SYNTHESIS OF 5-FERROCENYL-4-((4-NITROPHENYL)SULFENYL)-1*H*-PYRAZOLES BY ELECTROPHILIC CYCLIZATION

A THESIS SUBMITTED TO
THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES
OF
MIDDLE EAST TECHNICAL UNIVERSITY

BY

FULYA KARAHAN DAĞ

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR
THE DEGREE OF MASTER OF SCIENCE
IN
CHEMISTRY

JULY 2011

Approval of the thesis:

SYNTHESIS OF 5-FERROCENYL-4-((4-NITROPHENYL)SULFENYL)-1*H*-PYRAZOLES BY ELECTROPHILIC CYCLIZATION

submitted by **FULYA KARAHAN DAĞ** 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. Bekir Peynircioğlu
Chemistry Dept., METU _____

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

Prof. Dr. Cihangir Tanyeli
Chemistry Dept., METU _____

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

Assoc. Prof. Dr. Adnan Bulut
Chemistry Dept., Kırıkkale University _____

Date: 27.07.2011

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 : Fulya KARAHAN DAĞ

Signature :

ABSTRACT

SYNTHESIS OF 5-FERROCENYL-4-((4-NITROPHENYL)SULFENYL)-1*H*-PYRAZOLES BY ELECTROPHILIC CYCLIZATION

Karahan Dağ, Fulya

M. Sc., Department of Chemistry

Supervisor: Prof. Dr. Metin Zora

July 2011, 81 pages

Pyrazoles have been intensely studied in the design and synthesis of biologically active agents because they display considerable medicinal activities. Recent studies have shown that integration of a ferrocenyl unit with structural features of pyrazoles can result in the formation of the new products with enhanced or/and unexpected biological activity since several ferrocene derivatives have already been illustrated to be active against a number of tumors. Therefore, we have investigated the electrophilic cyclizations of the hydrazones to afford 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-substituted pyrazole derivatives. First, the requisite hydrazone derivatives were synthesized by the reactions of ferrocenyl propargyl aldehydes or ketones with a series of hydrazines. Then electrophilic cyclizations of these hydrazones were investigated by treating with 4-(nitrophenyl)sulfenyl chloride as electrophile. By employing these electrophilic cyclizations, a series of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-1*H*-pyrazoles, 5-ferrocenyl-4-((4-nitrophenyl) sulfenyl)-3-methyl-1*H*-pyrazoles and 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-3-phenyl-1*H*-pyrazoles have been synthesized in moderate to good yields.

Keywords: Pyrazole, Ferrocene, Hydrazone, Electrophilic Cyclization

ÖZ

5-FERROSENİL-4-((4-NİTROFENİL)SULFENİL)-1*H*-PİRAZOL TÜREVLERİNİN ELEKTROFİLİK HALKALAŞMA TEPKİMESİ İLE SENTEZİ

Karahan Dağ, Fulya
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Metin Zora

Temmuz 2011, 81 sayfa

Pirazollerin tıbbi uygulamalarda önemli bir yapı olarak yer edinmesi, bu maddeyi içeren, biyolojik olarak aktif, yeni yapıların tasarımı ve sentezi üzerine yoğun çalışmalar yapılmasına yol açmıştır. Bir diğer tarafta da ferrosenlerin farklı yapılara dahil edilmesi, bu yapıların aktivitelerinin önemli biçimde arttığını göstermiştir. Ferrosen içeren pirazollerin ise birçok tümör hücrelerine karşı aktif olması gibi yeni kullanım alanları da oluşturabileceği düşünülmüştür. Bu nedenle, bu çalışmada 5-ferrosenil-4-((4-nitrofenil)sulfenil)-1*H*-pirazol türevlerinin, alkinik hidrazon ve 4-(nitrofenil)sulfenil klorür'ün elektrofilik halkalaşma tepkimesi ile sentezi çalışılmıştır. İlk olarak alkinik aldehit veya ketonlar çeşitli hidrazinler ile tepkimeye sokularak, bir seri alkinik hidrazonlar sentezlenmiştir. Daha sonra bu hidrazonlar elektrofilik olan 4-(nitrofenil)sulfenil klorür ile muamele edilerek, halkalaşma tepkimesi gerçekleşmiştir. Bu sayede 5-ferrosenil-4-((4-nitrofenil)sulfenil)-1*H*-pirazol, 5-ferrosenil-4-((4-nitro fenil)sulfenil)-3-metil-1*H*-pirazol ve 5-ferrosenil-4-((4-nitrofenil)sulfenil)-3-fenil-1*H*-pirazol türevleri, orta veya yüksek verimlerle elde edilmiştir.

Anahtar Kelimeler: Pirazol, Ferrosen, Elektrofilik Halkalaşma, Hidrazon

To My Family,

ACKNOWLEDGEMENTS

I would like to present my sincere thanks to my supervisor Prof. Dr. Metin Zora for his endless guidance and support throughout my Master study at METU. He enlarged my vision about scientific outlook. Moreover, He was not only my supervisor in academic means but also I learned a lot from him about life, relations, too. His continuous efforts in my career will never be forgotten.

I also thank to Dr. Arif Kıvrak, as much as my supervisor. His energy was endless. He always came up with new ideas and encouraged us to go further. He answered all of our problems and always maintained the smile on his face.

This study could not have been completed without the support of Zora's research group members. I would like to thank especially to Deniz Demirci for his friendship and optimistic behaviour, Sedef Karabyıykoğlu, I learned a lot from her and I will always appreciate her. Yılmaz Kelgökmen, Ezel Dikmen for their help in this research and all other D-249 members for making laboratory life full of chat and fun.

I also should express my thanks to Melis Şardan, Tuba İnceöz, Merve Türkşanlı, Özlem Gökçe, and İmre Bilgel for their never ending friendship during my education life and for the further.

I would like to thank to Seda Karayılan and Zehra Uzunoğlu for their kind help in my routine and special NMR analysis.

I would like to thank to TUBİTAK for rewarding me with MSc Student Scholarship during my master studies.

I would like to thank to Graduate School of Natural and Applied Sciences where I worked as a research assistant. They provided me flexible working hours and a room

of mine. I also thank to Ceren Bora, Neşe Öztop, Gülden Eroğlu, and Alper İnce for making working life warmer.

Finally, I would like to thank to my family for everything. Especially, my mother, Leyla Karahan has the most important role in my life for these days, my father Yusuf Karahan, my lovely sister, Gülin Karahan, my husband, Bulent Dağ, for his being part of me, and Adalet and Seydi Dağ for their support.

TABLE OF CONTENTS

ABSTRACT……iv
ÖZ……...….v
ACKNOWLEDGEMENTS……...……vii
TABLE OF CONTENTS……ix
LIST OF TABLES……..xii
LIST OF FIGURES……...xiii
ABBREVIATIONS……..xvii
CHAPTERS
1. INTRODUCTION 1
1.1 Pyrazoles 6
1.1.1 Synthesis of pyrazoles 8
1.1.2 Biologically important pyrazole derivatives 11
1.2 Ferrocene and biologically active ferrocene derivatives 13
1.3 Ferrocenyl pyrazoles 18
1.4 Electrophilic cyclization reactions 21
1.5 The aim of the study 21
2. RESULTS AND DISCUSSION 23
2.1 Synthesis of 3-ferrocenylpropynal (41), 4-ferrocenyl-3-yne-2-butynone (44) and 3-ferrocenyl-1-phenyl-propynone (45) 23
2.2 Synthesis of alkynic hydrazones (51, 52, 53) 25
Structures of α,β-alkynic hydrazones are presented in Figure 37, which contain different substituents with ferrocenyl moiety. 28
2.3 Synthesis of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-1H-pyrazoles (55) ... 29
2.4 Synthesis of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl-3-phenyl-1H-pyrazoles 56 and 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-3-methyl-1H-pyrazoles 57 32
2.5 Proposed reaction mechanism for electrophilic cycliation of alkynic hydrazones with 4-(nitrophenyl)sulfenyl chloride. 37
3. CONCLUSION 39
4. EXPERIMENTAL 40

4.1 Synthesis of acetylferrocene (23) 41
4.2 Synthesis of (2-formyl-1-chlorovinyl)ferrocene (38) 41
4.3 Synthesis of ethynylferrocene (48) 42
4.4 Synthesis of 3-ferrocenylpropynal (41) 43
4.5 Synthesis of propargyl ketones (44, 45) 44
4.5.1 Synthesis of 1-methyl-3-ferrocenylprop-2-yn-1-one (44) 44
4.5.2 Synthesis of 1-phenyl-3-ferrocenylprop-2-yn-1-one (45) 44
4.6 General Procedure 1: Synthesis of alkynic hydrazones (51, 52, 53) 45
4.6.1 Synthesis of (*E*)- and (*Z*)-1-(3-ferrocenylprop-2-ynylidene)-2-phenyl-hydrazines (51-*E* and 51-*Z*) 45
4.6.2 Synthesis of (*Z*)-1-(2,5-diflorophenyl)-2-(3-ferrocenylprop-2-ynylidene) hydrazine (51-*Z*b) 46
4.6.3 Synthesis of (*Z*)-1-((4-trifloromethyl)phenyl)-2-(3-ferrocenylprop-2-ynylidene)hydrazine (51-*Z*c) 46
4.6.4 Synthesis of (*Z*)-1-(3-chloro-4-florophenyl)-2-(3-ferrocenylprop-2-ynylidene)hydrazine (51-*Z*d) 47
4.6.5 Synthesis of (*Z*)-1-phenyl-2-(4-ferrocenylbut-3-yn-2-ylidene)hydrazine (52-*Z*a) 47
4.6.6 Synthesis of (*Z*)-1-(2,5-diflorophenyl)-2-(4-ferrocenylbut-3-yn-2-ylidene) hydrazine (52-*Z*b) 48
4.6.7 Synthesis of (*Z*)-1-((4-trifloromethyl)phenyl)-2-(4-ferrocenylbut-3-yn-2-ylidene)hydrazine (52-*Z*c) 48
4.6.8 Synthesis of (*Z*)-1-(3-chloro-4-florophenyl)-2-(4-ferrocenylbut-3-yn-2-ylidene)hydrazine (52-*Z*d) 49
4.6.9 Synthesis of (*Z*)-1-(3-ferrocenyl-1-phenylprop-2-ynylidene)-2-phenyl hydrazine (53-*Z*a) 49
4.6.10 Synthesis of (*Z*)-1-(3-ferrocenyl-1-phenylprop-2-ynylidene)-2-(2,5-difloro phenyl)hydrazine (53-*Z*b) 50
4.6.11 Synthesis of (*Z*)-1-(3-ferrocenyl-1-phenylprop-2-ynylidene)-2-((4-trifloro methyl)phenyl)hydrazine (53-*Z*c) 50
4.6.12 Synthesis of (*Z*)-1-(3-ferrocenyl-1-phenylprop-2-ynylidene)-2-(3-chloro-4-florophenyl)hydrazine (53-*Z*d) 51

4.7 General Procedure 2: Synthesis of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-1H-pyrazoles (55, 56, 57) 51
4.7.1 Synthesis of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-1*H*-pyrazoles (55) 52
4.7.2 Synthesis of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-3-methyl-1*H*-pyrazoles (56) 53
4.7.3 Synthesis of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-3-phenyl-1*H*-pyrazoles (57) 55
REFERENCES 57
APPENDIX A. NMR Data 61

LIST OF TABLES

TABLES

Table 1. Synthesis of alkynic hydrazones **51-53**.....…..…….……....27

Table 2. Effect of temperature, solvent, base, and time on the synthesis of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-1-phenyl-1*H*-pyrazole **(55A)**……30

Table 3. Synthesis of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-1*H*-pyrazoles **55**…31

Table 4. Effect of temperature, solvent, base, and time on the synthesis of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-1*H*-pyrazoles **(57A)**……..……..……..33

Table 5. Synthesis of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-3-methyl-1*H*-pyrazoles **(56)** and 5-ferrocenyl-4-((4-nitro phenylsulfenyl-3-phenyl-1*H*-pyrazoles **(57)**……..34

LIST OF FIGURES

FIGURES

Figure 1. Some early heterocyclic compounds of natural origin……..……...2
Figure 2. Alkaloids used in tobacco industry……..3
Figure 3. Purine alkaloids……3
Figure 4. Structures of some vitamins…….4
Figure 5. Structure of penicilin G, phenothiazine, chlorpromazine…….5
Figure 6. Some examples of heterocycles used in food industry……..….5
Figure 7. Knorr pyrazole molecule framework synthesis..……..6
Figure 8. Synthesis of pure pyrazole core by decarboxylation of pyrazole-3,4,5-tricarboxylic acid (**1**)…….7
Figure 9. The first extracted natural pyrazole samples……7
Figure 10. Tautomeric forms for unsubstituted pyrazole…….8
Figure 11. Tautomeric forms for substituted pyrazole…….8
Figure 12. Pyrazole synthesis via condensation reaction of hydrazines with 1,3 dicarbonyl compounds **4** or α, β unsaturated aldehydes or ketones **5, 6, 7**…….….9
Figure 13. Synthesis of anti-inflammatory drug tepoxalin **12**……...10
Figure 14. Synthesis of 4-(5-p-tolyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzene sulfonamide (**13**)…….10
Figure 15. Synthesis of 5-(thiophen-2-yl)-1*H*-pyrazole **(14)** by ring closure precursor……11
Figure 16. Structures of chlorantroniliprole **16**, fipronil **17**, and paicer **18**……...12
Figure 17. Structures of sildenafil citrate **19,** celebrex **20,** DHODase enzyme **21**....13
Figure 18. Structure of ferrocene (**22**)……...14
Figure 19. Schematic of ferrocene preparation……..14
Figure 20. Basic substitution reactions of ferrocene (**22**)……..15
Figure 21. Ferrocenyl penicilins **27**……...16
Figure 22. Structures of tamoxifen **28**, hyroxytamoxifen **29,** ferrocifens **30**, and ferrocenophanes **31**…….16

Figure 23. Ferrocenyl derivatives of oxaliptalin **32,** dehydropyrazol **33,** cyanoacrylate **34…**……17
Figure 24. Structures of ferroquine **35** and ferrocene-tridimenol derivatives **36**…..18
Figure 25. Synthesis of ferrocenyl pyrazole derivatives with antitumor activity…..19
Figure 26. Ferrocenyl pyrazole formation through the reaction between (2-formly-1-chlorovinly)ferrocene **(38)** and hydrazines…….19
Figure 27. Synthesis of ferrocenyl pyrazoles **39, 40** by the reactions of 3-ferrocenylpropynal (**41**) with hydrazinium salts…….20
Figure 28. Synthesis of 4-iodo-5-ferrocenyl pyrazole derivative **43…**…….20
Figure 29. Schematic of electrophilic cyclization……..21
Figure 30. Synthesis of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-1*H*-pyrazoles **(47).**22
Figure 31. Synthesis of acetylferrocene **(31),** (2-formly-1-chlorovinly)ferrocene **(38)**, and ethynlferrocene **(48)**……23
Figure 32. Synthesis of 3-ferrocenylpropynal **(41)**……24
Figure 33. Synthesis of 4-ferrocenyl-3-yne-2-butyone **(44)…**……..25
Figure 34. Synthesis of 3-ferrocenyl-1-phenyl-propynone **(45)…**……25
Figure 35. Synthesis of *E* and *Z* isomers of hydrazones……26
Figure 36. Hydrazines **54a-54d** used in the synthesis of alkynic hydrazones……...28
Figure 37. ferrocenyl alkynic hydrazones used in electrophilic cyclization, **51-*Z*a-d, 52-*Z*a-d, 53-*Z*a-d…**……28
Figure 38. Structures of the synthesized 5-ferrocenyl-4-((4-nitrophenyl) sulfenyl)-1*H*-pyrazole derivatives **55A-D…**…….…….....32
Figure 39. Structures of the synthesized 3-methyl-4-(4-nitrophenylsulfenyl)-5-ferrocenyl-1*H*-pyrazole derivatives **56A-D** and 3-phenyl-4-(4-nitrophenyl sulfenyl)-5-ferrocenyl-1*H*-pyrazole derivatives **57A-D…**…….35
Figure 40. ^{1}H NMR spectrum of pyazole **56A…**……...37
Figure 41. ^{13}C NMR spectrum of pyrazole **56A…**……38
Figure 42. Mechanism for the formation of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-1*H*- pyrazoles **55-57**……39
Figure A1. ^{1}H NMR spectrum of **52*Z*-a**…….…….62
Figure A2. ^{13}C NMR spectrum of **52*Z*-a**…….…….....62

Figure A3. ^{1}H NMR spectrum of **52*Z*-b**……..63
Figure A4. ^{13}C NMR spectrum of **52*Z*-b**…….…63
Figure A5. ^{1}H NMR spectrum of **52*Z*-c**…….……...64
Figure A6. ^{13}C NMR spectrum of **52*Z*-c**……..64
Figure A7. ^{1}H NMR spectrum of **52*Z*-d**...…….…...65
Figure A8. ^{13}C NMR spectrum of **52*Z*-d**..…….……65
Figure A9. ^{1}H NMR spectrum of **53*Z*-a**……66
Figure A10. ^{13}C NMR spectrum of **53*Z*-a**…...66
Figure A11. ^{1}H NMR spectrum of **53*Z*-b**…..……67
Figure A12. ^{13}C NMR spectrum of **53*Z*-b**…...……...67
Figure A13. ^{1}H NMR spectrum of **53*Z*-c**…..…….....68
Figure A14. ^{13}C NMR spectrum of **53*Z*-c**…….……68
Figure A15. ^{1}H NMR spectrum of **53*Z*-d**..…….…...69
Figure A16. ^{13}C NMR spectrum of **53*Z*-d**…..…….……..69
Figure A17. ^{1}H NMR spectrum of **55A**…….…...70
Figure A18. ^{13}C NMR spectrum of **55A**…….……..70
Figure A19. ^{1}H NMR spectrum of **55B**……....71
Figure A20. ^{13}C NMR spectrum of **55B**……...71
Figure A21. ^{1}H NMR spectrum of **55C**……....72
Figure A22. ^{13}C NMR spectrum of **55C**…….…..72
Figure A23. ^{1}H NMR spectrum of **55D**……....73
Figure A24. ^{13}C NMR spectrum of **55D**…….…..73
Figure A25. ^{1}H NMR spectrum of **56A**…….…...74
Figure A26. ^{13}C NMR spectrum of **56A**…….……..74
Figure A27. ^{1}H NMR spectrum of **56B**…….…...75
Figure A28. ^{13}C NMR spectrum of **56B**…….……..75
Figure A29. ^{1}H NMR spectrum of **56C**……....76
Figure A30. ^{13}C NMR spectrum of **56C**……...76
Figure A31. ^{1}H NMR spectrum of **56D**……....77
Figure A32. ^{13}C NMR spectrum of **56D**…….…..77
Figure A33. ^{1}H NMR spectrum of **57A**……....78
Figure A34. ^{13}C NMR spectrum of **57A**…….…..78
Figure A35. ^{1}H NMR spectrum of **57B**…….…...79

Figure A36. ^{13}C NMR spectrum of **57B**……..……..79
Figure A37. ^{1}H NMR spectrum of **57C**……..……...80
Figure A38. ^{13}C NMR spectrum of **57C**……..……..80
Figure A39. ^{1}H NMR spectrum of **57D**……..……...81
Figure A40. ^{13}C NMR spectrum of **57D**……..……..81

ABBREVIATIONS

bn	billion
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
DCE	dichloroethane
DMF	dimethylformamide

CHAPTER 1

INTRODUCTION

Organic chemistry is a branch of chemistry that includes variety of studies related with reactions, properties, and structural aspects of carbon-based compounds. Although, to synthesize organic compounds could be better understood recently, in early times they seemed to be very complex structures to synthesize and could only be obtained from nature. Thus those structures were labeled as "vital compounds" [1]. Organic compounds play important role as proteins contributing to catalyze reactions in living organisms and also they constitute much of blood, tissue, muscle and skin [2]. In addition, in genetics, basic structures related with heredity are composed of organic compounds that control main processes in the cells. To extend this list, we meet them as food in our meals to eat, as drugs to heal diseases, as gasoline to drive off cars and so on [3].

Many organic compounds are found in cyclic structures. These cyclic organic compounds may have an element, like nitrogen, oxygen, etc., other than the carbon in their composition. Then, they are classified as *heterocyclic.* Heterocycles are widespread in organic chemistry. A recent analysis performed on the organic compounds registered in *Chemical Abstracts,* by the time June 2007, showed that many of 24.282.284 cyclic structure adopting compounds are heterocyclic [4]. Essential vitamins, coenzymes, hemoglobin, DNA, RNA are all made up of heterocyclic ring. Heterocycles also constitute remarkable place in medicine, agriculture, petroleum and dye industries. The source is not far or complicated. Nature presents great variety of heterocycles, especially, plants, microorganisms, marine animals are sources of nitrogen containing cyclic compounds [5].

Even if, many synthetic ways improved to synthesize them after years of research, early heterocyclic compounds were extracted from natural sources. Chronogically some examples to these early compounds are ordered as (Figure 1) [6]:

- Uric acid from human bladder stones in 1776.
- Alloxan by oxidation of uric acid in 1818.
- Quinoline from coal distillates in 1834.
- Melamine in 1834.
- Pyrole by runge in coal tar in 1834
- Pyridine on pyrolysis of bones in 1849
- Indole by degradation of indigo in 1866
- Furan by destructive distillation of of wood and cellulose in 1870.

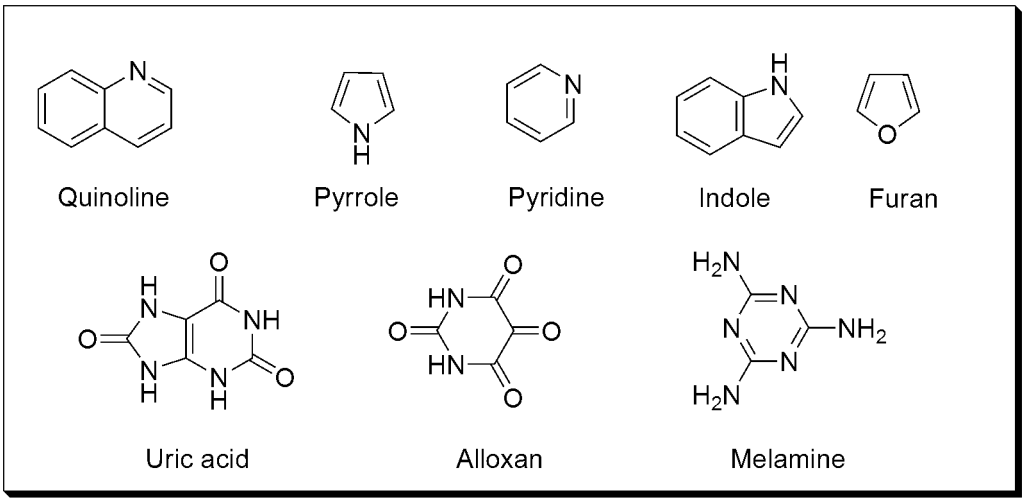


Figure 1. Some early heterocyclic compounds of natural origin.

Heterocyclic compounds containing nitrogen are weakly basic and can form salts by reaction with mineral acids. So isolated ones from plants are also known as alkaloids (alkali like). These types are mostly used in tobacco industry like nicotine, anabasine, and anatabine (Figure 2) [6].

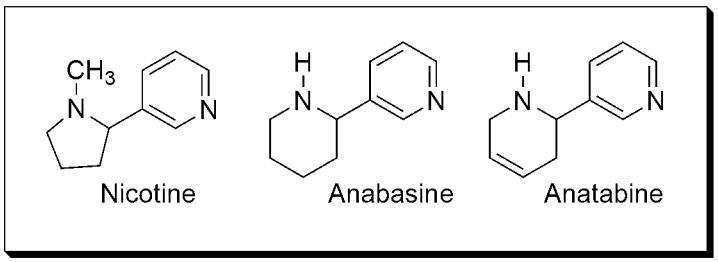


Figure 2. Alkaloids used in tobacco industry.

In daily life, most of the people at least taste the drinks tea, coffee, or cocoa. Having a delicious taste and aroma, these drinks reflect their effect as they bear caffeine, theobromine and theophylline, alkaloid derivatives of heterocyclic purine. These derivatives are extracted from tea leaves and the beans of coffee and tobacco. They are famous for their stimulant role in the central nervous system (Figure 3) [7].

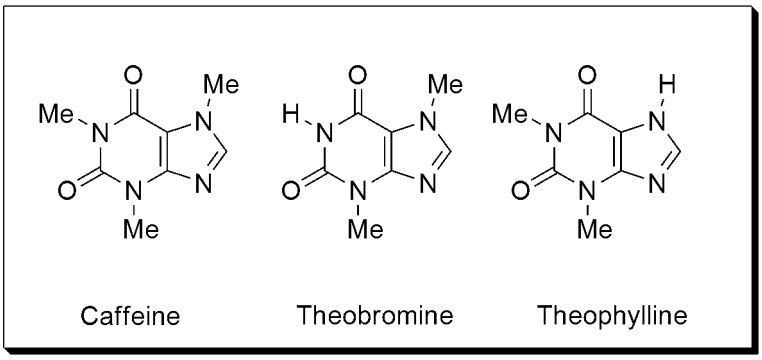


Figure 3. Purine alkaloids.

The structural variety can be best seen in vitamins and chemicals essentials for growth. Nucleic acids, amino acids essential for biological systems are all heterocyclic. Chlorophyll is the main component for photosynthesis process in higher plants, is also heterocyclic. Moreover vitamins that the human metabolism needs to

consume like, B1, B2, B3, B6 and C adopt heterocyclic ring structures, too. Some examples for vitamins are given in Figure 4 [7].

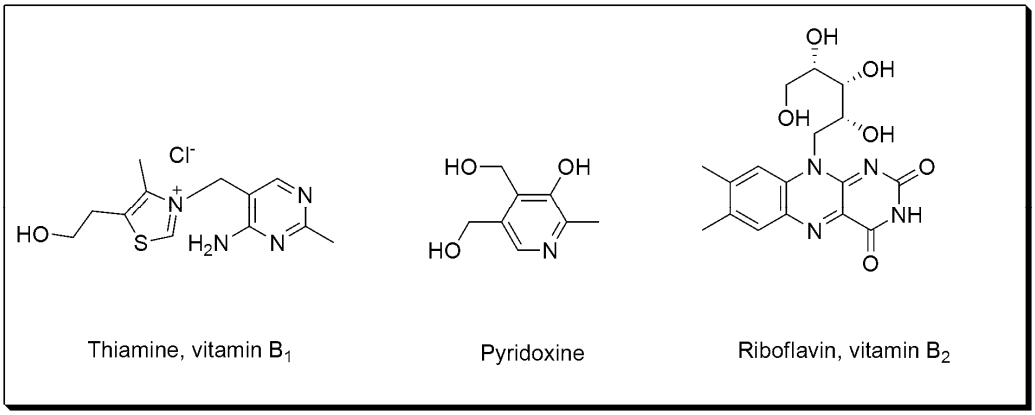


Figure 4. Structures of some vitamins.

Nitrogen and sulfur containing heterocycles attract attention in petroleum industry. For example, pyridine based heterocycles were extracted from coal. Besides, In the field of solar system chemistry, presence of pyridine carboxylic acid is noted in a meteorite found near Tagish Lake [8].

Heterocyclics found in nature also serve in pharmaceutical applications (antibiotic, neurotropic, cardiovascular, anticarcinogenic). The firstly discovered antibacterial, penicilin G, became very popular among drugs for its treatment bacterial infections. By means of this β-lactam drug, during world war II, many lives were saved. Even if there are numerous antibiotics today, it still keeps its fame. Moreover, by the introduction of phenothiazine derivatives, another important progress in heterocyclic chemistry has been made. In the beginning of 1950s this derivative was subjected to clinical tests for its treatment psychological disorders. Chlorpromazine constitutes the fundamental place in this class. It has been widely used for the treatment of schizophrenia by reducing the levels of aggressiveness (Figure 5) [6].

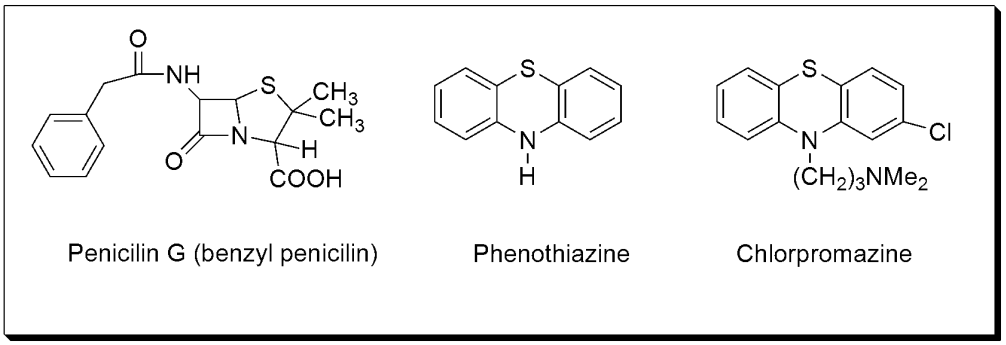


Figure 5. Structure of penicilin G, phenothiazine, chlorpromazine.

Heterocyclic compounds also became trend in food industry as dyes or aromas. Red erythrosine, yellow tartrazine, blue indigo carmine all contains heterocyclic moiety in their structure. Among these yellow tartrazine has a pyrazole core. Additionally, the smell of most food contains a bunch of constituents. Among these, for example, 8-methylpyrrolo[1,2-α]pyrazine is the primary source of the odor of roasted-meat (Figure 6) [7].

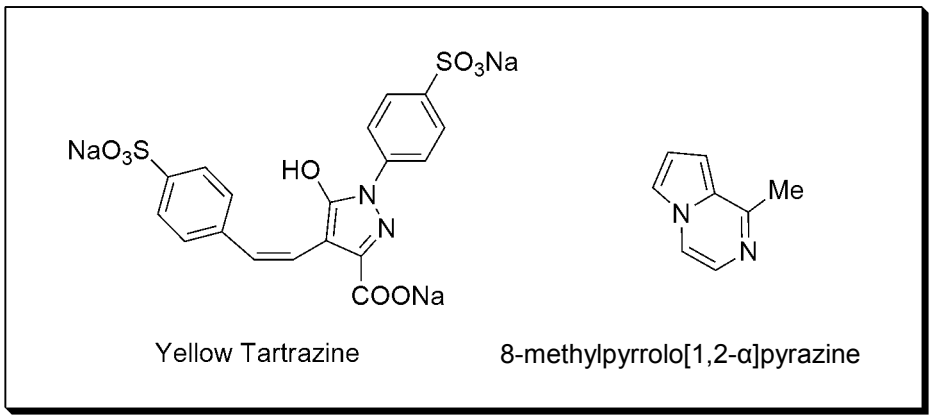


Figure 6. Some examples of heterocycles used in food industry.

In short, all of those facts clearly show that heterocyclic compounds are essential part of organic chemistry. Thus, those compounds attract special interest of researchers.

1.1 Pyrazoles

Five membered ring systems containing nitrogen atoms at 1,2-positions are named as pyrazoles [9]. Pyrazoles are found very scarce in nature. However, due to their biological activities especially in the fields of pharmacy, agriculture and technology, the synthesis of pyrazole derivatives has been studied by many researchers [10].

The first pyrazole derivative was prepared by Ludwig Knorr in 1883. He utilized Emil Fisher's discovery of phenylhydrazine. The condensation reaction between phenylhydrazine and 1,3-diketoester gave a substituted pyrazolone derivative, namely 1-phenyl-3-methyl-5-pyrazolone (Figure 7). When this intermediate was treated with methyl iodine, Knorr obtained antipyrine, which showed the characteristic properties as analgesic and antipyretic [11].

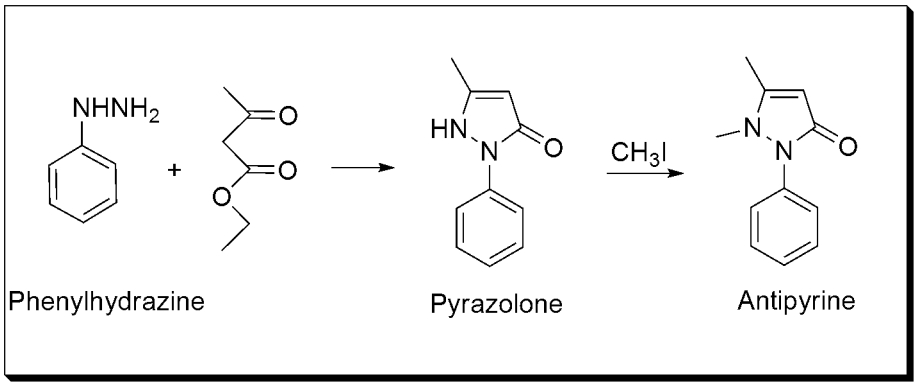


Figure 7. Knorr pyrazole molecule framework synthesis.

The pure pyrazole core could not be characterized until 1889, when Buchner obtained it by decarboxylation reaction of pyrazole-3,4,5-tricarboxylic acid (**1**) (Figure 8) [12].

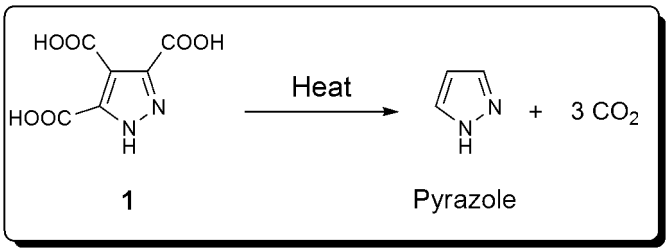


Figure 8. Synthesis of pure pyrazole core by decarboxylation of pyrazole-3,4,5-tricarboxylic acid (**1**).

Nobody knew pyrazole samples were found in nature until 1954 when Japanese researchers discovered the first pyrazole sample in nature. 3-*n*-Nonylpyrazole (**2**) was isolated from a plant grown in tropical Asia, Hauttuynia Cardata. Conducted experiments on this pyrazole derivative showed that it exhibits antimicrobial activity. Later on, a second pyrazole derivative, *levo*-*β*-(1-pyrazolyl) alanine (**3**), was extracted from watermelon seeds. This pyrazole was pyrazolic amino acid (Figure 9) [12].

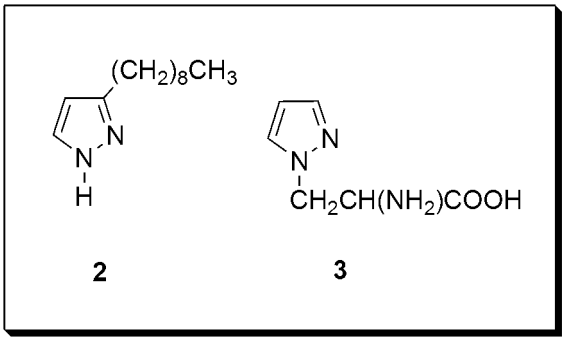


Figure 9. The first extracted natural pyrazole samples.

Having six delocalized π-electrons and planar conjugated ring structure, pyrazoles are also aromatic compounds like benzene ring. Hence, most of the information about pyrazole chemistry attained by comparing with benzenes [13]. Additionally, in the beginning of discovery, there aroused some structural problems due to

tautomerism of pyrazole ring. Accordingly, for unsubstituted pyrazoles three possible tautomeric forms could be written (Figure10) [12].

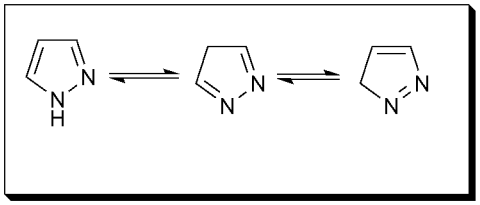


Figure 10. Tautomeric forms for unsubstituted pyrazole.

Pyrazole compounds having different substituents on two carbon atoms adjacent to the nitrogen atoms have possible five tautomeric forms (Figure 11) [12].

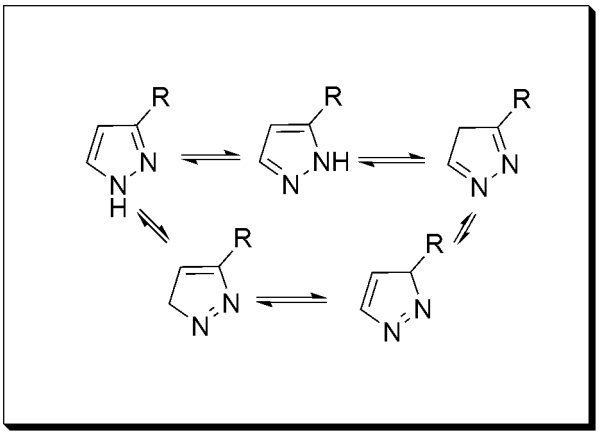


Figure 11. Tautomeric forms for substituted pyrazole.

1.1.1 Synthesis of pyrazoles

Synthesis of pyrazole derivatives are described by many different procedures in literature. The variety of substituents affects how the methodology, reactions,

transformations, synthetic routes, etc. will proceed [14]. Although there are many ways to assemble pyrazole rings, the cyclization through condensation reaction of 1,3-dicarbonyl ketone or aldehyde with a hydrazine is the most common one. Hydrazines act as bidendate nucleophile towards 1,3-dicarbonyl compounds **4** or α,β-unsaturated aldehydes or ketones **5-7** (Figure 12). The substitution pattern and symmetry can give the isomeric pyrazoles **8** and/or **9** [5,14].

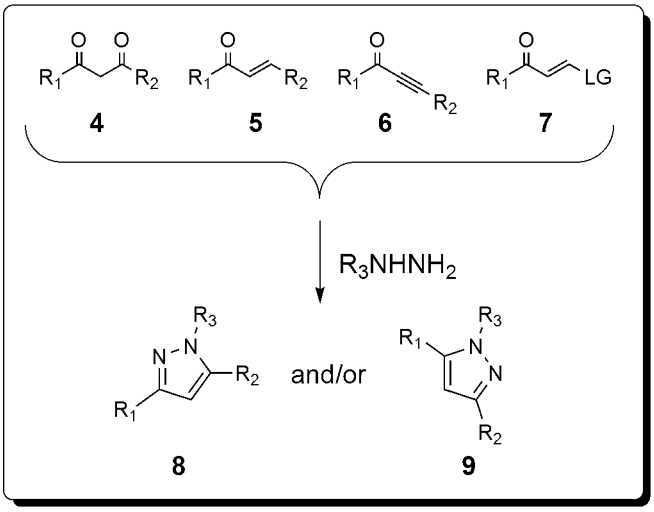


Figure 12. Pyrazole synthesis via condensation reaction of hydrazines with 1,3-dicarbonyl compounds **4** or α,β-unsaturated aldehydes or ketones **5**, **6**, **7**.

This common method has been utilized in the formation of various products. To exemplify, the cyclocondensation of 6-(4-chlorophenyl)-*N*-hydroxy-*N*-methyl-4,6-dioxohexanamide (**10**) with 4-methoxyphenylhydrazine (**11**) resulted in the formation of anti-inflammatory drug tepoxalin (**12**) (Figure 13) [15].

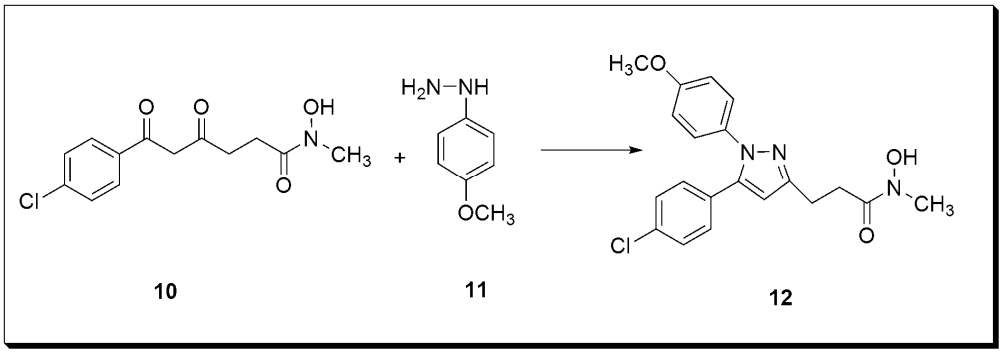


Figure 13. Synthesis of anti-inflammatory drug tepoxalin (**12**).

1,3-Dipolar cycloaddition of nitrile imines with alkynes or alkenes is secondly used methodology utilized for pyrazole synthesis. For this synthesis, firstly, nitrile imine generation is necessary. In situ generation of nitrile imines can be performed by base catalyzed elimination of hydrogen halide or benzene sulfonate as shown below, so that the resulting intermediate readily adds to alkenes and alkynes. Synthesis of 4-(5-*p*-tolyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzenesulfonamide (**13**) could be achieved through this way (Figure 14) [5].

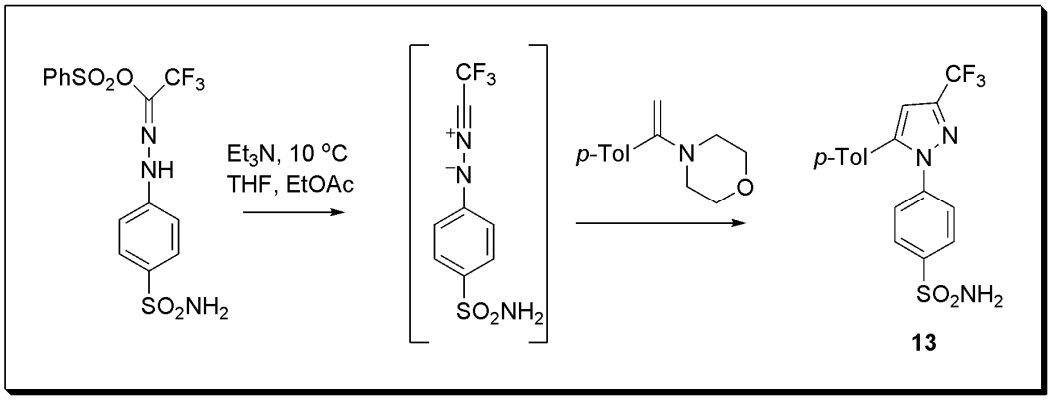


Figure 14. Synthesis of 4-(5-*p*-tolyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzenesulfonamide (**13**).

Among most of the routes for pyrazole syntheses, an essential one is the ring closure condensation reaction of a tosylhydrazone-phosphonate **14** with an aldehyde. Horner-Emmons has expressed this way as a sequence which starts by the intramolecular Michael addition and continuing with the loss of toluenesulfinate group which leaves the molecule aromatic and results in the formation of 5-substituted pyrazole compound such as 5-(thiophen-2-yl)-1*H*-pyrazole (**15**) (Figure 15) [16].

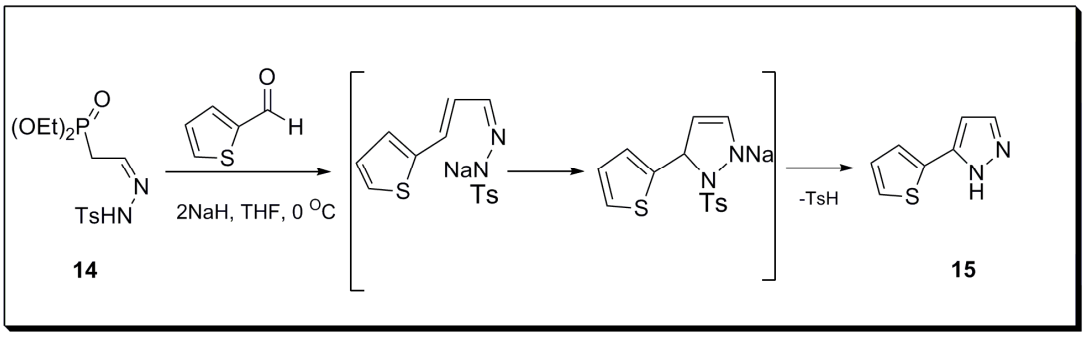


Figure 15. Synthesis of 5-(thiophen-2-yl)-1*H*-pyrazole (**14**) by ring closure precursor.

1.1.2 Biologically important pyrazole derivatives

Many biologically active compounds are composed of pyrazole ring in their frame. Pyrazole containing compounds constitute essential part for variety of industrial applications like agrochemistry, medicine, etc. In agriculture, they have potential use as insectices [6,17] or herbicides [7,18]. In medicine we met them in the structures of many analgesics, anti-inflammatory, antitumor, antimicrobial agents etc. [19]. Thus the research on pyrazolic compounds has been attractive since last decades and continuously new derivatives are taking place in literature [20].

Chlorantroniliprole (**16**) is used as crop protection agent against insects. It functions through activation of ryonadine receptors which leads to calcium release in muscles of insects. Another class of insecticides disrupts the central nervous system. Fipronil (**17**) shows activity in that means. This herbicide blocks the γ-aminobutric acid

(GABA) receptor/chloride channel in the neurologic system [6]. Pyrazole containing agents were also used in the elimination of unwanted plants. As known, the basic action in plant metabolism is chlorophyll synthesis which occurs in many steps. Disruption of any stage can inhibit this synthesis. Therefore herbicides functioning in that bioactivity are preferable. An example of this class of herbicides can be given as the pyrazole derivative Paicer (**18**) (Figure 16) [7].

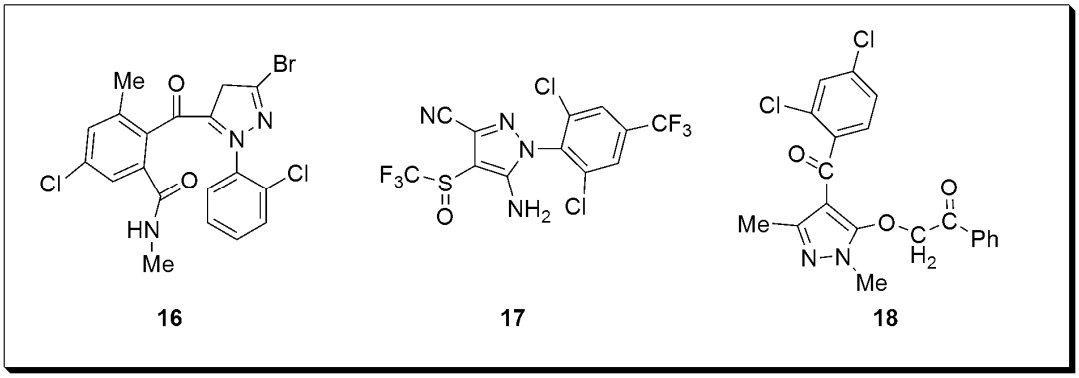


Figure 16. Structures of chlorantroniliprole (**16**), fipronil (**17**), and paicer (**18**).

Pyrazoles also constitute great portion in medicine. To exemplify, commercially called Viagra, scientifically sildenafil citrate (**19**) (Figure 17), is a pyrazole derivative containing molecule in its structure. This drug makes oral therapy for male erectile dysfunction by hindering the activity of phosphodiesterase enzyme existing in human *corpus cavernosum* [21].

Celebrex (**20**) has its marketplace in the pharmacies due to its use as anti-inflammatory drug for rheumatoid arthritis and acute pain. Celebrex functions by inhibiting the activity of cyclooxygenase-2 (COX-2) enzyme which takes part in reactions causing inflammation and pain in body (Figure 17) [22]. Another example for inhibitors is DHODase enzyme (**21**) (Dihydroorotate dehydrogenase) which plays a key role in the synthesis of pyrimidine. By this way, DHODase enzyme inhibits the termination of helicobacter pyroli bacterium cells which causes gastrointestinal disorders (Figure 17) [23].

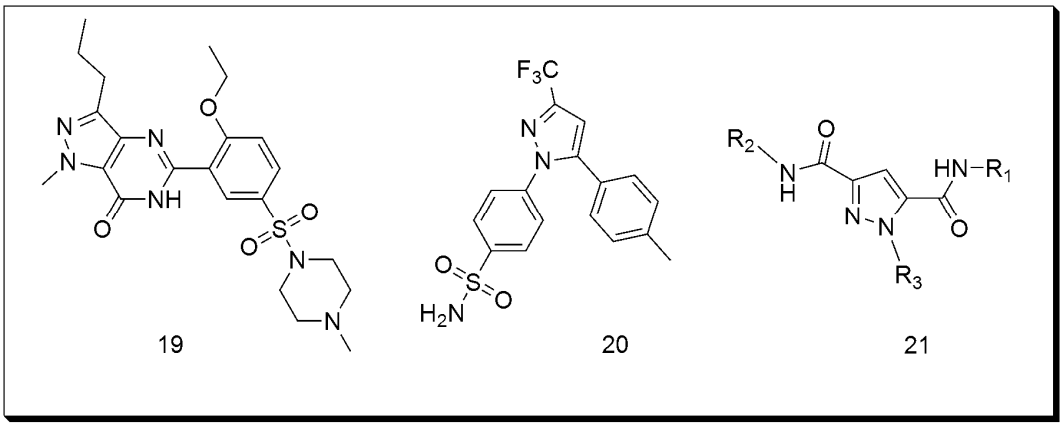
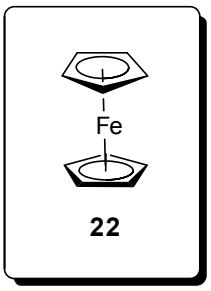


Figure 17. Structures of sildenafil citrate (**19**), celebrex (**20**) and DHODase enzyme (**21**).

1.2 Ferrocene and biologically active ferrocene derivatives

When a compound contains a moiety with a carbon-metal bond, then this compound classified as *Organometallic*. Research on this topic is increasing day by day, since they possess strong chemical and physical properties. To specify, being structurally stable, synthetically accessible, chemically versatile, ferrocene (**22**) has taken great interest among organometallic compounds (Figure 18) [24].

In very early 1950s, English chemists found out the orange powder organometallic compound *ferrocene* (**22**) which formed when cyclopentadiene reeved iron tubings. Keally, Pauson and Miller introduced this compound in 1951 and Pauson described the structure as bis-cyclopentadienyl-iron [$Fe(\sigma\text{-}C_5H_5)_2$], which was published in *Nature* [25]. However, this proposal was not obeying the 18 valance e^- rule. It had 10 valance electrons. Soon after, Wilkinson, Woodward, and Fischer developed sandwich like structure. Accordingly, it can be described as an 18-electron complex, having a π-bonded iron metal between two parallel cyclopentadienyl group and showing aromatic properties. It has a dipole moment zero and shows one typical C-H peak in IR spectrum. The stability makes this frame resistant to hydrolytic and oxidative cleavage. In relation to this improvement, "the discovery of ferrocene is accepted as the boom of organometallic chemistry" [26].



22

Figure 18. Structure of ferrocene (**22**).

Many synthetic methods have been developed to synthesize ferrocene (**22**). The easier and reasonable way to get ferrocene can be described as deprotonation of cyclopentadiene with KOH and treatment with $FeCl_2$ in DMSO (Figure 19) [27].

Figure 19. Preparation of ferrocene.

Exhibiting aromatic properties with electron abundance, this orange compound may undergo various simple and valuable reactions such as Friedel-Crafts acylation/alkylation, Vilsmeier formylation, dimethylamino-methylation and mercuration reactions (Figure 20) [28].

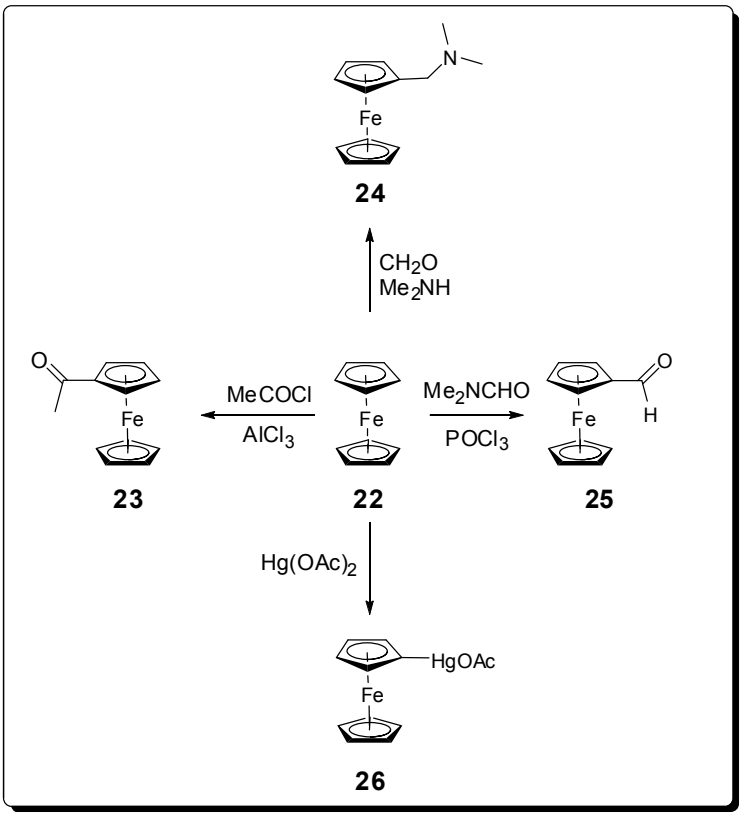


Figure 20. Basic reactions of ferrocene (**22**).

Ferrocenes possess strong chemical and physical properties like being neutral and non-toxic. From this point of view, replacing an aromatic constituent of a biological compound by ferrocene could change its activity. An important tangible result obtained when penicilins with ferrocene moiety **27** were synthesized by the research group of Edwards [29]. Formerly, certain bacteria were degrading the antibiotics of penicilin by producing β-lactamase enzyme. Ferrocene bearing penicilins **27** inhibited the activity of these bacteria (Figure 21) [29].

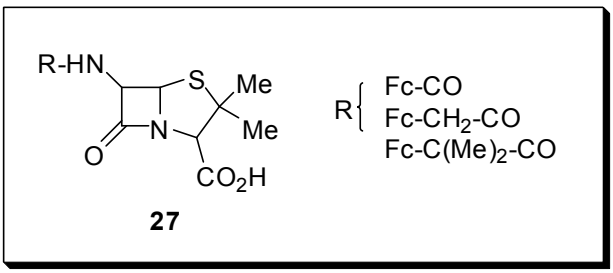


Figure 21. Ferrocenyl penicilins **27**.

Another step has taken toward this novelty when the research group of Jaouen synthesized ferrocifens (**30**), ferrocenyl analogues of tamoxifen (**28**) and hydroxytamoxifen (**29**). Tamoxifen (**28**) and hydroxytamoxifen (**29**) treats only hormone-dependent breast cancer cells [30]. Substitution of phenyl group by ferrocenyl moiety increased the lipophilicity of the compound which allowed the molecule to enter through the cells and they showed activity toward both hormone-dependent and hormone-independent breast cancer cells [31,32]. Later on, they introduced that ferrocenophane derivatives **31** of ferrocifens are more active against breast cancer cells (Figure 22) [33].

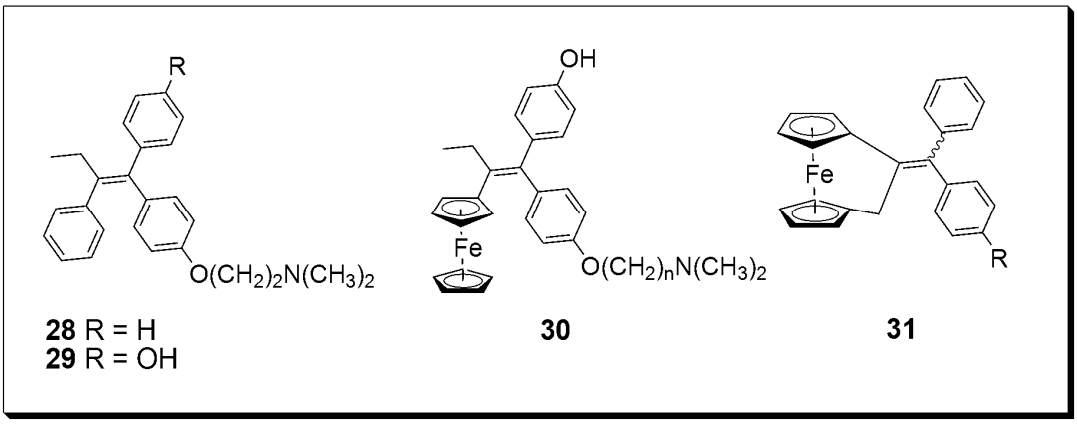


Figure 22. Structures of tamoxifen (**28**), hydroxytamoxifen (**29**), ferrocifen (**30**) and ferrocenophane (**31**).

Those advancements gave credit for research on the modification of active biological skeletons by organometallics. Accordingly, the complexes of ferrocenyl oxaliptalin **32** as anticancer drug [34], ferrocenyl dehydropyrazole **33** as antibacterial reagent [35], and ferrocenyl cyanoacrylate **34** as herbicide were used [36] (Figure 23).

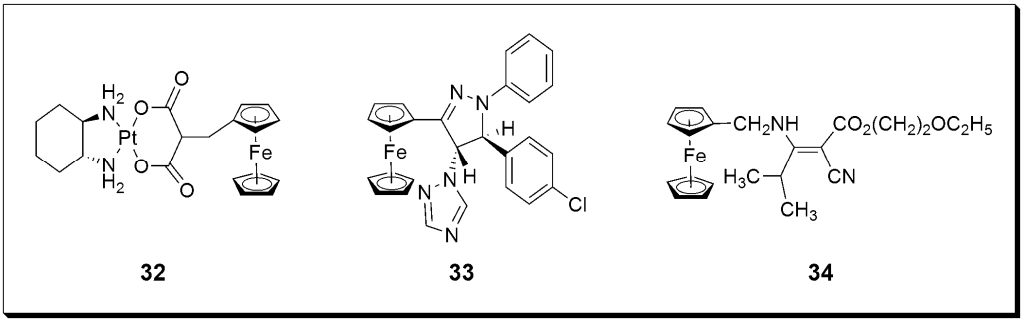


Figure 23. Ferrocenyl oxaliptalin **32**, ferrocenyl dehydropyrazole **33** and ferrocenyl cyanoacrylate **34**.

In addition to their significance in cancer treatment, ferrocene-substituted compounds also address most of the biological problems. To exemplify, *Plasmodium falciparum* known as a threatening malaria parasite. This parasite shows resistivity against antimalaria drugs chloroquine, mefloquine and quinine, so researches have been conducted on solving that problem [37]. The studies revealed that ferroquine derivatives **35** bears antimalarial property against this parasite (Figure 24) [38]. In addition to this finding, ferrocene-tridimenol analogues **36** shows effective regulatory role on plant growth (Figure 24) [39].

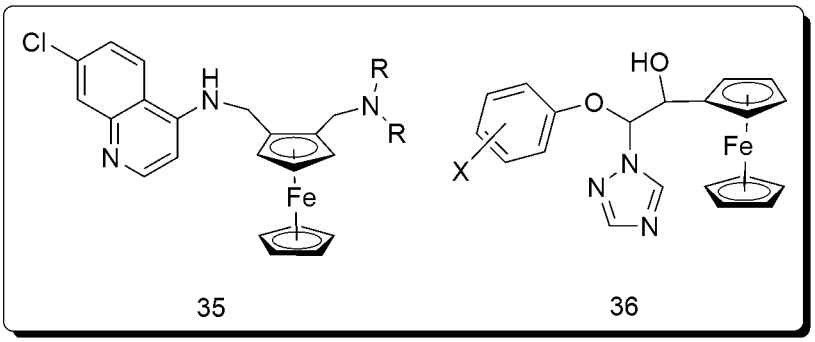


Figure 24. Structures of ferroquine **35** and ferrocene-tridimenol derivatives **36**.

1.3 Ferrocenyl pyrazoles

Both pyrazole and ferrocene derivatives constitute significant place in wide range applications which attracts the interest of most researchers on these topics. Due to their glamorous chemistry, linking these two promising units can generate very important structures with enhanced activity in many areas.

A recent study also has been conducted under the light of this idea. Accordingly, incorporation of pyrazole moiety into a ferrocene unit could develop novel antitumor agent. Researchers synthesized a class of ferrocenyl pyrazoles according to the pathway given in Figure 25 and conducted some bioactivity tests on the synthesized compounds. The results showed that most of the synthesized compounds, especially compound **37,** are promising antiproliferative agent against human *myelogenous leukemia* (Figure 25) [40].

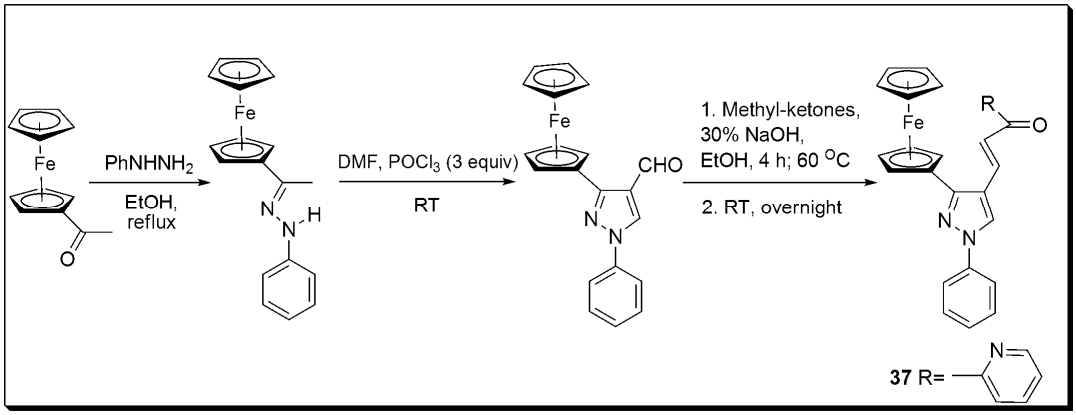


Figure 25. Synthesis of ferrocenyl pyrazole derivatives with antitumor activity.

Although, in literature, the sources on the studies of this topic are very rare, recently more interest has been shown [41-43]. Especially, Zora research group has studied widely on coexisting ferrocene-substituted pyrazole derivatives, and contribution to this field of research is noteworthy [41,42].

Among these studies, ferrocenyl pyrazole formation through the reaction between (2-formyl-1-chlorovinly)ferrocene (**38**) and hydrazines was the precursor of the method developed lately [41]. This reaction afforded two isomers of pyrazoles; 1-alkyl/aryl-5-ferrocenylpyrazole (**39**) and/or 1-alkyl/aryl-3-ferrocenylpyrazole (**40**). Although, mostly the first isomer was observed as the major one, according to substituent pattern, the ratios could change (Figure 26) [41].

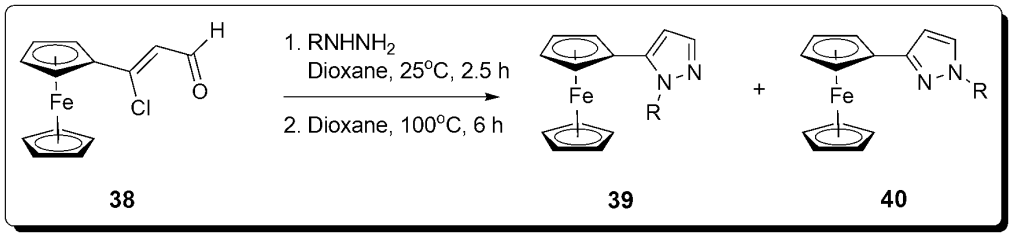


Figure 26. Ferrocenyl pyrazole formation through the reaction between (2-formyl-1-chlorovinly)ferrocene (**38**) and hydrazines.

In the pursuit of this formation, Zora research group has worked on the synthesis of pyrazoles **39** and **40** by the reaction between 3-ferrocenylpropynal (**41**) and hydrazinium salts (Figure 27). This method resulted in relatively higher yields of pyrazoles **39** and **40** [42].

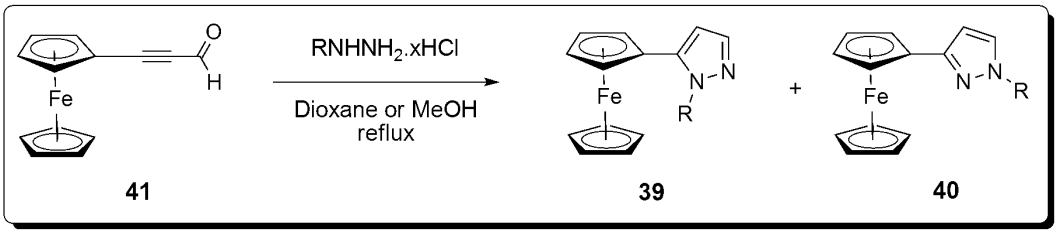


Figure 27. Synthesis of ferrocenyl pyrazoles **39** and/or **40** by the reaction of 3-ferrocenylpropynal (**41**) with hydrazinium salts.

Two methods mentioned above gave pyrazoles in two forms, so a new route was developed for regioselectivity to obtain major or only one type of pyrazoles. This has been possible by electrophilic cyclization reaction which is performed in very mild conditions and resulted in high regioselectivity. When 3-ferrocenylpropynal (**41**) reacts with hydrazine, unlike the reaction above, it does not form pyrazole, instead the formation of hydrazone **42** is observed. When treated with molecular iodine, this hydrazone undergo electrophilic cyclization to give 4-iodo-5-ferrocenylpyrazole derivatives **43** in high yields [44].

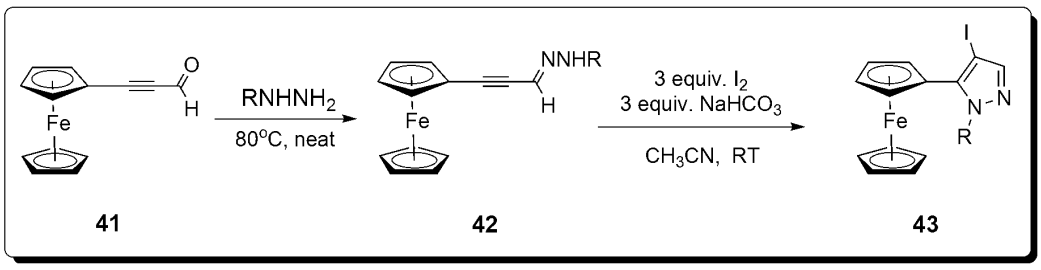


Figure 28. Synthesis of 4-iodo-5-ferrocenylpyrazole derivatives **43**.

1.4 Electrophilic cyclization reactions

When an electrophile attacks to carbon-carbon triple bond, there a cationic intermediate is formed which can easily undergo intramolecular cyclization onto aromatic ring [45]. So we can say the main ingredients for electrophilic cyclization are an alkynic species with functional substituents for cyclization and a highly electrophilic substance. This methodology can be used in various syntheses including bioactive polycyclic aromatic compounds and heterocyclic compounds. As a general route, electrophiles like ICl, NBS, *p*-$NO_2C_6H_4SCl$, $SeCl_2$, I_2, etc. are chosen to get relatively higher yields. The functional groups could be alkyl, aryl, vinyl, or benzyl group (Figure 29) [46,47].

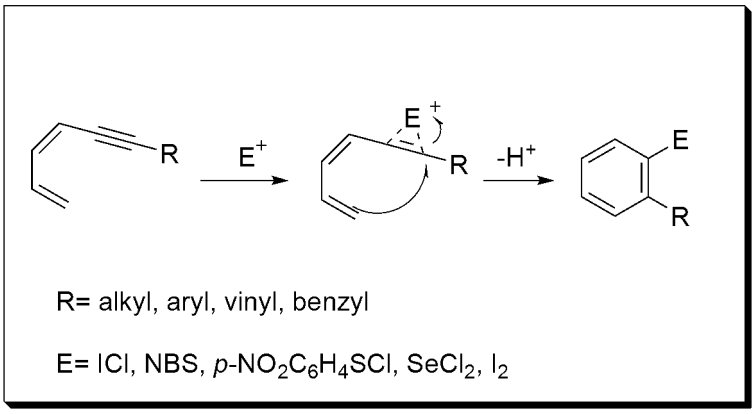


Figure 29. Schematic representation of electrophilic cyclization.

1.5 The aim of the study

Throughout their existance in chemistry, both pyrazoles and ferrocenes have been a research topic for most scientists due to their fascinating physical, chemical and biological properties. Recently, due to its magnetic and electronic properties, ferrocene has been introduced in many polymeric materials, catalysts, bio-organometallic substances, etc. [48]. On the other hand, pyrazoles show many biological and chemical activities. So the idea of bringing pyrazoles and ferrocene

together was inevitable. In the pursuit of this idea, Zora research group has studied on the synthesis of ferrocenenyl-substituted pyrazoles as mentioned above. Accordingly, 1-alkyl/aryl-5-ferrocenylpyrazoles (**39**) and 1-alkyl/aryl-3-ferrocenylpyrazoles (**40**) could be obtained from (2-formly-1-chlorovinly)ferrocene (**38**) and 3-ferrocenylpropynal (**41**) (Figures 26 and 27) [41,42]. Additionally, 5-ferrocenyl-4-iodopyrazoles (**43**) could be achieved through regioselective electrophilic cyclization of corresponding hydrazones with molecular iodine (Figure 28) [44].

In this study, the aim was to synthesize 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-1*H* pyrazoles **47** via electrophilic cyclization reaction of corresponding hydrazones with *p*-(nitrophenyl)sulfenyl chloride. For this purpose, first of all a group of hydrazones **46** will be synthesized by the reaction of hydrazines with ferrocenyl-substituted propargyl aldehyde **41** or ketones **44** and **45**. After the synthesis of hydrazones, the optimization studies of electrophilic cyclization reaction step will be carried out and then by following optimization conditions, a variety of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-1*H*-pyrazoles will be synthesized as described in Figure 30.

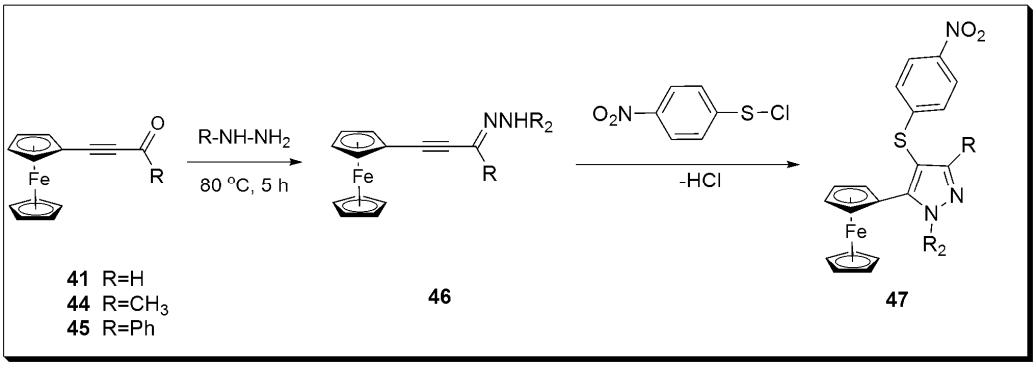


Figure 30. Synthesis of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-1*H*-pyrazoles (**47**).

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis of 3-ferrocenylpropynal (41), 4-ferrocenyl-3-yne-2-butynone (44) and 3-ferrocenyl-1-phenyl-propynone (45)

The first stage of the study constitutes the synthesis of starting materials, ferrocenyl propargyl aldehydes or ketones, in order to prepare the desired hydrazones used in the electrophilic cyclizations. First of all, ethynylferrocene (**48**) was synthesized as the common precursor for ferrocenyl-substituted propargyl aldehydes and ketones, starting from commercially available ferrocene (**22**) (Figure 31).

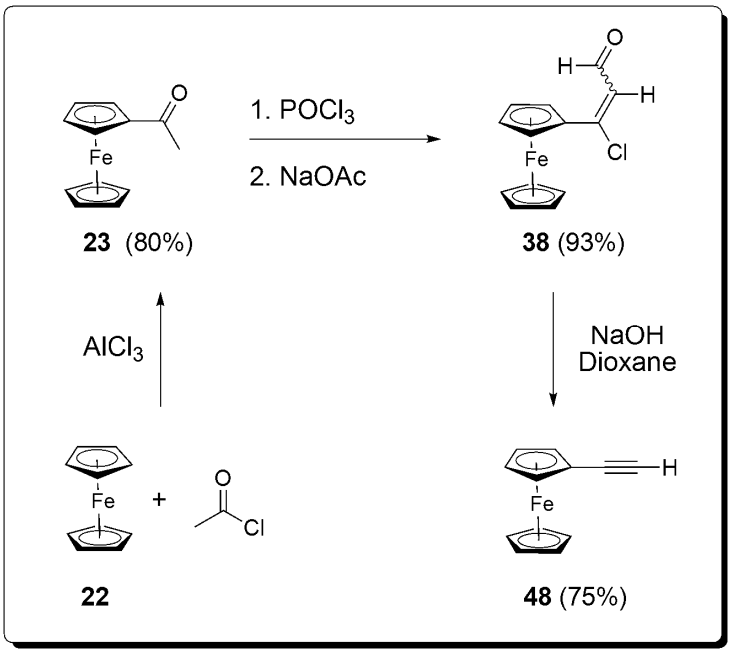


Figure 31. Synthesis of acetylferrocene (**23**), (2-formyl-1-chlorovinly)ferrocene (**38**) and ethynlferrocene (**48**).

In the first stage, acetylferrocene (**23**) was prepared via Friedel-Crafts acylation reaction (Figure 31) [49]. Acetylferrocene was then reacted with $POCl_3$ and NaOAc to give (2-formly-1-chlorovinly)ferrocene (**38**) [50]. The compound **38** was allowed to be refluxed with sodium hydroxide in dioxane, so that ethynylferrocene (**48**) was produced with 75% yield (Figure 31) [50].

Next step was the synthesis of 3-ferrocenylpropynal (**41**) and ferrocenyl propargyl ketones **44** and **45**. For the synthesis of **41**, ethynylferrocene (**48**) was first reacted with *n*-BuLi in THF at -40 ^{o}C under Argon. The resulting (ferrocenylethynyl)lithium intermediate **(49)** was then treated with DMF to give 3-ferrocenylpropynal (**41)**. This procedure afforded 3-ferrocenylpropynal in 82% yield (Figure 32) [51].

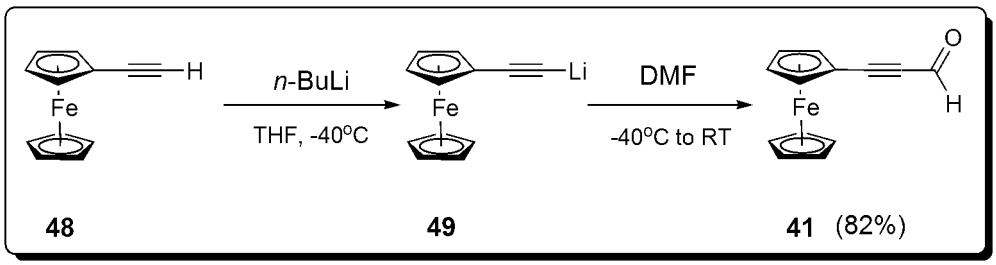


Figure 32. Synthesis of 3-ferrocenylpropynal (**41**).

Secondly, 4-ferrocenyl-3-yne-2-butyone (**44**) was synthesized through similar procedure. First, (ferrocenylethynyl)lithium (**49**) was formed in situ, which then treated with $ZnCl_2$ and acetyl chloride, respectively, in THF at -70 ^{o}C to afford 4-ferrocenyl-3-yne-2-butyone (**44**) (Figure 33) [52].

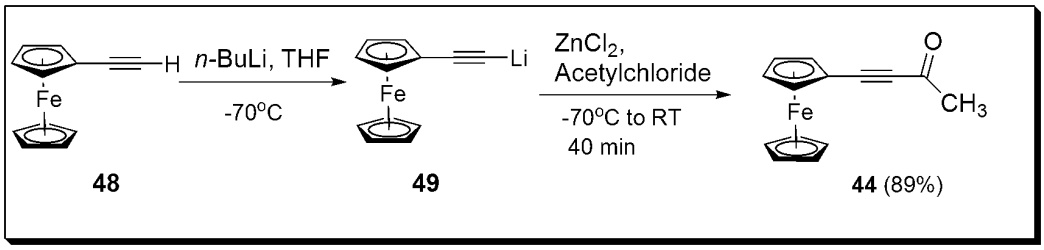


Figure 33. Synthesis of 4-ferrocenyl-3-yne-2-butyone (**44**).

As the third starting material, 3-ferrocenyl-1-phenyl-propynone (**45**) was synthesized. Benzoyl chloride (**50**) and ethynylferrocene (**48**) was reacted in the presence of $PdCl_2(PPh_3)_2$, Et_3N, CuI in anhydrous THF to afford 3-ferrocenyl-1-phenyl-propynone (**45**) with 80% yield (Figure 34) [53].

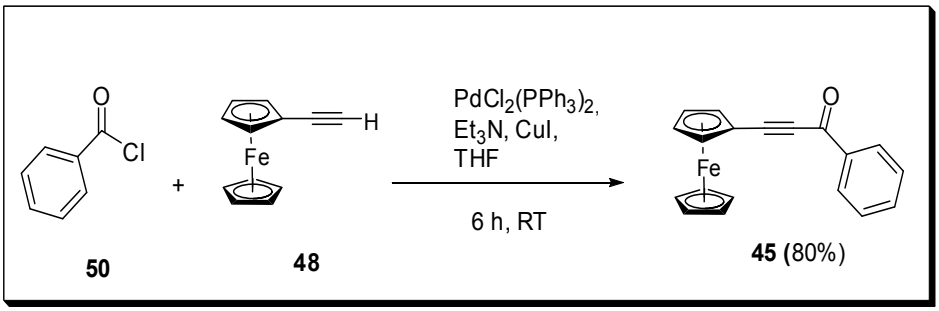


Figure 34. Synthesis of 3-ferrocenyl-1-phenyl-propynone **(45).**

2.2 Synthesis of alkynic hydrazones (51, 52, 53)

Subsequently, the reactions of various hydrazines with 3-ferrocenylpropynal (**41**), 4-ferrocenyl-3-yne-2-butyone (**44**) and 3-ferrocenyl-1-phenyl-propynone (**45**) were investigated in order to synthesize corresponding hydrazones. Initially, the reaction of phenylhydrazine with propargyl aldehydes and ketones were carried out as depicted in Figure 35. The reactions were held solvent free at 80 ^oC under Argon

[44]. However, in some cases where the reactants do not dissolve within each other by heating, we added one or two drops of dioxane. Accordingly, the condensation reactions yielded ***E*** and ***Z*** isomers of corresponding hydrazones **51-53**. These two isomers ***E*** and ***Z*** are both alkynic and can be easily separated by column chromatography.

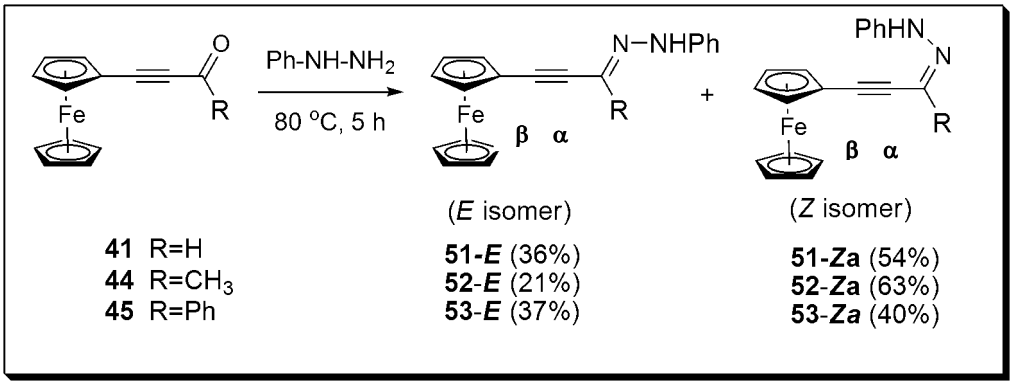
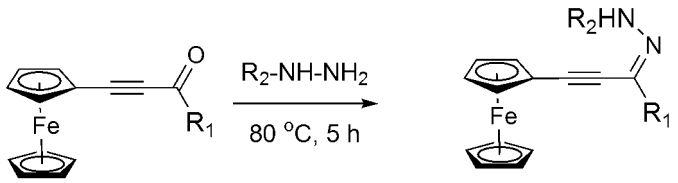


Figure 35. Synthesis of ***E*** and ***Z*** isomers of hydrazones.

A series hydrazones were synthesized by using this procedure (Table 1). In the synthesis of these hydrazones, commercially available hydrazines were employed (Figure 36). It should be mentioned that only ***Z*** isomers of hydrazones were isolated because it was realized that ***E*** isomers are not stable throughout the reaction and they tend to be partially converted into ***Z*** isomers. Longer reaction times decreased the yields of ***E*** isomers while the yields of ***Z*** isomers increased. This result proved that ***E*** isomers were converted into ***Z*** isomers. Additionally, during flash chromatography and standing at room temperature, this conversion was also observed. For this reason, the isolation of ***E*** isomers was not carried out [44]. Characterization of the isomers is possible by the analysis of their ^{13}C NMR data, which was confirmed through theoretical NMR predictions [44] and some literature sources of similar hydrazones [54]. As noted, for ***E*** isomers, α and β carbons resonate closely and the chemical shift difference is around 3-20 ppm. On the other hand, for ***Z*** isomers, those carbons resonate relatively in higher field and with more difference in chemical shifts like 22-30 ppm [44].

Table 1. Synthesis of α,β-alkynic hydrazones **51-53.**



41 R_1=H
44 R_1=CH_3
45 R_1=Ph

51 R_1=H
52 R_1=CH_3
53 R_1=Ph

Entry	*R_1*	*Hydrazine*	*R_2*	*Hydrazone*	*% Yield of Hydrazone*
1	H	**54a**	phenyl	**51-*Z*a**	54
2	H	**54b**	2,5-diflorophenyl	**51-*Z*b**	66
3	H	**54c**	4-(trifloromethyl)phenyl	**51-*Z*c**	82
4	H	**54d**	3-chloro-4-florophenyl	**51-*Z*d**	56
5	methyl	**54a**	phenyl	**52-*Z*a**	63
6	methyl	**54b**	2,5-diflorophenyl	**52-*Z*b**	66
7	methyl	**54c**	4-(trifloromethyl)phenyl	**52-*Z*c**	13
8	methyl	**54d**	3-chloro-4-florophenyl	**52-*Z*d**	53
9	phenyl	**54a**	phenyl	**53-*Z*a**	38
10	phenyl	**54b**	2,5-diflorophenyl	**53-*Z*b**	27
11	phenyl	**54c**	4-(trifloromethyl)phenyl	**53-*Z*c**	56
12	phenyl	**54d**	3-chloro-4-florophenyl	**53-*Z*d**	64

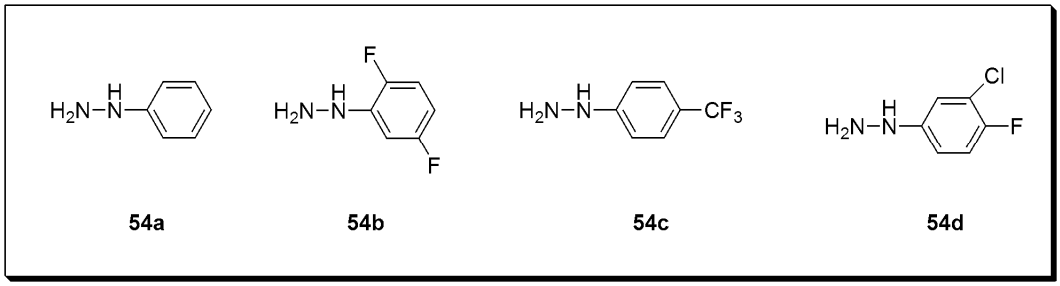


Figure 36. Structures of hydrazines **54a-d** used in the synthesis of alkynic hydrazones.

Structures of α,β-alkynic hydrazones are presented in Figure 37, which contain different substituents with ferrocenyl moiety.

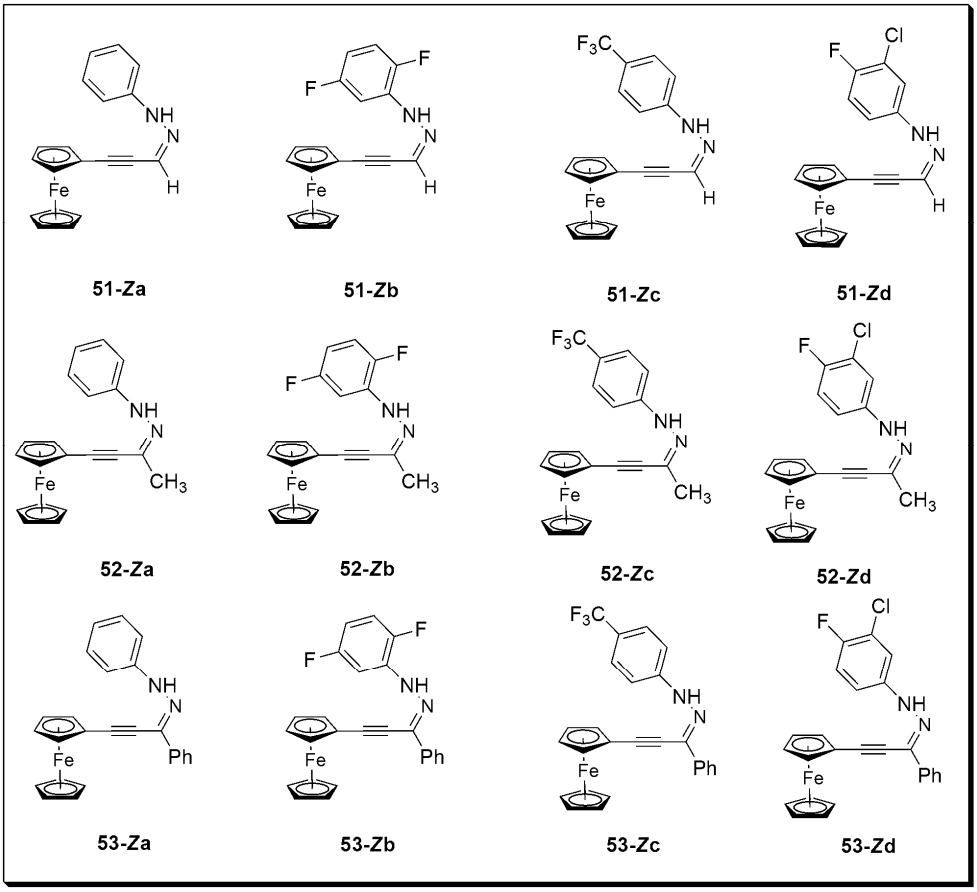


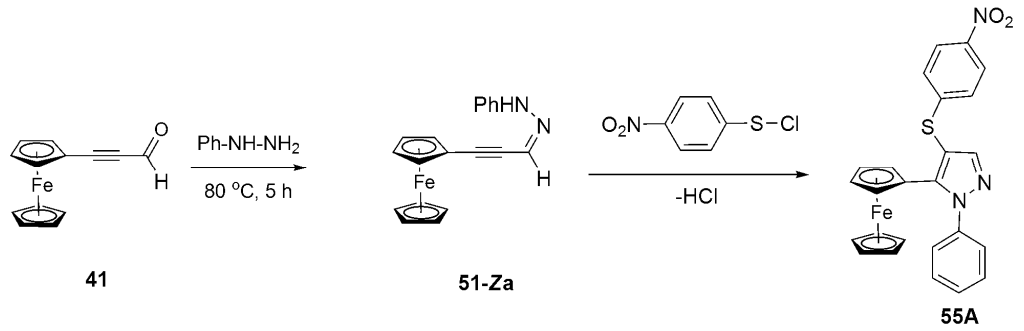
Figure 37. Ferrocenyl alkynic hydrazones **51-*Z*a-d, 52-*Z*a-d** and **53-*Z*a-d** employed in electrophilic cyclizations**.**

As can be noted from Table 1, the yields of *Z*-isomers of hydrazones vary from low to moderate and high yields (13 to 82%). The reason for this diversity can be expained by the effect of substituents.

2.3 Synthesis of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-1*H*-pyrazoles (55)

As the aim of our study, in the second part, the synthesis of targeted pyrazole derivatives was explored via electrophilic cyclization of alkynic hydrazone derivatives with 4-(nitrophenyl)sulfenyl chloride as electrophile. Accordingly, in order to find the optimal conditions, the synthesis of 5-ferrocenyl-4-((4-nitrophenyl)-sulfenyl)-1-phenyl-1*H*-pyrazole (**55**) was studied. Table 2 shows how the variables such as base, temperature, solvent and time affected the yield. All the reactions were controlled with TLC analysis. First of all, the reaction was performed in dichloromethane solvent in the absence of base at room temperature for 2 hours (Table 2, Entry 1). This experiment furnished the product with 70% yield. Then, the effect of base was searched. The addition of different bases such as $NaHCO_3$, K_2CO_3, Na_2CO_3 and LiCl did not increase the yield (Table 2, Entries 2, 5, 6, 7 and 11). Longer reaction time did not affect the yield in positive way (Table 2, Entry 3). Then the reaction was performed in different solvents; however, neither of acetonitrile nor dichloroethane gave satisfactory results (Table 2, Entries 10 and 13). The yield improvement studies were continued with reactions at different temperatures. Refluxing at 80 ^{o}C in acetonitrile decreased the yield too much. Moreover, the reaction at 35 ^{o}C and 0 ^{o}C in dichloromethane also did not increase the yield (Table 2, Entries 8, 9 and 12). Treating with excess amount of electrophile surprisingly decreased yield (Table 2, Entry 4). As a result, the group of hydrazones **51-*Z*a-d** derived from 3-ferrocenylpropynal (**41**) were put into electrophilic cyclization in dichloromethane at room temperature and for 2 hours.

Table 2. Effect of temperature, solvent, base, and time on the synthesis of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-1-phenyl-1*H*-pyrazole (**55A**)[a].

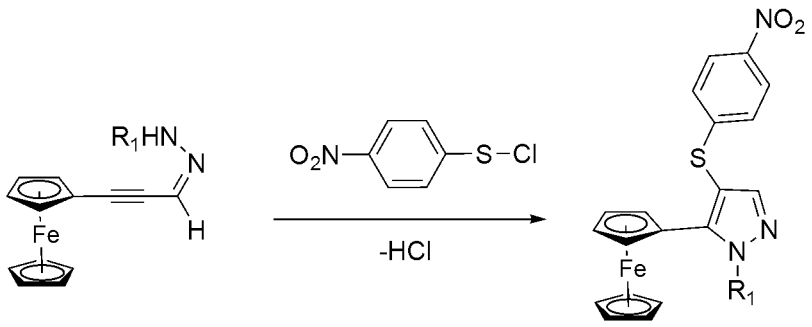


Entry	*Base*	*Temp.* (*°C*)	*Solvent*	*Time* (*h*)	*% Yield of 55*
1	**-**	**25**	**DCM**	**2**	**70**
2	2 equiv. $NaHCO_3$	25	DCM	2	69
3	-	25	DCM	4	62
4[b]	-	25	DCM	2	48
5	2 equiv. K_2CO_3	25	DCM	2	66
6	2 equiv. Na_2CO_3	25	DCM	2	64
7	2 equiv. LiCl	25	DCM	2	59
8	-	35	DCM	2	69
9	-	0	DCM	2	68
10	-	25	ACN	2	52
11	2 equiv. $NaHCO_3$	25	ACN	2	39
12	-	80	ACN	2	31
13	-	25	DCE	2	50
14	-	25	DCM	2	65

[a]All reactions were performed with 1.0 equiv. of alkynic hydrazone (**51-*Z*a**) and 2.0 equiv. of 4-(nitrophenyl)sulfenyl chloride. [b] 3.0 equiv. of 4-(nitrophenyl)sulfenyl chloride was used.

After these studies, We aimed to synthesize a variety of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-1*H*-pyrazole derivatives by the electrophilic cyclization reaction of 4-(nitrophenyl)sulfenyl chloride with hydrazones **51-*Z*a-d** listed in Figure 37**.** Four pyrazole derivatives were synthesized in this class (Table 3). Those pyrazoles were isolated with moderate to high yields (65-85%). The highest yield 85% was obtained with 4-(trifloromethyl)phenyl substituent at the first position.

Table 3. Synthesis of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-1*H*-pyrazoles (**55**).



51 **55**

Entry	R_1	*Product*	*% Yield*
1	phenyl	**55A**	70
2	2,5-diflorophenyl	**55B**	65
3	4-(trifloromethyl)phenyl	**55C**	85
4	3-chloro-4-florophenyl	**55D**	69

The structures of the synthesized pyrazoles in Table 3 are presented in Figure 38.

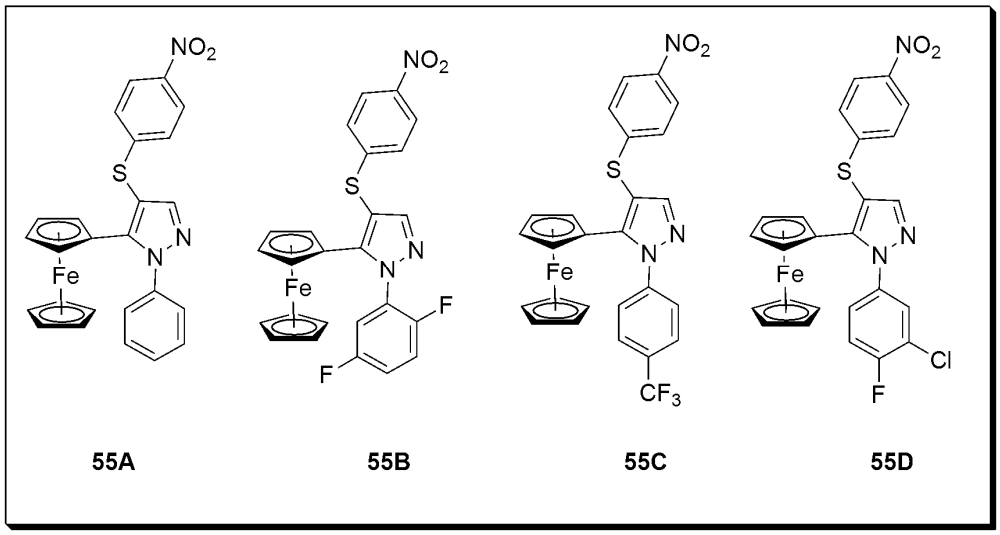
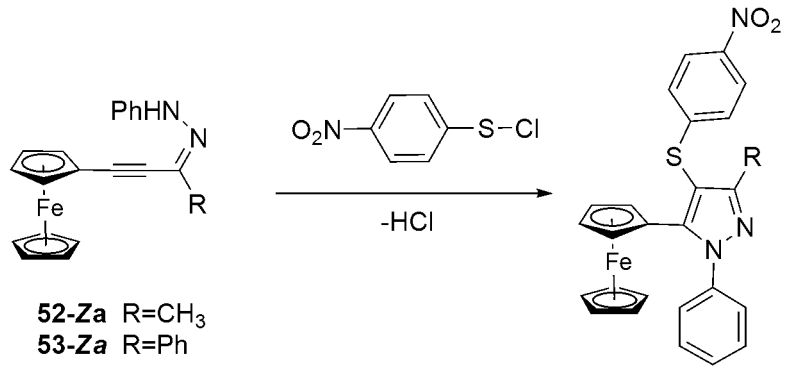


Figure 38. Structures of the synthesized 5-ferrocenyl-4-((4-nitrophenyl) sulfenyl)-1*H*-pyrazole derivatives **55A-D**.

2.4 Synthesis of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl-3-phenyl-1*H*-pyrazoles 56 and 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-3-methyl-1*H*-pyrazoles 57

As further studies, we carried out the electrophilic cyclization of ferrocenyl alkynic hydrazones with ketone precursor. For this type of pyrazole class, we needed a new optimization condition because the same procedure for electrophilic cyclization of hydrazones with aldehyde precursor did not give satisfactory yields in the formation of desired pyrazoles (Table 4, Entry 1). This observation made us to optimize the reaction conditions again. For optimization, we chose 3-ferrocenyl-1-phenyl-propynone (**45**) as hydrazone**.** The addition of the base $NaHCO_3$ increased the yield only by 3% (Table 2, Entry 2). Thus we preferred the reaction without base because this result was in agreement with the first optimization studies. Then solvent was changed from DCM to DCE (Table 4, Entry 3). The yield was relatively high as compared with Entry 1 of Table 4. As a result, we concluded that the pyrazoles derived from aldehyde precursor better resulted in DCM solution, whereas, from ketone precursor, DCE was more convenient. In further reactions of hydrazones with ketone precursors, i.e. **52-*Z*a-d** and **53-*Z*a-d**, DCE was preferred as the solvent.

Table 4. Effect of temperature, solvent, base, and time on the synthesis of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-1*H*-pyrazoles (**57A**)[a].



52-*Z*a R=CH_3
53-*Z*a R=Ph

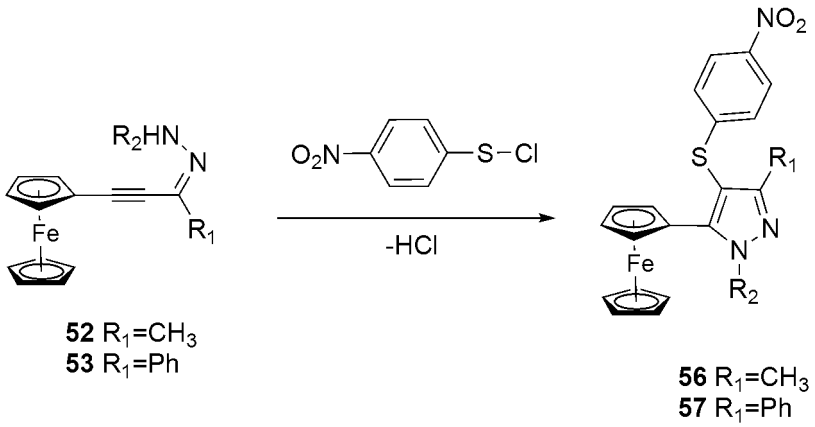
56A R=CH_3
57A R=Ph

Entry	*Base*	*Temp.* (^oC)	*Solvent*	*Time* (*h*)	*Yield of 57A (%)*
1	-	25	DCM	2	50
2	2 equiv. $NaHCO_3$	25	DCM	2	53
3	**-**	**25**	**DCE**	**2**	**64**

[a]All reactions were performed with 1.0 equiv. alkynic hydrazone (**53-*Z*a**), 2.0 equiv. 4-nitrophenylsulfenyl chloride.

Subsequently, 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-3-methyl-1*H*-pyrazoles **56A-D** and 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-3-phenyl-1*H*-pyrazoles **57A-D** were synthesized (Table 5). Among methyl-substituted pyrazoles at the third position, the maximum yield was obtained for that **56C** derived from 4-(trifloromethyl)phenyl-hydrazine (85%). However, for phenyl-substituted at the third position, pyrazole **57D** derived from 3-chloro-4-florophenylhydrazine gave the maximum yield (74%).

Table 5. Synthesis of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-3-methyl-1*H*-pyrazoles (**56**) and 5-ferrocenyl-4-((4-nitrophenylsulfenyl-3-phenyl-1*H*-pyrazoles (**57**).



52 R_1=CH_3
53 R_1=Ph

56 R_1=CH_3
57 R_1=Ph

Entry	R_1	R_2	*Product*	*% Yield*
1	methyl	phenyl	**56A**	82
2	methyl	2,5-diflorophenyl	**56B**	84
3	methyl	4-(trifloromethyl)phenyl	**56C**	85
4	methyl	3-chloro-4-florophenyl	**56D**	77
5	phenyl	phenyl	**57A**	64
6	phenyl	2,5-diflorophenyl	**57B**	71
7	phenyl	4-(trifloromethyl)phenyl	**57C**	50
8	phenyl	3-chloro-4-florophenyl	**57D**	74

The structures of the synthesized pyrazoles in Table 5 are shown in Figure 39.

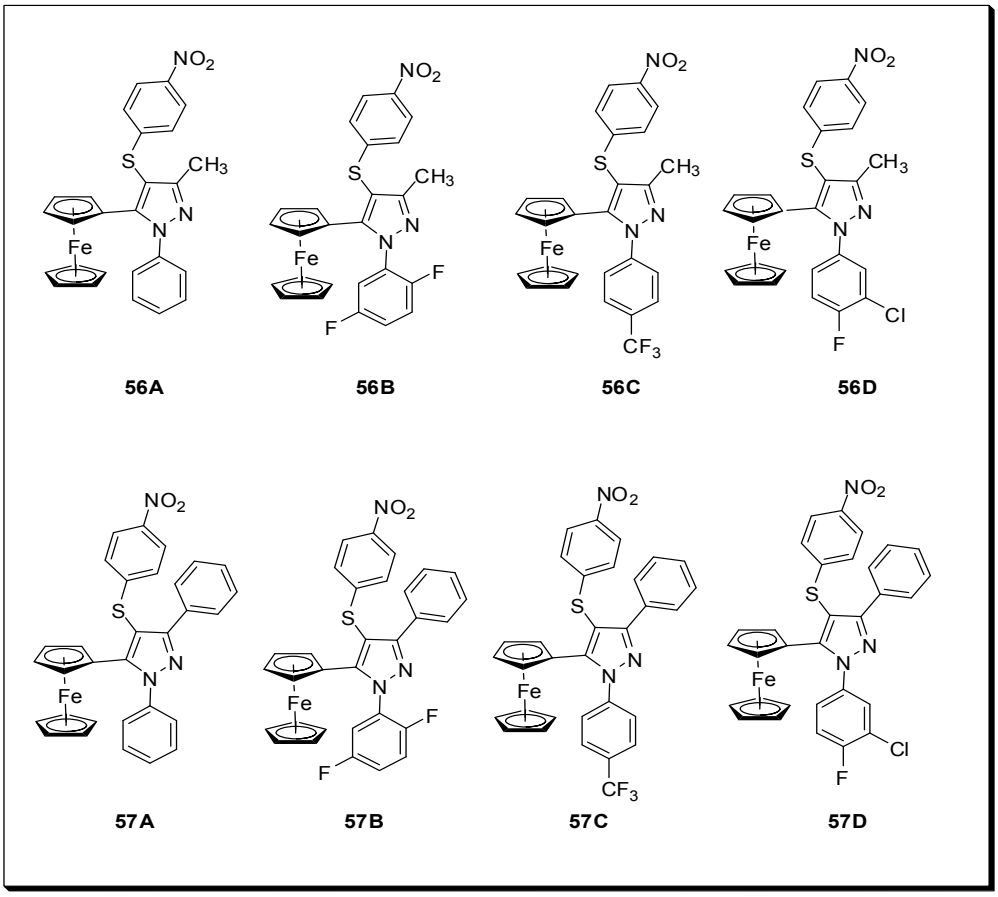


Figure 39. Structures of the synthesized 3-methyl-4-(4-nitrophenylsulfenyl)-5-ferrocenyl-1*H*-pyrazole derivatives **56A-D** and 3-phenyl-4-((4-nitrophenyl) sulfenyl)-5-ferrocenyl-1*H*-pyrazole derivatives **57A-D**.

The characterization of pyrazoles has been done by NMR spectroscopy. As an example, ^{1}H NMR spectrum of 1-phenyl-3-methyl-4-((4-nitrophenyl)sulfenyl)-5-ferrocenyl-1*H*-pyrazole (**56A**) is described in Figure 40. Ferrocene proton peaks characteristically appear around 4.0-4.5 ppm region of the spectrum. At 4.27 and 4.31 ppm, two pseudo triplet peaks appear for four protons of substituted cyclopentadienyl ring. The singlet peak at 4.12 ppm represents the protons of five protons of unsubstituted cyclopentadienyl ring. The methyl group locating at the third position of pyrazole shows a singlet peak at 2.38 ppm and the rest nine proton peaks belonging to phenyl groups resonates around 7.36-8.24 ppm.

.

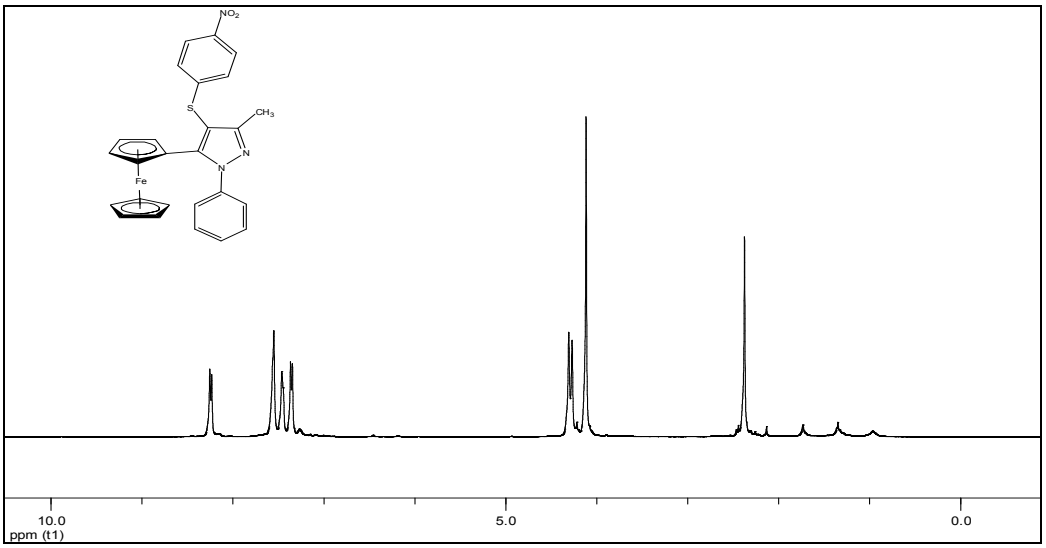


Figure 40. ^{1}H NMR spectrum of pyazole **56A.**

^{13}C NMR spectrum of 1-phenyl-3-methyl-4-(4-nitrophenyl)sulfenyl-5-ferrocenyl-1*H*-pyrazole (**56A**) is demonstrated in Figure 41. The presence of methyl group is proved by the peak which resonates at 11.9 ppm. The peaks at 72.6-68.9 ppm represents ferrocene carbons. Moreover, the C peak at 101.9 ppm belongs to the carbon of pyrazole core at which 4-nitrophenylsulfenyl group is attached. As a result, this spectra of ^{1}H and ^{13}C NMR are consistent with the indicated pyrazole structure.

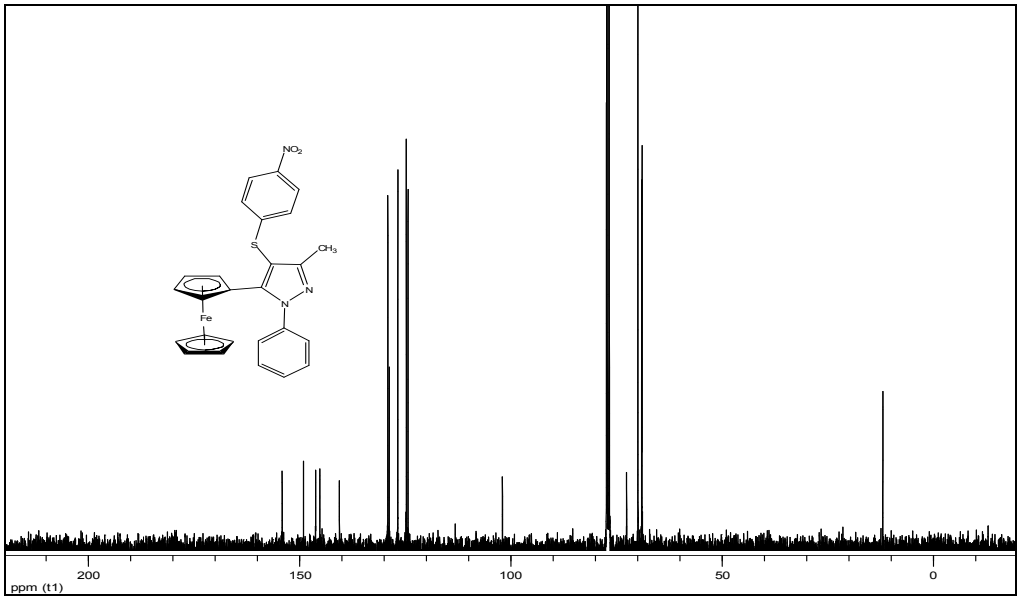


Figure 41. ^{13}C NMR spectrum of pyrazole **56A.**

2.5 Proposed reaction mechanism for electrophilic cycliation of alkynic hydrazones with 4-(nitrophenyl)sulfenyl chloride.

The mechanism proposed for the formation of 5-ferrocenyl-4-((4-nitrophenyl) sulfenyl)-1*H*-pyrazoles **55-57** is illustrated in Figure 42. The reaction of alkyne functionality of hydrazone with sulfur of 4-nitrophenylsulfenyl chloride gives the intermediate **58**, which initiates the electrophilic cyclization. The attack of secondary nitrogen to the carbon atom attached to sulfur atom yields the protonated pyrazole **59.** At the end, the abstraction of the proton by Cl^- ion results in the formation of desired pyrazoles. As we mentioned from the beginning, the mechanism is considered to follow from the ***Z*** isomer of hydrazone. However, it is known that ***E*** isomer is also converted to ***Z*** isomer during the course of the cyclization in the presence of electrophile.

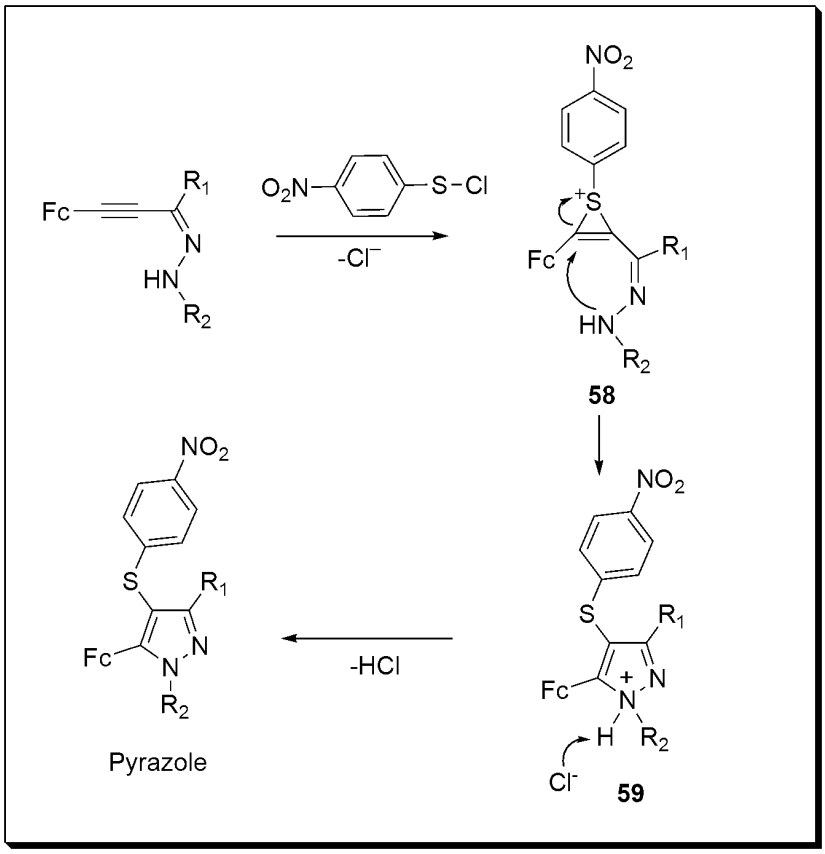


Figure 42. Mechanism proposed for the formation of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)- 1*H*- pyrazoles **55-57**.

CHAPTER 3

CONCLUSION

In summary, the synthesis of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-1*H*-pyrazoles by electrophilic cyclization reaction has been investigated in this study. The fact that both ferrocene and pyrazole containing compounds contribute to many fields like chemistry, biochemistry, medicine, agriculture, etc. has been one of the reason to study on the synthesis of coexisting compounds. The introduction of ferrocene moiety to pyrazole structure could have potential applications with enhanced activities.

In the first phase of the study, starting materials 3-ferrocenypropynal (**41**), 4-ferrocenyl-3-yne-2-butyone (**44**) and 3-ferrocenyl-1-phenyl-propynone (**45**) were synthesized. Later, those starting materials were treated with a series of hydrazines **54a-d** to get a library of alkynic hydrazones **51-53.**

In the second phase of the study, the synthesis of ferrocenyl pyrazoles was explored via electrophilic cyclization of alkynic hydrazones **51-53** with *p*-(nitrophenyl)-sulfenyl chloride as electrophile. This way, 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-1*H*-pyrazoles **51**, 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-3-methyl-1*H*-pyrazoles **52**, and 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-3-phenyl-1*H*-pyrazoles **53** were synthesized in moderate to good yields.

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 Synthesis of acetylferrocene (23)

In a dry flask, ferrocene (**22**) was put (2 g, 10.8 mmol). Under constant magnetic stirring and inert atmosphere, to the same flask DCM (9 ml) was added in order to dissolve ferrocene. Then acetyl chloride was added to the resulting orange/red solution. With careful immersion of flask into ice-water bath of 0-5 ^{o}C, anhydrous aluminum chloride (1.44 g, 10.8 mmol) was put in slowly in small proportions to the reaction flask. The reaction mixture was allowed to reach room temperature and stirred for 2 hours. Again the reaction mixture was cooled with the help of ice bath prior to the addition of cold pure water (4 x 0.5 ml), in that process, the reaction mixture was hydrolyzed. Another 3 ml of cold water was added as soon as possible. The hydrolyzed reaction mixture was extracted with DCM and collected organic extracts were washed with 5% NaOH solution and brine. The organic phase was dried over magnesium sulfate and applied high vacuum filtration. The resultant orange/red solid, after the evaporation of solvent by rotary evaporator, was purified by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent to give the final product acetylferrocene (**23**) (1.96 g, 80%)

22: ^{1}H NMR ($CDCl_3$): δ 4.60 (s, 2H), 4.32 (s, 2H), 4.02 (s, 5H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 79.2 (C), 72.3 (CH), 69.8 (CH), 69.5 (CH), 27.3 (CH_3). The spectral data are in agreement with those reported previously for this compound [55].

4.2 Synthesis of (2-formyl-1-chlorovinyl)ferrocene (38)

In a two necked round bottom flask, acetylferrocene (**23**) (2 g, 8.8 mmol) and then DMF (2.17 ml, 28.2 mmol) were put respectively under argon. The brown mixture was cooled to 0 ^{o}C by means of ice bath and stirred for 10 minutes. Separately, in a long flask having a dropping tap, DMF (2.17 ml, 28.2 mmol) and phosphorus oxychloride (2.21 ml, 28.2 mmol) were added at 0 ^{o}C and with good stirring. The resulting red complex was cautiously added to reaction flask of acetylferrocene dropwise over 30 minutes by immersion of dropping tap side of long flask into one of the necks. After the completion of the addition, the constituents of reaction

mixture were stirred at 0 ^{o}C for 2 hours until the dark brown to olive oil and finally dark blue colors were observed respectively. After the observation of dark blue, 20 ml of diethyl ether was added with continuos stirring followed by addition of sodium acetate trihydrate (10.18 g, 74.6 mmol) addition to the reaction flask in ice bath. Later, pure water (2 ml) was added and the color of organic layer was changed from colorless to ruby red, which was the sign of the formation of formyl derivative. The ice bath was removed and the reaction mixture was stirred for 1 hour before the addition of diethyl ether (2 ml). Stirring was continued for 3 hours more at room temperature for complete quenching. The reaction mixture was extracted with diethyl ether. The combined organic extracts were washed with saturated sodium bicarbonate solution. The organic phase was dried over by magnesium sulfate and filtrated by vacuum filtration. By rotary evaporator, the solvent was removed and we got the resulting orange/red solid as (2-formly-1-chlorovinly)ferrocene (**38**) (2.25 g, 93%)

38: ^{1}H NMR ($CDCl_3$): 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 are in agreement with those reported previously for this compound [50].

4.3 Synthesis of ethynylferrocene (48)

In a dry flask, (2-formly-1-chlorovinly)ferrocene (**38**) was replaced (1.3 g, 4.75 mmol). Under constant magnetic stirring and inert atmosphere, to the same flask anhydrous dioxane (15 ml) was added in order to dissolve (2-formly-1-chlorovinly)ferrocene. Then the reaction mixture was heated to reflux (approximately 80 ^{o}C). 5 minutes later, a boiling 1 N solution of NaOH (12.5 ml) was poured into the flask rapidly in one portion and the reaction was refluxed for another 25 minutes. After the reflux, the reaction mixture was allowed to cool to room temperature. The constituents in the flask were poured directly into ice and neutralized with 1 N HCl solution. The neutralization is controlled with litmus paper. The reaction mixture was extracted with hexane (5 x 5 ml). The combined organic extracts were washed with saturated sodium bicarbonate solution and water. The

organic phase was dried over by magnesium sulfate and filtrated by vacuum filtration. By rotary evaporator, the solvent was removed and ethynylferrocene (**48**) was purified by flash column chromatography on silica gel using pure hexane as the eluent. Finally we obtained the pure ethynylferrocene as orange crystals. (750 mg, 75%)

48: ^{1}H NMR ($CDCl_3$): δ 4.46 (s, 2H), 4.21 (s, 5H), 4.19 (s, 2H), 2.71 (s, 1H); ^{13}C ($CDCl_3$): δ 82.6 (C), 73.6 (C), 71.7 (CH), 70.0 (CH), 68.7 (CH), 63.9 (C). The spectral data are in agreement with those reported previously for this compound [51].

4.4 Synthesis of 3-ferrocenylpropynal (41)

Ethynylferrocene (**48**) (0.1 mol, 21 g) was dissolved in approximately 25 ml of dry THF. The solution flask was inserted into ethyl acetate/liquid nitrogen mixture in a dewar jacket equipped with a thermometer. By this way the solution was cooled to -40 ^{o}C for the slow addition of *n*-BuLi (1.6 M in hexane, 65.4 ml, 0.1 mol) by a glass syringe under constant argon flash of the system. After the addition of *n*-BuLİ, DMF (15.5 ml, 0.2 mol) was added rapidly in one portion and the reaction reaction was stirred for several minutes. Then the system was allowed to warm to room temperature. The constituents of the reaction flask were poured into a cold mixture of 10% KH_2PO_4 (540 ml, 0.4 mol) and diethyl ether (500 ml). The two phases were separated by extraction. The organic layer was washed with water (4 x 200 ml) and the aqueous phase was extracted with ether. The combined organic extracts were dried over by magnesium sulfate and filtrated by vacuum filtration. By rotary evaporator, the solvent was removed and corresponding aldehyde was purified by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate mixture as the eluent (19.6 g, 82%).

41: ^{1}H NMR ($CDCl_3$): δ 9.27 (s, 1H), 4.60 (s, 2H), 4.41 (s, 2H), 4.25 (s, 5H); ^{13}C NMR ($CDCl_3$): 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 [51,56].

4.5 Synthesis of propargyl ketones (44, 45)

4.5.1 Synthesis of 1-methyl-3-ferrocenylprop-2-yn-1-one (44)

Ethynylferrocene (**48**) (10 mmol) was dissolved in approximately 50 ml of dry THF in a 100 ml of two-necked round bottom flask having a magnetic stirrer in it. The solution was cooled to -70 ^{o}C for the slow addition of *n*-BuLi (1.6 M in hexane, 6.54 ml, 10 mmol) by a glass syringe under constant argon flash of the system. After the addition of *n*-BuLi, the system was allowed to warm to 0 ^{o}C and stirred for 30 min at this temperature. Later, the system was again cooled at -70 ^{o}C before adding $ZnCl_2$ (1 equiv, 1 mol L^{-1} solution in THF). The system was allowed to warm to room temperature and stirred for another 15 min. and then the system recooled at -70 ^{o}C prior to the addition of acetyl chloride (10 mmol) in one portion. The system was warmed up to room temperature again and the reaction was allowed to run for 40 min. Then the mixture was diluted with hexane (10 ml) and washed out with brine (3*10 ml). The combined organic extracts were dried over by magnesium sulfate and filtrated by vacuum filtration. By rotary evaporator, the solvent was removed and corresponding ketone (2.2 g, 89%) was purified by flash column chromatography on silica gel using 70:1 hexane/ethyl acetate mixture as the eluent [52].

44: ^{1}H NMR ($CDCl_3$): δ 4.59 (t, 2H), 4.39 (t, 2H), 4.26 (s, 5H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 86.3 (C), 73.1 (CH), 70.7 (CH), 70.4 (C), 32.5 (CH_3).

4.5.2 Synthesis of 1-phenyl-3-ferrocenylprop-2-yn-1-one (45)

Benzoyl chloride (421.5 mg, 3.0 mmol), $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol) and Et_3N (303 mg, 3.0 mmol) in anhydrous THF (5 mL) were stirred for 10 min under argon atmosphere at room temperature. To this mixture CuI (19 mg, 0.1 mmol) was added and the reaction mixture was stirred for additional 10 min prior to adding ethynyl ferrocene (**48**) (525 mg, 2.5 mmol). The reaction was allowed to run for 6 h at room temperature. After 6 h, ethyl acetate was added to the reaction mixture in order to combine organic phase and then washed with 0.1 N HCl and a saturated NH_4Cl

solution. The organic phase was separated, dried over by magnesium sulfate and filtrated by vacuum filtration. By rotary evaporator, the solvent was removed and corresponding ketone (706 mg, 90%) was purified by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate mixture as the eluent [53].

45: ^{1}H NMR ($CDCl_3$): δ 8.20 (d, 2H, *J* = 7.2 Hz), 7.63 (t, 1H, *J* = 7.6 Hz), 7.53 (t, 2H, *J* = 8.0 Hz), 4.70 (t, 2H, *J* = 2.0 Hz), 4.44 (t, 2H, *J* = 2.0 Hz), 4.30 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 173.6 (C), 137.3 (C), 133.7 (CH), 129.4 (CH), 128.6 (CH), 85.6 (C), 73.2 (CH), 70.8 (CH), 70.5 (C), 60.4 (C).

4.6 General Procedure 1: Synthesis of alkynic hydrazones (51, 52, 53)

The corresponding propargyl aldehyde (1 equiv.) or propargyl ketone (1 equiv.) and the accompanying hydrazine (1 equiv.) were added in a dry test tube. The contents of the reaction were heated to 80 ^{o}C, so that they both form a viscous mixture. The reaction was hold with continuous stirring for 3-5 hours under argon atmosphere. The product was purified by flash chromatography on silica gel by using 19:1 hexane/ethyl acetate as the eluent.

4.6.1 Synthesis of (*E*)- and (*Z*)-1-(3-ferrocenylprop-2-ynylidene)-2-phenyl-hydrazines (51-*E* and 51-*Z*)

General Procedure 1 was followed by using 3-ferrocenylpropynal (**41**) (500 mg, 2.10 mmol) and phenylhydrazine (0.21 ml, 2.10 mmol). The resultant mixture of isomers was separated by flash chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent, yielding hydrazones **51-*E*** (*E* isomer, 248 mg, 36%) and **51-*Z*** (*Z* isomer, 372 mg, 54%).

51-*E* (*E* isomer): ^{1}H NMR ($CDCl_3$): δ 7.95 (br s, 1H, NH), 7.27 (t, 2H, *J* = 7.9 Hz), 7.08 (d, 2H, *J* = 7.9 Hz), 7.03 (s, 1H), 6.90 (t, 1H, *J* = 7.3 Hz), 4.51 (s, 2H), 4.27 (s, 2H), 4.25 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 143.7 (CH), 129.3 (CH), 120.8 (CH), 120.4 (C), 113.1 (CH), 92.2 (C), 82.0 (C), 71.6 (CH), 70.1 (CH), 69.2 (CH), 64.3

(C). The spectral data are in agreement with those reported previously for this compound [44].

51-*Z*a (*Z* isomer): ^{1}H NMR ($CDCl_3$): δ 8.64 (br s, 1H, NH), 7.32 (t, 2H, *J* = 7.3 Hz), 7.13 (d, 2H, *J* = 7.6 Hz), 6.94 (t, 1H, *J* = 7.3 Hz), 6.55 (s, 1H), 4.57 (s, 2H), 4.35 (s, 2H), 4.29 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 143.7 (CH), 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). The spectral data are in agreement with those reported previously for this compound [44].

4.6.2 Synthesis of (*Z*)-1-(2,5-diflorophenyl)-2-(3-ferrocenylprop-2-ynylidene) hydrazine (51-*Z*b)

3-Ferrocenylpropynal (**41**) (105 mg, 0.44 mmol) and (2,5-diflorophenyl)hydrazine (**54b**) (63.6 mg, 0.44 mmol) were used in the pursuit of General Procedure 1 giving *Z* isomer **51-*Z*b** (106 mg, 66%).

51-*Z*b: ^{1}H NMR ($CDCl_3$): δ 8.84 (br s, 1H, NH), 7.27 (m, 1H), 7.03 (m, 1H), 6.69 (s, 1H), 6.53 (m, 1H), 4.59 (s, 2H), 4.38 (s, 2H), 4.30 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 159.8 (d, *J* = 239 Hz, C), 145.9 (d, *J* = 235.5 Hz, C), 133.3 (t, *J* = 11.3 Hz, C), 118.8 (CH), 115.5 (dd, *J* = 20 Hz, *J* = 10 Hz, CH), 105.6 (dd, *J* = 29.6 Hz, *J* = 20 Hz, CH), 103.8 (C), 101.9 (dd, *J* = 2.3 Hz, *J* = 28.4 Hz, CH), 75.9 (C), 71.9 (CH), 70.4 (CH), 69.9 (CH), 62.1 (C); IR (neat): 3325, 3093, 2189, 1633, 1521, 1452, 1342, 1247, 1182, 1153, 1118, 1004, 817, 754 cm^{-1}. The spectral data are in agreement with those reported previously for this compound [44].

4.6.3 Synthesis of (*Z*)-1-((4-trifloromethyl)phenyl)-2-(3-ferrocenylprop-2-ynylidene)hydrazine (51-*Z*c)

3-Ferrocenylpropynal (**41**) (72 mg, 0.3 mmol) and (4-(trifloromethyl)phenyl) hydrazine (**54c**) (53 mg, 0.3 mmol) were used in the pursuit of General Procedure 2 giving *Z* isomer **51-*Z*c** (97 mg, 82%).

51-*Z*c: ^{1}H NMR ($CDCl_3$): δ 8.74 (br s, 1H, NH), 7.55 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz 2H), 6.62 (s, 1H), 4.59 (s, 2H), 4.38 (s, 2H), 4.30 (s, 5H); ^{13}C NMR ($CDCl_3$): 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}. The spectral data are in agreement with those reported previously for this compound [44].

4.6.4 Synthesis of (*Z*)-1-(3-chloro-4-florophenyl)-2-(3-ferrocenylprop-2-ynylidene)hydrazine (51-*Z*d)

3-Ferrocenylpropynal (**41**) (66 mg, 0.28 mmol) and (3-chloro-4-florophenyl) hydrazine (**54d**) (44.5 mg, 0.28 mmol) were used in the pursuit of General Procedure 2 giving *Z* isomer **51-*Z*d** (59 mg, 56%).

51-*Z*d: ^{1}H NMR ($CDCl_3$): δ 8.50 (br s, 1H, NH), 7.20 (m, 1H), 7.06 (t, *J* = 8.6 Hz 1H), 6.92 (m, 1H), 6.55 (s, 1H), 4.56 (s, 2H), 4.36 (s, 2H), 4.28 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 153.2 (d, *J* = 600 Hz, C), 140.6 (C), 121.7 (d, *J* = 18.5 Hz, C), 117.1 (C), 116.9 (CH), 114.8 (CH), 112.2 (d, *J* = 6.2 Hz CH), 103.0 (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}. The spectral data are in agreement with those reported previously for this compound [44].

4.6.5 Synthesis of (*Z*)-1-phenyl-2-(4-ferrocenylbut-3-yn-2-ylidene)hydrazine (52-*Z*a)

4-Ferrocenylbut-3-yne-1-one (**44**) (60 mg, 0.24 mmol) and phenylhydrazine (**54a**) (26 mg, 0.24 mmol, 0.023 ml) were used in the pursuit of General Procedure 1 giving *Z* isomer **52-*Z*a** (52 mg, 63%).

52-*Z*a: ^{1}H NMR ($CDCl_3$): δ 8.16 (br s, 1H, NH), 7.17 (d, 2H, *J* = 8 Hz), 7.0 (d, 2H, *J* = 8 Hz), 6.78 (t, 1H, *J* = 7.2 Hz), 4.47 (s, 2H), 4.25 (s, 2H), 4.18 (s, 5H), 2.13 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 144.2 (C), 129.2 (CH), 124.5 (C), 120.0 (CH), 112.8

(CH), 101.4 (C), 77.7 (C), 71.7 (CH), 70.2 (CH), 69.6 (CH), 62.8 (C), 22.2 (CH_3); IR (neat): 3305.8 (w), 3093.3 (w), 2914.8 (w), 2180.7 (s), 1600.5 (vs), 1502.8 (vs), 1252.9 (m), 1201.6 (m), 1140.7 (m), 1105.7 (w), 1001.3 (w), 819.4 (m), 747.4 (m), 690.6 (m), 644.5 (w).

4.6.6 Synthesis of (*Z*)-1-(2,5-diflorophenyl)-2-(4-ferrocenylbut-3-yn-2-ylidene) hydrazine (52-*Z*b)

4-Ferrocenylbut-3-yne-1-one (**44**) (56mg, 0.22 mmol) and (2,5-diflorophenyl) hydrazine (**54b**) (31 mg, 0.22 mmol) were used in the pursuit of General Procedure 1 giving *Z* isomer **52-*Z*b** (55 mg, 66%).

52-*Z*b: ^{1}H NMR ($CDCl_3$): δ 8.46 (br s, 1H, NH), 7.22 (m, 1H), 6.97 (m, 1H), 6.43 (m, 1H), 4.57 (s, 2H), 4.35 (s, 2H), 4.27 (s, 5H), 2.22 (s, 3H); ^{13}C NMR ($CDCl_3$): δ (couldn't be obtained); IR (neat): 3325.5 (m), 2988.2 (w), 2919.6 (w), 2183.6 (s), 1636.7 (s), 1522.8 (vs), 1457.9 (m), 1331.5 (w), 1285.4 (w), 1244.4 (m), 1155.5 (vs), 1129.6 (m), 1105.9 (w), 834.9 (m), 825.8 (m), 784.2 (s), 732.8 (s).

4.6.7 Synthesis of (*Z*)-1-((4-trifloromethyl)phenyl)-2-(4-ferrocenylbut-3-yn-2-ylidene)hydrazine (52-*Z*c)

4-Ferrocenylbut-3-yne-1-one (**44**) (100 mg, 0.4 mmol) and (4-(trifloromethyl) phenyl) hydrazine (**54c**) (70 mg, 0.4 mmol) were used in the pursuit of General Procedure 1 giving *Z* isomer **52-*Z*c** (21 mg, 13%).

52-*Z*c: ^{1}H NMR ($CDCl_3$): δ 8.38 (br s, 1H, NH), 7.51 (d, 2H, J = 8.4 Hz), 7.12 (d, 2H, J = 8.4 Hz), 4.56 (s, 2H), 4.36 (s, 2H), 4.27 (s, 5H), 2.23 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 146.7 (C), 126.8 (C), 126.7 (C), 126.6 (C), 124.5 (CH), 121.9 (CH), 112.3 (C), 102.3 (C), 71.8 (CH), 70.3 (CH), 69.8 (CH), 62.3 (C), 22.3 (CH_3); IR (neat): 3300.8 (w), 2189.2 (w), 1612.7 (s), 1528.6 (m), 1483.9 (w), 1416.5 (w), 1323.7 (vs), 1265.0 (m), 1203.3 (w), 1102.5 (vs), 1061.7 (s), 821.0 (m).

4.6.8 Synthesis of (*Z*)-1-(3-chloro-4-florophenyl)-2-(4-ferrocenylbut-3-yn-2-ylidene)hydrazine (52-*Z*d)

4-Ferrocenylbut-3-yne-1-one (**44**) (51 mg, 0.2 mmol) and (3-chloro-4-florophenyl) hydrazine (**54d**) (32.5 mg, 0.2 mmol) were used in the pursuit of General Procedure 1 giving *Z* isomer (**52-*Z*d**) (62 mg, 78%).

52-*Z*d: ^{1}H NMR ($CDCl_3$): δ 8.13 (br s, 1H, NH), 7.17 (dd, 1H, J = 2.4 Hz), 7.04 (t, 1H, J = 8.8 Hz), 6.87 (m, 1H), 4.56 (s, 2H), 4.36 (s, 2H), 4.27 (s, 2H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 153.5 (C), 151.1 (C), 141.2 (C), 125.9 (C), 121.4 (d, CH, J = 73.6 Hz), 116.8 (d, CH, J = 89.2 Hz), 114.3 (CH), 111.8 (d, C, J = 25.2 Hz), 102.0 (C), 71.8 (CH), 70.3 (CH), 69.7 (CH), 62.4 (C), 22.3 (CH_3). IR (neat): 3308.1 (w), 2918.7 (w), 2183.0 (m), 1606.9 (m), 1501.4 (s), 1254.3 (m), 1214.6 (s), 1196.6 (s), 1142.2 (m), 1106.3 (w), 1041.2 (w), 1001.9 (w), 804.4 (m), 782.5 (m), 697.7 (w).

4.6.9 Synthesis of (*Z*)-1-(3-ferrocenyl-1-phenylprop-2-ynylidene)-2-phenyl hydrazine (53-*Z*a)

1-Phenyl-3-ferrocenylprop-2-yne-1-one (**45**) (100 mg, 0.32 mmol) and phenylhydrazine (**54a**) (35 mg, 0.32 mmol, 0.03 ml) were used in the pursuit of General Procedure 1 giving *Z* isomer **53-*Z*a** (48 mg, 38%).

53-*Z*a: ^{1}H NMR ($CDCl_3$): δ 8.7 (br s, 1H, NH), 7.97 (dd, 2H, J_1 = 7.2 Hz, J_2 = 1.6 Hz), 7.42 (t, 2H, J = 7.2 Hz), 7.34 (t, 3H, J = 7.6 Hz), 7.25 (t, 3H, J = 7.6 Hz), 4.64 (s, 2H), 4.38 (s, 2H), 4.31 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 157.0 (C), 143.8 (C), 136.0 (C), 129.4 (CH), 128.3 (CH), 128.1 (CH), 125.5 (CH), 120.9 (CH), 113.4 (CH), 75.6 (C), 71.9 (C), 70.3 (CH), 69.8 (CH), 64.8 (CH), 62.8 (C); IR (neat): 3308.4 (w), 2915.5 (w), 2182.5 (m), 1607.9 (m), 1504.3 (vs), 1255.8 (m), 1197.2 (m), 1145.7 (w), 1106.7 (w), 1040.9 (w), 804.7 (w), 697.4 (w).

4.6.10 Synthesis of (*Z*)-1-(3-ferrocenyl-1-phenylprop-2-ynylidene)-2-(2,5-difloro phenyl)hydrazine (53-*Z*b)

1-Phenyl-3-ferrocenylprop-2-yne-1-one (**45**) (82 mg, 0.26 mmol) and (2,5-diflorophenyl)hydrazine (**54b**) (38 mg, 0.26 mmol) were used in the pursuit of General Procedure 1 giving *Z* isomer **53-*Z*b** (30 mg, 27%).

53-*Z*b: ^{1}H NMR ($CDCl_3$): δ 8.89 (s, 1H, NH), 7.98 (d, *J* = 6.8 Hz, 2H), 7.43 (d, *J* = 7.6 Hz, 2H), 7.38 (d, *J* = 7.2 Hz, 2H), 7.02 (m, 1H), 6.52 (m, 1H), 4.65 (s, 2H), 4.40 (s, 2H), 4.31 (s, 5H); ^{13}C NMR ($CDCl_3$): δ (couldn't be obtained); IR (neat): 3316.9 (w), 2970.1 (vw), 2192.1 (m), 1630.6 (s), 1529.1 (vs), 1514.3 (vs), 1454.1 (m), 1330.9 (w), 1289.2 (w), 1245.6 (m), 1184.3 (m), 1156.9 (s), 1053.9 (w), 814.2 (w), 776.1 (s), 728.7 (m), 691.8 (w).

4.6.11 Synthesis of (*Z*)-1-(3-ferrocenyl-1-phenylprop-2-ynylidene)-2-((4-trifloro methyl)phenyl)hydrazine (53-*Z*c)

1-Phenyl-3-ferrocenylprop-2-yne-1-one (**45**) (84 mg, 0.27 mmol) and (4-(trifloro methyl)phenyl)hydrazine (**54c**) (47 mg, 0.27 mmol) were used in the pursuit of General Procedure 1 giving *Z* isomer **53-*Z*c** (71 mg, 56%).

53-*Z*c: ^{1}H NMR ($CDCl_3$): δ 8.72 (br s, 1H, NH), 7.91 (d, 2H, *J* = 7.6 Hz), 7.47 (d, 2H, *J* = 7.2 Hz), 7.36 (br s, 3H), 7.20 (d, 2H, *J* = 7.2 Hz), 4.58 (s, 2H), 4.32 (s, 2H), 4.24 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 146.2 (C), 135.4 (C), 128.9 (C), 128.5 (d, C, *J*=18 Hz), 128.3 (CH), 126.6 (CH), 125.7 (CH), 125.0 (CH), 112.9 (CH), 104.7 (C), 75.2 (C), 72.0 (CH), 70.2 (CH), 60.9 (CH), 62.2 (C); IR (neat) (couldn't be obtained).

4.6.12 Synthesis of (*Z*)-1-(3-ferrocenyl-1-phenylprop-2-ynylidene)-2-(3-chloro-4-florophenyl)hydrazine (53-*Z*d)

1-Phenyl-3-ferrocenylprop-2-yne-1-one (**45**) (82 mg, 0.26 mmol) and (3-chloro-4-florophenyl)hydrazine (**54d**) (42 mg, 0.26 mmol) were used in the pursuit of General Procedure 1 giving *Z* isomer **53-*Z*d** (76 mg, 64%).

53-*Z*d: ^{1}H NMR ($CDCl_3$): δ 8.49 (br s, 1H, NH), 7.97 (d, *J* = 7.2 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.37(d, *J* = 7.2 Hz, 1H), 7.32 (dd, *J* = 6.4 Hz, 1H), 7.06 (t, *J* = 8.8 Hz, 1H), 7.02 (m, 1H), 4.65 (t, *J* = 2.0 Hz, 2H), 4.40 (t, *J* = 2.0 Hz, 2H), 4.32 (s, 5H); ^{13}C NMR ($CDCl_3$); δ 154.0 (C), 140.7 (C), 135.6 (C), 128.5 (C), 128.4 (CH), 127.7 (CH), 125.6 (CH), 121.6 (d, C, *J* = 74.8 Hz), 116.9 (d, CH, *J* = 88.4 Hz), 114.8 (CH), 112.4 (d, CH, *J* = 25.6 Hz), 104.6 (C), 75.4 (C), 71.9 (CH), 70.3 (CH), 69.9 (CH), 62.4 (C); (IR (neat): 3317.1 (m), 2971.1 (w), 2194.6 (s), 1631.0 (vs), 1529.3 (vs), 1514.0 (vs), 1492.1 (m), 1453.8 (m), 1436.7 (m), 1245.9 (m), 1162.9 (s), 1106.3 (s), 1052.9 (w), 1009.9 (w), 814.0 (w), 728.5 (w), 692.1 (w).

4.7 General Procedure 2: Synthesis of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-1*H*-pyrazoles (55, 56, 57)

In a dry flask, the corresponding *Z*-isomer of hydrazones (1 equiv.) was dissolved with solvent. In another flask, (4-nitrophenyl)sulfenyl chloride (3 equiv.) was dissolved with the equal amount of solvent used for related hydrazone. Then (4-nitrophenyl)sulfenyl chloride solution was transferred into the first flask at once. The reaction was stirred under argon atmosphere for two hours at room temperature. After two hours, solvent was removed on a rotary evaporator and the resultant product was purified by flash chromatography on silica gel starting with 19:1 hexane/ethyl acetate and continuing with 9:1 hexane/ethyl acetate solution as the eluent.

4.7.1 Synthesis of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-1*H*-pyrazoles (55)

General Procedure 2 was followed by using corresponding hydrazone represented in Figure 37 (0.15 mmol) (**51-Za – 51-*Z*d**) and 4-(nitrophenyl)sulfenyl chloride (0.45 mmol) dissolved in DCM (10 ml)**.** After chromatographic purification, 4-((4-nitrophenyl)sulfenyl)-5-ferrocenyl-1*H*-pyrazoles **55A-D** presented in Figure 38 were isolated with indicated yields, The spectroscopic data for each are expressed below.

5-Ferrocenyl-4-((4-nitrophenyl)sulfenyl)-1-phenyl-1*H*-pyrazole (55A) (Table 3, Entry 1) : Yield: 70%; ^{1}H NMR ($CDCl_3$): δ 8.16 (d, 2H, *J* = 8.8 Hz), 7.79 (s, 1H), 7.49 (m, 3H), 7.39 (m, 2H), 7.32 (d, 2H, *J* = 8.8 Hz), 4.20 (s, 4H), 4.04 (s, 5H); ^{13}C NMR ($CDCl_3$); δ 149.4 (C), 146.6 (CH), 145.7 (C), 145.3 (C), 140.5 (C), 129.1 (CH), 128.9 (CH), 126.7 (CH), 124.9 (CH), 124.3 (CH), 103.0 (C), 72.1 (CH), 69.9 (CH), 69.1 (CH), 69.0 (C); IR (neat): 3090.7 (w), 2987.0 (w), 2907.3 (w), 1573.1 (m), 1499.3 (vs), 1471.4 (s), 1395.6 (m), 1335.8 (vs), 1208.2 (w), 1108.5 (w), 1068.6 (w), 996.8 (w), 845.2 (s), 769.5 (s), 737.5 (s), 689.7 (m).

5-Ferrocenyl-4-((4-nitrophenyl)sulfenyl)-1-(2,5-diflorophenyl)-1*H*-pyrazole (55B) (Table 3, Entry 2): Yield: 65%; ^{1}H NMR ($CDCl_3$): δ 8.19 (d, 2H, *J* = 7.2 Hz), 7.84 (s, 1H), 7.31 (d, 2H, *J* = 8.0 Hz), 7.30 (s, 1H), 7.28 (d, 2H, *J* = 12.4 Hz), 4.33 (s, 2H), 4.29 (s, 2H), 4.12 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 158.2 (d, C, *J* = 980 Hz), 153.6 (d, C, *J* = 1003 Hz), 148.8 (C), 147.8 (CH), 147.5 (C), 145.3 (C), 129.1 (C), 125.0 (CH), 124.3 (CH), 117.8 (CH), 116.4 (CH), 116.2 (C), 103.1 (CH), 71.8 (CH), 70.3 (CH), 69.8 (CH), 68.3 (C); IR (neat): 2979.1 (vs), 2891.3 (s), 1511.3 (s), 1399.6 (w), 1331.8 (m), 1248.1 (vw), 1068.6 (br), 813.3 (w), 765.5 (w), 669.7 (w).

5-Ferrocenyl-4-((4-nitrophenyl)sulfenyl)-1-((4-trifloromethyl)phenyl-1*H*-pyrazole (55C) (Table 3, Entry 3): Yield: 85%; ^{1}H NMR ($CDCl_3$): δ 8.18 (br s, 2H), 7.83 (s, 1H), 7.72 (br s, 2H), 7.50 (br s, 2H), 7.33 (br s, 2H), 4.26 (s, 2H), 4.16 (s, 2H), 4.09 (s, 5H); ^{13}C NMR ($CDCl_3$); δ 149.0 (C), 147.1 (C), 145.8 (C), 145.4 (C), 143.0 (CH), 130.4 (CH), 126.5 (C), 126.2 (C), 125.0 (CH), 124.4 (CH), 105.2 (CH), 104.5 (C), 72.0 (CH), 70.1 (CH), 69.3 (CH), 67.0 (C); IR (neat): 2919.2 (w),

2863.3 (w), 1583.1 (m), 1507.3 (s), 1467.4 (w), 1407.6 (w), 1339.8 (vs), 1156.3 (w), 1128.4 (s), 1048.6 (w), 940.9 (m), 849.2 (s), 825.3 (s), 737.5 (m), 589.9 (w).

5-Ferrocenyl-4-((4-nitrophenyl)sulfenyl)-1-(3-chloro-4-florophenyl)-1*H*-pyrazole (55D) (Table 3, Entry 4): Yield: 69%; ^{1}H NMR ($CDCl_3$): δ 8.17 (d, 2H, *J* = 8.4 Hz), 7.79 (s, 1H), 7.53 (d, 1H, *J* = 5.6 Hz), 7.31 (d, 2H, *J* = 8.0 Hz), 7.23 (d, 1H, *J* = 5.2 Hz), 7.22 (s, 1H), 4.26 (s, 2H), 4.20 (s,2H), 4.08 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 156.7 (C), 149.0 (C), 146.9 (CH), 145.9 (C), 145.3 (C), 128.9 (C), 126.4 (CH), 126.3 (CH), 125.0 (C), 124.3 (CH), 116.9 (CH), 116.7 (CH), 103.9 (C), 71.7 (CH), 70.1 (CH), 69.4 (CH), 69.1 (C); IR (neat): 3744.9 (w), 3645.1 (w), 3561.4 (w), 2975.1 (s), 2891.3 (s), 1503.3 (m), 1399.6 (m), 1331.8 (s), 1244.1 (w), 1060.6 (vs), 661.8 (m).

4.7.2 Synthesis of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-3-methyl-1*H*-pyrazoles (56)

General Procedure 2 was followed by using corresponding hydrazone represented in Figure 37 (0.15 mmol) (**52-*Z*a – 52-*Z*d**) and 4-nitrophenylsulfenyl chloride (0.45 mmol) dissolved in DCE (10 ml)**.** After chromatographic purification, 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-1*H*-pyrazoles **56A-D** presented in Figure 38 were isolated with indicated yields, The spectroscopic data for each are expressed below.

5-Ferrocenyl-4-((4-nitrophenyl)sulfenyl)-3-methyl-1-phenyl-1*H*-pyrazole (56A) (Table 5, Entry 1): Yield: 82%; ^{1}H NMR ($CDCl_3$): δ 8.24 (d, 2H, *J* = 8.4 Hz), 7.55 (s, 3H), 7.46 (s, 2H), 7.36 (d, 2H, *J* = 8.4 Hz), 4.31 (s, 2H), 4.27 (s,2H), 4.12 (s, 5H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 154.1 (CH), 149.0 (C), 146.2 (C), 145.2 (C), 140.5 (C), 129.1 (CH), 128.7 (CH), 126.7 (CH), 124.7 (CH), 124.3 (CH), 101.9 (C), 72.6 (CH), 69.9 (CH), 69.0 (CH), 68.9 (C), 11.9 (CH_3); IR (neat): 3094.7 (w), 2971.1 (w), 2894.4 (vw), 1579.1 (s), 1507.3 (vs), 1423.6 (w), 1331.8 (vs), 1112.5 (m), 1076.6 (s), 1000.8 (m), 913.1 (w), 853.2 (w), 817.3 (w), 737.5 (w), 689.7 (w).

5-Ferrocenyl-4-((4-nitrophenyl)sulfenyl)-3-methyl-1-(2,5-diflorophenyl)-1*H*-pyrazole (56B) (Table 5, Entry 2): Yield: 84%; ^{1}H NMR ($CDCl_3$): δ 8.13 (d, 2H, *J* = 8.0 Hz), 7.27 (s, 1H), 7.22 (d, 2H, *J* = 8.4 Hz), 7.18 (d, 2H, *J* = 8.0 Hz), 4.27 (s, 2H), 4.21 (s, 2H), 4.04 (s, 5H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 158.3 (d, C, *J* = 980 Hz), 155.14 (C), 153.7 (dd, C, *J* = 991.6 Hz), 148.5 (C), 148.3 (C), 145.3 (C), 129.4 (q, CH), 124.7 (CH), 124.4 (CH), 117.6 (m, CH), 116.5 (CH), 116.3 (C), 102.2 (CH), 72.0 (CH), 70.0 (CH), 69.5 (CH), 69.0 (C), 12.0 (CH_3); IR (neat): 2967.11 (vs), 2923.24 (vs), 2851.44 (w), 1583.11 (m), 1507.38 (vs), 1482.73 (w), 1410.69 (w), 1327.85 (vs), 1260.04 (vs), 1235.87 (m), 1092.53 (br), 1008.77 (s), 869.17 (w), 845.24 (w), 797.38 (vs), 737.55 (vs), 681.71 (w).

5-Ferrocenyl-4-((4-nitrophenyl)sulfenyl)-3-methyl-1-((4-trifloromethyl)phenyl)-1*H* -pyrazole (56C) (Table 5, Entry 3): Yield: 85%; ^{1}H NMR ($CDCl_3$): δ 8.17 (d, 2H, *J* = 8.4 Hz), 7.71 (d, 2H, *J* = 6.8 Hz), 7.48 (d, 2H, *J* = 6.8 Hz), 7.28 (d, 2H, *J* = 6.4 Hz), 4.26 (s, 2H), 4.20 (s, 2H), 4.09 (s, 5H), 2.30 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 154.8 (C), 148.6 (C), 148.4 (C), 145.3 (C), 145.2 (C), 126.5 (CH), 126.4 (C), 126.2 (CH), 126.1 (C), 124.7 (CH), 124.4 (CH), 103.5 (C), 72.5 (CH), 70.1 (CH), 69.3 (CH), 69.2 (C), 12.0 (CH_3); IR (neat): 3094.7 (w), 2935.2 (br), 1734.7 (m), 1615.0 (m), 1579.1 (s), 1419.5 (w), 1323.9 (vs), 1236.1 (w), 1164.3 (s), 1132.4 (s), 1100.5 (s), 1056.6 (s), 877.1 (w), 853.2 (s), 737.5 (m).

5-Ferrocenyl-4-((4-nitorphenyl)sulfenyl)-3-methyl-1-(3-chloro-4-florophenyl)-1*H*-pyrazole (56D) (Table 5, Entry 4): Yield: 77%; ^{1}H NMR ($CDCl_3$): δ 8.17 (d, 2H, *J* = 8.4 Hz), 7.52 (br s, 1H), 7.26 (d, 2H, *J* = 8.8 Hz), 7.20 (br s, 2H), 4.26 (s, 2H), 4.22 (s, 2H), 4.08 (s, 5H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 157.9 (d, C, *J* = 1001.6 Hz), 154.6 (C), 148.6 (C), 146.5 (C), 145.3 (C), 136.9 (d, C, *J* = 15.2 Hz), 128.9 (CH), 126.4 (d, CH, *J* = 29.6 Hz), 124.7 (C), 124.4 (CH), 121.6 (d, CH, *J* = 76.4 Hz), 116.7 (d, CH, *J* = 89.2 Hz) 102.9 (C), 72.3 (CH), 70.1 (CH), 69.3 (CH), 69.0 (C), 15.2 (CH_3); IR (neat): 3736.81 (s), 3657.11 (m), 3569.37 (m), 2963.12 (vs), 2927.22 (vs), 1587.10 (w), 1503.34 (w), 1399.64 (w), 1327.85 (w), 1264.03(vs), 1076.57 (vs), 1012.76 (vs), 885.13(vw), 797.38(vs), 741.54 (w), 665.76 (m).

4.7.3 Synthesis of 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-3-phenyl-1*H*-pyrazoles (57)

General Procedure 2 was followed by using corresponding hydrazone represented in Figure 37 (0.15 mmol) (**53-*Z*a – 53-*Z*d**) and 4-(nitrophenyl)sulfenyl chloride (0.45 mmol) dissolved in DCE (10 ml)**.** After chromatographic purification, 5-ferrocenyl-4-((4-nitrophenyl)sulfenyl)-1*H*-pyrazoles **57A-D** presented in Figure 38 were isolated with indicated yields, The spectroscopic data for each are expressed below.

5-Ferrocenyl-4-((4-nitorphenyl)sulfenyl)-1,3-diphenyl-1*H*-pyrazole (57A) (Table 5, Entry 5): Yield: 64%; ^{1}H NMR ($CDCl_3$): δ 8.15 (d, 2H, *J* = 8.8 Hz), 7.88-7.86 (m, 2H), 7.51-7.49 (m, 3H), 7.46-7.44 (m, 2H), 7.37-7.35 (m, 3H), 7.33 (d, 2H, *J* = 8.8 Hz), 4.21 (s, 4H), 4.08 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 155.1 (C), 149.5 (C), 147.3 (C), 145.2 (C), 140.5 (C), 131.8 (C), 129.1 (C), 128.9 (C), 128.6 (CH), 128.3 (CH), 128.0 (CH), 126.7 (CH), 124.8 (CH), 124.4 (CH), 100.7 (C), 72.5 (CH), 70.0 (CH), 69.2 (CH), 69.0 (C); IR (neat): 3728.9 (w), 3641.2 (w), 3553.4 (w), 2991.0 (vs), 2899.3 (s), 1575.1 (m), 1503.3 (s), 1476.4 (w), 1396.6 (w), 1327.8 (vs), 1100.5 (w), 1064.6 (br), 1000.8 (m), 829.3 (w), 765.5 (s), 737.5 (s), 689.7 (s), 661.8 (m).

5-Ferrocenyl-4-((4-nitrophenyl)sulfenyl)-3-phenyl-1-(2,5-diflorophenyl)-1*H*-pyrazole (57B) (Table 5, Entry 6): Yield: 74%; ^{1}H NMR ($CDCl_3$): δ 8.14 (d, 2H, *J* = 9.2 Hz), 7.84-7.81 (m, 2H), 7.44-7.40 (m, 2H), 7.37 (d, 1H, *J* = 1.2 Hz), 7.35 (d, 2H, *J* = 2.4 Hz), 7.29 (d, 2H, *J* = 8.8 Hz), 7.26 (s, 1H), 4.27 (s, 2H), 4.17 (s, 2H), 4.12 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 156.2 (C), 149.0 (C), 145.4 (C), 131.4 (C), 128.9 (C), 128.4 (C), 128.0(C), 124.9(C), 124.5 (CH), 119.6 (CH), 117.8 (CH), 116.5 (CH), 116.3 (CH), 100.9 (C), 72.0 (CH), 70.2 (CH), 69.6 (CH), 68.2 (C); IR (neat): 3102.7 (w), 2983.1 (s), 1619.0 (m), 1583.1 (vs), 1511.3 (vs), 1497.4 (w), 1410.3 (w), 1335.8 (vs), 1164.3 (s), 1132.4 (s), 1100.5 (s), 1064.6 (s), 996.8 (m), 845.2 (s), 741.5 (m).

5-Ferrocenyl-4-((4-nitrophenyl)sulfenyl)-3-phenyl-1-((4-trifloromethyl)phenyl)-1*H*-pyrazole (57C) (Table 5, Entry 7): Yield: 50%; ^{1}H NMR ($CDCl_3$): δ 8.14 (d, 2H, *J* = 8.8 Hz), 7.87 (m, 2H), 7.72 (d, 2H, *J* = 8.4 Hz), 7.54 (d, 2H, *J* = 8.4 Hz),

7.37 (d, 1H, *J* = 2.0 Hz), 7.36 (d, 2H, *J* = 2.0 Hz), 7.31 (d, 2H, *J* = 9.2 Hz), 4.27 (s, 2H), 4.17 (s, 2H), 4.12 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 155.7 (C), 149.0 (C), 147.5 (C), 146.3 (C), 145.3 (C), 143.1 (C), 142.0 (CH), 131.5 (CH), 128.9 (CH), 128.4 (C), 127.9 (CH), 128.6 (CH), 126.2 (CH), 124.8 (CH), 124.5 (CF_3), 102.2 (C), 72.4 (CH), 70.2 (CH), 69.5 (CH), 69.3 (C); IR (neat): 3732.9 (w), 2987.1 (s), 2895.3 (w), 1619.0 (w), 1571.1 (m), 1503.3 (s), 1407.6 (w), 1331.8 (vs), 1168.3 (m), 1132.4 (s), 1056.5 (s), 996.8 (m), 909.0 (s), 845.2 (s), 729.6 (s), 689.7 (s).

5-Ferrocenyl-4-((4-nitorphenyl)sulfenyl)-3-phenyl-1-(3-chloro-4-florophenyl)-1*H*-pyrazole (57D) (Table 5, Entry 8): Yield: 71%; ^{1}H NMR ($CDCl_3$): δ 8.05 (d, 2H, *J* = 9.2 Hz), 7.77-7.75 (m, 2H), 7.53-7.51 (m, 2H), 7.28 (d, 1H, *J* = 5.2 Hz), 7.27 (d, 1H, *J* = 2.0 Hz), 7.22 (d, 2H, *J* = 9.2 Hz), 7.17-7.15 (m, 1H), 7.14 (s, 1H), 4.19 (s, 2H), 4.12 (s, 2H), 4.03 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 159.2 (C), 156.7 (C), 155.6 (C), 149.0 (C), 147.6 (C), 145.3 (C), 131.5 (CH), 128.9 (d, CH, *J* = 23.2 Hz), 128.5 (CH), 127.9 (CH), 126.5 (d, CH, *J* = 29.8 Hz), 124.9 (C), 124.4 (CH), 121.6 (CH), 116.9 (CH), 116.7 (CH), 101.6 (C), 72.2 (CH), 70.2 (CH), 69.4 (CH), 69.3 (C); IR (neat): 2971.1 (s), 2907.3 (w), 1579.1 (s), 1507.3 (vs), 1497.1 (w), 1323.9 (vs), 1252.1 (s), 1080.6 (s), 1008.8 (s), 909.1 (w), 825.3 (s), 737.5 (w).

REFERENCES

[1] Roberts, D. J.; Caserio, M. C., *Basic Principles of Organic Chemistry,* 2nd Ed., Addison & Wesley: **1977**.

[2] Solomons, T. W. G.; Fryhle, C. B., *Organic Chemistry*, 8th Ed., Wiley & Sons: New York, **2004**.

[3] McMurry, J., *Organic Chemistry,* 7th Ed., Thomson and Brooks/Cole: New York, **2008**.

[4] Lipkus, A. H.; Yuan, Q.; Kucas, K. A.; Funk, S. A.; Bartelt III, W. F.; Schenck, R. J.; Trippe A. J., *J.Org. Chem.* **2008**, *73*, 4443.

[5] Joule, J. A.; Mills, K., *Heterocyclic Chemistry,* 5th Ed., Wiley & Sons: UK, **2010**.

[6] Quin, L. D.; Tyrell J. A., *Fundamentals of Heterocyclic Chemistry*, Wiley and Sons: New Jersey, **2010**.

[7] Pozharskii, A. F.; Soldatenkov, A. T.; Katrizky, A. R., *Heterocycles in Life and Society*, Wiley and Sons, **1997**.

[8] Pizzarello, S.; Huang, Y.; Becker, L.; Poreda, R. J.; Nieman, R. A.; Cooper, G.; Williams, M., *Science,* **2001**, 293, 2236

[9] Badger, G. M., *The chemistry of Heterocyclic compounds,* Academic Press: London, **1961**.

[10] Katritzky, A.; Rees, C.; Scriven , E. *In Comprehensive Heterocyclic Chemistry II*, Pergamon Press: Oxford, **1996**, Vol. 3, pp 1-75

[11] Li J., *Name Reactions in Heterocyclic Chemistry,* Wiley and Sons: New Jersey, **2005**.

[12] Behr, L. C.; Fusco, R.; Jarboe, C. H., *The Chemistry of Heterocyclic Compounds: Pyrazoles, Pyrazolines, Pyrazolidines, Inzadoles and Condensed Rings,* Wiley and Sons: London, **1967**.

[13] Krygowski, T. M.; Anulewicz, R.; Cyrafiski, M. K.; Puchala, A.; Rasata, D., *Tetrahedron,* **1998**, *54*, 12295.

[14] Fustero, S.; Simon-Fuentes, A.; Sanz-Cervera, J. F., *Org. Prep. Proceed. Int.,* **2009**, *41*, 253.

[15] Murray, W. V.; Hadden, S. K. *J. Org. Chem*. **1992**, *57*, 6662

[16] Almirante, N.; Cerri, A.; Fedrizzi, G.; Marazzi, G.; Santagostino, M. *Tetrahedron Let*. **1998**, *39*, 3287.

[17] (a) Parlok, J. J., *J. Heterocycl*. *Chem*. **1998**, *35*, 1493. (b) Okada, J.; Itaru, O.; Shuku, W.; Wada, M.; Fukuchi, T.; Yoshiya, K.; Takahashi Y. *ACS Symp*. *Ser*. **1998**, 168.

[18] (a) Frinkelstein, B. L.; Strok, C. J. *J. Pesticide Sci*. **1997**, *50*, 324. (b) Schallner, O.; Heinz, K. H.; Karl, K. J. Ger. Offen DE, 1997, 19615259; *Chem*. *Abstr*. **1997**, *127*, 346387.

[19] (a) Daidone, G.; Maggio, B.; Plescia, S.; Raffa, D.; Musiu, C.; Milia, C.; Perra, G.; Marongiu, M. E. *Eur*. *J. Med*. *Chem*. **1998**, *33*, 375. (b) Tsuji, K.; Nakamurana, K.; Konishi, N.; Tojo, T.; Ochi, T.; Scnoh, H.; Masuo, M. *Chem*. *Pharm*. *Bull*. **1997**, *45*, 987. (c) Nauduri, D.; Reddy, G. *Chem*. *Pharm*. *Bull*. **1998**, *46*, 1254. (d) Gajare, A. S.; Bhawsar, S. B.; Shingare, M. S. *Ind*. *J. Chem*. **1997**, *6*, 321. (e) Wise, L. D.; Butler, D. E.; Dewald, H. A.; Lustgarten, D. M.; Pattison, I. C.; Schweiss, D. N.; Coughenour, L. L.; Downs, D. A.; Heffner, T. G.; Pugsley, T. A. *J. Med*. *Chem*. **1987**, *30*, 1807. (f) Brune, K. *Med*. *Toxicol*. *(Suppl*. *1)* **1986**, *1*, 1.

[20] Olivera, R.; Sanmartin, R.; Dominguez, E. *J. Org*. *Chem*. **2000**, *65*, 7010.

[21] Dale, D. J.; Dunn, P. J.; Golightly, C.; Hughes, M. L.; Levett, P. C.; Pearce, A. K.; Searle, P. M.; Ward, G.; Wood, A. S. *Org*. *Process Res*. *Dev*. **2000**, *4*, 17.

[22] Gupton, J. T.; Clough, S. C.; Miller, R. B.; Norwood, B. K.; Hickenboth, C. R.; Chertudi, I. B.; Cutro, S. R.; Petrich, S. A.; Hicks, F. A.; Wilkinson, D. R.; Sikorski, J. A. *Tetrahedron* **2002**, *58*, 5467.

[23] McGowan, C. C.; Cover, T. L.; Blaser, M. J. *Gastroenterology* **1996**, *110*, 426.

[24] Eisch, J. J. *The Chemistry of Organometallic Compounds*, The Macmillan Company, **1967**.

[25] Keally, T.; Pauson, P. L. *Nature*, **1951**, *168*, 1039.

[26] Astruc, D. *Organometallic Chemistry and Catalysis*, Springer, **2007**.

[27] Shriver, D. F.; Atkins, P. W.; Overton, T. L.; Rourke, J. P.; Weller, M. T.; Armstrong, F. A., *Inorganic Chemistry*, 4th Ed., Oxford University Press: New York, **2006**.

[28] Little, W. F.; Scott, A., *Comprehensive Organometallic Chemistry*, Academic Press: New York, **1963**.

[29] Jaouen, G., *Bioorganometallics*, Wiley, VCH Verlag, **2006**.

[30] Cuzick, J.; Powles, T.; Veronesi, U.; Forbes, J.; Edwards, R.; Ashley, S.; Boyle, P., *Lancet* **2003**, *361*, 296.

[31] Vessieres, A.; Top, S.; Beck, W.; Hillarda, E.; Jaouen, G., *Dalton Trans..,* **2006**, 529.

[32] Jaouen, G.; Top, S.; Vessieres, A.; Leclercq, G.; Quivy, J.; Jin, L.; Croisy, A. *C. R. Acad. Sci. Paris Ser. IIc* **2000**, *3*, 89.

[33] Gormen, M.; Plazuk, D.; Pigeon, P.; Hillard, E. A.; Plamont, M.; Top, S.; Vessières, A.; Jaouen, G., *Tetrahedron Lett*. **2010**, *51*, 118.

[34] Rosenfeld, A.; Blum, J.; Gibson, D.; Ramu, A., *İnorg. Chim. Acta*., **1992**, *201*, 219-221.

[35] Fang, J.; Jin, Z.; Li, Z.; Liu, W. J., *Org. Chem.*, **2003**, 674, 1-9.

[36] Huikai, S.; Qingmin, W.; Rinqiu, H.; Heng, L.; Yonghong, L., *J. Org. Chem.,* **2002**, *655*, 182-185.

[37] (a) WHO. *Weekly Epidemiol. Rep*. **1996**, *3*, 17. (b) WHO. *Weekly Epidemiol. Rep*. **1996**, *4*, 25. (c) WHO. *Weekly Epidemiol. Rep*. **1996**, *5*, 37.

[38] Daher, W.; Biot, C.; Fandeur, T.; Jouin, H.; Pelinski, L.; Viscogliosi, E.; Fraisse, L.; Pradines, B.; Brocard, J.; Khalife, J.; Dive, D. *Malaria J*. **2006**, *5*,11.

[39] Pradines, B.; Brocard, J.; Khalife, J.; Dive, D., *Malaria J*. **2006**, *5*,11.

[40] Rotkavic, Z.; Juranic, Z. D.; Stanojkovic, T.; Manojlov, D.; Rodulovic, N.; Joksovic, M. D., *Bioorganic Chemistry,* **2010,** *38,* 26-32

[41] Zora, M.; Görmen, M. *J.Organomet. Chem.* **2007,** *692,* 5026

[42] Zora, M.; Pinar, A. N.; Odabaşoğlu, M.; Büyükgüngör, O.; Turgut, G. *J. Organomet. Chem*. **2008**, *693*, 145.

[43] Damljanovic, I.; Vukicevic, M.; Radulovic, N.; Palic, R.; Ellmerer, E.;

Ratkovic, Z.; Joksovic, M.D.; Vukicevic, R. D. *Bioorg*. *Med*. *Chem*. *Lett*. **2009**, *19*, 1093.

[44] (a) Kıvrak, A. Ph. D. Thesis, Middle East Technical University, Ankara, TR, 2010. (b) Zora, M.; Kivrak, A.; Yazici, C. *J. Org. Chem.* **2011**, DOI: 10.1021/jo201119e. (c) Zora, M.; Kivrak, A. *in Abstracts of Papers, 237th National Meeting of American Chemical Society*, Salt Lake City, UT, United States, March 22-26; 2009, (ORGN-236).

[45] (a) Kitamura, T.; Takachi, T.; Kawasato, H.; Taniguchi, H. *J. Chem. Soc.*, *Perkin Trans. 1* **1992**, 1969. (b) Furstner, A.; Mamane, V. *J. Org. Chem*. **2002**, *67*, 6264. (c) Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett*. **2003**, *5*, 1055. (d) Pastine, S. J.; Youn, S. W.; Sames, D., *Tetrahedron* **2003**, *59*, 8859.

[46] Yao, T.; Campo, M. A.; Larock, R. C., *J. Org. Chem.,* **2005,** *70*, 3511-3517.

[47] Yue, D.; Yao, T.; Larock, R. C., *J. Org. Chem.,* **2005,** *70,* 10292-10296

[48] Togni, A.; Hayashi, T., *Ferrocenes: Homogeneous Catalysis, Organic Synthesis, Materials Science,* VCH: Weinheim, **1995**.

[49] Gibson, S. E., *Transition Metals in Organic Synthesis*. Oxford Univercity Press: Oxford, **1997**.

[50] Polin, J.; Schottenberger, H.; Anderson, B.; Martin, S. F., *Org. Synth.* **1995**, *73,* 262.

[51] Journet, M. Y.; Cai, D.; DiMichele, L. M.; Larsen, R. D., *Tetrahedron Lett.* **1998**, *39,* 6427.

[52] Santos , A.; Castelani, P.; Bassora, B. K.; Junior, J. C. F.; Costa, E. C.; Comasset0, V. J., *Tetrahedron Lett,* **2005,** 61.

[53] Cacchi S.; Fabrizi G.; Filisti E., *Org. Lett.*, **2008**, *10*, 2629-2632.

[54] Dvorko, M. Y.; Glotova, T. E.; Albanov, A. I.; Chipanina, N. N.; Kazheva, O. N.; Shilov, G. V.; Dyachenko, O. A., *Mendeleev Commun*. **2008**, *18*, 48.

[55] Gibson, S. E., *Transition Metals in Organic Synthesis.* Oxford University Press: Oxford, **1997**.

[56] Doisneau, G.; Balavoine, G.; Fillebeen-Khan, T. *J. Organomet*. *Chem*. **1992**, *425*, 113.

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.

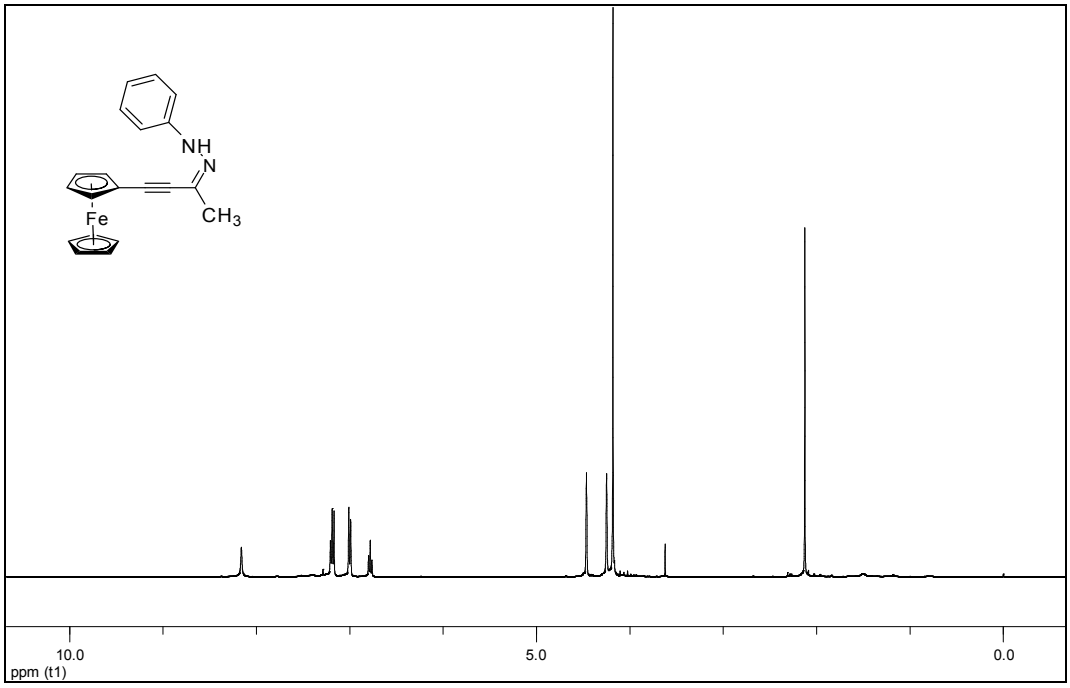


Figure A1. ^{1}H NMR spectrum of **52*Z*-a**

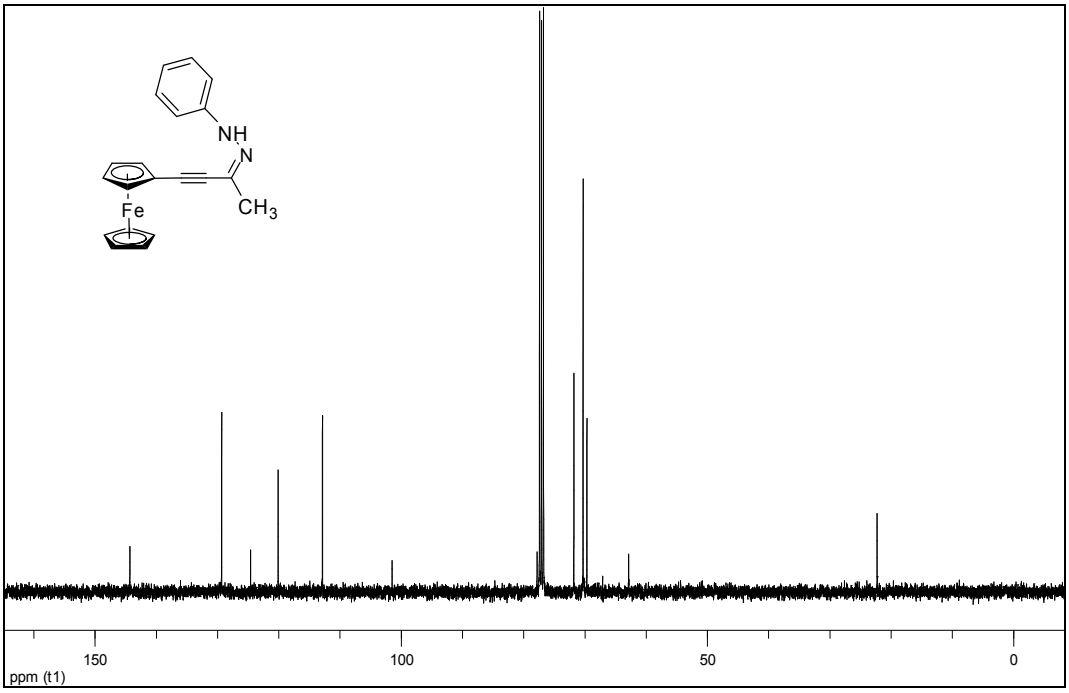


Figure A2. ^{13}C NMR spectrum of **52*Z*-a**.

.

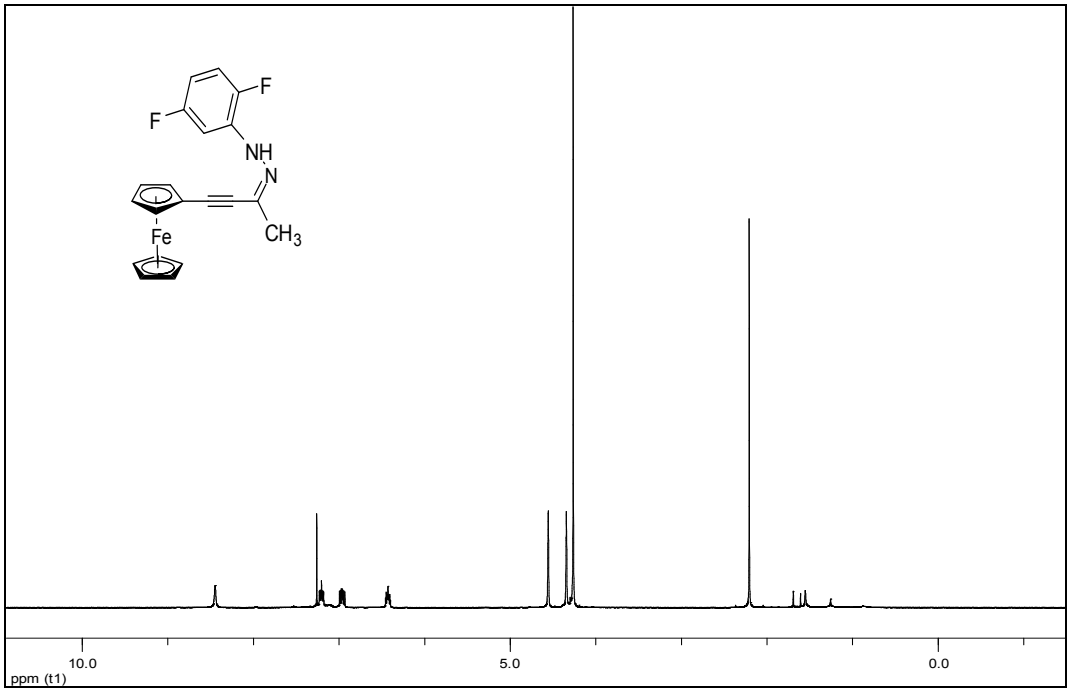


Figure A3. ^{1}H NMR spectrum of **52*Z*-b**.

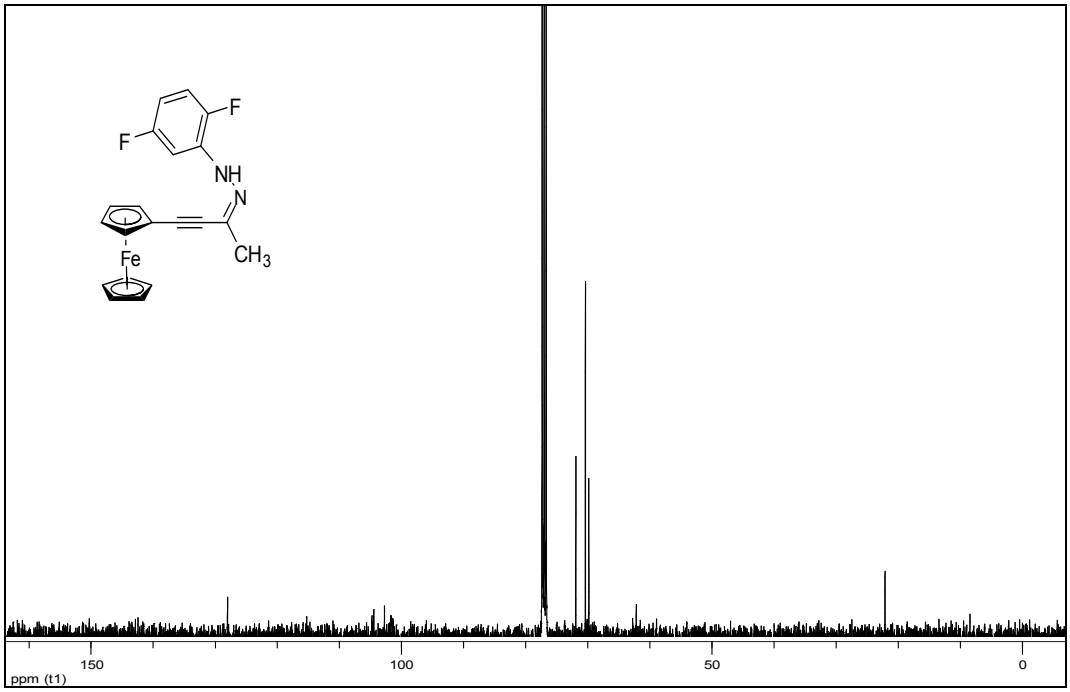


Figure A4. ^{13}C NMR spectrum of **52*Z*-b**.

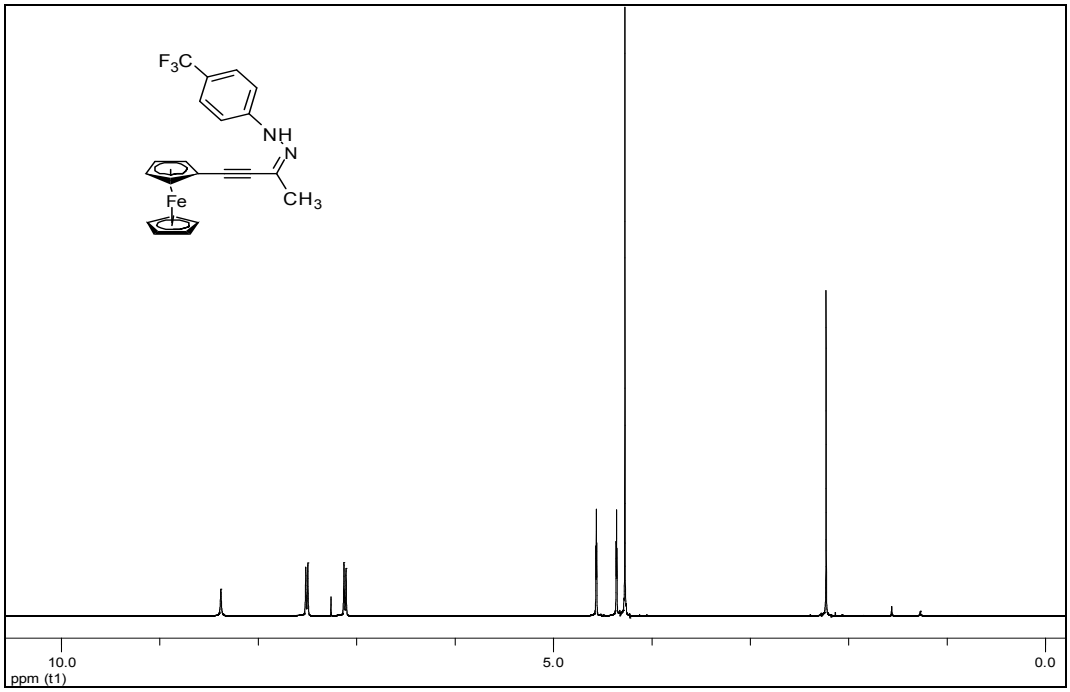


Figure A5. ^{1}H NMR spectrum of **52*Z*-c**.

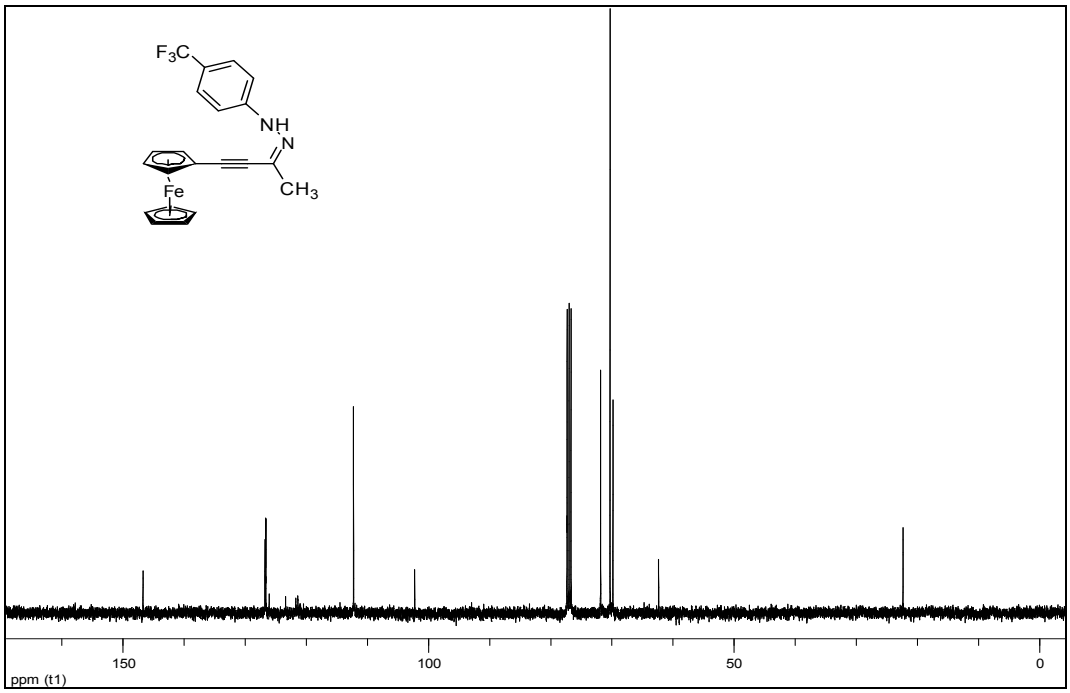


Figure A6. ^{13}C NMR spectrum of **52*Z*-c**.

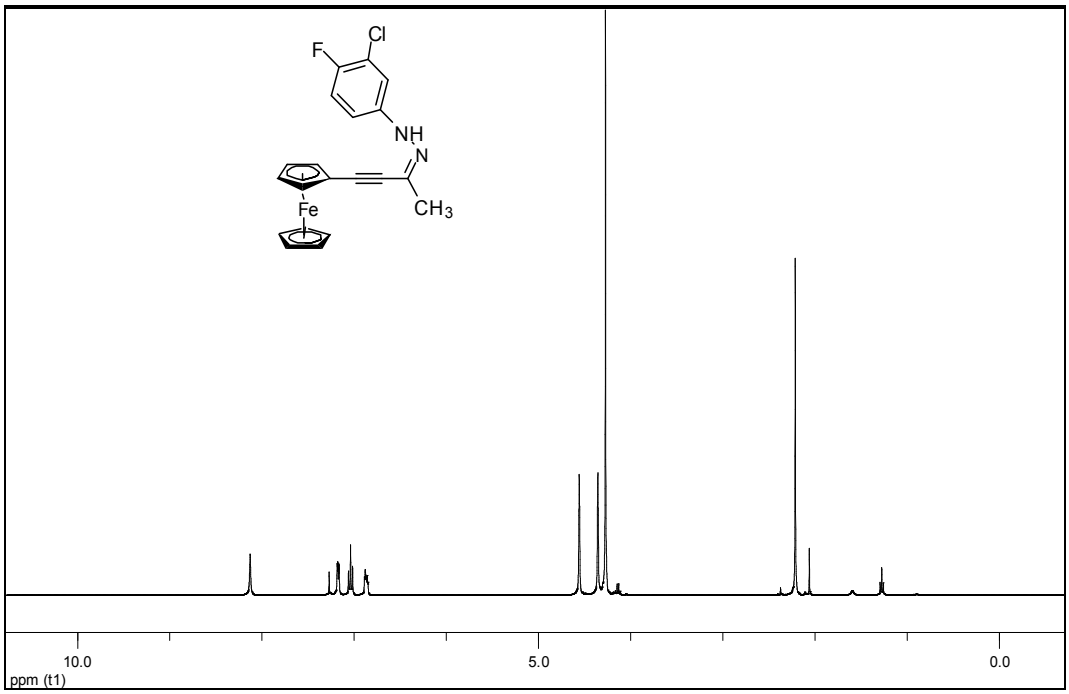


Figure A7. ^{1}H NMR spectrum of **52*Z*-d**.

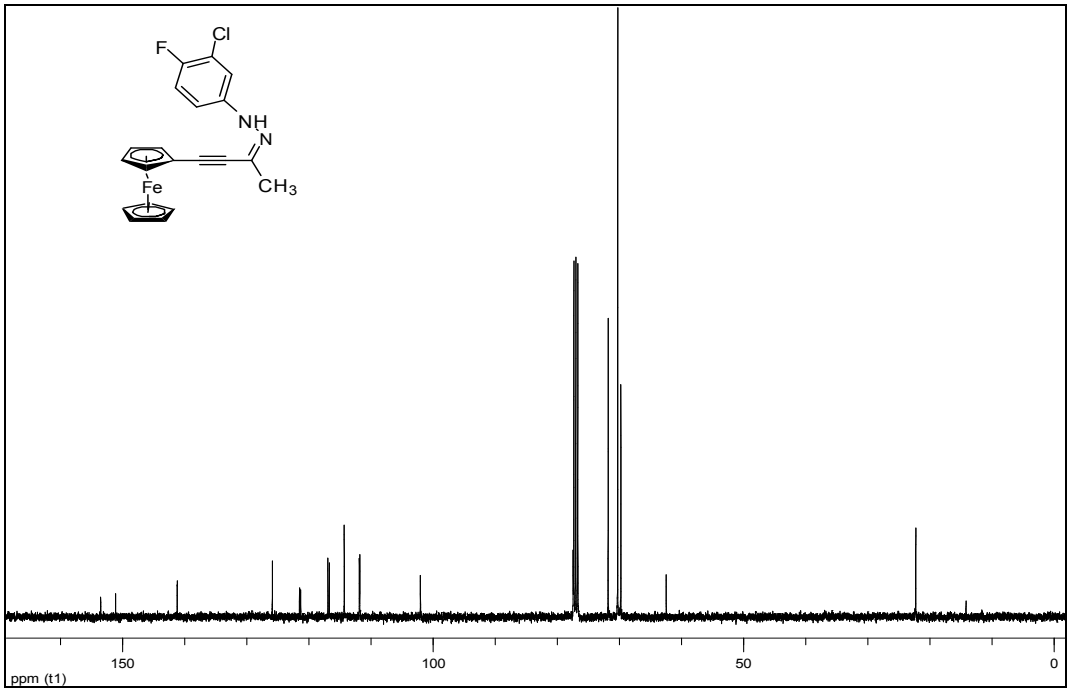


Figure A8. ^{13}C NMR spectrum of **52*Z*-d**.

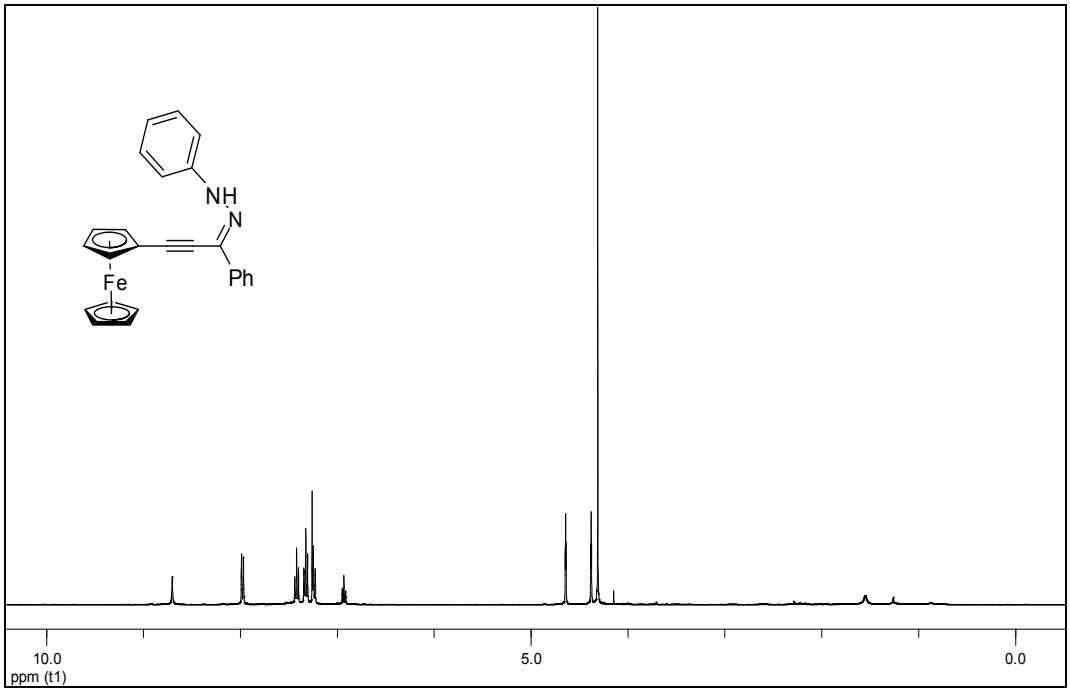


Figure A9. ^{1}H NMR spectrum of **53*Z*-a**.

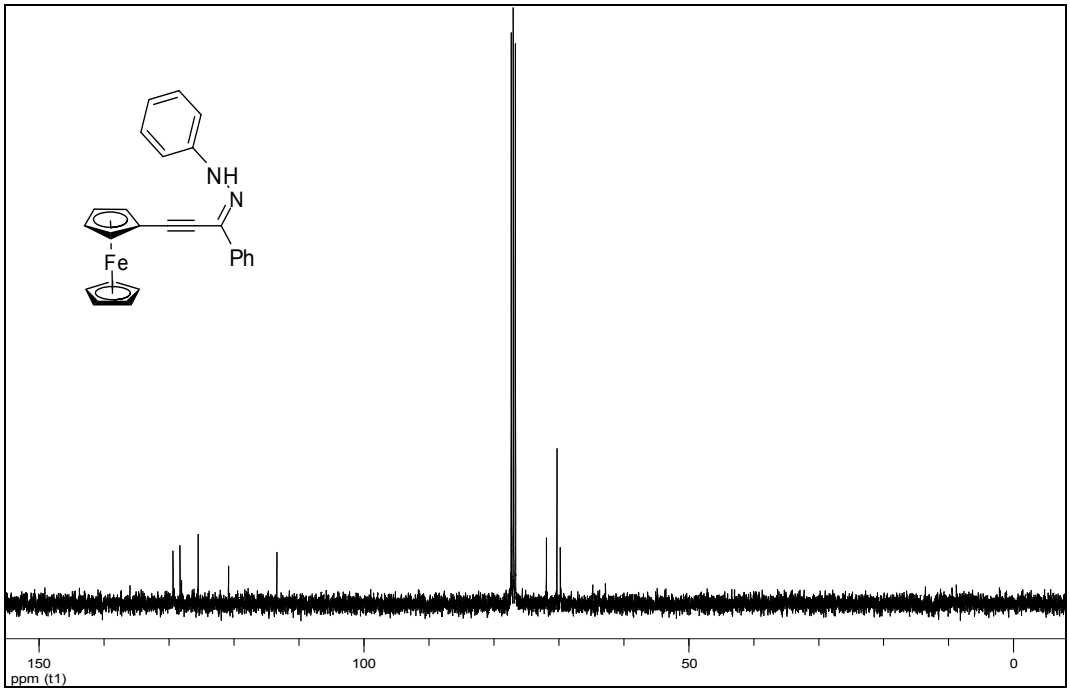


Figure A10. ^{13}C NMR spectrum of **53*Z*-a**.

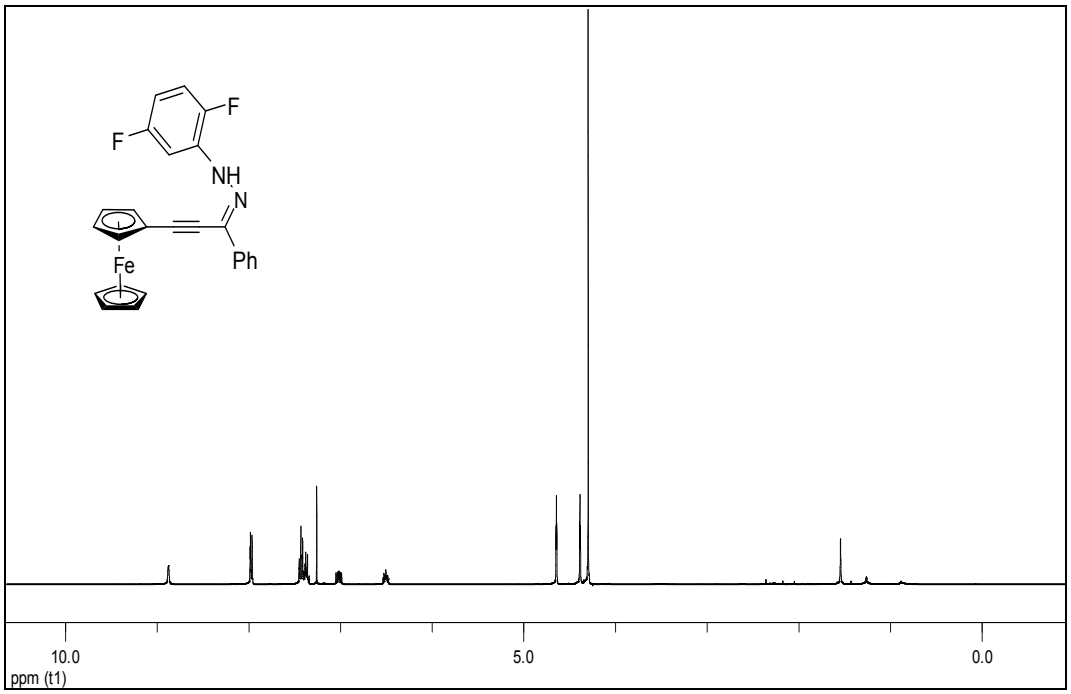


Figure A11. ^{1}H NMR spectrum of **53*Z*-b**.

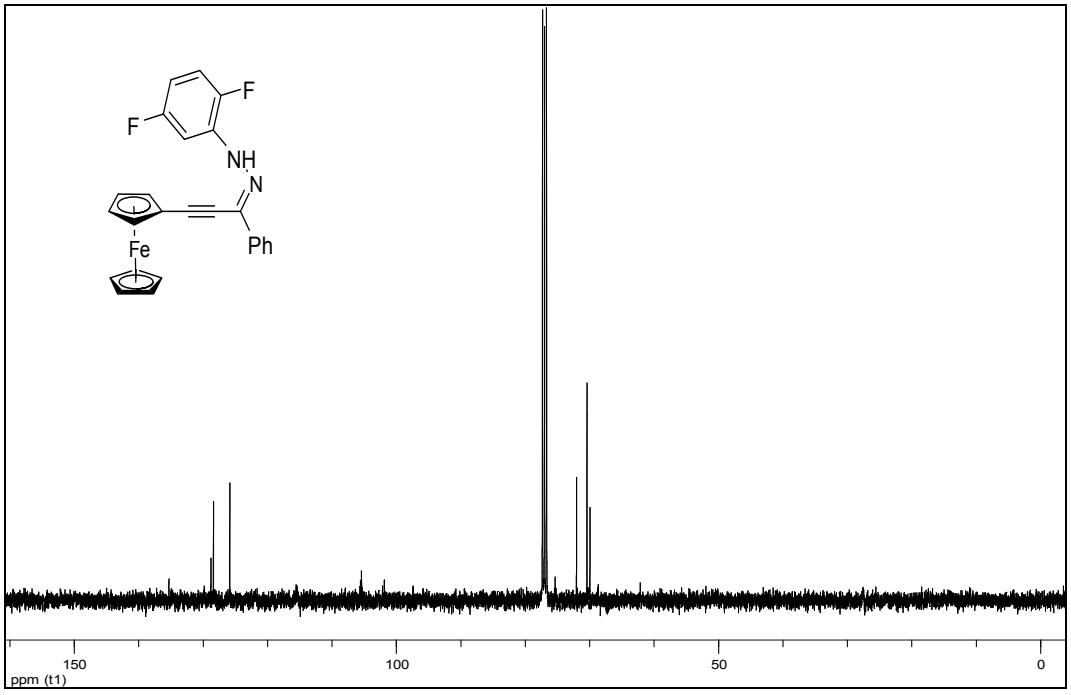


Figure A12. ^{13}C NMR spectrum of **53*Z*-b**.

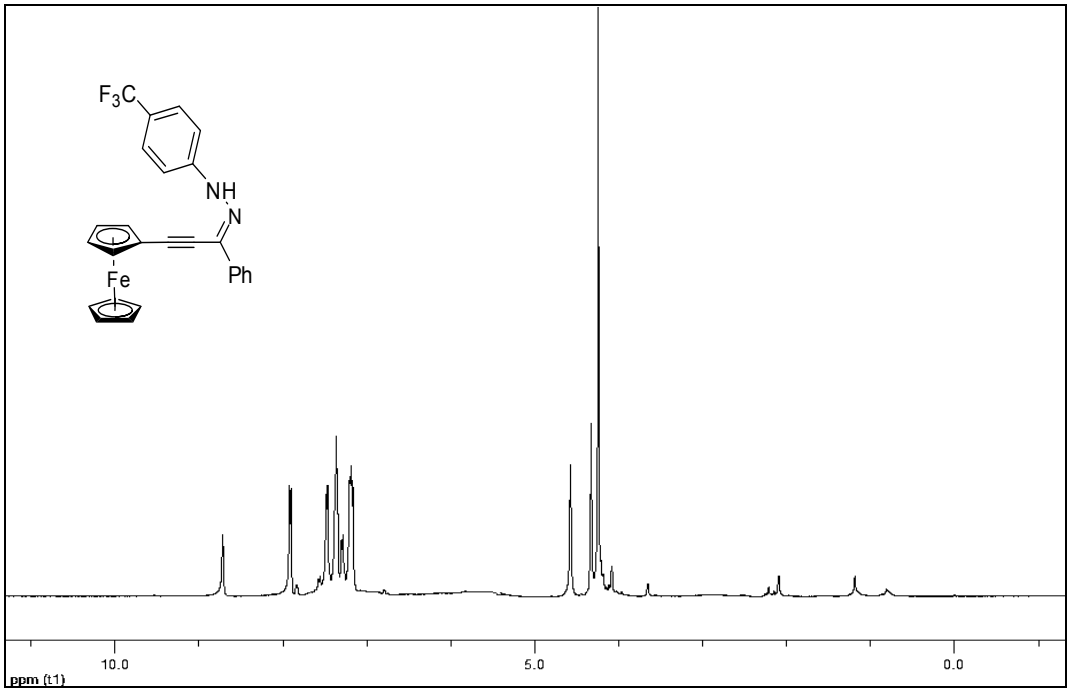


Figure A13. ^{1}H NMR spectrum of **53*Z*-c**.

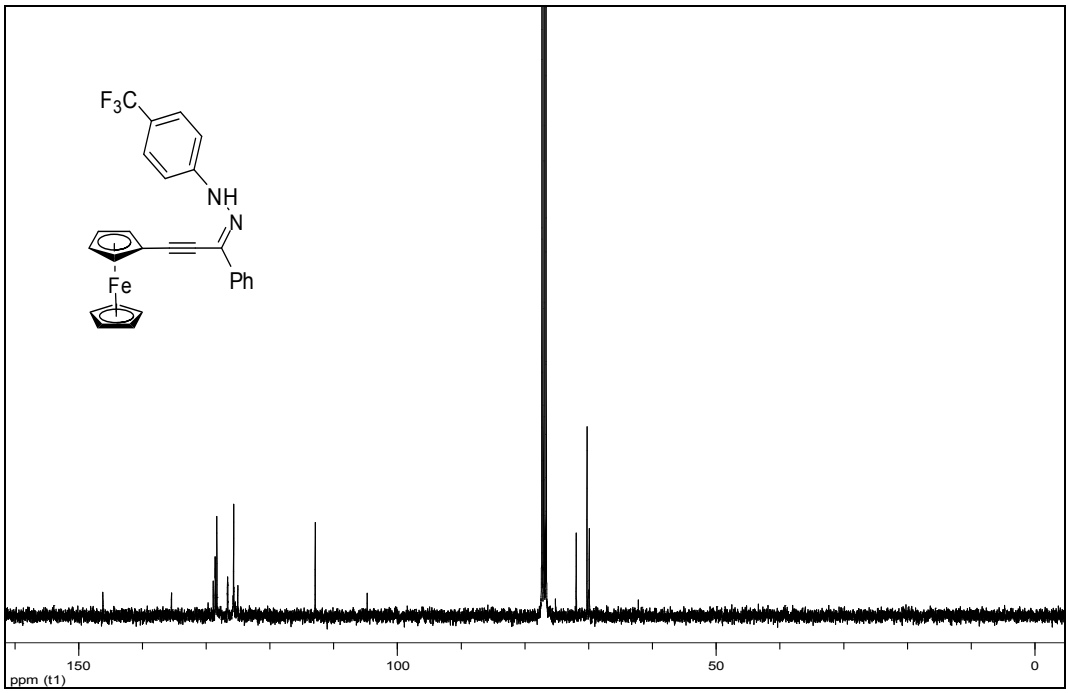


Figure A14. ^{13}C NMR spectrum of **53*Z*-c**.

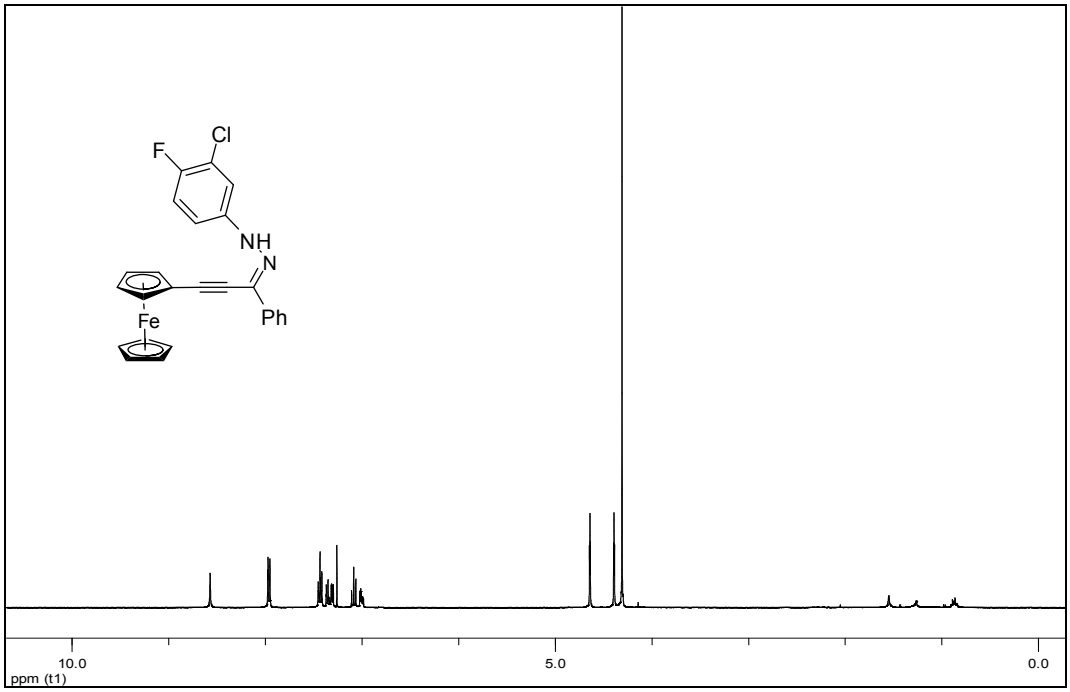


Figure A15. ^{1}H NMR spectrum of **53*Z*-d**.

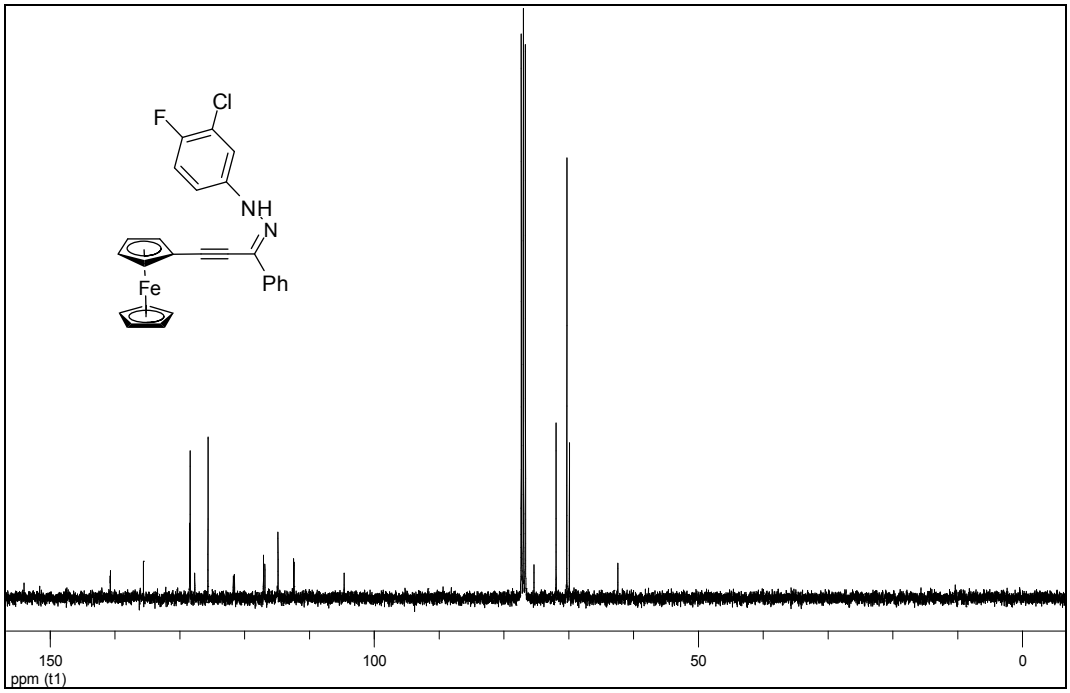


Figure A16. ^{13}C NMR spectrum of **53*Z*-d**.

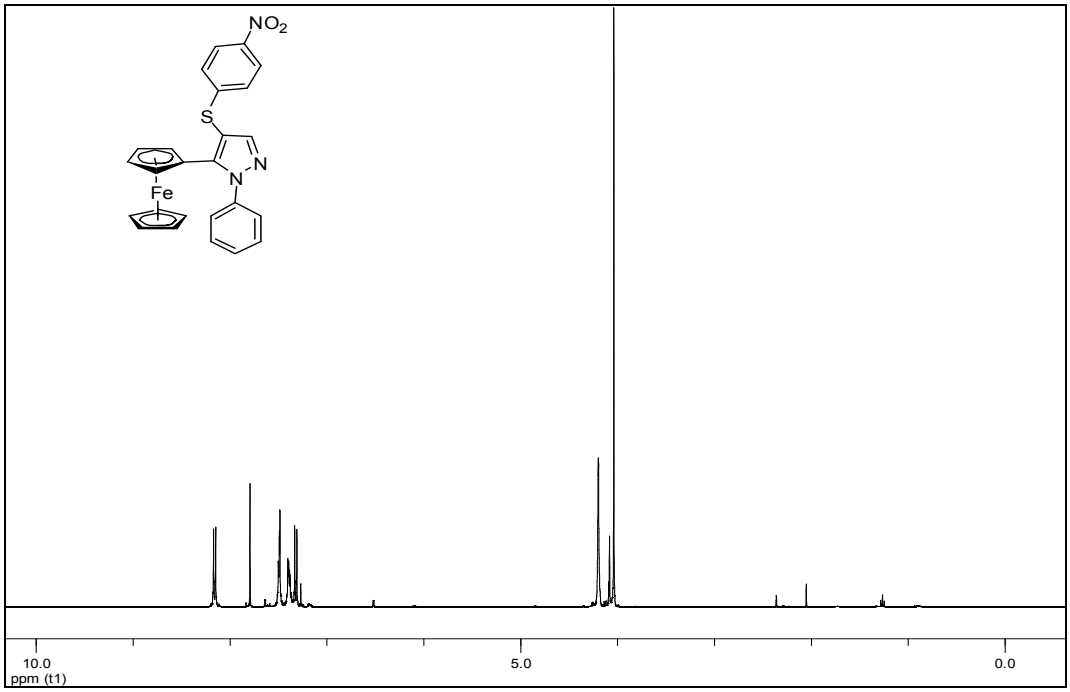


Figure A17. ^{1}H NMR spectrum of **55A**.

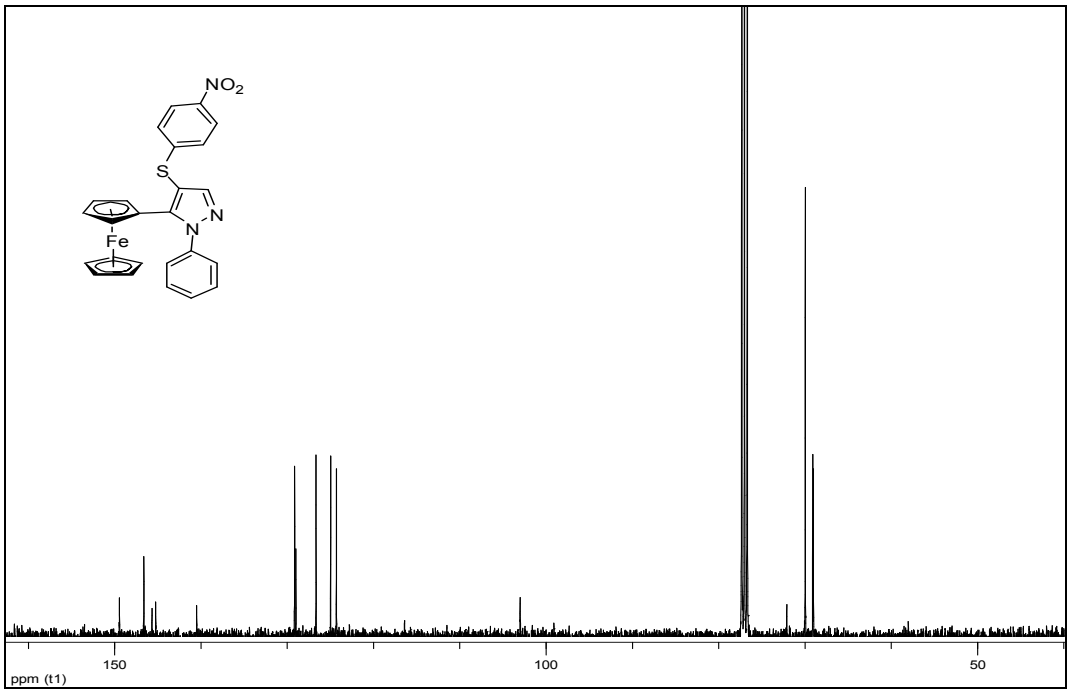


Figure A18. ^{13}C NMR spectrum of **55A**.

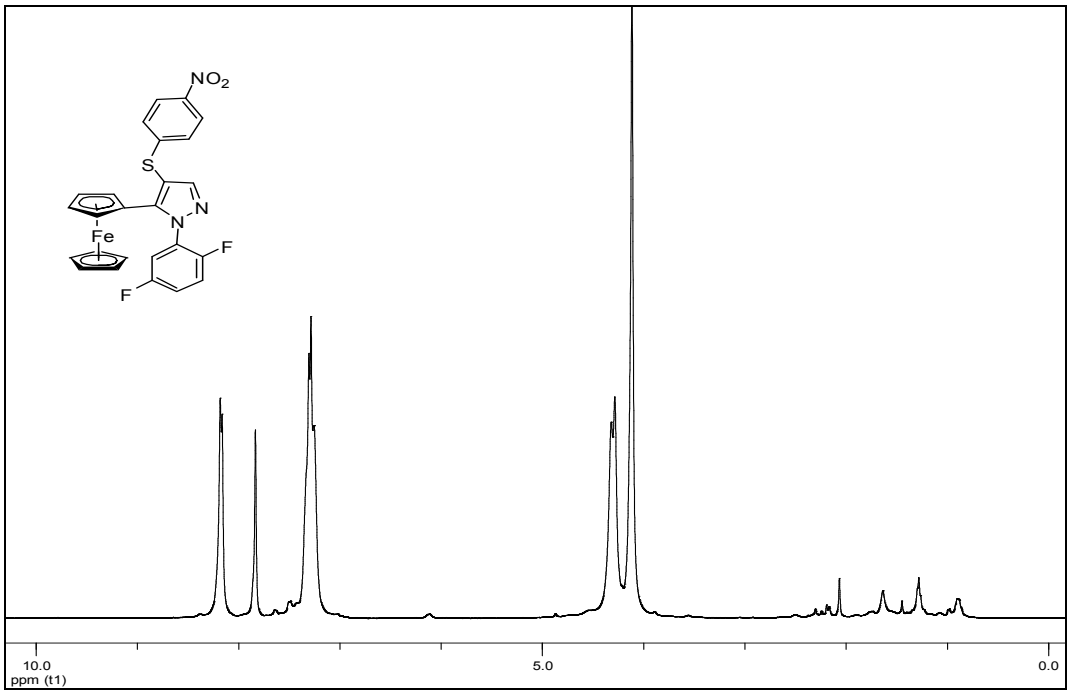


Figure A19. ^{1}H NMR spectrum of **55B**.

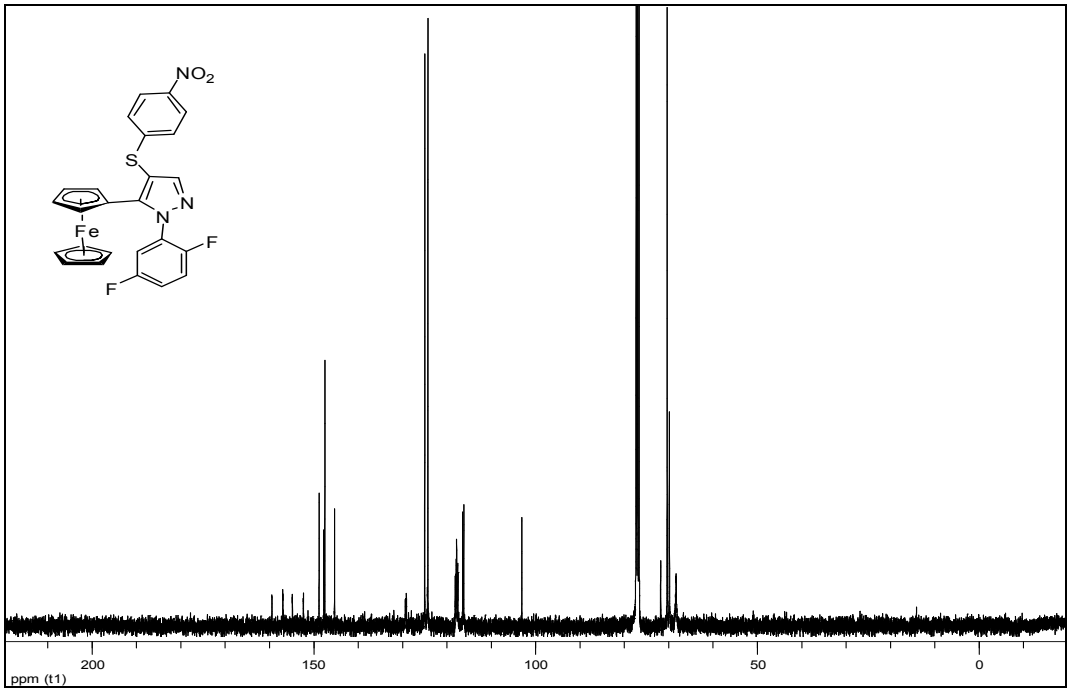


Figure A20. ^{13}C NMR spectrum of **55B**.

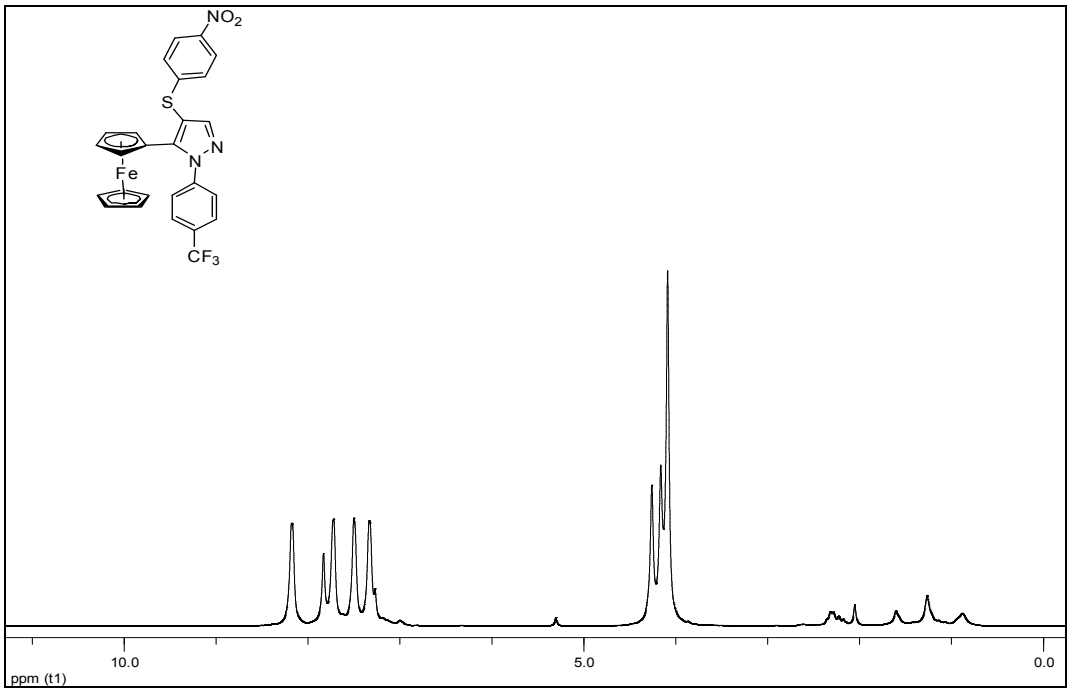


Figure A21. ^{1}H NMR spectrum of **55C**.

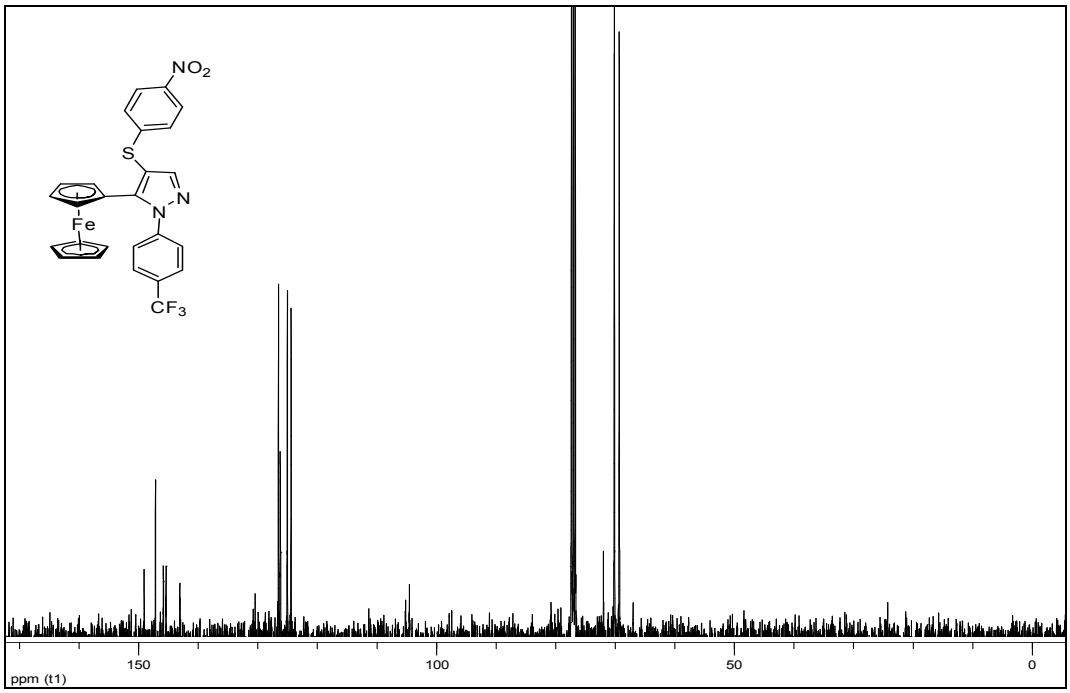


Figure A22. ^{13}C NMR spectrum of **55C**.

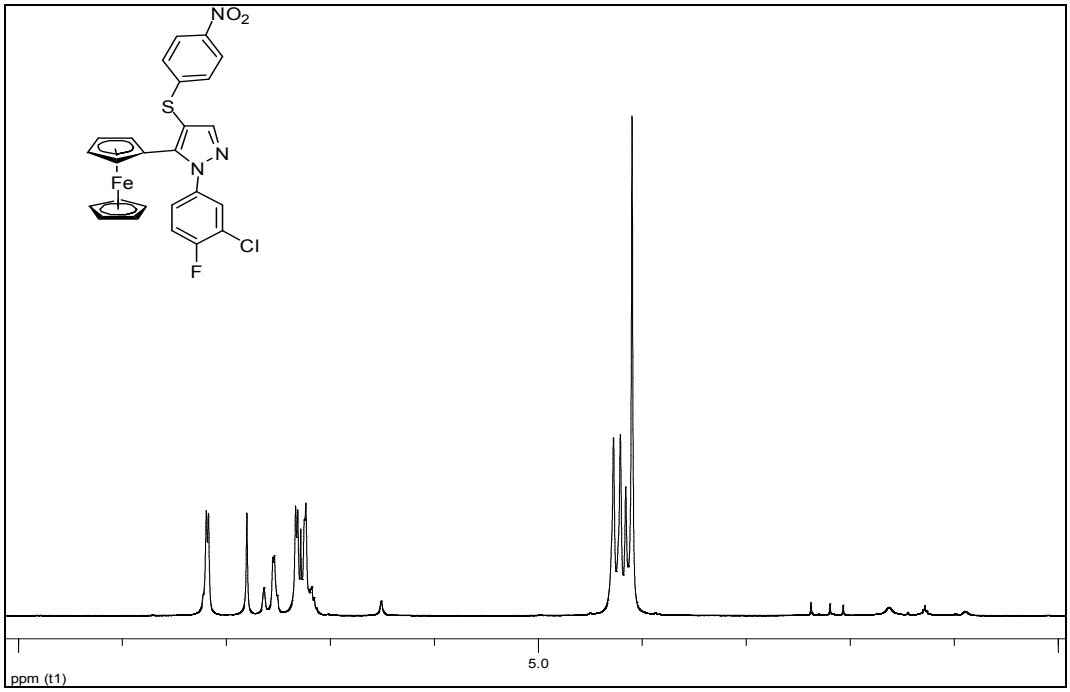


Figure A23. ^{1}H NMR spectrum of **55D**.

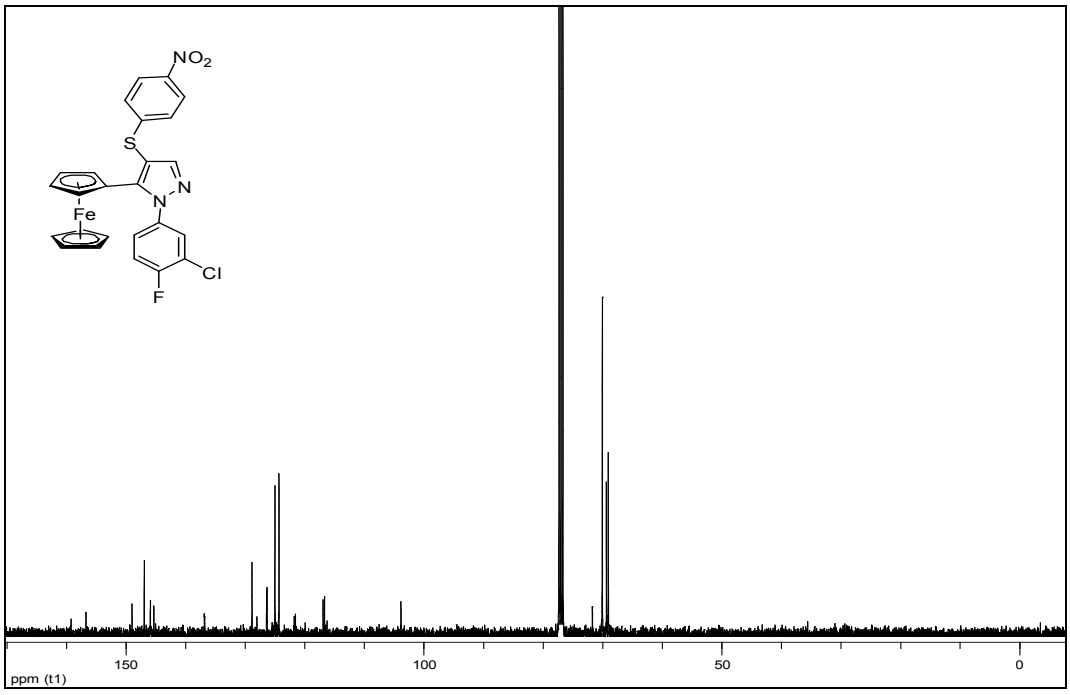


Figure A24. ^{13}C NMR spectrum of **55D**.

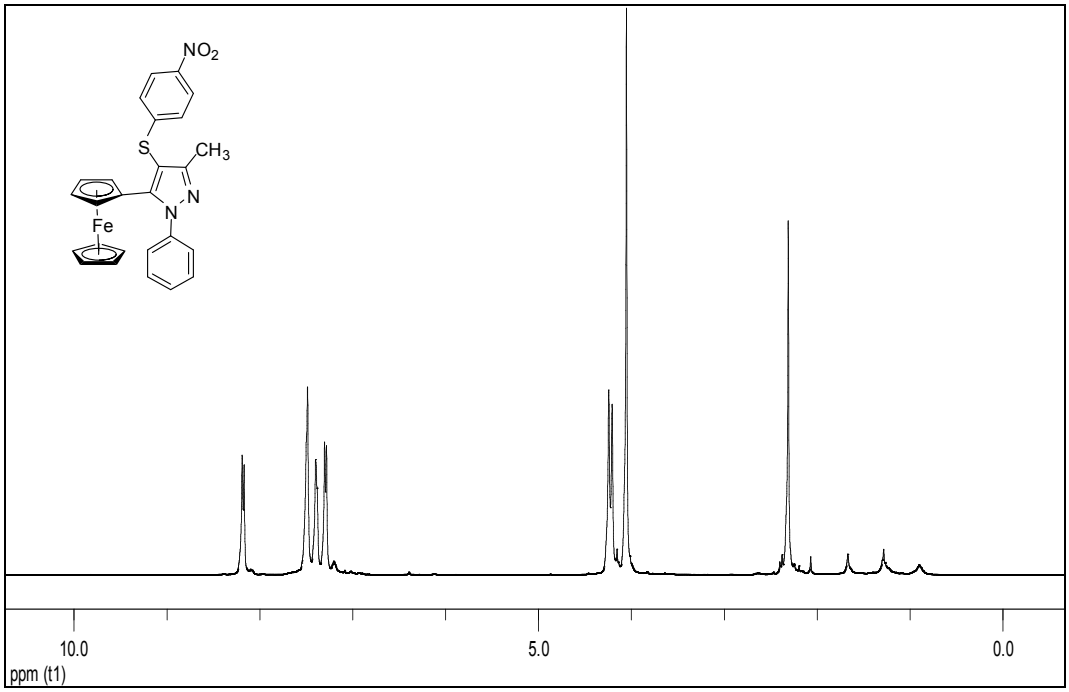


Figure A25. ^{1}H NMR spectrum of **56A**.

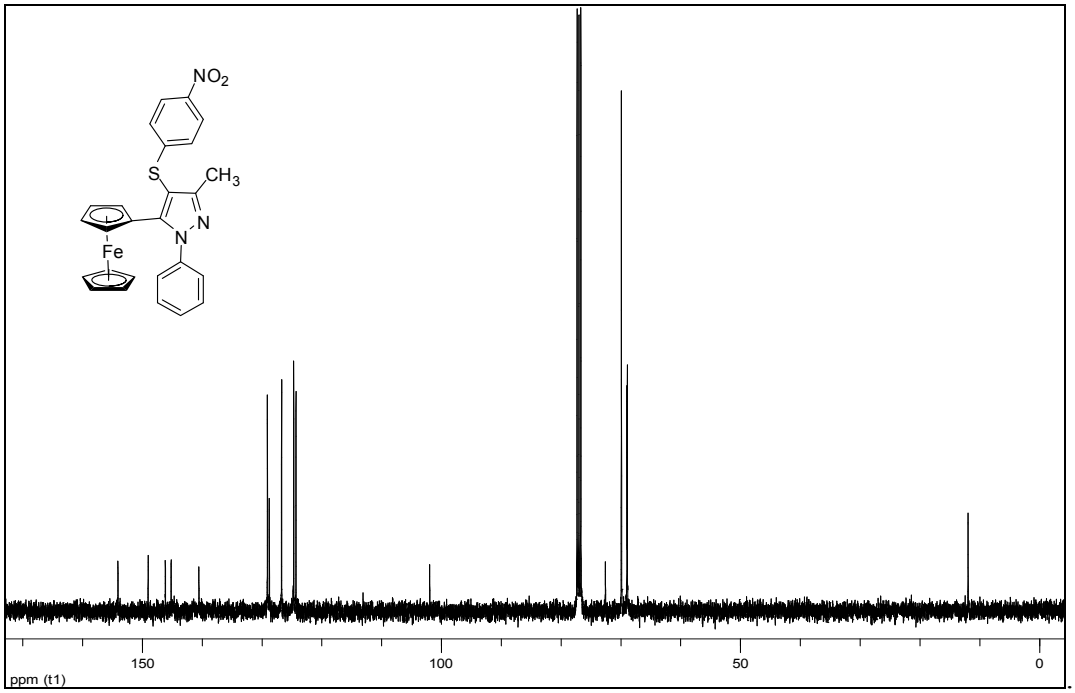


Figure A26. ^{13}C NMR spectrum of **56A**.

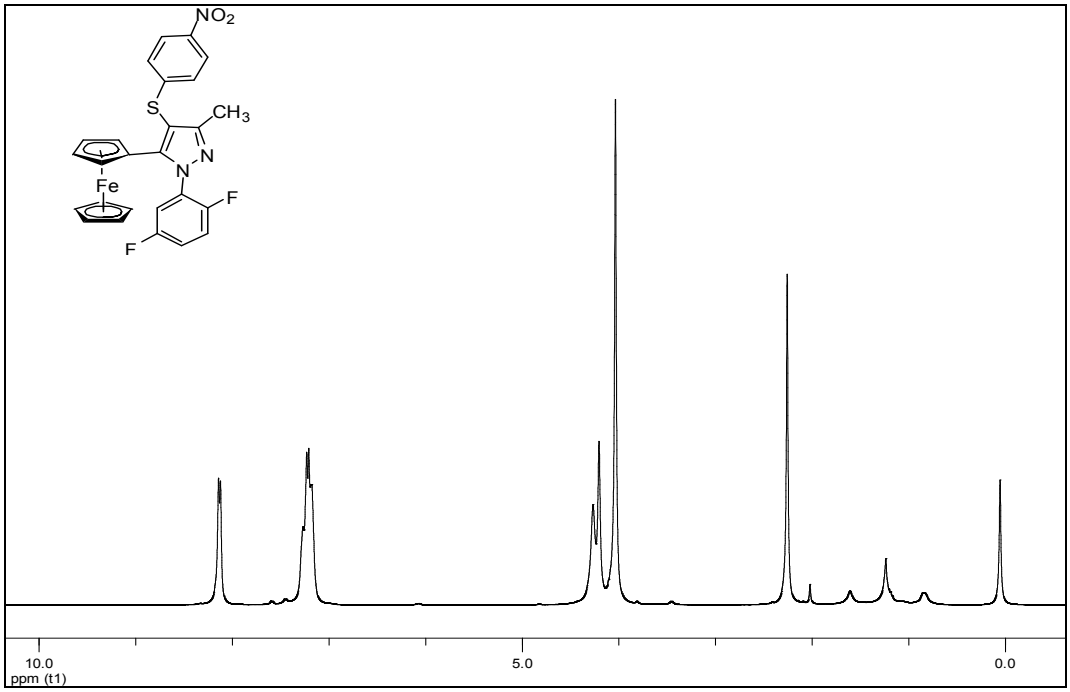


Figure A27. ^{1}H NMR spectrum of **56B**.

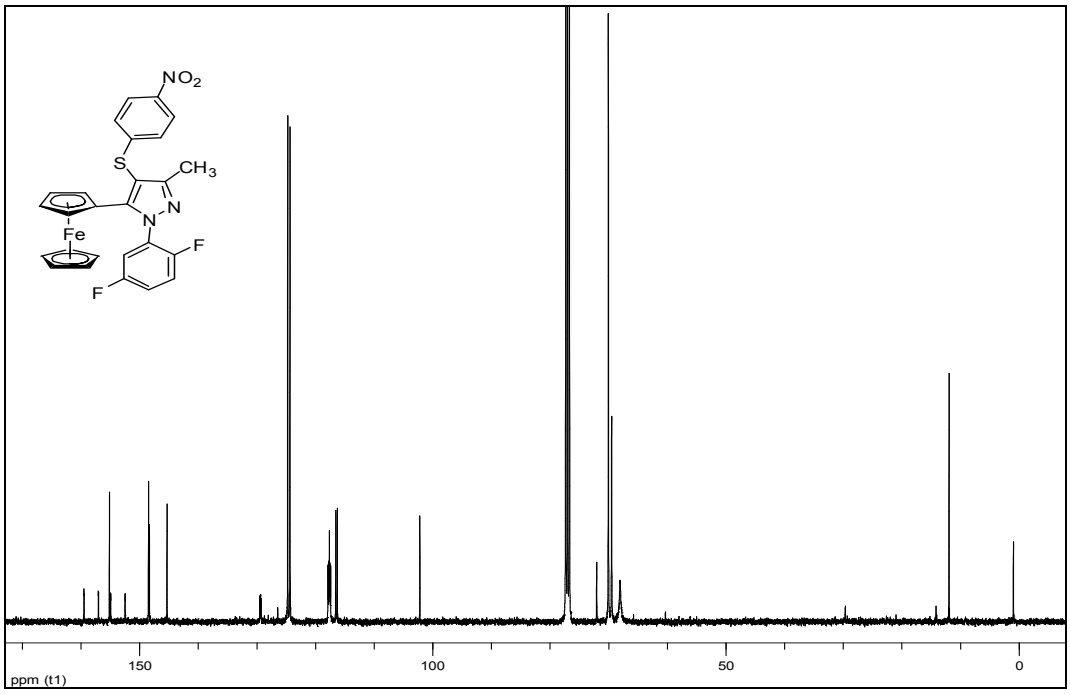


Figure A28. ^{13}C NMR spectrum of **56B**.

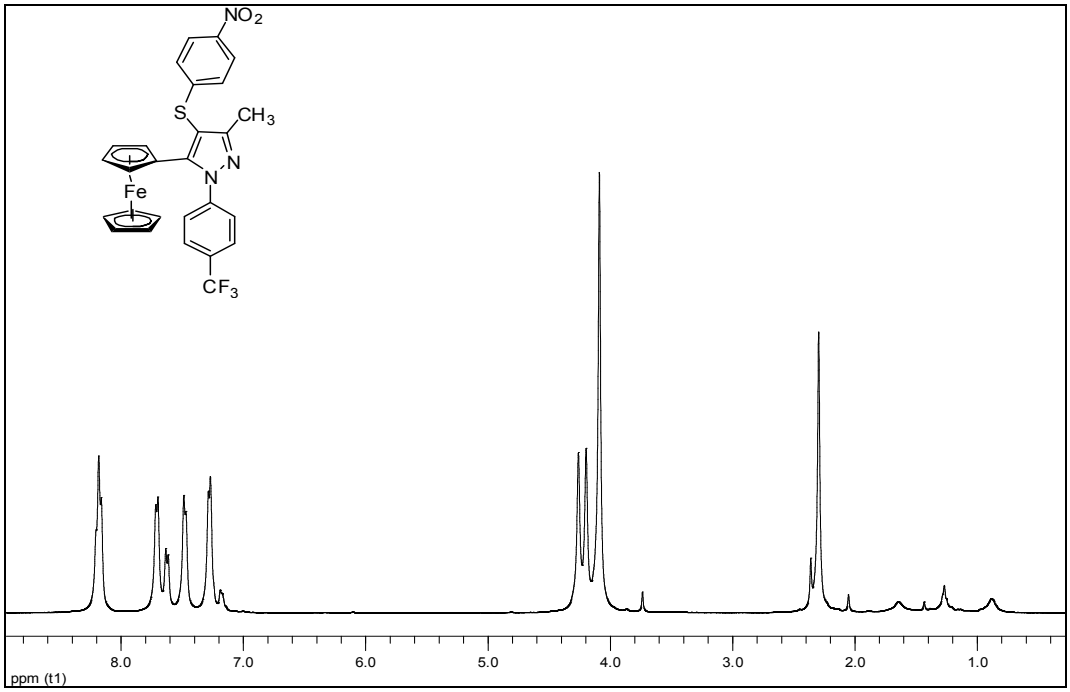


Figure A29. ^{1}H NMR spectrum of **56C**.

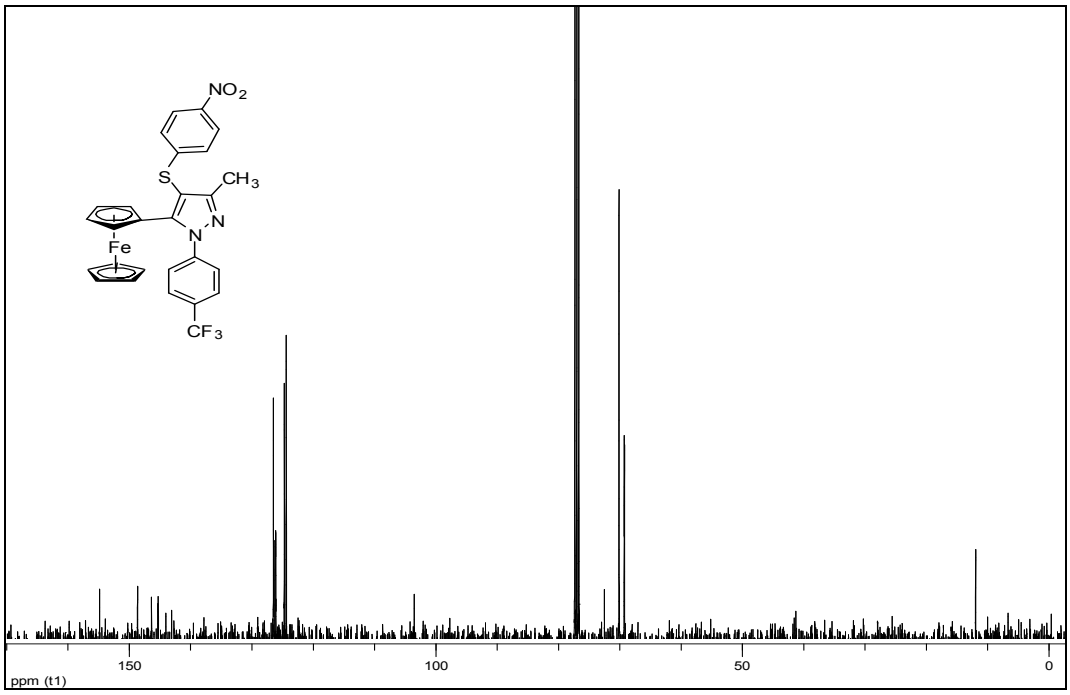


Figure A30. ^{13}C NMR spectrum of **56C**.

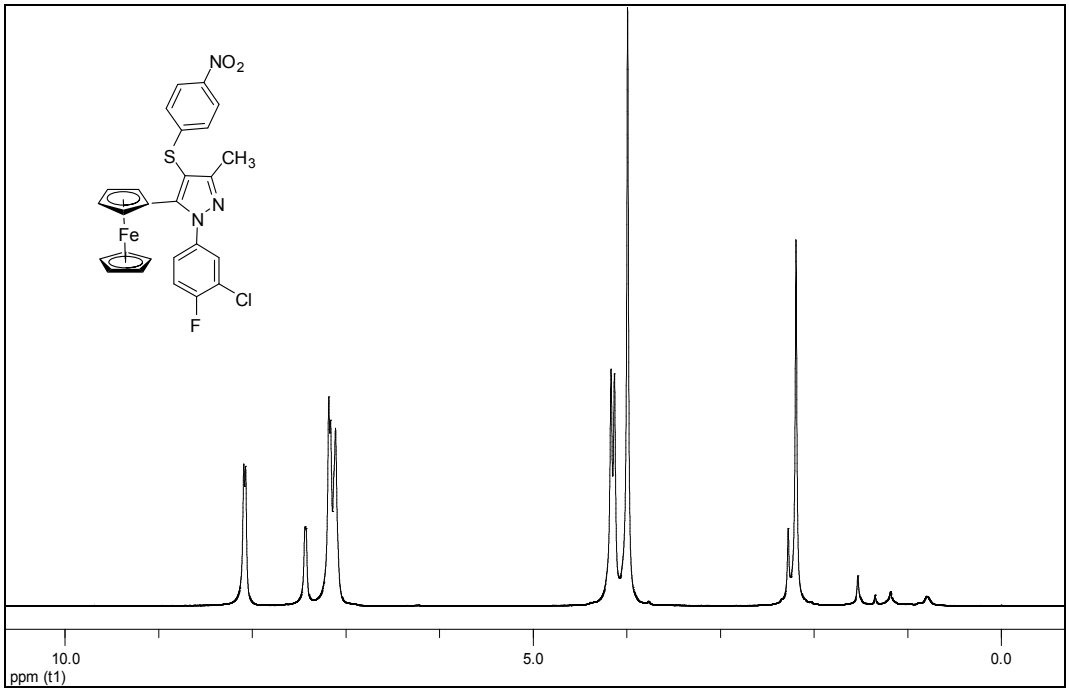


Figure A31. ^{1}H NMR spectrum of **56D**.

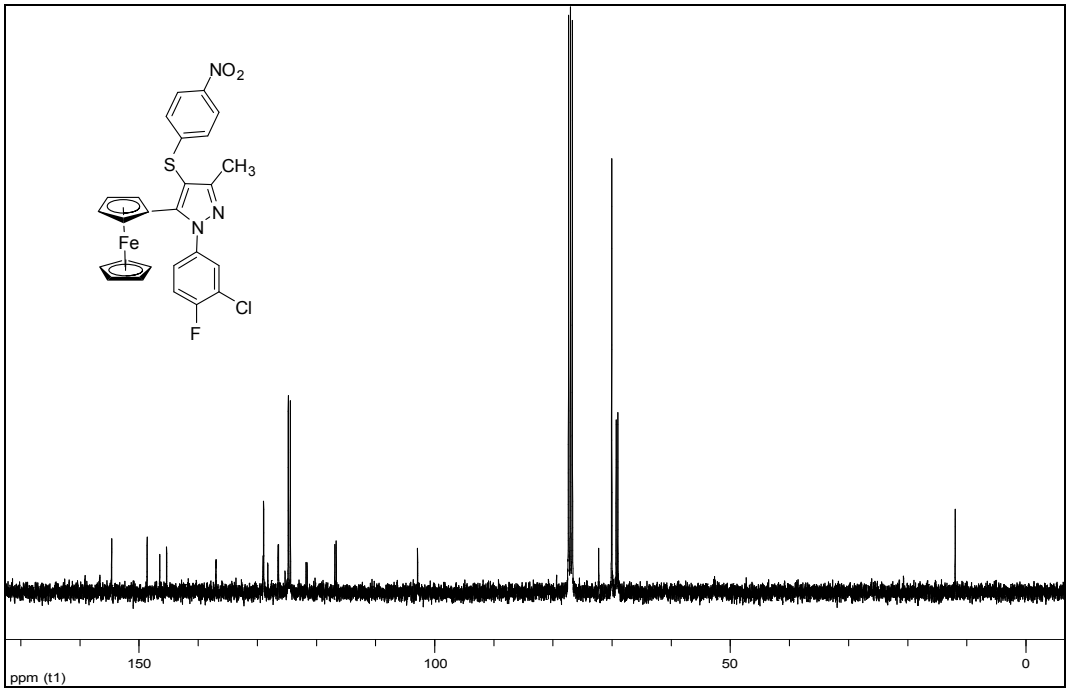


Figure A32. ^{13}C NMR spectrum of **56D**.

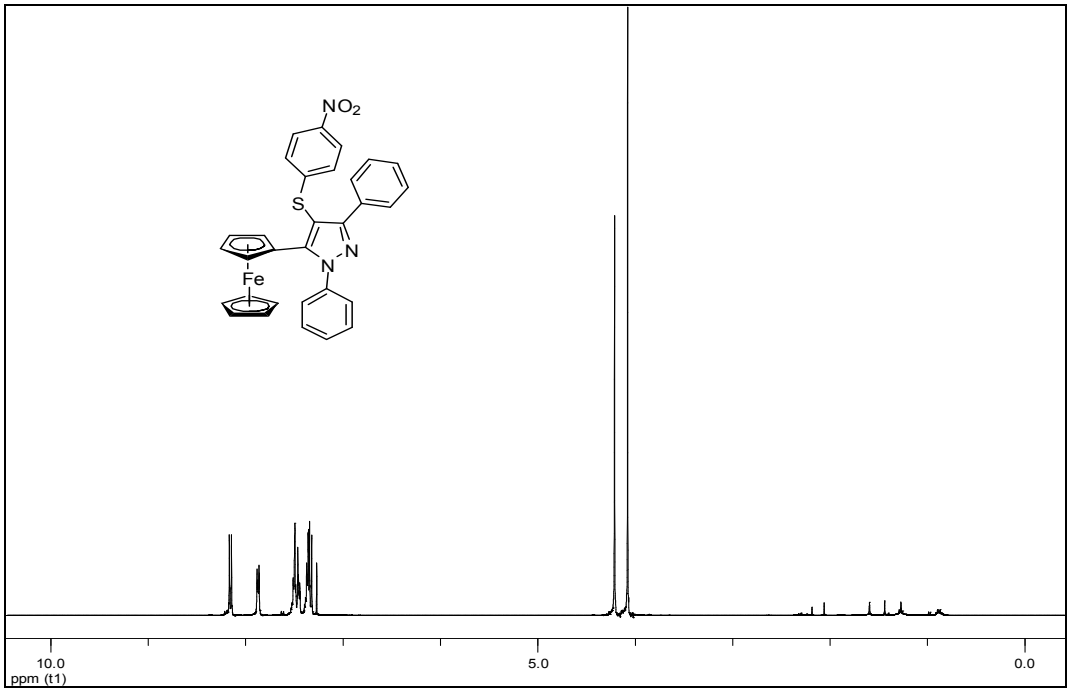


Figure A33. ^{1}H NMR spectrum of **57A**.

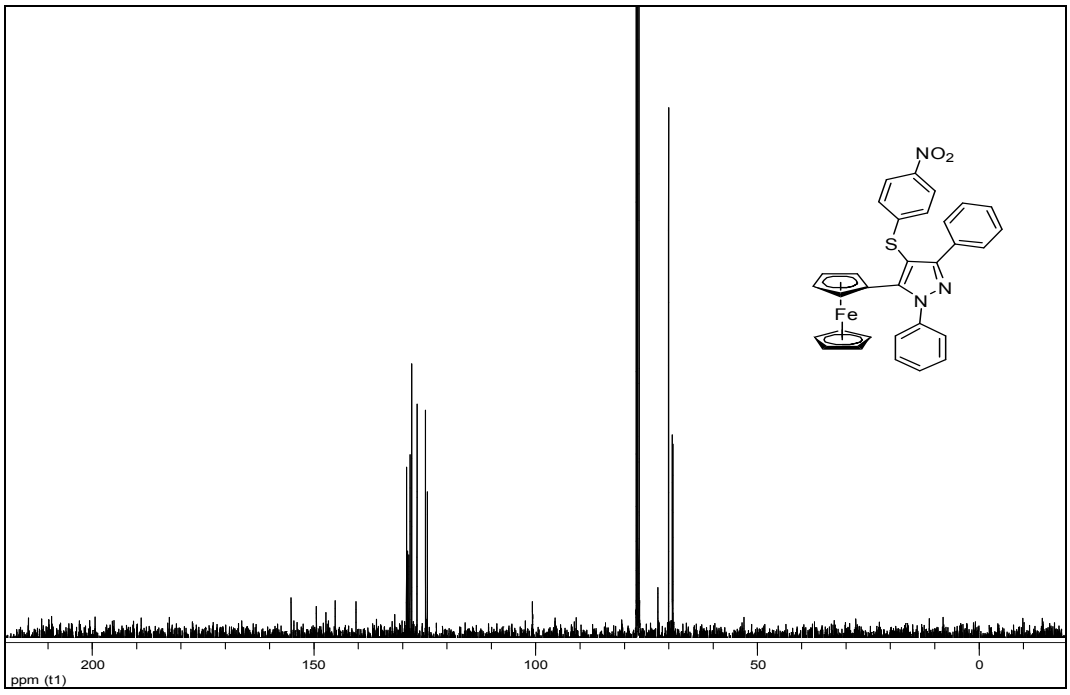


Figure A34. ^{13}C NMR spectrum of **57A**.

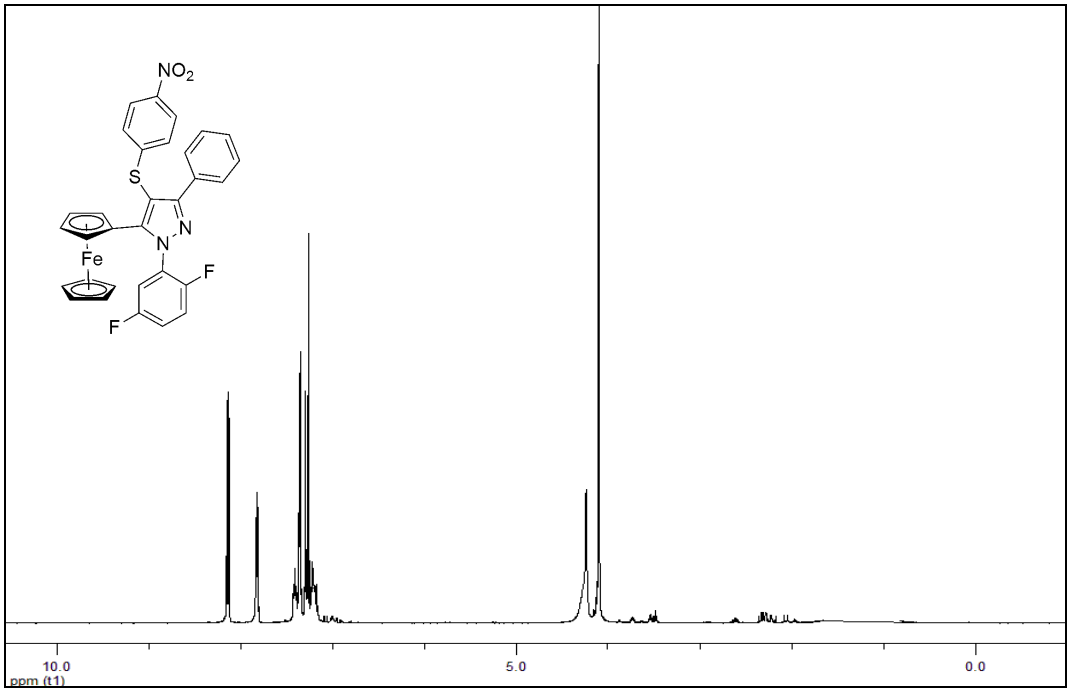


Figure A35. ^{1}H NMR spectrum of **57B**.

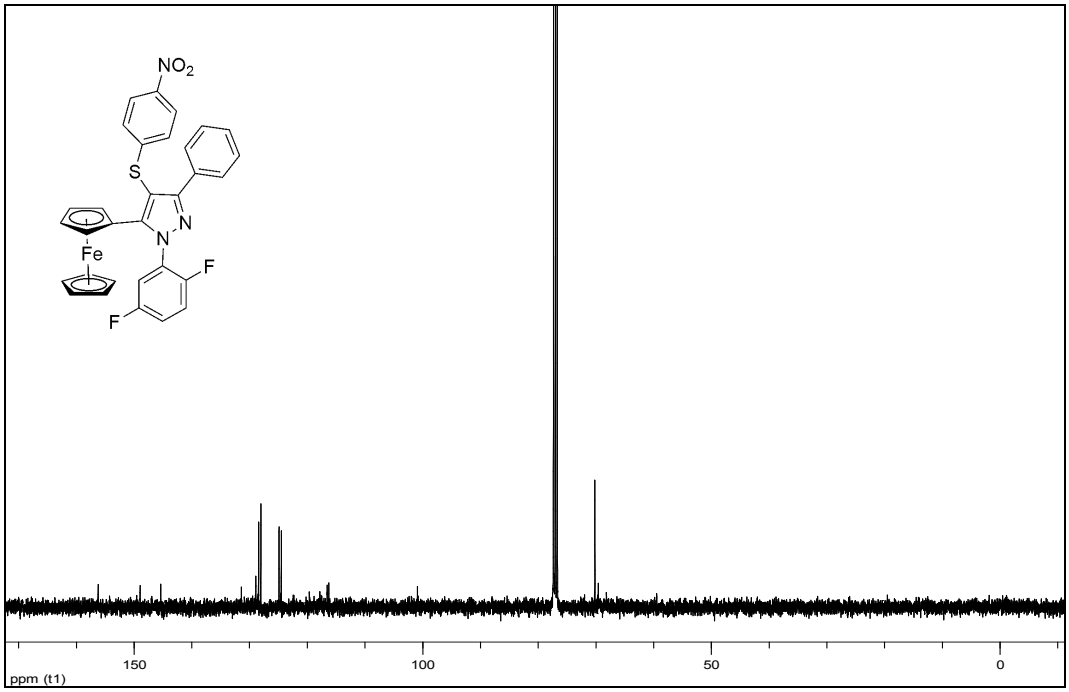


Figure A36. ^{13}C NMR spectrum of **57B**.

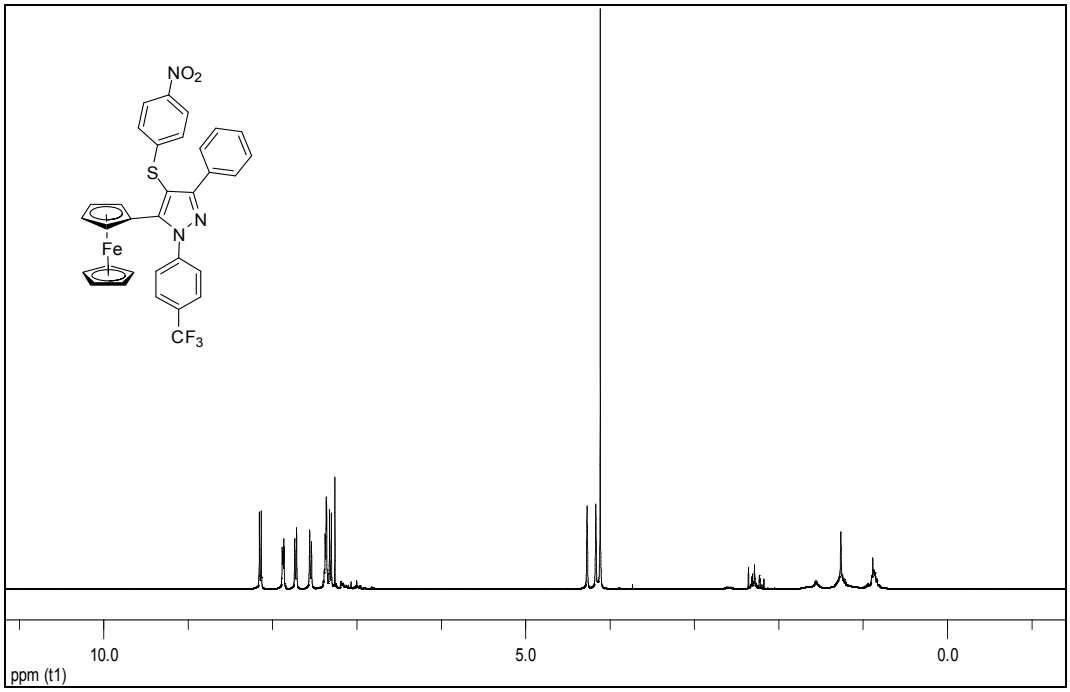


Figure A37. ^{1}H NMR spectrum of **57C**.

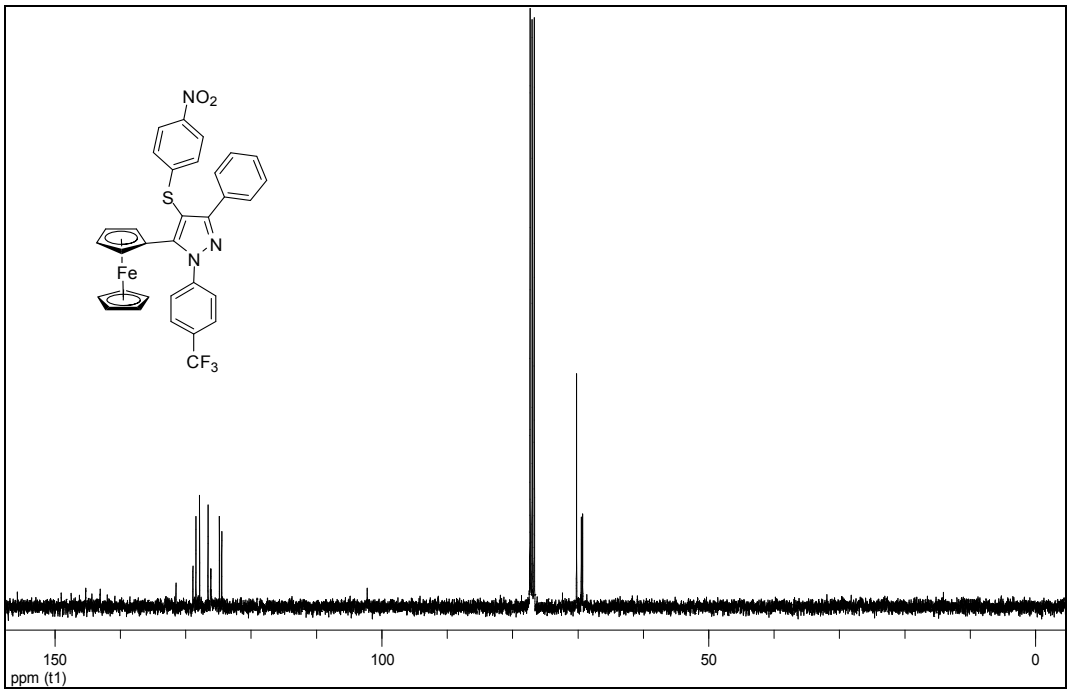


Figure A38. ^{13}C NMR spectrum of **57C**.

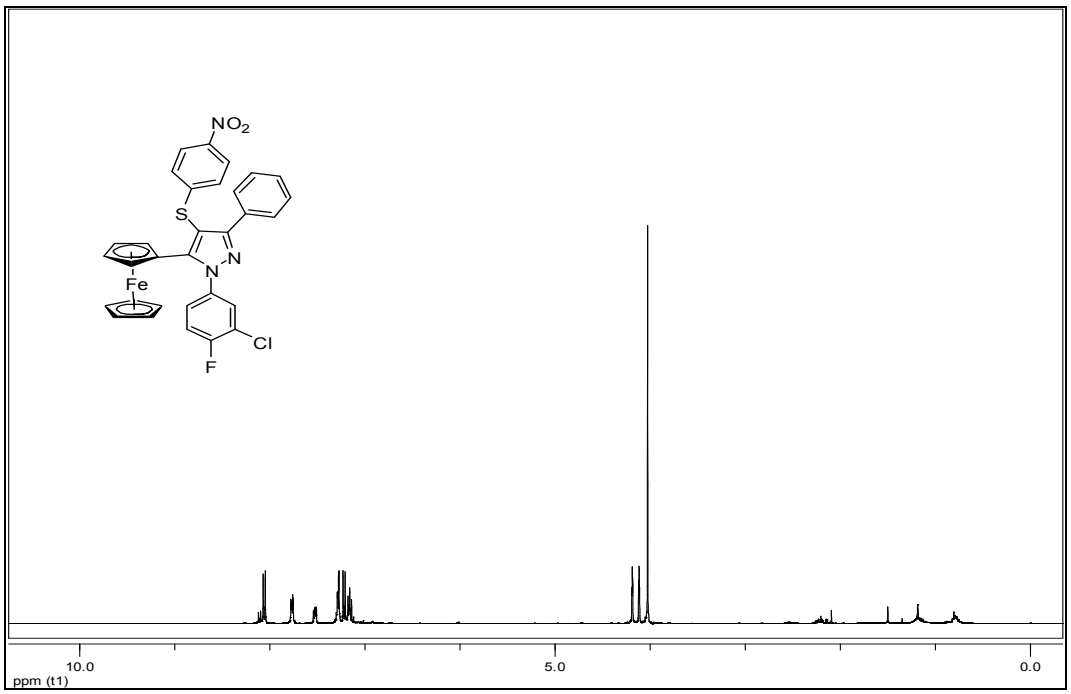


Figure A39. ^{1}H NMR spectrum of **57D**.

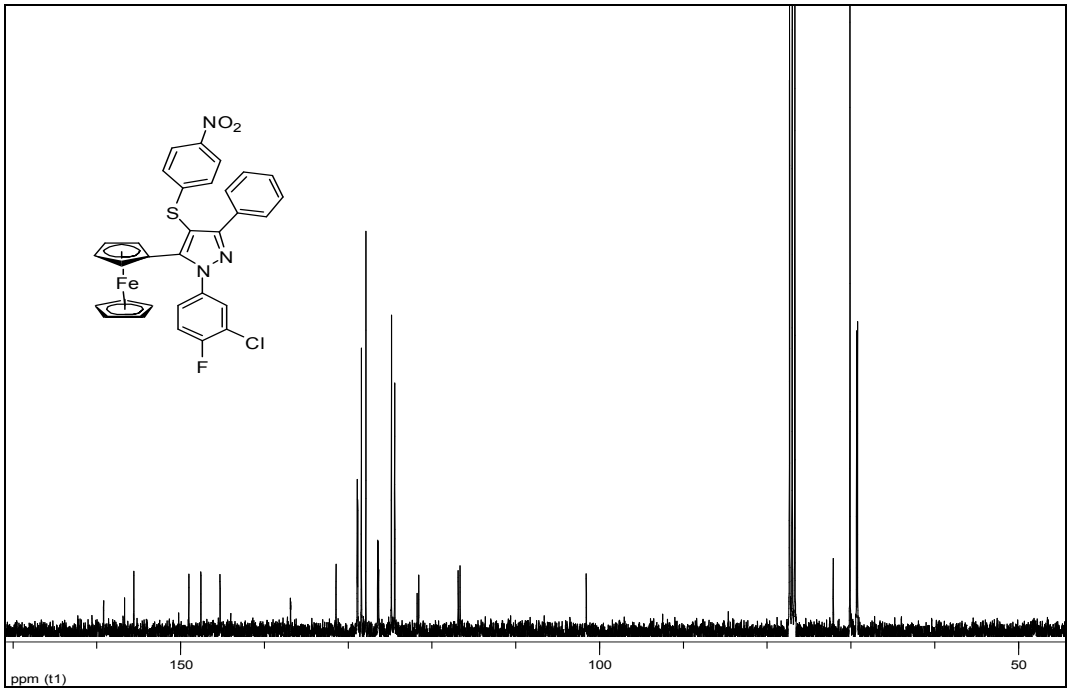


Figure A40. ^{13}C NMR spectrum of **57D**.