DEVELOPMENT OF NEW METHODS FOR THE SYNTHESIS OF PYRAZOLES, 4-IODOPYRAZOLES, ISOXAZOLES AND 1,2,4-OXADIAZOLES

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DEVELOPMENT OF NEW METHODS FOR THE SYNTHESIS OF PYRAZOLES, 4-IODOPYRAZOLES, ISOXAZOLES AND 1,2,4-OXADIAZOLES

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ABSTRACT

DEVELOPMENT OF NEW METHODS FOR THE SYNTHESIS OF PYRAZOLES, 4-IODOPYRAZOLES, ISOXAZOLES AND 1,2,4-OXADIAZOLES

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Synthesis of five-membered heteroaromatic compounds such as pyrazoles, isoxazoles and 1,2,4-oxadiazoles are important for pharmaceutical industry and material science due to their applications. Although there are many methods to prepare such compounds, new variants continue to appear since they exhibit a wide range of biological and medicinal activities.

In this thesis, new methods were developed for the synthesis of 4-iodopyrazoles, pyrazoles, isoxazoles, 1,2,4-oxadiazoles and/or 1,2,4-oxadiazepines. In the first part of the study, electrophilic cyclization of α,β-alkynic hydrazones by molecular iodine and copper iodide were investigated as new ways for the synthesis of 4-iodopyrazoles and pyrazoles, respectively. Initially, α,β-alkynic hydrazones were prepared by the reactions of propargyl aldehydes and ketones with hydrazines. Then α,β-alkynic hydrazones were treated with molecular iodine in the presence of $NaHCO_3$, which afforded 4-iodopyrazoles in good to excellent yields. Subsequently, the same reactions were carried out with CuI in the presence of NEt_3, which furnished corresponding pyrazoles in good yields. Moreover, ferrocenyl-substituted 4-iodopyrazoles and pyrazole derivatives were synthesized from corresponding α,β-alkynic hydrazones by using such electrophilic cyclizations.

In the second part of the study, the reactions between propargyl aldehydes and amidoximes were investigated. These reactions produced exclusively conjugate addition products. In one reaction, a new product was isolated in low yield and tentatively characterized as 7-pentyl-3-phenyl-1,2,4-oxadiazepine. Interestingly, under acidic and basic conditions, conjugate addition products afforded isoxazoles and 1,2,4-oxadiazoles, respectively. When conjugate addition products were treated with HCl, they afforded isoxazoles in good yields. On the other hand, when treated with bases such as KOH and NaH, conjugate addition products furnished 1,2,4-oxadiazoles in good to excellent yields. Reaction mechanism for the formation of isoxazoles and 1,2,4-oxadiazoles from conjugate addition products was also proposed.

In the last part of the study, one-pot reactions between propargyl aldehydes and amidoximes in the presence of KOH were investigated for the synthesis of 1,2,4-oxadiazoles. As anticipated, these one-pot reactions provided corresponding 1,2,4-oxadiazoles. One-pot reactions afforded oxadiazoles in slightly lower yields as compared to their two-step syntheses but they saved time and chemicals due to easy purification. More importantly, the synthesis of 5-ferrocenyl-1,2,4-oxadiazoles was achieved by one-pot procedure since the reaction of 3-ferrocenylpropanal with amidoximes did not yield corresponding conjugate addition products.

In summary, a variety of pyrazoles, 4-iodopyrazoles, isoxazoles, 1,2,4-oxadiazoles and/or 1,2,4-oxadiazepines were synthesized by new methods, which may have useful biological and medicinal activities.

Keywords: Pyrazole, 4-iodopyrazole, isoxazole, 1,2,4-oxadiazole, ferrocene, electrophilic cyclization

ÖZ

PİRAZOL, 4-İYODOPİRAZOL, İZOKSAZOL VE 1,2,4-OKSADİAZOLLERİN SENTEZİ İÇİN YENİ METOTLARIN GELİŞTİRİLMESİ

Kıvrak, Arif
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Ocak 2011, 302 sayfa

Pirazoller, izoksazoller ve 1,2,4-okzadiazoller gibi beşli halka yapısına sahip heteroaromatik bileşiklerin sentezi geniş uygulama alanlarından dolayı ilaç endüstrisi ve malzeme bilimi için oldukça önemlidir. Bu yapıların sentezi için birçok metot olmasına rağmen çok farklı biyolojik ve tıbbi özellikler göstermesinden dolayı yeni yöntemler bulunmaya devam etmektedir.

Bu tezde, 4-iyotpirazoller, pirazoller, izoksazoller, 1,2,4-oksadiazoller ve/veya 1,2,4-oksadiazepinlerin sentezi için yeni metotlar geliştirilmiştir. Çalışmanın birinci bölümünde α,β-alkinik hidrazonların moleküler iyot ve bakır iyodür ile elektrofilik halkalaşma tepkimelerinden 4-iyotpirazoller ve pirazoller elde edildiği bulunmuştur. İlk olarak, proparjil aldehit ve ketonların hidrazinler ile tepkimesinden α,β-alkinik hidrazonlar hazırlanmıştır. Daha sonra α,β-alkinik hidrazonlar $NaHCO_3$ ortamında moleküler iyot ile tepkimeye sokularak yüksek verimlerle 4-iyotpirazoller sentezlenmiştir. Aynı tepkime NEt_3 varlığında bakır iyodur ile gercekleştirildiğinde ise yüksek verimlerle pirazoller elde edilmiştir. Bunlara ek olarak, ferrosenil substitüye 4-iyodopirazol ve pirazol türevleri de elektrofilik halkalaşma tepkimeleri kullanılarak hidrazonlarından sentezlenmiştir.

İkinci bölümde ise proparjil aldehitlerin amidoksimlerle olan tepkimeleri araştırılmıştır. Bu tepkimeler çoğunlukla konjuge katılma ürünlerini üretmiştir. Sadece bir reaksiyonda düşük verimle yeni bir ürün izole edilmiş ve geçiçi olarak 7-pentil-3-fenil-1,2,4-okzadiazepin olarak tanımlanmıştır. İlginç olarak konjuge katılma ürünleri asidik ve bazik ortamlarda izoksazol ve 1,2,4-okzadiazol türevlerini üretmiştir. Konjuge katılma ürünleri HCl ile muamele edildiğinde iyi verimlerle izoksazolleri vermiştir. Diğer taraftan konjuge katılma ürünleri KOH ve NaH gibi bazlarla muamele edildiklerinde ise yüksek verimlerle 1,2,4-okzadiazolleri oluşturmaktadır. Konjuge katılma ürünlerinden izoksazol ve 1,2,4-okzadiazollerin oluşumu için mekanizma da önerilmiştir.

Çalışmanın son bölümünde ise KOH ortamında proparjil aldehitlerin amidoksimlerle olan tepkimeleriyle tek balonda 1,2,4-oksadiazollerin sentezi araştırılmıştır. Beklenildigi üzere tek balondaki tepkimeler 1,2,4-oksadiazolleri üretmiştir. Tek balonda elde edilen oksadiazol verimleri iki basamaklı yönteme göre biraz düşük verimlerle gerçekleşse de tek balon yönteminde zaman ve kimyasal kazancı söz konusudur, çünkü bu yöntemde daha az saflaştırma gerekmektedir. Daha da önemlisi konjuge katılma ürünleri üretmeyen 3-ferrosenilpropanaldan tek balon yöntemi ile 5-ferrosenil-1,2,4-oksadiazollerin sentezi gerçekleştirilmiştir.

Özetle, önemli faydalı biyolojik ve tıbbi aktiviteye sahip olabilecek pirazol, 4-iyotpirazol, izoksazol, 1,2,4-okzadiazol ve/veya 1,2,4-okzadiazpin türevleri yeni metotlarla sentezlenmiştir.

Anahtar Kelimeler: Pirazol, 4-iyodopirazol, izoksazol, 1,2,4-okzadiazol, ferrosen, elektrofilik halkalaşma

To my wife and my family

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ABBREVIATIONS

br	broad (spectral)
^{o}C	degrees Celcius
δ	chemical shift in parts per million downfield from
d	doublet (spectral)
Fc	ferrocenium ion
FT	fourier transform
g	gram(s)
h	hour(s)
Hz	hertz
IR	infrared
J	coupling constant
m	multiplet (spectral)
mL	milliliter(s)
min	minutes
mmole	millimole
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million (in NMR)
q	quartet (spectral)
r.t.	room temperature
s	singlet (spectral)
t	triplet (spectral)
THF	tetrahydrofuran
TLC	thin layer chromatography
DCM	dicholoromethane
DMAc	dimethylacetamide
DMF	dimethylformamide

ACN	acetonitrile
n-BuLi	Buthyl Lithium
$POCl_3$	Phosphorus oxychloride
$AlCl_3$	Aluminium chloride
DFT	density functional theory
NEt_3	triethylamine
HRMS	high resolution mass spectrometry

CHAPTER 1

INTRODUCTION

The science of organic chemistry is less than 200 years old while organic compounds and their reactions have been used for thousands of years [1]. In fact, we composed largely of organic compounds since we derived from and nourished by them. Importantly, we live in an age of organic chemistry since there is an excellent relationship between the applications of organic chemistry and the standard of living. Organic chemistry is a wide field which intersects with biology, biochemistry, medicine, pharmacology, polymer technology, agriculture and petroleum engineering.

Heterocyclic compounds are organic compounds which have at least one element other than carbon, such as oxygen, nitrogen or sulfur, within a ring skeleton. Heterocyclic compounds are not only found in natural products, such as aflatoxin B_1, caffeine, reserpine and biotin [2], but also obtained synthetically. Heterocyclic compounds are generally classified according to the number of atoms on the ring. Some examples for the known heterocyclics include 3-membered oxiranes and aziridines, 4-membered oxetanes and azetidines, 5-membered furans, pyrroles and thiophenes, and 6-membered pyridines [3].

Many alkaloids, vitamins, antibiotics and synthetic medicines as well as dyestuffs are heterocyclic compounds. The seven of the top 10 best selling prescription drugs include heterocyclic moieties in their structures, which emphasizes the importance of heterocyclic compounds for human life [4]. Therefore, the synthesis of heterocyclic compounds has attracted great attention in organic community for a long time because of their biological activities, properties and applications. Pyrazoles,

isoxazoles and 1,2,4-oxadiazoles are important classes of heterocyclic chemistry due to the broad range of biological activities they possess, which will be discussed in the following sections.

1. 1 Pyrazoles

Pyrazoles, which are five-membered two-nitrogen-containing heterocycles, are important organic compounds for pharmaceutical [5] and agrochemical industry [6] (Figure 1). Numerous compounds containing pyrazole moiety are known to exhibit anti-hyperglycemic [7], analgesic [8], anti-inflammatory [9], antipyretic [10], antibacterial [11], antimicrobial [12], antihypertensive [13] and antidepressant [14] activities. They are also used as herbicides [5c, 15] and dyestuffs [16].

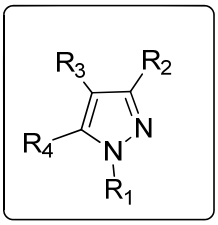


Figure 1. Structure of pyrazoles.

Pyrazoles are aromatic molecules due to their planar conjugated ring structures with six delocalized π-electrons. Therefore, many important properties of these molecules were analyzed by comparing with the properties of benzene derivatives [17]. Like other nitrogen involving heterocycles, different tautomeric structures can be written for pyrazoles. As shown in Figure 2, unsubstituted pyrazole can be represented in three tautomeric forms [18].

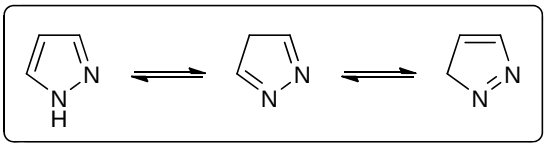


Figure 2. Tautomeric forms of unsubstituted pyrazole.

For the pyrazole derivatives in which two carbon atoms neighboring the nitrogen atoms on the ring have different substituents, five tautomeric structures are possible (Figure 3).

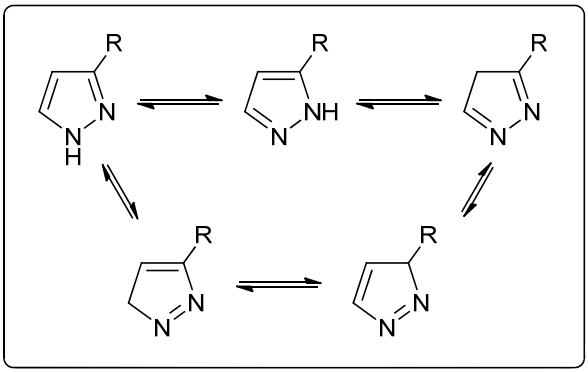


Figure 3. Five tautomeric forms of a substituted pyrazole derivative.

Naturally occurring pyrazoles were isolated after 1950s. First natural pyrazole, 3-*n*-nonylpyrazole, was obtained from *Houttuynia Cordata*, a plant of the *piperaceae* family from tropical Asia (Figure 4) [18]. This naturally occuring pyrazole showed antimicrobial activity. The other natural pyrazole derivative, *levo*-β-(1-pyrazolyl)alanine, was isolated from watermelon seeds (*Citrullus Vulgaris*) by Japanies researchers (Figure 4) [18].

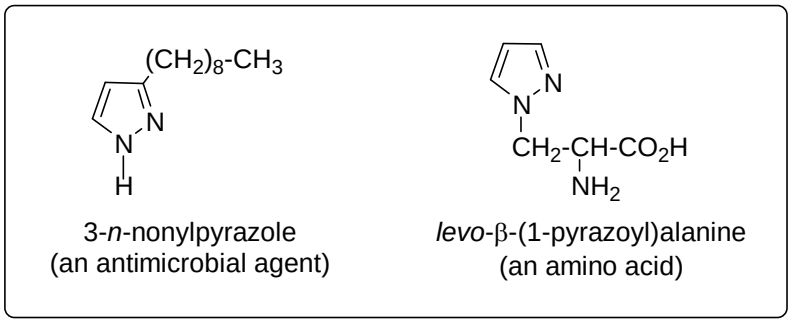


Figure 4. Some examples of naturally occuring pyrazoles.

Structures of some biologically important pyrazole containing drugs such as Zaleplon (**1**) [19] (marketed under the brand names Sonata and Starnoc), Viagra (**2**) [20], Zoniporide (**3**) [21], Celecoxib (**4**) [22], and Acomplia (**5**) [23] are depicted in Figure 5. Zaleplon (**1**) [19] affects the nervous system to treat insomnia where difficulty in falling a sleep is the primary complaint. Viagra (**2**) is well known drug developed by the pharmaceutical company Pfizer in 1998, which is the prime treatment for erectile dysfunction [20]. Zoniporide (**3**) having a pyrazole core structure is the selective inhibitor with the desired properties [21]. Another important example of biologically active pyrazole derivative is Celecoxib (**4**) (the brand name Celebrex), which is the selective cycloxygenase 2 (COX 2) inhibitor showing great promise as anti-inflammatory and analgesic agent [22]. Moreover, Celecoxib (**4**) has less undesirable side effect than the other known anti-inflammatory agents. Acomplia (Rimonabant) (**5**) is the first selective CB1 receptor blocker and has been used as an anti-obesity drug until 2009 [23]. Then, this drug was withdrawn by the European Medicines Agency because of its side effects.

Notably, many methods have been developed for preparation of substituted pyrazoles. In general, pyrazoles are synthesized by (*i*) the reaction of 1,3-diketones with hydrazines, (*ii*) 1,3-dipolar cycloaddition of diazo compounds with alkynes, and (*iii*) the reaction of α,β-unsaturated aldehydes and ketones with hydrazines [24].

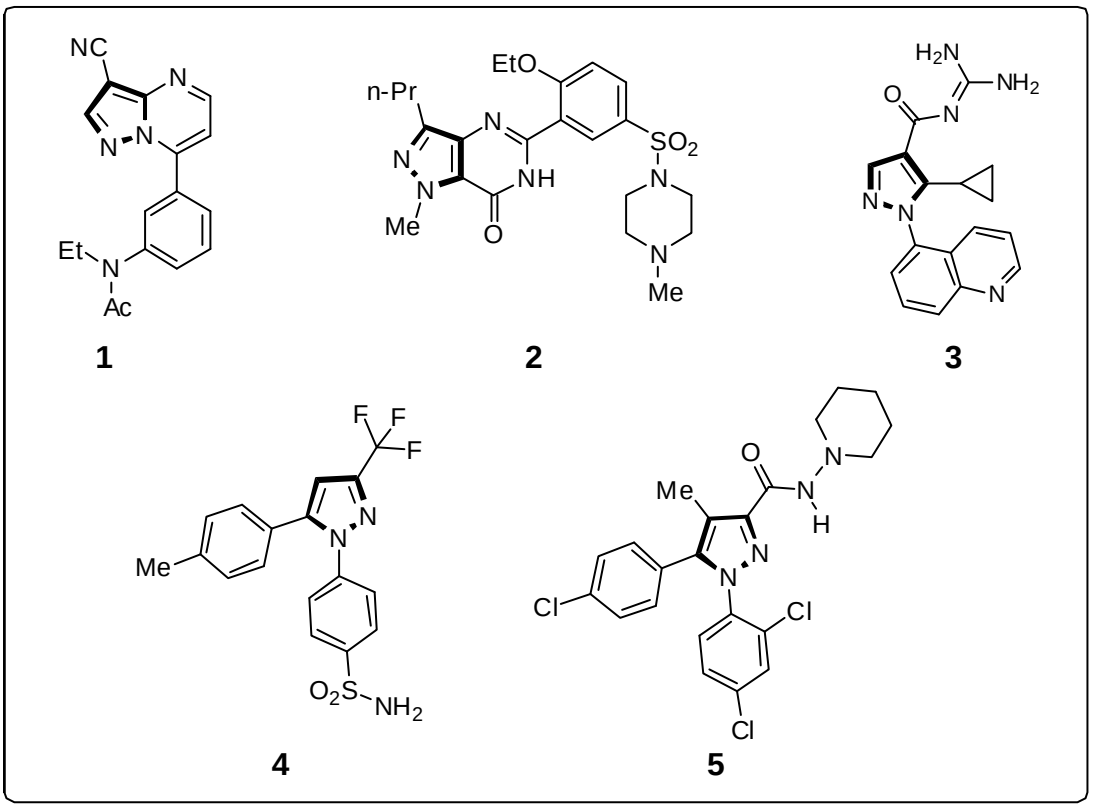


Figure 5. Structures of Zaleplon (**1**), Viagra (**2**), Zoniporide (**3**), Celecoxib (**4**) and Acomplia (**5**).

1.1.1 Synthesis of pyrazoles from 1,3-diketones and hydrazines

First synthetic method for the synthesis of pyrazole was explored by Knorr in 1883 [25], which employed the reactions of 1,3-dicarbonyl compounds **6** with arylhydrazines to afford pyrazoles derivatives **7** and **8** (Figure 6). It should be mentioned that the condensation of symmetrical or unsymmetrical 1,3-diketones with hydrazine or arylhydrazines in the presence of catalysts generally produced a mixture of two regioisomers. The yields of pyrazole isomers usually depend on the reaction conditions.

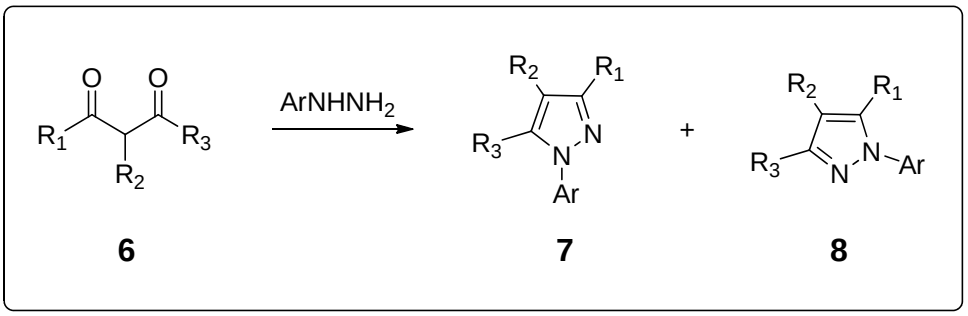


Figure 6. Synthesis of pyrazoles by the reaction between 1,3-diketones and arylhydrazines.

Many synthetic pathways were reported for the synthesis of pyrazole derivatives starting from 1,3-dicarbonyl compounds. Recently, an efficient one-pot synthesis of 3,5-disubstituted pyrazoles was achieved by employing enolates **9** and acid chlorides **10**. The reaction proceeded through the in situ generated 1,3-dicarbonyl compound **6** (Figure 7) [26].

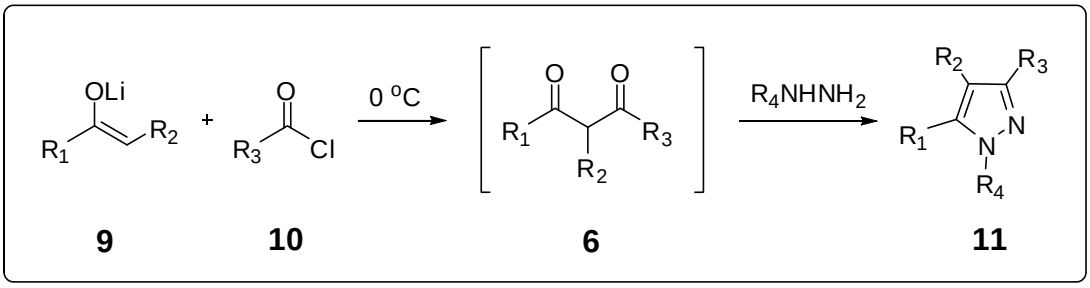
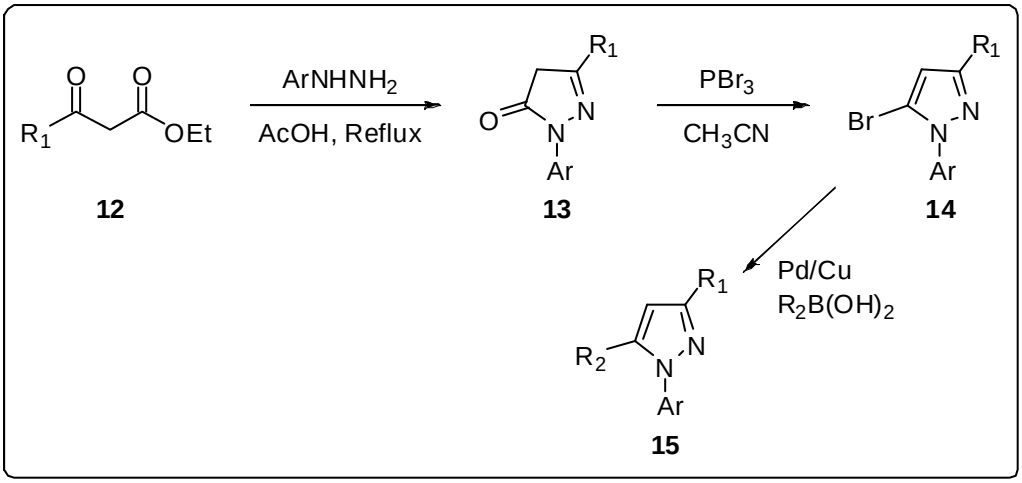


Figure 7. Synthesis of pyrazoles starting from enolates and acid chlorides.

Related with 1,3-diketones, Wang developed a new method for the synthesis of 1,3,5-trisubstituted pyrazoles starting from β-ketoesters **12** (Figure 8) [27]. The reaction first proceeded arylpyrazolones **13**, the subsequent treatment of which with PBr_3 and the palladium catalyzed cross-coupling of the resulting 5-bromopyrazoles

14 with arylboronic acids as well as with alkynes and vinyltins afforded pyrazoles **15** (Figure 8) [27].



12 **13** **14** **15**

Figure 8. Synthesis of pyrazoles starting from β-ketoesters.

Polar and protic solvents such as alcohols or acetic acid were usually used for cyclocondensation reactions between arylhydrazines and 1,3-diketones. However, when 1-arylbutane-1,3-diones **16** were allowed to react with arylhydrazine hydrochlorides in *N*,*N*-dimethylacetamide (DMA), pyrazole derivatives **17** were obtained with high regioselectivity over pyrazole isomers **18** (Figure 9) [28].

It is interesting to note that the reactions of 1,3-diketones **19** with acylhydrazines produced only 4,5-dihydro-5-hydroxypyrazole derivatives **20** with complete regioselectivity (Figure 10) [29]. Corresponding pyrazole derivatives **21** were obtained after thermally dehydration and deacylation of these compounds in the presence of sulfuric acid at 120 ^{o}C.

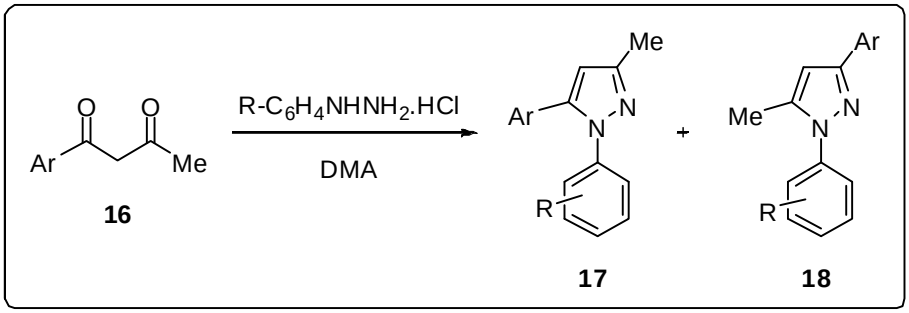


Figure 9. Synthesis of pyrazoles by the reaction of 1,3-diketones with arylhydrazine hydrochlorides in DMA.

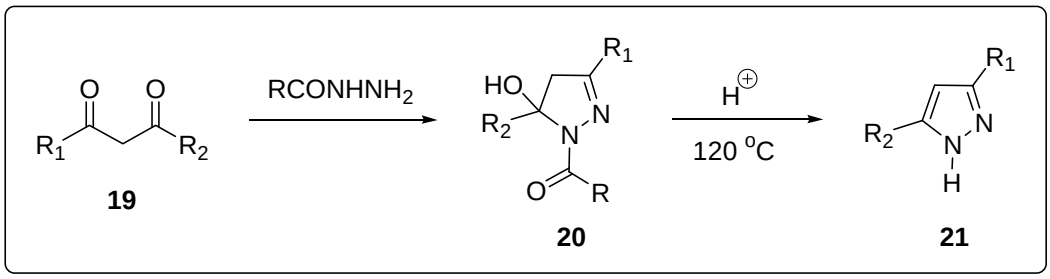


Figure 10. Synthesis of pyrazoles from 4,5-dihydro-5-hydroxypyrazoles **20**.

1.1.2 Synthesis of pyrazoles via 1,3-dipolar cycloaddition of diazoles with alkynes

Alkynes react with diazo compounds to afford pyrazoles *via* [3+2]-cycloaddition. Aggarwal reported one-pot 1,3-dipolar cycloaddition of diazoles with alkynes for the preparation of 3,5-disubstituted pyrazoles (Figure 11) [30]. First, diazo compounds **23** were in situ generated from tosylhydrazones of aldehydes **22** by treating with sodium hydroxide, which then underwent cycloaddition with terminal alkynes to produce pyrazole derivatives **21**.

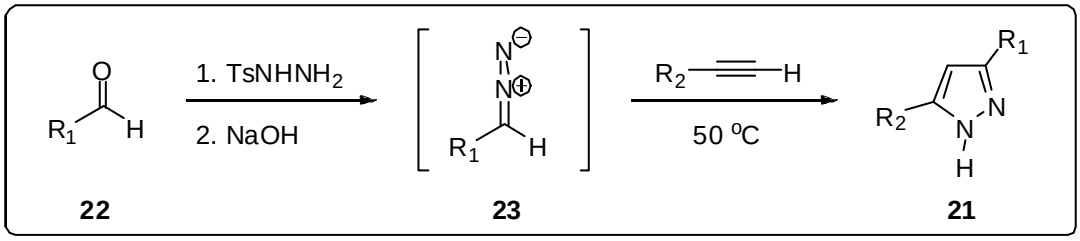


Figure 11. Synthesis of pyrazoles via 1,3-dipolar cycloaddition.

When the reaction was carried out between *N*-monosubstituted hydrazones **24** and nitroolefines **25**, 1,3,4,5-tetrasubstituted pyrazoles **26** were obtained in moderate to good yields (Figure 12) [31].

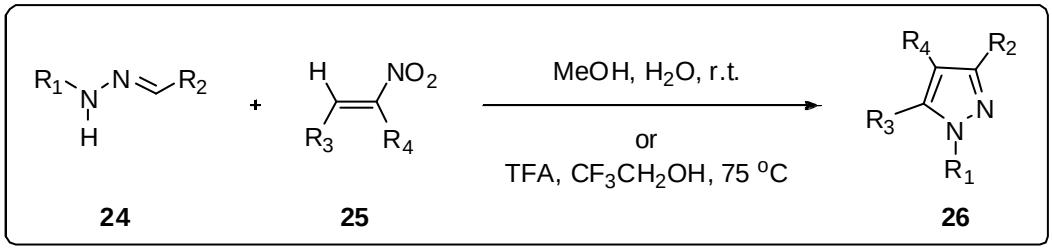


Figure 12. Synthesis of pyrazoles from hydrazones and nitroolefines.

1.1.3 Pyrazoles from the reaction of hydrazines with α,β-unsaturated aldehydes and ketones

Another strategy for the synthesis of pyrazoles is the cyclocondensation of an appropriate hydrazine with a carbonyl compound having two electrophilic carbons at the 1 and 3 locations [32]. Examples of such carbonyl compounds are given in Figure 13. Importantly, hydrazines behave like a bidentate nucleophile and react with these α,β-unsaturated aldehydes or ketones.

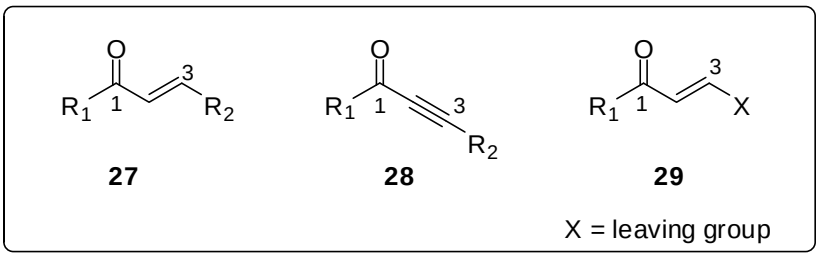


Figure 13. Examples of α,β-unsaturated carbonyl compounds.

Katritzky synthesized 1,3,5-trisubstituted pyrazoles **32** by the reaction of α-benzotriazolyl-α,β-unsaturated ketones **30** with hydrazines (Figure 14) [33]. During the course of the reaction, pyrazolines **31** were first produced and then oxidized to pyrazoles **32** by the elimination of benzotriazolyl group with sodium ethoxide.

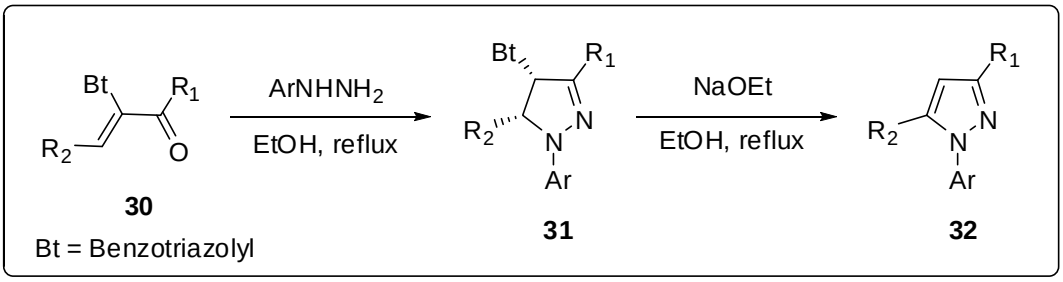


Figure 14. Synthesis of pyrazoles from α,β-unsaturated ketones and hydrazines.

β-Aminoenones such as **33** were also reacted with alkyl-, acetyl- and methoxy-carbonyl hydrazine as well as with semicarbazide to afford 1,3,5-trisubstituted pyrazole derivatives **34** as illustrated in Figure 15 [34].

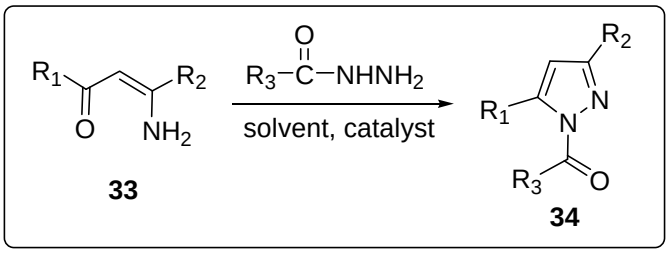


Figure 15. Synthesis of pyrazoles from β-aminoenones and hydrazines.

On the other hand, the reaction of α,β-unsaturated compounds like chalcones **35** with hydrogen peroxide gave epoxides **36** (Figure 16) [35]. Then, addition of hydrazine hydrate produced unstable pyrazoline intermediates **37**, dehydration of which yielded 3,5-disubstituted pyrazoles **38** (Figure 16). Silva research group reported that treatment of chalcones with diazomethane followed by oxidation of the resulting pyrazoline intermediates produced pyrazoles as well [36].

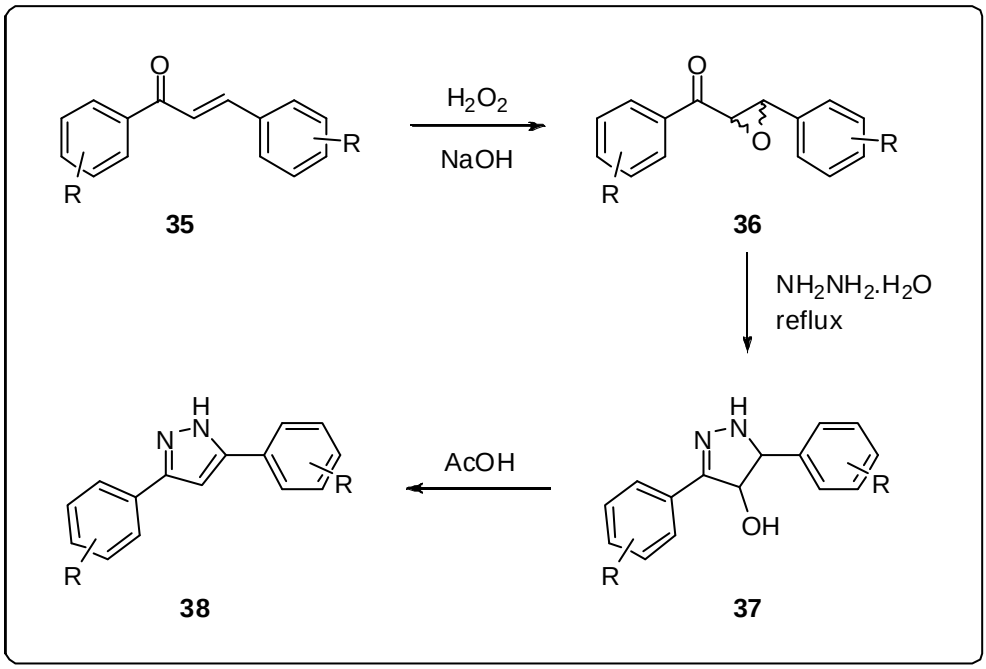


Figure 16. Synthesis of pyrazoles from chalcones.

The reactions of hydrazines with α,β-alkynic aldehydes and ketones (alkynals and alkynones) also produced pyrazole derivatives. For instance, the reactions between propargyl ketones **39** and metyl or aryl substituted hydrazines gave pyrazole isomers **40** and **41** (Figure 17) [37]. Notably, the regioselectivity of reaction was depended on the identity of hydrazine substitutents. For example, methyl substituted hydrazines afforded pyrazoles **40** as major products while aryl substituted hydrazines yielded pyrazoles **41** as major products (Figure 17).

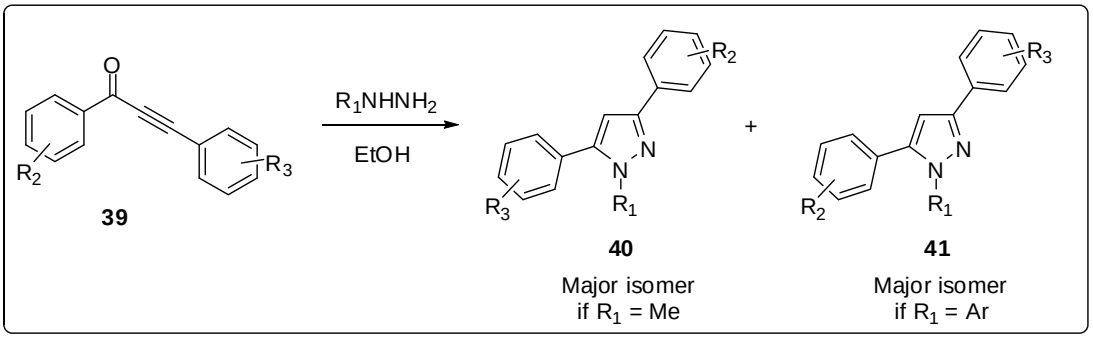


Figure 17. Synthesis of pyrazoles from alkynones and hydrazines.

Interestingly, 3,5-disubstituted pyrazoles **21** were synthesized from acid chlorides **42** and terminal alkynes **43** by employing one-pot coupling-cyclocondensation sequence (Figure 18) [38]. Sonogashira cross coupling reaction firstly produced the alkynone intermediate in the presence of palladium metal, and then addition of hydrazine gave the desired pyrazole derivatives **21**. However, the reaction did not tolerate the preparation of *N*-substituted pyrazoles.

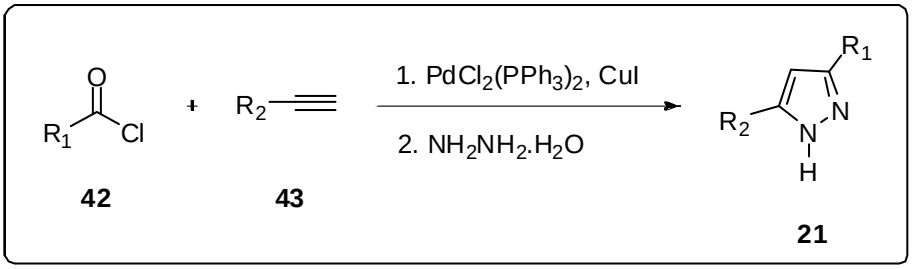


Figure 18. One pot **s**ynthesis of pyrazoles from terminal alkynes.

Recently, it has been reported that the presence of a ferrocenyl group on the structures of biologically active carbocyclic and heterocyclic compounds may increase the current biological activities or creates the totally new properties [39]. For this reason, Zora research group synthesized ferrocenyl substituted pyrazoles, namely 1-alkyl/aryl-5-ferrocenylpyrazoles (**46**) and/or 1-alkyl/aryl-3-ferrocenyl-pyrazoles (**50**), by employing the reaction between (2-formyl-1-chlorovinyl)-ferrocene (**44**) and hydrazines or hydrazine salts (Figure 19) [40]. In most cases, 1,5-pyrazole isomers **46** were obtained as the major or single product of these reactions.

Zora and coworkers also synthesized ferrocenyl substituted pyrazoles **49** and/or **50** from 3-ferrocenylpropynal **45** and hydrazine salts (Figure 19) [41]. In fact, these reactions gave pyrazoles **46** and/or **47** in relatively higher yields but the proportion of 1,3-pyrazole isomers **47** relatively increased as compared to those of 1,5-pyrazole isomers **46**. Expectedly, when hydrazinium salts are used, the medium becomes slightly acidic and pyrazoles are isolated in good yields. It appears that acidic medium favors the reaction but, in this case, a mixture of 1,5- and 1,3-pyrazole isomers **46** and **47** are obtained (Figure 19) [41].

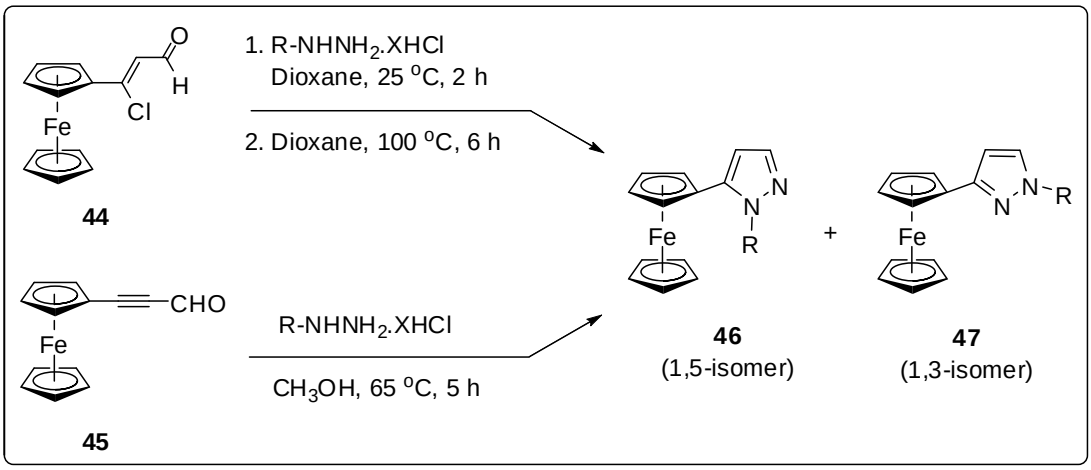


Figure 19. Synthesis of ferrocenyl substituted pyrazoles.

1.1.4 Other methods for the synthesis of pyrazoles

Pyrazoles were also synthesized by the reaction between *N*-tosyl-*N*-propargylhydrazine (**48**) and aryliodides or vinyltriflates in the presence of palladium catalyst (Figure 20) [42]. Initially, cyclocondensation led to the formation of *N*-tosyl-3-aryl(vinyl)pyrazoles **49**, detosylation of which then yielded 3-aryl(vinyl)-1*H*-pyrazoles **50**.

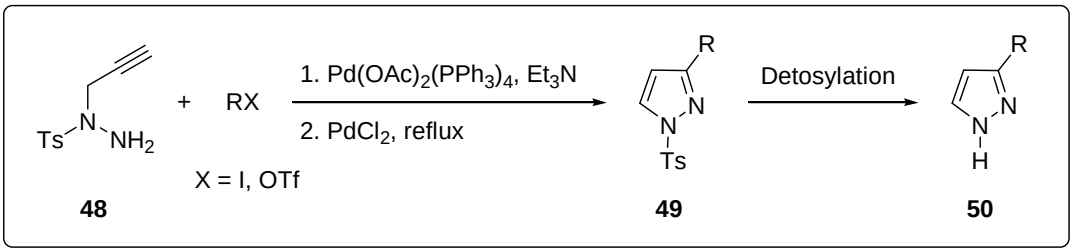


Figure 20. Synthesis of 3-aryl(vinyl)pyrazoles from *N*-tosyl-*N*-propargylhydrazines.

Santagostino developed a new method for the synthesis of pyrazoles through the cyclocondensation between diethoxyphosphorylacetaldehyde tosylhydrazone (**51**) and aldehydes (Figure 21) [43]. Hydrazone **51** was first allowed to react with

aromatic, unsaturated or enolizable aldehydes in the presence of NaH to form α,β–unsaturated tosylhydrazone salts **52**. Corresponding pyrazoles **50** were then isolated by refluxing conditions in moderate to good yields.

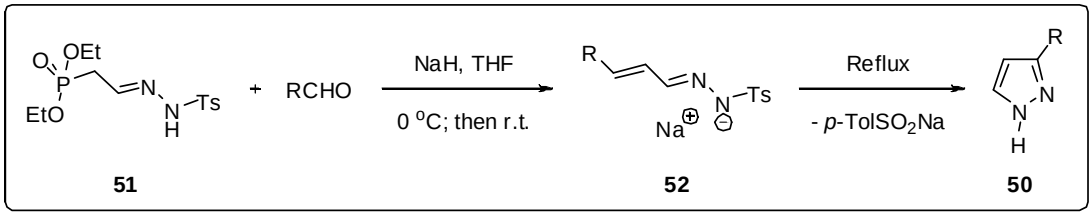


Figure 21. Synthesis of pyrazoles from diethoxyphosphorylacetaldehyde tosylhydrazone.

An efficient method for the synthesis of 3(5)-mono, 3,5-di- and 3,4,5-trisubstituted pyrazoles **56** was investigated by Buchwald (Figure 22) [44]. Protected hydrazine and haloenyne **53** first underwent amination reaction in the presence of Cu catalyst, and then intramolecular cyclization of **54** gave hydropyrazole **55**. Finally, deprotection with trifluoroacetic acid yielded pyrazole derivative **56** (Figure 22).

Suresh discovered a new synthetic pathway for the synthesis of 1,3,4,5-tetrasubtituted pyrazoles **59** starting from dialkyl azodicarboxylates **57**, 3-disubstituted allenoates **58** and triphenylphosphine (Figure 23) [45]. This cycloaddition was applied for the synthesis of variety of 1,4-dicarboalkoxy-substituted pyrazoles.

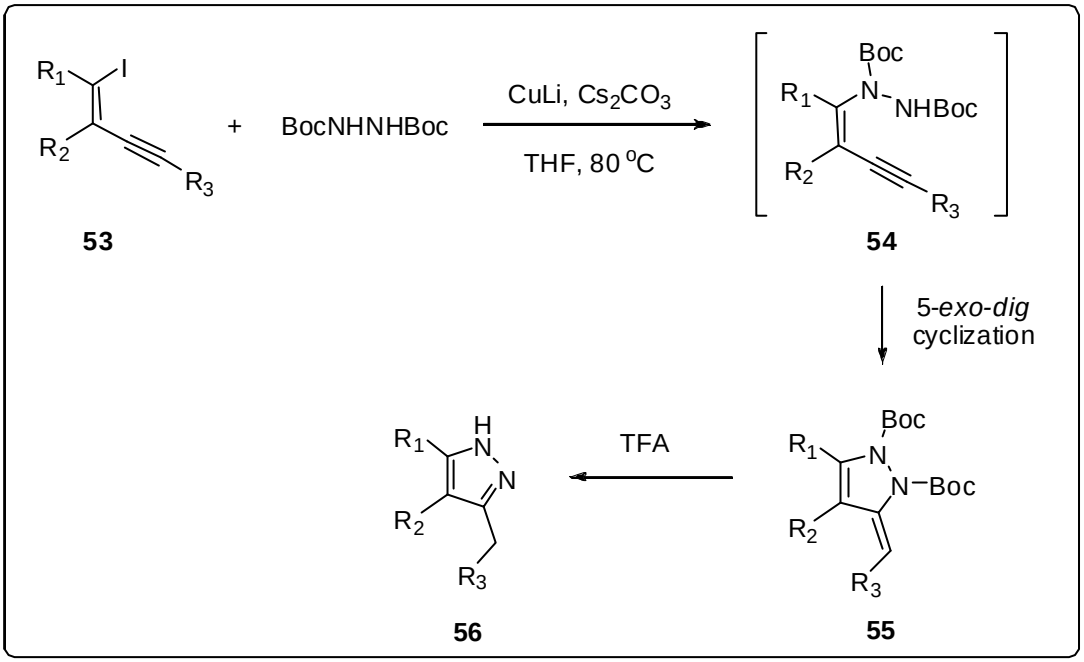


Figure 22. Synthesis of 3,4,5-trisubstituted pyrazoles from haloenynes.

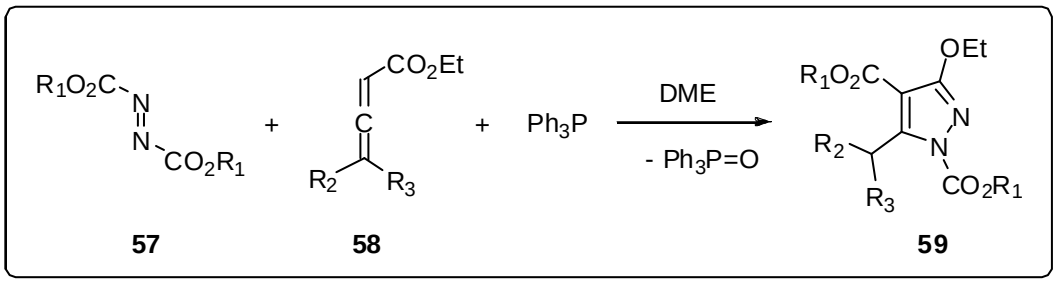


Figure 23. Synthesis of 1,3,4,5-tetrasubtituted pyrazoles **59** from dialkyl azodicarboxylates **57** and 3-disubstituted allenoates **58.**

1.1.5 Synthesis of iodopyrazoles

Halo-substituted pyrazoles, particularly iodo-substituted derivatives, are valuable organic precursors for the synthesis of highly substituted and biologically important derivatives through the Sonogashira, Suzuki-Miyaura and Heck cross-coupling reactions [46]. In addition, iodopyrazoles can be subjected to amination and halogen-

metal exchange reactions. It is noteworthy to mention that iodopyrazoles are generally prepared from other pyrazole derivatives by using a variety of iodination reagents (Figure 24), as will be discussed below.

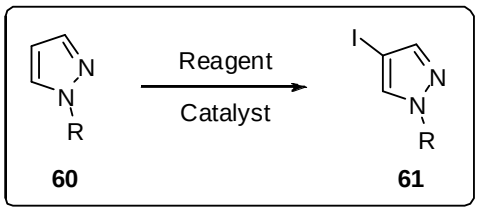


Figure 24. Iodination of pyrazoles.

There are many reagent and catalyst systems which are available for the preparation of halopyrazoles, including I_2, *N*-iodosuccinimide (NIS), *N*-bromosuccinimide (NBS), KI, HIO_3, iodobenzene diacetate (IBD) and ceric ammonium nitrate (CAN) [47]. In the presence of these reagents, pyrazole derivatives **60** undergo iodination reactions to form 4-iodopyrazoles **61** (Figure 24). The more reactive iodine monochloride (ICl) can also be used as an iodinating agent in such reactions [48]. 4-Iodopyrazoles **65** can be synthesized by using I_2/H_2O_2 system as well [49].

An interesting example for the synthesis of 5-halo-substituted pyrazoles **64** was reported by Janinas as shown in Figure 25 [50]. The reaction between diethyl 2-(ethoxymethylene)malonate (**62)** with hydrazine hydrochloride gave ethyl 3-ethoxy-1*H*-pyrazole-4-carboxylate (**63**), which then converted into 5-halopyrazole derivative **64** by treating with I_2/KI, NIS or NBS (Figure 25).

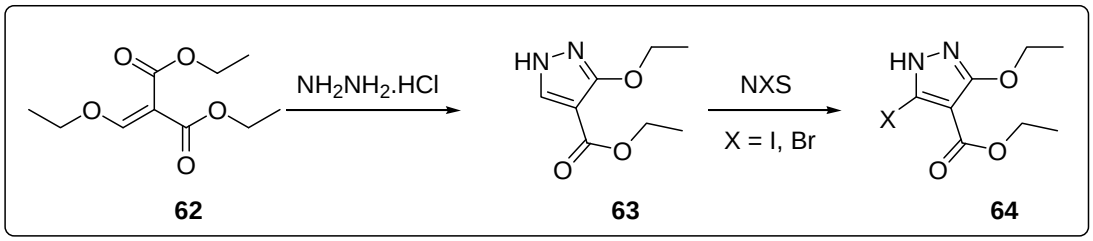


Figure 25. Synthesis of 5-halopyrazoles from dimethyl 2-(ethoxymethylene)-malonate (**62**).

Vedso sythesized 4-iodopyrazole derivative **66** by using ICl/K_2CO_3 system (Figure 26) [48], which underwent iodine-magnesium exchange with alkylmagnesium bromide to give heteroaryl magnesium bromide **67**. Then, introduction of electrophiles, such as benzaldehyde, DMF, TMSCl and benzoyl chloride, led to the formation of 4-substituted pyrazole derivatives **68** (Figure 26).

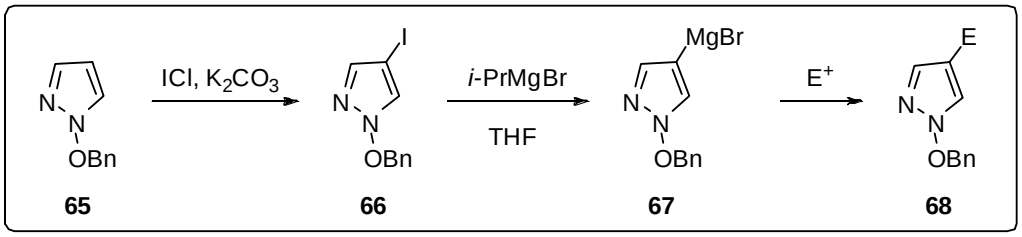


Figure 26. Synthesis of 4-iodopyrazoles and their functionalization by electrophiles via iodine-magnesium exchange sequence.

Iodo substitutent at C4 position of pyrazoles was allowed to react with boronic acids or terminal alkynes to produce functionalized derivatives. By utilizing this methodology, Stauffer prepared estrogene receptor pyrazoles **71** (Figure 27) [51]. After preparing 4-iodopyrazoles **70** with a solution of KI and I_2, they subjected this derivative to Suzuki-Miyaura coupling with boronic acids to synthesize the target pyrazoles **71**.

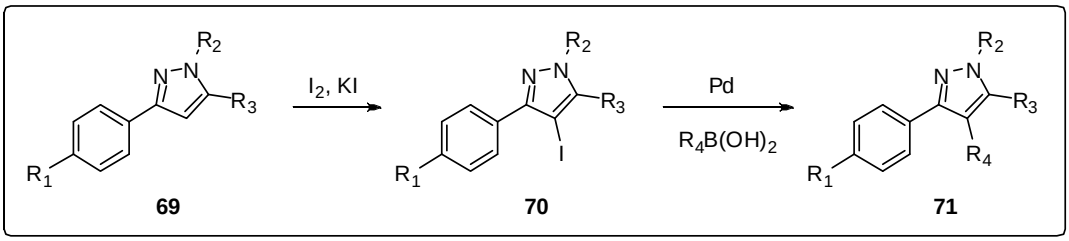


Figure 27. Synthesis of estrogene receptor pyrazoles **71**.

Similarly, Zora research group further functionalized 5-ferrocenyl-4-iodopyrazoles **72** by using Sonogashira and Suzuki-Miyaura cross-coupling reactions to prepare new derivatives which could be potentially active (Figure 28) [52]. For this reason, 4-iodopyrazoles **72** was treated with arylboronic acids and terminal alkynes in the presence of convenient palladium catalysts to synthesize 4-aryl-5-ferrocenylpyrazoles **73** and 4-alkynyl-5-ferrocenylpyrazoles **74** in good to excellent yields.

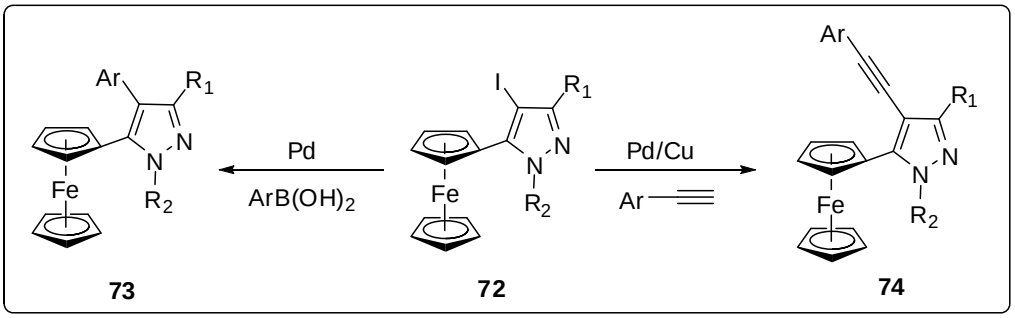


Figure 28. Synthesis of 4-aryl-5-ferrocenylpyrazoles **73** and 4-alkynyl-5-ferrocenylpyrazoles **74**.

Electrophilic cyclizations have been used for the synthesis of biologically active heterocyclic compounds such as isoxazoles, indoles, isochromenes and quinolines [53]. A new approach for the synthesis of halo-substituted pyrazoles can be realized by the electrophilic cyclization of corresponding propargyl aldehydes and ketones via their hydrazones. Surprisingly, regarding electrophilic cyclization of propargyl

aldehydes and ketones leading to 4-iodopyrazoles, there are few studies. Gonzalez-Nogel reported the synthesis of 4-iodo-5-silylpyrazoles **77** from hydrazones **76** with molecular iodine by using electrophilic cyclization (Figure 29) [54]. In this study, they were able to prepare only two derivatives of 4-iodo-5-silylpyrazoles **77** since the condensation of silylated acetylenic ketones with hydrazines was very complicated or the desilylation of acetylenic ketones occurred in acidic medium.

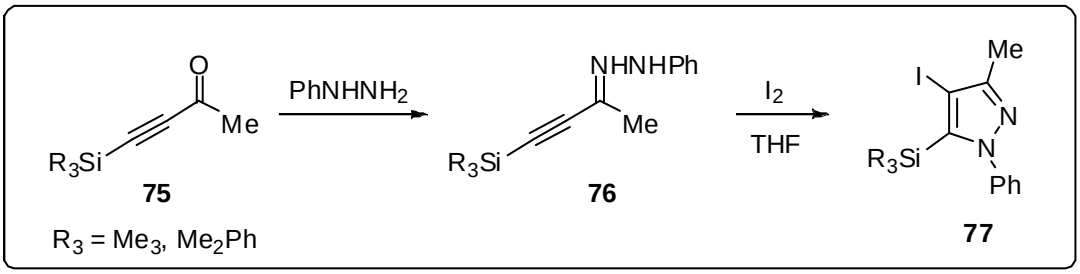


Figure 29. Synthesis of 4-iodo-5-silylpyrazoles.

Larock research group studied electrophilic cyclization of propargyl ketones **28** to synthesize corresponding 4-iodopyrazoles as well (Figure 30) [55]. Propargyl ketones **28** were treated with *N,N*-dimethylhydrazine to yield expected hydrazones **78** but they were not stable in reaction conditions. So the electrophilic cyclization of hydrazones **78** to 4-iodopyrazoles **79** could not be achieved. Alternatively, propargyl ketones were treated with *N*-acylhydrazine to produce dihydropyrazoles **80**, which upon dehydration followed by iodination provided 1-acetyl-4-iodopyrazoles **81** (Figure 30) [56]. It should be mentioned that second method does not involve electrophilic cyclization.

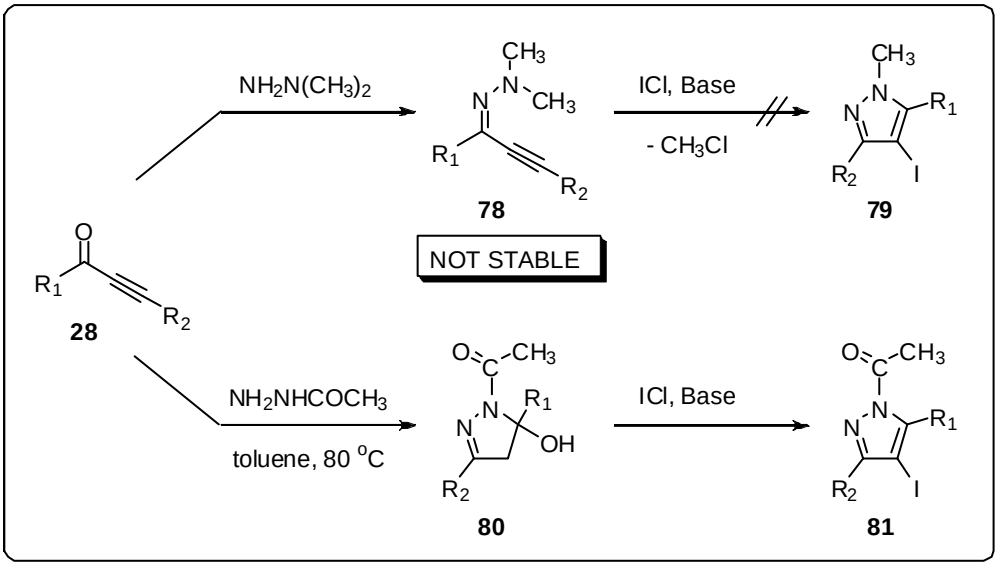


Figure 30. Synthesis of 1-acetyl-4-iodopyrazole derivatives.

Recently, Wada research group synthesized 4-iodo-2,3-dihydropyrazoles **83** and 4-iodopyrazoles **84** by electrophilic cyclization of propargylic hydrazides **82** (Figure 31) [56]. The reaction of hydrazides **82** with bis(2,4,6-collidine)iodonium(I) hexafluorophosphate ($I(coll)_2PF_6$) afforded 4-iodo-2,3-dihydropyrazoles **83** while treatment of hydrazides **82** with *N*-iodosuccinimide (NIS) in the presence boron trifluoride yielded 4-iodopyrazoles **84**.

In summary, the synthesis of pyrazoles has been studied by many research groups and the regioselectivity in these syntheses have been examined. Although organic chemists devised a broad range of methods for the synthesis of pyrazoles and new methods continue to appear, the design of new regioselective pyrazole forming reactions is still a compelling research topic.

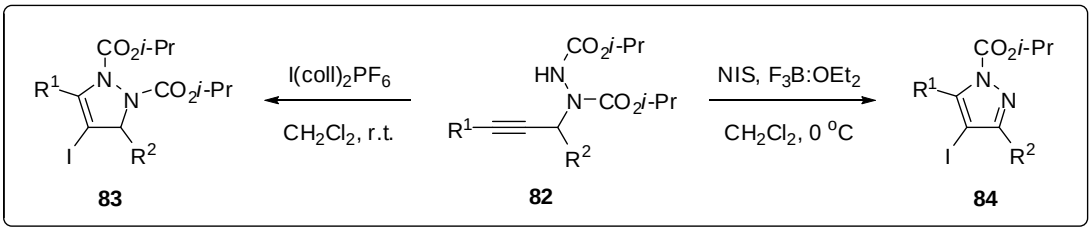


Figure 31. Iodocyclization of propargylic hydrazides **82** to afford 4-iodo-2,3-dihydropyrazoles **83** and 4-iodopyrazoles **84**.

1.2 Isoxazoles

Isoxazoles are five-membered ring heterocycles containing adjacent one oxygen and one nitrogen atom on the ring (Figure 32), and they constitute an important family of heterocyclic chemistry. Isoxazoles are present in the structures of many natural products and pharmaceutical agents [57]. In fact, isoxazoles have long been targeted in organic synthesis due to the broad spectrum of their biological and pharmacological activities, which include hypoglycemic, analgesic, anti-inflammatory, anti-bacterial, anti-infective and anti-tumor activities [58]. They have been also used as selective COX-2 inhibitors such as Valdecoxid (**85**) and β2-selective agonists such as Broxaterol (**86**) (Figure 33) [58c, 59]. Notably, Broxaterol (**86**) is a potential bronchodilatory agent in the therapy of asthma [59c].

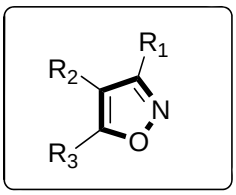


Figure 32. Structure of isoxazoles.

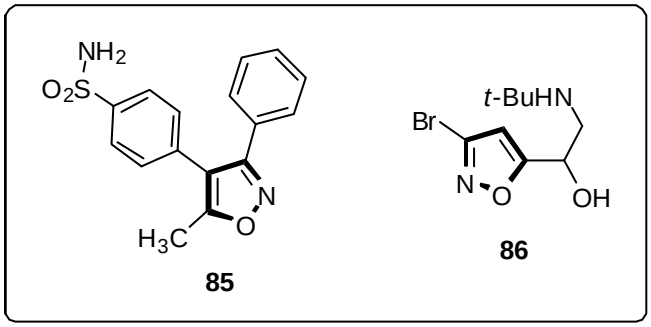


Figure 33. Structures of Valdecoxid (**85**) and Broxaterol (**86**).

Tuberculosis (TB), a life-treating chronic infection affecting the lungs, is caused by the mycobacterium tuberculosis. The World Health Organization reported that one-third of the world`s population is infected with mycobacterium tuberculosis, resulting in 1.3-1.7 million deaths from tuberculosis in 2007 [60]. Kozikowski designed new isoxazole-based antituberculosis drug candidates, the structures of which are shown in Figure 34. The results displayed that benzyloxy, benzylamino and phenoxy derivatives of 5-phenyl-3-isoxazolecarboxylic acid ethyl esters are highly potent and selective for anti-TB [61].

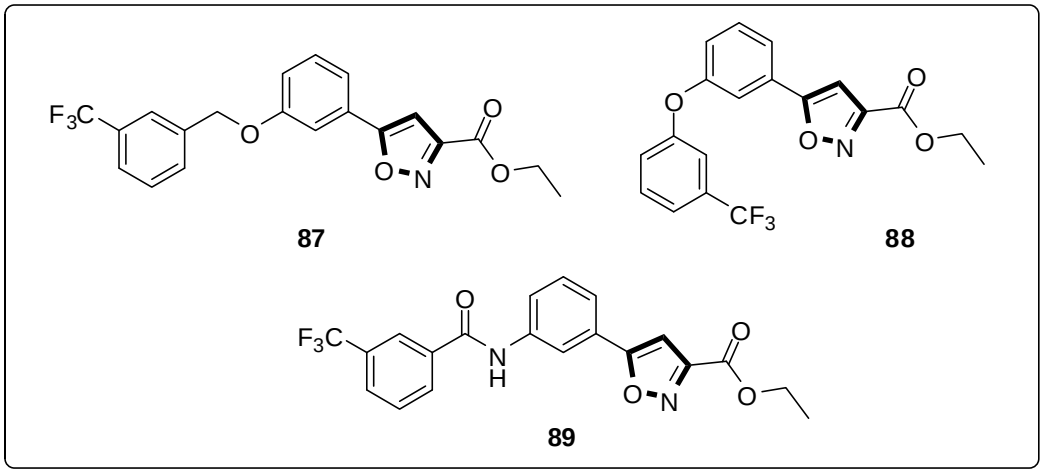


Figure 34. Structures of isoxazole-based antituberculosis drug candidates.

Recently, 3-aryl-4-isoxazolecarboxamide derivatives have been described as potent small molecule agonists of the human TGR5 G-protein coupled receptors, which can be used to treat metabolic disorders such as type II diabetes [62]. High-throughput screening (HTS) has identified that isoxazole-based derivatives **90** and **91** have been found to be novel TGR5 receptor agonists (Figure 35) [63].

Isoxazoles are present in the structures of tetracycline antibiotics as well, one example (**92**) of which is illustrated in Figure 35 [63].

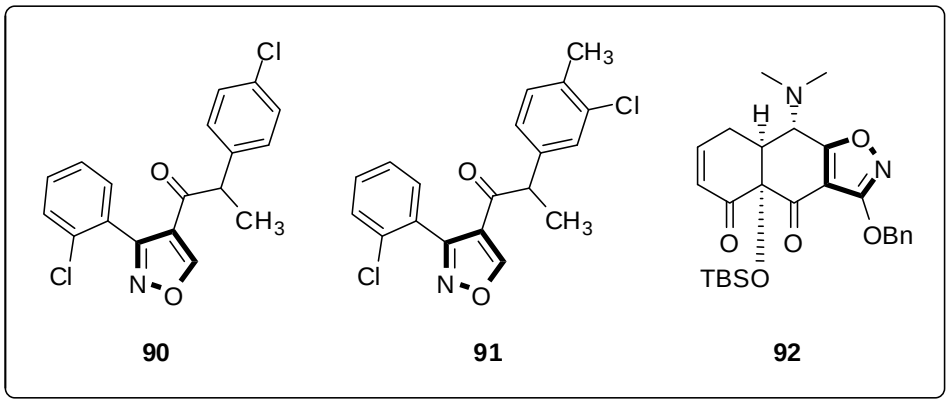


Figure 35. Structures of novel isoxazole-based TGR5 receptor agonists **90** and **91** and tetracycline antibiotic **92**.

Isoxazoles are also valuable building blocks for organic synthesis since they are not only converted into important synthetic units such as β-hydroxyketones, γ-aminoalcohols, α,β-unsaturated oximes, β-hydroxynitriles and aziridine esters [64], but also used in the synthesis of many natural products [57a, 65].

Isoxazoles are generally prepared by (*i*) the reaction of 1,3-diketones with hydroxylamines [66], (*ii*) 1,3-dipolar cycloaddition of nitrile oxides with alkynes [67], and (*iii*) the reaction of α,β-unsaturated aldehydes and ketones with hydroxylamines [68].

1.2.1 Synthesis of isoxazoles from 1,3-diketones and hydroxylamines

When treated with hydroxylamines, β-diketones produce isoxazole derivatives (Figure 36) [67]. When unsymmetrical 1,3-dicarbonyl components such as **6** are used, isoxazole isomers **93** and **94** are obtained. The ratio of isomers usually depends on the reaction conditions.

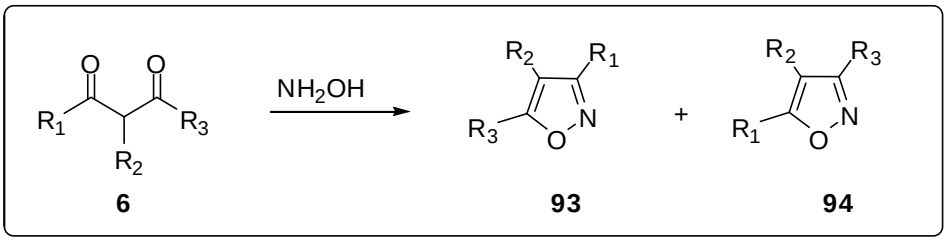


Figure 36. Synthesis of isoxazoles from 1,3-diketones.

When β-keto esters such as **95** react with hydroxylamine, these cyclocondensation reactions are called as Claisen isoxazole synthesis (Figure 37) [69]. 4,5-Disubstituted-3-hydroxyisoxazole derivatives **96** have been obtained from the reaction between β-keto esters **95** and hydroxylamine.

Krogsgaard-Larsen has prepared 3-hydroxyisoxazole derivatives **98** by using Claisen method (Figure 38) [70]. It has been reported that these kinds of isoxazoles behave as a $GABA_A$ receptor antagonist.

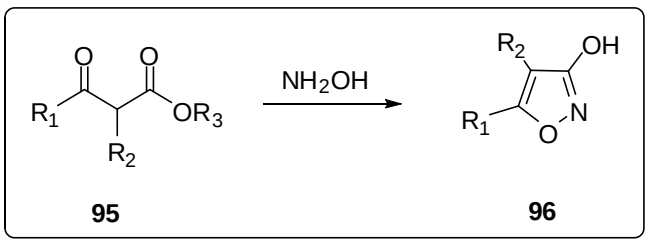


Figure 37. Synthesis of 3-hydroxyisoxazoles from β-keto esters.

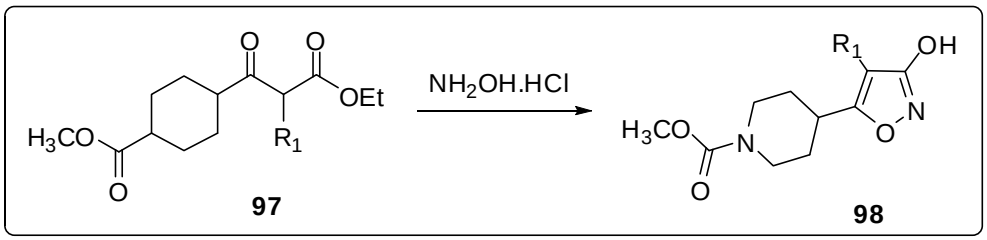


Figure 38. Synthesis of isoxazole-based $GABA_A$ receptor antagonists.

1.2.2 Synthesis of isoxazoles via 1,3-dipolar cycloadditon of nitrile oxides with alkynes

1,3-dipolar cycloaddition of nitrile oxides with alkynes is one of most common methods for the synthesis of aromatic isoxazole derivatives (Figure 39) [71]. However, these reactions usually yield two isomers of isoxazoles with different ratio.

The necessary starting 1,3-dipolar nitrile oxides **100** are generally prepared in situ by the base-catalysed elimination of hydrogen halide from halo-oximes **102**, or by the dehydration of nitro compounds **103** (Figure 40) [72]. Hydroxyiminoyl halides **102** (X = Cl, Br) are easily obtained by the reaction of corresponding aldehyde oximes with *N*-halosuccinimide (NXS).

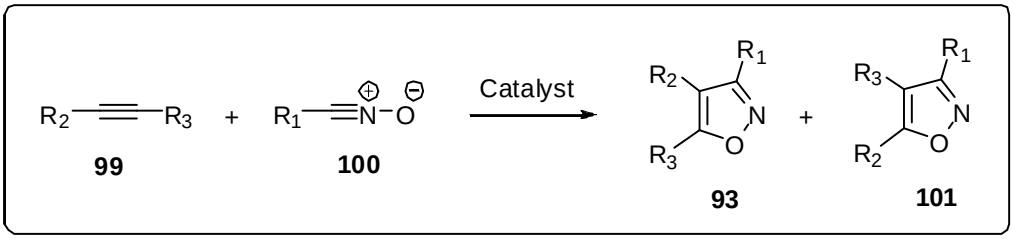


Figure 39. Synthesis of isoxazoles via 1,3-dipolar cycloaddition of nitrile oxides with alkynes.

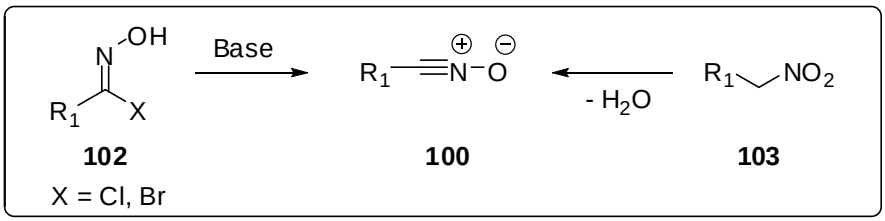


Figure 40. Preparation of nitrile oxides **100** from hydroxyiminoyl chlorides **102** and nitro compounds **103**.

Shang synthesized 5-ferrocenyl-3-arylisoxazole **106** by employing 1,3-dipolar cycloaddition of ethynylferrocene (**104**) with aryl-substituted nitrile oxides **105** [73]. As depicted in Figure 41, this cycloaddition showed regioselectivity for the formation of isoxazole derivatives **106**. It should be noted that 5-ferrocenylisoxazoles **112** displayed new properties for applications in organic synthesis, catalysis and electrochemistry due to quasi-reversible oxidation of iron atom [74].

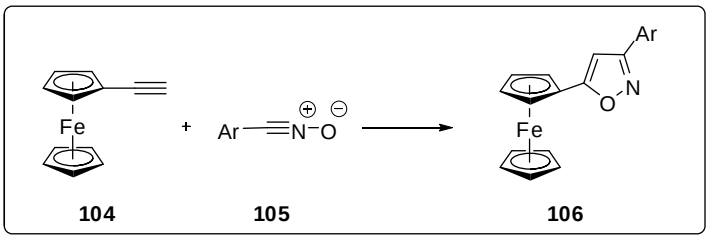


Figure 41. Synthesis of 5-ferrocenylisoxazoles from ethynylferrocene.

Microwave-assisted organic synthesis has received much interest in recent years. Rate enhancement, increased yield, improved purity and greater reproducibility are major advantages in using microwave reactors in organic synthesis [74]. Hence, isoxazoles have been also prepared under microwave irradiation. As shown in Figure 42, Müller has reported the synthesis of substituted isoxazoles **108** by employing one-pot three-component reaction including Sonogashira coupling of acid chlorides

42 with terminal alkynes **43**, followed by 1,3-dipolar cycloaddition of the resulting alkynones **28** with nitrile oxides **107** [75].

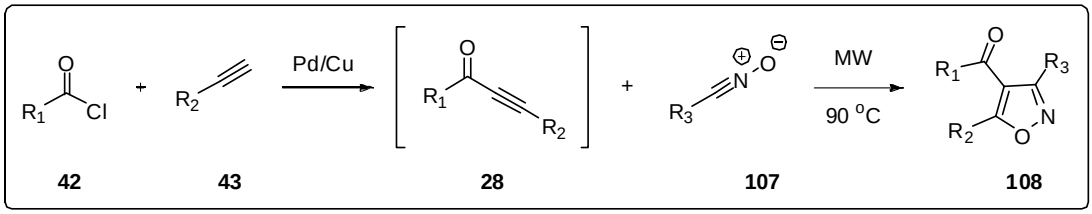


Figure 42. Microwave-assisted synthesis of isoxazoles.

1.2.3 Isoxazoles from the reaction of hydroxylamines with α,β-unsaturated aldehydes and ketones

α,β-Unsaturated carbonyl compounds such as **109** and **111** react with hydroxylamine to afford corresponding isoxazole derivatives (Figure 43) [76]. When treated with oxidizing reagents or catalysts, α,β-unsaturated oximes **110**, obtained from α,β-unsaturated ketones **109** and hydroxylamine, produce isoxazole derivatives **112**. When α or β-substituted α,β-unsaturated ketones **111** are treated with hydroxyl amines, two isomers of isoxazoles, **112** and **113**, are obtained (Figure 43).

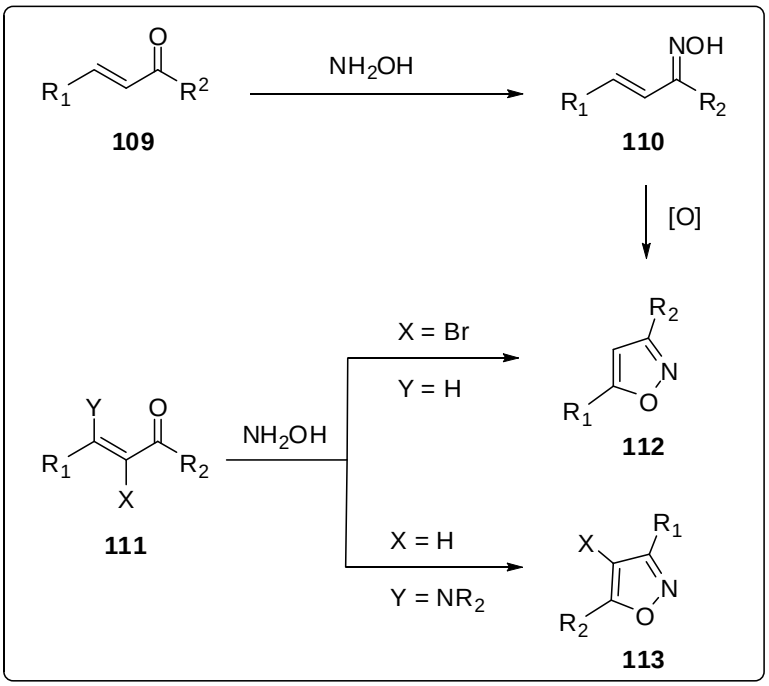


Figure 43. Synthesis of isoxazoles from α,β-unsaturated carbonyl compounds.

Recent studies showed that pyridinylisoxazoles **116** and **117** are potent inhibitors of p38 mitogen-activated protein (MAP) kinase. For this reasons, the synthesis of such isoxazoles were achieved from appropriate ethanones (Figure 44) [77]. The reaction of ethanone **114** with DMF and DMA in refluxing toluene yielded enaminoketones **115** and then addition of hydroxylamine hydrochloride afforded isoxazole derivative **117**. On the other hand, subsequent deprotonation of ethanone **114** with *n*-BuLi followed by ring closure through a 1,3-cycloaddition with the isobutyronitrile *N*-oxide yielded isoxazole derivative **116** (Figure 44) [78].

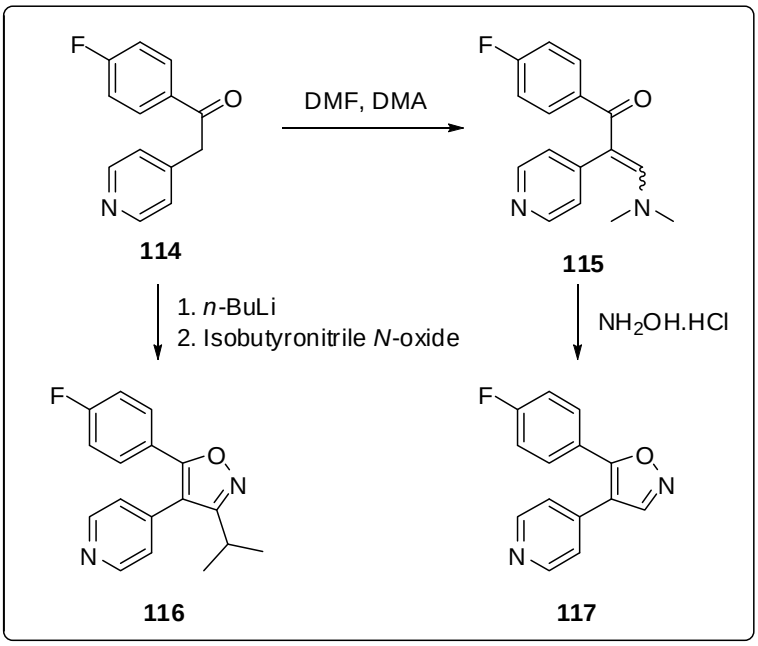


Figure 44. Synthesis of 4,5-disubstituted and 3,4,5-trisubstituted isoxazole derivatives.

Synthesis of highly substituted isoxazoles was reported by Larock research group (Figure 45) [78]. They prepared regioselectively 4-iodoisoxazoles **120** by electrophilic cyclization of *O*-methyloximes **119**, obtained from alkynones **118**, with iodine monochloride. 4-Iodoisoxazoles **120** were then allowed to undergo Sonogashira, Suzuki-Miyaura, Heck and carbonylative amidation cross-coupling reactions for the formation of poly-substituted isoxazole derivatives **121-124** (Figure 45).

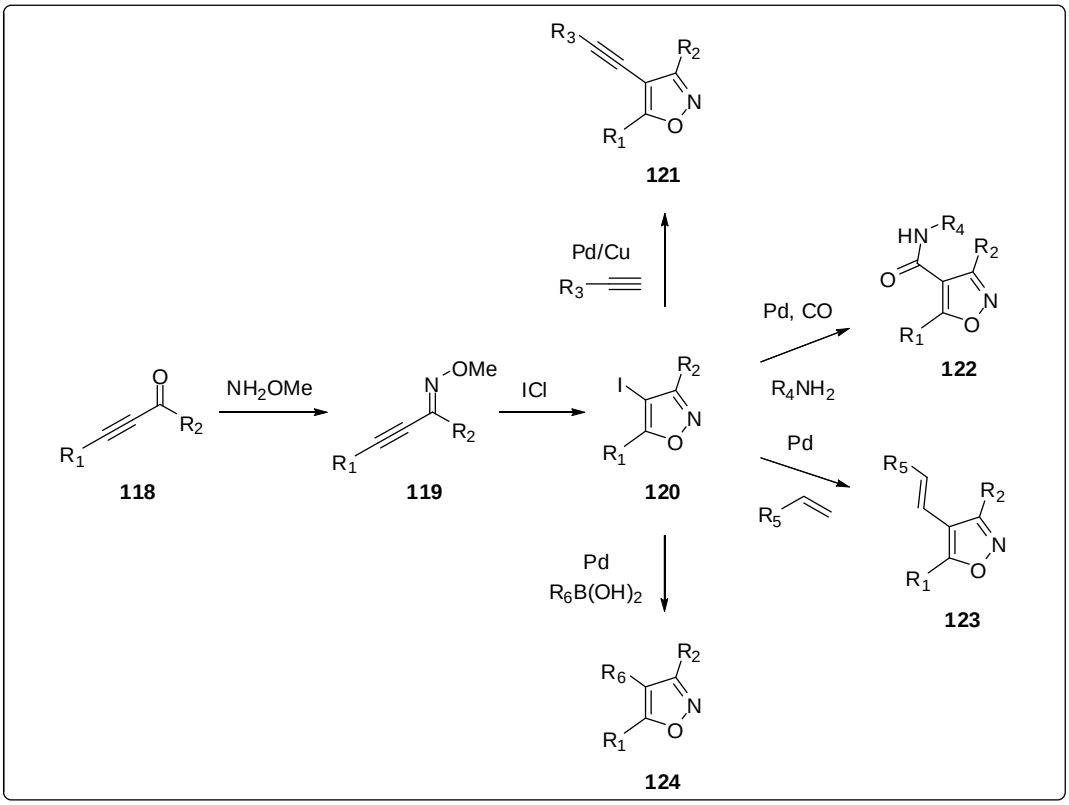


Figure 45. Synthesis of 4-iodoisoxazoles via electrophilic cyclization and their further functionalizations by Pd-catalyzed cross-coupling reactions.

Synthesis of isoxazoles was also achieved from keto-oximes. For instance, 5-trimethylsilanylmethylisoxazole derivative **127** was prepared by cyclization of 4-trimethylsilanyl-3-butynone oxime **126** with a mild base (Figure 46) [79]. Oxime **126** was obtained by the treatment of α-bromo-ketone oxime **125** with corresponding lithium acetylide.

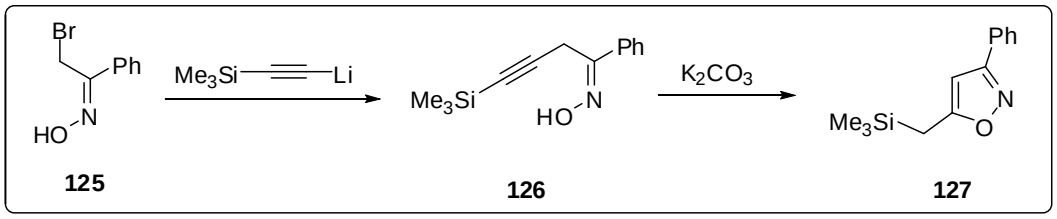


Figure 46. Synthesis of isoxazoles from keto-oximes.

π-Acidic transition metal-catalyzed intramolecular addition of a heteroatom to an alkyne and subsequent migration of the substituent is one of the most useful strategies for the synthesis of heterocyclic compounds [80]. Similar cyclization of alkynyl oxime ethers **128** was carried out for the synthesis of trisubstituted isoxazoles **130** by Miyata (Figure 47) [81]. Intramolecular addition of the oxygen atom in oxime **128** to alkyne functionality in the presence of gold catalyst gave the oxonium intermediate **129**, which then underwent Claisen-type sigmatropic rearrangement for the formation of 4-allyl-3,5-disubstituted isoxazoles **130** (Figure 47). Notably, 4-allyl-substituted isoxazoles are highly versatile building blocks for the synthesis of different heterocycles involving 4,7-dihydrobenzo[*d*]isoxazole, pyrano[4,3-*d*]isoxazole and 4*H*-benzo[3,4]cyclohept[1,2-*d*]isoxazole derivatives [82].

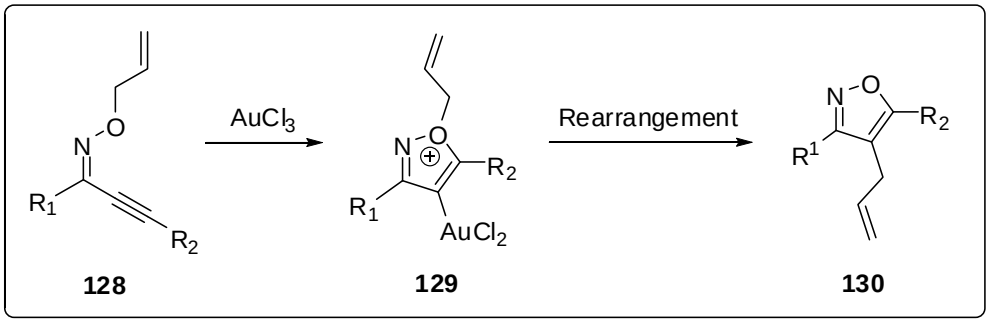


Figure 47. Synthesis of isoxazoles via Au-catalyzed cyclization followed by subsequent rearrangement.

1.2.4 Other methods for the synthesis of isoxazoles

Beam reported a new approach to prepare 3,5-disubstituted isoxazoles regioselectively by condensing lithiated oxime dianions with carboxylic acid derivatives followed by dehydrative cyclization under acidic conditions (Figure 48) [83]. When keto-oximes **131** were treated with *n*-BuLi, oxime dianions **132** were formed. The addition of esters or amides then produced 3,5-disubstituted isoxazoles **133** through *C*-formylation and ring closure sequence (Figure 48) [84].

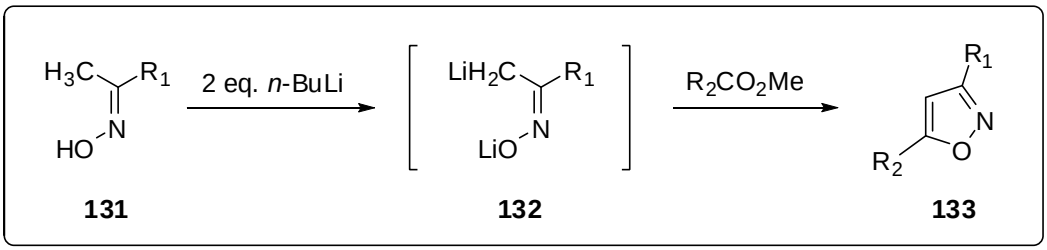


Figure 48. Synthesis of 3.5-disubstituted isoxazoles from keto-oximes

Kloetzer developed a method for the preparation of 3-aminoisoxazoles by the reaction of β-bromoacrylonitriles with hydroxyurea (Figure 49) [85]. Base-promoted elimination of HBr from 2,3-dibromopropionitriles **135**, prepared from acrylonitriles **134**, produced in situ β-bromoacrylonitriles **136**. Additon of hydroxyurea as an *N*-protected hydroxylamine then gave 3-aminoisoxazoles **137** (Figure 49).

Synthesis of 5-aminoisoxazoles **139** was also reported by Bourbeau via nucleophilic addition of lithiated alkyl nitriles **138** to *α*-chlorooximes **102** (Figure 50) [86]. Aminoisoxazoles **139** were also converted to isoxazoles **140** by diazotization reaction with sodium nitrite in the presence of acid [87]. Laufer synthesized 3,4-disubstituted isoxazoles as potential P-38 MAP kinase inhibitors by using this method [77, 88].

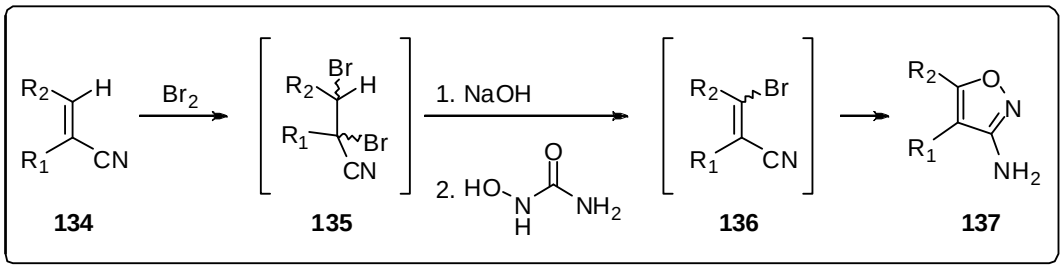


Figure 49. Synthesis of 3-aminoisoxazoles.

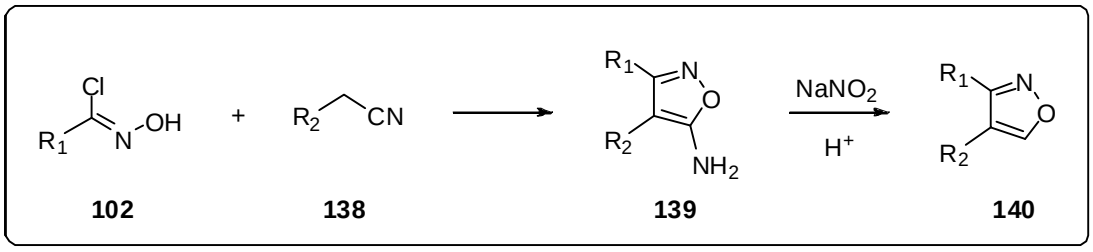


Figure 50. Synthesis of 3,4-disubstituted isoxazoles.

Highly reactive three-membered azirine **141** was utilized to synthesize mono-substituted isoxazoles such as **142** and **143** (Figure 51) [89]. When treated with Grubbs` catalyst, azirine **141** afforded 3-phenylisoxazole (**143**). On the contrary, under photochemical conditions, it yielded 2-phenyloxazole (**142**), an isomer of **143** [90].

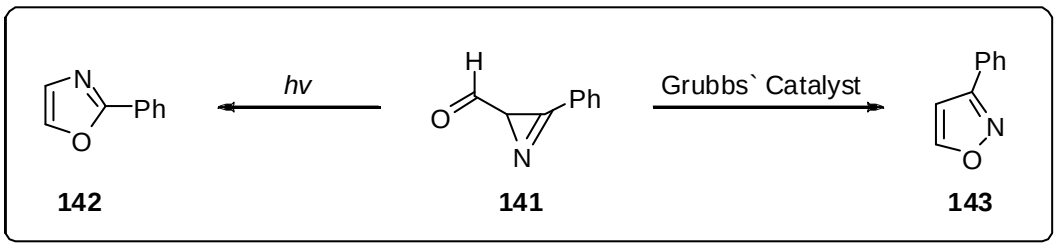


Figure 51. Synthesis of 3-phenylisoxazole and 2-phenyloxazole from an azirine.

1.3 1,2,4-Oxadiazoles

Oxadiazoles are five-membered heteroaromatic compounds including two nitrogen atoms and one oxygen atom on the ring. In fact, there are four isomeric structures for oxadiazoles; 1,2,4-oxadiazoles, 1,3,4-oxadiazoles, 1,2,5-oxadiazoles and 1,2,3-oxadiazoles (Figure 52) [91]. In particular, 1,2,4-oxadiazoles constitute an important class of heterocyclic compounds due to the wide range of biological activities they exhibit.

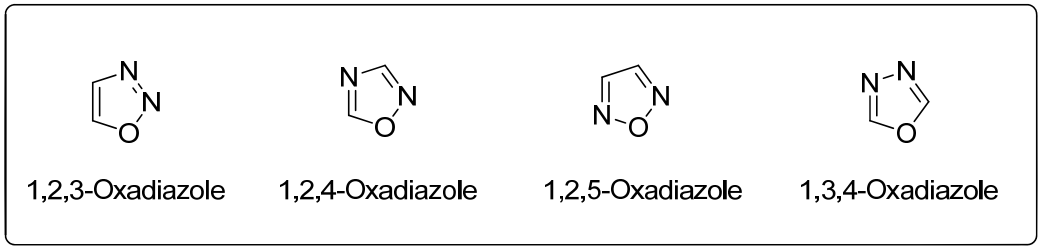


Figure 52. Isomeric structures of oxadiazoles.

First derivatives of 1,2,4-oxadiazoles were synthesized by Tremann and Kruger 125 years ago [92]. Since then, many articles have been published for the applications of 1,2,4-oxadiazoles in medicine [93] and material science (ionic liquids, liquid crystals, OLED) [94]. Structure-metabolism relationship studies often reveal that incorporation of one or more heteroatoms in an aromatic ring influences the chemical and biochemical reactivity of these compounds and therefore alter their metabolism [95].

1,2,4-Oxadiazoles have been described as good bioisosters of amide and esters [93a, 96]. Furthermore, they have been reported to have agonist for cortical muscarinic receptors [97], benzodiazepine [98], 5-HT_{1D} (5-hydroxytryptamine) [99], 5-HT_3 [100], histemic H_3 [101] and sphingosine-1-phosphate-1 ($S1P_1$) receptors [102]. They also display activity as anti-inflammatory [103], antiparasetic [104] and anti-tumor

agents [105], anti-diabetics (**145**) [106] (Figure 53), anti-asthmatics (**146**) [107] (Figure 53), and growth hormone secretagogues [108]. They exhibit signal transduction [109], monoamine oxidase [110], cell adhesion [111] and tryptase inhibitor properties [112]. Furthermore, they show activity against several breast and colorectal cancer cell lines (**144**) [93j, 113] (Figure 53), antagonist of the integrin $\alpha_v\beta_3$ [114], human nuetrophil elastase [115] and human DNA topoisomerases [116].

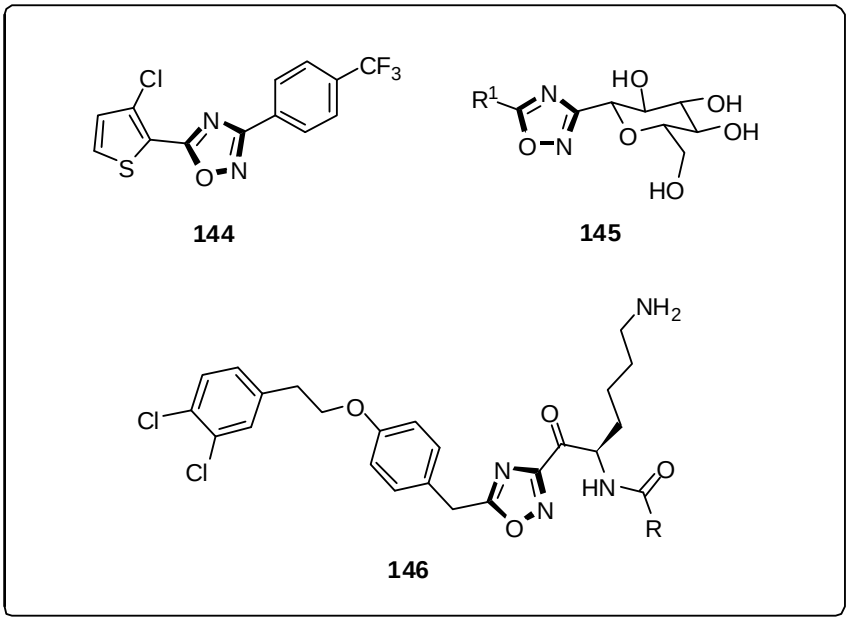


Figure 53. Examples of 1,2,4-oxadiazole-containing anti-cancer **144**, anti-diabetics **145** and anti-asthmatics **146** agents.

Recent studies have proved anti-inflammatory properties of 3,5-disubstituted-1,2,4-oxadiazoles. In addition, 1,2,4-oxadiazoles with long hydrocarbon chains at C-5 have been found to possess not only anti-inflammatory but also antitumor activities (Figure 54) [117]. Importantly, these compounds exhibit similar or more activity as compared with aspirin and ibuprofen.

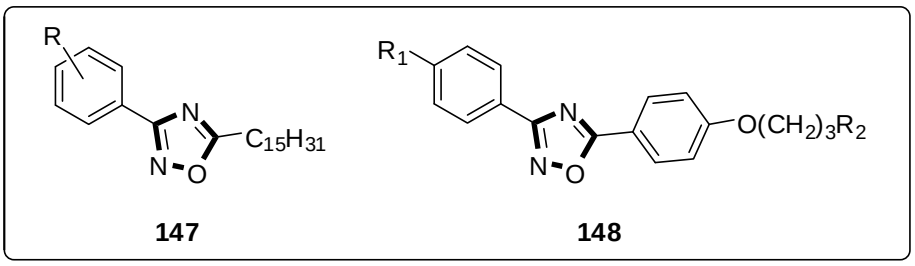


Figure 54. Examples of 1,2,4-oxadiazole-based anti-inflammatory agents.

In addition to anti-microbial activity, 1,2,4-oxadiazole derivatives **149** were found to have the best bioisosteric replacement for the methyl ester groups, which maintained of anti-HIV with submicromolar EC_{50} values [118]. 5-Thiocyano-substituted oxadiazoles displayed anti-bacterial properties, and particularly, 3-aryl-5-thiocyanomethyl-1,2,4-oxadiazole derivatives **150** were found to be potential drugs for the treatment of *Leishmaniasis* and *African trypanosomiasis* caused by the bite of certain species of sand fly or Tsetse fly (Figure 55) [119].

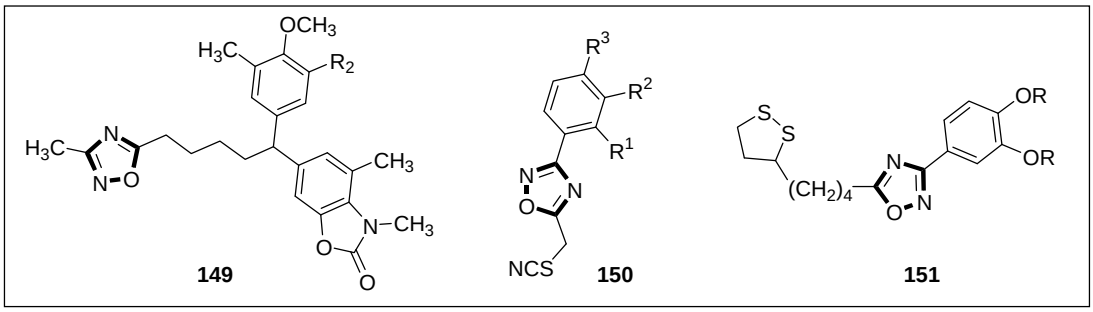


Figure 55. Examples of 1,2,4-oxadiazole-based anti-microbial and neuroprotecting agents.

1,2,4-Oxadiazoles are also used as neuroprotective agents for the therapy of Parkinsons` and Alzheimer`s diseases. 1,2,4-Oxadiazole derivatives **151** have been designed to be neuroprotective agents (Figure 55), since the derivatives of 1,2-dithiolane-3-pentanoic acid (α-lipoic acid) are neuroprotective antioxidants. For this

purpose, a series of 3,5-dialkyl/aryl-1,2,4-oxadiazoles containing lipoic acids have been prepared to find strong neuroprotective agents [120].

Polymers containing oxadiazole units, such as **152** and **153**, are known to have excellent thermal and hydrolytic stability in material applications since they are thermally degraded in the 300-400 ^{o}C range (Figure 56) [121]. Additionally, they are soluble in strong acids such as sulfuric acid and trifluoroacetic acid.

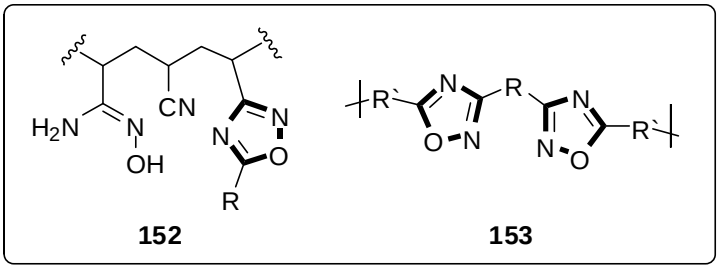


Figure 56. Examples of 1,2,4-oxadiazole-bearing polimers.

Photochemical reactivity of 1,2,4-oxadiazoles was examined in detail and it was shown that these heterocycles can be used as a synthon for the construction of other heterocyclic systems including different 1,2,4-oxadiazoles **155** [122], 1,2,4-triazines **156** [123], 1,2,4-triazoles **157** [124], indazoles **158** [125], quinazolinones **159** [126], *N*-imidoylaziridines **160** [127], 1,3,4-oxadiazoles **161** [128], *N*-benzoylbenzamidines **162** [123] (Figure 57). Some heterocycles like benzimidazoles [129], benzoxazoles [130] and quinolines [131] were also obtained after photochemical rearrangement of 1,2,4-oxadiazoles. The rearrangement of 1,2,4-oxadiazoles under photochemical conditions generally started with the cleavage of N-O bond, followed by different reaction pattern depending on the nature of the substituents on the ring (Figure 57).

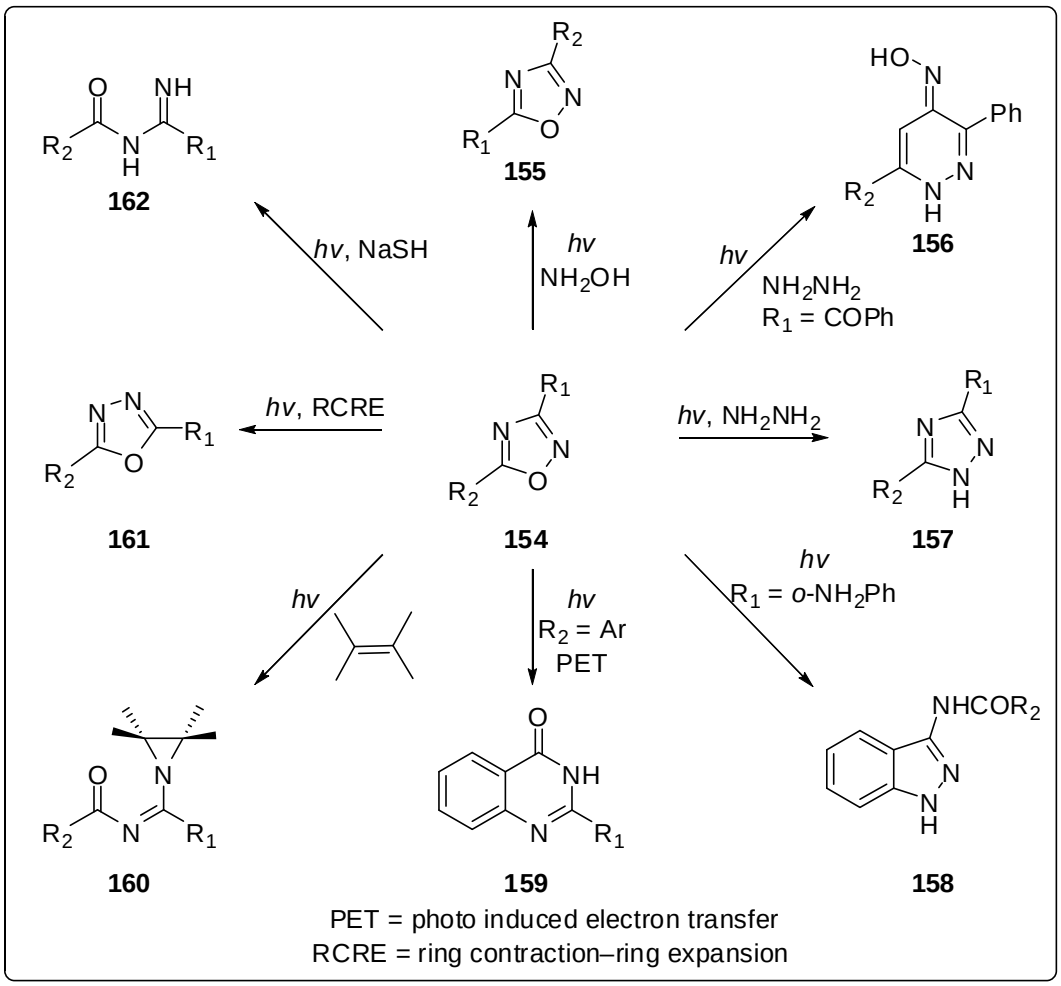


Figure 57. Photochemical rearrangements of 1,2,4-oxadiazoles.

1,2,4-Oxadiazoles are generally prepared by (*i*) 1,3-dipolar cycloadditon of nitrile oxides with nitriles and (*ii*) cyclocondensation of amidoximes with carbonyl-containing reactants; such as activated acids, acid chlorides and fluorides, acid anhydrides, esters and β-ketoesters [132].

1.3.1 Synthesis of 1,2,4-oxadiazoles via 1,3-dipolar cycloaddition of nitrile oxides with nitriles

It was previously mentioned that 1,3-dipolar cycloaddition reactions are one of the most common methods for the synthesis of heterocyclic compounds. 1,2,4-Oxadiazoles were also prepared by the cycloaddition between nitrile oxides and nitriles, and 3,5-disubstituted-1,2,4-oxadiazole derivatives were isolated from these reactions as illustrated in Figure 58 [133].

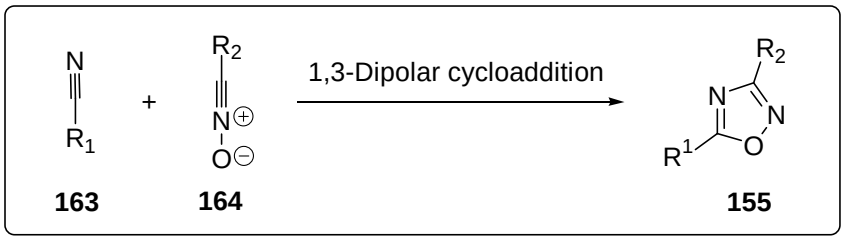


Figure 58. Synthesis of 1,2,4-oxadiazoles via 1,3-dipolar cycloaddition of nitrile oxides with nitriles.

Synthesis of 3-acyl-1,2,4-oxadiazoles **168** is important for the further functionalization of 1,2,4-oxadiazoles [122]. Itoh reported a rare example for the synthesis of such 1,2,4-oxadiazoles by using iron-catalyzed cycloaddition reaction with nitriles and carbonyl compounds. For this purpose, α-nitroketones **166** were first synthesized from methyl ketones **165** (Figure 59) [134]. Subsequent elimination of water gave in situ nitrile oxides **167**. Finally, 1,3-dipolar cycloaddition of nitrile oxides **167** with appropriate nitriles produced the desired 3-acyl-1,2,4-oxadiazoles **168** (Figure 59) [135].

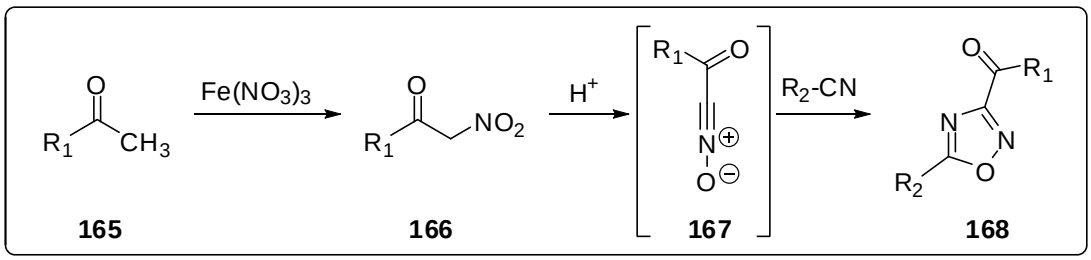


Figure 59. Synthesis of 3-acyl-1,2,4-oxadiazoles.

Augustine developed one-pot synthesis of 1,2,4-oxadiazoles from amidoximes and nitriles in the presence of PTSA/$ZnCl_2$ catalyst system as depicted in Figure 60 [136]. Interestingly, amidoximes **169** were used as a nitrile oxide precursor in this methodology.

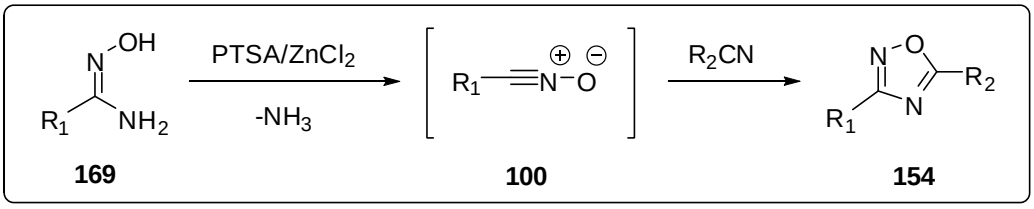


Figure 60. Synthesis of 1,2,4-oxadiazoles from amidoxime and nitriles.

1.3.2 Synthesis of 1,2,4-oxadiazoles by cyclocondensation of amidoximes with carboxylic acid derivatives

Cyclocondensation of amidoximes with carboxylic acids in the presence of a coupling reagent is most common method for the synthesis of 3,5-disubstituted-1,2,4-oxadiazoles **154** (Figure 61) [137]. The reaction consists of two steps; coupling and cyclization. Amidoximes **169** are often either commercially available or easily prepared by the reaction of nitriles with hydroxylamine [138]. Activated carboxylic acid derivatives, such as acid chlorides and fluorides, esters and anhydrides, are also used for the formation of *O*-acylated amidoxime intermediates **171**. *N*,*N*-Carbonyl-

diimidazole (CDI) [139], acyl-palladium complex [140], *N*,*N*-dicyclohexyl-carbodiimide (DCC) [141], (*N*,*N*-dimethylamino)isopropyl chloride (DIC) [142], 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) [109a, 143] and 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) are commonly used as coupling (activating) agents for carboxylic acids [144].

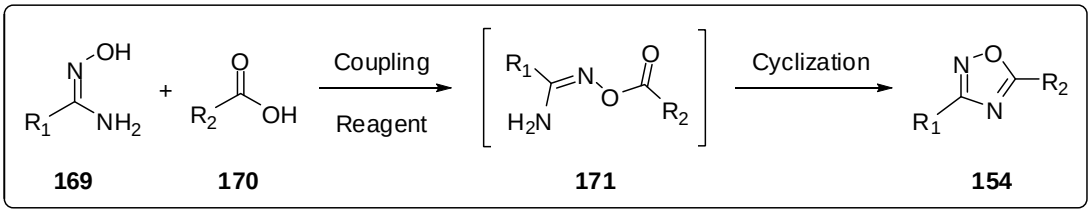


Figure 61. Synthesis of 1,2,4-oxadiazoles from amidoximes and carboxylic acids.

The reaction of aryl amidoximes **172** with succinic anhydride (**173)** in high boiling solvents or under microwave irradiation produced a mixture of 1,2,4-oxadiazole derivatives **174**, **175** and **176**, the former being the major product of the reaction (Figure 62) [145]. Oxadiazole derivatives **175** and **176** were obtained as minor products. Derivatives containing propionic acid units, such as **174**, are important building blocks for the synthesis of pharmaceuticals such as cannabinoid receptor 2 (CB2) [146] and niacin receptor agonists [147]. For this purpose, elaborated anti-inflammatory and anti-microbial derivatives of 1,2,4-oxadiazole peptidomimetics were prepared [148].

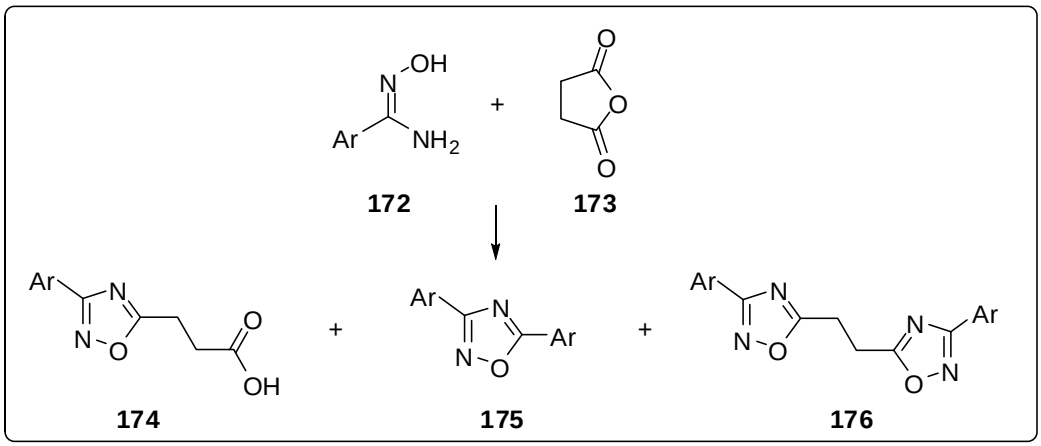


Figure 62. Synthesis of 1,2,4-oxadiazoles from amidoximes and succinic anhydride.

1.3.3 Other methods for the synthesis of 1,2,4-oxadiazoles

Reactions of amidoximes with aldehydes gave 4,5-dihydro-1,2,4-oxadiazoles **168**, instead of 1,2,4-oxadiazoles (Figure 63) [140, 149]. Then, oxidation of dihydrooxadiazoles **178** by using potassium permanganate, MnO_2 or sodium hypochlorite furnished 1,2,4-oxadiazoles **154**. Recently, Okimoto electrochemically oxidized dihydrooxadiazoles **178** to 1,2,4-oxadiazoles **154** in good yields [150].

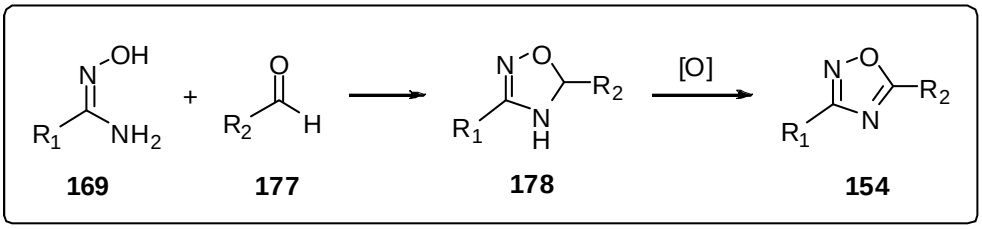


Figure 63. Synthesis of 1,2,4-oxadiazoles via oxidation of 4,5-dihydro-1,2,4-oxadiazoles.

1. 4 1,2,4-Oxadiazepines

1,2,4-Oxadiazepines are seven-membered ring heterocycles containing one oxygen and two nitrogen atoms on the ring. In fact, there are nine possible isomers of oxadiazepines (Figure 64). 1,2,3-, 1,2,4-, 1,2,5-, 1,2,6 and 1,2,7-Oxadiazepines are not known but few derivatives of their fused or benzo-fused analogs are known [151]. Oxadiazepines are also an important class of heterocyclic compounds due to their pharmaceutical and biological activities since the compounds containing oxadiazepine skeleton display antimicrobial, antifungal and anticancer activities [152].

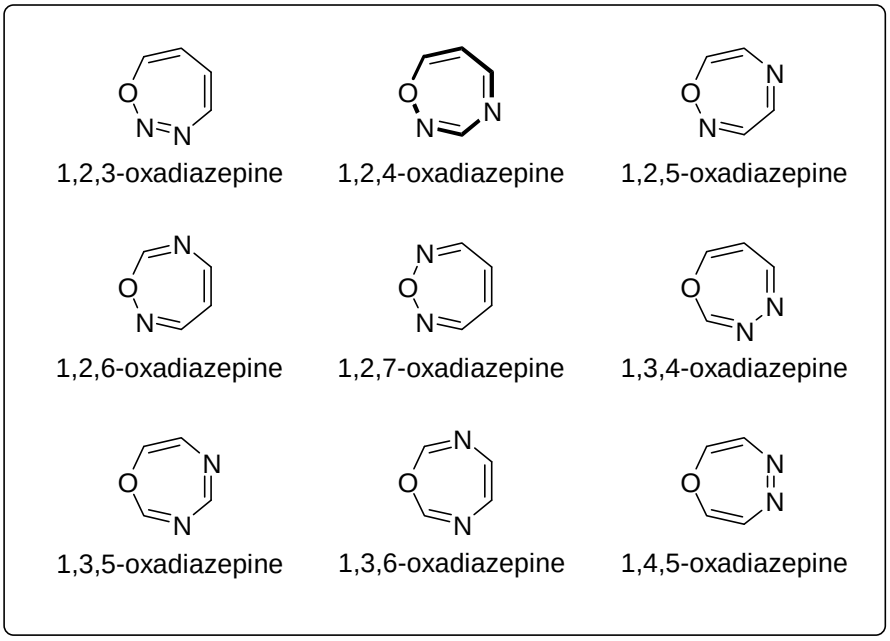
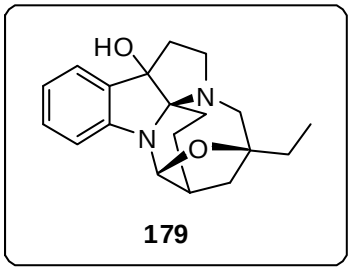


Figure 64. Isomers of oxadiazepines.

Recently, Lim has isolated a natural product including fused oxadiazepine-tetrahydrofuran moiety from *Malayan Tabernaemontana corymbosa* (Figure 65) [153].

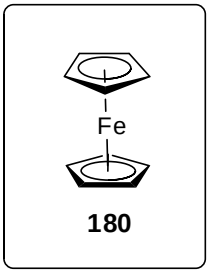


179

Figure 65. Structure of a naturally occurring fused oxadiazepine.

1.5 Ferrocene

Ferrocene, a double-cone sandwich structure, was synthesized from cyclopentadiene and $FeCl_2$ in 1951 by the research groups of Miller, Tebboth and Tremaine, and of Kealy and Pauson at the same time (Figure 66) [154]. However, the structure of ferrocene was proposed by Fischer, Wilkinson and Woodward in 1952.



180

Figure 66. Structure of ferrocene.

Ferrocene has many favorable chemical features that make it one of the most appealing compounds for the researchers during the last decades. It is neutral, highly stable and non-toxic, and also it carries many biochemically valuable properties like membrane permeation, solubility in a large array of solvents and enhanced redox abilities [155]. Interestingly, the incorporation of a ferrocene unit with the structural features of biologically active molecules increases the current activities of parent

compounds or creates totally new properties [156]. Therefore, there are many structural variations of established drugs with ferrocenyl moieties, such as ferrocenyl aspirin (**181**) [157], anti-malarial drug ferroquine (**182**) [158] and anti-cancer drug ferrocifen (**182**) [159] (Figure 67). For instance, ferrocifen (**183**) is more active than tamoxifen and effective on both hormone-dependent and hormone-independent breast cancer lines [160]. In addition, ferrocene salts, such as ferrocenium tetrafluoroborate **184** (Figure 67), are well known anticancer agents [161].

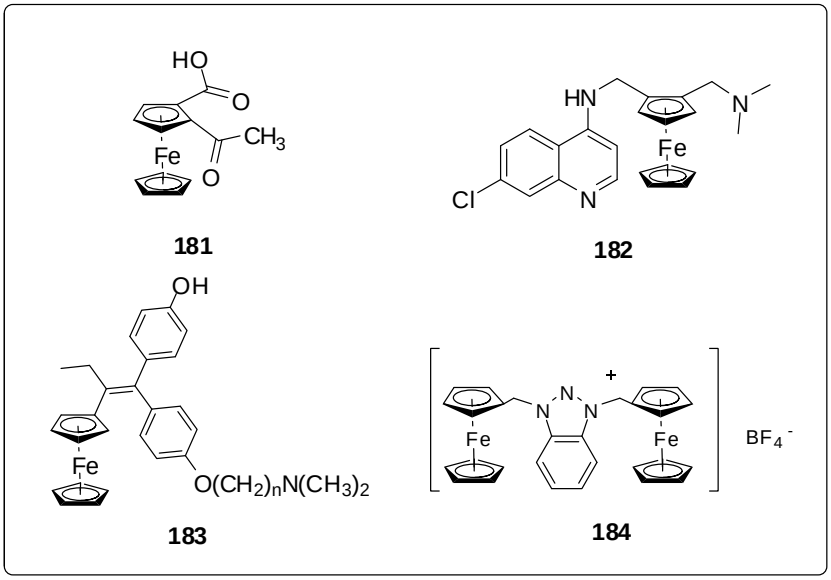


Figure 67. Structures of ferrocenyl aspirin **181**, ferroquine **182**, ferrocenyl hydroxytamoxifen **183** and ferrocenium tetrafluoroborate **184**.

1. 6 Aim of the study

In this study, we will investigate new methods for the synthesis of biologically important heteroaromatic compounds including pyrazoles, 4-iodopyrazoles, isoxazoles and 1,2,4-oxadiazoles and 1,2,4-oxadiazepines. First, we will employ electrophilic cyclizations of α,β-alkynic hydrazones **186**, obtained from propargyl aldehydes and ketones **118** and hydrazines **185**, to regioselectively produce

corresponding pyrazoles **187** and **188** (Figure 68). When treated with molecular iodine, acetylenic hydrazone derivatives **186** may undergo electrophilic cyclization and afford 4-iodopyrazoles **187**. We are particularly interested in the synthesis of 4-iodo-1,3,5-trisubstituted and 4-iodo-1,5-disubstituted pyrazoles since they may play an important role in the formation of biologically active pyrazole derivatives due to the resulting iodine-containing products. As mentioned previously, iodo-substituted pyrazoles are important precursors for the synthesis of highly substituted pyrazole derivatives via metal-catalyzed cross-coupling reactions.

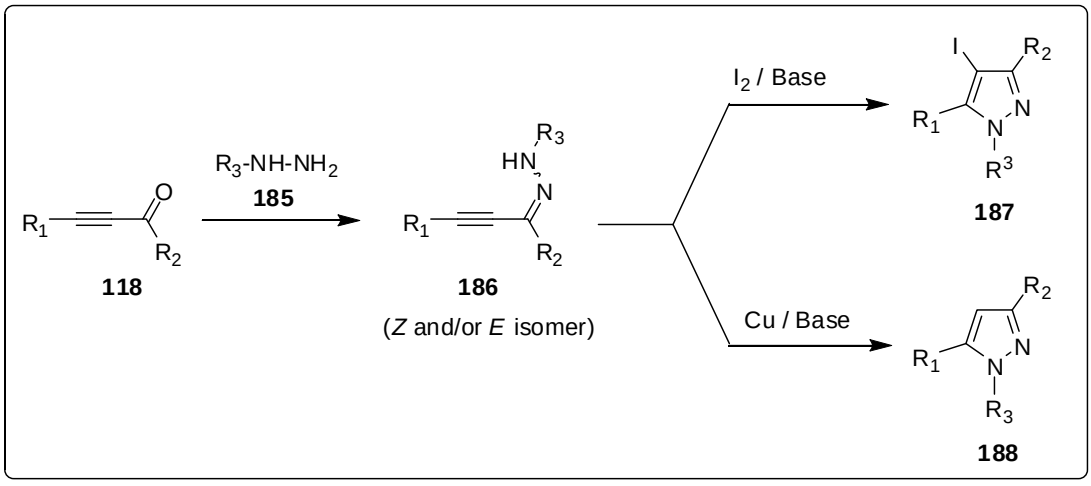


Figure 68. Synthesis of pyrazoles and 4-iodopyrazoles via electrophilic cyclization.

In the second part of the study, we will examine electrophilic cyclization of α,β-alkynic hydrazones **186** with CuI/Base system, a new electrophilic cyclization method. When treated with cuprous iodide in the presence of a base, acetylenic hydrazones **186** could be converted to corresponding pyrazole derivatives **188** (Figure 68).

In the third phase of the study, we will investigate the reactions of amidoximes **190** with propargyl aldehydes and ketones **118** for the synthesis of 1,2,4-oxadiazepines

193 (Figure 69). Initially, these reactions could produce conjugate addition products **191** before cyclization reactions. If we will not obtain oxadiazepine **193**, the cyclization would be carried out under basic or acidic conditions. We hyphothesize that conjugate addition products **191** may also give 1,2,4-oxadiazoles **192** or isoxazoles **112**. Interestingly, under basic conditions, conjugate addition products **191** could afford 1,2,4-oxadiazoles **192** along with methyl ketones. On the other hand, under acidic conditions, conjugate addition products **191** could furnish isoxazoles **112** (Figure 69). It should be mentioned that if these reactions produce isoxazoles and 1,2,4-oxadiazoles under acidic and basic conditions, respectively, they will be previously unknown reactions from the mechanistic point of view.

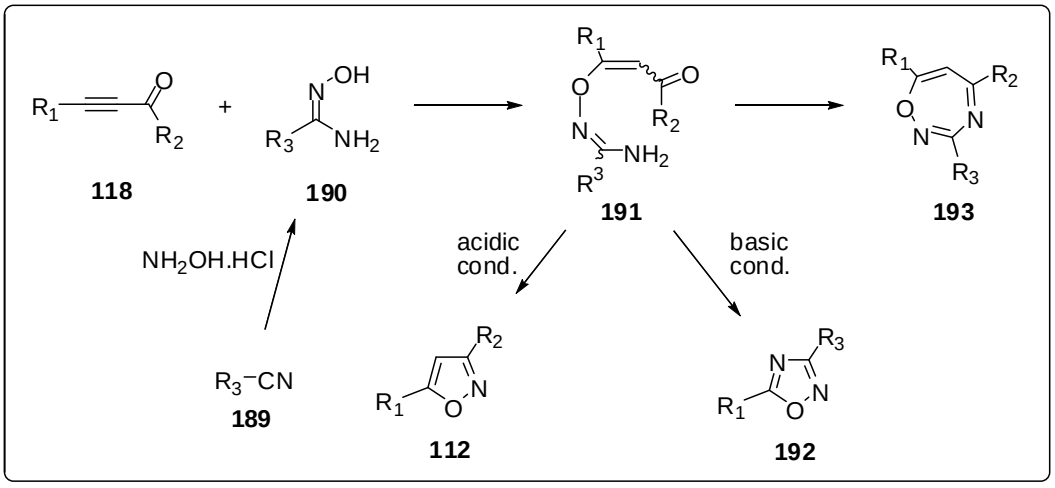


Figure 69. Synthesis of isoxazoles (**112**), 1,2,4-oxadiazoles (**192**) and 1,2,4-oxadiazepines (**193**).

It is concluded that the synthesis of these ring systems includes:

(*i*) Synthesis of propargyl aldehydes (alkynals) and ketones (alkynones) **118** from corresponding alkynes,

(*ii*) Synthesis of hydrazone derivatives **186** of propargyl aldehydes and ketones,

(*iii*) I_2-mediated electrophilic cyclization of hydrazone derivatives **186** to afford 4-iodopyrazoles **187**,

(*iv*) CuI-mediated electrophilic cyclization of hydrazones derivatives **186** to afford pyrazoles **188**,

(*v*) Synthesis of amidoxime derivatives **190** from corresponding nitriles,

(*vi*) Synthesis of conjugate addition (N'-((-3-oxo-1-aryl/alkylprop-1-en-1-yl)oxy)aryl) products **191** and/or 1,2,4-oxadiazepines **193** by the reaction of amidoximes **190** with propargyl aldehydes and ketones **118**,

(*vii*) Reaction of conjugate addition (*N*′-(3-oxopropenyloxy)benzimidamide) products **191** in acidic condition,

(*viii*) Reaction of conjugate addition (*N*′-(3-oxopropenyloxy)benzimidamide) products **191** in basic conditions,

In summary, in this thesis, the scope, limitations and mechanisms for the formation of 4-iodopyrazoles **187**, pyrazoles **188**, isoxazoles **112**, 1,2,4-oxadiazoles **192** and oxadiazepines **193** will be discussed in detail.

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis of propargyl aldehydes and ketones

2.1.1 Synthesis of propargyl aldehydes

In the first part of the study, propargyl aldehydes **118** were prepared from corresponding terminal alkynes **194** in good to high yields by using a standard literature procedure (Figure 70) [162]. Terminal alkynes **194** were first treated with *n*-BuLi in THF at -40 ^{o}C under argon. Then the resulting lithium alkynides **195** were allowed to react with DMF at room temperature for 1 h to afford propargyl aldehydes **118**. Note that a reverse quench into a phosphate buffer has proved to be the key for these high yielding formylation reactions. Proposed mechanism for the formation of propargyl aldehydes **118** is shown in Figure 70.

As depicted in Figure 71, six different derivatives of 3-aryl or alkyl substituted propargyl aldehydes were synthesized, the overall yields of which ranged from 52 to 94%. The best yield was obtained for 4-methoxyphenyl derivative **118c** while the lowest yield was found for thiophen-3-yl derivative **118d**.

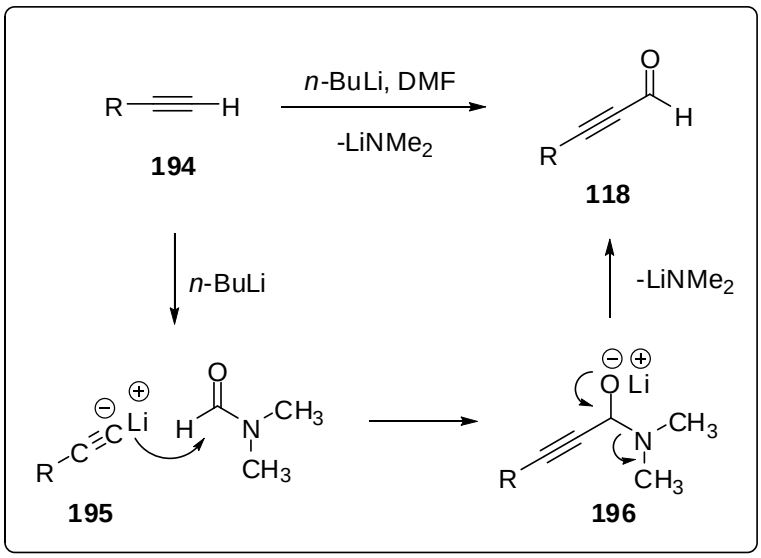


Figure 70. Proposed mechanism for the formation of propargyl aldehydes**.**

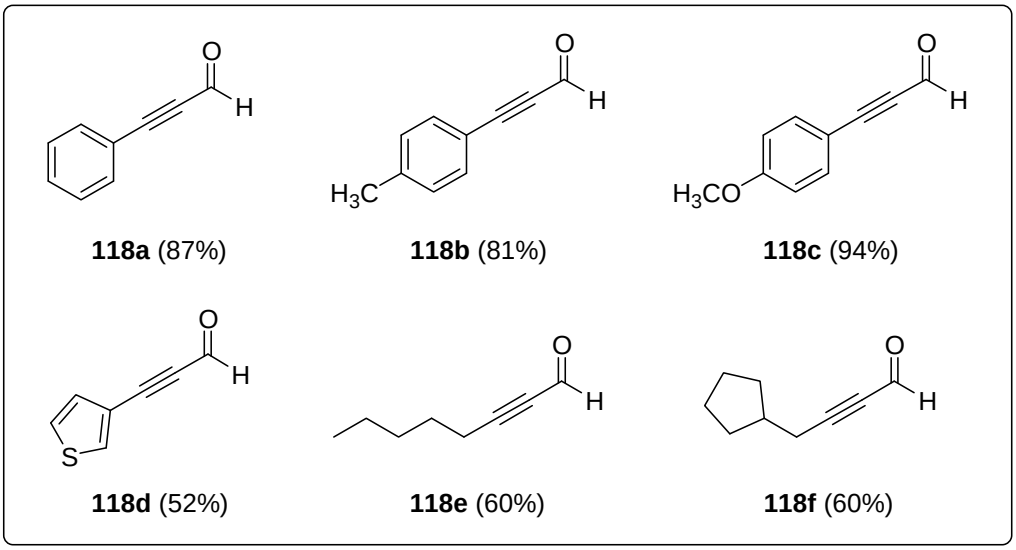


Figure 71. Structures of the synthesized propargyl aldehyde derivatives.

2.1.2 Synthesis of propargyl ketones

4-Phenylbut-3-yn-2-one (**118g**) was prepared from phenylacetylene (**194a**) by using a slightly different procedure (Figure 72) [163]. The treatment of phenylacetylene

(**194a**) with *n*-BuLi first yielded in situ lithium phenylacetylide, then the reaction of which with $ZnCl_2$ followed by acetyl chloride addition resulted in the formation of the desired propargyl ketone **118g** in 89% yield.

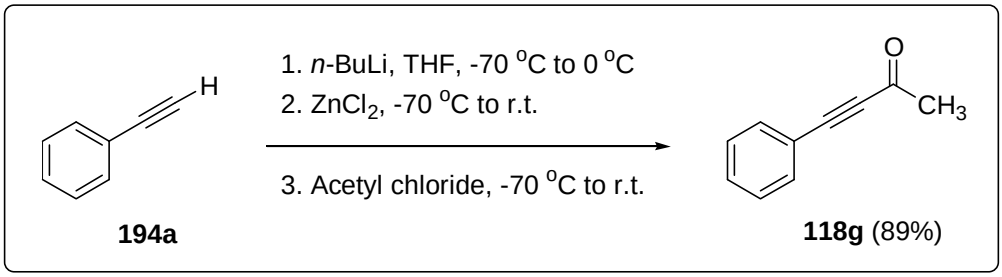


Figure 72. Synthesis of 4-phenylbut-3-yn-2-one (**118g**) from phenylacetylene (**194a**).

On the other hand, 1,3-diphenylprop-2-yn-1-one (**118h**) was prepared by a metal-catalyzed cross-coupling reaction [164]. The palladium-catalyzed Sonogashira coupling of benzoyl chloride (**197**) with phenylacetylene (**194a**) at room temperature easily produced the expected propargyl ketone **118h** in 98% yield (Figure 73).

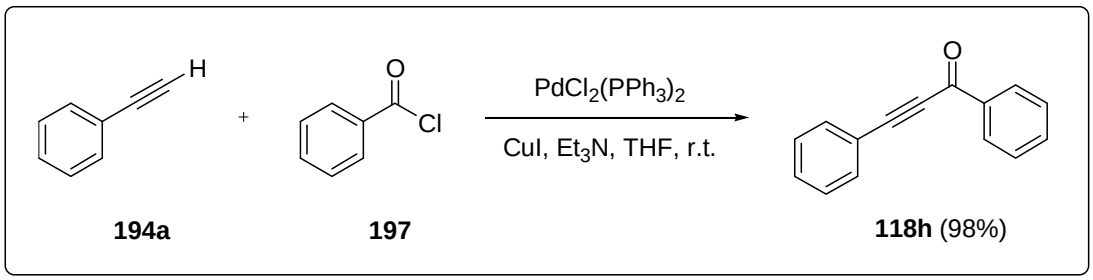


Figure 73. Synthesis of 1,3-diphenylprop-2-yn-1-one (**118h**) from phenylacetylene (**194a**).

2.1.3 Synthesis of 3-ferrocenylpropynal (45)

3-Ferrocenylpropynal (**45**) was synthesized from ferrocene (**180**) as shown in Figure 74. Acetylferrocene (**198**) was first prepared by Friedel-Crafts acylation of ferrocene (**180**) with acetyl chloride in the presence of $AlCl_3$ [165]. Acetylferrocene (**198**) was then treated with Vilsmeier-Haack reagent [166], formed in situ by the reaction between DMF and $POCl_3$, to yield (2-formyl-1-chlorovinyl)ferrocene (**44**) [167]. Subsequently, the reaction of compound **44** with sodium hydroxide in refluxing dioxane afforded ethynylferrocene (**104**) through addition-elimination reaction sequence. Finally, the formylation of ethynylferrocene (**104**) with DMF, according to a known procedure mentioned above [164], produced 3-ferrocenylpropynal (**45**) (Figure 74).

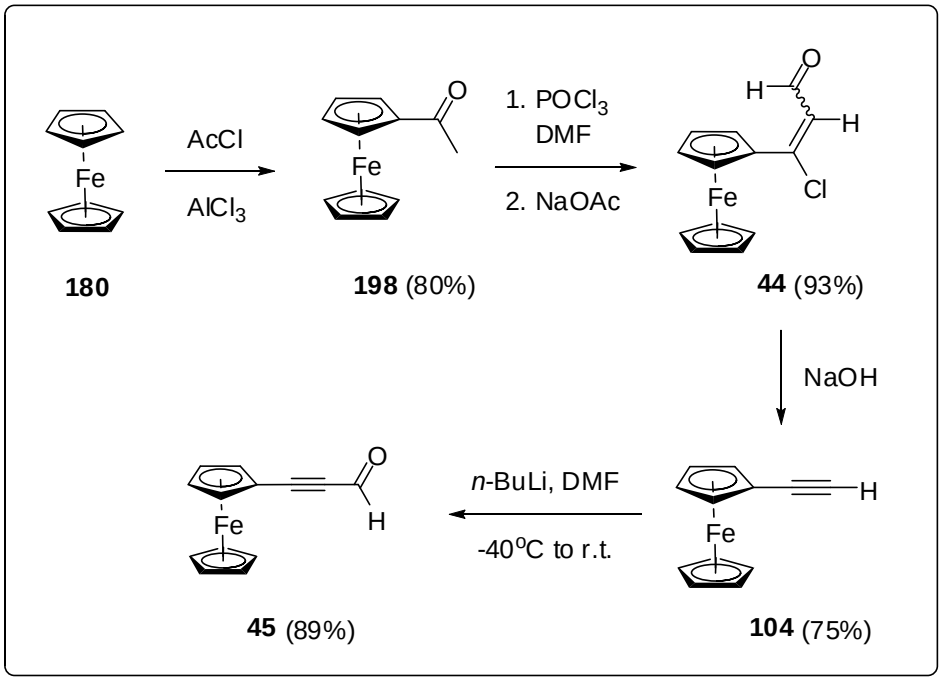


Figure 74. Synthesis of 3-ferrocenylpropynal (**45**).

2.2 Synthesis of α,β-alkynic hydrazones

After preparing propargyl aldehydes and ketones **118**, we synthesized corresponding α,β-alkynic hydrazones **186** by their reactions with aryl or alkyl substituted hydrazines **185** (Figure 75). These reactions were carried out with commercially available hydrazine derivatives **185** as shown in Figure 76.

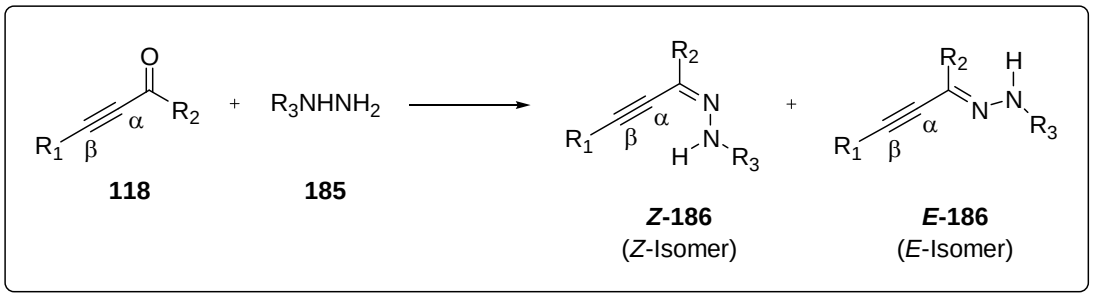


Figure 75. Synthesis of α,β-alkynic hydrazone derivatives.

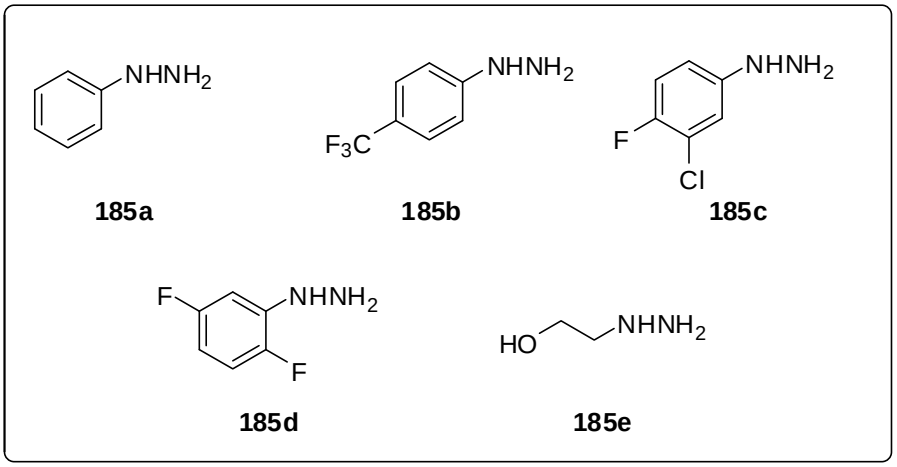


Figure 76. Structures of the employed hydrazine derivatives.

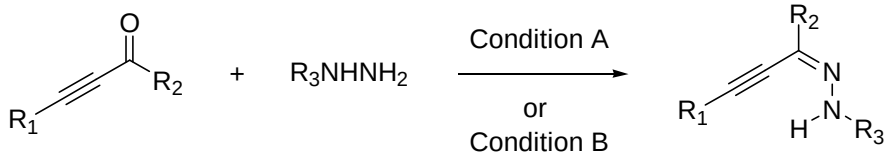
Condensation reactions between hydrazines **185** and propargyl aldehydes and ketones **118** were carried out in refluxing dioxane at 100 ^{o}C (condition A) or in the solvent-free (neat) manner at 80 ^{o}C (condition B). From these reactions, *Z* isomers of

α,β-alkynic hydrazones, ***Z*-186**, were obtained as major products while *E* isomers, ***E*-186**, were formed as minor products (Figure 75). Apparently, in the reaction conditions, *E* isomers ***E*-186** were not so stable that they started to convert into *Z* isomers ***Z*-186**. We observed that keeping the reaction time longer decreased the amount of *E* isomers ***E*-186** since they partially converted into *Z* isomers. Importantly, during column chromatography as well as on standing at room temperature in a solvent, most derivatives of *E* isomers ***E*-186** started to convert into *Z* isomers ***Z*-186**. For this reason, the isolation of *E* isomers ***E*-186** was not attempted. Results are summarized in Table 1.

These reactions were found to be general for a variety of hydrazone derivatives and tolerated the presence of aromatic, heteroaromatic and aliphatic substituents. Hydrazones were generally isolated in good to high yields. The highest yield (93%) was obtained for the synthesis of hydrazone ***Z*-186q** (Table 1, Entry 17) while the lowest yield (27%) was observed for the formation of hydrazone ***Z*-186w** (Table 1, Entry 23). Overall, 26 kinds of hydrazone derivatives were synthesized.

Hydrazones ***Z*-186a**, ***Z*-186c** and ***Z*-186n** were prepared by employing both conditions (A and B) as seen in Entries 1, 3 and 14 of Table 1. Clearly, the hydrazone-forming reactions in neat conditions (condition B) provide corresponding hydrazones in higher yields than those in refluxing dioxane (condition A). For instance, condition B afforded hydrazones ***Z*-186a**, ***Z*-186c** and ***Z*-186n** in approximately 17-20% higher yields than did condition A.

Table 1. Synthesis of α,β-alkynic hydrazone derivatives.



118 **185** ***Z*-186**

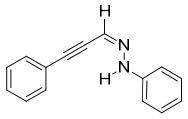
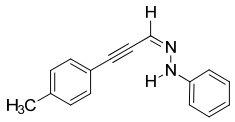
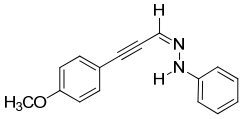
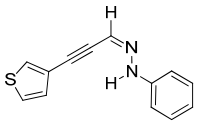
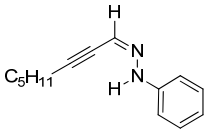
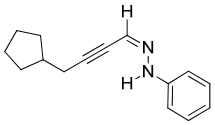
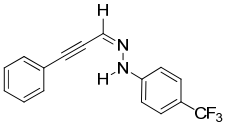
entry	alkynal or alkynone	hydrazine	condition[a]	α,β-alkynic hydrazone	% yield
1	118a	185a	A B	 *Z*-186a	61 81
2	118b	185a	B	 *Z*-186b	85
3	118c	185a	A B	 *Z*-186c	57 64
4	118d	185a	B	 *Z*-186d	54
5	118e	185a	B	 *Z*-186e	81
6	118f	185a	B	 *Z*-186f	60
7	118a	185b	B	 *Z*-186g	60

Table 1. Continued.

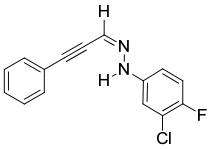
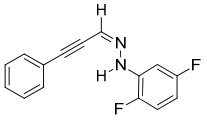
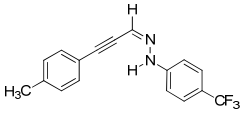
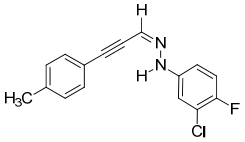
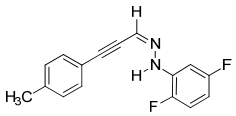
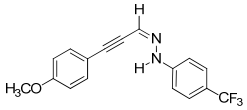
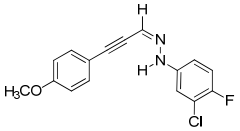
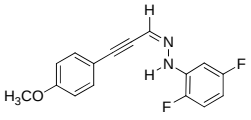
entry	alkynal or alkynone	hydrazine	condition[a]	α,β-alkynic hydrazone	% yield
8	118a	185c	B	 *Z*-186h	80
9	118a	185d	B	 *Z*-186i	71
10	118b	185b	B	 *Z*-186j	60
11	118b	185c	B	 *Z*-186k	77
12	118b	185d	B	 *Z*-186l	80
13	118c	185b	B	 *Z*-186m	52
14	118c	185c	A B	 *Z*-186n	63 82
15	118c	185d	B	 *Z*-186o	57

Table 1. Continued.

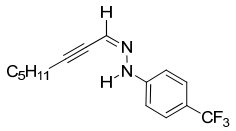
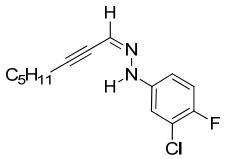
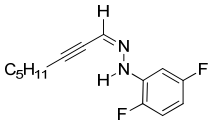
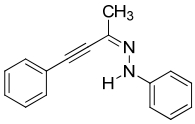
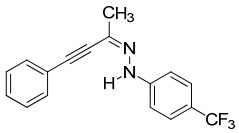
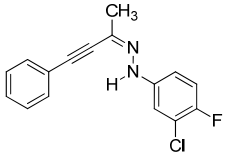
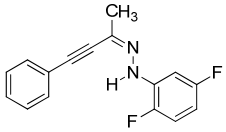
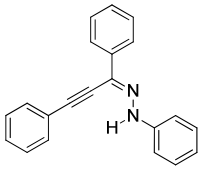
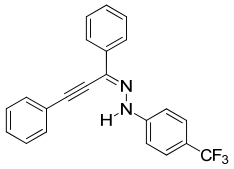
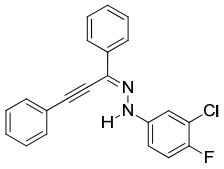
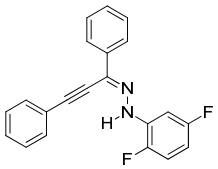
entry	alkynal or alkynone	hydrazine	condition[a]	α,β-alkynic hydrazone	% yield
16	118e	185b	B	 *Z*-186p	70
17	118e	185c	B	 *Z*-186q	93
18	118e	185d	B	 *Z*-186r	88
19	118g	185a	B	 *Z*-186s	69
20	118g	185b	B	 *Z*-186t	76
21	118g	185c	B	 *Z*-186u	87
22	118g	185d	B	 *Z*-186v	86

Table 1. Continued.

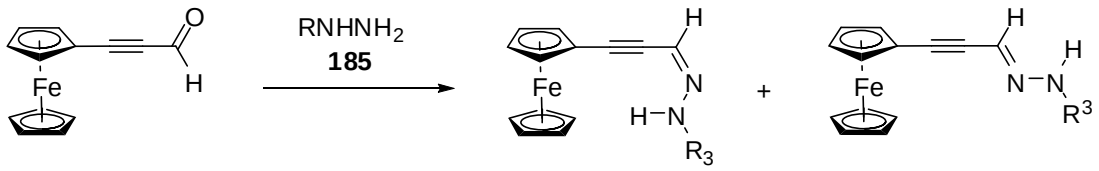
entry	alkynal or alkynone	hydrazine	condition[a]	α,β-alkynic hydrazone	% yield
23	118h	185a	B	 Z-186w	27
24	118h	185b	B	 Z-186x	52
25	118h	185c	B	 Z-186y	65
26	118h	185d	B	 Z-186z	36

[a]Condition A: Dioxane, 100 ^{o}C, 5h; Condition B: Neat, 80 ^{o}C, 5h.

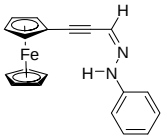
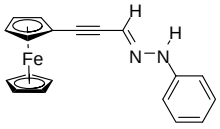
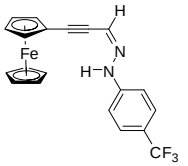
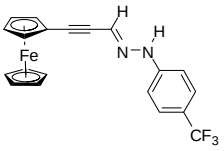
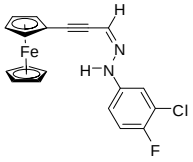
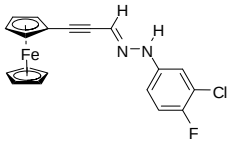
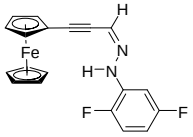
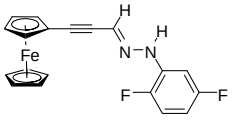
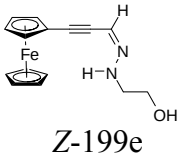
We also prepared ferrocenyl substituted α,β-alkynic hydrazones **199** by the reaction of 3-ferrocenylpropynal (**45**) with hydrazines **185** (Table 2). Importantly, we were able to isolate both *Z* and *E* isomers of ferrocenyl substituted hydrazones, ***Z*-199** and ***E*-199**. Interestingly, ferrocenyl substituted hydrazones ***Z*-199** and ***E*-199** were reasonably stable to purification and the conversion of hydrazones ***E*-199** into ***Z*-199** was quite slow. On the other hand, the reaction of 3-ferrocenylpropynal (**45**) with 2-

hydroxyethylhydrazine (**185e**) afforded exclusively *Z*-hydrazone ***Z*-199e** (Table 2).

Table 2. Synthesis of ferrocenyl-substituted α,β-alkynic hydrazone derivatives.



45 ***Z*-199** (*Z*-isomer) ***E*-199** (*E*-isomer)

entry	hydrazine	condition[a]	*Z*-hydrazone	% yield	*E*-hydrazone	% yield
1	185a	A		48		45
		B	*Z*-199a	54	*E*-199a	36
2	185b	A		45		30
		B	*Z*-199b	43	*E*-199b	50
3	185c	A		47		52
		B	*Z*-199c	40	*E*-199c	60
4	185d	A		58		42
		B	*Z*-199d	56	*E*-199d	40
5	185e	B		49		
			Z-199e			

[a]Condition A: Dioxane, 100 °C, 5h; Condition B: Neat, 80 °C, 5h.

Structures of *E* and *Z* isomers of alkynic hydrazone derivatives **199** have been assigned on the basis of their ^{1}H and ^{13}C NMR spectra (Figures 77 and 78). Notably, H atom of NH group in *E* isomers resonates in more upfield than that in *Z* isomers. For example, H peak of NH group in *E* isomer of 3-ferrocenylpropynal phenylhydrazone (***E*-199a**) appears around 8.00 ppm while that in its *Z* isomer (***Z*-199a**) come out around 8.67 ppm (Figure 77).

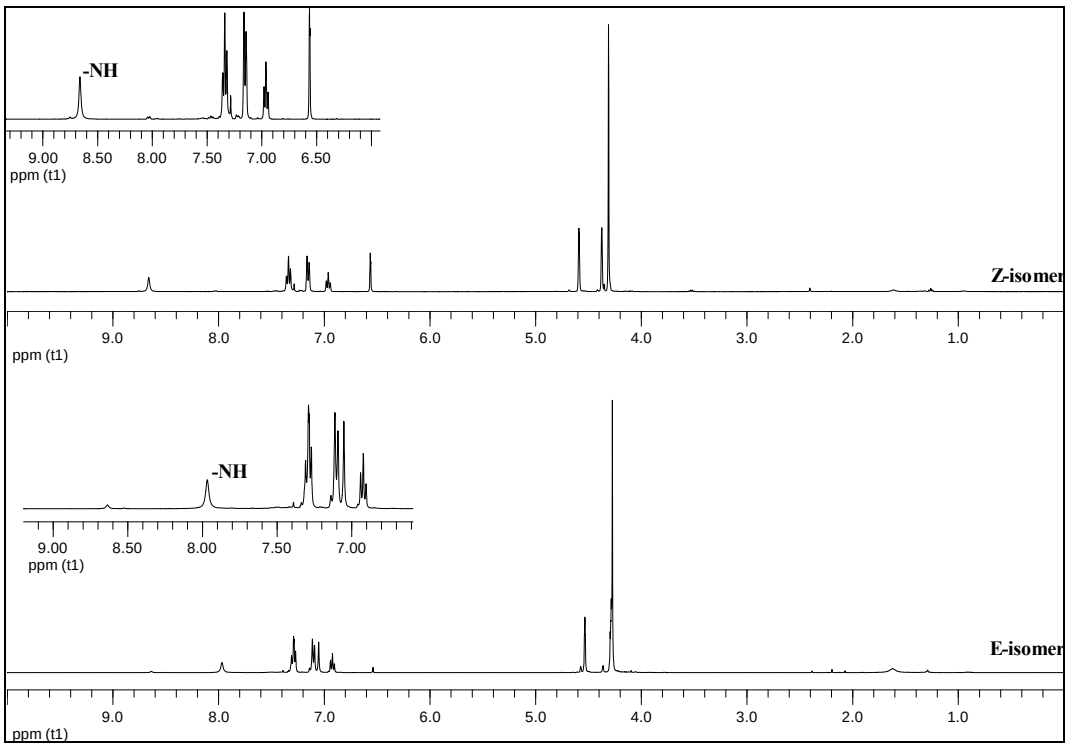


Figure 77. ^{1}H NMR spectra of *E* and *Z* isomers of 3-ferrocenylpropynal phenylhydrazone (**199a**).

Moreover, in the *E* isomer, two alkynic carbons, which we refer to as C_α and C_β carbons with respect to hydrazone functionality, resonate closely, and the chemical shift difference between C_α and C_β carbons is approximately 3 to 12 ppm. However, in the *Z* isomer, C_α carbon is

relatively upfield while C_β carbon is comparatively downfield, and the chemical shift difference between these carbons is around 22 to 30 ppm. In summary, the absolute value of chemical shift difference between C_α and C_β carbons in *E* isomer is generally smaller than that between respective C_α and C_β carbons in *Z* isomer, i.e. $|\Delta\delta(C_\alpha - C_\beta)_{E\text{-isomer}}| < |\Delta\delta(C_\alpha - C_\beta)_{Z\text{-isomer}}|$, which is consistent with both our theoretical NMR predictions and ^{13}C NMR data of similar alkynic hydrazones whose structures were unambiguously identified by X-ray analysis [168]. For instance, in *E* isomer of 3-ferrocenylpropynal phenylhydrazone (***E*-199a**), C_α and C_β carbons appear around 82.0 and 92.2 ppm while, in corresponding Z isomer (***Z*-199a**), they resonate around 76.5 and 102.4 ppm, respectively (Figure 78).

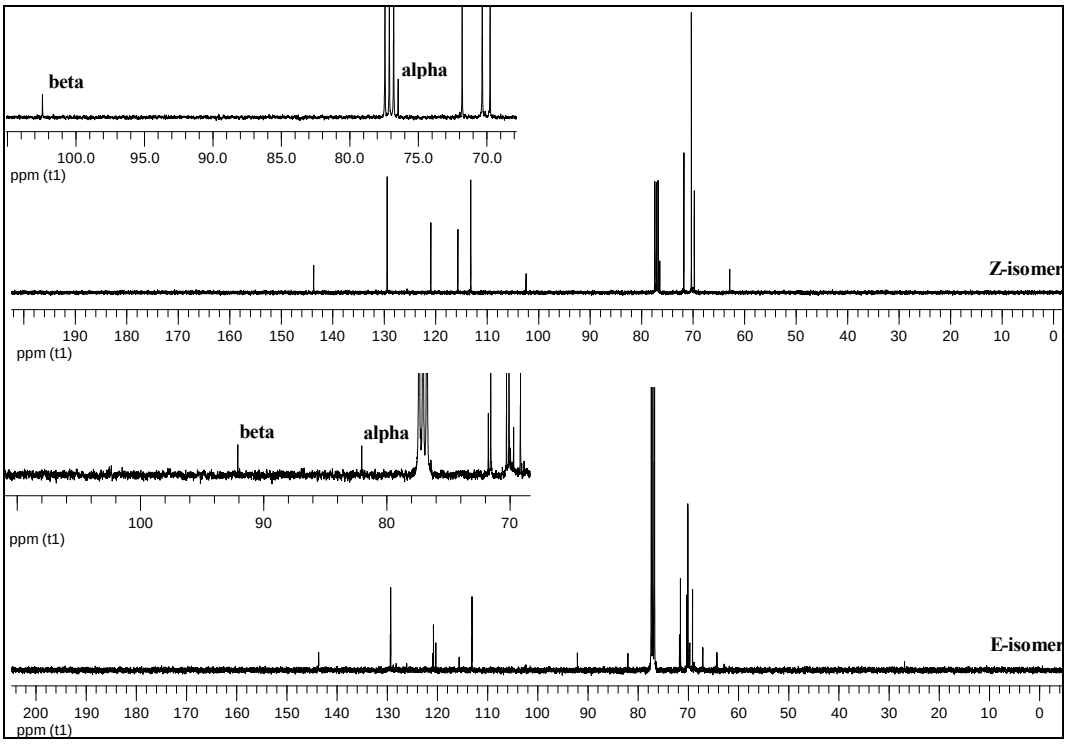


Figure 78. ^{13}C NMR spectra of *E* and *Z* isomers of 3-ferrocenylpropynal phenylhydrazone (**199a**).

We also calculated the relative energies of *E* and *Z* isomers of alkynic hydrazones **186a**, **186s** and **186w** to figure out the comparative stabilities of such hydrazones. We carried out the calculations at the density functional theory (DFT) level (B3LYP/6-31G*) [169,170] by using the Gaussian 98 program package [171]. Calculations indicated that unless there is a severe steric interaction, alkynic hydrazones adopt almost planar structures in their most stable conformations, thus maintaining the conjugation between their aromatic moieties (Figure 79). Notably, in *E* isomer of diphenylpropynone phenylhydrazone (***E*-186w**), phenyl group attached to hydrazone double bond deviates from planarity by 52.4° due to its severe steric interaction with H atom of NH group. Interestingly, in *Z* isomer of alkynic hydrazones, C_α carbon is in close proximity with H atom of NH group of hydrazone functionality in the range of 2.312–2.387 Å (Figure 75). This close proximity might be responsible for why H atom of NH group in *Z* isomers resonates at relatively more downfield than that in *E* isomers in ^{1}H NMR spectroscopy. In addition, this might be the reason why C_α carbon is relatively upfield while C_β carbon is relatively downfield in *Z* isomers as compared to those in *E* isomers in ^{13}C NMR spectroscopy mentioned above. We found that in gas phase, *E* isomer of phenylpropynal phenylhydrazone (***E*-186a**) is less stable than its *Z* isomer (***Z*-186a**) by 2.2 kcal/mol. On the other hand, *E* isomer of 4-phenyl-3-butyn-2-one phenylhydrazone (***E*-186s**) is 3.5 kcal/mol less stable than its *Z* isomer (***Z*-186s**) while *E* isomer of diphenylpropynone phenylhydrazone (***E*-186w**) is 6.1 kcal/mol less stable than corresponding *Z* isomer (***Z*-186w**). In summary, our calculations at the DFT level indicated that *E* isomers of alkynic hydrazones are less stable than corresponding *Z* isomers.

2.3 I_2-mediated electrophilic cyclization of α,β-alkynic hydrazones

2.3.1 Synthesis of 4-iodopyrazoles

After synthesizing necessary propargyl aldehydes and ketones, we investigated their electrophilic cyclizations by using molecular iodine. In this respect, molecular iodine has gained considerable importance as a mild and nontoxic Lewis acid catalyst since it catalyzes various organic reactions with high efficiency and selectivity [172].

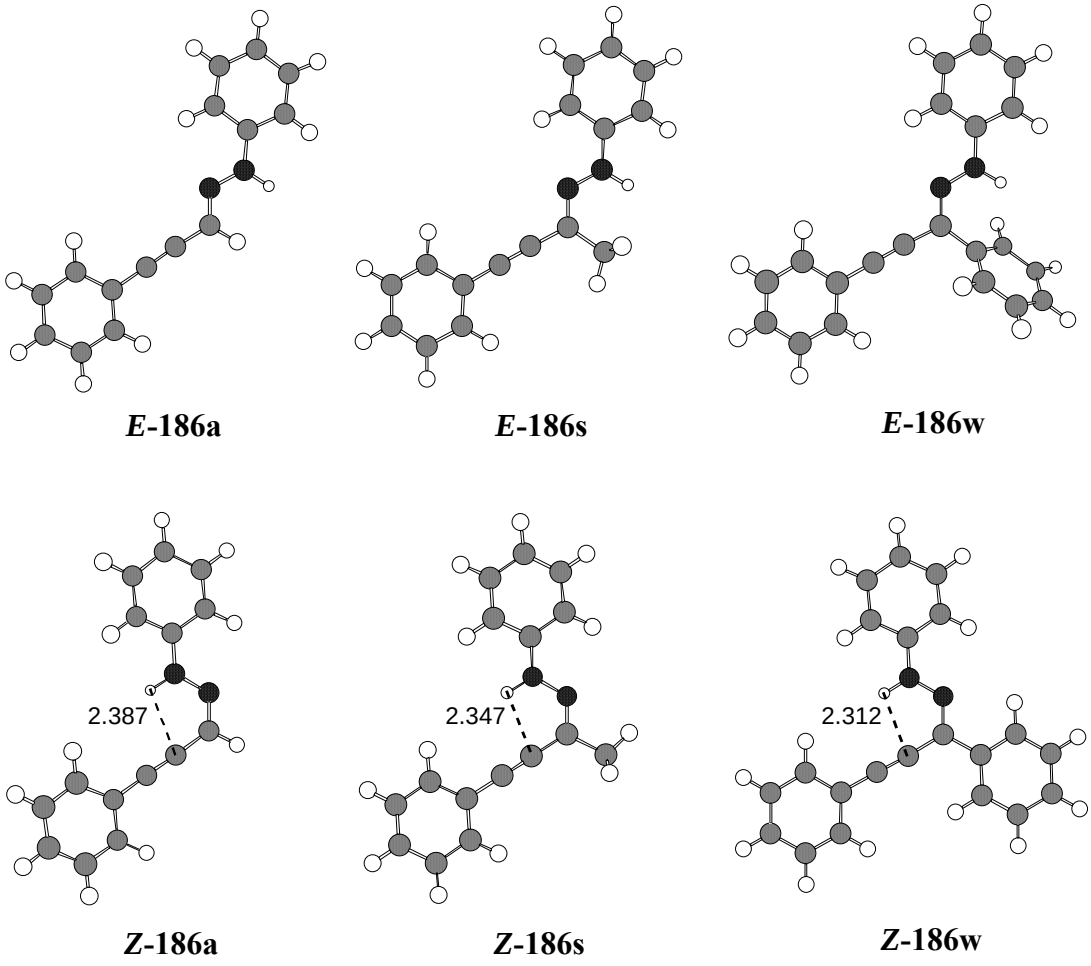
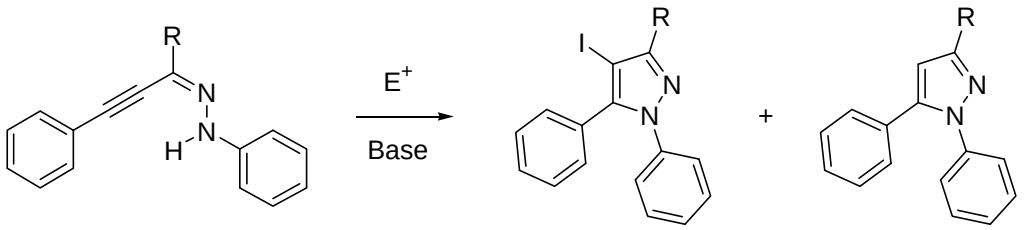


Figure 79. B3LYP/6-31G* optimized geometries for representative α,β-alkynic hydrazones with selected distances in angstroms.

Initially, as illustrated in Table 3, we optimized the reaction conditions by examining the iodocyclizations of propargyl aldehyde hydrazone ***Z*-186a** and propargyl ketone hydrazone ***Z*-186w**, Note that, in the light of literature studies [173], the reactions

were generally performed with excess amount (3 eq.) of molecular iodine and base. Interestingly, in the absence of iodine and base, hydrazone ***Z*-186a** in DCM did not yield any isolable product (Table 3, Entry 1). However, the reaction with I_2 in refluxing DCM produced 4-iodopyrazole **187a** and pyrazole **188a** in 72 and 7% yields, respectively (Table 3, Entry 2). When the reaction of ***Z*-186a** was carried out in the presence of excess I_2 and $NaHCO_3$ at room temperature, 4-iodopyrazole **187a** was obtained in 80% yield without formation of pyrazole **188a** (Table 3, Entry 3), which was the optimal yield of 4-iodopyrazole **187a**. On the other hand, the same reaction in acetonitrile at room temperature and 82 ^{o}C afforded 4-iodopyrazole **187a** in 61 and 66% yields, respectively (Table 3, Entries 4 and 5), which were less than optimal yield. Surprisingly, in the best condition found for propargyl aldehyde hydrazones, propargyl ketone hydrazone ***Z*-186w** yielded 4-iodopyrazole **187p** in only 15% yield (Table 3, Entry 6). However, when the same reaction was carried out in refluxing acetonitrile, 4-iodopyrazole **187p** was obtained in 66% yield (Table 3, Entry 7), which was the highest yield we found since the higher temperatures did not significantly increase the yield of 4-iodopyrazole **187p**.

Table 3. Iodocyclization of α,β-alkynic hydrazones ***Z*-186a** and ***Z*-186w**.



***Z*-186a** (R = H)
***Z*-186w** (R = Ph)

187a (R = H)
187p (R = Ph)

188a (R = H)
188t (R = Ph)

entry	hydrazone	E^+ (3 eq.)	base (3 eq.)	solvent	time (h)	temp. (^oC)	products (% yields)
1	***Z*-186a**	-	-	CH_2Cl_2	5	25	-
2	***Z*-186a**	I_2	-	CH_2Cl_2	3	40	**187a** (72) + **188a** (7)
3	***Z*-186a**	I_2	$NaHCO_3$	CH_2Cl_2	2	25	**187a** (80)
4	***Z*-186a**	I_2	$NaHCO_3$	CH_3CN	2	25	**187a** (61)
5	***Z*-186a**	I_2	$NaHCO_3$	CH_3CN	2	82	**187a** (66)
6	***Z*-186w**	I_2	$NaHCO_3$	CH_2Cl_2	2	25	**187p** (15)
7	***Z*-186w**	I_2	$NaHCO_3$	CH_3CN	2	82	**187p** (66)

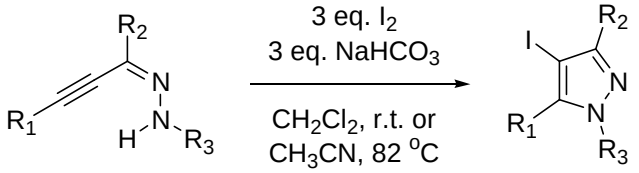
Subsequently, we investigated the scope and limitations of I_2-mediated electrophilic cyclizations of α,β-alkynic hydrazones ***Z*-186** for the synthesis of 4-iodopyrazoles **187**. Results are summarized in Table 4. Note that iodocyclizations of propargyl aldehyde hydrazones were performed in DCM at room temperature while those of propargyl ketone hydrazones were carried out in refluxing acetonitrile. As can be seen in Table 4, iodocyclizations were found to be general for a wide range of α,β-alkynic hydrazones and tolerated the presence of aliphatic, aromatic and heteroaromatic moieties with electron-withdrawing and electron-donating substituents. 1,5-Dialkyl/aryl-substituted 4-iodopyrazoles **187a-k** were isolated in 40 to 95% yields (Table 4, Entries 1-11) while 1,3,5-trialkyl/aryl-substituted 4-

iodopyrazoles **187l-r** were obtained in 66 to 93% yields (Table 4, Entries 12-18). Clearly, iodocyclizations leading to the formation of trialkyl/aryl-substituted 4-iodopyrazoles **187l-r** proceed well and provided them in good to high yields. In summary, 18 kinds of 4-iodopyrazole derivatives were synthesized.

2.3.2 Synthesis of 5-ferrocenyl-4-iodopyrazoles

We also synthesized 5-ferrocenyl-substituted 4-iodopyrazole derivatives **200** by electrophilic cyclization of β-ferrocenyl-α,β-alkynic hydrazones ***Z*-** and ***E*-199** since, as mentioned before, the presence of a ferrocene moiety in the structure may increase the current biological activities or bring entirely different medicinal activities [158]. We reoptimized the reaction conditions for the synthesis of 5-ferrocenyl-substituted 4-iodopyrazole derivatives, which are summarized in Table 5, because, under previously optimized conditions, iodocyclization of hydrazone ***Z*-199a** produced 5-ferrocenyl-4-iodopyrazole **200a** in 50% yield, accompanied by the formation of pyrazole **201a** in 27% yield (Table 5, Entry 1). In the absence of base, the reactions of hydrazones ***Z*-** and ***E*-199a** with I_2 in refluxing DCM yielded 4-iodopyrazole **200a** along with pyrazole in moderate yields (Table 5, Entries 2 and 3). In the presence of varying amounts of NEt_3, 4-iodopyrazole **200a** was obtained in 43-59% yield, typically with the formation of pyrazole **201a** in 7-14% yield (Table 5, Entries 4-6).

Table 4. Synthesis of 4-iodopyrazoles via electrophilic cyclization with I_2..[a]



***Z*-186** **187**

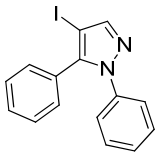
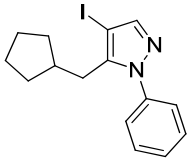
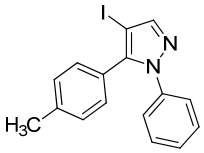
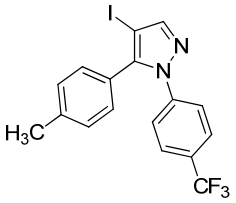
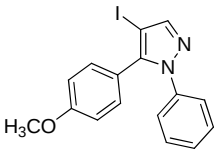
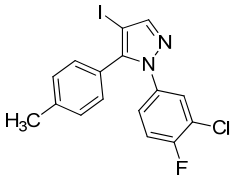
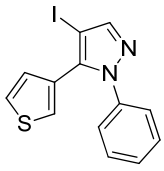
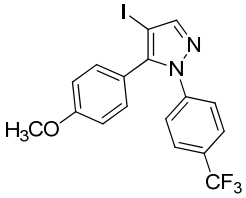
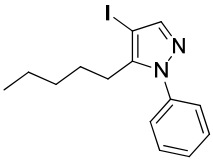
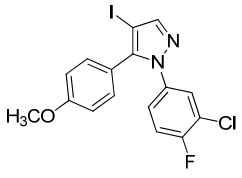
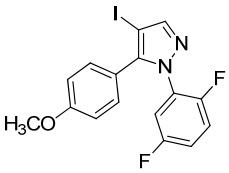
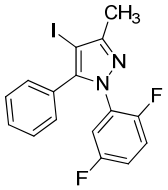
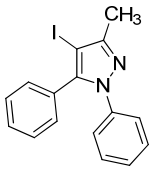
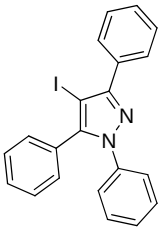
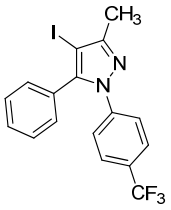
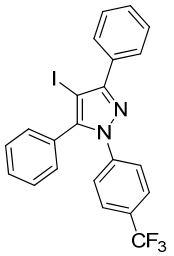
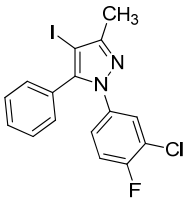
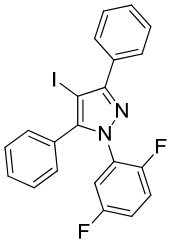
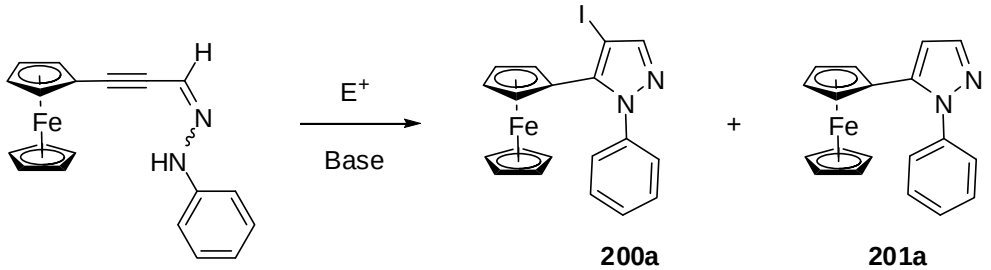
entry	hydrazone[b]	4-iodopyrazole	yield (%)	entry	hydrazone[b]	4-iodopyrazole	yield (%)
1	*Z*-186a	 187a	80	6	*Z*-186f	 187f	47
2	*Z*-186b	 187b	85	7	*Z*-186j	 187g	40
3	*Z*-186c	 187c	84	8	*Z*-186k	 187h	41
4	*Z*-186d	 187d	83	9	*Z*-186m	 187i	85
5	*Z*-186e	 187e	47	10	*Z*-186n	 187j	95

Table 4. Continued.[a]

entry	hydrazone[b]	4-iodopyrazole	yield (%)	entry	hydrazone[b]	4-iodopyrazole	yield (%)
11	*Z*-186o	 187k	74	15	*Z*-186v	 187o	86
12	*Z*-186s	 187l	92	16	*Z*-186w	 187p	66
13	*Z*-186t	 187m	93	17	*Z*-186x	 187q	89
14	*Z*-186u	 187n	81	18	*Z*-186z	 187r	74

[a]Reactions of ***Z*-186a-k** were carried out in CH_2Cl_2 at r.t. while those of ***Z*-186l-r** were performed in CH_3CN at 82 °C. [b]For the identity of R_1, R_2 and R_3 groups in hydrazones, see Table 1.

Table 5. Iodocyclization of β-ferrocenyl-α,β-alkynic hydrazones ***Z*-** and ***E*-199a**.



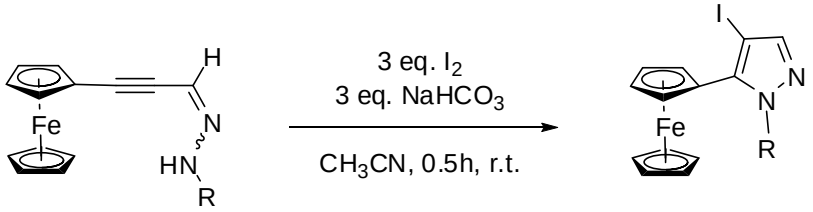
***Z*-** or ***E*-199a** **200a** **201a**

entry	hydrazone	I_2 (eq.)	base (eq.)	solvent	temp. (^oC)	time (h)	yield of **200a** (%)	yield of **201a** (%)
1	***Z*-199a**	3	$NaHCO_3$ (3)	CH_2Cl_2	25	2	50	27
2	***Z*-199a**	3	-	CH_2Cl_2	40	3	47	37
3	***E*-199a**	3	-	CH_2Cl_2	40	3	37	45
4[a]	***Z*-199a**	3	Et_3N (1.5)	CH_2Cl_2	40	3	43	-
5[b]	***Z*-199a**	3	Et_3N (3)	CH_2Cl_2	40	3	59	7
6	***E*-199a**	3	Et_3N (3)	CH_2Cl_2	40	3	56	14
7	***Z*-199a**	3	$NaHCO_3$ (3)	CH_3CN	25	0.5	90	**-**
8	***Z*-199a**	6	$NaHCO_3$ (3)	CH_3CN	25	0.5	91	-

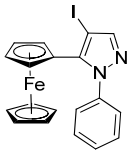
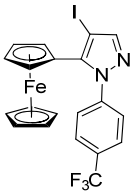
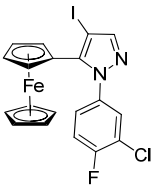
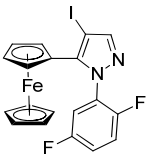
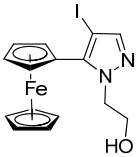
[a]Starting hydrazone ***Z*-199a** was recovered in 23% yield. [b]Starting hydrazone ***Z*-199a** was recovered in 14% yield.

We found that the reaction with 3 equivalents of I_2 and $NaHCO_3$ in acetonitrile at room temperature afforded 5-ferrocenyl-4-iodopyrazole **200a** in 30 minutes with 90% yield without the formation of any side products (Table 5, Entry 7). The use of excess amount (6 eq.) of I_2 did not increase the yield significantly (Table 5, Entry 8). In summary, iodocyclizations of β-ferrocenyl-α,β-alkynic hydrazones ***Z*-** and ***E*-199** were performed in acetonitrile at room temperature in the presence of 3 equivalents of I_2 and $NaHCO_3$. Results are shown in Table 6.

Table 6. Synthesis of 5-ferrocenyl-4-iodopyrazoles.



Z- or ***E-199*** **200**

entry	hydrazone	5-ferrocenyl-4-iodopyrazole	% yield
1	*Z*-199a *E*-199a	 200a	90 92
2	*Z*-199b *E*-199b	 200b	95 76
3	*Z*-199c *E*-199c	 200c	94 93
4	*Z*-199d *E*-199d	 200d	83 89
5	*Z*-199e	 200e	58

As depicted in Table 6, 5 kinds of 5-ferrocenyl-4-iodopyrazole derivatives **200** were synthesized in good to high yields. In most cases, *Z* and *E* isomers of the same hydrazones provided corresponding 5-ferrocenyl-4-iodopyrazoles in relatively similar yields (Table 6, Entries 1, 3 and 4). Apparently, during the course of the reactions, *E* isomers of hydrazones isomerized into *Z* isomers in the presence I_2 and/or $NaHCO_3$ since the cyclization occured from *Z* isomers of hydrazones, as will be discussed below.

The mechanism proposed for the formation of 4-iodopyrazoles is shown in Figure 80. The electrophilic cyclization reaction starts with the formation of iodonium ion **202** by the coordination of iodine to the triple bond of alkyne functionality. Then the attack of secondary nitrogen to the carbon atom bearing R_1 group forms the protonated pyrazole **203**. Finally, the abstraction of proton by $NaHCO_3$ results in the formation of 4-iodopyrazoles **187** and **200** (Figure 80).

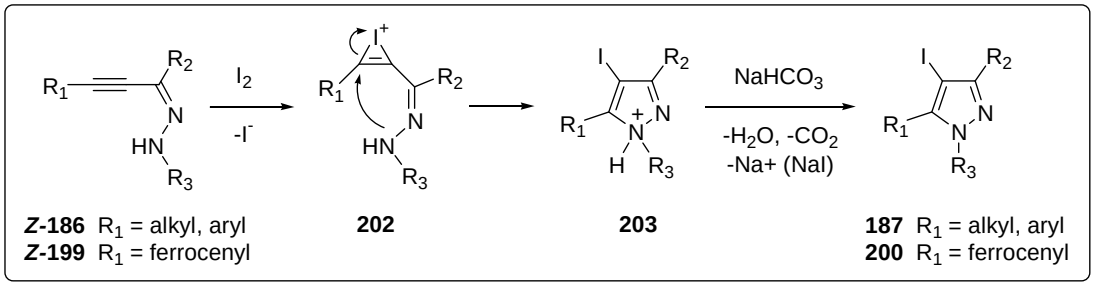


Figure 80. Proposed mechanism for the formation of 4-iodopyrazoles.

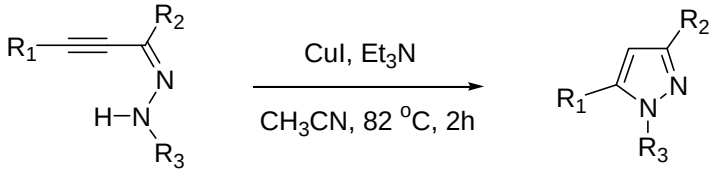
2.4. CuI-mediated electrophilic cyclization of α,β-alkynic hydrazones

The wide range of Cu-catalyzed transformations provide a promising alternative for the synthesis of heterocycles including indoles, furans and pyrroles, due to their high efficiency, mild reaction conditions and low cost [174]. Importantly, Cu-mediated intramolecular and intermolecular cyclizations lead to the formation of new carbon-nitrogen bonds [175].

In the light of our previous experience and literature studies, we found that when subjected to the electrophilic cyclization with copper iodide (CuI) in the presence of triethylamine, α,β-alkynic hydrazones **186** and **199** afforded corresponding di- or tri-substituted pyrazoles **188** and **201**. In the initial tries, electrophilic cyclization of hydrazone **186a** in acetonitrile at room temperature or in refluxing DCM did not happen and starting hydrazone **186a** was recovered. Then reaction conditions were optimized and best yields were obtained by equimolar amounts of CuI and NEt_3 in refluxing acetonitrile at 82 ^oC. Importantly, the reaction went to completion in a very short time such as 2 hours. Results from a systematic study are given in Table 7.

As illustrated in Table 7, electrophilic cyclizations with CuI/NEt_3 system were found to be general for a wide range of α,β-alkynic hydrazones and tolerated the presence of aliphatic, aromatic and heteroaromatic moieties with electron-withdrawing and electron-donating substituents. First, we investigated the synthesis of 1,5-dialkyl/aryl-substituted pyrazoles **188a-p**, which were obtained in 54 to 98% yields (Table 7, Entries 1-16). Second, we performed the synthesis of 1,3,5-trialkyl/aryl-substituted pyrazoles **188q-w** and isolated them in 57 to 96% yields (Table 7, Entries 17-23). Finally, we carried out the synthesis of 5-ferrocenyl-substituted pyrazoles **201a-d**, which were obtained in 44-86% yields (Table 7, Entries 24-27). Clearly, electrophilic cyclizations with CuI/NEt_3 system leading to the formation of 1,5-dialkyl/aryl- and 1,3,5-trialkyl/aryl-substituted pyrazoles **188** and **201** proceed well and provided them in good to high yields (Table 7). In summary, 27 kinds of pyrazole derivatives were synthesized.

Table 7. Synthesis of pyrazoles via electrophilic cyclization with CuI.



186 R_1 = alkyl, aryl
199 R_1 = ferrocenyl

188 R_1 = alkyl, aryl
201 R_1 = ferrocenyl

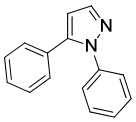
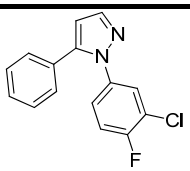
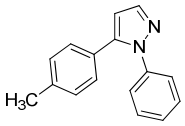
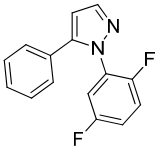
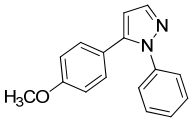
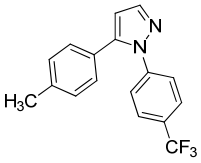
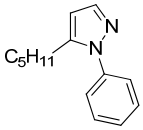
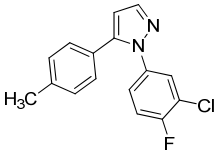
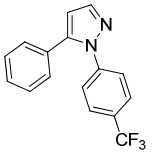
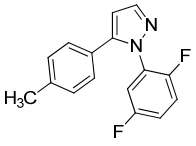
entry	hydrazone[a]	pyrazole	yield (%)	entry	hydrazone[a]	pyrazole	yield (%)
1	*Z*-186a	 188a	73	6	*Z*-186h	 188f	72
2	*Z*-186b	 188b	77	7	*Z*-186i	 188g	87
3	*Z*-186c	 188c	85	8	*Z*-186j	 188h	71
4	*Z*-186d	 188d	65	9	*Z*-186k	 188i	76
5	*Z*-186g	 188e	83	10	*Z*-186l	 188j	95

Table 7. Continued.

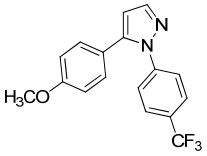
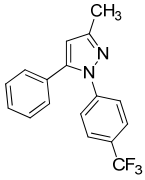
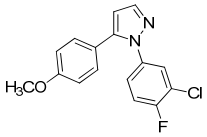
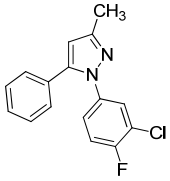
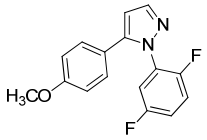
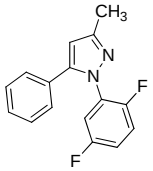
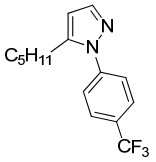
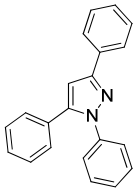
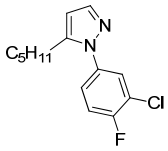
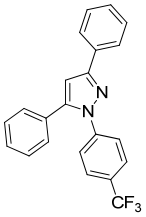
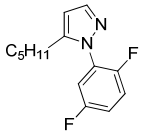
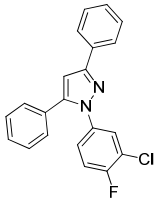
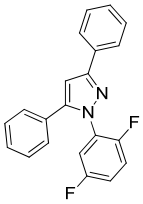
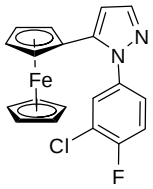
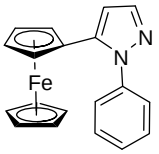
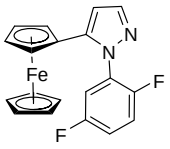
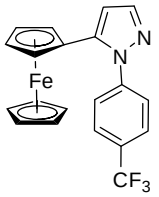
entry	hydrazone[a]	pyrazole	yield (%)	entry	hydrazone[a]	pyrazole	yield (%)
11	*Z*-186m	 188k	87	17	*Z*-186t	 188q	78
12	*Z*-186n	 188l	96	18	*Z*-186u	 188r	54
13	*Z*-186o	 188m	86	19	*Z*-186v	 188s	77
14	*Z*-186p	 188n	89	20	*Z*-186w	 188t	99
15	*Z*-186q	 188o	57	21	*Z*-186x	 188u	88
16	*Z*-186r	 188p	85	22	*Z*-186y	 188v	95

Table 7. Continued.

entry	hydrazone[a]	pyrazole	yield (%)	entry	hydrazone[a]	pyrazole	yield (%)
23	*Z*-186z	 188w	98	26	*Z*-199c	 201c	67
24	*Z*-199a	 201a	44	27	*Z*-199d	 201d	86
25	*Z*-199b	 201b	83				

[a]For the identity of R_1, R_2 and R_3 groups in hydrazones, see Table 1.

The mechanism proposed for the electrophilic cyclizations of α,β-alkynic hydrazones **186** and **199** with CuI to afford pyrazoles **188** and **201** is given in Figure 81, which displays similarities to that of I_2-mediated cyclization of α,β-alkynic hydrazones. First, the coordination of alkyne functionality of hydrazone to copper gives intermediate **204**. Then nucleophilic attack of secondary nitrogen atom yields protonated pyrazole **205**. Subsequently, proton exchange by NEt_3 via intermediacy of **206** results in the formation of pyrazole **207**. Finally, reductive elimination produces pyrazoles **187** and **200** with the regeneration of CuI catalyst (Figure 81).

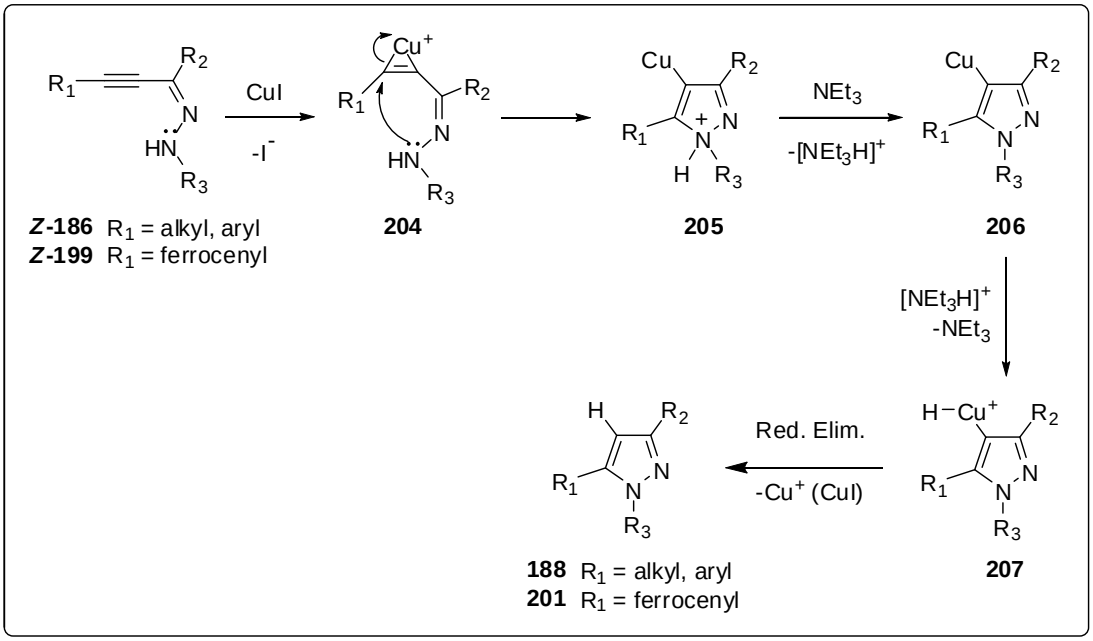


Figure 81. Proposed mechanism for the formation of pyrazoles.

2.5 Synthesis of amidoxime derivatives

Amidoxime derivatives were prepared by the reaction of hydroxylamine hydrochloride with nitriles in the presence of a base according to a literature procedure (Figure 82) [176]. Generally, equimolar amounts of hydroxylamine hydrochloride and triethyl amine were added to nitriles in ethanol and the resulting mixture was then refluxed with stirring. After removing solvent, products were purified by using flash chromatography. Structures of the synthesized amidoxime derivatives **190** were shown in Figure 83. It should be mentioned that amidoximes **190a-j** were synthesized from commercially available nitriles, the yields of which ranged from 35 to 87%. However, ferrocenyl amidoxime **190k** was prepared from cyanoferrocene which was synthesized by an efficient one-pot reaction between ferrocenecarboxaldehyde and $NH_2OH.HCl$ in the presence of KI/ZnO catalyst system in 85% yield [177]. Notably, ferrocenyl amidoxime **190k** was isolated in a very low yield (15%).

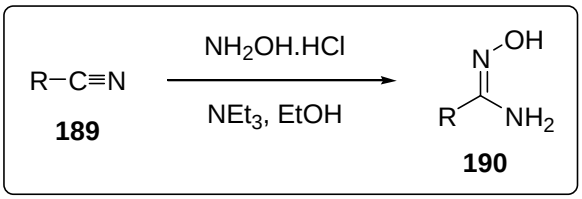


Figure 82. Synthesis of amidoximes.

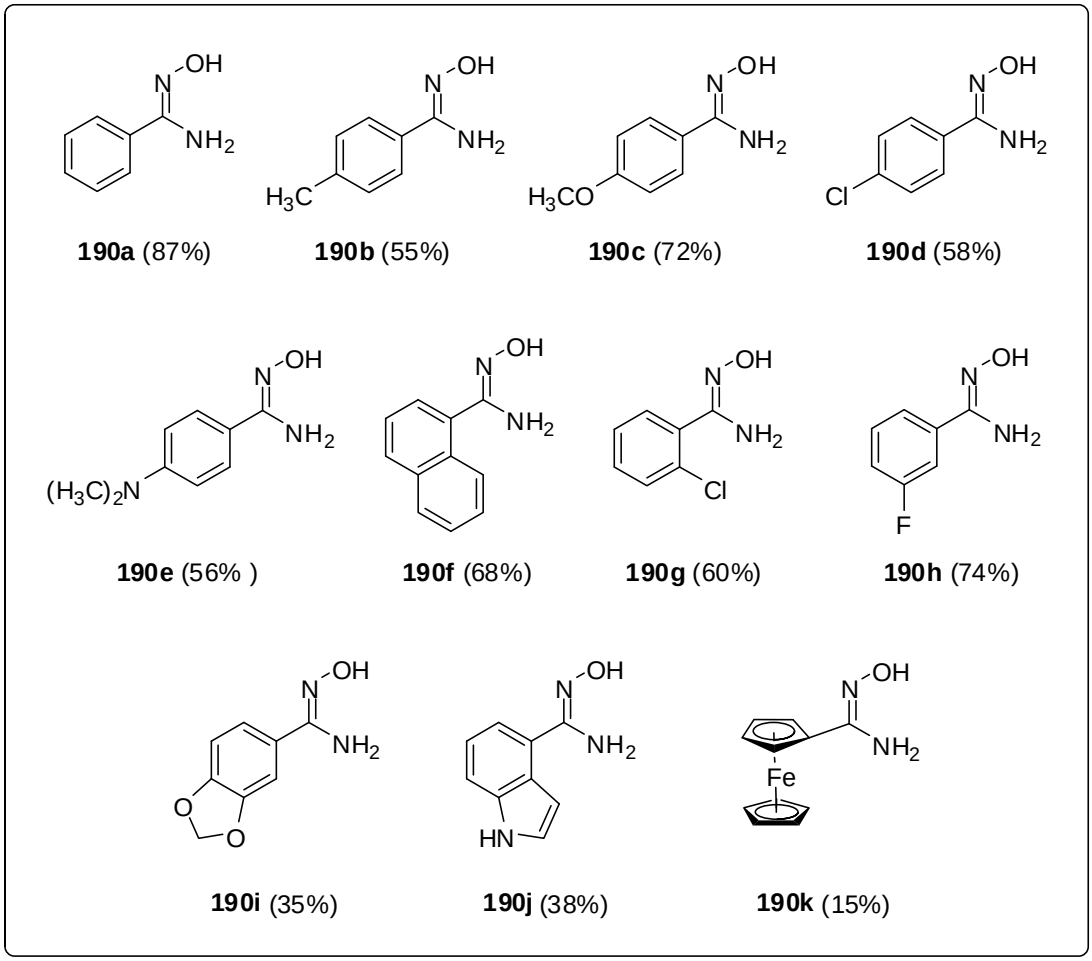
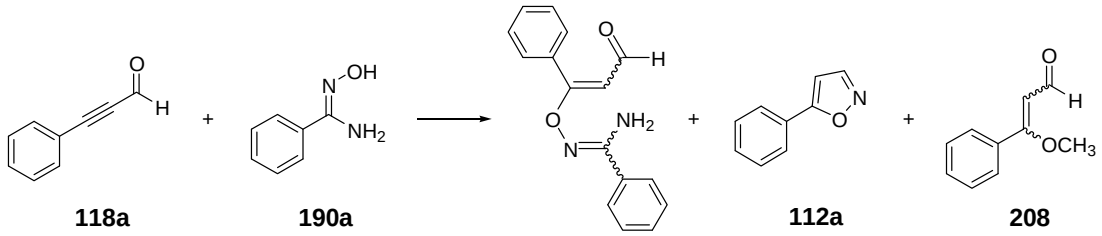


Figure 83. Structures of the synthesized amidoximes.

2.6 Synthesis of conjugate addition products 191

After preparing amidoxime derivatives **190**, we investigated their reactions with propagyl aldehydes and ketones **118**. For this reason, the reaction between propargyl aldehyde **118a** and benzamidoxime **190a** was first studied (Table 8). Expectedly, conjugate addition product **191a** was obtained as a single or the major product of the reactions in moderate to good yields (Table 8, Entries 1-5). In some cases, isoxazole **112a** and conjugate addition product of methanol, **208**, were also obtained but they formed in very low yields. Importantly, the reaction in refluxing methanol for 2 hours gave the highest yield of conjugate addition product **191a** (Table 8, Entry 4). Notably, higher temperatures such as in refluxing dioxane at 100 ^{o}C did not provide the higher yields of conjugate addition product **191a** (Table 8, Entry 5).

Table 8. Reaction of propargyl aldehyde **118a** with amidoxime **190a**.



118a **190a** **191a** **112a** **208**

entry	solvent	temp. (^{o}C)	time (h)	% yield of **191a**	% yield of **112a**	% yield of **208**
1	EtOH	78	1	60	5	11
2	MeOH	65	1	56	16	-
3	MeOH	65	1.5	73	13	-
4	MeOH	65	2	84	-	1
5	Dioxane	100	1.5	55	-	-

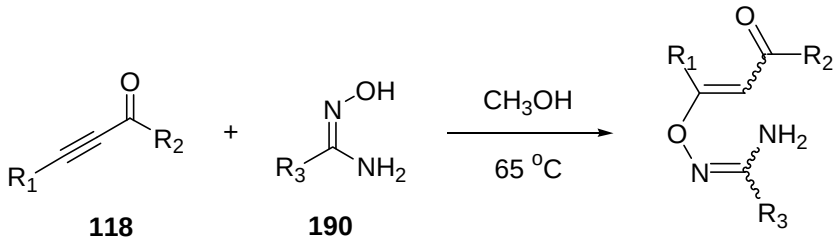
As anticipated, conjugate addition product **191** can practically exist in four different stereoisomeric forms since it bears two double bonds in its structure. Interestingly, from these reactions, conjugate addition product **191** was obtained as a single stereoisomer as proved by TLC analysis and ^{1}H and ^{13}C NMR spectra. However, the identity of the isolated stereoisomer could not be identified at present. Our studies on this matter are currently underway.

Subsequently, we synthesized a variety of conjugate addition products **191** including aromatic, heteroaromatic and aliphatic moieties. Results are collected in Table 9. The yields of conjugate addition products **191** changed from 53 to 92%.

It should be mentioned that the reaction between 3-ferrocenylpropynal (**45**) and benzamidoxime (**190a**) did not yield any of the expected conjugate addition product, and from this reaction, only conjugate addition product of methanol was isolated in 57% yield.

As indicated, the reaction of 2-octynal (**118e**) with benzamidoxime (**190a**) was performed at room temperature and conjugate addition product **191e** was obtained in 82% yield (Table 9, Entry 5). When the same reaction was carried out in refluxing methanol at 65 ^{o}C, a new product was isolated in 13% yield and tentatively characterized as 7-pentyl-3-phenyl-1,2,4-oxadiazepine (**193a**) (Figure 84). Isoxazole **112d** and conjugate addition products **190e** and **208** were also resulted from this reaction in varying amounts. When the reaction of 2-octynal (**118e**) with benzamidoxime (**190a**) was repeated two times under the same condition, the product that was tentatively characterized as oxadiazepine **193a** formed in 22 and 18% yields, respectively. Note that when the reaction was carried out in a different solvent such as dioxane, it gave only conjugate addition product **191e** in 47% yield without the formation of 1,2,4-oxadiazepine derivative. More importantly, 1,2,4-oxadiazepine formation was not observed in the reactions of other propargyl aldehydes and ketones.

Table 9. Synthesis of conjugate addition products.



118 **190** **191**

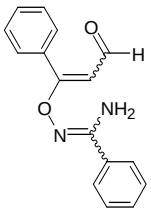
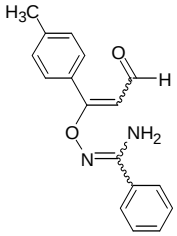
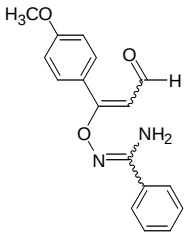
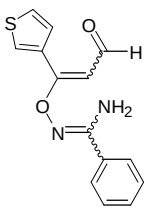
entry	alkynal or alkynone[a]	amidoxime	conjugate addition product	% yield
1	118a	190a	 191a	84
2	118b	190a	 191b	78
3	118c	190a	 191c	69
4	118d	190a	 191d	89

Table 9. Continued.

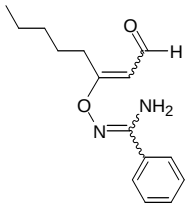
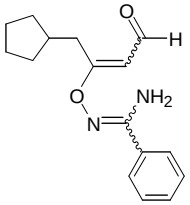
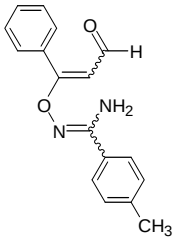
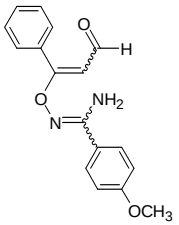
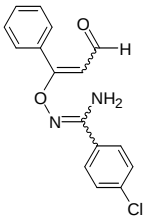
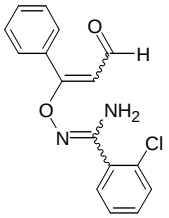
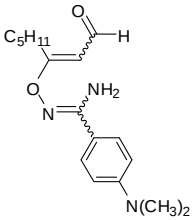
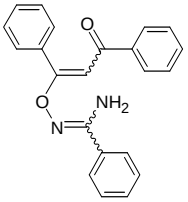
entry	alkynal or alkynone[a]	amidoxime	conjugate addition product	% yield
5[b]	118e	190a	 191e	82
6	118f	190a	 191f	92
7	118a	190b	 191g	53
8	118a	190c	 191h	84
9	118a	190d	 191i	70

Table 9. Continued.

entry	alkynal or alkynone[a]	amidoxime	conjugate addition product	% yield
10	118a	190g	 191j	60
11	118e	190e	 191k	50
12	118h	190	 191l	63

[a]For the structures of alkynals or alkynones, see Figure 83. [b]Reaction was carried out at room temperature.

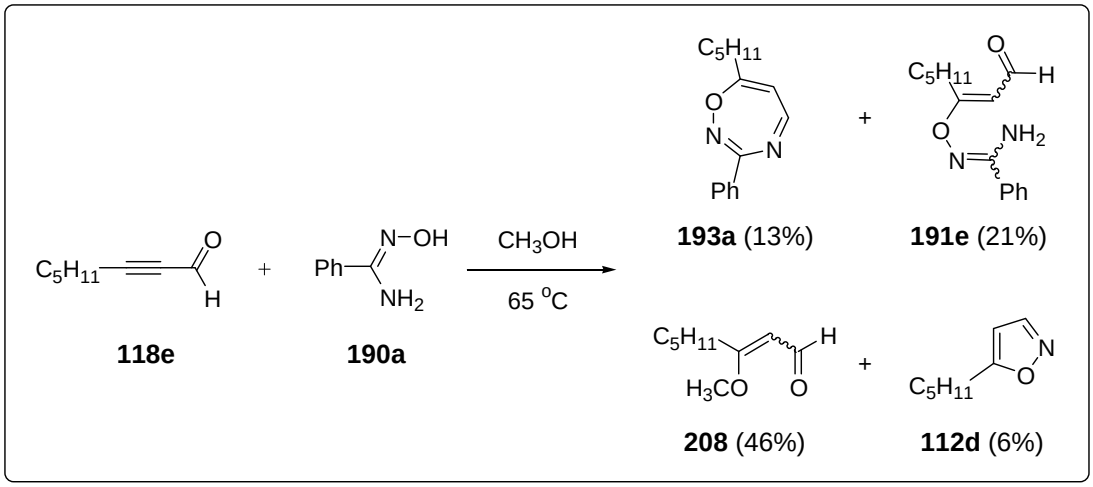


Figure 84. Reaction of 2-octynal (**118e**) with benzamidoxime (**190a**).

The structure of oxadiazepine was tentatively determined by their NMR and Mass spectra. Phenyl protons appear around 7.49 and 8.43 ppm (Figure 85). Hydrogens attached to C5 and C6 carbons resonate at 8.23 and 7.18 ppm, respectively, as doublets. COSY analysis showed that H5 is adjacent to H6. HMQC analysis indicated that C5 carbon resonates at 142.3 ppm while C6 carbon appears at 118.5 ppm. In HMBC spectra, C6 carbon (118.5 ppm) interacts with CH_2 protons. Moreover, C3 carbon peak at 156.7 ppm and C7 carbon peak at 160.9 ppm were identified by using HMBC. The mass of the proposed oxadiazepine structure was proved by HRMS analysis. The exact structure of this compound will be determined by X-ray single crystal analysis.

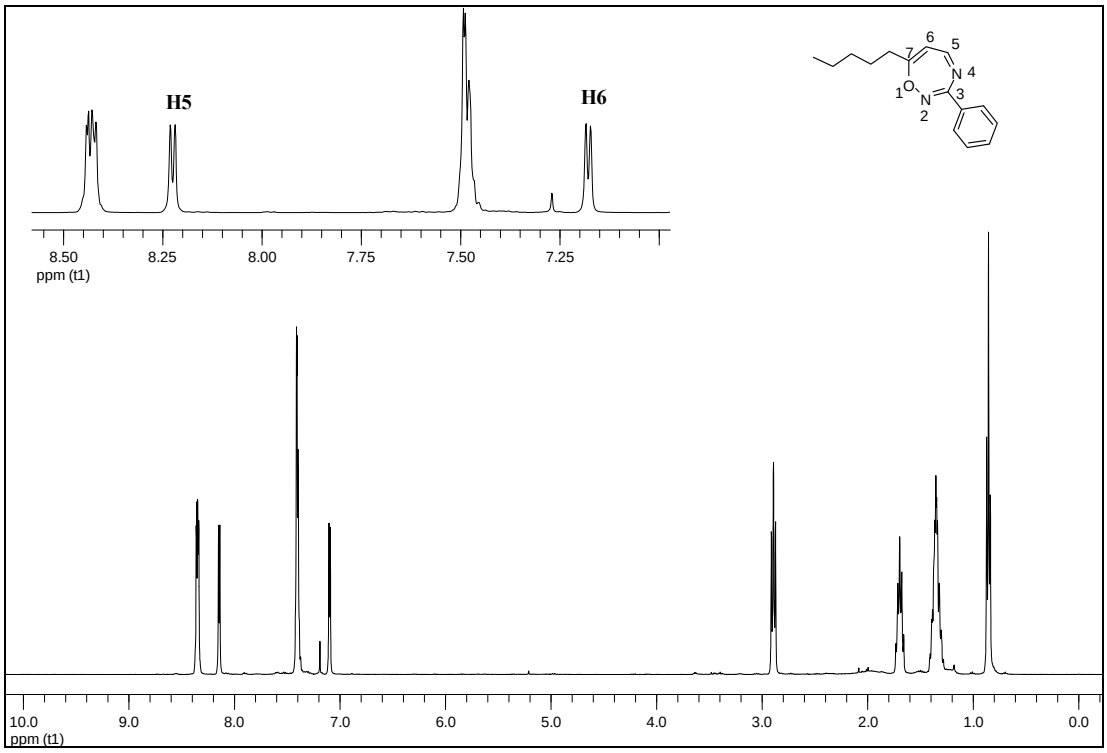


Figure 85. ^{1}H NMR spectra of 1,2,4-oxadiazepine **193a**.

We hypothesized that when the isolated conjugate addition products such as **191a** were heated at higher temperatures, they could be converted to seven-membered heterocycles such as **193a (**Figure 87). As anticipated, conjugate addition product **191a** was thermolyzed under refluxing in methanol or dioxane for hours but the expected product **193a** did not formed and the starting compound **191a** was recovered. In order to affect the formation of 1,2,4-oxadiazepines, the same reactions were then carried out in the presence of acid and base catalysts. Unexpectedly, the acid-catalyzed reactions of conjugate addition products **191** produced isoxazole derivatives **112** while the base-catalyzed reactions of **191** afforded 1,2,4-oxadiazole derivatives **192**, instead of oxadiazepines **193**, as will be discussed in the following parts.

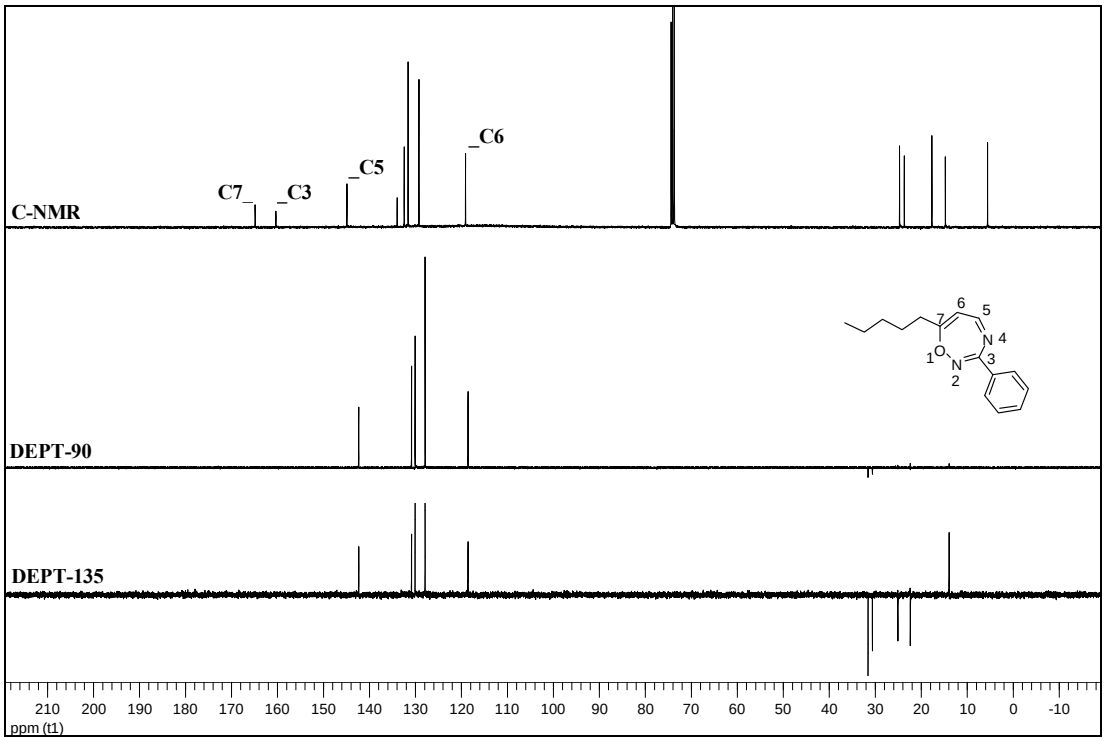


Figure 86. ^{13}C NMR, DEPT 90, and DEPT 135 spectra of oxadiazepine **193a**.

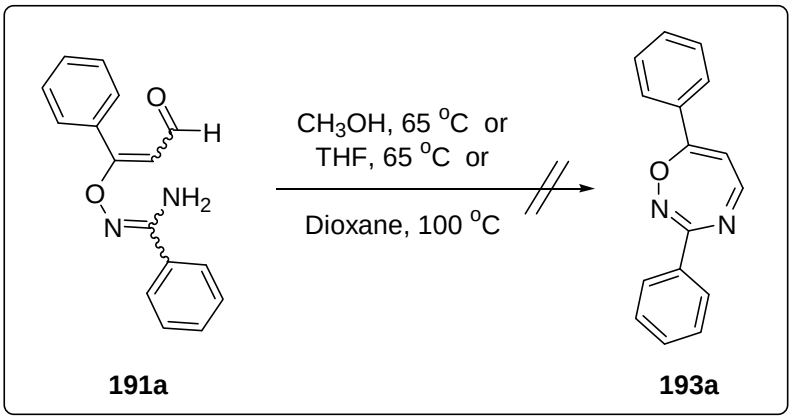
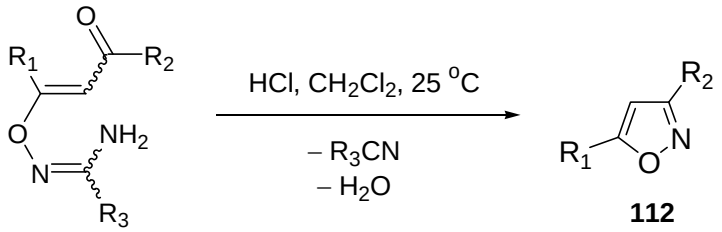


Figure 87. Thermolysis of conjugate addition product **191a**.

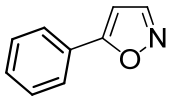
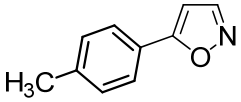
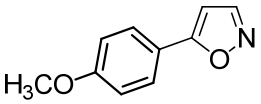
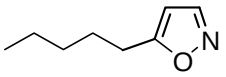
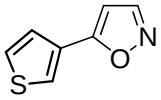
2.7. Synthesis of isoxazoles 112 from conjugate addition products 191

For the synthesis of oxadiazepines **193**, the reactions of conjugate addition products **191** were investigated in the presence of hydrochloric acid. Surprisingly, when the conjugate addition products **191** were treated with 2-3 drops of HCl in CH_2Cl_2 at room temperature for approximately 30 minutes, the reactions led to formation of isoxazoles **112** in good yields, without formation of any of the expected oxadiazepines **193**. The results are shown in Table 10. The formation of isoxazoles **112** from conjugated addition products **191** was observed for the first time and quite important from the mechanistic point of view. As seen in Table 10, all conjugated products **191** afforded corresponding isoxazoles **112**. When compound **191a** was employed, acid catalyzed reaction produced 5-phenylisoxazole (**112a**) in 96% yield, which was the highest yield obtained (Table 10, Entry 1). Interestingly, these reactions produced nitrile derivatives (R_3CN) as well, but effort was not spent to isolate them. However, the formation of nitriles in these reactions was proved by HPLC analysis of benzonitrile in the crude reaction mixture obtained in Entry 1 of Table 10. The lowest yield (67%) of isoxazoles was observed for the formation of 5-pentylisoxazole (**112d**) (Table 10, Entry 4). Thiophenyl-substituted isoxazole **112e** was obtained in 87% yield (Table 10, Entry 5). Apparently, the reaction tolerates the presence of aryl, heteroaryl and alkyl functionalities. Interestingly, when treated with acid, conjugate addition product **191l**, which contains a ketone functionality, underwent hydrolysis and afforded 1,3-diketone **209** in 96% yield (Figure 88). An amidoxime derivative, namely benzamidoxime (**190a**), was possibly resulted from this reaction as well, but, in the acidic conditions, it might be converted to salt form which escaped from isolation during column chromatography.

Table 10. Synthesis of isoxazoles.



191 **112**

entry	conjugate addition product	isoxazole	% yield
1	191a	 112a	96
2	191b	 112b	91
3	191c	 112c	78
4	191d	 112d	67
5	191e	 112e	87

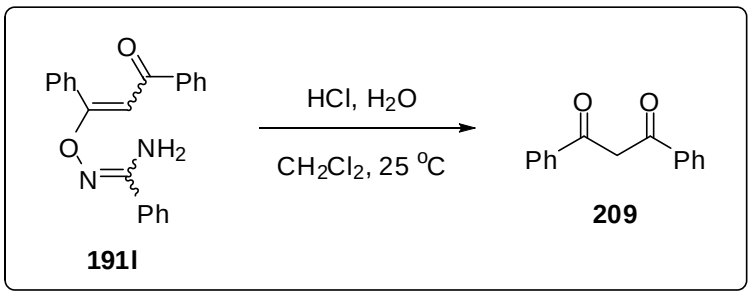


Figure 88. Acid catalyzed hydrolysis of conjugate addition product **191l**.

The proposed mechanism for the formation of isoxazoles **112** is given in Figure 89. The carbonyl moiety of **191** is first protonated to give compound **210**. Then intramolecular nucleophilic attack of secondary nitrogen at carbonyl group produces compound **211**, in which proton shift from iminium to hydroxyl group affords compound **212**. Subsequently, water elimination yields compound **213**. Finally, elimination of nitrile **189** from **213** gives isoxazole **112** (Figure 89).

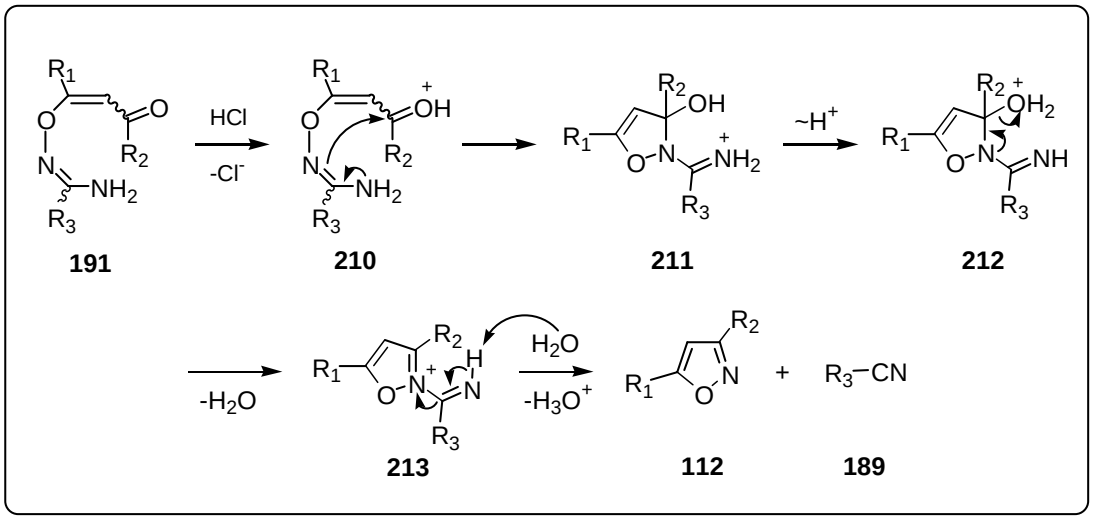


Figure 89. Proposed mechanism for the formation of isoxazoles **112**.

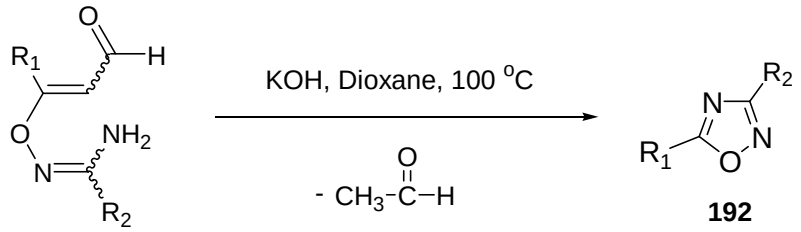
2.8. Synthesis of 1,2,4-oxadiazoles 192

2.8.1. Synthesis of 1,2,4-oxadiazoles 192 from conjugate addition products 191

For the synthesis of oxadiazepines **193**, the reactions of conjugate addition products **191** were investigated in the presence of bases as well. Interestingly, base catalyzed cyclizations of conjugate addition products **191** afforded 3,5-disubstituted-1,2,4-oxadiazoles **192** (Tables 11 and 12), without formation of oxadiazepines **193** and/or isoxazoles **112**. The formation of 1,2,4-oxadiazoles **192** from conjugated addition products **191** is a new method and quite important from synthetic and mechanistic point of view. Particularly, they are very important in material science and pharmaceutical industry as noted before [94-95].

In the first phase of the study, conjugated addition products **191** were treated with KOH under refluxing dioxane, which furnished 1,2,4-oxadiazoles **192** in good yields. The results are depicted in Table 13. Interestingly, these reactions produced acetaldehyde as side product along with 1,2,4-oxadiazoles **192**. Obviously, the formation of acetaldehyde in these reactions presents importance for clarification of the reaction mechanism. Although effort was not spent to isolate acetaldehyde from these reactions, its formation was proved by a parallel experiment as will be discussed in the following parts. As seen in Table 13, a variety of conjugate addition products were employed and all provided the expected 1,2,4-oxadiazoles, the yields of which ranged from 47 to 95%. Reaction times for the completion of reactions were determined by the frequent TLC analyses. Clearly, the oxadiazole-forming reaction tolerates the presence of aryl, heteroaryl and alkyl groups.

Table 11. Synthesis of 1,2,4-oxadiazoles via KOH-mediated reaction.



191 **192**

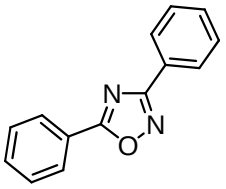
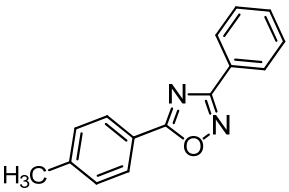
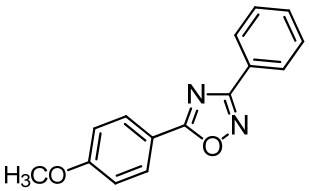
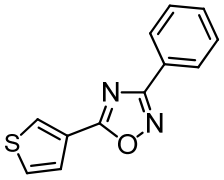
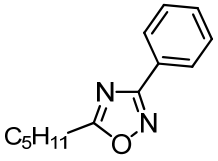
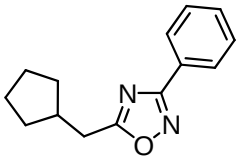
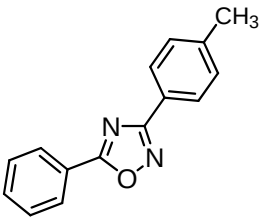
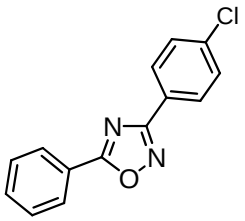
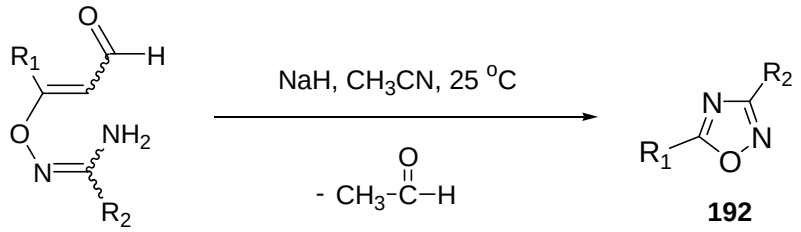
entry	conjugate addition product	time (h)	1,2,4-oxadiazole	% yield
1	191a	1	 192a	84
2	191b	2	 192b	80
3	191c	2	 192c	95
4	191d	10	 192d	68
5	191e	5	 192e	81

Table 11. Continued.

entry	conjugate addition product	time (h)	1,2,4-oxadiazole	% yield
6	191f	8	 192f	47
7	191g	3	 192g	93
8	191i	1	 192h	91

We thought that other bases such as NaH may also be used in such reactions. In the second phase of the study, the reactions of conjugate addition products **191** were carried out with excess NaH in acetonitrile at room temperature, which also produced 1,2,4-oxadiazoles **192** in good yields. The results are illustrated in Table 12. Notably, these reactions also furnished acetaldehyde as side product, which is very important from mechanistic point of view as stated before. As seen in Table 12, six different oxadiazole derivatives were synthesized by employing these reactions. The yields of oxadiazoles **192** altered from 79 to 93%. NaH-mediated oxadiazole-forming reactions also tolerated the presence of aryl, heteroaryl and alkyl groups.

Table 12. Synthesis of 1,2,4-oxadiazoles via NaH-mediated reaction.



191 **192**

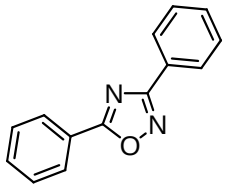
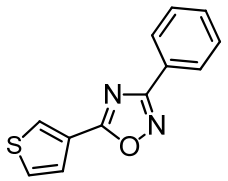
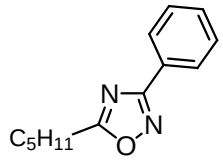
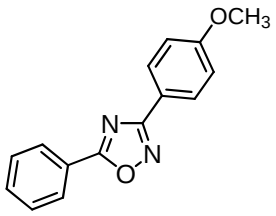
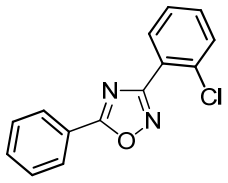
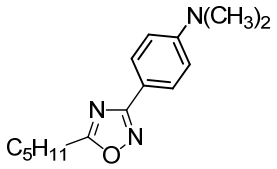
entry	conjugate addition product	time (h)	1,2,4-oxadiazole	% yield
1	191a	1	 192a	85
2	191d	0.5	 192d	83
3	191e	0.6	 192e	84
4	191h	0.5	 192i	85
5	191j	0.5	 192j	93

Table 12. Continued.

entry	conjugate addition product	time (h)	1,2,4-oxadiazole	% yield
6	**191k**	17	 **192k**	79

Yields of oxadiazoles resulted from NaH-mediated reactions were very comparable with those obtained with KOH Although handling NaH is relatively more difficult than KOH, NaH was found to be more reactive than KOH since, in most cases, the reactions with NaH went to completion in shorter times than those with KOH.

As mentioned above, oxadiazole-forming reactions afforded acetaldehyde as side product. Admittedly, isolation of acetaldehyde is difficult since it has a low boiling point (20.2 ^{o}C). For this reason, we thought that if a conjugate addition product containing a ketone functionality such as **191l** is employed, the reaction should then produce acetophenone (**214**) instead of acetaldehyde in addition to oxadiazole **192a** (Figure 91). As expected, oxadiazole **192a** and acetophenone (**214**) were isolated from this reaction. Importantly, the formation of acetophenone (**214**) helped us to propose a reaction mechanism (Figure 91) and indirectly proved the formation of acetaldehyde in the reactions present in Tables 13 and 14.

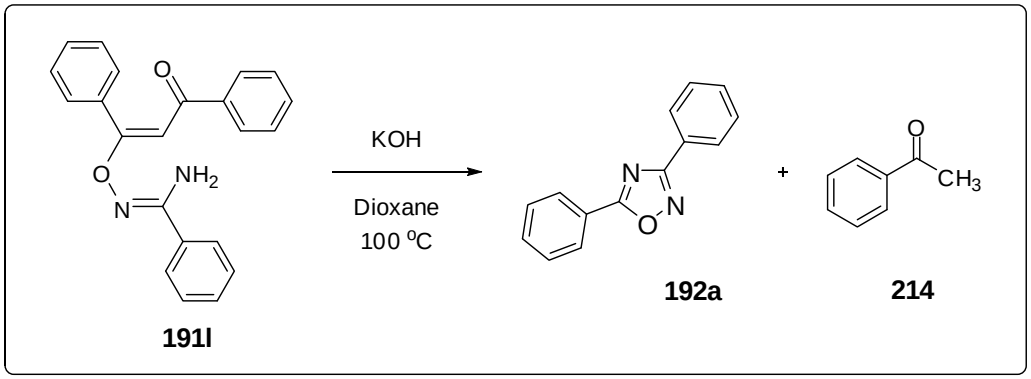


Figure 90. KOH-mediated reaction of conjugate addition product **191l**.

The proposed mechanism for the formation of 1,2,4-oxadiazoles **192** is shown in Figure 91. First, abstraction of a hydrogen from primary amine produces alkoxide **215**. Then intramolecular conjugate addition takes place to give five-membered compound **216**. Subsequently, hydrogen exchange yields compound **217**, which then furnish compound **218** upon keto-enol tautomerization. Finally, compound **218** undergoes rearrangement to afford 1,2,4-oxadiazole **192** and enolate **219**, the latter of which, after keto-enol tautomerization, provides acetaldehyde (**220**) or acetophenone (**214**) depending upon the identity of R_2 group (Figure 91).

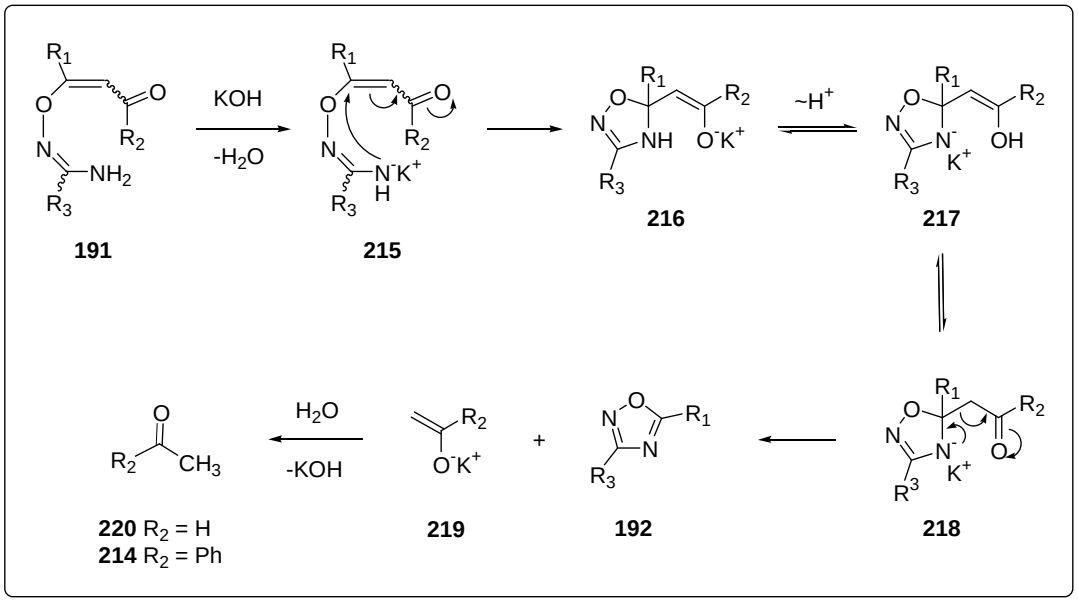
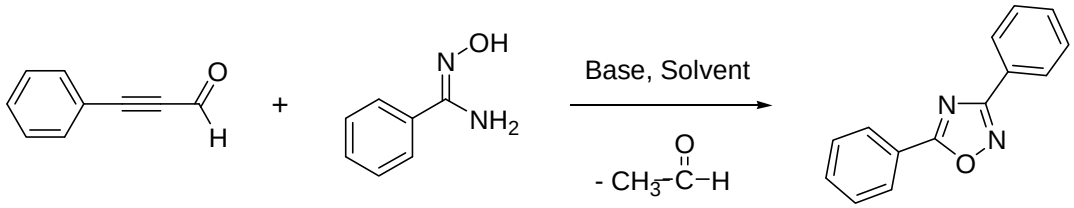


Figure 91. Proposed mechanism for the formation of 1,2,4-oxadiazoles **192**.

2.8.2. One pot synthesis of 1,2,4-oxadiazoles

Next, we investigated the possibility of the synthesis of 1,2,4-oxadiazoles directly from amidoximes **190** and propargyl aldehydes **118** in one-pot manner. For this reason, the reaction between propargyl aldehyde **118a** and amidoxime **190a** was performed in the presence of KOH and NaH as shown in Table 13. These reactions went to completion in very short time such as 0.5-1 h and afforded corresponding oxadiazoles in 53-61% yields. Notably, the reaction with KOH produced oxadiazole **192a** in slightly better yield as compared to that with NaH (Table 13). For this reason, one-pot synthesis of 1,2,4-oxadiazole were performed in refluxing dioxane in the presence of KOH (Table 14).

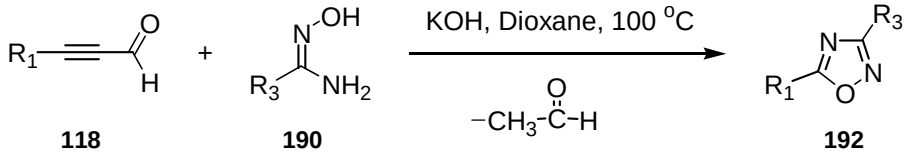
Table 13. Reaction of propargyl aldehyde **118a** with amidoxime **190a** in the presence of base.



118a **190a** **192a**

entry	base	solvent	temp. (^{o}C)	time (h)	% yield
1	1 eq. KOH	Dioxane	100	0.5-1	61
2	1.1 eq. NaH	CH_3CN	25	1	53

Table 14. One-pot synthesis of 1,2,4-oxadiazoles.



118 **190** **192**

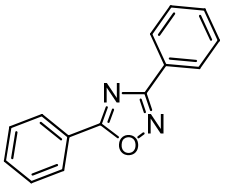
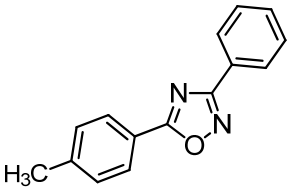
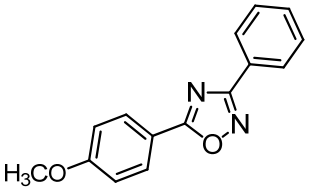
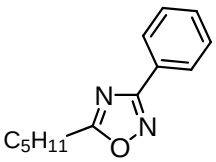
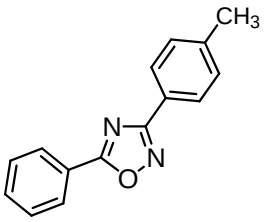
entry	alkynal	amidoxime	time (h)	1,2,4-oxadiazole	% yield
1	118a	190a	0.5	 192a	61
2	118b	190a	1	 192b	55
3	118c	190a	0.5	 192c	76
4	118e	190a	1	 192e	72
5	118a	190b	0.5	 192g	59

Table 14. Continued.

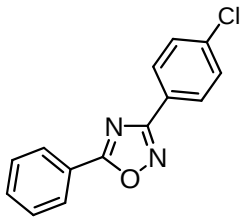
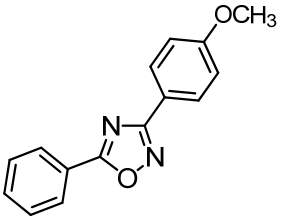
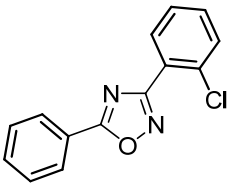
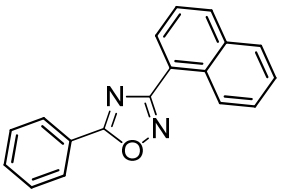
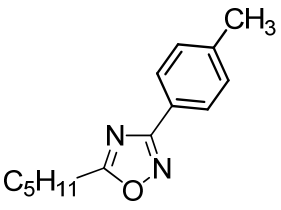
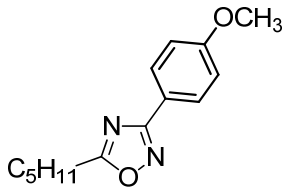
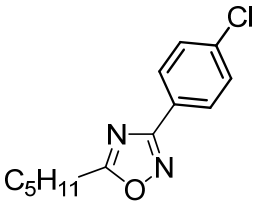
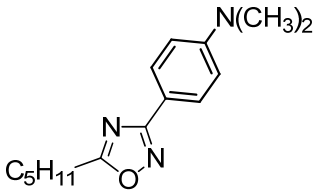
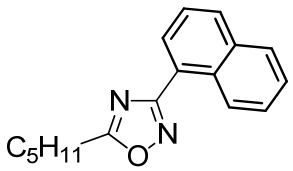
entry	alkynal	amidoxime	time (h)	1,2,4-oxadiazole	% yield
6	118a	190d	1	 192h	42
7	118a	190a	0.5	 192i	60
8	118a	190g	0.5	 192j	49
9	118a	190f	1	 192l	48
10	118e	190b	1	 192m	80

Table 14. Continued.

entry	alkynal	amidoxime	time (h)	1,2,4-oxadiazole	% yield
11	118e	190c	1	 192n	67
12	118e	190d	1	 192o	76
13	118e	190e	1	 192p	79
14	118e	190f	1	 192q	52

As seen in Table 14, a variety of 1,2,4-oxadiazole derivatives **192** were synthesized in one-pot manner. As expected, the reactions of propargyl aldehydes **118** with amidoximes **190** yielded in situ corresponding conjugate addition products which smoothly underwent to cyclization to form 3,5-disubstituted-1,2,4-oxadiazoles **192**. 1,2,4-Oxadiazoles were obtained in moderate to good yields Although one-pot syntheses gave slightly lower yields of oxadiazoles as compared to their two-step syntheses, they saved time and chemicals since they required less purification.

Notably, the reaction tolerated the presence of aryl and alkyl substituents. The yields of 3,5-diaryl-substituted 1,2,4-oxadiazoles ranged from 42 to 76% (Table 14, Entries 1-3 and 4-9). When 1-naphthyl-substituted amidoxime **190f** was allowed to react with 3-phenyl-substituted propargyl aldehyde **118a**, corresponding oxadiazole **192l** was isolated in 48% yield (Table 14, Entry 9). One-pot procedure was also carried out for the synthesis of 5-alkyl-3-aryl-1,2,4-oxadiazole derivatives (Table 14, Entries 4 and 10-14), which were resulted in 52 to 80% yields. As noted before, the reaction of 2-octynal (**118e**) with benzamidoxime (**190a**) in refluxing methanol produced four different products without formation of any oxadiazole product (Figure 84, p83). However, the same reaction in the presence of KOH in refluxing dioxane afforded only corresponding oxadiazole derivative **192e** in 72% yield (Table 14, Entry 4).

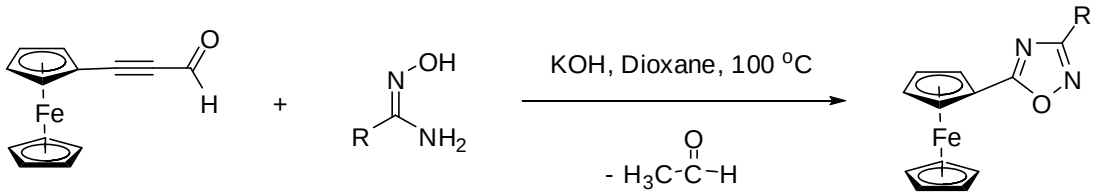
2.8.3. Synthesis of 3-aryl-5-ferrocenyl-1,2,4-oxadiazoles

As mentioned before, when treated with amidoximes, 3-ferrocenylpropynal (**45**) did not furnish any conjugate addition product. Therefore, one-pot procedure was employed for the synthesis of 5-ferrocenyl-1,2,4-oxadiazole derivatives **221** from 3-ferrocenylpropynal (**45**). Expectedly, treatment of ferrocenylpropynal (**45**) with amidoximes **190** in the presence of KOH at 100 ^{o}C provided 5-ferrocenyl-substituted 1,2,4-oxadiazoles (Table 15). As seen in Table 15, in most cases, the reaction went to completion in very short times, such as 0.5-2 h, and the longer reaction times decreased the yields of 5-ferrocenyl-1,2,4-oxadiazoles **221** (Table 15, Entries 1 and 4). Apparently, under higher reaction temperatures such as 100 ^{o}C, oxadiazoles started to be decomposed. For this reason, the reactions were checked by the frequent TLC analysis to find the appropriate times for each reaction.

Subsequently, the scope of the reaction was examined and a variety of 5-ferrocenyl-1,2,4-oxadiazole derivatives **221** was synthesized. In most cases, oxadiazoles were obtained in good yields. The highest yield (95%) was observed for oxadiazole derivative **221b** (Table 15, Entry 2). 1-Naphtyl-substituted oxadiazole **221f** was

isolated in 54% yield (Table 15, Entry 6). Fused-heteroaromatic-substituted oxadiazoles **221i** and **221j** were obtained in 82 and 44% yields, respectively (Table 15, Entries 9 and 10). Oxadiazole derivative **221k** which contains two ferrocenyl groups at 3 and 5 positions was also synthesized but it was obtained in 22% yield (Table 15, Entry 11).

Table 15. Synthesis of 5-ferrocenyl-1,2,4-oxadiazoles**.**



45 **190** **221**

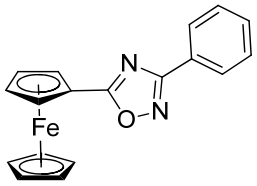
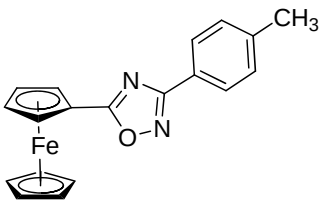
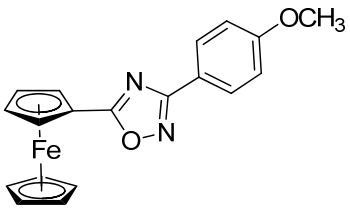
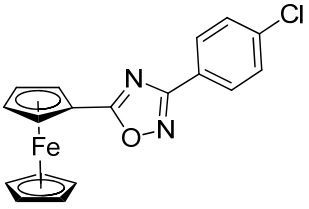
entry	amidoxime	time (h)	5-ferrocenyl-1,2,4-oxadiazole	% yield
1	190a	2 4 8	 221a	84 70 61
2	190b	3	 221b	95
3	190c	0.5	 221c	85
4	190d	1 4	 221d	90 69

Table 15 Continued.

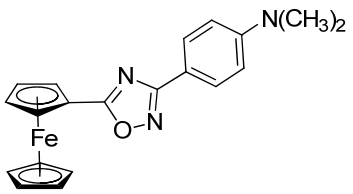
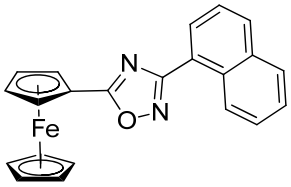
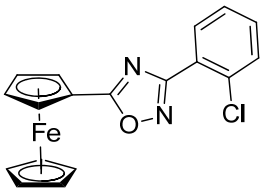
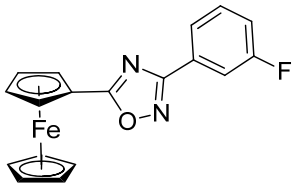
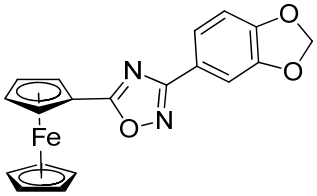
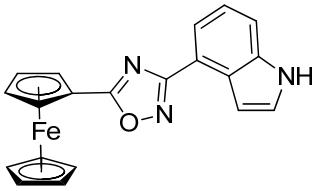
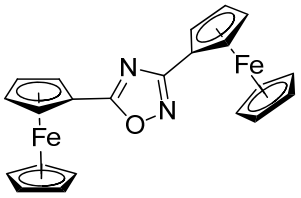
entry	amidoxime	time (h)	5-ferrocenyl-1,2,4-oxadiazole	% yield
5	190e	0.5	 221e	61
6	190f	0.5	 221f	54
7	190g	2	 221g	79
8	190h	0.5	 221h	78
9	190i	0.5	 221i	82
10	190j	0.5	 221j	44

Table 15. Continued.

entry	amidoxime	time (h)	5-ferrocenyl-1,2,4-oxadiazole	% yield
11	190k	0.5	 221k	22

CHAPTER 3

CONCLUSION

In summary, we have developed new methodologies for the synthesis of pyrazoles, 4-iodopyrazoles, isoxazoles and 1,2,4-oxadiazoles and 1,2,4-oxadiazepines from propargyl aldehyde and ketones.

In the first part of study, we have investigated electrophilic cyclizations of α,β-alkynic hydrazones **186**, obtained from propargyl aldehydes and ketones **118** and hydrazines **185**. As expected, these reactions produced the expected 4-iodopyrazoles **187** and pyrazoles **188** as the major or single product. The α,β-alkynic hydrazones **186** have been allowed to react with molecular iodine in the presence of base, this reaction gave 4-iodopyrazoles in good to excellent yields. When the reactions were carried out with CuI in the presence of base in acetonitrile, pyrazoles **188** were obtained in good yields. The electrophilic cyclization reactions were tolerated a varity of α,β-alkynic hydrazone derivatives **186** for the synthesis of 1,5-disubstituted-4-iodo-1*H*-pyrazoles, 1,3,5-trisubstituted-4-iodo-1*H*-pyrazoles, 1,5-disubstituted-1*H*-pyrazoles and 1,3,5-trisubstitued-1*H*-pyrazoles. As a result, 23 kinds of 4-iodopyrazoles and 27 kinds of pyrazoles have been isolated and characterized. In addition, Ferrocenyl substituted pyrazoles also have been synthesized via electrophilic cyclization reaction from corresponding α,β-alkynic hydrazones.

In the last part of the study, the reactions between propargyl aldehydes and amidoximes have been examined. It was found that these reactions produced the conjugate addition products **191** in stead of 1,2,4-oxadiazepines **193**. Isoxazoles **112** were yielded under the acidic reaction conditions and 1,2,4-oxadiazoles **192** were

formed under the basic conditions from the conjugate addition products **191**. The reaction mechanisms were proposed for the formation of these heteroaromatics.

Moreover, one-pot reaction of propargyl aldehydes and amidoximes with base has been applied for the synthesis of 1,2,4-oxadiazoles **192**, but these one-pot reactions gave relatively low yields. 3-Aryl-5-ferrocenyl-1,2,4-oxadiazoles have been synthesized by using one-pot procedure because ferrocenylpropanal and amidoximes did not produce the conjugate addition product. 11 Kind of new ferrocenyl substituted oxadiazoles were obtained by using this novel methodology.

In conclusion, synthesis of 4-iodopyrazoles and pyrazoles via electrophilic cyclization reactions were performed successfully. Especially, 4-iodopyrazoles would be new starting compound for the synthesis of biologically important structures by using metal catalyst coupling reactions.

CHAPTER 4

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Spectrospin Avance DPX400 Ultrashield (400 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from an internal TMS (trimethylsilane) reference. Coupling constants (*J*) are reported in hertz (Hz), and spin multiplicities are presented by the following symbols: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet). DEPT ^{13}C NMR information is given in parentheses as C, CH, CH_2 and CH_3. Infrared spectra (IR) were recorded on a NICOLET IS10 FTIR Spectrometer using attenuated total reflection (ATR). Band positions are reported in reciprocal centimeters (cm^{-1}). Band intensities are indicated relative to most intense band, and are listed as: br (broad), vs (very strong), s (strong), m (medium), w (weak), vw (very weak). Flash chromatography was performed using thick-walled glass columns and ''flash grade'' silica (Merck 230-400 mesh). Thin layer chromatography (TLC) was performed by using commercially prepared 0.25 mm silica gel plates and visualization was effected with short wavelength UV lamp. The relative proportions of solvents in chromatography solvent mixtures refer to the volume:volume ratio. All commercially available reagents were used directly without purification unless otherwise stated. All the solvents used in reactions distilled for purity. The inert atmosphere was created by slight positive pressure (ca. 0.1 psi) of argon. All glassware was dried in oven prior to use.

4.1 General procedure for the preparation of propargyl aldehydes (118)

Corresponding alkyne (50 mmol) was dissolved in dry THF (125 ml) and the solution was cooled to -40 ^{o}C under argon. *n*-Butyllithium (1.65 M in Hexanes, 30.3 ml, 50 mmol) was added dropwise over 2 min maintaining the temperature between -35 ^{o}C and -40 ^{o}C. After completion of the addition, anhydrous DMF (7.75 ml, 100 mmol) was added in one portion and the cold bath was removed. The reaction mixture was allowed to warm to room temperature and aged for 30 min. THF solution was poured into a vigorously stirred biphasic solution prepared from a 10% aqueous solution of KH_2PO_4 (270 ml, 200 mmol) and diethylether (250 ml) cooled over ice to 5 ^{o}C. Layers were separated and the organic extract was washed with water (2 x 200 mL). Combined organic layers were dried over $MgSO_4$, filtered and concentrated to give the crude propargyl aldehyde which was filtered through a pad of silica gel using 9:1 mixtures of hexanes/EtOAc as the eluent [164].

3-Phenylpropiolaldehyde (118a). 1-Ethynylbenzene (500mg, 3.88 mmol), *n*-BuLi (2.35 ml, 3.88 mmol), and DMF (0.62 ml, 7.76 mmol) was employed to afford 435 mg of the indicated product in 87% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.45 (s, 1H), 7.52-7.64 (m, 2H), 7.44-7.49 (m, 1H), 7.36-7.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9 (CH), 133.4 (CH), 131.4 (CH), 128.8 (CH), 119.6 (C), 95.3 (C), 88.9 (C). The spectral data was in agreement with those reported previously for this compound [178].

3-(*p*-Tolyl)propiolaldehyde (118b). 1-Ethynyl-4-methylbenzene (500mg, 4.3 mmol), *n*-BuLi (2.6 ml, 4.3 mmol), and DMF (0.67 ml, 8.6 mmol) was employed to afford 502 mg of the indicated product in 81% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.41 (s, 1H), 7.49 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9 (CH), 142.1 (C), 133.3 (CH), 129.5(CH), 116.3 (C), 95.9 (C), 88.5 (C), 21.7 (CH_3). The spectral data were in agreement with those reported previously for this compound [164].

3-(4-Methoxyphenyl)propiolaldehyde (118c). 1-Ethynyl-4-methoxybenzene (500mg, 3.78 mmol), *n*-BuLi (2.3 ml, 3.78 mmol), and DMF (0.60 ml, 8.6 mmol) was employed to afford 570 mg of the indicated product in 94% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.28 (s, 1H), 7.42 (d, J = 9.0 Hz, 2H), 6.80 (d, J = 9.0 Hz, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6 (CH), 162.2 (C), 135.4 (CH), 114.5 (CH), 111.2 (C), 96.5 (C), 88.7 (C), 55.5 (CH_3). The spectral data were in agreement with those reported previously for this compound [179].

3-(Thiophen-3-yl)propiolaldehyde (118d). 3-Ethynylthiophene (500mg, 4.62 mmol), *n*-BuLi (2.8 ml, 4.62 mmol), and DMF (0.73 ml, 9.24 mmol) was employed to afford 303 mg of the indicated product in 52% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.42 (s, 1H), 7.83 (s, 1H), 7.37 (m, 1H), 7.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6 (CH), 134.8 (CH), 130.3 (CH), 126.4 (CH), 118.8 (C), 90.5 (C), 88.9 (C). The spectral data were in agreement with those reported previously for this compound [180].

Oct-2-ynal (118e). Hept-1-yne (500mg, 5.21 mmol), *n*-BuLi (3.2 ml, 5.21 mmol), and DMF (0.82 ml, 10.42 mmol) was employed to afford 388 mg of the indicated product in 60% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.16 (s, 1H), 2.40 (t, J = 7.1 Hz, 3H), 1.55 (m, 2H), 1.31 (m, 4H), 0.90 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.2 (CH), 99.3 (C), 81.7 (C), 30.9 (CH_2), 27.2 (CH_2), 22.1 (CH_2), 19.1 (CH_2), 13.8 (CH_3). The spectral data were in agreement with those reported previously for this compound [181].

4-Cyclopentylbut-2-ynal (118f). Prop-2-yn-1-ylcyclopentane (500mg, 2.38 mmol), *n*-BuLi (1.45 ml, 2.38 mmol), and DMF (0.73 ml, 4.76 mmol) was employed to afford 377 mg of the indicated product in 60% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.18 (s, 1H), 2.42 (d, J = 6.8 Hz, 2H), 2.09 (m, 1H), 1.80 (m, 2H), 1.53 (m, 4H), 1.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1 (CH), 88.9 (C), 81.7 (C), 38.0 (CH_2), 32.0 (CH), 25.2 (CH_2), 25.0 (CH_2).

4.2 General procedure for the preparation of 4-phenylbut-3-yn-2-one (118g).

To a 100 mL two-necked round-bottomed flask equipped with magnetic stirring under nitrogen at -70 ^{o}C were added the terminal alkyne (10 mmol) and THF (50 mL). To the solution was slowly added *n*-butyllithium (1 equiv, 1.65 M solution in hexanes). The solution was warmed up to 0 ^{o}C, stirred at this temperature for 30 min and then cooled at -70 ^{o}C prior to the addition of a solution of $ZnCl_2$ (1 eq., 1 M solution in THF). The solution was warmed and stirred at room temperature for additional 15 min and then recooled at -70 ^{o}C. Acetyl chloride was added in one portion. The reaction mixture was warmed to room temperature and stirred for additional 40 min, then diluted with hexane (10 mL) and washed with brine (3x10 mL). The organic phase was dried over magnesium sulphate and filtered. The solvents were evaporated and the residue purified by silica gel column chromatography eluting with EtOAc/hexane yielding 1,3-diphenylprop-2-yn-1-one. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.55 (d, J = 8.3 Hz, 2H), 7.43 (t, J = 7.4 Hz, H), 7.36 (m, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 184. 3 (C), 133.0 (CH), 130.7 (CH), 128.6 (CH), 119.9 (C), 90.2 (C), 88.3 (C), 32.6 (CH_3).The spectral data were in agreement with those reported previously for this compound [163, 182].

4.3 General procedure for the preparation of 1,3-diphenylprop-2-yn-1-one (118h)

Benzoyl chloride (6 mmol), $PdCl_2(PPh_3)_2$ (0.1 mmol) and Et_3N (6 mmol) in THF (20 ml) were stirred for 10 min under argon atmosphere at room temperature. CuI (0.1 mmol) was added and the reaction mixtue was stirred for another 10 min before adding phenylacetylene (5 mmol). After 6 h at room temperature, THF is removed under reduced pressure and the crude mixture was extracted with ethyl acetate and 0.1 N HCl and a saturated NH_4Cl solution. The organic phase was dried over magnesium sulphate and filtered. The solvents were evaporated and the residue purified by silica gel column chromatography eluting with hexane/EtOAC yielding

1,3-diphenylprop-2-yn-1-one (98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (dd, J = 1.2 Hz, J = 8.2 Hz, 2H), 7.69 (d, J = 6.9 Hz, 2H), 7.64 (t, J = 7.4 Hz, 1H), 7.50 (m, 3H), 7.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.8 (C), 136.9 (C), 134.1 (CH), 133.1 (CH), 130.8 (CH), 129.6 (CH), 128.7 (CH), 128.6 (CH), 120.2 (C), 93.1 (C), 86.9 (C).The spectral data were in agreement with those reported previously for this compound [164].

4.4 Preparation of 3-ferrocenylpropynal (45).

4.4.1 Synthesis of acetylferrocene (198)

Ferrocene (**180**) (2g, 10.8 mmol) was dissolved in dry CH_2Cl_2 (9 mL) by constant stirring under argon. Then acetyl chloride (0.92ml, 11.8 mmol) was added to the resultant orange/red solution. The flask was immersed in a 0-5 ^{o}C ice-water bath. Anhydrous aluminum chloride (1.44 g, 10.8 mmol) was slowly added in small portions to the reaction flask. The reaction mixture was stirred at room temperature for 2 h and then it was recooled to 0-5 ^{o}C by a fresh ice-water bath. By the slow addition of cold water (4 x 0.5 ml), the reaction mixture was hydrolyzed. Then a further 3 ml of cold water was added more rapidly. The hydrolyzed reaction mixture was extracted with CH_2Cl_2 and combined organic extracts were washed with 5% NaOH solution followed by brine solution. The organic phase was dried over magnesium sulfate and filtered off. An orange/red solid was obtained after solvent was removed on rotary evaporator. The resultant solid was purified by flash column chromatography on silica gel using 9:1 hexane/ethylacetate as the eluent to give acetylferrocene (**198**) (1.96 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.60 (s, 2H), 4.32 (s, 2H), 4.02 (s, 5H), 2.17 (s, 3H); ^{13}C NMR (100 MHz,, $CDCl_3$): δ 79.2 (C), 72.3 (CH), 69.8 (CH), 69.5 (CH), 27.3 (CH_3). The spectral data is in agreement with those reported previously for this compound [183].

4.4.2 Synthesis of (2-formyl-1-chlorovinyl)ferrocene (44)

In a two necked flask, acetylferrocene (**198**) (2 g, 8.8 mmol) and DMF (2.17 ml, 28.2 mmol) were added under argon. The flask was cooled to 0 ^{o}C by ice-water bath and the brown reaction mixture was stirred for 10 minutes. Separately, in a round-bottom flask, DMF (2.17 ml, 28.2 mmol) was added and cooled to 0 ^{o}C under argon. Then cautiously phosphorus oxychloride (2.21 ml, 28.2 mmol) was added to DMF with good stirring. The resultant viscous red complex was slowly (over 30 minutes) transferred to the two neck flask containing acetylferrocene (**198**) and DMF by a dropping funnel. After the addition was completed, the contents of the flask were stirred at 0 ^{o}C for approximately 2 h until the color of reaction mixture changed from dark brown to olive green and then to dark blue. A 20 ml portion of diethyl ether was added, and the mixture was stirred vigorously. Then with continued cooling with ice-water bath, sodium acetate trihydrate (10.18 g, 74.6 mmol) was carefully added to the reaction flask in one portion followed by addition of water (2 ml). The ice water bath was removed and a color change in organic layer from colorless to ruby red, indicating the formation of formyl derivative, was observed. After 1 h, additional ether (2 ml) was added and the stirring was continued for 3 h at room temperature for complete quenching. The reaction mixture was extracted with diethyl ether. The organic extracts were combined and washed with saturated sodium bicarbonate solution. After dried by magnesium sulfate and filtered, organic phase was concentrated on rotary evaporator, yielding (2-formyl-1-chlorovinyl)ferrocene (**44**) (2.25 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.06 (d, 1H, J = 7.1 Hz), 6.38 (d, 1H, J = 7.1 Hz), 4.73 (t, 2H, J = 1.68 Hz), 4.54 (t, 2H, J = 1.68 Hz), 4.22 (s, 5H). The spectral data is in agreement with those reported previously for this compound [167].

4.4.3 Synthesis of ethynylferrocene (104)

In a dry flask, (2-formyl-1-chlorovinyl)ferrocene (**44**) (1.3 g, 4.75 mmol) was dissolved in anhydrous dioxane (15 mL) by flashing with argon and heated to reflux.

After approximately 5 minutes a boiling 1 N solution of sodium hydroxide (12.5 ml) was added rapidly in one portion and the reflux continued for another 25 minutes. Then refluxing was stopped and the mixture was allowed to cool to room temperature. The contents of the flask were poured directly into ice and neutralized with 1 N hydrochloric acid solution. The resultant mixture was extracted with hexane (5 x 5 ml). The organic phase was washed with sodium bicarbonate solution and water. The combined organic parts were dried over magnesium sulfate, filtered and the solvent was removed on rotary evaporator. The crude ethynylferrocene **(198)** was purified by flash chromatography on silica gel by using hexane as the eluent and the clear product was obtained as orange crystals (750 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.46 (s, 2H), 4.21 (s, 5H), 4.19 (s, 2H), 2.71 (s, 1H). The spectral data is in agreement with those reported previously for this compound.

4.4.4 3-Ferrocenylpropynal (45).

Ethynylferrocene (500mg, 3.78 mmol), *n*-BuLi (1.6 M in hexanes, 2.3 ml, 3.78 mmol), and DMF (0.40 ml, 8.6 mmol) was employed to afford 504 mg of the indicated product in 89% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.27 (s, 1H), 4.60 (s, 2H), 4.41 (s, 2H), 4.25 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2 (C), 99.5 (C), 87.7 (C), 73.3 (CH), 71.3 (CH), 70.6 (CH), 59.2 (C). The spectral data were in agreement with those reported previously for this compound [184].

4.5 General procedure for the synthesis of alkynic hydrazones 186 (Table 1)

Conditions A. A mixture of arylhydrazine (1 equiv.) and propargyl aldehydes or ketones (1 equiv.) in dioxane was heated at 100 ^{o}C in a round bottom flask equipped with condenser under argon for 5 h. After the reaction was over, the dioxane was removed under reduced pressure. The residue was purified by flash column

chromatography on silica gel using ethyl acetate/hexane as the eluent to afford the desired product.

Conditions B. A mixture of arylhydrazine (1 equiv.) and propargyl aldehydes or ketones (1 equiv.) in a round bottom flask was heated at 80 ^{o}C under argon for 5 h. After the reaction was over, the residue was purified by flash column chromatography on silica gel using ethyl acetate/hexane as the eluent to afford the desired product.

(*Z*)-1-Phenyl-2-(3-phenylprop-2-yn-1-ylidene)hydrazine (*Z*-186a) (Table 1, Entry 1). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 61% and 81% of the desired product for Condition A and Condition B, respectively. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (brs, 1H, NH), 7.53 (m, 2H), 7.40 (m, 3H), 7.29 (m, 2H), 7.10 (m, 2H), 6.92 (m, 1H), 6.62 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5 (C), 131.8 (CH), 129.5 (CH), 129.4 (CH), 128.6 (CH), 121.6 (C), 121.2 (CH), 114.7 (CH), 113.3 (CH), 101.9 (C), 79.6 (C); IR (neat): 3307, 3051, 3028, 2185, 1596, 1523, 1500, 1438, 1342, 1309, 1255, 1124, 1068, 764, 682 cm^{-1}; MS (ESI, *m/z*): 243.09 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{15}H_{12}N_2Na$: 243.0897 $[M+Na]^+$; Found: 243.0893.

(*Z*)-1-Phenyl-2-(3-(p-tolyl)prop-2-yn-1-ylidene)hydrazine (*Z*-186b) (Table 1, Entry 2). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 85% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (brs, 1H), 7.45 (d, J = 7.99 Hz, 2H), 7.31 (t, J = 7.7 Hz, 2H), 7.22 (d, J = 7.9 Hz, 2H), 7.13 (d, J = 8.2 Hz, 2H), 6.94 (t, J = 7.2 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6 (C), 139.9 (C), 131.7 (CH), 129.4 (CH), 129.3 (CH), 121.0 (CH), 118.5 (C), 114.9 (CH), 113.3 (CH), 102.3 (C), 79.1 (C), 21.6 (CH_3); IR (neat): 3317, 3053, 3029, 2918, 2189, 1598, 1531, 1508, 1348, 1253, 1122, 1068, 885, 810, 750, 688 cm^{-1}; MS (ESI, *m/z*): 257.11 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{16}H_{14}N_2Na$: 257.1054 $[M+Na]^+$. Found: 257.1049.

(*Z*)-1-(3-(4-Methoxyphenyl)prop-2-yn-1-ylidene)-2-phenylhydrazine (*Z*-186c) (Table 1, Entry 3). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 64% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (brs, 1H, NH), 7.48 (d, J = 8.7 Hz, 2H), 7.29 (t, J = 7.5 Hz, 2H), 7.11 (d, J = 8.2 Hz, 2H), 6.93 (m, 3H), 6.62 (s, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6 (C), 143.6 (C), 133.4 (CH), 129.3 (CH), 121.0 (CH), 115.2 (C), 114.3 (CH), 113.6 (C), 113.2 (C), 102.2 (C), 78.6 (C), 55.4 (CH_3); IR (neat): 3290, 3055, 2839, 2192, 1598, 1542, 1504, 1346, 1290, 1240, 1172, 1105, 1026, 885, 827, 748, 690 cm^{-1}; MS (ESI, *m/z*): 273.10 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{16}H_{14}N_2ONa$: 273.1003 $[M+Na]^+$; Found: 273.0998.

(*Z*)-1-Phenyl-2-(3-(thiophen-3-yl)prop-2-yn-1-ylidene)hydrazine (*Z*-186d) (Table 1, Entry 4). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 54% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (brs, 1H, NH), 7.51 (d, J = 1.9 Hz, 1H), 7.26 (m, 1H), 7.20 (m, 2H), 7.12 (d, J = 5.4 Hz, 1H), 7.02 (d, J = 8.3 Hz, 2H), 6.84 (t, J = 7.2 Hz, 1H), 6.51 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5 (C), 130.2 (CH), 129.7 (CH), 129.4 (CH), 126.1 (CH), 121.1 (CH), 120.7 (C), 114.7 (CH), 113.3 (CH), 97.0 (C), 79.3 (C); IR (neat): 3305, 3105, 3053, 2181, 1598, 1498, 1342, 1521, 1120, 1068, 856, 779, 748, 688 cm^{-1}; MS (ESI, *m/z*): 249.05 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{13}H_{10}N_2SNa$: 249.0462 $[M+Na]^+$; Found: 249.0457.

(*Z*)-1-(Oct-2-yn-1-ylidene)-2-phenylhydrazine (*Z*-186e) (Table 1, Entry 5). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 81% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (brs, 1H, NH), 7.19 (t, J = 7.68 Hz, 2H), 7.03 (d, J = 7.88 Hz, 2H), 6.81 (t, J = 7.20 Hz, 1H), 6.32 (s, 1H), 2.40 (t, J = 6.93 Hz, 2H), 1.55 (p, J = 7.15 Hz, 2H), 1.33 (m, 4H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8 (C), 129.3 (CH), 120.8 (CH), 115.8 (CH), 113.1 (CH), 104.3 (C), 71.9 (C), 31.2 (CH_2), 28.2 (CH_2), 22.2 (CH_2), 19.7 (CH_2), 14.0 (CH_3); IR (neat): 3307, 2954, 2929, 2858, 2196, 1600, 1535,1502, 1344, 1253,

1151, 1114, 1066, 883, 810, 746, 690 cm^{-1}; MS (ESI, *m/z*): 237.14 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{14}H_{18}N_2Na$: 237.1367 $[M+Na]^+$; Found: 237.1362.

(*Z*)-1-(4-Cyclopentylbut-2-yn-1-ylidene)-2-phenylhydrazine (*Z*-186f) (Table 1, Entry 6). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 60% of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 8.58 (s, 1H), 7.31 (m, 2H), 7.08 (d, J = 7.50 Hz, 2H), 7.0 (t, J = 7.26 Hz, 1H), 6.43 (s, 1H), 2.55 (d, J = 6.80 Hz, 2H), 2.16-2.27 (m, 1H), 1.95-1.88 (m, 2H), 1.77-1.61 (m, 4H), 1.43-1.35 (m, 2H); IR (neat): 3307, 2947, 2864, 2194, 1600, 1533, 1502, 1344, 1307, 1523, 1151, 114, 1066, 810, 764, 690 cm^{-1}; MS (ESI, *m/z*): 249.14 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{15}H_{18}N_2Na$: 249.1367 $[M+Na]^+$; Found: 249.1362.

(*Z*)-1-(3-Phenylprop-2-yn-1-ylidene)-2-(4-(trifluoromethyl)phenyl)hydrazine (*Z*-186g) (Table 1, Entry 7). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 60% of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 8.76 (brs, 1H, NH), 7.53 (m, 4H), 7.41 (m, 3H), 7.15 (d, J = 8.44 Hz, 2H), 6.69 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.0 (C), 131.8 (CH), 129.8 (CH), 128.7 (CH), 126.7 (m, CH), 124.6 (d, J = 269 Hz, C), 122.8 (q, J = 30 Hz, C), 121.2 (C), 116.9 (CH), 112.9 (CH), 102.5 (C), 79.0 (C). IR (neat): 3323, 3070, 3039, 2185, 1614, 1541, 1523, 1488, 1326, 1259, 1159, 1093, 1058, 819, 754, 686 cm^{-1}; MS (ESI, *m/z*): 311.08 $[M+Na]^+$, 289.10 $[M+H]^+$; HRMS (ESI): calcd. for $C_{16}H_{11}F_3N_2Na$: 311.0771 $[M+Na]^+$; Found: 311.0767; calcd. for $C_{16}H_{12}F_3N_2$: 289.0953 $[M+H]^+$; Found: 289.0947.

(*Z*)-1-(3-Chloro-4-fluorophenyl)-2-(3-phenylprop-2-yn-1-ylidene)hydrazine (*Z*-186h) (Table 1, Entry 8). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 80% of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 8.53 (brs, 1H, NH), 7.50 (m, 2H), 7.39 (m, 3H), 7.17 (m, 1H), 7.03 (m, 1H), 6.94 (m, 1H), 6.62 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.5 (d, J = 18 Hz, C), 139.9 (C), 131.3 (CH), 129.2 (CH), 128.2 (CH), 121.1 (d, J = 18 Hz, C), 120.8 (C), 116.4 (d, J = 22.5 Hz, CH), 115.5 (CH), 114.4 (CH), 111.8 (d, J = 25.2 Hz, CH), 101.8 (C),

78.6(C); IR (neat): 3313, 3053, 2183, 1604, 1533, 1504, 1488, 1440, 1344, 1257, 1207, 1101, 1047, 858, 802, 746, 682 cm^{-1}; MS (ESI, *m/z*): 295.04 $[M+Na]^+$, 273.06 $[M+H]^+$; HRMS (ESI): calcd. for $C_{15}H_{10}ClFN_2Na$: 295.0413 $[M+Na]^+$; Found: 295.0409; calcd. for $C_{15}H_{11}ClFN_2$: 273.0595 $[M+H]^+$; Found: 273.0589.

(*Z*)-1-(2,5-Difluorophenyl)-2-(3-phenylprop-2-yn-1-ylidene)hydrazine (*Z*-186i) (Table 1, Entry 9). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 71% of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 8.85 (brs, 1H, NH), 7.52 (m, 2H), 7.40 (m, 3H), 7.20 (m, 1H), 6.97 (m, 1H), 6.72 (s, 1H), 6.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8 (d, J = 240 Hz, C), 145.9 (d, J = 232 Hz, C), 133.1 (t, J = 11.5 Hz, C), 131.9 (CH), 129.8 (CH), 128.6 (CH), 121.2 (CH), 118.0 (CH), 115.5 (dd, J = 10.4 Hz, J = 20.4 Hz, CH), 106.0 (dd, J = 6.9 Hz, J = 24.5 Hz, CH), 103.0 (C), 102.0 (d, J = 28 Hz, CH), 79.0 (C); IR (neat): 3334, 3078, 2185, 1633, 1541, 1519, 1461, 1440, 1350, 1247, 1155, 1120, 975, 839, 796, 773, 748, 715, 680 cm^{-1}; MS (ESI, *m/z*): 279.07 $[M+Na]^+$, 257.09 $[M+H]^4$; HRMS (ESI): calcd. for $C_{15}H_{10}F_2N_2Na$: 279.0709 $[M+Na]^+$; Found: 279.0704; calcd. for $C_{15}H_{11}F_2N_2$: 257.0891 $[M+H]^+$; Found: 257.0885.

(*Z*)-1-(3-(*p*-Tolyl)prop-2-yn-1-ylidene)-2-(4-(trifluoromethyl)phenyl)hydrazine *(Z*-186j) (Table 1, Entry 10). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 60% of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 8.74 (brs, 1H), 7.51 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 7.9 Hz, 2H), 7.14 (d, J = 8.5 Hz, 2H), 6.67 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.1 (C), 140.3 (C), 131.8 (CH), 129.5 (CH), 126.7 (m, CH), 124.6 (d, J = 268 Hz, C), 122.6 (q, J = 32.5 Hz, C), 118.1 (C), 117.174 (CH), 112.80 (CH), 102.9 (C), 78.6 (C), 21.6 (CH_3); IR (neat): 3313, 3033, 2925, 2181, 1614, 1537, 1321, 1261, 1159, 1099, 1064, 840, 815 cm^{-1}; MS (ESI, *m/z*): 325.09 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{17}H_{13}F_3N_2Na$: 325.0929 $[M+Na]^+$; Found: 325.0924.

(*Z*)-1-(3-Chloro-4-fluorophenyl)-2-(3-(p-tolyl)prop-2-yn-1-ylidene)hydrazine (*Z*-186k) (Table 1, Entry 11). Purification by flash chromatography (1:9

EtOAc/Hexane) afforded 77% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (brs, 1H), 7.45 (d, J = 7.9 Hz, 2H), 7.18 (d, J = 7.9 Hz, 2H), 7.15 (m, 1H), 7.03 (t, J = 8.7 Hz, 1H), 6.90 (m, 1H), 6.61 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.5 (d, J = 18.9 Hz, C), 140.0 (C), 139.7 (C), 131.2 (CH), 128.9 (CH), 121.1 (d, J = 18.9 Hz, C), 117.7 (C), 116.4 (d, J = 22.1 Hz, CH), 115.7 (CH), 114.4 (CH), 111.8 (d, J = 6.9 Hz, CH), 102.2 (C), 78.2 (C), 21.1 (CH_3); IR (neat): 3301, 2918, 2858, 2177, 1604, 1531, 1500, 1342, 1251, 1205, 1101, 810, 740 cm^{-1}; MS (ESI, *m/z*): 309.06 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{16}H_{12}ClFN_2Na$: 309.0571 $[M+Na]^+$; Found: 309.0565.

(*Z*)-1-(2,5-Difluorophenyl)-2-(3-(p-tolyl)prop-2-yn-1-ylidene)hydrazine (*Z*-186l) (Table 1, Entry 12). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 80% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.87 (brs, 1H), 7.41 (d, J = 7.9 Hz, 2H), 7.19 (m, 1H), 7.18 (d, J = 7.7 Hz, 2H), 6.96 (m, 1H), 6.71 (s, 1H), 6.47 (m, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8 (d, J = 239.5 Hz, C), 145.9 (d, J = 234.5 Hz, C), 140.3 (C), 133.2 (t, J = 10.8 Hz, C), 131.8 (CH), 129.5 (CH), 118.3 (CH), 118.1 (C), 115.5 (dd, J = 9.7 Hz, 20.2 Hz, CH), 105.9 (dd, J = 6.9, J = 24.8 Hz, CH), 103.0 (C), 102.0 (dd, J = 28.8, J = 2.5 Hz, CH), 78.6 (C), 21.6 (CH_3); IR (neat): 3330, 3078, 2920, 2181, 1631, 1542, 1515, 1456, 1342, 1247, 1153, 1116, 1078, 844, 813, 794, 756 cm^{-1}; MS (ESI, *m/z*): 293.09 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{16}H_{12}F_2N_2Na$: 293.0866 $[M+Na]^+$; Found: 293.0861.

(*Z*)-1-(3-(4-Methoxyphenyl)prop-2-yn-1-ylidene)-2-(4-(trifluoromethyl)phenyl) hydrazine (*Z*-186m) (Table 1, Entry 13). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 52% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (brs, 1H, NH), 7.50 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.8 Hz, 2H), 7.13 (d, J = 8.5 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 6.67 (s, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8 (C), 146.2 (C), 133.5 (CH), 126.6 (m, CH), 124.6 (d, J = 271 Hz, C), 122.5 (q, J = 31.9 Hz, C), 117.4 (CH), 114.4 (CH), 113.2 (C), 112.8 (CH), 102.9 (C), 78.8 (C), 55.4 (CH_3); IR (neat): 3321, 2970, 2840, 2177, 1600, 1506,

1328, 1296, 1251, 1095, 1060, 1033, 823 cm^{-1}; MS (ESI, *m/z*): 341.09 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{17}H_{13}F_3N_2ONa$: 341.0877 $[M+Na]^+$; Found: 341.0872.

(*Z*)-1-(3-Chloro-4-fluorophenyl)-2-(3-(4-methoxyphenyl)prop-2-yn-1-ylidene) hydrazine (*Z*-186n) (Table 1, Entry 14). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 82% of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 8.71 (brs, 1H, NH), 7.50 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.67 (s, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8 (C), 146.2 (C), 133.5 (CH), 126.6 (m, CH), 124.6 (d, *J* = 271 Hz, C), 122.5 (q, *J* = 31.9 Hz, C), 117.4 (CH), 114.4 (CH), 113.2 (C), 112.8 (CH), 102.9 (C), 78.8 (C), 55.4 (CH_3); IR (neat): 3321, 2970, 2840, 2177, 1600, 1506, 1328, 1296, 1251, 1095, 1060, 1033, 823 cm^{-1}; MS (ESI, *m/z*): 341.09 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{16}H_{12}ClFN_2ONa$: 325.0520 $[M+Na]^+$; Found: 325.0514.

(*Z*)-1-(2,5-Difluorophenyl)-2-(3-(4-methoxyphenyl)prop-2-yn-1-ylidene) hydrazine (*Z*-186o) (Table 1, Entry 15). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 57% of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): *δ* 8.80 (brs, 1H, NH), 7.46 (d , *J* = 8.6 Hz, 2H), 7.20 (m, 1H), 6.96 (m, 1H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.70 (s, 1H), 6.47 (m,1H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 160.8 (C), 159.8 (d, *J* = 239 Hz, C), 145.8 (d, *J* = 235.8 Hz,C), 133.6 (CH), 133.5 (t, *J* = 11.3 Hz, C), 118.5 (CH), 115.5 (dd, *J* = 10 Hz, *J* = 20 Hz, CH), 114.4 (CH), 113.2 (C), 105.8 (dd, *J* = 7.4 Hz, *J* = 24.5 Hz, CH), 103.5 (C), 101.9 (dd, *J* = 29 Hz, *J* = 2.5 Hz, CH), 78.3 (C), 55.4 (CH_3); IR (neat): 3338, 2844, 2183, 1633, 1600, 1517, 1556, 1299, 1251, 1176, 1151, 1107, 1031, 852, 827, 800, 777, 756 cm^{-1}; MS (ESI, *m/z*): 309.08 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{16}H_{12}F_2N_2ONa$: 309.0815 $[M+Na]^+$; Found: 309.0810.

(*Z*)-1-(Oct-2-yn-1-ylidene)-2-(4-(trifluoromethyl)phenyl)hydrazine (*Z*-186p) (Table 1, Entry 16). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 70 % of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): *δ* 8.64 (brs, 1H, NH), 7.49 (d, *J* = 8.5 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.45 (s, 1H), 2.49 (td, *J* = 7.1

Hz, J = 1. 4 Hz, 2H), 1.63 (p, J = 7.4 Hz, 2H), 1.42 (m, 4H), 0.93 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.3 (C), 126.6 (m, CH), 124.6 (d, J = 269.5 Hz, C), 122.3 (q, J = 32.5 Hz, C), 117.9 (CH), 112.6 (CH), 105.0 (C), 71.5 (C), 31.1 (CH_2), 28.0 (CH_2), 22.2 (CH_2), 19.6 (CH_2), 13.3 (CH_3); IR (neat): 3315, 2958, 2933, 2861, 2198, 1614, 1527, 1481, 1317, 1263, 1157, 1109, 1060, 833 cm^{-1}; MS (ESI, *m/z*): 283.14 $[M+H]^+$; HRMS (ESI): calcd. for $C_{15}H_{18}F_3N_2$: 283.1422 $[M+H]^+$; Found: 283,1417.

(*Z*)-1-(3-Chloro-4-fluorophenyl)-2-(oct-2-yn-1-ylidene)hydrazine (*Z*-186q) (Table 1, Entry 17). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 93 % of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (brs, 1H, NH), 6.94 (m, 1H), 6.82 (t, J = 8.7 Hz, 1H), 6.66 (m, 1H), 6.20 (s, 1H), 2.25 (td, J = 1.0 Hz, J = 7.1 Hz, 2H), 1.44 (p, J = 7.4 Hz, 2H), 1.21 (m, 4H), 0.75 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.8 (J = 239.5 Hz, C), 140.72 (C), 121.5 (d, J = 18.3 Hz, C), 117.0 (CH), 116.8 (J = 22.8 Hz, CH), 114.7 (CH), 112.2 (J = 6.8 Hz, CH), 104.8 (C), 71.5 (C), 31.1 (CH_2), 28.1 (CH_2), 22.2 (CH_2), 19.7 (CH_2), 13.9 (CH_3); IR (neat): 3315, 2956, 2931, 2860, 2198, 1610, 1502, 1340, 1253, 1207, 1091, 844, 804, 731 cm^{-1}; MS (ESI, *m/z*): 267.11 $[M+H]^+$; HRMS (ESI): calcd. for $C_{14}H_{17}ClFN_2$: 267.1065 $[M+H]^+$; Found: 267.1059.

(*Z*)-1-(2,5-Difluorophenyl)-2-(oct-2-yn-1-ylidene)hydrazine (*Z*-186r) (Table 1, Entry 18). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 88 % of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (brs, 1H), 7.16 (m, 1H), 6.85 (m, 1H), 6. 48 (s, 1H), 6.43 (m, 1H), 2.48 (t, J = 6.87 Hz, 2H), 1.62 (p, 2H), 1.43 (m, 2H), 1.36 (m, 2H), 0.92 (t, J = 7.16 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7 (d, J = 203.6 Hz, C), 145.7 (d, J = 235.9 Hz, C), 133.4 (t, J = 11 Hz, C), 118.9 (CH), 115.4 (dd, J = 20.3, J = 10.4 Hz, CH), 105.5 (dd, J = 24.5 Hz, J = 7.4 Hz, CH), 105.4 (C), 101.9 (d, J = 31.5 Hz, CH), 71.4 (C), 31.0 (CH_2), 28.0 (CH_2), 22.2 (CH_2), 19.6 (CH_2), 13.8 (CH_3); IR (neat): 3328, 2958, 2931, 2862, 2198, 1631, 1542, 1517, 1456, 1338, 1288, 1244, 1157, 1107, 1066, 852, 790 cm^{-1}; MS (ESI, *m/z*): 273.12 $[M+Na]^+$, 251.14 $[M+H]^+$; HRMS (ESI): calcd. for

$C_{14}H_{16}F_2N_2Na$: 273.1178 $[M+Na]^+$; Found: 273.1174; calcd. for $C_{14}H_{17}F_2N_2$: 251.1360 $[M+H]^+$; Found: 251.1354.

(Z)-1-Phenyl-2-(4-phenylbut-3-yn-2-ylidene)hydrazine (*Z*-186s) (Table 1, Entry 19). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 69% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (brs, 1H), 7.57 (m, 2H), 7.43 (m, 3H), 7.30 (t, J = 8.0 Hz, 2H), 7.13 (d, J = 7.6 Hz, 2H), 6.91 (t, J = 7.3 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.2 (C), 131.8 (CH), 129.5 (CH), 129.3 (CH), 128.6 (CH), 123.7 (C), 121.6 (C), 120.3 (CH), 113.0 (CH), 101.2 (C), 81.0 (C), 22.2 (CH_3); IR (neat): 3056, 2923, 2200, 1670, 1598, 1504, 1442, 1363, 1253, 1155, 1072, 970, 758, 690 cm^{-1}; MS (ESI, *m/z*): 257.11 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{16}H_{14}N_2Na$: 257.1055 $[M+Na]^+$; Found: 257.1049. The spectral data were in agreement with those reported previously for this compound [185].

(*Z*)-1-(4-Phenylbut-3-yn-2-ylidene)-2-(4-(trifluoromethyl)phenyl)hydrazine (*Z*-186t) (Table 1, Entry 20). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 76% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (brs, 1H), 7.45 (d, J=7.6 Hz, 2H), 7.39 (d, J = 8.5 Hz, 2H), 7.32 (m, 3H), 7.02 (d, J = 8.4 Hz, 2H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.6 (C), 131.9 (CH), 129.7 (CH), 128.7 (CH), 126.6 (m, CH), 125.9 (C), 124.7 (d, J = 269.8 Hz, C), 121.8 (q, J = 32.9 Hz, C), 121.2 (C), 112.5 (CH), 101.7 (C), 80.4 (C), 22.3 (CH_3); IR (neat): 3313, 3082, 2989, 2918, 2360, 2177, 2162, 1612, 1527, 1488, 1325, 1311, 1267, 1153, 1099, 1062, 821, 748, 684 cm^{-1}; MS (ESI, *m/z*): 303.11 $[M+H]^+$; HRMS (ESI): calcd. for $C_{17}H_{14}F_3N_2$: 303.1109 $[M+Na]^+$; Found: 303.1104.

(*Z*)-1-(3-Chloro-4-fluorophenyl)-2-(4-phenylbut-3-yn-2-ylidene)hydrazine (*Z*-186u) (Table 1, Entry 21). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 87% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (brs, 1H), 7.54 (m, 2H), 7.42 (m, 3H), 7.17 (dd, J = 2.5 Hz, J = 6.3 Hz, 1H), 7.03 (t, J = 8.7 Hz, 1H), 6.88 (m, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.5 (d, J = 18.4 Hz, C), 141.0 (C), 131.8 (CH), 129.6 (CH), 128.7 (CH), 125.0 (C),

121.5 (d, J = 18.4 Hz, C), 121.3 (C), 116.8 (d, J = 21.8 Hz, CH), 114.5 (CH), 112.0 (d, J = 6.2 Hz, CH), 101.6 (C), 80.6(C), 22.2 (CH_3); IR (neat): 3309, 3055, 2916, 2360, 2165, 1606, 1556, 1506, 1442, 1259, 1209, 1186, 1153, 862, 804, 746, 680 cm^{-1}; MS (ESI, *m/z*): 309.06 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{16}H_{12}ClFN_2Na$: 309.0571 $[M+Na]^+$; Found: 309.0565.

(*Z*)-1-(2,5-Difluorophenyl)-2-(4-phenylbut-3-yn-2-ylidene)hydrazine (*Z*-186v) (Table 1, Entry 22). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 86% of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 8.54 (brs, 1H), 7.57 (m, 2H), 7.44 (m, 3H), 7.25 (m, 1H), 6.98 (m, 1H), 6.47 (m, 1H), 2.28 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8 (d, J = 239.8 Hz, C), 145.7 (d, J = 233.4 Hz, C), 133.7 (t, J = 12 Hz, C), 131.9 (CH), 129.7 (CH), 128.7 (CH), 127.2 (C), 121.2 (C), 115.3 (dd, J = 9.7 Hz, J = 20 Hz, CH), 105.0 (dd, J = 7 Hz, J = 24.8 Hz, CH), 102.2 (C), 101.6 (dd, J = 2.5 Hz, J = 30.4 Hz, CH), 80.4 (C), 22.1 (CH_3); IR (neat): 3327, 3066, 3045, 2921, 2173, 1633, 1521, 1460, 1247, 1151, 1130, 977, 854, 808, 754, 732, 684 cm^{-1}; MS (ESI, *m/z*): 293.09 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{16}H_{12}F_2N_2Na$: 293.0868 $[M+Na]^+$; Found: 293.0861.

(*Z*)-1-(1,3-Diphenylprop-2-yn-1-ylidene)-2-phenylhydrazine (*Z*-186w) (Table 1, Entry 23). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 27% of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 8.79 (brs, 1H), 8.06 (d, J = 7.9 Hz, 2H), 7.69 (m, 2H), 7.49 (m, 5H), 7.39 (m, 3H), 7.30 (d, J = 7.9 Hz, 2H), 7.0 (t, J = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6 (C), 135.9 (C), 132.0 (CH), 129.7 (CH), 129.4 (CH), 128.8 (CH), 128.5 (CH), 128.2 (CH), 125.7 (C), 125.6 (CH), 121.6 (CH), 121.1 (C), 113.6 (CH), 103.8 (C), 78.9 (C); IR (neat): 3298, 2928, 2360, 2160, 1600, 1517, 1490, 1442, 1259, 1168, 1072, 885, 748, 686 cm^{-1}; MS (ESI, *m/z*): 319.12 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{21}H_{16}N_2Na$: 319.1211 $[M+Na]^+$; Found: 319.1206.

(*Z*)-1-(1,3-Diphenylprop-2-yn-1-ylidene)-2-(4-(trifluoromethyl)phenyl)hydrazine (*Z*-186x) (Table 1, Entry 24). Purification by flash chromatography (1:9

EtOAc/Hexane) afforded 52% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (brs, 1H), 8.02 (d, J = 7.5 Hz, 2H), 7.67 (d, J = 7.6 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.49 (m, 5H), 7.39 (d, J = 7.3 Hz, 1H), 7.29 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.8 (C) 135.4 (C), 132.0 (CH), 129. (CH), 128.8 (CH), 128.5 (CH), 127.9 (C), 126.7 (m, CH), 125.9 (CH), 125.8 (CH), 123.8 (d, J = 175 Hz, (C), 122.6 (q, J = 32.2 Hz, C), 121.2 (C), 113.1 (CH), 104.2 (C), 78.5 (C); IR (neat): 3303, 3064, 3029, 2360, 2187, 1612, 1533, 1488, 1419, 1321, 1267, 1551, 1095, 1060, 829, 752, 682 cm^{-1}; MS (ESI, *m/z*): 387.11 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{22}H_{15}F_3N_2Na$: 387.1085 $[M+Na]^+$; Found: 387.1080.

(*Z*)-1-(3-Chloro-4-fluorophenyl)-2-(1,3-diphenylprop-2-yn-1-ylidene)hydrazine (*Z*-186y) (Table 1, Entry 25). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 65 % of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (brs, 1H), 7.98 (d, J = 7.6 Hz, 2H), 7.64 (m, 2H), 7.46 (m, 5H), 7.37 (d, J = 6.9 Hz, 1H), 7.31 (m, 1H), 7.09 (t, J = 8.7 Hz, 1H), 7.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0 (d, J = 240.5 Hz, C), 140.5 (C), 135.5 (C), 131.9 (CH), 129.8 (CH), 128.8 (CH), 128.6 (CH), 128.4 (CH), 126.9 (CH), 125.6 (CH), 121.6 (d, J = 18.5 Hz, C), 121.3 (C), 116.9 (d, J = 22.3 Hz, CH), 115.0 (CH), 112.6 (d, J = 6.2 Hz, CH), 104.1 (C), 78.6 (C); IR (neat): 3305, 3053, 3024, 2185, 1606, 1506, 1488, 1442, 1207, 1157, 835, 812, 752, 680 cm^{-1}; MS (ESI, *m/z*): 371.07 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{21}H_{14}ClFN_2Na$: 371.0727 $[M+Na]^+$; Found: 371.0722.

(*Z*)-1-(2,5-Difluorophenyl)-2-(1,3-diphenylprop-2-yn-1-ylidene)hydrazine (*Z*-186z) (Table 1, Entry 26). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 36% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.93 (brs, 1H), 8.01 (d, J = 7.5 Hz, 2H), 7.65 (m, 2H), 7.45 (m, 5H), 7.40 (m, 2H), 7.02 (m, 1H), 6.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4 (d, J = 239 Hz, C), 145.7 (d, J = 235.5 Hz, C), 134.7 (C), 132.8 (t, J = 11.5 Hz, C), 131.6 (CH), 129.4 (CH), 128.6 (C),128.4 (CH), 128.3 (CH), 128.0 (CH), 125.3 (CH), 120.7 (C), 115.0 (dd, J = 9.4 Hz, J = 20 Hz, CH), 105.3 (dd, J = 7.5 Hz, J = 24.6 Hz, CH), 104.3 (C), 101.6 (d, J = 29.1 Hz, CH), 78.0 (C); IR (neat): 3317, 3056, 2920, 2360,

2185, 1633, 1529, 1496, 1461, 1436, 1346, 1288 1247, 1182, 1157, 839, 785, 752, 729, 686 cm^{-1}; MS (ESI, *m/z*): 355.10 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{21}H_{14}F_2N_2Na$: 355.1023 $[M+Na]^+$; Found: 355.1017.

(*Z*)-1-Phenyl-2-(3-ferrocenylprop-2-yn-1-ylidene)hydrazine (*Z*-199a) (Table 2, Entry 1). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 48% and 54% of the indicated product by using Condition A and B, respectively. ^1H NMR (400 MHz, $CDCl_3$): δ 8.64 (brs, 1H, NH), 7.32 (t, J = 7.3 Hz, 2H), 7.13 (d, J = 7.6 Hz, 2H), 6.94 (t, J = 7.3 Hz, 1H), 6.55 (s, 1H), 4.57 (s, 2H), 4.35 (s, 2H), 4.29 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7 (C), 129.4 (CH), 120.4 (CH), 115.7 (CH), 113.2 (CH), 102.4 (C), 76.5 (C), 71.8 (CH), 70.3 (CH), 69.7 (CH), 62.9 (C); IR (neat): 3303, 2360, 2204, 2160, 1602, 1560, 1519, 1488, 1259, 1147, 1105, 1018, 999, 875, 810, 750, 692 cm^{-1}; MS (ESI, *m/z*): 351.06 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{19}H_{16}FeN_2Na$: 351.0559 $[M+Na]^+$; Found: 351.0555.

(*E*)-1-Phenyl-2-(3-ferrocenylprop-2-yn-1-ylidene)hydrazine (*E*-199a) (Table 2, Entry 1). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 45% and 36% of the indicated product by using Condition A and B, respectively. ^1H NMR (400 MHz, $CDCl_3$): δ 7.95 (brs, 1H, NH), 7.27 (t, J = 7.9 Hz, 2H), 7.08 (d, J = 7.9 Hz, 2H), 7.03 (s, 1H), 6.90 (t, J = 7.3 Hz, 1H), 4.51 (s, 2H), 4.27 (s, 2H), 4.25 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7 (C), 129.3 (CH), 120.8 (CH), 120.4 (C), 113.12 (CH), 92.2 (C), 82.0 (C), 71.6 (CH), 70.1 (CH), 69.2 (CH), 64.3 (C); IR (neat): 3305, 2204, 2160, 1602, 1560, 1519, 1490, 1348, 1261, 1147, 1105, 1018, 999, 875, 810, 750, 692 cm^{-1}; MS (ESI, *m/z*): 351.06 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{19}H_{16}FeN_2Na$: 351.0559 $[M+Na]^+$; Found: 351.0555.

(*Z*)-1-(3-(Ferrocenyl)prop-2-yn-1-ylidene)-2-(4-(trifluoromethyl)phenyl) hydrazine (*Z*-199b) (Table 2, Entry 2). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 45% and 43% of the indicated product by using Condition A and B, respectively. ^1H NMR (400 MHz, $CDCl_3$): δ 8.72 (brs, 1H, NH), 7.54 (d, J = 7.5 Hz, 2H), 7.16 (d, J = 7.6 Hz, 2H), 6.60 (s, 1H), 4.57 (s, 2H), 4.37 (s, 2H), 4.28 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.2 (C), 126.7 (m, CH), 124.6 (d, J =

269.5 Hz, C), 122.5 (q, *J* = 32.3 Hz, C), 117.8 (CH), 112.8 (CH), 103.2 (C), 76.0 (C), 71.9 (CH), 70.4 (CH), 69.9 (CH), 62.4 (C); IR (neat): 3325, 2187, 1614, 1542, 1523, 1323, 1263, 1091, 1058, 1001, 821 cm^{-1}. MS (ESI, *m/z*): 419.04 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{20}H_{15}F_3FeN_2Na$: 419.0433 $[M+Na]^+$; Found: 419.0429.

(*E*)-1-(3-(Ferrocenyl)prop-2-yn-1-ylidene)-2-(4-(trifluoromethyl)phenyl) hydrazine (*E*-199b) (Table 2, Entry 2). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 30% and 50% of the indicated product by using Condition A and B, respectively. ^1H NMR (400 MHz, $CDCl_3$): δ 8.09 (brs, 1H, NH), 7.51 (d, *J* = 7.2 Hz, 2H), 7.13 (d, *J* = 7.4 Hz, 2H), 7.09 (s, 1H), 4.53 (s, 2H), 4.29 (s, 2H), 4.26 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.2 (C), 126.6 (m, CH), 124.6 (d, *J* = 268.8 Hz, C), 122.4 (d, *J* = 33 Hz, C), 122.3 (CH), 112.6 (CH), 93.5 (C), 81.6 (C), 71.7 (CH), 70.2 (CH), 69.4 (CH), 63.6 (C); IR (neat): 3315, 2202, 1616, 1533, 1326, 1661, 1155, 1103, 1064, 894, 813 cm^{-1}; MS (ESI, *m/z*): 419.04 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{20}H_{15}F_3FeN_2Na$: 419.0433 $[M+Na]^+$; Found: 419.0429.

(*Z*)-1-(3-Chloro-4-fluorophenyl)-2-(3-ferrocenylprop-2-yn-1-ylidene)hydrazine (*Z*-199c) (Table 2, Entry 3). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 47% and 40% of the indicated product by using Condition A and B, respectively. ^1H NMR (400 MHz, $CDCl_3$): δ 8.50 (brs, 1H), 7.20 (m, 1H), 7.06 (t, J: 8.6 Hz, 1H), 6.92 (m, 1H), 6.55 (s, 2H), 4.56 (s, 2H), 4.36 (s, 2H), 4.28 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.6 (d, *J* = 239.5 Hz, C), 140.6 (C), 121.6 (d, *J* = 18.5 Hz, C), 117.1 C, 116.8 (CH), 114.8 (CH), 112.2 (d, *J* = 6.2 Hz, CH), 103.1 (C), 76.2 (C), 71.8 (CH), 70.3 (CH), 69.9 (CH), 62.5 (C); IR (neat): 3303, 3093, 2181, 1606, 1492, 1411, 1330, 1251, 1207, 1143, 1105, 1047, 1001, 812, 732 cm^{-1}; MS (ESI, *m/z*): 403.01 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{19}H_{14}ClFFeN_2Na$: 403.0076 $[M+Na]^+$; Found: 403.0072.

(*E*)-1-(3-Chloro-4-fluorophenyl)-2-(3-ferrocenylprop-2-yn-1-ylidene)hydrazine (*E*-199c) (Table 2, Entry 3). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 52% and 60% of the indicated product by using Condition

A and B, respectively. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (brs, 1H), 7.19 (m, 1H), 7.03 (m 2H), 6.86 (m, 1H), 4.52 (s, 2H), 4.28 (s, 2H), 4.26 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.6 (d, J = 239.5 Hz, C), 140.6 (C), 121.6 (d, J = 18.5 Hz, C), 117.1 C, 116.8 (CH), 114.8 (CH), 112.2 (d, J = 6.2 Hz, CH), 103.1 (C), 76.2 (C), 71.8 (CH), 70.3 (CH), 69.9 (CH), 62.5 (C); MS (ESI, *m/z*): 403.01 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{19}H_{14}ClFFeN_2Na$: 403.0076 $[M+Na]^+$; Found: 403.0072.

(*Z*)-1-(2,5-Difluorophenyl)-2-(3-ferrocenylprop-2-yn-1-ylidene)hydrazine (*Z*-199d) (Table 2, Entry 4). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 58% and 56% of the indicated product by using Condition A and B, respectively. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81 (brs, 1H), 7.23 (m, 1H), 7.00 (m, 1H), 6.64 (s, 1H), 6.50 (m, 1H), 4.57 (s, 2H), 4.36 (s, 2H), 4.28 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8 (d, J = 239 Hz, C), 145.9 (d, J = 235.5 Hz, C), 133.3 (t, J = 11.3 Hz, C), 118.9 (CH), 115.5 (dd, J = 20 Hz, J = 10 Hz, CH), 105.7 (dd, J = 24.5 Hz, J = 7.5 Hz, CH), 103.8 (C), 101.9 (dd, J = 2.3, J = 28.4 Hz, CH), 76.0 (C), 71.9 (CH), 70.4 (CH), 69.9 (CH), 62.2 (C); IR (neat): 3325, 3093, 2189, 1633, 1521, 1452, 1342, 1247, 1182, 1153, 1118, 1004, 817, 754 cm^{-1}; MS (ESI, *m/z*): 387.04 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{19}H_{14}F_2FeN_2Na$: 387.0371 $[M+Na]^+$; Found: 387.0367.

(*E*)-1-(2,5-Difluorophenyl)-2-(3-ferrocenylprop-2-yn-1-ylidene)hydrazine (E-199d) (Table 2, Entry 4). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 42% and 40% of the indicated product by using Condition A and B, respectively. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (brs, 1H), 7.27 (m, 1H), 7.13 (s, 1H), 6.95 (m, 1H), 6.47 (m, 1H), 4.59 (s, 2H), 4.32 (s, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7 (d, J = 239 Hz, C), 145.6 (d, J = 233 Hz, C), 133.0 (t, J = 11.9 Hz, C), 126.2 (CH), 115.4 (dd, J = 20 Hz, J = 9.5 Hz, CH), 105.7 (dd, J = 25 Hz, J = 7.5 Hz, CH), 102.2 (d, J = 31 Hz, CH), 93.7 (C), 81.4 (C), 71.7 (CH), 70.2 (CH), 69.5 (CH), 63.8 (C); IR (neat): 3321, 3087, 2185, 1631, 1517, 1450, 1338, 1290, 1244, 1184, 1157, 1107, 1001, 977, 815, 734 cm^{-1}; MS (ESI, *m/z*): 387.04 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{19}H_{14}F_2FeN_2Na$: 387.0371 $[M+Na]^+$; Found: 387.0367.

(*Z*)-2-(2-(3-Ferrocenylprop-2-yn-1-ylidene)hydrazinyl)ethanol (*Z*-199e) (Table 2, Entry 5). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 49% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.42 (s, 1H), 4.49 (s, 2H), 4.29 (s, 2H), 4.23 (s, 5H), 3.85 (t, 2H), 3.47 (t, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 116.9 (CH), 101.5 (C), 71.7 (CH), 70.2 (CH), 70.0 (C), 69.5 (CH), 63.1 (C), 62.3 (CH_2), 51.9 (CH_2); IR (neat): 3253 b, 2185, 1529, 1467, 1409, 1340, 1164, 1105, 1058, 1022, 1001, 815 cm^{-1}; MS (ESI, *m/z*): 319.05 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{15}H_{16}FeN_2ONa$: 319.0509 $[M+Na]^+$; Found: 319.0504.

4.6 General procedure for the synthesis of 4-iodopyrazoles

4.6.1 General procedure for the synthesis of 1,5-diaryl/alkyl-4-iodo-1*H*-pyrazole (187a-k) (Table 4)

To a stirred solution of iodine (0.75 mmol) and $NaHCO_3$ (0.75 mmol) in CH_2Cl_2 (5 mL) was added appropriate α,β-alkynic hydrazone (0.25 mmol) in CH_2Cl_2 (2 mL), and the solution was allowed to stir at room temperature under Argon for 2 h. After the reaction was over, the excess I_2 was removed by washing with a saturated aqueous solution of $Na_2S_2O_3$. The aqueous solution was then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under a vacuum to yield the crude product, which was purified by flash chromatography.

4-Iodo-1,5-diphenyl-1*H*-pyrazole (187a) (Table 4, Entry 1). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 80% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.29 (m, 3H), 7.19 (m, 5H), 7.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.5, 143.5, 139.9, 130.3, 129.6, 129.0, 128.8, 128.5, 127.6, 124.7, 62.3; IR (neat): 3029, 2923, 2852, 1595, 1492, 1444, 1377,

1066, 943, 844, 758 cm^{-1}; MS (ESI, *m/z*): 368.98 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{15}H_{11}IN_2Na$: 368.9865 $[M+Na]^+$; Found: 368.9859.

4-Iodo-1-phenyl-5-(*p*-tolyl)-1*H*-pyrazole (187b) (Table 4, Entry 2). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 85% of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 7.72 (s, 1H), 7.23 (m, 3H), 7.14 (m, 4H), 6.83 (d, J = 8.3 Hz, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9 (C), 145.3 (CH), 143.4 (C), 140.0 (C), 131.6 (CH), 128.8 (CH), 127.5 (CH), 124.7 (CH), 121.7 (C), 113.9 (CH), 62.2 (C), 55.2 (CH_3); IR (neat): 3101, 2914, 2852, 1595, 1496, 1434, 1380, 1315, 1068, 943, 914, 858, 815, 761 cm^{-1}; MS (ESI, *m/z*): 383.00 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{16}H_{13}IN_2Na$: 383.0021 $[M+Na]^+$; Found: 383.0016.

4-Iodo-5-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole (187c) (Table 4, Entry 3). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 84% of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 7.72 (s, 1H) , 7.23 (m, 3H), 7.14 (m, 4H), 6.83 (d, J = 8.3 Hz, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9 (C), 145.3 (CH), 143.4 (C), 140.0 (C), 131,6 (CH), 128.8 (CH), 127.5 (CH), 124.7 (CH), 121.7 (C), 113.9 (CH), 62.2 (C), 55.2 (CH_3); IR (neat): 2912, 1595, 1496, 1434, 1380, 1315, 1068, 943, 914, 858, 815, 761 cm^{-1}; MS (ESI, *m/z*): 399.00 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{16}H_{13}IN_2ONa$: 398.9970 $[M+Na]^+$; Found: 398.6665.

4-Iodo-1-phenyl-5-(thiophen-3-yl)-1*H*-pyrazole (187d) (Table 4, Entry 4). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 83% of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.29 (dd, J = 1.0 Hz, J = 2.9 Hz, 1H), 7.22 (m, 2H), 7.19 (m, 2H), 7.16 (d, J = 1.7 Hz, 1H), 7.14 (m, 1H), 6.79 (d, J=4.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.6 (CH), 139.9 (C), 139.4 (C), 129.3 (C), 128.9 (CH), 128.2 (CH), 127.9 (CH), 126.8 (CH), 125.8 (CH), 124.8 (CH), 62.2 (C); IR (neat): 3091, 2954, 2921, 2852, 1593, 1498, 1444, 1375, 1182,

1066, 943, 854, 786, 761 cm^{-1}; MS (ESI, *m/z*): 374.94 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{13}H_9IN_2SNa$: 374.9429 $[M+Na]^+$; Found: 374.9423.

4-Iodo-5-pentyl-1-phenyl-1*H*-pyrazole (187e) (Table 4, Entry 5). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 47% of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 7.59 (s, 1H), 7.44 (m, 3H), 7.35 (d, J = 7.6 Hz, 2H), 2.67 (t, J = 8 Hz, 2H), 1.44 (p, J = 7.39 Hz, 2H), 1.23 (m, 4H), 0.8 (t, J= 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.6 (C), 144.5 (CH), 139.9 (C), 129.2 (CH), 128.5 (CH), 125.5 (CH), 60.6 (C), 31.2 (CH_2), 28.2 (CH_2), 25.7 (CH_2), 22.0 (CH_2), 13.8 (CH_3); IR (neat): 2954, 2925, 2858, 1596, 1500, 1456, 1390, 1174, 933, 846, 761 cm^{-1}; MS (ESI, *m/z*): 363.03 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{14}H_{17}IN_2Na$: 363.0334 $[M+Na]^+$; Found: 363.0329.

5-(Cyclopentylmethyl)-4-iodo-1-phenyl-1*H*-pyrazole (187f) (Table 4, Entry 6). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 47% of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 7.59 (s, 1H), 7.43 (m, 3H), 7.36 (m, 2H), 2.74 (d, J = 7.6 Hz, 2H), 1.91 (p, 1H), 1.49 (m, 4H), 1.38 (m, 2H), 1.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.6 (CH), 144.3 (C), 140.2 (C), 129.2 (CH), 128.9 (CH), 125.8 (CH), 61.3 (C), 39.6 (CH), 32.7 (CH_2), 31.0 (CH_2), 24.6 (CH_2); MS (ESI, *m/z*): 375.03 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{15}H_{17}IN_2Na$: 375.0334 $[M+Na]^+$; Found: 375.0329.

4-iodo-5-(*p*-tolyl)-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (187g) (Table 4, Entry 7). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 40% of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 1H) , 7.56 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 7.9 Hz, 2H), 7.15 (d, J = 7.9 Hz, 2H) , 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.1 (CH), 143.9 (C), 142.5 (C), 139.5 (C), 130.0 (CH), 129.4 (CH), 129.2 (q, J = 32.5 Hz, C), 126.2 (C), 126.0 (m, CH), 124.3 (CH), 123.7 (d, J = 271 Hz, C), 63.6 (C), 21.4 (CH_3); MS (ESI, *m/z*): 450.99 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{17}H_{12}F_3IN_2Na$: 450.9895 $[M+Na]^+$; Found: 450.9889.

1-(3-Chloro-4-fluorophenyl)-4-iodo-5-(*p*-tolyl)-1*H*-pyrazole (187h) (Table 4, Entry 8). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 41% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.40 (dd, J = 2.30, 6.4 Hz), 7.18 (d, J = 7.9, 2H), 7.11 (d, J = 7.9 Hz, 2H), 6.99 (t, J = 8.7 Hz, 1H), 6.94 (m, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.0 (d, J = 249.5 Hz, C), 145.8 (CH), 143.8 (C), 139.5 (C), 136.4 (C), 130.0 (CH), 129.5 (CH), 126.9 (CH), 125.9 (C), 124.3 (d, J = 7.5 Hz, CH), 121.4 (d, J = 19.5 Hz, C), 116.5 (d, J = 22.5 Hz, CH), 62.9 (C), 21.5 (CH_3); IR (neat): 2921, 2850, 1598, 1498, 1438, 1406, 1384, 1259, 1230, 1053, 952, 867, 844, 813, 717 cm^{-1}; MS (ESI, *m/z*): 434.95 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{16}H_{11}ClFIN_2Na$: 434.9537 $[M+Na]^+$; Found: 434.9532.

4-Iodo-5-(4-methoxyphenyl)-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (187i) (Table 4, Entry 9). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 85% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (s, 1H) , 7.53 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.3 Hz, 2H), 7.16 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 8.5 Hz, 2H) , 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3 (C), 146.1 (CH), 143.7 (C), 142.6 (C), 131.5 (CH), 129.2 (q, J = 33.3 Hz, C), 126.0 (CH), 124.3 (CH), 123.7 (d, J = 271 Hz, C), 121,3 (C), 114.3 (CH), 63.6 (C), 55.3 (CH_3); IR (neat): 2966, 2939, 2839, 1612, 1544, 1519, 1490, 1377, 1323, 1249, 1166, 1109, 1058, 1028, 941, 831 cm^{-1}; MS (ESI, *m/z*): 466.98 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{17}H_{12}F_3IN_2ONa$: 466.9844 $[M+Na]^+$; Found: 466.9839.

1-(3-Chloro-4-fluorophenyl)-4-iodo-5-(4-methoxyphenyl)-1*H*-pyrazole (187j) (Table 4, Entry 10). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 95% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.42 (m, 1H), 7.18 (d, J = 8.5 Hz, 2H) , 7.01 (m, 2H) , 6.93 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3 (C), 157.0 (d , J = 248.5 Hz, C) , 145.8 (CH), 143.7 (CH), 136.5 (C), 131.5 (CH), 126.9 (CH), 124.2 (CH), 121.4 (d, J = 18.4 Hz, C), 121.0 (C), 116.5 (d, J = 22.1 Hz, CH), 114.3 (CH), 62.9 (C), 55.3 (CH_3);. IR (neat): 2933, 2837, 1612, 1542, 1498, 1434, 1375, 1249, 1176, 1029, 948, 831, 719

cm^{-1}; MS (ESI, *m/z*): 450.94 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{17}H_{15}ClIN_2ONa$: 450.9481 $[M+Na]^+$; Found: 450.9486.

1-(2,5-Difluorophenyl)-4-iodo-5-(4-methoxyphenyl)-1*H*-pyrazole (187k) (Table 4, Entry 11). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 74% of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.17 (d, J = 8.6 Hz, 2H), 7.12 (m, 1H), 6.99 (m, 2H), 6.84 (d, J = 8.6Hz, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2 (C), 158.0 (d, J = 244, C), 152.6 (d, J = 248.5 Hz, C), 146.5 (CH), 145.4 (CH), 130.9 (CH), 128.5 (C), 120.8 (C), 117.4 (dd , J = 9.1, J = 22.8 Hz, CH) , 116.9 (dd, J = 7.5 Hz, J = 23.8 Hz, CH), 115.8 (d, J = 25.7 Hz, CH), 113.9 (CH), 61.5 (C), 55.2 (CH_3); IR (neat): 2981, 2943, 1616, 1542, 1508, 1488, 1461, 1425, 1365, 1288, 1249, 1205, 1178, 1110, 1026, 952, 867, 815, 767 cm^{-1}; MS (ESI, *m/z*): 434.97 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{16}H_{11}F_2IN_2ONa$: 434.9782 $[M+Na]^+$; Found: 434.9776.

4.6.2 General Procedure for the synthesis of 4-iodo-1,3,5-aryl/alkyl-1*H*-pyrazole (187l-r) (Table 4)

To a stirred solution of the iodine (0.75 mmol) and $NaHCO_3$ (0.75 mmol) in CH_3CN (5 mL) was added appropriate α,β-alkynic hydrazone (0.25 mmol) in CH_3CN (2 mL), and the solution was allowed to stir 80 ^0C under argon for 2 h. After the reaction was over, the excess I_2 was removed by washing with a saturated aqueous solution of $Na_2S_2O_3$. The aqueous solution was then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under a vacuum to yield the crude product, which was purified by flash chromatography.

4-Iodo-3-methyl-1,5-diphenyl-1*H*-pyrazole (187l) (Table 4, Entry 12). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 92% of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (m, 3H), 7.28 (m, 5H), 7.21 (d, J = 8.4 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7 (C), 144.1

(C), 139.9 (C), 130.3 (C), 130.2 (CH), 128.8 (CH), 128.7 (CH), 128.4 (CH), 127.3 (CH), 124.7 (CH), 66.2 (C), 14.4 (CH_3); IR (neat): 2921, 2852, 1596, 1504, 1440, 1407, 1379, 1357, 1047, 966, 916, 840, 767 cm^{-1}; MS (ESI, *m/z*): 383.00 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{16}H_{13}IN_2Na$: 383.0021 $[M+Na]^+$; Found: 383.0016. The spectral data were in agreement with those reported previously for this compound [186].

4-Iodo-3-methyl-5-phenyl-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (187m) (Table 4, Entry 13). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 93% of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, J = 8.4, 2H), 7.43 (m, 3H), 7.34 (d, J = 8.4 Hz, 2H), 7.30 (m,2H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.5 (C), 144.3 (C), 142.6 (C), 130.1 (CH) , 129.9 (C), 129.3 (CH), 128.9 (q, J = 32.5 Hz , C), 128.8 (CH), 126.0 (m, CH), 124.1 (CH), 123.7 (d, J = 271.3 Hz, C), 67.7 (C), 14.4 (CH_3); IR (neat): 2958, 2925, 1614, 1519, 1492, 1444, 1402, 1357, 1319, 1164, 1124, 1064, 1045, 964, 844, 752 cm^{-1}; MS (ESI, *m/z*): 450.99 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{17}H_{12}F_3IN_2Na$: 450.9895 $[M+Na]^+$; Found: 450.9889.

1-(3-Chloro-4-fluorophenyl)-4-iodo-3-methyl-5-phenyl-1*H*-pyrazole (187n) (Table 4, Entry 14). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 81% of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, 4H), 7.17 (m, 2H), 6.87 (m, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9 (d, J = 248.5 Hz, C), 152.2 (C), 144.3 (C),136.5 (C), 130.1 (CH), 129.7 (C), 129.3 (CH), 128.7 (CH), 126.8 (CH), 124.1 (d, J = 7.5 Hz, CH), 121.4 (d, J = 19 Hz, C), 116.4 (d, J = 21.8 Hz, CH), 66.8 (C), 14.3 (CH_3);. IR (neat): 3041, 2920, 2850, 1596, 1502, 1444, 1400, 1380, 1359, 1263, 1230, 1172, 1134, 1047, 974, 869, 829, 771 cm^{-1}; MS (ESI, *m/z*): 412.97 $[M+H]^+$; HRMS (ESI): calcd. for $C_{16}H_{12}ClFIN_2Na$: 412.9718 $[M+Na]^+$; Found: 412.9712.

1-(2,5-Difluorophenyl)-4-iodo-3-methyl-5-phenyl-1*H*-pyrazole (187o) (Table 4, Entry 15). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 86%

of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (m, 3H), 7.30 (m, 2H), 7.16 (m, 2H), 6.99 (m, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158. (d, J = 244 Hz, C), 152.8 (C), 152.6 (d, J = 250 Hz, C), 146.0 (C), 129.4 (CH), 129.3 (C), 129.1 (CH), 128.9 (C), 128.4 (t, J = 10.7 Hz, C), 128.4 (CH), 117.4 (dd, J = 9.2 Hz, J = 22.5 Hz, CH), 116.7 (dd, J = 7.5 Hz, J = 24.1 Hz, CH), 115.7 (d, J = 25.5 Hz, CH), 65.6 (C), 14.5 (CH_3); IR (neat): 3080, 2923, 1623, 1508, 1488, 1434, 1394, 1352, 1251, 1195, 1166, 1043, 871, 819, 761, 750 cm^{-1}; MS (ESI, *m/z*): 418.98 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{16}H_{11}F_2IN_2Na$: 418.9833 $[M+Na]^+$; Found: 418.9837.

4-Iodo-1,3,5-triphenyl-1*H*-pyrazole (187p) (Table 4, Entry 16). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 66% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 7.3 Hz, 2H), 7.5 (m, 2H), 7.40 (m, 4H), 7.37 (m, 2H), 7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0 (C), 145.4 (C), 139.9 (C), 132.9 (C), 130.6 (CH), 130.3 (C), 129.1 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 127.5 (CH), 124.8 (CH), 63.6 (C); IR (neat): 3066, 2923, 1591, 1490, 1450, 1396, 1350, 1147, 1072, 1028, 960, 912, 758 cm^{-1}; MS (ESI, *m/z*): 445.02 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{21}H_{15}$ IN_2Na: 445.0178 $[M+Na]^+$; Found: 445.0172. The spectral data were in agreement with those reported previously for this compound [**Hata! Yer işareti tanımlanmamış.**c].

4-Iodo-3,5-diphenyl-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (187q) (Table 4, Entry 17). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 89% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 7.2 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H), 7.33 (m, 8H), 7.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7 (C), 145.6 (C), 142.5 (C), 132.4 (C), 130.5 (CH), 130.0 (C), 129.5 (CH), 159.2(q, J = 32.5 Hz, C), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 126.0 (m, CH), 124.3 (CH), 123.7 (d, J = 270.5 Hz, C), 65.0 (C); IR (neat): 3056, 2925, 1614, 1523, 1436, 1321, 1151, 1119, 1062, 1018, 960, 839, 761 cm^{-1}; MS (ESI, *m/z*): 513.01 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{22}H_{14}F_3IN_2Na$: 513.0051 $[M+Na]^+$; Found: 513.0046.

1-(2,5-Difluorophenyl)-4-iodo-3,5-diphenyl-1*H*-pyrazole (187r) (Table 4, Entry 18). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 74% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 7.4 Hz, 2H), 7.5 (m, 3H), 7.40 (m, 5H7.28 (m, 1H), 7.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.01 (d, J = 244.3 Hz, C), 154.2 (C), 152.6 (d, J = 244.5 Hz, C), 147.4 (C), 132.5 (C), 129.9 (CH), 129.3 (CH), 128.71 (C), 128.7 (C), 128.65 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 117.4 (dd , J = 9.2 Hz, J = 22.4 Hz, CH) , 117.0 (dd, J = 7.5 Hz, J = 23.6 Hz, CH), 115.9 (d, J = 25.7 Hz, CH), 62.9 (C); IR (neat): 2921, 2852, 1620, 1498, 1473, 1442, 1344, 1251, 1195, 1147, 1112, 1029, 972, 867, 812, 763 cm^{-1}; MS (ESI, *m/z*): 481.00 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{21}H_{13}F_2IN_2Na$: 480.9989 $[M+Na]^+$; Found: 480.9984.

4.6.3 General procedure for the synthesis of 1-aryl-5-ferrocenyl-4-iodo-1*H*-pyrazole (200) (Table 6)

To a stirred solution of the iodine (0.75 mmol) and $NaHCO_3$ (0.75 mmol) in CH_3CN (5 mL) was added appropriate α,β-alkynic hydrazone (0.25 mmol) in CH_3CN (2 mL), and the solution was allowed to stir at room temperature under Argon for 30 min. After the reaction was over, the excess I_2 was removed by washing with a saturated aqueous solution of $Na_2S_2O_3$. The aqueous solution was then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under a vacuum to yield the crude product, which was purified by flash chromatography.

5-Ferrocenyl-4-iodo-1-phenyl-1*H*-pyrazole (200a) (Table 6, Entry 1). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 90% of the indicated product from ***Z*-199a** and 92% of the indicated product from ***E*-199a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (s, 1H), 7.30 (m, 3H), 7.17 (m, 2H), 4.31 (s, 2H), 4.15 (s, 2H), 4.11 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7 (C), 141.1 (C), 140.8 (C), 128.2 (CH), 128.4 (CH), 126.4 (CH), 74.1 (C), 70.2 (CH), 69.2 (CH), 68.7 (CH), 59.6 (C); IR

(neat): 3080, 2921, 2850, 1595, 1496, 1394, 1377, 1213, 1103, 1029, 995, 943, 840, 813, 767 cm^{-1}; MS (ESI, *m/z*): 476.95 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{19}H_{15}FeIN_2Na$: 476.9527 $[M+Na]^+$; Found: 476.9522.

5-Ferrocenyl-4-iodo-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (200b) (Table 6, Entry 2) . Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 95% of the indicated product from ***Z*-199b** and 76% of the indicated product from ***E*-199b**. ^1H NMR (400 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 4.36 (s, 2H), 4.29 (s, 2H), 4.22 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147,5 (CH), 143.2 (C), 141.3 (C), 130.0 (q, J = 32 Hz, C), 126.2 (CH), 126,2 (m, CH), 123.7 (d, J = 271 Hz, C), 73.95 (C), 70.0 (CH), 69.1 (CH), 68.7 (CH), 60.8 (C); IR (neat): 3116, 2921, 1614, 1519, 1377, 1321, 1163, 1141, 1122, 1107, 1064, 941, 848, 823 cm^{-1}; MS (ESI, *m/z*): 544.94 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{20}H_{14}F_3FeIN_2Na$: 544.9401 $[M+Na]^+$; Found: 544.9396.

1-(3-Chloro-4-fluorophenyl)-5-ferrocenyl-4-iodo-1*H*-pyrazole (200c) (Table 6, Entry 3). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 94% of the indicated product from ***Z*-199c**, and 93% of the indicated product ***E*-199c**. ^1H NMR (400 MHz, $CDCl_3$): δ 7.69 (s, 1H), 7.41 (d, J = 4.8 Hz, 1H), 7.14 (m, 1H), 7.08 (s, 1H), 4.38 (s, 2H), 4.29 (s, 2H), 4.23 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1 (d, J = 249.3 Hz), 146.7, 140.9, 136.6, 128.0, 125.6 (d, J = 7.5 Hz), 120.9 (d, J = 19 Hz), 116.0 (d, J = 22.3 Hz), 72.9, 69.6, 68.5, 68.3, 59.6; MS (ESI, *m/z*): 528.90 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{28}H_{13}ClFFeIN_2Na$: 528.9043 $[M+Na]^+$; Found: 528.9038.

1-(2,5-Difluorophenyl)-5-ferrocenyl-4-iodo-1*H*-pyrazole (200d) (Table 6, Entry 4). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 83% of the indicated product from ***Z*-199d** and 89% of the indicated product from ***E*-199d**. ^1H NMR (400 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.17 (m, 3H), 6.51 (s, 1H), 4.24 (s, 4H), 4.11 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.1 (d, J = 244.6 Hz, C), 153.9 (d, J = 250.9 Hz, C), 143.6 (C), 141.2 (CH), 129.0 (C), 117.3 (m, CH x2), 116.6 (d, J =

25.2 Hz, CH), 105.9 (CH), 74.1 (C), 69.9 (CH), 69.0 (CH), 67.7 (CH); IR (neat): 3083, 2989, 2869, 1625, 1508, 1473, 1415, 1371, 1253, 1180, 1141, 1103, 999, 925, 879, 819, 794, 765 cm^{-1}; MS (ESI, *m/z*): 512.93 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{19}H_{13}F_2FeIN_2Na$: 512.9339 $[M+Na]^+$; Found: 512.9333.

2-(5-Ferrocenyl-4-iodo-1*H*-pyrazol-1-yl)ethanol (200e) (Table 6, Entry 5). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 58% of the indicated product from ***Z*-199e**. ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (s, 1H), 4.74 (s, 2H), 4.57 (b, 2H), 4.42 (s, 2H), 4.25 (s, 5H), 4.07 (b, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.4 (CH), 141.4 (C), 73.7 (C), 69.8 (CH), 69.2 (CH), 68.8 (CH), 61.7 (CH_2), 58.9 (C), 52.2 (CH_2); IR (neat): 3095, 2927, 2871, 1542, 1398, 1369, 1284, 1232, 1105, 1060, 1001, 960, 871, 819, 729 cm^{-1}; MS (ESI, *m/z*): 444.95 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{15}H_{15}FeIN_2ONa$: 444.9476 $[M+Na]^+$; Found: 444.9471.

4. 7 General procedure for the synthesis of pyrazoles (188/201) (Table 7)

To a stirred solution of the α,β-alkynic hydrazone (0.25 mmol) in CH_3CN (7 mL) under argon was added CuI (0.25 mmol) and Et_3N (0.25 mmol), and solution was allowed to stir under reflux for 2 h. After the reaction was over, solvent was evaporated, and the residue was purified by flash column chromatography on silica gel using ethyl acetate/hexane as the eluent to afford the desired product **188**.

1,5-Diphenyl-1*H*-pyrazole (188a) (Table 7, Entry 1). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 77 % of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 7.75 (s, J = 1.6 Hz, 1H), 7.32 (m, 8H), 7.27 (m, 2H), 6.53 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.0, 140.3, 140.2, 130.6, 128.9, 128.8, 128.4, 128.2, 127.4, 125.2, 107.8. The spectral data were in agreement with those reported previously for this compound [24a].

1-Phenyl-5-(*p*-tolyl)-1*H*-pyrazole (188b) (Table 7, Entry 2). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 85% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 1.4 Hz, 1H), 7.35 (m, 5H), 7.15 (m, 4H), 6.51 (d, J = 1.5 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.1 (C), 140.3 (C), 140.2 (CH), 138.1 (C), 129.2 (CH), 128.9 (CH), 128.7 (CH), 127.8 (C), 127.3 (CH), 125.2 (CH), 107.6 (CH), 21.2 (CH_3). IR (neat): 3124, 2979, 2869, 1596, 1496, 1446, 1382, 1128, 1072, 1022, 960, 923, 821, 785, 759 cm^{-1}; MS (ESI, *m/z*): 257.11 $[M+Na]^+$, 235.12 $[M+H]^+$; HRMS (ESI): calcd. for $C_{16}H_{14}N_2Na$: 257.1054 $[M+Na]^+$; Found: 257.1049; calcd. for $C_{16}H_{15}N_2$: 235.1236 $[M+H]^+$; Found: 235.1230. The spectral data were in agreement with those reported previously for this compound [187].

5-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazole (188c) (Table 7, Entry 3). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 85% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 1.0 Hz, 1H), 7.30 (m, 5H), 7.14 (d, J=8.67 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 6.43 (d, J = 1.0 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6 (C), 142.87 (C), 140.3 (C), 140.2 (CH), 130.0 (CH), 128.9 (CH), 127.3 (CH), 125.2 (CH), 123.0 (C), 113.9 (CH), 107.3 (CH), 55.3 (CH_3); IR (neat): 3134, 2929, 2835, 1598, 1496, 1442, 1384, 1288, 1245, 1178, 1130, 1029, 960, 925, 835, 786, 759, 692 cm^{-1}. The spectral data were in agreement with those reported previously for this compound [187].

5-Pentyl-1-phenyl-1*H*-pyrazole (188d) (Table 7, Entry 4). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 65% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 1.4 Hz, 1H), 7.40 (m, 5H), 6.19 (s, 1H), 2.62 (t, J = 7.6 Hz, 2H), 1.57 (p, J = 7.3 Hz, 2H), 1.26 (m, 4H), 0.83 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8 (C), 140.1 (C), 139.8 (CH), 129.0 (CH), 127.8 (CH), 125.4 (CH), 105.3 (CH), 31.4 (CH_2), 28.5 (CH_2), 26.2 (CH_2), 22.3 (CH_2), 13.3 (CH_3); IR (neat): 2954, 2929, 286, 1598, 1537, 1500, 1454, 1394, 1201, 1070, 1012, 923, 761, 694 cm^{-1}; MS (ESI, *m/z*): 237.14 $[M+Na]^+$, 215.15 $[M+H]^+$; HRMS (ESI):

calcd. for $C_{14}H_{18}N_2Na$: 237.1367 $[M+Na]^+$; Found: 237.1362; calcd. for $C_{14}H_{19}N_2$: 215.1549 $[M+H]^+$; Found: 215.1543.

5-Phenyl-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (188e) (Table 7, Entry 5). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 83% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.27 (m, 3H), 7.16 (m, 2H), 6.44 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3 (C), 142.8 (C), 141.1 (CH), 130.3 (C), 129.1 (q, J = 32.8 Hz, C), 128.9 (CH), 128.7 (CH), 128.6 (CH), 126.0 (CH), 124.8 (CH), 123.8 (d, J = 270.5 Hz, C), 108.9 (CH); IR (neat): 3085, 3064, 1618, 1521, 1452, 1421, 1379, 1321, 1164, 1101, 1060, 1014, 956, 920, 846, 827, 794, 758 cm^{-1}; MS (ESI, *m/z*): 311.08 $[M+Na]^+$, 289.10 $[M+H]^+$; HRMS (ESI): calcd. for $C_{16}H_{11}F_3N_2Na$: 311.0771 $[M+Na]^+$; Found: 311.0767; calcd. for $C_{16}H_{12}F_3N_2$: 289.0953 $[M+H]^+$; Found: 289.0947.

1-(3-Chloro-4-fluorophenyl)-5-phenyl-1*H*-pyrazole (188f) (Table 7, Entry 6). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 72% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 1.6 Hz, 1H), 7.50 (dd, J = 6.3, J = 2.1 Hz, 1H), 7.37 (m, 3H), 7.26 (m, 2H), 7.09 (m, 2H), 6.52 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1 (d, J = 248 Hz, C), 143.2 (C), 140.7 (CH), 136.7 (C), 130.0 (C), 128.8 (CH), 128.7 (CH), 128.6 (CH), 127.4 (CH), 124.7 (d, J = 7.5 Hz, CH), 123.4 (d, J = 18.6 Hz, C), 116.5 (d, J = 22.2 Hz, CH), 108.3 (CH); IR (neat): 2989, 2869, 2360, 1502, 1415, 1261, 1218, 1134, 1074, 925, 879, 823, 786, 756, 702 cm^{-1}; MS (ESI, *m/z*): 295.04 $[M+Na]^+$, 273.06 $[M+H]^+$; HRMS (ESI): calcd. for $C_{15}H_{10}ClFN_2Na$: 295.0413 $[M+Na]^+$; Found: 295.0409; calcd. for $C_{15}H_{11}ClFN_2$: 273.0595 $[M+H]^+$; Found: 273.0589.

1-(2,5-Difluorophenyl)-5-phenyl-1*H*-pyrazole (188g) (Table 7, Entry 7). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 87% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 1.2 Hz, 1H), 7.22 (m, 3H), 7.15 (m, 3H), 6.96 (m, 2H), 6.45 (d, J = 1.2 Hz, 1H); ^{13}C NMR (100 MHz,

$CDCl_3$): δ 158.3 (d, J = 244.6 Hz, C), 152.7 (d, J = 244.5 Hz, C), 145.0 (C), 141.5 (CH), 130.0 (C), 129.0 (t, J = 13.6 Hz, C), 128.6 (CH), 128.5 (CH), 127.8 (CH), 117.5 (dd, J = 22 Hz, J = 9 Hz, CH), 116.6 (dd, J = 24.1 Hz, J = 7.5 Hz, CH), 115.9 (d, J = 25.6 Hz, CH), 107.1 (CH); IR (neat): 3082, 1508, 1433, 1369, 1251, 1180, 1130, 923, 887, 871, 812, 763 cm^{-1}. The spectral data were in agreement with those reported previously for this compound [187].

5-(*p*-Tolyl)-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (188h) (Table 7, Entry 8). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 71% of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 1.4 Hz, 1H), 7.57 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 8.3 Hz, 2H), 6.48 (d, J = 1.4 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4 (C), 142.9 (C), 141.0 (CH), 138.7 (C), 129.4 (CH), 129.0 (d, J = 32.5 Hz, C), 128.7 (CH), 127.4 (C), 125.9 (m, CH), 124.8 (CH), 123.9 (d, J = 270 Hz, C), 108.6 (CH), 21.2 (CH_3); IR (neat): 2921, 1616, 1521, 1419, 1379, 1319, 1122, 1060, 956, 920, 844, 817, 777 cm^{-1}; MS (ESI, *m/z*): 325.09 $[M+Na]^+$, 303.11 $[M+H]^+$; HRMS (ESI): calcd. for $C_{17}H_{13}F_3N_2Na$: 325.0929 $[M+Na]^+$; Found: 325.0923; calcd. for $C_{17}H_{14}F_3N_2$: 303.1109 $[M+H]^+$; Found: 303.1104.

1-(3-Chloro-4-fluorophenyl)-5-(*p*-tolyl)-1*H*-pyrazole (188i) (Table 7, Entry 9). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 76% of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 1.4 Hz, 1H), 7.50 (dd, J = 1.9 Hz, J = 6.25 Hz, 1H), 7.13 (m, 4H), 7.08 (m, 2H), 6.47 (d, J = 1.6 Hz, 1H), 2.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.0 (d, J = 248.5 Hz, C), 143.9 (C), 140.7 (CH), 138.6 (C), 136.8 (C), 129.4 (CH), 128.6 (CH), 127.4 (CH), 127.1 (C), 124.8 (d, J = 6.9 Hz, CH), 121.4 (d, J = 19.7 Hz, C), 116.5 (d, J = 22.7 Hz, CH), 107.9 (CH), 21.2 (CH_3); IR (neat): 3066, 2923, 1496, 1417, 1257, 1220, 1136, 1082, 1058, 970, 923, 887, 817, 781, 713 cm^{-1}; MS (ESI, *m/z*): 309.06 $[M+Na]^+$, 287.08 $[M+H]^+$; HRMS (ESI): calcd. for $C_{16}H_{12}ClFN_2Na$: 309.0571 $[M+Na]^+$; Found: 309.0565; calcd. for $C_{16}H_{13}ClFN_2$: 287.0751 $[M+H]^+$; Found: 287.0746.

1-(2,5-Difluorophenyl)-5-(*p*-tolyl)-1*H*-pyrazole (188j) (Table 7, Entry 10). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 95% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 1.0 Hz, 1H), 7.20 (m, 1H), 7.09 (m, 4H), 7.02 (m, 2H), 6.48 (d, J = 1.0 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2 (d, J = 244 Hz, C), 152.8 (d, J = 247.3 Hz, C), 145.1 (C), 141.4 (CH), 138.5 (C), 129.3 (CH), 129.2 (t, J = 10.8 Hz, C), 127.7 (CH), 127.1 (CH), 117.5 (dd, J = 9, J = 22.4 Hz, CH), 116.5 (dd, J = 7.7, J = 23.2 Hz, CH), 115.9 (d, J = 25.8 Hz, CH), 106.9 (CH), 21.2 (CH_3); IR (neat): 3074, 2869, 2623, 1508, 1469, 1433, 1365, 1257, 1180, 1130, 923, 871, 821, 788, 765 cm^{-1}; MS (ESI, *m/z*): 293.09 $[M+Na]^+$, 271.10 $[M+H]^+$; HRMS (ESI): calcd. for $C_{16}H_{12}F_2N_2Na$: 293.0866 $[M+Na]^+$; Found: 293.0861; calcd. for $C_{16}H_{13}F_2N_2$: 271.1047 $[M+H]^+$; Found: 271.1041.

5-(4-Methoxyphenyl)-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (188k) (Table 7, Entry 11). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 87% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 1.2 Hz, 1H), 7.57 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 6.44 (d, J = 1 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9 (C), 143.2 (C), 142.9 (C), 141.0 (CH), 130.1 (CH), 129.1 (q, J = 32.5 Hz, C), 126.0 (m, CH), 124.8 (CH), 123.9 (d, J = 270 Hz, C), 122.6 (C), 114.2 (CH), 108.4 (CH), 55.3 (CH_3); IR (neat): 2846, 1614, 1521, 1498, 1456, 1419, 1384, 1323, 1251, 1161, 1120, 1101, 1062, 1029, 960, 923, 837, 792 cm^{-1}; MS (ESI, *m/z*): 341.09 $[M+Na]^+$, 319.11 $[M+H]^+$; HRMS (ESI): calcd. for $C_{17}H_{13}F_3N_2NaO$: 341.0878 $[M+Na]^+$; Found: 341.0872; calcd. for $C_{17}H_{14}F_3N_2O$: 319.1058 $[M+H]^+$; Found: 319.1053.

1-(3-Chloro-4-fluorophenyl)-5-(4-methoxyphenyl)-1*H*-pyrazole (188l) (Table 7, Entry 12). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 96% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 1.5 Hz, 1H), 7.48 (m, 1H), 7.14 (d, J = 8.6 Hz, 2H), 7.07 (m, 2H), 6.85 (d, J = 8.6 Hz, 2H), 6.43 (d, J = 1.3 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9 (C), 157.0

(d, J = 248.3 Hz, C), 143.1 (C), 140.7 (CH), 136.9 (C), 130.0 (CH), 127.4 (CH), 124.7 (d, J = 7.1 Hz, CH), 122.4 (C), 121.4 (d, J = 19.3 Hz, C), 116.5 (d, J = 22.6 Hz, CH), 114.2 (CH), 107.7 (CH), 55.3 (CH_3); IR (neat): 2960, 2840, 1610, 1548, 1496, 1467, 1442, 1419, 1375, 1301, 1245, 1174, 1134, 1080, 1028, 966, 923, 875, 833, 790, 719 cm^{-1}; MS (ESI, *m/z*): 325.05 $[M+Na]^+$, 303.07 $[M+H]^+$; HRMS (ESI): calcd. for $C_{16}H_{12}ClFN_2NaO$: 325.0520 $[M+Na]^+$; Found: 325.0514; calcd. for $C_{16}H_{13}ClFN_2O$: 303.0700 $[M+H]^+$; Found: 303.0695.

1-(2,5-Difluorophenyl)-5-(4-methoxyphenyl)-1*H*-pyrazole (188m) (Table 7, Entry 13). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 86% of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 7.72 (brs, 1H), 7.19 (m, 1H), 7.13 (d, J = 8.3 Hz, 2H), 7.02 (m, 2H) , 6.80 (d, J = 8.5 Hz, 2H), 6.45 (s,1H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8 (C), 158.2 (d, J = 244.3 Hz, C), 152.8 (d, J = 248.5 Hz, C), 144.9 (C), 141.4 (CH), 129.2 (CH), 129.0 (C), 122.4 (C), 117.5 (dd, J = 9 Hz, J = 22 Hz, CH), 116.5 (dd, J = 7.5 Hz, J = 24.3 Hz, CH), 115.9 (d, J = 25.8 Hz, CH) , 114.0 (CH), 106.6 (CH), 55.2 (CH_3); IR (neat): 3136, 3076, 2972, 2842, 1614, 1573, 1508, 1494, 1434, 1365, 1249, 1178, 1026, 925, 875, 835, 790, 765 cm^{-1}; MS (ESI, *m/z*): 309.08 $[M+Na]^+$, 287.10 $[M+H]^+$; HRMS (ESI): calcd. for $C_{16}H_{12}F_2N_2NaO$: 309.0815 $[M+Na]^+$; Found: 309.0810; calcd. for $C_{16}H_{13}F_2N_2O$: 287.0996 $[M+H]^+$; Found: 287.0990.

5-Pentyl-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (188n) (Table 7, Entry 14). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 89% of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8.31 Hz, 2H), 7.59 (s, 1H), 7.56 (d, J = 8.3 Hz, 2H), 6.23 (s, 1H), 2.67 (t, J = 7.82 Hz, 2H), 1.60 (p, J = 7.3 Hz, 2H), 1.28 (m, 4H), 0.84 (t, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0 (C), 142.9 (C), 140.6 (CH), 129.6 (q, J = 33.1 Hz, C), 126.3 (m, CH), 125.1 (CH), 123.9 (d, J = 270 Hz, C), 106.3 (CH), 31.3 (CH_2), 28.5 (CH_2), 26.4 (CH_2), 22.3 (CH_2), 13.8 (CH_3); IR (neat): 2958, 2931, 2862, 1618, 1523, 1463, 1419, 1394, 1321, 1164, 1122, 1064, 1010, 923, 844, 781 cm^{-1}; MS (ESI, *m/z*): 305.12 $[M+Na]^+$,

283.14 $[M+H]^+$; HRMS (ESI): calcd. for $C_{15}H_{17}F_3N_2Na$: 305.1240 $[M+Na]^+$; Found: 305.1236; calcd. for $C_{15}H_{18}F_3N_2$: 283.1422 $[M+H]^+$; Found: 283.1417.

1-(3-Chloro-4-fluorophenyl)-5-pentyl-1*H*-pyrazole (188o) (Table 7, Entry 15). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 57% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (s, 1H), 7.51 (m, 1H), 7.27 (m, 1H), 7.21 (t, J = 8.6 Hz, 1H), 6.18 (s, 1H), 2.59 (t, J = 7.8 Hz, 2H), 1.57 (p, J = 7.4 Hz, 2H), 1.27 (m, 4H), 0.84 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4 (J = 248.5 Hz, C), 144.0 (C), 140.3 (CH), 136.6 (C), 127.8 (CH), 125.0 (d, J = 9.5 Hz, CH), 121.6 (d, J = 18 Hz, C), 116.7 (d, J = 22.7 Hz, CH), 105.8 (CH), 31.3 (CH_2), 28.4(CH_2), 26.1 (CH_2), 22.3 (CH_2), 13.8 (CH_3); IR (neat): 2956, 2929, 2860, 1598, 1504, 1463, 1413, 1259, 1222, 1064, 923, 879, 819, 781, 731 cm^{-1}. MS (ESI, *m/z*): 289.09 $[M+Na]^+$, 267.11 $[M+H]^+$; HRMS (ESI): calcd. for $C_{14}H_{16}ClFN_2Na$: 289.0883 $[M+Na]^+$; Found: 289.0878; calcd. for $C_{14}H_{17}ClFN_2$: 267.1065 $[M+H]^+$; Found: 267.1059.

1-(2,5-Difluorophenyl)-5-pentyl-1*H*-pyrazole (188p) (Table 7, Entry 16). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 85% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (s, 1H), 7.14 (m, 2H), 7.05 (m, 1H), 6.17 (s, 1H), 2.49 (t, J = 7.73 Hz, 2H), 1.54 (p, 2H), 1.23 (m, 4H), 0.81 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2 (d, J = 244 Hz, C), 153.2 (d, J = 249.3 Hz, C), 145.6 (C), 141.0 (CH), 128.5 (m, C), 117.3 (dd, J = 22.7 Hz, J = 9 Hz, CH), 116.8 (dd, J = 23.4 Hz, J = 7.7 Hz, CH), 116.2 (d, J = 24.8 Hz, CH), 105.0 (CH), 31.2 (CH_2), 28.1 (CH_2), 25.4 (CH_2), 22.2 (CH_2), 13.8 (CH_3); IR (neat): 2956, 2931, 2862, 1625, 1596, 1510, 1458, 1377, 1251, 1174, 923, 894, 867, 813, 763 cm^{-1}; MS (ESI, *m/z*): 273.12 $[M+Na]^+$, 251.14 $[M+H]^+$; HRMS (ESI): calcd. for $C_{14}H_{16}F_3N_2Na$: 273.1178 $[M+Na]^+$; Found: 273.1174; calcd. for $C_{14}H_{17}F_3N_2$: 251.1360 $[M+H]^+$; Found: 251.1354.

3-Methyl-5-phenyl-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (188q) (Table 7, Entry 17). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 78%

of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.24 (m, 3H), 7.14 (m, 2H), 6.23 (s, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.4 (C), 144.0 (C), 142.9 (C), 130.5 (C) , 129.0 (q, J = 9.1 Hz , C), 128.7 (CH), 128.6 (CH) ,128. 5 (CH), 125.9 (m, CH) ,124.6 (CH), 124.6 (d, J = 270 Hz, C), 108.9 (CH), 13.5 (CH_3); IR (neat): 3060, 2925, 2850, 1616, 1519, 1496, 1448, 1411, 1361, 1323, 1162, 1105, 1062, 1036, 966, 840, 760 cm^{-1}; MS (ESI, *m/z*): 325.09 $[M+Na]^+$, 303.11 $[M+H]^+$; HRMS (ESI): calcd. for $C_{17}H_{13}F_3N_2Na$: 325.0929 $[M+Na]^+$; Found: 325.0923; calcd. for $C_{17}H_{14}F_3N_2$: 303.1109 $[M+H]^+$; Found: 303.1104.

1-(3-Chloro-4-fluorophenyl)-3-methyl-5-phenyl-1*H*-pyrazole (188r) (Table 7, Entry 18). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 54% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, J = 5.5 Hz, 1H), 7.35 (m, 3H), 7.24 (m, 2H), 7.05 (m, 2H), 6.32 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9 (J = 248.3 Hz, C), 149.9, 1443.9, 136.7, 131.4, 130.2, 128.6, 128.5, 127.2, 124.6 (d, J = 7.3 Hz), 121.3, 116.4 (d, J = 22.8 Hz), 108.2, 13.5; IR (neat): 3062, 2923, 1602, 1556, 1504, 1452, 1404, 1363, 1259, 1226, 1191, 1080, 1055, 1016, 977, 910, 875, 817, 759 cm^{-1}; MS (ESI, *m/z*): 309.06 $[M+Na]^+$, 287.08 $[M+H]^+$; HRMS (ESI): calcd. for $C_{16}H_{12}ClFN_2Na$: 309.0571 $[M+Na]^+$; Found: 309.0565; calcd. for $C_{16}H_{13}ClFN_2$: 287.0751 $[M+H]^+$; Found: 287.0746.

1-(2,5-Difluorophenyl)-3-methyl-5-phenyl-1*H*-pyrazole (188s) (Table 7, Entry 19). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 77% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, 3H), 7.23 (m, 3H), 7.02 (m, 2H) , 6.35 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2 (d, J = 241.5 Hz, C), 152.8 (d, J = 248.5 Hz, C), 150.7 (C), 145.8 (C), 130.2 (C), 129.1 (t, J = 10.6 Hz, C), 128.5 (CH), 128.4 (CH), 127.7 (CH), 117.4 (dd, J = 9.2 Hz, J = 22.9 Hz, CH), 116.3 (dd, J = 7.5 Hz, J = 23.9 Hz, CH), 115.8 (d, J = 25.1 Hz, CH), 107.1 (CH), 13.6 (CH_3); IR (neat): 3080, 2925, 1623, 1556, 1508, 1496, 1359, 1251, 1201, 1174, 1014, 981, 889, 871, 819, 800, 761 cm^{-1}; MS (ESI, *m/z*): 293.09 $[M+Na]^+$,

271.10 $[M+H]^+$; HRMS (ESI): calcd. for $C_{16}H_{12}F_2N_2Na$: 293.0861 $[M+Na]^+$; Found: 293.0861; calcd. for $C_{16}H_{13}F_2N_2$: 271.1047 $[M+H]^+$; Found: 271.1041.

1,3,5-Triphenyl-1*H*-pyrazole (188t) (Table 7, Entry 20). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 99% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.0 (d, J = 7.4 Hz, 2H), 7.49 (t, J = 7.5 Hz, 2H), 7.43 (m, 3H), 7.35 (m, 8H), 6.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.0 (C), 144.5 (C), 140.3 (C), 133.2 (C), 130.7 (C), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.3 (CH), 128.0 (CH), 127.4 (CH), 125.9 (CH), 125.4 (CH), 105.3 (CH); IR (neat): 3120, 2923, 1595, 1494, 1456, 1361, 1213, 1174, 1066, 970, 920, 791 cm^{-1}; MS (ESI, *m/z*): 297.14 $[M+H]^+$; HRMS (ESI): calcd. for $C_{21}H_{17}N_2$: 297.1392 $[M+H]^+$; Found: 297.1386.

3,5-Diphenyl-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (188u) (Table 7, Entry 21). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 88% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 7.3 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.34 (t, J=7.4 Hz, 2H),7.27 (m, 4H), 7.20 (m, 2H), 6.74 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7 (C), 144.7 (C), 142.9 (C), 132.7 (C), 130.3 (C), 129.0 (d, J = 33 Hz, C), 128.85 (CH), 128.8 (CH), 128.7 (CH), 128.3 (CH), 128.0 (CH) , 126.0 (m, CH) ,125.9 (CH), 124.8 (CH), 123.9 (d, J = 270 Hz, C), 106.3 (CH); IR (neat): 3064, 1612, 1550, 1523, 1483, 1458, 1409, 1363, 1323, 1166, 1107, 1056, 1016, 968, 916, 846, 810, 763 cm^{-1}; MS (ESI, *m/z*): 387.11 $[M+Na]^+$, 365.13 $[M+H]^+$; HRMS (ESI): calcd. for $C_{22}H_{15}F_3N_2Na$: 365.1266 $[M+Na]^+$; Found: 365.1260; calcd. for $C_{22}H_{16}F_3N_2$: 387.1085 $[M+H]^+$; Found: 387.1080.

1-(3-Chloro-4-fluorophenyl)-3,5-diphenyl-1*H*-pyrazole (188v) (Table 7, Entry 22). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 95% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, J = 6.8 Hz, 2H), 7.59 (m, 1H), 7.46 (m, 2H), 7.39 (m, 4H), 7.30 (m, 2H), 7.15 (m, 1H), 7.08 (m, 1H), 6.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1 (d, J = 248.5 Hz, C) , 152.5 (C), 144.6

(C) ,136.8 (C), 136.7 (CH), 132.7 (C), 130.1 (C), 128.8 (CH), 128.7 (CHx2), 128.5 (CH), 127.8 (CH), 125.9 (CH), 124.8 (d, J = 7.5 Hz, CH), 121.4 (d, J = 19.5 Hz, C), 116.5 (d, J = 21.8 Hz, CH), 105.7 (CH); IR (neat): 3060, 1602, 1550, 1498, 1460, 1402, 1363, 1257, 1230, 1209, 1178, 1072, 1028, 979, 954, 908, 875, 852, 817, 758 cm^{-1}; MS (ESI, *m/z*): 371.07 $[M+Na]^+$, 349.09 $[M+H]^+$; HRMS (ESI): calcd. for $C_{21}H_{14}ClFN_2Na$: 371.0727 $[M+Na]^+$; Found: 371.0722; calcd. for $C_{21}H_{15}ClFN_2$: 349.0908 $[M+H]^+$; Found: 349.0902.

1-(2,5-Difluorophenyl)-4-iodo-3,5-diphenyl-1*H*-pyrazole (188w) (Table 7, Entry 23). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 98% of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 7.5 Hz, 2H), 7.47 (t, J = 7.4 Hz, 2H), 7.35 (m, 7H), 7.06 (m, 2H), 6.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3 (d, J = 243.8, Hz, C), 153.2 (C), 152.8 (d, J = 247 Hz, C), 146.5 (C), 132.7 (C), 130.0 (C), 129.8 (t, J = 14.3 Hz, C), 128.7 (CH), 128.65 (CH), 128.6 (CH), 128.3 (CH), 127.8 (CH), 125.9 (CH), 117.5 (dd, J = 9.1 Hz, J = 22 Hz, CH), 116.6 (dd, J = 7.6 Hz, J = 23.2 Hz, CH), 116.0 (d, J = 25.5 Hz, CH), 104.6 (CH); IR (neat): 3078, 1625, 1602, 1546, 1508, 1487, 1456, 1359, 1253, 1215, 1176, 1076, 954, 889, 869, 812, 758 cm^{-1}; MS (ESI, *m/z*): 355.10 $[M+Na]^+$, 333.12 $[M+H]^+$; HRMS (ESI): calcd. for $C_{21}H_{14}ClF_2N_2Na$: 355.1023 $[M+Na]^+$; Found: 355.1017; calcd. for $C_{21}H_{15}ClF_2N_2$: 333.1203 $[M+H]^+$; Found: 333.1198.

5-Ferrocenyl-1-phenyl-1*H*-pyrazole (201a) (Table 7, Entry 24). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 44% of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 7.62 (s, 1H), 7.40 (m, 5H), 6.50 (s,1H), 4.17 (s, 2H), 4.14 (s, 2H), 4.05 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.5 (C), 140.4 (C), 140.0 (CH), 128.8 (CH), 128.0 (CH), 126.1 (CH), 106.8 (CH), 75.1 (C), 69.9 (CH), 68.8 (CH), 68.6 (CH). The spectral data were in agreement with those reported previously for this compound [41].

5-Ferrocenyl-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (201b) (Table 7, Entry 25). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 83% of the

indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.64 (d, J = 7.3 Hz, 2H), 7.49 (d, J = 7.2 Hz, 2H), 6.51 (s, 1H), 4.32 (s, 2H), 4.28 (s, 2H), 4.18 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143,0 (C), 141.7 (C), 140.8 (CH), 129.3 (q, J = 32.3 Hz, C), 125.8 (m, CH), 123.8 (d, J = 270.5 Hz, C), 108.7 (CH), 75.9 (C), 70.6 (CH), 69.8 (CH), 69.4 (CH); IR (neat): 1614, 1521, 1411, 1396, 1384, 1321, 1226, 1174, 1157, 1136, 1107, 1085, 1066, 1004, 972, 920, 871, 846, 817, 790 cm^{-1}; MS (ESI, *m/z*): 419.04 $[M+Na]^+$, 397.06 $[M+H]^+$, 396.05 [M]; HRMS (ESI): calcd. for $C_{20}H_{15}F_3FeN_2Na$: 419.0433 $[M+Na]^+$; Found: 419.0429; calcd. for $C_{20}H_{16}F_3FeN_2$: 397.0615 $[M+H]^+$; Found: 397.0610; calcd. for $C_{20}H_{15}F_3FeN_2$: 396,0536 [M]; Found: 396.0537.

1-(3-Chloro-4-fluorophenyl)-5-ferrocenyl-1*H*-pyrazole (201c) (Table 7, Entry 26). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 67% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (s, 1H), 7.50 (m, 1H), 7.17 (m, 2H), 6.48 (s, 1H), 4.29 (s, 2H), 4.23 (s, 2H), 4.15 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3 (d, J = 248.5 Hz, C), 1441.8 (C), 140.5 (CH), 136.9 (C), 128.1 (CH), 125.5 (d, J = 7.2 Hz, CH), 121.2 (d, J = 18.8 Hz, C), 116.4 (d, J = 22.5 Hz, CH), 107.5 (CH), 75.1 (C), 70.2 (CH), 69.2 (CH x 2); IR (neat): 3043, 1600, 1562, 1502, 1407, 1263, 1215, 1143, 1107, 1085, 1062, 1024, 1002, 975, 921, 867, 815, 783 cm^{-1}; MS (ESI, *m/z*): 403.01 $[M+Na]^+$, 381.03 $[M+H]^+$, 380.02 [M]; HRMS (ESI): calcd. for $C_{19}H_{14}ClFFeN_2Na$: 403.0076 $[M+Na]^+$; Found: 403.0072; calcd. for $C_{19}H_{15}ClFFeN_2$: 381.0258 $[M+H]^+$; Found: 381.0152; calcd. for $C_{19}H_{14}ClFFeN_2$: 380.0179 [M]; Found: 380.0179.

1-(2,5-Difluorophenyl)-5-ferrocenyl-1*H*-pyrazole (201d) (Table 7, Entry 27). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 86% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.17 (m, 3H), 6.51 (s, 1H), 4.24 (s, 4H), 4.11 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.1 (d, J = 244.6 Hz, C), 153.9 (d, J = 250.9 Hz, C), 143.6 (C), 141.2 (CH), 129.0 (m, C), 117.3 (m, CH x2), 116.6 (d, J = 25.2 Hz, CH), 105.9 (CH), 74.1 (C), 69.9 (CH), 69.0 (CH), 67.7 (CH); IR (neat): 3083, 2989, 2869, 1625, 1508, 1473, 1454, 1415, 1253, 1180,

1141, 1103, 999, 925, 879, 819, 794, 765 cm^{-1}; MS (ESI, *m/z*): 387.04 $[M+Na]^+$, 365.06 $[M+H]^+$; HRMS (ESI): calcd. for $C_{19}H_{14}F_2FeN_2Na$: 387.0371 $[M+Na]^+$; Found: 387.0367; calcd. for $C_{19}H_{15}F_2FeN_2$: 365.0553 $[M+H]^+$; Found: 365.0547.

4.8 General procedure for the preparation of amidoximes (190)

Hydroxylamine hydrochloride (15 mmol) was slowly added to a stirred solution of nitrile (10 mmol) and Et_3N (18 mmol) in absolute EtOH (15ml) and the solution was stirred under reflux when nitrile was over. The solvent was removed under reduced pressure to almost dryness. The crude product was extracted with EtOAc, and the combined organics were washed with water and brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel using ethyl acetate/hexane as the eluent to afford the desired product **190**.

***N'*-Hydroxybenzimidamide (190a).** Purification by flash chromatography (1:2 EtOAc/Hexane) afforded 87% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 7.4 Hz, 2H), 7.42 (m 3H), 4.94 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5 (C), 130.3 (C), 127.9 (CH), 126.6 (CH), 123.8 (CH). The spectral data were in agreement with those reported previously for this compound [188].

***N'*-Hydroxy-4-methylbenzimidamide (190b).** Purification by flash chromatography (1:2 EtOAc/Hexane) afforded 55% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7. 54 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 4.97 (brs, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7 (C), 140.2 (C), 129.5 (C), 129.3 (CH), 125.7 (CH), 21.3 (CH_3). The spectral data were in agreement with those reported previously for this compound [188b].

***N'*-Hydroxy-4-methoxybenzimidamide (190c).** Purification by flash chromatography (1:2 EtOAc/Hexane) afforded 72% of the indicated product. ^{1}H

NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 4.87 (brs, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0 (C), 152.6 (C), 127.2 (CH), 124.9 (C), 114.0 (CH), 55.4 (CH_3). The spectral data were in agreement with those reported previously for this compound [188b].

4-Chloro-*N'*-hydroxybenzimidamide (190d). Purification by flash chromatography (1:2 EtOAc/Hexane) afforded 58% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 4.88 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.8 (C), 136.1 (C), 130.9 (C), 128.9 (CH), 127.2 (CH). The spectral data were in agreement with those reported previously for this compound [188b].

4-(Dimethylamino)-*N'*-hydroxybenzimidamide (190e). Purification by flash chromatography (1:2 EtOAc/Hexane) afforded 56% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, J = 8.8 Hz, 2H), 6.69 (d, J = 8.9 Hz, 2H), 4.97 (bs, 2H), 2.99 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7 (C), 150.7 (C), 125.9 (CH), 118.0 (C), 110.8 (CH), 39.1 (CH_3). The spectral data were in agreement with those reported previously for this compound [137a].

***N'*-Hydroxy-1-naphthimidamide (190f).** Purification by flash chromatography (1:2 EtOAc/Hexane) afforded 68% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, J = 8.2 Hz, 2H), 7.90 (m, 2H),7.64 (d, J = 7.0 Hz, 1H), 7.50 (m. 2H), 7.48 (m, 1H), 5.06 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7 (C), 133.7 (C), 131.2 (C), 130.1 (CH), 128.4 (C), 128.3 (CH), 126.9 (CH), 126.8 (CH), 126.2 (CH), 125.4 (CH), 125.1 (CH). The spectral data were in agreement with those reported previously for this compound [189].

2-Chloro-*N'*-hydroxybenzimidamide (190g). Purification by flash chromatography (1:2 EtOAc/Hexane) afforded 60% of the indicated product with mixture of isomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, J = 7.4 Hz, 1H), 7.43 (m, 3H), 5.06 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7 (C), 133.7 (C), 132.6 (C), 131.0 (CH),

130.7 (CH), 130.2 (CH), 127.0 (CH). The spectral data were in agreement with those reported previously for this compound [190].

3-Fluoro-*N′*-hydroxybenzimidamide (190h). Purification by flash chromatography (1:2 EtOAc/Hexane) afforded 74% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (m, 3H), 7.14 (d, J = 8.1 Hz, 1H), 4.95 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8 (d, J = 245 Hz, C), 151.7 (C), 134.5 (d, J = 7.8 Hz, C), 130.3 (d, J = 8 Hz, CH), 121.5 (d, J = 2.5 Hz, CH), 116.9 (d, J = 20.5 Hz, CH), 113.2 (d, J = 23 Hz, CH). The spectral data were in agreement with those reported previously for this compound [148].

***N′*-Hydroxybenzo[d][1,3]dioxole-5-carboximidamide (190i).** Purification by flash chromatography (1:2 EtOAc/Hexane) afforded 35% of the indicated product. ^{1}H NMR (400 MHz, DMSO): δ 9.50 (s, 1H), 7.20 (m, 2H), 6.91 (d, J = 8.7 Hz, 1H), 6.03 (s, 2H), 5.71 (brs, 2H); ^{13}C NMR (100 MHz, DMSO): δ 150.5 (C), 147.8 (C), 147.1 (C), 127.4 (C), 119.3 (CH), 107.8 (CH), 105.7 (CH), 101.1 (CH_2). The spectral data were in agreement with those reported previously for this compound [191].

***N′*-hydroxy-1*H*-indole-4-carboximidamide (190j).** Purification by flash chromatography (1:2 EtOAc/Hexane) afforded 38% of the indicated product. ^{1}H NMR (400 MHz, DMSO): δ 11.1 (s, 1H), 9.54 (s, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.34 (s, 1H), 7.26 (d, J = 7.3 Hz, 1H), 7.11 (t, J = 7.8 Hz, 1H), 6.84 (s, 1H), 5.67 (brs, 1H); ^{13}C NMR (100 MHz, DMSO): δ 152.9 (C), 136.7 (C), 125.8 (CH), 125.6 (C), 125.4 (C), 120.8 (CH), 117.7 (CH), 112.7 (CH), 103.0 (CH). The spectral data were in agreement with those reported previously for this compound [192].

Ferrocenecarboxamide oxime (190k). Purification by flash chromatography (1:2 EtOAc/Hexane) afforded 15% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.69 (brs, 2H), 4.47 (s, 2H), 4.21 (s, 2H), 4.15 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9 (C), 73.4 (C), 69.7 (CH), 68.8 (CH), 67.7 (CH). The spectral data were in agreement with those reported previously for this compound [193].

4. 9 General procedure for the synthesis of conjugate addition products 191

Corresponding propargyl aldehyde/ketone (0.5 mmol) and amidoxime (0.5 mmol) in MeOH (10 mL) were stirrered under reflux for 2 h. After the reaction was over, solvent was evaporated, and the residue was purified by flash column chromatography on silica gel using ethyl acetate/hexane as the eluent to afford the desired product **191**.

***N'*-(((*E*)-3-Oxo-1-phenylprop-1-en-1-yl)oxy)benzimidamide (191a) (Table 9, Entry 1).** Purification by flash chromatography (1:3 EtOAc/Hexane) afforded 84% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.44 (d, J=8.5 Hz, 1H), 7.72 (d, J = 7.3 Hz, 2H), 7.54 (m, 3H), 7.46 (m, 5H), 6.51(d, J = 8.5 Hz, 1H), 5.34 (b, s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.0 (CH), 175.9 (C), 156.1 (C), 132.0 (C), 131.1 (CH), 130.9 (CH), 130.8 (C), 130.0 (CH), 128.8 (CH), 128.5 (CH), 126.5 (CH), 107.8 (CH); IR (neat): 3477, 3363, 3195, 3058, 2858, 1627, 1604, 1585, 1558, 1398, 1340, 1205, 1157, 114, 1080, 1026, 900, 844, 763 cm^{-1}; MS (ESI, *m/z*): 289.10 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{16}H_{14}N_2O_2Na$: 289.0953 $[M+Na]^+$; Found: 289.0947.

***N'*-(((*E*)-3-Oxo-1-(p-tolyl)prop-1-en-1-yl)oxy)benzimidamide (191b) (Table 9, Entry 2).** Purification by flash chromatography (1:3 EtOAc/Hexane) afforded 78% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.51 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 7.2 Hz, 2H), 7.48 (m, 5H), 7.30 (d, J = 7.8 Hz, 2H), 6.51(d, J = 8.4 Hz, 1H), 5.20 (b, s, 2H, NH_2), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.0 (CH), 175.8 (C), 155.8 (C), 141.4 (C), 131.1 (CH), 130.9 (C), 130.0 (CH), 129.2 (CH), 128.8 (CH), 126.4 (CH), 107.7 (CH), 21.5 (CH_3); IR (neat): 3490, 3338, 3182, 2837, 1633, 1585, 1558, 1506, 1394, 1338, 1209, 1157, 1110, 1020, 896, 837, 779,742 cm^{-1}; MS (ESI, *m/z*): 303.11 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{17}H_{16}N_2O_2Na$: 303.1109 $[M+Na]^+$; Found: 303.1104.

***N'*-(((*E*)-1-(4-Methoxyphenyl)-3-oxoprop-1-en-1-yl)oxy)benzimidamide (191c) (Table 9, Entry 3).** Purification by flash chromatography (1:3 EtOAc/Hexane) afforded 85% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.52 (d, J = 8.5 Hz, 1H), 7.75 (d, J = 7.6 Hz, 2H), 7.54 (d, J = 8.5 Hz, 2H), 7.46 (m, 3H), 7.00 (d, J = 8.7 Hz, 2H), 6.47 (d, J = 8.2 Hz, 1H), 5.14 (brs, 2H, NH_2), 3.88 (s, 3H); IR (neat): 3446, 3330, 3284, 3197, 2856, 1652, 1587, 1560, 1506, 1394, 1346, 1299, 1249, 1174, 1110, 1026, 898, 846, 777 cm^{-1}; MS (ESI, *m/z*): 319.11 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{17}H_{16}N_2O_3Na$: 319.1058 $[M+Na]^+$; Found: 319.1053.

***N'*-(((*E*)-3-Oxo-1-(thiophen-3-yl)prop-1-en-1-yl)oxy)benzimidamide (191d) (Table 9, Entry d).** Purification by flash chromatography (1:3 EtOAc/Hexane) afforded 89% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.67 (d, J = 8.4 Hz, 1H), 7.72 (m, 3H), 7.45 (m, 4H), 7.34 (d, J = 8.3 Hz, 1H), 6.51 (d, J = 8.3 Hz, 1H), 5.18 (brs, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.4 (CH), 170.2 (C), 155.8 (C), 132.8 (C), 131.2 (CH), 130.9 (C), 129.3 (CH), 128.9 (CH), 128.2 (CH), 126.45 (CH), 126.4 (CH), 108.3 (CH); IR (neat): 3469, 3292, 3157, 2866, 1627, 1600, 1579, 1560, 1521, 1419, 1390, 1357, 1313, 1191, 1157, 1101, 1072, 1028, 877, 846, 798, 779 cm^{-1}; MS (ESI, *m/z*): 295.05 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{14}H_{12}N_2O_2SNa$: 295.0515 $[M+Na]^+$; Found: 295.0512.

***N'*-(((*E*)-1-Oxooct-2-en-3-yl)oxy)benzimidamide (191e) (Table 9, Entry 5).** Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 80% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (d, J = 8.4 Hz, 1H), 7.66 (m, 2H), 7.39 (m, 3H), 6.26 (d, J = 8.2 Hz, 1H), 5.32 (b, s, 2H, NH_2), 2.70 (t, J = 7.5 Hz, 2H), 1.68 (m, 2H), 1.36 (m, 4H), 0.90 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.5 (CH), 178.6 (C), 155.6 (C), 131.0 (CH), 128.7 (CH), 126.4 (CH), 126.3 (C), 106.1 (CH), 31.4 (CH_2), 29.9 (CH_2), 28.4 (CH_2), 22.3 (CH_2), 13.9 (CH_3); IR (neat): 3485, 3309, 3165, 2947, 2927, 2860, 1633, 1604, 1585, 1566, 1456, 1398, 1328, 1217, 1161, 1085, 974, 920, 894, 844, 775 cm^{-1}; MS (ESI, *m/z*): 283.14 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{15}H_{20}N_2O_2Na$: 283.1422 $[M+Na]^+$; Found: 283.1417.

***N'*-(((*E*)-1-Cyclopentyl-4-oxobut-2-en-2-yl)oxy)benzimidamide (191f) (Table 9, Entry 6).** Purification by flash chromatography (1:3 EtOAc/Hexane) afforded 92% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (d, J = 8.4 Hz, 1H), 7.67 (m, 2H), 7.41 (m, 3H), 6.30 (d, J = 8.4 Hz, 1H), 5.29 (brs, 2H, NH_2), 2.70 (d, J = 7.4 Hz, 2H), 2.20 (m, 1H), 1.83 (m, 2H), 1.66 (m, 2H), 1.56 (m, 2H), 1.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.7 (CH), 178.3 (C), 155.7 (C), 130.9 (CH), 128.7 (CH), 126.4 (CH), 106.5 (CH), 39.5 (CH), 35.3 (CH_2), 32.5 (CH_2), 24.7 (CH_2); IR (neat): 3433, 3328, 2954, 2854, 1627, 1568, 1444, 1402, 1340, 1174, 1112, 902, 844, 773 cm^{-1}; MS (ESI, *m/z*): 295.14 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{16}H_{20}N_2O_2Na$: 295.1422 $[M+Na]^+$; Found: 295.1417.

4-Methyl-*N'*-(((*E*)-3-oxo-1-phenylprop-1-en-1-yl)oxy)benzimidamide (191g) (Table 9, Entry 7). Purification by flash chromatography (1:3 EtOAc/Hexane) afforded 53% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.51 (d, J = 8.5 Hz, 1H), 7.63 (m, 4H), 7.51 (m, 3H), 7.27 (d, J = 7.3 Hz, 2H), 6.54 (d, J = 8.4 Hz, 1H), 5.16 (brs, 2H, NH_2), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.9 (CH), 175.7 (C), 155.9 (C), 141.5 (C), 132.1 (C), 130.9 (CH), 130.0 (CH), 129.5 (CH), 128.5 (CH), 127.9 (C), 126.3 (CH), 107.9 (CH), 21.4 (CH_3); IR (neat): 3490, 3315, 3180, 2864, 1627, 1581, 1556, 1400, 1342, 1207, 1163, 1112, 1080, 891, 850, 821, 786, 758 cm^{-1}; MS (ESI, *m/z*): 303.11 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{17}H_{16}N_2O_2Na$: 303.1109 $[M+Na]^+$; Found: 303.1104.

4-Methoxy-*N*'-(((*E*)-3-oxo-1-phenylprop-1-en-1-yl)oxy)benzimidamide (191h) (Table 9, Entry 8). Purification by flash chromatography (1:3 EtOAc/Hexane) afforded 84% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.49 (d, J = 8.5 Hz, 1H), 7.68 (d, J = 8.7 Hz, 2H), 7.58 (m, 2H), 7.48 (m, 3H), 6.96 (d, J = 8.8 Hz, 2H), 6.52 (d, J = 8.5 Hz, 1H), 5.10 (b, s, 2H, NH_2), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.0 (CH), 175.9 (C), 161.9 (C), 155.9 (C), 132.1 (C), 130.9 (CH), 130.2 (CH), 128.4 (CH), 127.9 (CH), 123.0 (C), 114.2 (CH), 107.7 (CH), 55.4 (CH_3); IR (neat): 3477, 3336, 3195, 2829, 1633, 1600, 1583, 1560, 1519, 1446, 1409, 1392, 1338, 1305, 1251, 1155, 1110, 1072, 1022, 891, 829, 786, 758 cm^{-1}; MS

(ESI, *m/z*): 319.11 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{17}H_{16}N_2O_3Na$: 319.1058 $[M+Na]^+$; Found: 319.1053.

4-Chloro-*N'*-(((*E*)-3-oxo-1-phenylprop-1-en-1-yl)oxy)benzimidamide (191i) (Table 9, Entry 9). Purification by flash chromatography (1:3 EtOAc/Hexane) afforded 70% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.48 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.56 (m, 2H), 7.50 (m, 3H), 7.43 (d, J = 8.4 Hz, 2H), 6.49 (d, J = 8.4 Hz, 1H), 5.20 (b, s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.9 (CH), 175.6 (C), 154.9 (C), 137.3 (C), 131.9 (C), 130.9 (CH), 130.0 (CH), 129.3 (C), 129.1 (CH), 128.5 (CH), 127.7 (CH), 107.9 (CH); IR (neat): 3485, 3311, 3182, 2860, 1629, 1581, 1554, 1490, 1396, 1342, 1205, 1155, 1114, 1087, 1014, 894, 833, 771 cm^{-1}; MS (ESI, *m/z*): 323.08 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{16}H_{13}ClN_2O_2Na$: 323.0563 $[M+Na]^+$; Found: 323.0558.

2-chloro-N'-(3-oxo-1-phenylprop-1-enyloxy)benzimidamide (191j) (Table 9, Entry 10). Purification by flash chromatography (1:3 EtOAc/Hexane) afforded 60% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.85 (d, J = 8.3 Hz, 1H), 7.3-7.6 (m, 9H), 6.4 (d, J = 8.3 Hz, 1H), 5.3 (brs, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193 (CH), 175.5 (C), 155 (C), 132.5 (C), 131.7 (CH), 131.2 (CH), 131.0 (CH), 130.2 (CH), 130.0 (CH), 129.0 (C), 128.5 (CH), 127.2 (CH), 126.5 (C),107.9 (CH); MS (ESI, *m/z*): 323.08 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{16}H_{13}ClN_2O_2Na$: 323.0563 $[M+Na]^+$; Found: 323.0558.

4-(Dimethylamino)-*N'*-(1-oxooct-2-en-3-yloxy)benzimidamide (191k (Table 9, Entry 11) Purification by flash chromatography (1:3 EtOAc/Hexane) afforded 50% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.85 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.7 Hz, 2H), 6.68 (d, J = 8.2 Hz, 2H), 6.29 (d, J = 8.3 Hz, 1H), 5.03 (brs, 2H, NH_2), 3.00 (s, 6H), 2.71 (t, J = 7.5 Hz, 2H), 1.72 (m, 2H), 1.38 (m, 4H), 0.91 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.4 (CH), 178.6 (C), 155.7 (C), 152.2 (C), 127.3 (CH), 117.6 (C), 111.6 (CH), 106.1 (CH), 40.2 (CH_3), 31.4 (CH_2), 29.9 (CH_2), 28.4 (CH_2), 22.4 (CH_2), 13.9 (CH_3); IR (neat): 3429, 3317, 3222, 2964,

2965, 2840, 2765, 1631, 1579, 1542, 1396, 1332, 1218, 1170, 1087, 923, 858, 819, 734 cm^{-1}.

***N'*-(((*E*)-3-Oxo-1,3-diphenylprop-1-en-1-yl)oxy)benzimidamide (191l) (Table 9, Entry 12).** Purification by flash chromatography (1:3 EtOAc/Hexane) afforded 63% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 7.8 Hz, 2H), 7.79 (d, J = 7.4 Hz, 2H), 7.58 (d, J = 7.6 Hz, 2H), 7.47 (m, 6H), 7.40 (m, 4H), 5,17 (brs, 2h); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.6, 169.1, 155.5, 139.9, 134.2, 131.8, 131.0, 129.9, 129.4, 128.8, 128.7, 128.3, 128.2, 128.0, 126.5, 100,4. MS (ESI, *m/z*): 365.13 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{22}H_{18}N_2O_2Na$: 365.1266 $[M+Na]^+$; Found: 365.1260.

4. 10 General procedure for the synthesis of isoxazoles 112.

To a solution of **191** (0.25 mmol) in 10 mL of CH_2Cl_2 was added dropwise conc. HCl. The mixture was stirred at room temperature for appropriate time. After the reaction was over, the mixture was extracted with CH_2Cl_2 (2 x10 mL), and the organic phase was dried over $MgSO_4$ and filtered off. The residue was purified by flash column chromatography on silica gel using ethyl acetate/hexane as the eluent to afford the desired product **112**.

5-Phenylisoxazole (112a) (Table 10, Entry 1). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 96% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, J = 1.4 Hz, 1H), 7.8 (m, 2H), 7.45 (m, 3H), 6.51 (d, J = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4 (C), 130.2 (CH), 128.7 (CH), 127.0 (C), 126.1 (CH), 98.7 (CH). The spectral data were in agreement with those reported previously for this compound [194].

5-(*p*-Tolyl)isoxazole (112b) (Table 10, Entry 2). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 91% of the indicated product. ^{1}H

NMR (400 MHz, $CDCl_3$): δ 8.70 (d, J = 1.1 Hz, 1H), 7.59 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 7.9 Hz, 2H), 6.36 (d, J =1.5 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6 (C), 150.8 (CH), 140.5 (C), 129.7 (CH), 125.8 (CH), 124.6 (C), 98.0 (CH), 21.4 (CH_3). The spectral data were in agreement with those reported previously for this compound [195].

5-(4-Methoxyphenyl)isoxazole (112c) (Table 10, Entry 3). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 78% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, J=1.6 Hz, 1H), 7.73 (d, J = 8.9 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 6.39 (d, J = 1.6 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4 (C), 161.1 (C), 150.8 (CH), 127.5 (CH), 120.2 (C), 114.4 (CH), 97.2 (CH), 55.4 (CH_3). The spectral data were in agreement with those reported previously for this compound [196]].

5-Pentylisoxazole (112d) (Table 10, Entry 4). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 67% of the indicated product. The yield calculated from integration of NMR.

5-(Thiophen-3-yl)isoxazole (112e) (Table 10, Entry 5). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 87% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (s, 1H), 7.78 (s, 1H), 7.41 (m, 2H), 6.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6 (C), 150.6 (CH), 128.7 (C), 127.0 (CH), 125.4 (CH), 124.3 (CH), 98.4 (CH).

4. 11 General procedures for the synthesis of 1,2,4-oxadiazoles 192

4.11. 1 General procedure for the synthesis of 1,2,4-oxadiazoles 192 from conjugate addition products 191 in the presence of KOH (Table 11)

To a solution of **191** (0.25 mmol) in 10 mL of dioxane was added 1.0 equiv. of KOH. The mixture was stirred at 100 ^{o}C for appropriate time. After the reaction was over, the dioxane was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel using ethyl acetate/hexane as the eluent to afford the desired product.

3,5-Diphenyl-1,2,4-oxadiazole (192a) (Table 11, Entry 1). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 84% the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (m, 4H), 7.54 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7 (C), 168.9 (C), 132.7 (CH), 131.2 (CH), 129.1 (CH), 128.8 (CH), 128.2 (CH), 1278.6 (CH), 127.1 (C), 124.4 (C). The spectral data were in agreement with those reported previously for this compound [196].

3-Phenyl-5-(*p*-tolyl)-1,2,4-oxadiazole (192b) (Table 11, Entry 2). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 80% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (m, 2H), 7.98 (d, J = 8.2 Hz, 2H), 7.39 (m, 3H), 7.22 (d, J = 8.0 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9 (C), 168.9 (C), 143.4 (C), 131.1 (CH), 129.8 (CH), 128.8 (CH), 128.1 (CH), 127.5 (CH), 127.2 (C), 121.7 (C), 21.7 (CH_3). The spectral data were in agreement with those reported previously for this compound [138].

5-(4-Methoxyphenyl)-3-phenyl-1,2,4-oxadiazole (192c) (Table 11, Entry 3). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 95% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (m, 4H), 7.51 (m, 3H), 7.02 (d, J = 8.9 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6 (C), 168.8 (C), 163.2 (C), 131.0 (CH), 130.1 (CH), 128.8 (CH), 127.5 (CH), 127.2 (C), 116.9 (C), 114.5 (CH), 55.5 (CH_3). The spectral data were in agreement with those reported previously for this compound [197].

3-Phenyl-5-(thiophen-3-yl)-1,2,4-oxadiazole (192d) (Table 11, Entry 4). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 68% of the

indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, J = 2.8 Hz, 1H), 8.17 (m, 2H), 7.76 (d, J = 4.9 Hz, 1H), 7.52 (m, 3H), 7.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9 (C), 168.8 (C), 131.2 (CH), 130.1 (CH), 128.8 (CH), 127.5 (CH), 127.4 (CH), 127.0 (C), 126.7 (CH), 126.0 (C); IR (neat): 3015, 2921, 1596, 1527, 1444, 1352, 1253, 1211, 1126, 1068, 918, 858,736, 713, 688 cm^{-1}; MS (ESI, *m/z*): 251.03 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{12}H_8N_2OSNa$: 251.0255 $[M+Na]^+$; Found: 251.0250 [198].

5-Pentyl-3-phenyl-1,2,4-oxadiazole (192e) (Table 11, Entry 5). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 81% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (m, 2H), 7.48 (m, 3H), 2.94 (t, J = 7.6 Hz, 2H), 1.88 (m, 2H), 1.41 (m, 4H), 0.93 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.0 (C), 168.3 (C), 130.9 (CH), 128.8 (CH), 127.4 (CH), 127.1 (C), 31.2 (CH_2), 26.6 (CH_2), 26.3 (CH_2), 22.2 (CH_2), 13.8 (CH_3). The spectral data were in agreement with those reported previously for this compound [150].

5-(Cyclopentylmethyl)-3-phenyl-1,2,4-oxadiazole (192f) (Table 11, Entry 6). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 47% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (m, 2H), 7.49 (m, 3H), 2.95 (d, J = 7.4 Hz, 2H), 2.43 (m, 1H), 1.88 (m, 2H), 1.67 (m, 2H), 1.59 (m, 2H), 1.32 (m, 2H); ^{13}C NMR (100MHz, $CDCl_3$): δ 179.2 (C), 167.7 (C), 130.5 (CH), 128.3 (CH), 126.9 (CH), 126.6 (C), 37.5 (CH), 31.9 (CH_2), 24.5 (CH_2); MS (ESI, *m/z*): 251.12 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{14}H_{16}N_2ONa$: 251.1160 $[M+Na]^+$; Found: 251.1155.

5-Phenyl-3-(*p*-tolyl)-1,2,4-oxadiazole (192g) (Table 11, Entry 7). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 93% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, J = 7.1 Hz, 2H), 8.08 (d, J = 8.1 Hz, 2H), 7.57 (m, 3H), 7.32 (d, J = 7.9 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6 (C), 168.0 (C), 140.5 (C), 131.7 (CH), 129.6 (CH), 129.0 (CH), 128.2 (CH),

127.5 (CH), 124.4 (C), 124.2 (C), 20.6 (CH_3). The spectral data were in agreement with those reported previously for this compound [199].

3-(4-Chlorophenyl)-5-phenyl-1,2,4-oxadiazole (192h) (Table 11, Entry 8). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 91% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J = 7.4 Hz, 2H), 8.11 (d, J = 8.4 Hz, 2H), 7.60 (m, 1H), 7.54 (m, 2H), 7.47 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9 (C), 168.2 (C), 137.3 (C), 132.8 (CH), 129.2 (CH), 129.1 (CH), 128.8 (CH), 128.2 (CH), 125.5 (C), 124.2 (C). The spectral data were in agreement with those reported previously for this compound [200].

4.11. 2 General procedure for the synthesis of 1,2,4-oxadiazoles 192 from conjugate addition products 191 in the presence of NaH (Table 12)

To a solution of **191** (0.25 mmol) in 10 mL of anhydrous acetonitrile was added 1.05 equiv. of sodium hydride (60% suspension in mineral oil). The mixture was stirred at ambient temperature for appropriate time. Then, the mixture was filtrated and washed two times with diethylether (2 x 25 mL). The solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography on silica gel using ethyl acetate/hexane as the eluent to afford the desired product.

3,5-Diphenyl-1,2,4-oxadiazole (192a) (Table 12, Entry 1). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 85% of the indicated product. The spectral data were given the in previous section.

3-Phenyl-5-(thiophen-3-yl)-1,2,4-oxadiazole (192d) (Table 12, Entry 2). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 83% of the indicated product. The spectral data were given the in previous section.

5-Pentyl-3-phenyl-1,2,4-oxadiazole (192e) (Table 12, Entry 3). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 84% of the indicated product. The spectroscopic data were given the in previous section.

3-(4-Methoxyphenyl)-5-phenyl-1,2,4-oxadiazole (192i) (Table 12, Entry 4). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 85% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, J = 6.9 Hz, 2H), 8.12 (d, J = 8.8 Hz, 2H), 7.55 (m, 3H), 7.01 (d, J = 8.6 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.4 (C), 168.7 (C), 161.9 (C), 132.6 (CH), 129.1 (CH), 129.0 (CH), 128.1 (CH), 124.5 (C), 119.5 (C), 114.3 (CH), 55.4 (CH_3). The spectral data were in agreement with those reported previously for this compound [201].

3-(2-Chlorophenyl)-5-phenyl-1,2,4-oxadiazole (192j) (Table 12, Entry 5). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 93% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J = 7.9 Hz, 2H), 8.03 (dd, J = 7.2 Hz, J = 1.7, 1H), 7.54 (m, 4H), 7.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.3 (C), 167.8 (C), 133.6 (C), 132.9 (CH), 131.9 (CH), 131.6 (CH), 130.9 (CH), 129.1 (CH), 128.2 (CH), 126.9 (CH), 126.3 (C), 124.1 (C). The spectral data were in agreement with those reported previously for this compound [202].

***N*,*N*-Dimethyl-4-(5-pentyl-1,2,4-oxadiazol-3-yl)aniline (192k) (Table 12, Entry 6).** Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 79% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, J = 8.8 Hz, 2H), 6.75 (d, J = 8.8 Hz, 2H), 3.02 (s, 6H), 2.90 (t, J = 7.6 Hz, 2H), 1.86 (m, 2H), 1.40 (m, 4H), 0.92 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.3 (C), 168.3 (C), 152.0 (C), 128.6 (CH), 111.8 (CH), 40.2 (CH_3), 31.2 (CH_2), 26.6 (CH_2), 26.4 (CH_2), , 22.2 (CH_2), 13.8 (CH_3).

4.11.3 General procedure for the one-pot synthesis of 1,2,4-oxadiazoles 192 (Table 14)

To a stirred solution of propargyl aldehyde **118** (0.25 mmol) and amidoxime **190** (0.325 mmol) in dioxane (7 mL) was added KOH flakes (0.25 mmol), and the solution was allowed to stir at 100 ^{o}C under argon for appropriate time. After the reaction was over, the dioxane was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel using ethyl acetate/hexane as the eluent to afford the desired product.

3,5-Diphenyl-1,2,4-oxadiazole (192a) (Table 14, Entry 1). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 61% of the indicated product. The spectral data were given the in previous section.

3-Phenyl-5-(*p*-tolyl)-1,2,4-oxadiazole (192b) (Table 14, Entry 2). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 55% of the indicated product. The spectral data were given the in previous section..

5-(4-Methoxyphenyl)-3-phenyl-1,2,4-oxadiazole (192c) (Table 14, Entry 3). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 76% of the indicated product. The spectral data were given the in previous section.

5-Pentyl-3-phenyl-1,2,4-oxadiazole (192e) (Table 14, Entry 4). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 72% of the indicated product. The spectral data were given the in previous section.

5-Phenyl-3-(*p*-tolyl)-1,2,4-oxadiazole (192g) (Table 14, Entry 5). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 59% of the indicated product. The spectral data were given the in previous section.

3-(4-Chlorophenyl)-5-phenyl-1,2,4-oxadiazole (192h) (Table 14, Entry 6). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 42% of the indicated product. The spectral data were given the in previous section.

3-(4-Methoxyphenyl)-5-phenyl-1,2,4-oxadiazole (192i) (Table 14, Entry 7). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 60% of the indicated product. The spectral data were given the in previous section.

3-(2-Chlorophenyl)-5-phenyl-1,2,4-oxadiazole (192j) (Table 14, Entry 8). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 49% of the indicated product. The spectral data were given the in previous section.

3-(Naphthalen-1-yl)-5-phenyl-1,2,4-oxadiazole (192l) (Table 14, Entry 9). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 48% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.10 (d, J = 8.4 Hz, 1H), 8.42 (d, J = 7.1 Hz, 1H), 8.30 (d, J = 7.5 Hz, 2H), 8.03 (d, J = 8.2 Hz, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.70 (t, J = 7.1 Hz, 1H), 7.58 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3 (C), 170.8 (C), 135.4 (C), 134.7 (CH), 133.3 (CH), 132.2 (C), 130,9 (CH), 130.6 (CH), 130.1 (CH), 129.7 (CH), 129.0 (CH), 127.85 (CH), 127.8 (CH), 126.6 (CH), 125.7 (C), 125.5 (C); MS (ESI, *m/z*): 295.08 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{18}H_{12}N_2NaO$: 295.0847 $[M+Na]^+$; Found: 298.0842.

5-Pentyl-3-(*p*-tolyl)-1,2,4-oxadiazole (192m) (Table 14, Entry 10). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 80% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87(d, J = 7.9 Hz, 2H), 7.17 (d, J=7.9 Hz, 2H), 2.82 (t, J=7.5 Hz, 2H), 2.30 (s, 3H), 1.77 (m, 2H), 1.29 (m, 4H), 0.82 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.9 (C), 168.2 (C), 141.3 (C), 129.5 (CH), 127.3 (CH), 124.2 (C), 31.2 (CH_2), 26.6 (CH_2), 26.4 (CH_2), 22.2 (CH_3), 21.5 (CH_2), 13.8 (CH_3); IR (neat): 2956, 2929, 1589, 1568, 1411, 1363, 1180, 116, 902, 829, 740 cm^{-1}. MS (ESI, *m/z*): 253.13 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{14}H_{18}N_2NaO$: 253.1317 $[M+Na]^+$; Found: 253.1311.

3-(4-Methoxyphenyl)-5-pentyl-1,2,4-oxadiazole (192n) (Table 14, Entry 11). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 67% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H), 3.85 (s, 3H), 2.91 (td, J = 2.9 Hz, J = 7.5 Hz, 2H), 1.88 (m, 2H), 1.40 (m, 4H), 0.93 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.7 (C), 167.9 (C), 161.8 (C), 128.9 (CH), 119.5 (C), 114.2 (CH), 55.3 (CH_3), 31.2 (CH_2), 26.6 (CH_2), 26.3 (CH_2), 22.2 (CH_2), 13.8 (CH_3); IR (neat): 2956, 2933, 1614, 1591, 1569, 1483, 1423, 1363, 1301, 1251, 1172, 1107, 1029, 900, 839, 752 cm^{-1}; MS (ESI, *m/z*): 269.13 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{14}H_{18}N_2NaO_2$: 269.1266 $[M+Na]^+$; Found: 269.1260.

3-(4-Chlorophenyl)-5-pentyl-1,2,4-oxadiazole (192o) (Table 14, Entry 12). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 76% of the indicated product. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.99 (d, J = 8.5 Hz, 1H), 7.98 (d, J = 8.6 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 2.90 (m, 2H), 1.85 (m, 2H), 1.39 (m, 4H), 0.90 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.2 (C), 167.4 (C), 137.1 (C), 129.1 (CH), 128.7 (CH), 125.6 (C), 31.1 (CH_2), 26.5 (CH_2), 26.3 (CH_2), 22.2 (CH_2), 13.8 (CH_3); IR (neat): 2954, 2927, 1591, 1562, 1465, 1407, 1365, 1085, 1008, 904, 839, 785, 744 cm^{-1}; MS (ESI, *m/z*): 273.07 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{13}H_{15}N_2ClNaO$: 273.0771 $[M+Na]^+$; Found: 273.0767.

***N,N*-Dimethyl-4-(5-pentyl-1,2,4-oxadiazol-3-yl)aniline (192p) (Table 14, Entry 13).** Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 79% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, J = 8.8 Hz, 2H), 6.75 (d, J = 8.8 Hz, 2H), 3.02 (s, 3H), 2.90 (t, J = 7.6 Hz, 2H), 1.86 (m, 2H), 1.40 (m, 4H), 0.92 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.3 (C), 168.3 (C), 152.0 (C), 128.6 (CH), 111.8 (CH), 40.2 (CH_3), 31.2 (CH_2), 26.6 (CH_2), 26.4 (CH_2), 22.2 (CH_2), 13.8 (CH_3); MS (ESI, *m/z*): 282.16 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{15}H_{21}N_3NaO$: 282.1582 $[M+Na]^+$; Found: 282.1577.

3-(Naphthalen-1-yl)-5-pentyl-1,2,4-oxadiazole (192q) (Table 14, Entry 14). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 52% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (d, J = 9.0 Hz, 1H), 8.30 (d, J = 7.25 Hz, 1H), 8.00 (d, J = 8.2 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.67 (t, J = 7.1 Hz, 1H), 7.60 (M, 2H), 3.01 (t, J = 7.9 Hz, 2H), 1.95 (p, 2H), 1.44 (m, 4H), 0.97 (t, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.1 (C), 168.7 (C), 134.0 (C), 131.7 (CH), 130.7 (C), 129.3 (CH), 128.6 (CH), 127.5 (CH), 126.4 (CH), 126.3 (CH), 125.0 (CH), 124.1 (C), 31.3 (CH2), 26.5 (CH2), 26.4 (CH2), 22.2 (CH2), 13.9 (CH3); IR (neat): 2954, 2929, 1579, 1514, 1456, 1352, 1307, 1261, 1145, 1020, 900, 806, 775 cm^{-1}; MS (ESI, *m/z*): 289.13 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{17}H_{18}N_2NaO$: 289.1317 $[M+Na]^+$; Found: 289.1311.

4.11.4 General procedure for the one-pot synthesis of 3-aryl-5-ferrocenyl-1,2,4-oxadiazoles 221 (Table 15)

To a stirred solution of 3-ferrocenylpropynal (**45**) (0.25 mmol) and amidoxime **190** (0.325 mmol) in dioxane (7 mL) was added KOH flakes (0.25 mmol), and the solution was allowed to stir at 100 ^{o}C under argon for appropriate time. After the reaction was over, the dioxane was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel using ethyl acetate/hexane as the eluent to afford the desired product.

5-Ferrocenyl-3-phenyl-1,2,4-oxadiazole (221a) (Table 15, Entry 1). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 84% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (m, 2H), 7.52 (m, 3H), 5.08 (s, 2H), 4.56 (s, 2H), 4.22 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.3 (C), 168.7 (CH), 131.0 (CH) 128.8 (CH), 127.6 (CH), 127.2 (C), 71.5 (CH), 70.1 (CH), 69.1 (CH), 66.2 (C); IR (neat): 1595, 1583, 1477, 1444, 1352, 1274, 1139, 1109, 1024, 999, 904, 881, 819, 752 cm^{-1}.

5-Ferrocenyl-3-(*p*-tolyl)-1,2,4-oxadiazole (221b) (Table 15, Entry 2). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 95% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, J = 7.9 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 5.07 (s, 2H), 4.54 (s, 2H), 4.21 (s, 5H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.1 (C), 168.7 (C), 141.3 (C), 129.5 (CH), 127.5 (CH), 124.4 (C), 71.5 (CH), 70.1 (CH), 69.1 (CH), 66.3 (C), 21.6 (CH_3); IR (neat): 1595, 1575, 1409, 1346, 1278, 1143, 1103, 1029, 908, 881, 821, 759 cm^{-1}; MS (ESI, *m/z*): 344.06 $[M]^+$; HRMS (ESI): calcd. for $C_{19}H_{16}FeN_2O$: 364.0612 $[M]^+$; Found: 364.0607.

5-Ferrocenyl-3-(4-methoxyphenyl)-1,2,4-oxadiazole (221c) (Table 15, Entry 3). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 85% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09(d, J = 8.7 Hz, 2H), 7.01(d, J = 8.7 Hz, 2H), 5.06 (s, 2H), 4.53 (s, 2H), 4.20 (s, 5H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.9 (C), 168.4 (C), 161.9 (C), 133.9 (CH), 119.7 (C), 114.2 (CH), 71.5 (CH), 70.1 (CH), 69.1 (CH), 66.4 (C), 55.4 (CH_3); IR (neat): 1595, 1485, 1417, 1352, 1251, 1172, 1107, 1026, 1002, 900, 877, 817, 765 cm^{-1}; MS (ESI, *m/z*): 360.06 $[M]^+$; HRMS (ESI): calcd. for $C_{19}H_{16}FeN_2O_2$: 360.0561 $[M]^+$; Found: 360.0558.

3-(4-Chlorophenyl)-5-ferrocenyl-1,2,4-oxadiazole (221d) (Table 15, Entry 4). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 90% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 8.2 Hz, 2H), 5.05 (s, 2H), 4.55 (s, 2H), 4.20 (s, 5H); ^{13}C NMR (100MHz, $CDCl_3$): δ 179.6 (C), 167.9 (C), 137.1 (C), 129.1 (CH), 128.9 (CH), 125.7 (C), 71.7 (CH), 70.2 (CH), 69.1 (CH), 65.9 (C); IR (neat): 1591, 1571, 1473, 1404, 1348, 1278, 1143, 108, 1004, 910, 823, 761 cm^{-1}; MS (ESI, *m/z*): 364.01 $[M]^+$; HRMS (ESI): calcd. for $C_{18}H_{13}ClFeN_2O$: 364.0065 $[M]^+$; Found: 364.0061.

***N*,*N*-Dimethyl-4-(5-ferrocenyl-1,2,4-oxadiazol-3-yl)aniline (221e) (Table 15, Entry 5).** Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 61% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 8.8 Hz, 2H), 6.78 (d, J = 8.8 Hz, 2H), 5.06 (s, 2H), 4.53 (s, 2H), 4.21 (s, 5H), 3.05 (s, 6H); ^{13}C

NMR (100 MHz, $CDCl_3$): δ 178.4 (C), 169.8 (C), 152.2 (C), 128.7 (CH), 114.5 (C), 111.8 (CH), 71.3 (CH), 70.1 (CH), 69.0 (CH), 66.7 (C), 40.2 (CH_3); IR (neat): 1598, 1564, 1487, 1431, 1355, 1280, 1193, 1145, 1103, 1024, 1001, 89, 877, 819, 765 cm^{-1}; MS (ESI, *m/z*): 373.09 $[M]^+$; HRMS (ESI): calcd. for $C_{20}H_{19}FeN_3O$: 373.0877 $[M]^+$; Found: 373.0872.

5-Ferrocenyl-3-(naphthalen-1-yl)-1,2,4-oxadiazole (221f) (Table 15, Entry 6). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 54% of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 8.99 (d, J = 8.5 Hz, 1H), 8.34 (d, J = 7.1 Hz, 1H), 8.03 (d, J = 8.2 Hz, 1H), 7.95 (d, J = 8.1 Hz, 1H), 7.62 (m, 3H), 5.14 (s, 2H), 4.57 (s, 2H), 4.25 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.5 (C), 169.1 (C), 133.9 (C), 131.7 (CH), 130.8 (C), 129.3 (CH), 128.7 (CH), 127.5 (CH), 126.4 (CH), 126.3 (CH), 125.1 (CH), 124.2 (C), 71.7 (CH), 70.2 (CH), 69.2 (CH), 66.2 (C); IR (neat): 1600, 1595, 1577, 1353, 1305, 1261, 1149, 1028, 1002, 904, 879, 808, 777 cm^{-1}; MS (ESI, *m/z*): 403.05 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{22}H_{16}FeN_2ONa$: 403.0509 $[M+Na]^+$; Found: 403.0504.

3-(2-Chlorophenyl)-5-ferrocenyl-1,2,4-oxadiazole (221g) (Table 15, Entry 7). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 79% of the indicated product. ^1H NMR (400MHz, $CDCl_3$): δ 7.95 (dd, J = 1.9 Hz, J = 7.4 Hz, 1H), 7.56 (dd, J = 1.5 Hz, J = 7.9 Hz, 1H), 7.43 (m, 2H), 5.09 (s, 2H), 4.57 (s, 2H), 4.23 (s, 5H); ^{13}C NMR (100MHz, $CDCl_3$): δ 177.2 (C), 165.7 (C), 131.7 (C), 129.9 (CH), 129.7 (CH), 128.9 (CH), 125.0 (CH), 124.7 (C), 69.9 (CH), 68.4 (CH), 67.3 (CH), 63.9 (C); IR (neat): 1591, 1566, 1473, 1328, 1274, 1143, 1107, 1026, 1002, 908, 879, 823, 758 cm^{-1}; MS (ESI, *m/z*): 364.01 $[M]^+$; HRMS (ESI): calcd. for $C_{18}H_{13}ClFeN_2O$: 364.0065 $[M]^+$; Found: 364.0061.

5-Ferrocenyl-3-(3-fluorophenyl)-1,2,4-oxadiazole (221h) (Table 15, Entry 8). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 78% of the indicated product. ^1H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 7.7 Hz, 1H), 7.86 (d, J = 9.3 Hz, 1H), 7.48 (q, J = 7.8 Hz, 1H), 7.21 (td, J = 8.4 Hz, J = 2.1 Hz, 1H), 5.07 (s,

2H), 4.55 (s, 2H), 4.21 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.7 (C), 167.9 (C), 162.9 (d, J = 244.5 Hz, C), 130.5 (d, J = 33 Hz, CH), 129.3 (d, J = 8 Hz, C), 123.2 (d, J = 2.7 Hz, CH), 117.9 (d, J = 21.3 Hz, CH), 114.6 (d, J = 23 Hz, CH), 71.7 (CH), 70.2 (CH), 69.1 (CH), 65.9 (C); IR (neat): 1600, 1585, 1523, 1488, 1415, 1357, 1267, 1201, 1132, 1026, 1001, 877, 858, 821, 798, 763 cm^{-1}; MS (ESI, *m/z*): 348.04 $[M]^+$; HRMS (ESI): calcd. for $C_{18}H_{13}FFeN_2O$: 348.0361 $[M]^+$; Found: 348.0358.

3-(Benzo[d][1,3]dioxol-5-yl)-5-ferrocenyl-1,2,4-oxadiazole (221i) (Table 15, Entry 9). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 82% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8.0 Hz, 1H), 7.59 (s, 1H), 6.93 (d, J = 8.0 Hz, 1H), 6.05 (s, 2H), 5.05 (s, 2H), 4.55 (s, 2H), 4.21 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.0 (C), 168.3 (C), 149.9 (C), 148.1 (C), 122.4 (CH), 121.1 (C), 108.6 (CH), 107.6 (CH), 101.5 (CH_2), 71.5 (CH), 70.1 (CH), 69.1 (CH), 66.2 (C); IR (neat): 1591, 1456, 1325, 1238, 1134, 1103, 1035, 1008, 933, 881, 817, 761 cm^{-1}; MS (ESI, *m/z*): 397.03 $[M+Na]^+$; HRMS (ESI): calcd. for $C_{19}H_{14}FeN_2O_3Na$: 397.0251 $[M+Na]^+$; Found: 397.0246.

5-Ferrocenyl-3-(1H-indol-4-yl)-1,2,4-oxadiazole (221j) (Table 15, Entry 10). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 44% of the indicated product. ^{1}H NMR (400 MHz, *d*-DMSO): δ 11.48 (S, 1H), 7.88-7.10 (m, 5H), 5.1 2(s, 2H), 4.68 (s, 2H), 4.25 (s, 5H); ^{13}C NMR (100 MHz, *d*-DMSO): δ 177.8 (C), 168.5 (C), 136.4 (C), 127.0 (CH), 124.9 (C), 120.6 (CH), 120.0 (CH), 117.1 (C), 114.7 (CH), 102.3 (CH), 71.6 (CH), 69.8 (CH), 68.7 (CH), 65.6 (C); IR (neat): 3325, 3101, 1591, 1575, 1523, 1487, 1429, 1346, 1313, 1274, 1191, 1029, 1002, 893, 823, 761 cm^{-1}; MS (ESI, *m/z*): 369.06 $[M]^+$; HRMS (ESI): calcd. for $C_{20}H_{15}FeN_3O$: 369.0564 $[M]^+$; Found: 369.0559.

3,5-Diferrocenyl-1,2,4-oxadiazole (221k) (Table 15, Entry 11). Purification by flash chromatography (1:9 EtOAc/Hexane) afforded 22% of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.07 (s, 2H), 4.98 (s, 2H), 4.54 (s, 2H), 4.44 (s, 2H),

4.21 (s, 5H), 4.17 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.4 (C), 170.4 (C), 71.4 (CH), 70.4 (C), 70.2 (CH), 70.1 (CH), 69.8 (CH), 69.1 (CH), 68.4 (CH), 66.4 (C); IR (neat):1593, 1556, 1458, 1380, 1315, 1276, 1159, 1105, 1024, 999, 881, 813, 769 cm^{-1}; MS (ESI, *m/z*): 438.01 $[M]^+$; HRMS (ESI): calcd. for $C_{22}H_{18}Fe_2N_2O$: 438.0118 $[M]^+$; Found: 438.0113.

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APPENDIX A.

NMR DATA

NMR spectra were recorded on a Bruker Spectrospin Avance DPX400 Ultrashield (400 MHz) spectrometer

^{1}H and ^{13}C NMR spectra of products are given below.

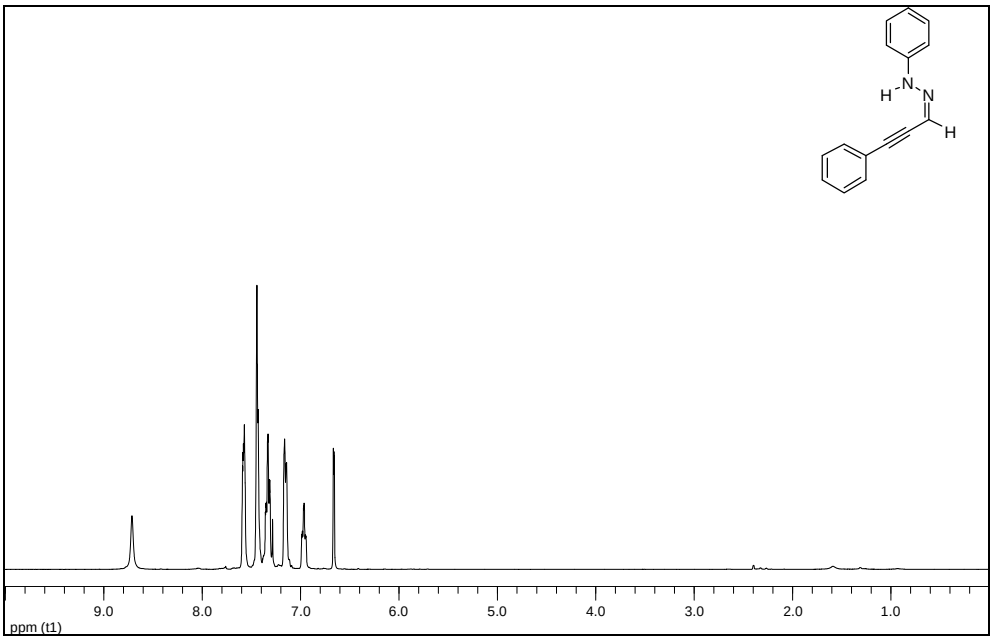

Figure A1. ^{1}H NMR spectra of ***Z*-186a.**

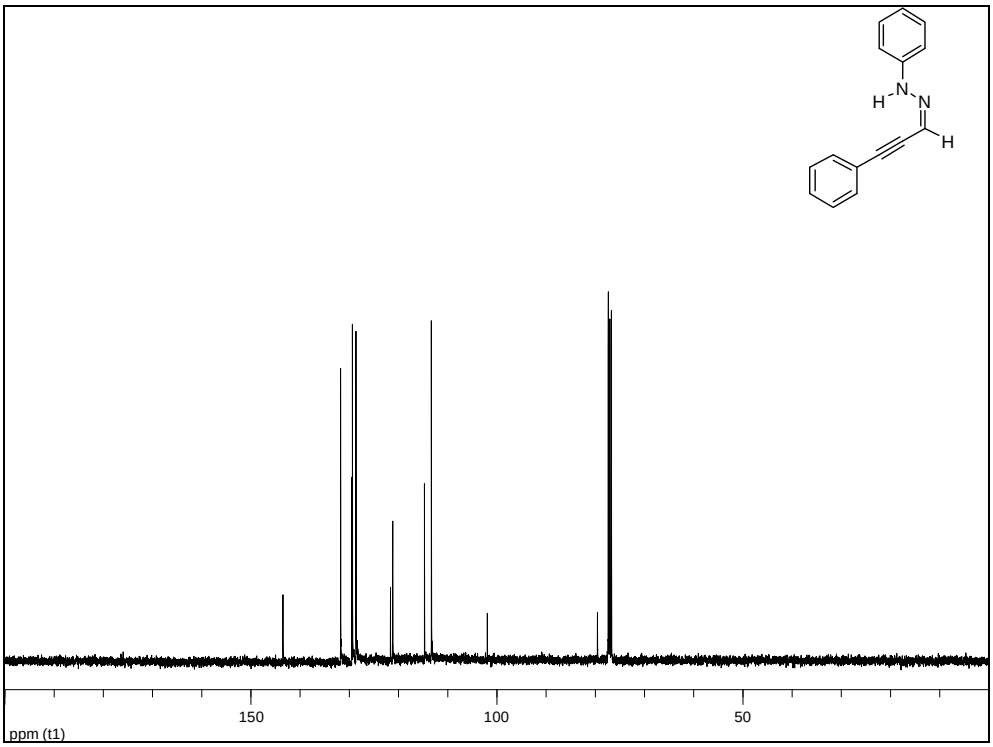

Figure A2. ^{13}C NMR spectra of ***Z*-186a**.

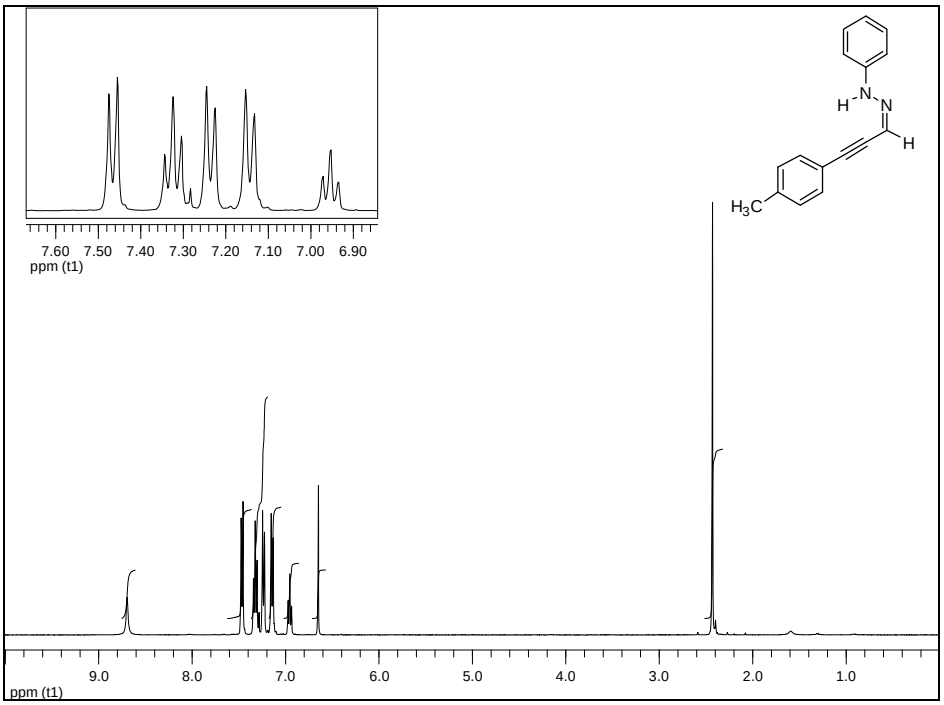

Figure A3. ^{1}H NMR spectra of ***Z*-186b.**

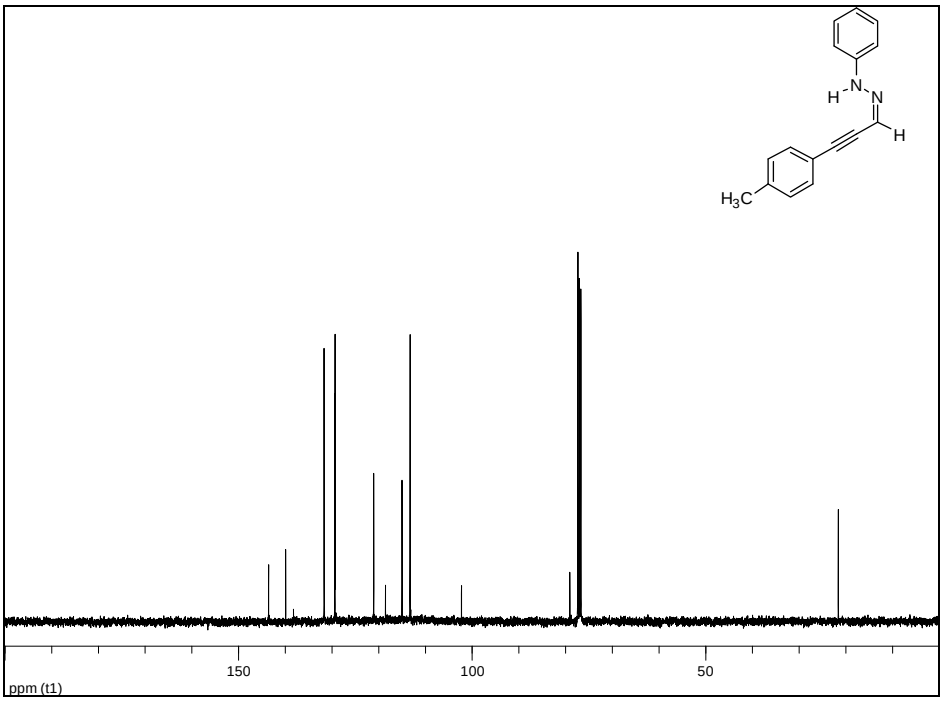

Figure A4. ^{13}C NMR spectra of ***Z*-186b.**

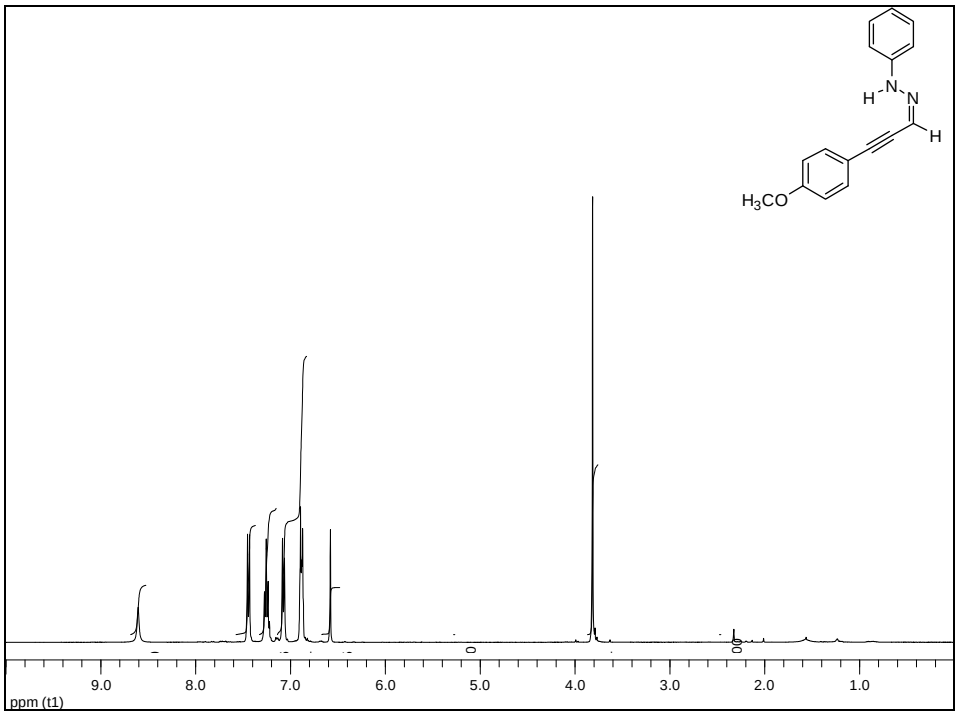

Figure A5. ^{1}H NMR spectra of ***Z*-186c.**

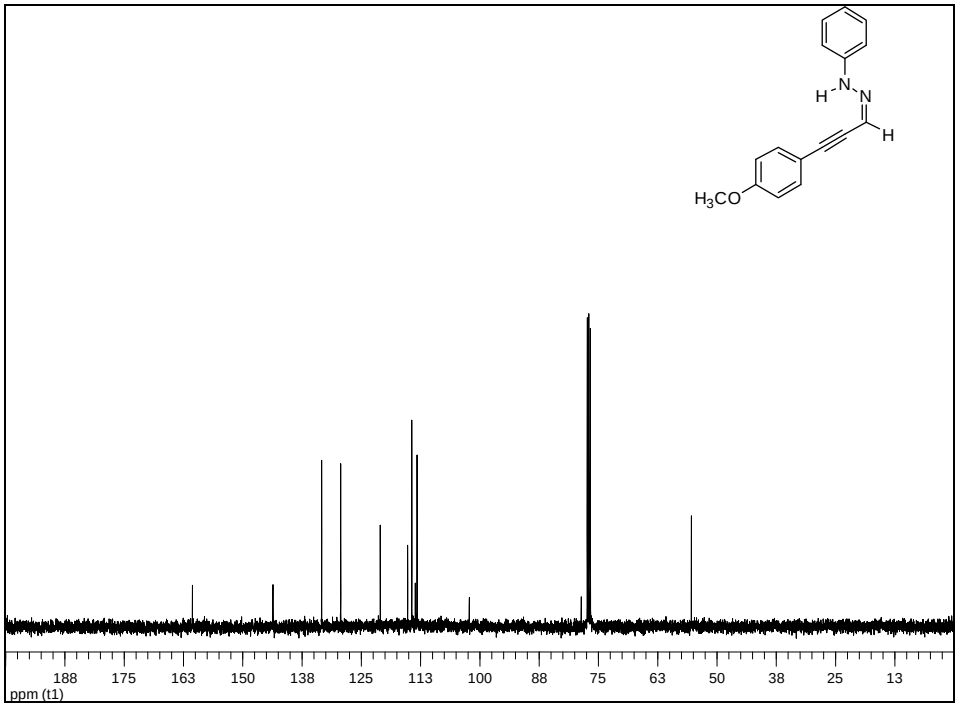

Figure A6. ^{13}C NMR spectra of ***Z*-186c.**

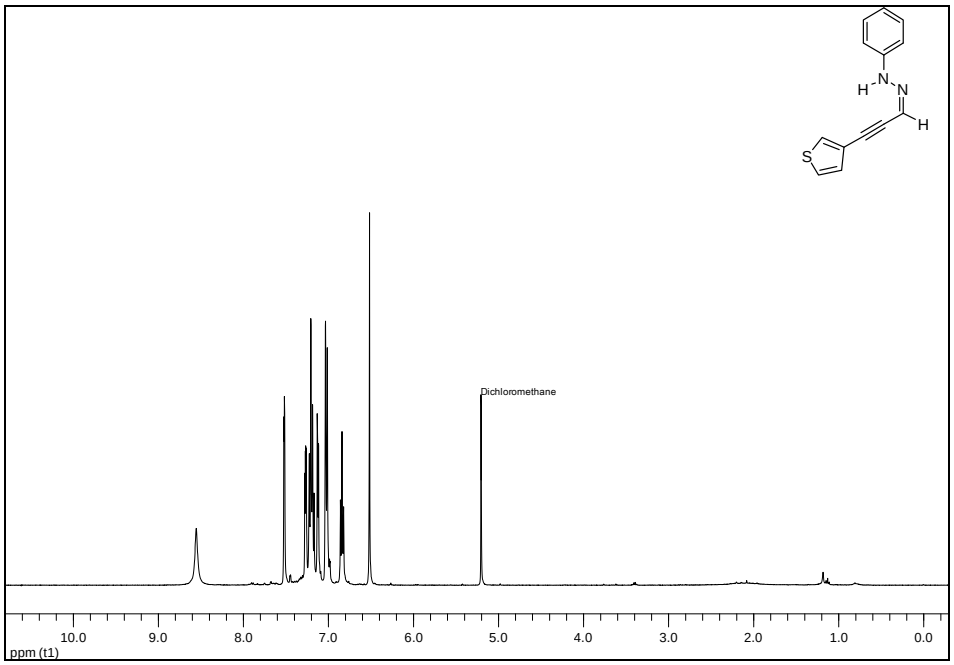

Figure A7. ^{1}H NMR spectra of ***Z*-186d.**

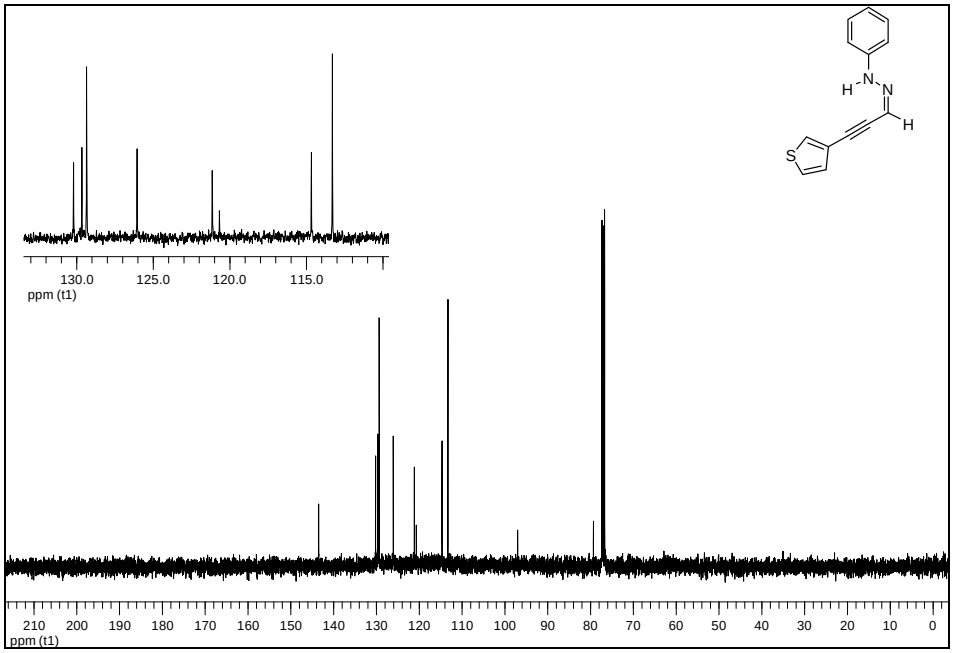

Figure A8. ^{13}C NMR spectra of ***Z*-186d.**

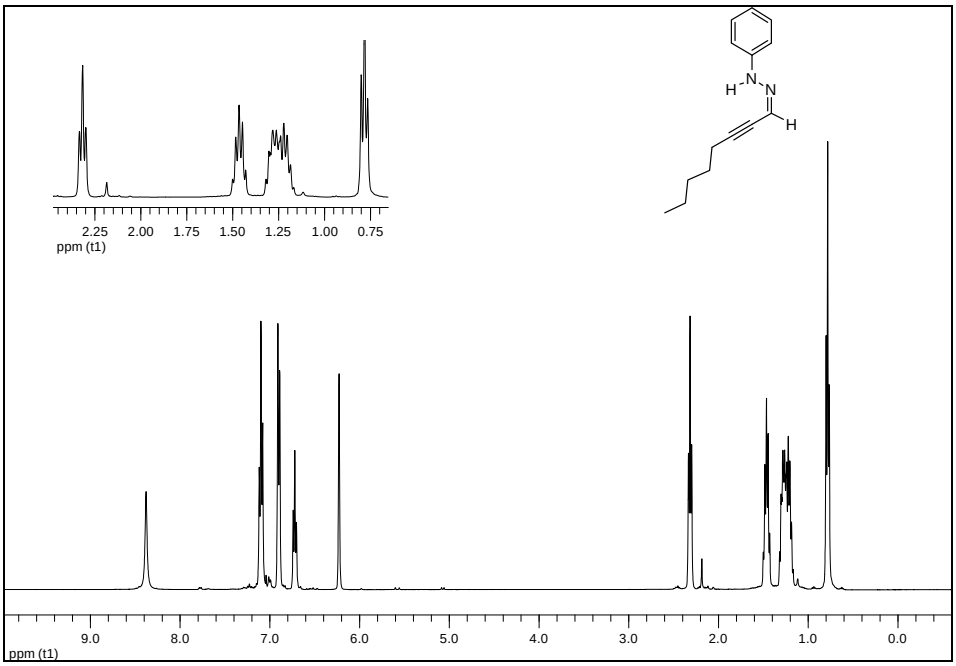

Figure A9. ^{1}H NMR spectra of ***Z*-186e.**

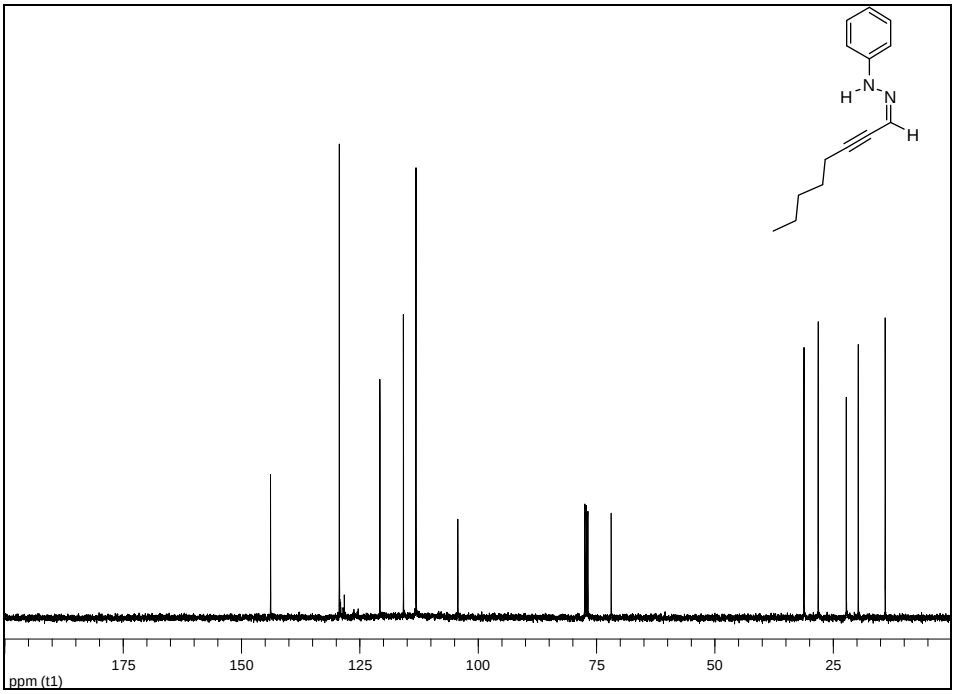

Figure A10. ^{13}C NMR spectra of ***Z*-186e.**

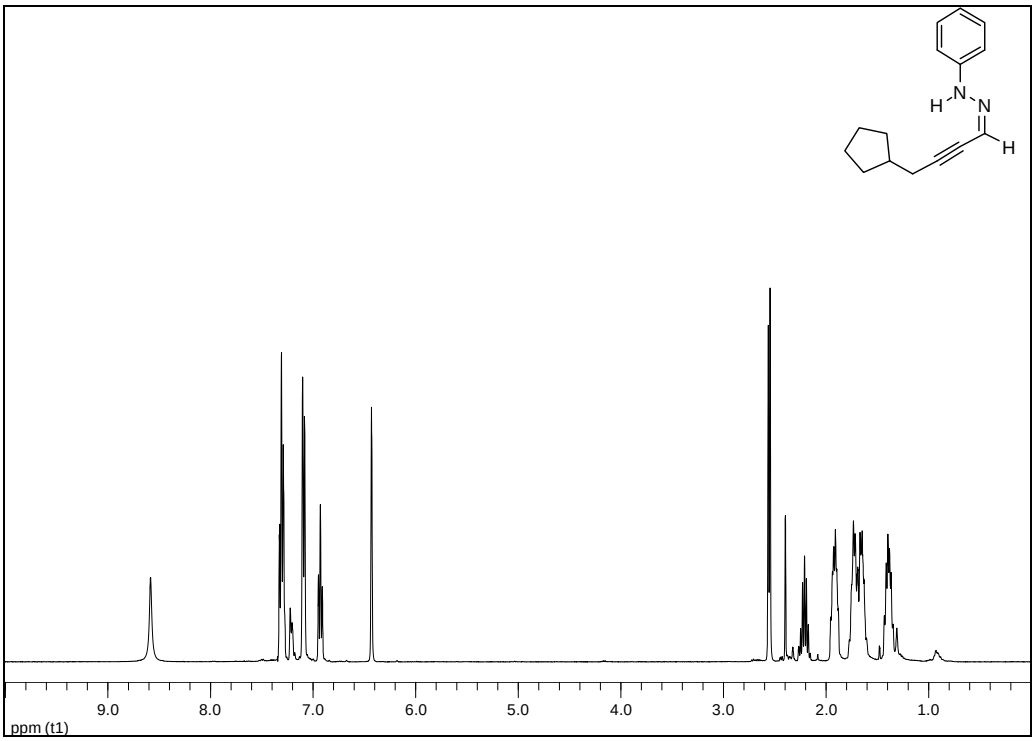

Figure A11. ^{1}H NMR spectra of ***Z*-186f.**

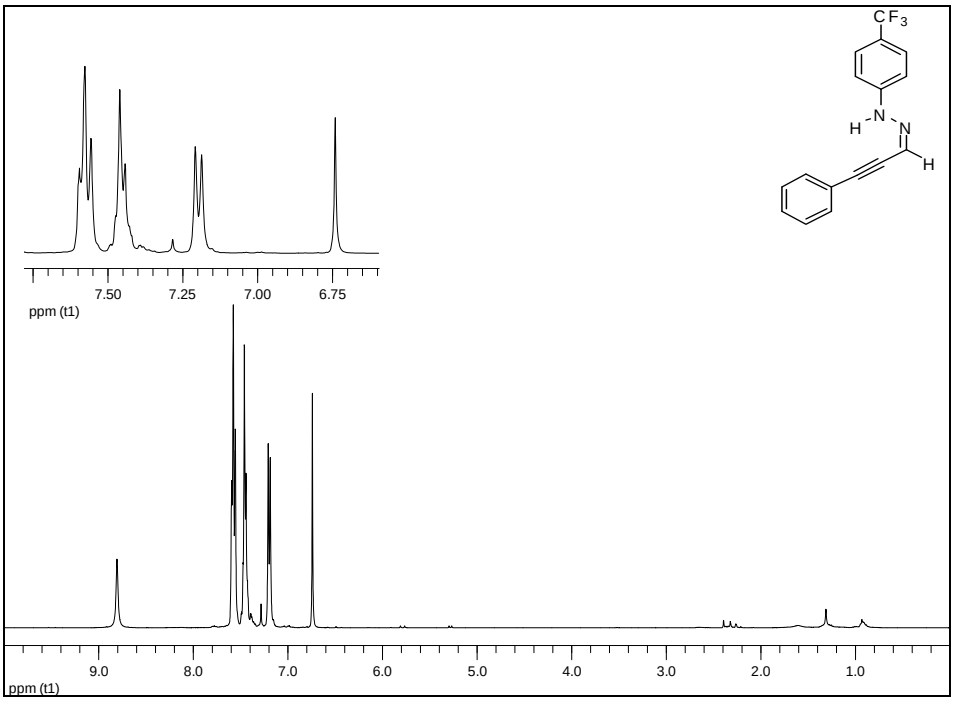

Figure A12. ^{1}H NMR spectra of ***Z*-186g.**

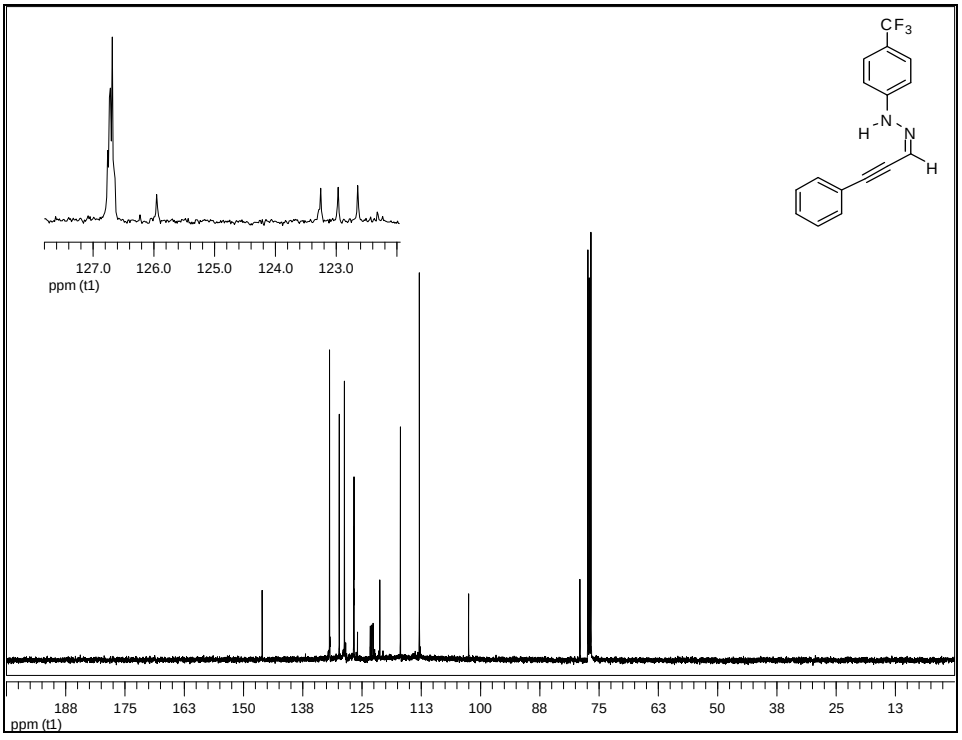

Figure A13. ^{13}C NMR spectra of ***Z*-186g.**

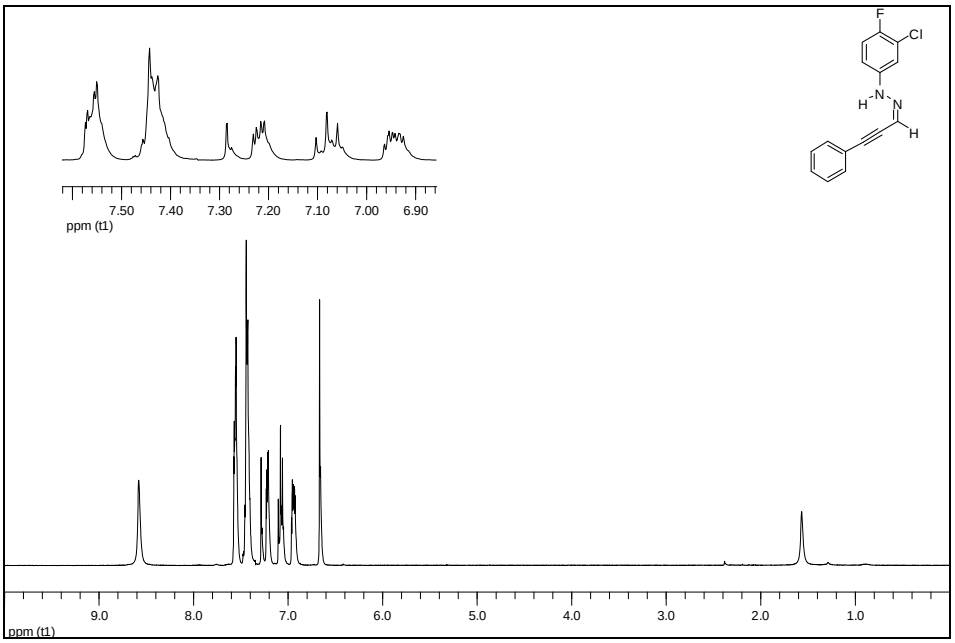

Figure A14. ^{1}H NMR spectra of ***Z*-186h.**

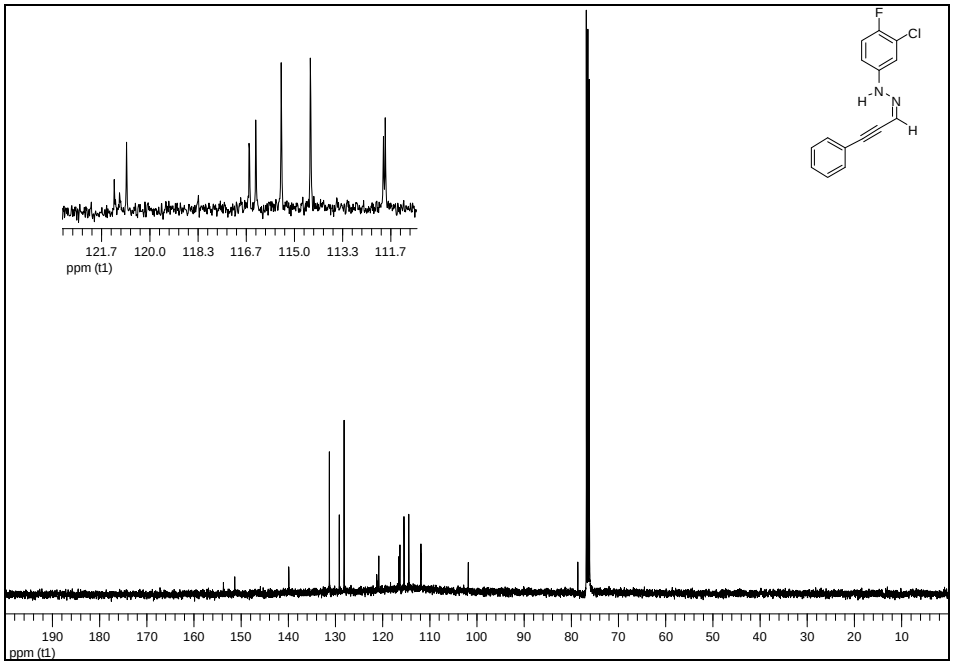

Figure A15. ^{13}C NMR spectra of ***Z*-186h.**

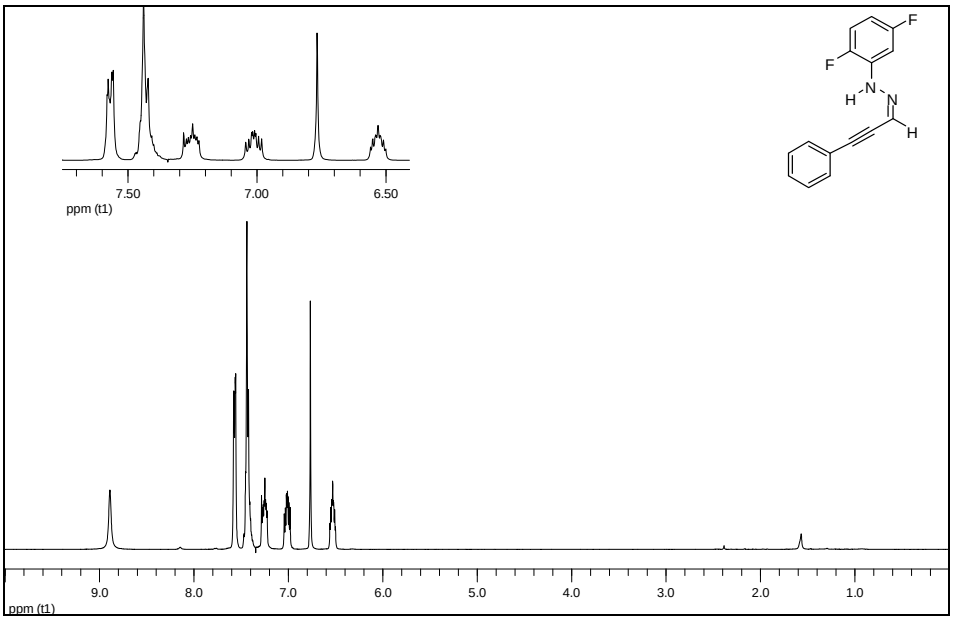

Figure A16. ^{1}H NMR spectra of ***Z*-186i.**

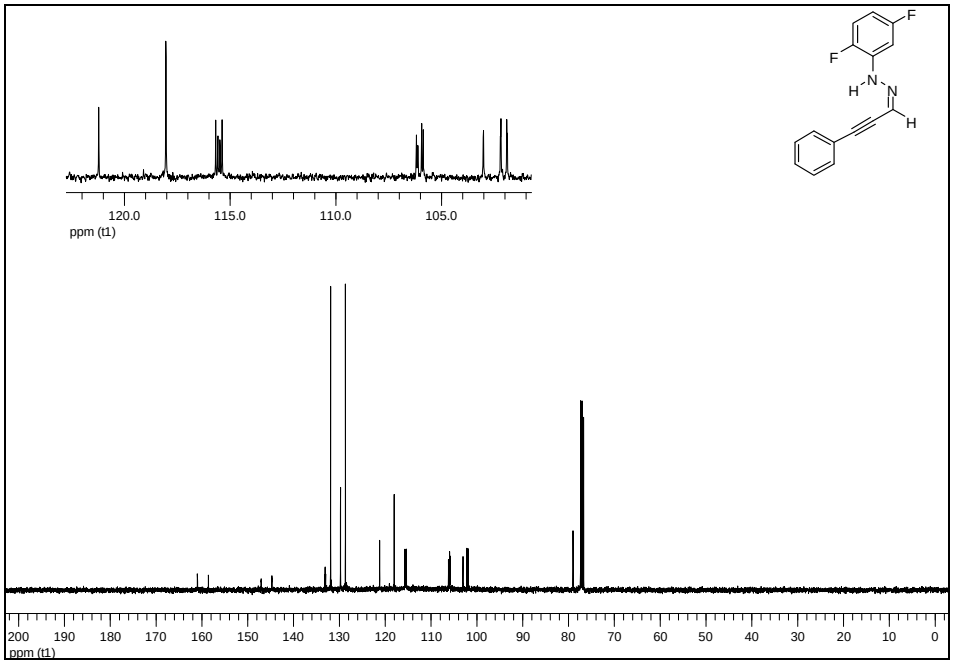

Figure A17. ^{13}C NMR spectra of ***Z*-186i.**

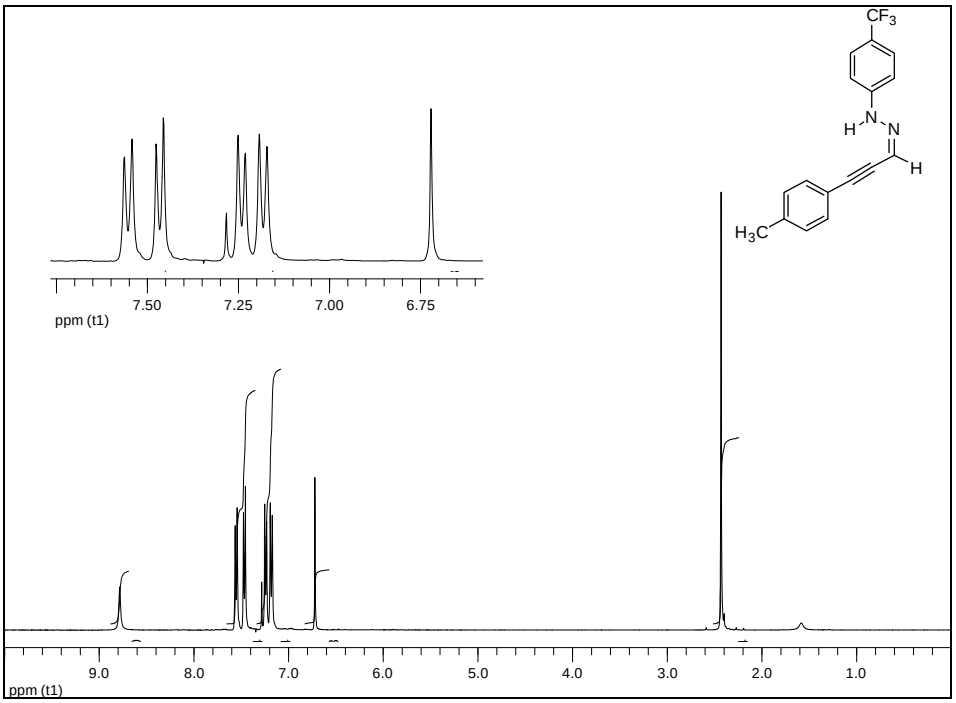

Figure A18. ^{1}H NMR spectra of ***Z*-186j**.

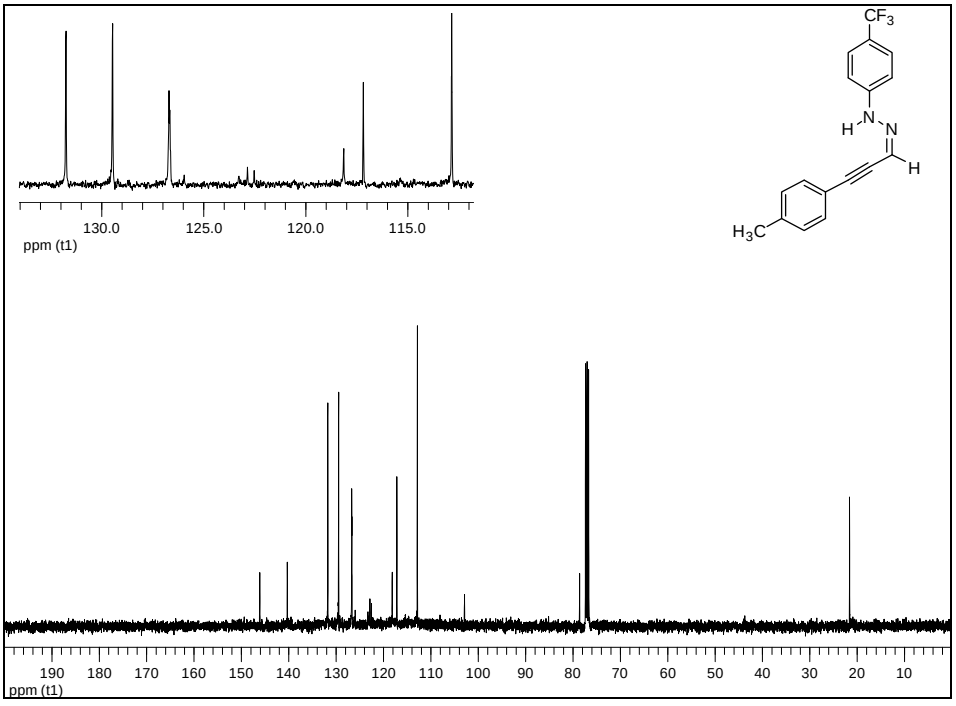

Figure A19. ^{13}C NMR spectra of ***Z*-186j.**

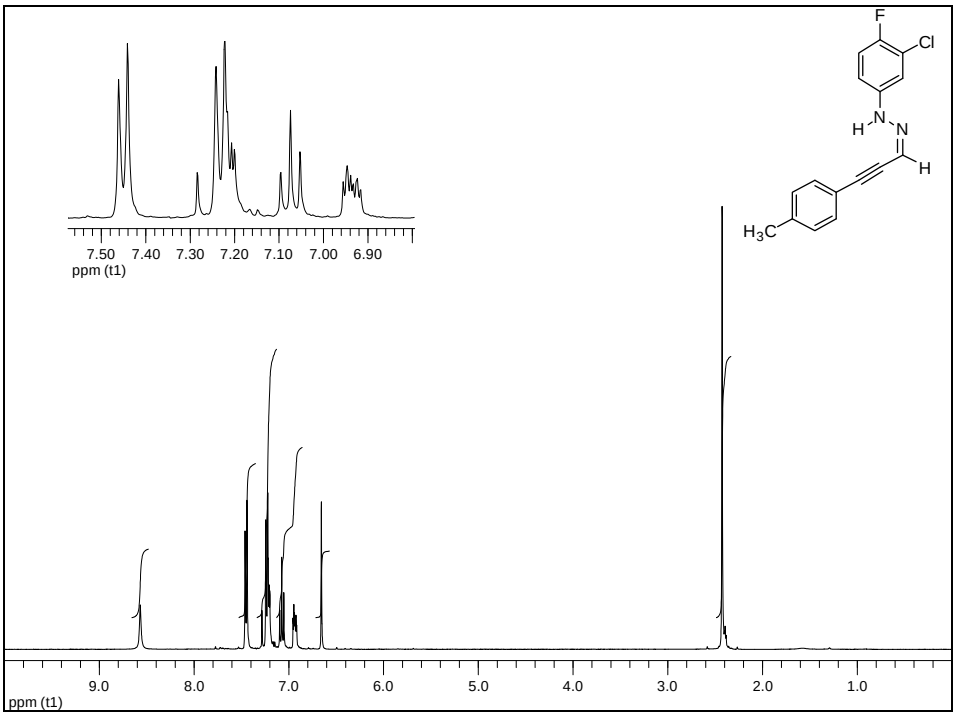

Figure A20. ^{1}H NMR spectra of ***Z*-186k**.

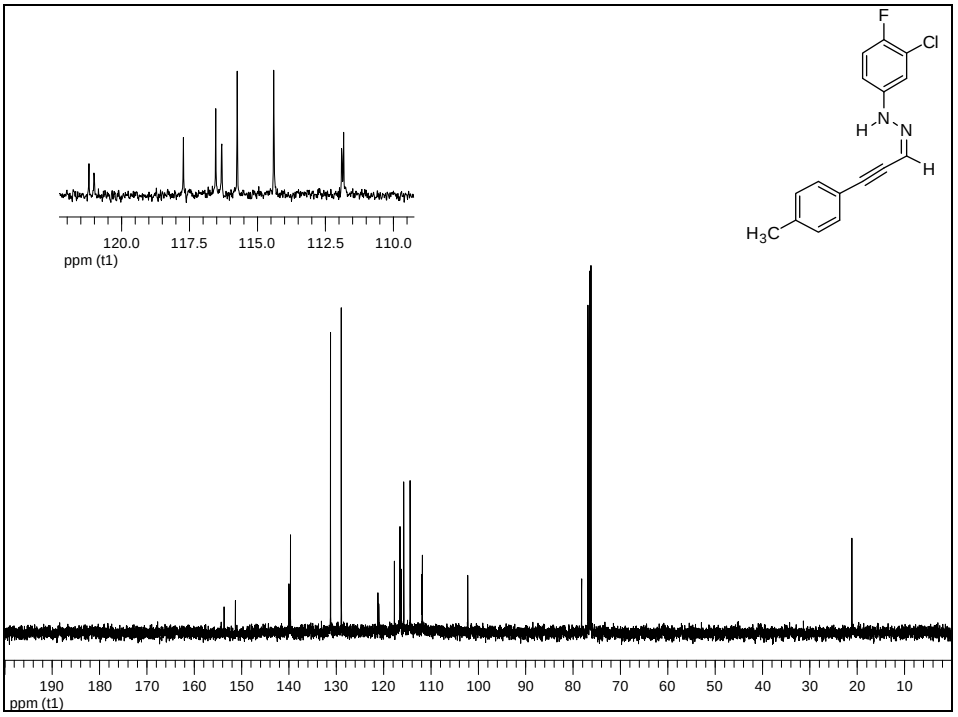

Figure A21. ^{13}C NMR spectra of ***Z*-186k.**

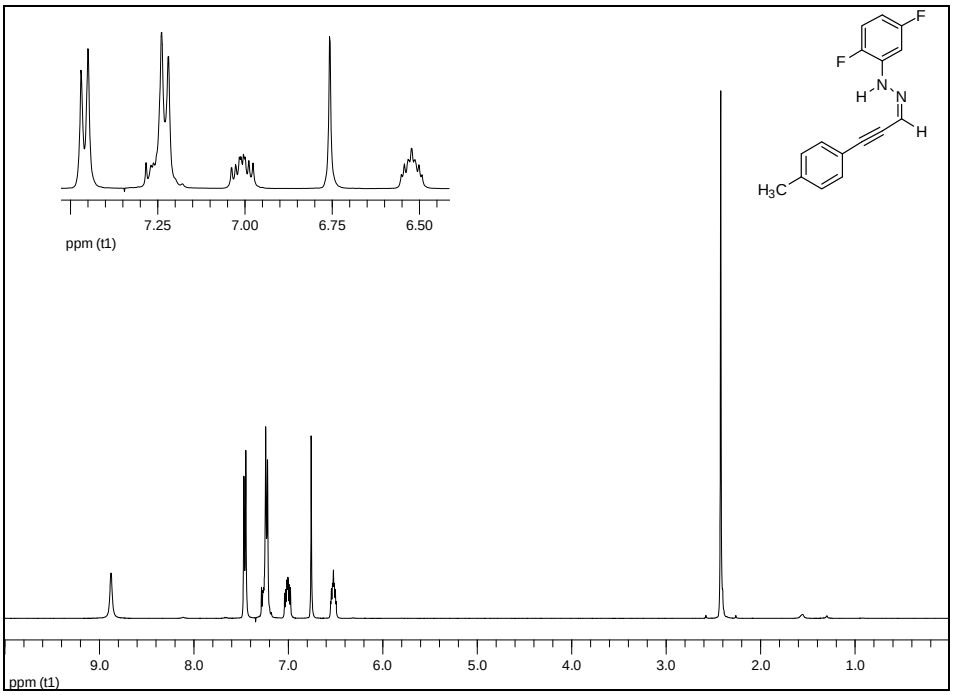

Figure A22. ^{1}H NMR spectra of ***Z*-186l**.

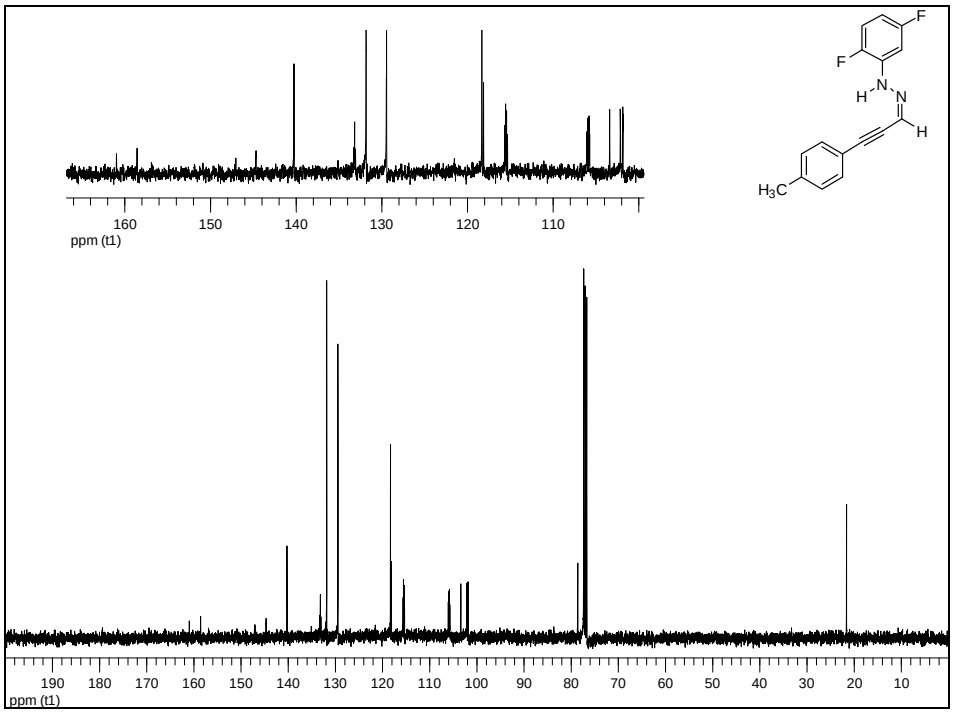

Figure A23. ^{13}C NMR spectra of ***Z*-186l**.

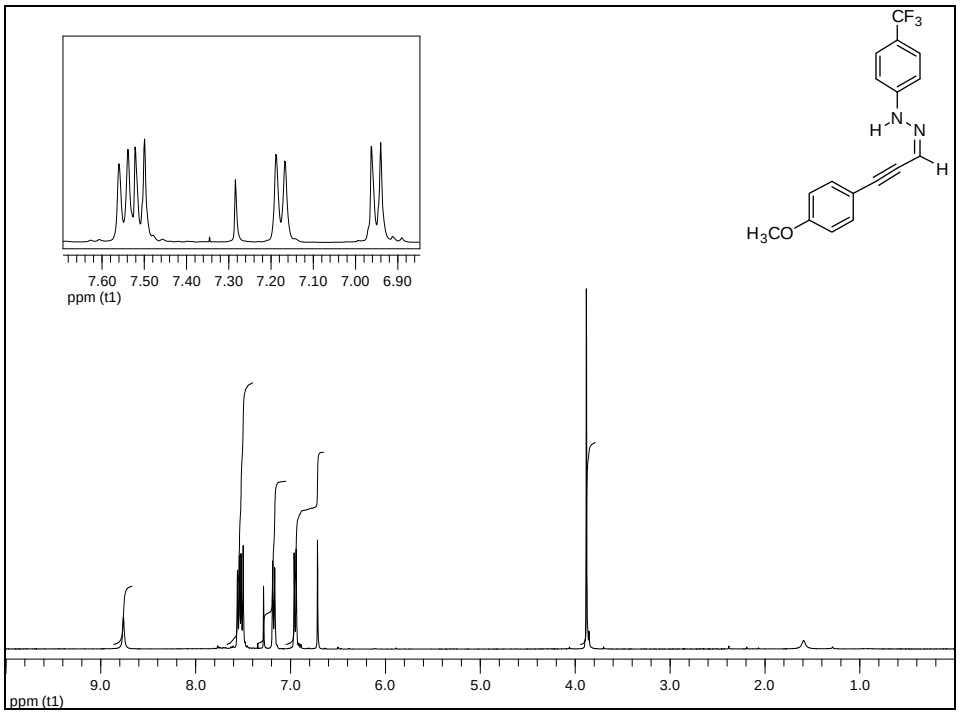

Figure A24. ^{1}H NMR spectra of ***Z*-186m**.

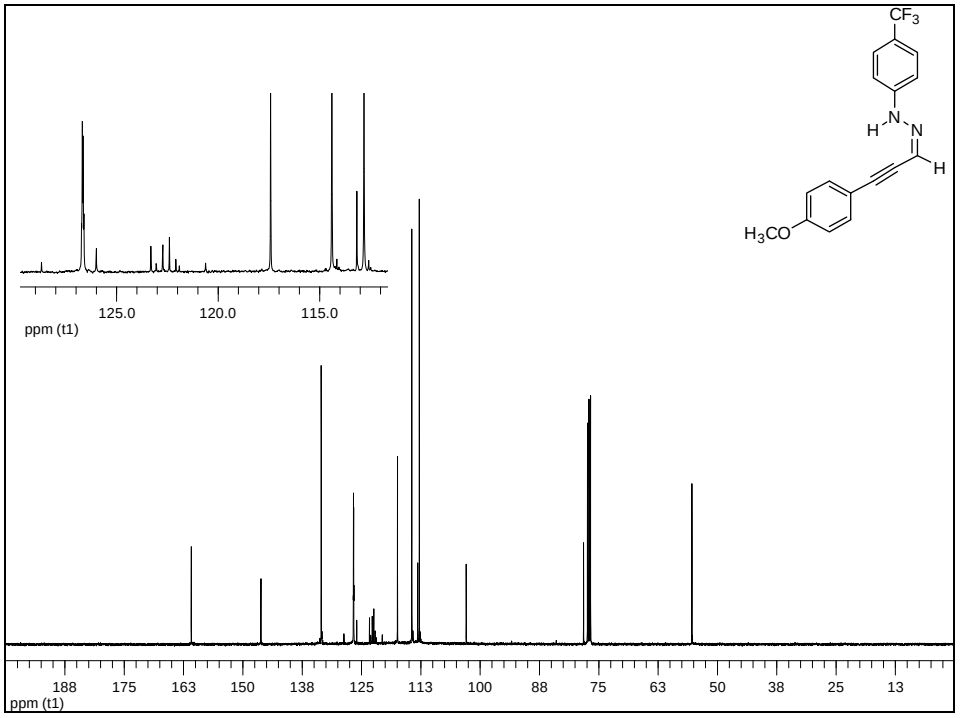

Figure A25. ^{13}C NMR spectra of ***Z*-186m**.

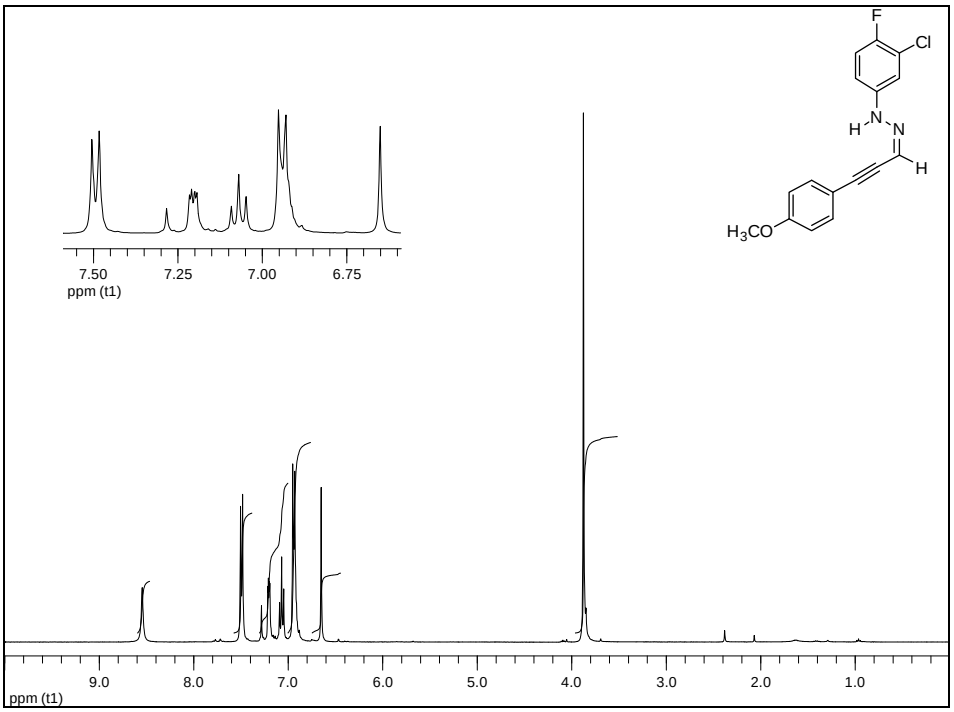

Figure A26. ^{1}H NMR spectra of ***Z*-186n**.

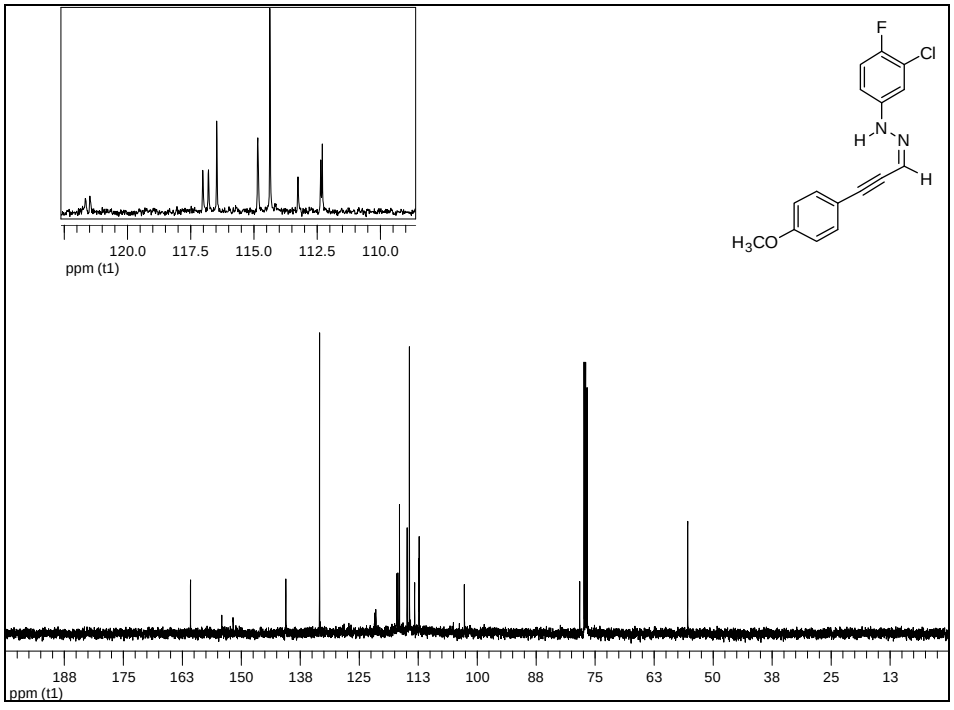

Figure A27. ^{13}C NMR spectra of ***Z*-186n.**

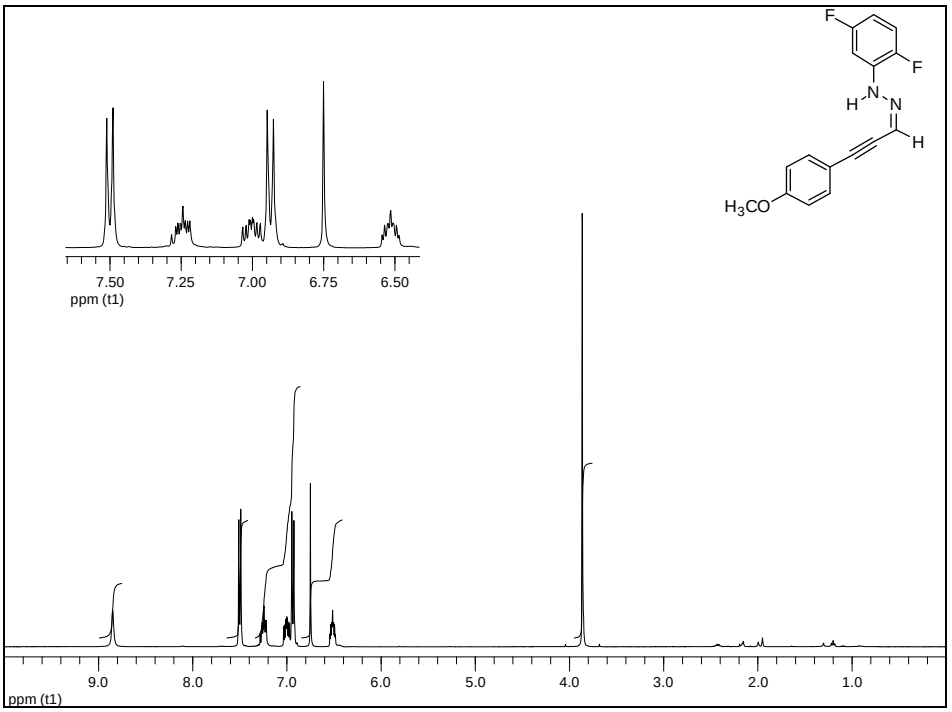

Figure A28. ^{1}H NMR spectra of ***Z*-186o**.

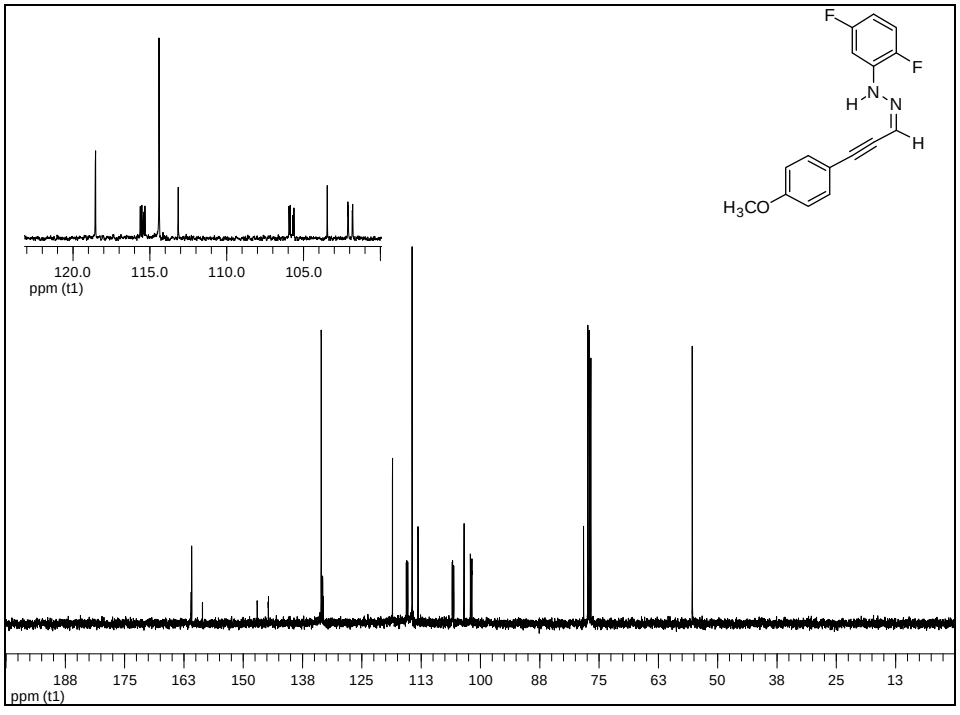

Figure A29. ^{13}C NMR spectra of ***Z*-186o.**

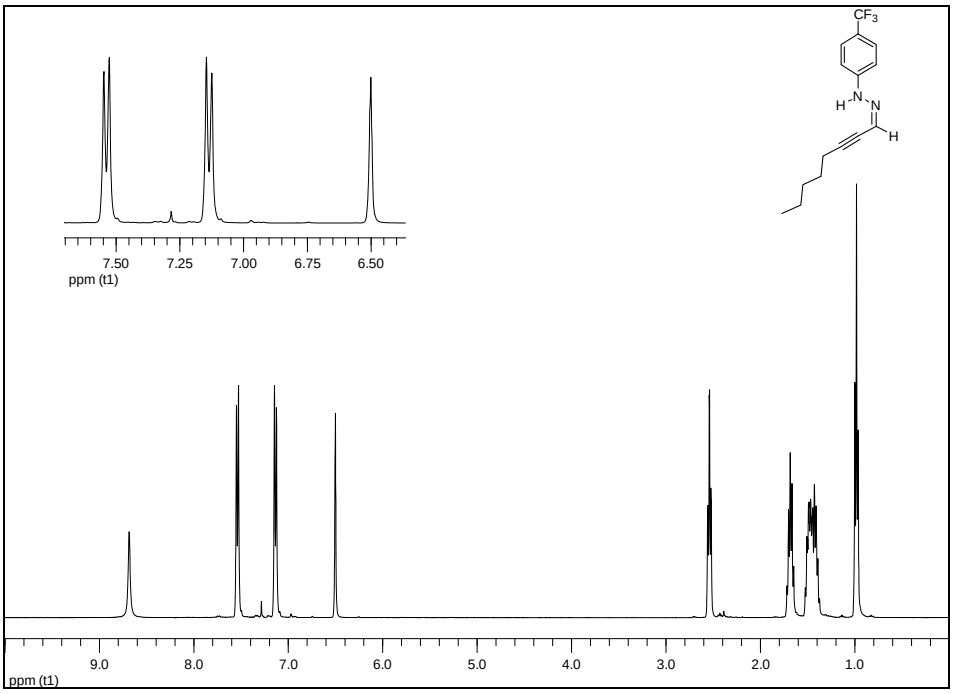

Figure A30. ^{1}H NMR spectra of ***Z*-186p**.

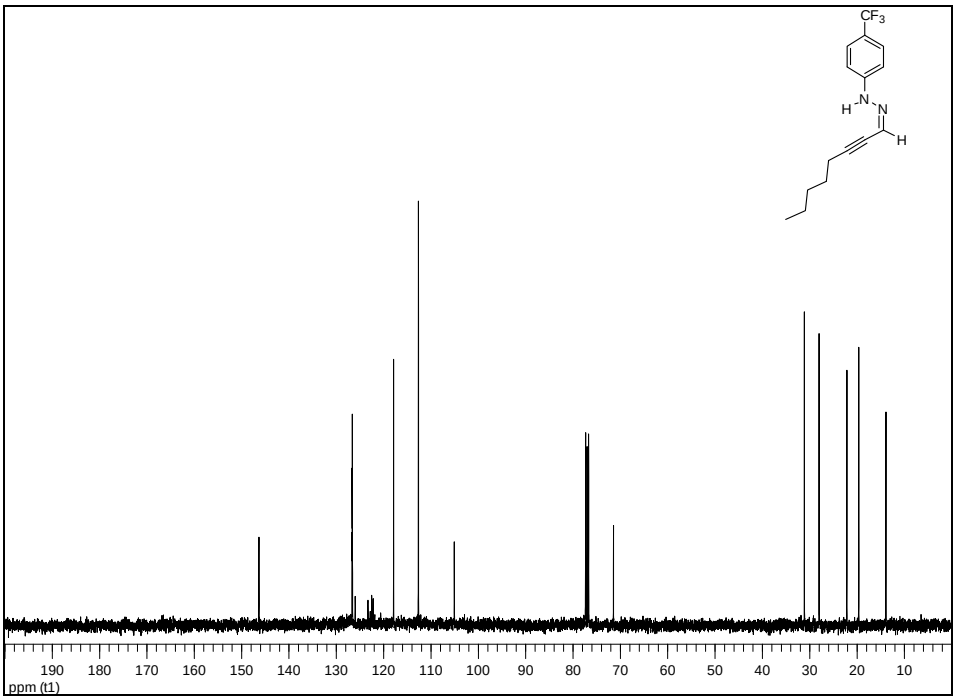

Figure A31. ^{13}C NMR spectra of ***Z*-186p.**

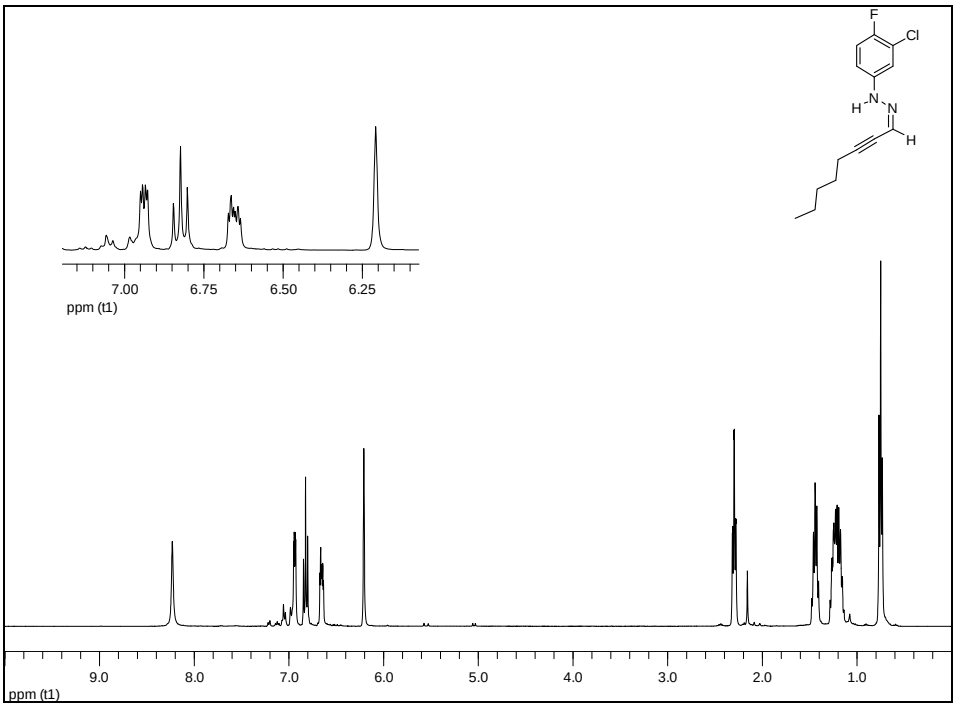

Figure A32. ^{1}H NMR spectra of ***Z*-186q**.

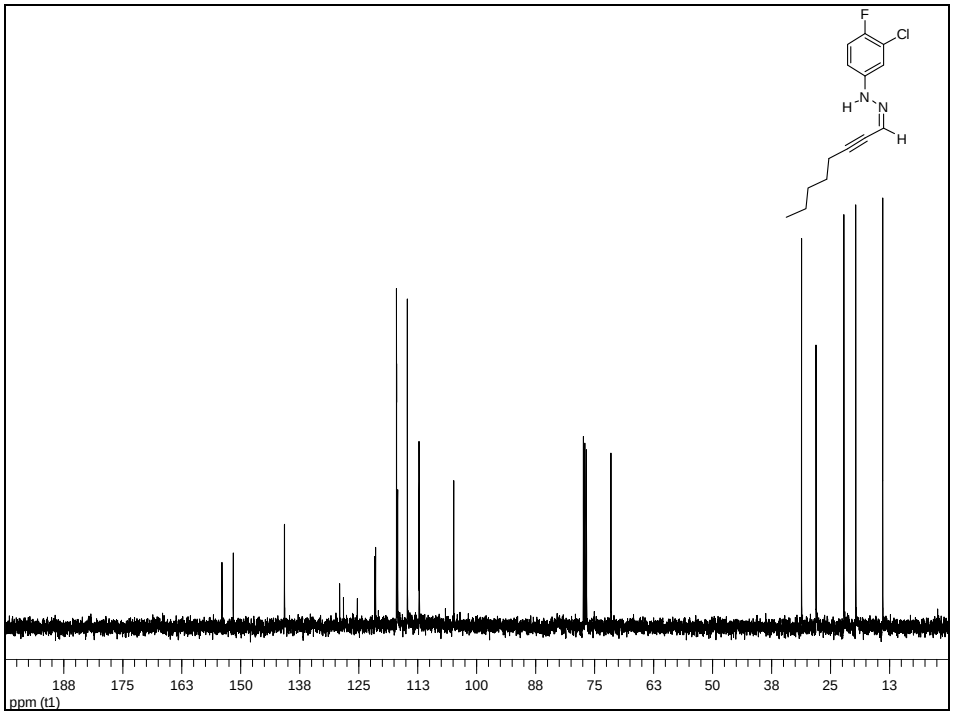

Figure A33. ^{13}C NMR spectra of ***Z*-186q.**

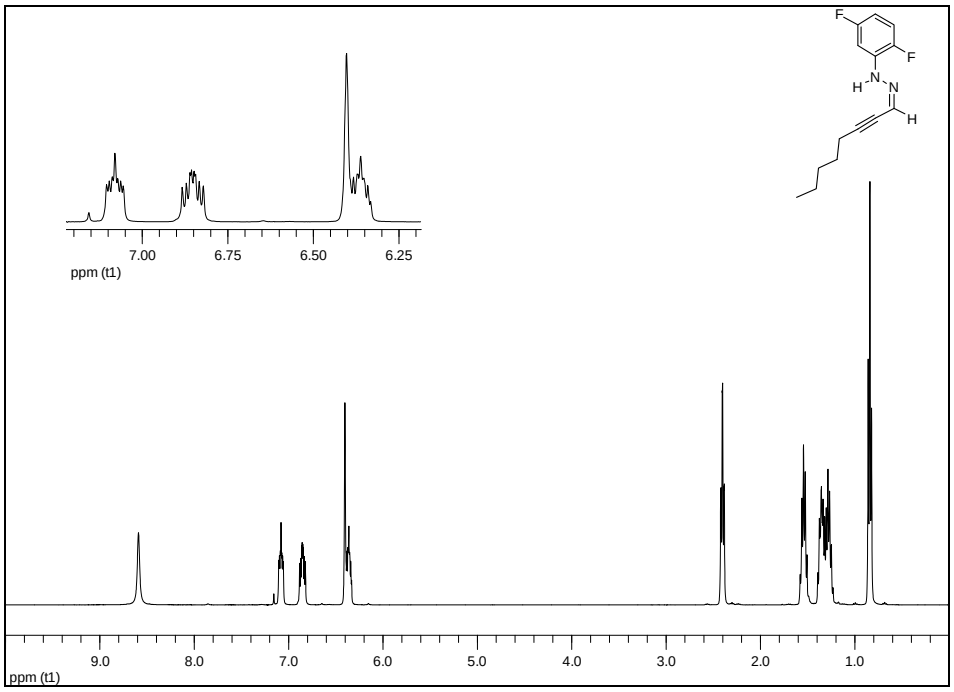

Figure A34. ^{1}H NMR spectra of ***Z*-186r**.

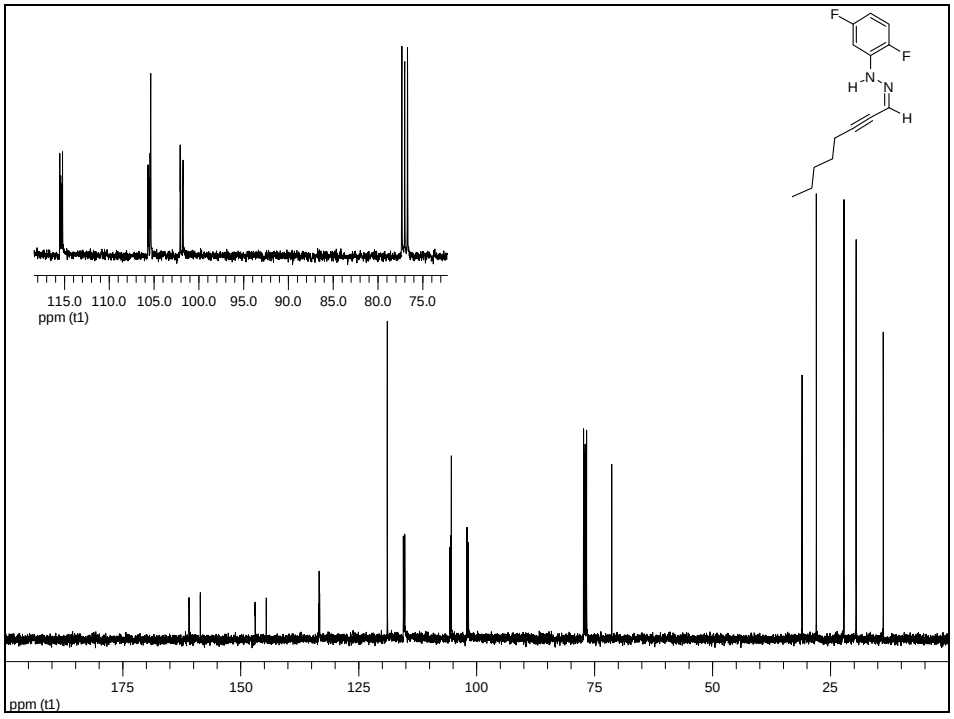

Figure A35. ^{13}C NMR spectra of ***Z*-186r**.

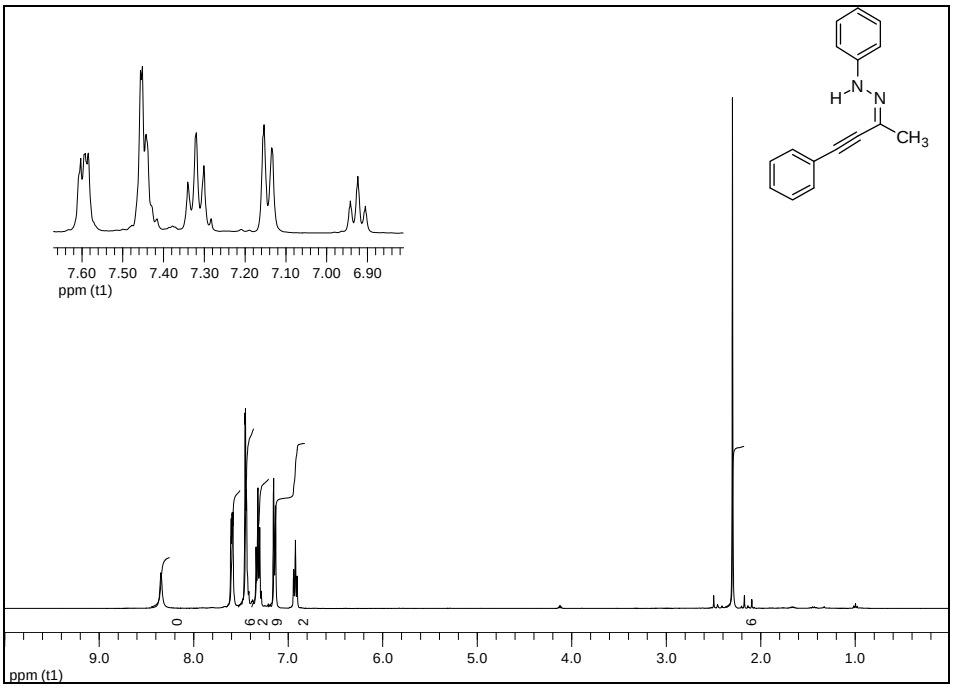

Figure A36. ^{1}H NMR spectra of ***Z*-186s**.

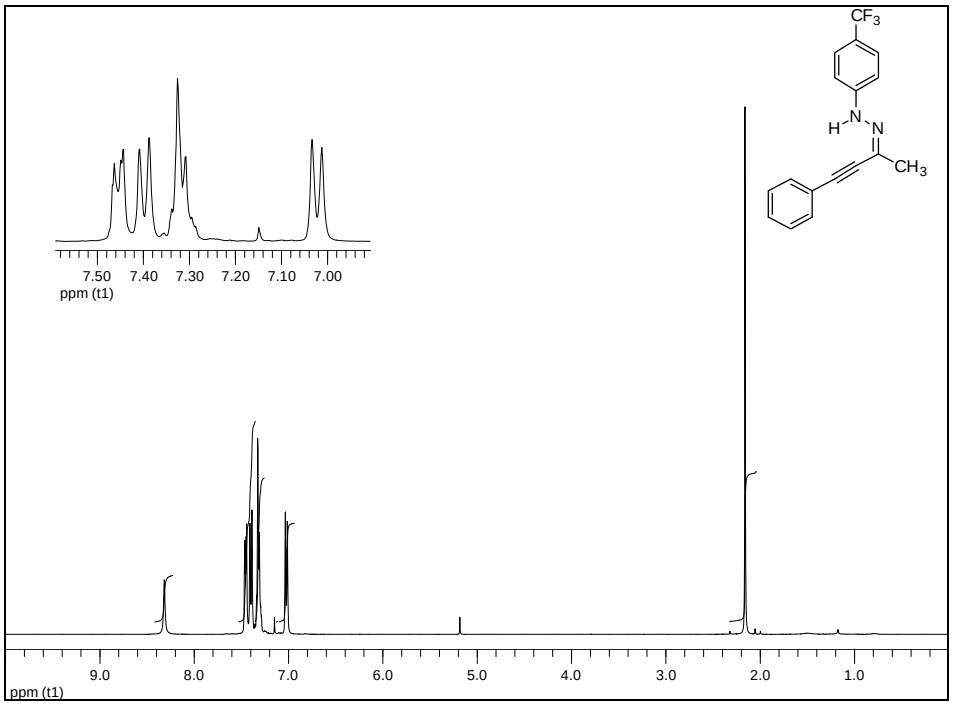

Figure A37. ^{1}H NMR spectra of ***Z*-186t**.

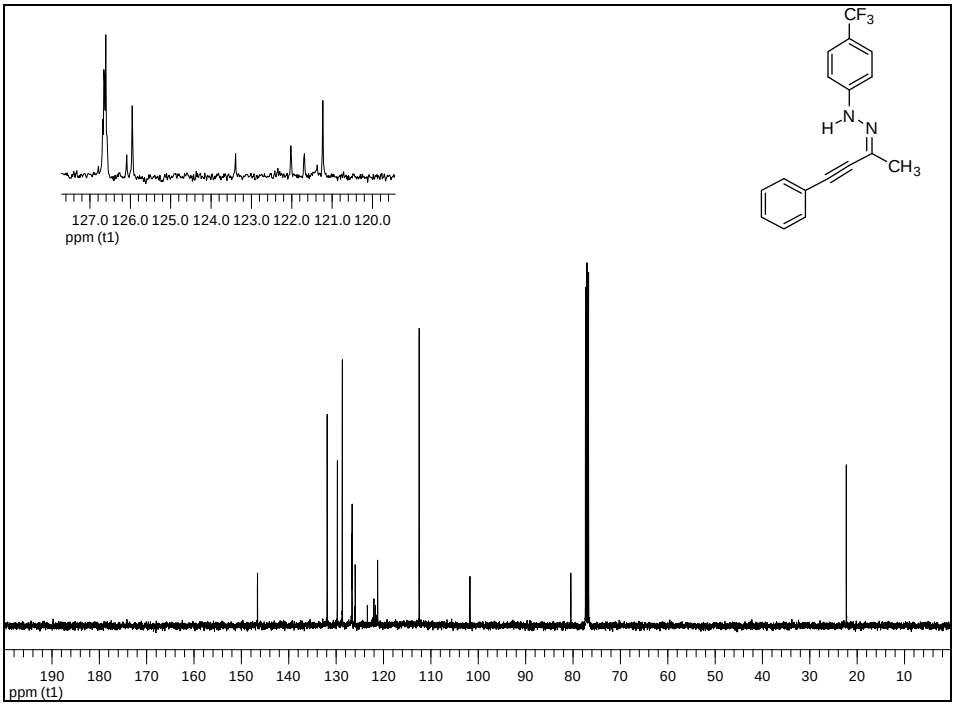

Figure A38. ^{13}C NMR spectra of ***Z*-186t**.

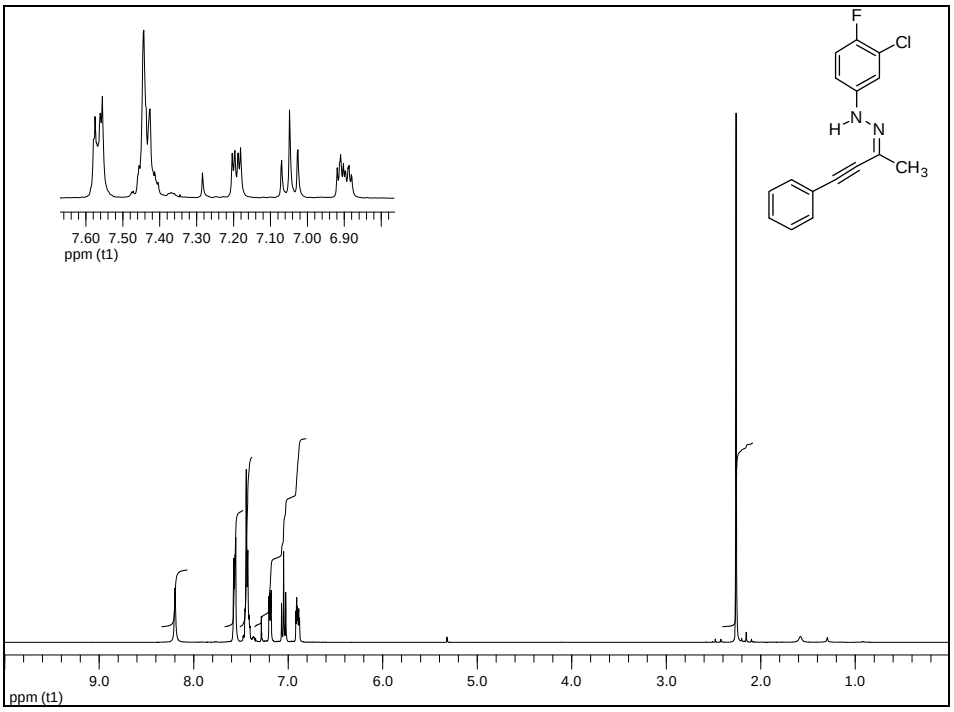

Figure A39. ^{1}H NMR spectra of ***Z*-186u**.

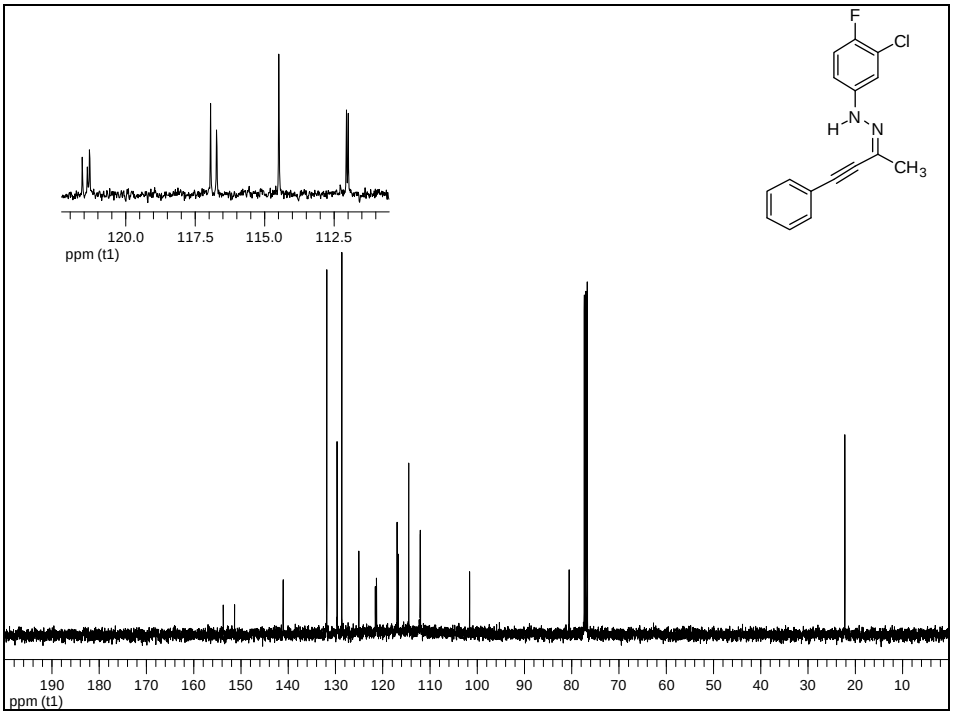

Figure A40. ^{13}C NMR spectra of ***Z*-186u**.

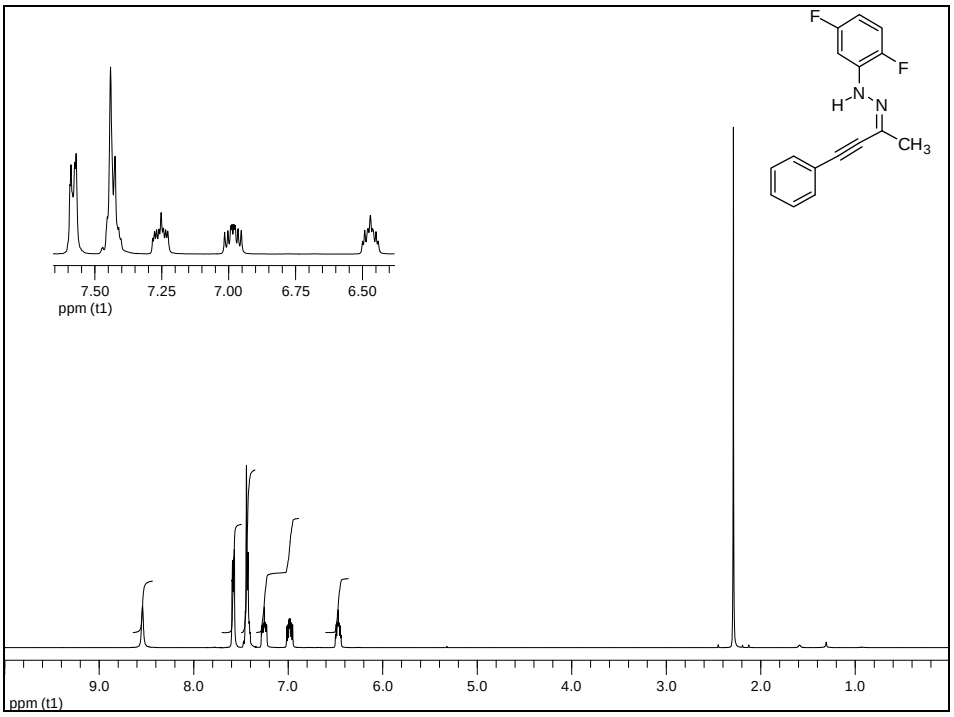

Figure A41. ^{1}H NMR spectra of ***Z*-186v.**

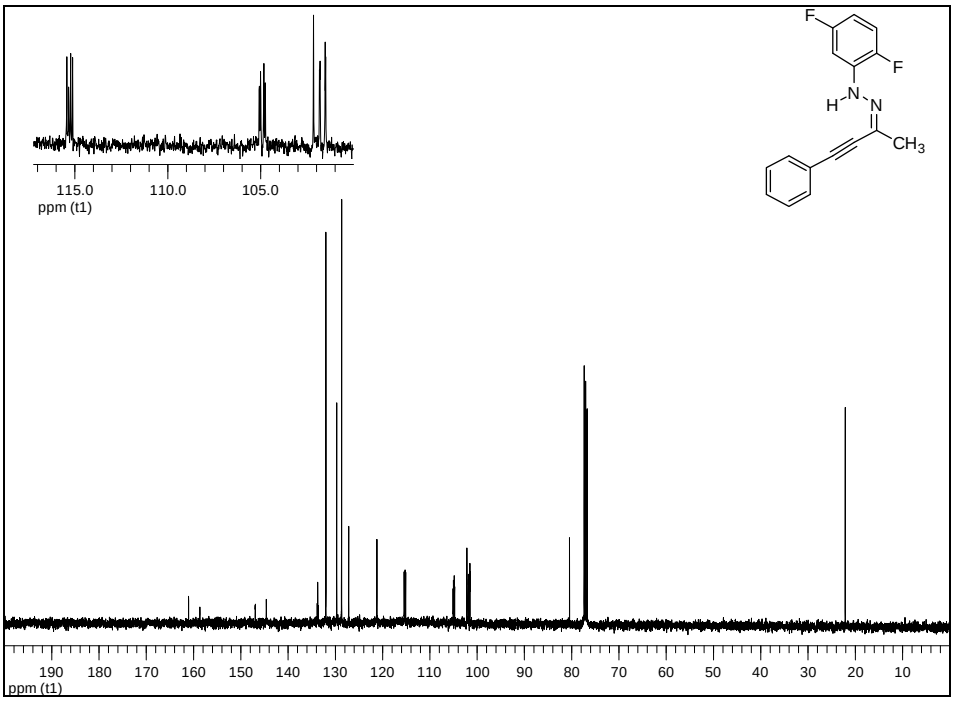

Figure A42. ^{13}C NMR spectra of ***Z*-186v.**

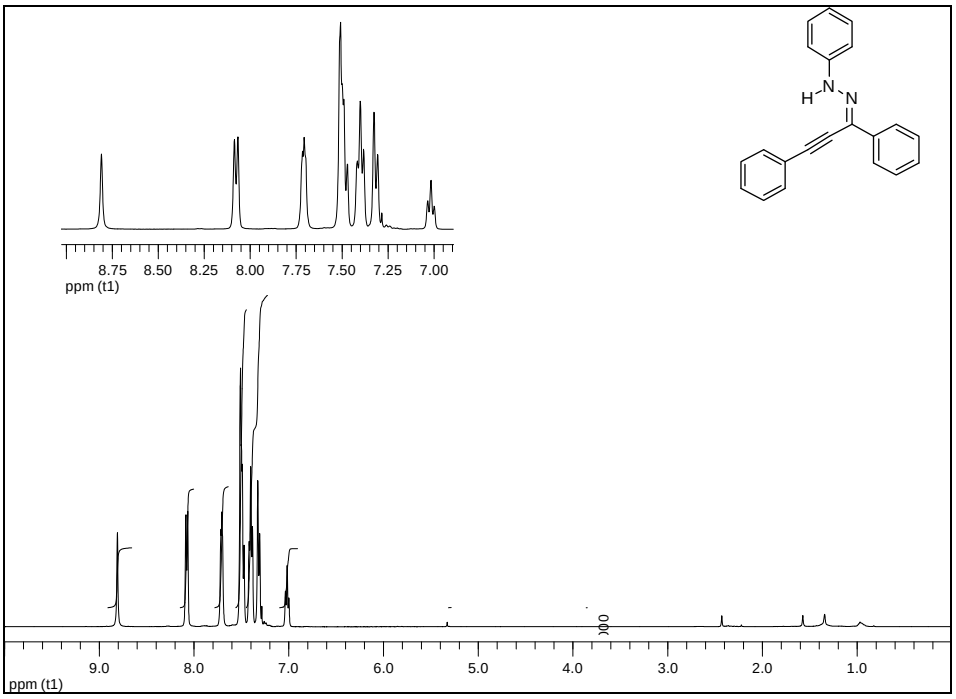

Figure A43. ^{1}H NMR spectra of ***Z*-186w**.

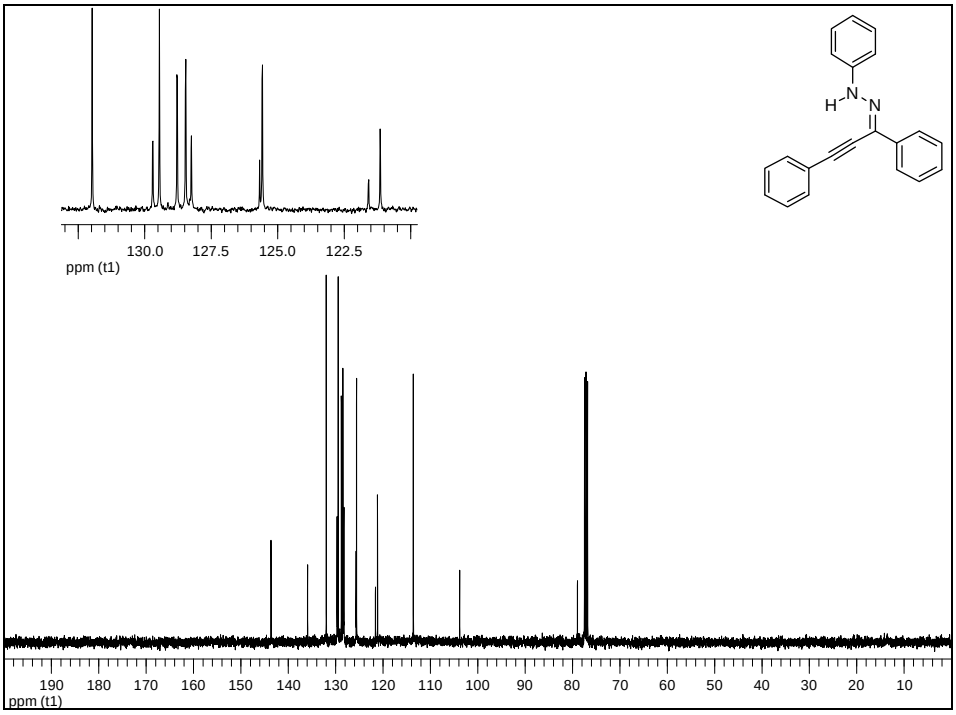

Figure A44. ^{13}C NMR spectra of ***Z*-186w**.

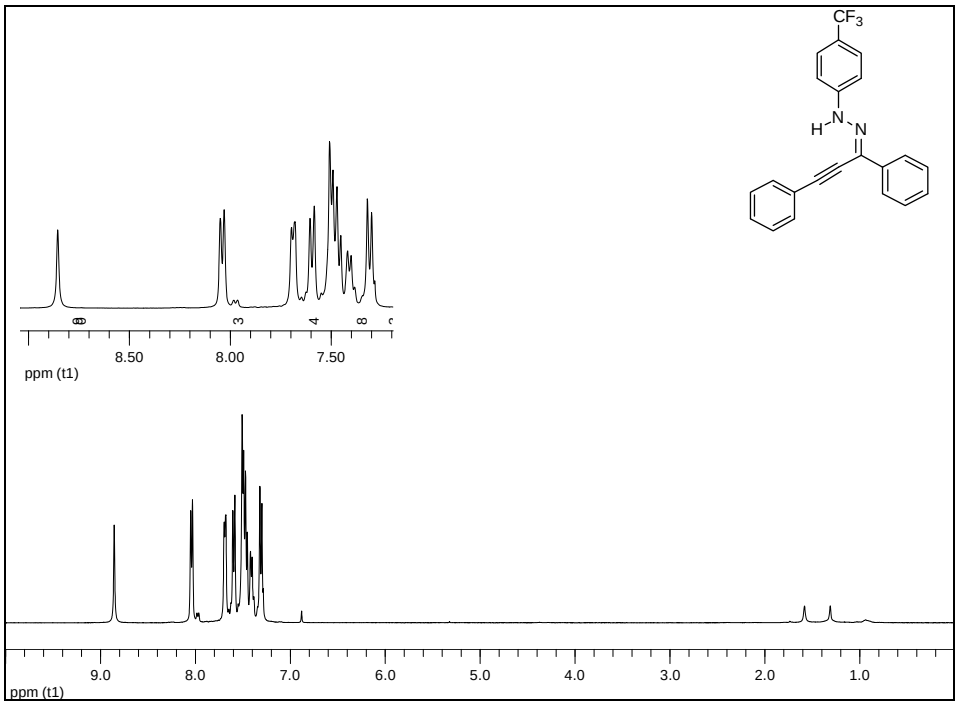

Figure A45. ^{1}H NMR spectra of ***Z*-186x**.

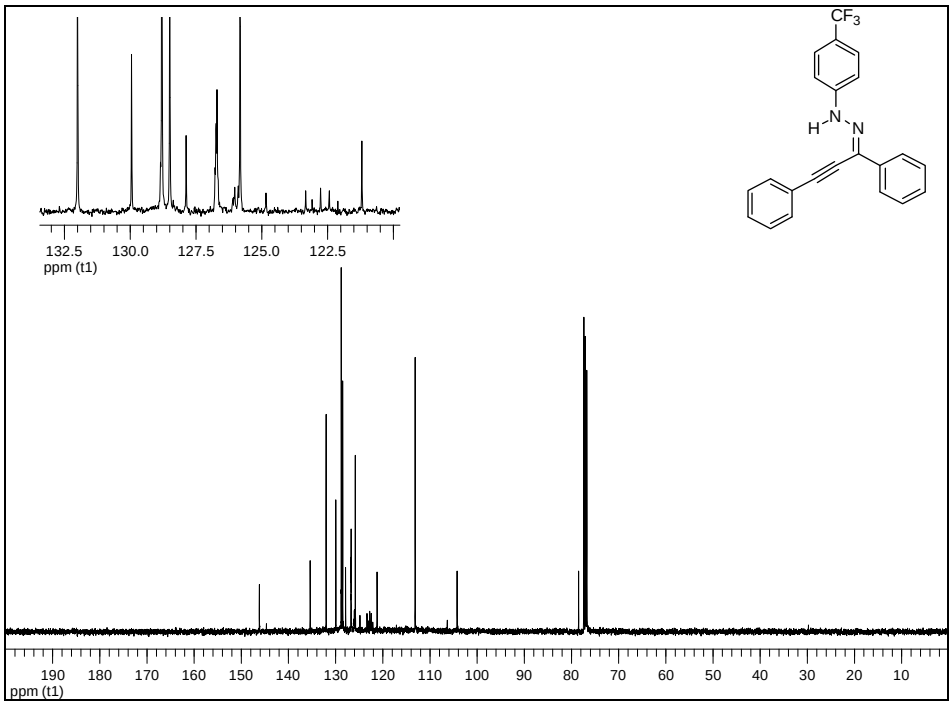

Figure A46. ^{13}C NMR spectra of ***Z*-186x**.

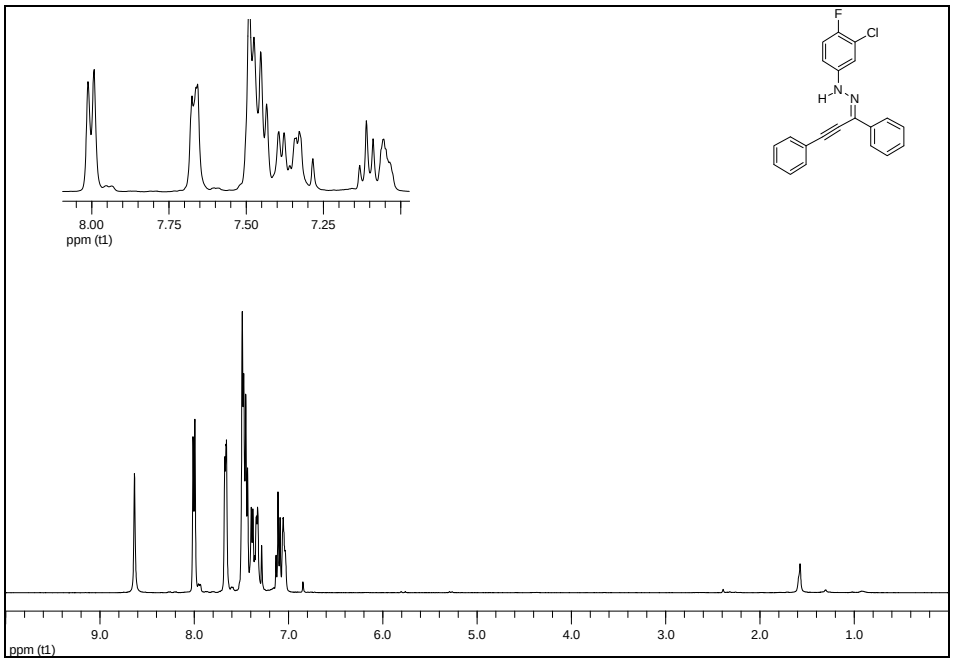

Figure A47. ^{1}H NMR spectra of ***Z*-186y**.

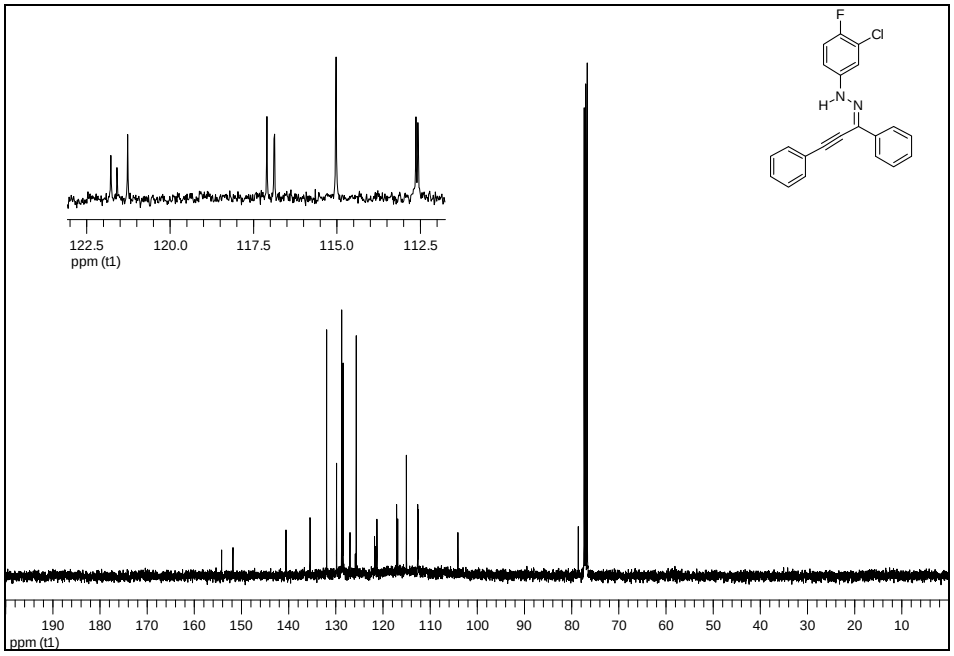

Figure A48. ^{13}C NMR spectra of ***Z*-186y**.

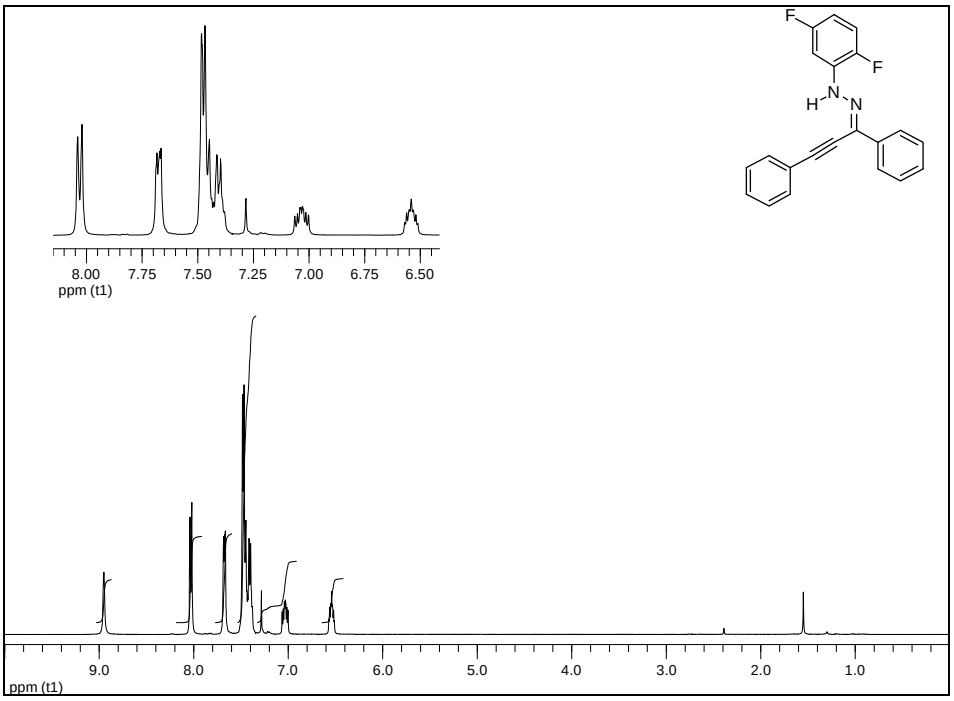

Figure A49. ^{1}H NMR spectra of ***Z*-186z**.

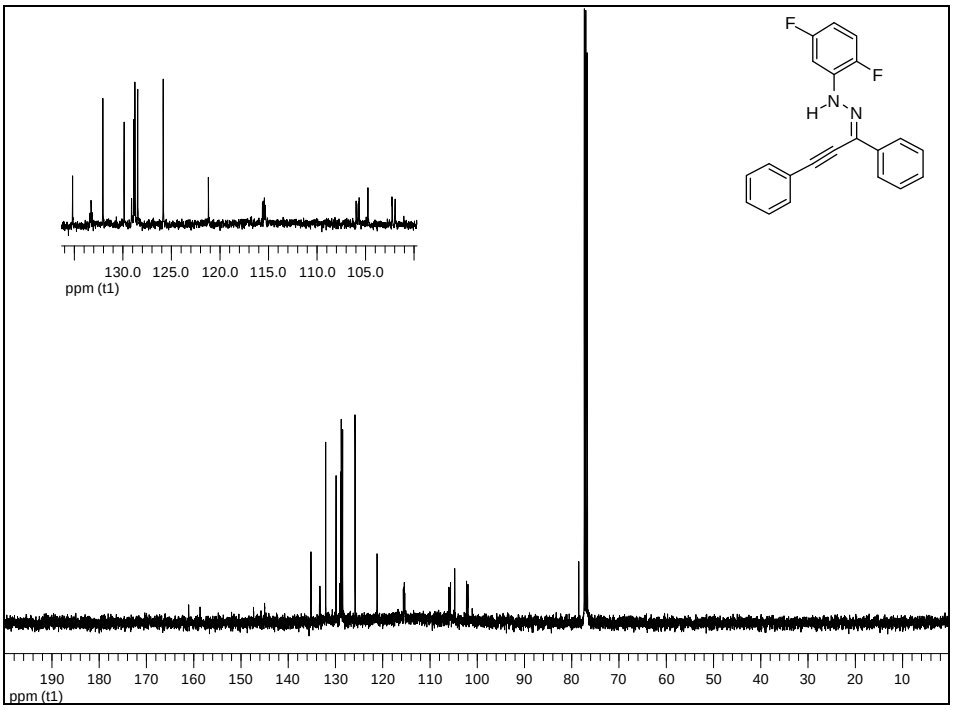

Figure A50. ^{13}C NMR spectra of ***Z*-186z**.

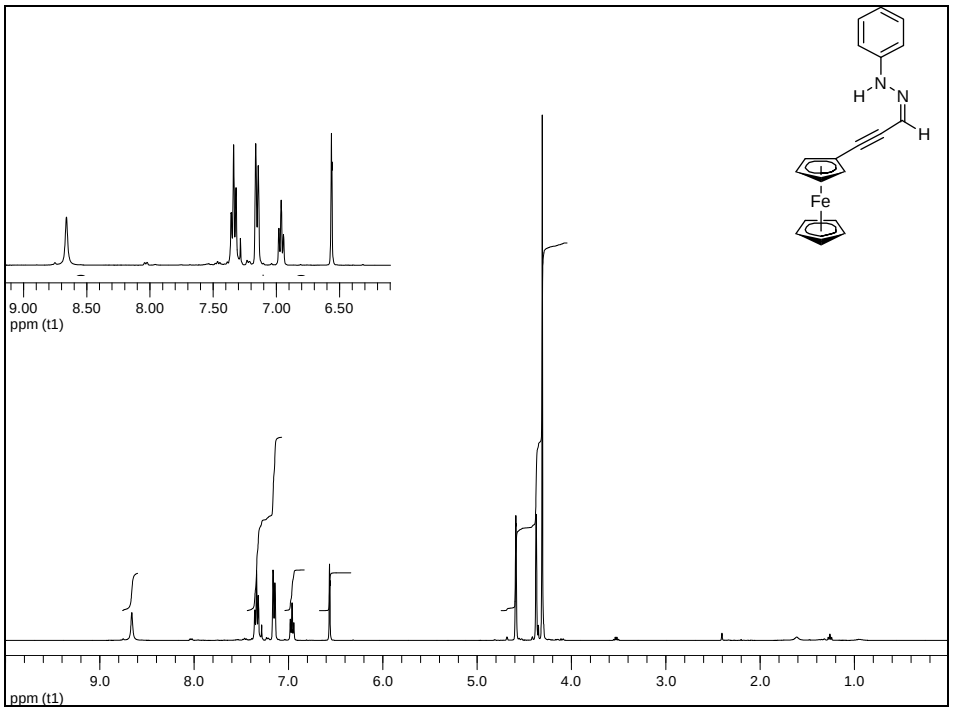

Figure A51. ^{1}H NMR spectra of ***Z*-199a.**

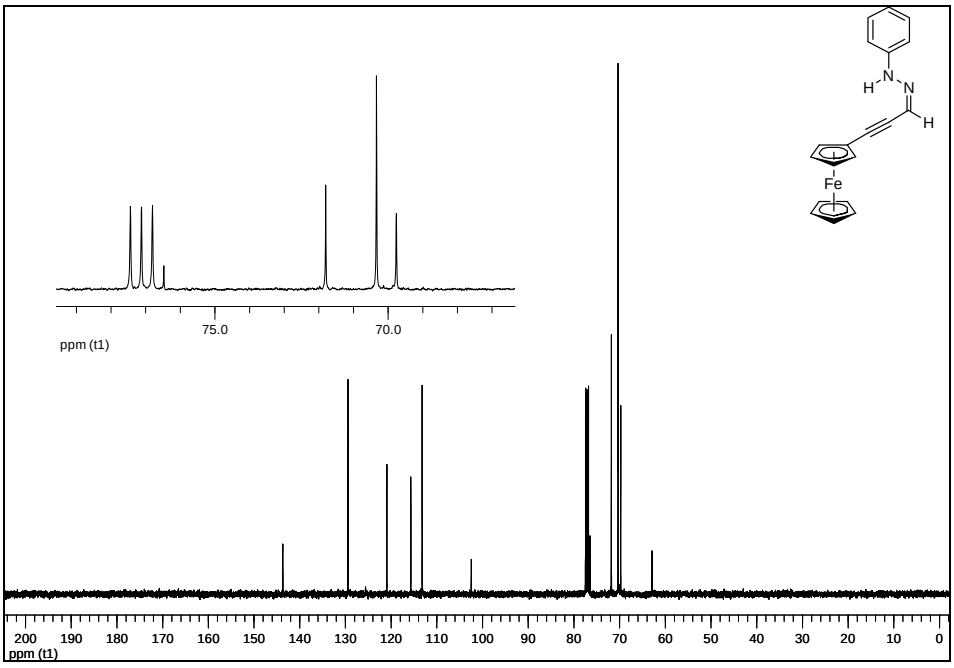

Figure A52. ^{13}C NMR spectra of ***Z*-199a.**

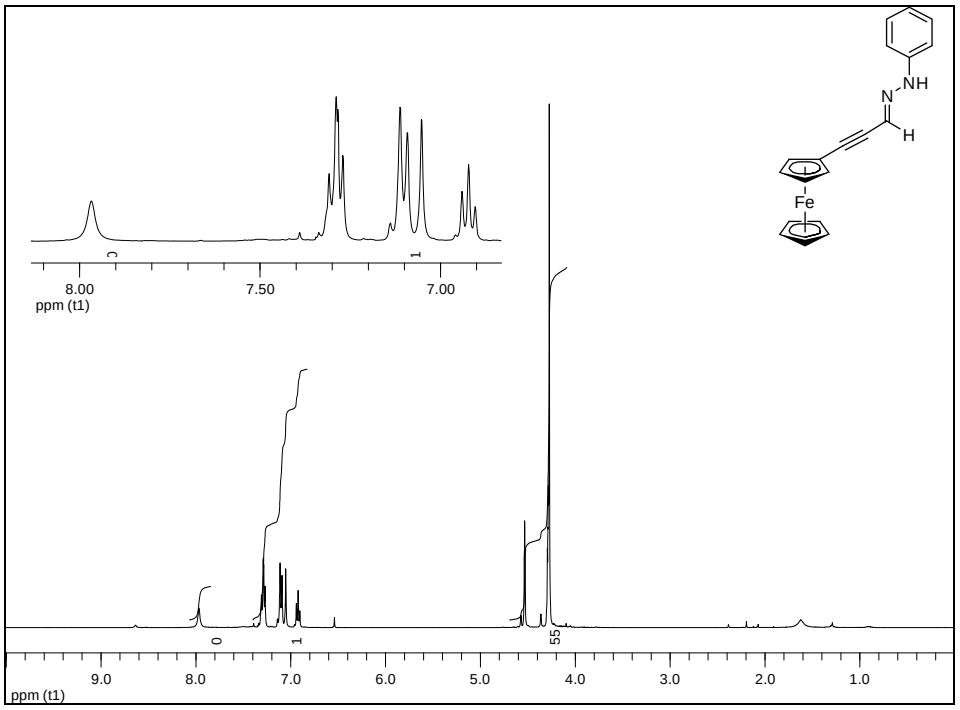

Figure A53. ^{1}H NMR spectra of ***E*-199a.**

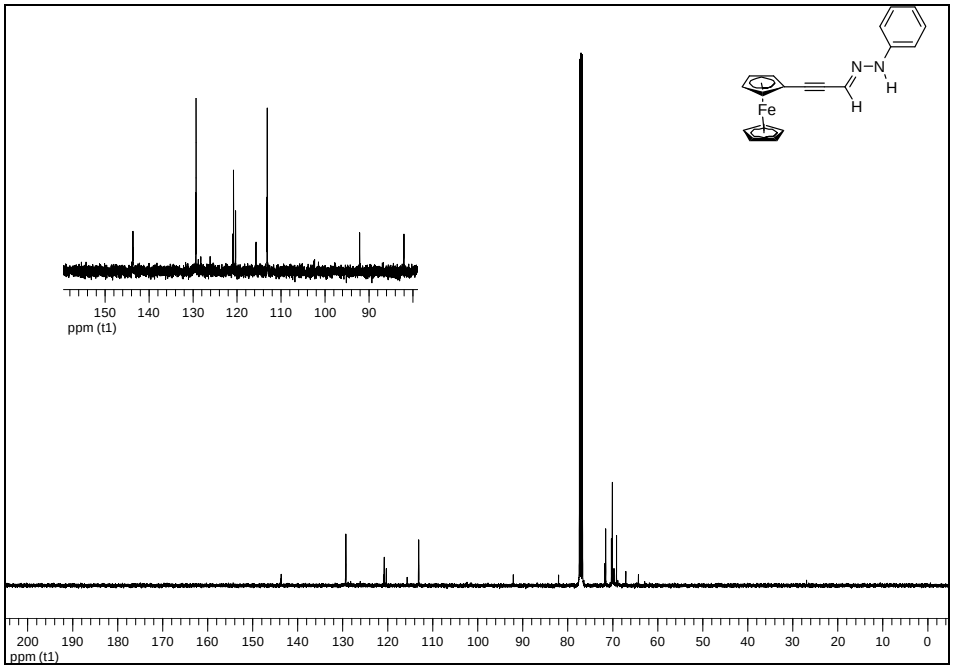

Figure A54. ^{13}C NMR spectra of ***E*-199a.**

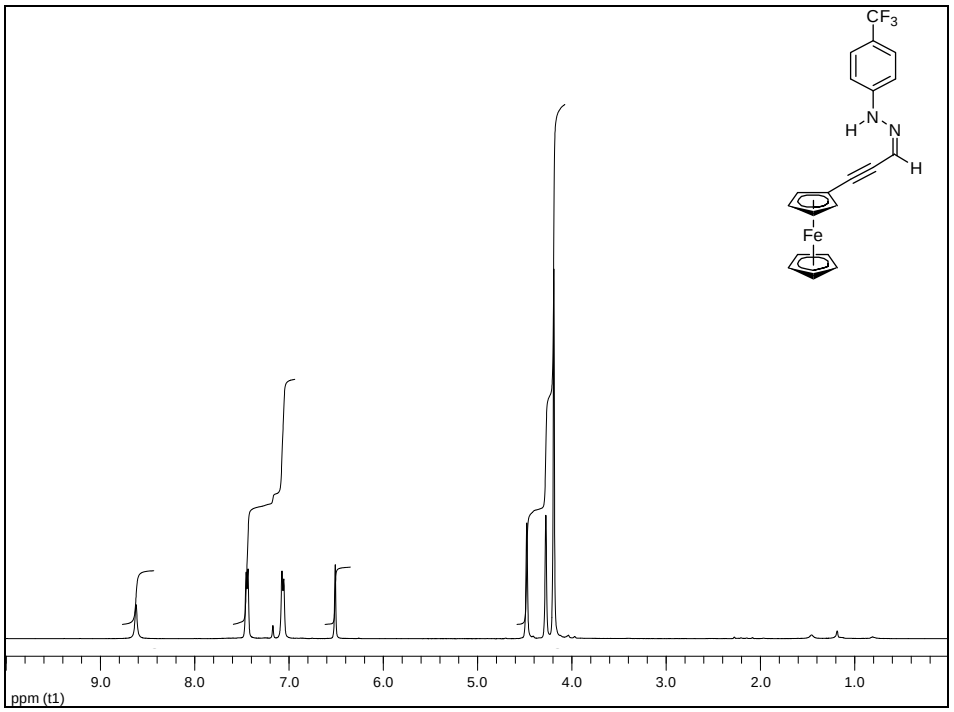

Figure A55. ^{1}H NMR spectra of ***Z*-199b**.

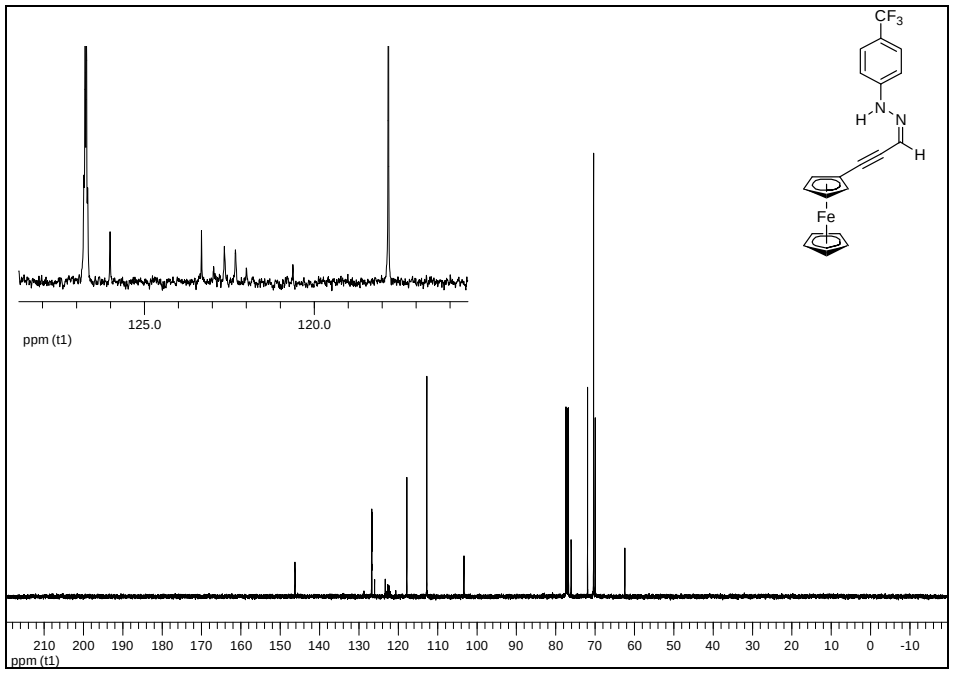

Figure A56. ^{13}C NMR spectra of ***Z*-199b.**

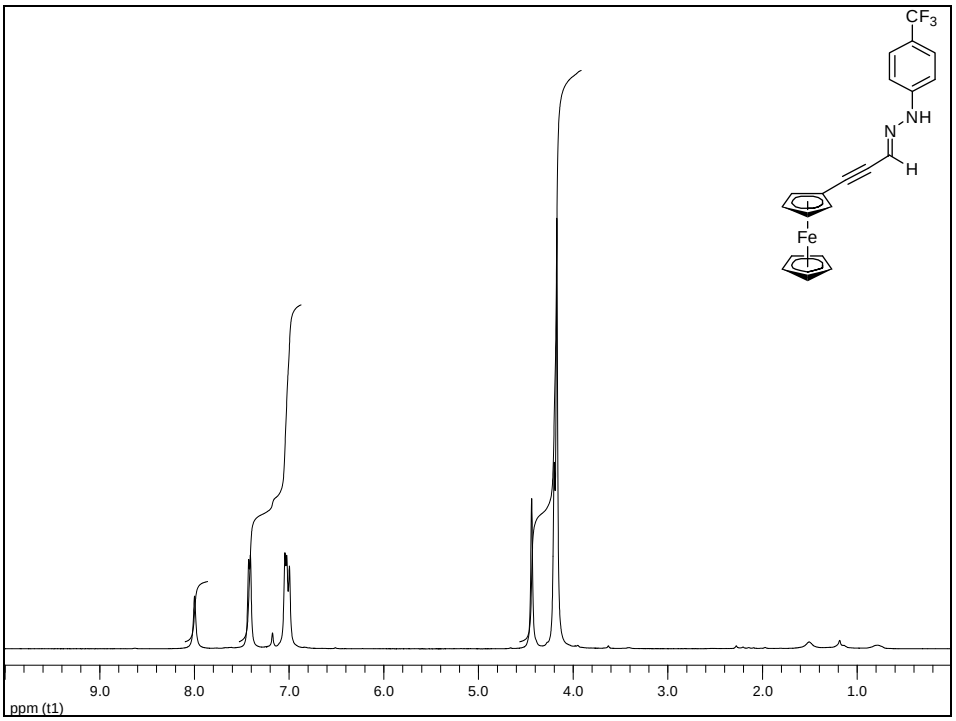

Figure A57. ^{1}H NMR spectra of ***E*-199b**.

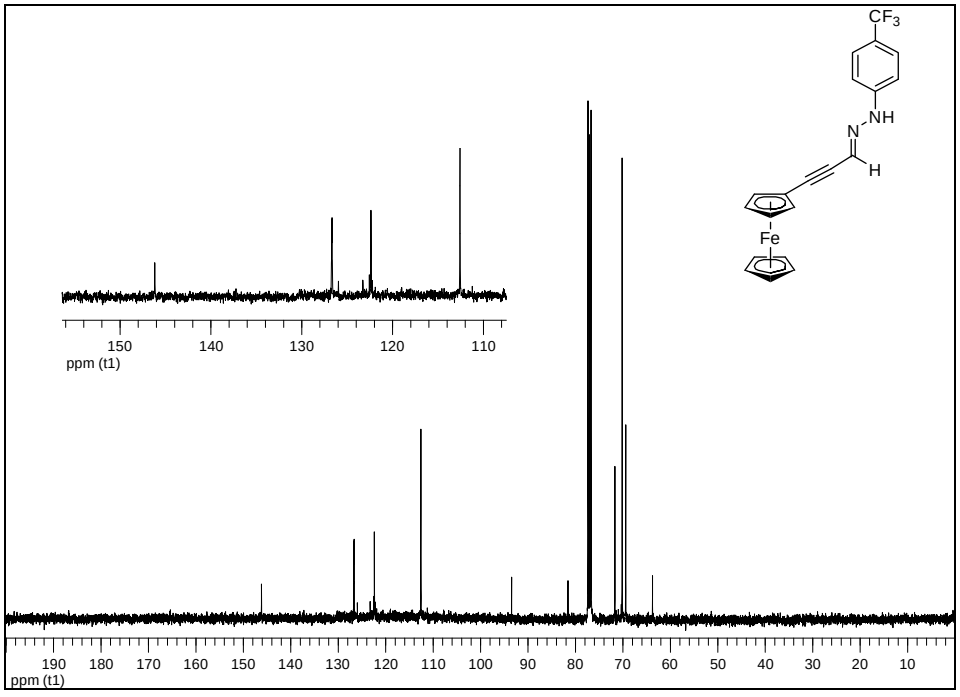

Figure A58. ^{13}C NMR spectra of ***E*-199b.**

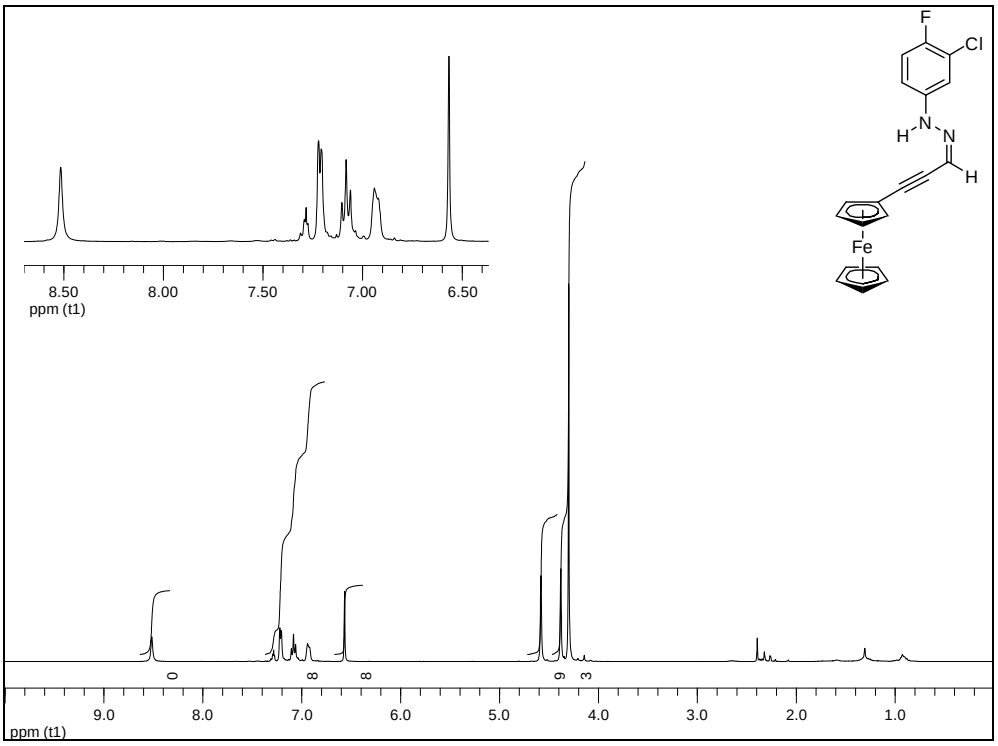

Figure A59. ^{1}H NMR spectra of ***Z*-199c**.

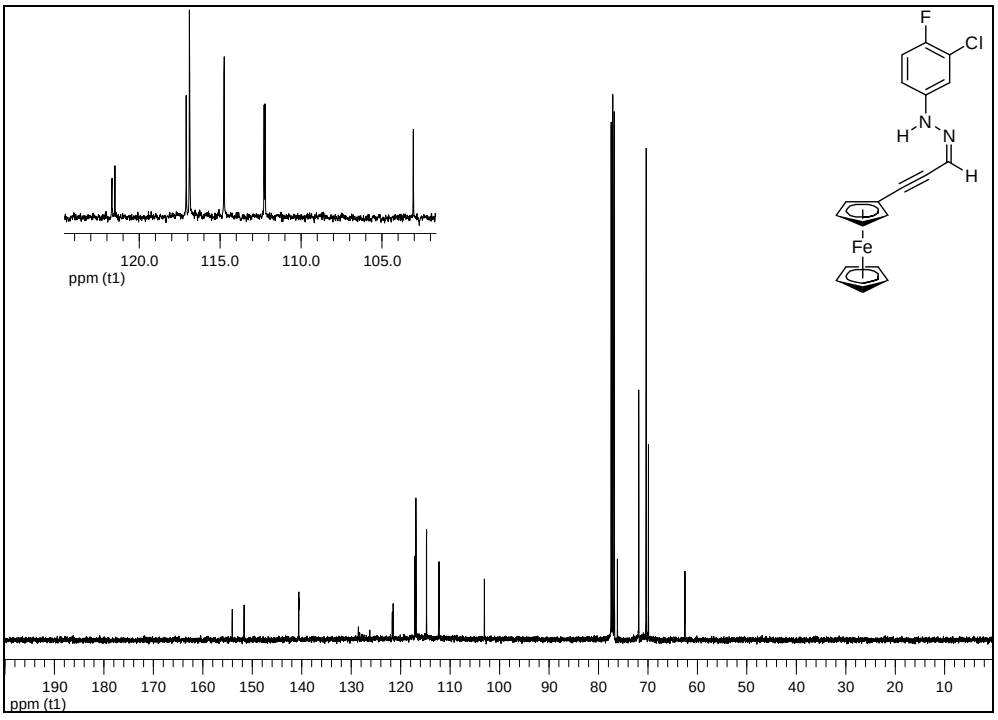

Figure A60. ^{13}C NMR spectra of ***Z*-199c.**

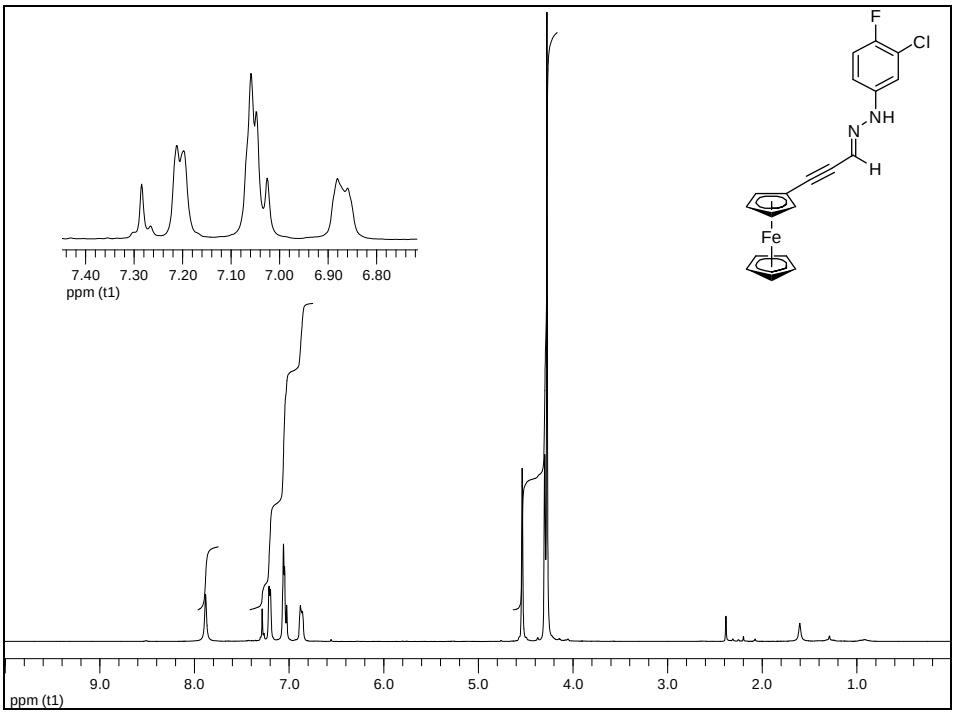

Figure A61. ^{1}H NMR spectra of ***E*-199c**.

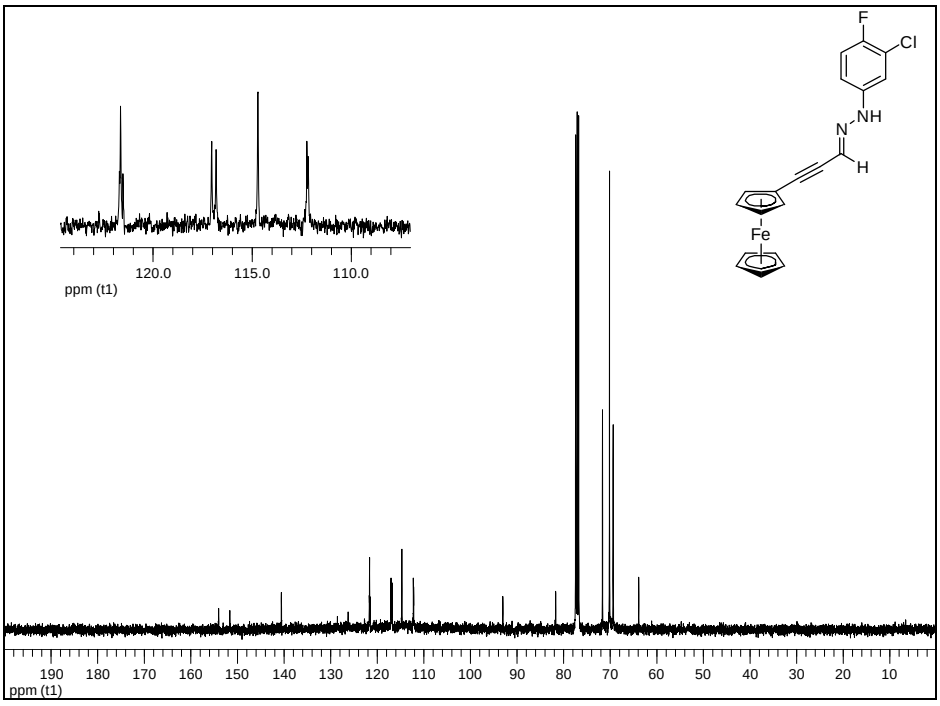

Figure A62. ^{13}C NMR spectra of ***E*-199c.**

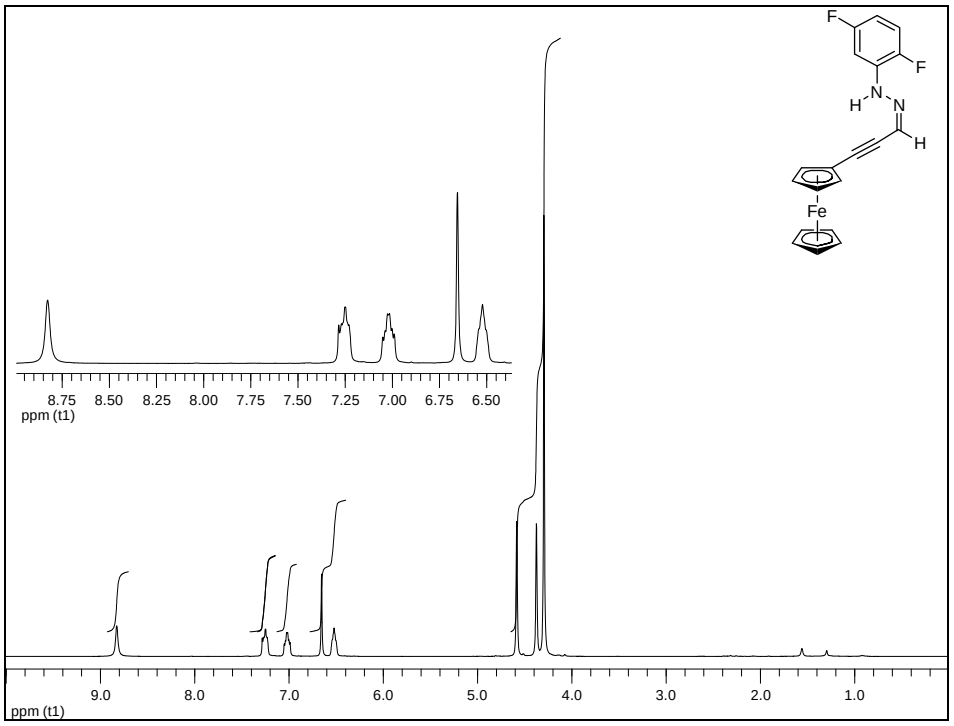

Figure A63. ^{1}H NMR spectra of ***Z*-199d**.

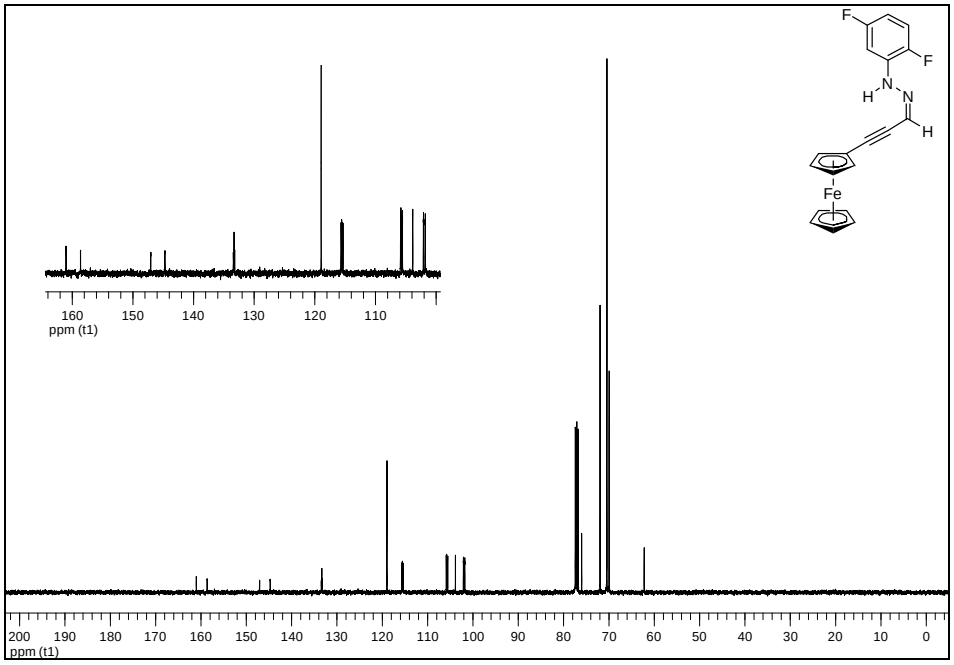

Figure A64. ^{13}C NMR spectra of ***Z*-199d.**

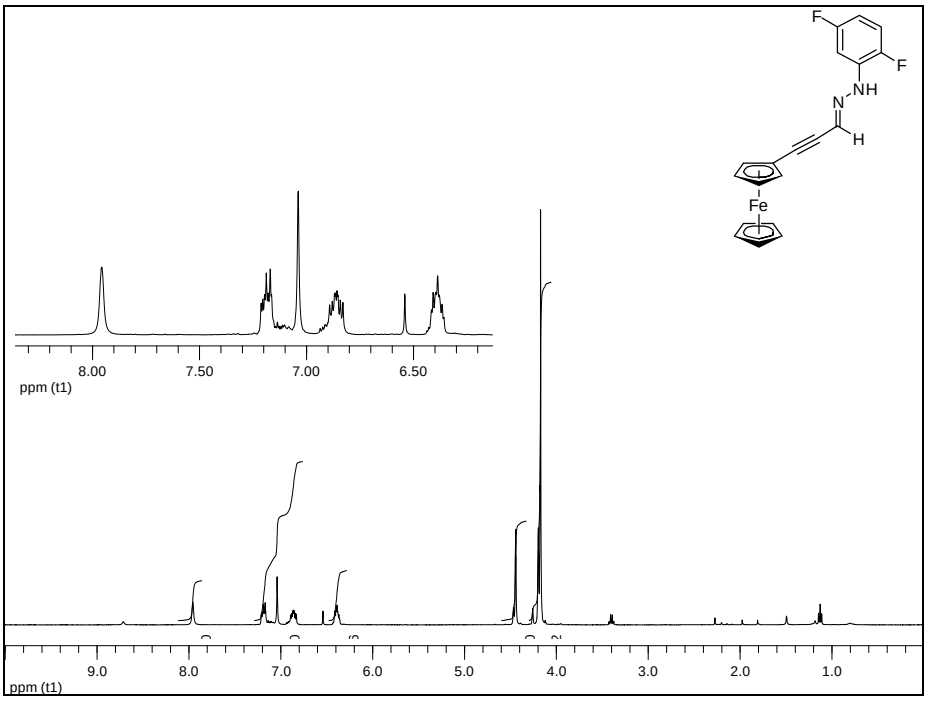

Figure A65. ^{1}H NMR spectra of ***E*-199d**.

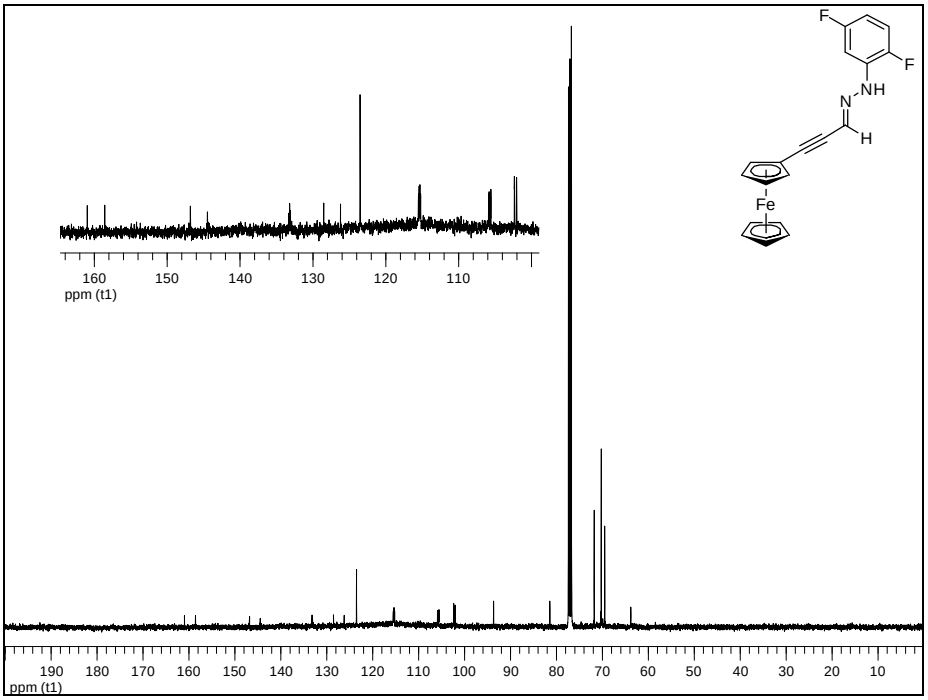

Figure A66. ^{13}C NMR spectra of ***E*-199d.**

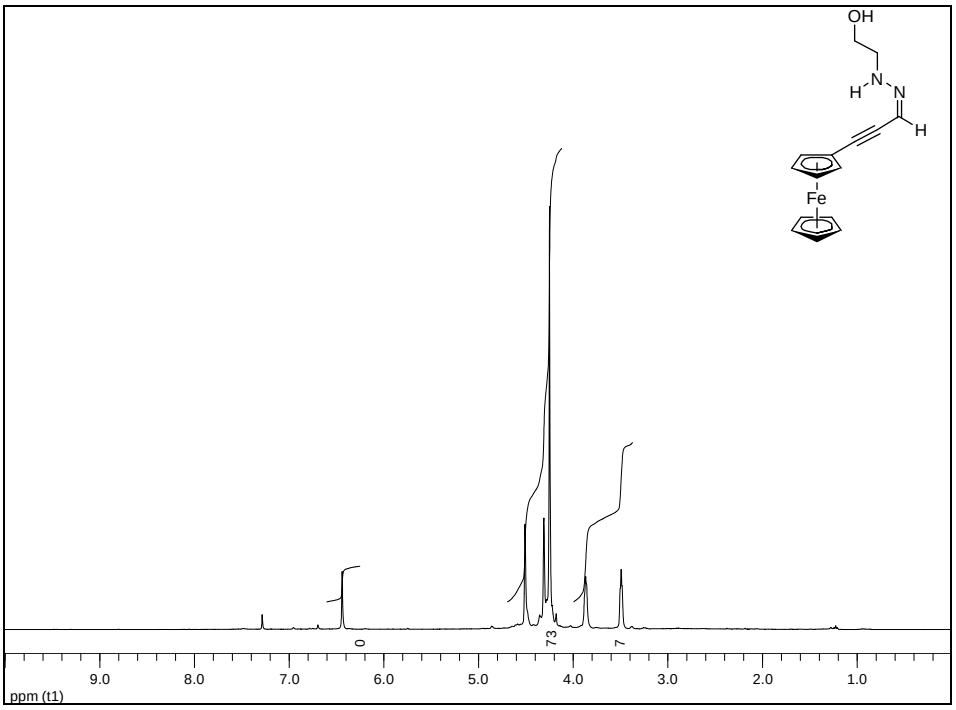

Figure A67. ^{1}H NMR spectra of ***Z*-199e**.

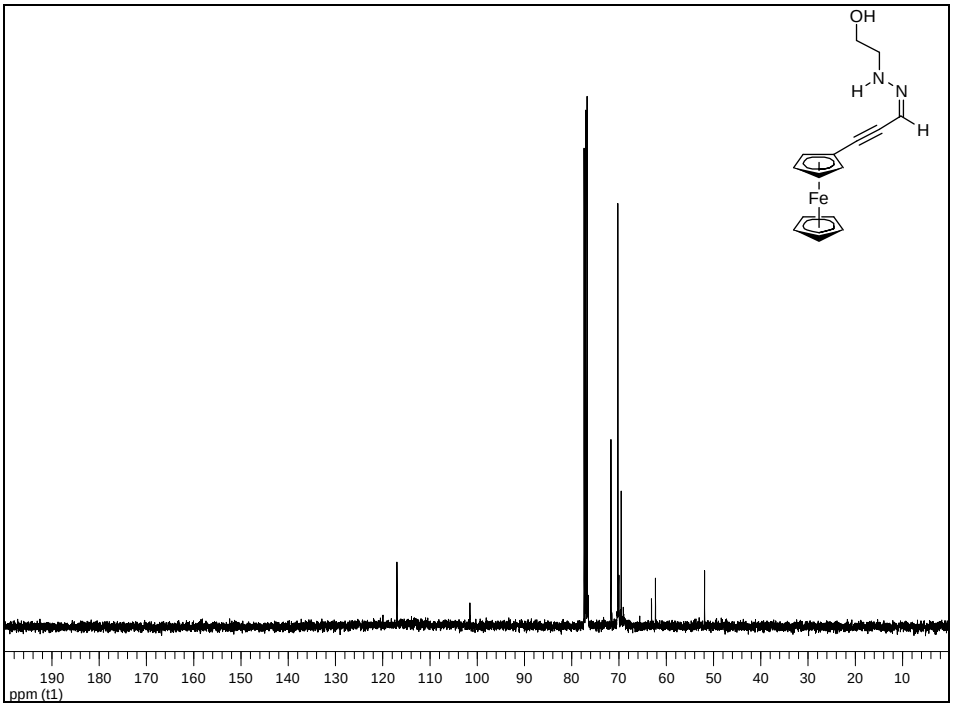

Figure A68. ^{13}C NMR spectra of ***Z*-199e.**

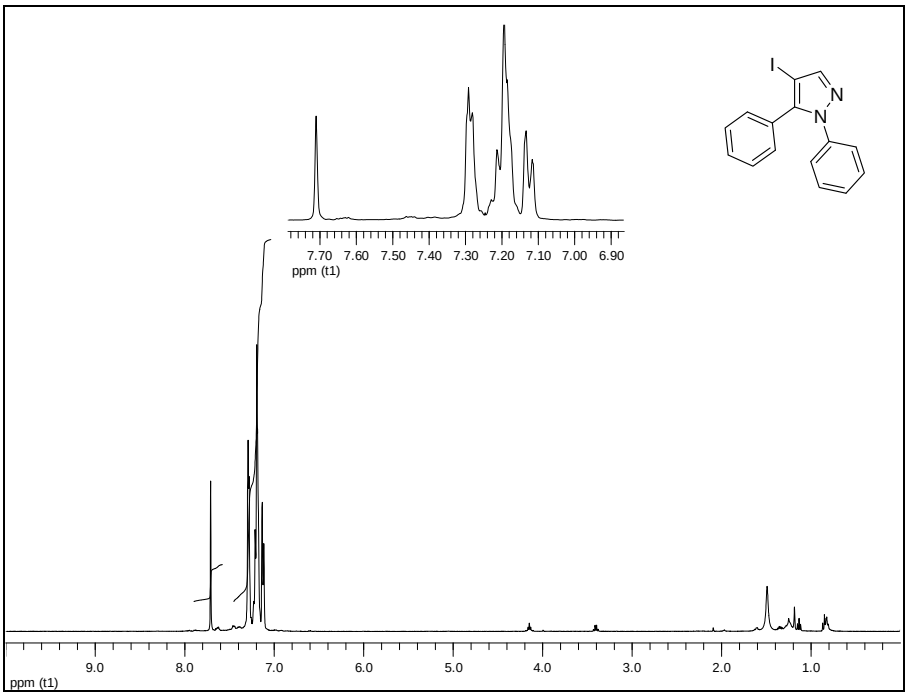

Figure A69. ^{1}H NMR spectra of **187a.**

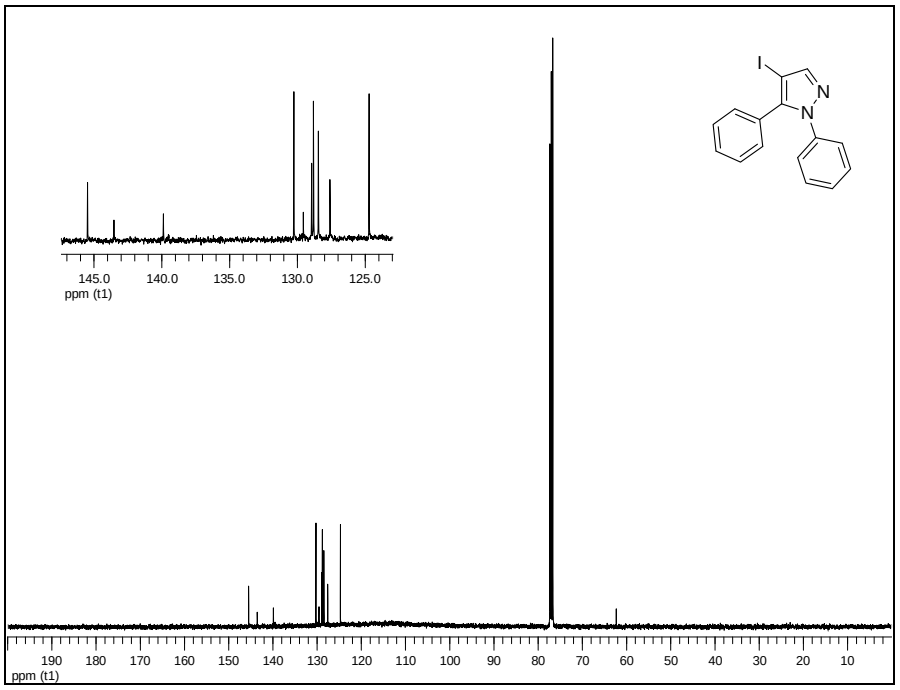

Figure A70. ^{13}C NMR spectra of **187a**.

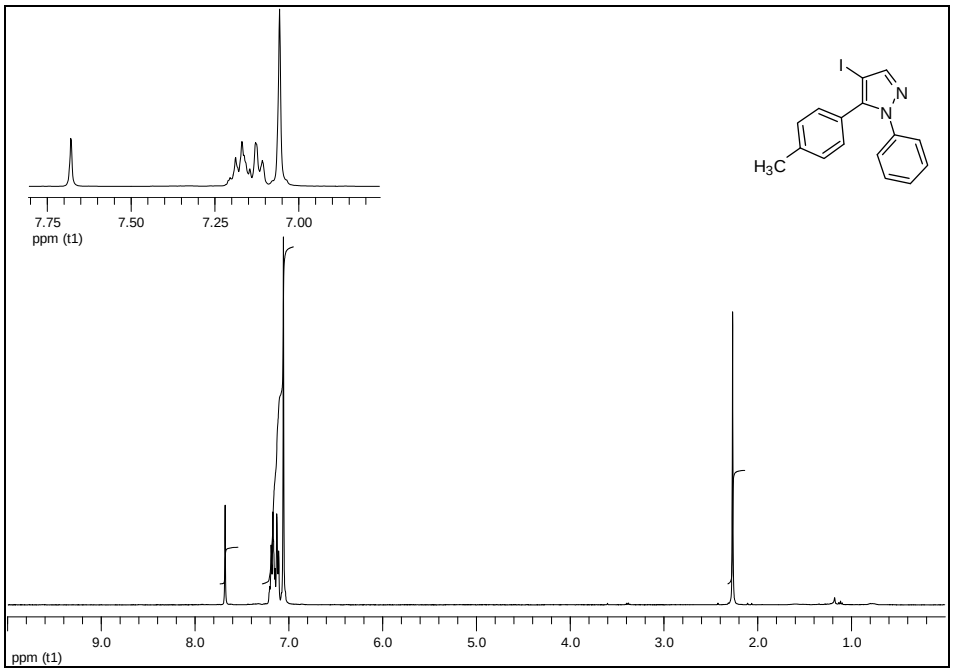

Figure A71. ^{1}H NMR spectra of **187b.**

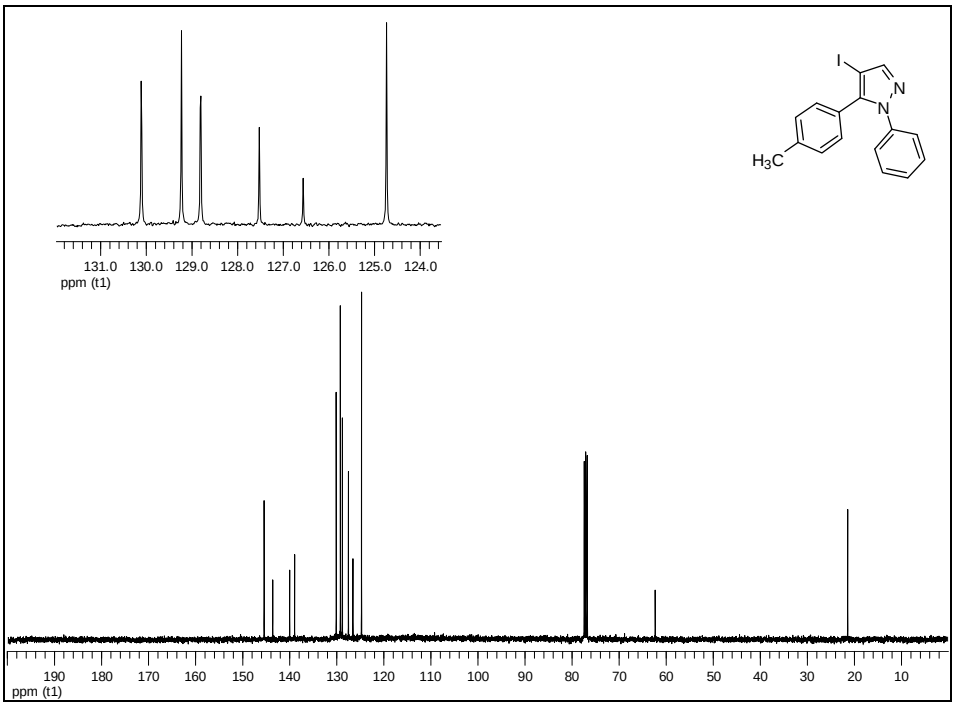

Figure A72. ^{13}C NMR spectra of **187b.**

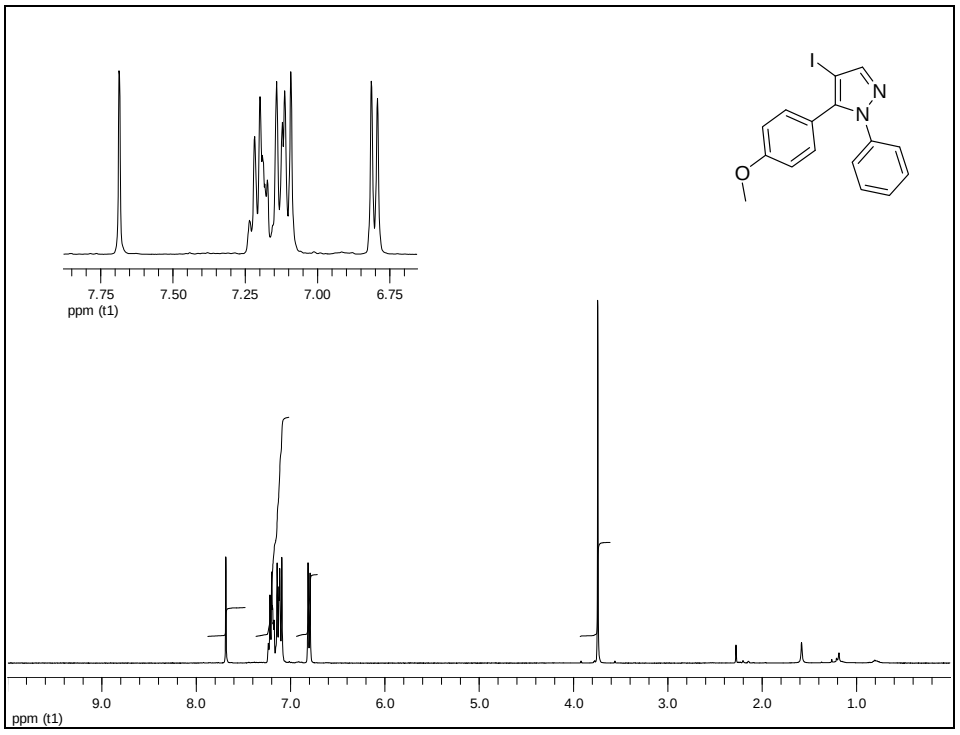

Figure A73. ^{1}H NMR spectra of **187c.**

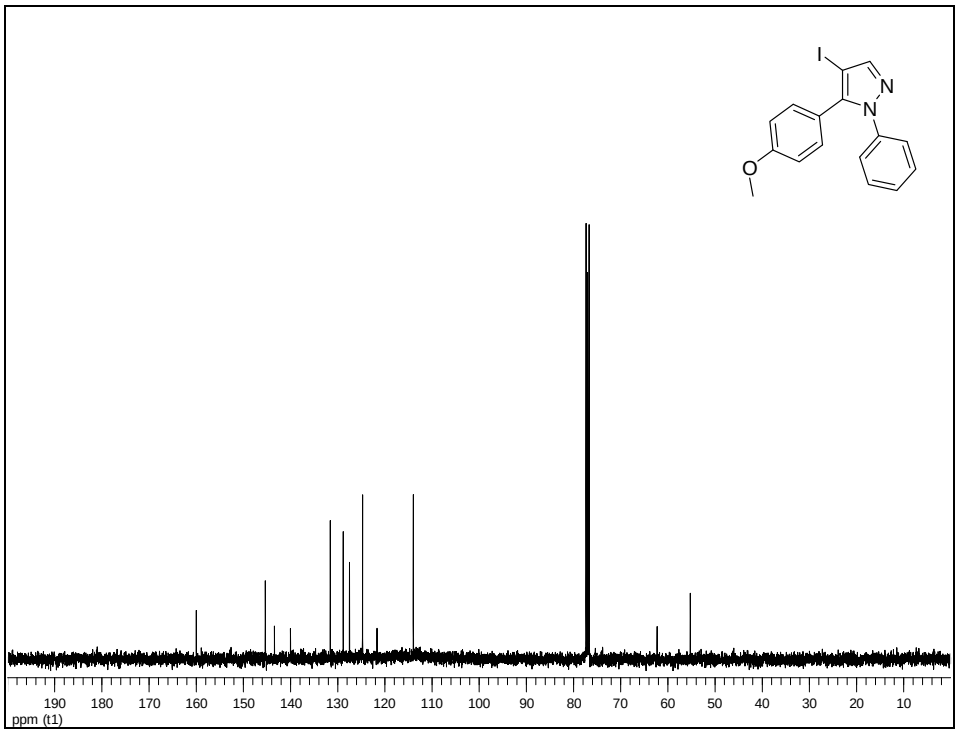

Figure A74. ^{13}C NMR spectra of **187c.**

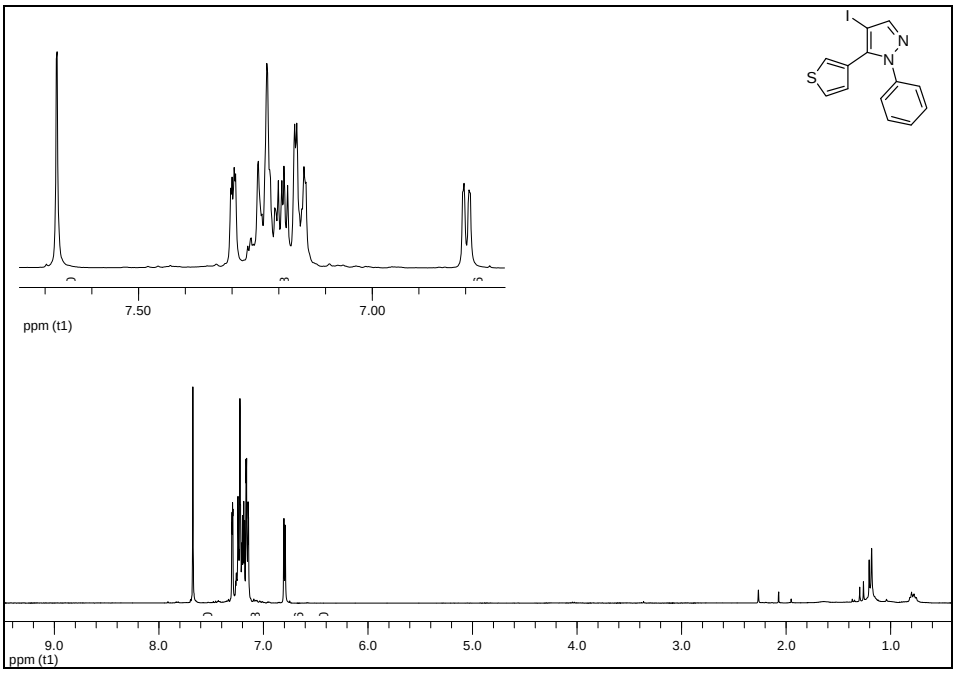

Figure A75. ^{1}H NMR spectra of **187d.**

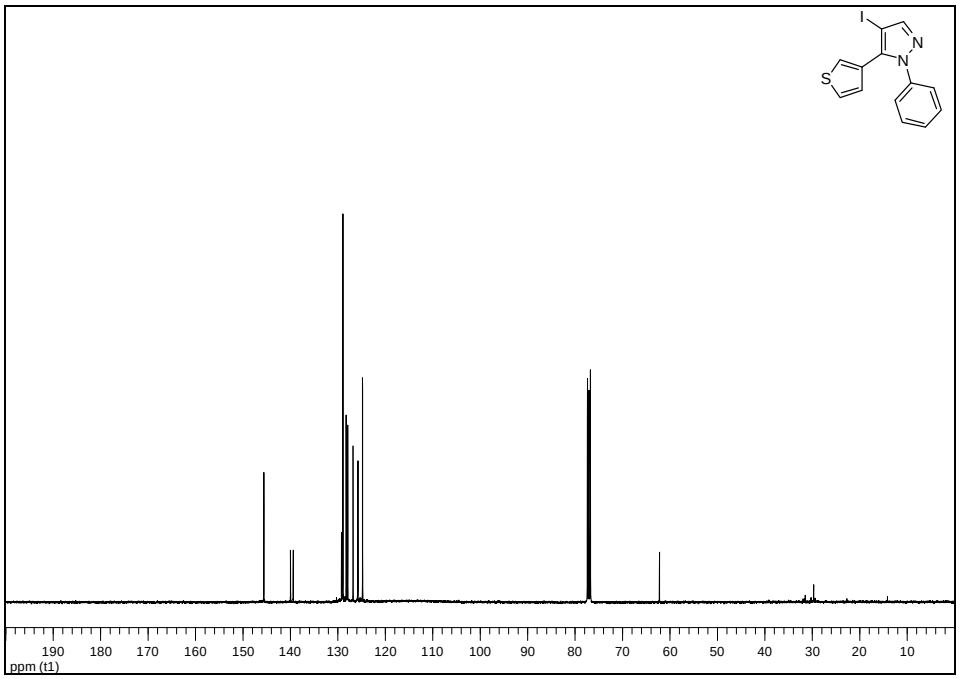

Figure A76. ^{13}C NMR spectra of **187d.**

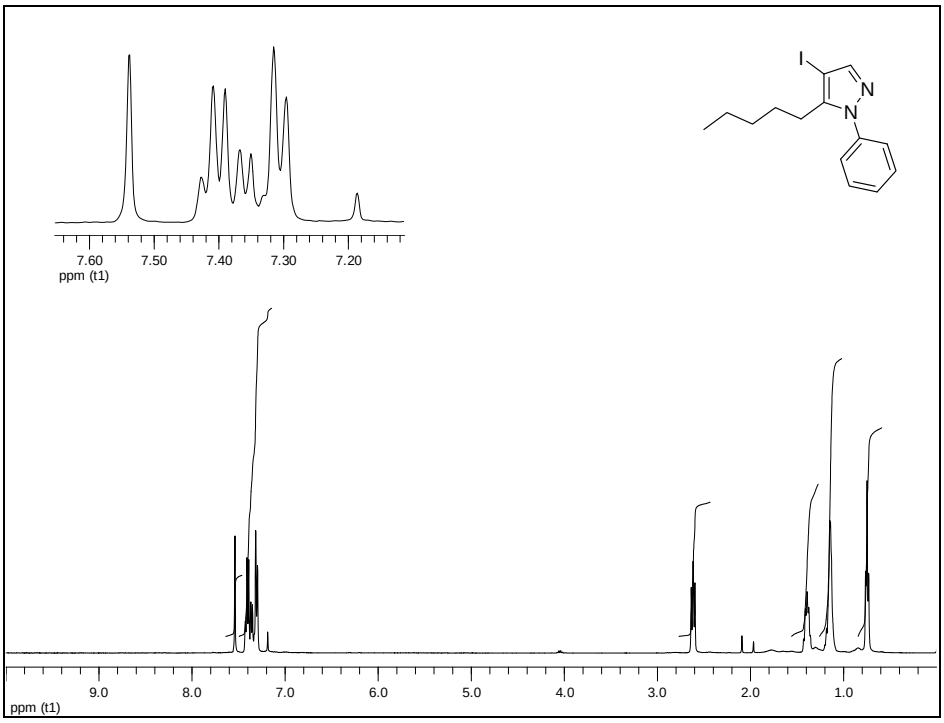

Figure A77. ^{1}H NMR spectra of **187e.**

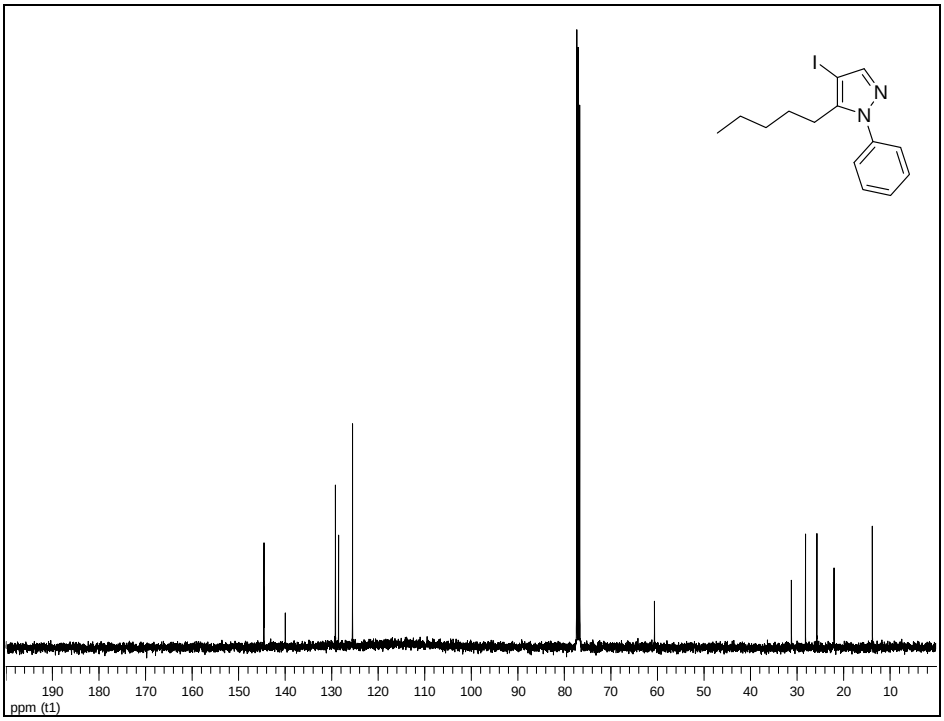

Figure A78. ^{13}C NMR spectra of **187e**

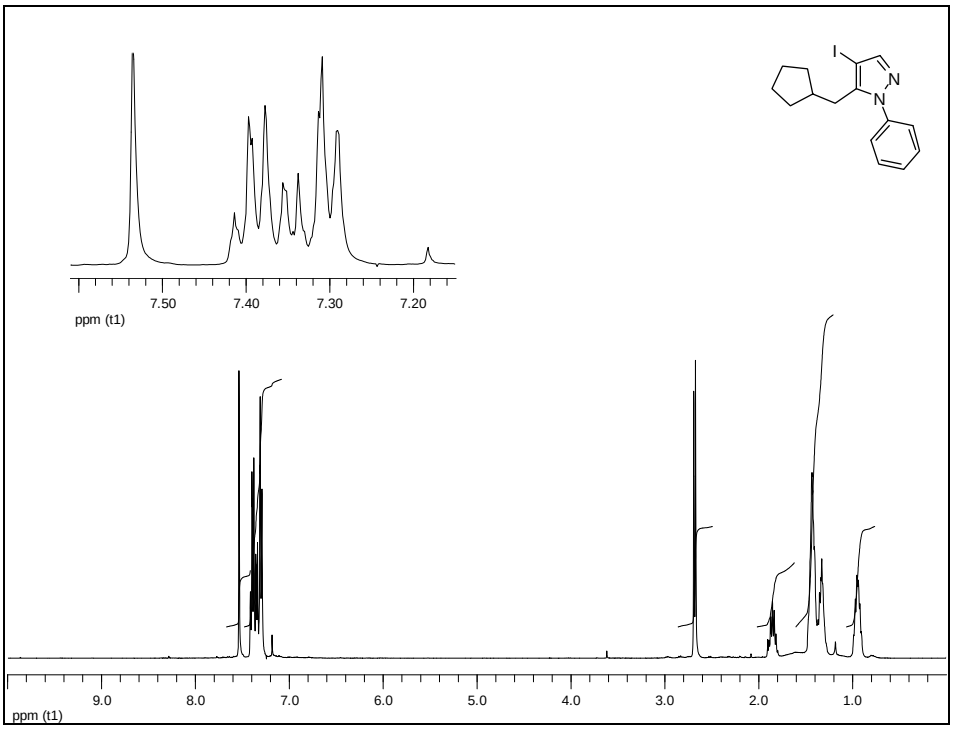

Figure A79. ^{1}H NMR spectra of **187f.**

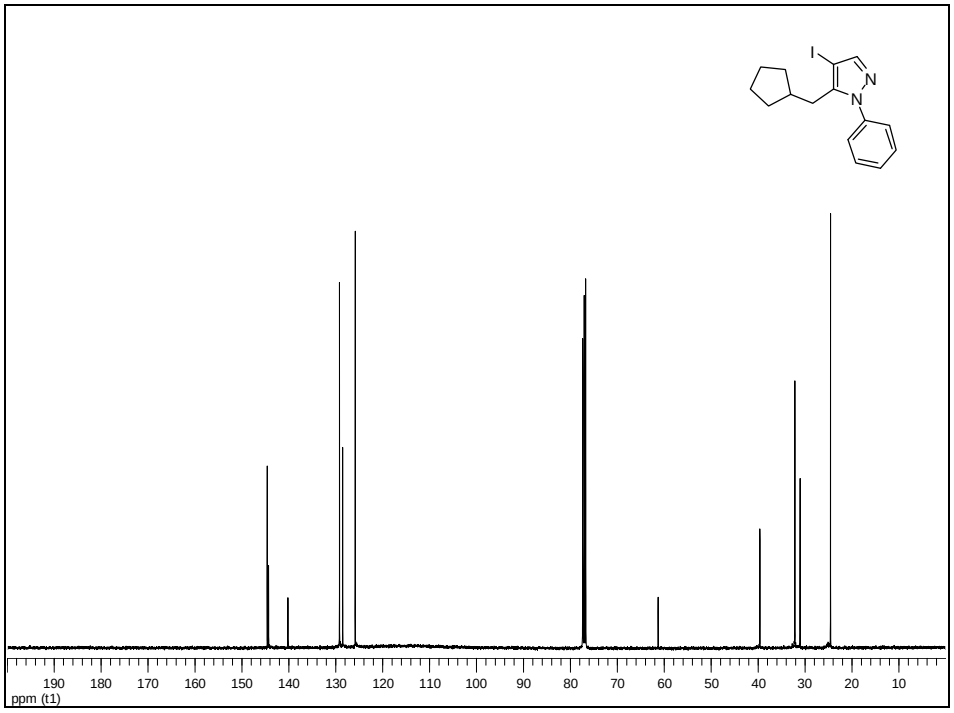

Figure A80. ^{13}C NMR spectra of **187f.**

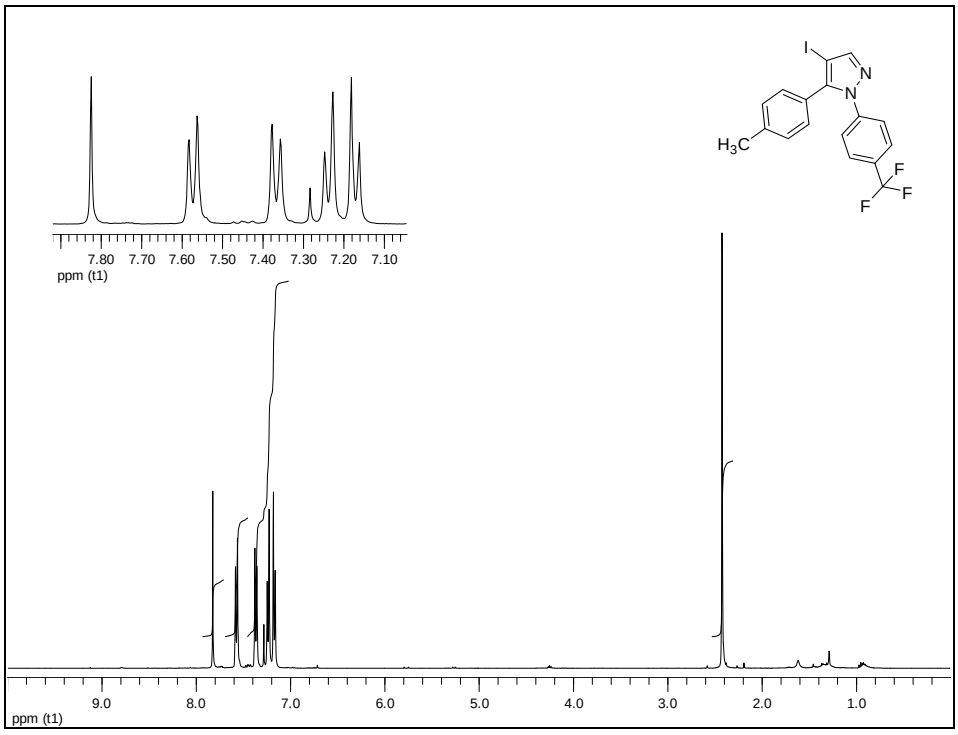

Figure A81. ^{1}H NMR spectra of **187g.**

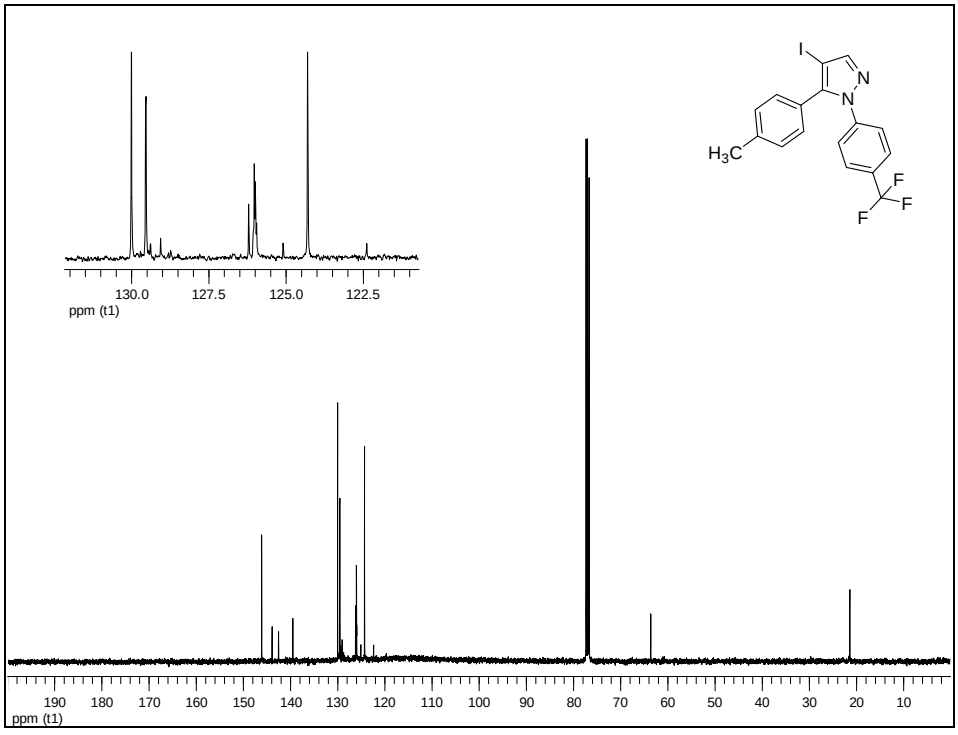

Figure A82. ^{13}C NMR spectra of **187g.**

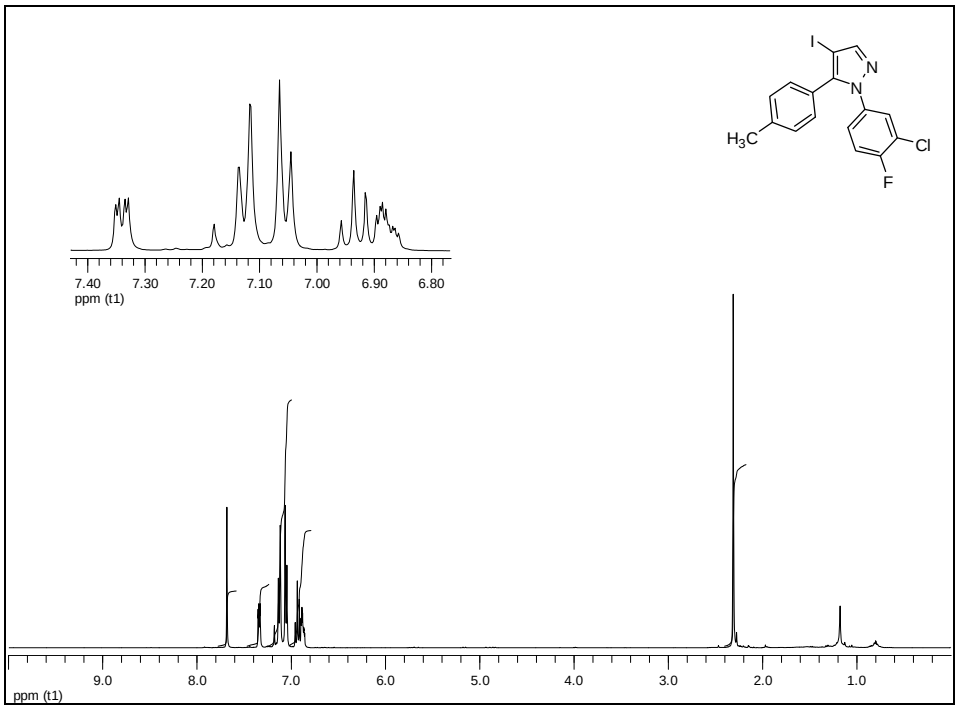

Figure A83. ^{1}H NMR spectra of **187h.**

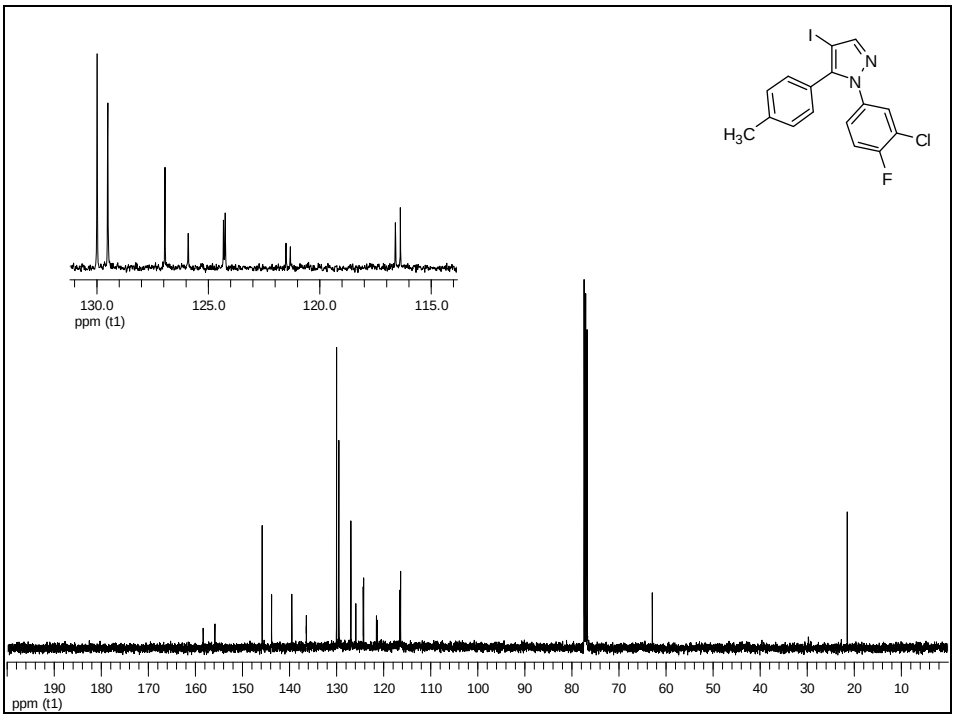

Figure A84. ^{13}C NMR spectra of **187h.**

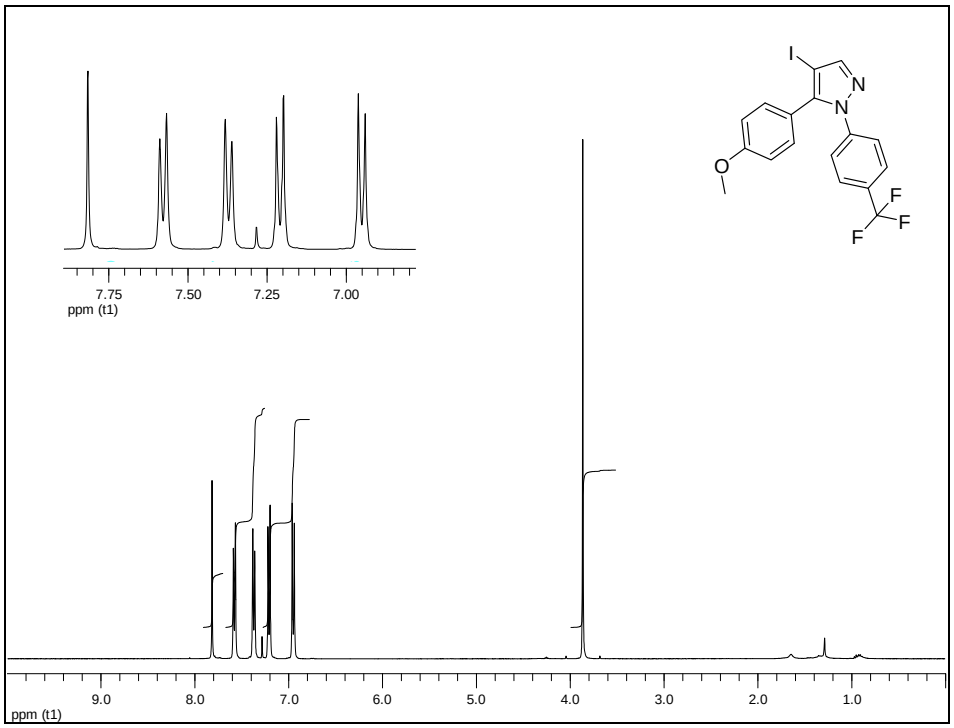

Figure A85. ^{1}H NMR spectra of **187i.**

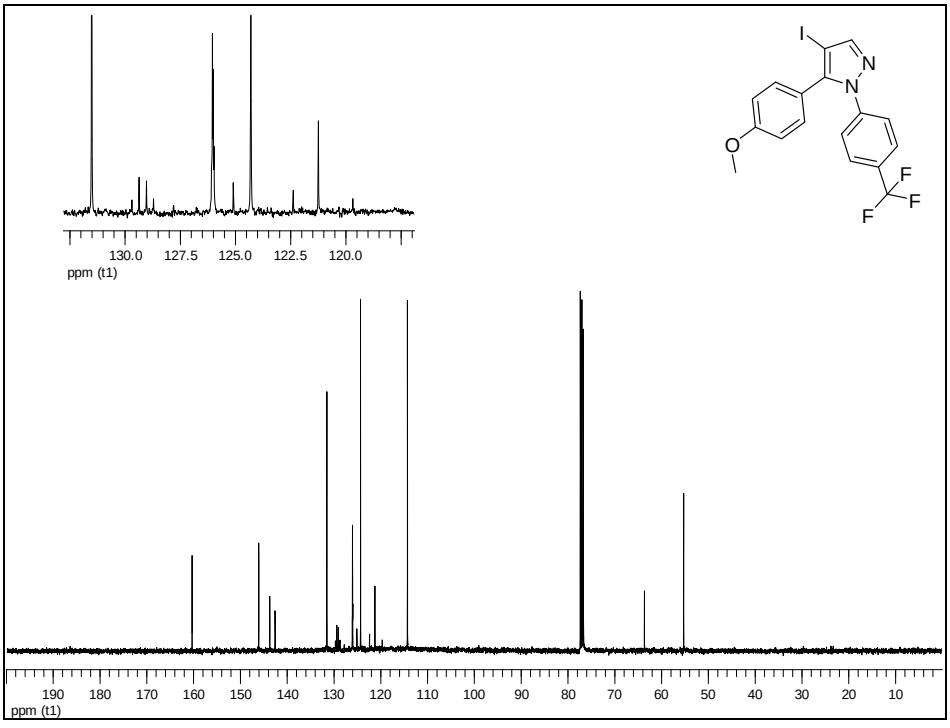

Figure A86. ^{13}C NMR spectra of **187i.**

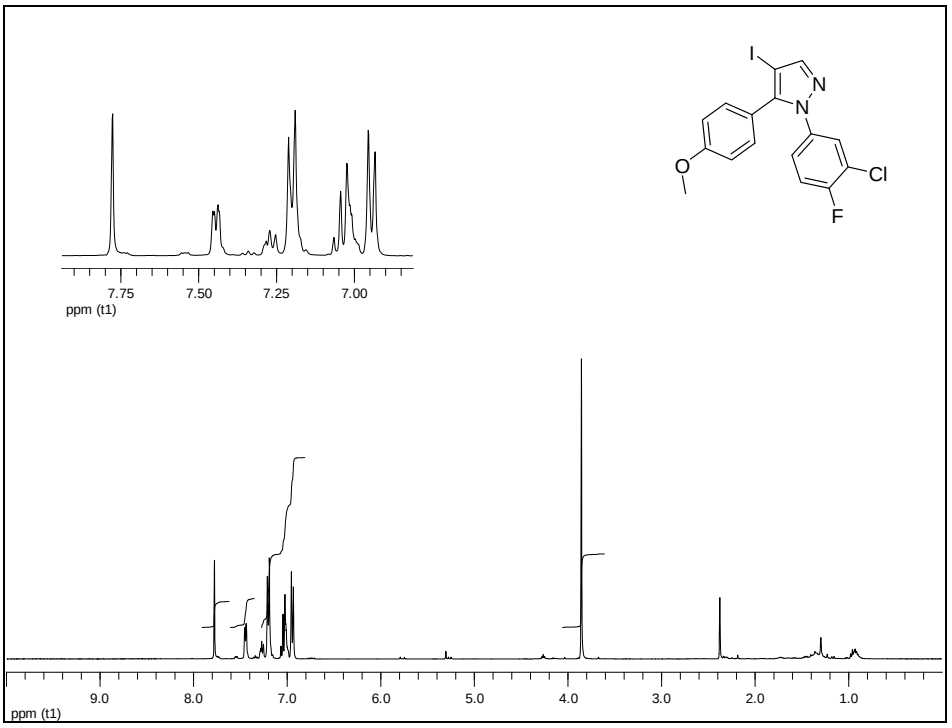

Figure A87. ^{1}H NMR spectra of **187j.**

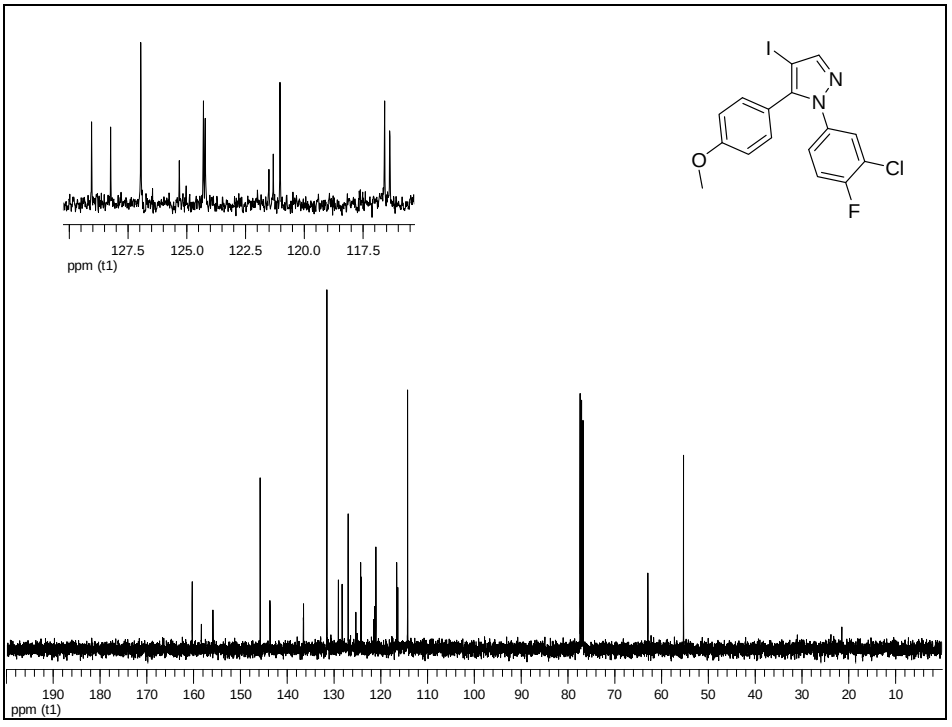

Figure A88. ^{13}C NMR spectra of **187j.**

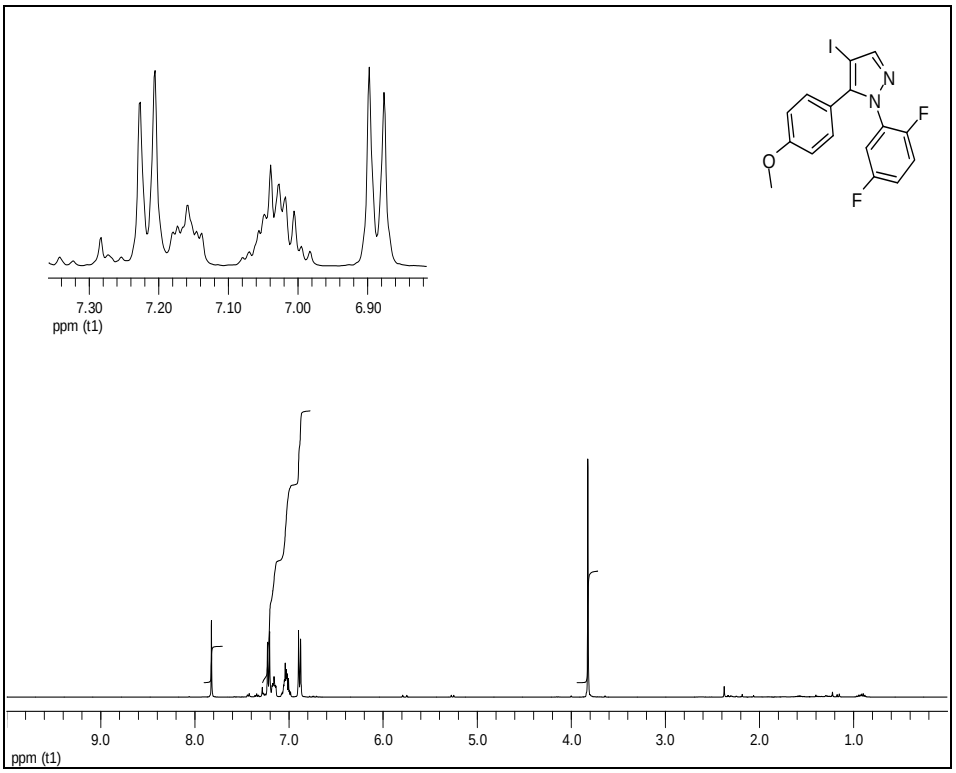

Figure A89. ^{1}H NMR spectra of **187k.**

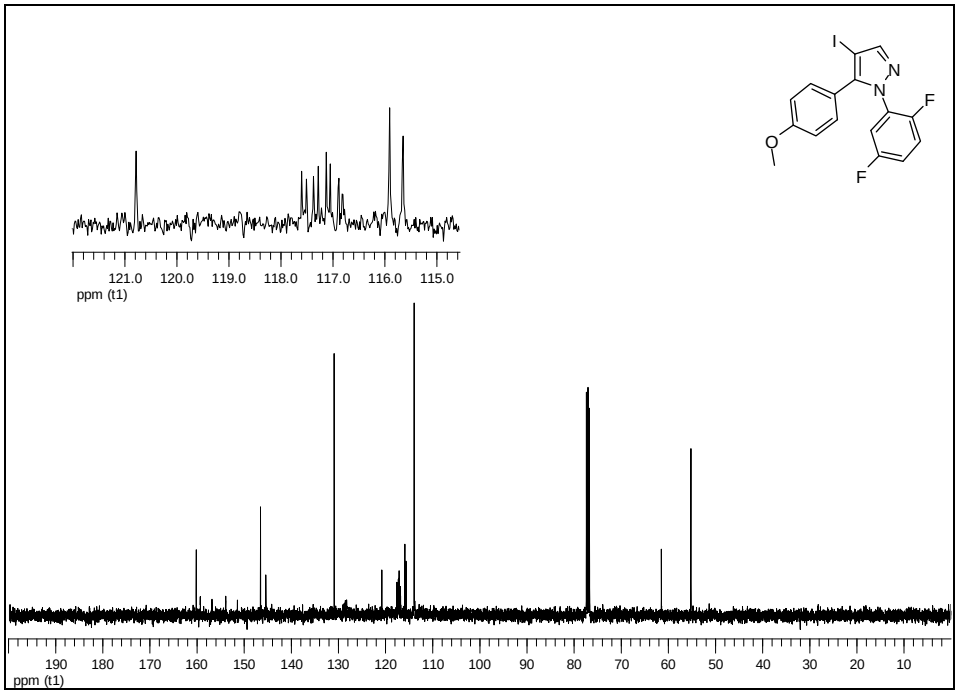

Figure A90. ^{13}C NMR spectra of **187k.**

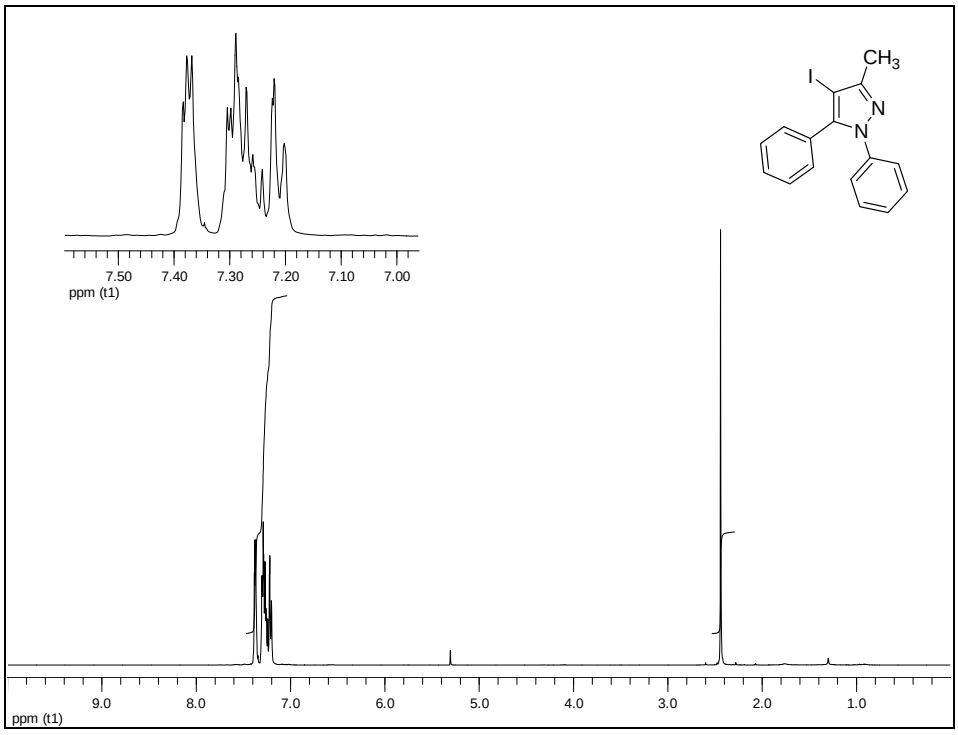

Figure A91. ^{1}H NMR spectra of **187l.**

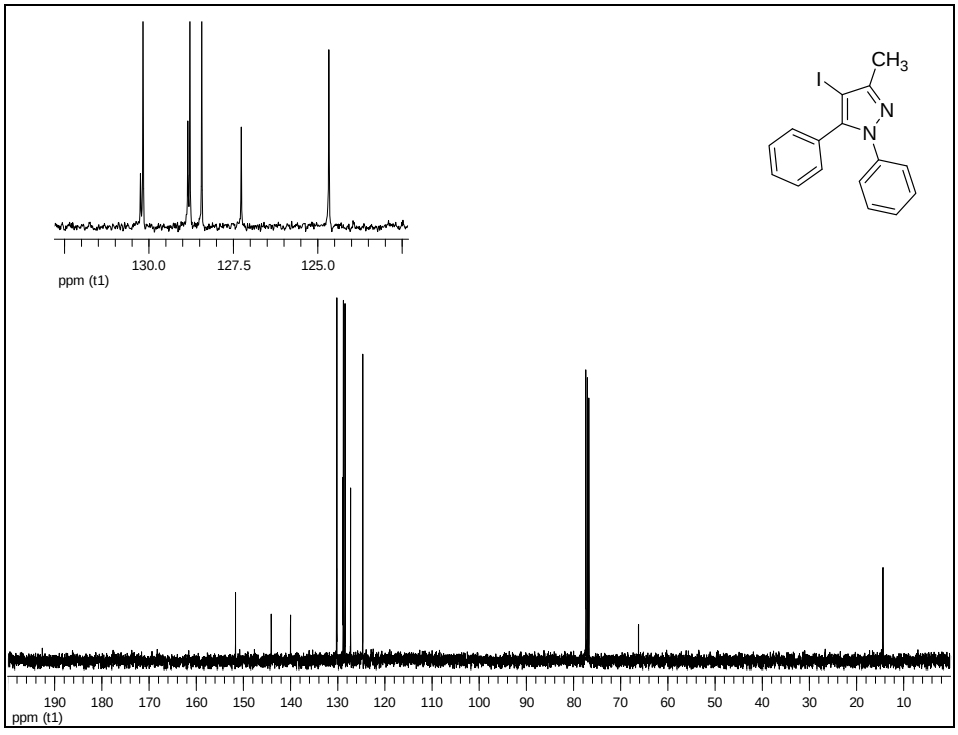

Figure A92. ^{13}C NMR spectra of **187l.**

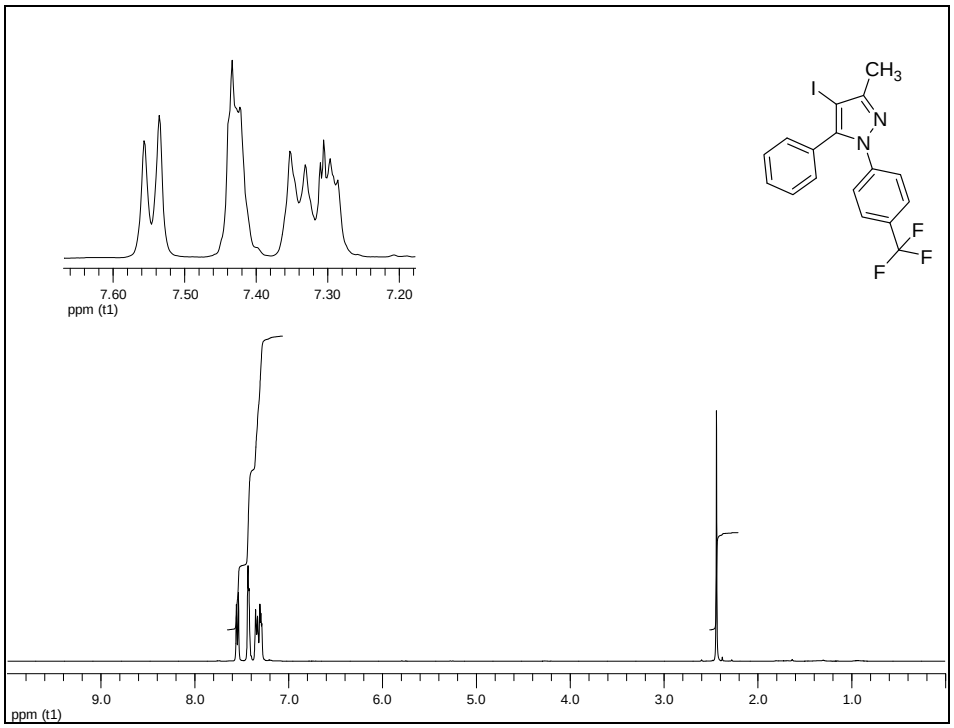

Figure A93. ^{1}H NMR spectra of **187m.**

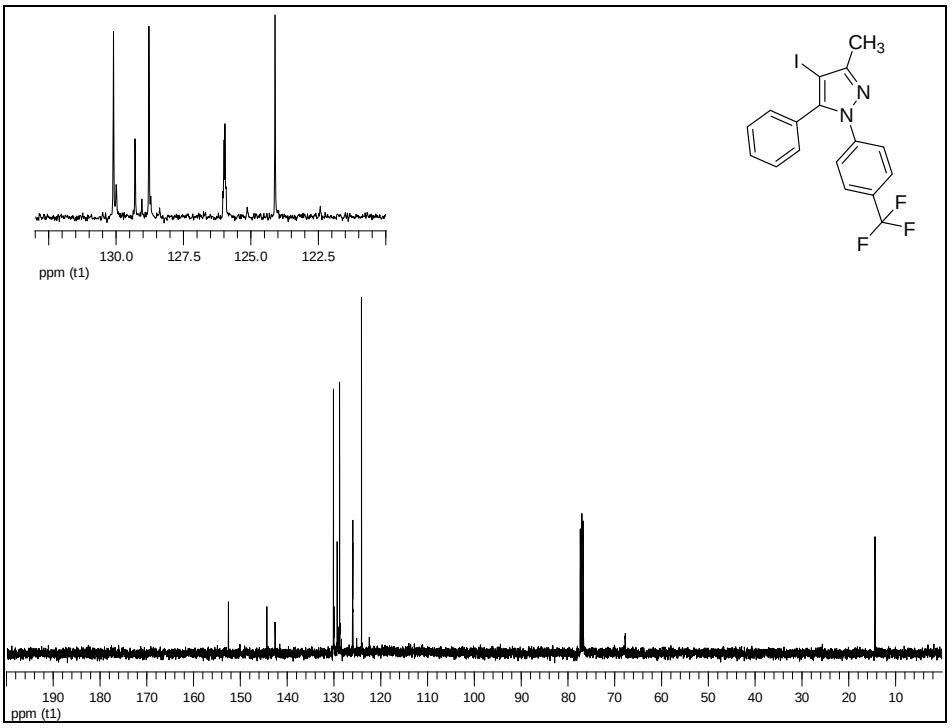

Figure A94. ^{13}C NMR spectra of **187m.**

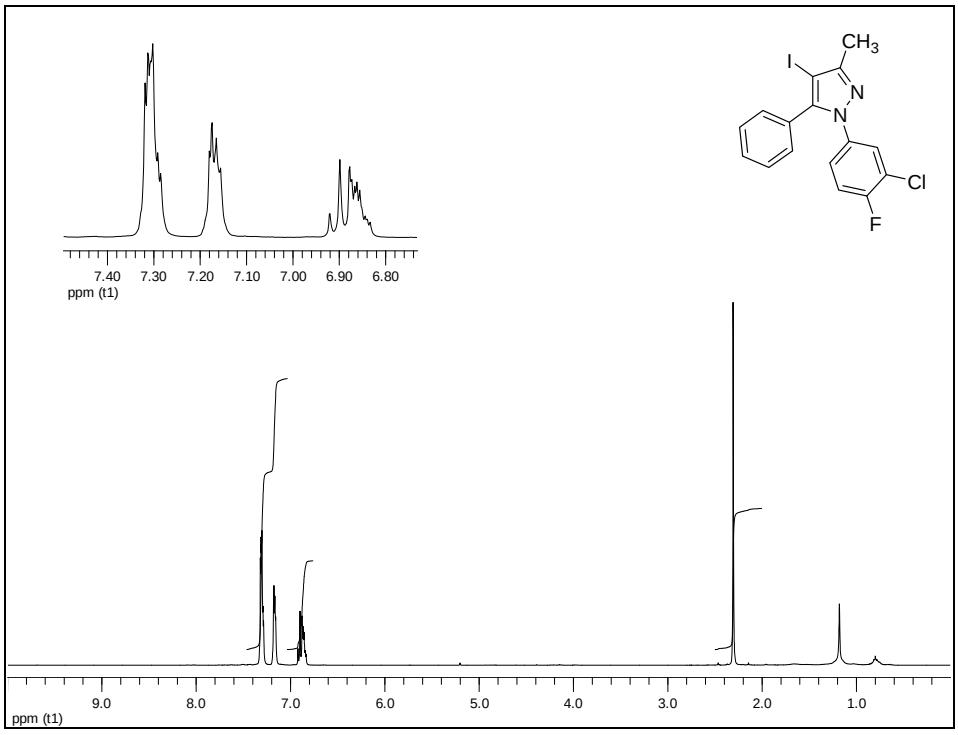

Figure A95. ^{1}H NMR spectra of **187n.**

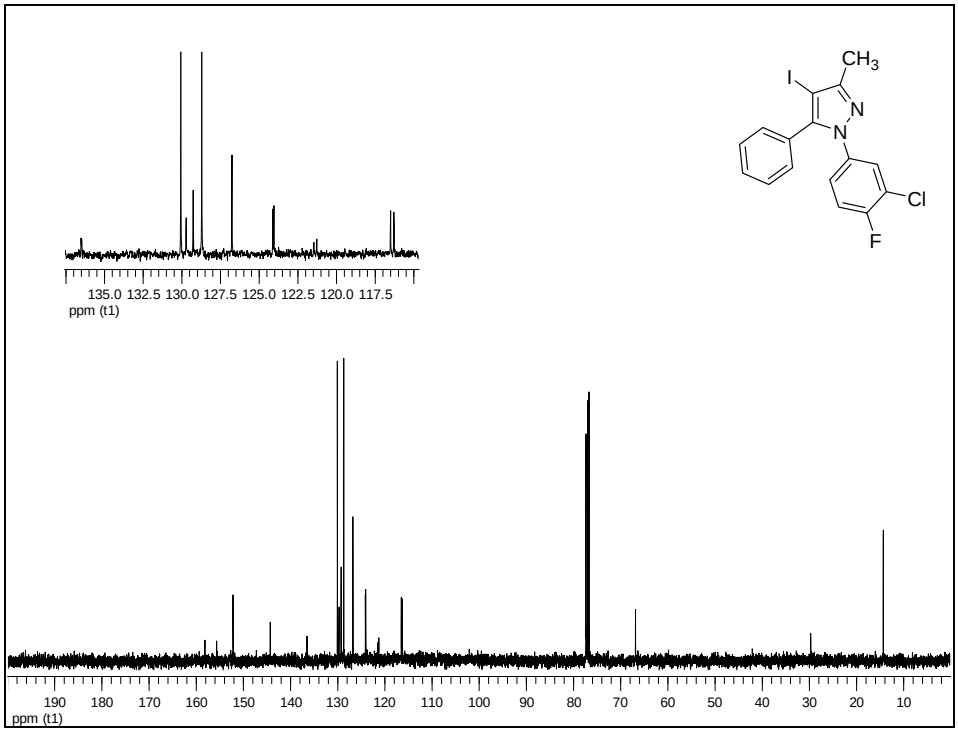

Figure A96. ^{13}C NMR spectra of **187n.**

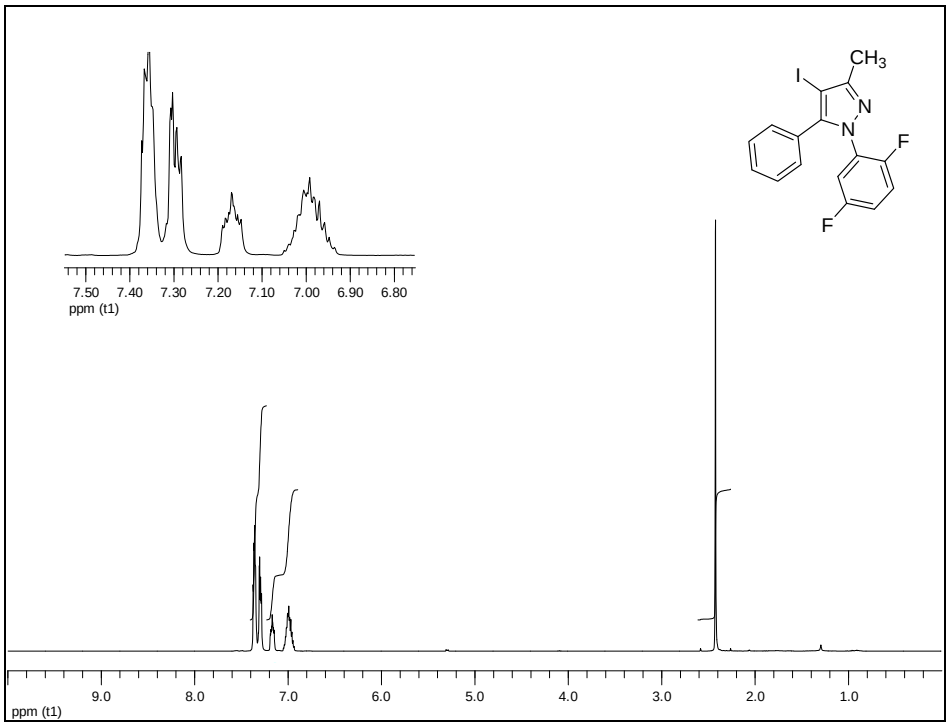

Figure A97. ^{1}H NMR spectra of **187o.**

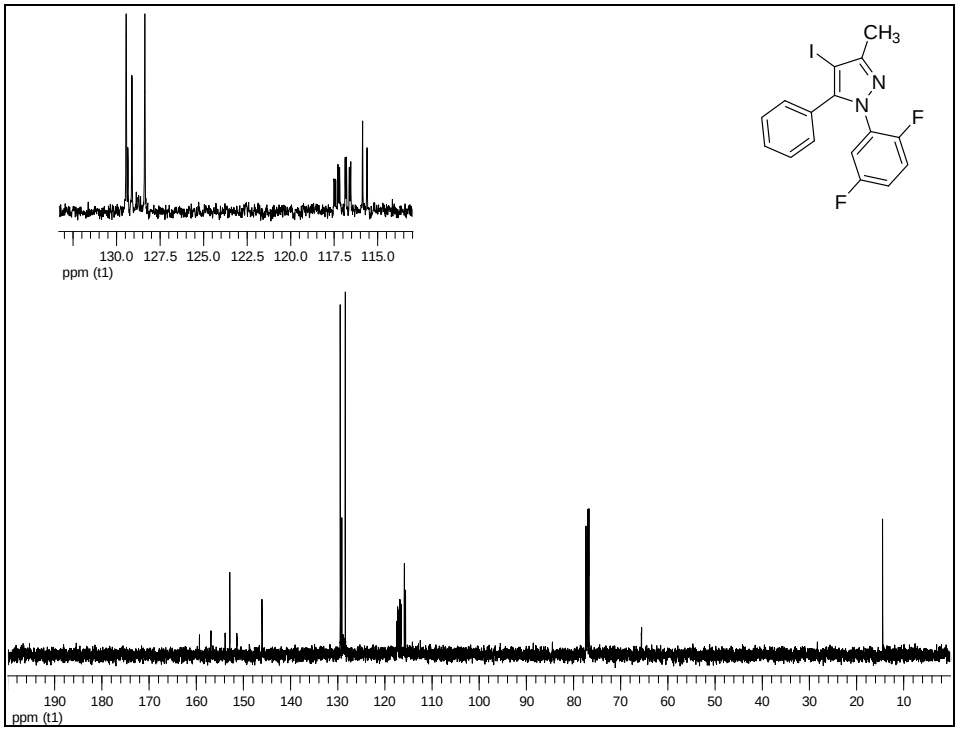

Figure A98. ^{13}C NMR spectra of **187o.**

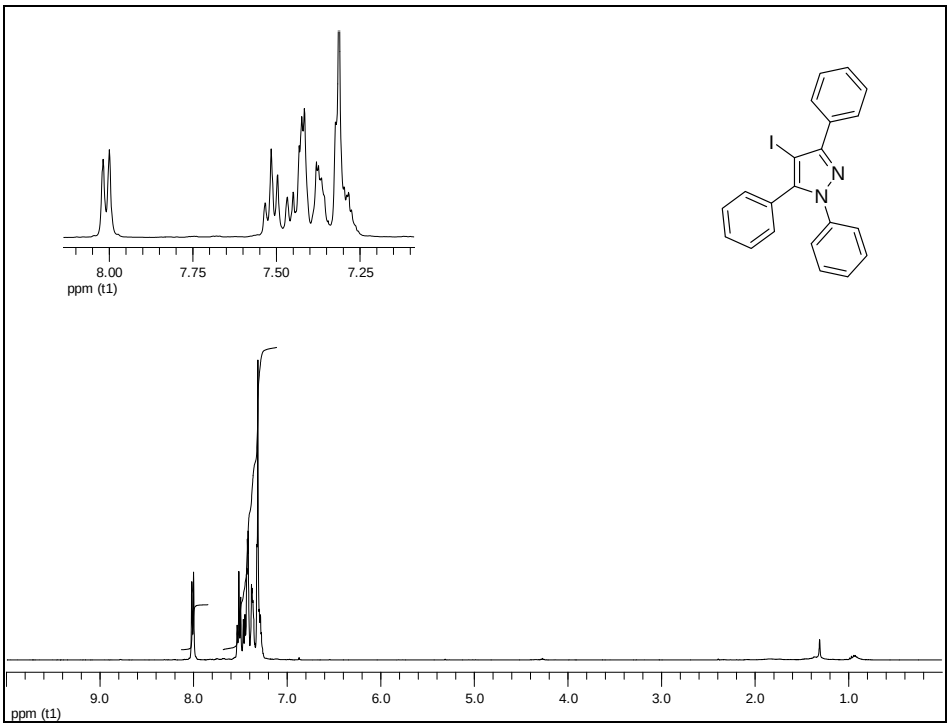

Figure A99. ^{1}H NMR spectra of **187p.**

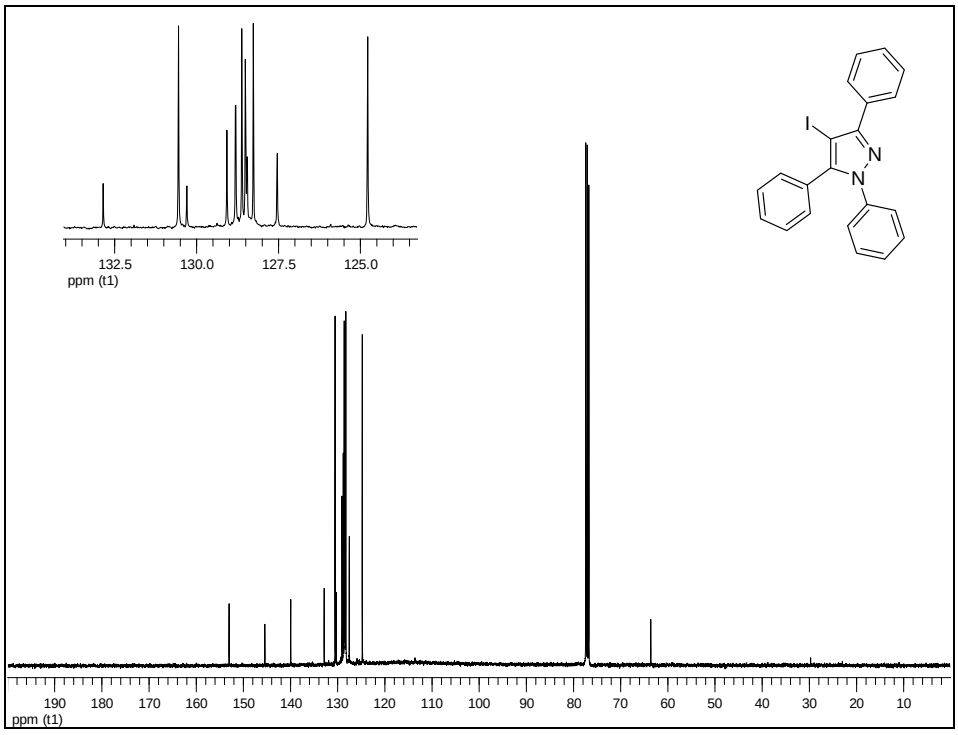

Figure A100. ^{13}C NMR spectra of **187p.**

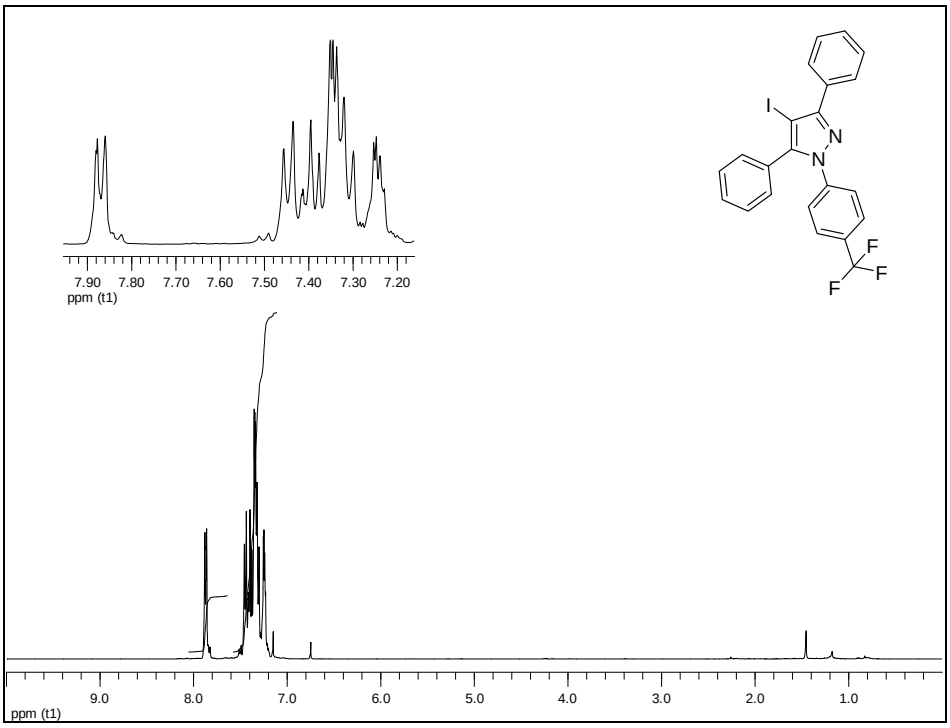

Figure A101. ^{1}H NMR spectra of **187q.**

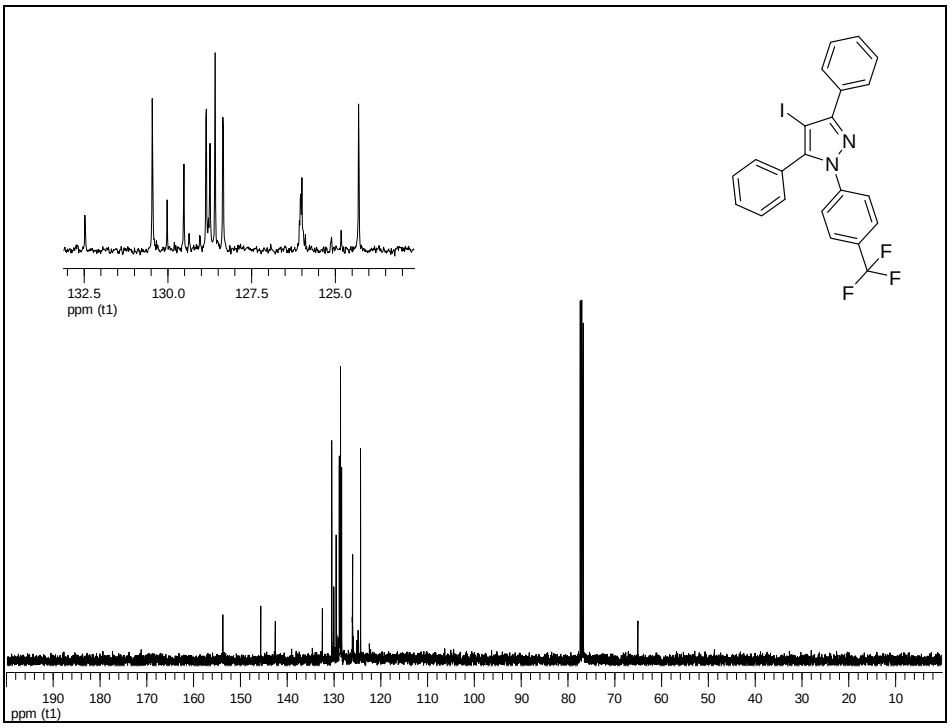

Figure A102. ^{13}C NMR spectra of **187q.**

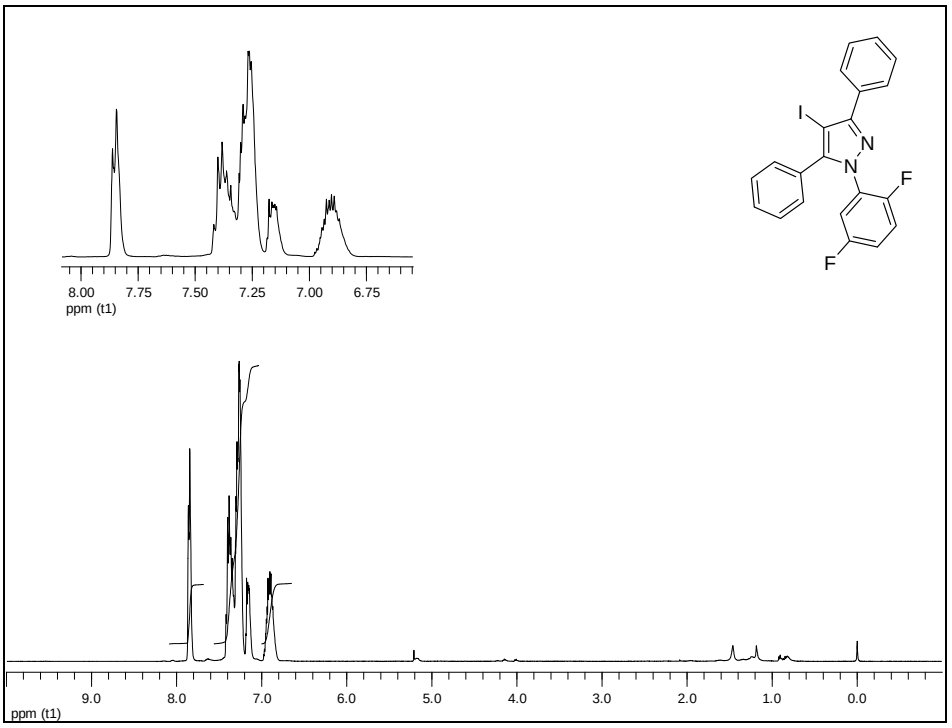

Figure A103. ^{1}H NMR spectra of **187r.**

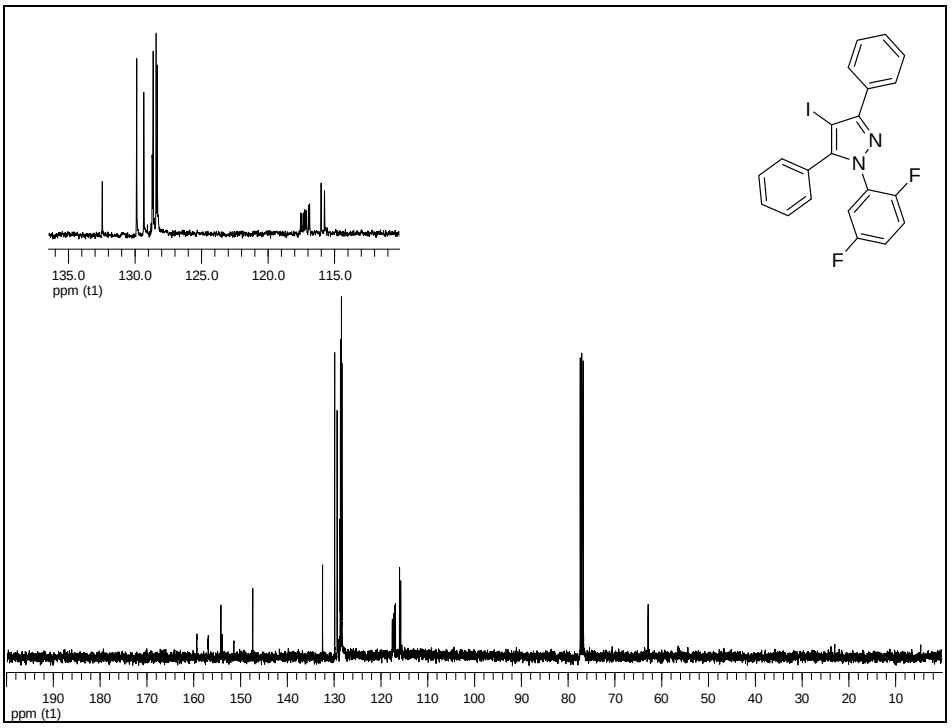

Figure A104. ^{13}C NMR spectra of **187r.**

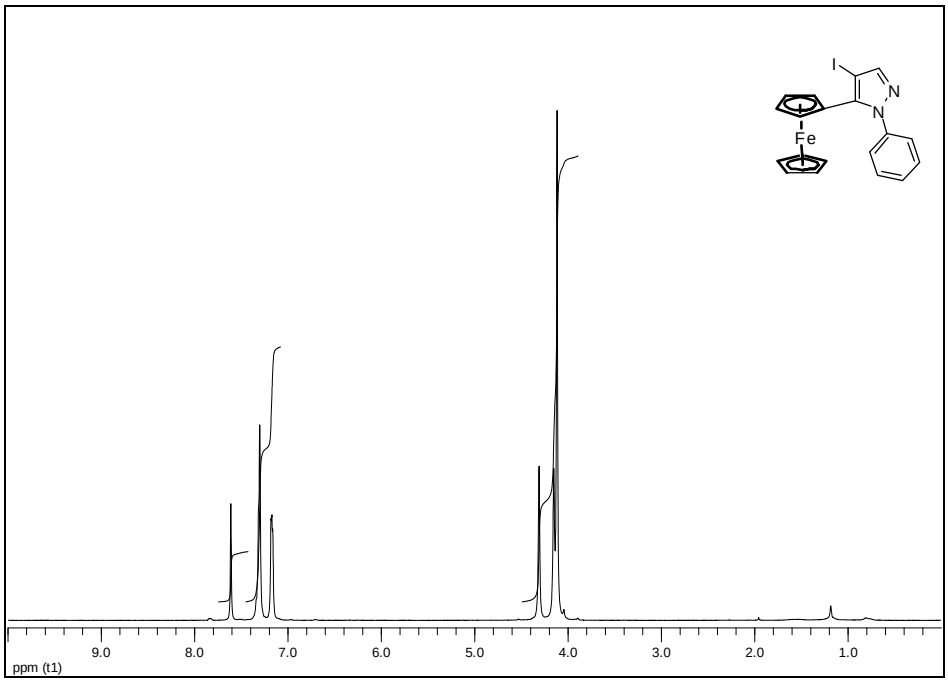

Figure A105. ^{1}H NMR spectra of **200a.**

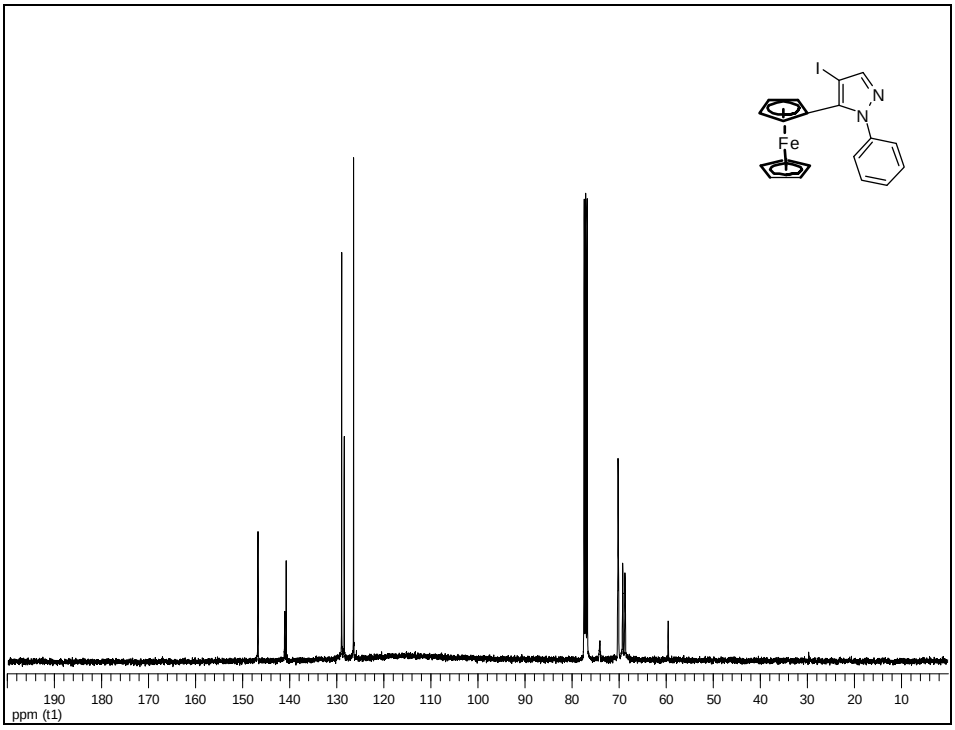

Figure A106. ^{13}C NMR spectra of **200a.**

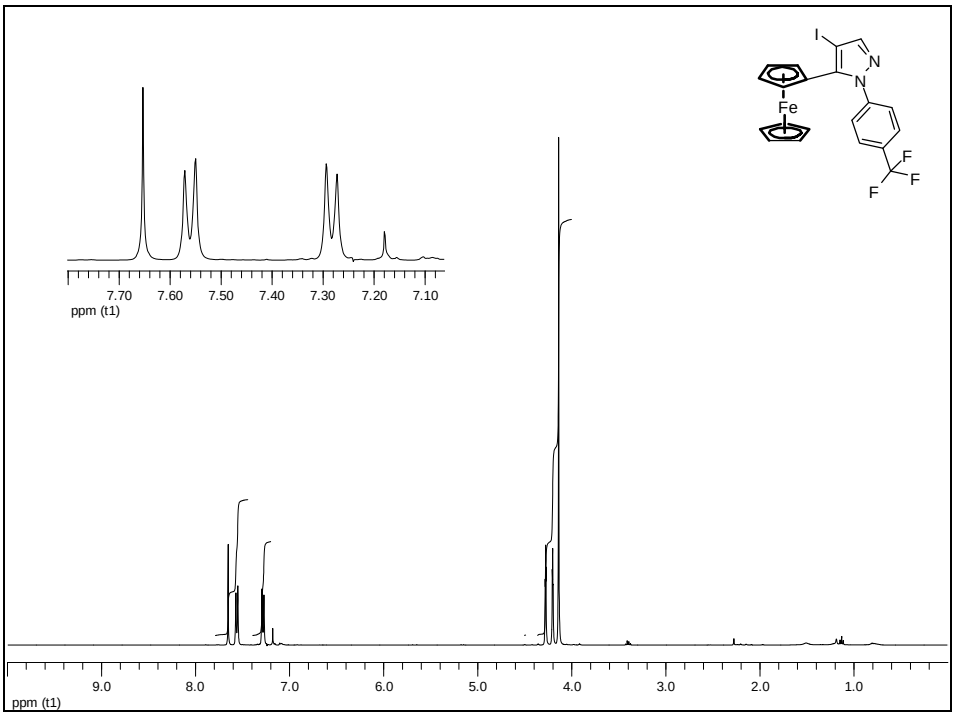

Figure A107. ^{1}H NMR spectra of **200b.**

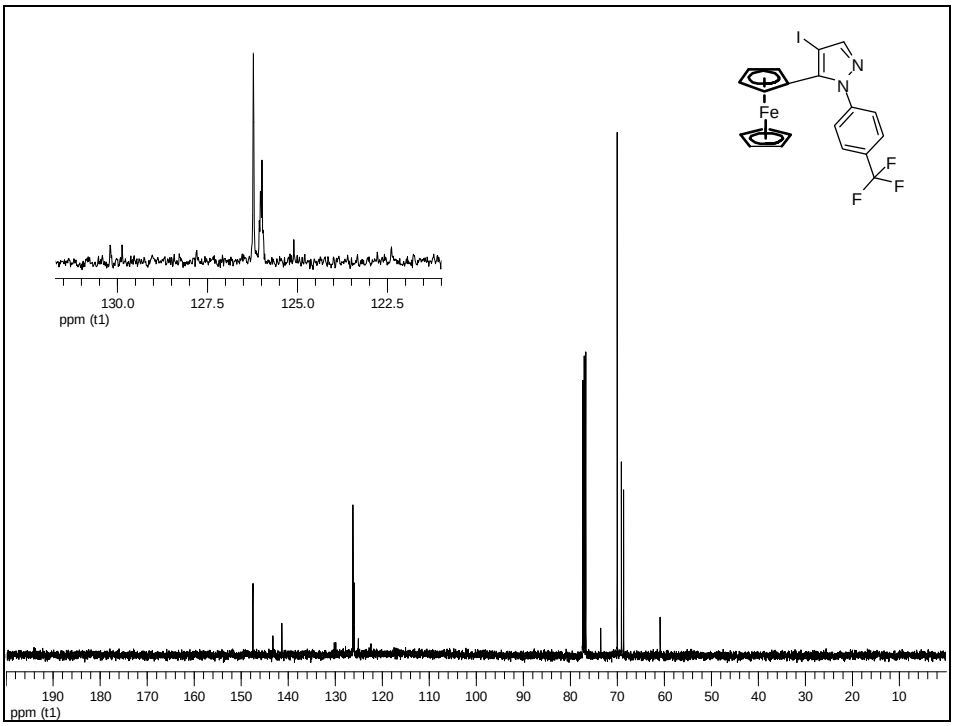

Figure A108. ^{13}C NMR spectra of **200b.**

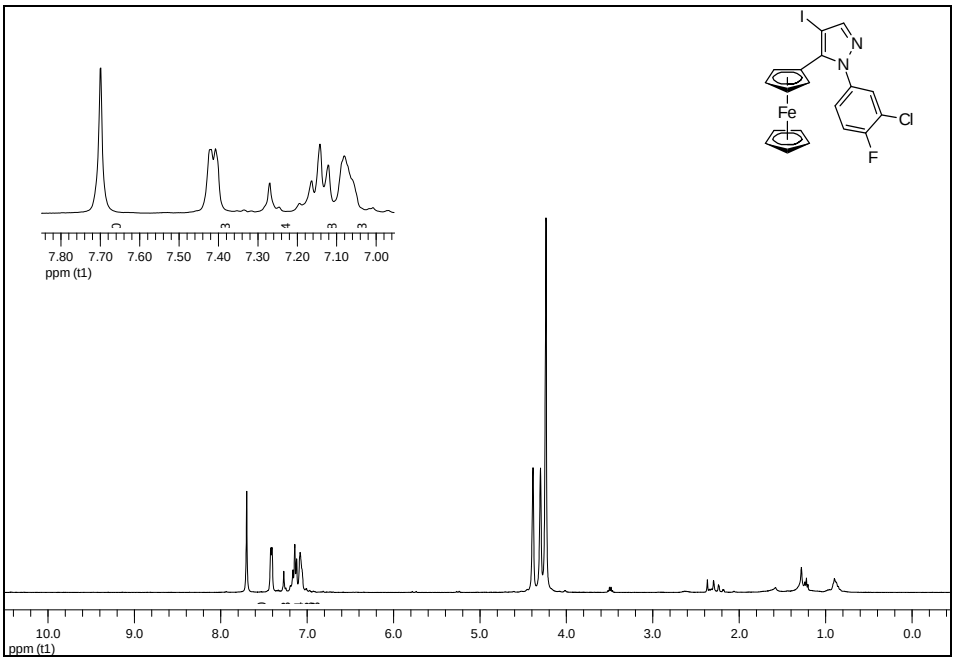

Figure A109. ^{1}H NMR spectra of **200c.**

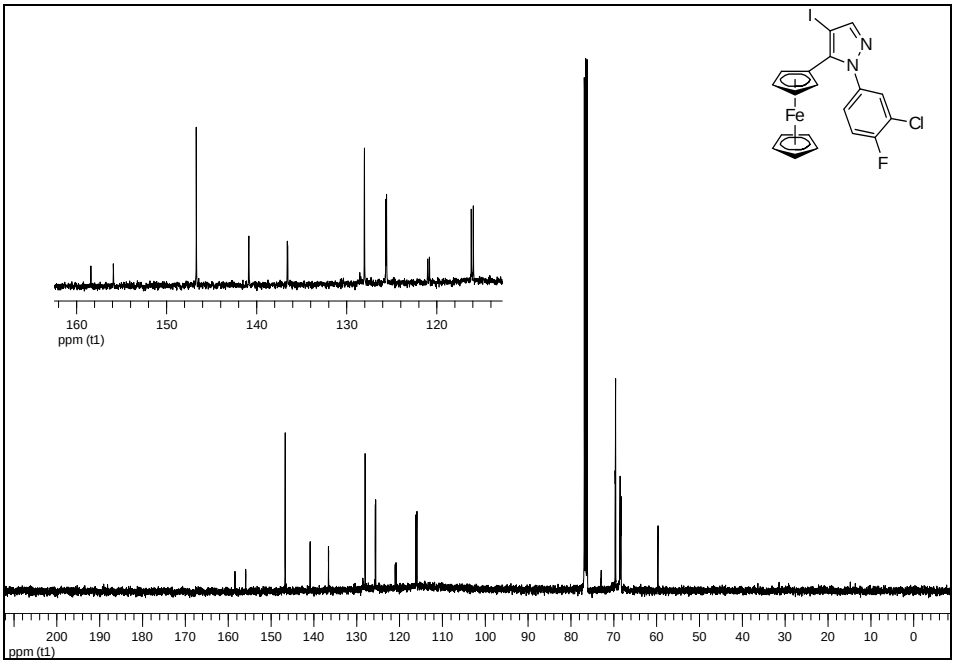

Figure A110. ^{13}C NMR spectra of **200c.**

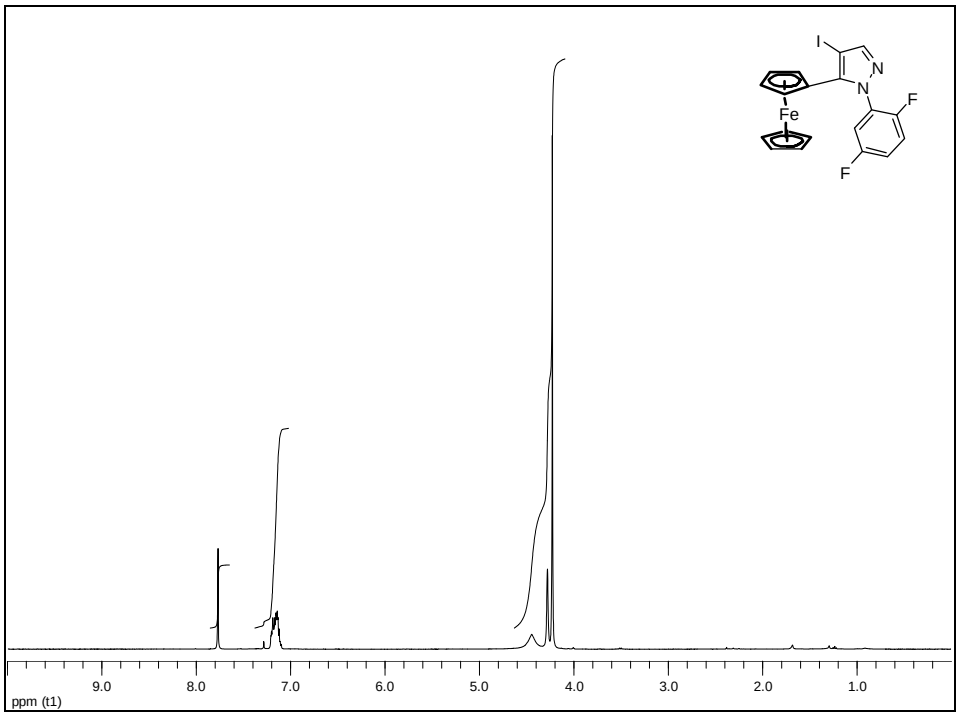

Figure A111. ^{1}H NMR spectra of **200d.**

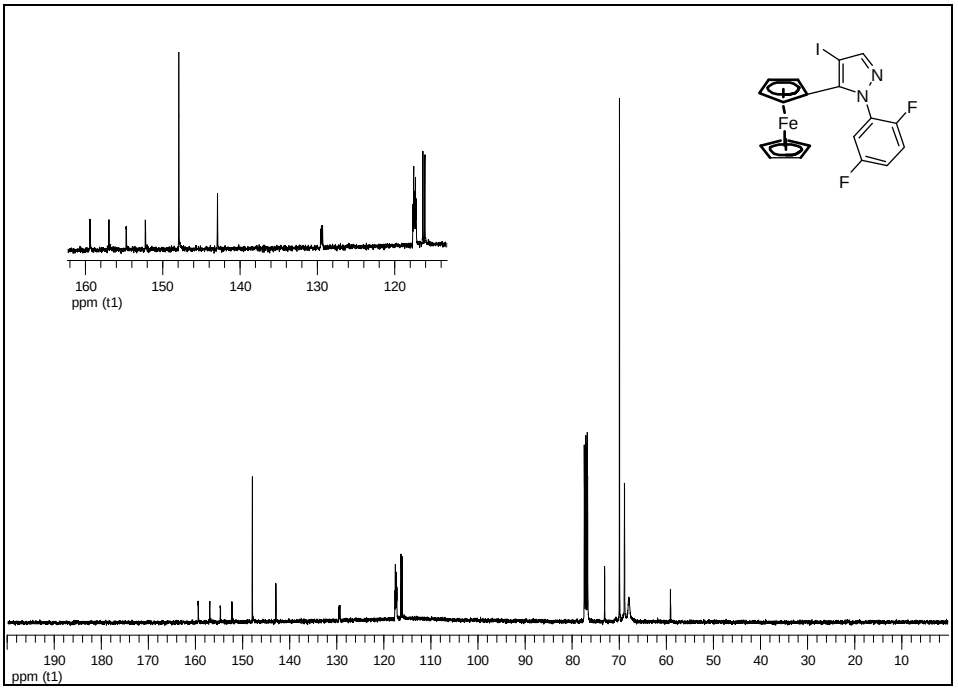

Figure A112. ^{13}C NMR spectra of **200d.**

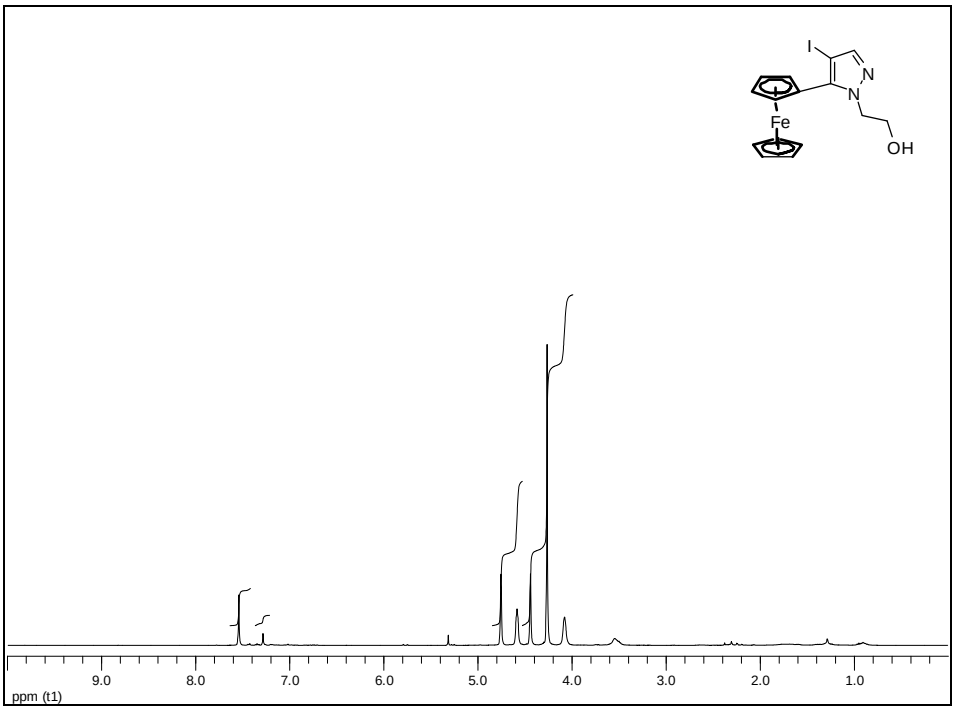

Figure A113. ^{1}H NMR spectra of **200e.**

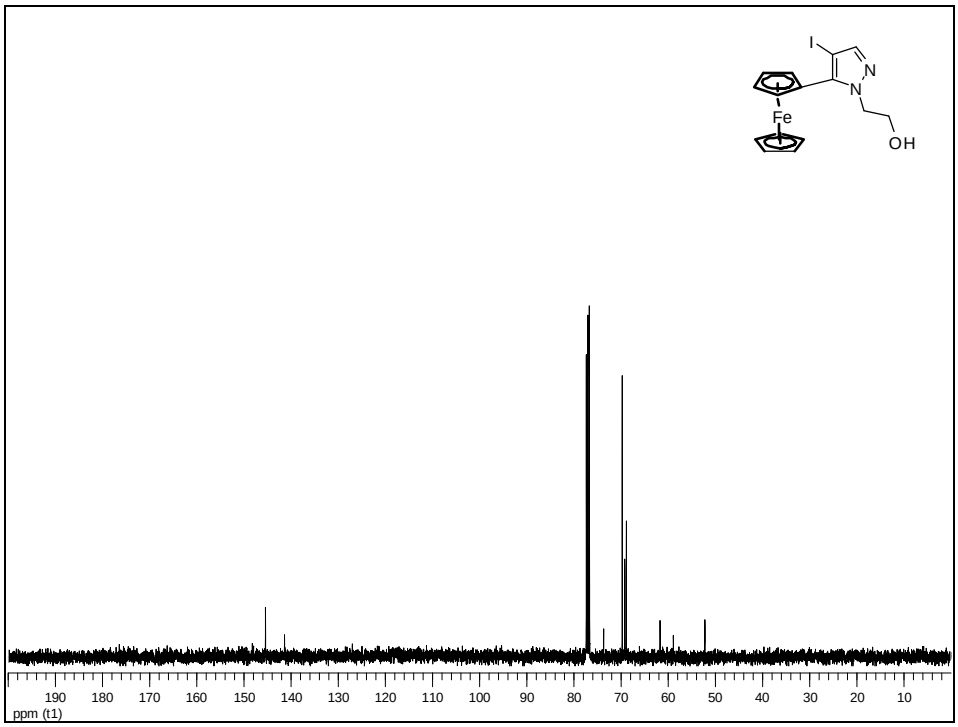

Figure A114. ^{13}C NMR spectra of **200e.**

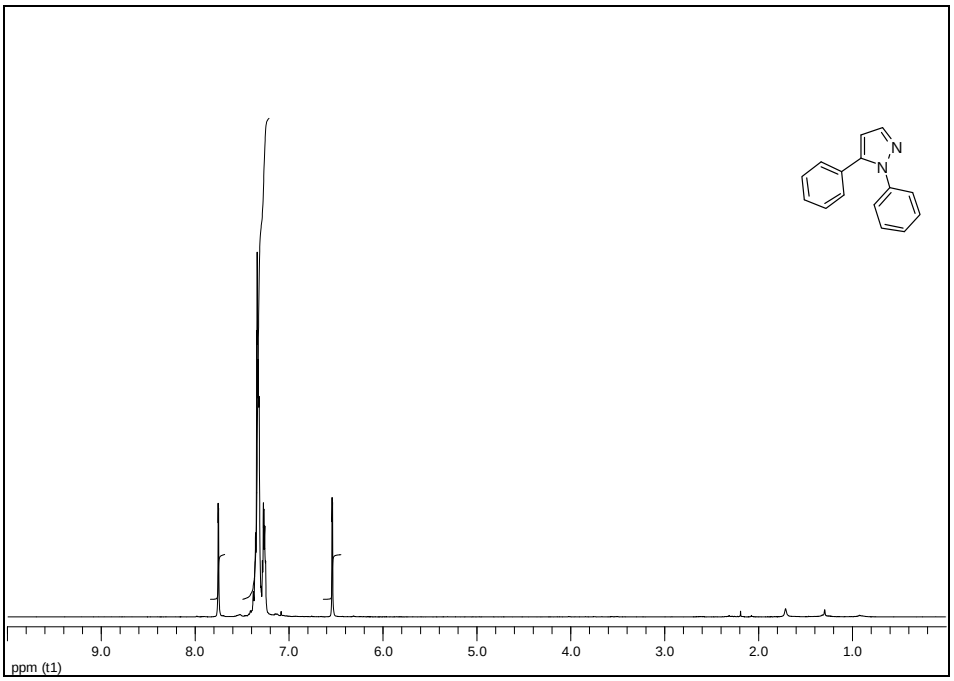

Figure A115. ^{1}H NMR spectra of **188a**.

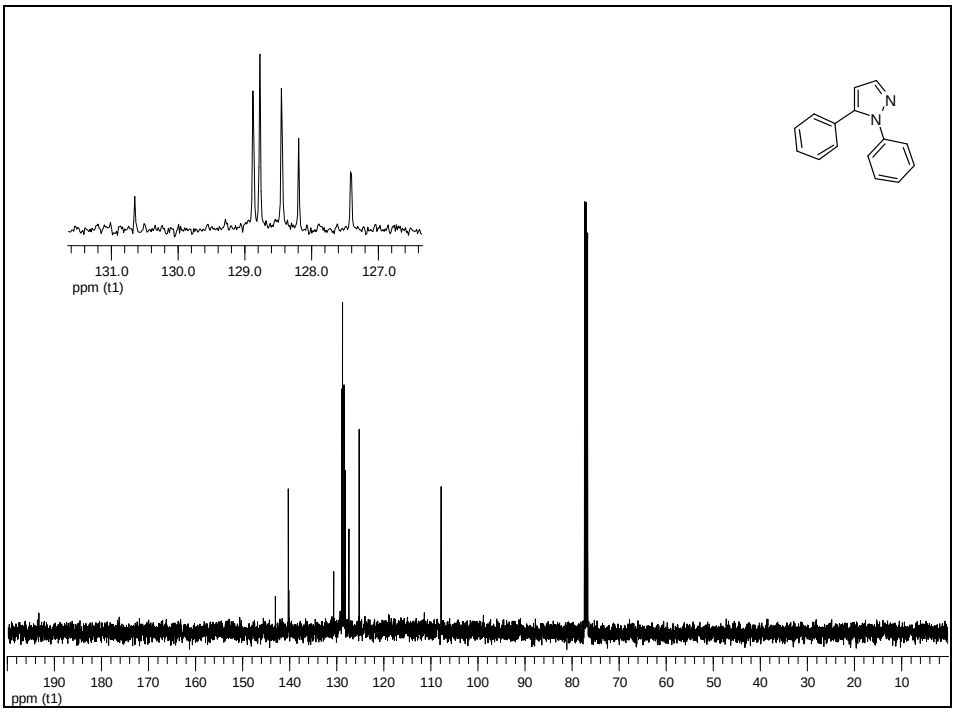

Figure A116. ^{13}C NMR spectra of **188a.**

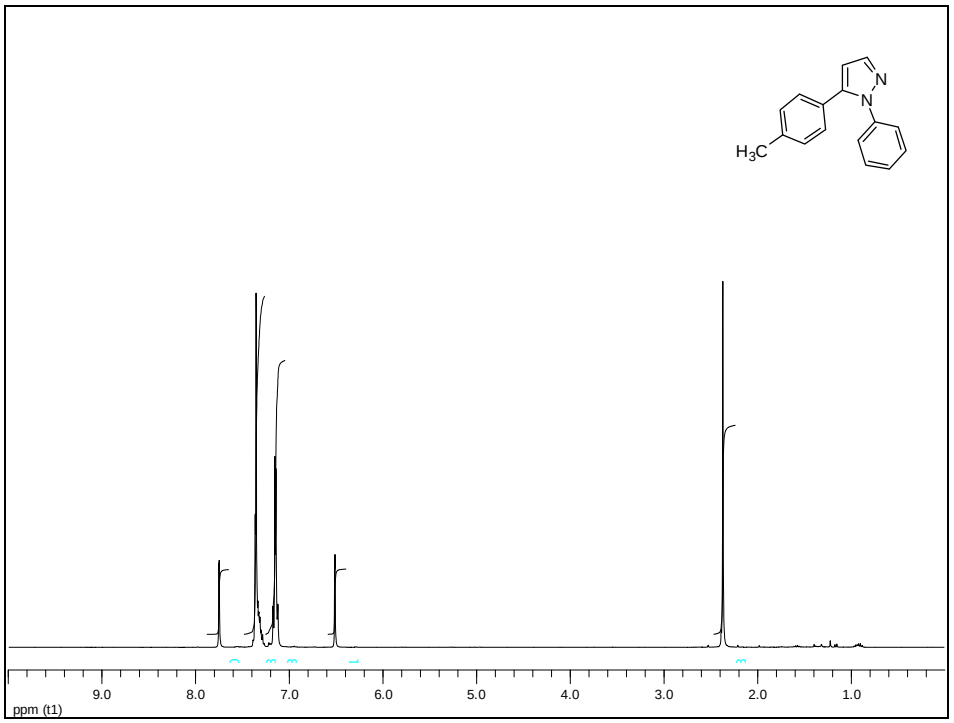

Figure A117. ^{1}H NMR spectra of **188b.**

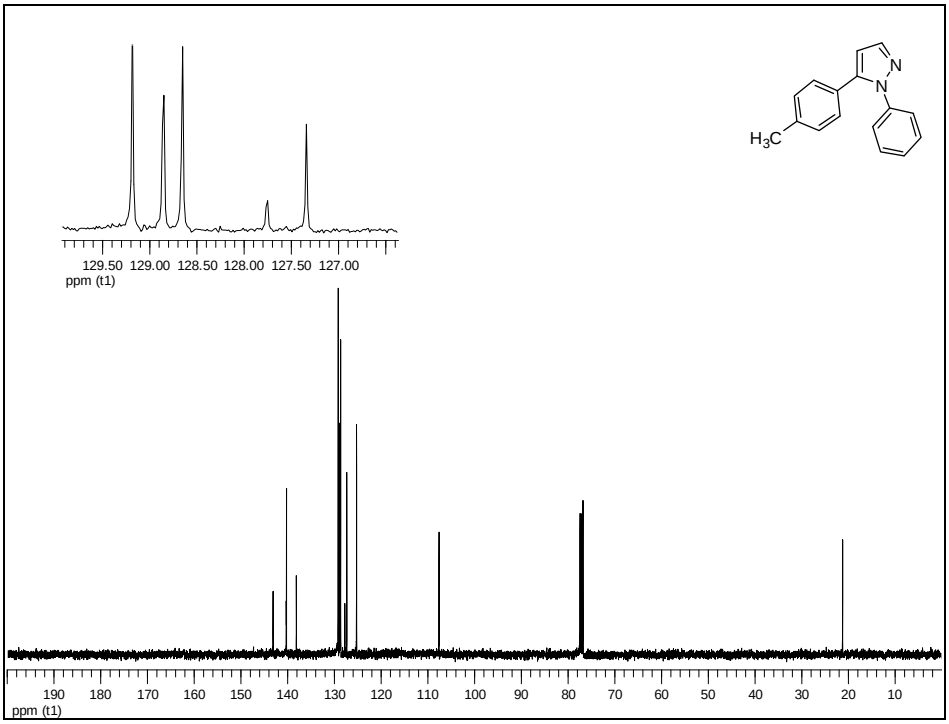

Figure A118. ^{13}C NMR spectra of **188b.**

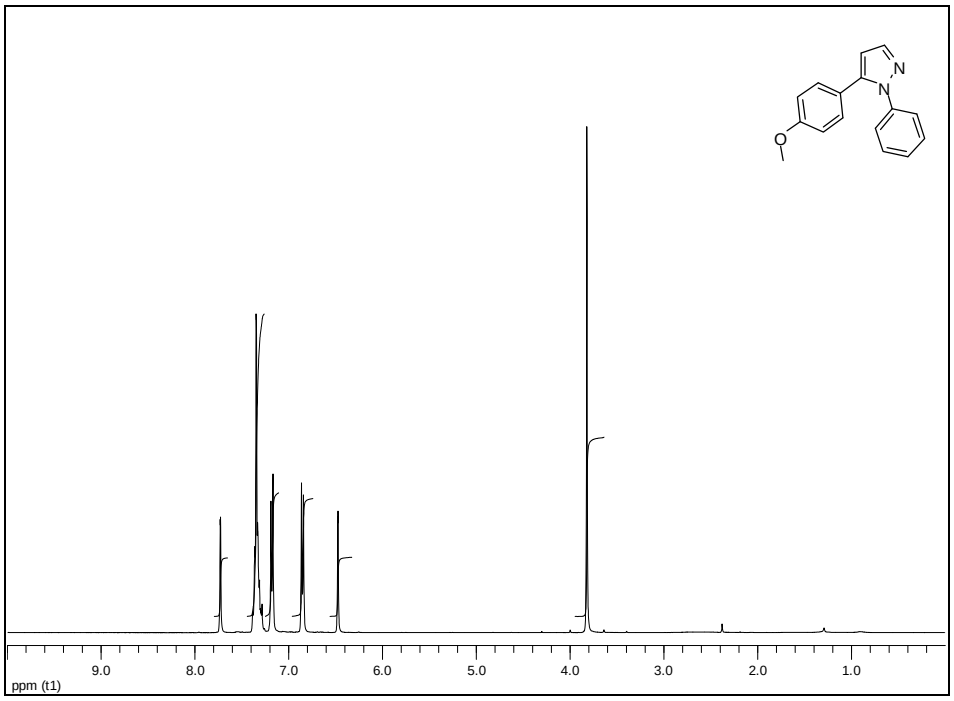

Figure A119. ^{1}H NMR spectra of **188c**.

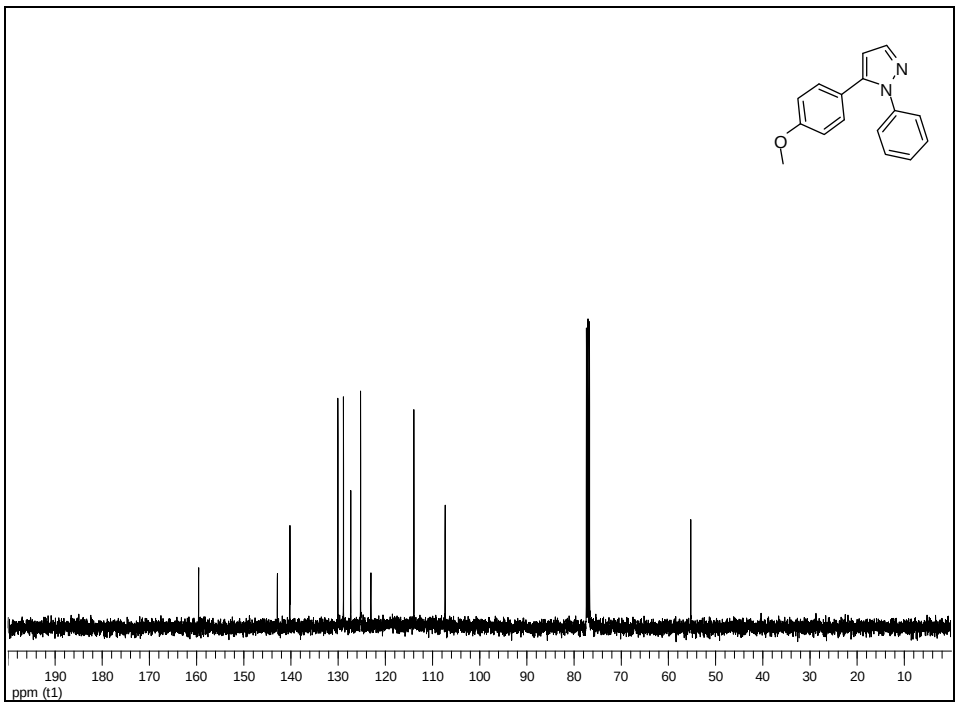

Figure A120. ^{13}C NMR spectra of **188c**.

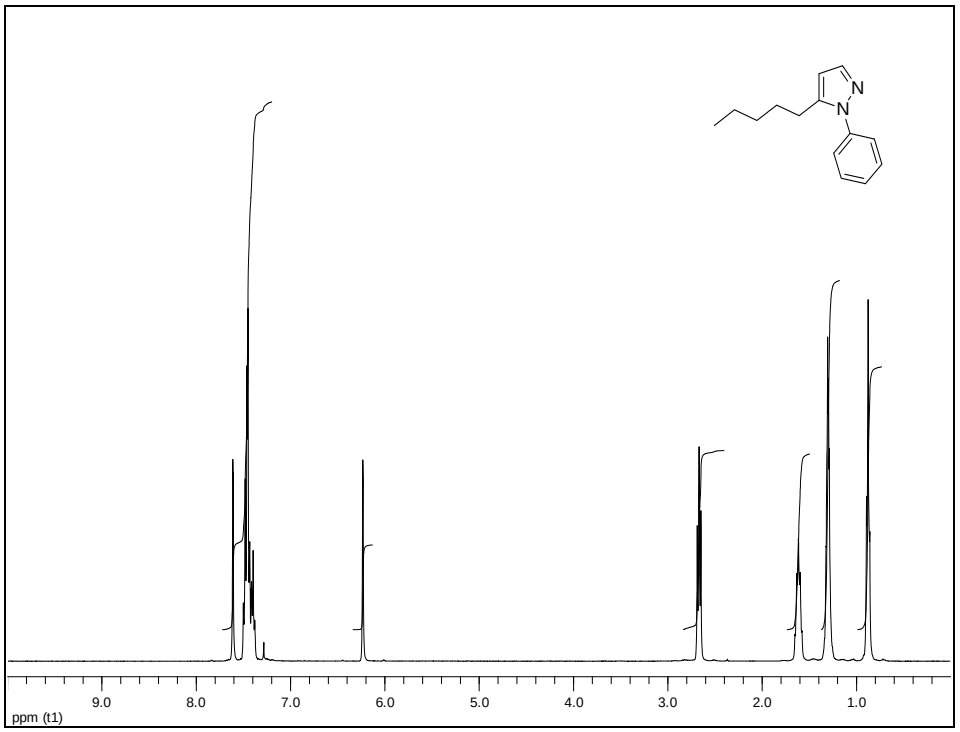

Figure A121. ^{1}H NMR spectra of **188d**.

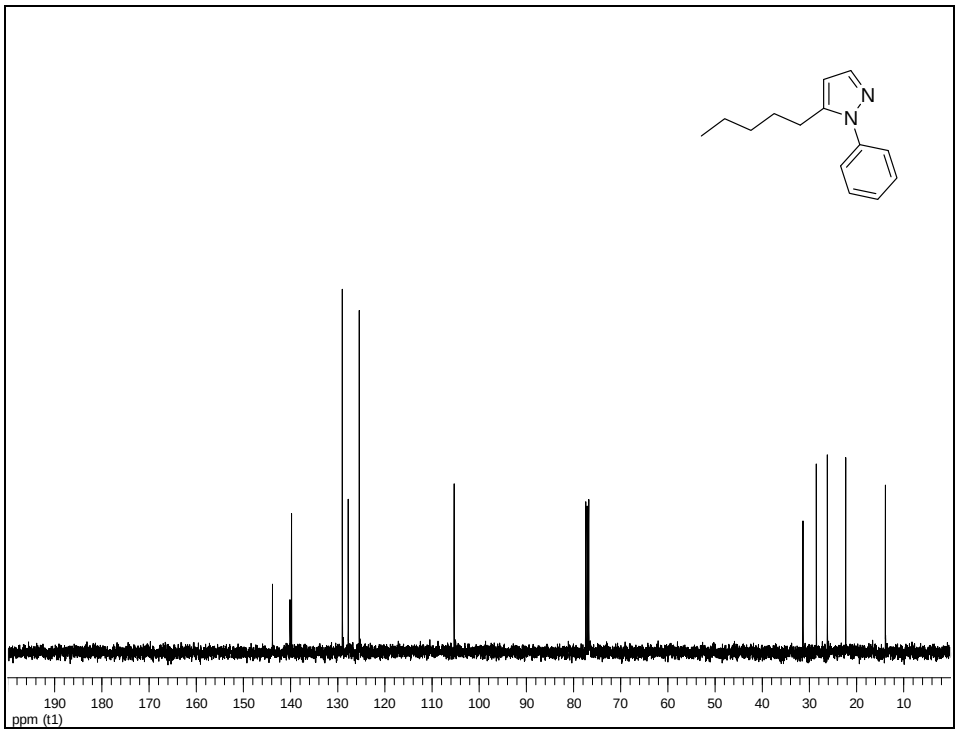

Figure A122. ^{13}C NMR spectra of **188d**.

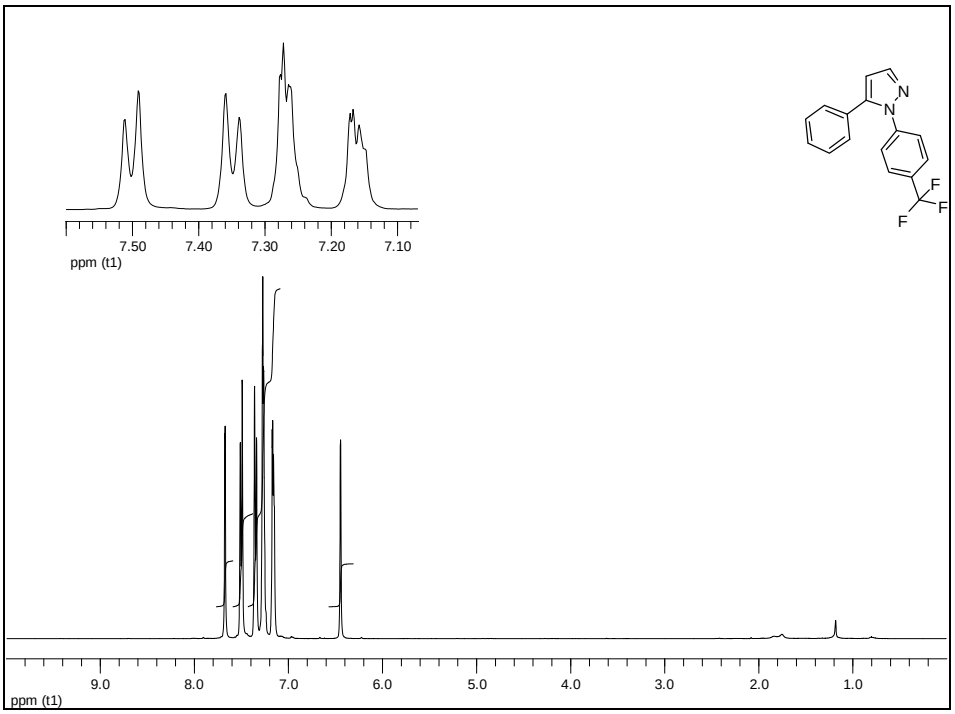

Figure A123. ^{1}H NMR spectra of **188e**.

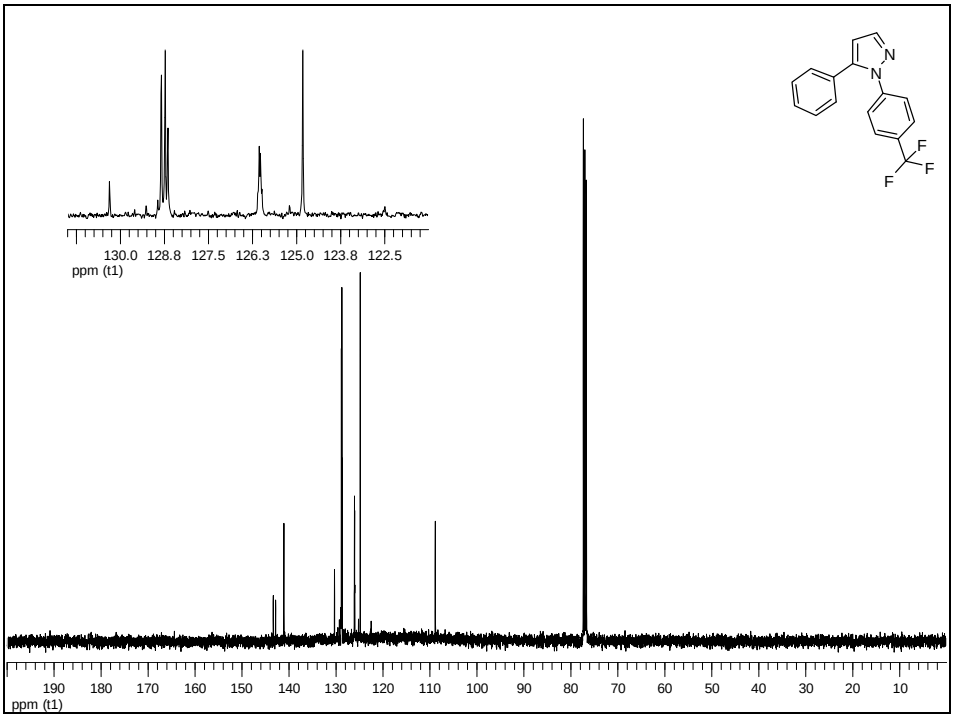

Figure A124. ^{13}C NMR spectra of **188e**.

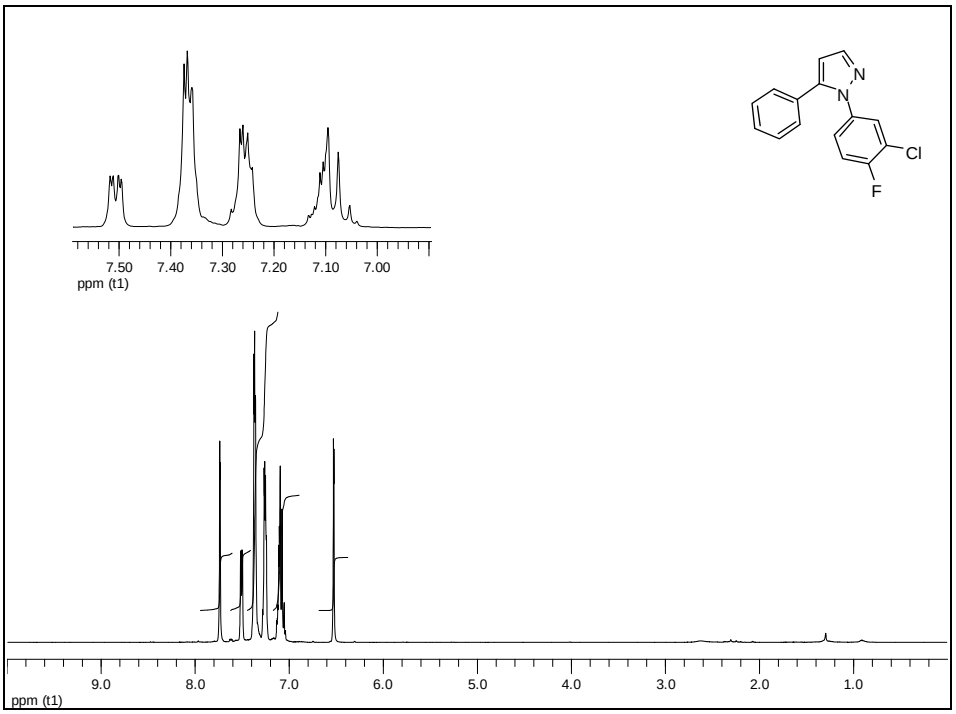

Figure A125. ^{1}H NMR spectra of **188f**.

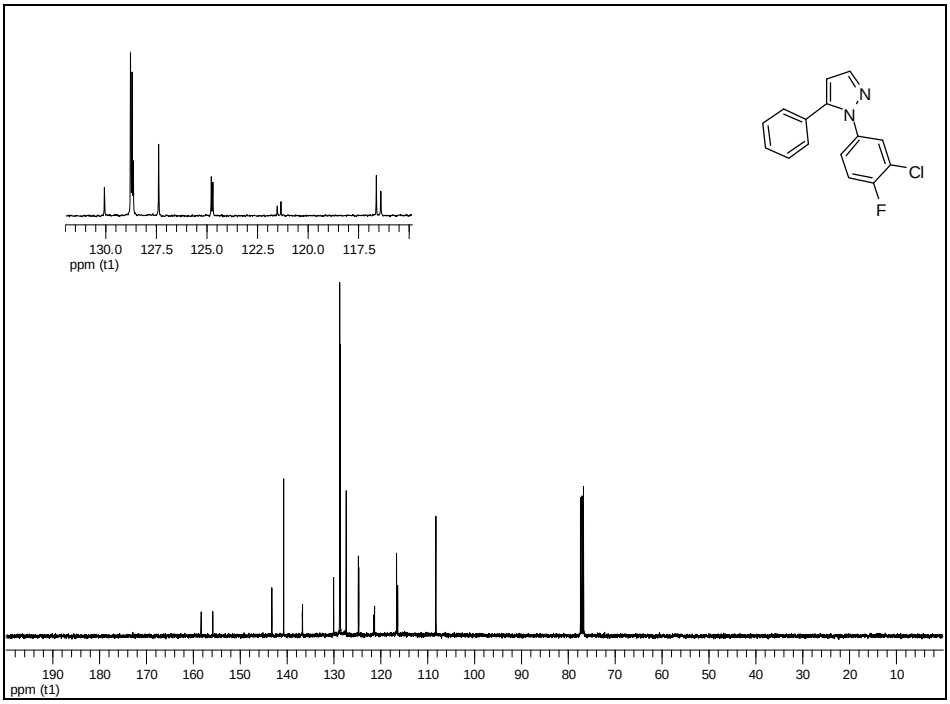

Figure A126. ^{13}C NMR spectra of **188f**.

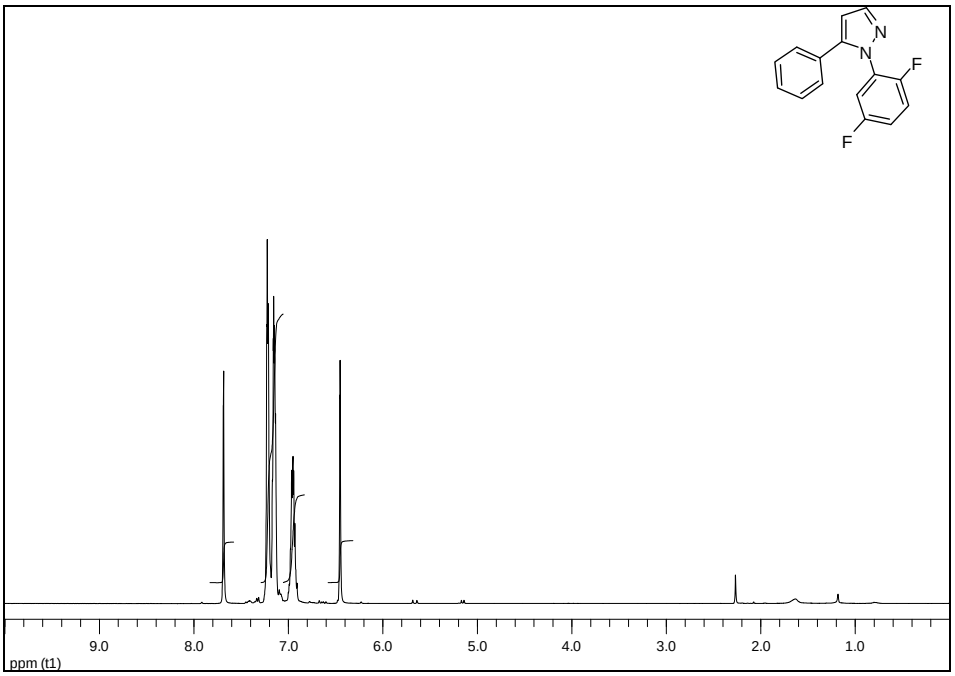

Figure A127. ^{1}H NMR spectra of **188g**.

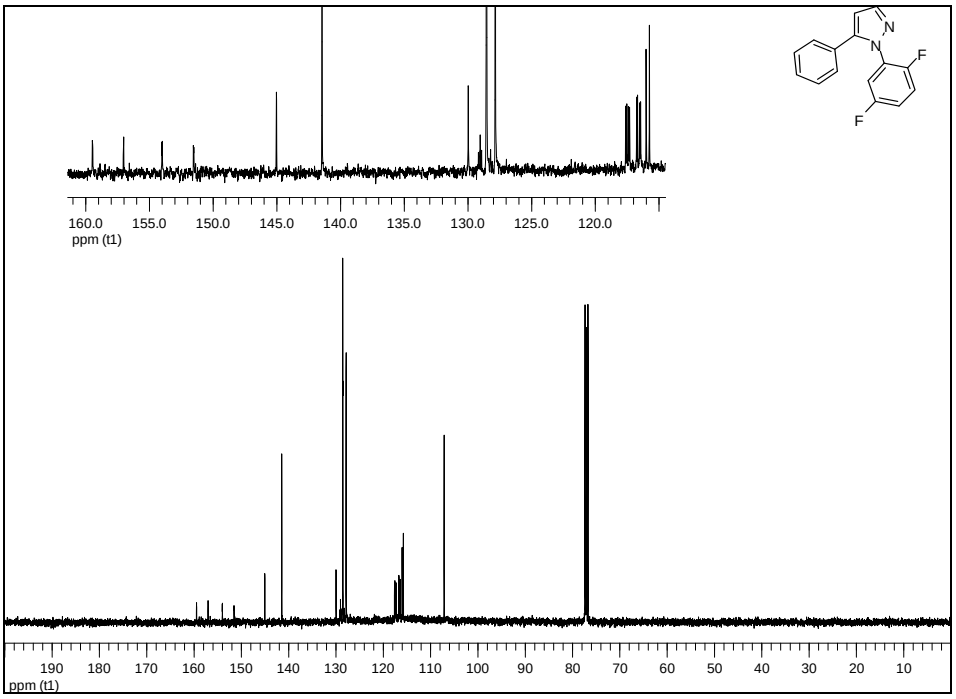

Figure A128. ^{13}C NMR spectra of **188g**.

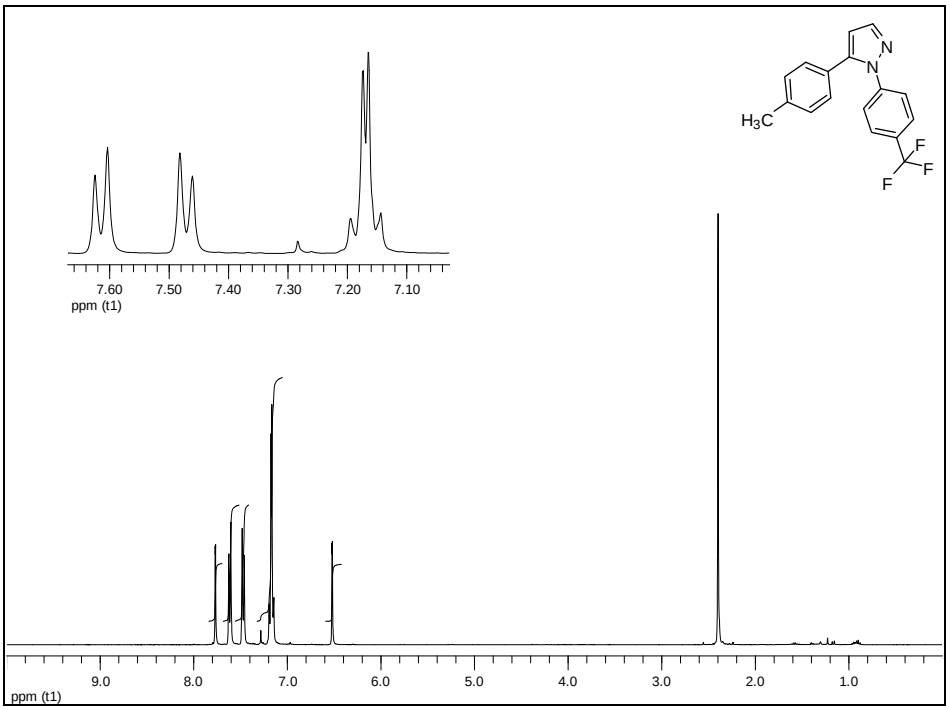

Figure A129. ^{1}H NMR spectra of **188h**.

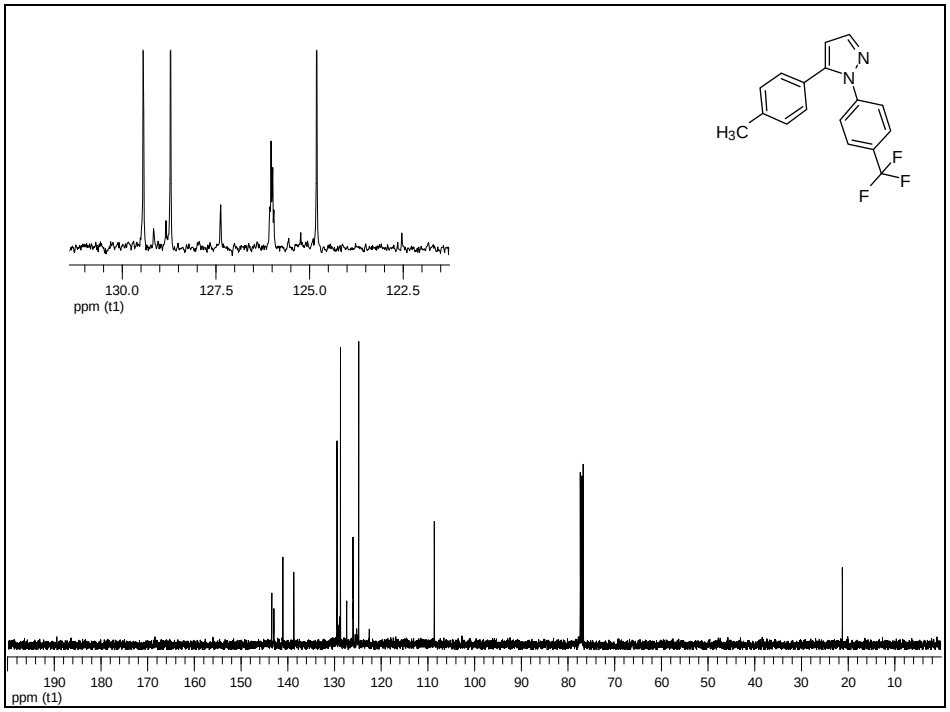

Figure A130. ^{13}C NMR spectra of **188h**.

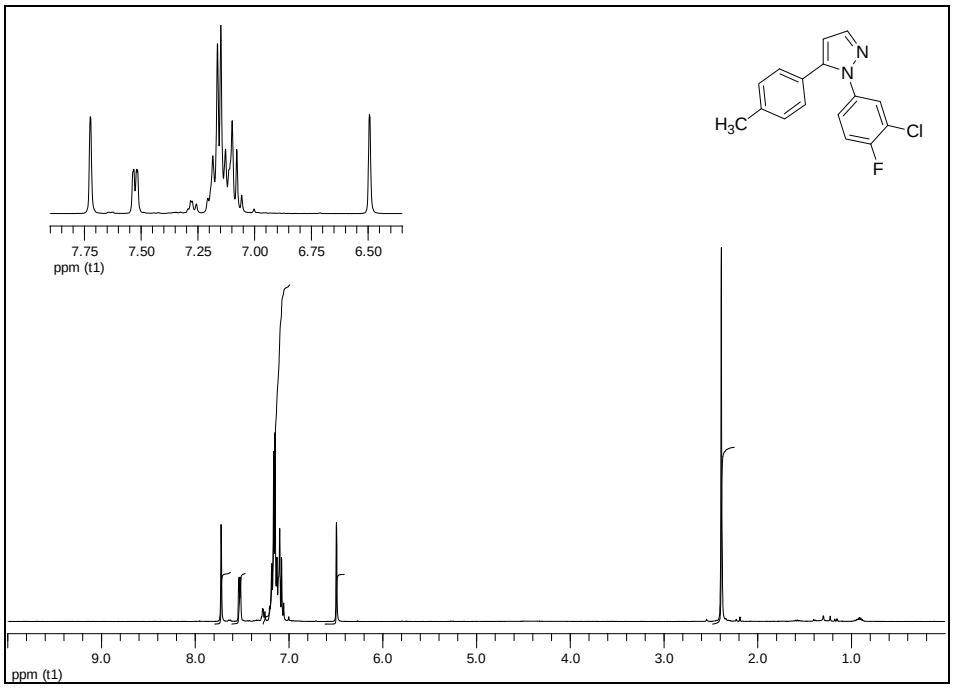

Figure A131. ^{1}H NMR spectra of **188i**.

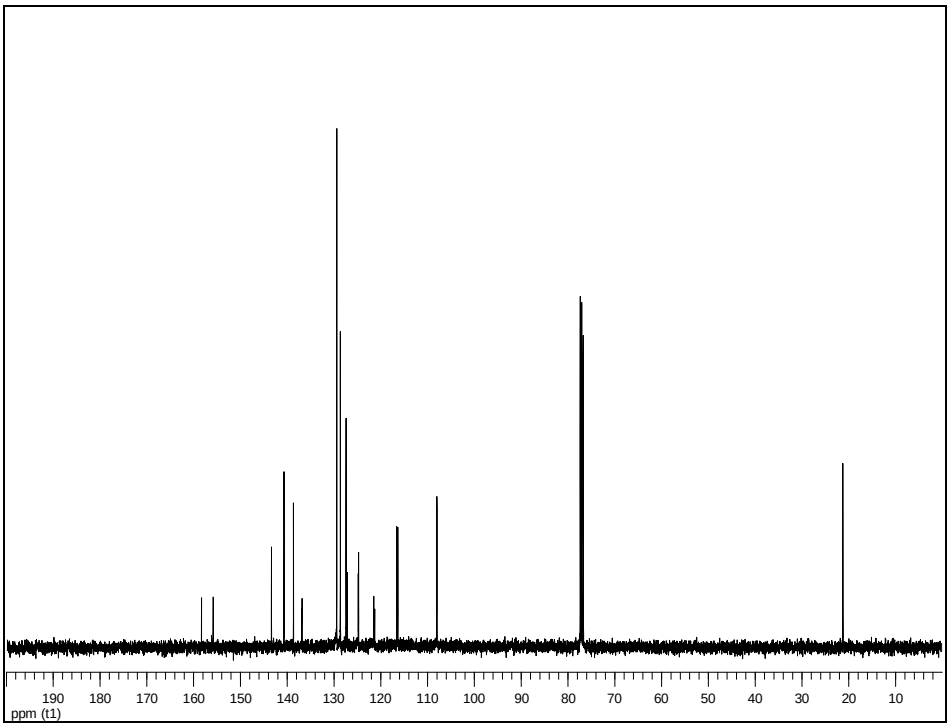

Figure A132. ^{13}C NMR spectra of **188i**.

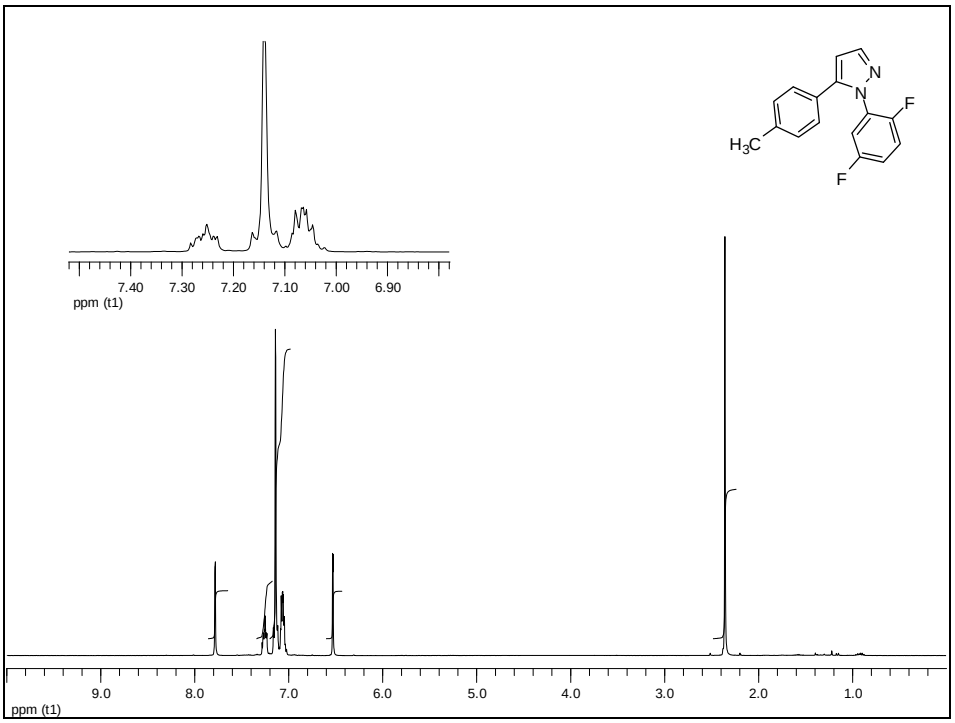

Figure A133. ^{1}H NMR spectra of **188j**.

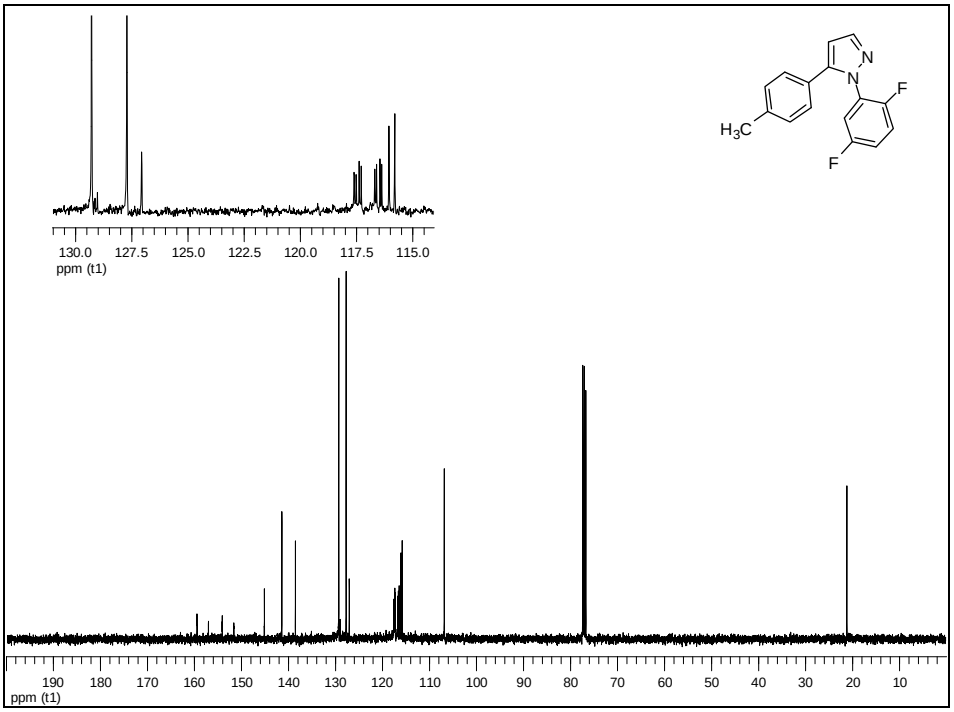

Figure A134. ^{13}C NMR spectra of **188j**.

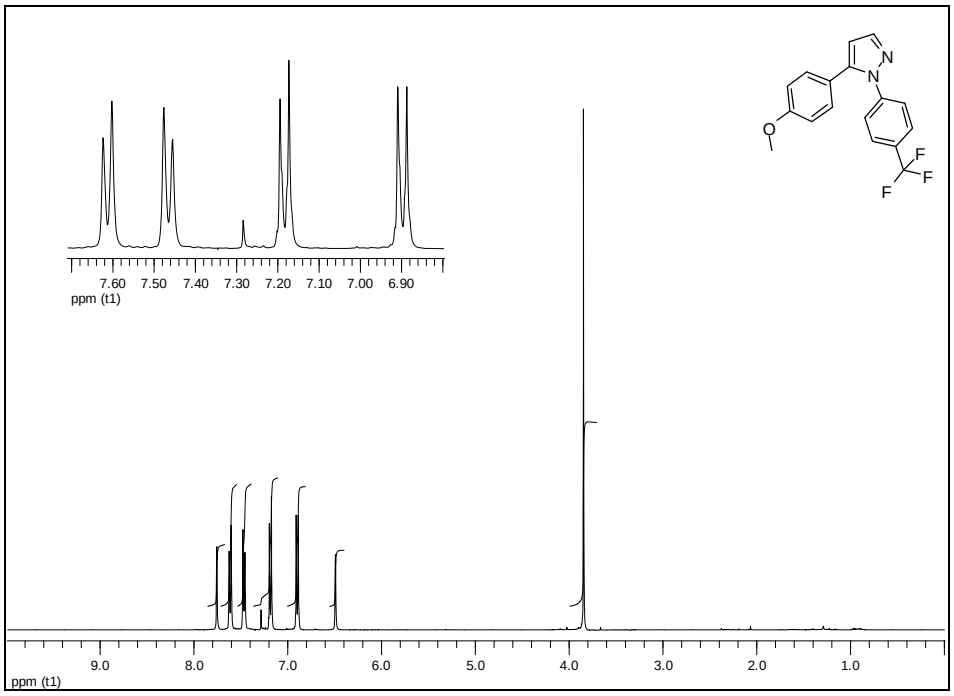

Figure A135. ^{1}H NMR spectra of **188k**.

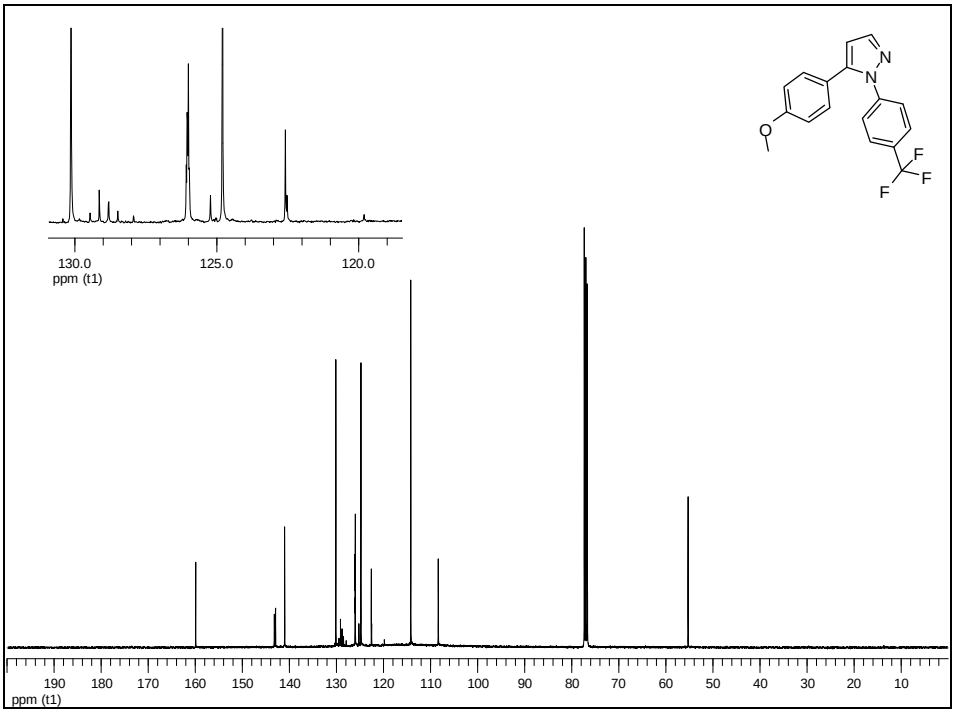

Figure A136. ^{13}C NMR spectra of **188k**.

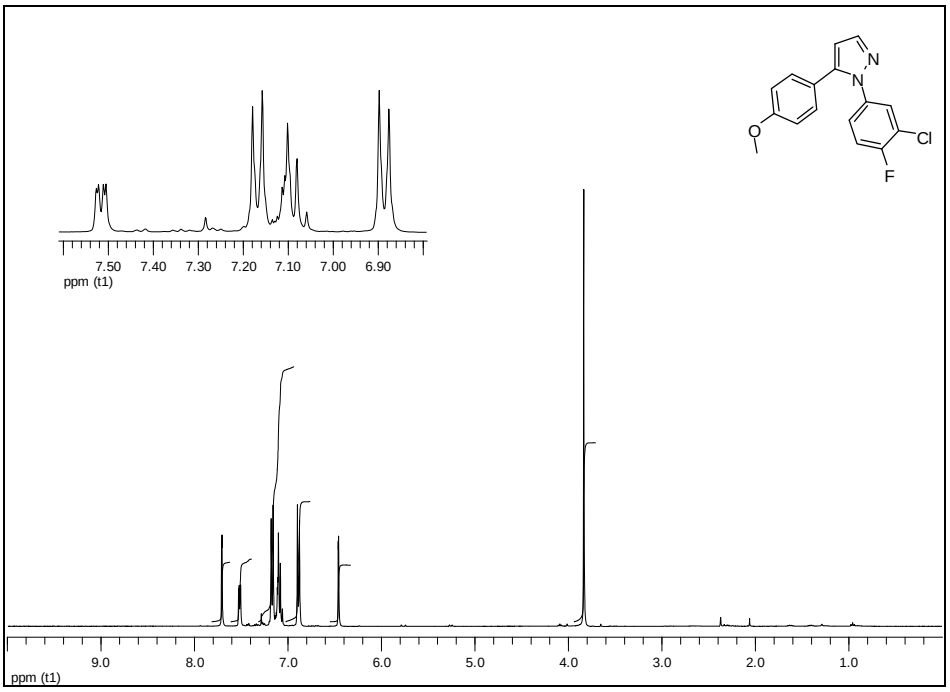

Figure A137. ^{1}H NMR spectra of **188l**.

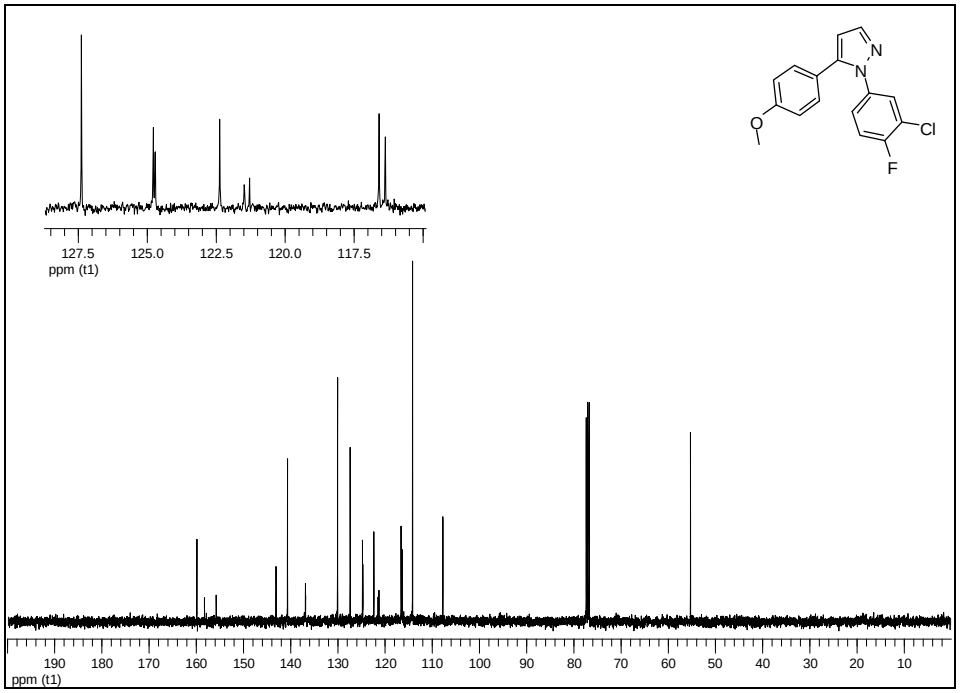

Figure A138. ^{13}C NMR spectra of **188l**.

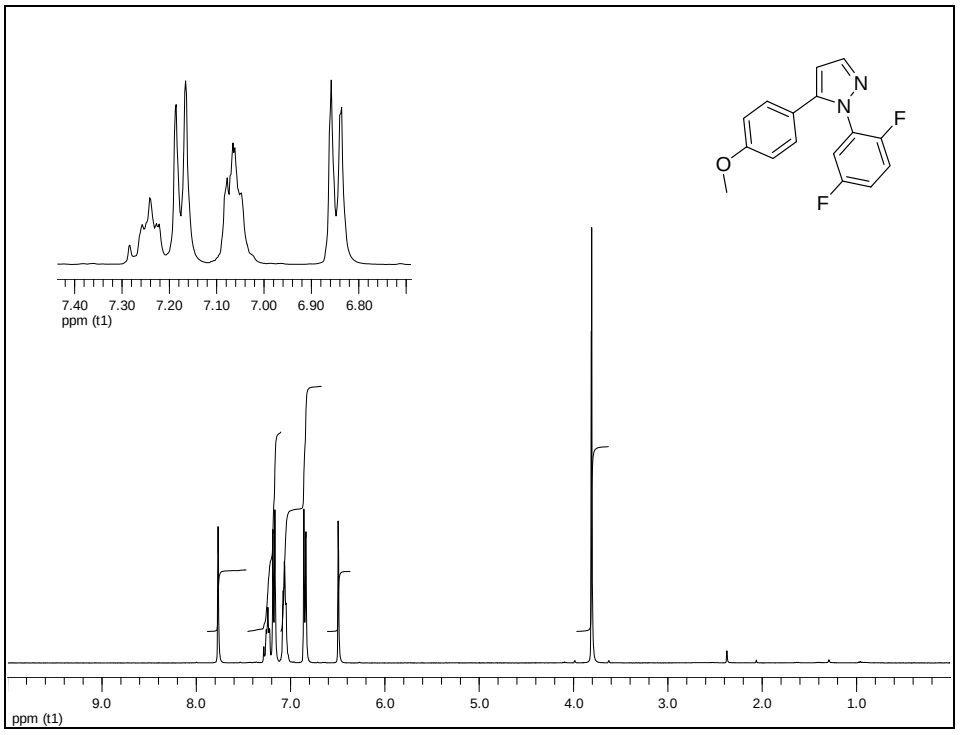

Figure A139. ^{1}H NMR spectra of **188m**.

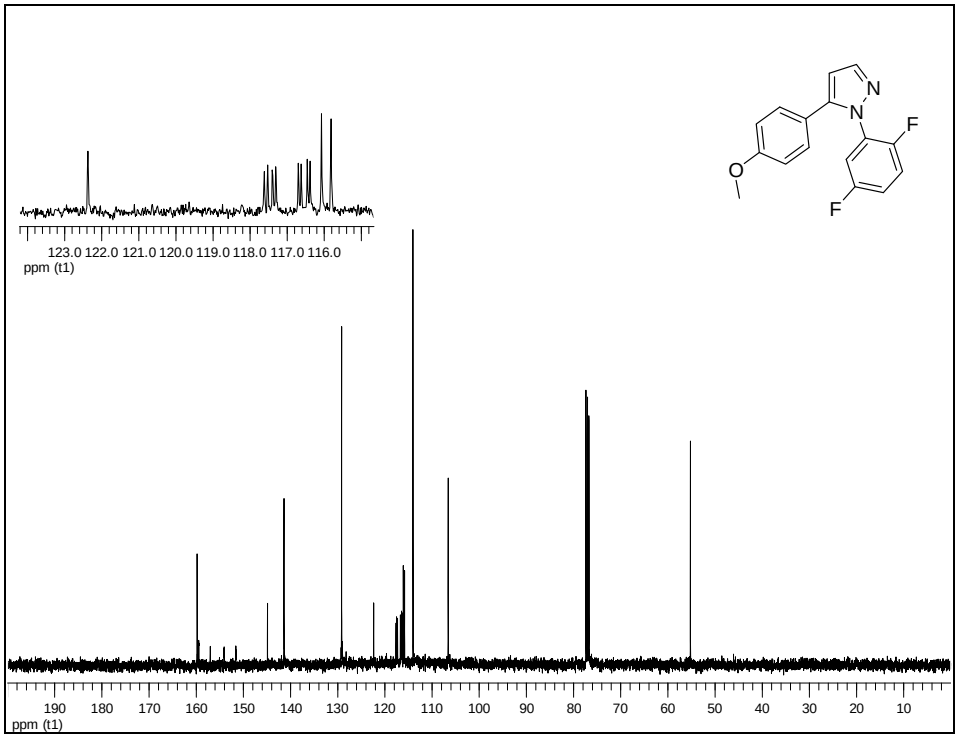

Figure A140. ^{13}C NMR spectra of **188m**.

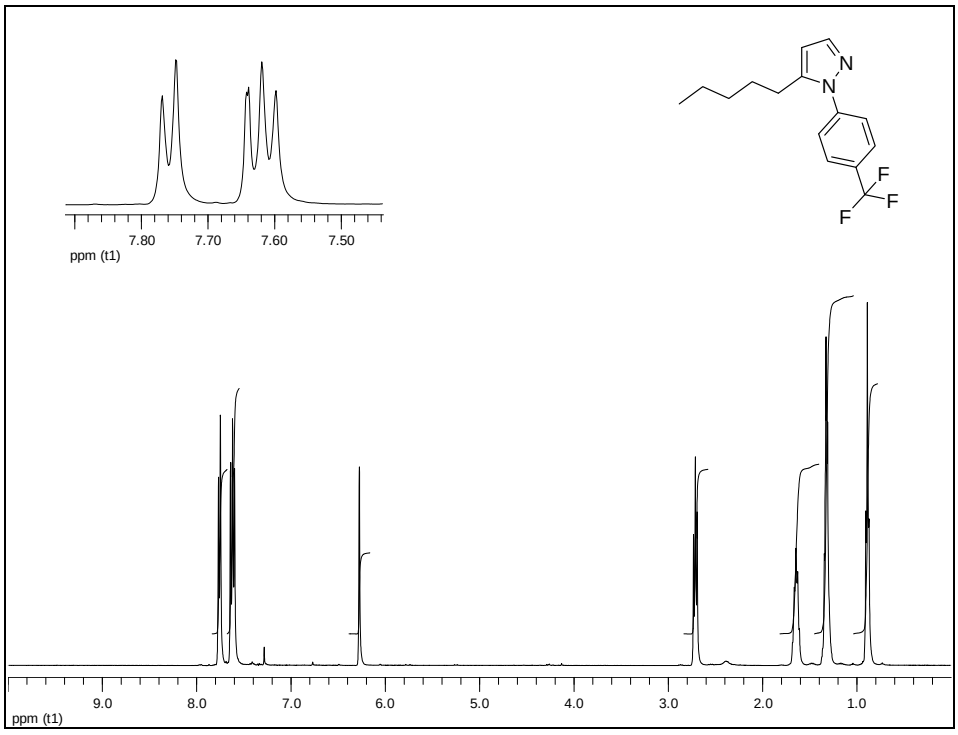

Figure A141. ^{1}H NMR spectra of **188n**.

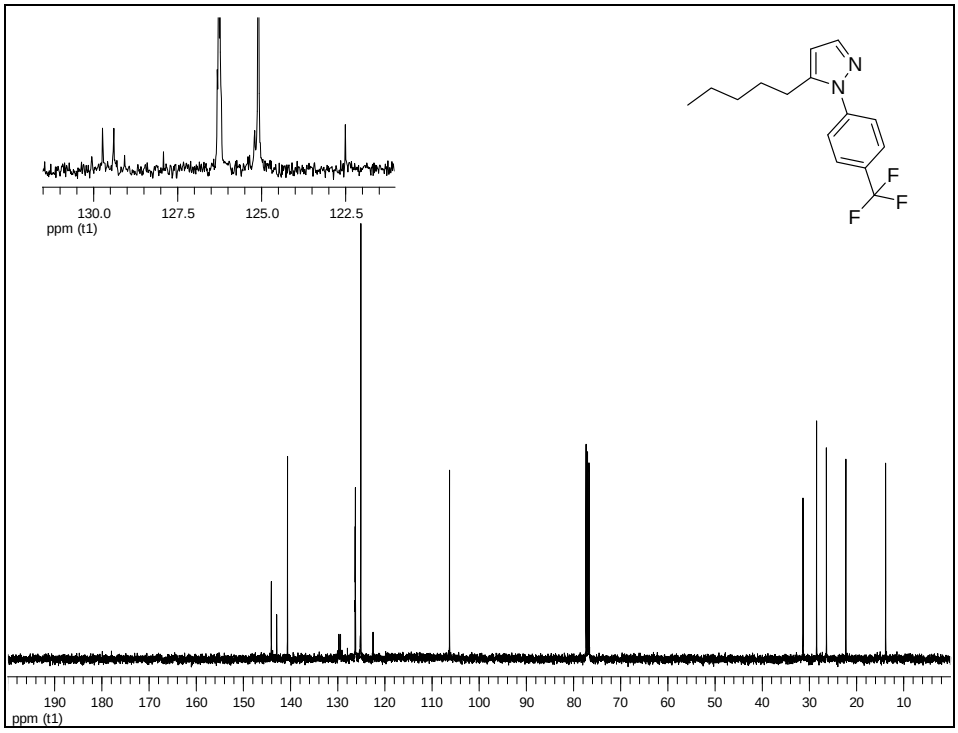

Figure A142. ^{13}C NMR spectra of **188n**.

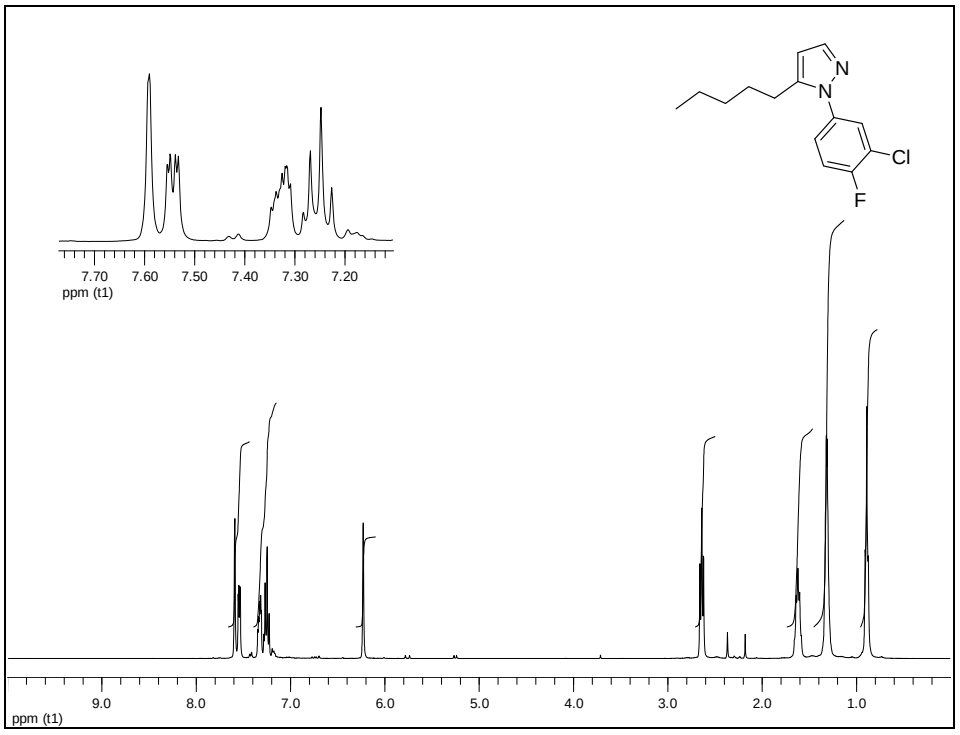

Figure A143. ^{1}H NMR spectra of **188o**.

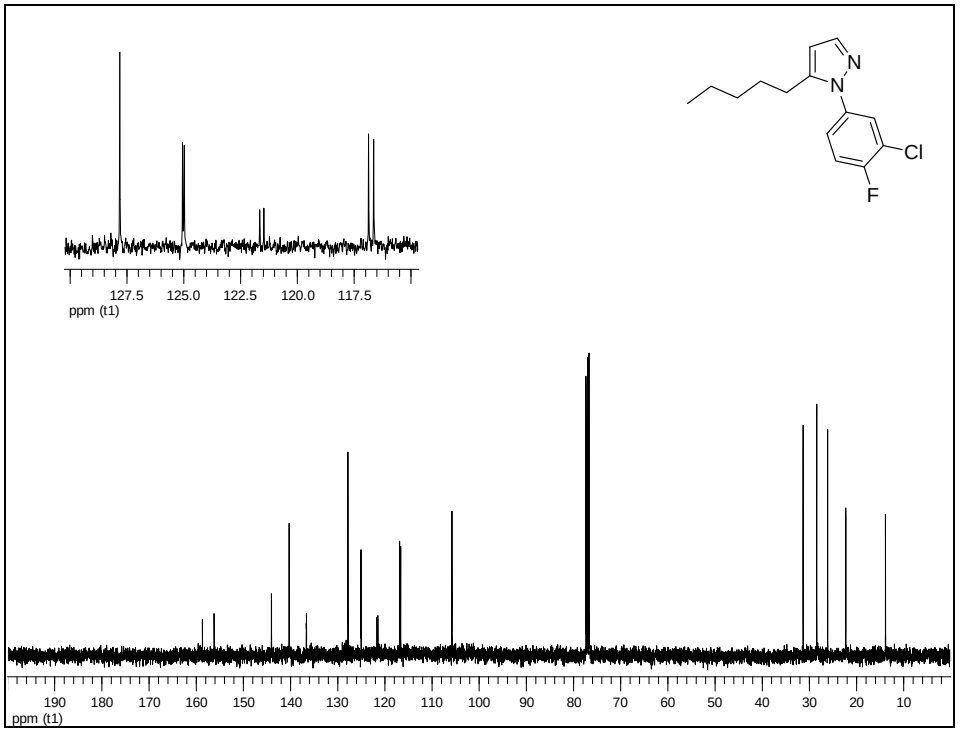

Figure A144. ^{13}C NMR spectra of **188o**.

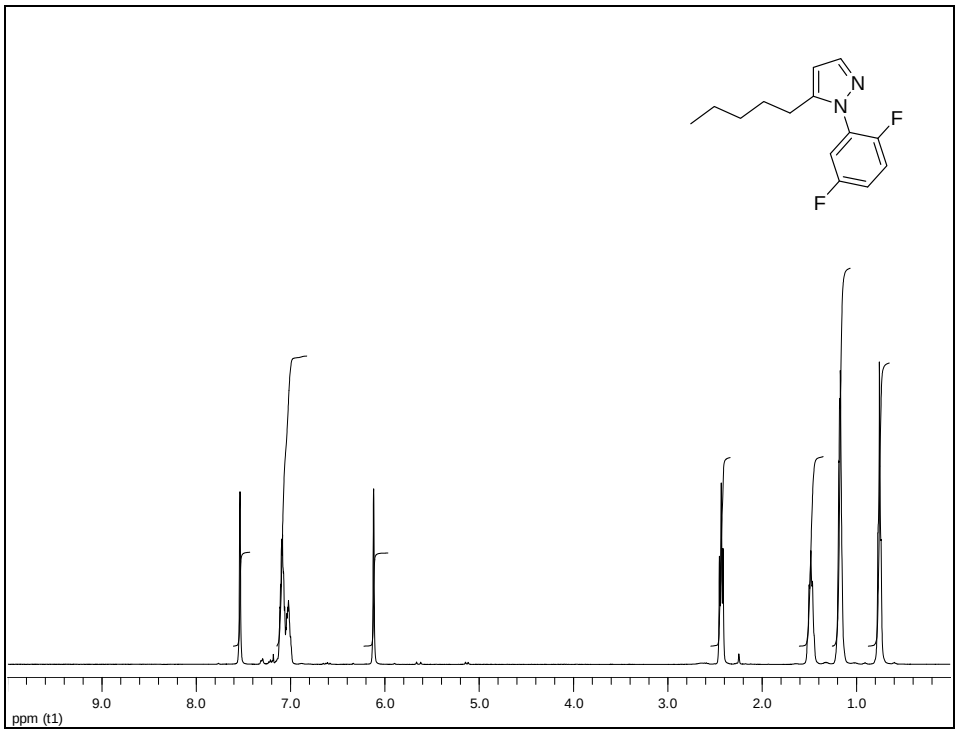

Figure A145. ^{1}H NMR spectra of **188p**.

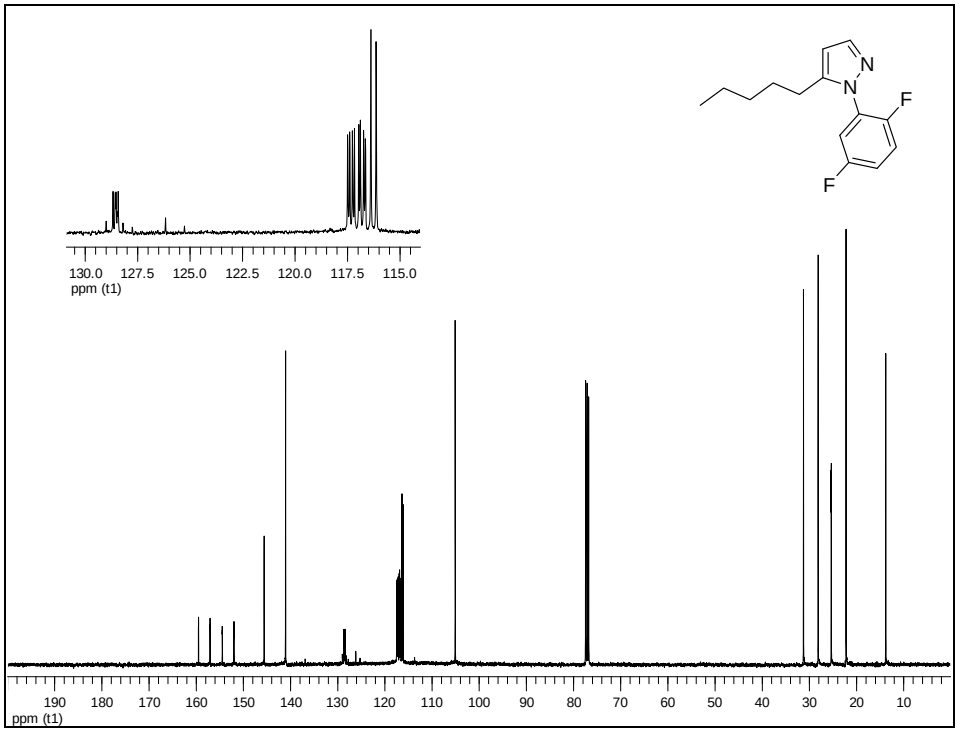

Figure A146. ^{13}C NMR spectra of **188p**.

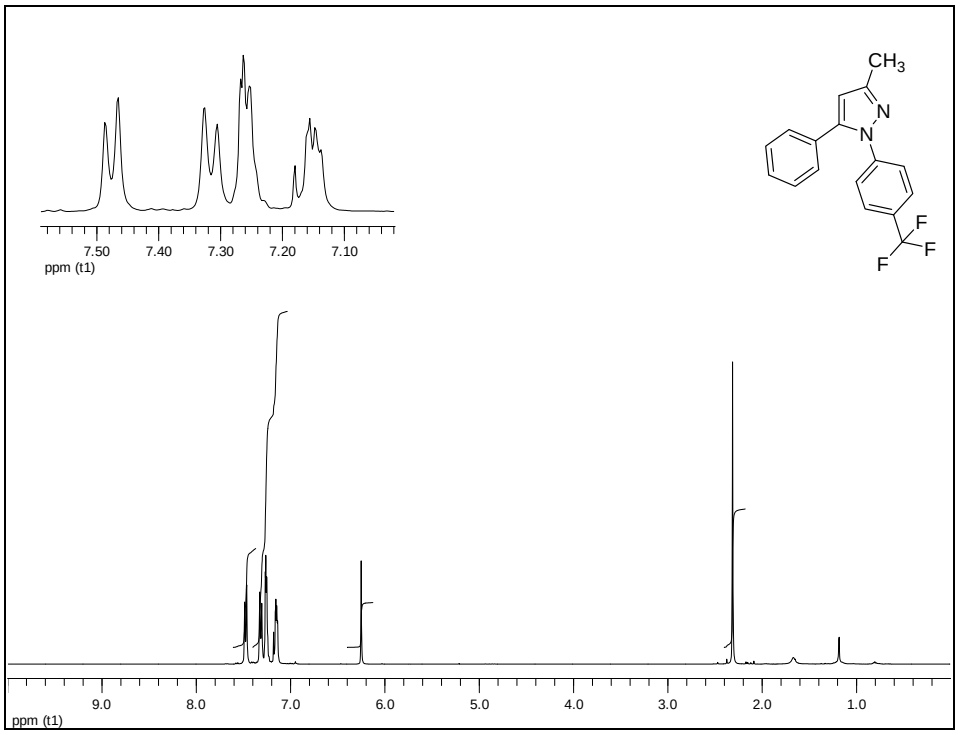

Figure A147. ^{1}H NMR spectra of **188q**.

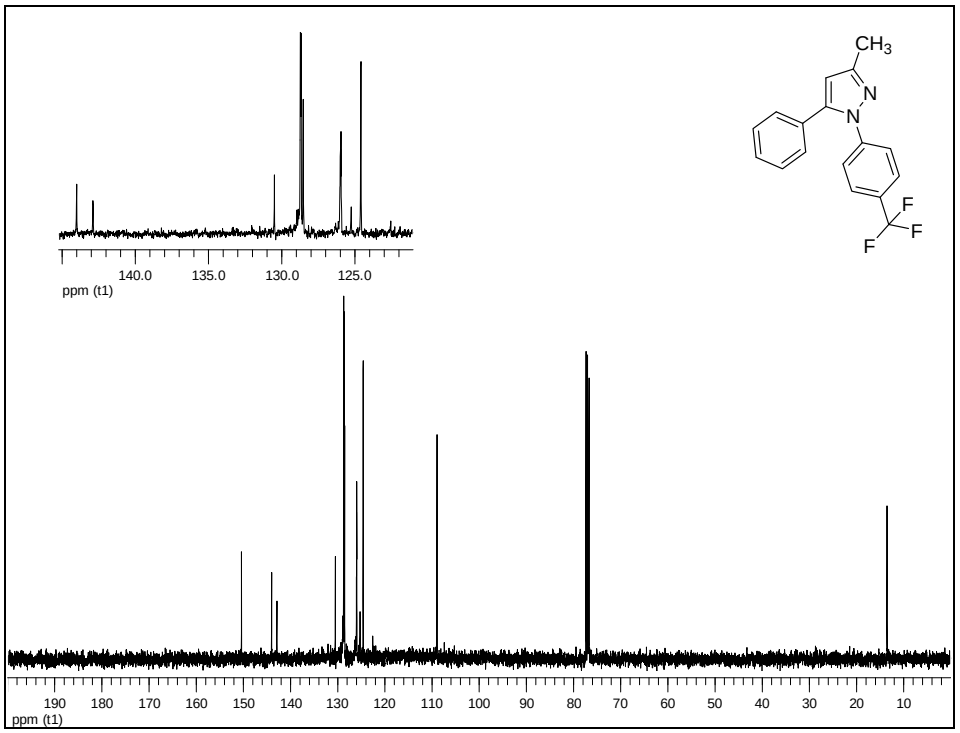

Figure A148. ^{13}C NMR spectra of **188q**.

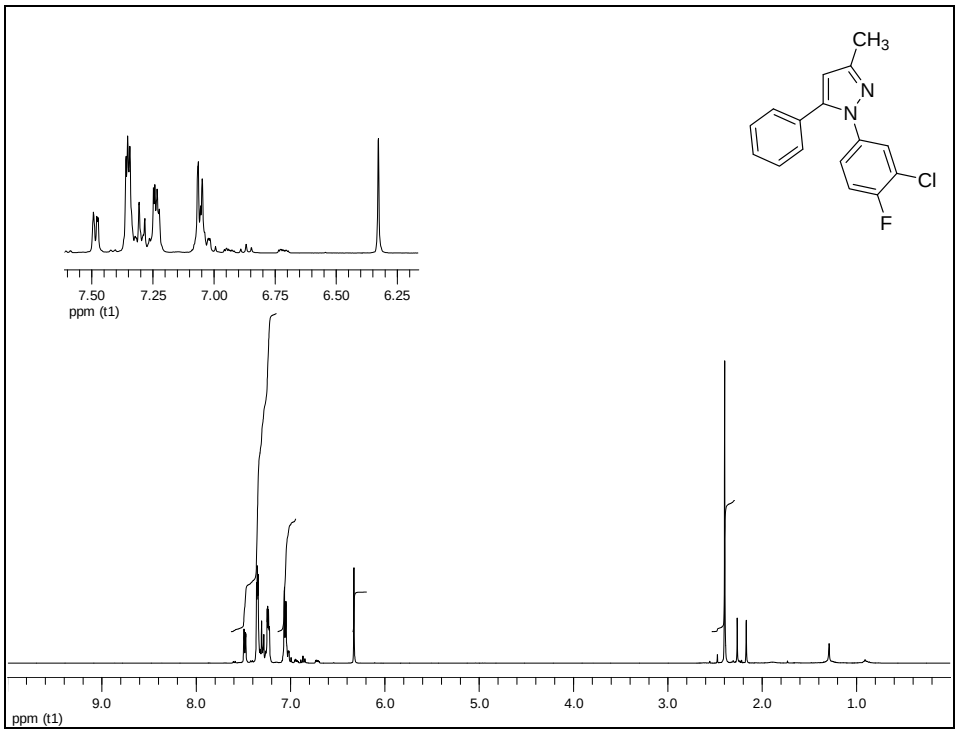

Figure A149. ^{1}H NMR spectra of **188r**.

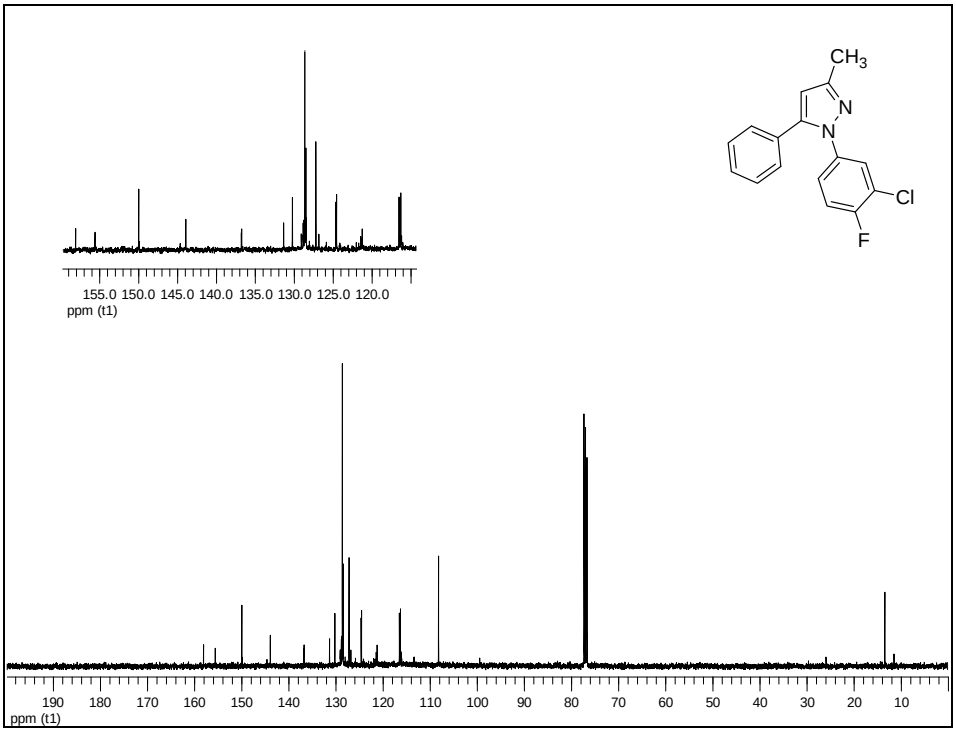

Figure A150. ^{13}C NMR spectra of **188r**.

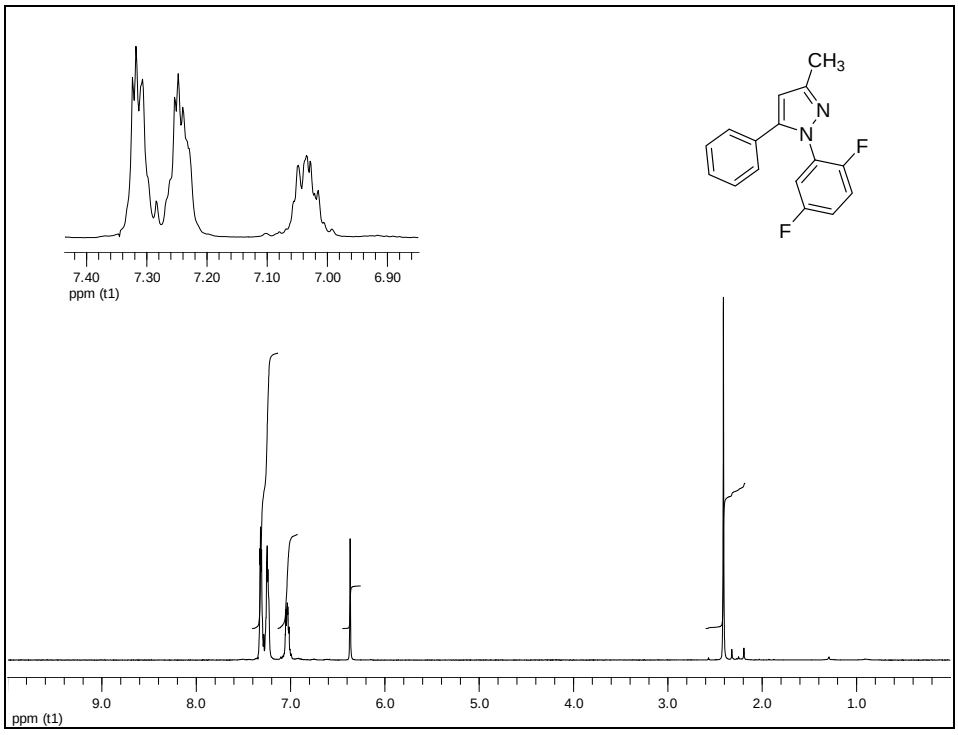

Figure A151. ^{1}H NMR spectra of **188s**.

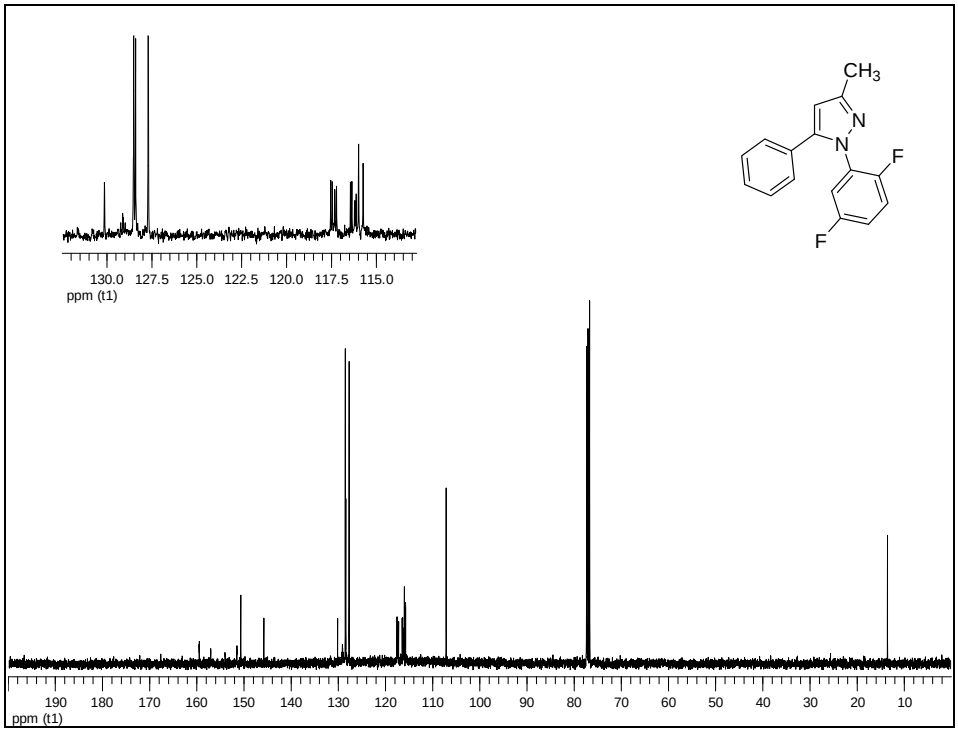

Figure A152. ^{13}C NMR spectra of **188s**.

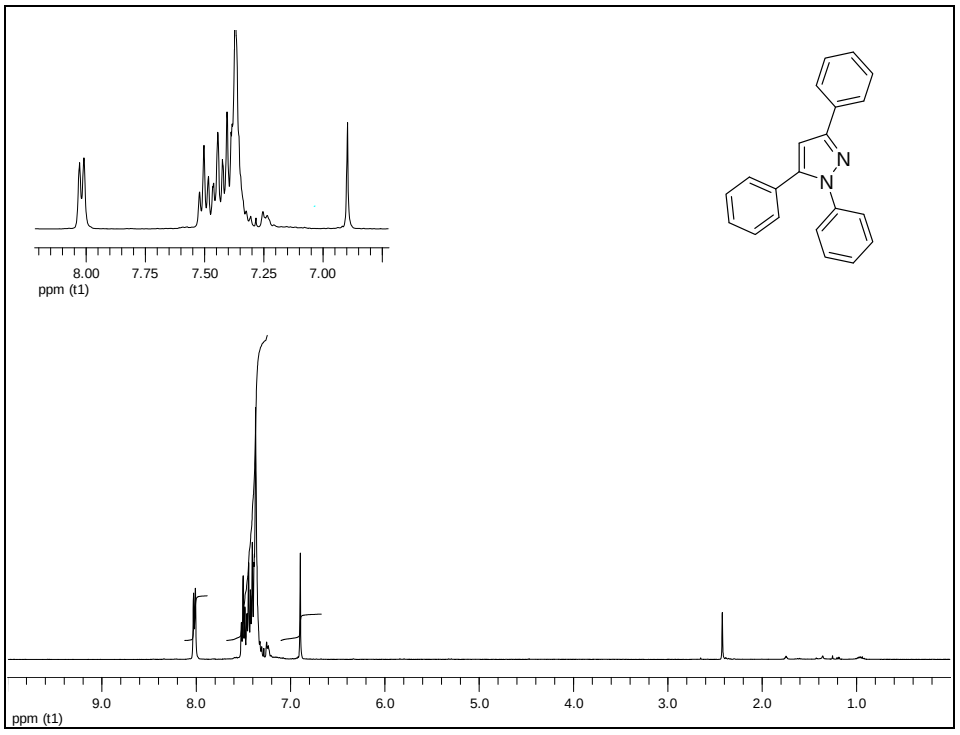

Figure A153. ^{1}H NMR spectra of **188t**.

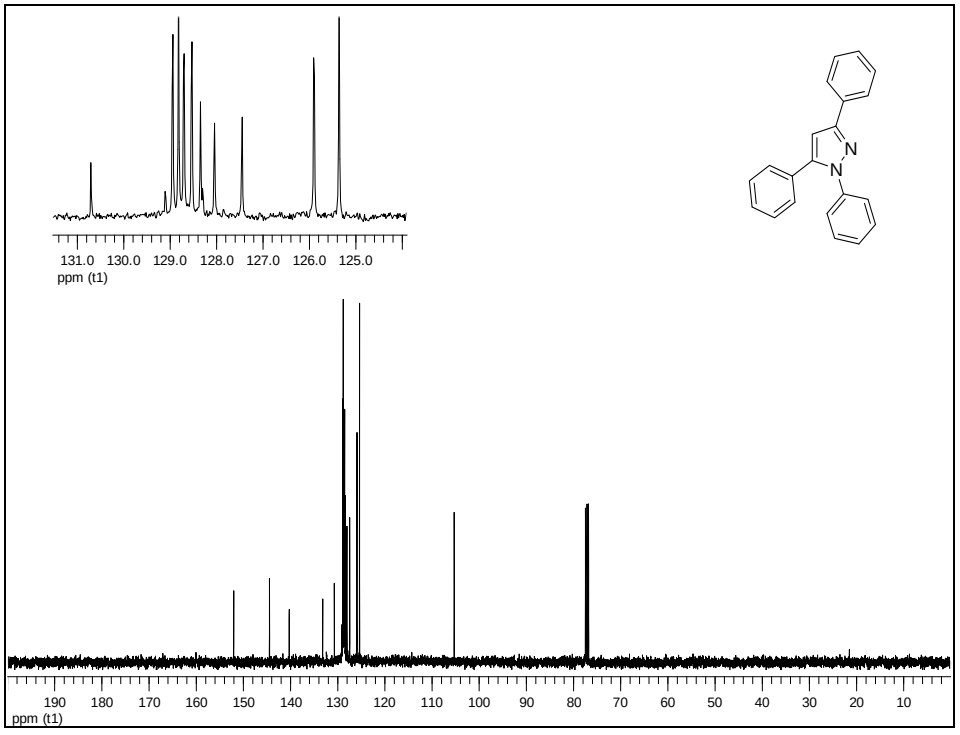

Figure A154. ^{13}C NMR spectra of **188t**.

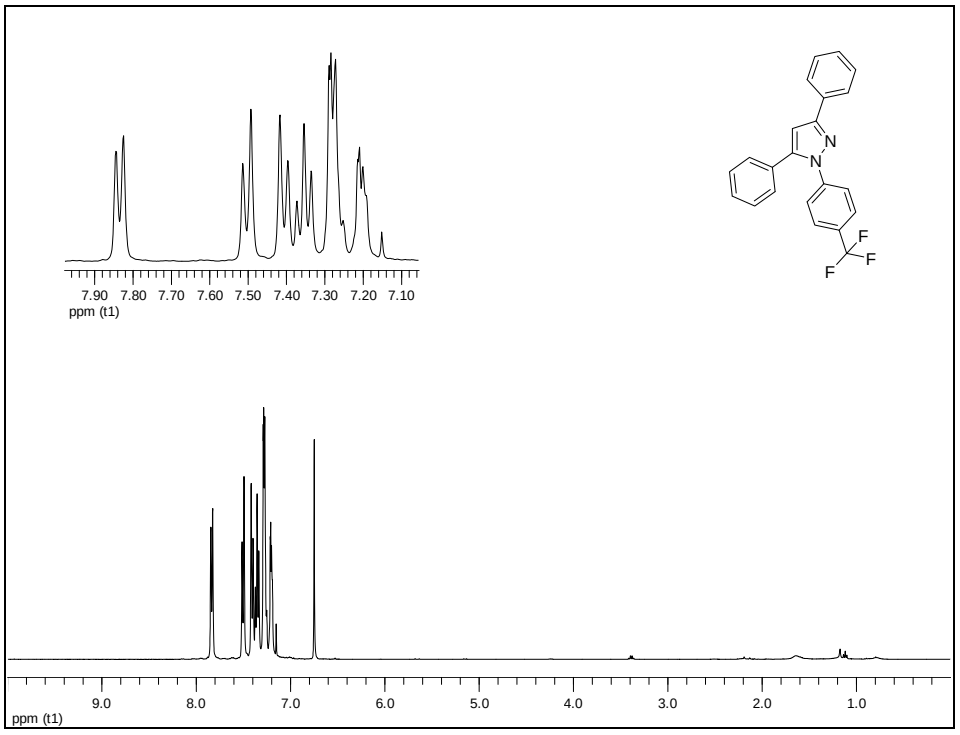

Figure A155. ^{1}H NMR spectra of **188u**.

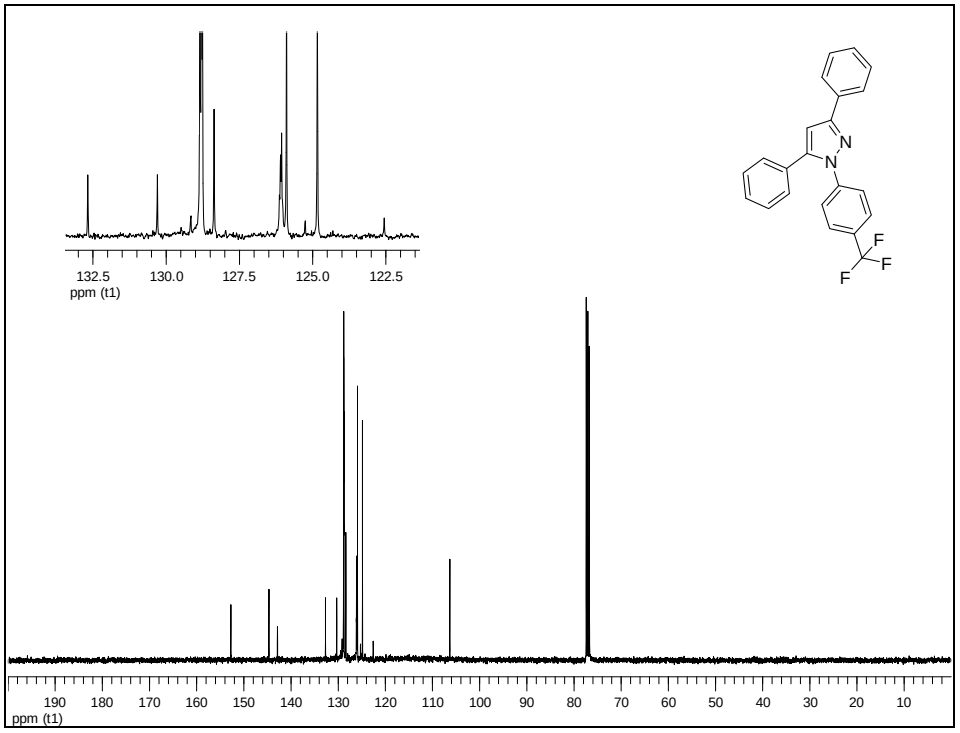

Figure A156. ^{13}C NMR spectra of **188u**.

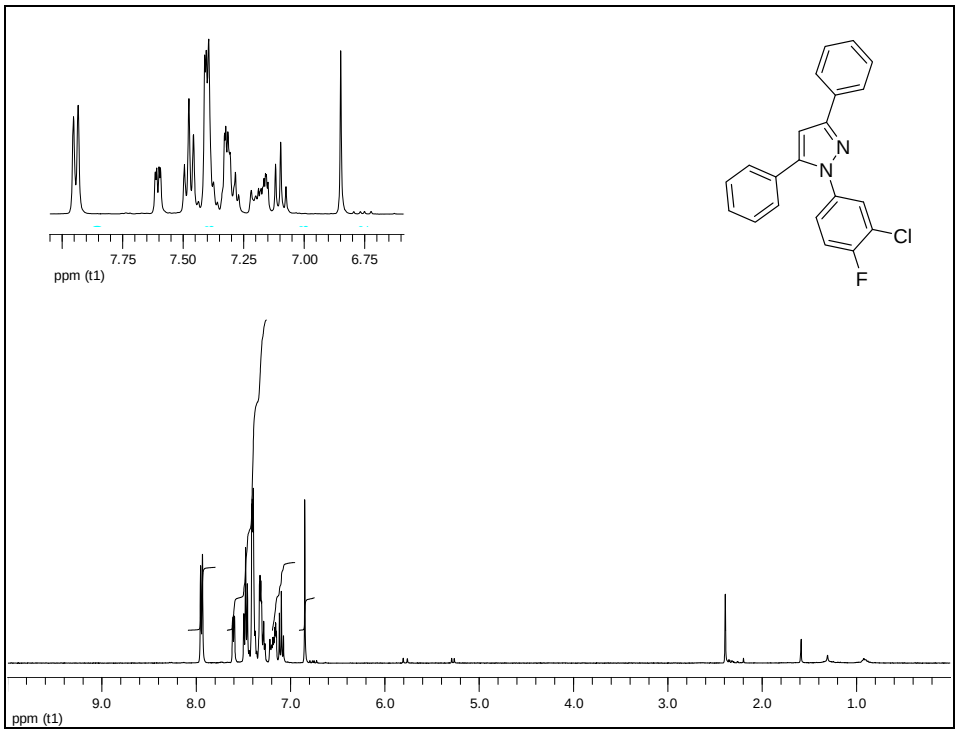

Figure A157. ^{1}H NMR spectra of **188v**.

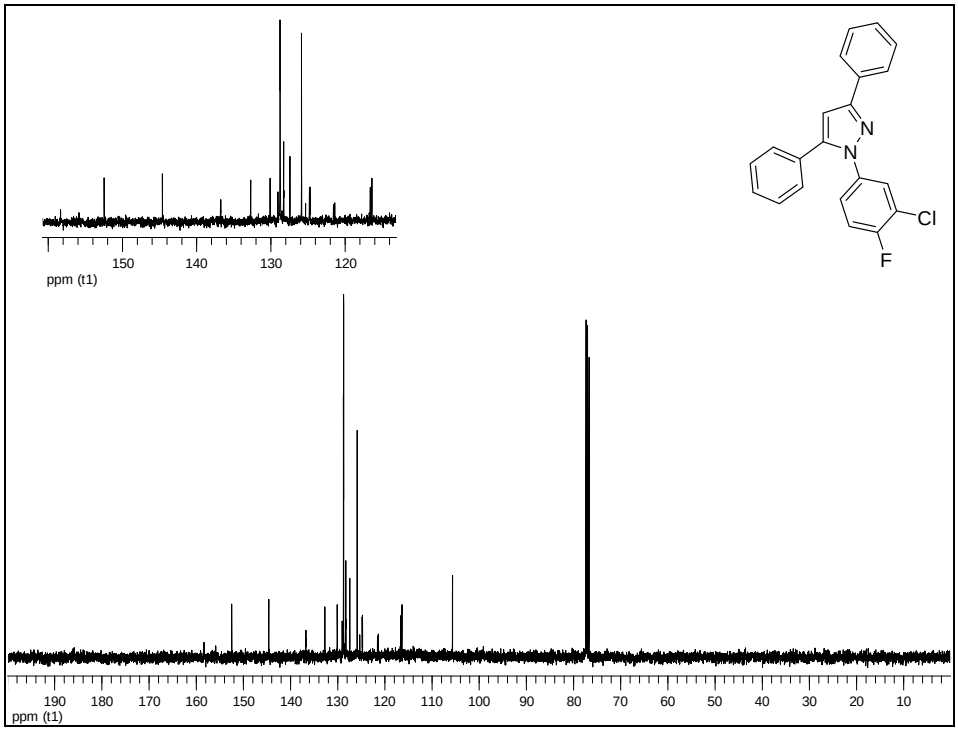

Figure A158. ^{13}C NMR spectra of **188v**.

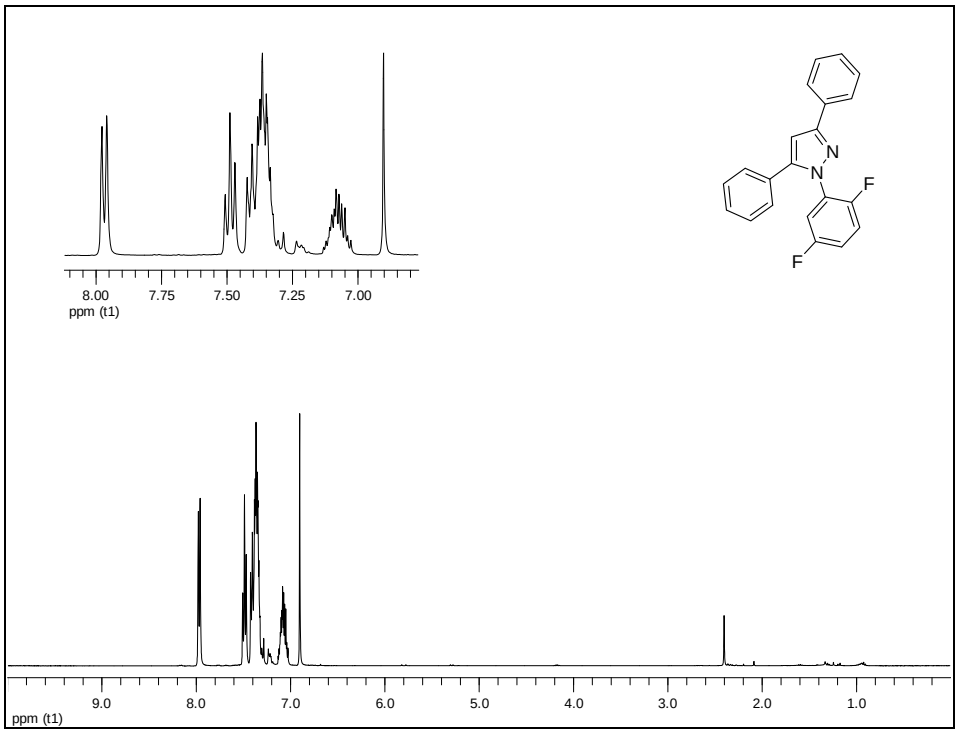

Figure A159. ^{1}H NMR spectra of **188w**.

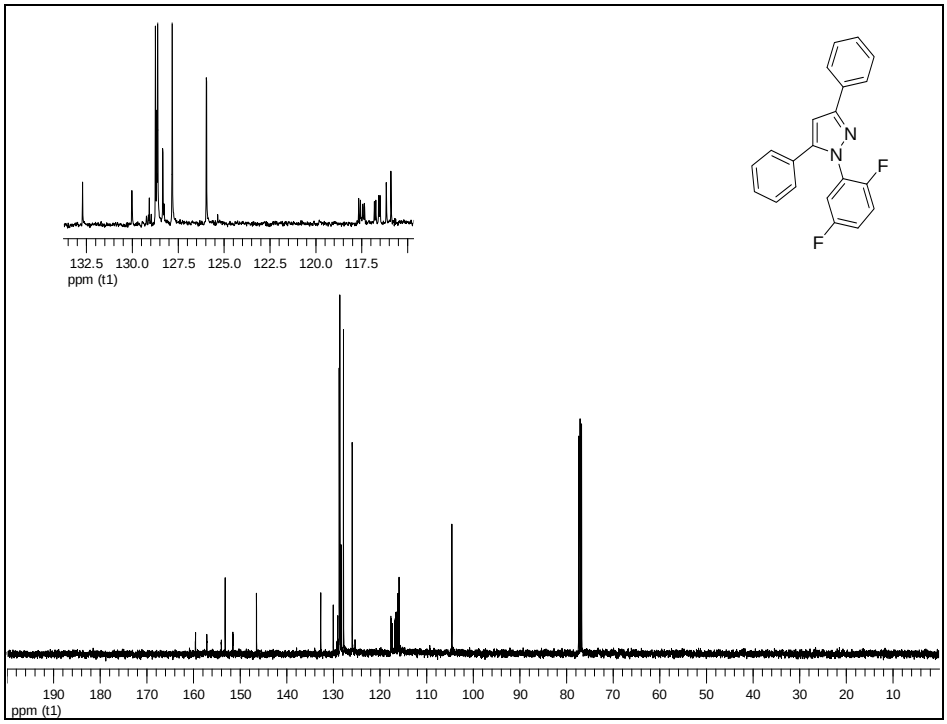

Figure A160. ^{13}C NMR spectra of **188w**.

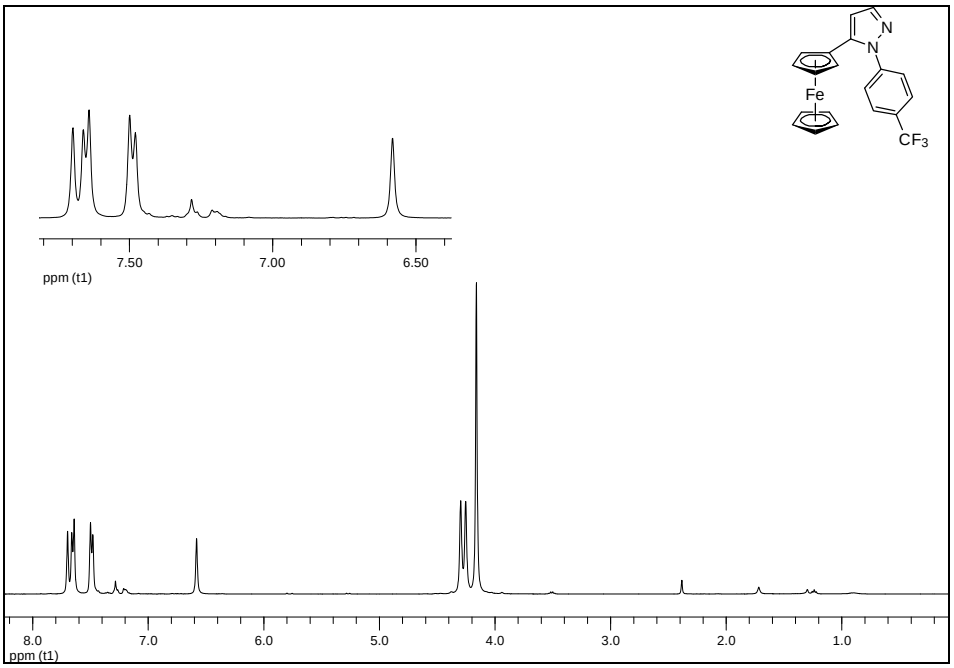

Figure A161. ^{1}H NMR spectra of **201b.**

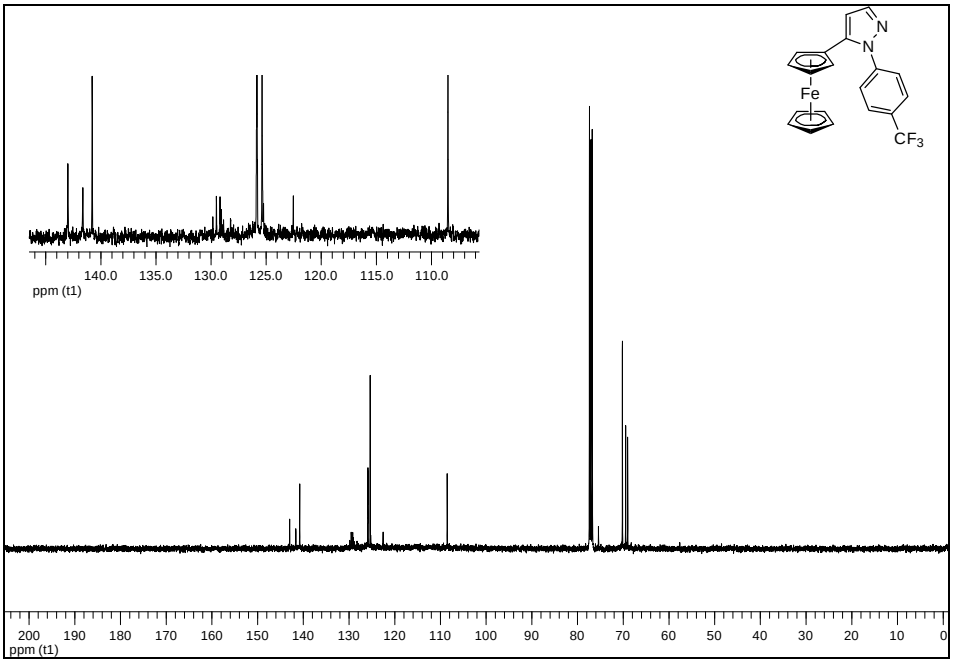

Figure A162. ^{13}C NMR spectra of **201b**.

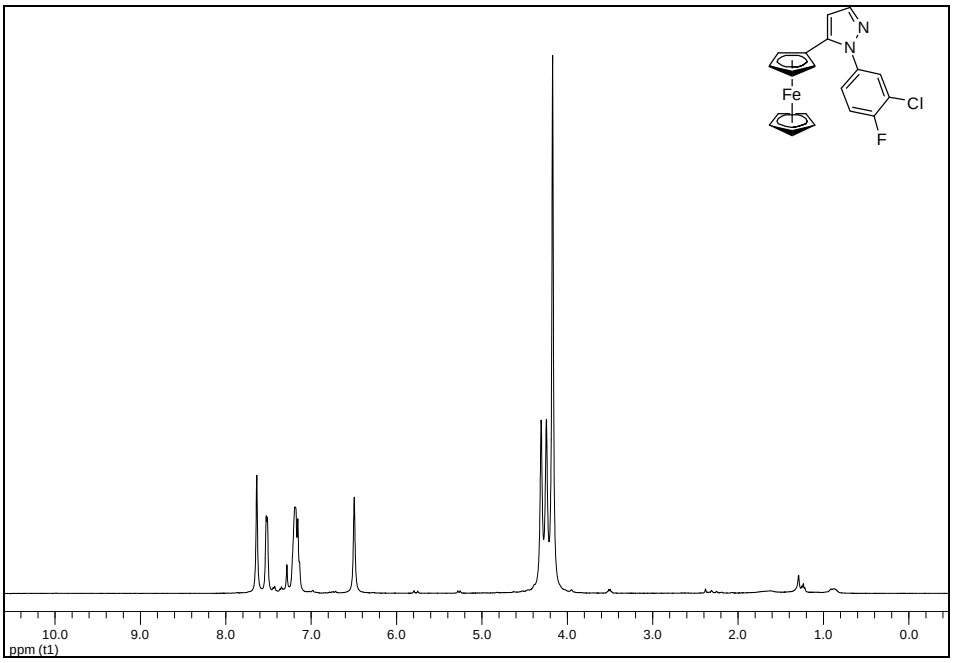

Figure A163. ^{1}H NMR spectra of **201c**.

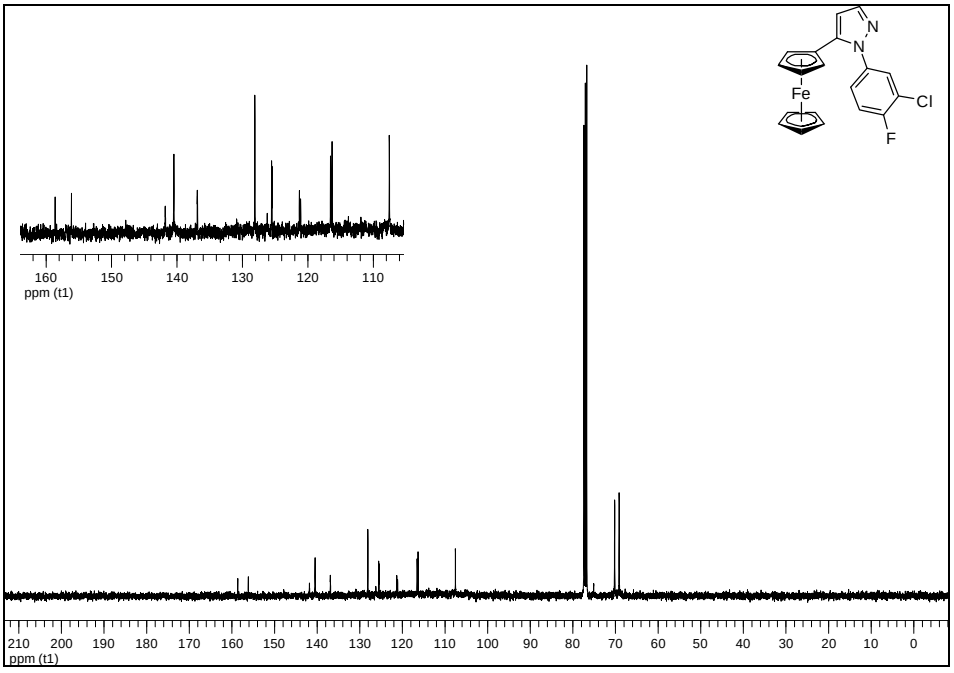

Figure A164. ^{13}C NMR spectra of **201c**.

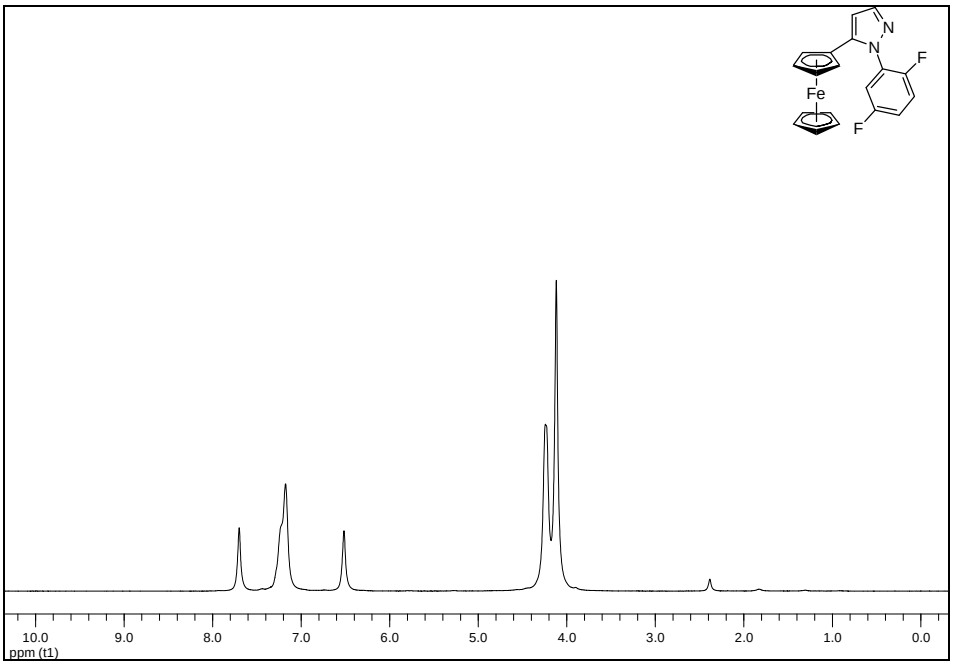

Figure A165. ^{1}H NMR spectra of **201d.**

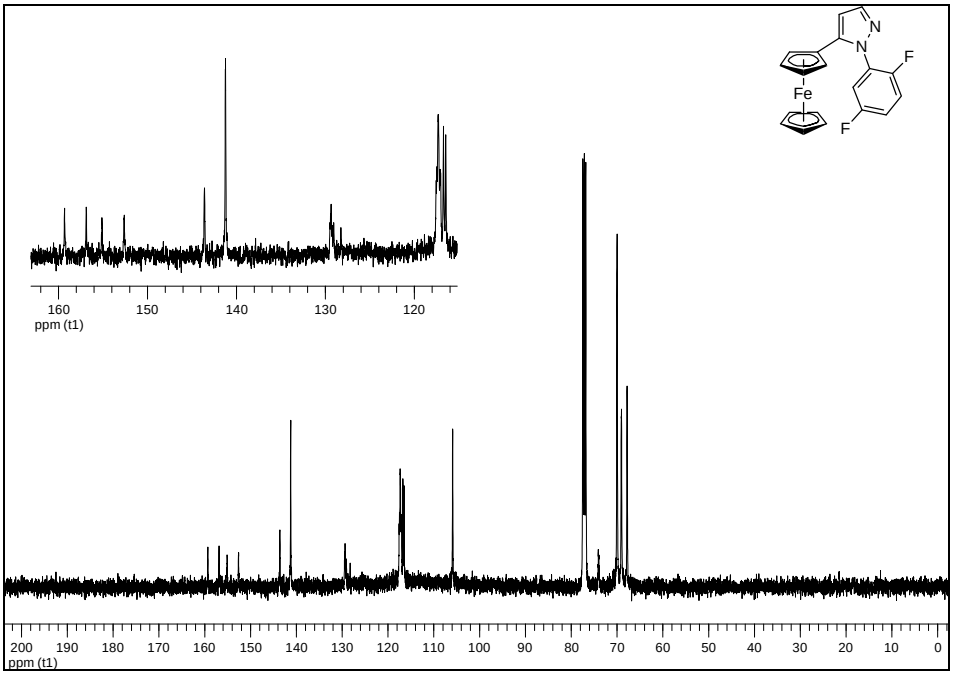

Figure A166. ^{13}C NMR spectra of **201d**.

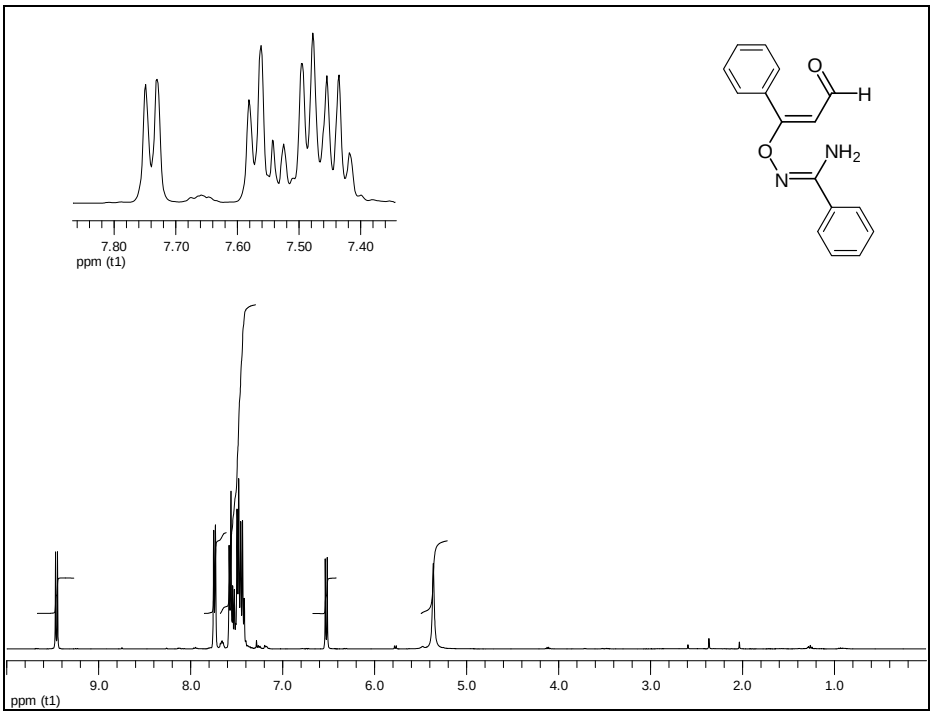

Figure A167. ^{1}H NMR spectra of **191a**.

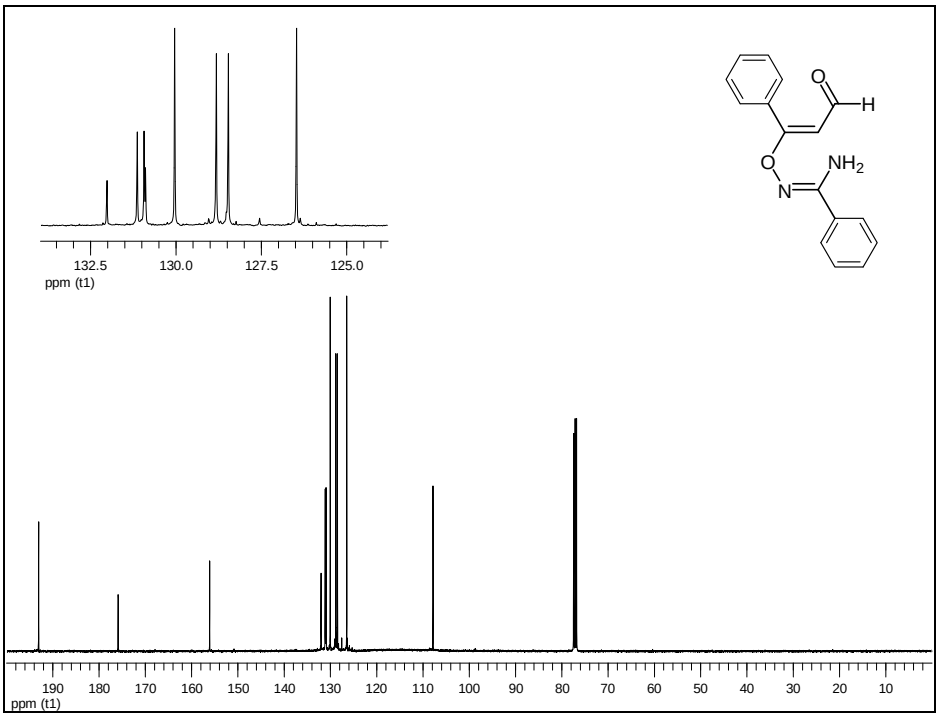

Figure A168. ^{13}C NMR spectra of **191a**.

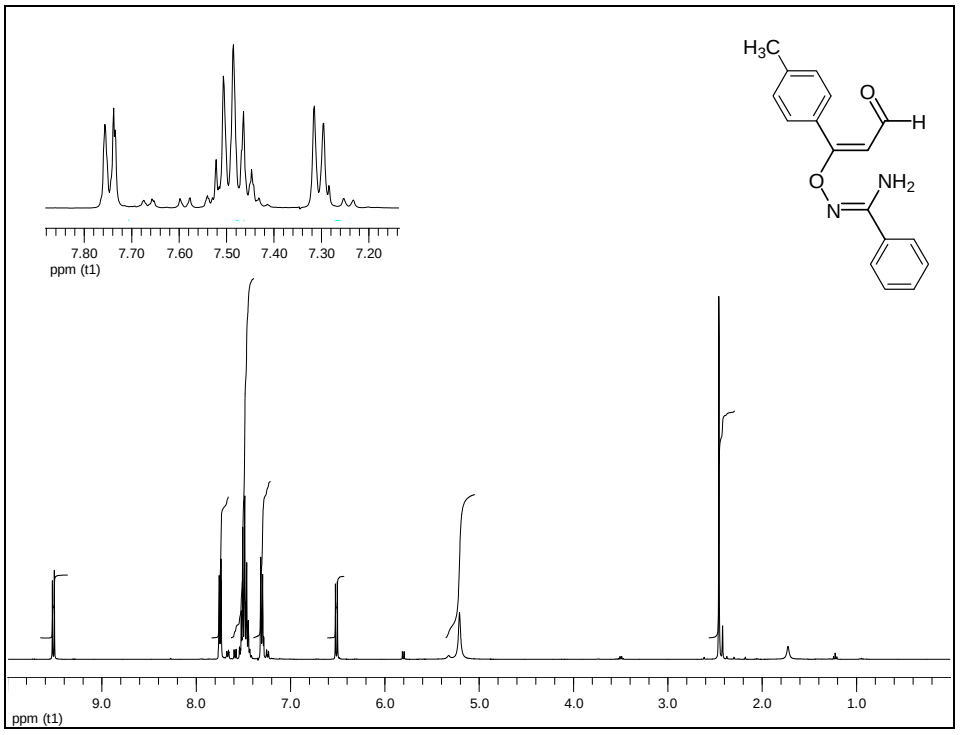

Figure A169. ^{1}H NMR spectra of **191b**.

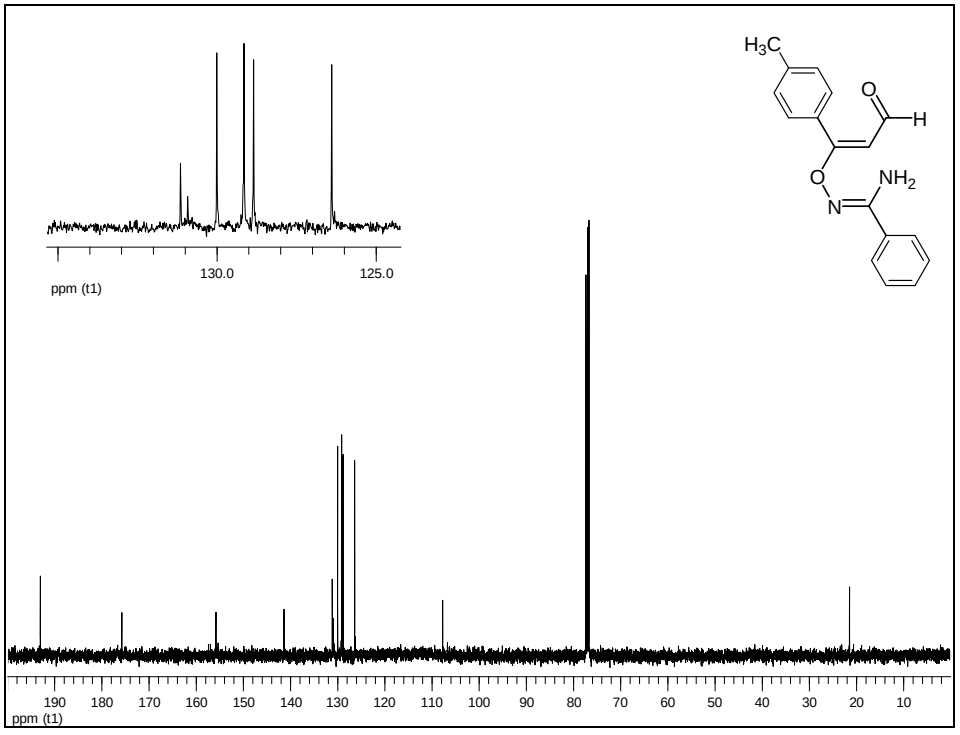

Figure A170. ^{13}C NMR spectra of **191b**.

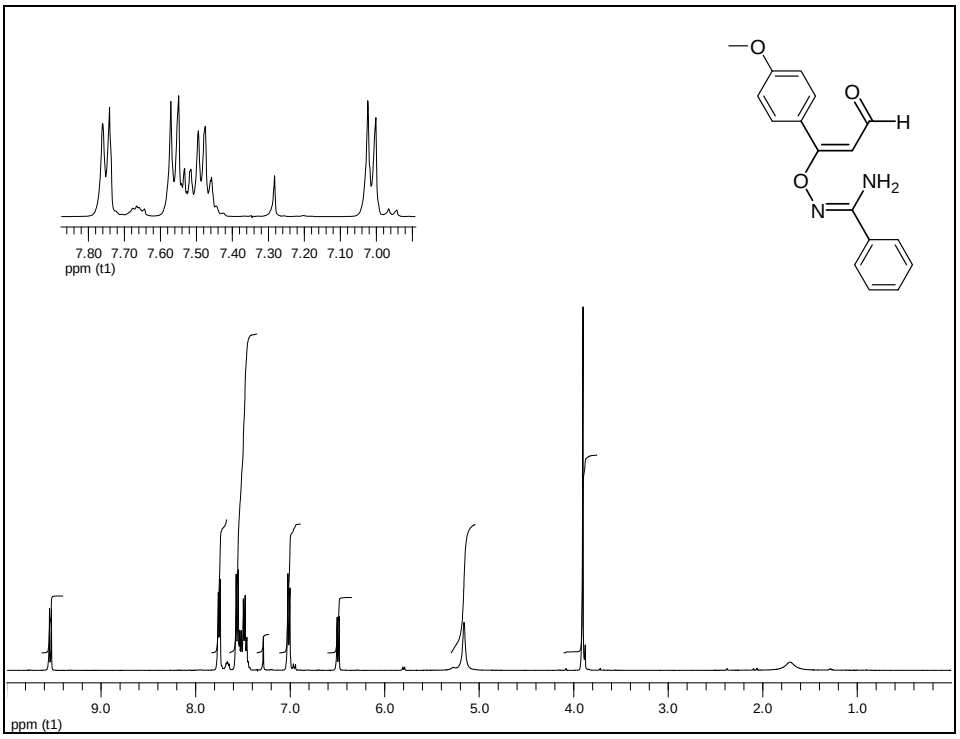

Figure A171. ^{1}H NMR spectra of **191c**.

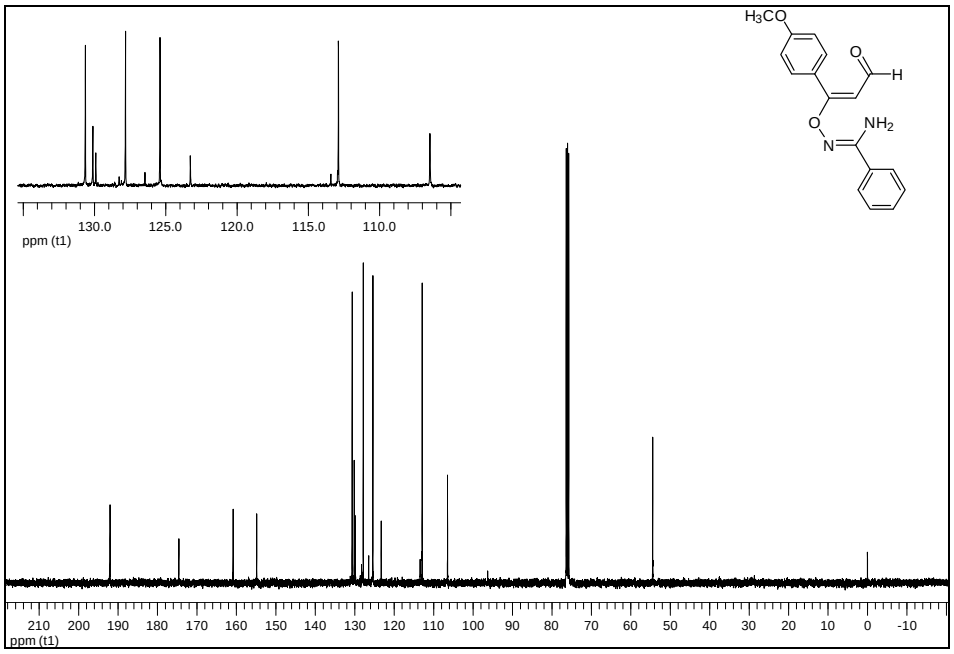

Figure A172. ^{13}C NMR spectra of **191c**.

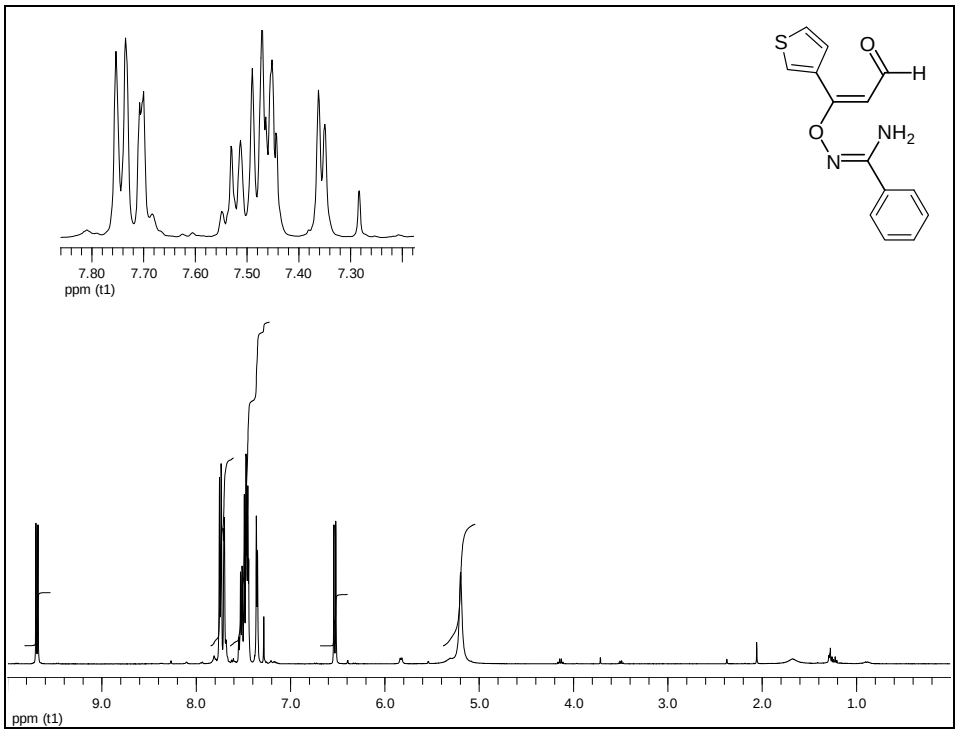

Figure A173. ^{1}H NMR spectra of **191d**.

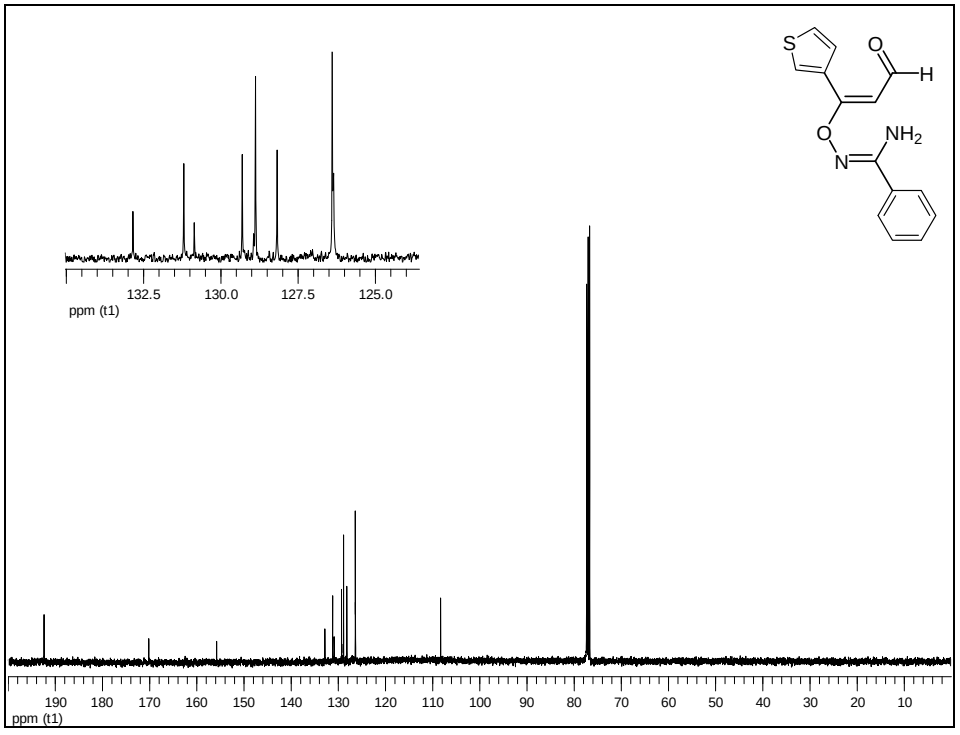

Figure A174. ^{13}C NMR spectra of **191d**.

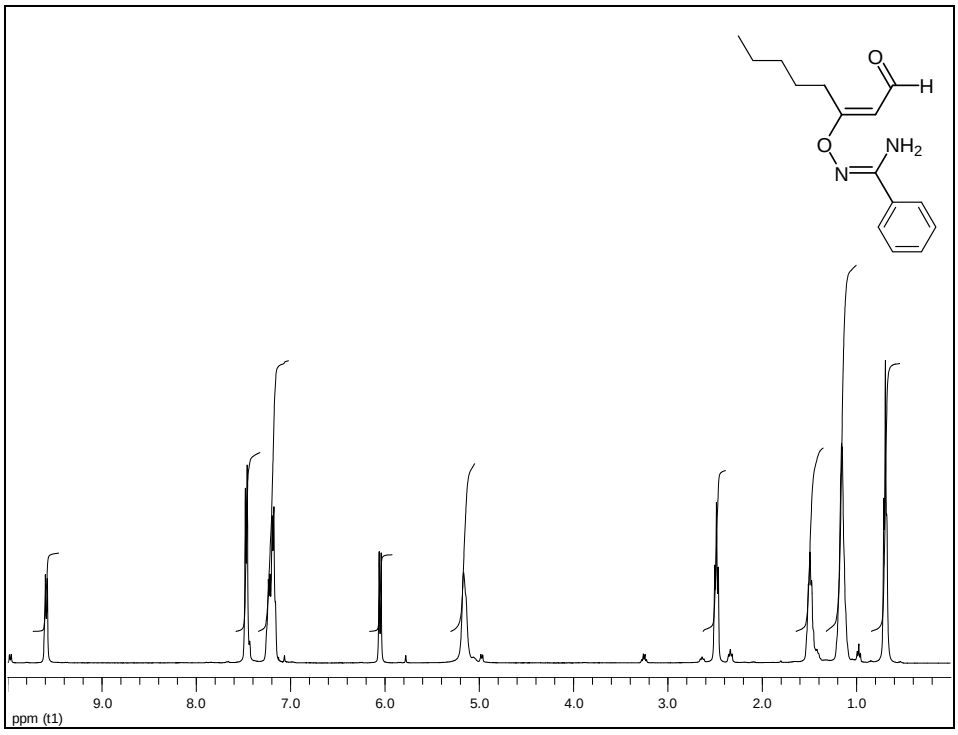

Figure A175. ^{1}H NMR spectra of **191e**.

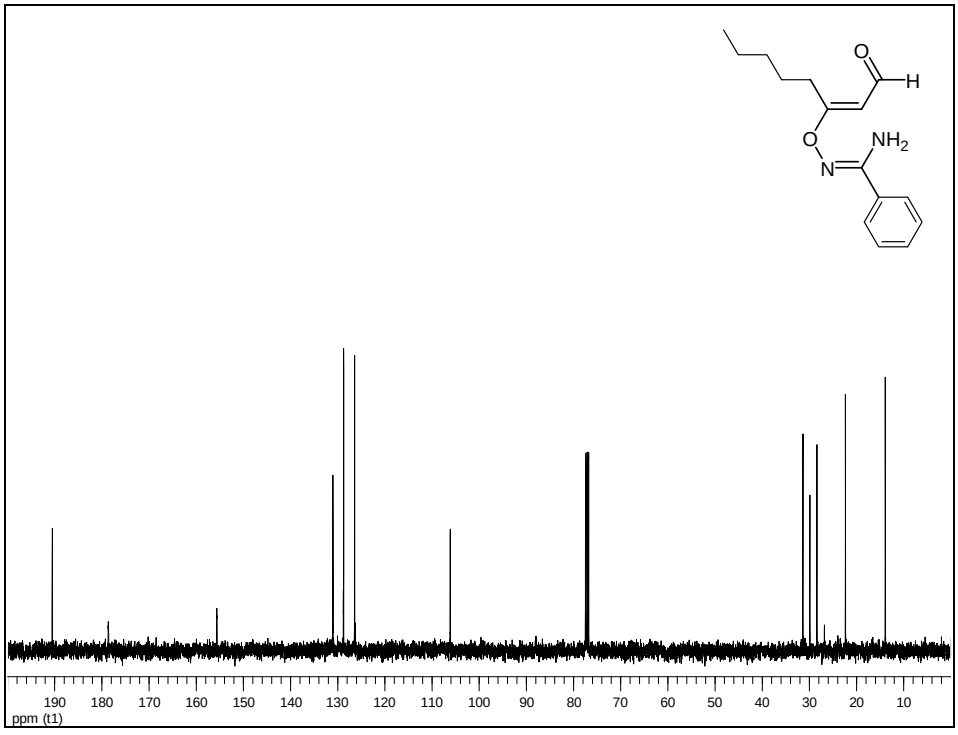

Figure A176. ^{13}C NMR spectra of **191e**.

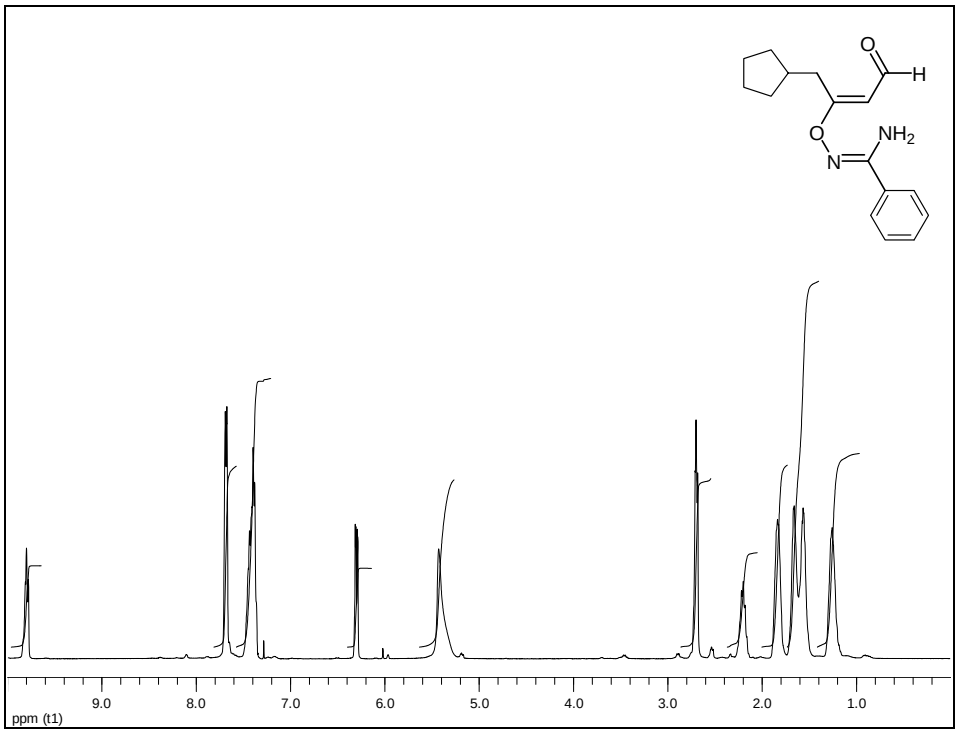

Figure A177. ^{1}H NMR spectra of **191f**.

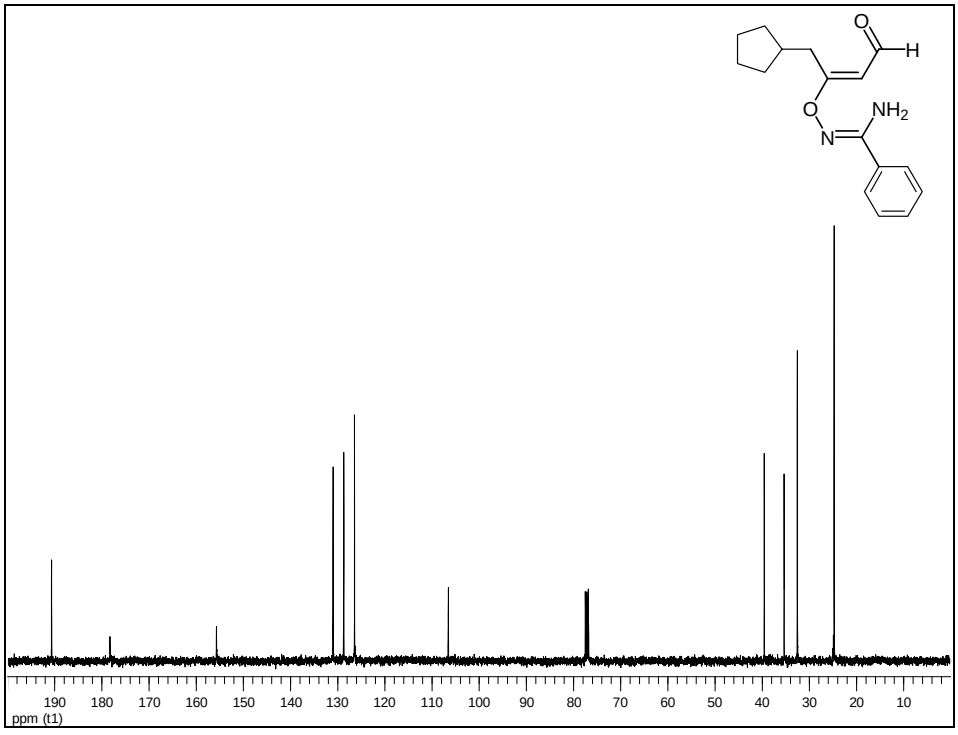

Figure A178. ^{13}C NMR spectra of **191f**.

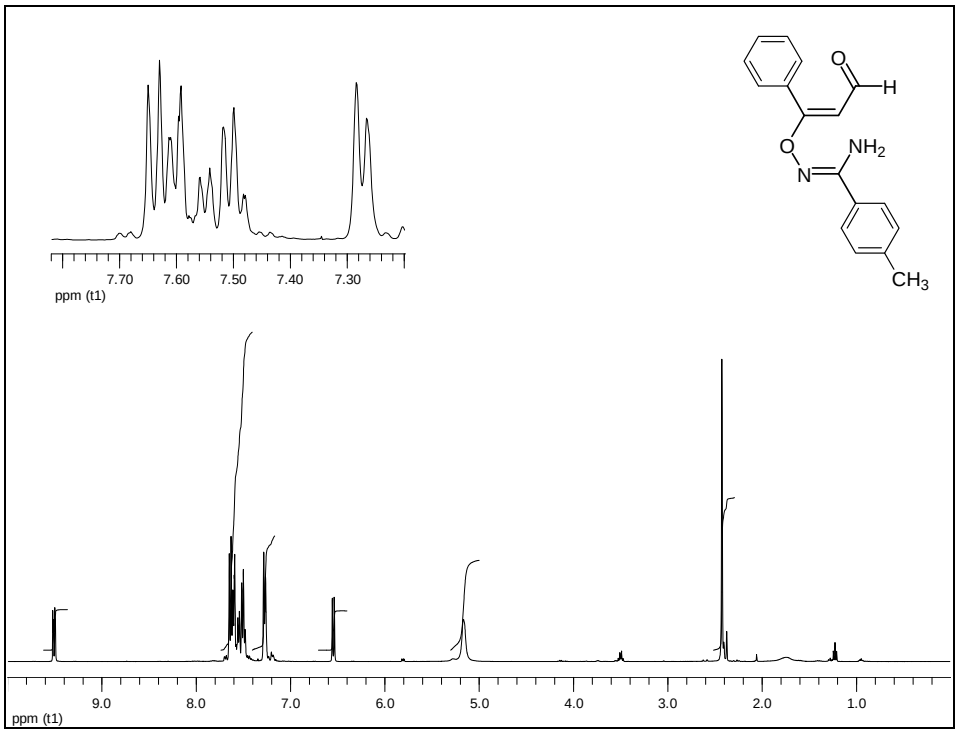

Figure A179. ^{1}H NMR spectra of **191g**.

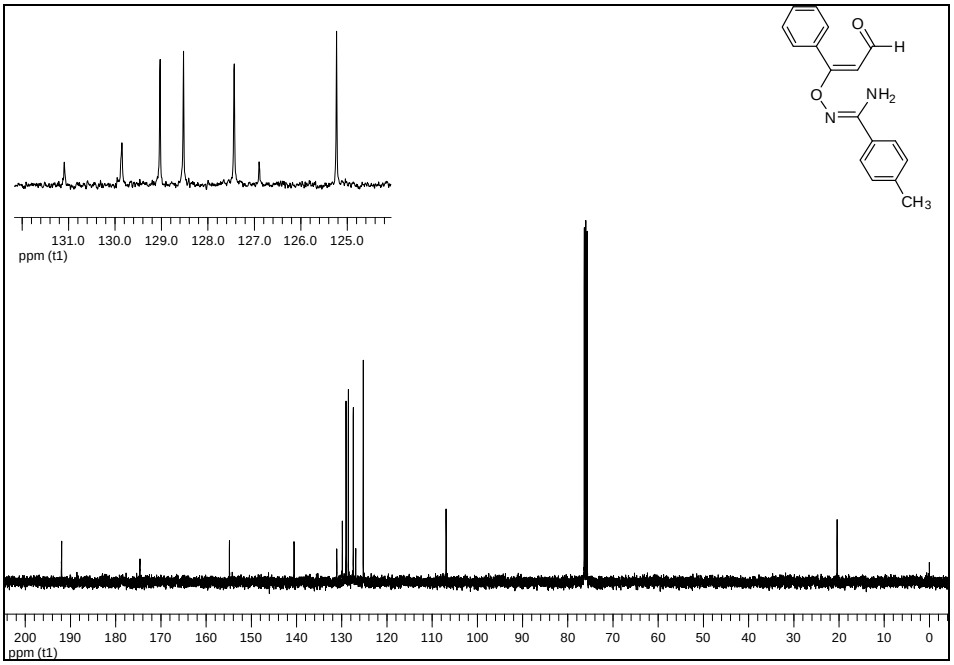

Figure A180. ^{13}C NMR spectra of **191g**.

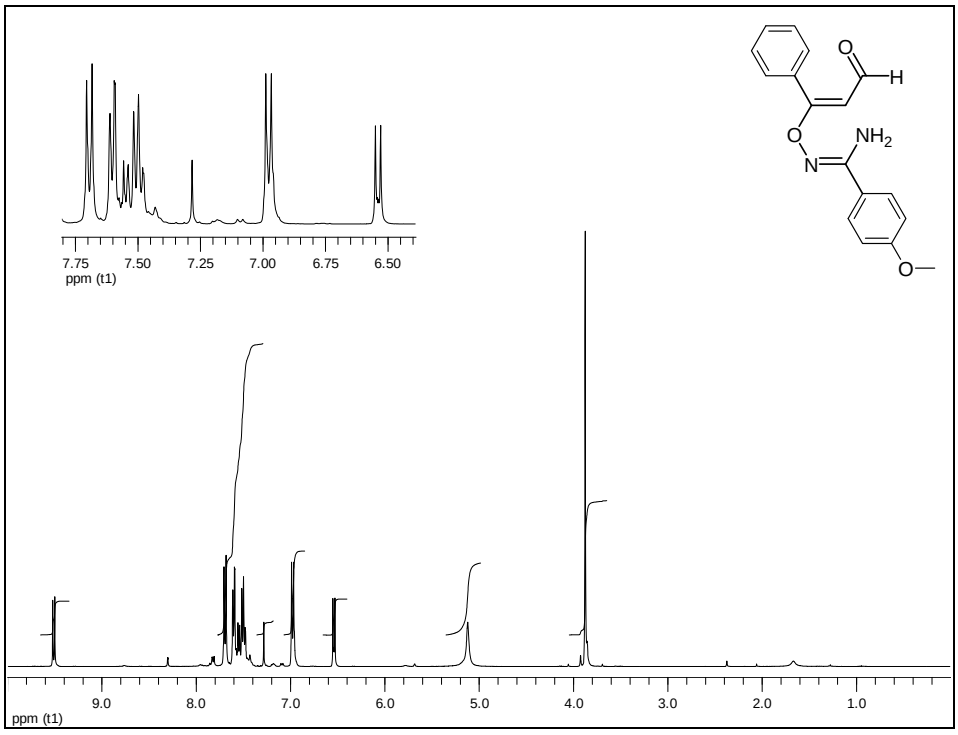

Figure A181. ^{1}H NMR spectra of **191h**.

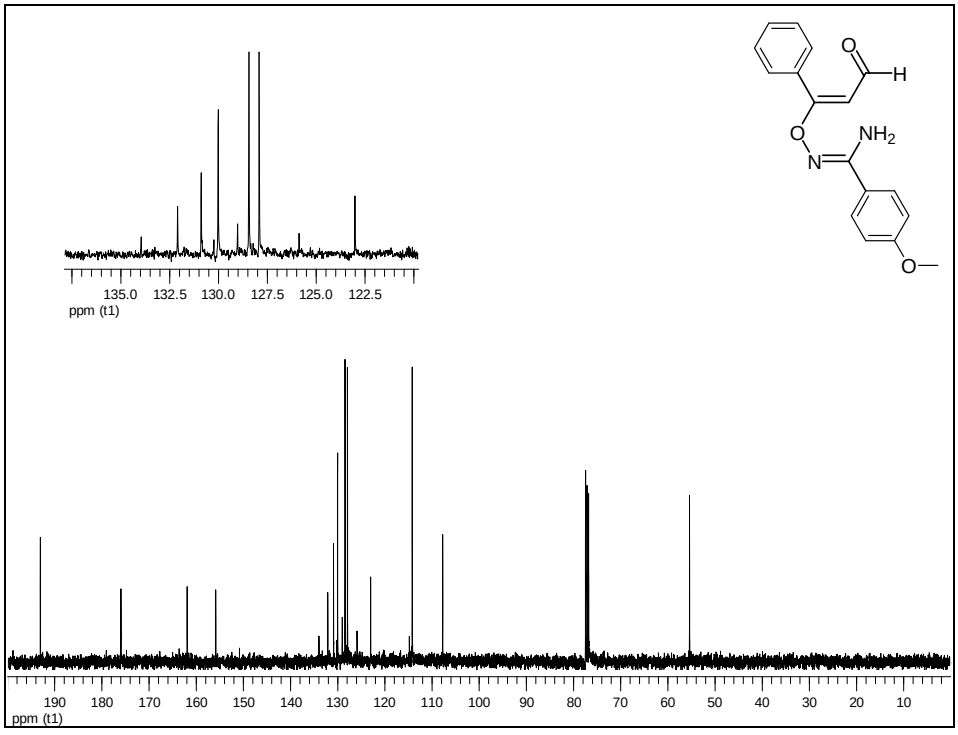

Figure A182. ^{13}C NMR spectra of **191h**.

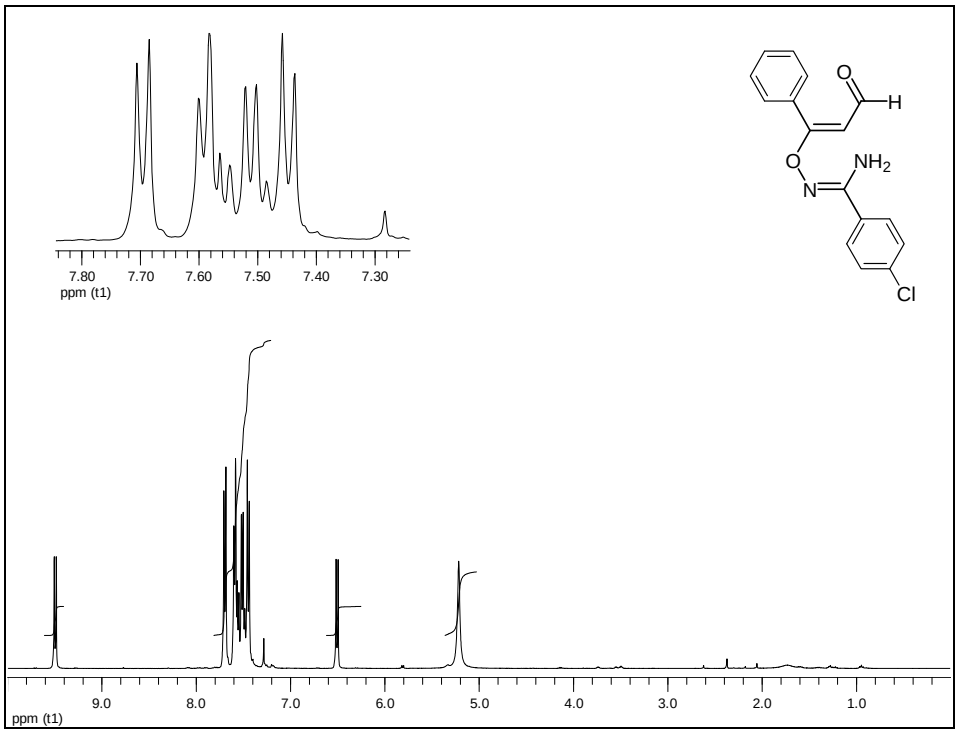

Figure A183. ^{1}H NMR spectra of **191i**.

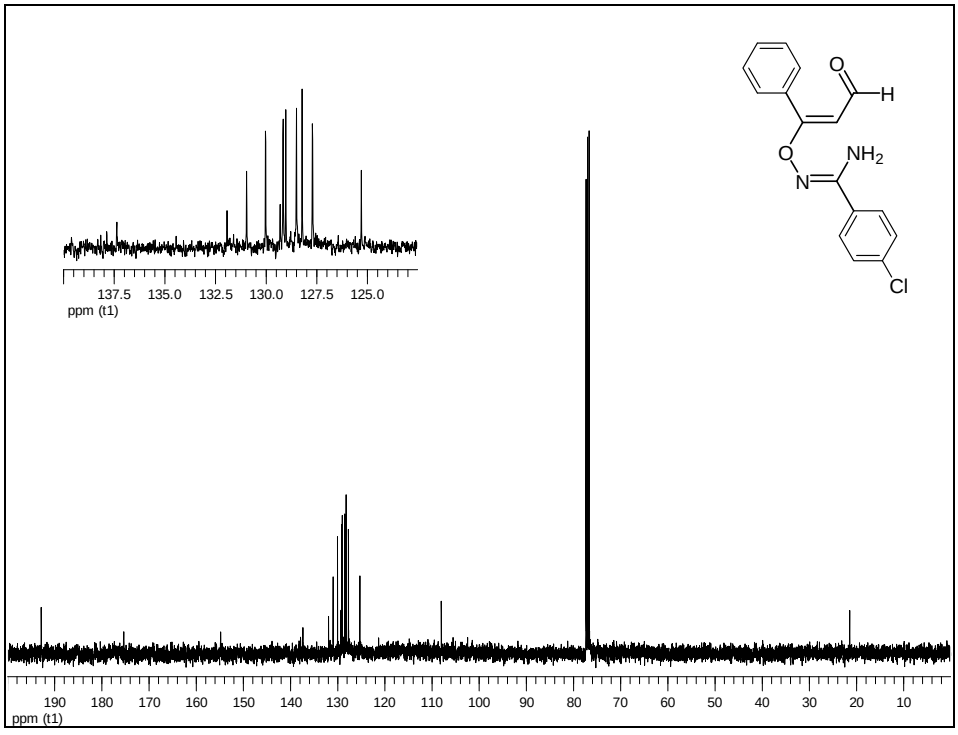

Figure A184. ^{13}C NMR spectra of **191i**.

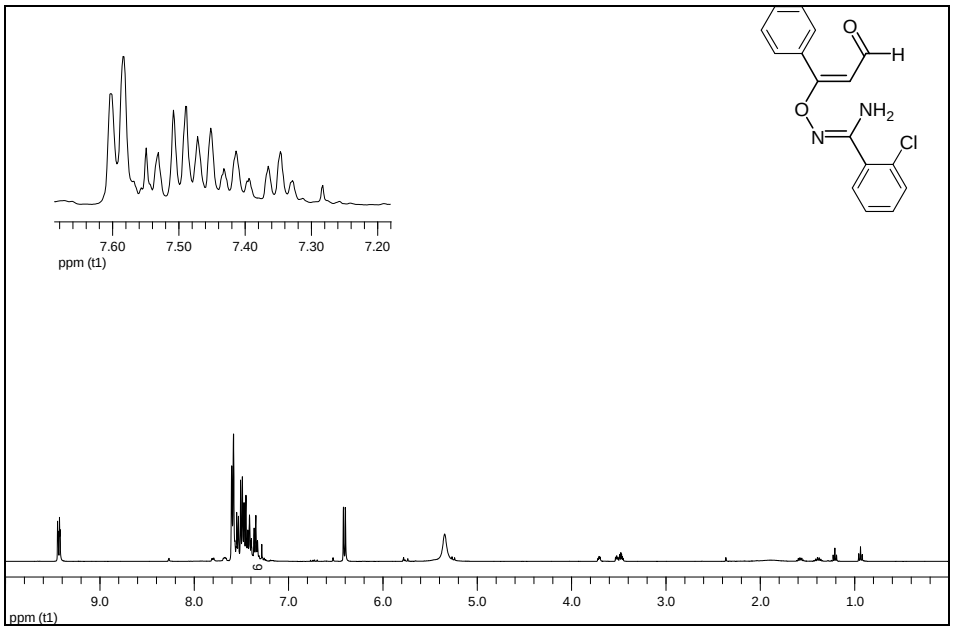

Figure A 185. ^{1}H NMR spectra of **191j**.

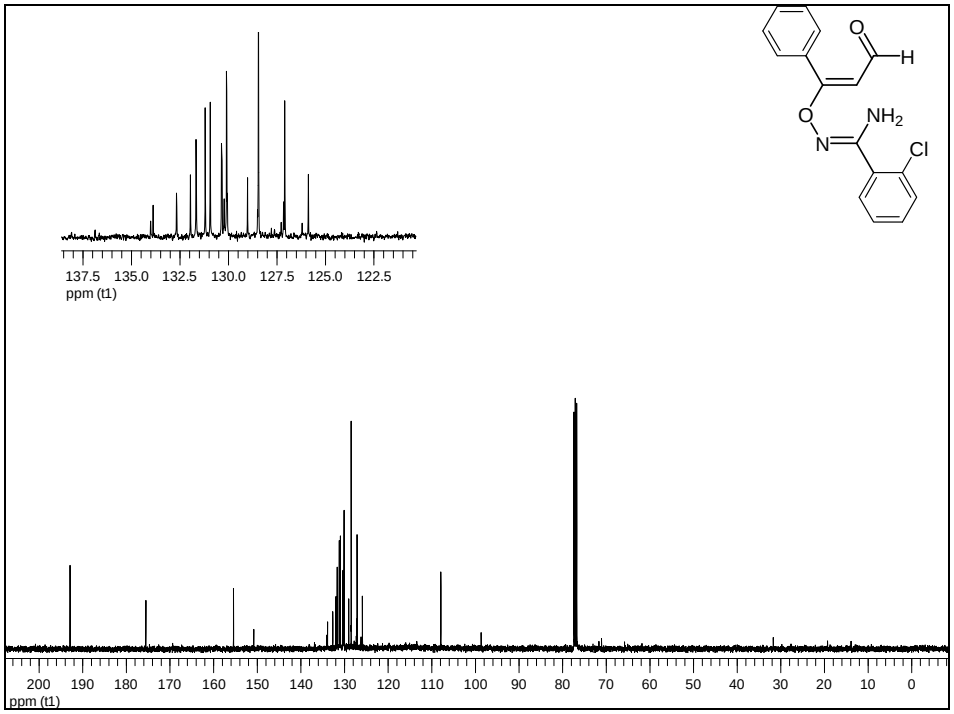

Figure A 186. ^{13}C NMR spectra of **191j**.

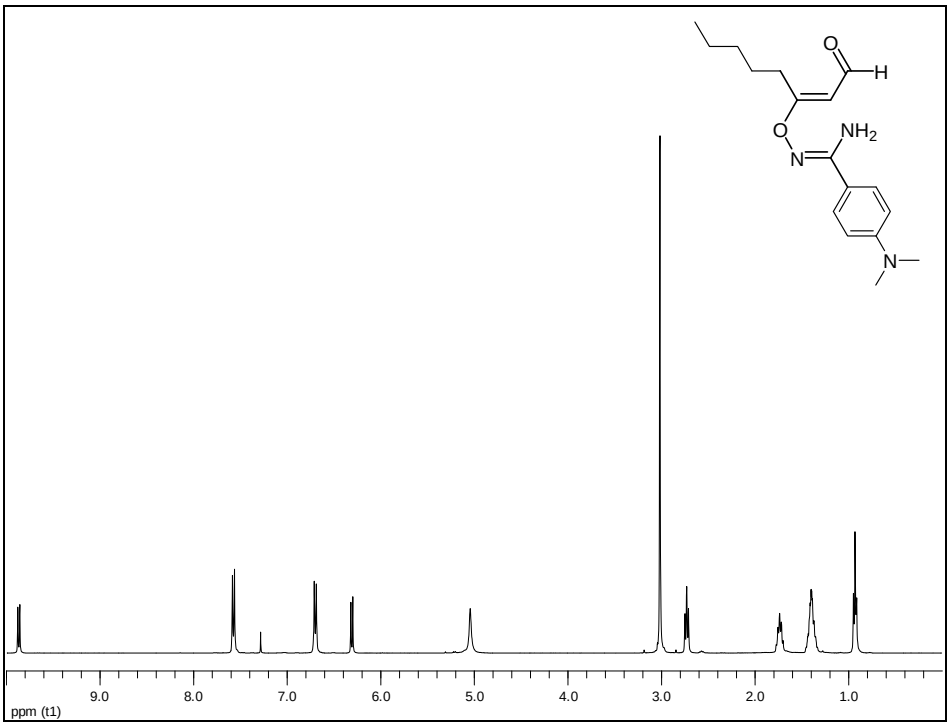

Figure A 187. ^{1}H NMR spectra of **191k**.

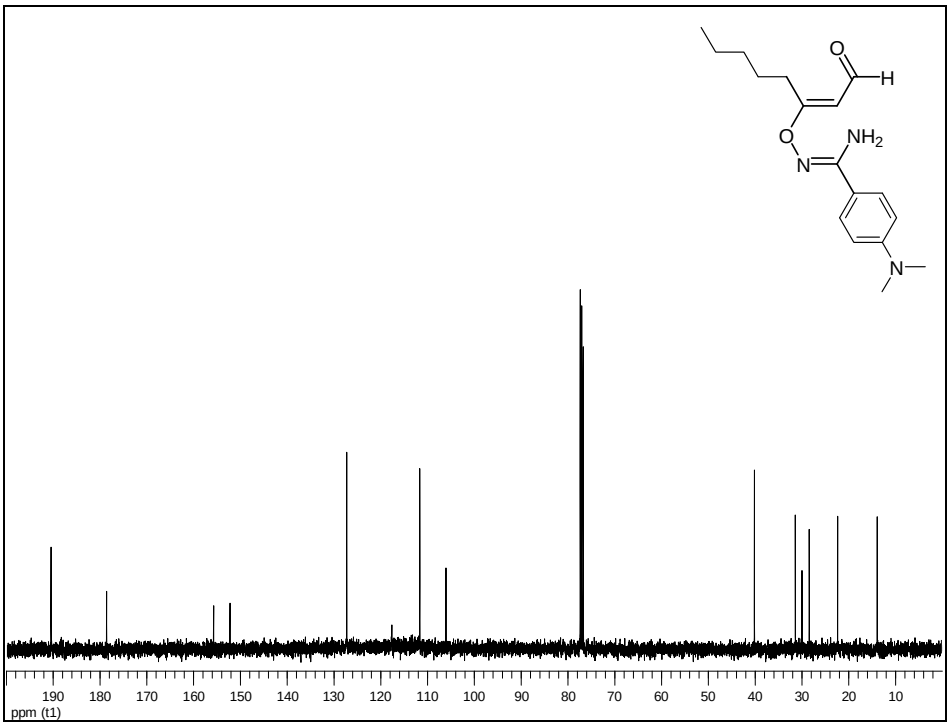

Figure A 188. ^{13}C NMR spectra of **191k**.

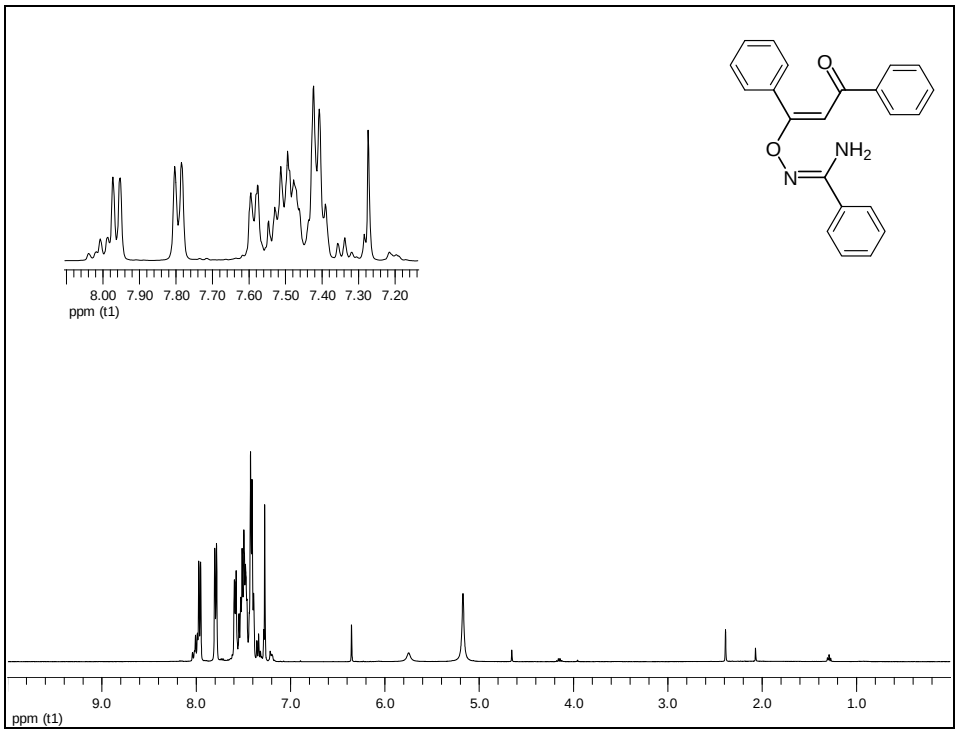

Figure A189. ^{1}H NMR spectra of **191l**.

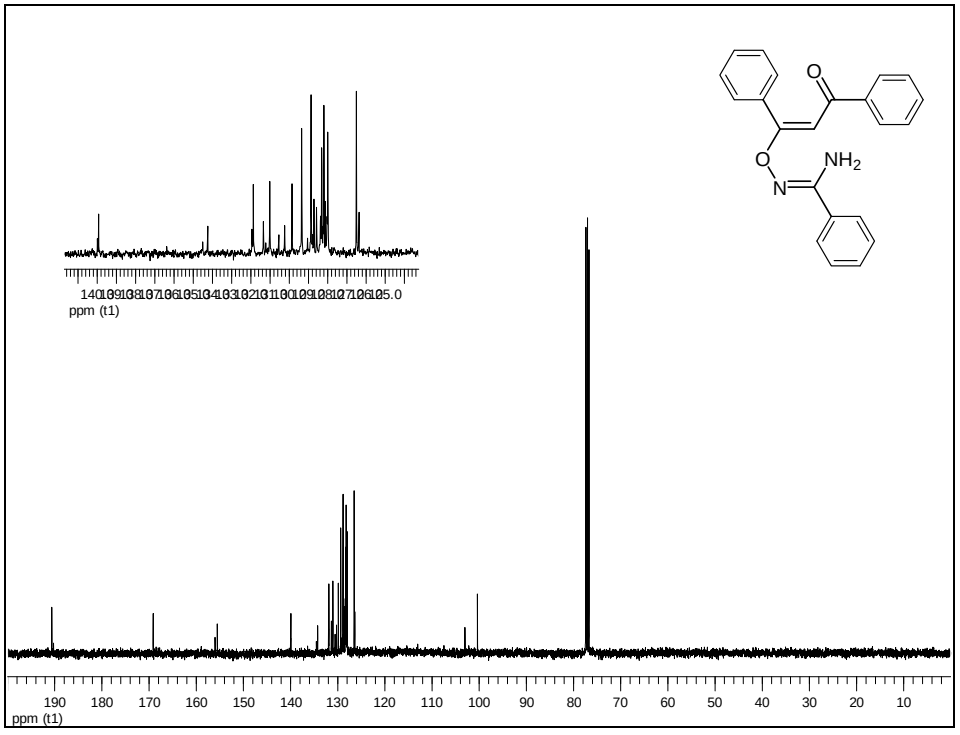

Figure A190. ^{13}C NMR spectra of **191l**.

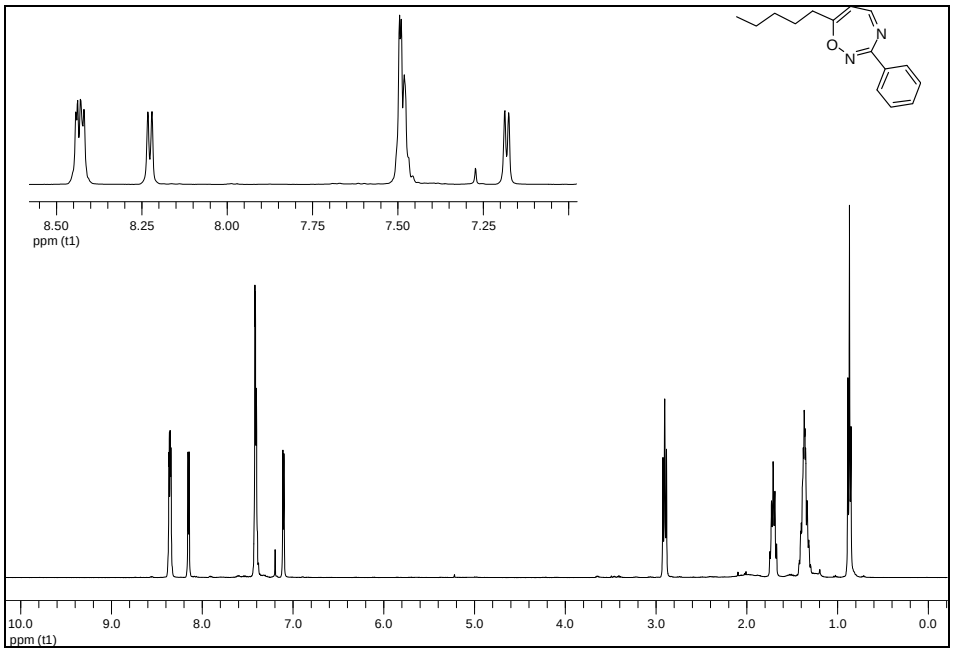

Figure A191. 1H NMR spectra of **193a**.

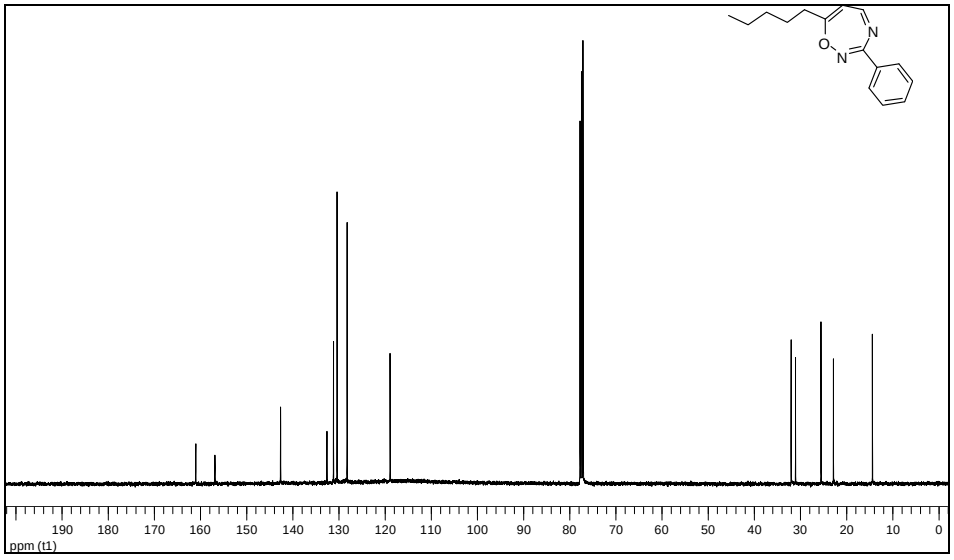

Figure A192. 13 C NMR spectra of **193a**.

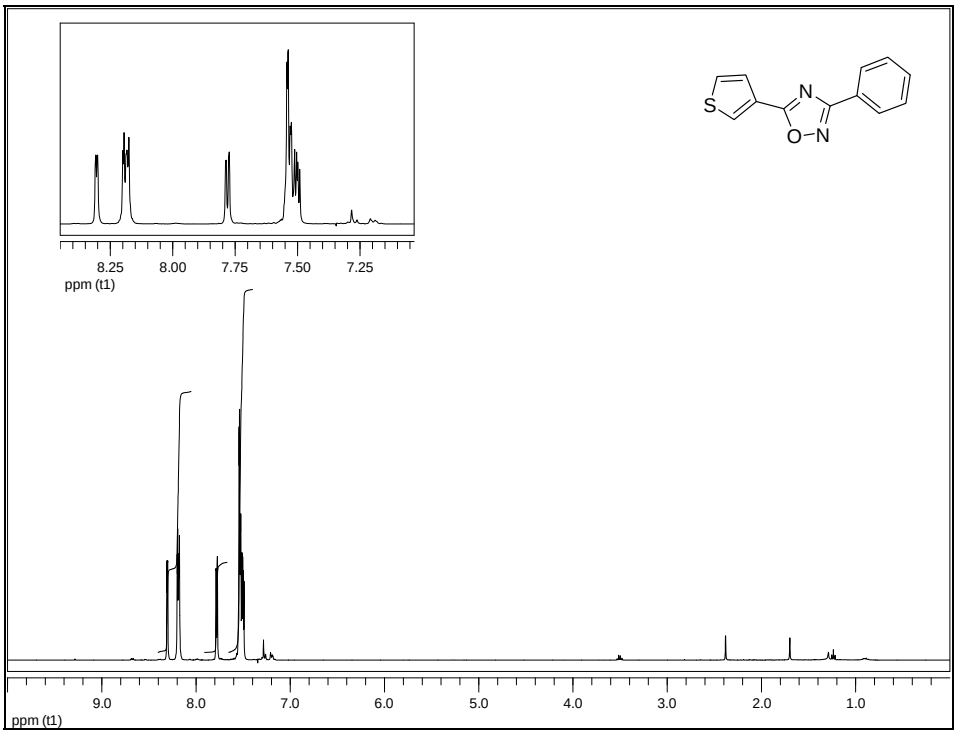

Figure A193. ^{1}H NMR spectra of **192d**.

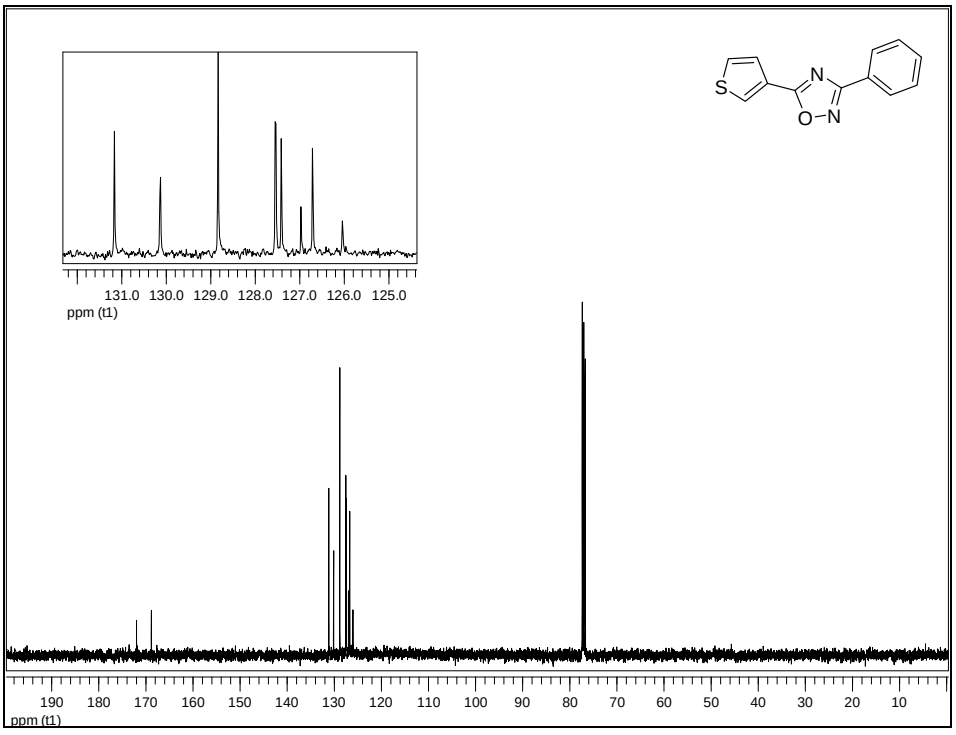

Figure A194. ^{13}C NMR spectra of **192d**.

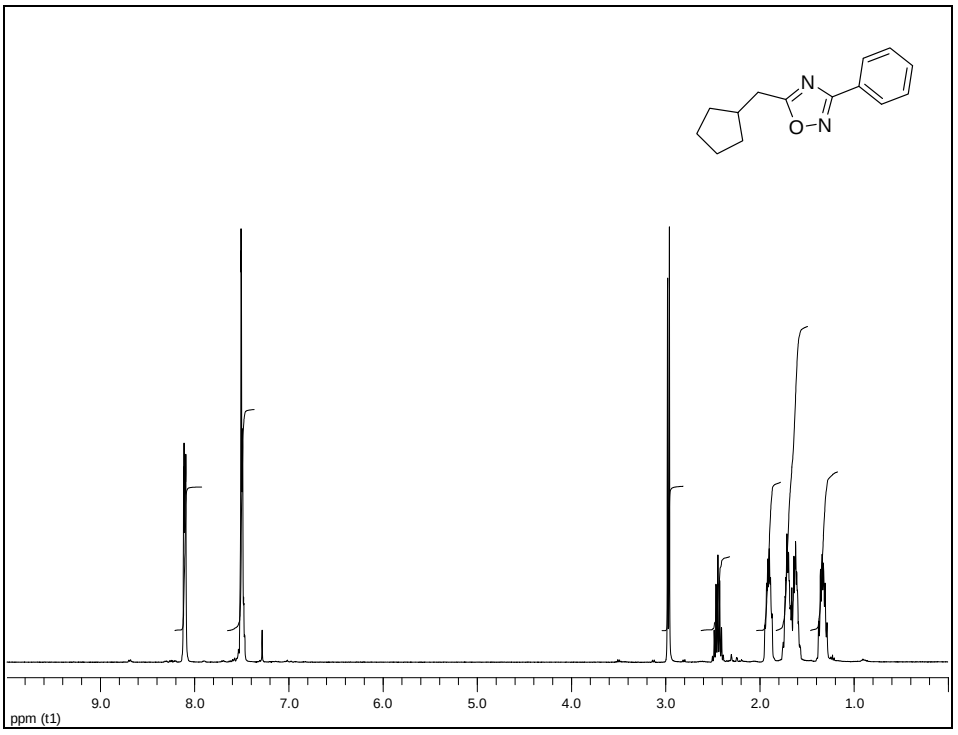

Figure A195. ^{1}H NMR spectra of **192f**.

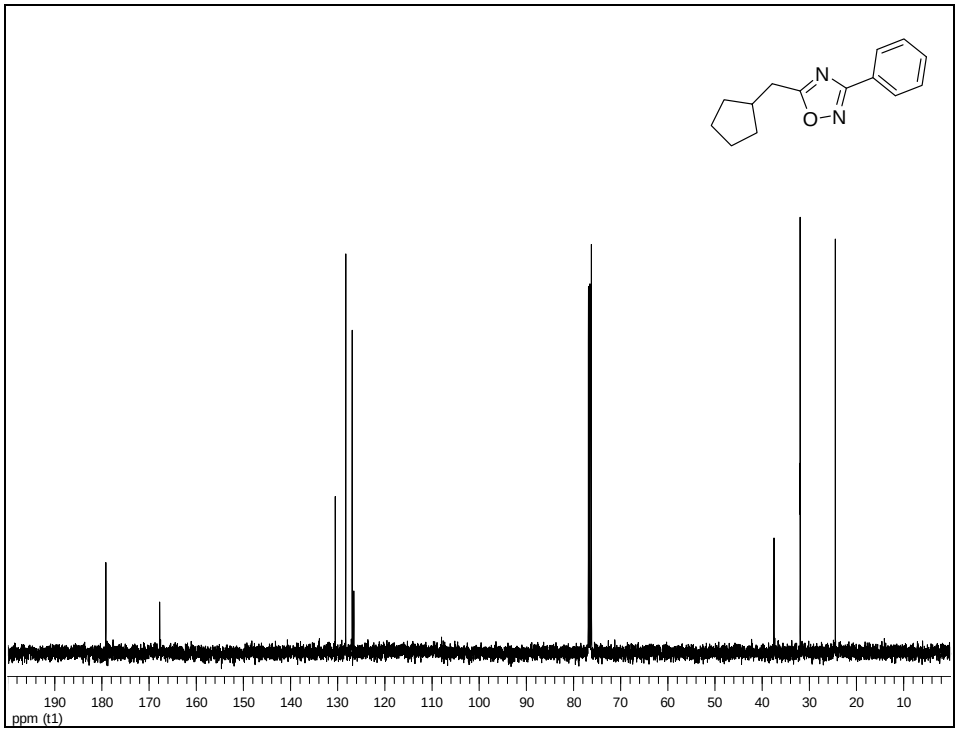

Figure A196. ^{13}C NMR spectra of **192f**.

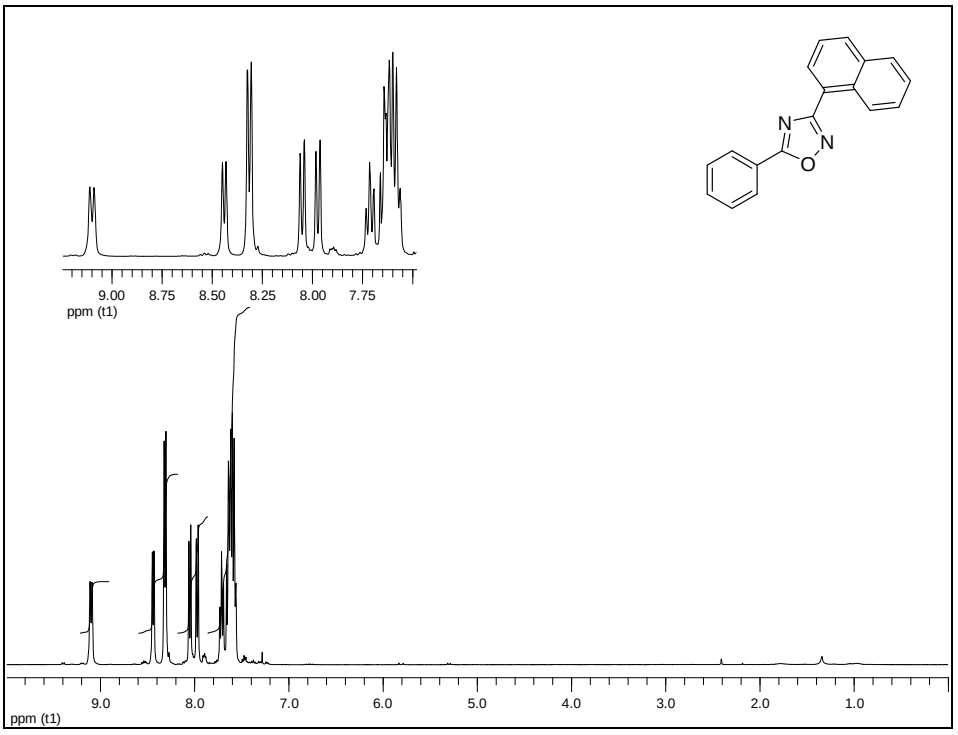

Figure A197. ^{1}H NMR spectra of **192l**.

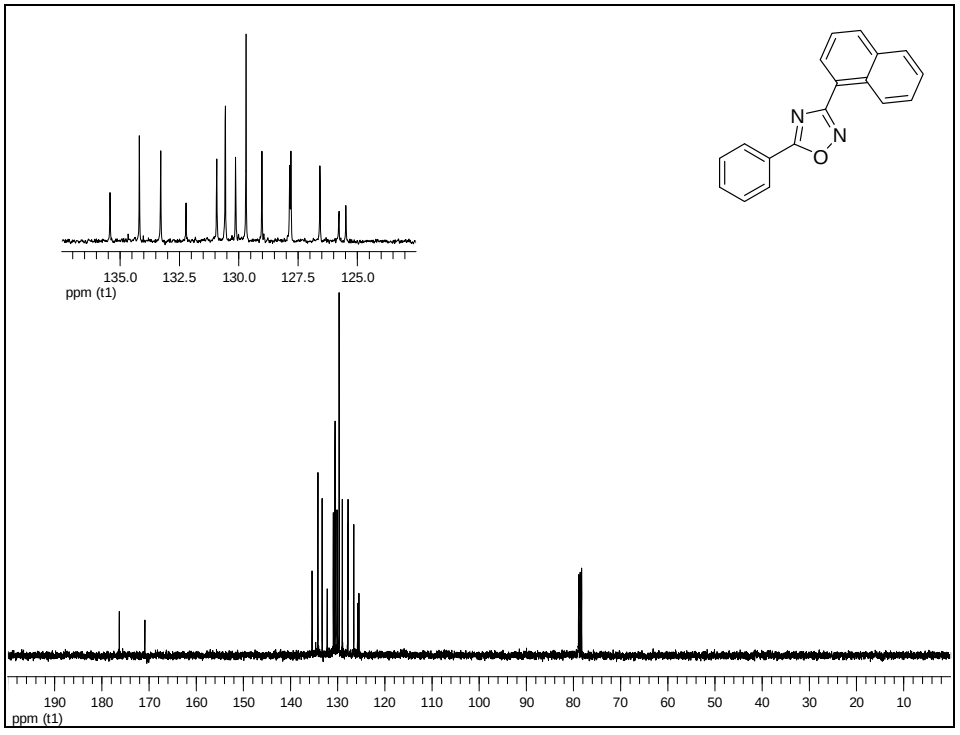

Figure A198. ^{13}C NMR spectra of **192l**.

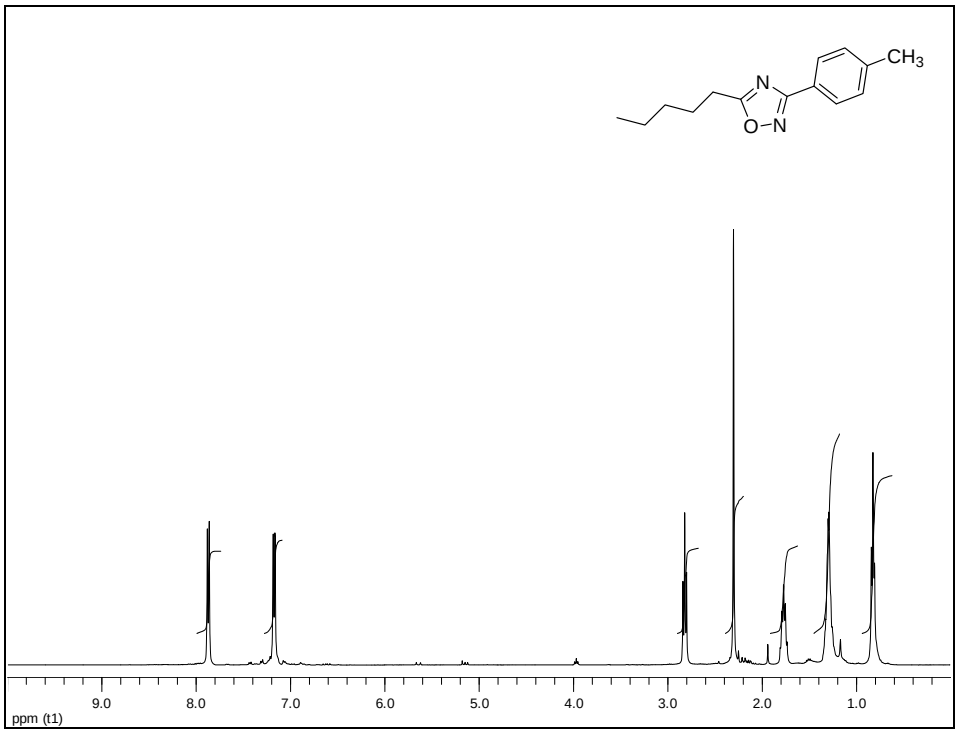

Figure A199. ^{1}H NMR spectra of **192m**.

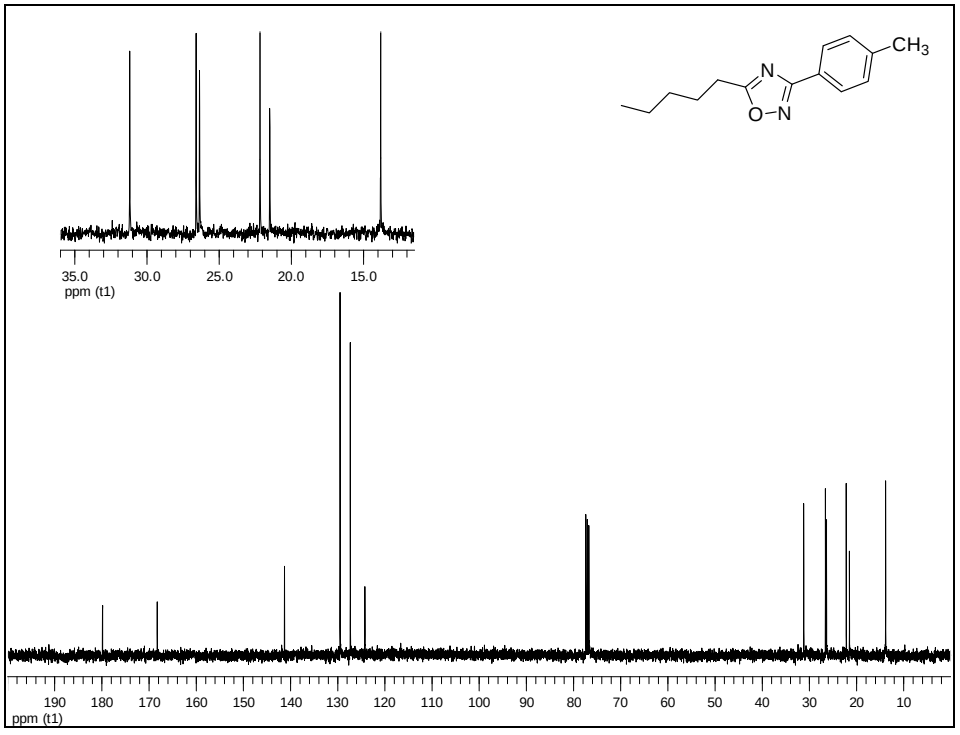

Figure A200. ^{13}C NMR spectra of **192m**.

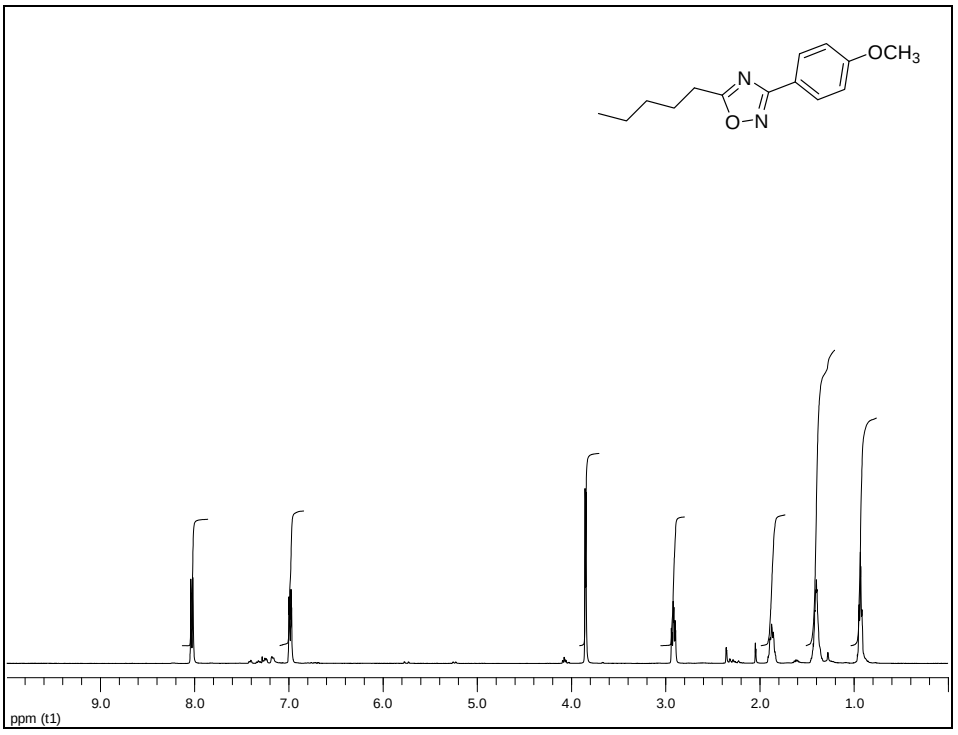

Figure A201. ^{1}H NMR spectra of **192n**.

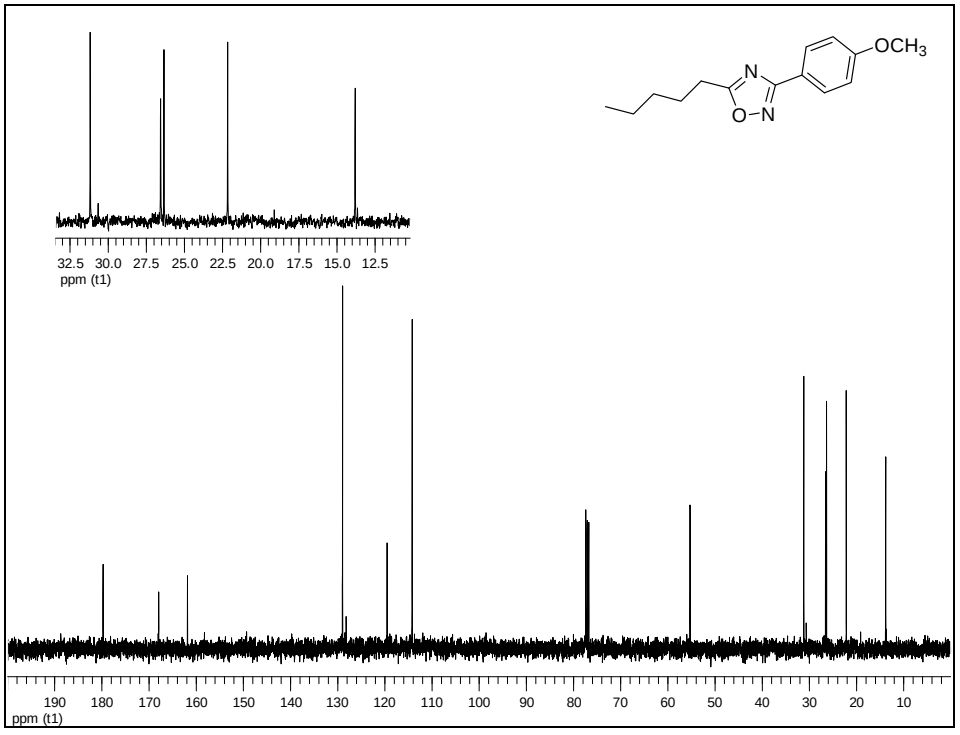

Figure A202. ^{13}C NMR spectra of **192n**.

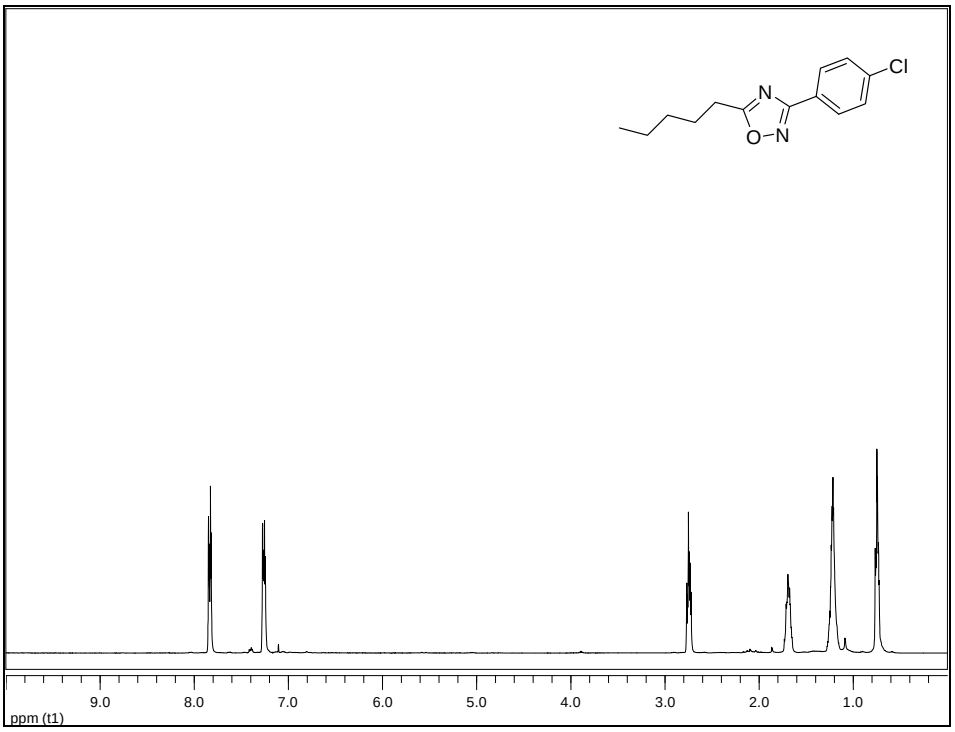

Figure A203. ^{1}H NMR spectra of **192o**.

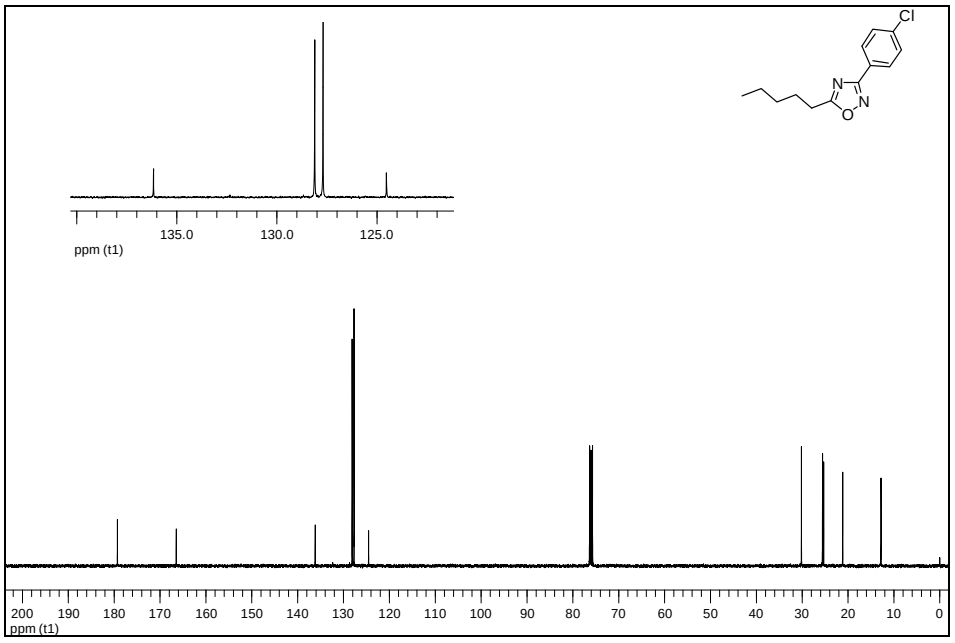

Figure A204. ^{13}C NMR spectra of **192o**.

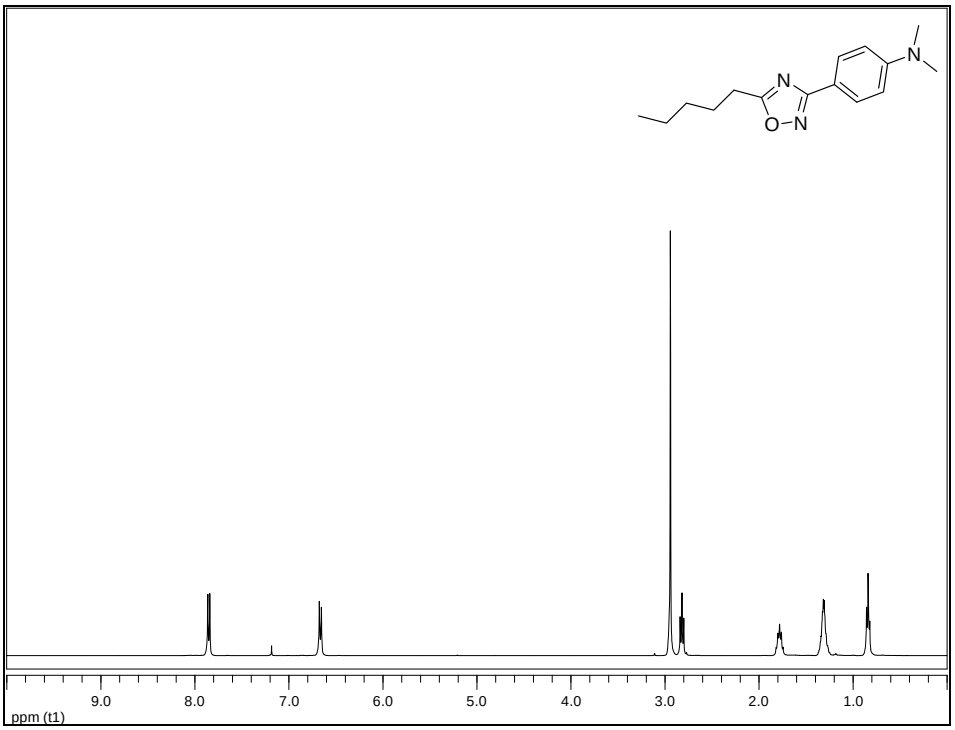

Figure A205. ^{1}H NMR spectra of **192p**.

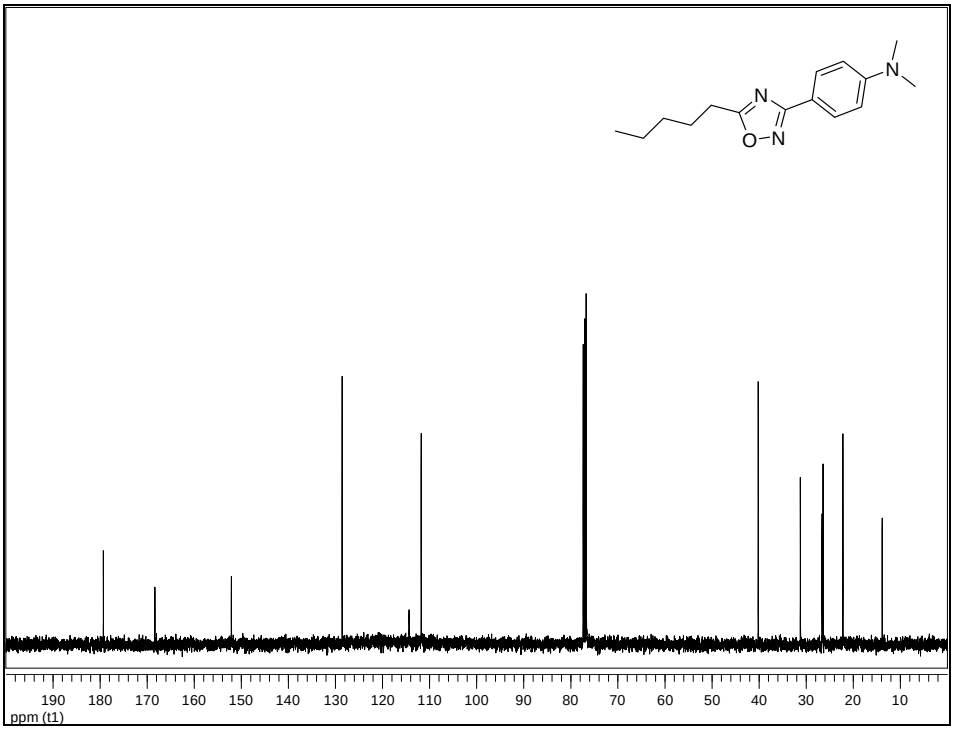

Figure A206. ^{13}C NMR spectra of **192p**.

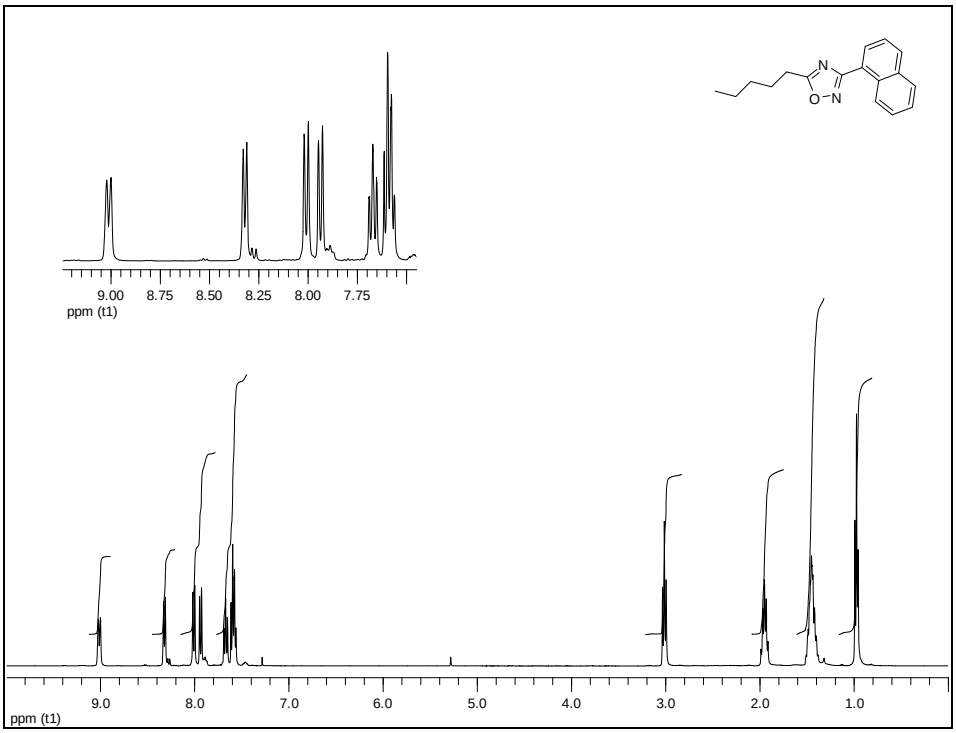

Figure A207. ^{1}H NMR spectra of **192q**.

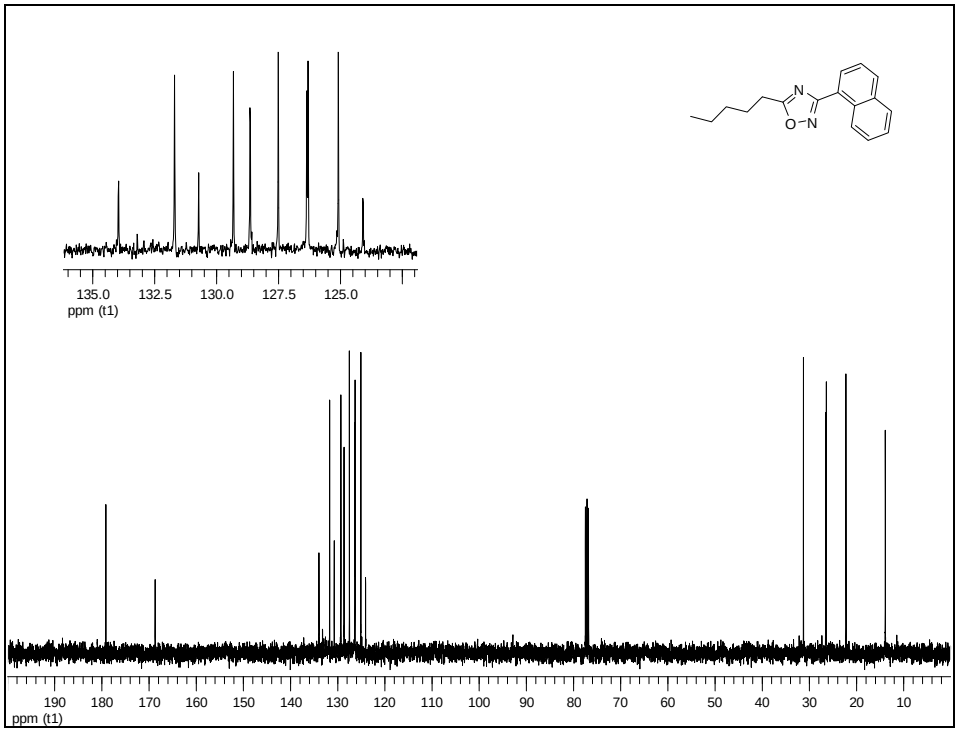

Figure A208. ^{13}C NMR spectra of **192q**.

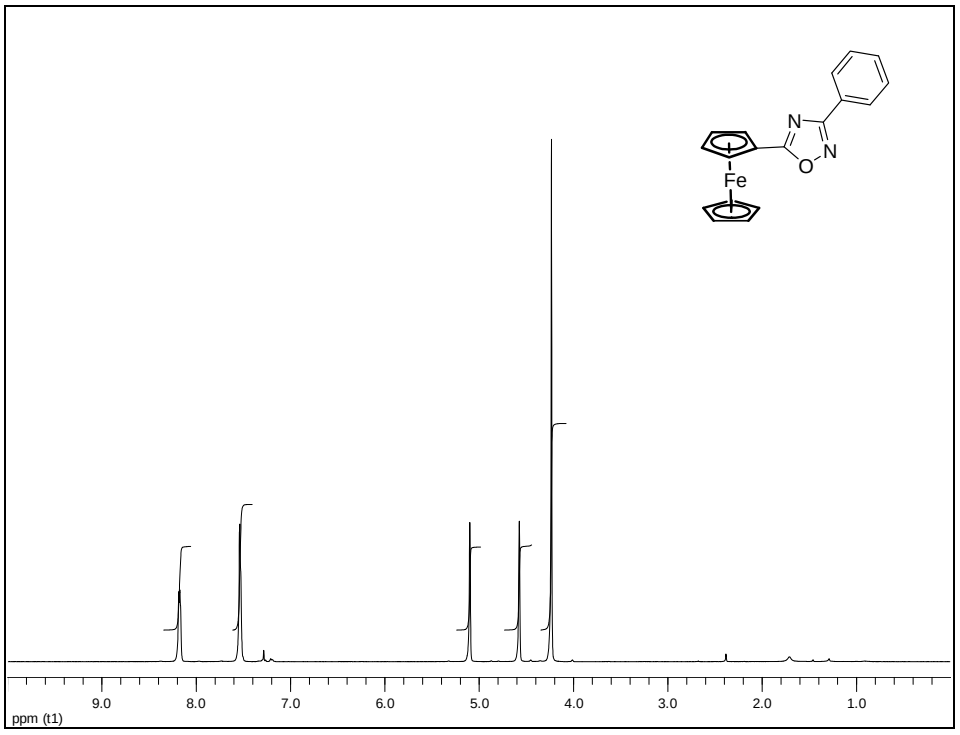

Figure A209. ^{1}H NMR spectra of **221a**.

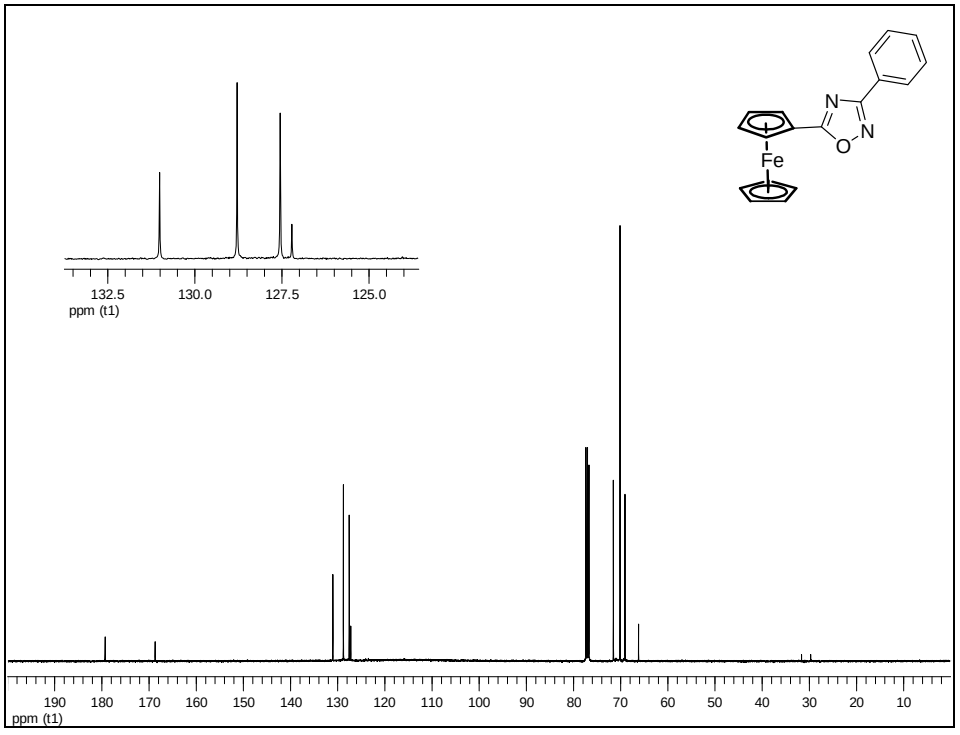

Figure A210. ^{13}C NMR spectra of **221a**.

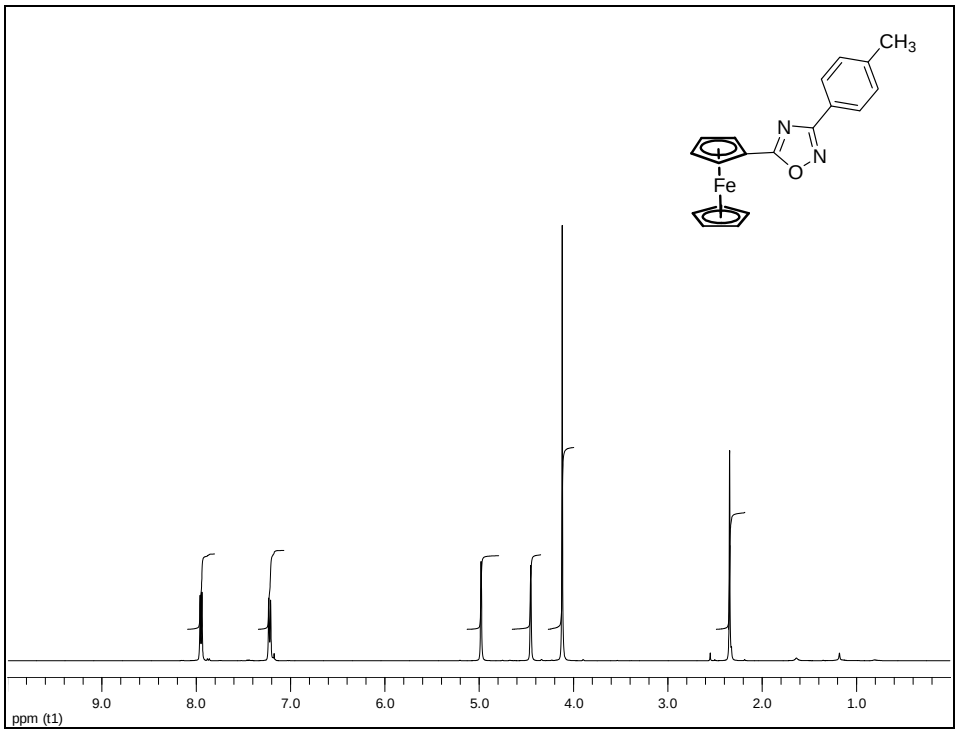

Figure A211. ^{1}H NMR spectra of **221b**.

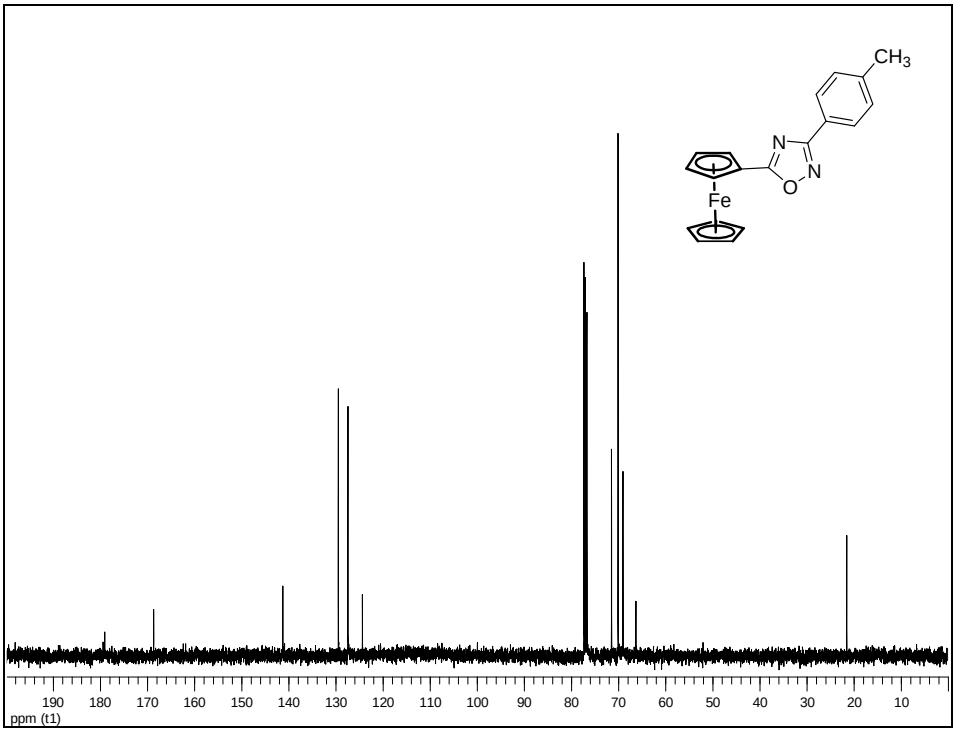

Figure A212. ^{13}C NMR spectra of **221b**.

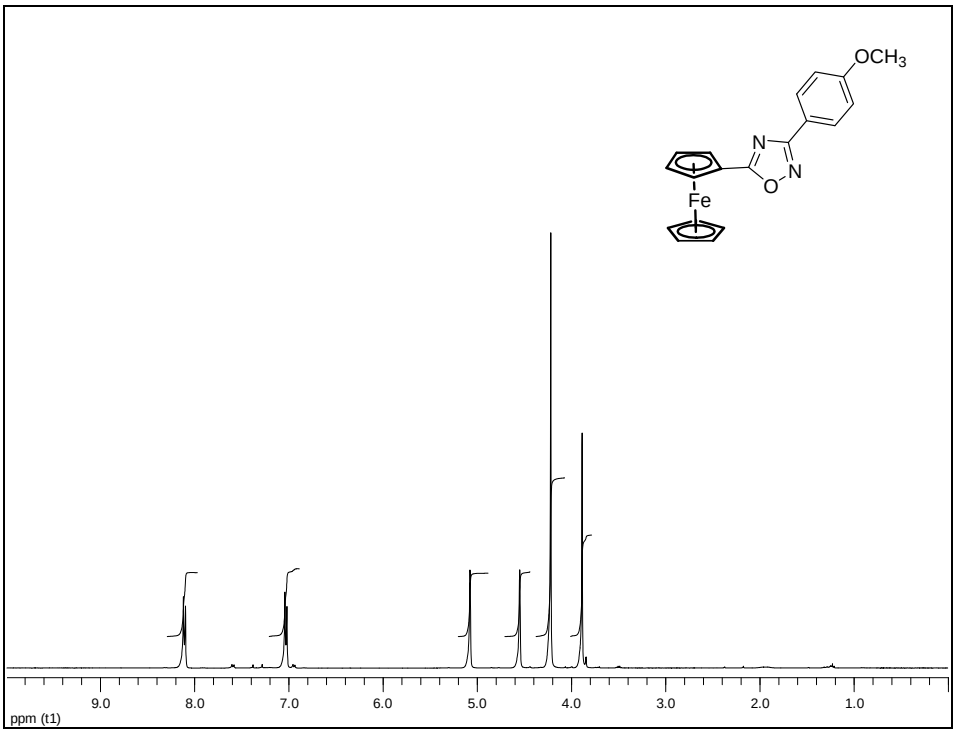

Figure A213. ^{1}H NMR spectra of **221c**.

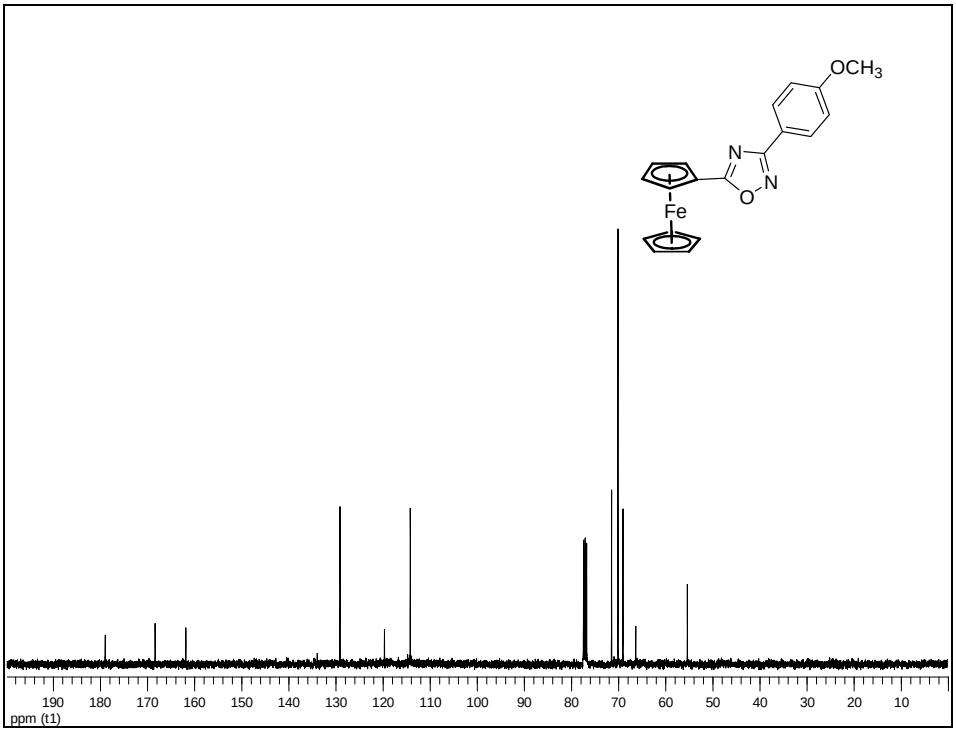

Figure A214. ^{13}C NMR spectra of **221c**.

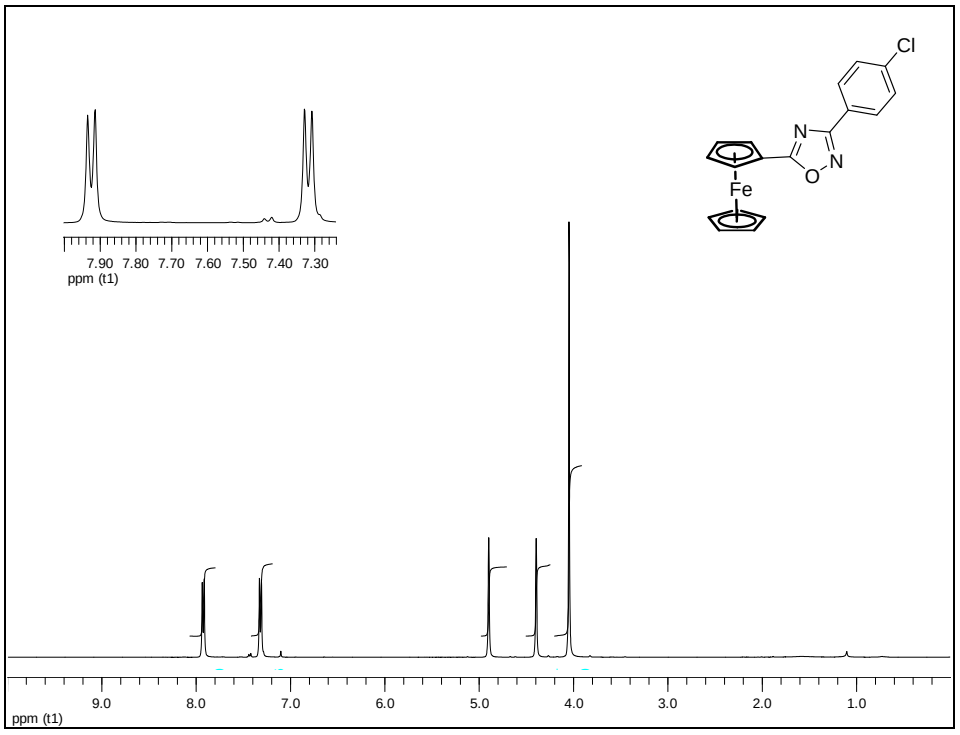

Figure A215. ^{1}H NMR spectra of **221d**.

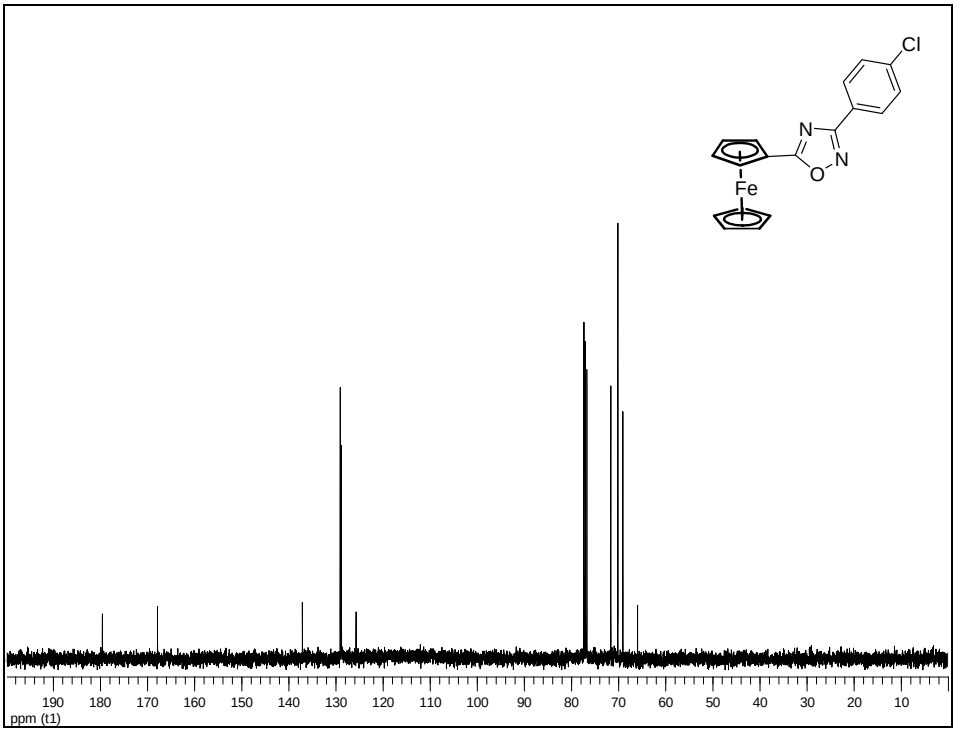

Figure A216. ^{13}C NMR spectra of **221d**.

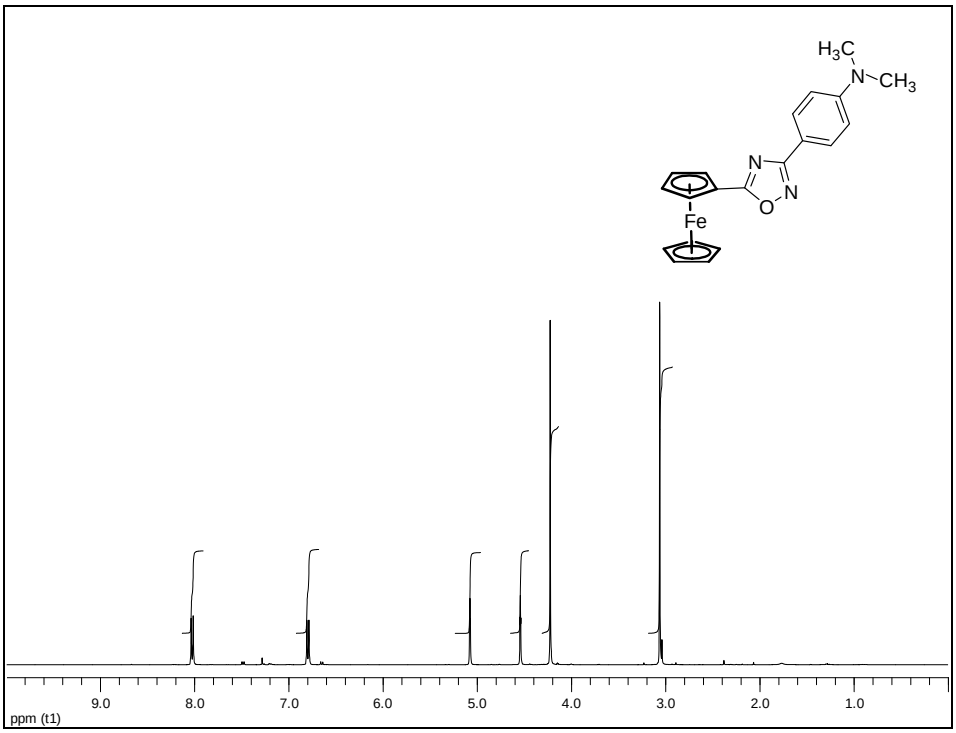

Figure A217. ^{1}H NMR spectra of **221e**.

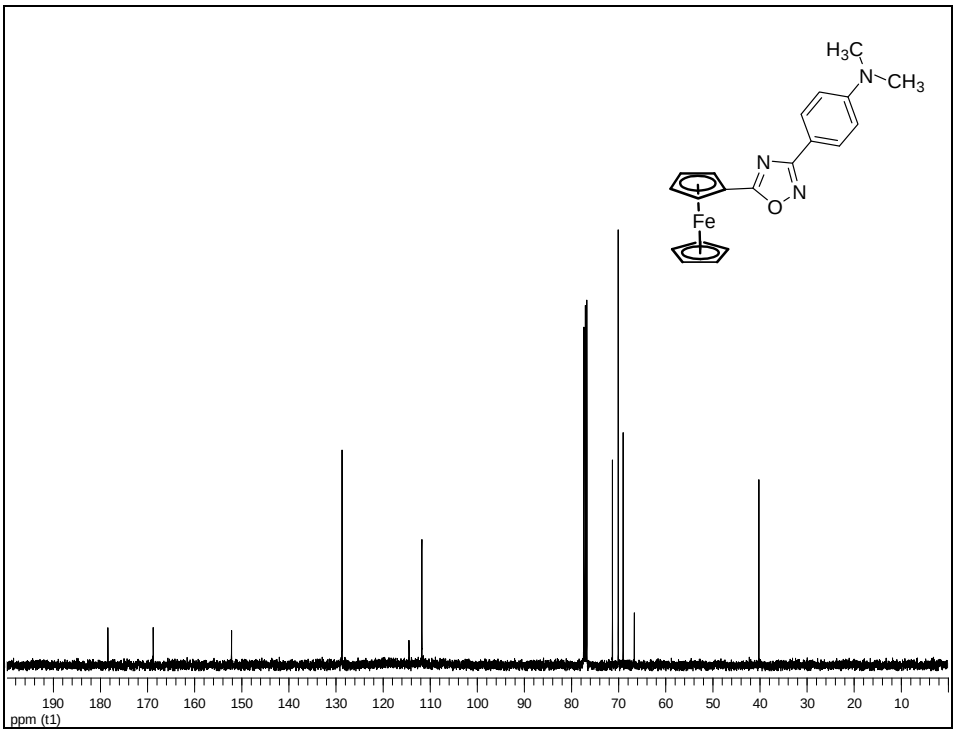

Figure A218. ^{13}C NMR spectra of **221e**.

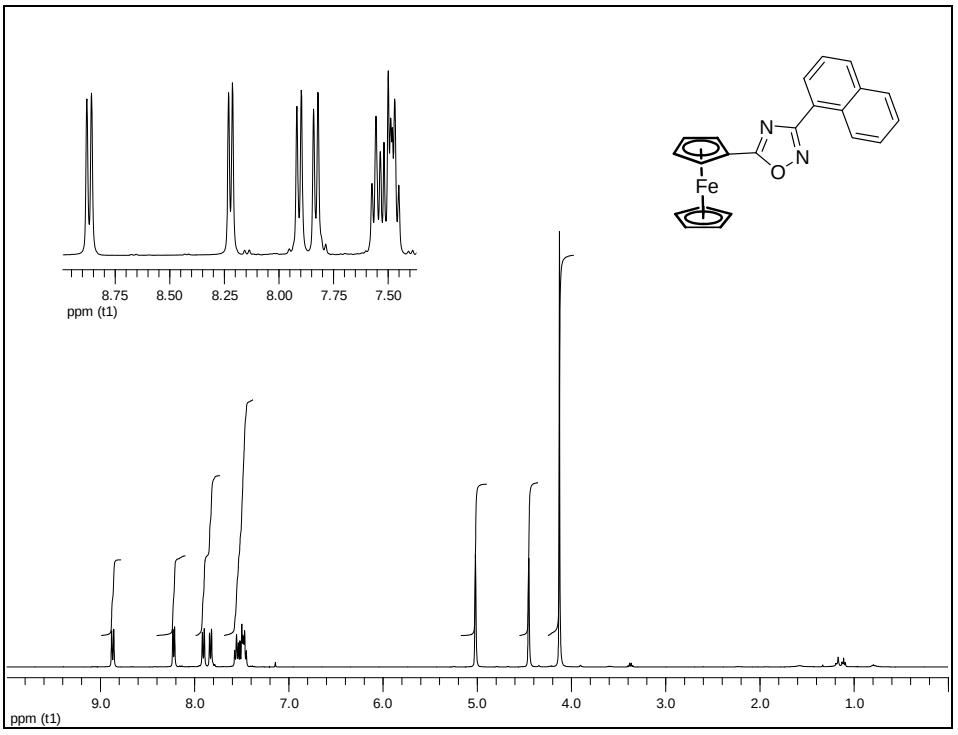

Figure A219. ^{1}H NMR spectra of **221f**.

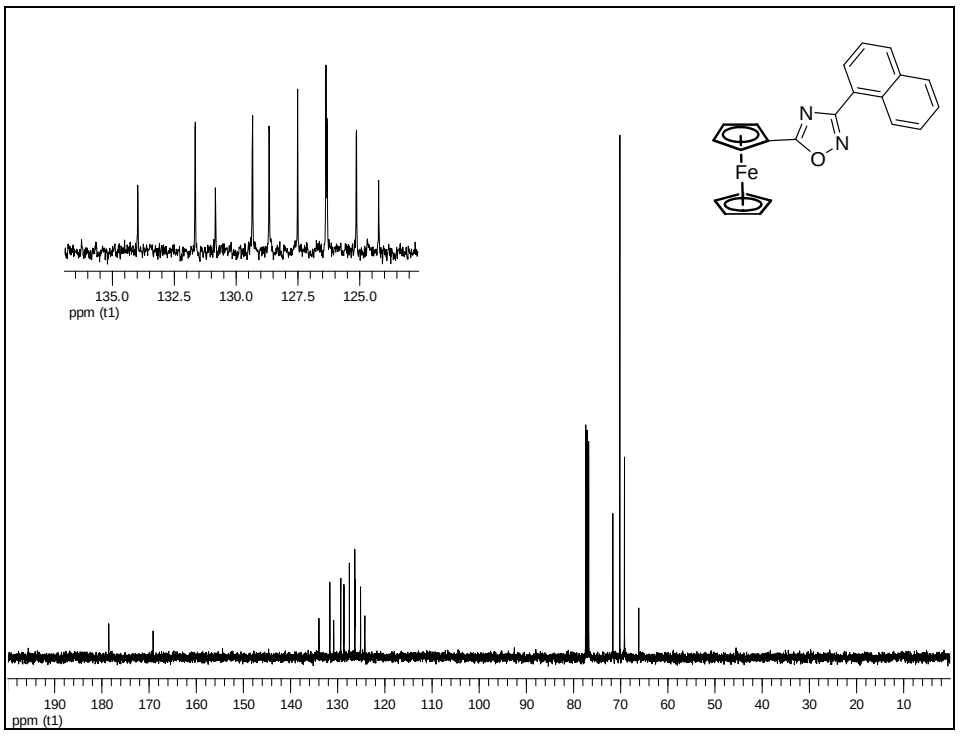

Figure A220. ^{1}H NMR spectra of **221f**.

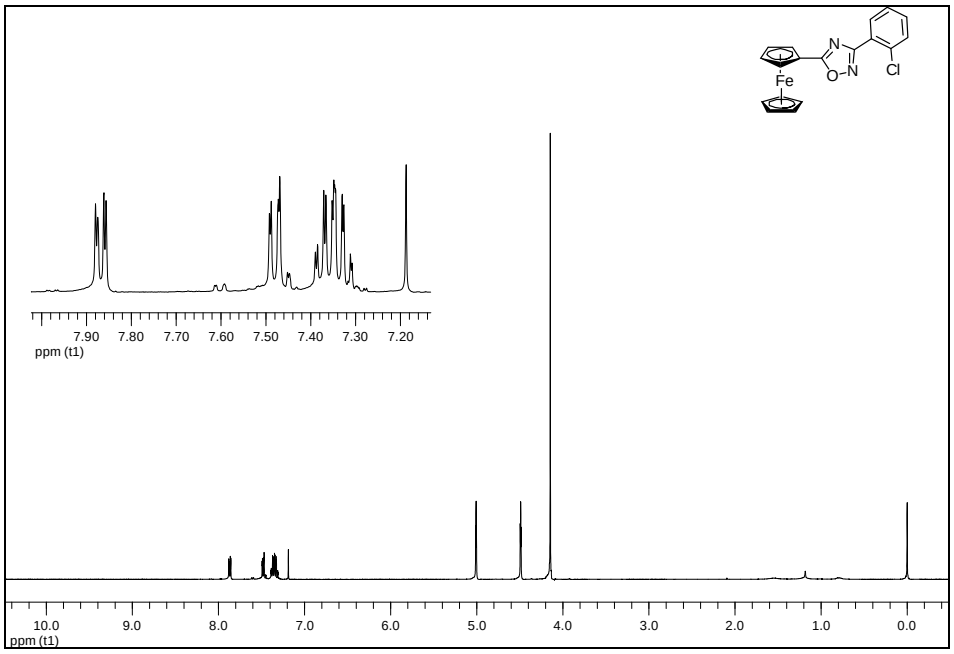

Figure A221. ^{1}H NMR spectra of **221g**.

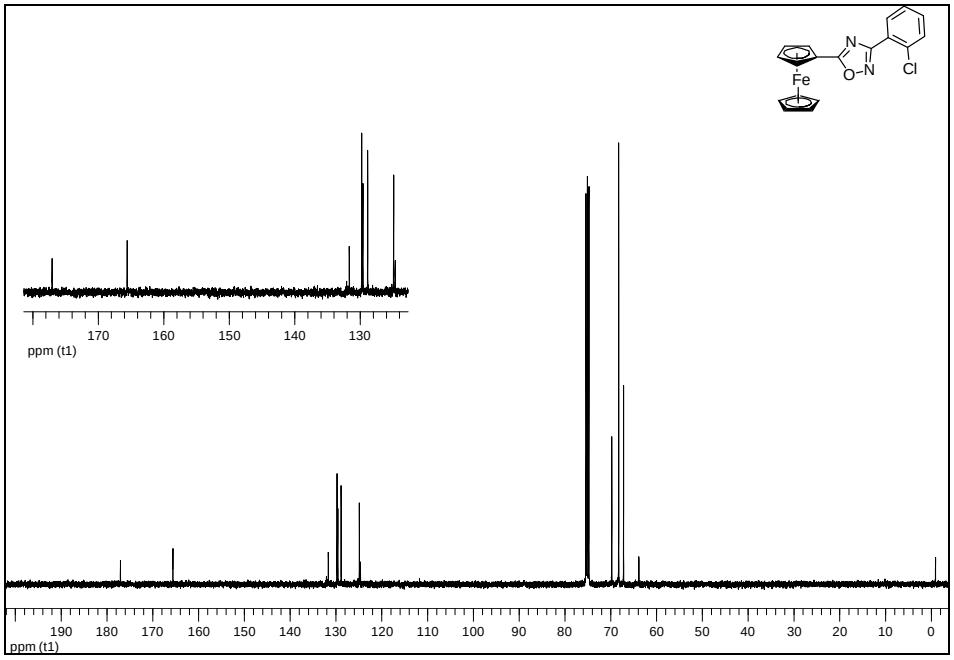

Figure A222. ^{13}C NMR spectra of **221g**.

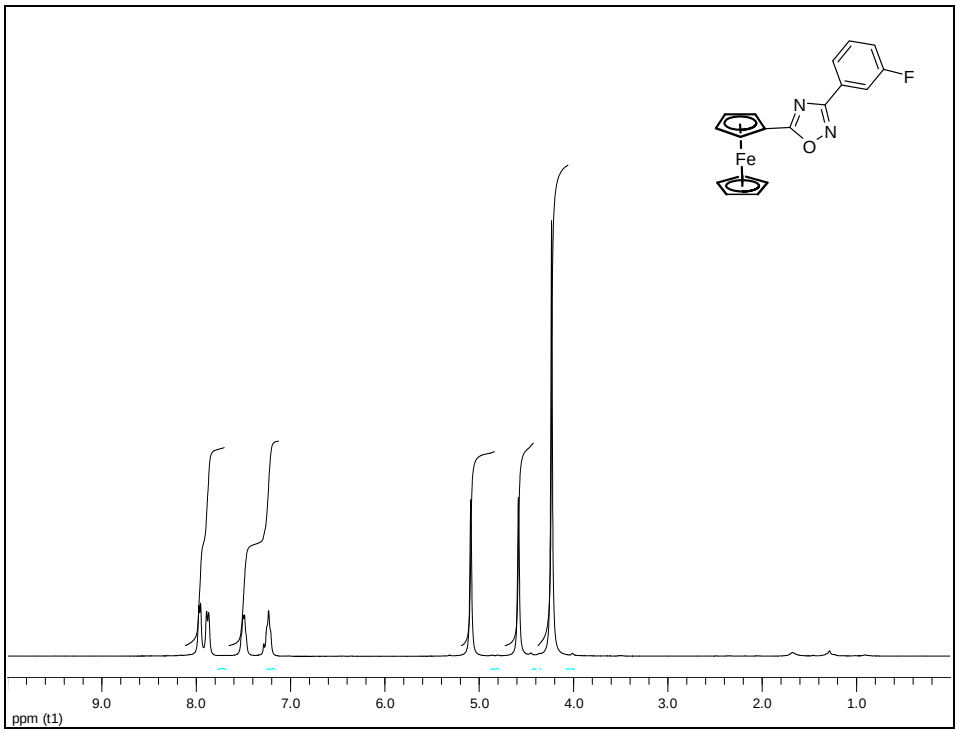

Figure A223. ^{1}H NMR spectra of **221h**.

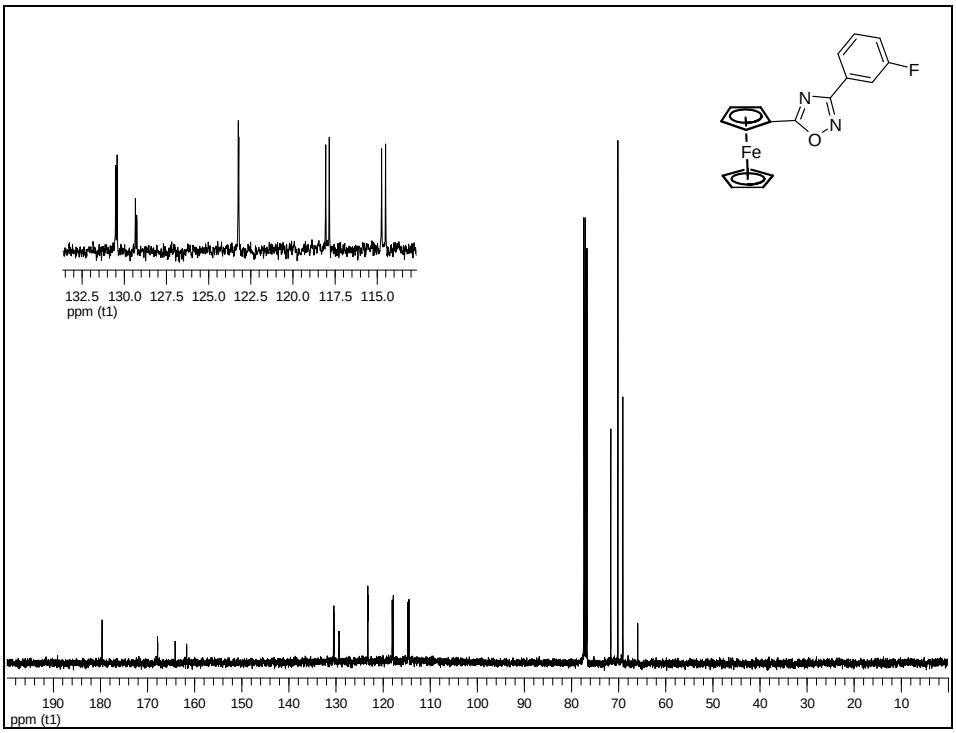

Figure A224. ^{13}C NMR spectra of **221h**.

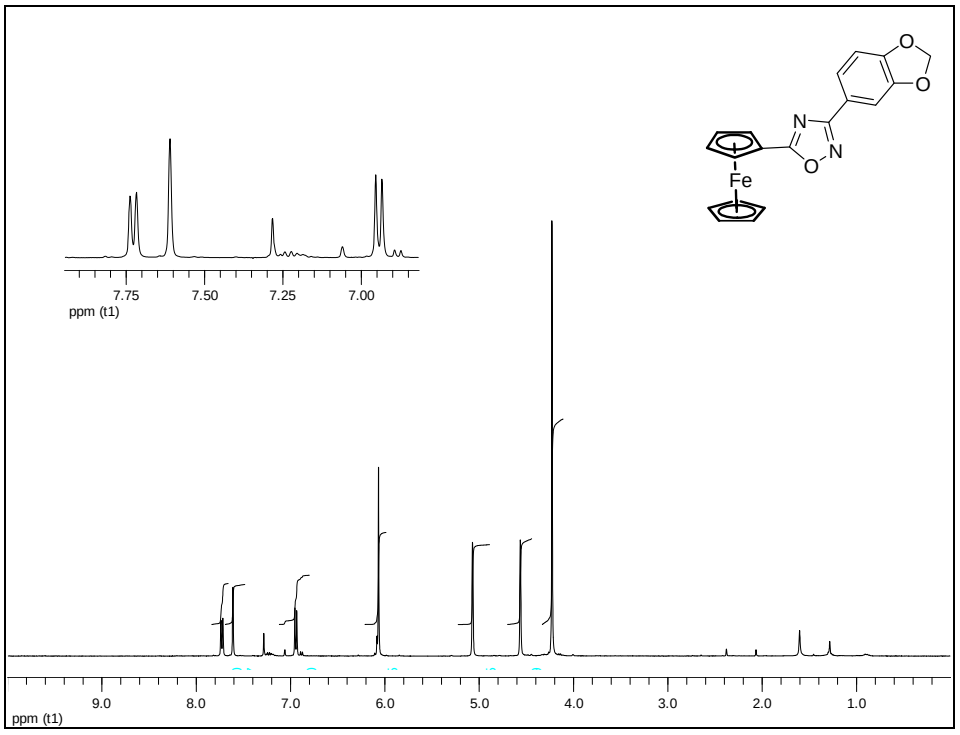

Figure A225. ^{1}H NMR spectra of **221i**.

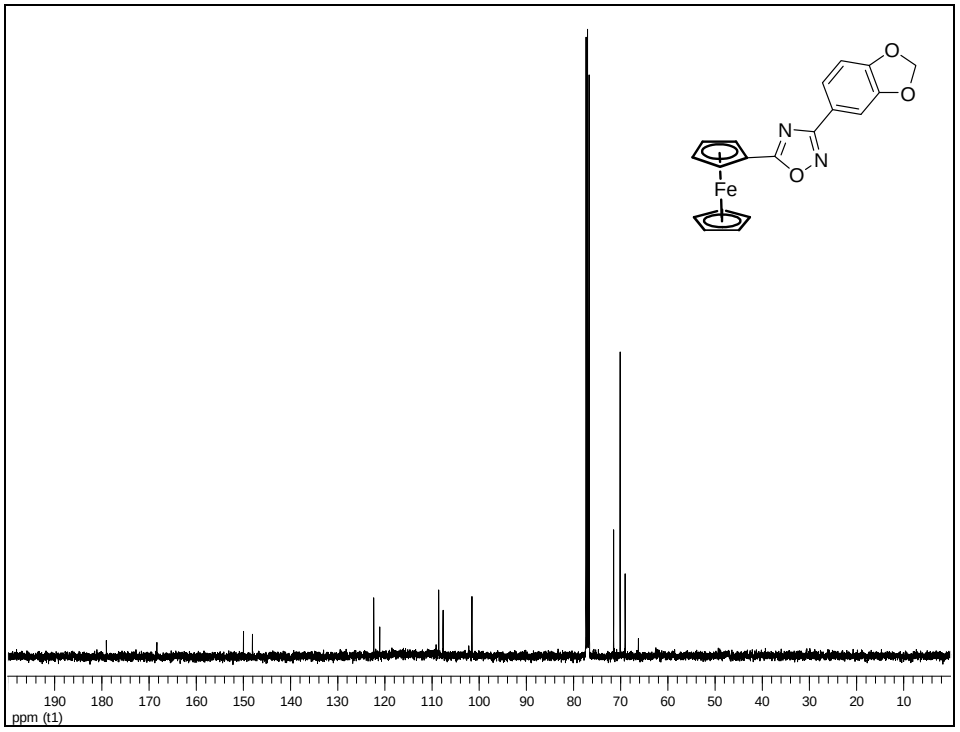

Figure A226. ^{13}C NMR spectra of **221i**.

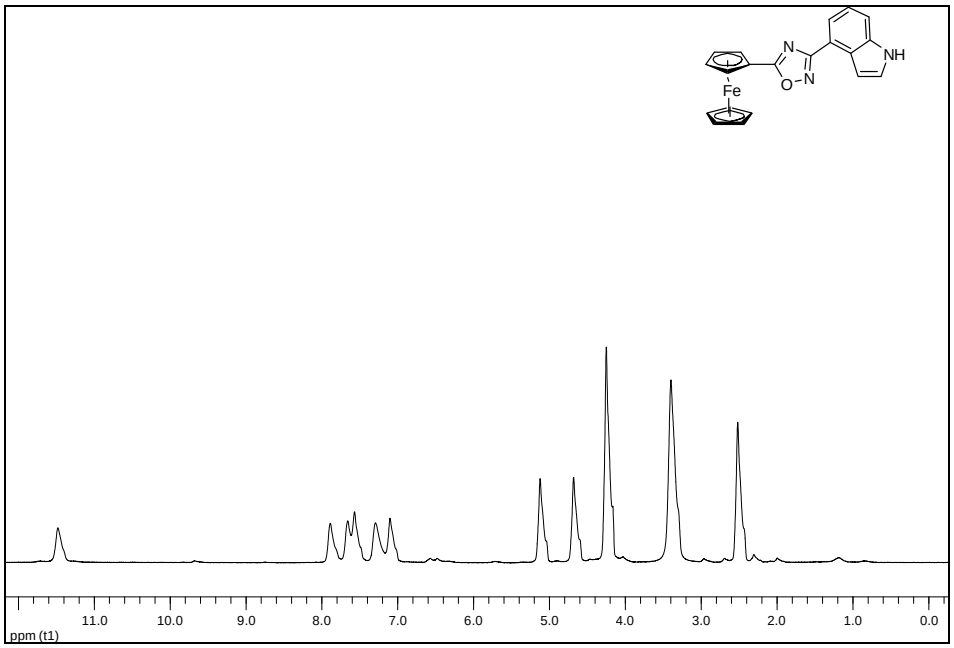

Figure A227. ^{1}H NMR spectra of **221j**.

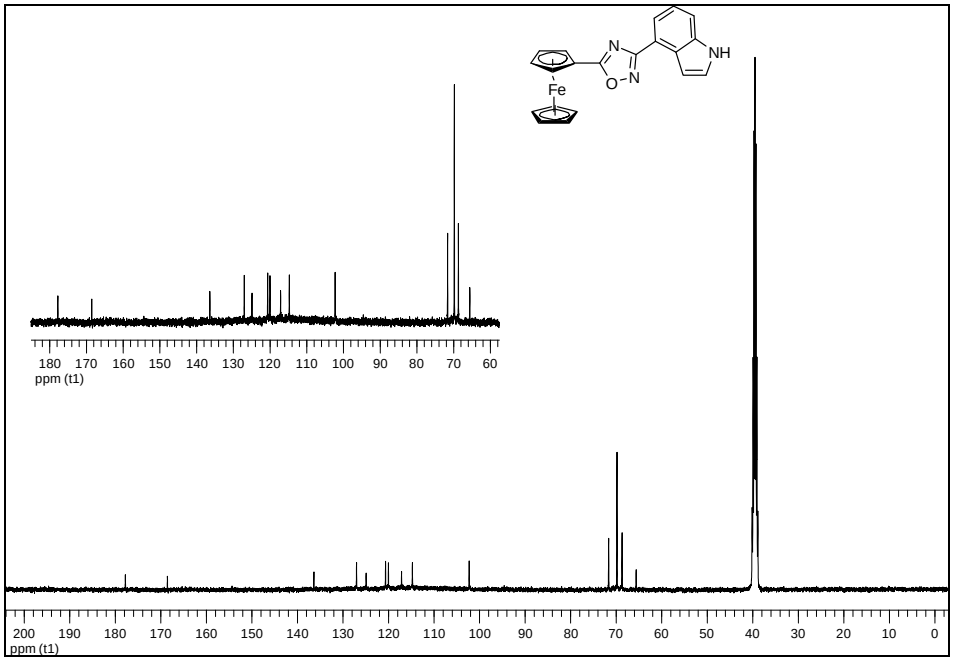

Figure A228. ^{13}C NMR spectra of **221j**.

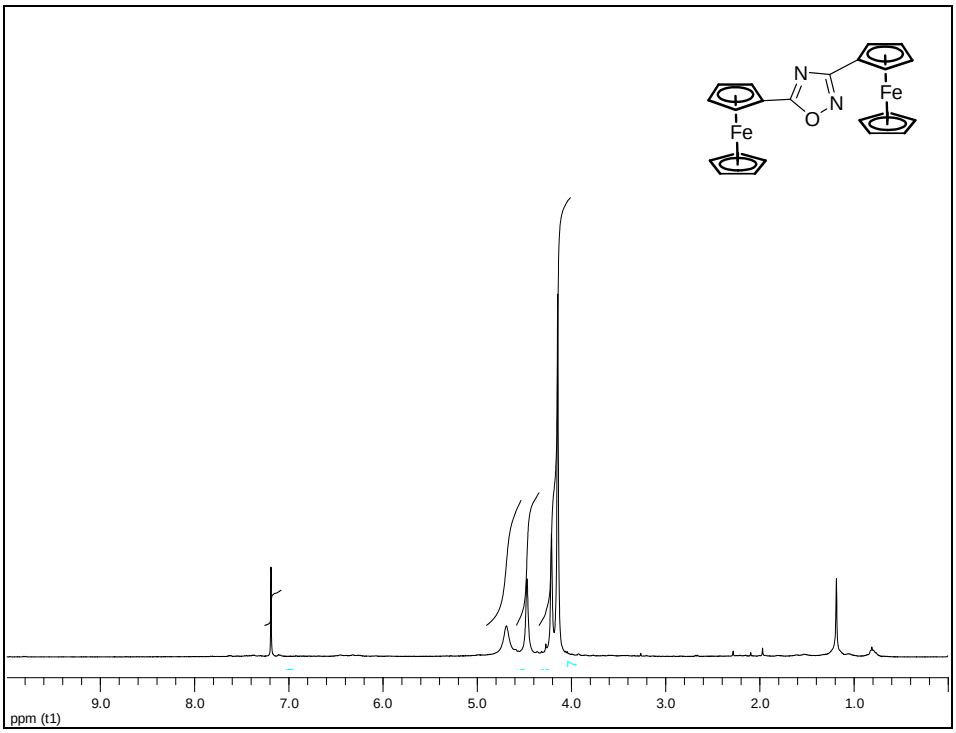

Figure A229. ^{1}H NMR spectra of **221k**.

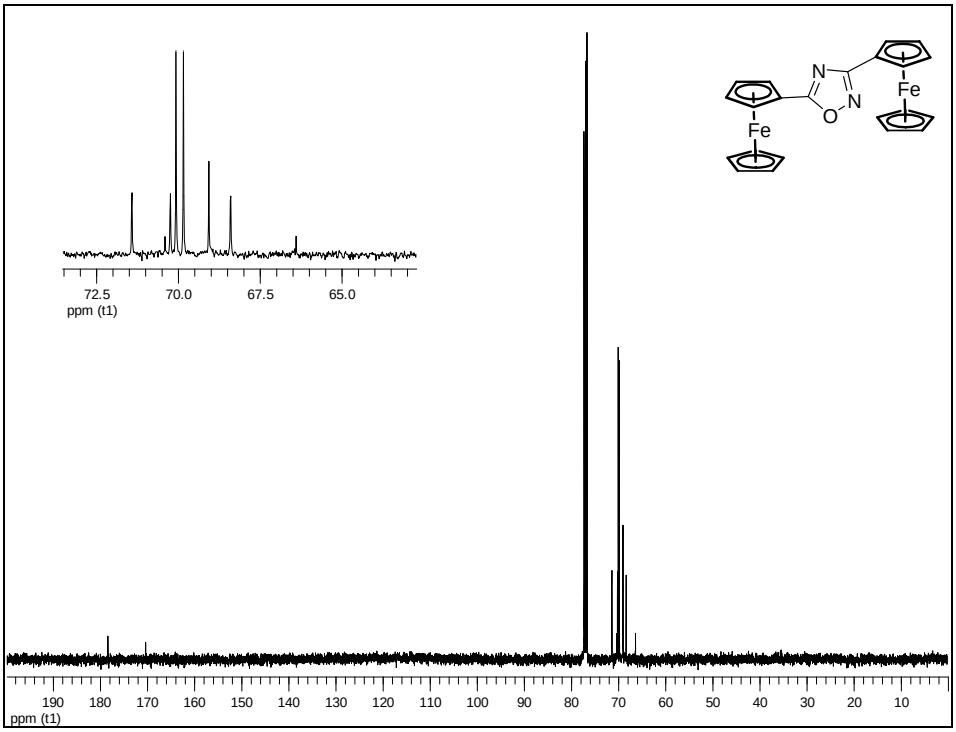

Figure A230. ^{13}C NMR spectra of **221k**.

CV

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1. A. Yurt, G. Bereket, A. Kıvrak, A. Balaban and B. Erk, Effect of schiff bases containing pyridyl group as corrosion inhibitors for low carbon steel in 0.1 M HCl, *Journal of Applied Electrochemistry* **2005,** *35*, 1025-1032.

2. Arif Kıvrak, **Metin Zora**, "Efficient one-pot synthesis of cyanoferrocene from ferrocenecarboxaldehyde using NH2OH.HCl/KI/ZnO/CH3OH system" *Journal of Organometallic Chemistry* **2007**, *692*, 2346-2349.

3. Arif Kivrak, Richard C. Larock, `Synthesis of Dihydrobenzisoxazoles by the [3+2] Cycloaddition of Arynes and Oxaziridines` *Journal of Organic Chemistry* **2010**, *75*, 7381-7387.

4. Buket Bezgin Çarbaş, Arif Kivrak, Metin Zora and Ahmet M. Önal, ` Synthesis of a novel fluorescent and ion sensitive monomer bearing quinoxaline moieties and its electropolymerization` *Reactive and Functional Polymers*, Manuscript submitted.

PRESENTATIONS

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1. G.Bereket, A.Yurt , **A.Kıvrak**, A.Balaban and B. Erk, '*HCl ortamında düşük karbon çeliğin korozyonuna Pridil grubu içeren Schiff Bazlarının etkisi*', 8. Uluslararası Korozyon Sempozyumu Bildiriler Kitabı, s.685, 9-12 Ekim 2003, Eskişehir.

2. G.Bereket, A.Yurt , **A.Kıvrak**, A.Balaban and B. Erk , "*Inhibiton of corrosion of carbon steel in HCl solutions by various Schiff bases*", 5th Internetional Conference of Advanced Batteries and Accumulators [ABA-5] 2004, Brno, Czech Republic.

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3. **Arif Kivrak**, Metin Zora, "*Efficient one-pot synthesis of cyanoferrocene from ferrocenecarboxaldehyde using NH2OH.HCl/KI/ZnO/CH3CN system*," 1st European Chemistry Congress, Budapest, Hungary; August 27-31, 2006; N-PO-178

4. **Arif Kivrak**, Metin Zora, "KI/ZnO: Ferrosenilnitril sentezi için yeni ve etkili katalizör sistemi," XX. Ulusal Kimya Kongresi, Erciyes Üniversitesi, Kayseri; 4-8 Eylül 2006; OKP-112.

5. **Arif Kıvrak**, Metin Zora, "*Synthesis of 3,7-disubstituted-1,2,4-oxadiazepine derivatives from arylamidoximes*," International Conference on Organic Chemistry, Erzurum, Turkey; June 5-9, 2007; PP-91, p 147.

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