SYNTHESIS OF 4-PHENYLSELENYL-1*H*-PYRAZOLES BY ELECTROPHILIC CYCLIZATION

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DENİZ DEMİRCİ

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submitted by **DENİZ DEMİRCİ** in partial fulfillment of the requirements for the degree of **Master of Science in Chemistry Department, Middle East Technical University** by,

Prof. Dr. Canan Özgen
Dean, Graduate School of **Natural and Applied Sciences** _____

Prof. Dr. İlker Özkan
Head of Department, **Chemistry** _____

Prof. Dr. Metin Zora
Supervisor, **Chemistry Dept., METU** _____

Examining Committee Members:

Prof. Dr. Metin Balcı
Chemistry Dept., METU _____

Prof. Dr. Metin Zora
Chemistry Dept., METU _____

Prof. Dr. Canan Ünaleroğlu
Chemistry Dept., Hacettepe University _____

Prof. Dr. Özdemir Doğan
Chemistry Dept., METU _____

Assist. Prof. Dr. Salih Özçubukçu
Chemistry Dept., METU _____

Date:

I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

Name, Last name : Deniz DEMİRCİ

Signature :

ABSTRACT

SYNTHESIS OF 4-PHENYLSELENYL-1*H*-PYRAZOLES BY ELECTROPHILIC CYCLIZATION

Demirci, Deniz

M. Sc., Department of Chemistry

Supervisor: Prof. Dr. Metin Zora

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In this study, the synthesis of 5-ferrocenyl/aryl-4-(phenylselenyl)-1*H*-pyrazole derivatives was investigated since the integration of ferrocenyl and selenium moieties into pyrazole derivatives may increase their current biological activities. Initially, the starting propargyl aldehydes were synthesized from corresponding acetylenes. Subsequently, propargyl aldehydes were reacted with hydrazines to yield corresponding hydrazones. Then the in situ synthesized hydrazones were subjected to electrophilic cyclization with phenylselenyl chloride, which afforded 5-ferrocenyl/aryl-4-(phenylselenyl)-1*H*-pyrazoles in one-pot manner. Subsequently, reaction conditions were optimized in terms of electrophile, base, temperature and solvent. Best results were obtained with phenylselenyl chloride and $NaHCO_3$ at room temperature in DCM for ferrocenyl substituted pyrazoles and DCE for aryl substituted pyrazoles. In summary, by employing the electrophilic cyclizations of in situ synthesized acetylenic hydrazones, a variety of 5-ferrocenyl/aryl-4-(phenylselenyl)-1*H*-pyrazole derivatives were synthesized in one-pot way in moderate to good yields.

Keywords: Pyrazole, Ferrocene, Phenylselenyl Chloride, Electrophilic Cyclization

ÖZ

4-FENİLSELENİL-1*H*-PİRAZOL TÜREVLERİNİN ELEKTROFİLİK HALKALAŞMA TEPKİMESİ İLE SENTEZİ

Demirci, Deniz

Yüksek Lisans, Kimya Bölümü

Tez Yöneticisi: Prof. Dr. Metin Zora

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Bu çalışmada, ferrosen ve selenyumun pirazol yapılarına bağlanması, pirazol türevlerinin sahip oldukları biyolojik aktiviteleri arttırabileceğinden dolayı 5-ferrosenil/aril-4-(fenilselenil)-1*H*-pirazol türevlerinin sentezi araştırılmıştır. İlk olarak, başlangıç maddeleri olan proparjil aldehitler asetilen türevlerinden sentezlenmiştir. Sonra proparjil aldehitlerin hidrazinlerle reaksiyonları sonucu ilgili hidrazonlar oluşturulmuştur. Tepkime ortamında üretilen bu hidrazonlar daha sonra fenilselenil klorür ile elektrofilik halkalaşma reaksiyonlarına maruz bırakılarak tek basamakta 5-ferrosenil/aril-4-(fenilselenil)-1*H*-pirazol türevleri sentezlenmiştir. Sonrada tepkime koşulları farklı elektrofil, baz, sıcaklık ve çözücü kullanılarak optimize edilmiştir. En iyi sonuçlar oda sıcaklığında fenilselenil klorür ve $NaHCO_3$ ile ferrosenil sübstiye pirazollar için DCM kullanılması ile aril sübstiye pirazoller için ise DCE kullanılması ile elde edilmiştir. Sonuç olarak bu projede asetilenik hidrazonların elektrofilik halkalaşmalarıyla bir seri 5-ferrosenil/aril-4-(fenilselenil)-1*H*-pirazol türevi tek basamakta orta ve yüksek verimlerde sentezlenmiştir.

Anahtar Kelimeler: Pirazol, Ferrosen, Fenilselenil Klorür, Elektrofilik Halkalaşma

Aileme,

To My Family,

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ABBREVIATIONS

br	broad (spectral)
δ	chemical shift in parts per million downfield from
d	doublet (spectral)
Fc	ferrocenyl
FT	fourier transform
Hz	hertz
IR	infrared
J	coupling constant
m	multiplet (spectral)
NMR	nuclear magnetic resonance
ppm	parts per million (in NMR)
q	quartet (spectral)
RT	room temperature
s	singlet (spectral)
t	triplet (spectral)
THF	tetrahydrofuran
TLC	thin layer chromatography
ACN	acetonitrile
DCM	dichloromethane
DCE	dichloroethane

CHAPTER 1

INTRODUCTION

Organic chemistry is a branch of science that deals with carbon compounds which constitute the main parts of the essential molecules such as proteins, enzymes, vitamins, lipids, carbohydrates and nucleic acids [1]. Beside these, the organic compounds that produced naturally like petroleum, natural gas, cotton, silk, food, medicine and that synthesized like fabrics, plastics, medicines and rubbers have also great importance in our life [2].

Most of the organic compounds are in the structure of ring systems. If the ring system is not built up fully with carbon and if it has elements other than carbon like oxygen, nitrogen or sulfur in its structure, it is called as heterocyclic compound. Heterocyclic ring systems have a great importance for organic chemistry because of their high usage in biological systems, medicines and materials (Figure 1) [3].

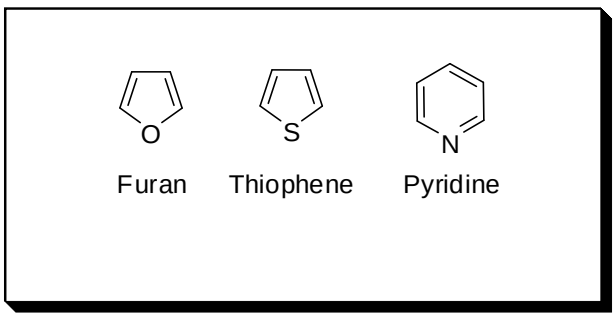


Figure 1. Examples of heterocyclic compounds.

Heterocyclic molecules are quite commonly encountered in nature and biological systems. Most of the known pharmaceutical preparations like antibiotics, neurotropics, cardiovasculars, anticarcinogenics are heterocyclic in nature. In addition, heterocyclic structures are used in agricultural processes, new plant development regulators and also pesticides widely. Beside these, heterocyclic fragments including polymers, fibers, pigments, colorants, organic metals and superconductors are synthesized and produced in tremendous amount in recent years [4].

All the living cells have DNA which is responsible from heredity and RNA which is responsible from the synthesis of proteins. DNA and RNA have the hereditary information codes cytosine, thymine, uracil, adenine, guanine and these vital codes have pyrimidine and purine nitrogen heterocyclic structures (Figure 2) [5].

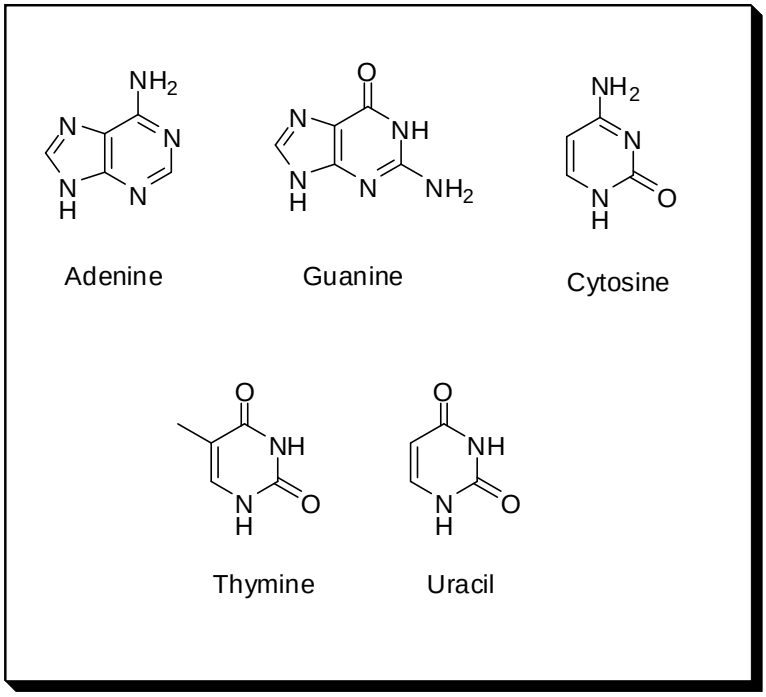


Figure 2. Nucleic acid pyrimidine and purine bases.

In the drug chemistry, heterocyclic compounds constitute the majority of the active parts of the medicines. For instance, a pain killer morphine has piperidine moiety in its structure (Figure 3). The hydrazide of isonicotinic acid (isoniazid) is used to cure tuberculosis (Figure 3). Moreover, in the structure of penicillin G, used as antibiotic, there are two heterocyclic systems which are five-membered thiazole ring and four-membered azetidine nucleus in the form of β-lactam (Figure 3) [5].

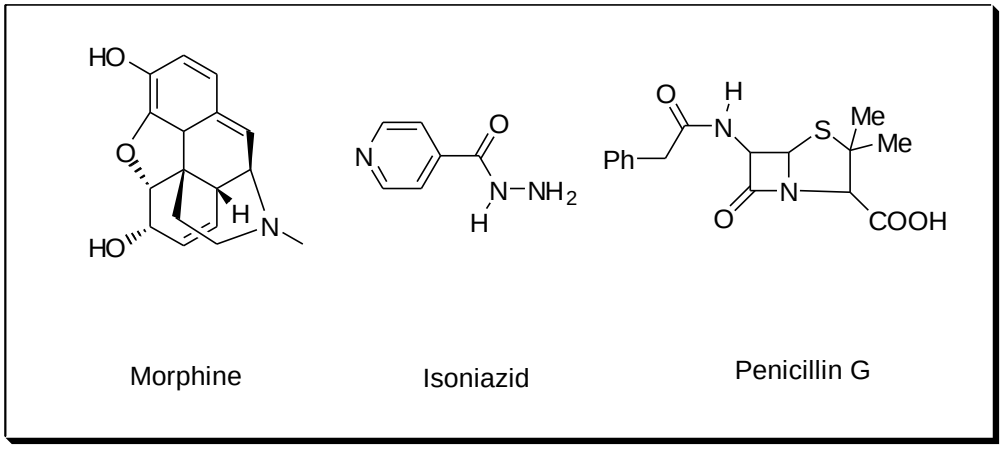


Figure 3. Examples of some heterocyclic structures used in drug chemistry.

Due to the facts mentioned above, heterocyclic chemistry is very important for the human life, and with the new studies and research on this subject, it will be easier to understand the topic and to solve problems related to science, technology, industry and also human life.

1.1 Pyrazoles

Pyrazoles are one of the important members of heterocyclic compounds with two adjacent nitrogens in a five-membered ring system. Because of their aromaticity and wide application in pharmaceutical and material industry, they have gained significant interest among the scientist [6].

The description of pyrazole was first made by Buchner in 1889, and it was synthesized by the decarboxylation of pyrazole-3,4,5-tricarboxylic acid (**1**) (Figure 4) [7].

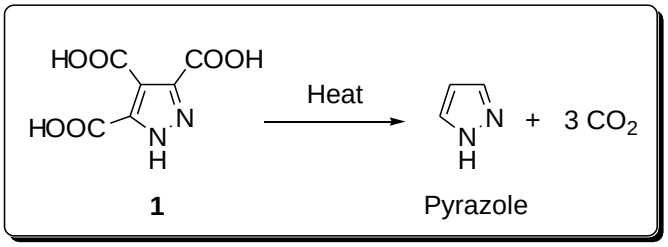


Figure 4. Synthesis of pyrazole by the decarboxylation of pyrazole-3,4,5-tricarboxylic acid (**1**).

From 1889 to 1954, it was thought that pyrazoles could not be obtained naturally. However, in 1954, Kosuge and Okeda extracted the first natural pyrazole derivative 3-*n*-nonylpyrazole (**2**) from a plant which is called as *Houttuynia Cordata*. The importance of this pyrazole derivative results from its antimicrobial activity [8]. Another natural pyrazole derivative which is *levo*-*β*-(1-pyrazolyl)alanine (**3**) was isolated from *Citrullus Vulgaris* that is watermelon seeds (Figure 5) [9].

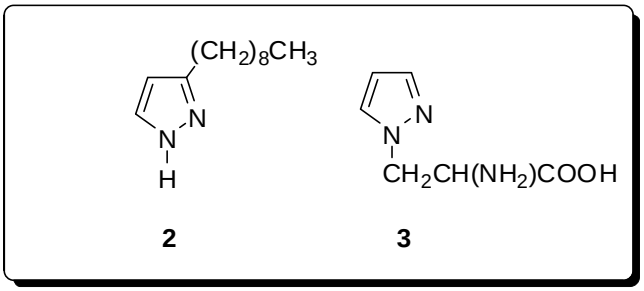


Figure 5. First isolated natural pyrazole derivatives.

According to the place of double bonds and substituents, pyrazoles can have different tautomeric forms. The presence of tautomeric and isomeric forms of pyrazoles can be proved by the nuclear magnetic resonance studies, rate of formation studies, UV absorption characteristics and some other physical properties like boiling point differences [10].

1.1.1 Biological importance of pyrazoles

Many of the biologically active compounds are in the heterocyclic structure. As a heterocycle, pyrazole ring shows a wide range of biological activities. Compounds including pyrazole ring in their structures have insecticide and herbicide properties. Moreover, they are used as antitumor, anti-inflammotary, antimicrobial, antipsychotic and analgesic agents [6]. For instance, pyrazole ring containing celecoxib (**4**) is used in the treatment of arthritis symptoms and related diseases [11]. DHODase (Dehydrorotate dehydrogenase) (**5**) has also pyrazole ring in its structure and is used as inhibitor to *Helicobacter Pylori* which causes stomach diseases such as ulcers and gastritis (Figure 6) [12].

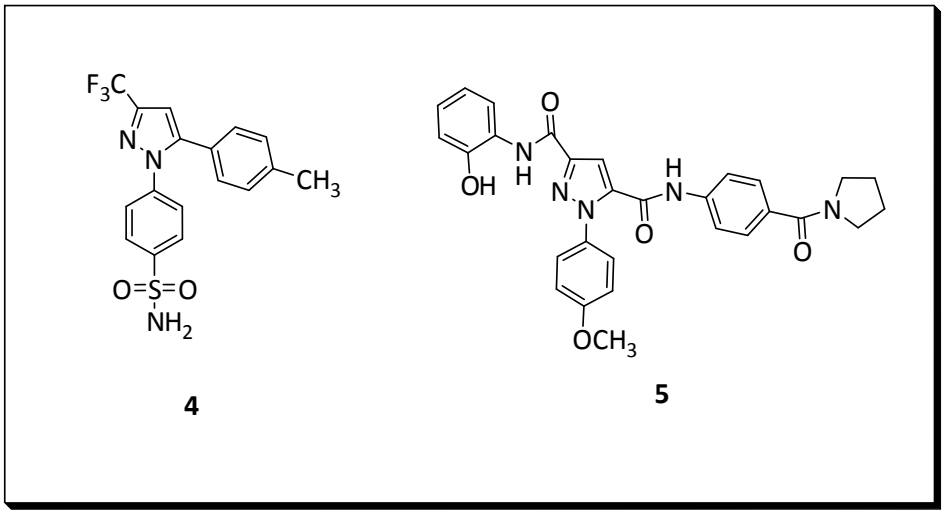


Figure 6. Structures of celecoxib (**4**) and DHODase (**5**).

In addition, fenpyroximate (**6**) is active as insecticide, pesticide and acaricide [13] while pyrazofurin (**7**) is active as antimicrobial, antiviral and anticancer agent (Figure 7) [14].

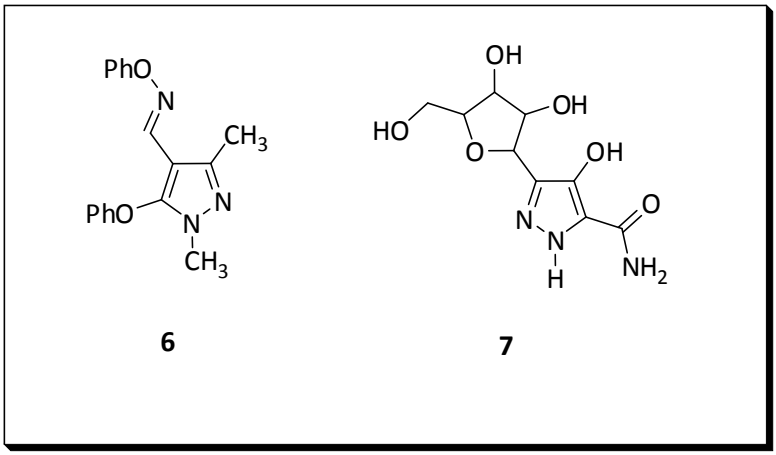


Figure 7. Structures of fenpyroximate (**6**) and pyrazofurin (**7**).

With the recent studies, the number of biologically active pyrazole containing compounds has been found increasing. For instance, Bondock research group has synthesized the substituted pyrazole derivative **8** in 2010 and showed its antifungal activity (Figure 8) [15]. Moreover, Radi has synthesized novel pyrazole compounds **9a-d** as antimicrobial, antibacterial and antifungal agents (Figure 8) [16].

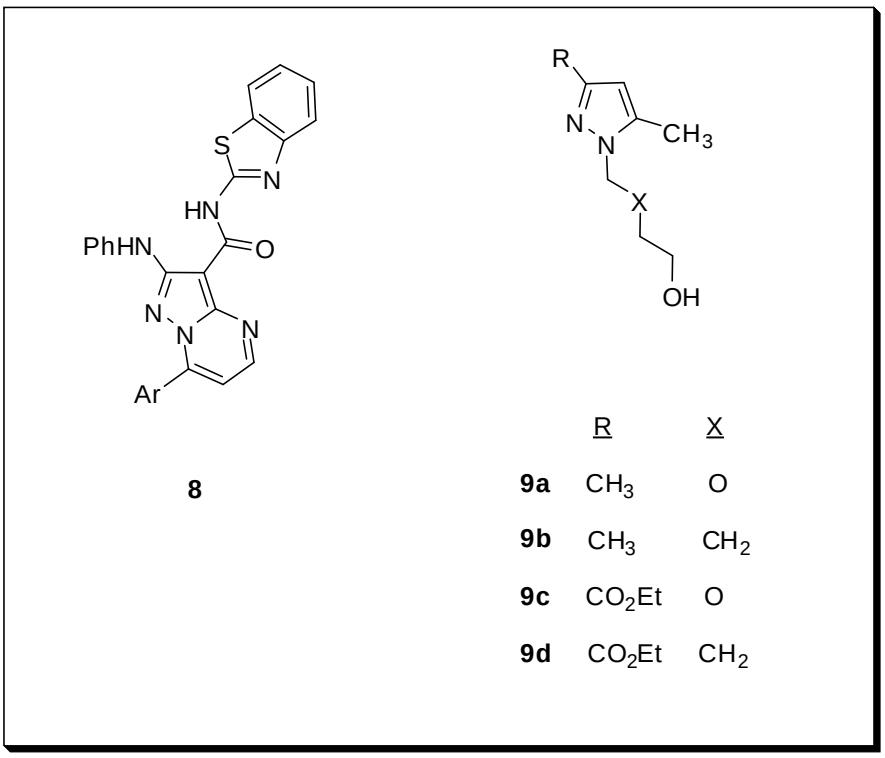


Figure 8. Biologically active pyrazole derivatives **8**, **9a**, **9b**, **9c** and **9d**.

It is the fact that pyrazole derivatives are important compounds for biological systems, medicines, agrochemicals and many fields of industrial products. However, pyrazoles are rarely found in nature and that makes the pyrazole synthesis crucial.

1.1.2 Synthesis of pyrazoles

Wide application areas of pyrazoles make them popular in research projects as well as in industry. Therefore, there are many studies in the literature, indicating many ways of synthesizing pyrazole derivatives. The most common method is the synthesis of pyrazoles by the reactions of β-dicarbonyl compounds with hydrazines. In this method, to obtain a single pyrazole, the starting material should be chosen symmetrical β-dicarbonyl compound. If the carbonyl groups are different from each other, a mixture of regioisomers is obtained. Regioselectivity of such reactions

depend upon the reaction conditions. An example to the synthesis of isomeric pyrazoles, such as **11a** and **11b**, can be given from unsymmetrical β-dicarbonyl compounds **10**. Gosselin research group has reported that the reaction of 1-arylbutane-1,3-diones **10** with arylhydrazine hydrochlorides under acidic conditions gave highly regioselective (99.8 : 0.2) isomers **11a** and **11b** (Figure 9) [10].

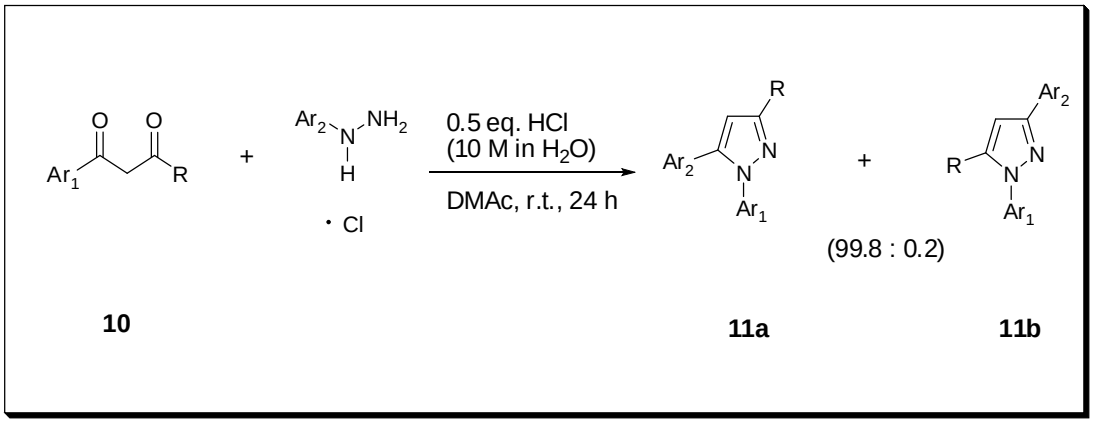


Figure 9. Synthesis of isomeric pyrazoles **11a** and **11b**.

Another commonly used method for the synthesis of pyrazole derivatives involves the condensation reaction of hydrazines with α,β-alkynic hydrazones, which are 1,3-dielectrophilic equivalents of 1,3-dicarbonyl compounds. When hydrazines are treated with 1,3-dicarbonyl compounds or with their equivalents, generally isomeric pyrazoles are formed. In fact, regioselective reactions depend on the identity of the hydrazine substituents. For instance, from the reaction of arylpropiolaldehyde **12** and methylhydrazine, only 1-methyl-3-aryl-1*H*-pyrazole **13** has been obtained (Figure 10) [17].

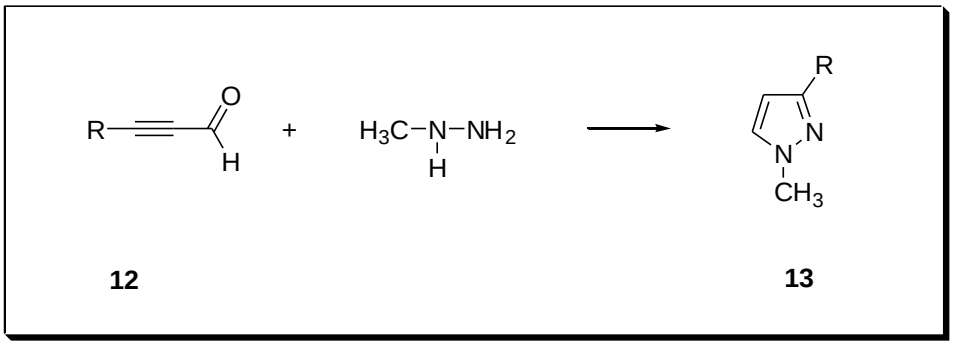


Figure 10. Regioselective synthesis of pyrazole derivatives **13** from arylpropiolaldehydes **12**.

Although the intermediate steps are not clearly known, pyrazole derivatives can also be synthesized from arylhydrazones **15** of aliphatic and aromatic aldehydes with β-ketoesters **14** in the presence of zinc chloride (Figure 11). Condensation of the reactants **14** and **15** at temperatures ranging from 120 to 140 °C in presence of $ZnCl_2$ gives the esters of pyrazole-4-carboxylic acids **16** [18].

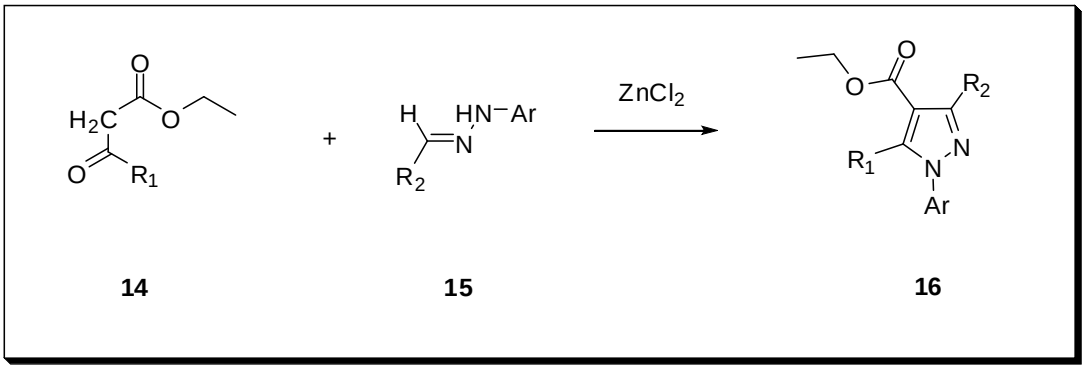


Figure 11. Synthesis of pyrazole derivatives **16** from β-ketoesters **14** and arylhydrazones **15**.

Another widely used method involves 1,3-dipolar cycloaddition of diazoalkanes or nitrilimines with alkenes or alkynes. Alkynes react with diazo compounds readily and give [3+2]-cycloaddition reaction. In 1,3-dipolar cycloaddition reactions, diazo

compounds, such as **18**, are first produced from tosylhydrazones of aldehydes **17** and then react with alkynes to generate the corresponding pyrazoles **19** (Figure 12) [19].

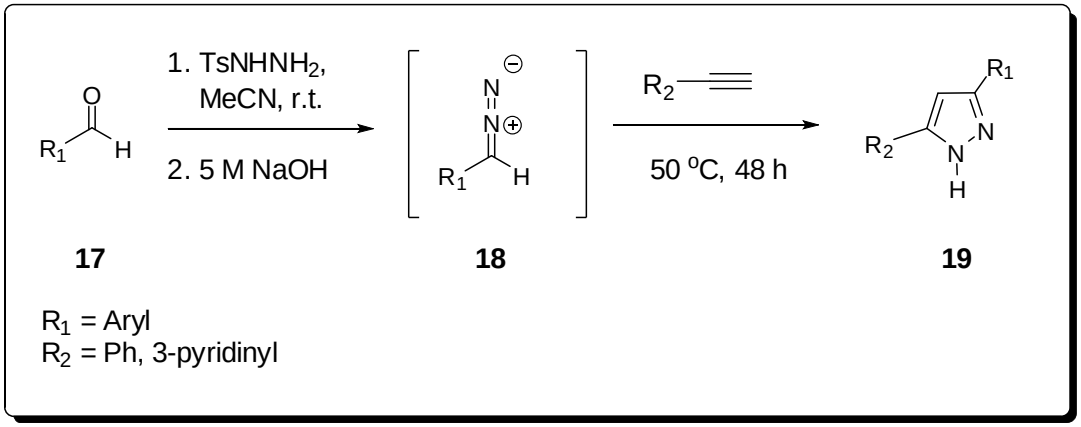


Figure 12. 1,3-Dipolar cycloaddition reactions of diazo compounds **18** with alkynes.

As mentioned before, pyrazoles have many important properties. Thus, chemists have developed many methodologies to synthesize new pyrazole derivatives so far and many studies are also being conducted. One of the recent studies is the microwave-assisted and continuous flow multistep synthesis of 4-(pyrazol-1-yl)carboxanilides **23**. In this study, Kappe and co-workers synthesized 1-(4-nitrophenyl)-1*H*-pyrazoles **22a** and 1-(4-bromophenyl)-1*H*-pyrazole **22b** by the cyclocondensation reaction of 4-(nitro/bromo)phenylhydrazines **21a** and **21b** with the enone **20** under acidic conditions (Figure 13). With some further reactions, Kappe and co-workers obtained 4-(pyrazol-1-yl)carboxanilides **23** [20].

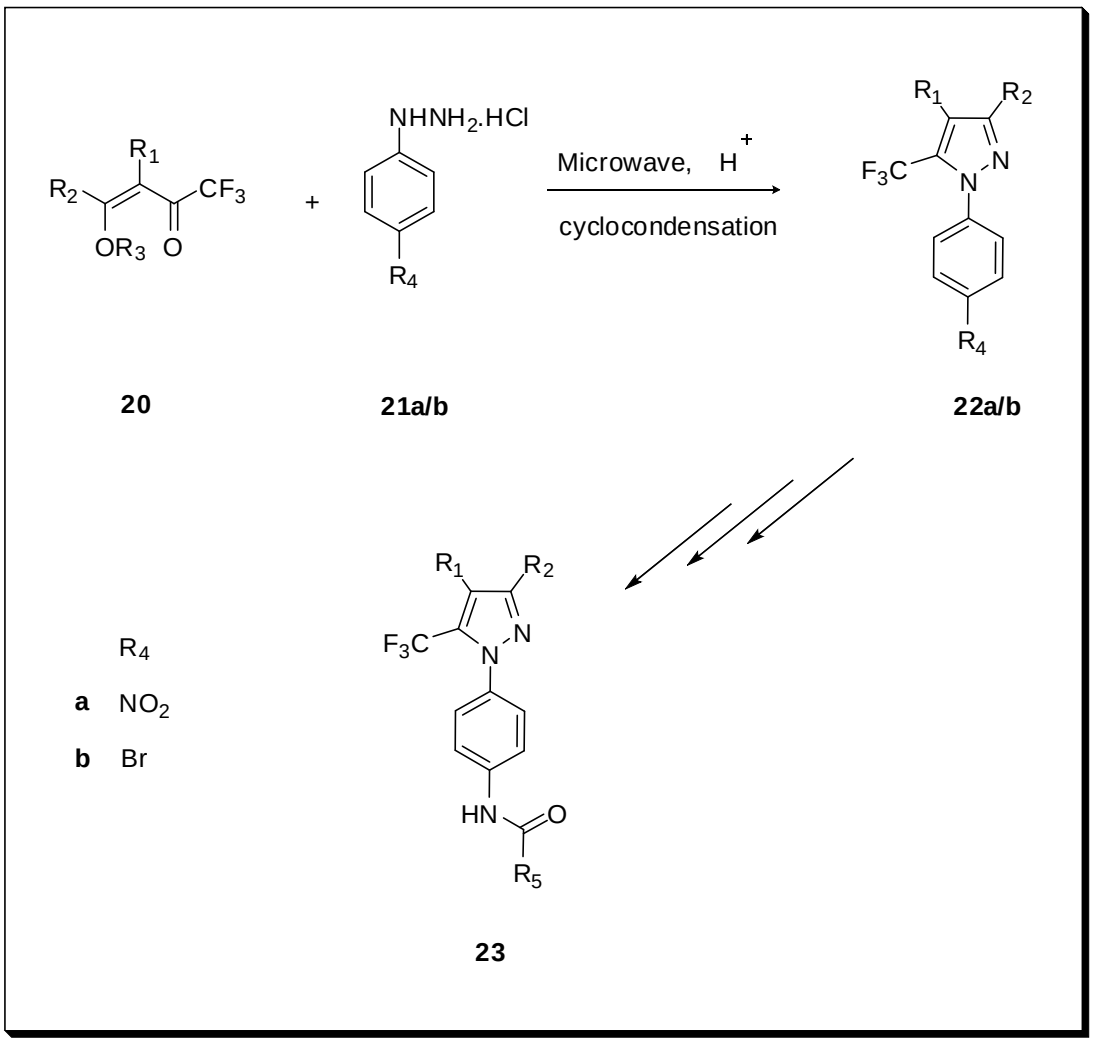


Figure 13. Synthesis of 4-(pyrazol-1-yl)carboxanilides (**23**).

In a recent study, Bertrand and co-workers synthesized pyrazole derivatives **25** from internal alkynes **24** and hydrazines by using a gold catalyst. They used a cyclic alkyl amino carbene-gold(I) catalyst (CAACAuCl) for hydroamination of alkynes or allenes (Figure 14) [21].

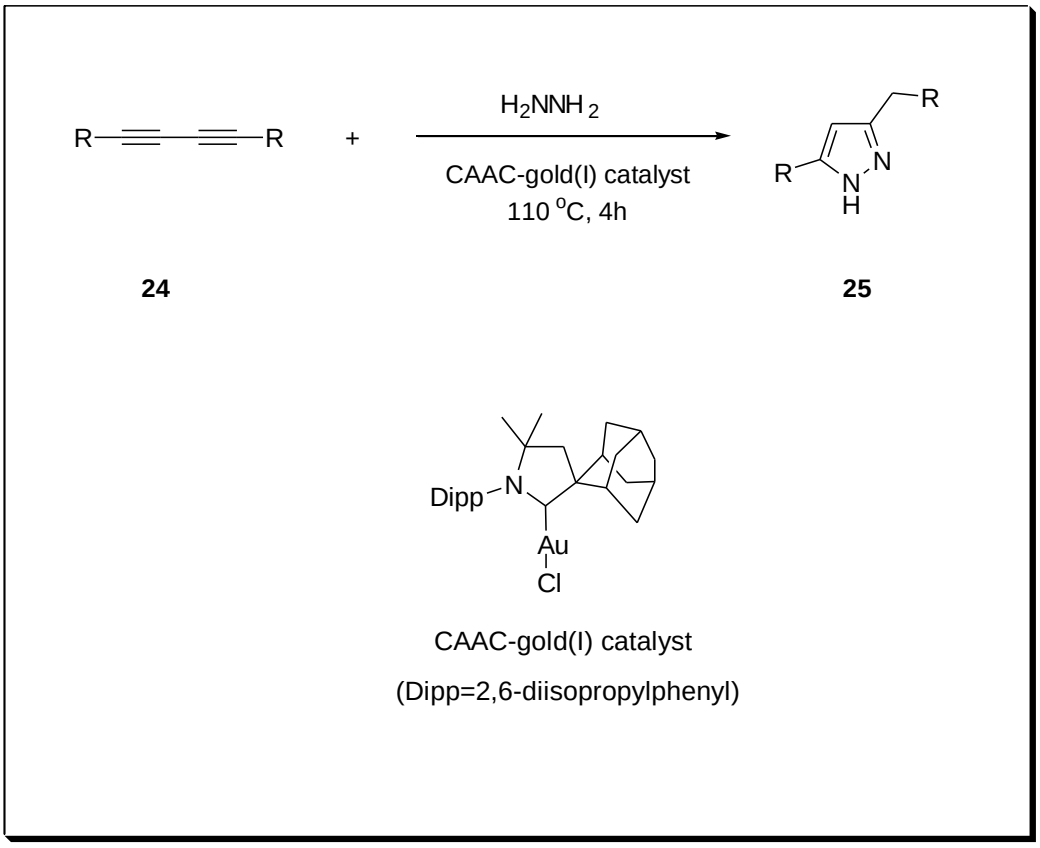


Figure 14. Synthesis of pyrazoles with gold catalyzed hydroamination of alkynes with hydrazines.

Kimpe and co-workers added new synthesis methods for fluorinated pyrazoles to the literature with their recent studies. They treated α-cyano-α-monofluoroketones **26a** with hydrazine to afford 3-amino-4-fluoropyrazoles **27** (Figure 15). In addition to that, the reaction of α-cyano-α,α-difluoroketones **26b** with hydrazine in refluxing isopropanol gave 3-unsubstituted 4-fluoropyrazoles **28** [22].

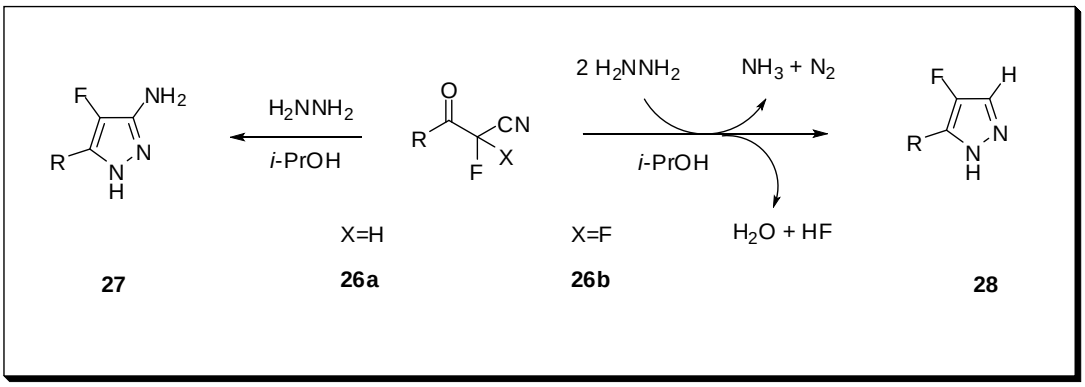


Figure 15. Synthesis of fluorinated pyrazole derivatives **27** and **28**.

Langer and co-workers reported one-pot synthesis of pyrazole-5-carboxylates **31** by the regioselective cyclizations of hydrazone dianions **29** with diethyl oxalate (**30**), as illustrated in Figure 16 [23].

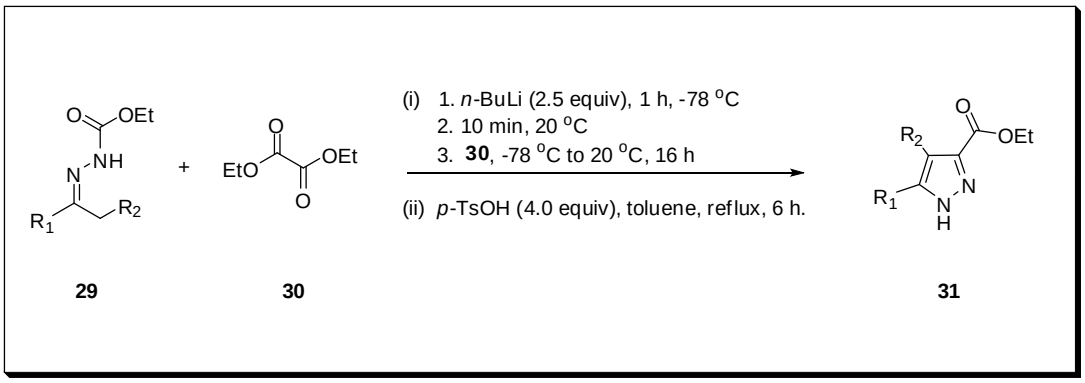
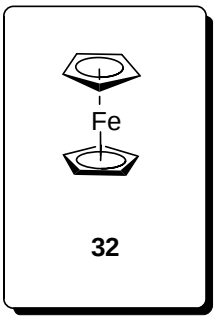


Figure 16. One-pot synthesis of pyrazole-5-carboxylates.

1.2 Ferrocene and biological importance of ferrocene derivatives

After the discovery of ferrocene (**32**) in 1951, many chemists have studied on ferrocene based research projects because ferrocene derivatives exhibit high stability and important biological activities such as antianemic, antibacterial, antitumor

properties and they are commonly used as ligands for asymmetric catalysis [24]. Ferrocene has a structure that iron metal centered between two cyclopentadienyl rings (Figure 13). It was synthesized first in 1951 separately by Miller, Tebboth and Tremaine, and also by Kealy and Pauson. However, the real double-cone sandwich structure was suggested by Fischer, Wilkinson and Woodward in 1952 (Figure 17) [25].



32

Figure 17. Structure of ferrocene (**32**).

The synthesis of ferrocene is achieved by the deprotonation of cyclopentadiene with KOH followed by the reaction of the resulting cyclopentadienyl anion with $FeCl_2$ in DMSO (Figure 18) [26].

32

Figure 18. Synthesis of ferrocene (**32**).

Since ferrocene behaves as electron rich aromatic compound, many derivatives can be synthesized from ferrocene. Friedel-Crafts acylation and alkylation,

dimethylamino-methylation, Vilsmeier formylation and mercuration reactions are some of the examples for the reactions of ferrocene (Figure 19) [27].

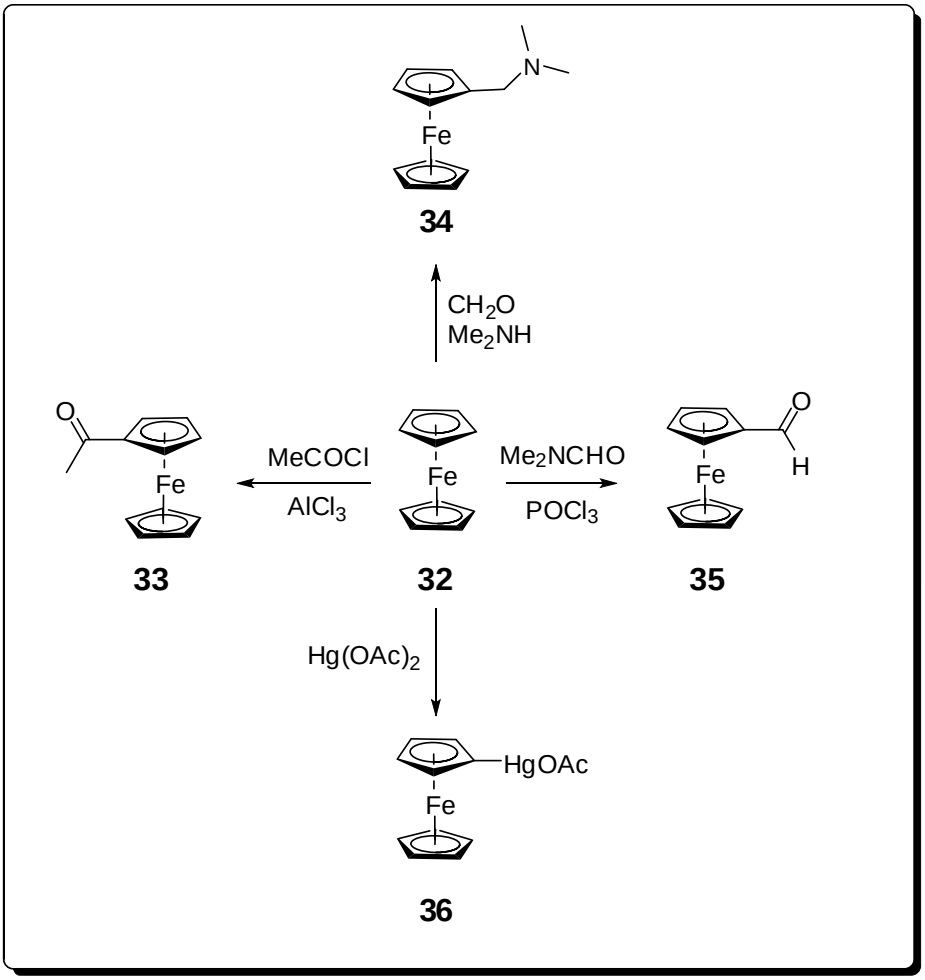


Figure 19. Typical substitution reactions of ferrocene (**32**).

Ferrocene has properties like enhanced redox ability, solubility in many solvents, membrane permeation and non-toxicology for body. These characteristics prompted chemists to study how to increase the biological activity of molecules by introducing ferrocene unit [28]. For instance, tamoxifen (**37**) and hydroxytamoxifen (**38**) are used in preventing hormone-dependent breast cancer (Figure 20) [29]. Jaouen and co-workers have synthesized new ferrocenyl derivative of tamoxifen and hydroxytamoxifen, which is called ferrocifen (**39**). They have showed that ferrocifen

(**39**) is more active than tamoxifen and hydroxytamoxifen. Even it can be used in both hormone-dependent and hormone-independent breast cancer. Notably, the best results against breast cancer cells were obtained by the ferrocenophane derivatives (**40**) in 2009 (Figure 20) [30].

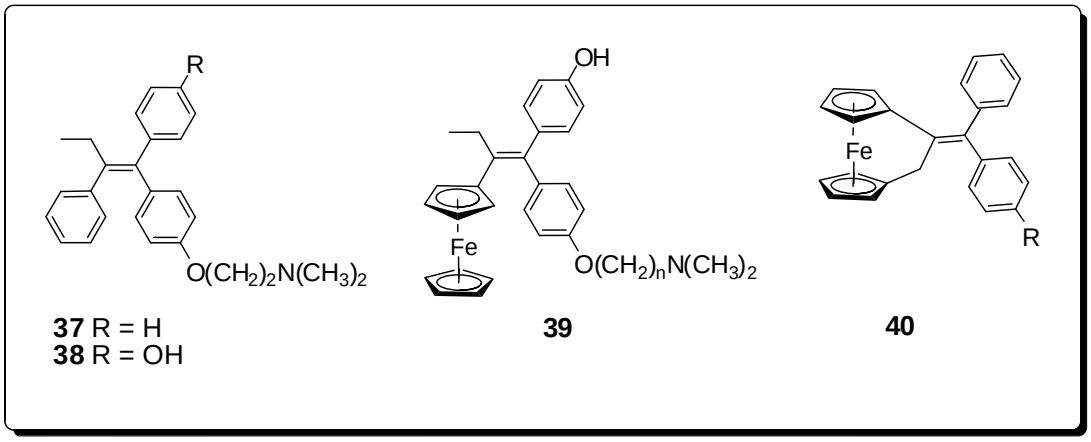


Figure 20. Structures of tamoxifens (**37**), hydroxytamoxifen (**38**), ferrocifens (**39**) and ferrocenophanes (**40**).

Another example of such studies is the synthesis of 5-alkyl-2-ferrocenyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-ones (**41**) (Figure 21). Zhao, Liu and their co-workers synthesized a series of novel pyrazole derivatives and showed that these compounds have inhibitory effects on A 549 lung cancer cell growth [31]. In 2008, they introduced ferrocene unit to their compounds and they synthesized a series of ferrocenyl substituted pyrazole derivatives (**41)** (Figure 21). They showed that ferrocenyl substituted pyrazole derivatives (**41**) are more effective on A 549 lung cancer cell growth than the other ones. In addition, they compared these compounds with a known anticancer drug, 5-FU, in the same conditions and they reached the results that ferrocenyl pyrazoles have more effective on the growth of A 549 cells than 5-FU (Figure 21) [32].

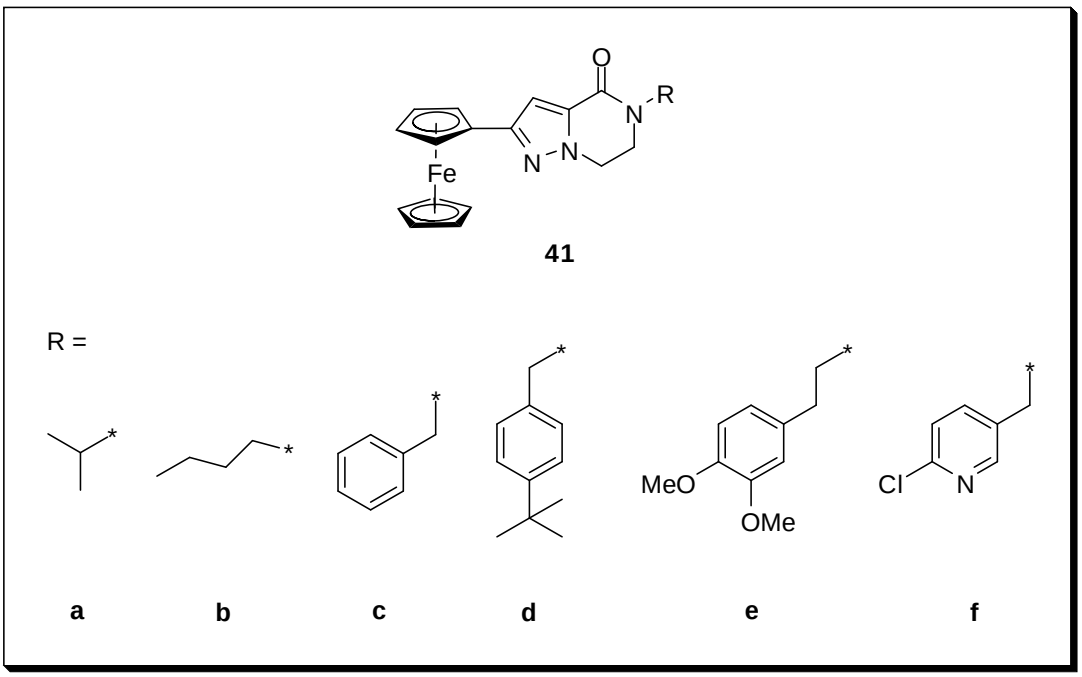


Figure 21. Derivatives of 5-alkyl-2-ferrocenyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-ones (**41**).

Under the light of these studies and knowledge from the literature, it has been thought that ferrocene-introduced pyrazole derivatives may have important biological activities. Therefore, many chemists have dealed with such studies more in the recent years [32].

1.3 Selenium and biological importance of selenium

The elemental selenium was discovered in 1817 by Berzelius [33]. Its atomic number is 34 and it has been classified both as metal and as nonmetal. It is widely distributed in the earth's crust [34]. The main sources of selenium for commercial applications are copper bearing ores and sulfur deposits. It can be also obtained as by-products of zinc, nickel and silver [35].

Selenium is an essential mineral for human body and it is required in small amounts. It is naturally found in plants, seafood, meat and meat products [36]. Recommended Dietary Allowance (RDA) is 20-40 μg/day for children and 55-60 μg/day for adults [37]. High dosage of selenium consumption may have toxicity effect and the symptoms can be fatigue, hair loss and white blotchy nails. On the other hand, deficiency of selenium may cause some diseases such as cardiomyopathy, cancer, endemic osteoarthropathy and anemia [38]. Keshan disease, a congestion cardiomyopathy in Chinese children, can be an example of selenium deficiency diseases [39].

Selenium is a very important trace element biologically because it is a component of some enzymes, proteins and nucleic acids. For example, selenocysteine aminoacid (**42**), which takes part in protein synthesis, has selenium in its structure (Figure 22) [40].

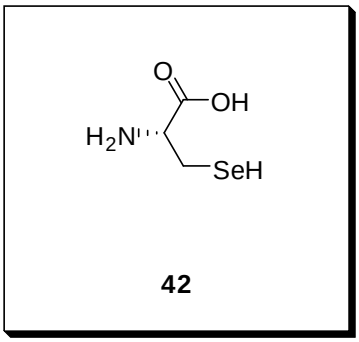
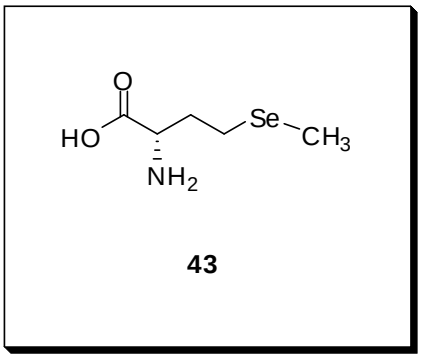


Figure 22. Structure of selenocysteine aminoacid (**42**).

The best-known biochemical function of selenium is its anti-oxidant role in the body. Being incorporated with glutathione peroxidase enzyme, it protects cells against peroxidation stress [41]. On the other hand, selenium has decreasing effects on the cancer hazard and the acquired immunodeficiency syndrome (AIDS). Also, it slows down the aging and favors the treatment of cardiological diseases [42].

These biologically important properties of selenium have attracted the interest of the chemists and many organoselenium compounds have been synthesized so far. Importantly, recent studies have shown that organoselenium compounds are seen less toxic than inorganic selenium forms [43]. An example of organoselenium compounds in medical usage can be ^{75}Se-selenomethionine (**43**), which is used in pancreatic scanning (Figure 23) [44].



43

Figure 23. Structure of selenomethionine (**43**) used in pancreatic scanning.

Many of the organoselenium compounds have been studied as potential antibacterial, antifungal, anesthetic, anti-inflammatory and anti-tumor agents [35]. For instance, 1*H*-purine-6(9*H*)-selenone (**44**) has antibacterial effect while 4-amino-1,2,5-selenadiazole-3-carboxylic acid (**45**) has antifungal property (Figure 24). Alkylseleno derivatives of falicaine (**46**) have anesthetic effect (Figure 24). Benzylselenovaleric acid (**47**) has anti-inflammatory activity and selenoguanine (**48**) has antitumor property (Figure 24) [35].

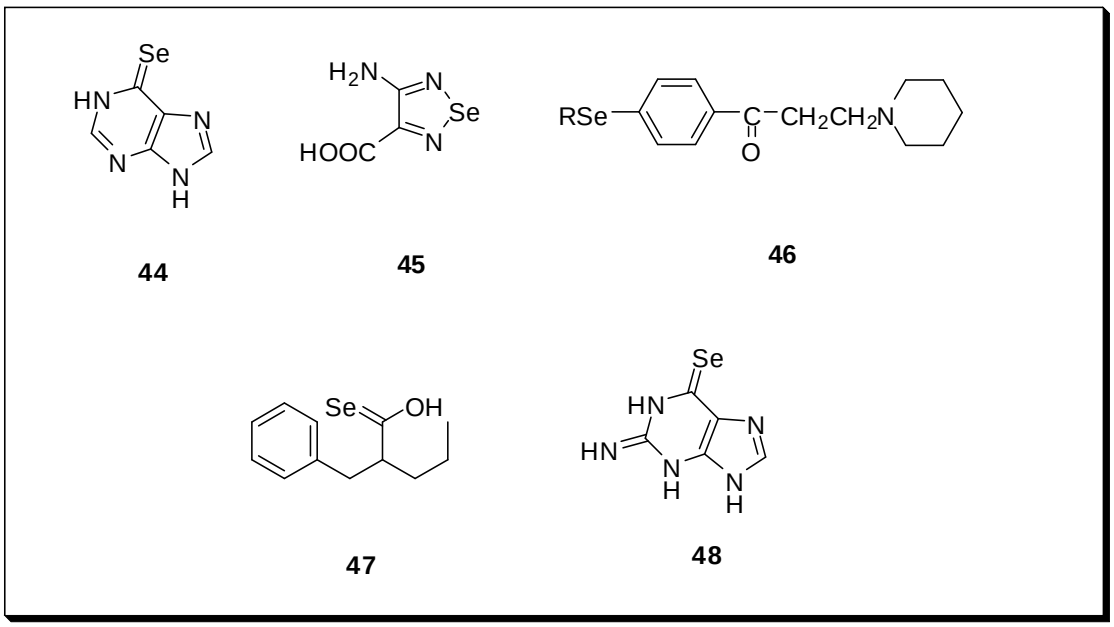


Figure 24. Examples of biologically active organoselenium compounds **44-48**.

1.4 Ferrocenyl pyrazoles

As mentioned before, ferrocene and pyrazoles have many fascinating biological properties. Their potentials in drug chemistry prompted Zora research group to combine them to synthesize new ferrocenyl pyrazole derivatives, which may have high biological activities [45]. The reaction of (2-formyl-1-chlorovinyl)ferrocene (**49**) with hydrazines was investigated to afford ferrocenyl pyrazoles (Figure 25). In these reactions, two isomers of pyrazoles, namely 1-alkyl/aryl-5-ferrocenylpyrazoles (**50**) and/or 1-alkyl/aryl-3-ferrocenylpyrazoles (**51**), were formed. In most cases, the former was the single or the major product of the reactions (Figure 25) [45].

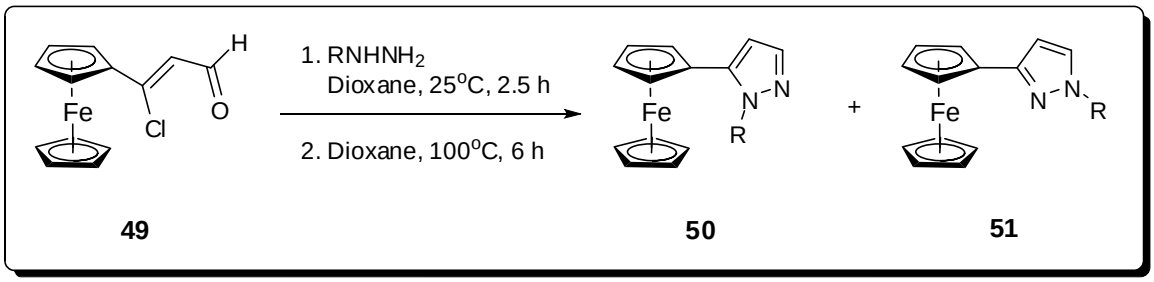


Figure 25. Synthesis of ferrocenyl pyrazoles by the reaction of (2-formyl-1-chlorovinyl)ferrocene (**49**) with hydrazines.

In addition to this study, they synthesized ferrocenyl pyrazoles **50** and **51** by the reaction of 3-ferrocenylpropynal (**52**) with hydrazinium salts (Figure 26) [46].

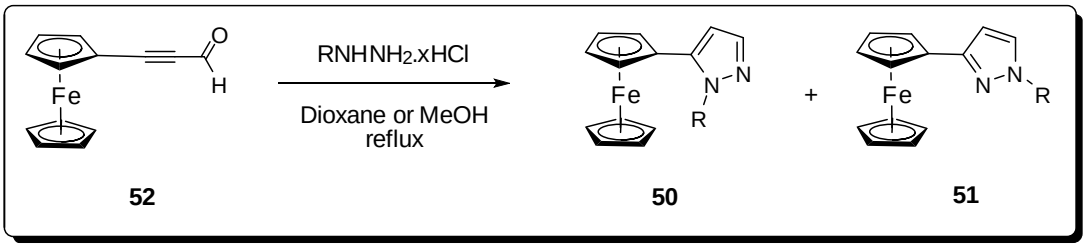


Figure 26. Synthesis of ferrocenyl pyrazoles by the reaction of 3-ferrocenylpropynal (**52**) with hydrazinium salts.

Moreover, Zora research group synthesized 3-ferrocenylpropynal hydrazones (**53** ***Z*,** **53** ***E***) by the reaction of 3-ferrocenylpropynal (**52**) with hydrazines and then examined their electrophilic cyclizations to pyrazoles derivatives (Figure 27). They showed that when treated with moleculer iodine and copper(I) iodide, 3-ferrocenylpropynal hydrazone (**53**) gave 5-ferrocenyl-4-iodopyrazoles (**54**) and 5-ferrocenylpyrazoles (**55**), respectively (Figure 27) [47, 48].

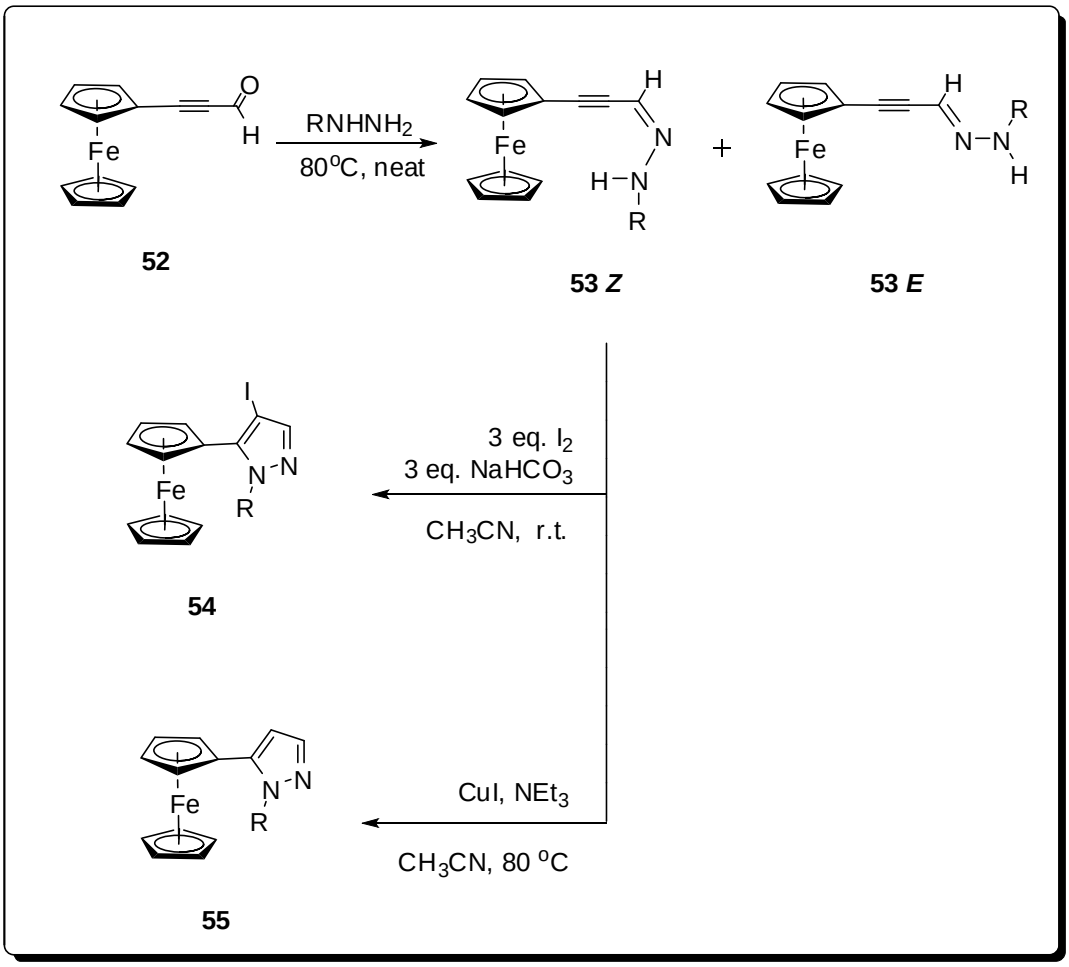


Figure 27. Synthesis of 5-ferrocenyl-4-iodopyrazoles **54** and 5-ferrocenylpyrazoles **55**.

1.5 Electrophilic cyclizations

Electrophilic cyclizations are known as the intramolecular cyclizations of nucleophile containing carbon-carbon unsaturated bonds in the presence of an electrophile. In such reactions, cationic intermediates are formed and they can easily undergo intramolecular cyclization to form more stable aromatic ring structures [49]. Most common used electrophiles are I_2, Br_2, ICl, NBS, NIS, *p*-$NO_2C_6H_4SCl$, $SeCl_2$, PhSeCl and as functional groups alkyl, aryl, vinyl or any benzyl groups can be chosen (Figure 28) [50].

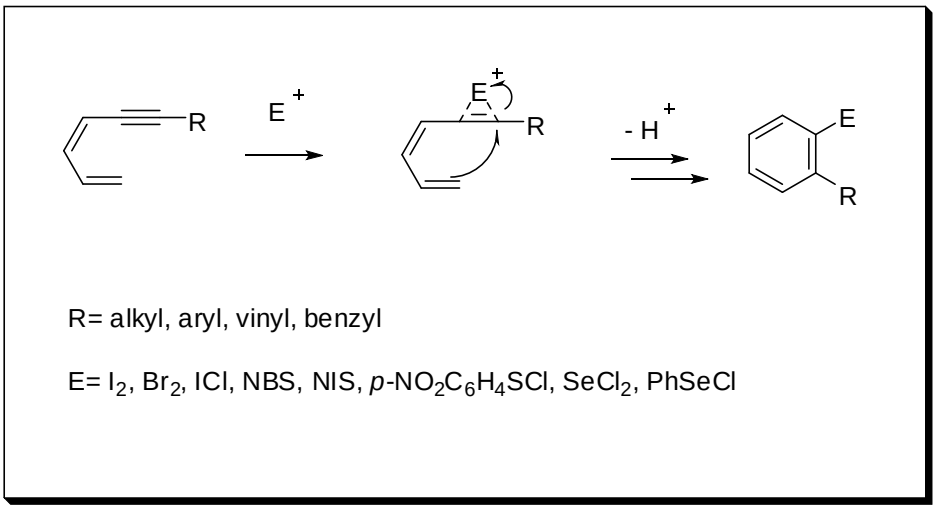


Figure 28. Schematic representation of electrophilic cyclizations.

1.6 The aim of the study

As mentioned before, pyrazoles have many biologically important properties and introducing both ferrocene and selenium moieties to pyrazoles that can provide new substances with enhanced biological activities. Although pyrazoles have been studied extensively, there are very few studies about ferrocenyl pyrazole derivatives. Zora research group has recently synthesized some ferrocenyl pyrazole derivatives [45-47].

In the light of these studies, the synthesis of 5-ferrocenyl/aryl-4-(phenylselenyl)-1*H*-pyrazole derivatives **69**-**81** has been aimed by employing the electrophilic cyclization of α,β-alkynic aldehydes **52**, **56**, **57**, **58** with phenylselenyl chloride (Figure 29).

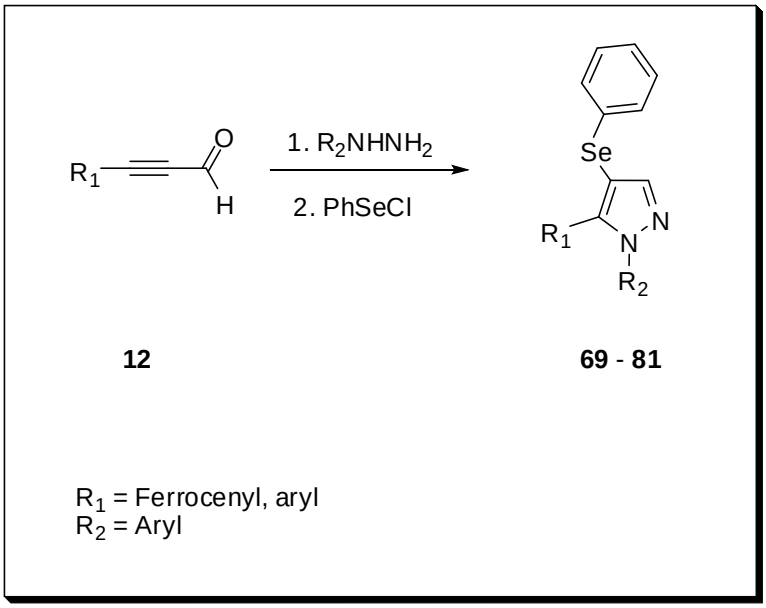


Figure 29. Synthesis of 5-ferrocenyl/aryl-4(phenylselenyl)-1*H*-pyrazole derivatives (**69** - **81**).

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis of ferrocenyl- and aryl-substituted propargyl aldehydes

In first part of the study, the synthesis of starting materials, 3-ferrocenylpropynal (**52**), 3-phenylpropiolaldehyde (**56**), 3-*p*-tolylpropiolaldehyde (**57**) and 3-(4-methoxyphenyl)propiolaldehyde (**58**), were carried out. For the synthesis of 3-ferrocenylpropynal (**52**), ethynylferrocene (**59**) was first synthesized starting from ferrocene (**32**) by using a known procedure from the literature (Figure 30). After the formation of ethynylferrocene (**59**), the formylation with DMF gave the desired starting material 3-ferrocenylpropynal (**52**) [48].

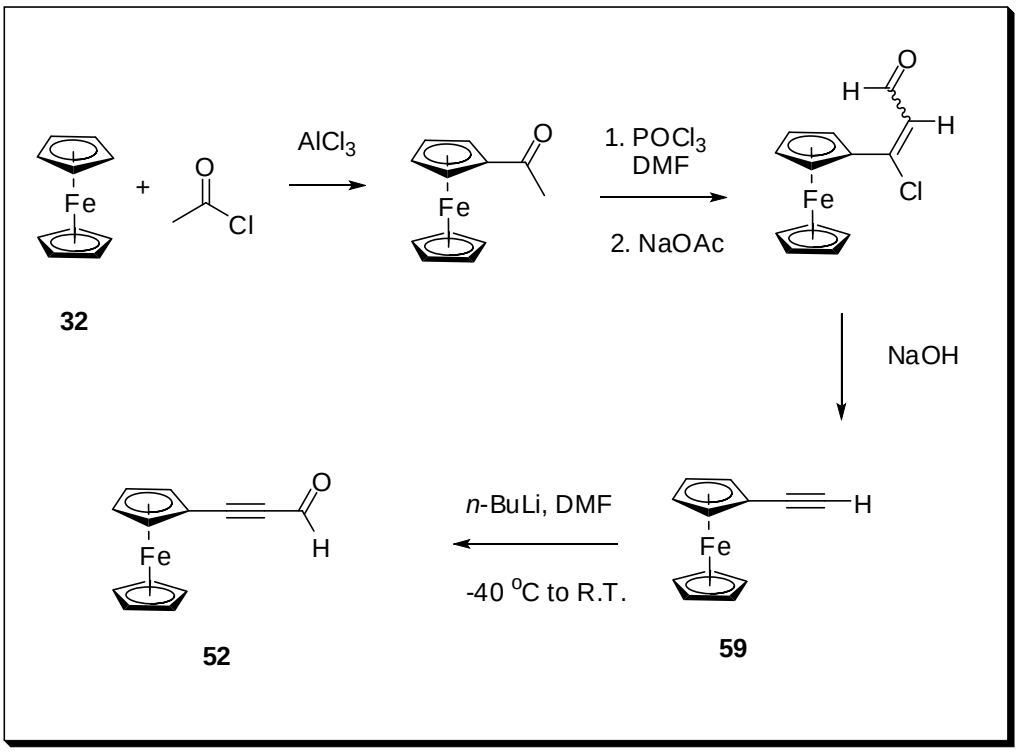


Figure 30. Synthesis of 3-ferrocenylpropynal (**52**).

3-Aryl substituted propargyl aldehydes (**56**, **57** and **58**) were synthesized from the corresponding terminal alkynes, ethynylbenzene (**60**), 1-ethynyl-4-methylbenzene (**61**) and 1-ethynyl-4-methoxybenzene (**62**). Terminal alkynes were first reacted with *n*-BuLi in THF at -40 °C and then with DMF to give 3-aryl substituted propargyl aldehydes (Figure 31) [51].

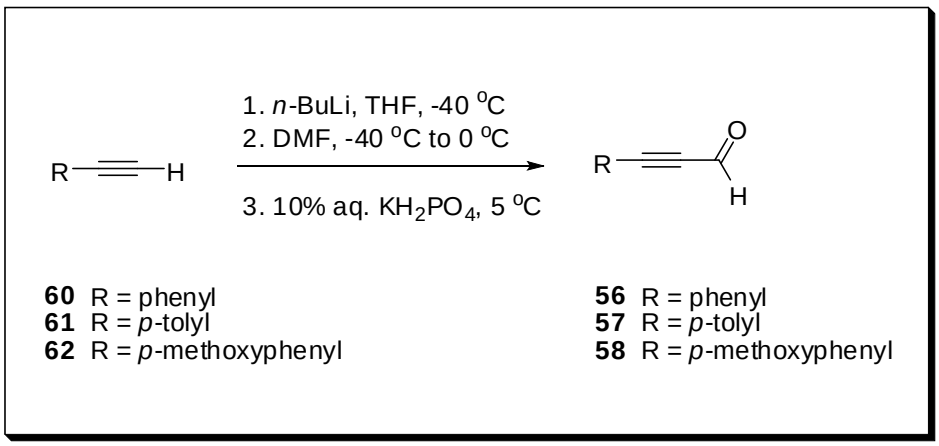


Figure 31. Synthesis of 3-aryl substituted propargyl aldehydes.

In summary, four different propargyl aldehydes, namely 3-ferrocenylpropynal (**52**), 3-phenylpropiolaldehyde (**56**), 3-*p*-tolylpropiolaldehyde (**57**) and 3-(4-methoxyphenyl)propiolaldehyde (**58**), were synthesized as depicted in Figure 32 [51].

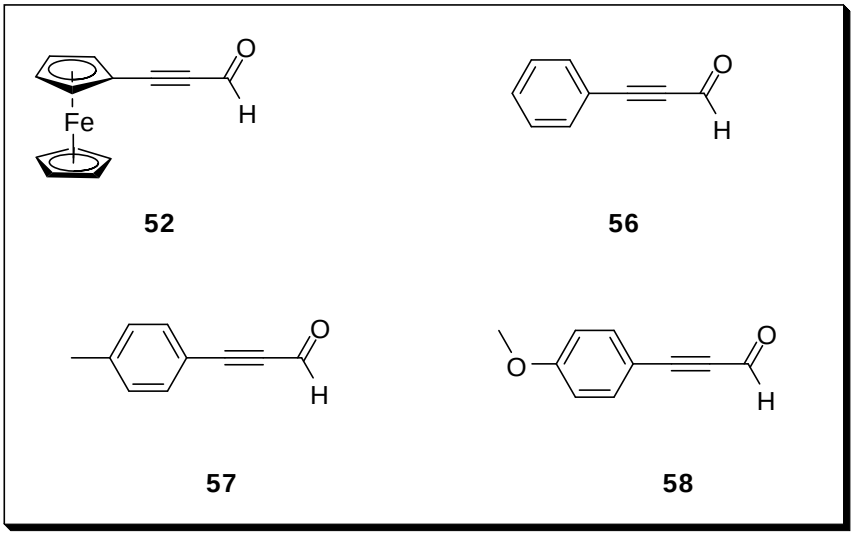


Figure 32. Structures of the synthesized propargyl aldehydes **52**, **56**, **57** and **58**.

2.2 Synthesis of 5-ferrocenyl and 5-aryl pyrazole derivatives

After the preparation of propargyl aldehydes, the synthesis of 5-ferrocenyl/aryl-4-(phenylselanyl)-1*H*-pyrazole derivatives (**69**-**81**) was performed with the commercially available hydrazine derivatives, namely phenylhydrazine (**63**), (4-(trifluoromethyl)phenyl)hydrazine (**64**), (3-chloro-4-fluorophenyl)hydrazine (**65**), (2,5-difluorophenyl)hydrazine (**66**) and (2-nitrophenyl)hydrazine (**67**), the structures of which are shown in Figure 33.

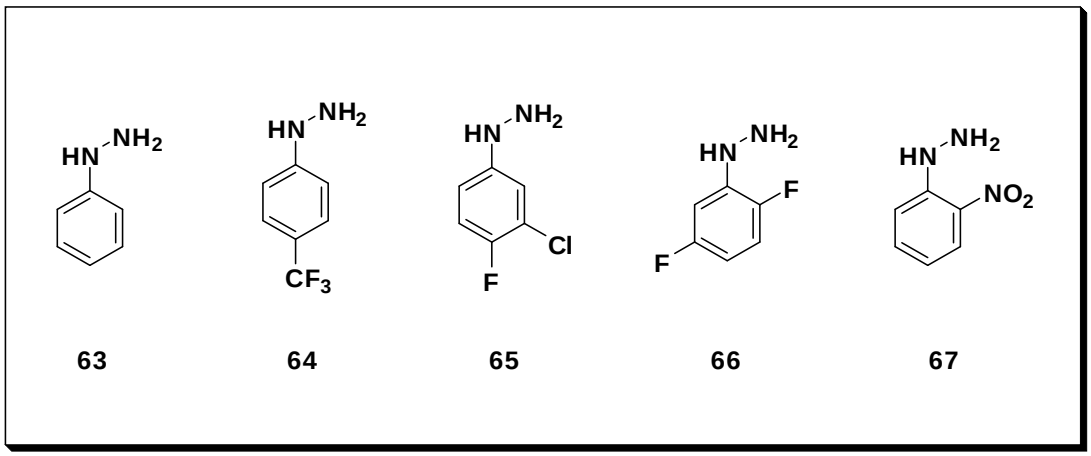


Figure 33. Hydrazine derivatives **63**-**67** employed in synthesis of 5-ferrocenyl/aryl-4-(phenylselanyl)-1*H*-pyrazole derivatives.

Condensation reactions of propargyl aldehydes with hydrazines were carried out at 80 ^{o}C under neat conditions for 1 hour. It is well known that the reactions of propargyl aldehydes with hydrazines give *E* and *Z* isomers of α,β-alkynic hydrazones **68** (Figure 34) [51]. *Z* isomers are the major products of these reactions and as time passes *E* isomers are turned to *Z* isomers. In addition, *E* isomers of aryl substituted hydrazones are turned to *Z* isomers easily but this conversion is slow for ferrocenyl substituted hydrazones [51]. For the synthesis of targeted pyrazoles, the requisite hydrazones were first synthesized in situ and then treated with PhSeCl for the electrophilic cyclization reactions of these hydrazones to afford corresponding 4-

(phenylselenyl)pyrazoles as depicted in Figure 34. In summary, 4-(phenylselenyl)-pyrazoles were synthesized in one-pot manner.

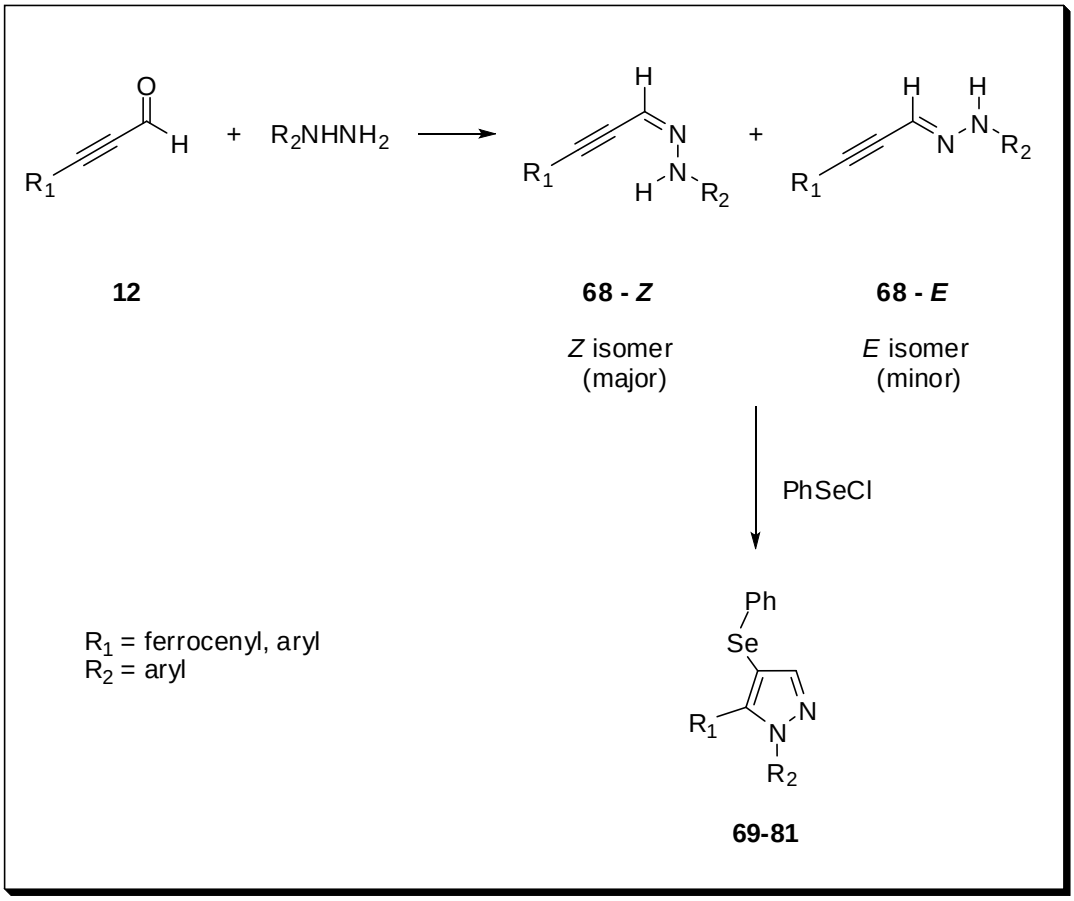
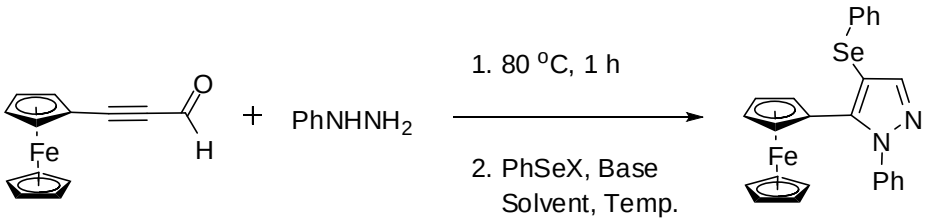


Figure 34. One-pot synthesis of pyrazoles **69**-**81** through the in situ prepared hydrazones **68**-***Z*** and/or **68**-***E***.

In order to optimize the reaction conditions, various reactions were performed for the high yields of 4-(phenylselenyl)pyrazoles. Optimization reactions were carried out with 3-ferrocenylpropynal (**52**) and phenylhydrazine (**63**) as illustrated in Table 1. Preparation of hydrazones was achieved under neat conditions at 80 ^{o}C. After the formation of hydrazones, the effect of base, electrophile, solvent and temperature was investigated for these in situ reactions. As seen in Table 1, the effect of base was depicted in entries 1-4, and $NaHCO_3$ was found to be the most efficient base. The effect of temperature was then investigated and CH_3CN was used as solvent.

Obviously, it was seen that temperature is not effective for these reactions (Entries 5 and 6). As noted in entries 3, 5 and 10, the effect of solvent was investigated and DCM was found as the most convenient solvent. As electrophile, PhSeBr were compared with PhSeCl for the same conditions. As depicted in Entries 7, 8 and 9, PhSeCl was observed to be more efficient than PhSeBr. To sum up, optimum conditions were obtained from the Entry 3 for the synthesis of ferrocenyl substituted pyrazoles. In other words, the reactions were carried out with PhSeCl in DCM in the presence of $NaHCO_3$ at room temperature.

Table 1. Optimization studies for the synthesis of 5-ferrocenyl-4-(phenylselenyl)pyrazoles.



Entry	X	Solvent	Temp. (°C)	Base (2 eq)	Yield (%)
1	Cl	DCM	R.T.	-	53
2	Cl	DCM	R.T.	Na_2CO_3	40
3	Cl	DCM	R.T.	$NaHCO_3$	70
4	Cl	DCM	R.T.	LiCl	43
5	Cl	CH_3CN	R.T.	$NaHCO_3$	60
6	Cl	CH_3CN	82	$NaHCO_3$	57
7	Br	DCE	R.T.	$NaHCO_3$	50
8	Br	DCM	R.T.	-	64
9	Br	DCM	R.T.	$NaHCO_3$	45
10	Cl	DCE	R.T.	$NaHCO_3$	58

We also investigated the synthesis of 4-(phenylselenyl)pyrazole **69** in stepwise manner and compared with its one-pot synthesis, as illustrated in Scheme 35. First, the reaction of 3-ferrocenylpropynal (**52**) with phenyl hydrazine (**63**) was employed, which yielded *E* and *Z* isomers of hydrazone **53**. After the isolation of *Z* isomer of hydrazone **53** by column chromatography in 54% yield, it was subjected to the reaction with phenylselenyl chloride and 4-(phenylselenyl)pyrazole **69** was obtained in 70% yield. In summary, the stepwise synthesis afforded pyrazole **69** in 38%

overall yield, which was lower than its one-pot synthesis (70% yield). As depicted in Figure 35, one-pot synthesis is more effective way of synthesizing 5-ferrocenyl-4-(phenylselenyl)pyrazoles and the synthesis of corresponding pyrazoles was performed in one-pot manner.

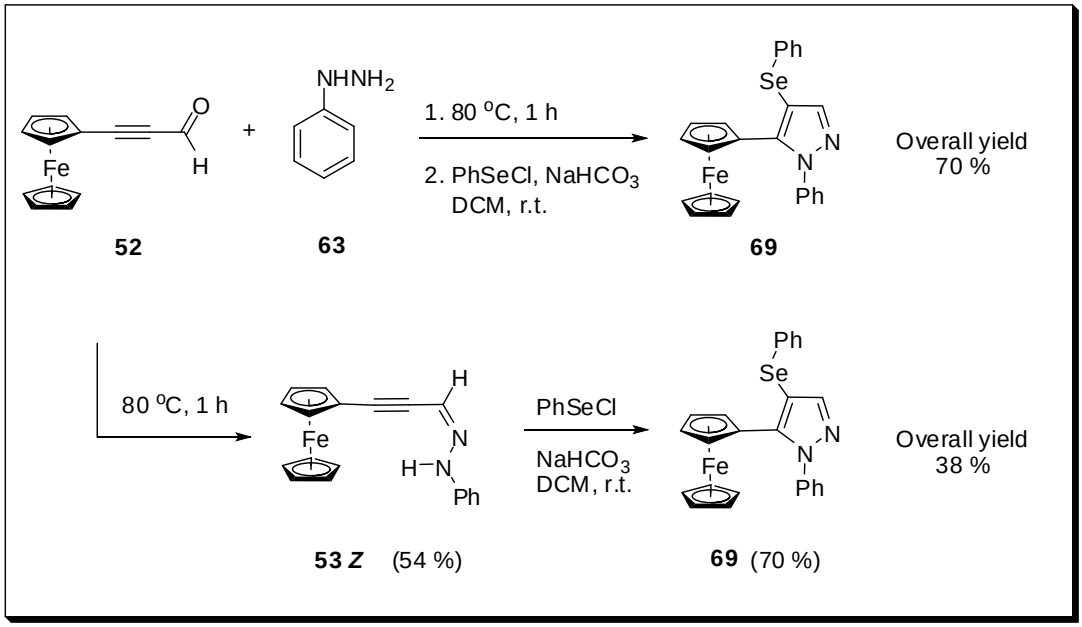


Figure 35. Comparison of one-pot and stepwise syntheses of pyrazole derivative **69**.

After the determination of optimum conditions, the synthesis of targeted pyrazoles was performed. At first, 5-ferrocenyl-4-(phenylselenyl)pyrazole derivatives **69-72** were synthesized in good yields. The highest yield (82%) was obtained for 1-(2,5-difluorophenyl)-4-(phenylselenyl)-5-ferrocenyl-1*H*-pyrazole (**72**) while the lowest yield (62%) was observed for 1-(4-(trifluoromethyl)phenyl)-4-(phenylselenyl)-5-ferrocenyl-1*H*-pyrazole (**70**). The structures and yields of ferrocenyl substituted pyrazoles are given in Figure 36.

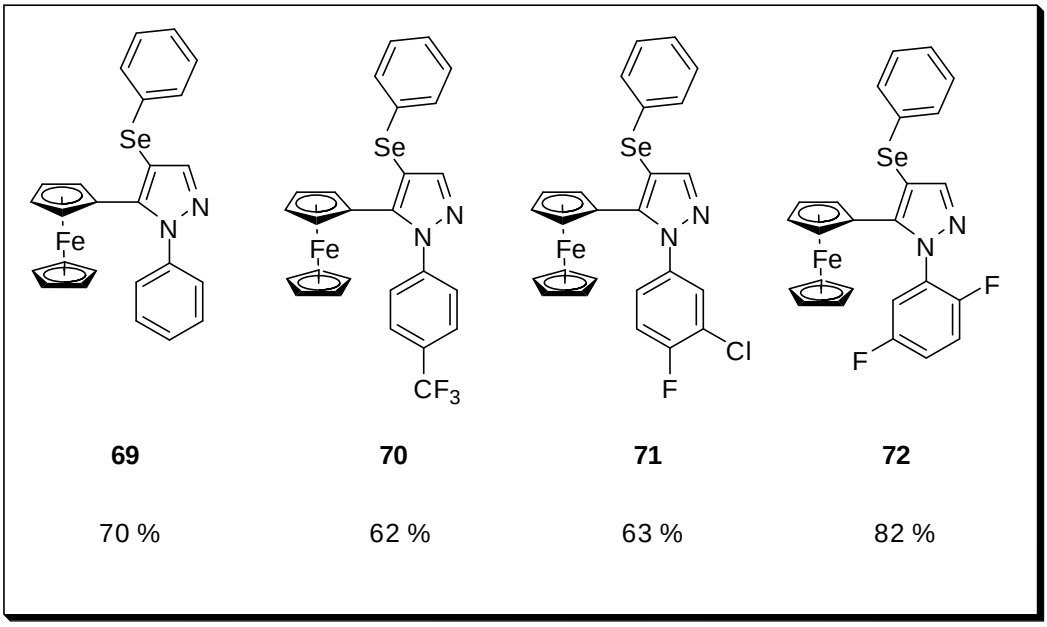
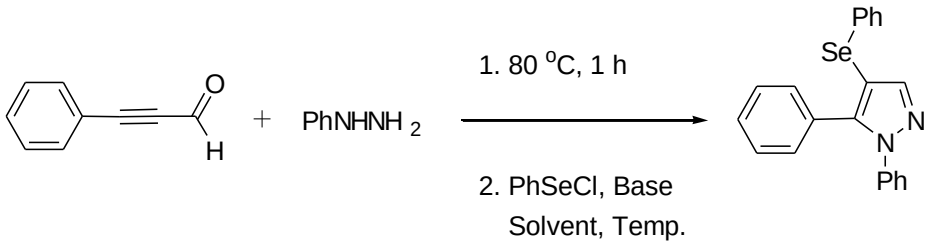


Figure 36. Structures of the synthesized ferrocenyl substituted pyrazoles **69**-**72**.

Next, the synthesis of aryl substituted pyrazoles was performed, but under the optimized conditions, the yields were found to be very low. For this reason, we decided to optimize the conditions for the synthesis of aryl substituted pyrazoles. The results are given in Table 2. Best conditions were observed as the same conditions with ferrocenyl substituted pyrazoles except the solvent. As seen in Table 2, the best solvent for aryl hydrazones was found to be DCE (Entry 5).

Table 2. Optimization studies for the synthesis of 5-aryl-4-(phenylselenyl)pyrazoles.



Entry	Solvent	Temp. (°C)	Base (2 eq)	Yield (%)
1	DCM	R.T.	$NaHCO_3$	42
2	CH_3CN	R.T.	$NaHCO_3$	58
3	CH_3CN	R.T.	K_2CO_3	50
4	CH_3CN	82	$NaHCO_3$	60
5	DCE	R.T.	$NaHCO_3$	68

After the optimization of the reaction conditions again, the synthesis of aryl substituted pyrazoles was carried out. 5-Aryl-4-(phenylselenyl)pyrazole derivatives **73-81** were synthesized in moderate to good yields. The highest yield (95%) was obtained for 1-(2-nitrophenyl)-4-(phenylselenyl)-5-(4-methoxyphenyl)-1*H*-pyrazole (**81**) while the lowest yield (25%) was observed for 1-(4-(trifluoromethyl)phenyl)-4-(phenylselenyl)-5-(4-methoxyphenyl)-1*H*-pyrazole (**80**). The structures and yields of aryl substituted pyrazoles are shown in Figure 37.

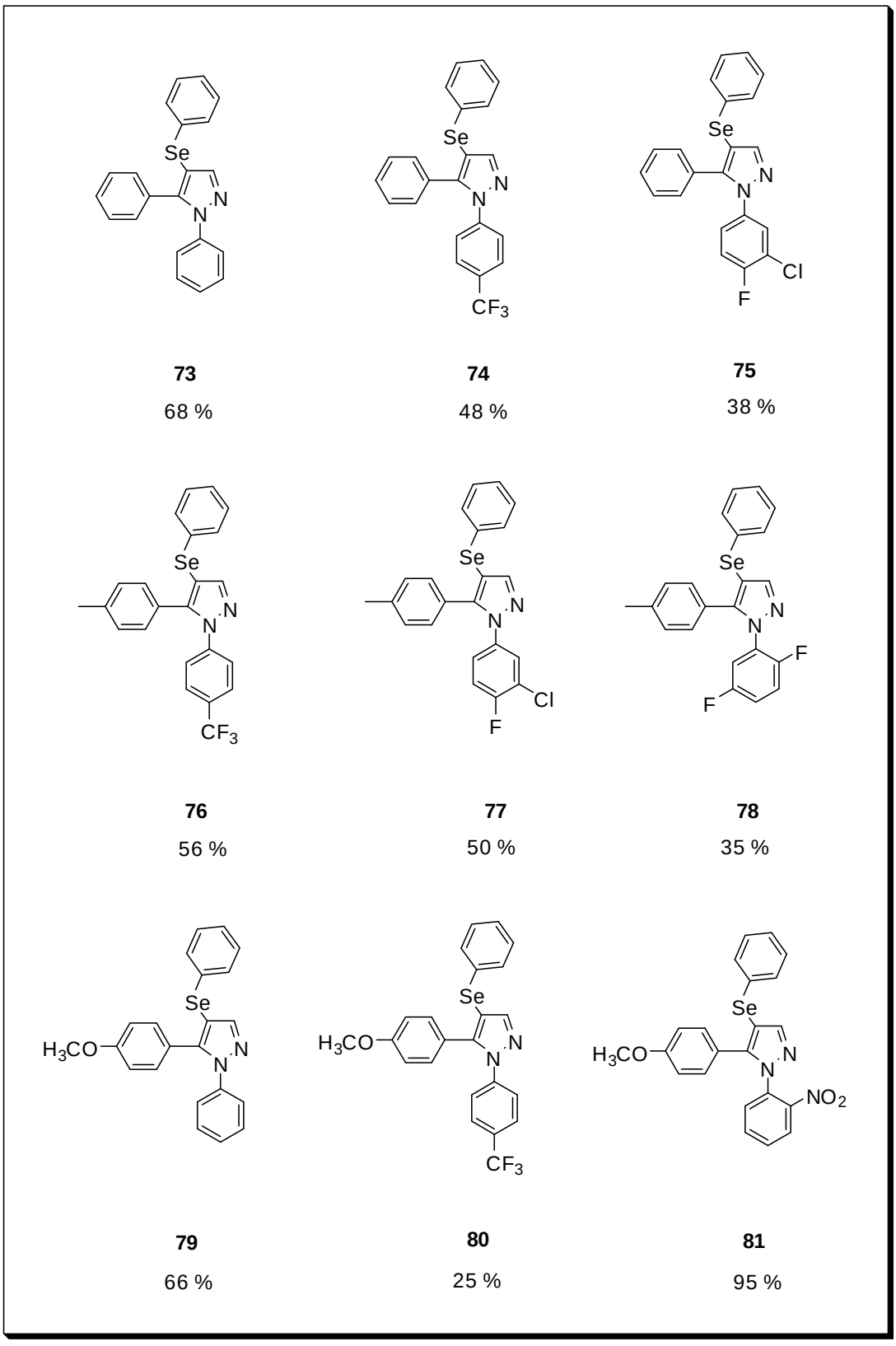


Figure 37. Structures of the synthesized aryl substituted pyrazoles **73-81**.

The structures of the synthesized pyrazole derivatives were identified by NMR spectroscopy. ^{1}H NMR spectrum of 1-phenyl-4-(phenylselenyl)-5-ferrocenyl-1*H*-pyrazole (**69**) is given in Figure 38. The characteristic ferrocene peaks are seen around the 4.0-4.5 ppm region of the spectrum. At 4.09 and 4.24 ppm, two pseudo triplet peaks appear for the four protons of substituted cyclopentadienyl ring and the singlet peak at 3.95 ppm represents the five protons of unsubstituted cyclopentadienyl ring. The proton located at the third position of pyrazole shows a singlet at 7.65 ppm and the ten protons of phenyl groups resonate around 7.38-7.31 ppm.

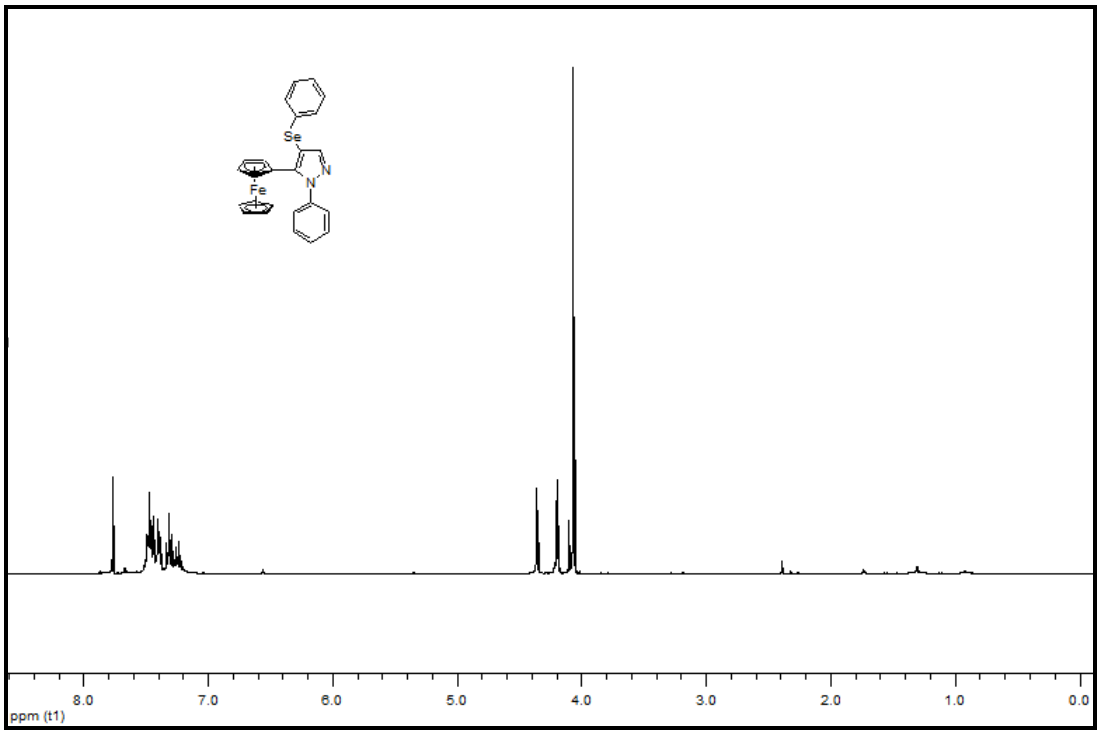


Figure 38. ^{1}H NMR spectrum of pyrazole **69**.

^{13}C NMR spectrum of 5-ferrocenyl-4-(phenylselenyl)-1-phenyl-1*H*-pyrazole (**69**) is shown in Figure 39. Ferrocene carbons give peaks around 73.5-68.5 ppm. The peak at 73.5 ppm belongs to carbon of ferrocene group attached to the pyrazole group. At 69.1 and 68.5 ppm, two peaks appear for the four carbons of substituted cyclopentadienyl ring and the peak at 69.7 ppm represents the five carbons of

unsubstituted cyclopentadienyl ring. The peak at 101.0 ppm belongs to the carbon of pyrazole core at which phenylselenyl group is attached and the peak at 143.8 ppm belongs to ferrocene attached carbon of pyrazole core. The only CH carbon of pyrazole group gives peak at 147.2 ppm. The peak at 139.9 ppm belongs to phenyl carbon attached to selenium and the peak at 140.9 ppm belongs to phenyl carbon attached to nitrogen of pyrazole group. The peaks of remaining six carbons of phenyl groups are around 133.5-126.1 ppm. As a result, ^{1}H and ^{13}C NMR spectra are consistent with the pyrazole structure **69**.

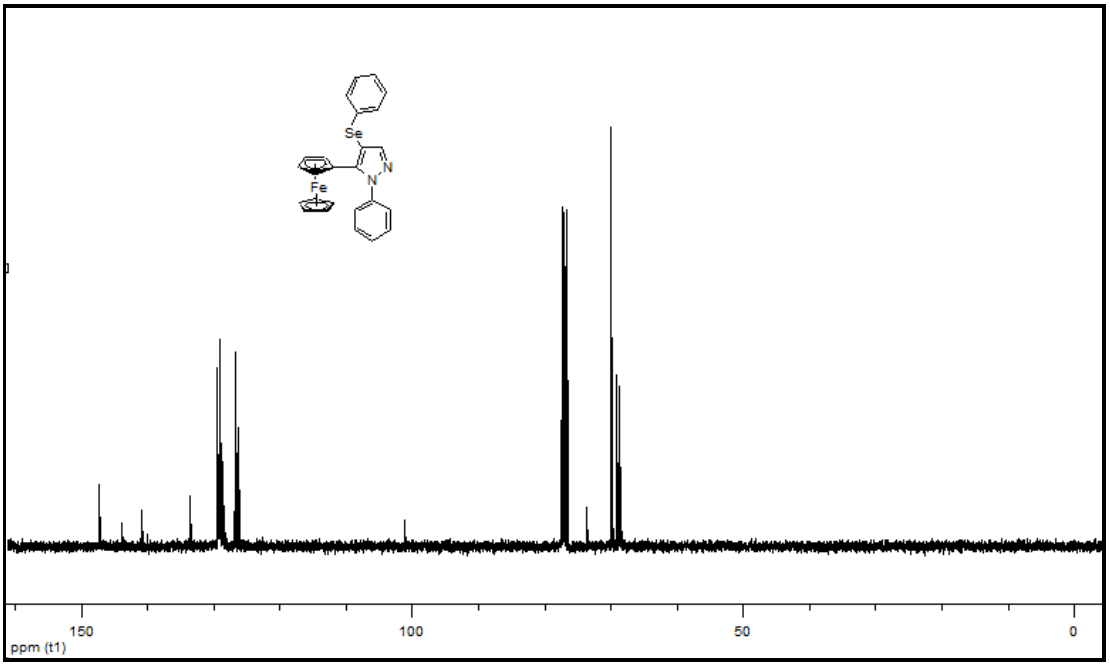


Figure 39. ^{13}C NMR spectrum of pyrazole **69**.

2.3 Proposed reaction mechanism for electrophilic cyclization of α,β-alkynic hydrazones with phenylselenyl chloride.

The proposed mechanism for the formation of 4-(phenyselenyl)pyrazole derivatives is demonstrated in Figure 40. Phenylselenyl chloride reacts with alkyne functionality of the hydrazone to afford the intermediate **82** which initiates the electrophilic

cyclization. Subsequently, secondary nitrogen attacks at the carbon adjacent to selenium atom to yield the protonated pyrazole **83**. Finally, the abstraction of the proton by base results in the formation of targeted pyrazoles (Figure 40).

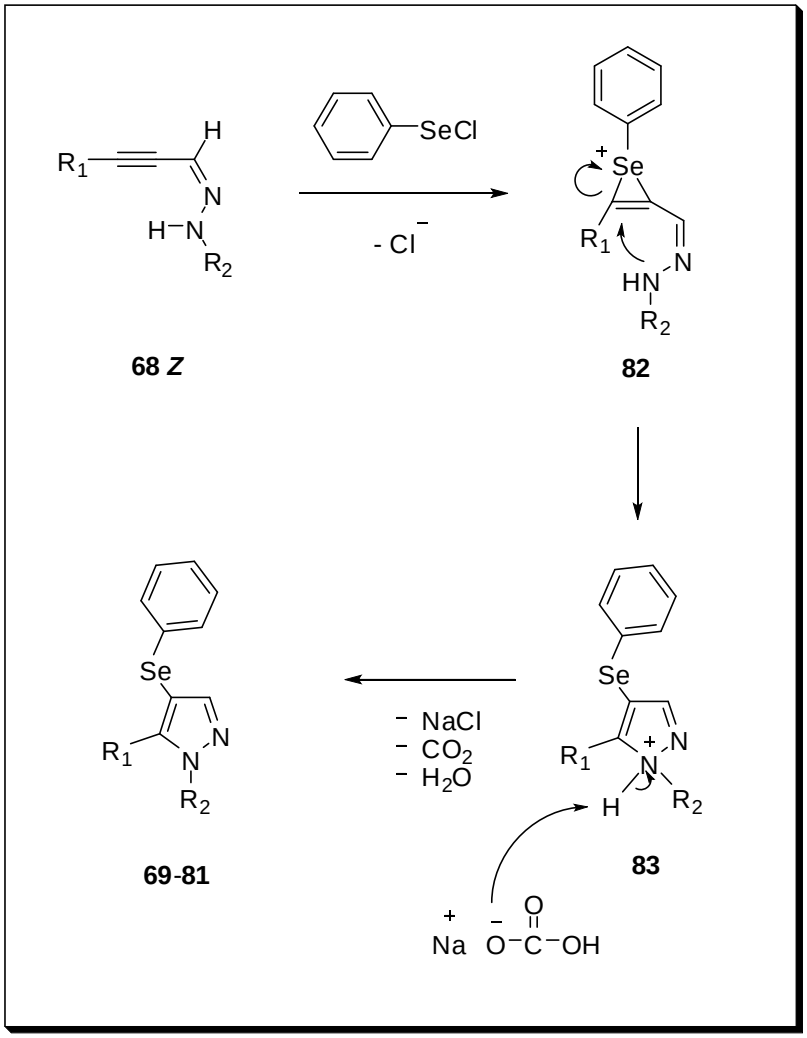


Figure 40. Proposed mechanism for the formation of 4-(phenyselenyl)pyrazoles.

CHAPTER 3

CONCLUSION

In summary, one-pot synthesis of 5-ferrocenyl/aryl-4-(phenylselenyl)-1*H*-pyrazole derivatives has been investigated.

For the first part of the study, starting materials 3-ferrocenylpropynal (**52**), 3-phenylpropiolaldehyde (**56**), 3-*p*-tolylpropiolaldehyde (**57**) and 3-(4-methoxyphenyl)propiolaldehyde (**58**) were synthesized.

In the second part, synthesized propargyl aldehydes were treated with corresponding hydrazines (**63**-**67**) and formation of hydrazones was achieved. In situ formed hydrazones subjected to electrophilic cyclizations with phenylselenyl chloride and pyrazole formations were observed. Then, reaction conditions were optimized for electrophilic cyclization reactions. Optimum conditions were determined as phenylselenyl chloride for electrophile, $NaHCO_3$ for base, room temperature, DCM solvent for ferrocenyl derivatives and DCE solvent for aryl derivatives.

Finally, series of 5-ferrocenyl/aryl-4-(phenylselenyl)-1*H*-pyrazole derivatives (**69**-**81**) were synthesized in one-pot manner via electrophilic cyclization reactions. The highest yield was obtained as 95% for 5-(4-Methoxyphenyl)-4-(phenylselenyl)-1-(2-nitrophenyl)-1*H*-pyrazole (**81**) and the lowest yield was obtained as 25% for 5-(4-Methoxyphenyl)-4-(phenylselenyl)-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (**80**).

The biological activity tests of these derivatives will be carried out by collaborative work.

CHAPTER 4

EXPERIMENTAL

The record of ^{1}H and ^{13}C NMR spectra were made on a Bruker Spectrospin Avance DPX400 Ultrashield (400 MHz) spectrometer. The chemical shifts of compounds were analyzed in parts per million (ppm) downfield from an internal TMS (trimethlsilane) reference. Coupling constants (*J)* were adjusted in hertz (Hz), and the spin multiplicities were represented as the following symbols: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet). DEPT ^{13}C NMR information was shown in parenthesis 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 were adjusted to reciprocal centimeters (cm^{-1}). The intensities of corresponding bands were represented according to the most intense band, and expressed as: br (broad), vs (very strong), s (strong), m (medium), w (weak), vw (very weak). The formations of the products were identified by applying Thin Layer Chromatography (TLC) on commercially prepared 0.25 mm silica gel plates and leaving the plates in solvent mixtures with relative polarity. The polarity of the solvents was adjusted as volume to volume ratio of hexane and ethyl acetate. Then the results were checked under the UV light. All reagents were used directly from their commercial state. The solvents put into reactions were distilled for the purpose of purity. The inert atmosphere was satisfied by slightly positive pressure (ca. 0.1 psi) of argon gas. All glassware and other equipments were dried in the oven before use.

4.1 General Procedure 1. Synthesis of propargyl aldehydes (52 and 56-58)

In approximately 25 ml of dry THF, corresponding alkyne (0.1 mol) was dissolved. The solution was cooled -40 ^{o}C under argon by using a dewar flask equipped with a thermometer and containing ethyl acetate/liquid nitrogen mixture. By flashing with argon, *n*-butyllithium (1.6 M in hexane, 65.4 ml, 0.1 mol) was cautiously added by a glass syringe slowly over 5 minutes, keeping the temperature between -35 and -40 ^{o}C. After the addition was completed, dry *N*,*N*-dimethylformamide (15.5 ml, 0.2 mol) was rapidly added in one portion and the cooling progress was stopped. The mixture was allowed to warm to room temperature. The contents of the reaction flask were poured into a cold mixture prepared from 10% aqueous KH_2PO_4 solution (540 ml, 0.4 mol) and diethylether (500 ml). Layers were separated by extraction. The organic phase was washed with water (4 x 200 ml) and the collected aqueous phase was further extracted with ether. The combined organic extracts were dried over $MgSO_4$ and filtered. The flash chromatography on silica gel by using hexane/ethyl acetate as the eluent afforded the corresponding propargyl aldehyde.

4.1.1 Synthesis of 3-ferrocenylpropynal (52)

General Procedure 1 was followed by using ethynylferrocene (**59**) (1 g, 4.74 mmol), *n*-butyllithium (1.6 M in hexane, 3.1 ml, 4.74 mmol) and dry *N*,*N*-dimethyl-formamide (0.75 ml, 9.5 mmol). The product was purified by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent (930 mg, 82%).

52: ^{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 are in agreement with those reported previously for this compound [53, 54].

4.1.2 Synthesis of 3-phenylpropynal (56)

General Procedure 1 was followed by using phenylacetylene (**60**) (1.1 ml, 10 mmol), *n*-butyllithium (1.6 M in hexane, 6.1 ml, 10 mmol) and dry *N*,*N*-dimethylformamide (1.54 ml, 20 mmol). The product was purified by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent (1.24 g, 97%).

56: ^{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 (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 are in agreement with those reported previously for this compound [55].

4.1.3 Synthesis of 3-*p*-tolylpropynal (57)

General Procedure 1 was followed by using 3-*p*-methylphenylacetylene (**61**) (500 mg, 4.3 mmol), *n*-butyllithium (1.6 M in hexane, 2.6 ml, 4.3 mmol) and dry *N*,*N*-dimethylformamide (0.67 ml, 8.6 mmol). The product was purified by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent (502 mg, 81%).

57: ^{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 (100 MHz, $CDCl_3$): δ 176.9 (CH), 142.1 (C), 133.3 (CH), 129.5 (CH), 116.3 (CH), 95.9 (C), 88.5 (C), 21.7 (CH_3). The spectral data are in agreement with those reported previously for this compound [56].

4.1.4 Synthesis of 3-*p*-(4-methoxyphenyl)propynal (58)

General Procedure 1 was followed by using 3-*p*-methoxyphenylacetylene (**62**) (500 mg, 3.78 mmol), *n*-butyllithium (1.6 M in hexane, 2.3 ml, 3.78 mmol) and dry *N*,*N*-dimethylformamide (0.60 ml, 8.6 mmol). The product was purified by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent (570 mg, 94%).

57: ^{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 (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 are in agreement with those reported previously for this compound [57].

4.2 General Procedure 2. Synthesis of 5-ferrocenyl-4-(phenylselenyl)-1-phenyl-1*H*-pyrazoles (69-72)

In a round-bottomed flask, appropriate propargyl aldehyde (0.1 mmol) and hydrazine (0.1 mmol) were reacted under neat condition at 80 °C for 1 h under argon. Formation of the corresponding hydrazones were followed with TLC analysis. After the formation of corresponding hydrazones in situ, a mixture of PhSeCl (0.2 mmol) and $NaHCO_3$ (0.2 mmol) in 5 ml of DCM were added to the reaction flask, and the resulting mixture was stirred for 1.5 h at room temperature under argon. The completion of the reaction was controlled with TLC analysis. After the reaction was over, DCM was removed under reduced pressure and the reaction mixture was extracted with ethyl acetate (3 x 30 mL). The organic phase was separated, dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography by using 19:1 hexane/ethyl acetate as the eluent to afford the corresponding pyrazole derivative.

4.2.1 5-Ferrocenyl-4-(phenylselenyl)-1-phenyl-1*H*-pyrazole (69)

General procedure 2 was followed by using ferrocenylpropargyl aldehyde (**52**) (50 mg, 0.21 mmol), phenylhydrazine (**63**) (22.7 mg, 0.21 mmol), phenylselenyl chloride (80.4 mg, 0.42 mmol) and $NaHCO_3$ (35.3 mg, 0.42 mmol). The product was purified by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent (71 mg, 70%).

69: ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.65 (s, 1H), 7.38-7.31 (m, 10H), 4.24 (s, 2H), 4.09 (s, 2H), 3.95 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): 147.2 (CH), 143.8 (C), 140.9 (C), 139.9 (C), 133.5 (CH), 129.2 (CH), 128.9 (CH), 128.5 (CH), 126.7 (CH),

126.1 (CH), 101.0 (C), 73.5 (C), 69.7 (CH), 69.1 (CH), 68.5 (CH); IR (neat): 3042.8 (w), 1735.9 (w), 1594.4 (m), 1569.5 (w), 1490.4 (s), 1473.8 (m), 1436.3 (w), 1403.0 (w), 1369.7 (s), 1328.1 (s), 1211.6 (w), 1140.8 (w), 1065.9 (w), 1024.3 (w), 990.9 (m), 949.4 (s), 911.9 (m), 874.4 (m), 820.3 (s), 745.4 (vs), 699.6 (s).

4.2.2 5-Ferrocenyl-4-(phenylselenyl)-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (70)

General procedure 2 was followed by using ferrocenylpropargyl aldehyde (**52**) (50 mg, 0.21 mmol), 4-(trifluoromethyl)-phenylhydrazine (**64**) (37 mg, 0.21 mmol), phenylselenyl chloride (80.4 mg, 0.42 mmol) and $NaHCO_3$ (35.3 mg, 0.42 mmol). The product was purified by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent (72 mg, 62%).

70: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.36 (t, J = 8.0 Hz, 4H), 7.21 (t, J = 7.2 Hz, 2H), 7.17 (d, J = 8.0 Hz, 1H), 4.20 (s, 2H), 4.15 (s, 2H), 4.02 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.5 (CH), 143.6 (d, J = 24.4 Hz, C), 133.0 (CH), 130.1 (d, J = 32.6 Hz, CH), 129.4 (d, J = 6.7 Hz, CH), 129.0 (C), 128.2 (C), 126.4 (d, J = 4.0 Hz, CH), 126.0 (d, J = 3.7 Hz, CH), 125.2 (d, J = 18.2 Hz, C), 122.4 (C), 103.0 (C), 73.5 (C), 70.1 (CH), 69.4 (CH), 68.8 (CH); IR (neat): 2917.9 (w), 2847.2 (w), 1735.9 (w), 1611.1 (m), 1573.6 (w), 1511.2 (m), 1477.9 (w), 1436.3 (w), 1390.5 (w), 1373.9 (m), 1323.9 (vs), 1161.6 (s), 1120.0 (vs), 1107.5 (vs), 1082.5 (s), 1015.9 (s), 945.2 (s), 812.0 (s), 841.2 (s), 741.9 (s), 687.2 (s).

4.2.3 5-Ferrocenyl-4-(phenylselenyl)-1-(3-chloro-4-fluorophenyl)-1*H*-pyrazole (71)

General procedure 2 was followed by using ferrocenylpropargyl aldehyde (**52**) (50 mg, 0.21 mmol) and 3-chloro-4-fluorophenylhydrazine (**65**) (34 mg, 0.21 mmol), phenylselenyl chloride (80.4 mg, 0.42 mmol) and $NaHCO_3$ (35.3 mg, 0.42 mmol).

The product was purified by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent (71 mg, 63%).

71: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (s, 1H), 7.42 (d, J = 6.8 Hz, 1H), 7.32 (d, J = 7.2 Hz, 1H), 7.22-7.14 (m, 5H), 7.10 (d, J = 6.4 Hz, 1H), 4.23 (s, 2H), 4.20 (s, 2H), 4.00 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7 (d, J = 244.5 Hz, C), 147.4 (CH), 143.9 (C), 137.2 (d, J = 3.7 Hz, C), 133.0 (CH), 129.4 (CH), 129.2 (CH), 128.9 (CH), 128.2 (C), 126.4 (d, J = 10.5 Hz, CH), 121.4 (d, J = 18.9 Hz, C), 116.6 (d, J = 10.2 Hz, CH), 101.9 (C), 73.3 (C), 70.0 (CH), 69.2 (CH), 68.9 (CH); IR (neat): 3098.7 (w), 2963.1 (w), 2923.2 (w), 2843.5 (w), 2237.2 (w), 1742.6 (s), 1658.9 (w), 1583.1 (s), 1499.3 (vs), 1475.4 (s), 1435.5 (m), 1399.6 (m), 1264.0 (s), 1228.1 (s), 1108.5 (m), 1020.7 (m), 956.9 (s), 865.2 (m), 817.3 (s), 745.5 (s).

4.2.4 5-Ferrocenyl-4-(phenylselenyl)-1-(2,5-difluorophenyl)-1*H*-pyrazole (72)

General procedure 2 was followed by using ferrocenylpropargyl aldehyde (**52**) (50 mg, 0.21 mmol) and 2,5-difluorophenylhydrazine (**66**) (30 mg, 0.21 mmol), phenylselenyl chloride (80.4 mg, 0.42 mmol) and $NaHCO_3$ (35.3 mg, 0.42 mmol). The product was purified by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent (90 mg, 82%).

72: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.22-7.08 (m, 6H), 4.32 (s, 2H), 4.14 (s, 2H), 3.99 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2 (d, J = 246.6 Hz, C), 153.7 (d, J = 246.6 Hz, C), 148.2 (CH), 145.7 (C), 133.0 (CH), 129.4 (CH), 129.0 (CH), 128.2 (C), 126.3 (CH), 125.2 (C), 117.5 (m, CH), 116.5 (d, J = 25 Hz, CH), 101.0 (C), 73.0 (C), 70.0 (CH), 69.1 (CH), 68.3 (CH); IR (neat): 2984.5 (w), 2360.2 (w), 1619.4 (w), 1573.6 (w), 1511.2 (s), 1469.6 (m), 1432.1 (w), 1394.7 (w), 1361.4 (w), 1253.2 (m), 1182.4 (m), 1107.5 (m), 1065.9 (w), 1011.8 (m), 961.8 (m), 899.4 (s), 866.1 (m), 824.5 (vs), 681.3 (vs).

4.3 General Procedure 3. Synthesis of 5-aryl-4-(phenylselenyl)-1-phenyl-1*H*-pyrazoles (73-81)

In a round-bottomed flask, appropriate propargyl aldehyde (0.1 mmol) and hydrazine (0.1 mmol) were reacted under neat condition at 80 °C for 1 h under argon. Formation of the corresponding hydrazones were followed with TLC analysis. After the formation of corresponding hydrazones in situ, a mixture of PhSeCl (0.2 mmol) and $NaHCO_3$ (0.2 mmol) in 5 ml of DCE were added to the reaction flask, and the resulting mixture was stirred for 1.5 h at room temperature under argon. The completion of the reaction was controlled with TLC analysis. After the reaction was over, DCE was removed under reduced pressure and the reaction mixture was extracted with ethyl acetate (3 x 30 mL). The organic phase was separated, dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography by using 19:1 hexane/ethyl acetate as the eluent to afford the corresponding pyrazole derivative.

4.3.1 1,5-Diphenyl-4-(phenylselenyl)-1*H*-pyrazole (73)

General procedure 3 was followed by using phenylpropargyl aldehyde (**56**) (62 mg, 0.48 mmol) and phenylhydrazine (**63**) (52 mg, 0.48 mmol), phenylselenyl chloride (183.9 mg, 0.96 mmol) and $NaHCO_3$ (80.6 mg, 0.96 mmol). The product was purified by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent (121.3 mg, 68%).

73: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.23-7.01 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.3 (CH), 145.8 (C), 139.8 (C), 133.1 (C), 130.1 (CH), 129.6 (CH), 129.3 (C), 129.1 (CH), 128.8 (CH), 128.7 (CH), 128.2 (CH), 127.5 (CH), 126.2 (CH), 124.8 (CH), 103.7 (C); IR (neat): 3090.7 (vw), 3070.8 (w), 3042.9 (w), 1746.6 (w), 1595.1 (m), 1571.1 (m), 1495.4 (vs), 1467.4 (s), 1439.5 (s), 1371.7 (s), 1068.6 (m), 1024.7 (m), 948.9 (s), 905.1 (m), 869.2 (m), 761.5 (s), 729.6 (s).

4.3.2 5-Phenyl-4-(phenylselenyl)-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (74)

General procedure 3 was followed by using phenylpropargyl aldehyde (**56**) (22 mg, 0.17 mmol) and 4-(trifluoromethyl)-phenylhydrazine (**64**) (30 mg, 0.17 mmol), phenylselenyl chloride (65.1 mg, 0.34 mmol) and $NaHCO_3$ (28.6 mg, 0.34 mmol). The product was purified by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent (36 mg, 48%).

74: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.48 (d, J = 7.6 Hz, 2H), 7.32-7.08 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.8 (CH), 145.9 (C), 142.5 (C), 132.6 (CH), 132.5 (C), 131.8 (CH), 130.1 (CH), 129.9 (CH), 129.1 (m, C), 129.0 (C), 128.5 (CH), 128.1 (C), 126.4 (CH), 126.0 (d, J = 3.7 Hz, CH), 124.5 (CH), 105.2 (C); IR (neat): 3058.8 (w), 2959.1 (w), 2855.4 (w), 2197.3 (w), 1674.8 (s), 1615.0 (s), 1575.1 (m), 1515.3 (m), 1475.4 (m), 1443.5 (m), 1379.7 (s), 1319.9 (vs), 1152.3 (s), 1116.5 (vs), 1060.6 (s), 948.9 (s), 833.3 (s), 741.5 (vs), 689.7 (s).

4.3.3 5-Phenyl-4-(phenylselenyl)-1-(3-chloro-4-fluorophenyl)-1*H*-pyrazole (75)

General procedure 3 was followed by using phenylpropargyl aldehyde (**56**) (52 mg, 0.4 mmol) and 3-chloro-4-fluorophenylhydrazine (**65**) (65 mg, 0.4 mmol), phenylselenyl chloride (153.2 mg, 0.8 mmol) and $NaHCO_3$ (67.2 mg, 0.8 mmol). The product was purified by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent (65 mg, 38%).

75: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.37 (d, J = 4.0 Hz, 1H), 7.27-7.06 (m, 10H), 6.93 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3 (C), 155.8 (CH), 146.6 (C), 145.9 (CH), 136.4 (CH), 132.7 (CH), 130.1 (C), 129.8 (C), 129.2 (CH), 128.8 (C), 128.5 (CH), 127.0 (C), 126.4 (CH), 124.3 (CH), 121.4 (CH), 116.5 (CH), 104.5 (C); IR (neat): 3689.0 (m), 2971.1 (vs), 2903.3 (vs), 1738.7 (m), 1670.9 (m), 1603.0 (m), 1571.1 (m), 1491.4 (vs), 1431.5 (m), 1407.6 (m), 1375.7 (m), 1260.0 (s), 1068.6 (s), 1048.6 (s), 956.9 (m), 821.3 (m), 761.5 (m), 729.6 (m), 689.7 (m).

4.3.4 5-*p*-Tolyl-4-(phenylselenyl)-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (76)

General procedure 3 was followed by using 3-*p*-tolylpropiol aldehyde (**57**) (35 mg, 0.24 mmol) and 4-(trifluoromethyl)-phenylhydrazine (**64**) (43 mg, 0.24 mmol), phenylselenyl chloride (91.9 mg, 0.48 mmol) and $NaHCO_3$ (40.3 mg, 0.48 mmol). The product was purified by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent (62 mg, 56%).

76: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 7.16-7.04 (m, 5H), 6.96 (d, J = 8.0 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.9 (CH), 146.1 (C), 142.6 (C), 139.2 (C), 132.8 (C), 129.9 (CH), 129.7 (CH), 129.3 (CH), 129.2 (CH), 128.9 (C), 126.3 (CH), 126.0 (m, C) 125.9 (CH), 125.1 (C), 124.5 (CH), 104.8 (C), 21.3 (CH_3); IR (neat): 3054.8 (w), 2915.3 (m), 2847.4 (w), 2193.3 (w), 1874.3 (vw), 1734.7 (w), 1670.9 (m), 1615.0 (s), 1575.1 (m), 1523.3 (m), 1471.4 (m), 1435.5 (m), 1419.6 (m), 1315.9 (vs), 1108.5 (vs), 1048.6 (s), 1012.8 (m), 944.9 (m), 849.2 (s), 821.3 (s), 733.6 (s), 685.7 (m), 653.8 (w).

4.3.5 5-*p*-Tolyl-4-(phenylselenyl)-1-(3-chloro-4-fluorophenyl)-1*H*-pyrazole (77)

General procedure 3 was followed by using 3-*p*-tolylpropiol aldehyde (**57**) (44 mg, 0.31 mmol) and 3-chloro-4-fluorophenylhydrazine (**65**) (50 mg, 0.31 mmol), phenylselenyl chloride (118.7 mg, 0.62 mmol) and $NaHCO_3$ (52.1 mg, 0.62 mmol). The product was purified by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent (68 mg, 50%).

77: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.40 (d, J = 4.0 Hz, 2H), 7.20-7.04 (m, 7H), 6.94 (t, J = 8.0 Hz, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.0 (d, J = 248.8 Hz, C), 146.6 (CH), 146.1 (C), 139.2 (C), 136.5 (C), 132.9 (C), 129.9 (CH), 129.7 (CH), 129.2 (CH), 129.1 (CH), 127.1 (CH), 126.3 (CH), 125.8 (C), 124.4 (d, J = 7.4 Hz, C), 121.4 (d, J = 18.8 Hz, CH), 116.4 (d, J = 22.3 Hz, CH), 104.3 (C), 21.3 (CH_3); IR (neat): 3681.0 (w), 2987.1 (w), 2919.3 (vw), 1742.6 (m), 1607.0 (w), 1575.1 (m), 1495.3 (vs), 1439.5 (m), 1407.6 (m), 1375.7

(w), 1264.0 (s), 1224.1 (vw), 1072.6 (vw), 1052.6 (m), 1024.7 (w), 956.9 (s), 813.3 (vs), 729.6 (s), 685.7 (m).

4.3.6 5-*p*-Tolyl-4-(phenylselenyl)-1-(2,5-difluorophenyl)-1*H*-pyrazole (78)

General procedure 3 was followed by using 3-*p*-tolylpropiol aldehyde (**57**) (44 mg, 0.31 mmol) and 2,5-difluorophenylhydrazine (**66**) (50 mg, 0.31 mmol), phenylselenyl chloride (118.7 mg, 0.62 mmol) and $NaHCO_3$ (52.1 mg, 0.62 mmol). The product was purified by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent (47 mg, 35%).

78: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.21-7.18 (m, 2H), 7.15-7.08 (m, 4H), 6.98 (d, J = 4.0 Hz, 4H), 6.94-6.89 (m, 2H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.1 (dd, J = 3.0 Hz, 243.8 Hz, C), 152.6 (dd, J = 3.0 Hz, 243.8 Hz, C), 147.9 (C), 147.3 (CH), 139.1 (C), 132.9 (C), 129.5 (CH), 129.3 (CH), 129.2 (CH), 128.9 (CH), 128.7 (d, J = 4.0 Hz, C), 126.3 (CH), 125.6 (C), 117.4 (dd, J = 9.2 Hz, 22.5 Hz, CH), 116.8 (dd, J = 7.8 Hz, 23.7 Hz, CH), 115.8 (d, J = 25.6 Hz, CH), 103.0 (C), 21.3 (CH_3); IR (neat): 3074.8 (w), 2979.1 (vw), 2911.3 (vw), 1738.7 (w), 1623.00 (m), 1571.1 (w), 1511.3 (vs), 1463.5 (m), 1427.6 (m), 1359.8 (m), 1248.1 (m), 1180.3 (m), 1116.5 (w), 1048.6 (vw), 964.9 (m), 885.1 (m), 877.2 (m), 817.3 (s), 765.5 (s), 737.6 (m), 689.7 (m), 653.8 (m).

4.3.7 5-(4-Methoxyphenyl)-4-(phenylselenyl)-1-phenyl-1*H*-pyrazole (79)

General procedure 3 was followed by using 3-(4-methoxyphenyl)propiol aldehyde (**58**) (25 mg, 0.16 mmol) and phenylhydrazine (**63**) (17 mg, 0.16 mmol), phenylselenyl chloride (61.3 mg, 0.32 mmol) and $NaHCO_3$ (26.9 mg, 0.32 mmol). The product was purified by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent (42 mg, 66%).

79: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.23-7.08 (m, 10H), 7.01 (d, J = 8.8 Hz, 2H), 6.73 (d, J = 8.8 Hz, 2H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8 (C), 146.4 (CH), 145.9 (C), 140.0 (C), 133.4 (C), 131.4 (CH), 129.4 (CH),

129.1 (CH), 128.8 (CH), 127.4 (CH), 126.1 (CH), 124.9 (CH), 121.5 (C), 113.7 (CH), 103.2 (C), 55.2 (CH_3); IR (neat): 3114.7 (w), 2839.5 (w), 2356.9 (vw), 1742.6 (w), 1611.0 (m), 1591.1 (m), 1575.1 (s), 1539.2 (m), 1495.4 (s), 1435.5 (s), 1367.7 (s), 1288.0 (m), 1236.1 (s), 1164.3 (s), 1104.5 (m), 1068.6 (m), 1020.7 (s), 956.9 (m), 825.3 (s), 757.5 (s), 729.6 (vs), 685.7 (vs).

4.3.8 5-(4-Methoxyphenyl)-4-(phenylselenyl)-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (80)

General procedure 3 was followed by using 3-(4-methoxyphenyl)propiol aldehyde (**58**) (54 mg, 0.34 mmol) and 4-(trifluoromethyl)-phenylhydrazine (**64**) (60 mg, 0.34 mmol), phenylselenyl chloride (130.2 mg, 0.68 mmol) and $NaHCO_3$ (57.1 mg, 0.68 mmol). The product was purified by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent (40 mg, 25%).

80: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.49 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.22-7.10 (m, 5H), 7.0 (d, J = 8.8 Hz, 2H), 6.8 (d, J = 8.8 Hz, 2H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2 (C), 146.9 (CH), 146.0 (C), 142.6 (C), 137.7 (C), 132.9 (C), 131.4 (CH), 129.7 (CH), 129.2 (CH), 126.4 (CH), 126.0 (m, CH), 125.1 (CH), 124.5 (CH), 121.1 (CH), 114.1 (C), 104.7 (C), 55.2 (CH_3); IR (neat): 3689.0 (m), 2959.1 (w), 2911.3 (w), 1734.7 (s), 1607.0 (s) 1535.2 (m), 1435.5 (m), 1371.7 (s), 1323.9 (vs), 1244.1 (s), 1160.3 (m), 1060.6 (w), 948.9 (m), 833.3 (m), 729.6 (m), 701.7 (m).

4.3.9 5-(4-Methoxyphenyl)-4-(phenylselenyl)-1-(2-nitrophenyl)-1*H*-pyrazole (81)

General procedure 3 was followed by using 3-(4-methoxyphenyl)propiol aldehyde (**58**) (78 mg, 0.49 mmol) and 2-nitrophenylhydrazine (**67**) (75 mg, 0.49 mmol), phenylselenyl chloride (187.7 mg, 0.98 mmol) and $NaHCO_3$ (82.3 mg, 0.98 mmol). The product was purified by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent (209 mg, 95%).

81: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.17 (d, J = 8.0 Hz, 2H), 7.12-7.06 (m, 3H), 6.99-6.92 (m, 5H), 6.74 (d, J = 8.8 Hz, 2H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1 (C), 158.2 (C), 155.7 (C), 146.6 (CH), 145.9 (C), 136.5 (C), 132.9 (CH), 131.3 (CH), 129.5 (CH), 129.1 (CH), 126.6 (CH), 124.3 (CH), 121.3 (C), 120.8 (CH), 116.4 (CH), 113.9 (CH), 104.0 (C), 55.1 (CH_3); IR (neat): 3673.1 (m), 2983.1 (m), 2903.3 (w), 1742.7 (vs), 1615.0 (s), 1575.1 (s), 1539.2 (m), 1491.4 (vs), 1431.6 (m), 1371.7 (m), 1252.1 (vs), 1168.3 (s), 1032.7 (s), 960.9 (s), 825.3 (s), 733.6 (s), 685.7 (m), 649.8 (m), 601.9 (m)

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APPENDIX A

NMR DATA

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Spectrospin Avance DPX400 Ultrashield at 400 and 100 MHz, respectively.

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

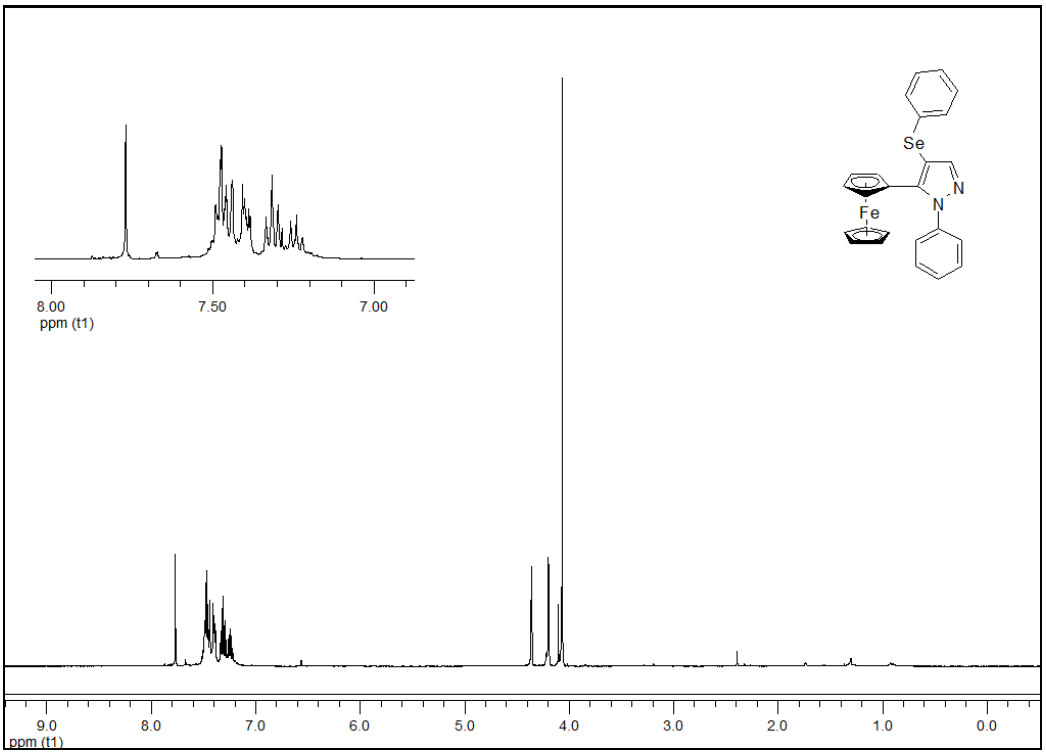

Figure A1. ^{1}H NMR spectrum of **69**

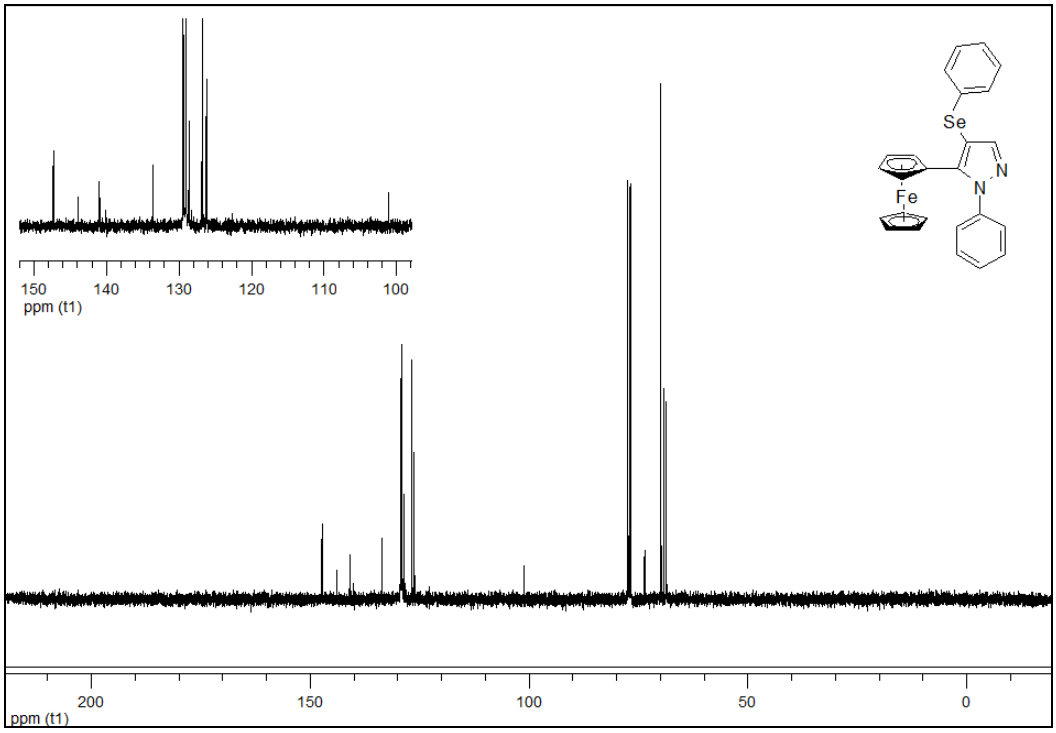

Figure A2. ^{13}C NMR spectrum of **69**.

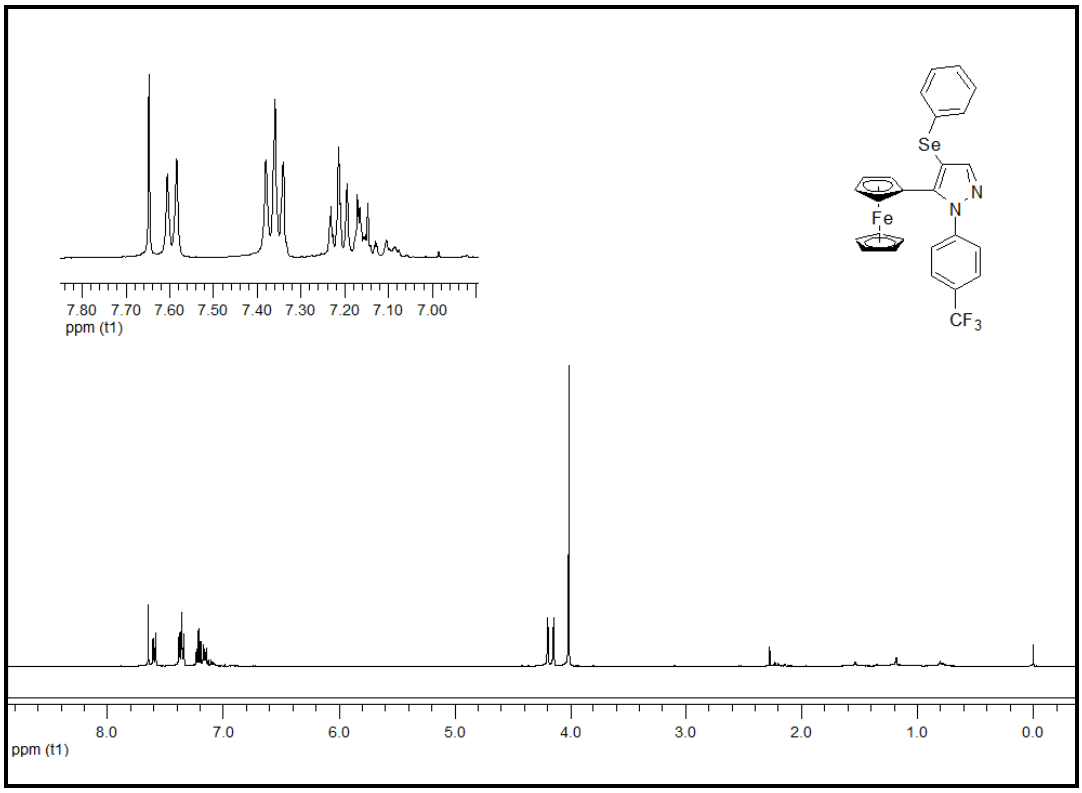

Figure A3. ^{1}H NMR spectrum of **70**

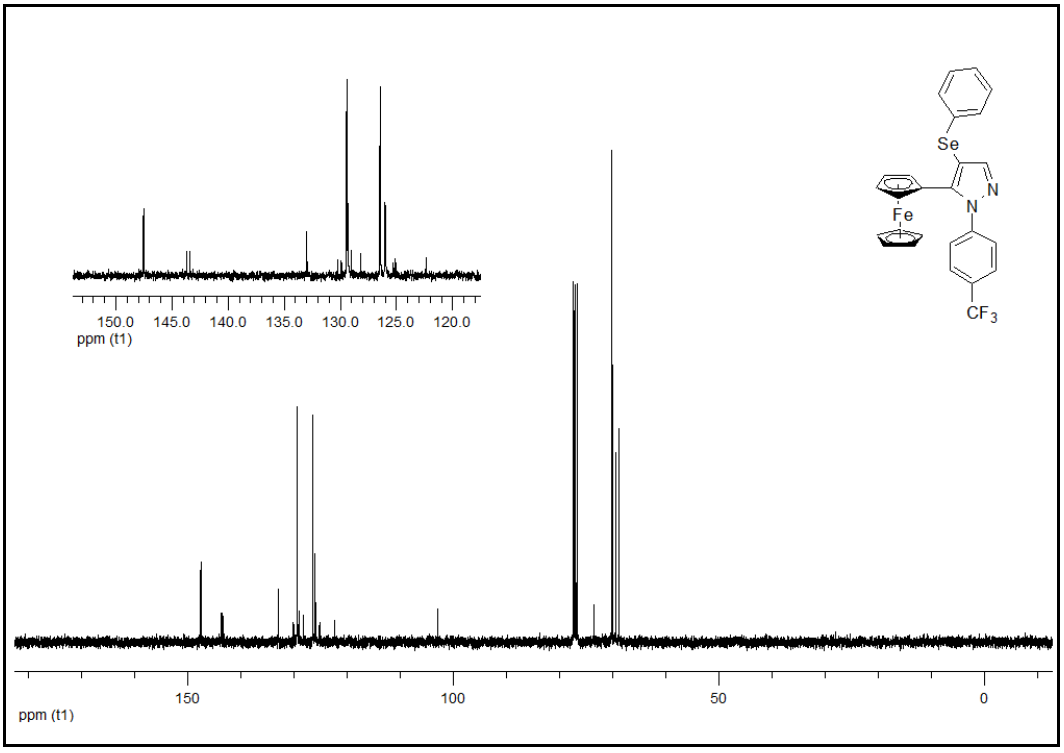

Figure A4. ^{13}C NMR spectrum of **70**.

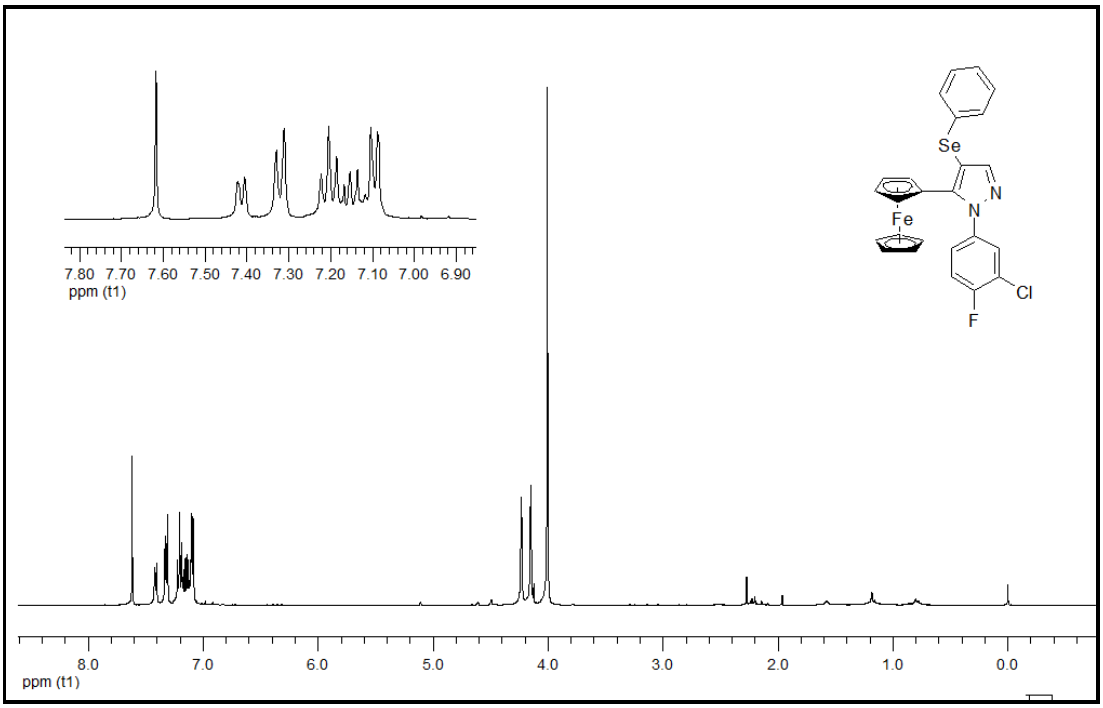

Figure A5. ^{1}H NMR spectrum of **71**

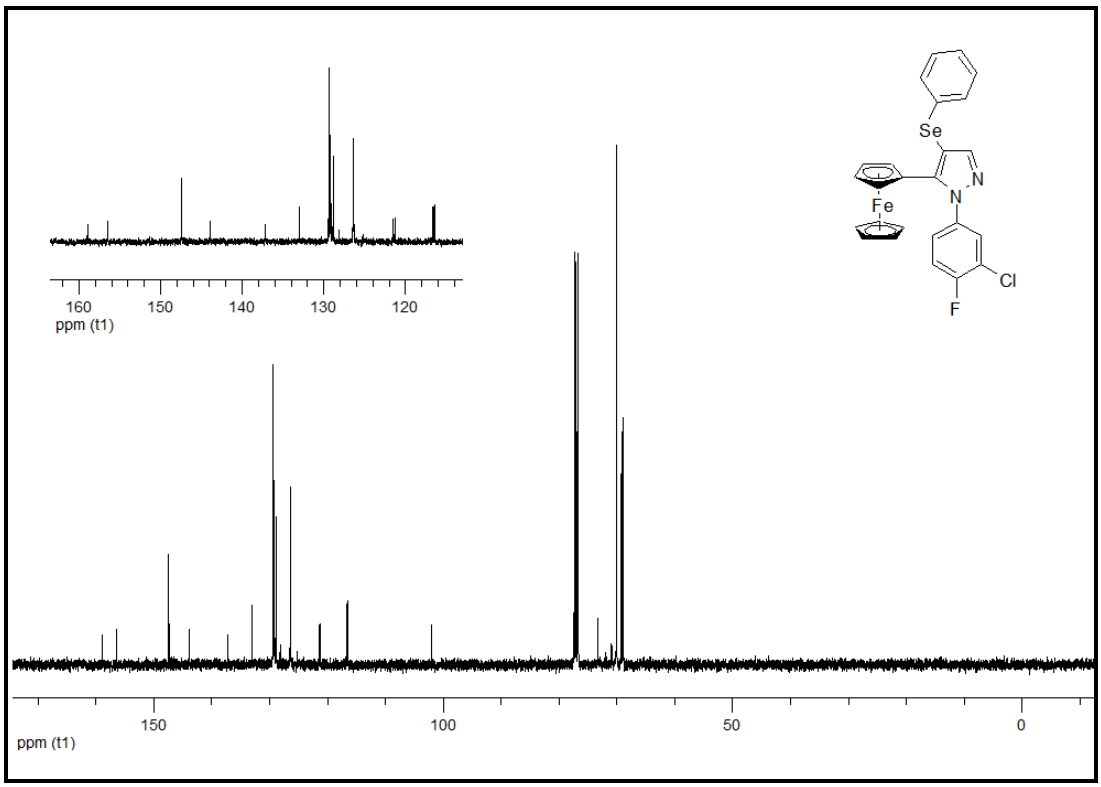

Figure A6. ^{13}C NMR spectrum of **71**.

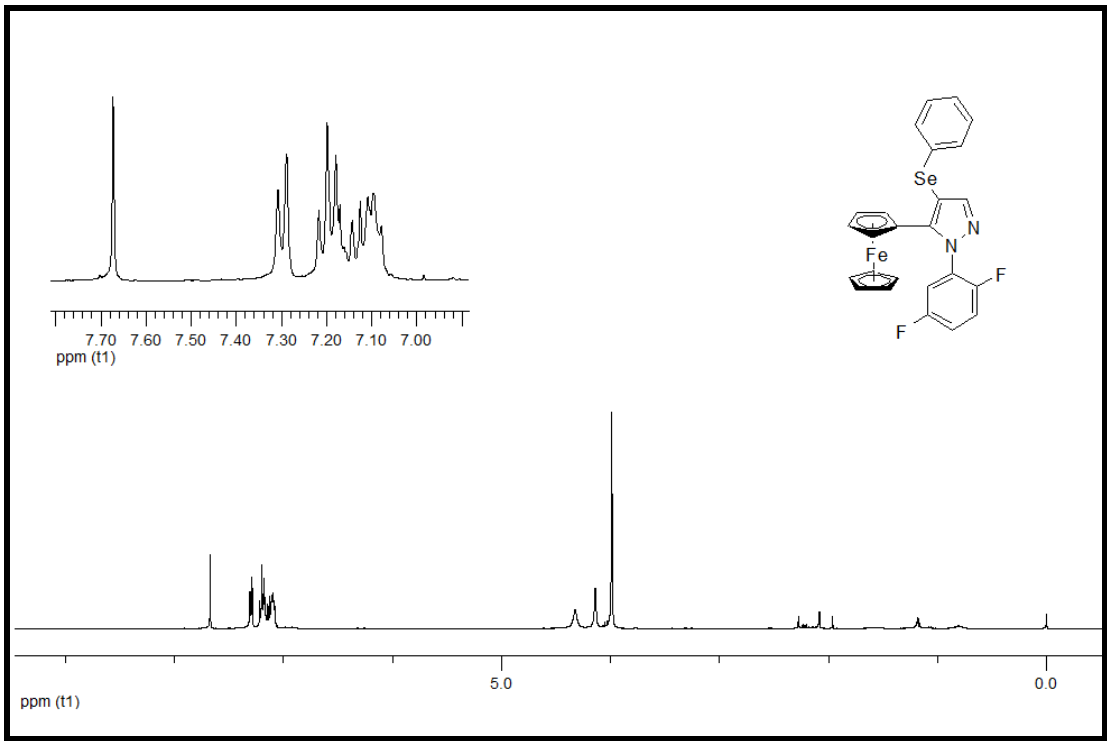

Figure A7. ^{1}H NMR spectrum of **72**

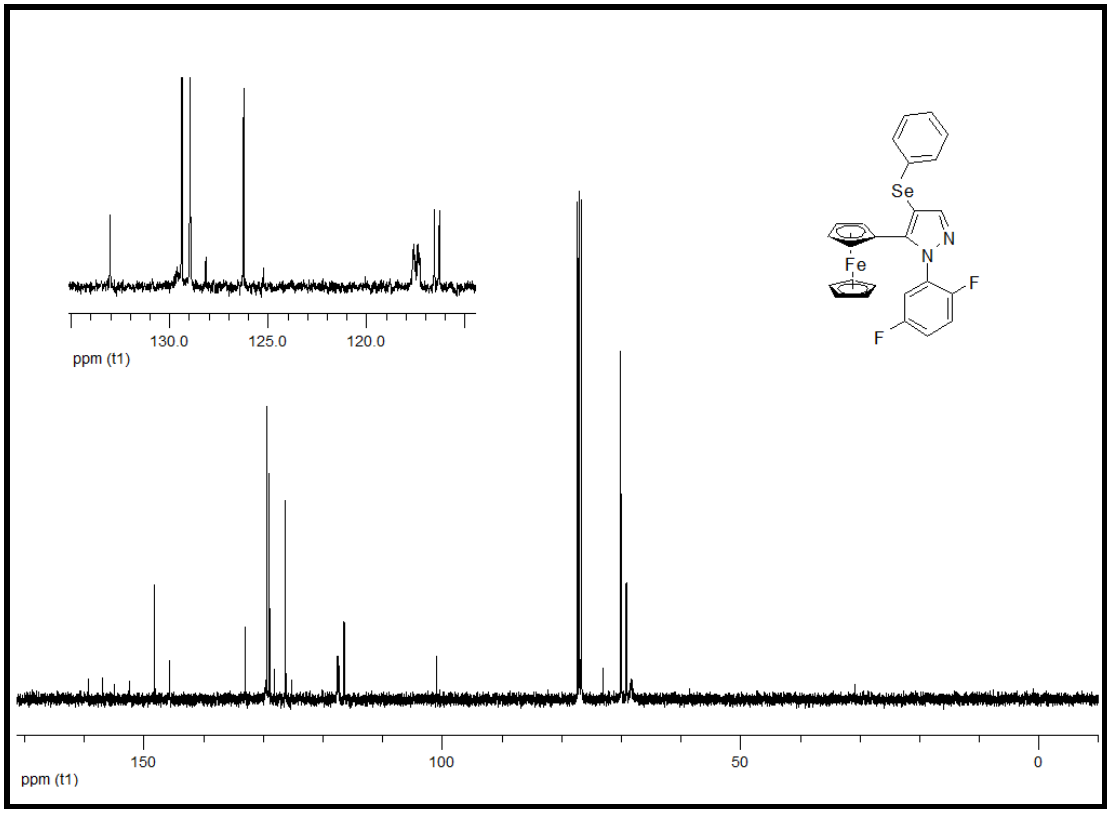

Figure A8. ^{13}C NMR spectrum of **72**.

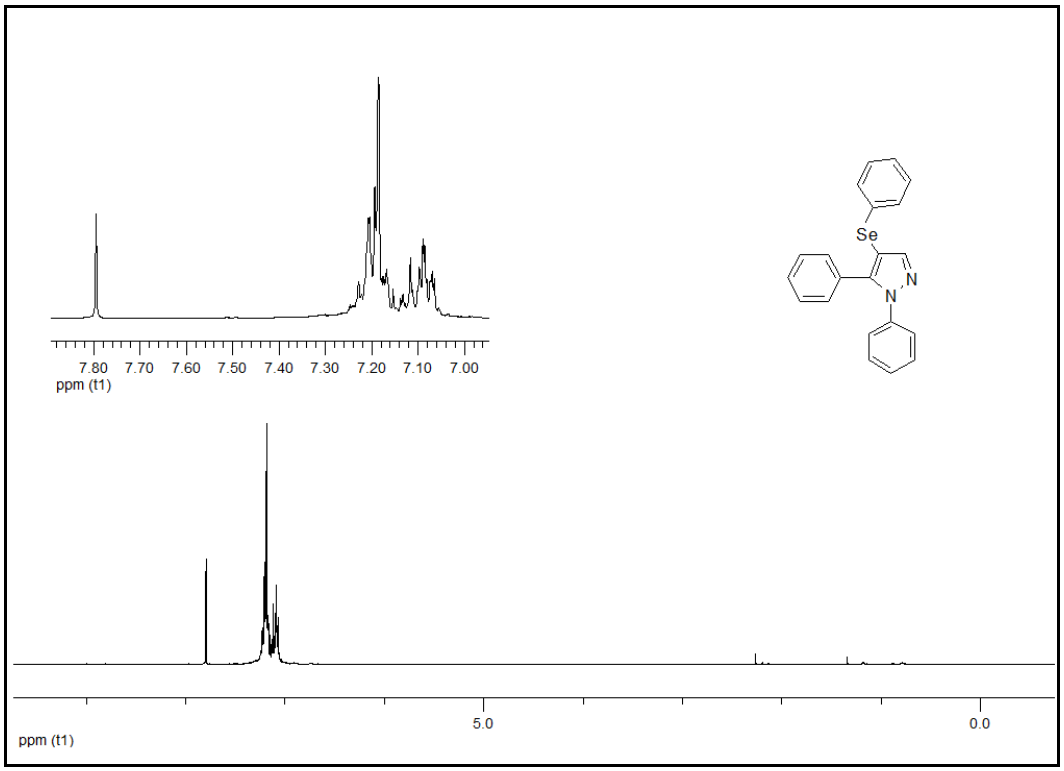

Figure A9. ^{1}H NMR spectrum of **73**

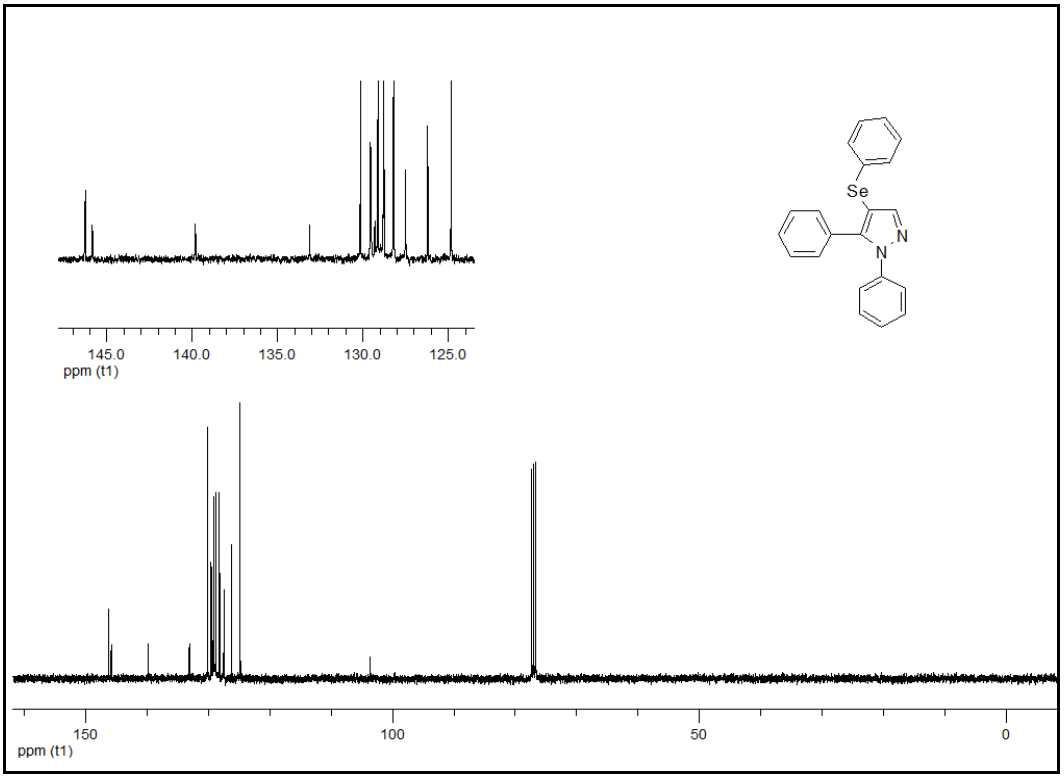

Figure A10. ^{13}C NMR spectrum of **73**.

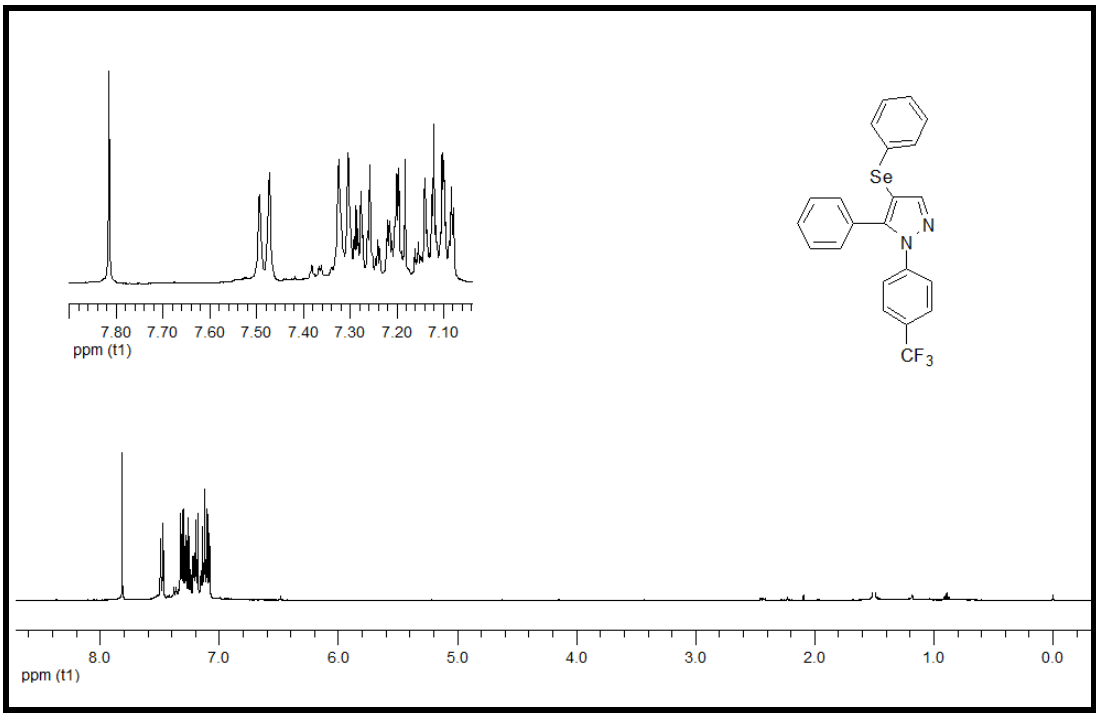

Figure A11. ^{1}H NMR spectrum of **74**

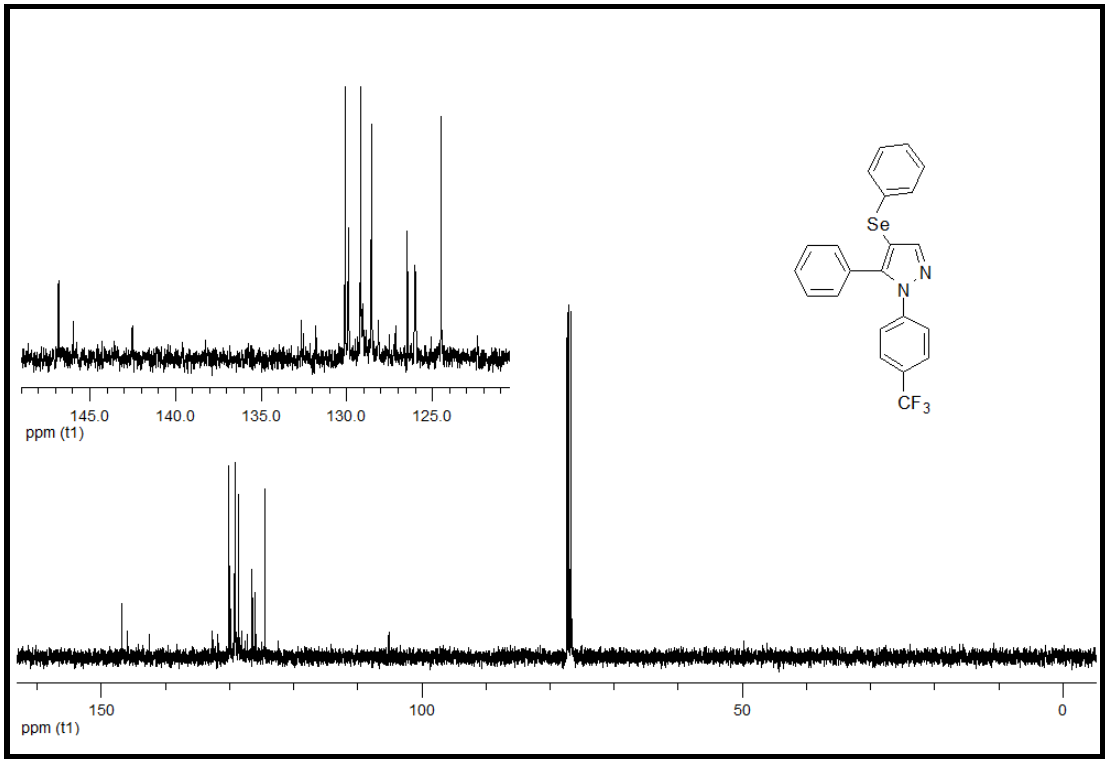

Figure A12. ^{13}C NMR spectrum of **74**.

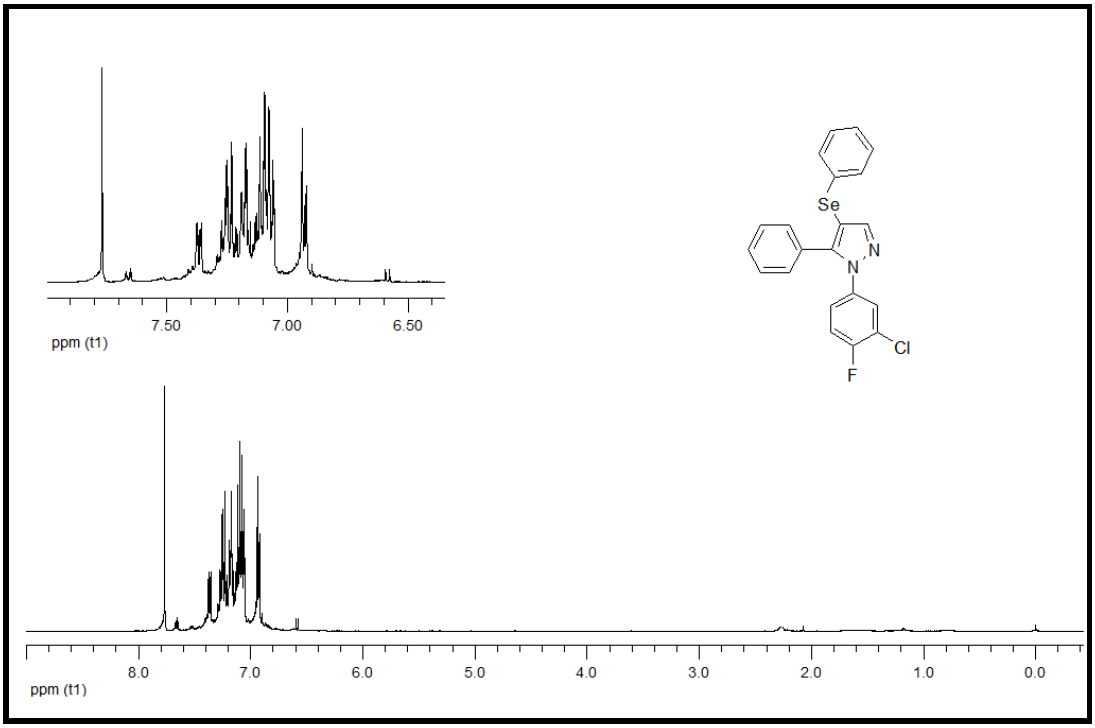

Figure A13. ^{1}H NMR spectrum of **75**

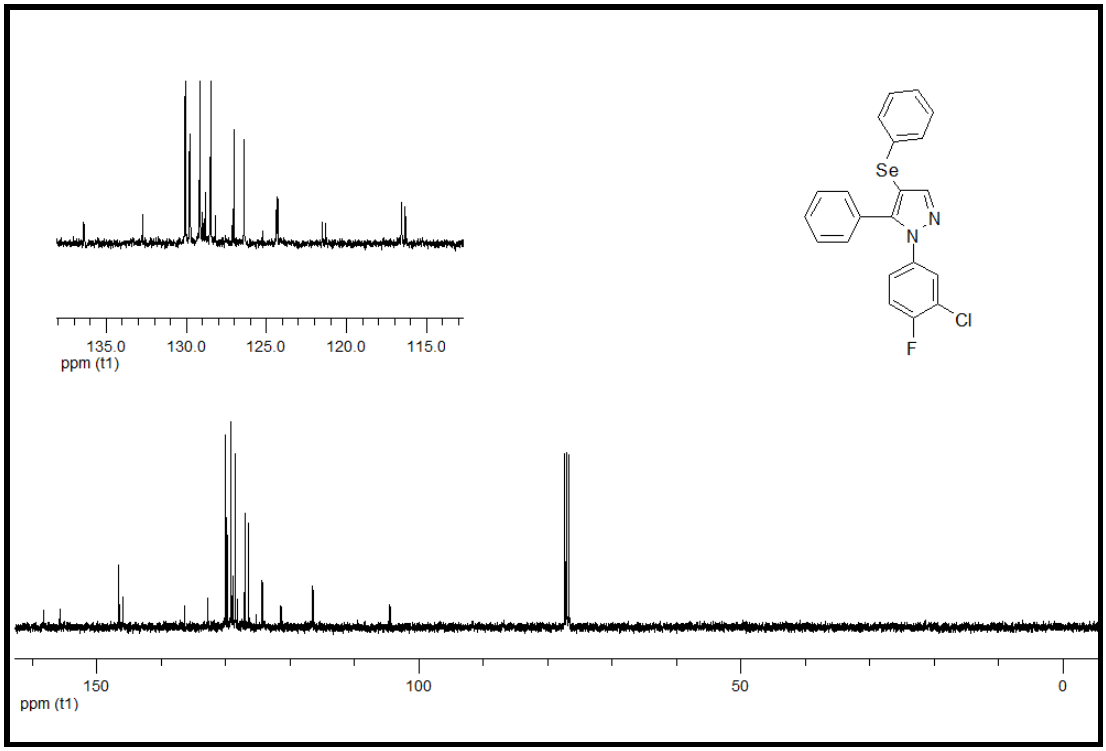

Figure A14. ^{13}C NMR spectrum of **75**.

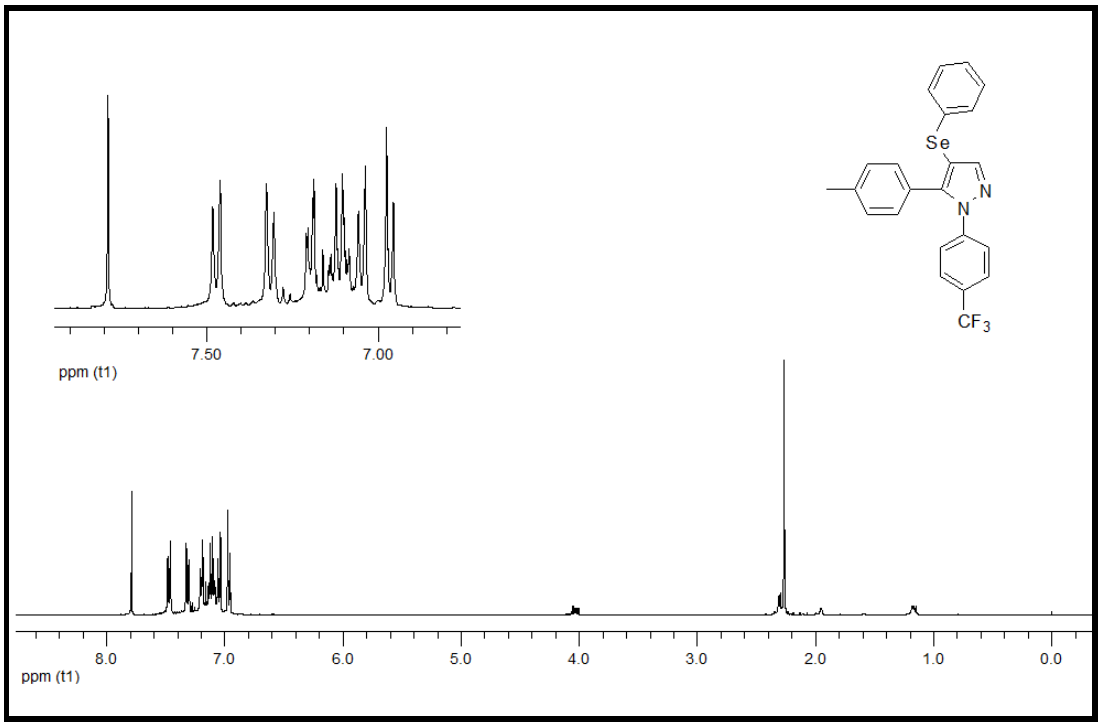

Figure A15. ^{1}H NMR spectrum of **76**

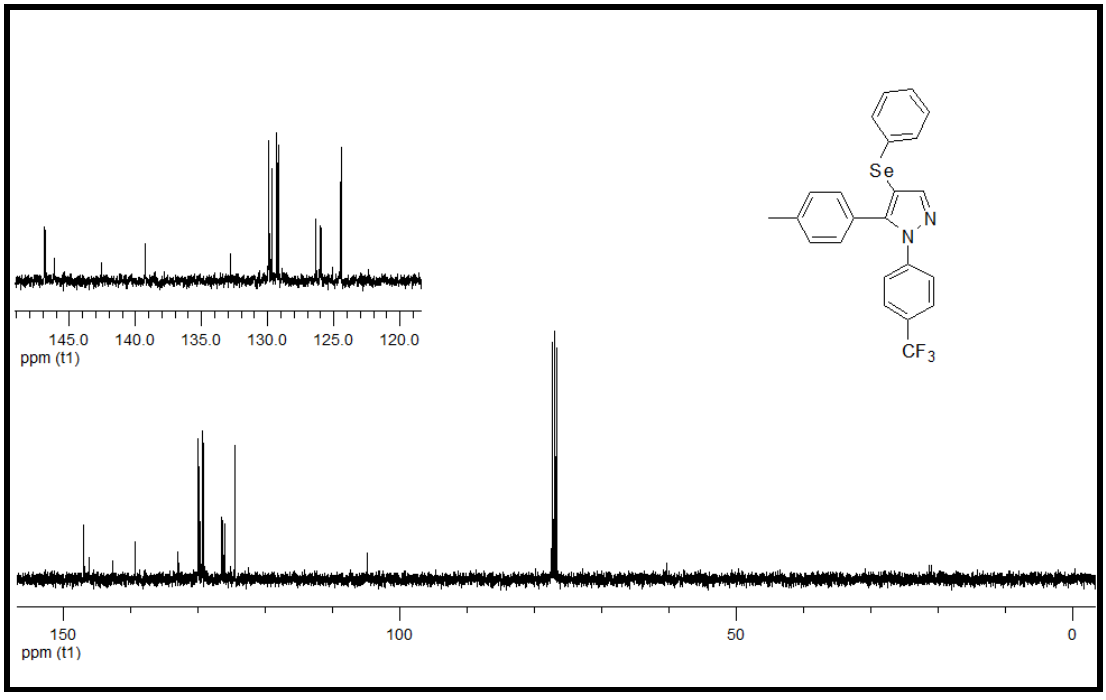

Figure A16. ^{13}C NMR spectrum of **76**.

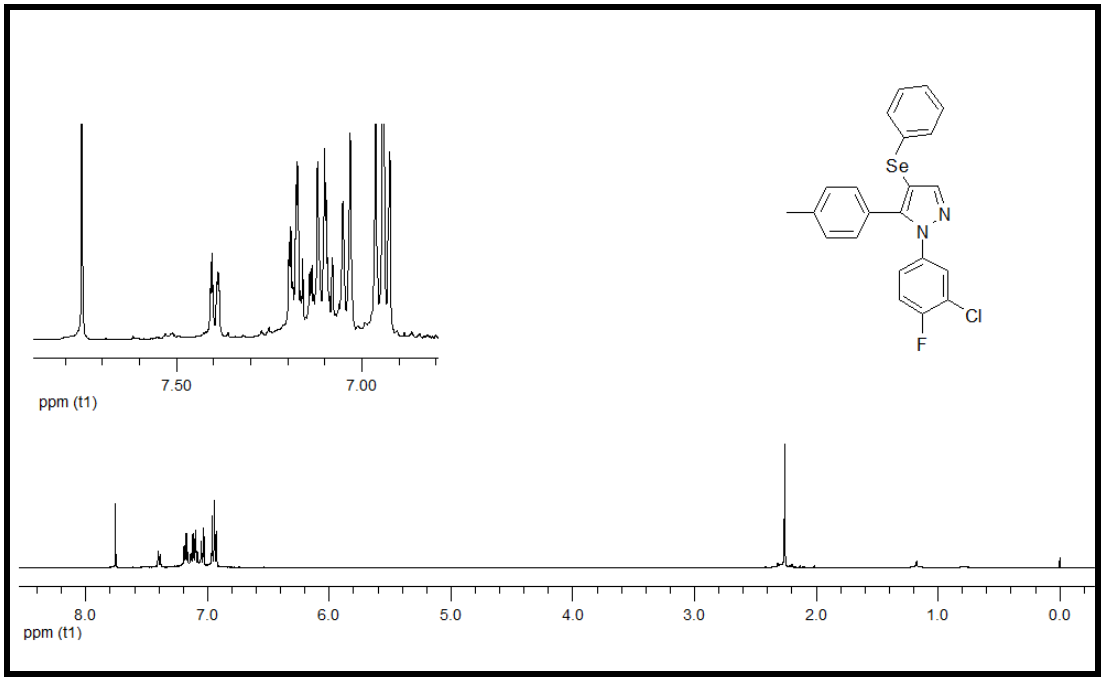

Figure A17. ^{1}H NMR spectrum of **77**

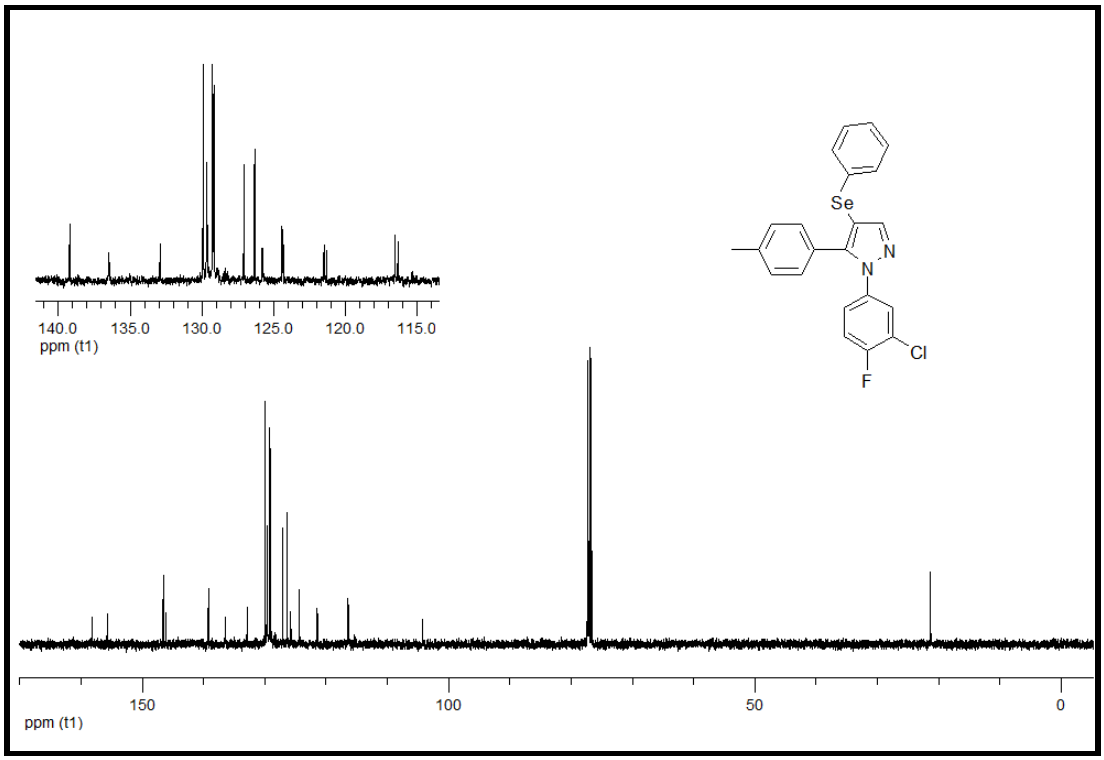

Figure A18. ^{13}C NMR spectrum of **77**.

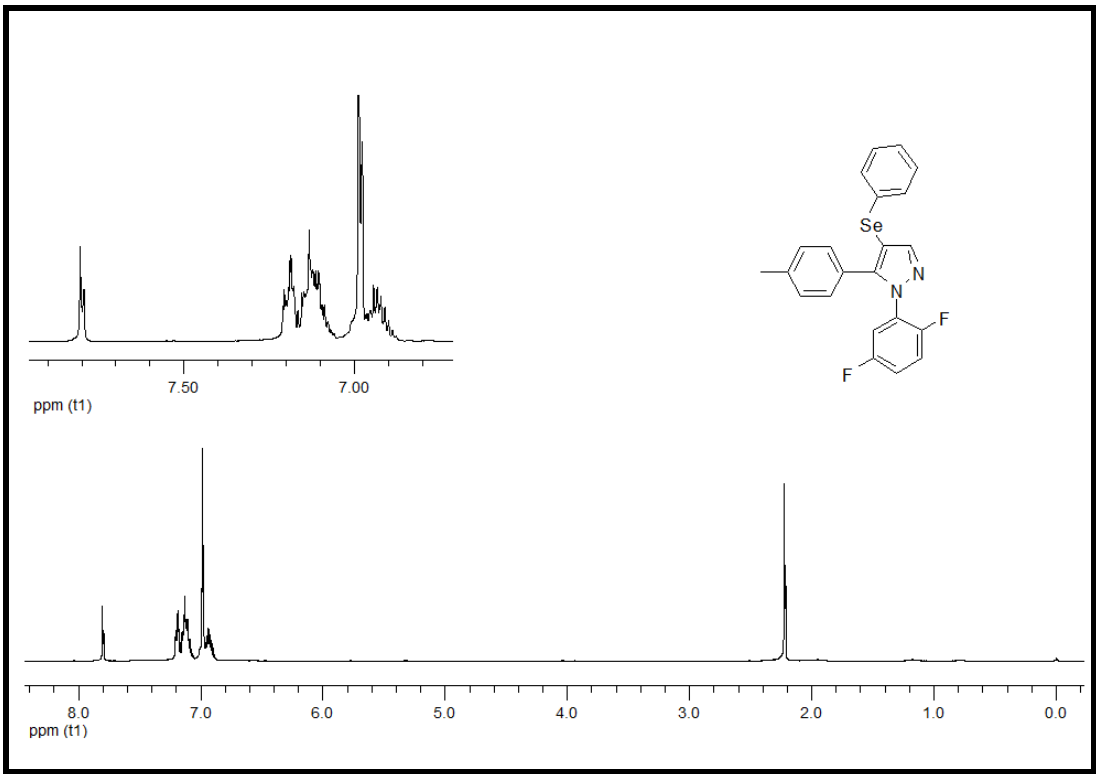

Figure A19. ^{1}H NMR spectrum of **78**

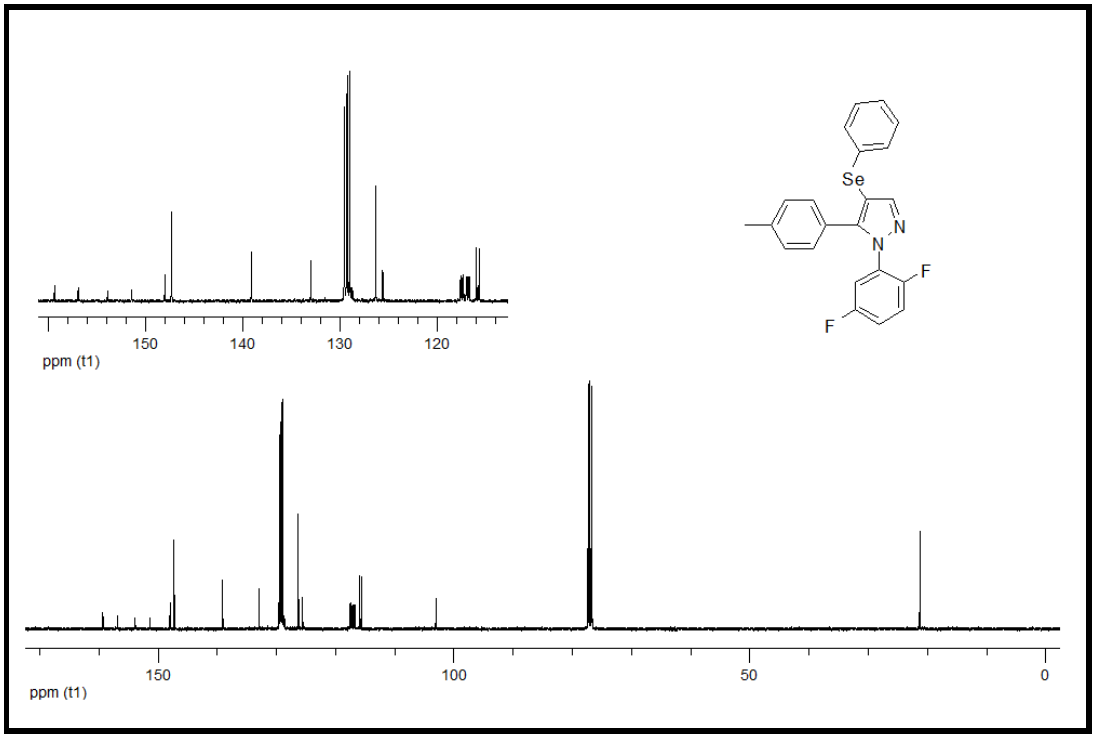

Figure A20. ^{13}C NMR spectrum of **78**.

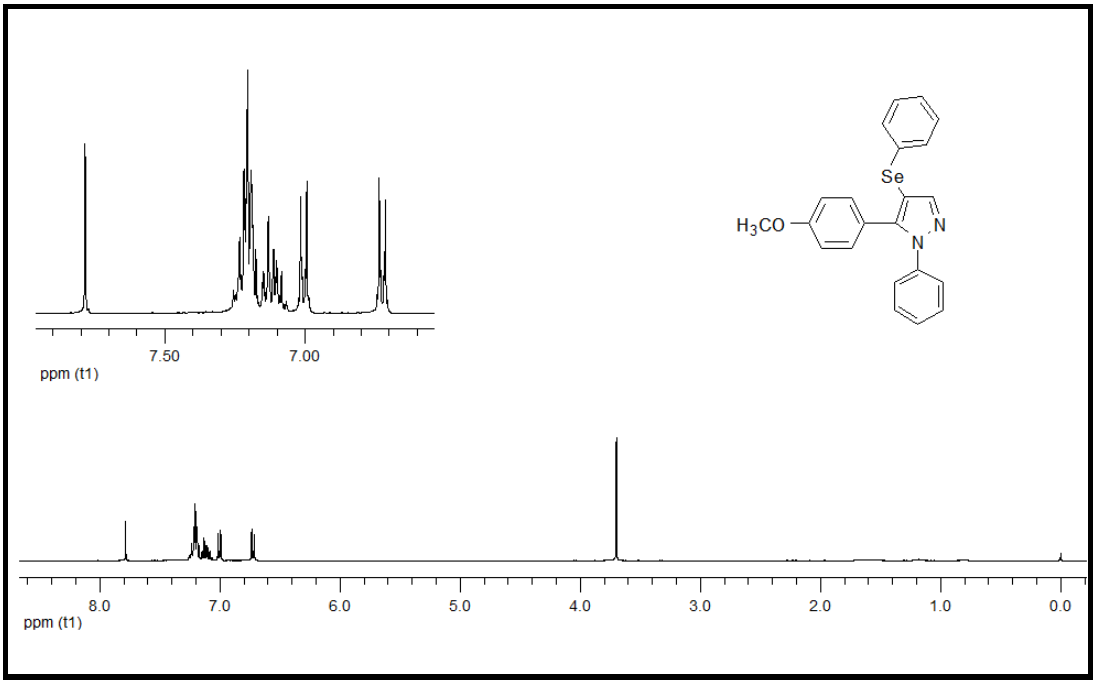

Figure A21. ^{1}H NMR spectrum of **79**

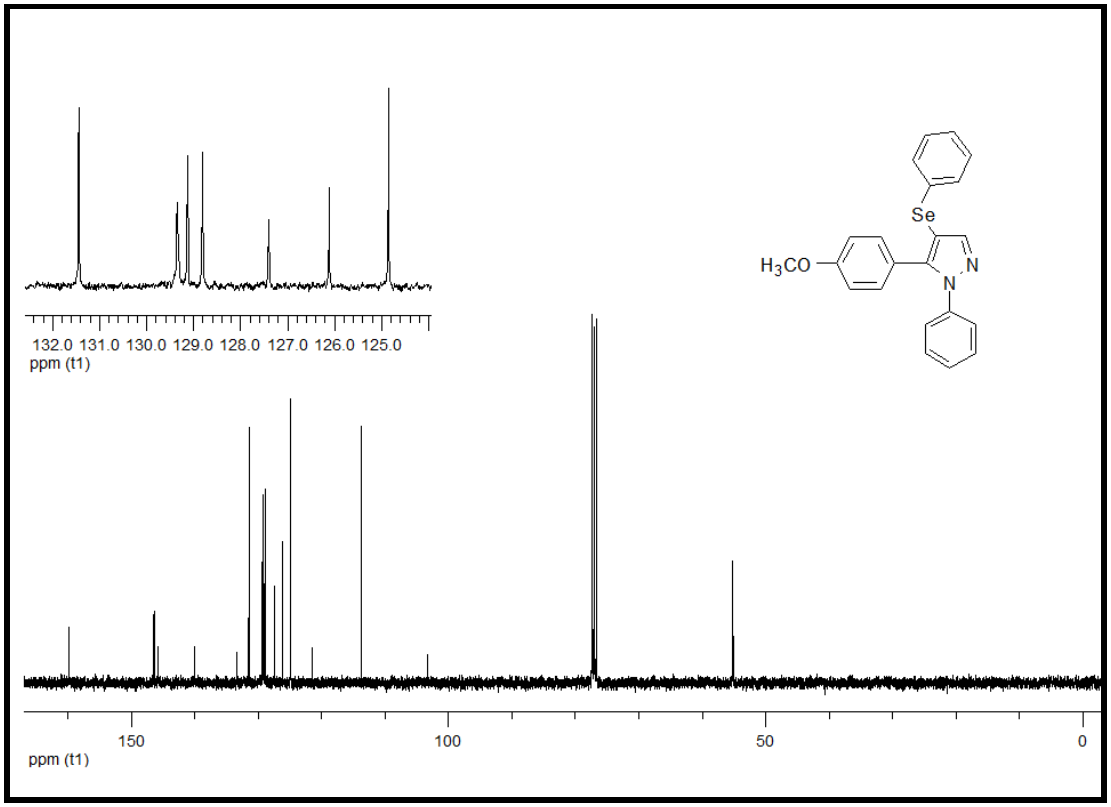

Figure A22. ^{13}C NMR spectrum of **79**

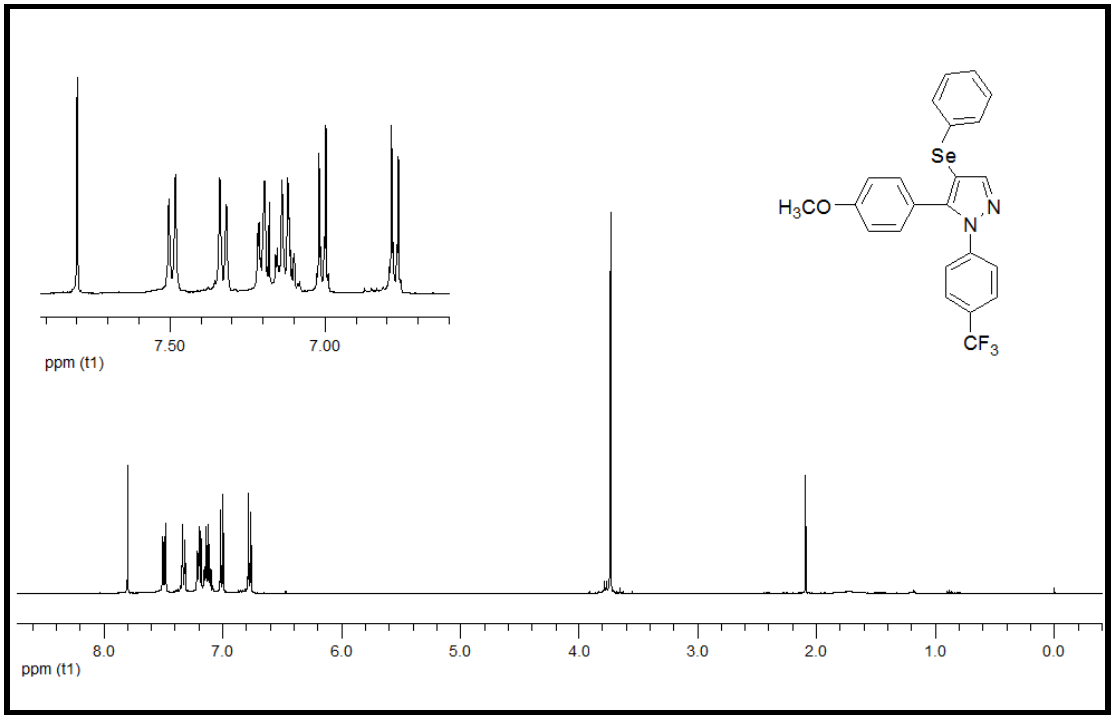

Figure A23. ^{1}H NMR spectrum of **80**

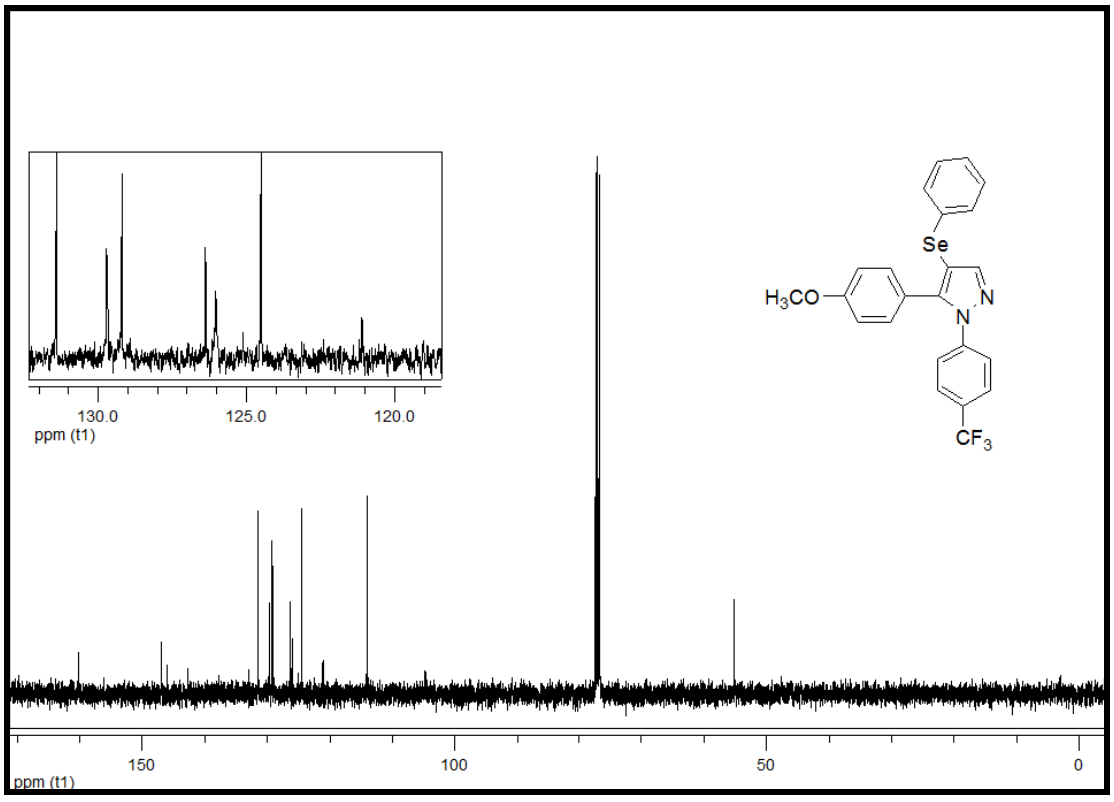

Figure A24. ^{13}C NMR spectrum of **80**

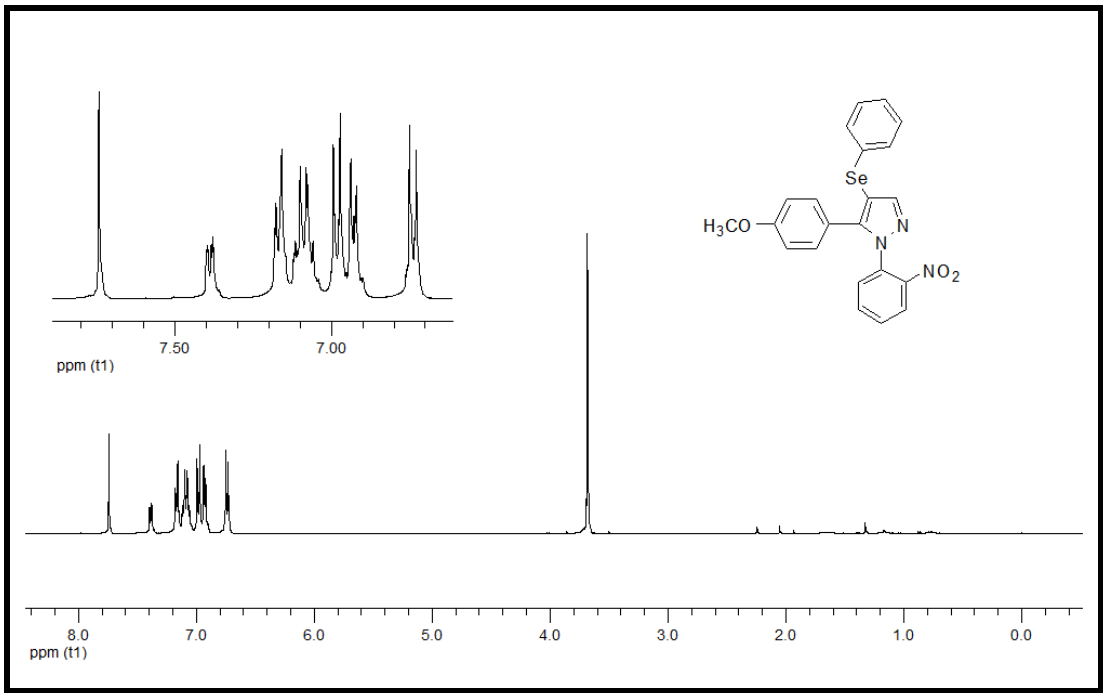

Figure A25. ^{1}H NMR spectrum of **81**

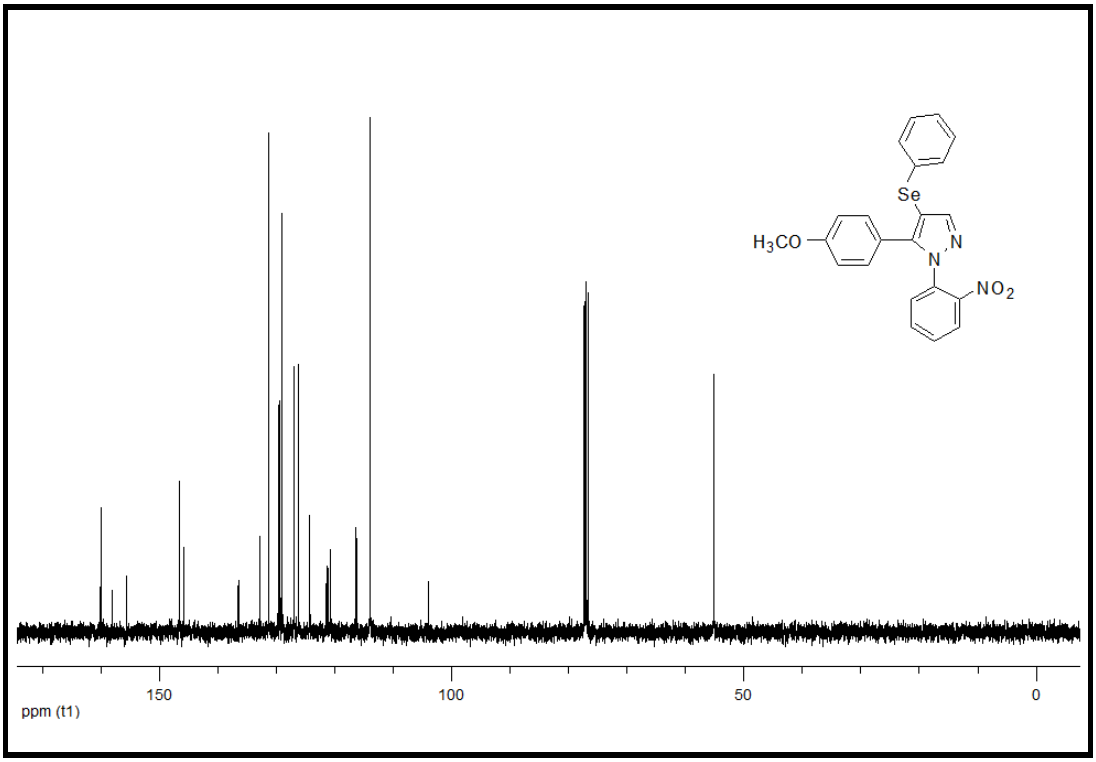

Figure A26. ^{13}C NMR spectrum of **81**