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A Study To Regioselectively Access Fluorinated Triazoles And Isoxazoles

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A STUDY TO REGIOSELECTIVELY ACCESS FLUORINATED TRIAZOLES AND ISOXAZOLES

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ABSTRACT

Fluorinated heterocycles have recently received a surge of interest in the field of medicinal chemistry. An incorporation of a fluorine atom into heterocyclic compounds can influence the overall dipole moment, pKa, and hydrogen bonding patterns. Currently, there is about twenty-five percent of fluorinated drugs in the market. Among these, fluorinated nitrogen heterocycles such as isoxazoles and triazoles, have been frequently found in medicinal agents. Both triazole and isoxazole rings have shown a wide range of biological activities as anti-cancer, anti-fungal, anti-viral, anti-bacterial, and anti-diabetic.

The objective of the thesis is to develop regioselective methods for mono-fluorination of disubstituted triazoles, both 1,4- and 1,5-regioisomer, and isoxazoles. These strategies focus on one-pot direct access to final mono-fluorinated triazoles and isoxazoles. Eventually, these fluorinated substrates will be screened against various biological targets.

Here, α-fluoronitroalkene was identified as a synthetic equivalent of α-fluoroalkyne, which undergoes 1,3-dipolar cycloaddition reaction to provide a direct regioselective access to 4-fluorotriazoles. The cycloaddition of α-fluoro-nitroalkenes with organic azides in the presence of trifluoroacetic acid generated 4-fluoro-1,5-disubstituted triazoles regioselectively.

Similarly, the optimization study of a regioselective method to generate 5-fluoro-1,4-disubstituted triazole was conducted. This reaction also utilized 1,3-dipolar cycloaddition to synthesize fluorinated triazole. However, difluoroalkene was used as a synthetic equivalent of α-

fluoroalkyne for this method. This resulted into the inversion of polarity affording a different regioisomer.

Also, a silver(I)-catalyzed reaction was studied to synthesize 4-fluoro-3,5-disubstituted isoxazole. An on-going optimization of cyclization reaction of oxime in presence of an electrophilic fluorinating source to furnish fluorinated isoxazole is discussed in detail.

DEDICATION

To my mentor, lab mates, family, and friends.

LIST OF ABBREVIATIONS OR SYMBOLS

°C	Celsius
n.o.	Not observed
NFSI	N-fluorobenzenesulfonimide
NMR	Nuclear magnetic resonance
rt	Room temperature
SAR	Structure–activity relationship
THF	Tetrahydrofuran
TLC	Thin layer chromatography
UV	Ultraviolet
TFA	Trifluoroacetic acid
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DCE	Dichloroethane
ACN	Acetonitrile
FDA	Food and Drug Administration
CuAAC	Copper(I)-catalyzed alkyne-azide cycloaddition
RuAAC	Ruthenium-catalyzed alkyne-azide cycloaddition
TEA	Triethyl amine
DIPEA	N, N-Diisopropylethylamine

S_NAr	Nucleophilic aromatic substitution
S_NV	Nucleophilic vinylic substitution
LiHMDS	Lithium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
TMEDA	Tetramethylethylenediamine

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Lastly, my heartfelt gratitude goes towards my parents who supported me to travel across the world to continue my education. Also, Swati and Deep, you guys have really been there to celebrate my highs and lift me up during my lows. Thank you!

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CHAPTER 1: INTRODUCTION

1.1 Fluorine

Fluorine is a small atom with a van der Waals radius of 1.47 Å, which is close to the 1.20 Å value for hydrogen.[1] However, it has high electronegativity of 3.98 on the Pauling electronegativity scale compared to 2.20 for hydrogen, 3.44 for oxygen, and 2.55 for carbon. These properties result in a highly polarized C−F bond which presents a strong dipole moment (μ C−F = 1.41 D).[1] Due to its unique properties, introduction of a fluorine atom into drug-like compounds can have a dramatic impact on a variety of properties and biological activities of these compounds.[2] Fluorine can alter the physicochemical properties and the binding affinity of a drug towards the receptor. It also results into an increase in metabolic stability and decrease the pKa value resulting into optimum bioavailability.[2]

1.2 Heterocycles in medicinal chemistry

Heterocycles are fundamental building blocks of most FDA approved drugs on the market today. They play a significant role in molecular properties such as the electronic distribution, three dimensionality, and scaffold rigidity.[3] These properties can influence the whole molecular properties such as lipophilicity, polarity, and hydrogen bonding capacity of molecules, which may lead to improved pharmacological, pharmacokinetic, toxicological, and physicochemical properties of drug candidates and ultimately the drug itself.[4]

Among 84% of FDA approved small-molecule drugs, at least one have nitrogen atom in them, and 59% have some sort of nitrogen heterocycle.[3] Some of the nitrogen containing heterocycles are shown below in Figure 1.

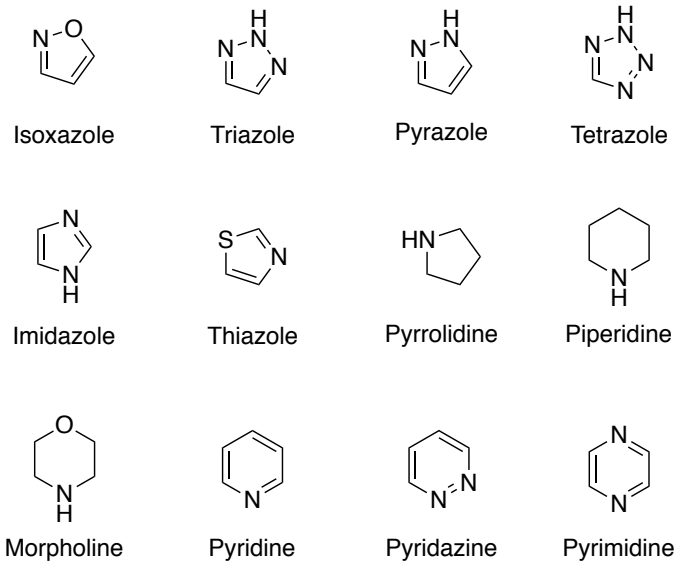


Figure 1: Few examples of nitrogen containing heterocycles

1.3 1,2,3-Triazoles

Among all the nitrogen-containing heterocycles, 1,2,3-triazoles have drawn considerable attention in the synthetic community. The application of triazoles have emerged in pharmaceutical research with anti-inflammatory, anti-microbial, anti-bacterial, anti-tubercular, anti-cancer, and anti-leishmanial properties as shown in Figure 2.[5] Triazoles are also used as fluorescent materials[6] and dyes.[7]

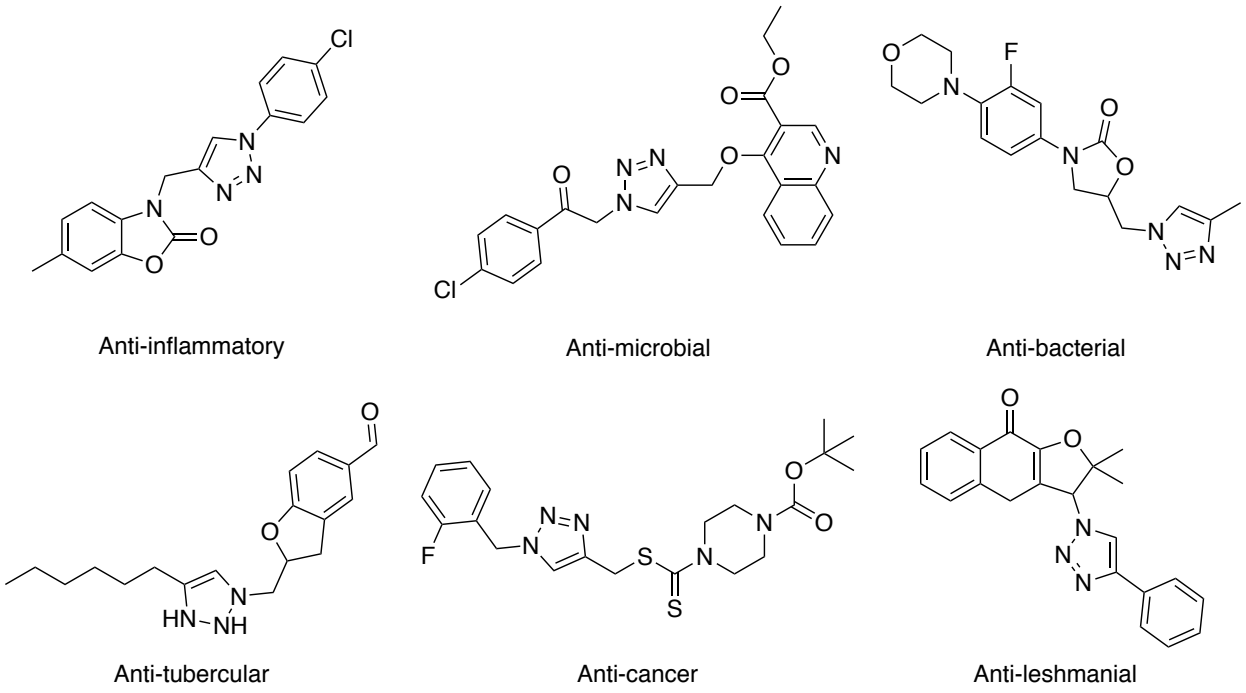


Figure 2: Pharmacologically active triazoles

There are mainly two types of 1,2,3-triazoles based on the position of the substituent on the nitrogen atom; 1H or 3H, and 2H-1,2,3-triazole (Figure 3).

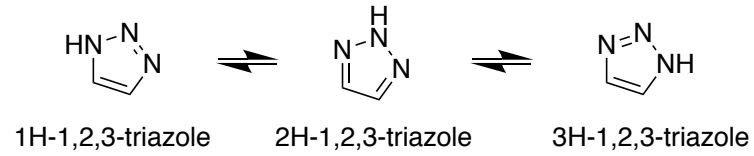


Figure 3: Types of 1,2,3-triazoles

The features possessed by the triazoles make them an important scaffold. 1,4-disubstituted 1,2,3-triazoles are good *trans*-amide bioisosteres because of high dipole moment, high H-bonding capabilities, and a higher metabolic stability than the amide bond (Figure 4).[8] Due to these properties, triazoles moiety has attracted the attention of synthetic chemists.

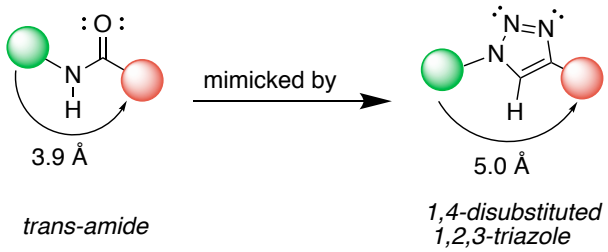
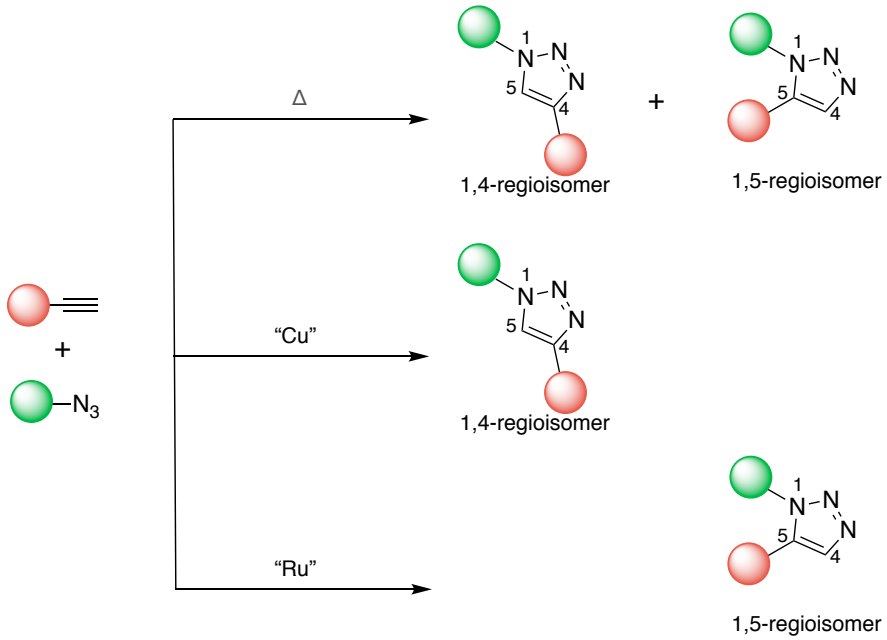


Figure 4: 1,4-disubstituted 1,2,3-triazole as a bioisostere of trans-amide

1,2,3-Triazoles were first synthesized by 1,3-dipolar cycloaddition of azides and alkynes at high temperature, also known as a Huisgen cycloaddition reaction.[9] This reaction is not often applied in organic synthesis due to the high temperature, poor regioselectivity, and low chemical yield. In 2001, Sharpless and Meldal introduced a regioselective copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) of 1,4-disubstituted 1,2,3-triazoles, which is popularly known as the "click reaction".[10] The CuAAC reaction is widely used in the chemical community because the reaction is quick, insensitive to water, and viable in a broad range of temperatures and functional groups. Soon after the discovery of the click reaction, ruthenium-catalyzed alkyne-azide cycloaddition (RuAAC) reaction was used to selectively form 1,5-disubstituted-1,2,3-triazoles.[11] However, this reaction has some limitations such as high reaction temperature, low yield, and the use of expensive metal catalysts.



Scheme 1: Types of 1,3-dipolar cycloaddition for the synthesis of 1,2,3-triazoles

1.4 Isoxazoles

Isoxazole is a significant heteroaromatic scaffold that are found in a wide range of biological activities such as anti-viral, anti-convulsant, anti-inflammatory, immune-modulatory, anti-cancer, anti-Alzheimer, anti-diabetic, and analgesic (Figure 5).[12] The isoxazole as a pharmacophore enforces the desired pharmacological activity due to the presence of two electronegative heteroatoms in 1,2-position. This results into many hydrogen bond interactions with a variety of receptors and enzymes unavailable to other ring systems.

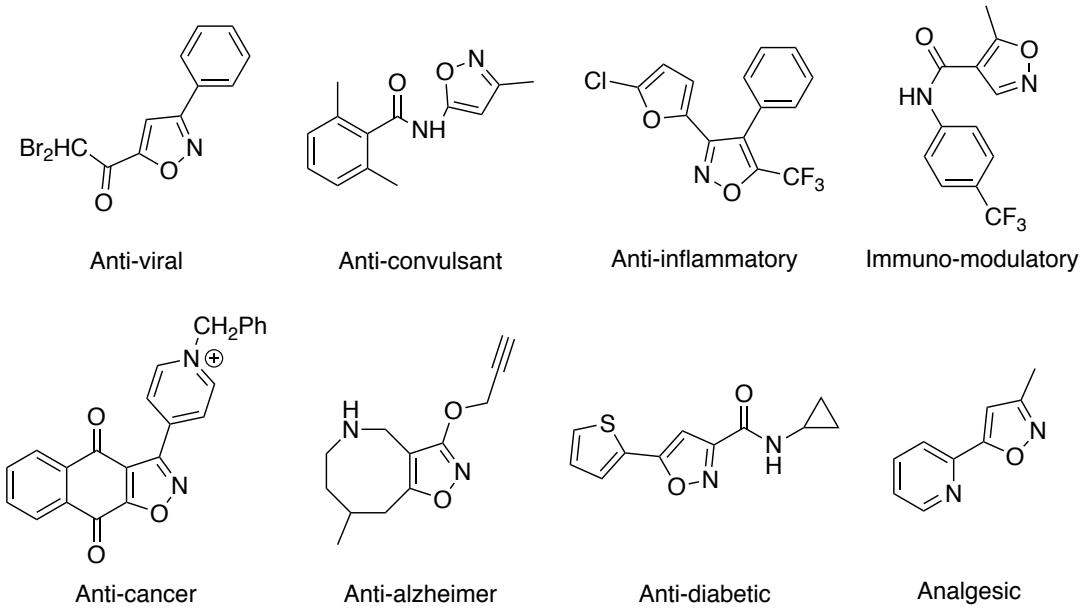
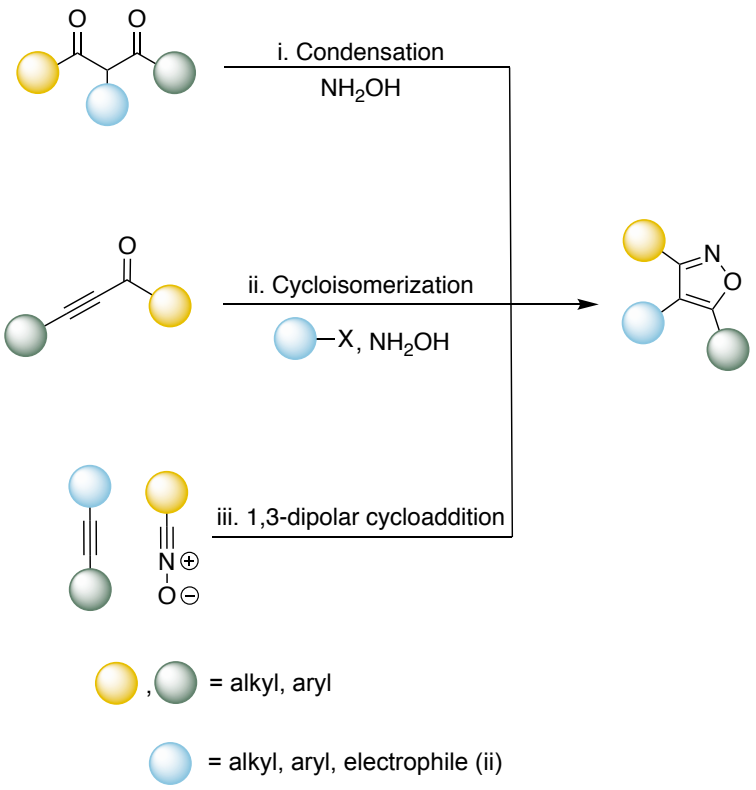


Figure 5: Pharmacologically active isoxazoles

The isoxazole ring can be constructed by several synthetic approaches. They can be classified into three types of reaction; condensation, 1,3-dipolar cycloaddition, and cycloisomerization (scheme 2). The isoxazoles were synthesized by condensation, which was first described by Claisen in 1888.[13] The reaction occurs between 1,3-dicarbonyl compound and hydroxylamine to form oxime, followed by cyclization to form isooxazoline. The isooxazoline then produces isoxazole after dehydration reaction. Similarly, Quilico reported the thermal dipolar cycloaddition between nitrile oxides and alkynes.[14] Later, Fokin reported copper-catalyzed 1,3-dipolar cycloaddition of hydroximoyl chlorides and terminal alkynes obtaining 3,5-disubstituted isoxazole with high yields and regioselectivity (>95:5).[15]



Scheme 2: Types of reaction for the synthesis of isoxazole

The synthesis of isoxazoles via electrophilic cycloisomerization of 1,3-disubstituted ynones has developed as one of the most efficient methods. This simple and mild procedure can directly introduce heteroatoms during the ring formation allowing straightforward preparation of highly valuable functionalized isoxazoles. In 2005, Larock proposed the first metal-free cycloisomerization synthesis of isoxazoles from ynones with *o*-methyl-hydroxylamine, followed by electrophilic cyclization of oximes.[16] The products were obtained in high yields and regioselectivity.

1.5 Fluorinated Heterocycles

The incorporation of a fluorine atom into heterocyclic compounds can influence the overall distribution of electron, which can alter the overall dipole moment, pKa, and hydrogen bonding

pattern of the compounds.[17] The application of fluorinated compounds can be commonly seen in pharmaceuticals, agrochemicals, material science, and positron emission tomography. Approximately 30 % of all agrochemicals and 20 % of all pharmaceuticals contain fluorine.[18] As a result, incorporation of fluorine into organic molecules have significantly attracted the interest of synthetic chemists. Even though addition of fluorine or fluorinated groups has been used to control the pharmacological properties of parent compounds, synthetic approaches remain challenging.[17]

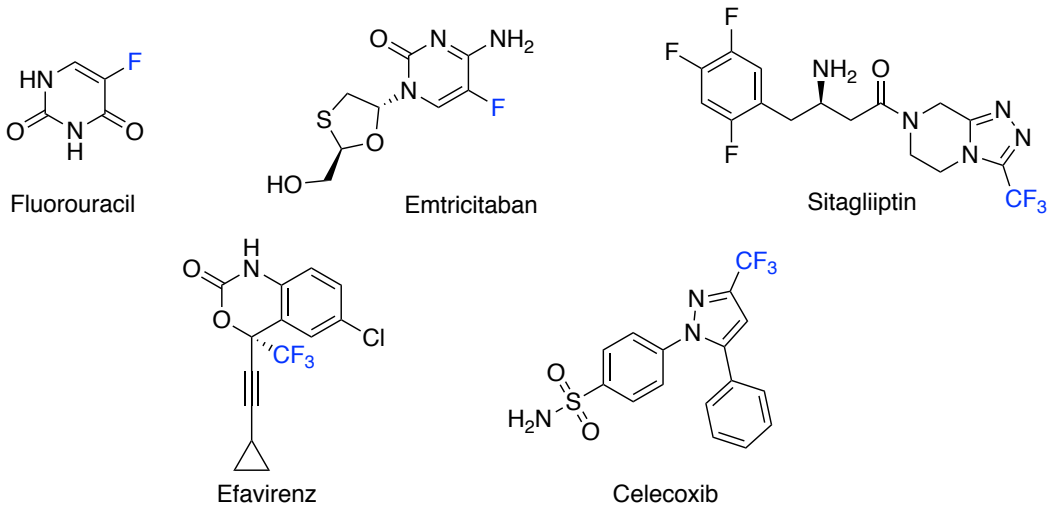


Figure 6: Few examples of drugs with fluorinated heterocyclic systems

1.6 Fluorinated 1,2,3-triazoles and isoxazoles

Fluorination of heterocycles is a relatively new and growing field in organic chemistry. There are scarce reports of studies on the mono-fluorination as well as trifluoromethylation of 1,2,3-triazoles. Similarly, mono-fluorination of isoxazole is also a novel field with very limited biological studies. There are comparatively more studies conducted on the trifluoromethylated isoxazoles, where they have found to exhibit a wide range of bioactivities, such as (R,S)-2-amino-

3-(3-hydroxy-5-trifluoromethylisoxazol-4-yl)propanoic acid (trifluoro-AMPA) acts as highly potent AMPA receptor agonist,[19] 5-trifluoromethyl-2-isoxazoline derivatives as veterinary medicines,[20] and 3-(5-chlorofuran-2-yl)-4-phenyl-5-trifluoromethylisoxazole acts as selective cyclooxygenase-1 (COX-1) inhibitor (Figure 7).[21]

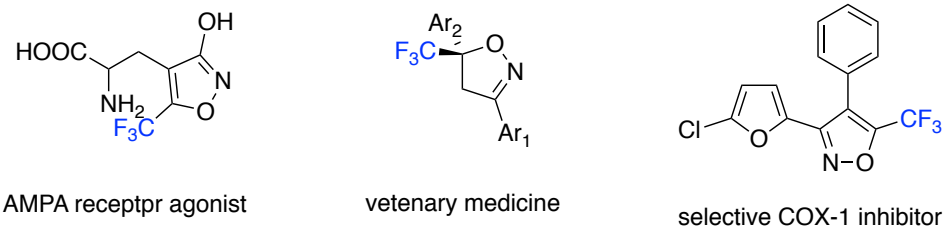


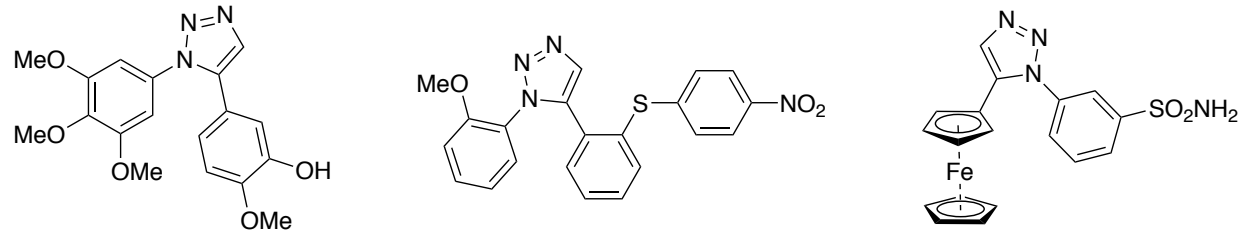
Figure 7: Few examples of trifluoromethylated isoxazoles

Thus, the novelty and limited studies of fluorine-containing heterocycles inspired us to develop new synthetic methods especially towards mono-fluorinated heterocycles. The method development and optimization to fluorinate 1,2,3-triazoles and isoxazoles will be discussed in detail in the following chapters.

CHAPTER 2: SYNTHESIS OF 4-FLUORO-1,5-DISUBSTITUTED-1,2,3-TRIAZOLES

2.1 Introduction

1,2,3-Triazoles are heterocycles of great importance and their chemistry has grown immensely in the past two decades.[4] Both 1,4- and 1,5-disubstituted-1,2,3-triazoles possess a wide range of biological activities and are commonly used in drug design. The study of the 1,5-disubstituted regioisomer was of a great interest to us because it is less prevalent in chemistry community and drug discovery which is accessed by Ru-catalyzed alkyne-azide cycloaddition,[11] whereas 1,4-disubstituted regioisomer are more prevalent and easily accessed by copper(I) catalyzed azide alkyne cycloaddition.[22] Some medicinal examples of 1,5-disubstituted-1,2,3-triazoles are shown in Figure 8.



combretastatin triazole analog
antitubulin

RN-18 triazole analog
antiretroviral

carbonic anhydrase inhibitor
anticancer

Figure 8: Some examples of 1,5-disubstituted-1,2,3-triazoles

Fluorination of the triazoles could be of great importance, as the incorporation of fluorine can have significant effect on the chemical and biological properties of the compounds.[2] In this chapter, we focused on the synthesis of 4-fluoro-1,5-disubstituted-1,2,3-triazoles. Until now, there no reports to synthesize fluorinated 1,5-disubstituted-triazoles.

Initially, we thought of performing a 1,3-dipolar cycloaddition between fluoro-alkyne and organic azide to form fluorinated triazole. However, fluoroalkynes are found to be very elusive due to their instability. They undergo spontaneous [2+2] cycloaddition to form 4 membered ring, which again undergoes [4+2] cycloaddition to produce fluorinated benzene derivatives as shown in figure 9.[23]

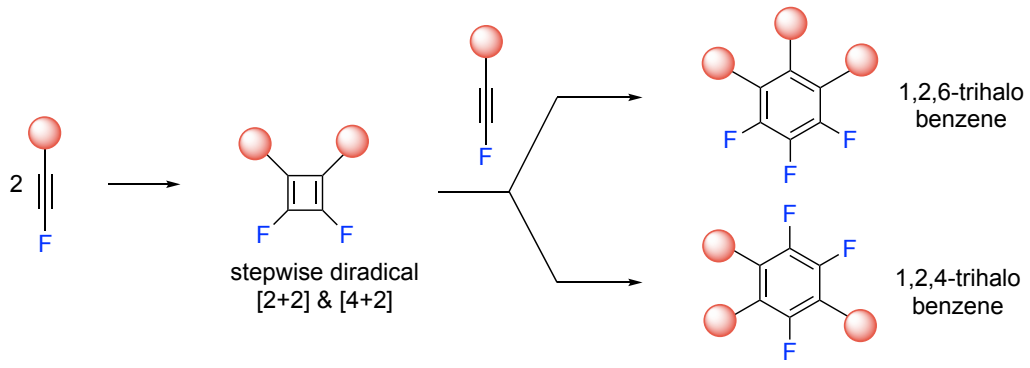


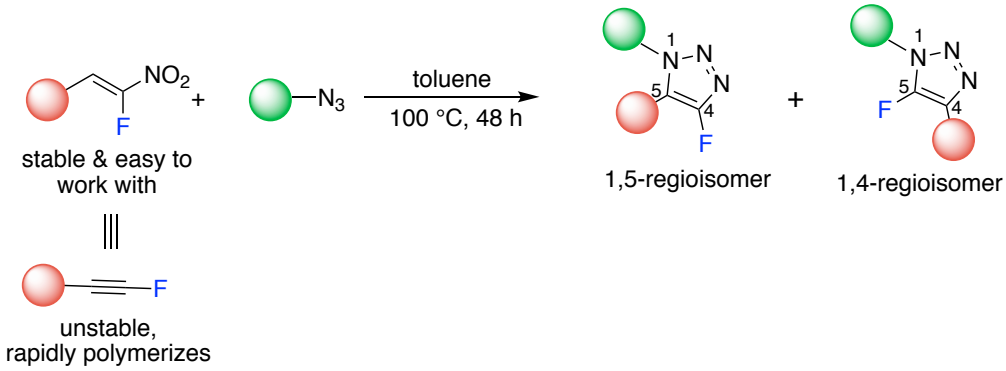
Figure 9: Spontaneous oligomerization of fluoroalkynes

2.2 Hypothesis

Therefore, in order to preclude fluoroacetylene as a starting precursor, we hypothesized that α-fluoroalkenes with a leaving group such as Br, CN, and NO_2 at the geminal position could be used as synthetic equivalents of α-fluoroalkynes.

We first screened α-fluorobromoalkene with azides in the presence of (i) various bases such as triethyl amine (TEA), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and

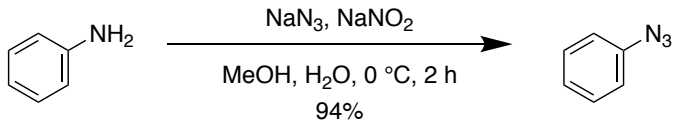
tetramethylethylenediamine (TMEDA), (ii) acid such as acetic acid, and (iii) different heating conditions from rt to rt-100 °C. However, the reaction did not go forward. Similarly, α-fluorocyanoalkene was screened in the presence of (i) trifluoroacetic acid (TFA) and (ii) various heating conditions from rt to rt-100 °C, but the desired product did not form. When α-fluoronitroalkene was heated to 100 °C with organic azide, [3+2] cycloaddition reaction occurred to form a mixture of 1,4- and 1,5-regioisomer of fluorinated triazole as shown in scheme 3. Since fluorinated 1,5-regioisomer has not been reported, we focused on the optimization to regioselectively access 1,5-regioisomer.



Scheme 3: α-Fluoronitroalkenes as synthetic equivalents of α-fluoroalkynes

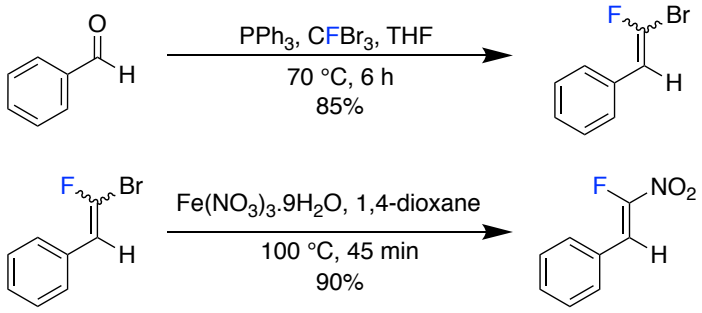
2.3 Synthesis of model substrates

We used azidobenzene (**2a**) as a model azide substrate for optimization. Aniline was reacted with sodium nitrite and hydrochloric acid to form corresponding diazonium salt. This reaction was followed by azidation reaction in presence of sodium azide to produce azidobenzene as shown in Scheme 4.[22]



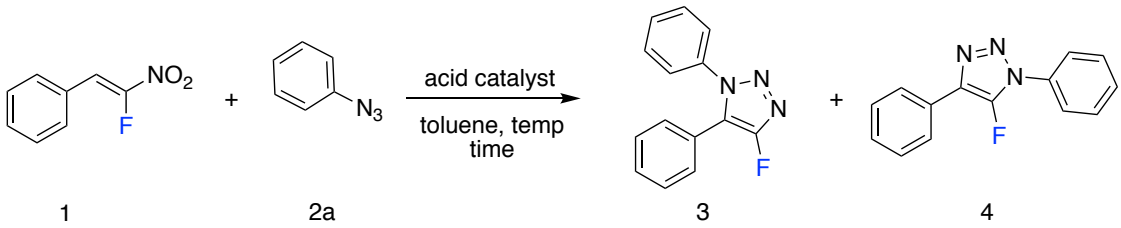
Scheme 4: Synthesis of azidobenzene

Also, when we screened various leaving groups such as bromo, nitro, and cyano, we found out that nitro was the best leaving group. Therefore, we used (*Z*)-(2-fluoro-2-nitrovinyl)benzene as a α-fluoronitroalkenes substrate for optimization step, which was synthesized in two steps.[24] We started with the corresponding aldehydes in presence of tribromofluoromethane and triphenyl phosphine in refluxing THF to form a mixture of *E* and *Z* isomers in 1:1 ratio of (2-bromo-2-fluorovinyl)benzene (**1-SM**). Then, (*Z*)-(2-fluoro-2-nitrovinyl)benzene (**1**) was synthesized by a radical-based nitration-debromination condition using ferric nitrate nonahydrate as shown below in Scheme 5.



Scheme 5: Synthesis of (2-fluoro-2-nitrovinyl)benzene

2.4 Optimization



1 2a 3 4

Table 1: Optimization for the synthesis of 4-fluoro triazole

entry	catalyst (equiv.)	temp (°C)	time (h)	yield(%)[b]	
				3	**4**
1	-	100	48	10	3
2	$Cu(OTf)_2$ (0.2)	100	24	19	n.o.
3	$Zn(OTf)_2$ (0.2)	100	24	16	n.o.
4	$Sc(OTf)_3$ (0.2)	100	24	25	n.o.
5	$Yb(OTf)_3$ (0.2)	100	24	11	n.o.
6	$Fe(OTf)_3$ (0.2)	100	24	8	n.o.
7	$Ce(OTf)_3$ (0.2)	100	24	22	n.o.
8	$BF_3 \bullet (OEt)_2$ (0.3)	100	24	28	8
9	AcOH (0.3)	100	48	42	10
10	PTSA (0.5)	100	48	31	<5
11	10-CSA (0.5)	100	48	36	<5
12	TFA (0.3)	100	48	60	n.o.
13	TFA (0.5)	110	48	74	n.o.
14	TFA (0.8)	100	48	69	n.o.
15	H_3PO_4 (0.5)	110	48	45	7
16	$MeSO_3H$ (0.5)	110	48	68	n.o.
17	NH_2SO_3 (0.5)	110	48	20	<5

[a]Standard reaction conditions: 1 equiv. of fluoronitroalkene **1a** (0.15 mmol), 2 equiv. of phenyl azide **2a** 0.30 mmol), and 0.5 equiv. of TFA were mixed in 2 M toluene and heated at 110 °C. [b] Isolated yield. PTSA = *p*-toluenesulfonic acid, TFA = trifluoroacetic acid 10-CSA = 10-camphorsulfonic acid. n.o.: not observed

We found 1 equiv. of α-fluoronitroalkene **1** and 2 equiv. of phenyl azide **2a** when heated at 100 °C in toluene resulted in the formation of a mixture of regioisomers, 1,5-disubstituted- and 1,4-disubstituted-fluoro-1,2,3-triazoles, in 5:2 ratio (entry 1, Table 1). The ratio of the regioisomeric products was determined by ^{19}F NMR. The ^{19}F NMR value for **3** and **4** are -145.1 and -150.4 ppm respectively.

It has been evident that the nitroalkenes can undergo regioselective nucleophilic addition as well as regioselective cycloaddition reaction in the presence of an acid catalyst.[25] Thus, we decided to screen the reaction with different Lewis acids. When we screened of our standard substrates in the presence of 20 mol% of $Cu(OTf)_2$ in toluene at 100 °C over 24 h (entry 2), it resulted in the selective formation of the 1,5 disubstituted 4-fluoro 1,2,3-triazole in 19% yield. Furthermore, screening of other Lewis acid such as $Zn(OTf)_2$, $Sc(OTf)_3$, $Yb(OTf)_3$, $Fe(OTf)_3$, $Ce(OTf)_3$, $BF3{\bullet}(OEt)_2$ (entries 3–8) did not lead to improvements in yield. However, an increase in yield up to 42% was observed with the formation of 1,5-disubstituted along with 10% in yield of 1,4-disusbtituted when we used 30 mol% AcOH as a catalyst (entry 9). Furthermore, we screened other Brønsted acids such as $MeSO_3H$, H_3PO_4, *p*-TSA·H_2O, and TFA with our standard substrates. Among these, TFA showed the best catalytic activity with an increase in yield up to 60% of selective one isomer **3** (entry 12). A gradual increase in yield was observed when the amount of TFA was increased from 30 mol% to 50 mol%. Further increase in yield was observed by raising temperature from 100 to 110 °C (entry 13). However, changing the solvents to DMF, DMSO, DCE, 1,4-dioxane, ACN, and THF resulted in lower yields.

Therefore, the optimized condition was found to be α-fluoronitroalkene **1** (1 equiv.) and phenyl azide **2a** (2 equiv.) with 50 mol% of TFA in 2M toluene when heated to 110 °C for 48 h, which regioselectively produced 1,5-diaryl-4-fluoro-1,2,3-triazole **3** in 74% yield.

2.4 Substrate scope

With the optimized condition in hand, we explored the substrate scope around aryl azides as shown in Figure 10. We noticed that *para*-substituted phenyl azides with electron-donating groups such as methyl (**3b**), *t*-butyl (**3c**), and methoxy (**3d**) gave the desired products in 51–58% yields. However, the yields dropped with electron withdrawing groups such as fluoro (**3e**) and cyano (**3f**) at the *para*-position as well as cyano (**3h**) and methoxy (**3i**) at the *meta*-position. The lower yield corresponded to unreacted starting materials as observed in ^{19}F NMR spectra and TLCs. Also, the combretastatin triazole analogue **3k** was prepared in 55% yield using this method.

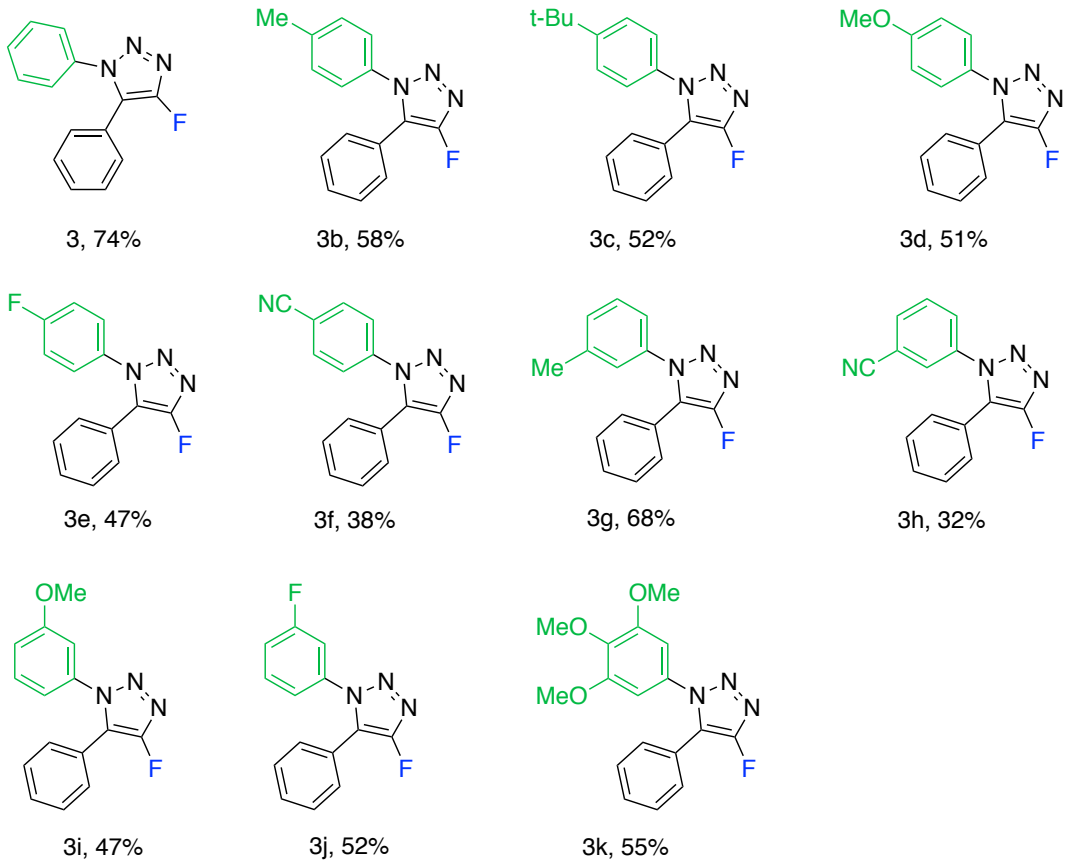


Figure 10: Substrate scope with respect to aryl azides

Next, the scope of the reaction for benzyl azides were examined (Figure 11). Both electron-donating group such as methyl (**3m**), *t*-butyl (**3n**), methoxy (**3o**) and electron withdrawing group such as cyano (**3p**), bromo (**3q**) at the *para*-position of benzyl azides were gave desired regioselective products in 51–63%. We also found methoxy group at *meta*-position such as **3r** gave similar results. Also, disubstituted fluoro at *ortho* and *para*-position in benzyl azide gave good yield using this method.

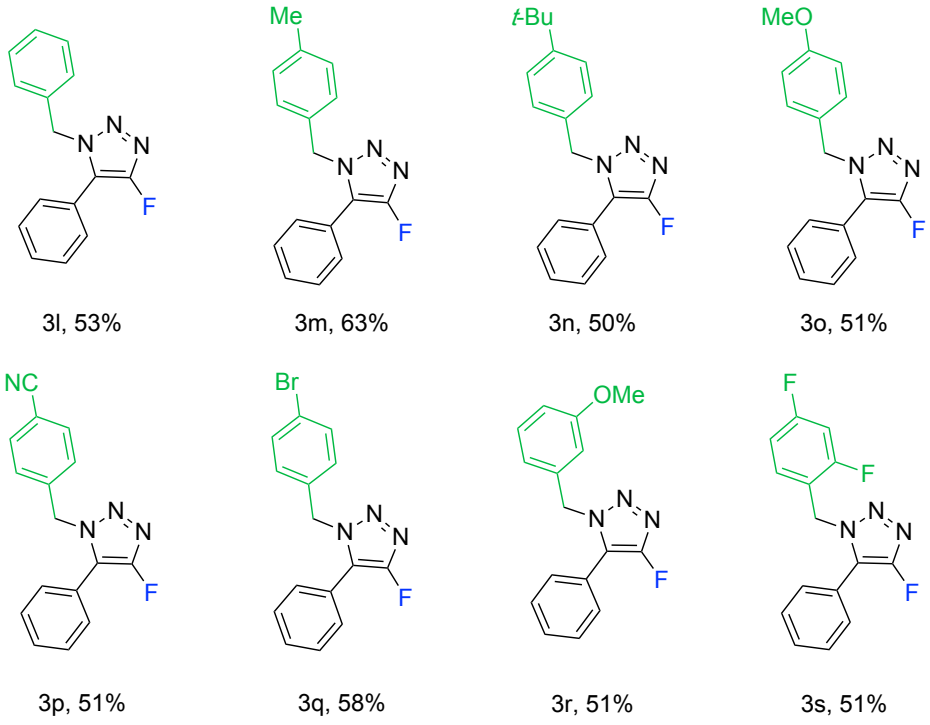


Figure 11: Substrate scope with respect to benzyl azides

We were also excited to use this method with aliphatic azides (**3t**–**3y**), which resulted in the formation of corresponding triazoles in 49–53% yields. Triazole analogues of azidothiamidine (**3x**), estrone (**3y**), and bis-triazole (**3z**) were also synthesized using our optimized conditions (Figure 12).

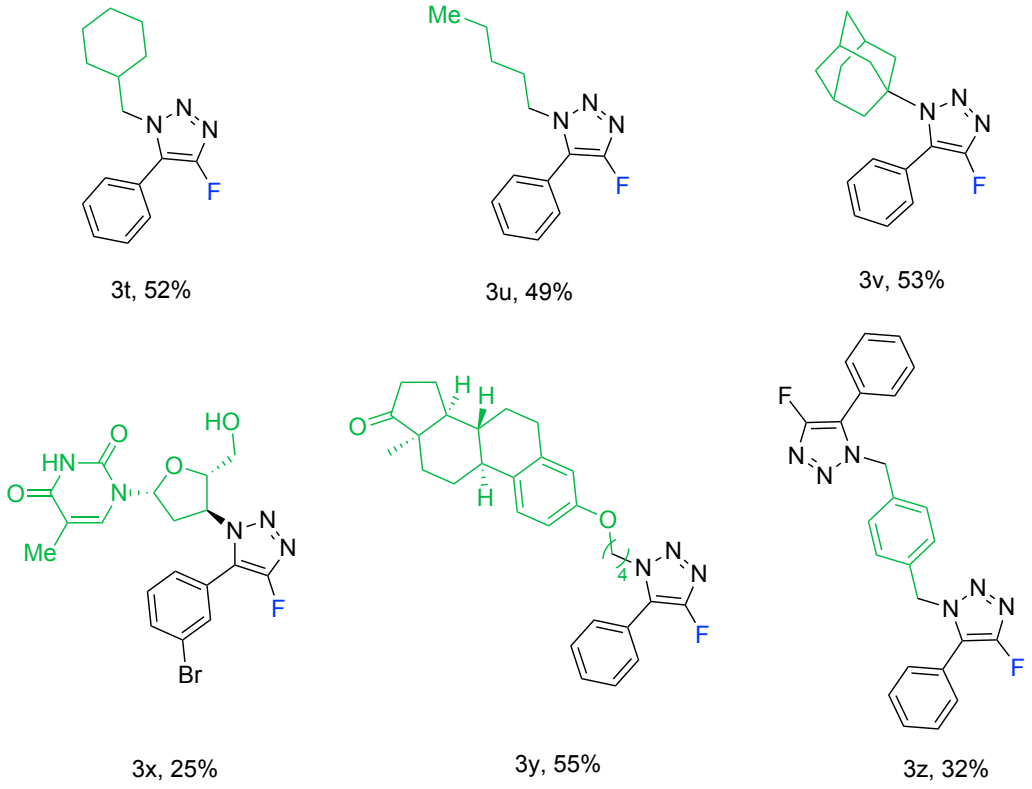


Figure 12: Substrate scope with respect to aliphatic azides

The scope of the reaction was further examined with the substitution patterns on α-fluoronitroalkenes (Figure 13). Overall, both electron donating and withdrawing groups at *para*-position in α-fluoronitroalkene showed good to moderate reactivity. The substrates with electron donating groups such as methyl (**4a**) and methoxy (**4b**) afforded better yields (54–73%) compared to the substrates containing electron withdrawing groups such as cyano (**4c**) and trifluoromethyl

(**4d**) (44–46%). The substituents at the *meta*-position afforded low yields (45–55%) irrespective of the substitution of electron donating and withdrawing group on α-fluoronitroalkene (**4e**–**4h**).

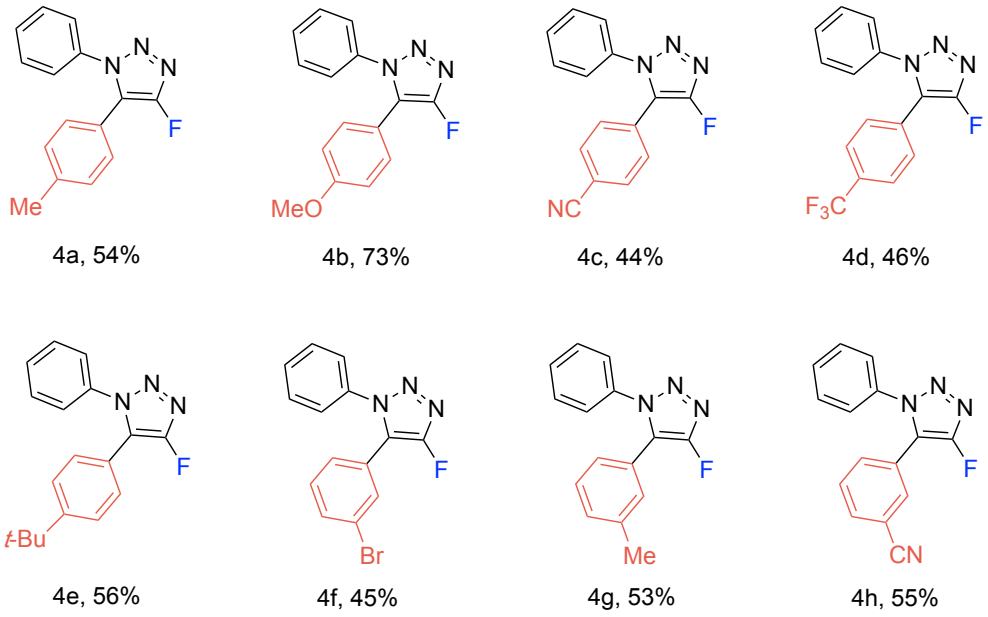


Figure 13: Substrate scope with respect to α-fluoronitroalkenes

2.5 Proposed mechanism

A plausible mechanism for this reaction is proposed in Figure 14. Initially, α-fluoronitroalkene and organic azide undergo regioselective [3+2] cycloaddition to form triazoline intermediate. Then, the nitro group is rapidly eliminated as nitrous acid to form the 1,5-disubstitued triazole. The regioselective cycloaddition occurs due to the presence of a strong electron withdrawing nitroa group, which is further activated by TFA. Without the presence of TFA in reaction condition, a mixture of 1,5 and 1,4-regioisomers are obtained in 5:2 ratio, as determined by ^{19}F NMR.

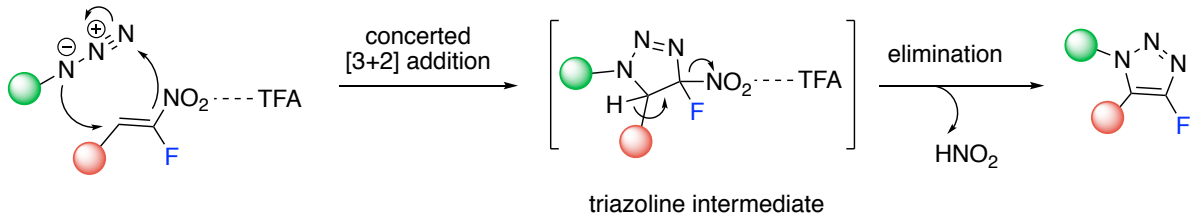


Figure 14: A proposed mechanism

The triazoline intermediate was attempted to probe via ^{19}F NMR in deuterated toluene at 90 °C. However, the intermediate could not be monitored by ^{19}F NMR. Therefore, the transient intermediate is believed to rapidly eliminate nitrous acid to form the triazole product. To prove the formation of triazoline intermediate, we synthesized fluoronitroalkene with methyl substitution in β-carbon. However, the cycloaddition did not take place between β-methyl fluoronitroalkene and organic azide.

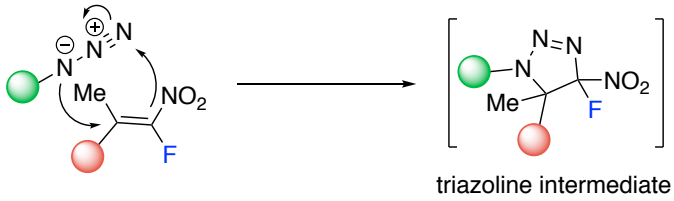


Figure 15: An attempt to form methyl substituted triazoline intermediate

2.6 Limitations

This fluorination method has many limitations such as the requirement of high temperature of 110 °C, very acidic environment, and long reaction hours up to 72 h. Using this method, we were not able to form respective triazole from N-Azidoacetylgalactosamine (GalNAz), 4-azidopyridine, 4-azido-7-chloroquinoline, and 3-azido-9-ethyl-9H-carbazole. Such high temperature and acidic environment can result into decomposition or undesired side reactions.

2.7 Conclusion

In conclusion, we have effectively used α-fluoronitroalkenes as a synthetic equivalent of α-fluoroalkynes in a regioselective [3 + 2] cycloaddition with organic azides to afford 4-fluoro triazoles. This novel method was used to synthesize a broad-range of 4-fluoro-1,5-substituted-1,2,3-triazoles in decent yields and high regioselectivity. α-Fluoronitroalkenes could be further used to synthesize other fluorinated heterocycles. Eventually, these fluorinated-triazoles will be screened against various biological targets.

CHAPTER 3: SYNTHESIS OF 5-FLUORO-1,4-DISUBSTITUTED-1,2,3-TRIAZOLES

3.1 Introduction

After the discovery of copper (I)- catalyzed azide–alkyne cycloaddition reaction (CuAAC), there was an increase in the production of a large number of 1,4-disubstituted-1,2,3-triazoles in very high yields.[26] The 1,4-disubstituted triazoles are commonly studied for their wide range of biological activities such as anticonvulsant, anti-Alzheimer's, and nicotinic acetylcholine receptors (nAChR) as shown in Figure 16.

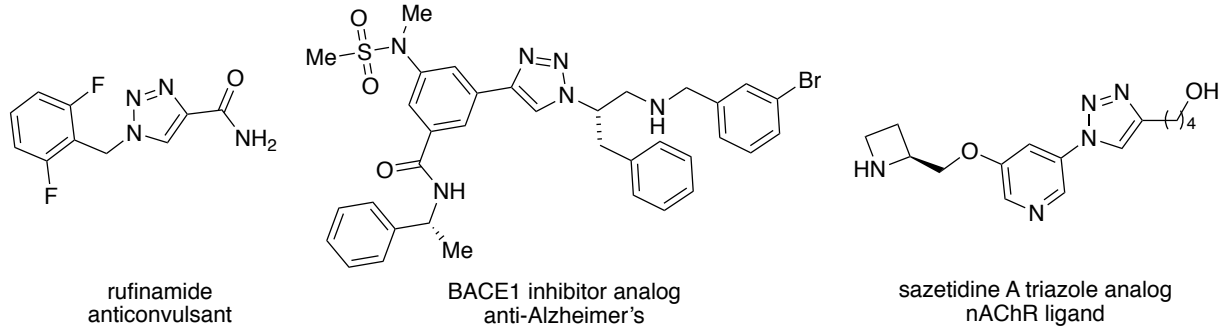
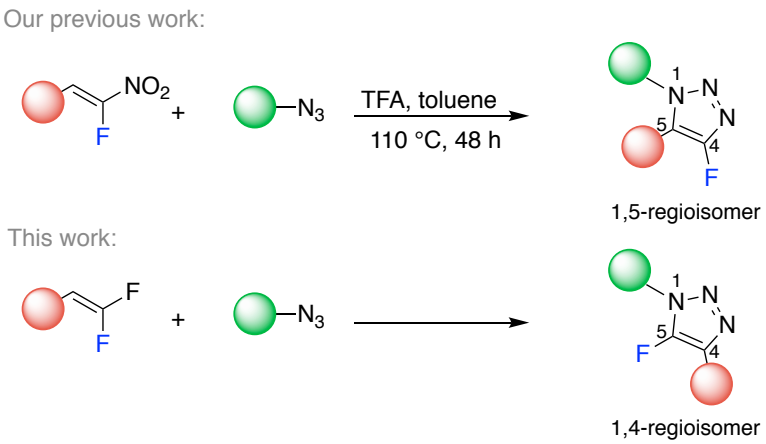


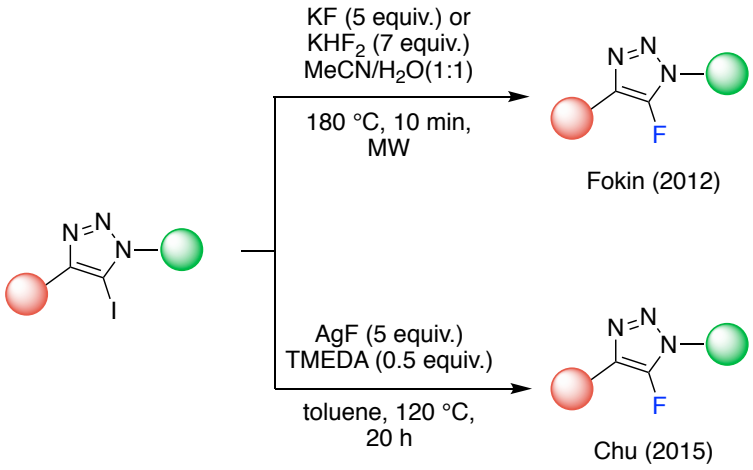
Figure 16: Examples of 1,4-disubstituted-1,2,3-triazoles

Previously in chapter 2, we showed that α-fluoronitroalkenes can serve as synthetic surrogates of α-fluoroalkynes in [3+2] cycloaddition reactions with organic azides facilitated by a catalytic amount of trifluoroacetic acid (TFA) to regioselectively access 4-fluoro-1,5-disubstituted-1,2,3-triazoles. Using the similar strategy, we were curious to study [3+2] cycloaddition reaction using difluoroalkene with organic azides.



Scheme 6: Synthetic surrogates of α-fluoroalkynes in [3+2] cycloaddition reactions

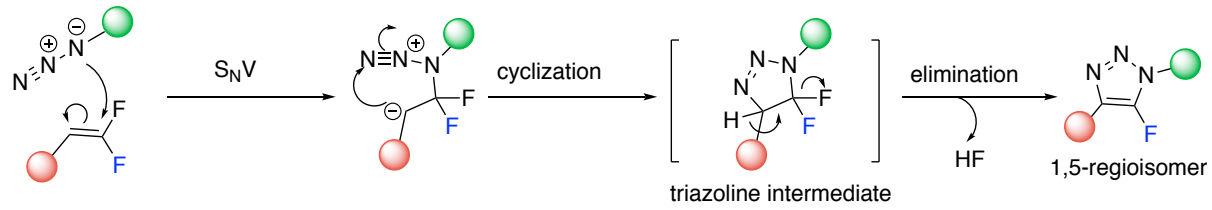
We were particularly keen in the study of a direct access to fluorinated 1,4-disubstituted triazoles since there are limited synthesis in literature precedents.[27,28] The existing methods first synthesize iodinated triazole, followed by a halogen exchange with fluoride either with potassium fluoride[27] or silver(I) fluoride[28] to afford fluorinated triazoles as shown below in Scheme 7. Therefore, there are no direct method for the synthesis of 5-fluorinated-1,4-disubstituted-1,2,3-triazoles.



Scheme 7: Halogen exchange from iodo-triazole to fluoro-triazoles

3.2 Hypothesis

During the optimization of [3+2] cycloaddition reaction using fluoroalkenes with leaving group in the geminal position, we observed polarity inversion when the leaving group were changed from strong electron withdrawing group such as nitro to inductively electron withdrawing group like fluoro (Scheme 7). Therefore, we hypothesized that difluoroalkenes can undergo nucleophilic vinylic substitution (S_NV) by organic azide, followed by cycloaddition reaction to form triazoline intermediate. The fluoro group eliminates as hydrogen fluoride accessing 5-fluoro-1,4-disubstituted-1,2,3-triazoles regioselectively as shown in scheme 8.

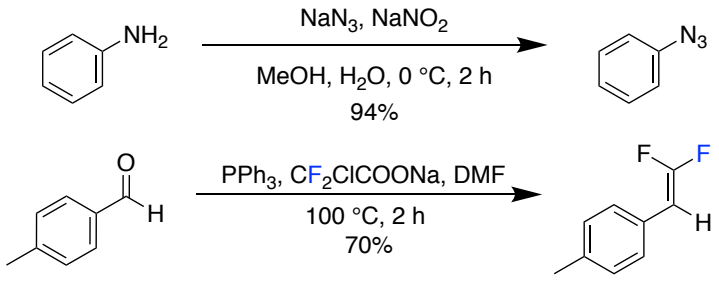


Scheme 8: Regioselective access to 5-fluoro-1,4-disubstituted-1,2,3-triazoles

3.3 Synthesis of model substrates

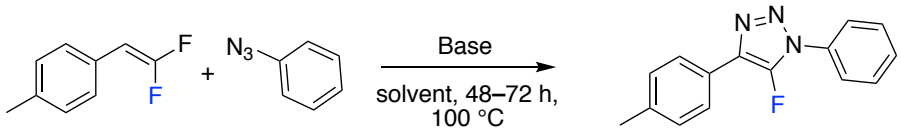
We used azidobenzene (**2a)** as an organic azide substrate for the optimization. Aniline was reacted with sodium nitrite and hydrochloric acid to form corresponding diazonium salt. This reaction was followed by azidation reaction in presence of sodium azide to produce azidobenzene as shown in Scheme 9.[22]

Also, 1-(2,2-difluorovinyl)-4-methylbenzene was chosen as a substrate for optimization step. The corresponding aldehydes was reacted with sodium 2-chloro-2,2-difluoroacetate and triphenyl phosphine in refluxing DMF to obtain 1-(2,2-difluorovinyl)-4-methylbenzene (**5)** as shown below in Scheme 9.[29]



Scheme 9: Synthesis of phenyl azide and difluoroalkene

3.4 Optimization



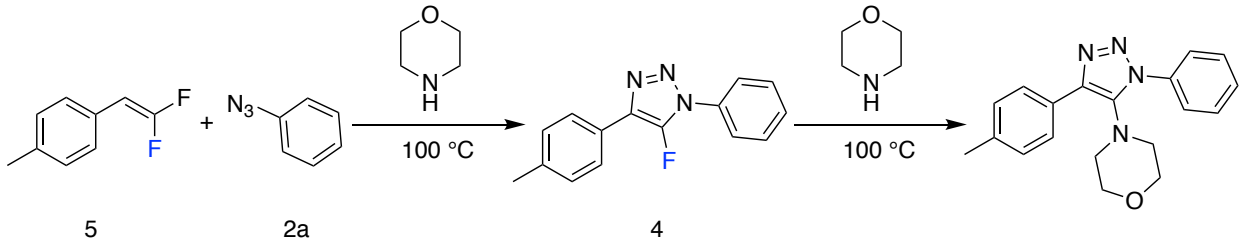
5 2a 4

Table 2: Optimization for the synthesis of 5-fluoro triazole

entry	catalyst (equiv.)	solvent (0.6 M)	time (h)	yield(%)[c] **4**
1	-	toluene	48	13[b]
2	-	morpholine	48	37
3	-	piperidine	48	31
4	-	TEA	72	14
5	-	pyridine	72	7
6	-	DIPEA	72	7
7	-	4-formyl morpholine	72	<5
8	morpholine (4)	toluene	48	<5
9	piperidine (4)	toluene	48	5
10	morpholine (8)	toluene	48	<5
11	LiHMDS (1)	toluene	48	15
12	LDA (1)	toluene	48	9

[a]Standard reaction conditions: 1 equiv. of difluoroalkene **5**, 2 equiv. of phenyl azide **2a**, and base were mixed in 0.6 M solvent and heated at 110 °C. [b]Isolated yield. [c] NMR yield.

We found 1 equiv. of difluoroalkene **5** and 2 equiv. of phenyl azide **2a** when heated at 100 °C in toluene resulted in regioselective formation of 5-fluorinated-1,4-disubstituted 1,2,3-triazoles **4** (entry 1, Table 2). The product **4** appeared at -150.4 ppm in ^{19}F NMR. Then, we screened the reaction using various bases such as morpholine, piperidine, triethyl amine (TEA), pyridine, *N*,*N*-diisopropylethylamine (DIPEA), and 4-formyl morpholine (entry 2-7). In case of morpholine, we observed an increased yield of 37% by aliquot ^{19}F NMR. However, we noticed a nucleophilic aromatic substitution (S_NAr) of fluorine by morpholine resulting into complete conversion of respective morpholine substituted triazole as shown in scheme 10.



Scheme 10: S_NAr reaction of fluorotriazole by morpholine

Fluorotriazole also underwent S_NAr reaction when piperidine was used as a solvent (entry 3). Therefore, in order to avoid the nucleophilic substitution, we tried to limit the amount of morpholine and piperidine in the reaction by using 4-8 equivalence of the base in toluene (entry 8-10). However, this resulted in ≤5% yield. To avoid the nucleophilic substitution of fluorine, we also screened non-nucleophilic bases such as lithium bis(trimethylsilyl)amide (LiHMDS) and lithium diisopropylamide (LDA) (entry 11-12). There was a slight increase of yield up to 15%. Other non-nucleophilic bases will be screened to further the optimization.

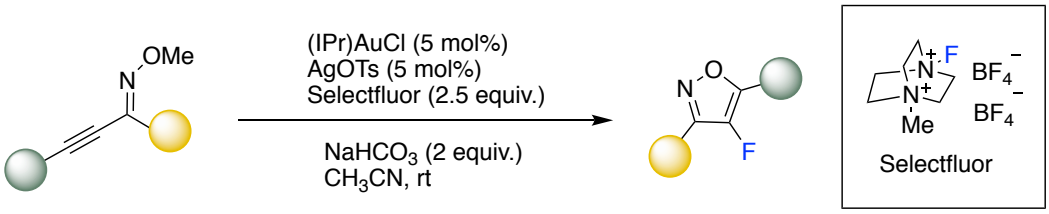
3.6 Conclusion

Thus, we have preliminary results on [3+2] cycloaddition reaction with difluoroalkene and organic azides to regioselectively access 5-fluorinated 1,4-disubstituted 1,2,3-triazoles. Further optimization and investigation of this reaction will be continued in our laboratory. This methodology will provide a novel direct method to access 5-fluoro-disubstituted triazoles.

CHAPTER 4: SYNTHESIS OF 4-FLUORO 3,5-DISUBSTITUTED ISOXAZOLES

4.1 Introduction

Isoxazole is a significant heteroaromatic scaffold that has shown a wide range of biological activities such as anticancer, antiviral, analgesic, antibiotic, and antidepressant.[30] In particular, fluoroisoxazoles have been found to have broad applications ranging from medicinal to material chemistry.[31] Despite such importance of fluorinated isoxazoles, their synthetic routes are limited due to difficulty faced during fluorination. In 2014, Ryu presented a gold-catalyzed cascade cyclization−fluorination of O-methyl oximes to give fluorinated isoxazoles at room temperature (Scheme 10).[30]



Scheme 11: Direct Synthesis of 4-Fluoroisoxazoles via Gold-Catalysis[30]

Since there are scarce reports to synthesize fluorinated isoxazole, we are determined to discover an alternative reaction to access 4-fluoro isoxazole.

4.2 Hypothesis

Recently, Miyata and co-workers reported a silver-catalyzed synthesis of disubstituted isoxazoles by cyclization of alkynyl oxime ethers.[32] Taking clue from the article, we hypothesized that the use of silver(I) activates the carbon-carbon triple bond of the oxime and cyclizes to generate an oxonium intermediate. Upon addition of electrophilic fluorinating source, silver eliminates to generate fluorinated isoxazole as shown in Figure 17.

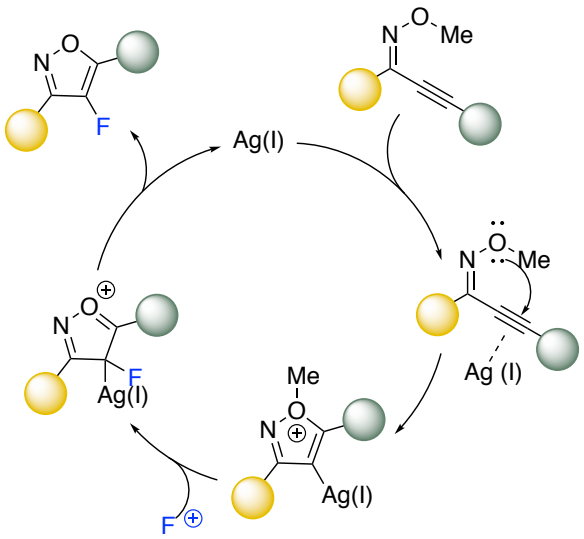
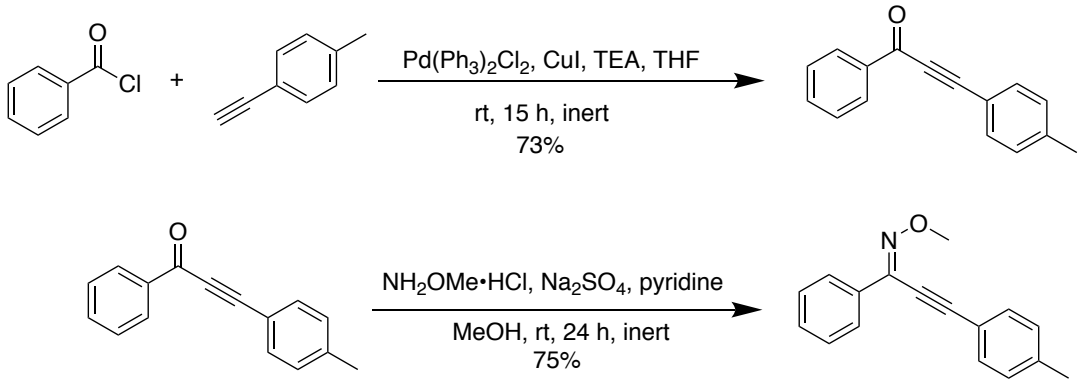


Figure 17: Silver-catalyzed synthesis of fluorinated disubstituted isoxazoles

4.3 Synthesis of model substrate



Scheme 12: Synthesis of O-methyl oxime

For preliminary investigation, we chose (*Z*)-1-phenyl-3-(p-tolyl)prop-2-yn-1-one *O*-methyl oxime **6** as a model substrate, which was prepared by two steps. The first step was the palladium/copper catalyzed Sonogashira coupling of an acid chloride with a terminal acetylene, resulting into internal ynone.[33] Then, *O*-methyl oximes was readily prepared by stirring the internal ynone in the presence of methoxylamine hydrochloride, pyridine, and Na_2SO_4 at room temperature using methanol as the solvent.[34]

4.4 Optimization

First, we carried out cyclization reaction with oxime **6** in presence of silver tetrafluoroborate ($AgBF_4$) and 2,6-dichloro-1-fluoropyridiniumtetrafluoroborate ($Py.Cl_2.F$) stirring in THF in an inert atmosphere at 80 °C for 48 hours (Table 3, entry 1). This reaction provided a mixture of fluorinated isoxazole **7** and protonated isoxazole **8** in <5% and 12% respectively. The ratio of the products 7 and 8 was determined by ^1H NMR. The product was also confirmed by ^{19}F NMR value, which shows a diagnostic peak at -179 ppm. We carried out the reaction in acetonitrile (entry 2), which gave us a cleaner reaction profile as suggested by TLC and NMR, with mixture of **7** and **8** in 11% and 6% respectively. Since the formation of **7** was increased in comparison to **8**, we did further optimization of the reaction in acetonitrile by increasing the equivalence of $AgBF_4$ from 0.5 to 1 (entry 3 and 4). The reaction with 1 equiv. $AgBF_4$ gave a good result with mixture of **7** and **8** in 45% and 32% respectively. With preliminary data in hand, we began an investigation of multiple silver catalysts and their equivalents: AgOTf (0.5 equiv.), AgOTs (0.5 equiv.), $AgNO_3$ (0.2 equiv.), and $AgSbF_6$ (0.5 equiv.) (entry 5-8). Yet, $AgBF_4$ (1 equiv.) in acetonitrile gave the best outcome (entry 4).

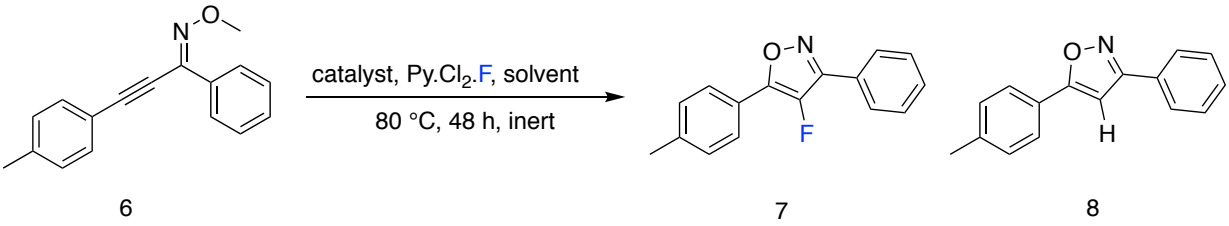


Table 3: Optimization for the Ag(I) catalyzed synthesis of 4-fluoro isoxazole

S.N.	Ag Catalyst, equiv.	Solvent, M	Yield (%)[b]	
			7	**8**
1	$AgBF_4$, 0.2	THF, 0.7	<5	12
2	$AgBF_4$, 0.2	MeCN, 0.7	11	6
3	$AgBF_4$, 0.5	MeCN, 0.7	36	60
4	$AgBF_4$, 1	MeCN, 0.7	45	32
5	AgOTf, 0.5	MeCN, 0.7	<5	n.o.
6	AgOTs, 0.5	MeCN, 0.7	<5	12
7	$AgNO_3$, 0.2	MeCN, 0.7	n.o.	n.o.
8	$AgSbF_6$, 0.5	MeCN, 0.7	24%	20%

[a]Standard reaction conditions: 1 equiv. of oxime **6**, 2 equiv. of $Py.Cl_2.F$, and Ag catalyst was heated to 80 °C for 48 h. [b] isolated yield. n.o.: not observed.

We further investigated various electrophilic fluorinating sources such as selectfluor, N-fluorobenzenesulfonimide (NFSI), and 1-fluoropyridinium tetrafluoroborate (Py.F) (Figure 18).

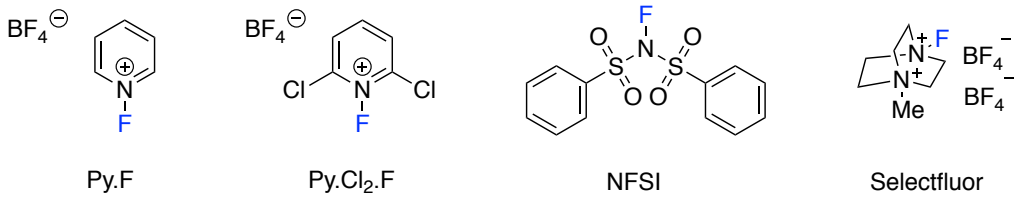
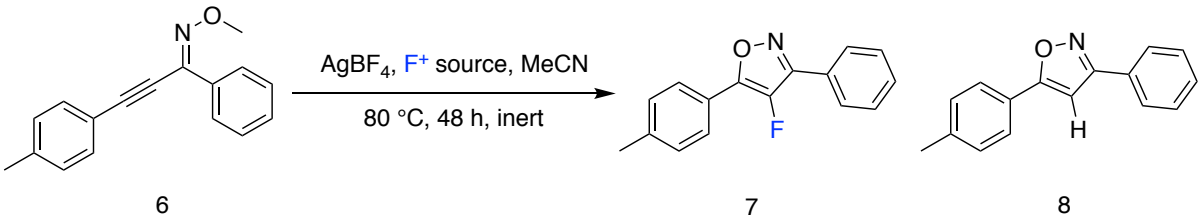


Figure 18: Various electrophilic fluorine sources

The reactions were catalyzed by silver tetrafluoroborate ($AgBF_4$) stirring in THF in an inert atmosphere at 80 °C for 48 hours (Table 4). For this optimization set, THF was used as a

solvent for better solubility. However, the fluorinating agents selectfluor, NFSI, and Py.F did not result into the formation of fluoro-isoxazole.



6 7 8

Table 4: Optimization with fluorinating sources for the synthesis of 4-fluoro isoxazole

S.N.	F^+ source (2 equiv.)	Yield (%)[b]	
		7	**8**
1	Selectfluor	n.o.	n.o.
2	NFSI	n.o.	13%
3	Py.F	n.o.	n.o.

[a]Standard reaction conditions: 1 equiv. of oxime **6**, 2 equiv. of electrophilic fluorine source, and 0.2 equiv. of $AgBF_4$ was heated to 80 °C for 48 h.
[b] isolated yield. n.o.: not observed.

4.5 Conclusion

Therefore, we have preliminary results on one-pot silver-catalyzed cyclization−fluorination of (*Z*)-2-alkynone *O*-methyl oxime to yield fluorinated isoxazole. The optimization of this reaction will be continued in our laboratory. This methodology will provide an alternative procedure to access 4-fluoro disubstituted isoxazole. The optimized reaction may have application in medicinal chemistry to the synthesize of bioactive fluorinated isoxazoles.

LIST OF REFERENCES

REFERENCES

(1) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58*, 8315–8359.

(2) Hemalatha, K.; Madhumitha, G.; Al-Dhabi, N. A.; Arasu, M. V. Importance of Fluorine in 2,3-Dihydroquinazolinone and Its Interaction Study with Lysozyme. *J. Photochem. Photobiol. B Biol.* **2016**, *162*, 176–188.

(3) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. Rings in Drugs. *J. Med. Chem.* **2014**, *57*, 5845–5859.

(4) Gomtsyan, A. Heterocycles in Drugs and Drug Discovery. *Chem. Heterocycl. Compd.* **2012**, *48*, 7-10.

(5) Dheer, D.; Singh, V.; Shankar, R. Medicinal Attributes of 1,2,3-Triazoles : Current Developments. *Bioorg. Chem.* **2017**, *71*, 30–54.

(6) Song, S.; Ko, Y.-G.; Lee, H.; Wi, D.; Ree, B. J.; Li, Y.; Michinobu, T.; Ree, M. High-Performance Triazole-Containing Brush Polymers via Azide–Alkyne Click Chemistry: A New Functional Polymer Platform for Electrical Memory Devices. *Npg Asia Mater.* **2015**, *7*, 228-241.

(7) Duan, T.; Fan, K.; Fu, Y.; Zhong, C.; Chen, X.; Peng, T.; Qin, J. Triphenylamine-Based Organic Dyes Containing a 1,2,3-Triazole Bridge for Dye-Sensitized Solar Cells via a 'Click' Reaction. *Dye. Pigment.* **2012**, *94*, 28–33.

(8) Bonandi, E.; Christodoulou, M. S.; Fumagalli, G.; Perdicchia, D.; Rastelli, G.; Passarella, D. The 1,2,3-Triazole Ring as a Bioisostere in Medicinal Chemistry. *Drug Discov. Today* **2017**, *22*, 1572–1581.

(9) Huisgen, R. 1,3-Dipolar Cycloaddition. *Proc. Chem. Soc.* **1961**, 357–396.

(10) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. Click Chemistry: Diverse Chemical Function from a Few Good Reactions. *Angew. Chemie Int. Ed.* **2001**, *40*, 2004–2021.

(11) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V; Jia, G. Ruthenium-Catalyzed Cycloaddition of Alkynes and Organic Azides. *J. Am. Chem. Soc.* **2005**, *127*, 15998–15999.

(12) Sysak, A.; Obmińska-Mrukowicz, B. Isoxazole Ring as a Useful Scaffold in a Search for New Therapeutic Agents. *Eur. J. Med. Chem.* **2017**, *137*, 292–309.

(13) Claisen, L.; Lowman, O. Zur Kenntniss Des Benzoylacetons. *Berichte der Dtsch. Chem. Gesellschaft*. **1888**, *21*, 1149–1157.

(14) Quilico, A. Advances in Nitrile Oxides Chemistry. *Experientia.* **1970**, *26*, 1169-1183.

(15) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. Copper(I)-Catalyzed Synthesis of Azoles. DFT Study Predicts Unprecedented Reactivity and Intermediates. *J. Am. Chem. Soc.* **2005**, *127*, 210–216.

(16) Waldo, J. P.; Larock, R. C. Synthesis of Isoxazoles via Electrophilic Cyclization. *Org. Lett.* **2005**, *7*, 5203–5205.

(17) Tarui, A.; Sato, K.; Omote, M.; Ando, A. Synthesis of Fluorinated Heterocycles Designed to Deliver the Modified Bioactive Behavior: Synthetic Use of Ethyl Bromodifluoroacetate, Ethyl Dibromofluoroacetate and Fluorine Containing Vinylsilanes. *J. Synth. Org. Chem.*

Japan. **2014**, *72*, 680–691.

(18) Manteau, B.; Pazenok, S.; Vors, J.-P.; Leroux, F. R. New Trends in the Chemistry of α-Fluorinated Ethers, Thioethers, Amines and Phosphines. *J. Fluor. Chem.* **2010**, *131*, 140–158.

(19) Madsen, U.; Ebert, B.; Krogsgaard-Larsen, P.; Wong, E. H. F. Synthesis and Pharmacology of (RS)-2-Amino-3-(3-Hydroxy-5-Trifluoromethyl-4-Isoxazolyl)Propionic Acid, a Potent AMPA Receptor Agonist. *Eur. J. Med. Chem.* **1992**, *27*, 479–484.

(20) Kawai, H.; Okusu, S.; Tokunaga, E.; Shibata, N. Enantioselective Synthesis of 5-Trifluoromethyl-2-Isoxazolines and Their N-Oxides by [Hydroxy(Tosyloxy)Iodo]Benzene-Mediated Oxidative N–O Coupling. *European J. Org. Chem.* **2013**, *2013*, 6506–6509.

(21) Vitale, P.; Tacconelli, S.; Perrone, M. G.; Malerba, P.; Simone, L.; Scilimati, A.; Lavecchia, A.; Dovizio, M.; Marcantoni, E.; Bruno, A.; et al. Synthesis, Pharmacological Characterization, and Docking Analysis of a Novel Family of Diarylisoxazoles as Highly Selective Cyclooxygenase-1 (COX-1) Inhibitors. *J. Med. Chem.* **2013**, *56*, 4277–4299.

(22) Tao, C.-Z.; Cui, X.; Li, J.; Liu, A.-X.; Liu, L.; Guo, Q.-X. Copper-Catalyzed Synthesis of Aryl Azides and 1-Aryl-1,2,3-Triazoles from Boronic Acids. *Tetrahedron Lett.* **2007**, *48*, 3525–3529.

(23) Yao, Z.-K.; Yu, Z.-X. Mechanisms of the Thermal Cyclotrimerizations of Fluoro- and Chloroacetylenes: Density Functional Theory Investigation and Intermediate Trapping Experiments. *J. Am. Chem. Soc.* **2011**, *133*, 10864–10877.

(24) Motornov, V. A.; Muzalevskiy, V. M.; Tabolin, A. A.; Novikov, R. A.; Nelyubina, Y. V; Nenajdenko, V. G.; Ioffe, S. L. Radical Nitration-Debromination of α-Bromo-α-

Fluoroalkenes as a Stereoselective Route to Aromatic α-Fluoronitroalkenes—Functionalized Fluorinated Building Blocks for Organic Synthesis. *J. Org. Chem.* **2017**, *82*, 5274–5284.

(25) Zefirov, N. S.; Chapovskaya, N. K.; Kolesnikov, V. V. Synthesis of 1,2,3-Triazoles by Reaction of Azide Ion with Aβ-Unsaturated Nitro-Compounds and Nitriles. *J. Chem. Soc. D Chem. Commun.* **1971**, *17*, 1001–1002.

(26) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. Click-Chemie: Diverse Chemische Funktionalität Mit Einer Handvoll Guter Reaktionen. *Angew. Chemie*. **2001**, *113*, 2056–2075.

(27) Worrell, B. T.; Hein, J. E.; Fokin, V. V. Halogen Exchange (Halex) Reaction of 5-Iodo-1,2,3-Triazoles: Synthesis and Applications of 5-Fluorotriazoles. *Angew. Chemie Int. Ed.* **2012**, *51*, 11791–11794.

(28) Wang, D.; Sun, W.; Chu, T. Synthesis of 5-Fluorotriazoles by Silver-Mediated Fluorination of 5-Iodotriazoles. *European J. Org. Chem.* **2015**, *2015*, 4114–4118.

(29) Faqua, S. A.; Duncan, W. G.; Silverstein, R. M. A One-Step Synthesis of 1,1-Difluoroolefins from Aldehydes by a Modified Wittig Synthesis. *Tetrahedron Lett.* **1964**, *5*, 1461–1463.

(30) Jeong, Y.; Kim, B.-I.; Lee, J. K.; Ryu, J.-S. Direct Synthesis of 4-Fluoroisoxazoles through Gold-Catalyzed Cascade Cyclization–Fluorination of 2-Alkynone O-Methyl Oximes. *J. Org. Chem.* **2014**, *79*, 6444–6455.

(31) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II–III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends

and Therapeutic Areas. *Chem. Rev.* **2016**, *116*, 422–518.

(32) Ueda, M.; Ikeda, Y.; Sato, A.; Ito, Y.; Kakiuchi, M.; Shono, H.; Miyoshi, T.; Naito, T.; Miyata, O. Silver-Catalyzed Synthesis of Disubstituted Isoxazoles by Cyclization of Alkynyl Oxime Ethers. *Tetrahedron.* **2011**, *67*, 4612–4615.

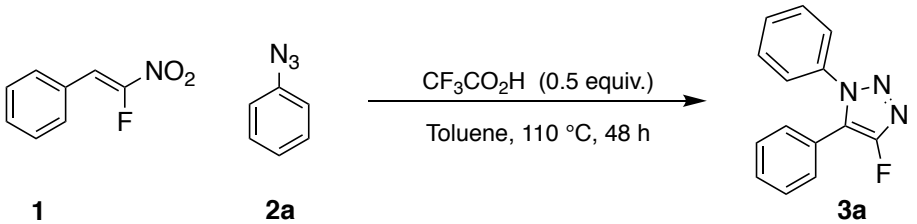
(33) Tohda, Y.; Sonogashira, K.; Hagihara, N. A Convenient Synthesis of 1-Alkynyl Ketones and 2-Alkynamides. *Synthesis (Germany)*. **1977**, *11*, 777-778.

(34) Beak, P.; Basha, A.; Kokko, B.; Loo, D. The Geometry of Displacements at Nonstereogenic Atoms: The Formal Displacement of Alkoxide from Alkoxyamines by Organolithium Reagents. *J. Am. Chem. Soc.* **1986**, *108*, 6016–6023.

APPENDIX

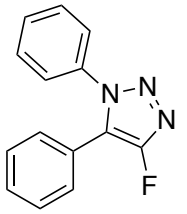
APPENDIX

1. Chapter 1



1 **2a** **3a**

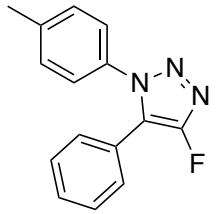
To an oven-dry screw-capped reaction tube with a magnetic stir bar was added α-fluoronitroalkene (1 equiv.) and corresponding azide (2 equiv.). The mixture was dissolved in toluene (0.4 mL) followed by TFA (0.5 equiv.) was added dropwise. The reaction mixture was purged with Argon and stirred at 110 °C for 48–96 h. After completion of the reaction (confirmed by TLC chromatography) the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with DCM (20 mL X 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in *vacuo*. The product was obtained after purification by column chromatography on silica gel by using DCM as eluent.



4-Fluoro-1,5-diphenyl-1H-1,2,3-triazole (3a):

α-Fluoronitroalkene (80 mg, 0.48 mmol), phenylazide (110 mg, 0.96 mmol), TFA (18 μL, 0.24 mmol) and toluene (0.4 mL). Reaction time is 48 h. The product was purified by column chromatography (DCM as eluent) affording **3a** (85 mg, 74% yield) as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.34 (m, 3H), 7.32–7.26 (m, 5H), 7.19–7.11 (m, 2H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -145.14. **^{13}C NMR** (101 MHz, CDCl3) δ 158.66 (d, J = 247.5 Hz), 136.78, 129.82, 129.58, 129.52, 129.03, 128.67, 128.65, 125.02, 124.32 (d, J = 4.2 Hz), 119.70 (d, J = 28.3 Hz). **IR** (ν, cm^{-1}): 2342, 2678, 2899. **HRMS**: $C_{14}H_{10}FN_3$ $[M]^-$; calculated: 239.0859, found: 239.0854.

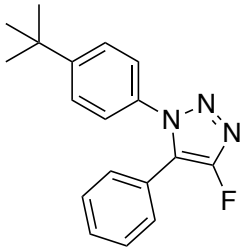


4-Fluoro-5-phenyl-1-(p-tolyl)-1H-1,2,3-triazole (3b):

α-Fluoronitroalkene (80 mg, 0.48 mmol), 1-azido-4-methylbenzene (130 mg, 0.96 mmol), TFA (18 μL, 0.24 mmol) and toluene (0.4 mL). Reaction time is 48 h. The product was purified by column chromatography (DCM as eluent) affording **3b** (70 mg, 58% yield) as an off-white oil.

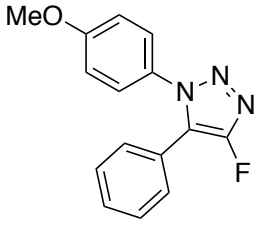
^{1}H NMR (400 MHz, MeOD-*d*) δ 7.42–7.36 (m, 3H), 7.33–7.29 (m, 2H), 7.28–7.23 (m, 4H), 2.40 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -145.22. **^{13}C NMR** (101 MHz, $CDCl_3$) 158.55 (d, *J* =

247.1 Hz), 140.04, 134.30, 130.08, 129.38, 128.94, 128.56, 124.79, 124.37 (d, J = 4.2 Hz), 119.56 (d, J = 28.2 Hz), 21.21. **IR** (ν, cm^{-1}): 2357, 3062. **HRMS**: $C_{15}H_{12}FN_3$ $[M + Cs]^+$; calculated: 386.0070, found: 386.0089.



1-(4-(*tert*-Butyl)phenyl)-4-fluoro-5-phenyl-1H-1,2,3-triazole (3c):

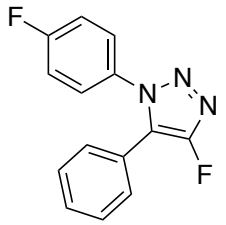
α-Fluoronitroalkene (80 mg, 0.48 mmol), 1-azido-4-(tert-butyl)benzene (170 mg, 0.96 mmol), TFA (18 μL, 0.24 mmol) and toluene (0.4 mL). Reaction time is 48 h. The product was purified by column chromatography (DCM as eluent) affording **3c** (74 mg, 54% yield) as a pale-yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (d, J = 8.7 Hz, 2H), 7.43–7.38 (m, 3H), 7.31 (d, J = 8.7 Hz, 2H), 7.29–7.26 (m, 2H), 1.37 (s, 9H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -145.19. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.73 (d, J = 247.3 Hz), 153.24, 134.35, 129.48, 129.07, 128.77 (d, J = 2.0 Hz), 126.56, 124.61 (d, J = 4.1 Hz), 124.57, 119.65 (d, J = 28.2 Hz), 35.02, 31.36. **IR** (ν, cm^{-1}): 2867, 2959, 3060. **HRMS**: $C_{18}H_{18}FN_3$ $[M + Cs]^+$; calculated: 428.0539, found: 428.0539.



4-Fluoro-1-(4-methoxyphenyl)-5-phenyl-1H-1,2,3-triazole (3d):

α-Fluoronitroalkene (80 mg, 0.48 mmol), 1-azido-4-methoxybenzene (140 mg, 0.96 mmol), TFA (18 µL, 0.24 mmol) and toluene (0.4 mL). Reaction time is 48 h. The product was purified by column chromatography (DCM followed by DCM/EtOAc = 9:1 as eluent) affording **3d** (66 mg, 51% yield) as a pale-yellow oil.

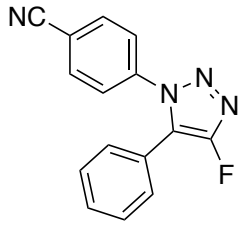
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.37 (m, 3H), 7.31 (d, *J* = 8.9 Hz, 2H), 7.29–7.25 (m, 2H), 6.97 (d, *J* = 8.9 Hz, 2H), 3.87 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -145.13. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.55, 158.63 (d, *J* = 247.2 Hz), 129.89, 129.45, 129.06, 128.67 (d, *J* = 2.2 Hz), 126.56, 124.56 (d, *J* = 4.2 Hz), 119.7 (d, *J* = 28.2 Hz), 114.74, 55.72. **IR**(ν, cm^{-1}): 2850, 2921, 3057. **HRMS**: $C_{15}H_{12}FN_3O$ $[M + Cs]^+$; calculated: 402.0019, found: 402.0018.



1-(4-(*tert*-Butyl)benzyl)-4-fluoro-5-phenyl-1H-1,2,3-triazole (3e):

α-Fluoronitroalkene (100 mg, 0.60 mmol), 1-azido-4-fluorobenzene (164 mg, 1.20 mmol), TFA (23 µL, 0.30 mmol) and toluene (0.4 mL). Reaction time is 48 h. The product was purified by column chromatography (DCM as eluent) affording **3e** (73 mg, 47% yield) as a pale yellow oil.

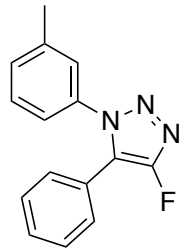
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.39 (m, 3H), 7.37 (t, 2H), 7.25–7.21 (m, 2H), 7.15 (t, 2H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -110.69, -144.91. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.09 (d, *J* = 250.9 Hz), 158.71 (d, *J* = 247.9 Hz), 132.99 (d, *J* = 3.3 Hz), 129.76, 129.23, 128.75 (d, *J* = 2.1 Hz), 127.08 (d, *J* = 8.9 Hz), 124.20 (d, *J* = 4.1 Hz), 119.90 (d, *J* = 28.3 Hz), 116.78 (d, *J* = 23.3 Hz). **IR** (ν, cm^{-1}): 2852, 2920, 3020, 3060. **HRMS**: $C_{14}H_9F_2N_3$ $[M + H]^+$; calculated: 258.0843, found: 258.0849.



3-(4-Fluoro-5-phenyl-1H-1,2,3-triazol-1-yl)benzonitrile (3f):

α-Fluoronitroalkene (50 mg, 0.30 mmol), 1-azido-4-cyanobenzene (86 mg, 0.60 mmol), TFA (12 µL, 0.15 mmol) and toluene (0.4 mL). Reaction time is 48 h. The product was purified by column chromatography (DCM followed by DCM/EtOAc = 9:1 as eluent) affording **3f** (29 mg, 38% yield) as an off-white oil.

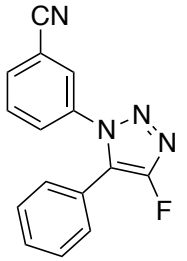
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.6 Hz, 2H), 7.54 (d, *J* = 8.7 Hz, 2H), 7.48–7.39 (m, 3H), 7.26–7.23 (m, 2H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -144.45. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.92 (d, *J* = 249.1 Hz), 139.97, 133.64, 130.26, 129.51, 128.92 (d, *J* = 1.8 Hz), 125.22, 123.74 (d, *J* = 4.0 Hz), 119.98 (d, *J* = 28.9 Hz), 117.59, 113.70. **IR** (ν, cm^{-1}): 2358, 2852, 2922. **HRMS**: $C_{15}H_9FN_4$ $[M + H]^+$; calculated: 265.0890, found: 265.0922.



4-Fluoro-5-phenyl-1-(m-tolyl)-1H-1,2,3-triazole (3g):

α-Fluoronitroalkene (80 mg, 0.48 mmol), 1-azido-3-methylbenzene (130 mg, 0.96 mmol), TFA (18 µL, 0.24 mmol) and toluene (0.4 mL). Reaction time is 48 h. The product was purified by column chromatography (DCM as eluent) affording **3g** (82 mg, 68% yield) as an off-white solid. **m.p.** 94-95 °C.

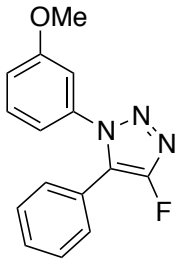
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.36 (m, 3H), 7.33–7.29 (m, 2H), 7.28–7.24 (m, 3H), 7.08 (d, *J* = 7.0 Hz, 1H), 2.38 (s, 3H). **^{19}F NMR** (471 MHz, $CDCl_3$) δ -145.08. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.71 (d, *J* = 247.4 Hz), 140.02, 136.82, 130.64, 129.51, 129.30, 129.04, 128.69 (d, *J* = 2.2 Hz), 125.69, 124.52 (d, *J* = 4.2 Hz), 122.18, 119.70 (d, *J* = 28.2 Hz), 21.40. **IR** (ν, cm^{-1}): 2342, 2865, 2960, 3057. **HRMS**: $C_{15}H_{12}FN_3$ $[M + Cs]^+$; calculated: 386.0070, found: 386.0083.



3-(4-Fluoro-5-phenyl-1H-1,2,3-triazol-1-yl)benzonitrile (3h):

α-Fluoronitroalkene (80 mg, 0.48 mmol), 1-azido-3-cyanobenzene (140 mg, 0.96 mmol), TFA (18 µL, 0.24 mmol) and toluene (0.4 mL). Reaction time is 48 h. The product was purified by column chromatography (DCM followed by DCM/EtOAc = 9:1 as eluent) affording **3h** (40 mg, 32% yield) as a pale yellow oil.

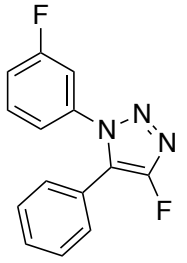
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.76 (m, 1H), 7.72 (d, *J* = 1.9 Hz, 1H), 7.66–7.59 (m, 2H), 7.48–7.40 (m, 3H), 7.27–7.19 (m, 2H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -144.49. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.65 (d, *J* = 248.8 Hz), 137.37, 133.20, 130.71, 130.20, 129.43, 128.98, 128.74 (d, *J* = 1.9 Hz), 128.02, 123.43 (d, *J* = 4.0 Hz), 119.97 (d, *J* = 29.1 Hz), 117.14, 113.94. **IR** (ν, cm^{-1}): 2358, 2852, 2922. **HRMS**: $C_{15}H_9FN_4$ $[M]^-$; calculated: 264.0811, found: 264.0827.



4-Fluoro-1-(3-methoxyphenyl)-5-phenyl-1H-1,2,3-triazole (3i):

α-Fluoronitroalkene (80 mg, 0.48 mmol), 1-azido-3-methoxybenzene (140 mg, 0.96 mmol), TFA (18 µL, 0.24 mmol). The product was purified by column chromatography (DCM followed by DCM/EtOAc = 9:1 as eluent) affording **3i** (61 mg, 47% yield) as an off-white solid. **m.p.** 85–86 °C.

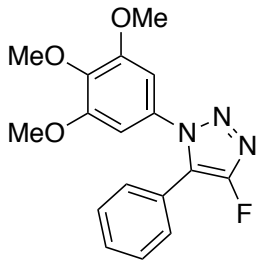
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.36 (m, 3H), 7.32 (t, *J* = 8.1 Hz, 1H), 7.28–7.24 (m, 2H), 7.02–6.98 (m, 1H), 6.95 (t, *J* = 2.3 Hz, 1H), 6.89 (d, *J* = 7.9 Hz, 1H), 3.75 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -145.23. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.33, 158.65 (d, *J* = 247.4 Hz), 137.72, 130.30, 129.56, 129.04, 128.69 (d, *J* = 2.1 Hz), 124.36 (d, *J* = 4.1 Hz), 119.72 (d, *J* = 28.2 Hz), 117.11, 115.87, 110.55, 55.61. **IR** (ν, cm^{-1}): 2345, 2685, 2850, 2921. **HRMS**: $C_{15}H_{12}FN_3O$ $[M]^+$; calculated: 269.0964, found: 269.0994.



4-Fluoro-1-(3-fluorophenyl)-5-phenyl-1H-1,2,3-triazole (3j):

α-Fluoronitroalkene (80 mg, 0.48 mmol), 1-azido-3-cyanobenzene (130 mg, 0.96 mmol), TFA (18 µL, 0.24 mmol). The product was purified by column chromatography (DCM as eluent) affording **3j** (64 mg, 52% yield) as an off-white oil.

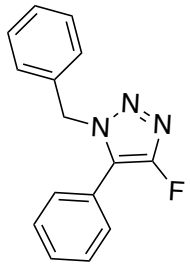
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.37 (m, 5H), 7.24 (d, *J* = 3.6 Hz, 1H), 7.19–7.13 (m, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -110.11, -145.01. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.75 (d, *J* = 249.5 Hz), 158.76 (d, *J* = 248.0 Hz), 137.99 (d, *J* = 9.9 Hz), 131.00 (d, *J* = 8.9 Hz), 129.89, 129.26, 128.81 (d, *J* = 1.9 Hz), 124.07 (d, *J* = 4.1 Hz), 120.71 (d, *J* = 3.5 Hz), 119.89 (d, *J* = 28.8 Hz), 116.98 (d, *J* = 21.0 Hz), 112.75 (d, *J* = 25.2 Hz). **IR** (ν, cm^{-1}): 2836, 2939, 2956, 3001, 3059. **HRMS**: $C_{14}H_9F_2N_3$ $[M + H]^+$; calculated: 258.08372, found: 258.0843.



4-Fluoro-5-phenyl-1-(3,4,5-trimethoxyphenyl)-1H-1,2,3-triazole (3k):

α-Fluoronitroalkene (80 mg, 0.48 mmol), 1-azido-3-cyanobenzene (200 mg, 0.96 mmol), TFA (18 µL, 0.24 mmol). The product was purified by column chromatography (DCM as eluent) affording **3k** (87 mg, 55% yield) as an off-white oil.

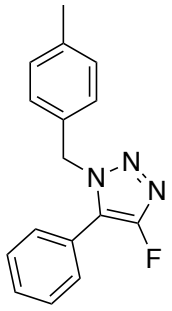
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.37 (m, 3H), 7.32–7.23 (m, 2H), 6.58 (s, 2H), 3.88 (s, 3H), 3.71 (s, 6H). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -144.88. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.61 (d, *J* = 247.7 Hz), 153.64, 138.92, 132.26, 129.63, 129.06, 128.77 (d, *J* = 2.1 Hz), 124.44 (d, *J* = 4.2 Hz), 119.68 (d, *J* = 28.5 Hz), 102.52, 61.13, 56.31. **IR** (ν, cm^{-1}): 2336, 2830, 2934. **HRMS**:$C_{17}H_{16}FN_3O_3$ $[M + Cs]^+$; calculated: 462.0230, found: 462.0223.



1-Benzyl-4-fluoro-5-phenyl-1H-1,2,3-triazole (3l):

α-Fluoronitroalkene (100 mg, 0.6 mmol), benzyl azide(159 mg, 1.20 mmol), TFA (23 µL, 0.3 mmol) and toluene (0.4 mL). The product was purified by column chromatography (DCM as eluent) affording **3l** (80 mg, 53% yield) as an off-white oil.

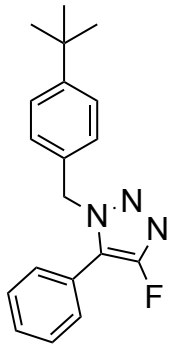
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, J = 5.1, 2.0 Hz, 3H), 7.32–7.21 (m, 5H), 7.14–6.93 (m, 2H), 5.49 (s, 2H). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -145.68. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.56 (d, J = 246.1 Hz), 134.76, 129.92, 129.23, 129.05 (d, J = 1.8 Hz), 129.01, 128.53, 127.27, 124.34 (d, J = 3.9 Hz), 120.07 (d, J = 29.7 Hz), 53.52. **IR** (ν, cm^{-1}): 2850, 2921. **HRMS**: $C_{15}H_{12}FN_3$ $[M]^+$; calculated: 254.1108, found: 254.1093.



4-Fluoro-1-(4-methylbenzyl)-5-phenyl-1H-1,2,3-triazole (3m):

α-Fluoronitroalkene (80 mg, 0.48 mmol), 1-(azidomethyl)-4-methylbenzene (140 mg, 0.96 mmol), TFA (18 µL, 0.24 mmol) and toluene (0.4 mL). The product was purified by column chromatography (DCM as eluent) affording **3m** (81 mg, 63% yield) as a colorless oil.

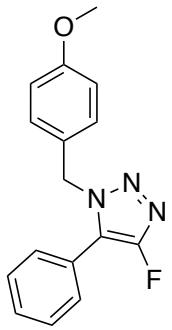
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.40 (m, 3H), 7.31–7.24 (m, 2H), 7.09 (d, *J* = 7.8 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 5.44 (s, 2H), 2.31 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -145.86. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.62 (d, *J* = 246.4 Hz), 138.42, 131.81, 129.90, 129.70, 129.24, 129.14 (d, *J* = 1.6 Hz), 127.31, 124.52 (d, *J* = 3.8 Hz), 119.99 (d, *J* = 29.8 Hz), 53.39, 21.24. **IR** (ν, cm^{-1}): 2836, 2939, 2956, 3001. **HRMS**: $C_{16}H_{14}FN_3$ [M + Cs]+; calculated: 400.0225, found: 400.0226.



1-(4-(tert-butyl)benzyl)-4-fluoro-5-phenyl-1H-1,2,3-triazole (3n):

α-Fluoronitroalkene (80 mg, 0.48 mmol), 1-(azidomethyl)-4-(tert-butyl)benzene (180 mg, 0.96 mmol), TFA (18 μL, 0.24 mmol). The product was purified by column chromatography (DCM as eluent) affording **3n** (74 mg, 50% yield) as a pale yellow oil.

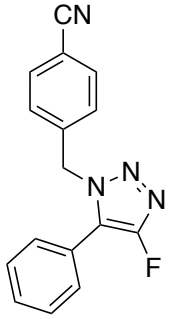
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (t, *J* = 3.3 Hz, 3H), 7.30 (td, *J* = 7.9, 7.5, 2.8 Hz, 4H), 7.11–6.97 (m, 2H), 5.46 (s, 2H), 1.29 (d, *J* = 1.5 Hz, 9H). **^{19}F NMR** (471 MHz, $CDCl_3$) δ -145.85. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.44 (d, *J* = 245.9 Hz), 151.50, 131.69, 129.77, 129.12, 129.02 (d, *J* = 1.5 Hz), 127.09, 125.80, 124.34, 119.91 (d, *J* = 29.7 Hz), 53.09, 34.54, 31.22. **IR** (ν, cm^{-1}): 2342, 2865, 2960, 3057. **HRMS**: $C_{19}H_{20}FN_3$ [M + H]+ ; calculated: 310.1719, found: 310.1692.



4-Fluoro-1-(4-methoxybenzyl)-5-phenyl-1H-1,2,3-triazole (3o):

α-Fluoronitroalkene (80 mg, 0.48 mmol), 1-(azidomethyl)-4-methoxybenzene (160 mg, 0.96 mmol), TFA (18 µL, 0.24 mmol). The product was purified by column chromatography (DCM as eluent) affording **3o** (69 mg, 51% yield) as a pale yelow oil.

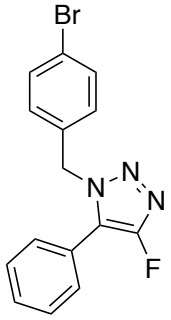
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.44 (m, 3H), 7.30–7.23 (m, 2H), 7.02 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 5.43 (s, 2H), 3.77 (s, 3H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -145.80; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.74, 158.61 (d, J = 246.2 Hz), 129.91, 129.24, 129.18 (d, J = 1.5 Hz), 128.89, 126.76, 124.50 (d, J = 4.0 Hz), 119.88 (d, J = 29.8 Hz), 114.35, 55.40, 53.16. **IR** (ν, cm^{-1}): 2922, 2852, 2358. **HRMS**: $C_{16}H_{14}FN_3O$ $[M + Cs]^+$; calculated: 416.0175, found: 416.0171.



4-((4-Fluoro-5-phenyl-1H-1,2,3-triazol-1-yl)methyl)benzonitrile (3p):

α-Fluoronitroalkene (80 mg, 0.48 mmol), 4-(azidomethyl)benzonitrile (150 mg, 0.96 mmol), TFA (18 µL, 0.24 mmol) and toluene (0.4 mL). The product was purified by column chromatography (DCM as eluent) affording **3p** (68 mg, 51% yield) as a pale yellow oil.

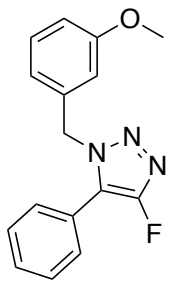
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.4 Hz, 2H), 7.49–7.44 (m, 3H), 7.25–7.22 (m, 2H), 7.19 (d, *J* = 8.0 Hz, 2H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -145.08. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.61 (d, *J* = 247.2 Hz), 139.74, 132.90, 130.33, 129.51, 128.95 (d, *J* = 1.5 Hz), 128.04, 123.94 (d, *J* = 3.8 Hz), 120.33 (d, *J* = 29.6 Hz), 118.22, 112.79, 52.91. **IR** (ν, cm^{-1}): 2336, 2830, 2934. **HRMS**: $C_{16}H_{11}FN_4$ $[M + Cs]^+$; calculated: 411.0020, found: 411.0022.



1-(4-Bromobenzyl)-4-fluoro-5-phenyl-1H-1,2,3-triazole (3q):

α-Fluoronitroalkene (80 mg, 0.48 mmol), 1-(azidomethyl)-4-bromobenzene (200 mg, 0.96 mmol), TFA (18 μL, 0.24 mmol) and toluene (0.4 mL).The product was purified by column chromatography (DCM as eluent) affording **3q** (92 mg, 58% yield) as a pale yellow oil.

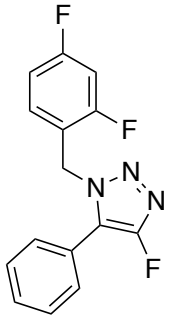
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.46 (m, 3H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.28–7.24 (m, 2H), 6.97 (d, *J* = 8.5 Hz, 2H), 5.46 (s, 2H). **^{19}F NMR** (471 MHz, $CDCl_3$) δ -145.22. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.59 (d, *J* = 246.7 Hz), 133.71, 132.22, 130.10, 129.36, 129.06, 129.04, 124.21 (d, *J* = 3.9 Hz), 122.76, 120.09 (d, *J* = 29.8 Hz), 52.90. **IR** (ν, cm^{-1}): 2854, 2922, 2951. **HRMS**: $C_{15}H_{11}BrFN_3$ $[M + H]^+$; calculated: 332.0023, found: 332.0018.



4-Fluoro-1-(3-methoxybenzyl)-5-phenyl-1H-1,2,3-triazole (3r):

α-Fluoronitroalkene (80 mg, 0.48 mmol), 1-(azidomethyl)-3-methoxybenzene (160 mg, 0.96 mmol), TFA (18 µL, 0.24 mmol).The product was purified by column chromatography (DCM as eluent) affording **3r** (69 mg, 51% yield) as a pale yellow oil.

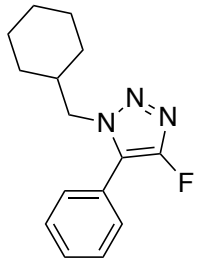
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.40 (m, 3H), 7.31–7.25 (m, 2H), 7.20 (t, *J* = 7.9 Hz, 1H), 6.82 (dd, *J* = 8.2, 2.6 Hz, 1H), 6.68–6.57 (m, 2H), 5.46 (s, 2H), 3.72 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -145.73. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.12, 158.59 (d, *J* = 246.3 Hz), 136.29, 130.13, 129.94, 129.26, 129.11 (d, *J* = 1.7 Hz), 124.43 (d, *J* = 4.0 Hz), 120.10 (d, *J* = 29.7 Hz), 119.50, 114.22, 112.77, 55.36, 53.48. **IR** (ν, cm^{-1}): 2830, 2908., 2934. **HRMS**:$C_{16}H_{14}FN_3O$ [M + Cs]$^{+}$; calculated: 416.0175, found: 416.0160.



1-(2,4-Difluorobenzyl)-4-fluoro-5-phenyl-1H-1,2,3-triazole (3s):

α-Fluoronitroalkene (80 mg, 0.48 mmol), 1-(azidomethyl)-2,4-difluorobenzene (160 mg, 0.96 mmol), TFA (18 µL, 0.24 mmol).The product was purified by column chromatography (DCM as eluent) affording **3s** (70 mg, 51% yield) as a colorless oil.

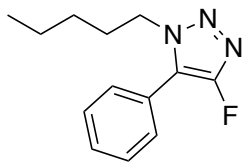
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.46 (m, 3H), 7.31 (dd, *J* = 6.5, 3.0 Hz, 1H), 7.13–7.00 (m, 1H), 6.90–6.73 (m, 2H), 5.53 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.03, -113.95, -145.56. **^{13}C NMR** (101 MHz, CDCl3) δ 163.14 (dd, *J* = 251.0, 11.9 Hz), 160.09 (dd, *J* = 250.8, 12.1 Hz), 158.52(d, *J* = 246.6 Hz), 130.67 (dd, *J* = 9.9, 4.8 Hz), 130.12, 129.38, 128.93 (d, *J* = 1.5 Hz), 124.05 (d, *J* = 4.0 Hz), 120.21 (d, *J* = 29.8 Hz), 117.90 (dd, *J* = 14.4, 3.9 Hz), 112.11 (dd, *J* = 21.5, 3.8 Hz), 104.24 (t, *J* = 25.3 Hz), 46.57 (d, *J* = 4.2 Hz). **IR** (ν, cm^{-1}): 2850, 2921. **HRMS**: $C_{15}H_{10}F_3N_3$ $[M]^-$; calculated: 289.0779, found: 289.0755.



1-(Cyclohexylmethyl)-4-fluoro-5-phenyl-1H-1,2,3-triazole (3t):

α-Fluoronitroalkene (80 mg, 0.48 mmol), (azidomethyl)cyclohexane (130 mg, 0.96 mmol), TFA (18 µL, 0.24 mmol). The product was purified by column chromatography (DCM as eluent) affording **3t** (65 mg, 52% yield) as a colorless oil.

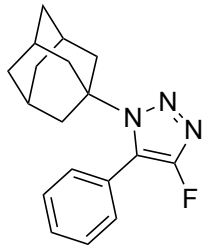
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.49 (m, 3H), 7.40–7.38 (m, 2H), 4.14 (d, *J* = 7.3 Hz, 2H), 1.90–1.73 (m, 1H), 1.64 (tdd, *J* = 12.5, 10.6, 8.4, 4.9 Hz, 3H), 1.56–1.51 (m, 2H), 1.19–1.07 (m, 3H), 0.92–0.82 (m, 2H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -146.73. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.50 (d, *J* = 245.5 Hz), 129.80, 129.38, 129.07 (d, *J* = 1.5 Hz), 124.90 (d, *J* = 4.0 Hz), 120.03 (d, *J* = 29.6 Hz), 55.76, 38.22, 30.49, 26.10, 25.52. **IR** (ν, cm^{-1}): 2358, 2852, 2922. **HRMS**: $C_{15}H_{18}FN_3$ $[M]^+$; calculated: 260.1563, found: 260.1577.



4-Fluoro-1-pentyl-5-phenyl-1H-1,2,3-triazole (3u):

α-Fluoronitroalkene (80 mg, 0.48 mmol), 1-azidopentane (110 mg, 0.96 mmol), TFA (18 μL, 0.24 mmol).The product was purified by column chromatography (DCM as eluent) affording **3u** (55 mg, 49% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.50 (m, 3H), 7.43–7.40 (m, 2H), 4.34–4.30 (m, 2H), 1.83 (t, *J* = 6.3 Hz, 2H), 1.27–1.24 (m, 4H), 0.85 (d, *J* = 5.2 Hz, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -146.54. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.52 (d, *J* = 245.7 Hz), 129.82, 129.39, 128.89 (d, *J* = 1.6 Hz), 124.79 (d, *J* = 4.0 Hz), 119.59 (d, *J* = 29.9 Hz), 49.95, 29.40, 28.53, 22.05, 13.83. **IR**(ν, cm^{-1}): 2358, 2852, 2922. **HRMS** $C_{13}H_{16}FN_3$ $[M]^+$; calculated: 234.1407, found: 234.1385.

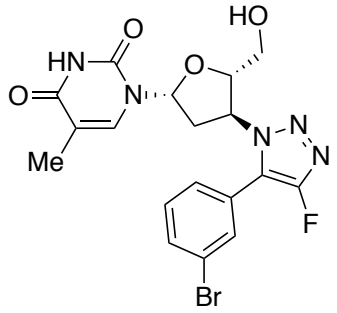


1-((3s,5s,7s)-adamantan-1-yl)-4-fluoro-5-phenyl-1H-1,2,3-triazole (3v):

α-Fluoronitroalkene (80 mg, 0.48 mmol), (3s,5s,7s)-1-azidoadamantane (250 mg, 0.96 mmol), TFA (18 μL, 0.24 mmol). The product was purified by column chromatography (DCM as eluent) affording **3v** (75 mg, 49% yield) as an off-white solid. **m.p.** 132–133 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 –7.45 (m, 3H), 7.38–7.33 (m, 2H), 2.23–2.17 (m, 5H), 2.13 (t, *J* = 3.2 Hz, 3H), 1.72–1.65 (m, 4H), 1.63–1.58 (m, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -146.62. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.85 (d, *J* = 245.2 Hz), 131.20, 130.00, 128.70, 127.08 (d, *J* =

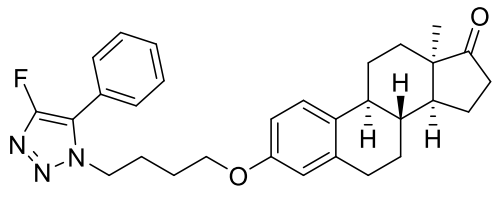
3.6 Hz), 119.31 (d, J = 31.6 Hz), 64.60, 42.56, 35.81, 29.67. **IR** (ν, cm^{-1}) 2342, 2678, 2899. **HRMS**: $C_{18}H_{20}FN_3$ $[M + Cs]^+$; calculated: 430.0695, found: 430.0678.



1-((2R,4S,5S)-4-(5-(3-Bromophenyl)-4-fluoro-1H-1,2,3-triazol-1-yl)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (3x):

(*Z*)-1-Bromo-3-(2-fluoro-2-nitrovinyl)benzene (138 mg, 0.56 mmol), 1-((2R,4S,5S)-4-azido-5-(hydroxymethyl) tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (100 mg, 0.37 mmol), TFA (14.4 µL, 0.187 mmol) and toluene (0.4 mL). The product was purified by column chromatography (EtOAc as eluent) affording **3x** (43 mg, 25% yield) as a white solid. **m.p.** 124–126 °C.

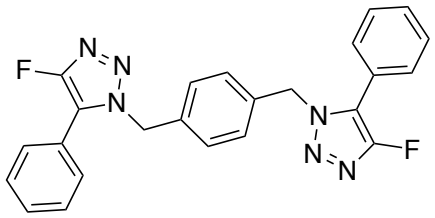
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.68 – 7.63 (m, 1H), 7.57 (t, J = 1.8 Hz, 1H), 7.43 (t, J = 7.9 Hz, 1H), 7.37 – 7.32 (m, 1H), 7.27 (d, J = 1.4 Hz, 1H), 6.20 (t, J = 6.9 Hz, 1H), 5.35 – 5.28 (m, 1H), 4.58 (dt, J = 4.1, 2.0 Hz, 1H), 3.94 (dd, J = 12.5, 2.4 Hz, 1H), 3.58 (dd, J = 12.5, 2.4 Hz, 1H), 3.08 – 2.97 (m, 1H), 2.89 – 2.77 (m, 1H), 1.91 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -145.54. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.22, 158.57 (d, J = 248.4 Hz), 150.71, 138.33, 136.98, 133.49, 132.15, 131.18, 127.91, 123.59, 119.26 (d, J = 29.7 Hz), 111.43, 89.75, 85.22, 61.94 (d, J = 6.6 Hz), 60.09, 37.45, 12.57. **IR**(ν, cm^{-1}): 2852, 2923, 3061, 3384. **HRMS**: $C_{18}H_{18}FN_5O_4$ $[M]^+$; calculated: 388.1421, found: 388.1397.



(8R,9S,13R,14S)-3-(4-(4-fluoro-5-phenyl-1H-1,2,3-triazol-1-yl)butoxy)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one (3y):

α-Fluoronitroalkene (60 mg, 0.36 mmol), (13S)-3-(4-azidobutoxy)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one (180 mg, 0.50 mmol), TFA (14 μL, 0.18 mmol).The product was purified by column chromatography (DCM:EtOAc = 9:1 as eluent) affording **3y** (92 mg, 53% yield) as a yellow oil.

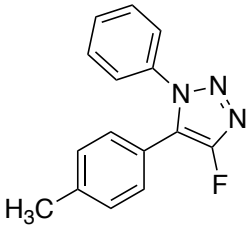
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.38 (m, 3H), 7.33 (dd, *J* = 7.4, 2.2 Hz, 2H), 7.13–7.03 (m, 1H), 6.54 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.47 (d, *J* = 2.7 Hz, 1H), 4.34 (t, *J* = 7.3 Hz, 2H), 3.80 (t, *J* = 6.0 Hz, 2H), 2.89–2.65 (m, 2H), 2.42 (dd, *J* = 19.0, 8.7 Hz, 1H), 2.31 (dt, *J* = 9.0, 3.1 Hz, 1H), 2.21–2.13 (m, 1H), 2.06 (dt, *J* = 18.9, 8.8 Hz, 1H), 2.01–1.91 (m, 4H), 1.87 (dd, *J* = 9.1, 2.6 Hz, 1H), 1.67 (dt, *J* = 8.7, 6.1 Hz, 2H), 1.60–1.48 (m, 2H), 1.47–1.36 (m, 4H), 0.83 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -145.75. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 221.09, 158.52 (d, *J* = 246.0 Hz), 156.77, 137.89, 132.34, 129.89, 129.46, 128.89, 126.45, 124.61 (d, *J* = 4.1 Hz), 119.70 (d, *J* = 29.7 Hz), 114.56, 112.14, 66.75, 50.50, 49.61, 48.12, 44.07, 38.46, 35.98, 31.68, 29.74, 26.63, 26.59, 26.18, 26.03, 21.69, 13.96. **IR** (ν, cm^{-1}): 2090, 2330, 2858, 2925, 3052. **HRMS**: $C_{30}H_{34}FN_3O_2$ $[M+H]^+$; calculated: 488.2707, found: 488.2701.



1,4-Bis((4-fluoro-5-phenyl-1H-1,2,3-triazol-1-yl)methyl)benzene (3z):

α-Fluoronitroalkene (231 mg, 1.38 mmol), 1,4-bis(azidomethyl)benzene (130 mg, 0.69 mmol), TFA (26.6 µL, 0.345 mmol). The product was purified by column chromatography (DCM as eluent) affording **3z** (96 mg, 32% yield) as an off-white oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.42 (m, 6H), 7.26–7.21 (m, 4H), 7.03 (s, 4H), 5.49 (s, 4H). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -145.42. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.56 (d, J = 246.5 Hz), 135.14, 130.08, 129.33, 128.98 (d, J = 1.5 Hz), 127.91, 124.19 (d, J = 3.9 Hz), 120.11 (d, J = 29.6 Hz), 53.03. **IR** (ν, cm^{-1}): 2856, 2924, 3055. **HRMS**: $C_{24}H_{18}F_2N_6$ $[M]^-$; calculated: 268.0858, found: 268.0886.

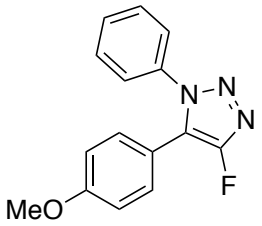


4-Fluoro-1-phenyl-5-(p-tolyl)-1H-1,2,3-triazole (4a):

(*Z*)-1-(2-Fluoro-2-nitrovinyl)-4-methylbenzene (100 mg, 0.55 mmol), azidobenzene (132 mg, 1.10 mmol), TFA (21.3 µL, 0.28 mmol).The product was purified by column chromatography (DCM as eluent) affording **4a** (75 mg, 54% yield) as a cololess solid. **m.p.** 94-96 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 7.1 Hz, 3H), 7.37 (d, J = 5.7 Hz, 2H), 7.21–7.08 (m, 4H), 2.36 (s, 3H). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -145.38. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.59

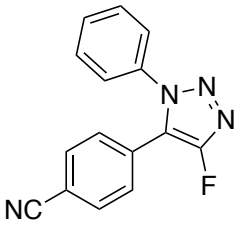
(d, J = 247.2 Hz), 139.79, 136.89, 129.79, 129.59, 128.57 (d, J = 2.0 Hz), 125.12, 125.06, 121.35 (d, J = 4.1 Hz), 119.85 (d, J = 28.3 Hz), 21.47. **IR** (ν, cm^{-1}): 2923, 3016, 3367. **HRMS**: $C_{15}H_{12}FN_3$ $[M + Cs]^+$; calculated: 386.0070, found: 386.0051.



4-Fluoro-5-(4-methoxyphenyl)-1-phenyl-1H-1,2,3-triazole (4b):

(*Z*)-1-(2-Fluoro-2-nitrovinyl)-4-methoxybenzene (70 mg, 0.36 mmol), azidobenzene (85 mg, 0.71 mmol), TFA (14 μL, 0.36 mmol).The product was purified by column chromatography (DCM as eluent) affording **4b** (70 mg, 73% yield) as an off white solid. **m.p.** 76–78 °C.

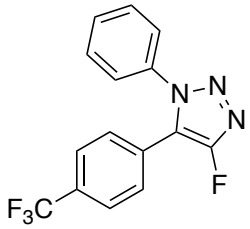
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.45 (m, 3H), 7.44–7.36 (m, 2H), 7.16 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -145.82. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.39, 158.35 (d, J = 246.2 Hz), 136.84, 130.07 (d, J = 2.0 Hz), 129.72, 129.54, 125.00, 119.66 (d, J = 28.6 Hz), 116.34 (d, J = 4.2 Hz), 114.54, 55.35. **IR** (ν, cm^{-1}): 2923, 3016, 3367. **HRMS**: $C_{15}H_{12}FN_3O$ $[M + Cs]^+$; calculated: 561.0620, found: 561.0615.



4-(4-Fluoro-1-phenyl-1*H*-1,2,3-triazol-5-yl)benzonitrile (4c):

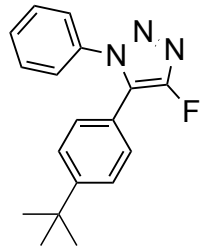
(*Z*)-4-(2-fluoro-2-nitrovinyl)benzonitrile (45 mg, 0.23 mmol), azidobenzene (56 mg, 0.47 mmol), TFA (9 μL, 0.12 mmol). The product was purified by column chromatography (DCM as eluent) affording **4c** (27 mg, 44% yield) as an off-white solid. **m.p.** 125–127 °C.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.65 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 10.3 Hz, 3H), 7.35 (d, *J* = 8.4 Hz, 4H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -142.81. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.00 (d, *J* = 250.2 Hz), 136.36, 132.79, 130.48, 129.99, 129.02, 128.87 (d, *J* = 4.5 Hz), 125.15, 118.05 (d, *J* = 27.6 Hz), 117.94, 113.26. **IR** (ν, cm^{-1}): 2341, 2679, 2899. **HRMS:** $C_{15}H_9FN_4$ [M]+; calculated: 264.0811, found: 264.0845.



4-Fluoro-1-phenyl-5-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (4d):

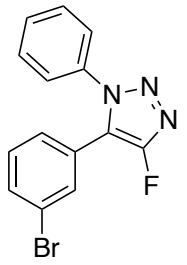
(*Z*)-1-(2-Fluoro-2-nitrovinyl)-4-(trifluoromethyl)benzene (101 mg, 0.425 mmol), azidobenzene (101 mg, 0.85 mmol), TFA (16.4 µL, 0.21 mmol) and toluene (0.4 mL). The product was purified by column chromatography (DCM as eluent) affording **4c** (28 mg, 46% yield) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.57–7.47 (m, 3H), 7.42–7.34 (m, 4H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -63.54, -143.66. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.00 (d, *J* = 249.3 Hz), 136.53, 130.30, 129.91, 128.92 (d, *J* = 2.2 Hz), 126.09 (q, *J* = 3.7 Hz), 125.17, 125.10, 125.04, 122.34, 118.45 (d, *J* = 28.1 Hz). **IR** (ν, cm^{-1}): 2110, 2331, 2850, 2918, 3062. **HRMS:** $C_{15}H_9F_4N_3$ $[M]^-$; calculated: 307.0733, found: 307.0741.



5-(3-(*tert*-Butyl)phenyl)-4-fluoro-1-phenyl-1H-1,2,3-triazole (4e):

(*Z*)-1-(*tert*-Butyl)-4-(2-fluoro-2-nitrovinyl)benzene (50 mg, 0.22 mmol), azidobenzene (53 mg, 0.45 mmol), TFA (8.6 μL, 0.11 mmol).The product was purified by column chromatography (DCM as eluent) affording **4e** (37 mg, 56% yield) as a colorless oil.

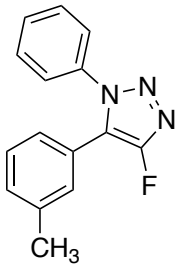
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.45 (m, 3H), 7.43–7.35 (m, 5H), 7.21–7.11 (m, 1H), 1.31 (d, *J* = 1.9 Hz, 9H). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -145.07. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.62 (d, *J* = 247.3 Hz), 152.74, 136.95, 129.72, 129.52, 128.20 (d, *J* = 2.2 Hz), 125.95, 125.10, 121.30 (d, *J* = 4.3 Hz), 119.69 (d, *J* = 28.2 Hz), 34.82, 31.14. **IR** (ν, cm^{-1}): 2958, 3060. **HRMS**: $C_{18}H_{18}FN_3$ $[M + Cs]^+$; calculated: 428.0539, found: 428.0550.



5-(3-Bromophenyl)-4-fluoro-1-phenyl-1*H*-1,2,3-triazole (4f):

(*Z*)-1-Bromo-3-(2-fluoro-2-nitrovinyl)benzene (46 mg, 0.19 mmol), azidobenzene (45 mg, 0.37 mmol), TFA (7.2 μL, 0.09 mmol).The product was purified by column chromatography (DCM as eluent) affording **4f** (27 mg, 45% yield) as a pale yellow oil.

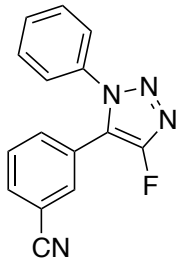
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.47 (m, 5H), 7.40–7.34 (m, 2H), 7.10 (d, *J* = 8.3 Hz, 2H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -144.36.**^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.73 (d, *J* = 248.5 Hz), 136.65, 132.48, 130.15, 130.12, 129.85, 125.14, 124.12, 123.38 (d, *J* = 4.3 Hz), 118.93, 118.74 (d, *J* = 7.5 Hz), 116.09. **IR** (ν, cm^{-1}): 2958, 3060. **HRMS**: $C_{14}H_9BrFN_3$ $[M + Cs]^+$; calculated: 449.9018, found: 449.9011.



4-Fluoro-1-phenyl-5-(m-tolyl)-1H-1,2,3-triazole (4g):

(*Z*)-1-(2-fluoro-2-nitrovinyl)-3-methylbenzene (50 mg, 0.28 mmol), azidobenzene (66 mg, 0.55 mmol), TFA (11 µL, 0.14 mmol).The product was purified by column chromatography (DCM as eluent) affording **4g** (37 mg, 53% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.37 (m, 5H), 7.32–7.16 (m, 2H), 7.11 (s, 1H), 6.99 (d, J = 7.5 Hz, 1H), 2.33 (s, 3H). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -145.20. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.61 (d, J = 247.2 Hz), 138.90, 136.82, 130.31, 129.75, 129.50, 129.23 (d, J = 2.2 Hz), 128.85, 125.78 (d, J = 1.9 Hz), 124.97, 124.18 (d, J = 4.2 Hz), 119.83 (d, J = 28.3 Hz), 21.36. **IR**(ν, cm^{-1}): 2855, 2921, 3064. **HRMS**: $C_{15}H_{12}F_1N_3$ $[M + Cs]^+$; calculated: 386.0070, found: 386.0051.

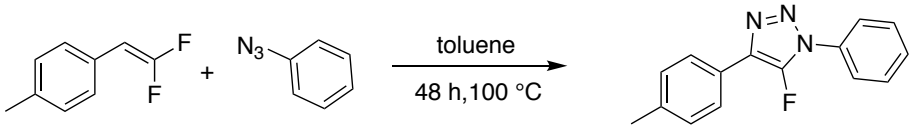


3-(4-Fluoro-1-phenyl-1*H*-1,2,3-triazol-5-yl)benzonitrile (4h):

(*Z*)-3-(2-Fluoro-2-nitrovinyl)benzonitrile (100 mg, 0.52 mmol), azidobenzene (124 mg, 0.55 mmol), TFA (20 µL, 0.26 mmol).The product was purified by column chromatography (DCM as eluent) affording **4h** (75 mg, 55% yield) as a pale yellow oil.

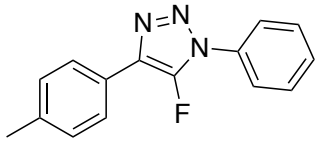
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.47 (m, 4H), 7.44–7.41 (m, 1H), 7.40–7.36 (m, 2H), 7.28–7.21 (m, 1H), 7.15–7.09 (m, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -144.03. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.84 (d, J = 249.5 Hz), 136.14, 132.89, 132.64 (d, J = 2.3 Hz), 131.77 (d, J = 2.2 Hz), 130.50, 130.10, 129.98, 125.88 (d, J = 4.4 Hz), 125.04, 117.68 (d, J = 27.9 Hz), 117.66, 113.61. **IR** (ν, cm^{-1}): 2357, 2922, 3062. **HRMS**: $C_{15}H_9FN_4$ $[M + Cs]^+$; calculated: 396.9866, found: 396.9824.

2. Chapter 2



5 2a 4

To an oven-dry screw-capped reaction tube with a magnetic stir bar, 1-(2,2-difluorovinyl)-4-methylbenzene (50 mg, 1 Equiv., 0.32 mmol) was charged with azidobenzene (77 mg, 2 Equiv., 0.65 mmol) in toluene (0.4 mL). The reaction tube was then flushed with Argon and stirred for at 100 ºC for 48 h to afford 5-fluoro-1-phenyl-4-(p-tolyl)-1H-1,2,3-triazole **4** (11mg, 13%) as a clear oil.

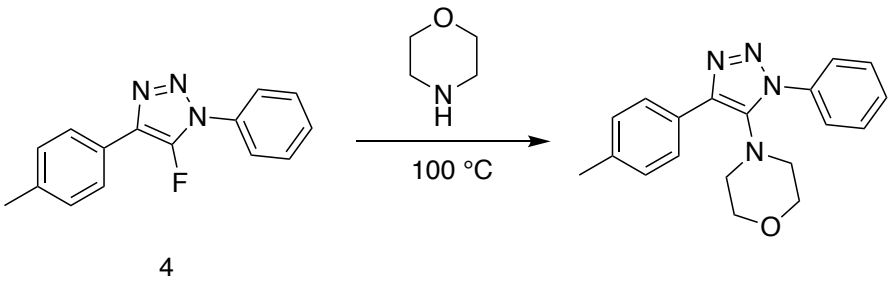


4

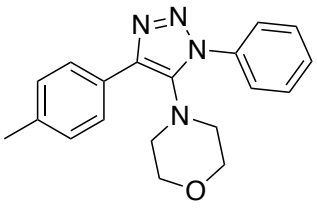
5-fluoro-1-phenyl-4-(p-tolyl)-1H-1,2,3-triazole (4):

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.81 (d, J = 8.1 Hz, 2H), 7.73 (d, J = 7.9 Hz, 2H), 7.57 (d, J = 8.1 Hz, 2H), 7.55–7.46 (m, 1H), 7.30 (d, J = 8.0 Hz, 2H), 2.41 (s, 3H). **^{19}F NMR** (471 MHz, $CDCl_3$) δ -150.85.

Nucleophilic aromatic substitution by morpholine:



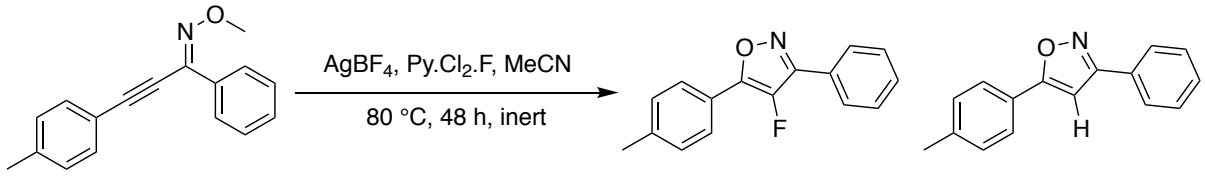
4



4-(1-phenyl-4-(p-tolyl)-1H-1,2,3-triazol-5-yl)morpholine:

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71 – 7.66 (m, 2H), 7.64–7.60 (m, 2H), 7.58–7.50 (m, 3H), 7.31–7.23 (m, 2H), 3.67–3.54 (m, 4H), 2.97–2.82 (m, 4H), 2.41 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.54, 138.45, 138.10, 136.78, 129.48, 129.44, 129.19, 128.55, 128.36, 125.14, 66.99, 50.58, 21.46.

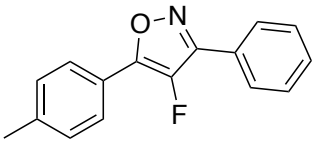
3. Chapter 3



6 7 8

To an oven-dry screw-capped reaction tube with a magnetic stir bar was charged with (*Z*)-1-phenyl-3-(p-tolyl)prop-2-yn-1-one *O*-methyl oxime (1 Eq, 30 mg, 0.12 mmol) and 2,6-dichloro-

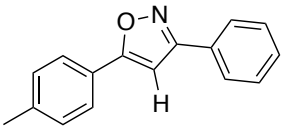
1-fluoropyridin-1-ium tetrafluoroborate (2 Eq, 61 mg, 0.24 mmol). The reaction vial was then degassed and gassed with Argon three times. The vial was taken to the glove box for the addition of (tetrafluoro-l5-boraneyl)silver (4.7 mg, 0.2 Eq, 24 μmol) followed by the addition of MeCN (0.4 M, 0.7 mL) via syringe reaction. Then, the reaction mixture was then stirred at 80 °C for 48 h affording **7** (3.4 mg, 11%) and **8** (1.7 mg, 6%).



7

4-fluoro-3-phenyl-5-(p-tolyl)isoxazole (7):

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.97–7.91 (m, 1H), 7.79–7.74 (m, 2H), 7.54–7.46 (m, 2H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.31 (s, 1H), 2.43 (s, 3H). **^{19}F NMR** (471 MHz, $CDCl_3$) δ -178.22.



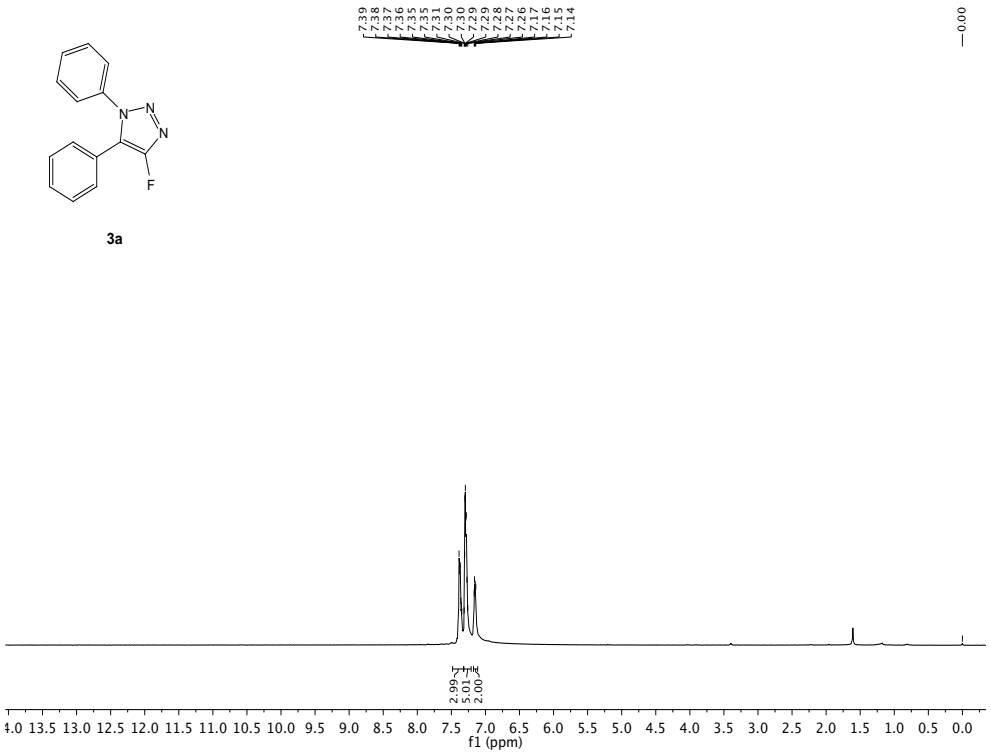
8

3-phenyl-5-(p-tolyl)isoxazole (8):

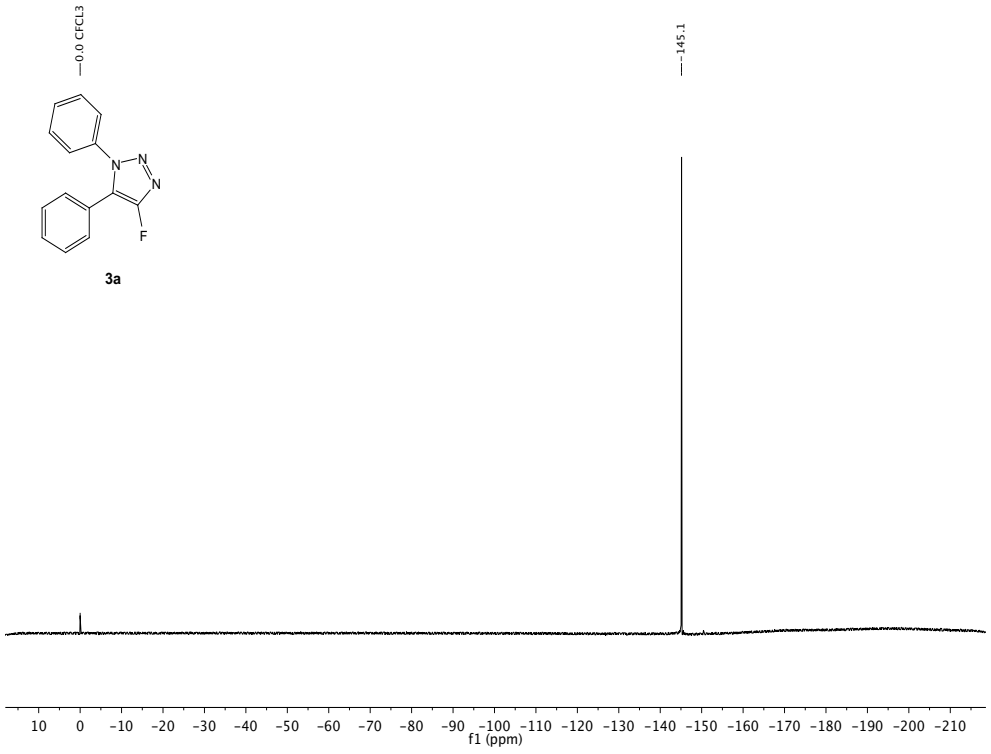
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.91–7.85 (m, 2H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.52–7.44 (m, 3H), 7.30 (d, *J* = 7.9 Hz, 2H), 6.78 (s, 1H), 2.42 (s, 3H).

4. NMR Spectra

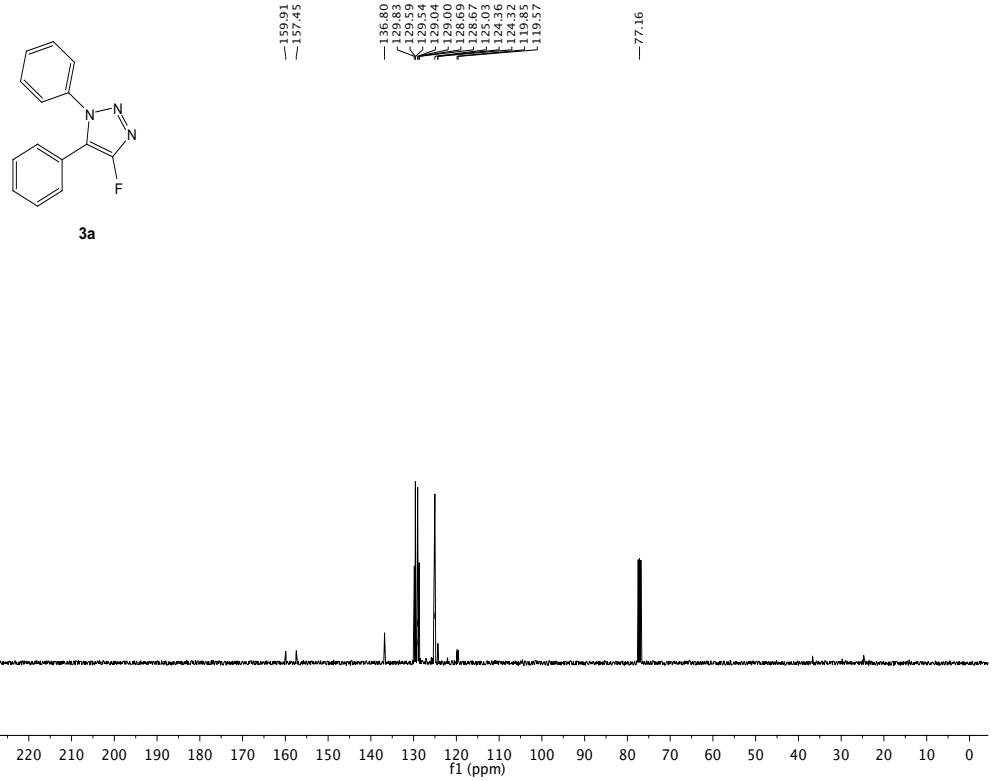
^{1}H NMR of **3a**



^{19}F NMR of **3a**

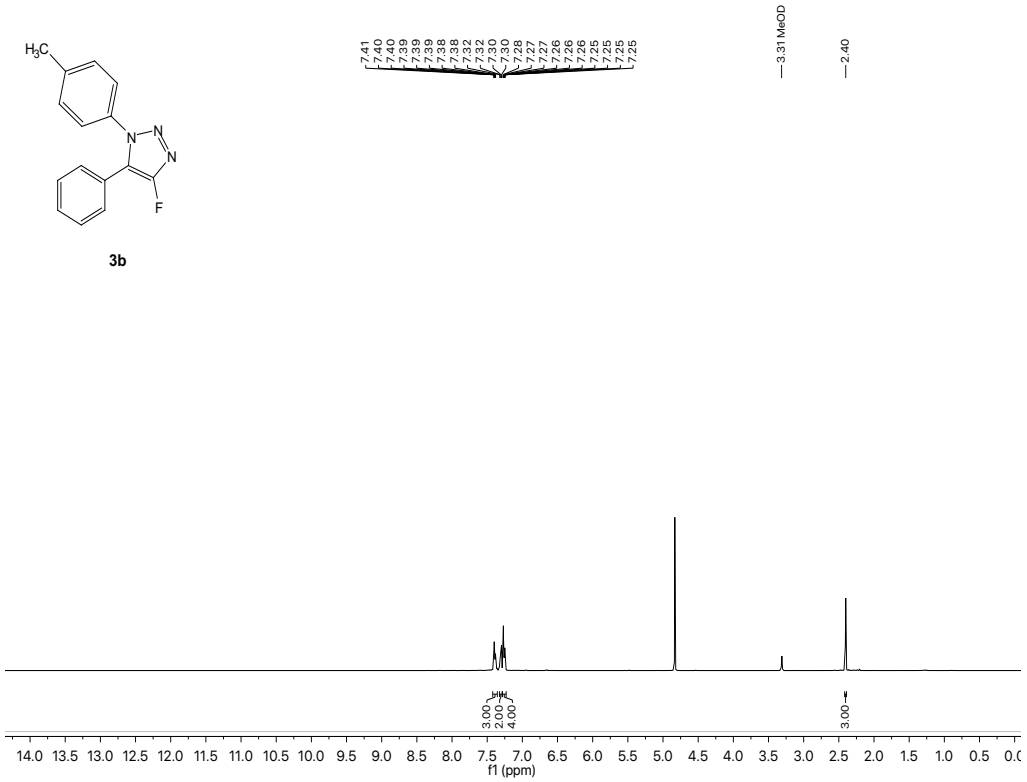


^{13}C NMR of **3a**



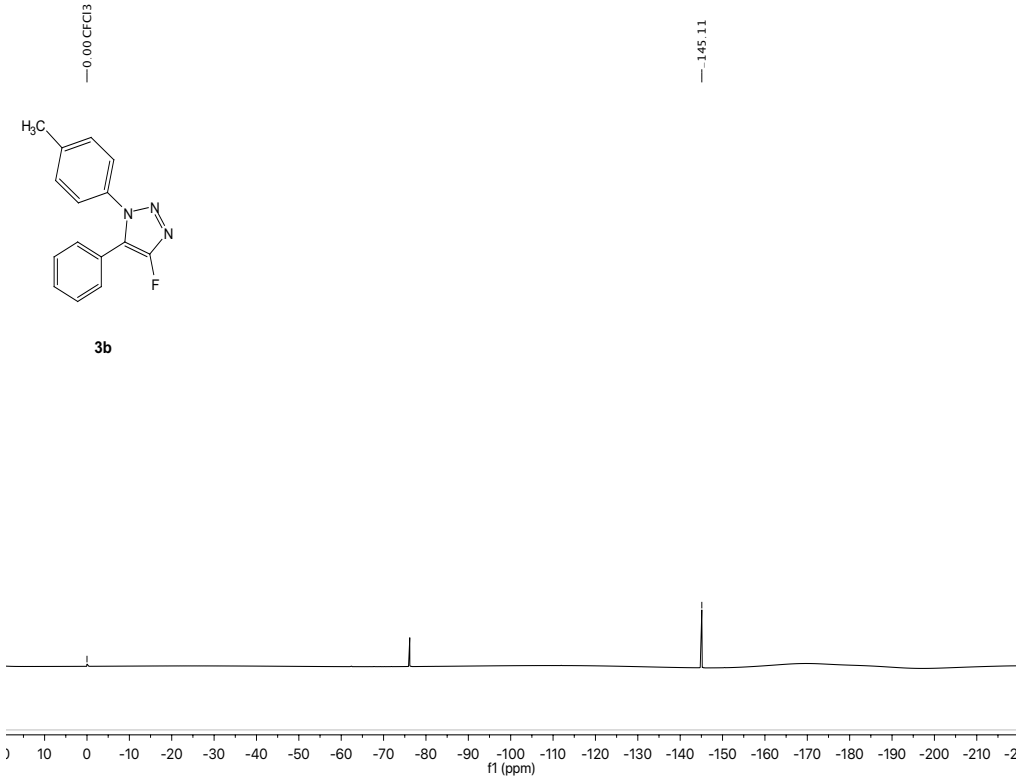
3a

^{1}H NMR of **3b**

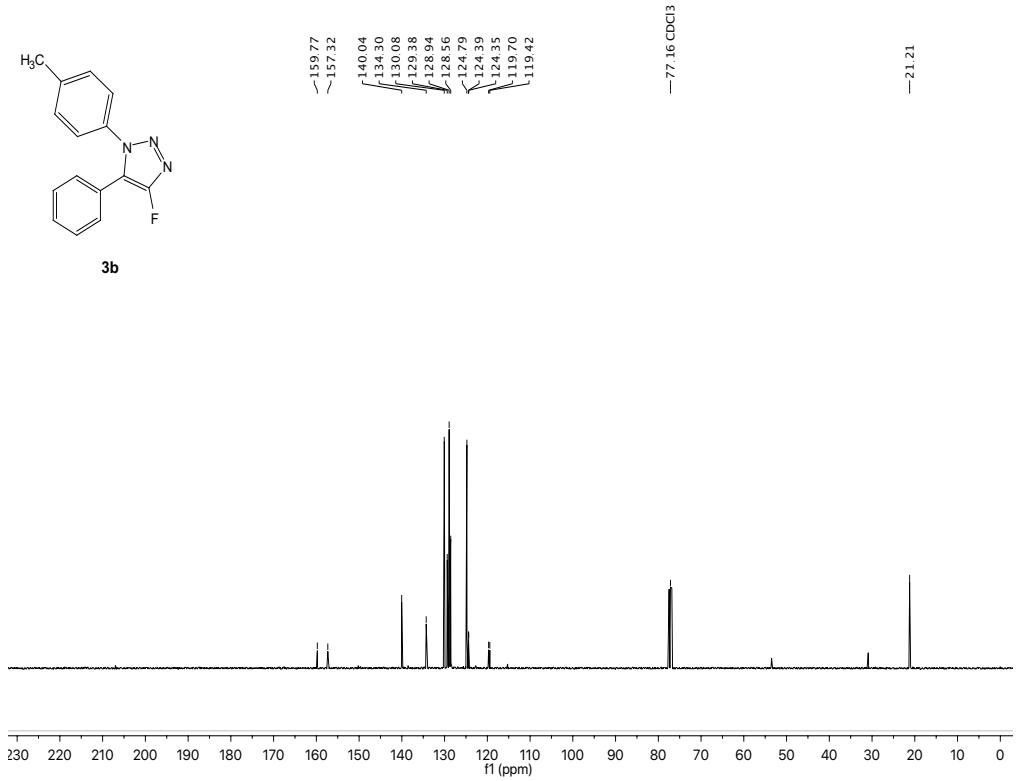


3b

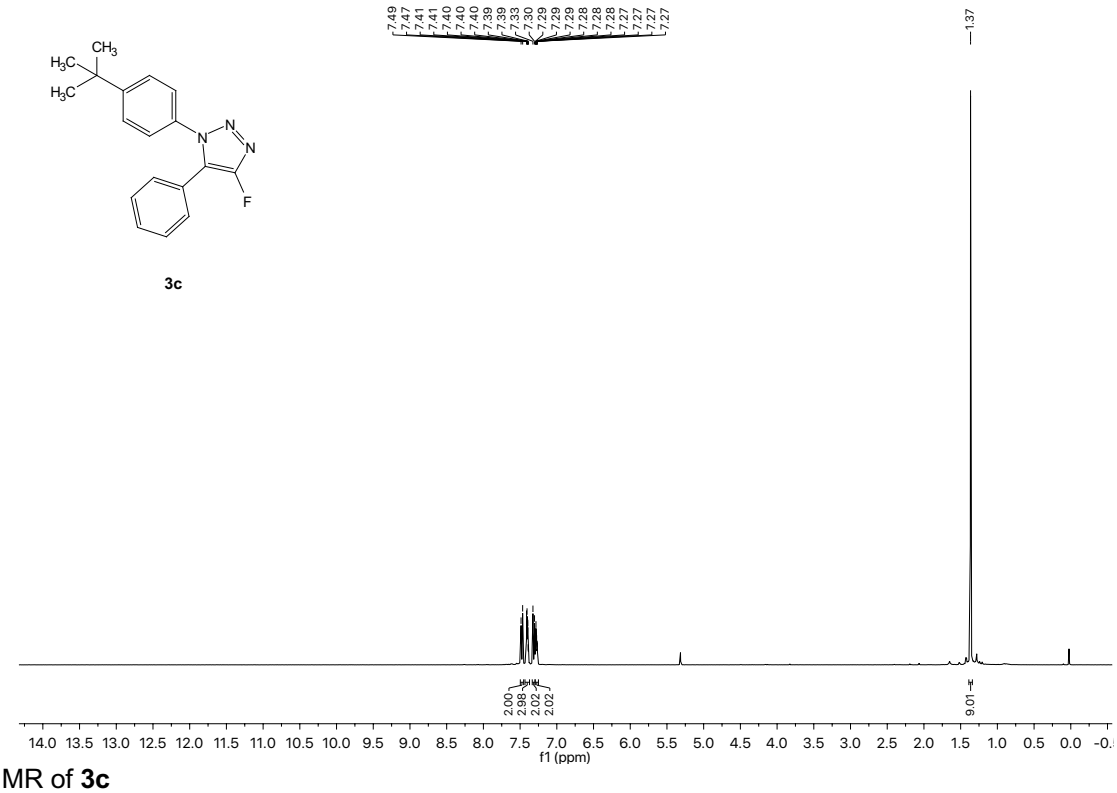
^{19}F NMR of **3b**



^{13}C NMR of **3b**

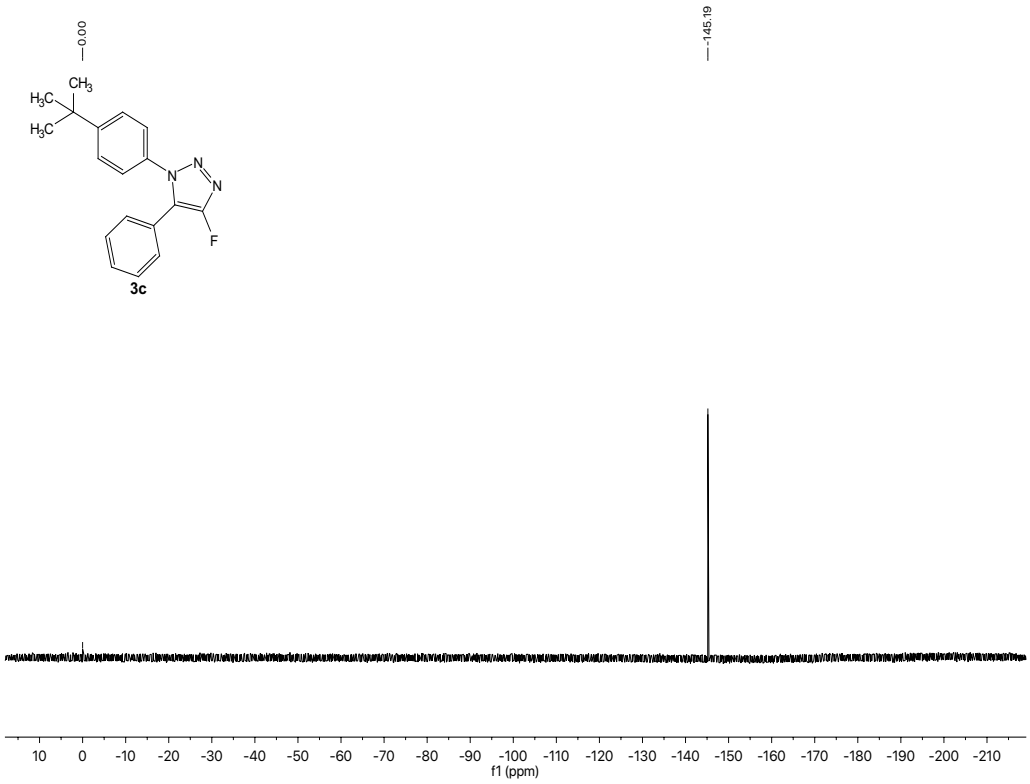


^{1}H NMR of **3c**



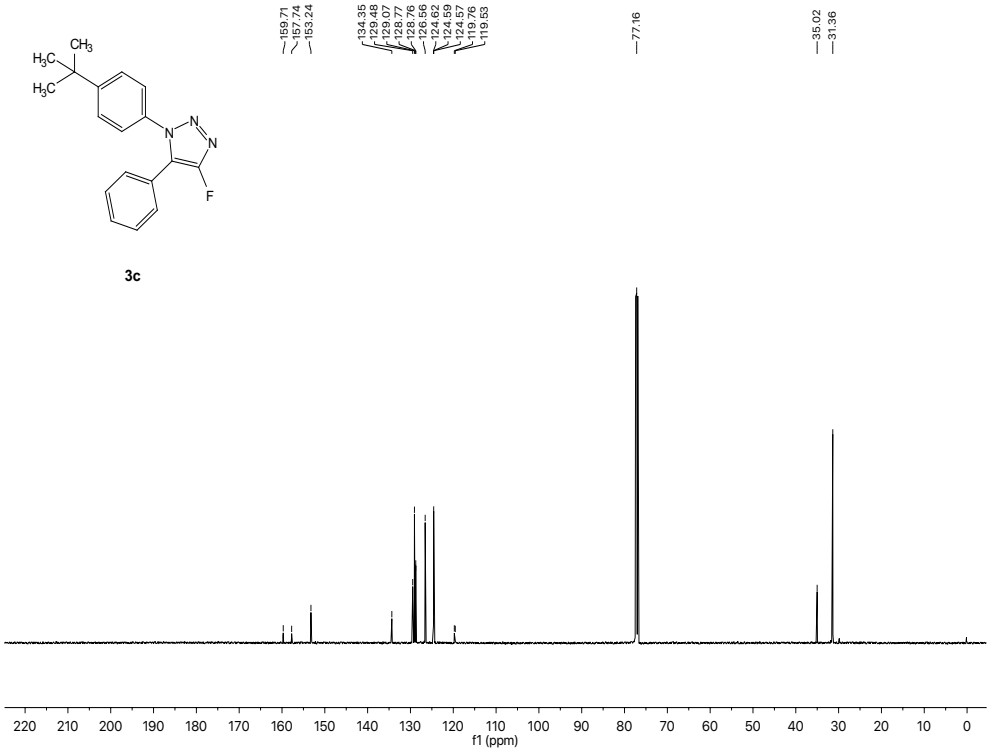
3c

^{19}F NMR of **3c**

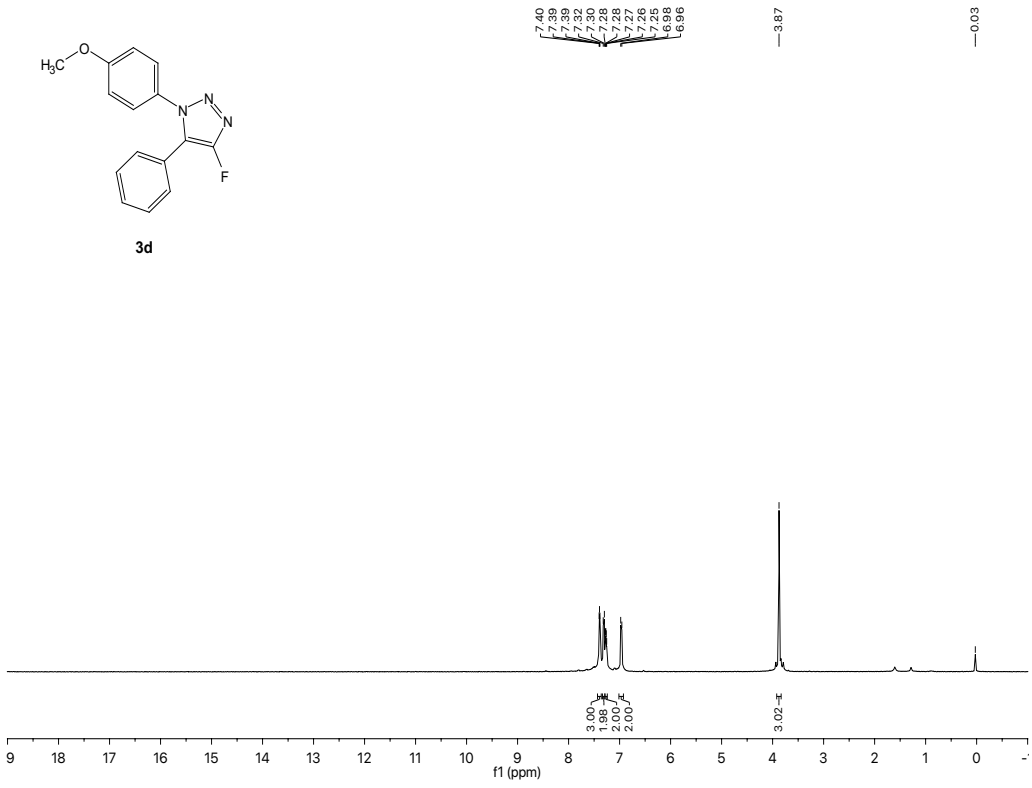


3c

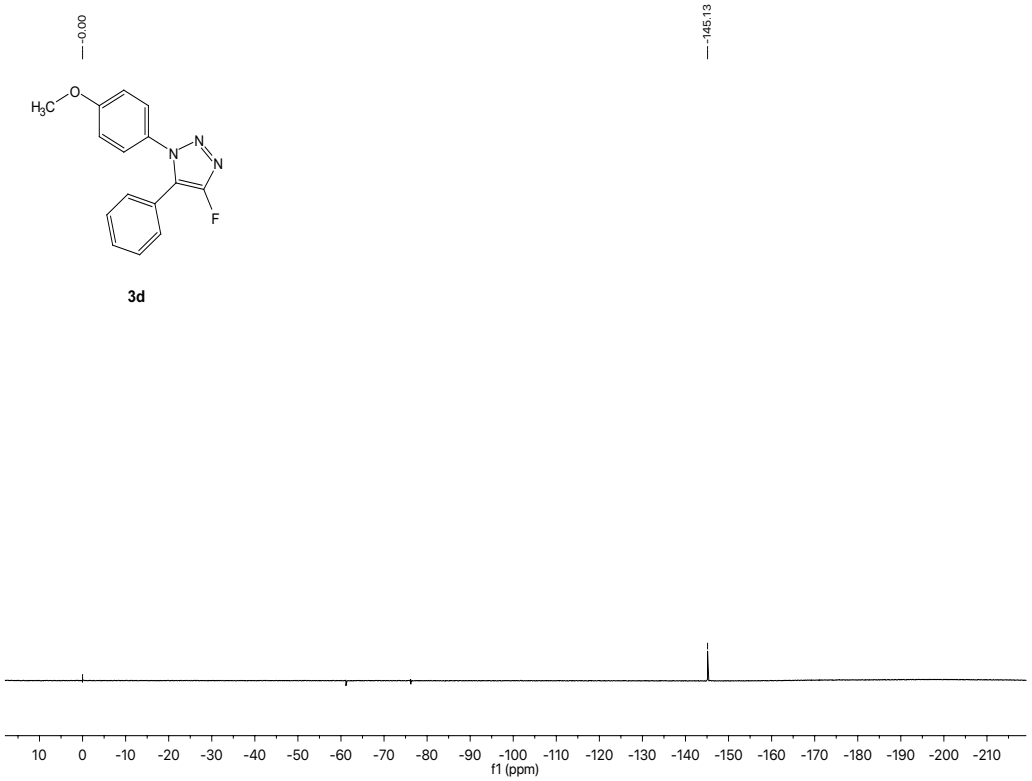
^{13}C NMR of **3c**



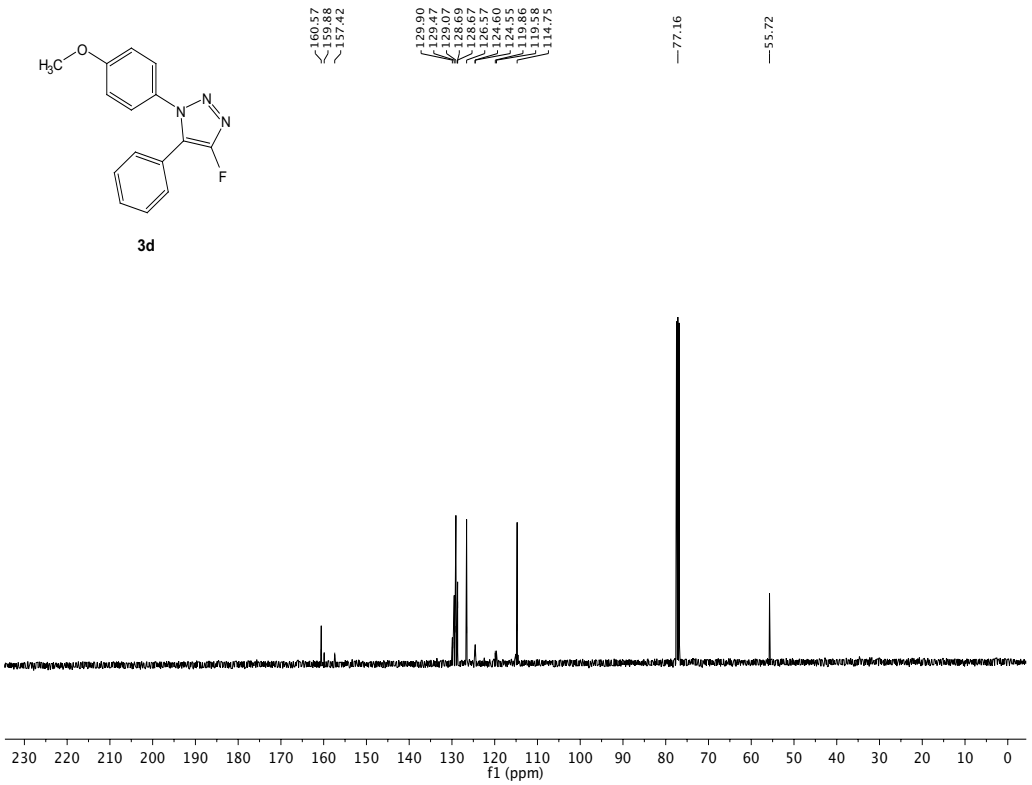
^{1}H NMR of **3d**



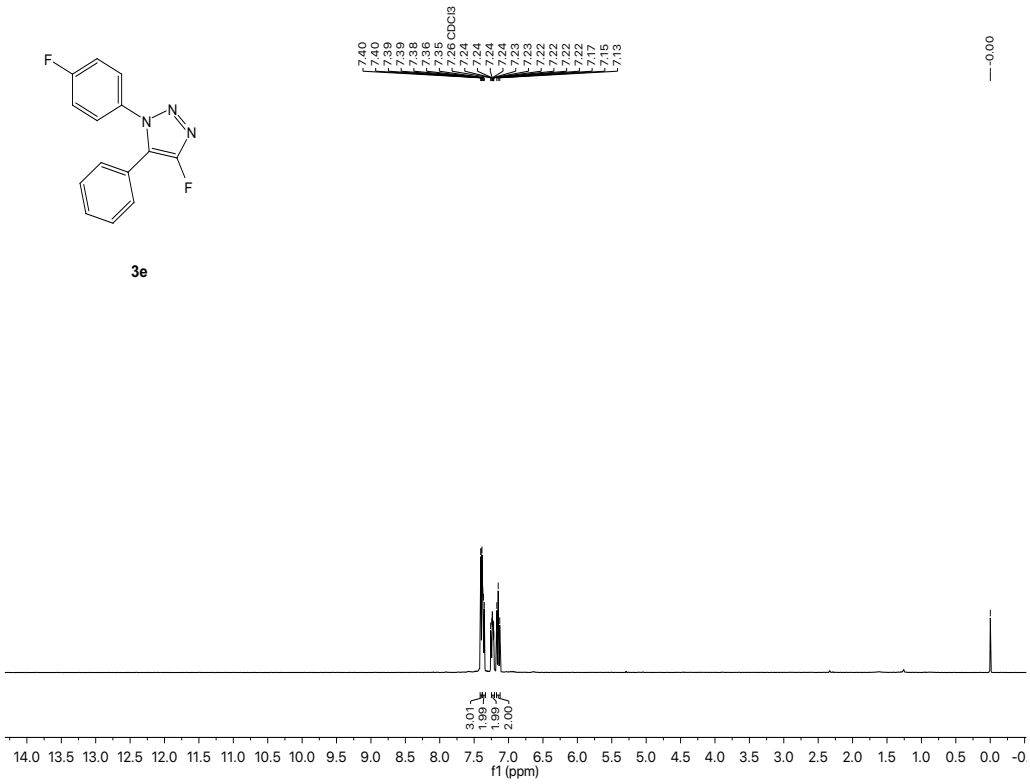
^{19}F NMR of **3d**



^{13}C NMR of **3d**

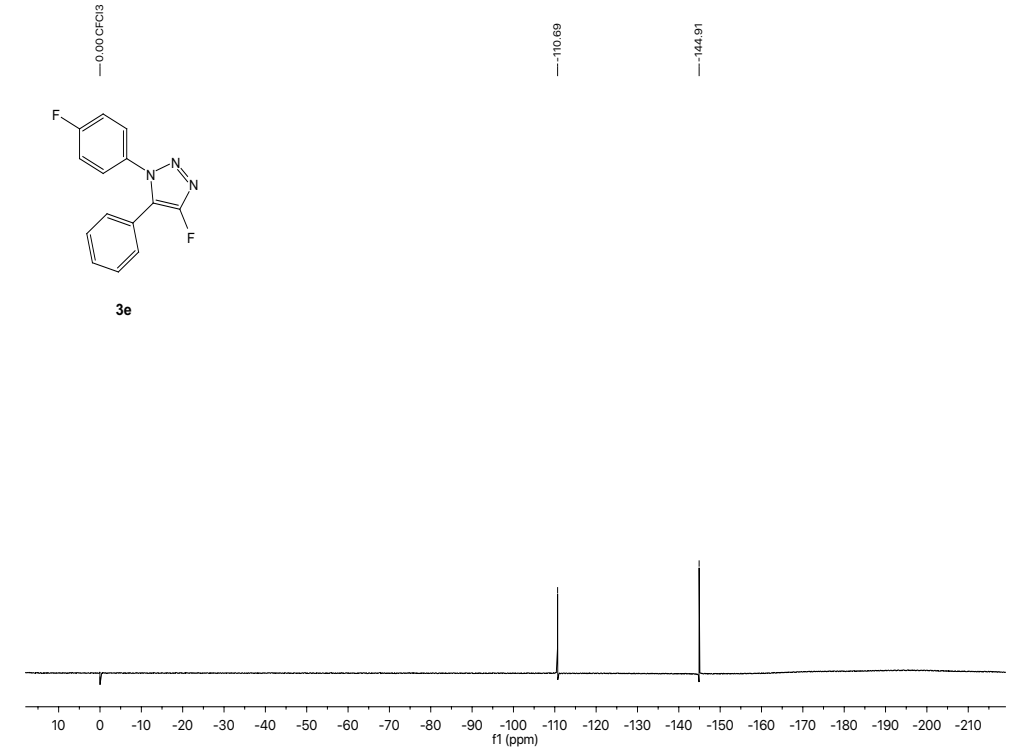


^{1}H NMR of **3e**



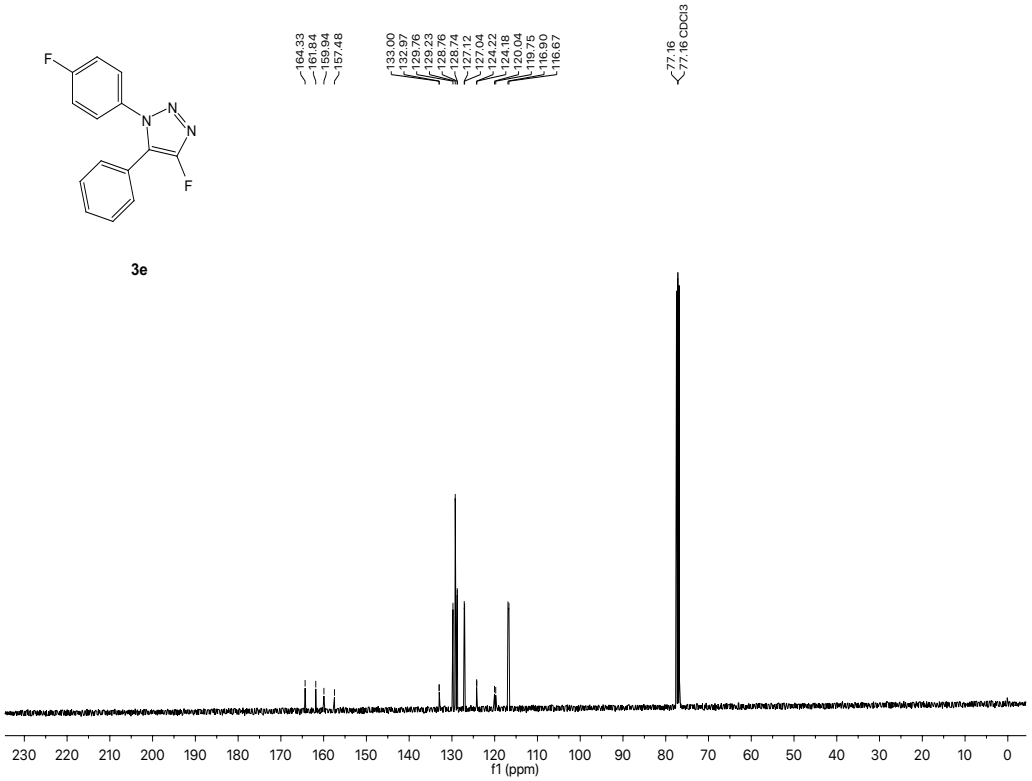
3e

^{19}F NMR of **3e**

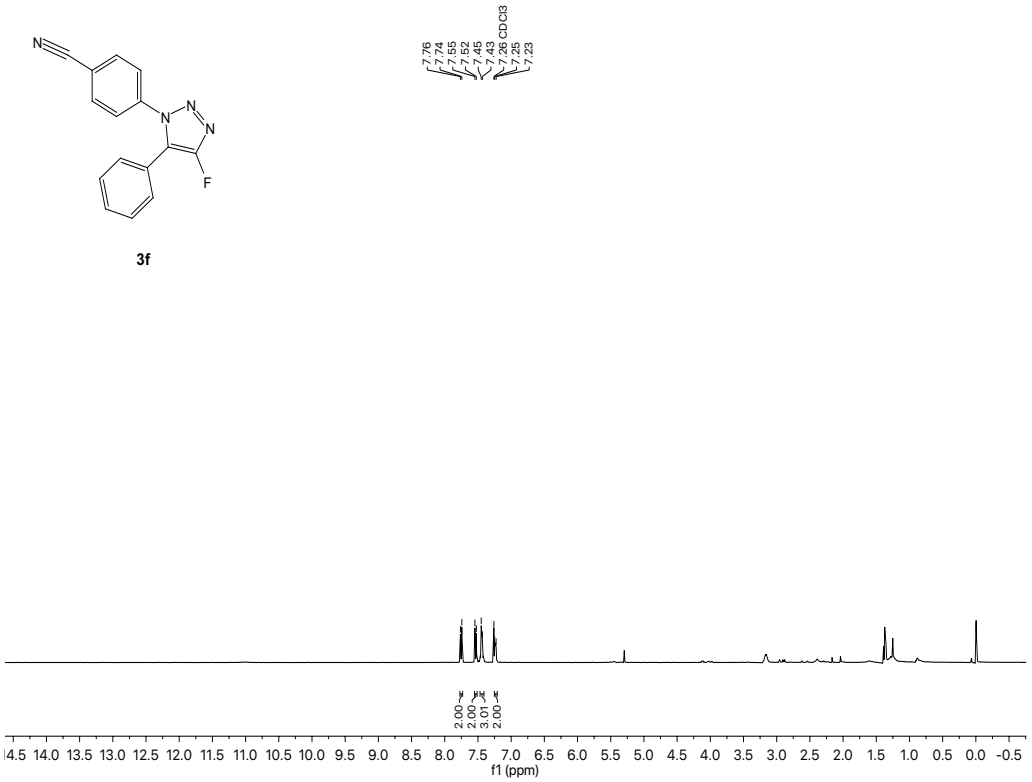


3e

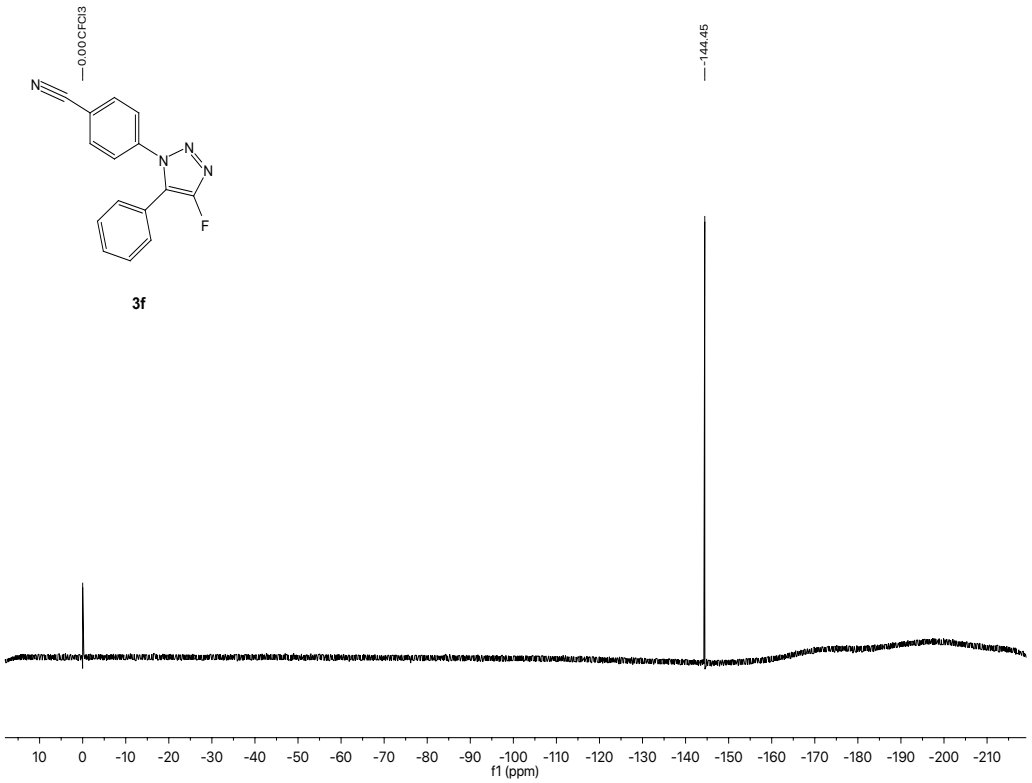
^{13}C NMR of **3e**



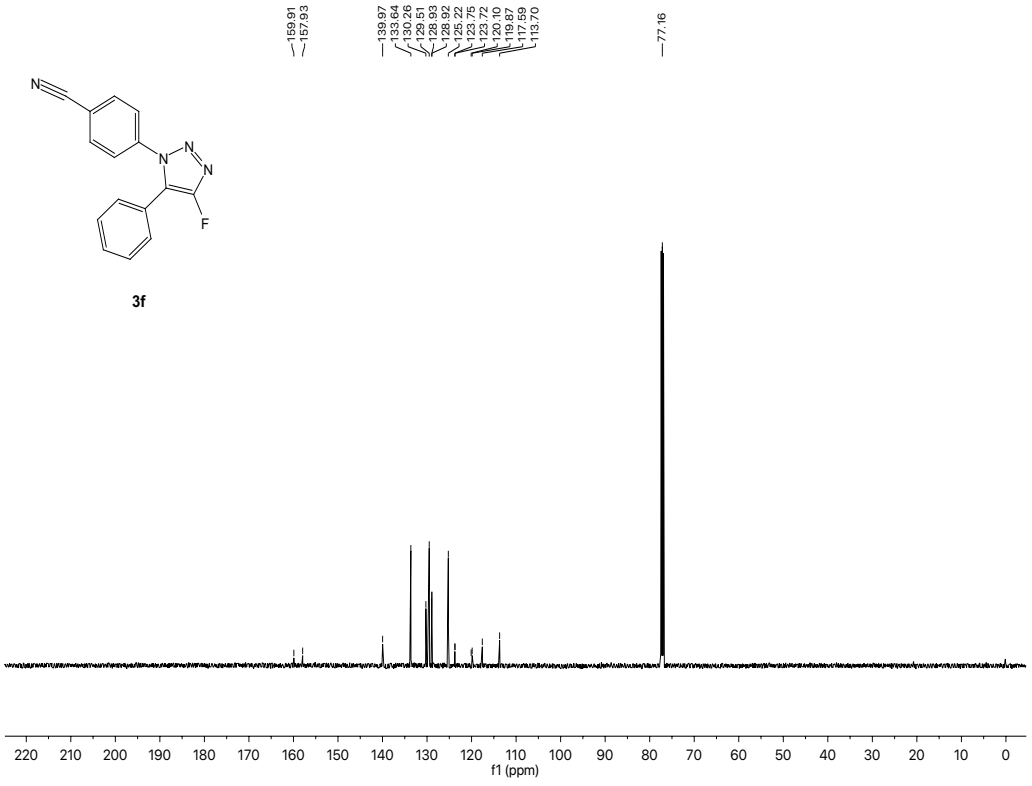
^{1}H NMR of **3f**



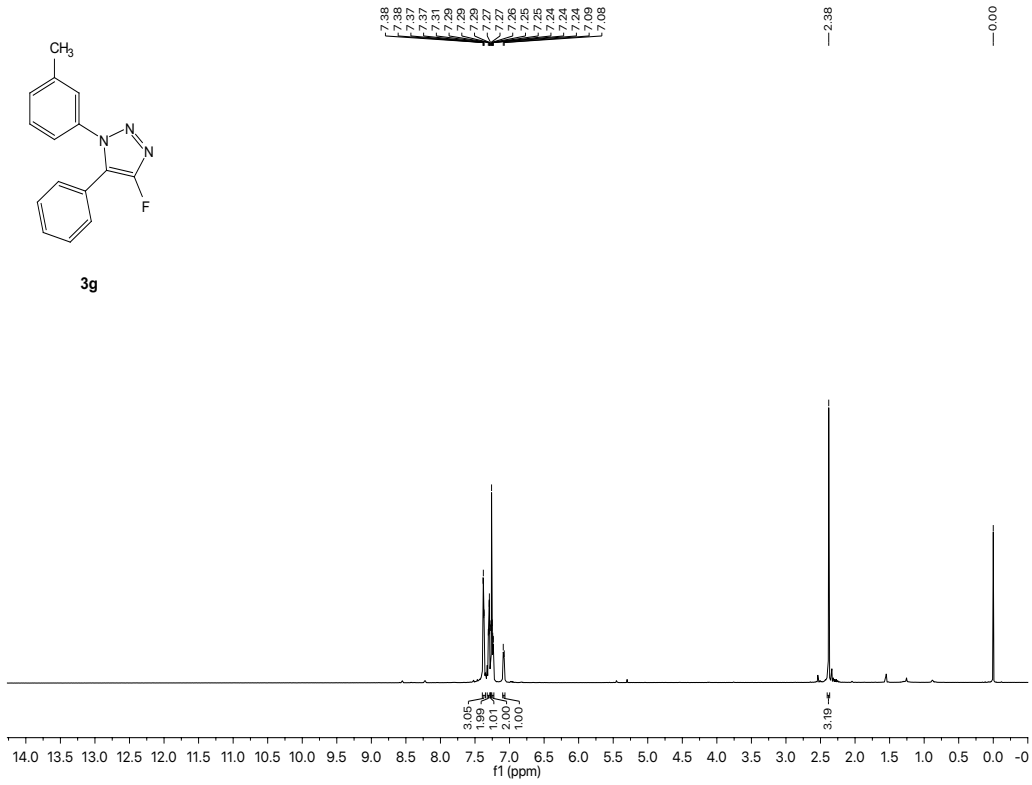
^{19}F NMR of **3f**



^{13}C NMR of **3f**

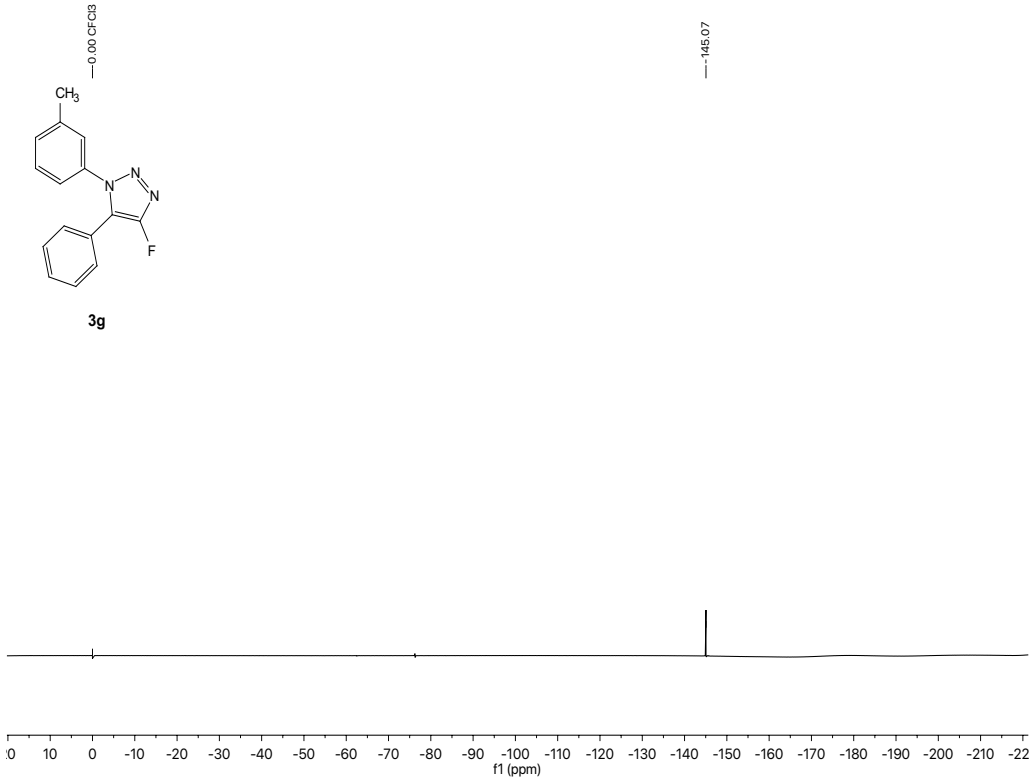


^{1}H NMR of **3g**



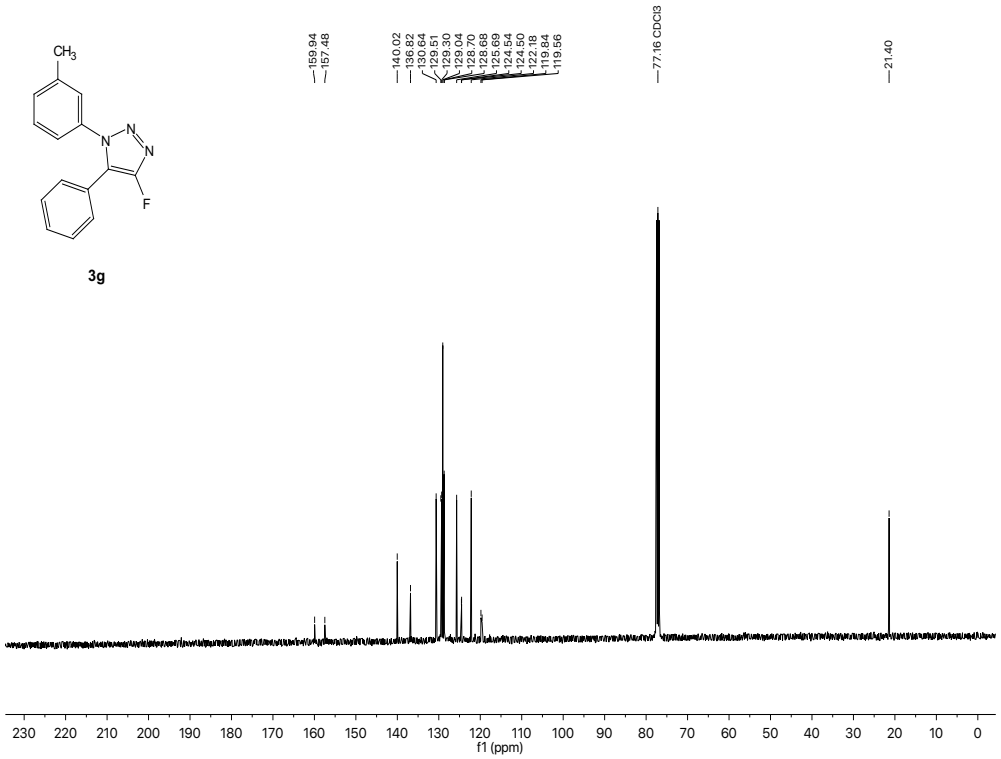
3g

^{19}F NMR of **3g**



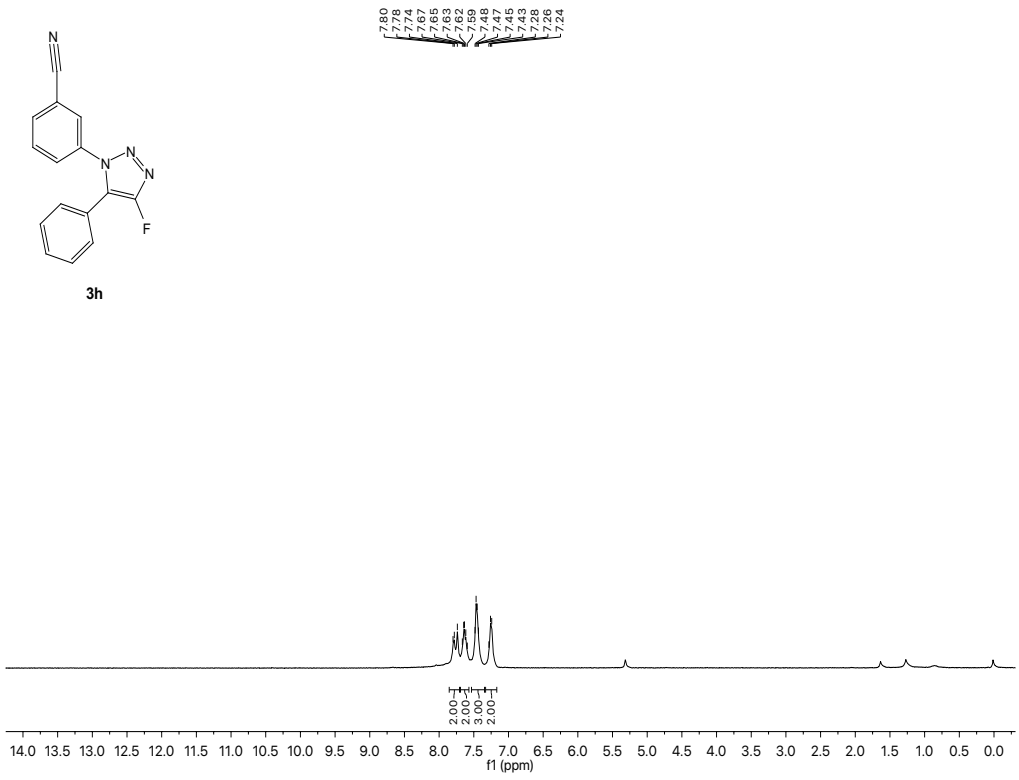
3g

^{13}C NMR of **3g**



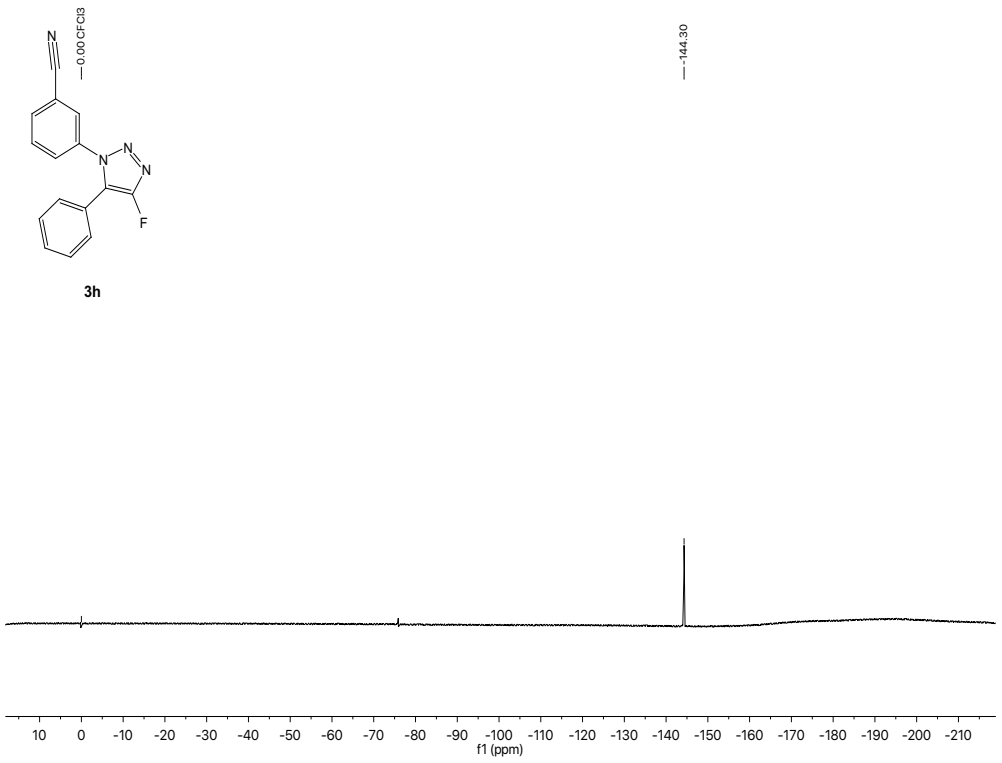
3g

^{1}H NMR of **3h**



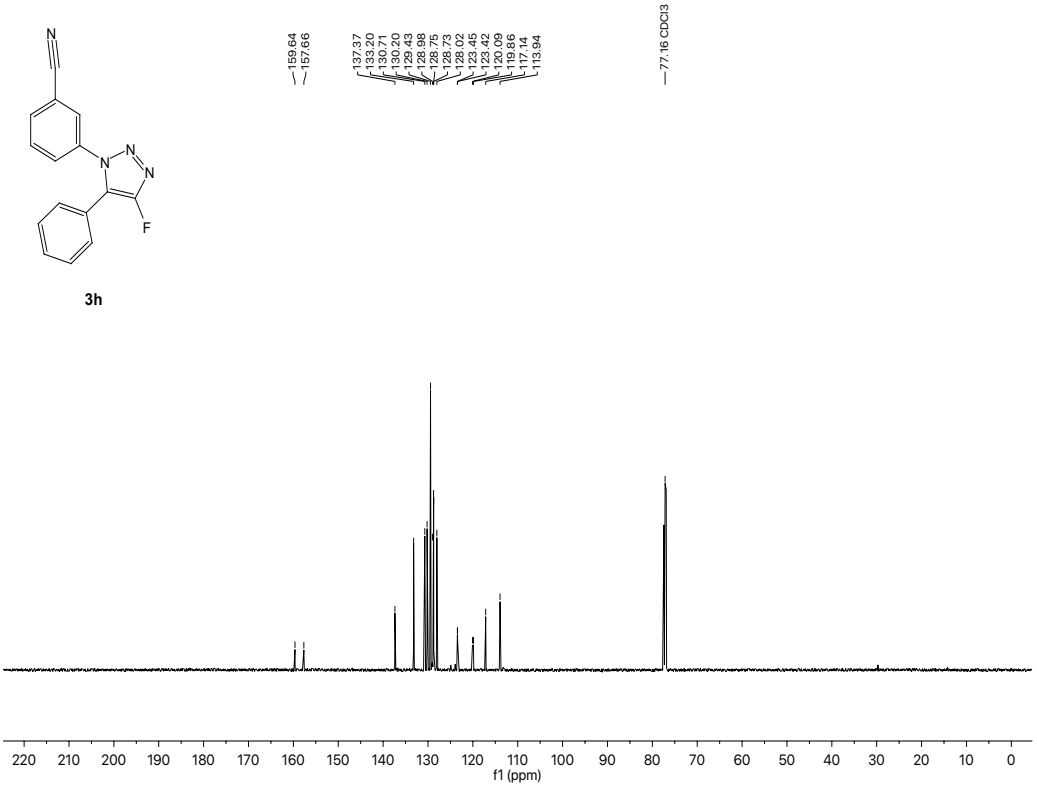
3h

^{19}F NMR of **3h**



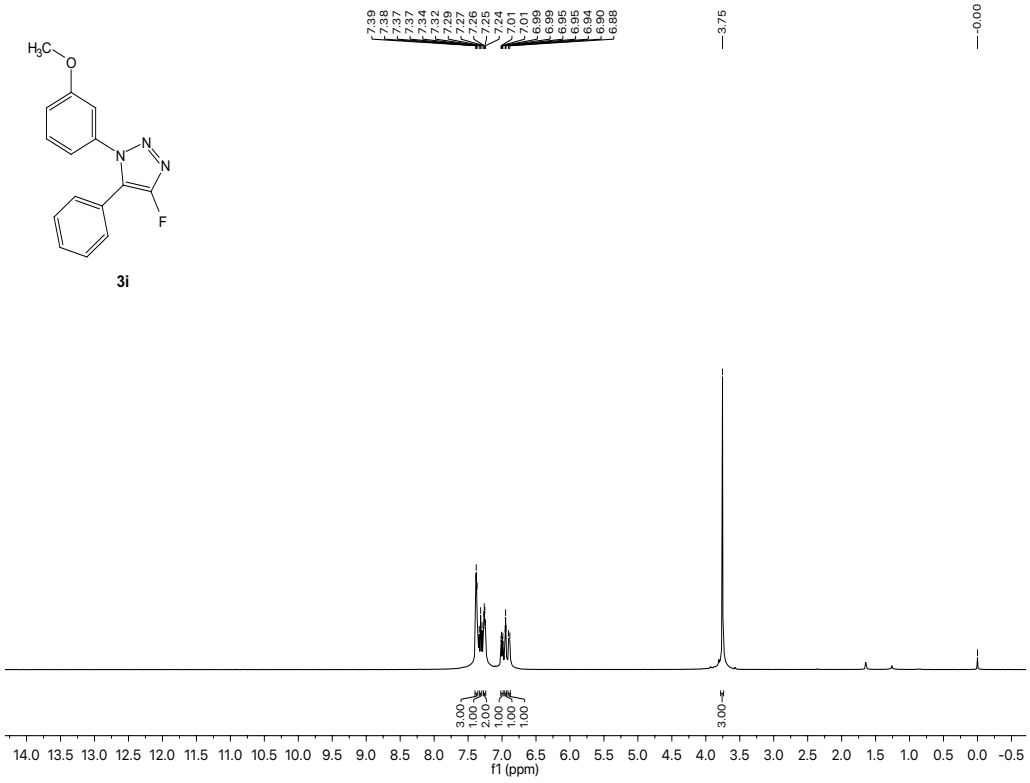
3h

^{13}C NMR of **3h**



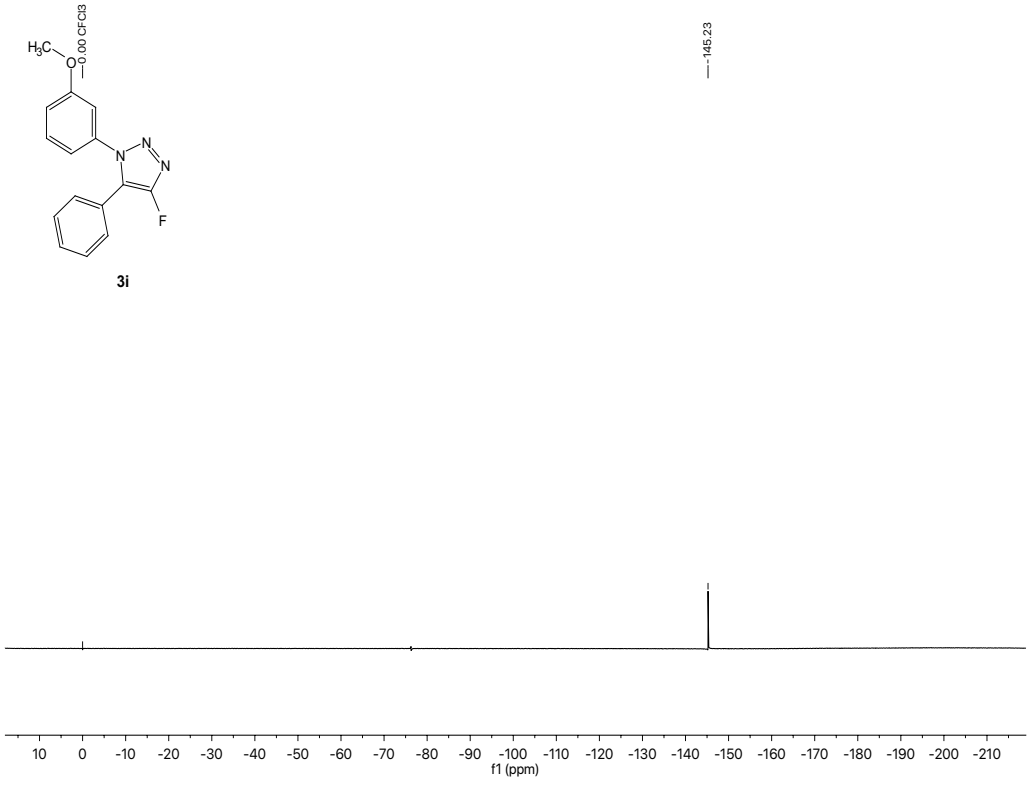
3h

^{1}H NMR of **3i**



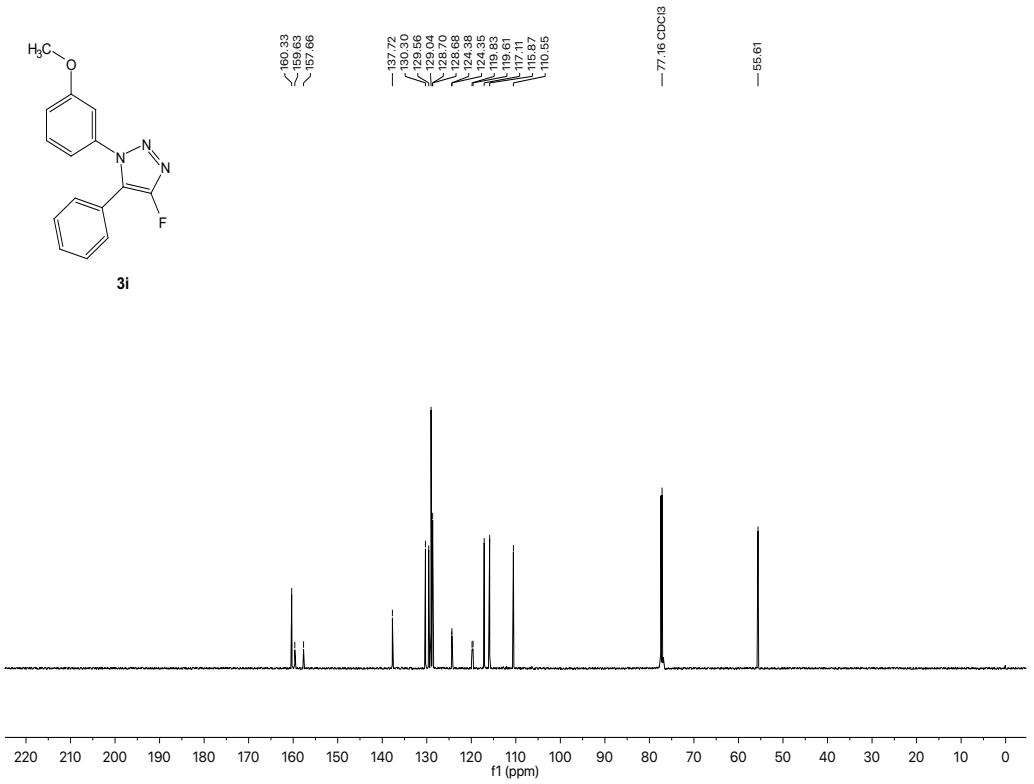
3i

^{19}F NMR of **3i**

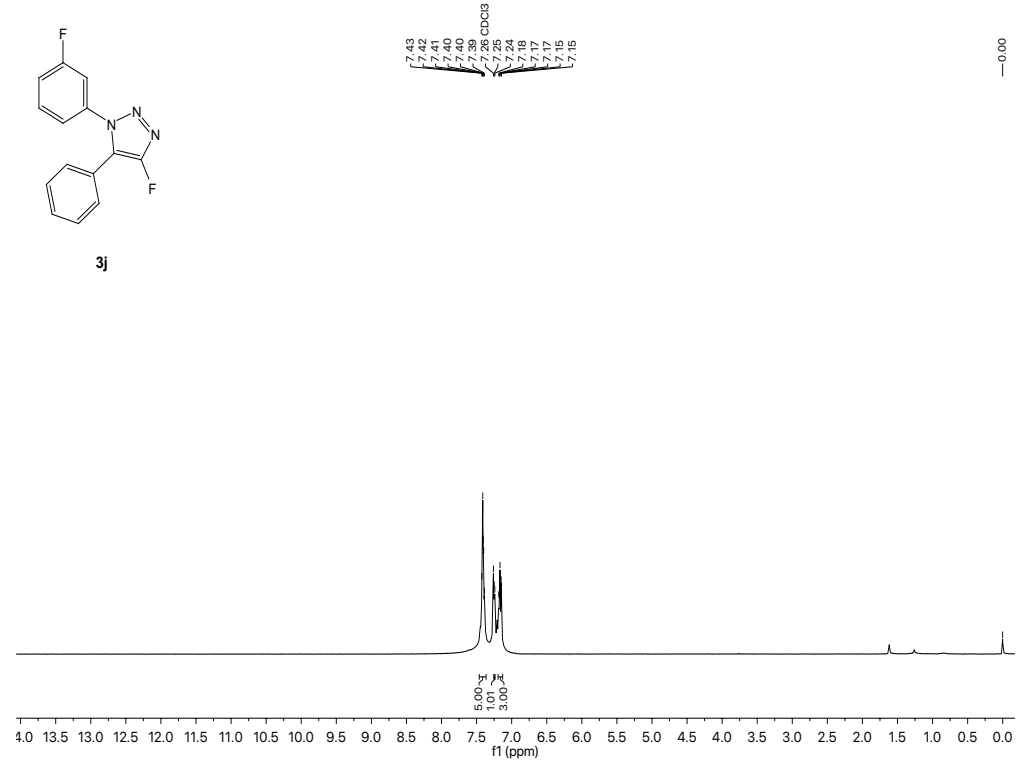


3i

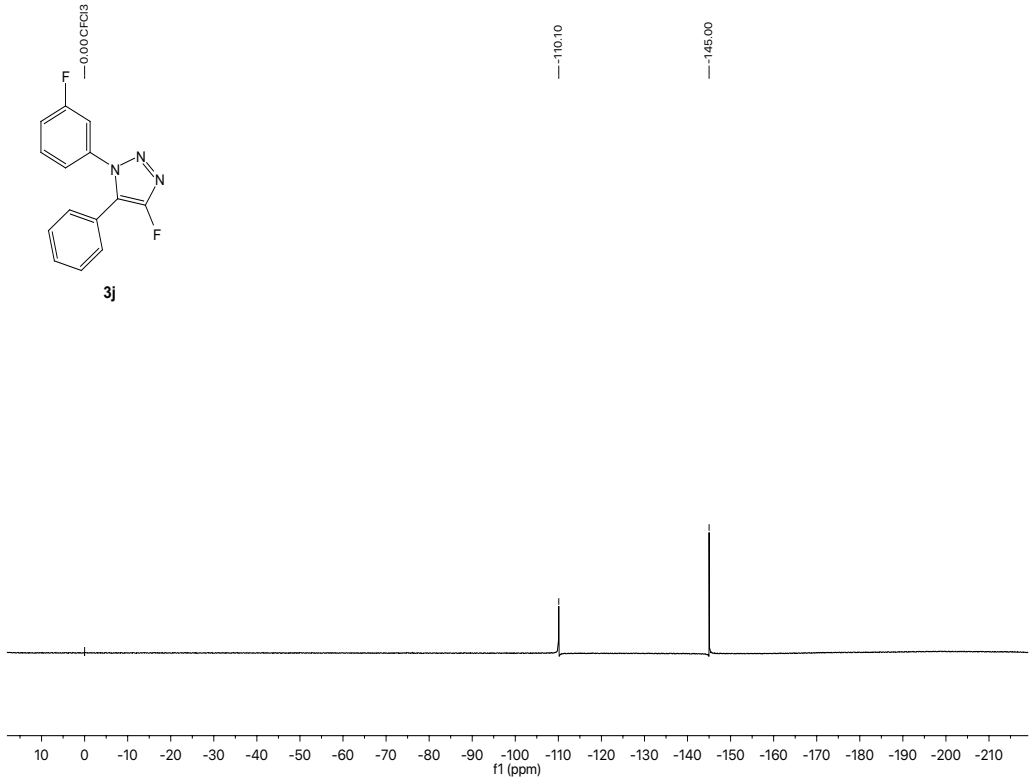
^{13}C NMR of **3i**



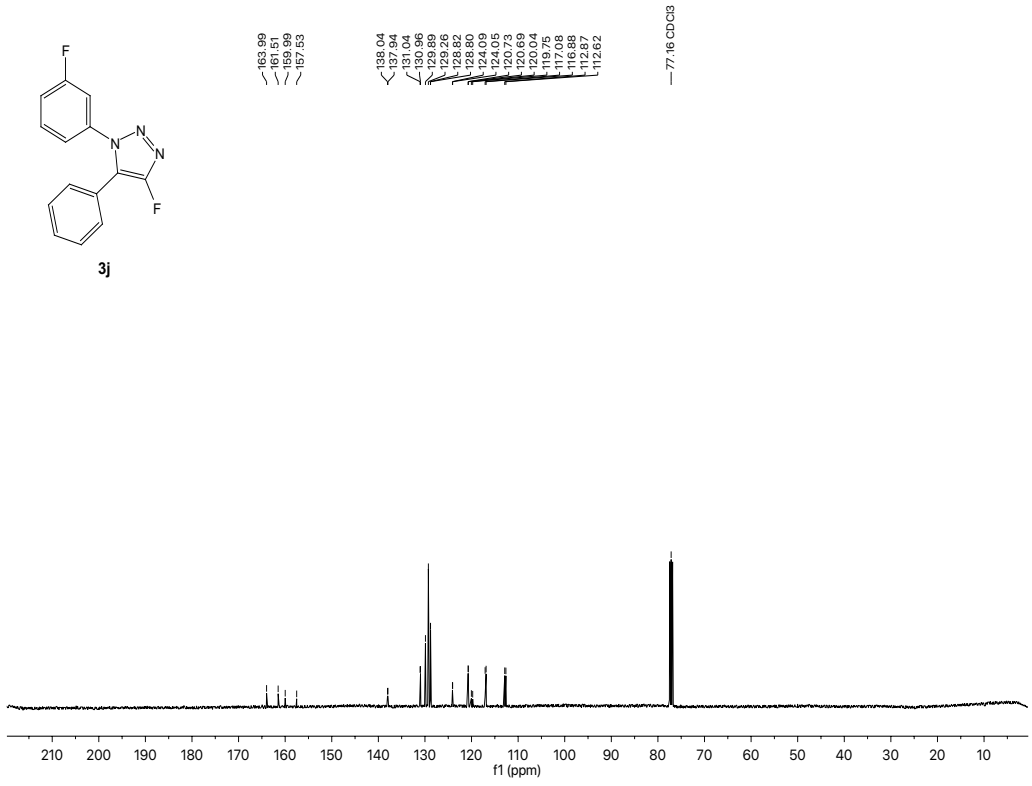
^{1}H NMR of **3j**



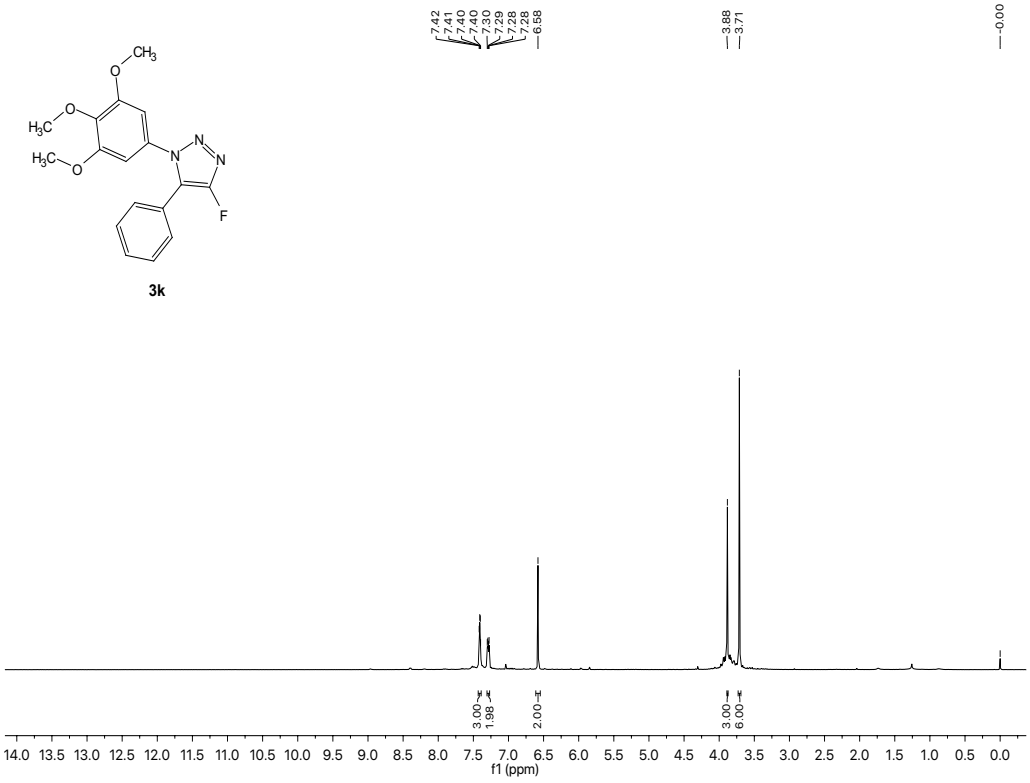
^{19}F NMR of **3j**



^{13}C NMR of **3j**

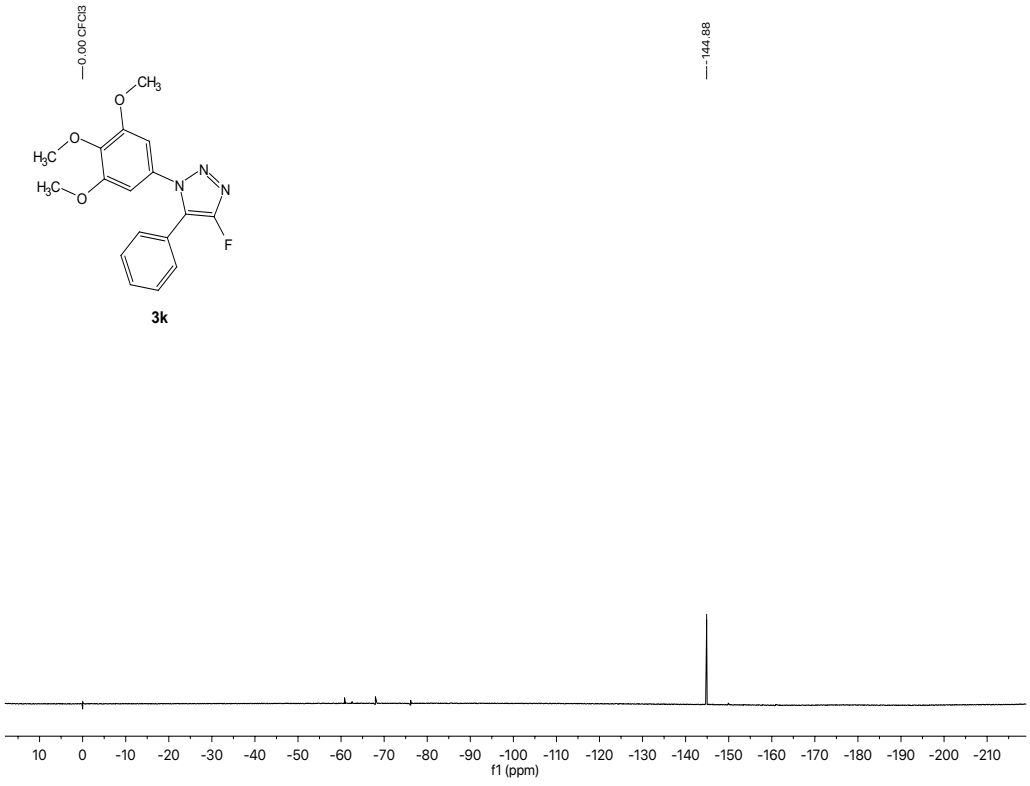


^{1}H NMR of **3k**



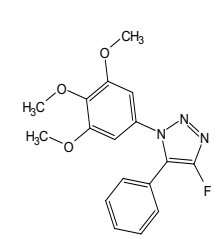
3k

^{19}F NMR of **3k**



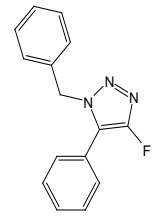
3k

^{13}C NMR of **3k**



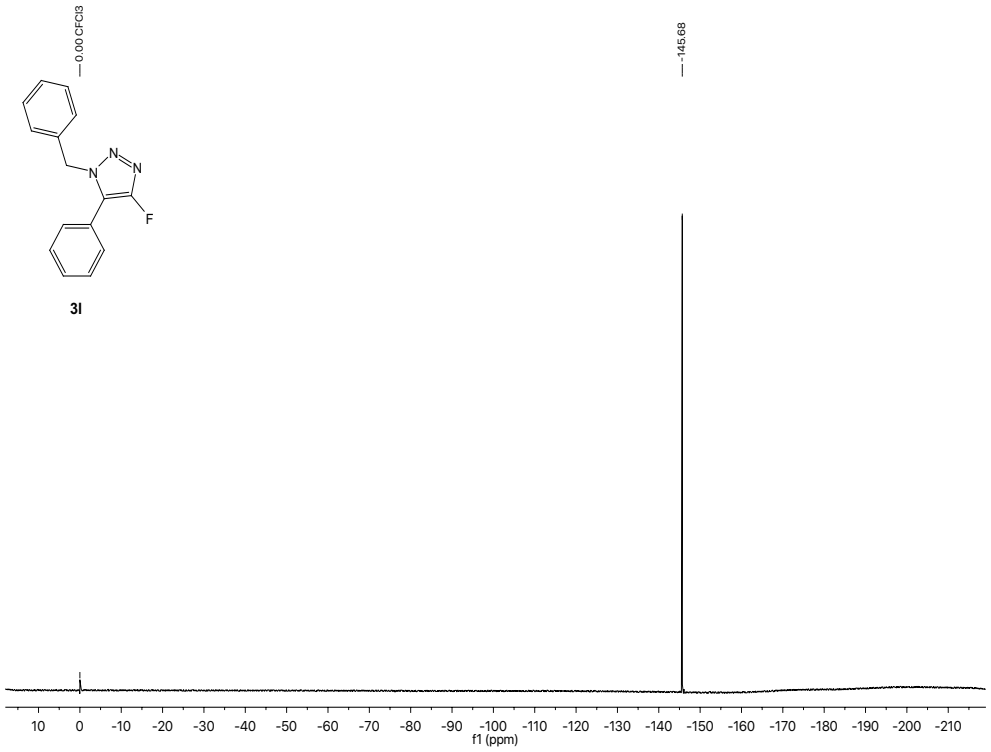
3k

^{1}H NMR of **3l**

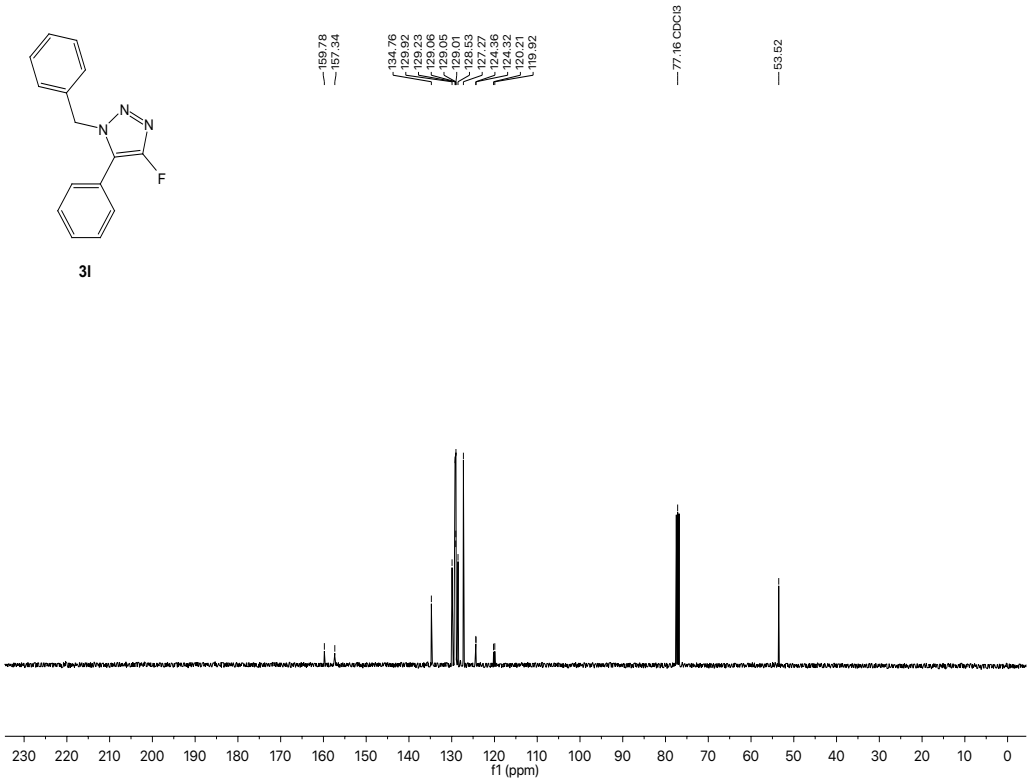


3l

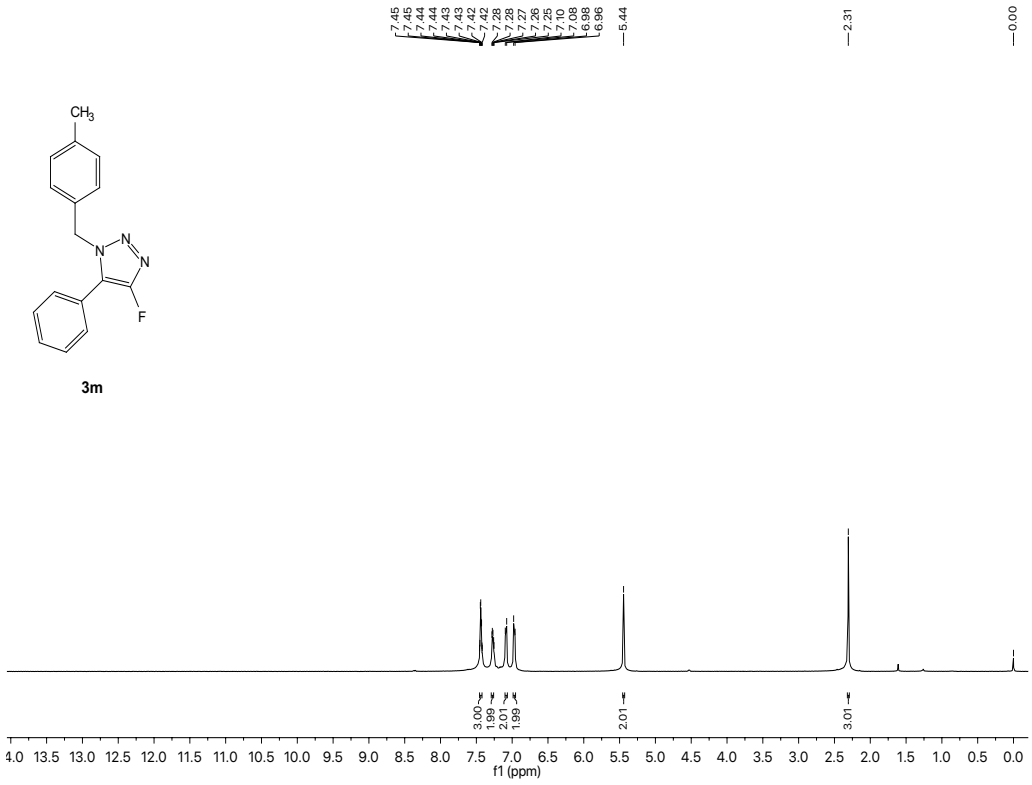
^{19}F NMR of **3l**



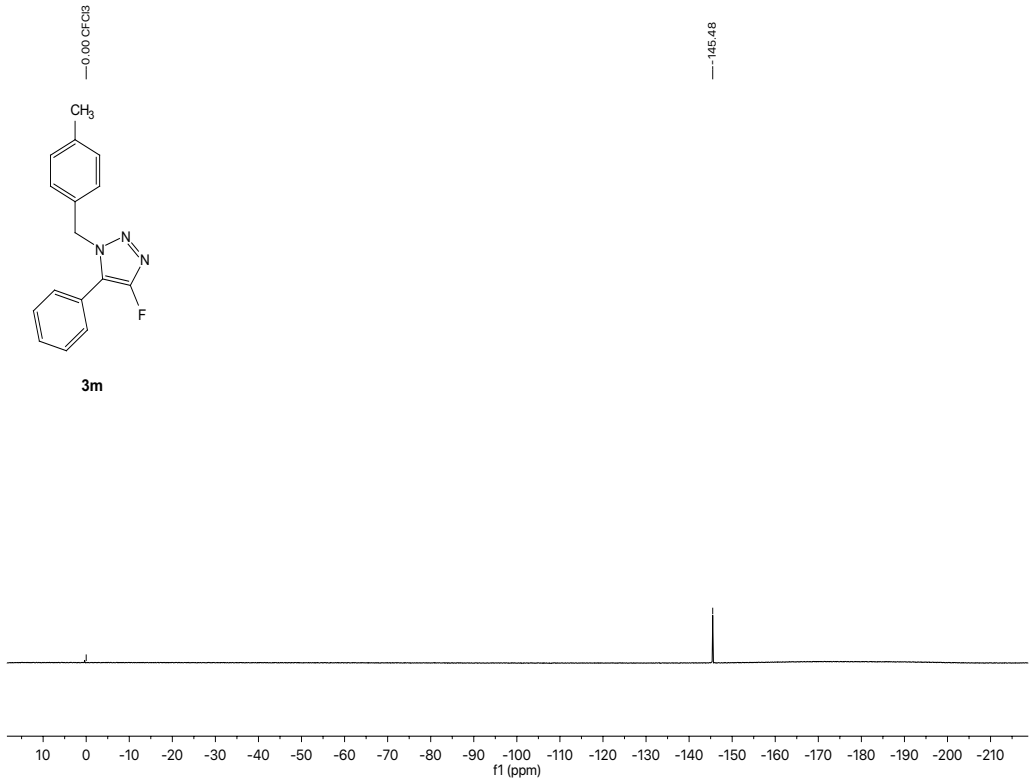
^{13}C NMR of **3l**



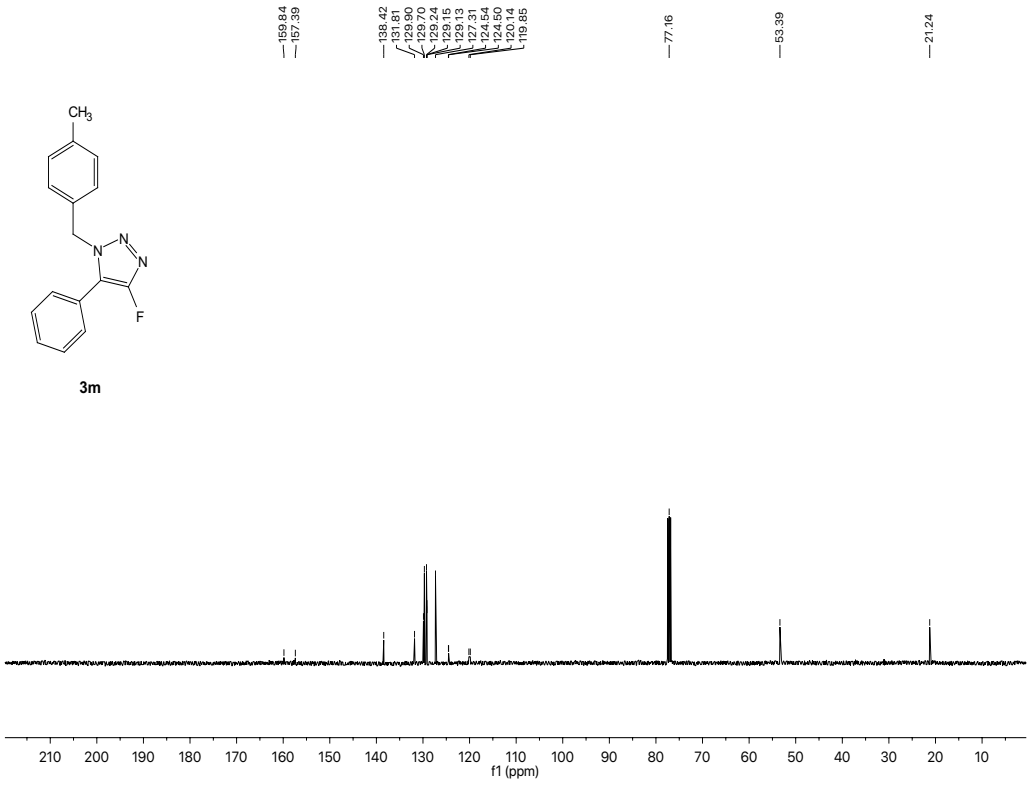
^{1}H NMR of **3m**



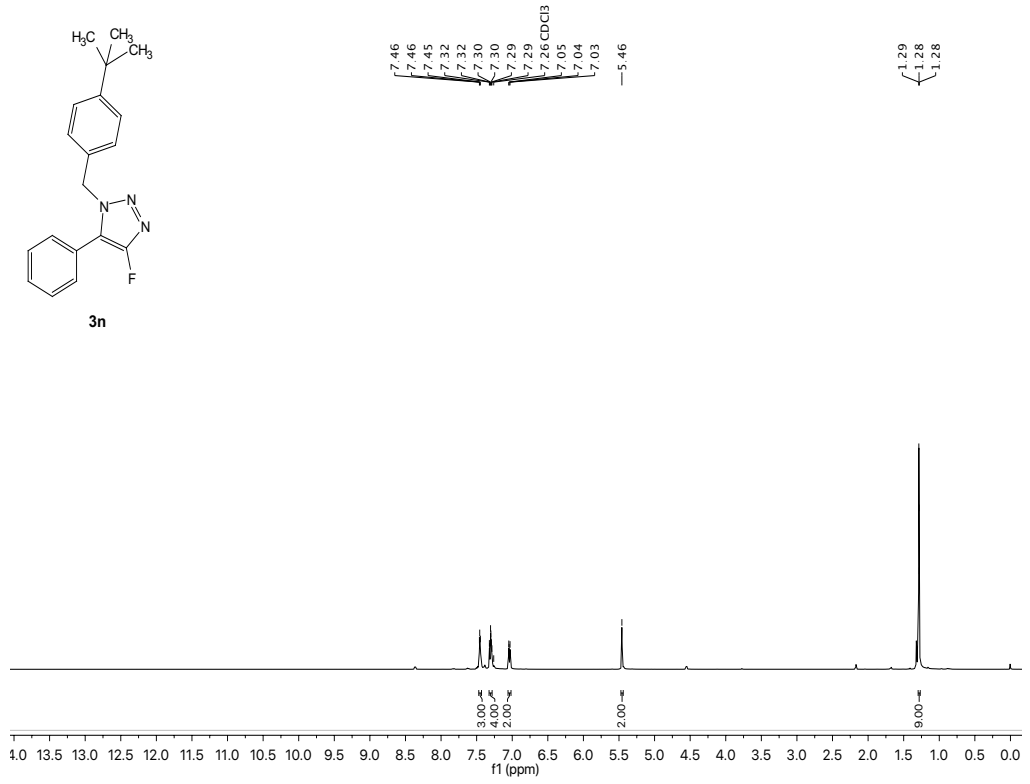
^{19}F NMR of **3m**



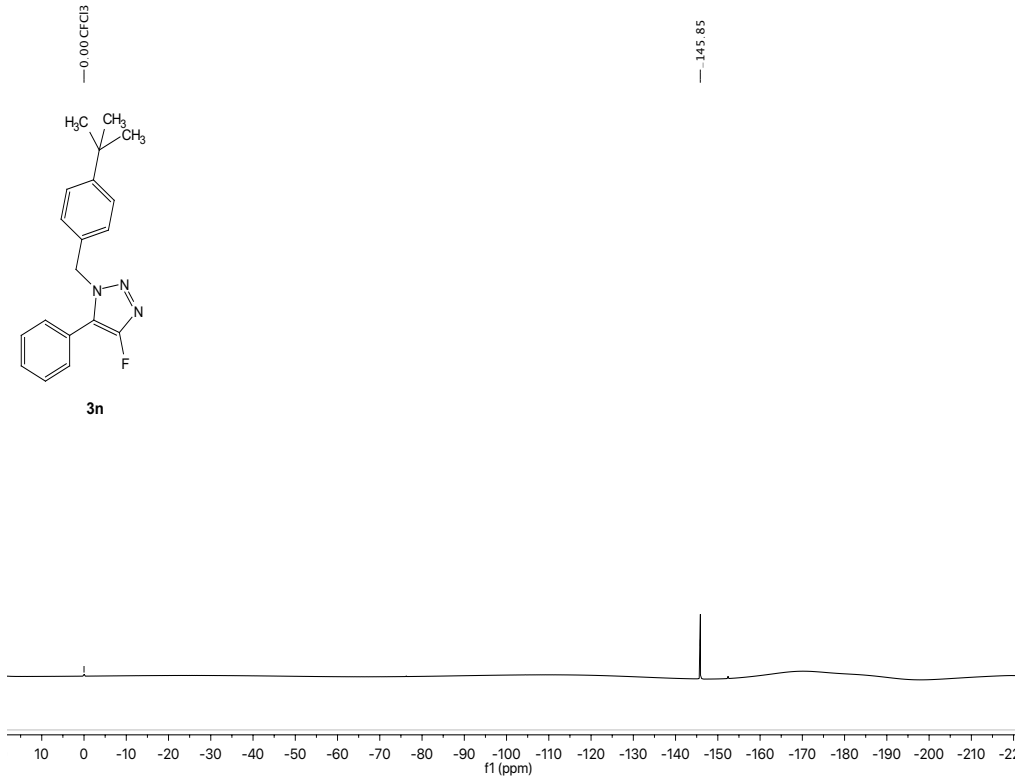
^{13}C NMR of **3m**



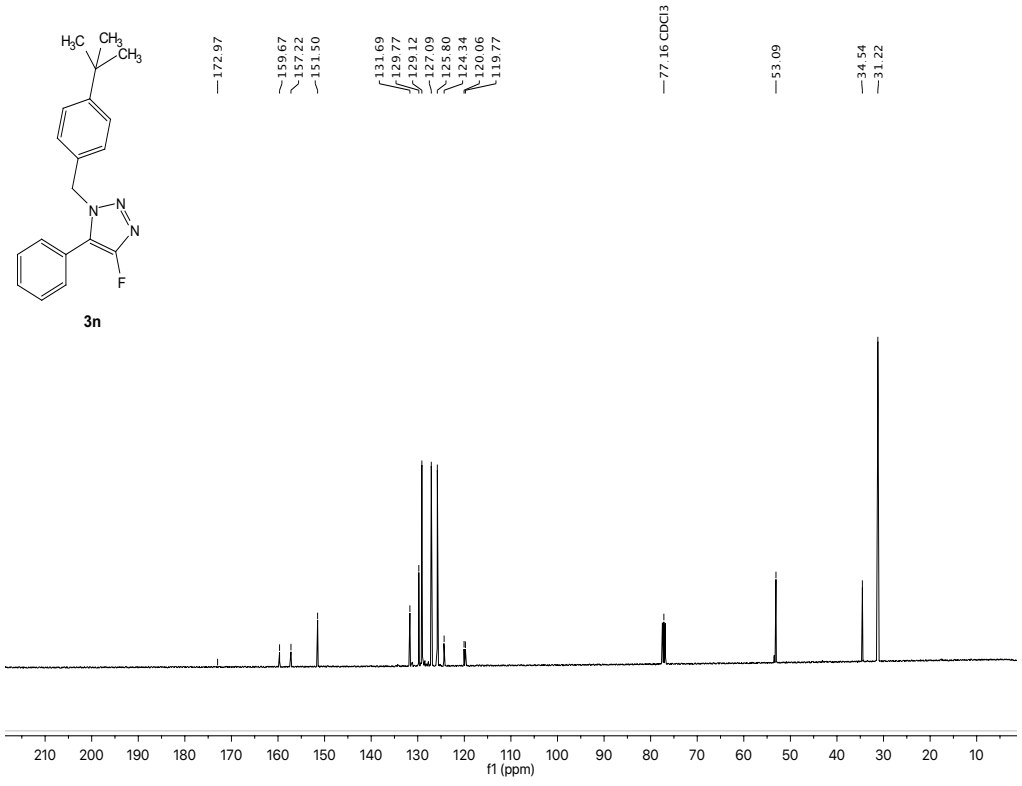
^{1}H NMR of **3n**



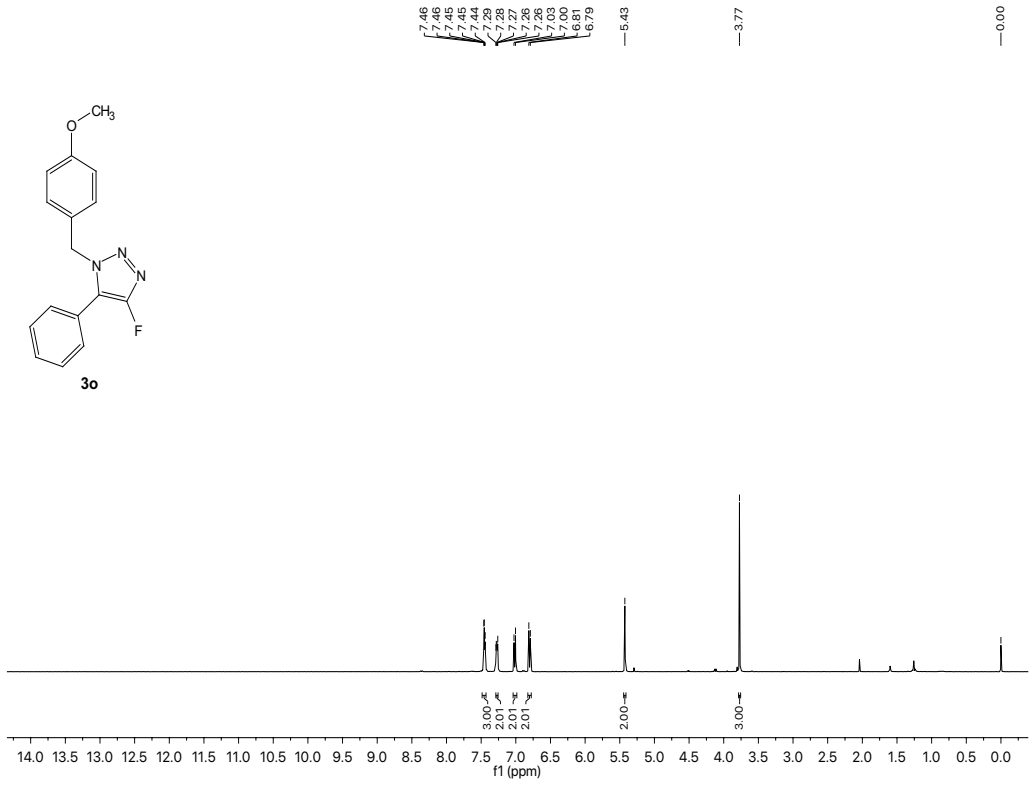
^{19}F NMR of **3n**



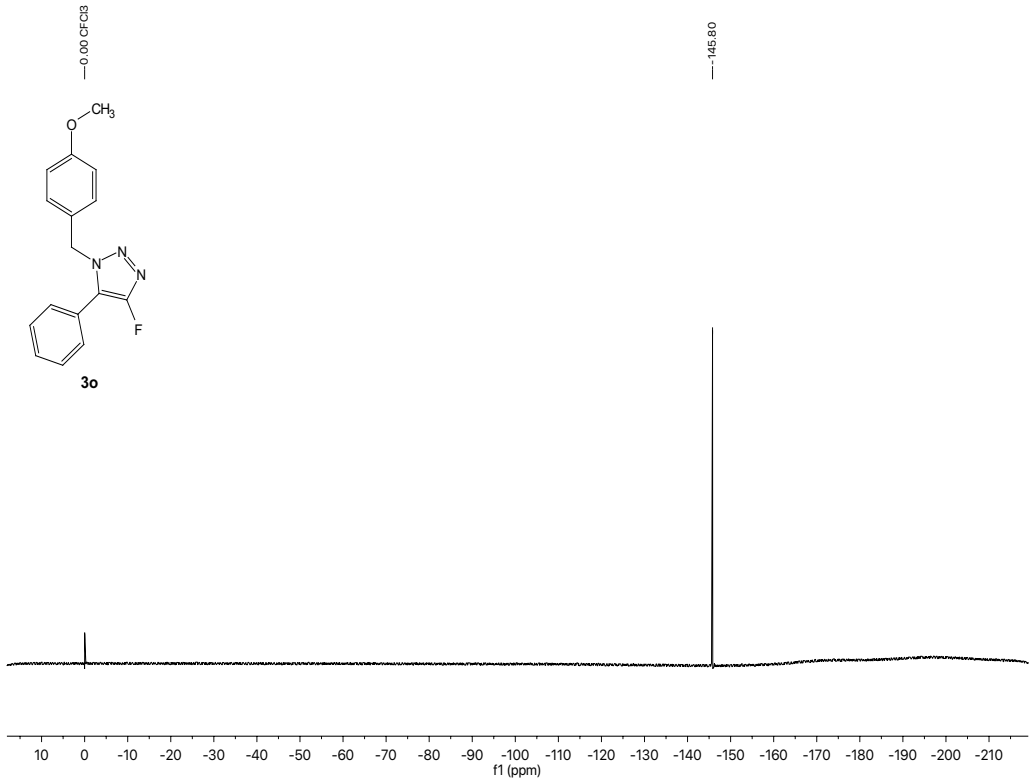
^{13}C NMR of **3n**



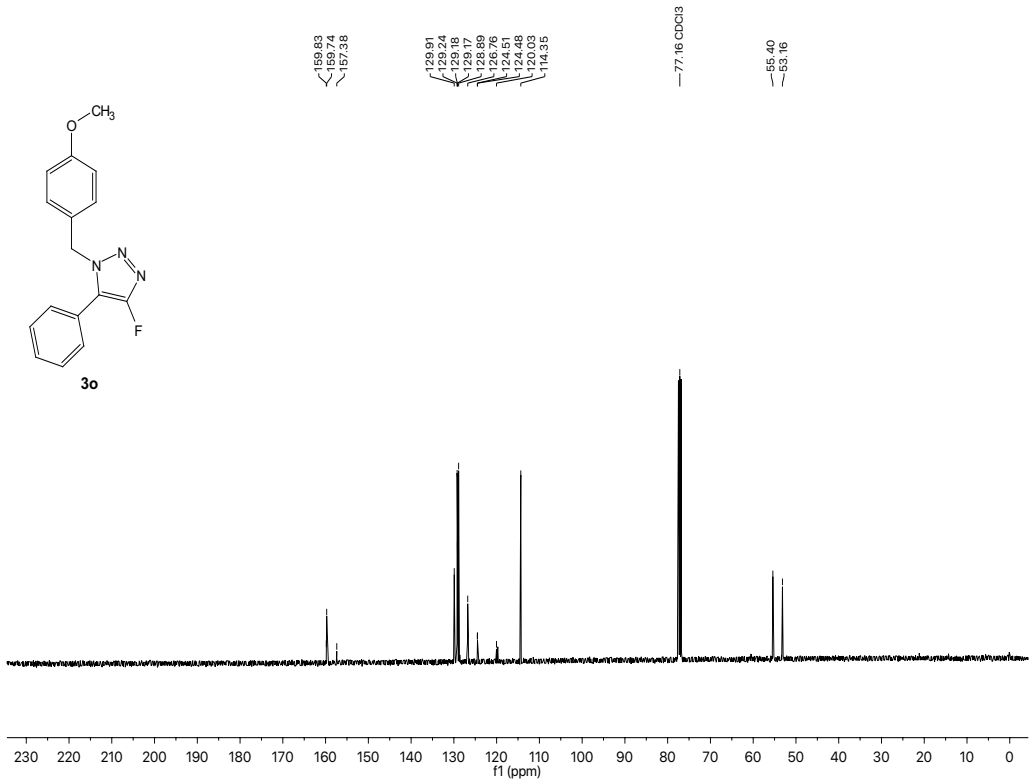
^{1}H NMR of **3o**



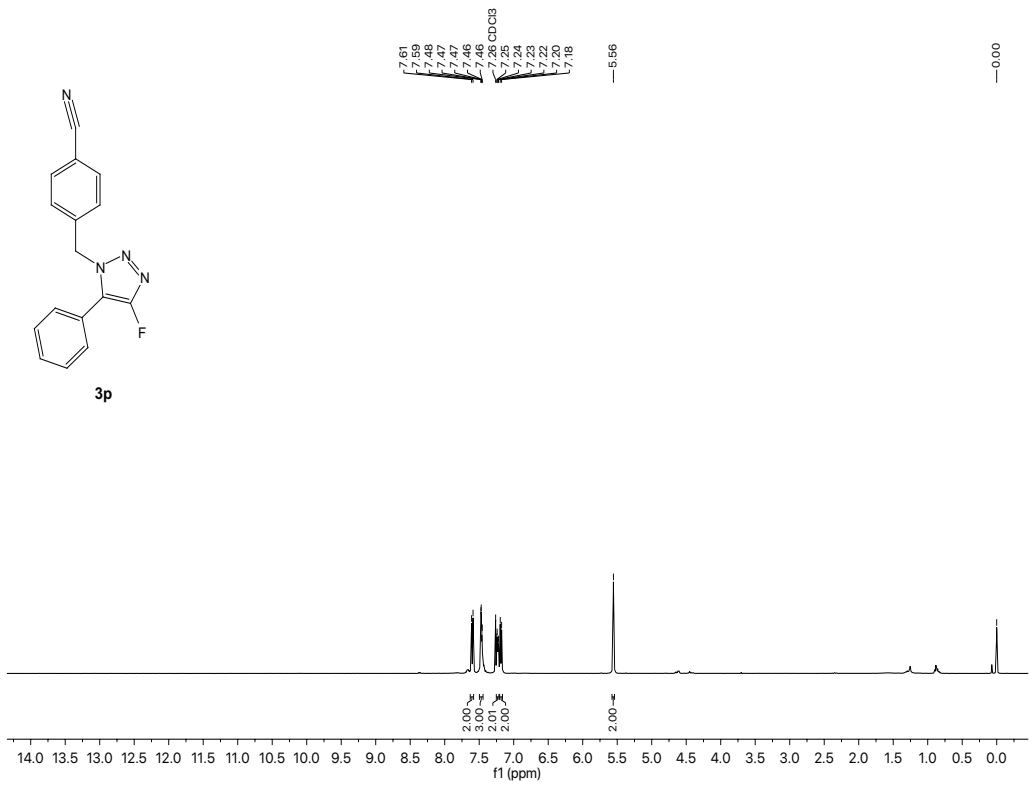
^{19}F NMR of **3o**



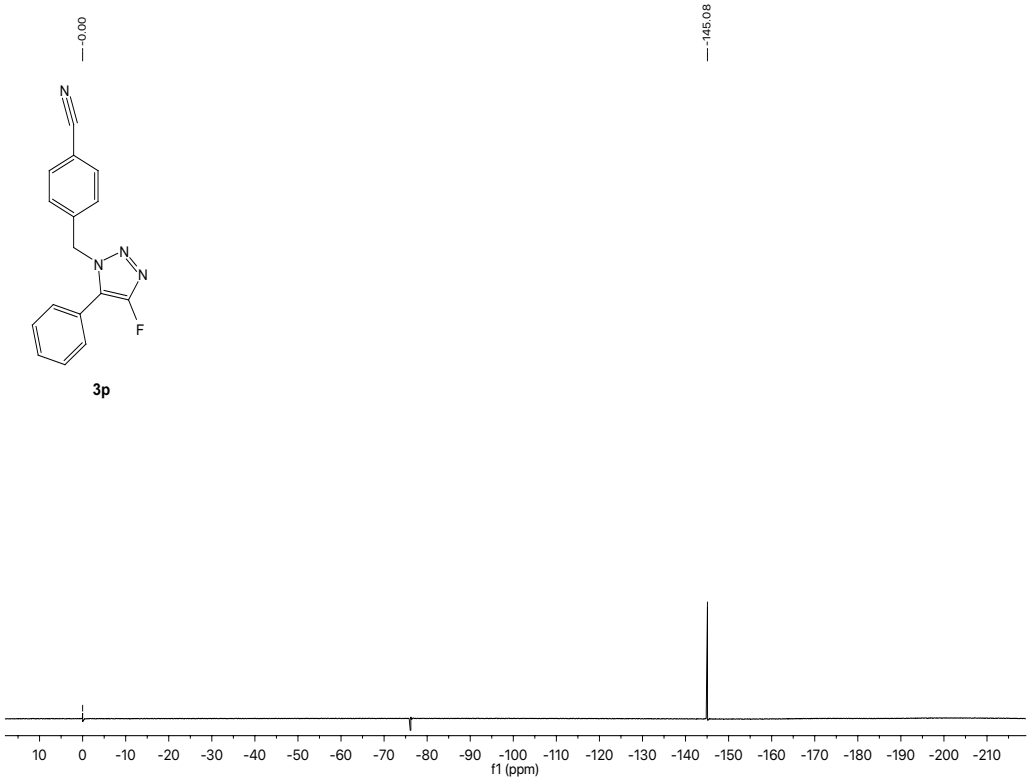
^{13}C NMR of **3o**



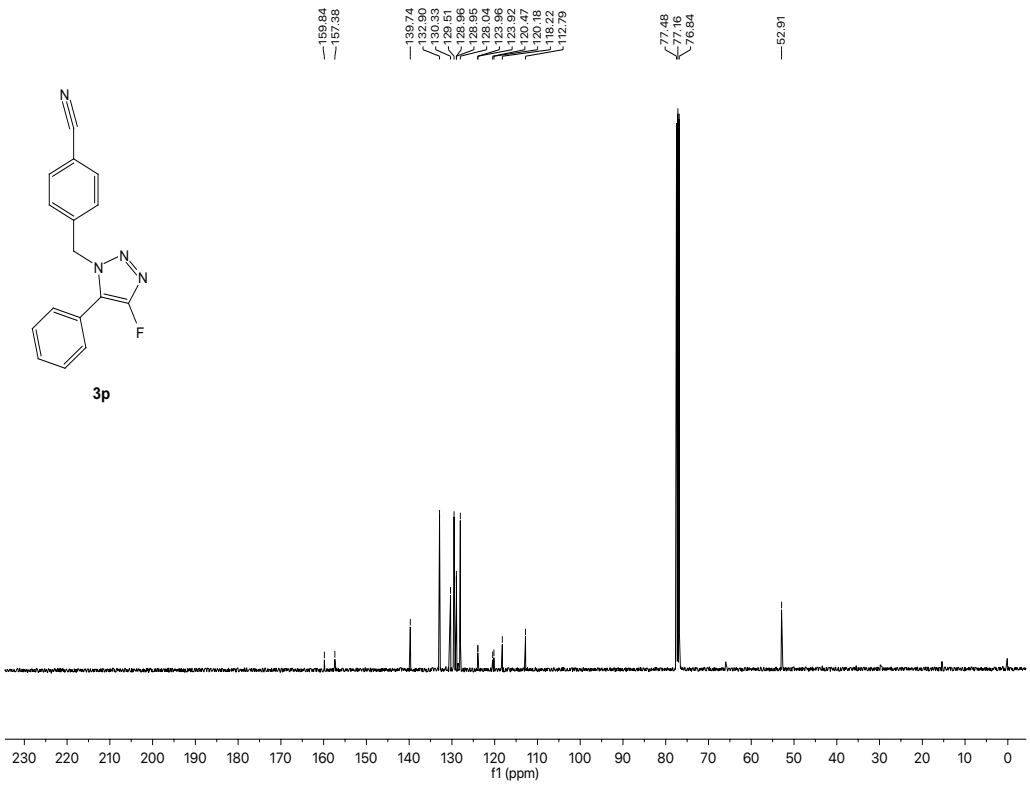
^{1}H NMR of **3p**



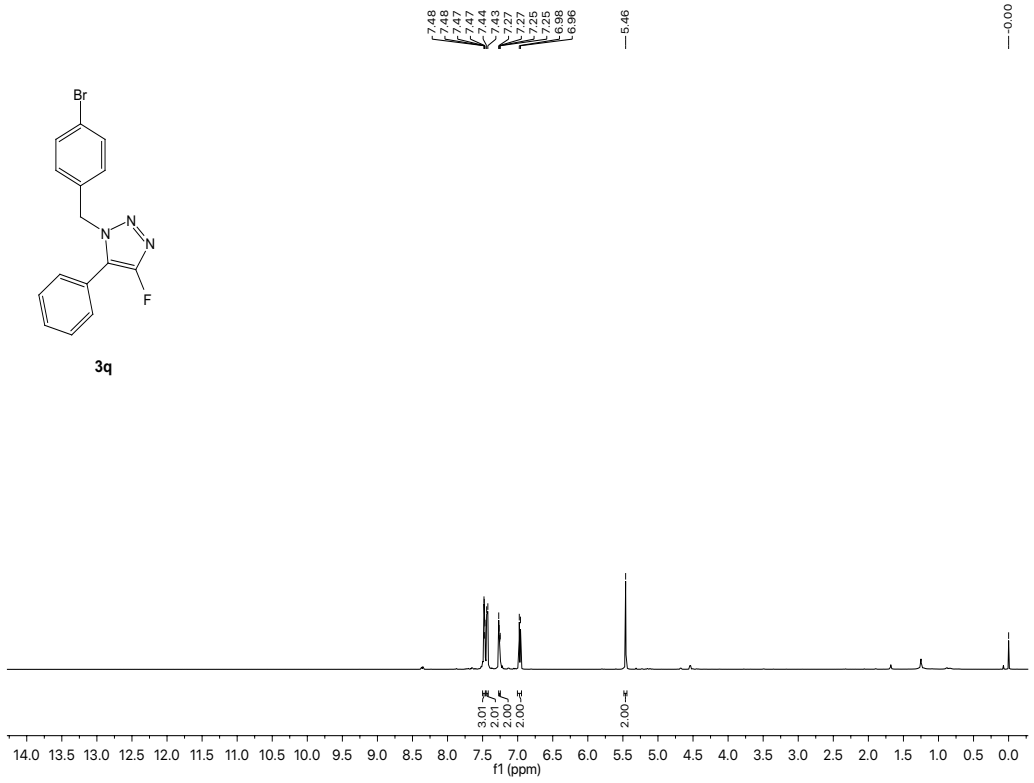
^{19}F NMR of **3p**



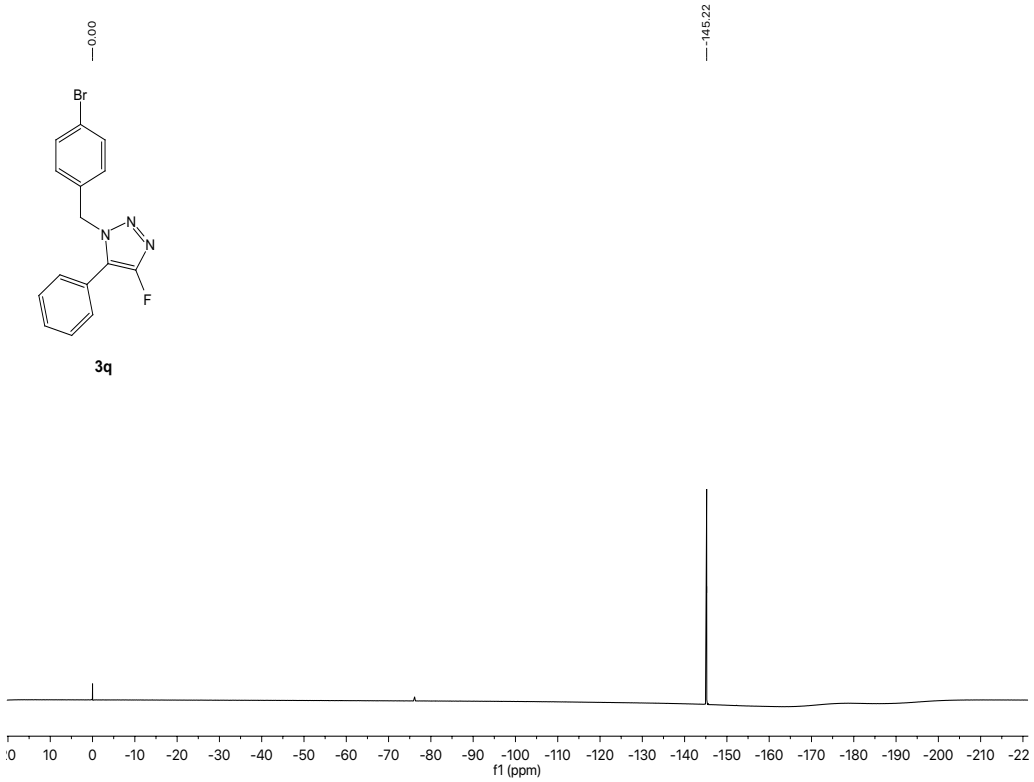
^{13}C NMR of **3p**



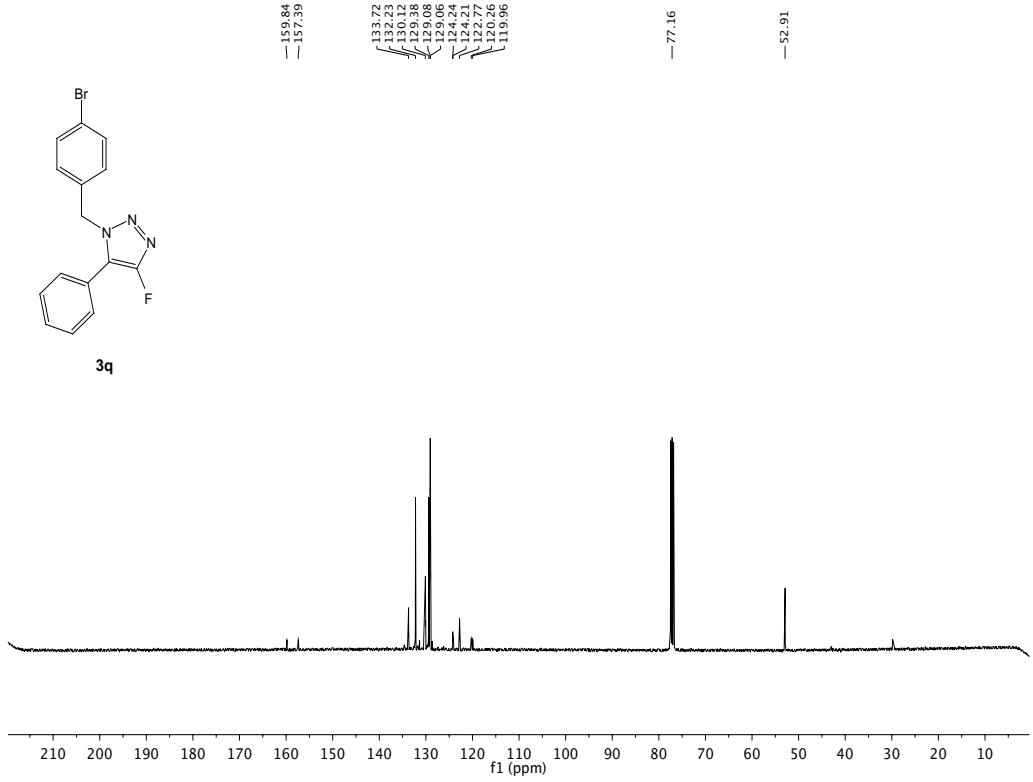
^{1}H NMR of **3q**



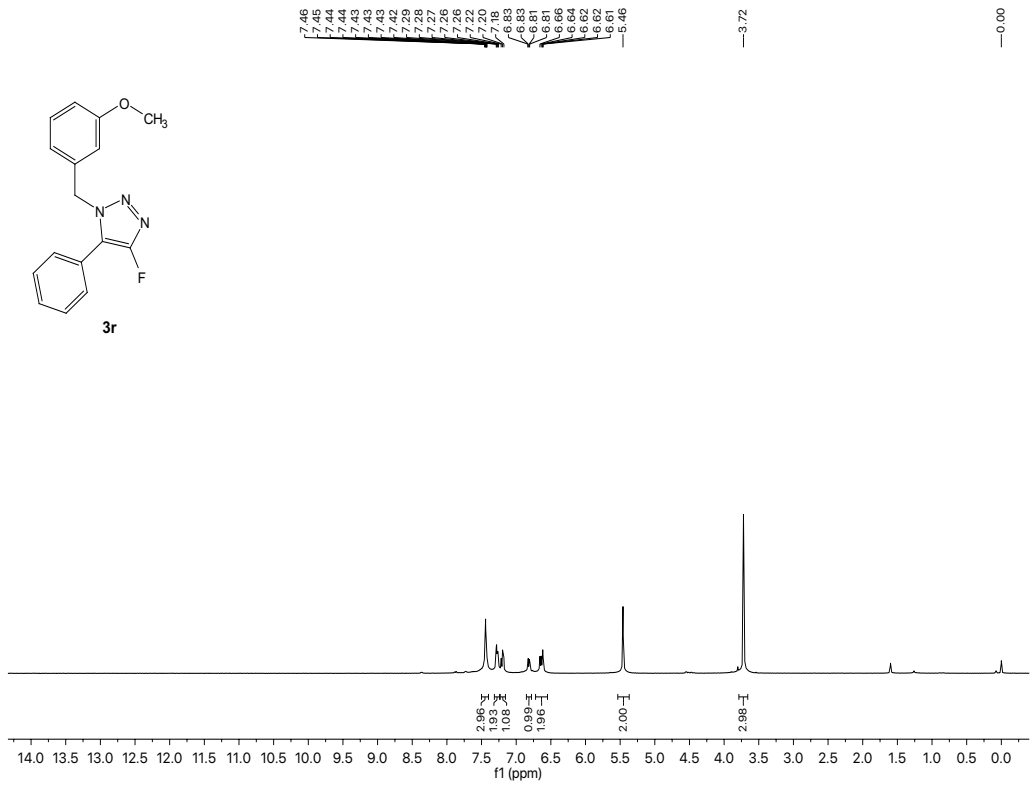
^{19}F NMR of **3q**



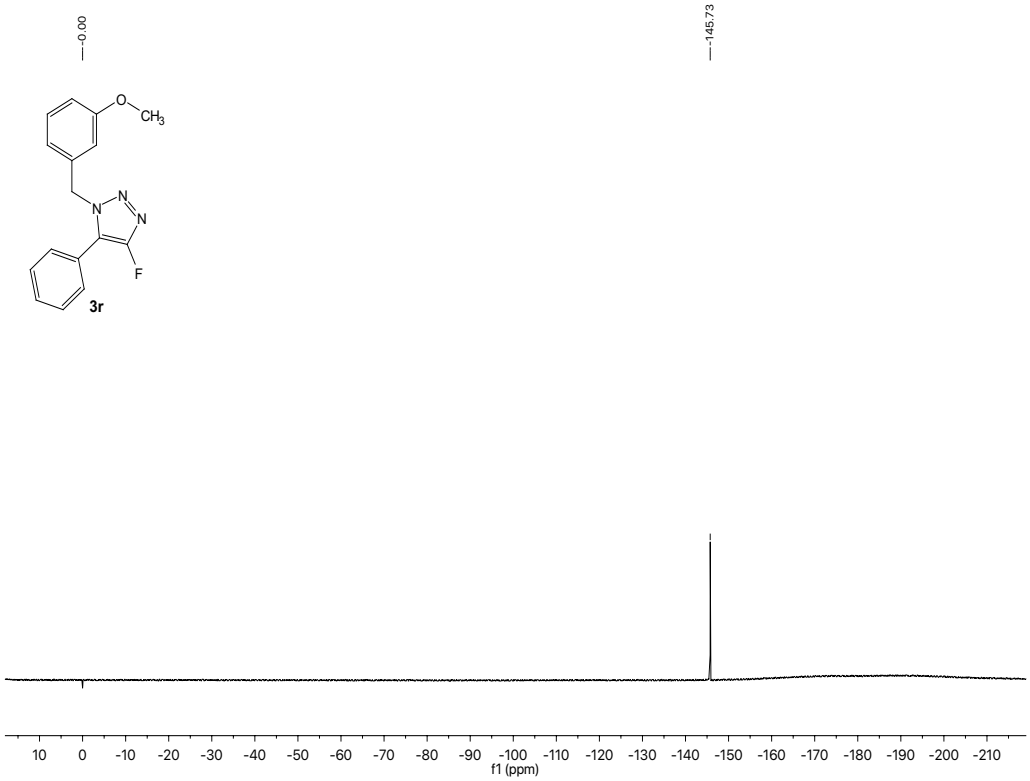
^{13}C NMR of **3q**



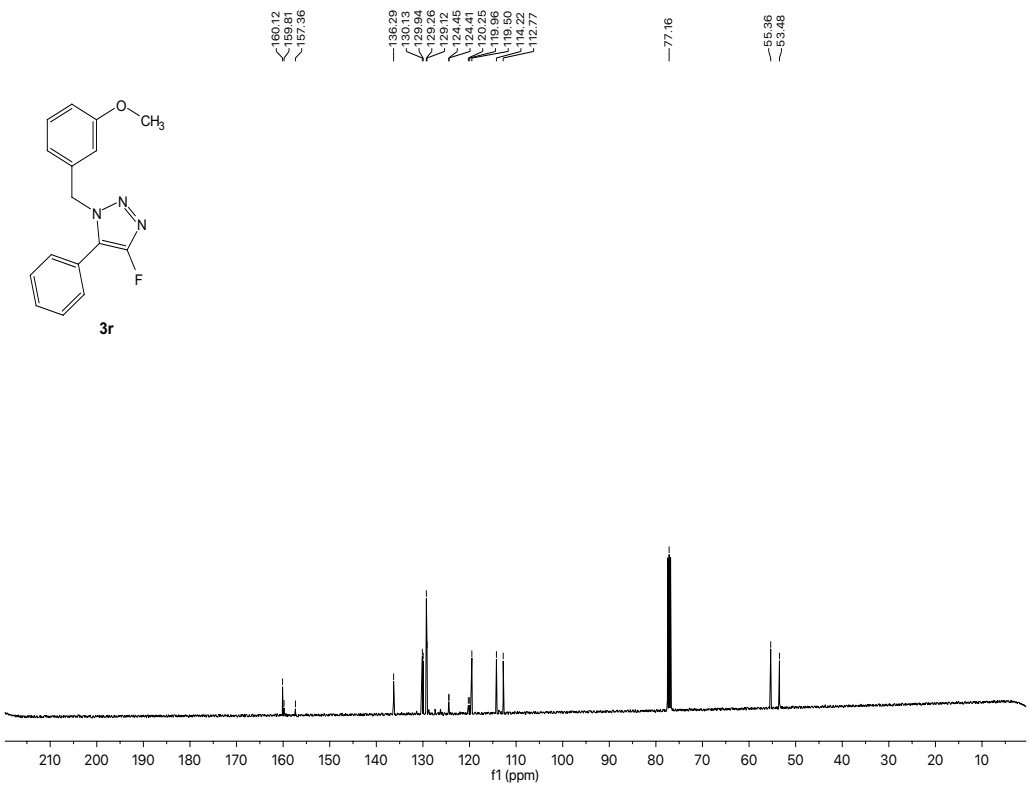
^{1}H NMR of **3r**



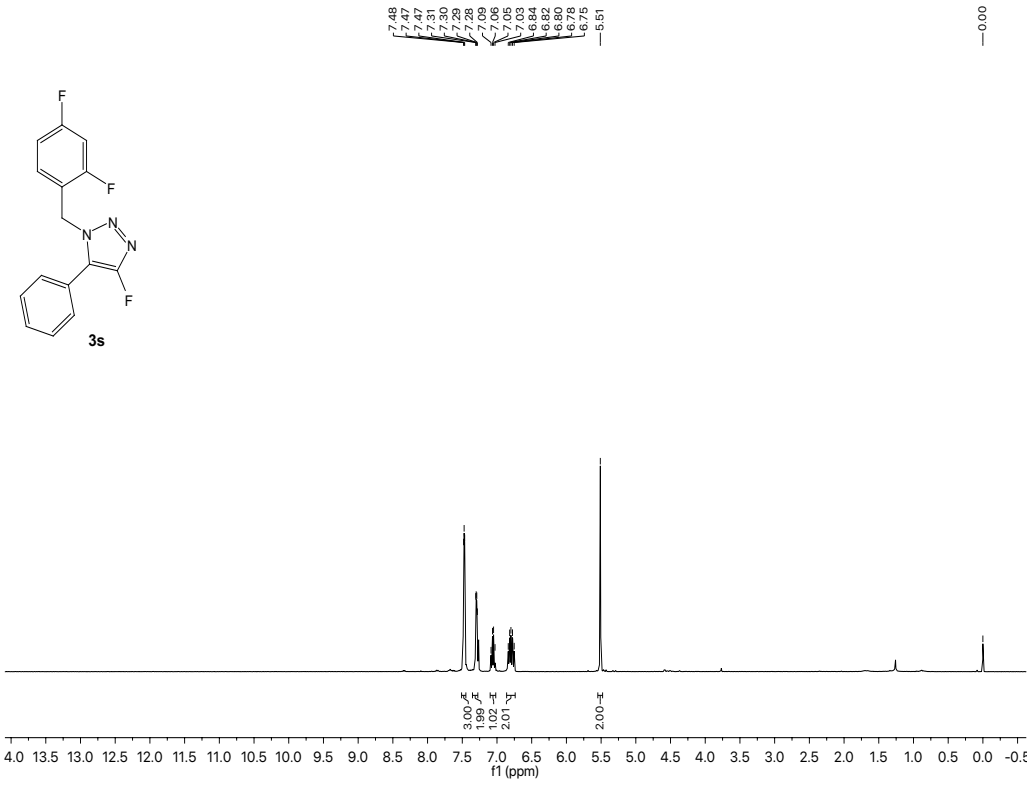
^{19}F NMR of **3r**



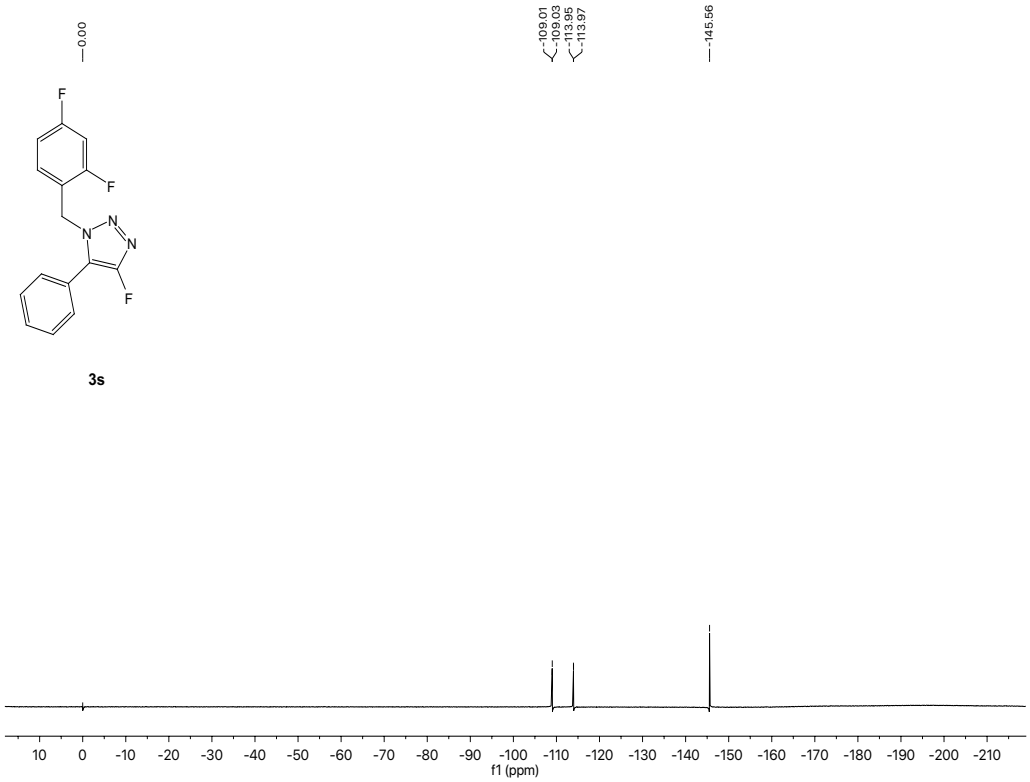
^{13}C NMR of **3r**



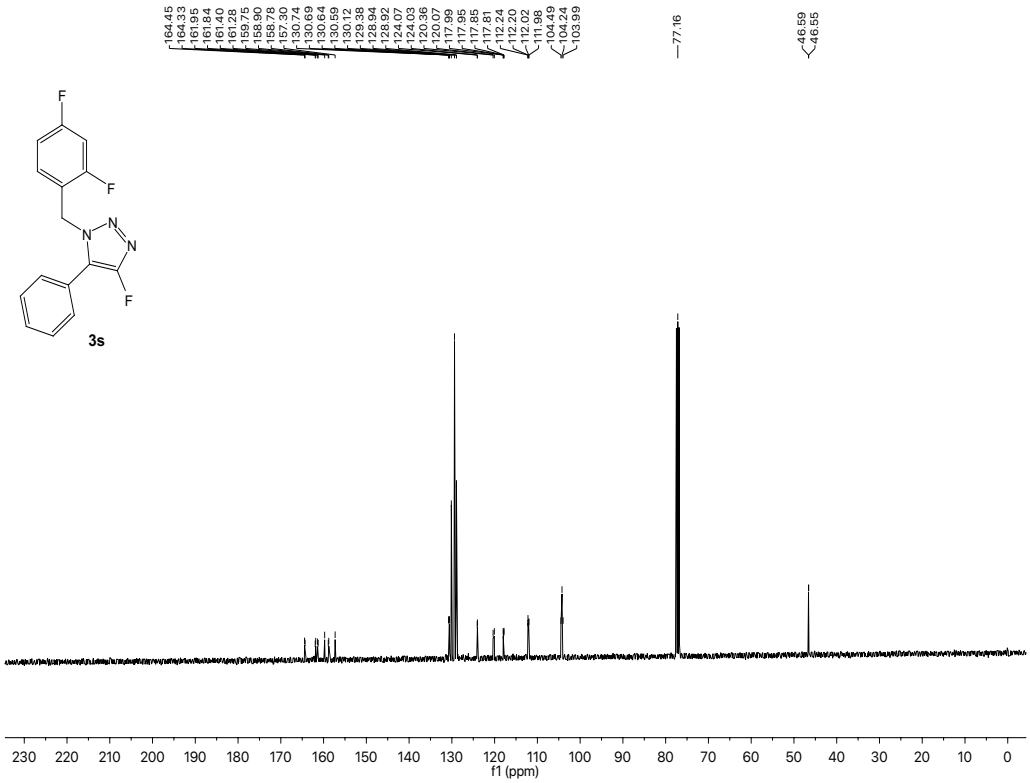
^{1}H NMR of **3s**



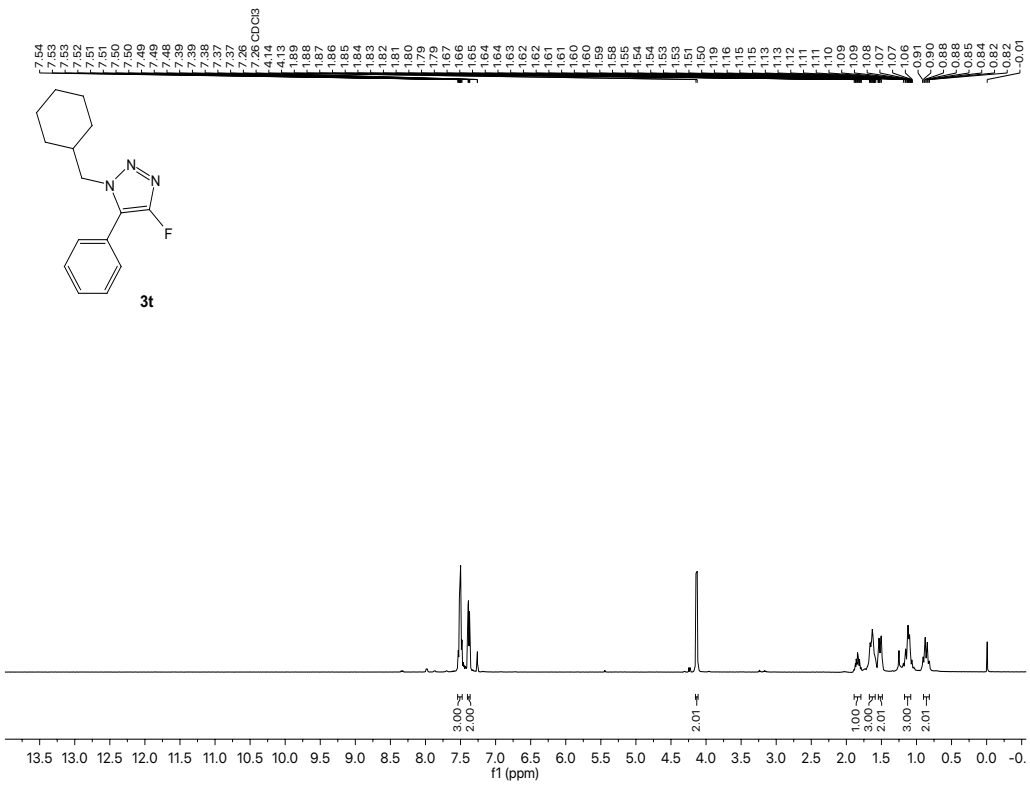
^{19}F NMR of **3s**



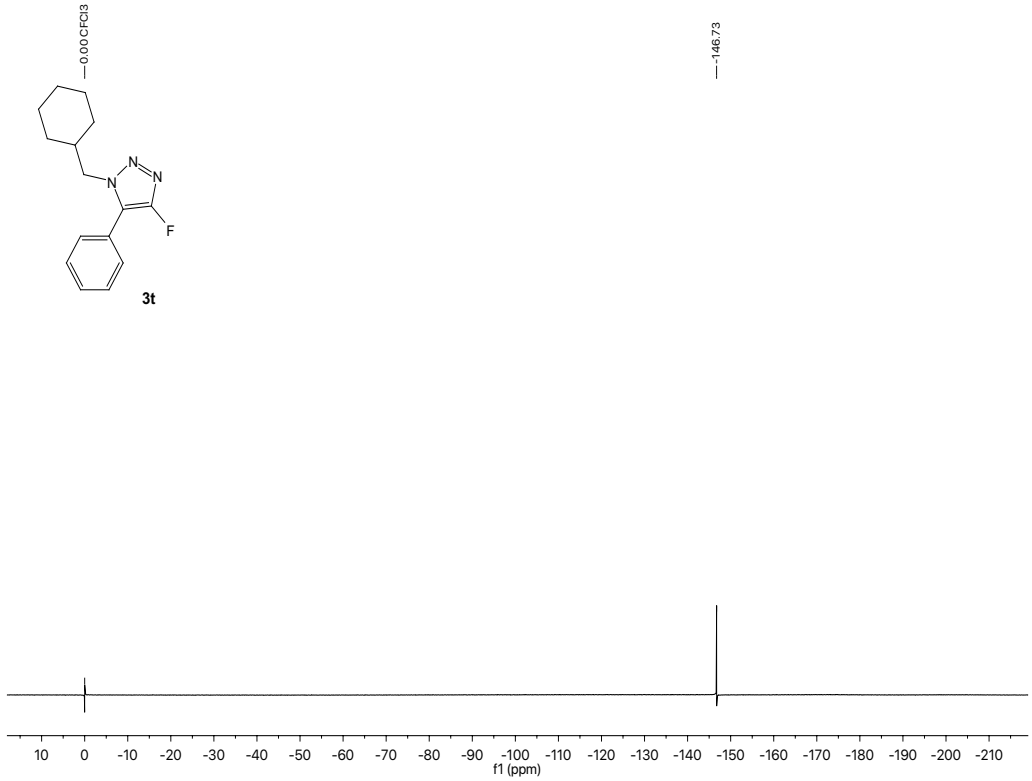
^{13}C NMR of **3s**



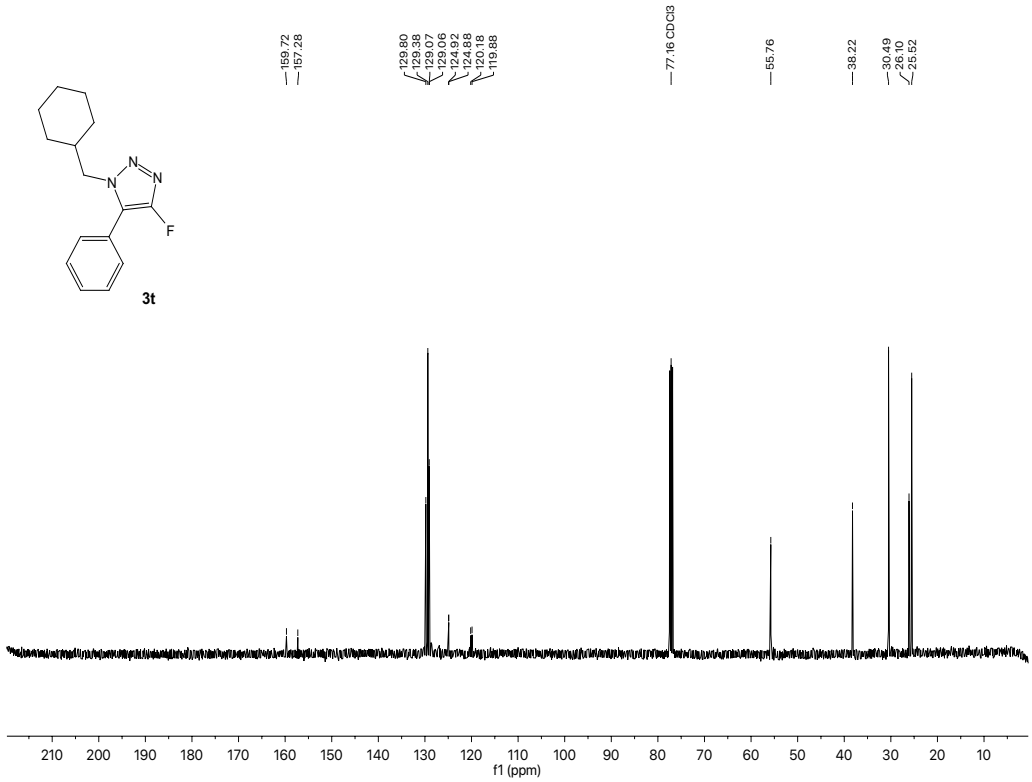
^{1}H NMR of **3t**



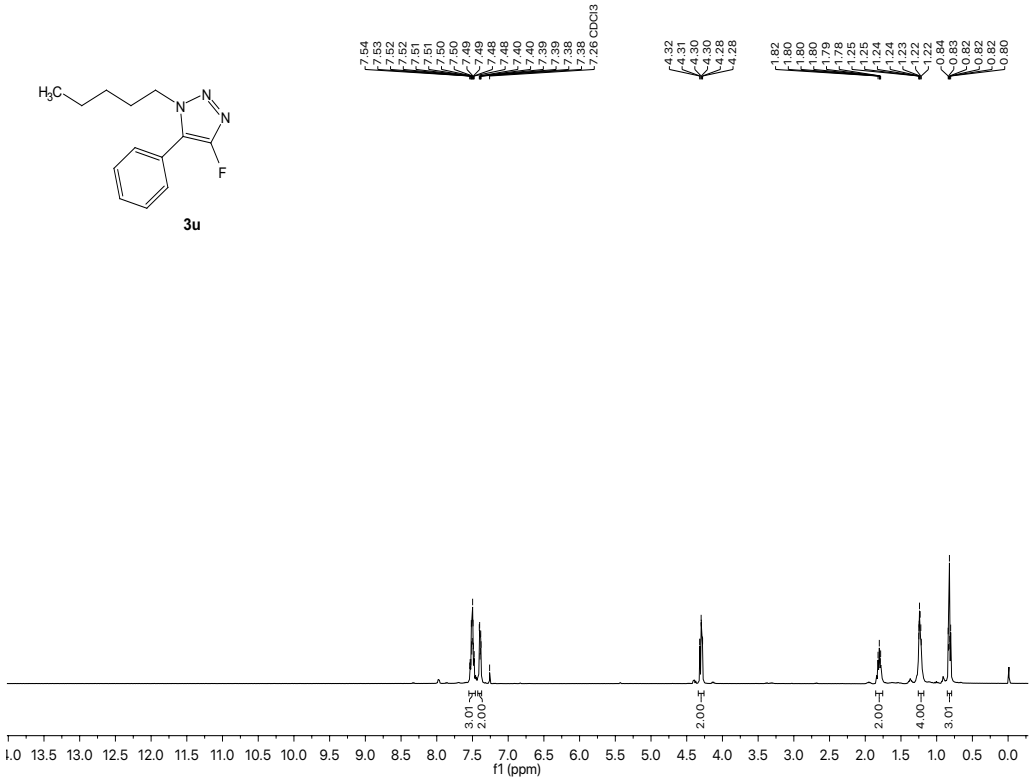
^{19}F NMR of **3t**



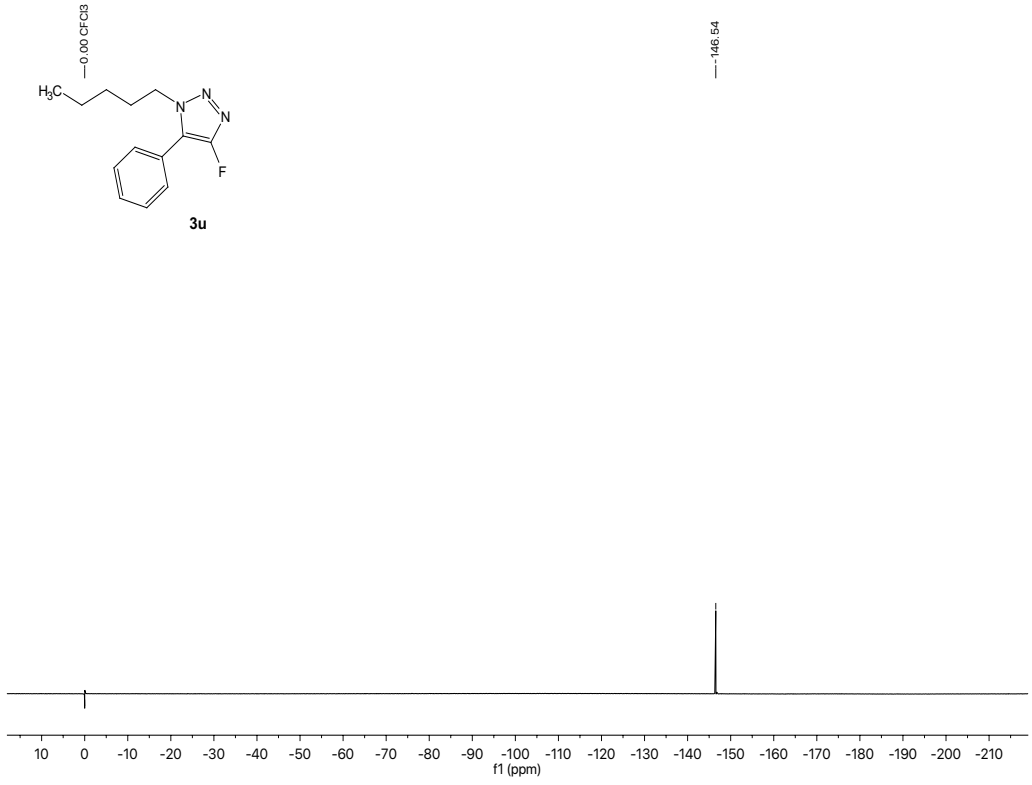
^{13}C NMR of **3t**



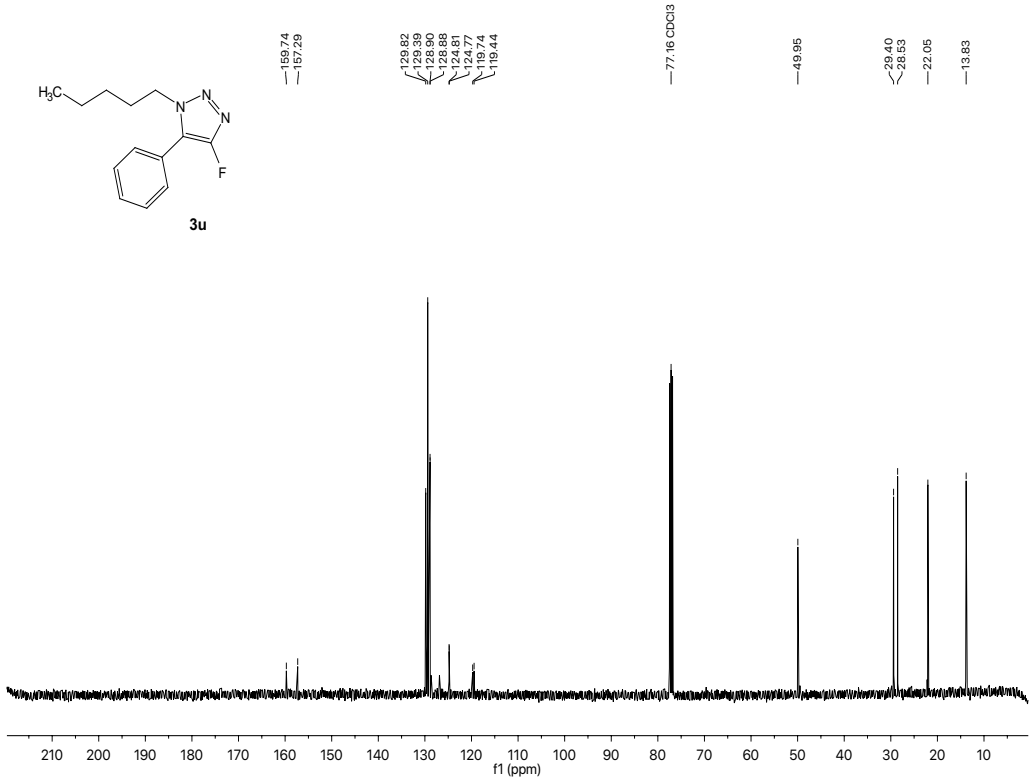
^{1}H NMR of **3u**



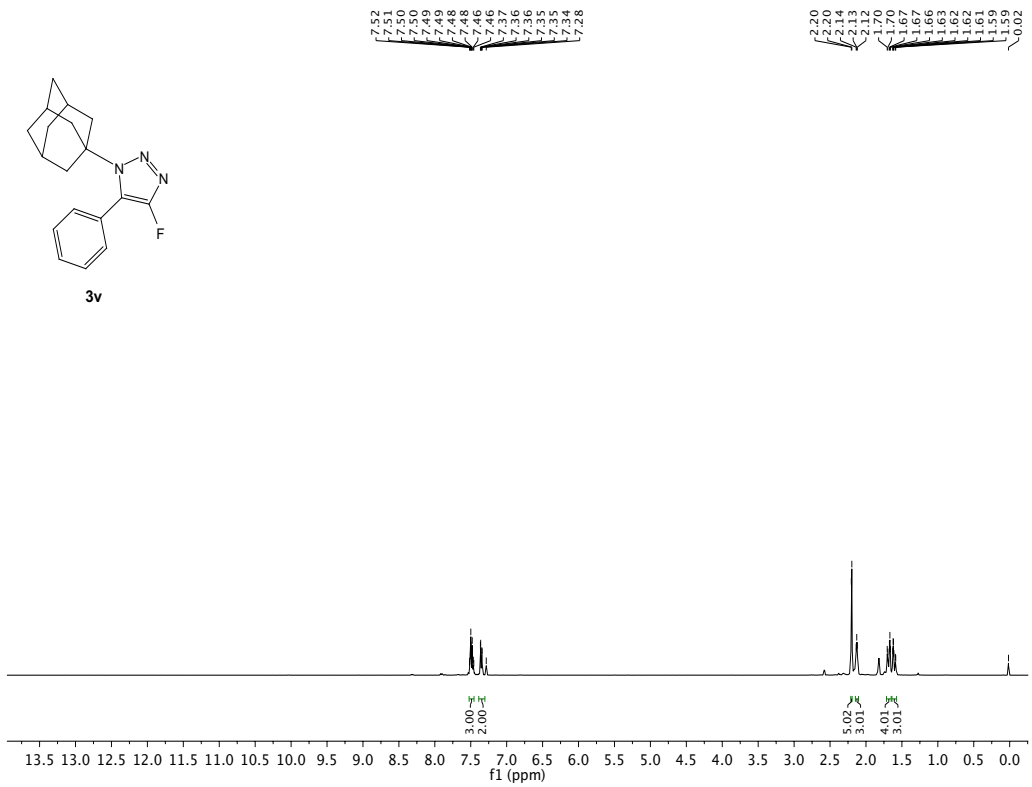
^{19}F NMR of **3u**



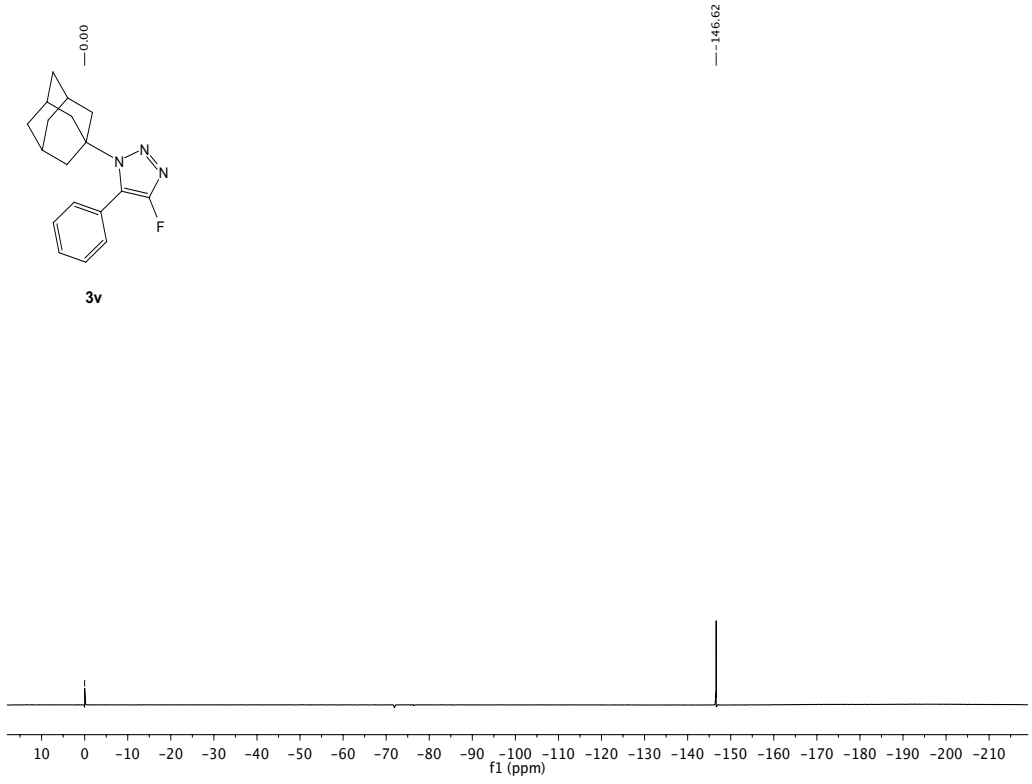
^{13}C NMR of **3u**



^{1}H NMR of **3v**



^{19}F NMR of **3v**



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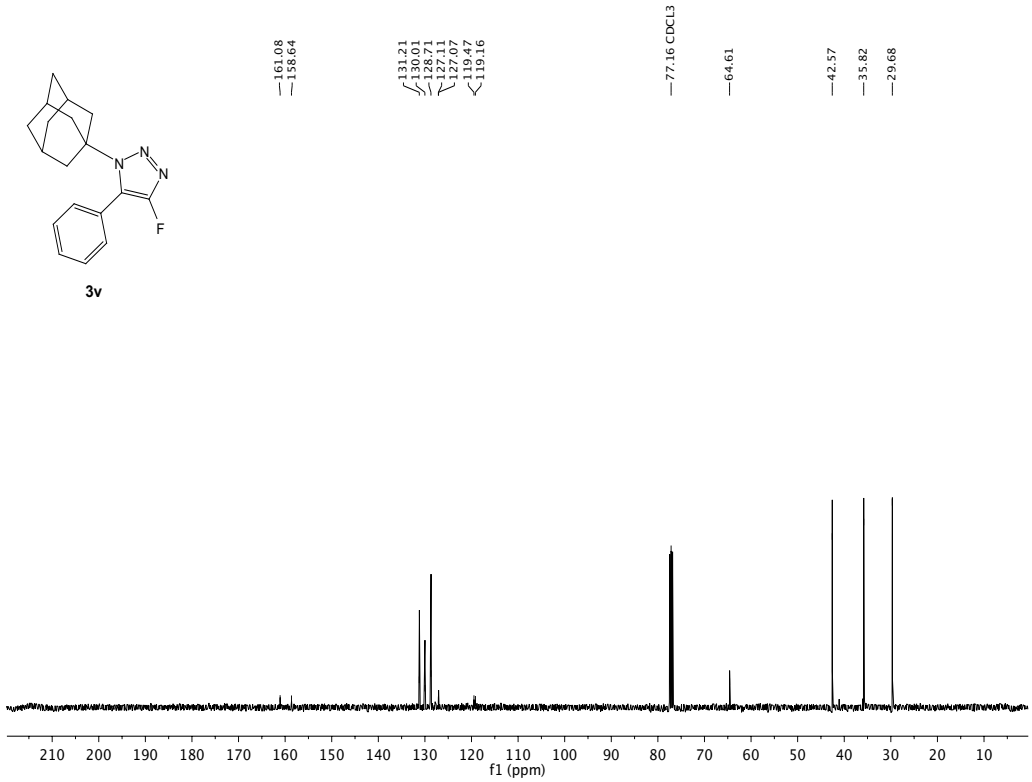
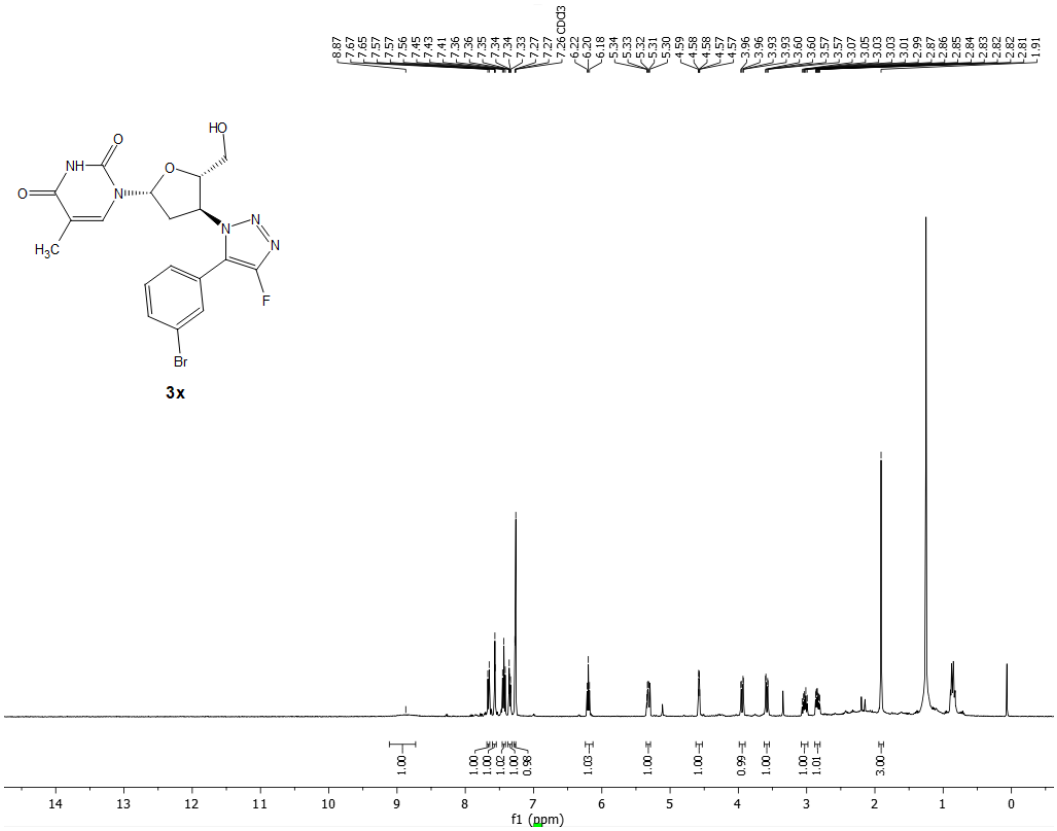
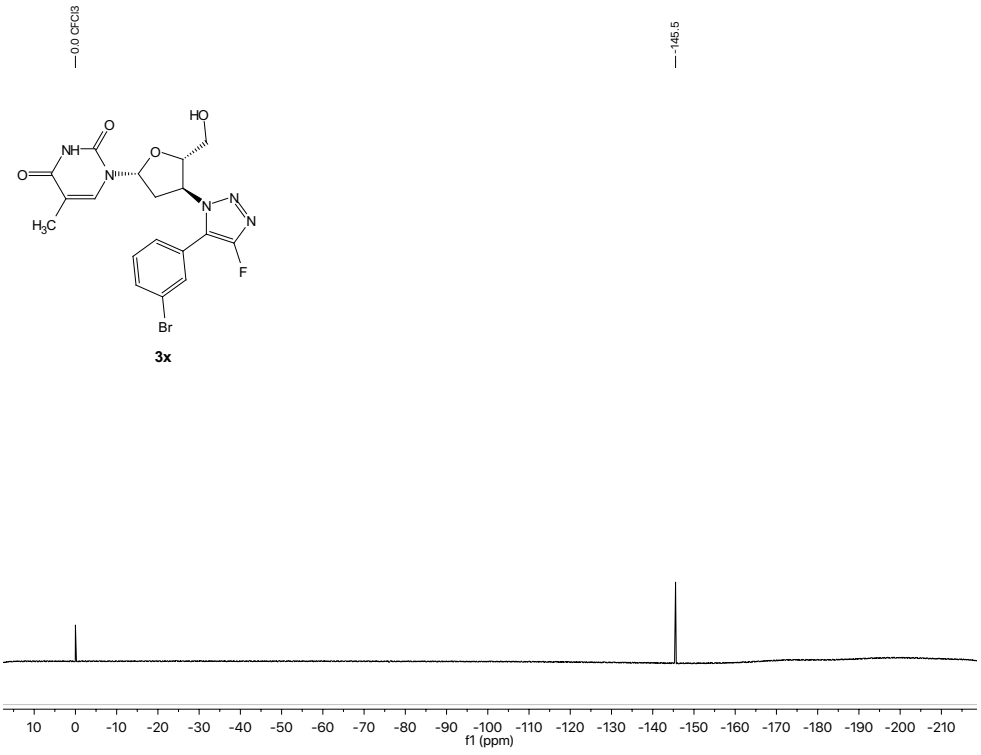


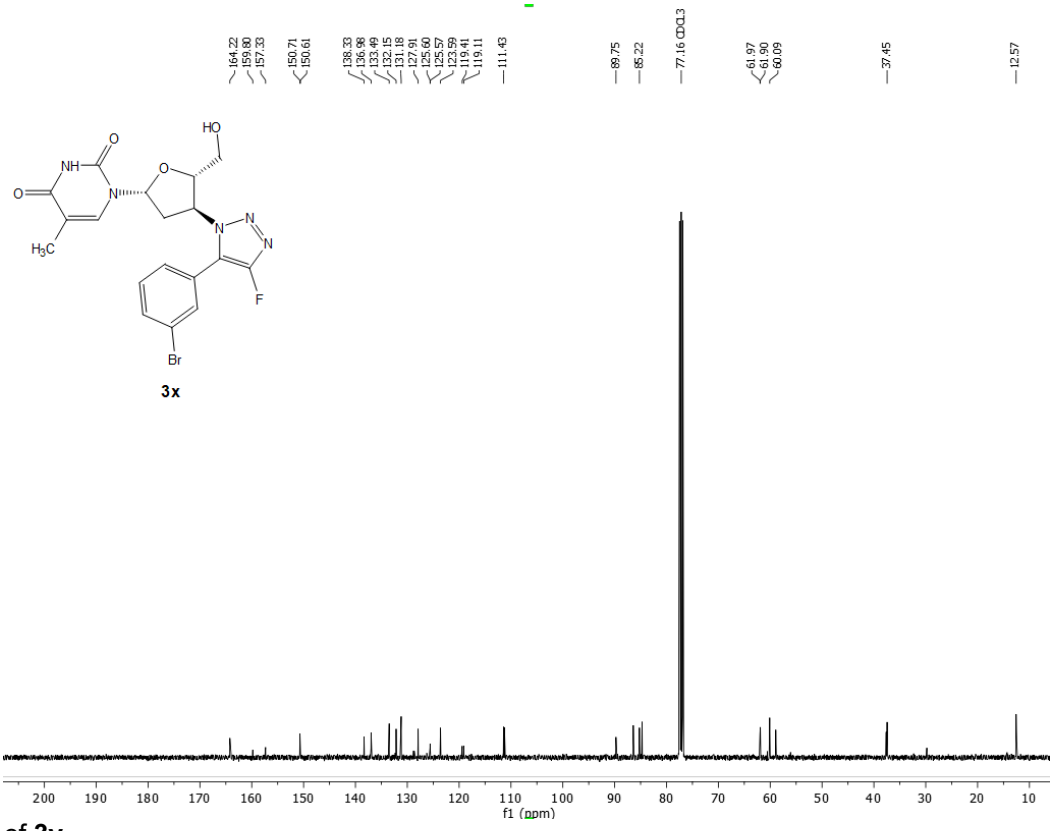
^{1}H NMR of **3x**



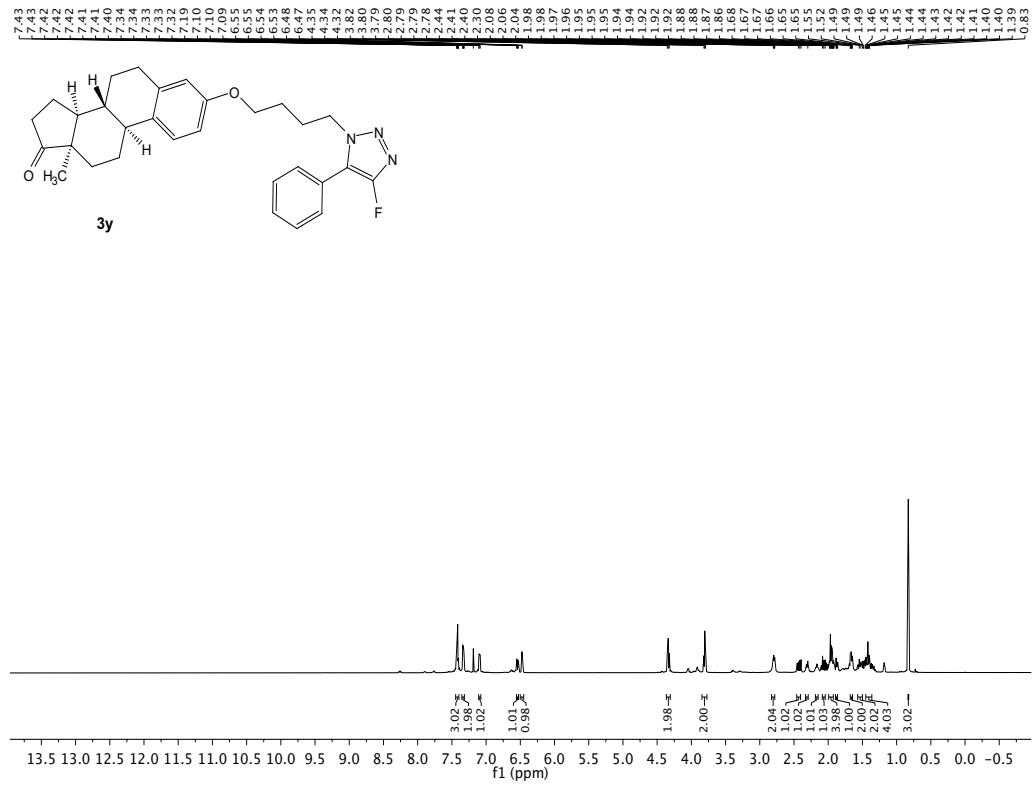
^{19}F NMR of **3x**



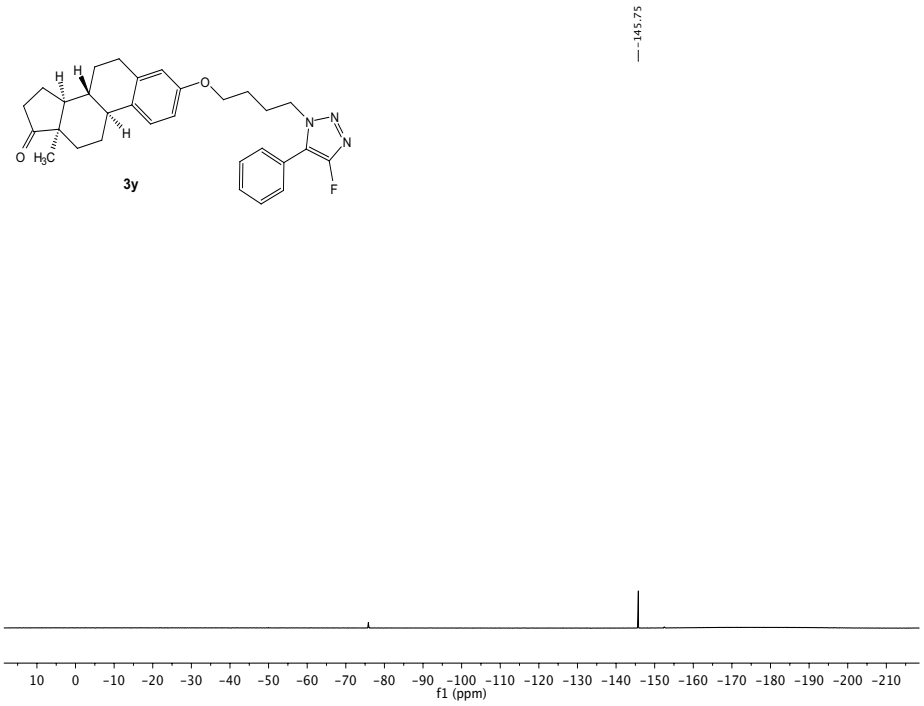
^{13}C NMR of **3x**



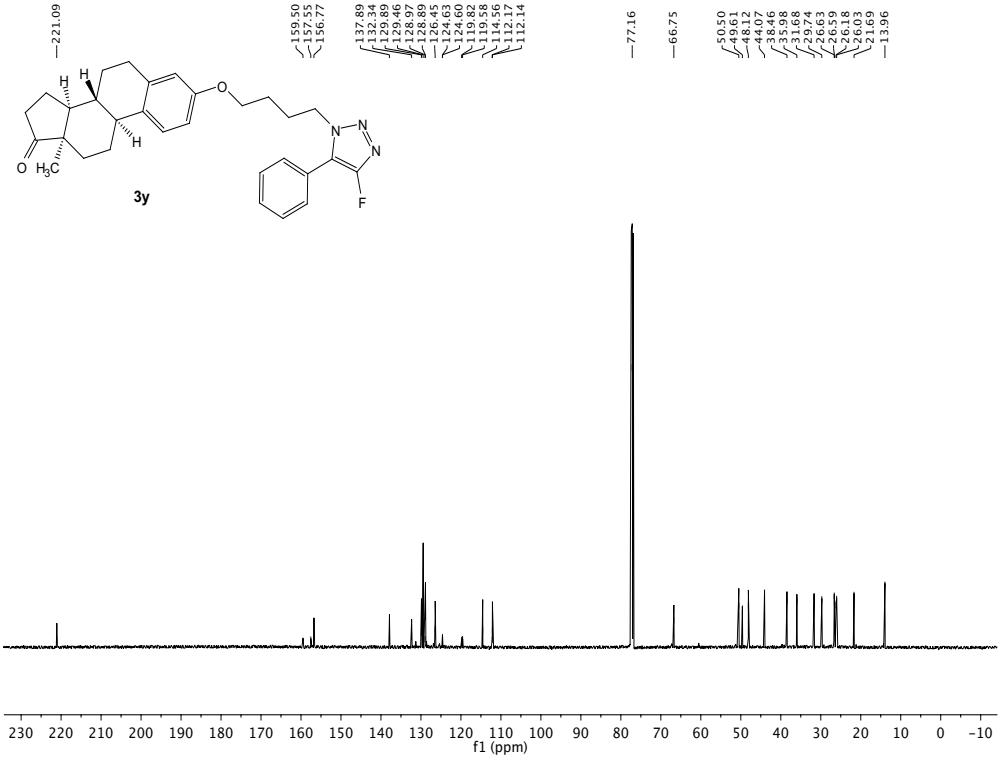
^{1}H NMR of **3y**



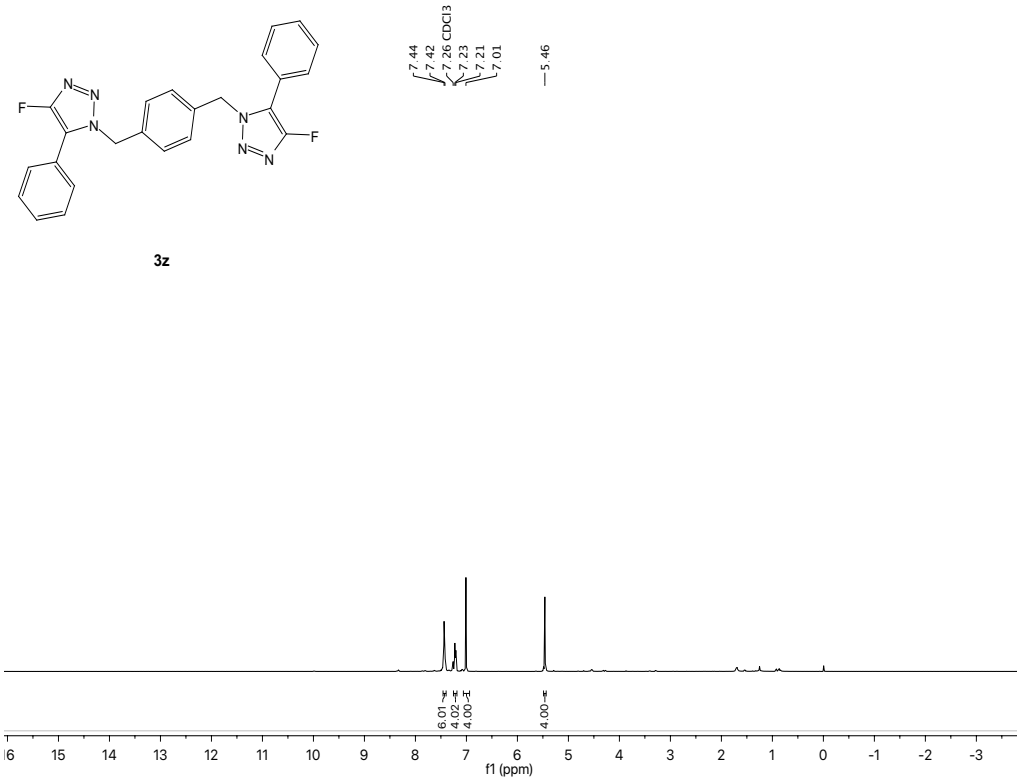
^{19}F NMR of **3y**



^{13}C NMR of **3y**



^{1}H NMR of **3z**



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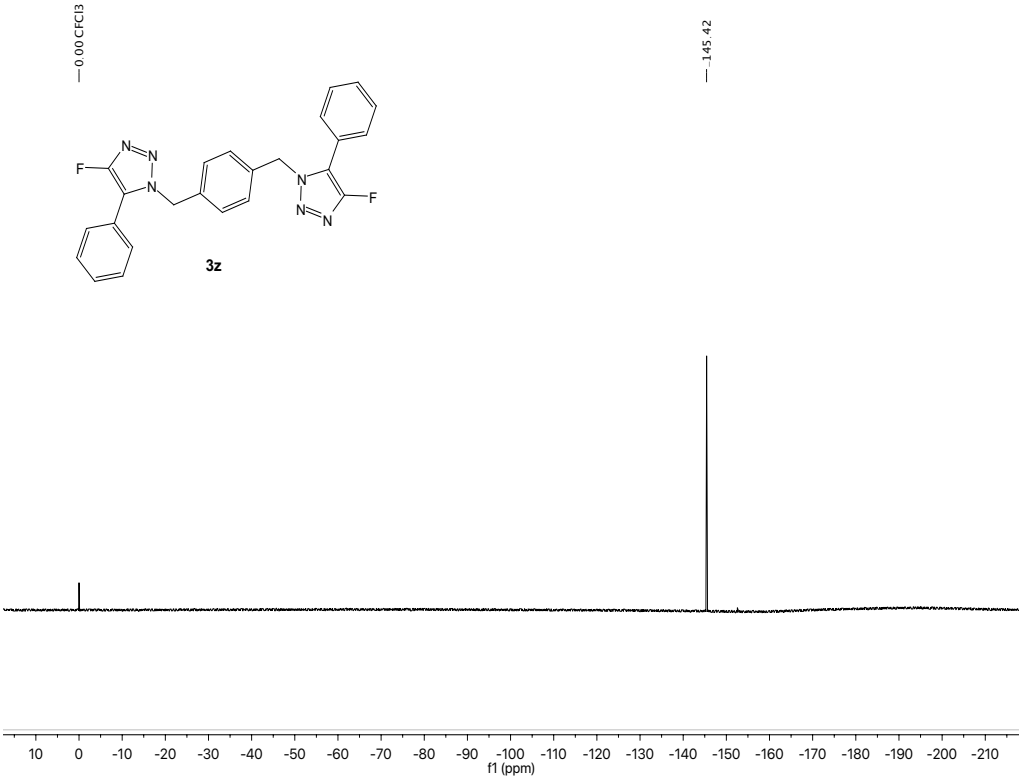
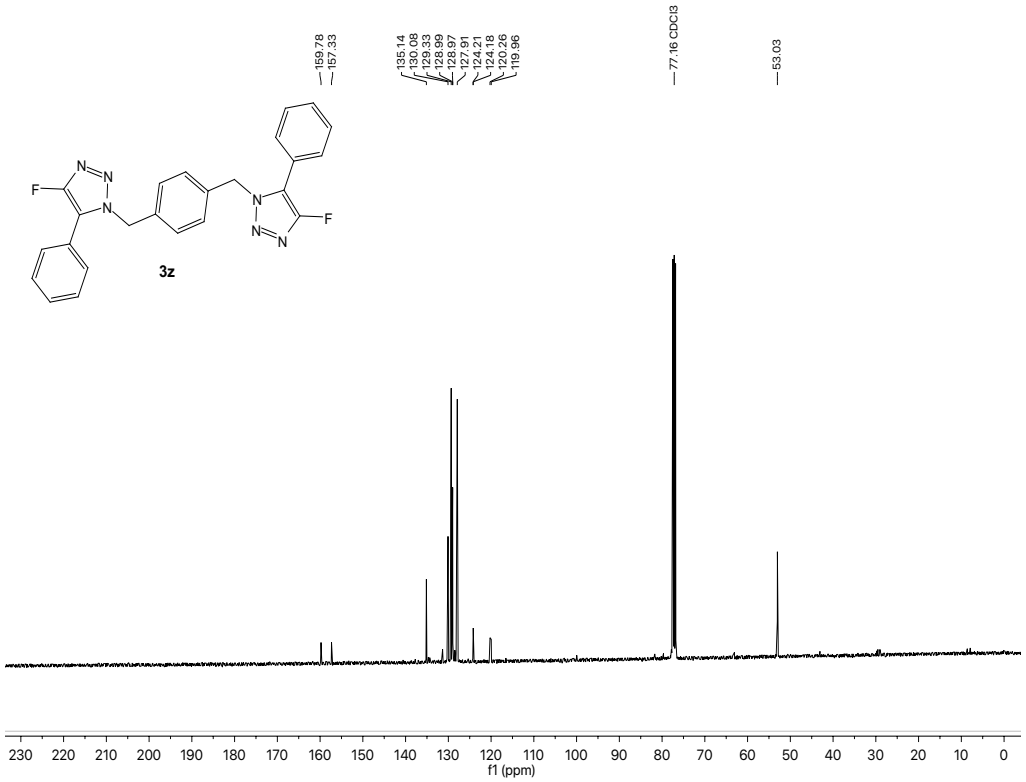
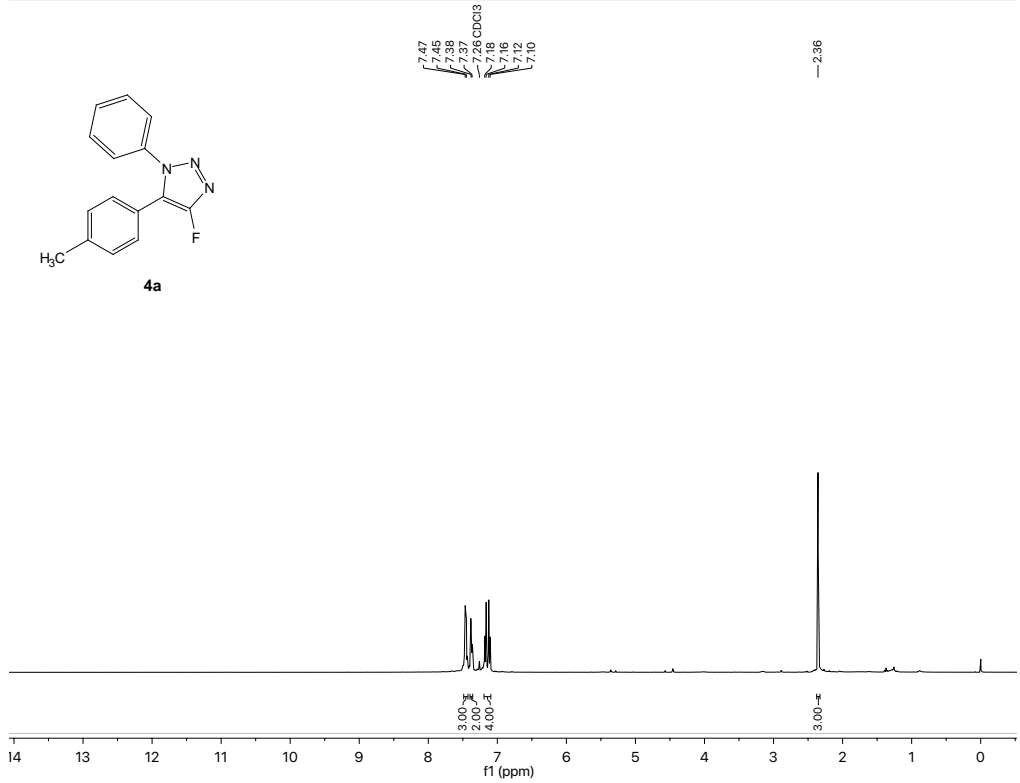


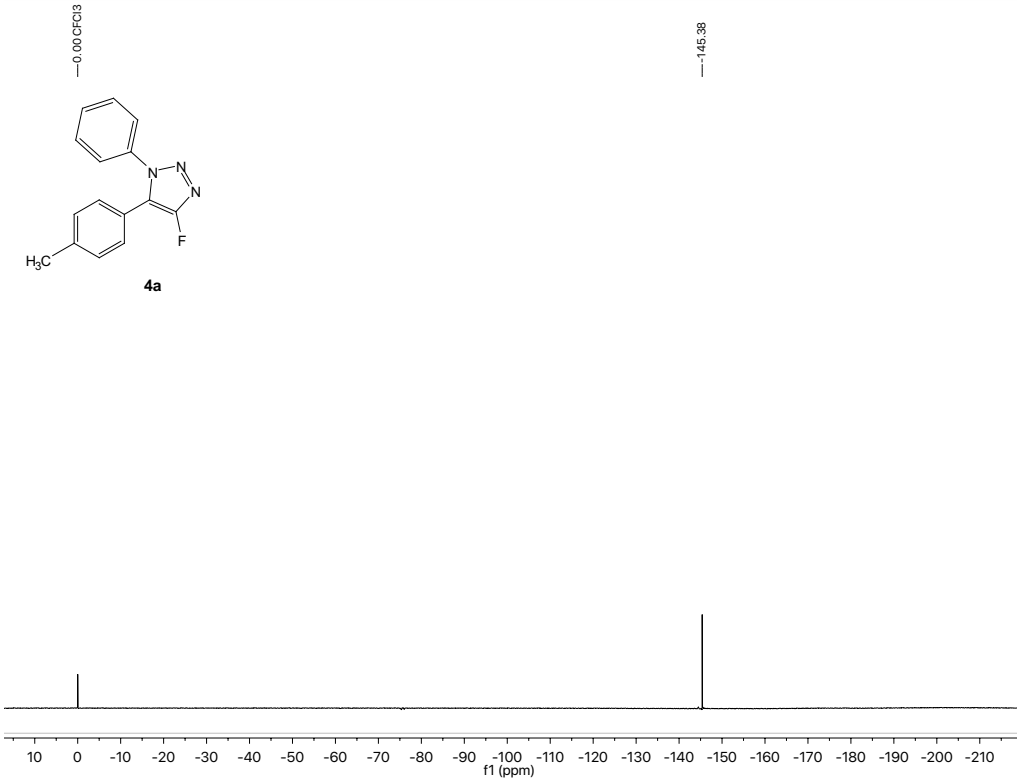
^{13}C NMR of **3z**



^{1}H NMR of **4a**

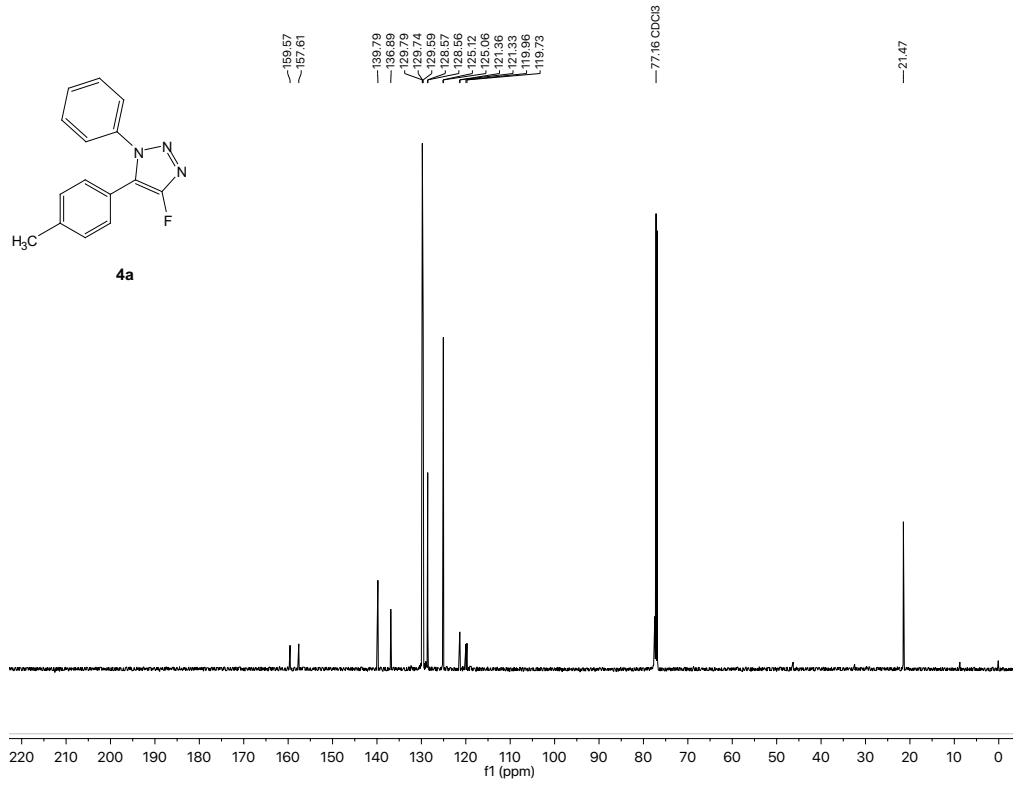


^{19}F NMR of **4a**



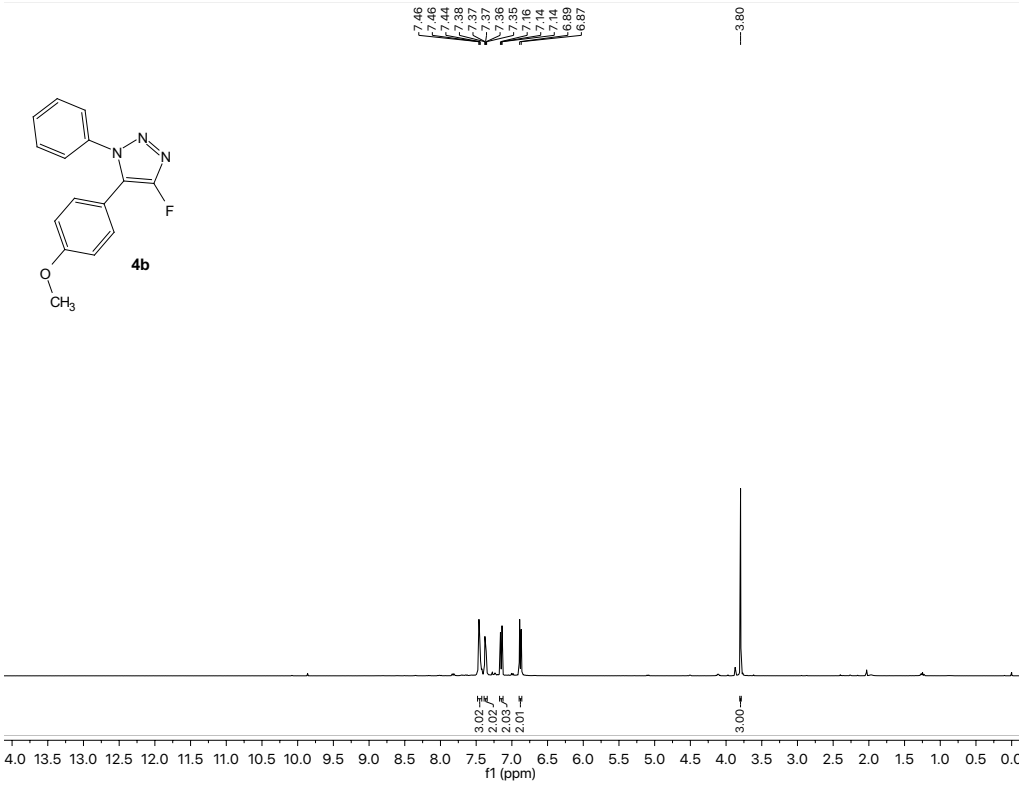
4a

^{13}C NMR of **4a**

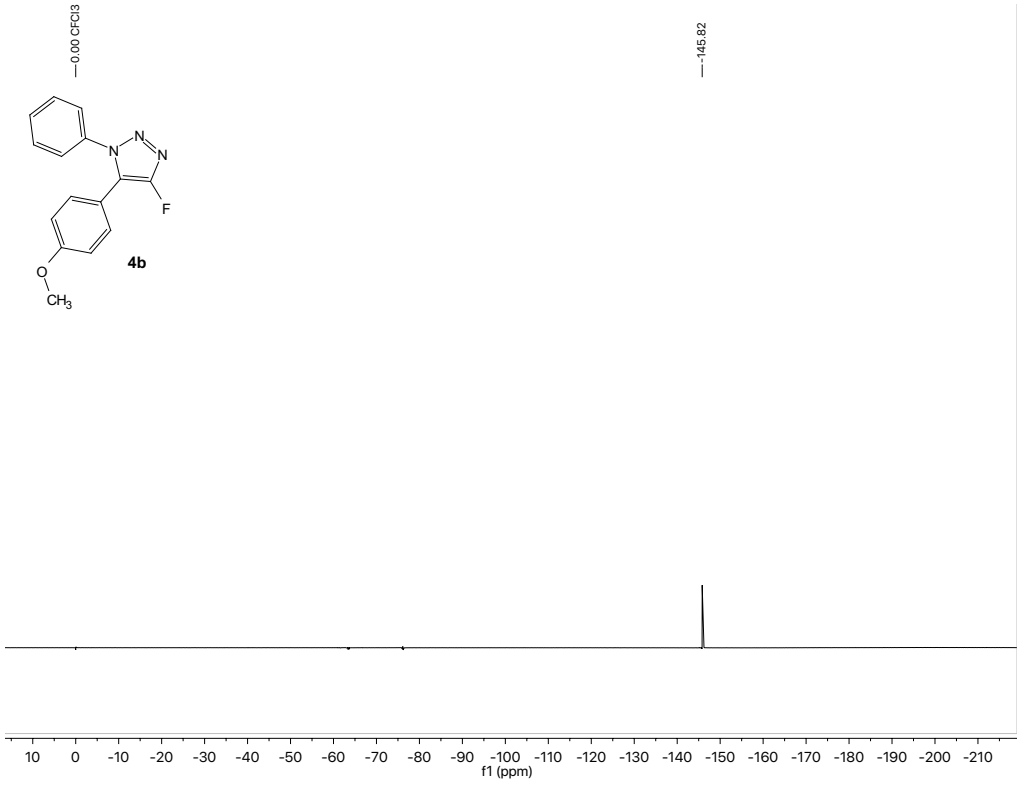


4a

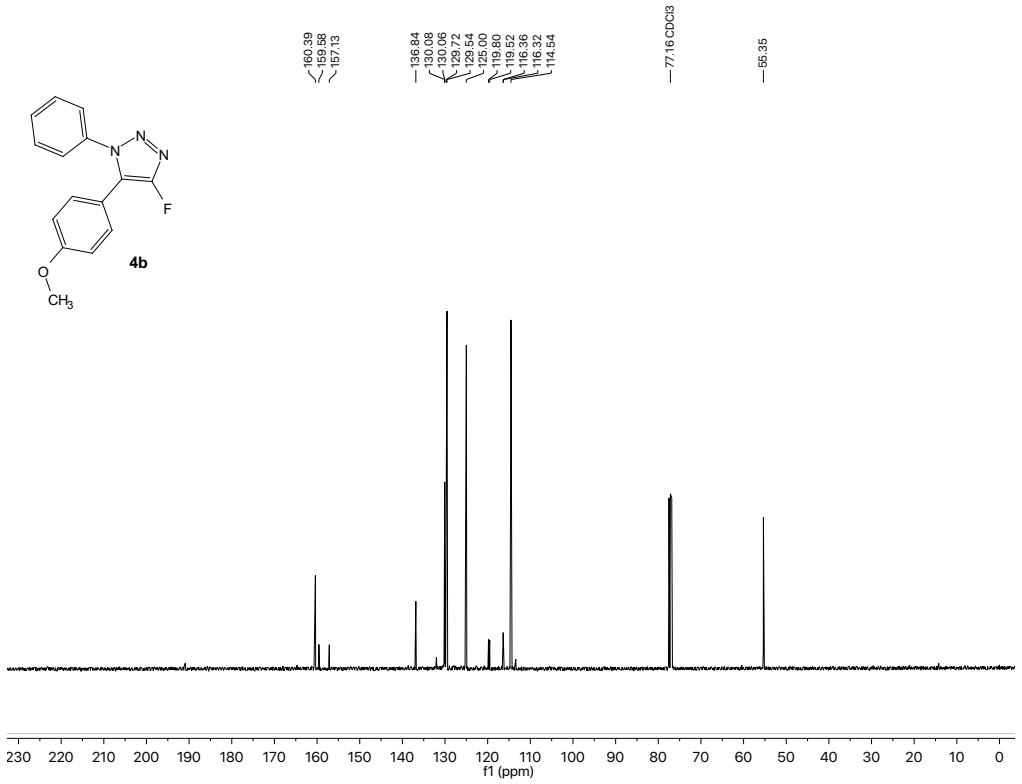
^{1}H NMR of **4b**



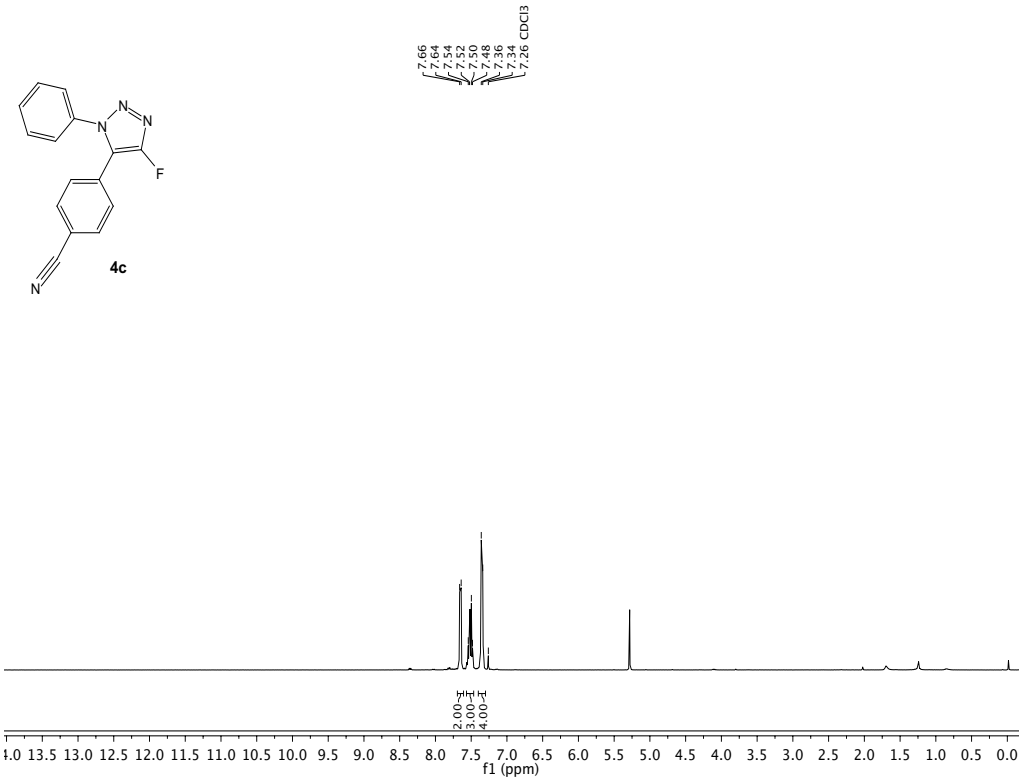
^{19}F NMR of **4b**



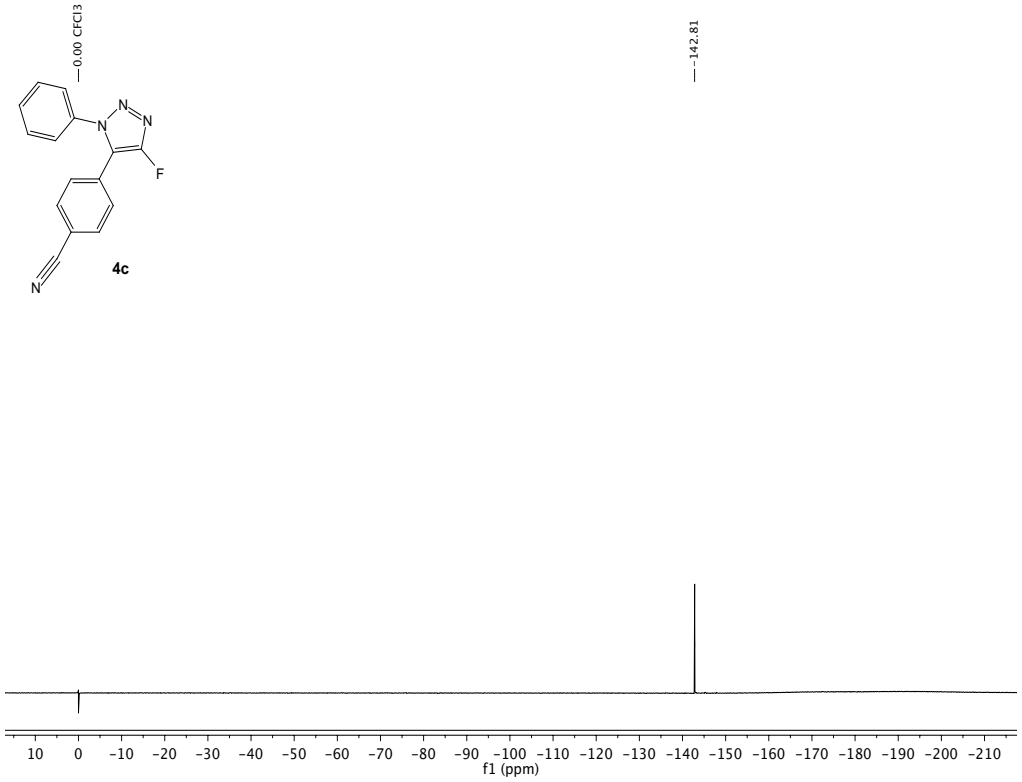
^{13}C NMR of **4b**



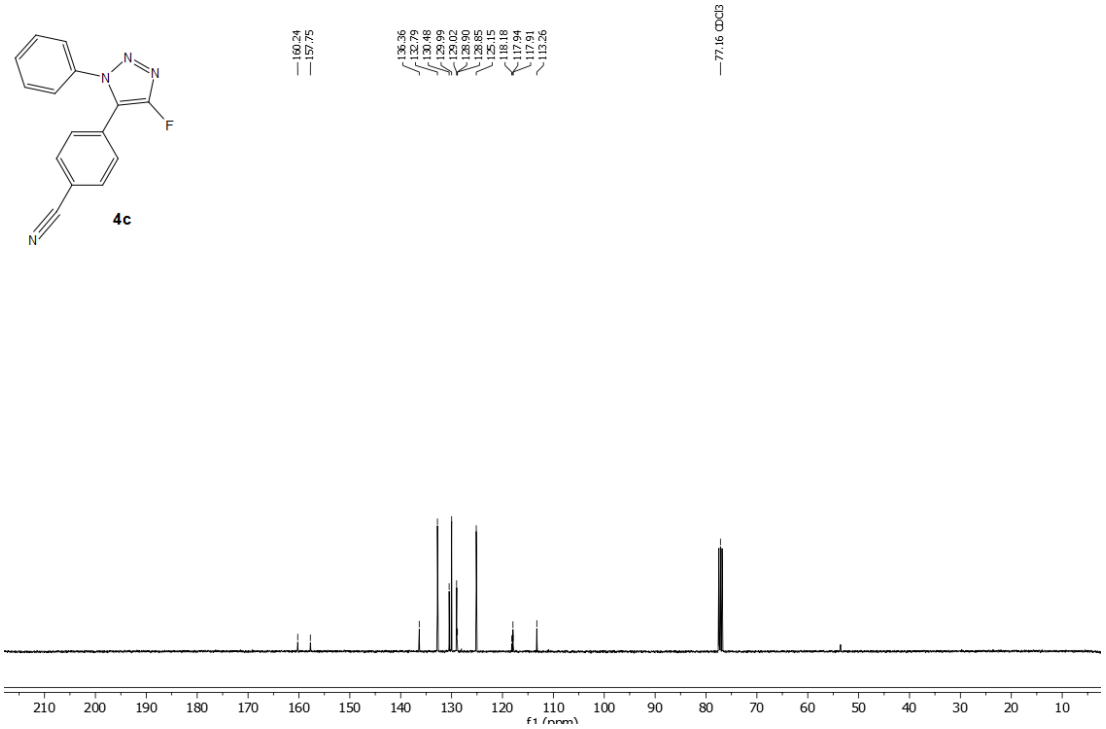
^{1}H NMR of **4c**



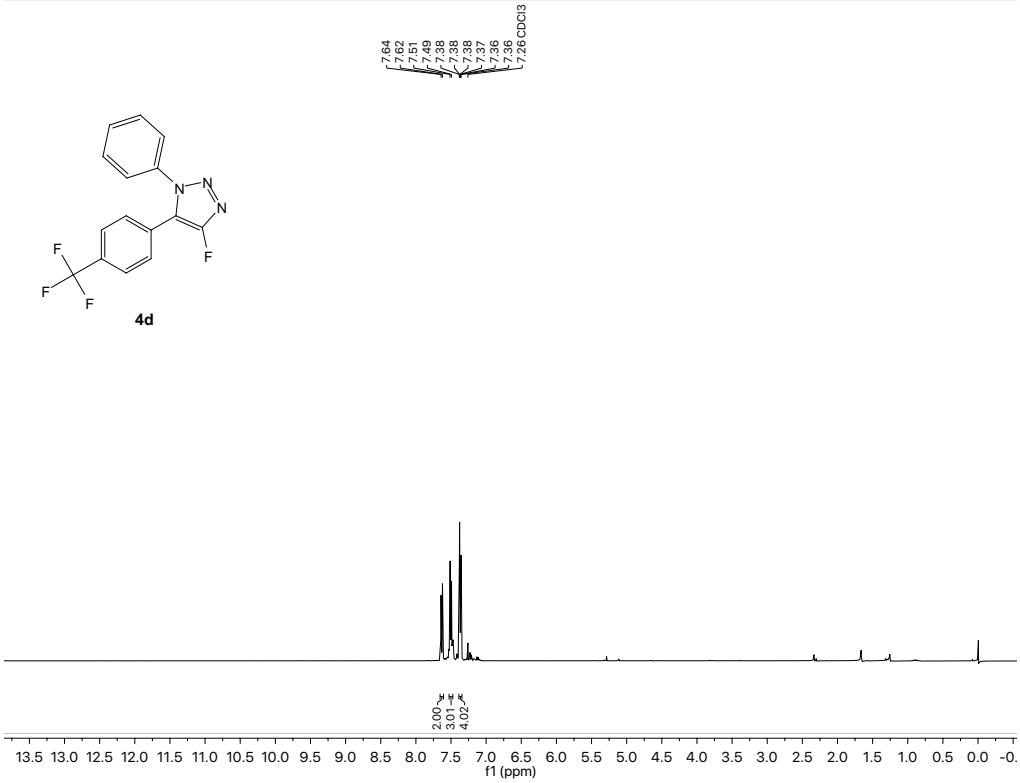
^{19}F NMR of **4c**



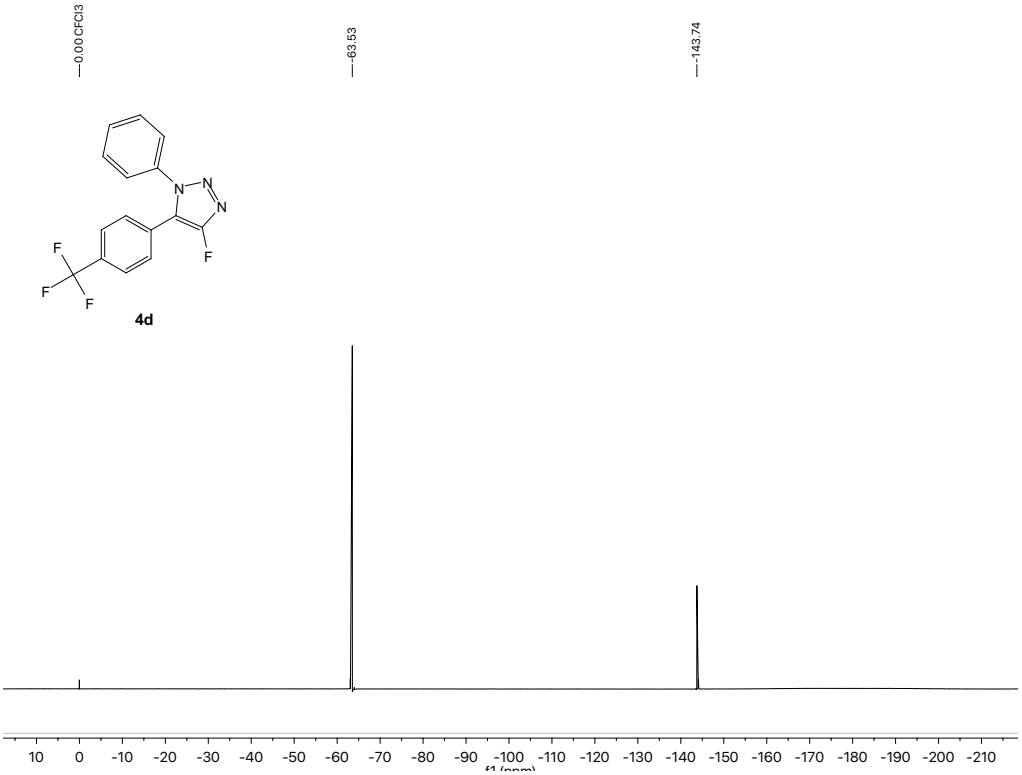
^{13}C NMR of **4c**



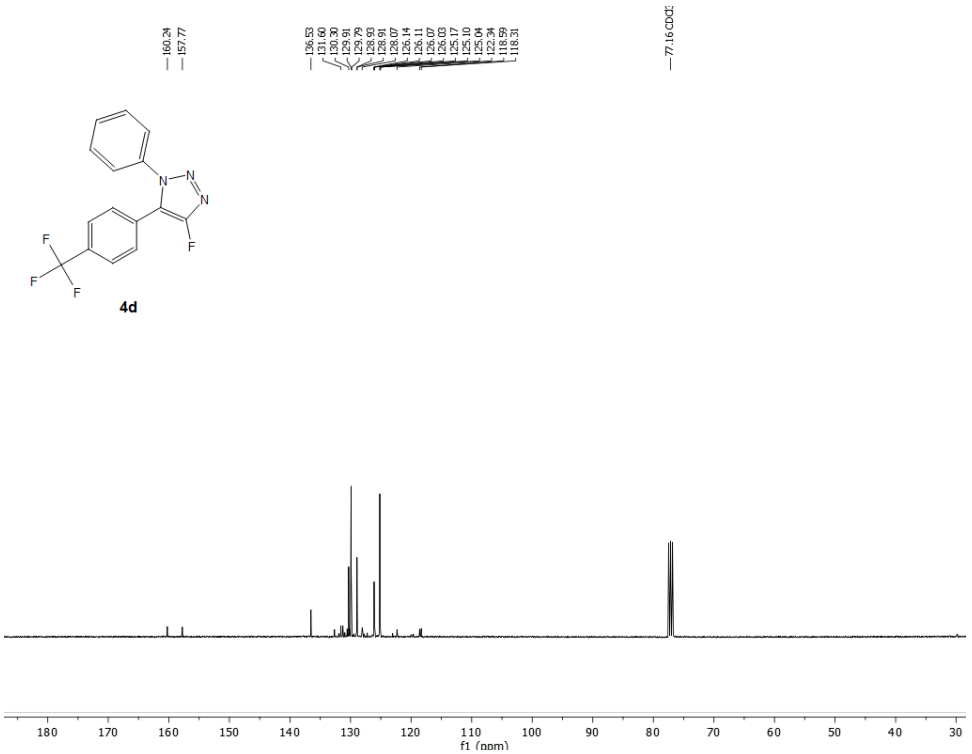
^{1}H NMR of **4d**



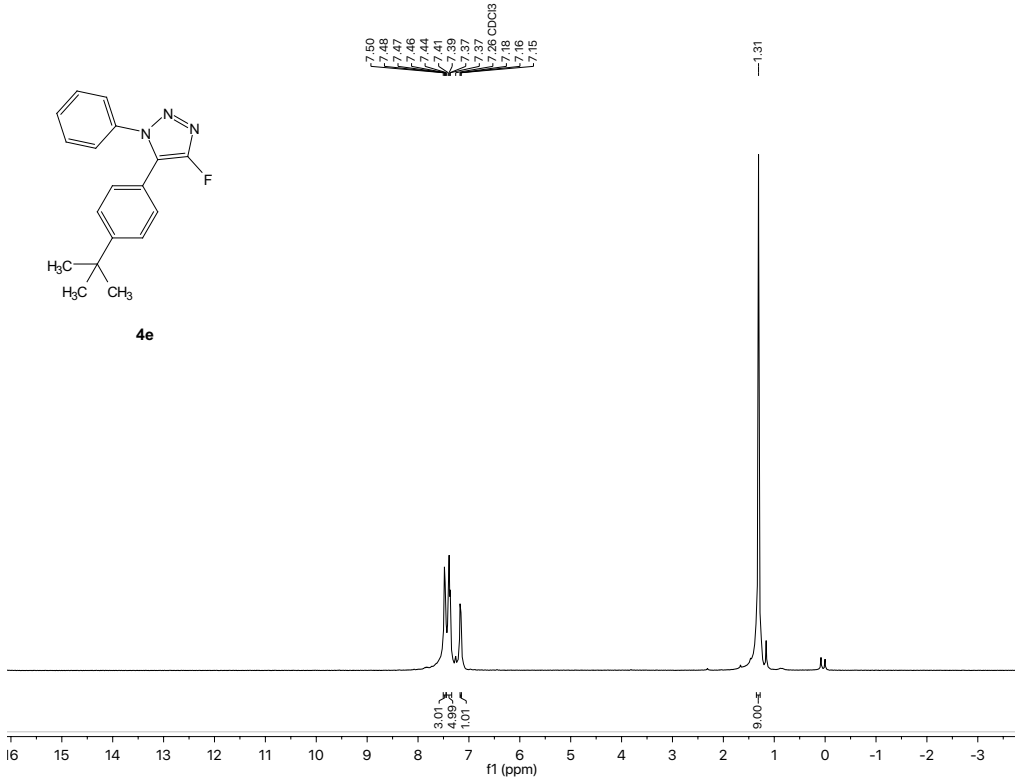
^{19}F NMR of **4d**



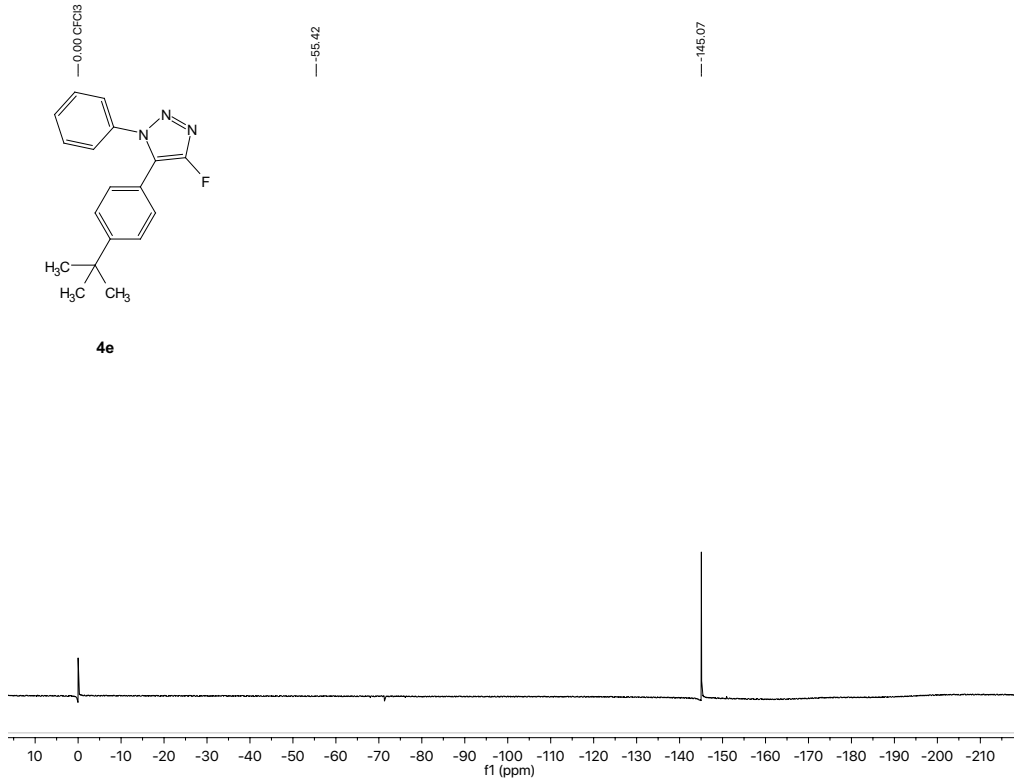
^{13}C NMR of **4d**



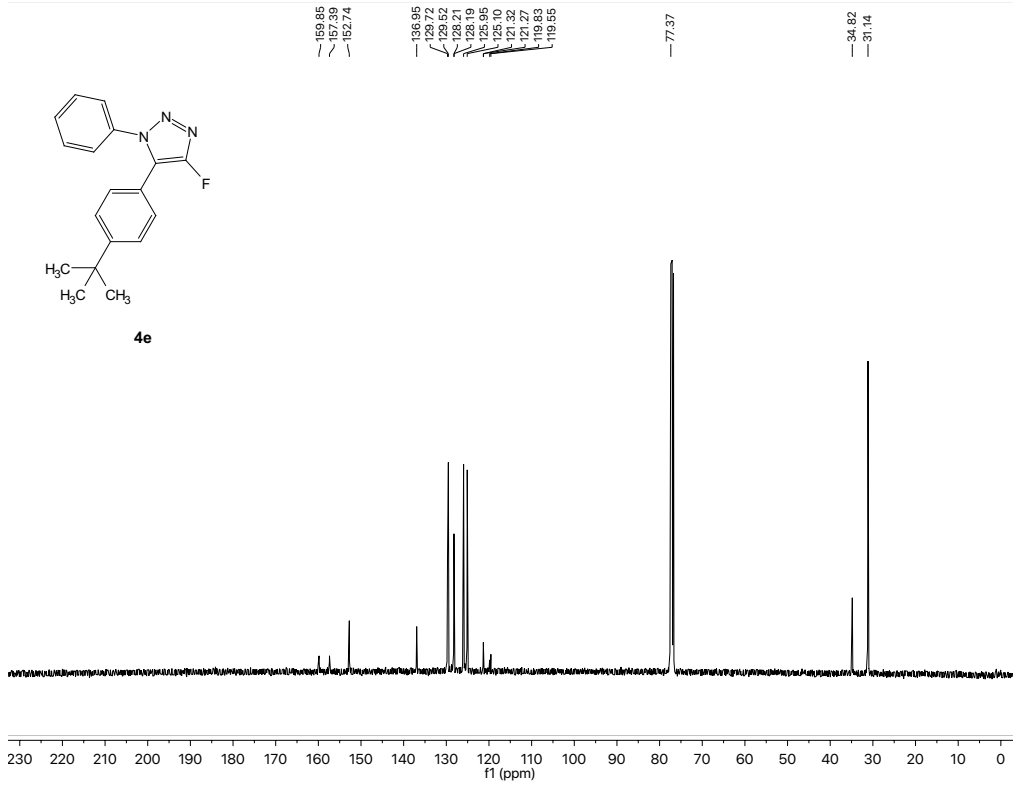
^{1}H NMR of **4e**



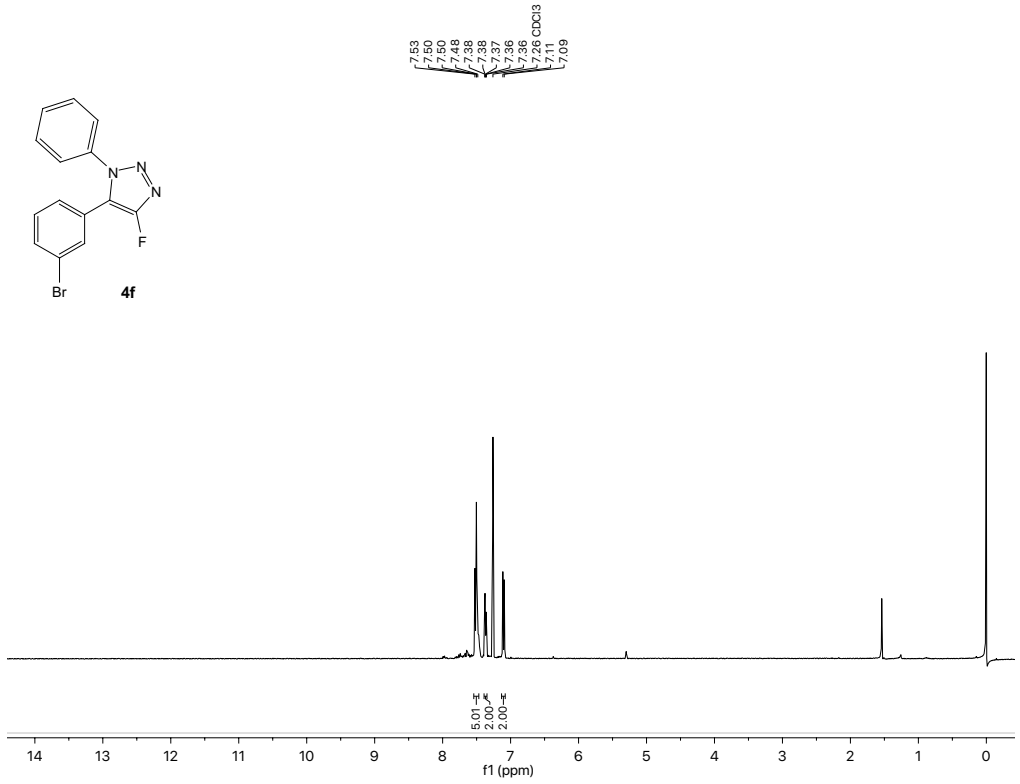
^{19}F NMR of **4e**



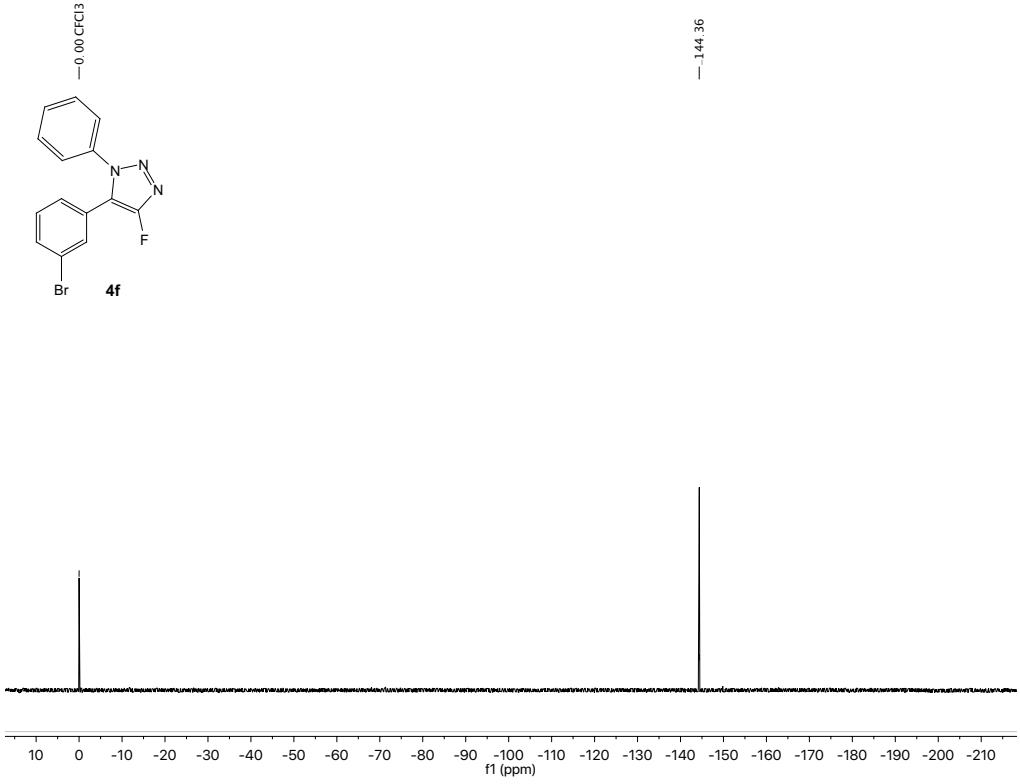
^{13}C NMR of **4e**



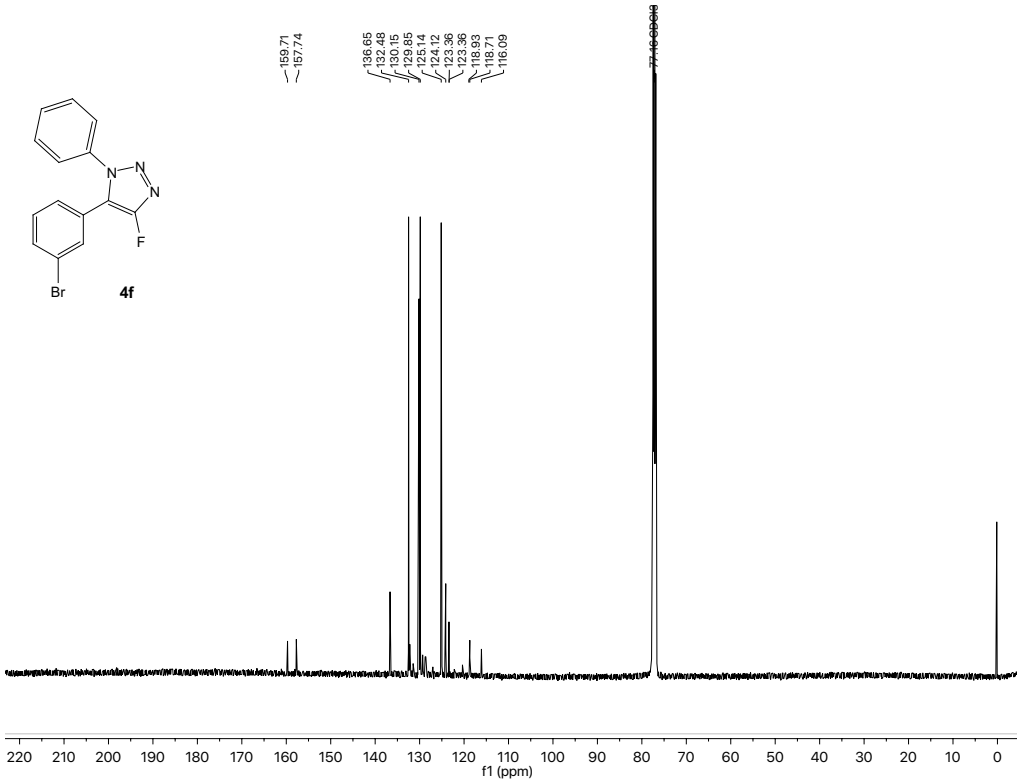
^{1}H NMR of **4f**



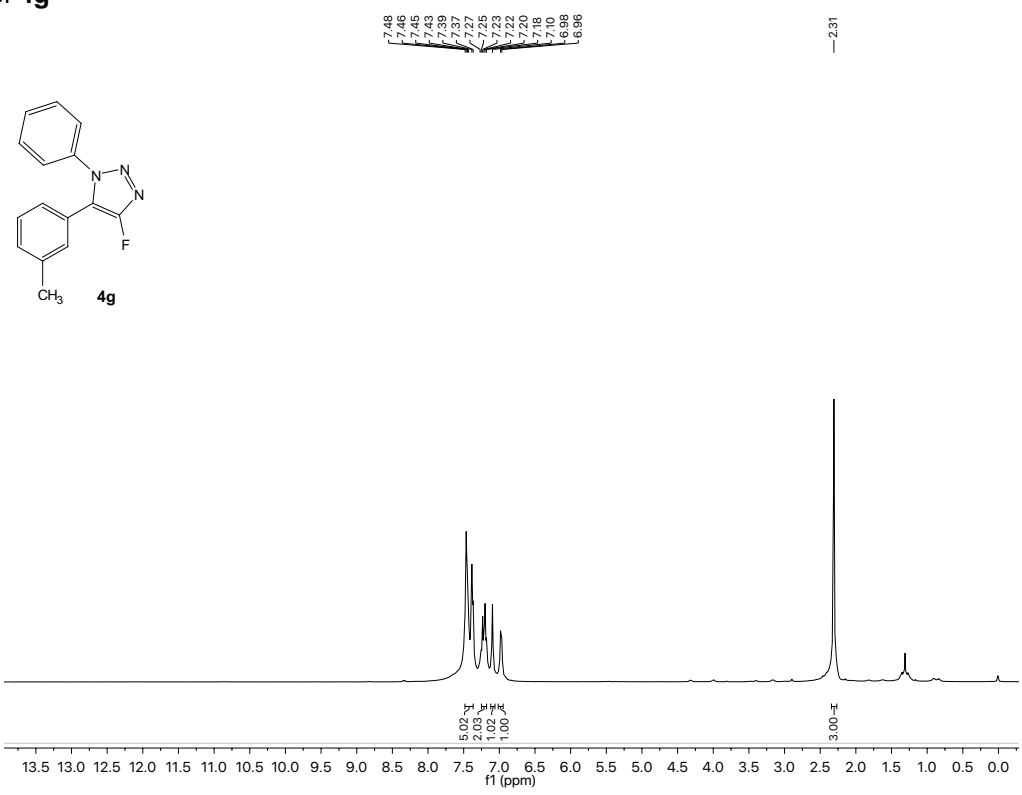
^{19}F NMR of **4f**



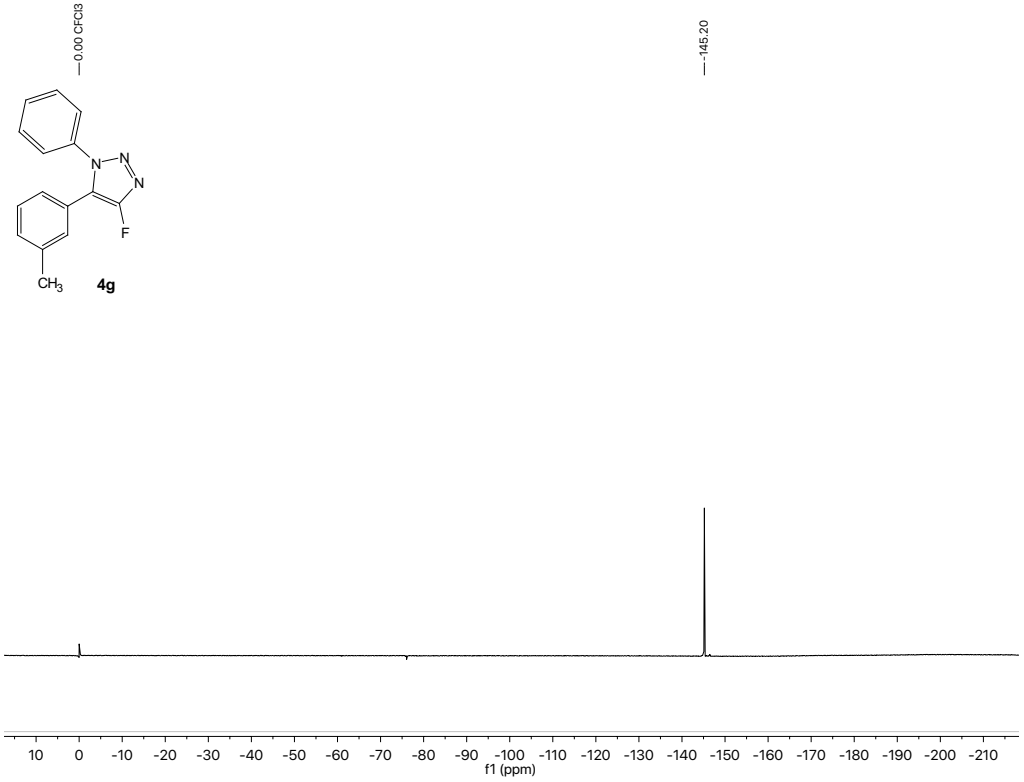
^{13}C NMR of **4f**



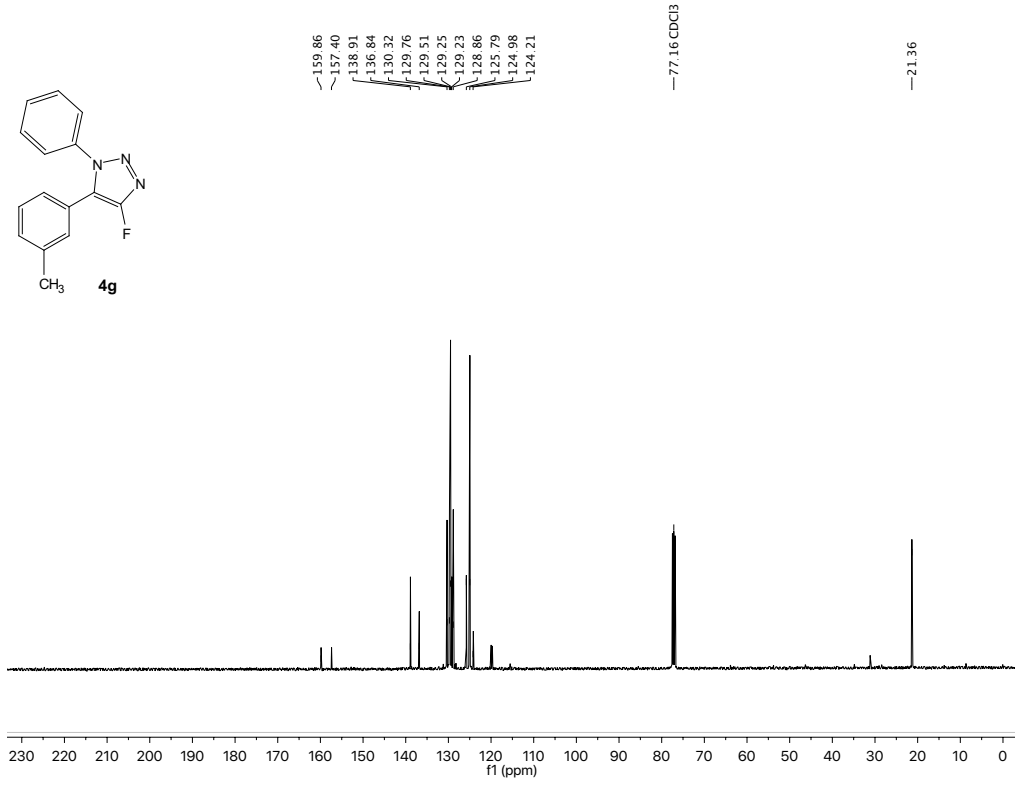
^{1}H NMR of **4g**



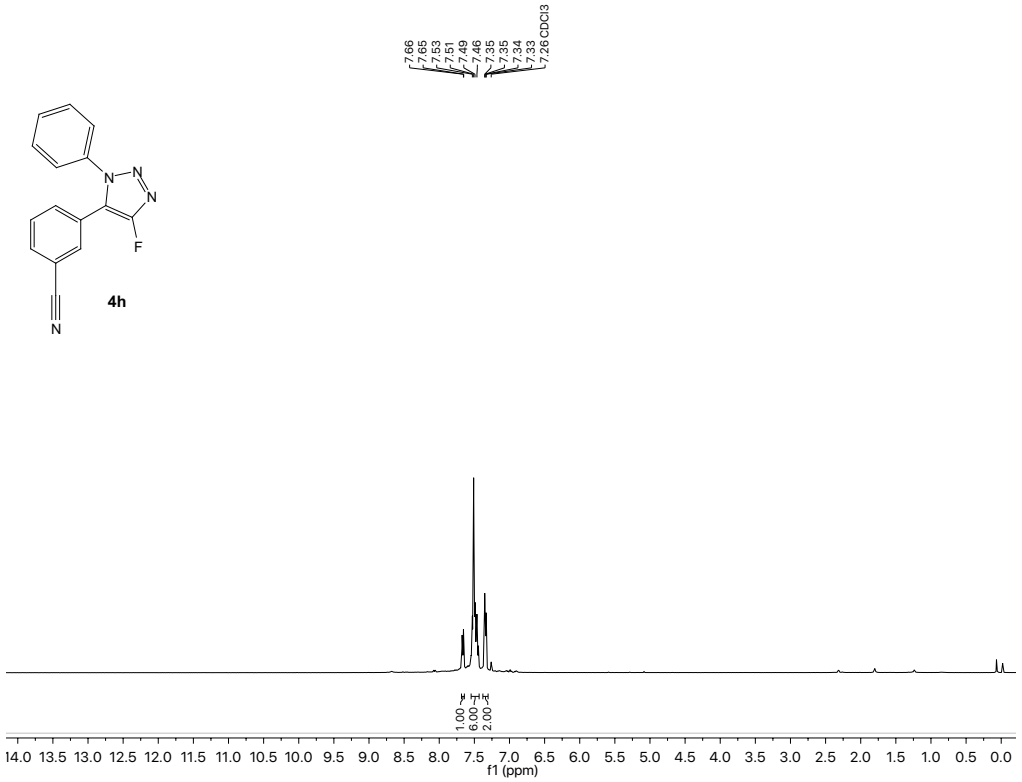
^{19}F NMR of **4g**



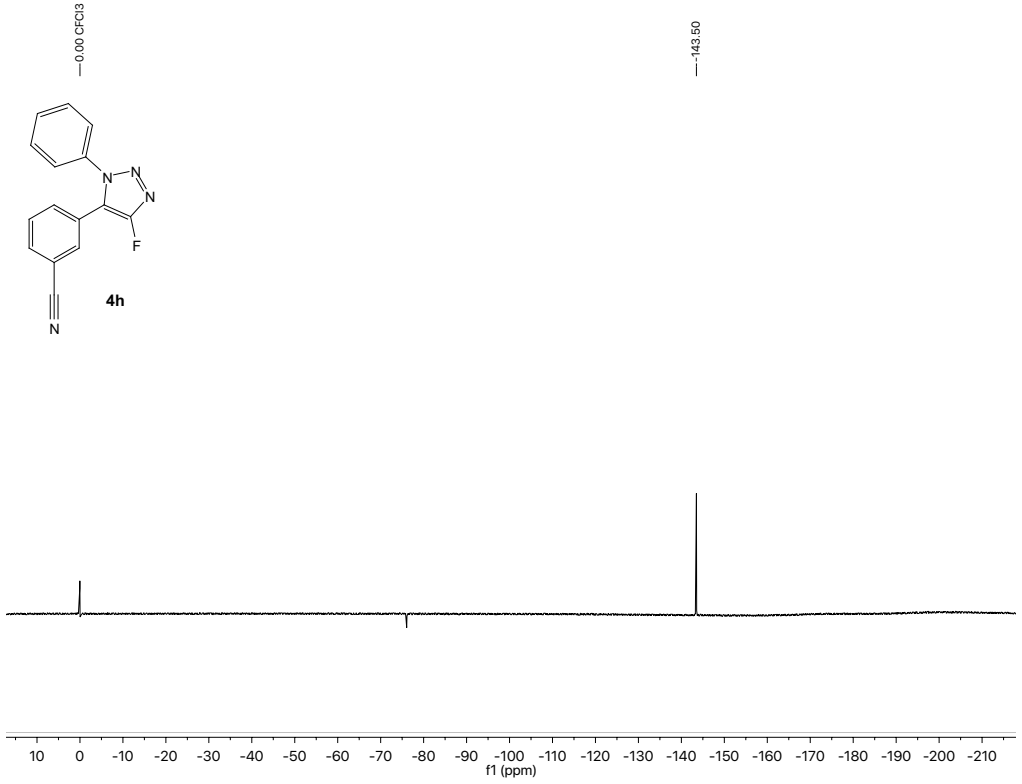
^{13}C NMR of **4g**



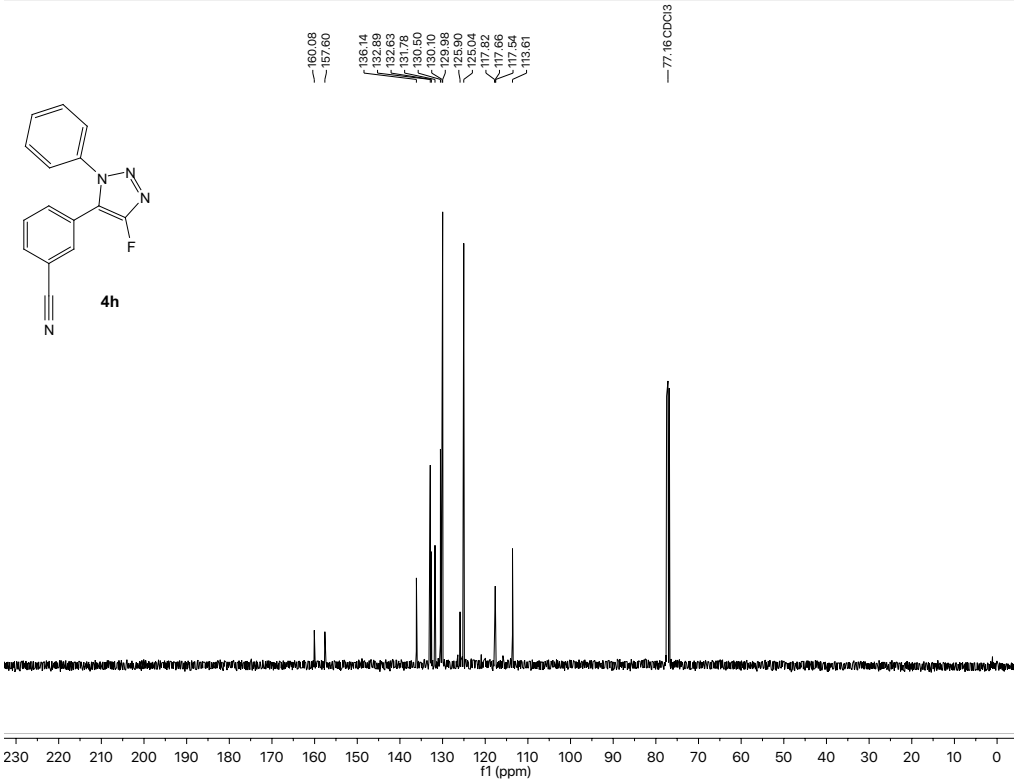
^{1}H NMR of **4h**



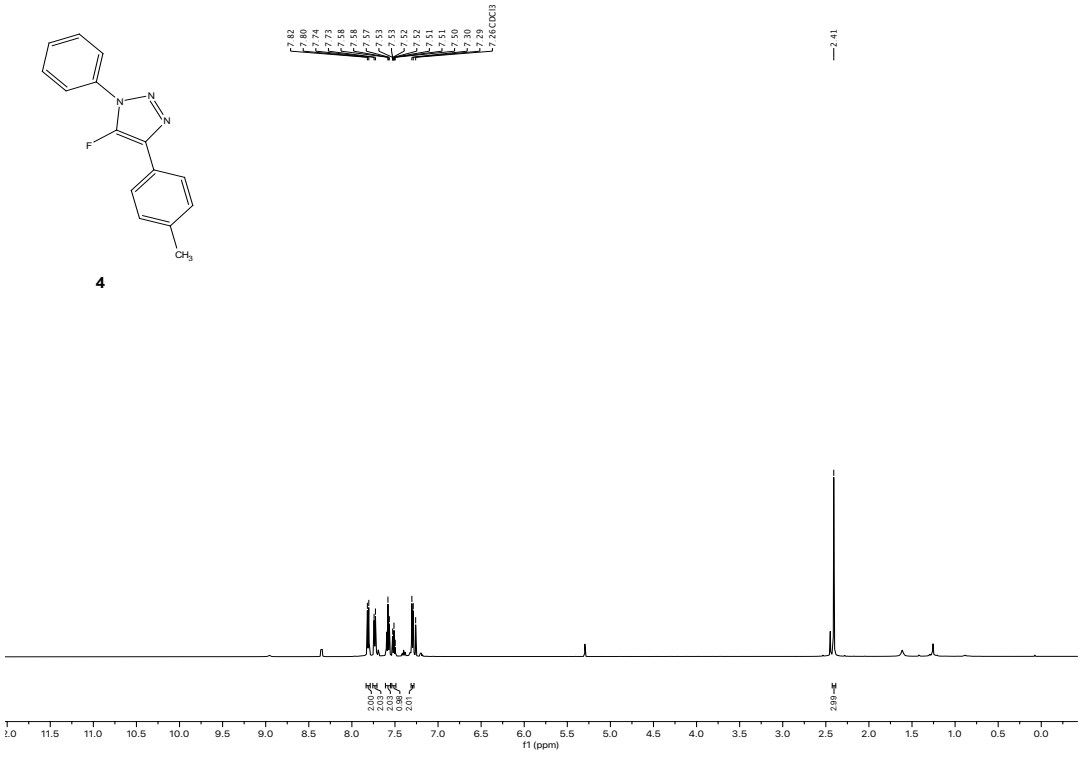
^{19}F NMR of **4h**



^{13}C NMR of **4h**

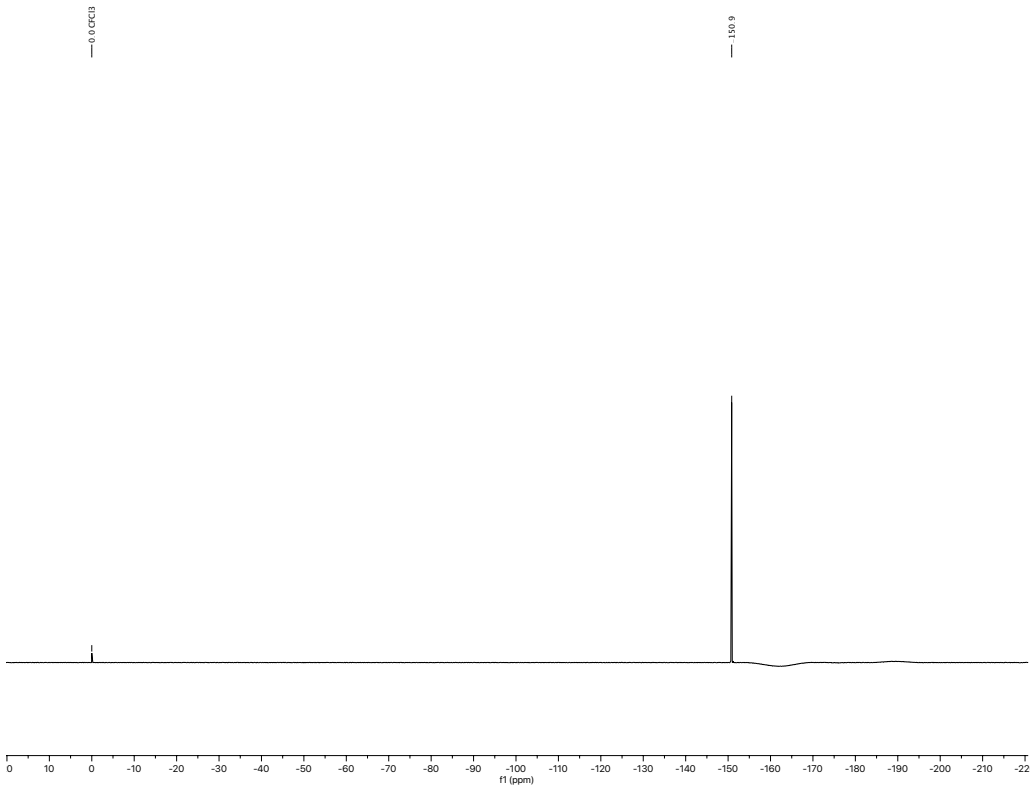

160.08
157.60
136.14
132.89
132.63
131.78
130.50
130.10
129.98
125.90
125.04
117.82
117.66
117.54
113.61
77.16 CDCl3
F
N
4h
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

^{1}H NMR of **4**

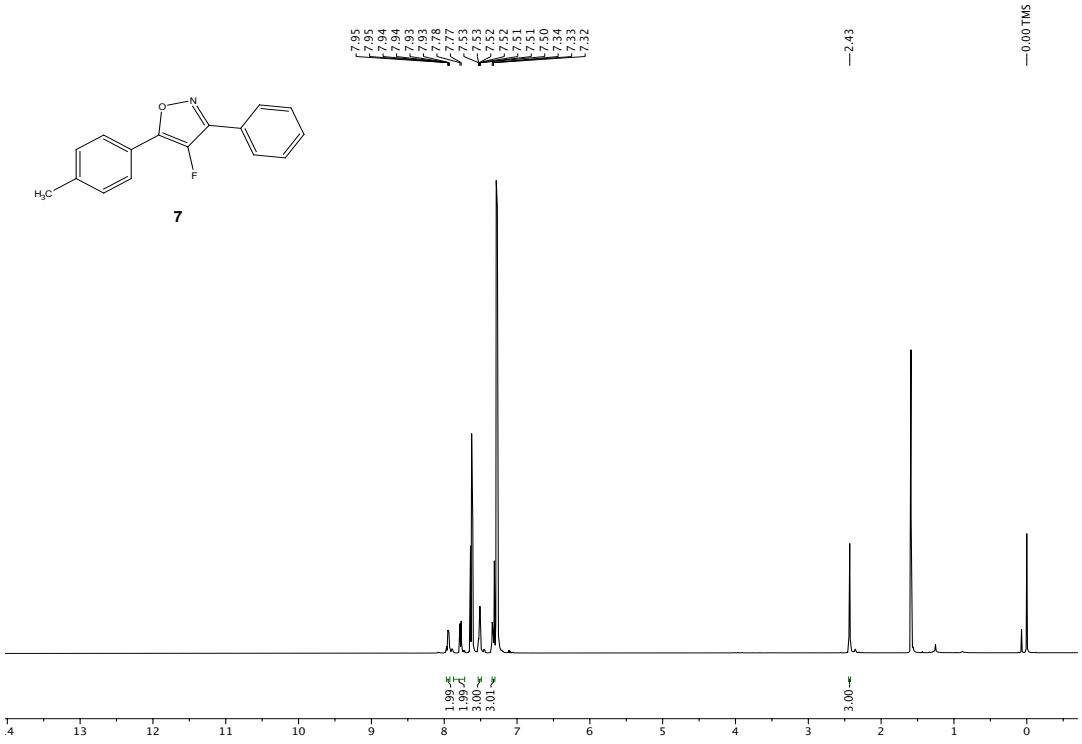


4

^{19}F NMR of **4**

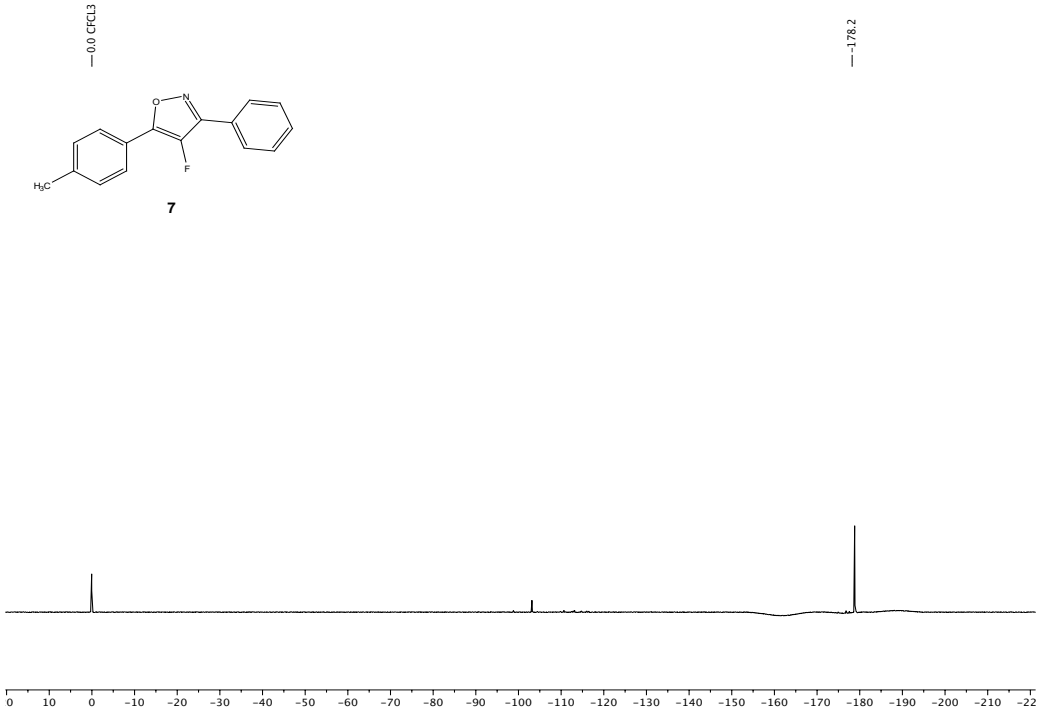


^{1}H NMR of **7**

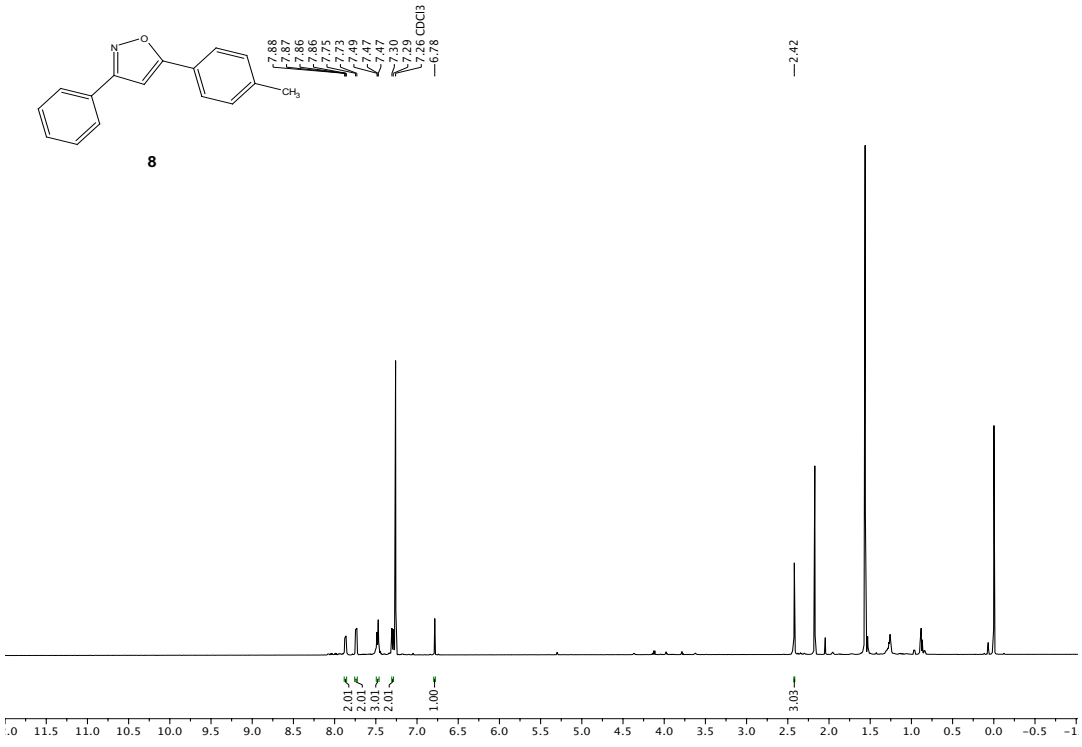


**This product contains 1,3-dichlorobenzene as impurity.

^{19}F NMR of **7**



^{1}H NMR of **8**


7.88
7.87
7.86
7.86
7.75
7.73
7.49
7.47
7.30
7.29
7.26 CDCl3
6.78
2.42
CH3
2.01
2.01
3.01
2.01
1.00
3.03

8

VITA

EDUCATION

- **B.Sc. in Biochemistry (Honors)** January 2015 – May 2017
  The University of Mississippi, Oxford, MS
  Thesis: Modification of Panobinostat to increase its therapeutic potential to cure Multiple Myeloma (Advisor: Dr. Davita Watkins)

- **B.Sc. in Biology (Minor in Music)** August 2013 – December 2014
  Mississippi University for Women, Columbus, MS

PUBLICATIONS

- Jana, S.; **Adhikari, S.**; Cox, M.R.; Roy, S. Fluorinated 1,2,3-Triazoles from 1-Fluoronitro alkenes as Surrogates of 1-Fluoroalkynes via Regioselective Cycloaddition Reactions with Organic Azides. *ChemRxiv*. Preprint.
- Stoddard, S.V.; May, X.A.; Rivas, F.; Dodson, K.; Vijayan, S.; **Adhikari, S.**; Parker, K.; Watkins, D.L. Design of Potent Panobinostat Histone Deacetylase Inhibitor Derivatives: Molecular Considerations for Enhanced Isozyme Selectivity between HDAC2 and HDA8. *Molecular Informatics*, **2018**, *38*, 3.
- Stoddard, S.V.; Balasubramaniam, S.; May, X.A.; Vijayan, S.; Goldman, L.; Dodson, K.; **Adhikari, S.**; Rivas, F.; Watkins, D.L. Design and Synthesis of Diazine-based Panobinostat Analogues for HDAC8 Inhibition. Submitted.

ACADEMIC ACHIEVEMENTS & AWARDS

- Joseph Sam and Lewis Nobles Graduate Research Award, 2018−2019.
- The University of Mississippi Student Travel Grant Award, 2018.
- American Chemical Society Outstanding Undergraduate Award, 2017.

SERVICES

- Professional skills workshop chair, Biomolecular sciences student advocates, School of Pharmacy, University of Mississippi, 2018-2019.
- Advisory board, Nepalese student association, University of Mississippi, 2017−2019.
- Executive officer, Nepalese student association, University of Mississippi, 2016−2017.