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The acidic sulfonimidation of aryl–oxazolines and the electrophilic fluorination of aryl–oxazolines

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Written by
David Gutierrez
Bachelors of Science in Chemistry
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This thesis is written under the guidance of the Faculty Advisory Committee, and approved by all its members, has been accepted in partial fulfillment of the requirements for the

Master of Science in Chemistry
at the
University of San Francisco

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Abstract

Aryl oxazolines have been employed as directing groups for several different coupling reactions. In the exploration of using phenyl oxazoline as a directing group for electrophilic fluorination, it was discovered that acidic sulfonimide nucleophiles including dibenzenesulfonimide, o–benzenesulfonimide, dimethanesulfonimide, and N–(methylsulfonyl)–benzenesulfonamide are discovered to open a variety of alkyl, aryl and heteroaryl–2–oxazoline rings to provide the sulfonimidation products in refluxing 1,4–dioxane. The electron rich 2–oxazoline substrates worked well for the nucleophilic ring opening reactions while no reaction took place for the electron poor 2–oxazoline substrates. 4,4–dimethyl–2–phenyl–2–oxazoline was thus rationally designed inhibit sulfonimidation and to act as a removable ortho directing group for the palladium catalyzed C–H electrophilic fluorination of arenes. Using NFSI as the fluorinating agent, and a Pd(II), Ag(I) catalytic system, electrophilic C(sp2–H) ortho–fluorination took place on a variety of aryl substrates to afford the corresponding mono and di–fluorinated products. The oxazoline directing group was then hydrolyzed unmasking the carboxcylic acid moiety, demonstrating the synthetic utility of this reaction.

Chapter 1 The sulfomindation of aryl oxazolines via acidic nucleophilic addition of sulfonimides.

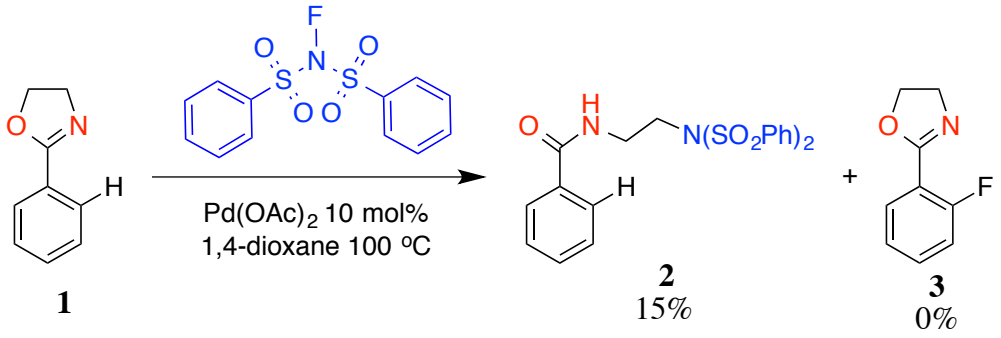
1.1 Introduction

Oxazolines are useful building blocks and ring opening reaction of oxazolines are well known.[1,2] For example, 2–substituted 1,3–oxazolines, have been used as starting monomers in the cationic polymerization reactions intended for making poly(ethylene imines) of various compositions and molecular weights.[3,4] Another approach is through nucleophilic ring opening of oxazolines such as 2–phenyl–2–oxazoline to give products. A variety of nucleophiles have been applied in this type of transformation. Thiophenols[5] and thiols[6] have been used as S–nucleophiles and phenols[7] as O–nucleophiles, C–nucleophiles in the form of stabilized carbanions have been also used to open oxazoline rings with the aid of methyl triflate.[8] Halides as nucleophiles generally react with oxazolines in the form of TMS–X.[9] Other nucleophiles that have been used to open oxazoline rings also include selenium[10] and tellurium[11] containing nucleophiles. More interestingly, N–nucleophiles have found synthetic utility in opening oxazoline rings. For instance, imidazole was used to open the oxazoline ring,[12] as was azide in form of $TMSN_3$.[13] In the presence of a Brønsted–Lowry or Lewis acid, amines such as diphenylamine bring about a nucleophilic ring opening of 2–ethyl–2–oxazoline at high temperature offering a synthesis of unsymmetrically substituted ethylenediamines.[14]

In the development of ortho directed palladium–catalyzed electrophilic fluorination using dimethyl oxazoline as DG it was discovered that N–fluorobenzenesulfonimide (NFSI) is able to act as an acidic nucleophile and ring open unsubsitituted oxazolines. NFSI a typical fluorinating agent, up to our knowledge, has not been previously reported in the literature as a nucleophile. The two electron with drawing sulfonyl groups render the nitrogen atom electron deficient and typically non–nucleophilic.

N–fluorobenzenesulfonimide (NFSI) is an electrophilic fluorinating agent that permits the incorporation of fluorine into neutral molecules as well as nucleophilic substrates ranging in strength from very reactive organometallic species to highly stabilized malonate anions. The use of NFSI does not involve any special equipment or techniques in handling, and it does not attack glass like most fluoride–containing reagents.[15]

In the process of pursuing our on going interest in fluorination via C–H activation, it was discovered that N–fluorobenzenesulfonimide (NFSI) was able to open the oxazoline ring on **1** to afford sulfonimide **2** in 15% yield (Scheme1). The importance of sulfonimides as important bioisosteres of carboxylic acids in medicinal chemistry,[16-19] led to the exploration of the scope and limitations of this unique ring–opening sulfonimidation reaction.

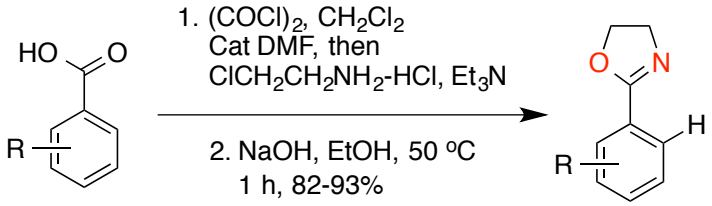


1 **2** 15% **3** 0%

Scheme 1: In the process of investigating electrophilic fluorination, no fluorination occurred. Instead ring opening of oxazoline was the predominate product

1.2 Results and discussion

The acidic dibenzenesulfonimide [$HN(SO_2Ph)_2$] was able to serve as a nucleophile to convert 2–phenyl–2–oxazoline into sulfonimide in 93% yield. Different oxazoline substrates were investigated. The oxazoline derivatives were prepared via a 2–step sequence consisting of amide formation from carboxylic acid chloride and 2–chloroethylamine•HCl,[20] followed by ring closure of the resulting amido–chloride with the aid of NaOH (Scheme 2).[21]



Scheme 2: Synthesis of aryl oxazolines from carboxylic acids via a 2–step sequence.

Initially the solvent effect for transformation of **1** to **5** was screened. When the reaction was heated in polar solvents including DMF and DMSO no reaction was observed even at 150 °C for a prolonged period of time. The reaction took place in solvents such as EtOH, *n*–BuOH and isopentanol. The reaction did stall at approximately 70% conversion. In ethereal solvents the reaction went to completion. Solvents such as methyl *t*–butyl ether (MTBE), THF, and 1,4–dioxane all gave complete conversion to the desired product. Because 1,4–dioxane had the highest boiling point, it was selected as the solvent of choice.

Observations of the solvent on the effect of the addition reaction could be attributed to the solvation effect of the nucleophile. Polar solvents such as DMF and DMSO can solvate the nucleophilic sulfonimide and dispersing the negative charge on the nitrogen throughout the molecule and thus lower the energy of the nucleophile. However ethereal solvents such as 1,4–dioxane can have an opposite effect. The lower dielectric constant of the ethereal solvents can presumably cause the negative charge to reside largely on the nitrogen of the imide. This lack of electron distribution causes the nucleophile to be

"harder" and more reactive than in polar solvents.

Stark differences were observed for electron rich and electron poor 2–oxazoline substituted aryls (Table 1). The reaction between 2–phenyl–2–oxazoline **1** and dibenzenesulfonimide in refluxing 1,4–dioxane gave 93% yield and the same reaction for 2 (p–methoxyphenyl)–2–oxazoline **5** gave 72%. 2–ethyl–2–oxazoline **3** behaved similarly to 2–phenyl–2–oxazoline, **1**, and all the reactions were complete within 2 hours. Substrates containing The electron rich hetero–aryls thiophene **7**, **9**, and furan **11**, and **13** reacted smoothly with $HN(SO_2Ph)_2$. However, this methodology did not work for electron poor substrates. For example, no reaction was observed when 2–(4–nitrophenyl)–2–oxazoline **15** and $HN(SO_2Ph)_2$ were heated together. The same phenomenon was observed for another electron–poor substrate 2–(pyridin–4–yl)–2–oxazoline **17**, derived from isonicotinic acid. The experimental results of these substituted aryl oxazolines were used in establishing a mechanism for this addition reaction.

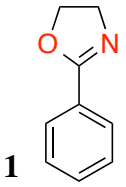
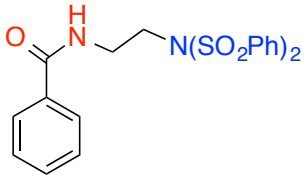
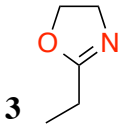
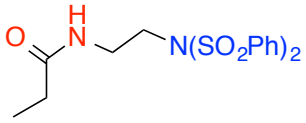
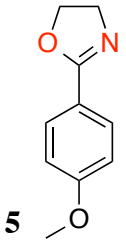
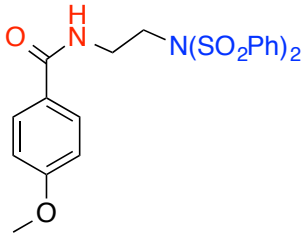
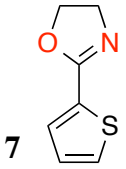
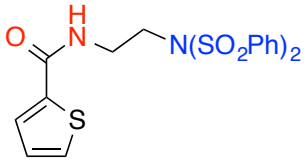
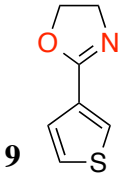
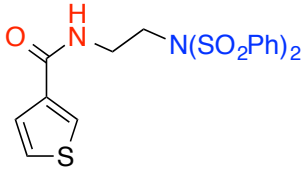
Substrates	Products	Reaction Time (min)	Yield
 **1**	 **2**	45	93
 **3**	 **4**	30	75
 **5**	 **6**	90	72
 **7**	 **8**	120	93
 **9**	 **10**	120	94

Table 1: Sulfonimidation of substituted oxazolines via nucleophilic ring opening with dibenzenesulfonimide

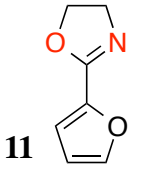
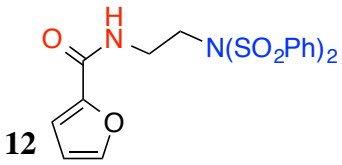
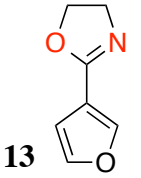
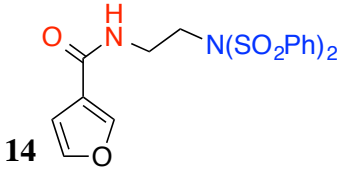
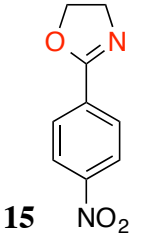
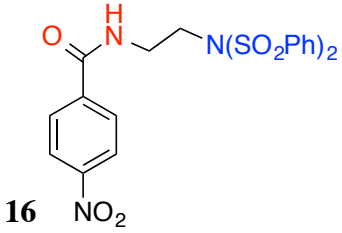
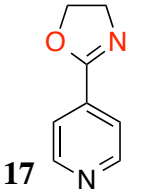
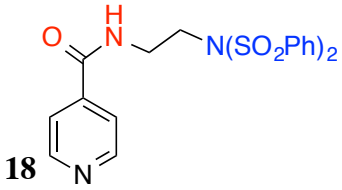
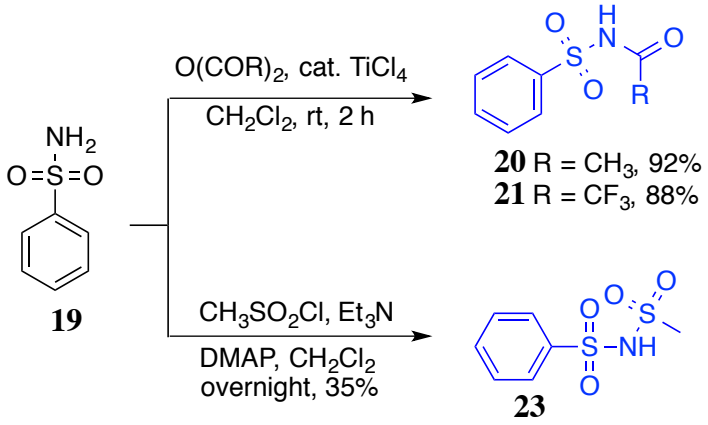
Substrates	Products	Reaction Time (min)	Yield
 **11**	 **12**	120	73
 **13**	 **14**	120	73
 **15**	 **16**	360	0
 **17**	 **18**	360	0

Table1 cont'd: Sulfonimidation of substituted oxazolines via nucleophilic ring opening with dibenzenesulfonimide

Before the mechanism could be further elucidated additional imide nucleophiles for this ring opening reaction were explored. The N–(phenylsulfonyl)acetamide **20** was prepared by treating a suspension of benzenesulfonamide **19** in CH_2Cl_2 with acetic anhydride in the presence of a catalytic amount of $TiCl_4$.[22] 2,2,2–Trifluoro–N–(phenylsulfonyl)acetamide **21** was synthesized in the same manner using trifluoroacetic anhydride.[22] N–(methylsulfonyl)benzenesulfonamide **23** was assembled in 35% yield by the reaction between benzenesulfonamide and methanesulfonyl chloride in the presence of Et_3N and a catalytic amount of DMAP (Scheme 3). Unfortunately, the resulting ring opened products, from these nucleophiles, were not stable on silica gel and less than 27% of products were able to be isolated.



Scheme 3: Preparation of additional sulfonimide nucleophiles

The reaction conditions for the preparation of **23** were surprisingly the only method to prepare this compound. However the cyclic arylsulfonimide dimethanesulfonimide and mixed sulfonimide all worked well in the ring opening reaction. Further, both nucleophiles dimethanesulfonimide and mixed sulfonimide worked on alkyl, aryl and hetero–aryloxazolines to produce the ring opening products with yields ranging from 56% to 84% (Table 2). However other imides such as phthalimide and benzenesulfonamide did not yield any ring opened product.

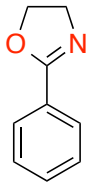
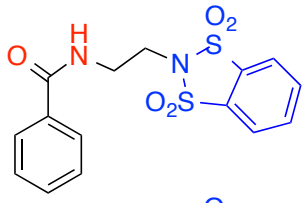
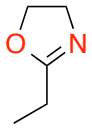
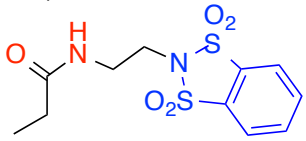
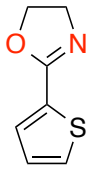
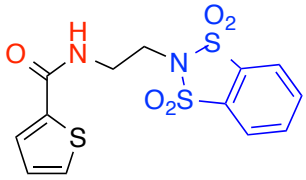
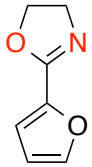
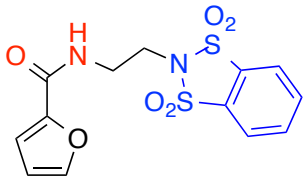
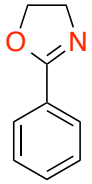
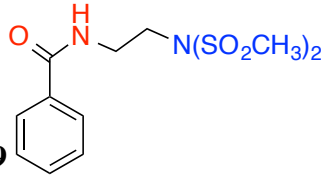
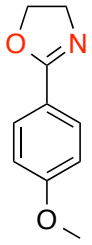
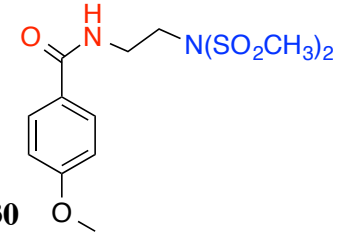
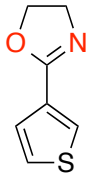
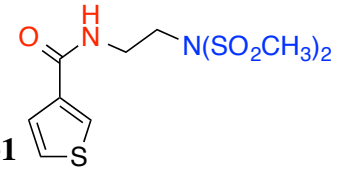
Substrates	Products	Reaction Time (min)	Yield
1 	**25** 	45	95
3 	**26** 	30	89
7 	**27** 	120	95
11 	**28** 	120	80
1 	**29** 	120	56
5 	**30** 	100	62
9 	**31** 	95	70

Table 2: Sulfonimidation of substituted oxazolines via nucleophilic ring opening reaction with additional sulfonimide nucleophiles

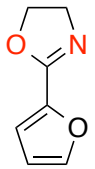
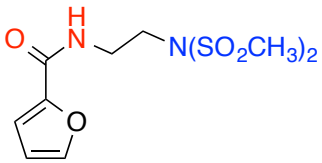
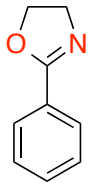
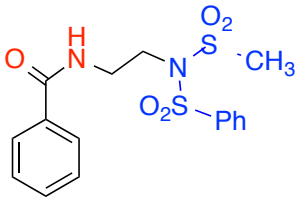
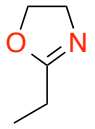
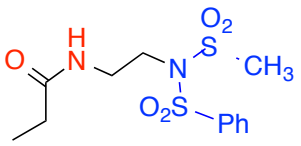
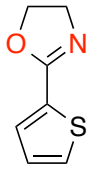
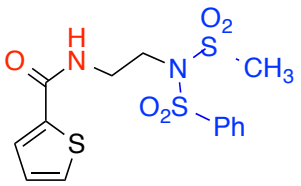
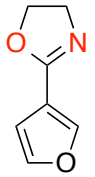
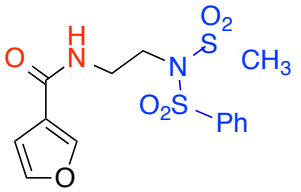
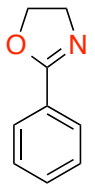
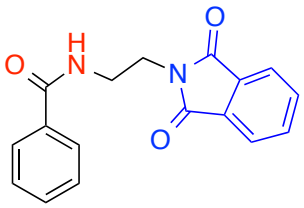
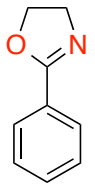
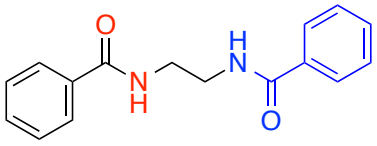
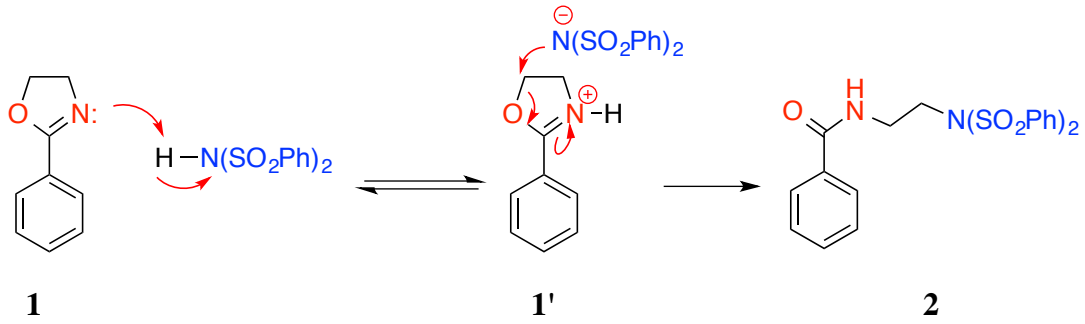
Substrates	Products	Reaction Time (min)	Yield
11 	**32** 	85	61
1 	**33** 	90	84
3 	**34** 	75	78
7 	**35** 	60	70
13 	**36** 	50	59
1 	**37** 	360	0
1 	**38** 	360	0

Table 2 cont'd: Sulfonimidation of substituted oxazolines via nucleophilic ring opening reaction with additional sulfonimide nucleophiles.

The experimental results indicate that the reaction is driven by the acidity of the substituted oxazoline and the acidity of the reactive sulfonimide. 2–Phenyl–2–oxazoline has a pKa of 4.4.[23] Electron donating substituents donate electrons to the oxazoline ring, increasing the pKa and promoting

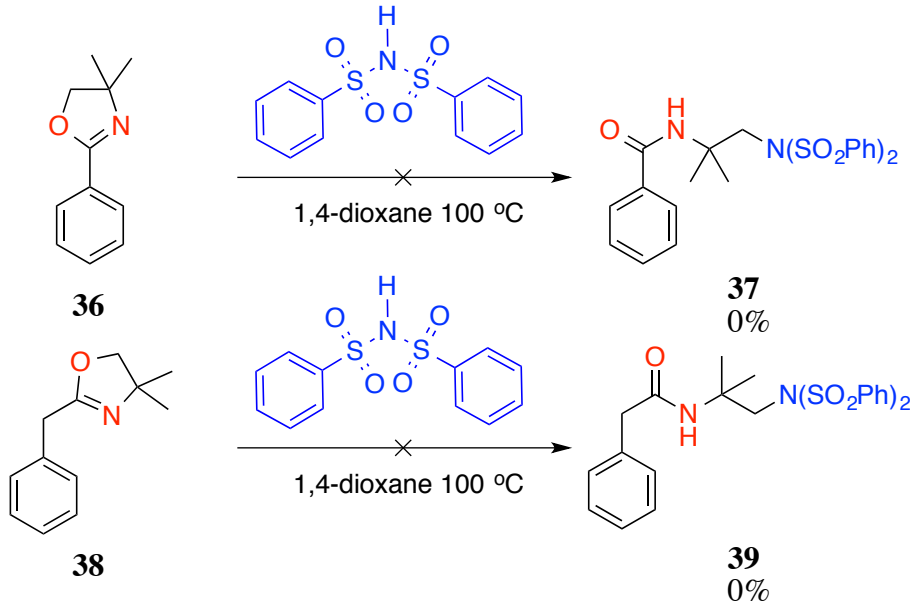
protonation.[23] On the other hand, electron accepting 2–substituents withdraw electrons from the oxazoline ring so that the nitrogen is no longer as basic as 2–phenyl–2–oxazoline and the reaction does not proceed. The two powerful electron withdrawing phenylsulfonyl groups, in NHSI render the NH proton on the molecule exceptionally acidic with a pKa value of 1.45, approximately as strong as phosphoric acid.[24] As a result, dibenzenesulfonimide is acidic enough to protonate the nitrogen atom on the oxazoline **1'** (Scheme 4). Indeed, moved to the baseline on TLC when $HN(SO_2Ph)_2$ were stirred in 1,4 dioxane at room temperature. The intermediacy of protonated oxazoline accounts for the disparity between electron rich and electron poor oxazolines.



Scheme 4: Proposed reaction mechanism

To further confirm the intermediacy of protonated oxazoline, the addition of 1 equivalent of sodium hydride to the reaction did not yield any ring–opened product. Indicating that the protonation of the oxazoline nitrogen is essential for the reaction. This also indicates a specific acid catalysis. The $(PhSO_2)_2N^-$ anion[25] can then serve as a nucleophile to open the oxazoline ring in an SN2 fashion to furnish the imidation product **2**. It is suspected that a nucleophile with similar acidity to $HN(SO_2Ph)_2$ would be more amenable to such transformations. Nucleophiles such as phthalimide and benzenesulfonamide have pKa's of 8.3 and 10.1 respectively, and are too basic to furnish intermediate. However the cyclicarylsulfonimide dimethanesulfonimide and mixed sulfonimide presumably have acidities near the pKa of NHSI. The relatively moderate yields for reactions involving alkylsulfonimides can possibly be attributed to alkylsulfonimides being less acidic than aryl–sulfonimides.

Sterically hindered oxazolines did not react in attempted ring openings using this methodology. This is most likely due to the fact that steric hindrance of the a neopentyl carbon cannot accommodate the bulky nucleophile, $(PhSO_2)_2N^-$ (Scheme 5).



Scheme 5: Unreactive sterically hindered aryl oxazolines.

Many efforts were made to react the sulfonimide products with other nucleophiles such as azide, but these invariably produced the ring closed oxazoline, the very starting materials to make those linear amide sulfonimides. This is not completely surprising because once the NH bond on the amide encounters even weak basic conditions, the intramolecular ring–closure prevails because it is very much more kinetically favored than the intermolecular SN2 substitution, especially considering that sulfonimides are such good leaving groups. Therefore, the synthetic utility of the linear ring opening products are limited to their corresponding linear forms.

1.3 Conclusion

It was discovered that acidic sulfonimides can serve as nucleophiles to open 2–substituted oxazolines. This methodology of sulfonimidation works more efficiently for oxazoline substrates with an electron rich 2–substituent, while no reaction took place for oxazolines with electron poor 2 substituents. The resulting linear amide–sulfonimides may serve as bioisosteres of carboxylic acids in drug discovery.

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Chapter 2: The electrophilic fluorination of aryl oxazolines

2.1 Introduction

The introduction of fluorine has been widely used in medicinal chemistry, to boost potency, increase membrane permeability, modulate pKa, and block metabolic sites on potential drug molecules.[26] In addition, ^{18}F–Labeled compounds are indispensable as radionuclides in radiotracers for positron emission tomography (PET). These unique properties make the introduction of fluorine to bioactive molecules intriguing. The construction of C–F bonds is very challenging,[27,28] particularly in a selective late stage synthesis. However, recently there have been advances in ortho directed palladium catalyzed electrophilic fluorination of arenes via C–H activation.[28] In 2006 Sanford used 8–methylquinolines and phenyl–pyridines to accomplish this transformation in acceptable yields and under microwave conditions.[29] The Xu group has also shown that a wide variety of N–heterocyclic DGs such as quinoxaline, pyrazole, and benzo[d]oxazole can promote selective mono–ortho–fluorination using trifluoroacetic acid as an additive.[30] A more expansive investigation into the electrophilic fluorination of aryls using benzo[d]oxazole and pyrazole as DGs has also been established.[31,32] Experimental studies of the electrophilic fluorination of arylpyrazoles has shown evidence of an alternative mechanism to the standard Pd(II)/Pd(IV) process, suggesting a possible oxidative addition of N–fluorobenzenesulfonimide (NFSI) to Pd(II).[30,32] Despite these recent advances in ortho directed palladium catalyzed electrophilic fluorination via C–H activation, many of the initial DGs were heteroaryls thus not easily removable thus limiting their synthetic utility. However a set of removable non–heteroaryl DGs have since been developed. The Xu group was able to demonstrate that O–methyloxime as a DG for ortho–fluorination of arenes at moderate temperatures.[33] They also demonstrated the selective ortho–mono–fluorination of 2–phenoxylpyridines via a six–membered cyclopalladation step.[34] Yu has reported the fluorination of arenes using the –C(O)NHC$_6$F$_4$CF$_3$ amide–DG, and was able to achieve selective mono–fluorination by increasing the acidity of the benzamide DG.[35] Other benzamides such as oxalyl amide[36] and triflamides[37] have also been shown to be suitable DGs for selective mono ortho–fluorination. These DGs are labile and their removal makes the aryls amenable for further synthetic transformations but most of the benzamides suffer from their large size and poor atom economy. Thus the development of a directing group that is both an N–heterocycle and removable with good atom is needed.

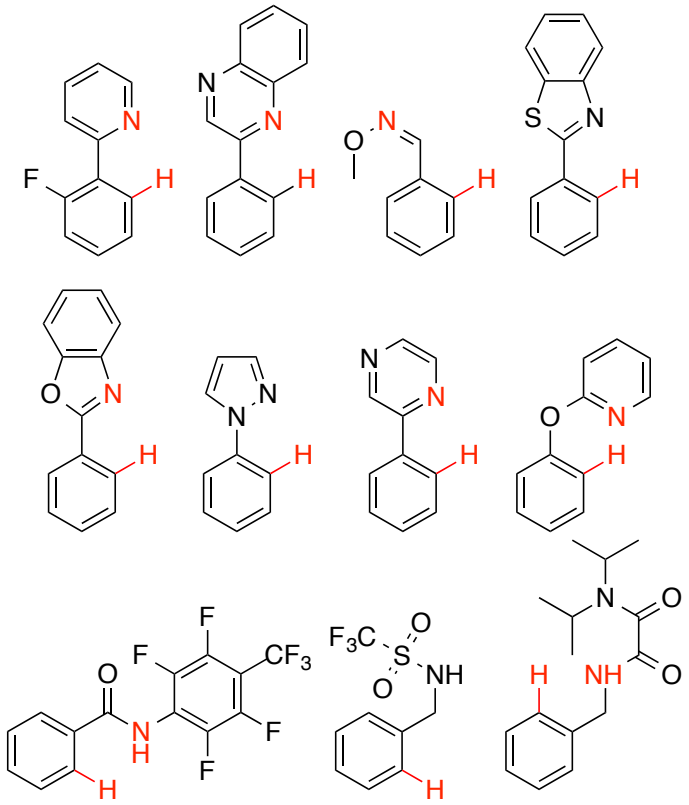
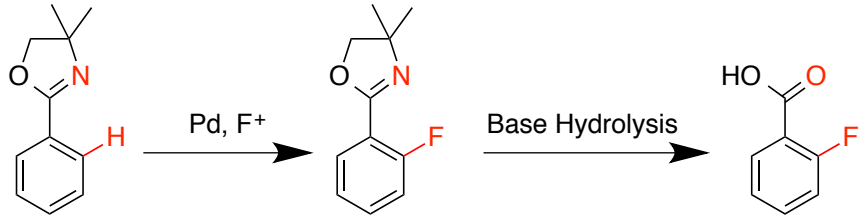


Figure 1: Examples of N–heterocylic and benzamide directing groups used for ortho directed fluorination

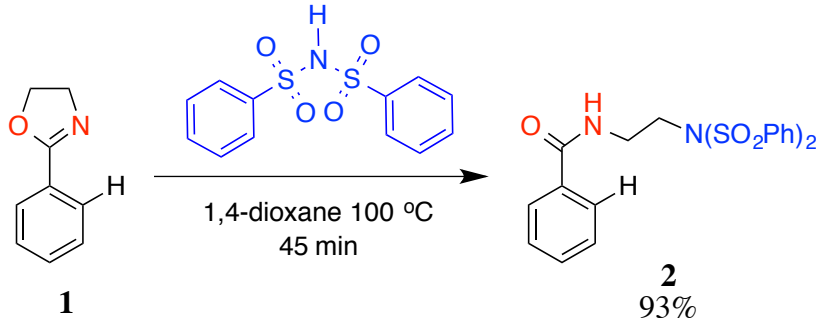
Oxazolines are versatile ligands and directing groups in organic synthesis and useful building blocks. Oxazolines have been extensively used as chiral ligands for asymmetric synthesis.[1,2] Aryl–2–oxazolines have served as an important class of directing groups for metalation via complex–induced proximity effect (CIPE), also known as directed ortho–metalation (DoM), pioneered by Meyers, Beak, and Snieckus, et al.[38,39] Aryloxazolines have been shown to be suitable DGs for C–C bond formation via C–H activation. Aryl–oxazolines have been fluorinated via ortho–metalation using magnesate bases and by lithiation.[40] Oxazolines have also been shown to be amenable to further synthetic transfromations by hydrolysis to the carboxylic acid, with good atom economy.[41] The development of a palladium catalyzed oxazoline ortho directed electrophilic fluorination takes advantage of the heterocyclic moiety to direct fluorination for late stage synthesis and can be hydrolyzed with good atom economy (Scheme 1).



Scheme 1: Oxazoline directed C–H bond fluorination and hydrolysis

2.2 Results and Discussion

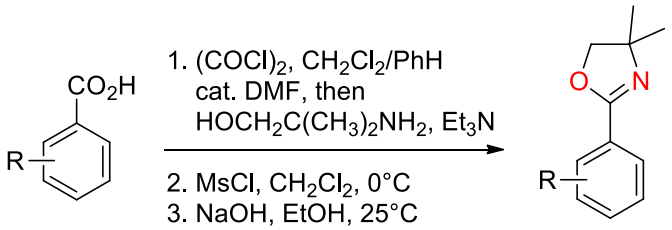
The investigation into fluorination began using 4,4–Dimethyl–2–phenyl–2–oxazoline because we have previously shown that ring opening occurred on 2–phenyl–oxazoline, **1**, when N–fluorobenzenesulfonimide (NFSI) was used as the electrophilic fluorine source and produces the corresponding sulfonimides **2**, as the predominate product (Scheme 2).[42] The dimethyl substituents add steric bulk to the oxazline and this was expected to hinder the ring opening reaction.



1 **2** 93%

Scheme 2: Sulfonamidation via nucleophilic ring opening of 2–oxazolines with acidic sulfonimides

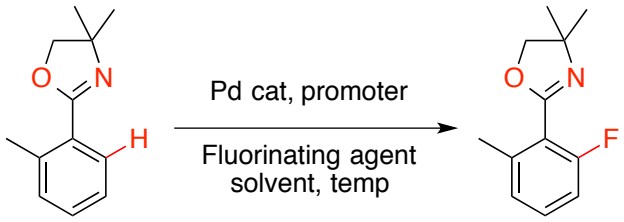
The 4,4–dimethyl oxazoline derivatives were prepared using standard procedures. The corresponding benzoic acid was converted to the acyl chloride using oxalyl chloride and catalytic DMF, followed by formation of the amide using 2–amino–2–methyl–1–propanol. The corresponding alcohol was then mesylated and then cyclized using NaOH in ethanol in high yield (Scheme 3).



Scheme 3: Procedures for the formation of substituted aryl oxazolines

With the oxazoline in hand the model substrate **3** with several fluorinating agents (**A**, **B**, **C**, **D**, **E**, and **F**) that have been shown to be successful fluorinating agents (Table 1). DMF was initially used as the solvent of choice for the fluorination reactions because this polar solvent was shown to retard the ring opening of phenyl oxazolines.[42] $Pd(OAc)_2$ catalyst was used and TFA as an additive. NFSI (**A**) and Selectfluor (**B**) afforded the fluorinated product **4** in 28% and 13%, respectively (entry 1–2). The four 1–fluoropyridinium–based fluorinating agents including $[PyF]BF_4$ (**C**), $[Cl_2PyF]OTf$ (**D**), complex **E**, and $[Me_2PyF]BF_4$ (**F**) all failed to produce more than a trace amount of the desired product (entries 3–6).

NFSI was selected as the fluorinating agent of choice and it was determined that five equivalents of TFA was needed to promote the fluorination reaction (Appendix B). A selection of Pd(II) and Pd(0) catalysts were screened (entry 8–12). Pd(0) catalysts gave low conversion to the fluorinated product (entry 8 and 11). Surprisingly $Pd(TFA)_2$ did not give a significant boost in conversion (entry 7). This is in contrast to previously know reports, as using TFA along with $Pd(TFA)_2$ increases amount of fluorination.[30] $Pd(NO_3)_2$ gave the best conversion to (entry 12). As a result of this catalyst giving superior conversion, a series of nitrates were screened as promoters but the use of KNO_3 and $Ca(NO_3)_2$ completely halted the reaction (entry 13–14). $Ag(NO_3)$ gave the best conversion of all the screened nitrates (entry 15). Other silver salts were screened however none of these silver sources showed any effectiveness at promoting the reaction (entry 16–17). No trace of fluorinated product was detected when no additive was used. However it does appear that that the silver nitrate salt is unique in its ability to promote fluorination. Solvents that have promoted other fluorination reactions were then screened. Trifluorotoluene, 1,2–dichloroethane, ethyl acetate, and dioxane, gave no reaction. Nitromethane was able to give conversion to desired product **4** but acetonitrile gave the full conversion to the fluorinated product. It was also concluded that using acetonitrile as the solvent only 50–mol% of $AgNO_3$ was needed to give full conversion to the desired product.



3 **4**

Entry	Pd cat.	F^+ source	Promoter	Solvent	Yield (**3**:**4**)[a]
1[b]	$Pd(OAc)_2$	A	TFA	DMF	72:28
2[b]	$Pd(OAc)_2$	B	TFA	DMF	87:13
3[b]	$Pd(OAc)_2$	C	TFA	DMF	NR
4[b]	$Pd(OAc)_2$	D	TFA	DMF	NR
5[b]	$Pd(OAc)_2$	E	TFA	DMF	NR
6[b]	$Pd(OAc)_2$	F	TFA	DMF	NR
7[b]	$Pd(TFA)_2$	A	TFA	DMF	71:29

8[b]	$Pd(dba)_2$	A	TFA	DMF	90:10
9[b]	$PdCl_2$	A	TFA	DMF	NR
10[b]	$Pd(OTf)_2$	A	TFA	DMF	82:18
11[b]	$Pd(PPh_3)_4$	A	TFA	DMF	66:34
12[b]	$Pd(NO_3)_2$	A	TFA	DMF	60:40
13[c]	$Pd(NO_3)_2$	A	KNO_3	DMF	92:8
14[c]	$Pd(NO_3)_2$	A	$Ca(NO_3)_2$	DMF	89:11
15[c]	$Pd(NO_3)_2$	A	$AgNO_3$	DMF	51:49
16[c]	$Pd(NO_3)_2$	A	AgTFA	DMF	100:0
17[c]	$Pd(NO_3)_2$	A	AgOAc	DMF	93:7
18[d]	$Pd(NO_3)_2$	A	$AgNO_3$	Dioxane	NR
19[d]	$Pd(NO_3)_2$	A	$AgNO_3$	DCE	NR
20[d]	$Pd(NO_3)_2$	A	$AgNO_3$	$PhCF_3$	NR
21[d]	$Pd(NO_3)_2$	A	$AgNO_3$	CH_3NO_2	73:27
22[d]	$Pd(NO_3)_2$	A	$AgNO_3$	EtOAc	NR
23[e]	$Pd(NO_3)_2$	A	$AgNO_3$	CH_3CN	0:100

Pd (20 mol %) aryloxazoline (0.1 mmol), NFSI (0.15 mmol), solvent (1 mL). [a]GCMS conversions using dodecane as an internal standard. [b]TFA (0.5 mmol) 150 ^{o}C. [c]Additive (0.5mmol) 150 ^{o}C. [d]AgNO3 (0.5mmol) 100 ^{o}C. [e]$AgNO_3$ (50 mol%) 80 ^{o}C.

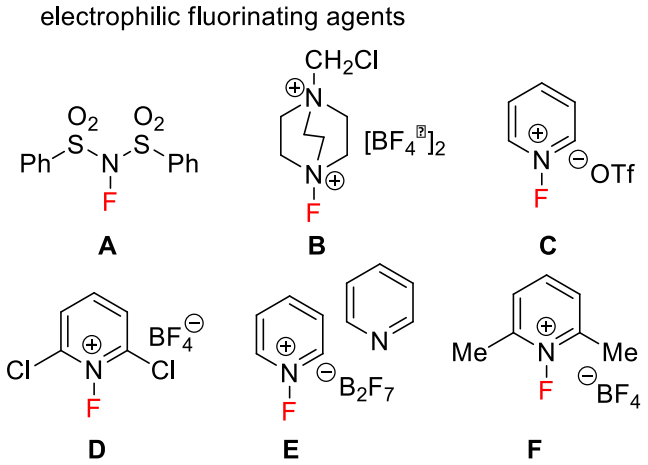


Table 1: Optimization of palladium–catalyzed fluorination of aryl 4,4–dimethyloxazoline 3

Using the optimized reaction conditions (Table 2) the scope of the reaction was then explored. Electron rich oxazolines showed moderate to good yields of fluorinated products. The fluorination of 2–o–tolyl substrate **4a** and 2–o–methoxyl substrate **4b**, gave moderate yields of fluorinated product. When the electron rich 4–p–methoxyl **4i** was fluorinated the 2,6–difluorination product **5i** was the major product with trace amounts of the monofluorinated observed by GCMS. Surprisingly 4–p–methyl **4h** was only able to be fluorinated once despite increasing the amount of fluorinating agent used to 5 equivalents and increasing reaction time.

Electron deficient oxazolines were not able to be fluorinated as readily as electron rich oxazolines. The unsubsititued oxazoline **4f** gave the monofluorinated product in predominate yield **4c**, 46%, and gave minor conversion to the difluoro product, 5%. Similar results were observed when the reaction was carried out in nitromethane. This experimental result is in contrast of other fluorination reactions which show nitromethane further promote fluorination and even promote difluorination reactions. The fluorination of 2–o–fluoro derivative **5c** gave only 19% isolated yield of the desired difluoro product **5c**. This result was unexpected given the amount of difluorination occurring on **4f**. The extremely deactivated 2–o–nitro oxazoline **4k**, was completely unable to be fluorinated and 4–p–chloro substituted aryloxazoline **4l**, showed only 13% GCMS conversion to the mono fluorinated product **5l**, and no difluoro product was observed. The stark lack of reactivity observed for the fluorination of electron deficient aryloxazolines than electron rich oxazolines is precedent for fluorination reactions.[30]

The differences in the reactivity of electron rich and electron deficient oxazolines could be presumably attributed to the basicity of the nitrogen on the oxazoline. The 4,4–dimethyl–2–phenyl–2–oxazoline **4h**, has a pKa of 4.4 and the substituent effect on the aryl can either increase or decrease the basicity of the nitrogen.[23] Electron donating substituents on aryls increase the basicity of the oxazolines

and thus increase its ability to facilitate the fluorination reaction. Where as electron poor aryls decrease the basicity of the nitrogen and shifts the equilibrium to the left.

Other effects of substituted aryl oxazolines were also investigated. Ortho chloro and bromo halides **4d** and **4e** were tolerated in the reaction and gave good to moderate yields respectively. The fluorination of 3–m–tolyl **4g** was low yielding and gave predominantly the less sterically hindered product **5g**. The naphthalene derivative **4j** gave impressive yield of the monofluorinated product **5j** at the 2–position, 88% and 7% of the 2,8–difluorinated product **5k**. However increasing the amount of NFSI to 5 equivalents and prolonged reaction time did not increase the amount of difluorinated product **5k**. **5k** is an interesting product because it represents a C–H activation at the 8 position of the naphthalene resulting in a 6–member palladacyclic intermediate which then undergoes fluorination.

The location of fluorination of the naphthalene substrate was done using cosy spectra. Using the 2–dimensional NMR a confirmation on the location of the electrophilic fluorination could take place

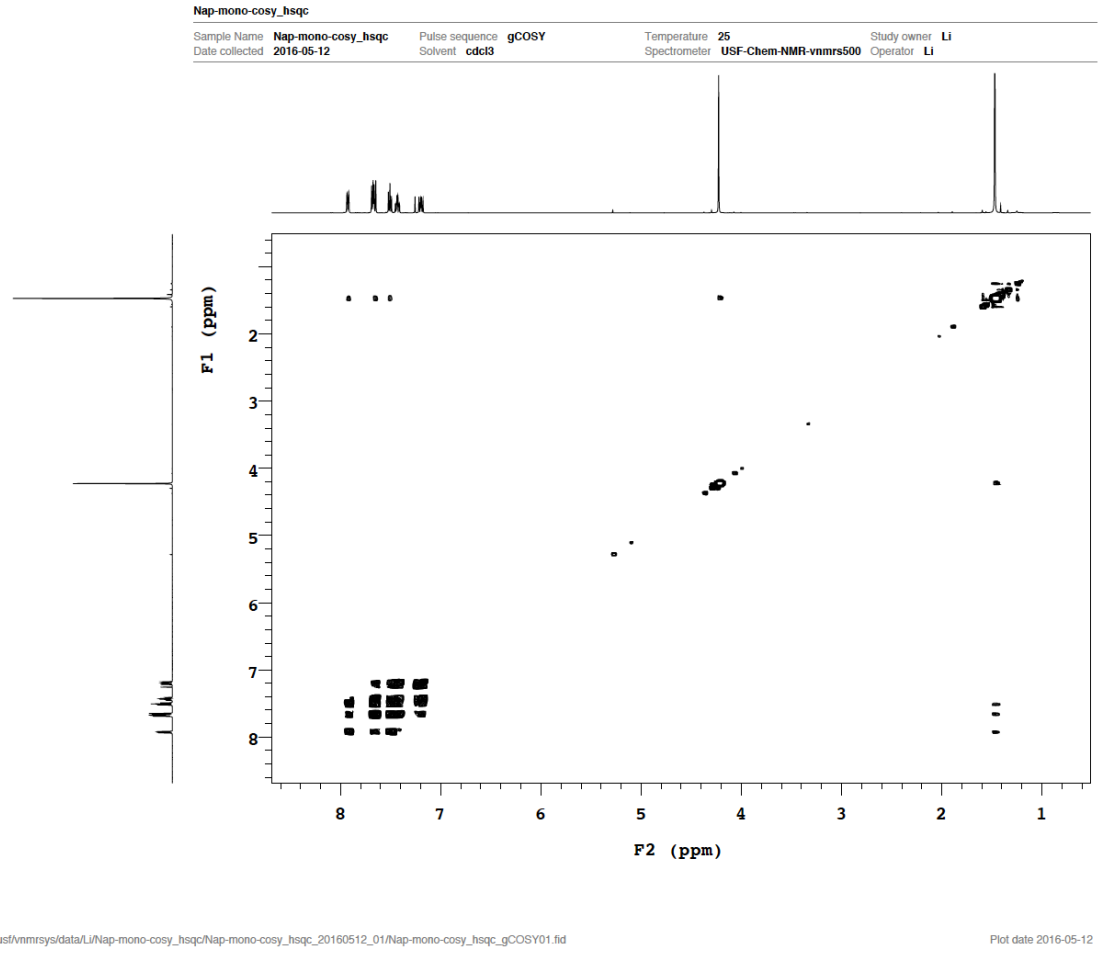
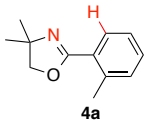
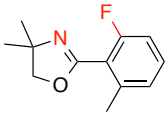
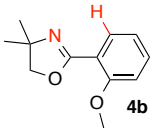
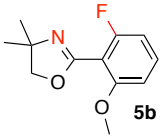
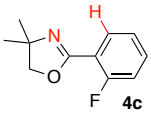
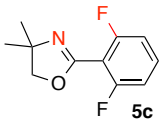
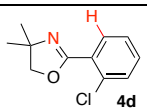
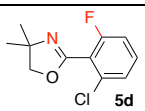
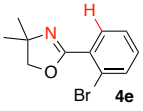
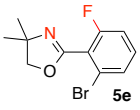
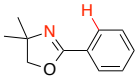
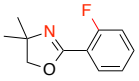
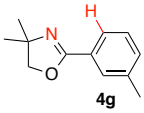
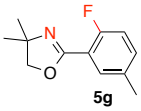
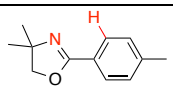
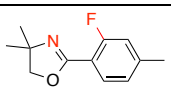
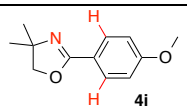
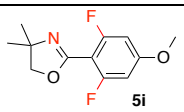
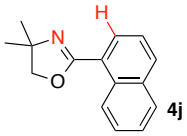
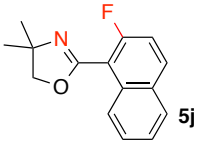
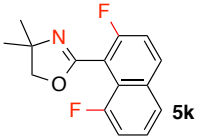
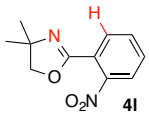
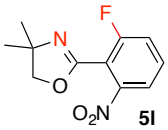
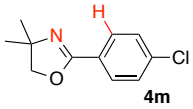
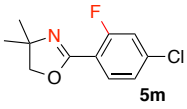


Figure 2: Cosy Spectra of fluorinated compound **5j**

Entry	Substrate	Product	Yield
1	 4a	 5a	100[b] (65)
2	 4b	 5b	97[b] (42)
3	 4c	 5c	27[b] (19)
4	 4d	 5d	63[b] (68)
5	 4e	 5e	47[b] (37)
6	 4f	 4c	46[b] (48)
7	 4g	 5g	19[b] (12)
8	 4h	 5h	17[bc] (23)

9	 **4i**	 **5i**	100[bc] (92)
9	 **4j**	 **5j**	91[b] (88)
		 **5k**	(7)
10	 **4l**	 **5l**	0[b]
11	 **4m**	 **5m**	13[b]

[a]Reaction conditions; Substrate **4** (0.5 mmol), NFSI (1.5 equiv), $Pd(NO_3)_2$ (20 mol%), $AgNO_3$ (50 mol%) in MeCN at 80 [o]C for 24 h. [b]GCMS conversion using dodecane as internal standard. Percent of isolated yields in parenthesis. [c]2.5 equivalents NFSI

Table 2: Palladium–catalyzed fluorination of aryl 4,4–dimethyloxazolines substituted arenes

2–Dimensional NMR was also used in determing that fluorination of the *m*–tolyl substituted aryl oxazoline **5g** was fluorinated in the less sterically hindered position.

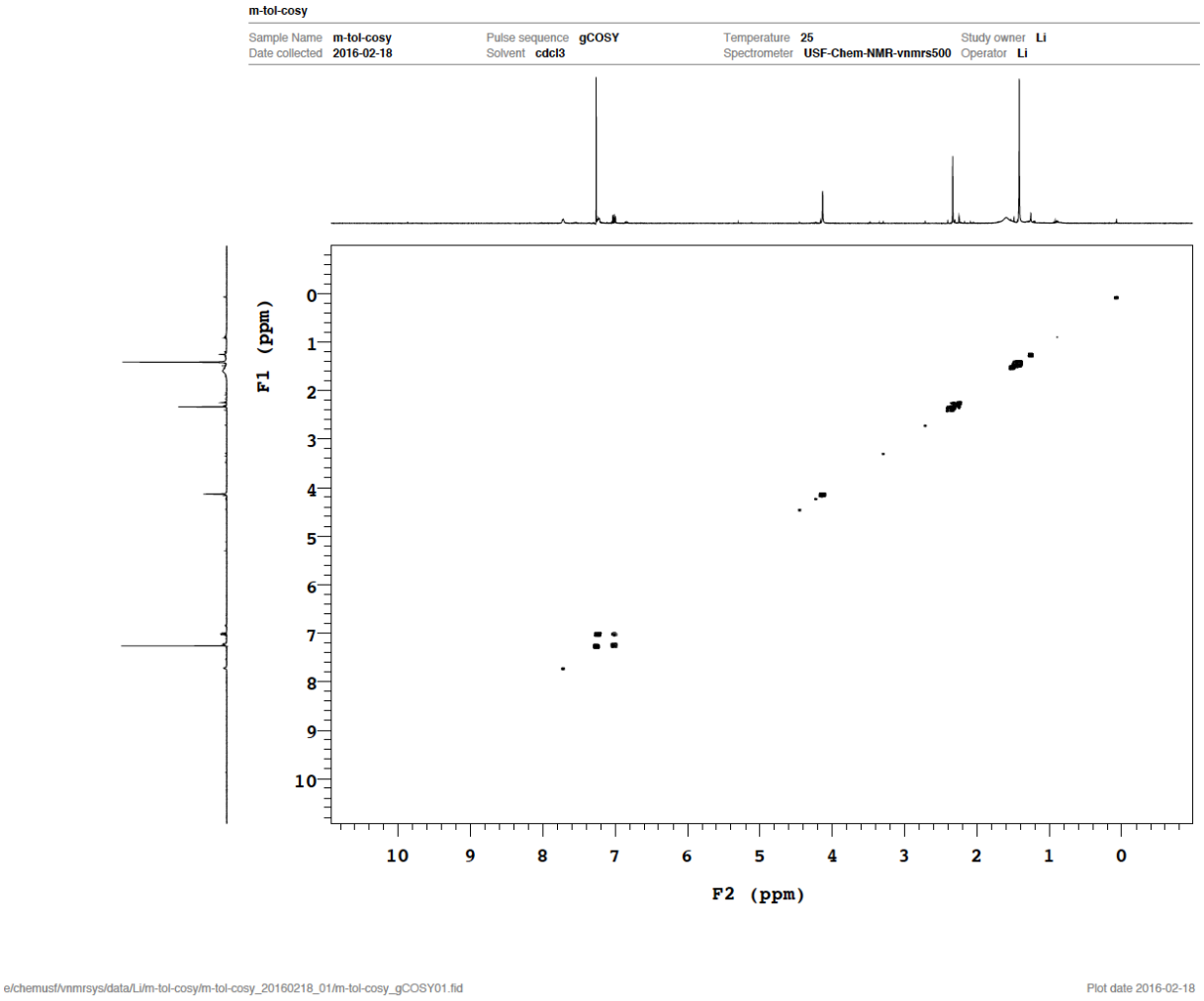
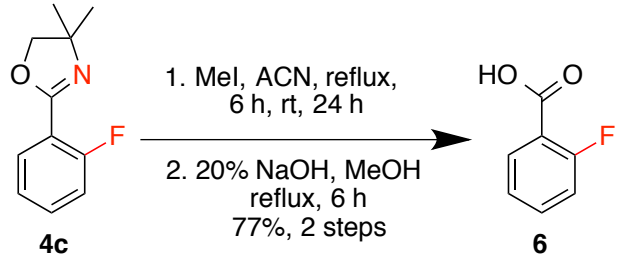


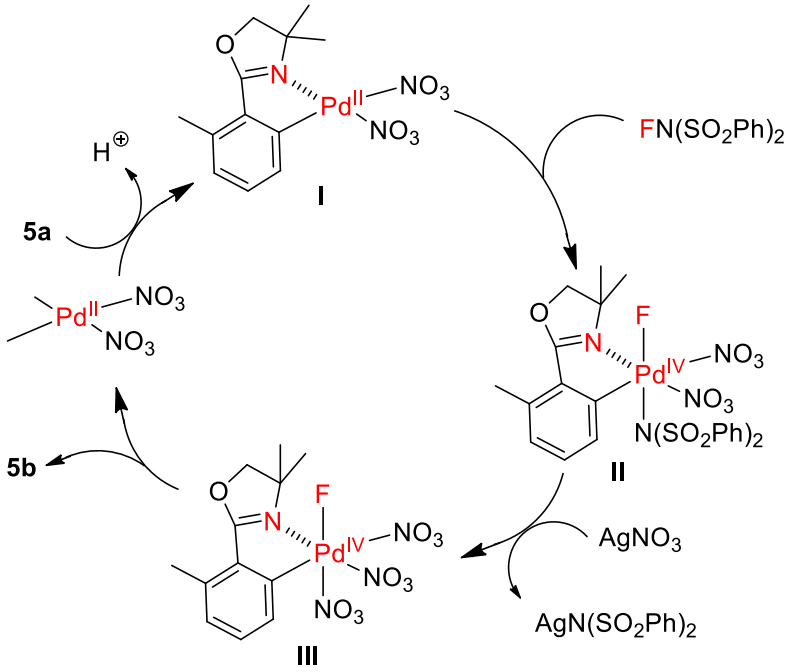
Figure 3: 2–D Cosy proton proton NMR of compound **5g** used in determing fluorination of the less sterically hindered postion

The oxazoline was converted to the corresponding acid using a 2–step sequence.[41] The treatment of **4c** with methyl iodide followed by basic hydrolysis using NaOH afforded 2–fluorobenzoic acid **6** in 77% in 2 steps (Scheme 4).



Scheme 4: Removal of oxazoline directing group

Many investigators have forwarded mechanistic insight for palladium catalyzed electrophilic C–H fluorination.[30,32,43] Based on the experimental results reported above and compared to the results other groups have reported, a plausible mechanism is proposed based on *Hierso's* catalytic cycle, which has been supported by experimental, and mass spectrometric analysis.[32] As shown in Scheme 5, C–H activation of substrate **4a** by $Pd(NO_3)_2$ assembles Pd(II) complex **I**. Ligand exchange between **I** and the second substrate **5a** affords complex **II**. Oxidative addition of NFSI to **II** then produces Pd(IV) complex **III**, which undergoes reductive elimination to deliver fluorinated product **6a** and Pd(II) complex IV. Another ligand exchange between **IV** and HNO_3 then delivers Pd(II) complex **I** to continue the next catalytic cycle.



Scheme 5: Proposed mechanism for the electrophilic fluorination

2.3 Conclusion

In conclusion we have reported an ortho directed palladium catalyzed electrophilic fluorination reaction using oxazoline as a removable directing group. The aryl substituents can efficiently promote the fluorination reaction and the reaction conditions are tolerant to chloro and bromo halides. The reaction conditions can be used for late stage fluorination, or the oxazoline can be hydrolyzed to give the corresponding acid.

2.4 References

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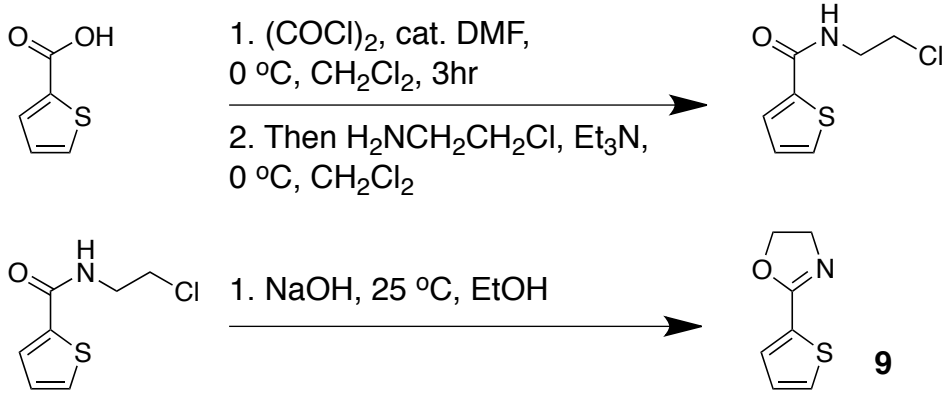
Chapter 3: Appendix A
3.1 General Methods

All reactions were performed in anhydrous solvents under a N_2 atmosphere. Solvents were purchased from Alfa Aesar and utilized without further purifications. Phenyl–2–oxazoline (**1**), 2–ethyl–2–oxazoline (**3**), dibenzenesulfonimide, bistrifluoroacetamide, and dimethanesulfonimide are commercially available and were used without further purifications. Analytical thin–layer chromatography (TLC) was carried out using Silica G TLC plates, 200 μM with UV254 (SORBENT Technologies), with visualization by UV or iodine. Flash chromatography was performed using standard grade silica gel (60 Å, 230–400 mesh; SORBENT Technologies). Melting Points were taken using Vernier Melt Station LabQuest 2 and were not corrected. NMR spectra were acquired using an Agilent VNMRS spectrometer equipped with one NMR probe (500 MHz for ^{1}H, 125 MHz for ^{13}C, 470 MHz for ^{19}F). Spectra were processed using MNova software (Mestrelab). Chemical shifts are reported in parts per million (ppm), coupling constants (*J*) in Hz and are calibrated to residual protonated solvent. Infrared spectra of neat samples were acquired using a PerkinElmer Spectrum 100 FT–IR spectrometer, with solid samples analyzed using a Universal ATR (attenuated total reflectance) sampling accessory. GC–MS was performed on a Hewlett Packard HP6890 Series GC System and a 5973 Mass Selective Detector.

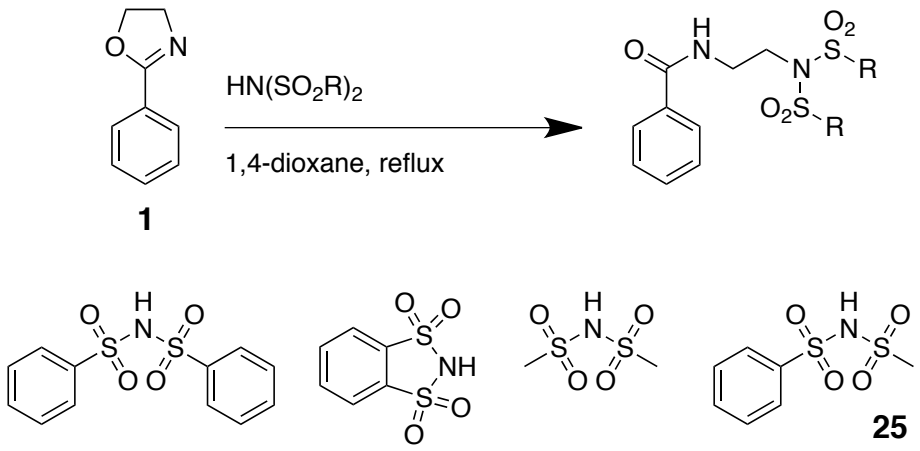
3.2 Preparations of Aryl–2–oxazolines



The following synthesis of **9** is exemplary of all oxazoline derivatives synthesized. 2–Thiophene Carboxcylic acid (1 gram 7.8 mmol) was dissolved in 10mL of anhydrous methylene chloride and cooled to 0 ^{o}C; 5 drops of DMF was added to the suspension. Oxalyl chloride (1.98 grams 15.8 mmol) was added drop wise to the reaction mixture. The reaction was warmed to room temperature and stirred for 3 h. The solvent was removed *in vacuo* and the residue was dried for 1 h on high vacuum. The residue was dissolved in 5mL of methylene chloride and added drop wise to a suspension of chloroethylamine•HCl (1.08 g 9.4 mmol), triethylamine (2.52g g 24 mmol) in 7mL of methylene chloride at 0 ^{o}C. The reaction stirred for 3 h and was warmed to room temperature. The reaction was diluted with

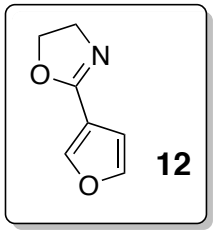
methylene chloride and washed once with sat. aq. ammonium chloride and washed twice with brine. The organic layer was dried over $MgSO_4$, filtered, then concentrated. The crude reaction mixture was purified by flash chromatography in a solvent system of hexane: ethyl acetate 2/1, respectively, to afford the amide intermediate. The thiophene amide intermediate (1.07 g 5.7 mmol) and sodium hydroxide (0.286g 7.2 mmol) was added to a reaction flask dissolved in ethanol and heated to 50 ^{o}C for 1 hour. The reaction was diluted with ethyl acetate and washed twice with brine. The organic layer was dried over $MgSO_4$, filtered, and then concentrated.

3.3 Preparation of Sulfonimides



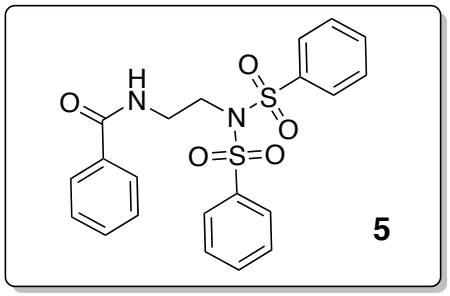
The aryl–2–oxazoline substrate (0.30 mmol) was dissolved in 3 mL of 1,4–dioxane. After addition of sulfonimide (0.45 mmol), the resulting solution was refluxed for 30 min to 2 h until reaction was judged complete by TLC (hexane: ethyl acetate). The reaction was cooled, diluted with ethyl acetate, washed once with sat. aq. ammonium chloride, and twice with brine. The organic layer was concentrated *in vacuo*. The crude product was purified using flash chromatography (hexane: ethyl acetate) to obtain the desired ring opened product.

3.4 Characterization of New Compounds

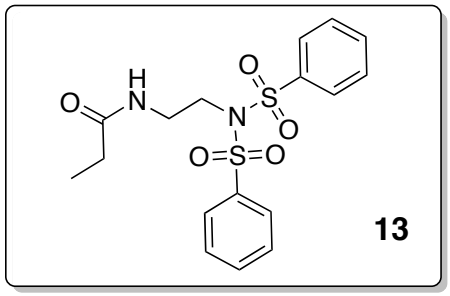


2–(furan–3–yl)–4,5–dihydrooxazole
Yellow oil (73% yield), m.p. 36– 39 ^{o}C; FTIR (neat, ATR, cm^{-1}) 3091,1668, 1517, 1353, 1272, 1151, 1113, 1063, 976, 927 869, 843, 750; ^{1}H NMR (500 MHz, Chloroform–*d*) δ 7.88 (s, 1H), 7.43 (t, *J* = 1.7 Hz, 1H), 6.76 (dd, *J* = 1.8, 0.8 Hz, 1H), 4.36 (t, *J* = 9.4 Hz, 2H), 3.99 (t, *J* = 9.4 Hz, 2H); ^{13}C NMR (126 MHz, $cdcl_3$) δ 159.98, 144.77, 143.80, 115.68, 109.53, 67.42, 54.76; HRMS (ESI, m/z) calcd for $C_7H_7N_1O_2$: 137.0477, found: 137.0476.

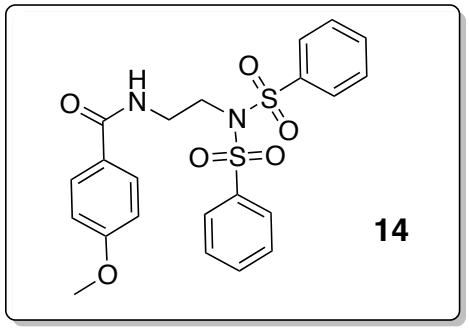
3.5 Characterization data for Sulfonimides



N–(2–(*N*–(Phenylsulfonyl)phenylsulfonamido)ethyl)benzamide
White solid (93% yield), m.p. 81.2–83.3 ^{o}C; FTIR (neat, ATR, cm^{-1}) 3312, 3071, 2990, 1725, 1737, 1642, 1544, 1492 1448, 1371, 1353, 1160, 1169, 882, 825 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform–*d*) δ 8.00 (dd, *J* = 8.5, 1.3 Hz, 4H), 7.74 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.65 – 7.56 (m, 2H), 7.53 – 7.43 (m, 5H), 7.41 – 7.34 (m, 2H), 6.91 (s, 1H), 3.98 (t, *J* = 5.8 Hz, 2H), 3.72 (q, *J* = 5.6 Hz, 2H); ^{13}C NMR (125 MHz, cdcl$_3$) δ 167.69, 139.19, 134.26, 133.98, 131.64, 129.34, 128.62, 128.28, 127.06, 47.51, 39.52; HRMS (ESI, m/z) calcd for $C_{21}H_{20}N_2O_5S_2$: 444.0814, found: 444.0815.

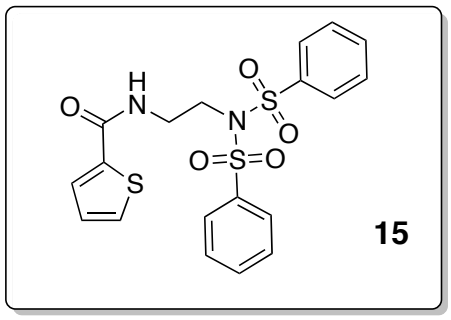


N–(2–(*N*–(Phenylsulfonyl)phenylsulfonamido)ethyl)propionamide
White solid (75% yield), m.p. 113.3–119.5 ^{o}C; FTIR (neat, ATR, cm^{-1}) 3274, 1644, 1539, 1447,1368, 1166, 1083, 833 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform–*d*) δ 7.98 (dd, *J* = 8.4, 1.1 Hz, 4H), 7.70 – 7.63 (m, 2H), 7.59 – 7.51 (m, 4H), 5.97 (s, 1H), 3.87 (t, *J* = 5.8 Hz, 2H), 3.54 (q, *J* = 5.7 Hz, 2H), 2.16 (q, *J* = 7.6 Hz, 2H), 1.09 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 174.19, 139.21, 134.14, 129.24, 128.24, 47.53, 38.80, 29.55, 9.58; HRMS (ESI, m/z) calcd for $C_{17}H_{20}N_2O_5S_2$: 396.0814, found: 396.08084.

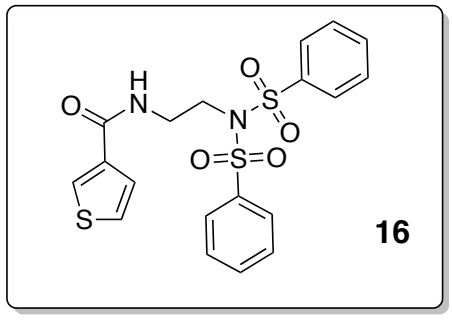


4–Methoxy–*N*–(2–(*N*–(phenylsulfonyl)phenylsulfonamido)ethyl)benzamide
White solid (72% yield), m.p. 139.2–140.0 ^{o}C; FTIR (neat, ATR, cm^{-1}) 3317, 1634, 1605, 1548, 1447,1372, 1260, 1128, 1084, 883, 834 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform–*d*) δ 8.00 (d, *J* = 7.8 Hz, 4H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 2H), 7.51 (t, *J* = 7.7 Hz, 4H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.76 (s, 1H), 3.97 (t, *J* = 5.7 Hz, 2H), 3.82 (s, 3H), 3.71 (q, *J* = 5.6 Hz, 2H); ^{13}C NMR (126 MHz, cdcl$_3$) δ

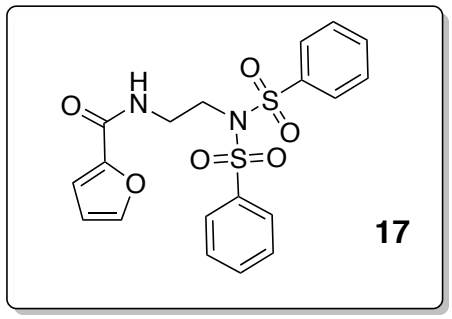
167.22, 162.34, 139.26, 134.29, 129.38, 128.91, 128.33, 126.36, 113.85, 55.50, 47.62, 39.47; HRMS (ESI, m/z) calcd for $C_{22}H_{22}N_2O_6S_2$: 474.0919, found: 474.0912.



N–(2–(*N*–(Phenylsulfonyl)phenylsulfonamido)ethyl)thiophene–2–carboxamide
White solid (93% yield), m.p. 117.3–119.8 °C; FTIR (neat, ATR, cm^{-1}) 3270, 2259, 1626, 1563, 1448, 1372, 1167, 1127, 1083, 870, 857, 809 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform–*d*) δ 8.02 (d, *J* = 7.2 Hz, 4H), 7.67 – 7.62 (m, 2H), 7.54 (t, *J* = 7.9 Hz, 4H), 7.46 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.43 (dd, *J* = 3.8, 1.2 Hz, 1H), 7.04 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.67 (s, 1H), 3.97 (t, *J* = 5.8 Hz, 2H), 3.71 (q, *J* = 5.5 Hz, 2H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 162.21, 139.25, 138.75, 134.36, 130.31, 129.45, 128.38, 128.23, 127.79, 47.50, 39.40; HRMS (ESI, m/z) calcd for $C_{19}H_{18}N_2O_5S_3$: 450.0378, found: 450.0373.

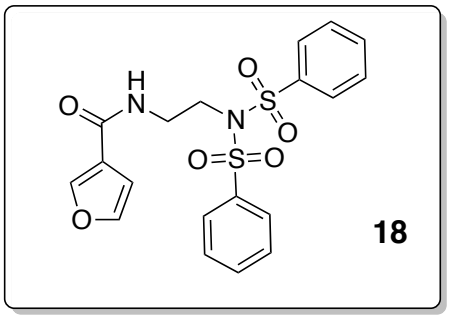


N–(2–(*N*–(Phenylsulfonyl)phenylsulfonamido)ethyl)thiophene–3–carboxamide
White solid (94% yield), m.p. 145.1–145.9 °C; FTIR (neat, ATR, cm^{-1}) 3294, 1633, 1551, 1448, 1369, 1295, 1166, 1083, 861, 830 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform–*d*) δ 8.01 (d, *J* = 7.8 Hz, 4H), 7.83 (s, 1H), 7.64 (t, *J* = 7.5 Hz, 2H), 7.53 (t, *J* = 7.7 Hz, 4H), 7.36 (d, *J* = 5.0 Hz, 1H), 7.30 (s, 1H), 6.70 (s, 1H), 3.97 (t, *J* = 5.7 Hz, 2H), 3.70 (d, *J* = 5.7 Hz, 2H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 163.30, 139.20, 137.19, 134.35, 129.42, 128.56, 128.35, 126.55, 126.24, 47.54, 39.21; HRMS (ESI, m/z) calcd for $C_{19}H_{18}N_2O_5S_3$: 450.0378, found: 450.0372.

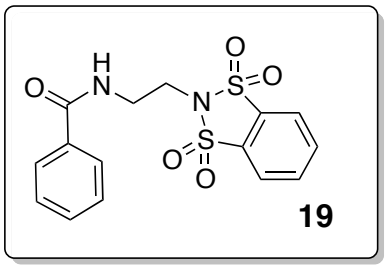


N–(2–(*N*–(phenylsulfonyl)phenylsulfonamido)ethyl)furan–2–carboxamide

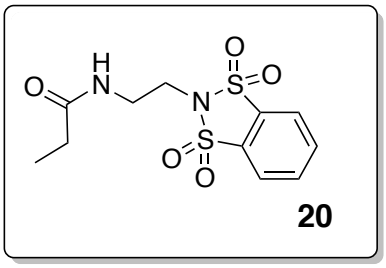
White solid (73% yield), m.p. 124.1–125.3 ^{o}C; FTIR (neat, ATR, cm^{-1}) 3269, 1647, 1597, 1537, 1446, 1368, 1350, 1323, 1300, 1177, 1167, 1129, 1077, 1010, 873, 810 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform–*d*) δ 8.05 – 7.99 (m, 4H), 7.67 – 7.61 (m, 2H), 7.57 – 7.49 (m, 4H), 7.42 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.08 (dd, *J* = 3.4, 0.8 Hz, 1H), 6.75 (s, 1H), 6.48 (dd, *J* = 3.5, 1.8 Hz, 1H), 3.96 (t, *J* = 6.1 Hz, 2H), 3.68 (q, *J* = 6.0 Hz, 2H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 158.75, 147.74, 144.28, 139.40, 134.24, 129.37, 128.39, 114.46, 112.17, 47.70, 38.95; HRMS (ESI, m/z) calcd for $C_{19}H_{18}N_2O_6S_2$: 434.0606, found: 434.0599



N–(2–(*N*–(Phenylsulfonyl)phenylsulfonamido)ethyl)furan–3–carboxamide
White solid (90% yield), m.p. 121.8–125.3 ^{o}C; FTIR (neat, ATR, cm^{-1}) 3254, 2261, 1638, 1589, 1542, 1449, 1373, 1350, 1169, 1127, 1084, 1024, 864 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform–*d*) δ 8.03 – 7.97 (m, 4H), 7.89 (dd, *J* = 1.6, 0.9 Hz, 1H), 7.69 – 7.62 (m, 2H), 7.57 – 7.51 (m, 4H), 7.39 (t, *J* = 1.8 Hz, 1H), 6.59 (dd, *J* = 1.9, 0.9 Hz, 1H), 6.52 (s, 1H), 3.95 (t, *J* = 5.4 Hz, 2H), 3.67 (q, *J* = 5.3 Hz, 2H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 162.94, 144.97, 143.86, 139.20, 134.38, 129.44, 128.37, 122.38, 108.41, 47.50, 38.96; HRMS (ESI, m/z) calcd for $C_{19}H_{18}N_2O_6S_2$: 434.0606, found: 434.0602.

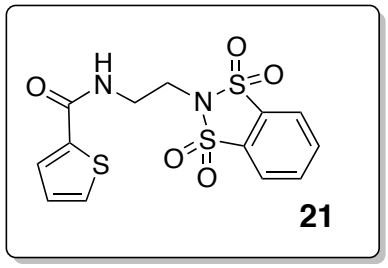


N–(2–(1,1,3,3–Tetraoxidobenzo[d][1,3,2]dithiazol–2–yl)ethyl)benzamide
White solid (95% yield), m.p. 162–164 ^{o}C; FTIR (neat, ATR, cm^{-1}) 3337, 1635, 1536, 1337, 1320, 1203, 11,39, 1125, 1069, 947, 797, 761, 721 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform–*d*) δ 8.08 – 7.73 (m, 5H), 7.55 – 7.32 (m, 3H), 6.81 (s, 1H), 4.06 (br. s, 2H), 3.91 (br. s, 2H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 167.93, 135.21, 135.14, 134.12, 131.77, 128.69, 127.23, 122.47, 42.03, 39.15; HRMS (ESI, m/z) calcd for, $C_{15}H_{14}N_2O_5S_2$: 366.0344, found: 366.0340.

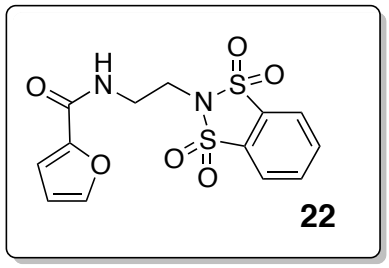


N–(2–(1,1,3,3–Tetraoxidobenzo[d][1,3,2]dithiazol–2–yl)ethyl)propionamide

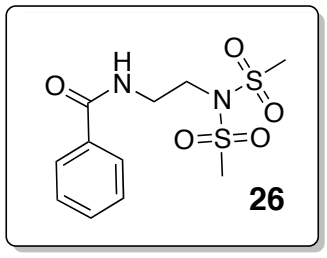
White solid (89% yield), m.p. 114–117 °C; FTIR (neat, ATR, cm^{-1}) 3270, 1638, 1551, 1335, 1198, 1167, 1091, 811, 764, 730 cm^{-1}; ^1H NMR (500 MHz, Chloroform–*d*) δ 8.05 – 8.00 (m, 2H), 7.99 – 7.91 (m, 2H), 6.04 (s, 1H), 4.00 – 3.86 (m, 2H), 3.78 – 3.55 (m, 2H), 2.27 (q, *J* = 7.6 Hz, 2H), 1.18 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 174.45, 135.33, 135.11, 122.45, 42.17, 38.57, 29.72, 9.64; HRMS (ESI, m/z) calcd for, $C_{11}H_{14}N_2O_5S_2$: 318.0344, found: 318.0339.



N–(2–(1,1,3,3–tetraoxidobenzo[d][1,3,2]dithiazol–2–yl)ethyl)thiophene–2–carboxamide
White solid (95% yield), m.p. 158–162 °C; FTIR (neat, ATR, cm^{-1}) 3318, 1629, 1547, 1442, 1336, 1203, 1138, 1072, 969, 788, 766, 723 cm^{-1}; ^1H NMR (500 MHz, Chloroform–*d*) δ 8.07 – 8.00 (m, 2H), 7.98 – 7.90 (m, 2H), 7.56 (dd, *J* = 3.8, 1.2 Hz, 1H), 7.48 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.06 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.66 (s, 1H), 4.08 – 4.02 (m, 2H), 3.93 – 3.86 (m, 2H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 162.29, 138.56, 135.22, 135.17, 130.53, 128.58, 127.79, 122.51, 42.10, 39.07; HRMS (ESI, m/z) calcd for, $C_{13}H_{12}N_2O_5S_3$: 371.9908, found: 371.9903.

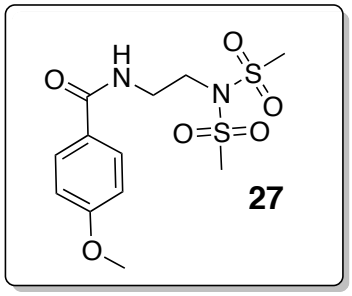


N–(2–(1,1,3,3–tetraoxidobenzo[d][1,3,2]dithiazol–2–yl)ethyl)furan–2–carboxamide
White solid (80% yield), m.p. 108–110 °C; FTIR (neat, ATR, cm^{-1}) 3314, 1647, 1569, 1532, 1443, 1336, 1202, 1140, 1075, 1046, 1021, 794, 753, 727 cm^{-1}; ^1H NMR (500 MHz, Chloroform–*d*) δ 8.05 – 7.99 (m, 2H), 7.97 – 7.88 (m, 2H), 7.44 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.13 (dd, *J* = 3.5, 0.8 Hz, 1H), 6.91 (s, 1H), 6.48 (dd, *J* = 3.5, 1.7 Hz, 1H), 4.03 – 3.99 (m, 2H), 3.92 – 3.86 (m, 2H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 158.80, 147.70, 144.44, 135.29, 135.11, 122.51, 114.77, 112.20, 41.92, 38.28; HRMS (ESI, m/z) calcd for, $C_{13}H_{12}N_2O_6S_2$: 356.0137, found: 356.0131.

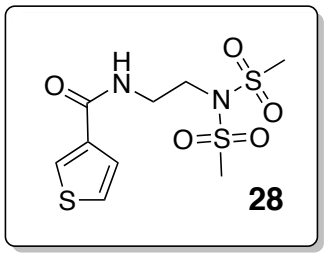


N–(2–(*N*–(Methylsulfonyl)methylsulfonamido)ethyl)benzamide
White solid (56%). m.p. 167–169 °C; FTIR (neat, ATR, cm^{-1}) 3271, 1628, 1543, 1353, 1152, 1068, 967, 900, 795, 759, 671 cm^{-1}; ^1H NMR (500 MHz, Chloroform–*d*) δ 7.82 (d, *J* = 7.6 Hz, 2H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 6.61 (s, 1H), 4.05 (t, *J* = 5.5 Hz, 2H), 3.79 (q, *J* = 5.6 Hz, 2H), 3.33 (s,

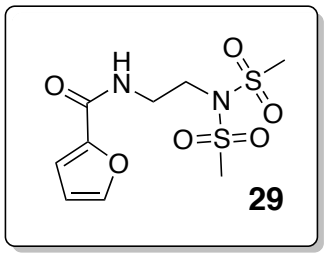
6H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 168.13, 134.05, 131.90, 128.85, 127.10, 47.32, 43.84, 38.93; HRMS (ESI, m/z) calcd for, $C_{11}H_{16}N_2O_5S_2$: 320.0501, found: 320.0498.



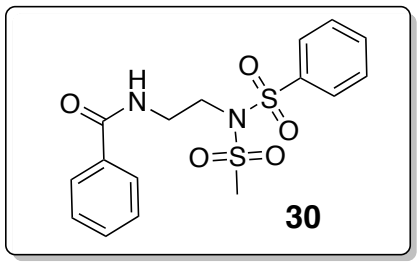
4–Methoxy–*N*–(2–(*N*–(methylsulfonyl)methylsulfonamido)ethyl)benzamide
White solid (62%), m.p. 128–130 °C; FTIR (neat, ATR, cm^{-1}) 3218, 1626, 1605, 1507, 1344, 1324, 1256, 1153,1071, 1028, 961, 851, 802, 786, 757 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform–*d*) δ 7.80 – 7.78 (m, 1H), 7.78 – 7.76 (m, 1H), 6.94 – 6.93 (m, 1H), 6.92 – 6.90 (m, 1H), 6.56 (s, 1H), 4.03 (t, *J* = 5.4 Hz, 2H), 3.84 (s, 3H), 3.76 (q, *J* = 5.5 Hz, 2H), 3.32 (s, 6H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 167.60, 162.52, 128.94, 126.30, 114.03, 55.54, 47.37, 43.81, 38.88; HRMS (ESI, m/z) calcd for, $C_{12}H_{18}N_2O_6S_2$: 350.0606, found: 350.0600.



N–(2–(*N*–(Methylsulfonyl)methylsulfonamido)ethyl)thiophene–3–carboxamide
White solid (70%). m.p. 197–199 °C; FTIR (neat, ATR, cm^{-1}) 3249, 1619, 1546, 1350, 1309, 1151, 1073, 959, 893, 790, 698 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform–*d*) δ 7.54 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.50 (dd, *J* = 4.9, 1.2 Hz, 1H), 7.09 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.47 (s, 1H), 4.03 (t, *J* = 5.4 Hz, 2H), 3.76 (q, *J* = 5.6 Hz, 2H), 3.33 (s, 6H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 162.54, 138.48, 130.61, 128.49, 127.93, 47.18, 43.84, 38.95. HRMS (ESI, m/z) calcd for, $C_9H_{14}N_2O_5S_3$: 326.0065, found: 326.0062.



N–(2–(N–(methylsulfonyl)methylsulfonamido)ethyl)furan–2–carboxamide
White solid (61%), m.p. 166–169 °C; FTIR (neat, ATR, cm^{-1}) 3235, 1641, 1569, 1538, 1352, 1319, 1153 1073, 959, 868, 794 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform–*d*) δ 7.47 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.12 (dd, *J* = 3.5, 0.8 Hz, 1H), 6.72 (s, 1H), 6.50 (dd, *J* = 3.5, 1.7 Hz, 1H), 4.00 (t, *J* = 6.2 Hz, 2H), 3.74 (q, *J* = 5.8 Hz, 2H), 3.33 (s, 6H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 158.98, 147.62, 144.54, 114.80, 112.28, 47.25, 43.67, 38.54; HRMS (ESI, m/z) calcd for, $C_9H_{14}N_2O_6S_2$: 310.0293, found: 310.0289.



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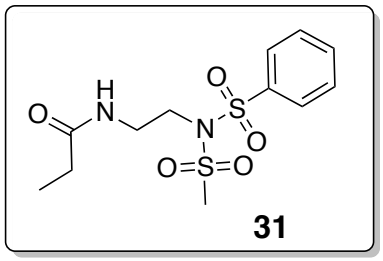
N–(2–(*N*–(Methylsulfonyl)phenylsulfonamido)ethyl)benzamide
White solid (84%), m.p. 138–141 ^{o}C; FTIR (neat, ATR, cm^{-1}) 3364, 1643, 1541, 1369, 1362, 1314, 1290, 1152, 1086, 976, 899, 791, 781, 723 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform–*d*) δ 8.05 – 7.99 (m, 2H), 7.85 – 7.79 (m, 2H), 7.68 – 7.61 (m, 1H), 7.58 – 7.47 (m, 3H), 7.47 – 7.40 (m, 2H), 6.79 (s, 1H), 3.98 (d, *J* = 6.0 Hz, 2H), 3.75 (q, *J* = 5.5 Hz, 2H), 3.42 (s, 3H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 167.93, 138.75, 134.45, 134.03, 131.83, 129.41, 128.80, 128.39, 127.11, 47.37, 44.95, 39.22; HRMS (ESI, m/z) calcd for, $C_{16}H_{18}N_2O_5S_2$: 382.0657, found: 382.0653



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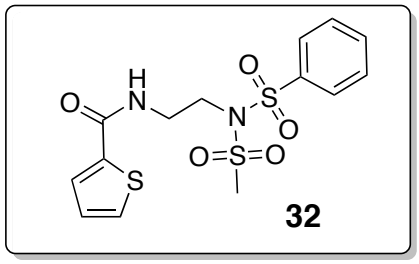
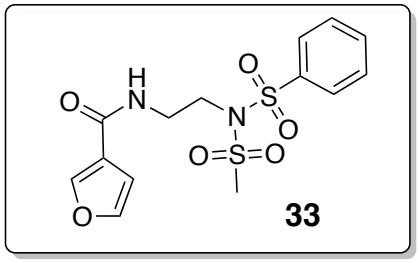
N–(2–(*N*–(Methylsulfonyl)phenylsulfonamido)ethyl)propionamide
White solid (78%), m.p, 130–133 ^{o}C; FTIR (neat, ATR, cm^{-1}) 3282, 1647, 1539, 1448, 1431, 1360, 1346, 1164, 1070, 964, 900, 796, 725, 681 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform–*d*) δ 8.01 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.69 – 7.64 (m, 1H), 7.59 – 7.53 (m, 2H), 5.88 (s, 1H), 3.85 (t, *J* = 5.7 Hz, 2H), 3.56 (q, *J* = 5.6 Hz, 2H), 3.43 (s, 3H), 2.24 (q, *J* = 7.6 Hz, 2H), 1.16 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 174.49, 138.94, 134.40, 129.40, 128.41, 47.55, 44.89, 38.48, 29.90, 9.82; HRMS (ESI, m/z) calcd for, $C_{12}H_{18}N_2O_5S_2$: 334.0657, found: 334.0653



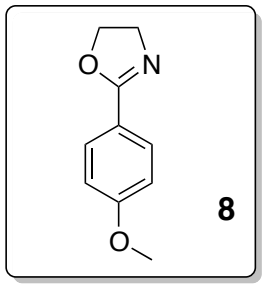
32

N–(2–(*N*–(methylsulfonyl)phenylsulfonamido)ethyl)thiophene–2–carboxamide
White solid (70%), m.p. 123–125 ^{o}C; FTIR (neat, ATR, cm^{-1}) 3269, 1610.1549, 1361, 1347, 1320, 1265, 1085, 1065, 967, 895, 853, 819, 783, 735, 728 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform–*d*) δ 8.02 (dd, *J* = 8.7, 1.5 Hz, 2H), 7.68 – 7.61 (m, 1H), 7.57 – 7.50 (m, 3H), 7.48 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.07 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.71 (s, 1H), 3.95 (t, *J* = 5.7 Hz, 2H), 3.71 (q, *J* = 5.5 Hz, 2H), 3.42 (s, 3H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 162.28, 138.52, 138.49, 134.31, 130.36, 129.27, 128.25, 128.24, 127.74, 47.08, 44.81, 39.07; HRMS (ESI, m/z) calcd for, $C_{14}H_{16}N_2O_5S_3$: 388.0221, found: 388.0218.

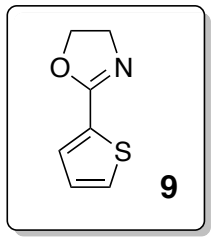


N–(2–(*N*–(Methylsulfonyl)phenylsulfonamido)ethyl)furan–3–carboxamide
White solid (70%), m.p. 123–125 °C; FTIR (neat, ATR, cm^{-1}) 3254, 3150, 1637, 1585, 1539, 1449, 1361, 1348, 1338, 1318, 1128, 1088, 1069, 1031, 965, 873, 809, 753, 725, 682, 674 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform–*d*) δ 8.00 (d, *J* = 7.4 Hz, 2H), 7.96 (s, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 2H), 7.42 (s, 1H), 6.66 (d, *J* = 1.9 Hz, 1H), 6.55 (s, 1H), 3.92 (t, *J* = 5.7 Hz, 2H), 3.67 (q, *J* = 5.5 Hz, 2H), 3.41 (s, 3H); ^{13}C NMR (126 MHz, $cdcl_3$) δ 163.13, 145.06, 143.97, 138.66, 134.46, 129.41, 128.35, 122.37, 108.41, 47.24, 44.92, 38.66; HRMS (ESI, m/z) calcd for, $C_{14}H_{16}N_2O_6S_2$:372.0450, found: 372.0446.

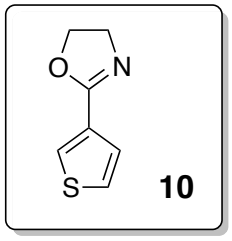
3.6 Characterization of known Compounds



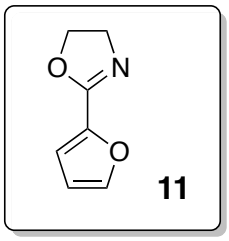
2–(4–methoxyphenyl)–4,5–dihydrooxazole
White solid, m.p. 40.8–42.3 °C; FTIR (neat, ATR, cm^{-1}) 1644, 1606, 1510, 1253, 1166, 1068, 1021, 939, 844, 672; ^{1}H NMR (500 MHz, Chloroform–*d*) δ 7.88 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 4.39 (t, *J* = 9.5 Hz, 2H), 4.02 (t, *J* = 9.4 Hz, 2H), 3.83 (s, 3H); 13C NMR (126 MHz, cdcl3) δ 162.15, 129.99, 128.94, 120.35, 113.80, 67.64, 55.45, 54.92.



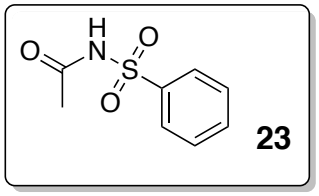
2–(thiophen–2–yl)–4,5–dihydrooxazole
White solid, m.p. 59–60 °C; FTIR (neat, ATR, cm^{-1}) 1643, 1430, 1246, 1051, 1013, 925, 851, 729, 692; ^{1}H NMR (500 MHz, Chloroform–*d*) δ 7.58 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.44 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.07 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.42 (t, *J* = 9.4 Hz, 2H), 4.03 (t, *J* = 9.4 Hz, 2H); ^{13}C NMR (126 MHz, $cdcl_3$) δ 160.51, 130.49, 130.25, 129.83, 127.68, 68.16, 55.12.



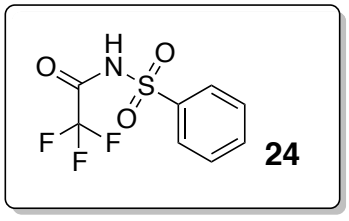
2–(thiophen–3–yl)–4,5–dihydrooxazole
White solid, m.p. 73–74 ºC; FTIR (neat, ATR, cm^{-1}) 3107, 3070, 1651, 1421, 1317, 1258, 1064, 951, 702; ^{1}H NMR (500 MHz, Chloroform–*d*) δ 7.87 (d, *J* = 3.3 Hz, 1H), 7.51 (d, *J* = 5.1 Hz, 1H), 7.31 (dd, *J* = 5.1, 3.0 Hz, 1H), 4.38 (t, *J* = 9.4 Hz, 2H), 4.02 (t, *J* = 9.5 Hz, 2H); ^{13}C NMR (126 MHz, $cdcl_3$) δ 161.16, 130.06, 128.66, 127.30, 126.24, 67.55, 54.91.



2–(furan–2–yl)–4,5–dihydrooxazole
White solid, m.p. 76–79 ºC; FTIR (neat, ATR, cm^{-1}) 3099, 1673, 1563, 1480, 1352, 1172, 1096, 1013, 954, 774, 706 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform–*d*) δ 7.54 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.94 (d, *J* = 3.4 Hz, 1H), 6.48 (dd, *J* = 3.5, 1.8 Hz, 1H), 4.41 (t, *J* = 9.6 Hz, 2H), 4.06 (t, *J* = 9.4 Hz, 2H); ^{13}C NMR (126 MHz, $cdcl_3$) δ 157.09, 145.26, 143.24, 114.27, 111.60, 67.87, 55.04.

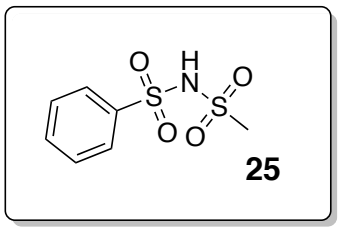


N–(phenylsulfonyl)acetamide
White solid, m.p. 128–131 ºC; FTIR (neat, ATR, cm^{-1}) 3112, 2902, 1702, 1686, 1459, 1352, 1160, 1090, 934, 858, 762, 687 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform–*d*) δ 9.38 (s, 1H), 8.11 – 7.99 (m, 2H), 7.68 – 7.60 (m, 1H), 7.57 – 7.51 (m, 2H), 2.07 (s, 3H); ^{13}C NMR (126 MHz, $cdcl_3$) δ 169.00, 138.54, 134.17, 129.16, 128.29, 23.60.



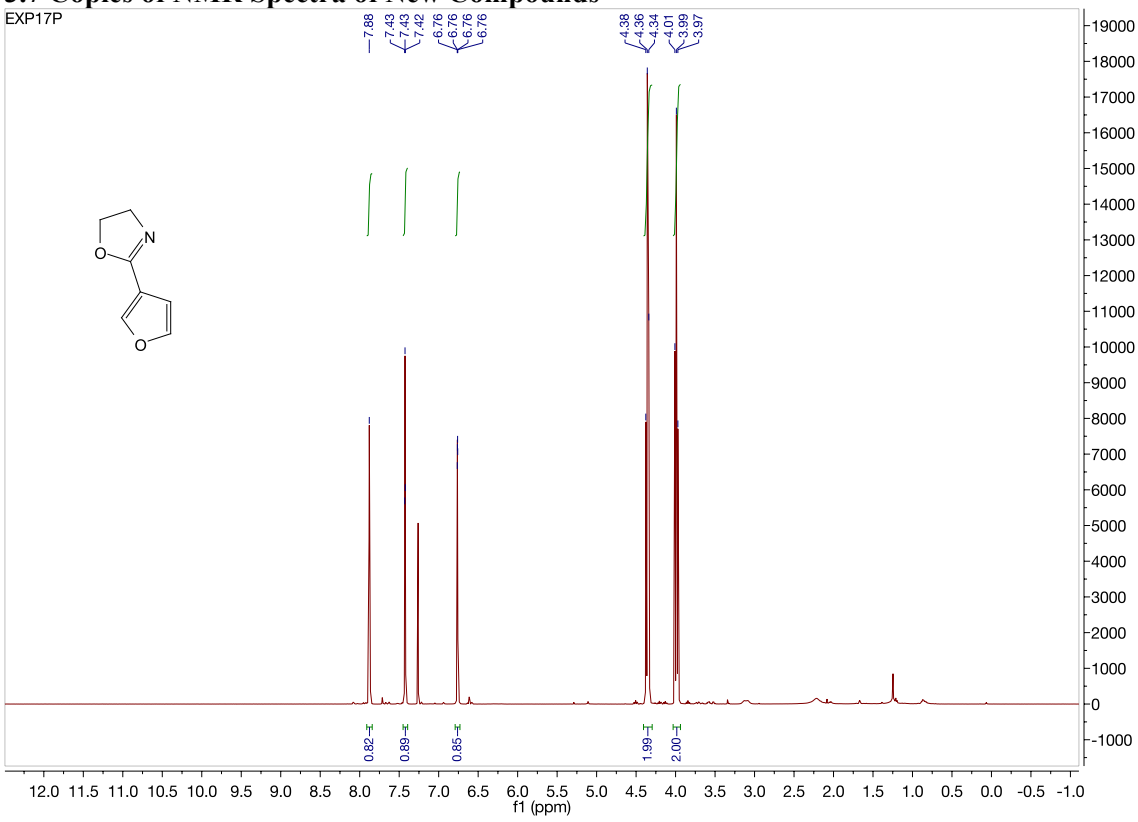
2,2,2–trifluoro–*N*–(phenylsulfonyl)acetamide
White solid, m.p. 139–142 ºC; FTIR (neat, ATR, cm^{-1}) 3223, 1772, 1467, 1360, 1154, 1116, 1081, 887, 826, 757, 679 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform–*d*) δ 8.79 (br. s, 1H), 8.14 – 8.10 (m, 2H), 7.78 –

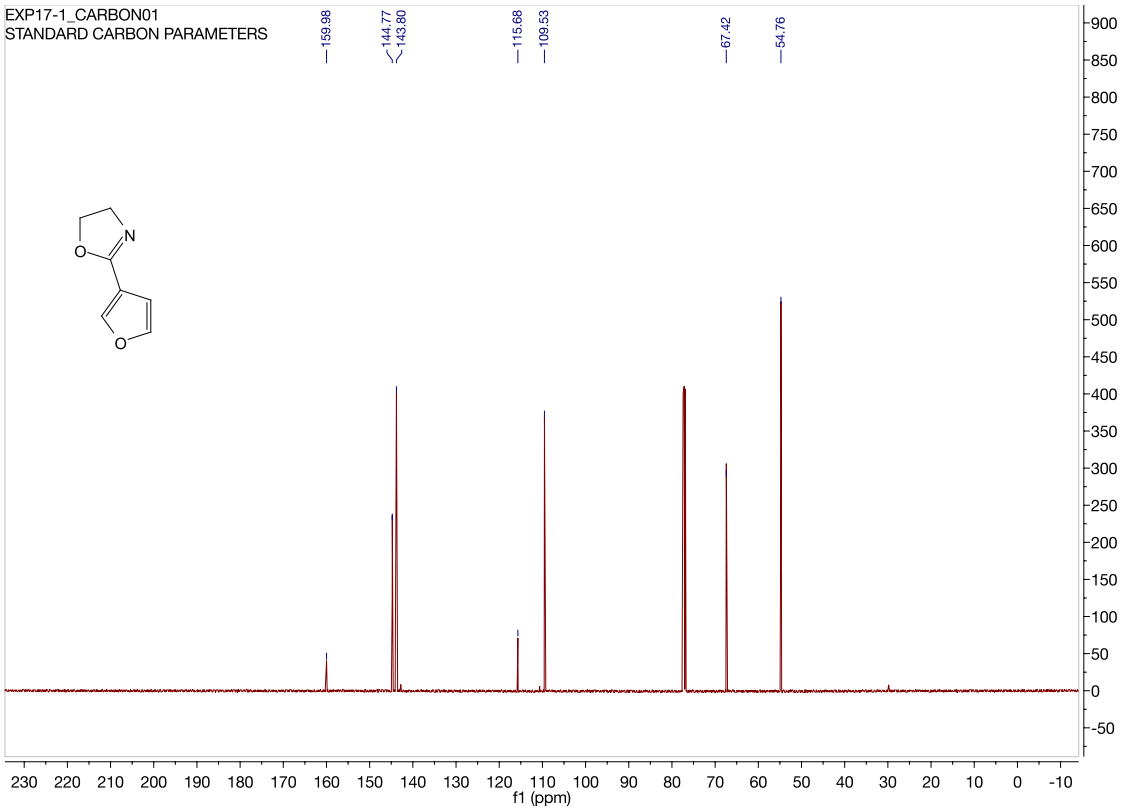
7.71 (m, 1H), 7.65 – 7.56 (m, 2H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 154.20, 153.87, 136.88, 135.38, 129.57, 128.97; ^{19}F NMR (470 MHz, cdcl$_3$) δ –75.64.



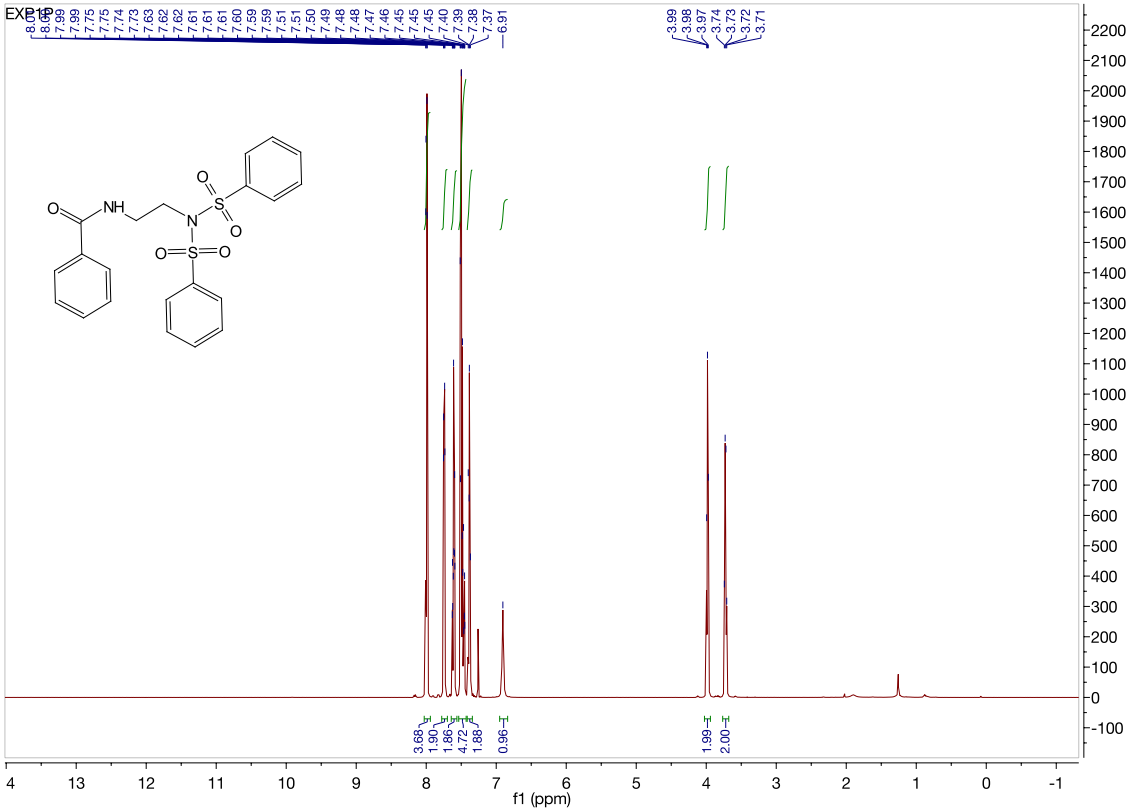
N–(methylsulfonyl)benzenesulfonamide
White solid, m.p. 138–142 ºC; FTIR (neat, ATR, cm^{-1}) 3210, 1453, 1348, 1088, 973, 864, 758 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform–*d*) δ 8.02 – 7.98 (m, 2H), 7.70 – 7.64 (m, 1H), 7.59 – 7.54 (m, 2H), 3.38 (s, 3H); ^{13}C NMR (126 MHz, cdcl$_3$) δ 139.25, 134.44, 129.38, 128.11, 44.16.

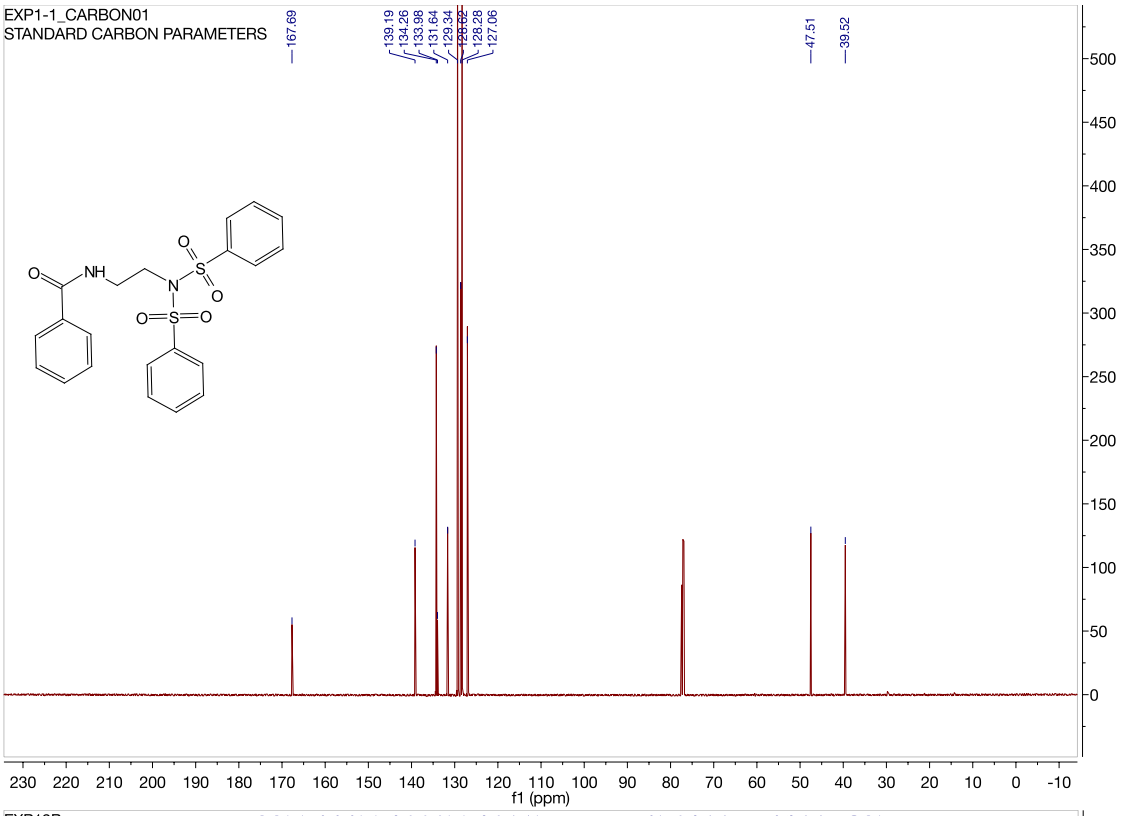
3.7 Copies of NMR Spectra of New Compounds

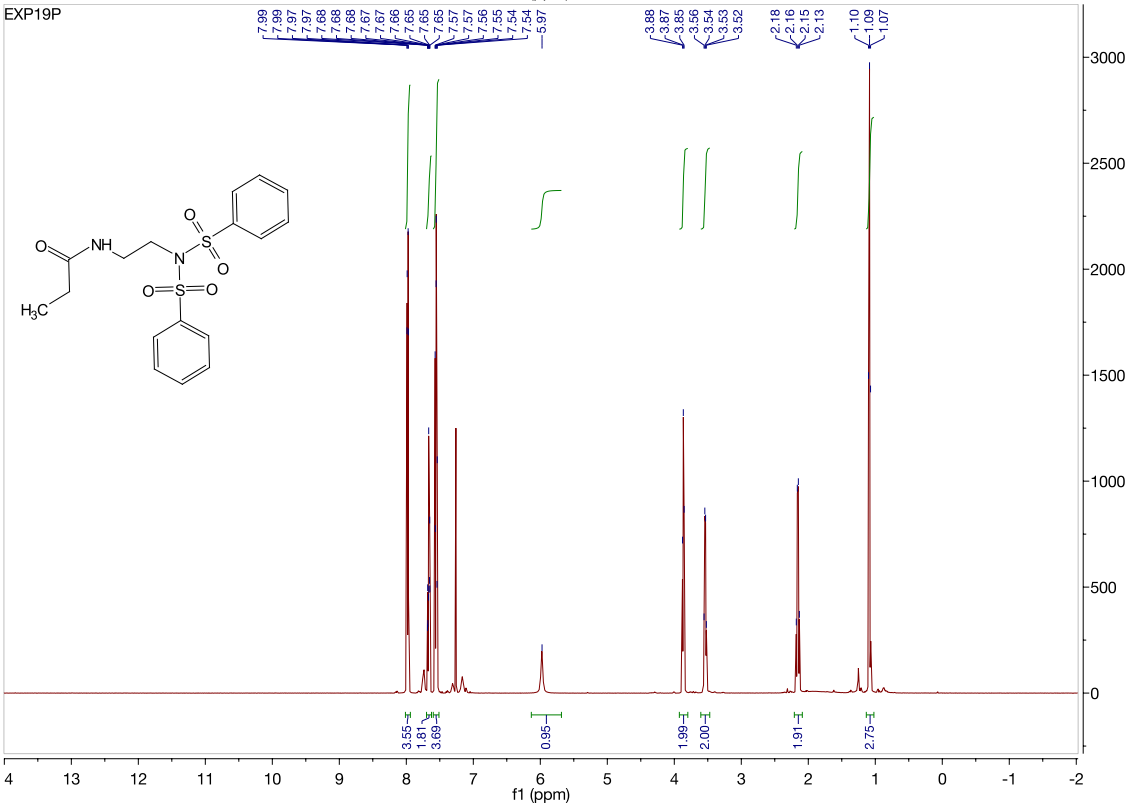


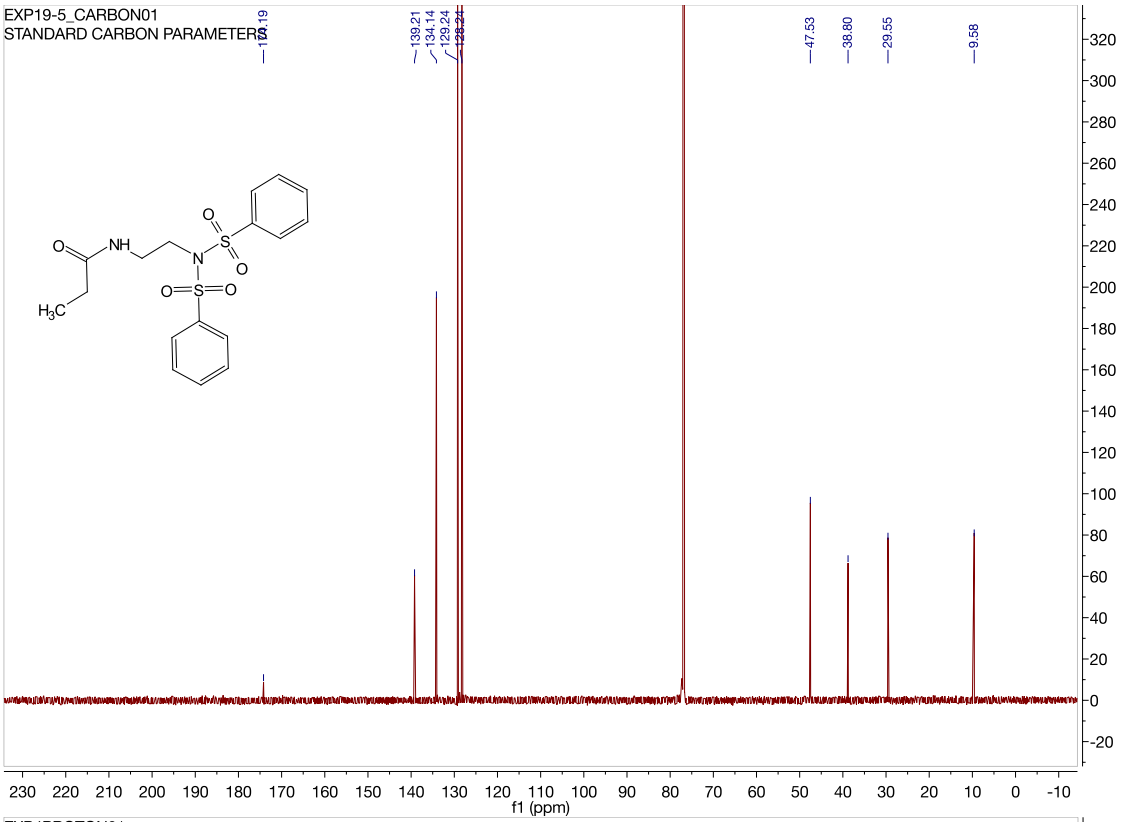


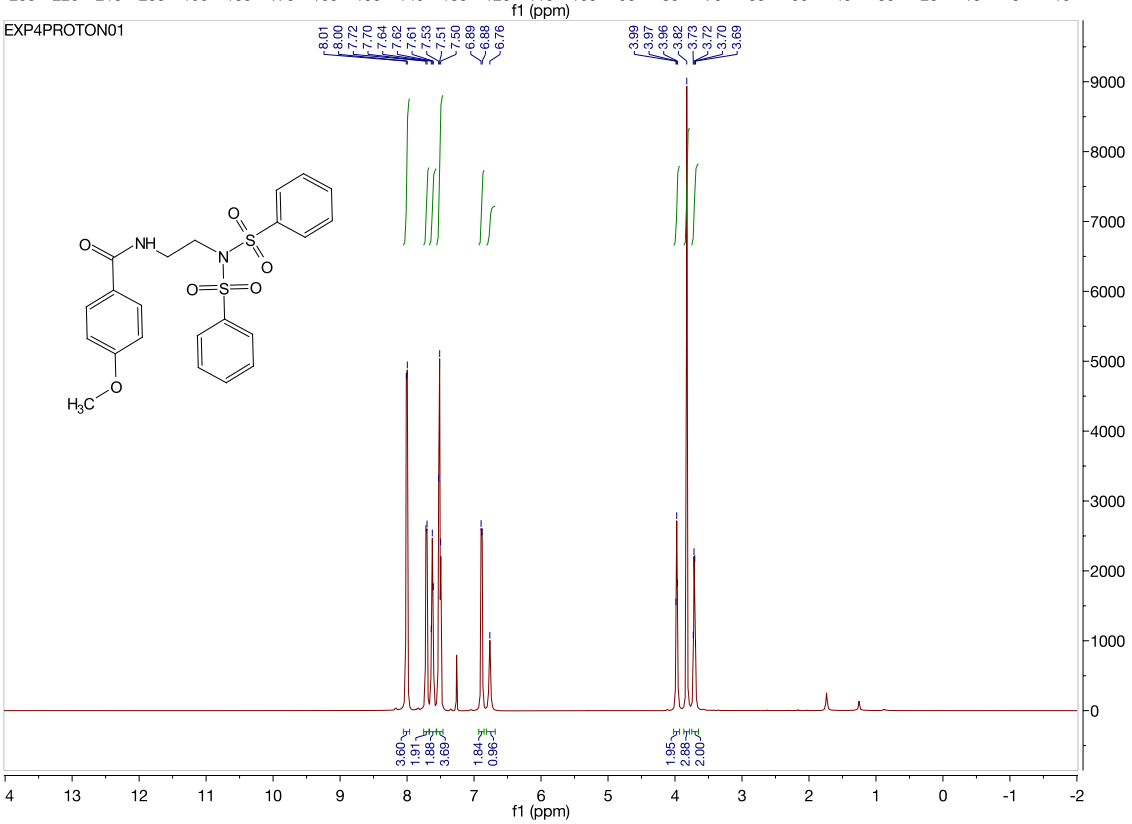
3.8 Copies of NMR for New Sulfonimides

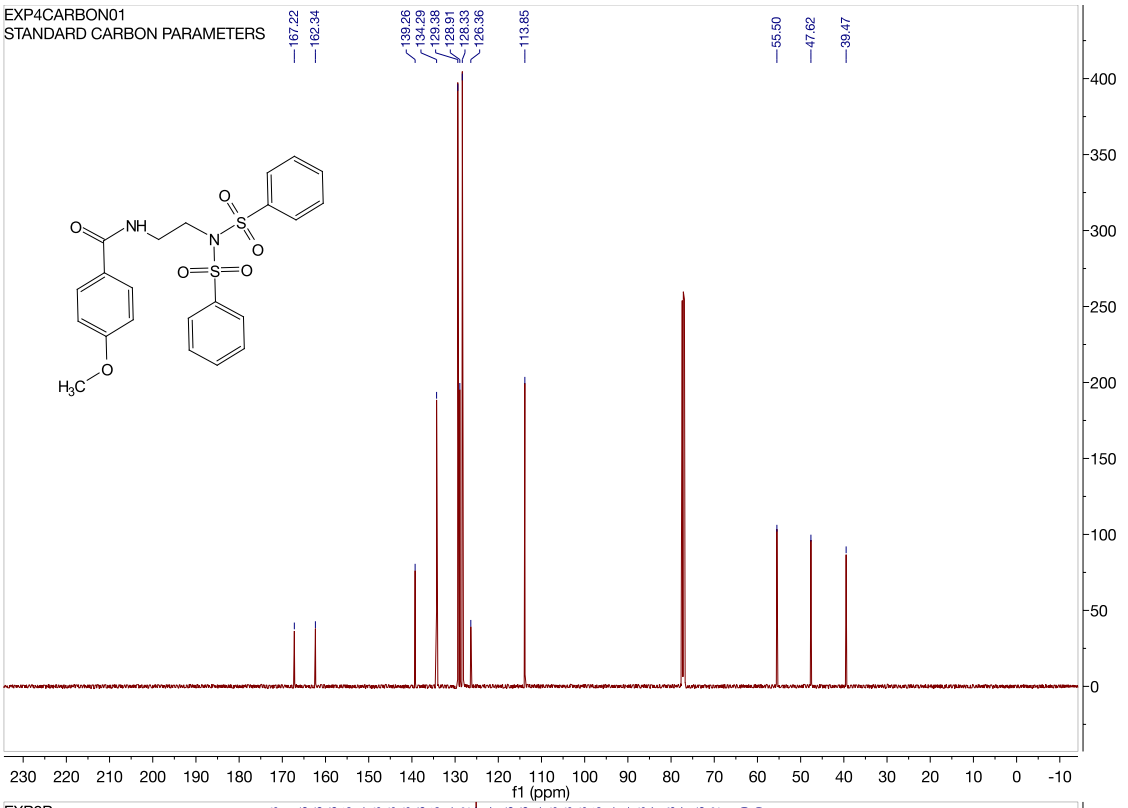


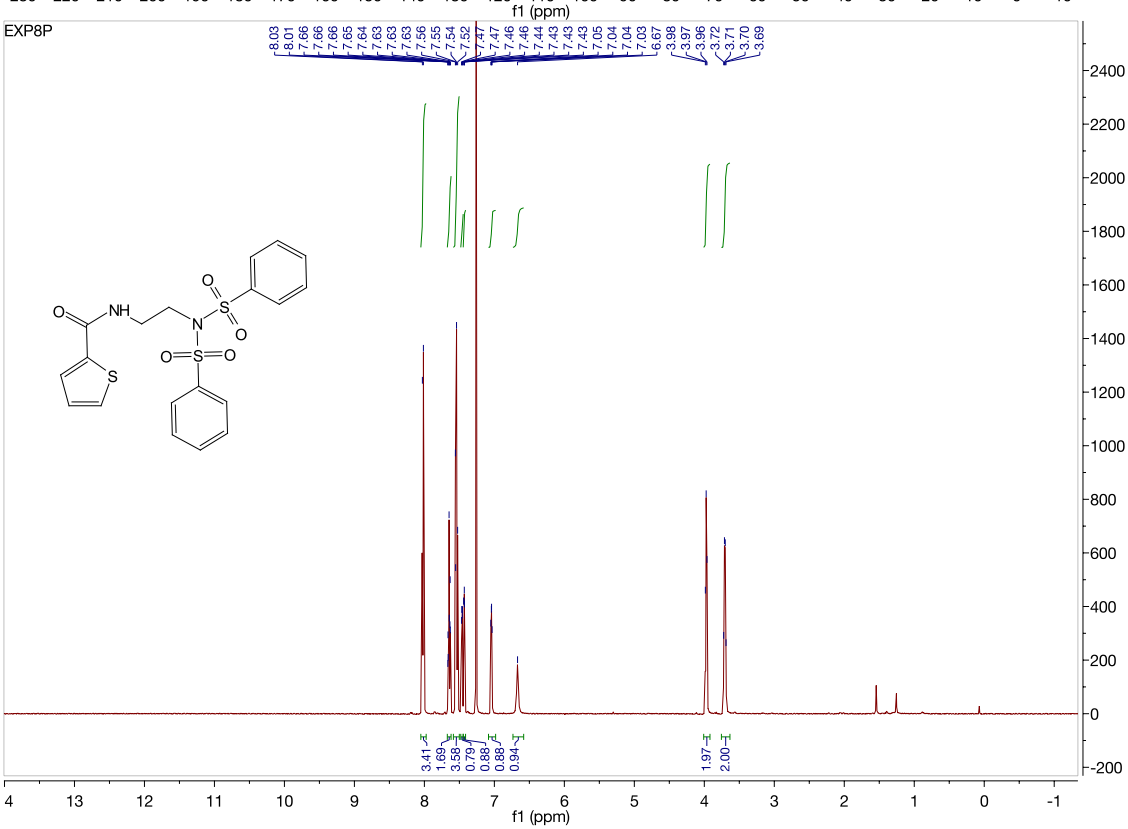

EXP1-1_CARBON01
STANDARD CARBON PARAMETERS
167.69
139.19
134.26
133.98
131.64
129.34
128.82
128.28
127.06
47.51
39.52
f1 (ppm)

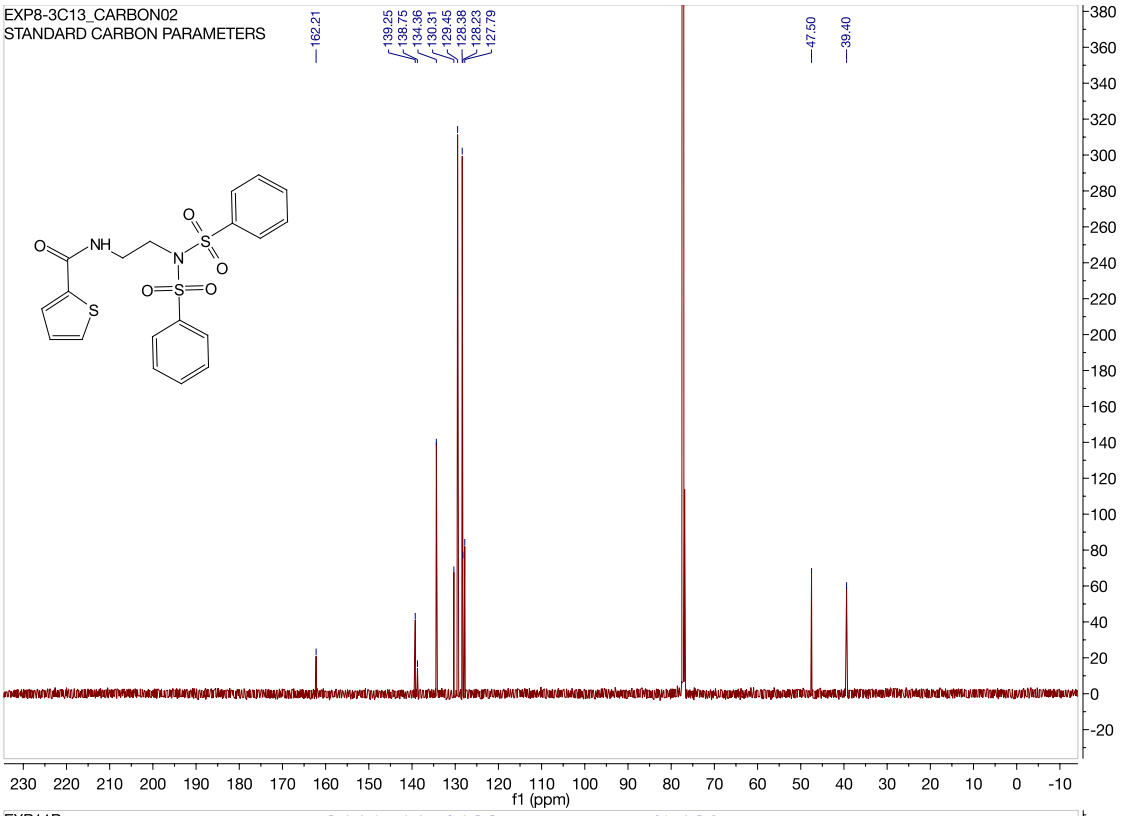

EXP19P
7.99
7.97
7.68
7.67
7.66
7.65
7.57
7.56
7.55
7.54
5.97
3.88
3.87
3.85
3.56
3.54
3.53
3.52
2.18
2.16
2.15
2.13
1.10
1.09
1.07
3.55
1.81
3.69
0.95
1.99
2.00
1.91
2.75
f1 (ppm)

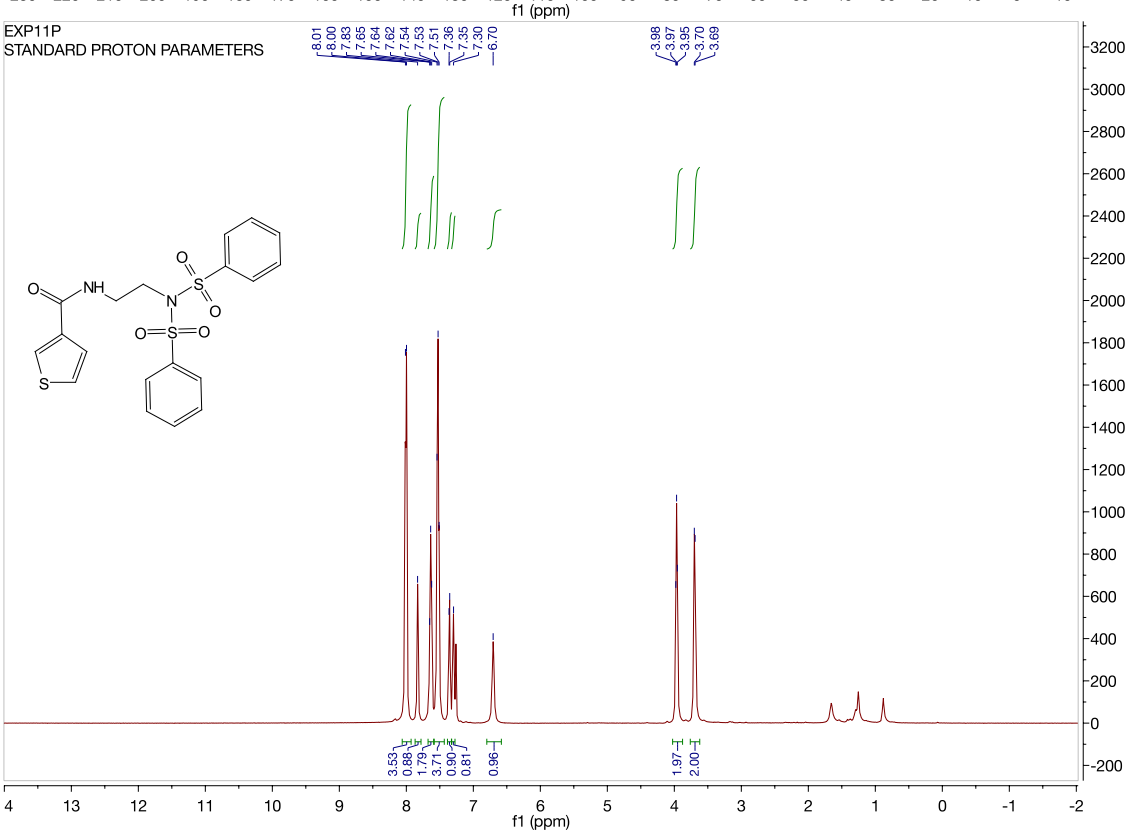

EXP19-5_CARBON01
STANDARD CARBON PARAMETERS
139.21
134.14
129.24
47.53
38.80
29.55
9.58
f1 (ppm)

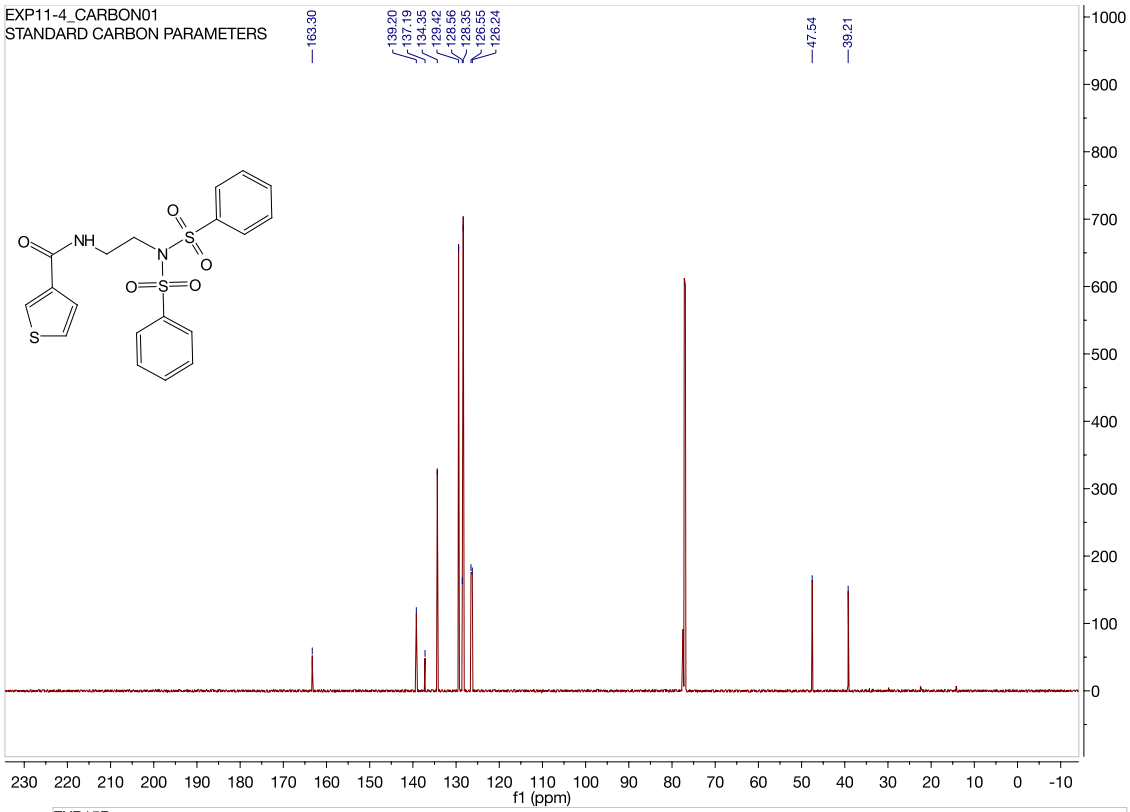

EXP4PROTON01
8.01
8.00
7.72
7.70
7.64
7.62
7.61
7.53
7.51
7.50
6.89
6.88
6.76
3.99
3.97
3.96
3.82
3.73
3.72
3.70
3.69
3.60
1.91
1.88
3.69
1.84
0.96
1.95
2.88
2.00
f1 (ppm)

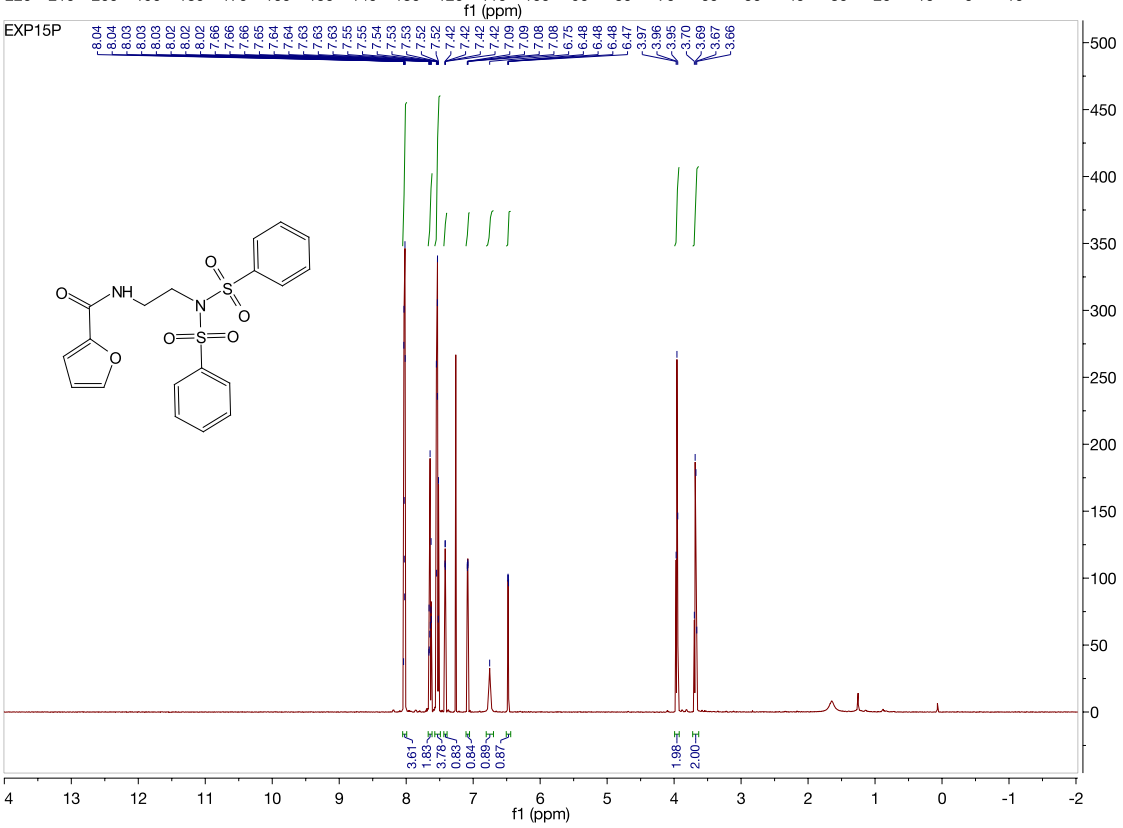

EXP4CARBON01
STANDARD CARBON PARAMETERS
167.22
162.34
139.26
134.29
129.38
128.91
128.33
126.36
113.85
55.50
47.62
39.47
f1 (ppm)

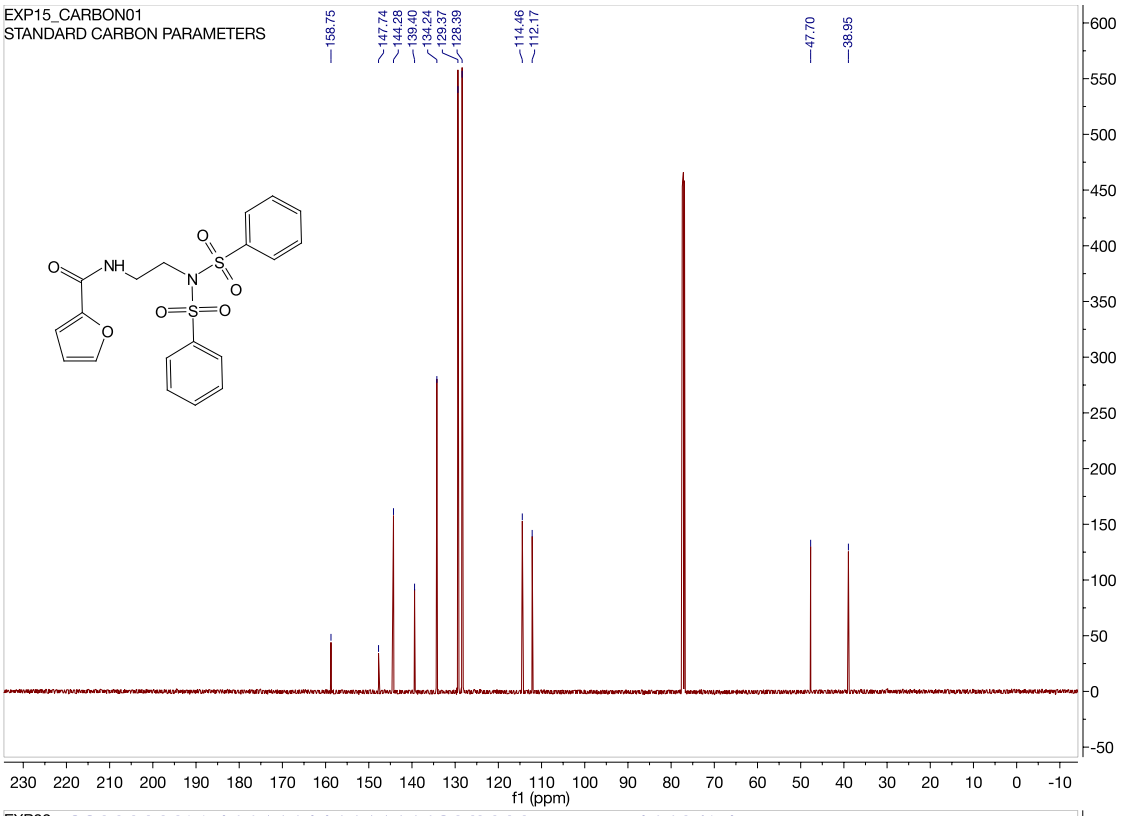

EXP8P
8.03
8.01
7.66
7.66
7.66
7.66
7.65
7.64
7.63
7.63
7.63
7.56
7.55
7.54
7.52
7.47
7.47
7.46
7.46
7.44
7.43
7.43
7.43
7.05
7.04
7.04
7.03
6.67
3.98
3.97
3.96
3.72
3.71
3.70
3.69
3.41
1.69
3.58
0.79
0.88
0.88
0.94
1.97
2.00
f1 (ppm)

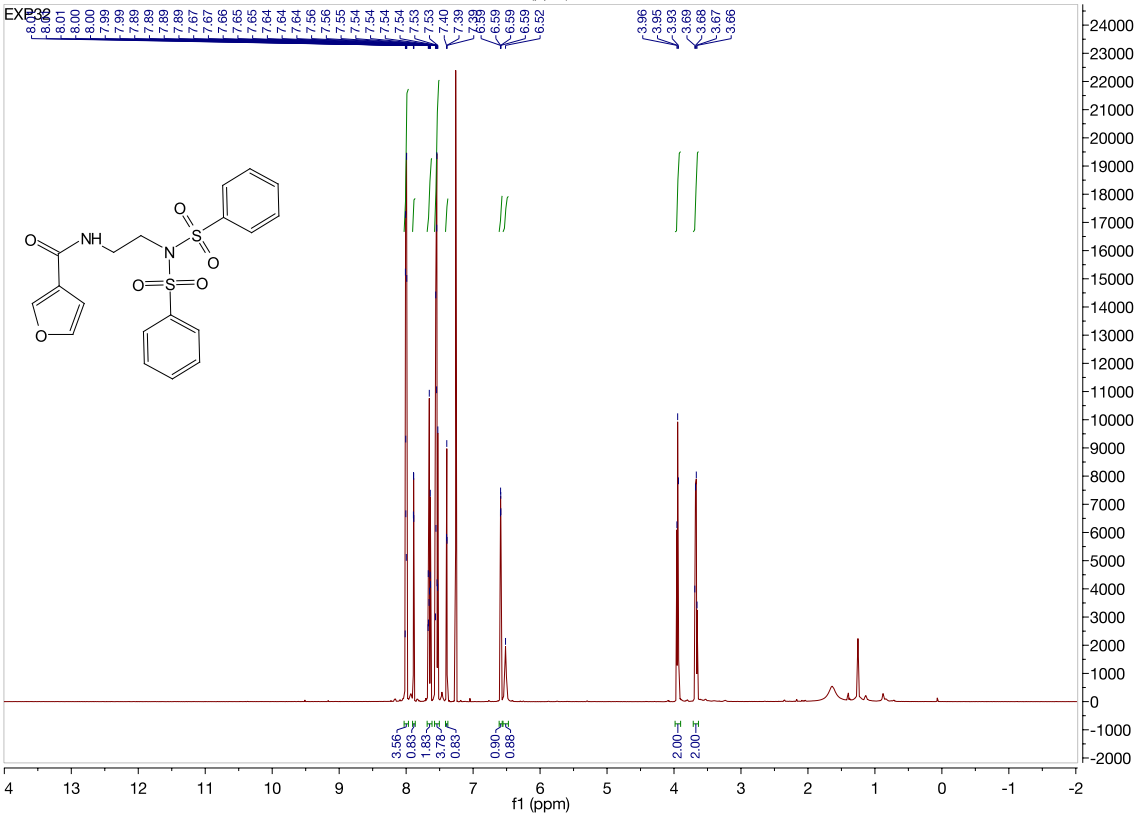

EXP8-3C13_CARBON02
STANDARD CARBON PARAMETERS
162.21
139.25
138.75
134.36
130.31
129.45
128.38
128.23
127.79
47.50
39.40
f1 (ppm)

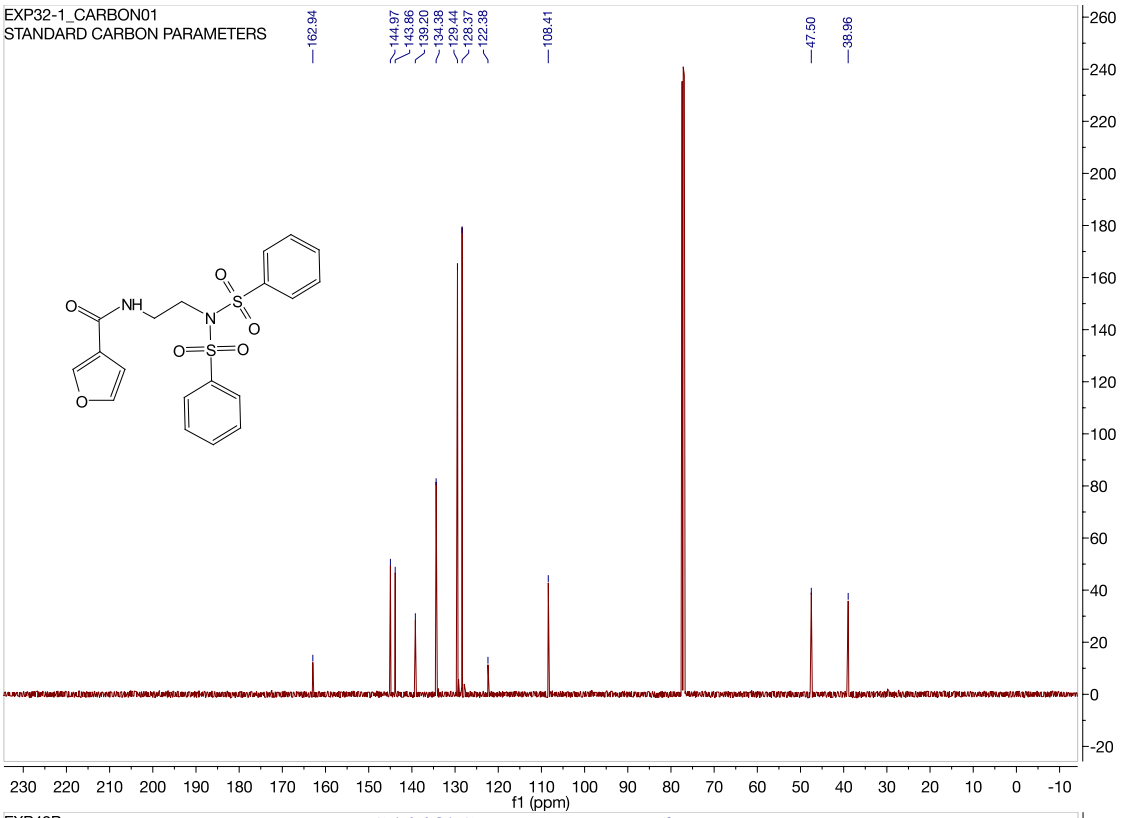

EXP11P
STANDARD PROTON PARAMETERS
8.01
8.00
7.83
7.65
7.64
7.62
7.54
7.53
7.51
7.36
7.35
7.30
6.70
3.98
3.97
3.95
3.70
3.69
3.53
0.88
1.79
3.71
0.90
0.81
0.96
1.97
2.00
f1 (ppm)

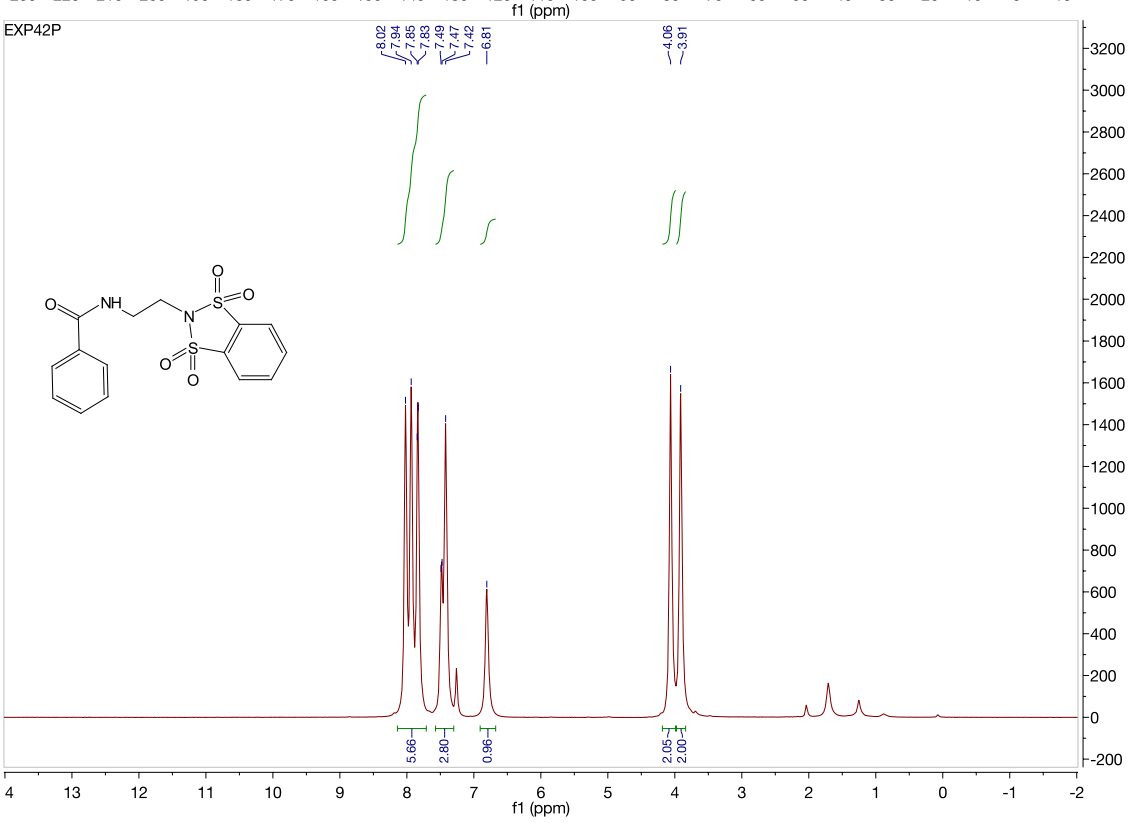

EXP11-4_CARBON01
STANDARD CARBON PARAMETERS
163.30
139.20
137.19
134.35
129.42
128.56
128.35
126.55
126.24
47.54
39.21
f1 (ppm)

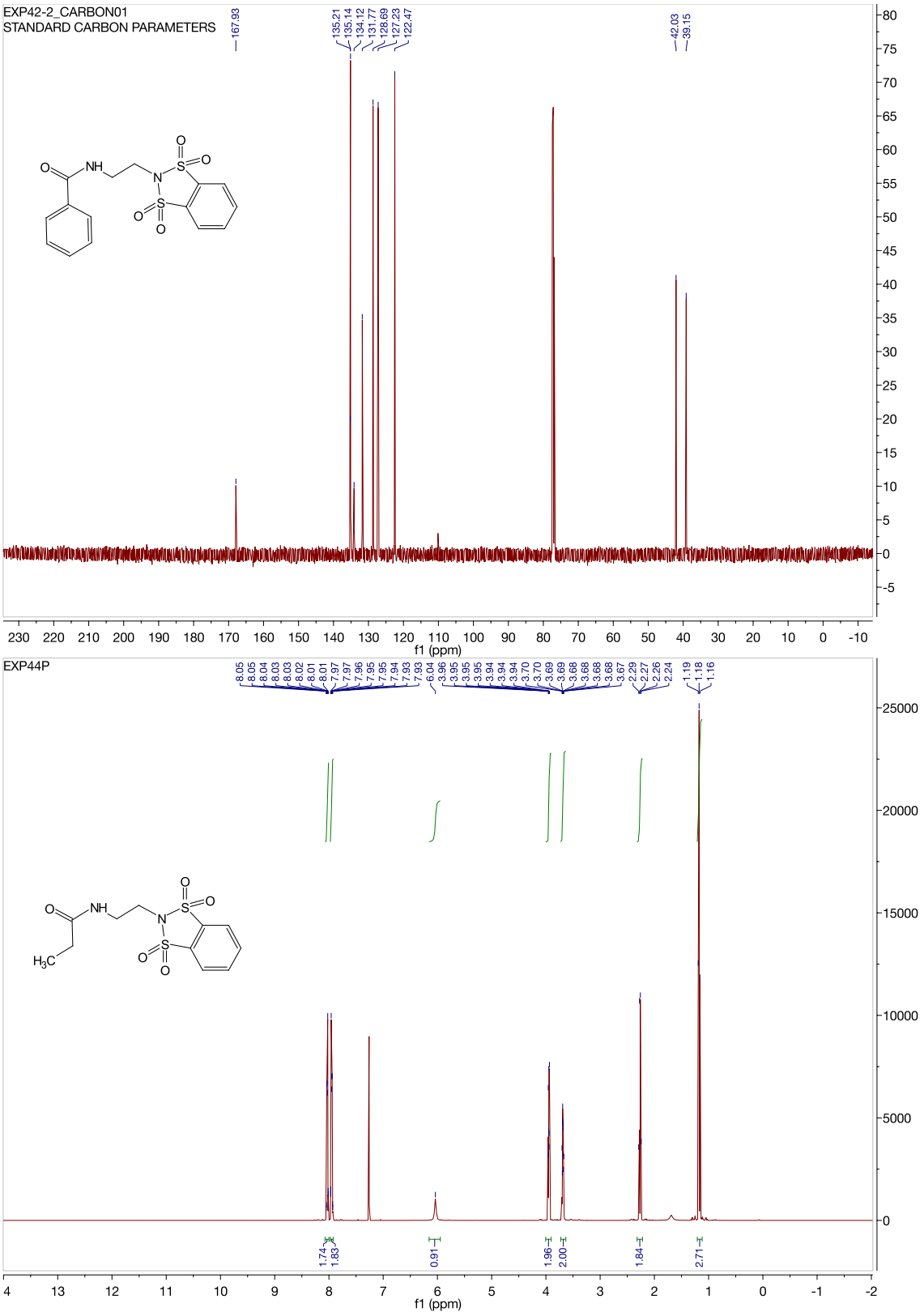

EXP15P
f1 (ppm)

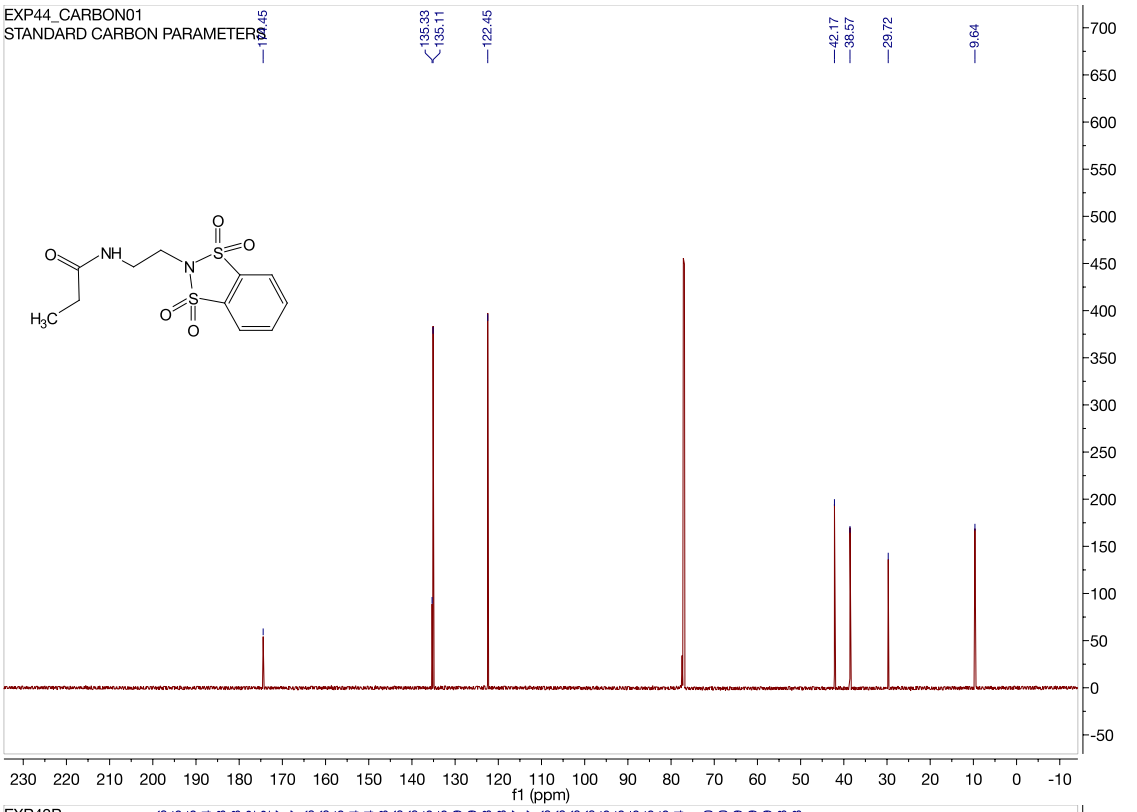

EXP15_CARBON01
STANDARD CARBON PARAMETERS
158.75
147.74
144.28
139.40
134.24
129.37
128.39
114.46
112.17
47.70
38.95
f1 (ppm)

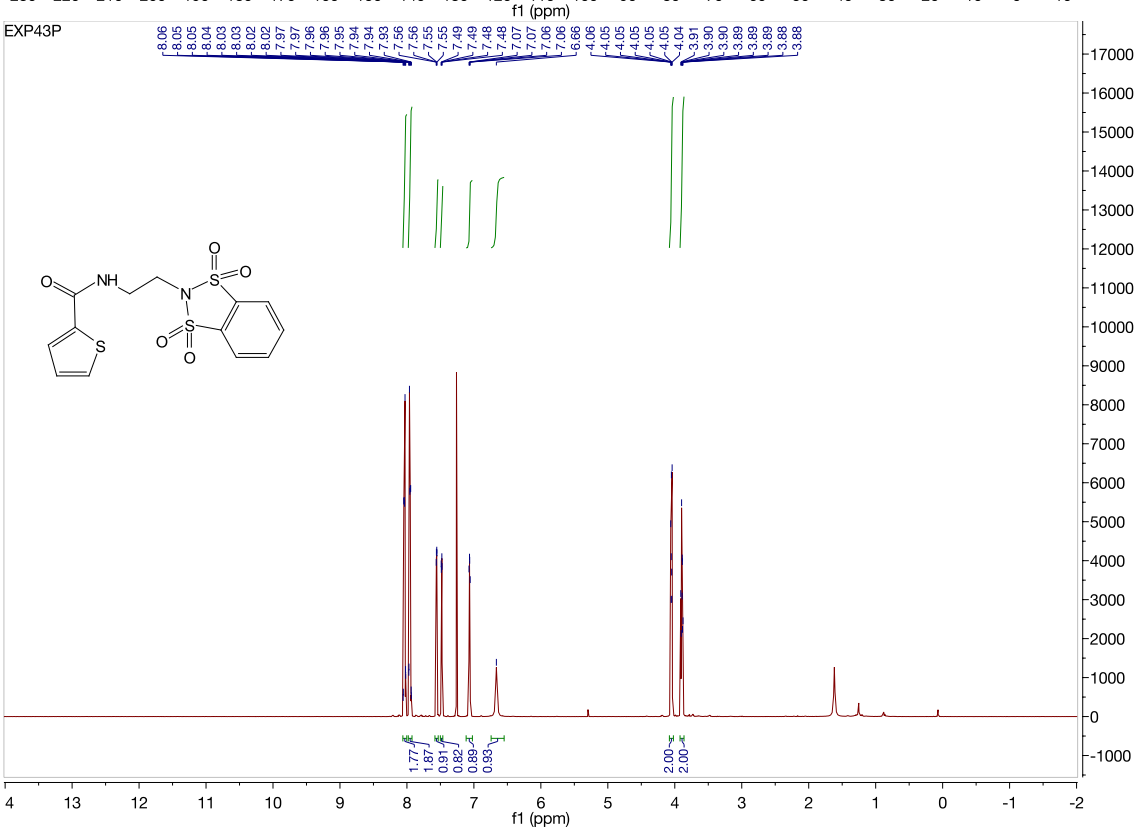

EXP32
f1 (ppm)

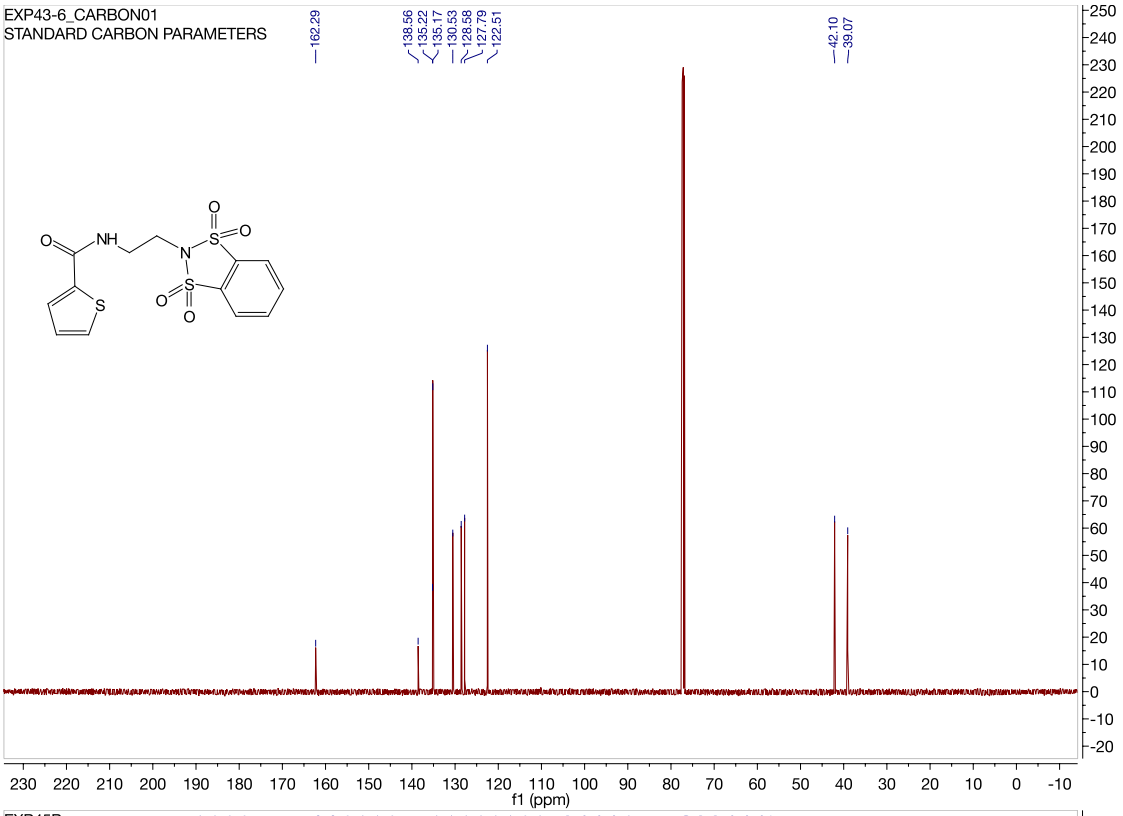

EXP32-1_CARBON01
STANDARD CARBON PARAMETERS
162.94
144.97
143.86
139.20
134.38
129.44
128.37
122.38
108.41
47.50
38.96
f1 (ppm)

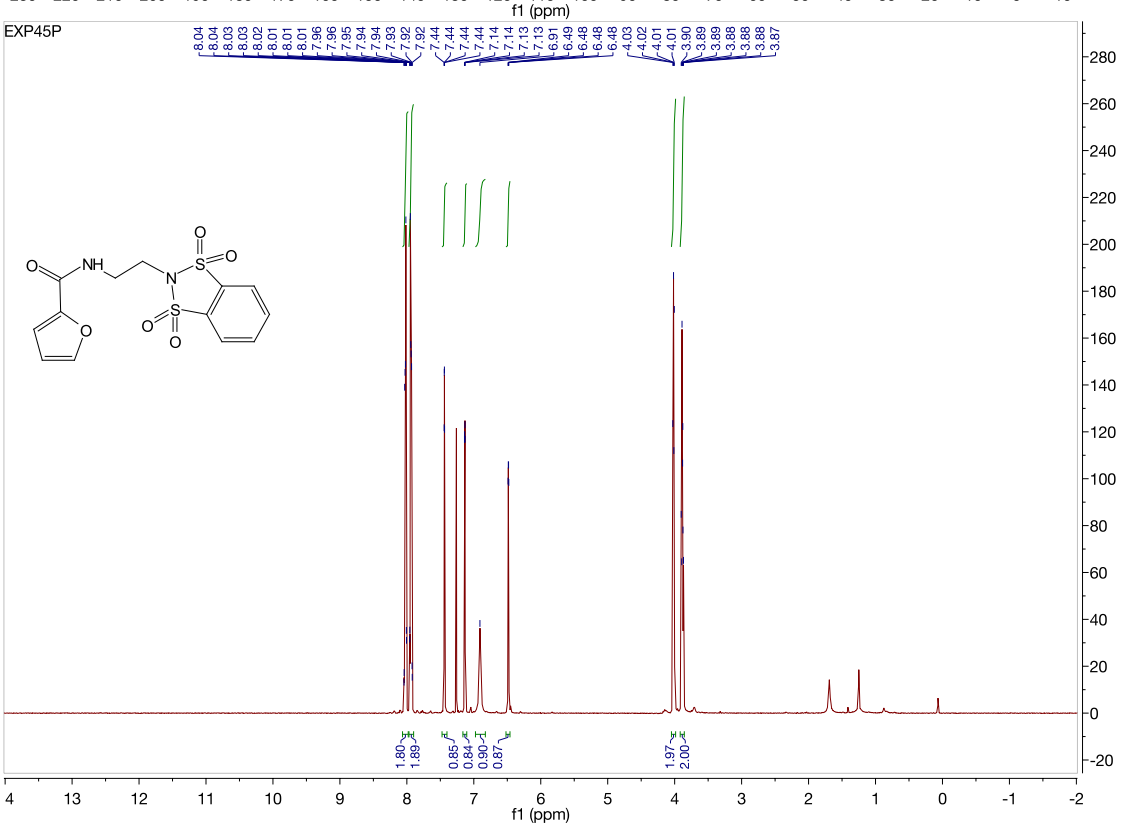

EXP42P
8.02
7.94
7.85
7.83
7.49
7.47
7.42
6.81
4.06
3.91
5.66
2.80
0.96
2.05
2.00
f1 (ppm)

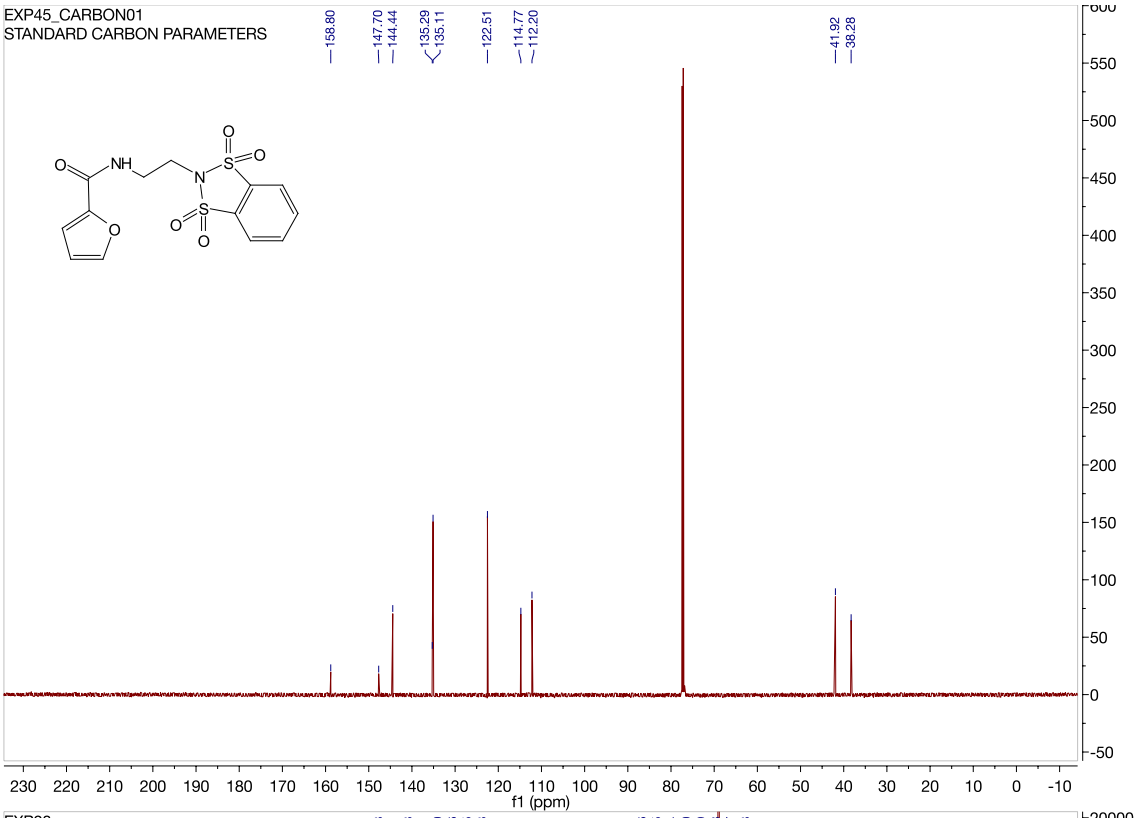

EXP42-2_CARBON01
STANDARD CARBON PARAMETERS
167.93
135.21
135.14
134.12
131.77
128.69
127.23
122.47
42.03
39.15
f1 (ppm)
EXP44P
8.05
8.05
8.04
8.03
8.03
8.02
8.01
8.01
7.97
7.97
7.96
7.95
7.95
7.94
7.93
7.93
6.04
3.96
3.95
3.95
3.95
3.94
3.94
3.94
3.70
3.70
3.69
3.69
3.68
3.68
3.68
3.67
2.29
2.27
2.26
2.24
1.19
1.18
1.16
1.74
1.83
0.91
1.96
2.00
1.84
2.71
f1 (ppm)

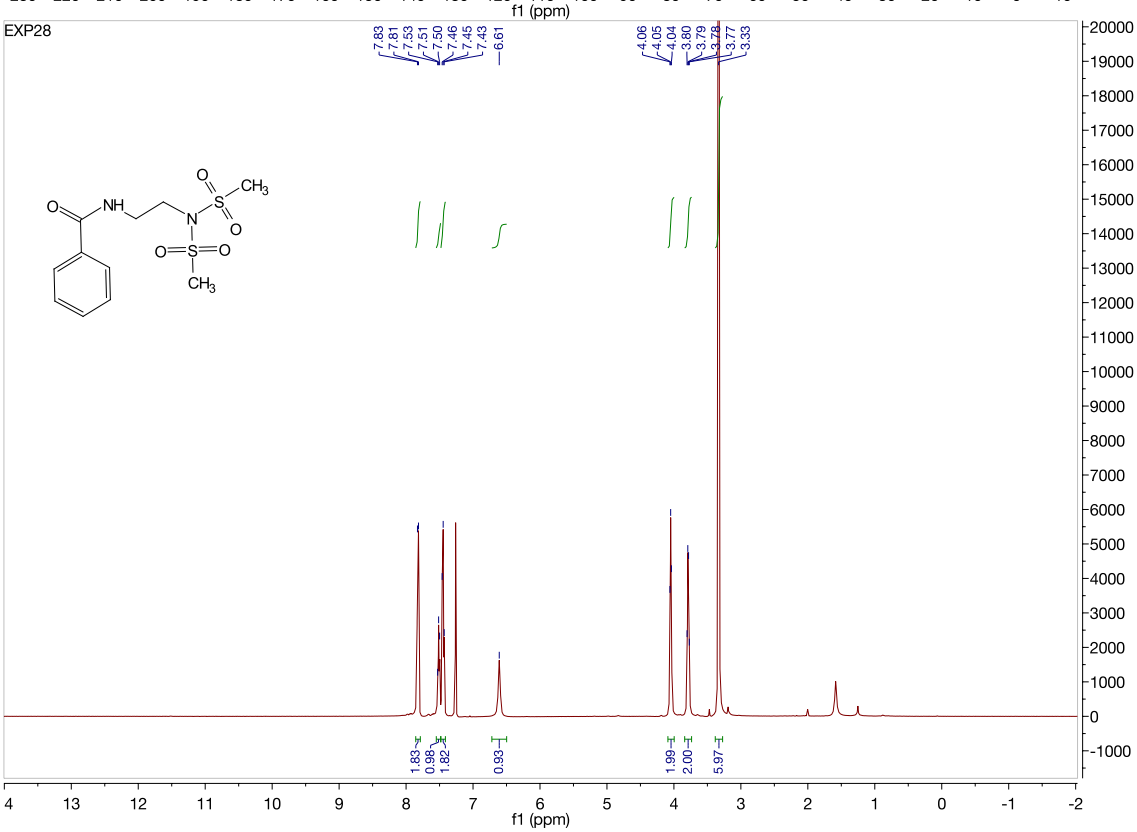

EXP44_CARBON01
STANDARD CARBON PARAMETER
135.33
135.11
122.45
42.17
38.57
29.72
9.64
f1 (ppm)

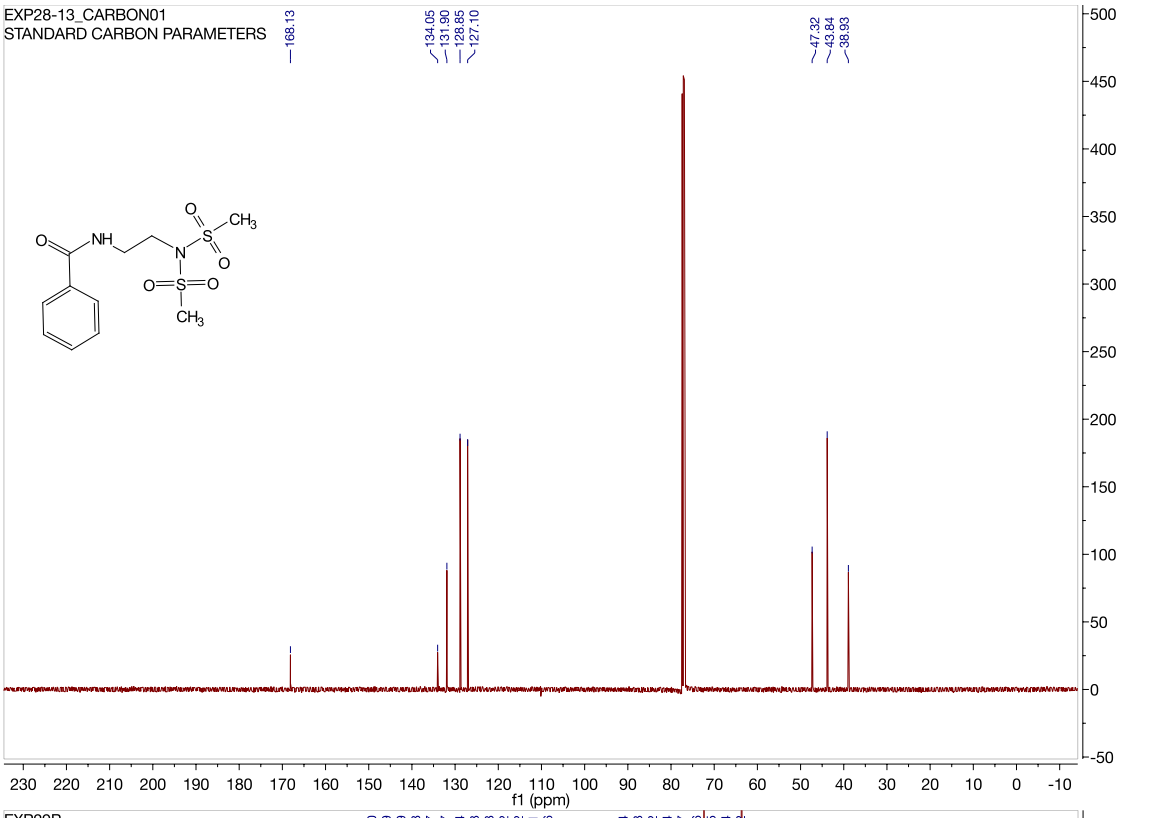

EXP43P
f1 (ppm)

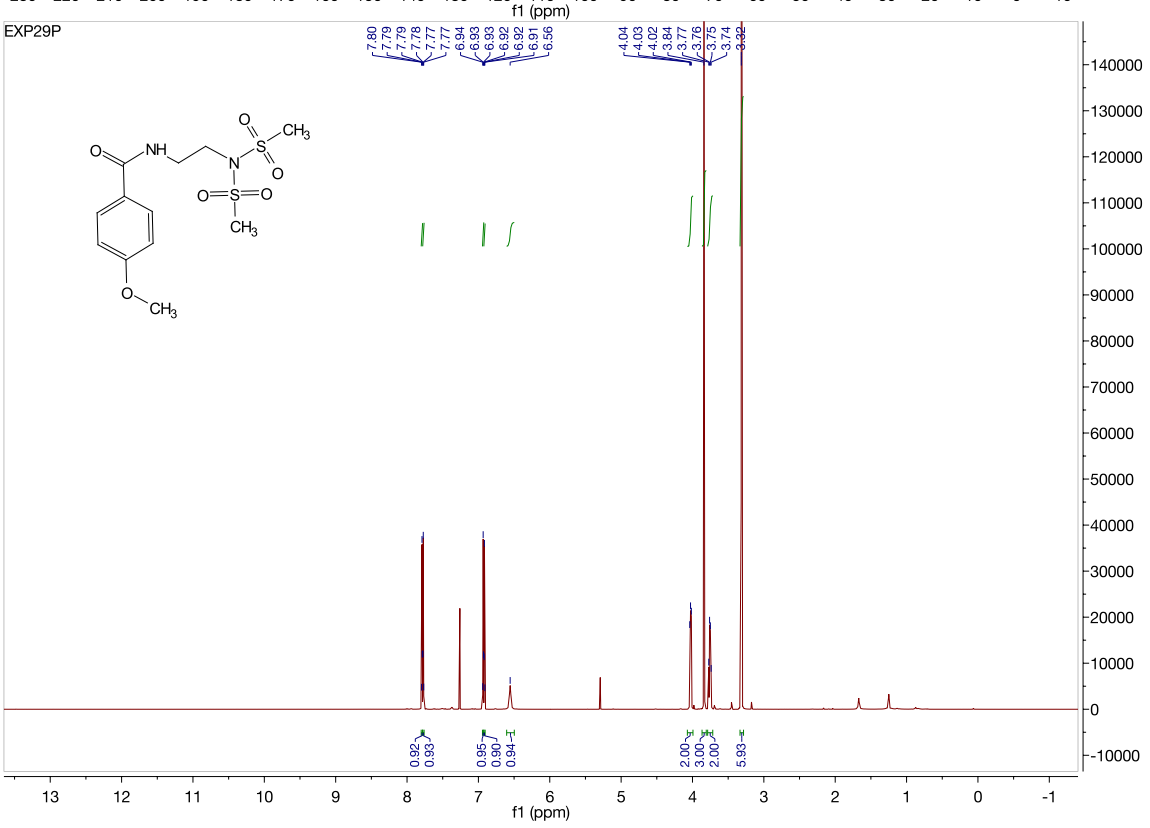

EXP43-6_CARBON01
STANDARD CARBON PARAMETERS
162.29
138.56
135.22
135.17
130.53
128.58
127.79
122.51
42.10
39.07
f1 (ppm)

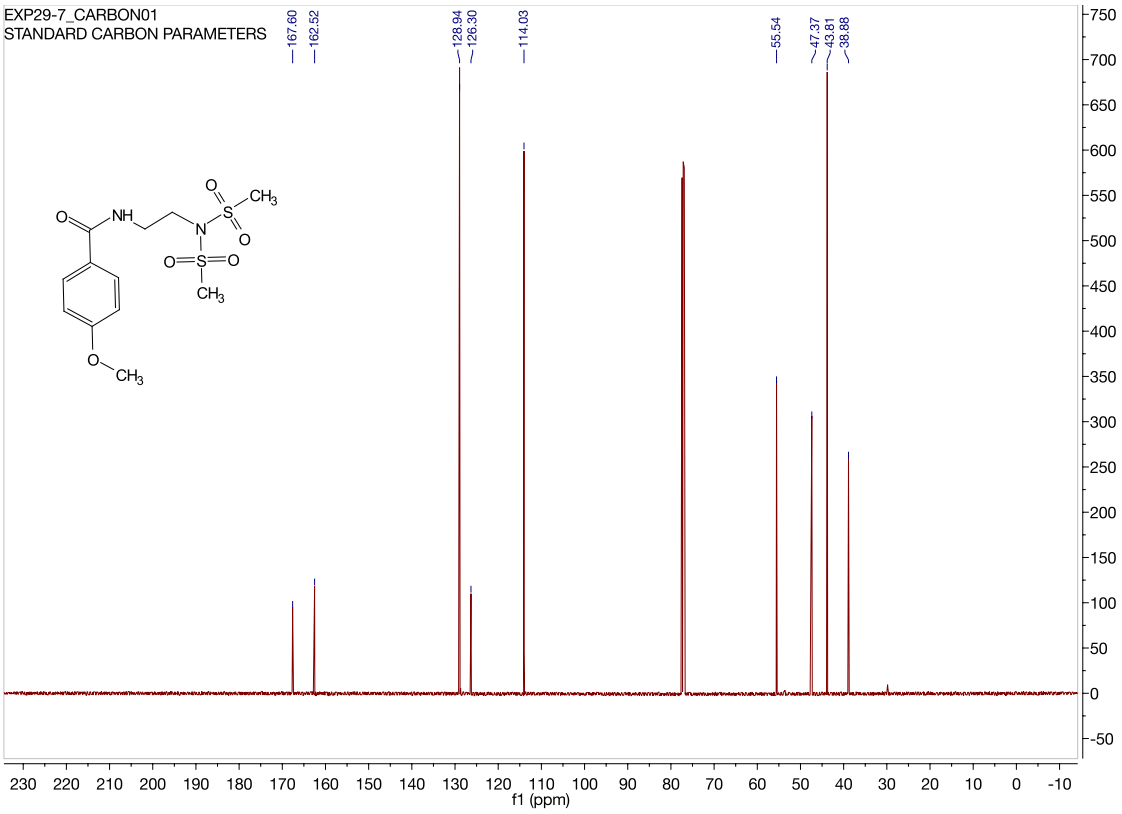

EXP45P
f1 (ppm)

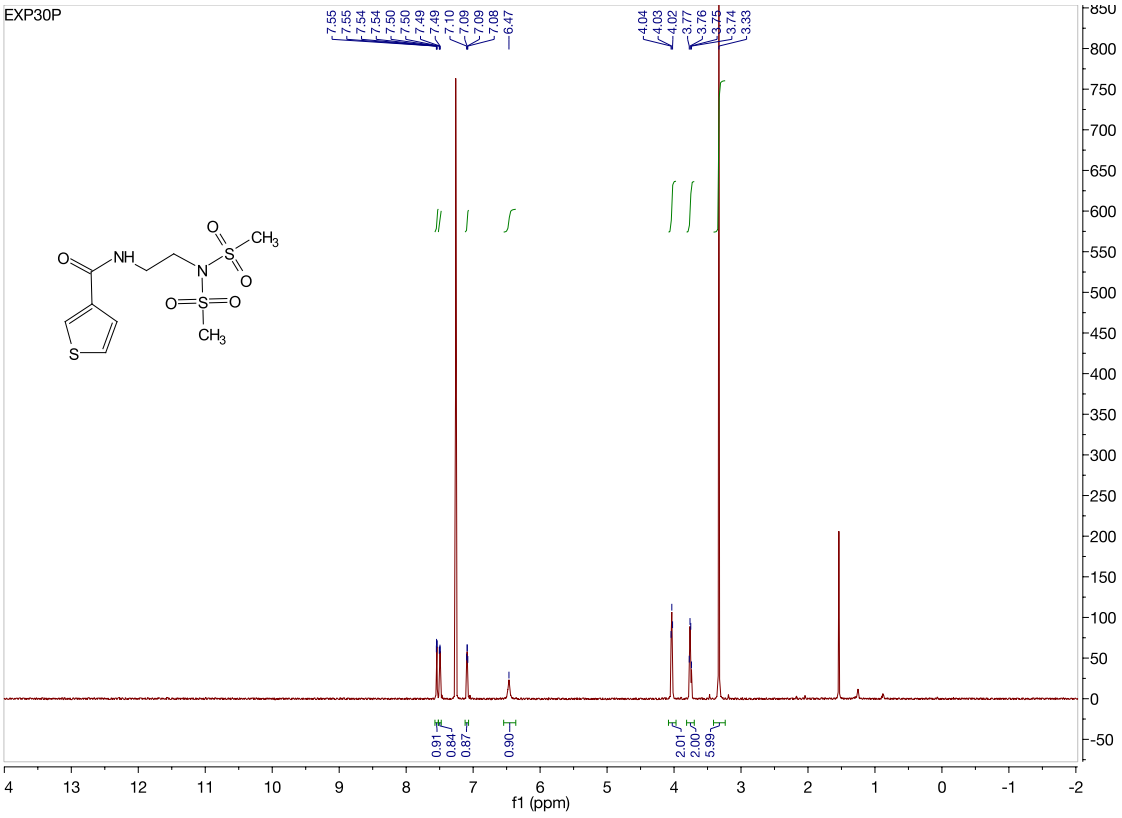

EXP45_CARBON01
STANDARD CARBON PARAMETERS
158.80
147.70
144.44
135.29
135.11
122.51
114.77
112.20
41.92
38.28
f1 (ppm)

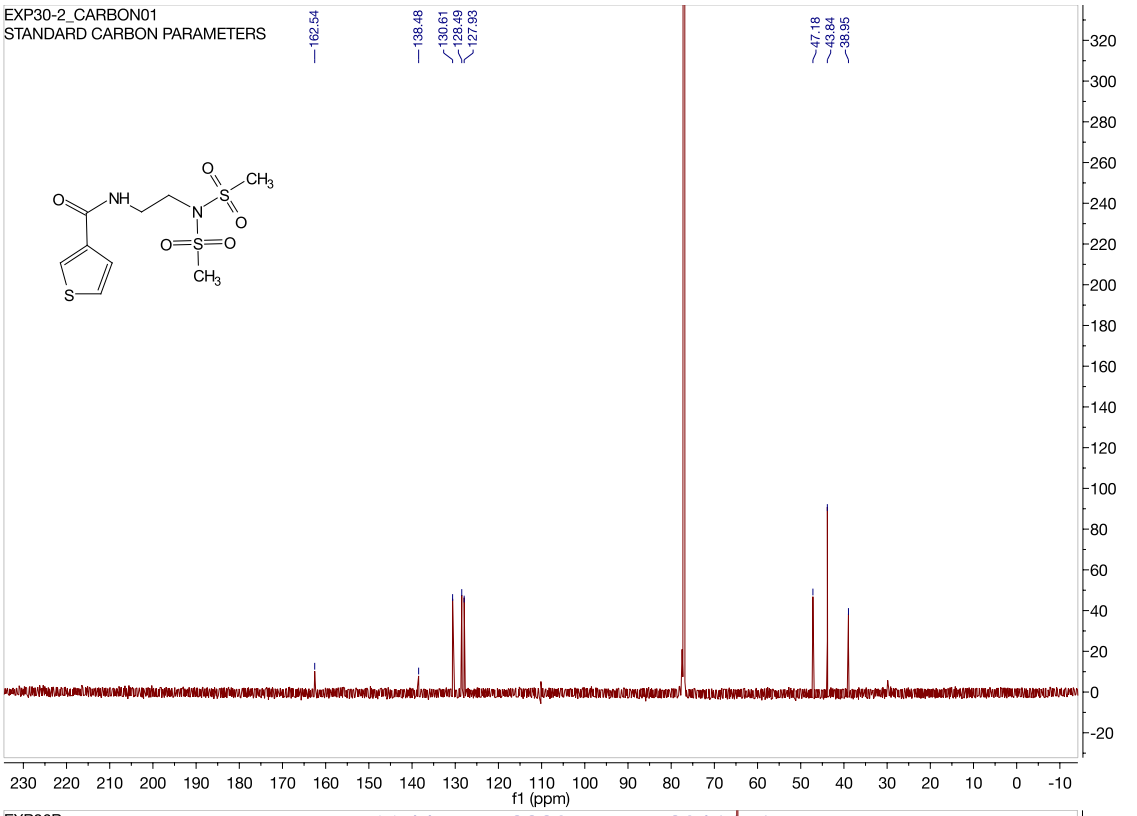

EXP28
7.83
7.81
7.53
7.51
7.50
7.46
7.45
7.43
6.61
4.06
4.05
4.04
3.80
3.79
3.78
3.77
3.33
1.83
0.98
1.82
0.93
1.99
2.00
5.97
f1 (ppm)

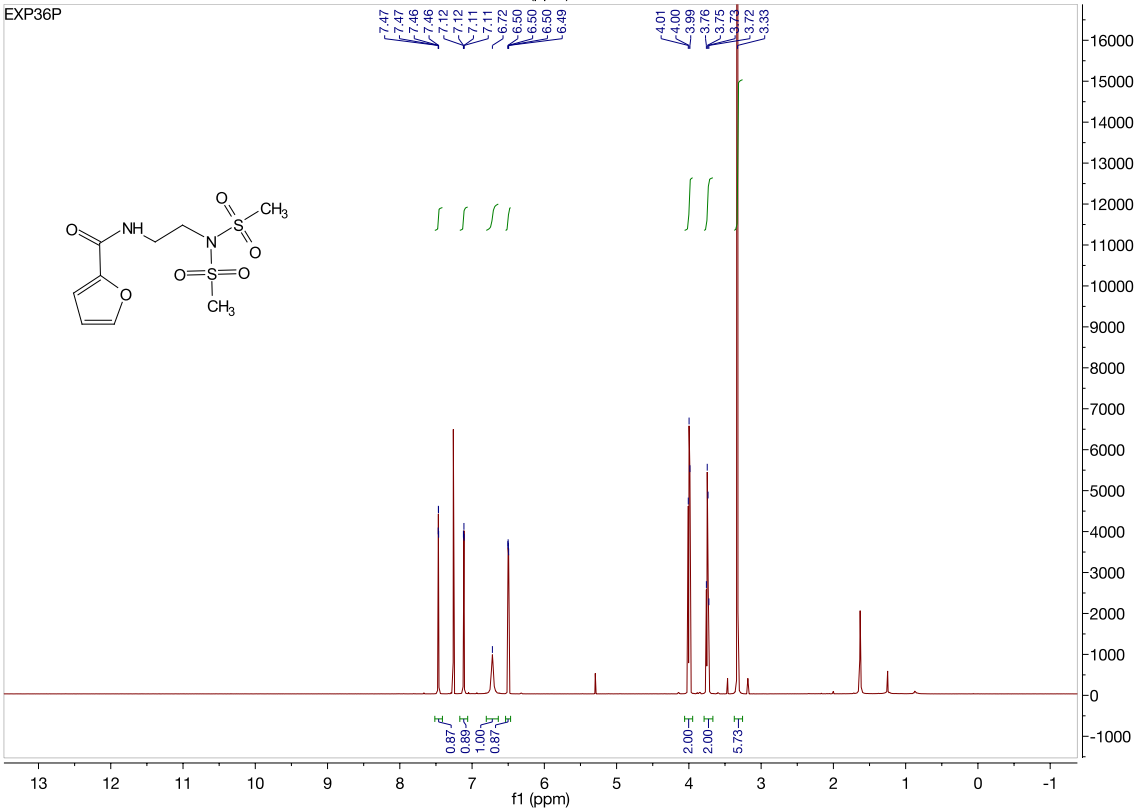

EXP28-13_CARBON01
STANDARD CARBON PARAMETERS
168.13
134.05
131.90
128.85
127.10
47.32
43.84
38.93
f1 (ppm)

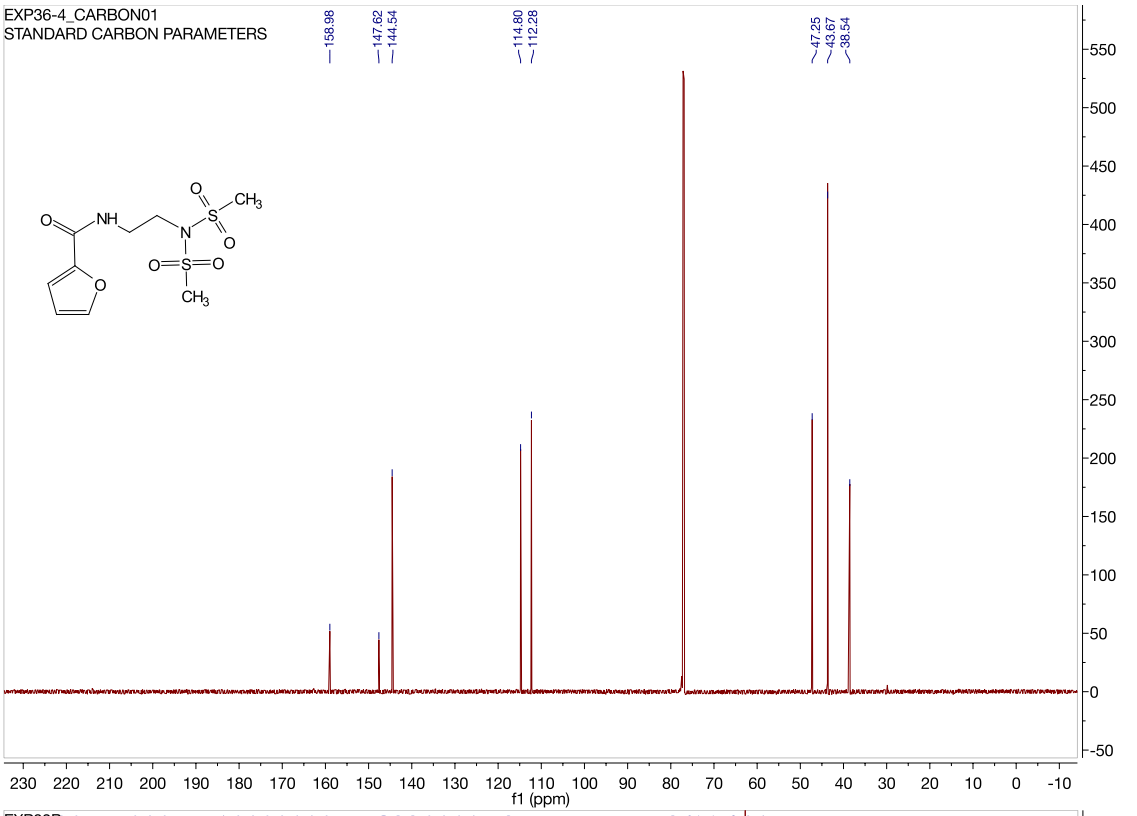

EXP29P
7.80
7.79
7.79
7.78
7.77
7.77
6.94
6.93
6.93
6.92
6.92
6.91
6.56
4.04
4.03
4.02
3.84
3.77
3.76
3.75
3.74
3.32
0.92
0.93
0.95
0.90
0.94
2.00
3.00
2.00
5.93
f1 (ppm)

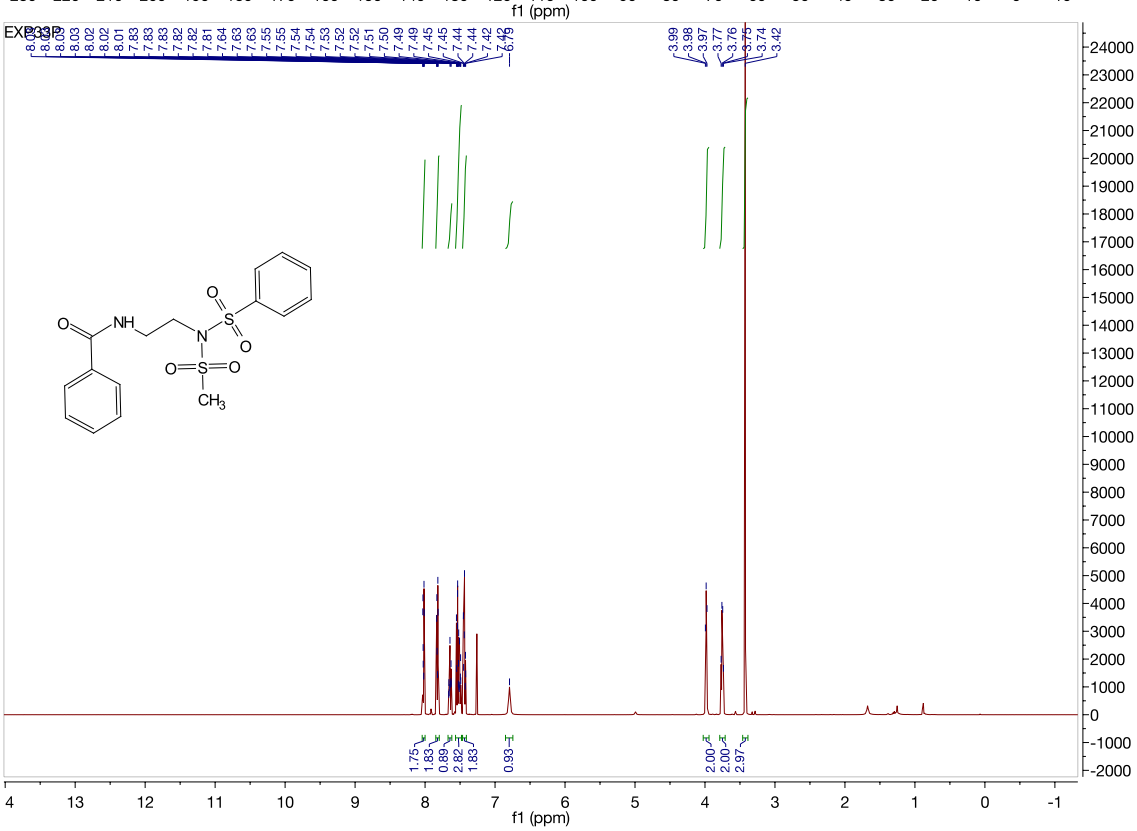

EXP29-7_CARBON01
STANDARD CARBON PARAMETERS
167.60
162.52
128.94
126.30
114.03
55.54
47.37
43.81
38.88
f1 (ppm)

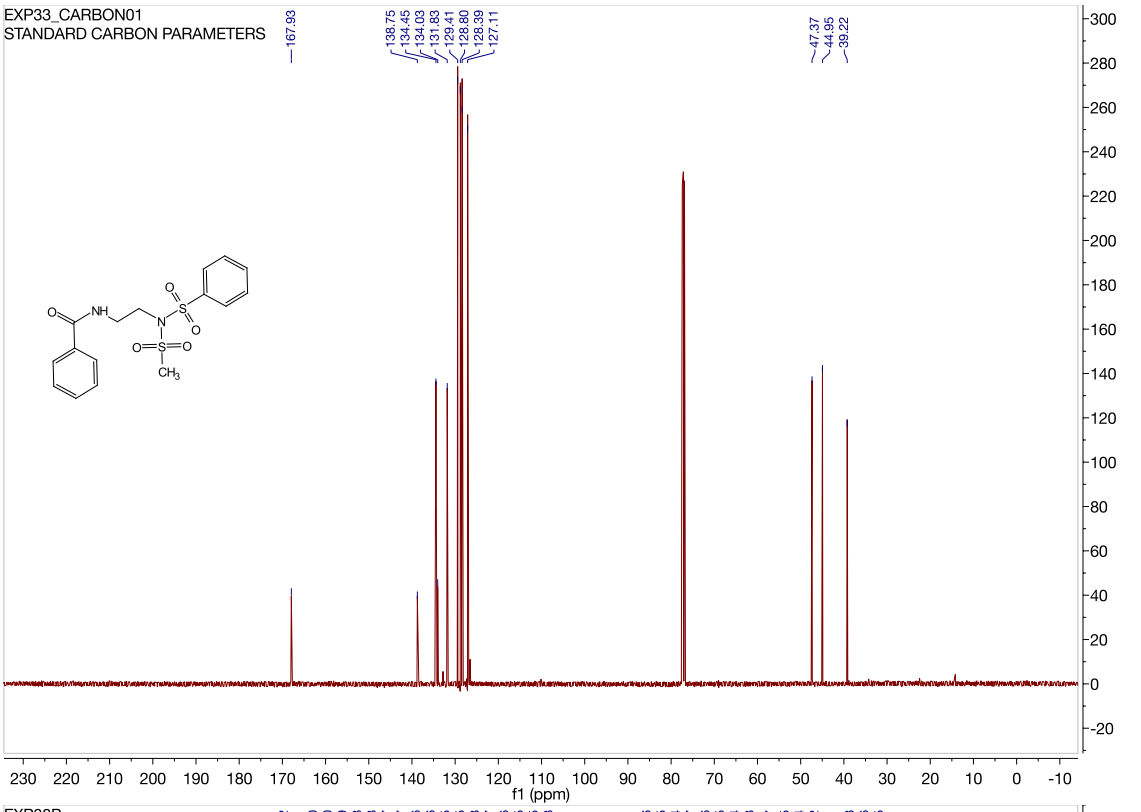

EXP30P
7.55
7.55
7.54
7.54
7.50
7.50
7.49
7.49
7.10
7.09
7.09
7.08
6.47
4.04
4.03
4.02
3.77
3.76
3.75
3.74
3.33
0.91
0.84
0.87
0.90
2.01
2.00
5.99
f1 (ppm)

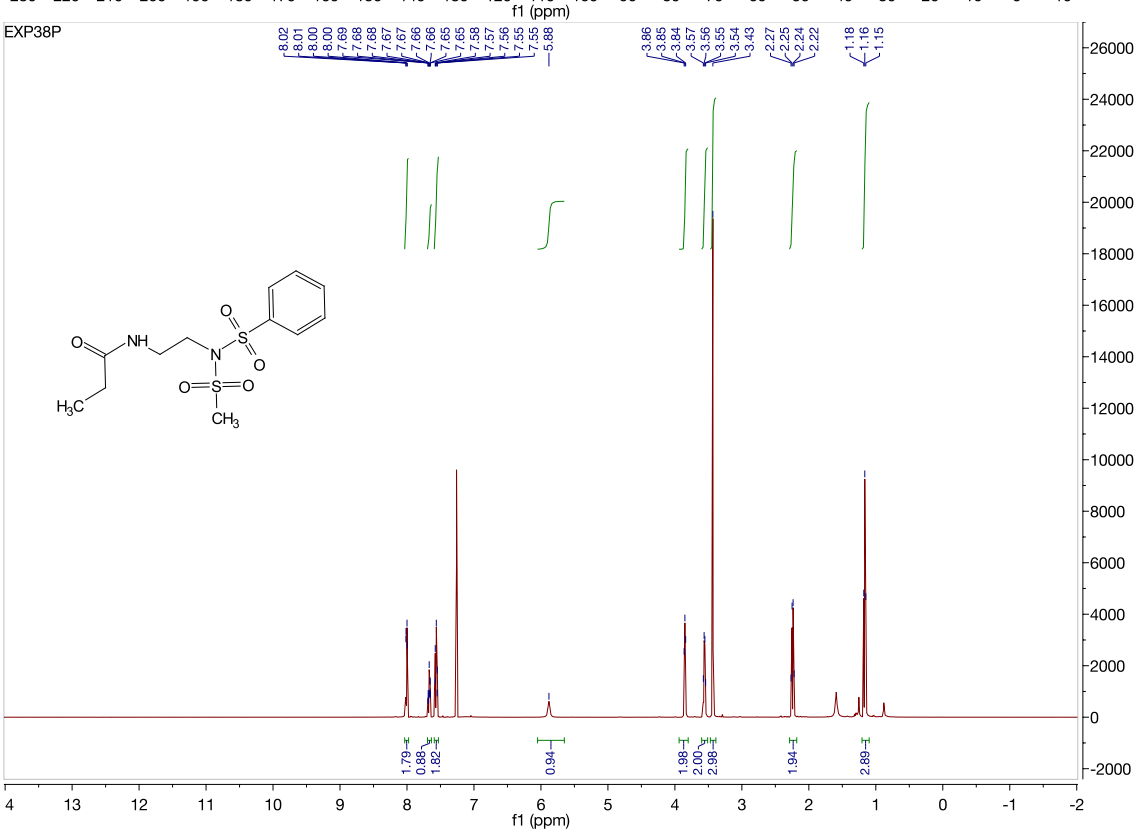

EXP30-2_CARBON01
STANDARD CARBON PARAMETERS
162.54
138.48
130.61
128.49
127.93
47.18
43.84
38.95
f1 (ppm)

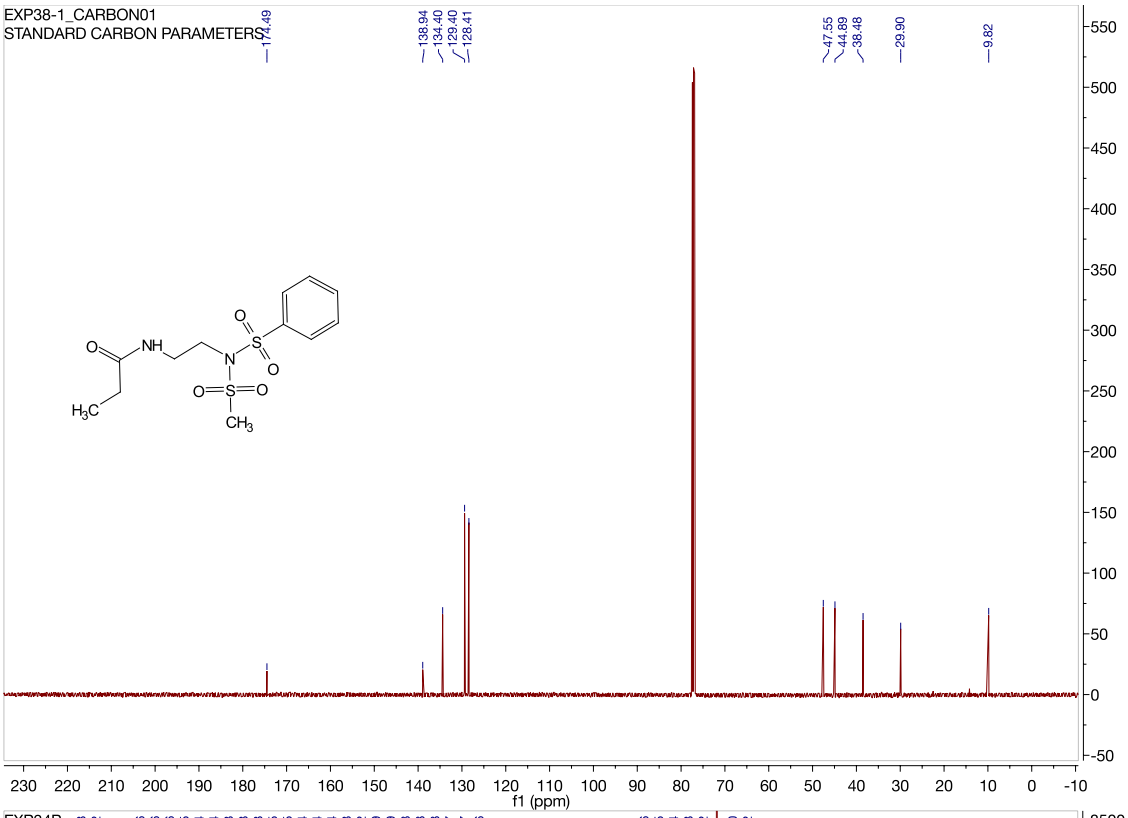

EXP36P
7.47
7.47
7.46
7.46
7.12
7.12
7.11
7.11
6.72
6.50
6.50
6.50
6.49
4.01
4.00
3.99
3.76
3.75
3.73
3.72
3.33
0.87
0.89
1.00
0.87
2.00
2.00
5.73
f1 (ppm)

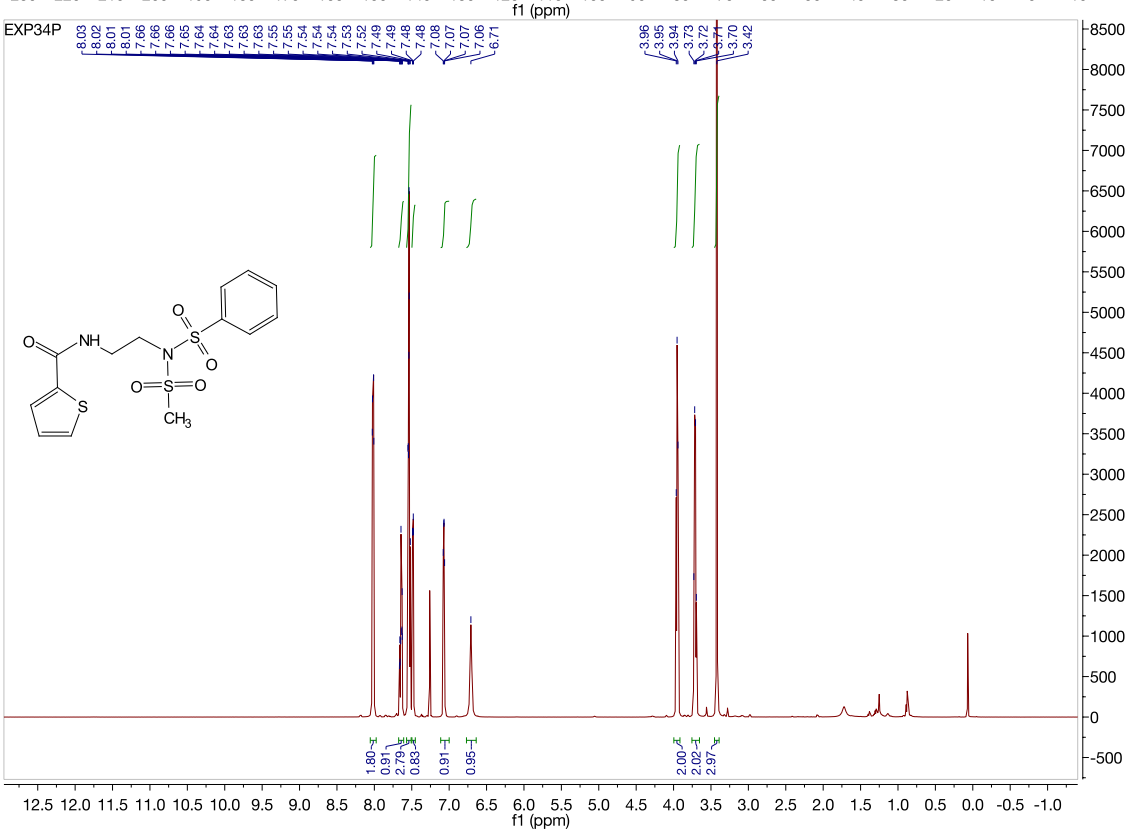

EXP36-4_CARBON01
STANDARD CARBON PARAMETERS
158.98
147.62
144.54
114.80
112.28
47.25
43.67
38.54
f1 (ppm)

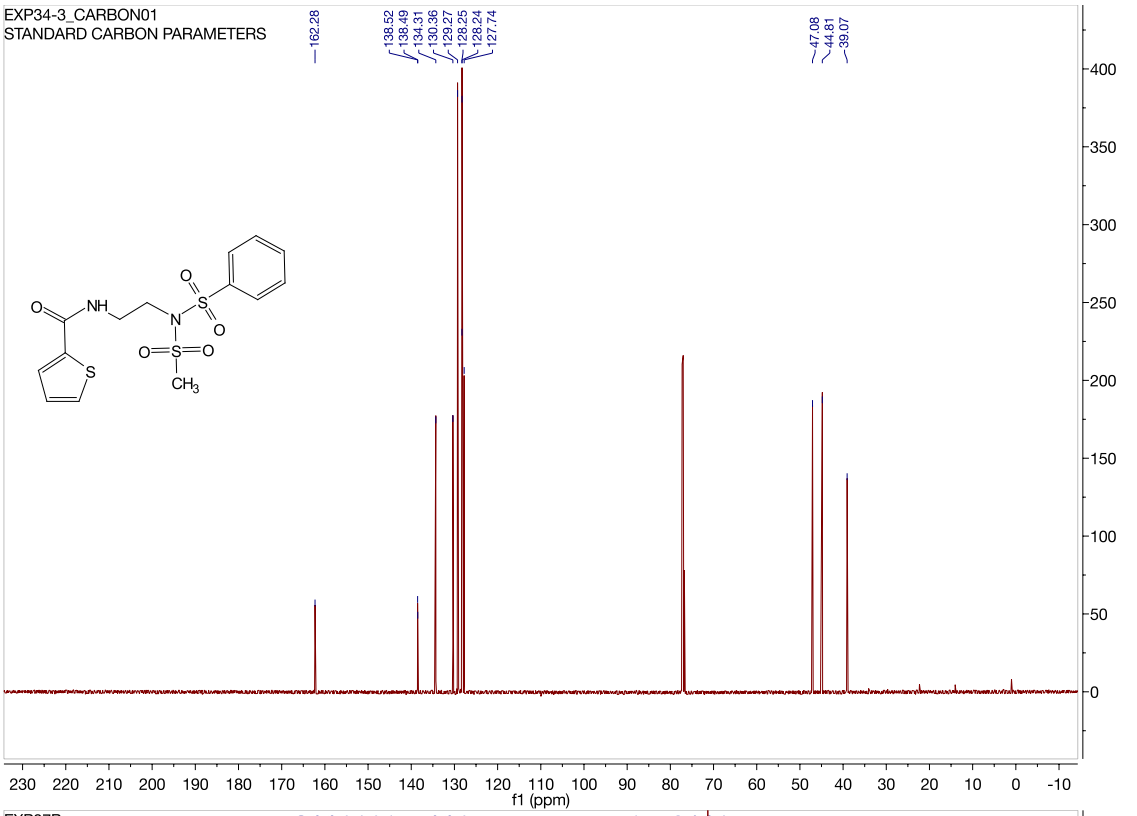

EXP333
f1 (ppm)

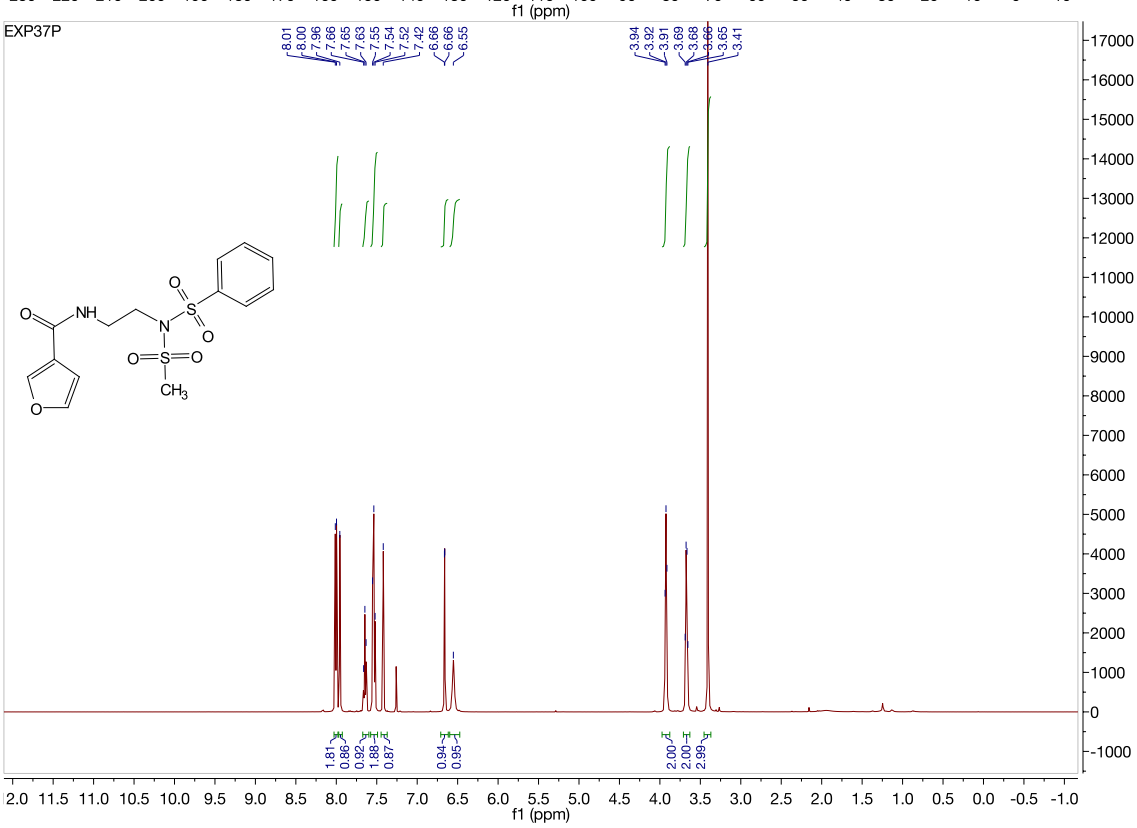

EXP33_CARBON01
STANDARD CARBON PARAMETERS
167.93
138.75
134.45
134.03
131.83
129.41
128.90
128.39
127.11
47.37
44.95
39.22
f1 (ppm)

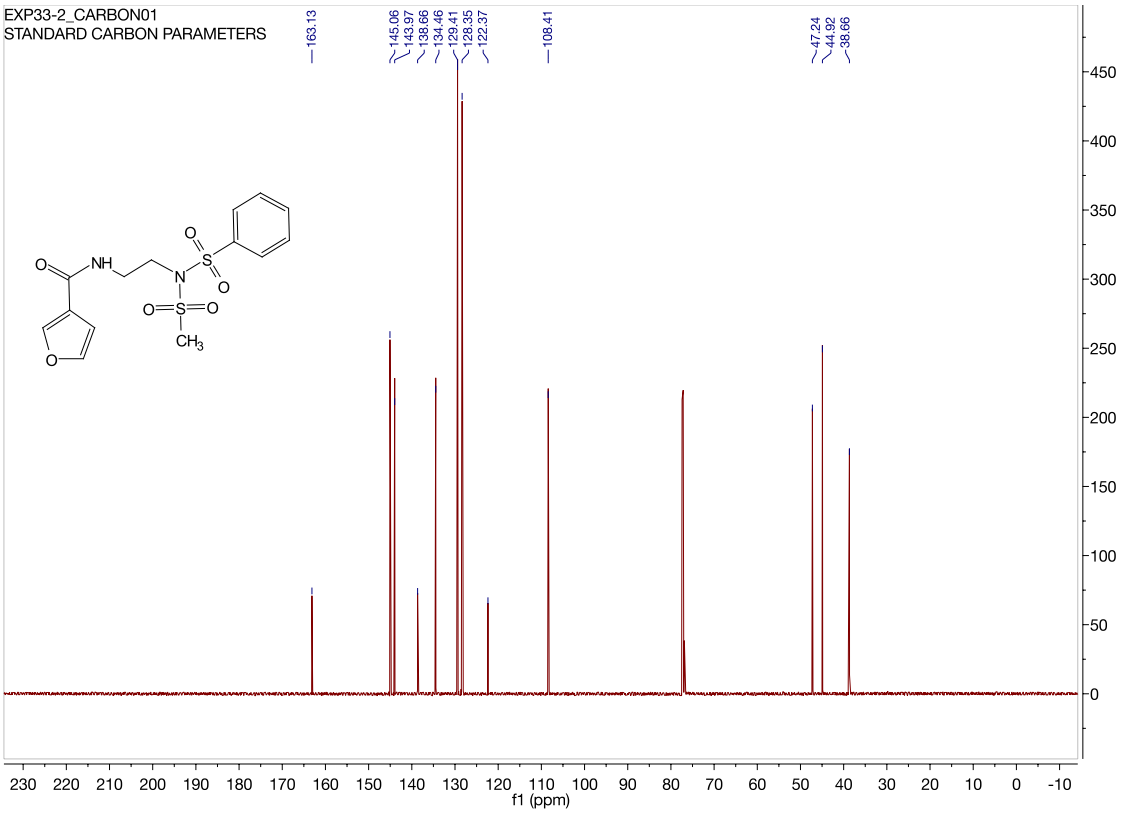

EXP38P
8.02
8.01
8.00
8.00
7.69
7.68
7.68
7.67
7.67
7.66
7.66
7.65
7.65
7.58
7.57
7.56
7.55
7.55
5.88
3.86
3.85
3.84
3.57
3.56
3.55
3.54
3.43
2.27
2.25
2.24
2.22
1.18
1.16
1.15
1.79
0.88
1.82
0.94
1.98
2.00
2.98
1.94
2.89
f1 (ppm)


EXP38-1_CARBON01
STANDARD CARBON PARAMETERS
174.49
138.94
134.40
129.40
128.41
47.55
44.89
38.48
29.90
9.82
f1 (ppm)

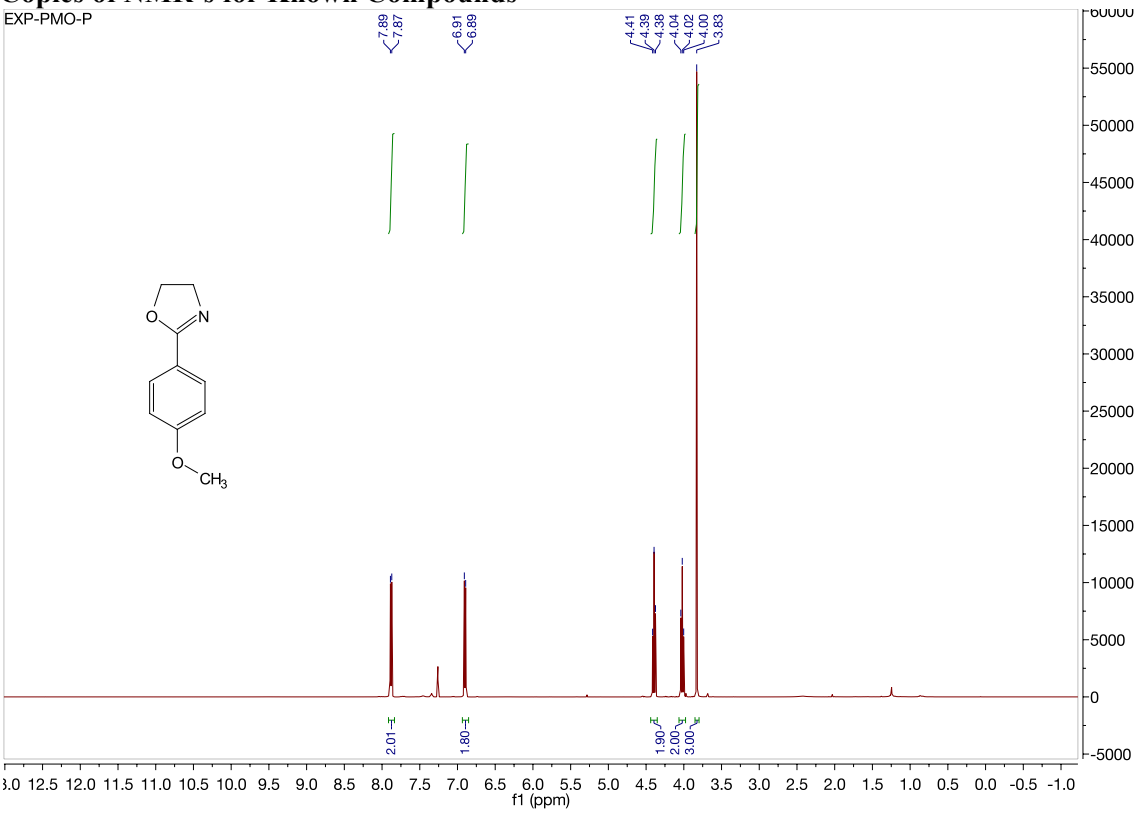

EXP34P
f1 (ppm)

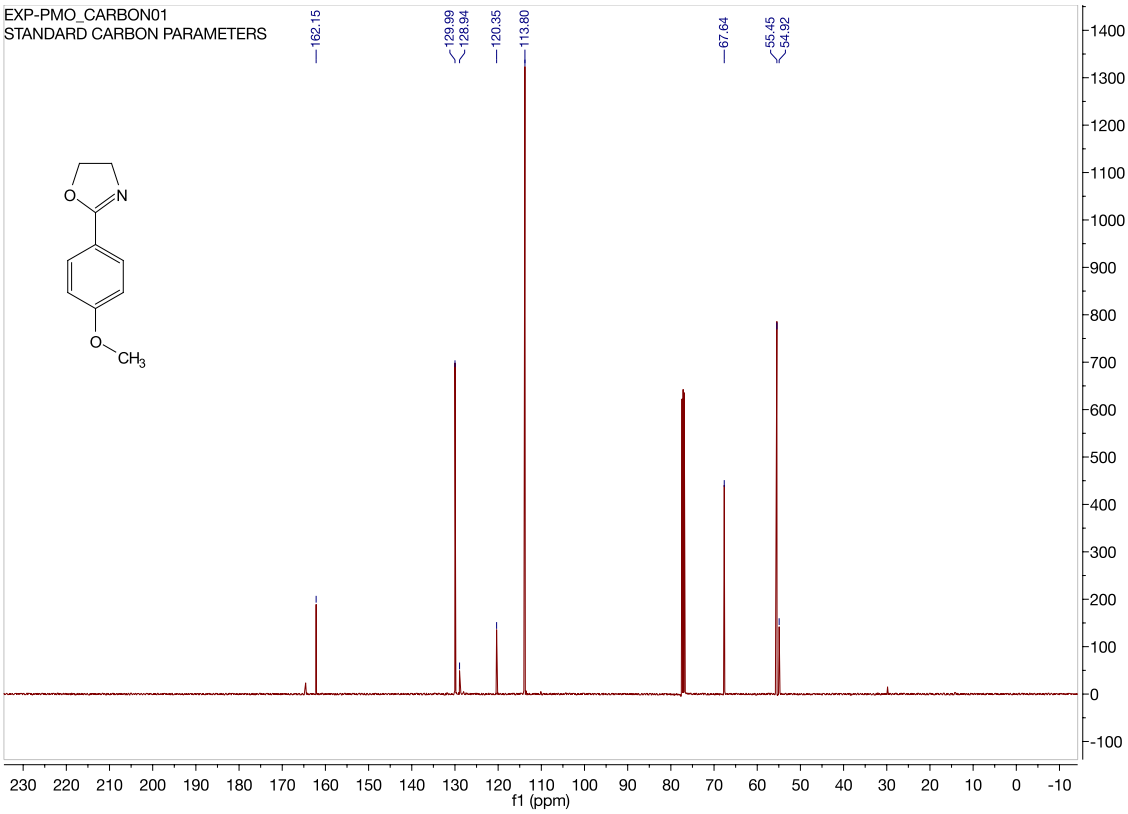

EXP34-3_CARBON01
STANDARD CARBON PARAMETERS
162.28
138.52
138.49
134.31
130.36
129.27
128.25
128.24
127.74
47.08
44.81
39.07
f1 (ppm)

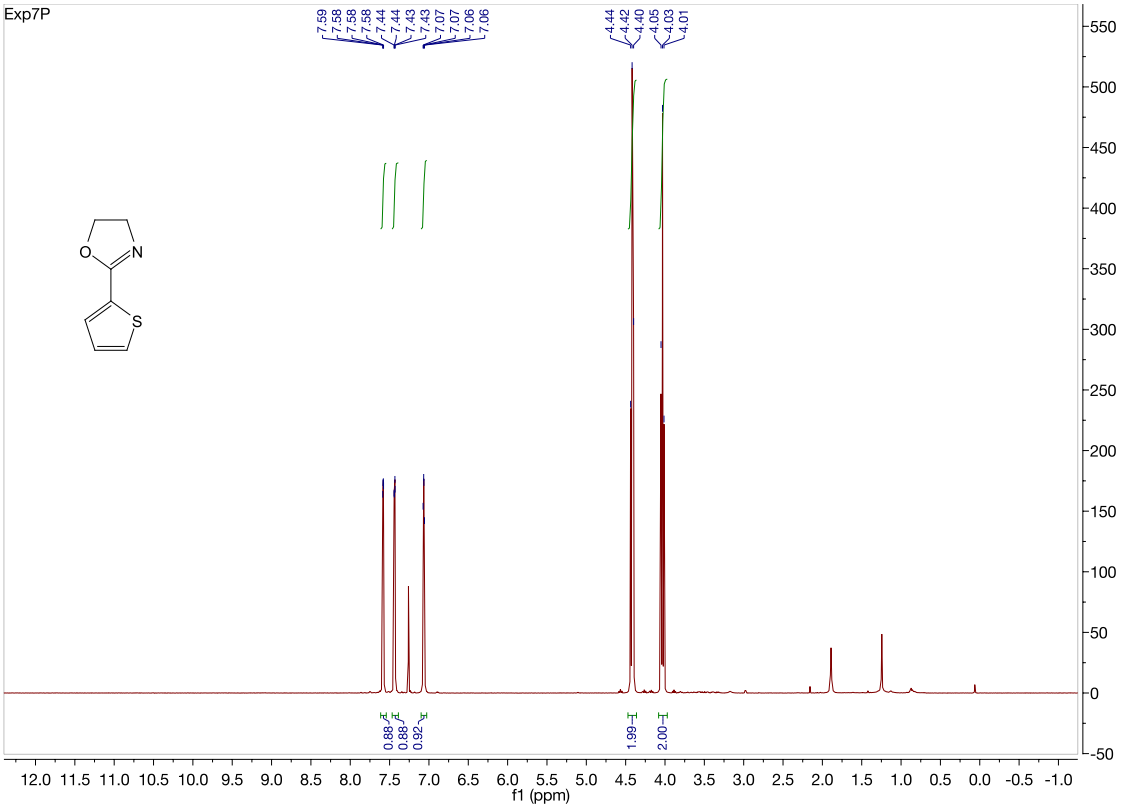

EXP37P
8.01
8.00
7.96
7.66
7.65
7.63
7.55
7.54
7.52
7.42
6.66
6.66
6.55
3.94
3.92
3.91
3.69
3.68
3.66
3.65
3.41
1.81
0.86
0.92
1.88
0.87
0.94
0.95
2.00
2.00
2.99
f1 (ppm)

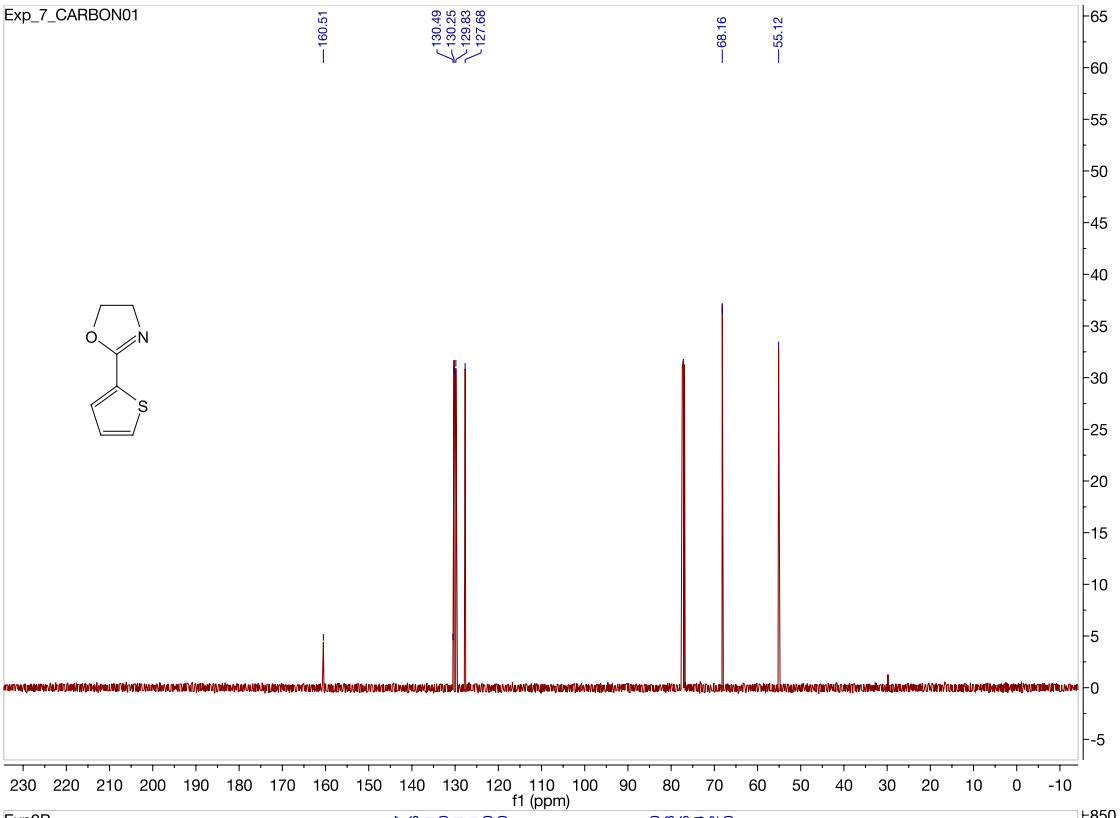


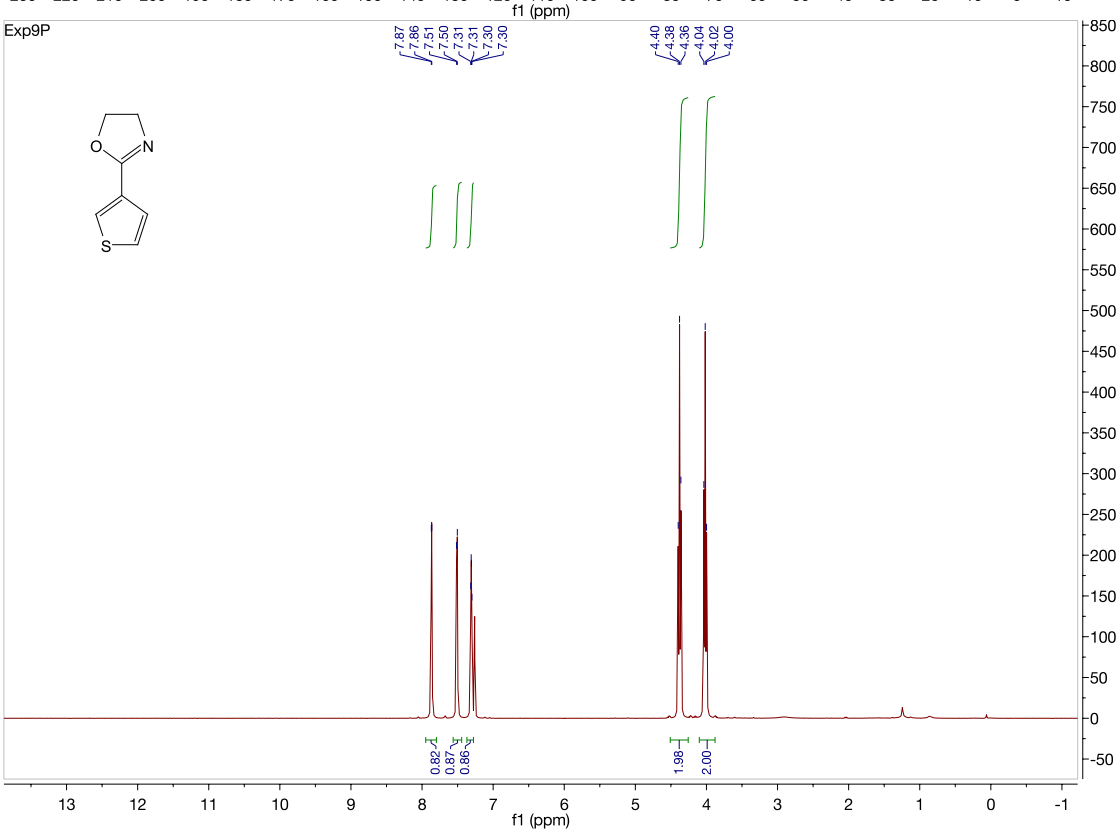
3.9 Copies of NMR's for Known Compounds

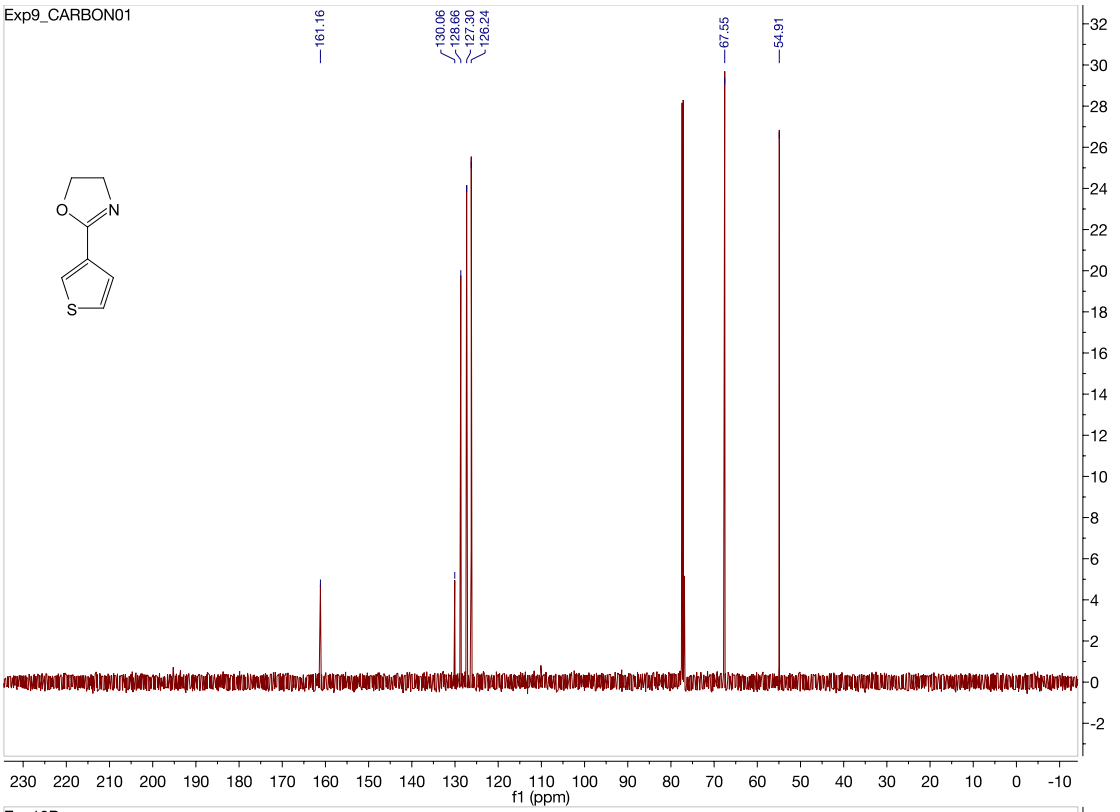


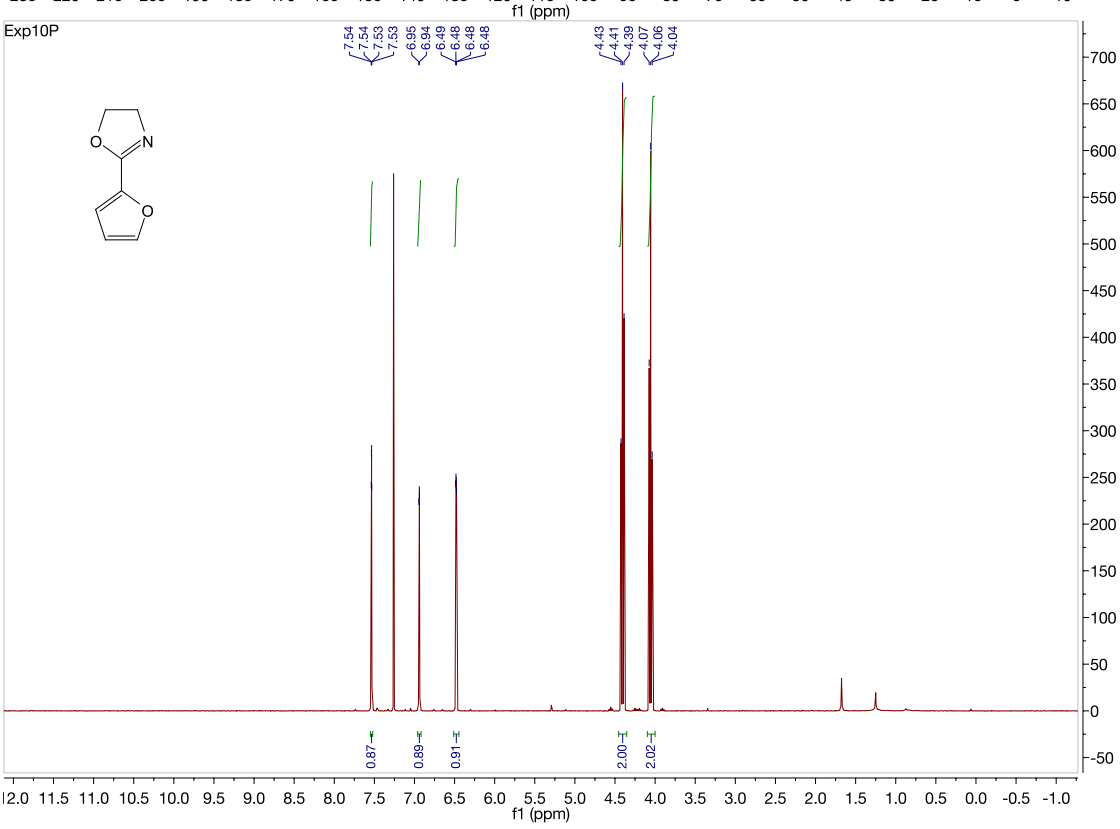

EXP-PMO_CARBON01
STANDARD CARBON PARAMETERS
162.15
129.99
128.94
120.35
113.80
67.64
55.45
54.92
O
N
O
CH3
f1 (ppm)

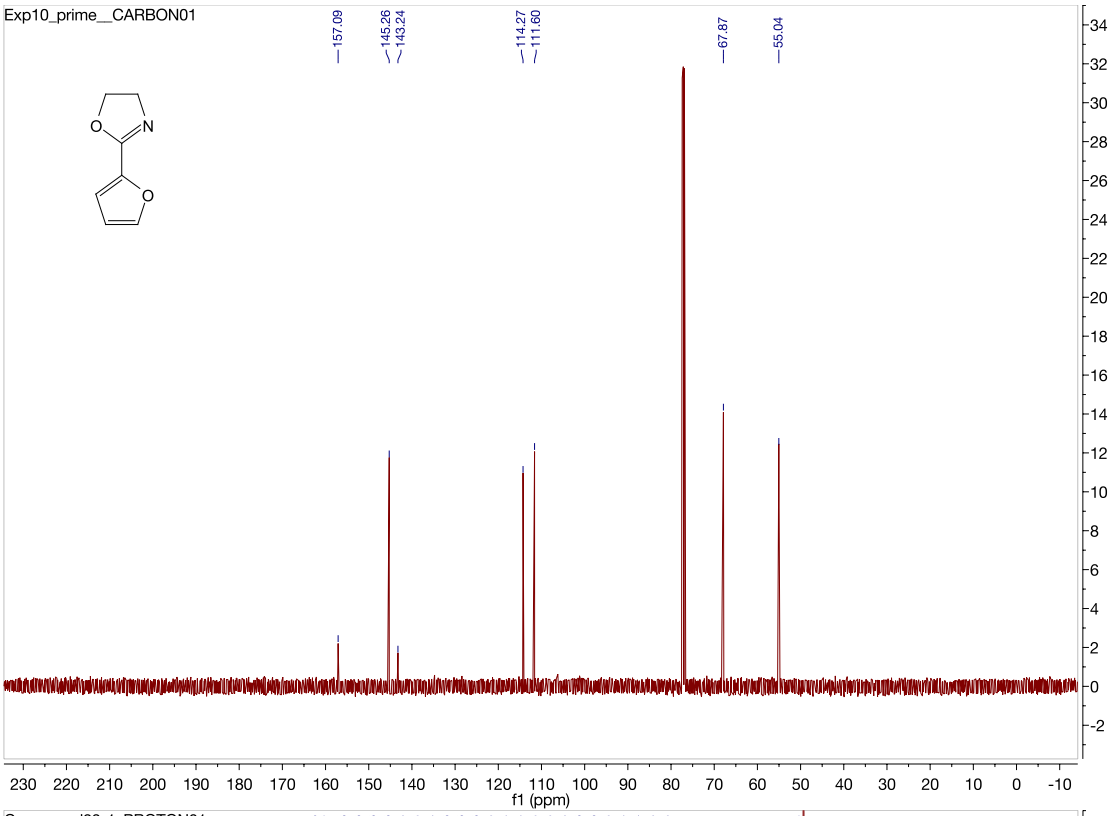

Exp7P
7.59
7.58
7.58
7.58
7.58
7.44
7.44
7.43
7.43
7.07
7.07
7.06
7.06
4.44
4.42
4.40
4.05
4.03
4.01
0.88
0.88
0.92
1.99
2.00
O
N
S
f1 (ppm)

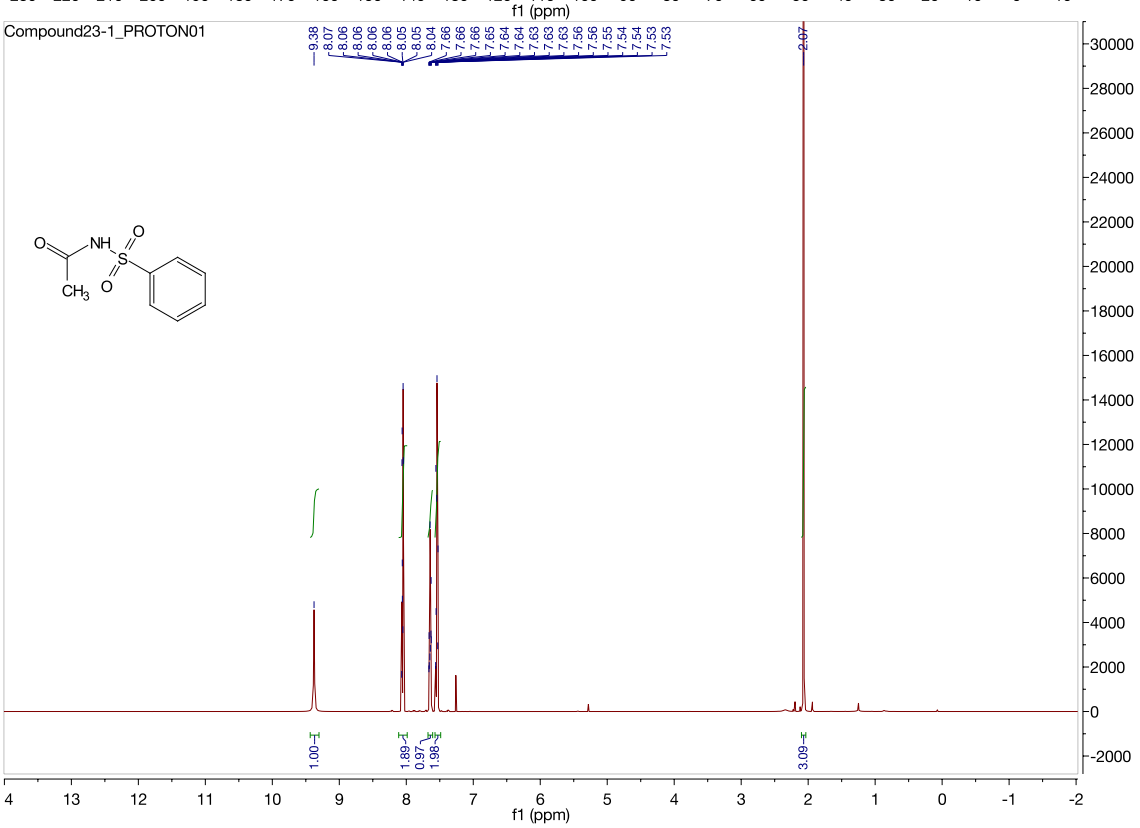

Exp_7_CARBON01
160.51
130.49
130.25
129.83
127.68
68.16
55.12
O
N
S
f1 (ppm)

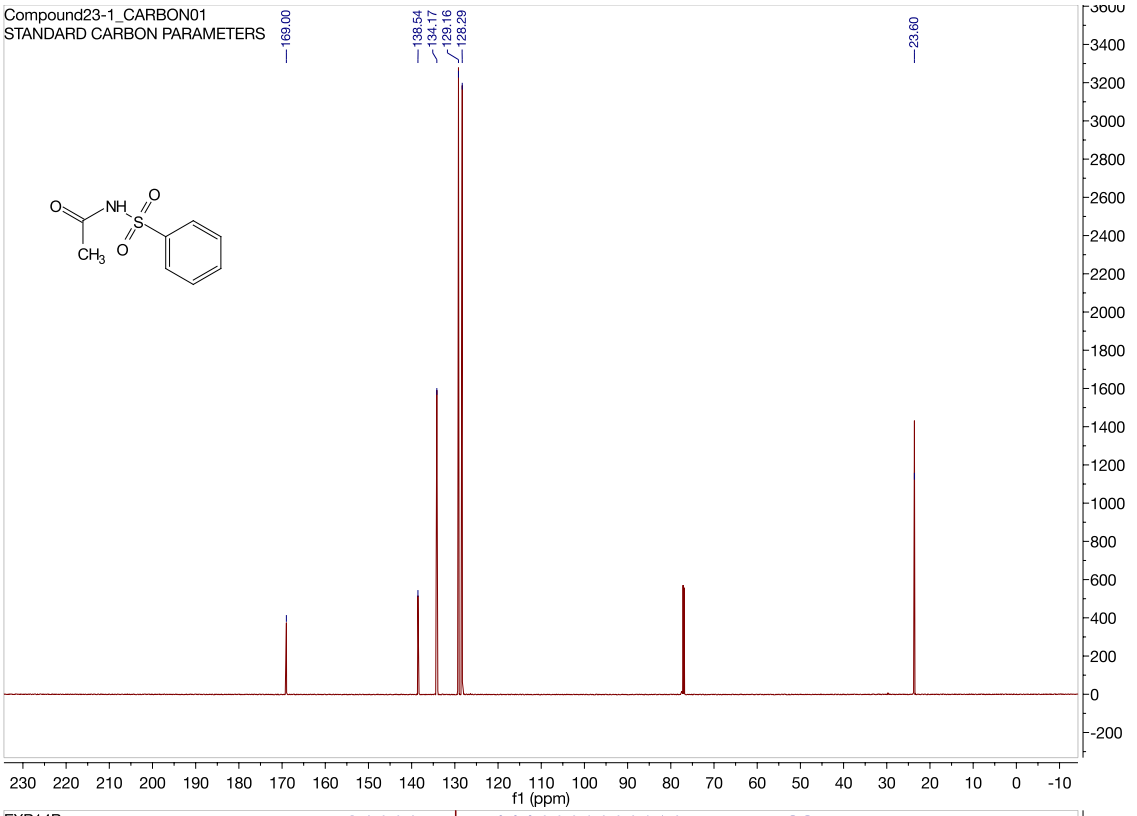

Exp9P
7.87
7.86
7.51
7.50
7.31
7.31
7.30
7.30
4.40
4.38
4.36
4.04
4.02
4.00
0.82
0.87
0.86
1.98
2.00
O
N
S
f1 (ppm)

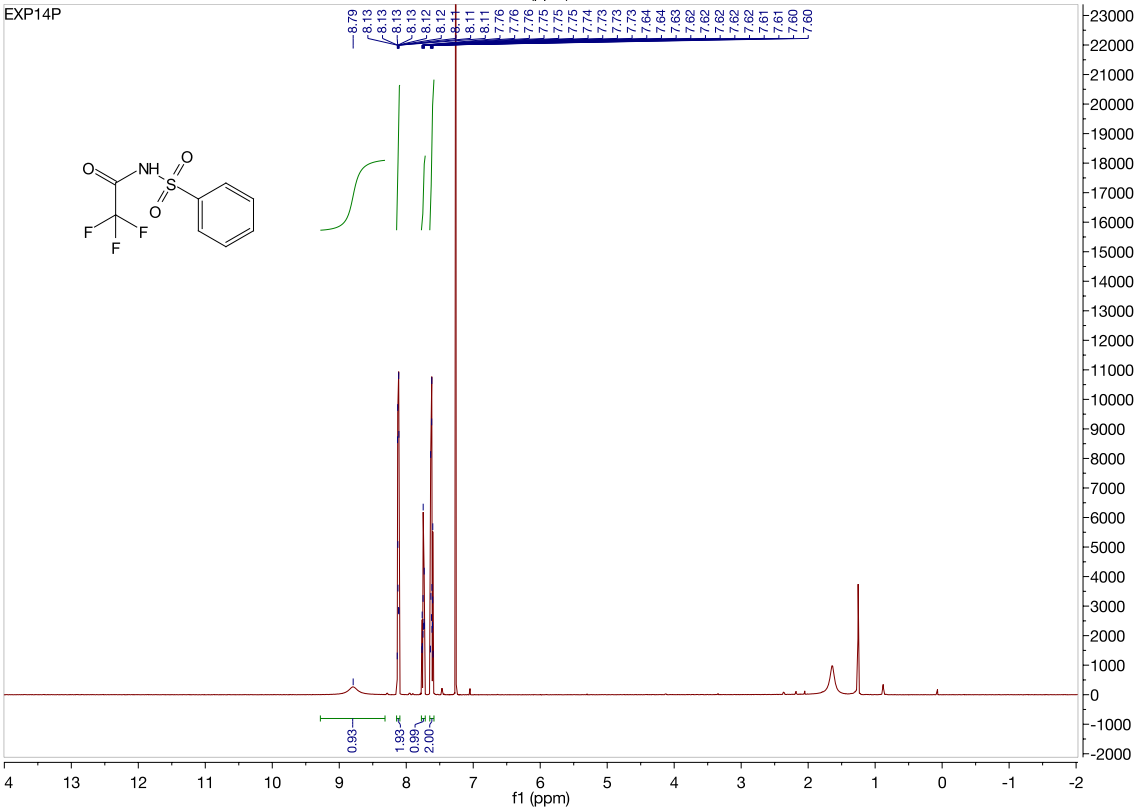

Exp9_CARBON01
161.16
130.06
128.66
127.30
126.24
67.55
54.91
O
N
S
f1 (ppm)

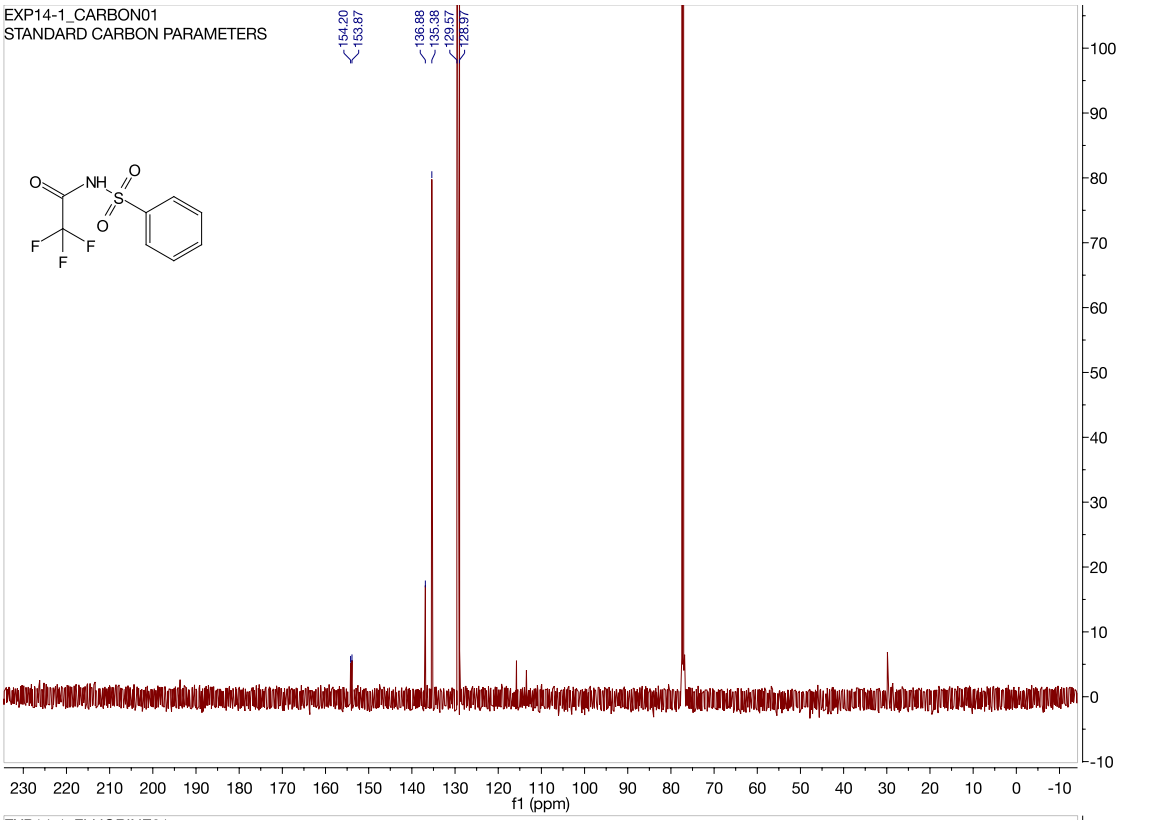

Exp10P
7.54
7.54
7.53
7.53
6.95
6.94
6.49
6.48
6.48
6.48
4.43
4.41
4.39
4.07
4.06
4.04
0.87
0.89
0.91
2.00
2.02
O
N
O
f1 (ppm)

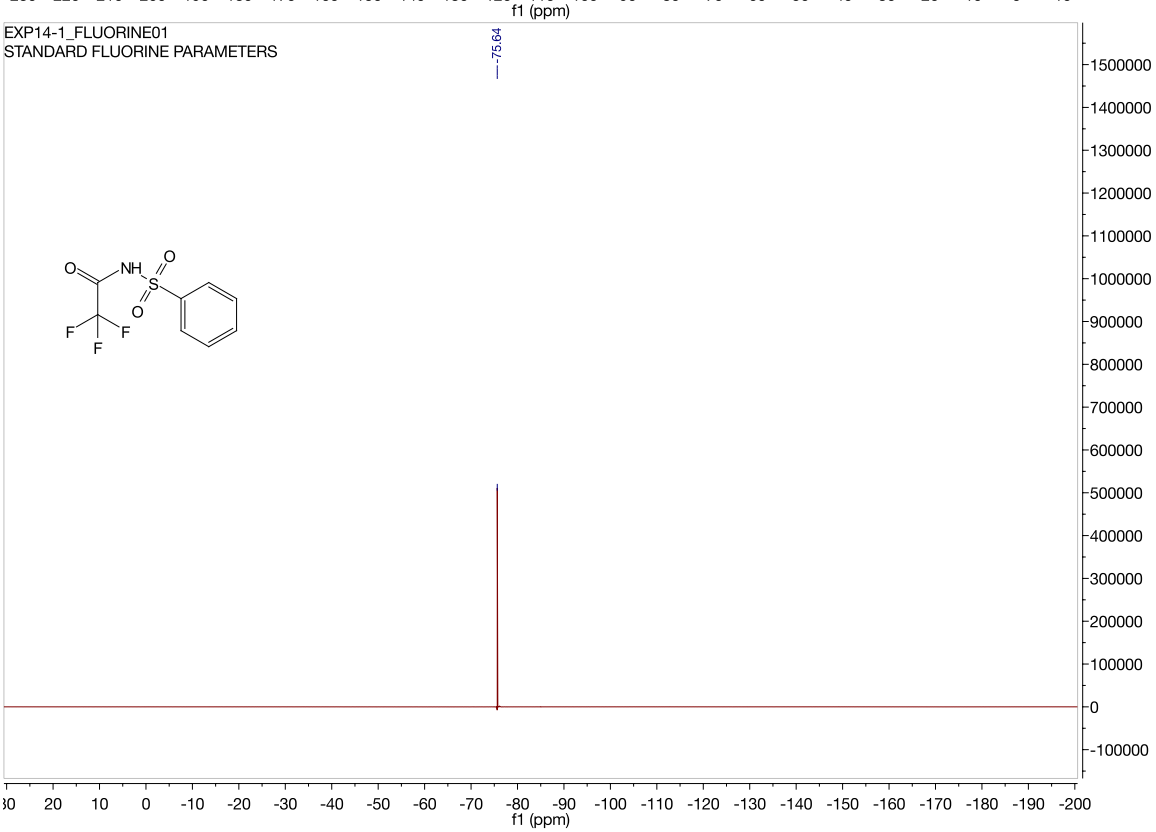

Exp10_prime__CARBON01
157.09
145.26
143.24
114.27
111.60
67.87
55.04
f1 (ppm)

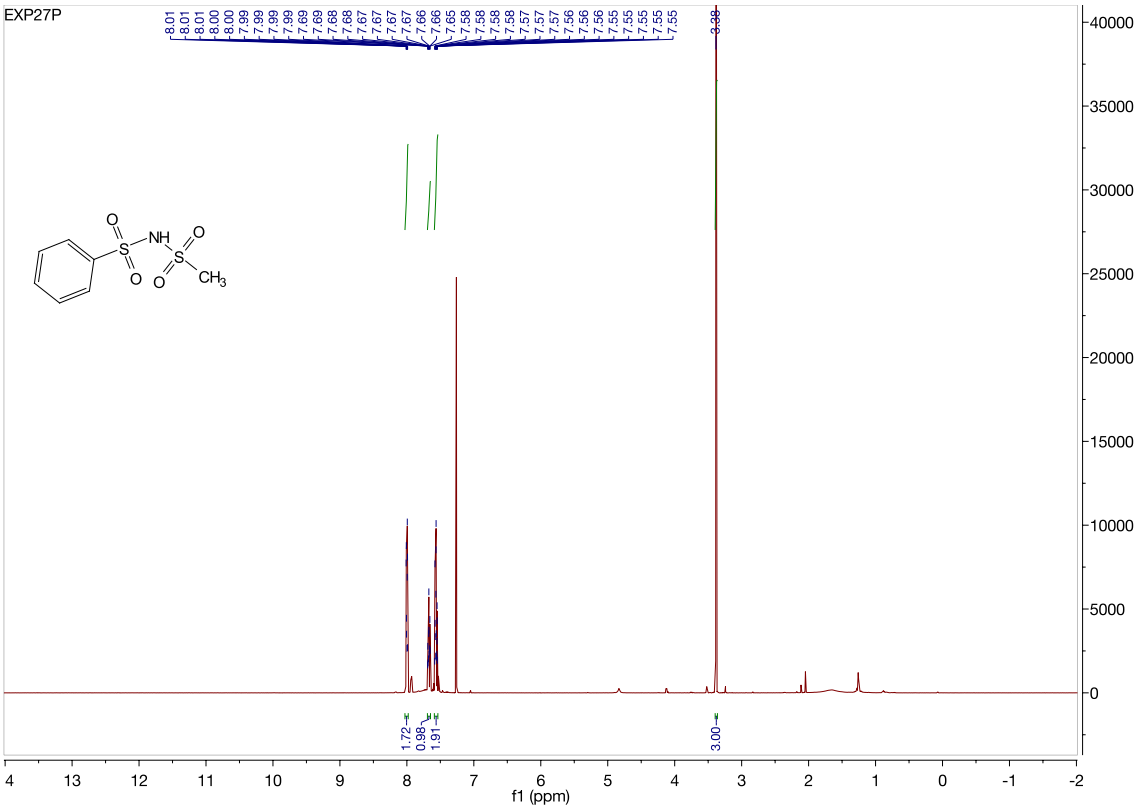

Compound23-1_PROTON01
9.38
8.07
8.06
8.05
8.04
7.66
7.65
7.64
7.63
7.56
7.55
7.54
7.53
2.07
1.00
1.89
0.97
1.98
3.09
f1 (ppm)

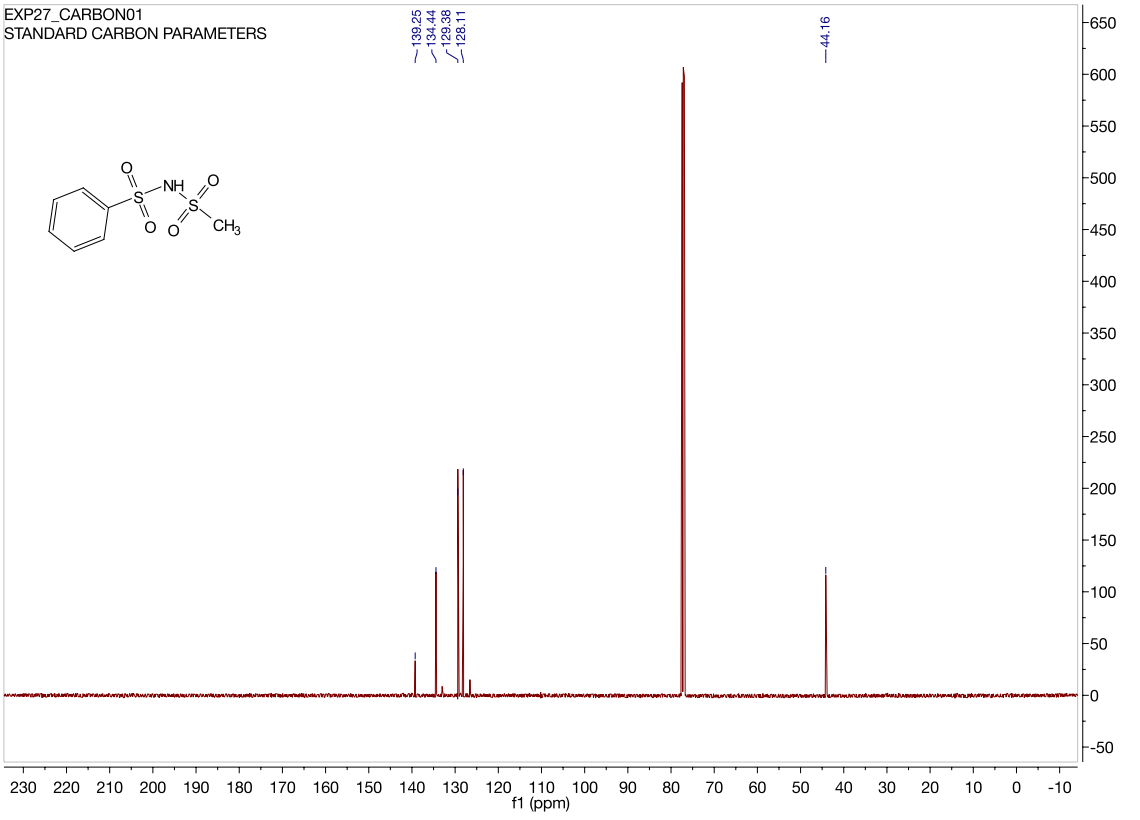

Compound23-1_CARBON01
STANDARD CARBON PARAMETERS
169.00
138.54
134.17
129.16
128.29
23.60
f1 (ppm)


EXP14P
8.79
8.13
8.12
8.11
7.76
7.75
7.74
7.73
7.64
7.63
7.62
7.61
7.60
0.93
1.93
0.99
2.00
f1 (ppm)


EXP14-1_CARBON01
STANDARD CARBON PARAMETERS
154.20
153.87
136.88
135.38
129.57
128.97
f1 (ppm)


EXP14-1_FLUORINE01
STANDARD FLUORINE PARAMETERS
-75.64
f1 (ppm)


EXP27P
8.01
8.01
8.01
8.00
8.00
7.99
7.99
7.99
7.99
7.69
7.69
7.68
7.68
7.67
7.67
7.67
7.67
7.66
7.66
7.65
7.58
7.58
7.58
7.58
7.57
7.57
7.57
7.56
7.56
7.56
7.55
7.55
7.55
7.55
7.55
3.98
NH
CH3
1.72
0.98
1.91
3.00
f1 (ppm)


EXP27_CARBON01
STANDARD CARBON PARAMETERS
139.25
134.44
129.38
128.11
44.16
NH
CH3
f1 (ppm)

Chapter 4: Appendix B

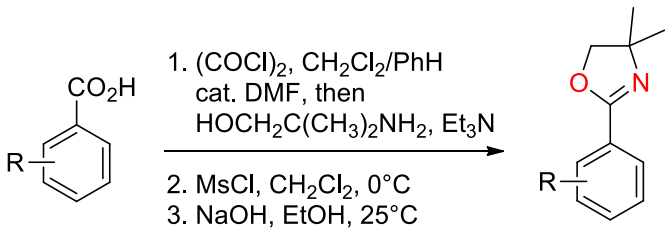
4.1 General Methods

All reactions were performed in anhydrous solvents under a N_2 atmosphere. Solvents were purchased from Alfa Aesar and utilized without further purifications. Analytical thin–layer chromatography (TLC) was carried out using Silica G TLC plates, 200 mM with UV254 (SORBENT Technologies), with visualization by UV or iodine. Flash chromatography was performed using standard grade silica gel (60 Å, 230–400 mesh; SORBENT Technologies). Melting Points were taken using Vernier Melt Station LabQuest 2 and were not corrected. NMR spectra were acquired using an Agilent VNMRS spectrometer equipped with one NMR probe (500 MHz for ^{1}H, 125 MHz for ^{13}C, 470 MHz for ^{19}F). Spectra were processed using MNova software (Mestrelab). Chemical shifts are reported in parts per million (ppm), coupling constants (*J*) in Hz and are calibrated to residual protonated solvent. Infrared spectra of neat samples were acquired using a PerkinElmer Spectrum 100 FT–IR spectrometer, with solid samples analyzed using a Universal ATR (attenuated total reflectance) sampling accessory. GC–MS was performed on a Hewlett Packard HP6890 Series GC System and a 5973 Mass Selective Detector.

4.2 General Procedures for Fluorination

As a typical experiment, the oxazoline derivative **5** (0.5 mmol), NFSI (X mmol), $Pd(NO_3)_2$ (0.1 mmol), and $AgNO_3$ (0.25 mmol) were charged into an oven dried reaction vial, equipped with a magnetic stirring bar and sealed. The reaction vial was evacuated and purged several times with nitrogen. Anhydrous acetonitrile (5 mL) was added, and the microwave vial purged several times with nitrogen. The microwave vial was placed in a heating block at 80°C and reactants were allowed to stir for 24 hr. After cooling to room temperature, the reaction mixture was filtered through a plug of silica, using ethyl acetate and then washed twice with 3% triethylamine in water solution, twice with brine and then the organic layer was dried over $MgSO_4$ and filtered. The organic layer was concentrated *in vacuo* and the residue and was analyzed by gas chromatography using dodecane as an internal standard to determine the conversion of the fluorinated product. The crude product was purified by silica gel column chromatography using an appropriate ratio of the eluent.

4.3 General Procedures for Preparations of Aryl–2–oxazolines



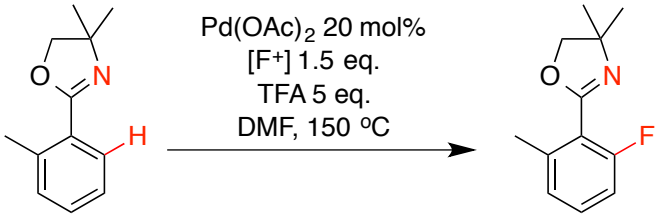
Aryl acid (10 mmol) was dissolved in 20 mL of dried methylene chloride and cooled to 0^oC; 5 drops of DMF was added to the suspension. Oxalyl chloride (12 mmol) was added drop wise to the reaction mixture. The reaction was warmed to room temperature and stirred for 3 h. The solvent was removed *in vacuo* and the residue was dried for 1 h on high vacuum. The residue was dissolved in 15mL of methylene chloride and added drop wise to a suspension of 2–amino–2–methyl–1–propanol (1.39 g, 12 mmol), triethylamine (2.02 g, 20 mmol) in 35 mL of methylene chloride at 0^oC. The reaction stirred for 3 h and was warmed to rt. The reaction was diluted with methylene chloride and washed once with dilute HCl and washed twice with brine. The organic layer was dried, ($MgSO_4$) filtered, and concentrated *in vacuo* to give the crude amide intermediate. The crude amide intermediate (2.07 g 10 mmol) was dissolved in 50 mL of DCM and triethylamine (1.21 g, 12 mmol) was added. The reaction was stirred for 30 min at 0^oC. Mesylchloride (1.37 g, 12 mmol) was added drop wise and the reaction warmed to room temperature and stirred for 3 h. The reaction was diluted with DCM and washed twice with dilute HCl and twice with brine. The organic layer was was dried, ($MgSO_4$) filtered, and concentrated *in vacuo* to give the crude mesylate intermediate. The crude mesylate product was purified via flash chromatography in a gradient of hexane ethyl acetate respectively. The purified product was then diluted in 20 mL of ethanol and sodium hydroxide (480 mg, 9.3 mmol) was added and the reaction was stirred for 30 min. The reaction mixture was diluted with ethyl acetate and washed 3 times with brine. The organic layer was dried over $MgSO_4$ filtered and concentrated *in vacuo* to afford the product after flash chromatography.

4.4 Procedure for Removal of Directing group.

To a solution of the 2–(2–Fluorophenyl)–4,4–dimethyl–4,5–dihydrooxazole (6b) (38 mg, 0.2 mmol) in CH_3CN (3 mL) was added methyl iodide (1 mL, 16 mmol) and the mixture was heated to reflux for 6 h. The reaction mixture was then cooled to room temperature and stirred overnight. The reaction mixture was concentrated and the residue was triturated with Et_2O. Methanol (3 mL) was added to the residue. NaOH (80 mg, 2 mmol) and heated to reflux for 6 h. The reaction mixture was cooled to room temperature and concentrated. The aqueous phase was washed several times with DCM, and then acidfied to pH 1 using 1M HCl. The aqueous phase was extracted with twice with DCM. The combined organic phase was washed with brine, dried ($MgSO_4$) and concentrated to afford 22 mg (77%) of the benzoic acid, as an off white solid.

4.5 Screening of Fluorination Conditions

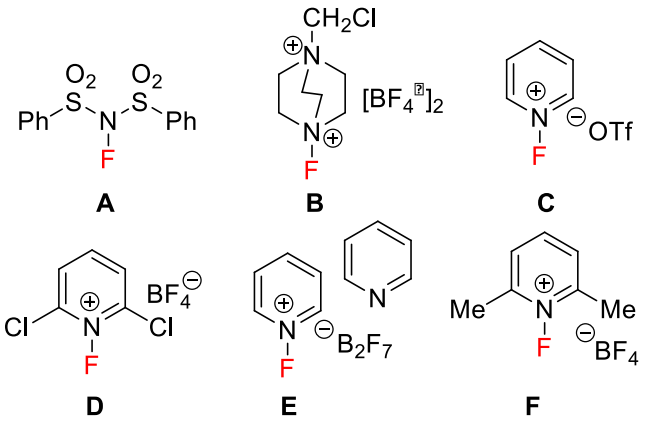
4.5.1 Screening of Fluorinating agents



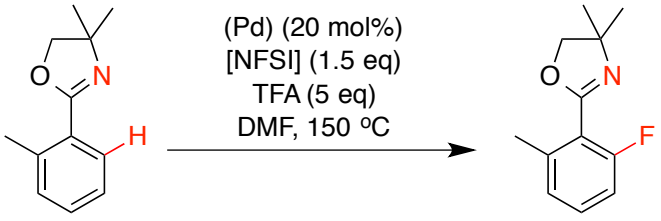
Entry	Fluorine Source	%SM	%Fluorination
1	**A**	72	28
2	**B**	87	13
3	**C**	100	0
4	**D**	100	0
5	**E**	100	0
6	**F**	100	0

[a] Reaction conditions(0.1 mmol), [Pd] (20 mol%), [F+] (0.15 mmol), trifluoracetic acid (0.5 mmol) DMF (1 mL), 150 °C, under nitrogen, 24 h. [b] GCMS conversion using dodecane as internal standard.

electrophilic fluorinating agents



4.5.2 Screening of Palladium Catalysts

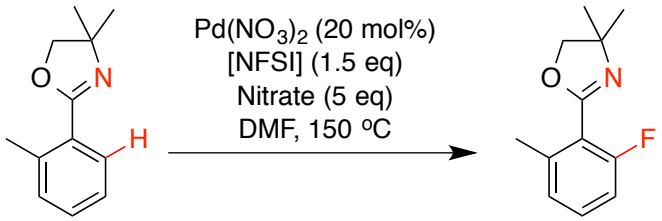


Entry	Pd Catalyst	%SM	%Fluorination[b]
1	$Pd(TFA)_2$	71	29
2	$Pd(dba)_2$	90	10
3	$PdCl_2$	NR	0

4	$Pd(OTf)_2$	82	18
5	$Pd(PPh_3)_4$	66	34
6	$Pd(NO_3)_2$	60	40

[a] Reaction conditions(0.1 mmol), [Pd] (20 mol%), NFSI (0.15 mmol), trifluoracetic acid (0.5 mmol) DMF (1 mL), 150 °C, under nitrogen, 24 h. [b] GCMS conversion using dodecane as internal standard.

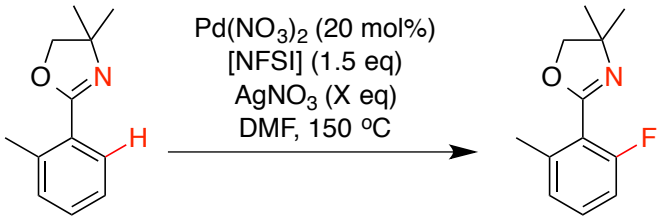
4.5.3 Screening of Nitrate salts



Entry	Nitrate Salt	%SM	%Fluorination
1	$AgNO_3$	53	47
2	$Ca(NO_3)_2$	89	11
3	KNO_3	92	8
4	$Cu_2(NO_3)$	83	17
5	$Na(NO_3)$	93	7

[a] Reaction conditions(0.1 mmol), $Pd(NO_3)_2$ (20 mol%), NFSI (0.15 mmol), Nitrate salt (0.5 mmol) DMF (1 mL), 150 °C, under nitrogen, 24 h. [b] GCMS conversion using dodecane as internal standard.

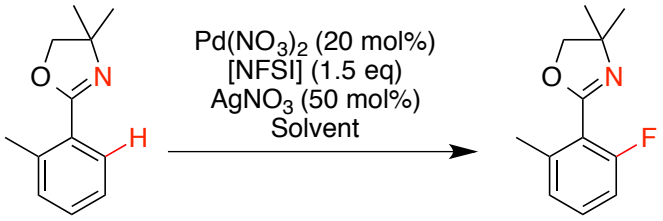
4.5.4 Additive loading



Entry	Eq $AgNO_3$	%SM	%Fluorination
1	5	53	47
2	2	52	48
3	0.5	51	49
4	0	100	0

[a] Reaction conditions (0.1 mmol), $Pd(NO_3)_2$ (20 mol%), NFSI (0.15 mmol), $AgNO_3$ (X mmol) DMF (1 mL), 150 °C, under nitrogen, 24 h. [b] GCMS conversion using dodecane as internal standard.

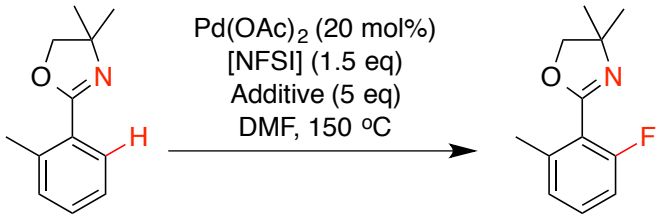
4.5.5 Solvent Screening



Entry	Solvent	Temperature °C	%SM	%Fluorination
1	Acetonitrile	80	0	100
2	Dioxane	100	84	16
3	DMF	150	51	49
4	CF3–toluene	80	91	9
5	Nitromethane	100	21	71
6	Dichloroethane	80	66	33
7[c]	THF	65	0	0
8	NMP	150	73	27
9	EtOAc	75	100	0
10	DMSO	150	55	45

[a] Reaction conditions(0.1 mmol), $Pd(OAc)_2$ (20 mol%), NFSI (0.15 mmol), $AgNO_3$ (50 mol%) Solvent (1 mL), 150 °C, under nitrogen, 24 h. [b] GCMS conversion using dodecane as internal standard. [c] Starting material decomposition

4.5.6 Screening of other Additives

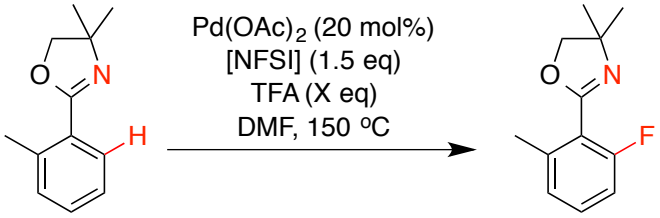


Entry	Promoter	%SM	%Fluorination
1	TFA	72	28
2	Pivalic Acid	96	4
3	Triflic Acid	95	5
4	Dichloroacetic acid	84	16
5	Chlorodifluorocacetic acid	83	17
6	Mesic acid	82	18

7	Tosic Acid	100	0
8	Difluoroacetic acid	81	19
14	L–Proline	100	0
15	NMP	100	0

[a] Reaction conditions(0.1 mmol), $Pd(OAc)_2$ (20 mol%), NFSI (0.15 mmol), $AgNO_3$ (50 mol%) Solvent (1 mL), 150 °C, under nitrogen, 24 h. [b] GCMS conversion using dodecane as internal standard.

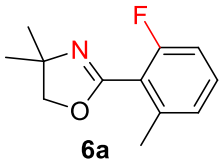
4.5.7 Acid additive loading



Entry	Eq TFA	%SM	%Fluorination
1	10	86	14
2	5	72	28
3	2	89	11
4	0.5	91	9
5	0	100	0

[a] Reaction conditions(0.1 mmol), $Pd(OAc)_2$ (20 mol%), NFSI (0.15 mmol), Trifluoroacetic acid (X mmol) DMF (1 mL), 150 °C, under nitrogen, 24 h. [b] GCMS conversion using dodecane as internal standard.

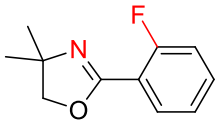
4.6 Characterization of Fluorinated Compounds



6a

2–(2–Fluoro–6–methylphenyl)–4,4–dimethyl–4,5–dihydrooxazole (6a)

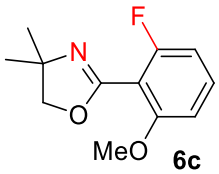
Yellow oil 68 mg, 65% yield; Flash chromatography solvent system Et_2O/Hex (1:1) R_f= 0.52; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.23 (m, 1H), 7.00 (d, *J* = 7.7 Hz, 1H), 6.93 (t, *J* = 8.9 Hz, 1H), 4.13 (s, 2H), 2.41 (s, 3H), 1.43 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.01 (d, *J* = 250.4 Hz), 158.70, 140.03 (d, *J* = 2.2 Hz), 131.18 (d, *J* = 9.1 Hz), 125.83 (d, *J* = 3.2 Hz), 113.11 (d, *J* = 21.5 Hz), 79.24, 68.16, 28.47, 19.62 (d, *J* = 2.3 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ –114.12; HRMS–ESI (m/z): calcd for $C_{12}H_{14}FNO$ (M+H): 207.1059, found



6b

2–(2–Fluorophenyl)–4,4–dimethyl–4,5–dihydrooxazole (6b)

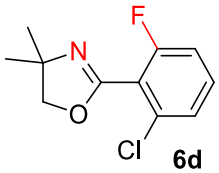
White solid, 44 mg, 46% yield; Flash chromatography solvent system Et_2O/Hex (1:4) R_f= 0.26; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 – 7.81 (m, 1H), 7.50 – 7.39 (m, 1H), 7.20 – 7.08 (m, 2H), 4.11 (s, 2H), 1.41 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.19 (dd, *J* = 257.6, 2.9 Hz), 159.15 (d, *J* = 12.3 Hz), 133.59 – 132.40 (m), 131.49 – 131.02 (m), 124.01 (t, *J* = 3.3 Hz), 116.71 (dd, *J* = 22.1, 3.0 Hz), 79.02 (d, *J* = 7.9 Hz), 67.82, 28.44; ^{19}F NMR (470 MHz, $CDCl_3$) δ –109.49;



6c

2–(2–Fluoro–6–methoxyphenyl)–4,4–dimethyl–4,5–dihydrooxazole (6c)

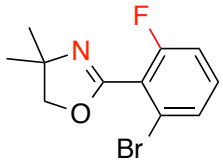
Clear oil; 47 mg, 42% yield; Flash chromatography solvent system EtOAc/Hex (1:3) R_f= 0.42; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (td, *J* = 8.5, 6.5 Hz, 1H), 6.76 – 6.65 (m, 2H), 4.13 (s, 2H), 3.85 (s, 3H), 1.42 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.51 (d, *J* = 250.7 Hz), 159.28 (d, *J* = 6.5 Hz), 156.43, 131.84 (d, *J* = 10.6 Hz), 108.17 (d, *J* = 21.9 Hz), 106.79 (d, *J* = 3.1 Hz), 79.14, 68.11, 56.54, 28.41; ^{19}F NMR (470 MHz, $CDCl_3$) δ –112.49; HRMS–ESI (m/z): calcd for $C_{12}H_{14}FNO_2$ (M+H): 223.1009, found



6d

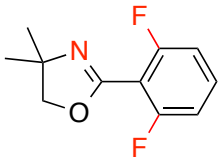
2–(2–Chloro–6–fluorophenyl)–4,4–dimethyl–4,5–dihydrooxazole (4d)

Yellow oil, 77 mg, 68% yield; Flash chromatography solvent system Et_2O/Hex (1:1) R_f= 0.61; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 1H), 7.24 – 7.20 (m, 1H), 7.07 – 6.99 (m, 1H), 4.16 (s, 2H), 1.43 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.09 (d, *J* = 254.2 Hz), 156.31, 134.73 (d, *J* = 4.1 Hz), 132.51 – 131.04 (m), 125.51 (d, *J* = 3.9 Hz), 118.32 (d, *J* = 18.8 Hz), 114.40 (d, *J* = 21.5 Hz), 79.56 (d, *J* = 6.2 Hz), 68.56, 28.29; ^{19}F NMR (470 MHz, $CDCl_3$) δ –110.68; HRMS–ESI (m/z): calcd for $C_{11}H_{11}ClFNO$ (M+H): 227.0513, found

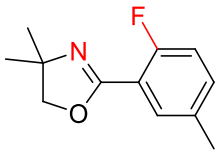


2–(2–bromo–6–fluorophenyl)–4,4–dimethyl–4,5–dihydrooxazole

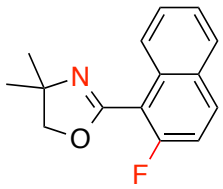
Yellow oil 47 mg, 37% yield; Flash chromatography solvent system Et_2O/Hex (1:4) R_f= 0.38; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.30 – 7.22 (m, 1H), 7.08 (t, *J* = 8.7 Hz, 1H), 4.16 (s, 2H), 1.44 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.93 (d, *J* = 255.0 Hz), 157.31, 132.20 (dd, *J* = 9.6, 3.1 Hz), 128.60 (d, *J* = 3.6 Hz), 123.21 (d, *J* = 3.3 Hz), 114.94 (d, *J* = 21.4 Hz), 79.65, 68.60, 28.25; ^{19}F NMR (470 MHz, $CDCl_3$) δ –110.01; HRMS (ESI, m/z) calcd for $C_{11}H_{12}BrNO$, 253.0102; found:



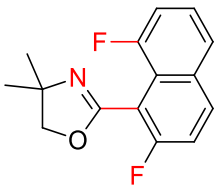
2–(2,6–Difluorophenyl)–4,4–dimethyl–4,5–dihydrooxazole (6e)
Clear oil, 20 mg, 19% yield. Flash chromatography solvent system Et_2O/Hex (1:4) R_f= 0.32. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.31 (m, 1H), 7.00 – 6.80 (m, 2H), 4.12 (s, 2H), 1.41 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.26 (dd, *J* = 255.6, 6.2 Hz), 154.65, 132.17 (t, *J* = 10.4 Hz), 111.90 (dd, *J* = 20.8, 4.5 Hz), 107.77 (t, *J* = 17.9 Hz), 79.20, 68.30, 28.38; ^{19}F NMR (470 MHz, $CDCl_3$) δ –109.58, –109.59, –109.59, –109.61.



2–(2–Fluoro–5–methylphenyl)–4,4–dimethyl–4,5–dihydrooxazole (6x)
Clear oil, 13 mg, 12% yield. Flash chromatography solvent system Et_2O/Hex (1:4) R_f= 0.21. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 – 7.65 (m, 1H), 7.22 (dd, *J* = 8.2, 4.0 Hz, 1H), 7.01 (dd, *J* = 10.6, 8.5 Hz, 1H), 4.12 (s, 2H), 2.33 (s, 3H), 1.41 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.84, 159.31 (d, *J* = 254.9 Hz), 133.57, 131.36, 116.42, 116.25, 79.21, 71.81, 67.24, 28.24, 20.40; ^{19}F NMR (470 MHz, $CDCl_3$) δ –114.85; HRMS–ESI (m/z): calcd for $C_{12}H_{14}FNO$ (M+H): 207.1059, found

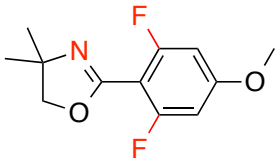


2–(2–Fluoronaphthalen–1–yl)–4,4–dimethyl–4,5–dihydrooxazole
White solid, 106 mg, 88% yield; Flash chromatography solvent system EtOAc/Hex (1:1) R_f= 0.43; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.4 Hz, 1H), 7.75 – 7.62 (m, 2H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.49 – 7.40 (m, 1H), 7.24 – 7.17 (m, 1H), 4.25 (s, 2H), 1.49 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.54, 158.40 (d, *J* = 253.6 Hz), 135.43 (d, *J* = 4.2 Hz), 130.42 (d, *J* = 3.1 Hz), 129.09, 126.43 (d, *J* = 8.6 Hz), 125.91, 124.50 (d, *J* = 4.1 Hz), 123.44, 121.35 (d, *J* = 13.6 Hz), 111.94 (d, *J* = 21.9 Hz), 80.27, 67.81, 28.19; ^{19}F NMR (470 MHz, $CDCl_3$) δ –76.02, –113.74, –113.75, –113.77, –113.77, –113.78; HRMS (ESI, m/z) calcd for $C_{15}H_{14}FNO$ 243.1059; found:



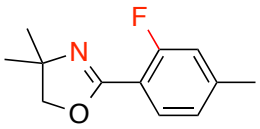
2–(2,8–Difluoronaphthalen–1–yl)–4,4–dimethyl–4,5–dihydrooxazole
Yellow solid, 8 mg, 6% yield. Flash chromatography solvent system EtOAc/Toluene (1:4) R_f= 0.29; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (dd, 1H), 7.90 (d, J = 8.3 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.66 – 7.59 (m, 1H), 7.47 – 7.36 (m, 1H), 3.98 (s, 2H), 1.65 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.21, 169.11 (d, *J* = 213.5 Hz), 161.06, 158.21 (d, *J* = 261.3 Hz), 138.71 (d, *J* = 5.3 Hz), 135.61 (d, *J* = 2.4 Hz), 133.55, 129.35, 129.20 (d, *J* = 7.9 Hz), 126.60, 126.00 (d, *J* = 22.3 Hz), 125.40 (d, *J* = 4.6 Hz), 124.44 (d,

J = 3.9 Hz), 119.30, 114.84 (d, *J* = 21.6 Hz), 111.71 (d, *J* = 21.1 Hz), 69.85, 68.53, 62.49, 53.96, 29.85, 23.42; ^{19}F NMR (470 MHz, $CDCl_3$) δ –102.17, –102.18, –102.20, –102.21; HRMS (ESI, m/z) calcd for $C_{15}H_{13}F_2NO$ 261.0965; found :



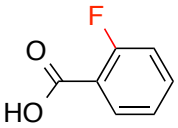
2–(2,6–difluoro–4–methoxyphenyl)–4,4–dimethyl–4,5–dihydrooxazole

Yellow oil 110 mg, 92% yield. Flash chromatography solvent system Et_2O/Hex (1:1) R_f= 0.36; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.50 (d, *J* = 10.1 Hz, 2H), 4.14 (s, 2H), 3.82 (s, 3H), 1.44 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.15 (dd, *J* = 255.0, 9.2 Hz), 105.66 – 95.31 (m), 71.83, 67.42, 55.99, 28.09; ^{19}F NMR (470 MHz, $CDCl_3$) δ –106.75, –106.77; HRMS (ESI, m/z) calcd for $C_{12}H_{13}F_2NO_2$, 241.0914; found:



2–(2–fluoro–4–methylphenyl)–4,4–dimethyl–4,5–dihydrooxazole

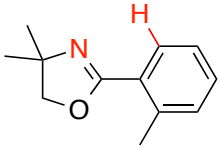
Clear oil 18 mg, 17% yield. Flash chromatography solvent system Et_2O/Hex (1:4) R_f= 0.19; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (s, 1H), 6.96 (dd, *J* = 18.5, 9.9 Hz, 2H), 4.11 (s, 2H), 2.37 (s, 2H), 1.41 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.86, 161.04 (d, *J* = 257.6 Hz), 159.83, 143.65, 131.03, 129.64, 124.85 (d, *J* = 3.6 Hz), 117.09 (d, *J* = 21.7 Hz), 112.44 (d, *J* = 3.9 Hz), 112.26, 79.00 (d, *J* = 27.8 Hz), 67.59 (d, *J* = 96.9 Hz), 28.21, 21.40; ^{19}F NMR (470 MHz, $CDCl_3$) δ -110.55, -110.57; HRMS–ESI (m/z): calcd for $C_{12}H_{14}FNO$ (M+H): 207.1059, found



2–fluro–benzoic acid

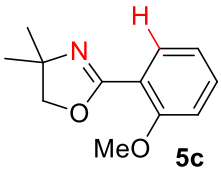
Yellow solid g, 22mg, 77% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 – 7.99 (m, 1H), 7.59 (tdd, *J* = 8.4, 6.6, 1.6 Hz, 1H), 7.28 – 7.15 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.11, 170.08, 163.84, 161.75, 135.80, 135.73, 132.90, 124.26, 124.22, 117.75, 117.67, 117.40, 117.22; ^{19}F NMR (470 MHz, $CDCl_3$) δ -108.09, -108.10, -108.10, -108.11, -108.13, -108.14.

4.7 Characterization of Oxazoline Derivatives



4,4–Dimethyl–2–(*o*–tolyl)–4,5–dihydrooxazole (5a)

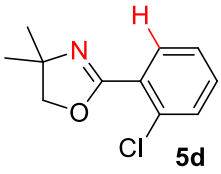
Yellow oil, 1.280 g, 68% yield; Flash chromatography solvent system EtOAc/Hex (1:2) R_f = 0.47; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.7 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.24 – 7.17 (m, 2H), 4.07 (s, 2H), 2.56 (s, 3H), 1.39 (s, 7H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.41, 138.20, 132.14, 132.11, 128.94, 128.33, 127.93, 125.40, 79.22, 79.19, 67.59, 28.56, 28.53, 21.35.



5c

2–(2–Methoxyphenyl)–4,4–dimethyl–4,5–dihydrooxazole (5c)

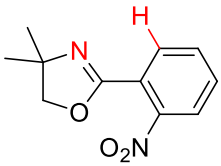
Yellow solid, 0.861 g, 42% yield; Melting point 73–75 ^{o}C; Flash chromatography solvent system EtOAc/Hex/MeOH (4:6:1) R_f = 0.39; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.7 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 9.3 Hz, 2H), 4.11 (s, 2H), 3.90 (s, 3H), 1.41 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.68, 158.61, 132.55, 131.53, 120.41, 111.90, 79.22, 67.43, 56.28, 28.43.



5d

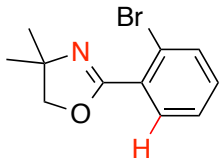
2–(2–Chlorophenyl)–4,4–dimethyl–4,5–dihydrooxazole (5d)

Yellow oil 1.422 g, 68% yield; Flash chromatography solvent system EtOAc/Hex (1:2) R_f = 0.42; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.4 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 4.16 (s, 2H), 1.43 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.59, 131.61, 131.55, 130.70, 130.67, 126.72, 126.69, 79.68, 67.86, 28.35, 28.32;



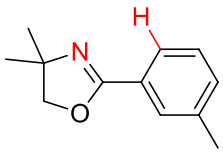
4,4–Dimethyl–2–(2–nitrophenyl)–4,5–dihydrooxazole (5x)

Yellow solid, 1.153 g, 61% yield; Flash chromatography solvent system EtOAc/Hex (1:1) R_f = 0.48; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 6.1 Hz, 1H), 7.66 – 7.53 (m, 2H), 4.10 (s, 2H), 1.38 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.02, 149.10, 132.71, 131.44, 131.21, 124.10, 80.32, 68.35, 28.04.

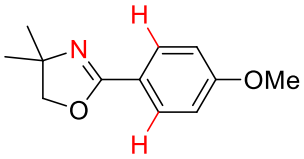


2–(2–bromophenyl)–4,4–dimethyl–4,5–dihydrooxazole

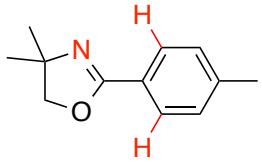
Yellow solid, 1.442 g, 57% yield; Melting point 36–38 ^{o}C; Flash chromatography solvent system EtOAc/Hex (1:1) R_f = 0.65. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 – 7.49 (m, 3H), 7.27 – 7.15 (m, 4H), 4.06 (s, 2H), 1.33 (s, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.45, 133.38, 131.33, 131.03, 130.17, 126.87, 121.62, 79.16, 67.90, 28.10.



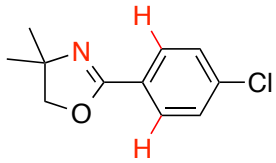
4,4–Dimethyl–2–(*m*–tolyl)–4,5–dihydrooxazole (5x)
Yellow oil 1.247 g, 66% yield; Flash chromatography solvent system EtOAc/Hex (1:1) R_f= 0.42; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.70 (d, *J* = 6.4 Hz, 1H), 7.32 – 7.21 (m, 2H), 4.08 (s, 2H), 2.36 (s, 3H), 1.36 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.41, 138.20, 132.14, 132.11, 128.94, 128.91, 128.33, 128.30, 127.93, 125.40, 125.36, 79.22, 67.59, 28.56, 28.53, 21.35;



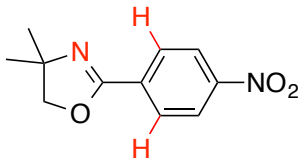
2–(4–Methoxyphenyl)–4,4–dimethyl–4,5–dihydrooxazole (5x)
Yellow oil 0.841 g, 41% yield; Flash chromatography solvent system EtOAc/Hex/MeOH (4:6:1) R_f = 0.32. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.9 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 4.07 (s, 2H), 3.83 (s, 3H), 1.36 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.10, 130.07, 130.06, 120.67, 113.75, 67.53, 55.48, 28.59.



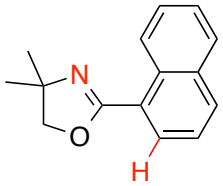
4,4–dimethyl–2–(*p*–tolyl)–4,5–dihydrooxazole
Clear oil 1.191 g 63%, yield; Flash chromatography solvent system EtOAc/Hex (1:1) R_f= 0.48; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 4.03 (s, 2H), 2.32 (s, 3H), 1.33 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.11, 141.43, 128.93, 128.16, 125.20, 78.97, 67.38, 28.39, 21.48;



2–(4–chlorophenyl)–4,4–dimethyl–4,5–dihyrooxazole
Yellow oil 1.087 g, 52% yield; Melting point 31–33 °C; Flash chromatography solvent system EtOAc/Hex (1:2) R_f= 0.44; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.8 Hz, 1H), 7.34 (d, *J* = 7.0 Hz, 1H), 4.08 (s, 1H), 1.35 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.31, 137.43, 129.67, 128.63, 126.59, 79.35, 28.45;



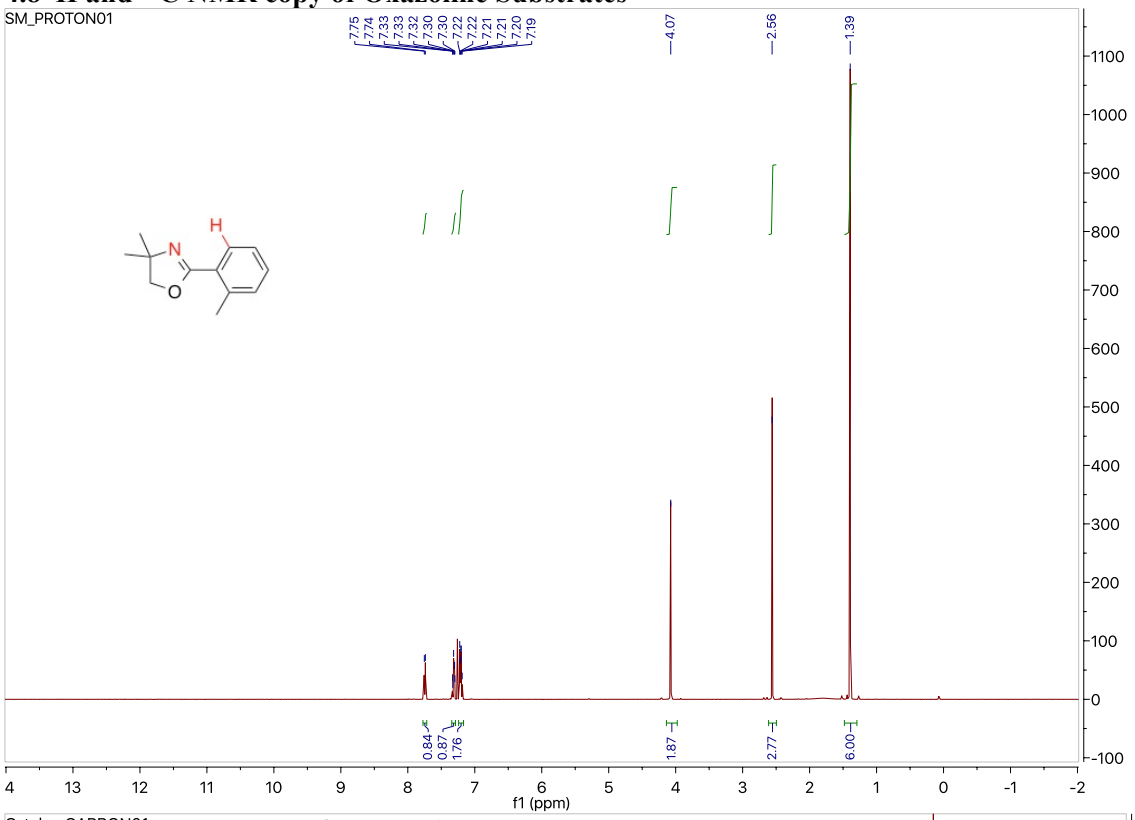
4,4–dimethyl–2–(4–nitrophenyl)–4,5–dihyrooxazole
Yellow oil 1.298 g, 59% yield; Melting point 96–97 °C; Flash chromatography solvent system EtOAc/Hex (1:2) R_f= 0.42. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25, 8.24, 8.11, 8.10, 4.16, 1.40. ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.48, 149.46, 133.62, 129.32, 123.46, 79.67, 68.09, 28.26.

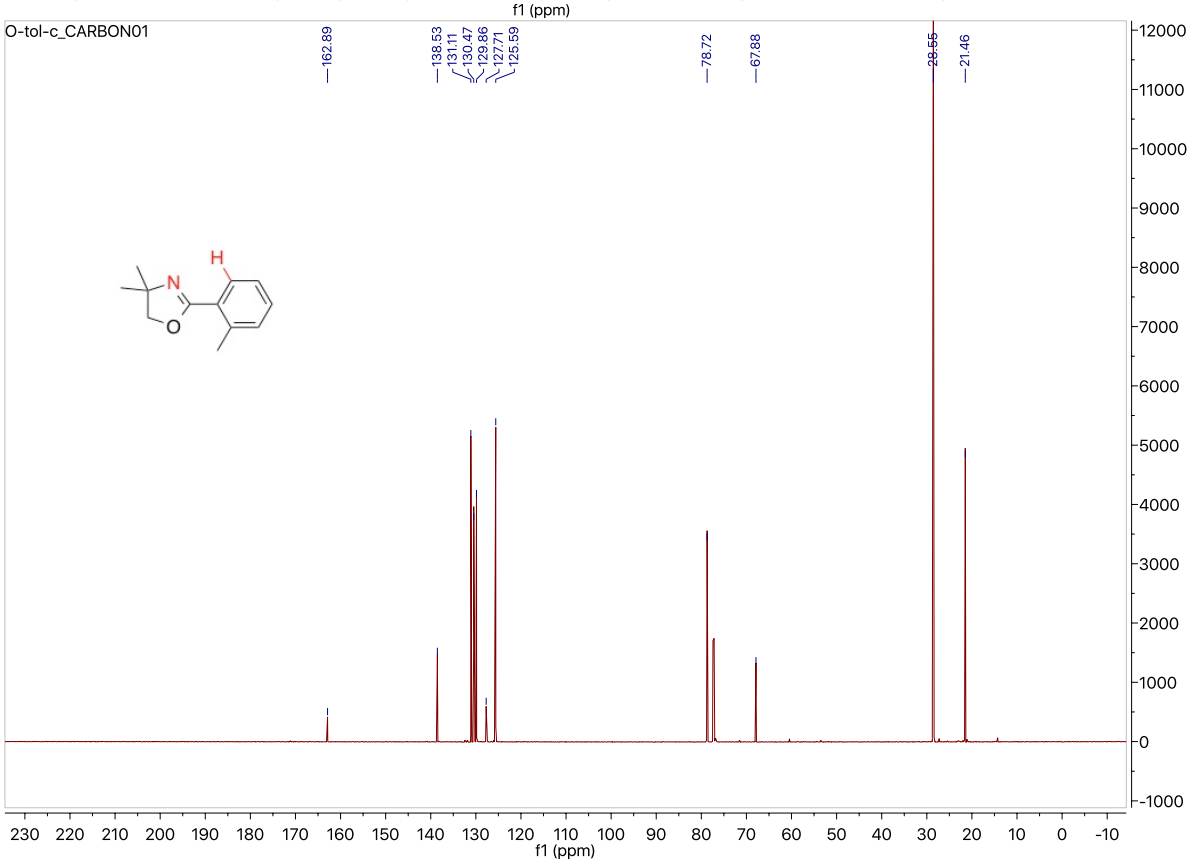


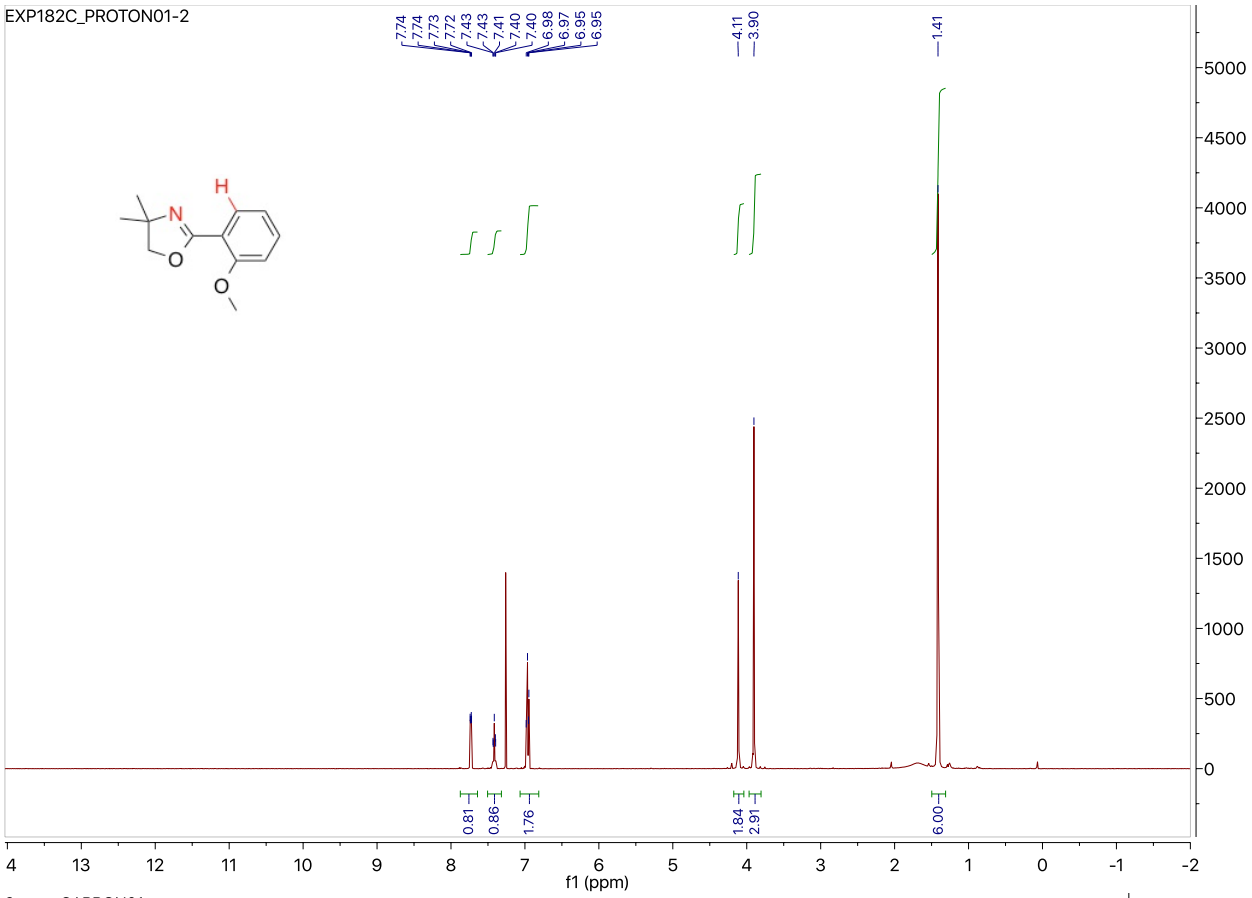
4,4–dimethyl–2–(naphthalene–1–yl)–4,5–dihydrooxazole

Yellow oil 1.531 g, 68% yield; Melting point 46–47 ^{o}C; Flash chromatography solvent system EtOAc/Hex (1:2) R_f= 0.52; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.07 (d, *J* = 8.7 Hz, 1H), 8.07 (d, *J* = 7.1 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.55 – 7.45 (m, 2H), 4.16 (s, 2H), 1.49 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.09, 133.79, 131.79, 131.26, 128.92, 128.47, 127.35, 126.43, 126.13, 125.02, 124.73, 78.47, 68.42, 28.66.

4.8 ^{1}H and ^{13}C NMR copy of Oxazoline Substrates



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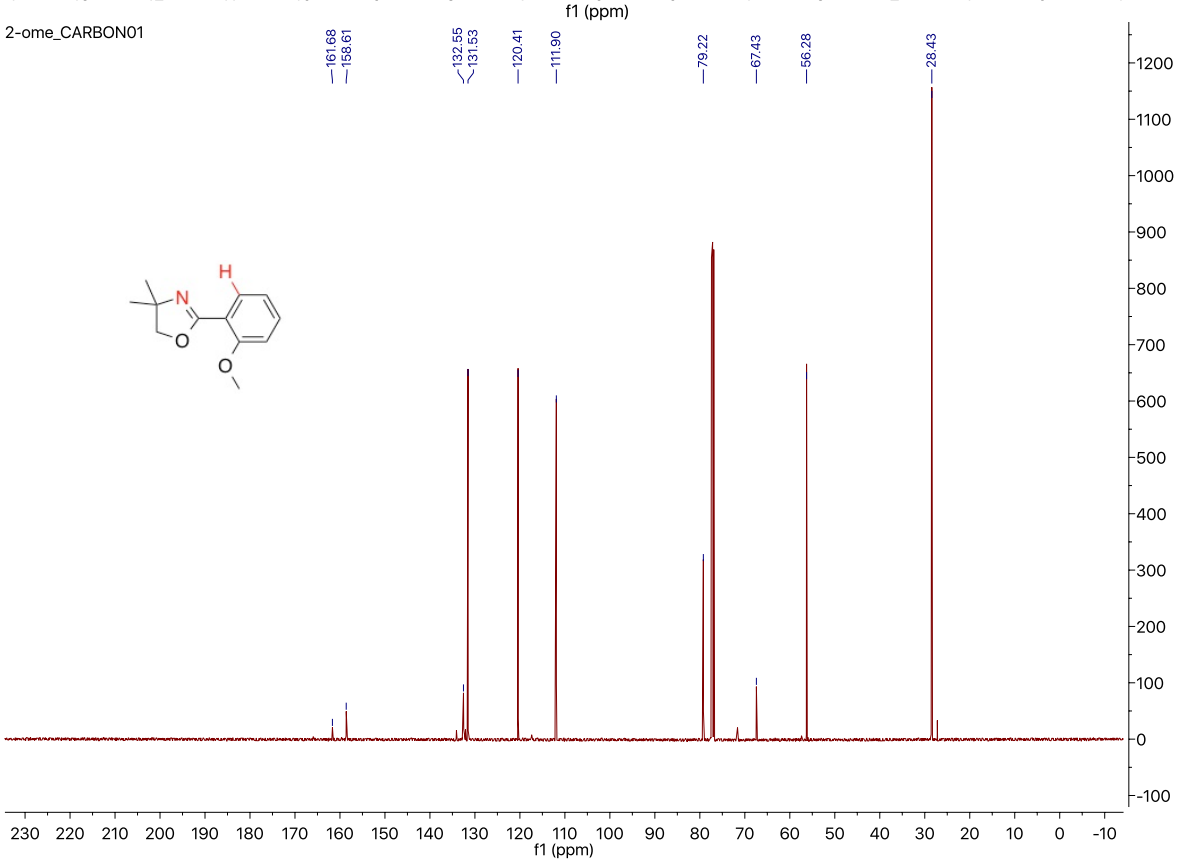
7.73
7.72
7.43
7.43
7.41
7.40
7.40
6.98
6.97
6.95
6.95
4.11
3.90
1.41
0.81
0.86
1.76
1.84
2.91
6.00
f1 (ppm)


2-ome_CARBON01
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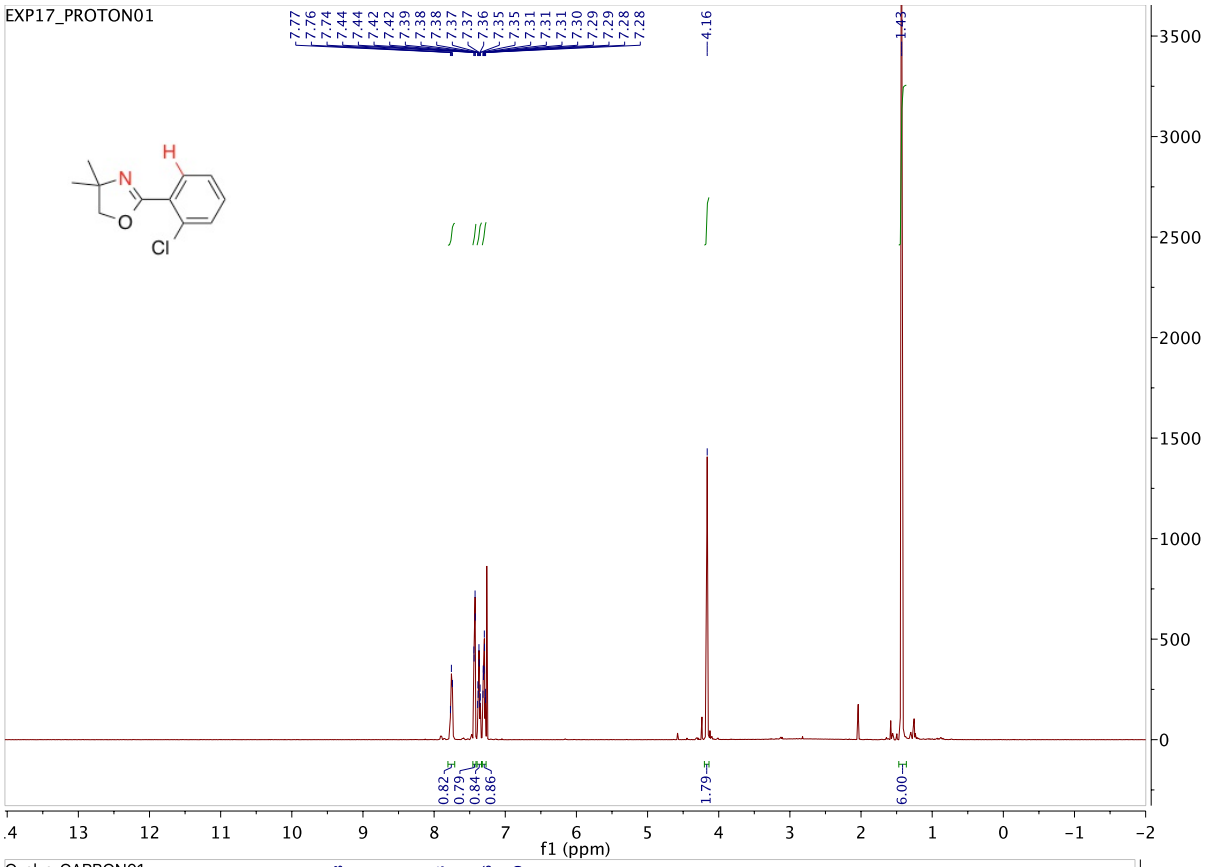
120.41
111.90
79.22
67.43
56.28
28.43
f1 (ppm)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7.31
7.31
7.30
7.29
7.29
7.28
7.28
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H
N
O
Cl
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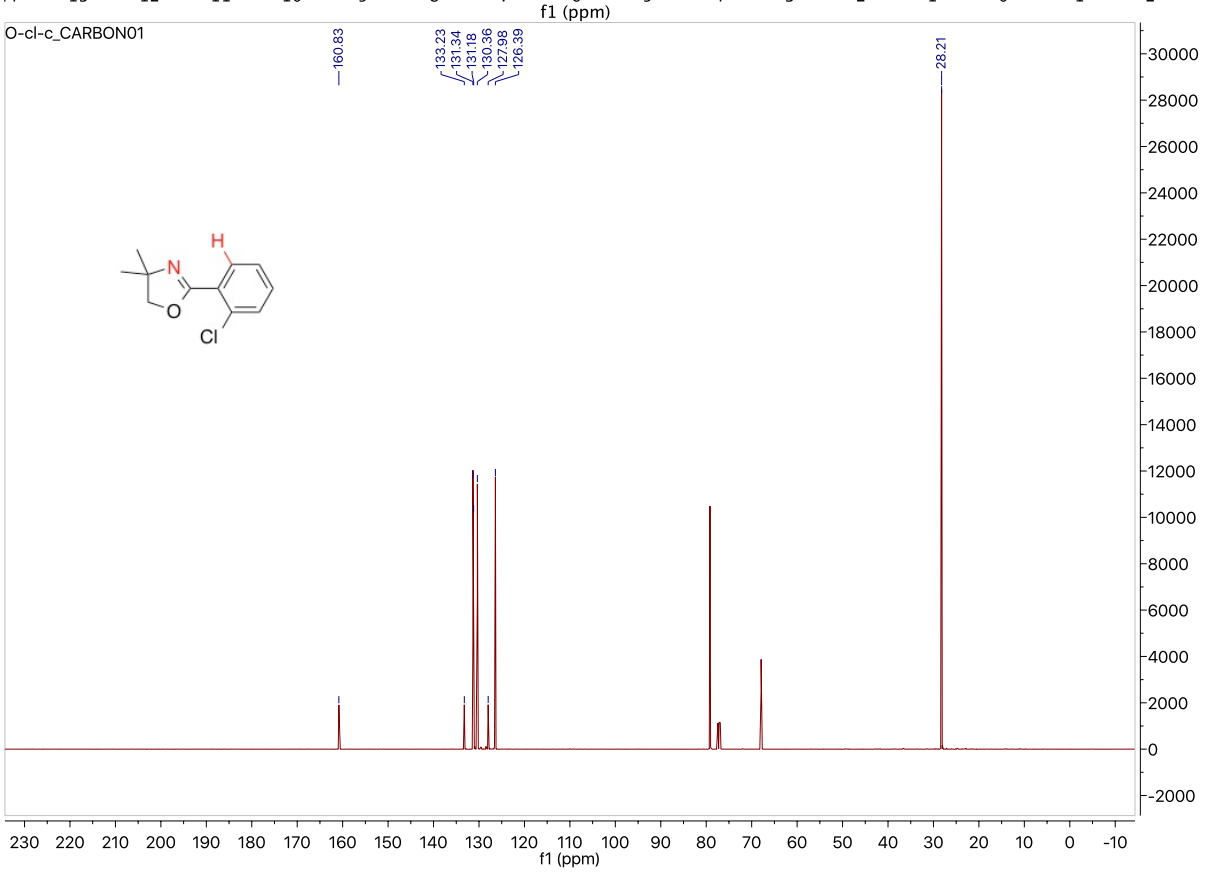
6.00
f1 (ppm)


O-cl-c_CARBON01
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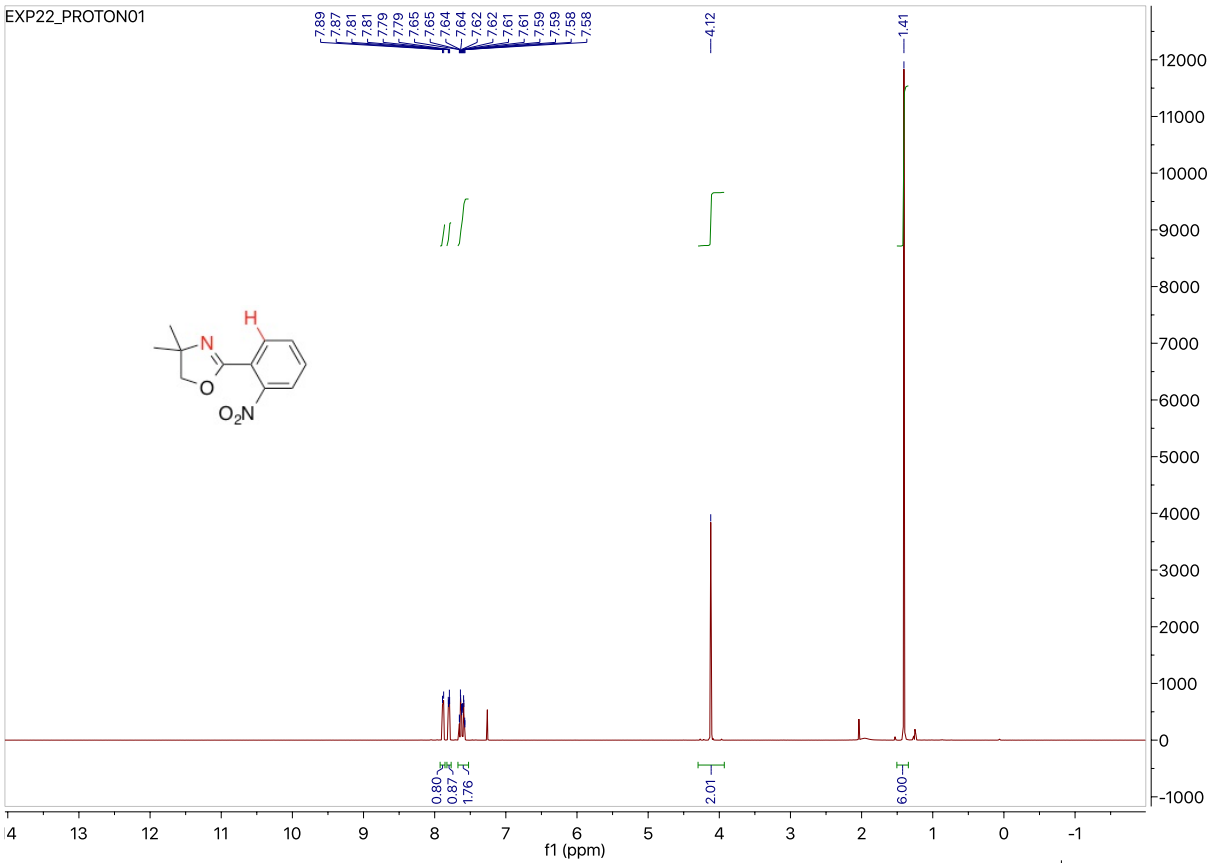
28.21
H
N
O
Cl
f1 (ppm)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7.64
7.64
7.62
7.62
7.61
7.61
7.59
7.59
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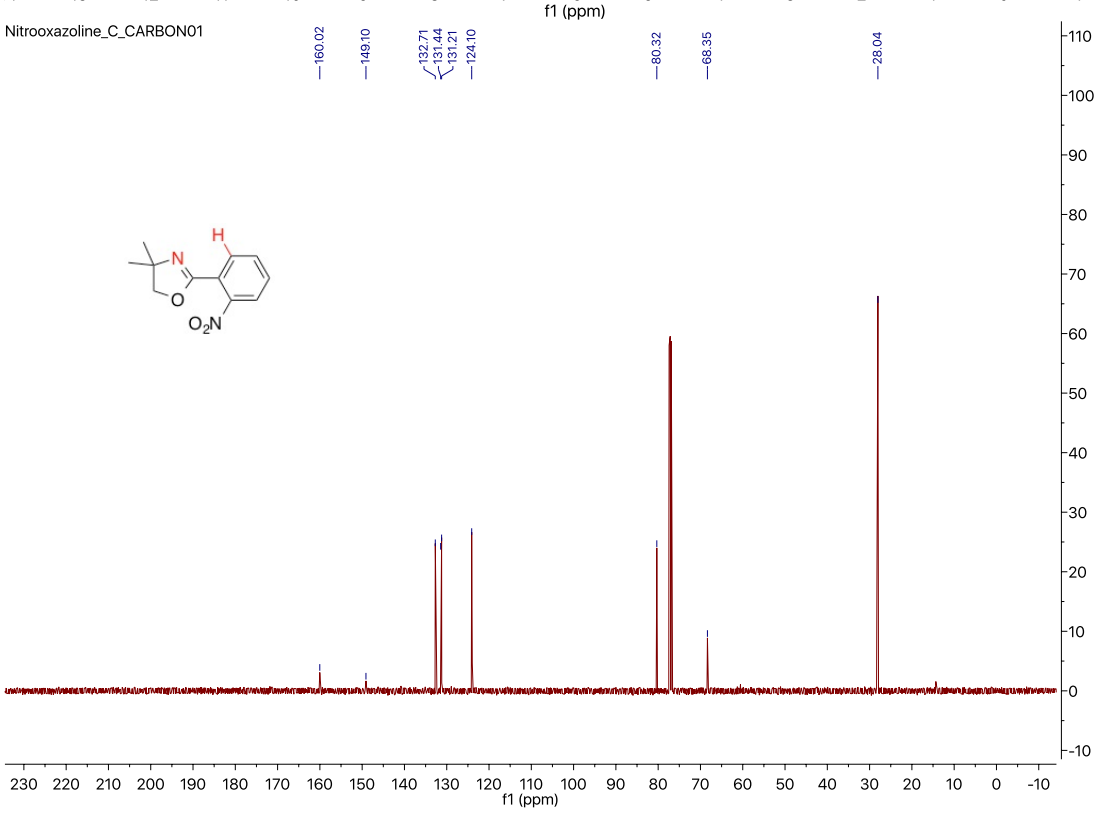
7.58
4.12
1.41
0.80
0.87
1.76
2.01
6.00
f1 (ppm)


Nitrooxazoline_C_CARBON01
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131.44
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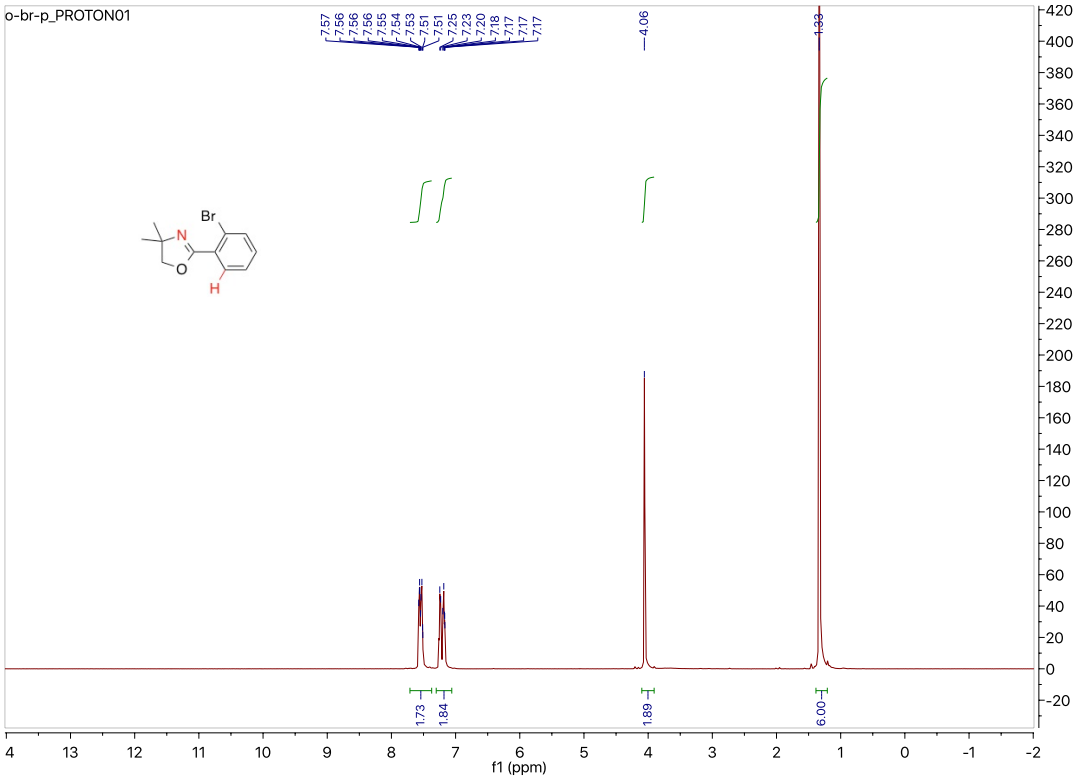
80.32
68.35
28.04
f1 (ppm)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7.56
7.56
7.56
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7.51
7.51
7.25
7.23
7.20
7.18
7.17
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7.17
4.06
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Br
N
O
H
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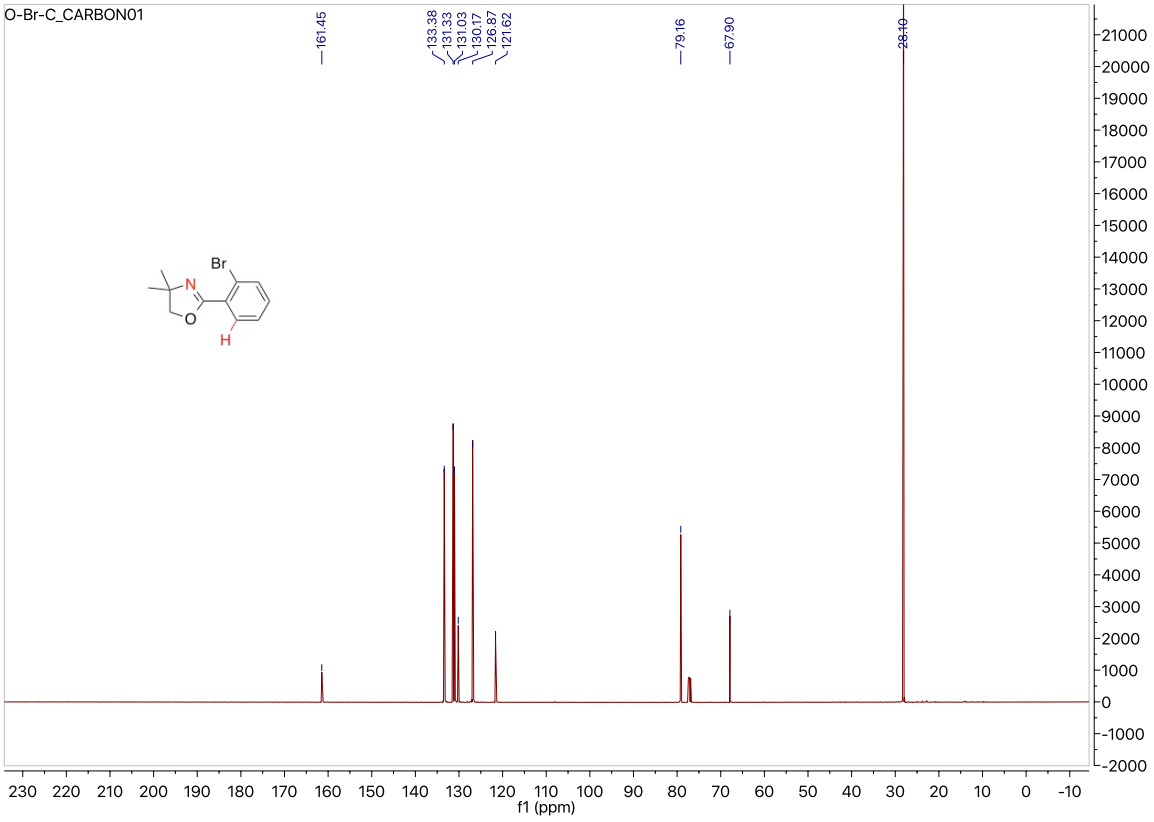
6.00
f1 (ppm)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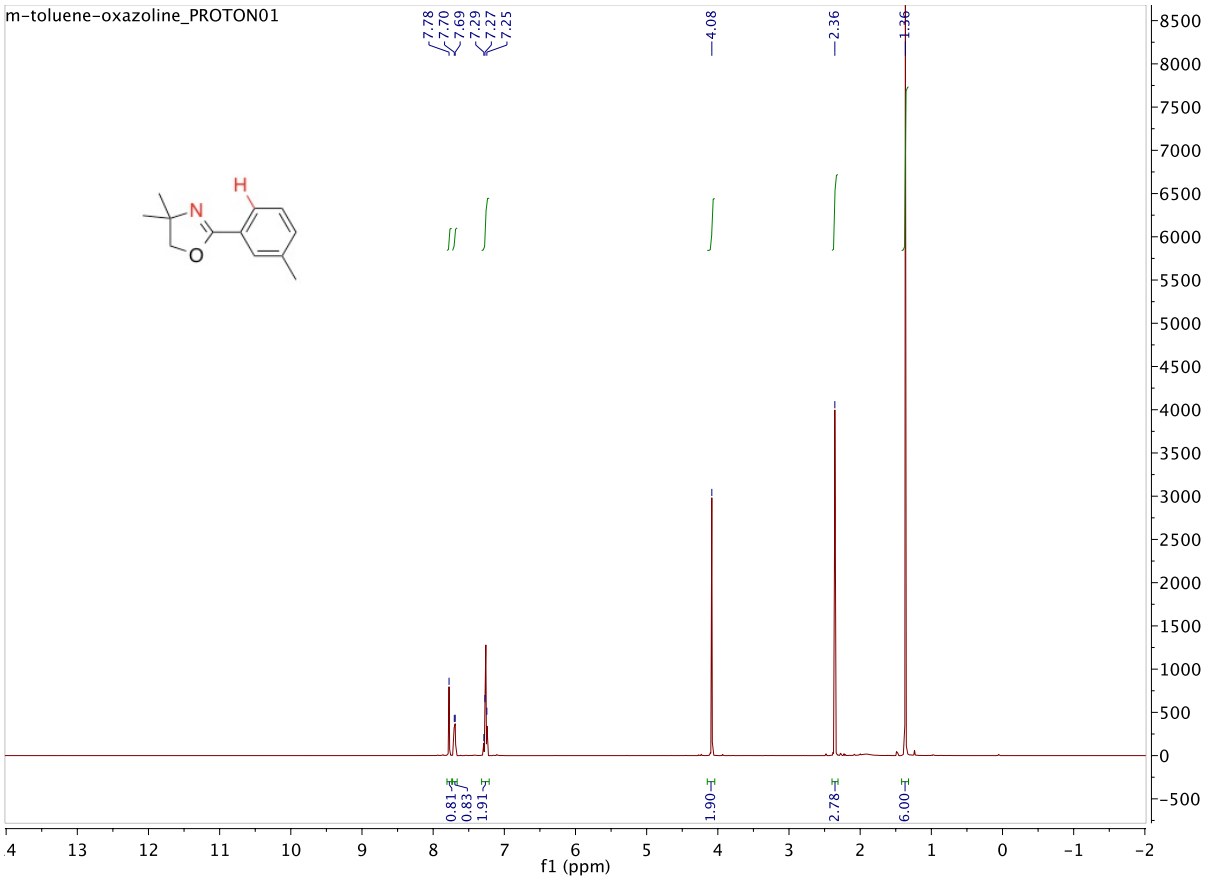
133.38
131.33
131.03
130.17
126.87
121.62
79.16
67.90
28.10
Br
N
O
H
f1 (ppm)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7.69
7.29
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7.25
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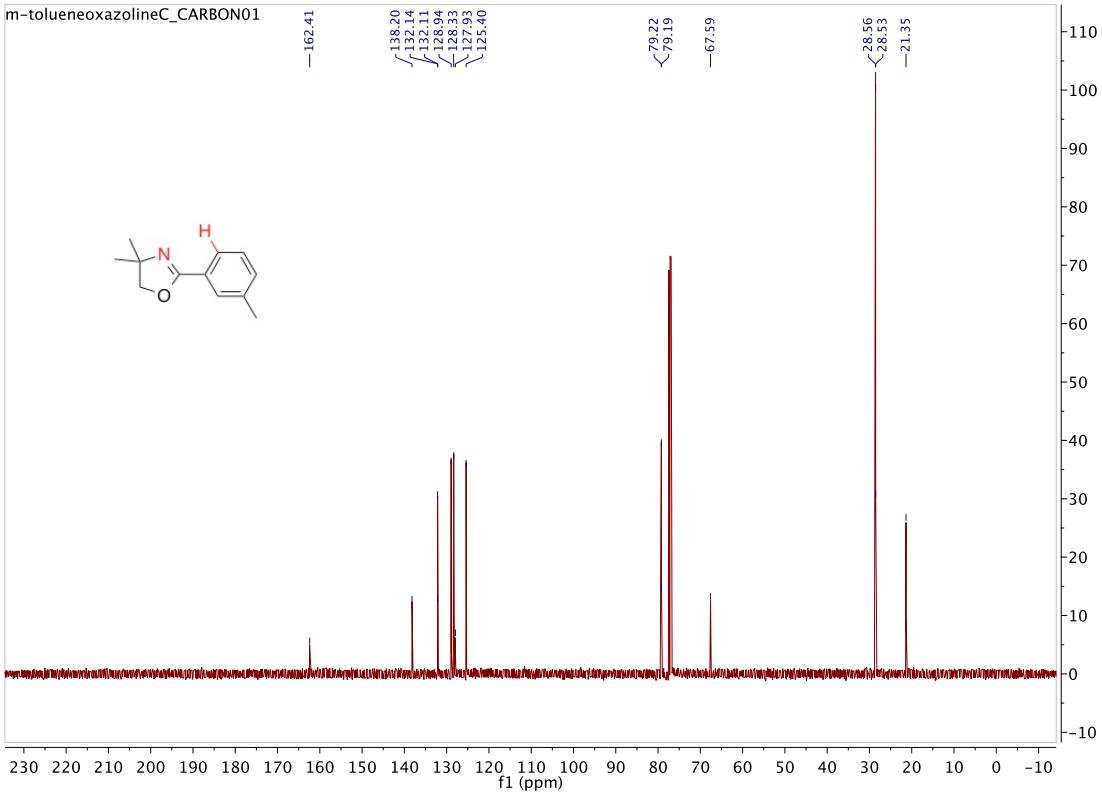
2.36
1.36
0.81
0.83
1.91
1.90
2.78
6.00
f1 (ppm)


m-tolueneoxazolineC_CARBON01
162.41
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132.11
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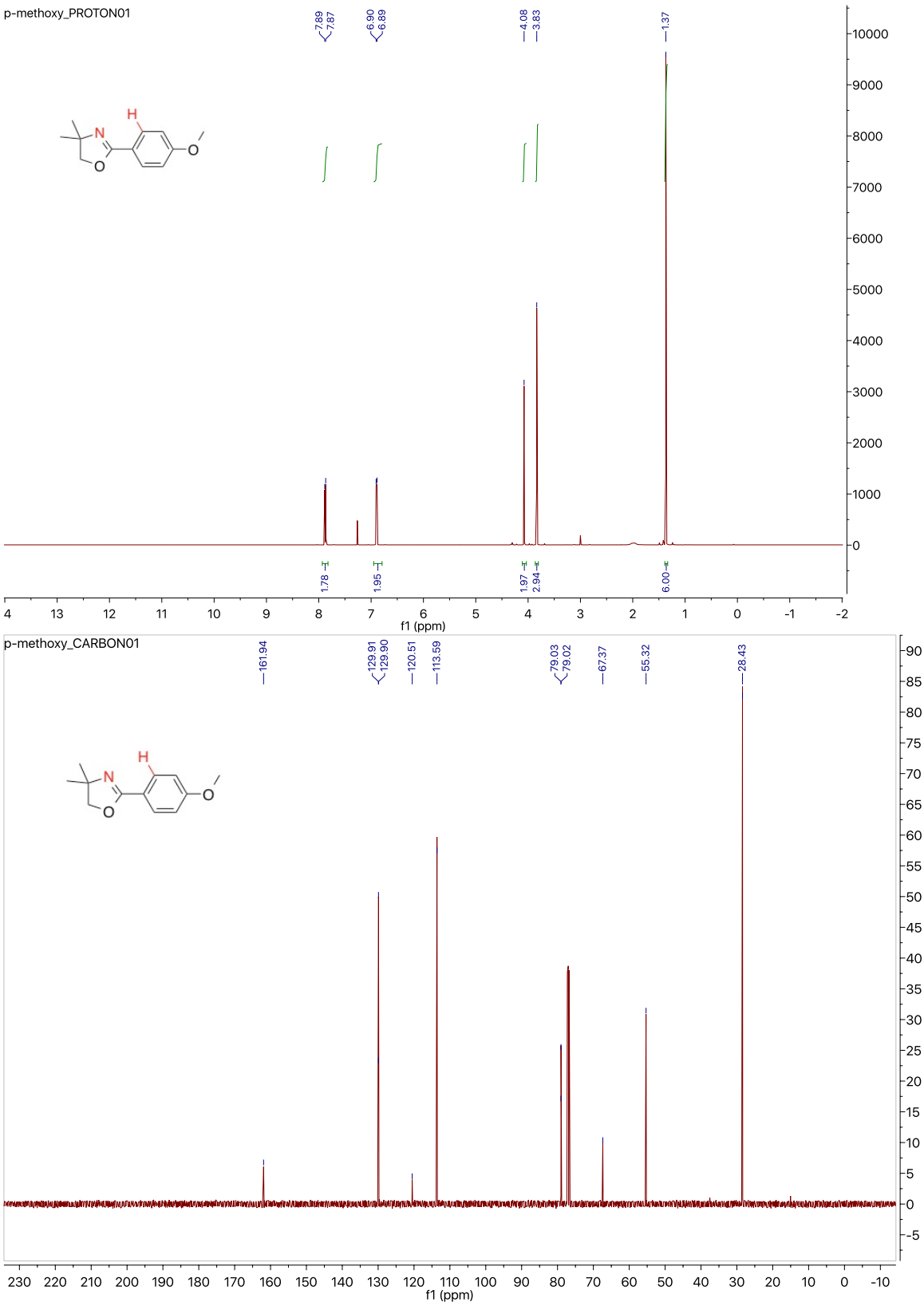
67.59
28.56
28.53
21.35
f1 (ppm)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6.00
f1 (ppm)
p-methoxy_CARBON01
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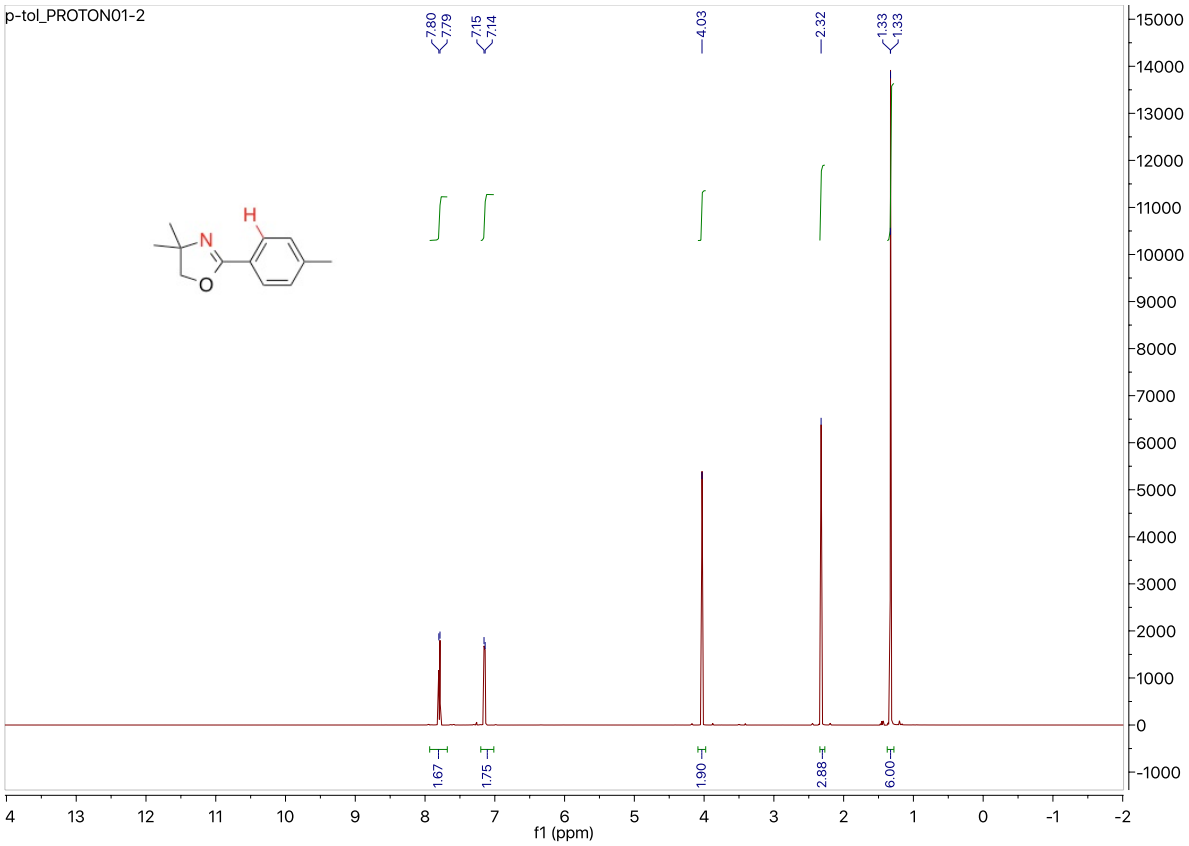
129.90
120.51
113.59
79.03
79.02
67.37
55.32
28.43
f1 (ppm)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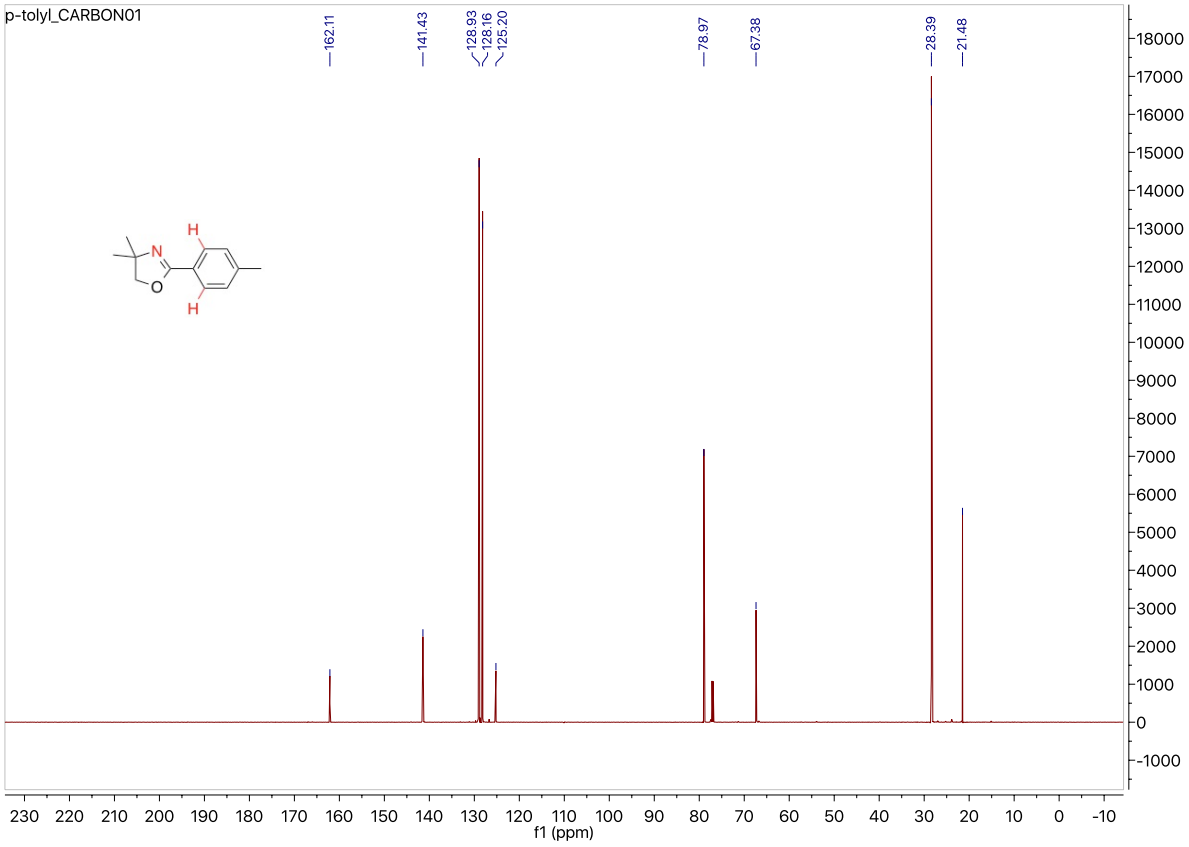
f1 (ppm)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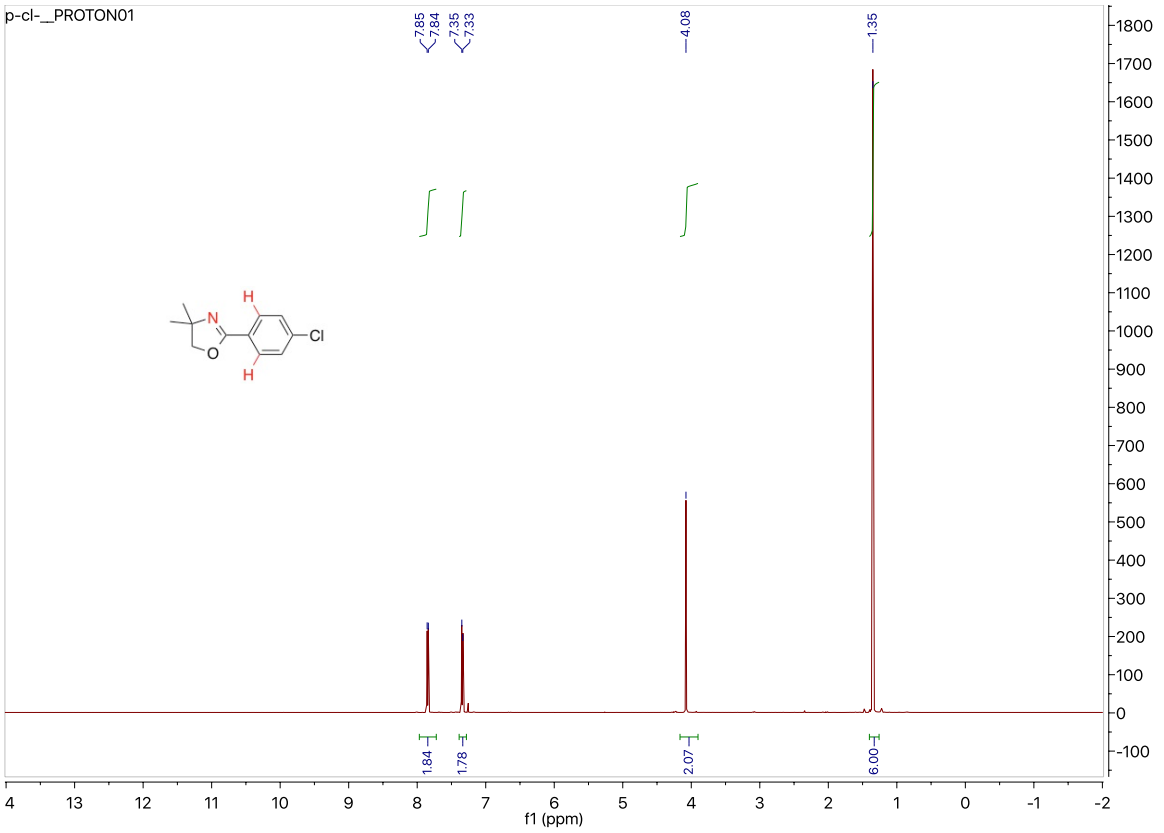
21.48
f1 (ppm)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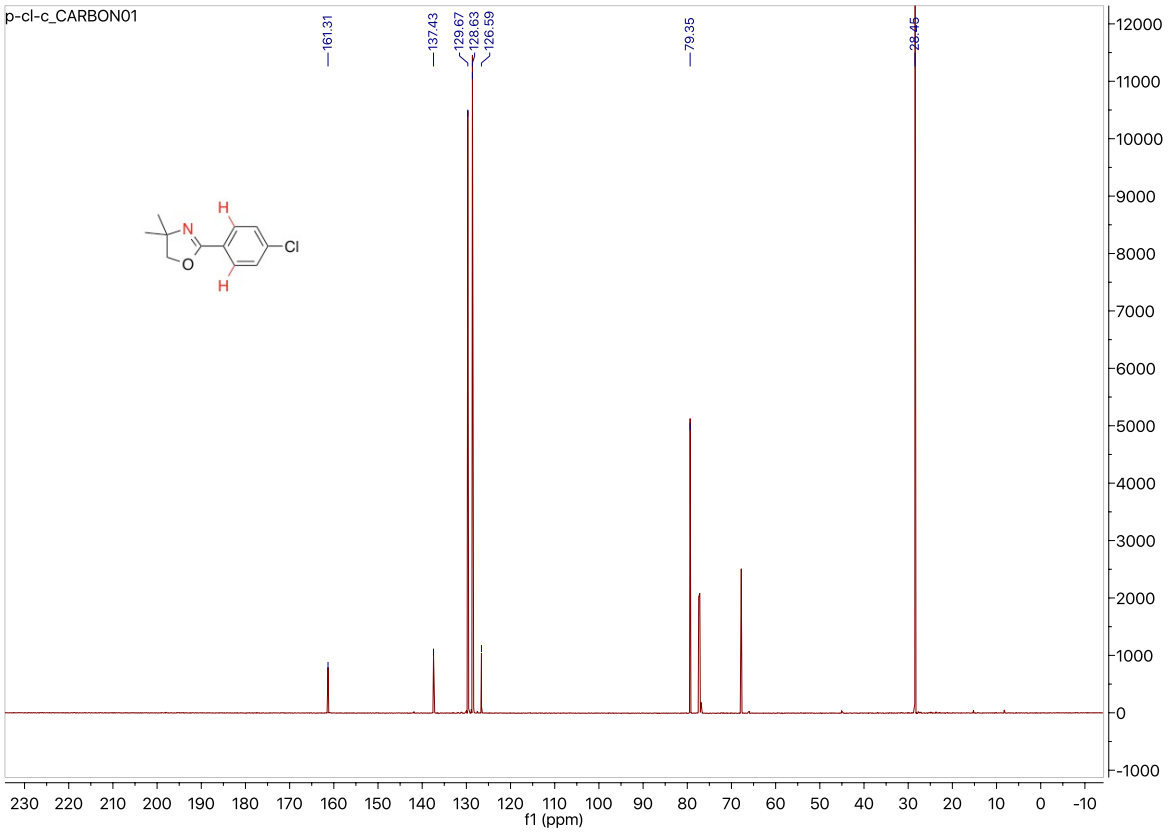
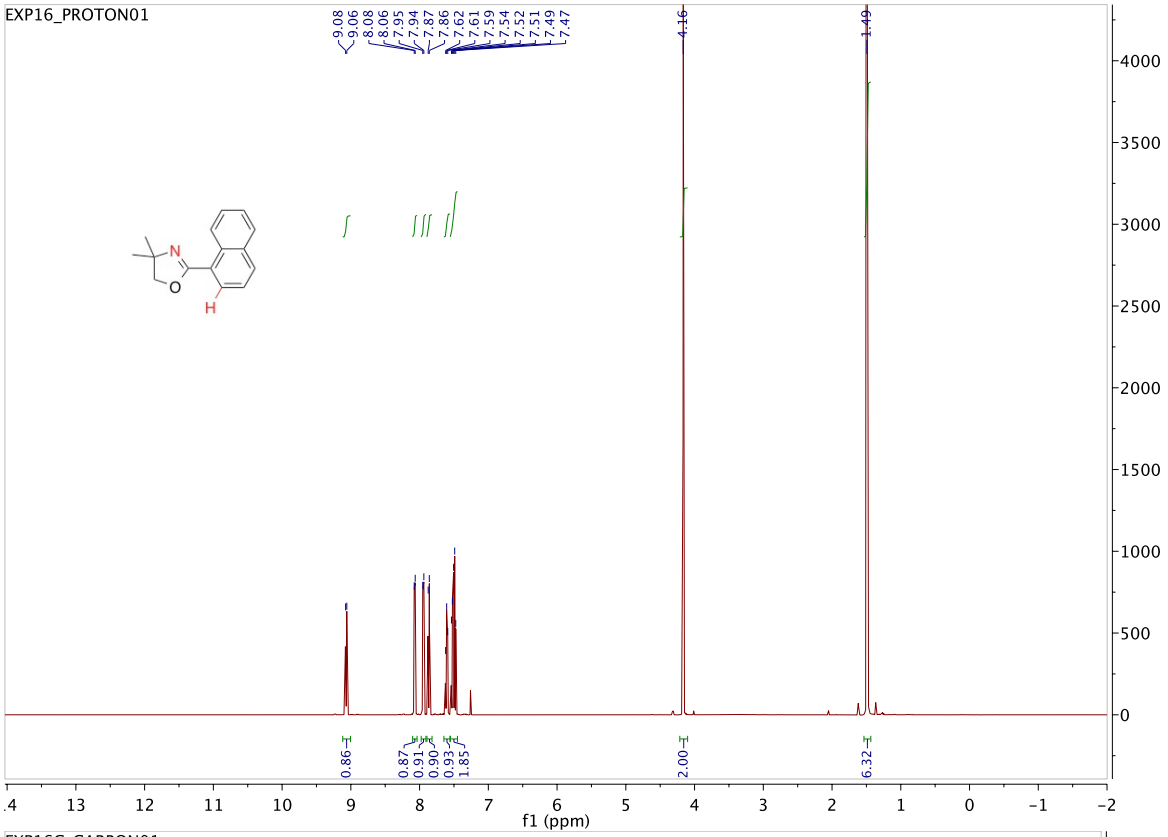
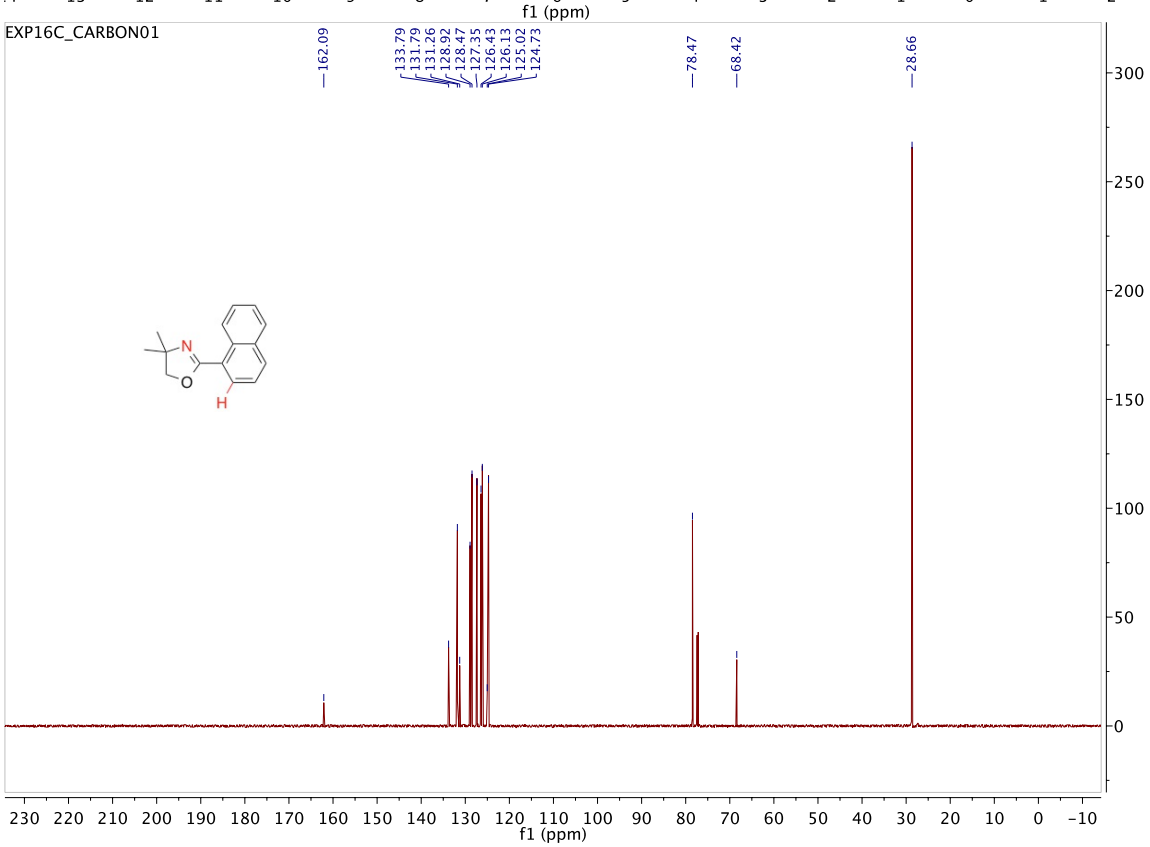
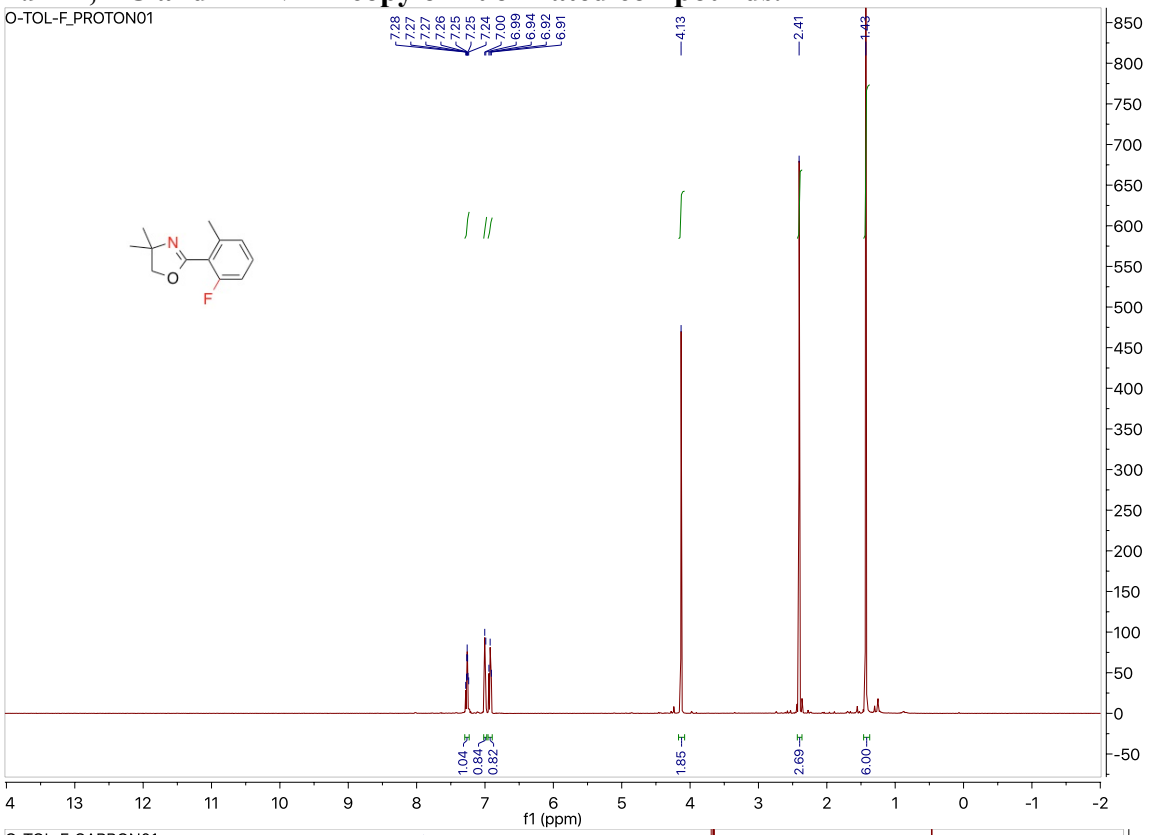
7.84
7.35
7.33
4.08
1.35
1.84
1.78
2.07
6.00
f1 (ppm)

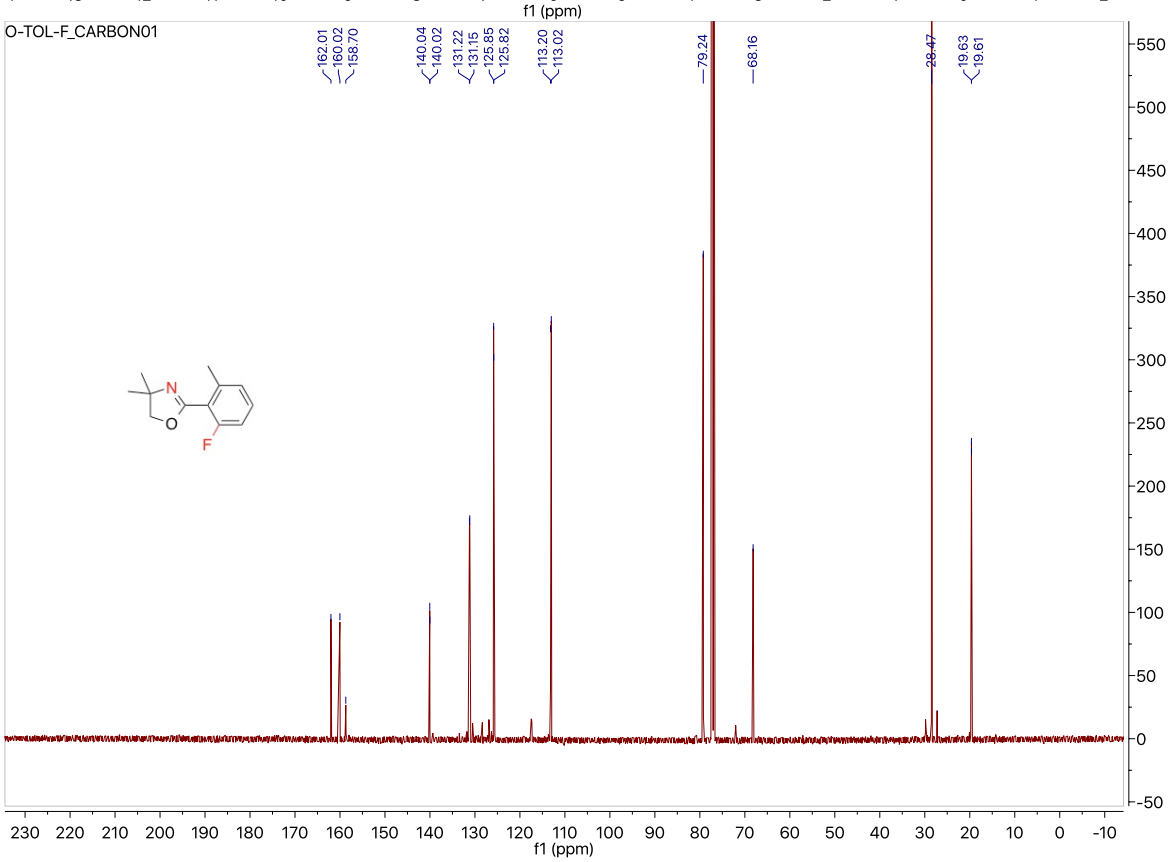

p-cl-c_CARBON01
161.31
137.43
129.67
128.63
126.59
79.35
28.46
f1 (ppm)

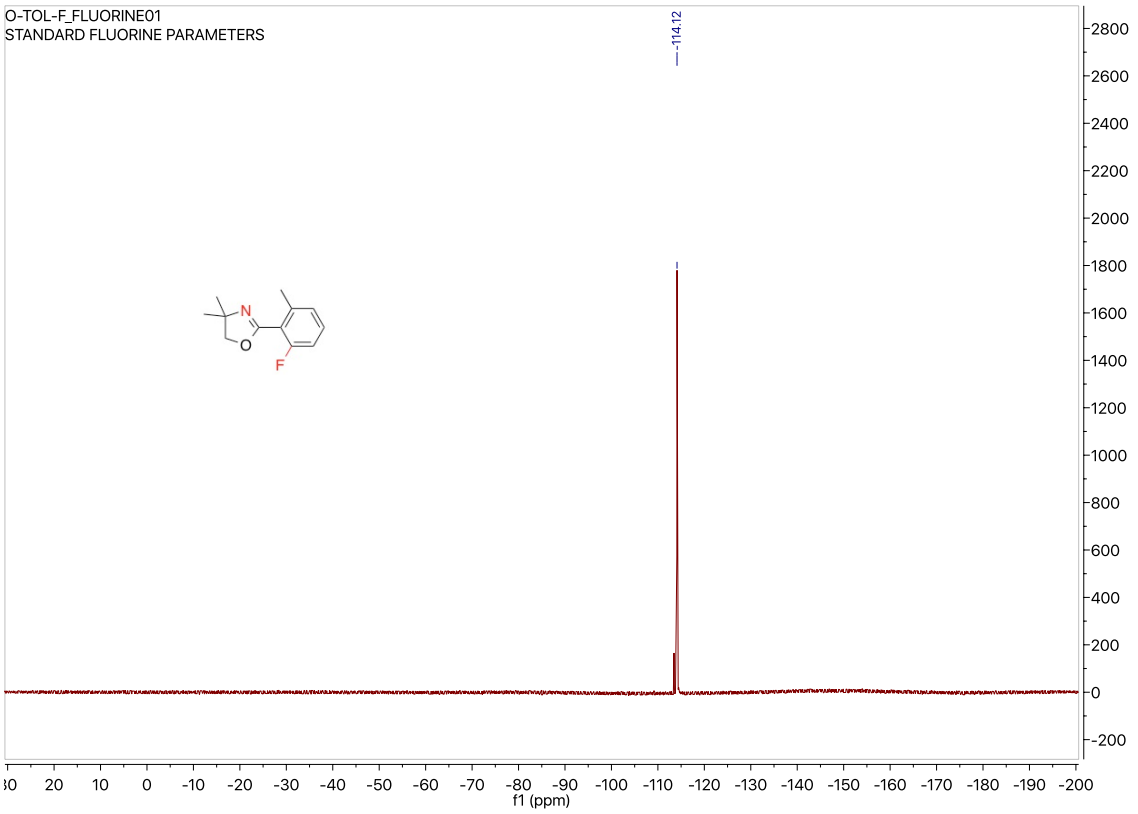

EXP16_PROTON01
9.08
9.06
8.08
8.06
7.95
7.94
7.87
7.86
7.62
7.61
7.59
7.54
7.52
7.51
7.49
7.47
4.16
1.49
0.86
0.87
0.91
0.90
0.93
1.85
2.00
6.32
f1 (ppm)

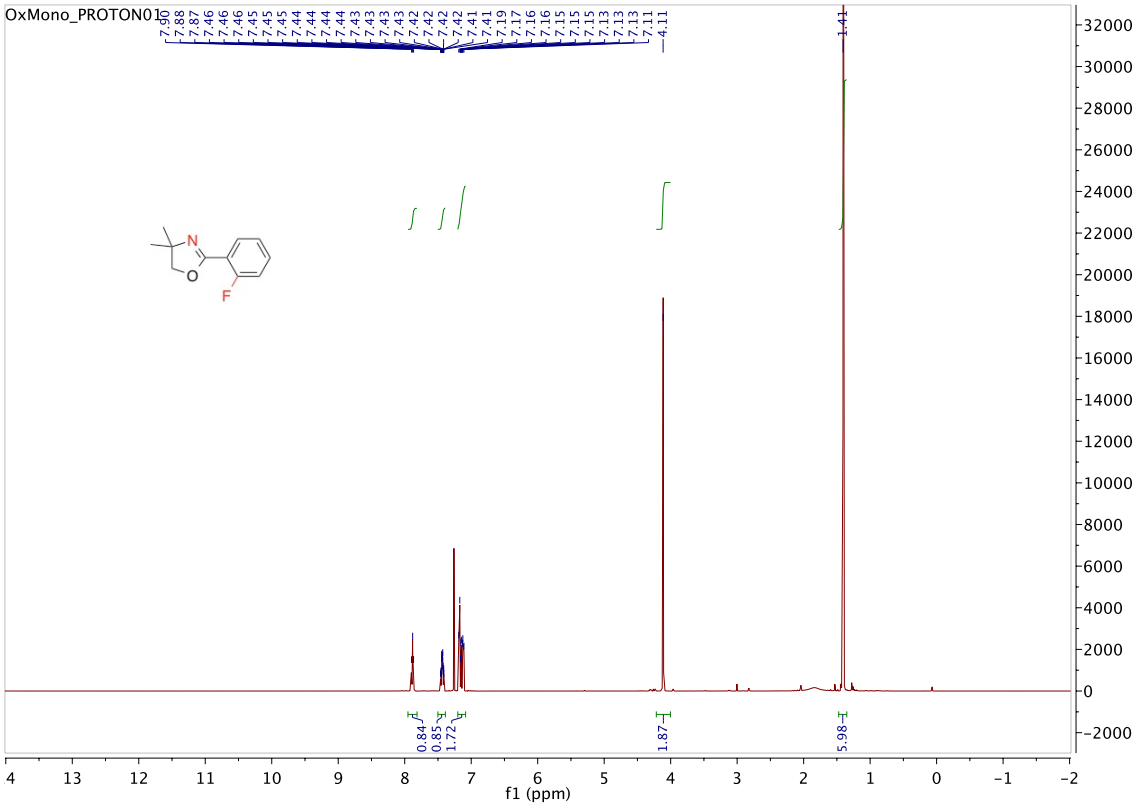

EXP16C_CARBON01
162.09
133.79
131.79
131.26
128.92
128.47
127.35
126.43
126.13
125.02
124.73
78.47
68.42
28.66
f1 (ppm)

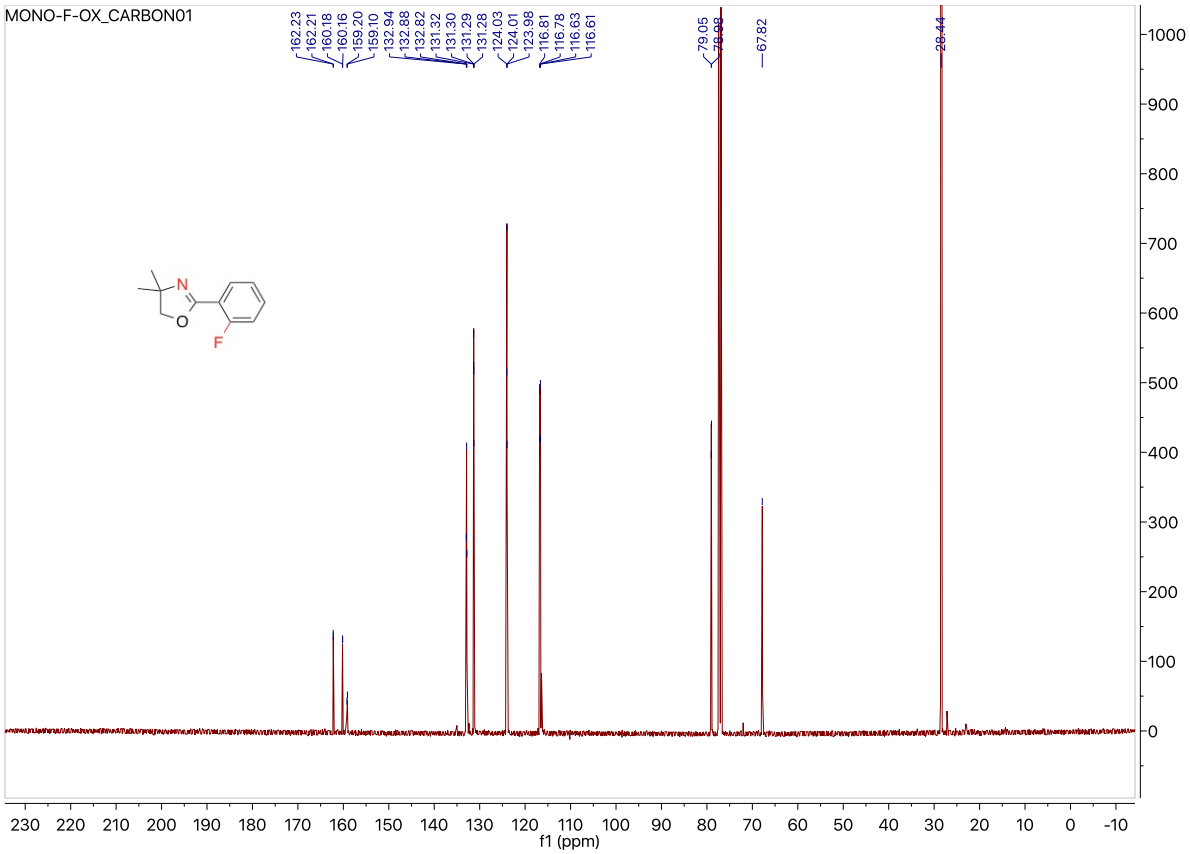
4.9 ^{1}H, ^{13}C and ^{19}F NMR copy of fluorinated compounds.

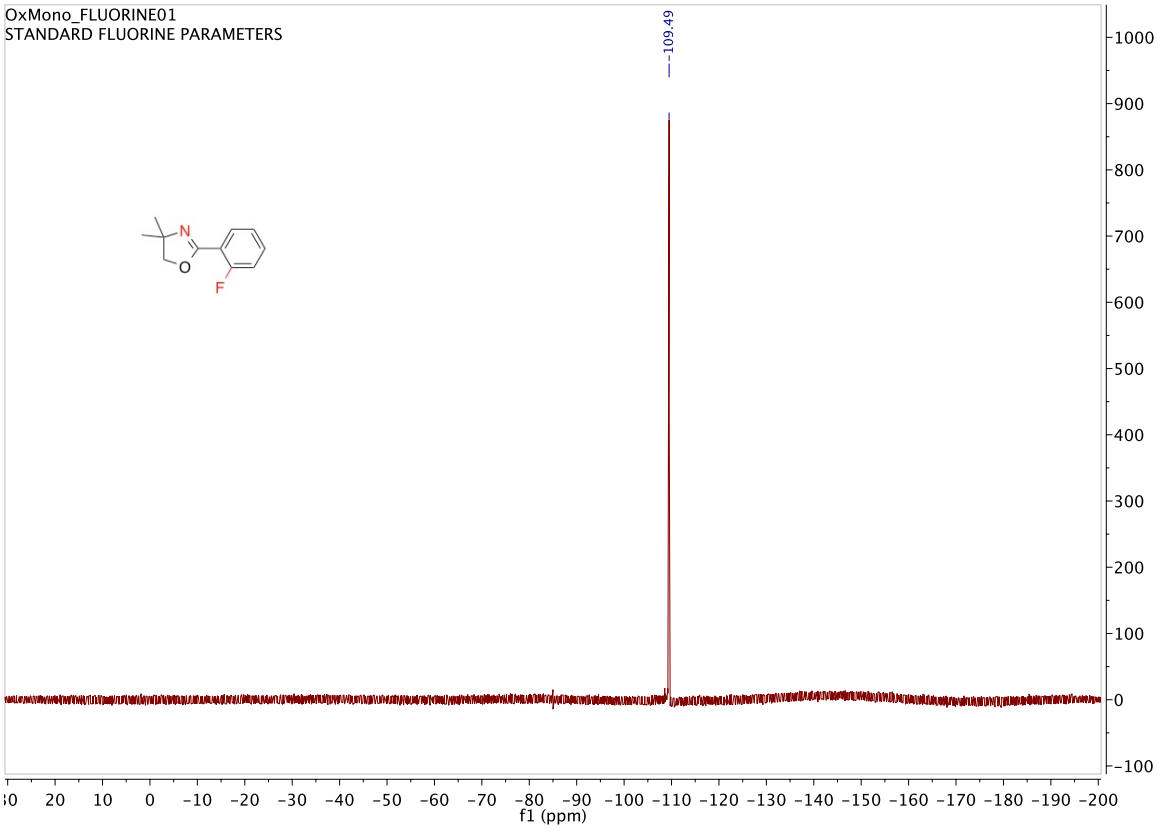


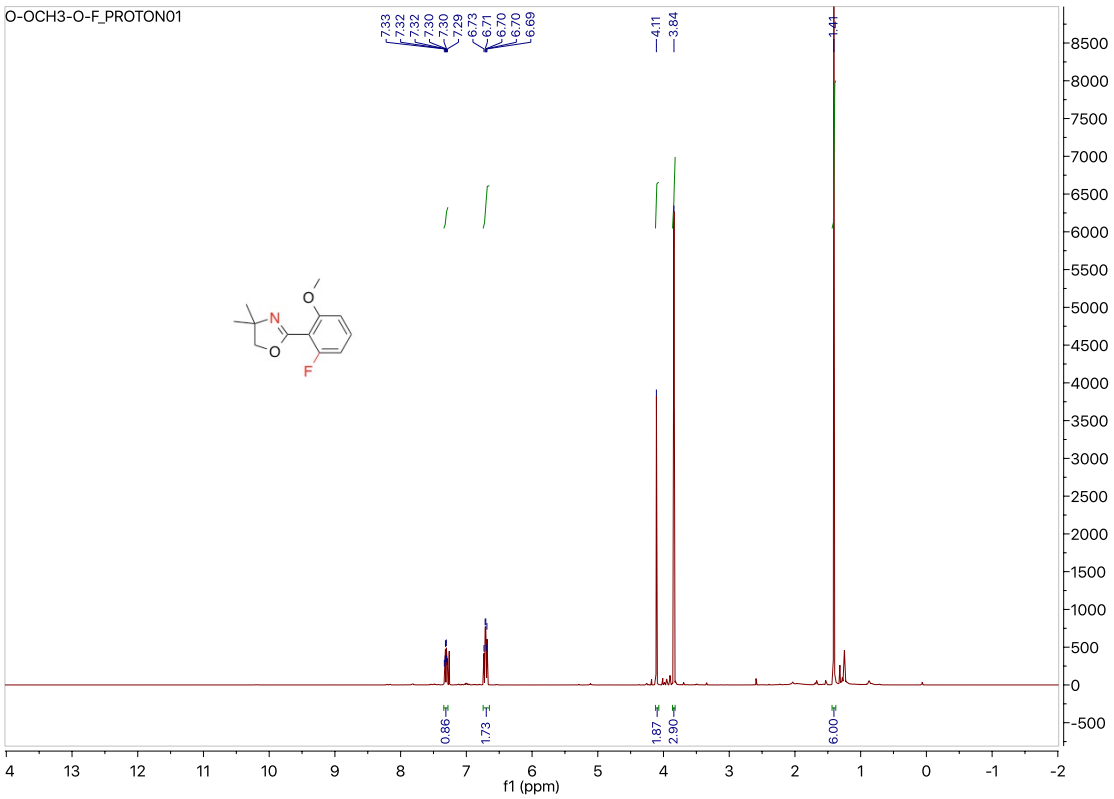


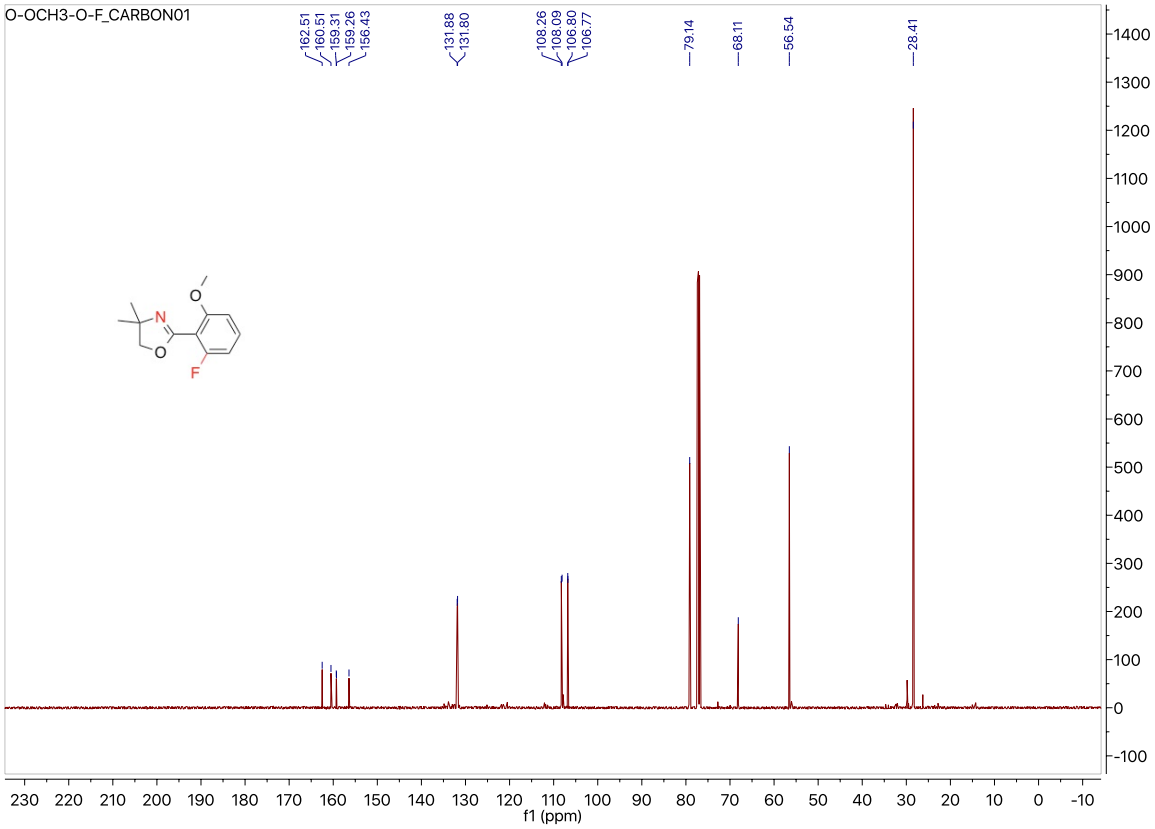

O-TOL-F_FLUORINE01
STANDARD FLUORINE PARAMETERS
-114.12
f1 (ppm)

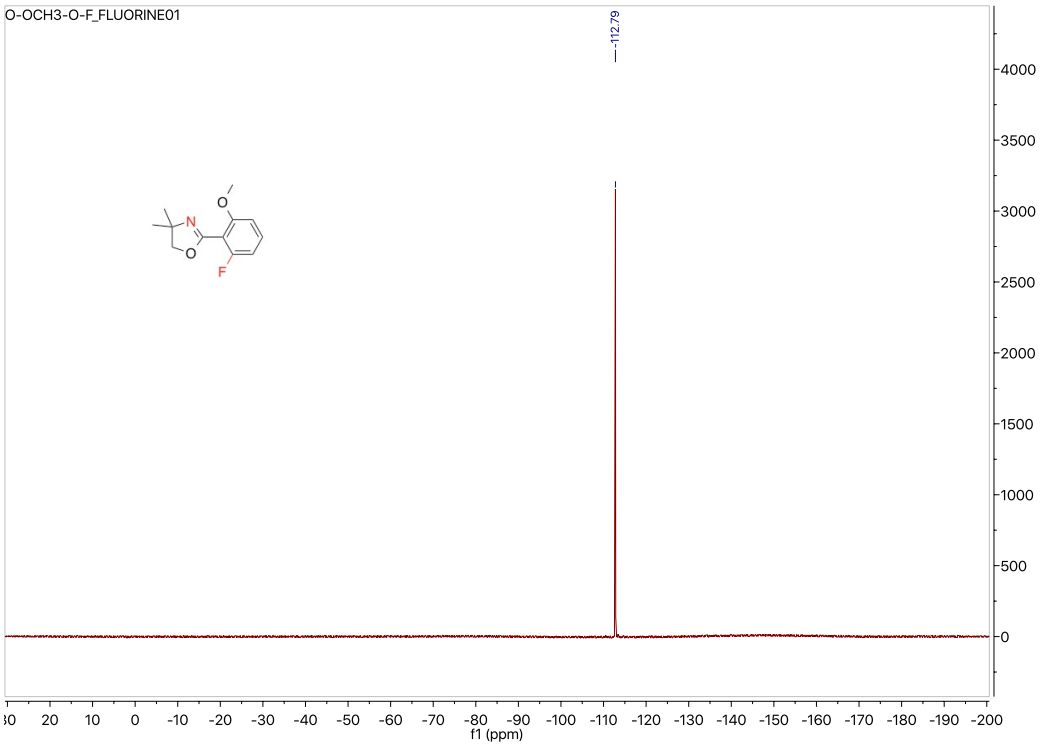

OxMono_PROTON01
7.90
7.88
7.87
7.46
7.46
7.46
7.45
7.45
7.45
7.44
7.44
7.44
7.44
7.43
7.43
7.43
7.43
7.42
7.42
7.42
7.42
7.41
7.41
7.19
7.17
7.16
7.16
7.15
7.15
7.15
7.13
7.13
7.13
7.11
4.11
1.41
0.84
0.85
1.72
1.87
5.98
f1 (ppm)

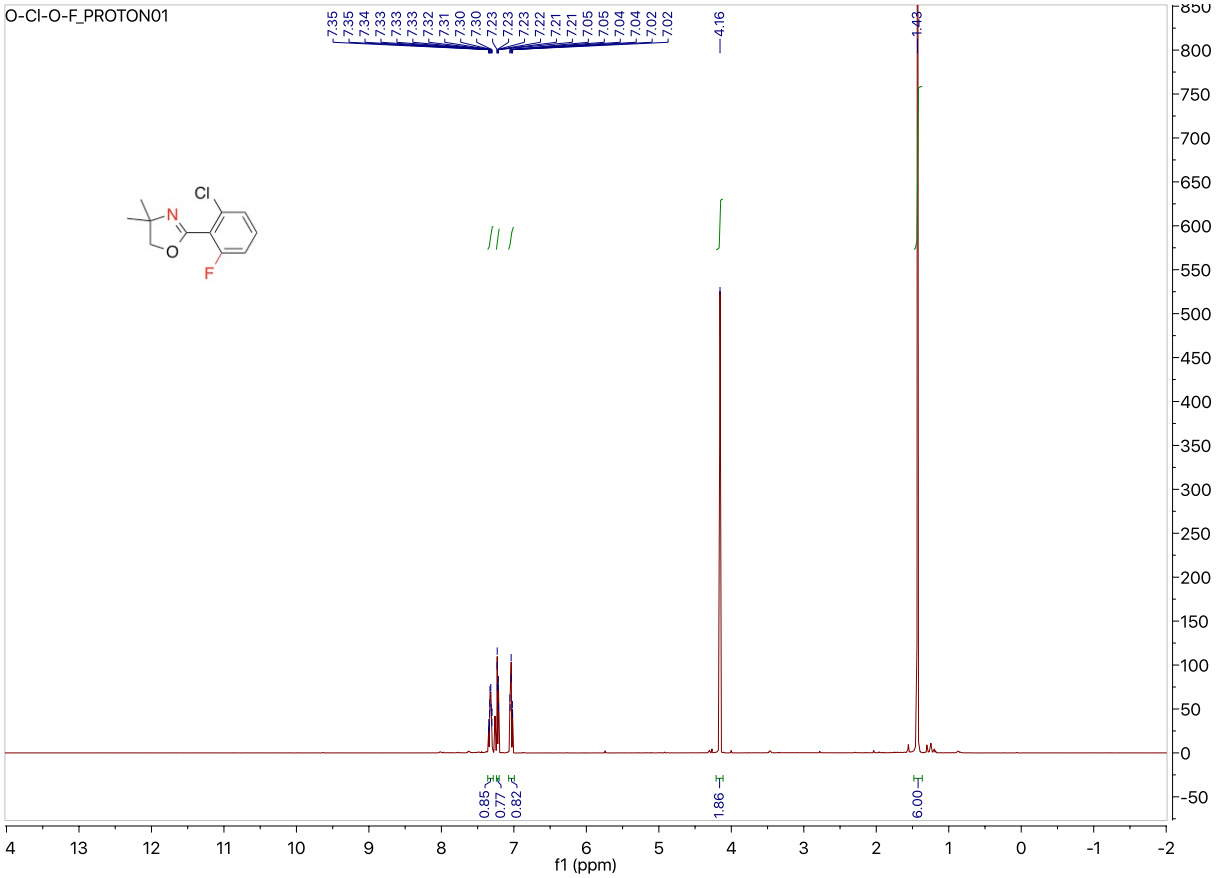

MONO-F-OX_CARBON01
162.23
162.21
160.18
160.16
159.20
159.10
132.94
132.88
132.82
131.32
131.30
131.29
131.28
124.03
124.01
123.98
116.81
116.78
116.63
116.61
79.05
78.88
67.82
28.44
N
O
F
1000
900
800
700
600
500
400
300
200
100
0
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

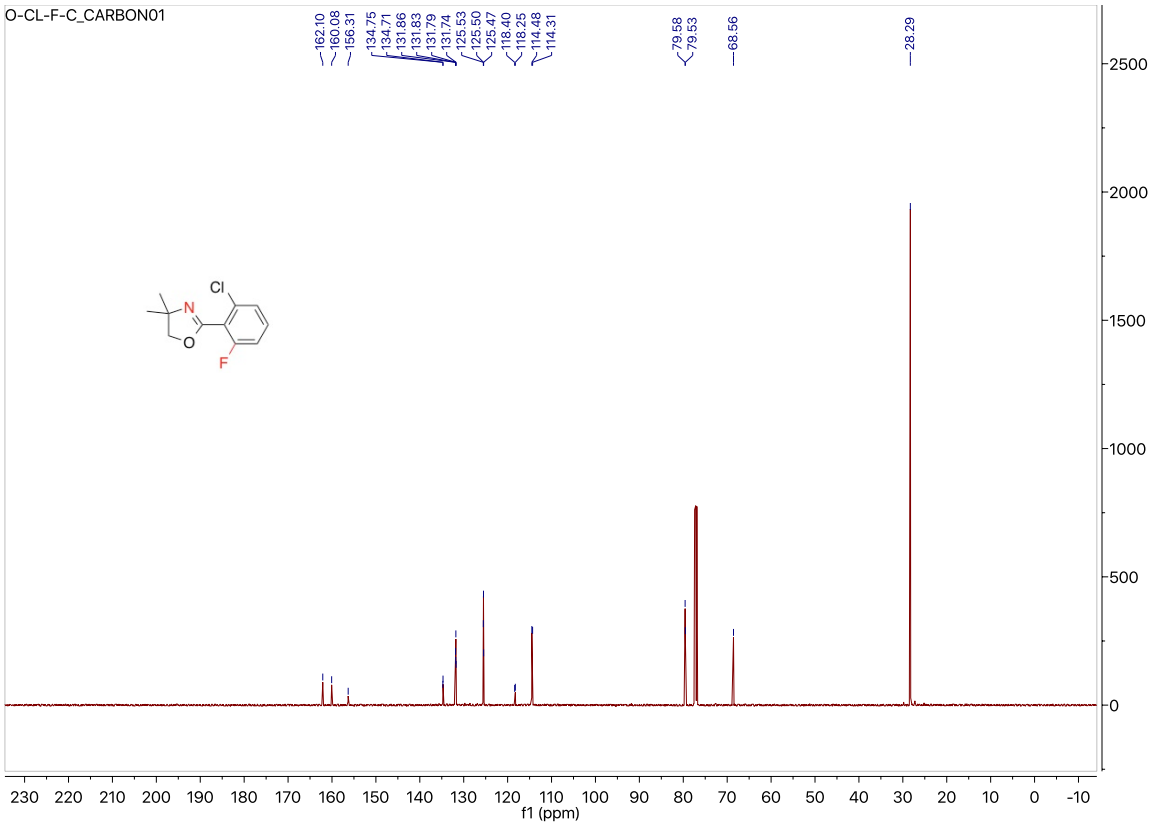

OxMono_FLUORINE01
STANDARD FLUORINE PARAMETERS
-109.49
N
O
F
1000
900
800
700
600
500
400
300
200
100
0
-100
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

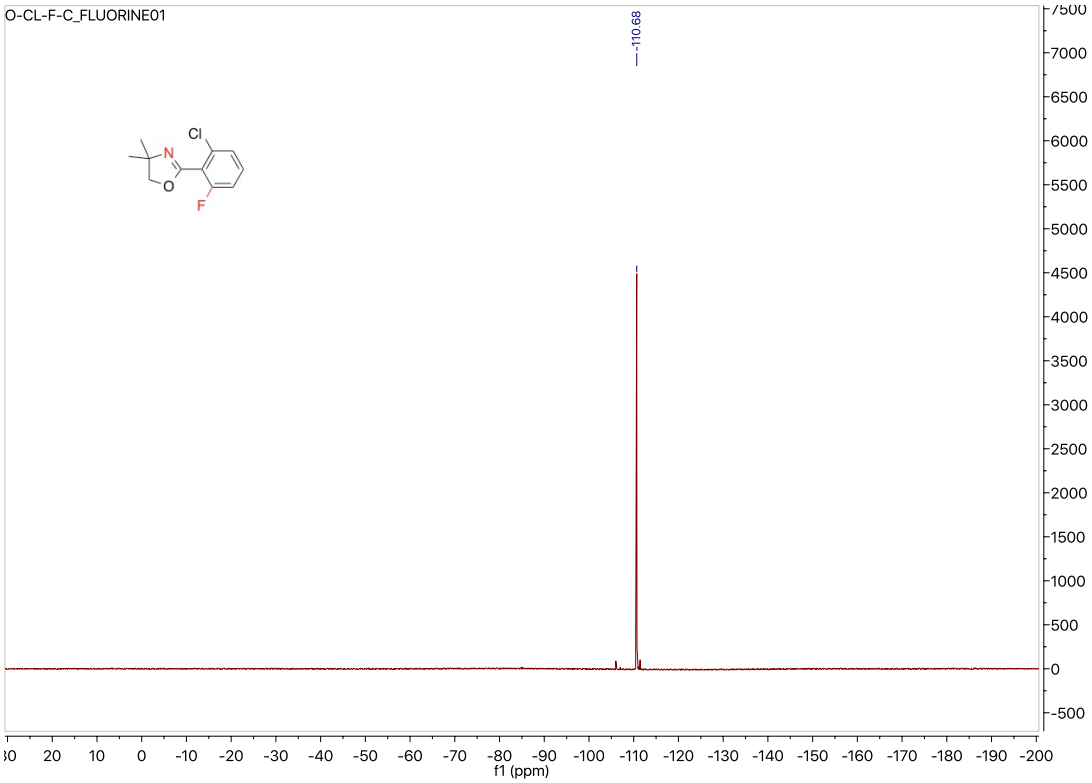

O-OCH3-O-F_PROTON01
7.33
7.32
7.32
7.30
7.30
7.29
6.73
6.71
6.70
6.70
6.69
4.11
3.84
1.41
0.86
1.73
1.87
2.90
6.00
f1 (ppm)

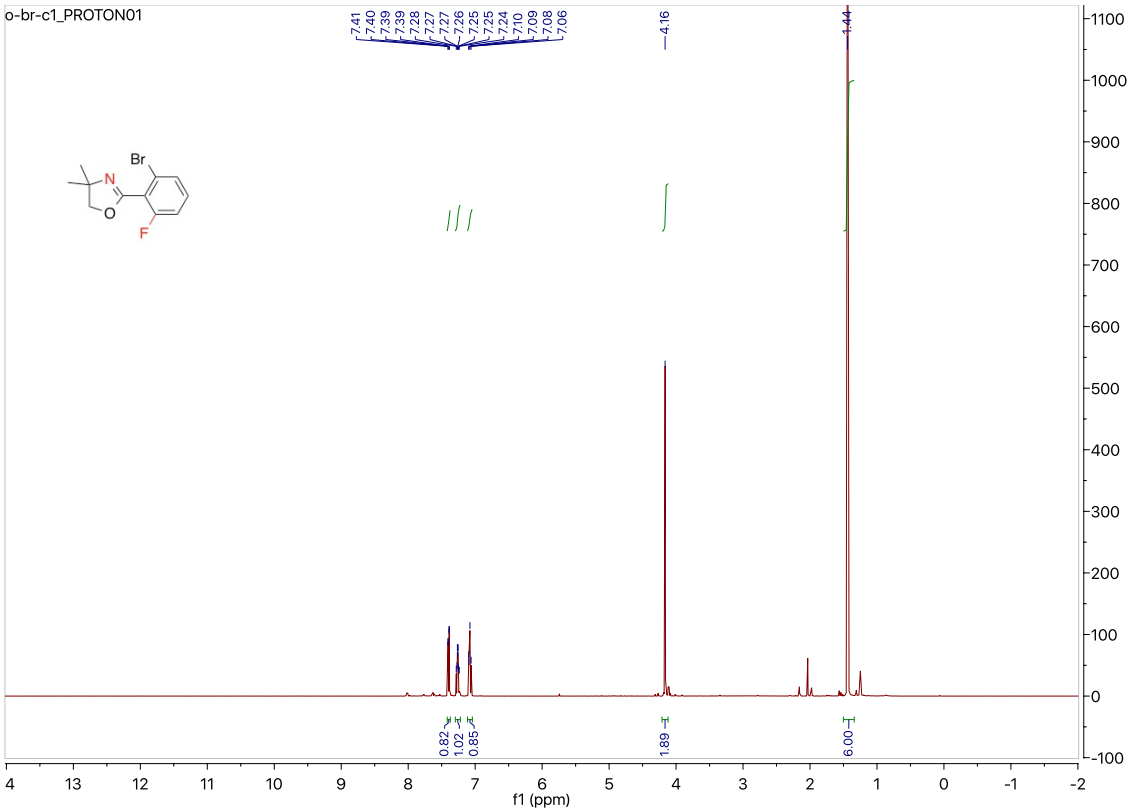

O-OCH3-O-F_CARBON01
162.51
160.51
159.31
159.26
156.43
131.88
131.80
108.26
108.09
106.80
106.77
79.14
68.11
56.54
28.41
f1 (ppm)

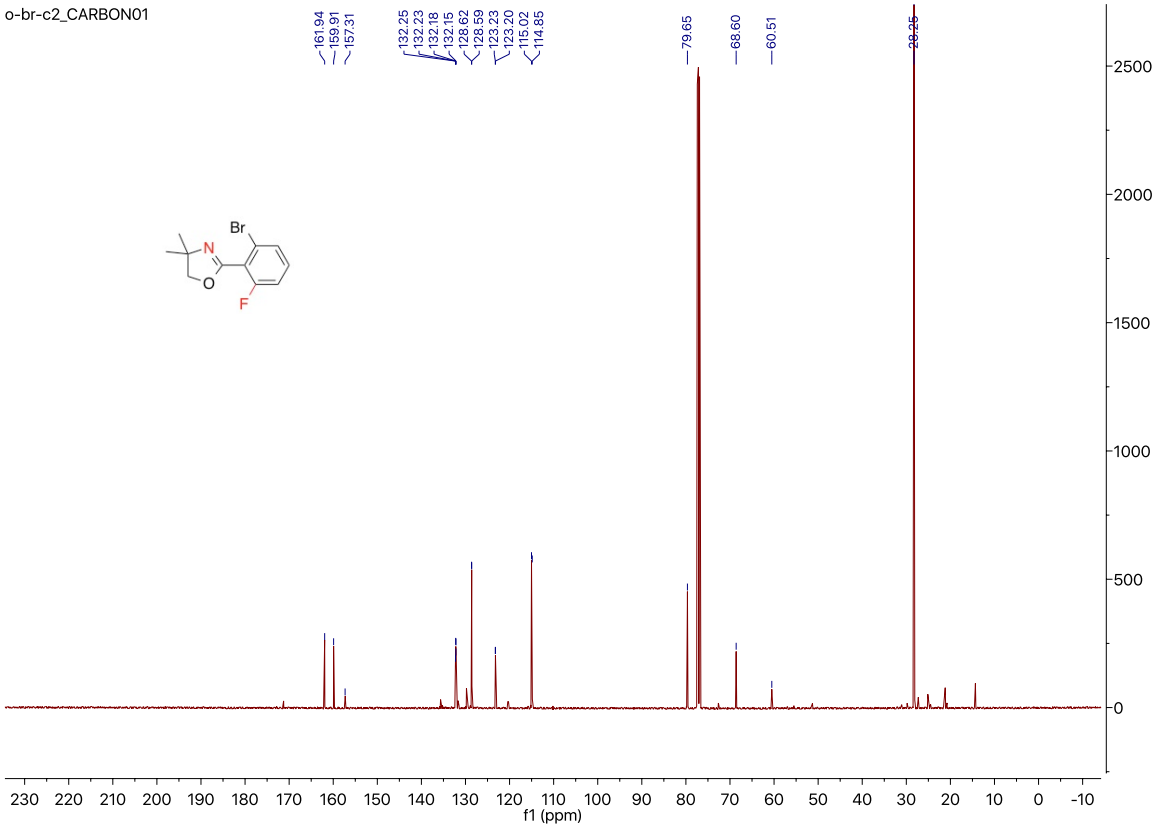

O-OCH3-O-F_FLUORINE01
-112.79
f1 (ppm)

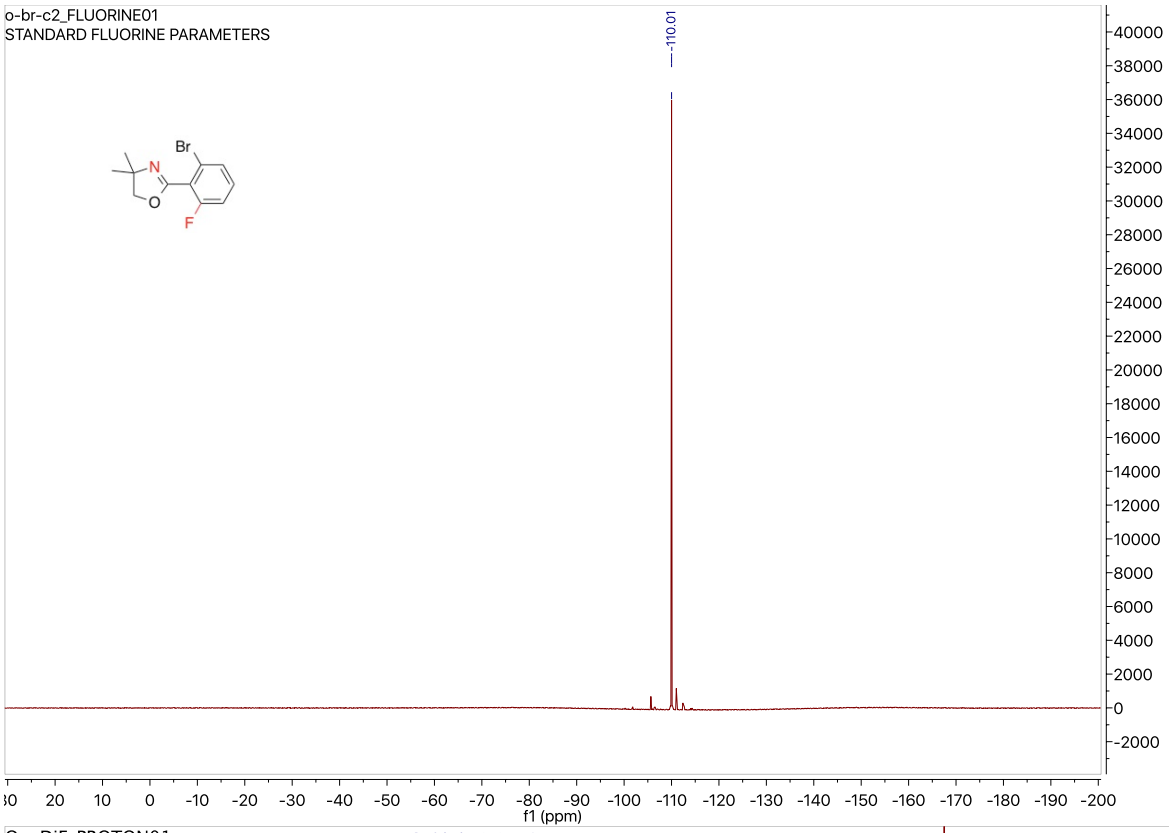

O-Cl-O-F_PROTON01
7.35
7.35
7.34
7.33
7.33
7.33
7.32
7.31
7.30
7.30
7.23
7.23
7.23
7.22
7.21
7.21
7.05
7.05
7.04
7.04
7.02
7.02
4.16
1.43
0.85
0.77
0.82
1.86
6.00
f1 (ppm)

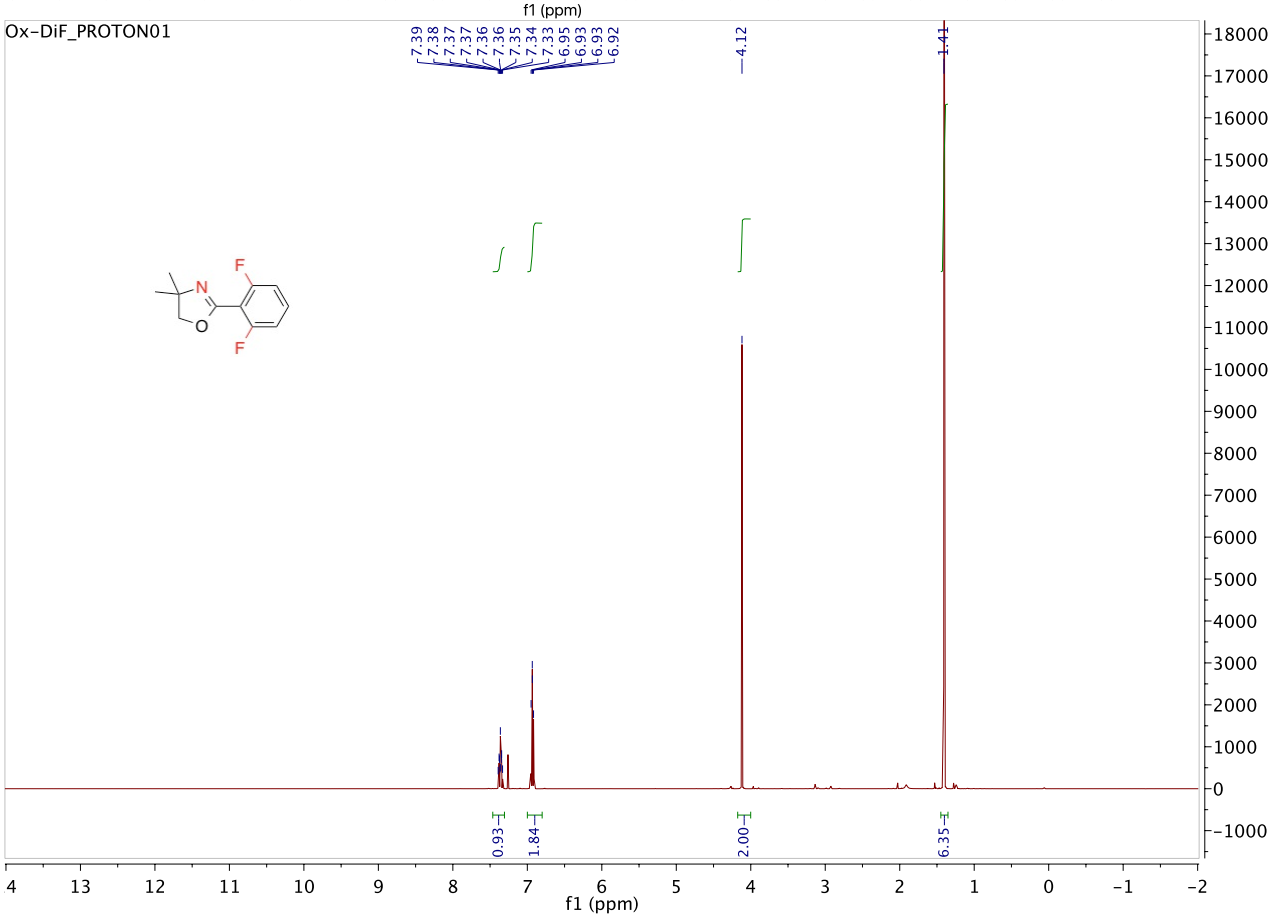

O-CL-F-C_CARBON01
162.10
160.08
156.31
134.75
134.71
131.86
131.83
131.79
131.74
125.53
125.50
125.47
118.40
118.25
114.48
114.31
79.58
79.53
68.56
28.29
Cl
N
O
F
2500
2000
1500
1000
500
0
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

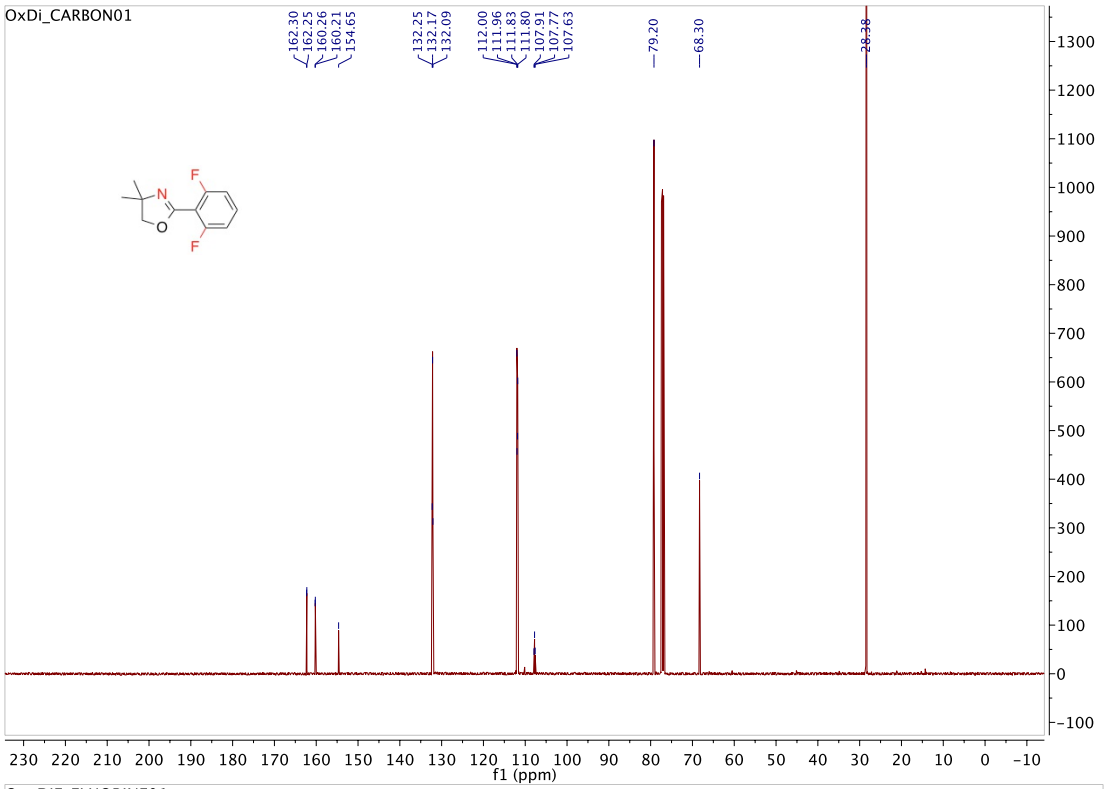

O-CL-F-C_FLUORINE01
-110.68
Cl
N
O
F
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

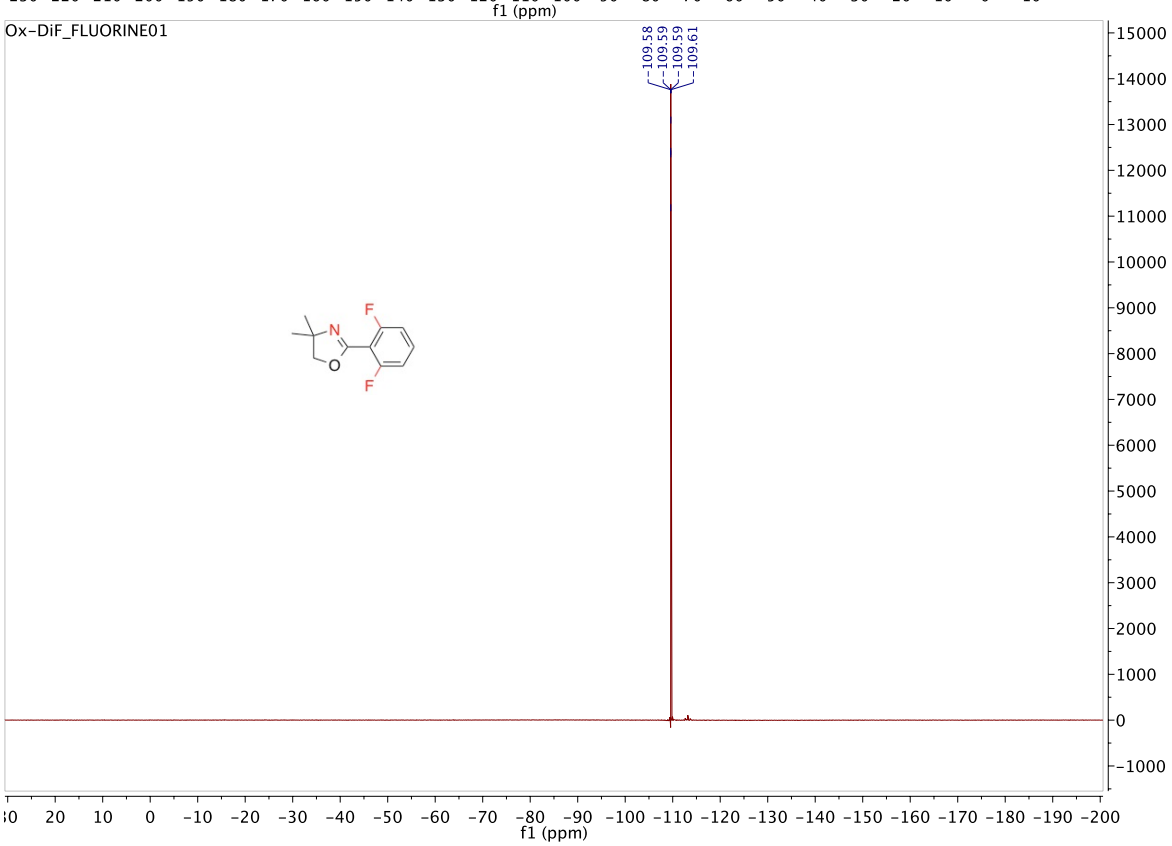

o-br-c1_PROTON01
7.41
7.40
7.39
7.39
7.28
7.27
7.27
7.26
7.25
7.25
7.24
7.10
7.09
7.08
7.06
4.16
1.44
Br
N
O
F
0.82
1.02
0.85
1.89
6.00
f1 (ppm)

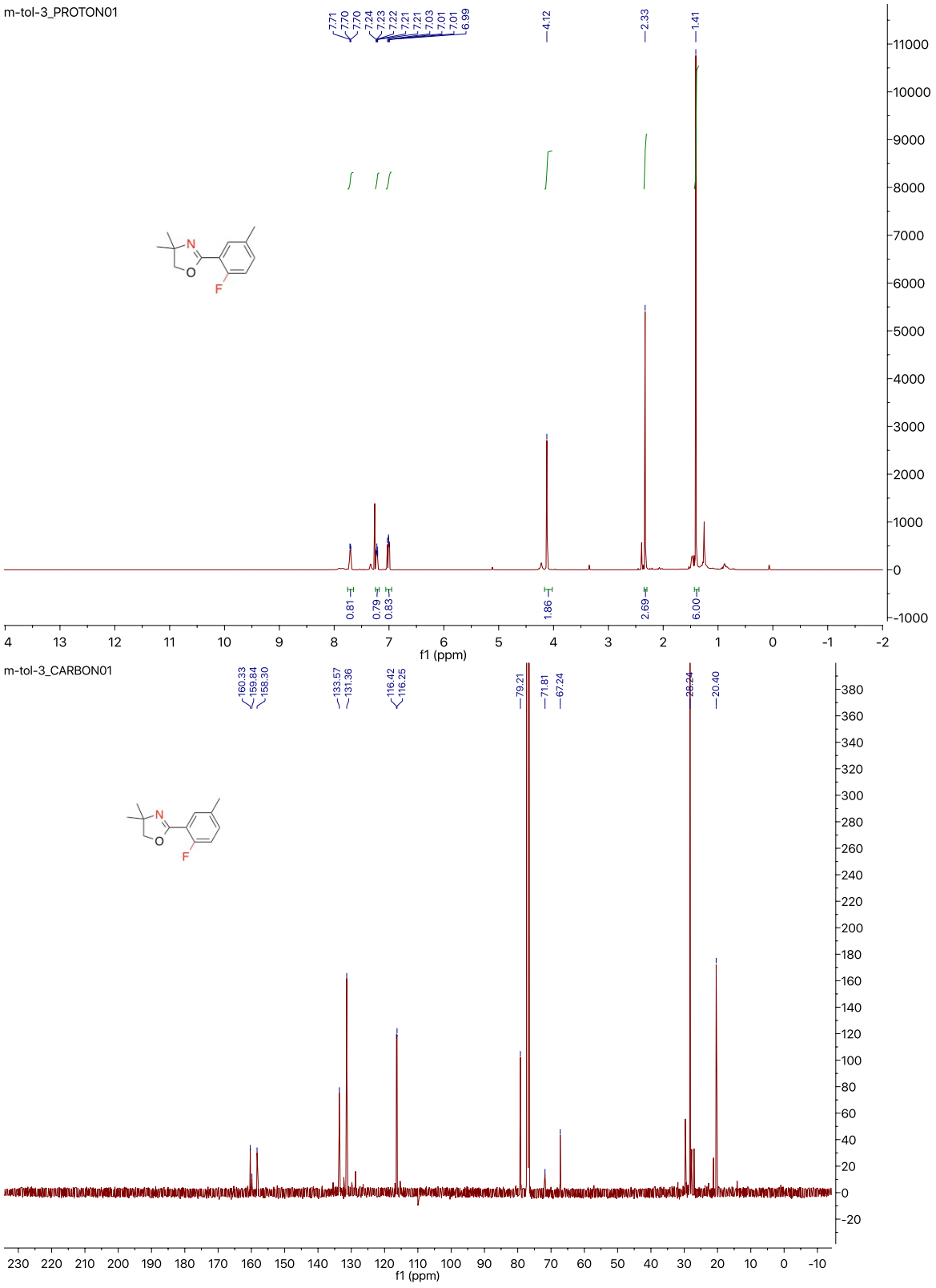

o-br-c2_CARBON01
161.94
159.91
157.31
132.25
132.23
132.18
132.15
128.62
128.59
123.23
123.20
115.02
114.85
79.65
68.60
60.51
28.25
Br
N
O
F
f1 (ppm)

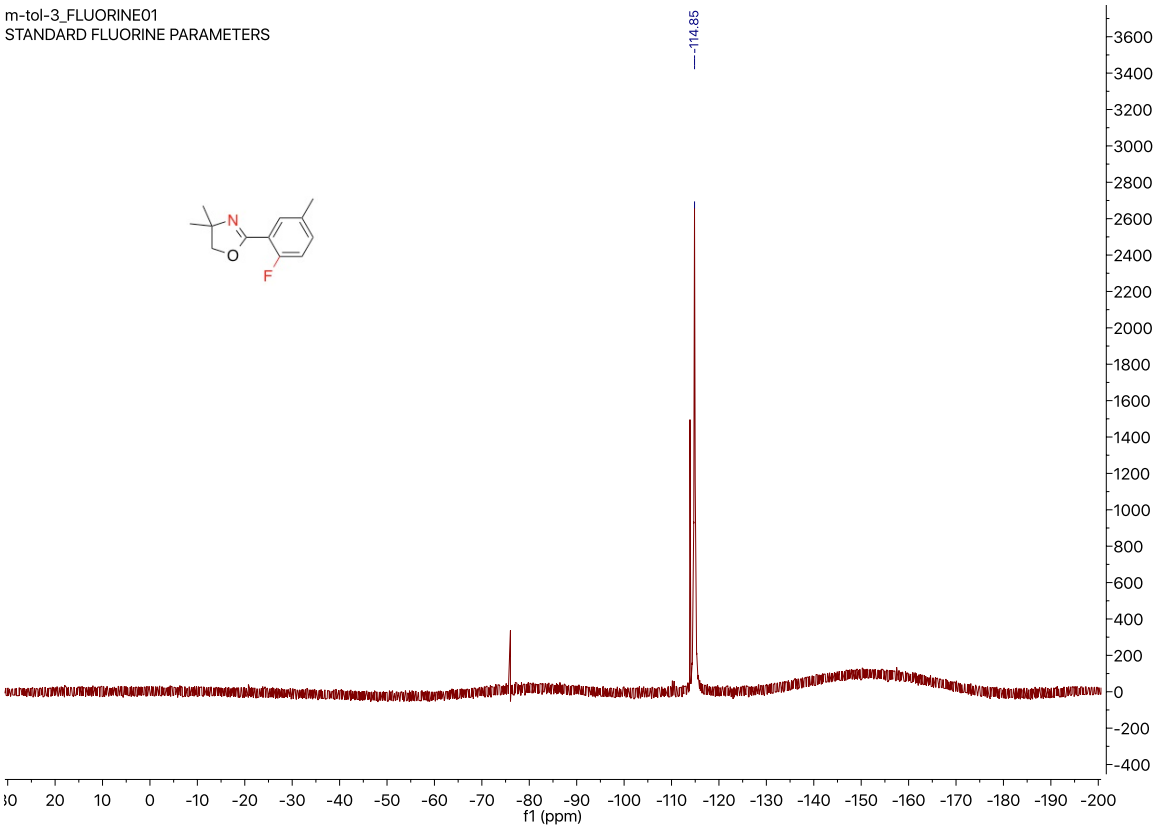

o-br-c2_FLUORINE01
STANDARD FLUORINE PARAMETERS
-110.01
Br
N
O
F
f1 (ppm)

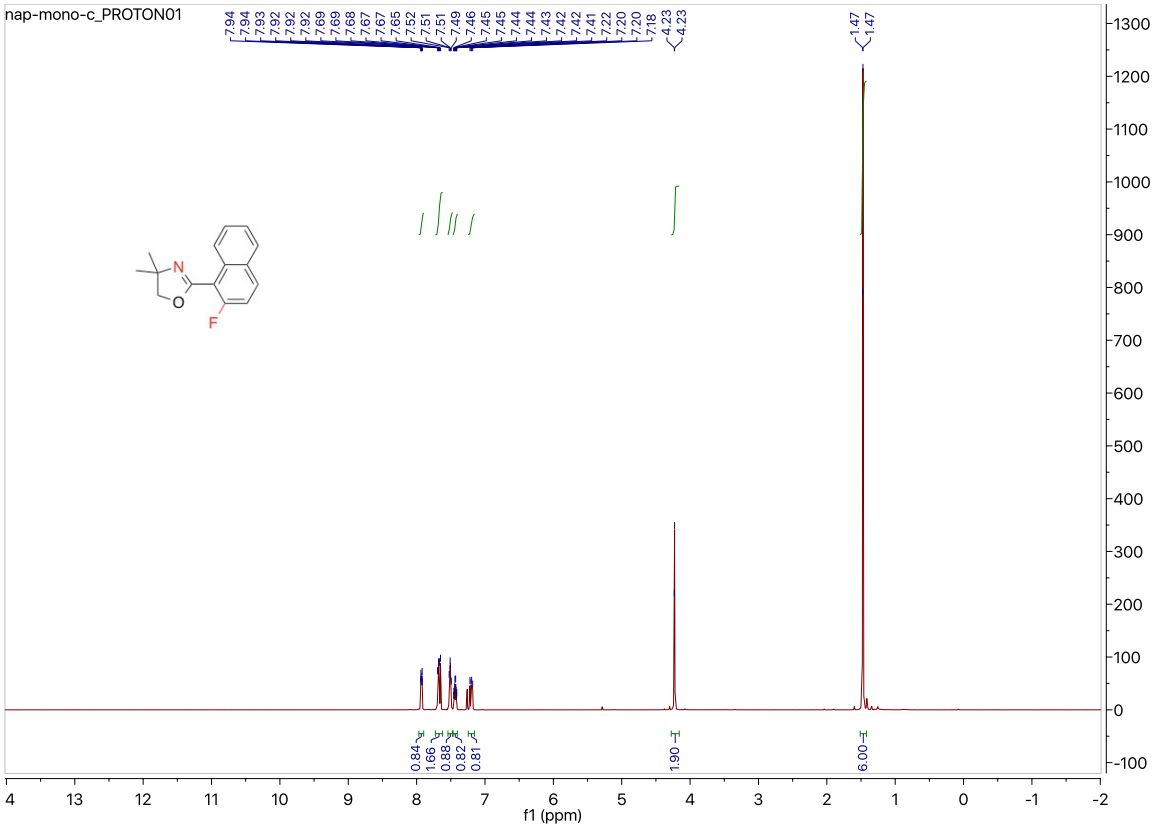

Ox-DiF_PROTON01
7.39
7.38
7.37
7.37
7.36
7.36
7.35
7.34
7.33
6.95
6.93
6.93
6.92
4.12
1.41
F
N
O
F
0.93
1.84
2.00
6.35
f1 (ppm)

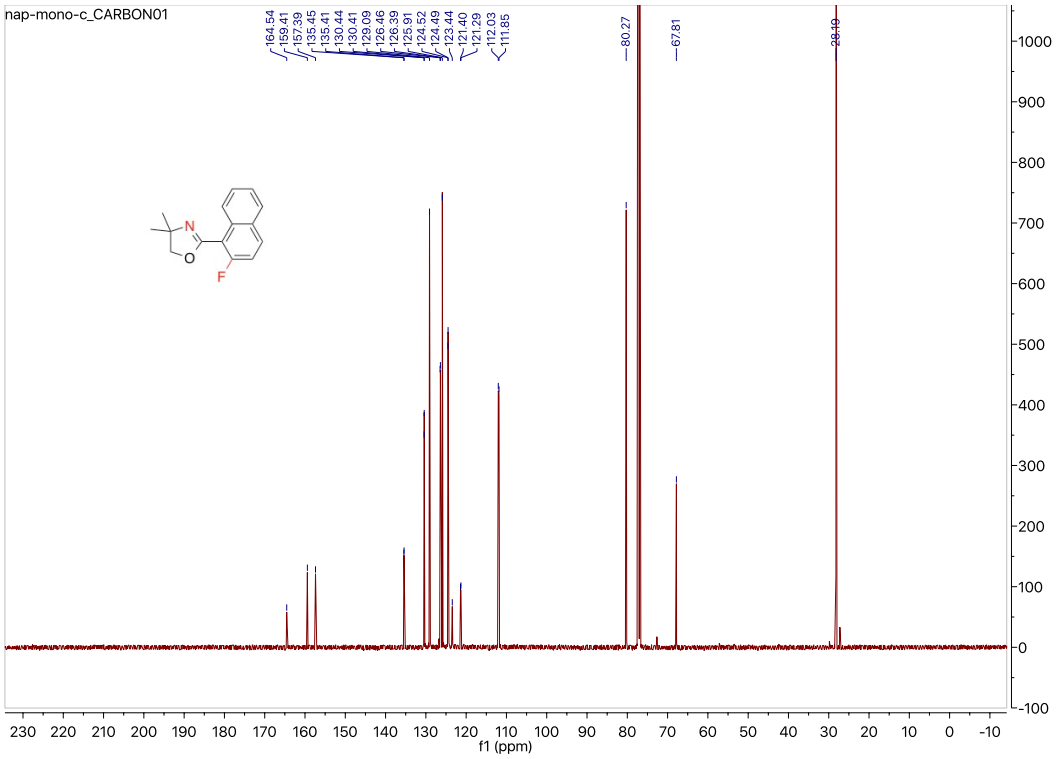

OxDi_CARBON01
162.30
162.25
160.26
160.21
154.65
132.25
132.17
132.09
112.00
111.96
111.83
111.80
107.91
107.77
107.63
79.20
68.30
28.38
f1 (ppm)

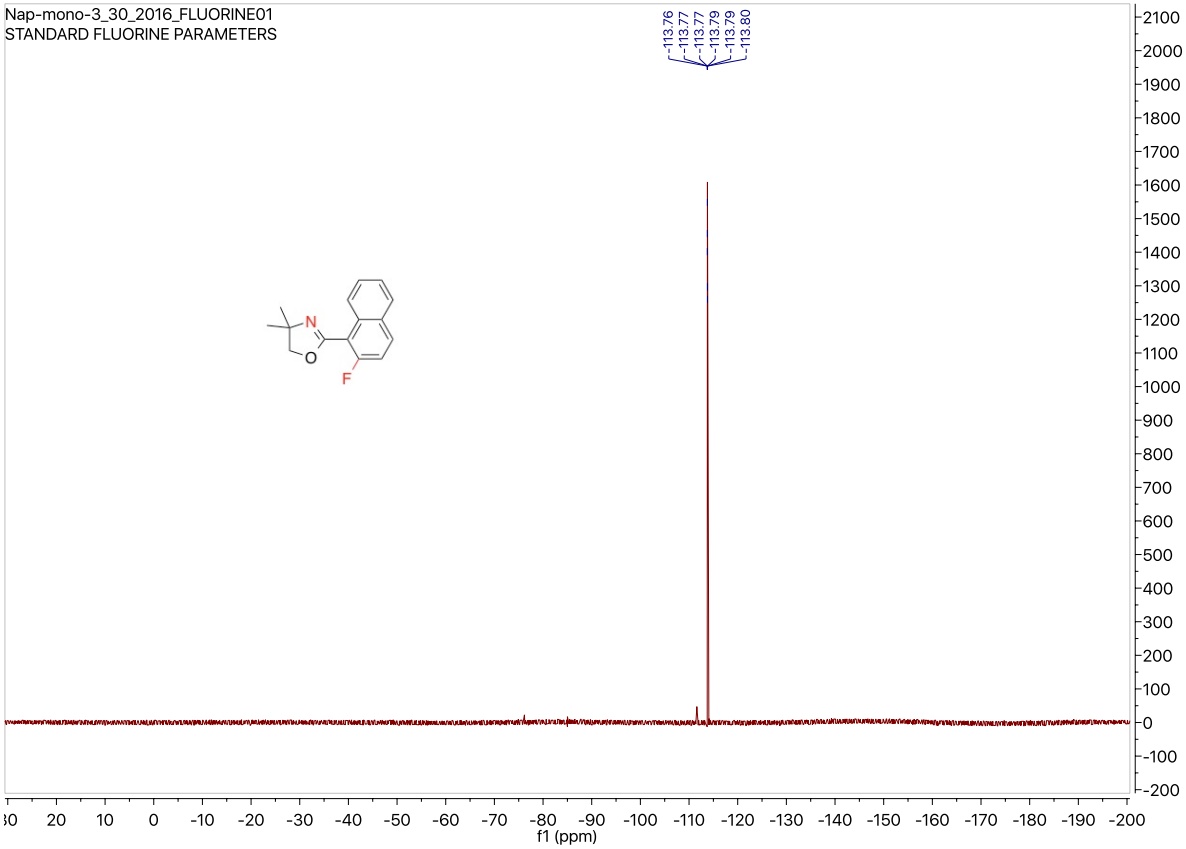

Ox-DiF_FLUORINE01
109.58
109.59
109.59
109.61
f1 (ppm)

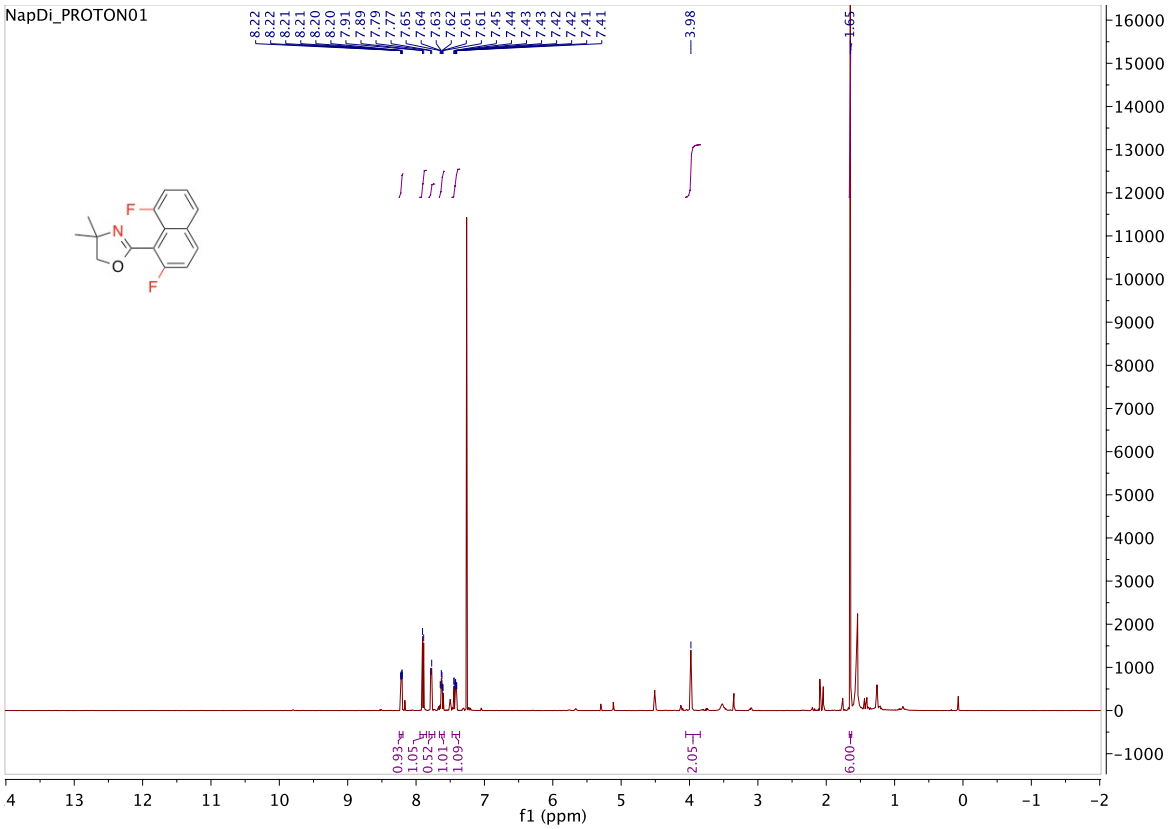

m-tol-3_PROTON01
7.71
7.70
7.70
7.24
7.23
7.22
7.21
7.21
7.03
7.01
7.01
6.99
4.12
2.33
1.41
0.81
0.79
0.83
1.86
2.69
6.00
f1 (ppm)
m-tol-3_CARBON01
160.33
159.84
158.30
133.57
131.36
116.42
116.25
79.21
71.81
67.24
28.24
20.40
f1 (ppm)

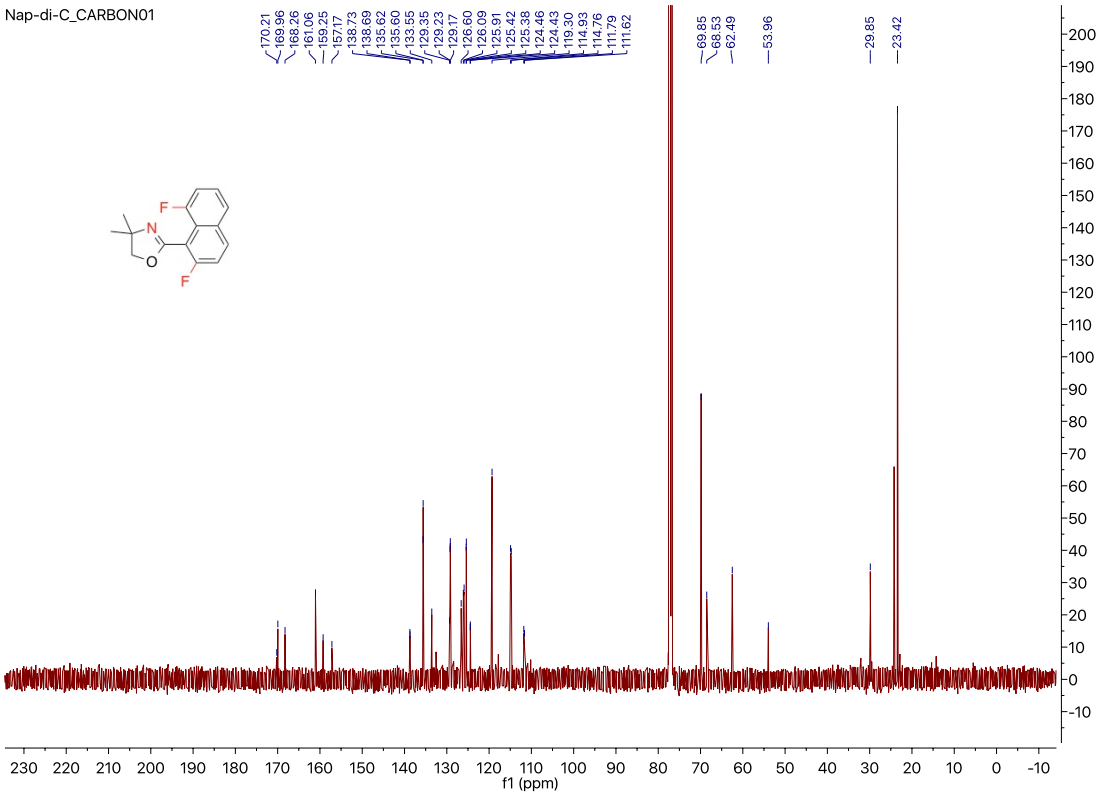

m-tol-3_FLUORINE01
STANDARD FLUORINE PARAMETERS
-114.85
f1 (ppm)

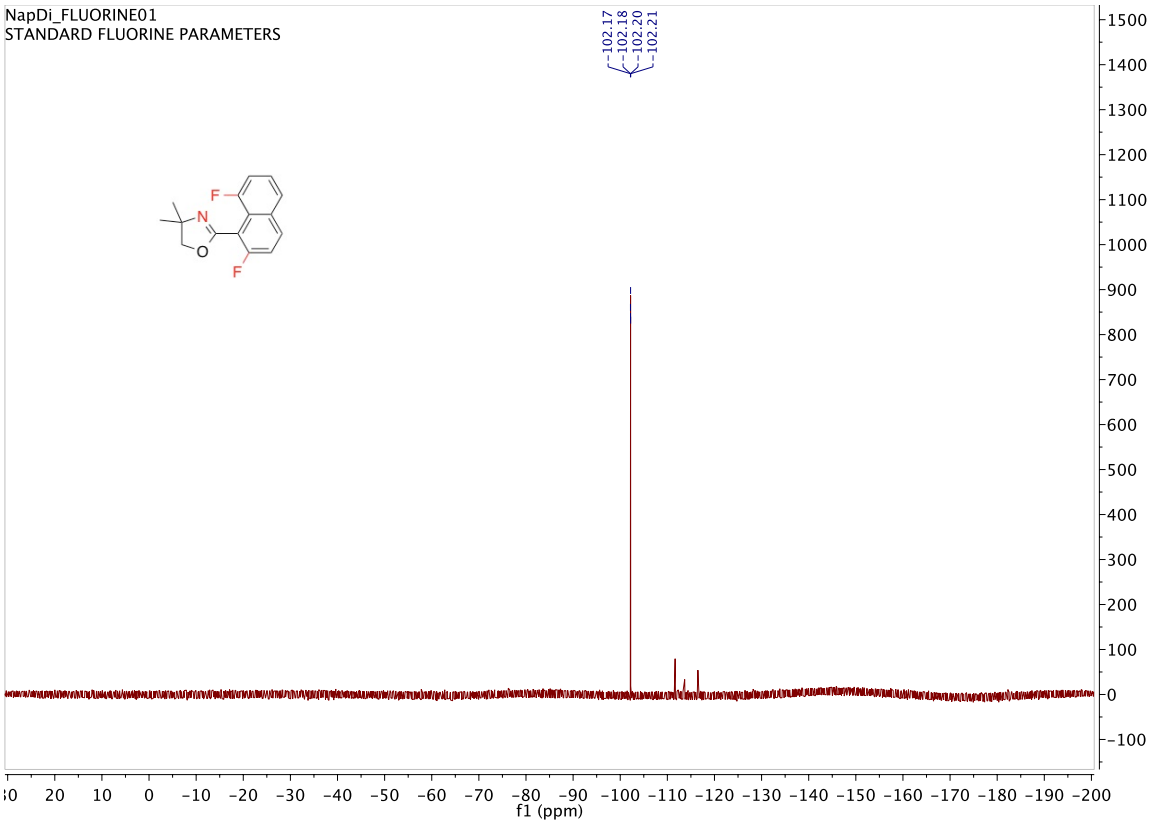

nap-mono-c_PROTON01
7.94
7.94
7.93
7.92
7.92
7.92
7.69
7.69
7.68
7.67
7.67
7.65
7.52
7.51
7.51
7.49
7.46
7.45
7.45
7.44
7.44
7.43
7.42
7.42
7.41
7.22
7.20
7.20
7.18
4.23
4.23
1.47
1.47
0.84
1.66
0.88
0.82
0.81
1.90
6.00
f1 (ppm)

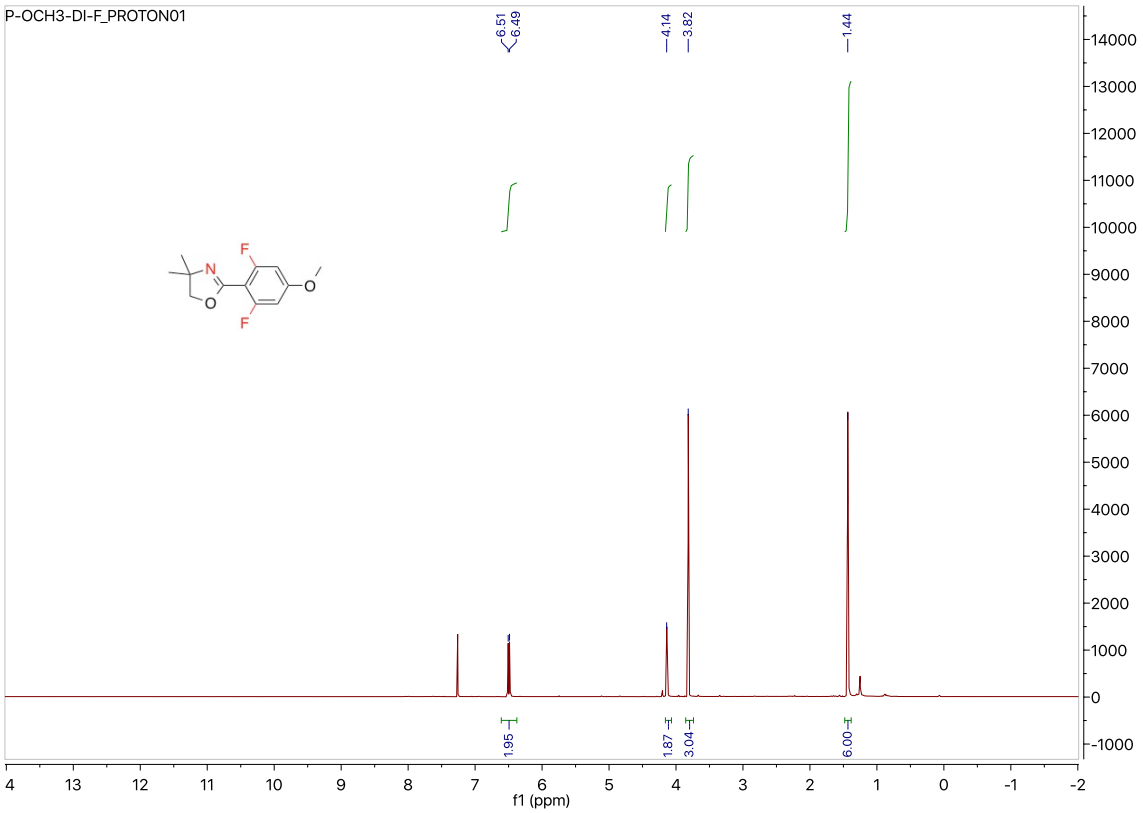

nap-mono-c_CARBON01
164.54
159.41
157.39
135.45
135.41
130.44
130.41
129.09
126.46
126.39
125.91
124.52
124.49
123.44
121.40
121.29
112.03
111.85
80.27
67.81
28.19
f1 (ppm)

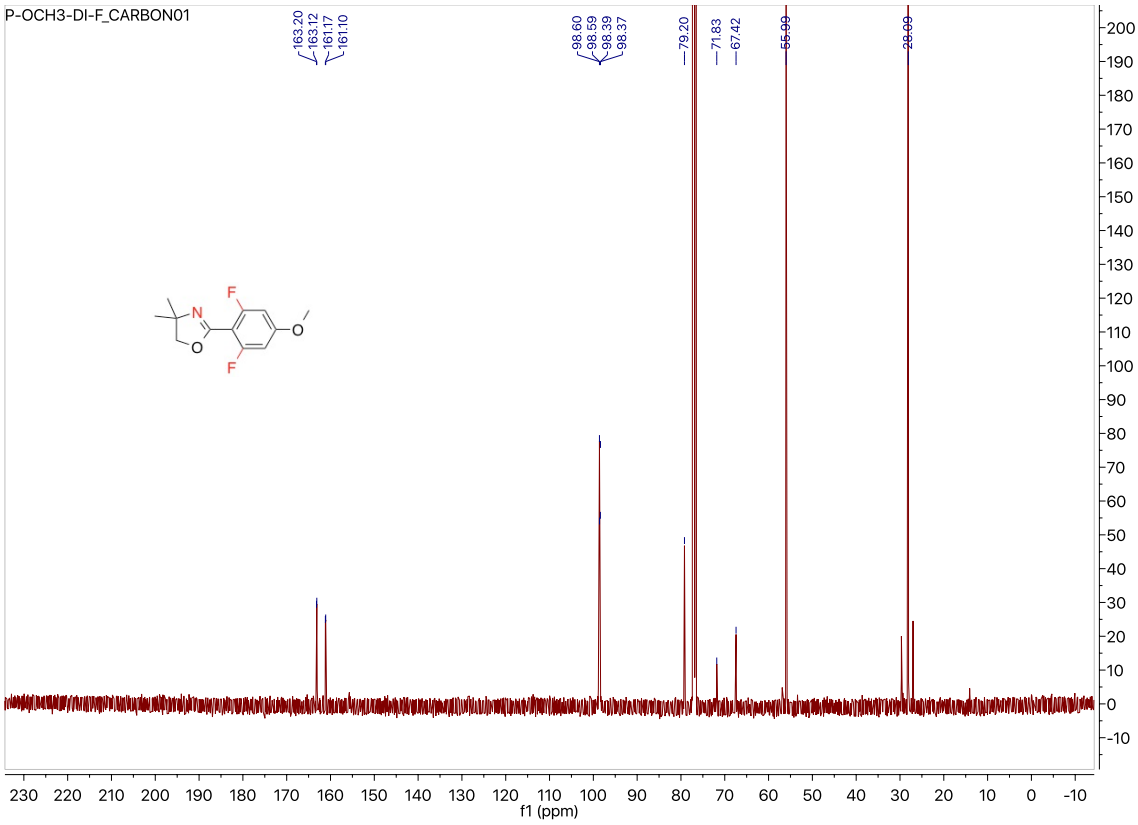

Nap-mono-3_30_2016_FLUORINE01
STANDARD FLUORINE PARAMETERS
-113.76
-113.77
-113.77
-113.77
-113.79
-113.79
-113.80
f1 (ppm)

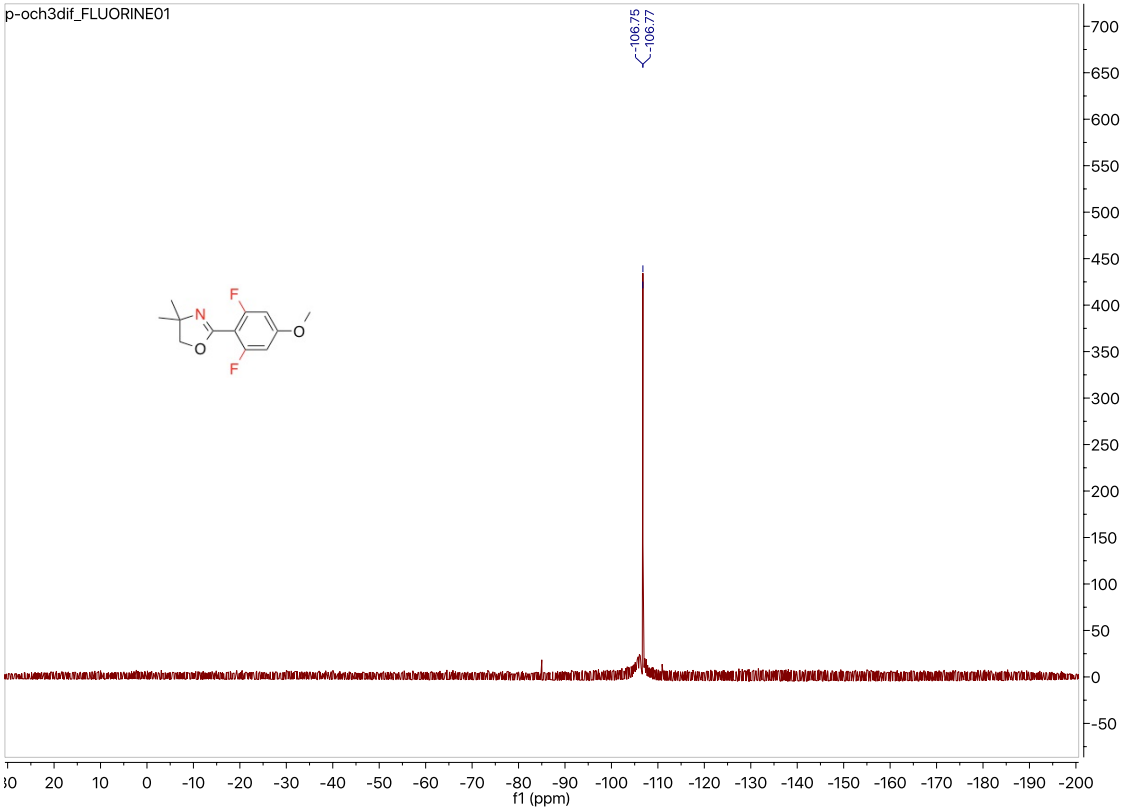

NapDi_PROTON01
8.22
8.22
8.21
8.21
8.20
8.20
7.91
7.89
7.79
7.77
7.65
7.64
7.63
7.62
7.61
7.61
7.45
7.44
7.43
7.43
7.42
7.42
7.41
7.41
3.98
1.65
F
N
O
F
0.93
1.05
0.52
1.01
1.09
2.05
6.00
f1 (ppm)

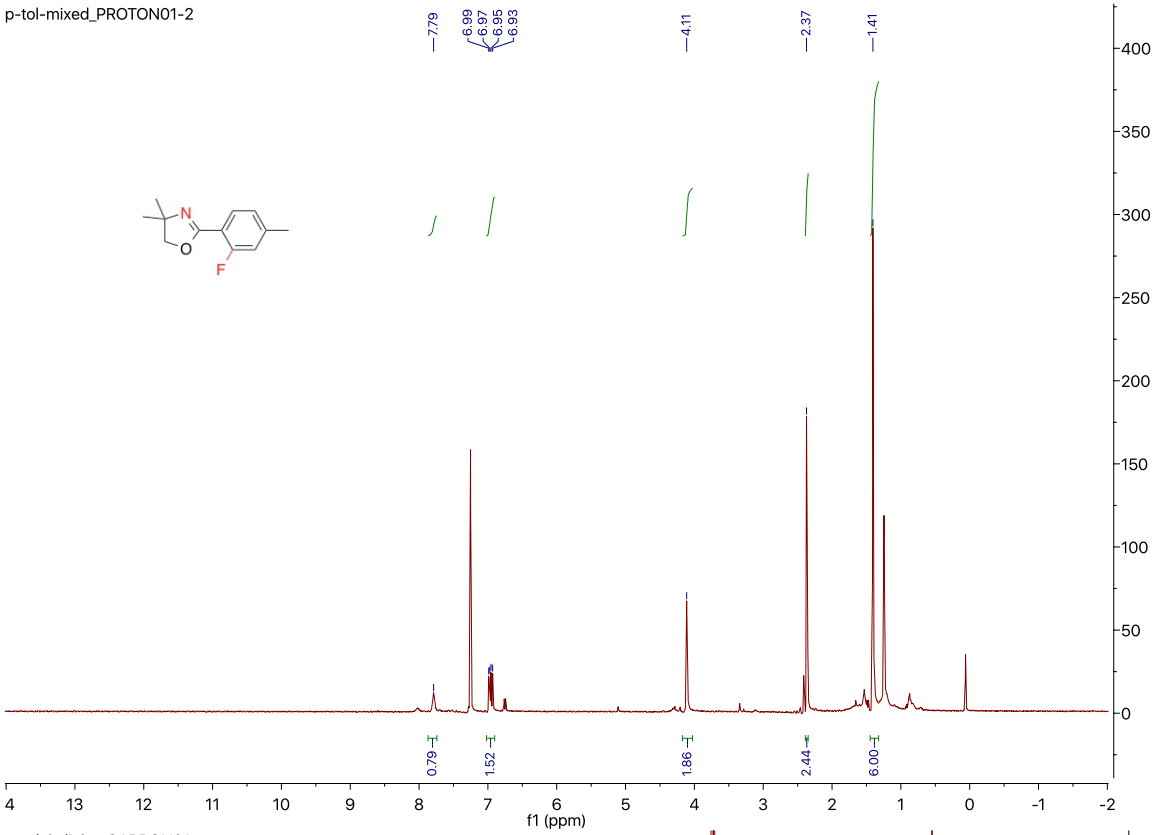

Nap-di-C_CARBON01
170.21
169.96
168.26
161.06
159.25
157.17
138.73
138.69
135.62
135.60
133.55
129.35
129.23
129.17
126.60
126.09
125.91
125.42
125.38
124.46
124.43
119.30
114.93
114.76
111.79
111.62
69.85
68.53
62.49
53.96
29.85
23.42
F
N
O
F
f1 (ppm)

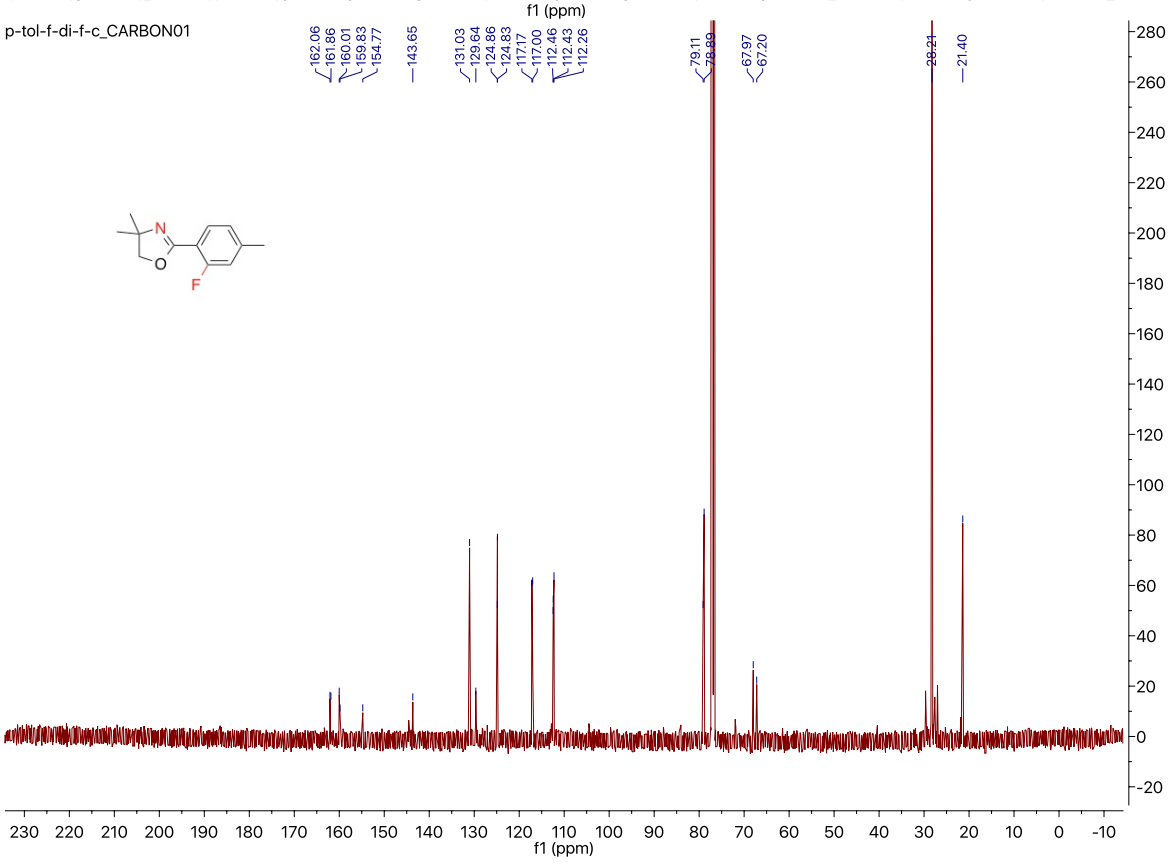

NapDi_FLUORINE01
STANDARD FLUORINE PARAMETERS
-102.17
-102.18
-102.20
-102.21
F
N
O
F
f1 (ppm)

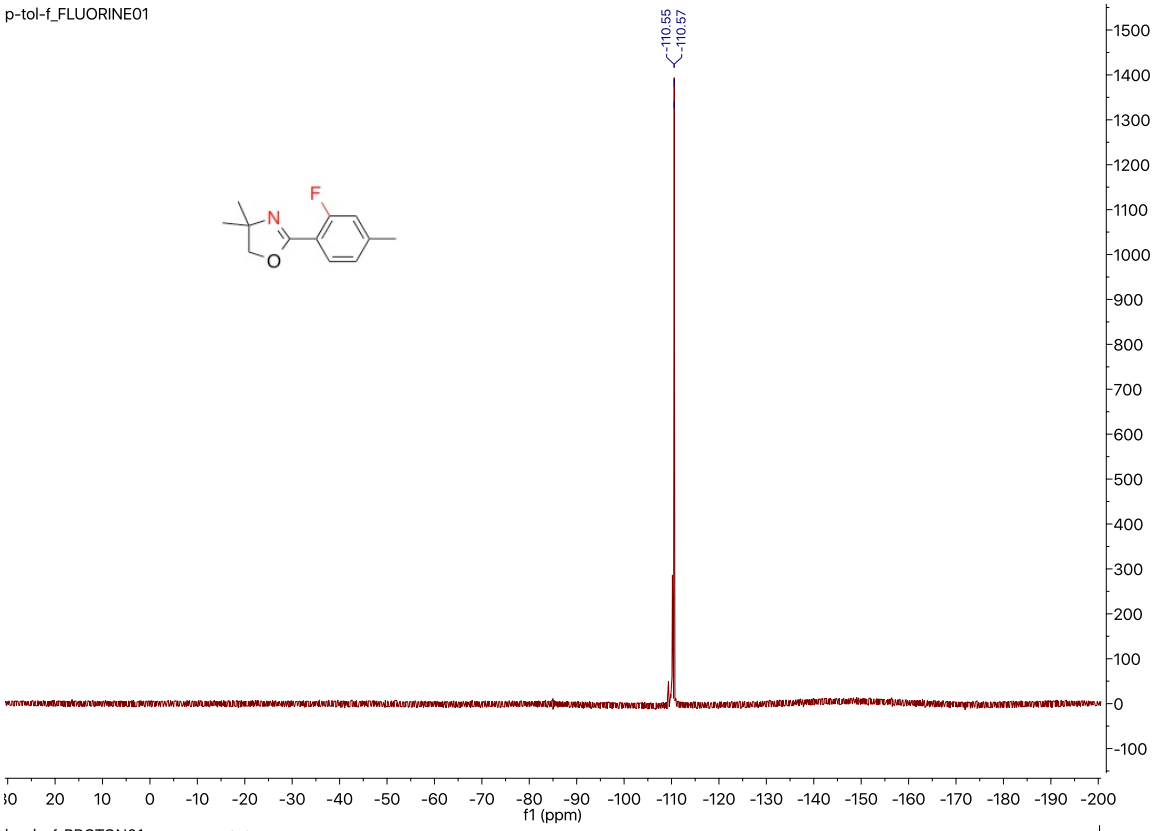

P-OCH3-DI-F_PROTON01
6.51
6.49
4.14
3.82
1.44
F
N
O
O
F
1.95
1.87
3.04
6.00
f1 (ppm)

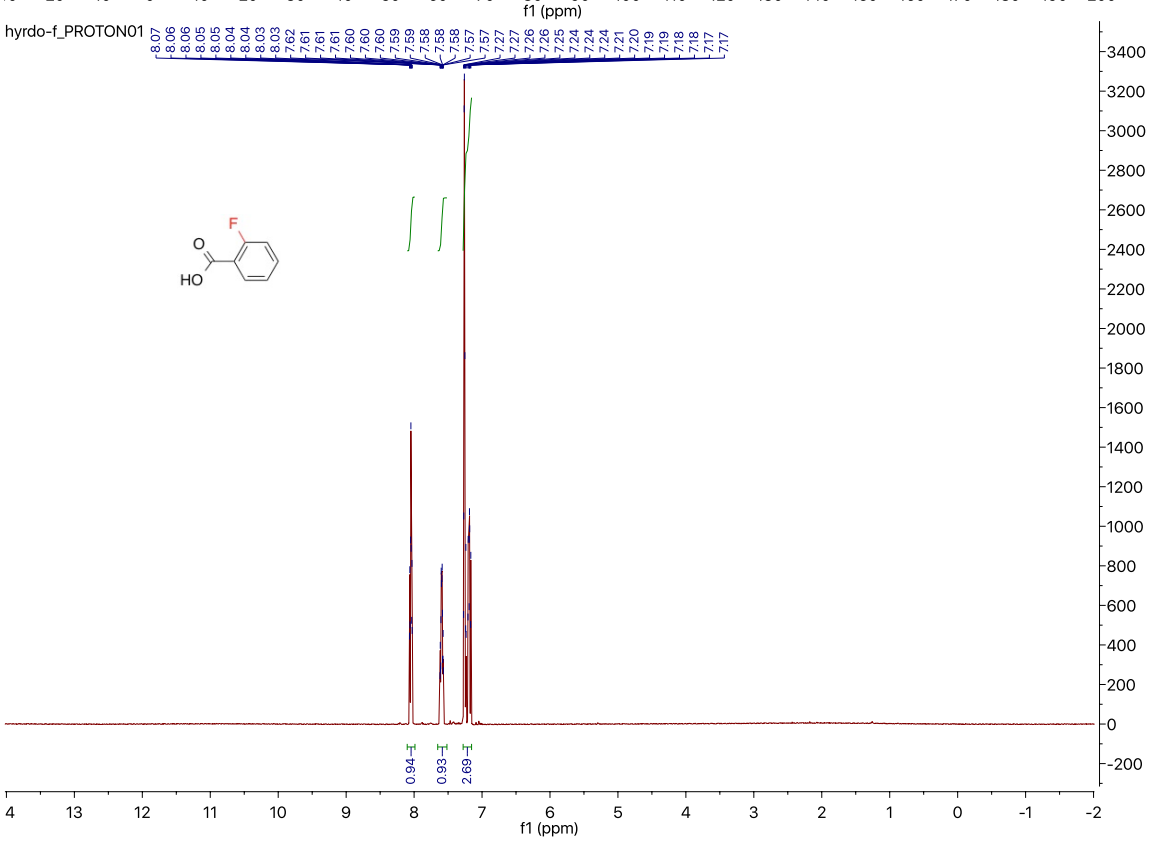

P-OCH3-DI-F_CARBON01
163.20
163.12
161.17
161.10
98.60
98.59
98.39
98.37
79.20
71.83
67.42
55.00
28.09
f1 (ppm)

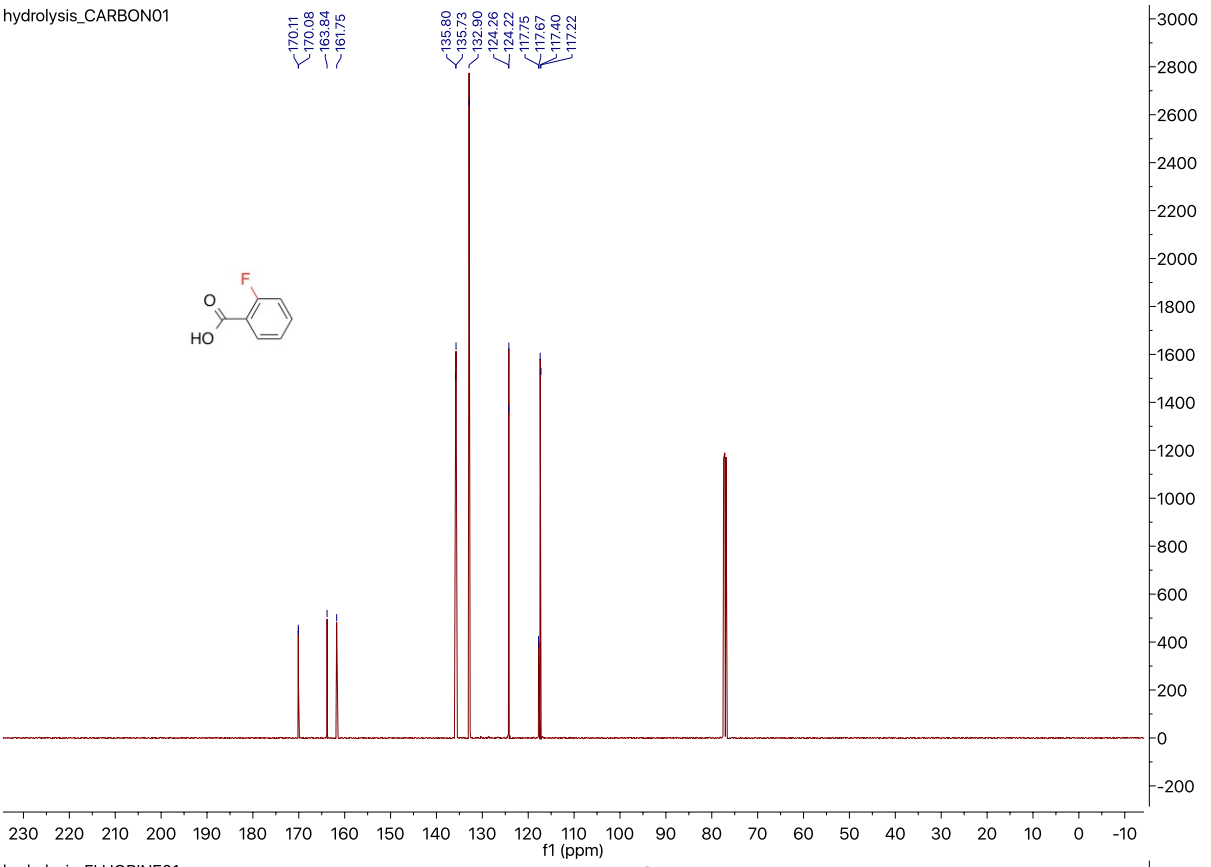

p-och3dif_FLUORINE01
-106.75
-106.77
f1 (ppm)

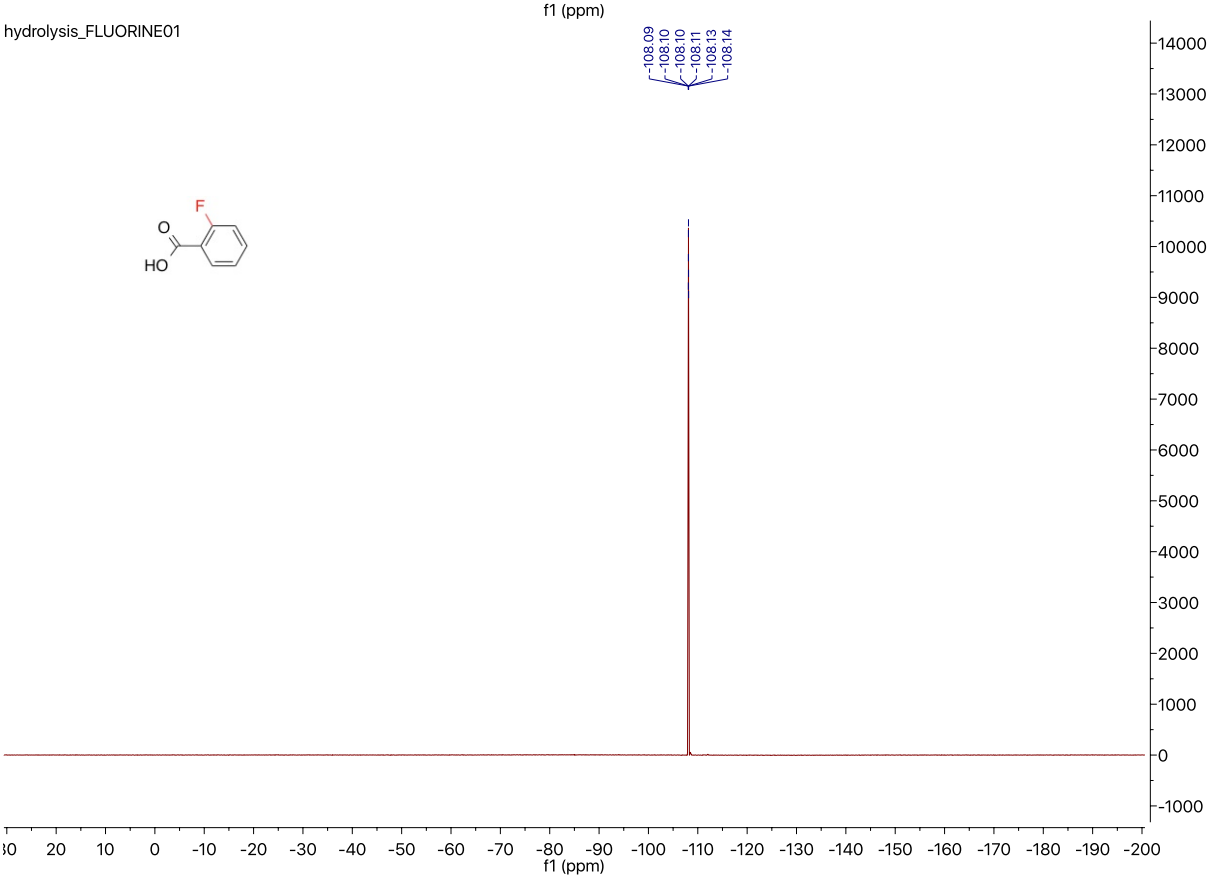

p-tol-mixed_PROTON01-2
7.79
6.99
6.97
6.95
6.93
4.11
2.37
1.41
0.79
1.52
1.86
2.44
6.00
f1 (ppm)


p-tol-f-di-f-c_CARBON01
162.06
161.86
160.01
159.83
154.77
143.65
131.03
129.64
124.86
124.83
117.17
117.00
112.46
112.43
112.26
79.11
78.89
67.97
67.20
28.21
21.40
f1 (ppm)


p-tol-f_FLUORINE01
-110.55
-110.57
F
N
O
f1 (ppm)


hyrdo-f_PROTON01
F
O
HO
0.94
0.93
2.69
f1 (ppm)


hydrolysis_CARBON01
170.11
170.08
163.84
161.75
135.80
135.73
132.90
124.26
124.22
117.75
117.67
117.40
117.22
F
O
HO
f1 (ppm)


hydrolysis_FLUORINE01
-108.09
-108.10
-108.10
-108.11
-108.13
-108.14
F
O
HO
f1 (ppm)