PALLADIUM-CATALYZED CYCLIZATION OF DRUG CANDIDATES

By

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PALLADIUM-CATALYZED

CYCLIZATION OF

DRUG CANDIDATES

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Abstract: Ovarian cancer is both difficult to detect and difficult to treat, therefore the discovery of new therapies is important. Retinoids (retinoic acid derivatives) are known to induce cellular apoptosis in various cancers, especially in ovarian cancer. Retinoids are also highly cytotoxic to healthy cells, however. SHetA2 leads a class of retinoids known as Flexible Heteroarotinoids (Flex-Hets) that have low toxicity to healthy cells while retaining anti-cancer activity. Rigorous studies of the structure-activity relationship of retinoids and heteroarotinoids have determined that 5-membered heterocyclic Ring A systems in SHetA2 analogs might exhibit anti-cancer activity as well as improved water solubility. The synthetic challenge in preparing these molecules led to the investigation of a new synthetic route for preparing SHetA2 analogs. This new route involves cyclizing tethered alkenes *via* a reductive Heck reaction using the Jeffery conditions. This reaction is known to prepare heterocycles that contain structural characteristics essential to SHetA2 analog anti-cancer activity. This study synthesized a new class of heteroarotinoids using this method, then explored other ways in which the method could be applied to the greater project. The method was also employed to synthesize a previously known heterarotinoid, OHet72, as well as a new analog of that compound. In addition, the synthesis of bacterioferritin-inhibiting antibiotics was explored, including the preparation of a specific substrate designed to provide insight into a problem observed in the synthesis of previous analogs. This substrate required a new synthetic approach, and was designed to eliminate the possibility of various side reactions occurring. This study explored the preparation of 4-((5-chloro-2-hydroxybenzyl)amino)isoindolin-1-one and whether similar side reactions were observed.

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CHAPTER I

SYNTHESIS OF HETEROAROTINOIDS FOR ANTI-CANCER ACTIVITY

1.1 Introduction

Ovarian cancer has been dubbed a "silent killer" because 80% of patients fail to exhibit symptoms before the disease has reached advanced stages.[1] In fact, ovarian cancer poses the highest mortality rate among gynecological cancers, with around 13,940 deaths and 21,750 diagnoses annually in the United States.[2] Effective treatment and drug options for this disease remain elusive.

Retinoids, including retinoic acid (**1**) (Figure 1.1), and their synthetic analogs are known to induce cellular differentiation and apoptosis.[3] Consequently, medicinal chemists regard these compounds as potential anti-cancer agents; however, the toxicity of retinoids towards healthy cells remains a problem.[4] One class of synthetic retinoid analogs, Flexible Heteroarotinoids (Flex-Hets), has been shown to retain anti-cancer activity without toxicity to healthy cells.[5] The parent compound in this series is SHetA2 (**3**) (Figure 1.1), which displays activity towards various cancers, including ovarian cancer.[6]

Heteroarotinoids have been known for more than three decades.[7] Several reviews have addressed this type of class of heterocycles, many of which have anti-cancer properties.[6, 8-9]

The initial theory was that a heteroarotinoid system might exhibit reduced toxicity compared[10] to retinoic acid (**1**), which was the primary model.[7] However, it has been documented that retinoids are quite toxic,[11] and thus, have limited utility at this time. One of the original heteroarotinoids was **2**[7] which contained a highly conjugated system as in **1**. Many modifications of the basic structure have appeared in the literature,[9] and have led to the compound **3**, which is awaiting clinical trial for the prevention of ovarian cancer.

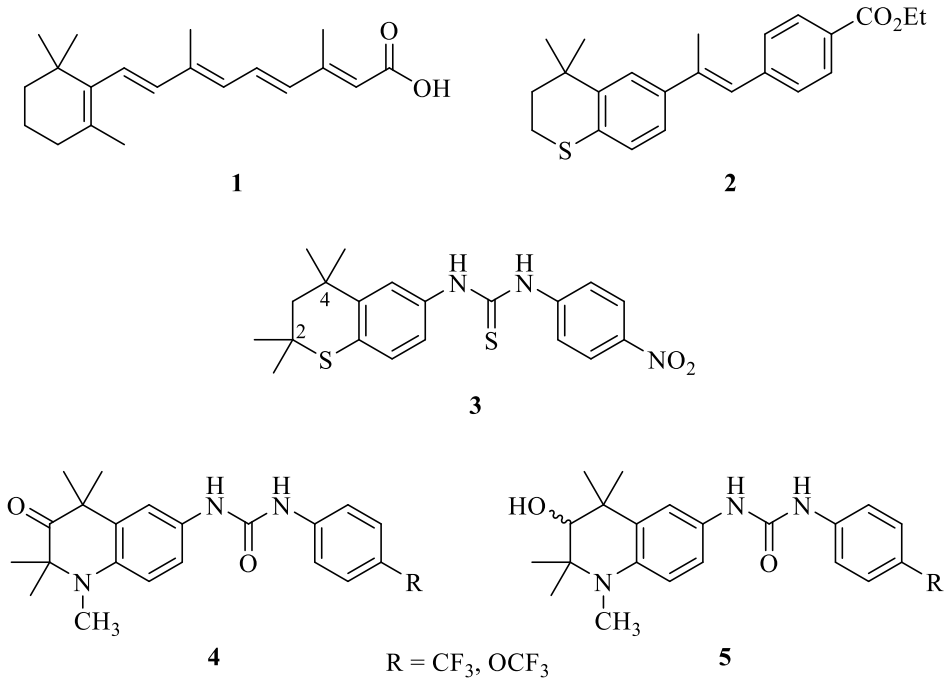


Figure 1.1: Structure of Retinoic Acid **1**, and its evolution into heteroarotinoids.

A toxicity assessment of **3** in rats and dogs revealed no observed adverse effect level (NOAEL) at 500 mg/kg/day and 1500 mg/kg/day, respectively.[12] A recent study of the pharmacokinetics and interspecies scaling of oral-bioavailability resulted in an estimate that a capsule containing 170 mg of SHetA2 for a person (based on 2 mg/kg for an 85 kg individual) was conceivable.[13] Additional research is required to substantiate this dosage for humans.

The major metabolites for SHetA2 have been identified.[14] Two such metabolites, **6** and **7**, are illustrated below. It was reasoned that such systems might be responsible, or partially responsible, for the biological activity derived from SHetA2. Speculation was that related compounds, such as **4** and **5**, might hold promise for useful activity.

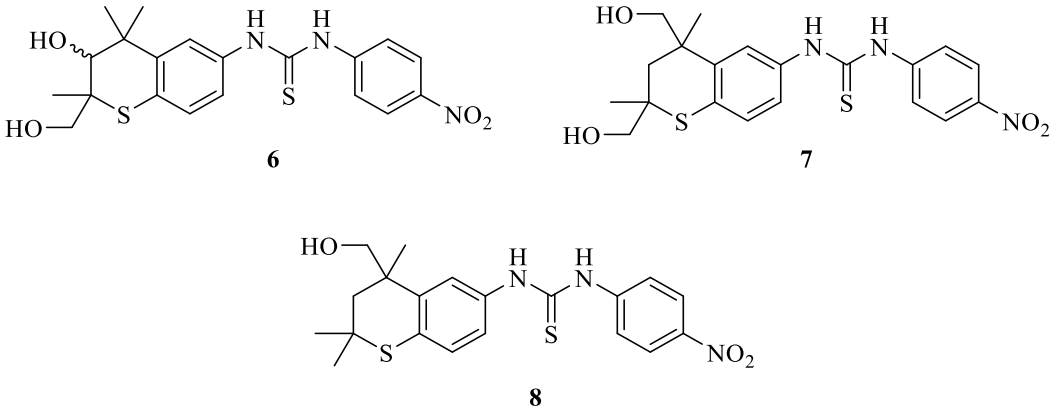


Figure 1.2: Metabolites of SHetA2.

The preparations of **4** and **5** have been consummated, and the work has been accepted for publication.[15] Although not an exact match for compound **7**, compounds **4** and **5** have the added capability to be solubilized by acid addition to the nitrogen atom, which should increase aqueous solubility. Moreover, several early examples in the heteroarotinoid family had enhanced activity with a urea linker over that with a thiourea linker, the former being included in **4** and **5**.[15] Thus, members of **4** had improved activity over SHetA2 in both IC_{50} and efficacy values (2.58 ± 0.1 and 90.1 ± 1.4 for the system with CF_3 and 2.4 ± 0.2 and 91.3 ± 1.3 for the system with OCF_3, respectively). These data compared well with that for SHetA2 (3.17 ± 0.05 and 84.3 ± 0.7, respectively). Unexpectedly, members of **5** had reduced activity compared to SHetA2.

It is known that SHetA2 interacts with the heat shock protein mortalin.[16] Obviously, the binding site in mortalin has considerable restrictions, based on data from the above experiments. Hydrophobic interaction of the top geminal dimethyl group appears to be important for binding to

mortalin. Because of the nearness in structure of **8** to the metabolite **7**, the synthesis of **8** was accomplished.[17] However, it did not possess activity better than SHetA2.[18]

An investigation was initiated by altering the alkyl groups at the 2-position and the 4-position, changing the heteroatom in the fused ring, and changing the linker to a urea.[19] Replacing the methyl groups on the fused ring with ethyl groups resulted in a marked improvement in the IC_{50} (50% inhibitory concentration) values as well as the efficacy values for all members of **9-11**. The IC_{50} values and efficacy values were as follows: for **9** (R = NO_2, 2.17 and 93.2%, R = CF_3, 2.45 and 92.4%), for **10** (R = NO_2, 2.05 and 93.7%, R = CF_3, 2.43 and 93.3%), and for **11** (R = NO_2, 2.09 and 91.4% and for R = CF_3, 2.0 and 91.4%). By comparison, the data for SHetA2 were 3.17 and 93.9, respectively, for IC_{50} and efficacy values. Clearly the presence of oxygen in the fused ring, a urea linker, and the ethyl groups at both C-2 and C-4 are significant constructs for enhanced biological activity.

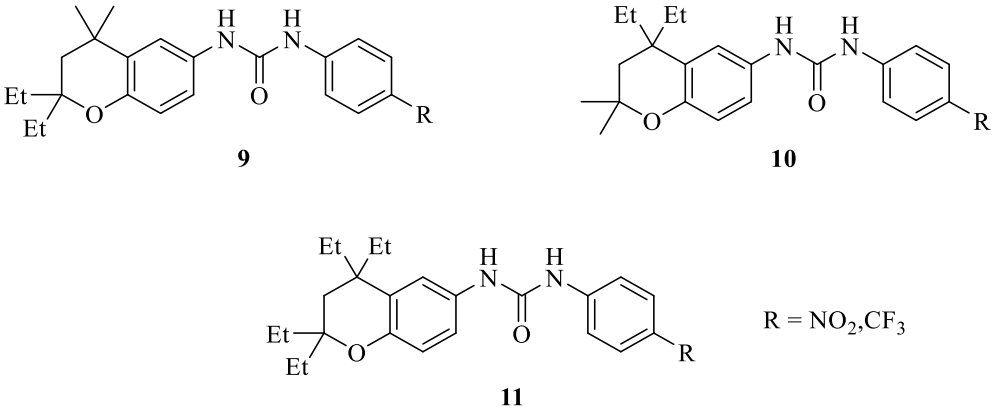
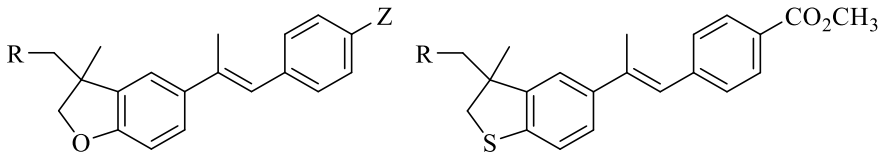


Figure 1.3: Compounds that identified important structural characteristics.

It occurred to us that a different fused ring size might well influence activity. Systems **12** and **13** are known,[20-21] and members of **12** actually induce differentiation of human promyelocytic cells (HL-60 cells).[20] To date, members of **13**[21] have not yet been screened for activity.



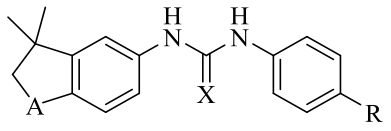
12 **13**

$Z = CO_2H, CO_2CH_3$
R = H, OH

Figure 1.4: Retinoids featuring a 5-membered fused ring.

However, a possibility existed that systems **14** might exhibit useful anti-cancer activity and they were targeted for synthesis as shown in the next chapter of this dissertation.

A = O, S
X = O, S
$R = NO_2, CF_3, OCF_3$



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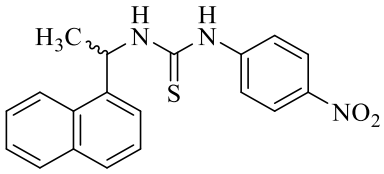

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Figure 1.5: Structure of target derivatives and a noteworthy compound.

It is noteworthy that a recent observation of a novel fused ring unit bonded to a chiral center, which, in turn, was bonded to a thiourea linker attached to a phenyl ring showed strong activity against several breast cell lines.[22] Compound **15** displayed activity during a cell cycle analysis involving human breast cancer cell lines MCF-7, T47D, and MDA-MB-453 when treated with 5.0 μM of the (*S*)-isomer. The publication summarizes considerable biology/chemistry of heteroarotinoids. Thus, the field remains viable for further development.

In order to further develop SHetA2 analogs as anti-cancer therapeutics, derivatives similar to **14** need to be synthesized. These analogs must further explore diversification of the functionality of the heteroatom-containing Ring A system, the linker unit, and the Ring B system (Figure 1.6).

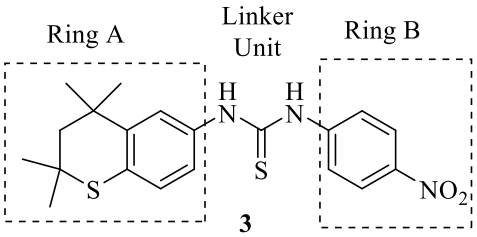

Figure 1.6: The composition of SHetA2 and its analogs.

Ideal analogs would retain or improve upon the potency and efficacy of SHetA2, while displaying improved solubility (especially in water) and reduced potential for mutagenic metabolites forming by way of the -NO_2 group.

This study will address the synthesis of fused, five-membered rings in the Ring A system. The rings are also functionalized with both urea and thiourea linker units, and with various electron withdrawing groups (EWG) bound to the Ring B system. Specifically, the study involves the development of efficient synthetic approaches to indoline and dihydrofuran-containing SHetA2 analogs (Figure 1.7).

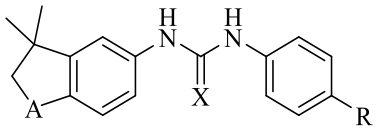

Figure 1.7: Target heteroarotinoids in this study.

Additionally, this study will discuss a new synthesis of OHet72 (**16**), a previously prepared heteroarotinoid (Figure 1.8). OHet72 is classified as a receptor-specific heteroarotinoid, and is known to inhibit tumor growth.[23]

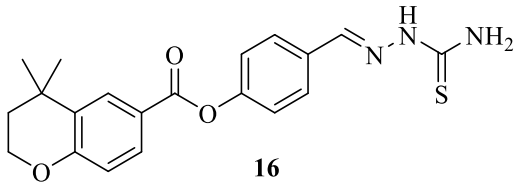

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Figure 1.8: OHet72, a heteroarotinoid of renewed interest.

Finally, this study will show the synthesis of a dihydrofuran analog **17** of OHet72 (**16**) (Figure 1.9). The purpose of synthesizing this analog was to demonstrate that the method used to synthesize OHet72 (**16**) and several prior analogs was sufficiently versatile to access many candidates for this project.

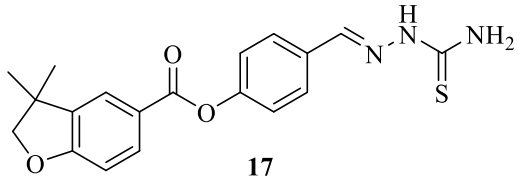

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Figure 1.9: A dihydrofuran analog of OHet72.

This study aims to introduce and demonstrate a facile, effective synthetic route to synthesize modified Ring A systems (Figure 1.6) that are of importance to anti-cancer activity. The reaction of interest is an intramolecular cyclization *via* a ligand-free, palladium catalyzed reductive Heck using the Jeffery conditions. From the time it was originally reported in the early 1970's, the Mizoroki-Heck reaction has been a powerful tool in organic synthesis due to its ability to generate aryl-alkyl C-C bonds (Figure 1.10).[24-25] Due to the numerous and diverse applications of the Mizoroki-Heck reaction, many studies have been performed aimed at expanding the reaction's scope. Catellani catalytically obtained H-transfer from various hydride sources to form reduced products of the Mizoroki-Heck reaction.[26] Jeffery reported adding tetraalkylammonium salts to the Mizoroki-Heck reaction resulting in significant lowering of the reaction temperature.[27] Larock synthesized nitrogen heterocycles by performing the Mizoroki-Heck reaction on alkenes tethered

to *o*-haloanilines.[28] By employing the Jeffery conditions, and, when applicable, hydride sources, Larock prepared various nitrogen heterocycles at relatively mild temperatures (80 – 90 °C) and in good to excellent yields.[28] Liu and coworkers report this method as pathway to synthesize a wide array of heterocycles.[29]

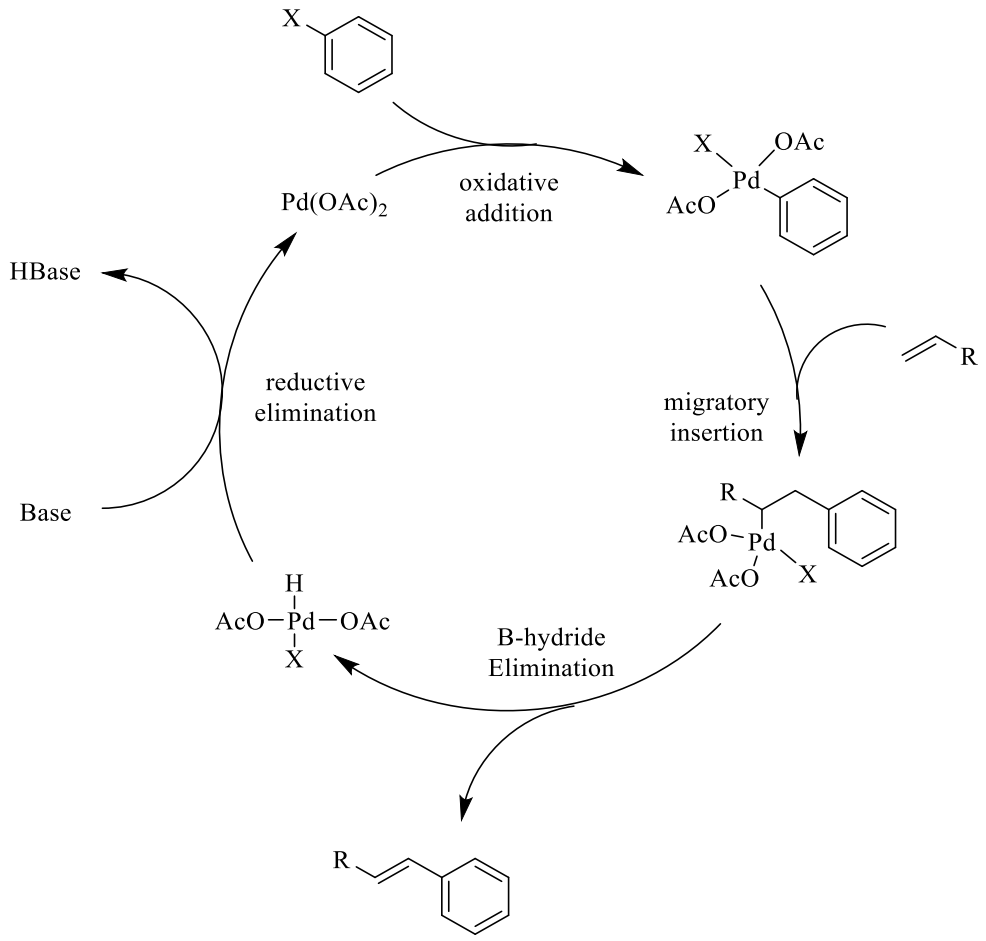


Figure 1.10: The catalytic cycle of a classic Heck reaction.

The classic Mizoroki-Heck reaction is characterized by the retention of the alkene in the cross-coupled product. The regeneration of the alkene occurs due to a β-hydride elimination (Figure 1.10), which is considered the thermodynamically favored process.[30] In order to obtain the reduced product, several adjustments must be made to the reaction, specifically the processes reported by Catellani and Jeffery.[26-27] Addition of a hydride source and use of tetraalkylammonium salts to

lower the heat input to the reaction introduces a competing mechanism.[31] With these conditions, β-hydride elimination is in competition with a ligand exchange of a hydride for a halogen, followed by subsequent C-H bond formation upon reductive elimination of the catalyst.[32] Lastly, the reductive product can be further favored by the use of an alkene void of a β-hydrogen (Figure 1.11).[33]

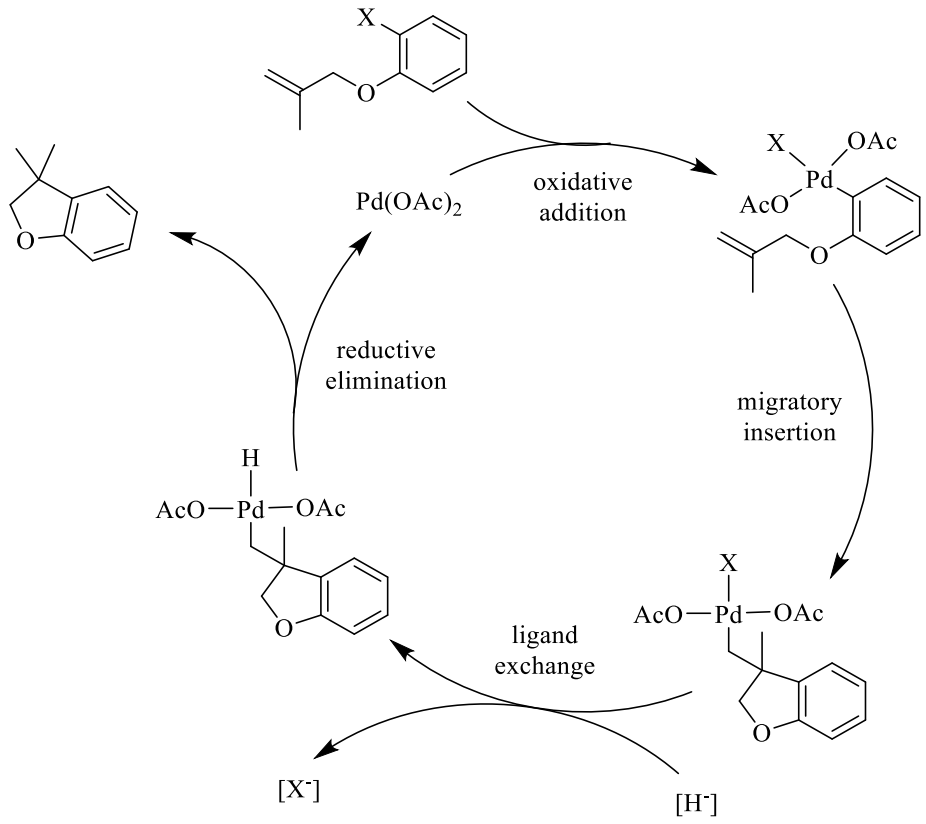


Figure 1.11: A possible catalytic cycle for an intramolecular reductive Heck cyclization.

One advantage of this method is the tolerance, and even requirement of, the presence of water, thus avoiding rigorously anhydrous reagents and reaction conditions.[29] A second advantage is the ability of the reaction to tolerate various functional groups.[29] This makes the method versatile, and therefore potentially very useful in the synthesis of SHetA2 analogs. The Jeffery conditions are essential to the success of this reaction. The tetraalkylammonium salt used in the Jeffery procedure functions both as a phase-transfer catalyst[27] and as a palladium nano-particle stabilizing

agent.[34] By using and studying this method, heterocycles can be synthesized that includes the top germinal dimethyl groups that are essential to anti-cancer activity in heteroarotinoids.

1.2 Synthesis of Indoline SHetA2 Analogs

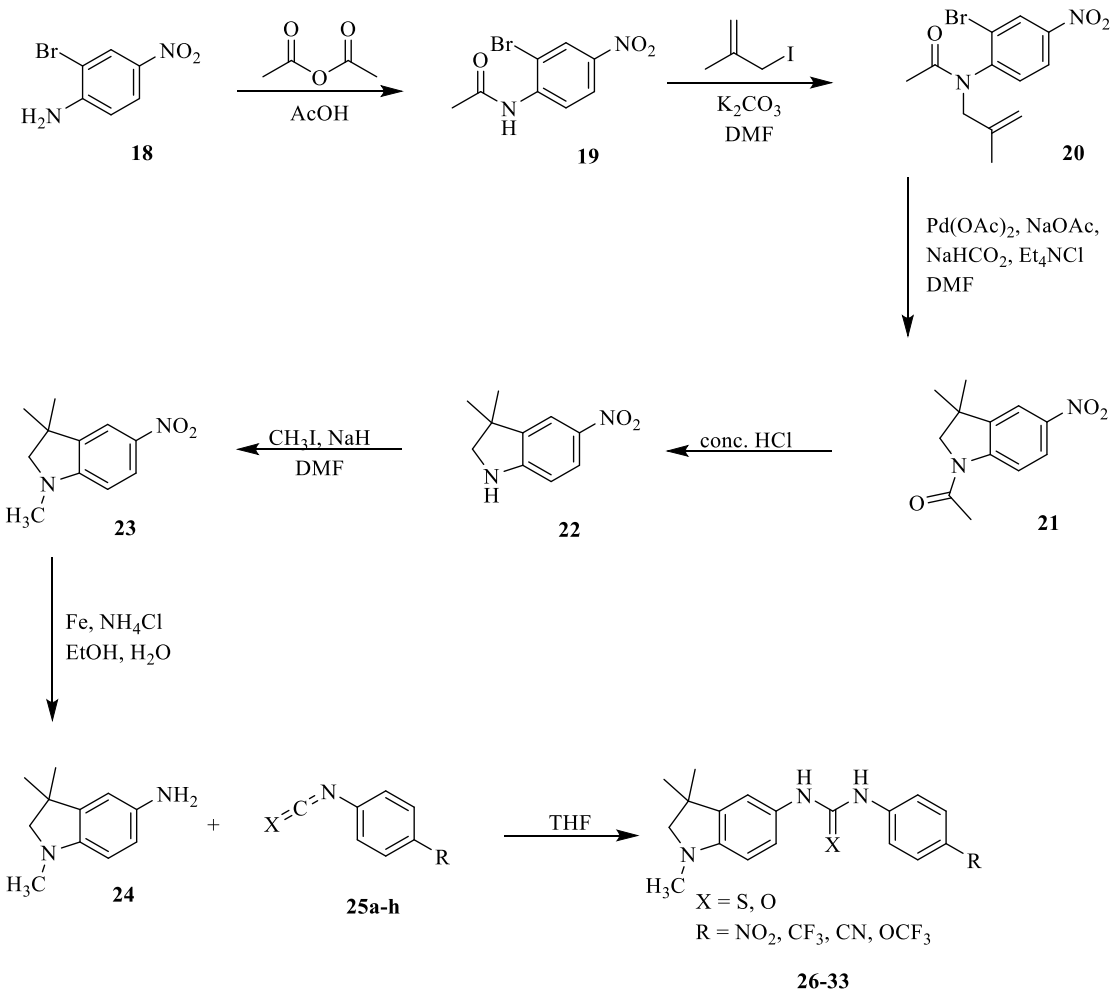
Interest in fused indoline-containing SHetA2 analogs developed due to the potential of this functional group to increase the solubility of SHetA2, and thus its potency, similar to **4** and **5**. The potential usefulness of **4, 5,** and **12** also increased interest. Making this adjustment to the Ring A system would also reveal the importance of the structure of Ring A in anti-cancer activity.

With these goals established, we designed and synthesized sixteen SHetA2 analogs characterized by a fused, *N*-methylindoline Ring A system, urea and thiourea linker units, and 4-NO_2, CN, CF_3, and OCF_3 functionalized Ring B systems. We now report the synthesis and biological activity of these Flex-Hets against the ovarian cancer cell line A2780. These new heteroarotinoids were appraised relative to SHetA2.

1.2.1 Results and Discussion

Synthesis of fused, *N*-methylindoline SHetA2 analogs required 7 steps. First, 2-bromo-4-nitroaniline (**18**) was treated with acetic anhydride in glacial acetic acid at room temperature to afford the acetamide product **19** in 84% yield. Subsequent alkylation of **19** with 3-iodo-2-methylprop-1-ene at 60 °C led to the formation of the tertiary amide **20** in quantitative yield. Cyclization of **20** *via* a reductive Heck reaction using Jeffery conditions at 85 °C afforded the cyclic amide **21** in 85% yield.[35] Amide **21** was hydrolyzed with refluxing 20% HCl to afford indoline **22** in 94% yield. Indoline **22** was methylated but treatment with NaH followed by dropwise addition of methyl iodide to generate *N*-methylindoline **23** in quantitative yields. Treating **23** with iron and ammonium chloride in a refluxing ethanol-water mixture (4:1) afforded aniline derivative **24** in 80% yield. Finally, aniline derivative **24** was treated by dropwise addition of isocyanates and isothiocyanates **25a-h** to afford the SHetA2 analogs **26-33** in 21-75% yields (Scheme 1.1). Reaction

yields in the final step were dependent upon the purity of the commercial isocyanates and isothiocyanates.



Scheme 1.1: The synthesis of Indoline SHetA2 Analogs.

All products **26-33** were purified on a 10 inch silica gel column, eluting with 10% ether in hexanes, increasing the polarity on a gradient to 50% ether in hexanes. All products were subsequently dried under vacuum at 60 °C for 24 hours.

The biological effects of the compounds were determined by cytotoxicity assay of the human A2780 ovarian cancer cell line (Table 1.1). All compounds showed decreased potency and significantly decreased efficacy compared to SHetA2. Compound **26** showed the highest efficacy of the candidates, with 44.87% efficacy of SHetA2. Compound **26** is functionalized with a urea

linker unit and a -NO_2 group on Ring B, indicating that one or both of those functionalities lead to improved efficacy. With no otherwise observable trend in the differences in potency and efficacy when varying the linker unit and the Ring B functionality, this study demonstrated the importance of the Ring A structure in the biological activity of SHetA2 analogs. Unfortunately, the synthesized fused *N*-methylindoline derivatives were marginal in anti-cancer activity.

Compound	X =	R =	Potency IC_{50} (μM)	Maximal Activity (% growth inhibition)	Efficacy (%SHetA2)
SHetA2	S	NO_2	3.45±0.10	80.76±2.41	100%
26	O	NO_2	6.14±0.20	36.24±3.13	44.87%
27	S	NO_2	5.91±0.26	21.58±2.66	26.72%
28	S	CF_3	6.15±0.26	18.43±2.25	22.82%
29	O	CF_3	6.34±0.26	28.21±2.99	34.93%
30	S	CN	3.51±0.26	20.59±1.85	25.50%
31	O	CN	3.89±0.23	19.19±2.10	23.76%
32	S	OCF_3	3.74±0.27	18.34±2.14	22.71%
33	O	OCF_3	5.95±0.30	22.79±3.18	28.22%

Table 1.1: The biological activity of indoline SHetA2 analogs relative to SHetA2.

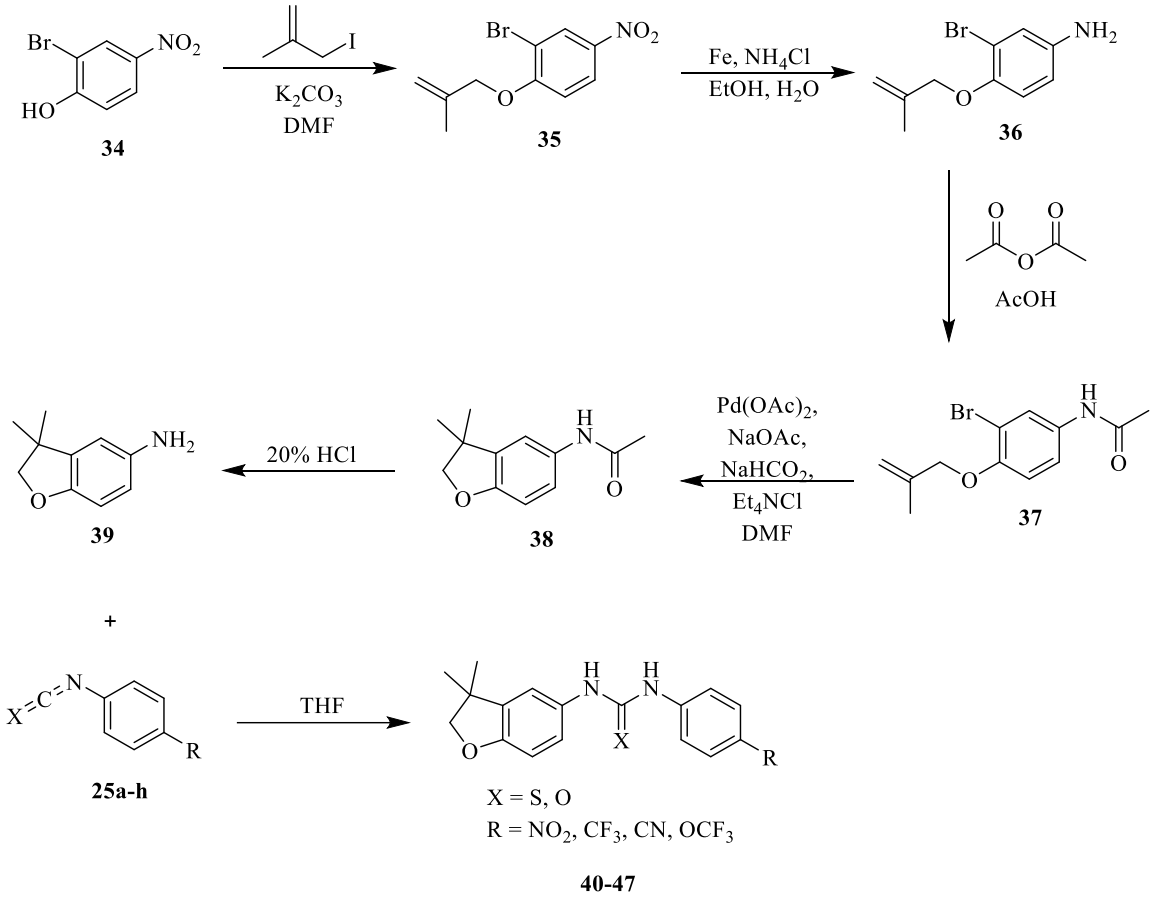
1.3 Synthesis of Dihydrofuran SHetA2 Analogs

Interest in fused dihydrofuran-containing SHetA2 analogs were developed with the desire to increase the solubility of SHetA2, and thus its potency. The usefulness of **9-11** also increased interest. Making this adjustment to the Ring A system could also reveal the importance of the structure of Ring A in anti-cancer activity.

With these goals in mind, we designed and synthesized sixteen SHetA2 analogs characterized by a fused, dihydrofuran Ring A system, urea and thiourea linker units, and 4-NO_2, CN, CF_3, and OCF_3 functionalized Ring B systems. We now report the synthesis and biological activity of these Flex-Hets against the ovarian cancer cell line A2780. These new heteroarotinoids were evaluated relative to SHetA2.

1.3.1 Results and Discussion

Synthesis of fused dihydrofuran analogs required 6 steps. First, 2-bromo-4-nitrophenol (**34**) was alkylated with 3-iodo-2-methylprop-1-ene to produce **35** in 72% yield.



Scheme 1.2: The synthesis of dihydrofuran SHetA2 analogs.

Nitrated ether **35** was treated with iron and ammonium chloride in a refluxing ethanol-water mixture (4:1) to afford **36** in 92% yield. Amide **37** was realized by treatment of the aniline analog **36** with acetic anhydride in glacial acetic acid at room temperature and was isolated in 89% yield. Cyclization of **37** *via* a reductive Heck reaction using Jeffery conditions afforded cyclic ether **38** in 95% yield. The aniline **39** was obtained in 82% yield by treatment of **38** with refluxing 20% HCl. Finally, **39** was treated with dropwise addition of isocyanates and isothiocyanates **25a-h** to afford the SHetA2 analogs **40-47** in 24-95% yields (Scheme 1.2). Reaction yields in the final step were dependent upon the purity of the commercial isocyanates and isothiocyanates. All products **40-47** were purified on a 10 inch silica gel column, eluting with 10% ether in hexanes, and

increasing the polarity on a gradient to 50% ether in hexanes. All products were subsequently dried under vacuum at 60 °C for 24 hours.

Compound	X =	R =	Potency IC_{50} (μM)	Maximal Activity (% growth inhibition)	Efficacy (%SHetA2)
SHetA2	S	NO_2	3.45±0.10	80.76±2.41	100%
40	S	NO_2	4.14±0.40	21.36±3.51	26.45%
41	O	NO_2	6.09±0.12	62.98±3.72	77.98%
42	S	CN	1.63±0.30	15.01±2.23	18.59%
43	O	CN	1.31±0.40	19.54±2.65	24.20%
44	O	CF_3	3.60±0.17	35.48±2.51	43.93%
45	S	CF_3	6.15±0.21	25.31±2.54	32.34%
46	O	OCF_3	1.38±0.06	44.69±1.01	55.34%
47	S	OCF_3	7.95±0.32	17.65±3.39	21.85%

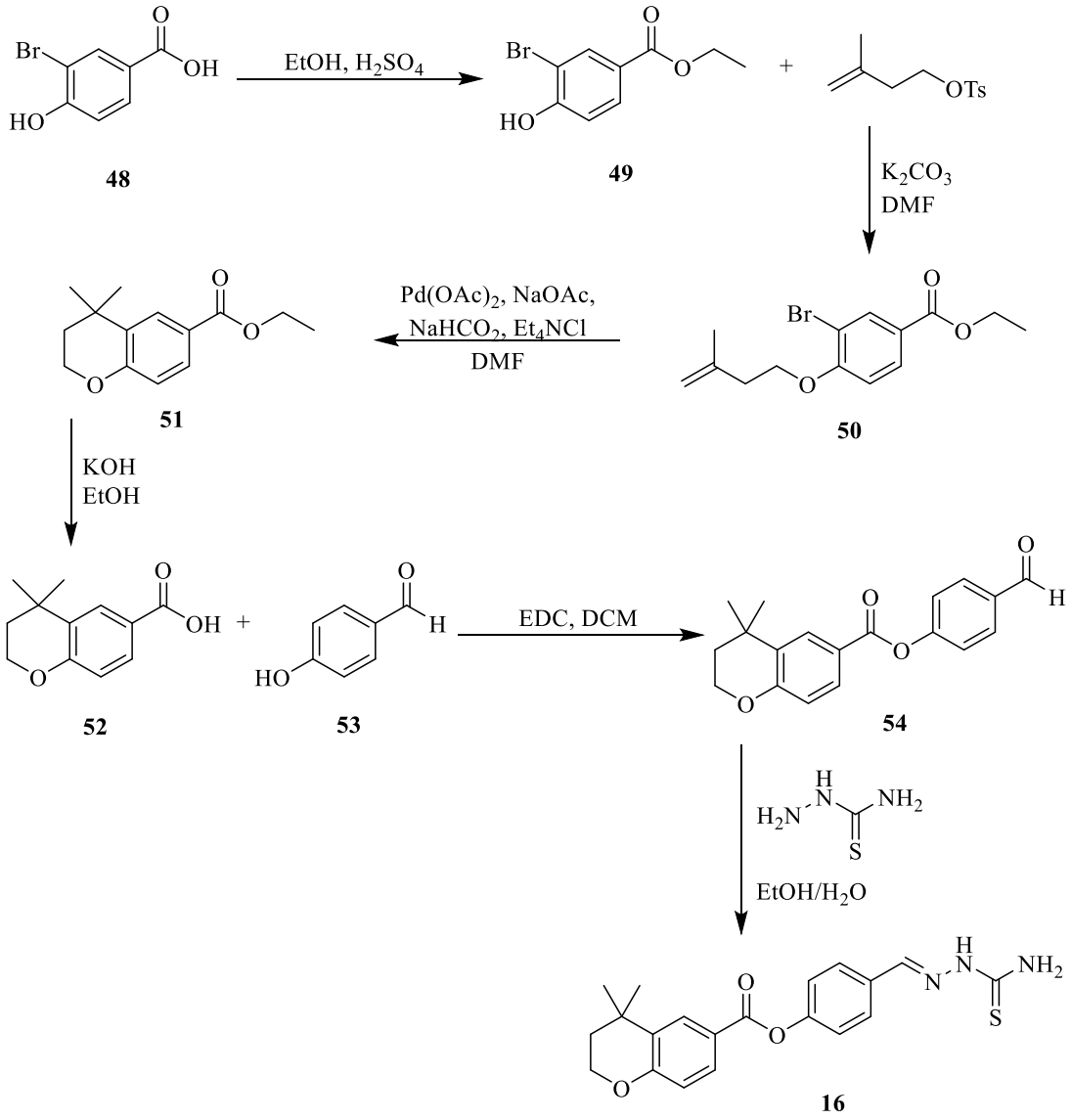
Table 1.2: The biological activity data of dihydrofuran SHetA2 analogs relative to SHetA2.

The biological effects of the compounds were determined by cytotoxicity assay against the human A2780 ovarian cancer cell line (Table 1.2). Compound **41** showed decreased potency and viable efficacy, compared to SHetA2. Compound **41** contains a urea linker unit and a 4-NO_2 group on Ring B, similar to indoline analog **26**, but with improved efficacy compared to SHetA2. This is an indication that the dihydrofuran-containing Ring A system provides better activity than the indoline-containing Ring A system when combined with active linker and Ring B units. Compound **46** showed marked potency compared to SHetA2, and provided sufficient efficacy to be noteworthy. The influence in Ring B functionality by -OCF_3 was noted, along with the urea linker unit. Compounds **42** and **43** showed improved potency relative to SHetA2, but much lower efficacy. This class of SHetA2 analogs revealed that this functionality of the Ring A system can provide compounds with improved potency and acceptable efficacy to SHetA2.

1.4 Synthesis of OHet72 *via* a Reductive Heck Cyclization

Interest in OHet72 (**16**) as an anti-cancer agent remains high. Herein, we report a facile synthesis of OHet72 using an intramolecular reductive Heck reaction using Jeffery conditions to cyclize the chroman ring.

1.4.1 Results and Discussion



Scheme 1.3: The synthetic route to OHet72 *via* a reductive Heck cyclization.

Synthesis of OHet72 (**16**) required 6 steps. First, 3-bromo-4-hydroxybenzoic acid (**48**) was converted to ester **49** by refluxing in ethanol with a catalytic amount of H_2SO_4, and ester **49** was recovered in 86% yield. Phenol **49** was then alkylated with 3-methylbut-3-en-1-yl 4-methylbenzenesulfonate, and ether **50** was produced in 81% yield. Cyclization of **50** *via* a reductive Heck using Jeffery conditions afforded chroman derivative **51** in 94% yield. Ester **51**

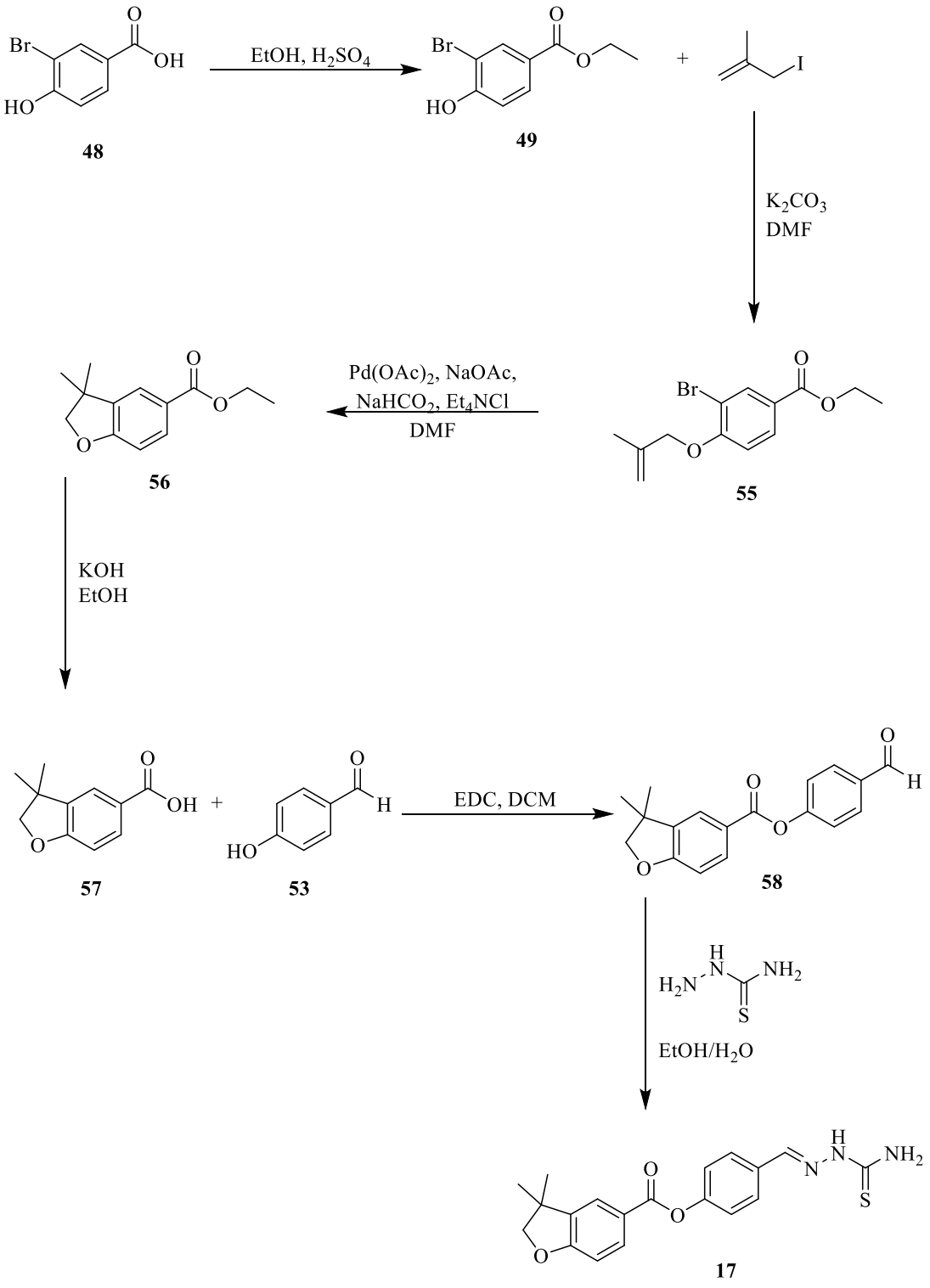
was next hydrolyzed to carboxylic acid **52** with KOH in ethanol at 89% yield. Ester-aldehyde **54** was obtained by treating carboxylic acid **52** and 4-hydroxybenzaldehyde (**53**) in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and 4-dimethylaminopyridine (DMAP). A yield of 64% was obtained for **54**. Finally, OHet72 (**16**) was realized by adding aqueous thiosemicarbazide to ester-aldehyde **54** in refluxing ethanol.

1.5 Synthesis of Furan OHet72 Derivative via a Reductive Heck Cyclization

Renewed interest in OHet72 (**16**) presented the opportunity to synthesize new analogs of the compound. Herein we report a synthesis for a dihydrofuran-containing analog of OHet72 (**17**), employing the Jeffery variant of the reductive Heck to cyclize the furan ring.

1.5.1 Results and Discussion

Synthesis of the dihydrofuran-containing analog **17** required 5 steps from a known precursor. First, ethyl 3-bromo-4-hydroxybenzoate (**49**) was alkylated with 3-iodo-2-methylprop-1-ene in 98% yield. The ether product **55** was cyclized by employing an intramolecular reductive Heck under the Jeffery conditions to afford the benzofuran derivative **56** in 50% yield. In the cyclization step, a significant amount of rearranged enol ether byproduct was observed. The yield of the cyclized product was maximized when the palladium catalyst was added before heating, and then heating at 95 °C. The cyclized ester **56** was treated with KOH in ethanol to obtain carboxylic acid **57** in 96% yield after neutralization. Ester-aldehyde **58** was next obtained by esterification of carboxylic acid **57** and 4-hydroxybenzaldehyde (**53**) with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and 4-dimethylaminopyridine (DMAP). A yield of 94% was realized for **58**. Finally, OHet72 analog **17** was acquired by addition of aqueous thiosemicarbazide to ester-aldehyde **58** in refluxing ethanol.



Scheme 1.4: The synthetic approach to a dihydrofuran analog of OHet72.

1.6 Conclusion

In summary, we have synthesized 18 heteroarotinoids by employing a powerful cyclization method. Additionally, in an attempt to improve the anti-cancer activity of SHetA2 (**3**), 16 heteroarotinoids were assessed in a cytotoxicity assay of the human A2780 ovarian cancer cell line.

1.6.1 Synthesis of Indoline SHetA2 Analogs

In this study, we synthesized Flex-Hets with an *N*-methylindoline Ring A system, including urea and thiourea linker units, as well as 4-NO_2, CN, CF_3, and OCF_3 substituents in Ring B (**26-33**). These compounds were evaluated for anti-cancer activity against the human A2780 ovarian cancer cell line. None of the prepared compounds showed useful activity, but a new method for the synthesis of analogs was developed.

1.6.2 Synthesis of Dihydrofuran SHetA2 Analogs

In this study, we synthesized Flex-Hets with a dihydrofuran Ring A system, including urea and thiourea linker units, and 4–NO_2, CN, CF_3, and OCF_3 groups in Ring B to yield **40-47**. These compounds were evaluated for anti-cancer activity against the human A2780 ovarian cancer cell line. Compounds **41** and **46** showed useful efficacy, and compounds **42** and **43** also showed improved potency from SHetA2. A useful method for the synthesis of heterocyclic analogs also was developed.

1.6.3 Synthesis of OHet72 via a Reductive Heck Cyclization

In this study, we employed the method discovered in previous studies to synthesize OHet72 (**16**). By using this facile, efficient method, we were able to synthesize OHet72 (**16**) on a multi-gram scale.

1.6.4 Synthesis of Furan OHet72 Derivative via a Reductive Heck Cyclization

In this study, we were able to synthesize an analog of OHet72 **17** by employing our facile, efficient method.

1.7 Chemistry

1.7.1 Synthesis of Indoline SHetA2 Analogs

***N*-(2-Bromo-4-nitrophenyl)acetamide (19).**

2-Bromo-4-nitroaniline (**18**, 5.0 g, 23.0 mmol) was dissolved in acetic acid (50 mL), and acetic anhydride (10 mL) was added. The mixture was stirred at room temperature for 18 hours, at which time TLC analysis (1:1 ether-hexane) indicated complete consumption of the starting material. The reaction mixture was poured into water (100 mL), at which time a yellow precipitate formed rapidly. The precipitate was collected *via* vacuum filtration and washed with copious amounts of water. The solid was dried under vacuum to yield **19** (5.00 g, 84%) as a yellow solid, mp 119-120 °C. IR: 3216, 1656, 1589, 1313 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (d, J = 9.2 Hz, 1H), 8.46 (d, J = 2.5 Hz, 1H), 8.26 (dd, J = 9.2, 2.5 Hz, 1H), 7.89 (br s, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 143.2, 141.3, 127.9, 124.2, 120.2, 11.8, 25.2.

***N*-(2-Bromo-4-nitrophenyl)-N-(2-methylallyl)acetamide (20).**

N-(2-Bromo-4-nitrophenyl)acetamide (**19**, 5.00 g, 19.30 mmol) was dissolved in DMF (60 mL), and potassium carbonate (10.60 g, 77.20 mmol) was added. The mixture was stirred at room temperature under a N_2 atmosphere for 10 minutes, at which time 3-iodo-2-methylprop-1-ene (7.00 g, 38.6 mmol) was added in one portion. The mixture was heated to 60 °C for 18 hours, after which time TLC analysis (1:2 ether-hexane) indicated completion of the reaction. The reaction mixture was poured into water (100 mL) and extracted with ethyl actetate (3 x 75 mL). The combined organic extracts were washed with water (2 x 75 mL) and brine (75 mL), dried

(Na_2SO_4), and concentrated under vacuum to afford **20** (6.02 g, 99%) as an orange oil. IR: 1652, 1583, 1513, 1317 cm-$^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, J = 2.5 Hz, 1H), 8.24 (dd, J = 8.6, 2.5 Hz, 1H), 7.41 (d, J = 8.6 Hz, 1H), 4.96 (d, J = 14.5 Hz, 1H), 4.86 (s, 1H), 4.66 (s, 1H), 3.52 (d, J = 14.5 Hz, 1H), 1.87 (s, 3H), 1.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 147.5, 147.2, 140.0, 131.5, 129.2, 124.8, 123.5, 115.0, 52.7, 22.6, 20.6.

1-(3,3-Dimethyl-5-nitroindolin-1-yl)ethan-1-one (21).

N-(2-Bromo-4-nitrophenyl)-N-(2-methylallyl)acetamide (**21**, 4.40 g, 14.0 mmol) was dissolved in DMF (50 mL) and stirred at room temperature under a N_2 atmosphere for five minutes. To the reaction mixture was added sodium acetate (2.84 g, 35.0 mmol), sodium formate (1.19 g, 17.50 mmol), and tetraethylammonium chloride (2.33 g, 14.0 mmol). The resultant mixture was stirred at room temperature for an additional 10 minutes under a N_2 atmosphere. Palladium acetate (0.30 g, 10 mol%) was added in a single portion, along with 10 drops of water. The mixture was heated to 80 °C for 18 hours. TLC analysis was inconclusive as to the completion of the reaction. However, the presence of palladium particles in solution indicated likely completion. The reaction mixture was poured over a 1 cm Celite pad. The remaining solution was then poured into water (150 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with water (2 x 50 mL), brine (75 mL), dried (Na_2SO_4), and concentrated under vacuum to afford **8** (2.78 g, 85%) as a yellow solid, mp 183-184 °C. IR: 1674, 1571, 1375 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, J = 9.0 Hz, 1H), 8.15 (dd, J = 9.0, 2.4 Hz, 1H), 8.00 (d, J = 2.4 Hz, 1H), 3.91 (s, 2H), 2.28 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 146.9, 143.9, 141.7, 124.9, 118.0, 116.4, 64.1, 40.1, 28.7, 24.3.

3,3-Dimethyl-5-nitroindoline (22).

1-(3,3-Dimethyl-5-nitroindolin-1-yl)ethan-1-one (**21**, 2.70 g, 11.50 mmol) was placed in 20% HCl (50 mL), and heated to 110 °C. After one hour, all solid had dissolved, indicating reaction

completion. The mixture was poured into 1 M NaOH (150 mL). The aqueous mixture was extracted with ethyl acetate (3 x 75 mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), and concentrated under vacuum to afford **22** (2.07 g, 94%) as a yellow solid, mp 74-76 °C. IR: 3388, 1558, 1363 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (dd, J = 8.7, 2.3 Hz, 1H), 7.90 (d, J = 2.3 Hz, 1H), 6.49 (d, J = 8.7 Hz, 1H), 4.45 (br s, 1H), 3.49 (s, 2H), 1.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9, 139.2, 138.2, 126.1, 118.9, 106.6, 61.7, 41.1, 27.9.

1,3,3-Dimethyl-5-nitroindoline (23).

A suspension of sodium hydride in DMF was prepared by washing 60% NaH (0.25 g, 6.00 mmol) in mineral oil with hexane three times, and then diluted with DMF (5 mL). 3,3-Dimethyl-5-nitroindoline (**22**, 1.00 g, 5.2 mmol) was dissolved in DMF (10 mL), and added at room temperature to the NaH suspension *via* an addition funnel over 5 minutes. After all the NaH had been consumed, methyl iodide (0.80 g, 5.70 mmol) in DMF (5 mL) was added *via* an addition funnel. The reaction mixture was heated to 40 °C for 1 hour, at which time TLC analysis (1:2 ether-hexane) indicated completion of the reaction. The reaction was quenched slowly with brine (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water (3 x 30 mL), brine (30 mL), dried (Na_2SO_4), and concentrated under vacuum to afford **23** (1.05 g, 99%) as a yellow oil. IR: 1551, 1359 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.08 (dd, J = 8.8, 2.3 Hz, 1 H), 7.83 (d, J = 2.3 Hz, 1H), 6.29 (d, J = 8.8 Hz, 1H), 3.36 (s, 2H), 2.92 (s, 3H), 1.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9, 139.2, 138.2, 126.1, 118.9, 106.6, 61.7, 41.1, 37.4, 27.9

1,3,3-Trimethylindolin-5-amine (24).

1,3,3-Trimethyl-5-nitroindoline (**23**, 1.05 g, 5.10 mmol) was placed in an ethanol-water mixture (4:1, 60 mL). Iron powder (1.15 g, 20.4 mmol) and ammonium chloride (0.35 g, 6.375 mmol) were added, and the mixture was heated at 85 °C for 2 hours, at which time TLC analysis (1:1

ether-hexane) indicated complete consumption of the starting material. The reaction mixture was filtered through a 1 cm Celite pad, which was washed with additional ethanol. The volume of ethanol was reduced under vacuum, and then the mixture was diluted with saturated sodium bicarbonate (100 mL). The aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with a brine and sodium bicarbonate mixture (1:1, 50 mL), dried (Na_2SO_4), and the solvent removed under vacuum to afford **24** (0.90 g, 80%) as a purple oil. IR: 3421, 3347 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.49 (dd, J = 75 Hz, 1H), 6.36 (d, J = 7.5 Hz, 1H), 3.23 (br s, 2H), 2.96 (s, 2H), 2.67 (s, 3H), 1.26 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.5, 140.8, 138.5, 114.3, 71.1, 40.4, 37.4, 27.1.

1-(4-Nitrophenyl)-3-(1,3,3-trimethylindolin-5-yl)urea (26).

1,3,3-Trimethylindolin-5-amine (**24**, 0.090 g 0.51 mmol) was dissolved in THF (5 mL). The resultant solution was cooled to 0 °C in an ice bath while stirring under a N_2 atmosphere. 1-Isocyanato-4-nitrobenzene (**25a**, 0.094 g, 0.57 mmol) dissolved in THF (5 mL) was added dropwise over a period of 15 minutes. Upon completion of the addition, the solution was allowed to warm to room temperature and was stirred at room temperature for 24 hours, at which time TLC analysis (100% ether) indicated the complete consumption of the amine. The solvent was removed under vacuum, and the resultant solid was loaded onto an eight inch silica column. Elution with ether-hexane (gradient increasing from 10% ether to 50% ether) yielded **26** (0.125g, 72%) as a yellow solid, mp 204-206 °C. IR: 3304, 3192, 1541, 1334 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.29 (s, 1H), 8.52 (s, 1H), 8.17 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 8.8 Hz, 2H), 7.17 (s, 1H), 7.02 (d, J = 8.3 Hz, 1H), 6.46 (d, J = 8.3 Hz, 1H), 2.99 (s, 2H), 2.66 (s, 3H), 1.23 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.6, 148.5, 147.3, 141.1, 139.7, 130.2, 125.6, 119.5, 117.6, 114.8, 107.8, 70.5, 40.2, 36.6, 27.5.

1-(4-Nitrophenyl)-3-(1,3,3-trimethylindolin-5-yl)thiourea (27).

1,3,3-Trimethylindolin-5-amine (**24**, 0.086 g, 0.48 mmol) was dissolved in THF (5 mL). The resultant solution was cooled to 0 °C in an ice bath while stirring under a N_2 atmosphere. 1-Isothiocyanato-4-nitrobenzene (**25b**, 0.098 g, 0.54 mmol) dissolved in THF (5 mL) was added dropwise over a period of 15 minutes. Upon completion of the addition, the solution was allowed to warm to room temperature and was stirred at room temperature for 24 hours, at which time TLC analysis (100% ether) indicated the complete consumption of the amine. The solvent was removed under vacuum, and the resultant solid was loaded onto an eight inch silica column. Elution with ether-hexane (gradient increasing from 10% ether to 50% ether) yielded **27** (0.128 g, 75%) as a red solid, mp 156-158 °C. IR: 3330, 3195, 1545, 1337 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 8.8 Hz, 2H), 7.69 (s, 1H), 7.01 (d, J = 8.4 Hz, 1H), 6.88 (s, 1H), 6.45 (d, J = 8.4 Hz, 1H), 3.20 (s, 2H), 2.81 (s, 3H), 1.31 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.7, 152.2, 144.3, 141.6, 126.4, 124.4, 122.7, 120.3, 107.1, 69.9, 40.3, 35.1, 27.5.

1-(4-(Trifluoromethyl)phenyl)-3-(1,3,3-trimethylindolin-5-yl)thiourea (28).

1,3,3-trimethylindolin-5-amine (**24**, 0.086 g, 0.48 mmol) was dissolved in THF (5 mL). The resultant solution was cooled to 0 °C in an ice bath while stirring under a N_2 atmosphere. 1-Isothiocyanato-4-(trifluoromethyl)benzene (**25c**, 0.107 g, 0.54 mmol) dissolved in THF (5 mL) was added dropwise over a period of 15 minutes. Upon completion of the addition, the solution was allowed to warm to room temperature and was stirred at room temperature for 24 hours, at which time TLC analysis (100% ether) indicated the complete consumption of the amine. The solvent was removed under vacuum, and the resultant solid was loaded onto an eight inch silica column. Elution with ether-hexane (gradient increasing from 10% ether to 50% ether) yielded **28** (0.091 g, 51%) as a grey solid, mp 161-163 °C. IR: 3321, 3186 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.58 (coincident d, J = 8.4 Hz, 2H and s, 1H), 7.02 (dd, J = 8.2, 2.2, 1H), 6.90 (d, J = 2.2 Hz, 1H), 6.45 (d, J = 8.2 Hz, 1H), 3.18 (s, 2H), 2.80 (s,

3H), 1.31 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.1, 152.0, 141.4, 141.4, 127.6, 127.3, 126.3, 125.9, 125.8, 123.8, 120.3, 107.1, 70.0, 40.3, 35.2, 27.5.

1-(4-(Trifluoromethyl)phenyl)-3-(1,3,3-trimethylindolin-5-yl)urea (29).

1,3,3-Trimethylindolin-5-amine (**24**, 0.080 g, 0.46 mmol) was dissolved in THF (5 mL). The resultant solution was cooled to 0 °C in an ice bath while stirring under a N_2 atmosphere. 1-Isocyanato-4-(trifluoromethyl)benzene (**25d**, 0.092 g, 0.50 mmol) dissolved in THF (5 mL) was added dropwise over a period of 15 minutes. Upon completion of the addition, the solution was allowed to warm to room temperature and was stirred at room temperature for 24 hours at which time TLC analysis (100% ether) indicated the complete consumption of the amine. The solvent was removed under vacuum, and the resultant solid was loaded onto an eight inch silica column. Elution with ether-hexane (gradient increasing from 10% ether to 50% ether) yielded **29** (0.079 g, 48%) as a white solid, mp 185-187 °C. IR: 3362, 3238 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, J = 8.7 Hz, 1H), 7.46 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 8.1 Hz, 1H), 6.93 (d, J = 2.2 Hz, 1H), 6.72 (s, 1H), 6.44 (d, J = 8.1 Hz, 1H), 6.25 (s, 1H), 3.14 (s, 2H), 2.78 (s, 3H), 1.30 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.4, 141.8, 140.9, 126.2, 125.6, 124.9, 124.6, 122.9, 118.8, 118.5, 70.2, 40.3, 35.7, 27.3.

1-(4-Cyanophenyl)-3-(1,3,3-trimethylindolin-5-yl)thiourea (30).

1,3,3-Trimethylindolin-5-amine (**24**, 0.072 g, 0.41 mmol) was dissolved in THF (5 mL). The resultant solution was cooled to 0 °C in an ice bath while stirring under a N_2 atmosphere. 4-Isothiocyanatobenzonitrile (**25e**, 0.072 g, 0.45 mmol) dissolved in THF (5 mL) was added dropwise over a period of 15 minutes. Upon completion of the addition, the solution was allowed to warm to room temperature and was stirred at room temperature for 24 hours, at which time TLC analysis (100% ether) indicated the complete consumption of the amine. The solvent was

removed under vacuum, and the resultant solid was loaded onto an eight inch silica column. Elution with ether-hexane (gradient increasing from 10% ether to 50% ether) yielded **30** (0.085 g, 62%) as a white solid, mp 158-160 °C. IR: 3306, 3188, 2234 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.71 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 8.5 Hz, 2H), 7.01 (dd, J = 8.1, 2.2 Hz, 1H), 6.45 (d, J = 2.2 Hz, 1H), 3.19 (2, 2H), 2.80 (s, 3H), 1.30 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.7, 152.1, 142.5, 141.5, 132.7, 126.4, 124.3, 123.4, 120.3, 118.7, 108.4, 107.1, 69.9, 40.3, 35.2, 27.5.

1-(4-Cyanophenyl)-3-(1,3,3-trimethylindolin-5-yl)urea (31).

1,3,3-Trimethylindolin-5-amine (**24**, 0.072 g 0.41 mmol) was dissolved in THF (5 mL). The resultant solution was cooled to 0 °C in an ice bath while stirring under a N_2 atmosphere. 4-Isocyanatobenzonitrile (**25f**, 0.065 g, 0.45 mmol) dissolved in THF (5 mL) was added dropwise over a period of 15 minutes. Upon completion of the addition, the solution was allowed to warm to room temperature and was stirred at room temperature for 24 hours, at which time TLC analysis (100% ether) indicated the complete consumption of the amine. The solvent was removed under vacuum, and the resultant solid was loaded onto an eight inch silica column. Elution with ether-hexane (gradient increasing from 10% ether to 50% ether) gave **31** (0.094 g, 72%) as a white solid, mp 212-214 °C. IR: 3356, 3218, 2221 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.04 (s, 1H), 8.45 (s, 1H), 7.70 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 2.2 Hz, 1H), 7.00 (dd, J = 8.2, 2.2 Hz, 1H), 6.45 (d, J = 8.2 Hz, 1H), 2.99 (s, 2H), 2.66 (s, 3H), 1.23 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.8, 140.1, 133.7, 130.4, 119.9, 119.4, 118.2, 114.7, 107.8, 103.2, 70.5, 40.3, 36.7, 27.5.

1-(4-(Trifluoromethoxy)phenyl)-3-(1,3,3-trimethylindolin-5-yl)thiourea (32).

1,3,3-Trimethylindolin-5-amine (**24**, 0.072 g, 0.41 mmol) was dissolved in THF (5 mL). The resultant solution was cooled to 0 °C in an ice bath while stirring under a N_2 atmosphere. 1-

Isothiocyanato-4-(trifluoromethoxy)benzene (**25g**, 0.100 g, 0.45 mmol) dissolved in THF (5 mL) was added dropwise over a period of 15 minutes. Upon completion of the addition, the solution was allowed to warm to room temperature and was stirred at room temperature for 24 hours, at which time TLC analysis (100% ether) indicated the complete consumption of the amine. The solvent was removed under vacuum, and the resultant solid was loaded onto an eight inch silica column. Elution with ether-hexane (gradient increasing from 10% ether to 50% ether) yielded **32** (0.034 g, 21%) as a yellow solid, mp 131-133 °C. IR: 3312, 3201 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.50 (d, J = 8.5 Hz, 2H), 7.47 (s, 1H), 7.19 (d, J = 8.5 Hz, 2H), 7.02 (dd, J = 8.2, 2.2 Hz, 1H), 6.90 (d, J = 2.2 Hz, 1H), 6.44 (d, J = 8.2 Hz, 1H), 3.17 (s, 2H), 2.79 (s, 3H), 1.30 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.2, 150.1, 144.8, 139.5, 139.4, 129.8, 125.6, 124.8, 121.5, 119.5, 107.2, 70.3, 40.3, 36.2, 27.5.

1-(4-(trifluoromethoxy)phenyl)-3-(1,3,3-trimethylindolin-5-yl)urea (33).

1,3,3-Trimethylindolin-5-amine (**24**, 0.072 g 0.41 mmol) was dissolved in THF (5 mL). The resultant solution was cooled to 0 °C in an ice bath while stirring under a N_2 atmosphere. 1-Isocyanato-4-(trifluoromethoxy)benzene **25g** (0.092 g, 0.45 mmol) dissolved in THF (5 mL) was added dropwise over a period of 15 minutes. Upon completion of the addition, the solution was allowed to warm to room temperature and was stirred at room temperature for 24 hours, at which time TLC analysis (100% ether) indicated the complete consumption of the amine. The solvent was removed under vacuum, and the resultant solid was loaded onto an eight inch silica column. Elution with ether-hexane (gradient increasing from 10% ether to 50% ether) yielded **33** (0.043 g, 27%) as a yellow solid, mp 176-178 °C. IR: 3369, 3224 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.71 (s, 1H), 8.30 (s, 1H), 7.53 (d, J = 9.0 Hz, 2H), 7.25 (s, J = 9.0 Hz, 2H), 7.15 (d, J = 2.1 Hz, 1H), 6.99 (dd, J = 8.2, 2.1 Hz, 1H), 6.44 (d, J = 8.2 Hz, 1H), 2.98 (s, 2H), 2.65 (s, 3H), 1.22 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.3, 148.2, 142.7, 139.9, 139.7, 130.9, 122.2, 122.1, 119.5, 119.2, 114.6, 107.8, 70.6, 39.5, 36.7, 27.5.

1.7.2 Synthesis of Dihydrofuran SHetA2 Analogs

2-Bromo-1-((2-methylallyl)oxy)-4-nitrobenzene (35).

2-Bromo-4-nitrophenol (**34**, 5.0 g, 22.9 mmol) was dissolved in DMF (100 mL), and potassium carbonate (12.60 g, 91.6 mmol) was added. The mixture was stirred under a N_2 atmosphere for 10 minutes. 3-Iodo-2-methylprop-1-ene (6.26 g, 34.4 mmol) was added in a single portion, and the reaction was stirred under N_2 at room temperature for 18 hours, at which time TLC analysis (1:4 ether-hexane) indicated completion of the reaction. The mixture was poured into water (200 mL), and the aqueous layer was extracted with ether (3 x 100 mL). The combined organic layers were washed with water (3 x 100 mL) and brine (100 mL), dried (Na_2SO_4) and concentrated under vacuum to afford **35** (4.32 g, 73%) as a tan solid, mp 40-42 °C. IR: 1538, 1516, 1345, 1241 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.47 (d, J = 2.7, 1H), 8.18 (dd, J = 9.1, 2.7, 1H), 6.94 (d, J = 9.1, 1H), 5.17 (s, 1H), 4.61 (s, 2H), 1.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0, 141.5, 138.9, 129.1, 124.6, 113.9, 112.2, 112.0, 73.2, 19.2.

3-Bromo-4-((2-methylallyl)oxy)aniline (36).

2-Bromo-1-((2-methylallyl)oxy)-4-nitrobenzene (**35**, 4.0 g, 14.72 mmol) was dissolved in an ethanol/water mixture (100 ml, 4:1). Ammonium chloride (1.0 g, 18.4 mmol) and iron metal (3.3 g, 58.8 mmol) were added, and the mixture was heated at 85 °C for one hour, at which time TLC analysis (1:1 ether-hexane) indicated complete consumption of the starting material. The reaction mixture was filtered through a 1 cm Celite pad. The volume was reduced under vacuum, and the aqueous portion was diluted with saturated aq. $NaHCO_3$ (100 mL). The aqueous layer was extracted with ether (3 x 75 mL), and the combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), and concentrated under vacuum to afford **36** (3.27 g, 92%) as a red oil. IR: 3423, 3348, 1521, 1243 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.88 (d, J = 2.6 Hz, 1H), 6.71 (d, J = 8.6 Hz, 1H), 6.53 (dd, J = 8.6, 2.6 Hz, 1H), 5.12 (s, 1H), 4.97 (s, 1H), 4.37 (s, 2H), 3.46 (br s,

2H), 1.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.1, 141.4, 140.9, 120.1, 115.7, 114.9, 113.2, 112.7, 73.6, 19.5.

***N*-(3-Bromo-4-((2-methylallyl)oxy)phenyl)acetamide (37).**

3-Bromo-4-((2-methylallyl)oxy)aniline (**36**, 3.0 g, 12.38 mmol) was dissolved in glacial acetic acid (20 mL), and 10mL of acetic anhydride were added. The reaction was stirred at room temperature for two hours, at which time TLC analysis indication completion of the reaction. The reaction mixture was poured into water (100 mL), and extracted with ether (3 x 75 mL). The combined organic layers were washed with water (3 x 100 mL), saturated aq. $NaHCO_3$ (3 x 100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated under vacuum to afford **37** (3.13 g, 89%) as a tan solid, mp 86-88 °C. IR: 3243, 1659 1523, 1239 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (br s, 1H), 7.68 (d, J = 2.6 Hz, 1H), 7.38 (dd, J = 8.8, 2.6 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 5.13 (s, 1H), 4.99 (s, 1H), 4.44 (s, 1H), 2.14 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 151.9, 140.2, 131.9, 125.6, 120.6, 113.6, 113.0, 112.0, 72.8, 24.3, 19.4.

***N*-(3,3-Dimethyl-2,3-dihydrobenzofuran-5-yl)acetamide (38).**

N-(3-Bromo-4-((2-methylallyl)oxy)phenyl)acetamide (**37**, 3.00 g, 10.58 mmol) was dissolved in DMF (40 mL), and sodium acetate (2.18 g, 26.25 mmol), sodium formate (0.86 g, 12.68 mmol), and tetraethylammonium chloride (2.10 g, 12.68 mmol) were added. The mixture was stirred under N_2 for 10 minutes, and then palladium acetate (0.240 g, 10 mol%) and a few drops of water were added. The reaction was heated to 90 °C for 18 hours, and then filtered through a 1 cm Celite pad. The mixture was diluted with water (150 mL) and extracted with ether (3 x 75mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), and concentrated under vacuum to afford **38** (2.05 g, 95%) as a tan solid, mp 124-126 °C. IR: 3239, 1661, 1231 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J = 2.3 Hz, 1 H), 7.18 (br s, 1H), 7.05

(dd, J = 8.5, 2.3 Hz, 1H), 6.71 (d, J = 8.5 Hz, 1H), 4.22 (s, 2H), 2.14 (s, 3H), 1.33 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 156.0, 137.2, 131.0, 120.5, 115.8, 109.5, 84.8 42.2, 27.4, 24.3.

3,3-Dimethyl-2,3-dihydrobenzofuran-5-amine (39).

N-(3,3-Dimethyl-2,3-dihydrobenzofuran-5-yl)acetamide (**38**, 2.00 g 10.27 mmol) was placed in 50 mL of 20% HCl and stirred for one hour at 90 °C. At this time, all the material was dissolved, indicating completion of the reaction. The mixture was poured into 100 mL of 1 M NaOH solution. The aqueous solution was then extracted with ethyl acetate (3 x 50 mL), and the combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), and concentrated under vacuum to afford **39** (1.30 g, 82%) as a brown oil. IR: 3423, 3348, 1239 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.60 (d, J = 8.2, 1.4 Hz, 1H), 6.50 (d, J = 2.4 Hz, 1H), 6.47 (dd, J = 8.2, 2.4 Hz, 1H), 4.16 (d, J = 8.5, 1H), 3.41 (s, 2H), 2.14 (s, 3H), 1.33 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 140.0, 137.5, 114.7, 110.2, 109.7, 84.3, 42.2, 27.2.

1-(3,3-Dimethyl-2,3-dihydrobenzofuran-5-yl)-3-(4-nitrophenyl)thiourea (40).

3,3-Dimethyl-2,3-dihydrobenzofuran-5-amine (**39**, 0.062 g, 0.377 mmol) was dissolved in THF (5 mL). The resultant solution was cooled to 0 °C in an ice bath while stirring under a N_2 atmosphere. 1-Isothiocyanato-4-nitrobenzene (**25a**, 0.075 g, 0.415 mmol) dissolved in THF (5 mL) was added dropwise over a period of 15 minutes. Upon completion of the addition, the solution was allowed to warm to room temperature and was stirred at room temperature for 24 hours, at which time TLC analysis (100% ether) indicated the complete consumption of the amine. The solvent was removed under vacuum, and the resultant solid was loaded onto an eight inch silica column. Elution with ether-hexane (gradient increasing from 10% ether to 50% ether) yielded **40** (0.070 g, 54%) as a white solid, mp 178-180 °C. IR: 3308, 3195, 1542, 1334 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.23 (s, 1H), 10.07 (s, 1H), 8.18 (d, J = 9.1 Hz, 2H), 7.82 (d, J = 9.1 Hz, 2H), 7.24 (d, J = 2.3 Hz, 1H), 7.12 (dd, J = 8.4, 2.3 Hz, 1H), 6.75 (d, J = , 8.4 Hz, 1H),

4.23 (s, 2H), 1.28 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 180.0, 156.9, 146.9, 142.6, 137.3, 132.2, 125.2, 124.8, 121.9, 120.1, 109.4, 82.5, 40.0, 27.6.

1-(3,3-Dimethyl-2,3-dihydrobenzofuran-5-yl)-3-(4-nitrophenyl)urea (41).

3,3-Dimethyl-2,3-dihydrobenzofuran-5-amine (**39**, 0.062 g, 0.377 mmol) was dissolved in THF (5 mL). The resultant solution was cooled to 0 °C in an ice bath while stirring under a N_2 atmosphere. 1-Isocyanato-4-nitrobenzene (**25b**, 0.068 g, 0.415 mmol) dissolved in THF (5 mL) was added dropwise over a period of 15 minutes. Upon completion of the addition, the solution was allowed to warm to room temperature and was stirred at room temperature for 24 hours, at which time TLC analysis (100% ether) indicated the complete consumption of the amine. The solvent was removed under vacuum, and the resultant solid was loaded onto an eight inch silica column. Elution with ether-hexane (gradient increasing from 10% ether to 50% ether) yielded **41** (0.073 g, 72%) as a yellow solid, mp 219-221°C. IR: 3336, 3199, 1546, 1329 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.35 (s, 1H), 8.68 (s, 1H), 8.18 (d, J = 8.9 Hz, 2H), 7.79 (d, J = 8.9 Hz, 2H), 7.37 (s, 1H), 7.07 (d, J = 8.5 Hz, 1H), 6.71 (d, J = 8.5 Hz, 1H), 4.19 (s, 2H), 1.29 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.9, 152.6, 147.1, 141.2, 137.4, 132.5, 125.6, 119.7, 117.8, 115.0, 109.5, 84.2, 42.2, 27.6.

1-(4-Cyanophenyl)-3-(3,3-dimethyl-2,3-dihydrobenzofuran-5-yl)thiourea (42).

3,3-Dimethyl-2,3-dihydrobenzofuran-5-amine (**39**, 0.068 g, 0.41 mmol) was dissolved in THF (5 mL). The resultant solution was cooled to 0 °C in an ice bath while stirring under a N_2 atmosphere. 4-Isothiocyanatobenzonitrile (**25c**, 0.083 g, 0.52 mmol) dissolved in THF (5 mL) was added dropwise over a period of 15 minutes. Upon completion of the addition, the solution was allowed to warm to room temperature and was stirred at room temperature for 24 hours, at which time TLC analysis (100% ether) indicated the complete consumption of the amine. The

solvent was removed under vacuum, and the resultant solid was loaded onto an eight inch silica column. Elution with ether-hexane (gradient increasing from 10% ether to 50% ether) yielded **42** (0.090 g, 67%) as a white solid, mp 158-160 °C. IR: 3299, 3183, 2231 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (br s, 1H), 7.68 (d, J = 8.7, 2H), 7.64 (br s, 1H), 7.61 (d, J = 8.7 Hz, 2H), 7.08 (dd, J = 8.3, 2.3 Hz, 1H), 7.04 (d, J = 2.3, 1H), 6.85 (d, J = 8.3 Hz, 1H), 4.32 (s, 2H), 1.36 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 180.0, 156.8, 144.7, 137.3, 133.2, 133.1, 132.2, 125.2, 122.7, 120.2, 119.6, 109.4, 105.5, 84.5, 40.1, 27.6.

1-(4-Cyanophenyl)-3-(3,3-dimethyl-2,3-dihydrobenzofuran-5-yl)urea (43).

3,3-Dimethyl-2,3-dihydrobenzofuran-5-amine (**39**, 0.068 g, 0.41 mmol) was dissolved in THF (5 mL). The resultant solution was cooled to 0 °C in an ice bath while stirring under a N_2 atmosphere. 4-Isocyanatobenzonitrile (**25d**, 0.075 g, 0.52 mmol) dissolved in THF (5 mL) was added dropwise over a period of 15 minutes. Upon completion of the addition, the solution was allowed to warm to room temperature and was stirred at room temperature for 24 hours, at which time TLC analysis (100% ether) indicated the complete consumption of the amine. The solvent was removed under vacuum, and the resultant solid was loaded onto an eight inch silica column. Elution with ether-hexane (gradient increasing from 10% ether to 50% ether) yielded **43** (0.0120 g, 95%) as a white solid, mp 188-190 °C. IR: 3349, 3204, 2226 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 8.7 Hz, 2H), 7.48 (d, J = 8.7 Hz, 2H), 7.12 (d, J = 2.2 Hz, 1H), 6.99 (dd, J = 8.4, 2.2 Hz, 1H), 6.89 (br s, 1H), 6.78 (d, J = 8.4 Hz, 1H), 6.52 (br s, 1H), 4.27 (s, 2H), 1.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.5, 153.5, 142.8, 138.3, 133.9, 133.3, 133.2, 129.3, 119.1, 119.0, 110.2, 105.7, 85.0, 42.1, 27.4.

1-(3,3-Dimethyl-2,3-dihydrobenzofuran-5-yl)-3-(4-(trifluoromethyl)phenyl)urea (44).

3,3-Dimethyl-2,3-dihydrobenzofuran-5-amine (**39**, 0.068 g, 0.41 mmol) was dissolved in THF (5 mL). The resultant solution was cooled to 0 °C in an ice bath while stirring under a N_2

atmosphere. 1-Isocyanato-4-(trifluoromethyl)benzene (**25e**, 0.097 g, 0.51 mmol) dissolved in THF (5 mL) was added dropwise over a period of 15 minutes. Upon completion of the addition, the solution was allowed to warm to room temperature and was stirred at room temperature for 24 hours, at which time TLC analysis (100% ether) indicated the complete consumption of the amine. The solvent was removed under vacuum, and the resultant solid was loaded onto an eight inch silica column. Elution with ether-hexane (gradient increasing from 10% ether to 50% ether) yielded **44** (0.037 g, 24%) as a grey solid, mp 221-223 °C. IR: 3304, 3191 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.00 (s, 1H), 8.55 (s, 1H), 7.65 (d, J = 8.6 Hz, 2H), 7.61 (d, J = 8.6 Hz, 2H), 7.36 (d, J = 1.5 Hz, 1H), 7.05 (dd, J = 8.4, 1.5 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H), 4.18 (s, 2H), 1.29 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.7, 153.0, 144.2, 137.4, 132.8, 126.5, 126.4, 122.1, 119.5, 118.1, 114.8, 109.5, 84.2, 42.2, 27.6.

1-(3,3-Dimethyl-2,3-dihydrobenzofuran-5-yl)-3-(4-(trifluoromethyl)phenyl)thiourea (45).

3,3-Dimethyl-2,3-dihydrobenzofuran-5-amine (**39**, 0.068 g, 0.41 mmol) was dissolved in THF (5 mL). The resultant solution was cooled to 0 °C in an ice bath while stirring under a N_2 atmosphere. 1-Isocyanato-4-(trifluoromethyl)benzene (**25f**, 0.105 g, 0.52 mmol) dissolved in THF (5 mL) was added dropwise over a period of 15 minutes. Upon completion of the addition, the solution was allowed to warm to room temperature and was stirred at room temperature for 24 hours, at which time TLC analysis (100% ether) indicated the complete consumption of the amine. The solvent was removed under vacuum, and the resultant solid was loaded onto an eight inch silica column. Elution with ether-hexane (gradient increasing from 10% ether to 50% ether) yielded **45** (0.085 g, 52%) as a white solid, mp 152-154 °C. IR: 3289, 3178 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.94 (s, 1H), 9.85 (s, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 2.2 Hz, 1H), 7.10 (dd, J = 8.4, 2.2 Hz, 1H), 6.74 (d, J = 8.4, Hz, 1H), 4.22 (s, 2H), 1.28 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 180.3, 156.8, 144.0, 137.2, 132.3, 126.2, 126.0, 125.3, 123.2, 120.2, 109.3, 84.5, 42.1, 27.6.

1-(3,3-Dimethyl-2,3-dihydrobenzofuran-5-yl)-3-(4-(trifluoromethoxy)phenyl)urea (46).

3,3-Dimethyl-2,3-dihydrobenzofuran-5-amine (**39**, 0.086 g, 0.525 mmol) was dissolved in THF (5 mL). The resultant solution was cooled to 0 °C in an ice bath while stirring under a N_2 atmosphere. 1-Isocyanato-4-(trifluoromethoxy)benzene (**25h**, 0.128 g, 0.631 mmol) dissolved in THF (5 mL) was added dropwise over a period of 15 minutes. Upon completion of the addition, the solution was allowed to warm to room temperature and was stirred at room temperature for 24 hours, at which time TLC analysis (100% ether) indicated the complete consumption of the amine. The solvent was removed under vacuum, and the resultant solid was loaded onto an eight inch silica column. Elution with ether-hexane (gradient increasing from 10% ether to 50% ether) yielded **46** (0.097 g 48%) as a white solid, mp 224-226 °C. IR: 3341, 3193 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.76 (s, 1H), 8.46 (s, 1H), 754 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 2.3 Hz, 1H), 7.26 (d, J = 8.8 Hz, 2H), 7.04 (dd, J = 8.6, 2.3 Hz, 1H), 6.68 (d, J = 8.5 Hz, 1H), 4.18 (s, 2H), 1.28 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.5, 153.2, 142.9, 142.9, 139.7, 137.3, 133.0, 122.1, 119.7, 114.7, 109.5, 84.2, 42.2, 27.6.

1-(3,3-Dimethyl-2,3-dihydrobenzofuran-5-yl)-3-(4-(trifluoromethoxy)phenyl)thiourea (47).

3,3-Dimethyl-2,3-dihydrobenzofuran-5-amine (**39**, 0.086 g, 0.525 mmol) was dissolved in THF (5 mL). The resultant solution was cooled to 0 °C in an ice bath while stirring under a N_2 atmosphere. 1-Isothiocyanato-4-(trifluoromethoxy)benzene (**25h**, 0.138 g, 0.631 mmol) dissolved in THF (5 mL) was added dropwise over a period of 15 minutes. Upon completion of the addition, the solution was allowed to warm to room temperature and was stirred at room temperature for 24 hours at which time TLC analysis (100% ether) indicated the complete consumption of the amine. The solvent was removed under vacuum, and the resultant solid was

loaded onto an eight inch silica column. Elution with ether-hexane (gradient increasing from 10% ether to 50% ether) yielded **47** (0.079 g, 37%) as a white solid, mp 148-150 °C. IR: 3307, 3195 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.69 (s, 1H), 9.68 (s, 1H), 7.56 (d, J = 9.0 Hz, 2H), 7.31 (d, J = 9.0 Hz, 2H), 7.20 (d, J = 2.3 Hz, 1H), 7.08 (dd, J = 8.5, 2.3 Hz, 1H), 6.73 (d, J = 8.5 Hz, 1H), 4.22 (s, 2H), 1.28 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 180.5, 156.7, 144.9, 139.3, 137.3, 132.4, 125.7, 125.4, 121.9, 121.5, 120.3, 109.3, 84.5, 42.0, 27.6.

1.7.3 Synthesis of OHet72 *via* a Reductive Heck Cyclization

Ethyl 3-bromo-4-hydroxybenzoate (49).

3-Bromo-4-hydroxybenzoic acid (**48**, 15.00 g, 69.1 mmol) was dissolved in ethanol (200 mL), and 1 mL of concentrated H_2SO_4 was added. The solution was heated at reflux for 3 days, and then the volume was reduced under vacuum. The residue was poured into water (200 mL), and the aqueous layer was extracted with ether (3 x 150 mL). The combined organic layers were washed with saturated aq. $NaHCO_3$ (50 mL) and brine (100 mL), and dried (Na_2SO_4). Removal of the solvent under vacuum gave **49** (14.61 g, 86%) as a white solid, mp 102-104 °C IR: 3244, 1677, 1289 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, J = 2.0 Hz, 1H), 7.93 (dd, J = 8.5, 2.0 Hz, 1H), 7.05 (d, J = 8.5 Hz, 1H), 5.92 (br s, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 156.0, 133.8, 131.0, 124.4, 115.7, 110.0, 61.1, 14.3.

Ethyl 3-bromo-4-((3-methylbut-3-en-1-yl)oxy)benzoate (50).

Ethyl 3-bromo-4-hydroxybenzoate (**49**, 14.5 g, 59.2 mmol) and 3-methylbut-3-en-1-yl 4-methylbenzenesulfonate (12.13 g, 59.2 mmol) were dissolved in dimethylformamide (DMF) (50 mL), and K_2CO_3 (32.72 g, 237.0 mmol) was added. The reaction mixture was stirred under N_2 at 80 °C for 18 hours, at which time TLC analysis indicated complete consumption of the starting phenol. The reaction mixture was cooled to room temperature and then poured into water (200 mL). The aqueous layer was extracted with ether (3 x 100 mL), and the combined organic layers

were washed with water (3 x 100 mL), saturated aq. $NaHCO_3$ (100 mL), brine (100 mL), and dried (Na_2SO_4). Removal of the solvent under vacuum gave the **50** (15.03 g, 81%) as a clear oil. IR: 1712, 1555 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J = 2.1 Hz, 1H), 7.96 (dd, J = 8.6, 2.1 Hz, 1H), 6.90 (d, J = 8.6 Hz, 1H), 4.88 (s, 1H), 4.82 (s, 1H), 4.35 (q, J = 7.1 Hz, 2H), 4.19 (t, J = 6.8 Hz, 2H), 2.59 (t, J = 7.1 Hz, 2H), 1.85 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 158.8, 141.7, 134.8, 130.5, 124.0, 112.6, 111.8, 111.7, 68.1, 61.0, 36.9, 23.0, 14.3.

Ethyl 4,4-dimethylchromane-6-carboxylate (51).

Ethyl 3-bromo-4-((3-methylbut-3-en-1-yl)oxy)benzoate (**50**, 14.75 g, 47.1 mmol) was dissolved in DMF (30 mL), and sodium acetate (9.60 g, 118 mmol), sodium formate (3.84 g, 56.5 g), and tetraethylammonium chloride (9.37 g, 56.5 mmol) were added to form a slurry. Water (2 mL), and $Pd(OAc)_2$ (1.06 g, 10 mol%) were added, and the reaction mixture was heated at 95 °C under N_2 for 18 hours. The mixture was cooled and filtered through a 1 cm Celite pad, and then partitioned between water (200 mL) and ether (100 mL). The aqueous layer was extracted with ether (2 x 100 mL) and the three combined organic layers were washed with water (3 x 100 mL), brine (100 mL), and dried (Na_2SO_4). Solvent was removed under vacuum to afford **51** (10.40 g, 94%). as a clear oil. IR: 1695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 2.1 Hz, 1H), 7.75 (dd, J = 8.6, 2.1 Hz, 1H), 6.79 (d, J = 8.6 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 4.24 (t, J = 5.3 Hz, 2H), 1.85 (t, J = 5.4 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H), 1.85 (t, J = 5.4 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H), 1.36 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 157.7, 131.4, 129.1, 128.8, 122.5, 116.9, 63.4, 60.6, 37.1, 30.8, 30.6, 14.4.

4,4-Dimethylchromane-6-carboxylic acid (52).

Ethyl 4,4-dimethylchromane-6-carboxylate (**51**, 10.00 g, 42.7 mmol) was placed in an ethanol-water mixture (2:1, 150 mL), and KOH (4.80 g, 85.5 mmol) was added. The reaction was stirred

at 80° C for 3 hours, at which time TLC analysis indicated the reaction was completed. The volume was reduced under vacuum, and the residue was acidified with 1 M HCl to pH 2, and then the aqueous layer was extracted with DCM (3 x 100 mL). The combined organic layers were washed with brine (100 mL) and dried (Na_2SO_4), and concentrated under vacuum to afford **52** (7.85 g, 89%) as a white solid, mp 223-225 °C. IR: 3602-2563, 1685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 2.1 Hz, 1H), 7.83 (dd, J = 8.6, 2.1 Hz, 1H), 6.83 (d, J = 8.6 Hz, 1H), 4.27 (t, J = 5.4 Hz, 2H), 1.86 (t, J = 5.4 Hz, 2H), 1.37 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 158.6, 131.6, 130.0, 129.6, 121.2, 117.1, 63.5, 37.0, 30.8, 30.6.

4-Formylphenyl 4,4-dimethylchromane-6-carboxylate (54).

4,4-Dimethylchromane-6-carboxylic acid (**52**, 7.54 g, 36.6 mmol) and 4-hydroxybenzaldehyde (**53**, 4.46 g, 36.6 mmol) were dissolved in DCM (20 mL). 4-Dimethylaminopyridine (DMAP) (11.16 g, 91.5 mmol) was added, followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (7.02 g, 36.6 mmol). The reaction mixture was stirred at room temperature for 24 hours, and then washed with 1 M HCl (2 x 100 mL), saturated aq. $NaHCO_3$ (100 mL) and brine (100 mL), and then dried (Na_2SO_4). Concentration under vacuum afforded a tan, oily solid. The material was recrystallized from ethanol (15 mL) to afford **54** (7.26 g, 64%) as a cream-colored solid, mp 127-128 °C. IR: 2832, 2726, 1731, 1695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.03 (s, 1H), 8.14 (d, J = 2.1 Hz, 1H), 7.97 (d, J = 8.6 Hz, 2H), 7.92 (dd, J = 8.6, 2.1 Hz, 1H), 7.40 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.6 Hz, 1H), 4.30 (t, J = 5.5 Hz, 2H), 1.89 (t, J = 5.5 Hz, 2H), 1.40 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.0, 164.5, 158.8, 156.0, 133.9, 131.9, 131.2, 130.0, 129.6, 122.7, 120.7, 117.4, 63.6, 36.9, 30.8, 30.7.

4-Formylphenyl 4,4-dimethylchromane-6-carboxylate thiosemicarbazone (16).

4-Formylphenyl 4,4-dimethylchromane-6-carboxylate (**54**, 3.00 g, 9.7 mmol) was suspended in ethanol (20 mL), and the mixture was heated to 78 °C until a clear solution was formed. To the

hot solution was added thiosemicarbazide (0.970 g, 10.6 mmol) in water (81 mL) with three drops of glacial acetic acid. The solution was allowed to stir and slowly cool to room temperature overnight. At this time, white crystals were noted in the flask, so the mixture was further cooled to -20 °C for 24 hours. The mixture was allowed to warm to room temperature for 1 hour before collecting the crystals *via* vacuum filtration. The white crystals were dried under vacuum overnight to afford the final dried product **16** (2.80 g, 76%) mp 187-189 °C. IR: 3436, 3402, 3263, 3166, 1729, 1601 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.47 (s, 1H), 8.22 (br s, 1H), 8.07 (d, J = 1.8 Hz, 1H), 8.07 (br s, 1H), 7.91 (d, J = 8.6 Hz, 2H), 7.85 (dd, J = 8.6, 1.8 Hz, 1H), 7.31 (d, J = 0.6 Hz, 2H), 6.92 (d, J = 8.6 Hz, 1H), 4.28 (t, J = 5.4 Hz, 2H), 1.86 (t, J = 5.4 Hz, 2H), 1.35 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 178.5, 164.7, 158.7, 152.3, 141.8, 132.5, 132.4, 129.8, 129.7, 128.9, 122.8, 121.0, 117.7,63.7, 36.6, 30.8, 30.7.

1.7.4 Synthesis of Furan OHet72 Derivative via a Reductive Heck Cyclization

Ethyl 3-bromo-4-((2-methylallyl)oxy)benzoate (55).

Ethyl 3-bromo-4-hydroxybenzoate (**49**, 2.00 g, 8.16 mmol) was dissolved in DMF (10 mL), and 3-iodo-2-methylprop-1-ene (1.78 g, 9.80 mmol) and K_2CO_3 (4.50 g, 32.65 mmol) were added. The mixture was heated at 60 °C for 4 hours, at which time TLC analysis indicated complete consumption of the starting material. The reaction mixture was poured into water (100 mL), and the aqueous layer was extracted with ether (3 x 50mL). The combined organic layers were washed with water (3 x 75 mL) and brine (75 mL), and then dried (Na_2SO_4). The solvent was removed under vacuum to afford **55** (2.40 g, 98%) as a yellow oil. IR: 1716, 1595 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, J = 2.1 Hz, 1H), 7.95 (dd, J = 8.6, 2.1 Hz, 1H), 6.88 (d, J = 8.6 Hz, 1H), 5.17 (s, 1H), 4.56 (s, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.86 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 158.5, 139.6, 134.8, 130.4, 124.1, 113.3, 112.2, 111.9, 72.6, 61.0, 19.3, 14.4.

Ethyl 3,3-dimethyl-2,3-dihydrobenzofuran-5-carboxylate (56).

Ethyl 3-bromo-4-((2-methylallyl)oxy)benzoate (**55**, 2.00 g, 6.70 mmol) was dissolved in DMF (10 mL), and sodium acetate (1.37 g, 16.7 mmol), sodium formate (0.550 g, 8.00 mmol), $PhEt_3NCl$ (1.83 g, 8.00 mmol), and $Pd(OAc)_2$ (7.5 mg, 0.5 mol%) were added. The reaction was heated to 95 °C for 18 hours. The reaction mixture was cooled to room temperature over 2 hours and then diluted with ether (100 mL) and filtered through a 1 cm Celite pad. The organic layer was washed with water (3 x 100 mL) and brine (100 mL), and then dried (Na_2SO_4). The solvent was removed under vacuum to afford a yellow oil. Crude NMR analysis indicated the presence of both the cyclized product and the enol ether rearrangement by-product. The mixture was purified *via* column chromatography on silica, eluting with 10% ether in hexanes. The cyclized product **56** eluted first as a yellow oil (0.725 g, 50%). IR: 1698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.89 (dd, J = 8.4, 1.8 Hz, 1H), 7.80 (d, J = 1.8 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 4.31 (s, 2H), 1.38 (t, J = 7.1 Hz, 3H), 1.37 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 164.2, 137.1, 131.9, 125.1, 121.8, 109.5, 85.6, 60.6, 41.6, 27.6, 14.4.

3,3-Dimethyl-2,3-dihydrobenzofuran-5-carboxylic acid (57).

Ethyl 3,3-dimethyl-2,3-dihydrobenzofuran-5-carboxylate (**56**, 0.625 g, 2.84 mmol) was dissolved in ethanol (20 mL), and KOH (0.500 g, 8.92 mmol) was added. The reaction was stirred at room temperature for 3 hours, at which time TLC analysis indicated the reaction was completed. The volume was reduced under vacuum, and the residue was acidified with 1 M HCl to pH 2. The aqueous layer was extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), and concentrated under vacuum to afford **57** (0.525 g, 96%) as a white solid, mp 162-165 °C. IR: 3572-2525, 1668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (dd, J = 8.4, 1.8 Hz, 1H), 7.87 (d, J = 1.8 Hz 1H), 6.83 (d, J = 8.4 Hz, 1H), 4.34 (s, 2H), 1.38 (s,

6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 164.1, 137.2, 131.9, 125.0, 121.9, 109.6, 85.5, 41.5, 27.7.

4-Formylphenyl 3,3-dimethyl-2,3-dihydrobenzofuran-5-carboxylate (58).

3,3-Dimethyl-2,3-dihydrobenzofuran-5-carboxylic acid (**57**, 0.450 g, 2.34 mmol) and 4-hydroxybenzaldehyde (**53**, 0.286 g, 2.34 mmol) were dissolved in DCM (20 mL). 4-Dimethylaminopyridine (DMAP) (0.715 g, 5.86 mmol) was added, followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (0.450 g, 2.34 mmol). The reaction mixture was stirred at room temperature for 24 hours and was then washed with 1 M HCl (2 x 50 mL), saturated aq. $NaHCO_3$ (50 mL), and brine (50 mL), and then dried (Na_2SO_4) and concentrated under vacuum to afford **58** (0.650 g, 94%) as a cream-colored solid, mp 85-87 °C. IR: 2742, 1722, 1696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.03 (s, 1H), 8.06 (dd, J = 8.4, 1.9 Hz 1H), 7.97 (d, J = 8.5 Hz, 2H), 7.94 (d, J = 1.9 Hz, 1H), 7.40 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.4 Hz, 1H), 4.37 (s, 2H), 1.41 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.0, 164.3, 156.0, 137.5, 133.9, 132.0, 131.2, 125.1, 122.6, 121.4, 109.8, 85.6, 41.6, 27.7.

4-Formylphenyl 3,3-dimethyl-2,3-dihydrobenzofuran-5-carboxylate thiosemicarbazone (17).

4-Formylphenyl 3,3-dimethyl-2,3-dihydrobenzofuran-5-carboxylate (**58**, 0.500 g, 1.69 mmol) was suspended in ethanol (10 mL), and the mixture was heated to 78 °C until a clear solution was formed. To the hot solution was added thiosemicarbazide (0.184 g, 2.03 mmol) in water (21 mL) with one drop of glacial acetic acid. The solution was allowed to stir and slowly cool to room temperature overnight. At this time, white crystals were noted in the flask. The mixture was further cooled to -20 °C for 24 hours. The resulting mixture was allowed to warm to room temperature for 2 hours before collecting the crystals *via* vacuum filtration. The white crystals were dried under vacuum overnight to afford the final dried product (**17**, 0.467 g, 75%) mp 186-

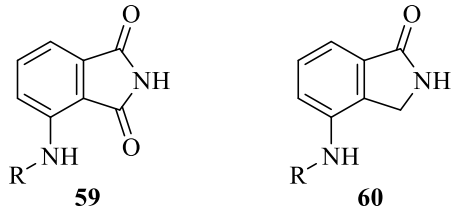
188 °C. IR: 3439, 3275, 3138, 2887, 1713, 1598 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.46 (s, 1H), 8.21 (br s, 1H), 8.08 (s, 1H), 8.06 (br s, 1H), 7.98 (d, J= 1.9 Hz, 1H), 7.96 (dd, J = 8.6 Hz, 1.9, 1H), 7.91 (d, J = 8.6 Hz, 2H), 7.31 (d, J = 8.6 Hz, 2H), 6.97 (d, J = 8.6 Hz, 2H), 4.38 (s, 2H), 1.36 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 178.5, 164.6, 164.1, 152.3, 141.8, 138.3, 132.4, 132.1, 129.0, 125.3, 122.8, 121.7, 110.2, 85.4, 41.6, 27.7.

CHAPTER II

SYNTHESIS OF A POTENTIAL ANTIBIOTIC

2.1 Introduction

Carbapenem-resistant bacterial infections is one of the most pressing health crises in the world today. According to the CDC's 2019 Antibiotic Resistance Threat Report, over 2.8 million antibiotic-resistant bacterial infections occur in the United States alone each year, resulting in over 35,000 deaths.[36] In order to counteract this rapidly developing issue, new bacterial cell membrane molecular targets need to be considered. Strategies to interrupt bacterial iron homeostasis have shown promise in this regard.[37]

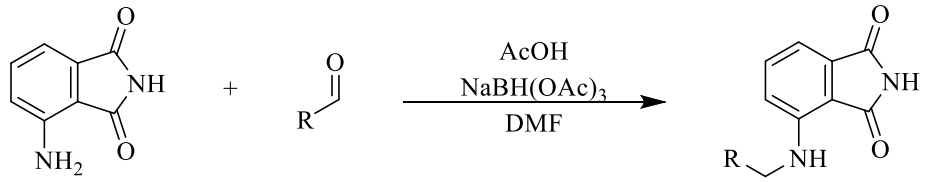


59 **60**

Figure 2.1: 4-Aminoisoindoline fragments.

The derivatives of 4-aminoisoindoline-1,3-dione (**59**) have been shown to interfere with the iron storage protein bacterioferritin (BfrB) in *P. aeruginosa* and therefore make promising synthetic targets.[38] This study will address the synthesis of a unique derivative of **59**.

The compound of interest in this study is a derivative of 4-aminoisoindolin-1-one **60**, and was designed to provide insight into problems observed in the synthesis of 4-aminoisoindoline-1,3-dione derivatives. It was suspected that during the reductive amination used to assemble 4-aminoisindoline-1,3-dione derivatives, unknown side reactions could occur making difficult separation of products and by-products (Scheme 2.1).



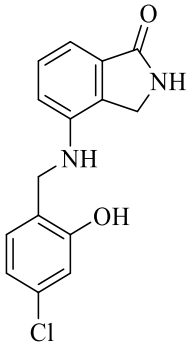
61 **62** **63**

Scheme 2.1: Synthesis of 4-aminoisoindoline derivatives *via* a reductive amination.

By synthesizing lactone derivative **60**, it can be determined if these side reactions are occurring. If by-products are not formed, and the derivative retains biological activity, 4-aminoisoindolin-1-one derivatives could be useful in future studies.

2.2 Synthesis of a 4-Aminoisoindolin-1-one Derivative

Interest in 4-aminoisoindolin-1-one functionalized antibiotic candidate **64** has developed because such a compound could provide information about the binding of the isoindoline unit to



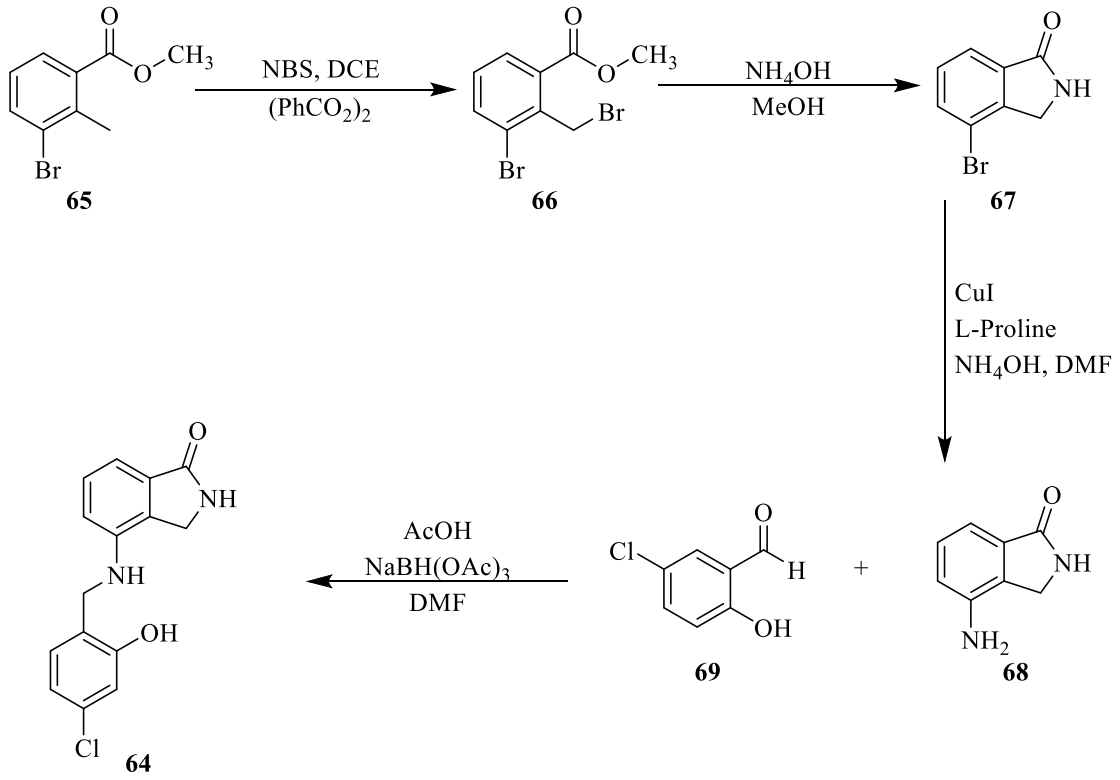
64

Figure 2.2: 4-Aminoisoindolin-1-one functionalized antibiotic candidate.

BfrB as well as information about side reactions occurring within the synthesis.[38]

2.2.1 Results and Discussion

4-((5-Chloro-2-hydroxybenzyl)amino)isoindolin-1-one (**64**) required 4 steps to prepare (Scheme 2.2). Important precursor 4-bromoisoindolin-1-one (**67**) was synthesized by following the literature procedure by Maugeri and coworkers.[39]



Scheme 2.2: The synthetic approach to 4-((5-Chloro-2-hydroxybenzyl)amino)isoindolin-1-one.

The toluoyl ester **65** was halogenated at a benzylic position *via* radical addition to afford the benzyl bromide ester **66** in quantitative yields. Next, **66** was exposed to ammonia inside a sealed tube and generated lactam **67** in 93% yield. Aniline derivative **56** was prepared *via* Ullmann coupling of **67** with ammonia to afford **68** in 65% yield. Finally, **64** was realized *via* reductive amination of aniline derivative **68** and aldehyde **69**.

2.3 Conclusion

In summary, an isoindolin-1-one antibiotic candidate was synthesized.

2.4 Chemistry

Methyl 3-bromo-2-(bromomethyl)benzoate (66).

Methyl 3-bromo-2-methylbenzoate (**65**, 5.00 g, 21.8 mmol) was dissolved in 1,2-dichloroethane (DCE) (100 mL). N-Bromosuccinimide (NBS) (4.27 g, 24 mmol) and benzoyl peroxide (20 mg) were added. The flask was partially wrapped in foil and placed under a heat lamp so that the mixture reached reflux. After 30 minutes, TLC analysis indicated complete consumption of the starting material. The volume was reduced under vacuum, and then the solution was diluted with dichloromethane (DCM) (200 mL). The organic layer was then washed with water (100 mL), $NaHCO_3$ solution (100 mL), brine (100 mL), and then dried (Na_2SO_4). Removal of the solvent under vacuum afforded **66** (6.70 g, >99%) as a clear oil in quantitative yield. IR: 1723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (dd, J = 7.8, 1.3 Hz, 1H), 7.75 (dd, J = 7.9, 1.3 Hz, 1H), 7.22 (t, J = 7.9 Hz, 1H), 5.12 (s, 2H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 142.5, 133.8, 137.3, 129.8, 129.2, 123.9, 51.5, 26.7.

4-Bromoisoindolin-1-one (67).

Methyl 3-bromo-2-(bromomethyl)benzoate (**66**, 6.70 g, 21.7 mmol) was dissolved in methanol (30 mL) in a large sealed tube. Aqueous ammonia (29%, 35 mL) was added, and the mixture was heated at 60 °C overnight. The tube was opened carefully after cooling, and the volume of solution was reduced under vacuum, and the residue was dissolved in ethyl acetate (150 mL). The organic layer was washed with water (2 x 100 mL), brine (100 mL), and dried (Na_2SO_4). The solvent was removed under vacuum to afford **67** (4.30 g, 93%) as a white solid, mp 207-209 °C. IR: 3328, 1639 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.81 (br s, 1H), 7.82 (dd, J = 7.7, 0.9 Hz,

1H), 7.70 (dd, J = 7.7, 0.9 Hz, 1H), 7.47 (t, J = 7.7 Hz, 1H), 4.31 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.9, 144.5, 135.9, 132.2, 127.8, 126.3, 122.0, 45.4.

4-Aminoisoindolin-1-one (68).

4-Bromoisoindolin-1-one (**67**, 1.50 g, 7.1 mmol) was dissolved in dimethylformamide (DMF) (4 mL) inside a sealed tube. Aqueous ammonia (29%, 20mL), CuI (0.675 g, 3.55 mmol), and L-proline (0.815 g, 7.1 mmol) were added, and the mixture was heated to 110 °C for 24 hours, at which time the solution turned from green to blue. The mixture was poured into $NaHCO_3$ solution (100 mL), and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were then washed with water (3 x 50 mL) and brine (50 mL), and dried (Na_2SO_4). The solvent was removed under vacuum to afford a brown solid. The product was purified *via* column chromatography using pyrone-treated silica gel, and eluting with 10% ethyl acetate in DCM. The product **68** (0.680 g, 65%) was recovered as a yellow solid, mp 174-176 °C. IR: 3451, 3358, 3325, 1621 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 (br s, 1H), 7.14 (t, J = 7.6 Hz, 1H), 6.85 (dd, J = 7.5, 0.9 Hz, 1H), 6.75 (dd, J = 7.7, 0.9 Hz, 1H), 5.37 (br s, 2H), 4.11 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.9, 144.4, 131.9, 130.8, 127.8, 119.5, 117.3, 44.1.

4-((5-Chloro-2-hydroxybenzyl)amino)isoindolin-1-one (64).

4-Aminoisoindolin-1-one (**68**, 0.200 g, 1.35 mmol), 5-chloro-2-hydroxybenzaldehyde (**69**, 0.423 g, 2.70 mmol), and acetic acid (0.190 mL) were placed in DMF (1.5 mL) under a N_2 atmosphere. Upon stirring, a slurry formed quickly, and the solution was heated to 90°C for 1 hour. During the hour, another 1.5 mL of DMF were added, and a clear solution resulted. The mixture was then cooled to 0 °C, and sodium triacetoxyborohydride [$NaBH(OAc)_3$] (0.860 g, 4.05 mmol) was added portion-wise over 15 minutes. The mixture was warmed to 90 °C for 3 hours, and then cooled to room temperature and stirred overnight, at which time TLC analysis indicated complete consumption of the starting amine. The mixture was carefully poured into water (50 mL), and the

aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with $NaHCO_3$ solution (2 x 50 mL), water (2 x 50 mL), and brine (50mL), and then dried (Na_2SO_4). The solvent was removed under vacuum to afford a yellow residue. The product was purified *via* column chromatography using pyrone-treated silica gel. Elution with 10% ethyl acetate in hexanes afforded the excess aldehyde **69**. Elution with 10% ethyl acetate in DCM, followed by increasing the gradient to 30% ethyl acetate, 5% methanol in DCM eluted the product **64** (0.281 g, 72%) as a yellow solid, mp 183-186 °C. IR: 3456, 3341, 3324, 1623 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.92 (s, 1H), 8.40 (br s, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.15 (d, J = 2.9 Hz, 1H), 7.08 (dd, J = 8.4, 2.8 Hz, 1H), 6.88 (d, J = 7.5 Hz, 1H), 6.84 (d, J = 8.6 Hz, 1H), 6.52 (d, J = 7.7 Hz, 1H), 6.19 (t, J = 6.1 Hz, 1H), 4.30 (d, J = 6.0 Hz, 2H), 4.23 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.2, 154.3, 143.9, 133.6, 129.4, 129.2 128.3, 127.6, 127.5, 123.0, 116.9, 111.9, 110.7, 44.0, 41.0.

CHAPTER III

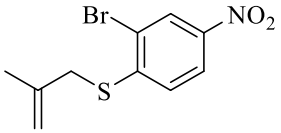
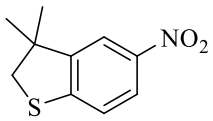
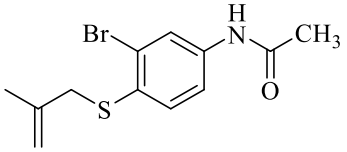
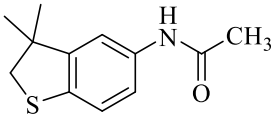
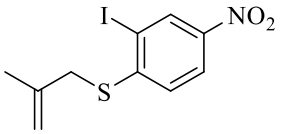
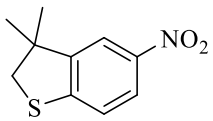
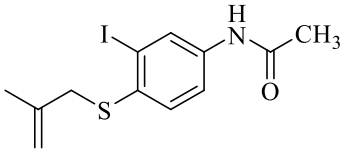
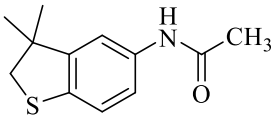
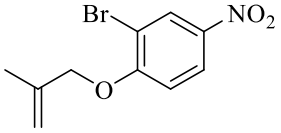
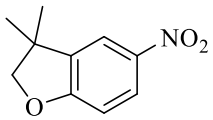
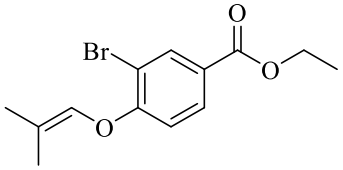
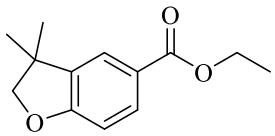
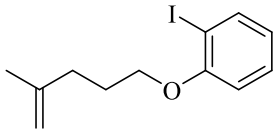
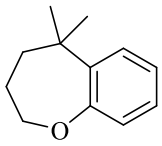
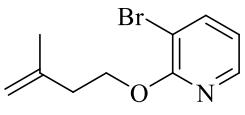
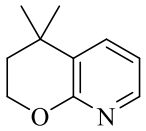
MISCELLANEOUS CYCLIZATION ATTEMPTS

3.1 Summary

Numerous attempts were made to cyclize Ring A systems that could be of interest as SHetA2 analogs. These attempts were made to better understand the scope of the reductive Heck reaction using the Jeffery conditions. If a sufficiently broad scope could be established, this reaction would prove to be an exceptionally powerful tool for the synthesis of SHetA2 analogs. The conditions established by Liu and co-workers[29] proved ineffective in initial attempts to form the heterocycles in Table 3.1, thus adjustments were made. The initial conditions incorporated 2.5 equivalents (relative to the alkene starting material) of NaOAc as a base, 1.2 equivalents of $NaHCO_2$ as a reductant, 1.2 equivalents of a tetraalkylammonium salt, and catalytic $Pd(OAc)_2$ in DMF at 85 °C to cyclize the material. These conditions have proven useful to synthesize **26**-**33** and **40**-**47**. Altering the conditions proved effective in the synthesis of **17.**

Attempts at altering the conditions to enable cyclization were numerous, and incorporated nearly all possible combinations of the adjusted conditions. The adjusted conditions initially involved using K_2CO_3 or Et_3N both in addition to, and in place of NaOAc, as the base. Secondly, high and low catalyst loadings were incorporated, including 10 mol% $Pd(OAc)_2$ and 0.5 mol% $Pd(OAc)_2$. Thirdly, the temperature of the reaction mixture was varied, including 65 °C, 75 °C, 85 °C, and 95 °C. Lastly, the reaction time was varied from 3 to 6 to 12 to 18 to 24 hours. The

aforementioned conditions were not exhausted for each example, but sufficient combinations were employed to determine the compatibility of the reaction with the substrate.

Substrate	Target Heterocycle	Typical Result
		Decomposition
		No Reaction
		Decomposition
		Mixture Obtained
		Decomposition
		No Reaction
		Mixture Obtained
		Mixture Obtained

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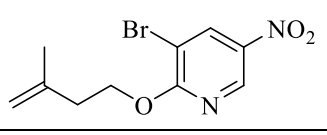
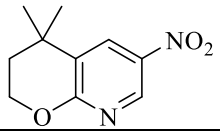
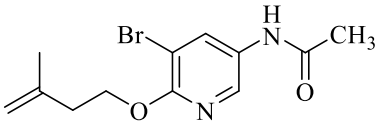
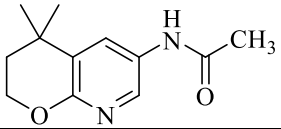
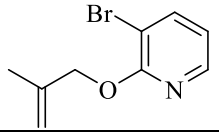
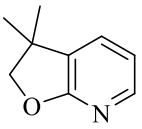
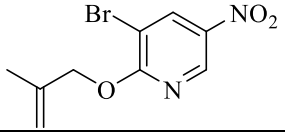
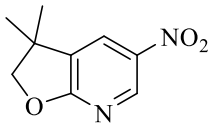
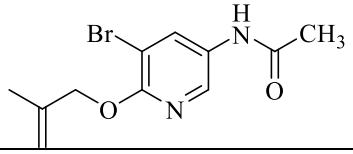
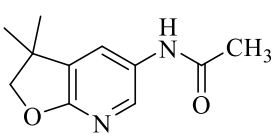
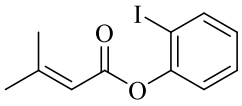
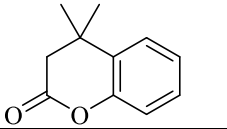
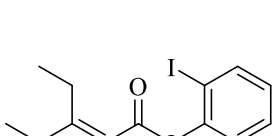
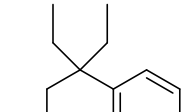
		Decomposition
		Decomposition
		Mixture Obtained
		Decomposition
		Decomposition
		Decomposition
		Decomposition

Table 3.1: Attempts made at expanding the scope of the reductive Heck cyclization.

Unfortunately, most substrates were prone to decompose, regardless of the reaction conditions. Several cases resulted in a mixture of cyclized material and starting material, but the crude yields were poor (<40%), and separation of the product proved exceptionally difficult. Each example in Table 3.1 features some characteristic that could prevent the desired cyclization from occurring, including functional groups thought to poison palladium catalysts,[40] electron deficient aromatic rings, sterically hindered alkenes, and thermodynamically unfavorable ring sizes. While the reductive Heck reaction using the Jeffery conditions has proven to be a powerful tool to

synthesize N- and O-containing heterocycles relevant as SHetA2 analogs, several limitations exist, and were discovered in this study.

CHAPTER IV

CONCLUSIONS

4.1 Summary

This study used a potentially powerful, previously unused method to synthesize anti-cancer drug candidates: an intramolecular reductive Heck cyclization using the Jeffery conditions. The nature of this reaction presented an interesting opportunity to discover a versatile method to synthesize SHetA2 (**3**) analogs. The reaction is known to prepare N- and O-containing heterocycles, and is capable of installing benzylic, geminal dimethyl groups, both of which are important to this study. This study also attempted to explore the scope of the reaction by initiating cyclizations of other substrates, many of which are not well understood.

Upon investigation, a method was established that proved capable of synthesizing N- and O-containing Ring A systems for SHetA2 analogs. The method proved to be effective for the preparation of 5- and 6-membered heterocycles with good functional group tolerance and good yields. This discovery lead us to conclude that this versatile method can be used to synthesize many future analogs of interest. Unfortunately, some apparent limitations of the reaction could not be overcome, as numerous cyclization attempts of S-containing heterocycles, pyridine substrates, and lactones proved incompatible.

Finally, this study produced a method to synthesize a potential antibiotic that could retain activity and minimizes likely side reactions in the synthesis. Testing of the compound will ultimately determine its usefulness.

REFERENCES

1. Berek, J. S., Ovarian Cancer. In *Practical Gynecologic Oncology*, Berek, J. S., Hacker N. F., Ed. Lippincott Williams and Wilkins: Philadelphia, PA, USA, 2005; pp 443-511
2. https://www.cancer.org/content/dam/CRC/PDF/Public/8773.00.pdf. Key Statistics for Ovarian Cancer. Source: American Cancer Society.
3. Alvarez, R.; Vaz, B.; Gronemeyer, H.; de Lera A. R. Functions, therapeutic applications, and synthesis of retinoids and carotenoids. *Chem. Rev.* **2014,** *114*, 1-125.
4. Brown, C. W.; Liu, S.; Klucik, J.; Berlin, K. D.; Brennan, P. J.; Kaur, D.; Benbrook, D. M. Novel heteroarotinoids as potential antagonists of *Mycobacterium bovis* BCG. *J. Med. Chem.* **2004,** *47*, 1008-1017.
5. Le, T. C.; Berlin, K. D.; Benson, S. D.; Eastman, M. A.; Bell-Eunice, G.; Nelson, A. C.; Benbrook D. M. Heteroarotinoids with anti-cancer activity against ovarian cancer cells. *Open. Med. Chem. J.* **2007,** *1*, 11-23.
6. Nammalwar, B.; Berlin, K. D.; Bunce R. A. SHetA2 - a mini review of a promising anticancer drug. *JSM Chem.* **2013,** *1*, 1005.
7. Waugh, K. M.; Berlin, K. D.; Ford, W. T.; Holt, E. M.; Carroll, J. P.; Schomber, P. R.; Schiff, L. J. Synthesis and characterization of selected heteroarotinoids. pharmacological activity as assessed in vitamin a deficient hamster tracheal organ cultures. Single crystal X-ray diffraction analysis of 1-(1-1-dioxa-3,4-dihydro-4,4-dimethyl-2*H*-1-benzothiopyran-6-yl)ethanone and ethyl (E)-4-[2-(3,4-dihydro-4,4-dimethyl-2*H*-1-benzothiopyran-6-yl)-1-propenyl]benzoate. *J. Med. Chem* **1985,** *27*, 116-124.

8. Benbrook, D. M. Refining retinoids with heteroatoms. *Mini Rev. Med. Chem* **2002,** *3*, 277-283.

9. Shengquan, L.; Zhou, G.; Lo, S. N. H.; Louie, M.; Rajagopalan, V. SHetA2, a new cancer-preventive drug candidate. IN TECH , 2016, Chapter 2 in ANTI-CANCER DRUGS-NATURE. Janeza Trdine 9, 51000 Rijeka, CROATIA [DOI-10.5772/65365] ISBN: 978-953-51-2813-7.

10. Benbrook, D. M.; Madler, M. M.; Spruce, L. W.; Birckbichler, P. J.; Nelson, E, C.; Subramanian, S.; Weerasekare, G. M.; Gale, J. B.; Patterson, Jr., M. K.; Wang, B.; Wang, W.; Lu, S.; Rowland, T. C.; DiSivestro, P.; Lindamood, C.; Hill, D. L.; and Berlin, K. D. Biologically active heteroarotinoids exhibit anticancer activity and decreased toxicity. *J. Med. Chem* **1997,** *40*, 3567-3583.

11. Orfanes, C. E.; Brown-Falcoz, O.; Farber, E. M.; Grupper, D.; Polano, M.; Schuppli, R. "Retinoids: Advances in Basic Research and Therapy". Springer-Verlag: New York, 1981.

12. Detrisac, C.; Pereira, M.; Martin-Jimenez, T.; Onua, E.; Banerjee, A.; van Breemen, R. B.; Nikolic, D.; Chen, L.; Lyubimov, A. V. Oral toxicity and pharmacokinetic studies of SHeA2, a new preventive agent, in rats and dogs. *Drug Chem. Toxicol.* **2013,** *36*, 284-295.

13. Sharma, A.; Benbrook, D. M.; Woo, S. Pharmacokinetics and interspecies scaling of a novel, orally-bioavailable anti-cancer drug, SHetA2. PLOS One, **2018**. 13, e0194046/1-e0194046/17.

14. Liu, Z.; Zhang, Y.; Hua, Y. F.; Covey, J. M.; Benbrook, D. M.; Chan, K. K. Metabolism of a sulfur-containing heteroarotinoid antitumor agent, SHetA2, using liquid chromatography/tandem mass spectrometry. *Rapid Comm. Mass Spectrom.* **2008,** *22,* 3371-3381.

15. Gnanasekaran, K. K.; Pouland, T.; Bunce, R. A.; Berlin, K. D.; Absukhuna, S.; Bhandan, D.; Mashayekhi, M.; Zhou, Z.; Benbrook, D. M. Flexhets: Tetrahydroquinoline units in heteroarotinoids convey anti-cancer properties. *Bioorg. & Med. Chem.* **2020,** *28*, In Press. doi: https://10.1016/j.bmc.2019.115244

16. Benbrook, D. M.; Nammalwar, B.; Long, A.; Matsumoto, H.; Singh, A.; Bunce, R. A.; Berlin, K. D. SHetA2 interference with mortalin binding to p66she and p53 identified using drug-conjugate magnetic microspheres. *Invest. New Drugs* **2014,** *32*, 412-423.

17. Nammalwar, B.; Bunce, R. A.; Benbrook, D. M.; Lu, T.; Li, Hui-Fang; Ya-Dong, C.; Berlin, K. D. Synthesis of *N*-[3,4-dihydro-4-(acetoxymethyl)-2,2,4-trimethyl-2*H*-1-benzothiopyran-6-yl]-*N*'-(4-nitrophenyl)thiourea and *N*-[3,4-(dihydromethyl)-2,2,4-trimethyl-2H-1benzothiopyran-6-ly]-*N*'(4-nitrophenyl)thiourea, a major metabolite of *N*-{3,4-dihydro-2,2,4,4-tetramethyl-2*H*-1-enzothiopyran-6-yl)-*N*'-(4-nitrophenyl) thiourea. *Phosphorus Sulfur Silicon Relat. Elem.* **2011,** *186,* 189-204.

18. Private communication from the National Cancer Institute of the National Institutes of Health.

19. Watts Jr., F. M.; Pouland, , T.; Bunce,, R. A.; Berlin, K. D.; Benbrook, D. M.; Mashayekhi, M.; Bhandari, D.; Zhou, D. Activity of oxygen-versus sulfur-containing analogs of the Flex-Het anticancer agent SHetA2. *Eur. J. Med. Chem.* **2018,** *158*, 720-732.

20. Spruce, L. W.; Rajadhyaksha, S. N.; Berlin, K. D.; Gale, J. B.; Miranda, E. T.; Ford, W. T.; Blossey, E. C.; Verma, A. K.; Hossain, M. B. van der Helm, D.; Breitman, T. R. Heteroarotinoids. Synthesis, characterization and biological activity in terms of an assessment of these systems to inhibit induction of ornithine decarboxylase activity and to induce terminal differentiation of HL-60 cells. *J. Med. Chem* **1987,** *30,* 1474-1482.

21. Gale, J. B.; Klucik, J.; Subramanian, S.; Berlin, K. D. Synthesis of methyl (*E*)-4-[2,3-dihydro-3-methyl-3-hydroxymethylbenzo[b]thien-5-yl)-1-propenyl]benzoate [(*E*-**3**], methyl (*E*)-4-[2-(2,3-dihydro-3-methyl-3-hydroxymethyl-5-benzofuranl)-1-propenyl]-benzoate [(*E*)-**4**], and methyl (*E*)-4-[2-(2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-3-hydroxy-1-propenyl]benzoate [(*E*)-**7**] as potential metabolites of selected hetero-arotinoids with fused, fived-membered rings. *Org. Prep. & Proc. Intern.* **2001,** *33*, 487-499.

22. Ginn, E.; Baek, J.; Zou, H.; Fallatach, M. M. J.; Liu, S.; Sevigny, M. B.; Louis, M. Enantiomer of the novel flexible heteroarotinoid, SL-1-09, blocks cell cycle progression in breast cancer cells. *Eur. J. Pharmacol.* **2019,** *862*, 172634.

23. Benbrook, D. M.; Kamelle, S. A.; Guruswamy, S. B.; Lightfoot, S. A.; Rutledge, T. L.; Gould, N. S.; Hannafon, B. N.; Dunn, S. T.; Berlin, K. D. Flexible heteroarotinoids (Flex-Hets) exhibit improved therapeutic ratios as anti-cancer agents over retinoic acid receptor agonists. *Invest. New Drugs* **2005,** *23*, 417-428.

24. Mizoroki, T.; Mori, K.; Atsumu, O. Arylation of olefins with aryl iodide catalyzed by palladium. *Bull. Chem. Soc. Jpn* **1971,** *44*, 581.

25. Heck, R. F.; Nolley Jr., J. P. Palladium-catalyzed vinylic hydrogen substitution reactions with aryl, benzyl, and styryl halides. *J. Org. Chem.* **1972,** *37*, 2320-2322.

26. Catellani, M.; Chiusoli, G. P.; Giroldini, W.; Giuseppe, S. New transition metal-catalyzed C-C coupling reactions initiated by C-X bond cleavage and terminated by H-transfer. *J. Organomet. Chem.* **1980,** *199*, C21-C23.

27. Jeffery, T. Palladium-catalyzed vinylation of organic halides under solid-liquid phase transfer conditions. *J. Chem. Soc., Chem. Commun.* **1984**, 1287-1289.

28. Larock, R. C.; Srinivasan, B. Synthesis of nitrogen heterocycles *via* palladium-catalyzed intramolecular cyclization. *Tet. Lett.* **1987,** *28*, 5291-5294.

29. Liu, P.; Huang, L.; Lu, Y.; Dilmeghani, M.; Baum, J.; Xiang, T.; Adams, J.; Tasker, A.; Larsen, R.; Faul M. M. Synthesis of heterocycles via ligand-free palladium catalyzed reductive heck cyclization. *Tet. Lett.* **2007,** *48*, 2307-2310.

30. Heck, R. F. *Palladium Reagents in Organic Synthesis*. Academic Press Inc.: New York, NY, USA, 1985.

31. Cacchi, S. The palladium-catalyzed hydroarylation and hydrovinylation of carbon-carbon multiple bonds: new perspectives in organic synthesis. *Pure Appl. Chem.* **1990,** *62*, 713-722.

32. Arcadi, A.; Marinelli, F.; Bernocchi, E.; Cacchi, S.; Ortar, G. Palladium-catalyzed preparation of exo-aryl derivatives of the norbornane skeleton. *J. Organomet. Chem.* **1989,** *368* (2), 249-256.

33. Larock, R. C.; Johnson, P. L. Palladium-catalysed intermolecular arylation and alkenylation of bicyclic alkenes. *J. Chem. Soc., Chem. Commun.* **1989**, 1368-1370.

34. Reetz, M. T.; Helbig, W.; Quaiser, S. A.; Stimming, U.; Breurer, N.; Vogel, R. Visualization of surfactants on nanostructured palladium clusters by a combination of STM and high-resolution TEM. *Science* **1995,** *267*, 367-369.

35. Bakthavatchalam, R.; Blum, C. A.; Chenard, B. L. Substituted bicyclic quinazolin-4-ylamine derivatives. WO 2005023807. Mar. 17, 2005.

36. https://www.cdc.gov/drugresistance/biggest-threats.html. Biggest Threats and Data, 2019 AR Threats Report. Source: Centers for Disease Control and Prevention.

37. Ballouche, M.; Cornelis, P.; Baysse, C. Iron metabolism: a promising target for antibacterial strategies. *Recent Pat. Anti-Infect. Drug Discovery* **2009,** *4*, 190-205.

38. Hewage, A. N. D. P.; Yao, H.; Nammalwar, B.; Gnanasekaran, K. K.; Lovell, S.; Bunce, R. A.; Eshelman, K.; Phaniraj, S. M.; Lee, M. M.; Peterson, B. R.; Battaile, K. P.; Reitz, A. B.; Rivera M. Small molecule inhibitors of the BfrB-Bfd interaction decrease *Pseudomonas aeroginosa* fitness and potentiate fluoroquinolone activity. *J. Am. Chem. Soc.* **2019,** *141*, 8171-8184.

39. Maugeri, C.; Alisi, M. A.; Apicella, C.; Cellai, L.; Dragone, P.; Fioravanzo, E.; Florio, S.; Fulotti, G.; Mangano, G.; Obrato, R.; Luisi, R.; Pompei, R.; Rincicotti, V.; Russo, V.; Vitiello, M.; Cazzolla N. New anti-viral drugs for the treatment of the common cold. *Bioorg. Med. Chem.* **2008,** *16*, 3091-3107.

40. Forzatti, P.; Lietti, L. Catalyst deactivation. *Catal. Today* **1999,** *52*, 165-181.

APPENDICES

APPENDIX A: Common Abbreviations

NOAEL – No observed adverse effect level

IC_{50} – Half maximal inhibitory concentration

DMF – dimethylformamide

DCM – dichloromethane, methylene chloride

DCE – 1,2-dichloroethane

DMAP – 4-dimethylaminopyridine

EDC – 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

TLC – thin layer chromatography

$CDCl_3$ – deuterated chloroform

DMSO-d_6 – deuterated dimethylsulfoxide

EtOH – ethanol

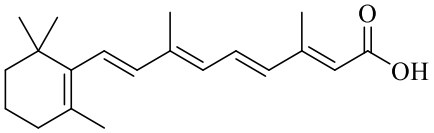
AcOH – acetic acid

NaOAc – sodium acetate

$Pd(OAc)_2$ – palladium (II) acetate

NBS – *N*-bromosuccinimide

APPENDIX B: Index of Molecules



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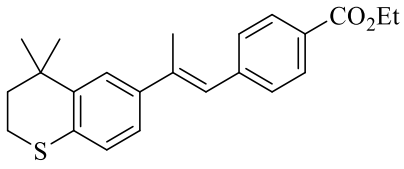

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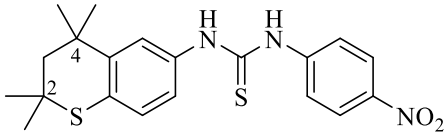

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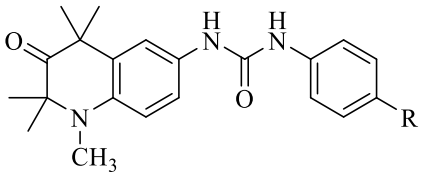

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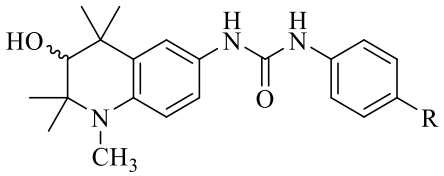

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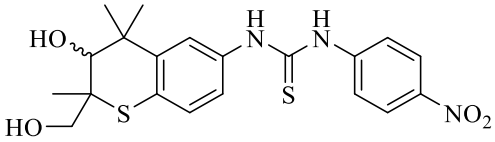

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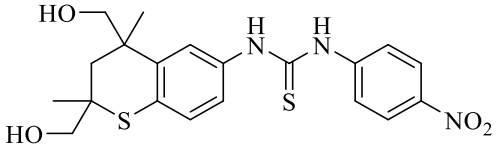

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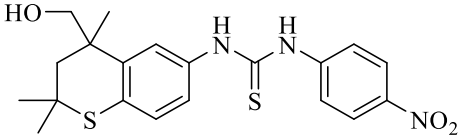

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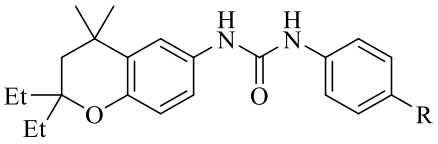

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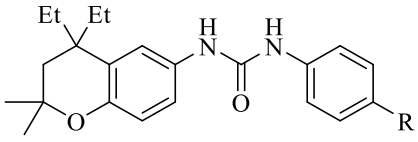

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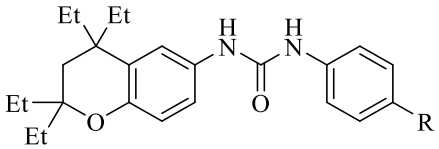
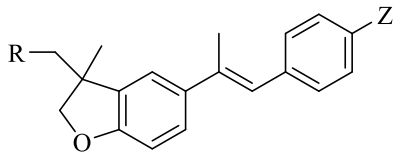


R = NO_2,CF_3

11



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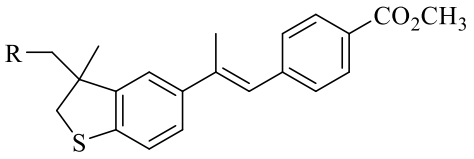


13

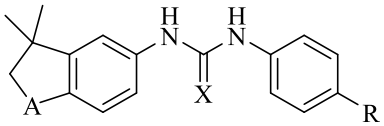
Z = CO_2H, CO_2CH_3

R = H, OH

A = O, S

X = O, S

R = NO_2, CF_3, OCF_3



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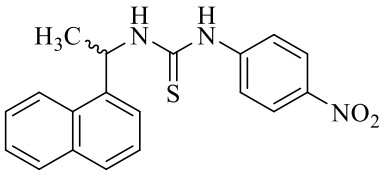

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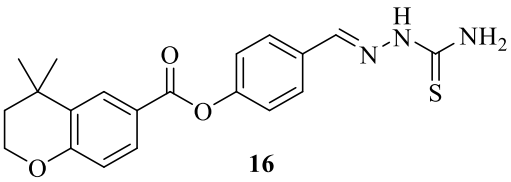

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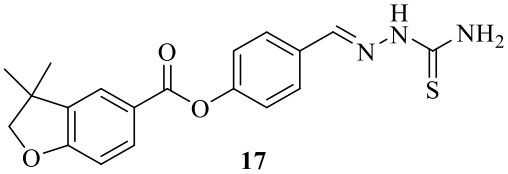

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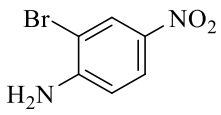

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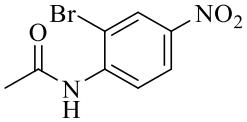

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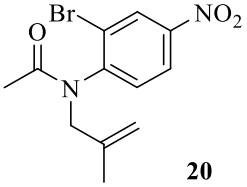

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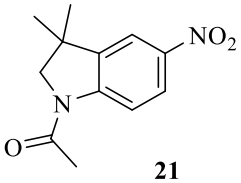

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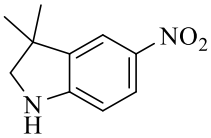

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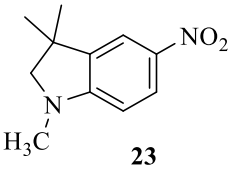

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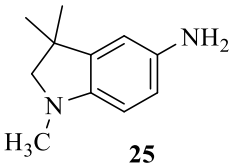

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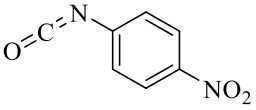

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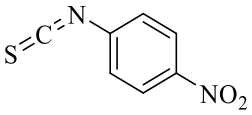

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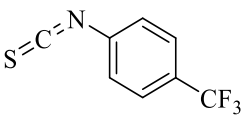

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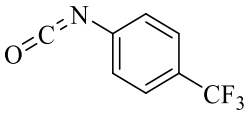

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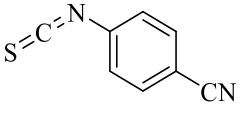

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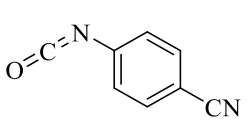

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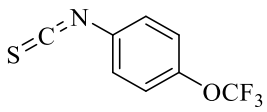

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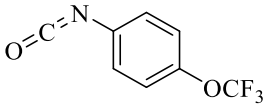

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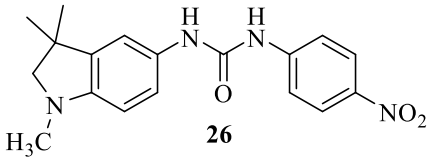

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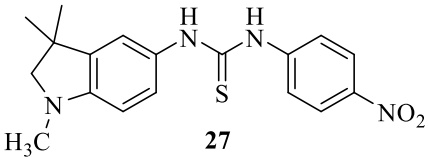

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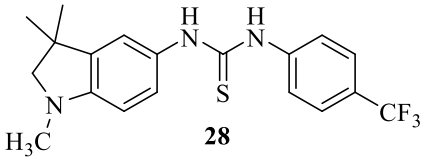

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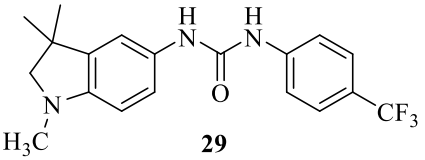

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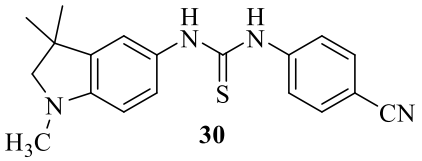

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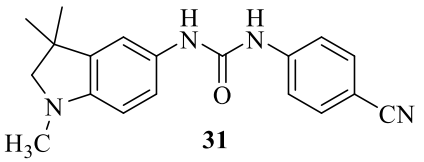

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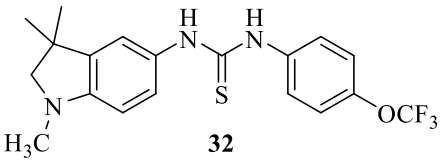

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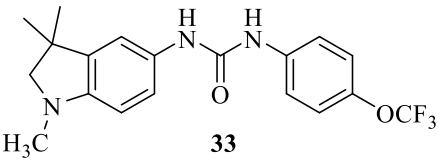

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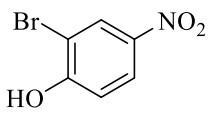

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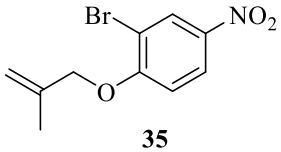

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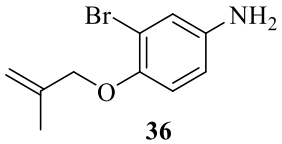

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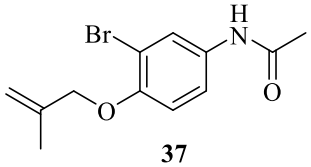

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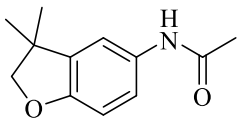

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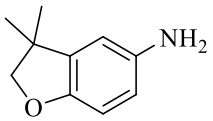

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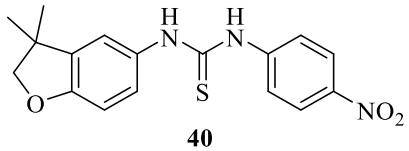

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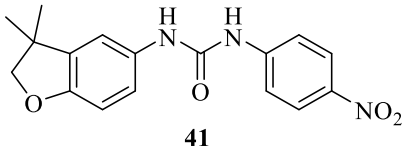

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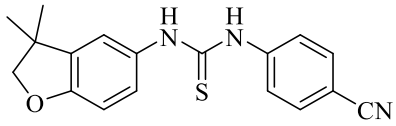

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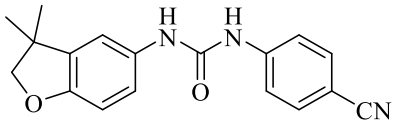

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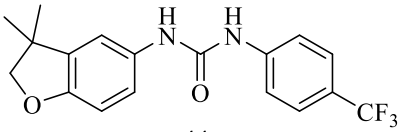

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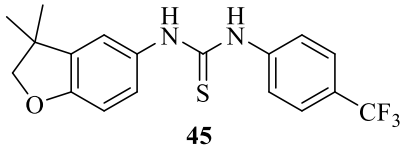

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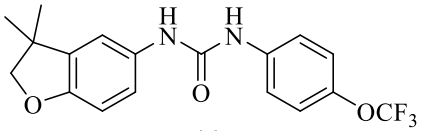

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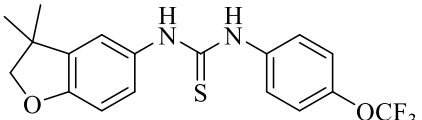

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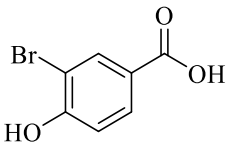

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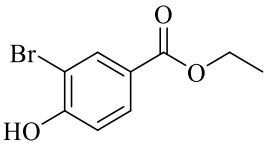

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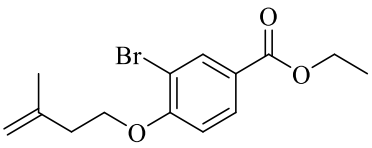

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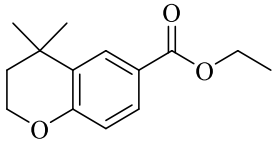

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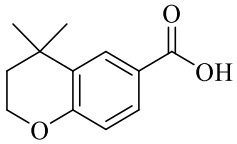

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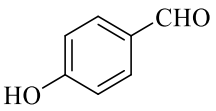

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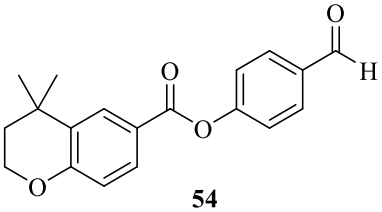

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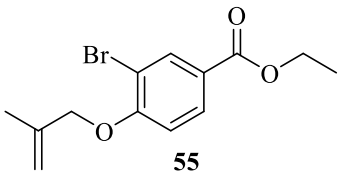

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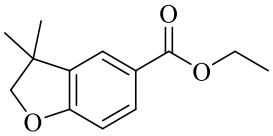

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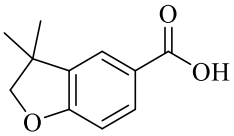

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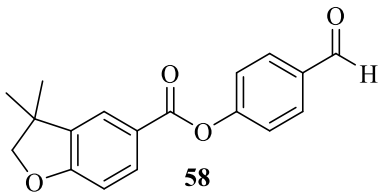

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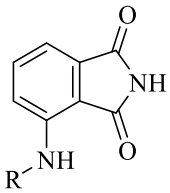
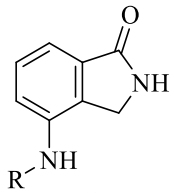


59



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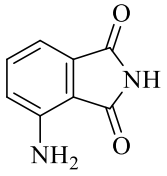
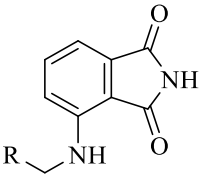
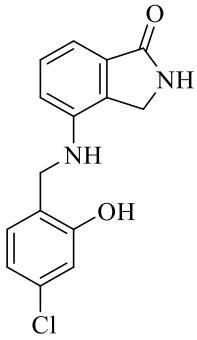


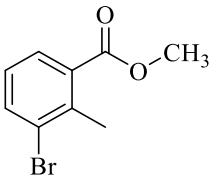
61



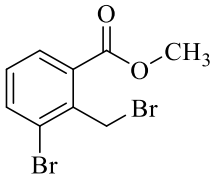
63



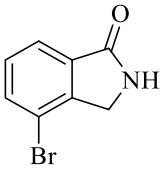
64



65



66



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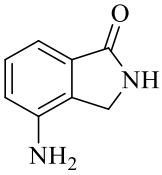
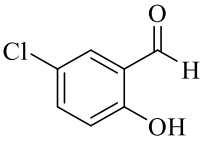


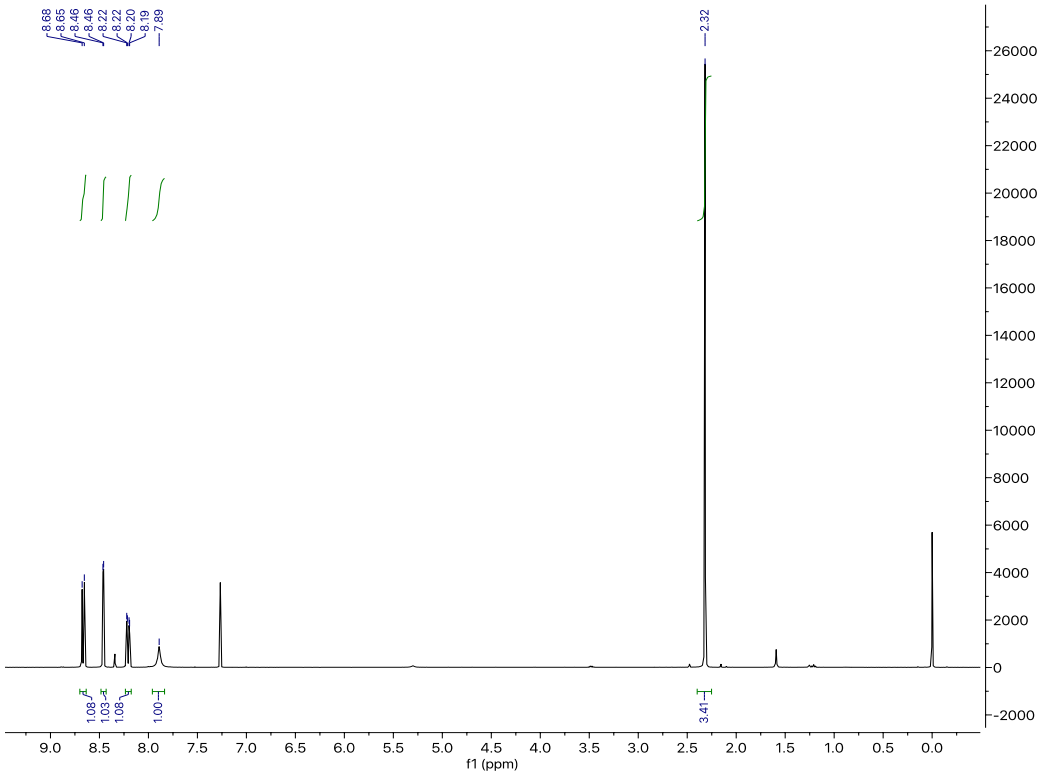
68

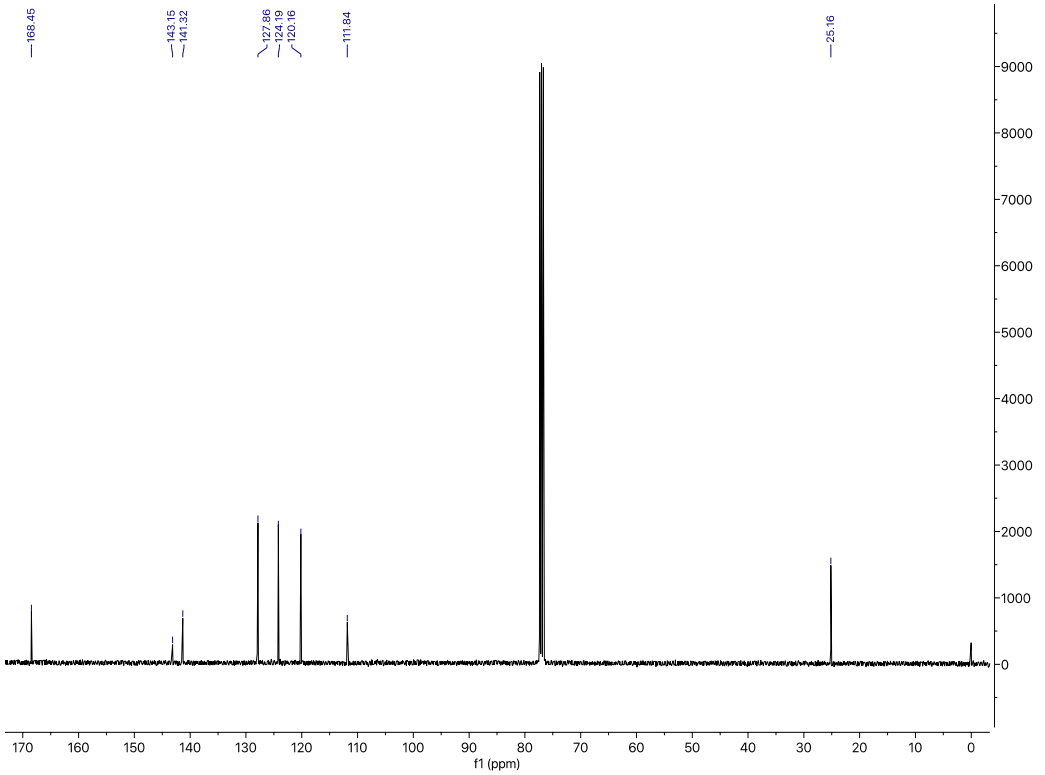


69

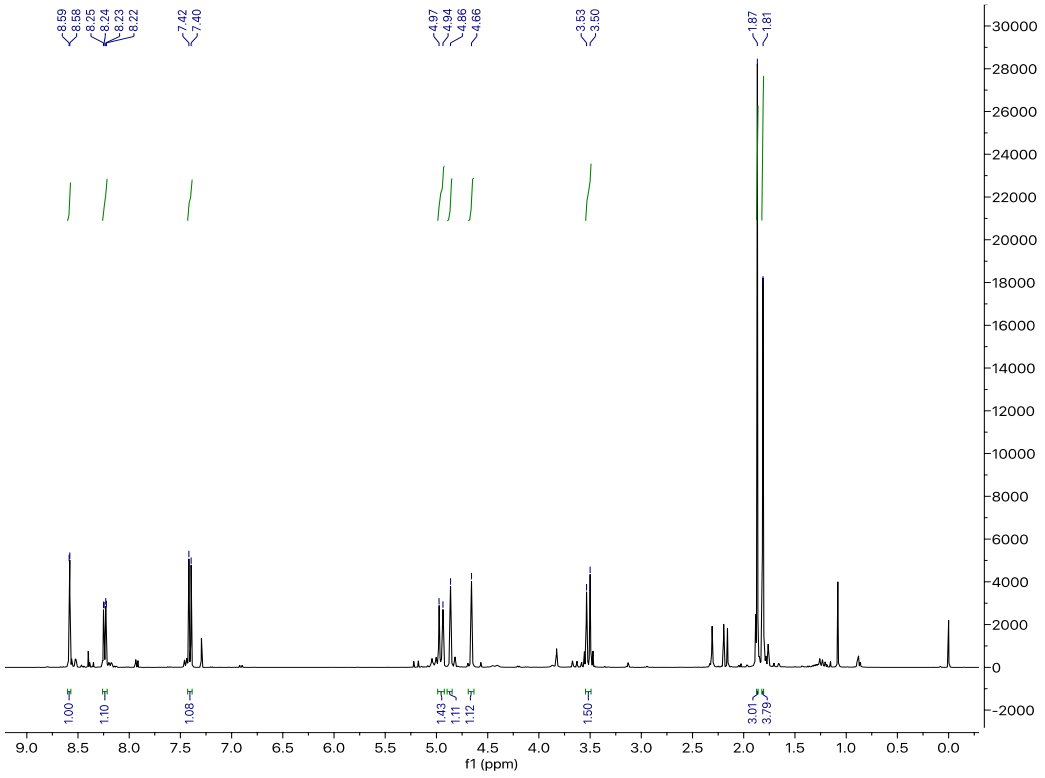
APPENDIX C: Spectral Data for Indoline SHetA2 Analogs

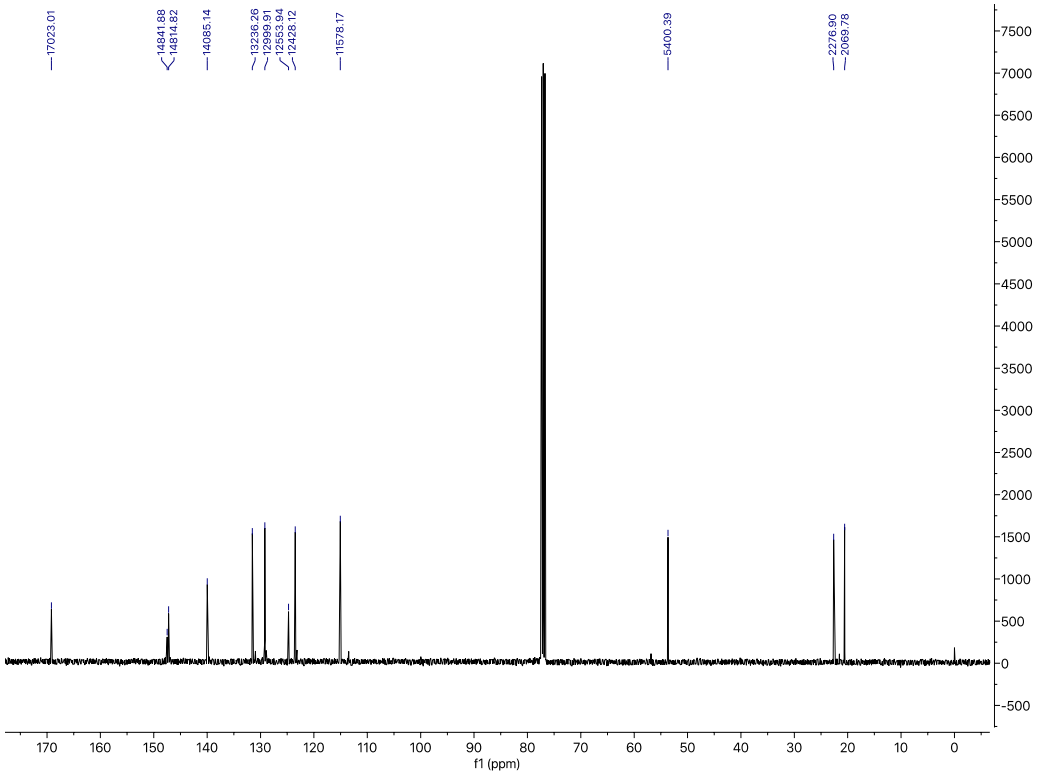
***N*-(2-Bromo-4-nitrophenyl)acetamide**



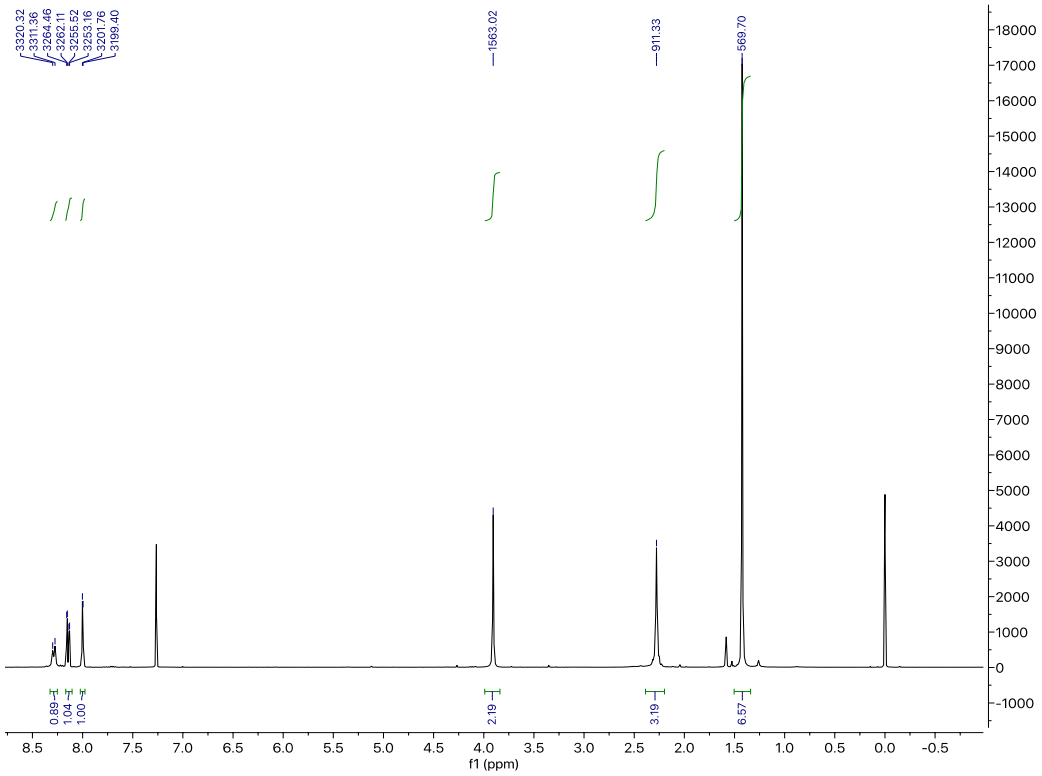


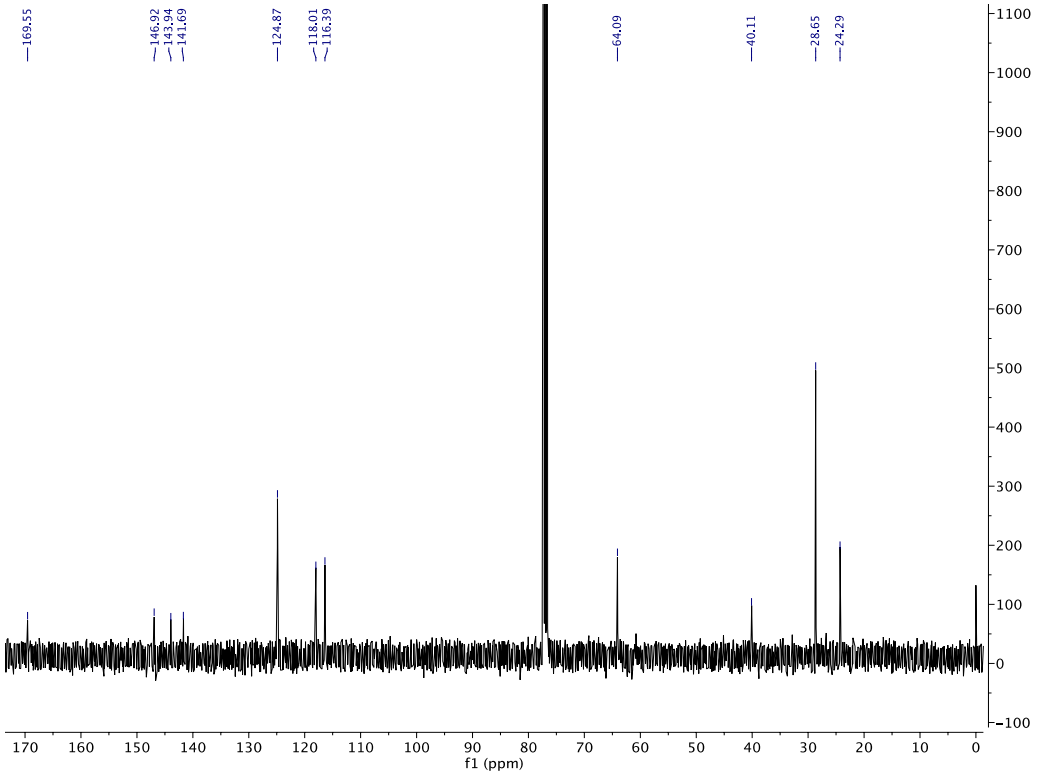
_N_-(2-Bromo-4-nitrophenyl)-N-(2-methylallyl)acetamide (20)



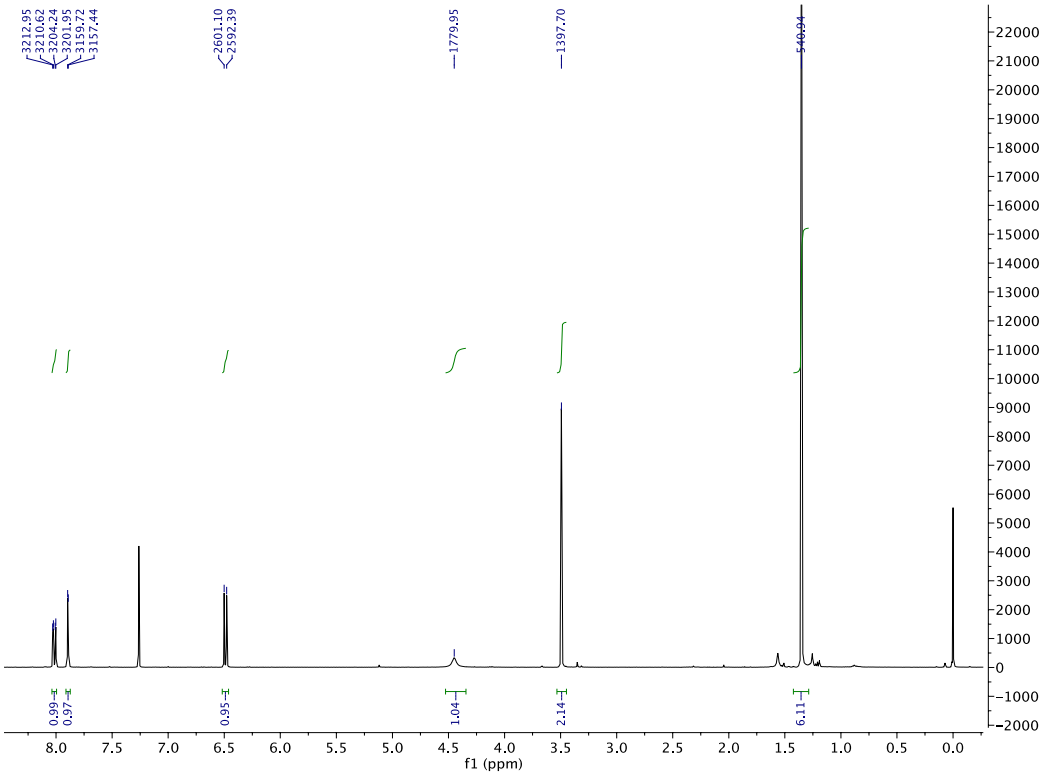


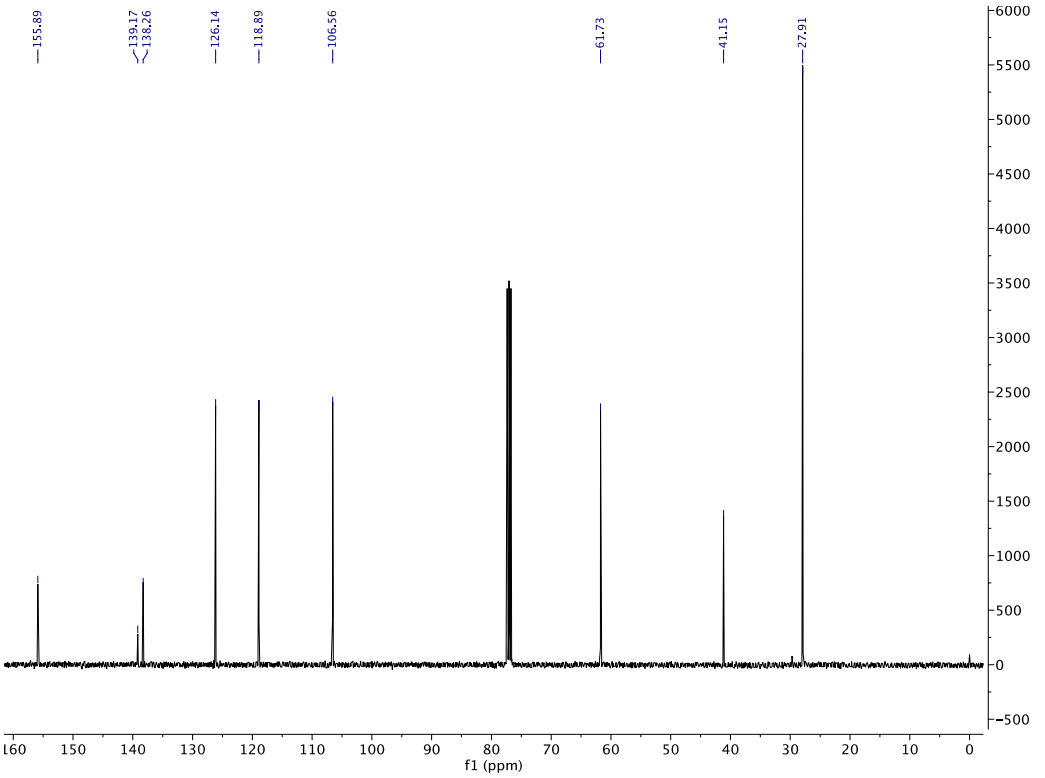
1-(3,3-Dimethyl-5-nitroindolin-1-yl)ethan-1-one (21)



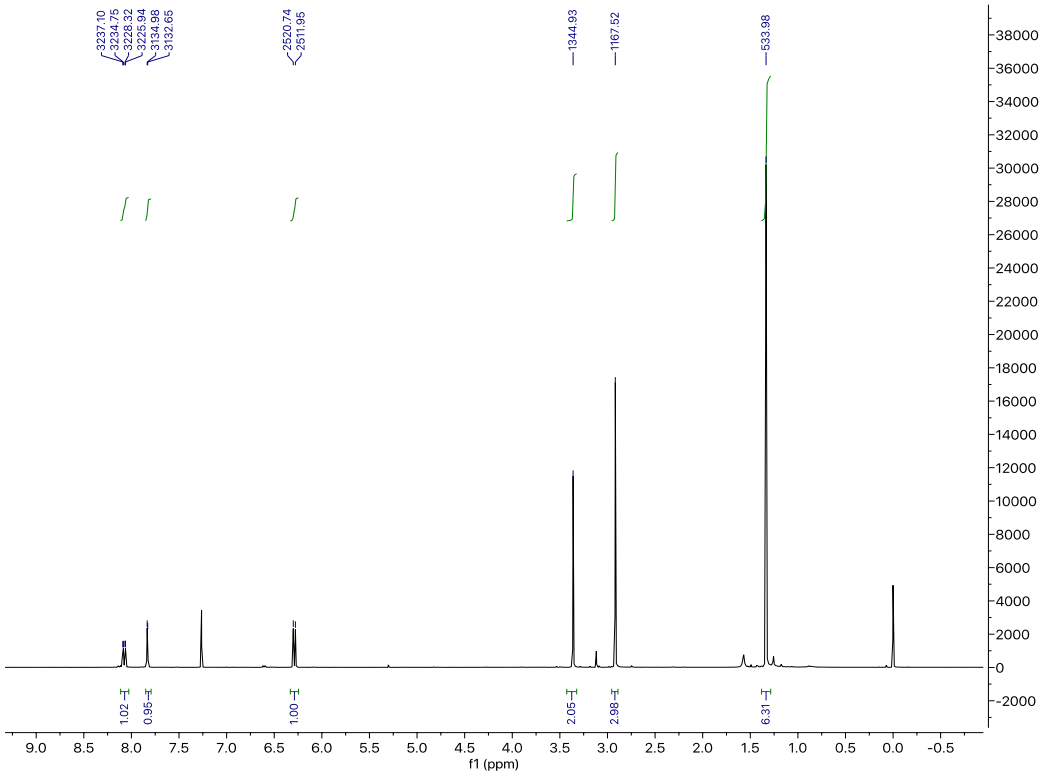


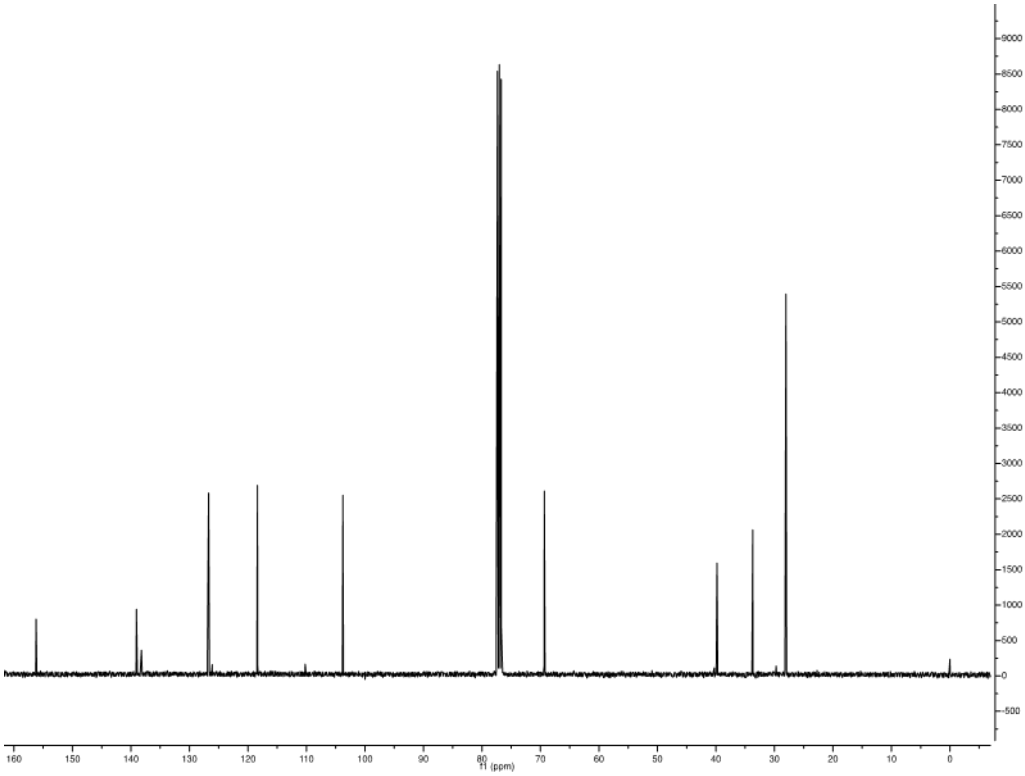
3,3-Dimethyl-5-nitroindoline (22)



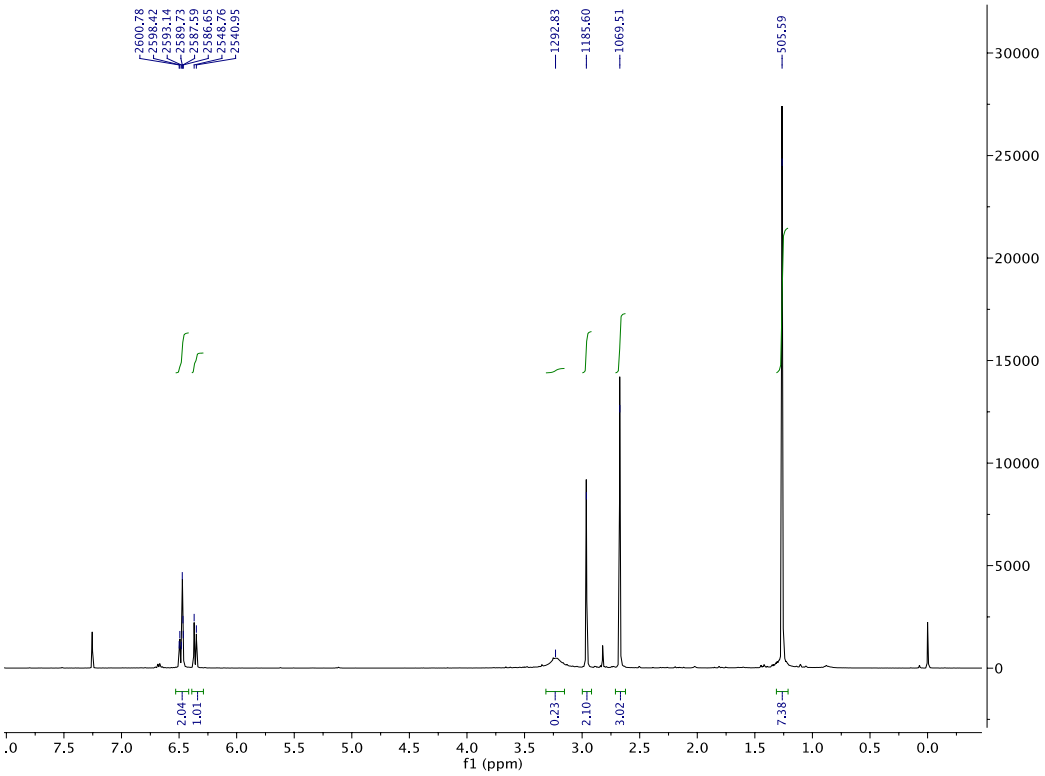


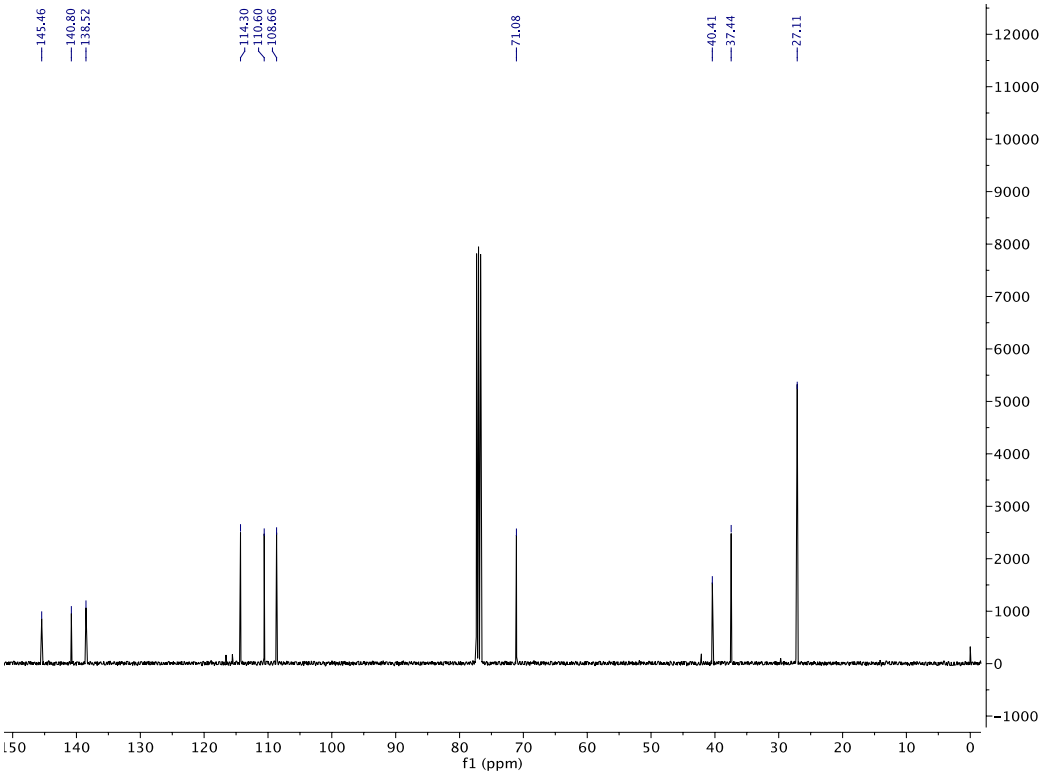
1,3,3-Dimethyl-5-nitroindoline (23)



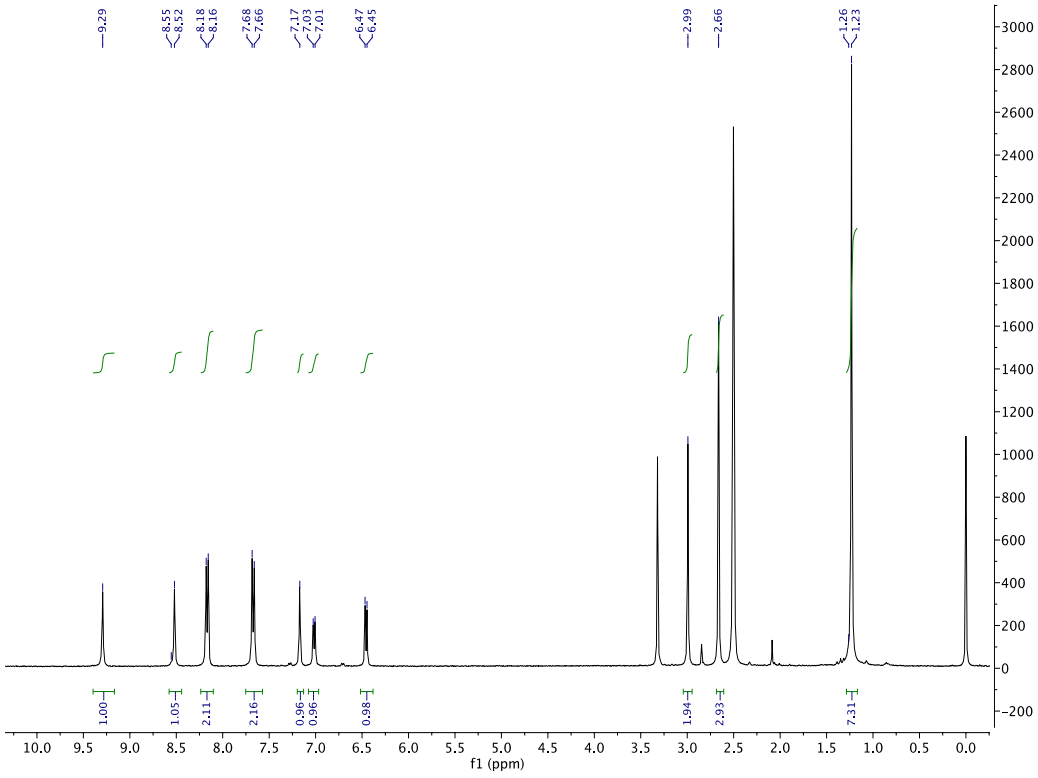


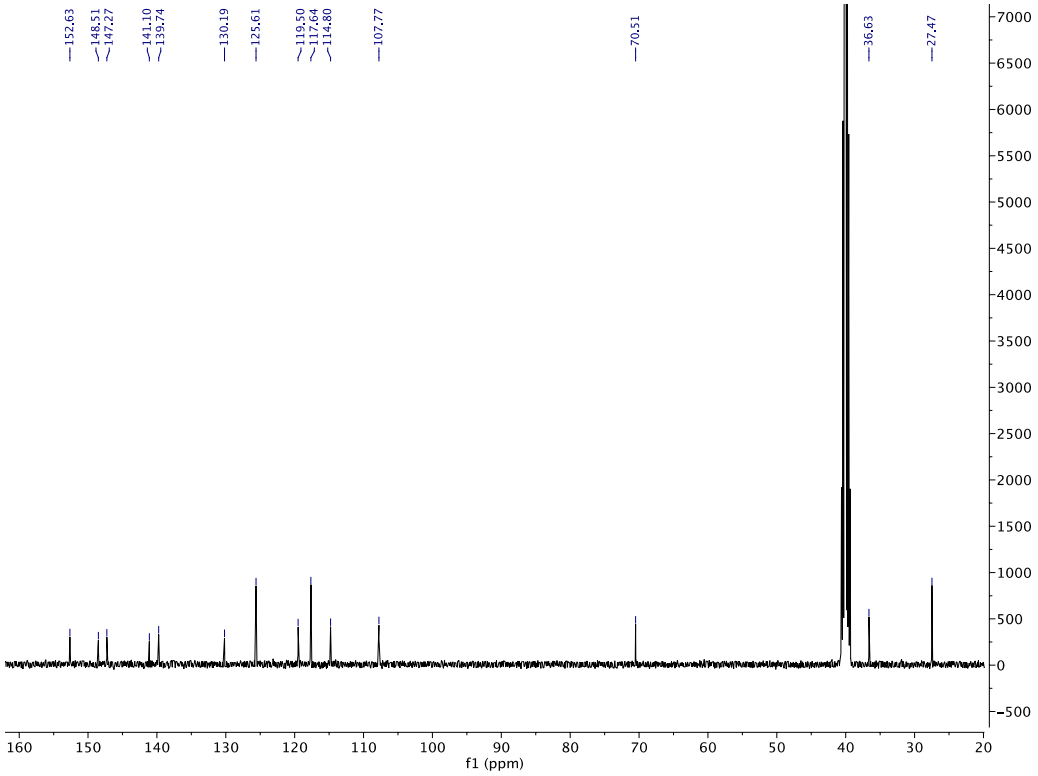
1,3,3-Trimethylindolin-5-amine (24)



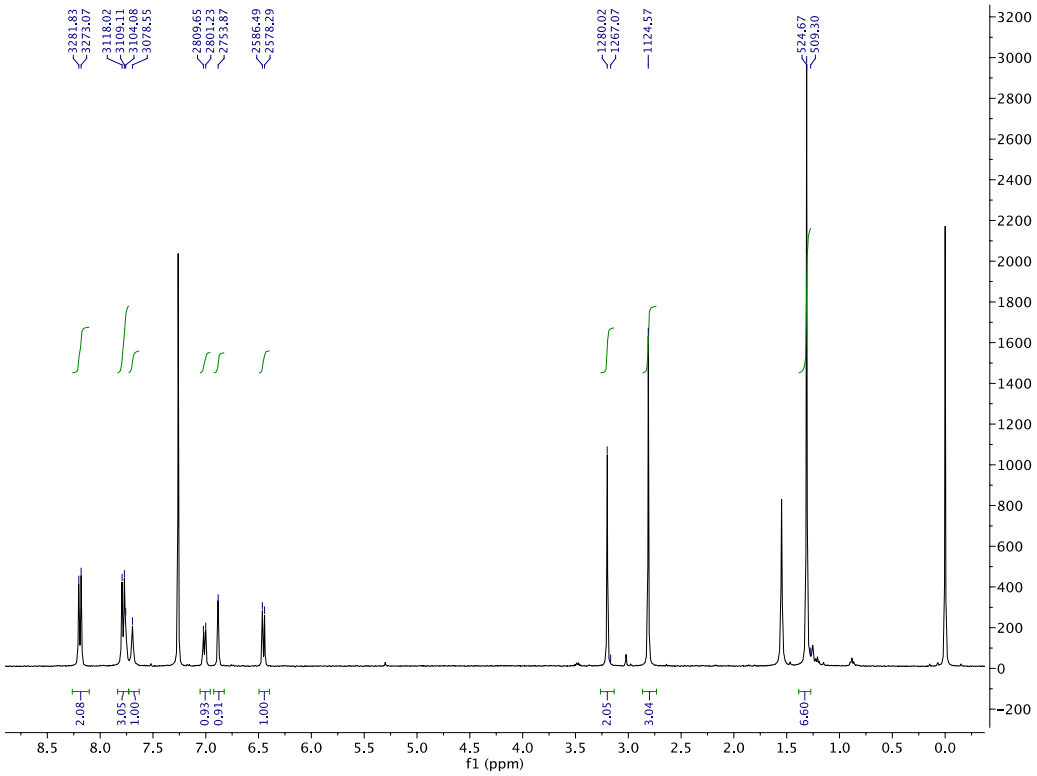


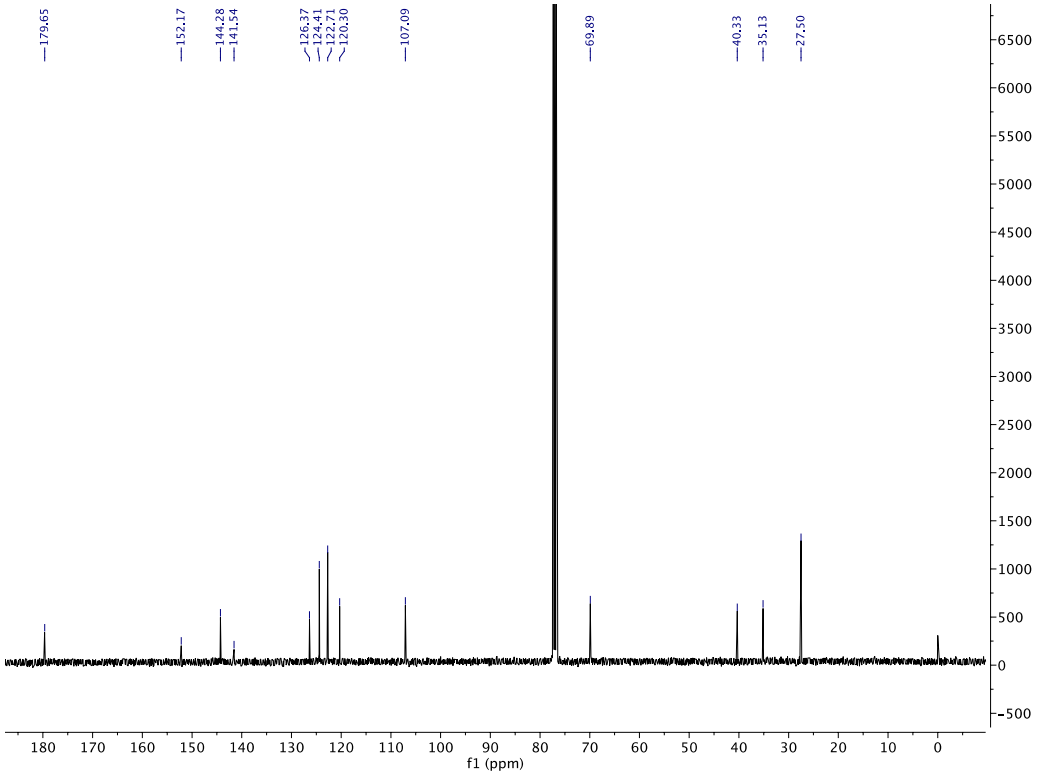
1-(4-Nitrophenyl)-3-(1,3,3-trimethylindolin-5-yl)urea (26)



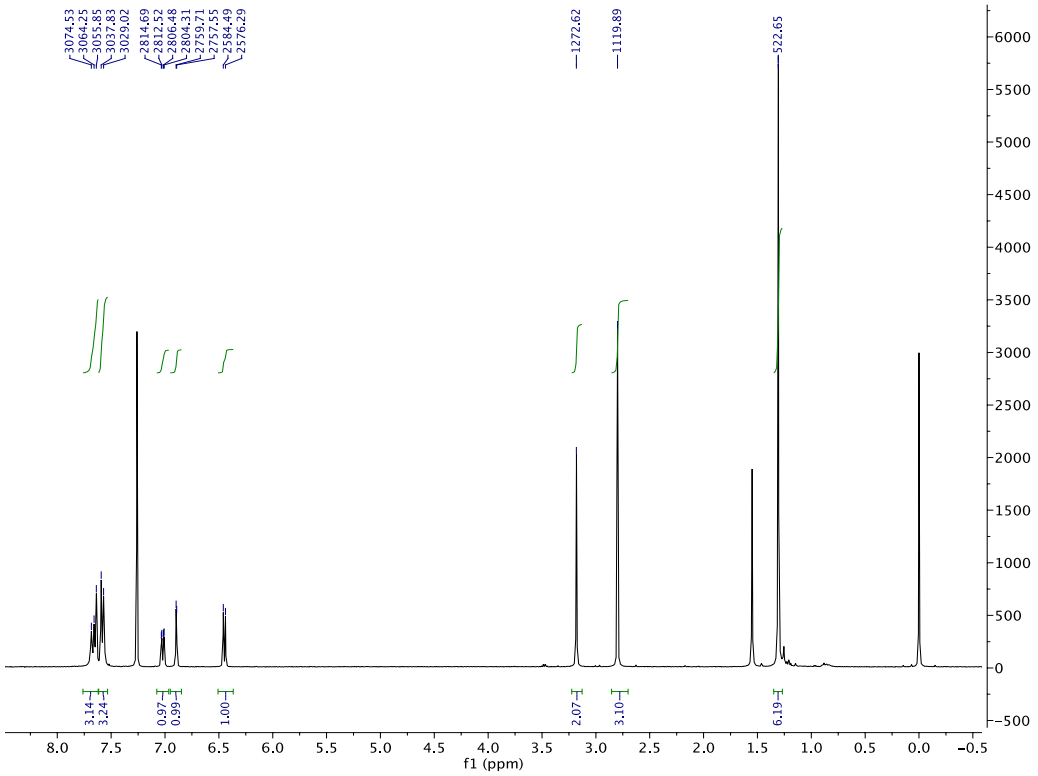


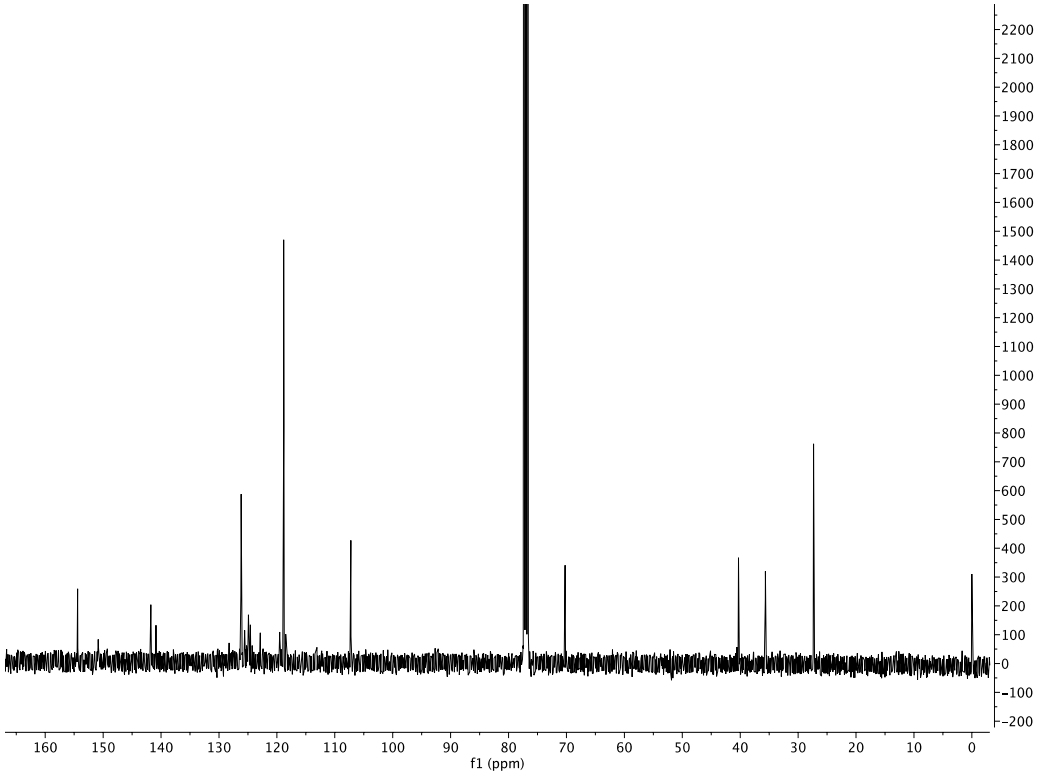
1-(4-Nitrophenyl)-3-(1,3,3-trimethylindolin-5-yl)thiourea (27)



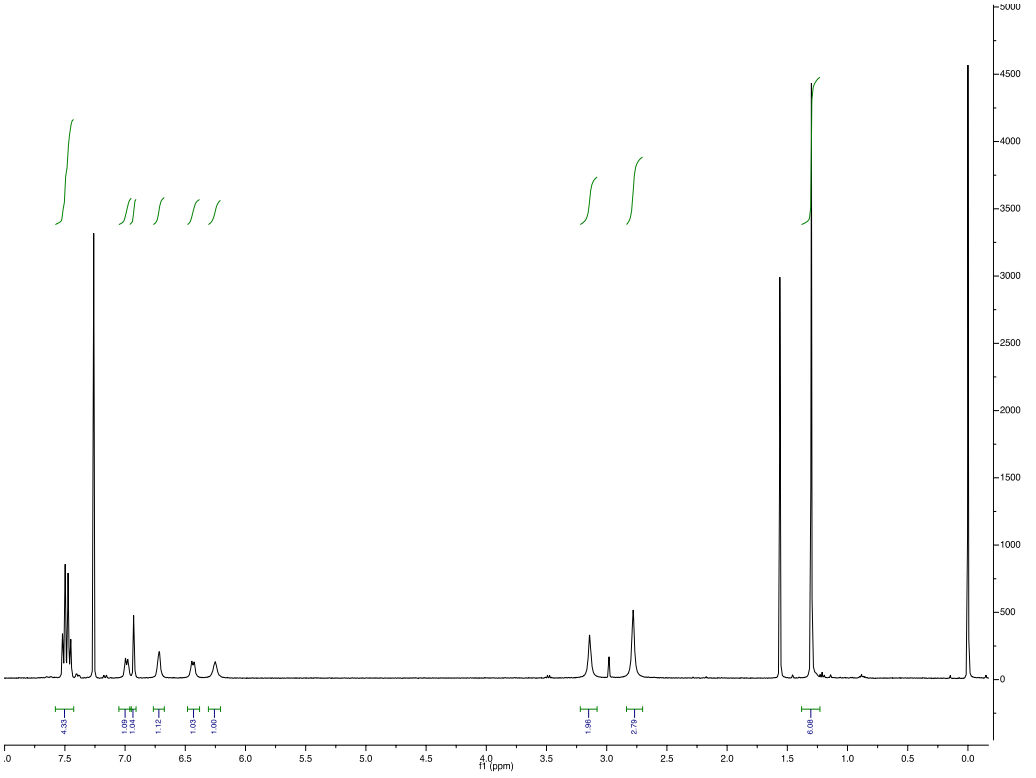


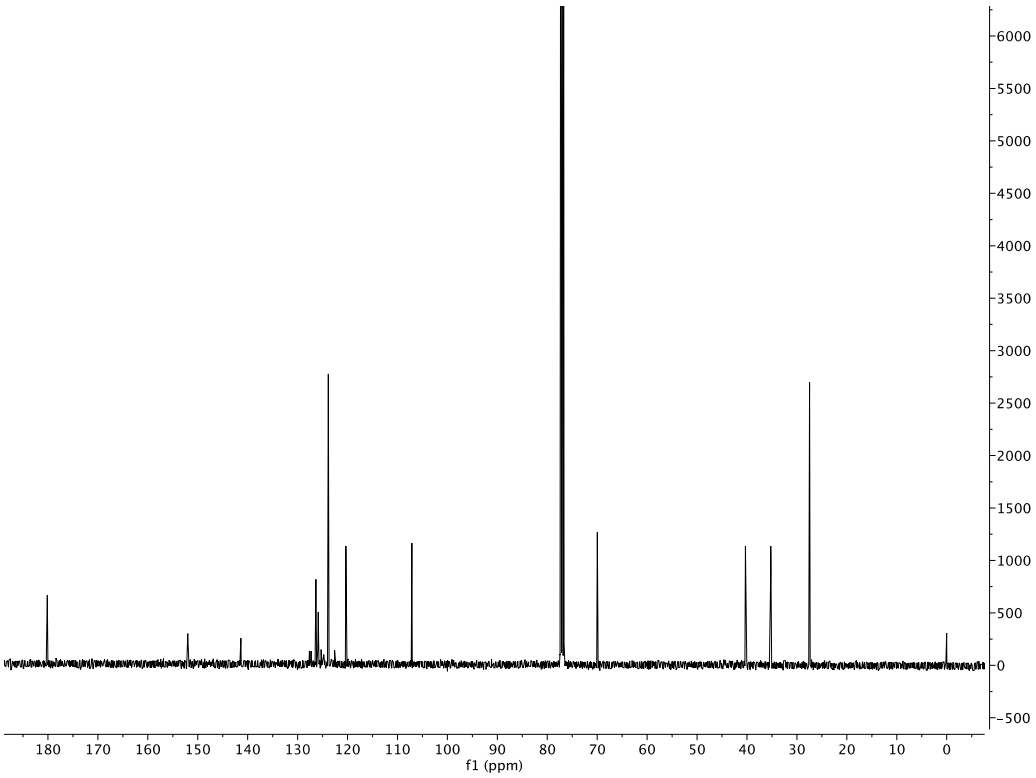
1-(4-(Trifluoromethyl)phenyl)-3-(1,3,3-trimethylindolin-5-yl)thiourea (28)



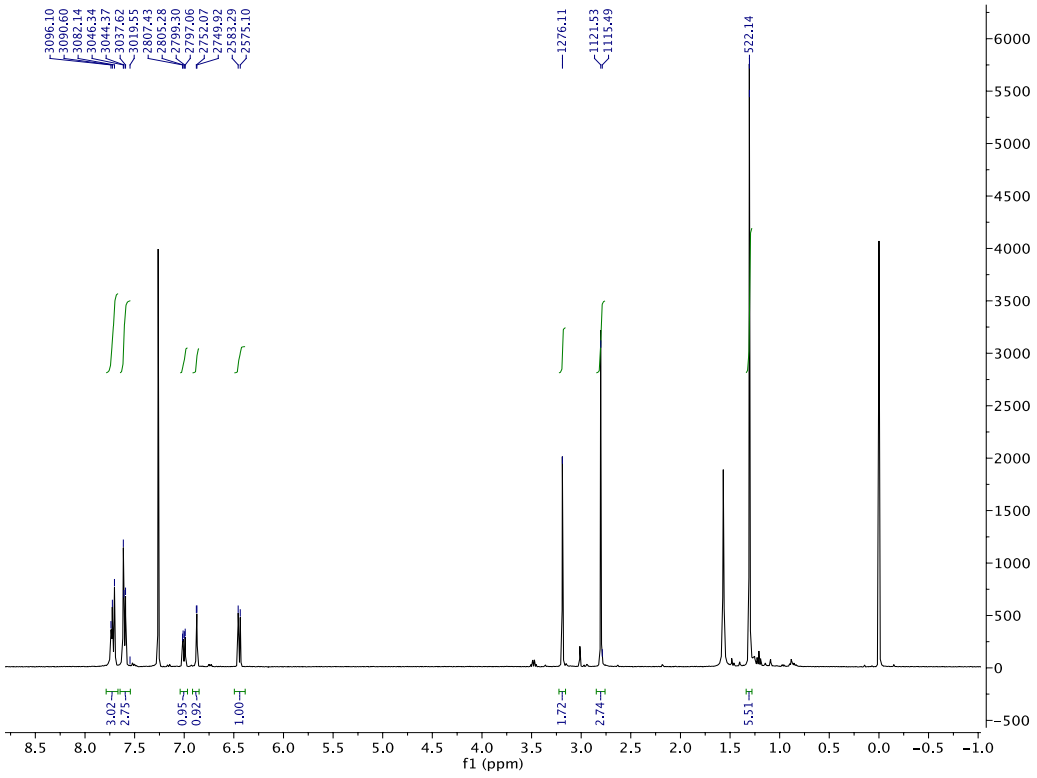


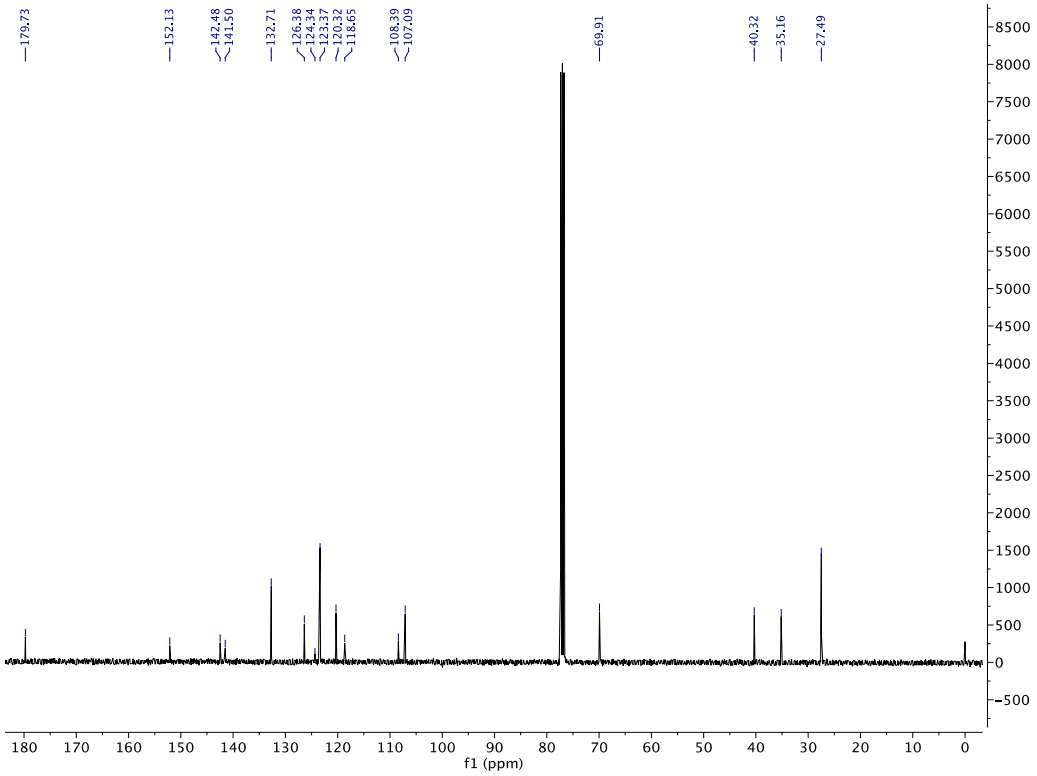
1-(4-(Trifluoromethyl)phenyl)-3-(1,3,3-trimethylindolin-5-yl)urea (29)



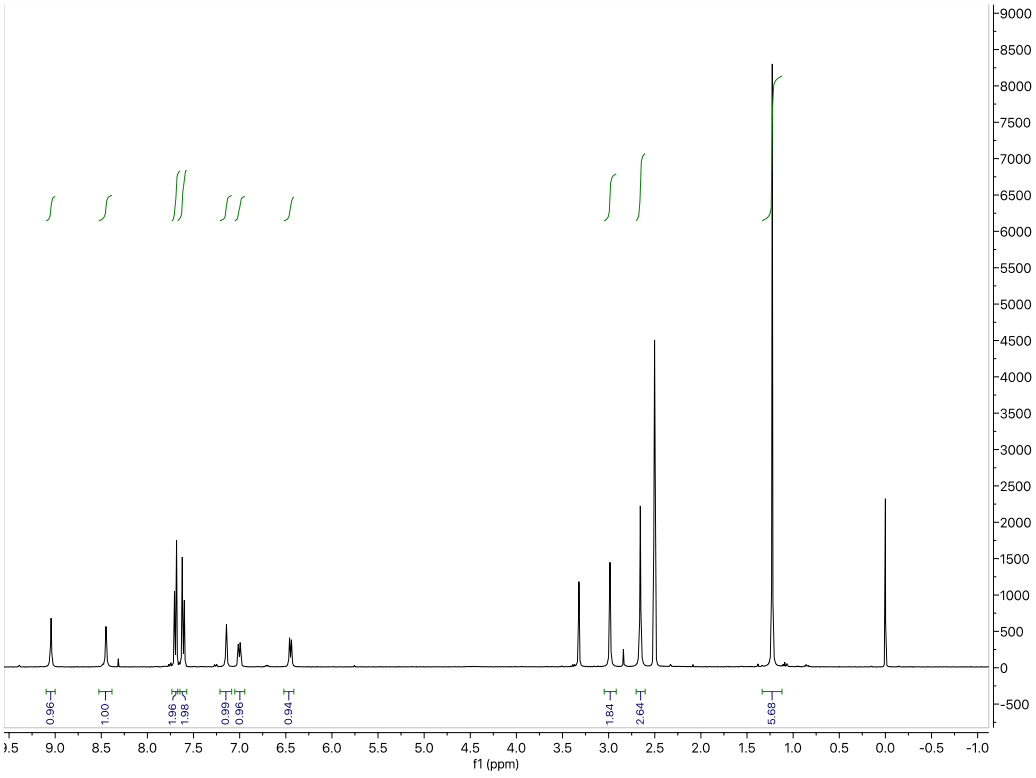


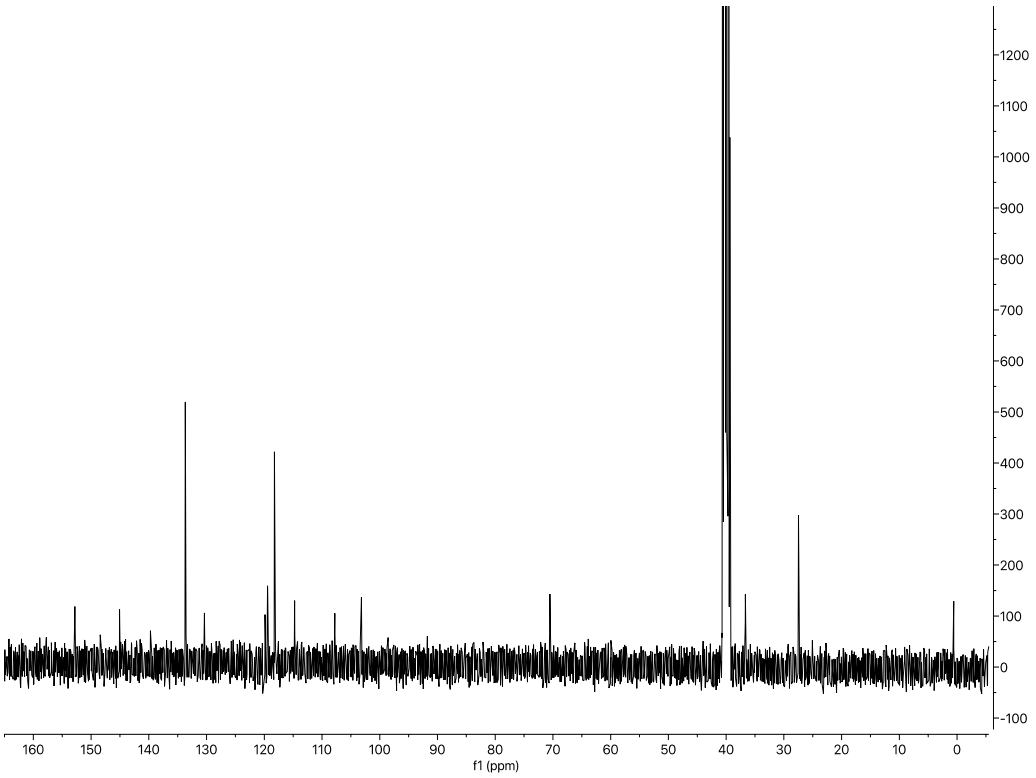
1-(4-Cyanophenyl)-3-(1,3,3-trimethylindolin-5-yl)thiourea (30)



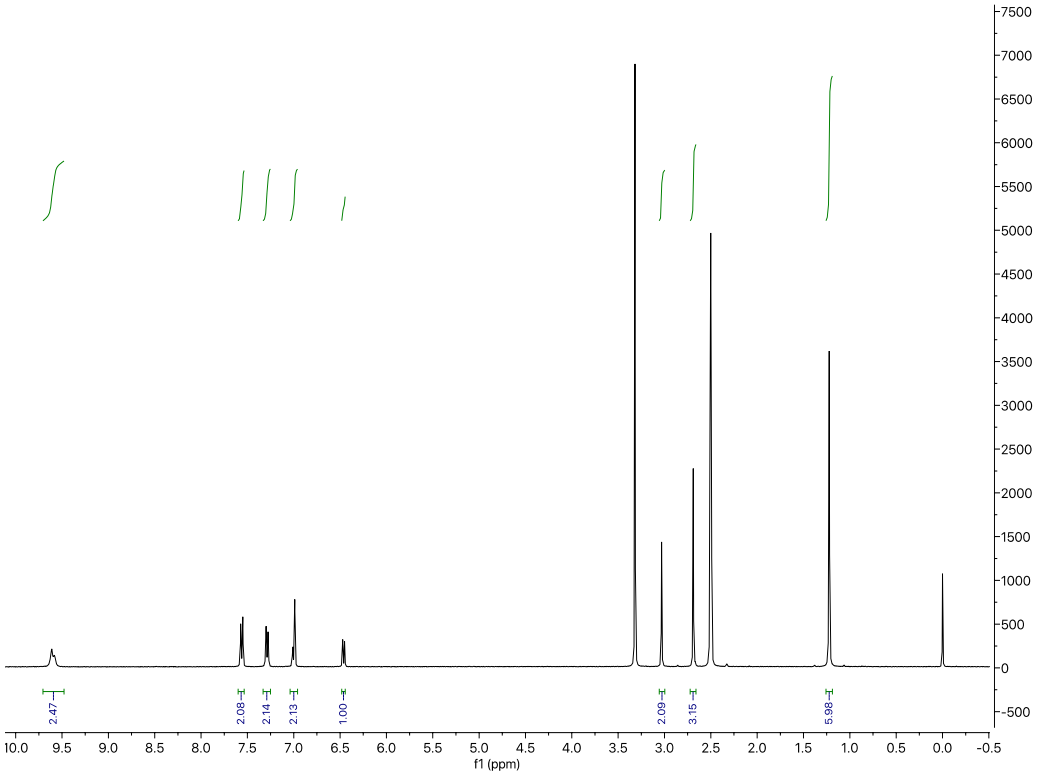


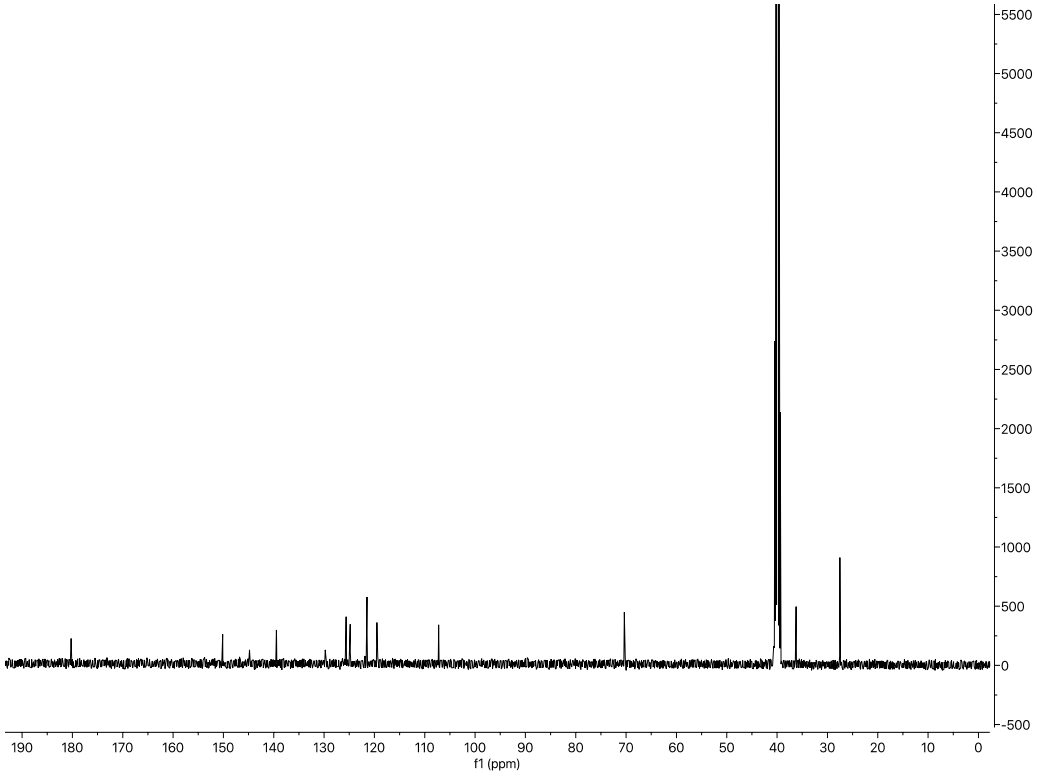
1-(4-Cyanophenyl)-3-(1,3,3-trimethylindolin-5-yl)urea (31)



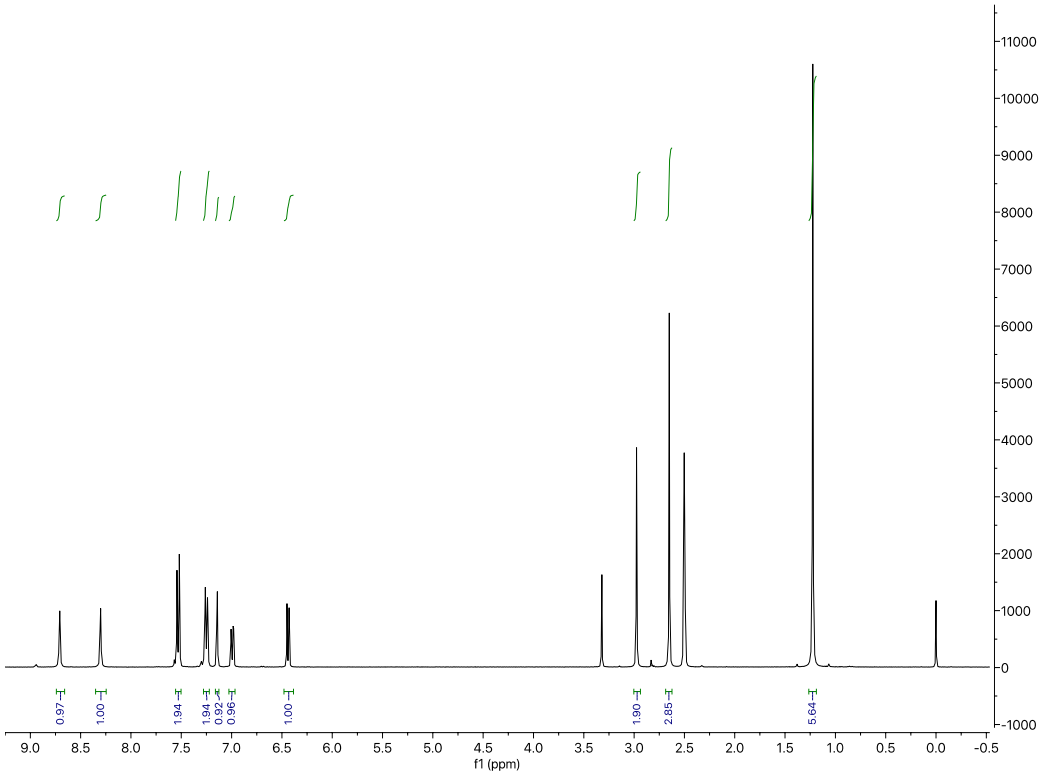


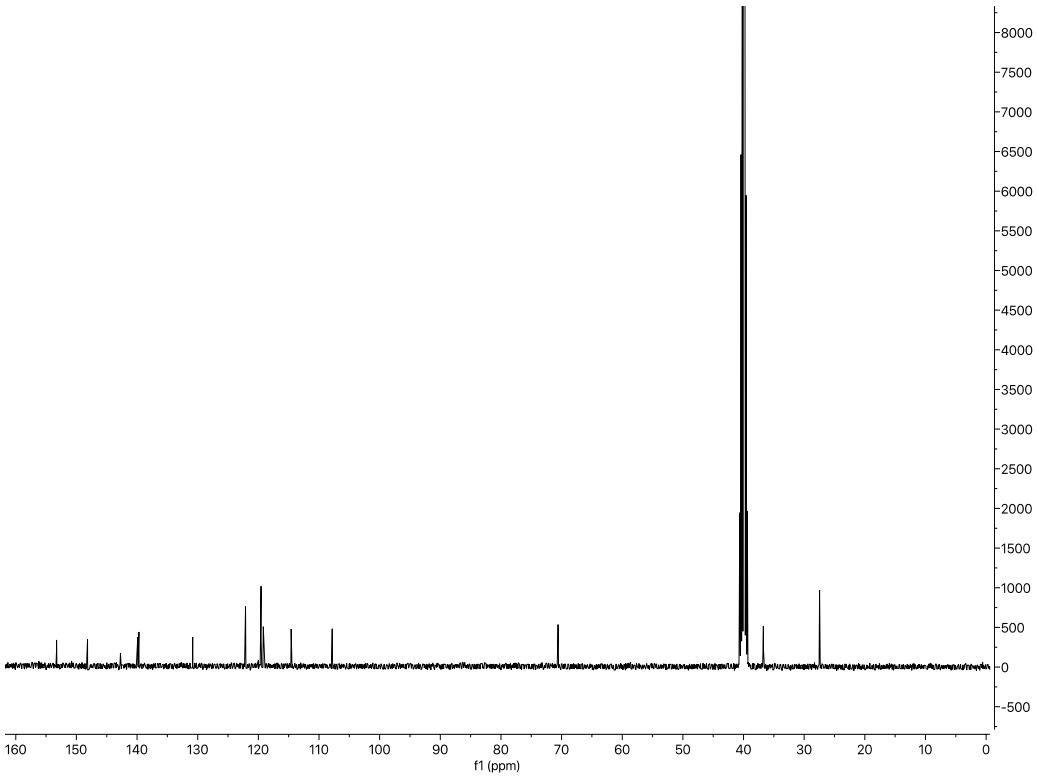
1-(4-(Trifluoromethoxy)phenyl)-3-(1,3,3-trimethylindolin-5-yl)thiourea (32)





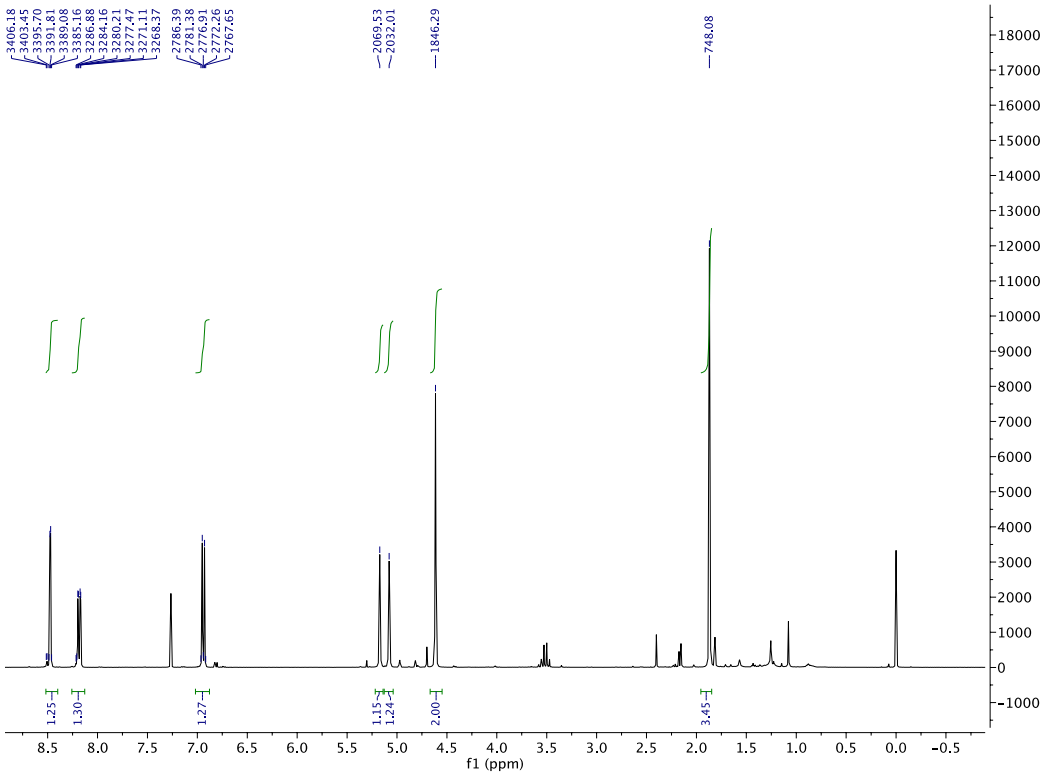
1-(4-(Trifluoromethoxy)phenyl)-3-(1,3,3-trimethylindolin-5-yl)urea (33)

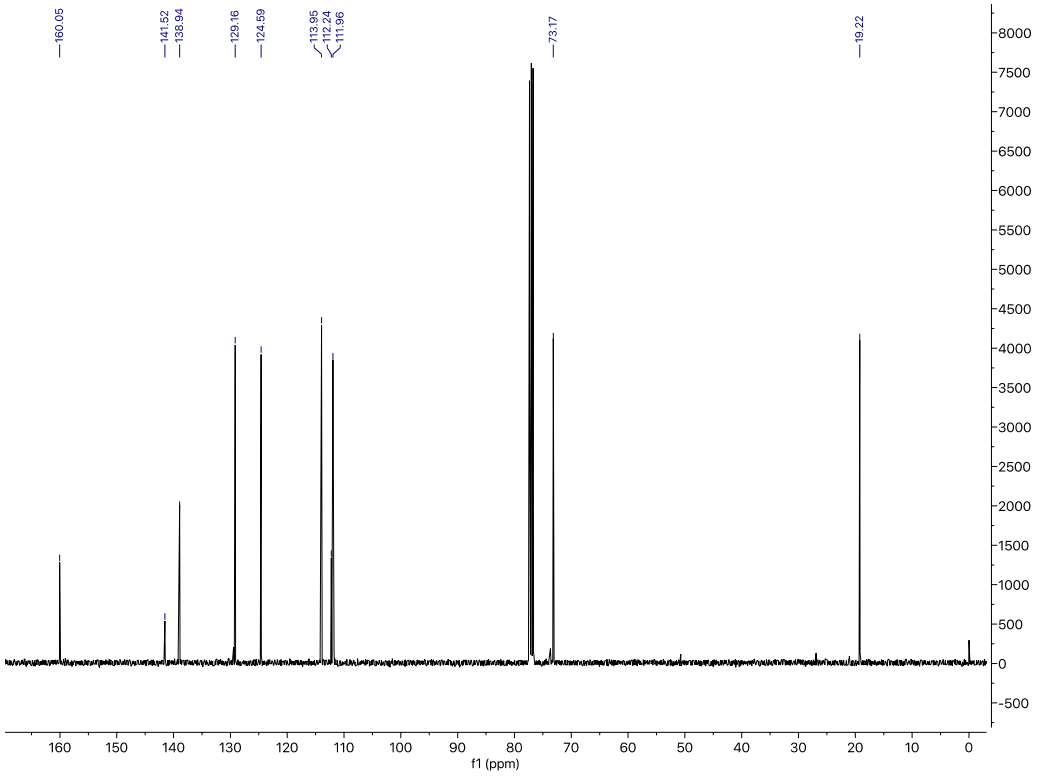




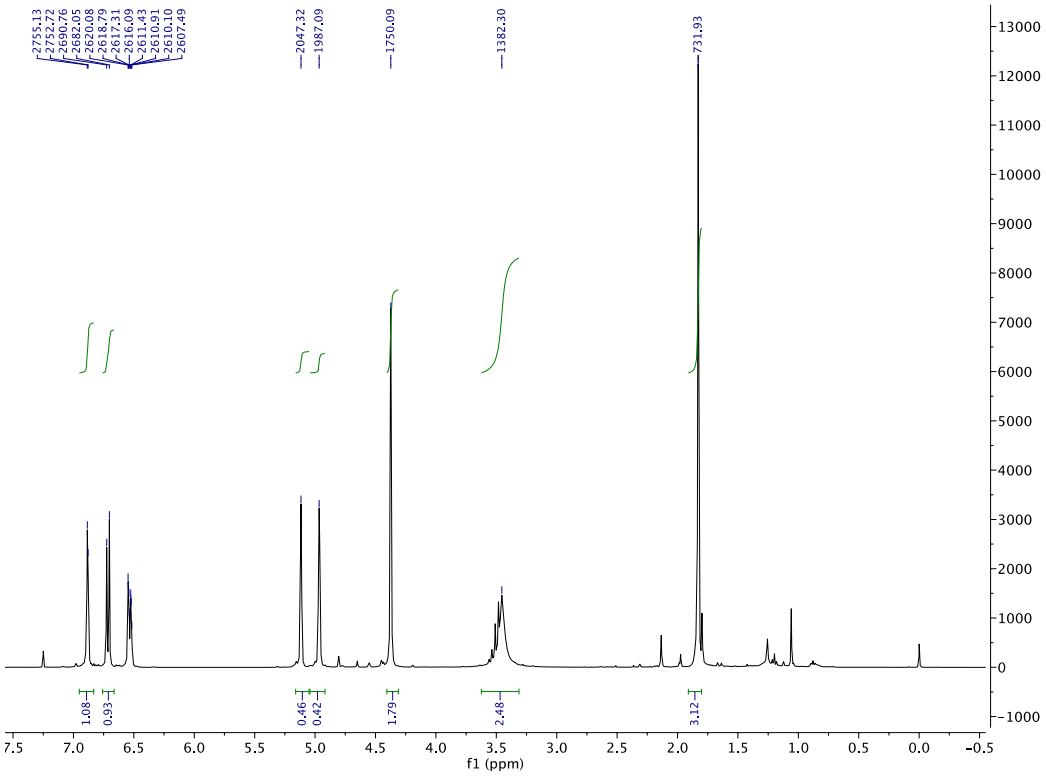
APPENDIX D: Spectral Data for Dihydrofuran SHetA2 Analogs

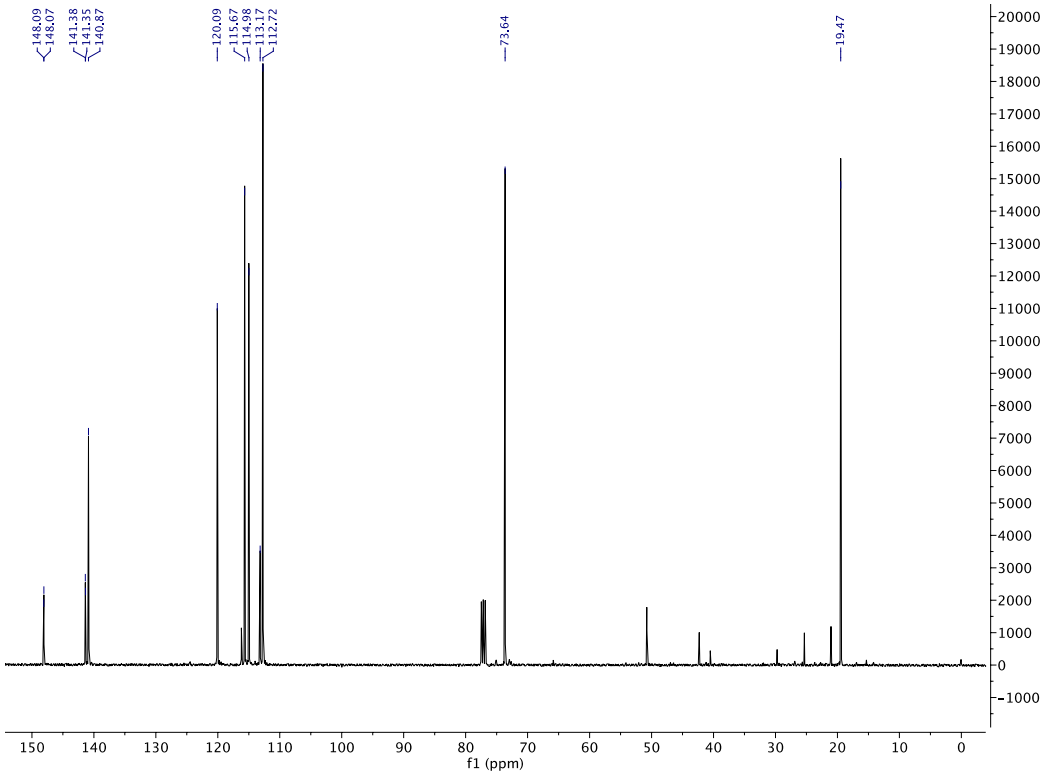
2-Bromo-1-((2-methylallyl)oxy)-4-nitrobenzene (35)



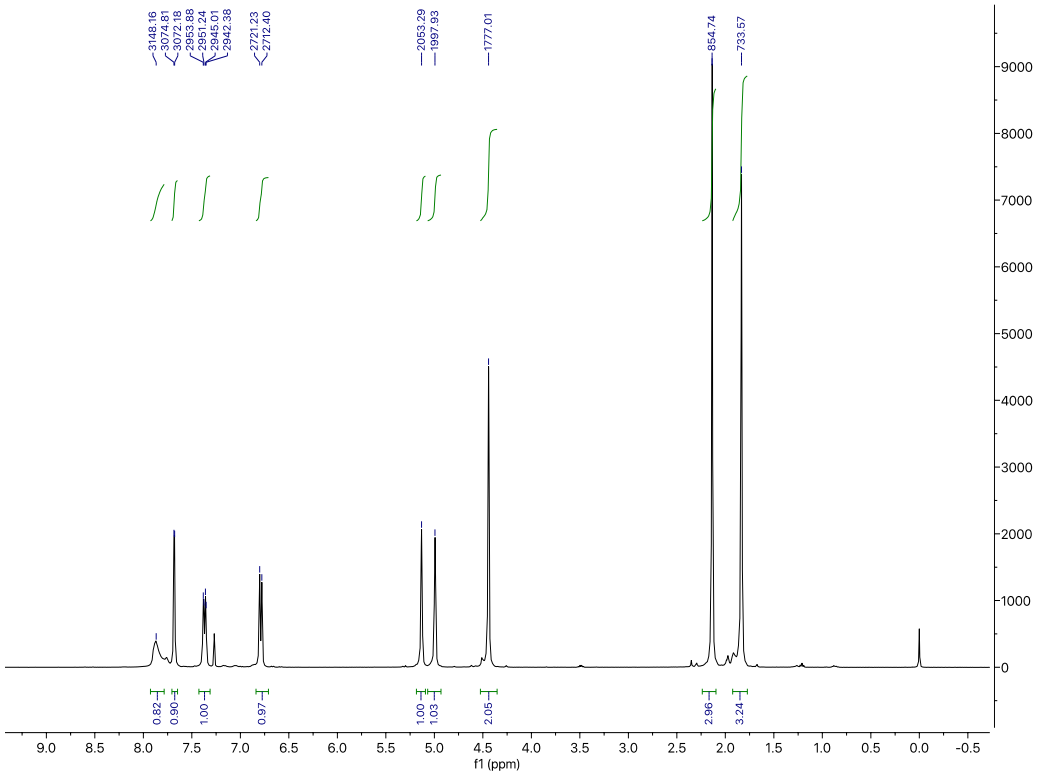


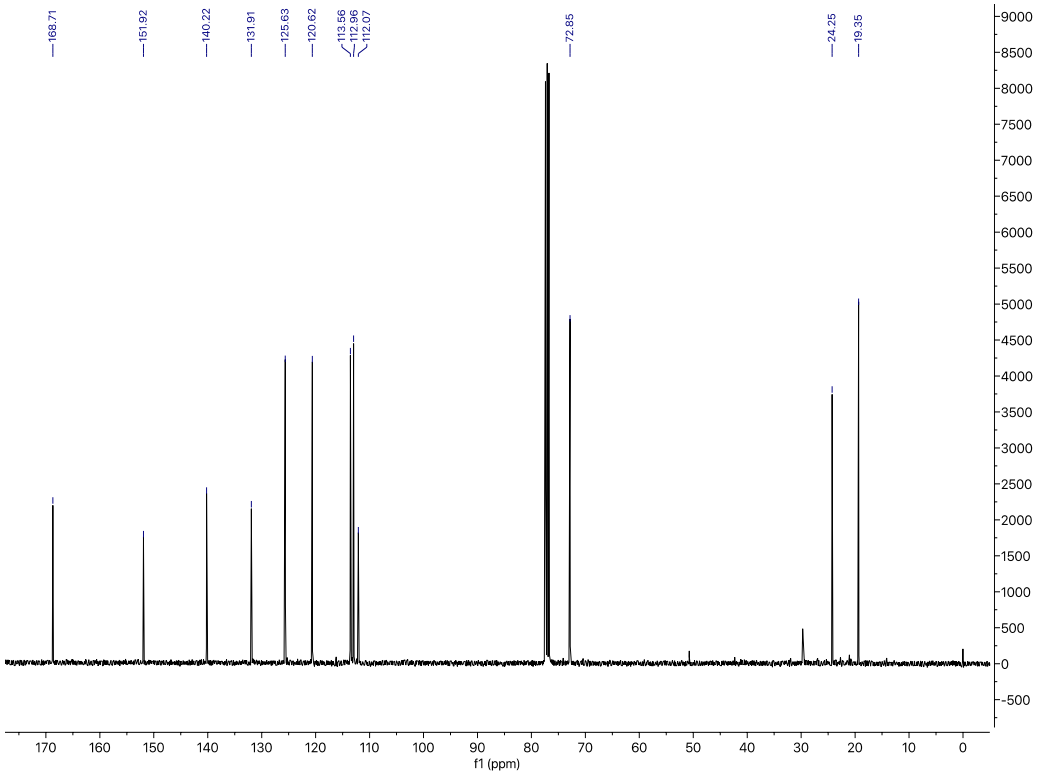
3-Bromo-4-((2-methylallyl)oxy)aniline (36)



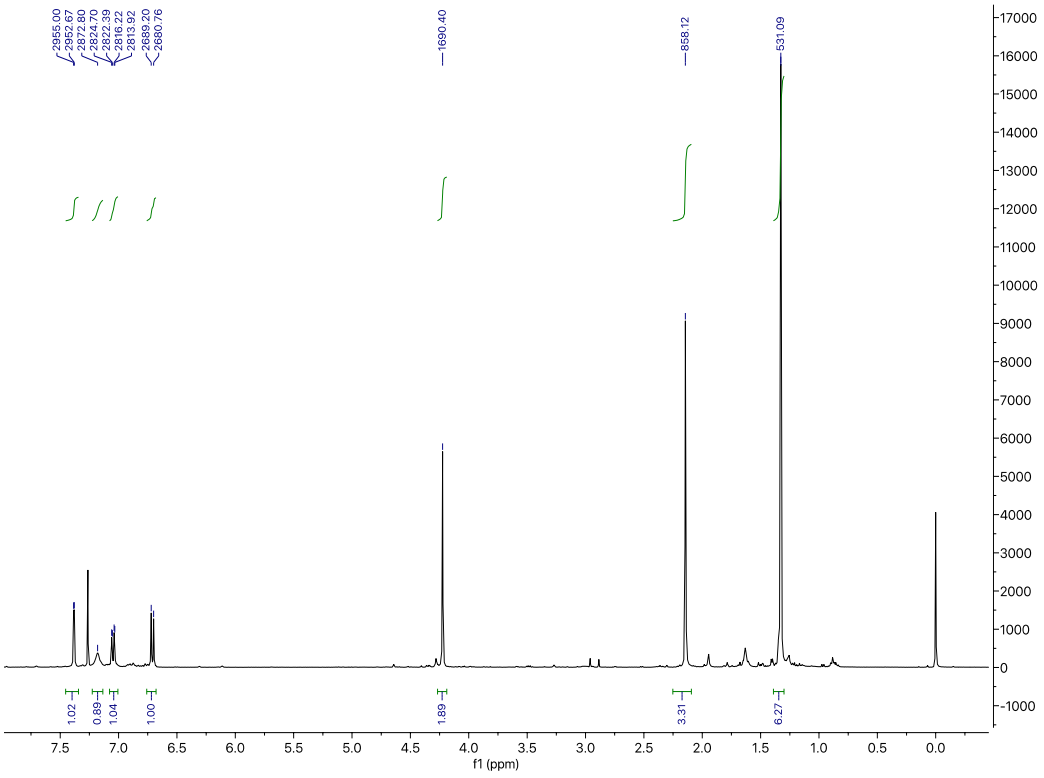


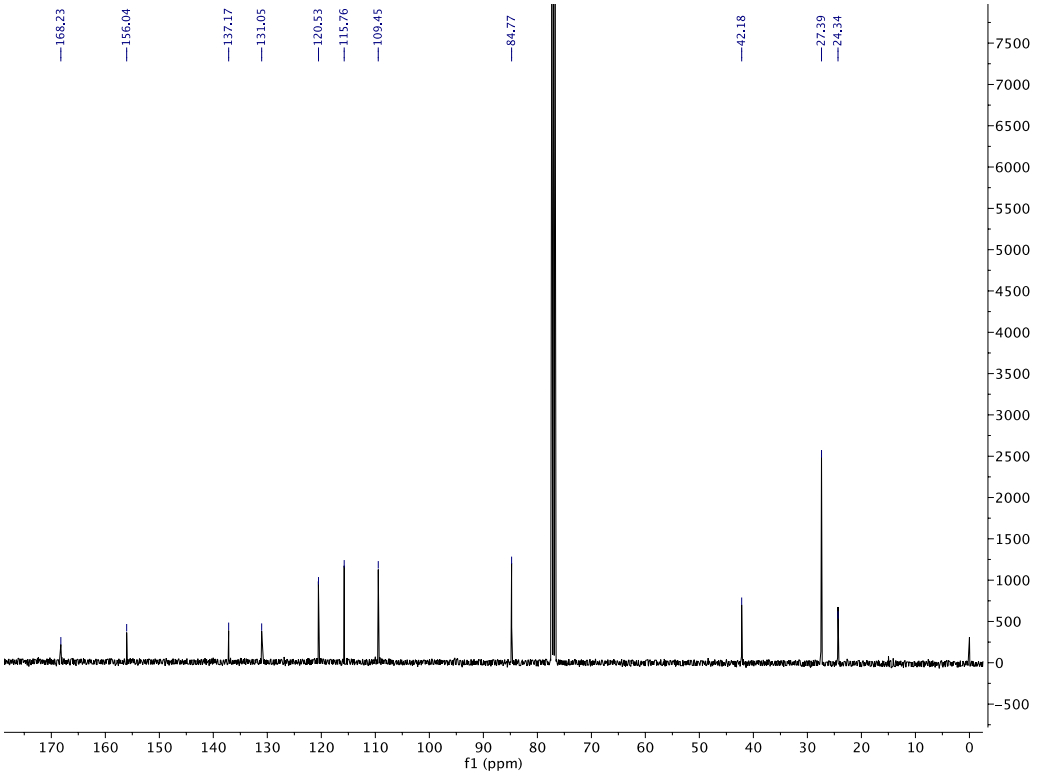
_N_-(3-Bromo-4-((2-methylallyl)oxy)phenyl)acetamide (37)



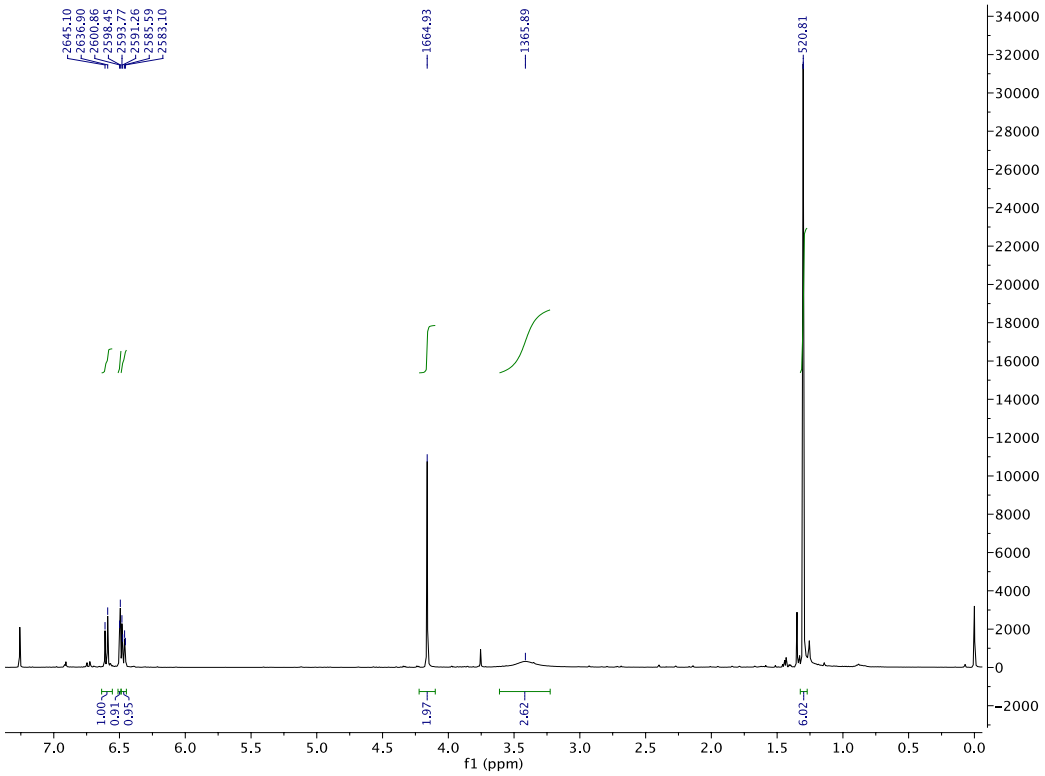


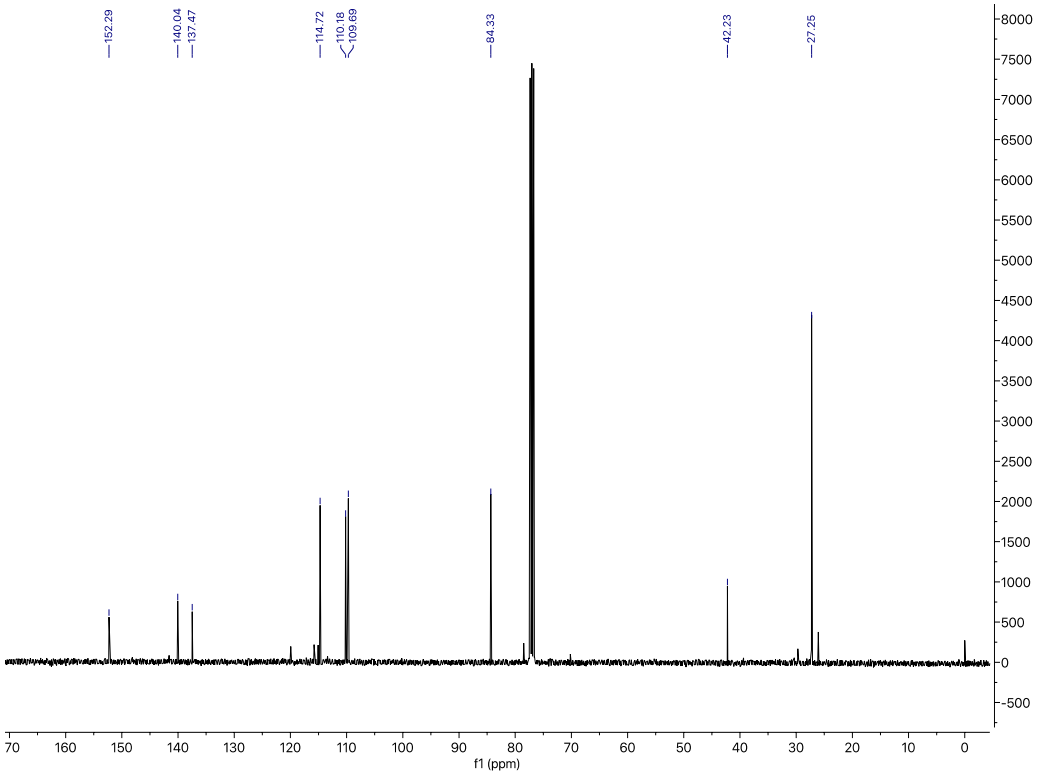
_N_-(3,3-Dimethyl-2,3-dihydrobenzofuran-5-yl)acetamide (38)



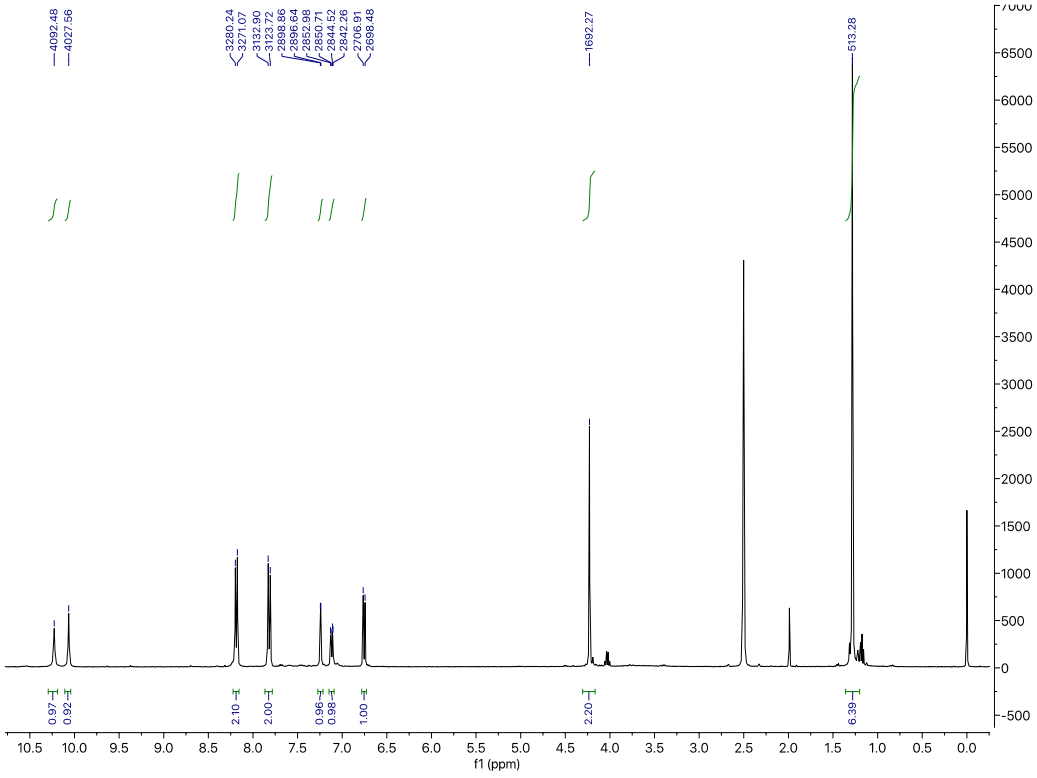


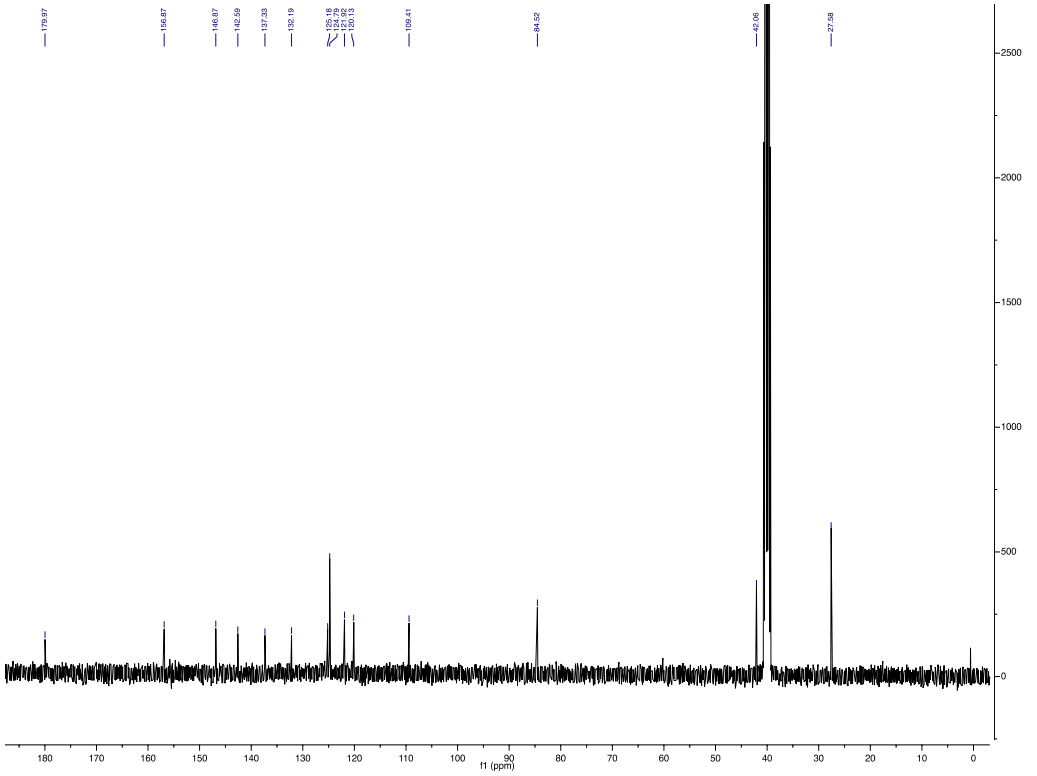
3,3-Dimethyl-2,3-dihydrobenzofuran-5-amine (39)



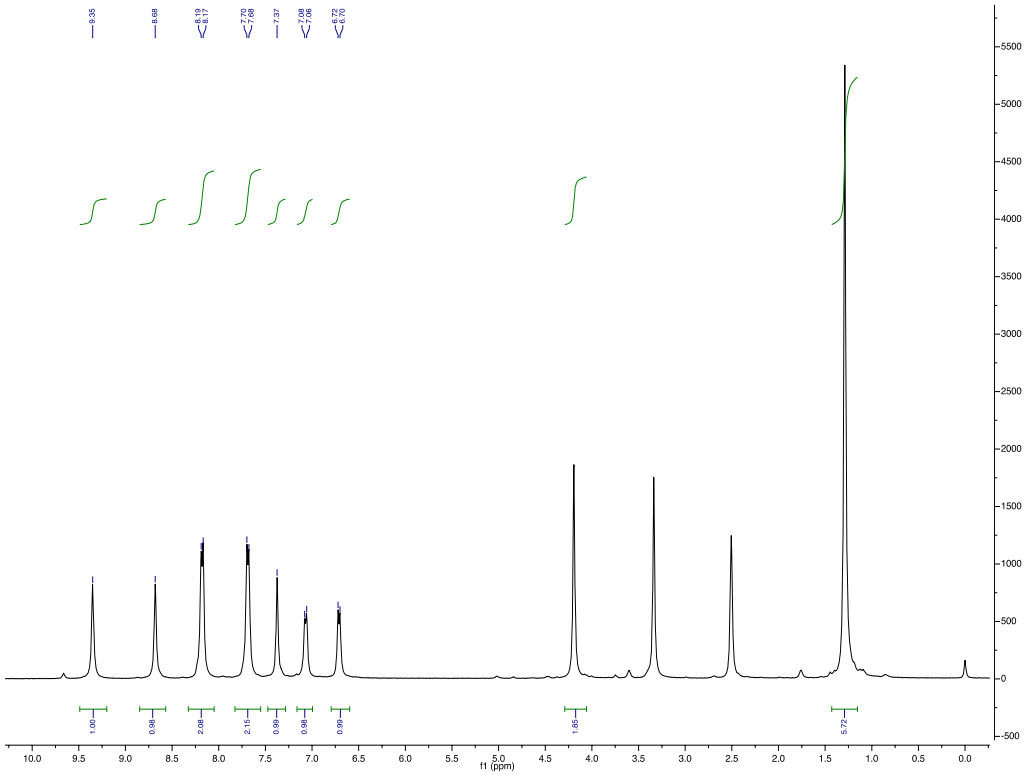


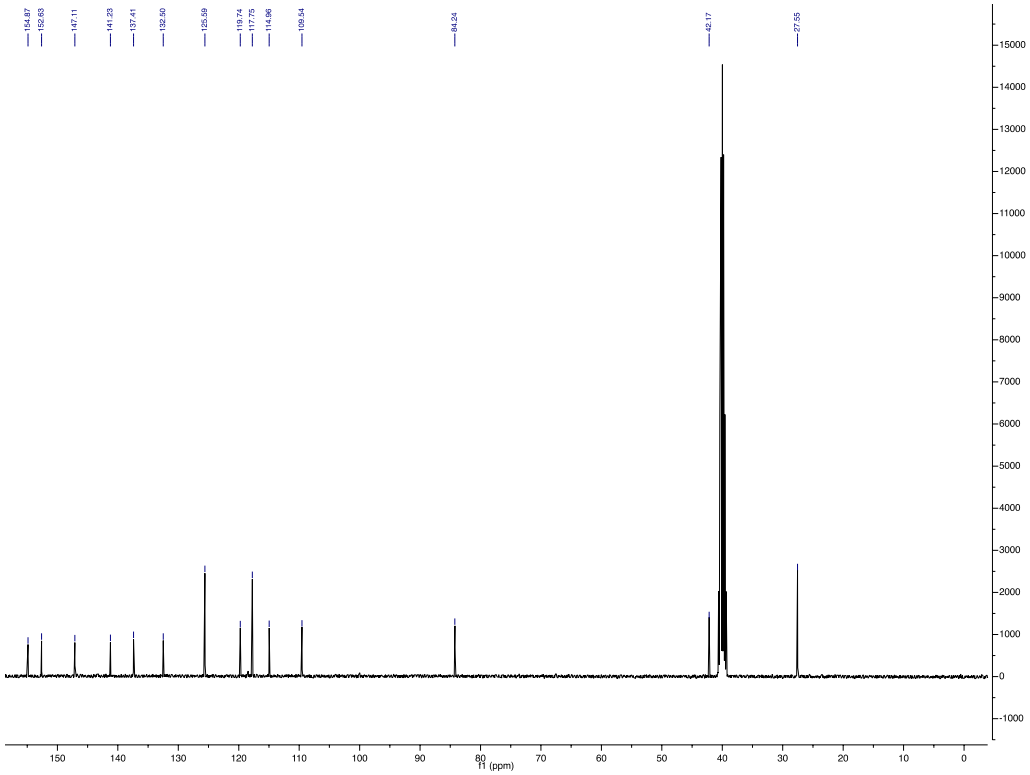
1-(3,3-Dimethyl-2,3-dihydrobenzofuran-5-yl)-3-(4-nitrophenyl)thiourea (40)



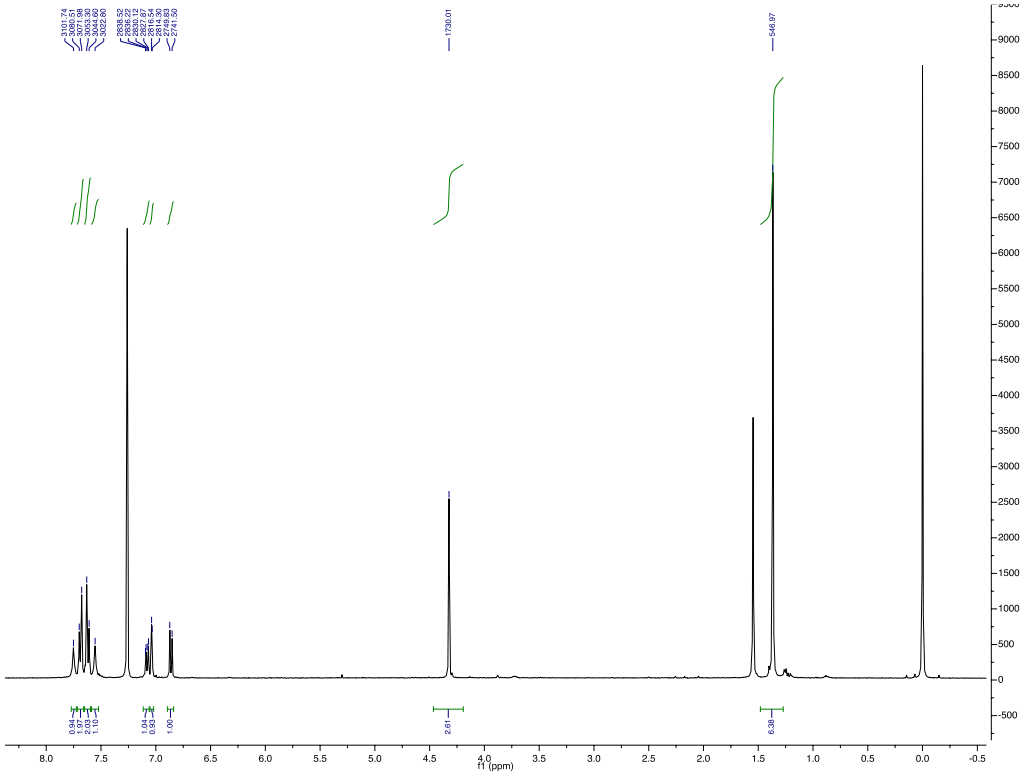


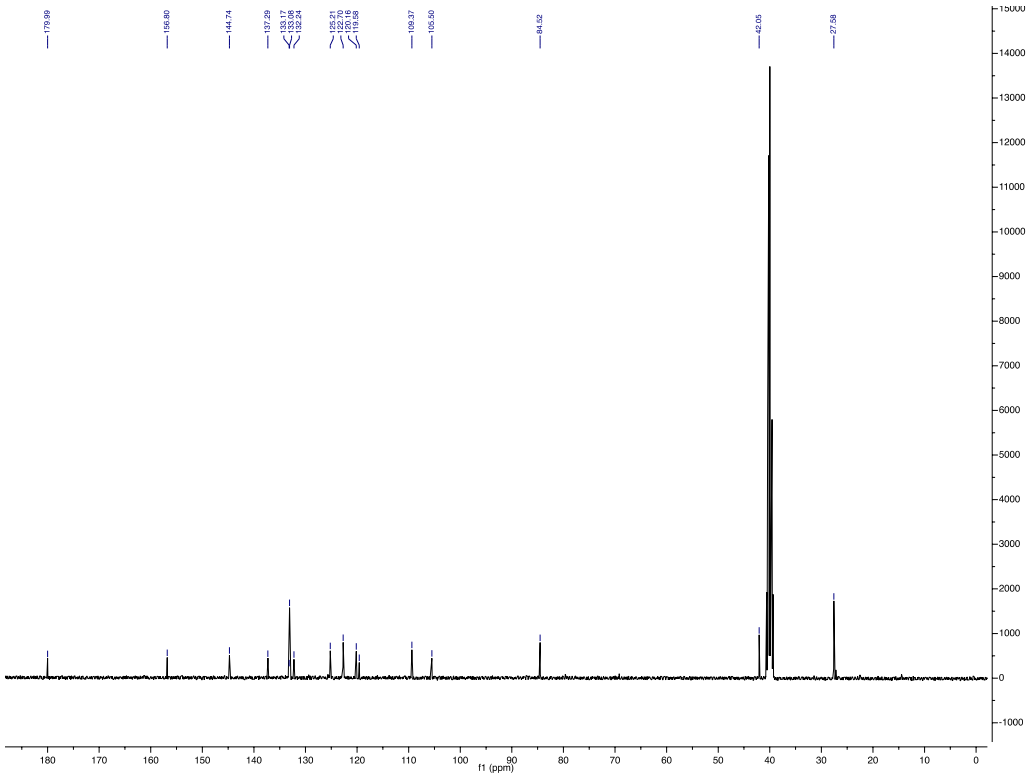
1-(3,3-Dimethyl-2,3-dihydrobenzofuran-5-yl)-3-(4-nitrophenyl)urea (41)



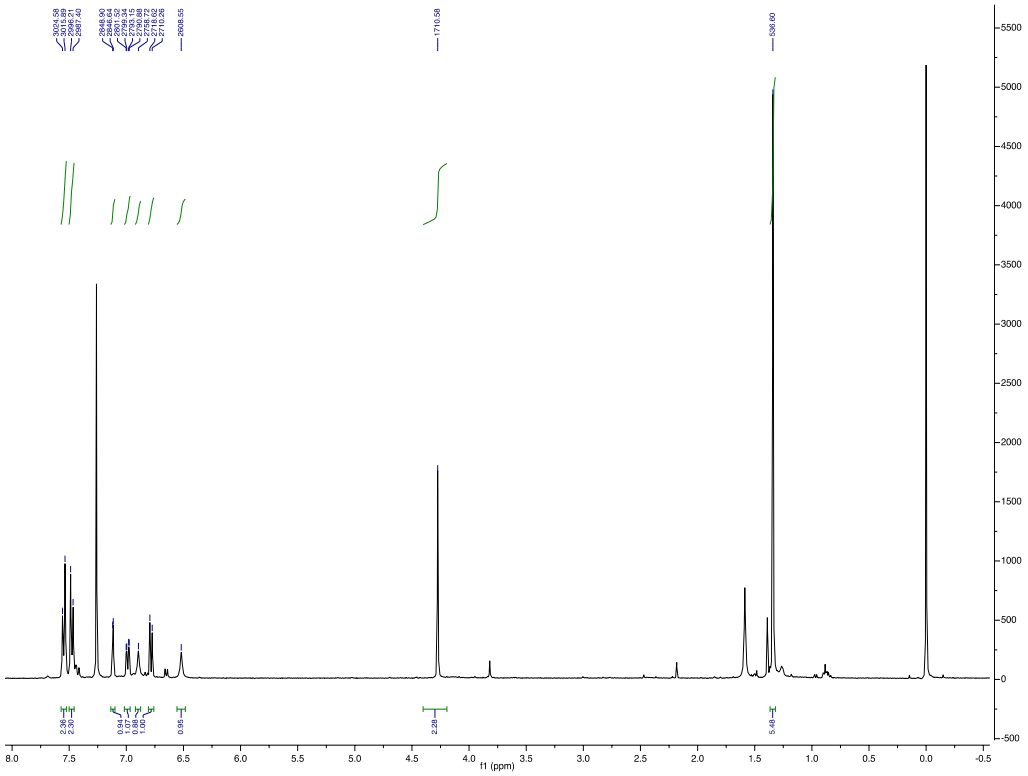


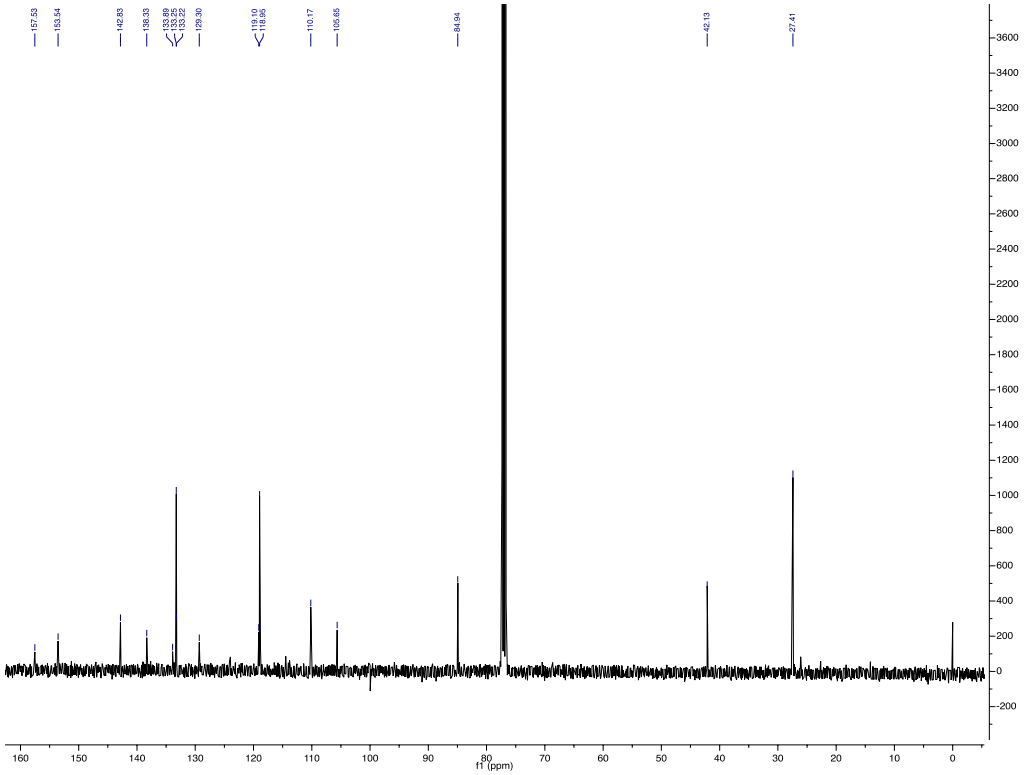
1-(4-Cyanophenyl)-3-(3,3-dimethyl-2,3-dihydrobenzofuran-5-yl)thiourea (42)



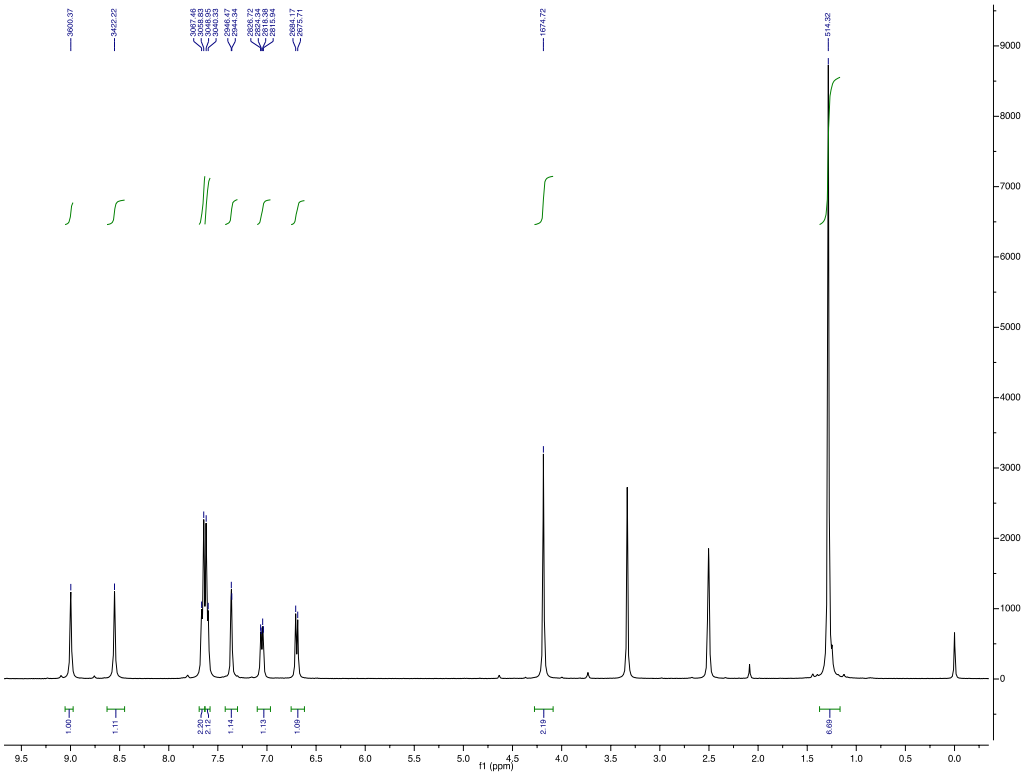


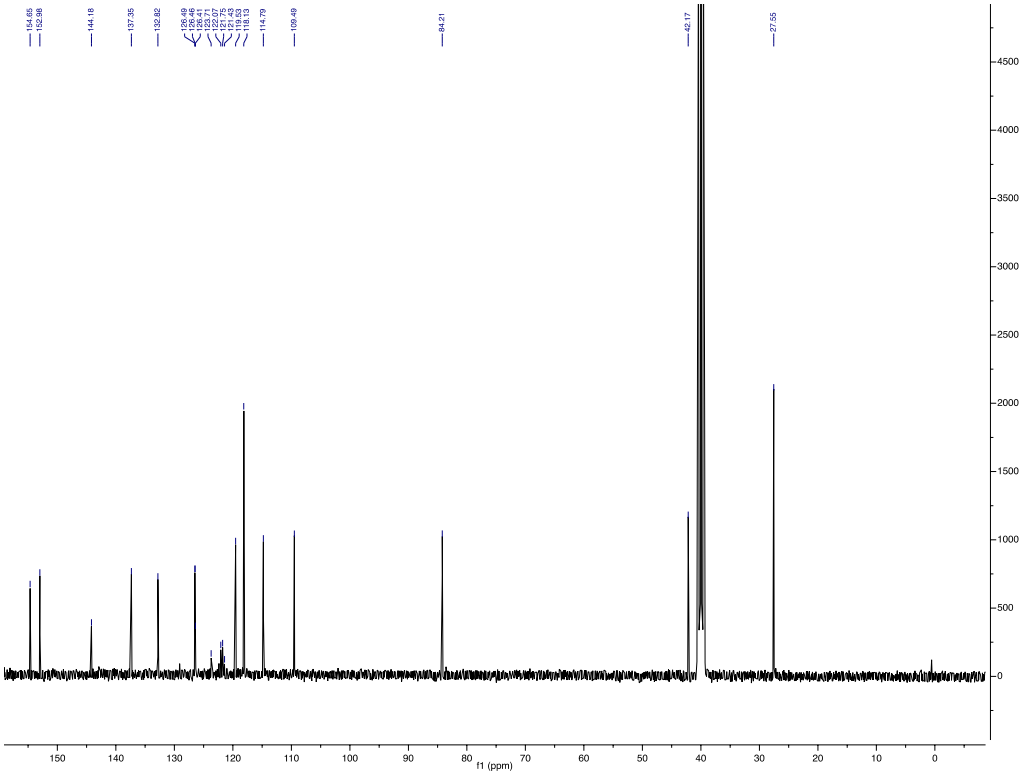
1-(4-Cyanophenyl)-3-(3,3-dimethyl-2,3-dihydrobenzofuran-5-yl)urea (43)



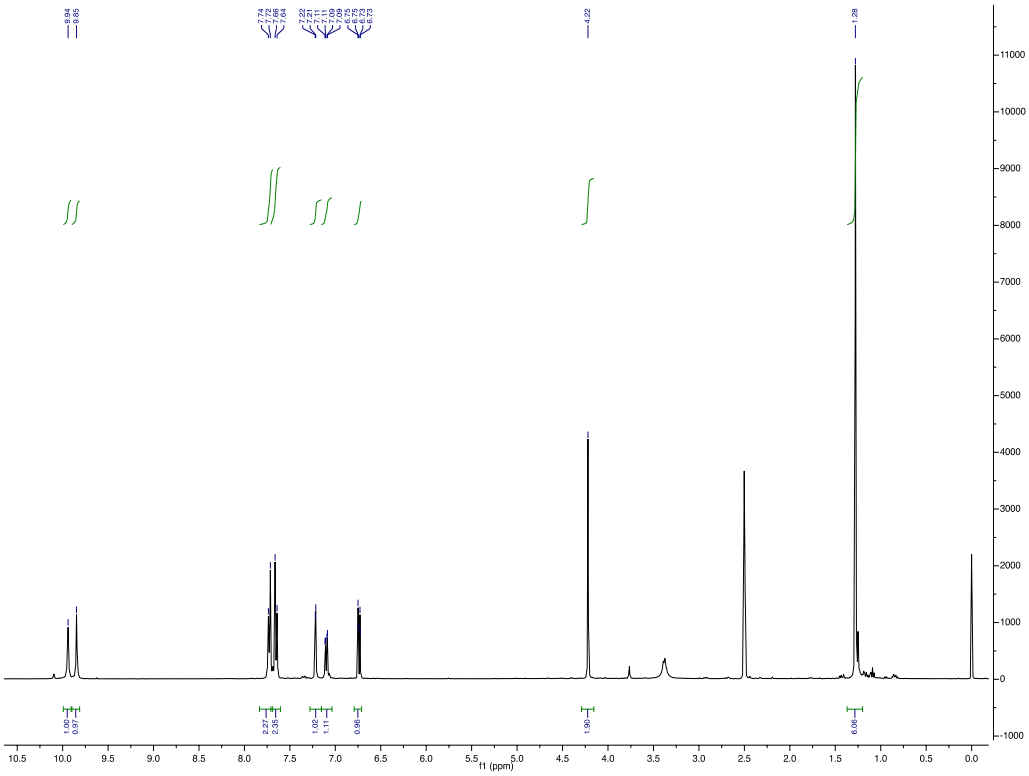


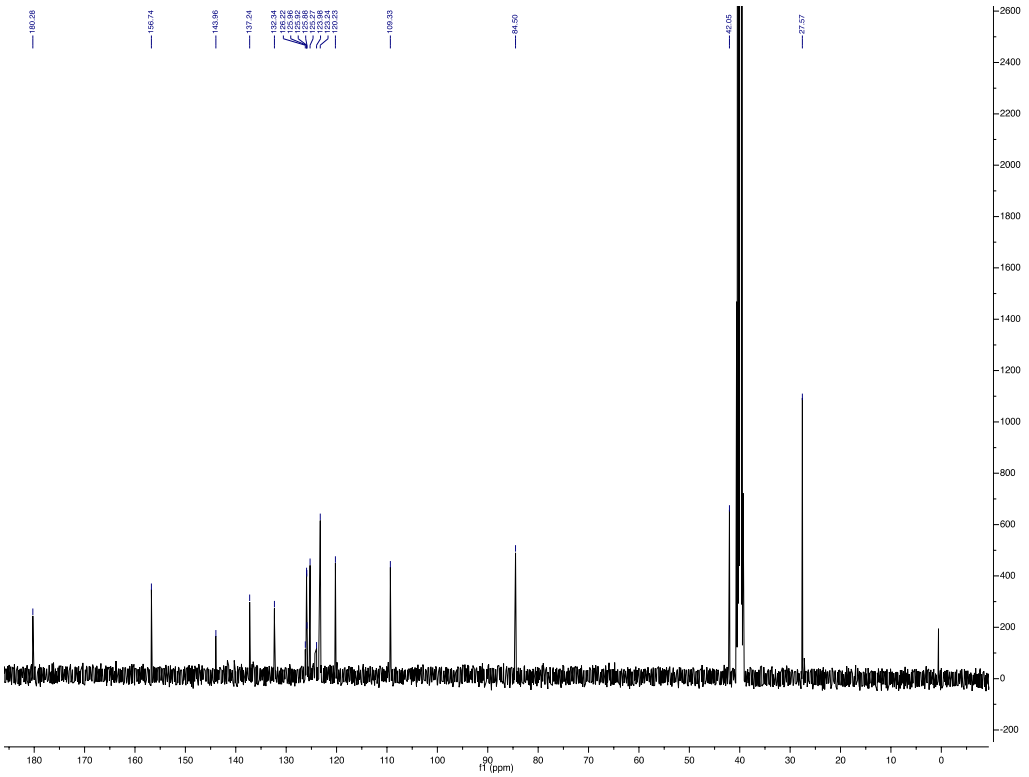
1-(3,3-Dimethyl-2,3-dihydrobenzofuran-5-yl)-3-(4-(trifluoromethyl)phenyl)urea (44)



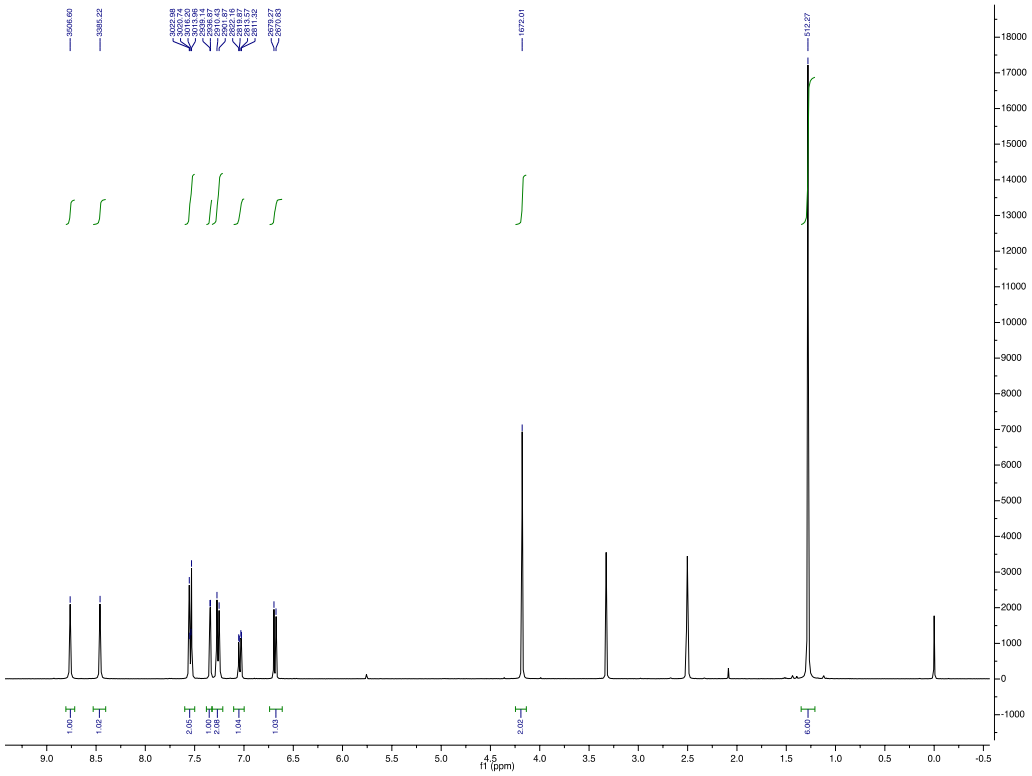


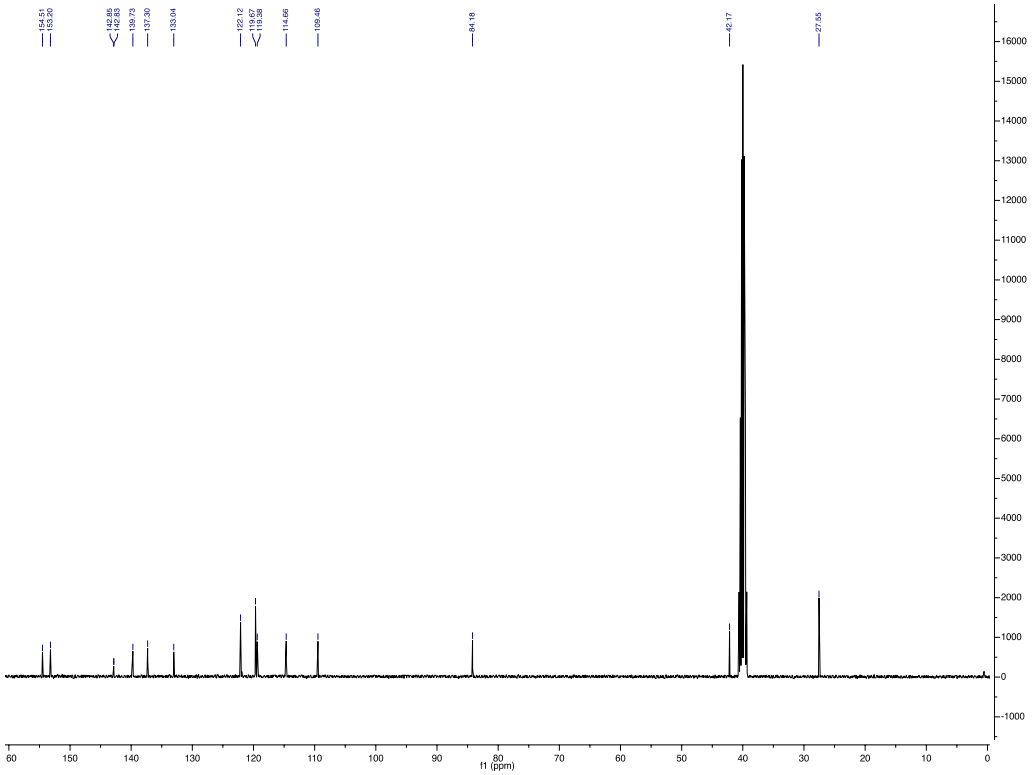
1-(3,3-Dimethyl-2,3-dihydrobenzofuran-5-yl)-3-(4-(trifluoromethyl)phenyl)thiourea (45)



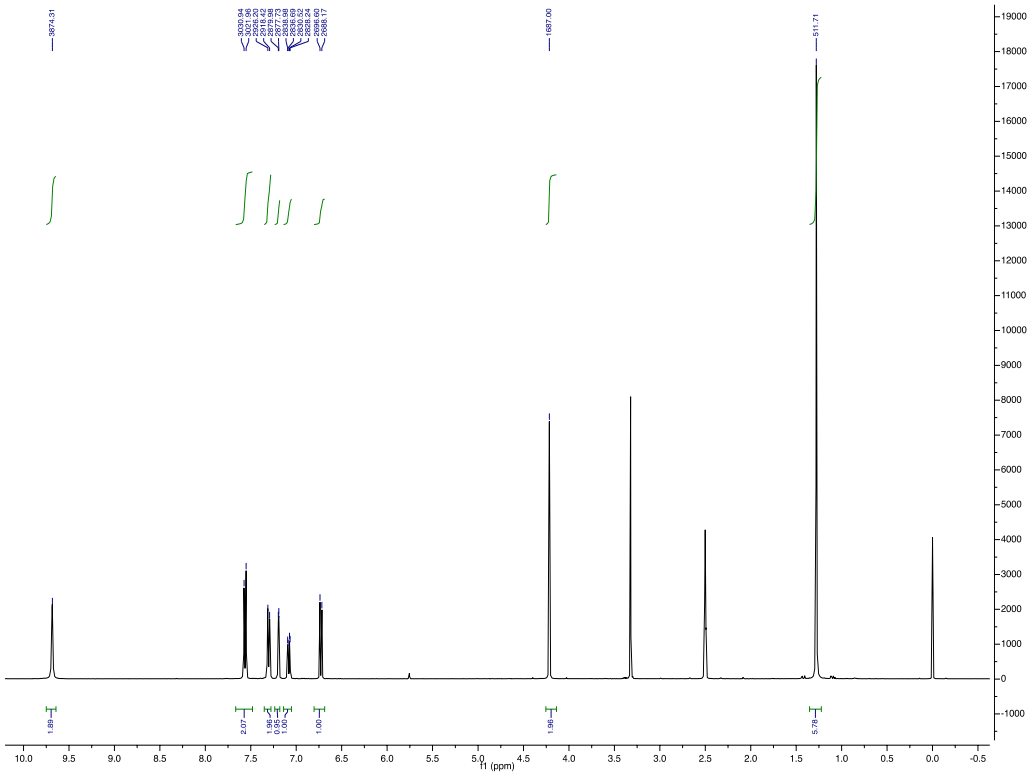


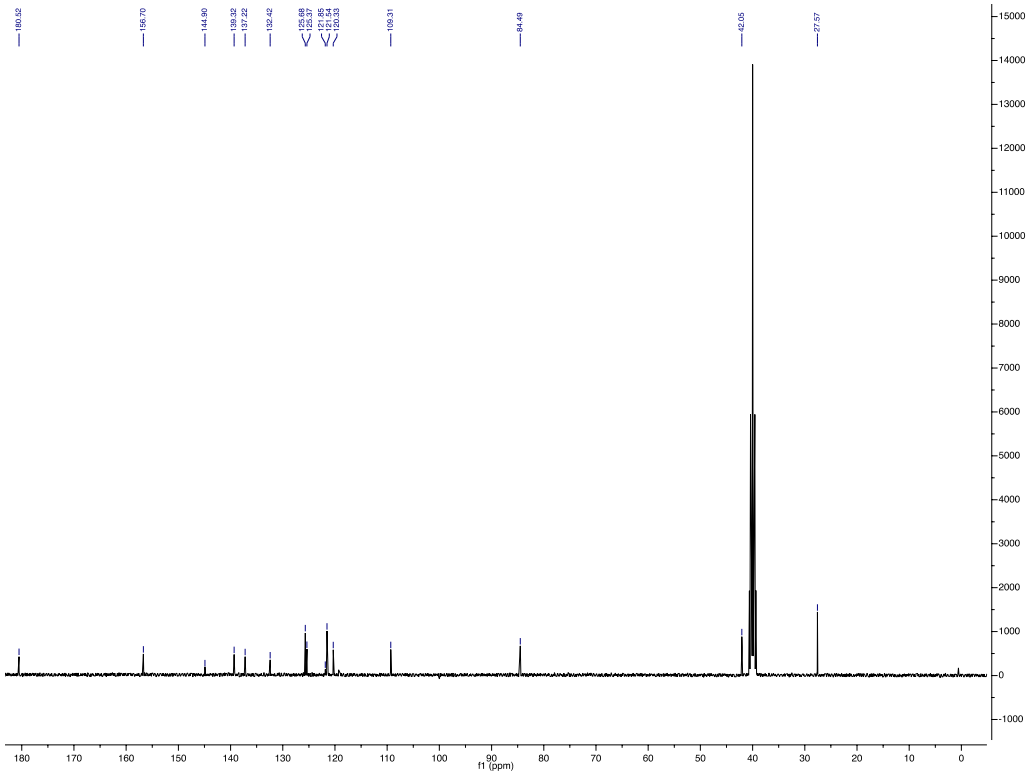
1-(3,3-Dimethyl-2,3-dihydrobenzofuran-5-yl)-3-(4-(trifluoromethoxy)phenyl)urea (46)





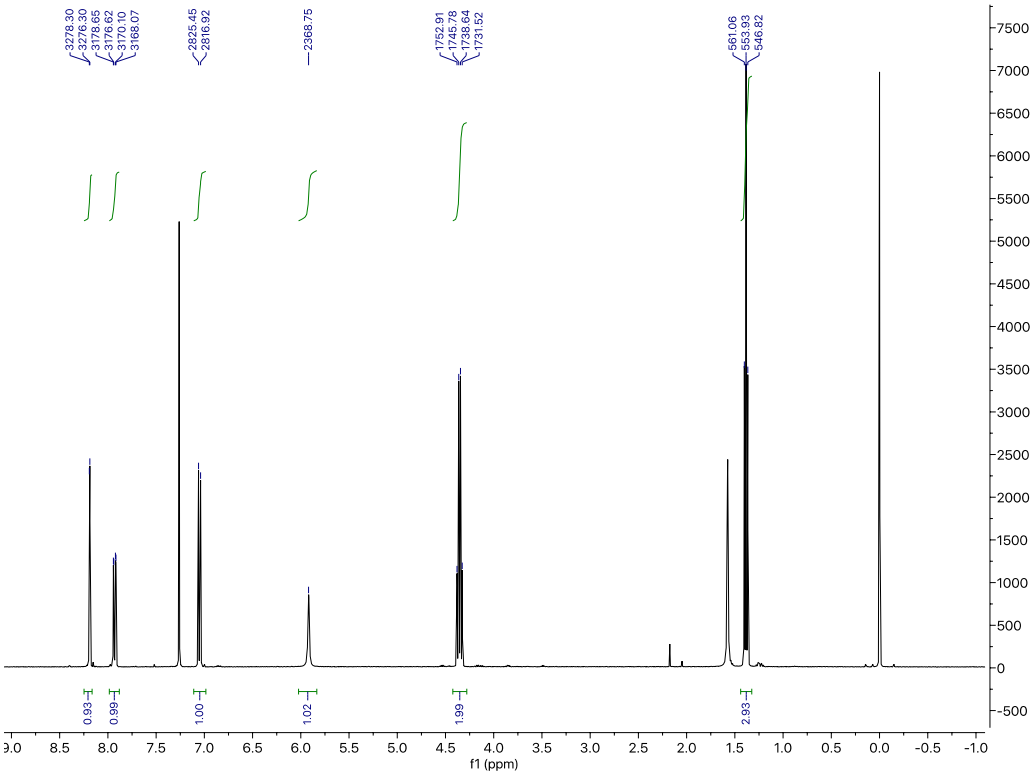
1-(3,3-Dimethyl-2,3-dihydrobenzofuran-5-yl)-3-(4-(trifluoromethoxy)phenyl)thiourea (47)

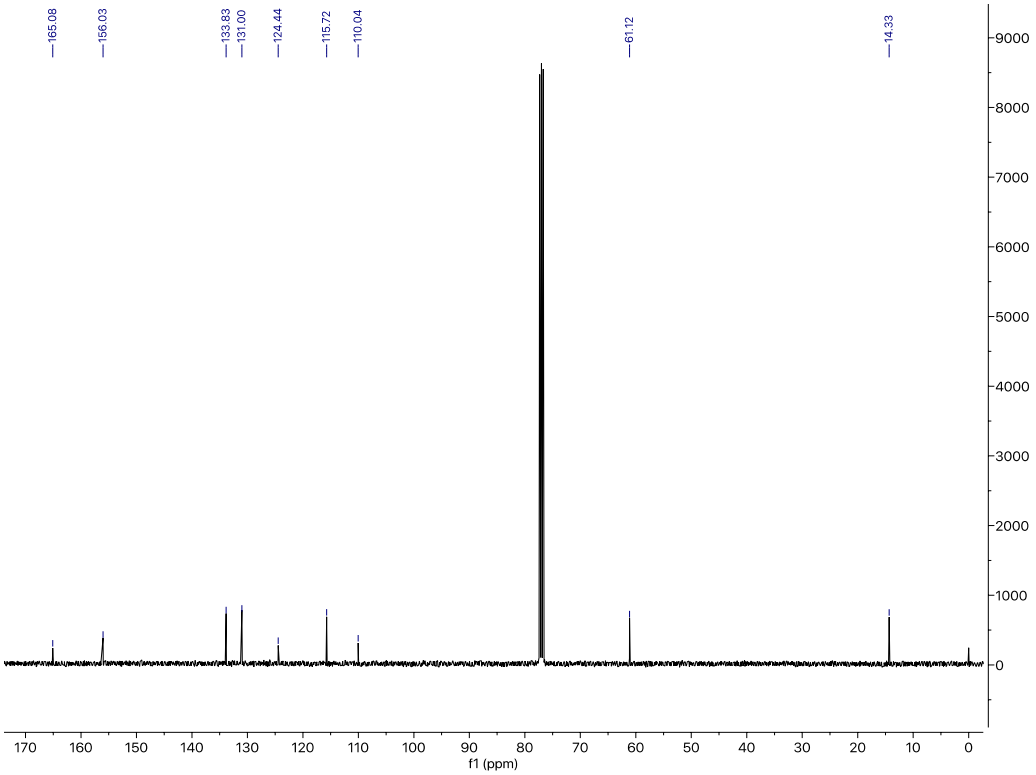




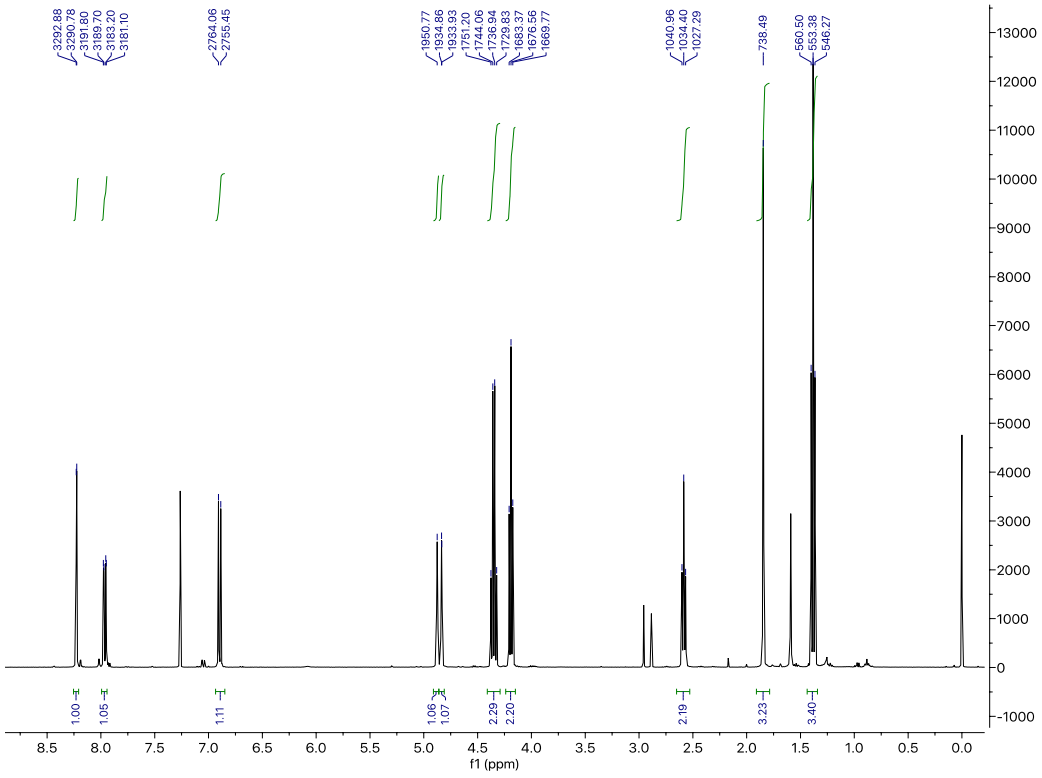
APPENDIX E: Spectral Data for OHet72

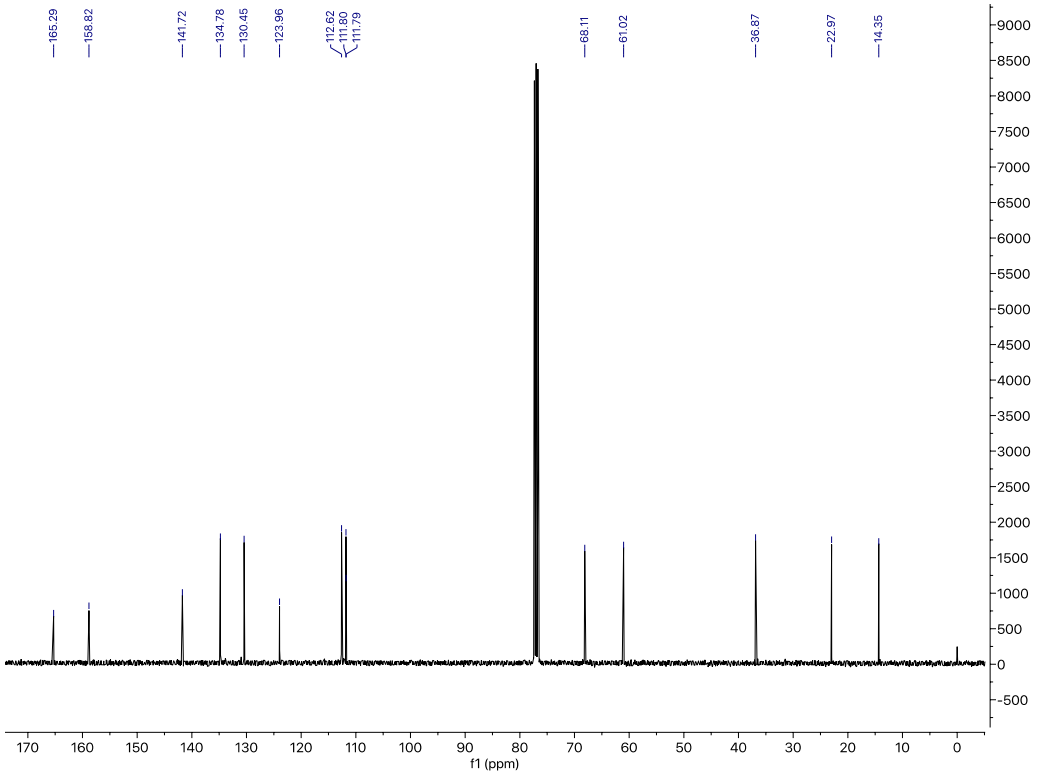
Ethyl 3-bromo-4-hydroxybenzoate (49)



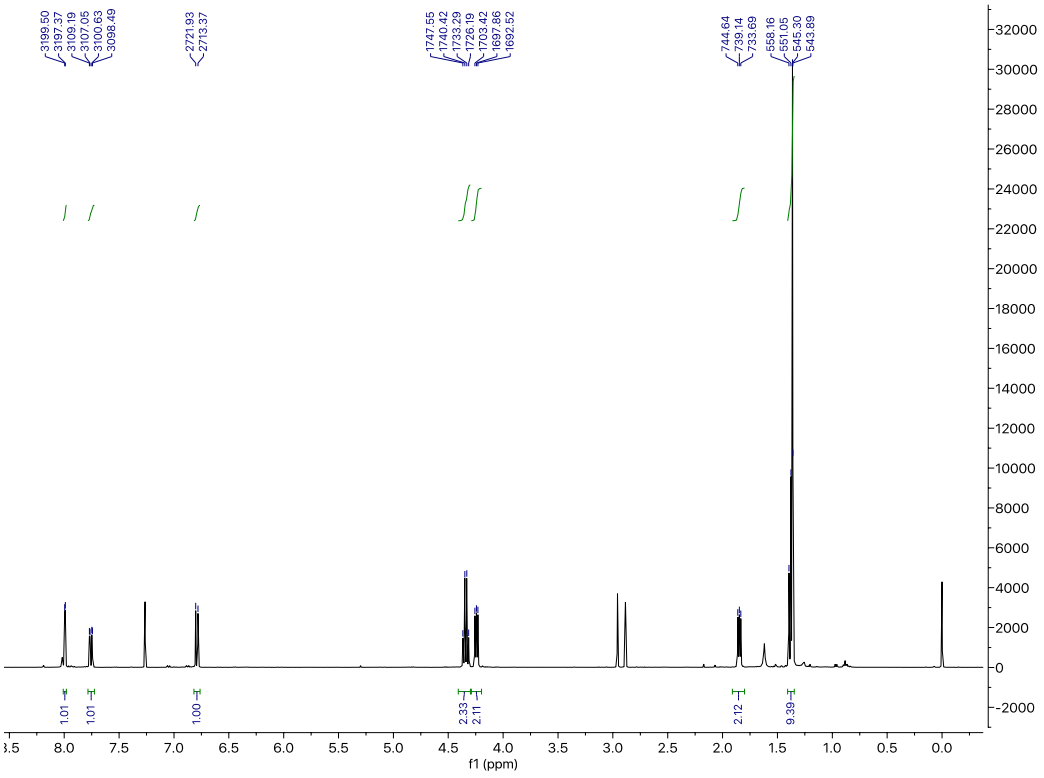


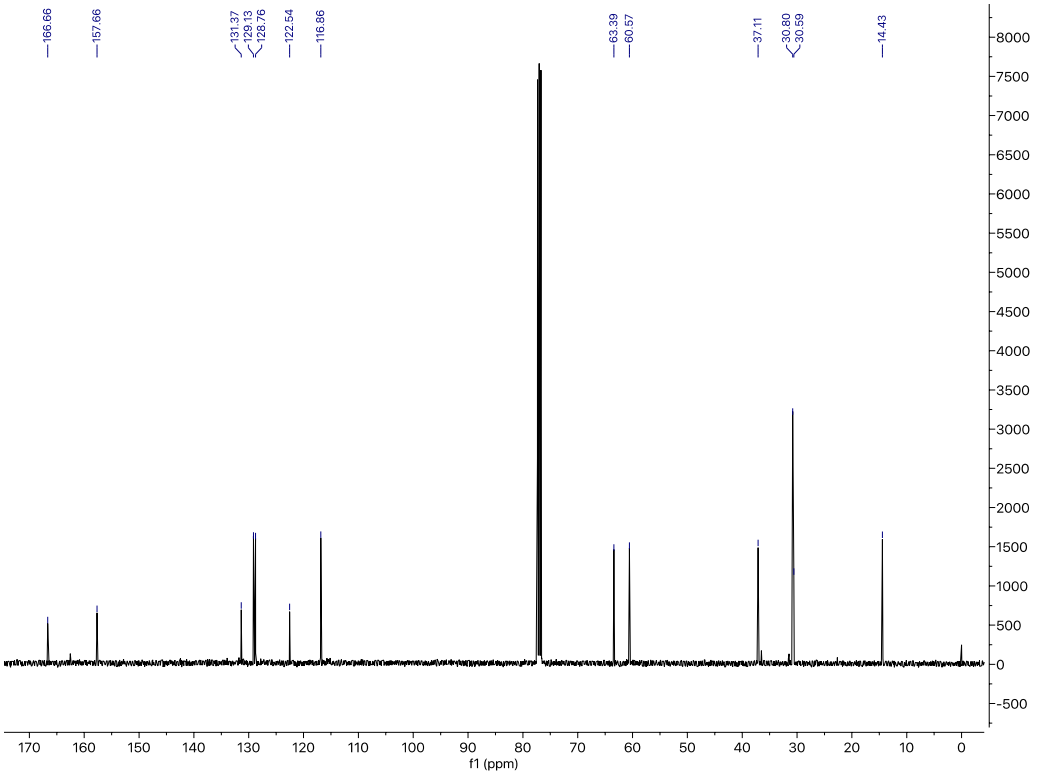
Ethyl 3-bromo-4-((3-methylbut-3-en-1-yl)oxy)benzoate (50)



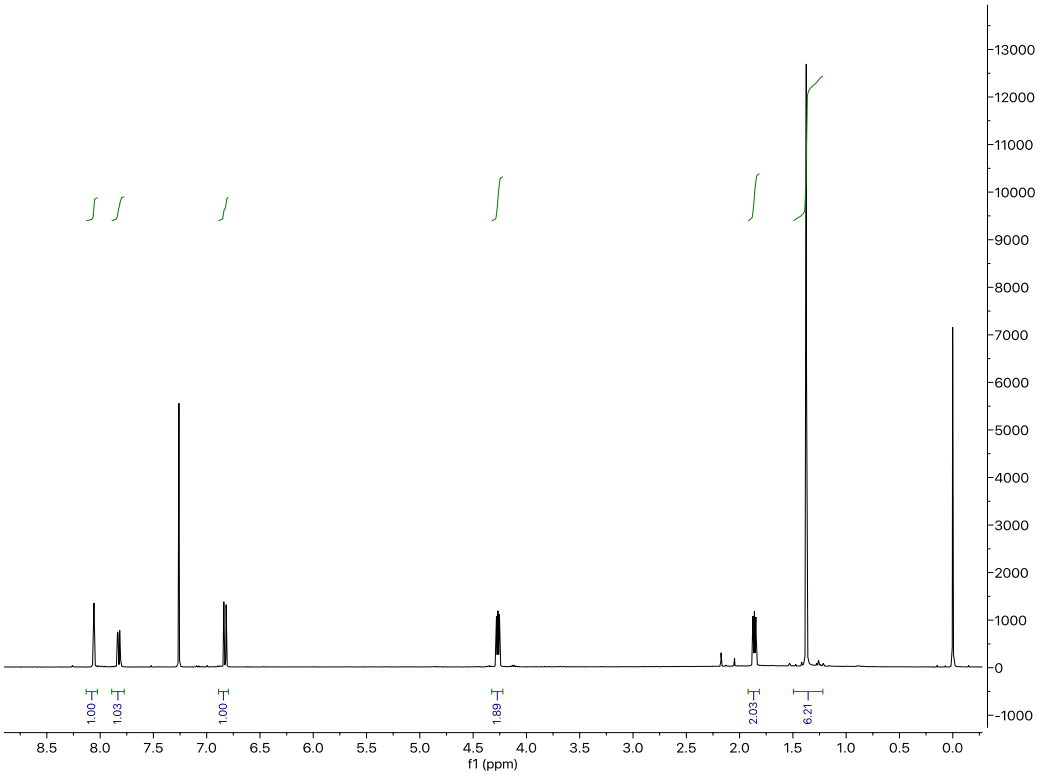


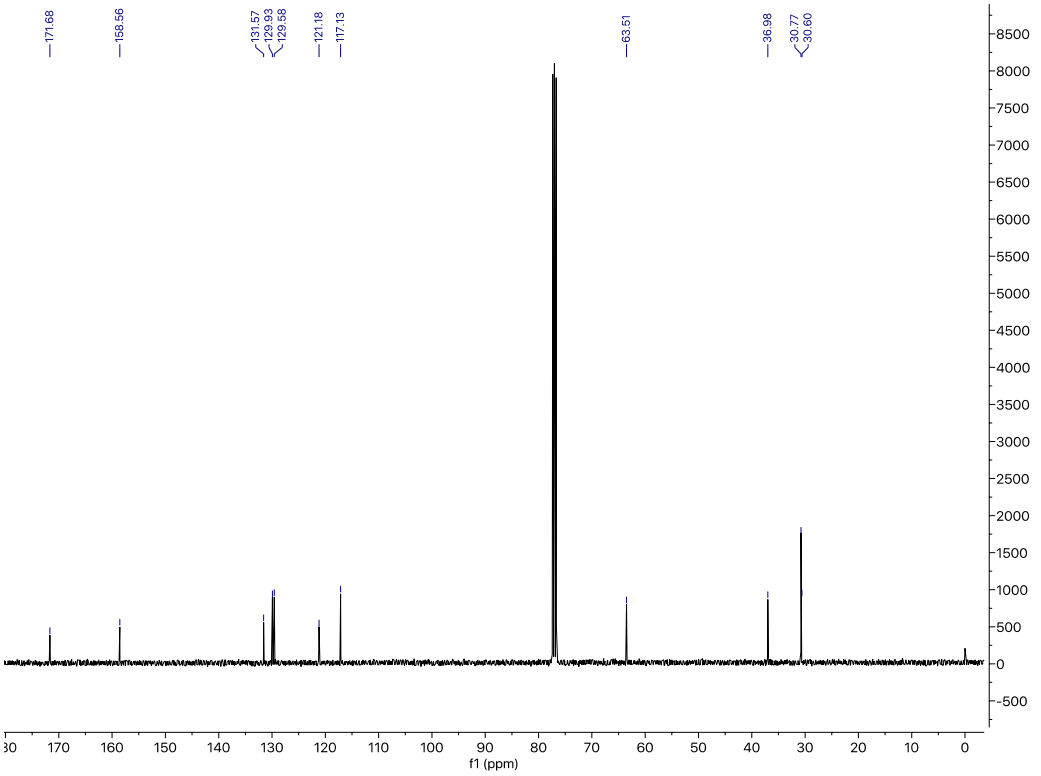
Ethyl 4,4-dimethylchromane-6-carboxylate (51)



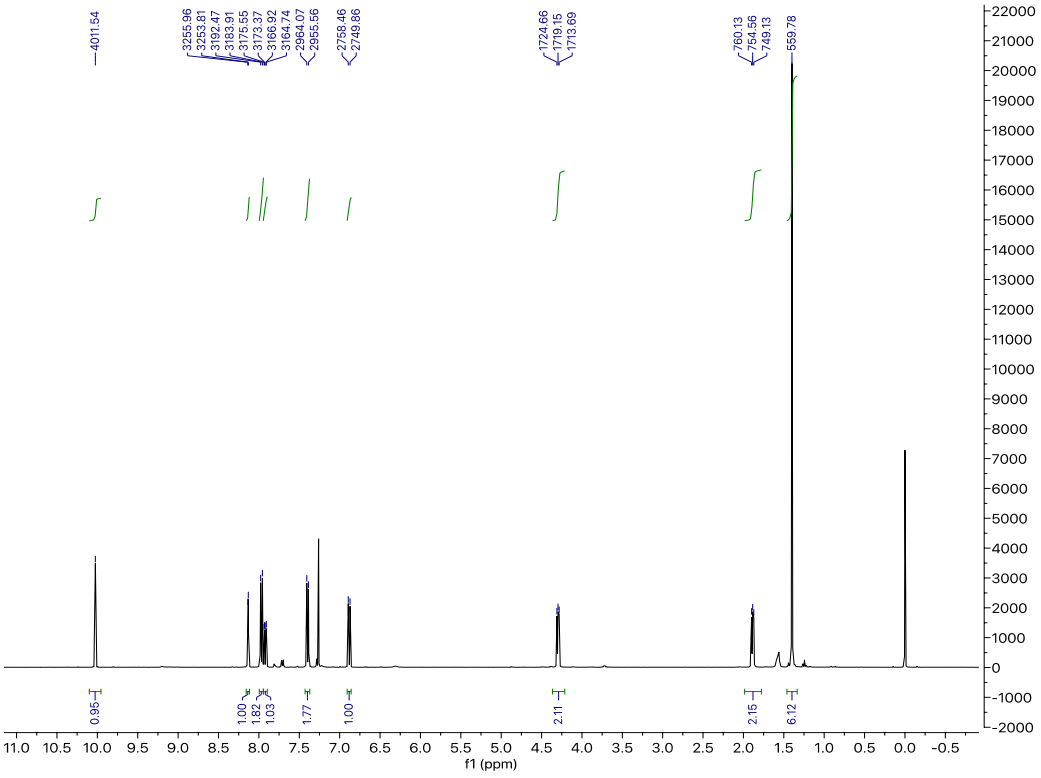


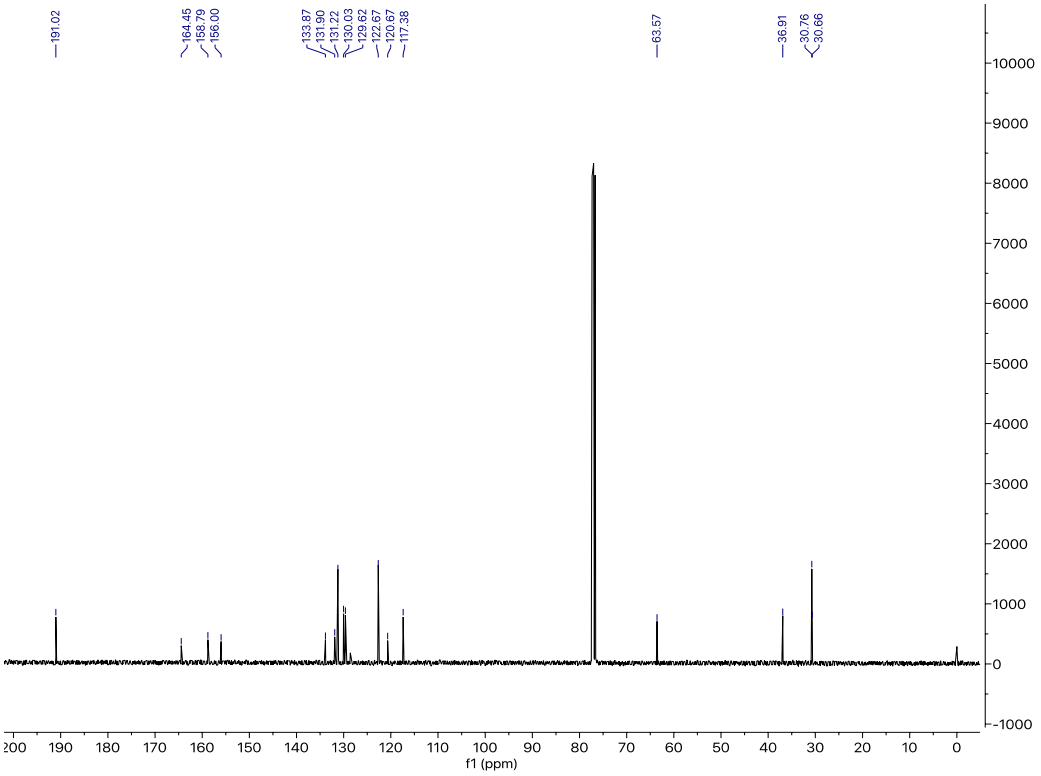
4,4-Dimethylchromane-6-carboxylic acid (52)



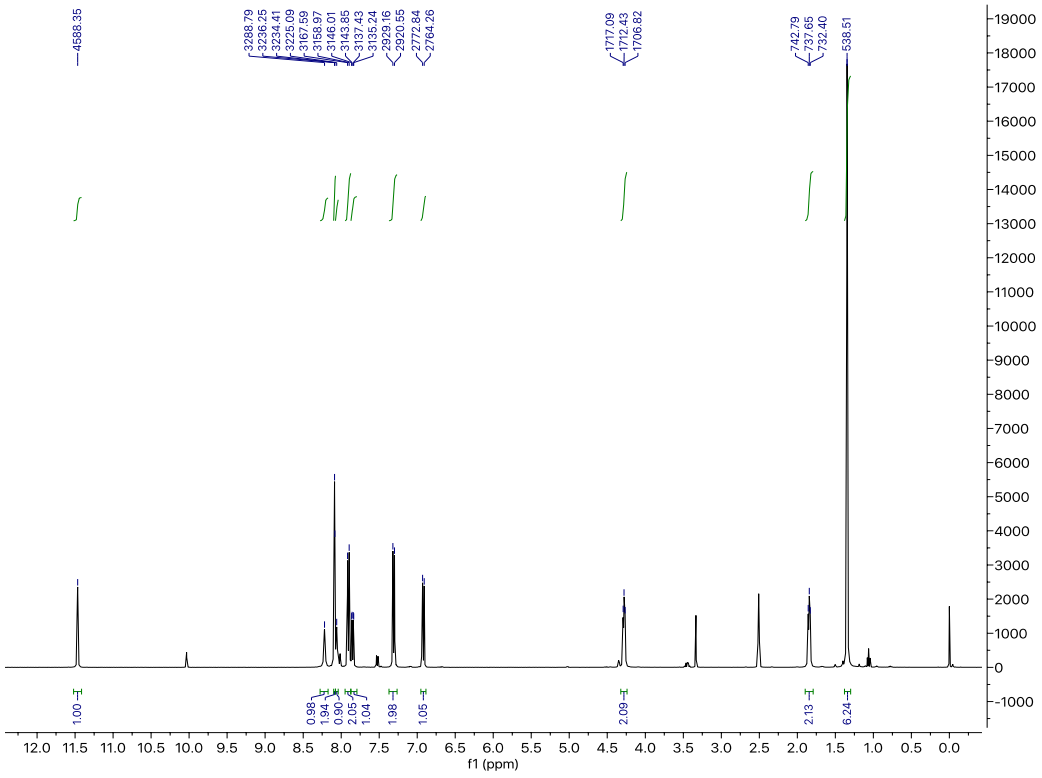


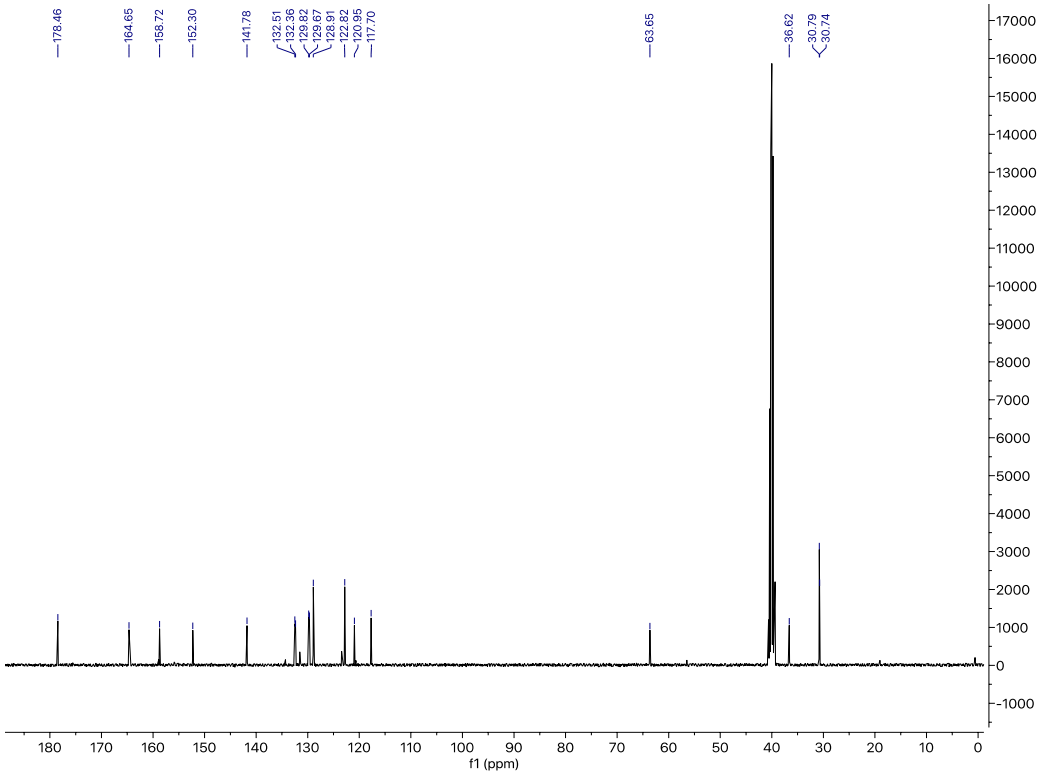
4-Formylphenyl 4,4-dimethylchromane-6-carboxylate (54)





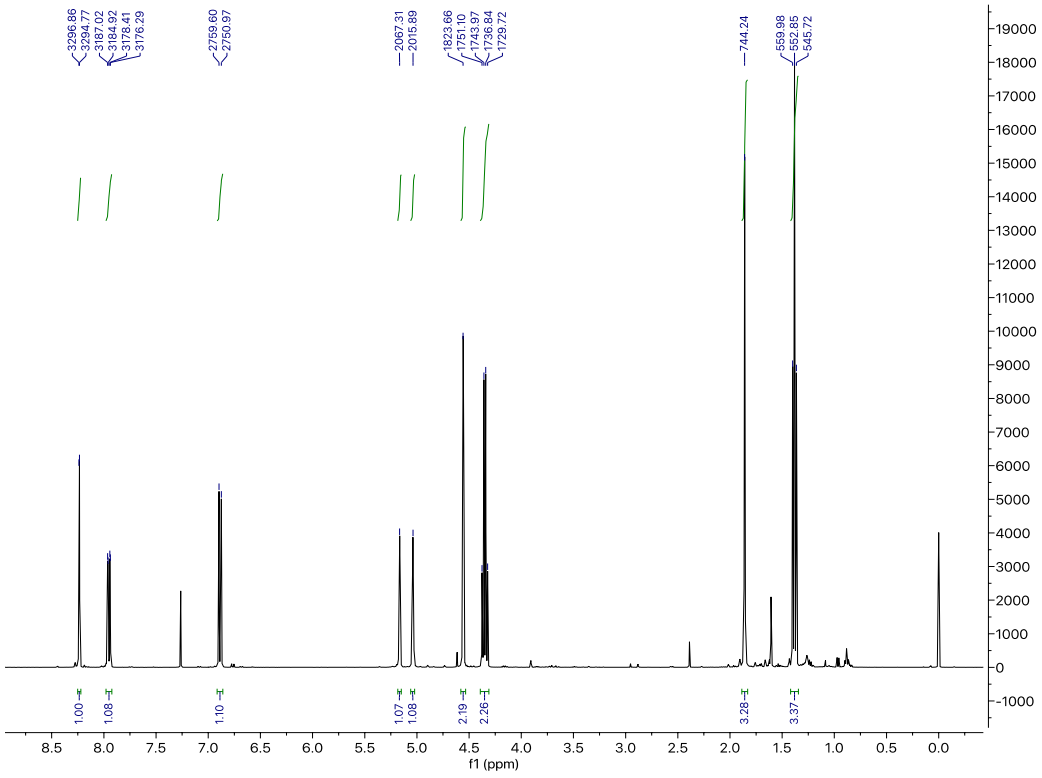
4-Formylphenyl 4,4-dimethylchromane-6-carboxylate thiosemicarbazone (16)

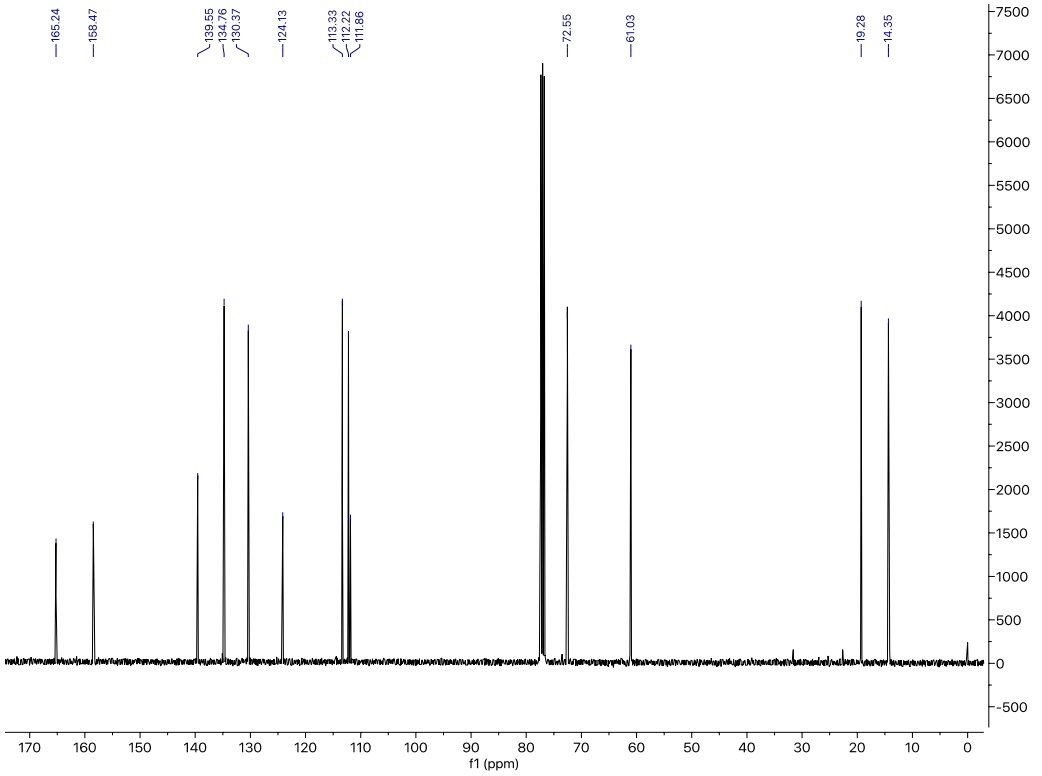




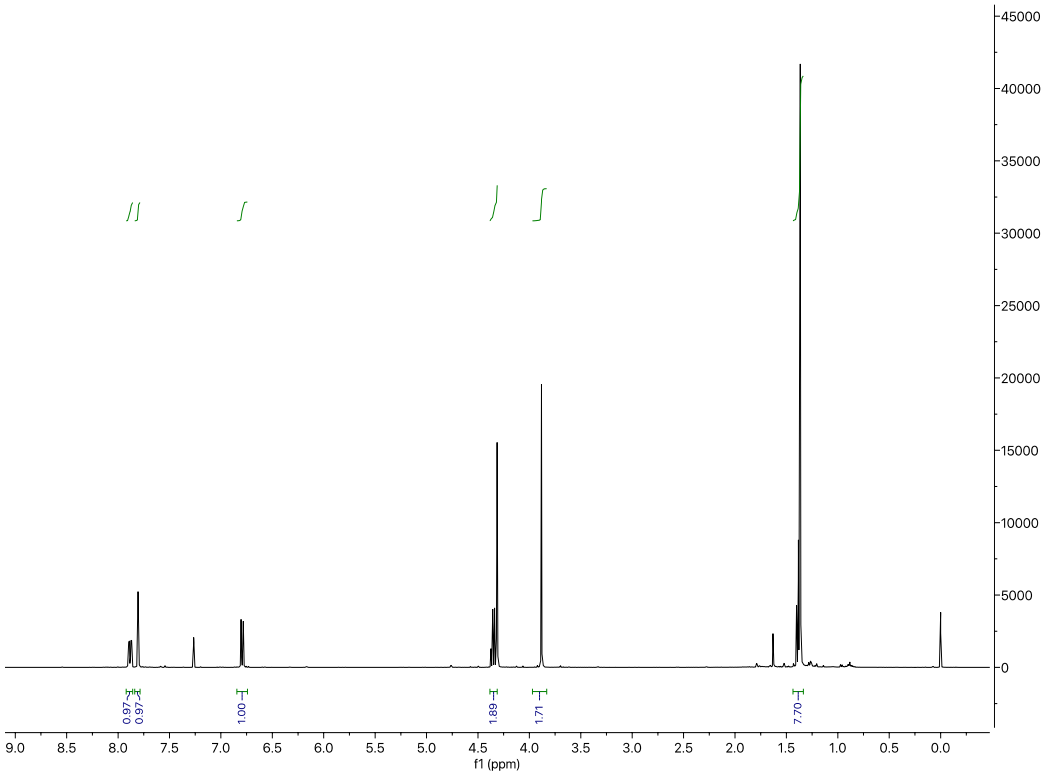
APPENDIX F: Spectral Data for a Dihydrofuran OHet72 Analog

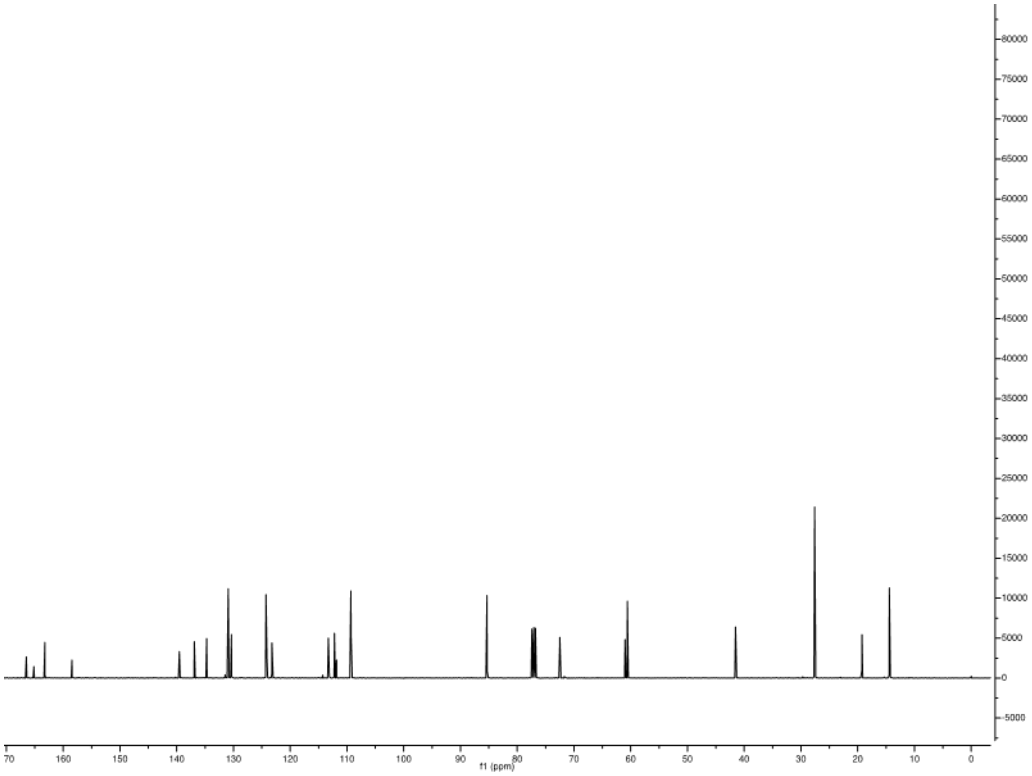
Ethyl 3-bromo-4-((2-methylallyl)oxy)benzoate (55)



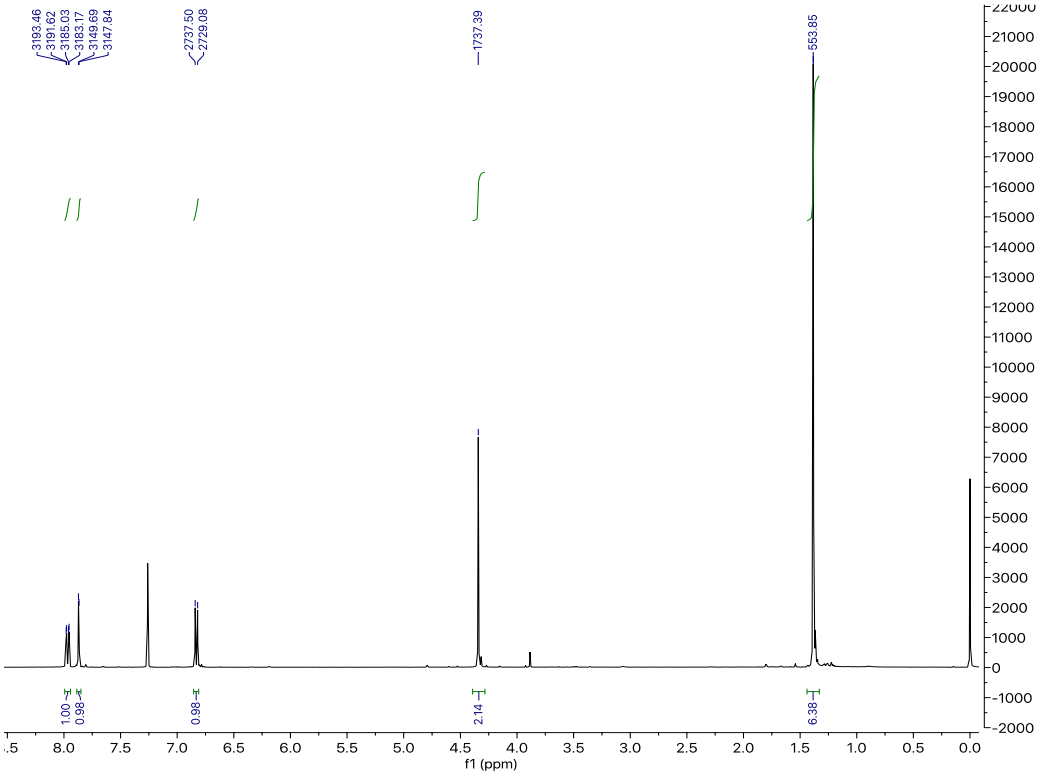


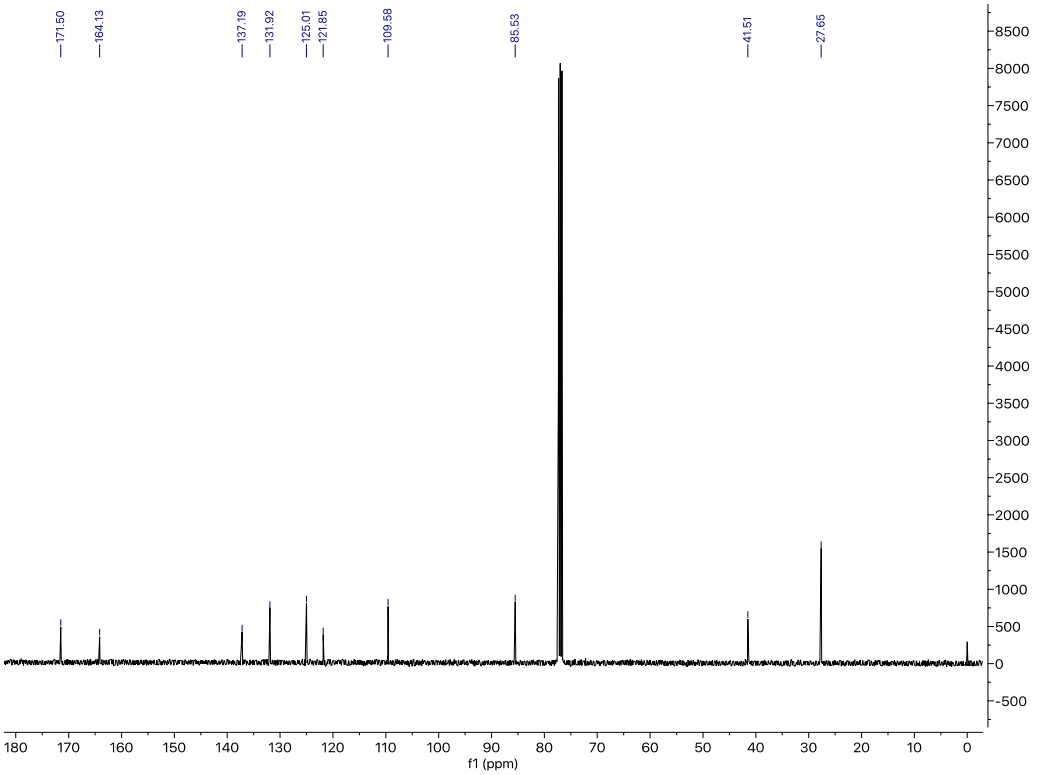
Ethyl 3,3-dimethyl-2,3-dihydrobenzofuran-5-carboxylate (56)



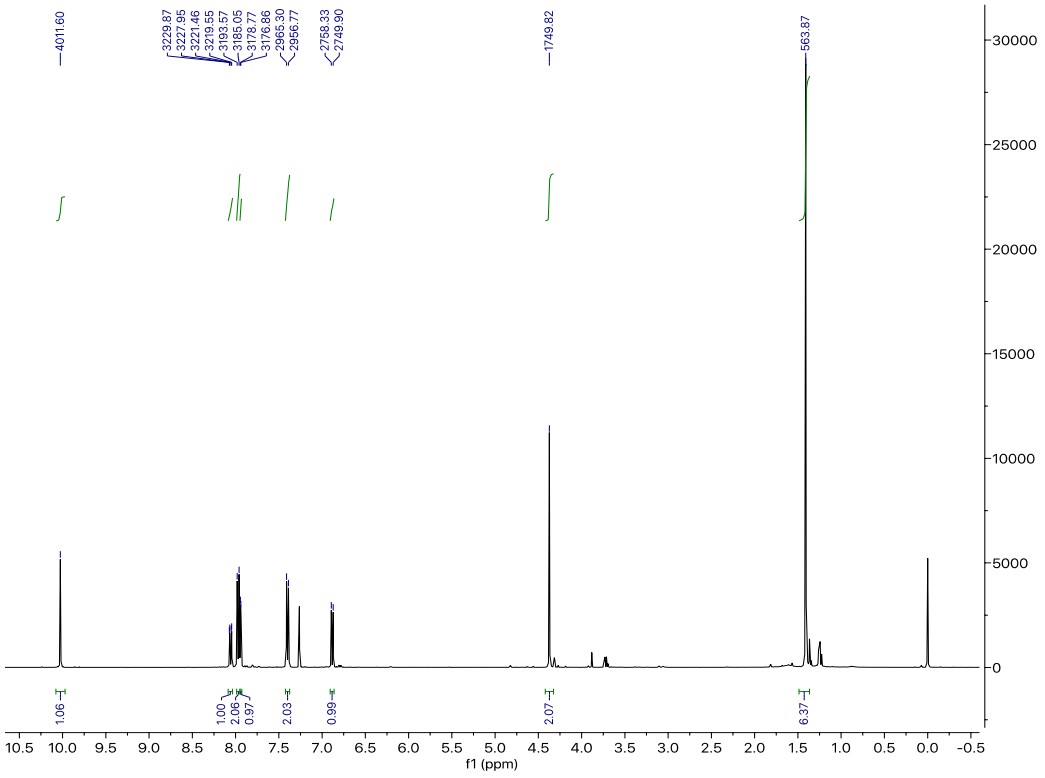


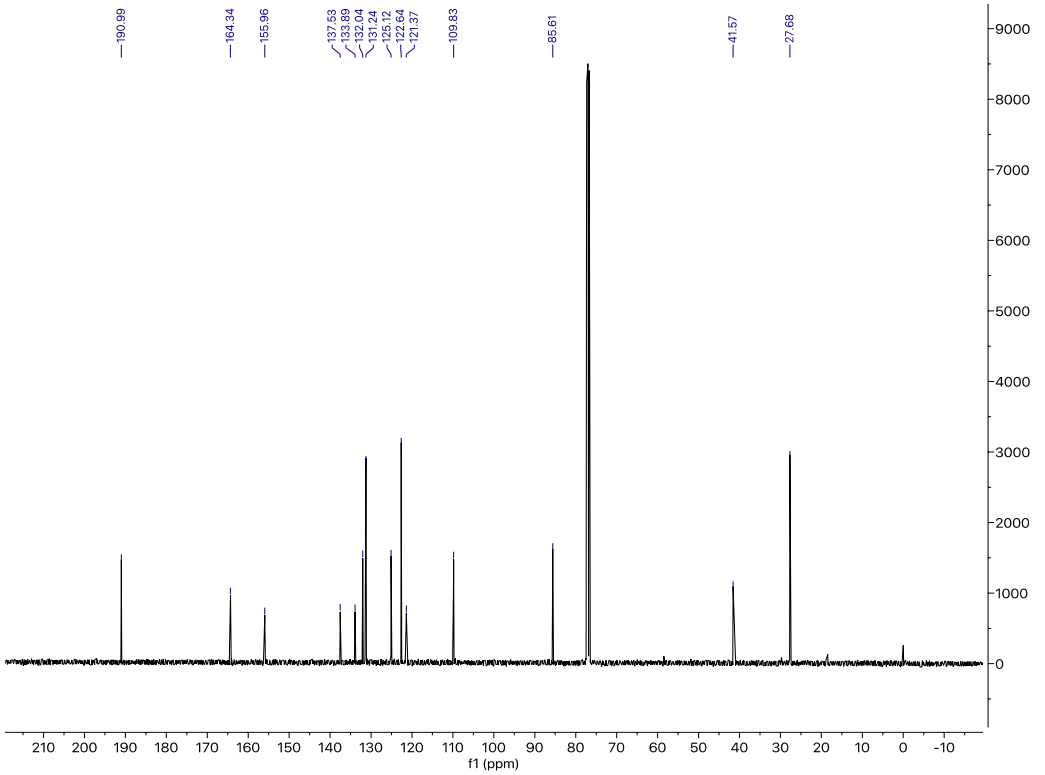
3,3-Dimethyl-2,3-dihydrobenzofuran-5-carboxylic acid (57)



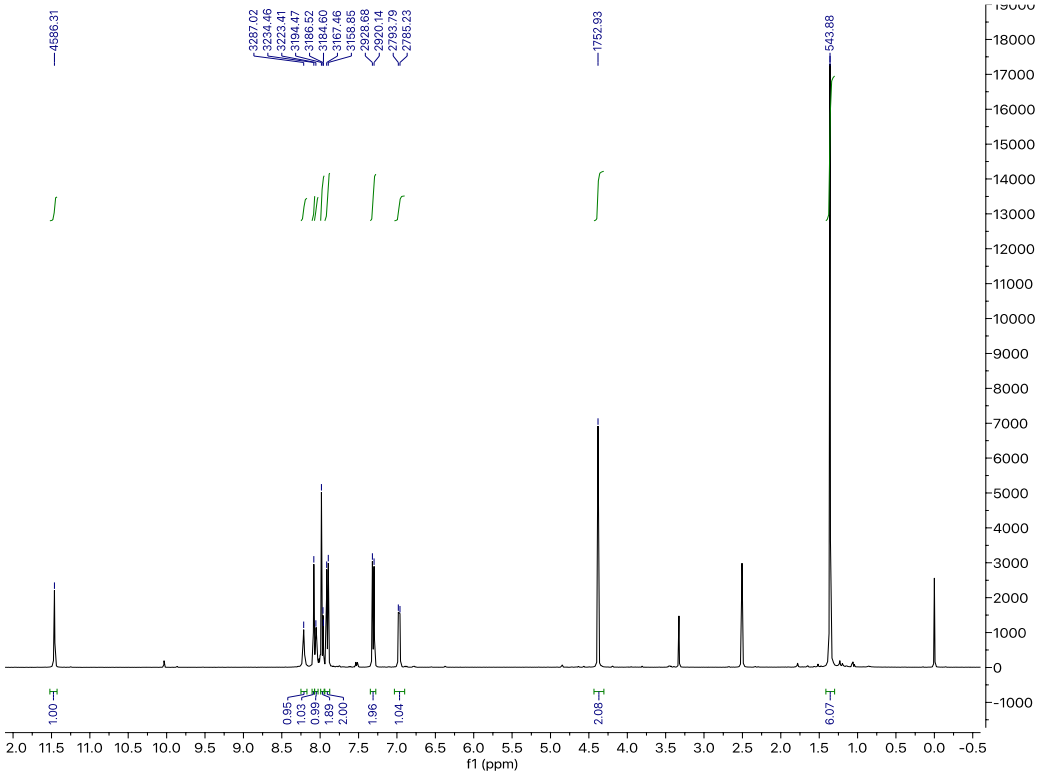


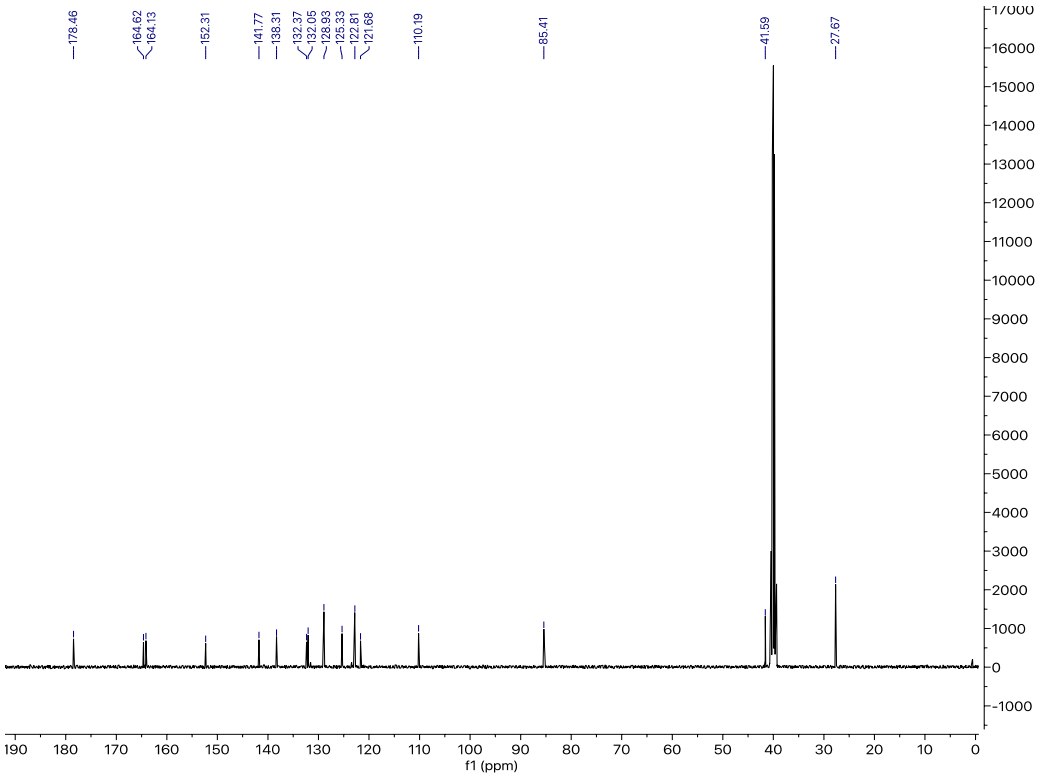
4-Formylphenyl 3,3-dimethyl-2,3-dihydrobenzofuran-5-carboxylate (58)





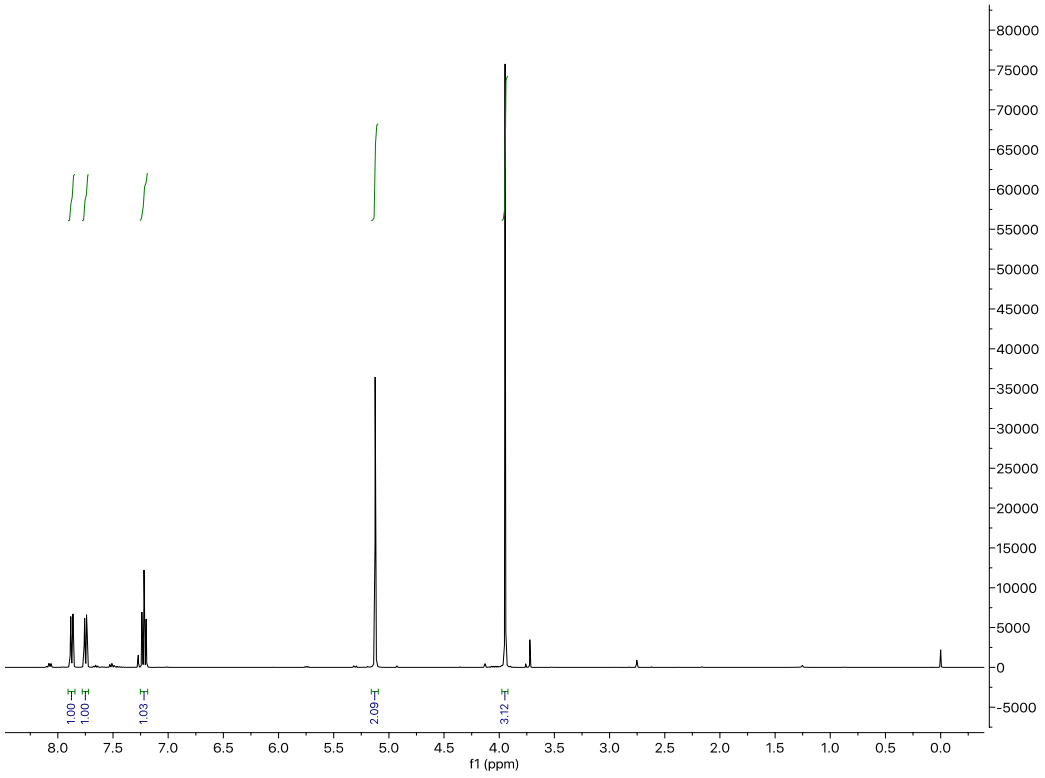
4-Formylphenyl 3,3-dimethyl-2,3-dihydrobenzofuran-5-carboxylate thiosemicarbazone (17)

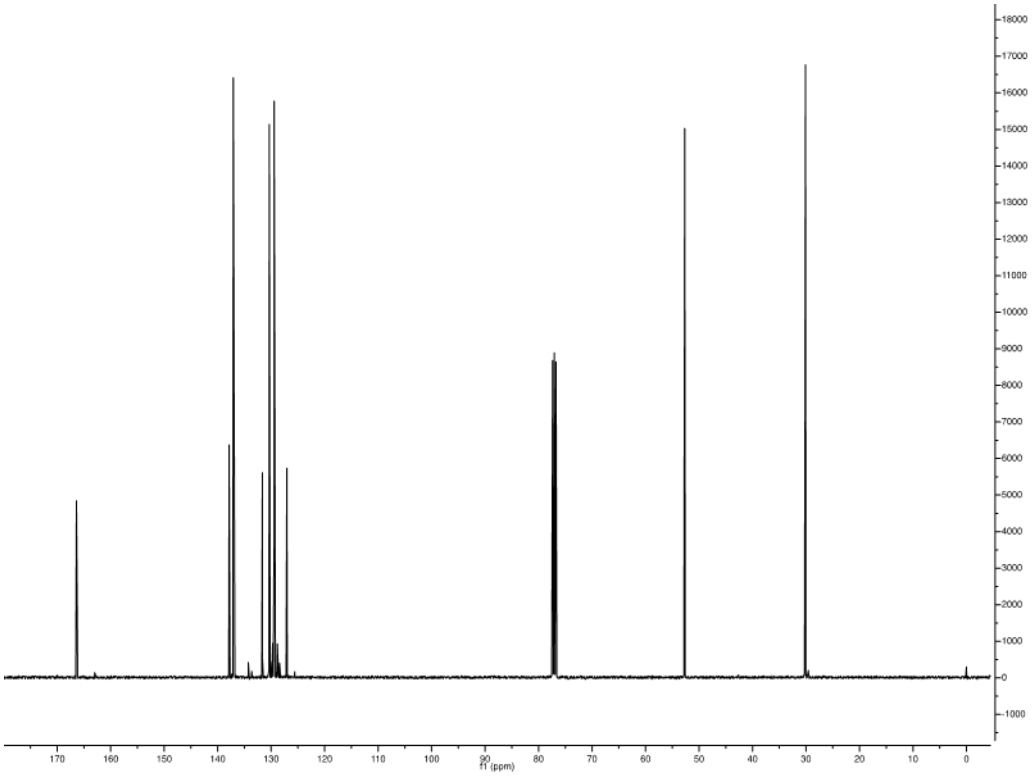




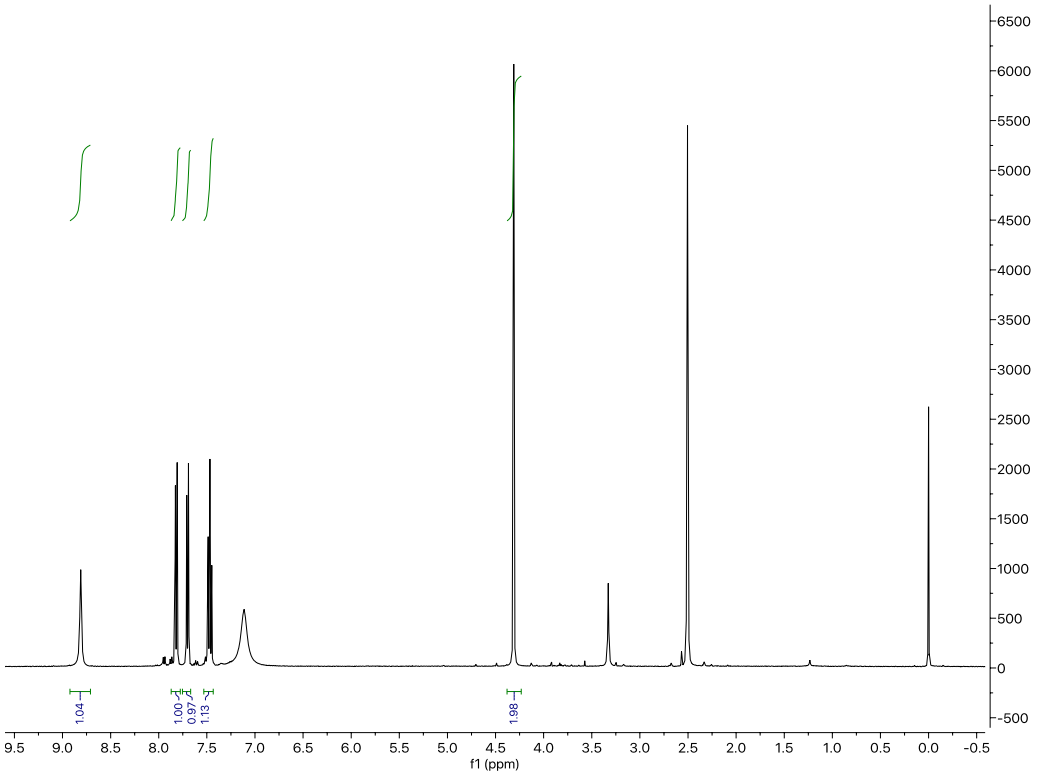
APPENDIX G: Spectral Data for a 4-Aminoisoindolin-1-one Antibiotic

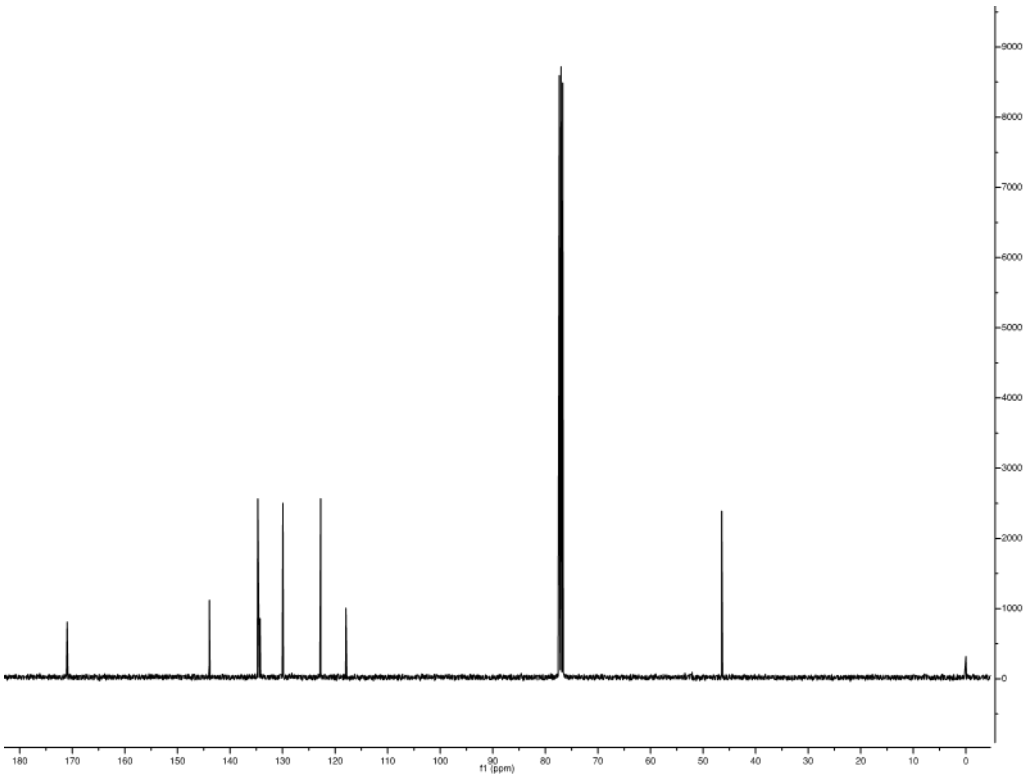
Methyl 3-bromo-2-(bromomethyl)benzoate (66)



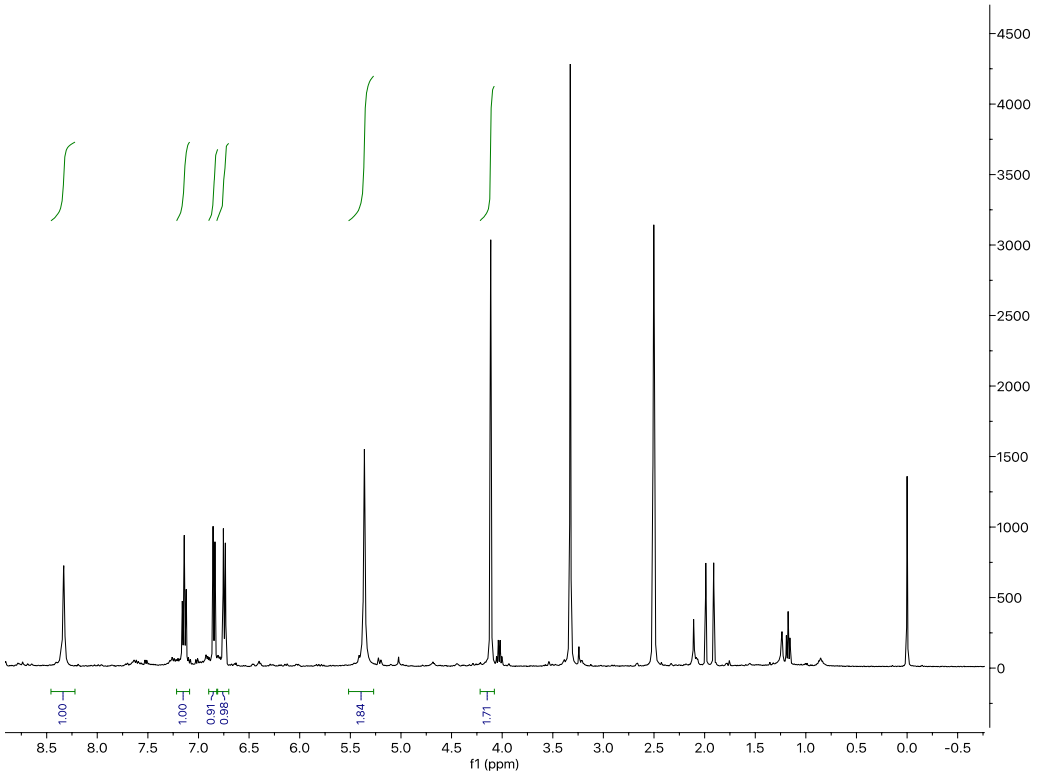


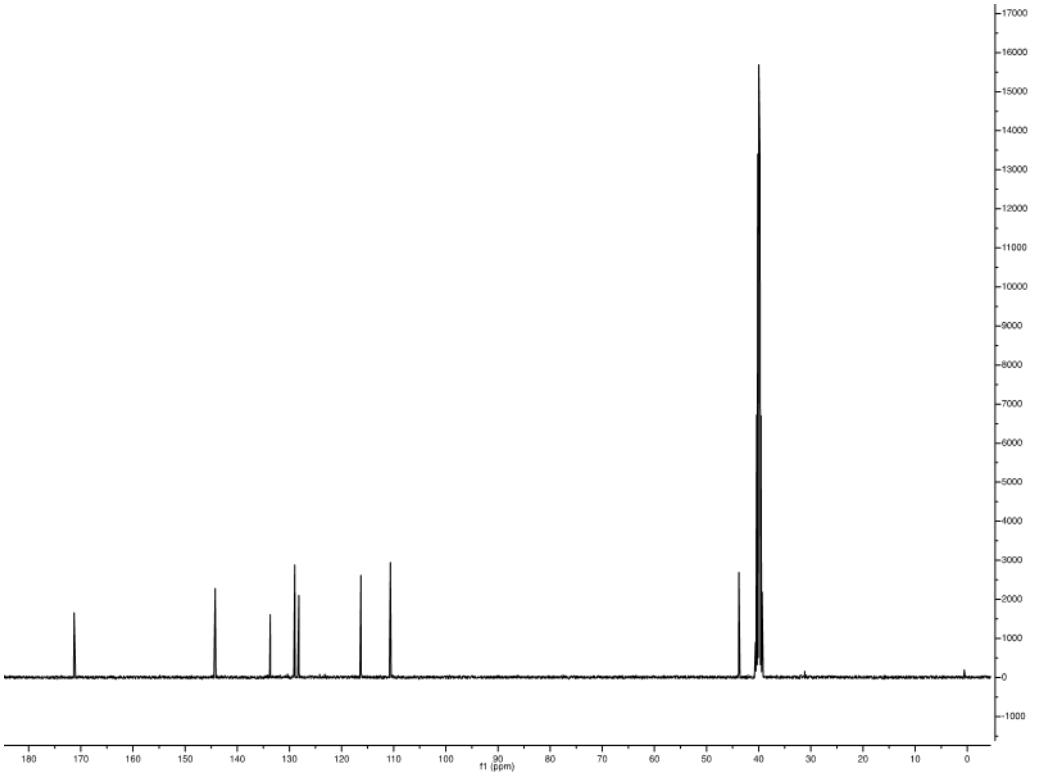
4-Bromoisoindolin-1-one (67)



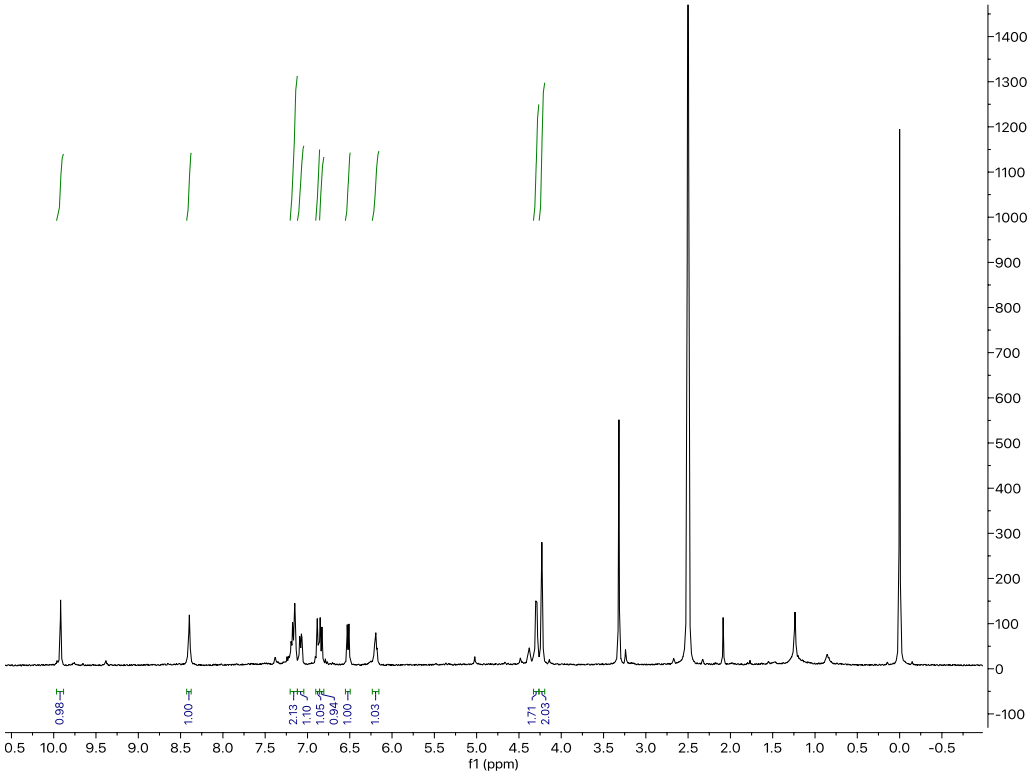


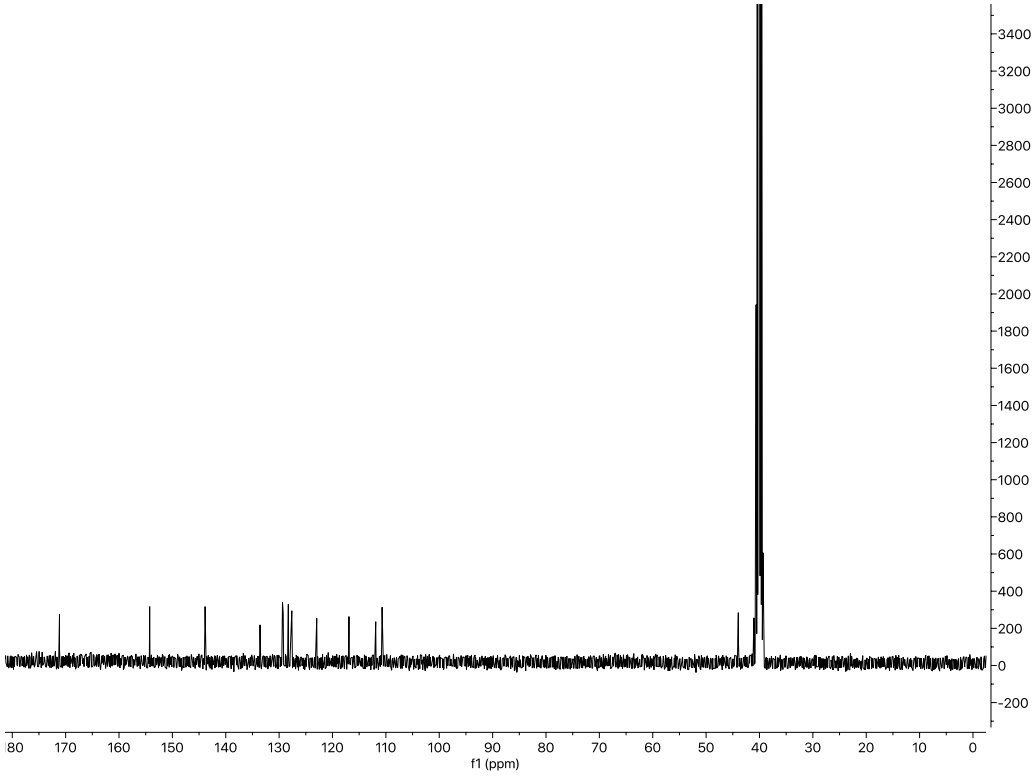
4-Aminoisoindolin-1-one (68)





4-((5-Chloro-2-hydroxybenzyl)amino)isoindolin-1-one (64)





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