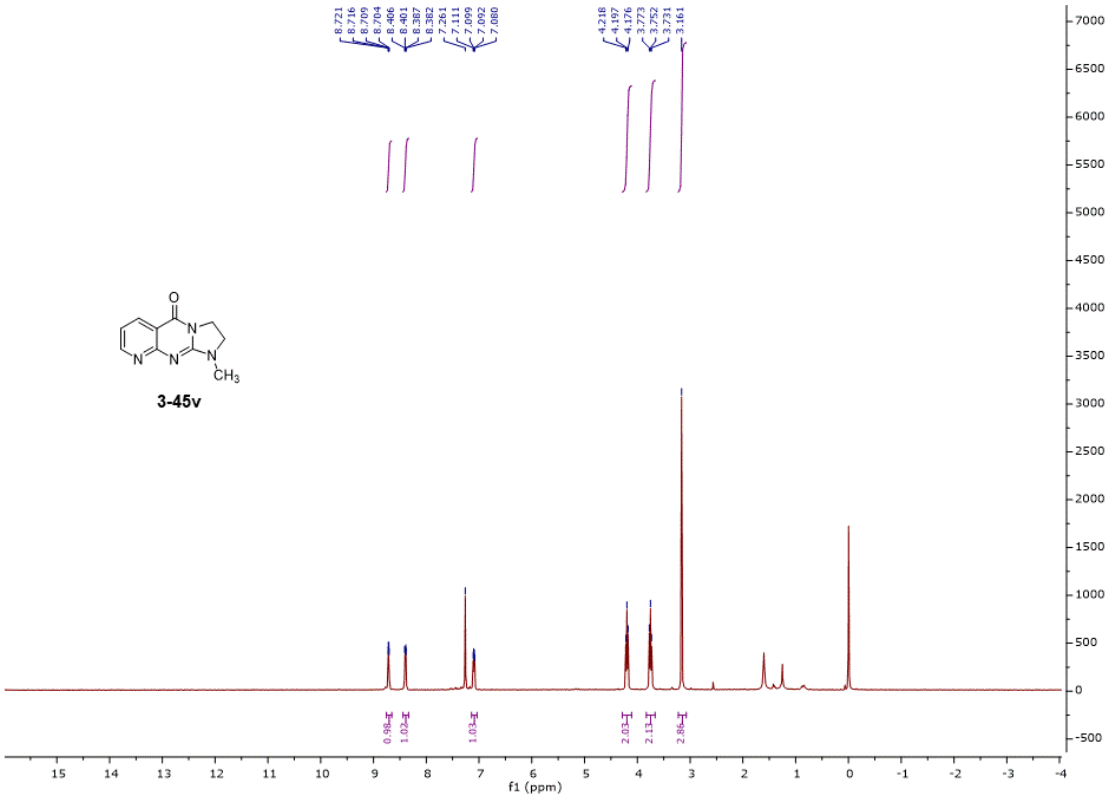

162.64
155.80
149.88
134.35
126.86
124.32
123.33
119.30
64.61
61.48
29.80
29.19
24.46
23.92
(±)-3-45s
f1 (ppm)

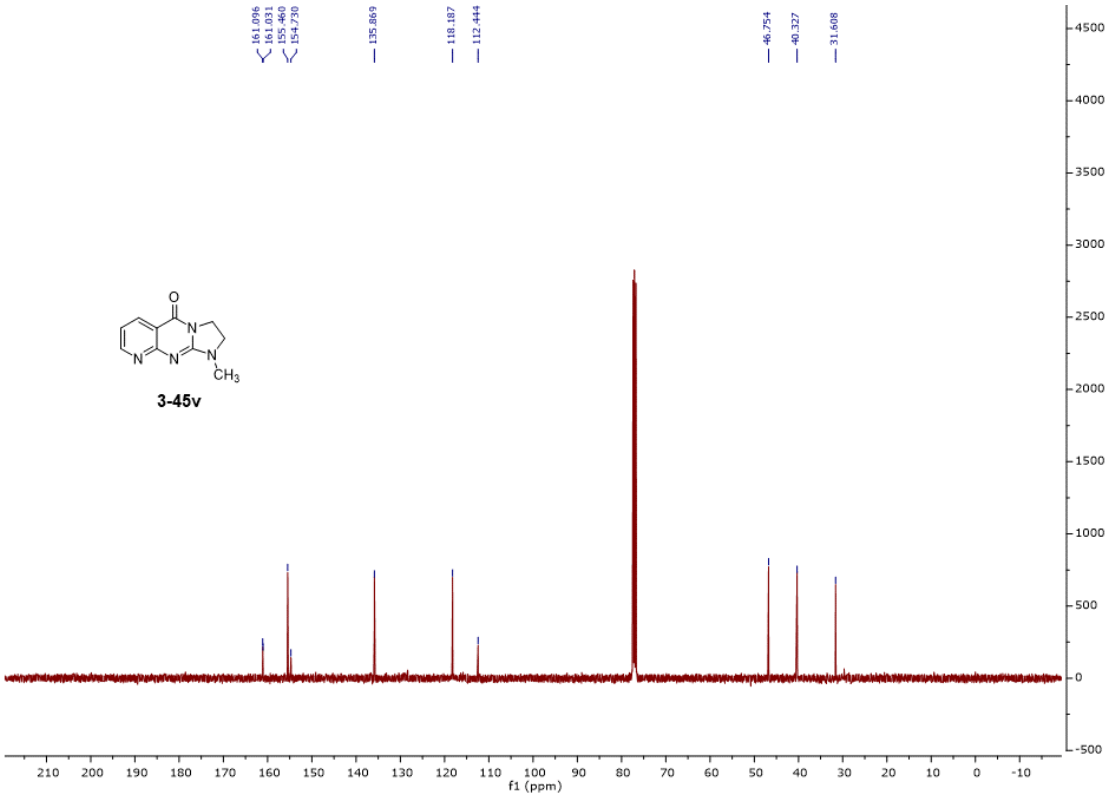

3-45t
f1 (ppm)

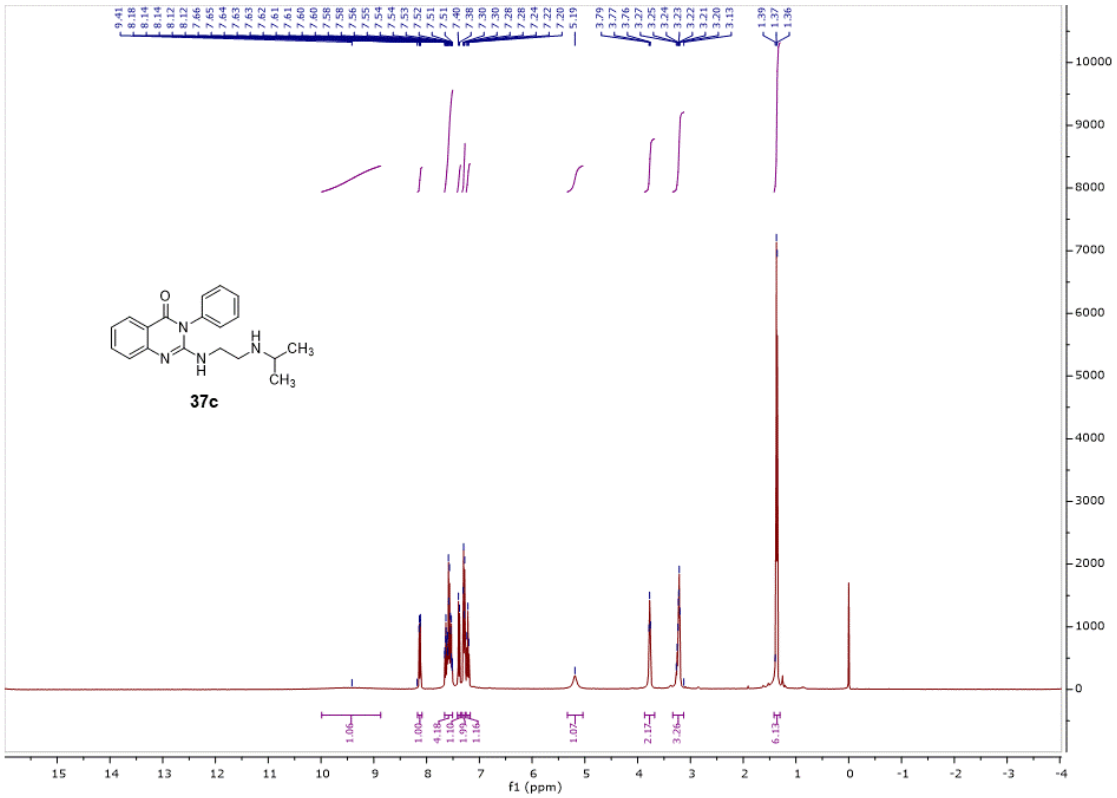

161.19
154.67
150.35
134.53
126.87
124.27
123.07
117.95
42.77
40.17
3-45t
f1 (ppm)

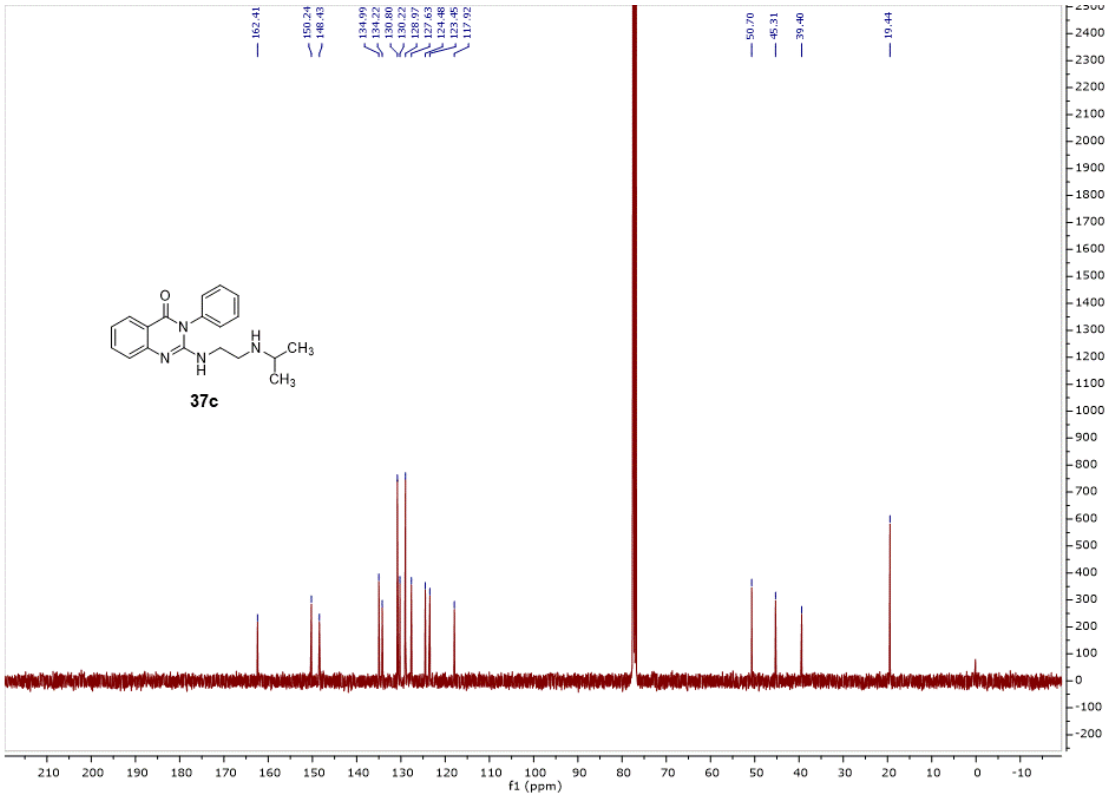

8.08
8.06
7.56
7.55
7.54
7.54
7.52
7.52
7.33
7.31
7.12
7.10
7.08
4.13
4.11
4.10
3.47
3.45
3.44
3.25
2.13
2.12
2.10
2.09
2.07
1.00
1.08
1.07
1.04
2.14
2.09
3.14
2.10
3-45u
f1 (ppm)

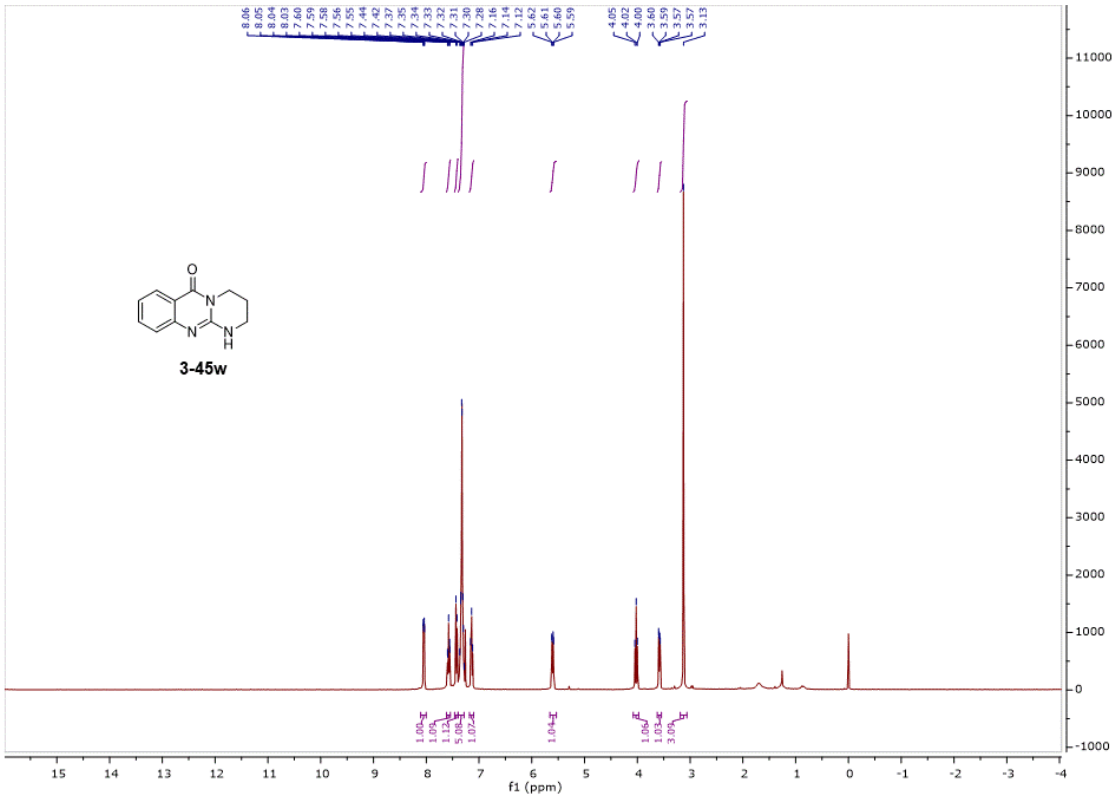

162.57
149.57
149.42
134.27
126.99
124.67
122.00
116.49
48.04
39.95
37.65
20.94
3-45u
f1 (ppm)

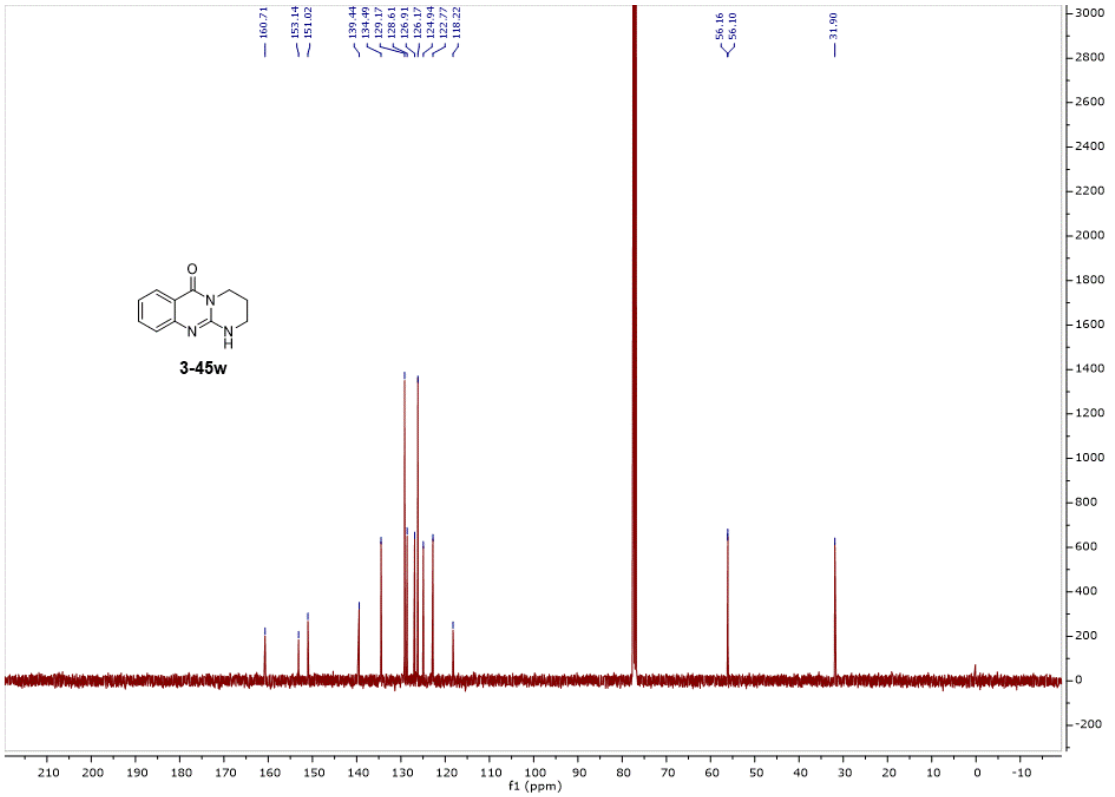

8.721
8.716
8.709
8.704
8.406
8.401
8.387
8.382
7.261
7.111
7.099
7.092
7.080
4.218
4.197
4.176
3.773
3.752
3.731
3.161
0.98
1.02
1.03
2.03
2.13
2.86
3-45v
f1 (ppm)

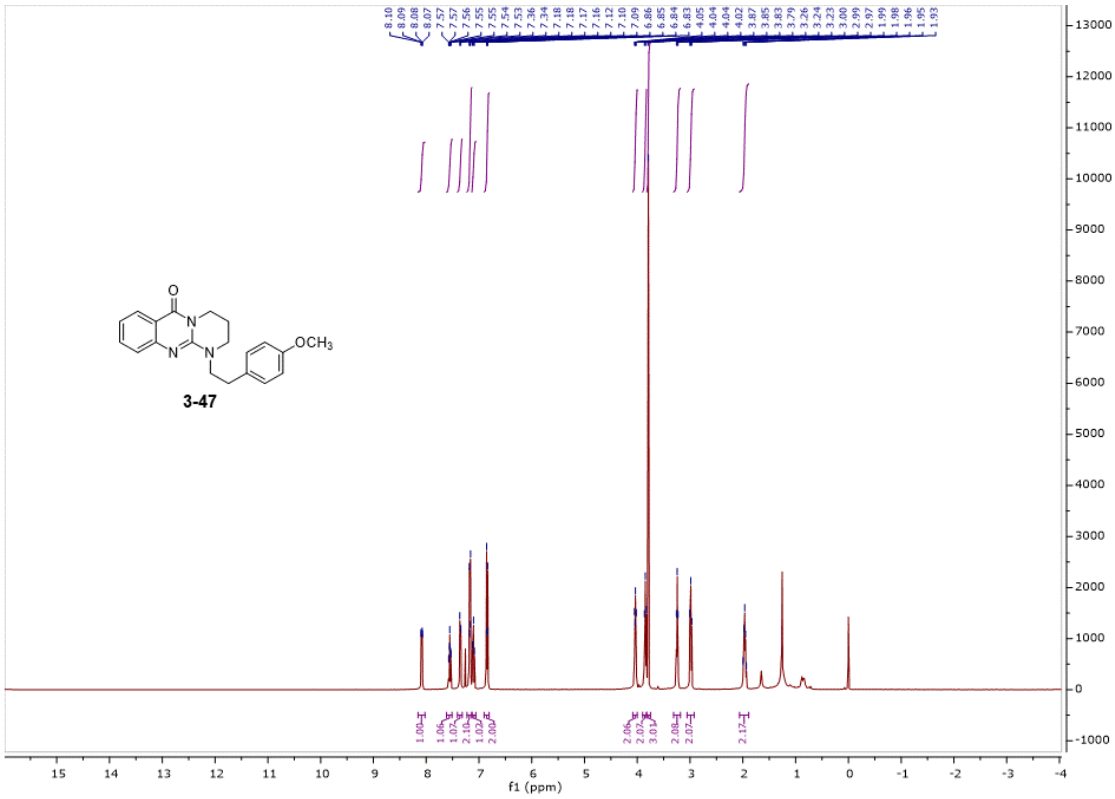

161.096
161.031
155.460
154.730
135.869
118.187
112.444
46.754
40.327
31.608
3-45v
f1 (ppm)

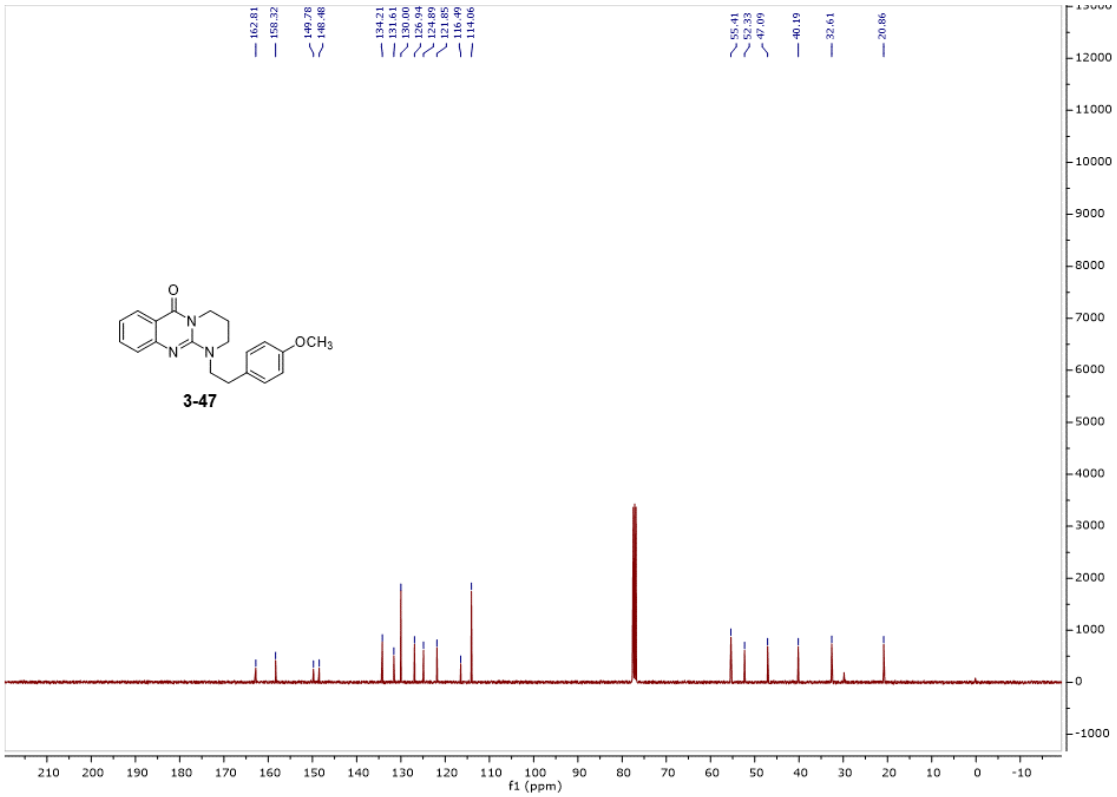

37c
f1 (ppm)

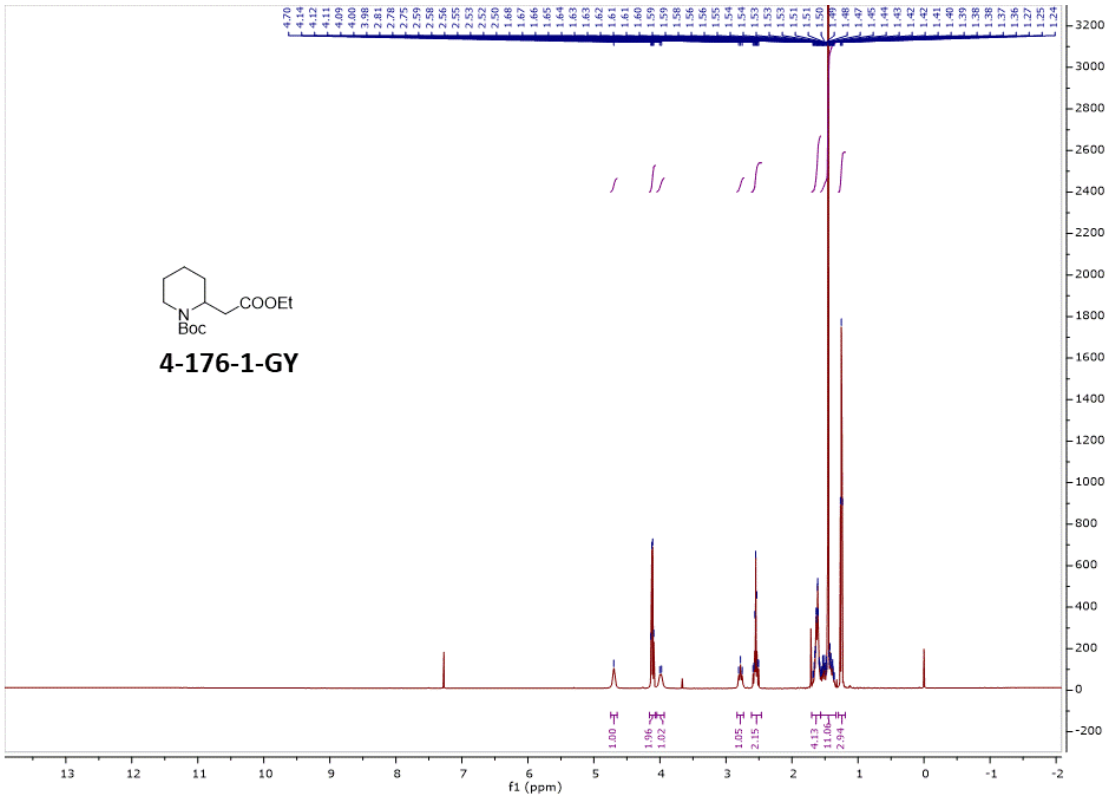

162.41
150.24
148.43
134.99
134.22
130.80
130.22
126.97
125.53
124.48
123.45
117.92
50.70
45.31
39.40
19.44
37c
f1 (ppm)

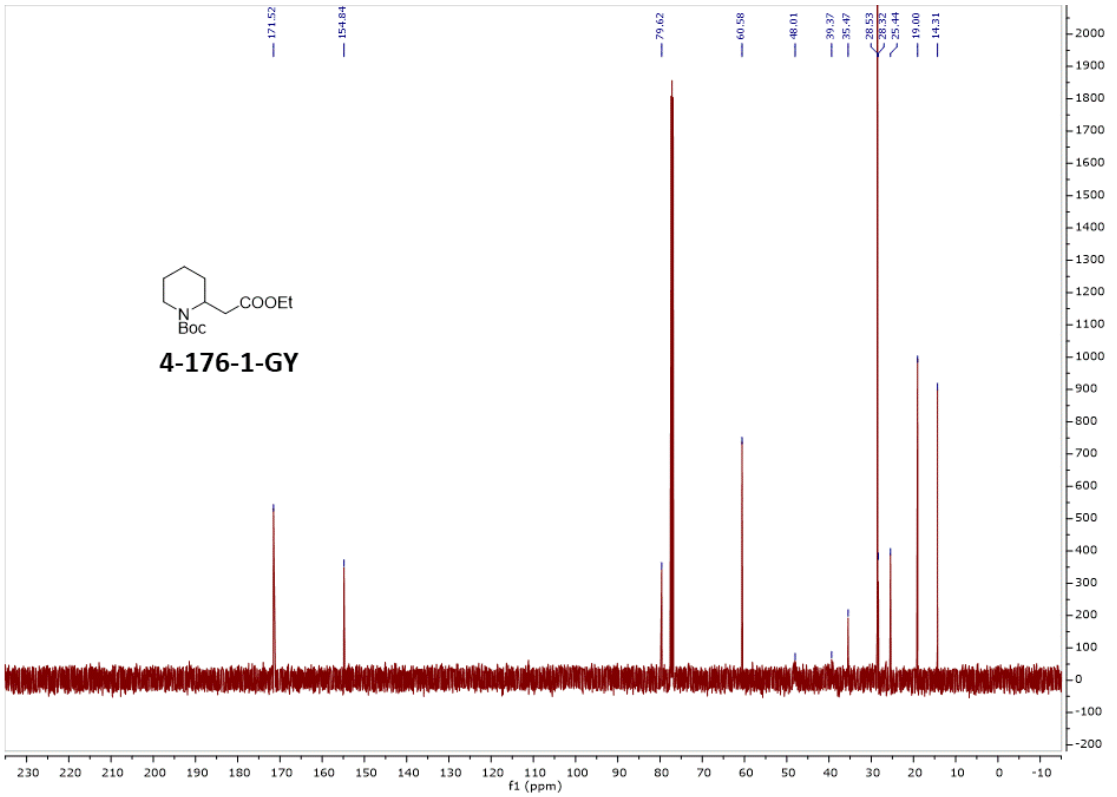

8.06
8.05
8.04
8.03
7.60
7.59
7.58
7.56
7.55
7.44
7.42
7.37
7.35
7.34
7.33
7.32
7.31
7.30
7.28
7.16
7.14
7.12
5.62
5.61
5.60
5.59
4.05
4.02
4.00
3.60
3.59
3.57
3.57
3.13
3-45w
f1 (ppm)

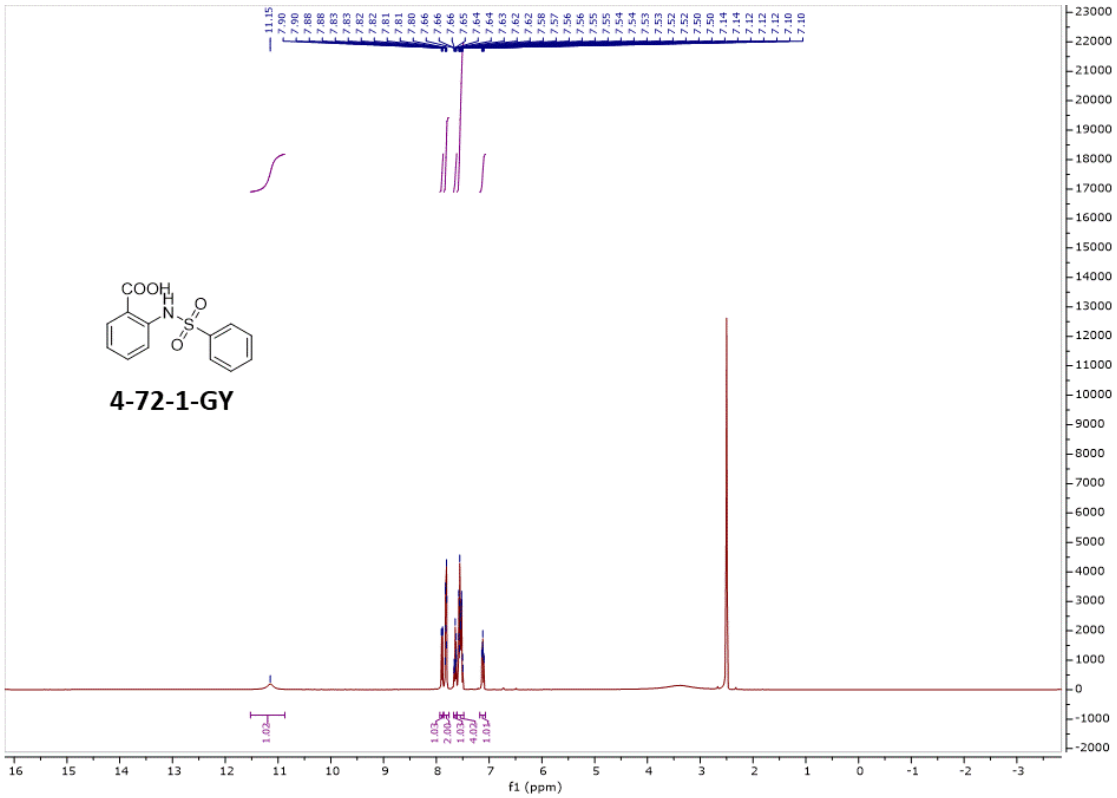

160.71
153.14
151.02
139.44
134.49
129.17
128.61
126.91
126.17
124.94
122.77
118.22
56.16
56.10
31.90
3-45w
f1 (ppm)

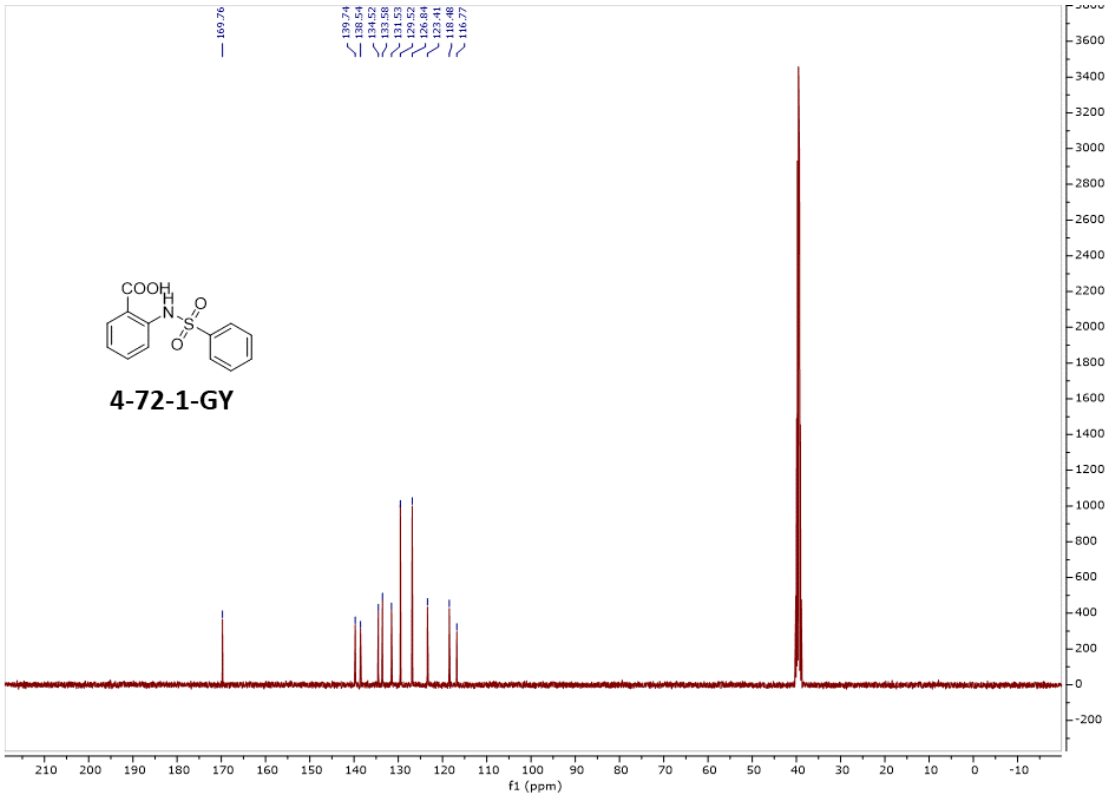

OCH3
3-47
f1 (ppm)

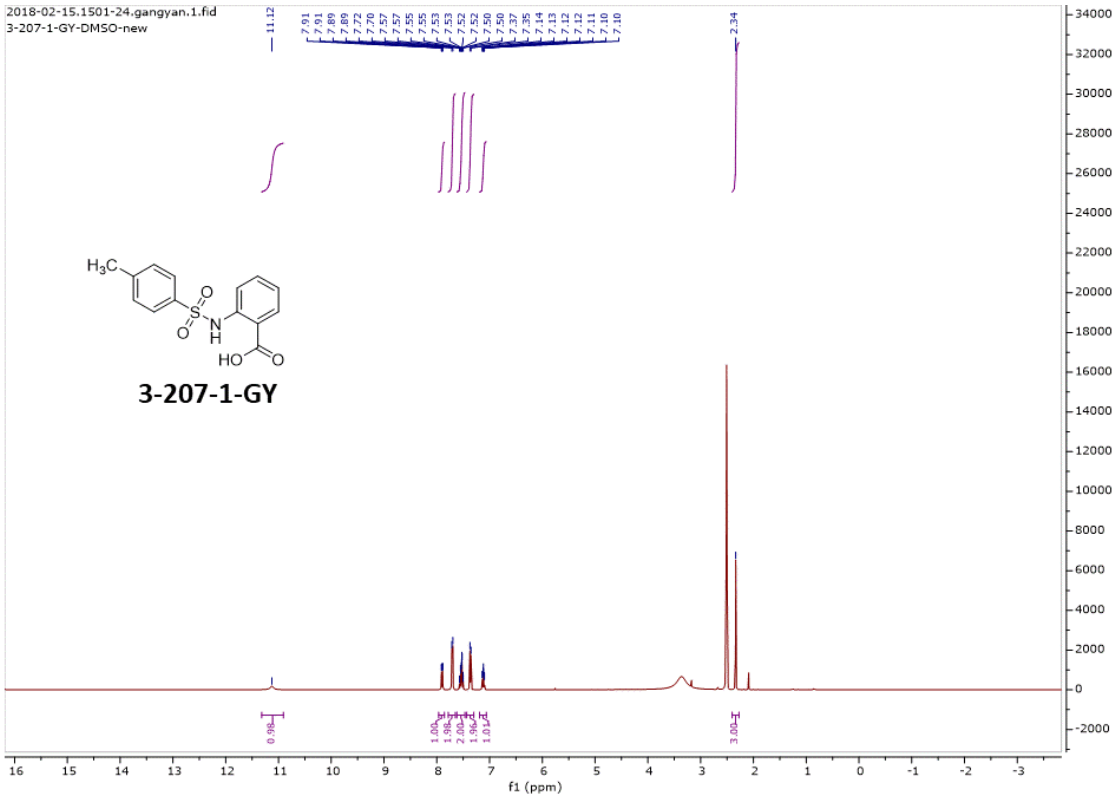

162.81
158.32
149.78
148.48
134.21
131.61
130.00
126.94
124.89
121.85
116.49
114.06
55.41
52.33
47.09
40.19
32.61
20.86
OCH3
3-47
f1 (ppm)

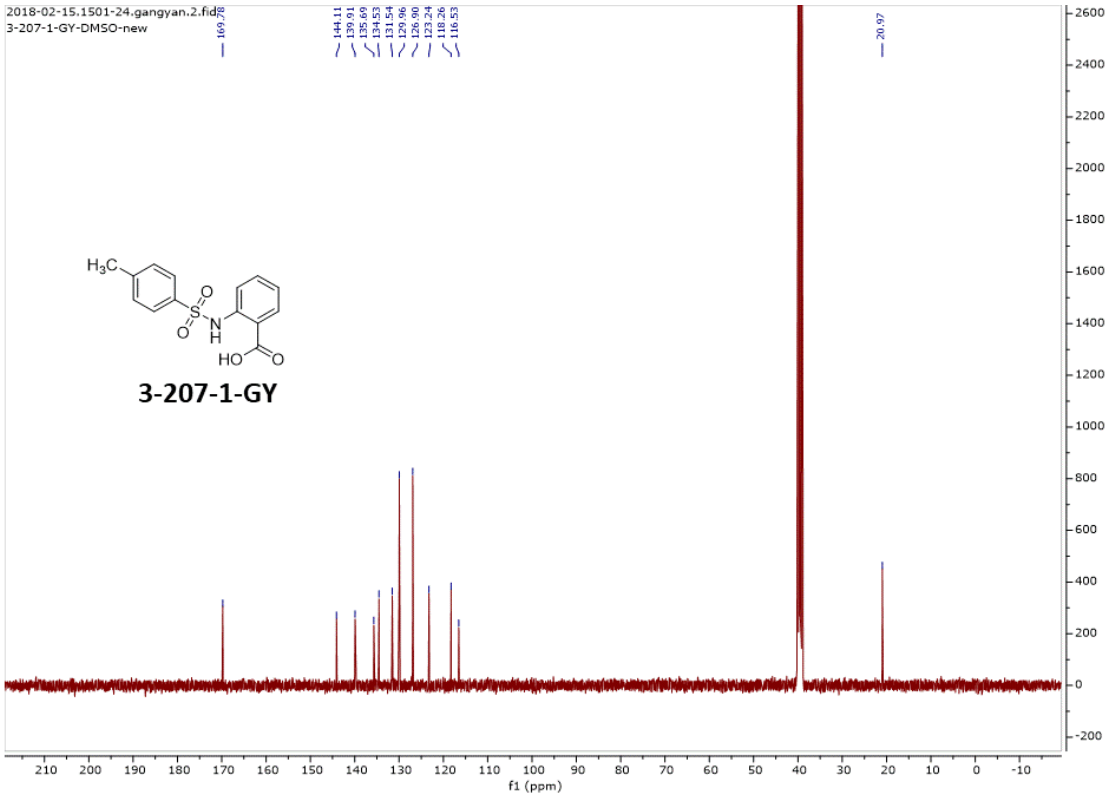

COOEt
N
Boc
4-176-1-GY
f1 (ppm)

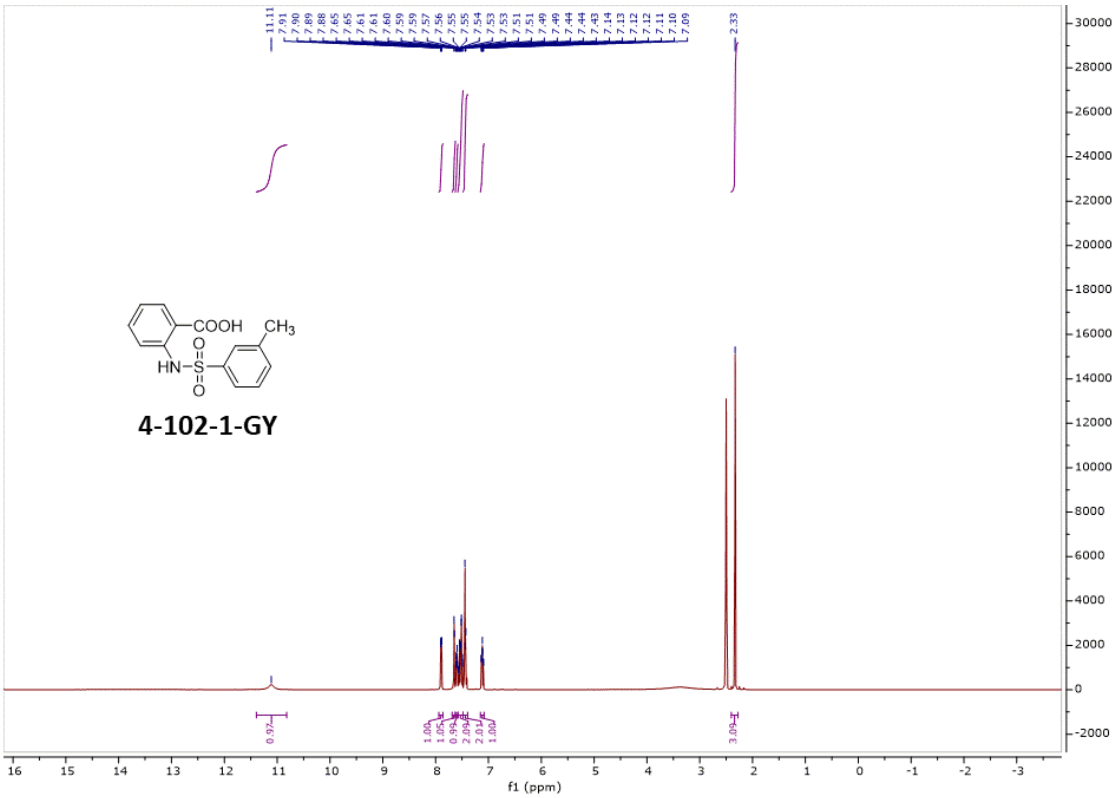

171.52
154.84
79.62
60.58
48.01
39.37
35.47
28.53
28.32
25.44
19.00
14.31
COOEt
N
Boc
4-176-1-GY
f1 (ppm)


11.15
7.90
7.88
7.83
7.82
7.81
7.80
7.66
7.65
7.64
7.63
7.62
7.58
7.57
7.56
7.55
7.54
7.53
7.52
7.50
7.14
7.12
7.10
COOH
H
N
S
O
O
4-72-1-GY
1.02
1.03
2.00
1.03
4.02
1.01
f1 (ppm)

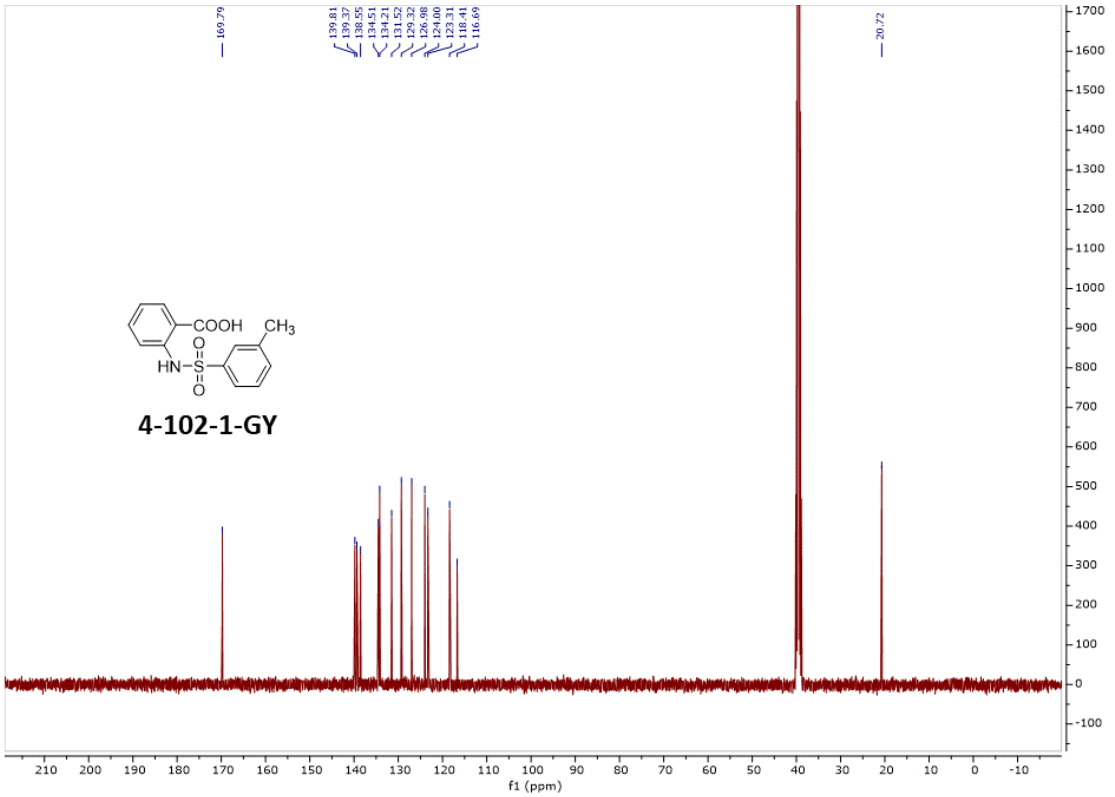

169.76
139.74
138.54
134.52
133.68
131.53
129.52
126.84
123.41
118.48
116.77
COOH
H
N
S
O
O
4-72-1-GY
f1 (ppm)


2018-02-15.1501-24.gangyan.1.fid
3-207-1-GY-DMSO-new
11.12
7.91
7.91
7.89
7.89
7.72
7.70
7.57
7.57
7.55
7.55
7.53
7.53
7.52
7.52
7.50
7.50
7.37
7.35
7.14
7.13
7.12
7.12
7.11
7.10
7.10
2.34
H3C
S
O
O
N
H
HO
O
3-207-1-GY
f1 (ppm)

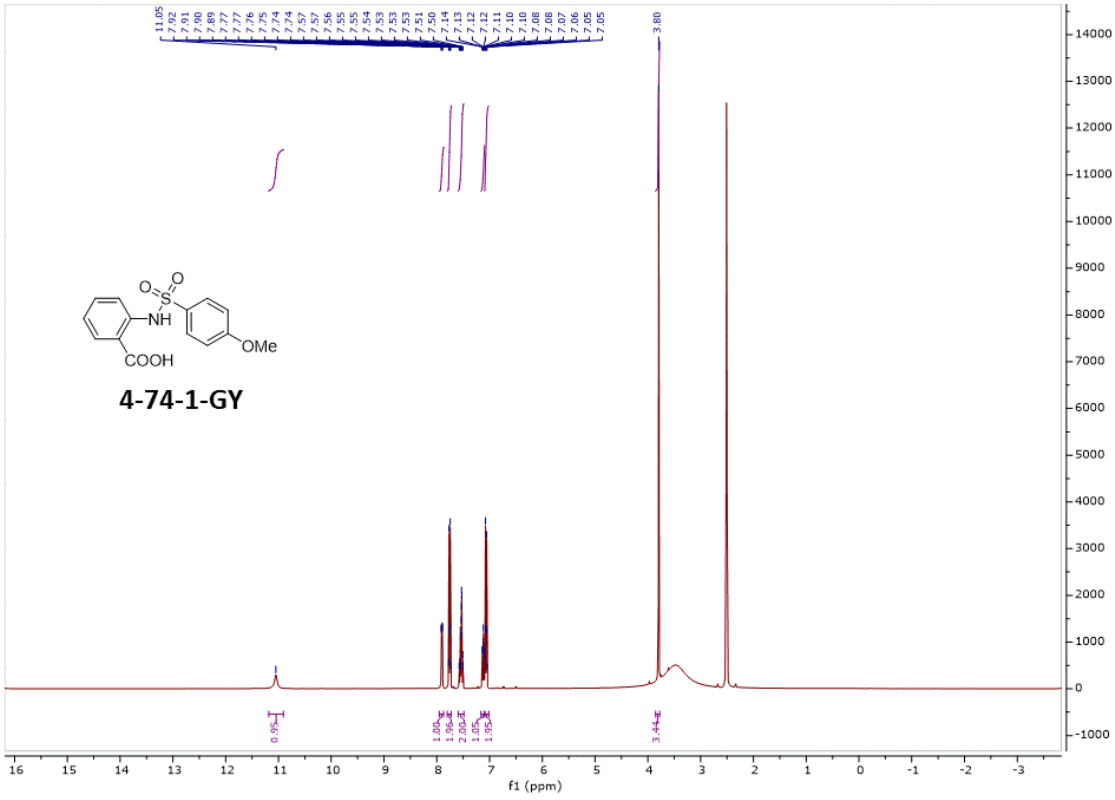

2018-02-15.1501-24.gangyan.2.fid
3-207-1-GY-DMSO-new
169.78
144.11
139.91
135.69
134.53
131.54
129.96
126.90
123.24
118.26
116.53
20.97
H3C
O
S
O
N
H
HO
O
3-207-1-GY
f1 (ppm)


11.11
7.91
7.90
7.89
7.88
7.65
7.65
7.61
7.61
7.60
7.59
7.59
7.57
7.56
7.55
7.55
7.54
7.53
7.53
7.51
7.51
7.49
7.49
7.44
7.44
7.43
7.14
7.13
7.12
7.12
7.11
7.10
7.09
2.33
COOH
CH3
HN
S
O
O
0.97
1.00
1.05
0.99
2.09
2.01
1.00
3.09
f1 (ppm)

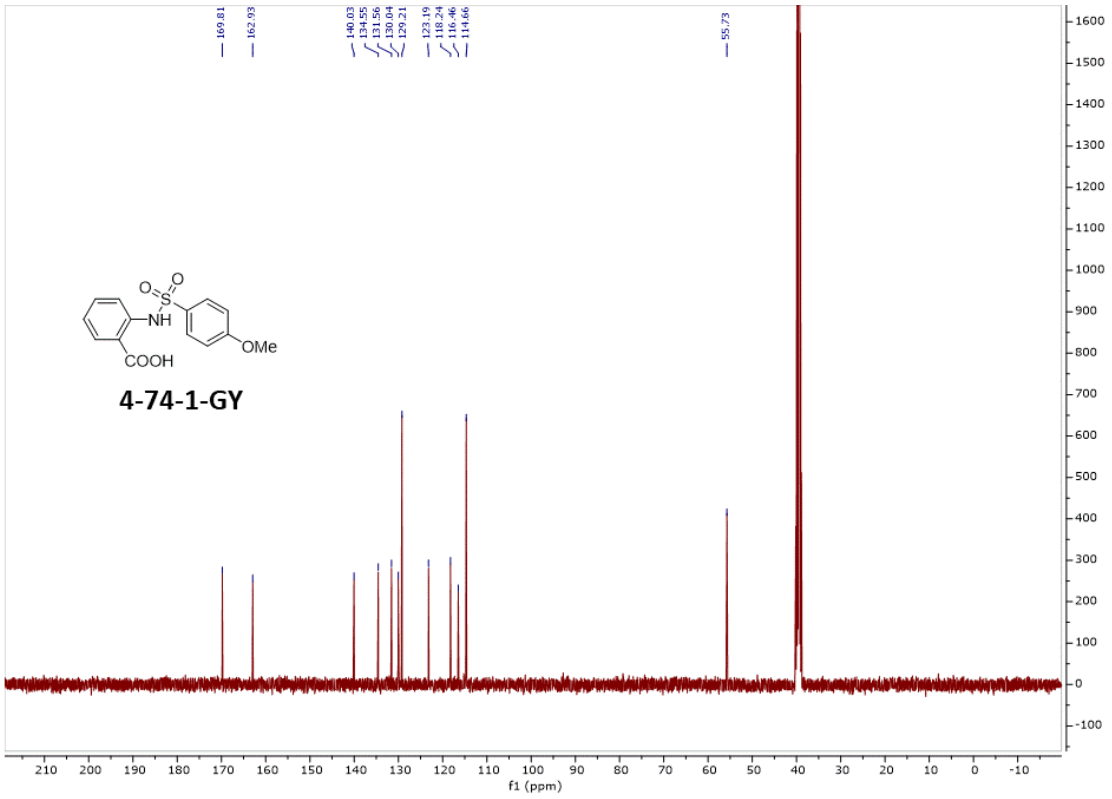
**4-102-1-GY**



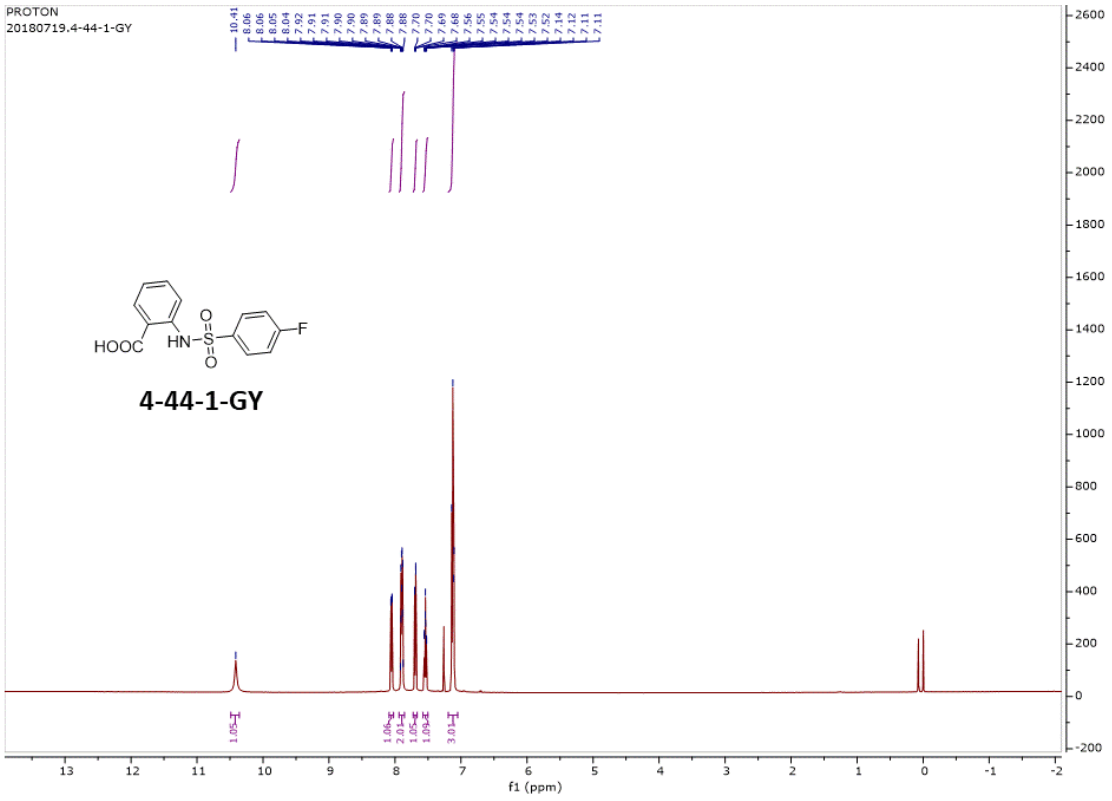

**4-102-1-GY**



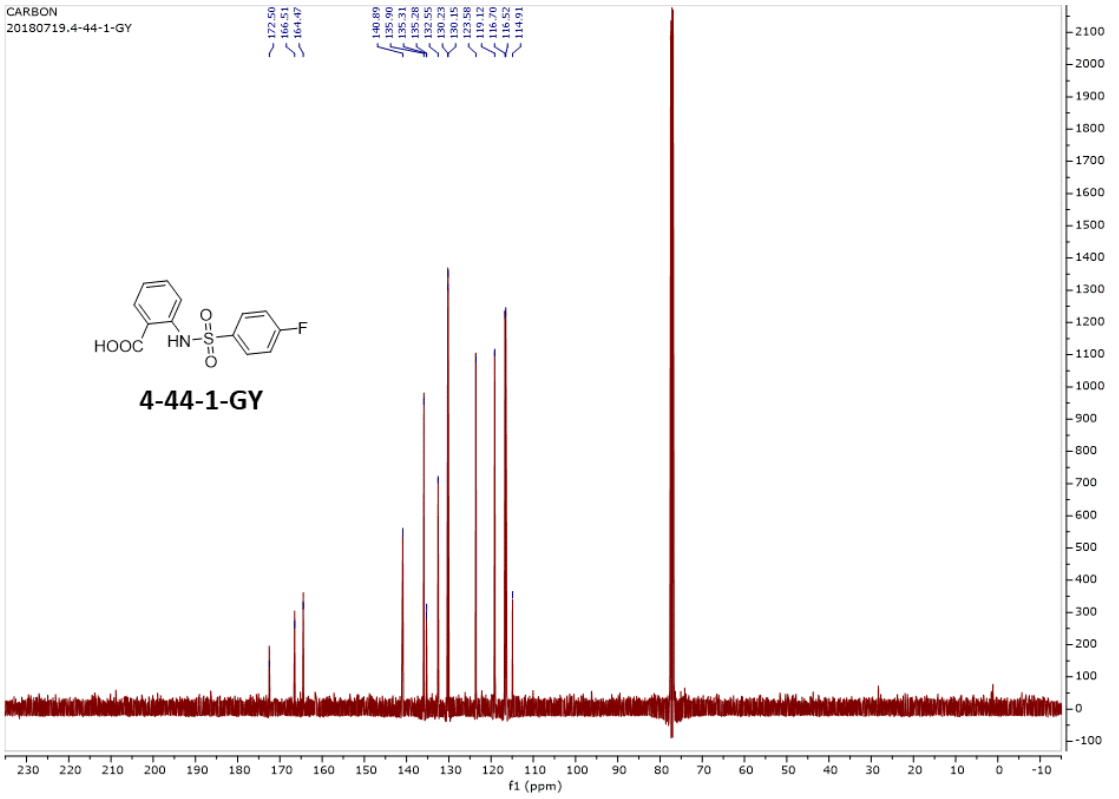

**4-74-1-GY**

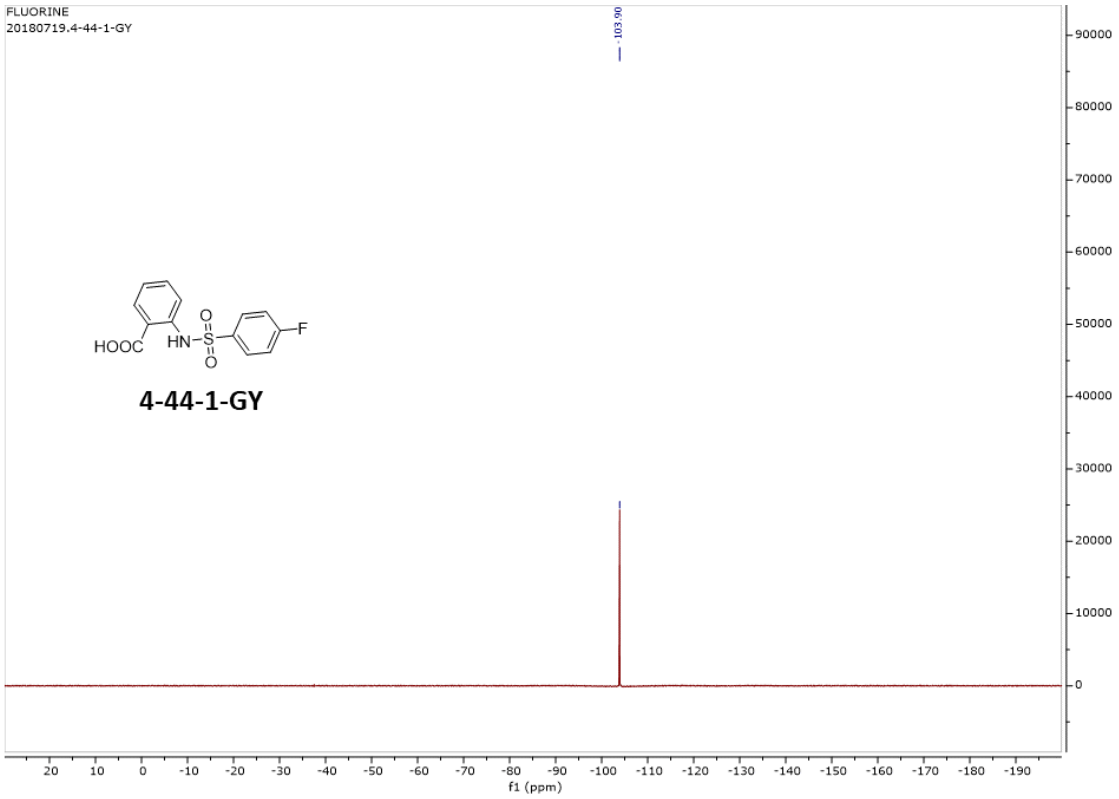


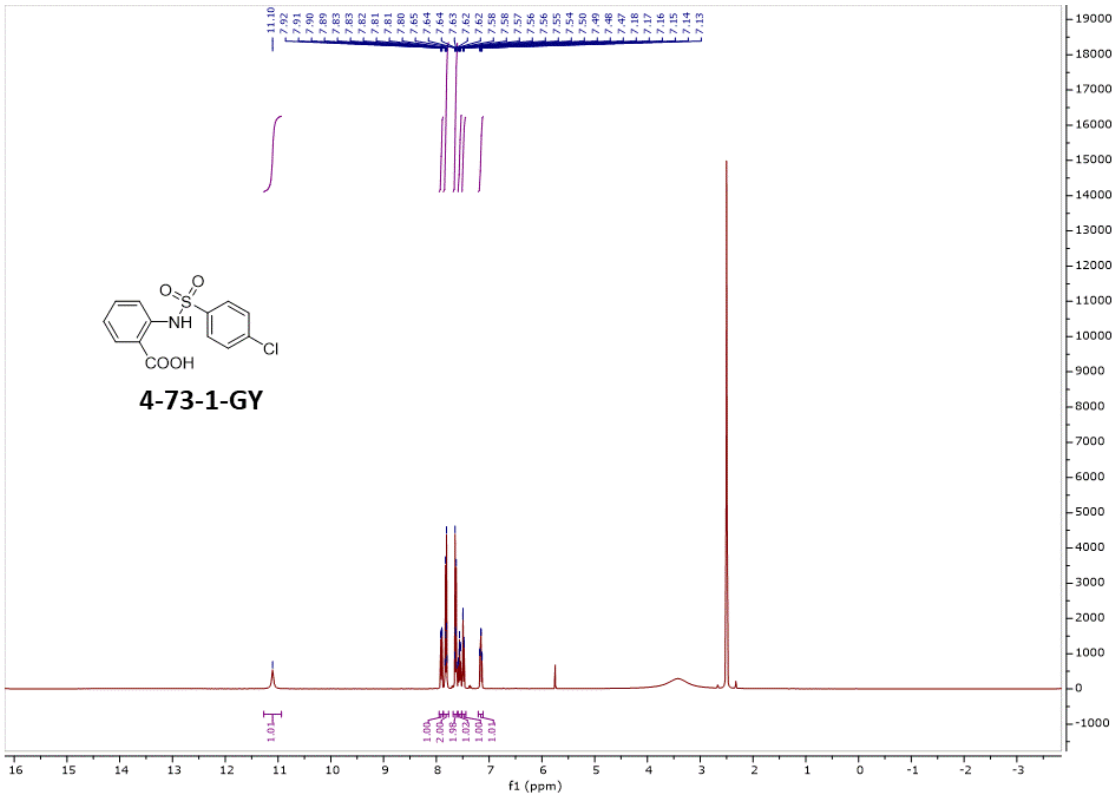

**4-74-1-GY**

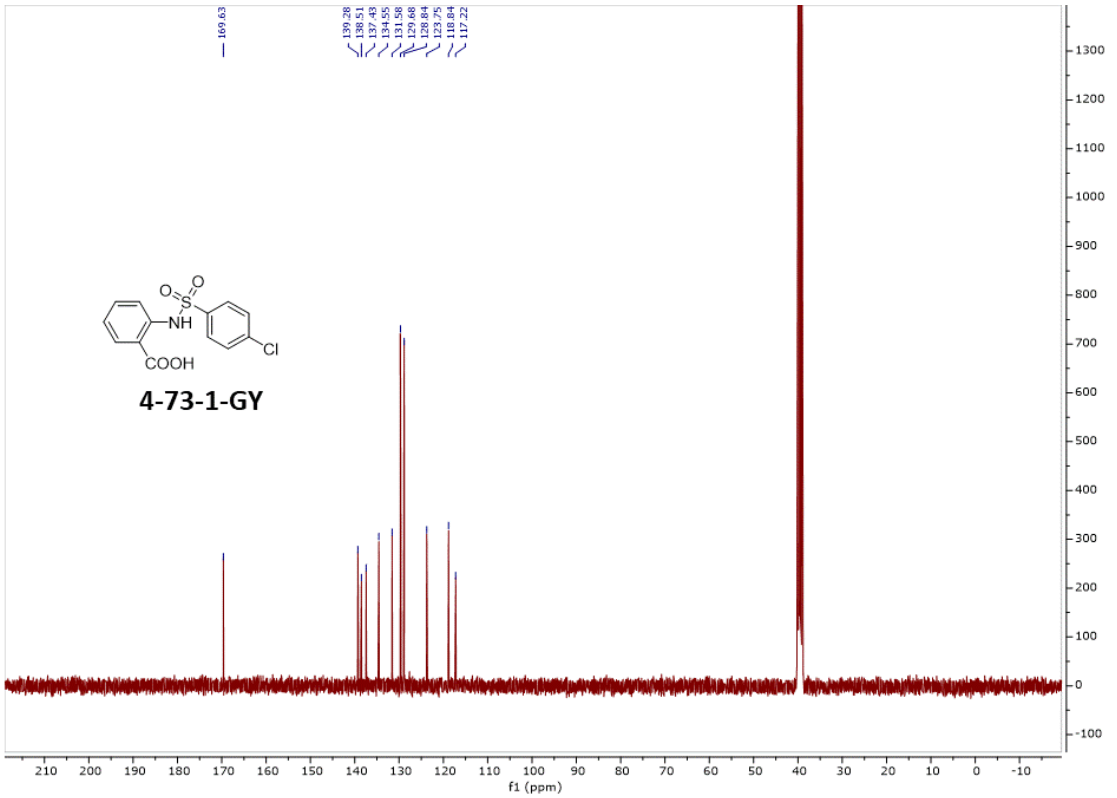


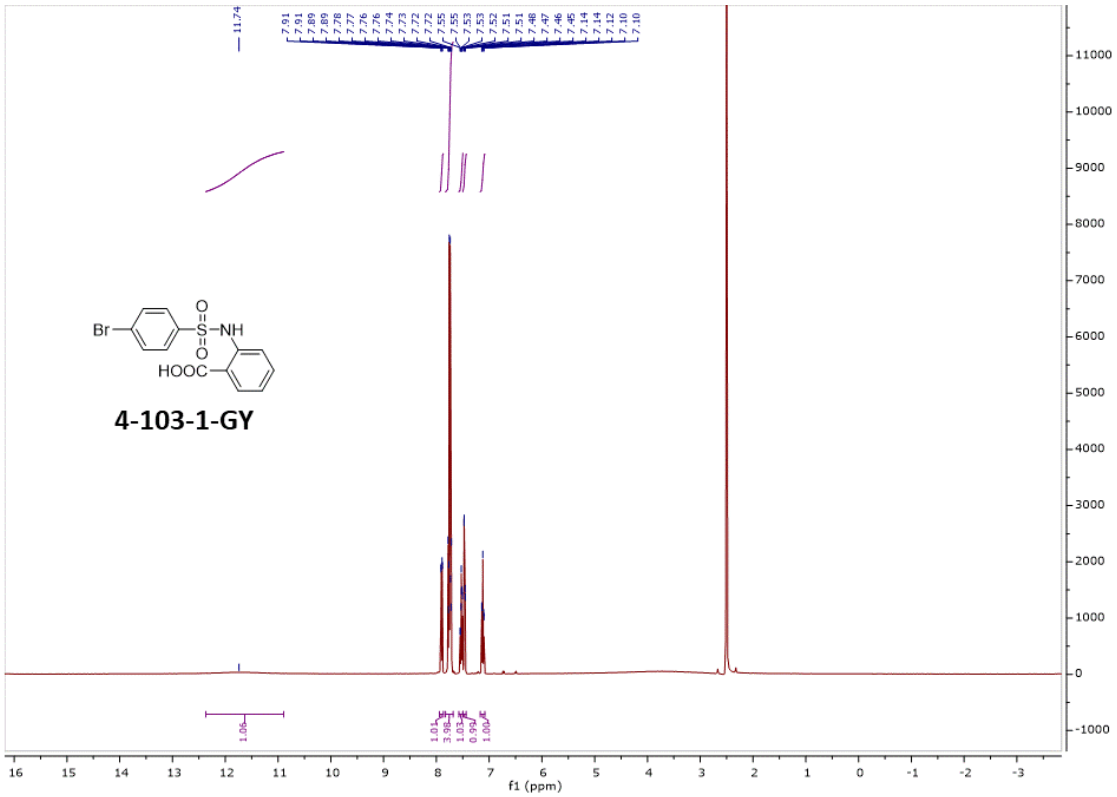

**4-44-1-GY**

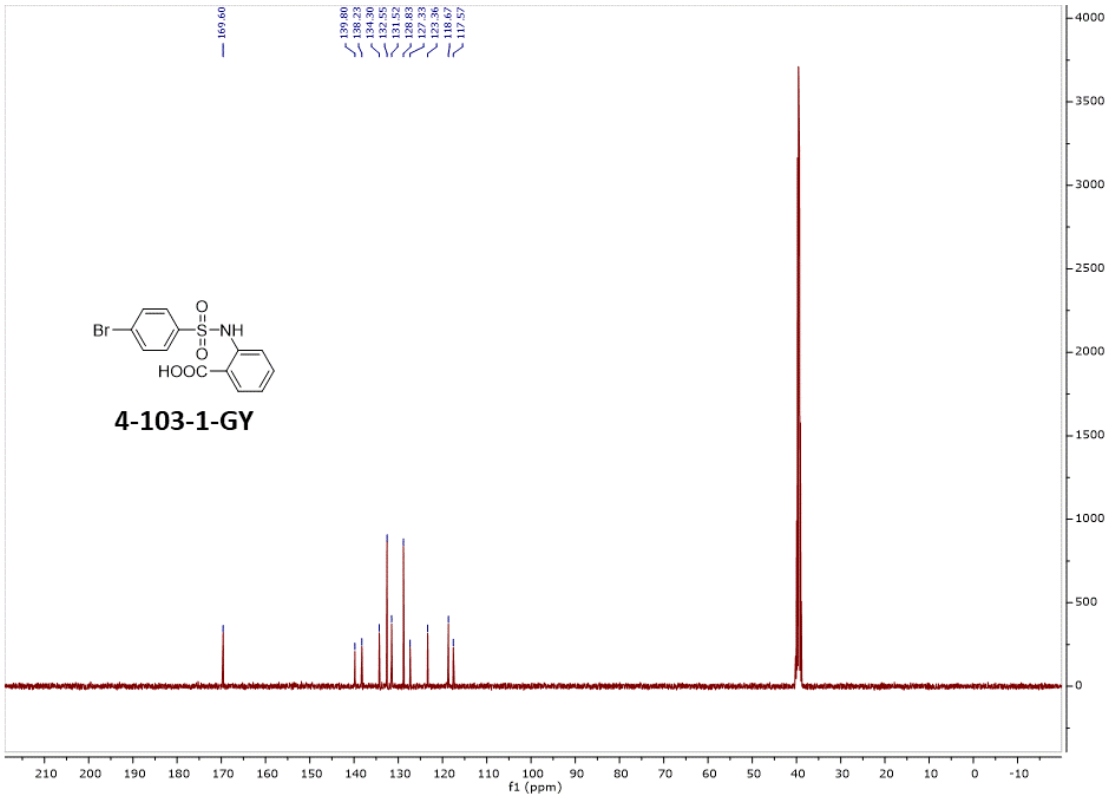

CARBON
20180719.4-44-1-GY
172.50
166.51
164.47
140.89
135.90
135.31
135.28
132.55
130.23
130.15
123.58
119.12
116.70
116.52
114.91
HOOC
HN
S
O
O
F
4-44-1-GY
f1 (ppm)

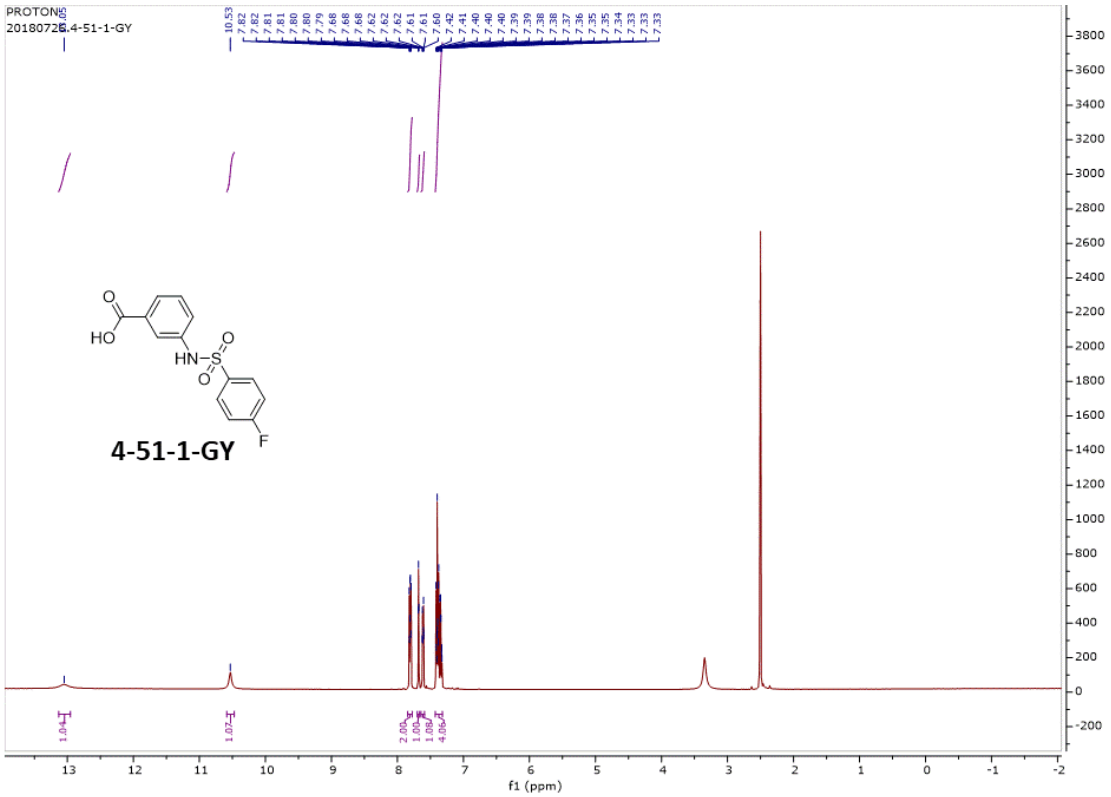

FLUORINE
20180719.4-44-1-GY
-103.90
HOOC
HN
S
O
O
F
4-44-1-GY
f1 (ppm)

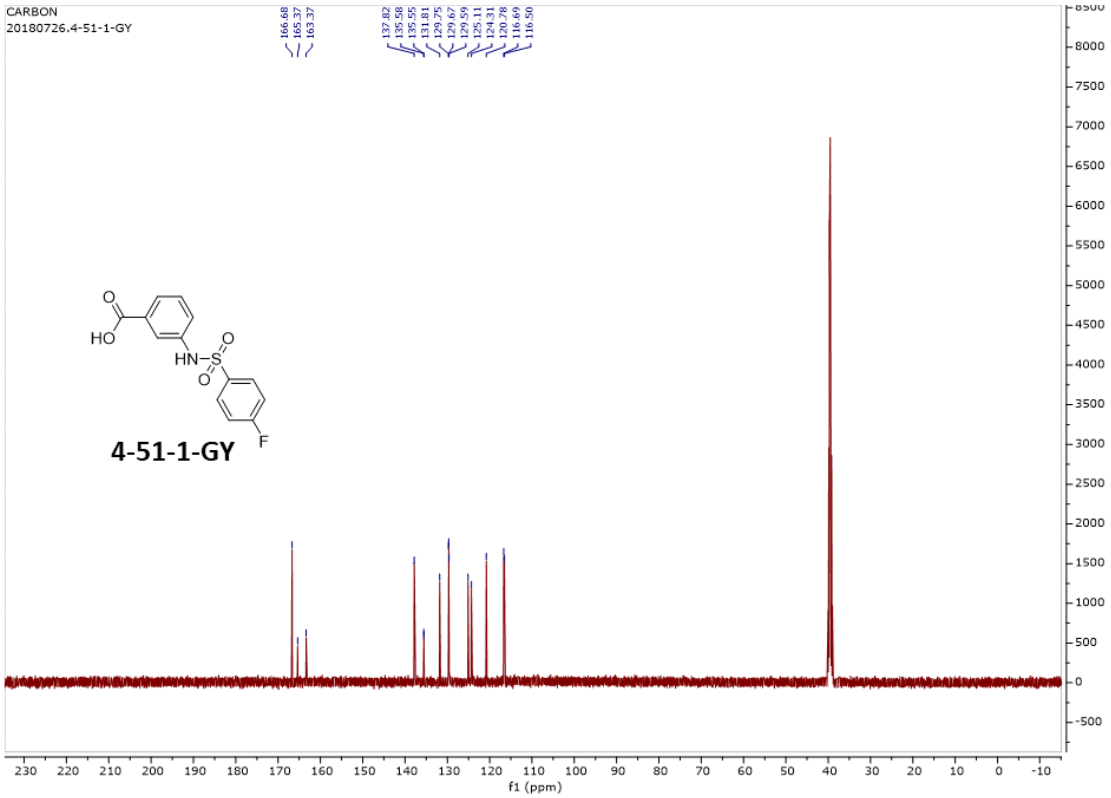

11.10
7.92
7.91
7.90
7.89
7.83
7.83
7.82
7.81
7.81
7.80
7.65
7.64
7.64
7.63
7.62
7.62
7.58
7.58
7.57
7.56
7.56
7.55
7.54
7.50
7.49
7.48
7.47
7.18
7.17
7.16
7.15
7.14
7.13
1.01
1.00
2.00
1.98
1.02
1.00
1.01
f1 (ppm)
NH
COOH
Cl
4-73-1-GY

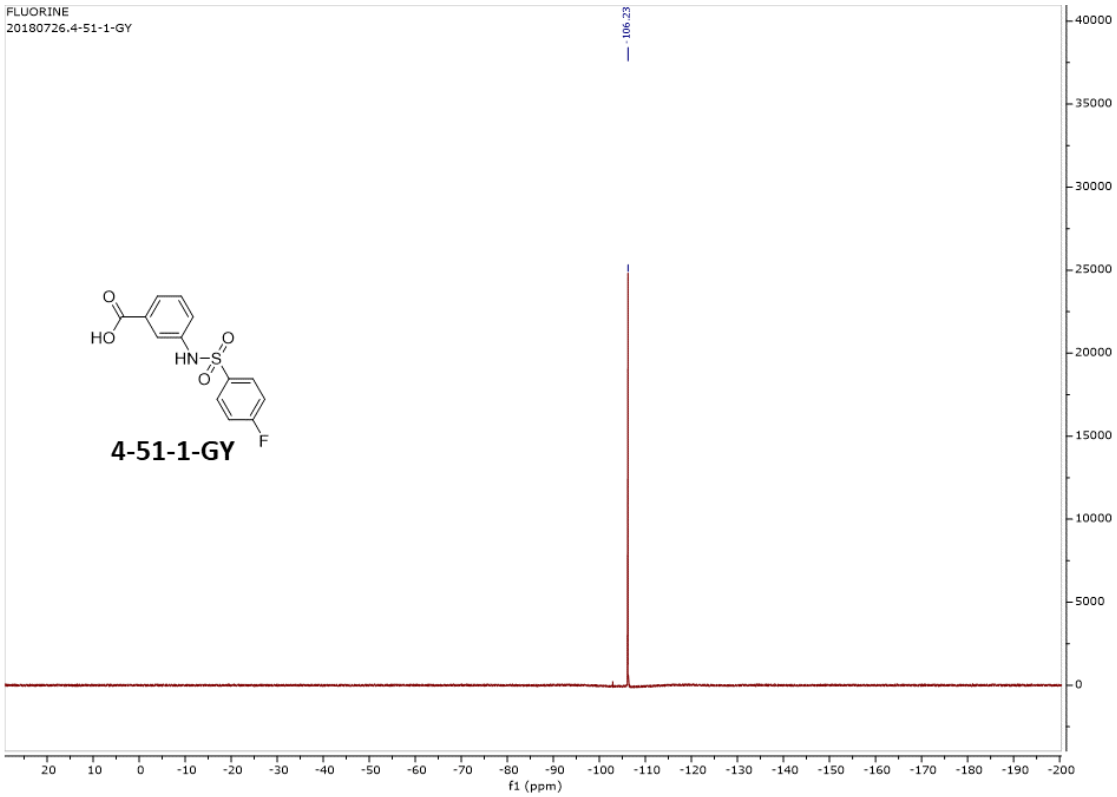

169.63
139.28
138.51
137.48
134.55
131.58
129.68
128.84
123.75
118.84
117.22
f1 (ppm)
NH
COOH
Cl
4-73-1-GY

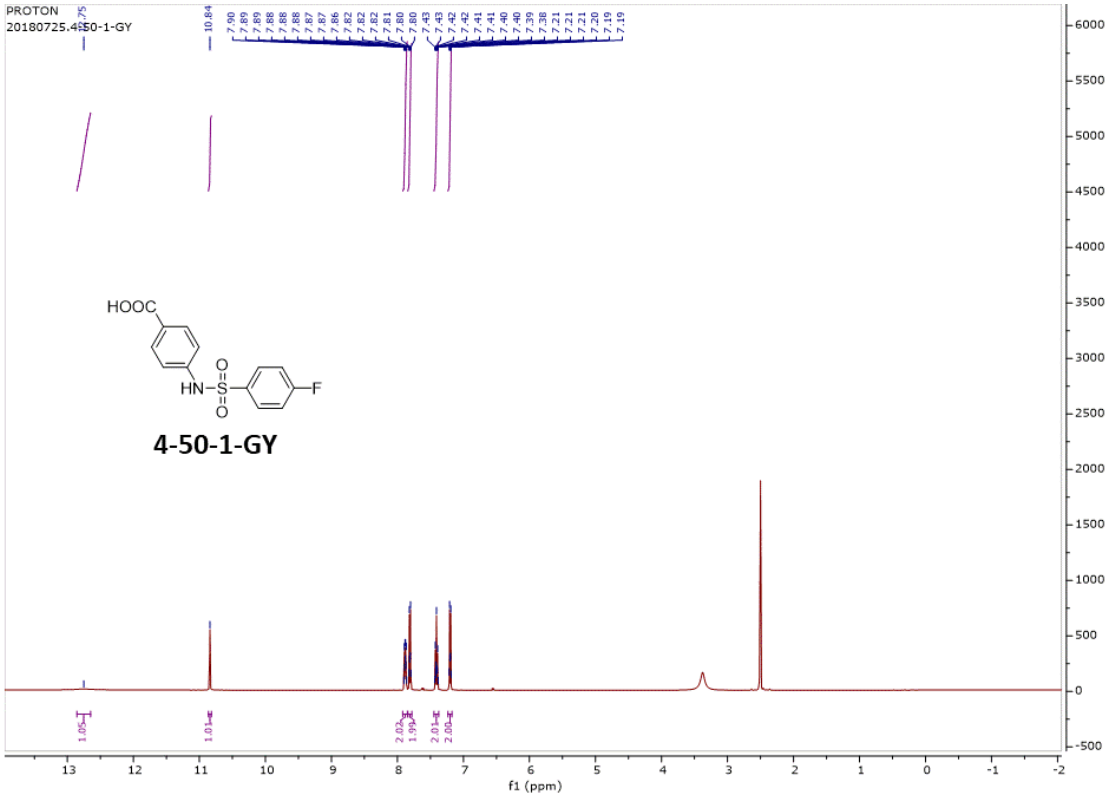

11.74
7.91
7.91
7.89
7.89
7.78
7.77
7.76
7.76
7.74
7.73
7.72
7.72
7.55
7.53
7.53
7.52
7.51
7.51
7.48
7.47
7.46
7.45
7.14
7.14
7.12
7.10
7.10
Br
O
S
NH
O
HOOC
4-103-1-GY
1.06
1.01
3.98
1.03
0.99
1.00
f1 (ppm)

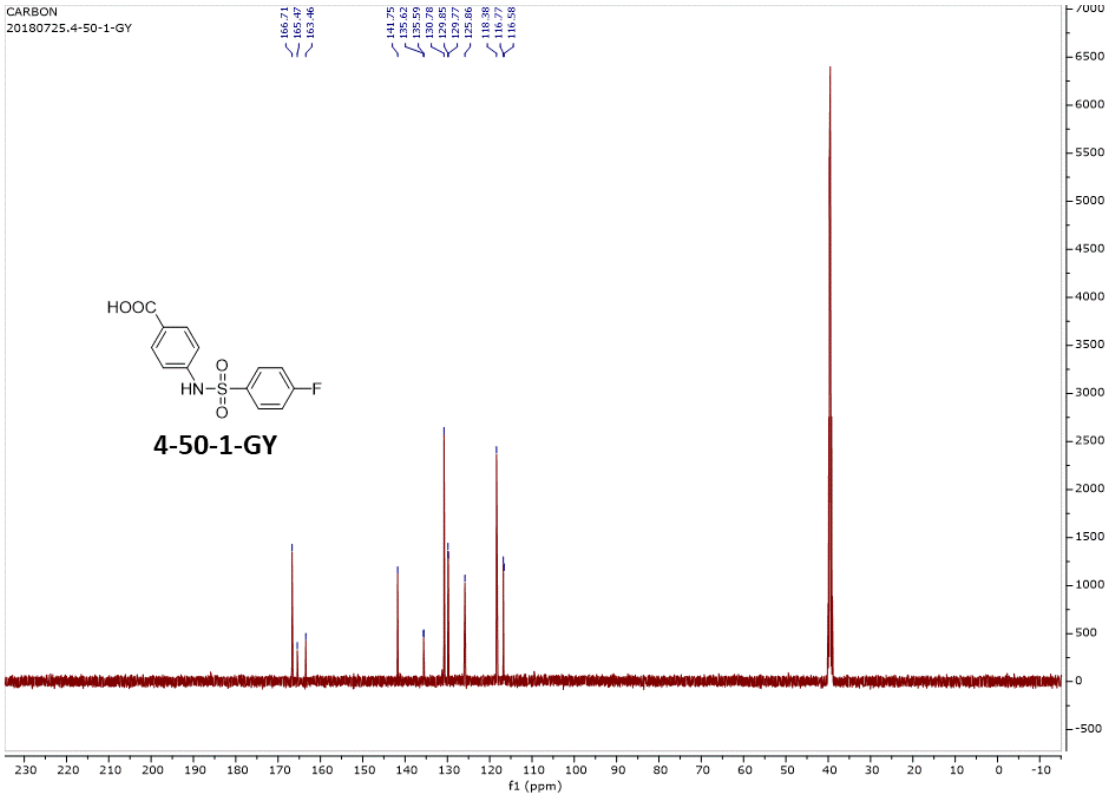

169.60
139.80
138.23
134.30
132.55
131.52
128.83
127.33
123.36
118.67
117.57
Br
O
S
NH
O
HOOC
4-103-1-GY
f1 (ppm)

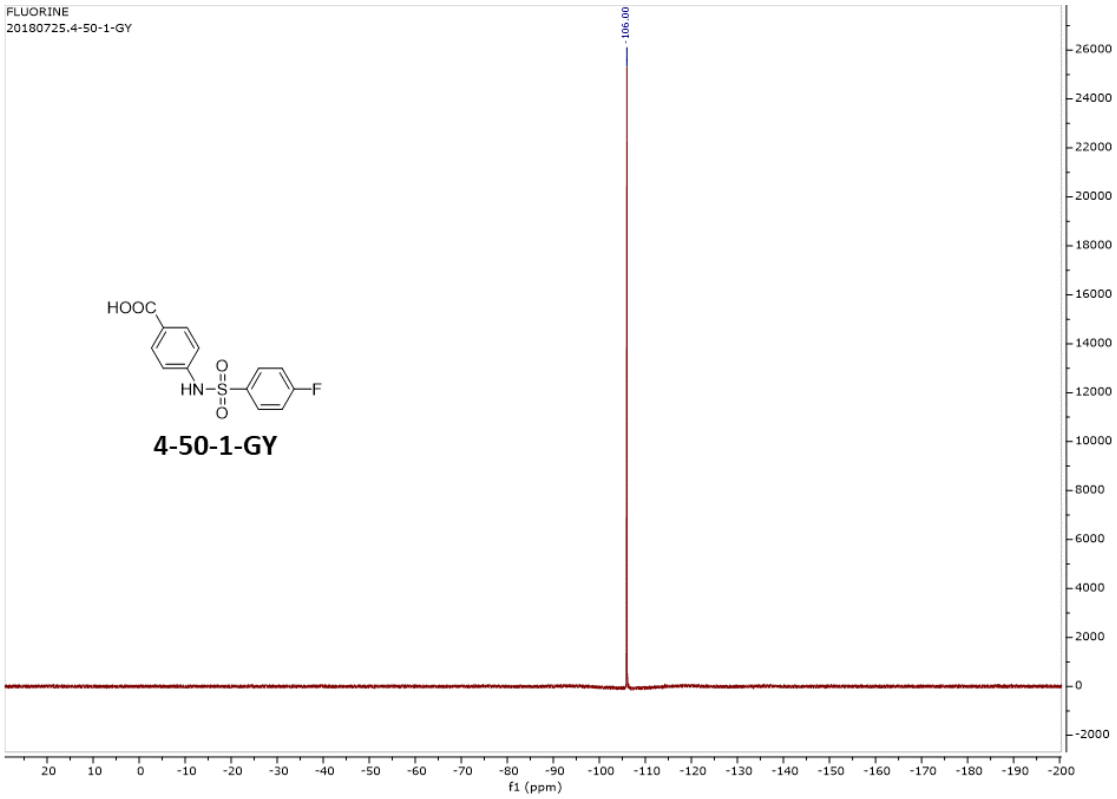

PROTON
20180726.4-51-1-GY
4-51-1-GY
f1 (ppm)

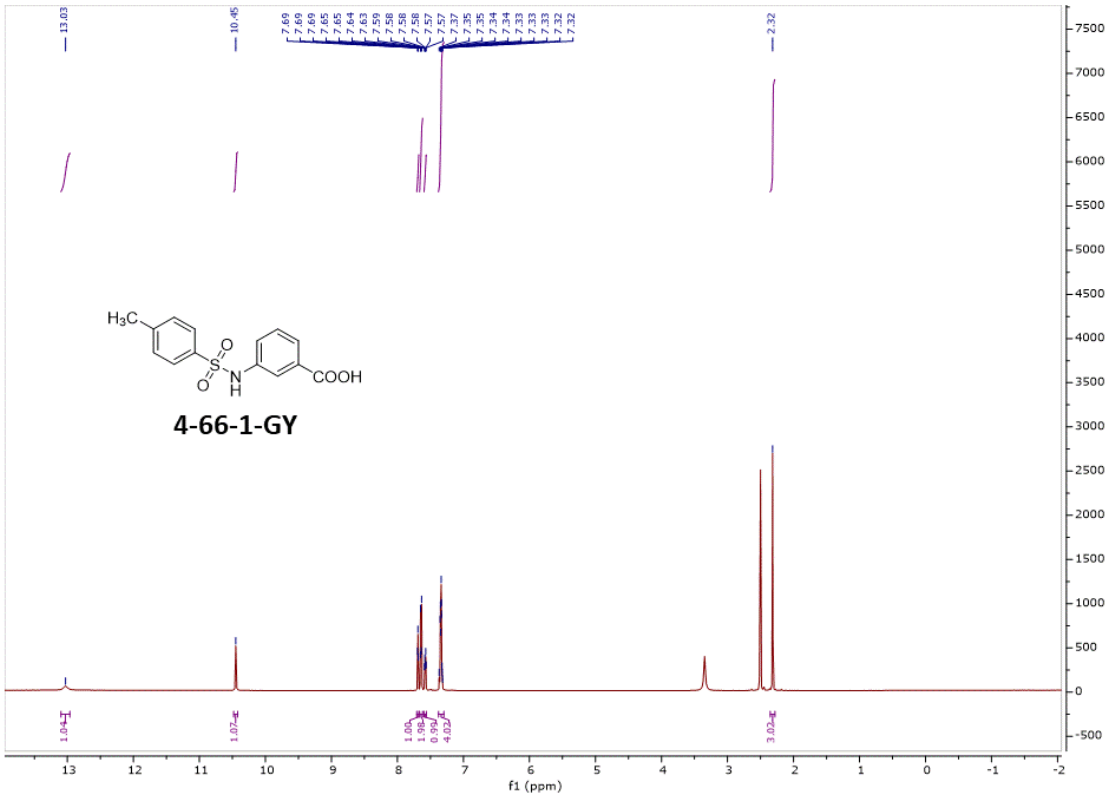

CARBON
20180726.4-51-1-GY
4-51-1-GY
f1 (ppm)

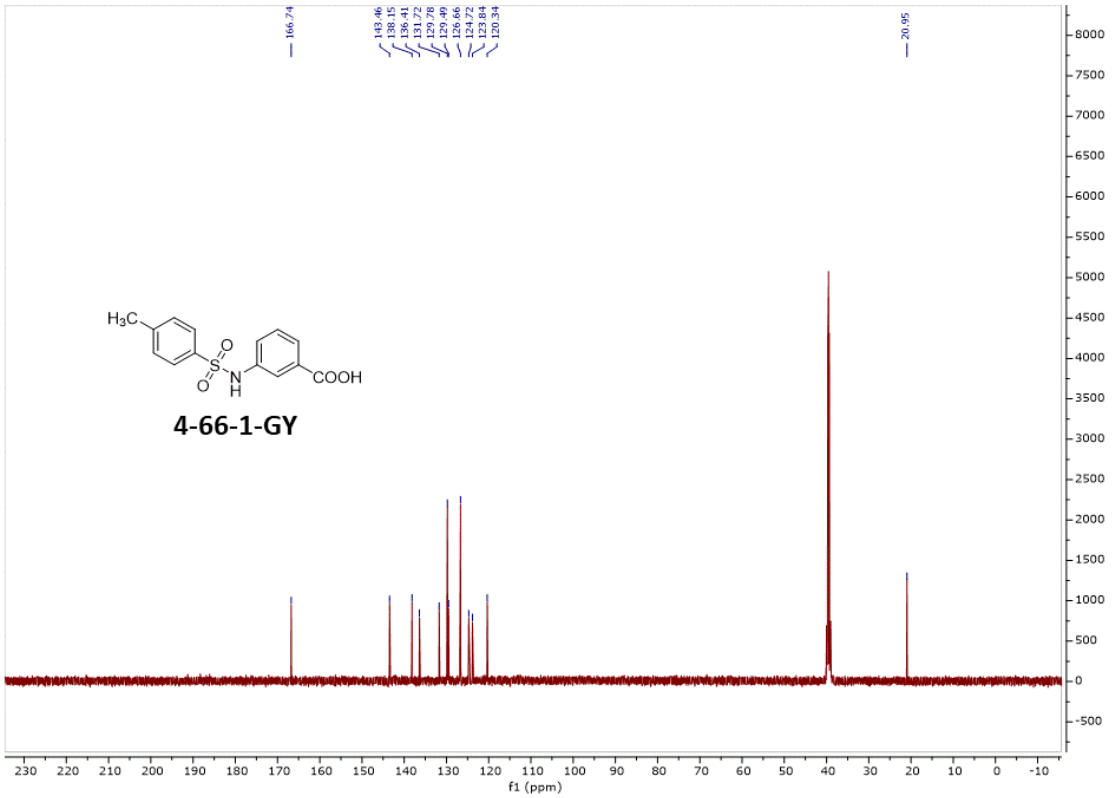

FLUORINE
20180726.4-51-1-GY
-106.23
HO
HN
S
O
O
F
4-51-1-GY
f1 (ppm)

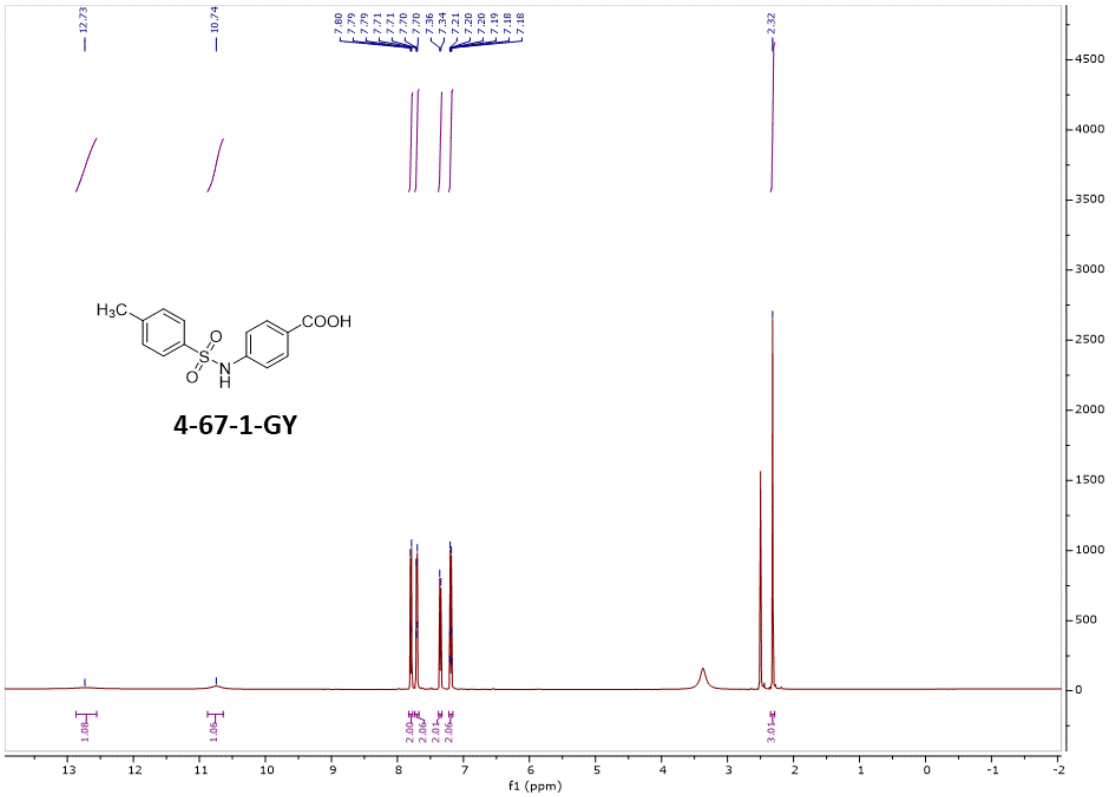

PROTON
20180725.4-50-1-GY
10.84
7.90
7.89
7.88
7.87
7.86
7.82
7.81
7.80
7.43
7.42
7.41
7.40
7.39
7.38
7.21
7.20
7.19
HOOC
HN
S
O
O
F
4-50-1-GY
1.05
1.01
2.03
1.94
2.01
2.00
f1 (ppm)

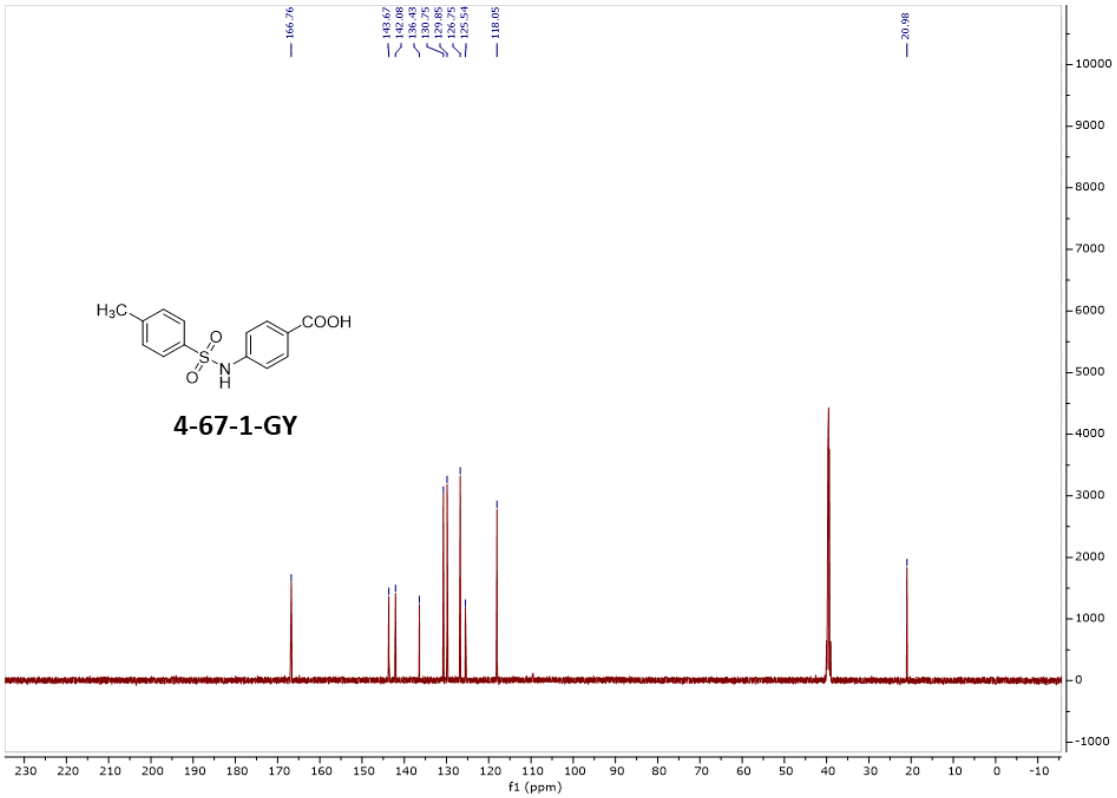

CARBON
20180725.4-50-1-GY
166.71
165.47
163.46
141.75
135.62
135.59
130.78
129.85
129.77
125.86
118.38
116.77
116.58
HOOC
HN
S
O
O
F
4-50-1-GY
f1 (ppm)

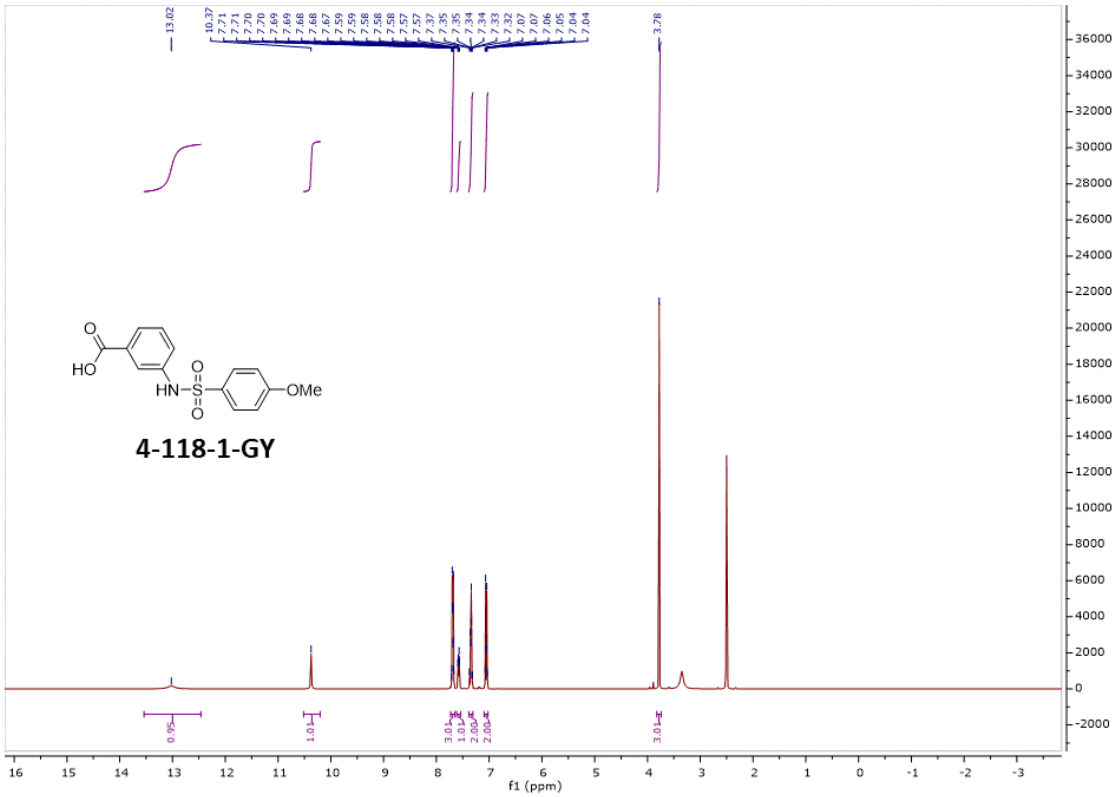

FLUORINE
20180725.4-50-1-GY
-106.00
HOOC
HN
S
O
O
F
4-50-1-GY
f1 (ppm)

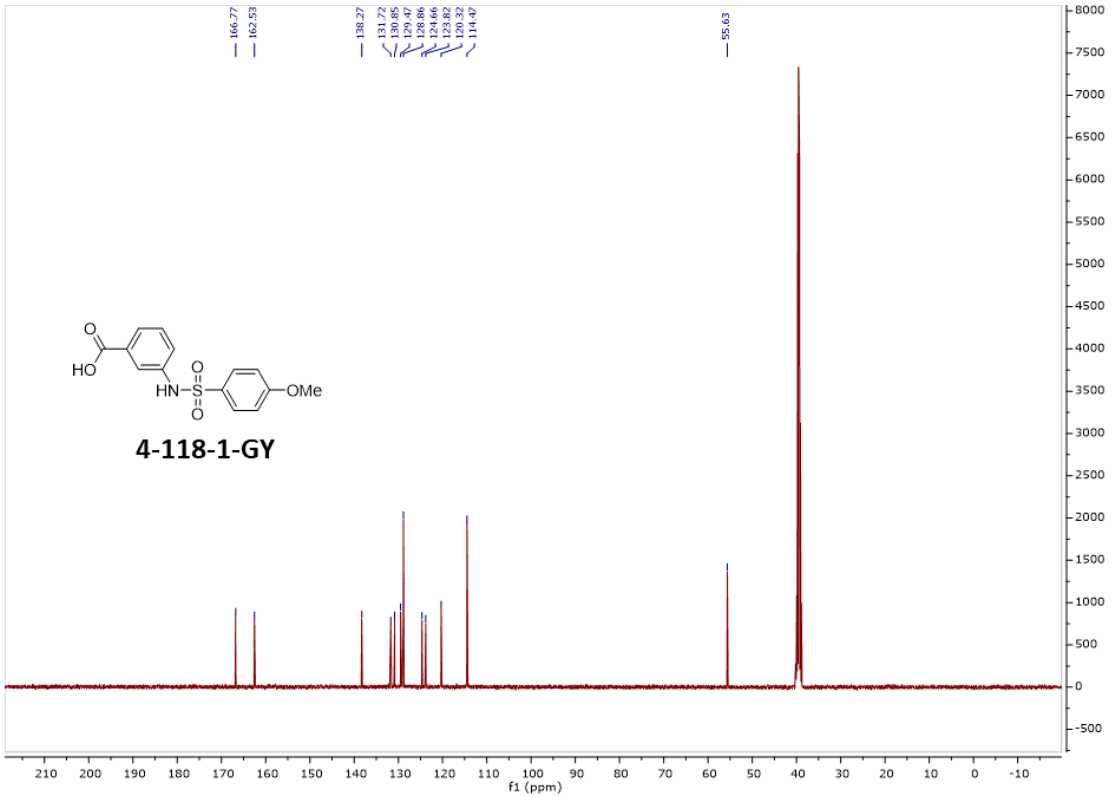

13.03
10.45
7.69
7.69
7.69
7.65
7.65
7.64
7.63
7.59
7.58
7.58
7.58
7.57
7.57
7.37
7.35
7.35
7.34
7.34
7.33
7.33
7.33
7.32
7.32
2.32
H3C
O
S
O
N
H
COOH
4-66-1-GY
1.04
1.07
1.00
1.98
0.99
4.02
3.02
f1 (ppm)

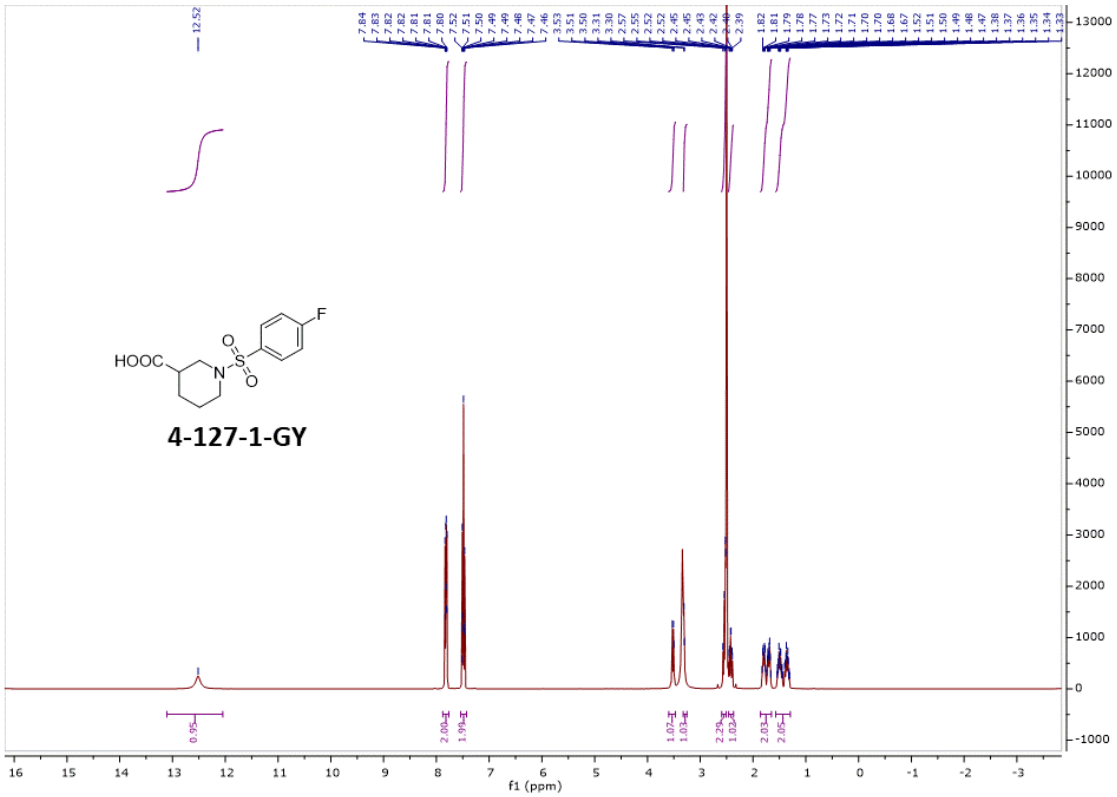

166.74
143.46
138.15
136.41
131.72
129.78
129.49
126.66
124.72
123.84
120.34
20.95
H3C
O
S
O
N
H
COOH
4-66-1-GY
f1 (ppm)

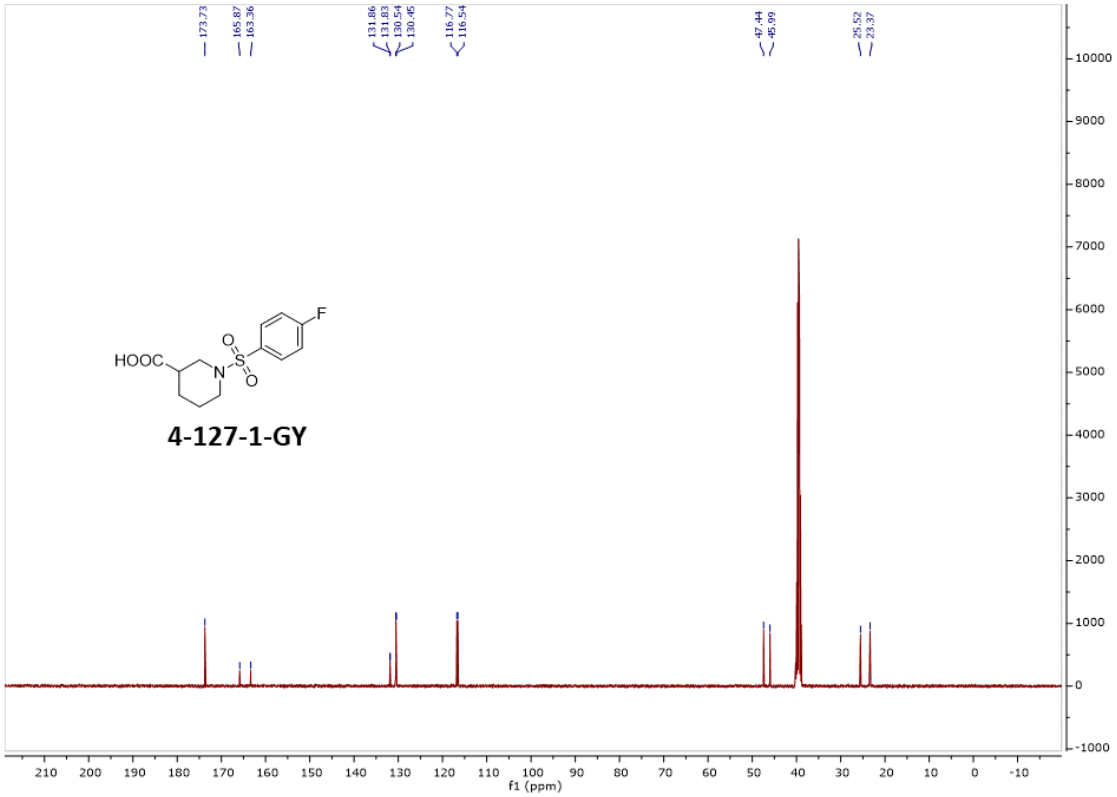

12.73
10.74
7.80
7.79
7.79
7.71
7.71
7.70
7.70
7.36
7.34
7.21
7.20
7.20
7.19
7.18
7.18
2.32
H3C
COOH
O
S
O
N
H
4-67-1-GY
1.08
1.06
2.00
2.06
2.01
2.06
3.01
f1 (ppm)

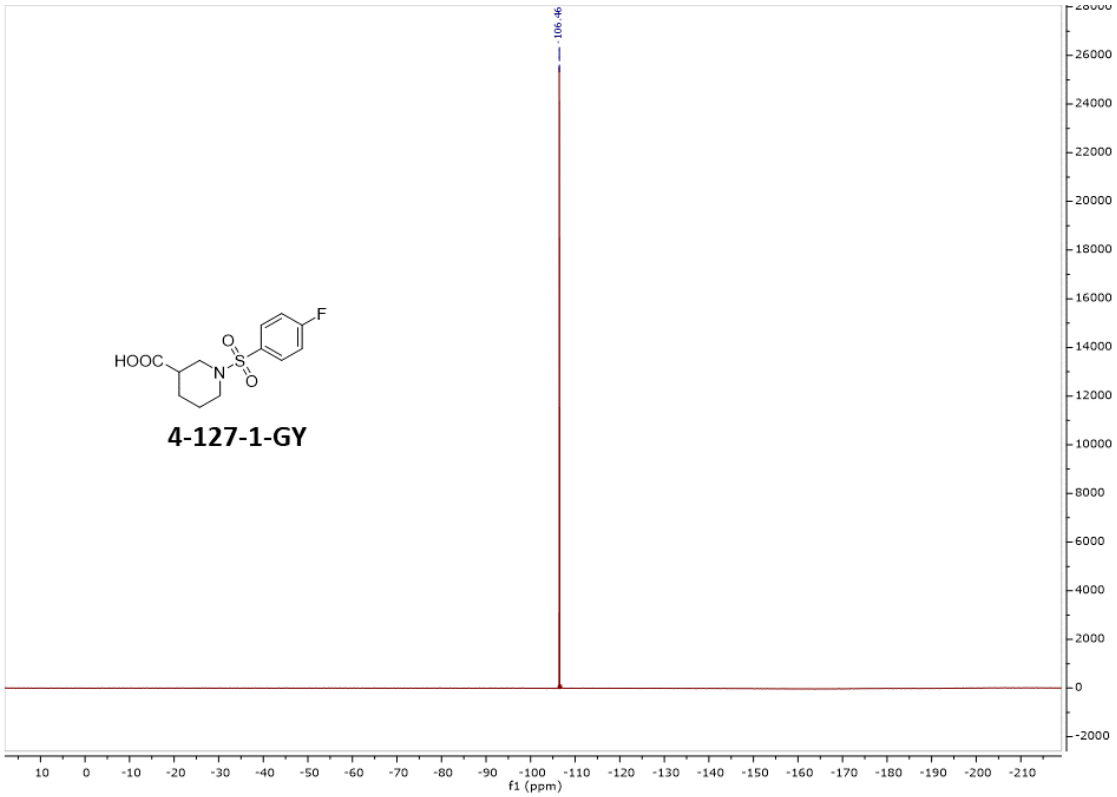

166.76
143.67
142.06
136.43
130.75
129.85
126.75
125.54
118.05
20.98
H3C
COOH
O
S
O
N
H
4-67-1-GY
f1 (ppm)

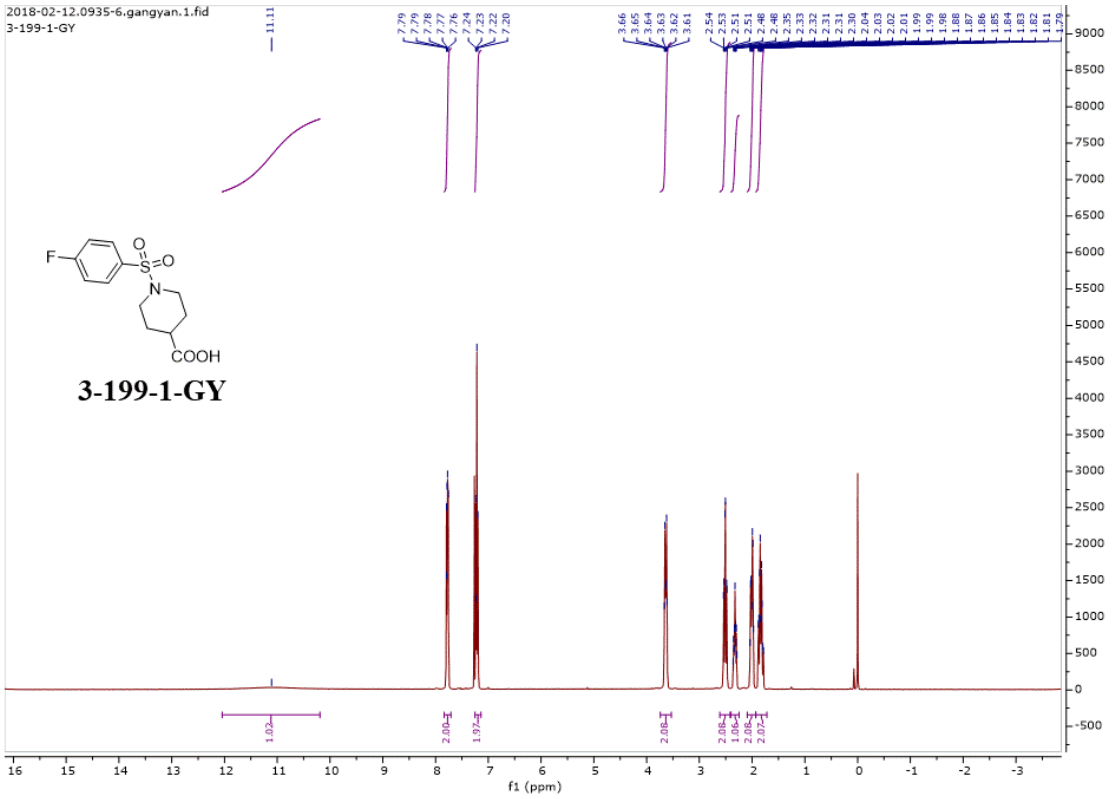

13.02
10.37
7.71
7.71
7.70
7.70
7.69
7.69
7.68
7.68
7.67
7.59
7.59
7.58
7.58
7.58
7.57
7.57
7.37
7.35
7.35
7.34
7.34
7.33
7.32
7.07
7.07
7.06
7.05
7.04
7.04
3.76
HO
HN
S
O
O
OMe
4-118-1-GY
0.95
1.01
3.01
1.01
2.00
2.00
3.01
f1 (ppm)

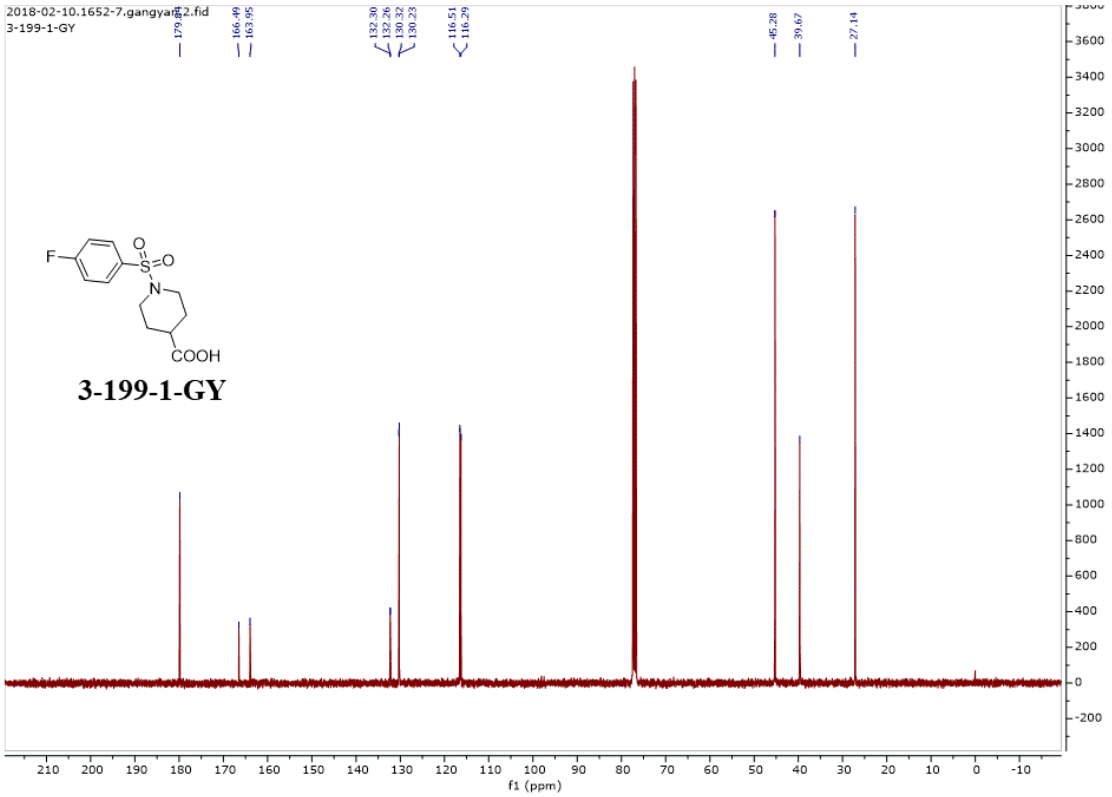

166.77
162.53
138.27
131.72
130.85
129.47
128.86
124.66
123.82
120.32
114.47
55.63
HO
HN
S
O
O
OMe
4-118-1-GY
f1 (ppm)

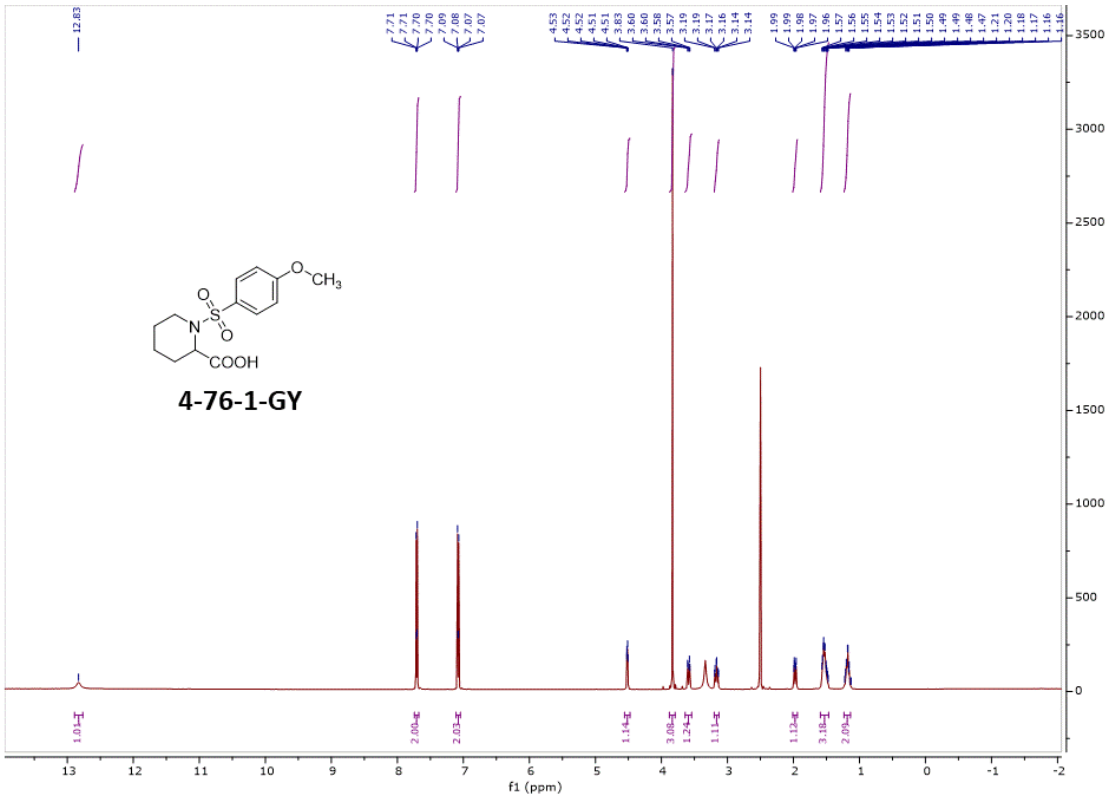

HOOC
F
4-127-1-GY
f1 (ppm)

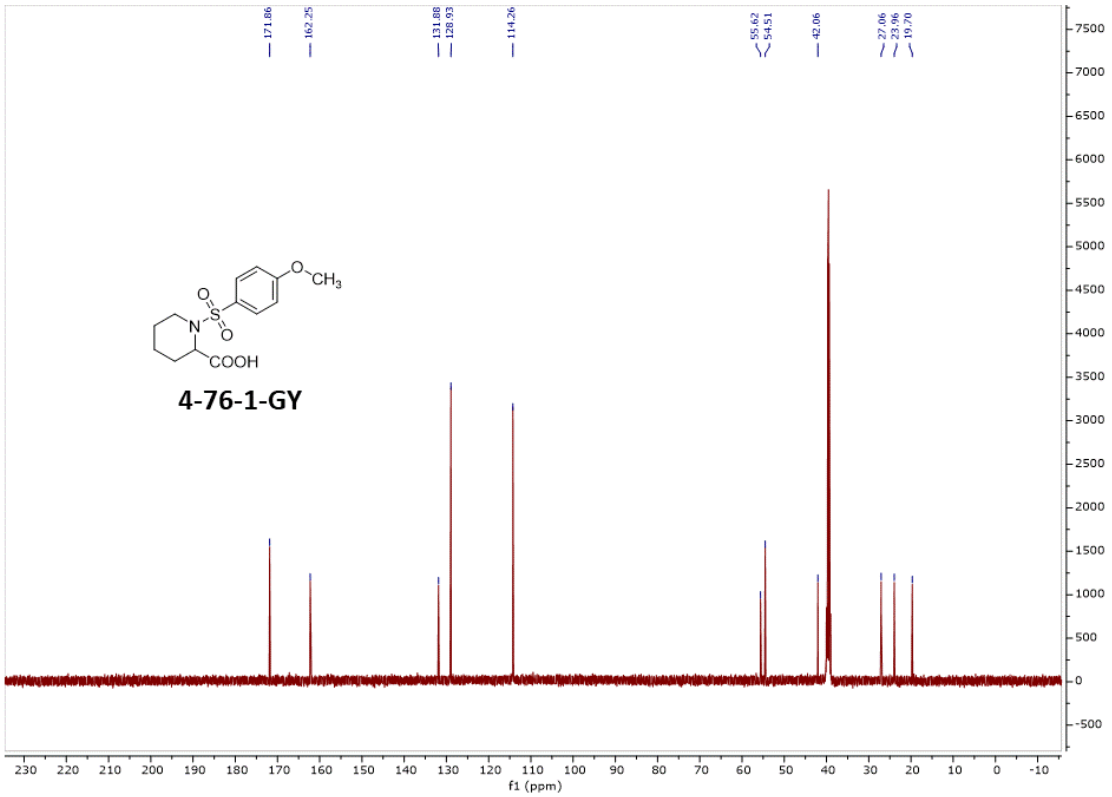

HOOC
F
4-127-1-GY
f1 (ppm)

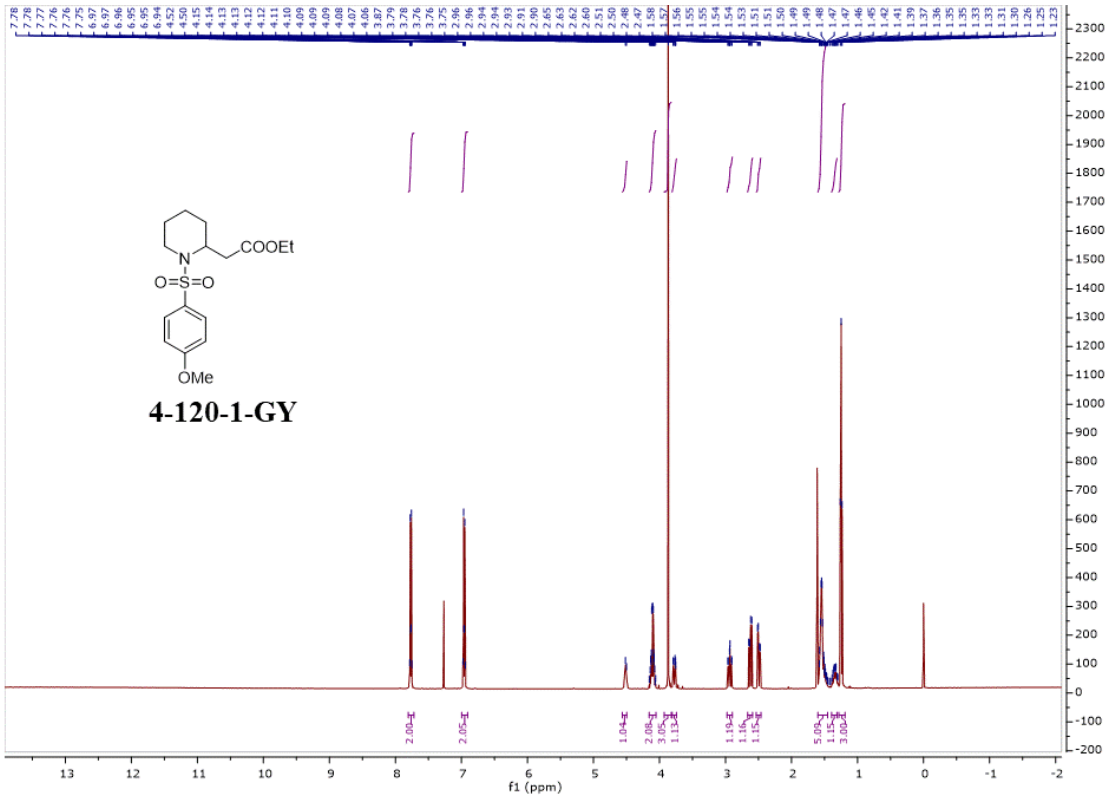

-106.46
HOOC
F
O
S
O
N
4-127-1-GY
f1 (ppm)

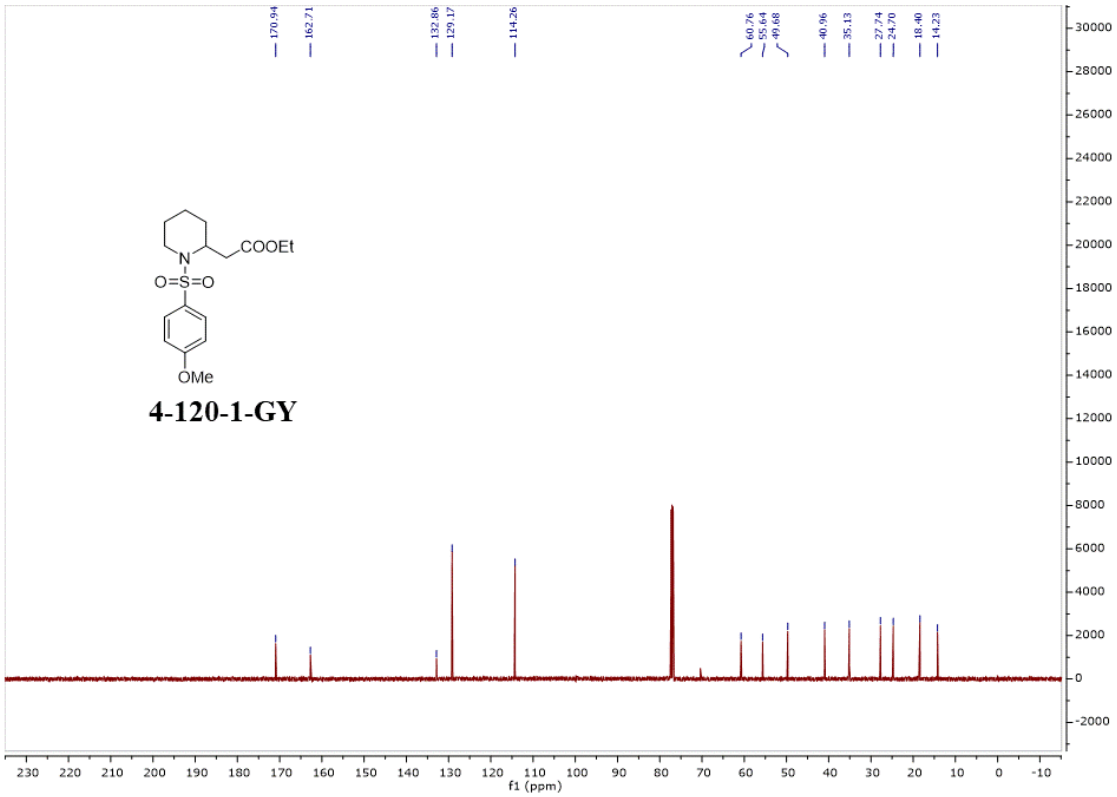

2018-02-12.0935-6,gangyan.1.fid
3-199-1-GY
11.11
7.79
7.78
7.77
7.76
7.24
7.23
7.22
7.20
3.66
3.65
3.64
3.63
3.62
3.61
2.54
2.53
2.51
2.48
F
O
S
O
N
COOH
3-199-1-GY
1.02
2.00
1.97
2.08
2.08
1.06
2.08
2.07
f1 (ppm)


2018-02-10.1652-7.gangyan2.fid
3-199-1-GY
179.84
166.49
163.95
132.30
132.26
130.32
130.23
116.51
116.29
45.28
39.67
27.14
F
O
S
O
N
COOH
3-199-1-GY
f1 (ppm)

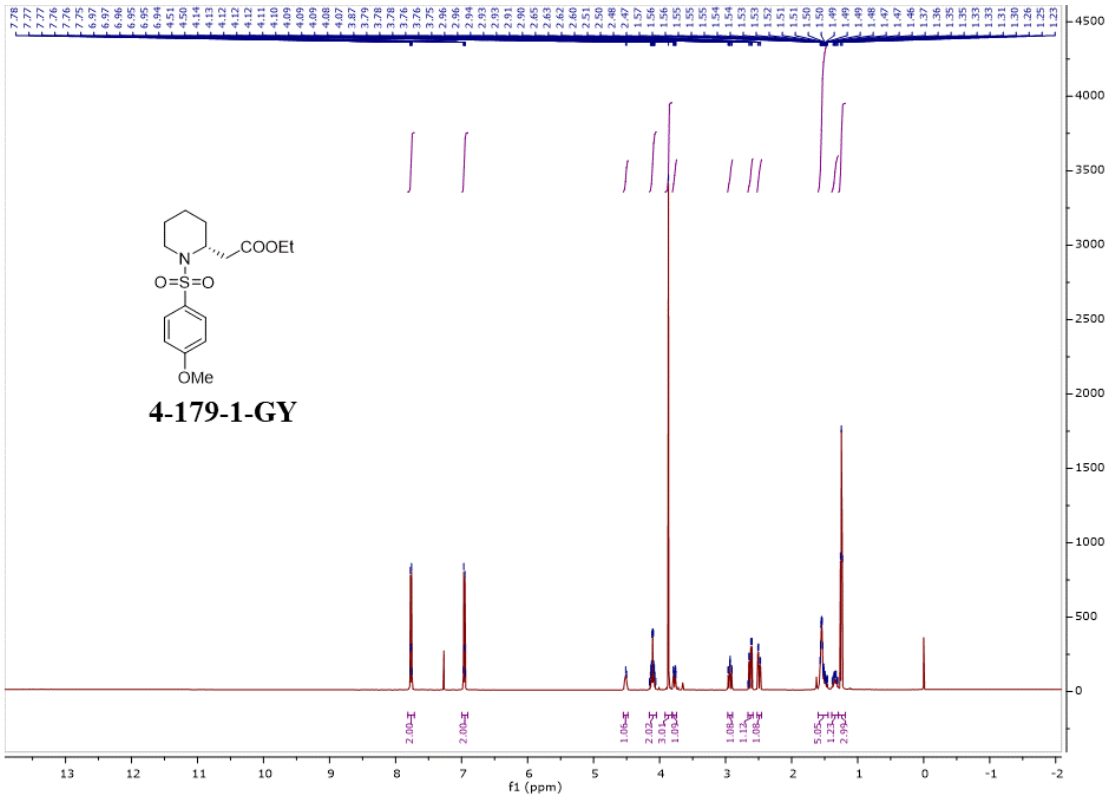

12.83
7.71
7.71
7.70
7.70
7.08
7.08
7.07
7.07
4.53
4.52
4.52
4.51
4.51
3.83
3.60
3.60
3.58
3.57
3.19
3.19
3.17
3.16
3.14
3.14
1.99
1.99
1.98
1.97
1.96
1.57
1.56
1.55
1.54
1.53
1.52
1.51
1.50
1.49
1.49
1.48
1.47
1.21
1.20
1.18
1.17
1.16
1.16
O
CH3
O
S
O
N
COOH
4-76-1-GY
1.01
2.00
2.03
1.14
3.08
1.24
1.11
1.12
3.18
2.09
f1 (ppm)


171.86
162.25
131.88
128.93
114.26
55.62
54.51
42.06
27.06
23.96
19.70
O
CH3
O
S
O
N
COOH
4-76-1-GY
f1 (ppm)

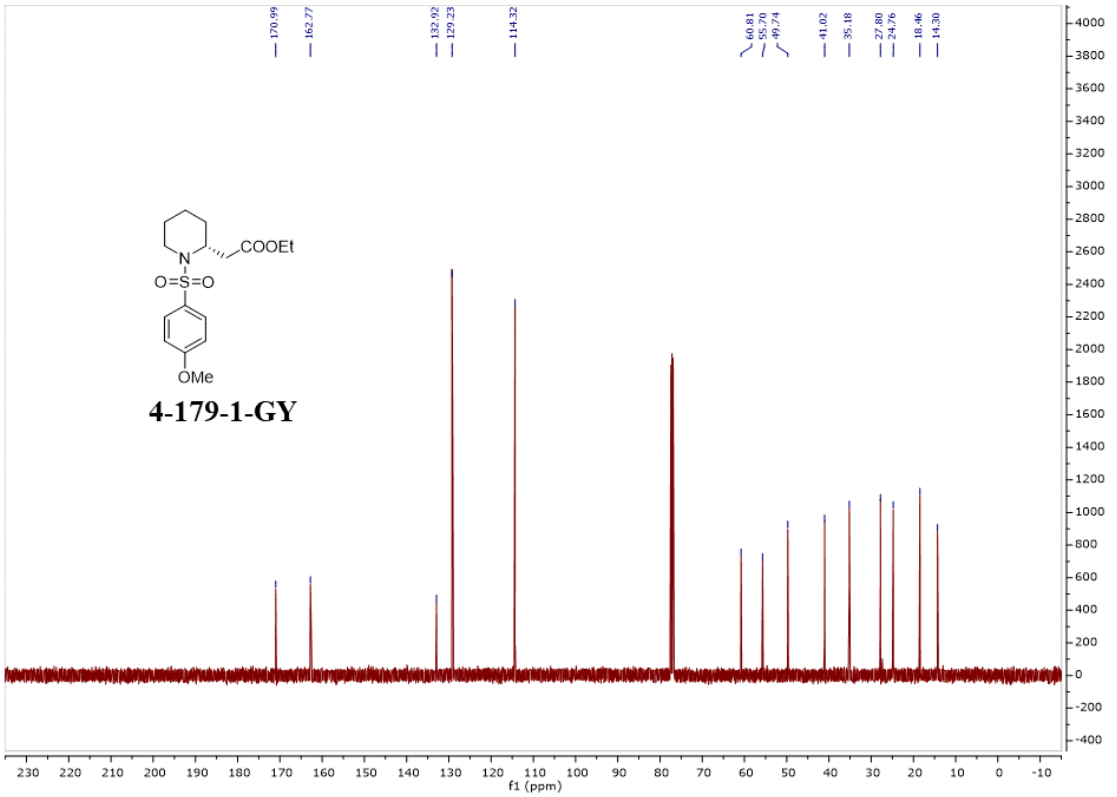

COOEt
N
O=S=O
OMe
4-120-1-GY
f1 (ppm)

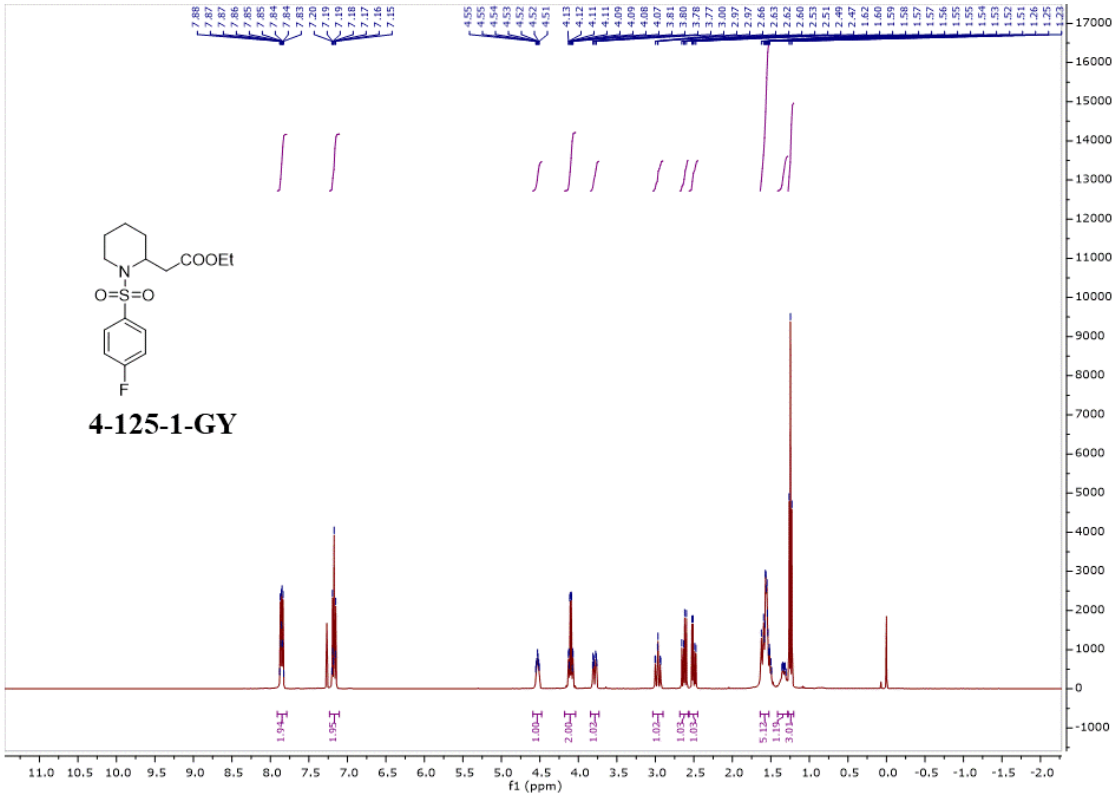


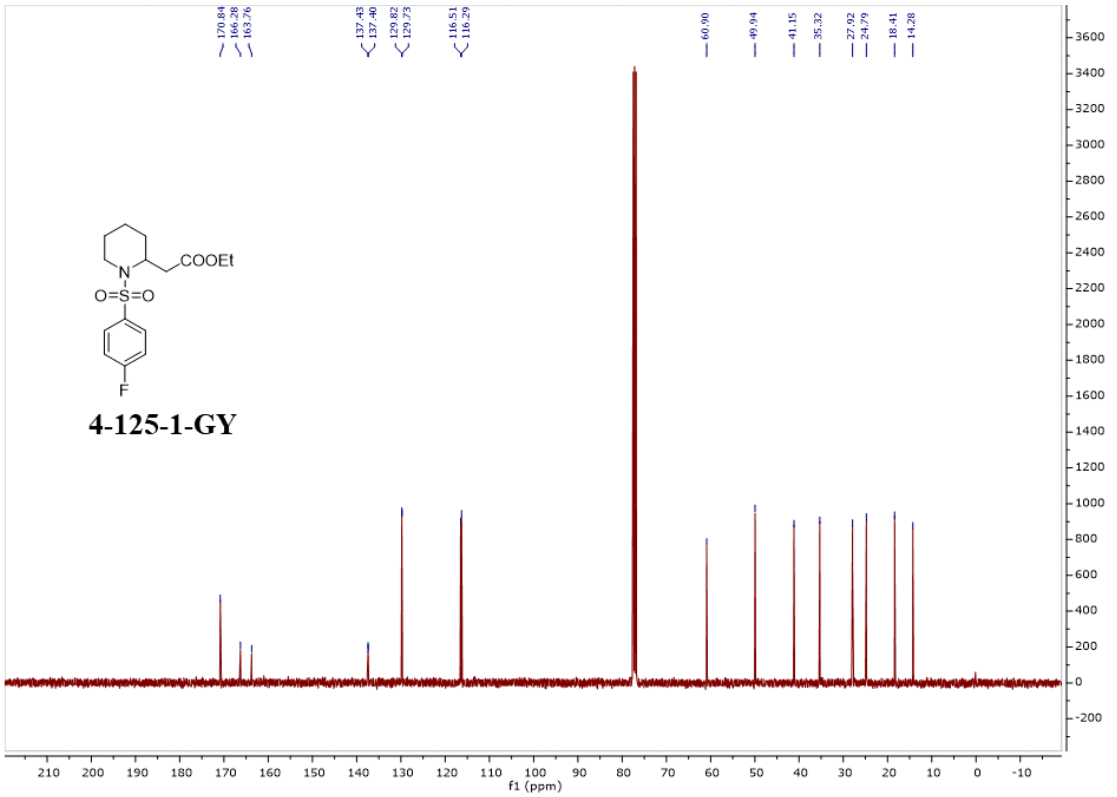

**4-120-1-GY**

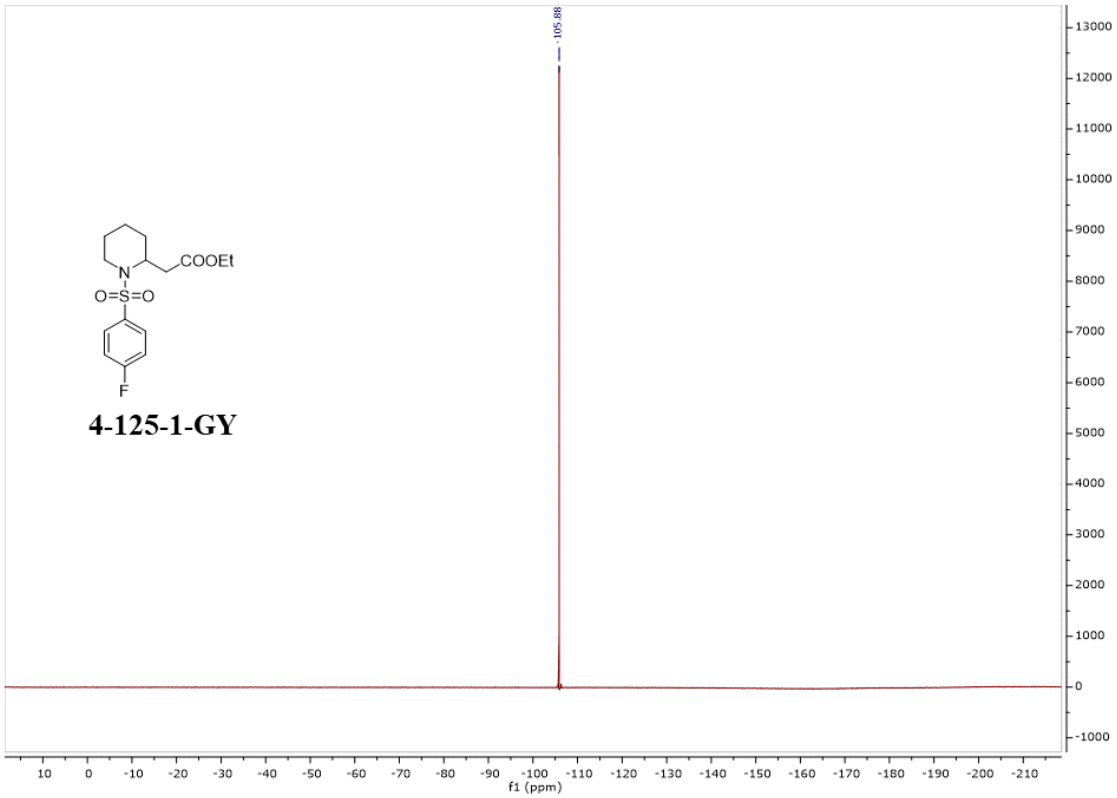


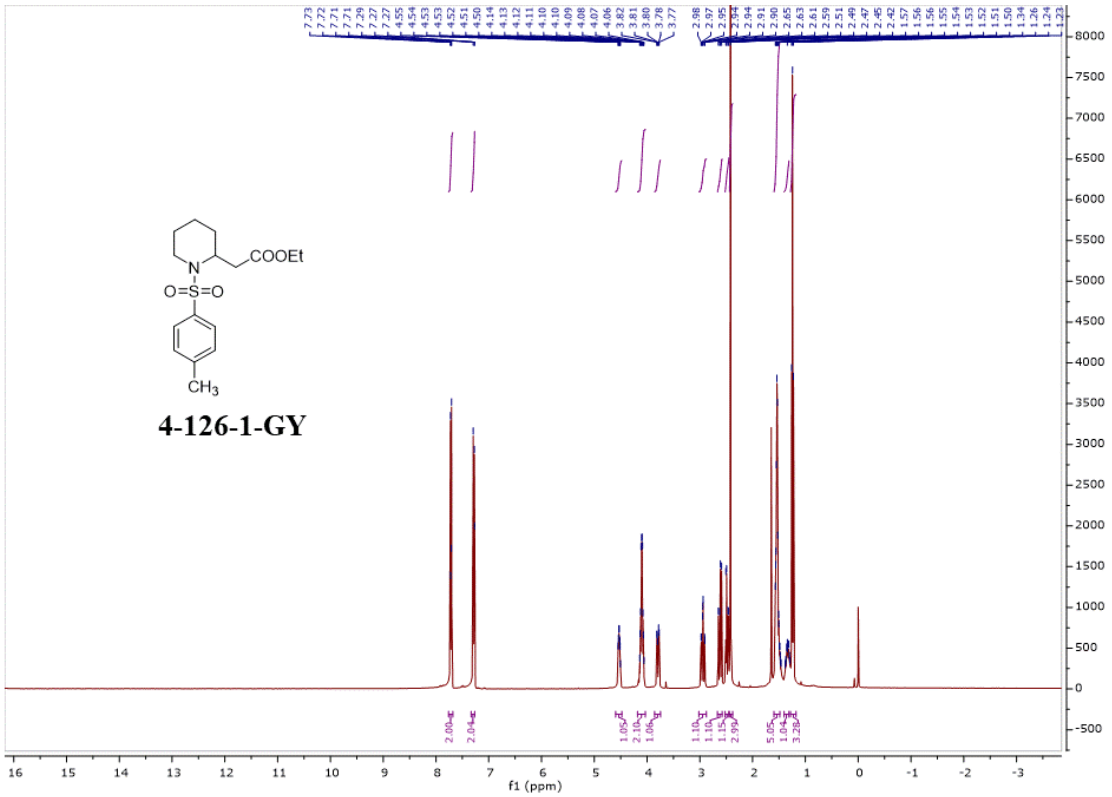

**4-179-1-GY**

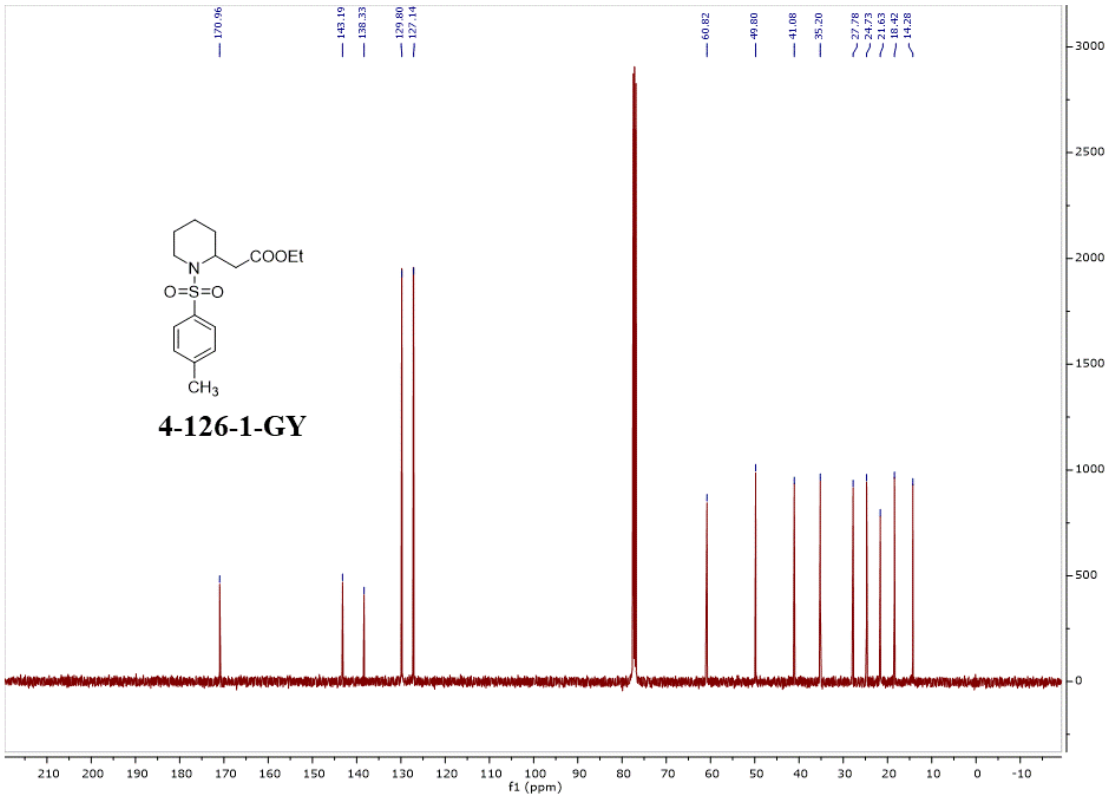

170.99
162.77
132.92
129.23
114.32
60.81
55.70
49.74
41.02
35.18
27.80
24.76
18.46
14.30
COOEt
N
O=S=O
OMe
4-179-1-GY
f1 (ppm)

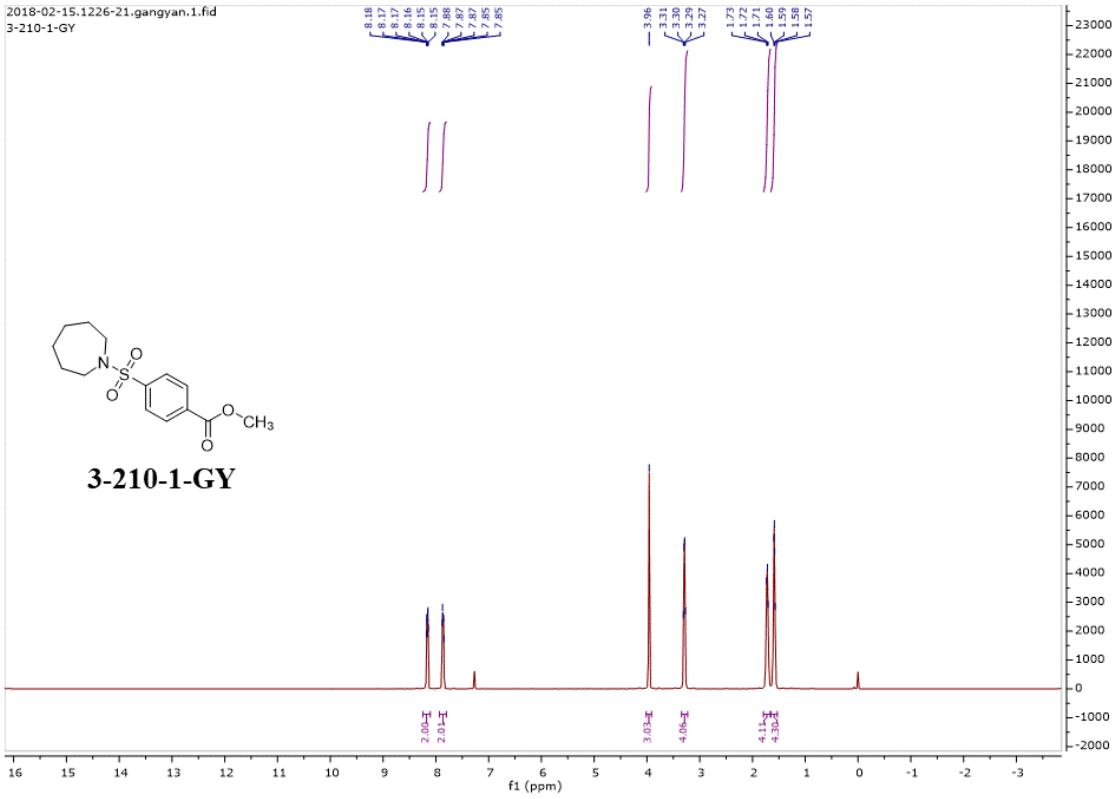

COOEt
N
O=S=O
F
4-125-1-GY
f1 (ppm)

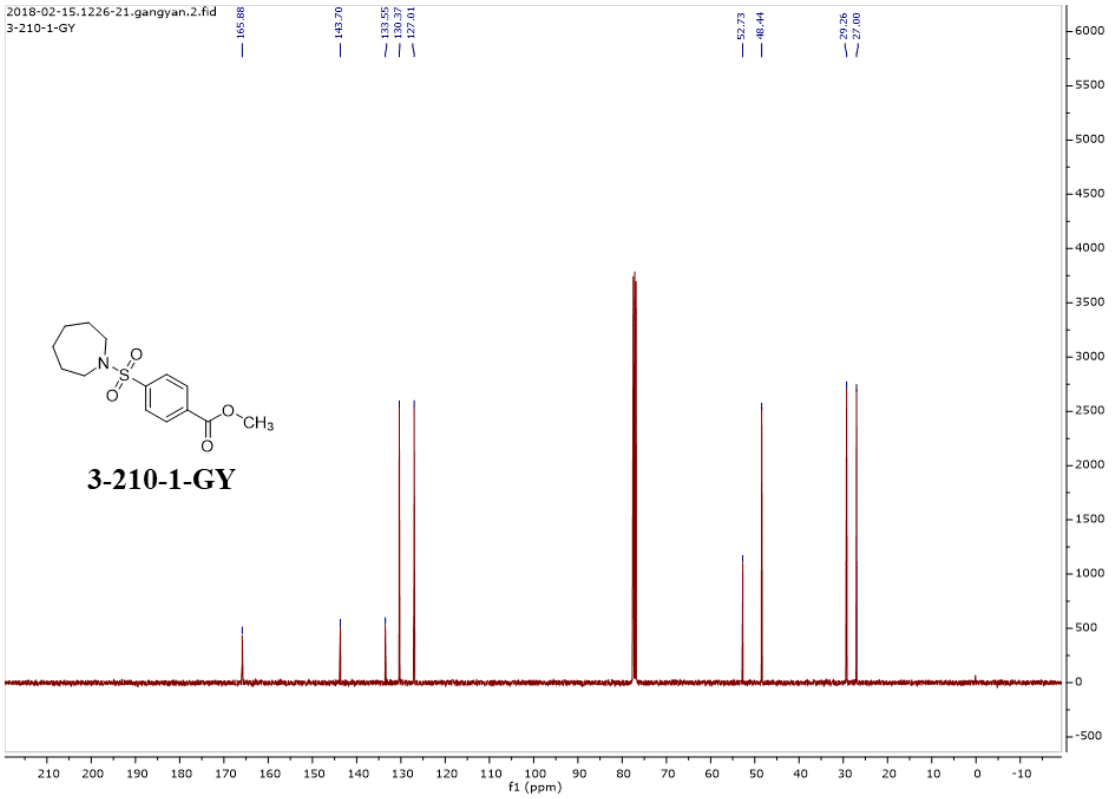

170.84
166.28
163.76
137.43
137.40
129.82
129.73
116.51
116.29
60.90
49.94
41.15
35.32
27.92
24.79
18.41
14.28
COOEt
N
O=S=O
F
4-125-1-GY
f1 (ppm)

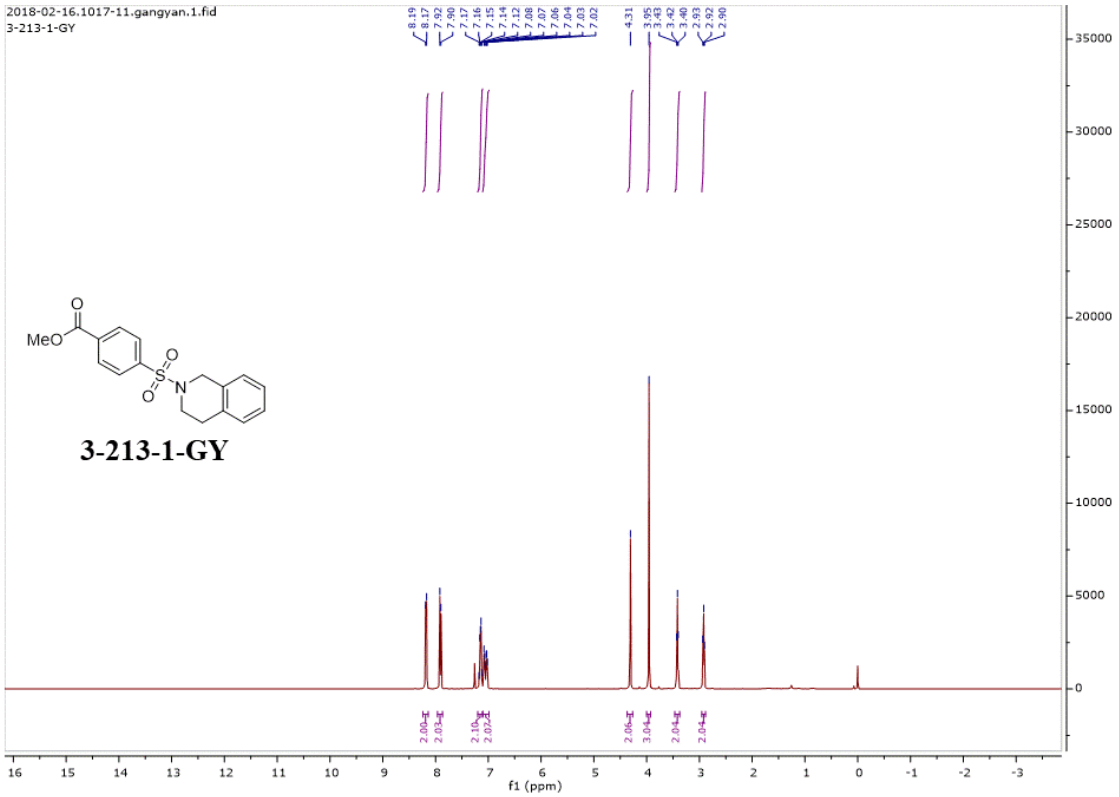

105.88
COOEt
N
O=S=O
F
4-125-1-GY
f1 (ppm)

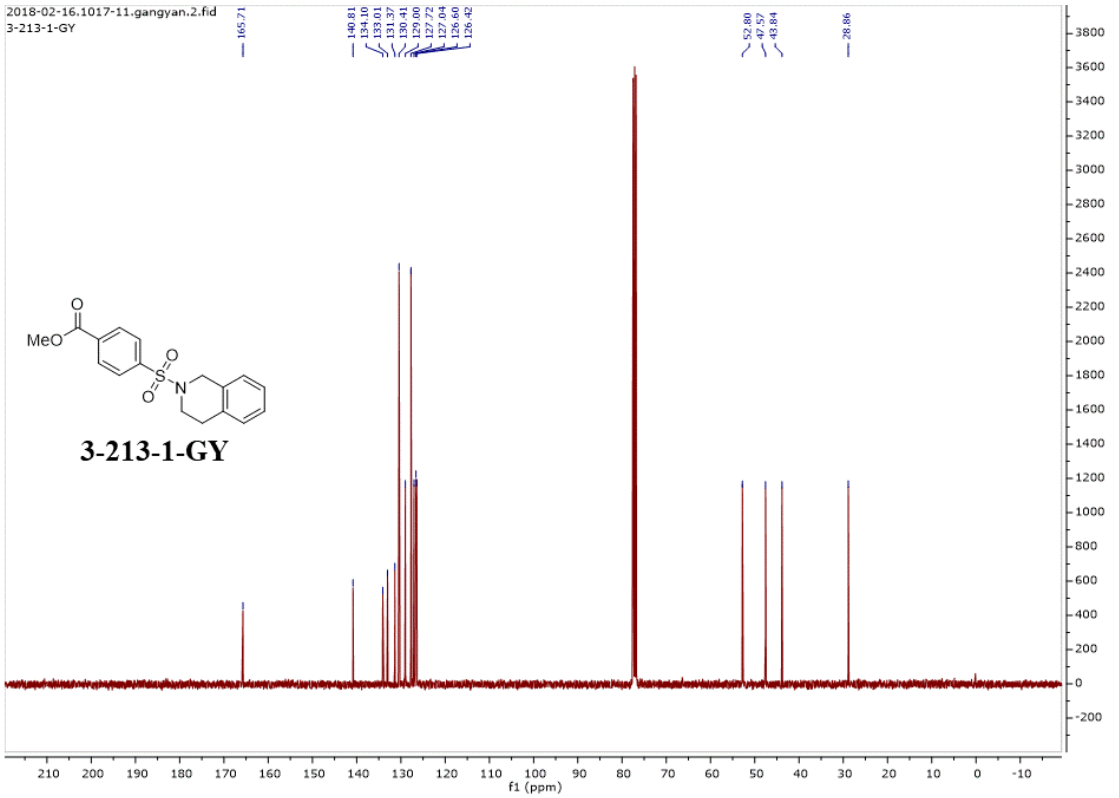

COOEt
N
O=S=O
CH3
4-126-1-GY
f1 (ppm)

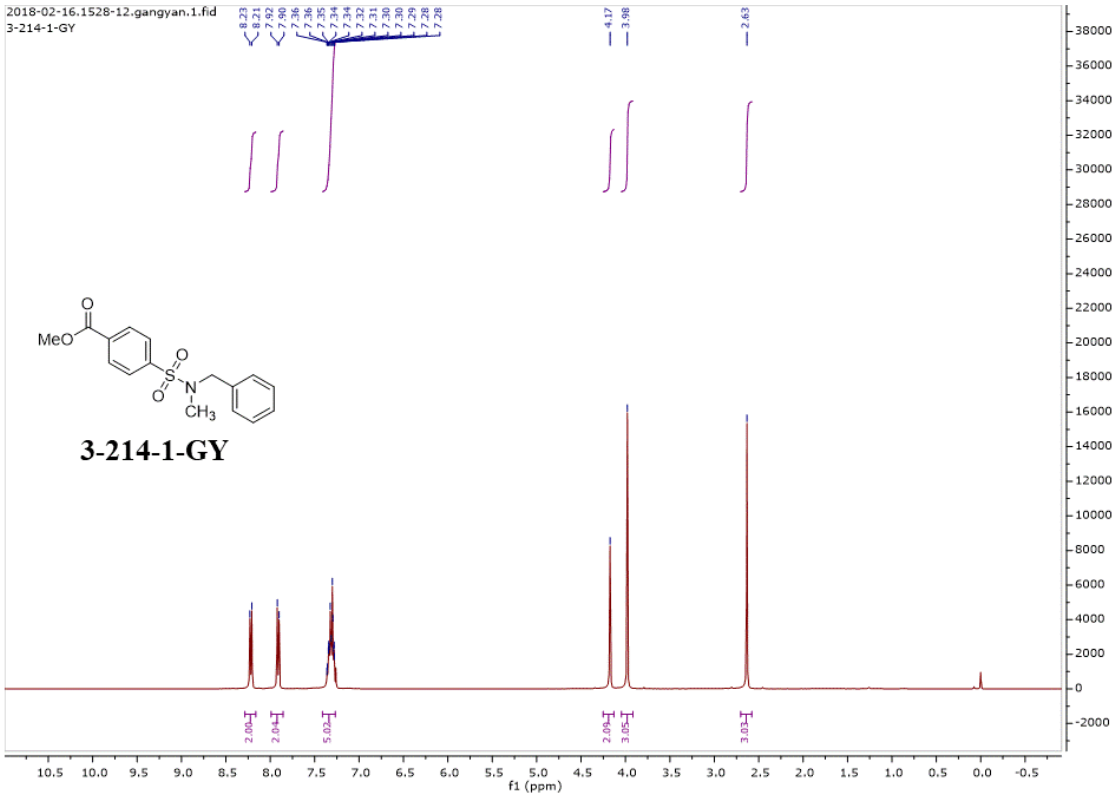

170.96
143.19
138.33
129.80
127.14
60.82
49.80
41.08
35.20
27.78
24.73
21.63
18.42
14.28
COOEt
N
O=S=O
CH3
4-126-1-GY
f1 (ppm)

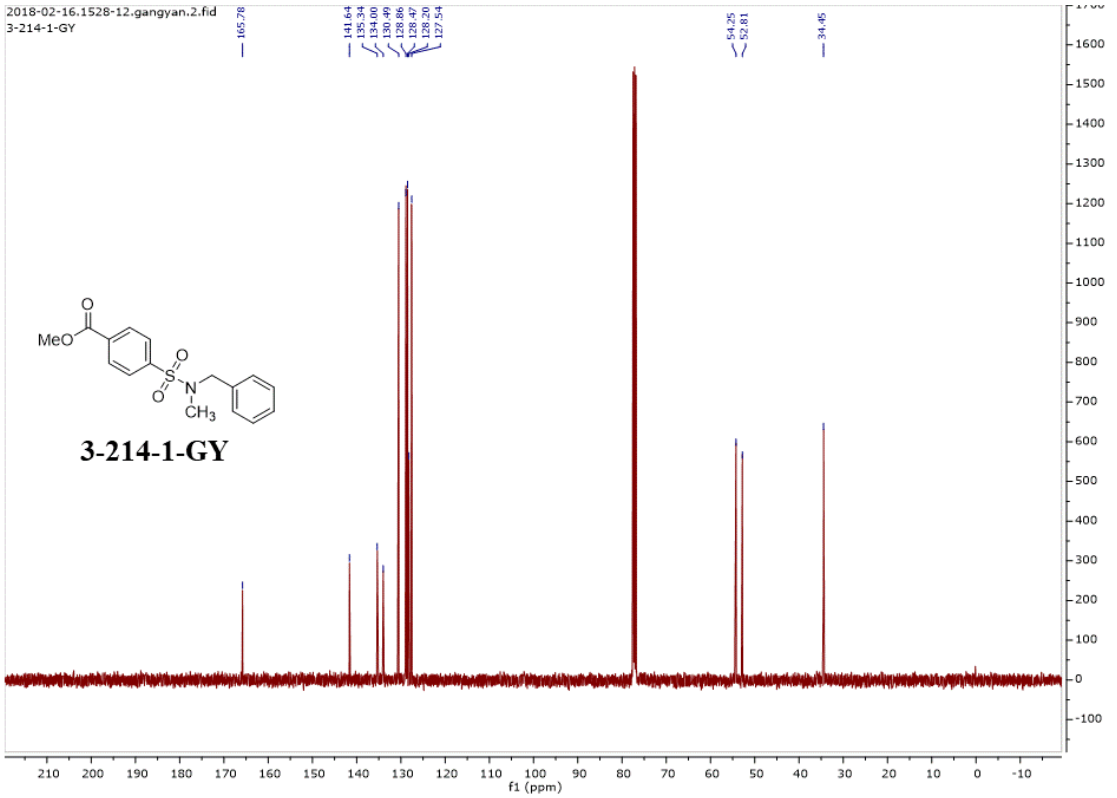

2018-02-15.1226-21.gangyan.1.fid
3-210-1-GY
8.18
8.17
8.17
8.16
8.15
8.15
7.88
7.87
7.87
7.85
7.85
3.96
3.31
3.30
3.29
3.27
1.73
1.72
1.71
1.60
1.59
1.58
1.57
2.00
2.01
3.03
4.06
4.11
4.30
f1 (ppm)
3-210-1-GY

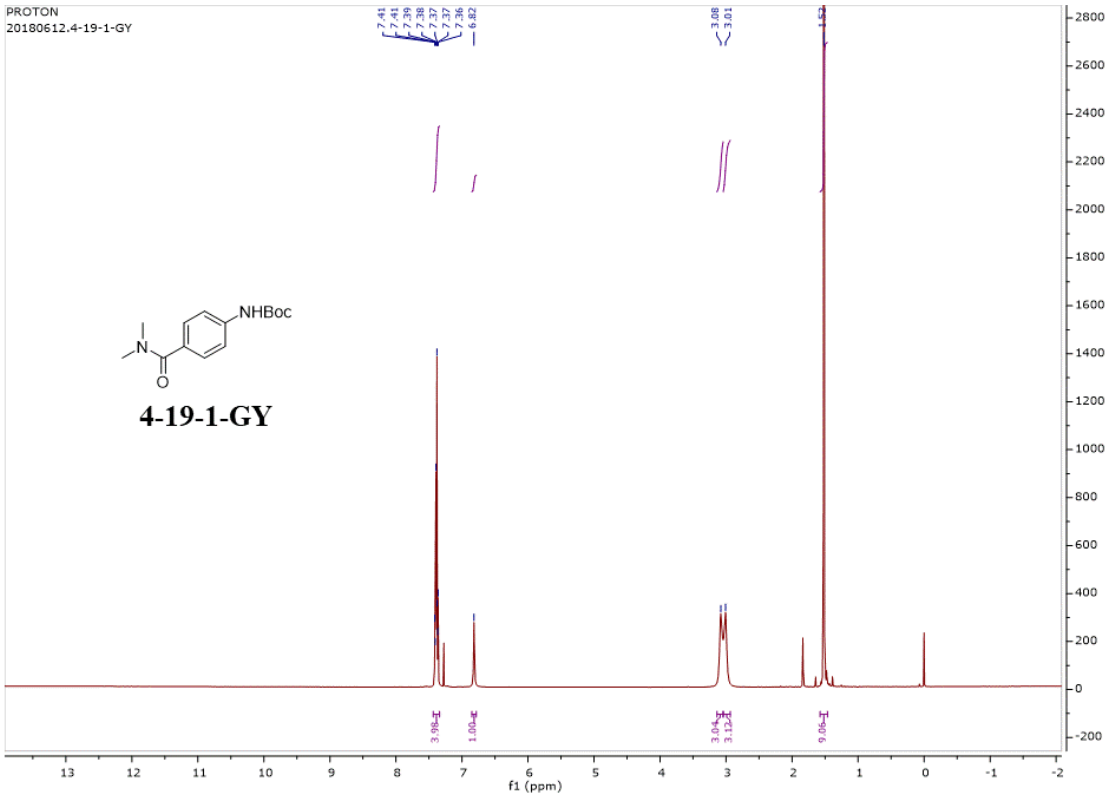

2018-02-15.1226-21.gangyan.2.fid
3-210-1-GY
165.88
143.70
133.55
130.37
127.01
52.73
48.44
29.26
27.00
f1 (ppm)
3-210-1-GY

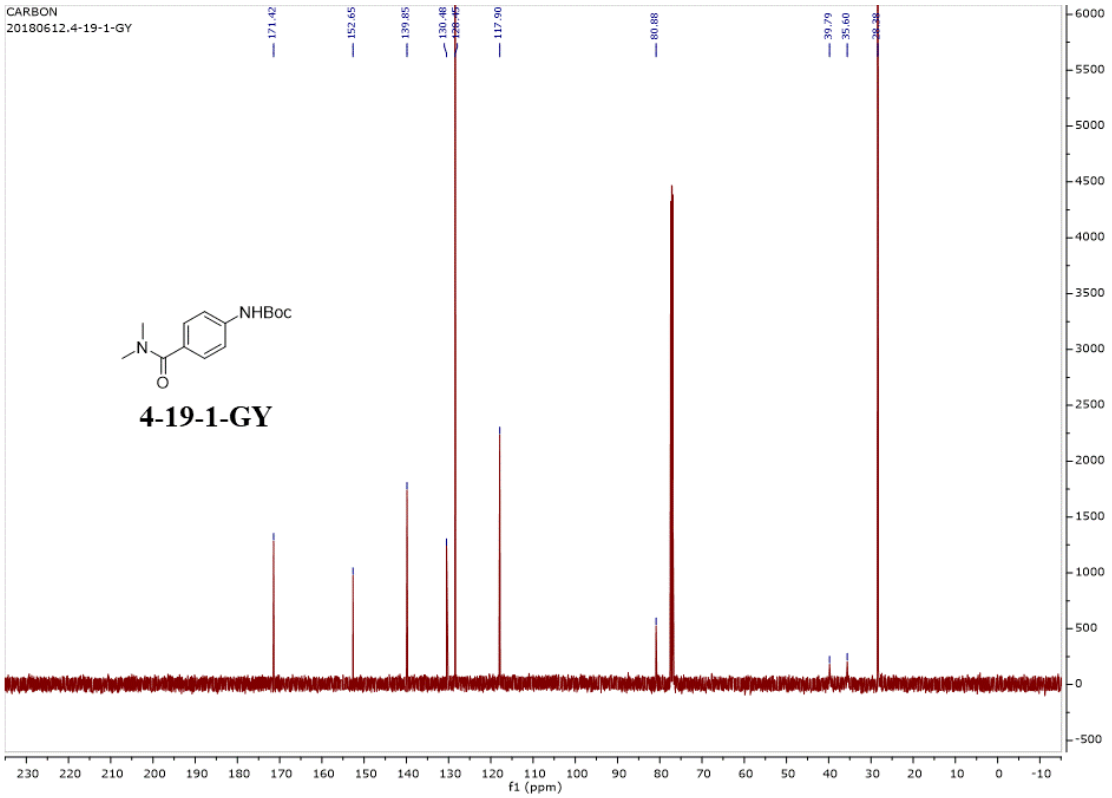

2018-02-16.1017-11.gangyan.1.fid
3-213-1-GY
8.19
8.17
7.92
7.90
7.17
7.16
7.15
7.14
7.12
7.08
7.07
7.06
7.04
7.03
7.02
4.31
3.95
3.43
3.42
3.40
2.93
2.92
2.90
MeO
3-213-1-GY
2.04
2.03
2.10
2.02
2.06
3.04
2.04
2.04
f1 (ppm)

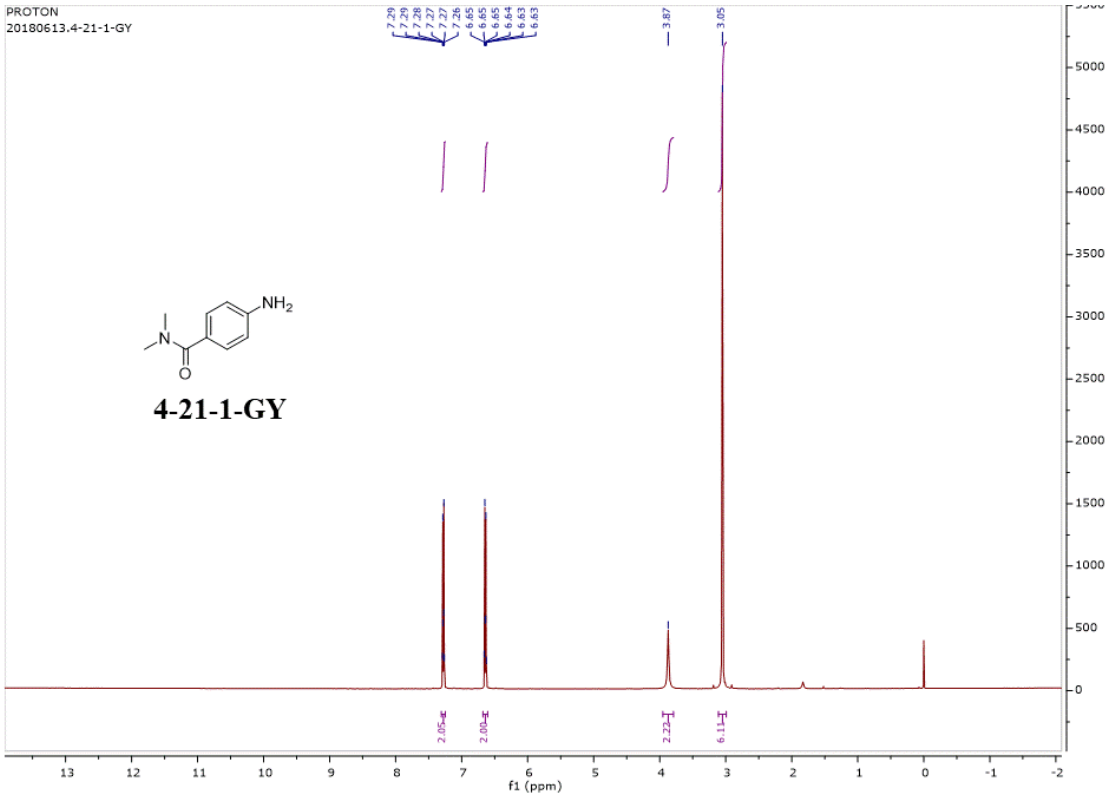

2018-02-16.1017-11.gangyan.2.fid
3-213-1-GY
165.71
140.81
134.10
133.01
131.37
130.41
129.00
127.72
127.04
126.66
126.42
52.80
47.57
43.84
28.86
MeO
3-213-1-GY
f1 (ppm)

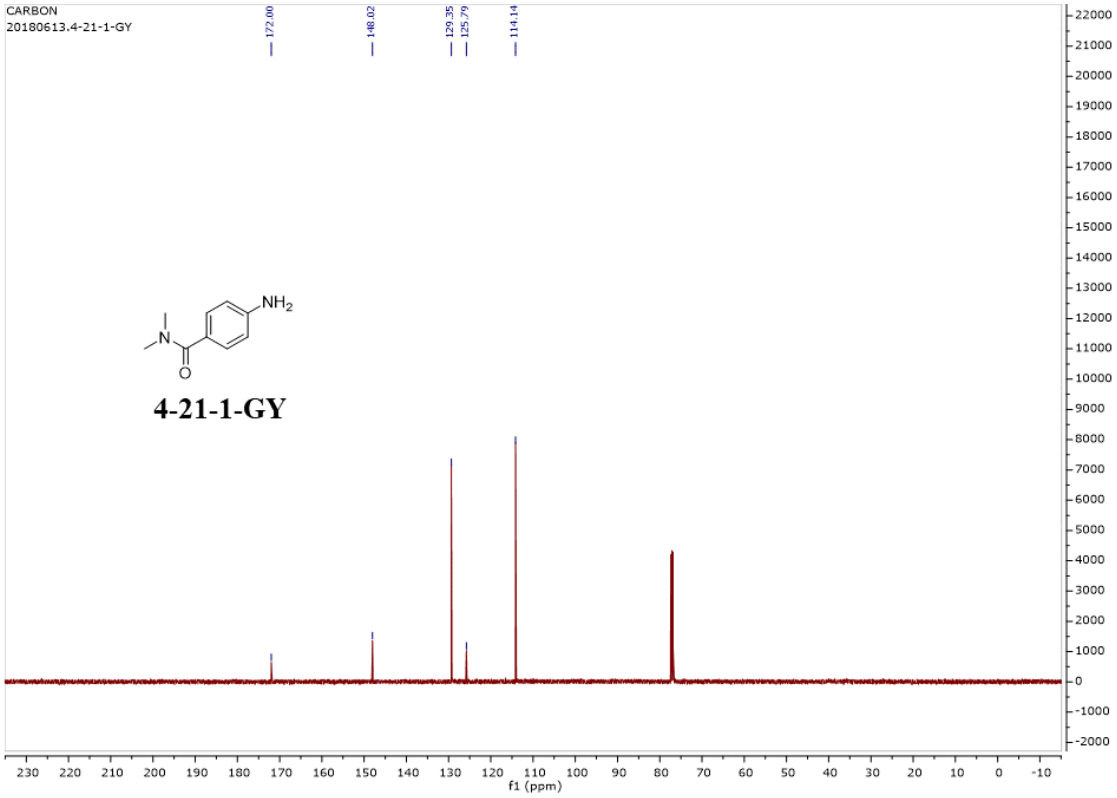

2018-02-16.1528-12.gangyan.1.fid
3-214-1-GY
8.23
8.21
7.92
7.90
7.36
7.36
7.35
7.34
7.34
7.32
7.31
7.30
7.30
7.29
7.28
7.28
4.17
3.98
2.63
MeO
O
O
S
N
CH3
3-214-1-GY
2.00
2.04
5.02
2.04
3.05
3.03
f1 (ppm)

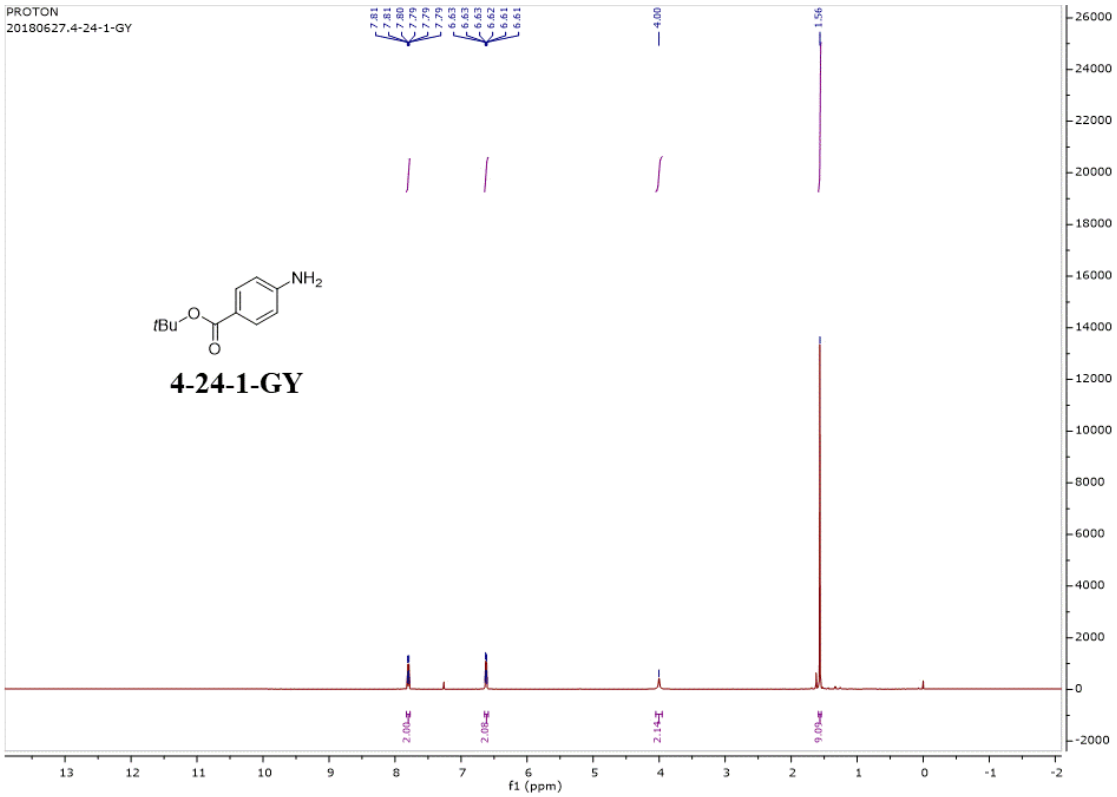

2018-02-16.1528-12.gangyan.2.fid
3-214-1-GY
165.78
141.64
135.34
134.00
130.49
129.86
128.47
128.20
127.54
54.25
52.81
34.45
MeO
O
O
S
N
CH3
3-214-1-GY
f1 (ppm)

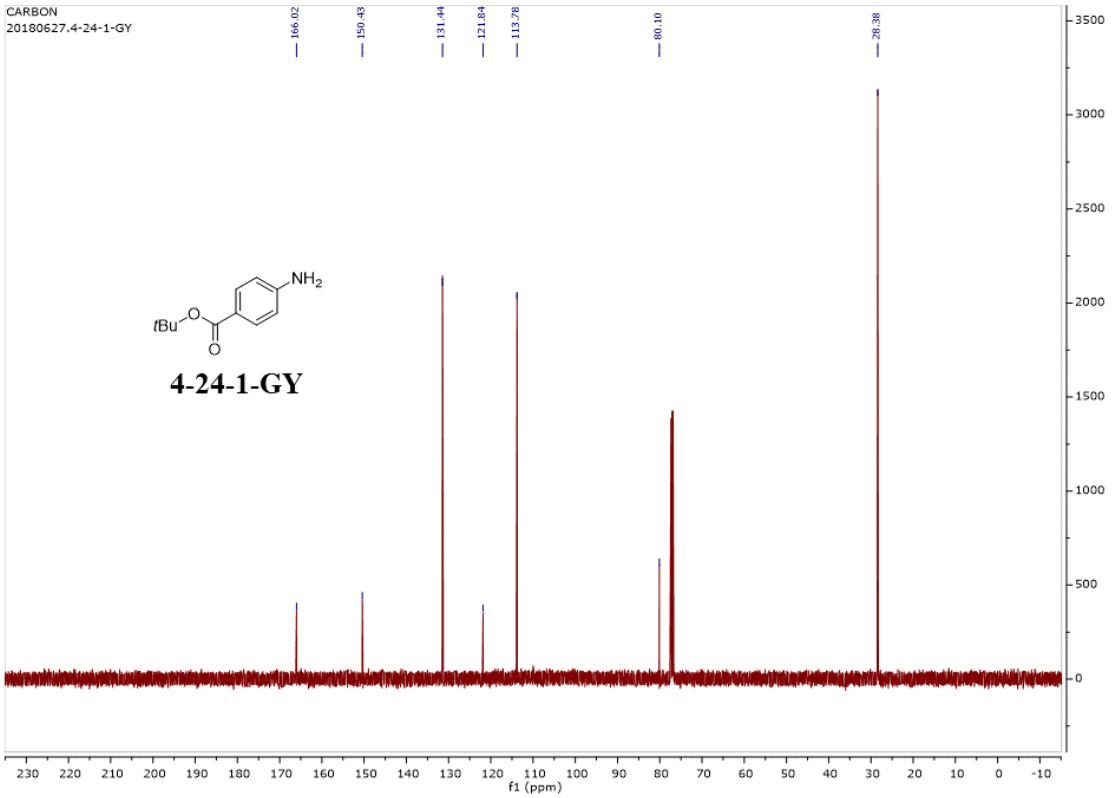

PROTON
20180612.4-19-1-GY
7.41
7.41
7.39
7.38
7.37
7.37
7.36
6.82
3.08
3.01
1.52
NHBoc
4-19-1-GY
3.98
1.00
3.04
3.12
9.06
f1 (ppm)

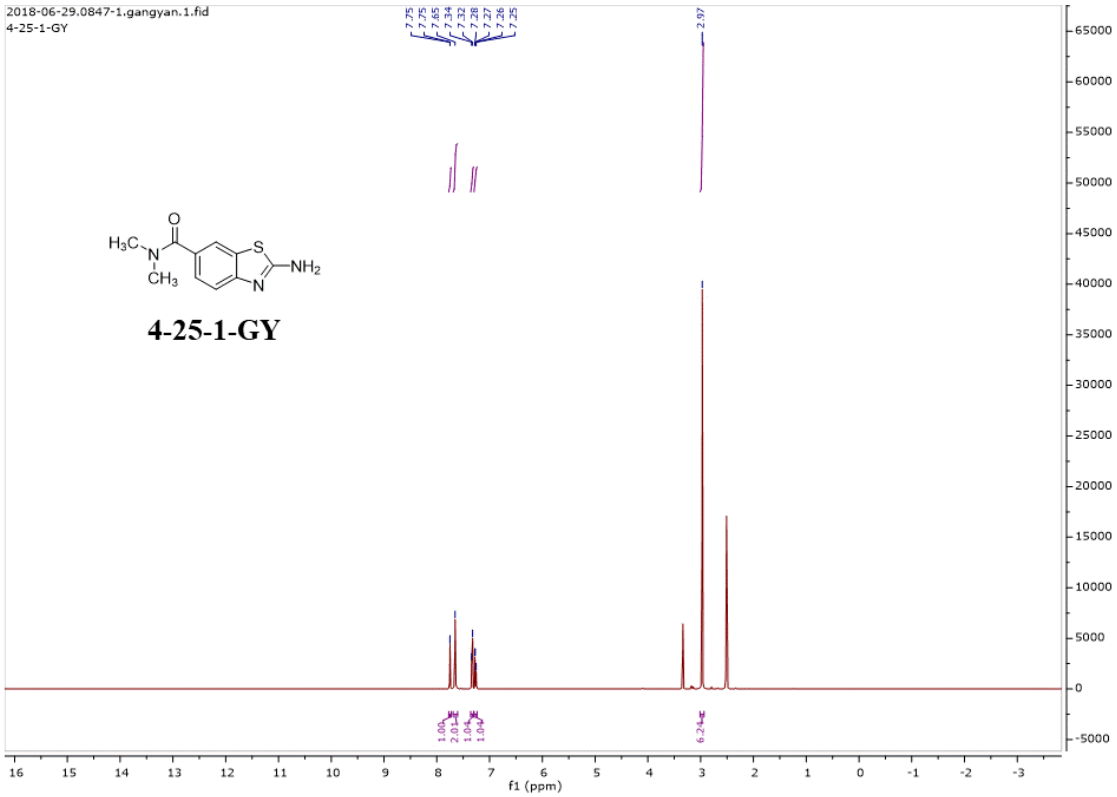

CARBON
20180612.4-19-1-GY
171.42
152.65
139.85
130.48
117.90
80.88
39.79
35.60
28.38
NHBoc
4-19-1-GY
f1 (ppm)


PROTON
20180613.4-21-1-GY
7.29
7.29
7.28
7.27
7.27
7.26
6.65
6.65
6.64
6.63
6.63
3.87
3.05
NH2
4-21-1-GY
2.05
2.00
2.22
6.11
f1 (ppm)

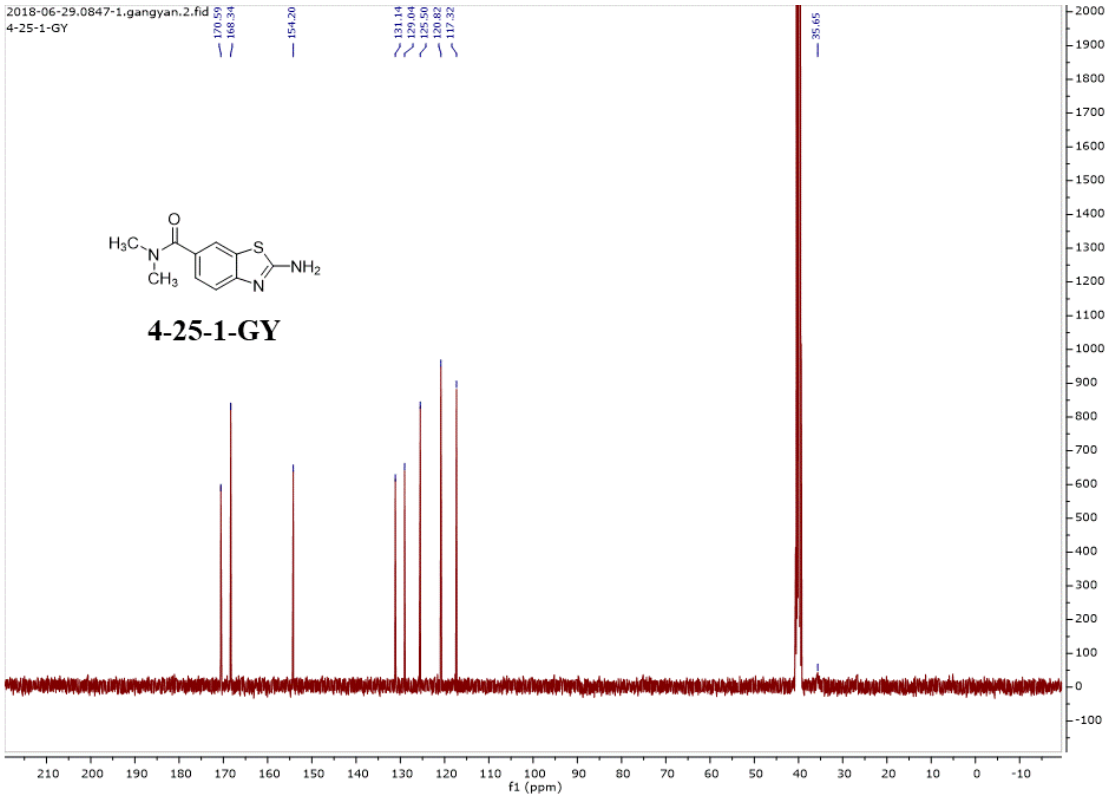

CARBON
20180613.4-21-1-GY
172.00
148.02
129.35
125.79
114.14
NH2
4-21-1-GY
f1 (ppm)


PROTON
20180627.4-24-1-GY
7.81
7.81
7.80
7.79
7.79
7.79
6.63
6.63
6.63
6.62
6.61
6.61
4.00
1.56
NH2
tBu
O
O
4-24-1-GY
2.00
2.08
2.14
9.09
f1 (ppm)

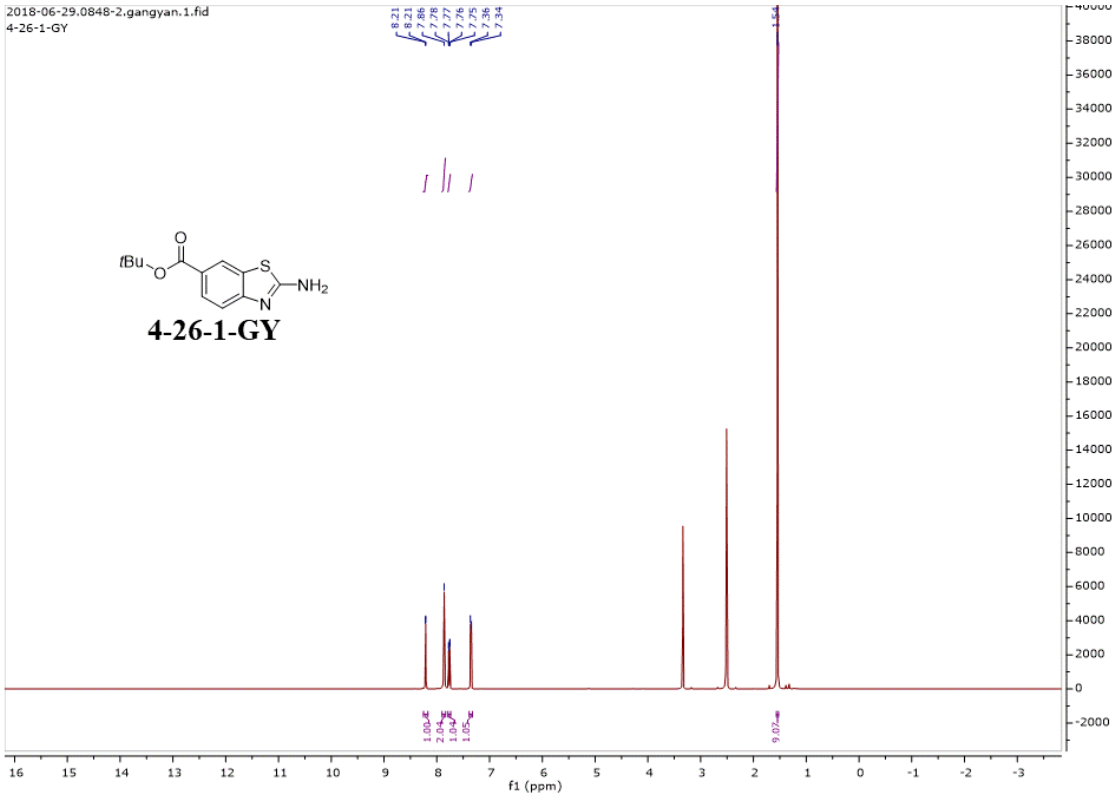

CARBON
20180627.4-24-1-GY
166.02
150.43
131.44
121.84
113.78
80.10
28.38
NH2
tBu
O
O
4-24-1-GY
f1 (ppm)

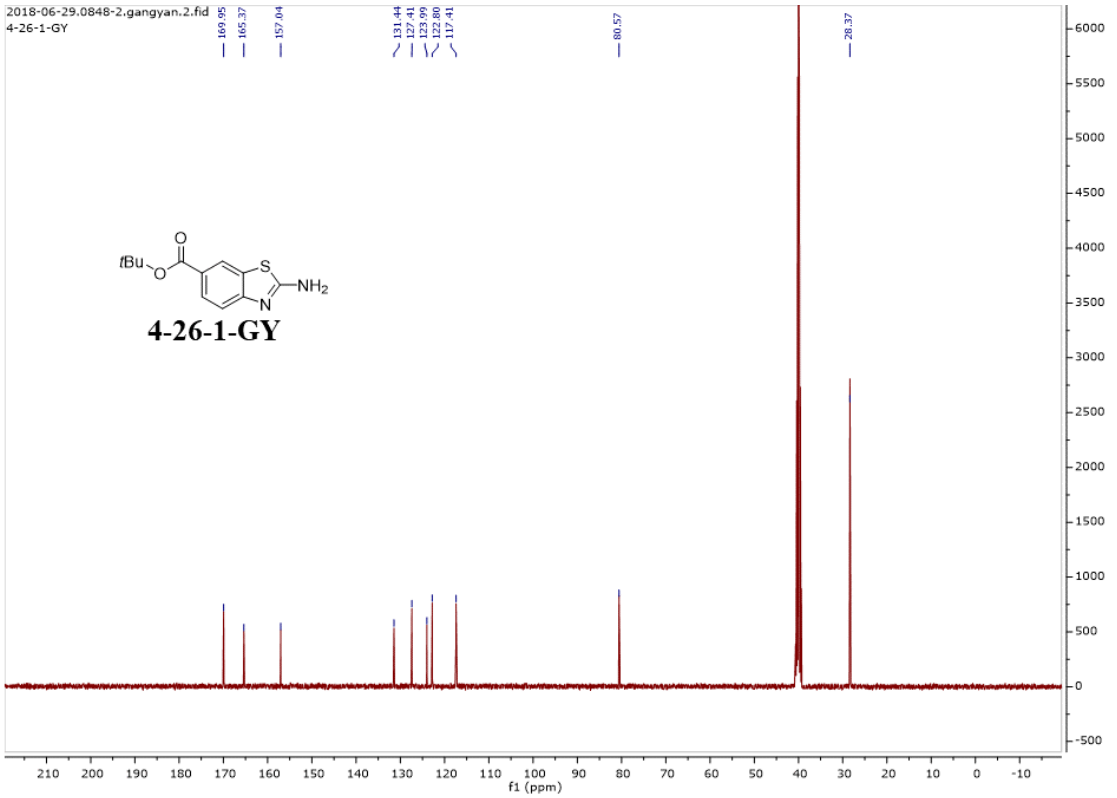


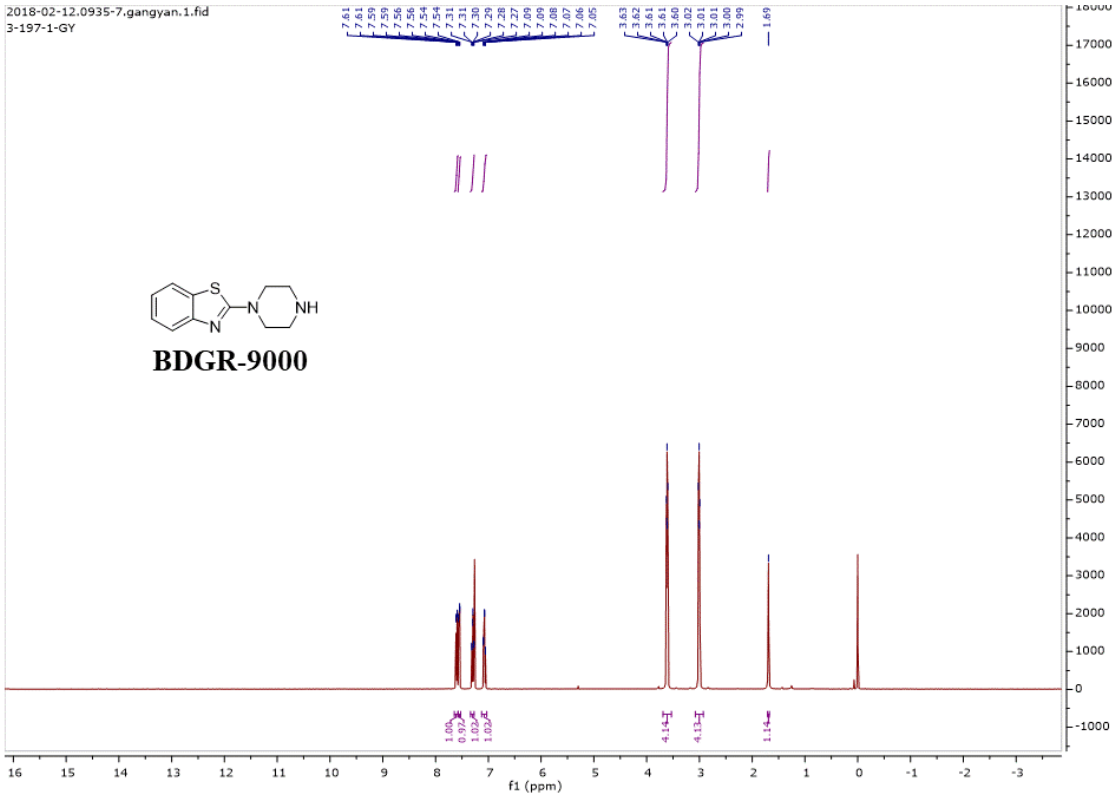

**4-25-1-GY**

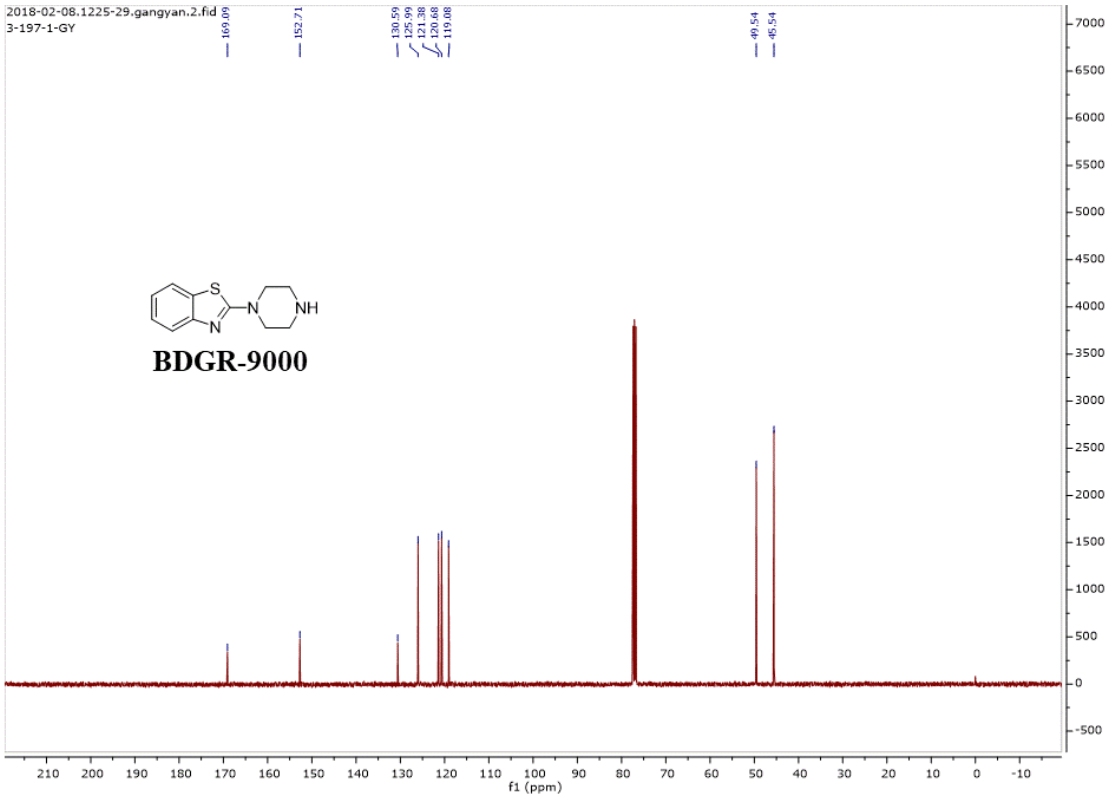


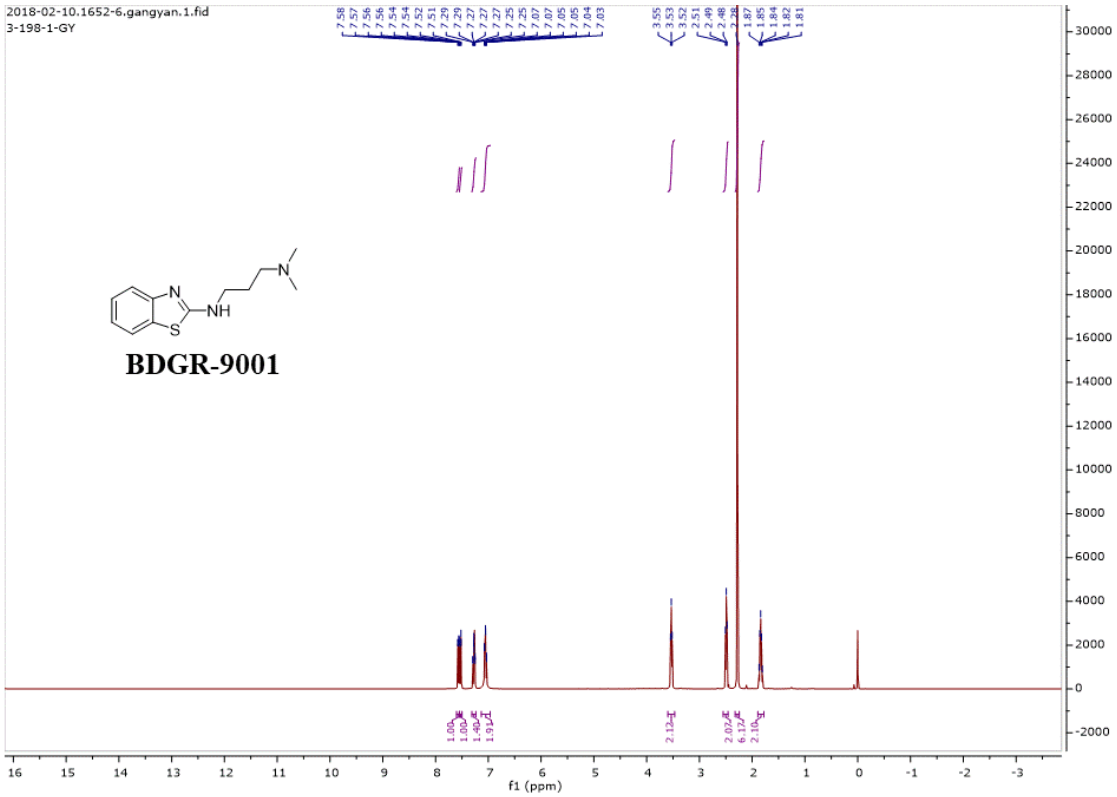

**4-25-1-GY**

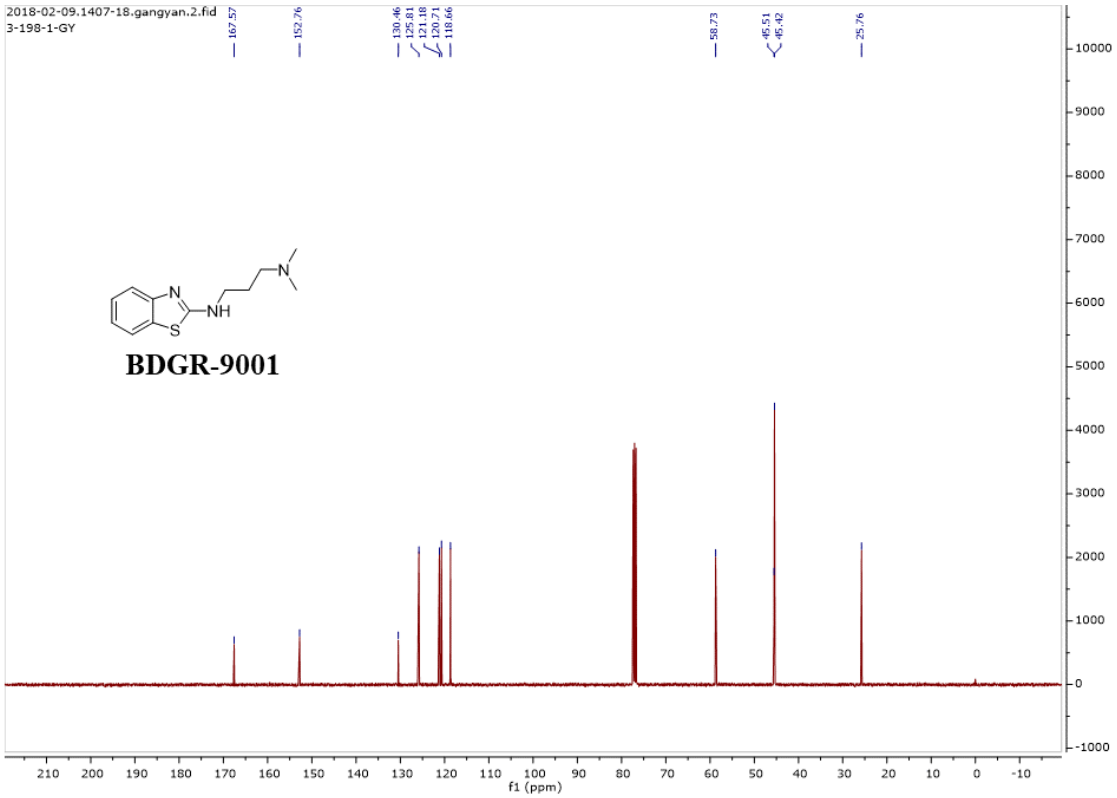

2018-06-29.0848-2.gangyan.1.fid
4-26-1-GY
8.21
8.21
7.86
7.78
7.77
7.76
7.75
7.36
7.34
1.54
tBu
O
O
S
N
NH2
4-26-1-GY
1.00
2.04
1.04
1.05
9.07
f1 (ppm)

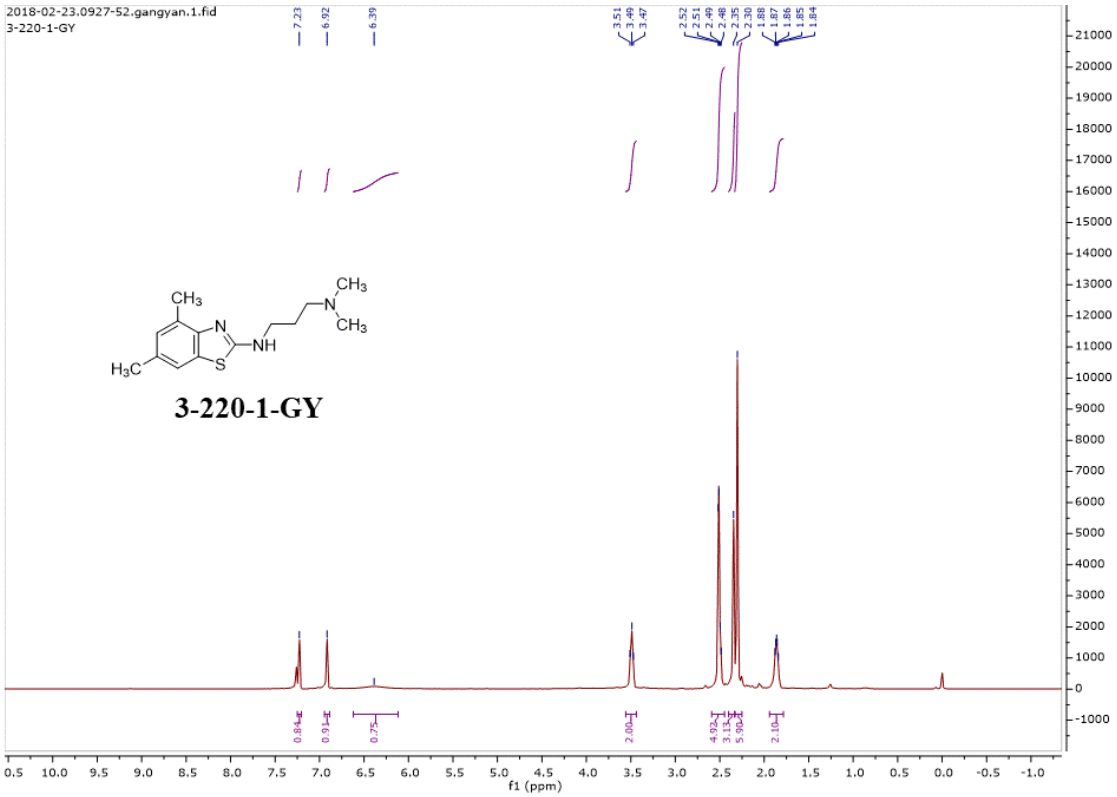

2018-06-29.0848-2.gangyan.2.fid
4-26-1-GY
169.95
165.37
157.04
131.44
127.41
123.99
122.80
117.41
80.57
28.37
tBu
O
O
S
N
NH2
4-26-1-GY
f1 (ppm)

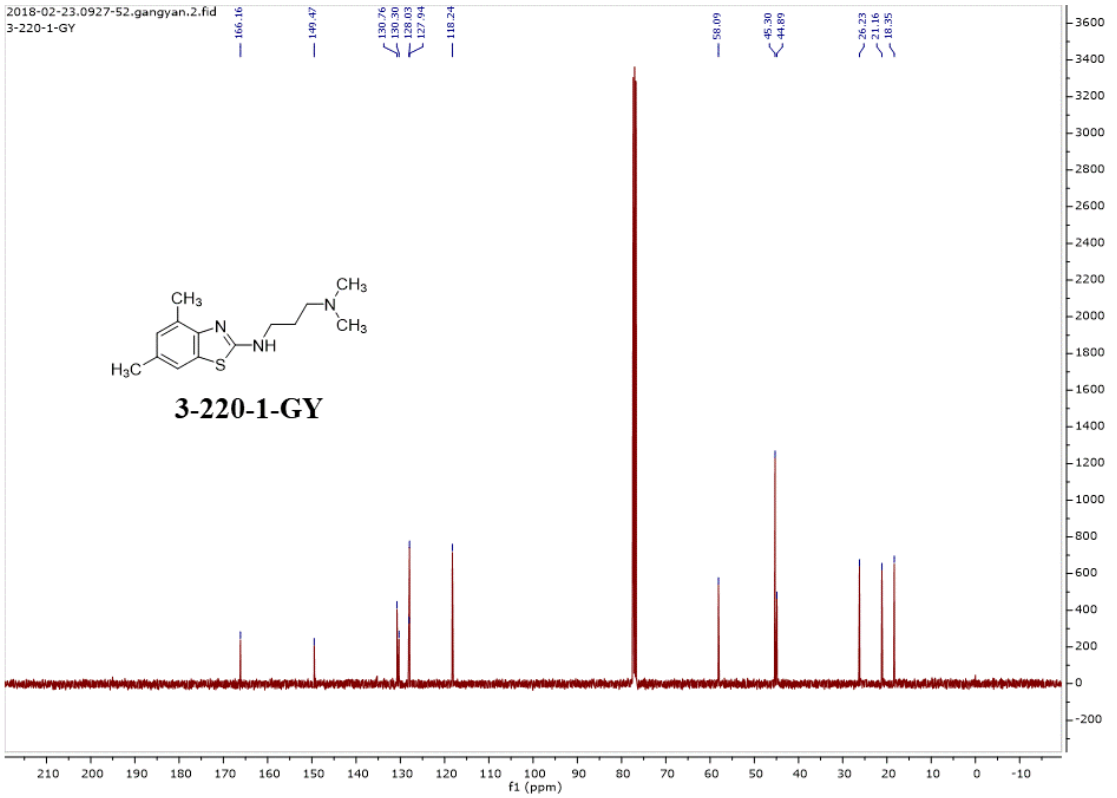

2018-02-12.0935-7.gangyan.1.fid
3-197-1-GY
BDGR-9000
f1 (ppm)

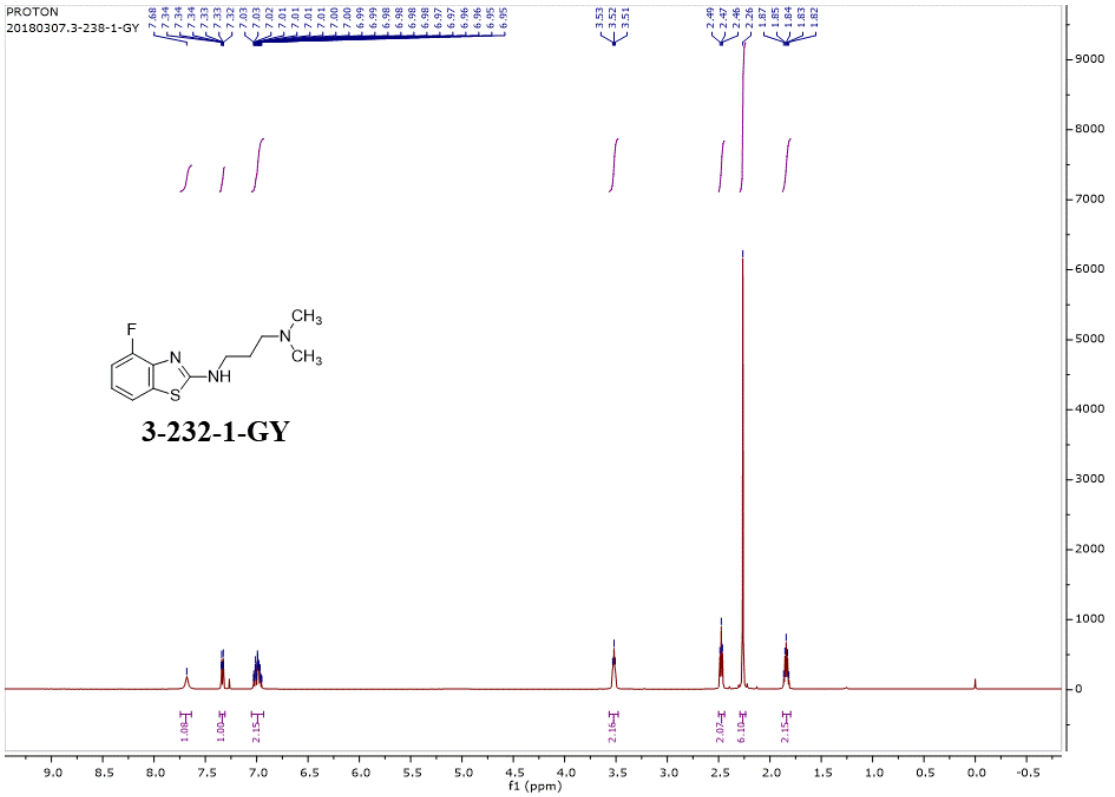

2018-02-08.1225-29.gangyan.2.fid
3-197-1-GY
BDGR-9000
f1 (ppm)

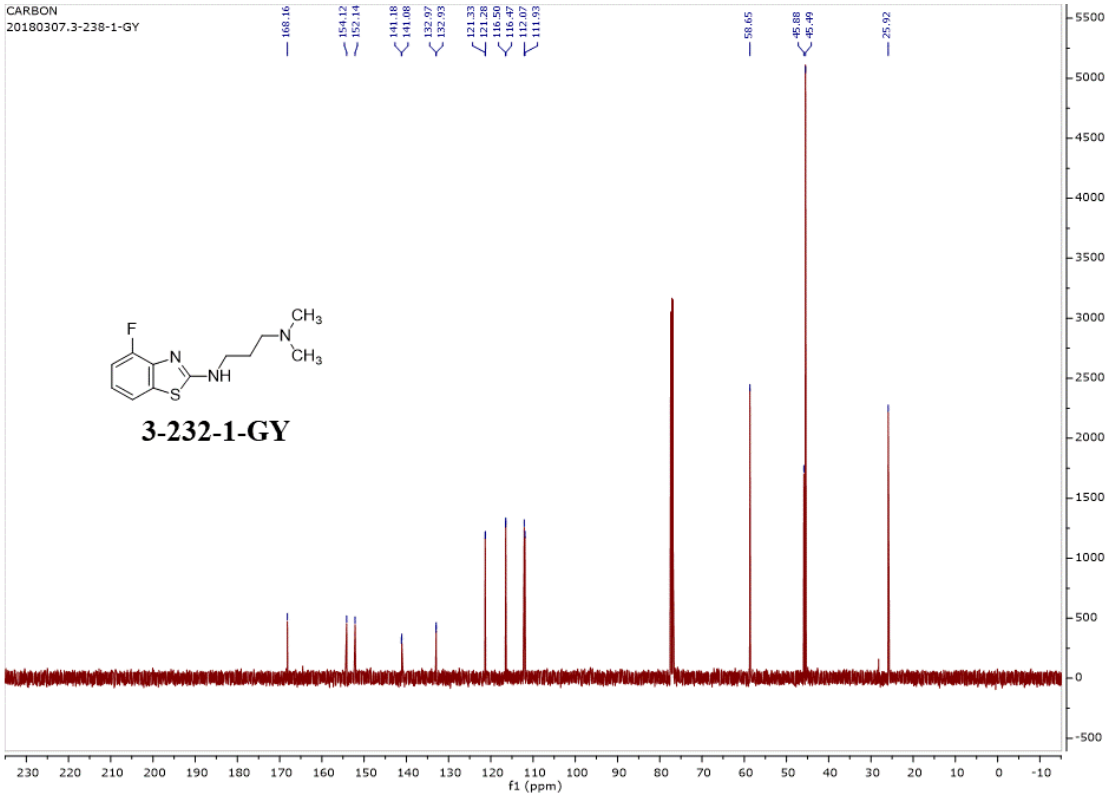

2018-02-10.1652-6.gangyan.1.fid
3-198-1-GY
BDGR-9001
f1 (ppm)

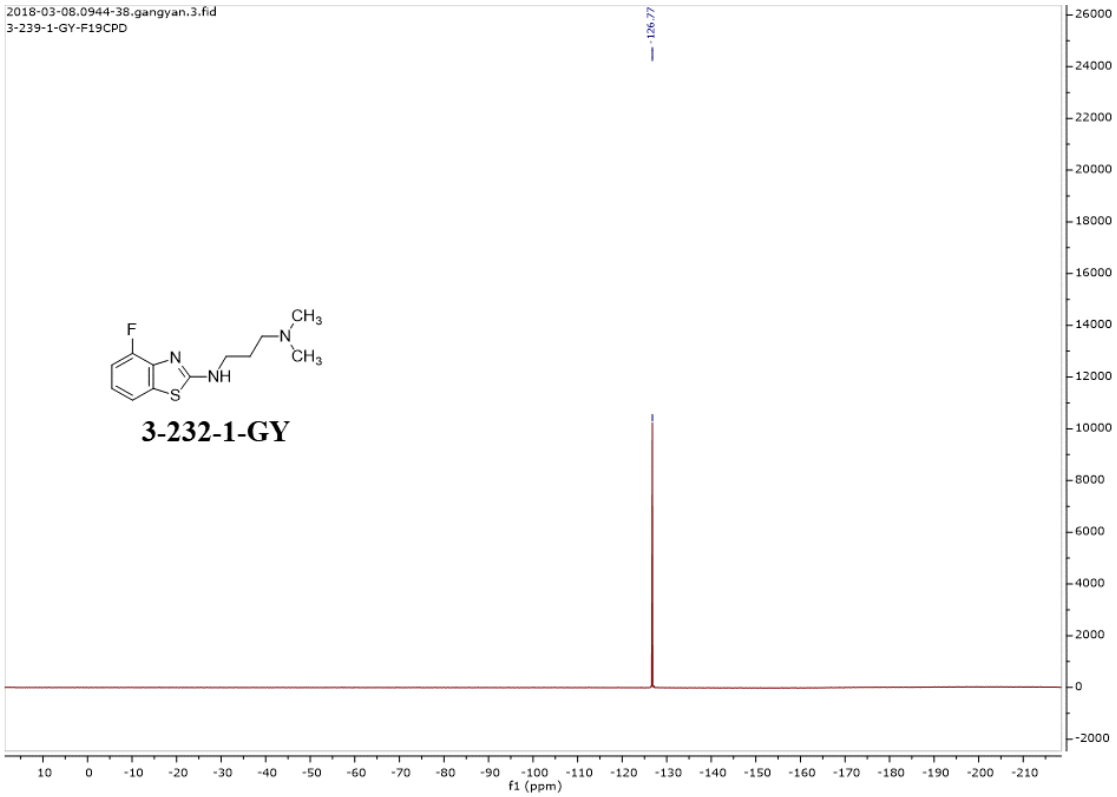

2018-02-09.1407-18.gangyan.2.fid
3-198-1-GY
BDGR-9001
f1 (ppm)


2018-02-23.0927-52.gangyan.1.fid
3-220-1-GY
7.23
6.92
6.39
3.51
3.49
3.47
2.52
2.51
2.49
2.48
2.35
2.30
1.88
1.87
1.86
1.85
1.84
CH3
N
CH3
CH3
NH
H3C
S
3-220-1-GY
0.84
0.91
0.75
2.00
4.92
3.13
5.90
2.10
f1 (ppm)

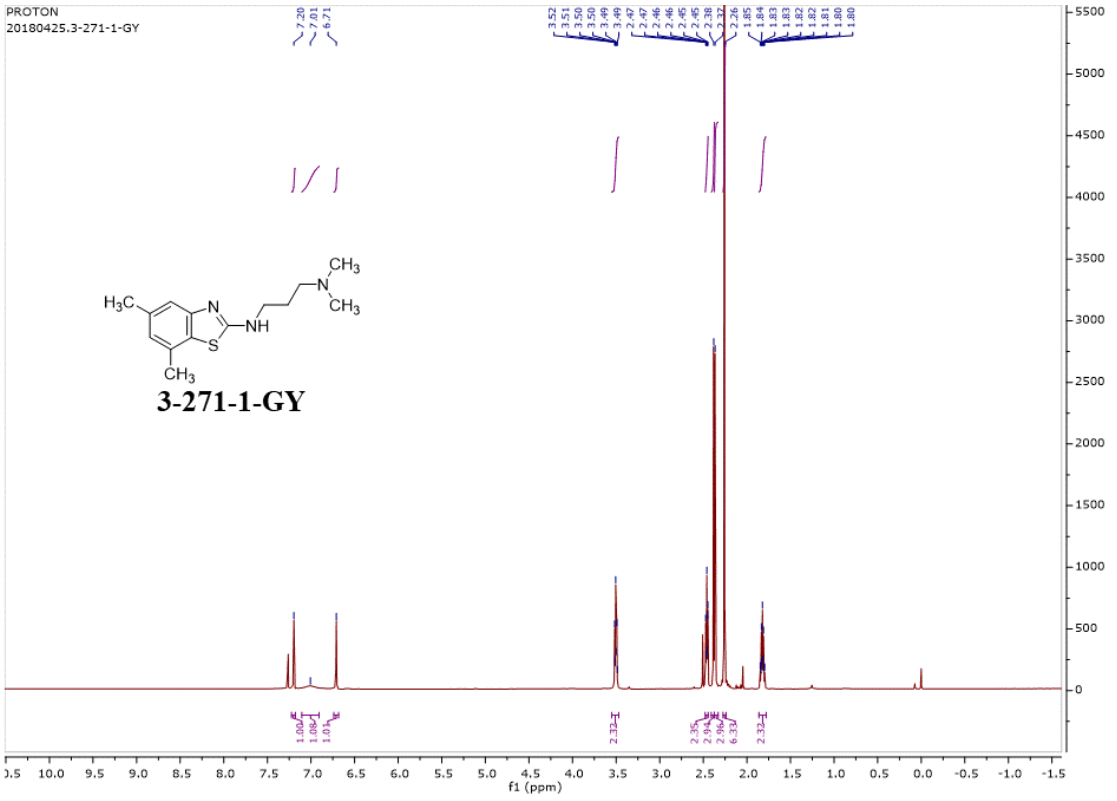

2018-02-23.0927-52.gangyan.2.fid
3-220-1-GY
166.16
149.47
130.76
130.30
128.03
127.94
118.24
58.09
45.30
44.89
26.33
21.16
18.35
CH3
N
CH3
CH3
NH
H3C
S
3-220-1-GY
f1 (ppm)


PROTON
20180307.3-238-1-GY
F
N
S
NH
CH3
N
CH3
3-232-1-GY
f1 (ppm)

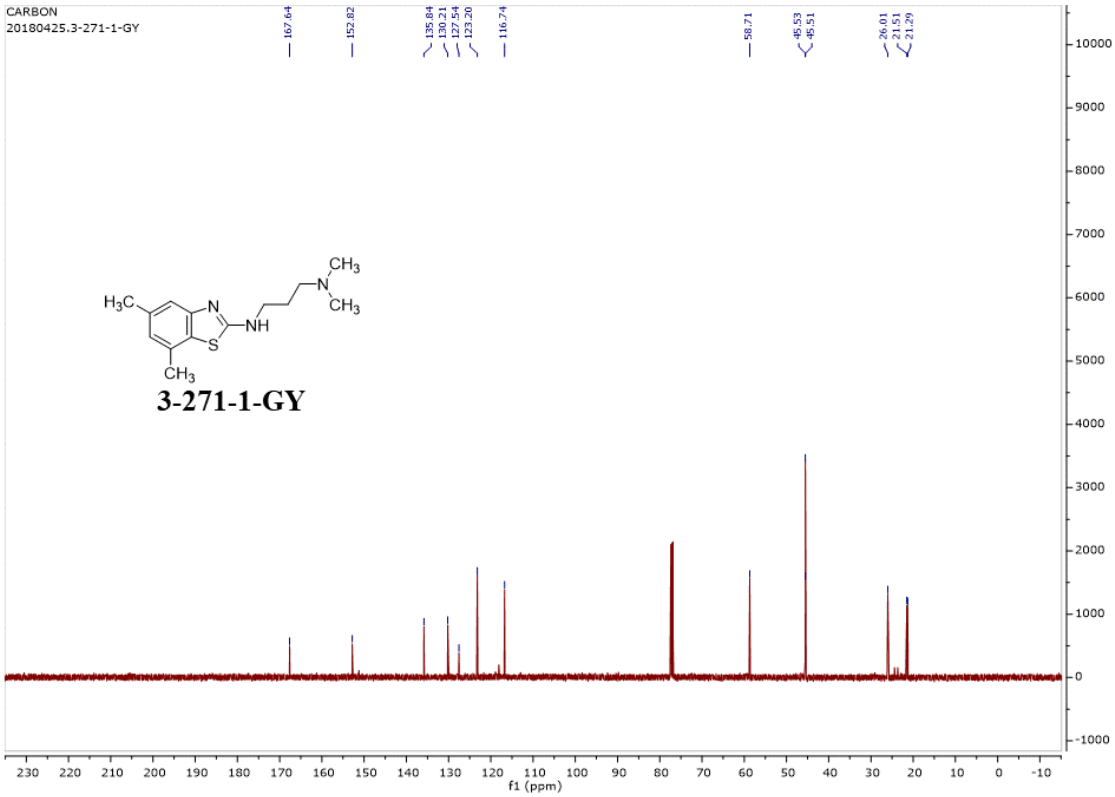

CARBON
20180307.3-238-1-GY
F
N
S
NH
CH3
N
CH3
3-232-1-GY
f1 (ppm)




**3-232-1-GY**

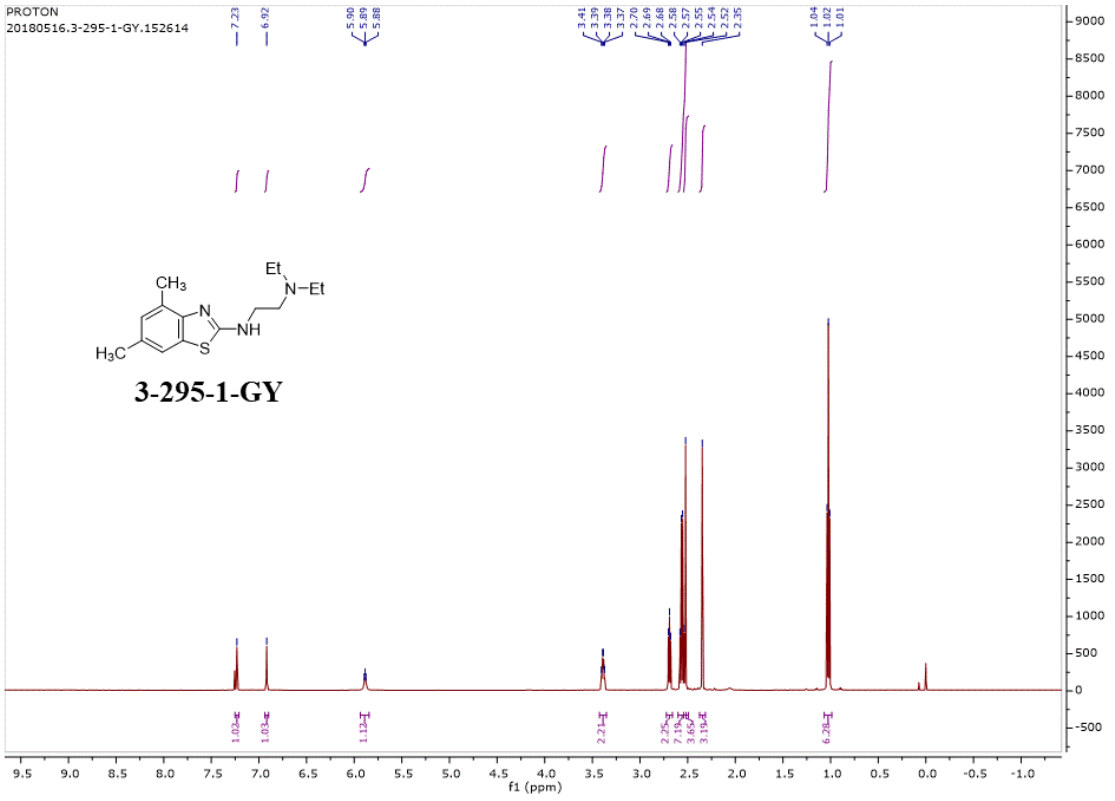



**3-271-1-GY**



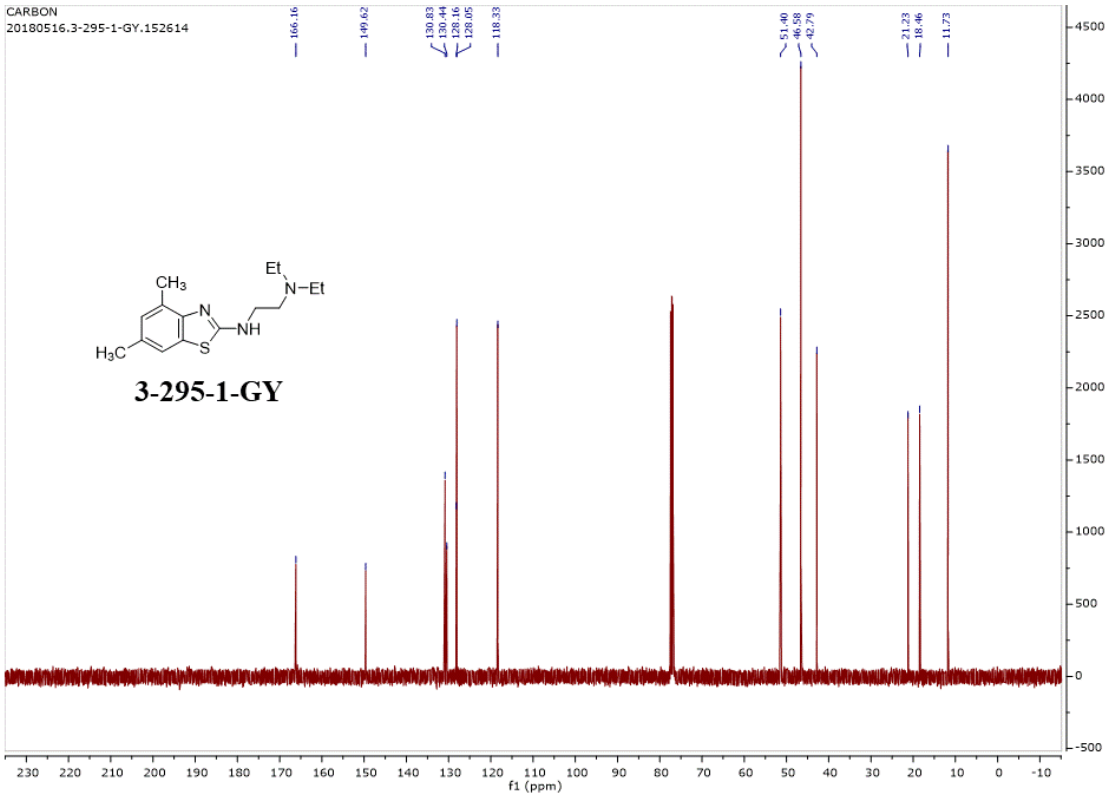



**3-271-1-GY**



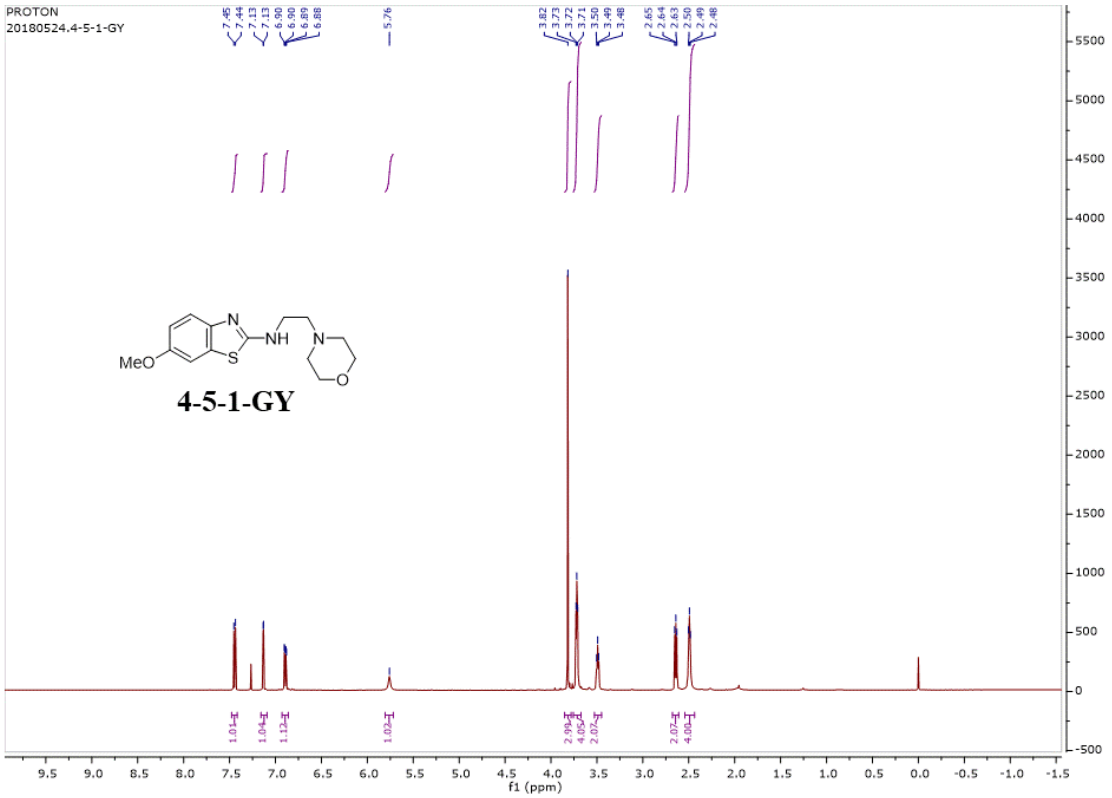



**3-295-1-GY**



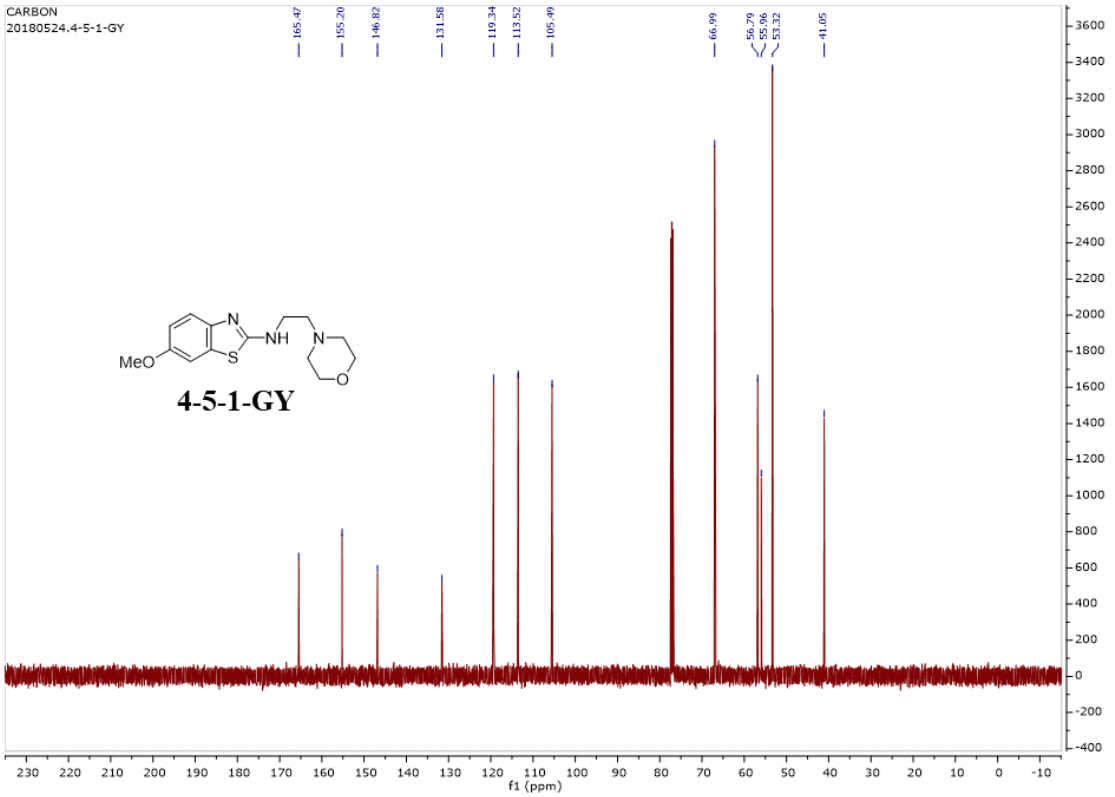


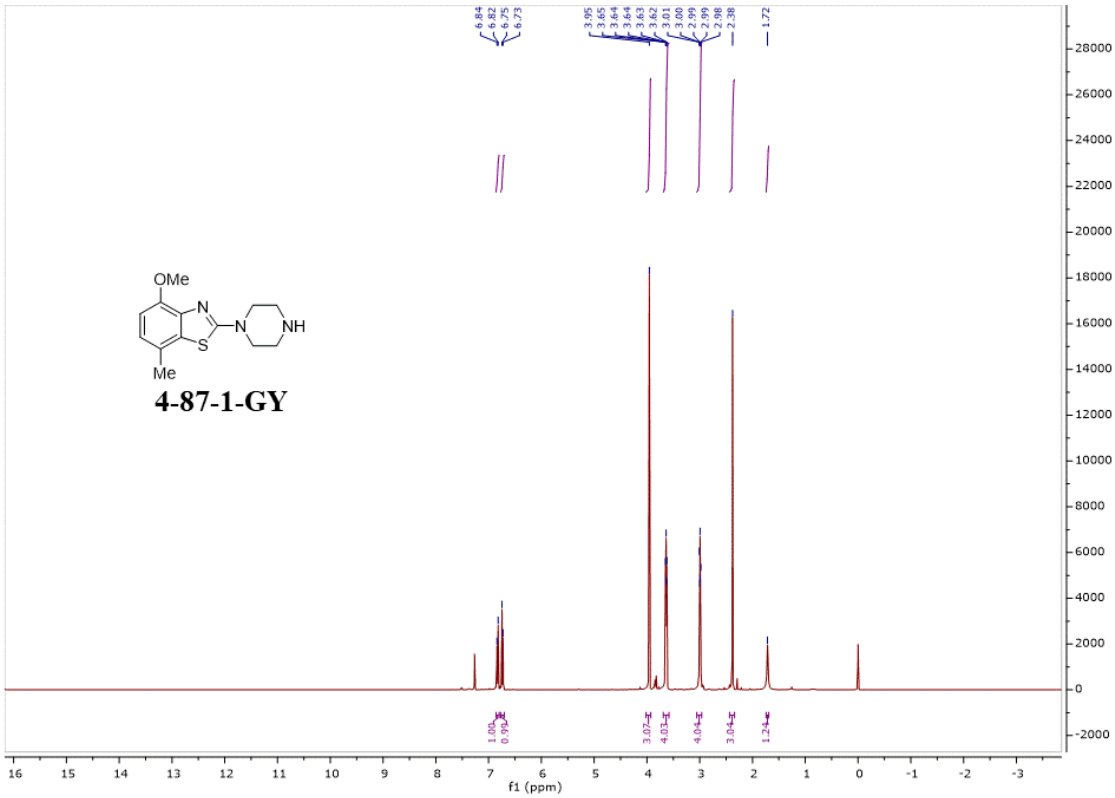

**3-295-1-GY**

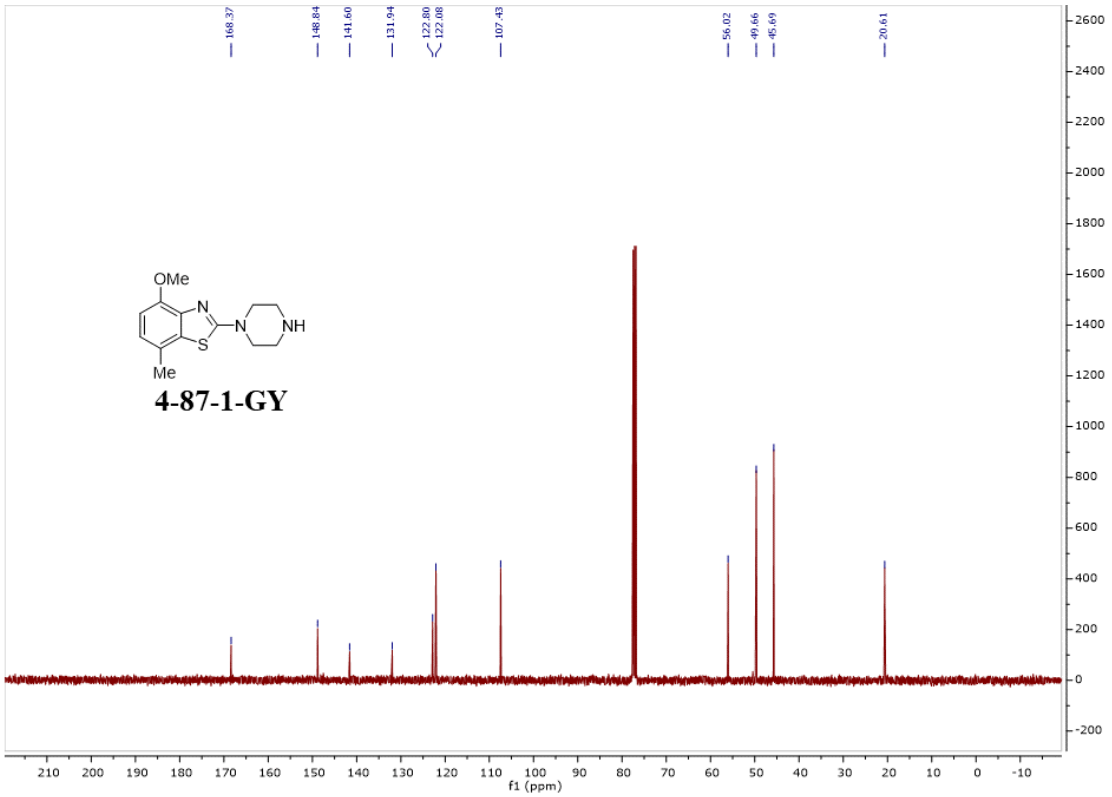


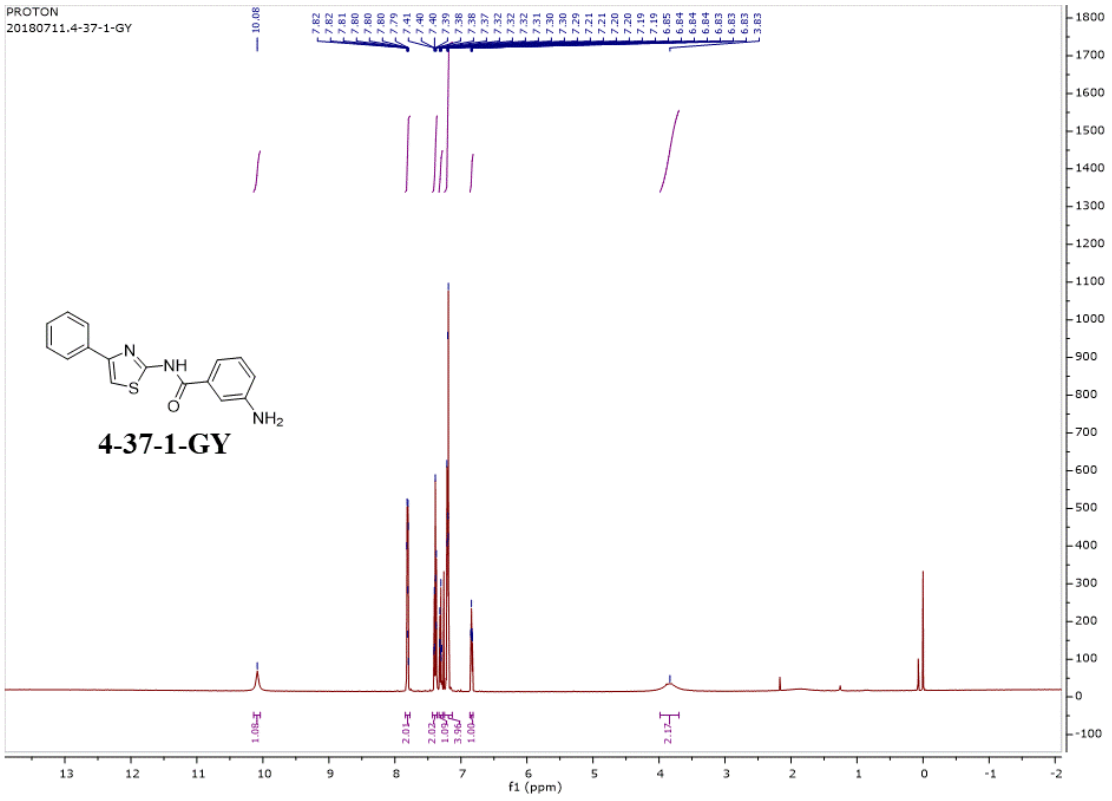


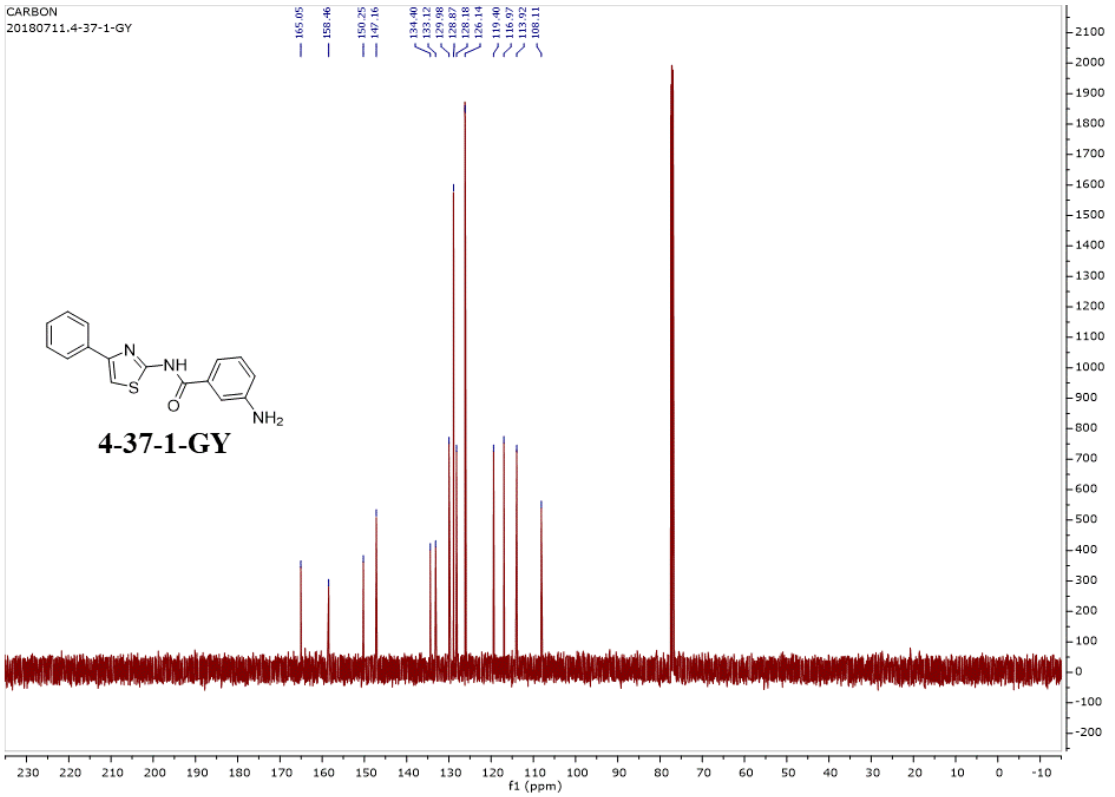

**4-5-1-GY**

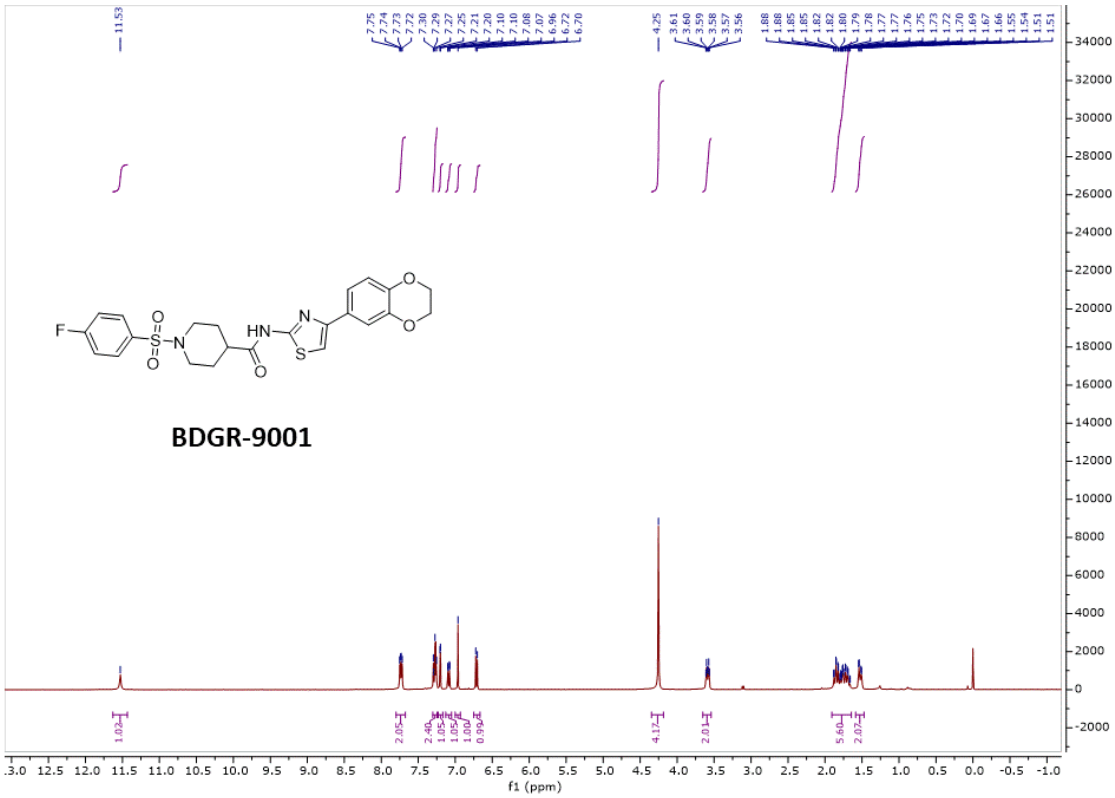

CARBON
20180524.4-5-1-GY
165.47
155.20
146.82
131.58
119.34
113.52
105.49
66.99
56.79
55.96
53.32
41.05
MeO
N
NH
N
S
O
4-5-1-GY
f1 (ppm)

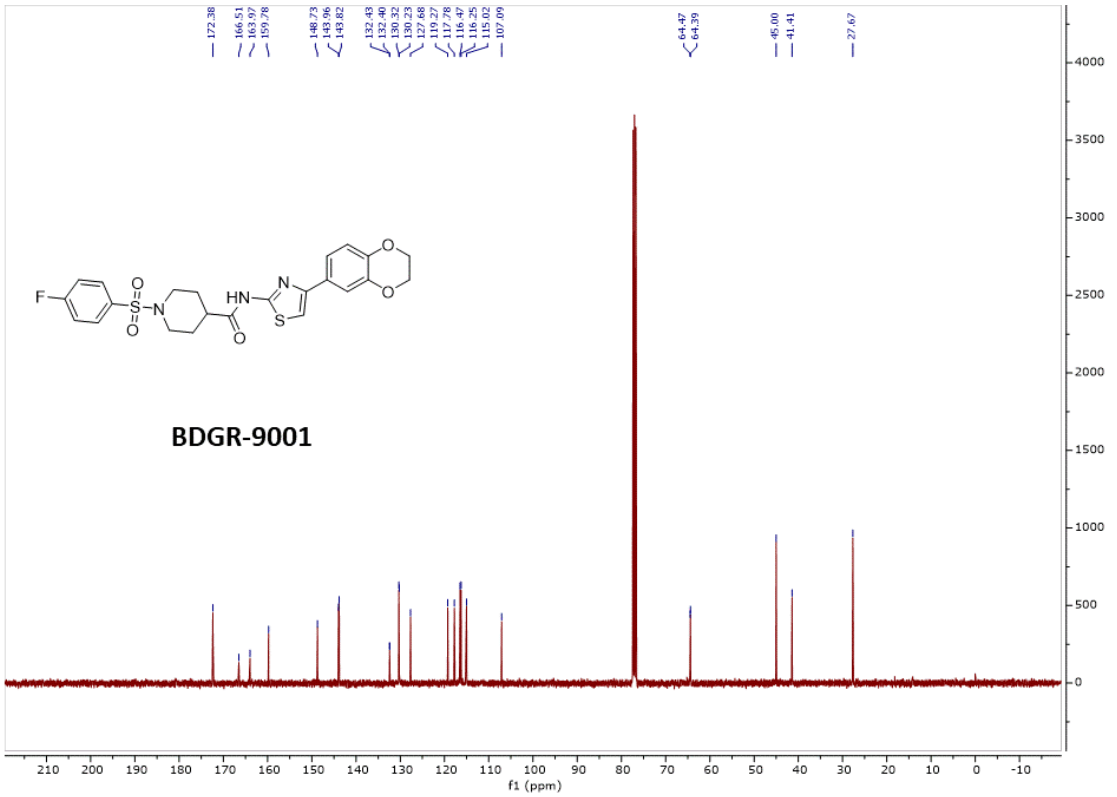

6.84
6.82
6.75
6.73
3.95
3.65
3.64
3.64
3.63
3.62
3.01
3.00
2.99
2.99
2.98
2.38
1.72
OMe
N
N
NH
S
Me
4-87-1-GY
1.00
0.99
3.07
4.03
4.04
3.04
1.24
f1 (ppm)

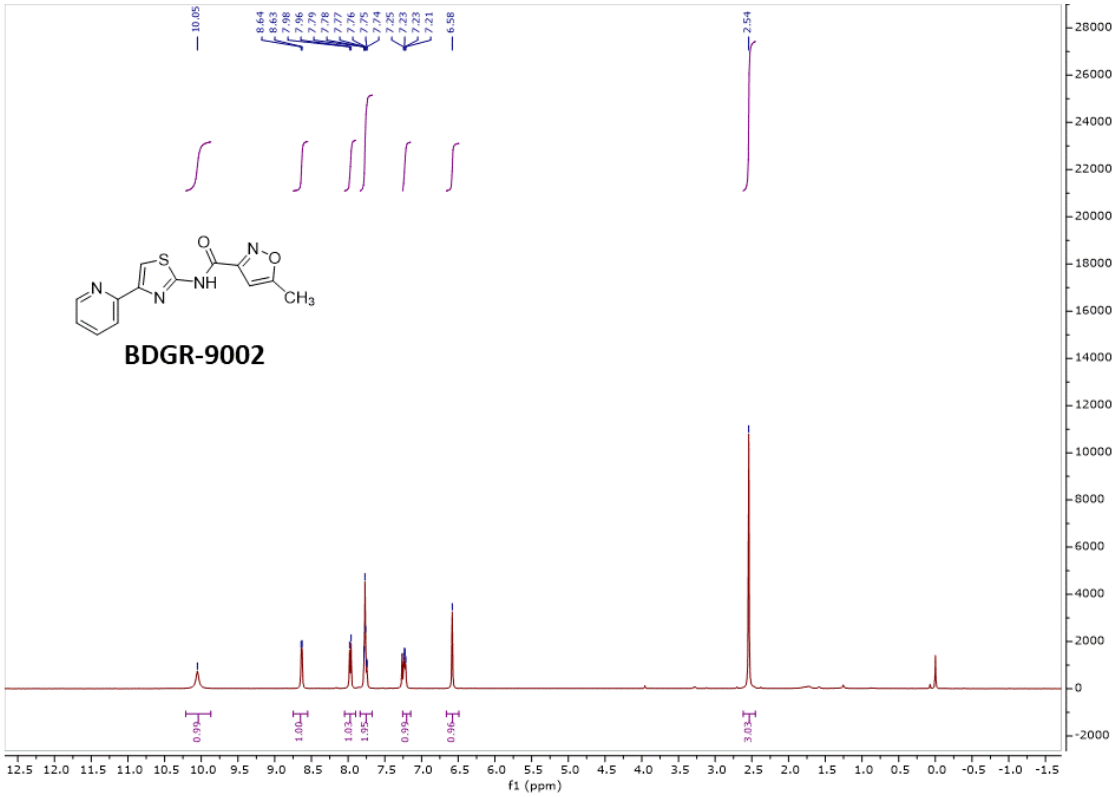

168.37
148.84
141.60
131.94
122.80
122.08
107.43
56.02
49.66
45.69
20.61
OMe
N
S
N
NH
Me
4-87-1-GY
f1 (ppm)

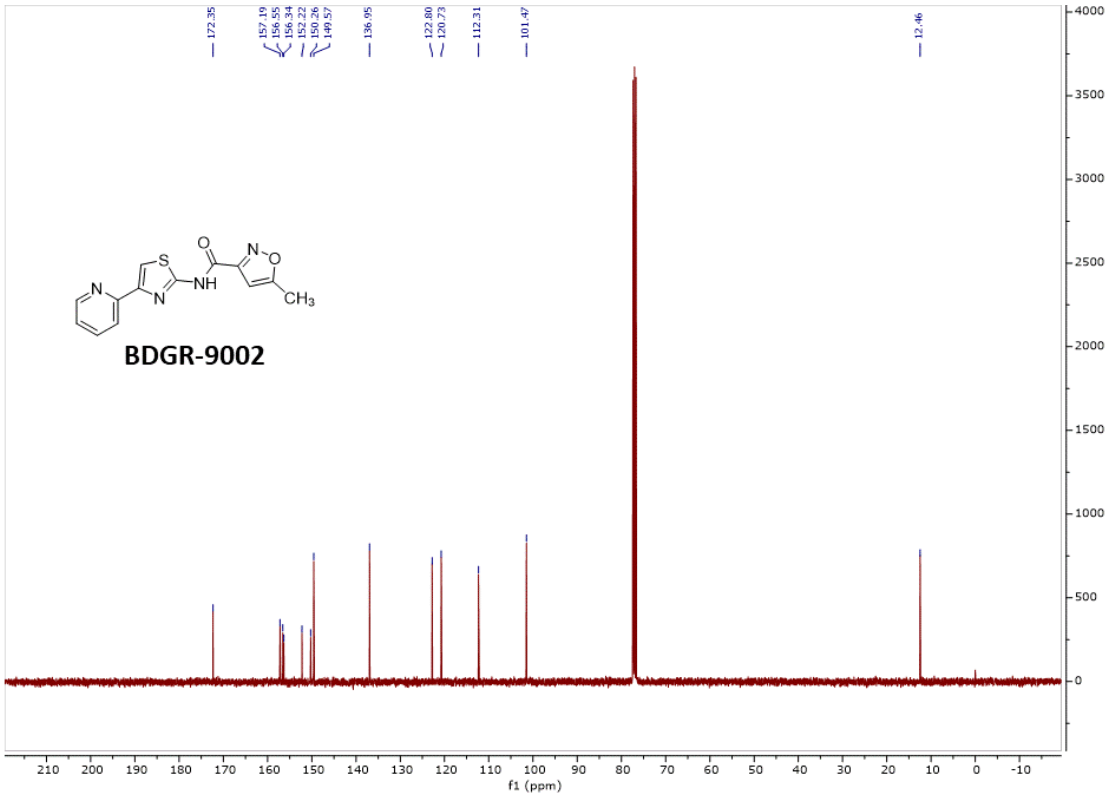

PROTON
20180711.4-37-1-GY
10.08
7.82
7.81
7.80
7.79
7.41
7.40
7.39
7.38
7.37
7.32
7.31
7.30
7.29
7.21
7.20
7.19
6.85
6.84
6.83
3.83
1.08
2.01
2.02
1.09
3.96
1.00
2.17
N
S
NH
O
NH2
4-37-1-GY
f1 (ppm)

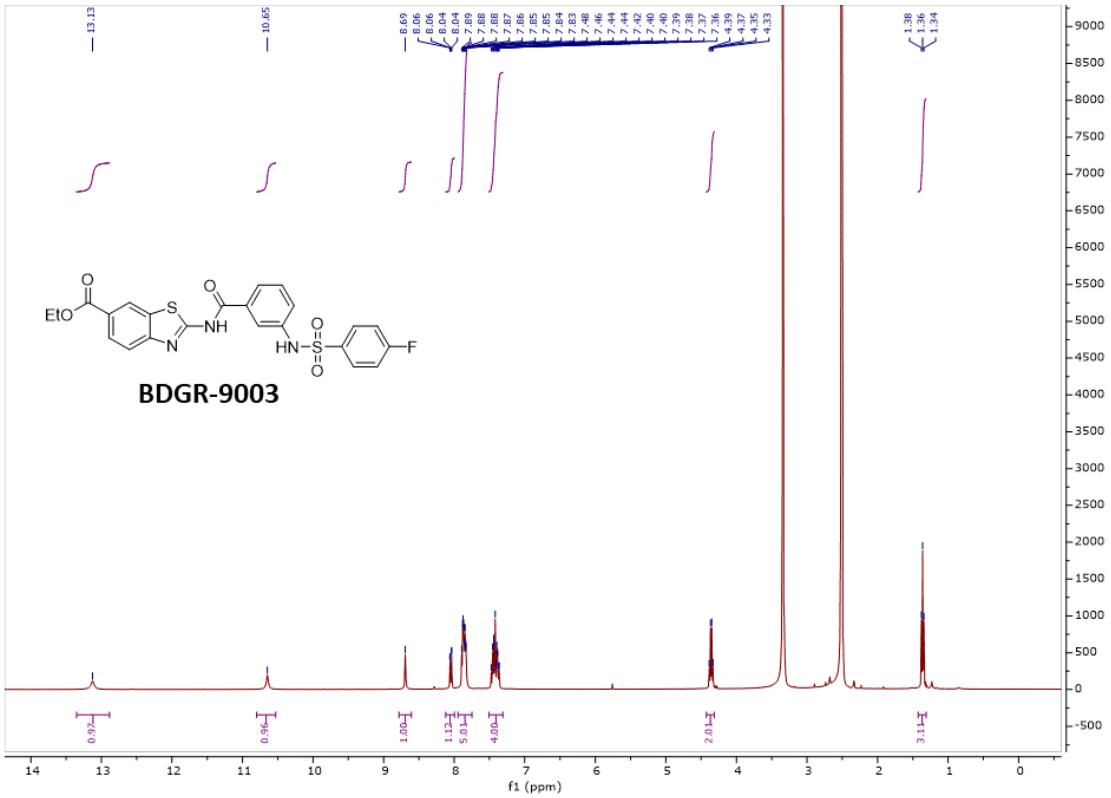

CARBON
20180711.4-37-1-GY
165.05
158.46
150.25
147.16
134.40
133.12
129.98
128.87
128.18
126.14
119.40
116.97
113.92
108.11
4-37-1-GY
f1 (ppm)

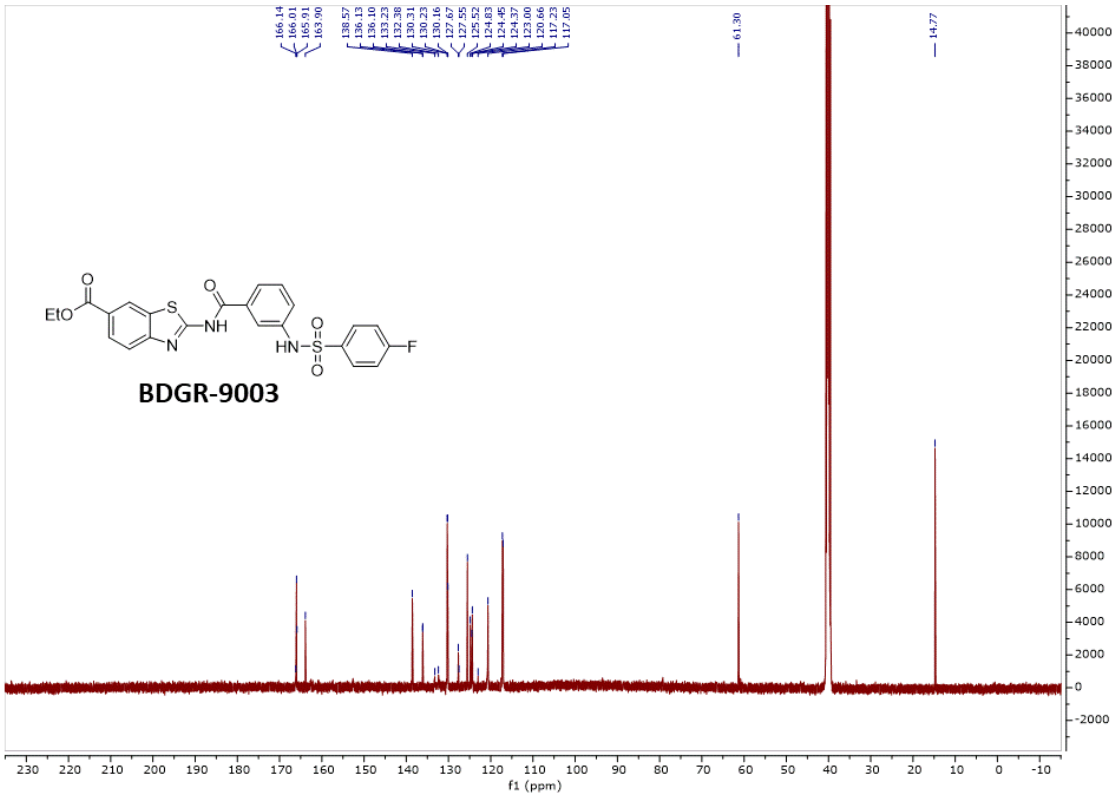

11.53
7.75
7.74
7.73
7.72
7.30
7.29
7.27
7.25
7.21
7.20
7.10
7.10
7.08
7.07
6.96
6.72
6.70
4.25
3.61
3.60
3.59
3.58
3.57
3.56
1.88
1.88
1.85
1.85
1.82
1.82
1.80
1.79
1.78
1.77
1.77
1.76
1.75
1.73
1.72
1.70
1.69
1.67
1.66
1.55
1.54
1.51
1.51
BDGR-9001
1.02
2.05
2.40
2.05
1.05
1.00
0.99
4.17
2.01
5.60
2.07
f1 (ppm)

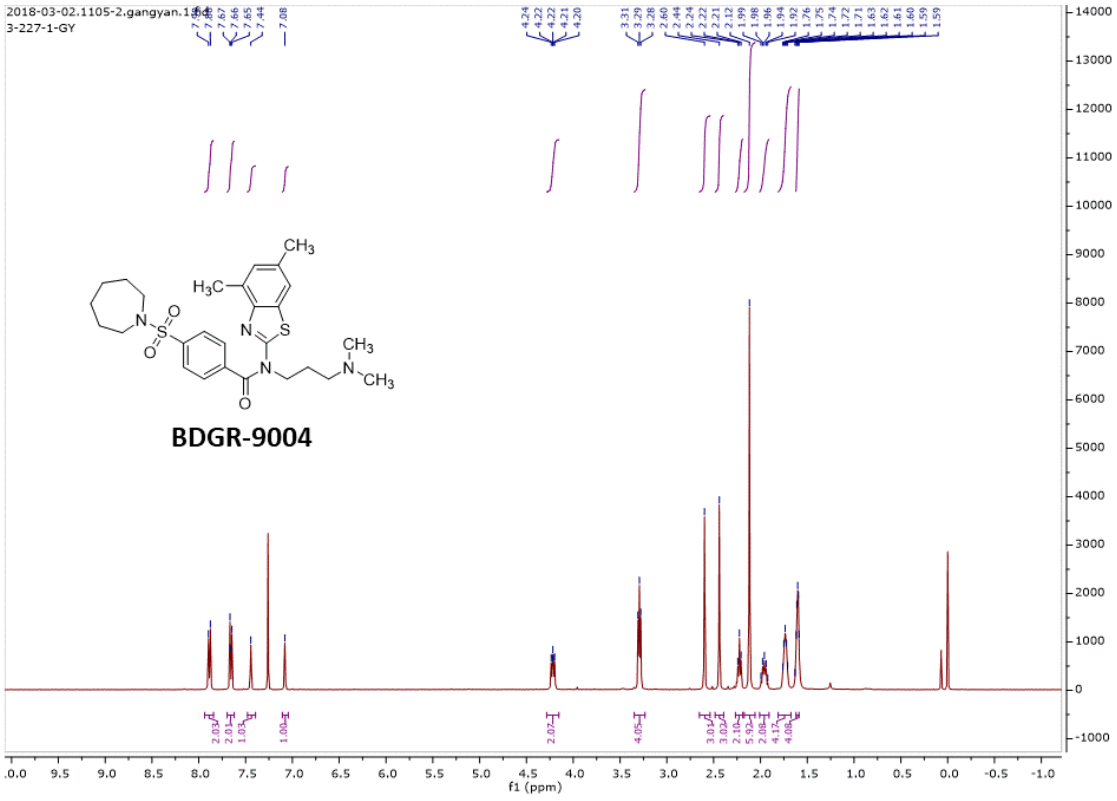

172.38
166.51
163.97
159.78
148.73
143.96
143.82
132.43
132.40
130.32
130.23
127.68
119.27
117.78
116.47
116.25
115.02
107.09
64.47
64.39
45.00
41.41
27.67
F
O
S
O
N
HN
N
S
O
O
BDGR-9001
f1 (ppm)

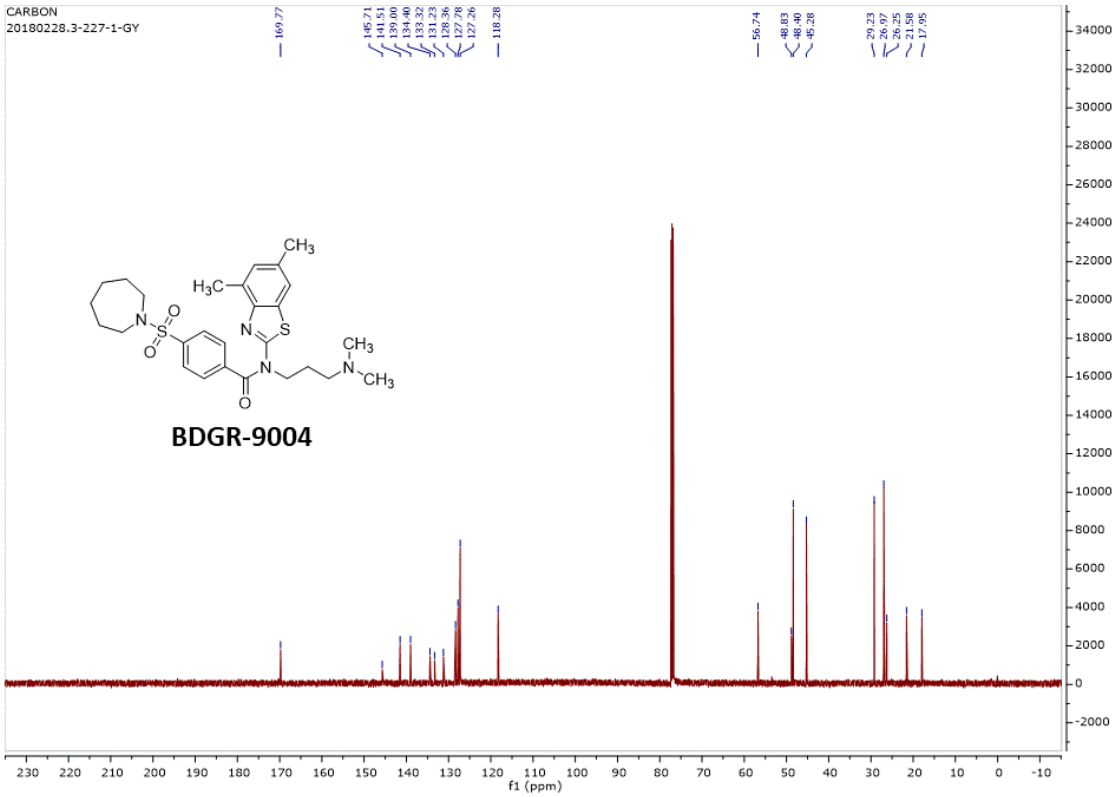

10.05
8.64
8.63
7.98
7.96
7.79
7.78
7.77
7.76
7.75
7.74
7.25
7.23
7.23
7.21
6.58
2.54
N
S
N
O
NH
N
O
CH3
BDGR-9002
0.99
1.00
1.03
1.95
0.99
0.96
3.03
f1 (ppm)


172.35
157.19
156.55
156.34
152.22
150.26
149.57
136.95
122.80
120.73
112.31
101.47
12.46
BDGR-9002
f1 (ppm)

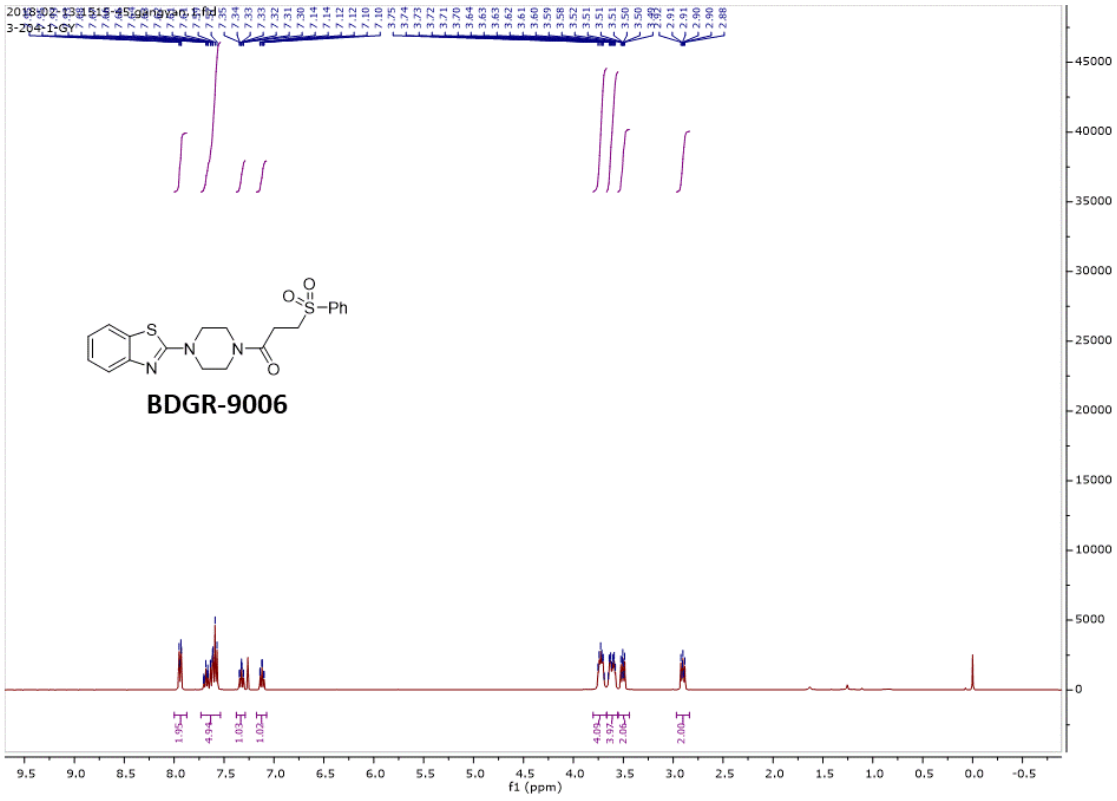

13.13
10.65
8.69
8.06
8.06
8.04
8.04
7.89
7.88
7.88
7.87
7.86
7.85
7.85
7.84
7.83
7.48
7.46
7.44
7.44
7.42
7.40
7.40
7.39
7.38
7.37
7.36
4.39
4.37
4.35
4.33
1.38
1.36
1.34
BDGR-9003
0.97
0.96
1.00
1.12
5.01
4.00
2.01
3.11
f1 (ppm)


166.14
166.01
165.91
163.90
138.57
136.13
135.10
133.23
132.38
130.31
130.23
130.16
127.67
127.55
125.52
124.83
124.45
124.37
123.00
120.66
117.23
117.05
61.30
14.77
EtO
S
N
NH
O
HN
S
O
O
F
BDGR-9003
f1 (ppm)

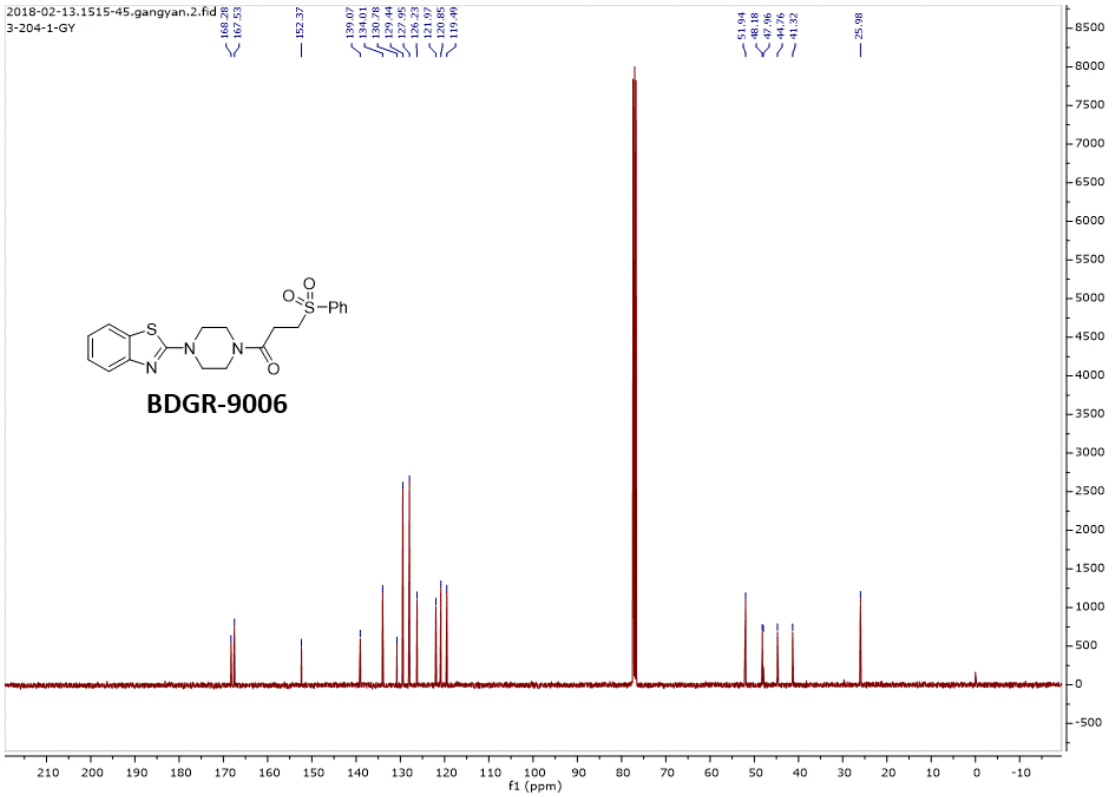

2018-03-02.1105-2.gangyan.1H
3-227-1-GY
7.68
7.67
7.66
7.65
7.44
7.08
4.24
4.22
4.22
4.21
4.20
3.31
3.29
3.28
2.60
2.44
2.24
2.22
2.21
2.12
1.99
1.98
1.96
1.94
1.92
1.76
1.75
1.74
1.72
1.71
1.63
1.62
1.61
1.60
1.59
1.59
CH3
H3C
N
S
N
O
S
O
O
N
CH3
N
CH3
BDGR-9004
2.03
2.01
1.03
1.00
2.07
4.05
3.01
3.02
2.10
2.02
2.08
4.12
4.08
f1 (ppm)




**BDGR-9004**

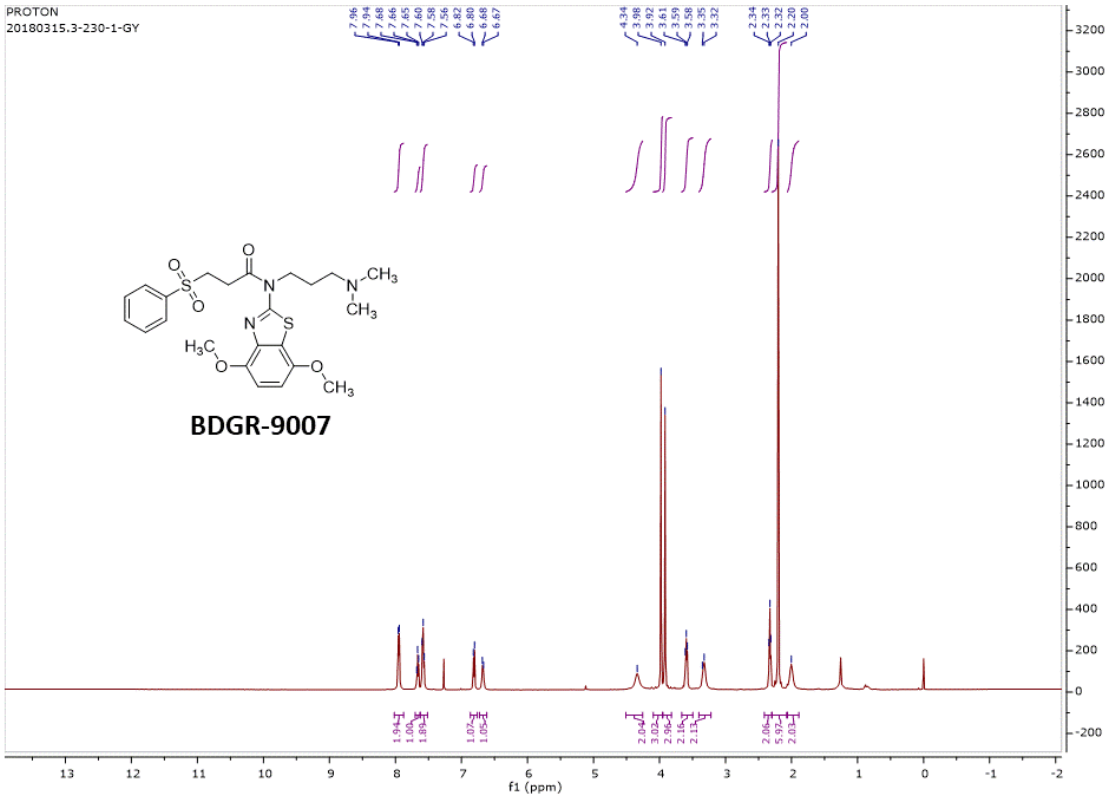



**BDGR-9006**



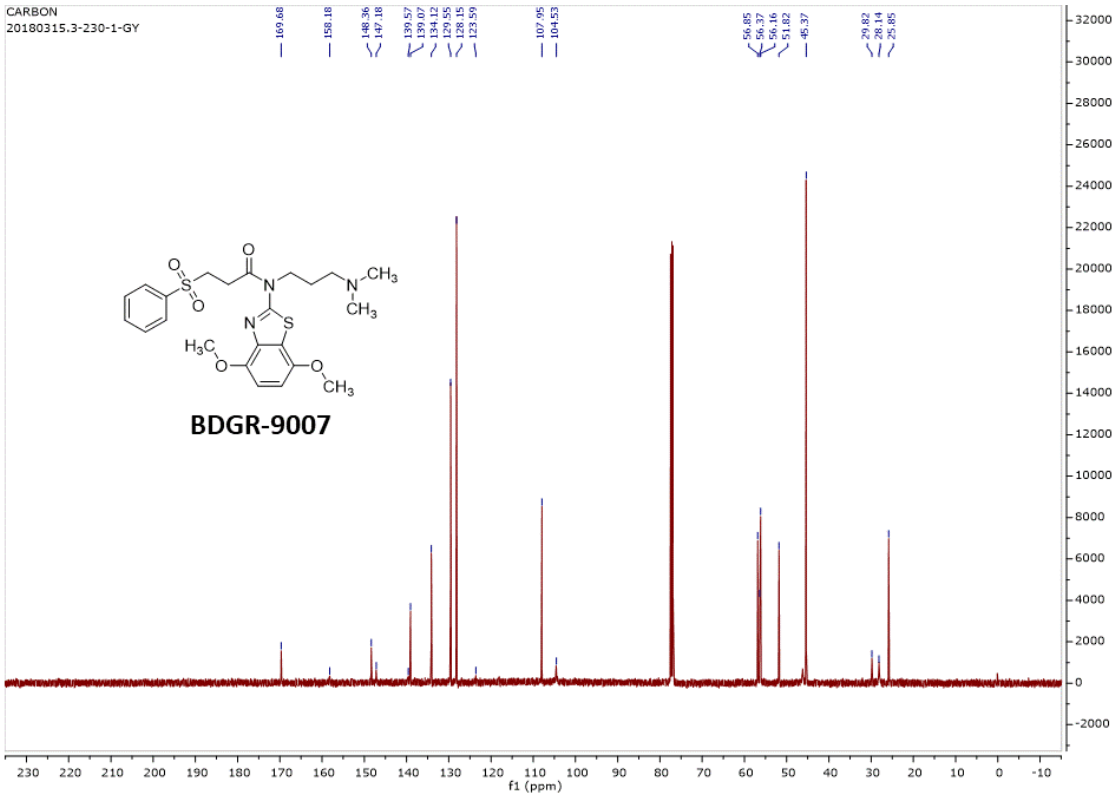



**BDGR-9006**

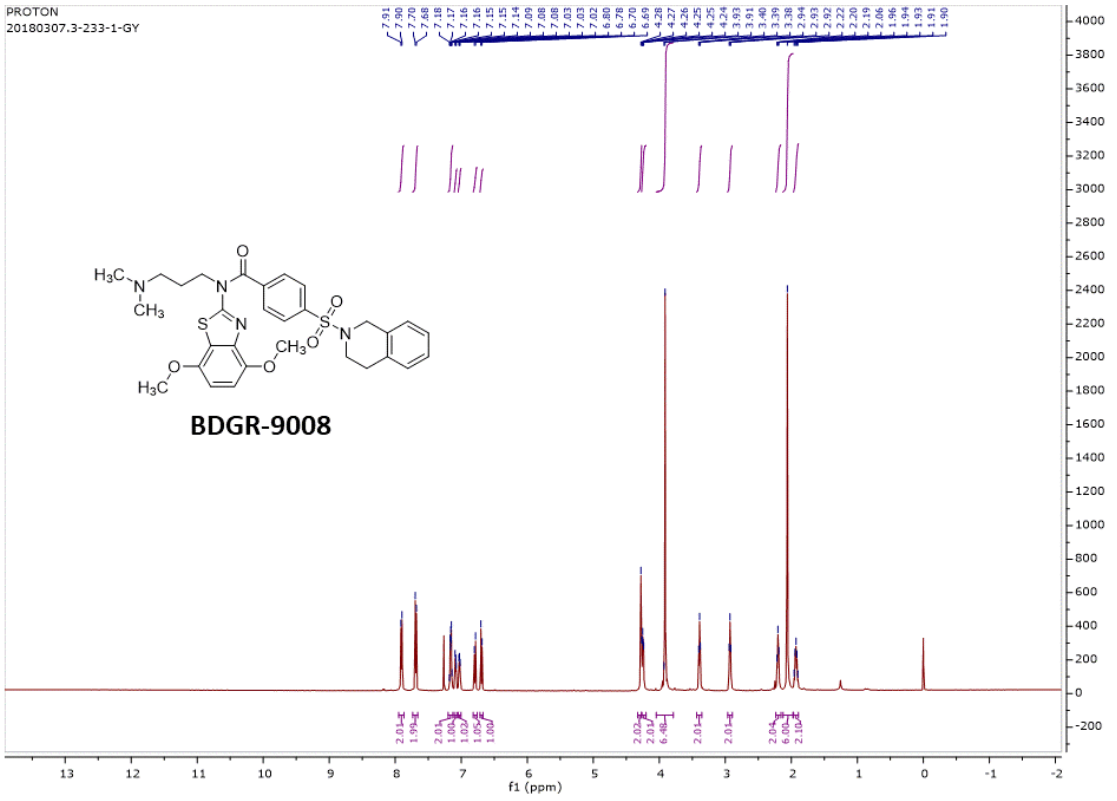




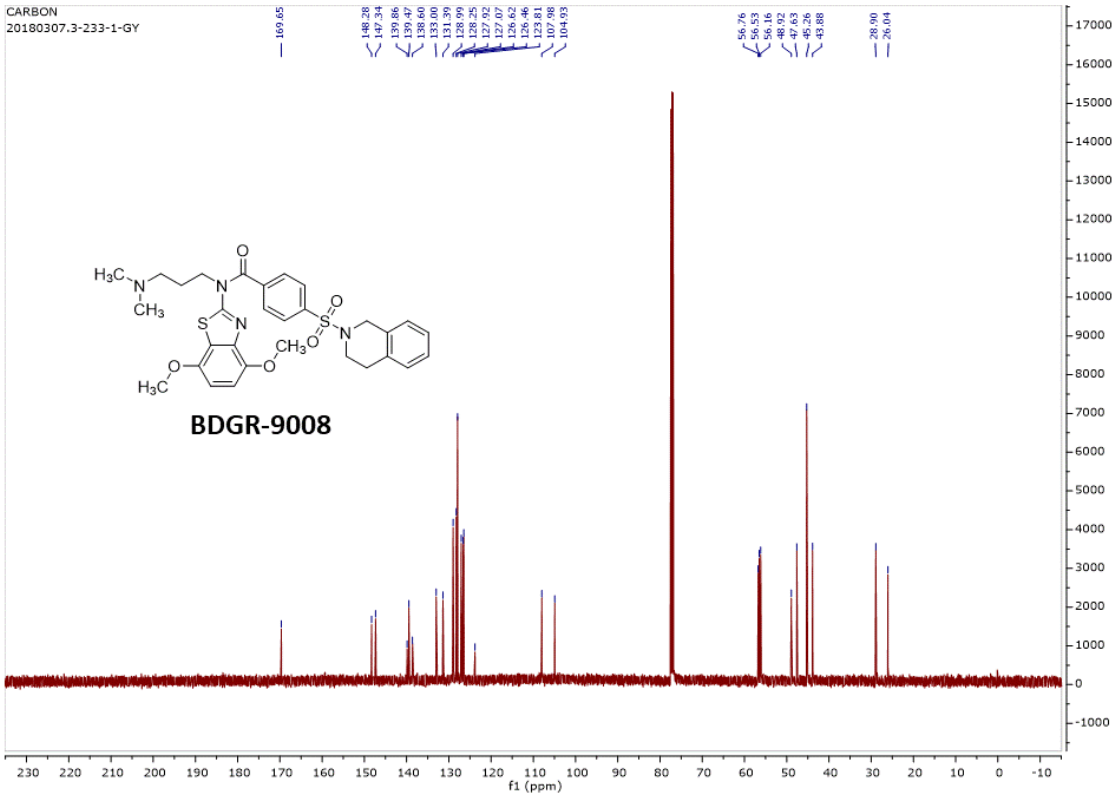

**BDGR-9007**

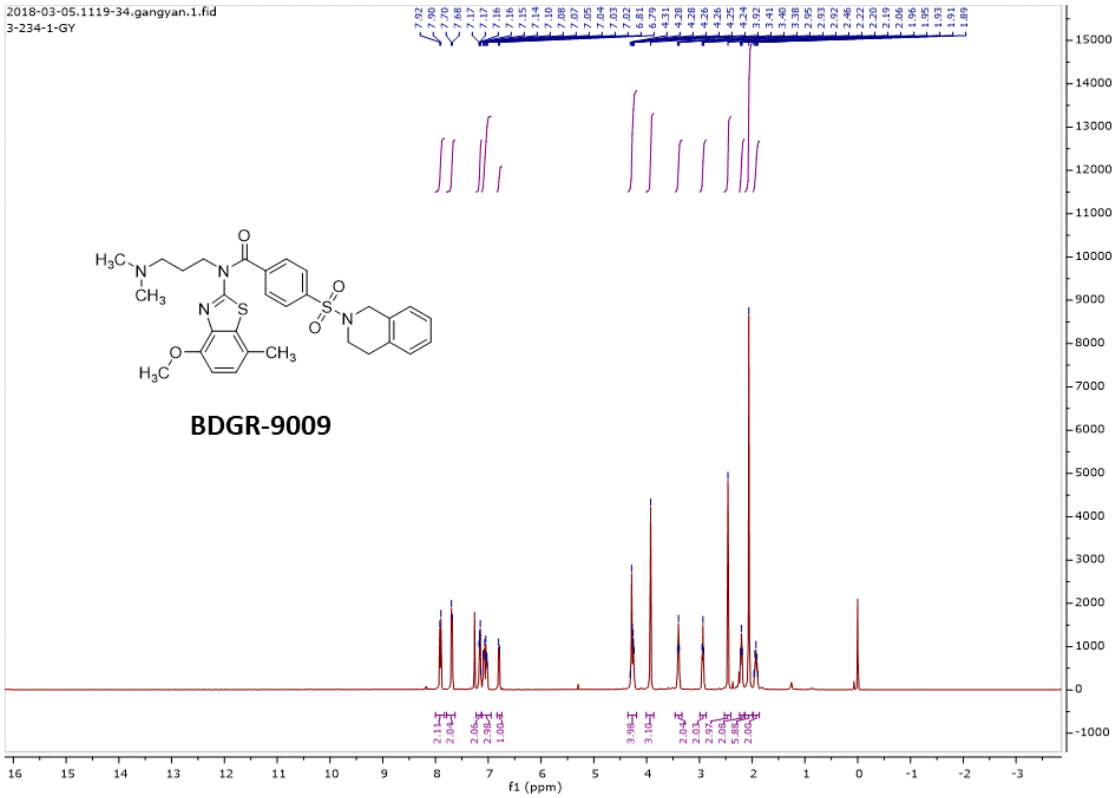


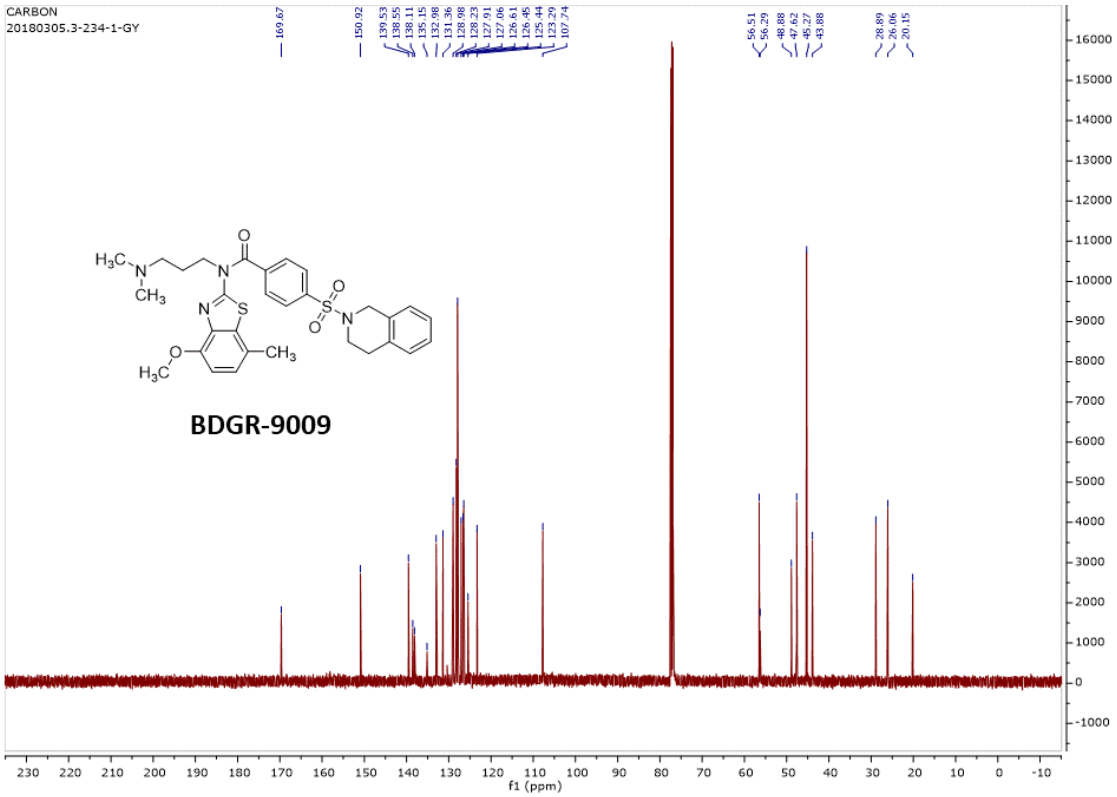

**BDGR-9007**

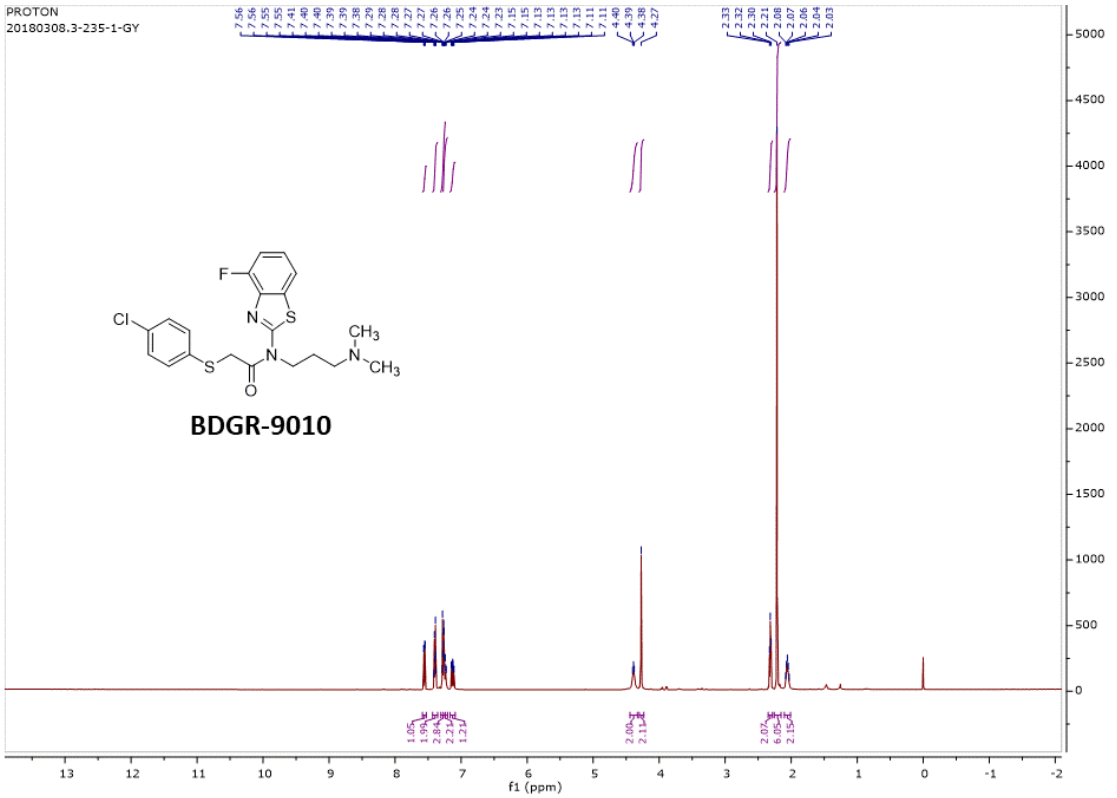


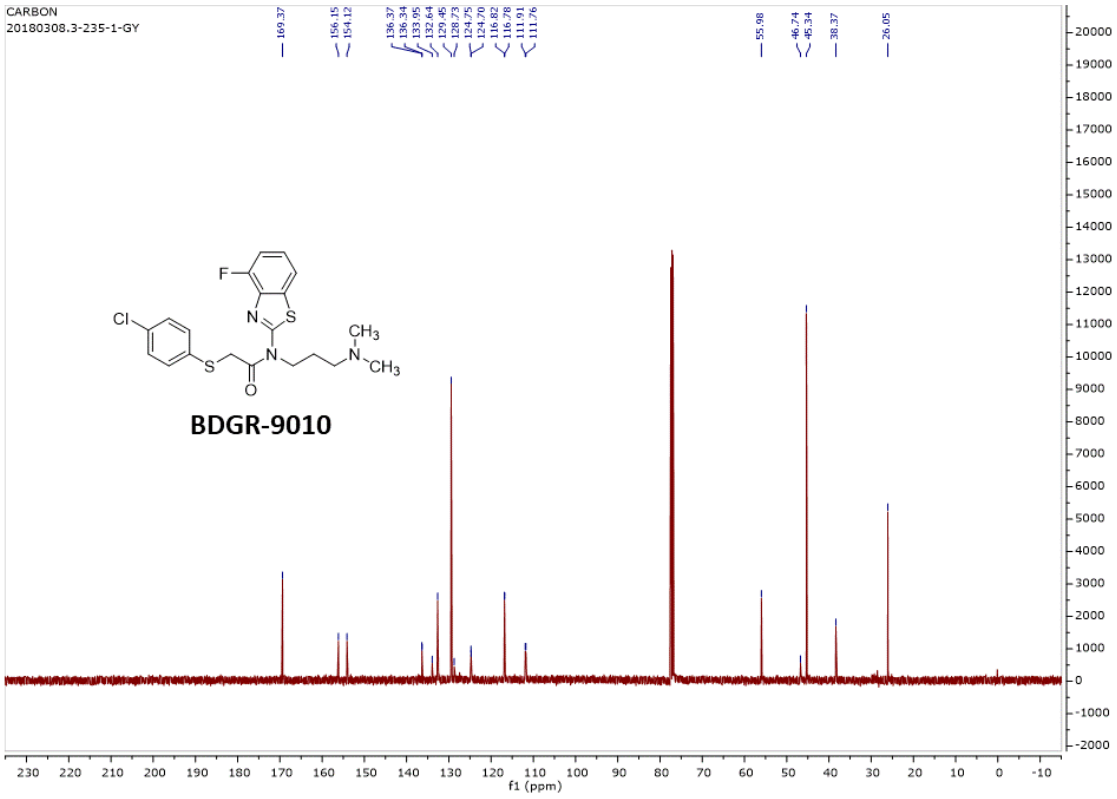

**BDGR-9008**

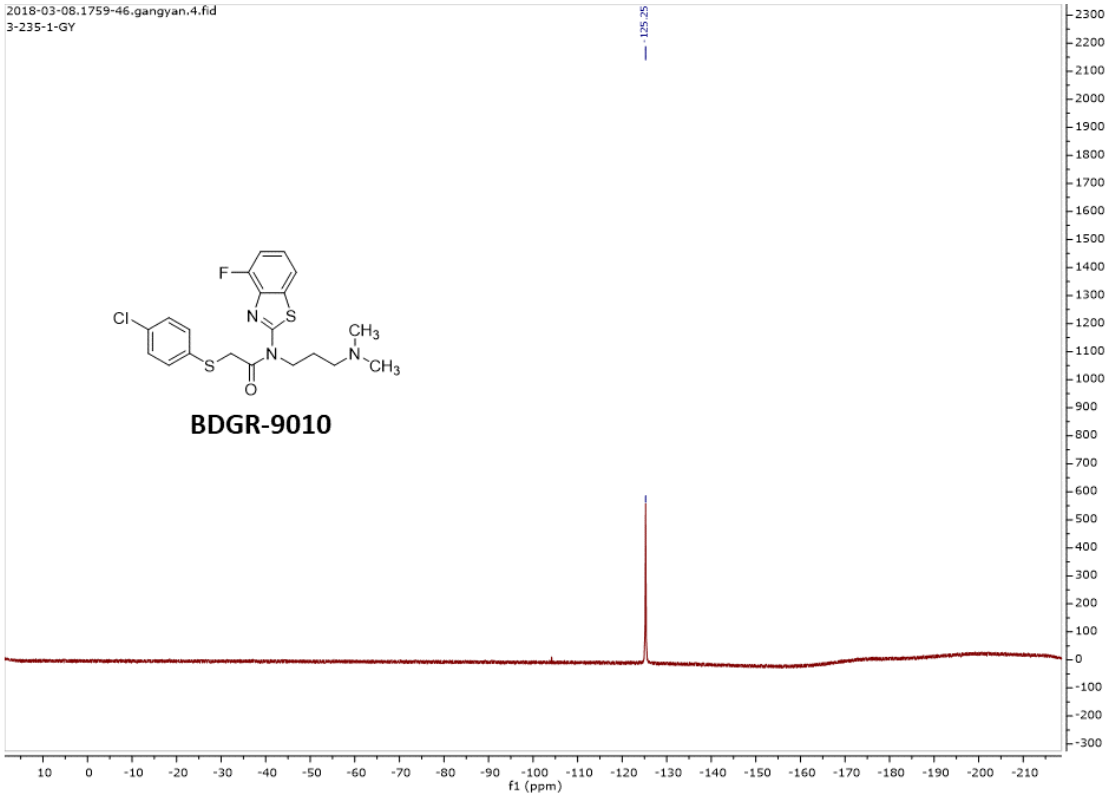

CARBON
20180307.3-233-1-GY
BDGR-9008
f1 (ppm)

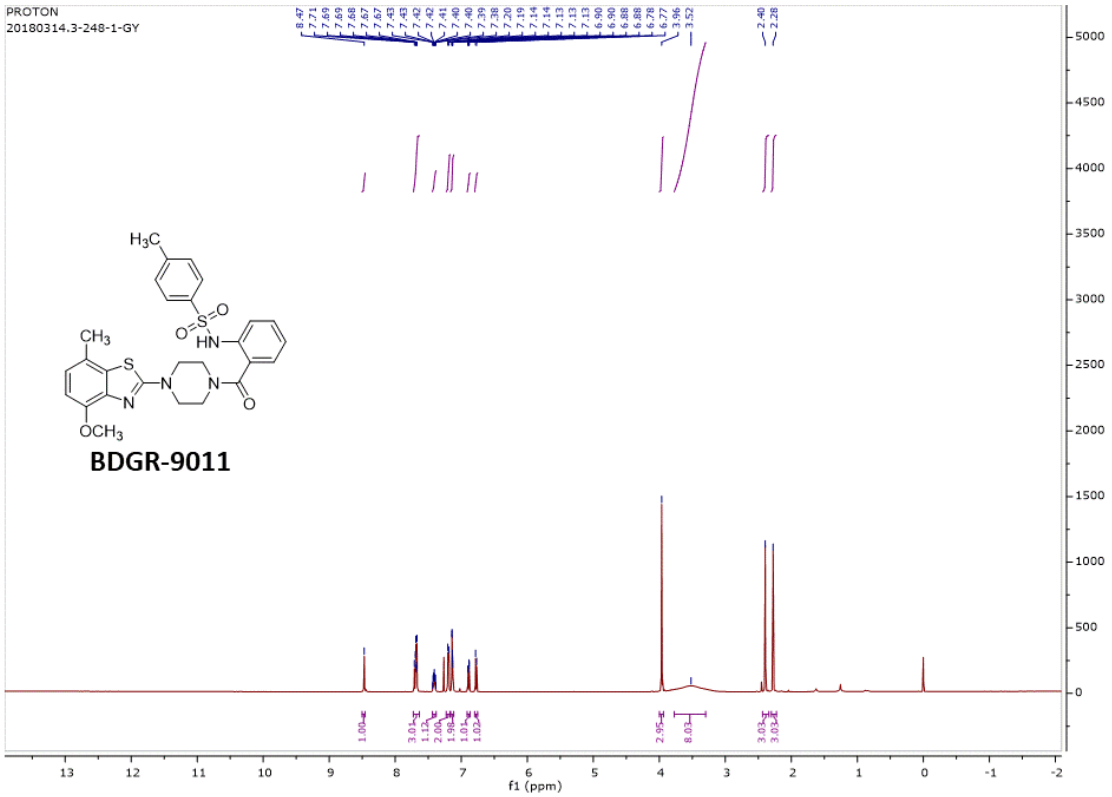

2018-03-05.1119-34.gangyan.1.fid
3-234-1-GY
BDGR-9009
f1 (ppm)

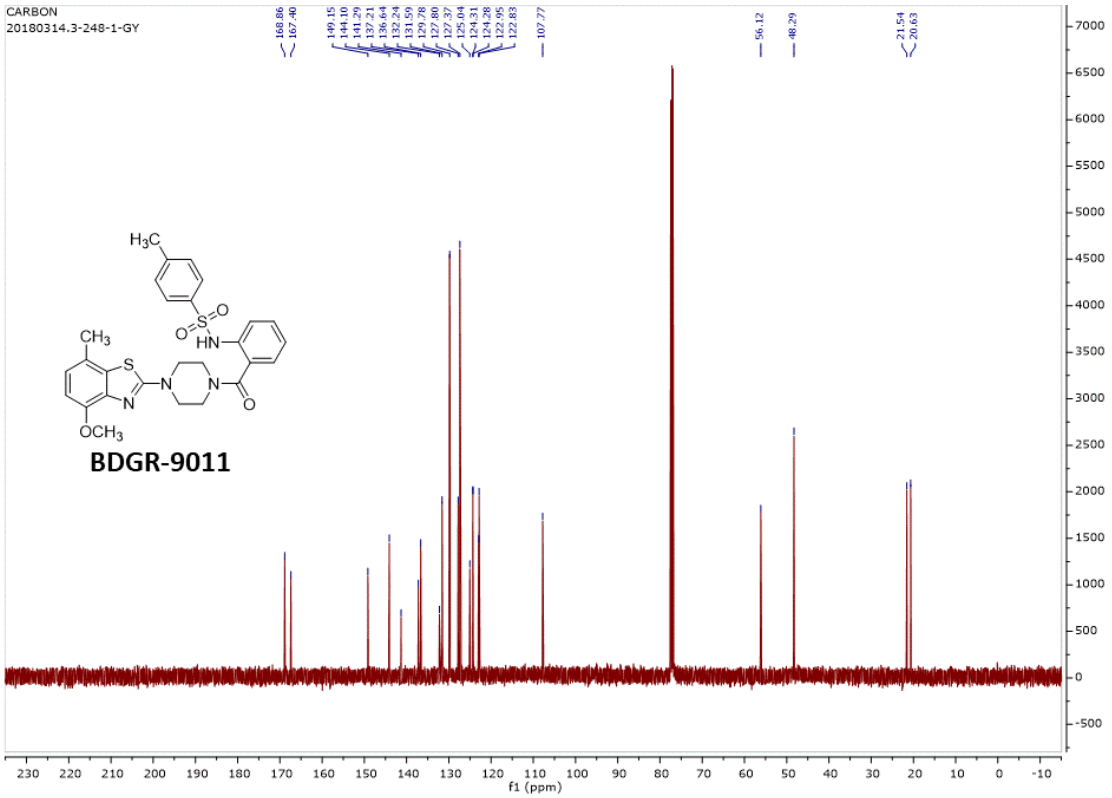

CARBON
20180305.3-234-1-GY
BDGR-9009
f1 (ppm)

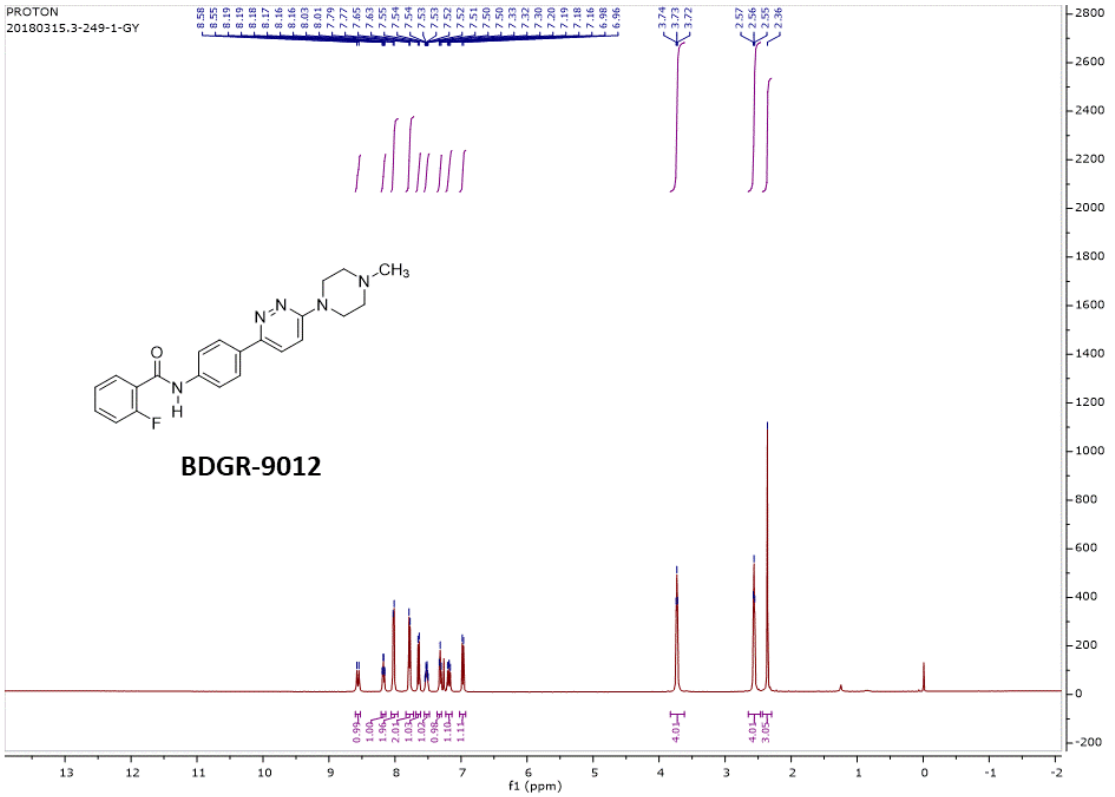

PROTON
20180308.3-235-1-GY
BDGR-9010
f1 (ppm)

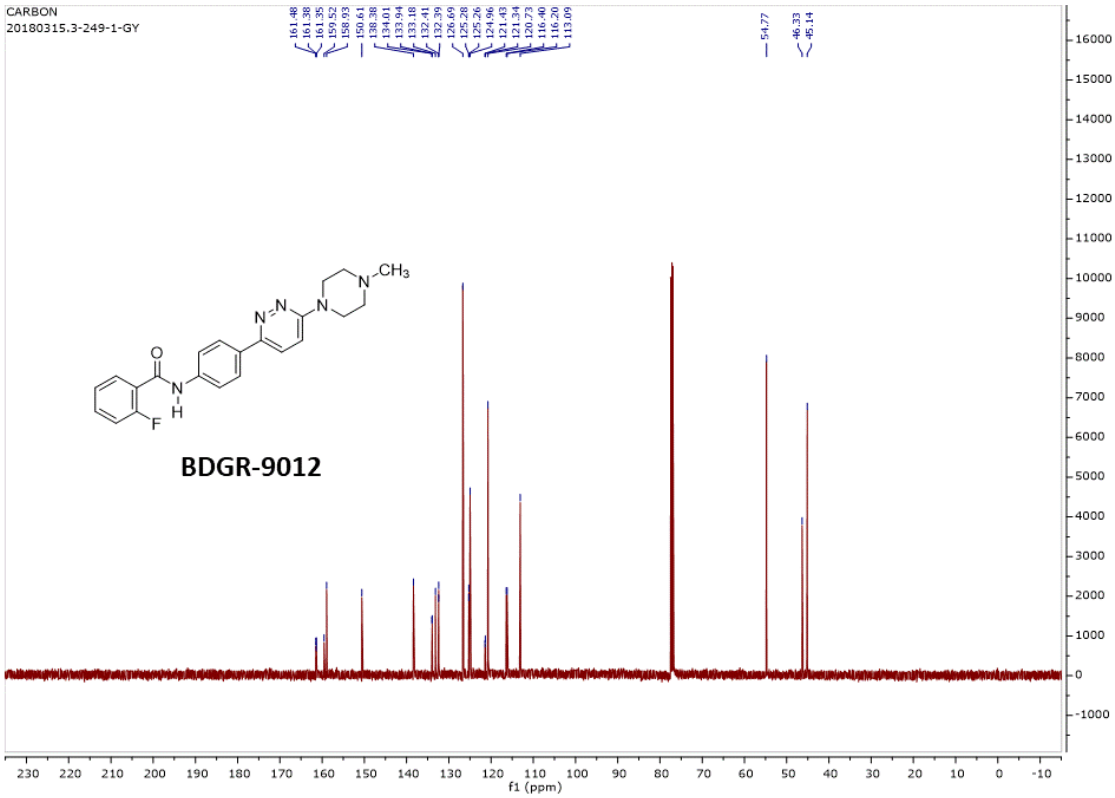

CARBON
20180308.3-235-1-GY
169.37
156.15
154.12
136.37
136.34
133.95
132.64
129.45
129.23
124.75
124.70
116.82
116.78
111.91
111.76
55.98
46.74
45.34
38.37
26.05
BDGR-9010
f1 (ppm)

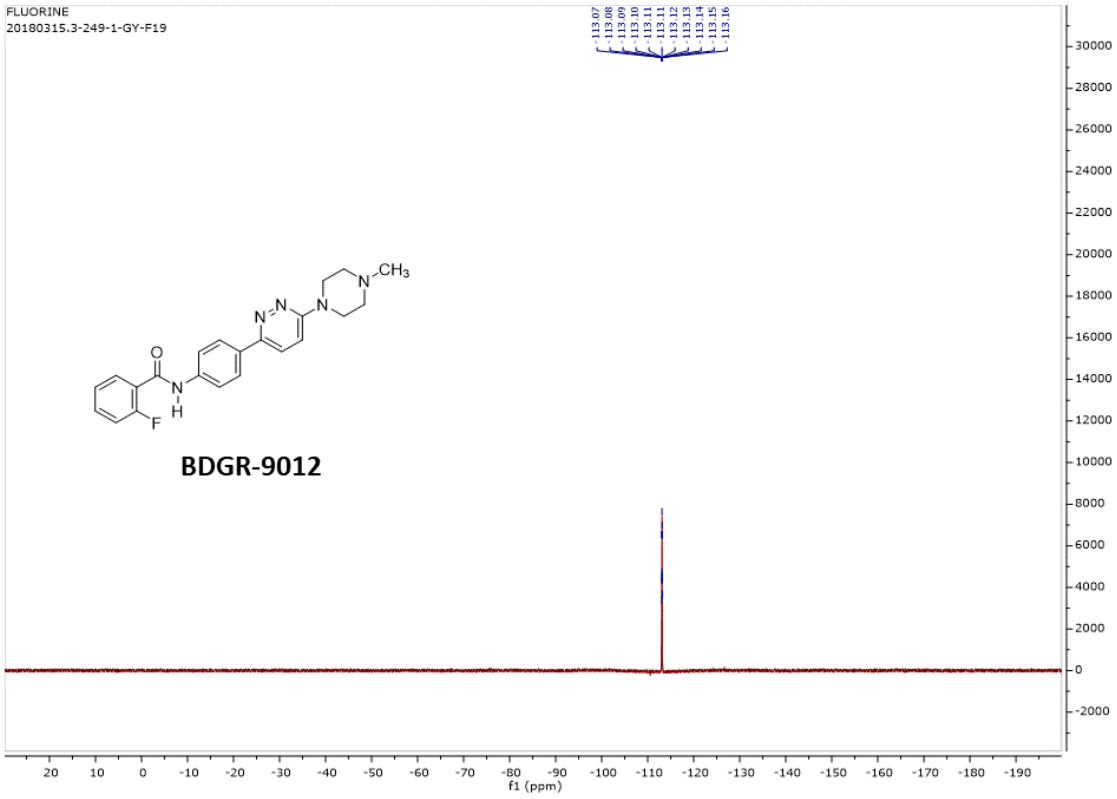

2018-03-08.1759-46.gangyan.4.fid
3-235-1-GY
125.25
BDGR-9010
f1 (ppm)

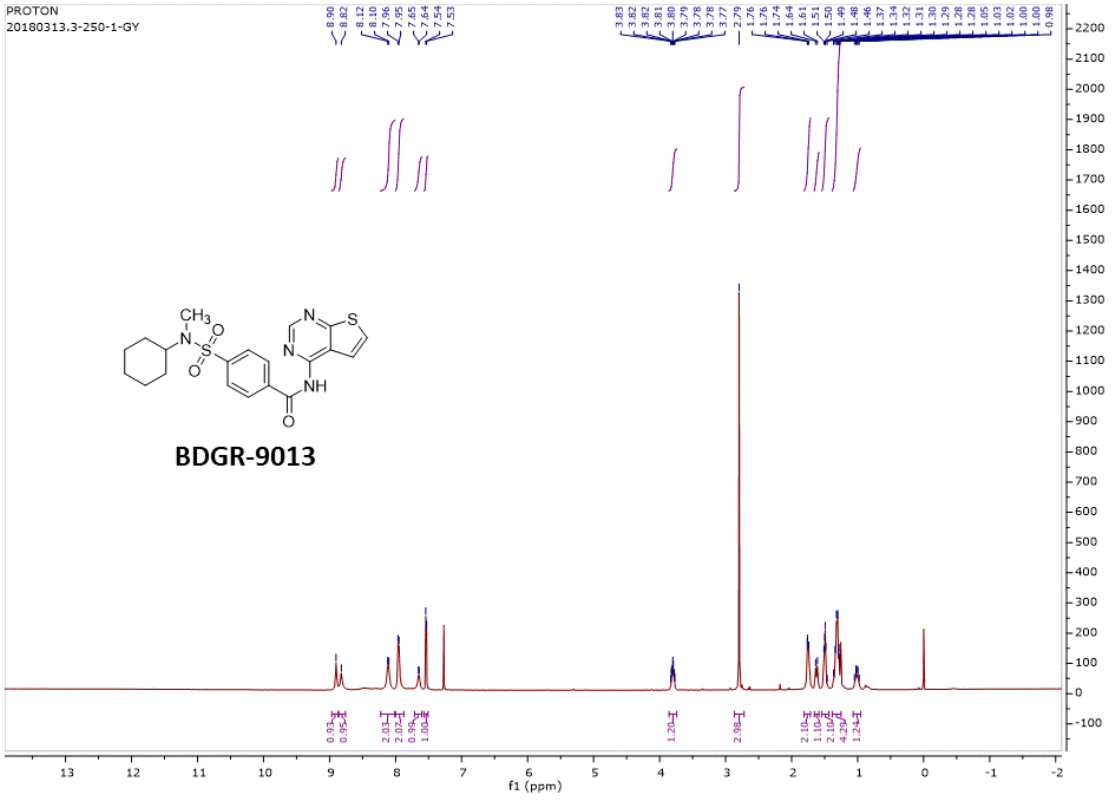

PROTON
20180314.3-248-1-GY
BDGR-9011
f1 (ppm)

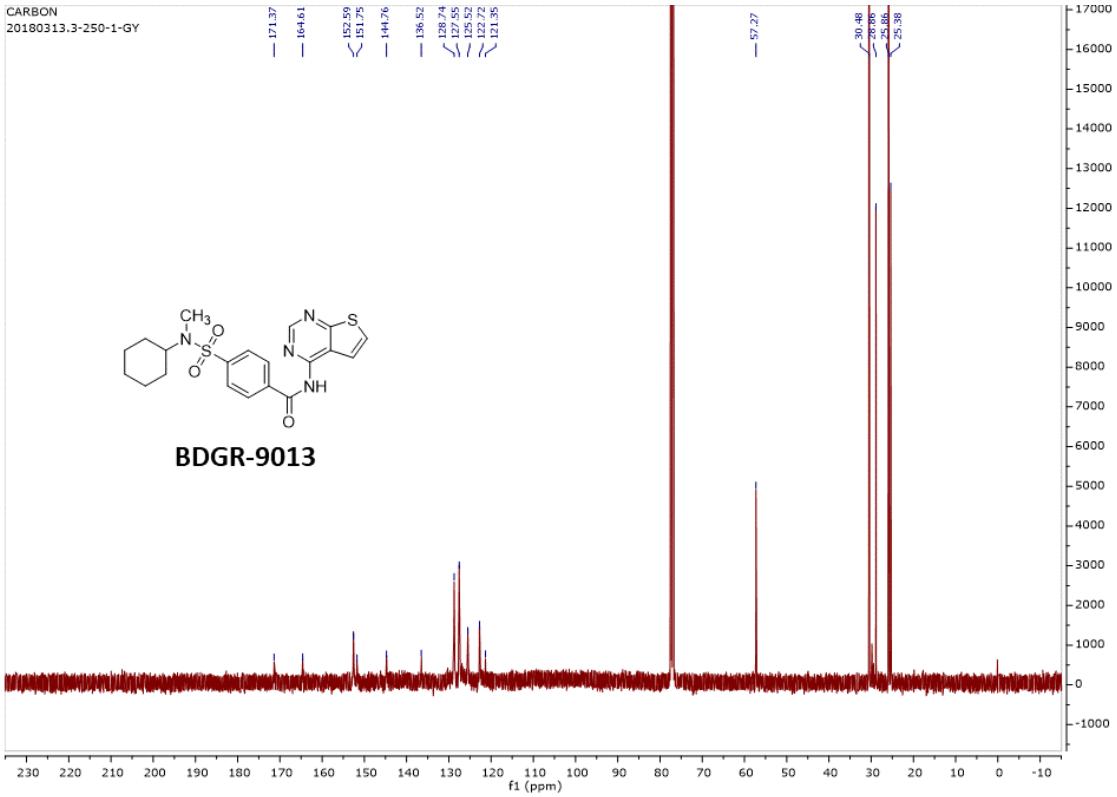

CARBON
20180314.3-248-1-GY
BDGR-9011
f1 (ppm)

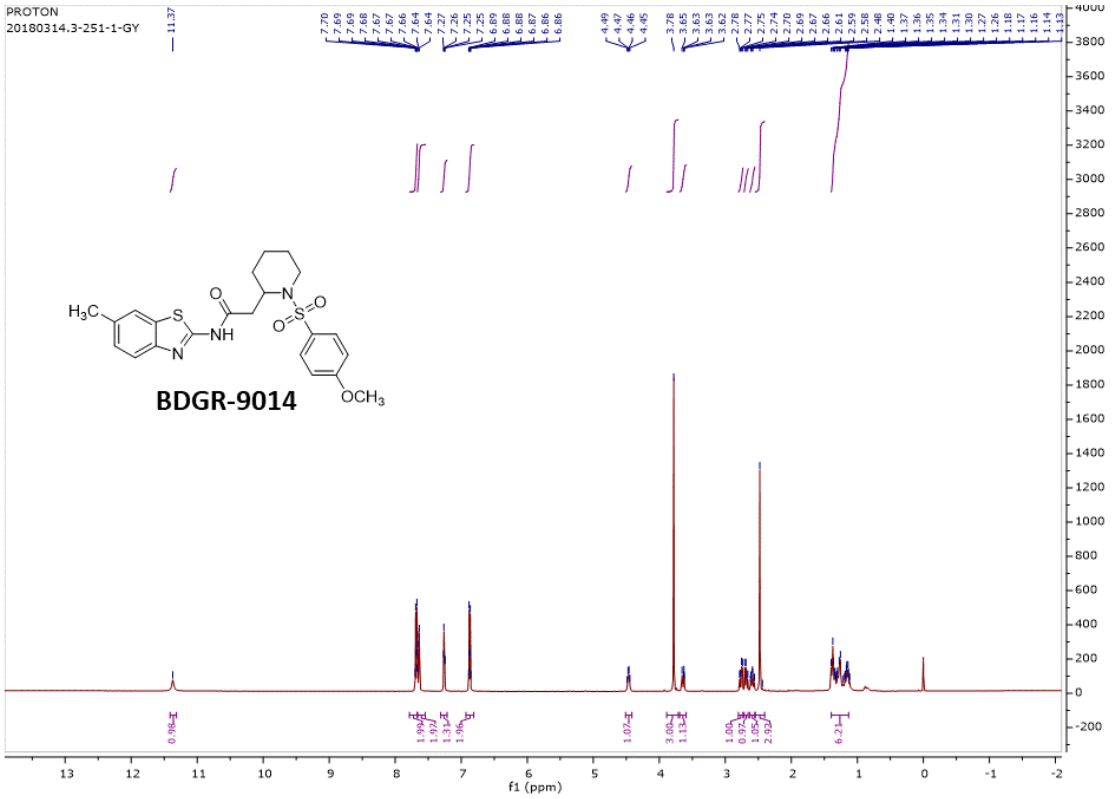

PROTON
20180315.3-249-1-GY
BDGR-9012
f1 (ppm)

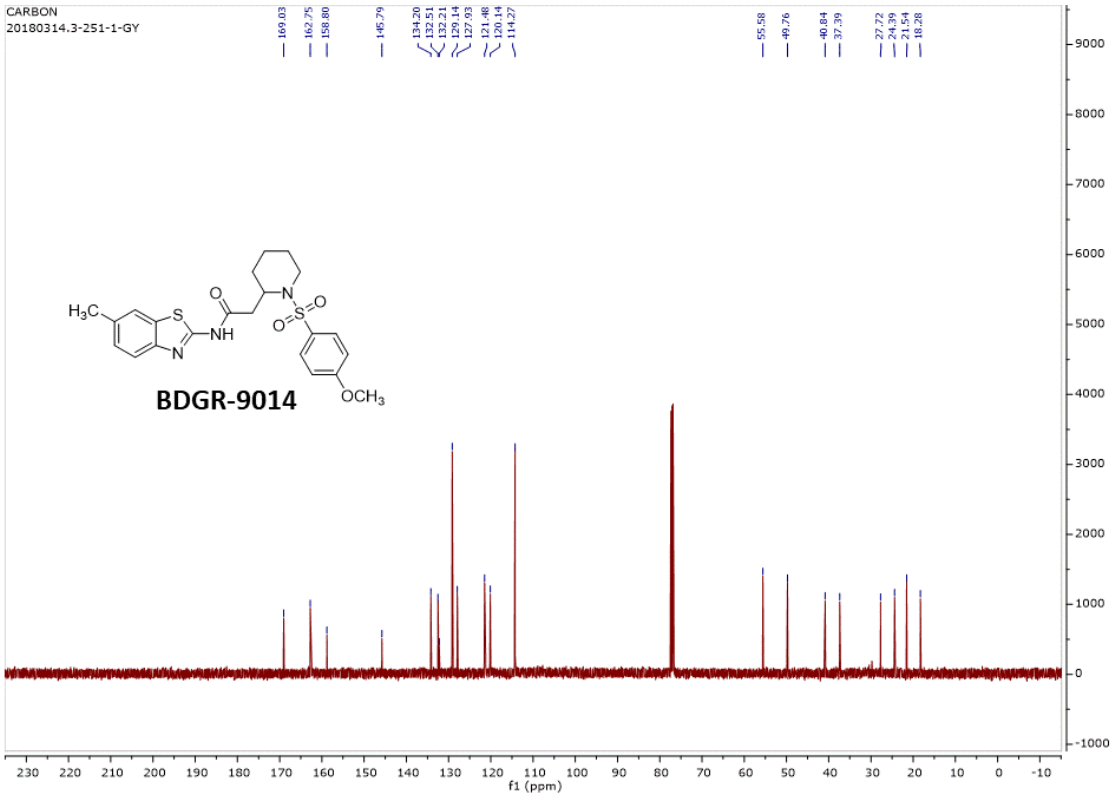

CARBON
20180315.3-249-1-GY
BDGR-9012
f1 (ppm)

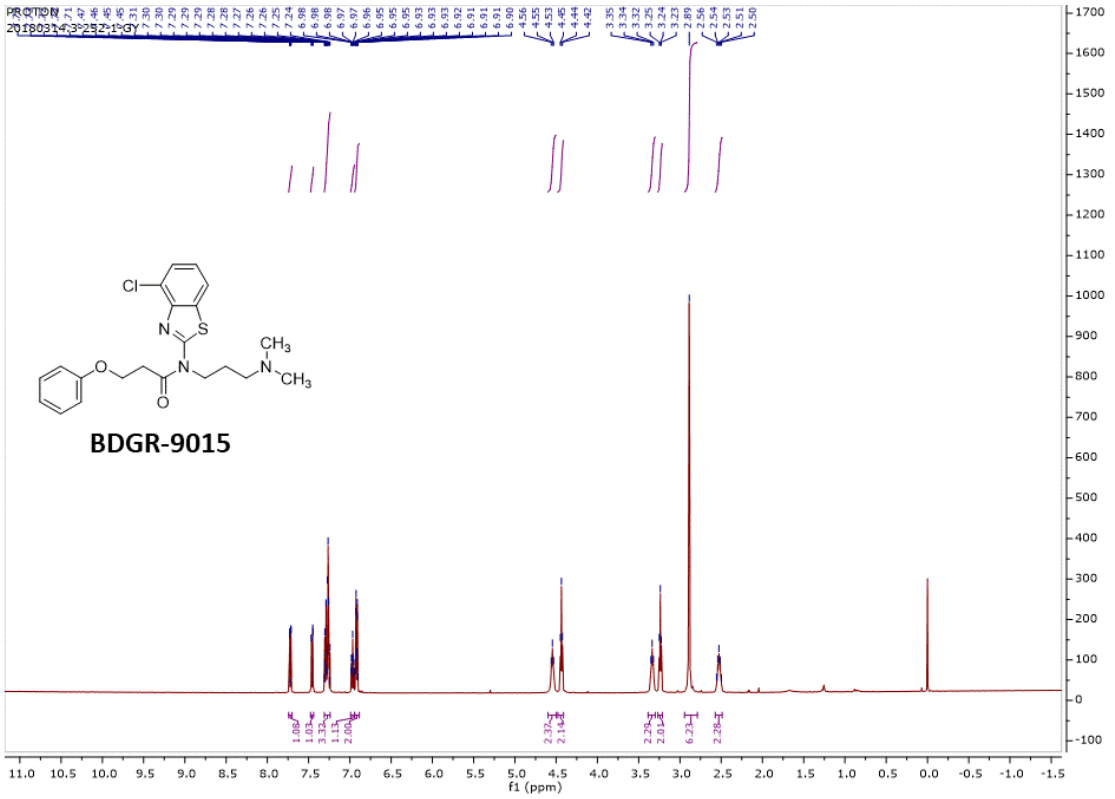

FLUORINE
20180315.3-249-1-GY-F19
BDGR-9012
f1 (ppm)

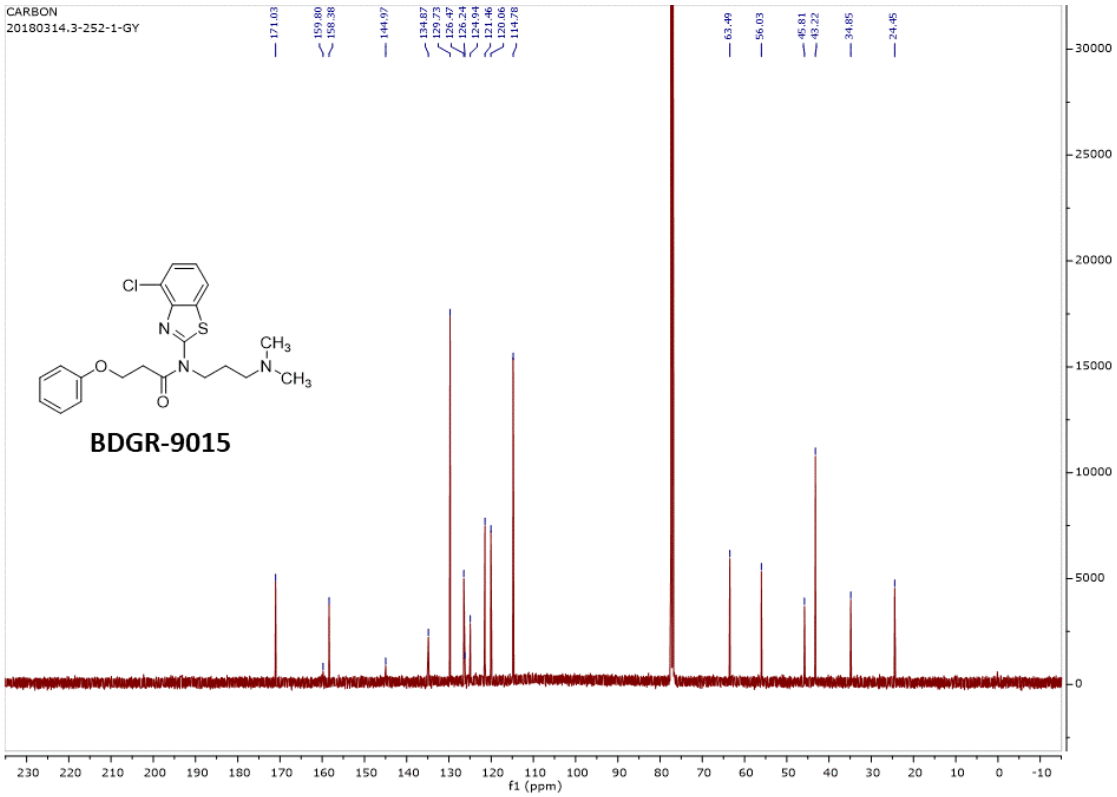

PROTON
20180313.3-250-1-GY
BDGR-9013
f1 (ppm)

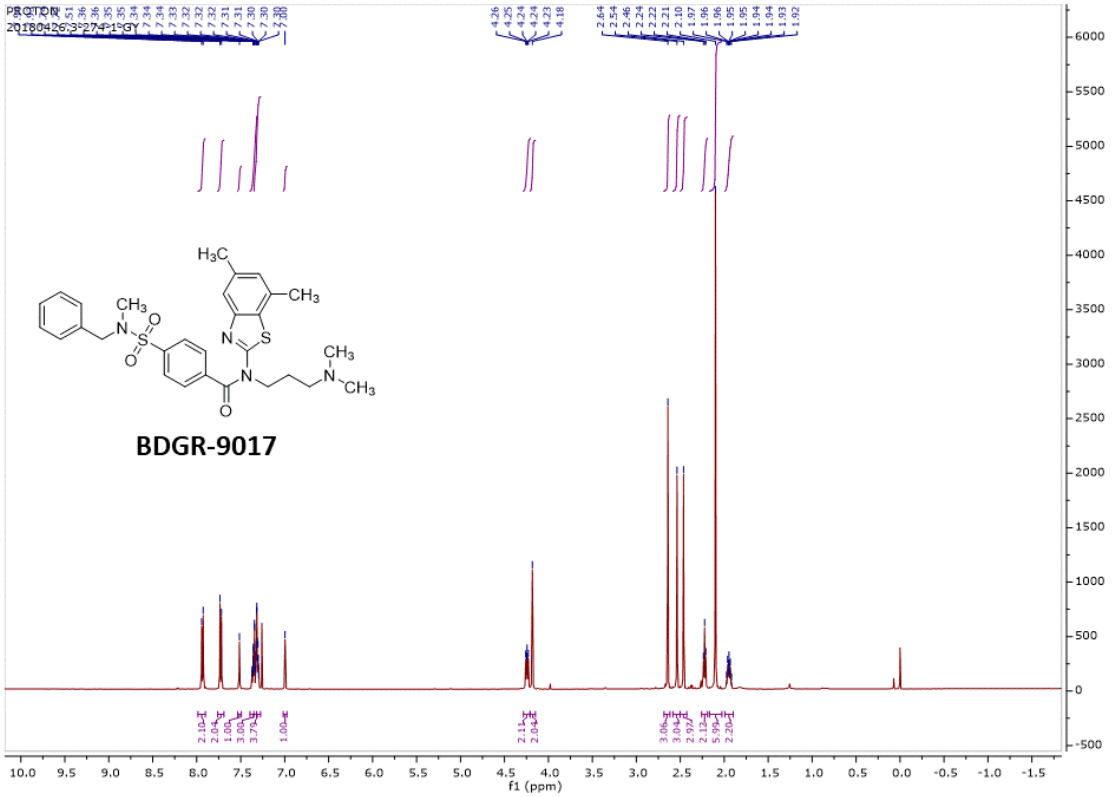

CARBON
20180313.3-250-1-GY
171.37
164.61
152.59
151.75
144.76
136.52
128.74
127.55
125.52
122.72
121.35
57.27
30.48
28.86
25.86
25.38
BDGR-9013
f1 (ppm)

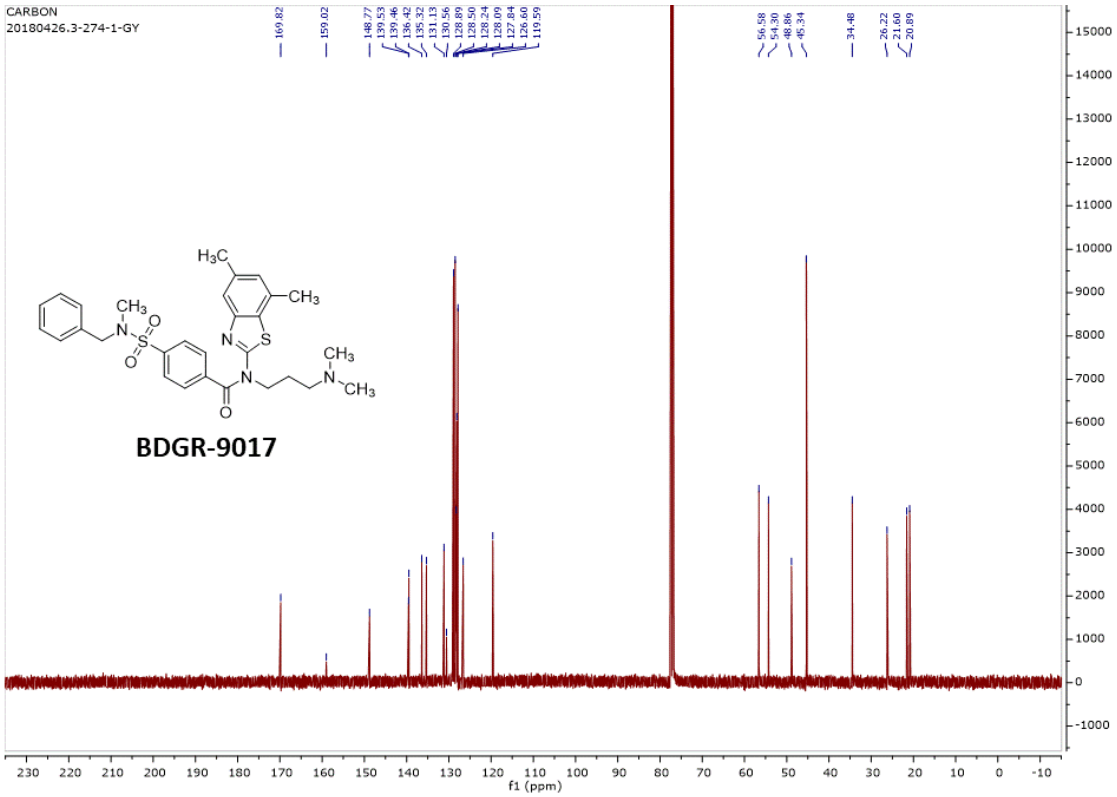

PROTON
20180314.3-251-1-GY
11.37
BDGR-9014
f1 (ppm)


CARBON
20180314.3-251-1-GY
169.03
162.75
158.80
145.79
134.20
132.51
132.21
129.14
127.93
121.48
120.14
114.27
55.58
49.76
40.84
37.39
27.72
24.39
21.54
18.28
BDGR-9014
f1 (ppm)

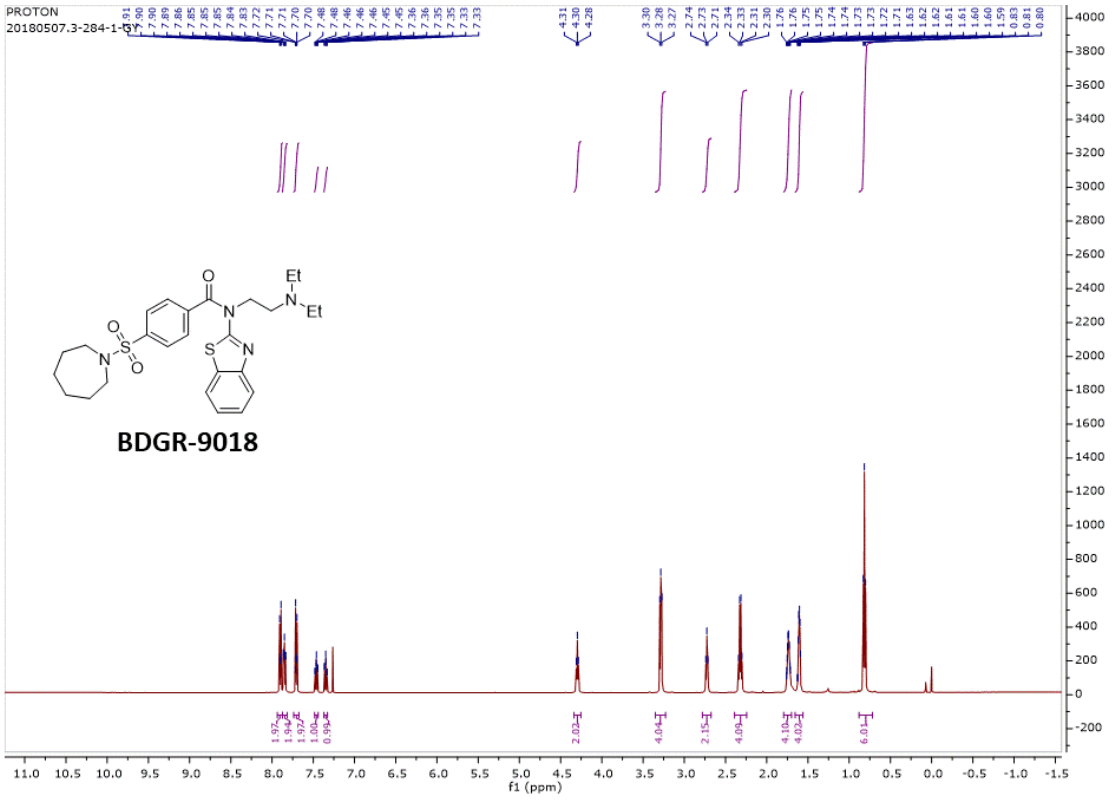

PROTON
20180314.3-252-1-GY
BDGR-9015
f1 (ppm)


CARBON
20180314.3-252-1-GY
BDGR-9015
f1 (ppm)

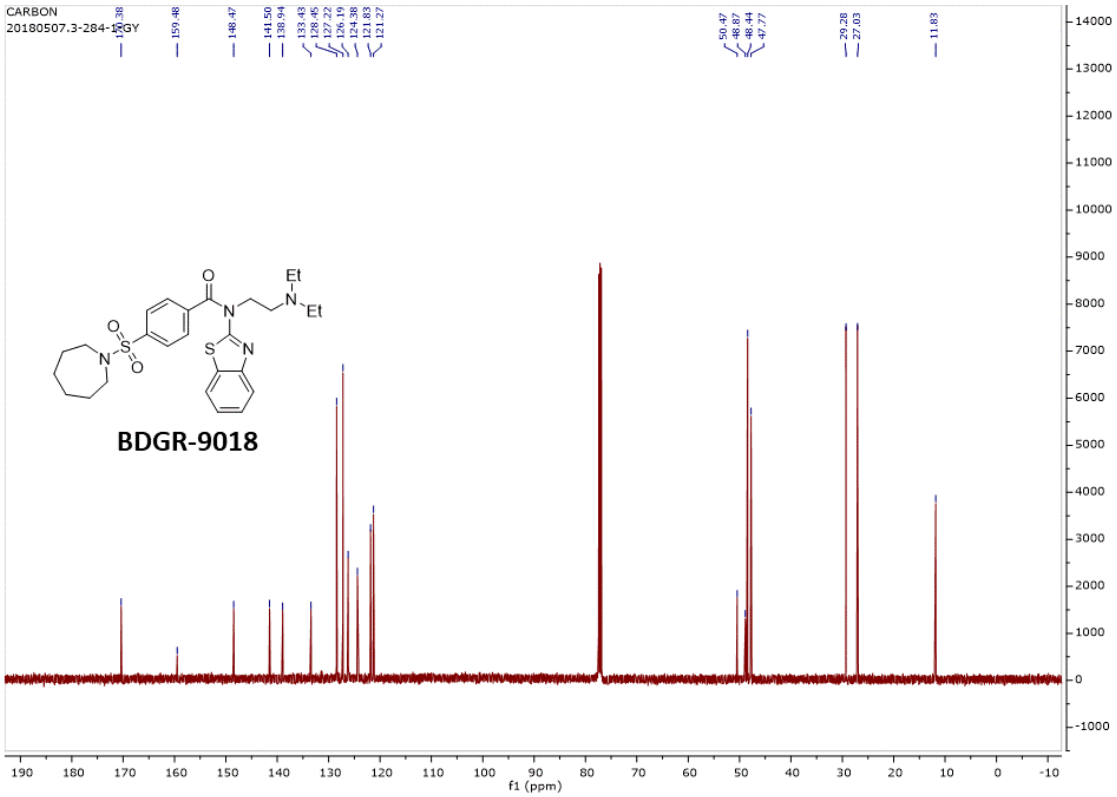

PROTON
BDGR-9017
f1 (ppm)

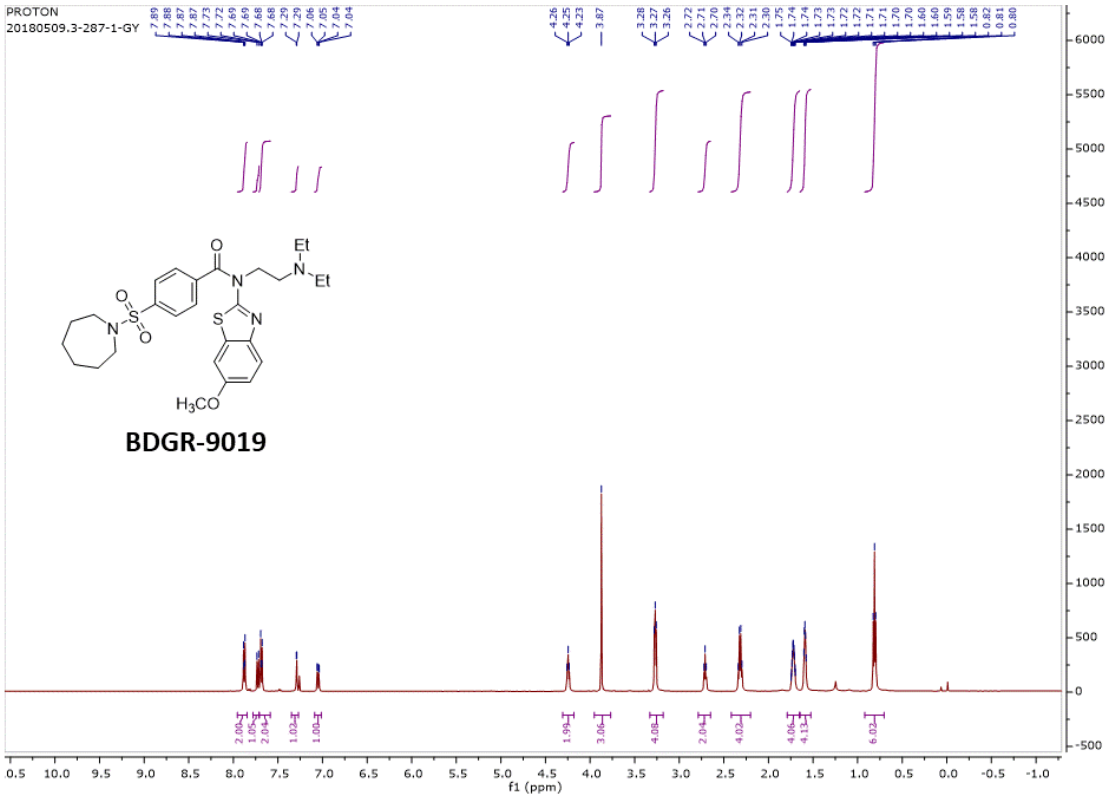


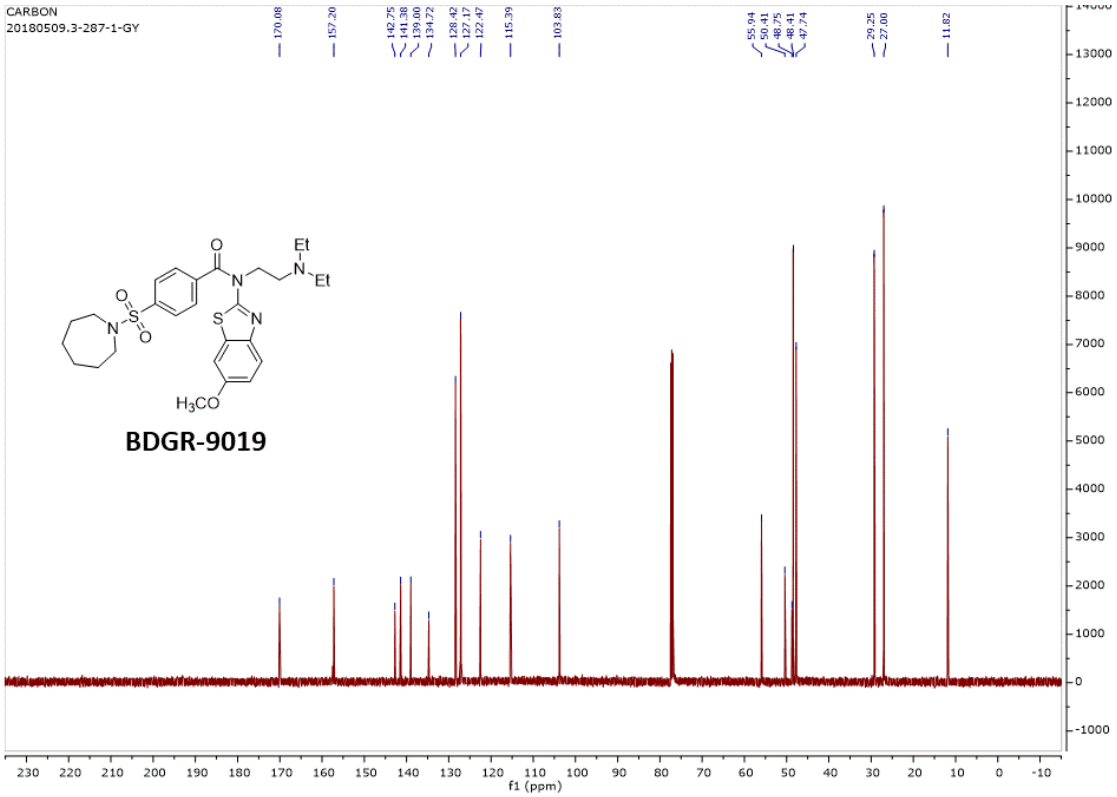

**BDGR-9017**

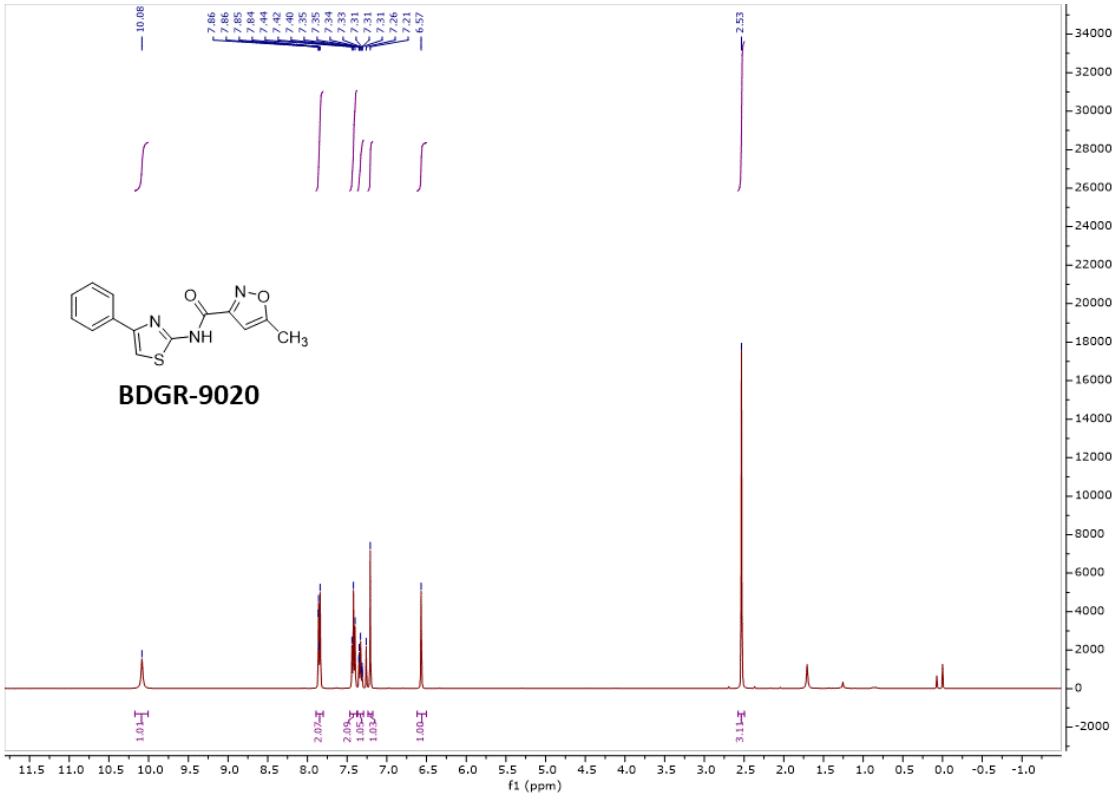


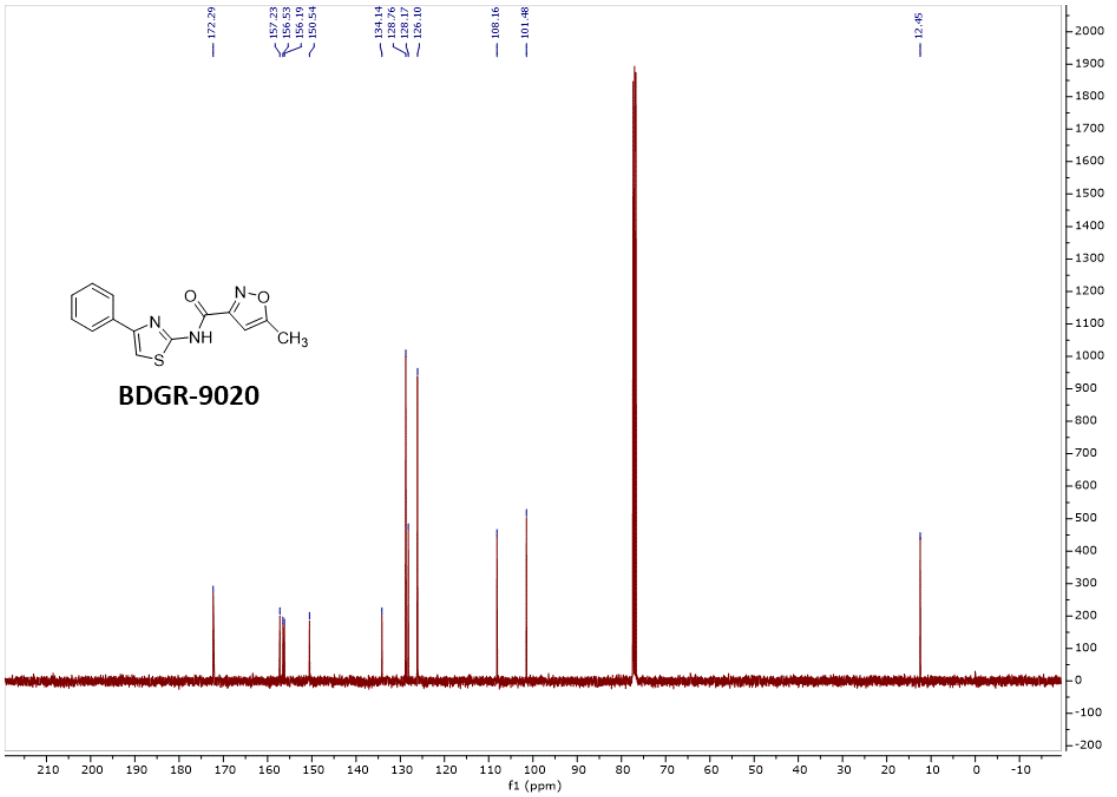

**BDGR-9018**

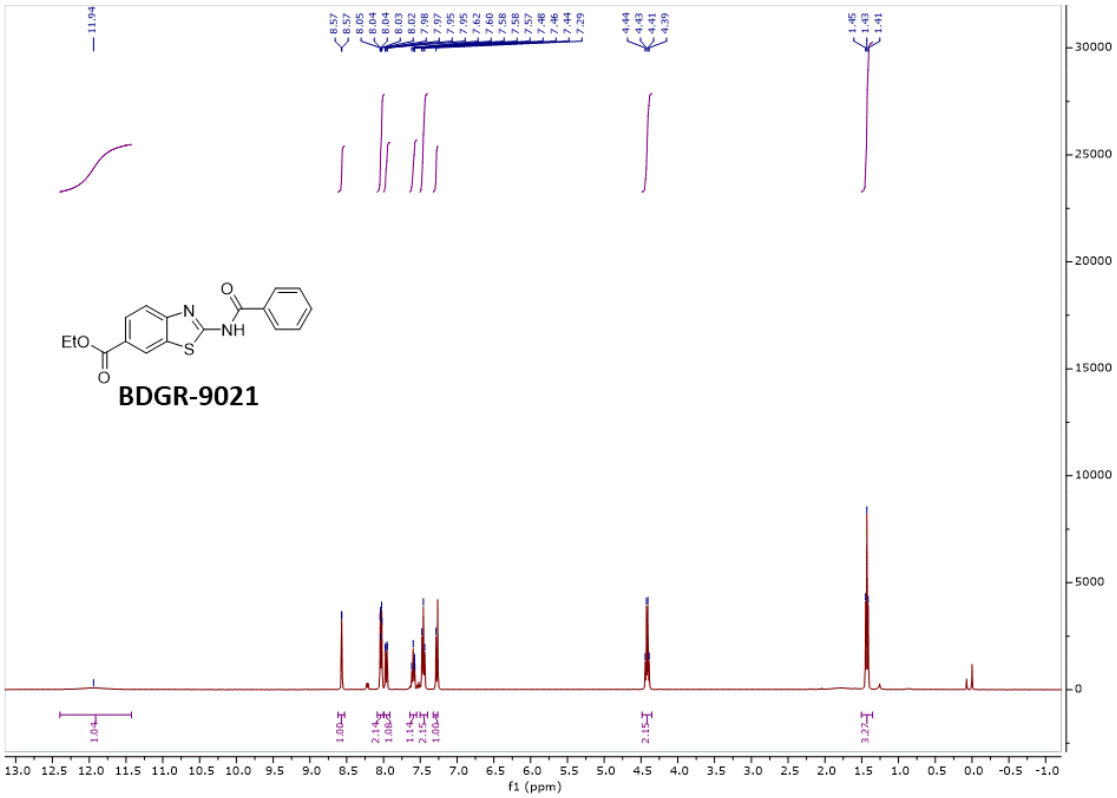

CARBON
20180507.3-284-1-GY
BDGR-9018
f1 (ppm)

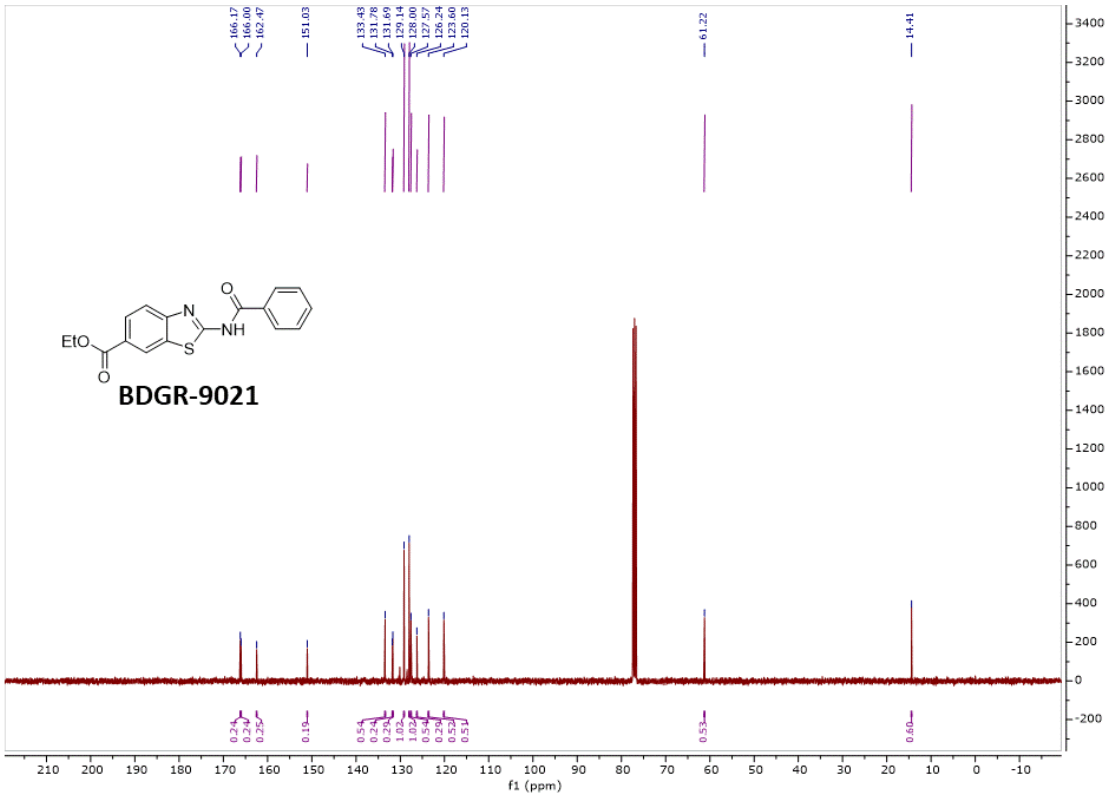

PROTON
20180509.3-287-1-GY
BDGR-9019
f1 (ppm)

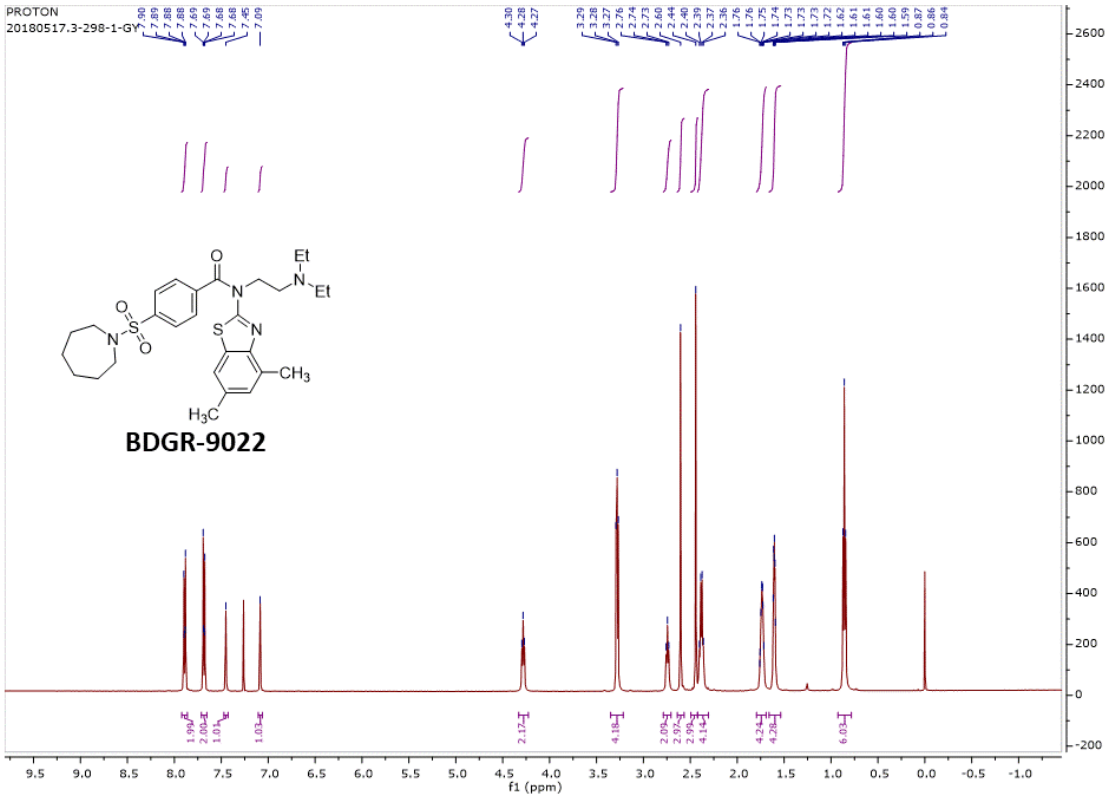

CARBON
20180509.3-287-1-GY
170.08
157.20
142.75
141.38
139.00
134.72
128.42
127.17
122.47
115.39
103.83
55.94
50.41
48.35
48.41
47.74
29.25
27.00
11.82
BDGR-9019
f1 (ppm)

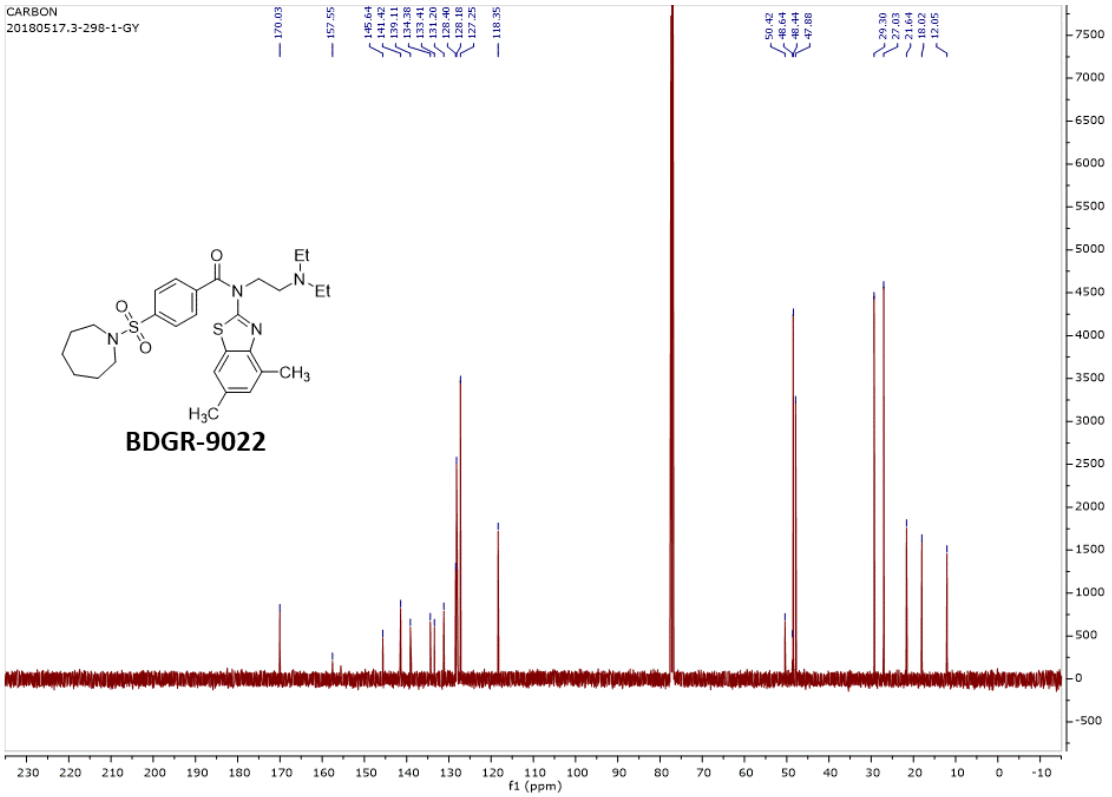

10.08
7.86
7.86
7.85
7.84
7.44
7.42
7.40
7.35
7.35
7.34
7.33
7.31
7.31
7.31
7.26
7.21
6.57
2.53
BDGR-9020
1.01
2.07
2.09
1.05
1.03
1.00
3.11
f1 (ppm)

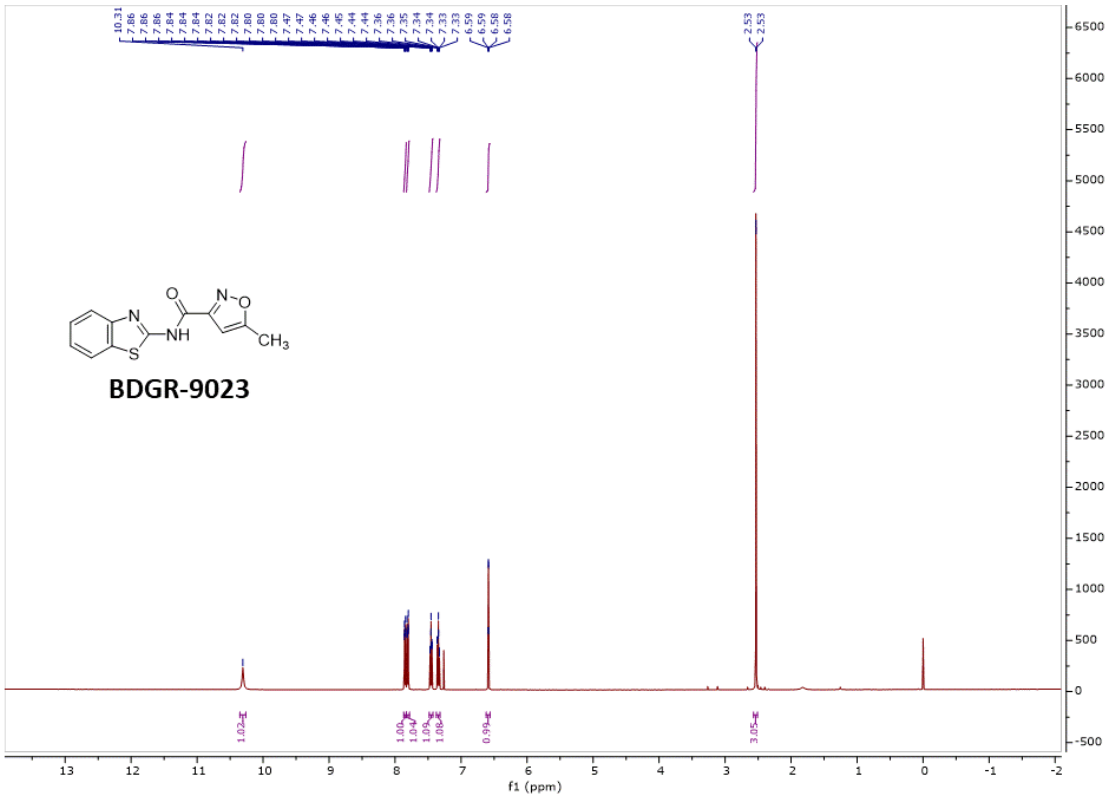

172.29
157.23
156.53
156.19
150.54
134.14
128.76
128.17
126.10
108.16
101.48
12.45
BDGR-9020
f1 (ppm)

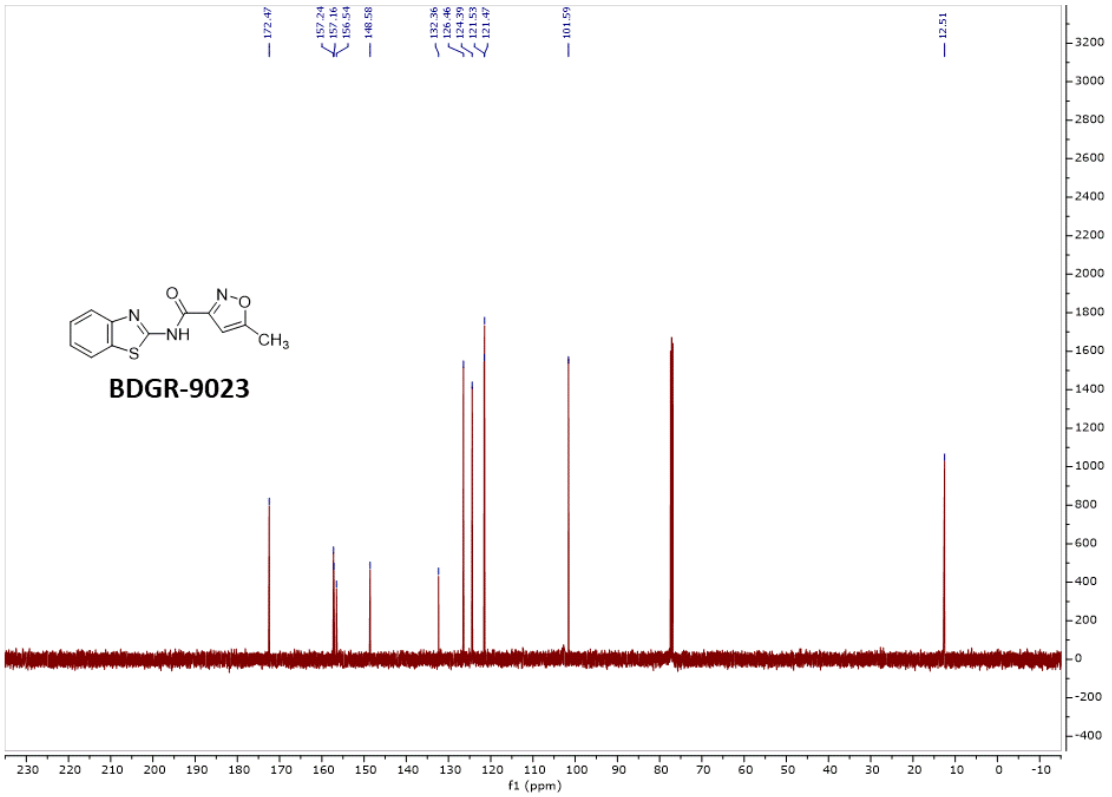

11.94
8.57
8.57
8.05
8.04
8.04
8.03
8.02
7.98
7.97
7.95
7.95
7.62
7.60
7.58
7.58
7.57
7.48
7.46
7.46
7.44
7.29
4.44
4.43
4.41
4.39
1.45
1.43
1.41
BDGR-9021
f1 (ppm)

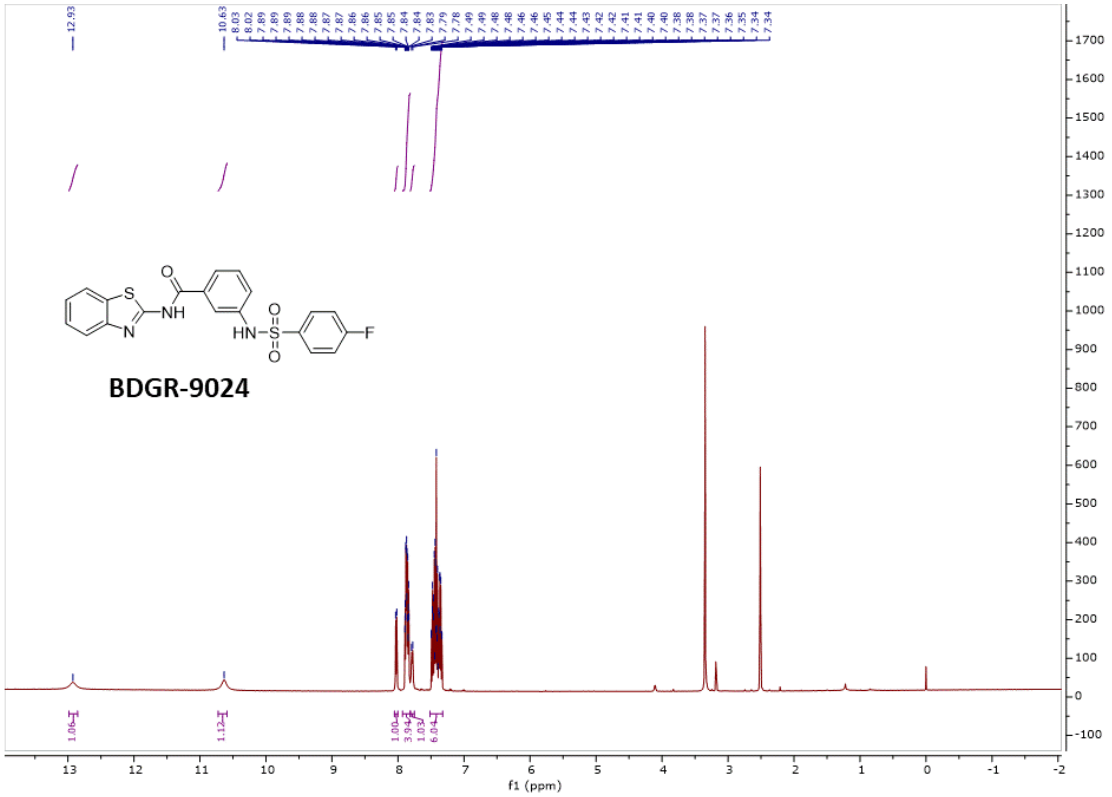

166.17
166.00
162.47
151.03
133.43
131.78
131.69
130.14
128.00
127.57
126.24
123.60
120.13
61.22
14.41
EtO
O
N
NH
S
O
BDGR-9021
f1 (ppm)

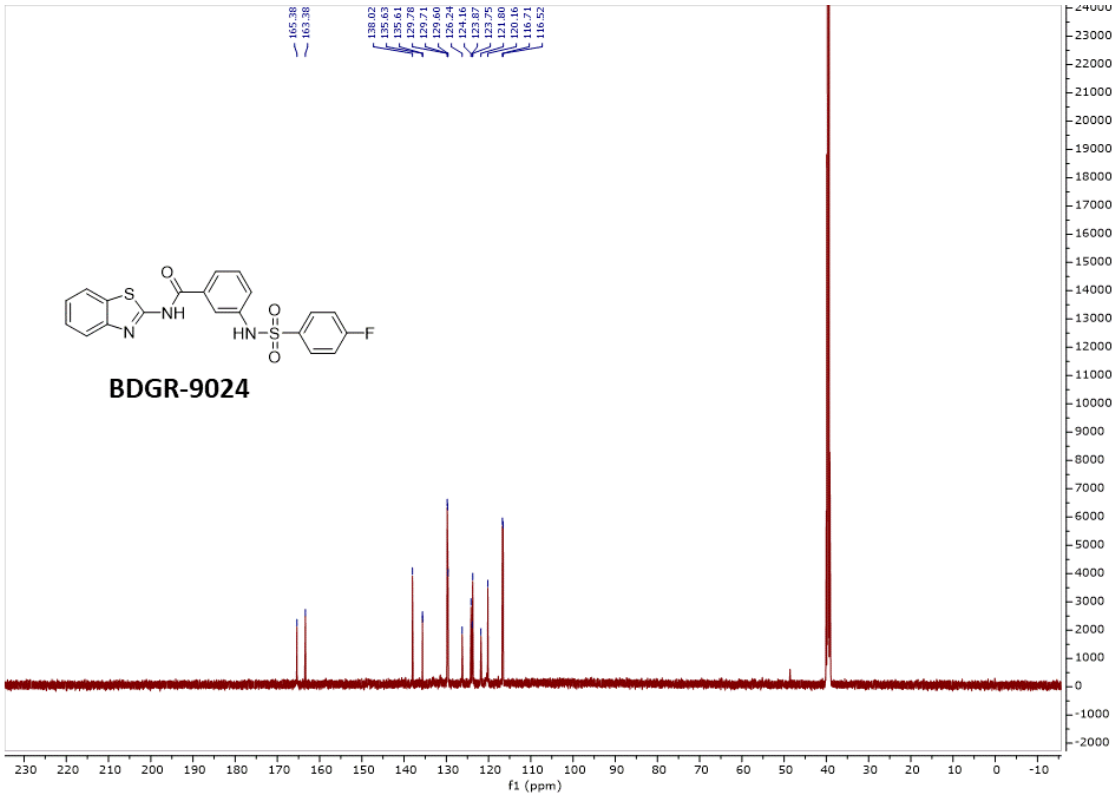

PROTON
20180517.3-298-1-GV
7.90
7.89
7.88
7.88
7.69
7.69
7.68
7.68
7.45
7.09
4.30
4.28
4.27
3.29
3.28
3.27
2.76
2.74
2.73
2.60
2.44
2.40
2.39
2.37
2.36
1.76
1.76
1.75
1.74
1.73
1.73
1.73
1.72
1.62
1.61
1.61
1.60
1.60
1.59
0.87
0.86
0.84
Et
N
Et
O
N
S
O
O
S
N
CH3
H3C
BDGR-9022
f1 (ppm)

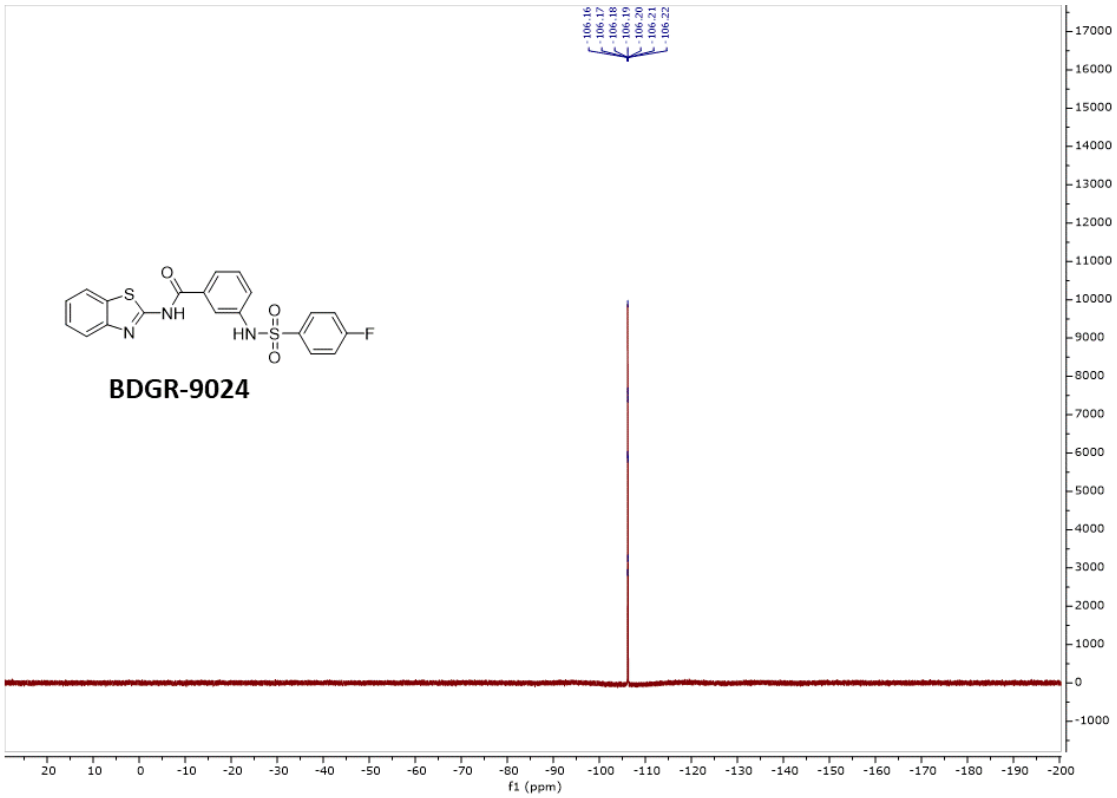

CARBON
20180517.3-298-1-GY
170.03
157.55
145.64
141.42
139.11
134.38
133.41
131.20
128.40
128.18
127.25
118.35
50.42
48.64
48.44
47.88
29.30
27.03
21.64
18.02
12.05
BDGR-9022
f1 (ppm)

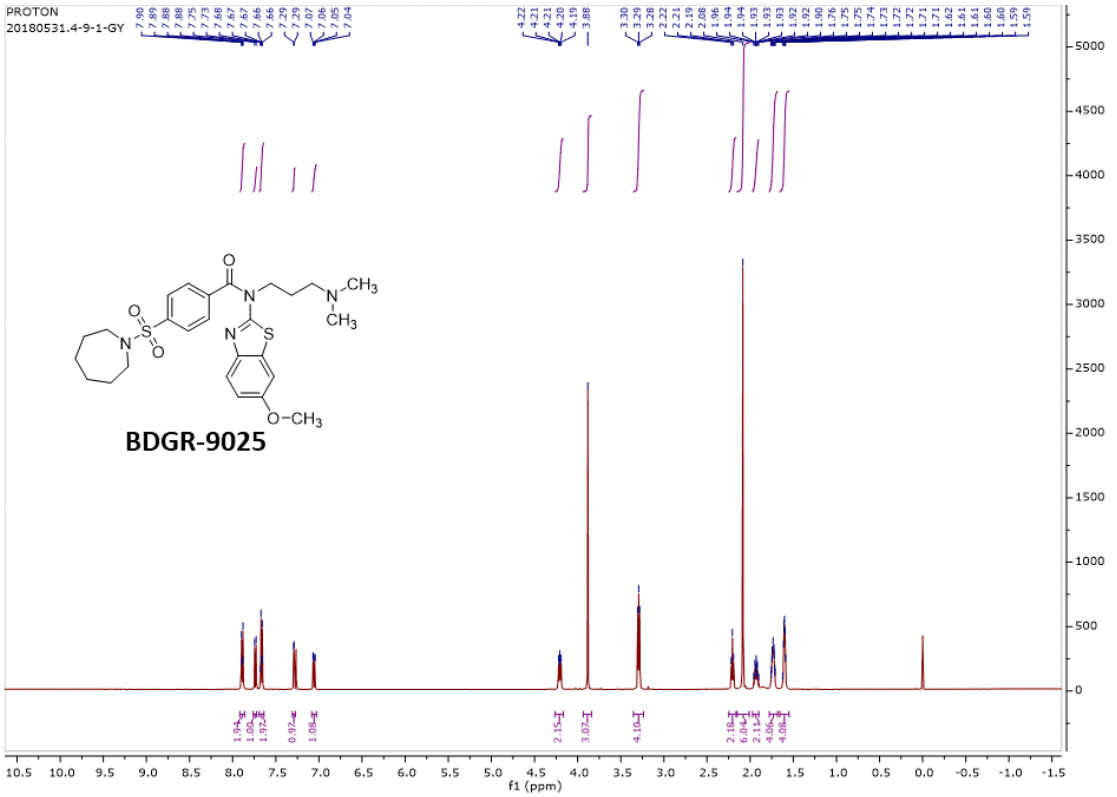

10.31
7.86
7.84
7.82
7.80
7.47
7.46
7.45
7.44
7.36
7.35
7.34
7.33
6.59
6.58
2.53
BDGR-9023
f1 (ppm)

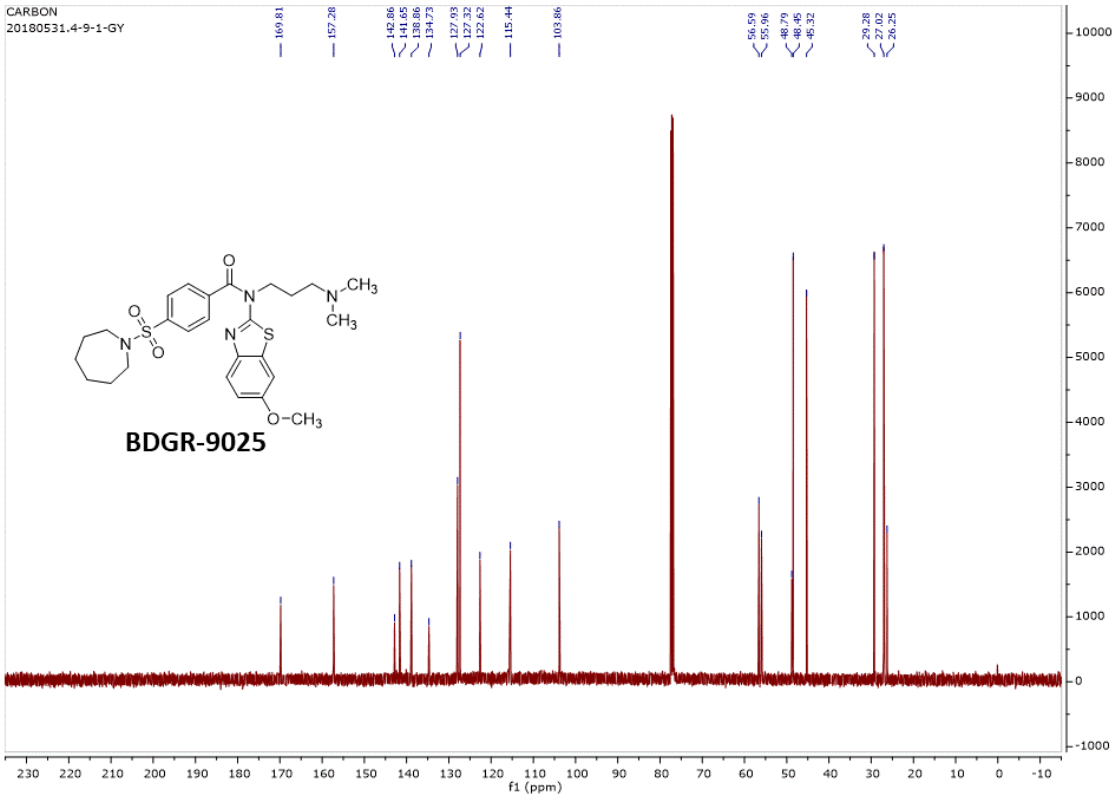

172.47
157.24
157.16
156.54
148.58
132.36
126.46
124.39
121.53
121.47
101.59
12.51
BDGR-9023
f1 (ppm)

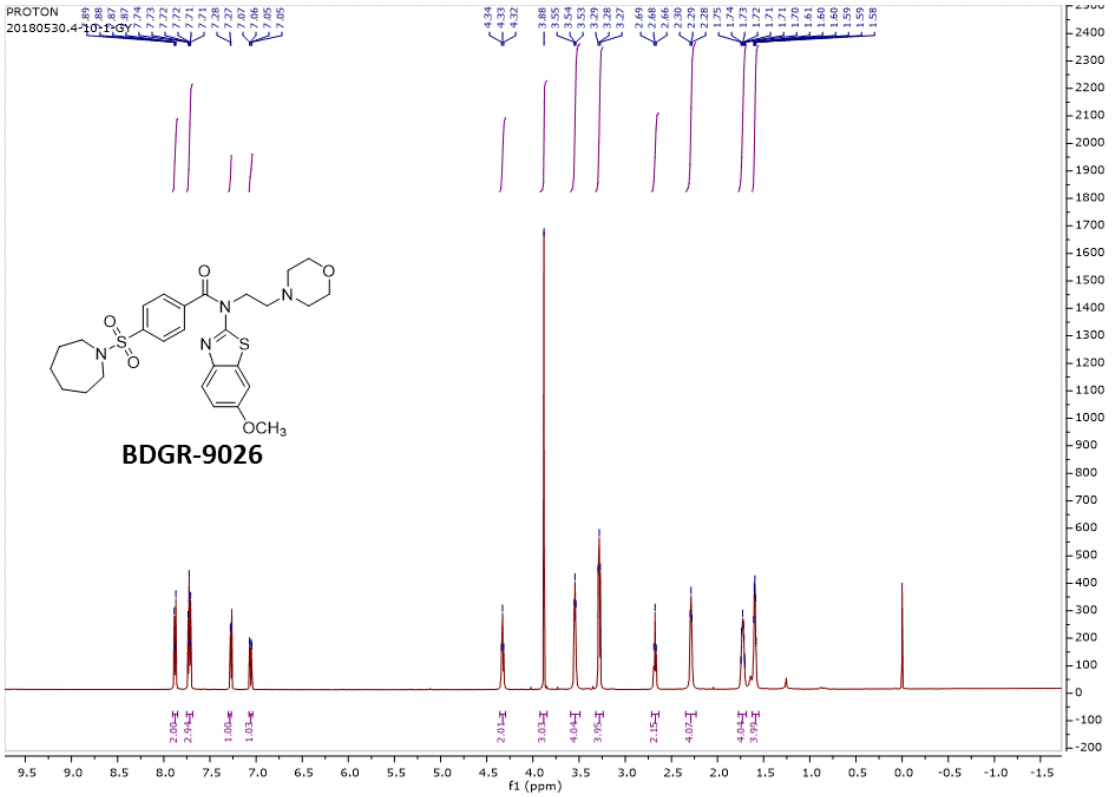

12.93
10.63
BDGR-9024
f1 (ppm)

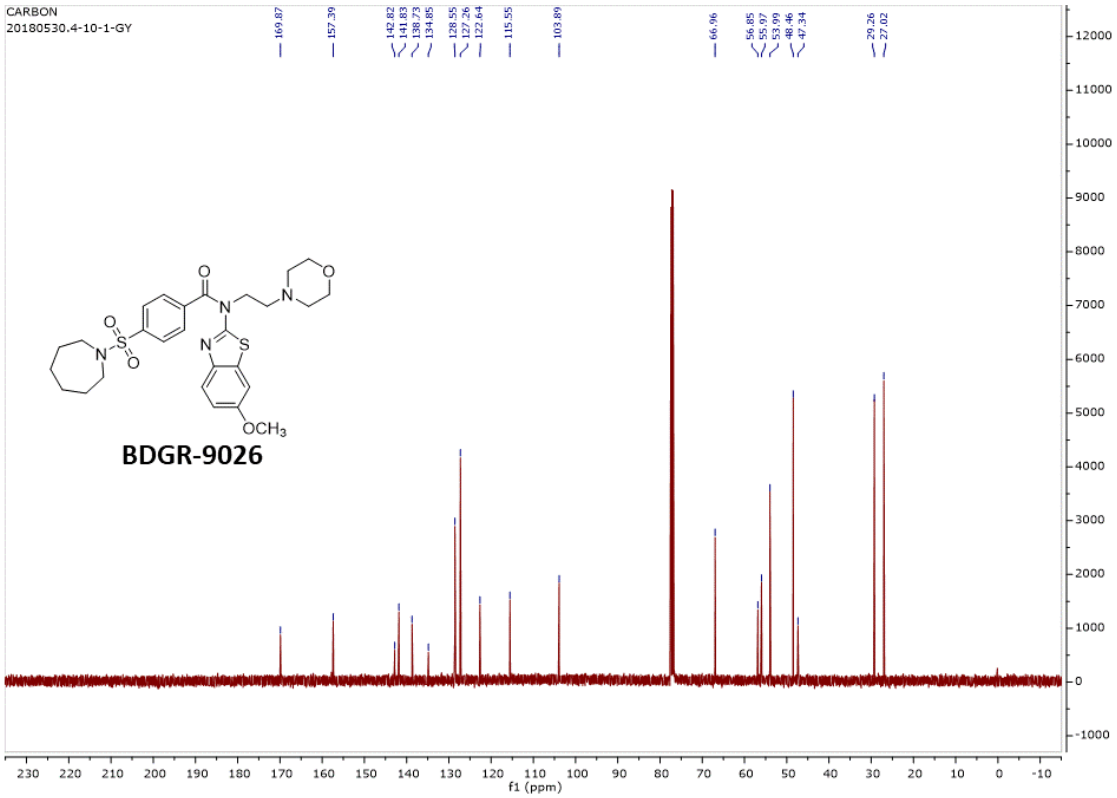

165.38
163.38
138.02
135.63
135.61
129.78
129.71
129.60
126.24
124.16
123.87
123.75
121.80
120.16
116.71
116.52
BDGR-9024
f1 (ppm)

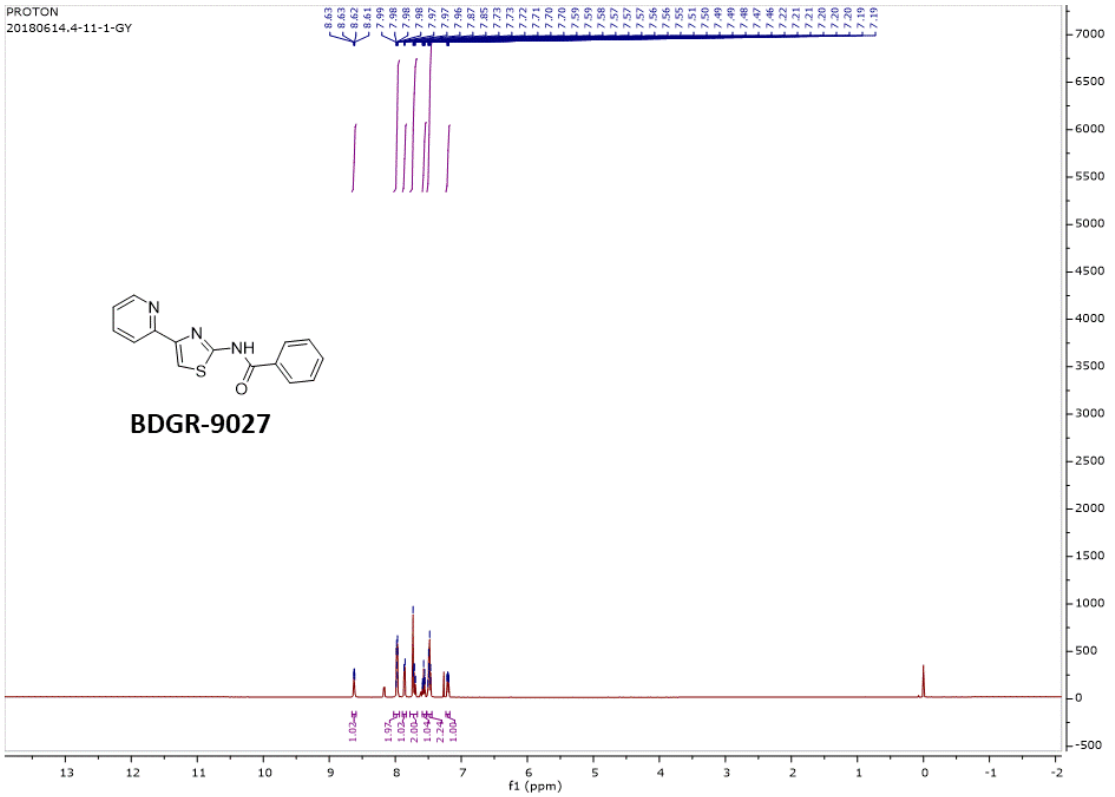

106.16
106.17
106.18
106.19
106.20
106.21
106.22
BDGR-9024
f1 (ppm)

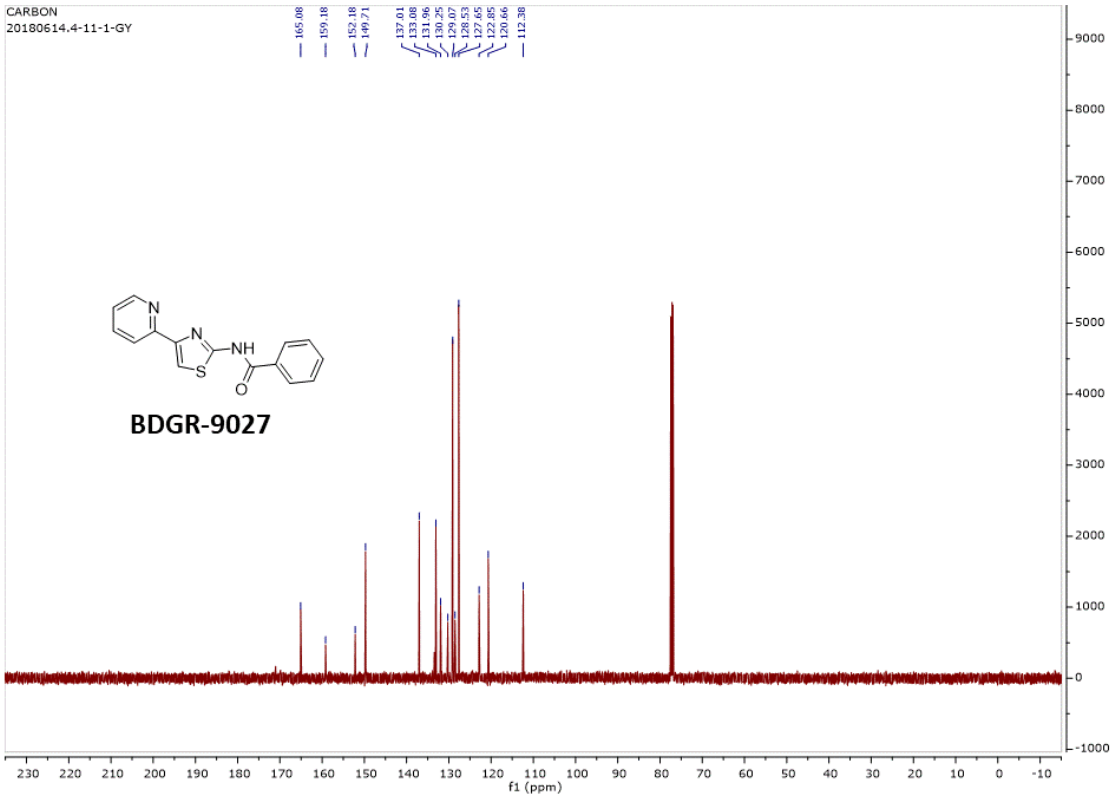

PROTON
20180531.4-9-1-GY
BDGR-9025
f1 (ppm)

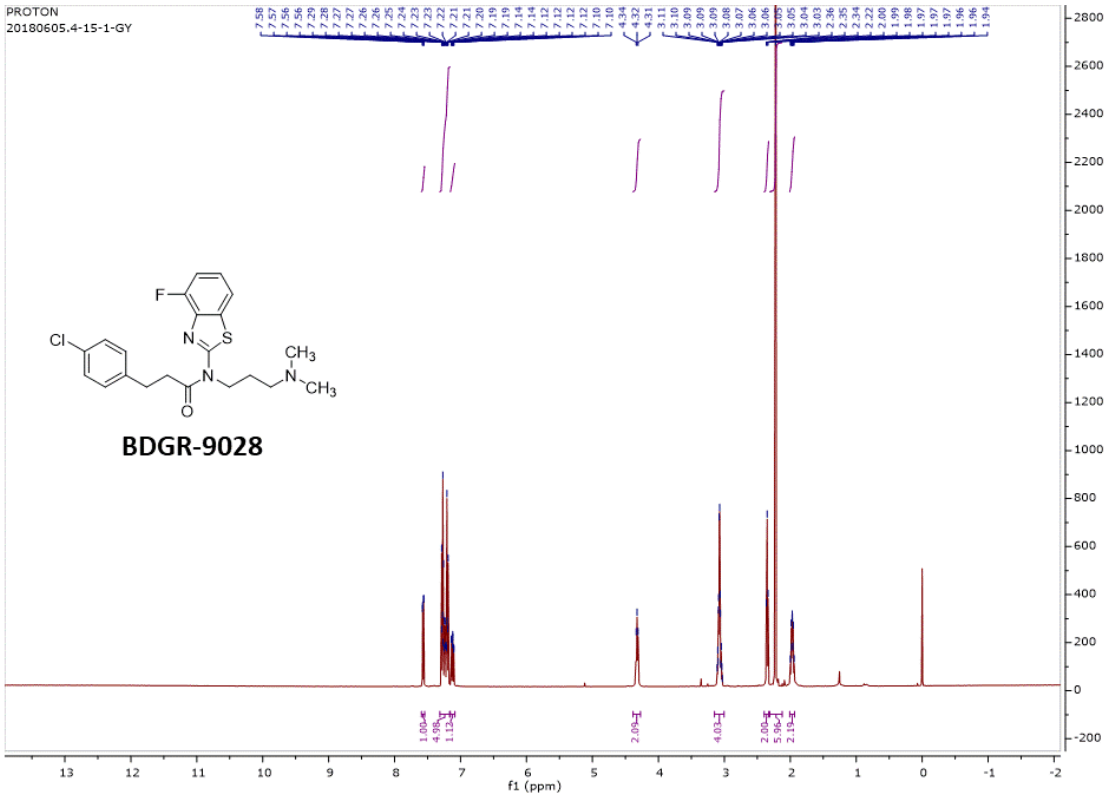

CARBON
20180531.4-9-1-GY
BDGR-9025
f1 (ppm)

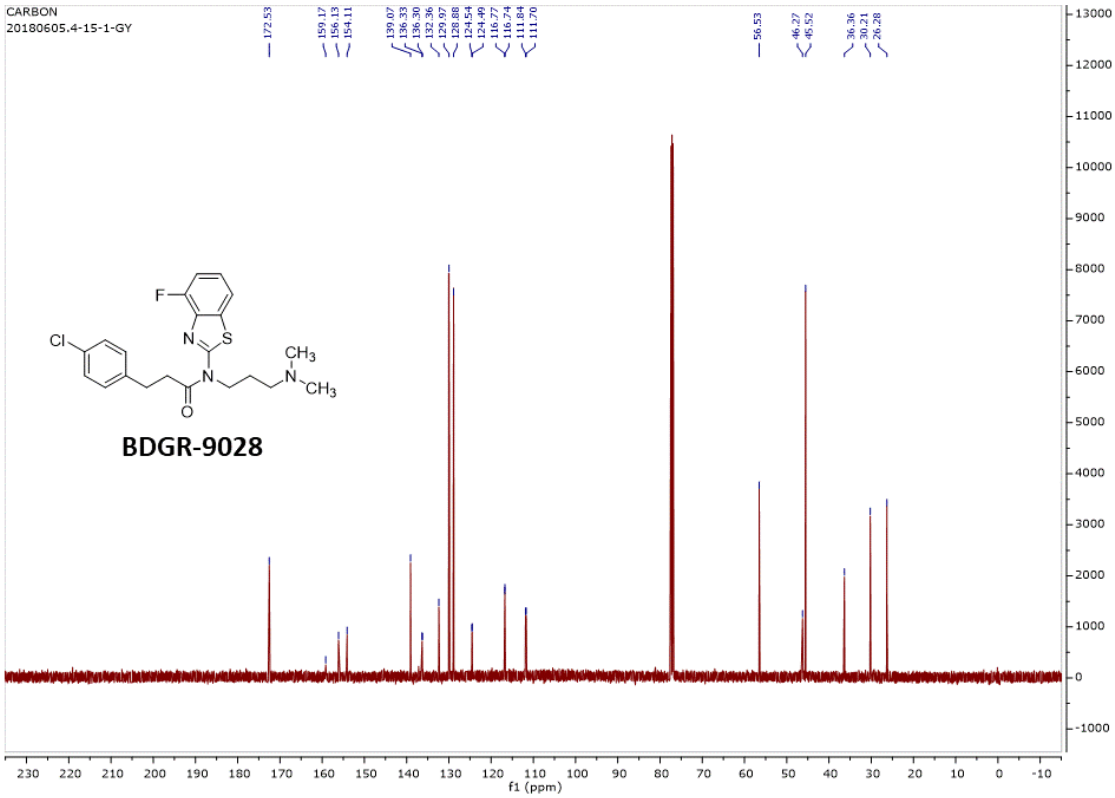

PROTON
20180530.4-10-1-GY
BDGR-9026
f1 (ppm)

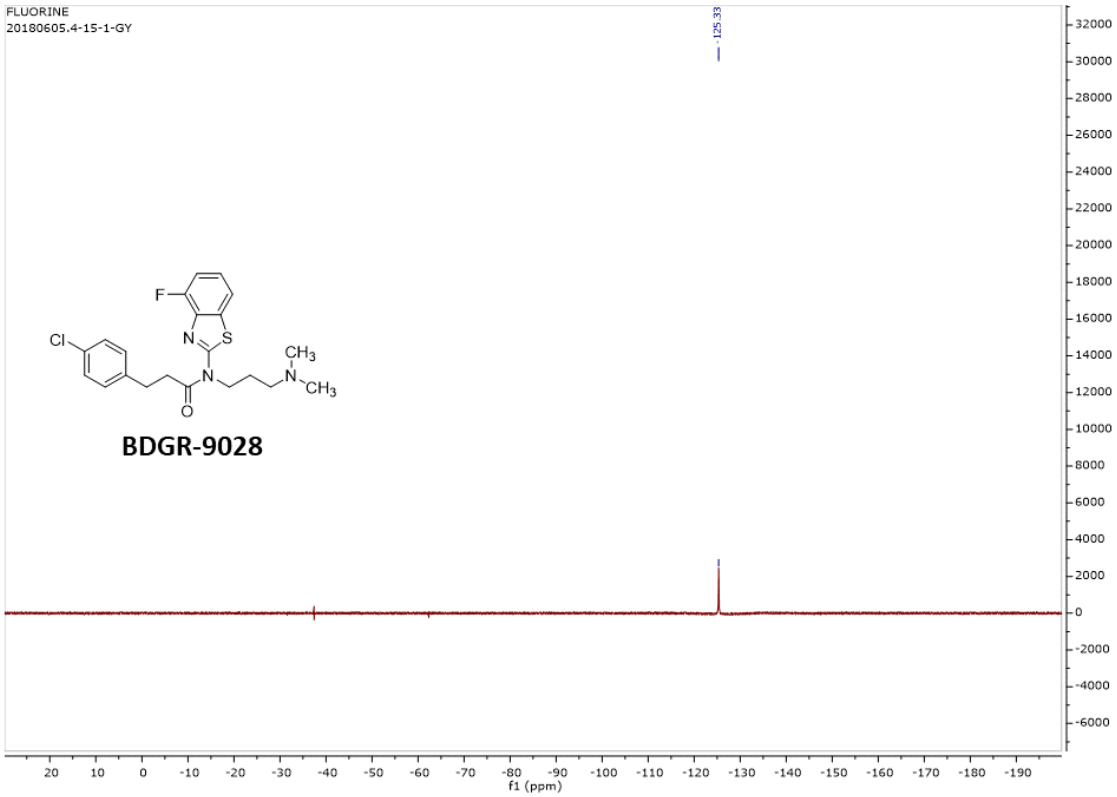

CARBON
20180530.4-10-1-GY
BDGR-9026
f1 (ppm)

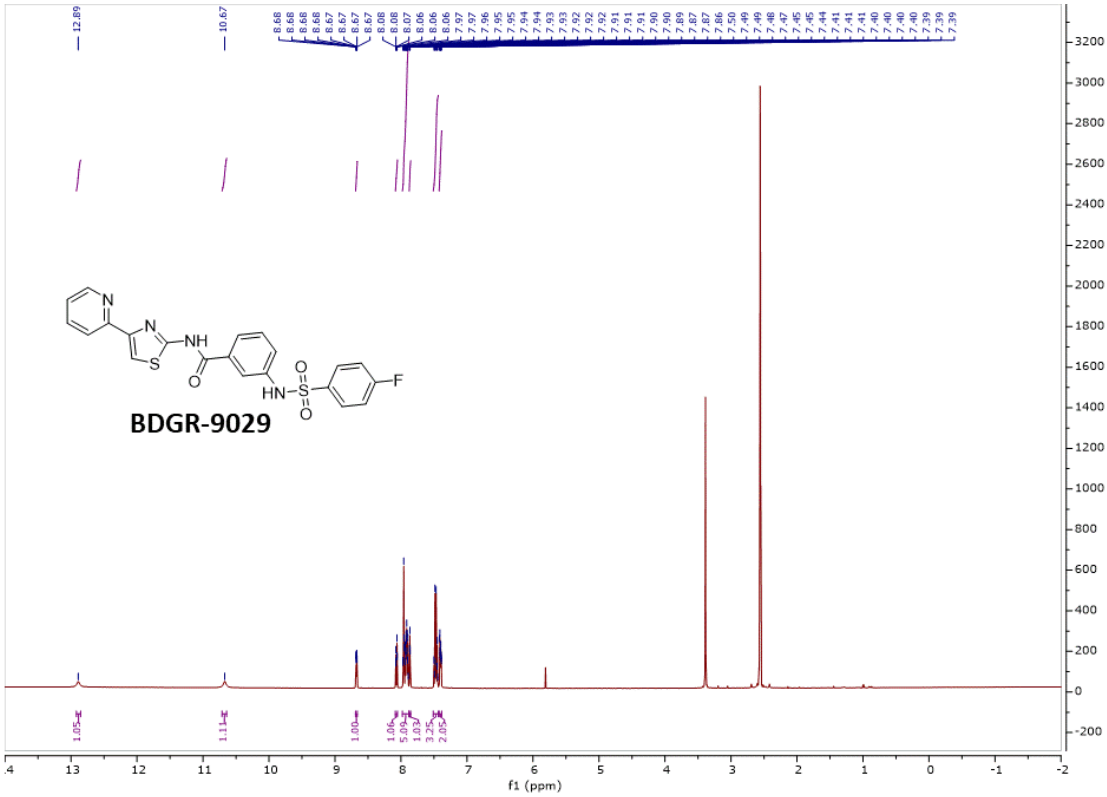

PROTON
20180614.4-11-1-GY
BDGR-9027
f1 (ppm)

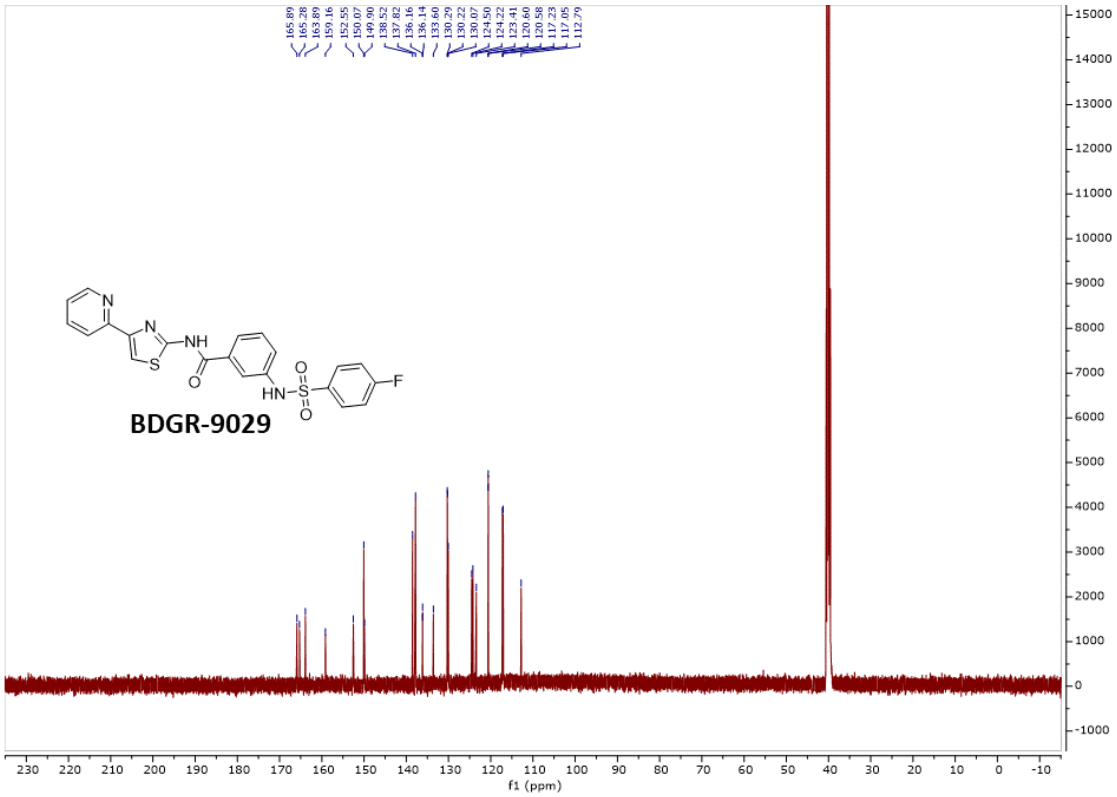

CARBON
20180614.4-11-1-GY
BDGR-9027
f1 (ppm)

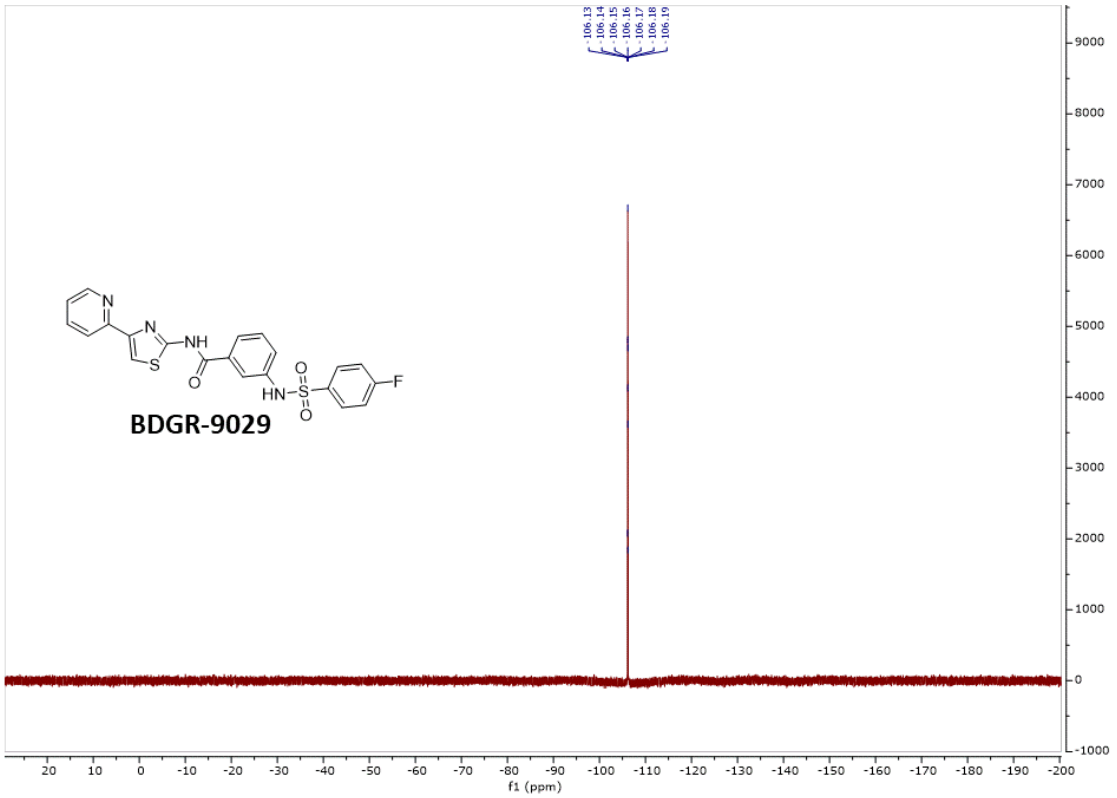

PROTON
20180605.4-15-1-GY
BDGR-9028
f1 (ppm)

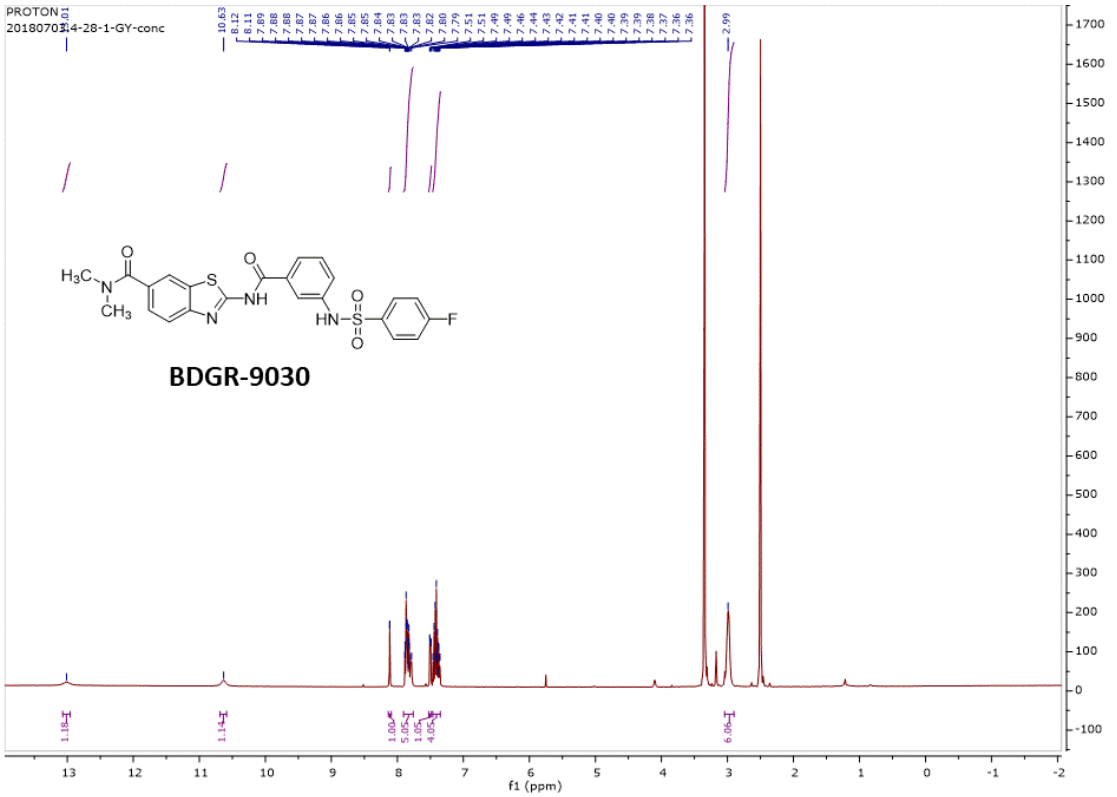

CARBON
20180605.4-15-1-GY
BDGR-9028
f1 (ppm)

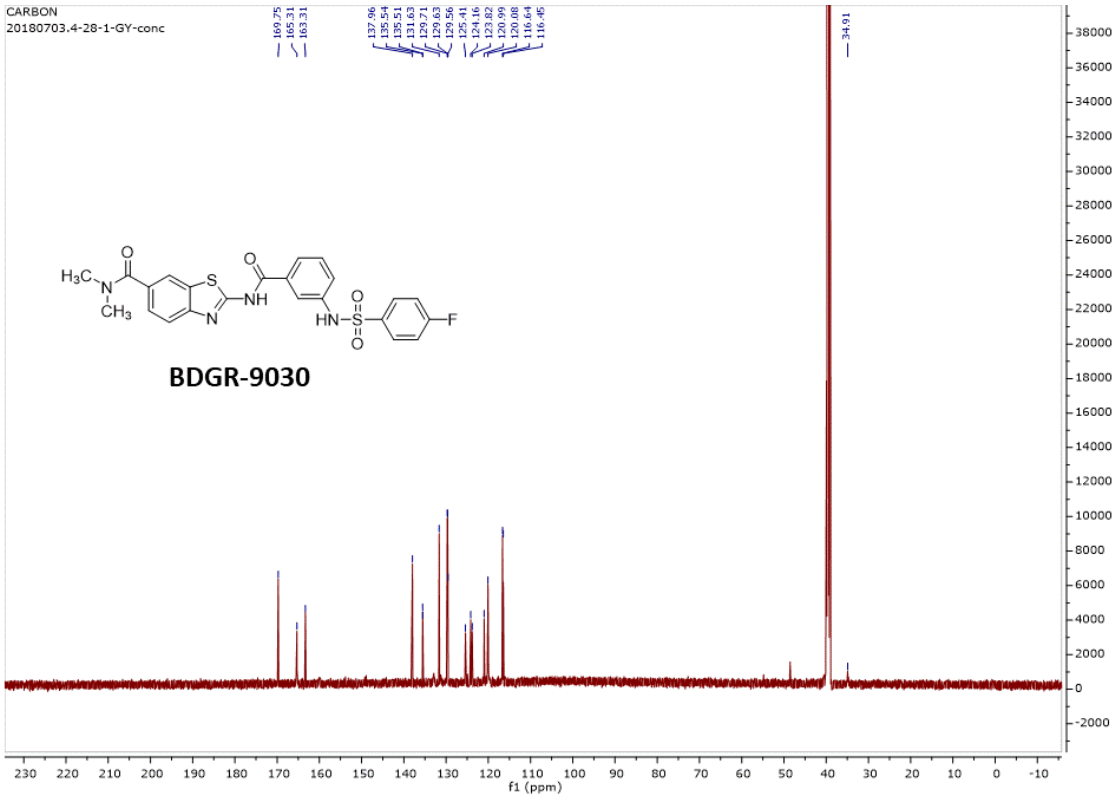

FLUORINE
20180605.4-15-1-GY
-125.33
BDGR-9028
f1 (ppm)

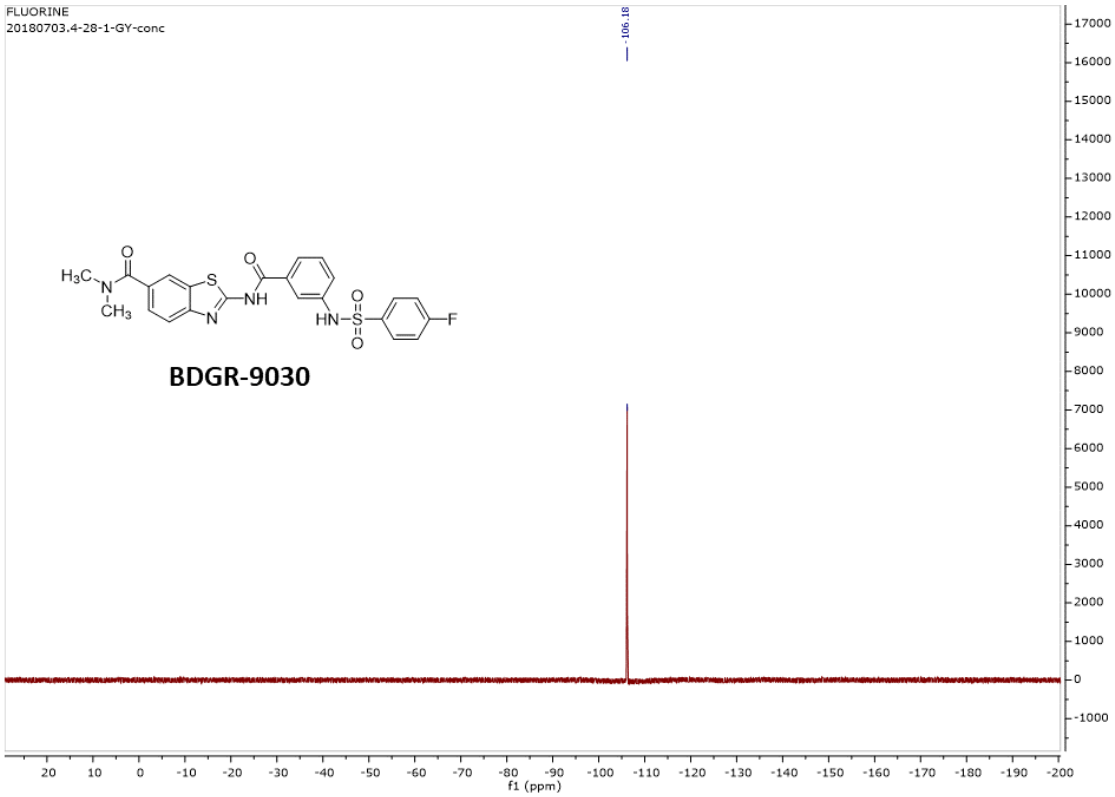

12.89
10.67
BDGR-9029
f1 (ppm)

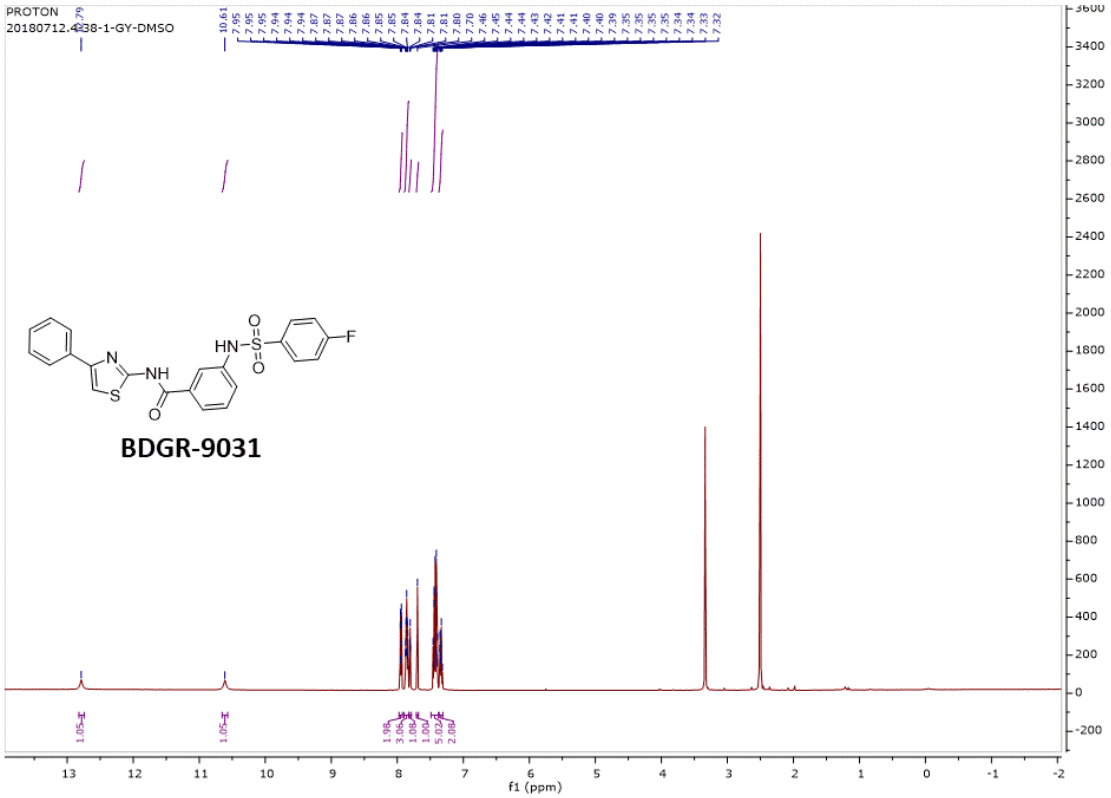

165.89
165.28
145.89
143.16
152.55
150.07
149.90
138.52
137.82
136.16
136.14
133.60
130.29
130.22
130.07
124.50
124.22
123.41
120.60
120.58
117.23
117.05
112.79
BDGR-9029
f1 (ppm)

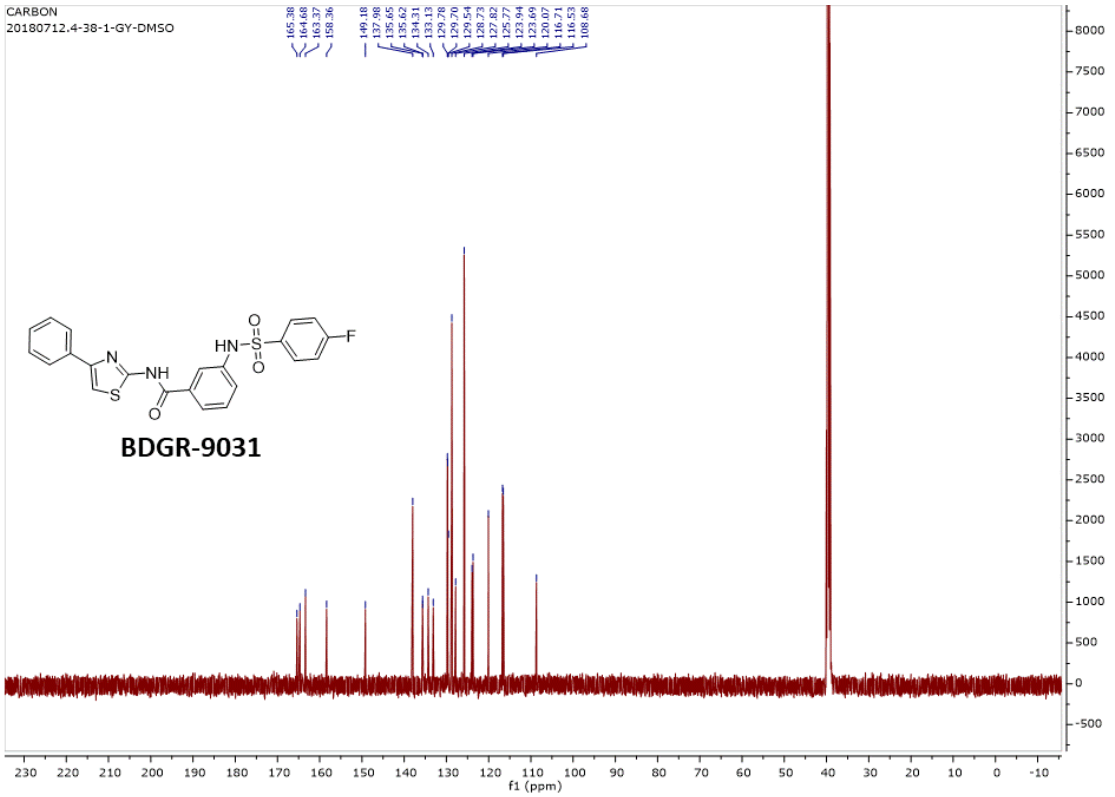

106.13
106.14
106.15
106.16
106.17
106.18
106.19
BDGR-9029
f1 (ppm)

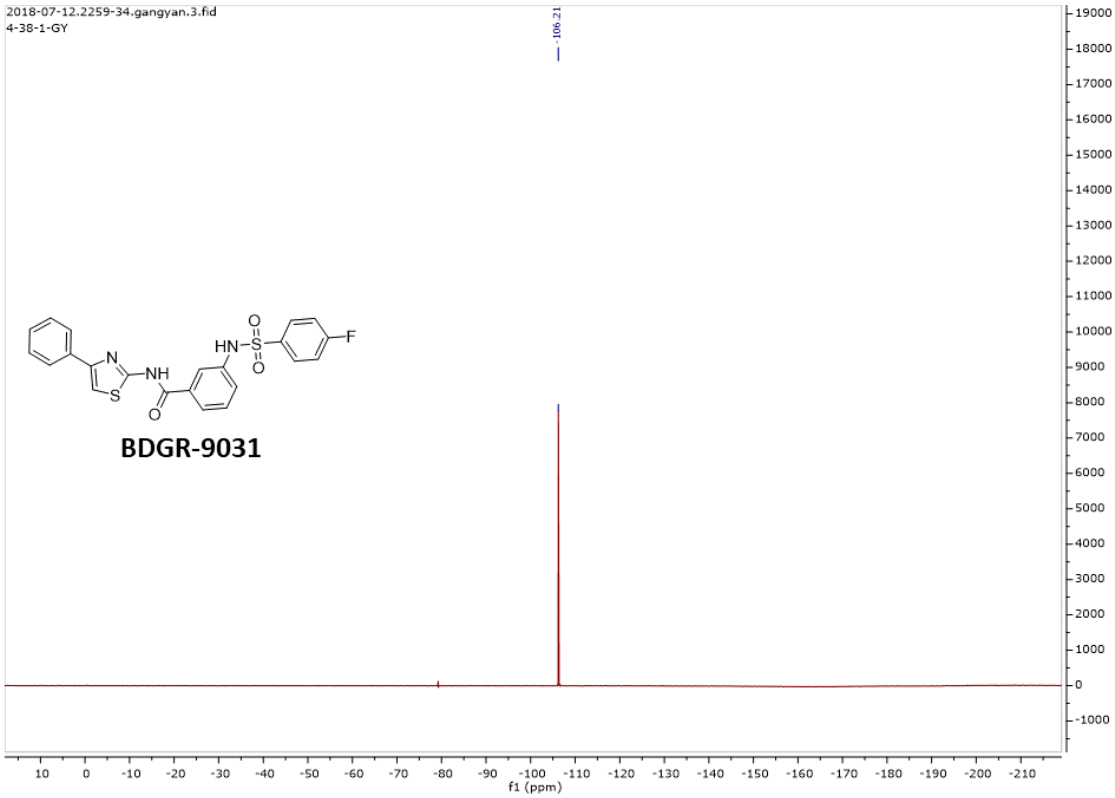

PROTON
20180703.4-28-1-GY-conc
BDGR-9030
f1 (ppm)

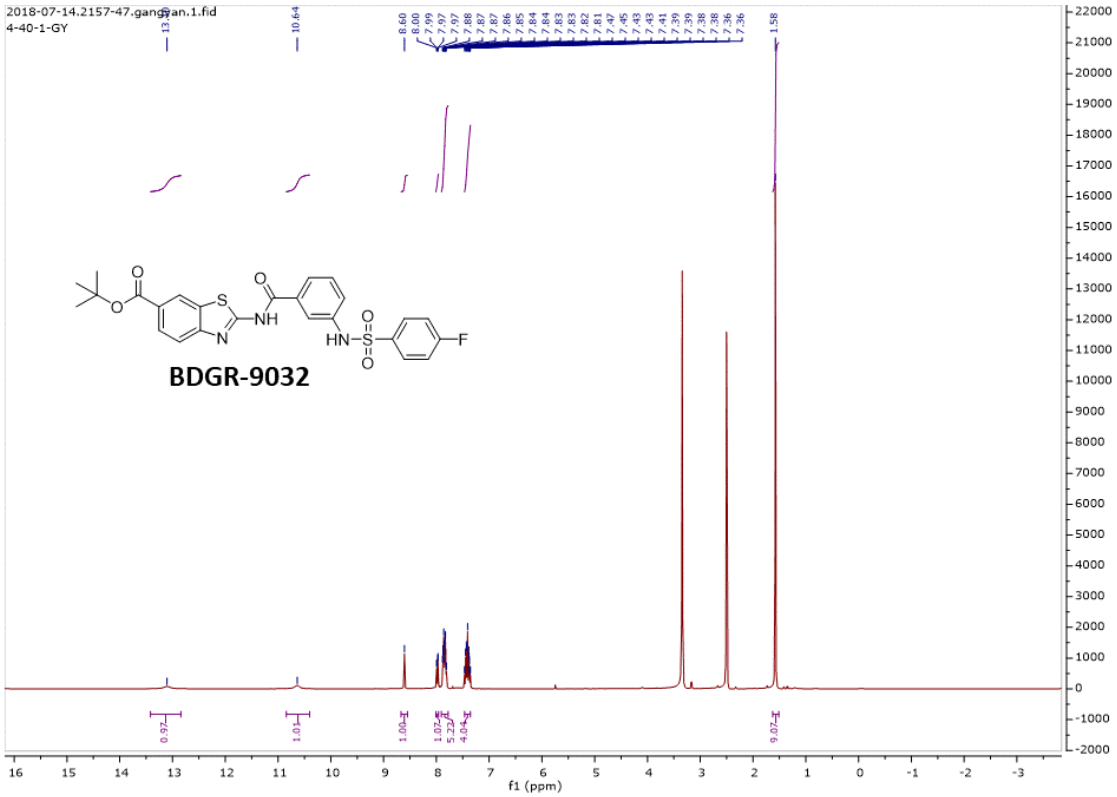

CARBON
20180703.4-28-1-GY-conc
BDGR-9030
f1 (ppm)

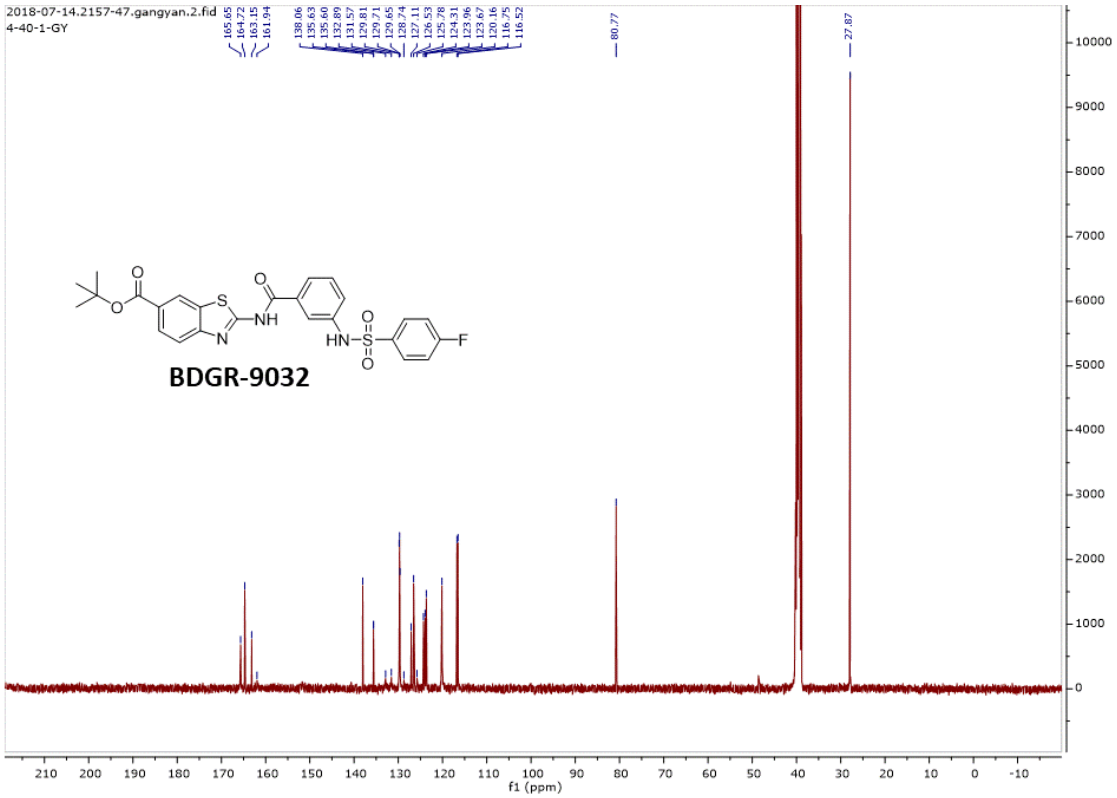

FLUORINE
20180703.4-28-1-GY-conc
-106.18
BDGR-9030
f1 (ppm)

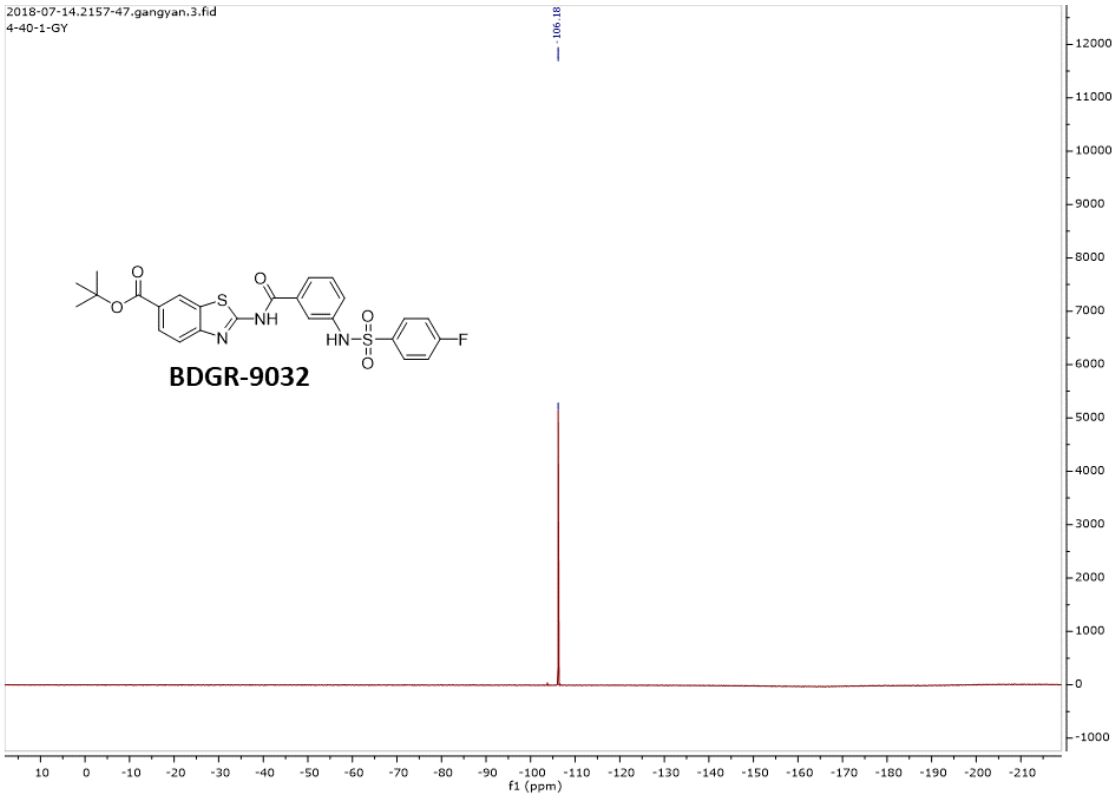

PROTON
20180712.4-38-1-GY-DMSO
BDGR-9031
f1 (ppm)

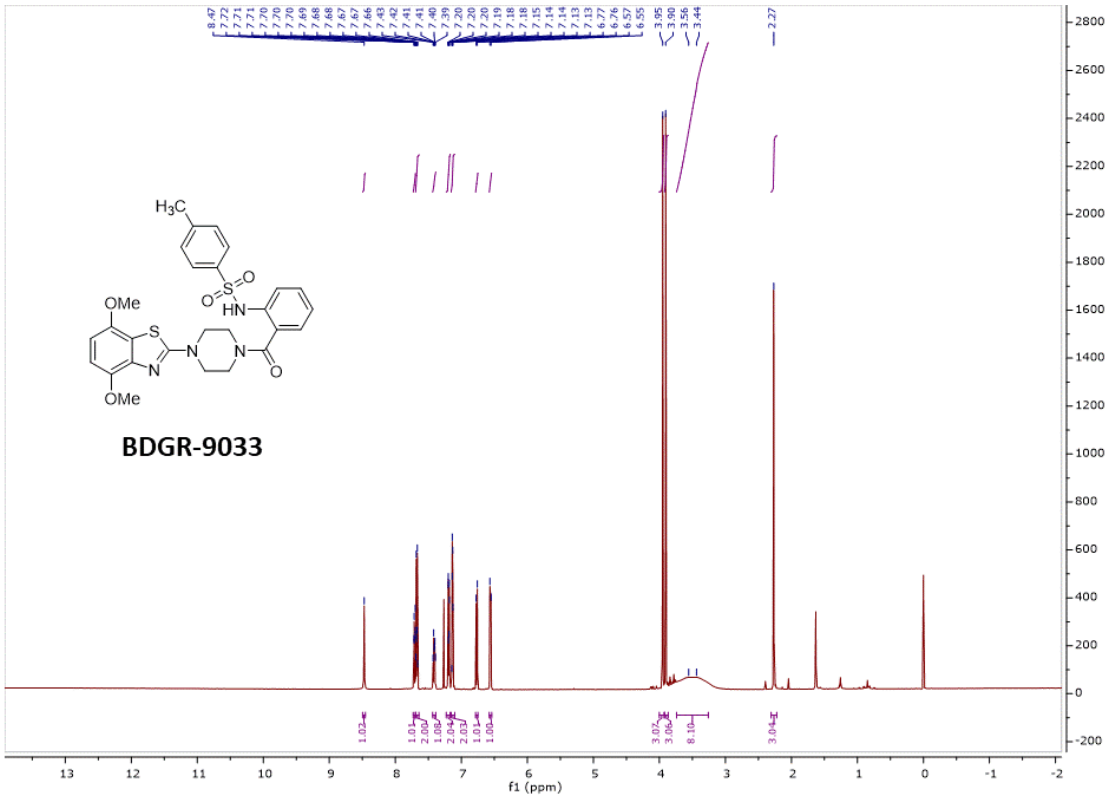

CARBON
20180712.4-38-1-GY-DMSO
165.38
164.68
163.37
150.36
149.18
137.98
135.65
135.62
134.31
133.13
129.78
129.70
129.54
128.73
127.82
125.77
123.94
123.69
120.07
116.71
116.53
108.68
BDGR-9031
f1 (ppm)

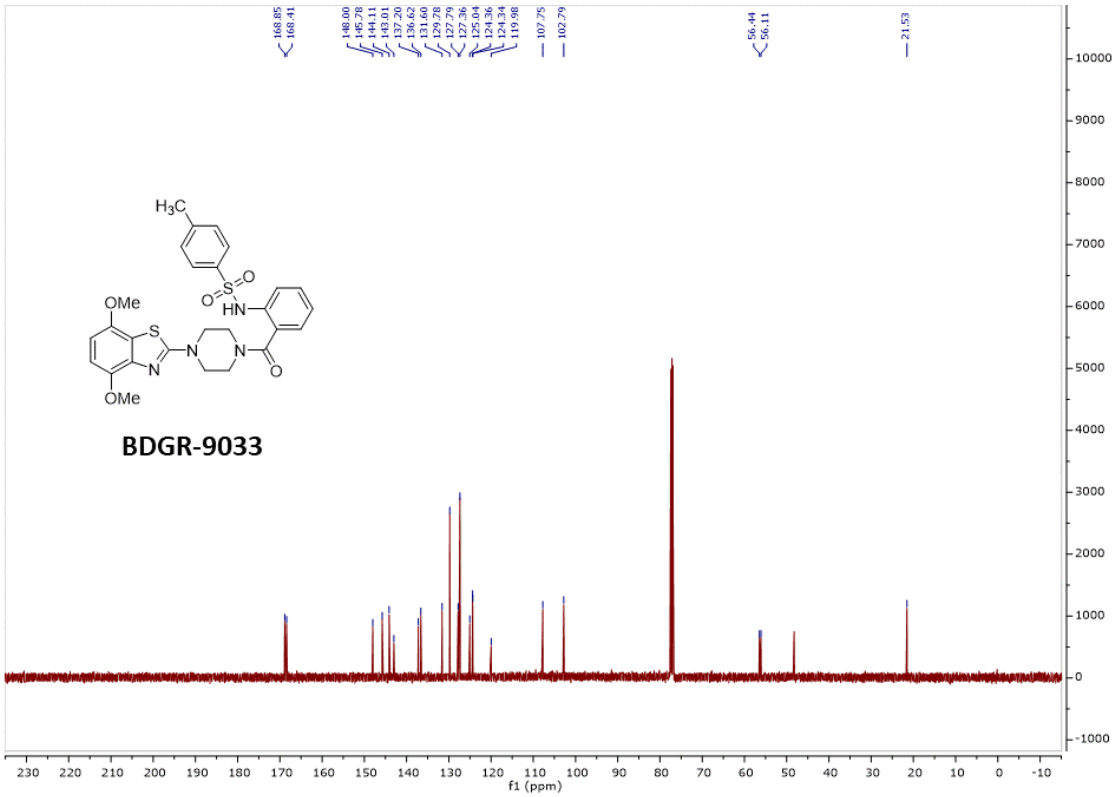

2018-07-12.2259-34.gangyan.3.fid
4-38-1-GY
106.21
BDGR-9031
f1 (ppm)

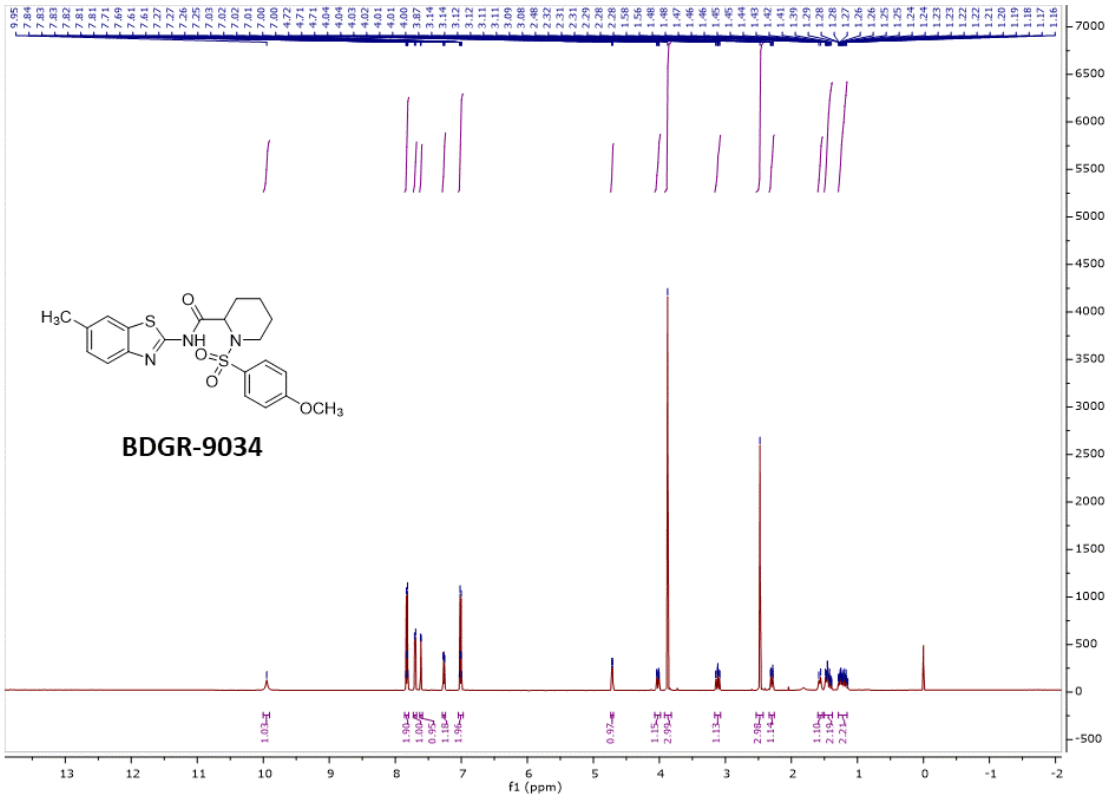

2018-07-14.2157-47.gangyan.1.fid
4-40-1-GY
BDGR-9032
f1 (ppm)

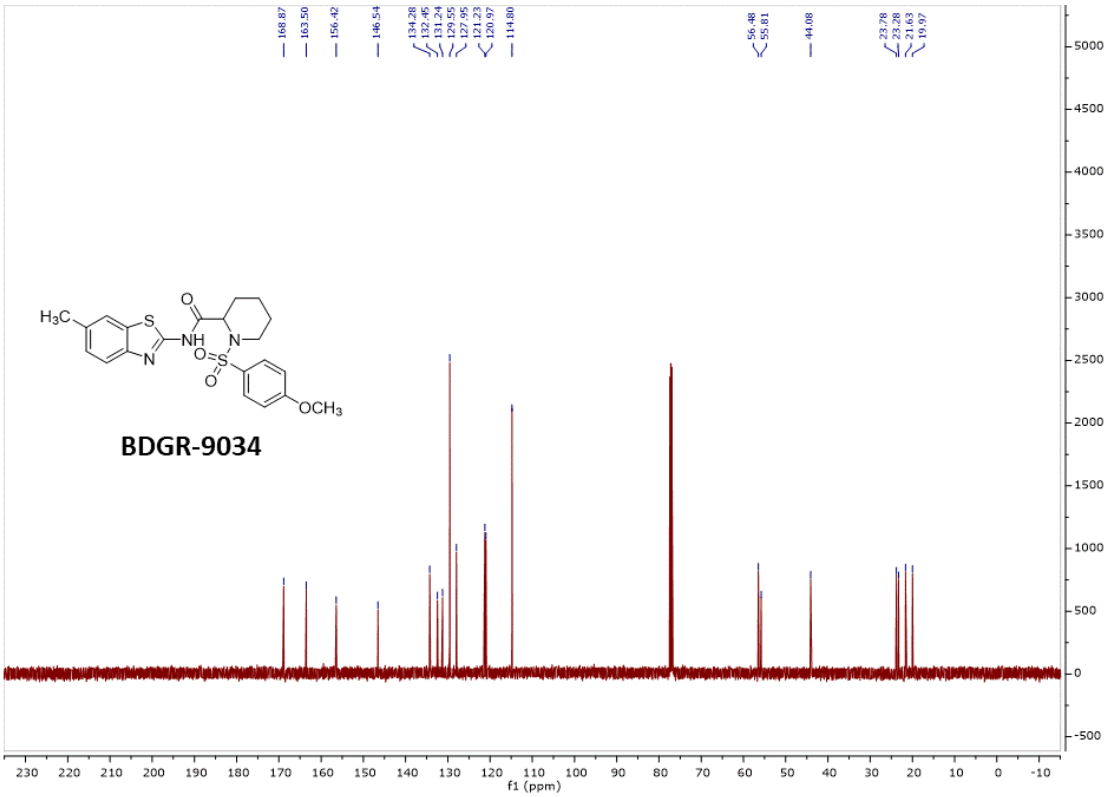

2018-07-14.2157-47.gangyan.2.fid
4-40-1-GY
BDGR-9032
f1 (ppm)

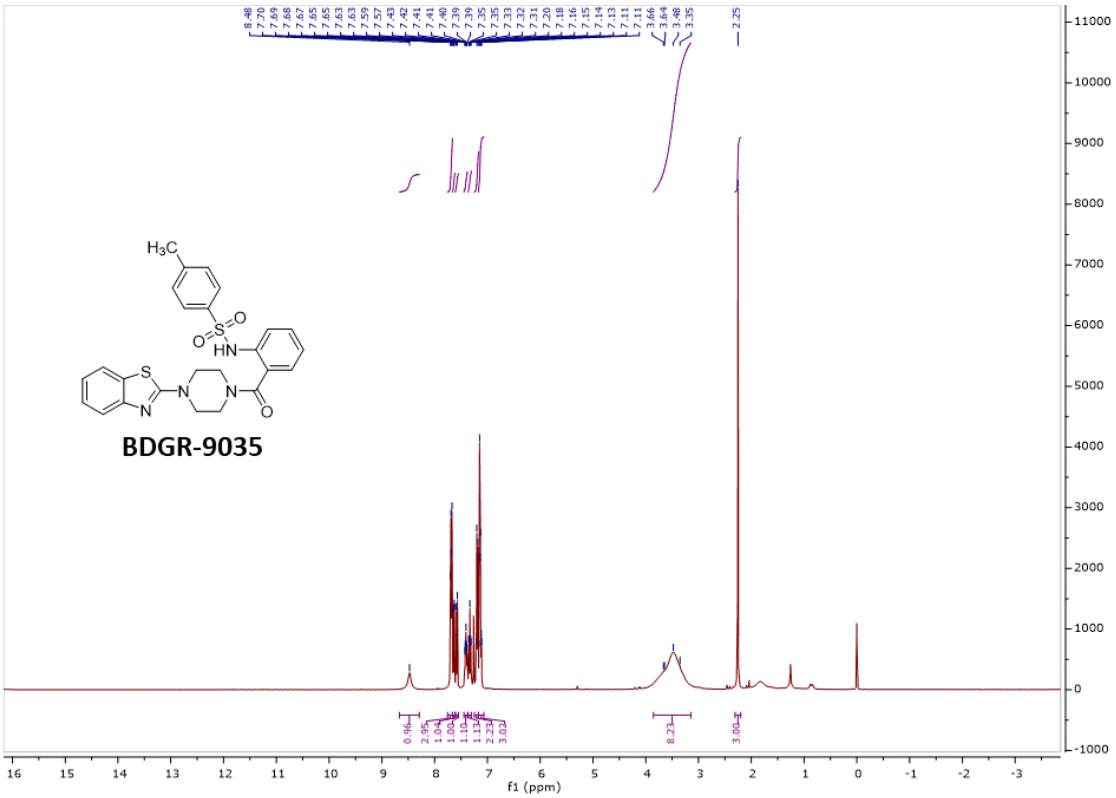

2018-07-14.2157-47.gangyan.3.fid
4-40-1-GY
-106.18
BDGR-9032
f1 (ppm)

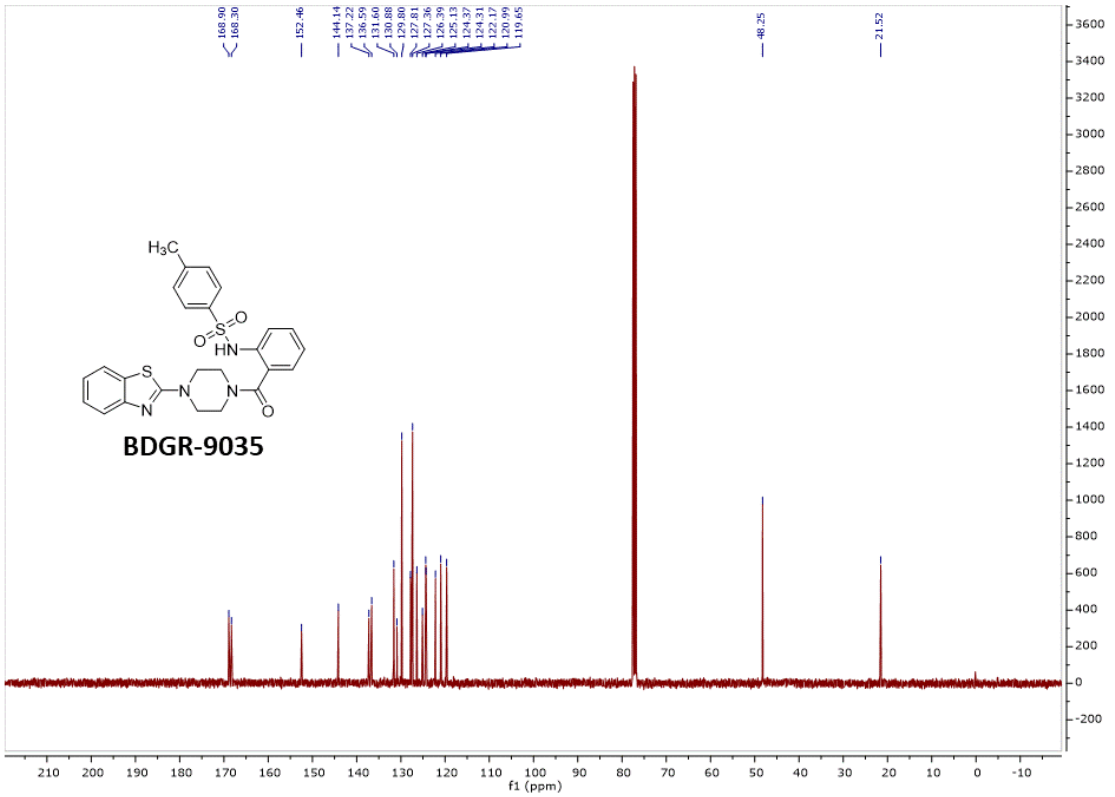

BDGR-9033
f1 (ppm)

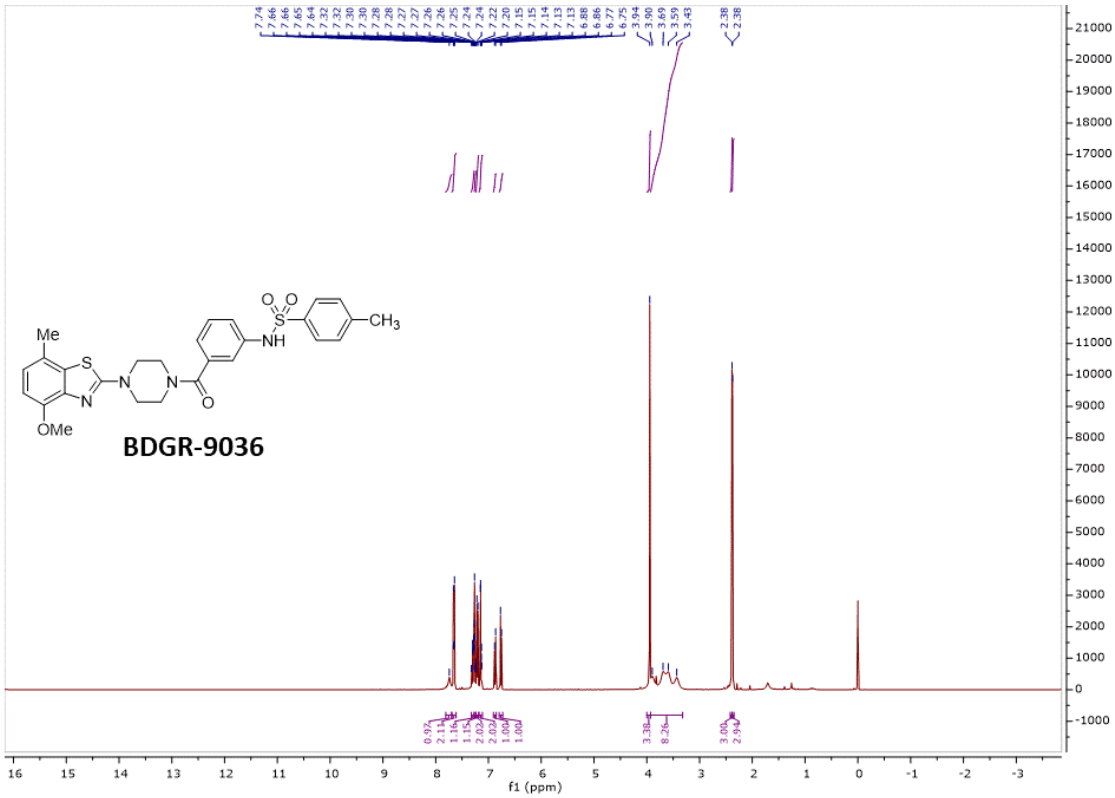

BDGR-9033
f1 (ppm)

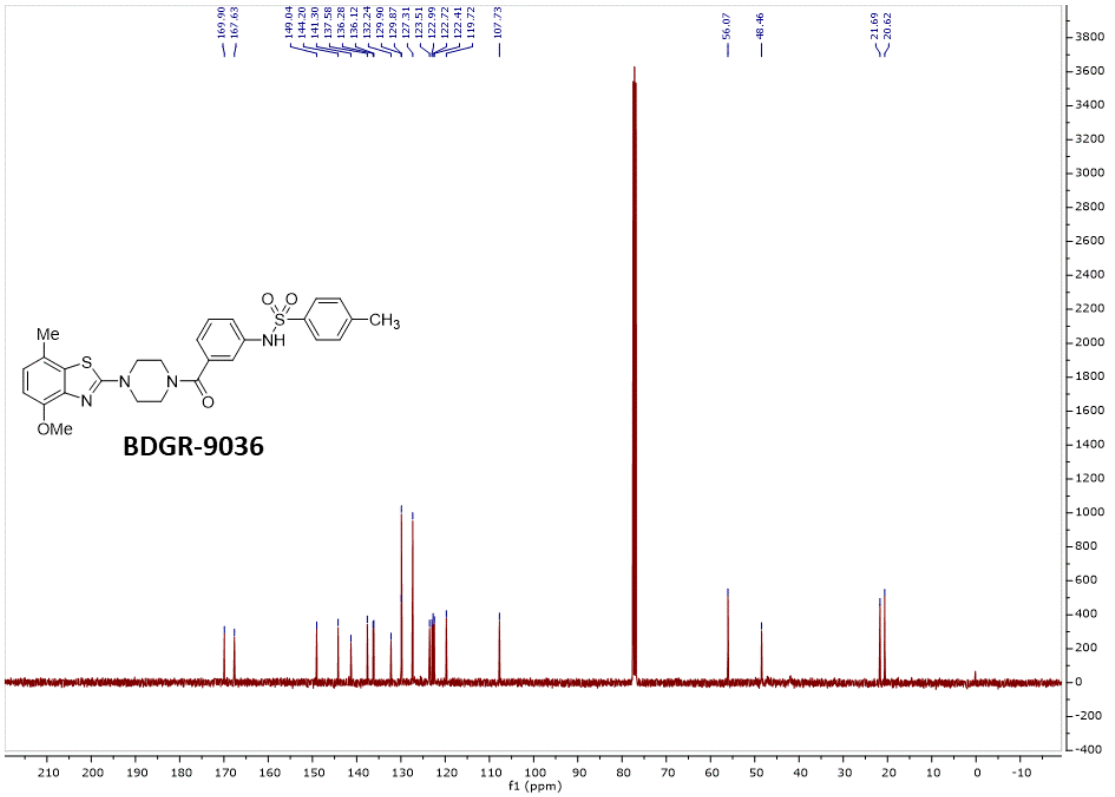

BDGR-9034
f1 (ppm)


BDGR-9034
f1 (ppm)

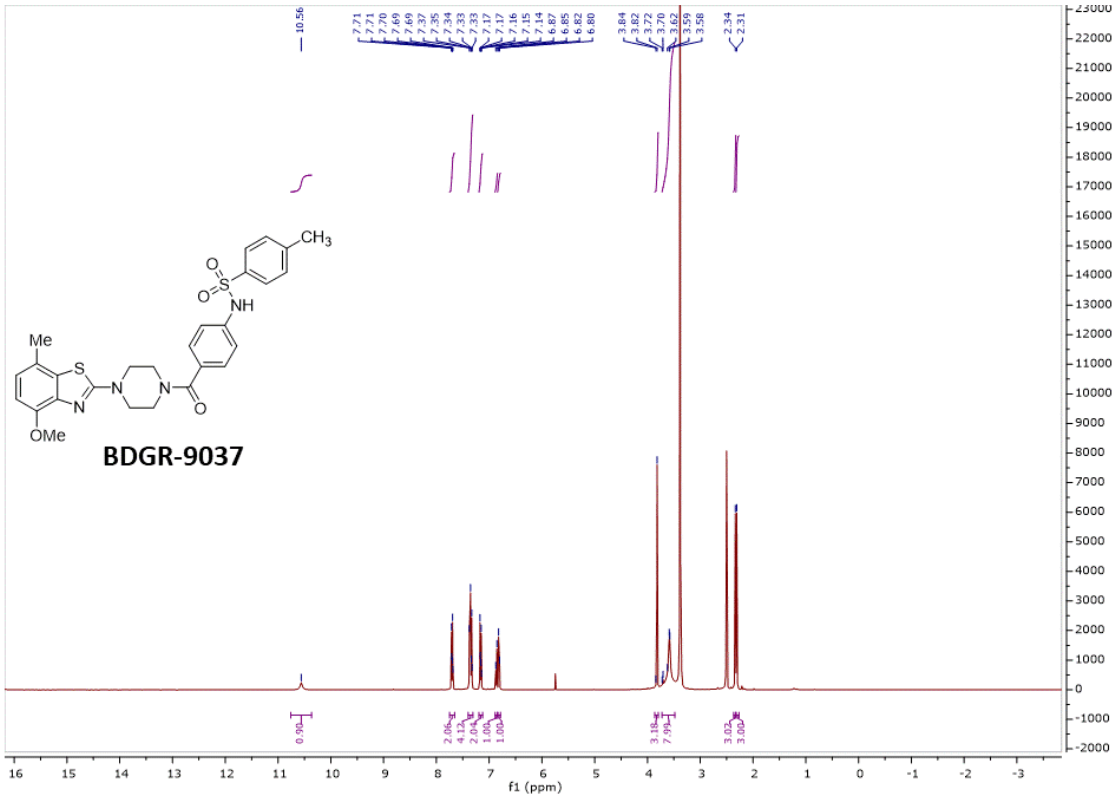

BDGR-9035
f1 (ppm)


BDGR-9035
f1 (ppm)

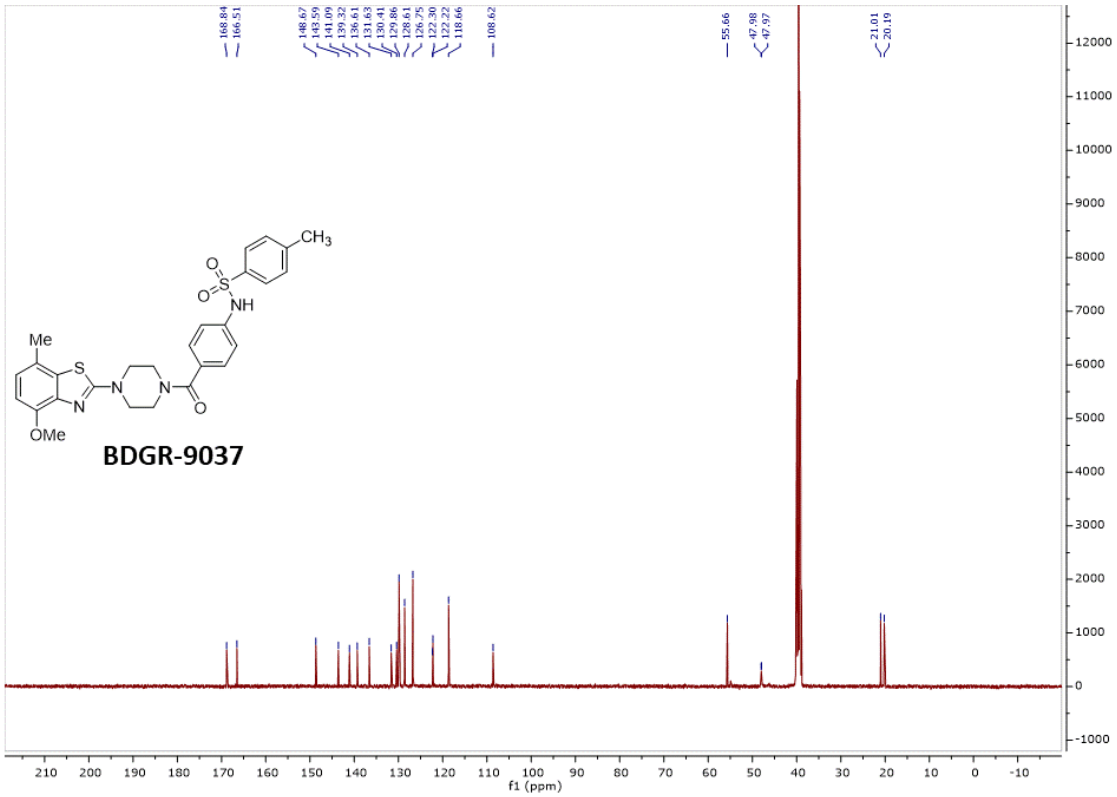

BDGR-9036
f1 (ppm)



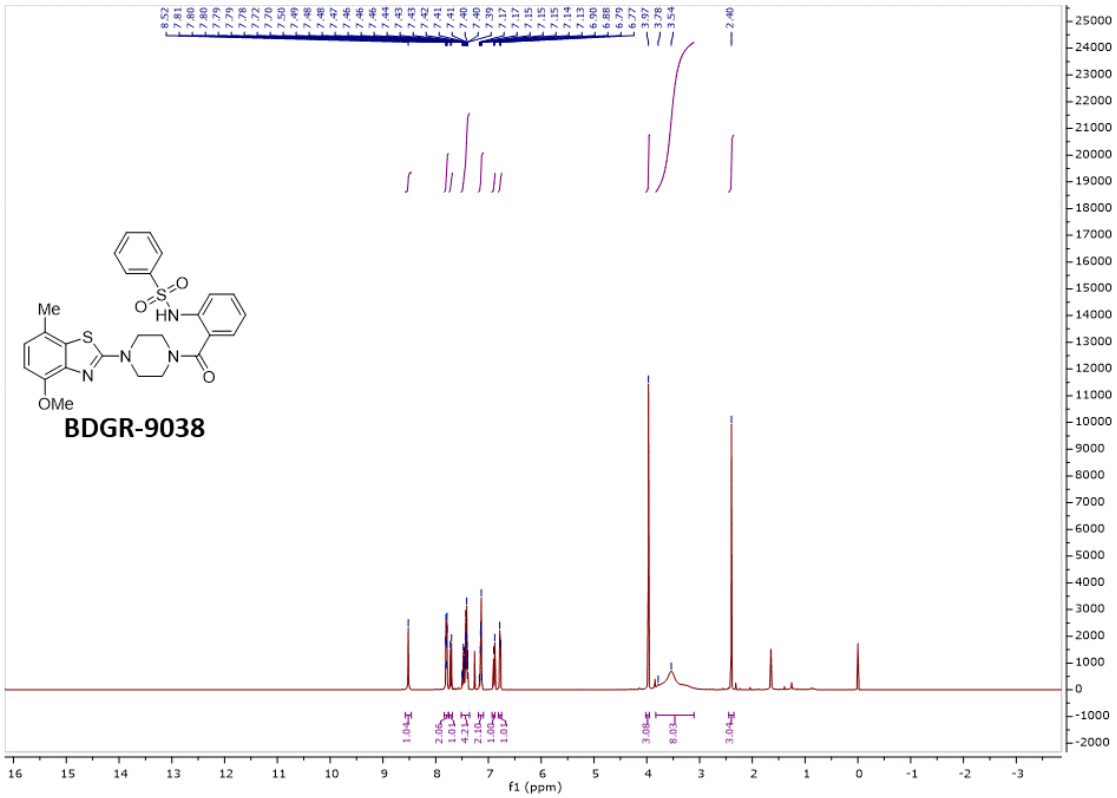

**BDGR-9036**



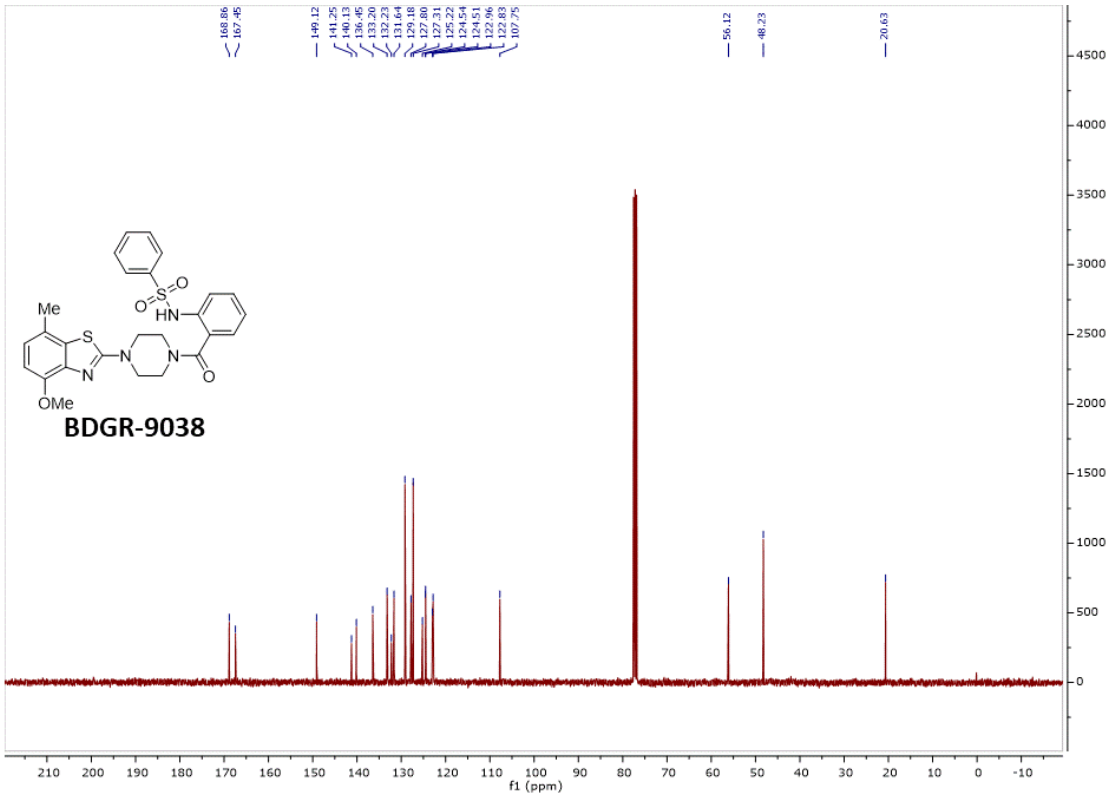

**BDGR-9037**

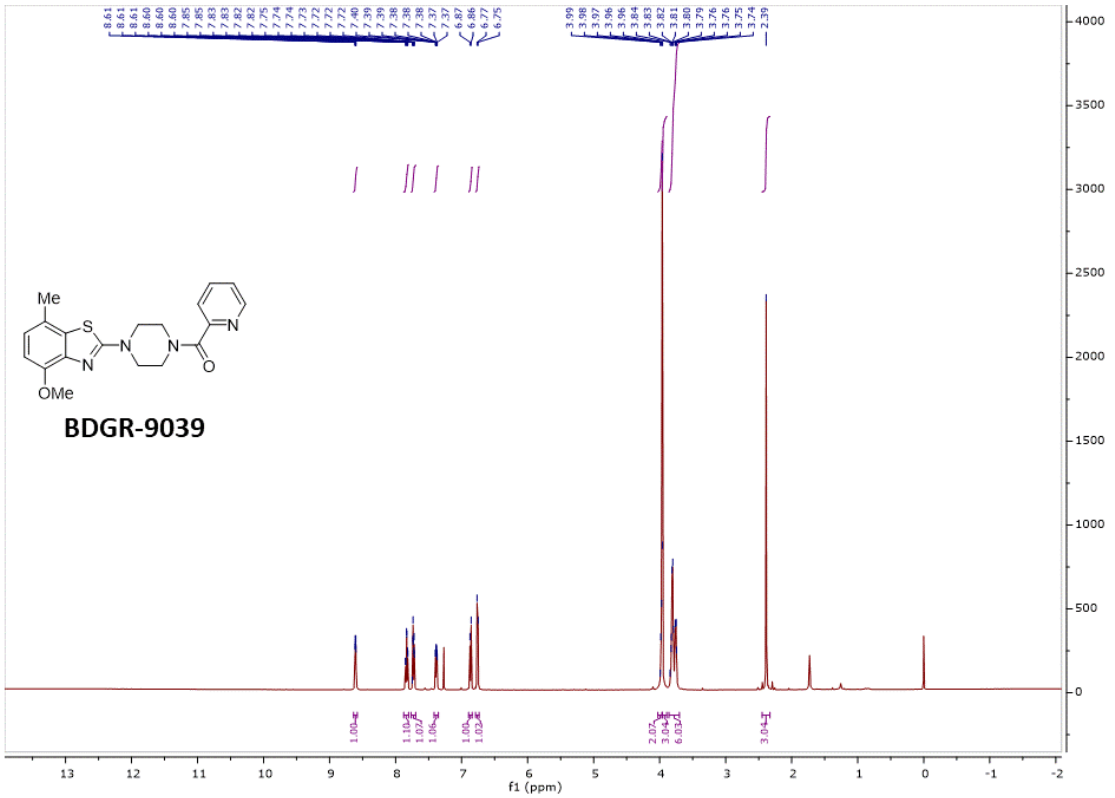


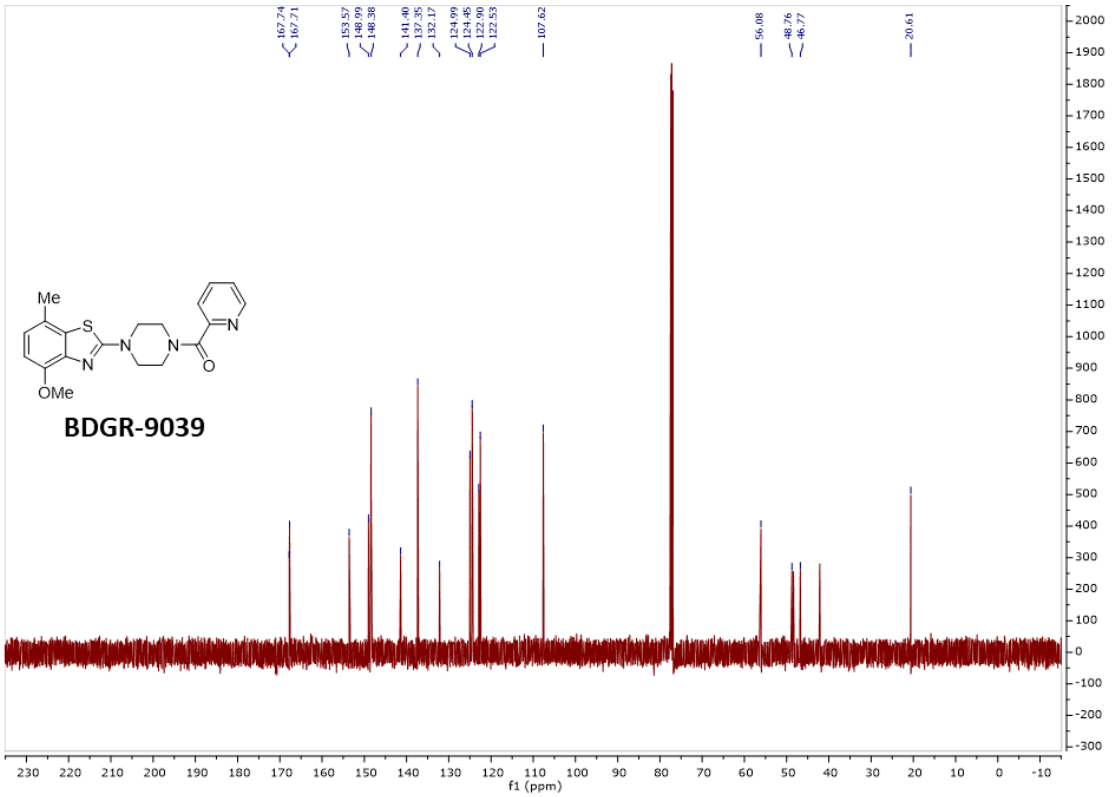

**BDGR-9037**

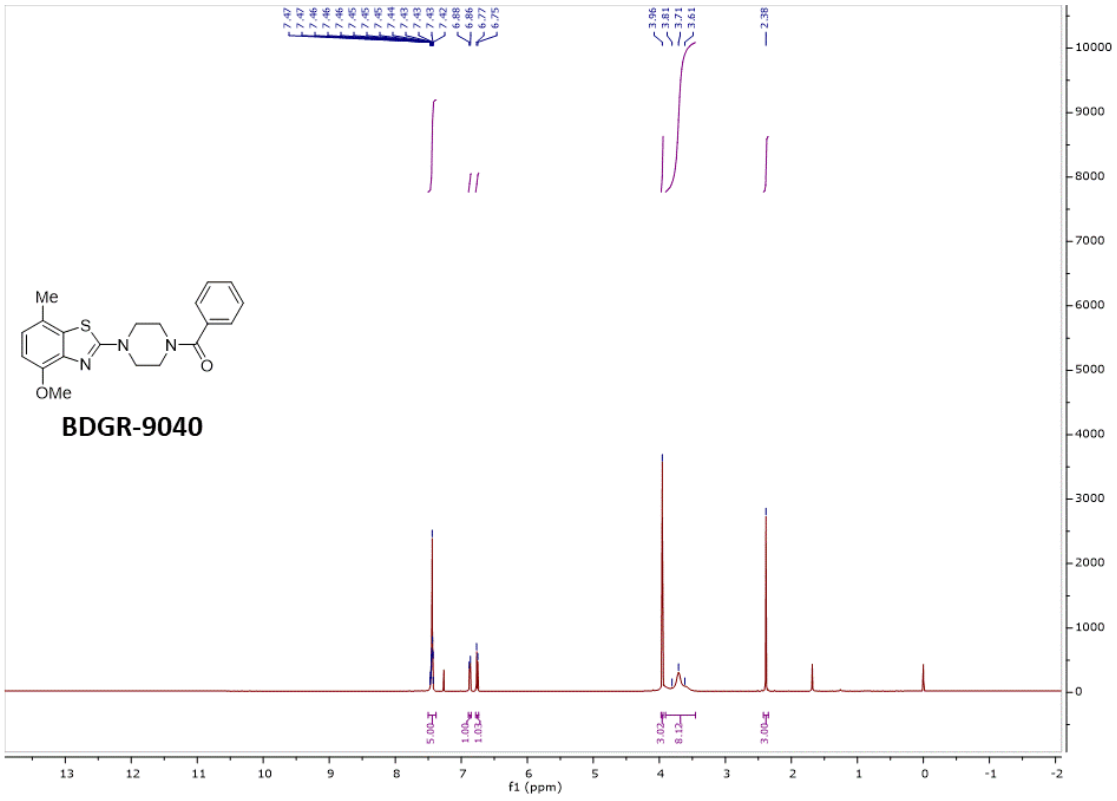


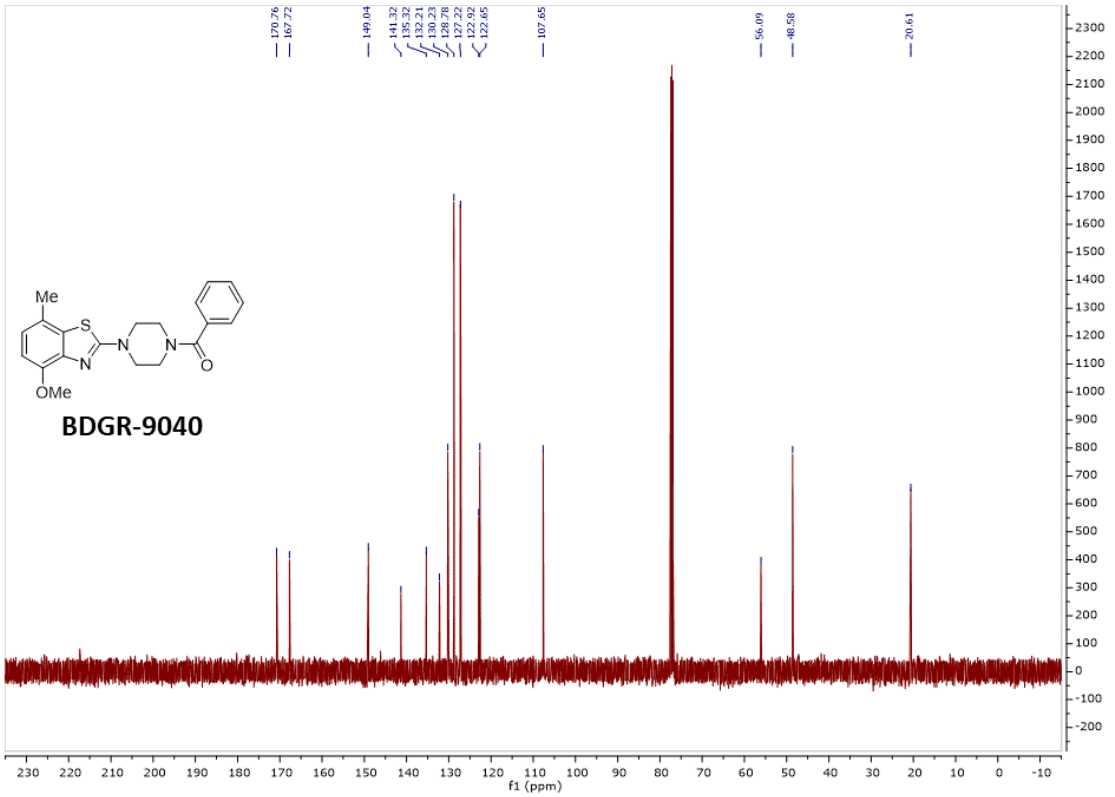

**BDGR-9038**

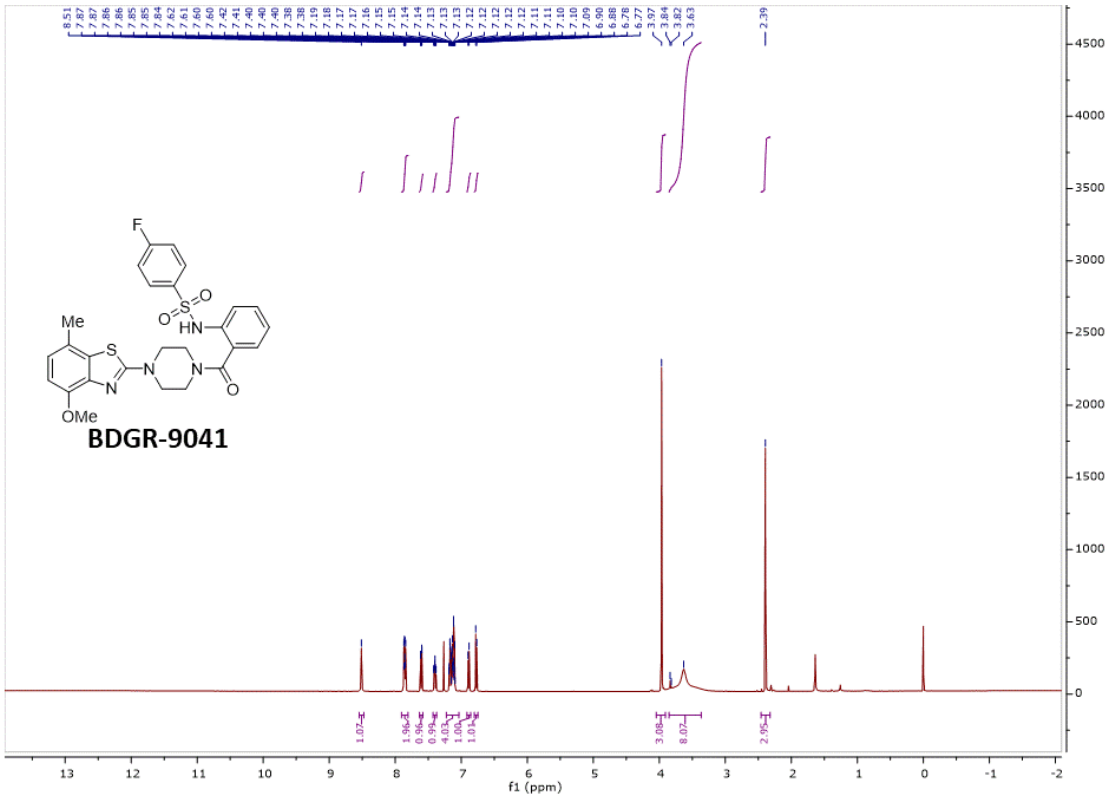

Me
S
N
N
N
HN
O
O
S
O
OMe
BDGR-9038
f1 (ppm)

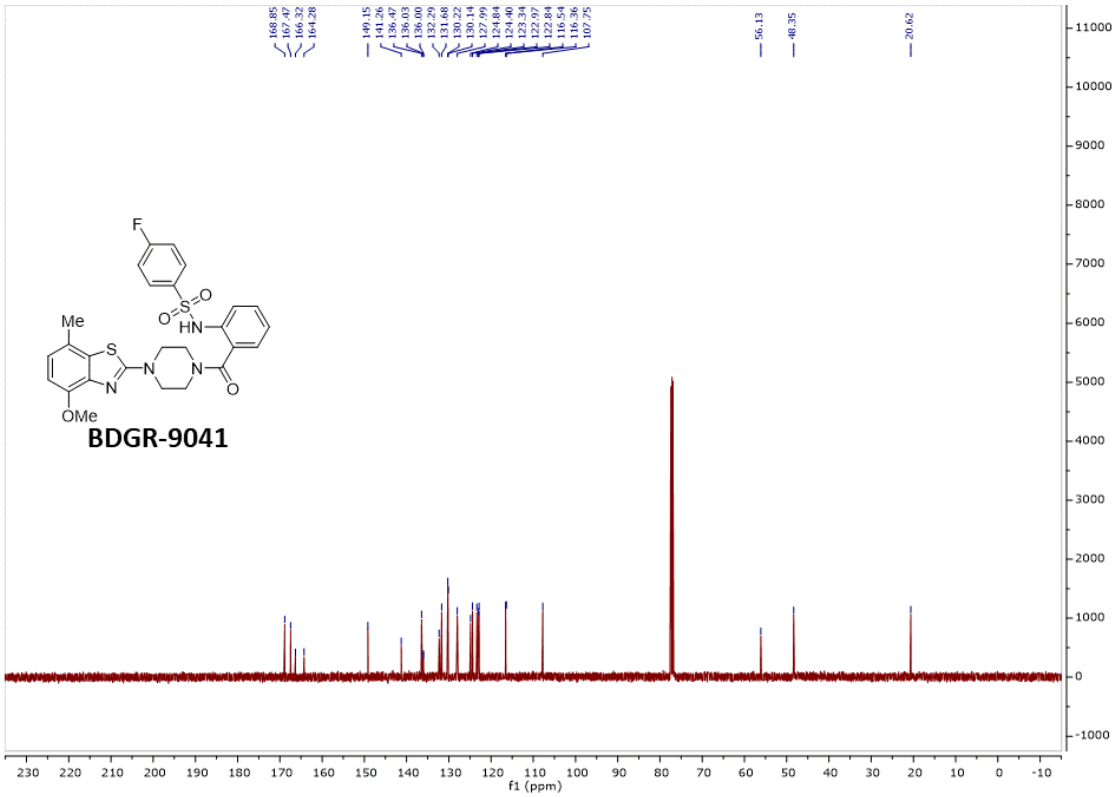

Me
S
N
N
N
O
OMe
BDGR-9039
f1 (ppm)

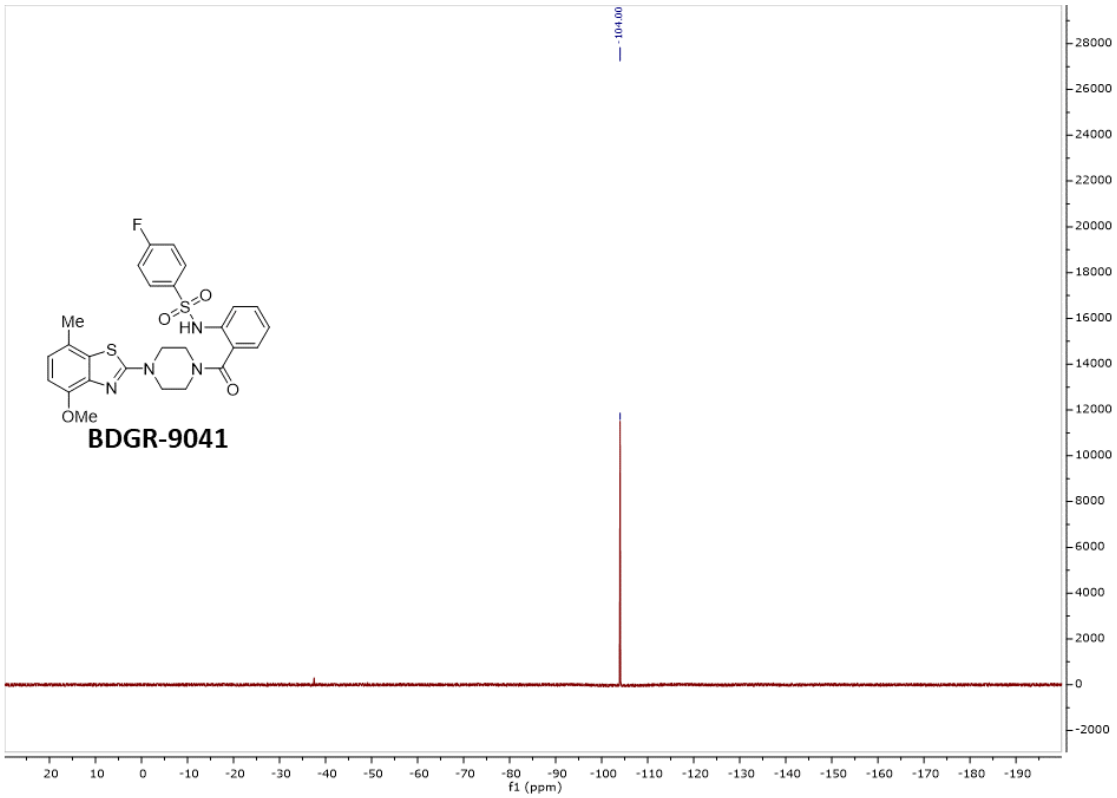

Me
S
N
N
N
O
OMe
BDGR-9039
167.74
167.71
153.57
148.99
148.38
141.40
137.35
132.17
124.99
124.45
122.90
122.53
107.62
56.08
48.76
46.77
20.61
f1 (ppm)

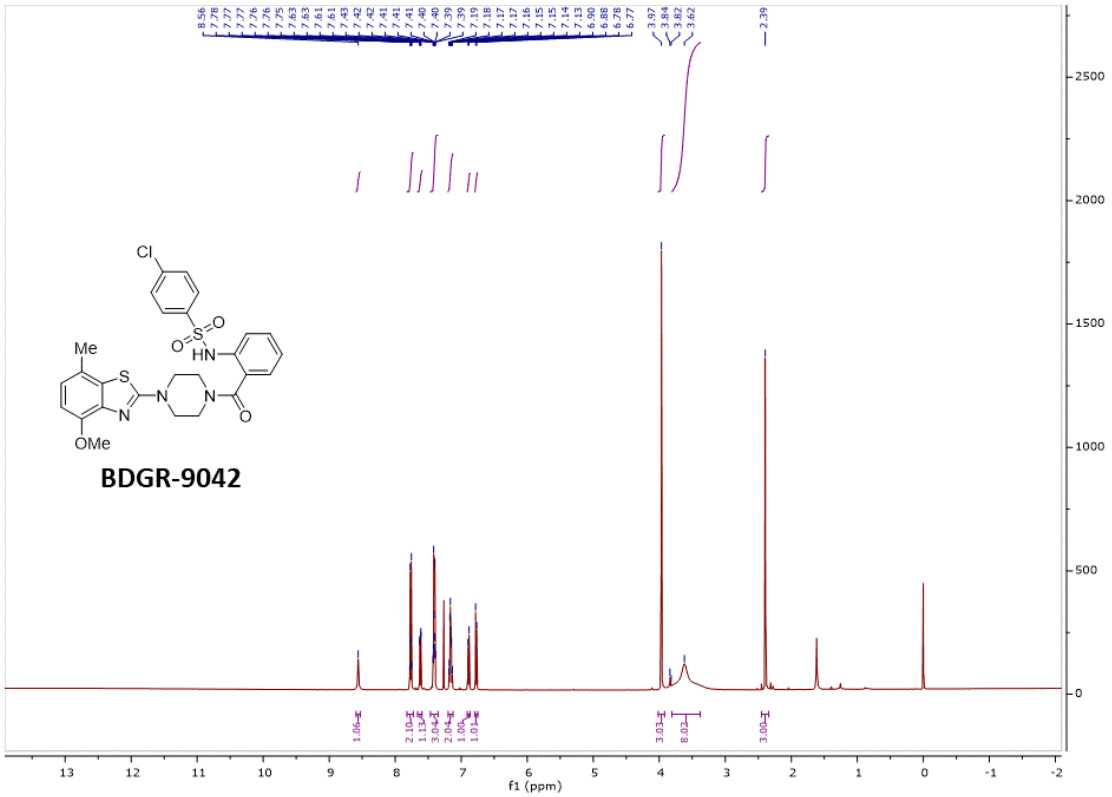

Me
S
N
N
O
OMe
BDGR-9040
7.47
7.47
7.46
7.46
7.46
7.45
7.45
7.45
7.44
7.43
7.43
7.43
7.42
6.88
6.86
6.77
6.75
3.96
3.81
3.71
3.61
2.38
5.00
1.00
1.03
3.02
8.12
3.00
f1 (ppm)

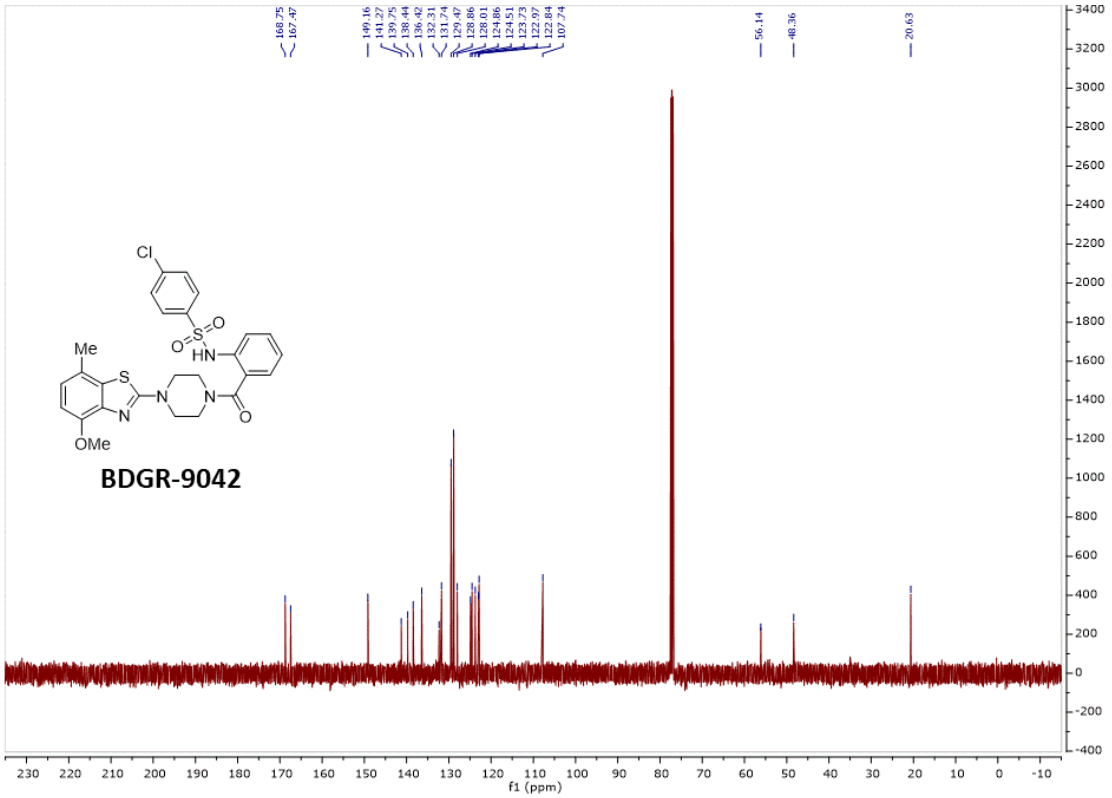

170.76
167.72
149.04
141.32
135.32
132.21
130.23
128.78
127.22
122.92
122.65
107.65
56.09
48.58
20.61
Me
S
N
N
N
O
OMe
BDGR-9040
f1 (ppm)

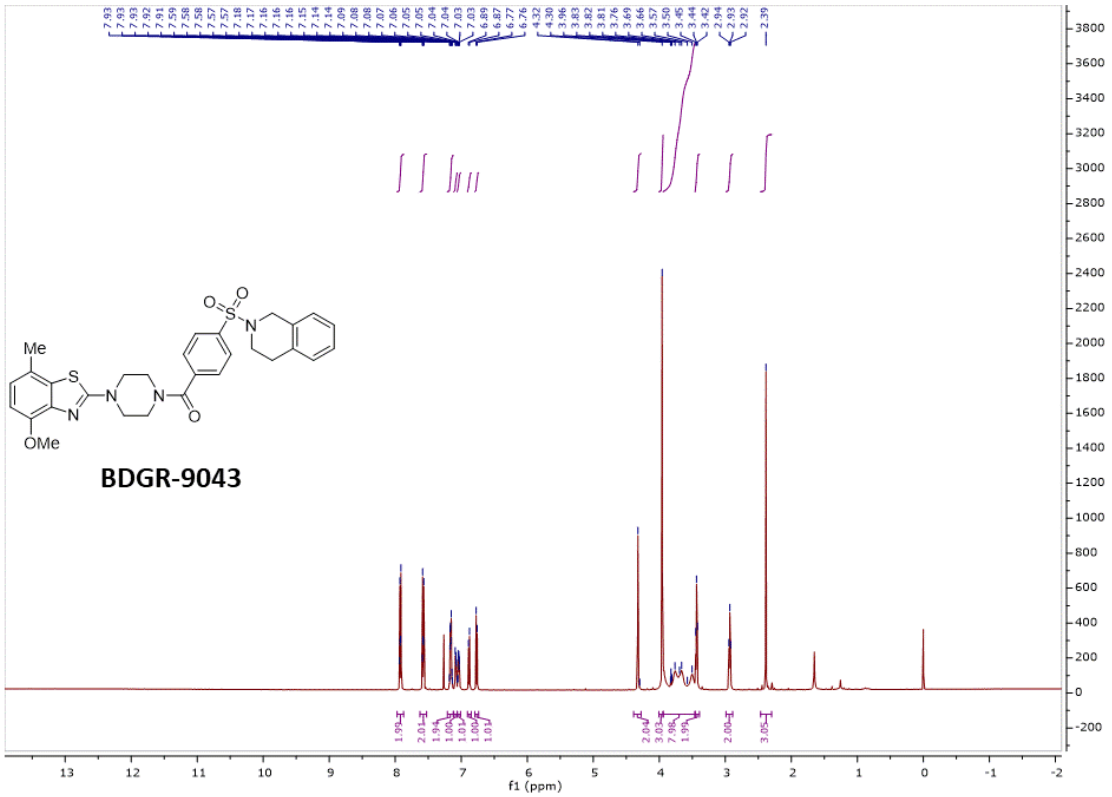

F
O
S
O
HN
Me
S
N
N
N
O
OMe
BDGR-9041
2.39
f1 (ppm)

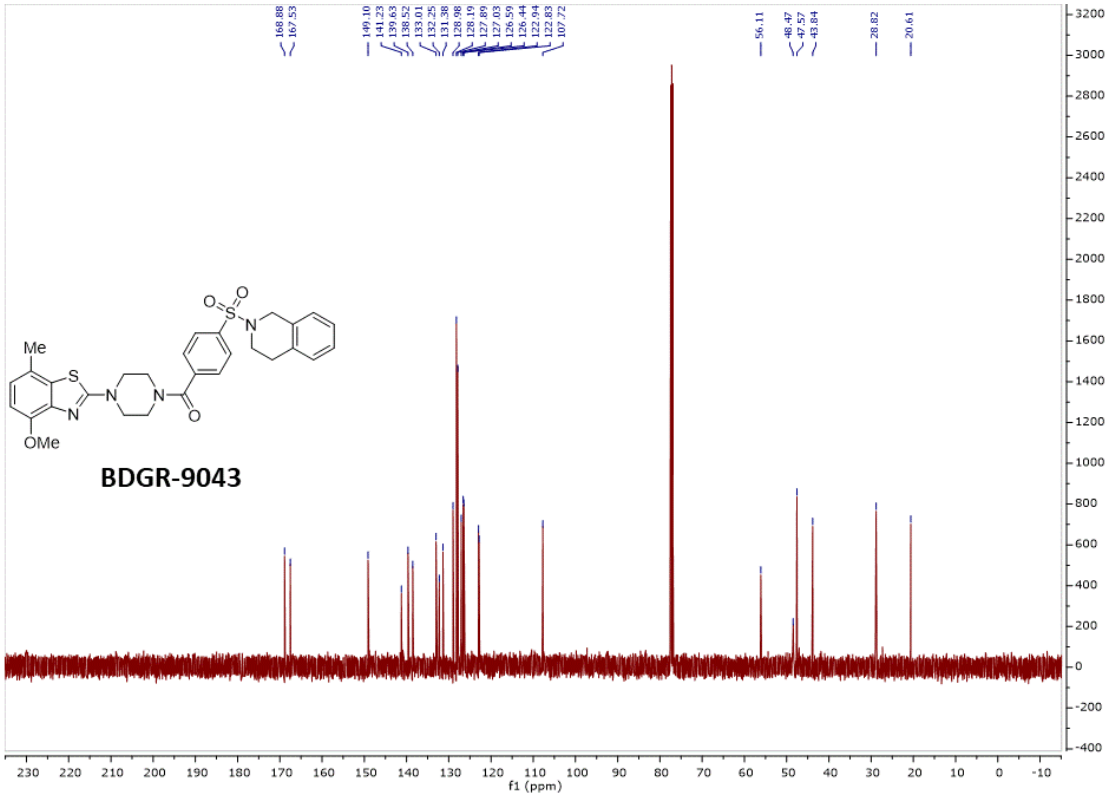

160.85
167.47
166.32
164.28
149.15
141.26
136.47
136.03
136.00
132.29
131.68
130.22
130.14
127.99
124.84
124.40
123.34
122.97
122.84
116.54
116.36
107.75
56.13
48.35
20.62
F
O
S
O
HN
Me
S
N
N
N
O
OMe
BDGR-9041
f1 (ppm)

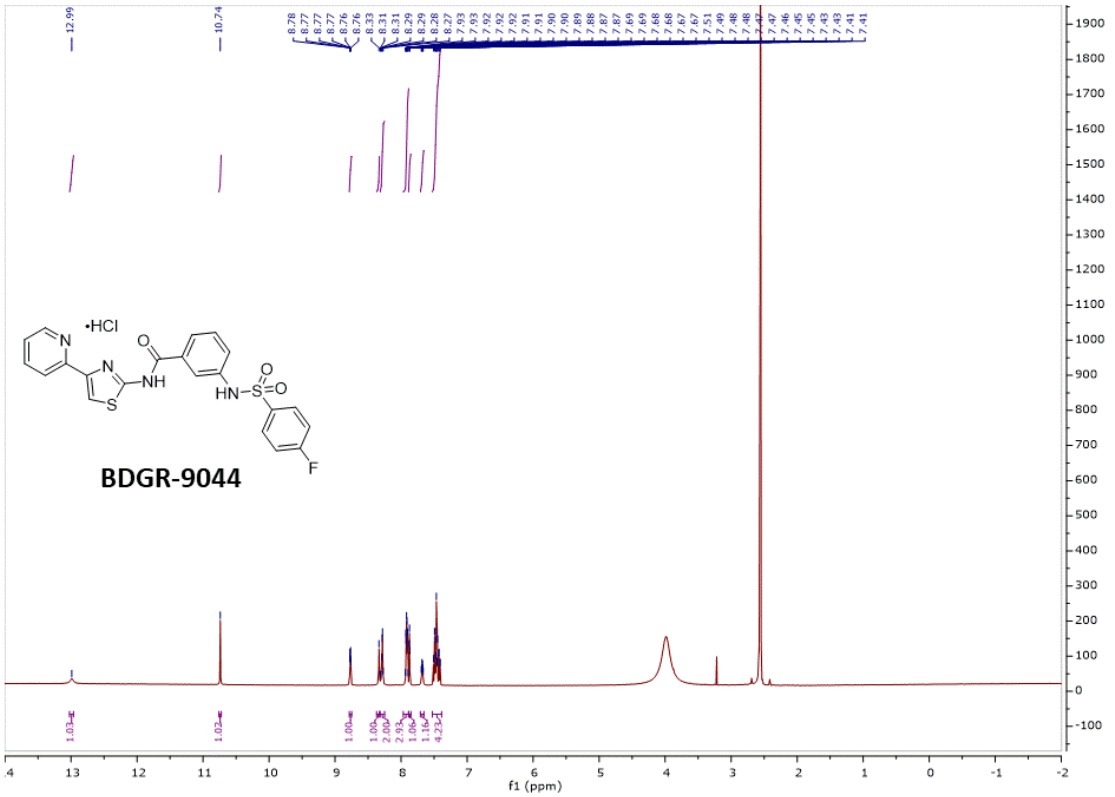

-104.00
F
O
S
O
HN
Me
S
N
N
N
O
OMe
BDGR-9041
f1 (ppm)

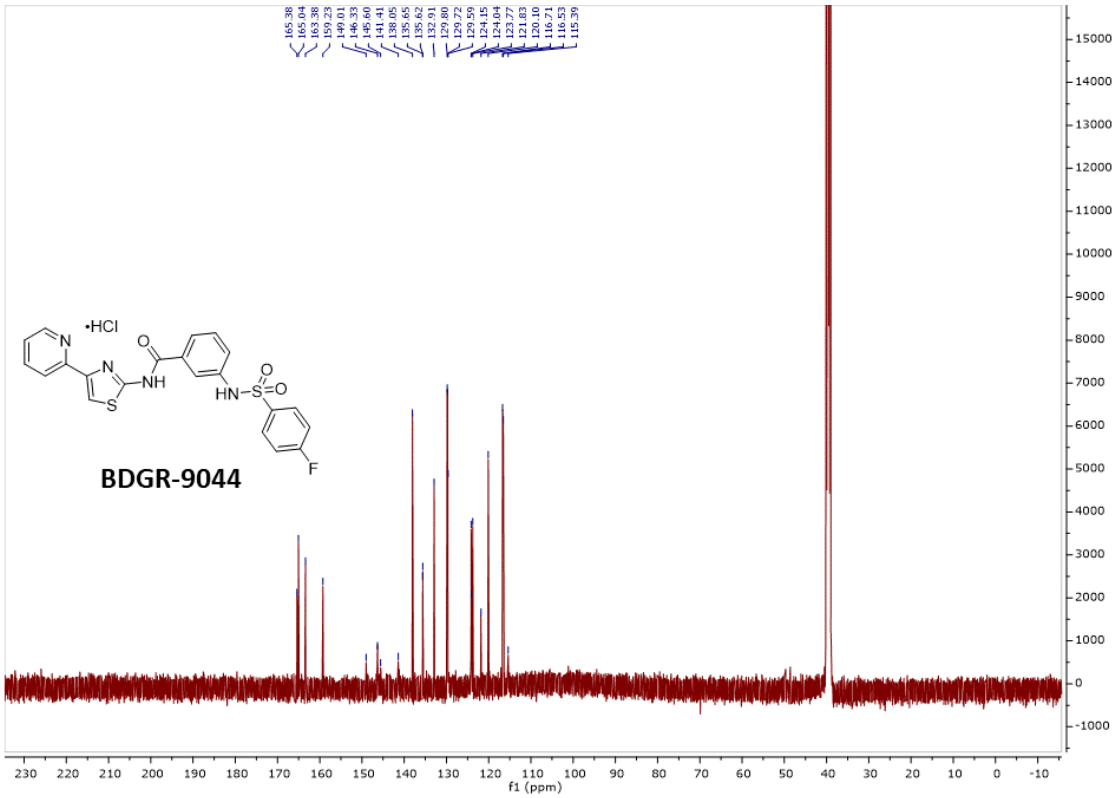

Cl
O
S
O
HN
Me
S
N
N
N
O
OMe
BDGR-9042
f1 (ppm)

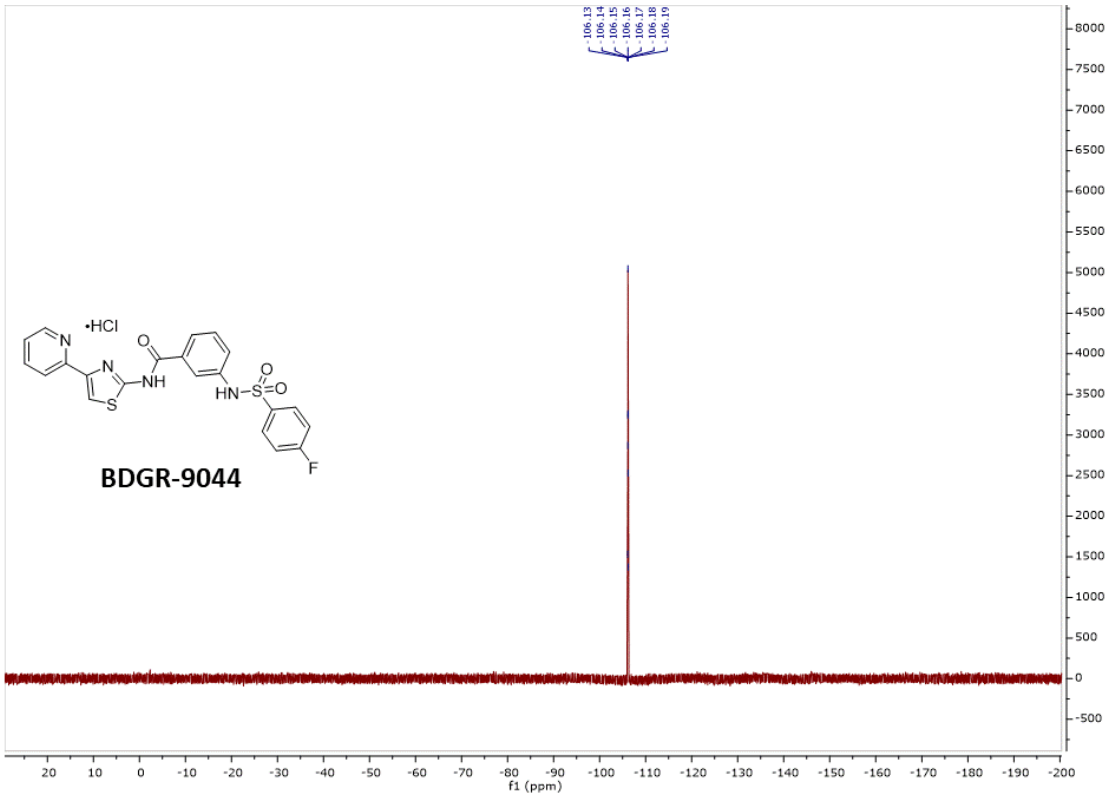

Cl
O
S
O
HN
Me
S
N
N
N
O
OMe
BDGR-9042
f1 (ppm)

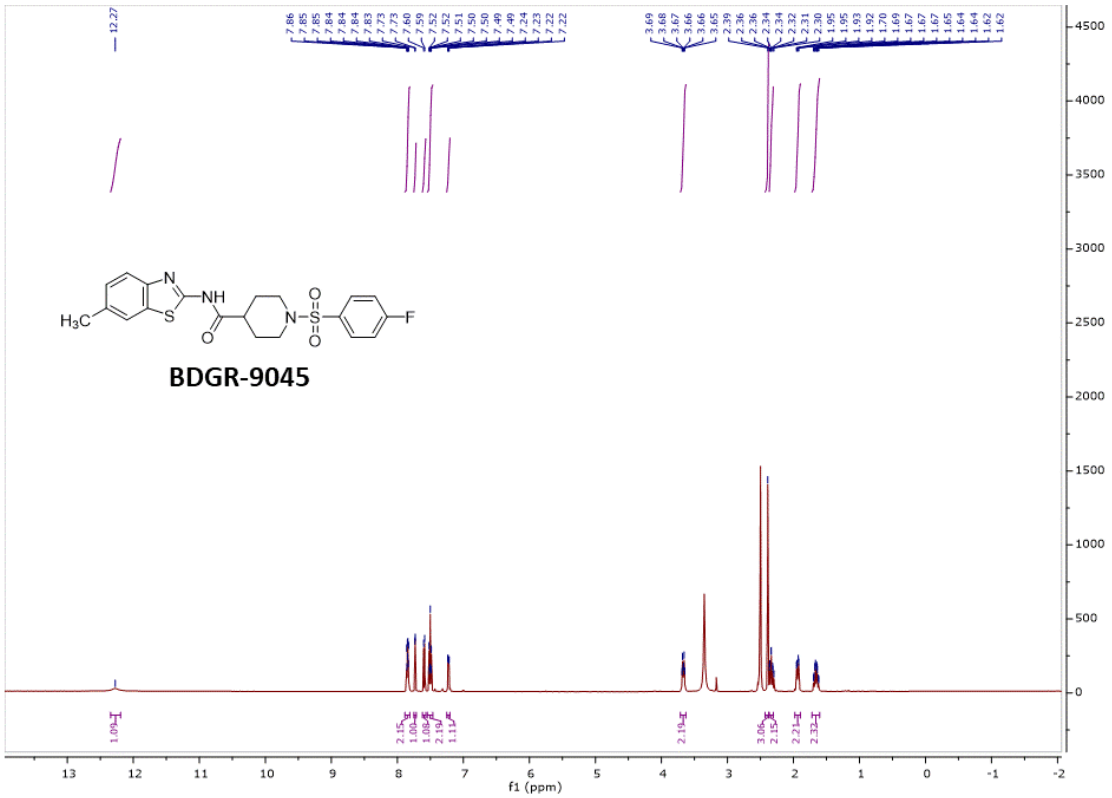

BDGR-9043
f1 (ppm)

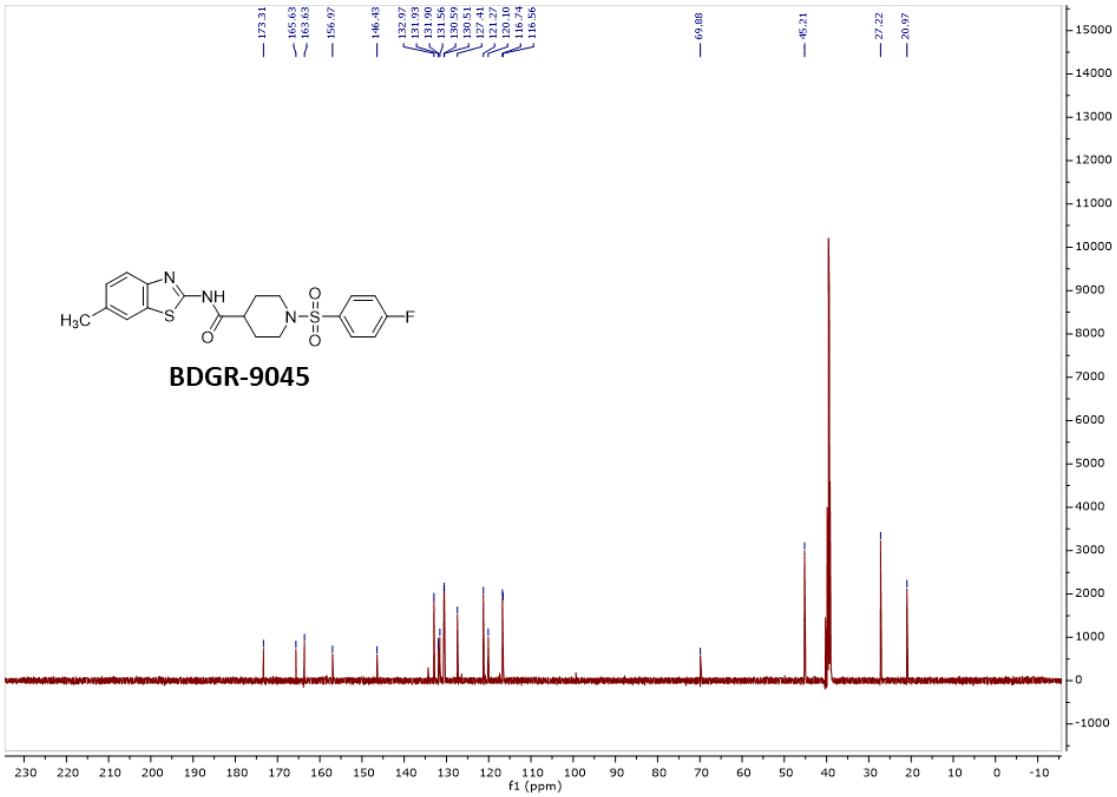

BDGR-9043
f1 (ppm)

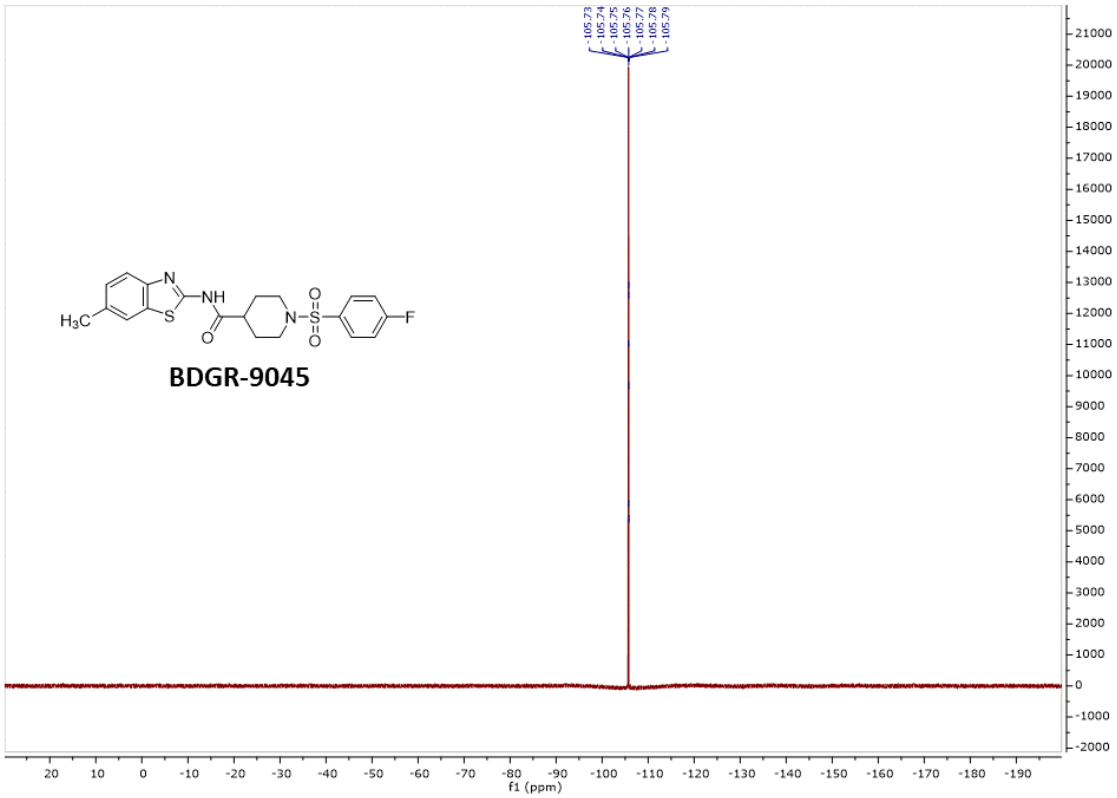

12.99
10.74
8.78
8.77
8.77
8.77
8.76
8.76
8.33
8.31
8.31
8.29
8.29
8.28
8.27
7.93
7.93
7.92
7.92
7.92
7.92
7.91
7.91
7.90
7.90
7.89
7.88
7.87
7.87
7.69
7.69
7.68
7.68
7.67
7.67
7.51
7.49
7.48
7.48
7.47
7.46
7.45
7.45
7.43
7.43
7.41
7.41
•HCl
N
O
NH
HN
S
O
O
F
BDGR-9044
1.03
1.02
1.00
1.00
2.00
2.05
1.06
1.16
4.23
f1 (ppm)

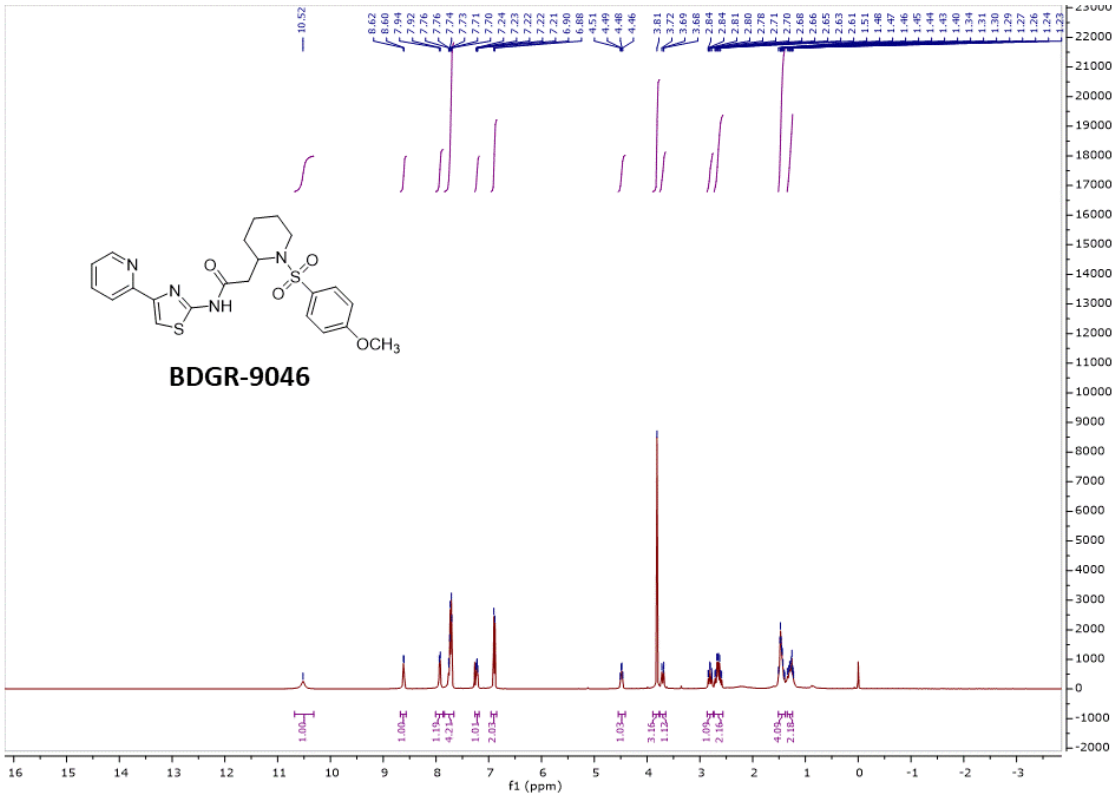

165.38
165.04
163.38
159.23
149.01
146.33
145.60
141.41
138.05
135.65
135.62
132.91
129.80
129.72
129.59
129.15
124.04
123.77
121.83
120.10
116.71
116.53
115.39
•HCl
N
O
NH
HN
S
O
O
F
BDGR-9044
f1 (ppm)

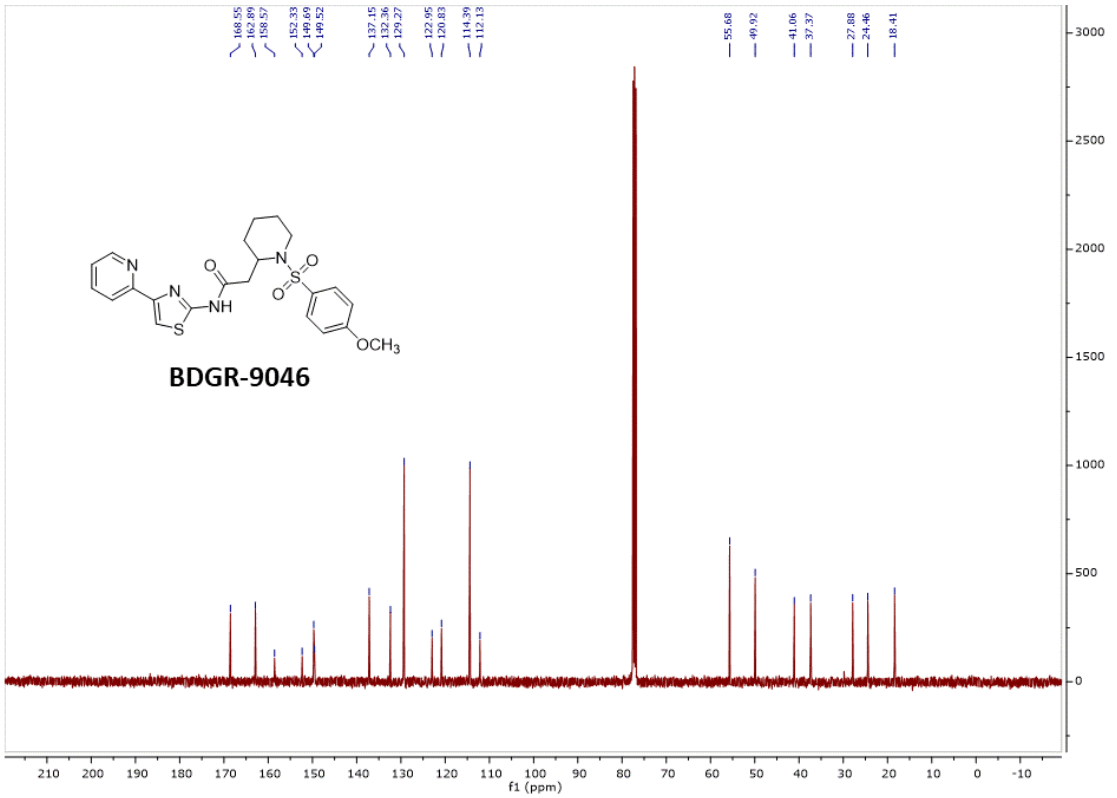

•HCl
BDGR-9044
f1 (ppm)

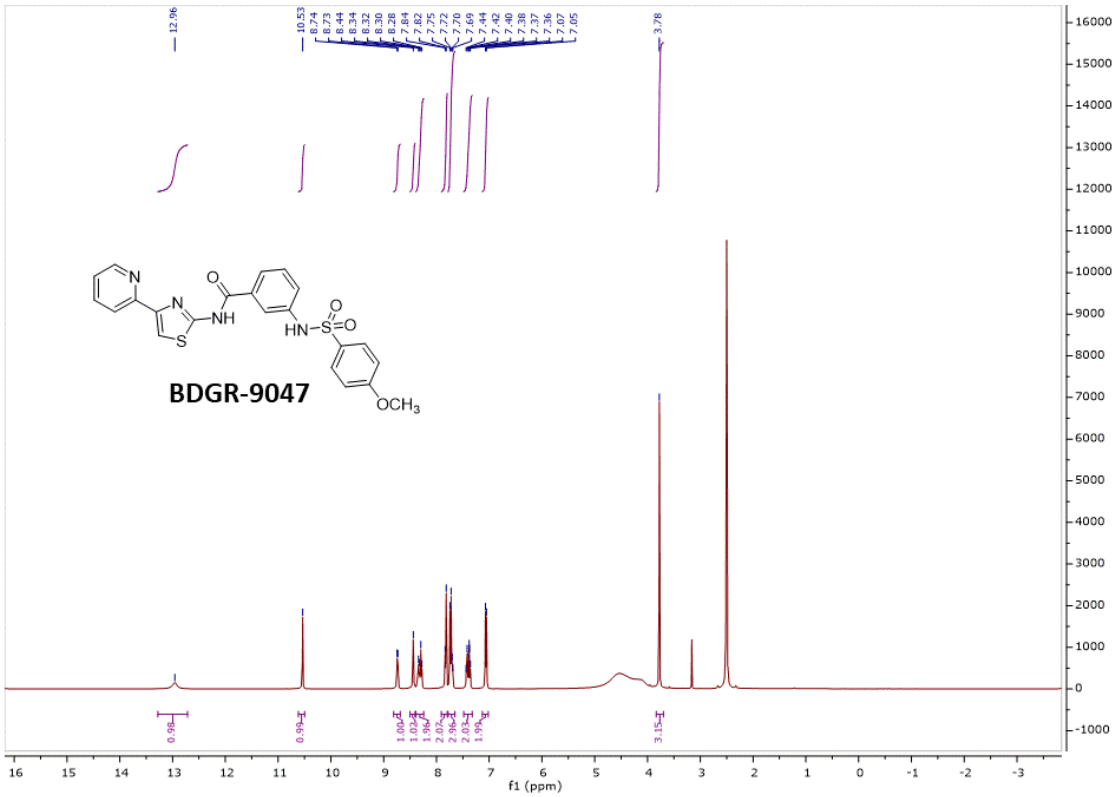

BDGR-9045
f1 (ppm)

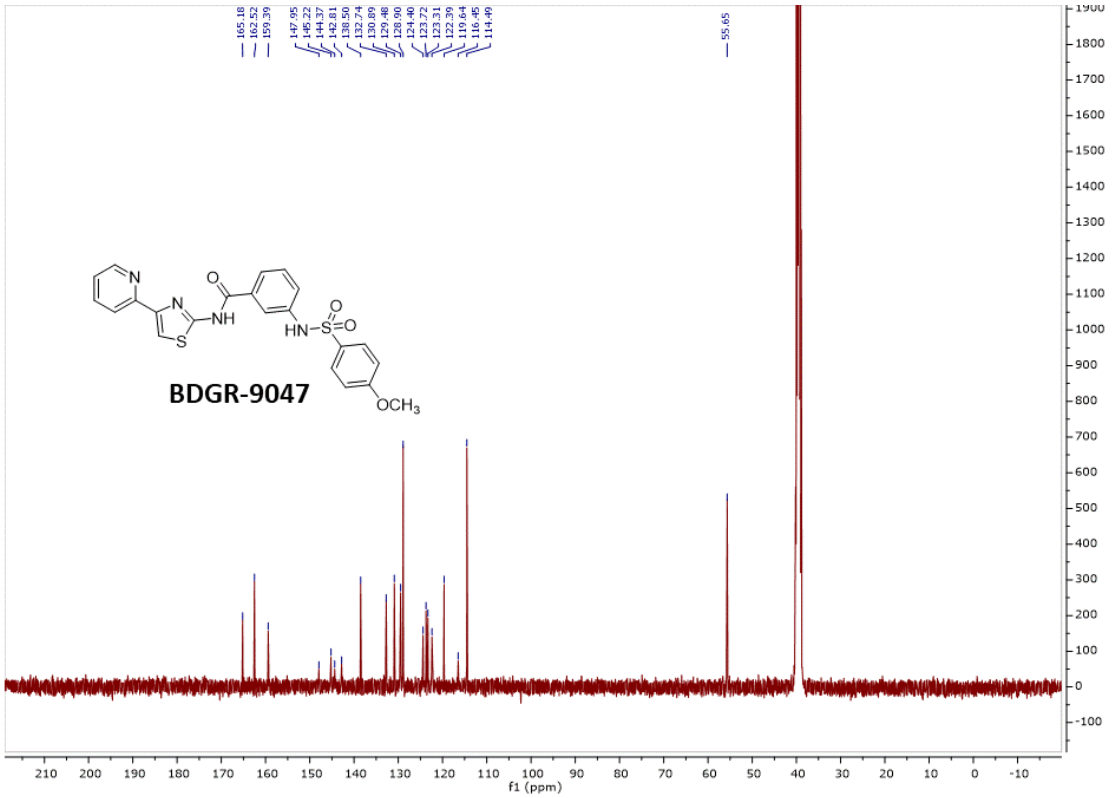

173.31
165.63
163.63
156.97
146.43
132.97
131.93
131.90
131.56
130.59
130.51
127.41
121.27
120.10
116.74
116.56
69.88
45.21
27.22
20.97
BDGR-9045
f1 (ppm)

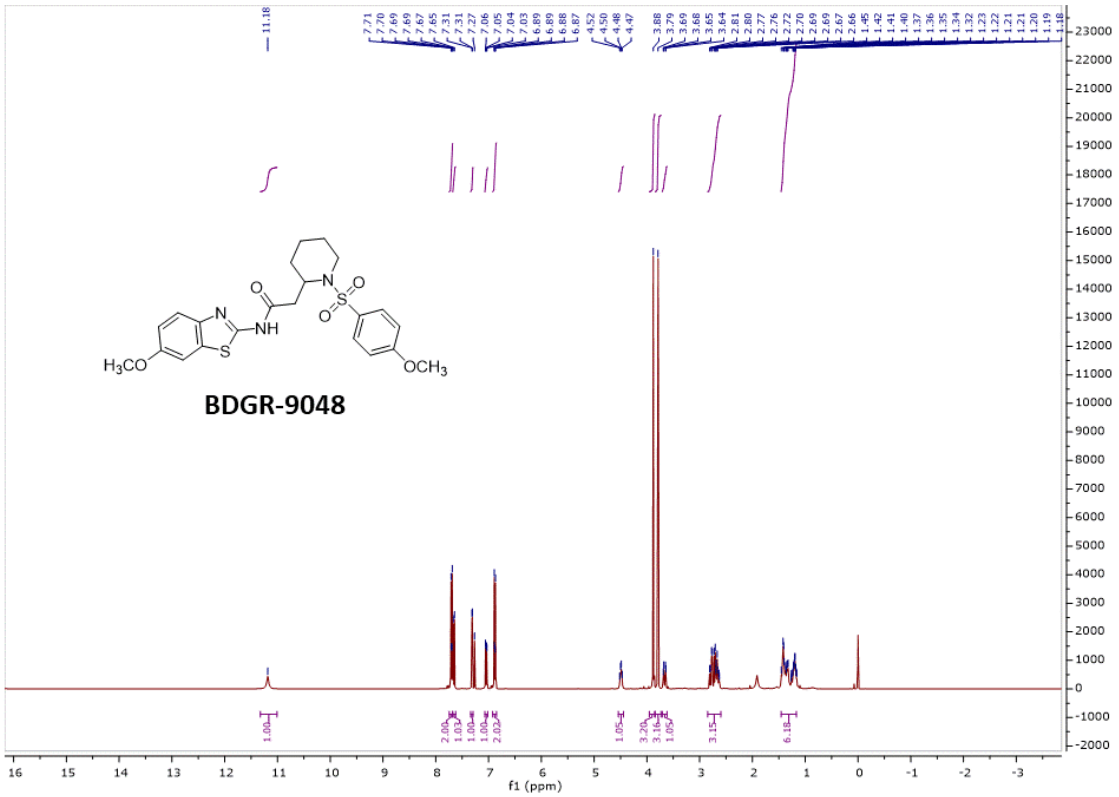

-105.73
-105.74
-105.75
-105.76
-105.77
-105.78
-105.79
BDGR-9045
f1 (ppm)

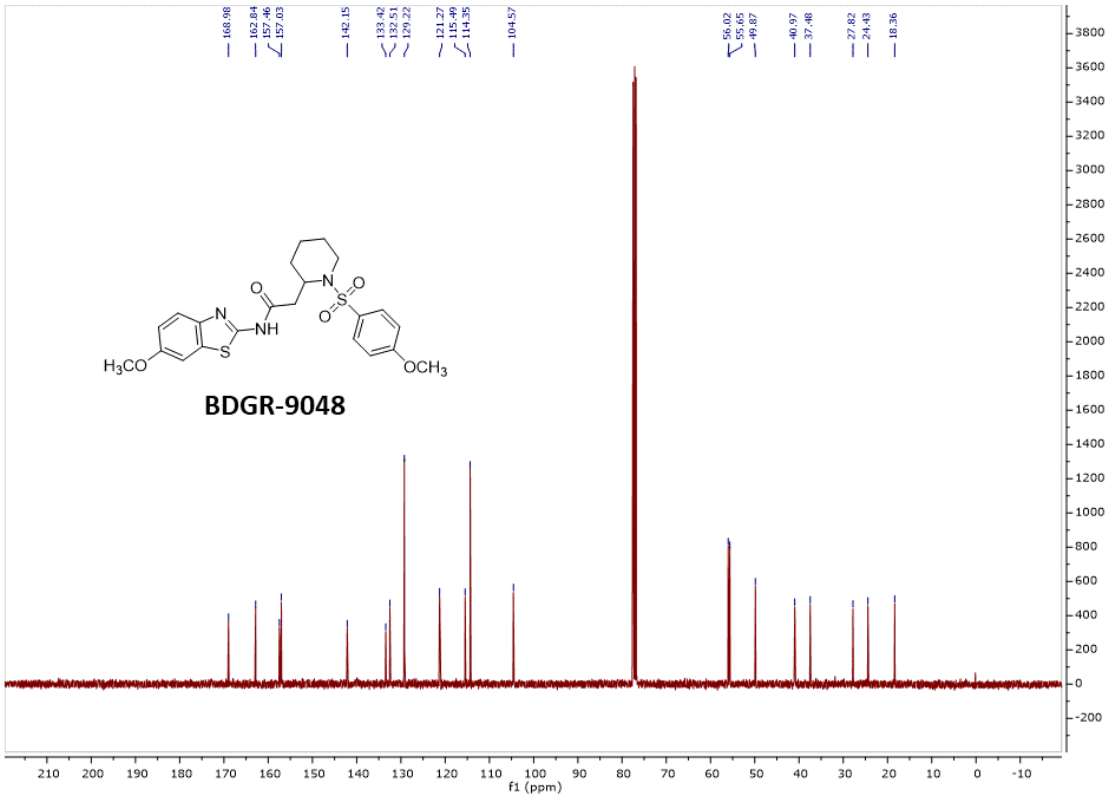

BDGR-9046
f1 (ppm)

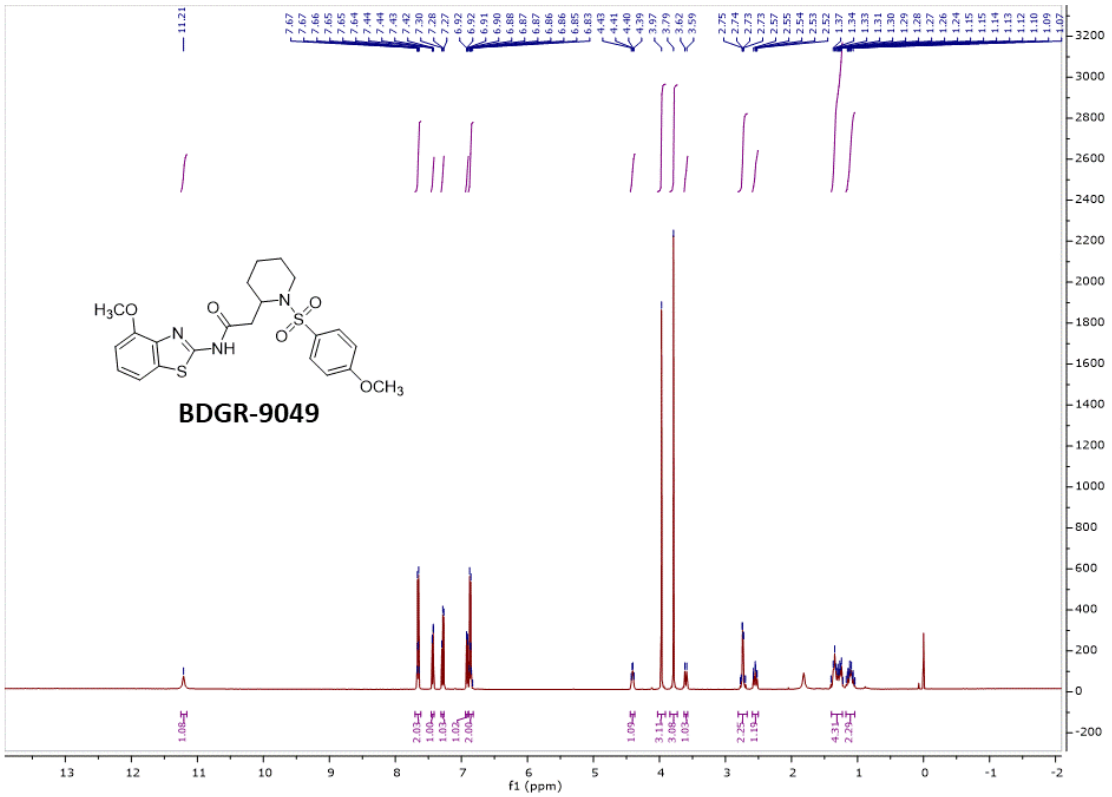

BDGR-9046
f1 (ppm)

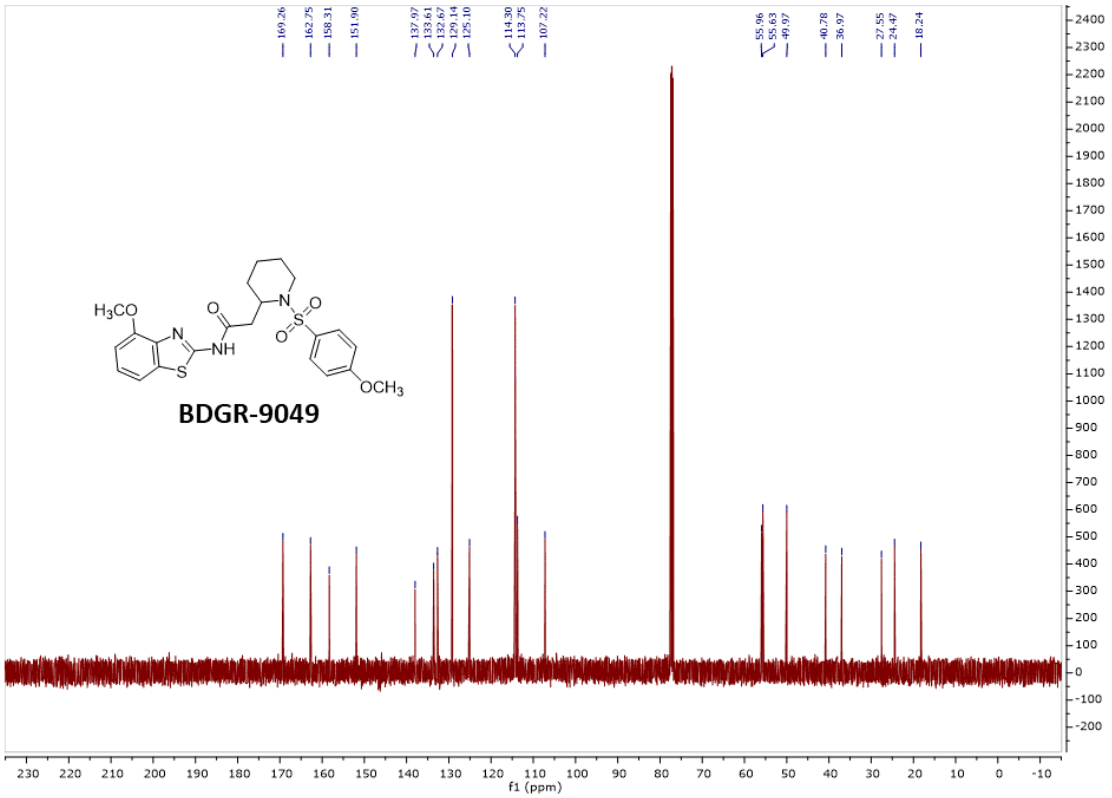

12.96
10.53
8.74
8.73
8.44
8.34
8.32
8.30
8.28
7.84
7.82
7.75
7.72
7.70
7.66
7.44
7.42
7.40
7.38
7.37
7.36
7.07
7.05
3.78
BDGR-9047
f1 (ppm)

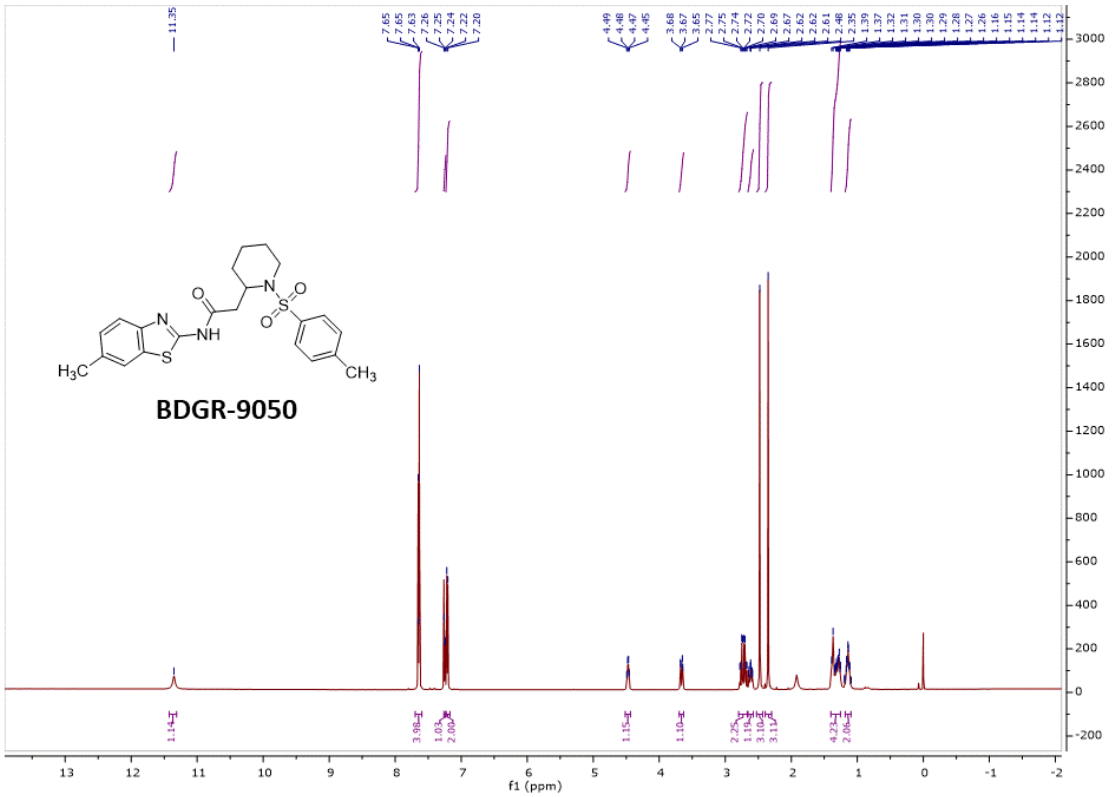

165.18
162.52
159.39
147.95
145.22
144.37
142.81
138.50
132.74
130.89
129.48
128.90
124.40
123.72
123.31
122.39
119.64
116.45
114.49
55.65
BDGR-9047
f1 (ppm)

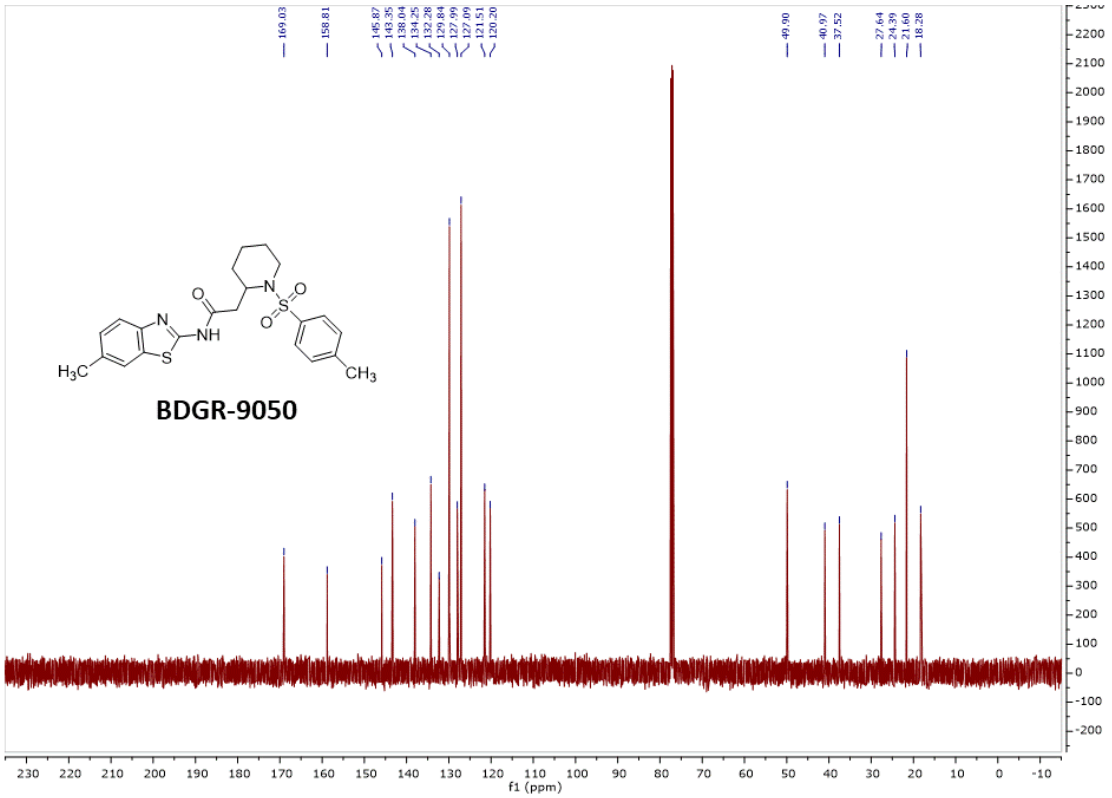

BDGR-9048
f1 (ppm)

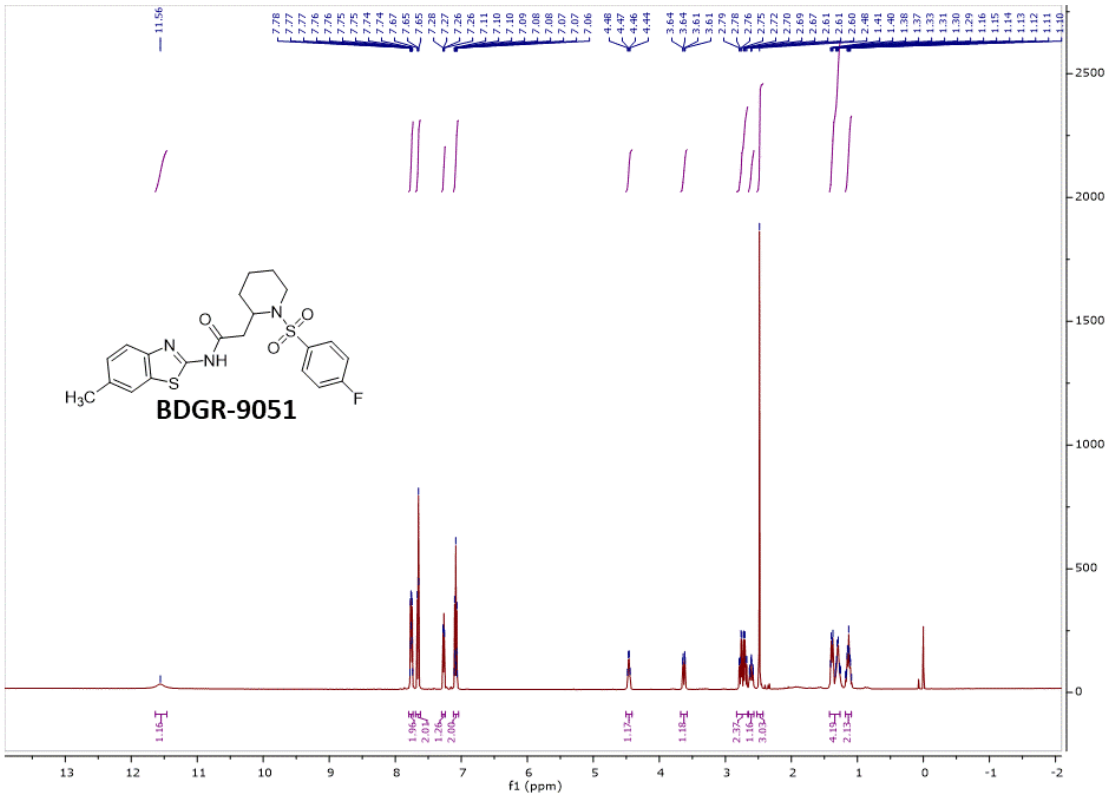

BDGR-9048
f1 (ppm)

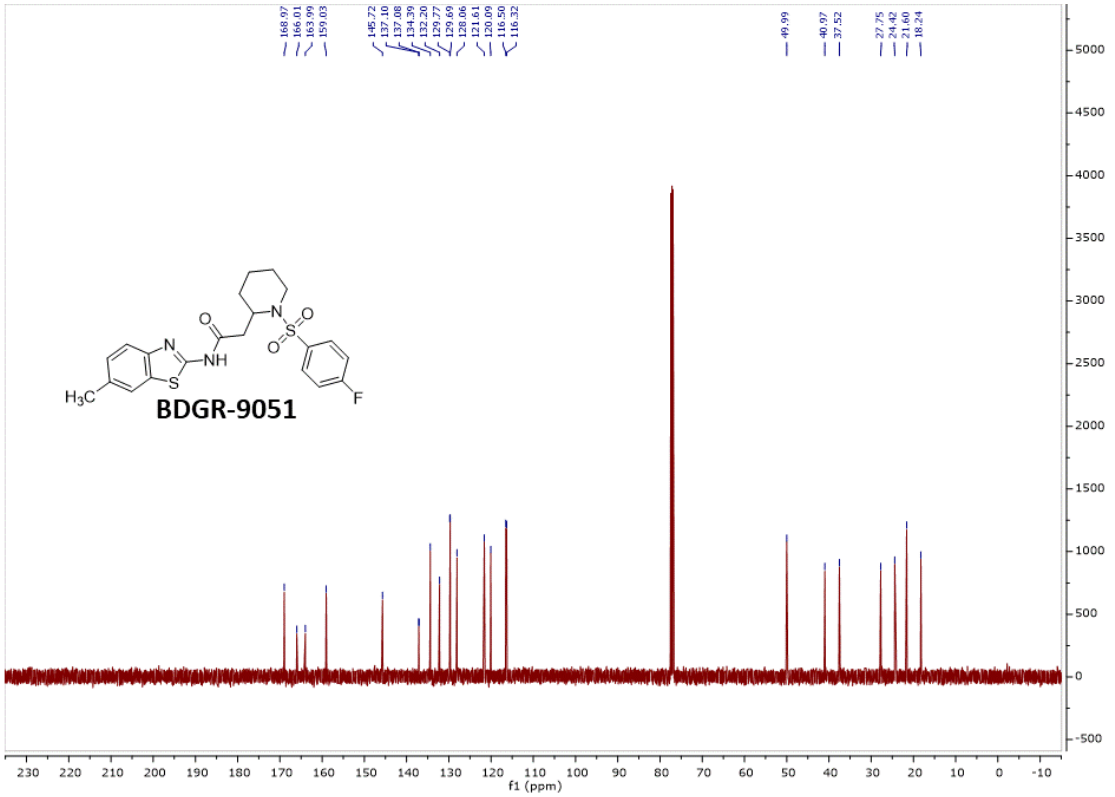

BDGR-9049
f1 (ppm)

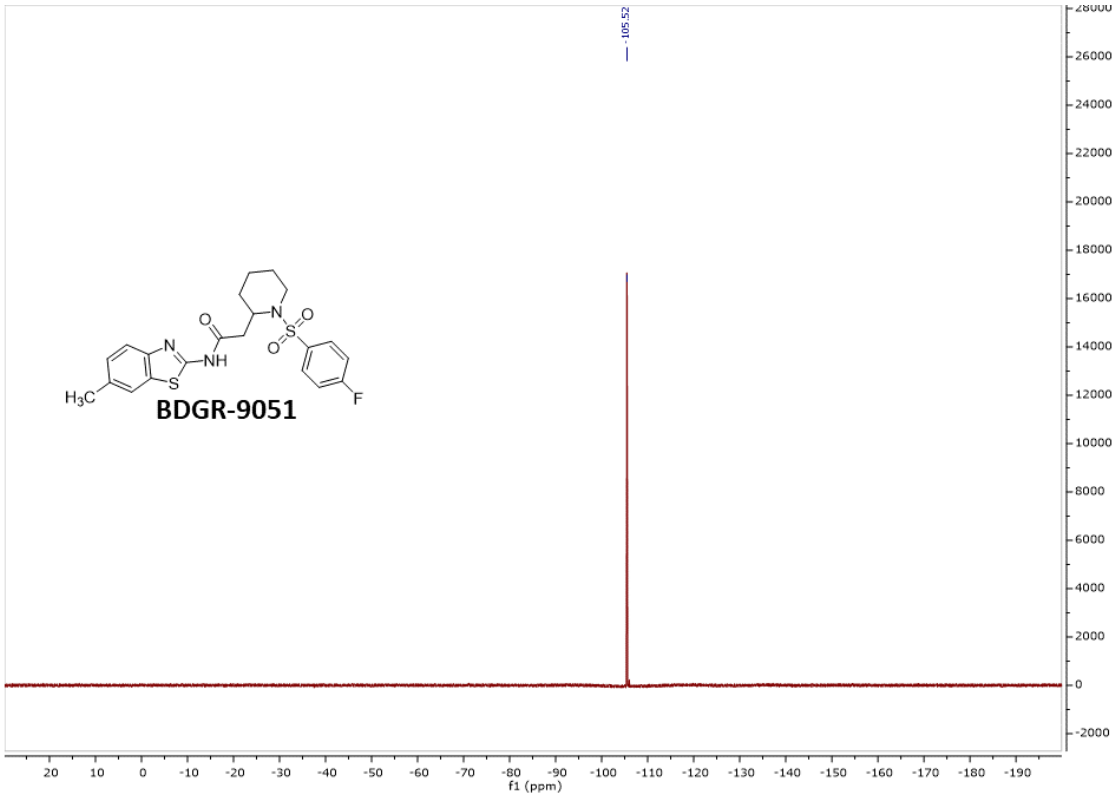

BDGR-9049
f1 (ppm)

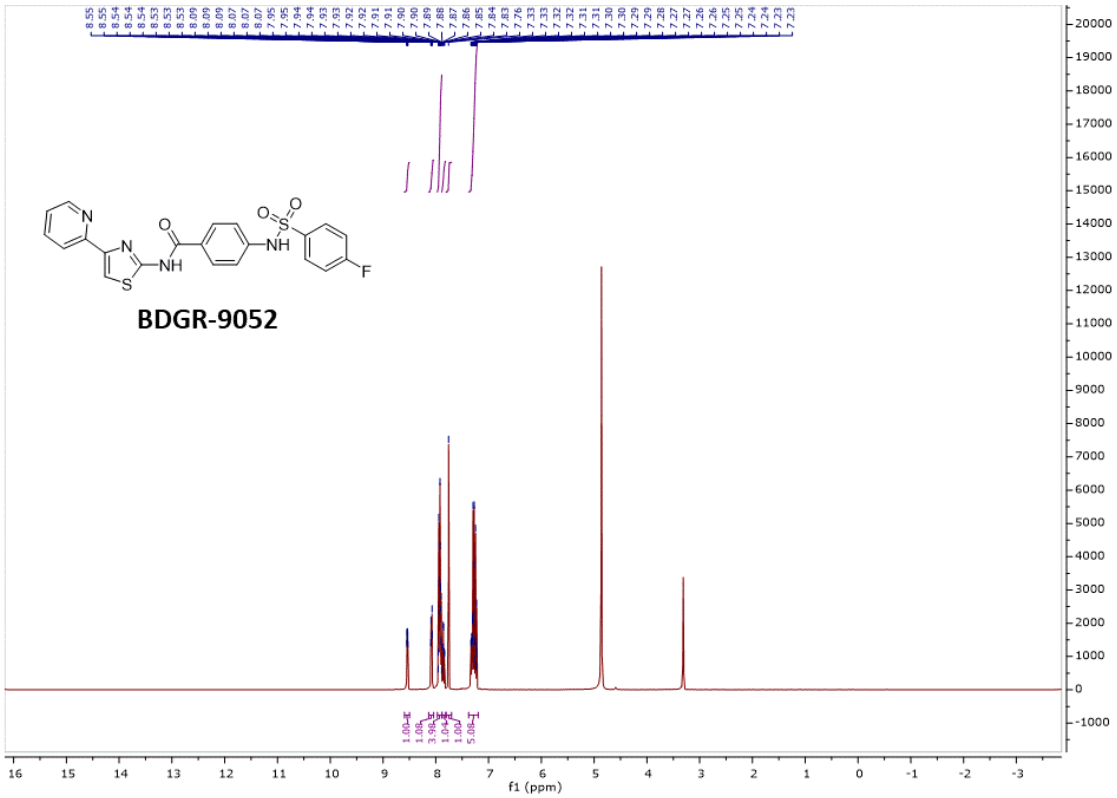

BDGR-9050
f1 (ppm)

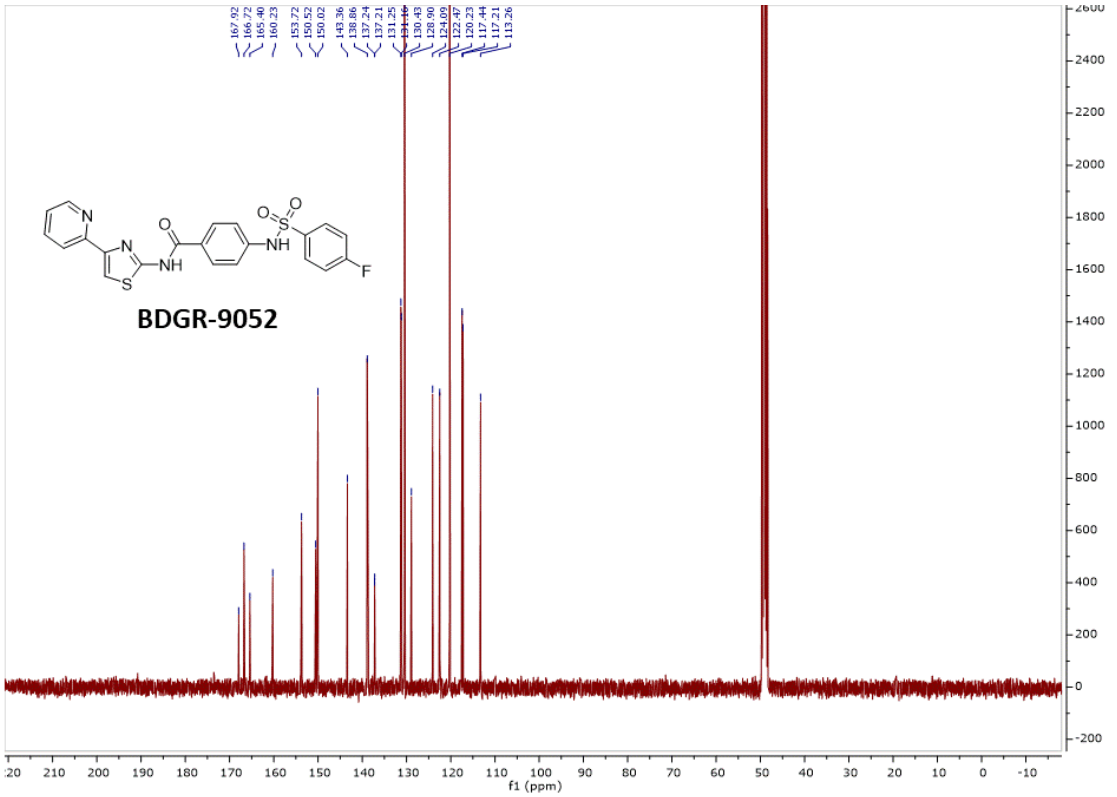

BDGR-9050
f1 (ppm)

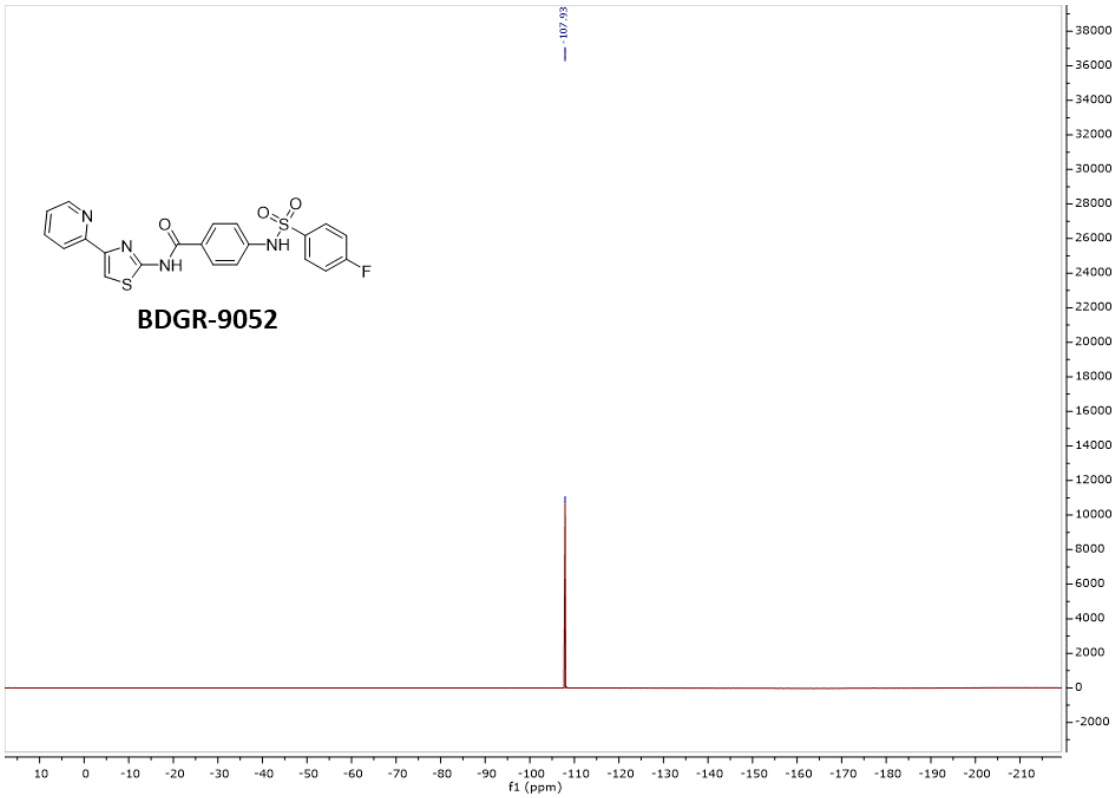

BDGR-9051
f1 (ppm)

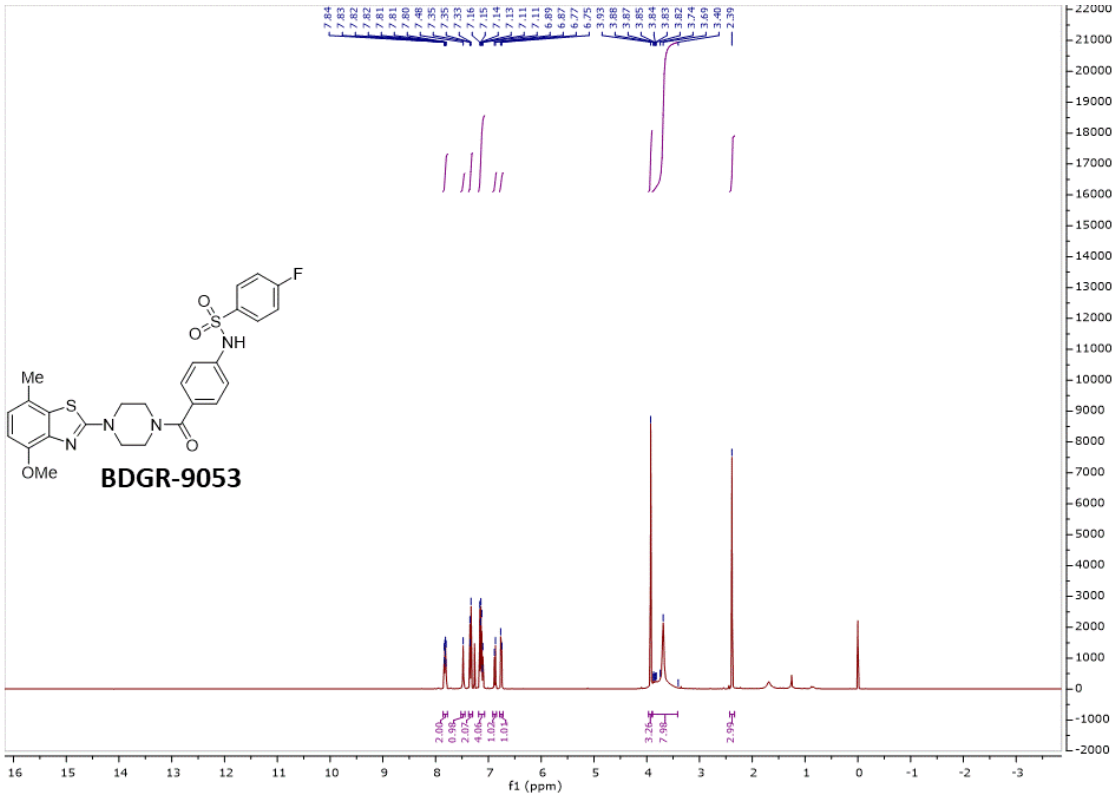

BDGR-9051
f1 (ppm)

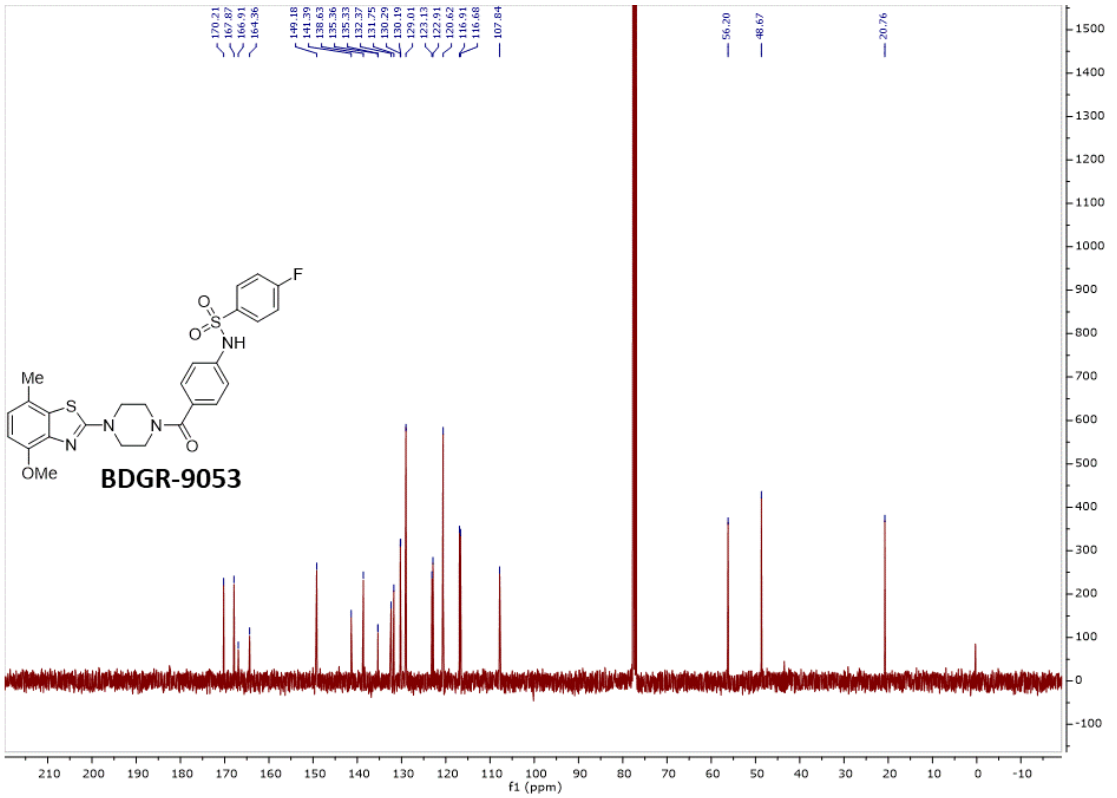

-105.52
BDGR-9051
f1 (ppm)

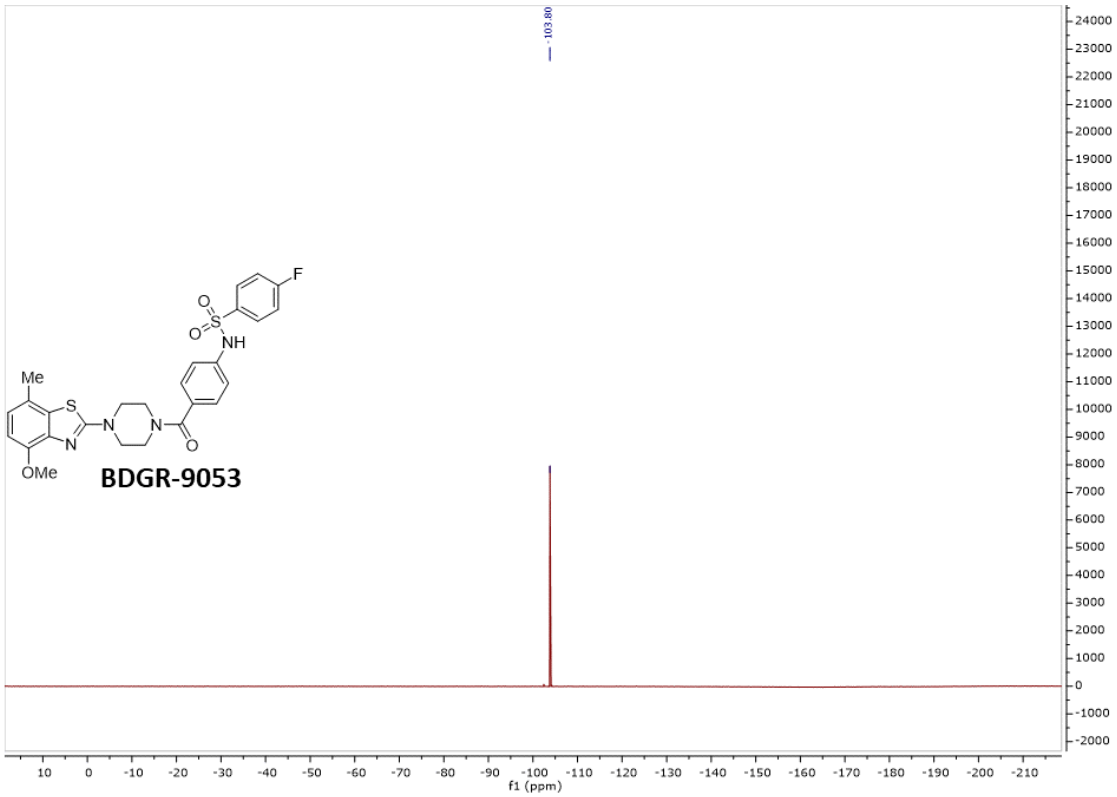

BDGR-9052
f1 (ppm)

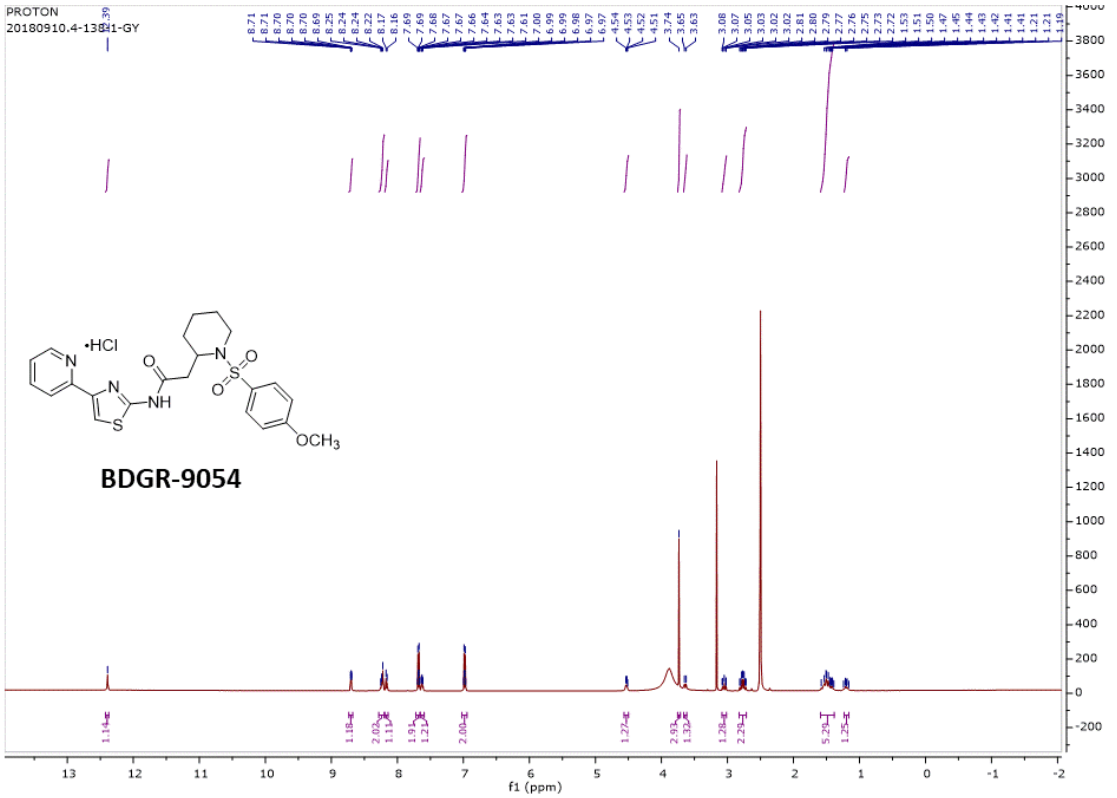

167.92
166.72
165.40
160.23
153.72
150.52
150.02
143.36
138.86
137.24
137.21
131.25
131.16
130.43
128.90
124.09
122.47
120.23
117.44
117.21
113.26
BDGR-9052
f1 (ppm)

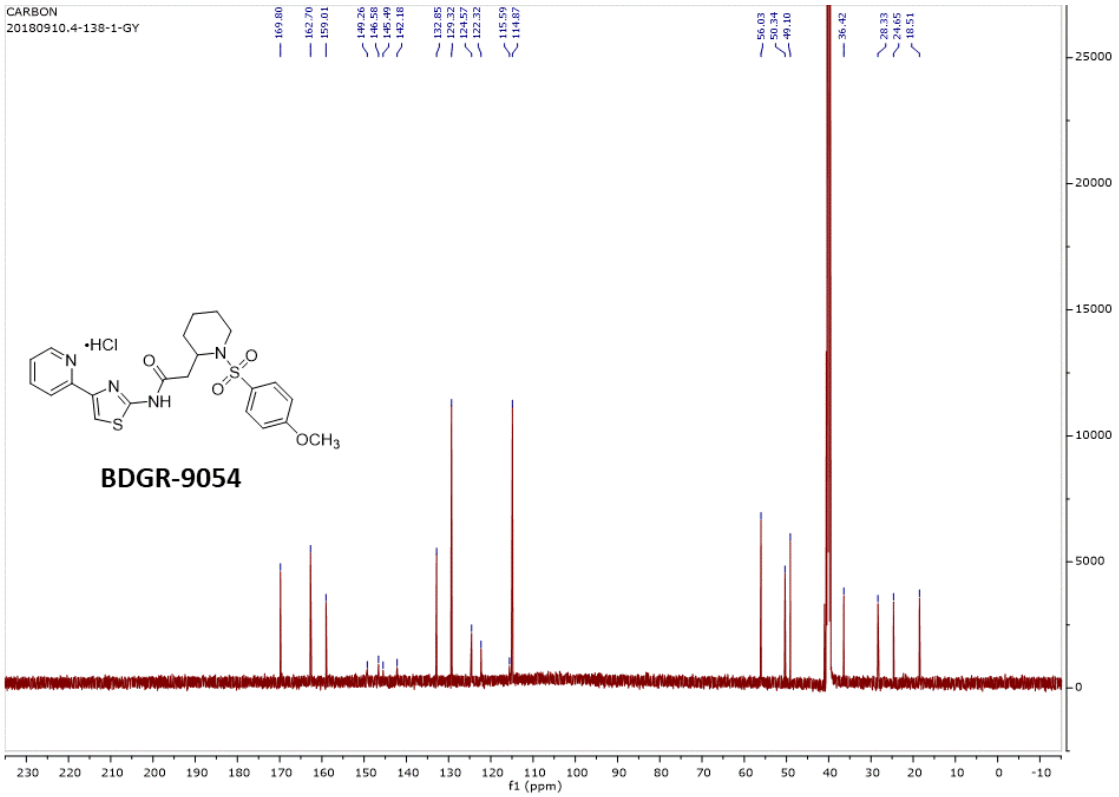

-107.93
BDGR-9052
f1 (ppm)

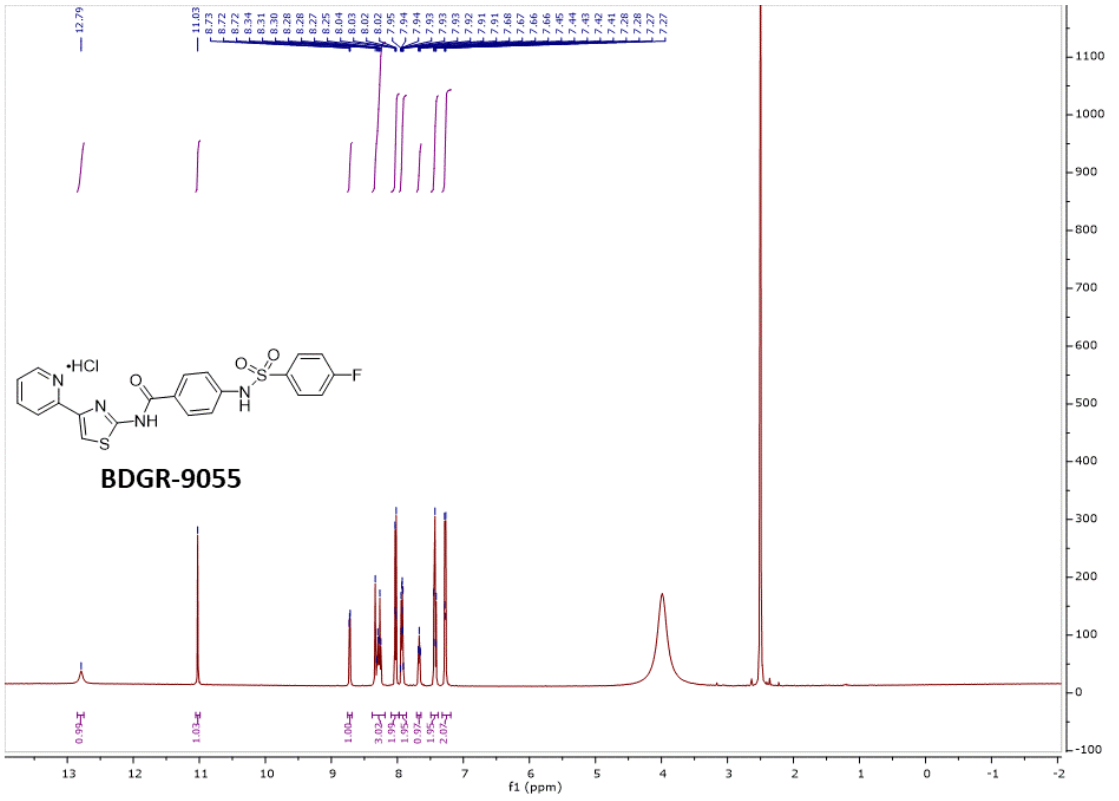

BDGR-9053
f1 (ppm)

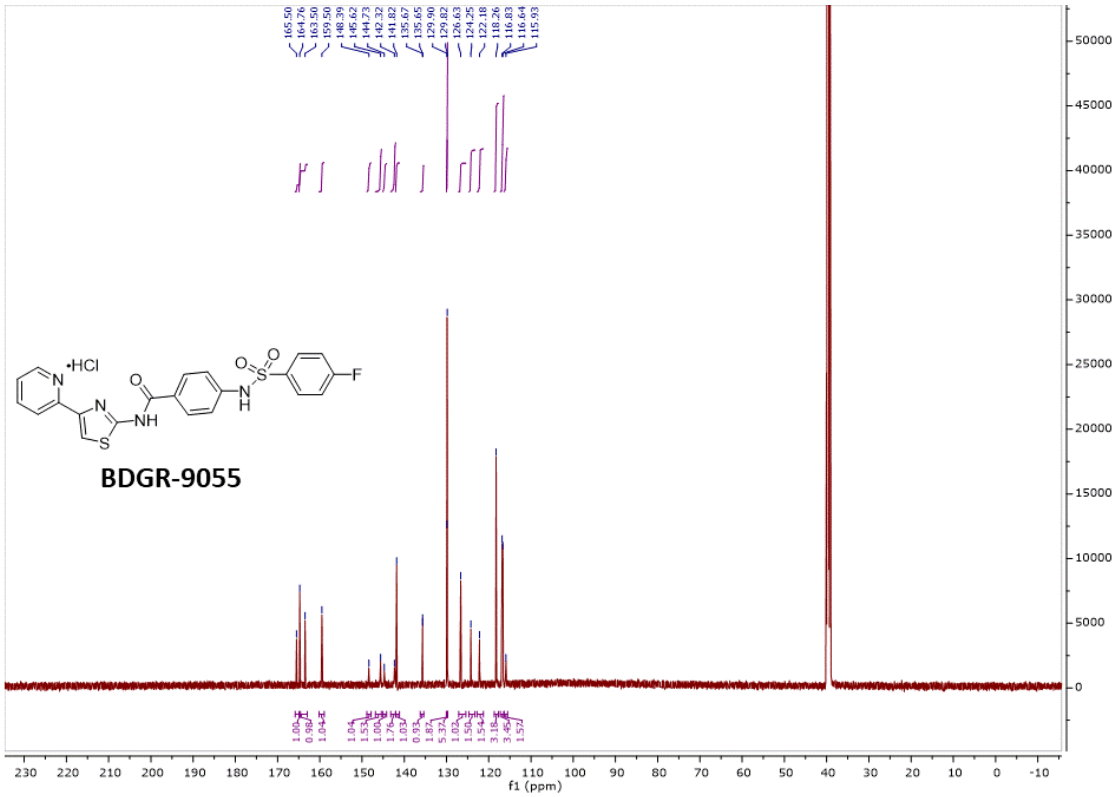

BDGR-9053
f1 (ppm)

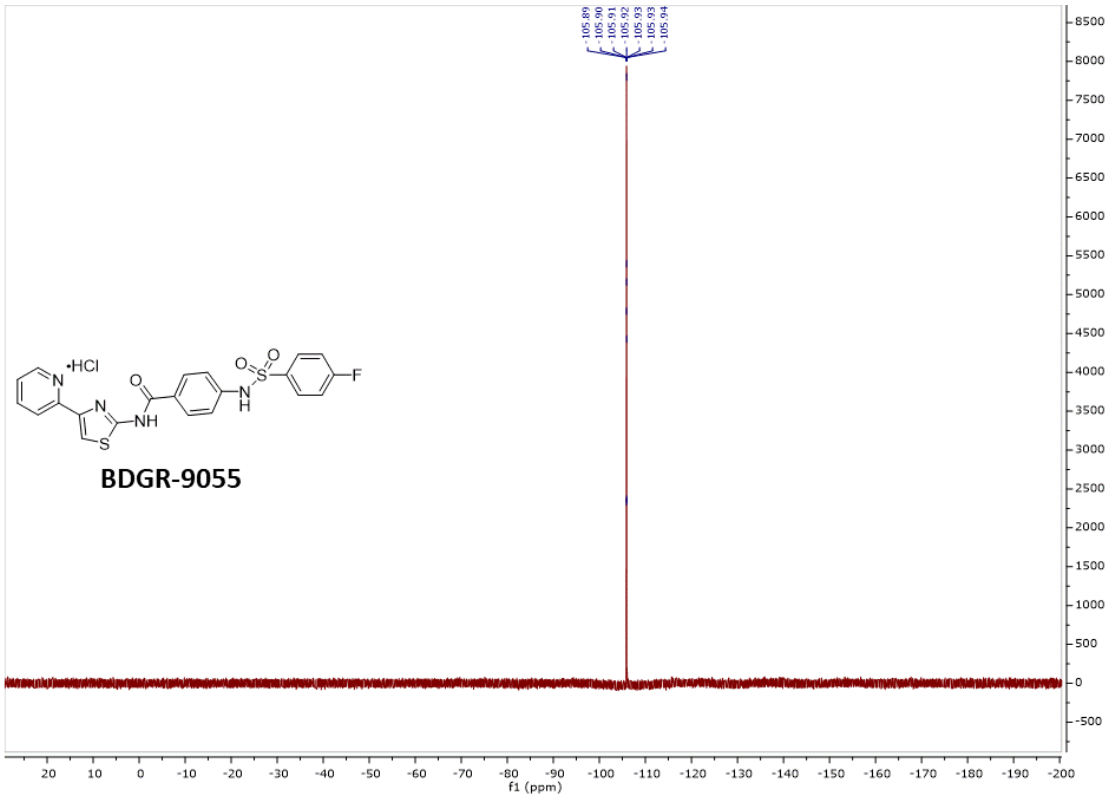

-103.80
F
O
S
O
NH
Me
S
N
N
N
O
OMe
BDGR-9053
f1 (ppm)

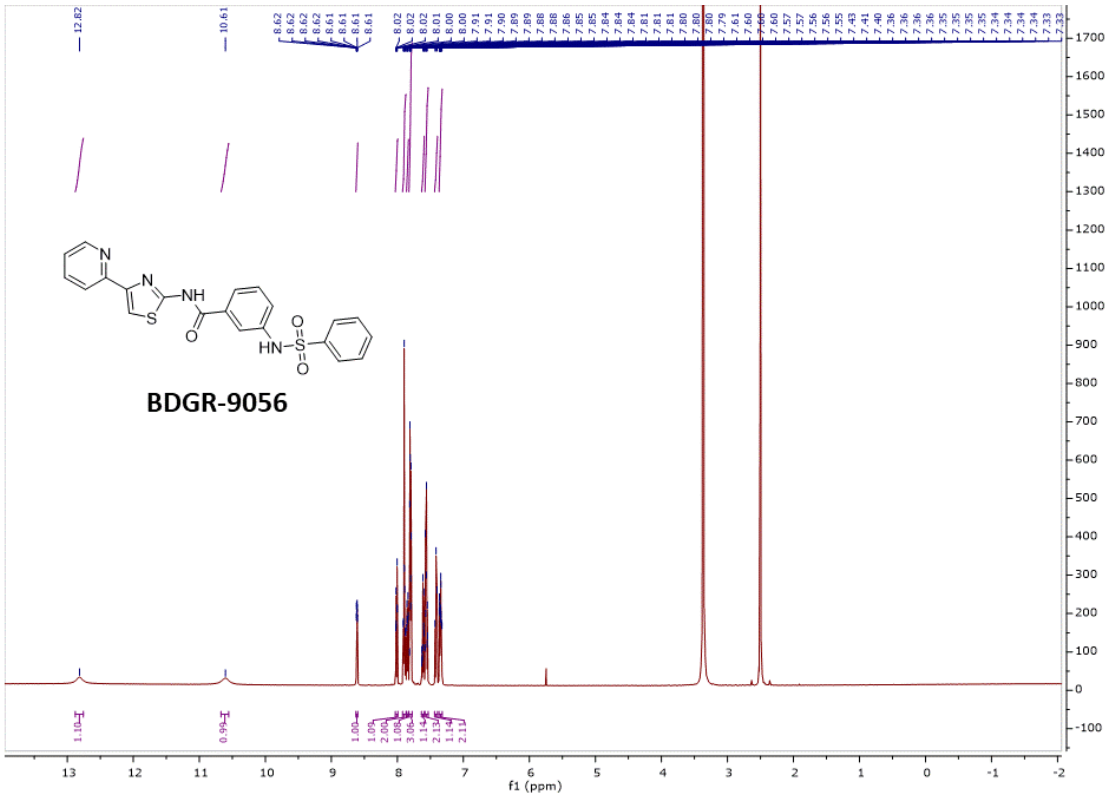

PROTON
20180910.4-1381-GY
•HCl
N
N
S
NH
O
N
O
S
O
OCH3
BDGR-9054
f1 (ppm)

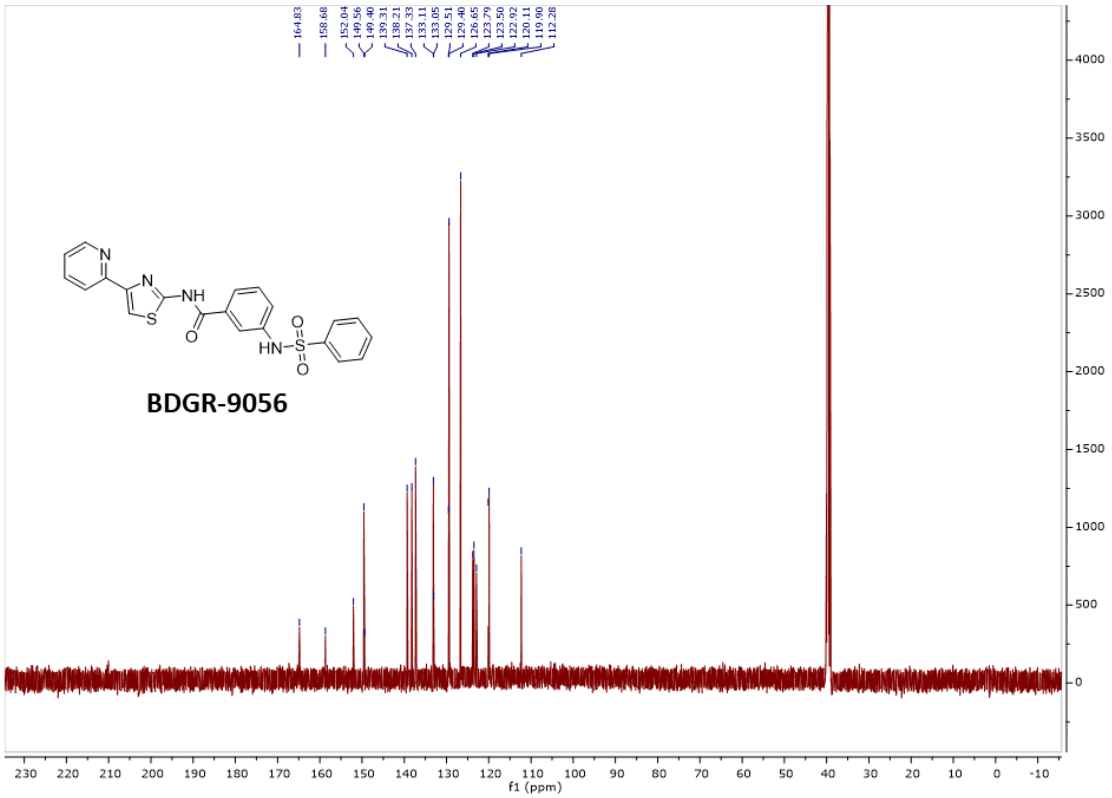

CARBON
20180910.4-138-1-GY
169.80
162.70
159.01
149.26
146.58
145.49
142.18
132.85
129.32
124.57
122.32
115.59
114.87
56.03
50.34
49.10
36.42
28.33
24.65
18.51
·HCl
NH
OCH3
BDGR-9054
f1 (ppm)

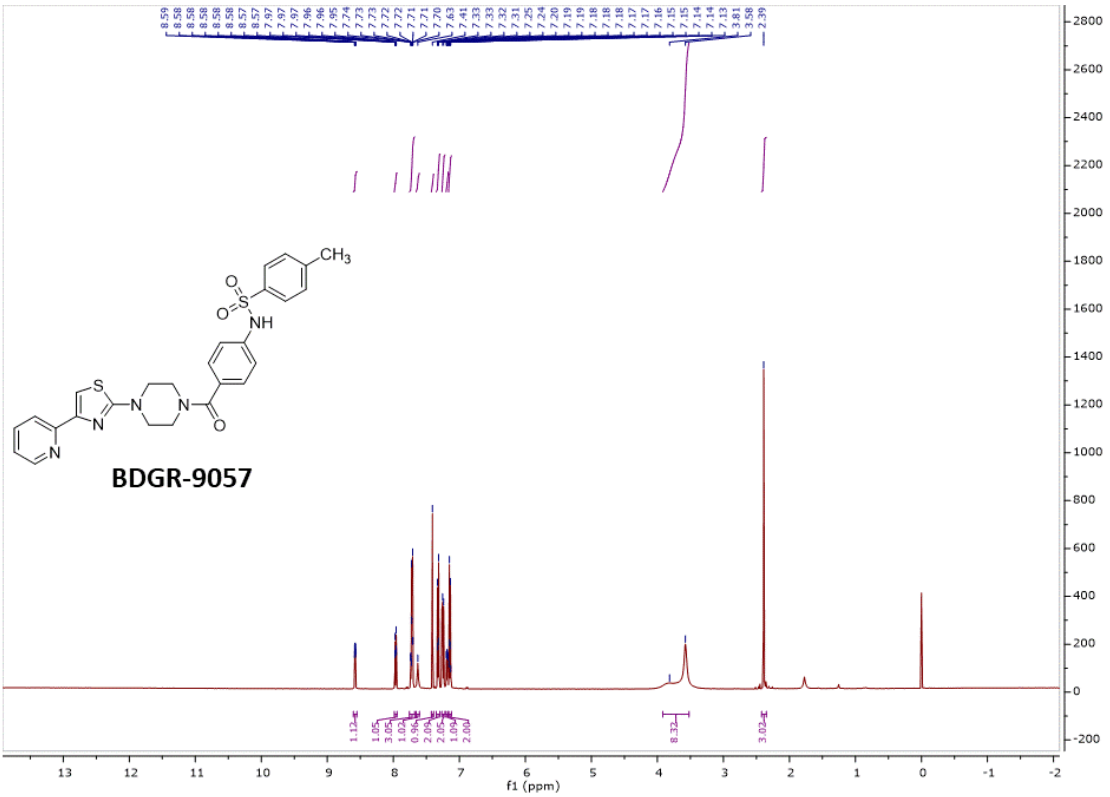

12.79
11.03
·HCl
NH
F
BDGR-9055
f1 (ppm)

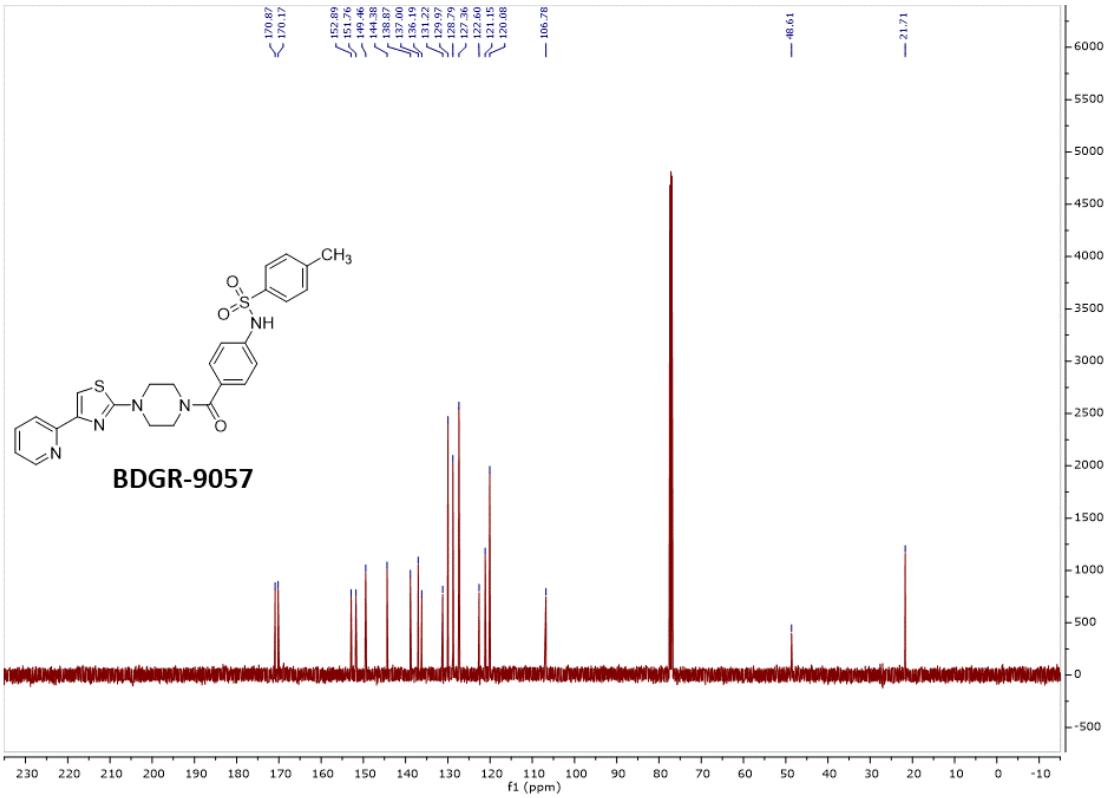

165.50
164.76
163.50
159.50
148.39
145.62
144.73
142.32
141.82
135.67
135.65
129.90
129.82
126.63
124.35
122.18
118.26
116.83
116.64
115.93
1.00
0.98
1.04
1.04
1.53
1.00
1.76
1.03
0.93
1.87
5.32
1.70
1.55
1.54
3.18
3.45
1.57
·HCl
BDGR-9055
f1 (ppm)

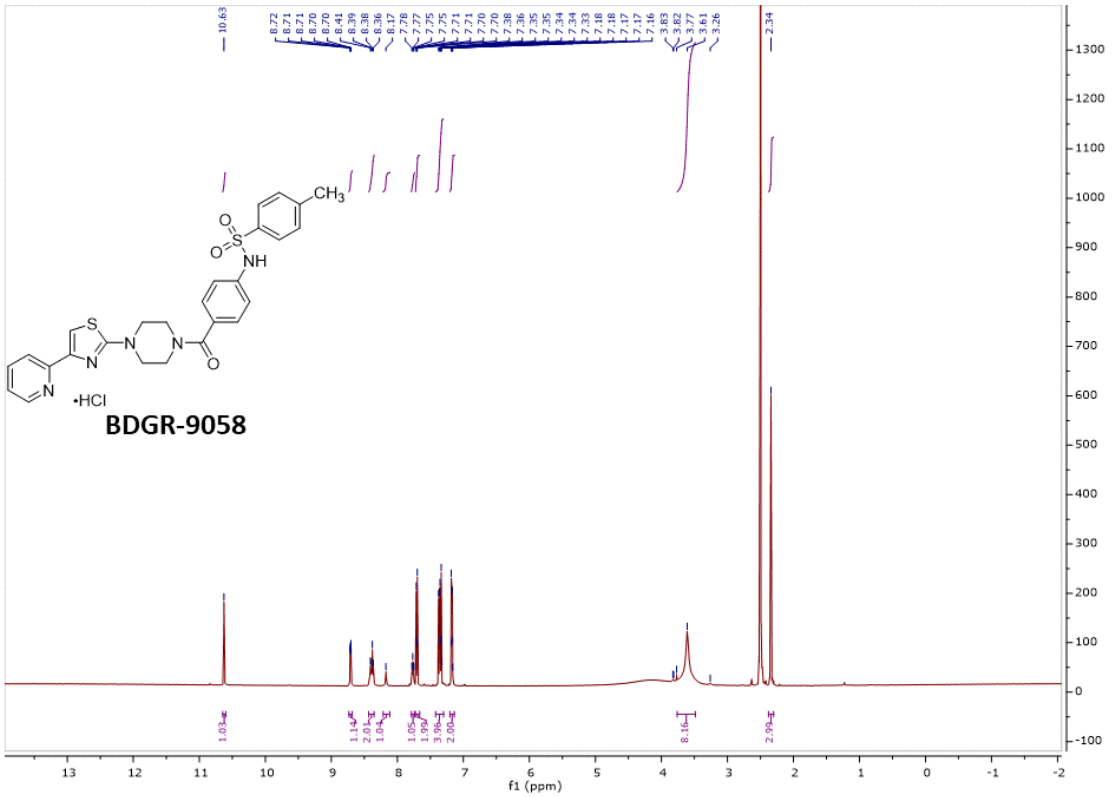

105.89
105.90
105.91
105.92
105.93
105.93
105.94
·HCl
BDGR-9055
f1 (ppm)

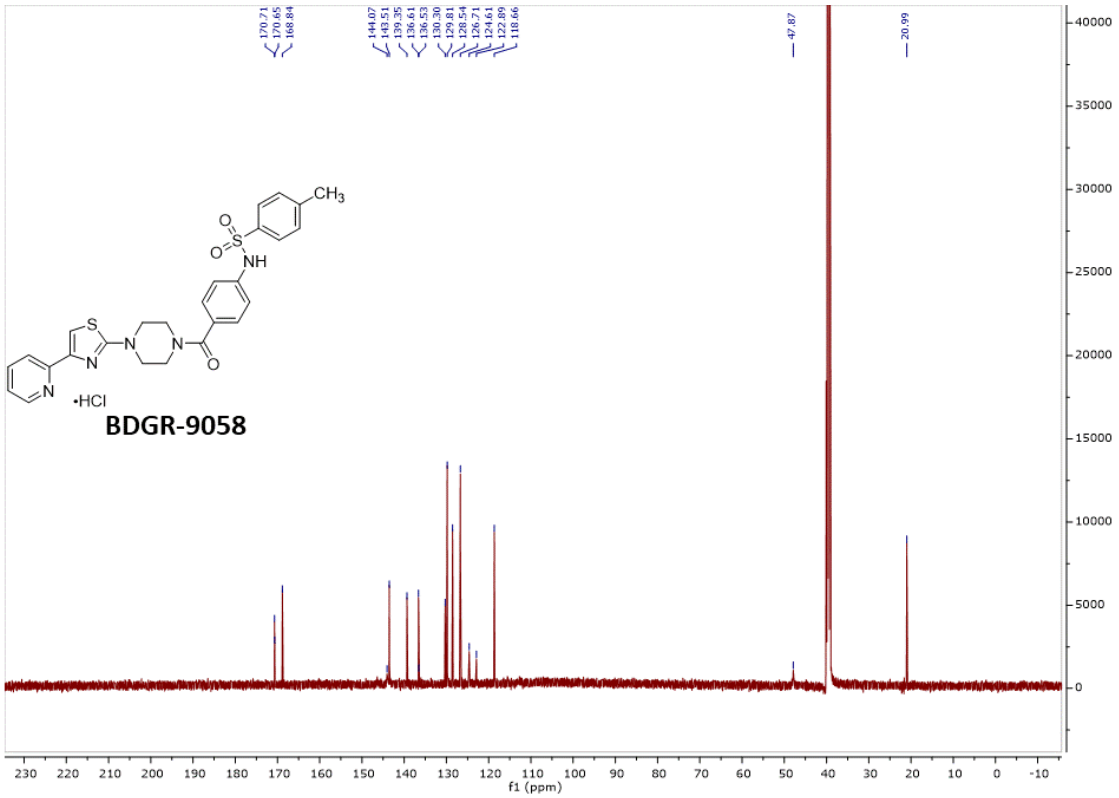

BDGR-9056
f1 (ppm)

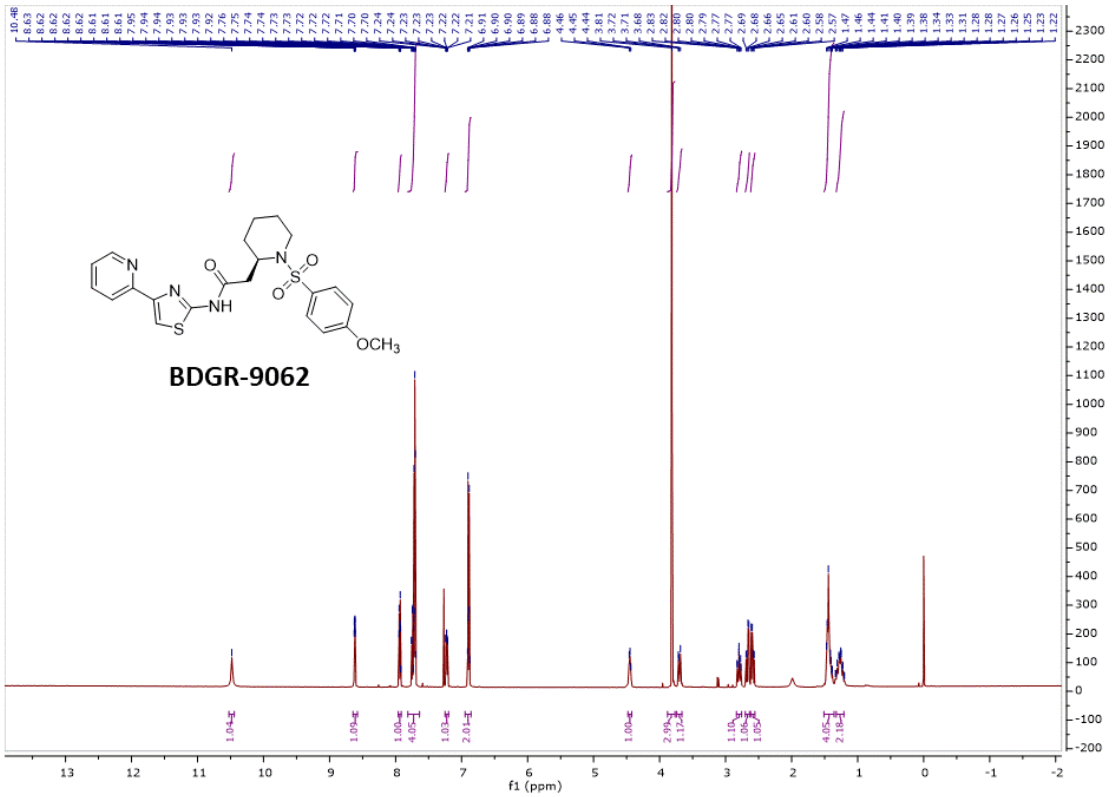

BDGR-9056
f1 (ppm)

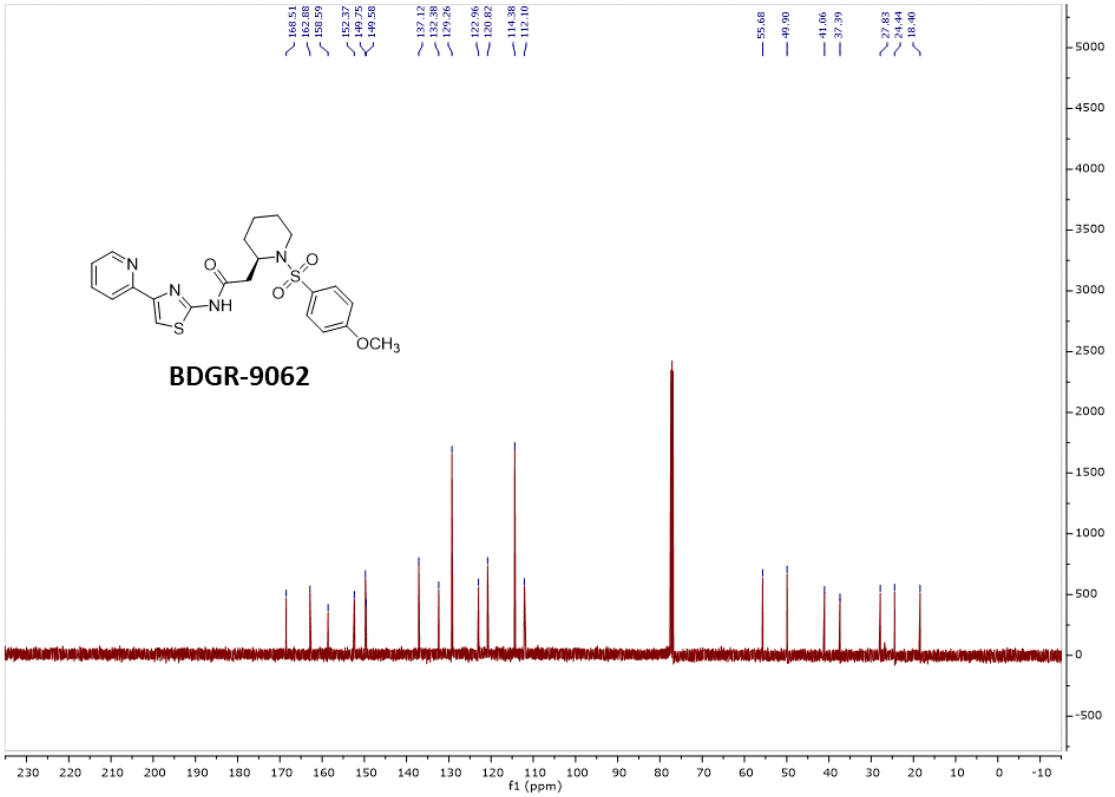

BDGR-9057
f1 (ppm)

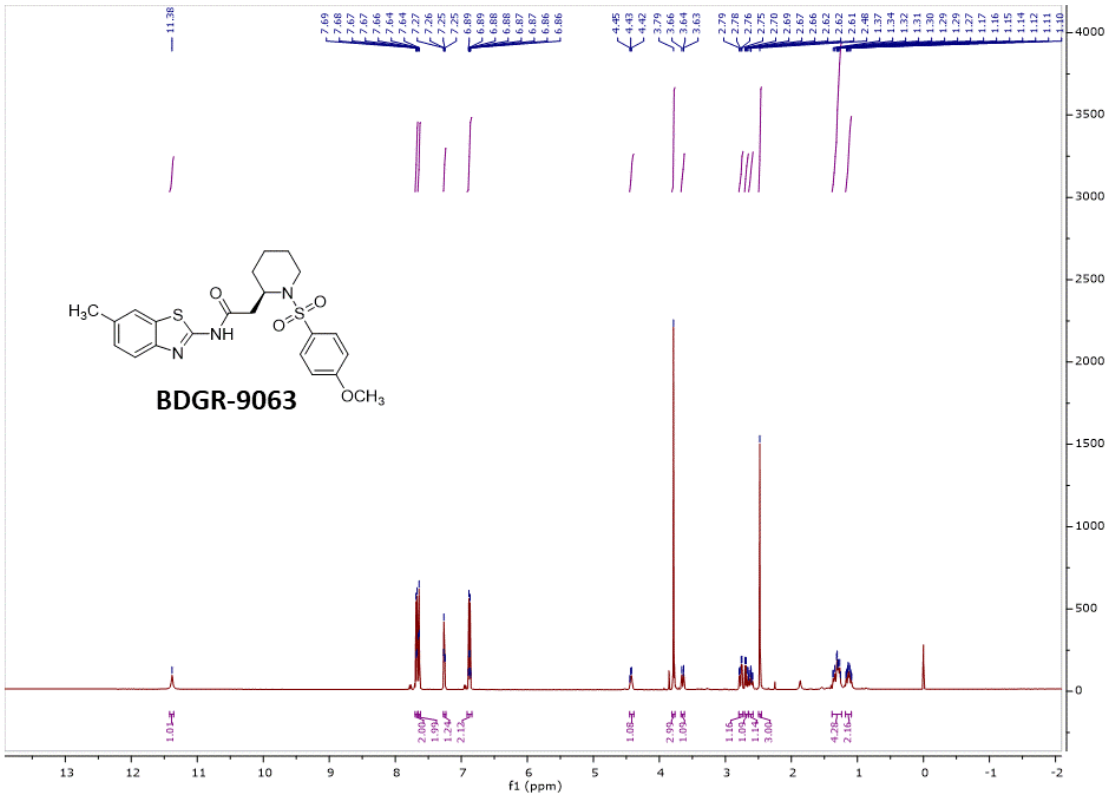

BDGR-9057
f1 (ppm)

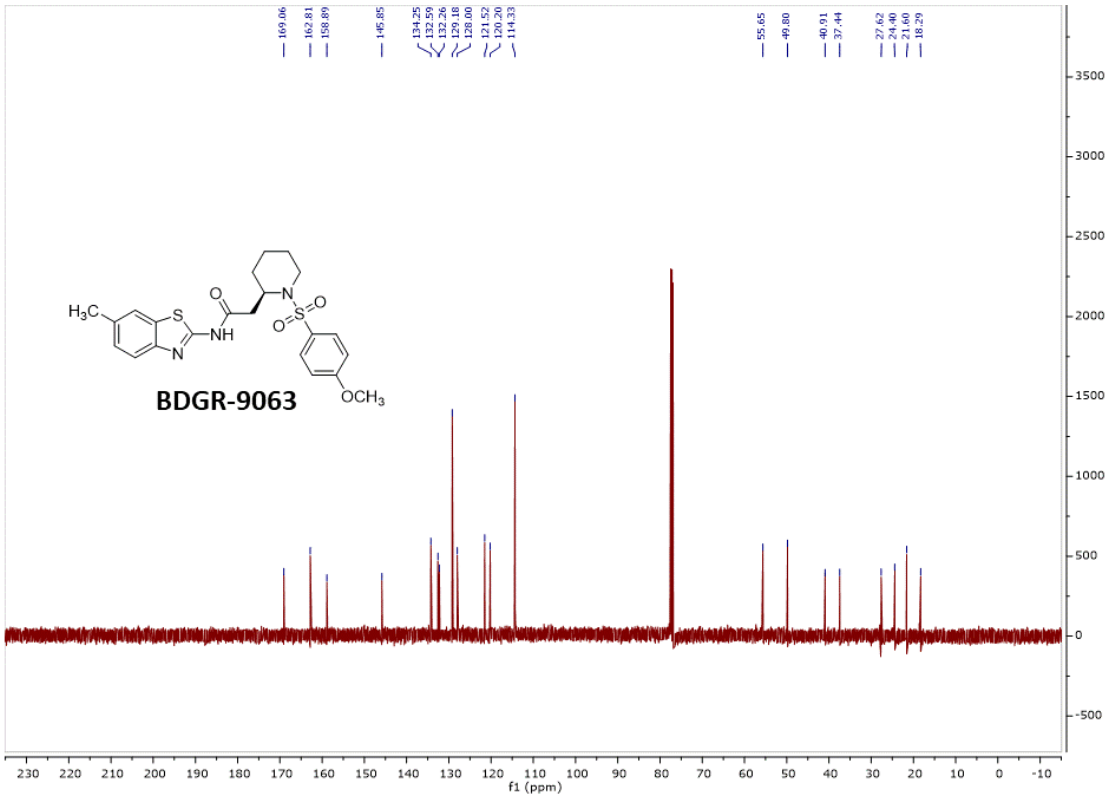

10.63
8.72
8.71
8.71
8.70
8.70
8.41
8.39
8.38
8.36
8.17
7.78
7.77
7.75
7.75
7.71
7.71
7.70
7.70
7.38
7.36
7.35
7.35
7.34
7.34
7.33
7.18
7.16
7.17
7.17
7.16
3.83
3.82
3.77
3.61
3.26
2.34
CH3
O
S
O
NH
S
N
N
N
O
•HCl
BDGR-9058
1.03
1.14
2.01
1.04
1.05
1.99
3.96
2.00
8.16
2.99
f1 (ppm)

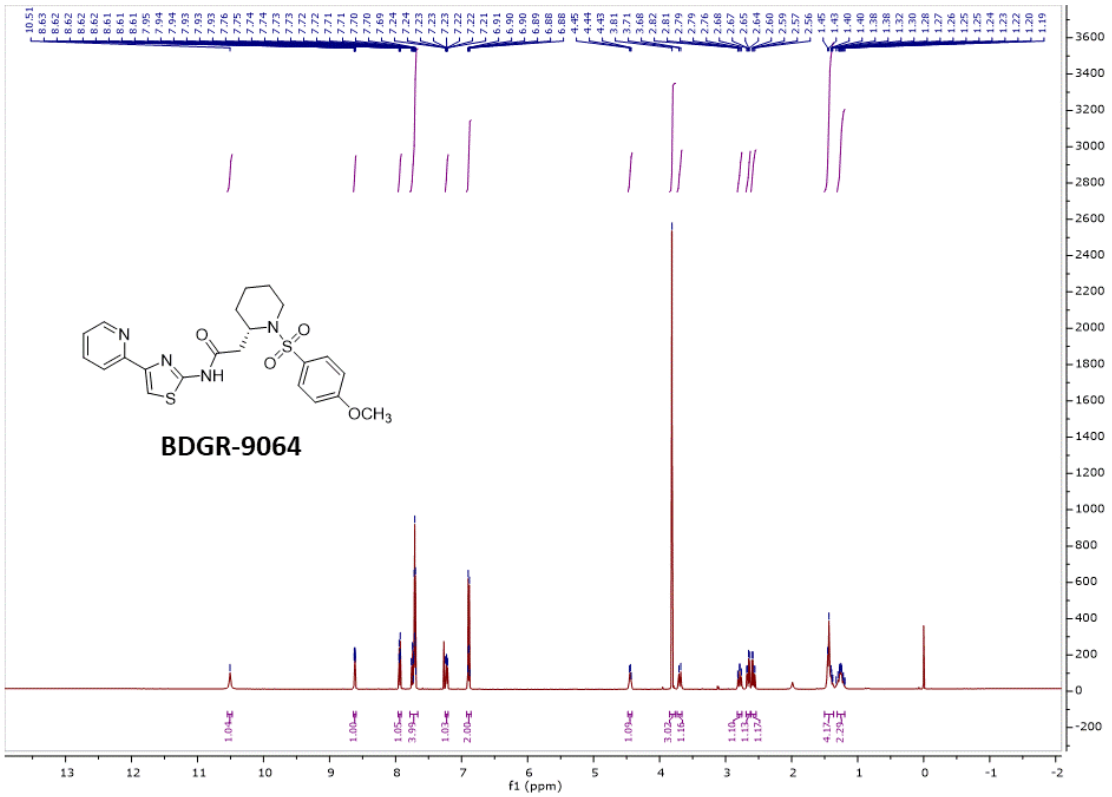

170.71
170.65
168.84
144.07
143.51
139.35
136.61
136.53
130.30
129.81
128.54
126.71
124.61
122.89
118.66
47.87
20.99
CH3
O
S
O
NH
S
N
N
N
O
•HCl
BDGR-9058
f1 (ppm)

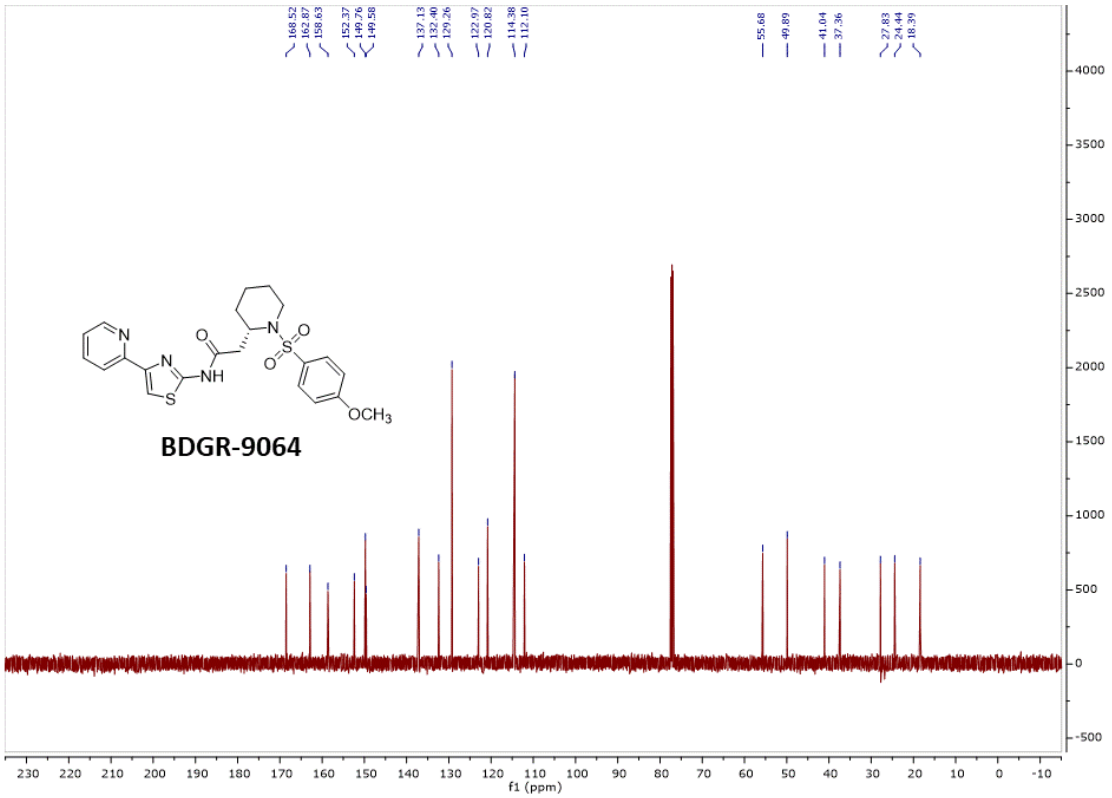

BDGR-9062
f1 (ppm)

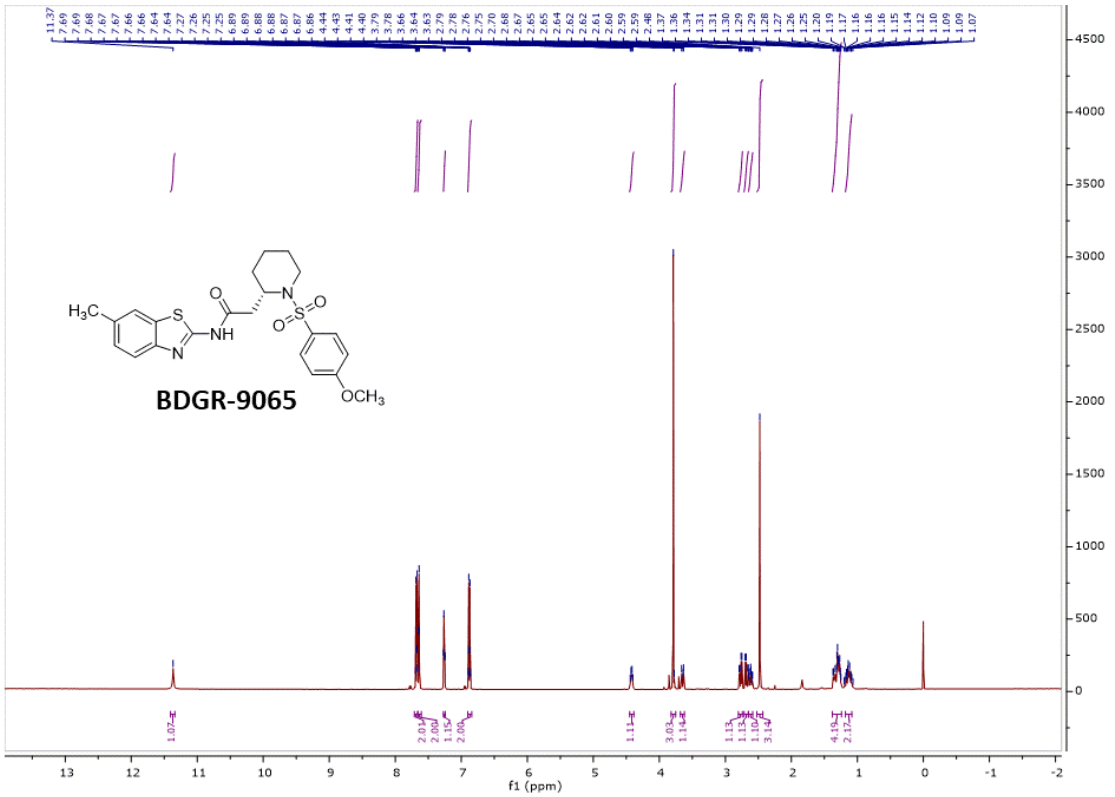

BDGR-9062
f1 (ppm)

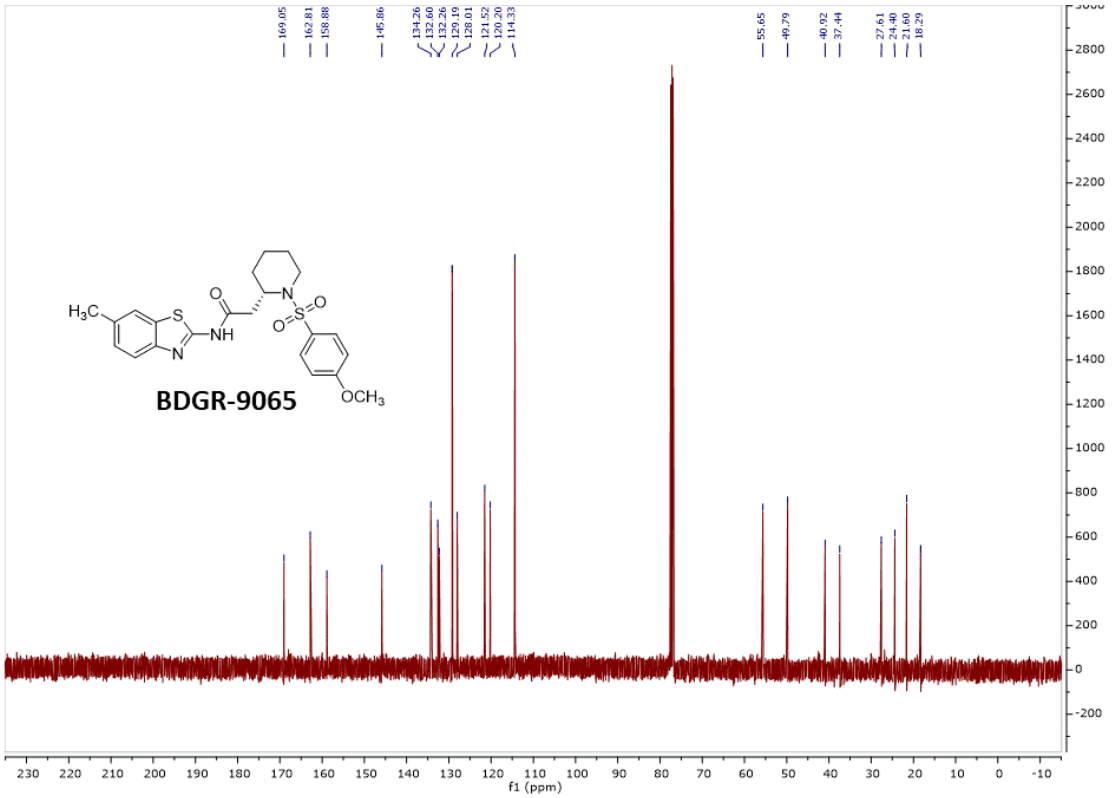

BDGR-9063
f1 (ppm)

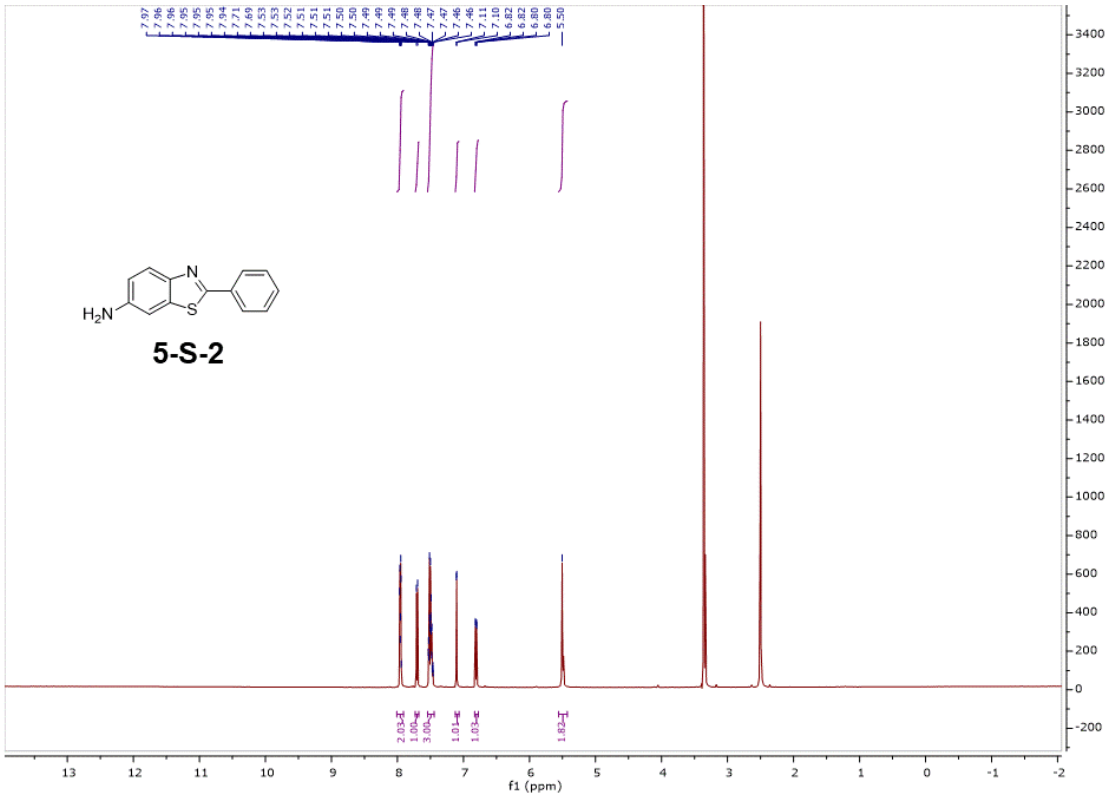

BDGR-9063
f1 (ppm)

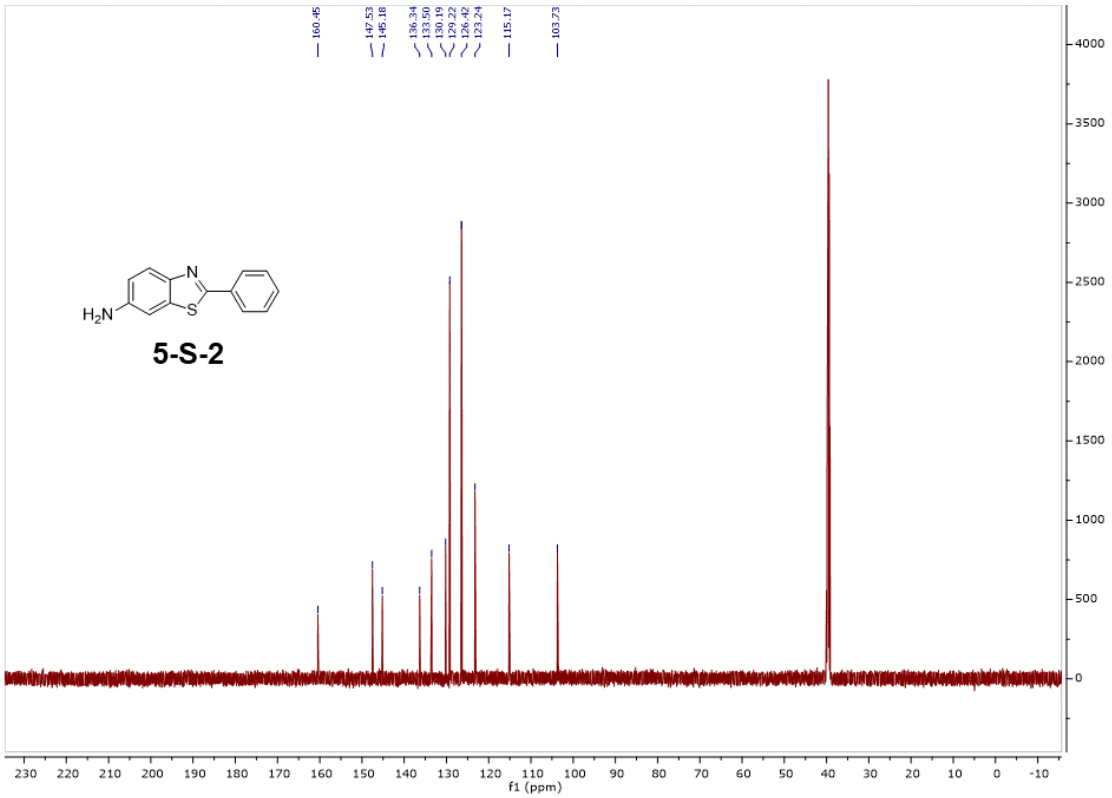

BDGR-9064
f1 (ppm)

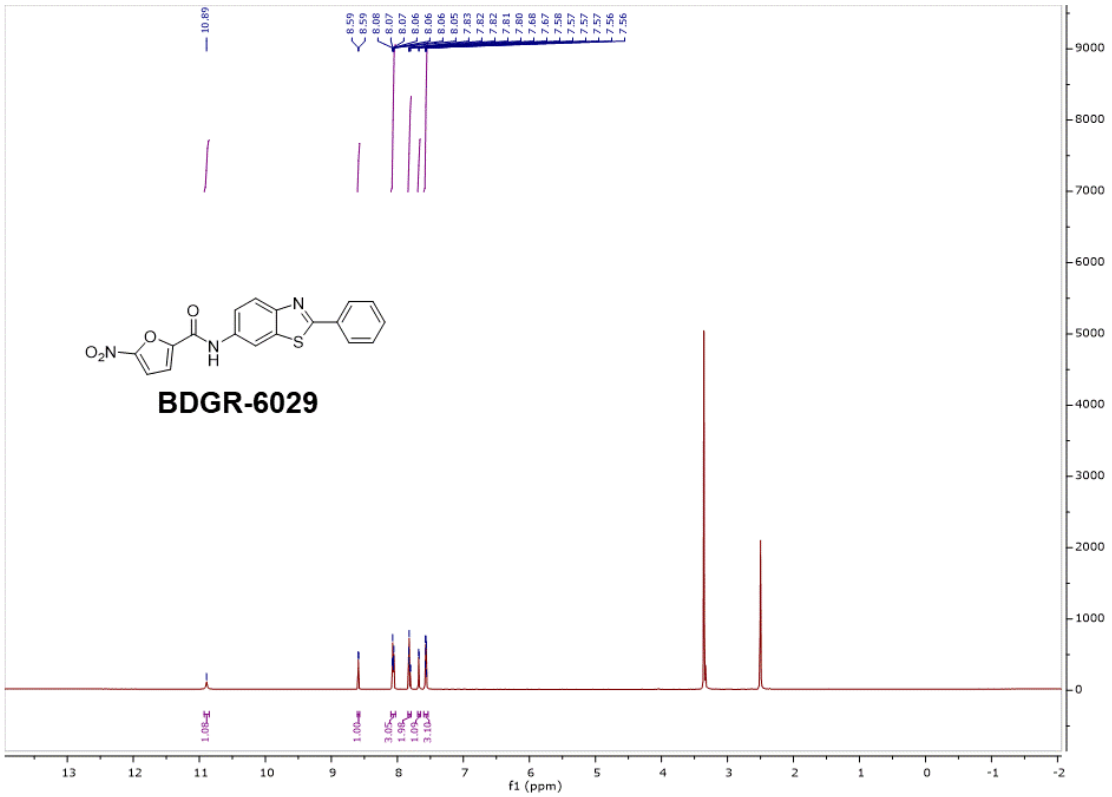

BDGR-9064
f1 (ppm)

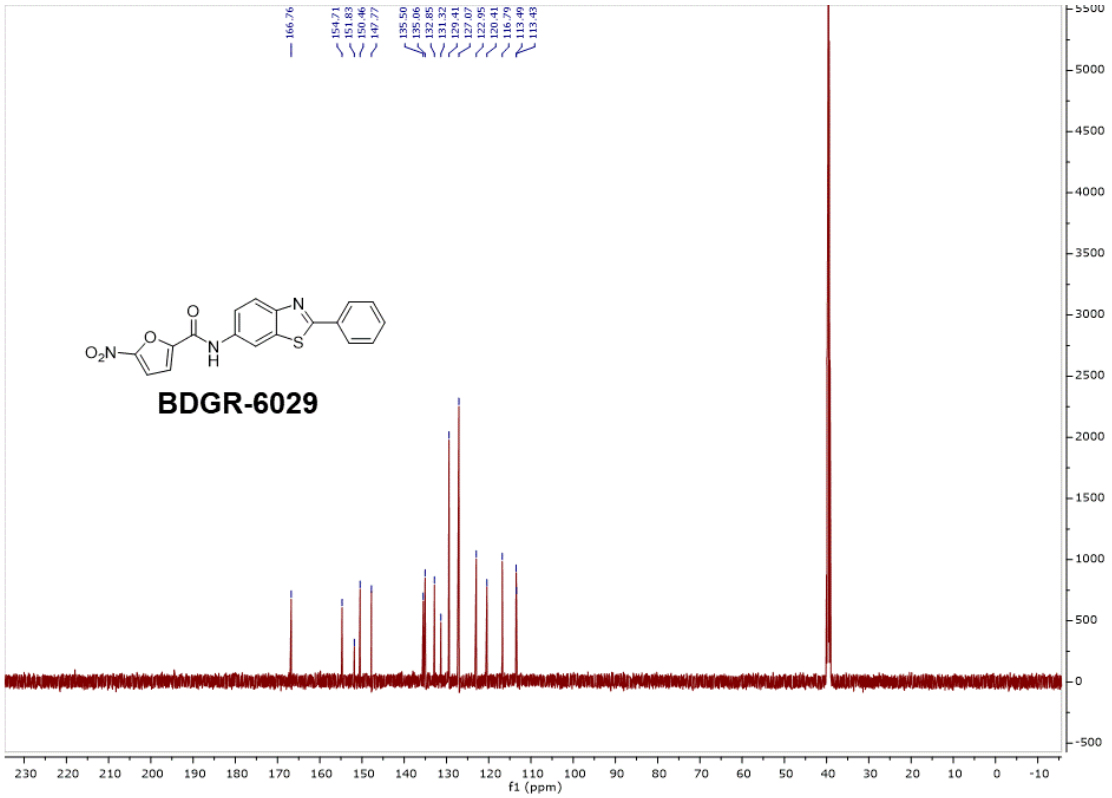

BDGR-9065
f1 (ppm)

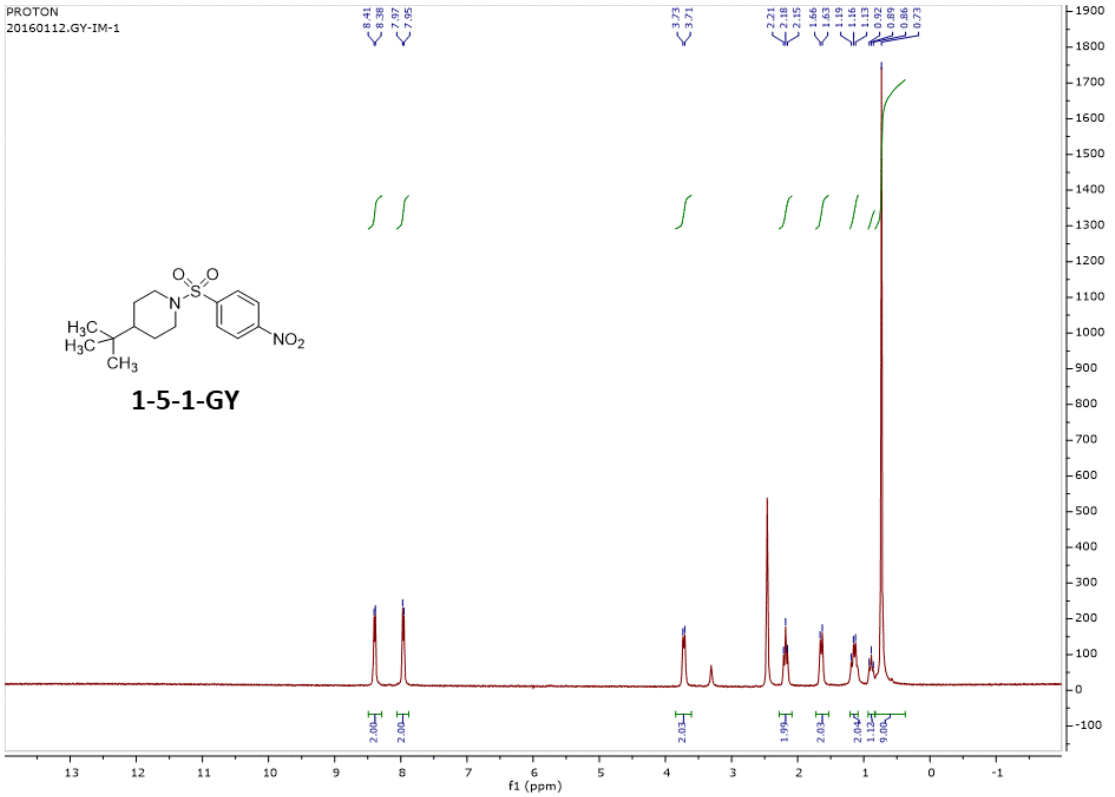

BDGR-9065
f1 (ppm)


7.97
7.96
7.96
7.95
7.95
7.95
7.94
7.71
7.69
7.53
7.53
7.52
7.51
7.51
7.51
7.50
7.50
7.49
7.49
7.49
7.48
7.48
7.47
7.47
7.46
7.46
7.11
7.10
6.82
6.82
6.80
6.80
5.50
2.03
1.00
3.00
1.01
1.03
1.83
H2N
N
S
5-S-2
f1 (ppm)


160.45
147.53
145.18
136.34
133.50
130.19
129.22
126.42
123.24
115.17
103.73
H2N
N
S
5-S-2
f1 (ppm)

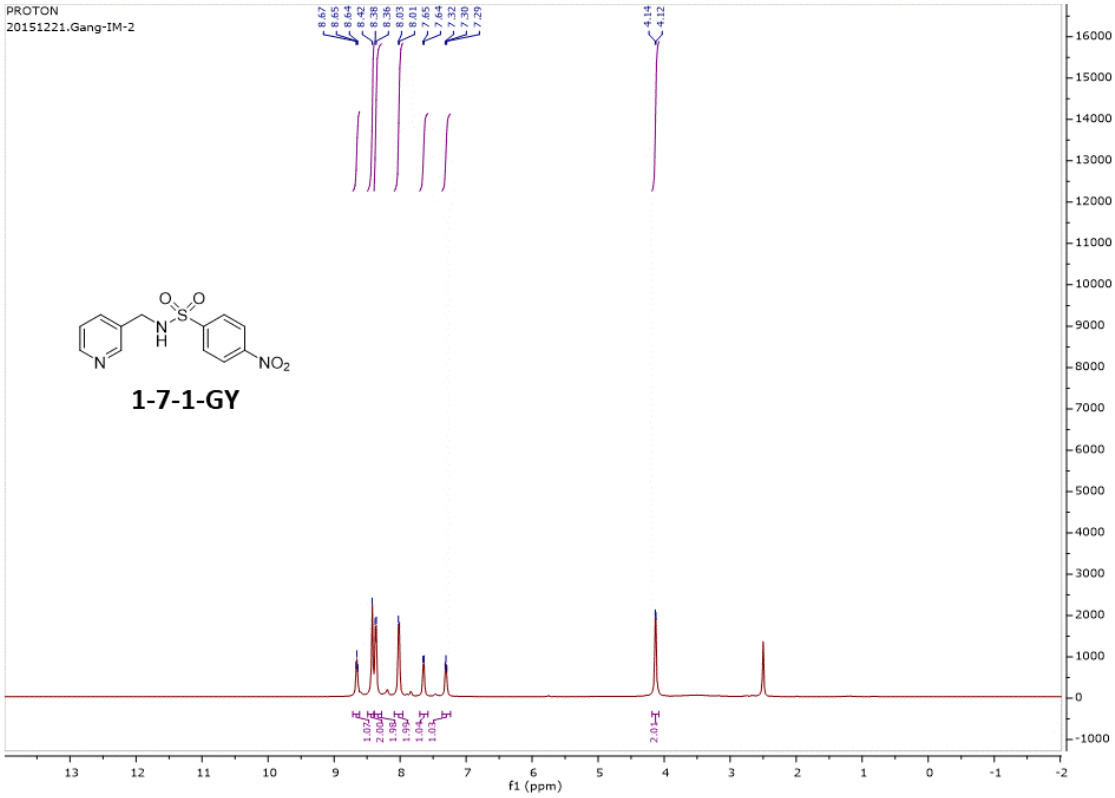

10.89
8.59
8.59
8.08
8.07
8.07
8.06
8.06
8.06
8.06
8.05
7.83
7.82
7.82
7.81
7.80
7.68
7.67
7.58
7.57
7.57
7.57
7.56
7.56
O2N
O
N
H
S
BDGR-6029
f1 (ppm)


166.76
154.71
151.83
150.46
147.77
135.50
135.06
132.85
131.32
129.41
127.07
122.95
120.41
116.79
113.49
113.43
O2N
O
N
H
S
BDGR-6029
f1 (ppm)


PROTON
20160112.GY-IM-1
f1 (ppm)

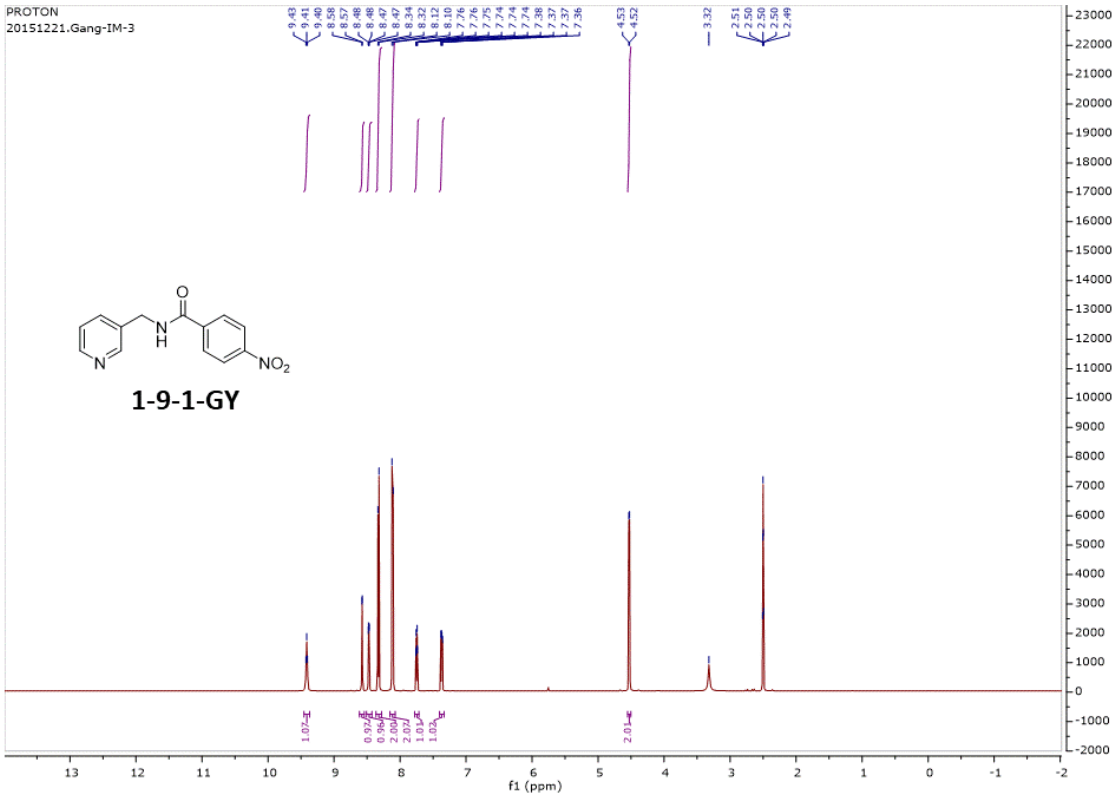


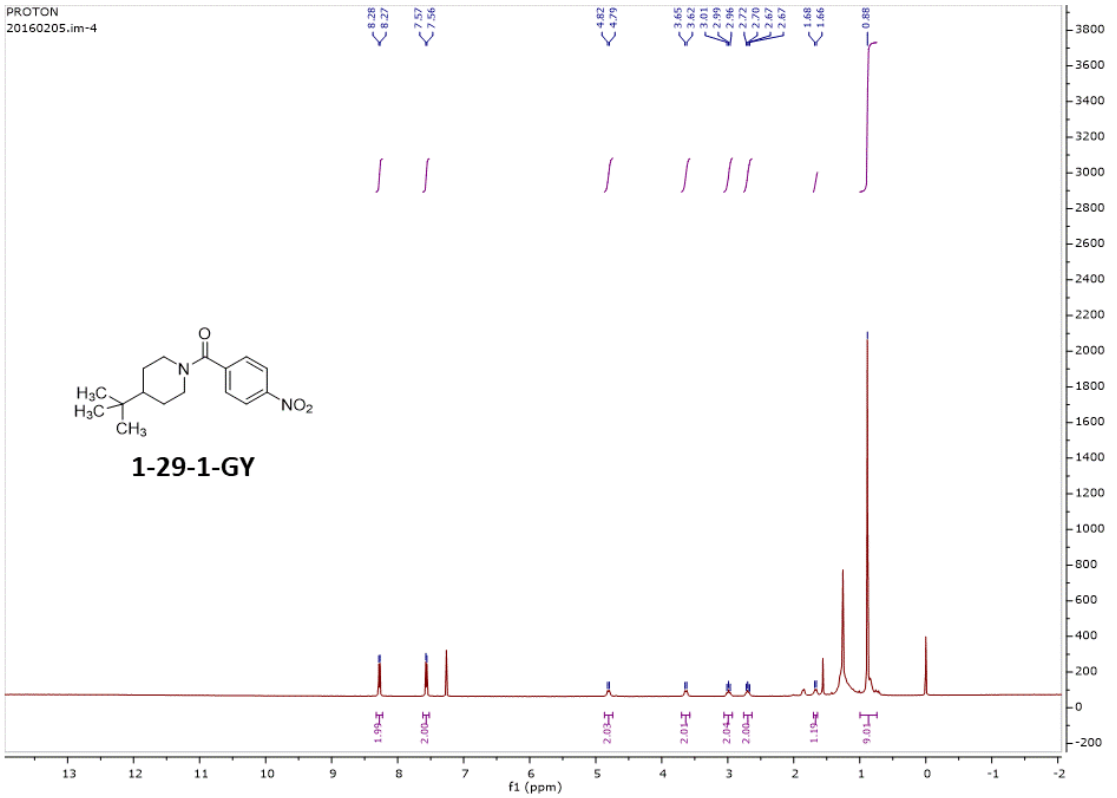
**1-5-1-GY**

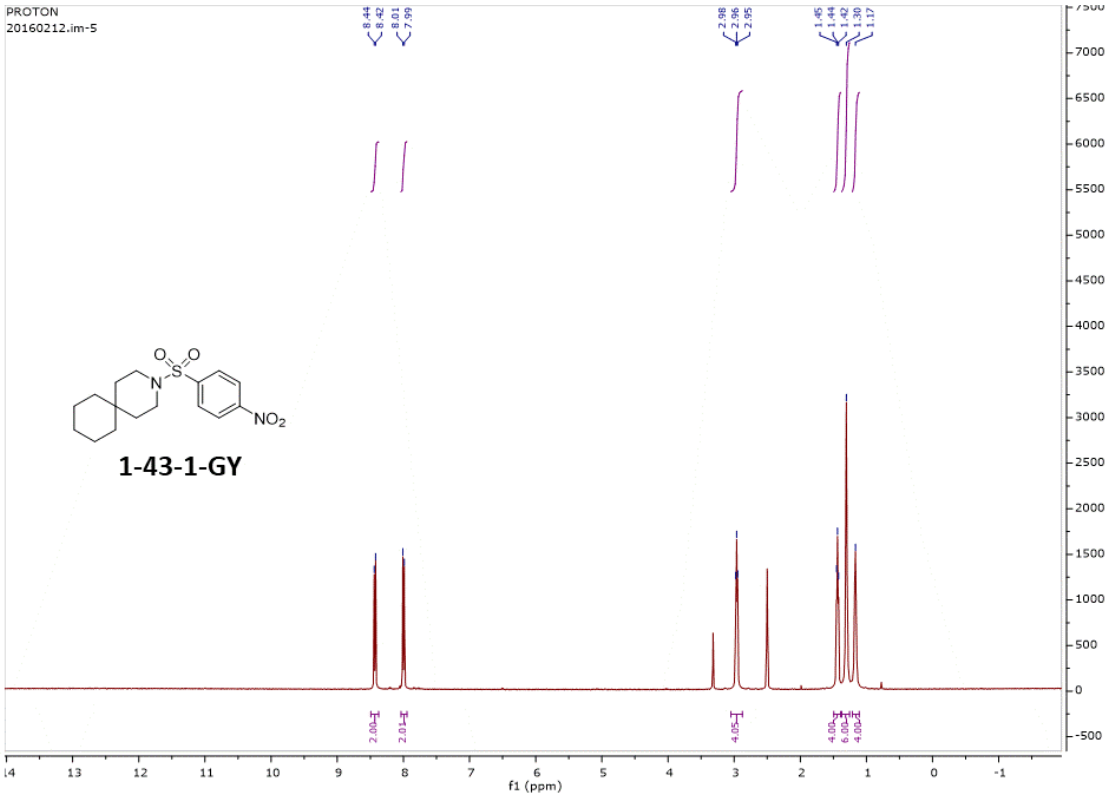

PROTON
20151221.Gang-IM-2
f1 (ppm)

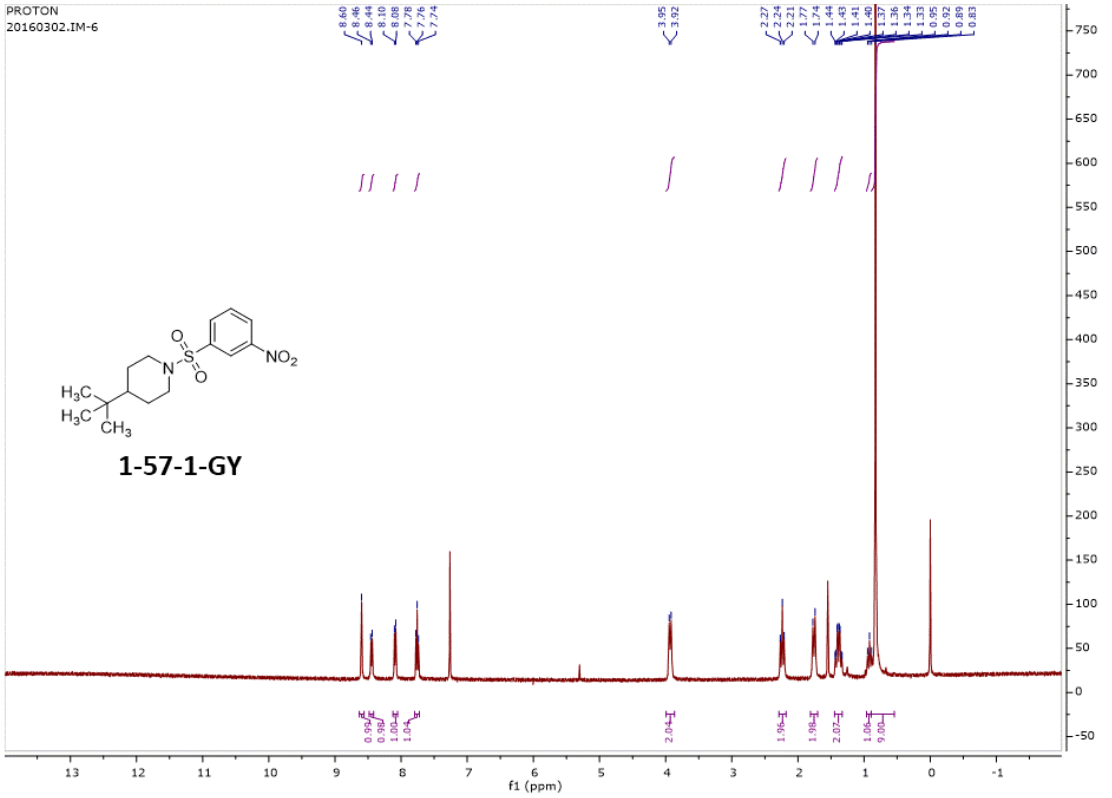


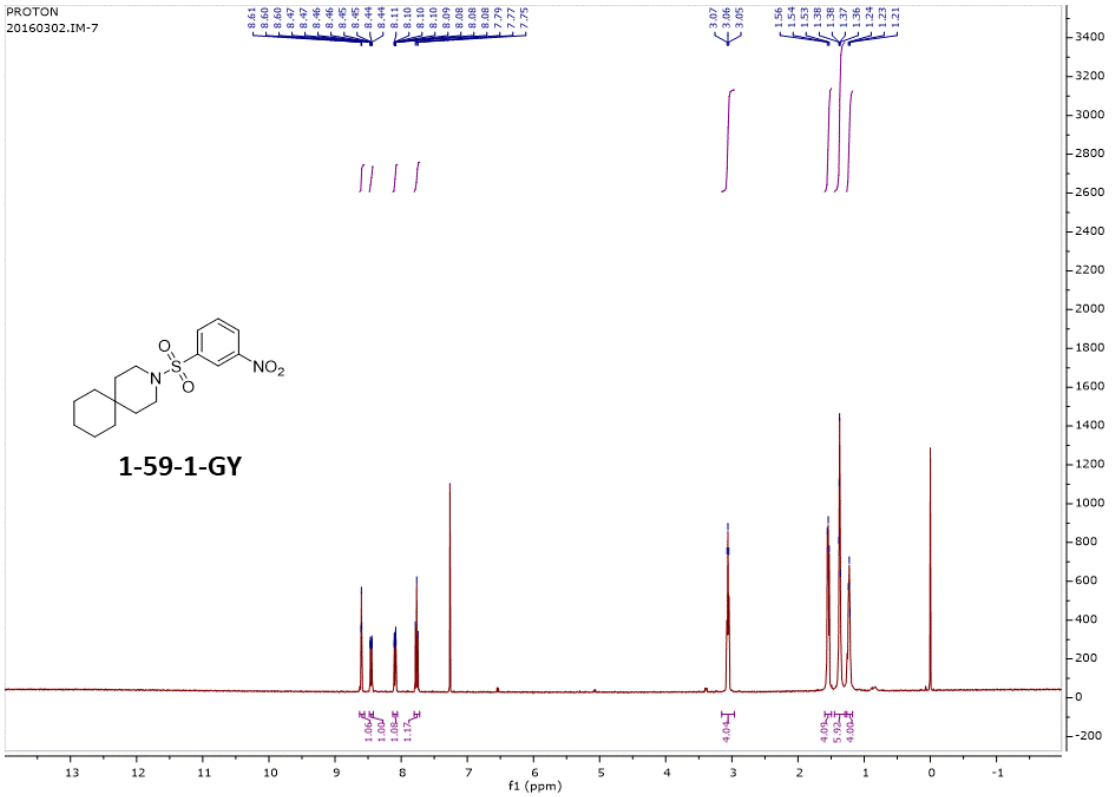
**1-7-1-GY**

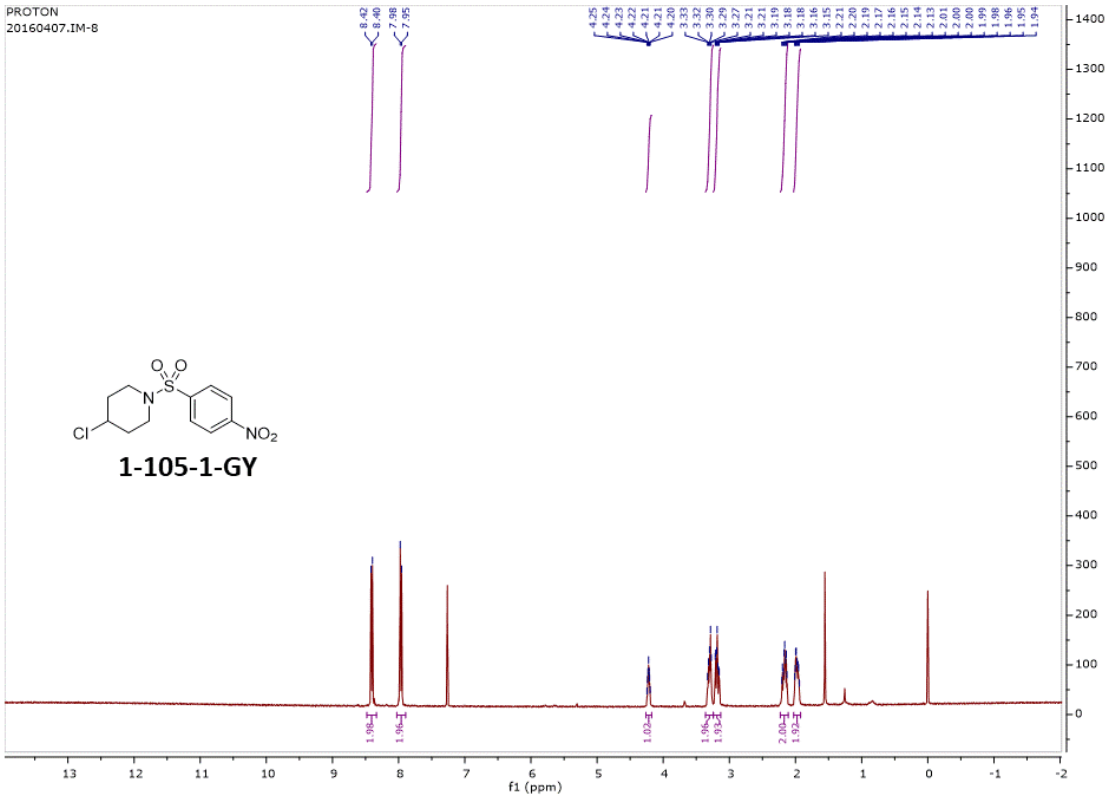

PROTON
20151221.Gang-IM-3
O
N
H
N
NO2
1-9-1-GY
f1 (ppm)

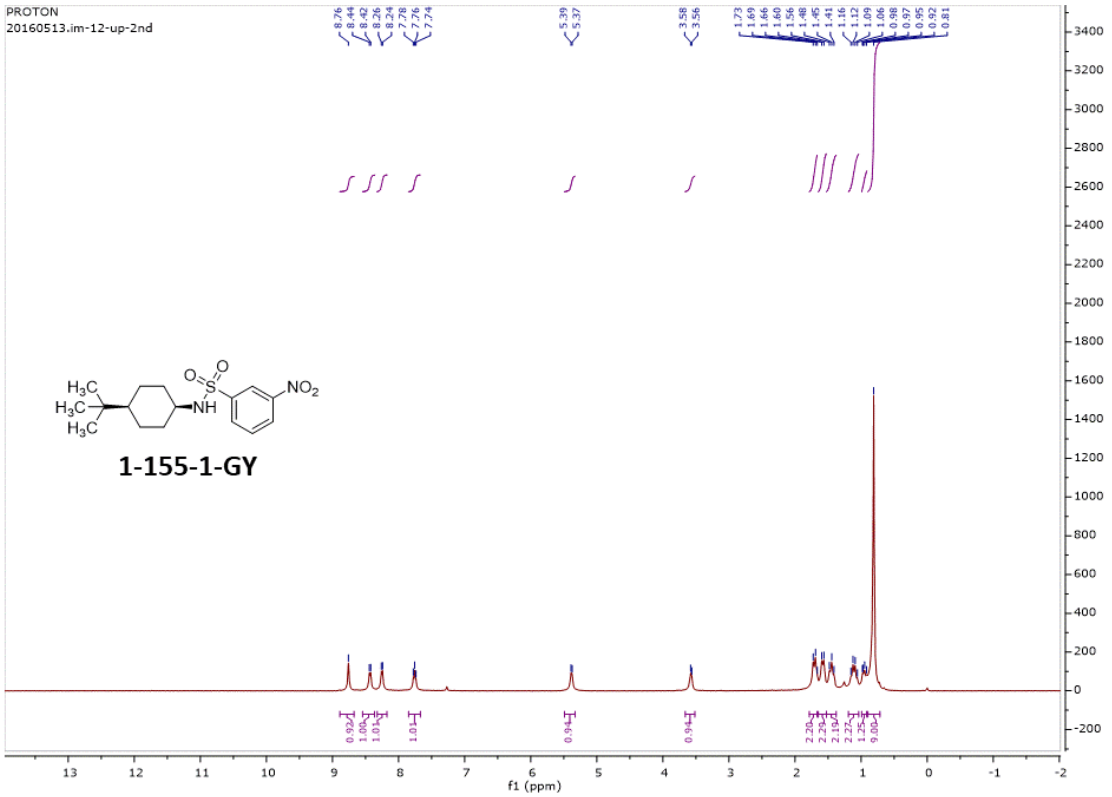

PROTON
20160205.im-4
O
N
H3C
H3C
CH3
NO2
1-29-1-GY
f1 (ppm)


PROTON
20160212.im-5
1-43-1-GY
f1 (ppm)


PROTON
20160302.IM-6
1-57-1-GY
f1 (ppm)

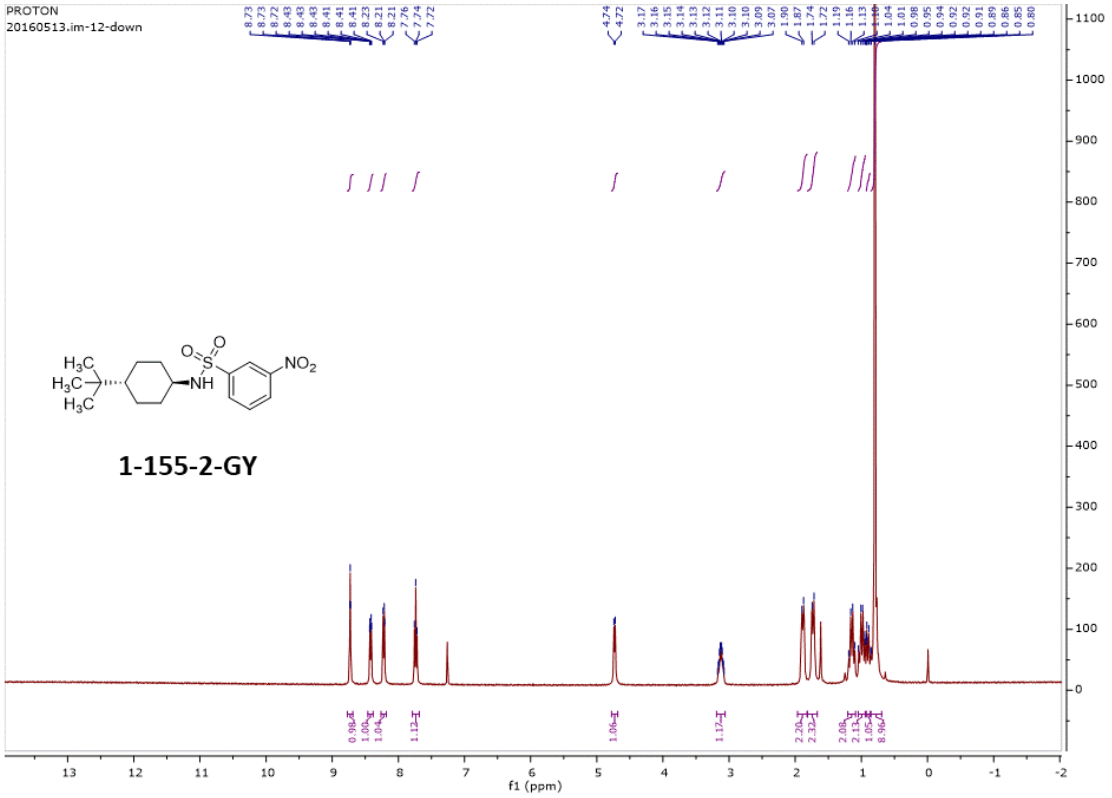

PROTON
20160302.IM-7
1-59-1-GY
f1 (ppm)


PROTON
20160407.IM-8
1-105-1-GY
f1 (ppm)



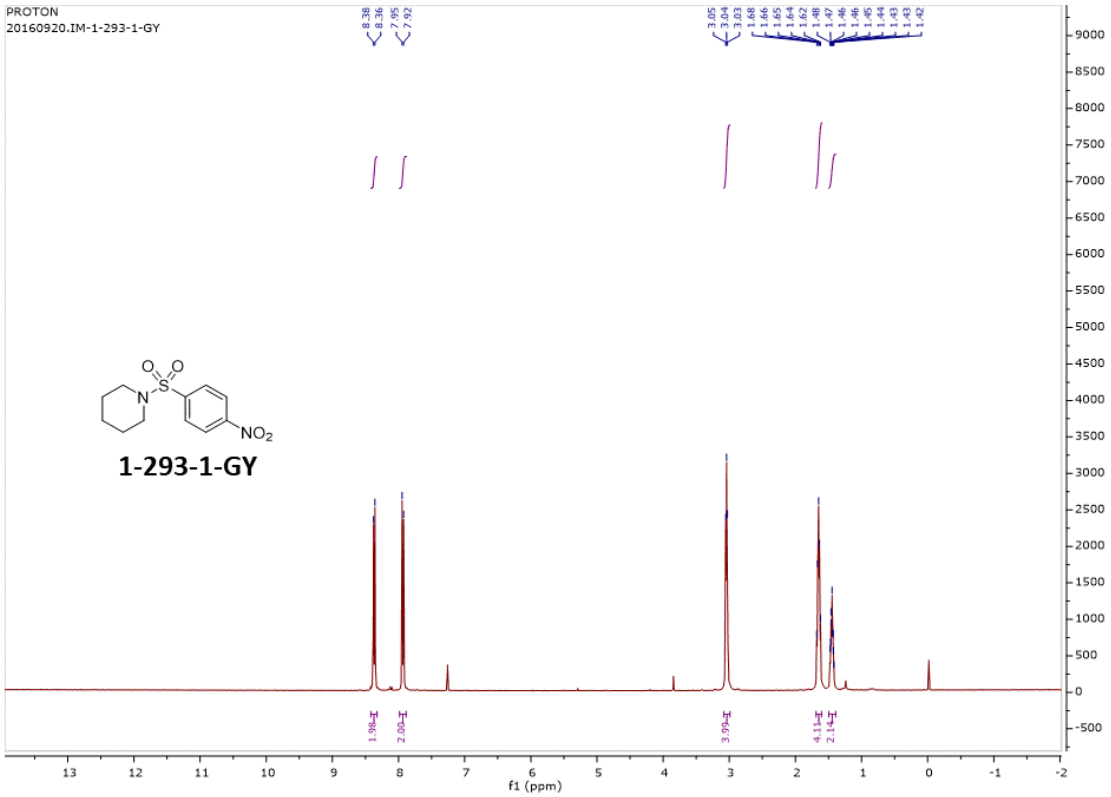


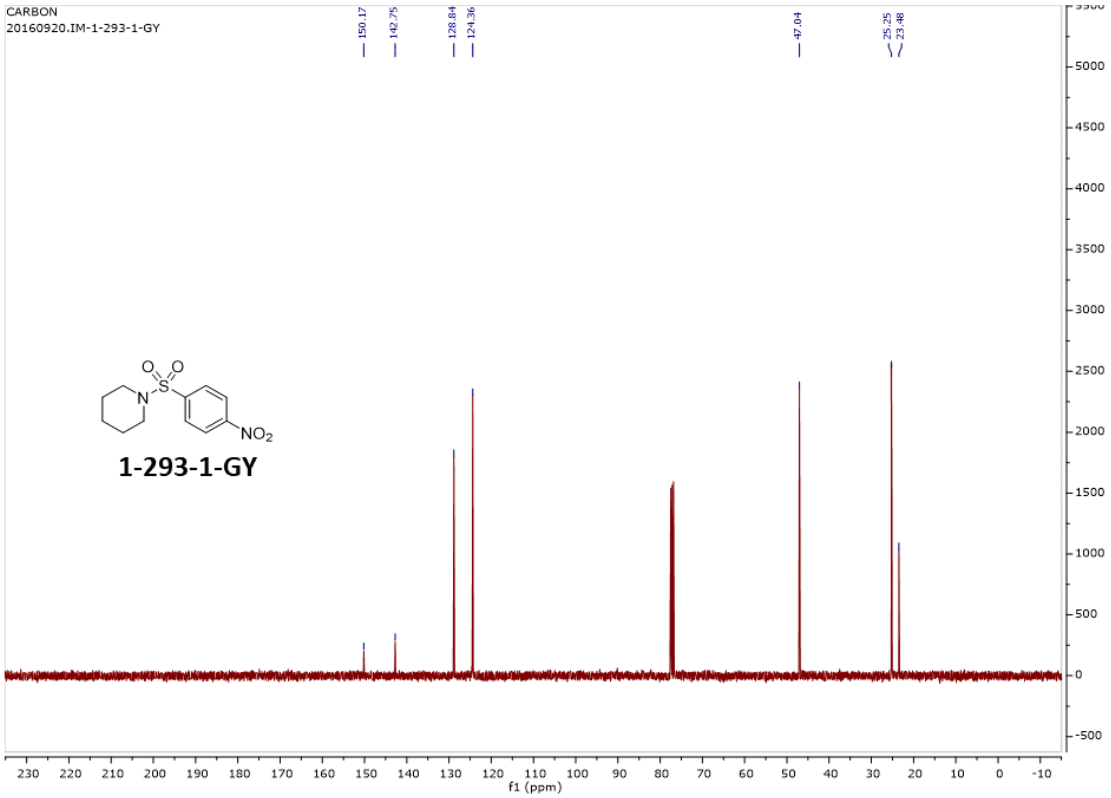

**1-155-1-GY**

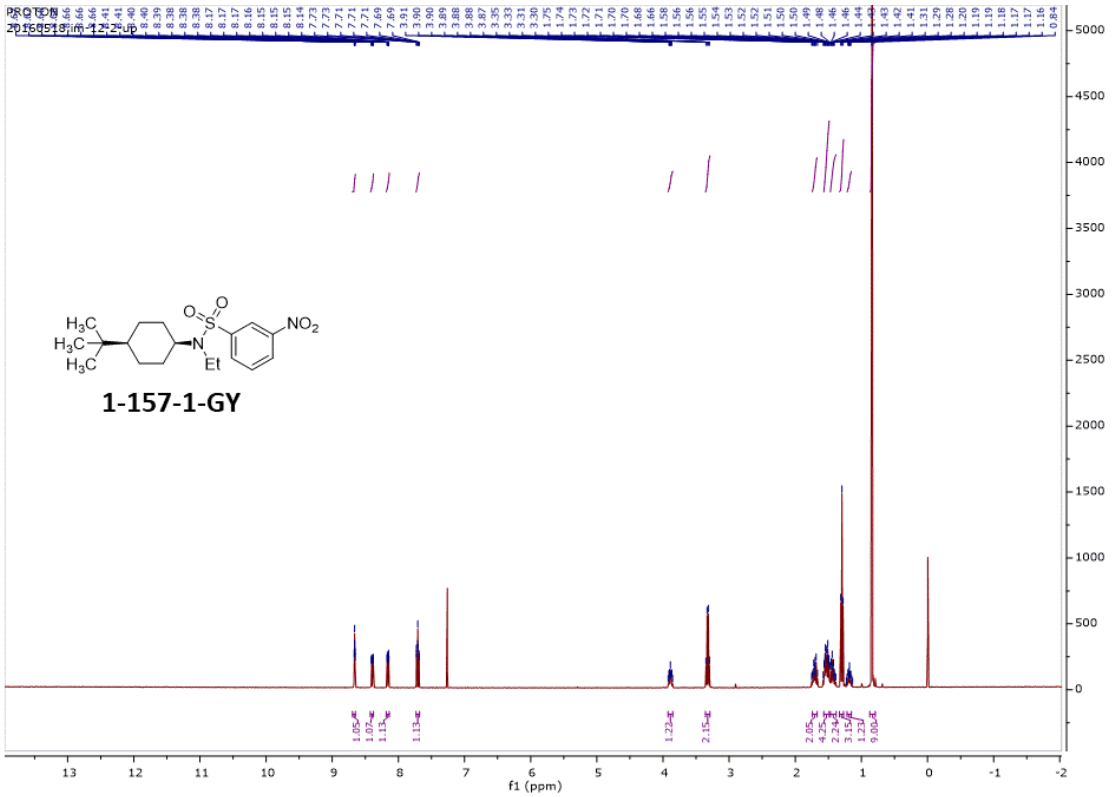


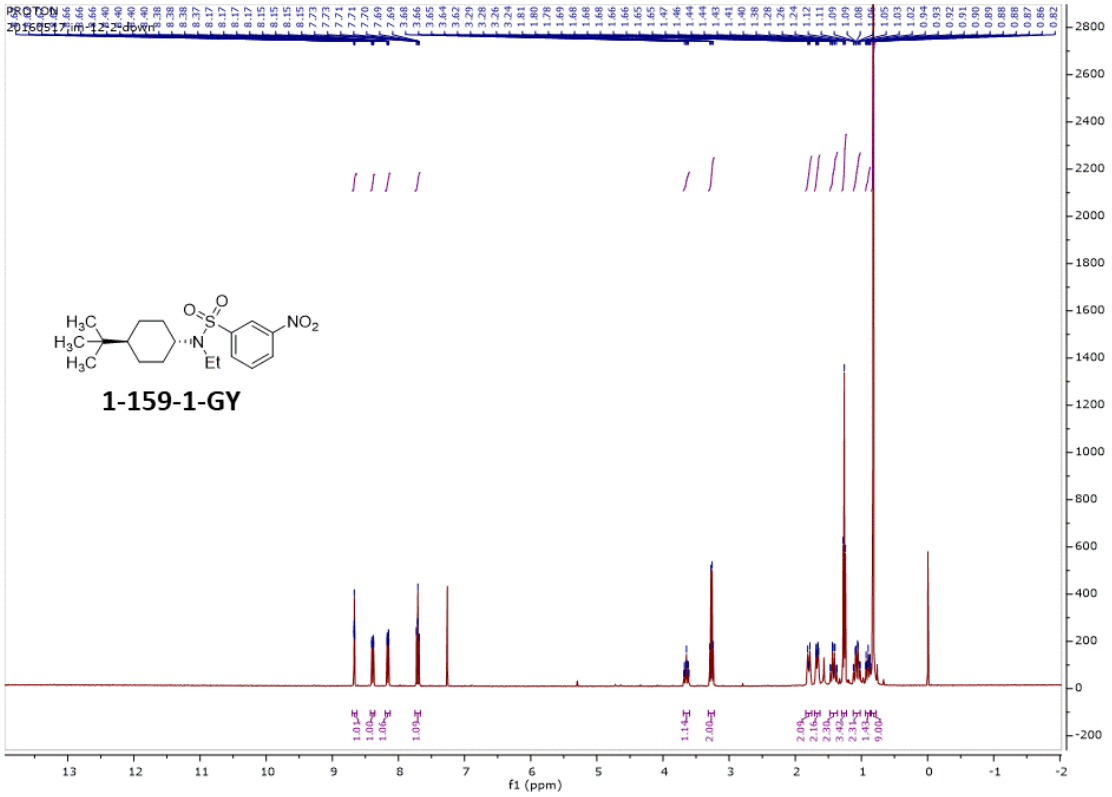


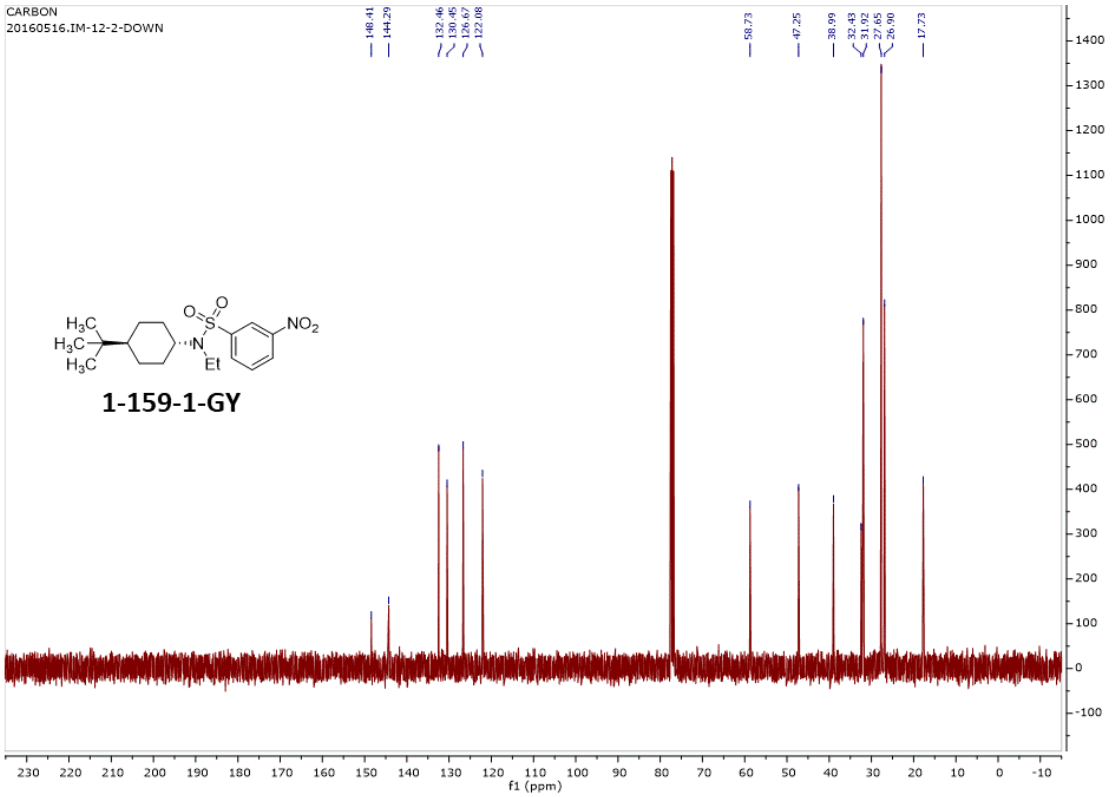

**1-155-2-GY**


PROTON
20160920.IM-1-293-1-GY
8.38
8.36
7.95
7.92
3.05
3.04
3.03
1.68
1.66
1.65
1.64
1.62
1.48
1.47
1.46
1.46
1.45
1.44
1.43
1.43
1.42
1.98
2.00
3.99
4.11
2.14
f1 (ppm)
1-293-1-GY


CARBON
20160920.IM-1-293-1-GY
150.17
142.75
128.84
124.36
47.04
25.25
23.48
f1 (ppm)
1-293-1-GY

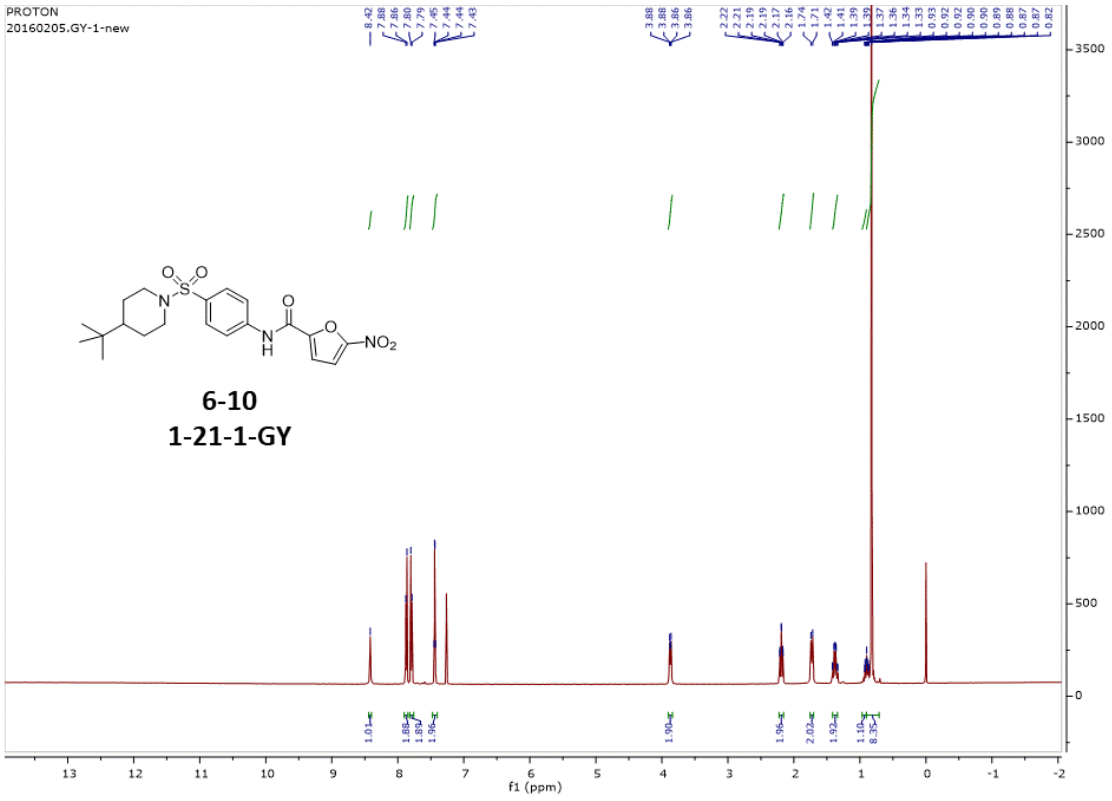

PROTON
20160518-jm-1-2-2-up
1-157-1-GY
f1 (ppm)


PROTON
20160517-jm-1-2-2-down
1-159-1-GY
f1 (ppm)



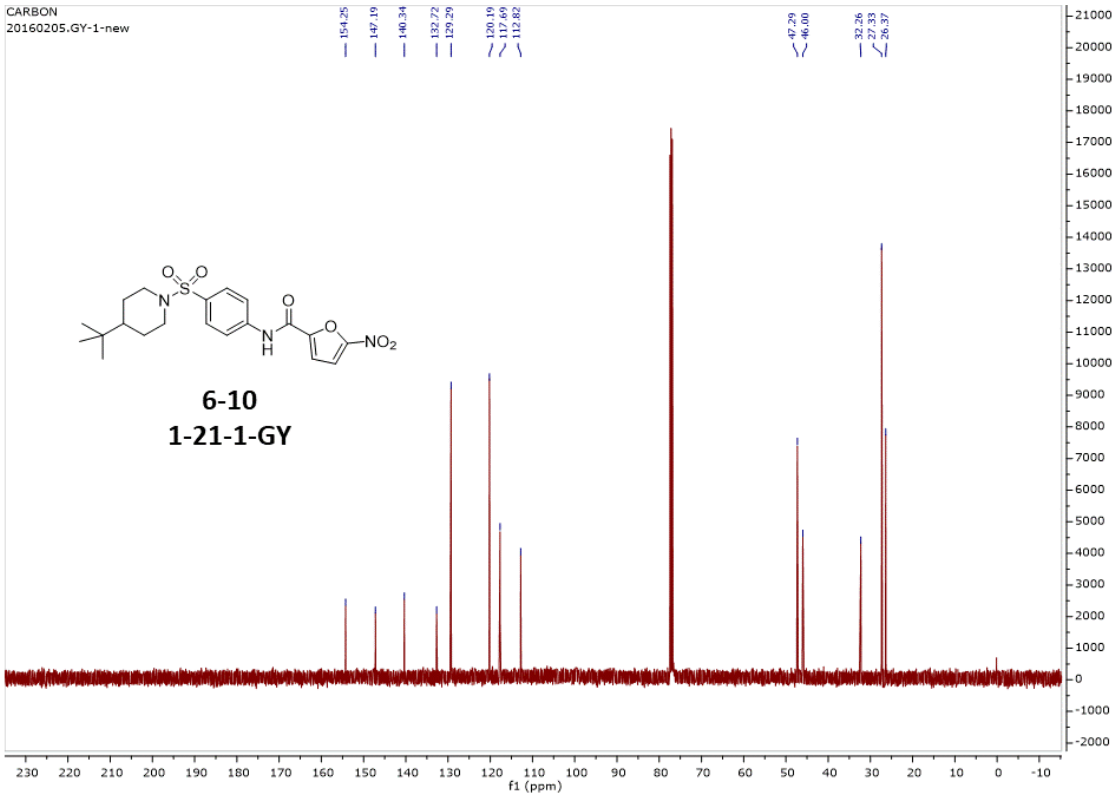



**1-159-1-GY**

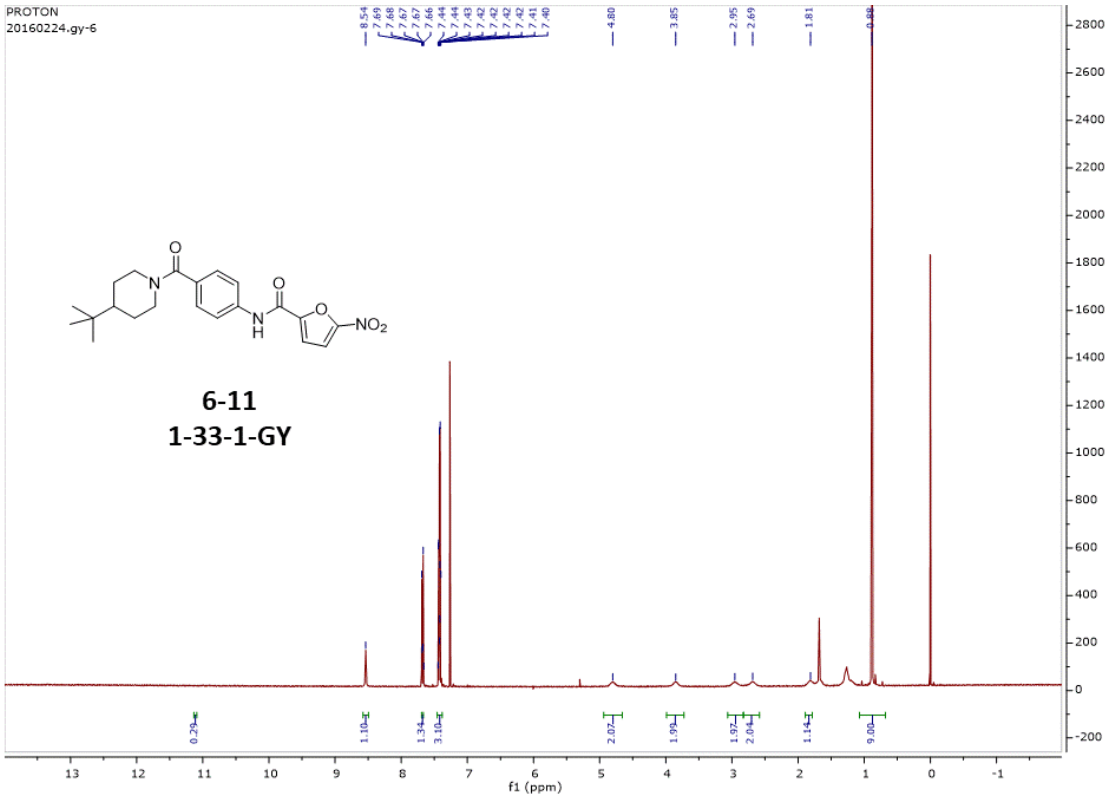




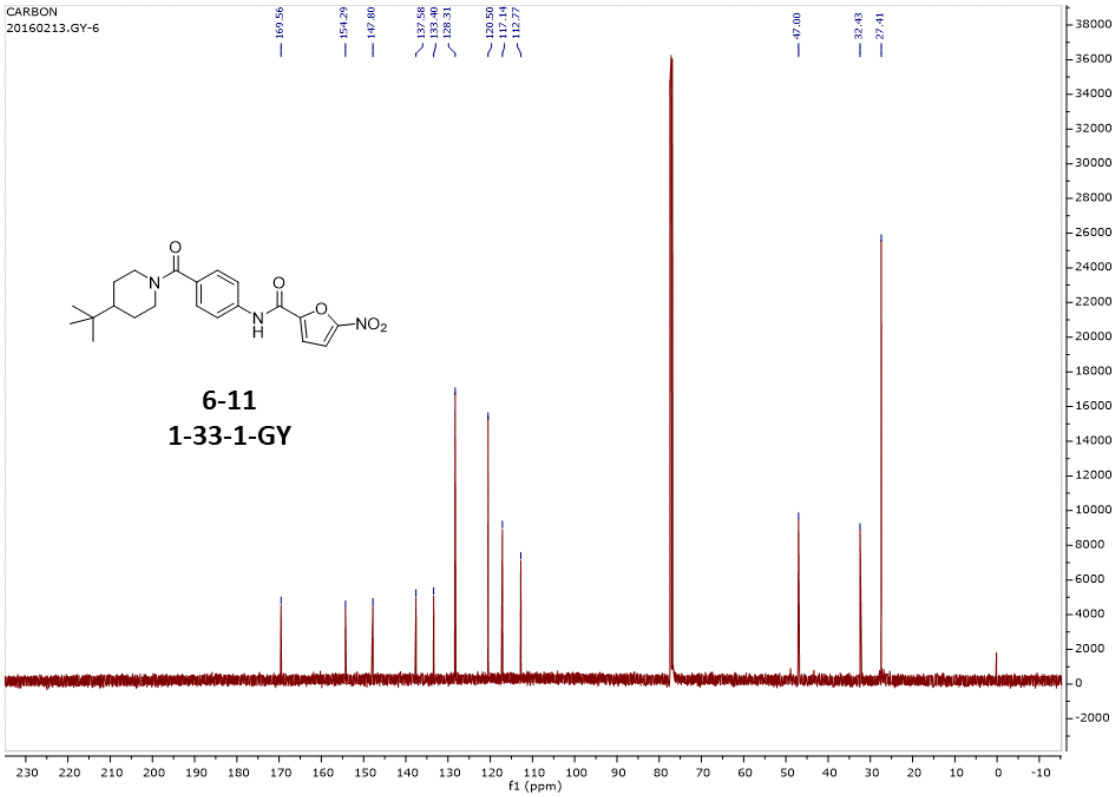

**6-10**
**1-21-1-GY**



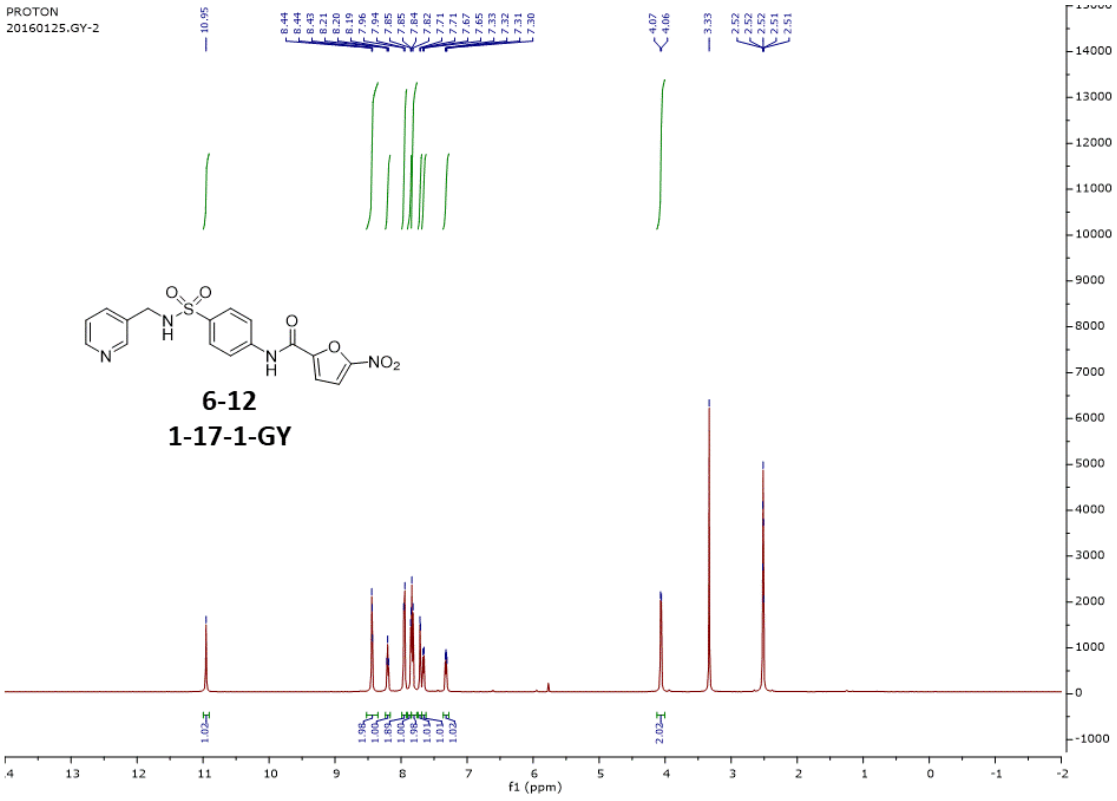

**6-10**
**1-21-1-GY**



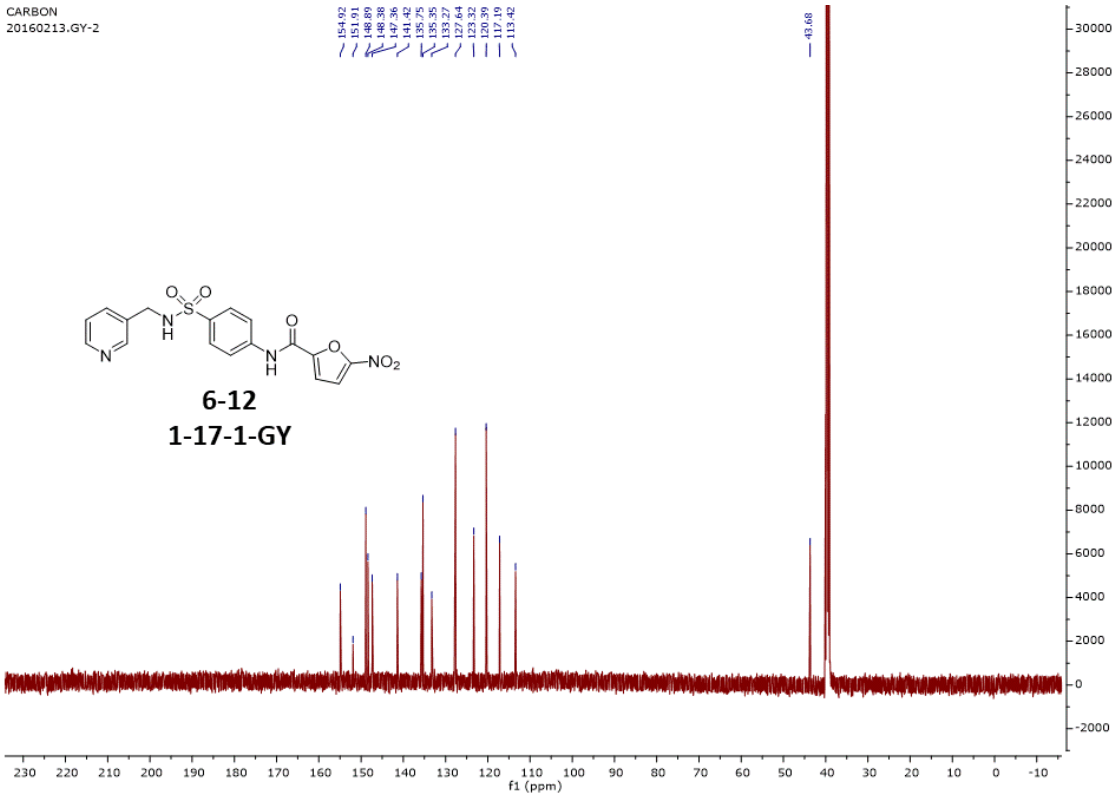

**6-11**
**1-33-1-GY**

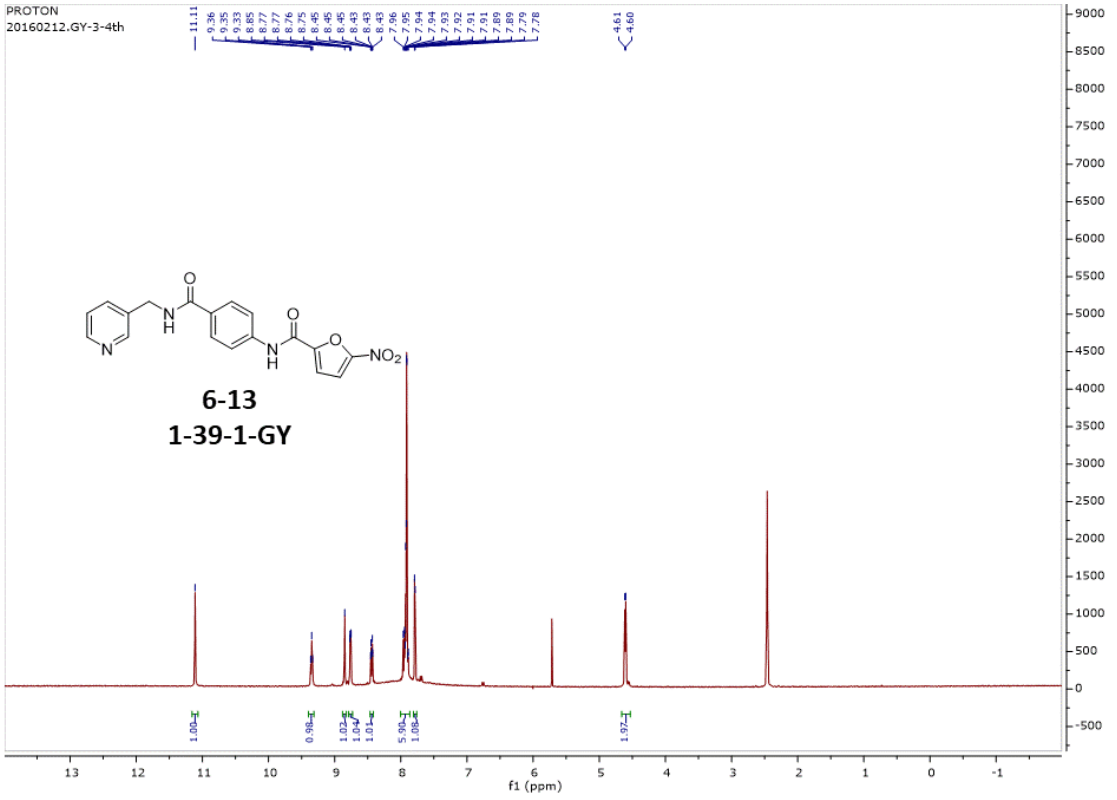


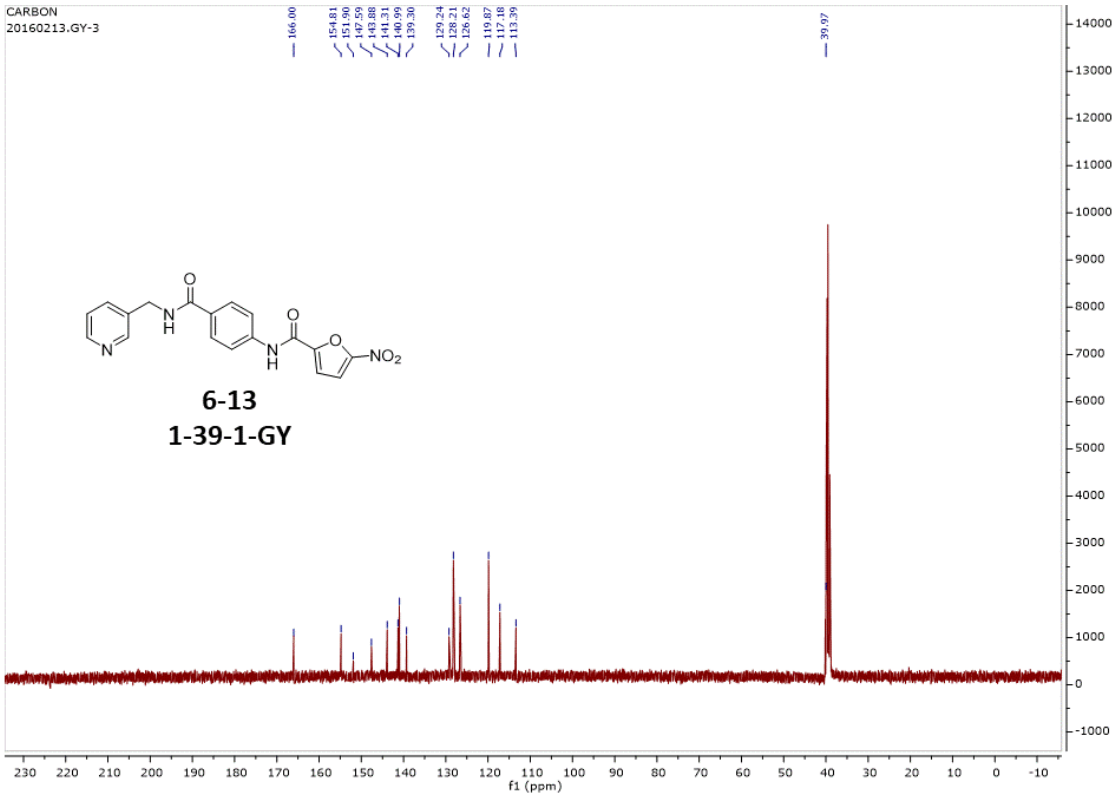

**6-11**
**1-33-1-GY**



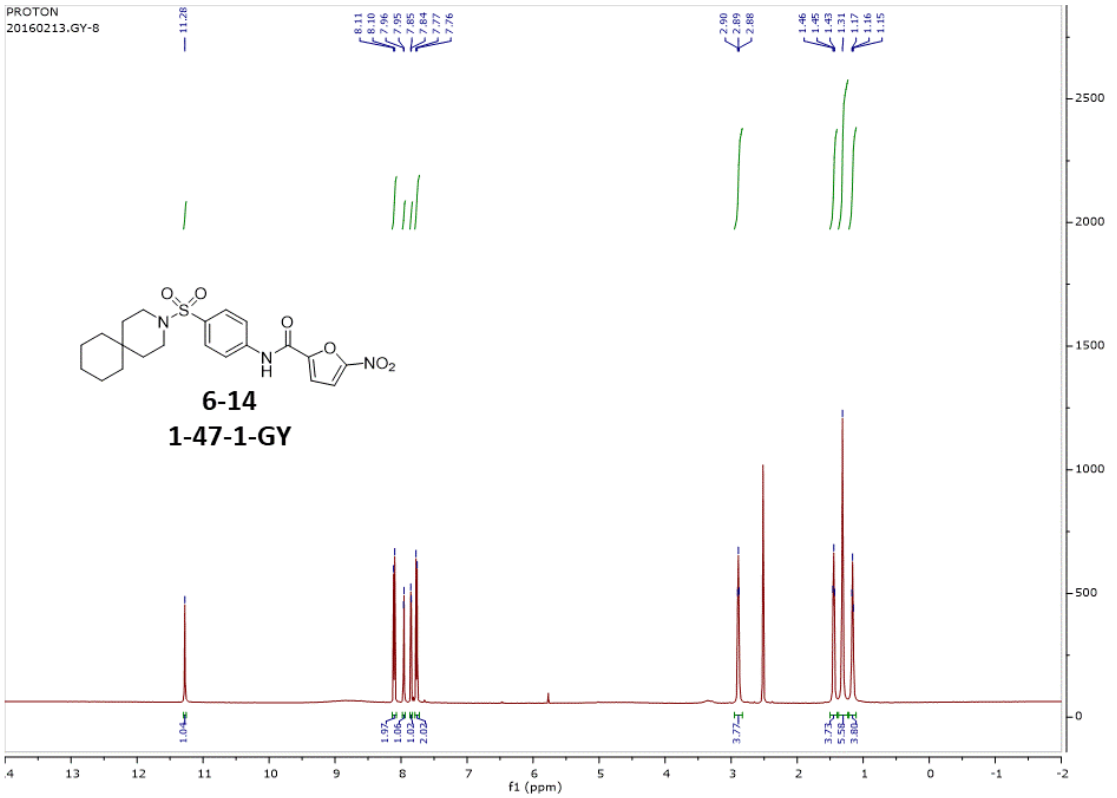

**6-12**
**1-17-1-GY**


CARBON
20160213.GY-2
154.92
151.91
148.89
148.38
147.36
141.42
135.75
135.35
133.27
127.64
123.32
120.39
117.19
113.42
43.68
6-12
1-17-1-GY
f1 (ppm)

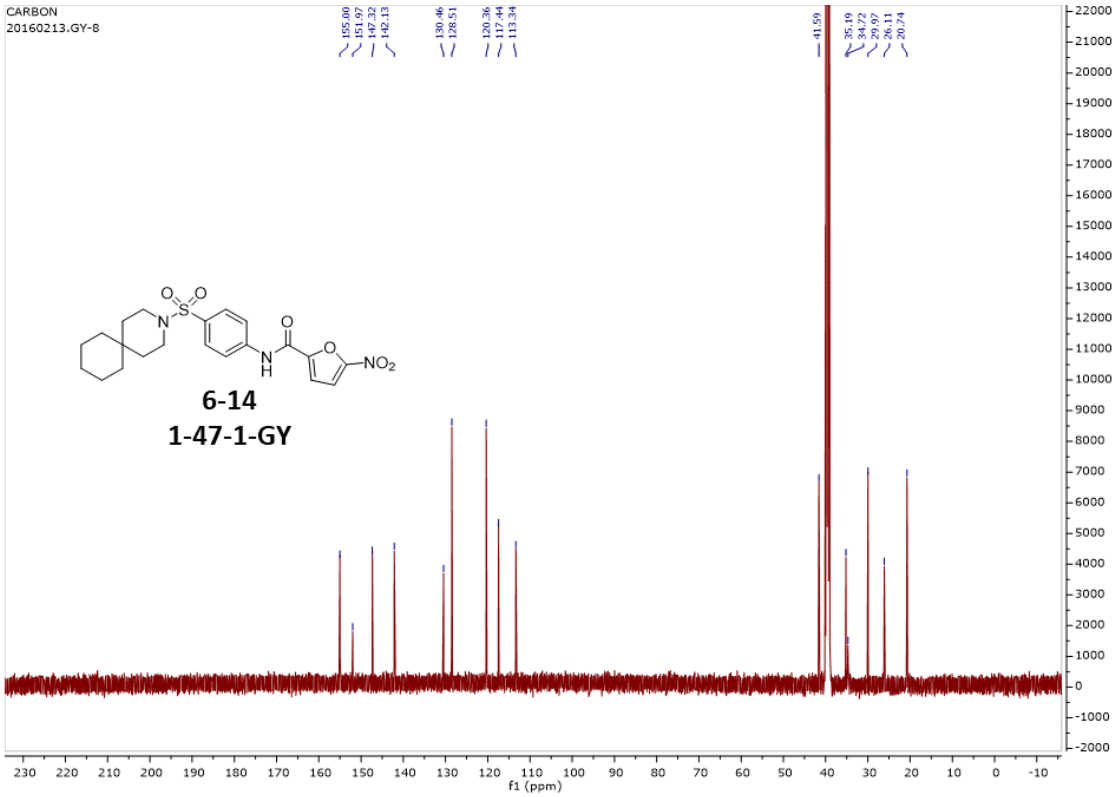

PROTON
20160212.GY-3-4th
11.11
9.36
9.35
9.33
8.85
8.77
8.77
8.76
8.75
8.45
8.45
8.45
8.43
8.43
8.43
7.96
7.95
7.94
7.94
7.93
7.92
7.91
7.81
7.80
7.79
7.78
4.61
4.60
1.00
0.98
1.02
1.04
1.01
5.90
1.08
1.97
6-13
1-39-1-GY
f1 (ppm)



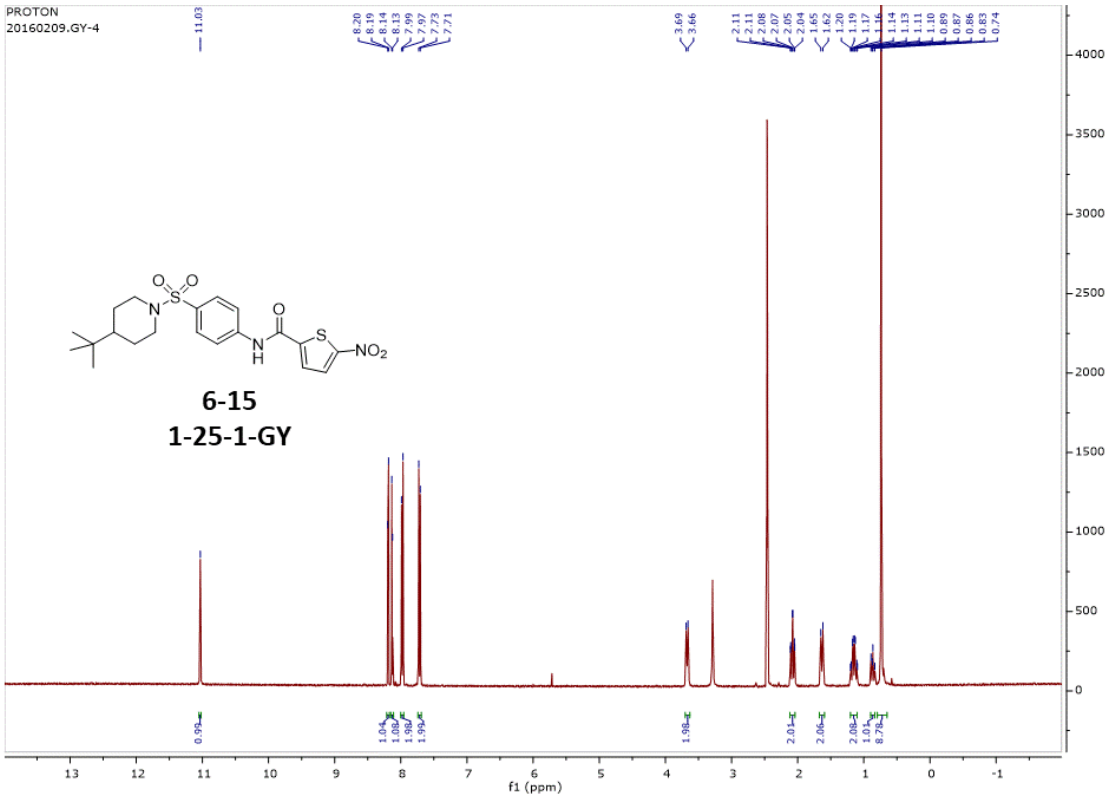

**6-13**
**1-39-1-GY**



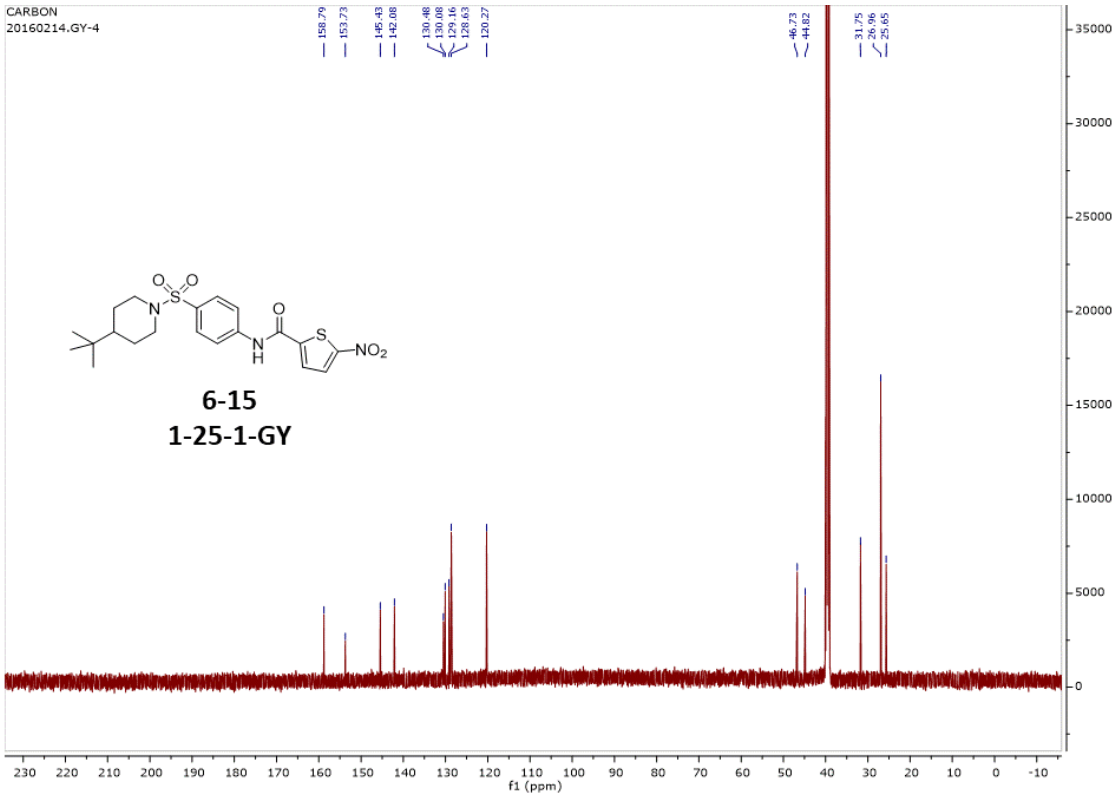

**6-14**
**1-47-1-GY**



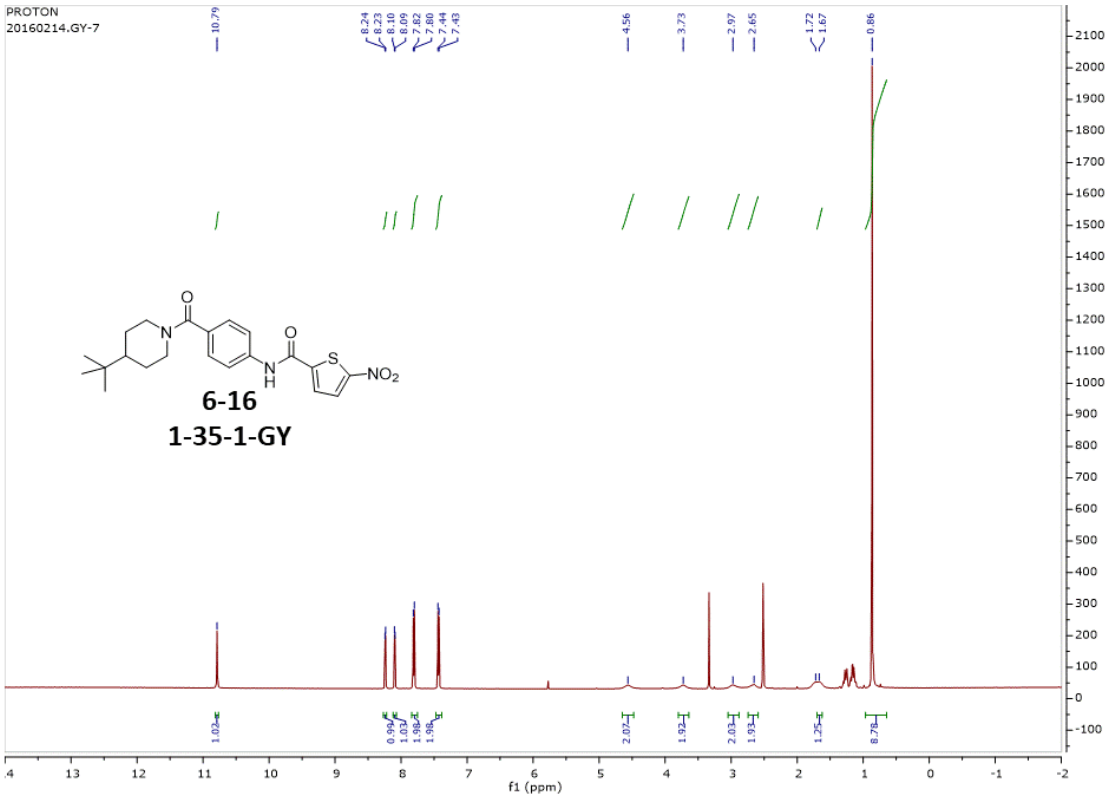

**6-14**
**1-47-1-GY**



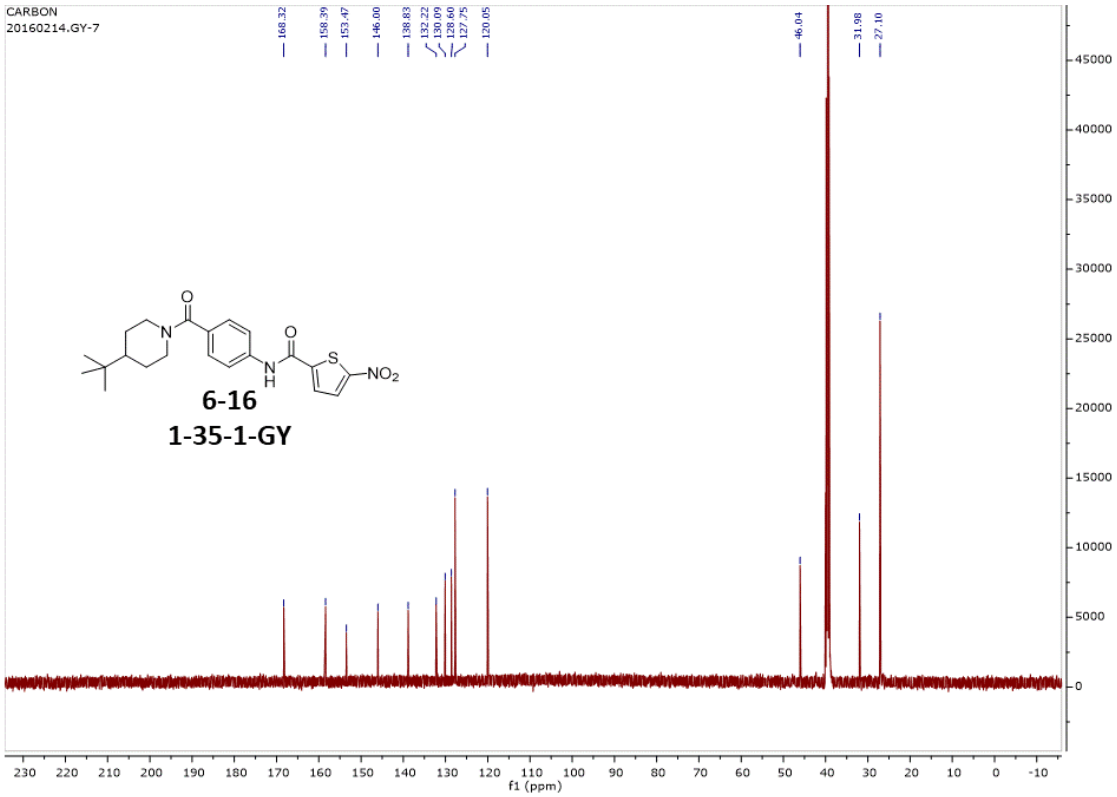

**6-15**
**1-25-1-GY**



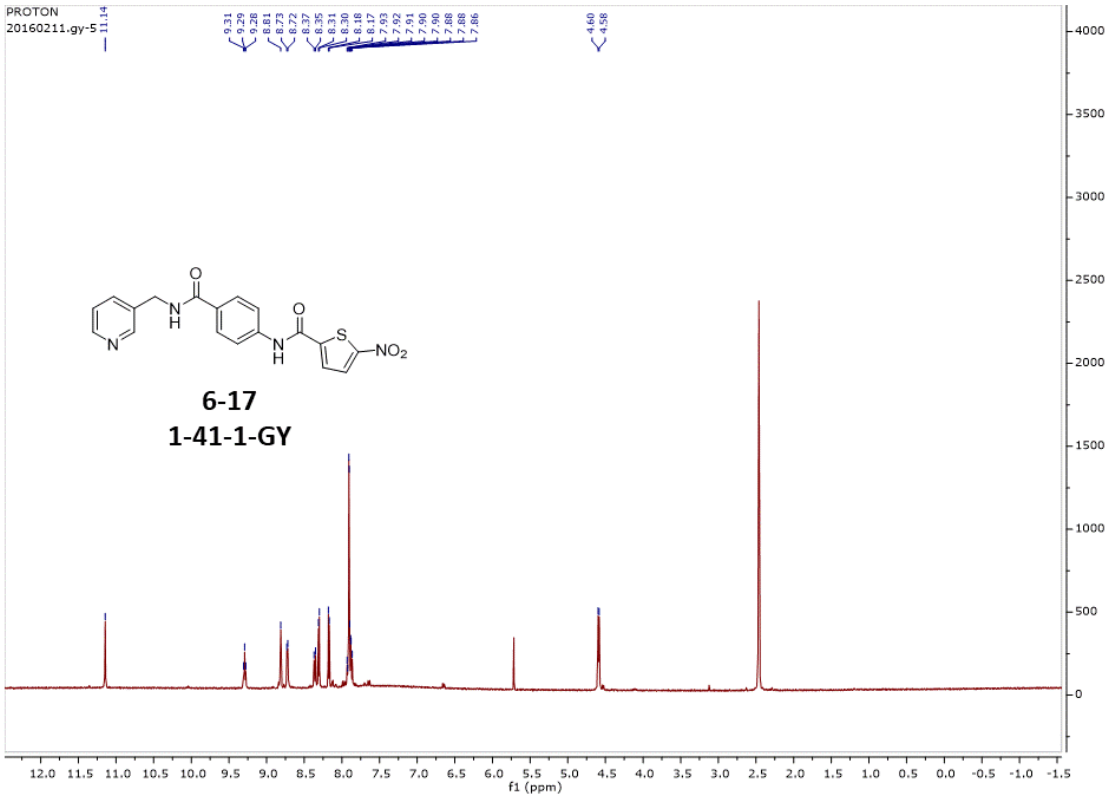

**6-15**
**1-25-1-GY**



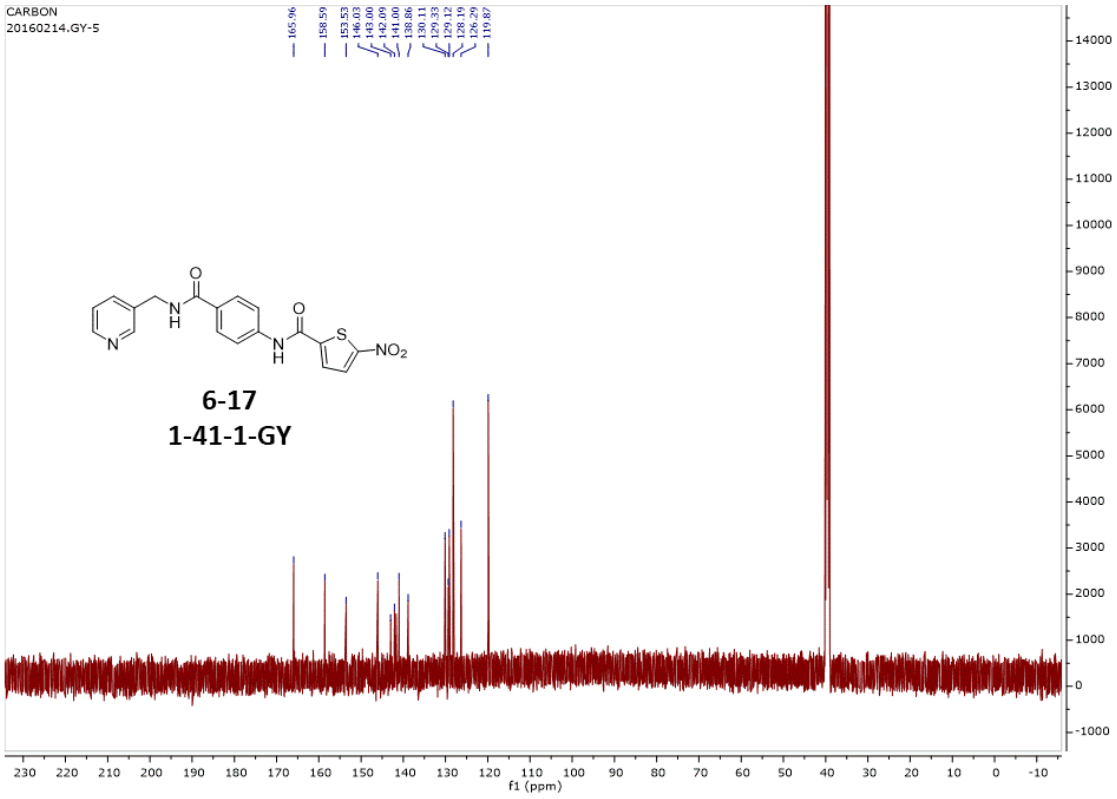

**6-16**
**1-35-1-GY**

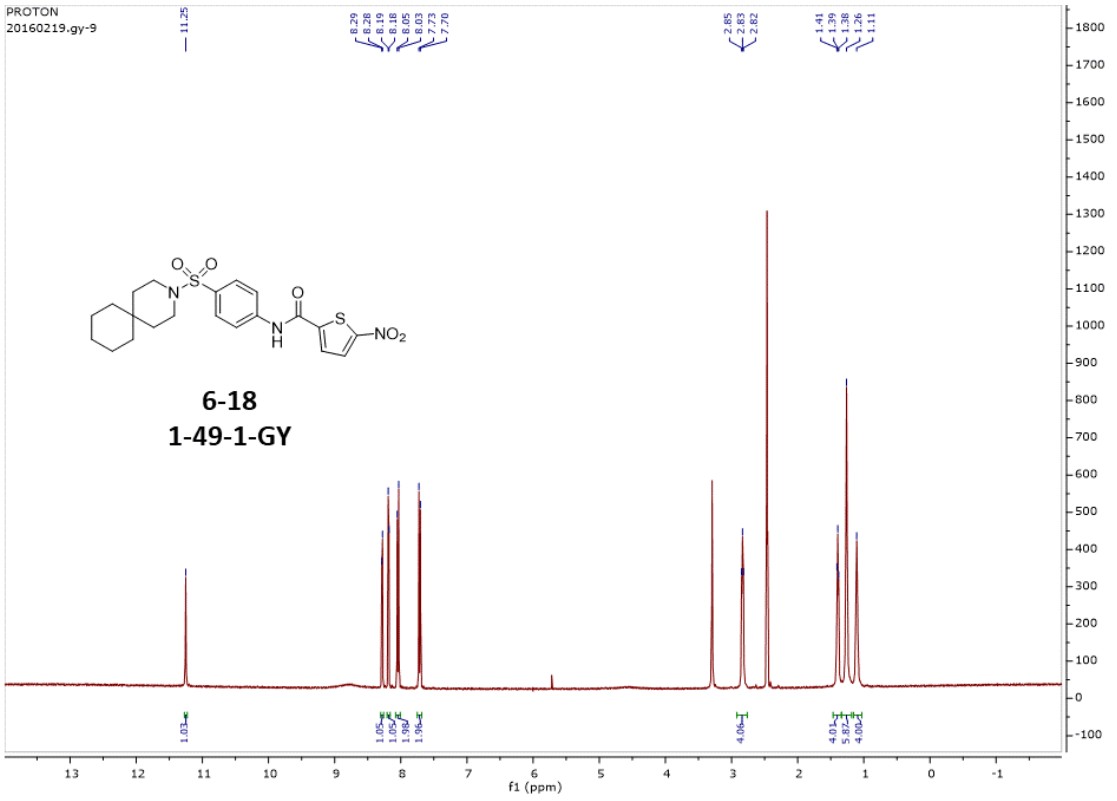


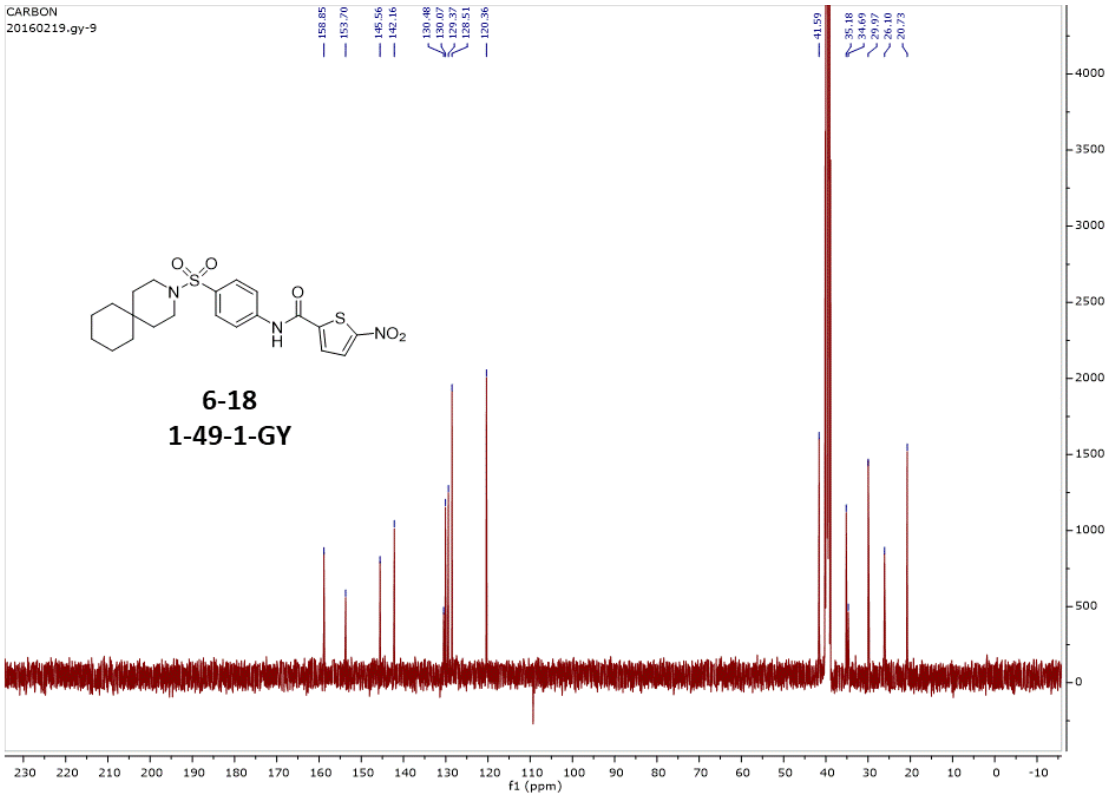

**6-16**
**1-35-1-GY**



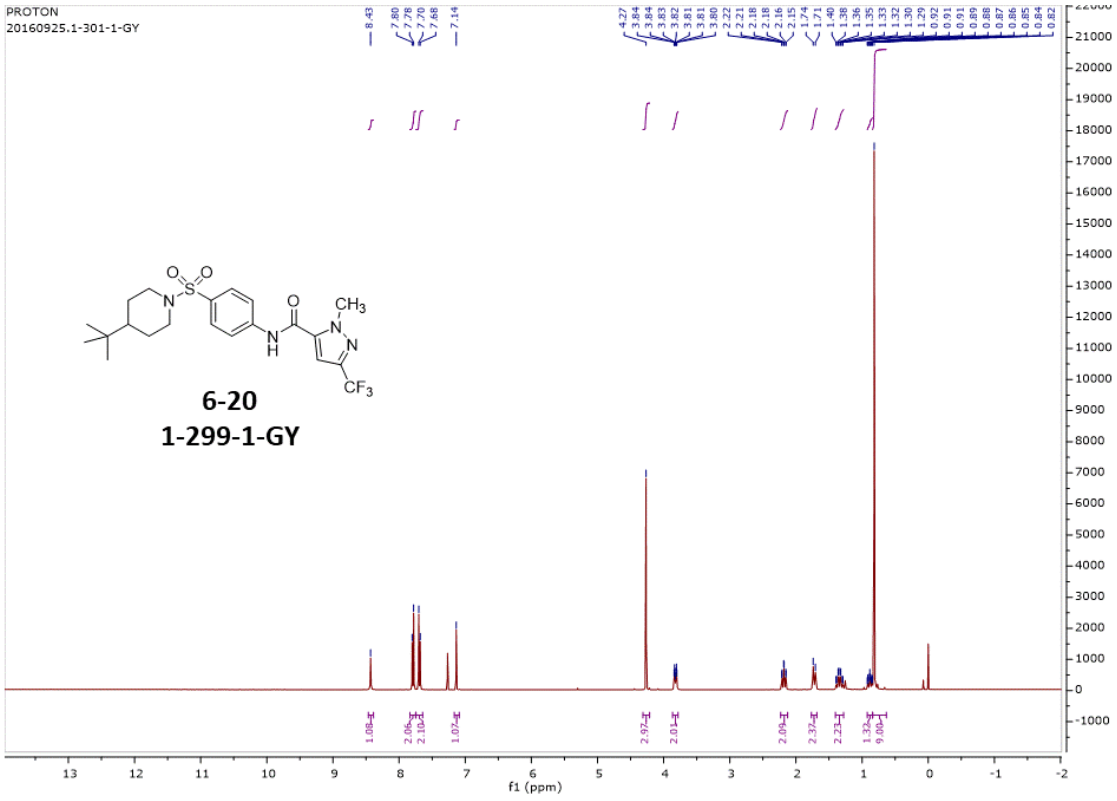

**6-17**
**1-41-1-GY**


CARBON
20160214.GY-5
165.96
158.59
153.53
146.03
143.00
142.09
141.00
138.86
130.11
129.33
129.12
128.19
126.29
119.87
O
N
H
N
O
N
H
S
NO2
6-17
1-41-1-GY
f1 (ppm)

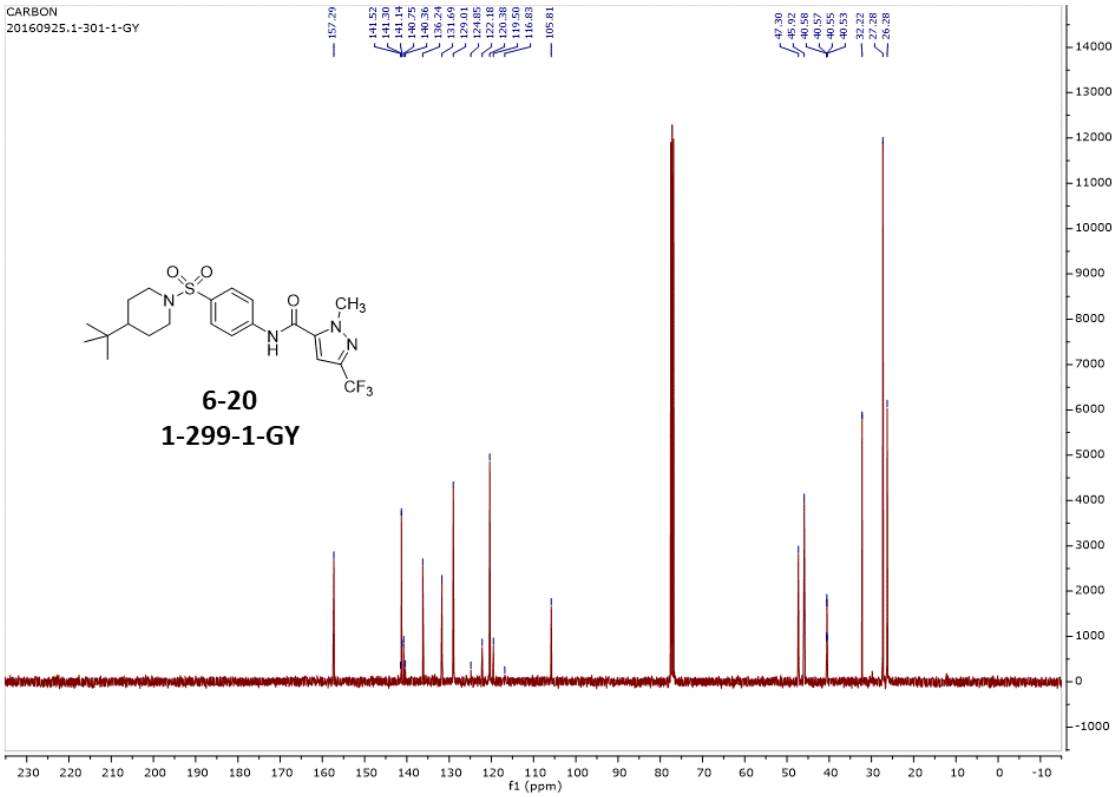

PROTON
20160219.gy-9
11.25
8.29
8.28
8.19
8.18
8.05
8.03
7.73
7.70
2.85
2.83
2.82
1.41
1.39
1.38
1.26
1.11
1.03
1.05
1.05
1.98
1.96
4.06
4.01
5.82
4.00
O
S
O
N
O
N
H
S
NO2
6-18
1-49-1-GY
f1 (ppm)



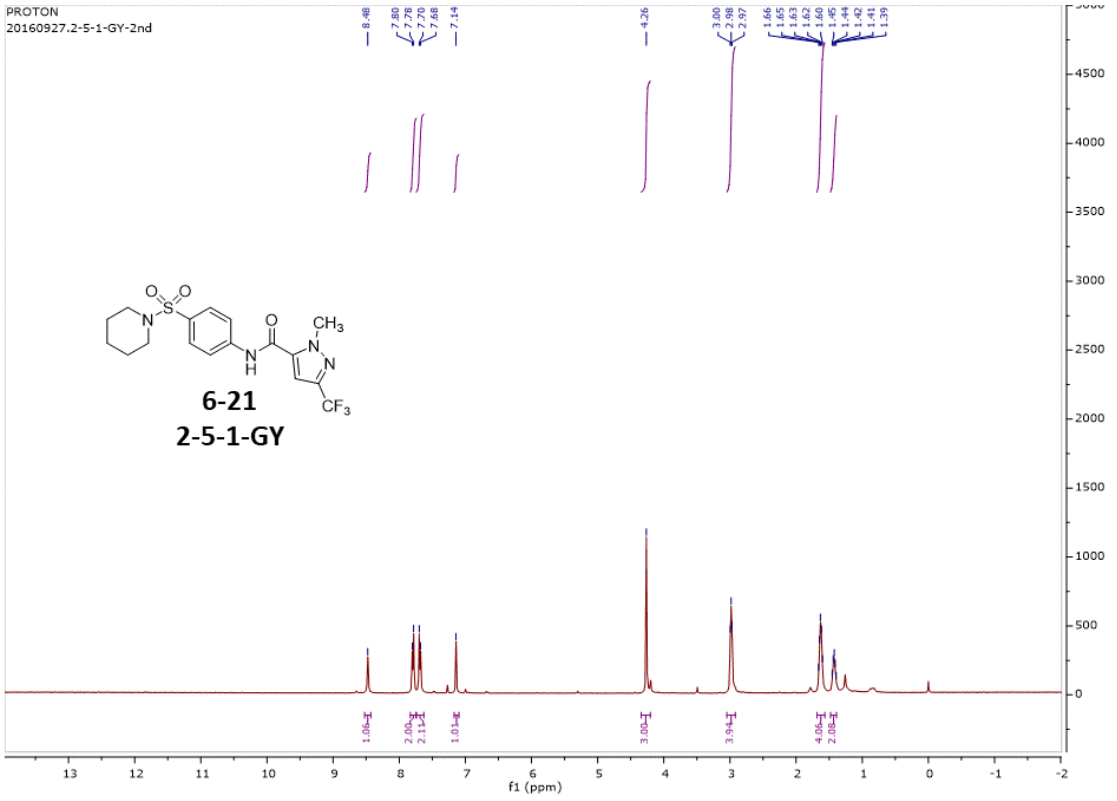

**6-18**
**1-49-1-GY**



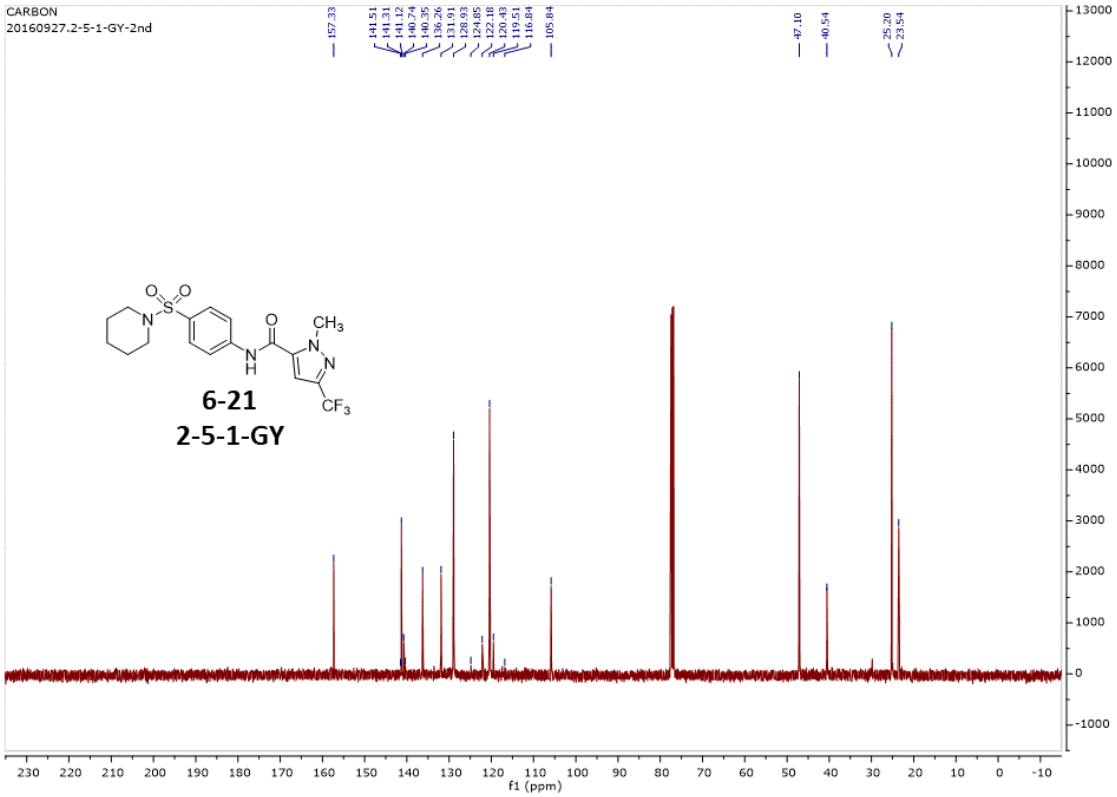

**6-20**
**1-299-1-GY**



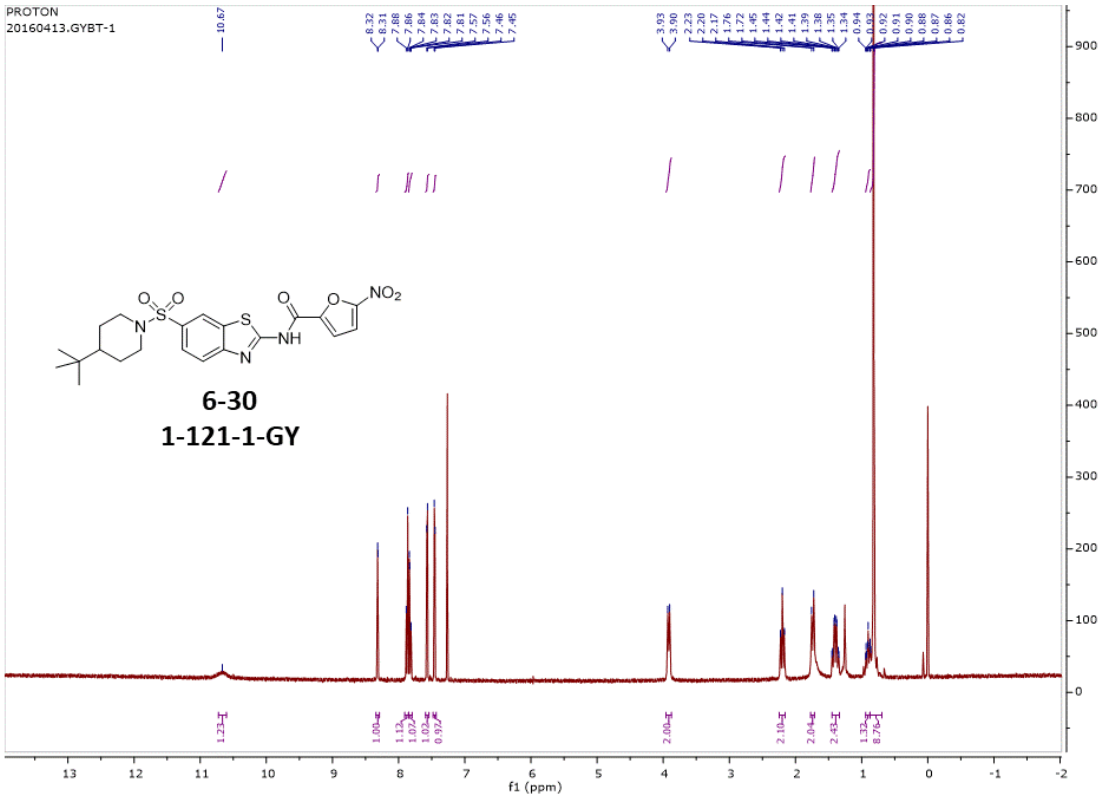

**6-20**
**1-299-1-GY**



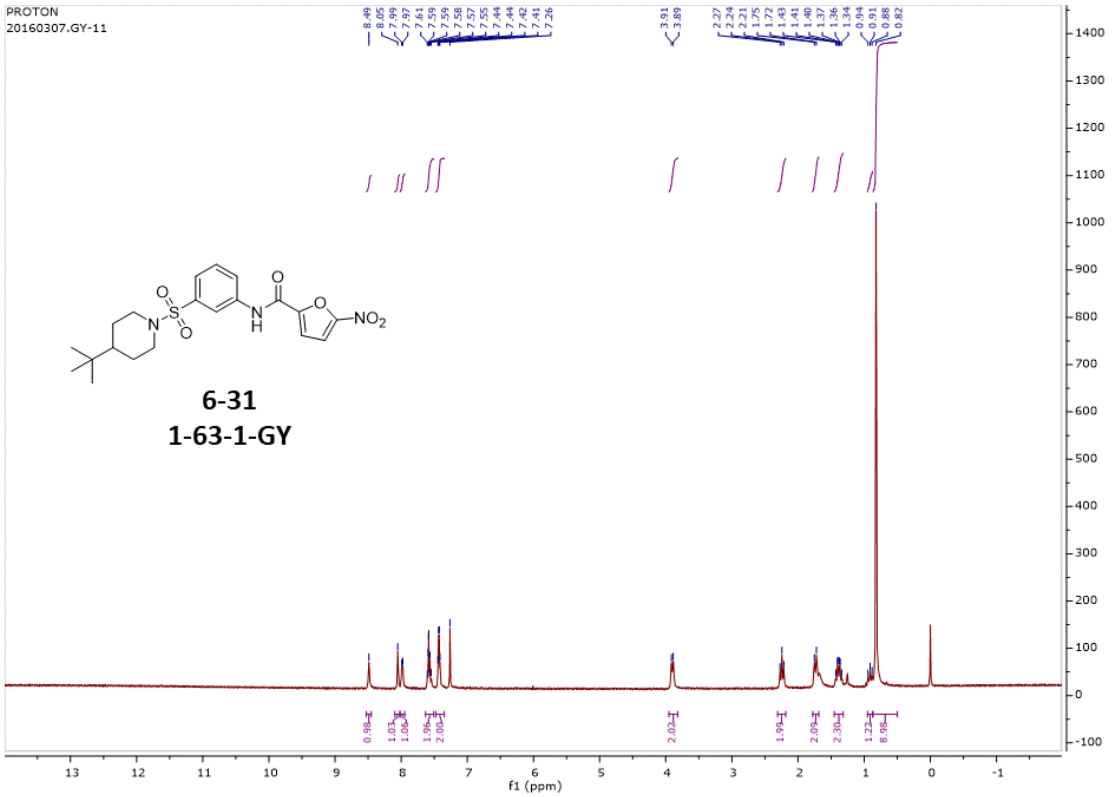

**6-21**
**2-5-1-GY**

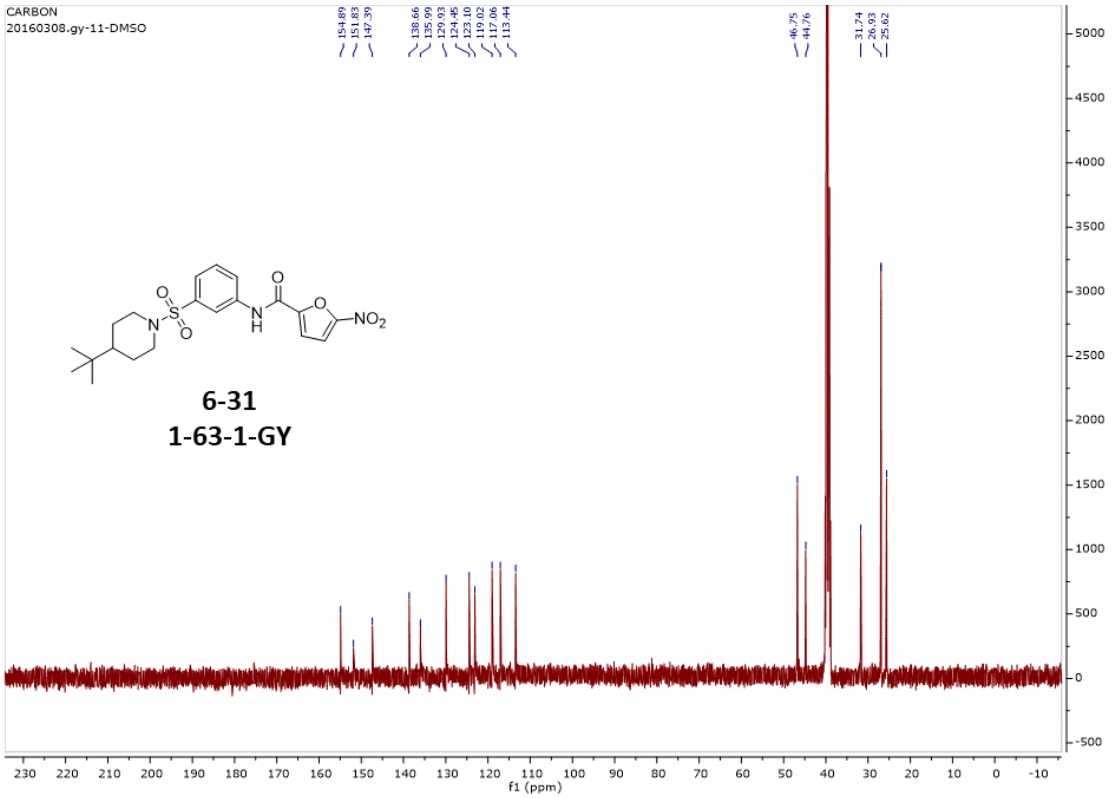


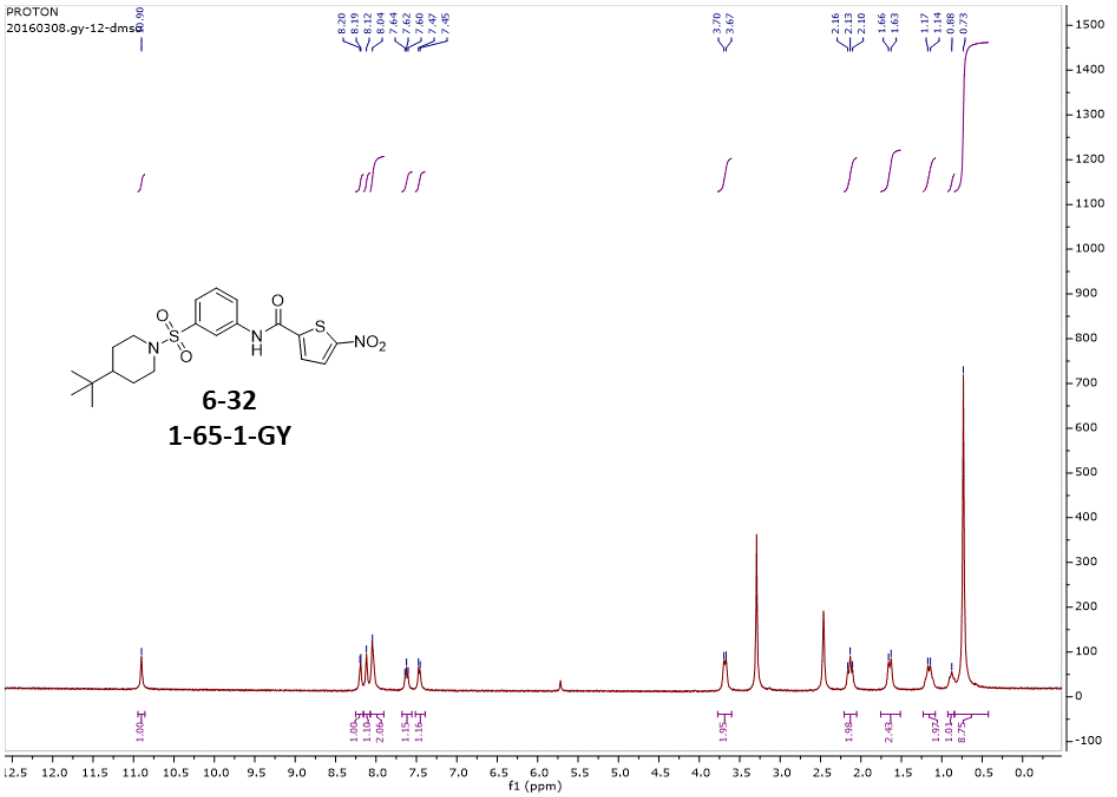

**6-21**
**2-5-1-GY**

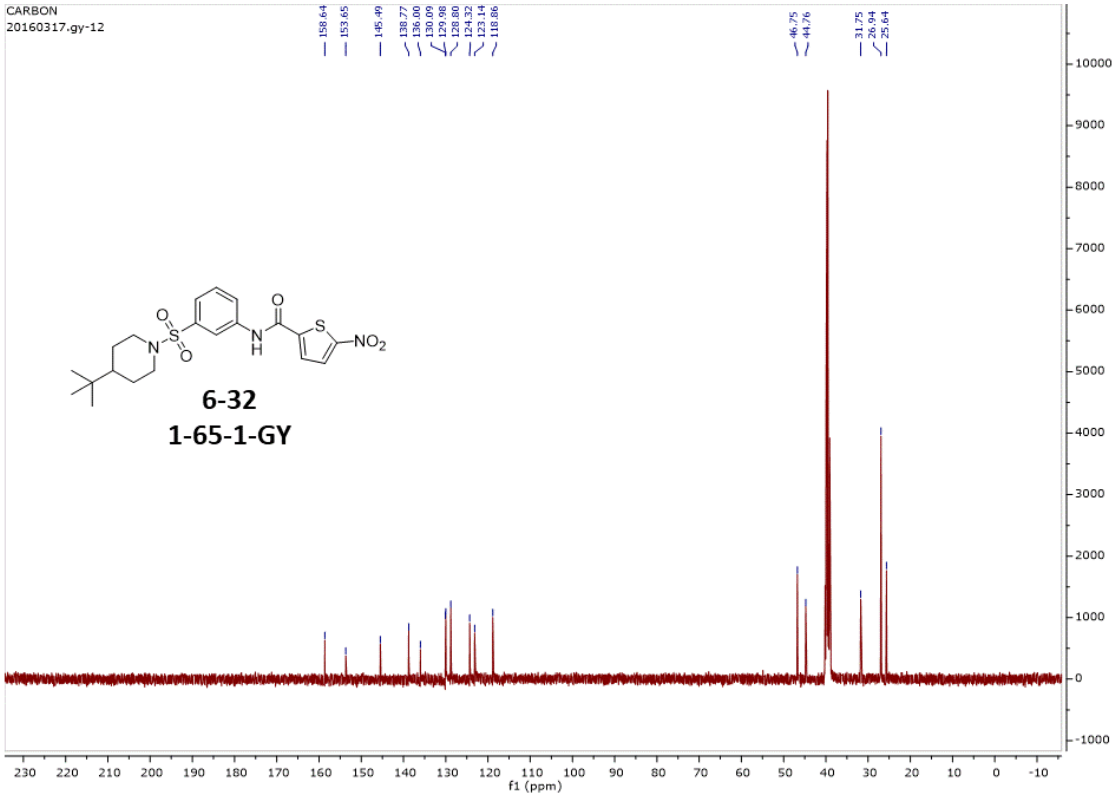


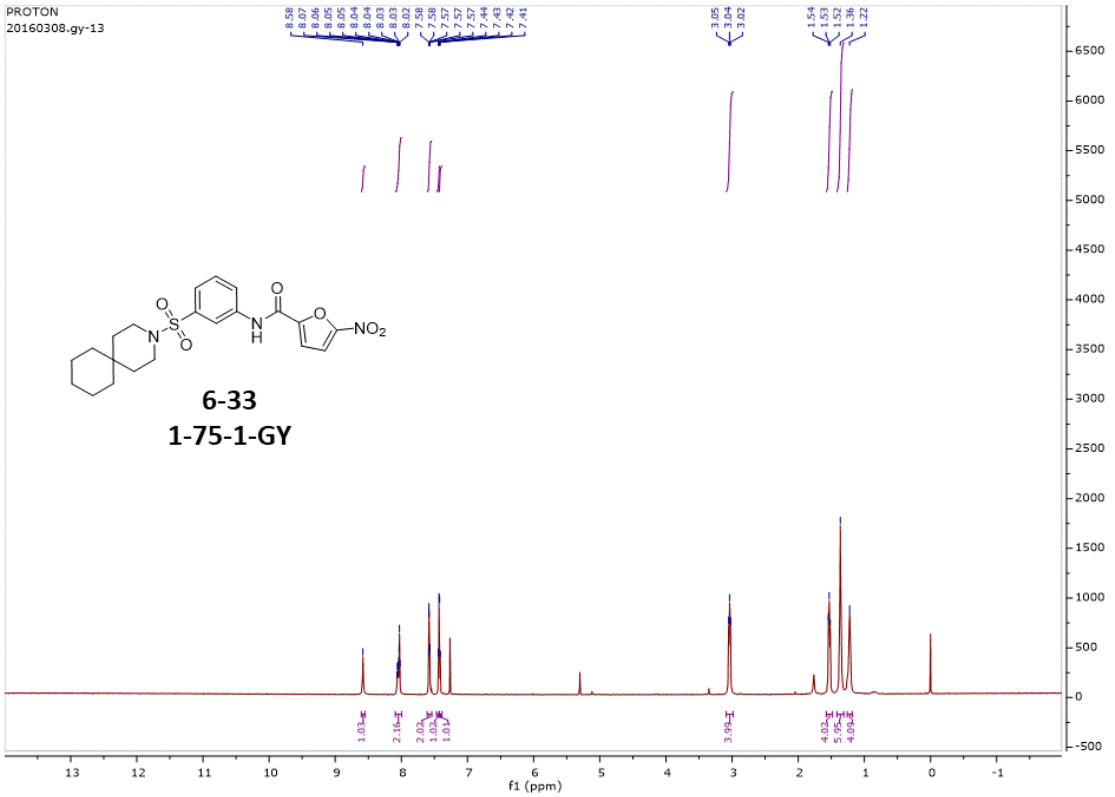

**6-30**
**1-121-1-GY**

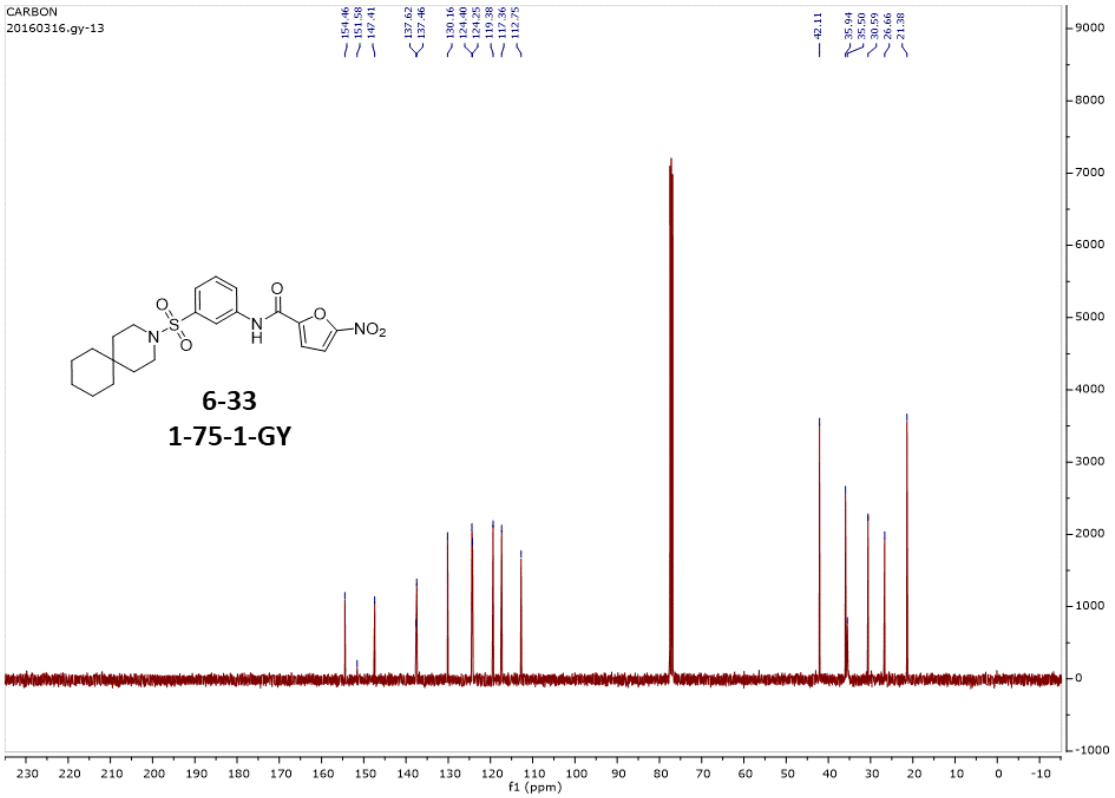

PROTON
20160307.GY-11
6-31
1-63-1-GY
f1 (ppm)

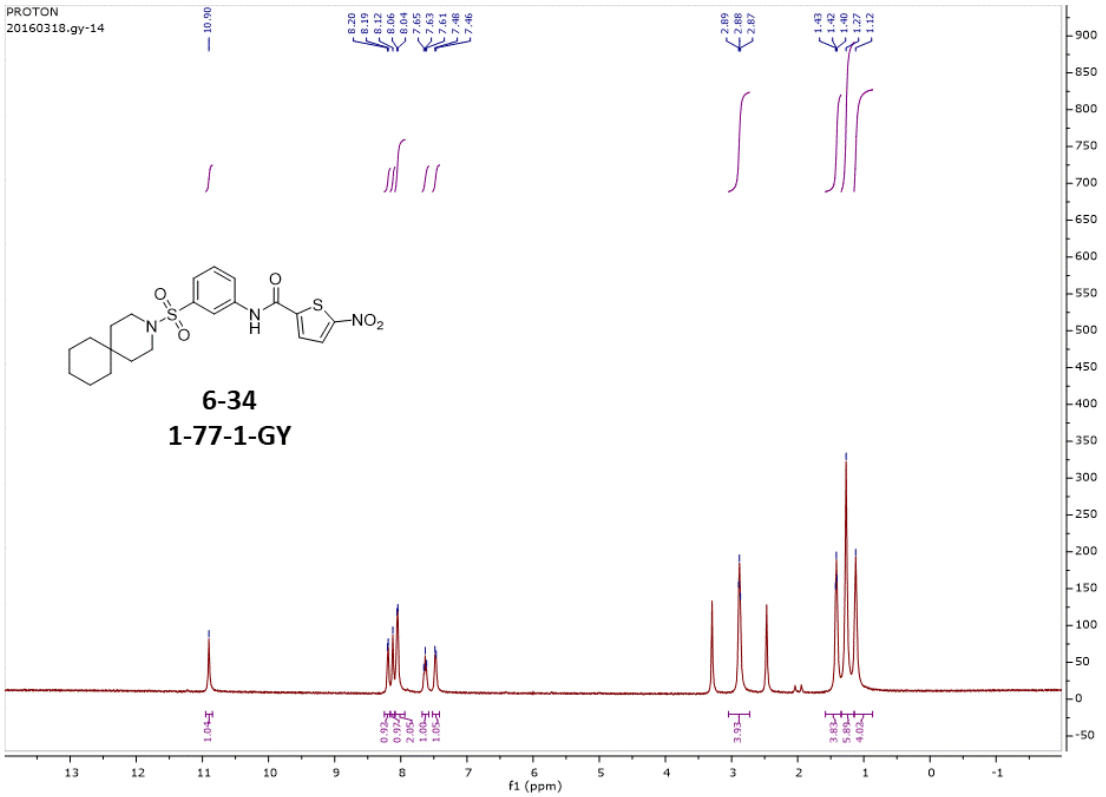

CARBON
20160308.gy-11-DMSO
6-31
1-63-1-GY
f1 (ppm)

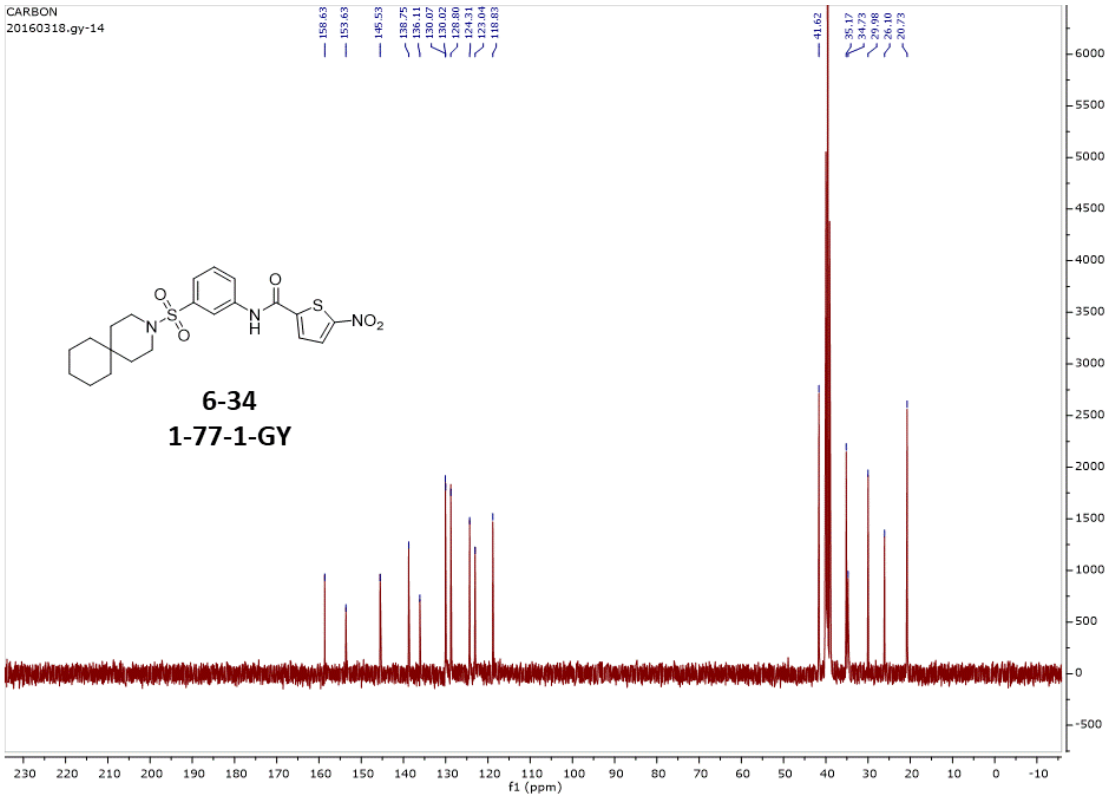

PROTON
20160308.gy-12-dmso
6-32
1-65-1-GY
f1 (ppm)

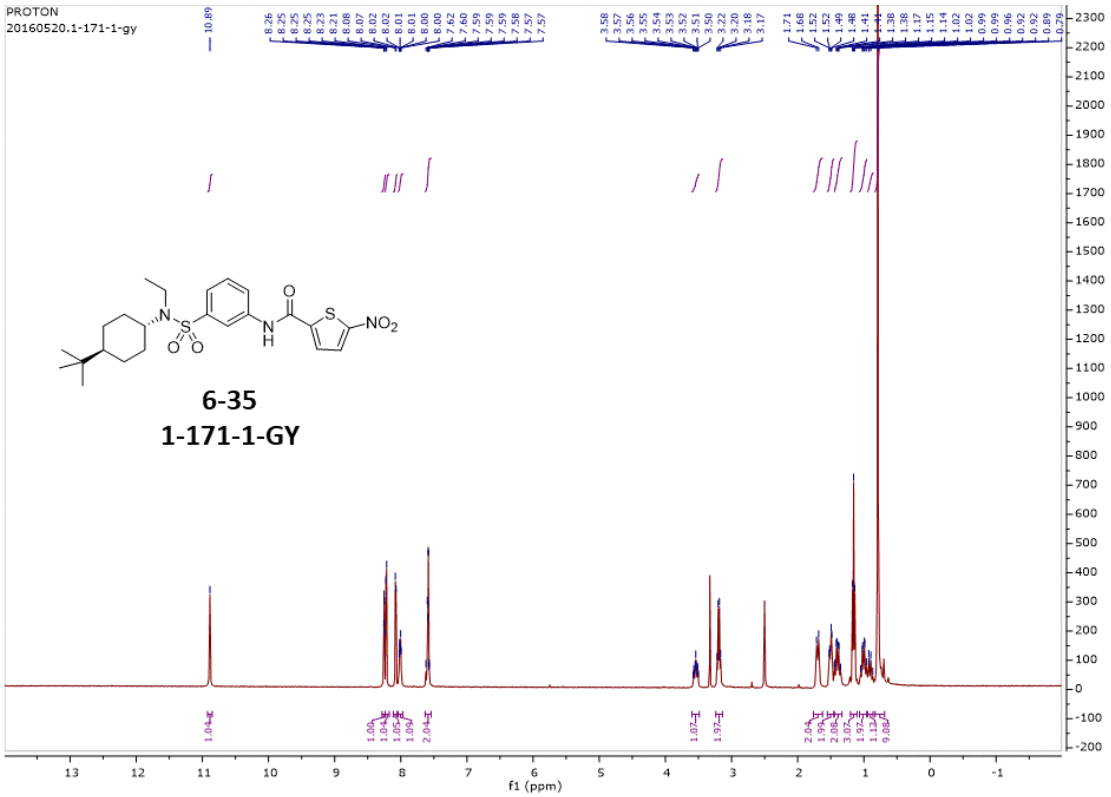

CARBON
20160317.gy-12
6-32
1-65-1-GY
f1 (ppm)

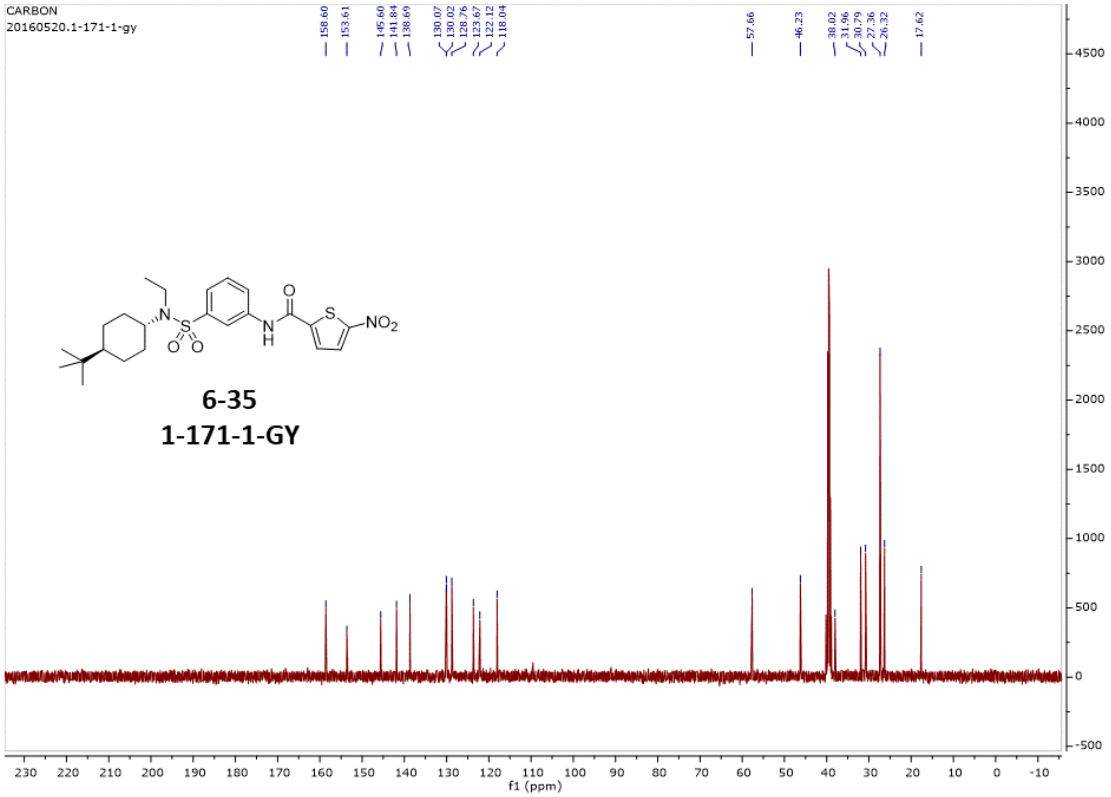

PROTON
20160308.gy-13
6-33
1-75-1-GY
f1 (ppm)

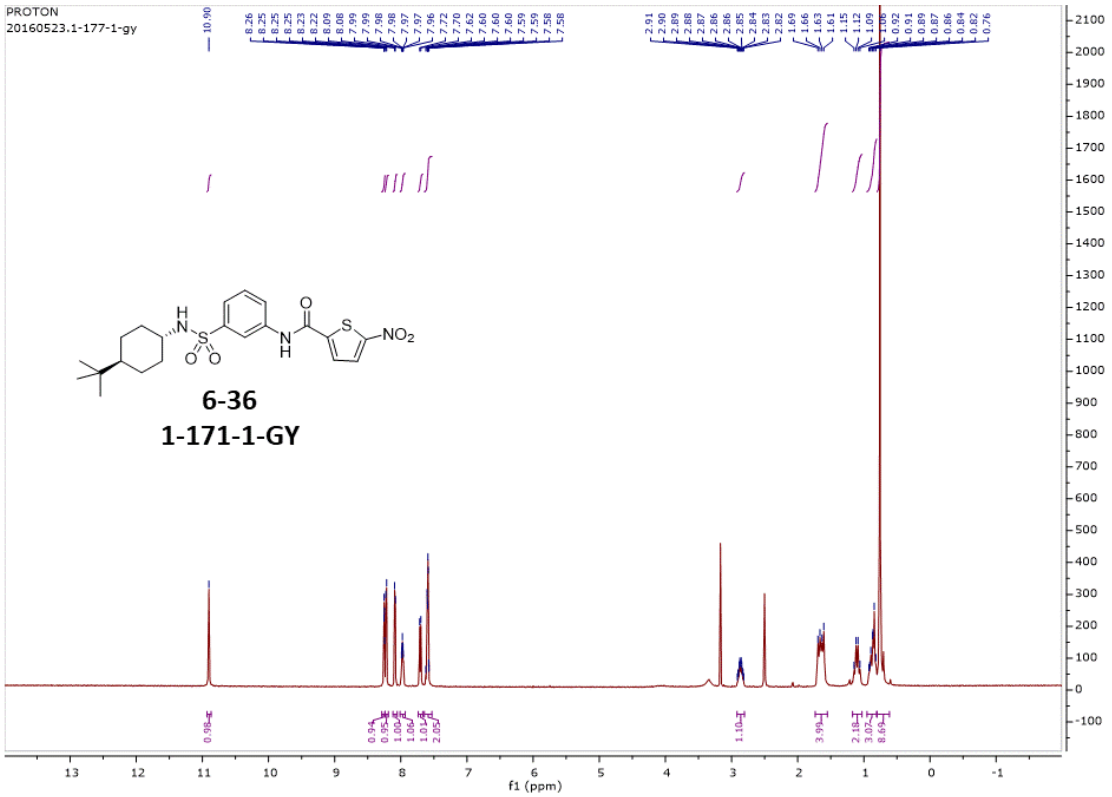

CARBON
20160316.gy-13
6-33
1-75-1-GY
f1 (ppm)

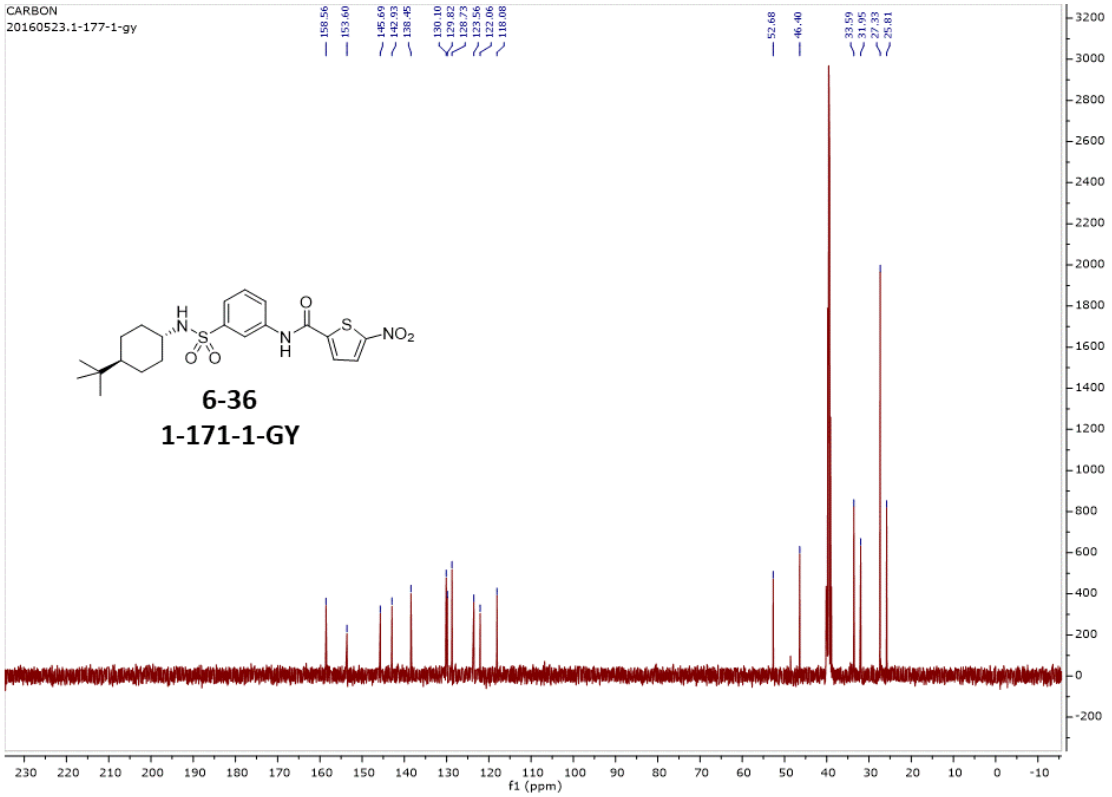

PROTON
20160318.gy-14
6-34
1-77-1-GY
f1 (ppm)

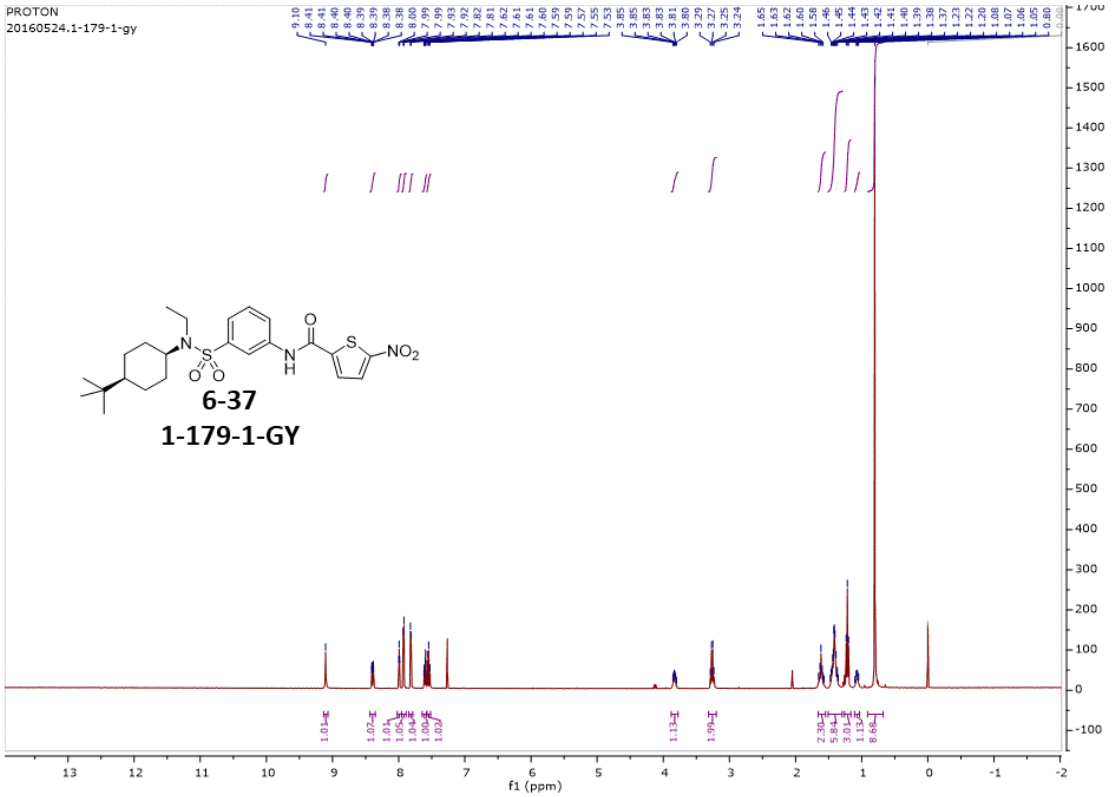

CARBON
20160318.gy-14
6-34
1-77-1-GY
f1 (ppm)

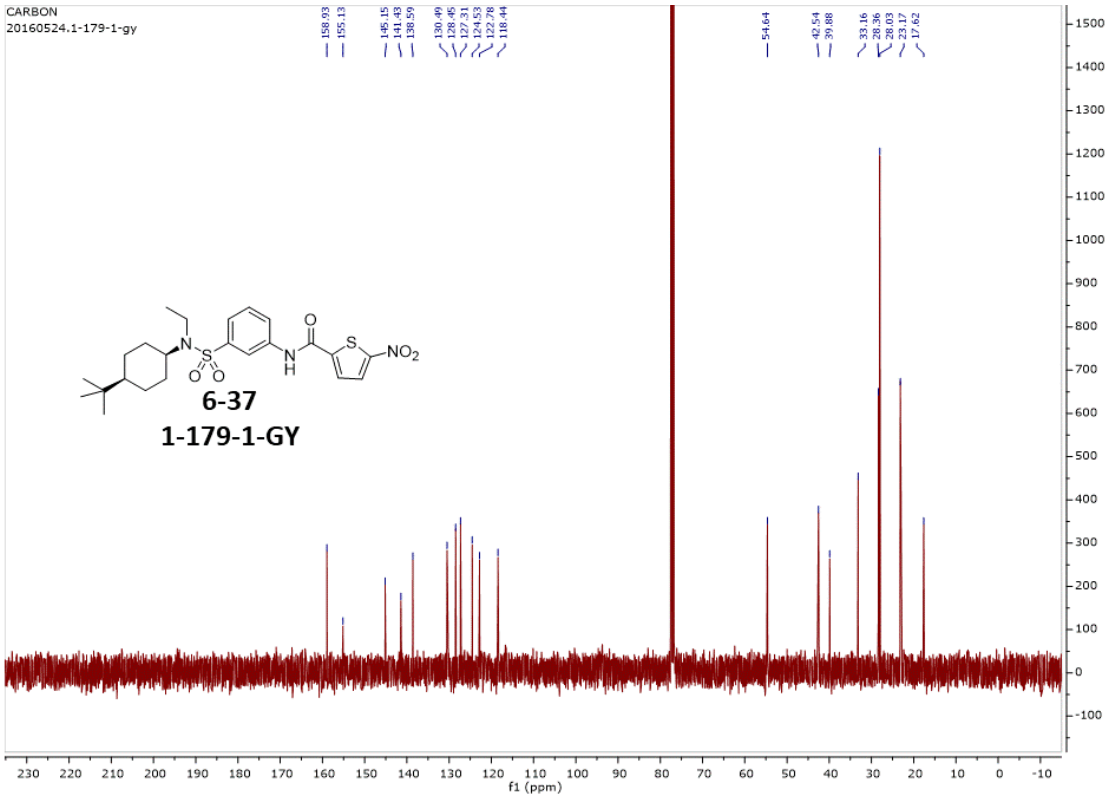

PROTON
20160520.1-171-1-gy
6-35
1-171-1-GY
f1 (ppm)

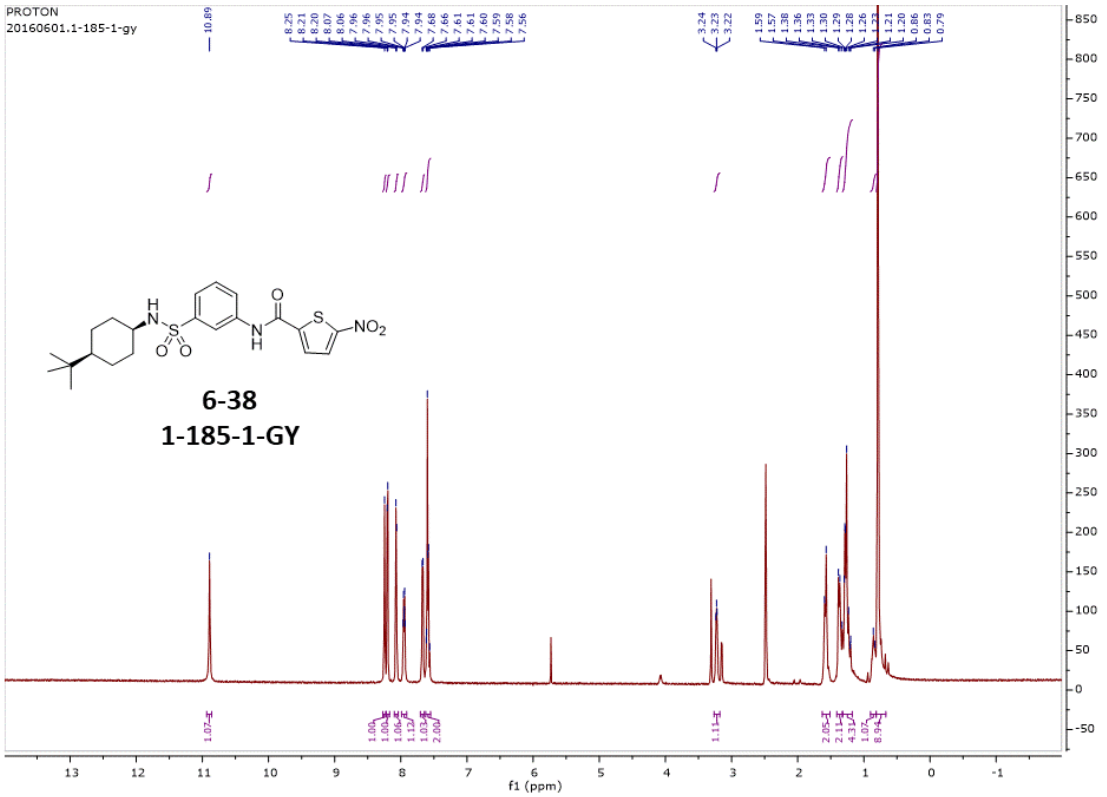

CARBON
20160520.1-171-1-gy
6-35
1-171-1-GY
f1 (ppm)

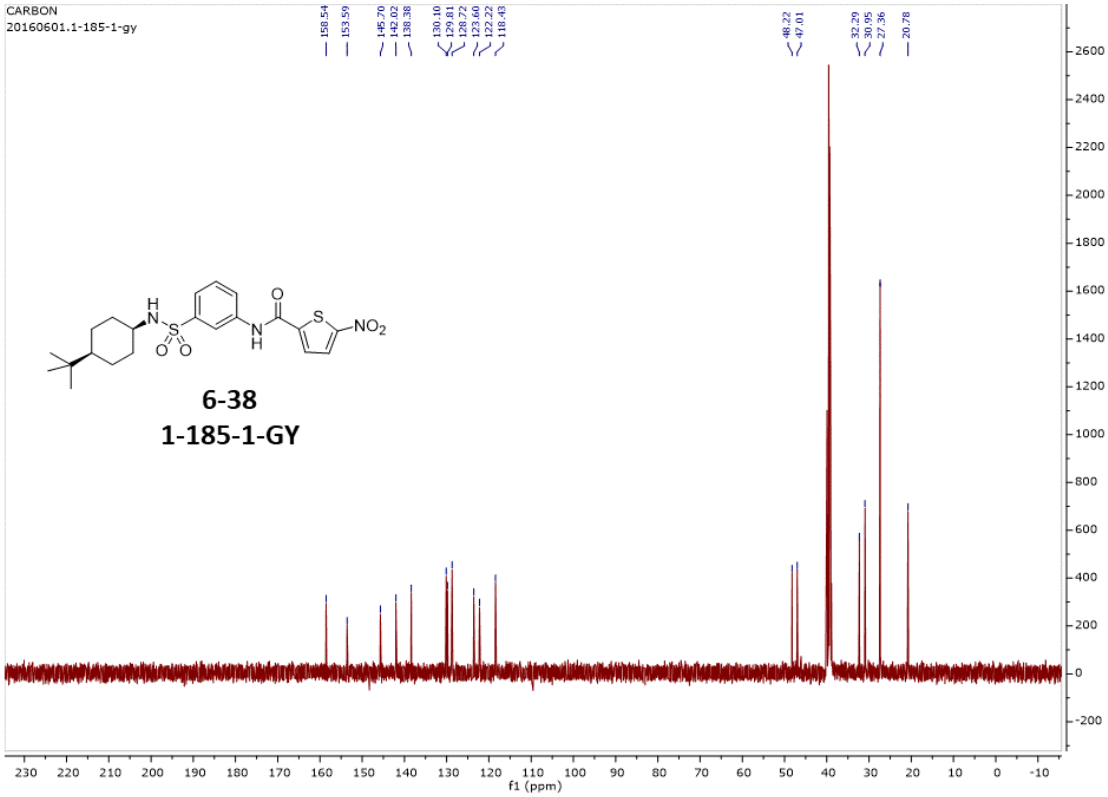

PROTON
20160523.1-177-1-gy
6-36
1-171-1-GY
f1 (ppm)

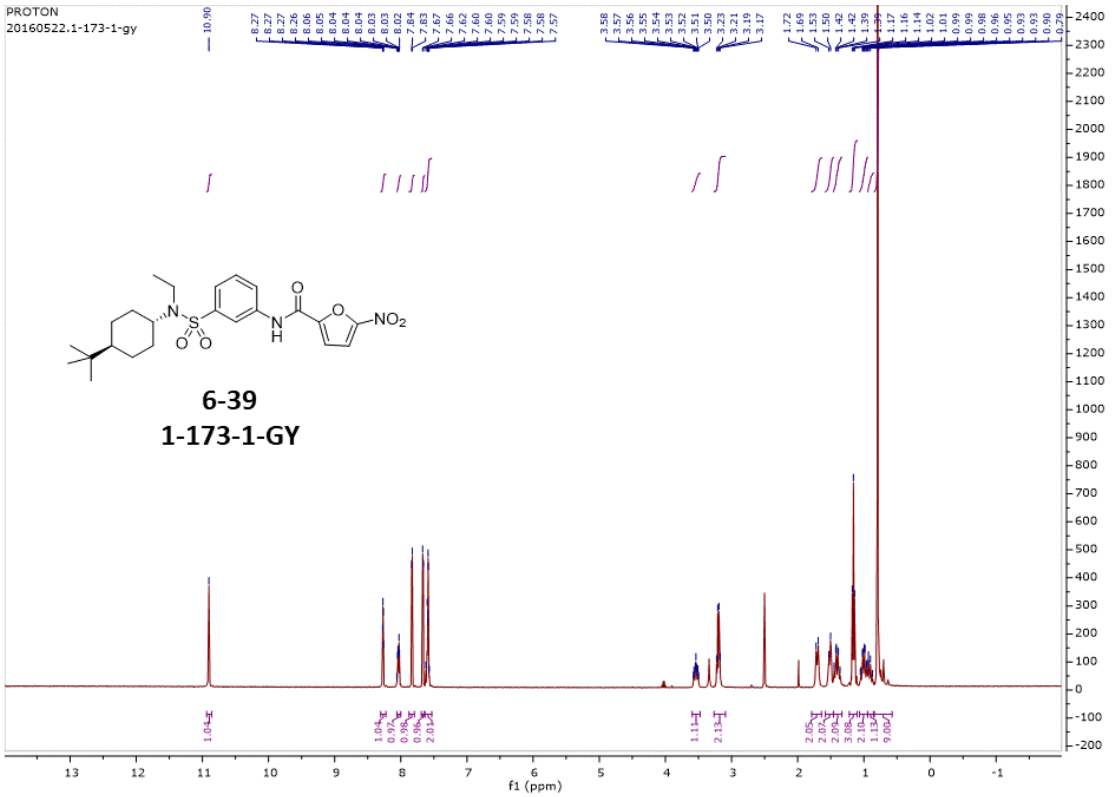

CARBON
20160523.1-177-1-gy
6-36
1-171-1-GY
f1 (ppm)

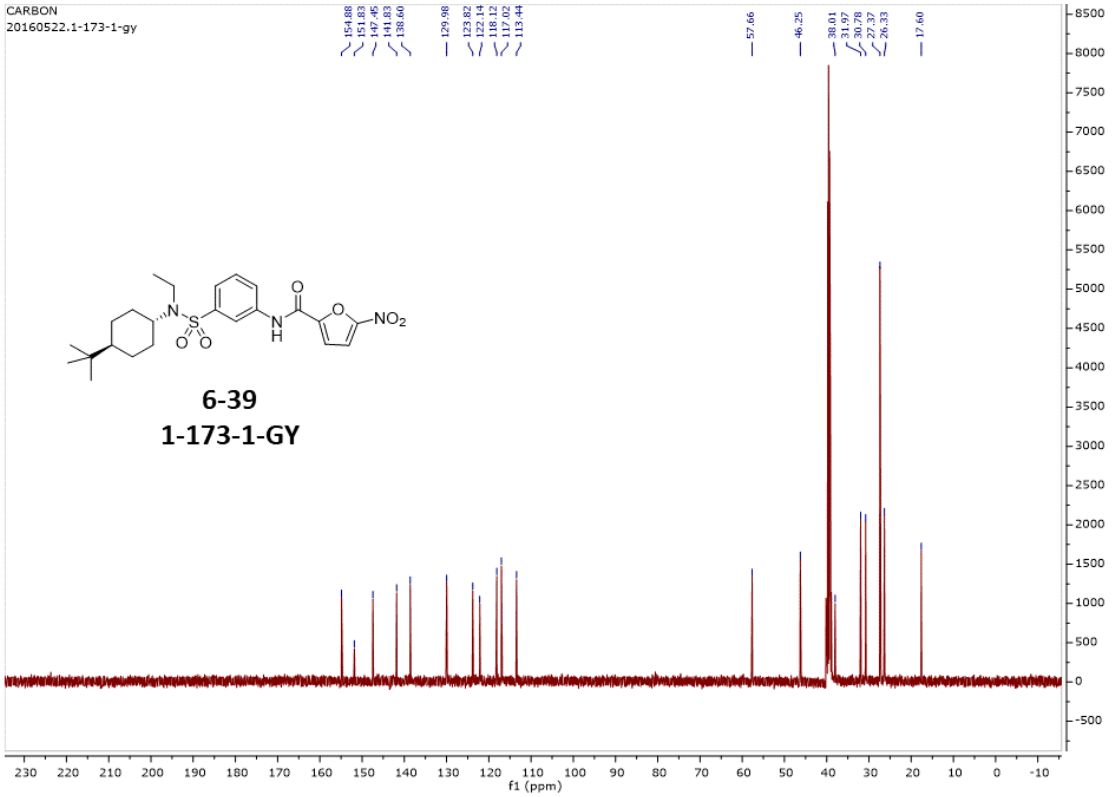

PROTON
20160524.1-179-1-gy
6-37
1-179-1-GY
f1 (ppm)

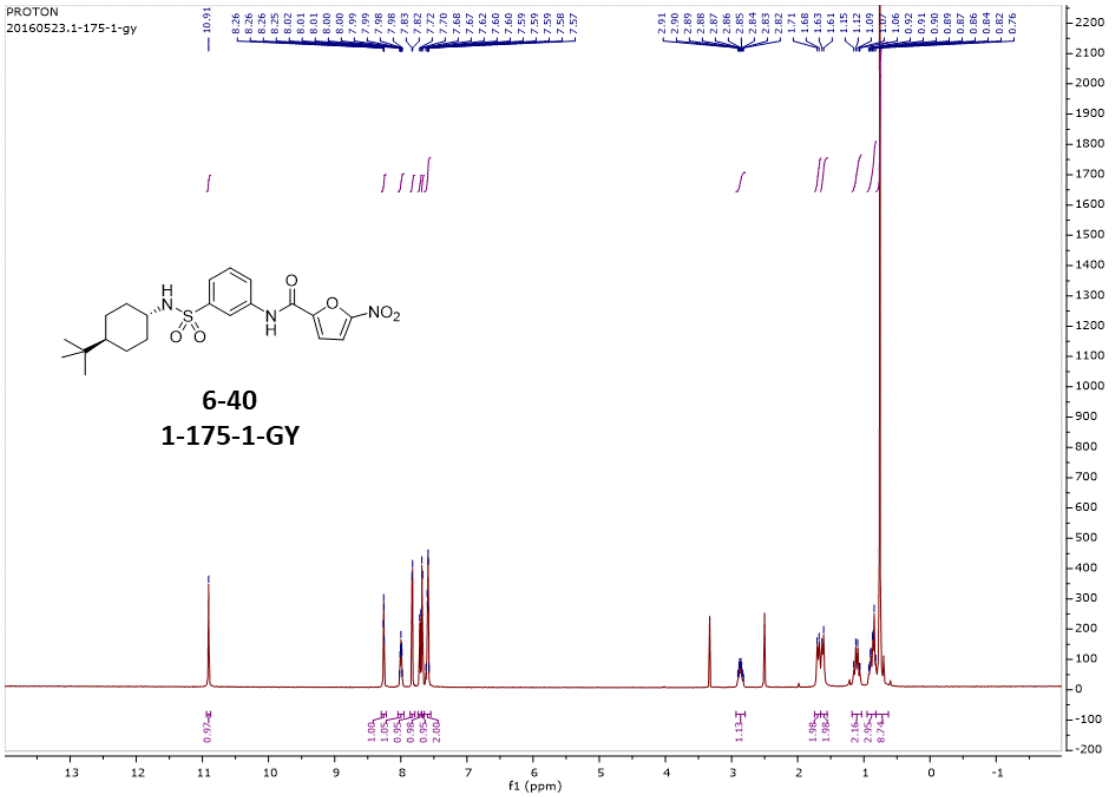

CARBON
20160524.1-179-1-gy
6-37
1-179-1-GY
f1 (ppm)

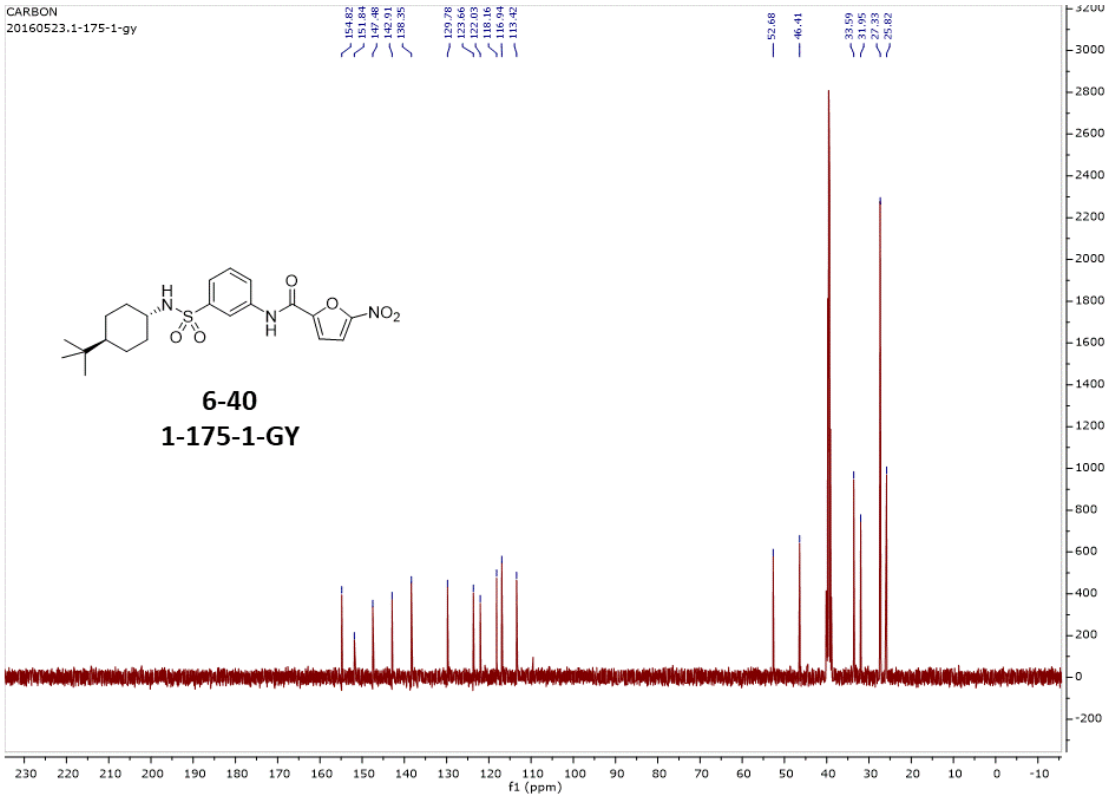

PROTON
20160601.1-185-1-gy
6-38
1-185-1-GY
f1 (ppm)

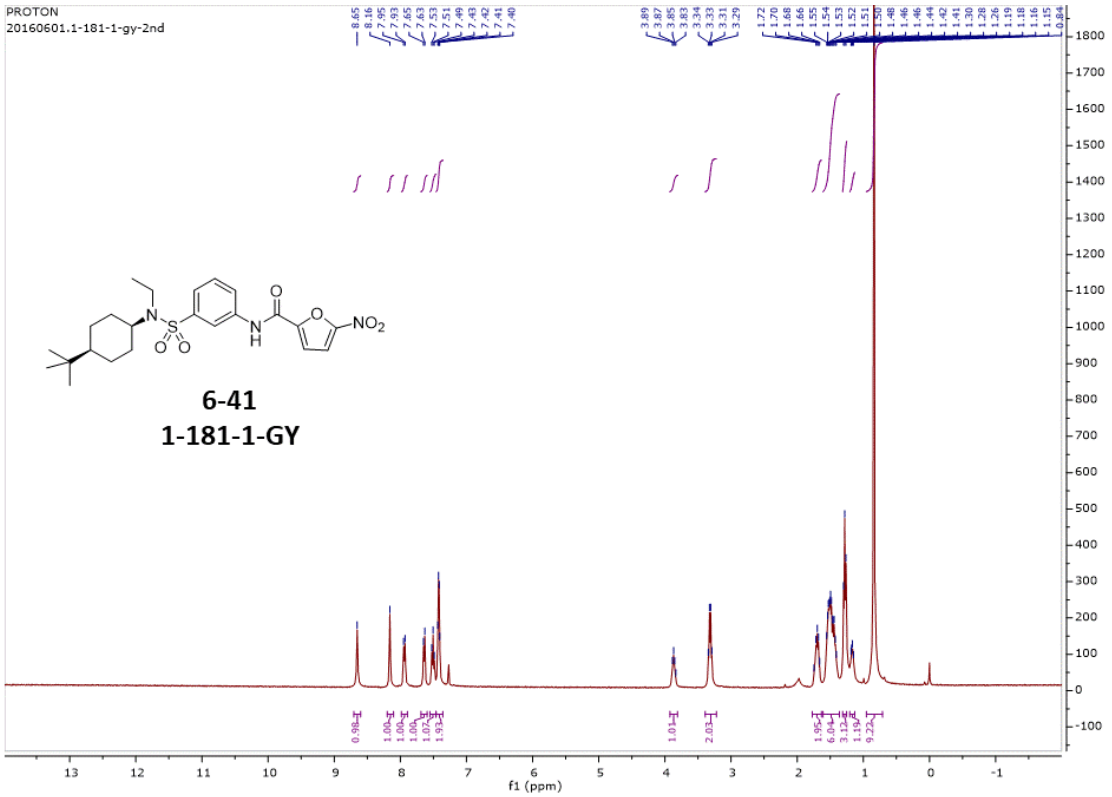

CARBON
20160601.1-185-1-gy
6-38
1-185-1-GY
f1 (ppm)

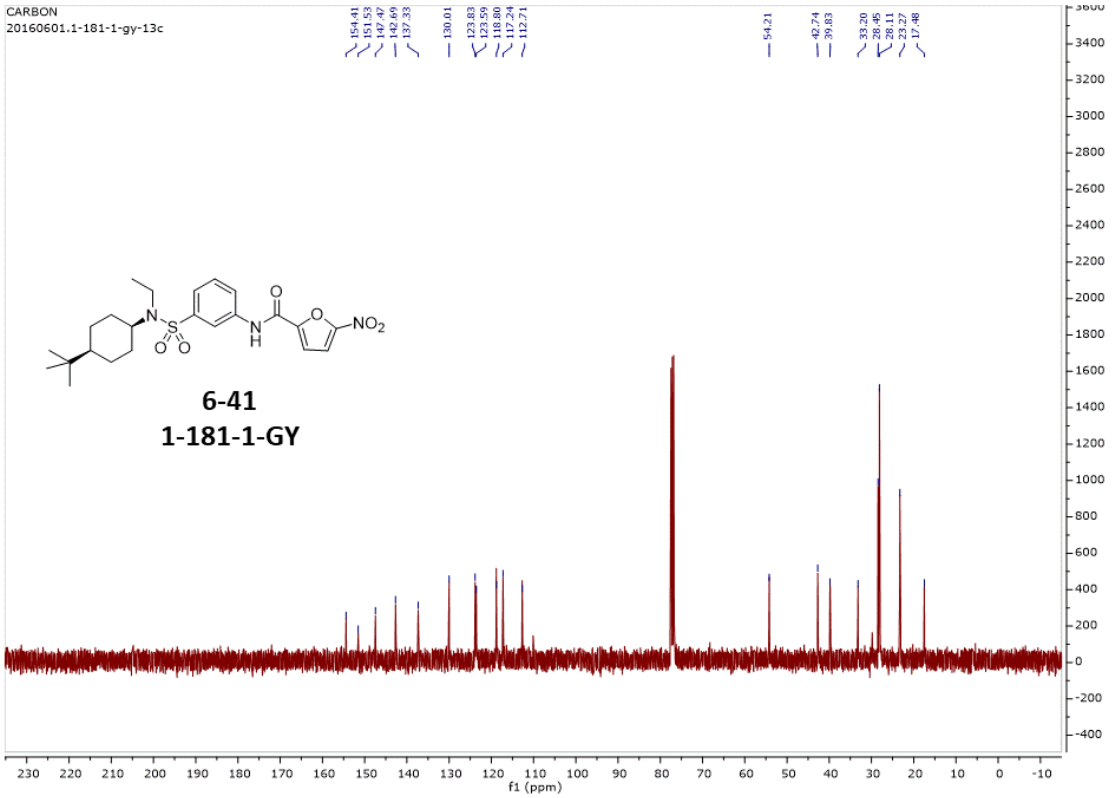

PROTON
20160522.1-173-1-gy
6-39
1-173-1-GY
f1 (ppm)

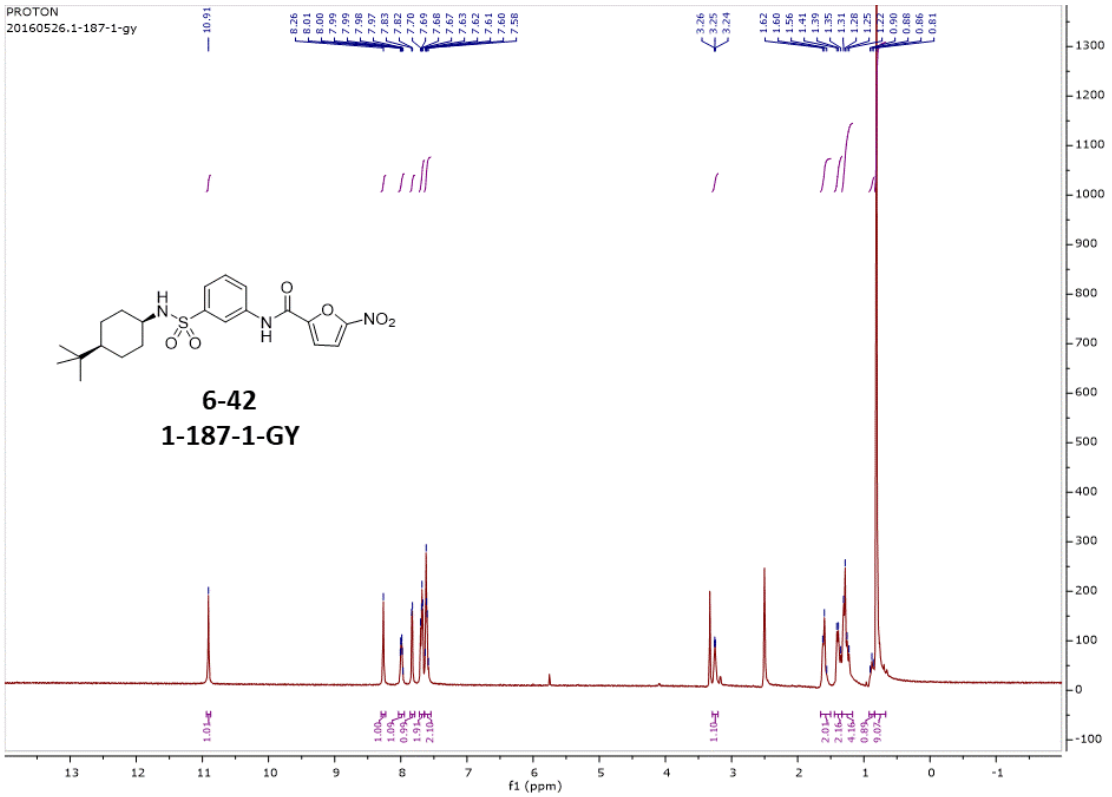

CARBON
20160522.1-173-1-gy
6-39
1-173-1-GY
f1 (ppm)

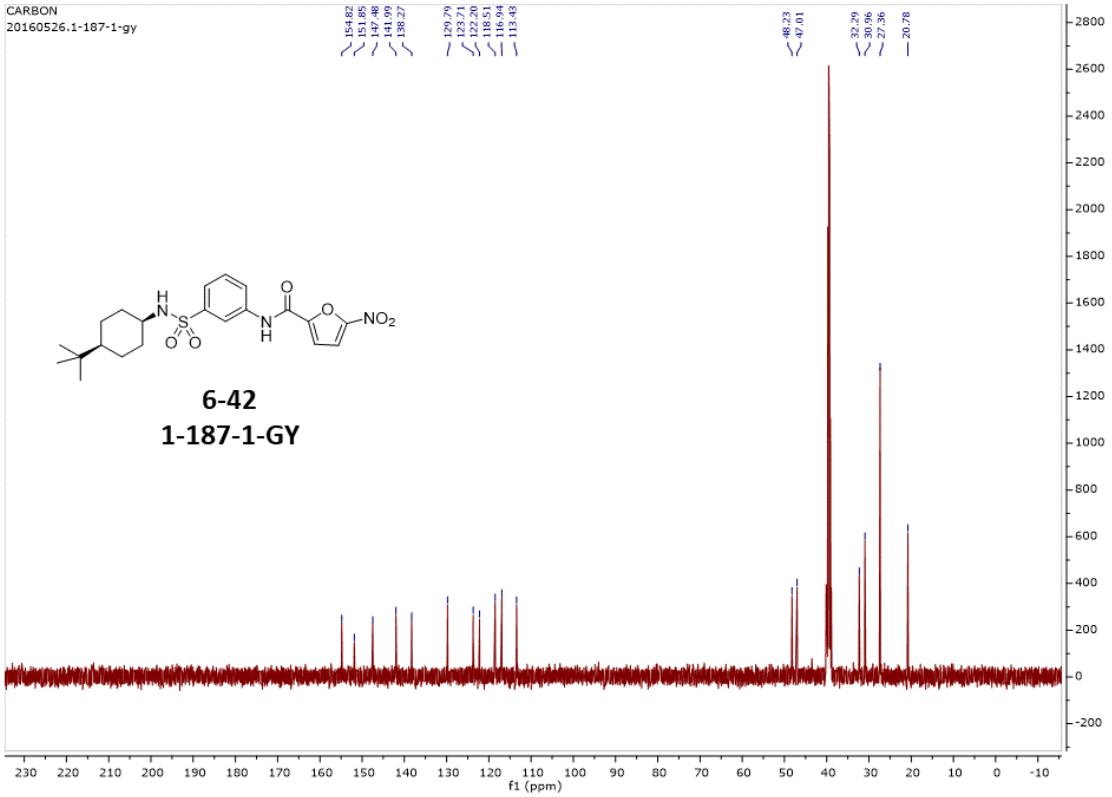

PROTON
20160523.1-175-1-gy
6-40
1-175-1-GY
f1 (ppm)

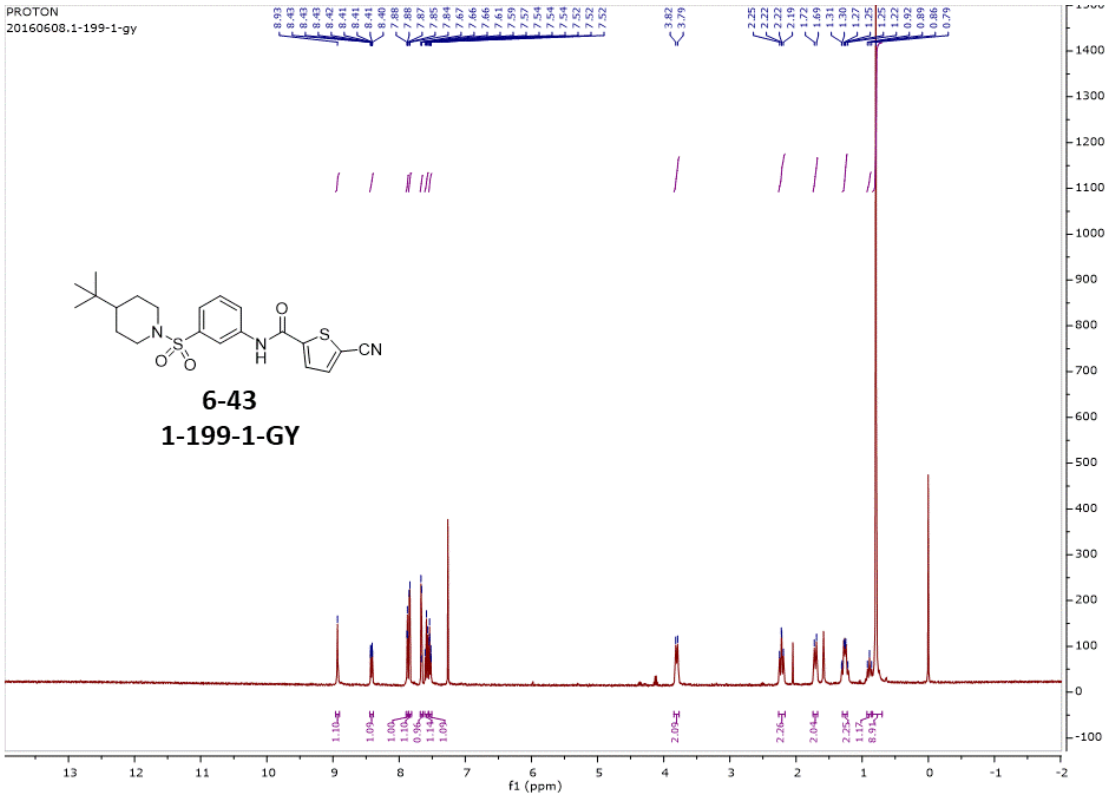

CARBON
20160523.1-175-1-gy
6-40
1-175-1-GY
f1 (ppm)

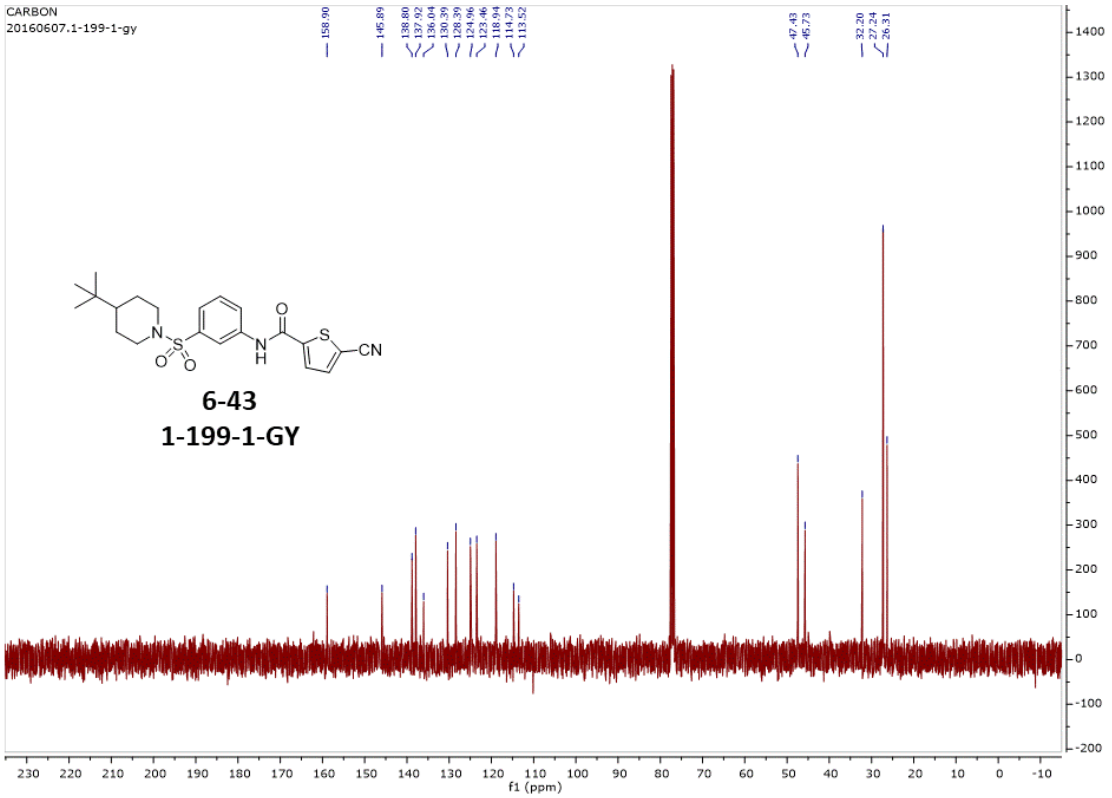

PROTON
20160601.1-181-1-gy-2nd
6-41
1-181-1-GY
f1 (ppm)

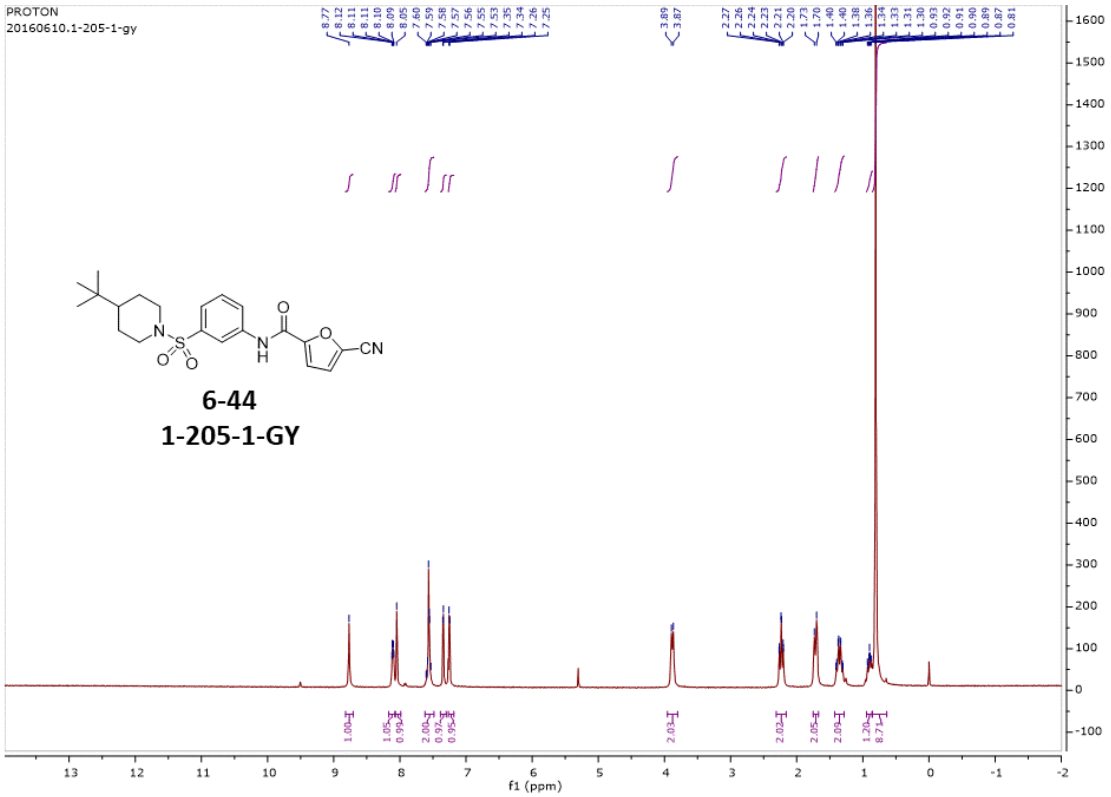

CARBON
20160601.1-181-1-gy-13c
6-41
1-181-1-GY
f1 (ppm)

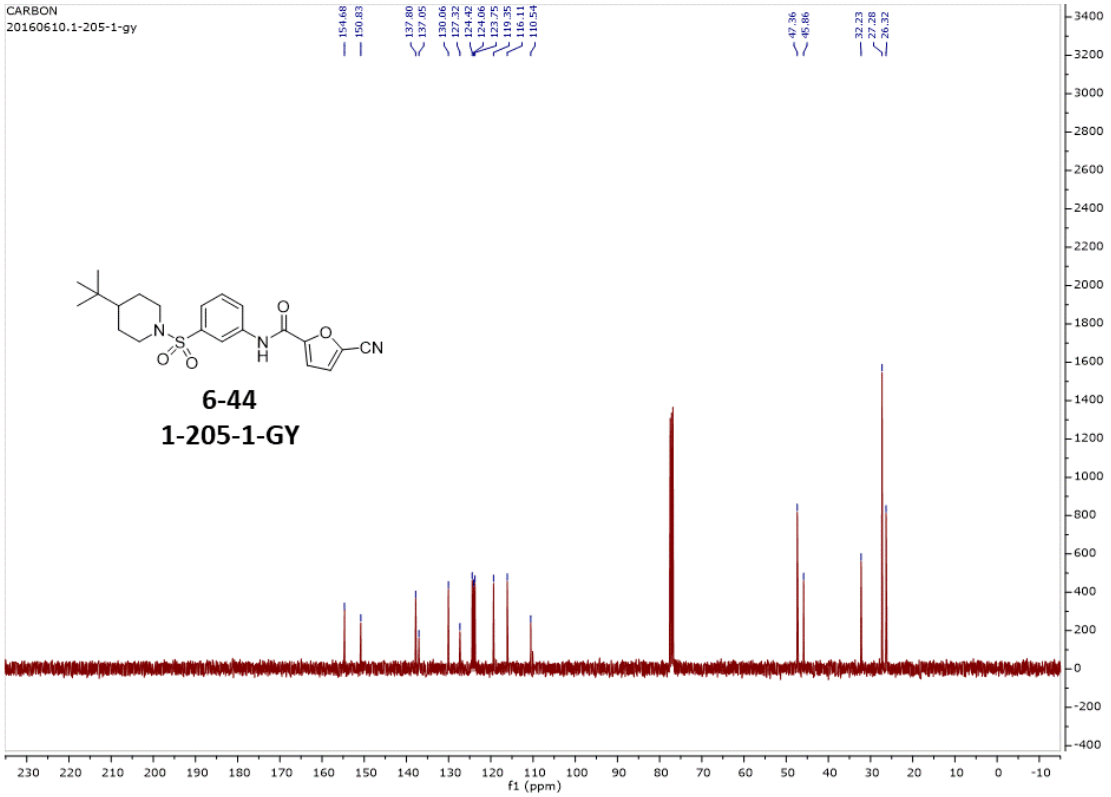

PROTON
20160526.1-187-1-gy
6-42
1-187-1-GY
f1 (ppm)

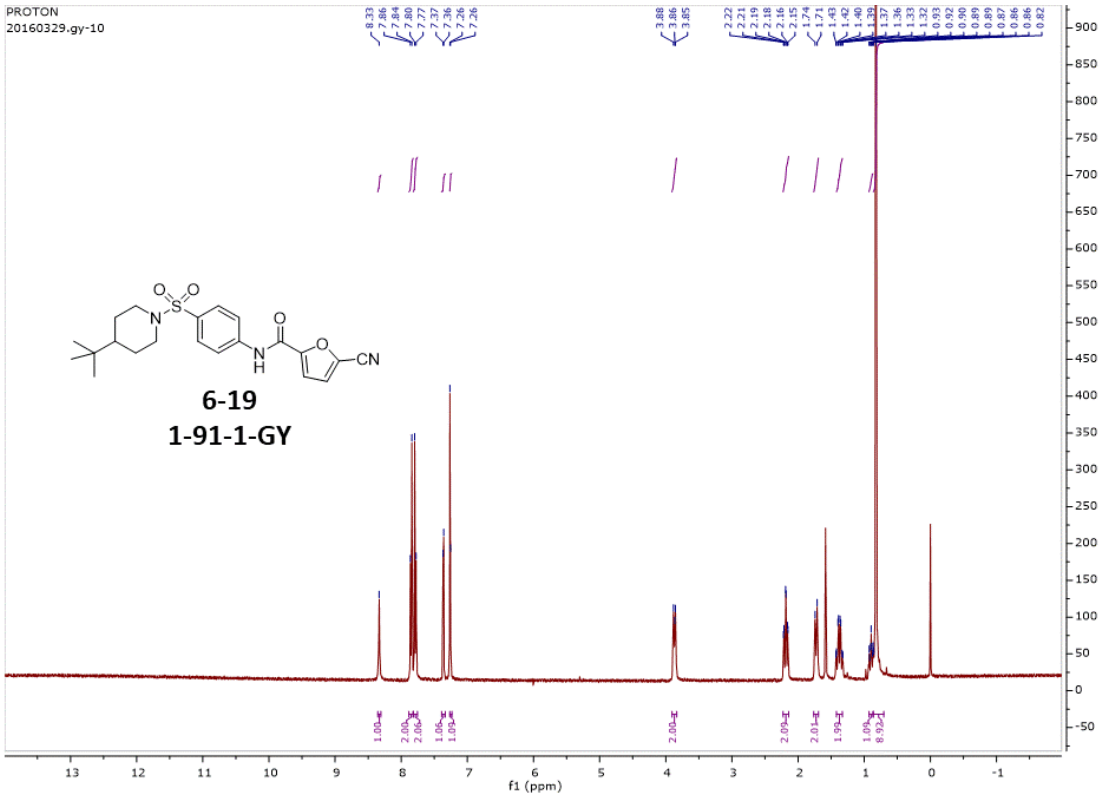

CARBON
20160526.1-187-1-gy
6-42
1-187-1-GY
f1 (ppm)

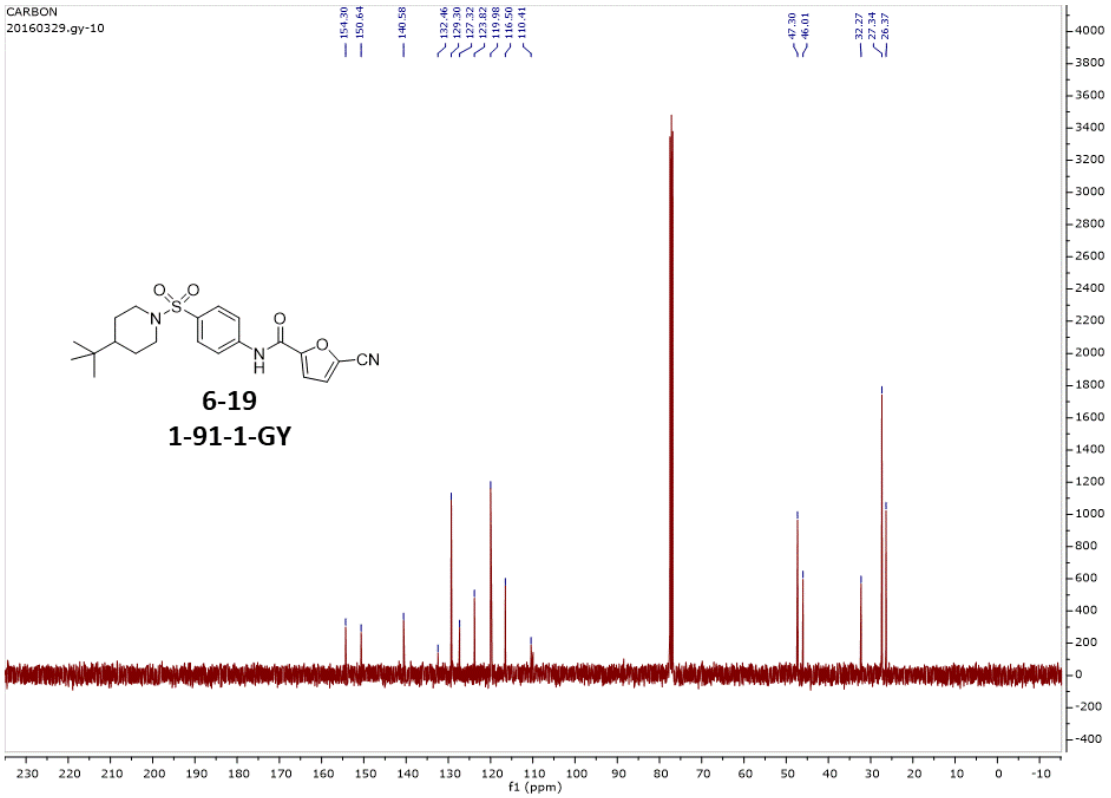

PROTON
20160608.1-199-1-gy
6-43
1-199-1-GY
f1 (ppm)

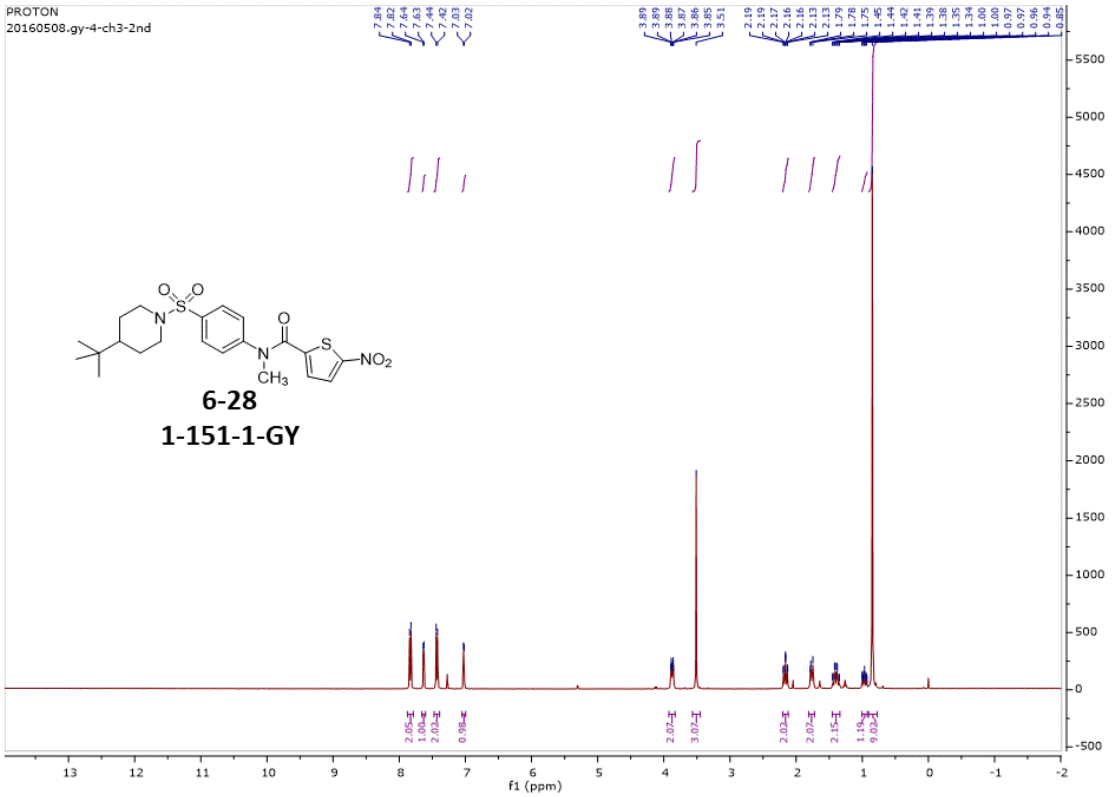

CARBON
20160607.1-199-1-gy
6-43
1-199-1-GY
f1 (ppm)

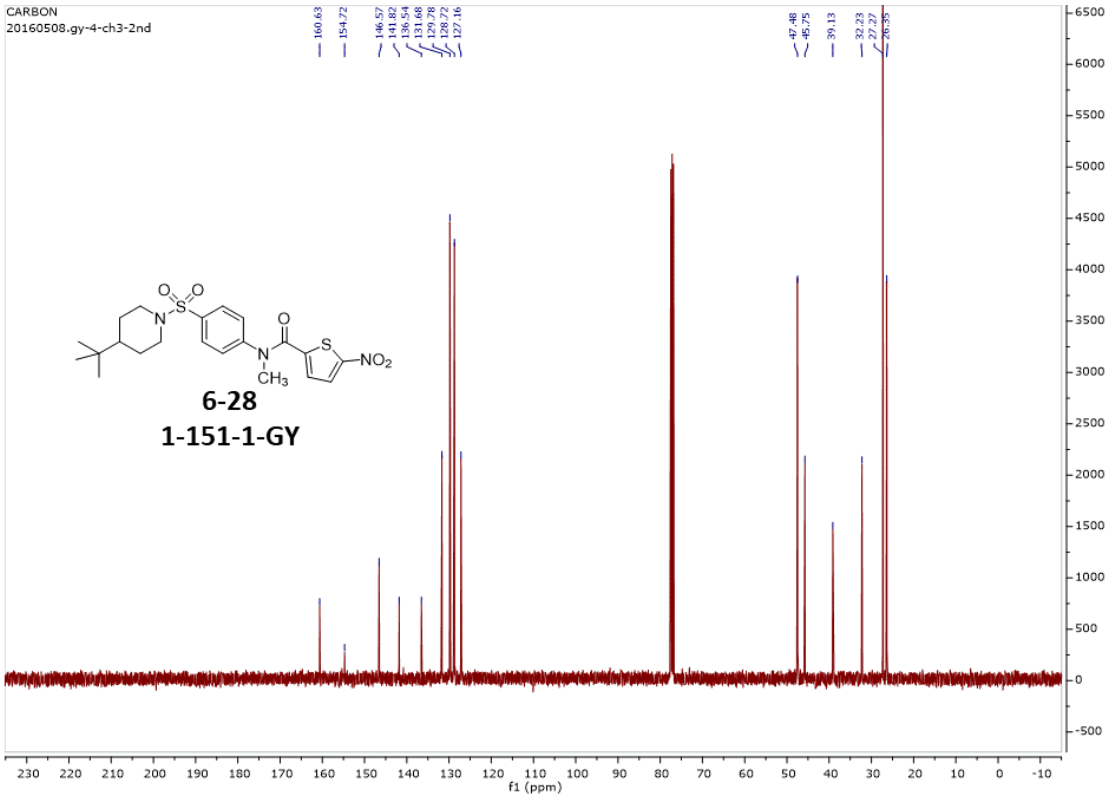

PROTON
20160610.1-205-1-gy
6-44
1-205-1-GY
f1 (ppm)

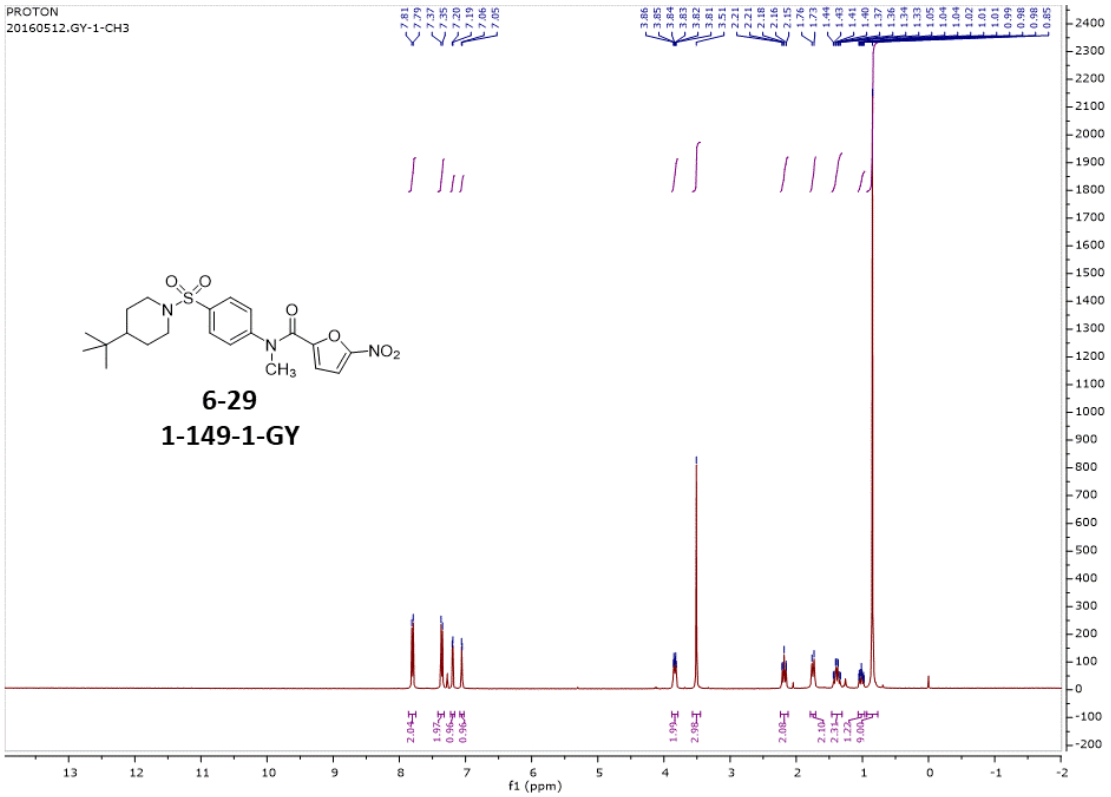

CARBON
20160610.1-205-1-gy
6-44
1-205-1-GY
f1 (ppm)

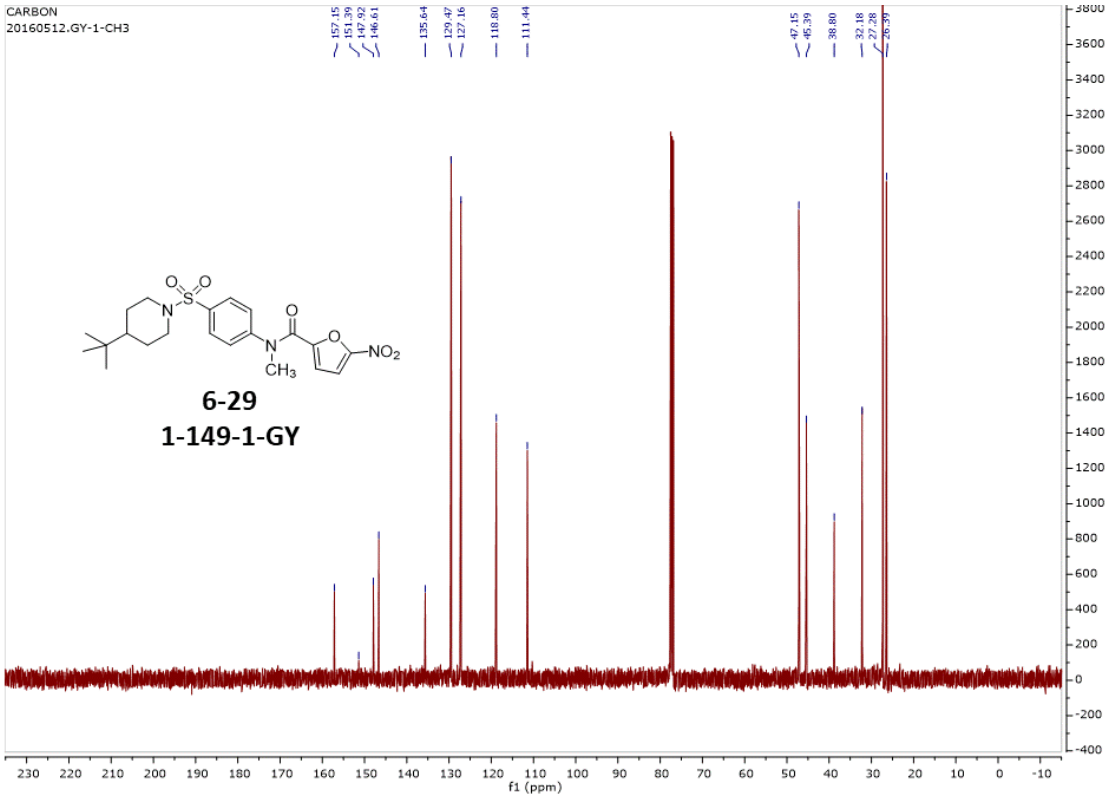

PROTON
20160329.gy-10
6-19
1-91-1-GY
f1 (ppm)

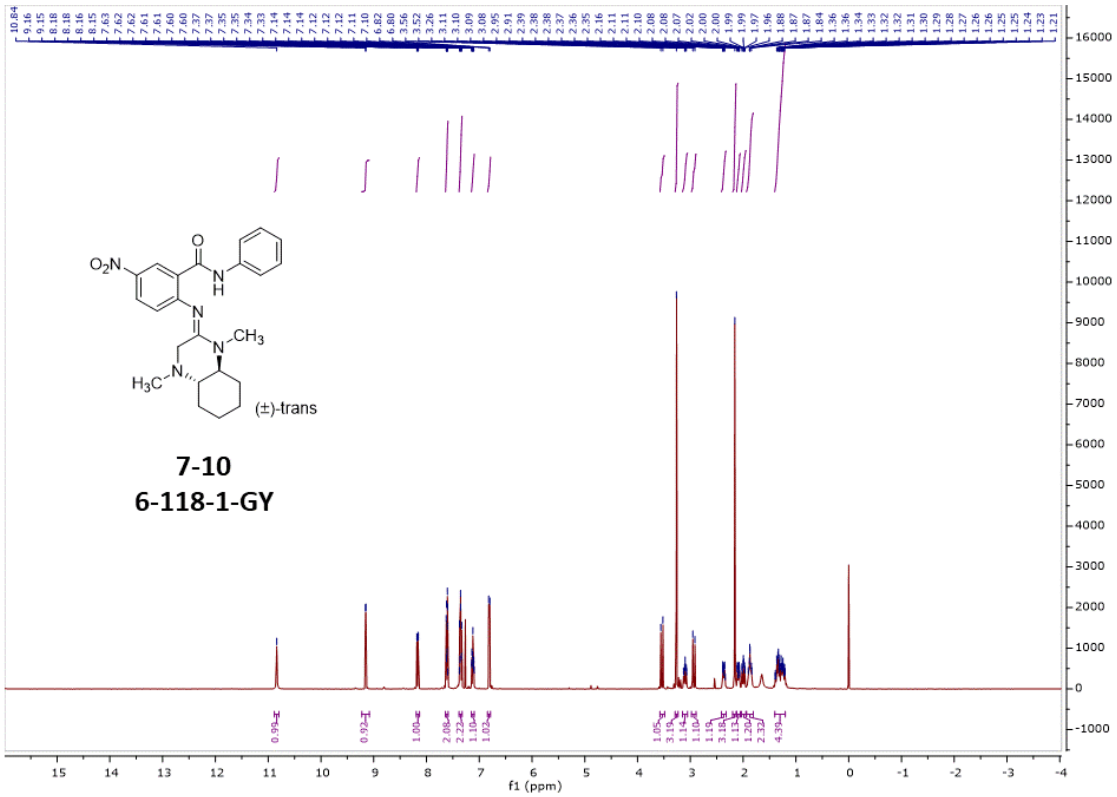

CARBON
20160329.gy-10
6-19
1-91-1-GY
f1 (ppm)

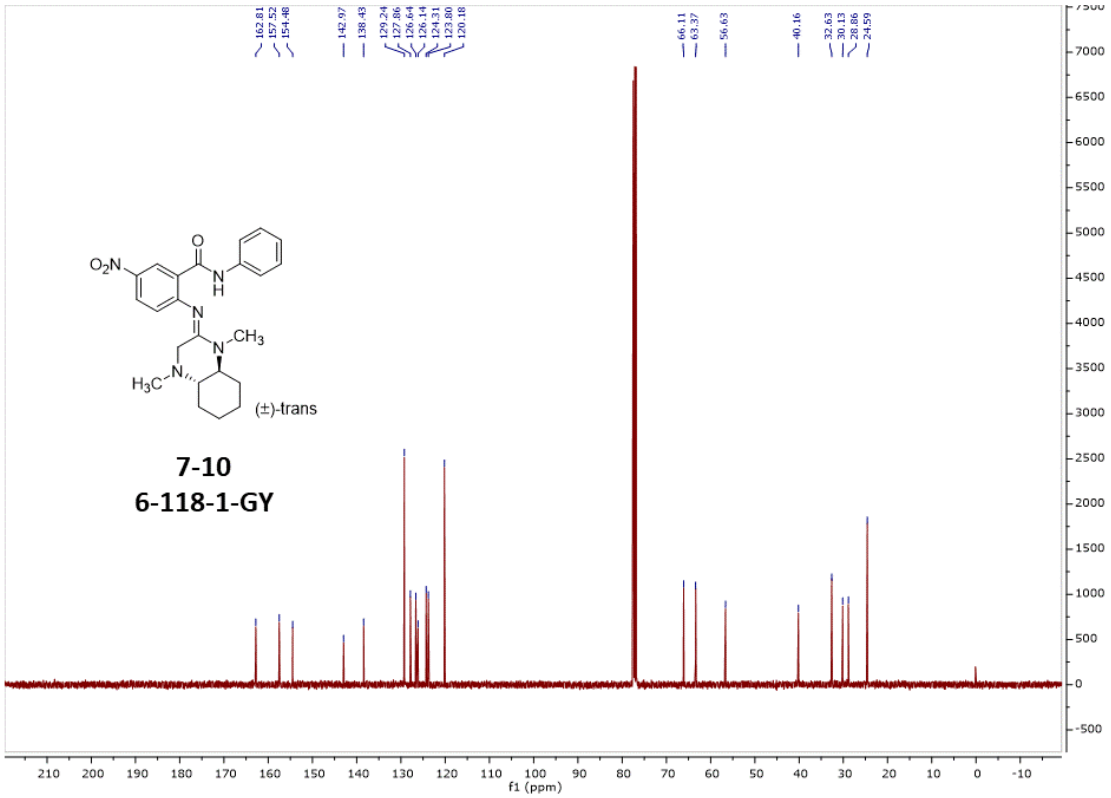

PROTON
20160508.gy-4-ch3-2nd
6-28
1-151-1-GY
f1 (ppm)

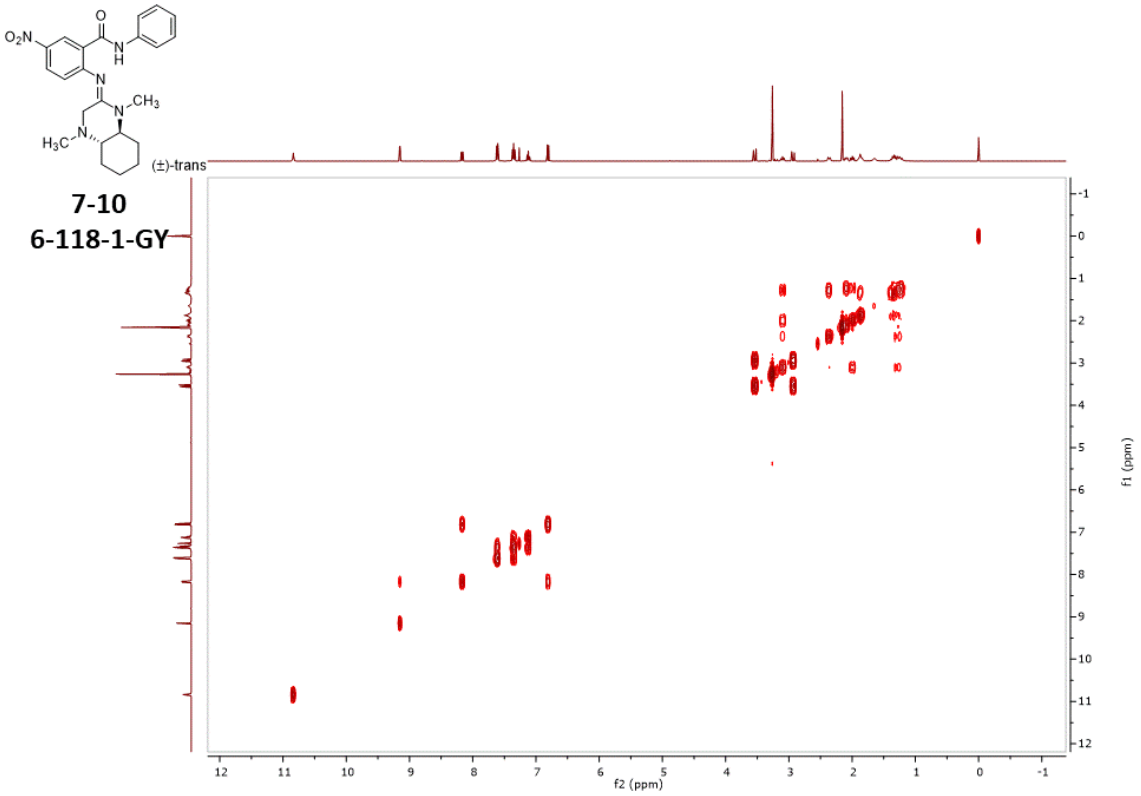

CARBON
20160508.gy-4-ch3-2nd
6-28
1-151-1-GY
f1 (ppm)

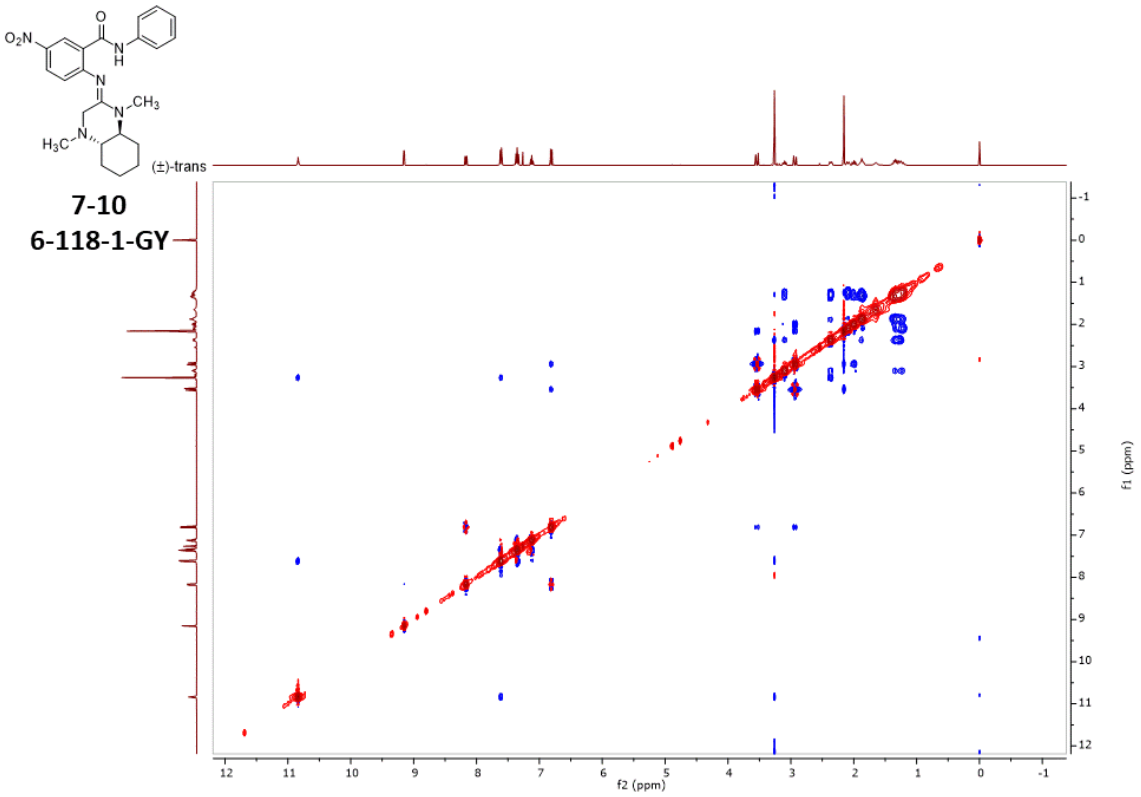

PROTON
20160512.GY-1-CH3
6-29
1-149-1-GY
f1 (ppm)

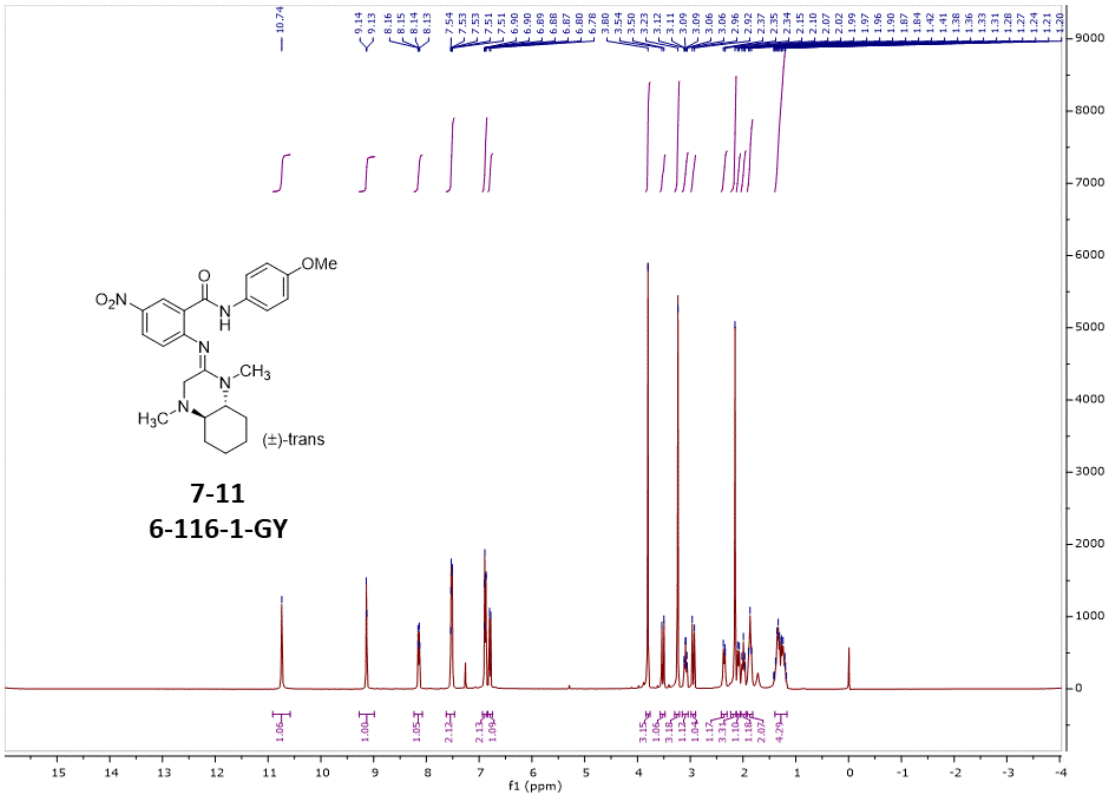

CARBON
20160512.GY-1-CH3
6-29
1-149-1-GY
f1 (ppm)

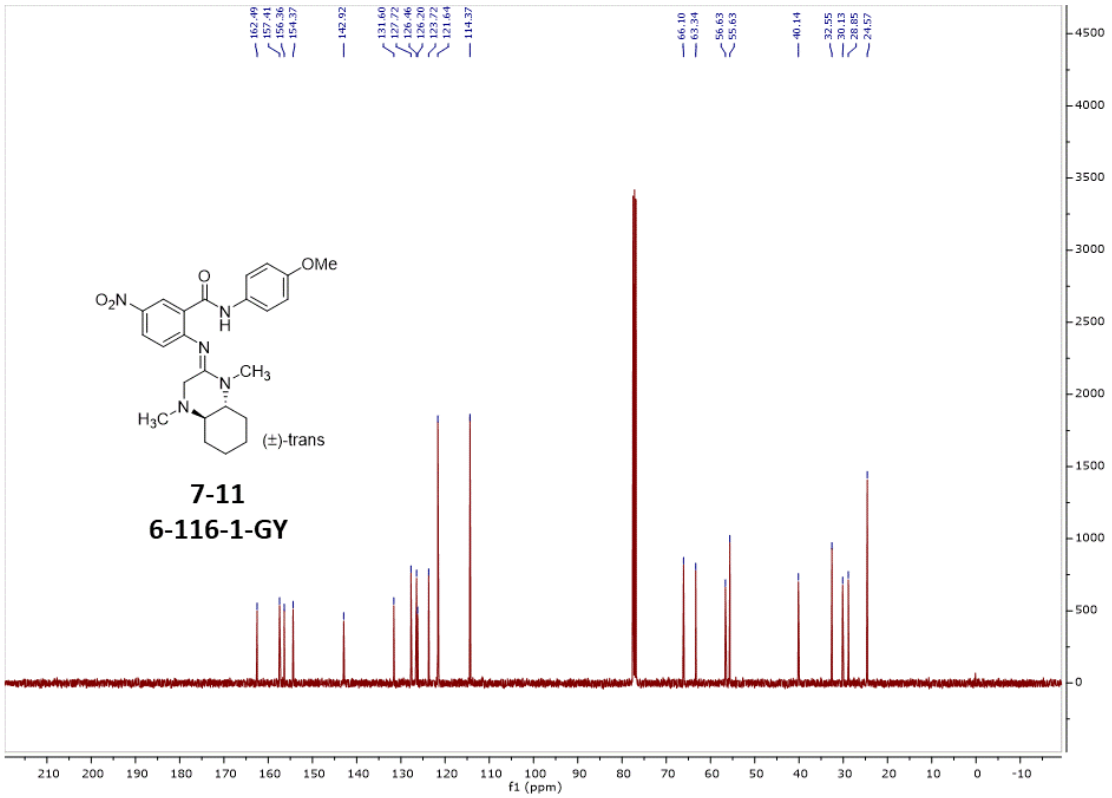

(±)-trans
7-10
6-118-1-GY
f1 (ppm)

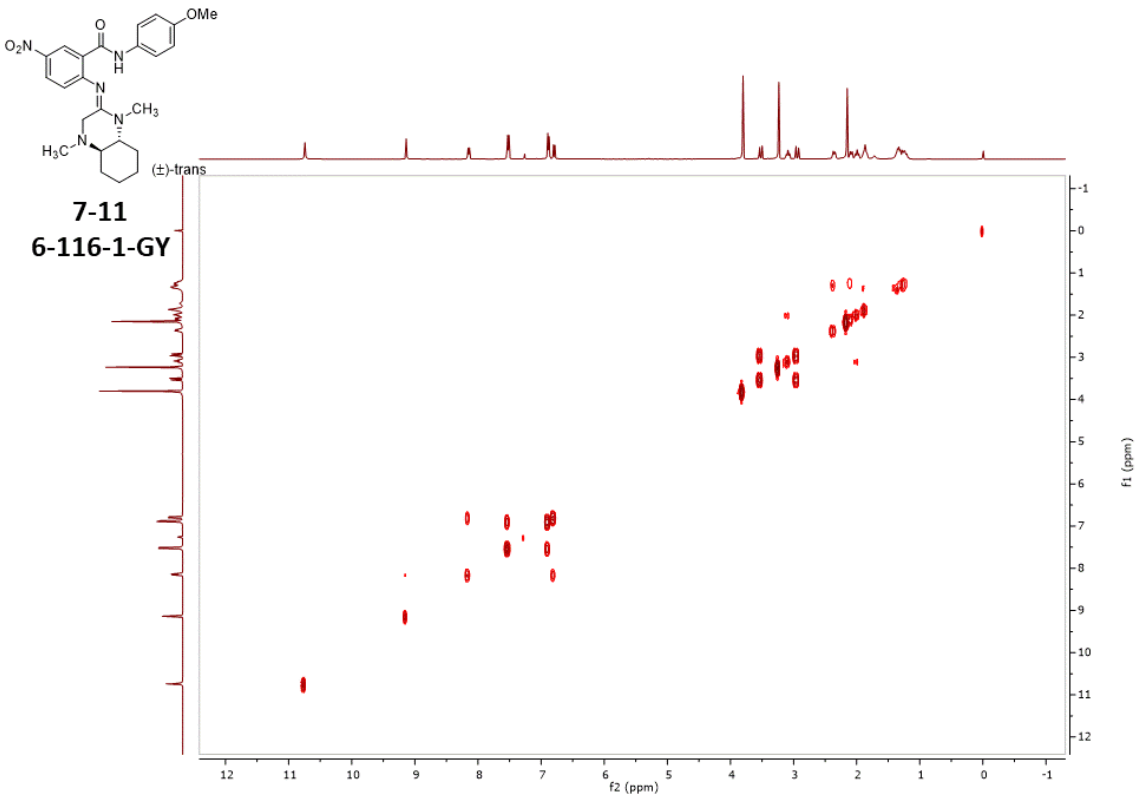

(±)-trans
7-10
6-118-1-GY
f1 (ppm)

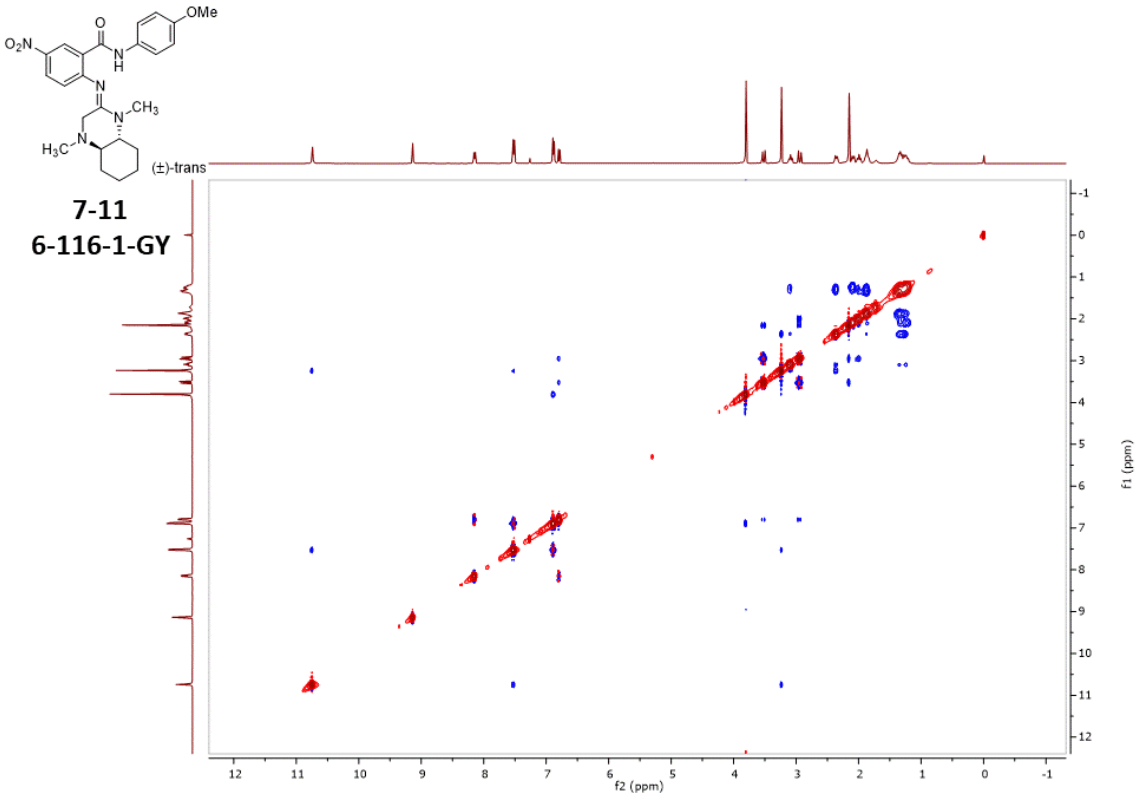

(±)-trans
7-10
6-118-1-GY
f2 (ppm)
f1 (ppm)

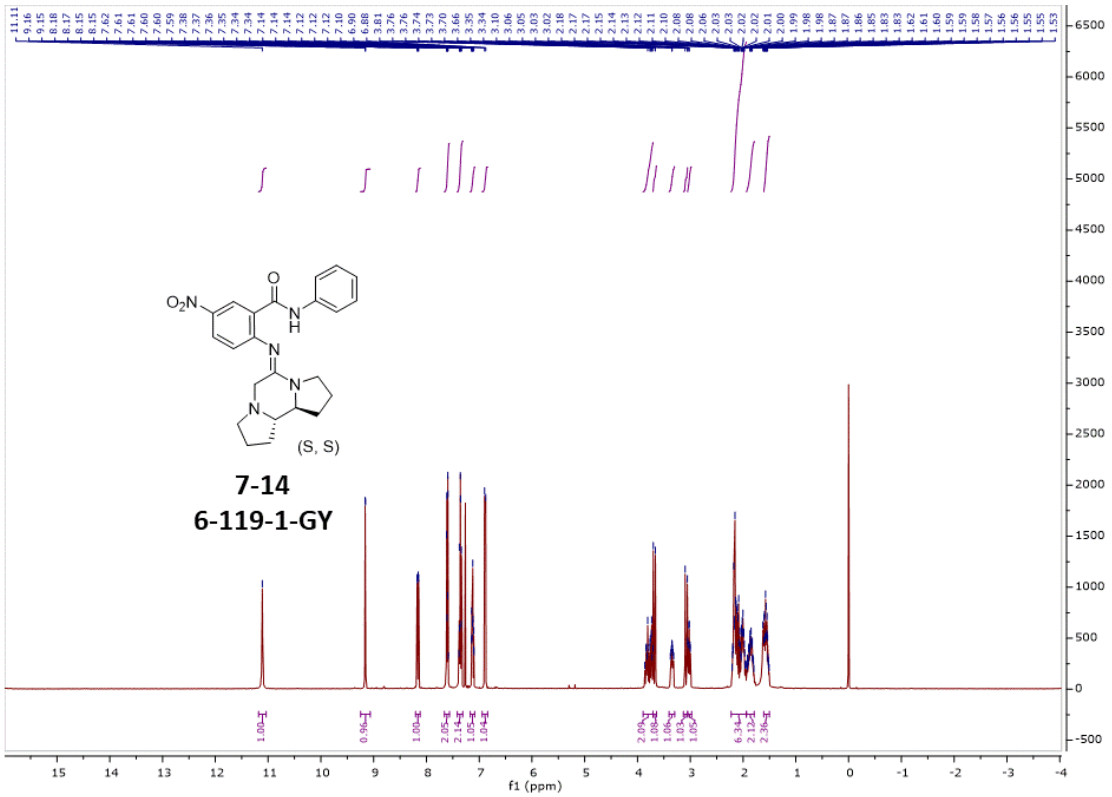

(±)-trans
7-10
6-118-1-GY
f2 (ppm)
f1 (ppm)

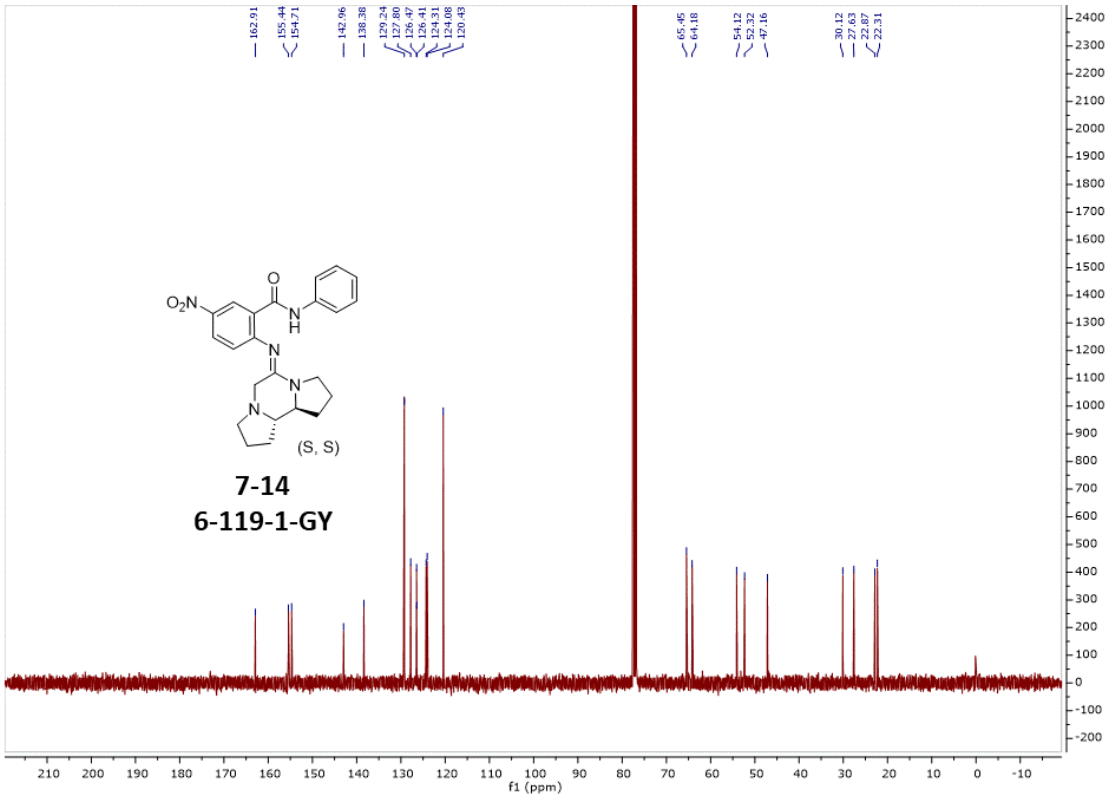

OMe
O2N
O
N
H
N
CH3
N
H3C
(±)-trans
7-11
6-116-1-GY
f1 (ppm)

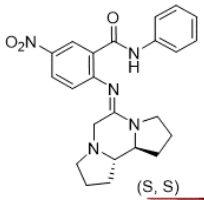

OMe
O2N
O
N
H
N
CH3
N
H3C
(±)-trans
7-11
6-116-1-GY
f1 (ppm)


OMe
O2N
O
N
H
N
CH3
H3C
N
(±)-trans
7-11
6-116-1-GY
f2 (ppm)
f1 (ppm)

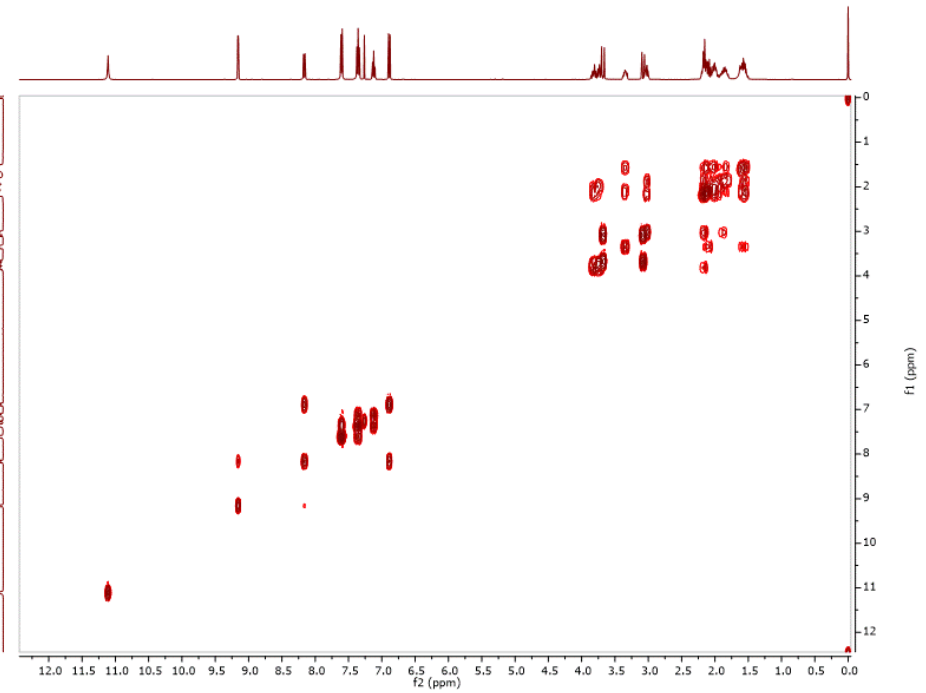

OMe
O2N
O
N
H
N
CH3
H3C
N
(±)-trans
7-11
6-116-1-GY
f2 (ppm)
f1 (ppm)

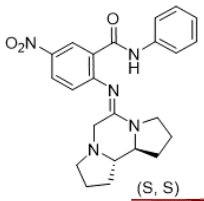

(S, S)
7-14
6-119-1-GY
f1 (ppm)


(S, S)
7-14
6-119-1-GY
f1 (ppm)

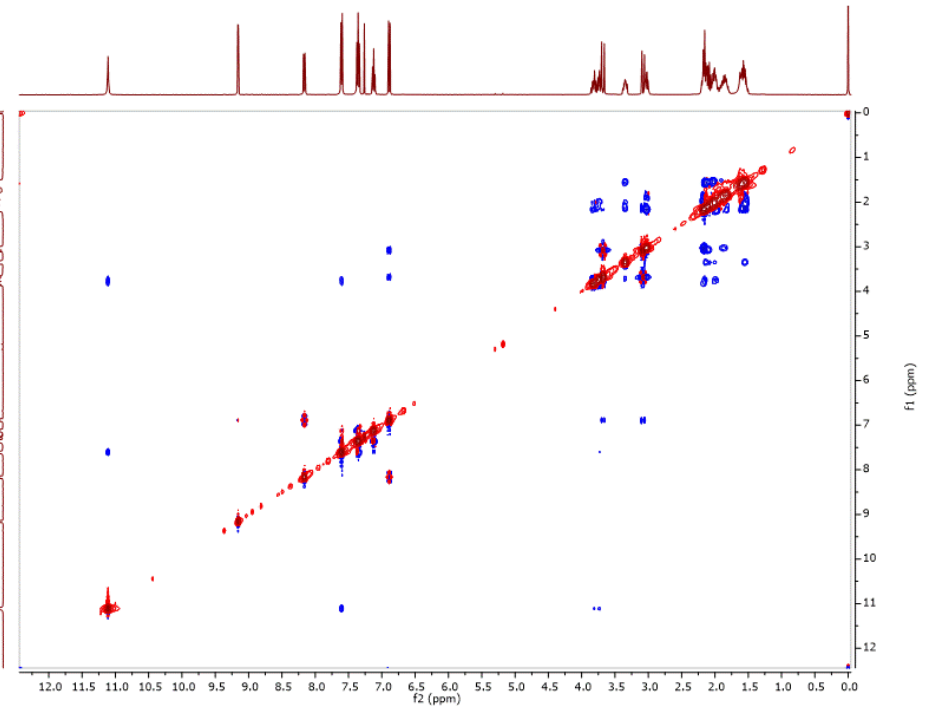


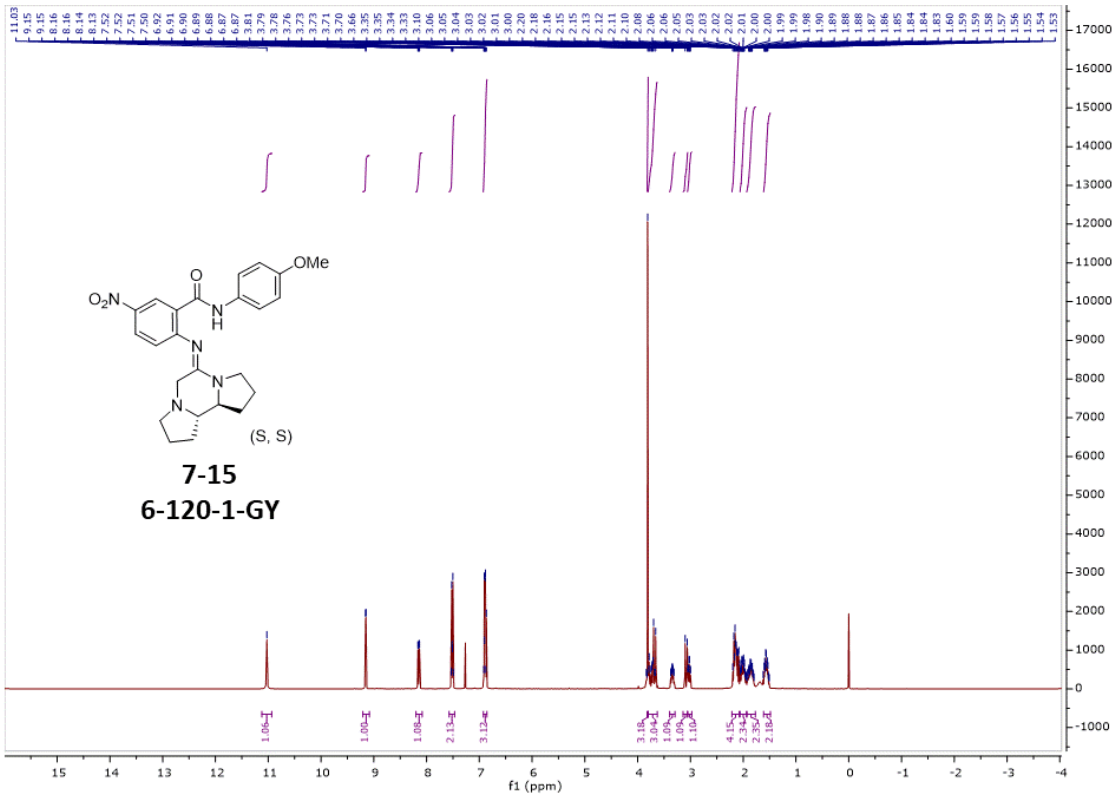

**7-14**
**6-119-1-GY**

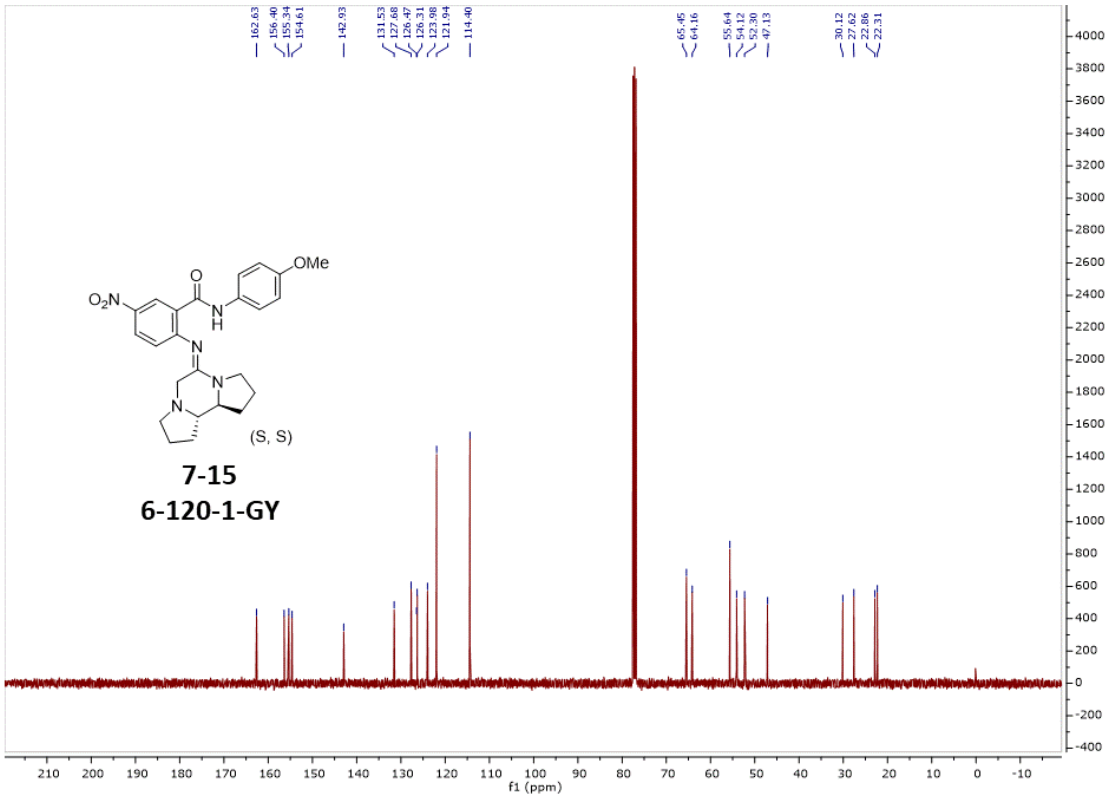


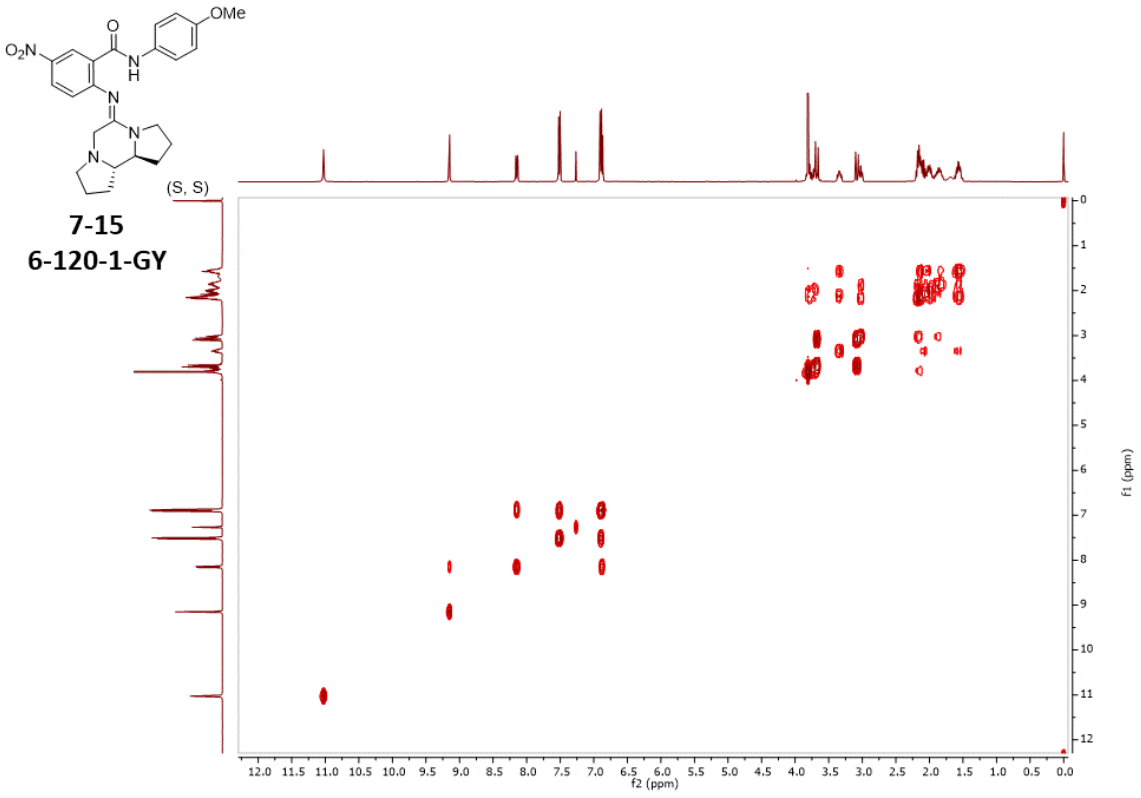



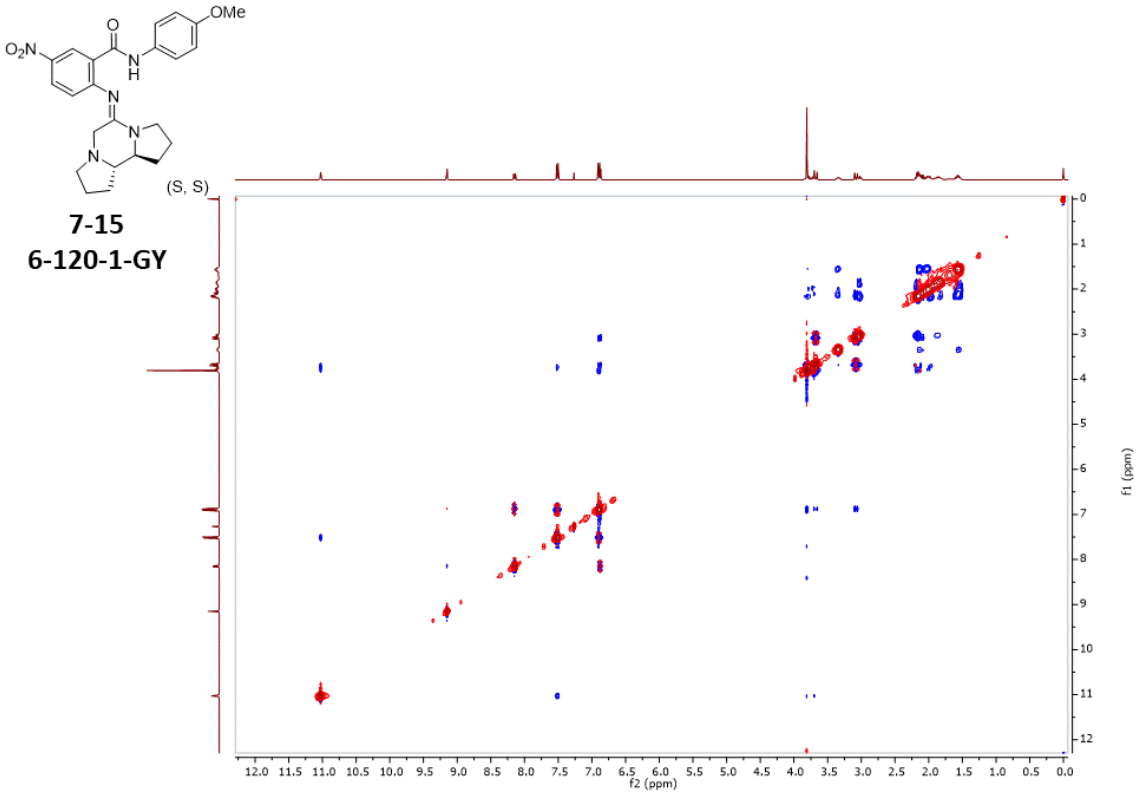

**7-14**
**6-119-1-GY**




OMe
$O_2N$
O
N
H
N
N
(S, S)
7-15
6-120-1-GY
f1 (ppm)


OMe
$O_2N$
O
N
H
N
N
(S, S)
7-15
6-120-1-GY
f1 (ppm)


OMe
O
N
H
$O_2N$
N
N
N
(S, S)
7-15
6-120-1-GY
f2 (ppm)
f1 (ppm)


OMe
O
N
H
$O_2N$
N
N
N
(S, S)
7-15
6-120-1-GY
f2 (ppm)
f1 (ppm)