

SYNTHESIS OF NOVEL POTENTIALLY BIOACTIVE 3-(3-SUBSTITUTED PHENYL-1,2,4-OXADIAZOLYL-5-METHYL)-1-IMIDAZOLIDINE-2,4-DIONES AND 5-NITRO-2-((3-SUBSTITUTED PHENYL-1,2,4-OXADIAZOL-5-YL)METHYLTHIO)-1*H*-BENZO[*d*]IMIDAZOLES

GÜLSÜN ÖZER

JANUARY 2012

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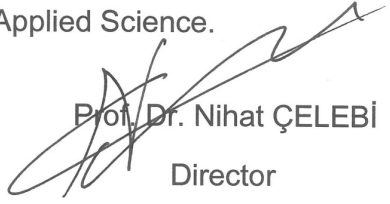
by

GÜLSÜN ÖZER

THESIS SUBMITTED TO
THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES
OF
THE ABANT İZZET BAYSAL UNIVERSITY
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE
OF
MASTER OF SCIENCE
IN
THE DEPARTMENT OF CHEMISTRY

JANUARY 2012

Approval of the Graduate School of Natural and Applied Science.


Prof. Dr. Nihat ÇELEBİ

Director

I certify that this thesis satisfies all the requirements as a thesis for the degree of Master of Science.


Prof. Dr. Çetin BOZKURT

Head of Department

This is to certify that we have read this thesis and that in our opinion it is fully adequate, in scope and quality as a thesis for the degree of Master of Sciences.


Prof. Dr. Yaşar DÜRÜST

Supervisor

Examining Committee Members

1. Prof. Dr. Yaşar DÜRÜST



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3. Prof. Dr. Mustafa ARSLAN



ABSTRACT

SYNTHESIS OF NOVEL POTENTIALLY BIOACTIVE 3-(3-SUBSTITUTED PHENYL-1,2,4-OXADIAZOLYL-5-METHYL)-1-IMIDAZOLIDINE-2,4-DIONES AND 5-NITRO-2-((3-SUBSTITUTED PHENYL-1,2,4-OXADIAZOL-5-YL)METHYLTHIO)-1*H*-BENZO[*d*]IMIDAZOLES

ÖZER, GÜLSÜN
M.Sc., Department of Chemistry
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January 2012, 174 pages

This work is aimed to assemble of novel 3-(3-substituted phenyl-1,2,4-oxadiazolyl-5-methyl)-1-imidazolidine-2,4-diones (hydantoins) and, 5-nitro-2-((3-substituted-phenyl-1,2,4-oxadiazol-5-yl)methylthio)-1*H*- benzo[*d*]imidazoles. In order to achieve this, firstly, *p*-substituted aromatic monoamidoximes used for the synthesis of 3,5-disubstituted-1,2,4-oxadiazoles were synthesized from *p*-substituted benzonitriles. Then these amidoximes were used in order to prepare 5-(chloromethyl)-3-aryl-1,2,4-oxadiazoles. These chloromethyl oxadiazoles were easily reacted with heterocycles having N-H or S-H groups such as 1-methyl hydantoin and 5-nitro-2-mercaptobenzimidazole when bases such as potassium carbonate and NaOH, respectively, were used for removing protons on nitrogen and sulfur atoms. The reaction products of 5-(chloromethyl)-3-aryl-1,2,4-oxadiazoles with 1-methylhydantoin are *N*-substituted products; and with 5-nitro-2-mercaptoimidazole, *S*-substitution products were obtained and structurally determined by physical (melting

points, R_f values) and spectroscopic data, namely, IR, NMR (^1H -NMR and ^{13}C -NMR) and LC-MS spectra. In addition, X-Ray diffraction data was used to resolve full structure. Since all of these novel compounds carry potent biactive groups like oxadiazole, hydantoin and sulfanyl-nitro-benzimidazole, we are planning to examine their bioactivity assays in collaboration with well-equipped international laboratories in the near future.

Keywords: amidoxime, 1,2,4-oxadiazole, hydantoin, 1-methylhydantoin, mercaptobenzimidazole, 5-nitro-2-mercaptobenzimidazole

ÖZET

YENİ POTANSİYEL BİYOAKTİF 3-(3-SÜBSTİTÜE FENİL-1,2,4-OKSADİAZOLİL-5-METİL)-1-İMİDAZOLİDİN-2,4-DİONLARIN VE 5-NİTRO-2-((3-SÜBSTİTÜE FENİL-1,2,4-OKSADİAZOL-5-İL)-1*H*-BENZO[*d*]İMİDAZOLLERİN SENTEZİ

ÖZER, GÜLSÜN
Yüksek Lisans, Kimya Bölümü
Tez Danışmanı: Prof. Dr.Yaşar DÜRÜST

Ocak 2012, 174 Sayfa

Bu çalışmada yeni 3-(3-sübstitüe fenil-1,2,4-oksadiazolil-5-metil)-1-imidazolidin-2,4-dionların (hidantoinler) ve 5-nitro-2-((3-substitue fenil-1,2,4-oksadiazol-5-il)metiltiyo)-1*H*-benzo[*d*]imidazollerin oluşturulması amaçlanmıştır. Bunun için, öncelikle, 3,5-disubstitue-1,2,4-oksadiazollerin sentezi için kullanılan *p*-substite aromatik monoamidoksimler *p*-sübstitüe benzonitril türevlerinden sentezlendi. Azot ve kükürt atomları üzerindeki protonları uzaklaştırmak için potasyum karbonat ve sodyum hidroksit gibi bazlar kullanıldığında, bu klorometil oksadiazoller, 1-metil hidantoin ve 5-nitro-2-merkaptobenzimidazol gibi N-H veya S-H gruplarını içeren heterosiklik yapılarla kolaylıkla tepkimeye girmişlerdir. 5-(Klorometil)-3-aril-1,2,4-oksadiazollerin 1-metilhidantoin ile tepkimesinden *N*-substitue ve 5-nitro-2-merkaptobenzimidazol ile tepkimesinden *S*-substitue ürünler elde edilmiştir. Bunların yapısal özellikleri, fiziksel (erime noktaları, R_f değerleri) ve IR, NMR (^1H NMR and ^{13}C NMR) and LC-MS gibi spektroskopik yöntemlerle belirlendi.

Buna ek olarak, tam yapı tayini yapmak için X-ışını kırınımı kullanıldı. Bu yeni bileşiklerin tümü oksadiazol, hidantoin ve sülfanil-nitro-benzimidazol gibi potansiyel biyoaktif gruplar içerdiği için, ileride daha donanımlı uluslararası laboratuvarlarda bu maddelerin biyolojik aktivitelerini incelemeyi planlıyoruz.

Anahtar Kelimeler: Amidoksim, 1,2,4-oksadiazol, Hidantoin, 1-metilhidantoin, Merkaptobenzimidazol, 5-nitro-2-merkaptobenzimidazol

TO MY FAMILY AND MY LITTLE NEPHEW

ACKNOWLEDGEMENTS

I would like to thank my supervisor, Prof. Dr. Yaşar DÜRÜST for his guidance, encouragements and his enthusiasm throughout this study and writing up. It has been a privilege and pleasure to work for him.

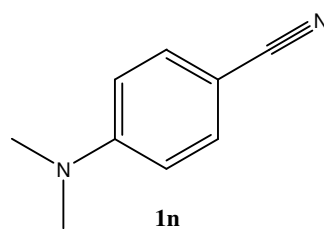
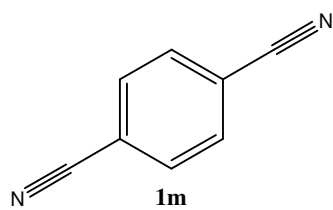
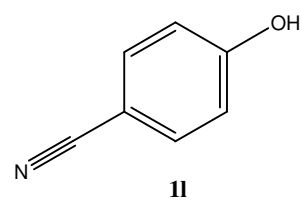
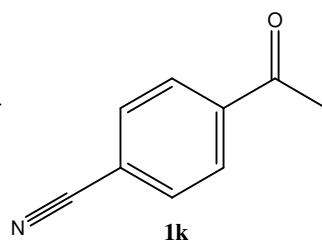
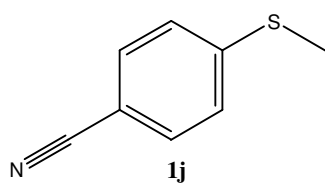
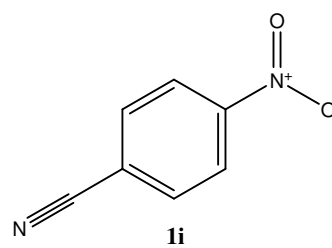
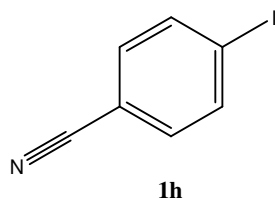
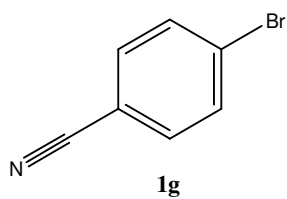
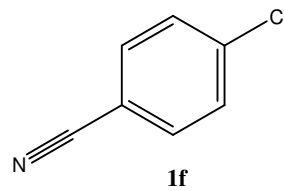
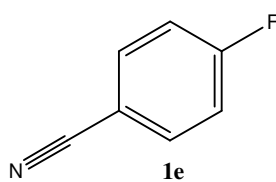
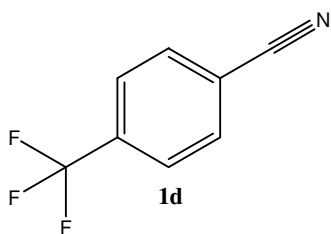
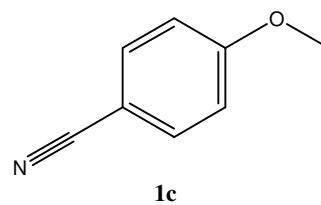
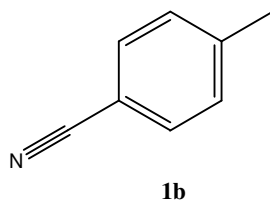
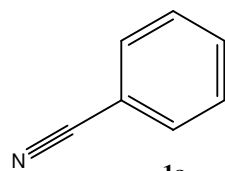
Gratitude is also extended to the Department of Chemistry of A.İ.B.U. for providing the necessary equipment and chemicals which made this work possible, and all the members of the department who aided in the completion of the work.

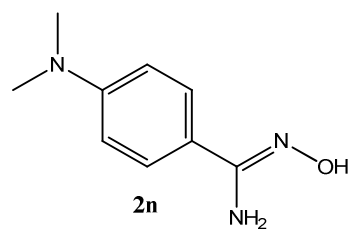
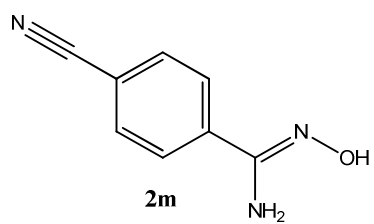
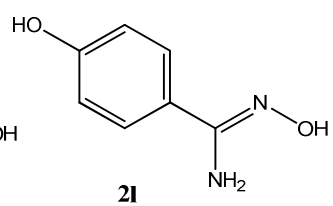
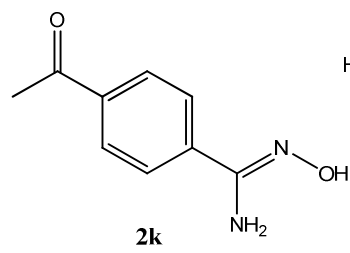
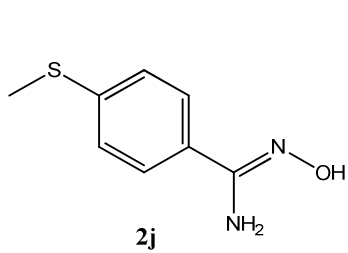
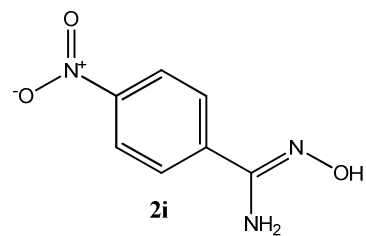
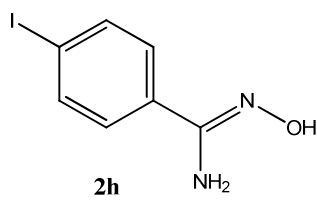
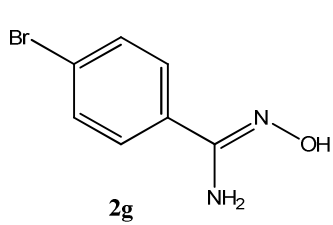
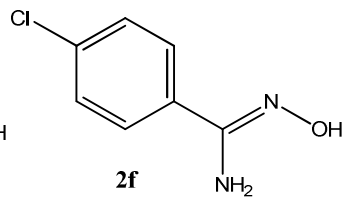
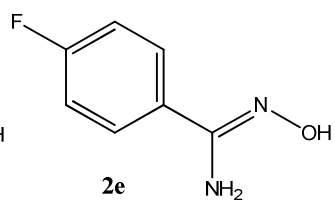
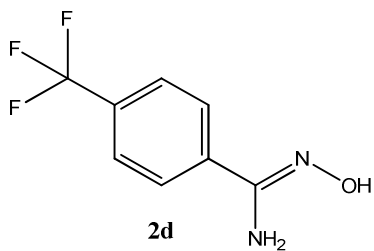
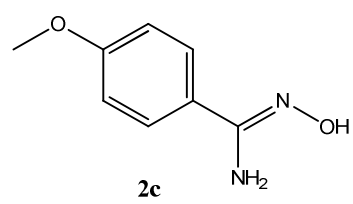
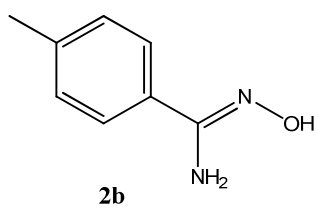
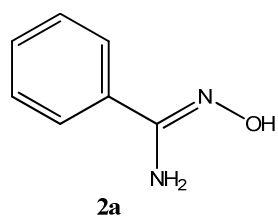
I would also like to thank Uzman Berrak ÇELEBİ, Assist. Prof. Dr. Cevher ALTUĞ, Assist. Prof. Dr. Muhammet YILDIRIM, Dr. Dilek METE, Akın SAĞIRLI, Esra CANER, Emine Özge GÖZLÜKAYA, Hamza KARAKUŞ. Also, I would like to thank Metin ALKAN and Mahmut İNCEEL for their technical supports.

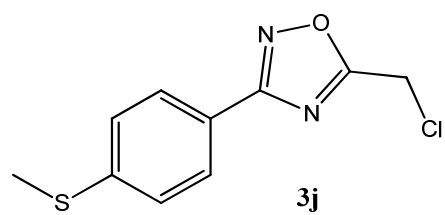
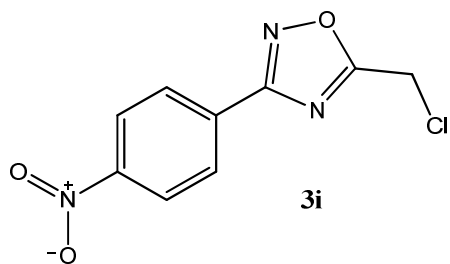
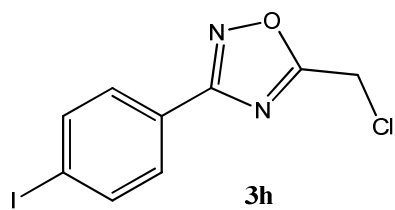
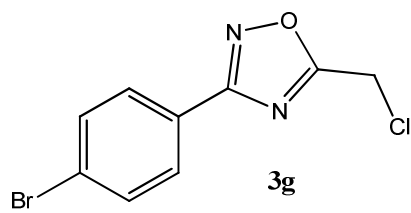
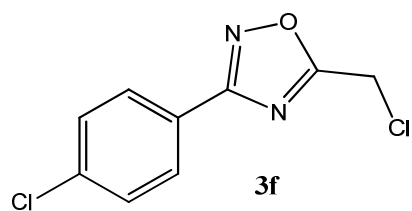
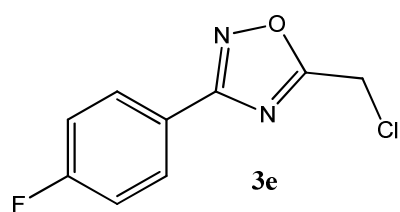
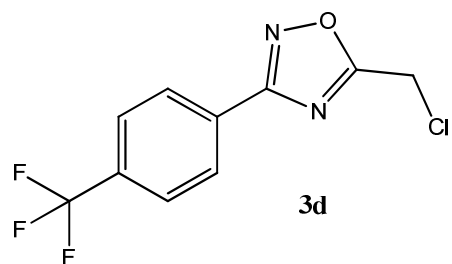
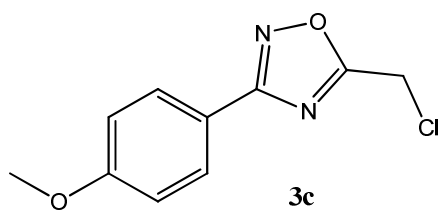
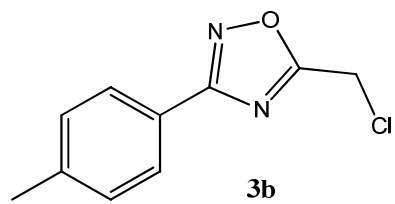
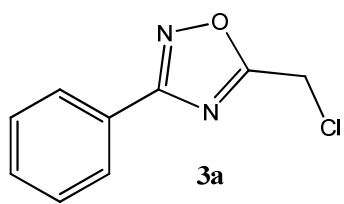
Sincere gratitudes go to Dr.Frank R.Fronczek (Department of Chemistry, Louisiana State University, Baton Rouge, LA, USA) for X-Ray data and Professor Hakan Göker (Faculty of Pharmacy, Ankara University, Ankara) for NMR and LC-MS spectra.

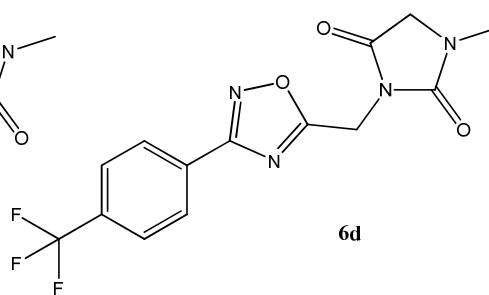
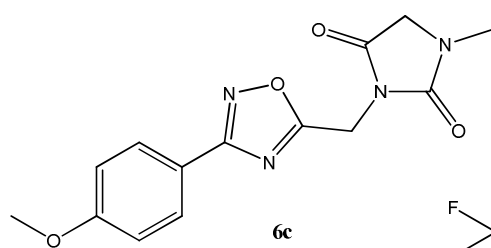
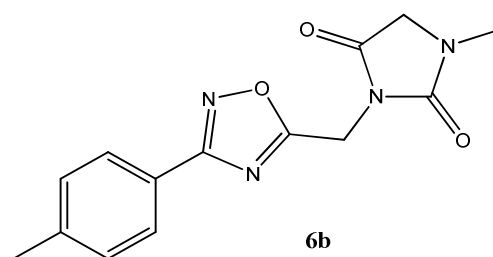
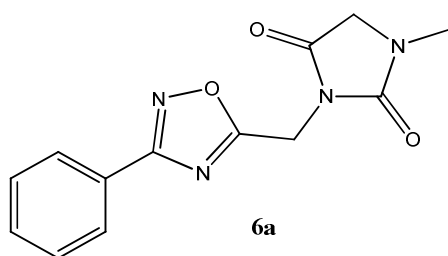
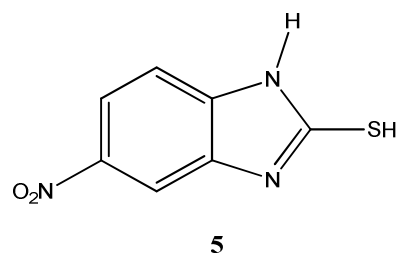
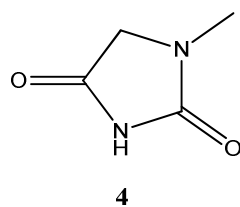
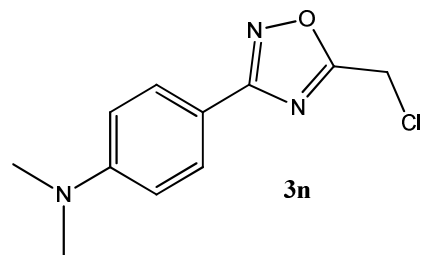
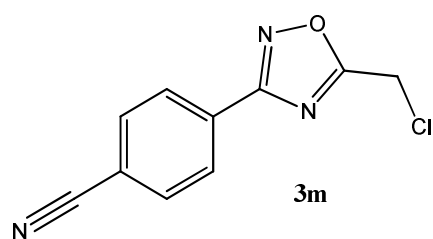
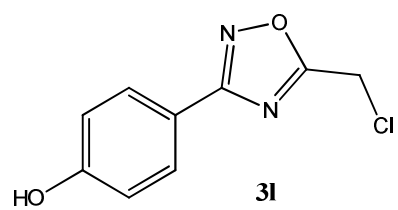
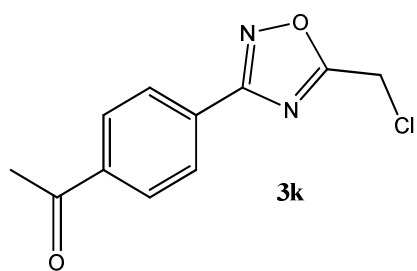
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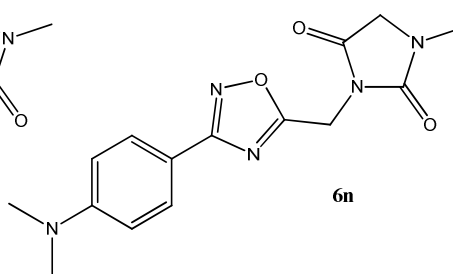
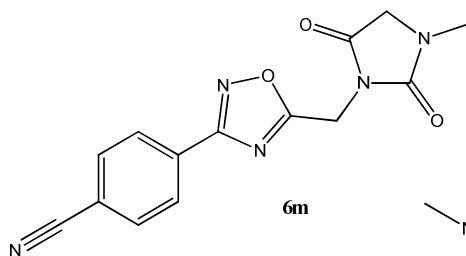
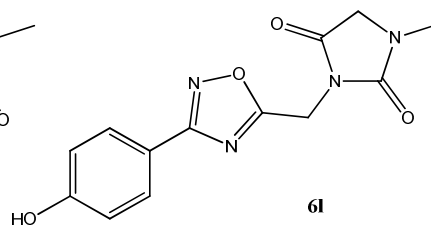
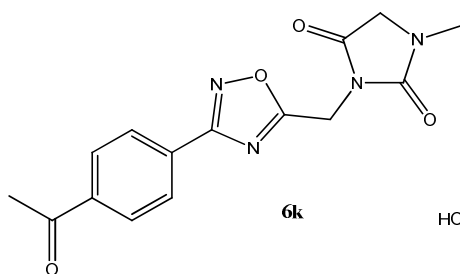
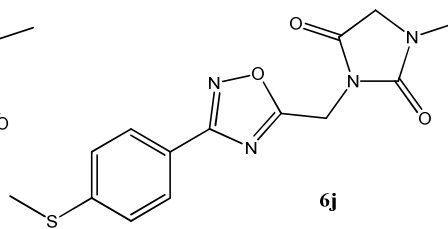
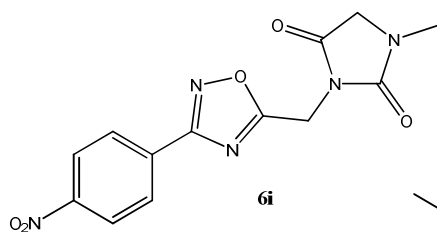
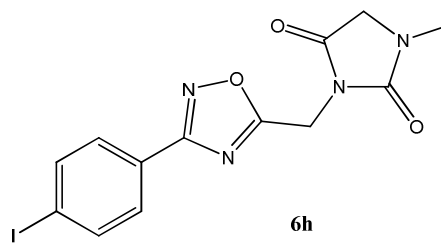
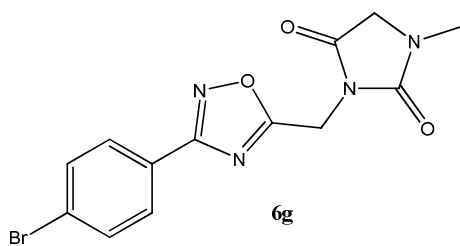
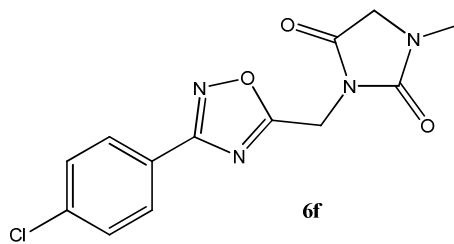
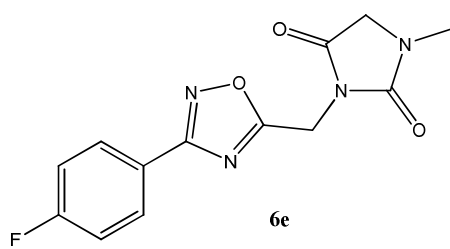
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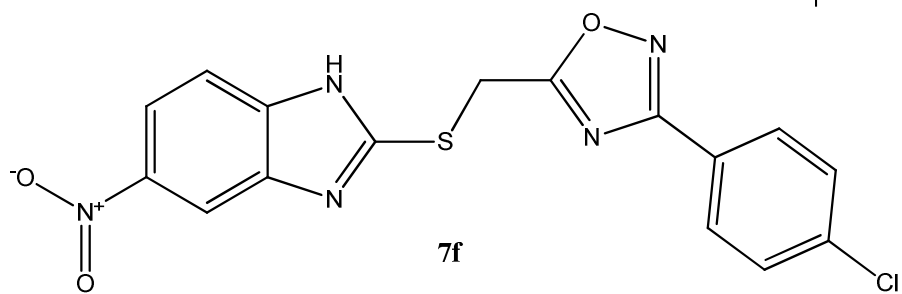
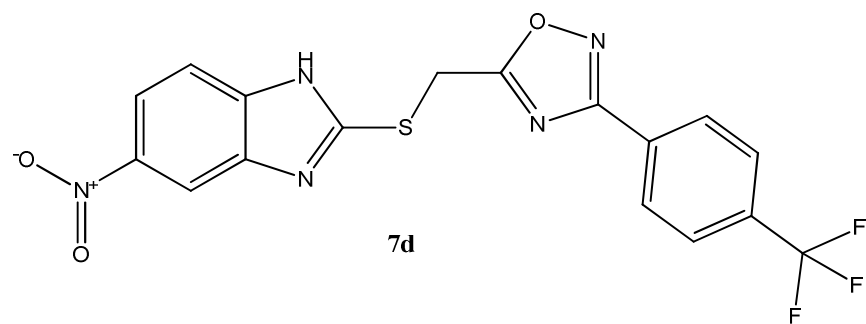
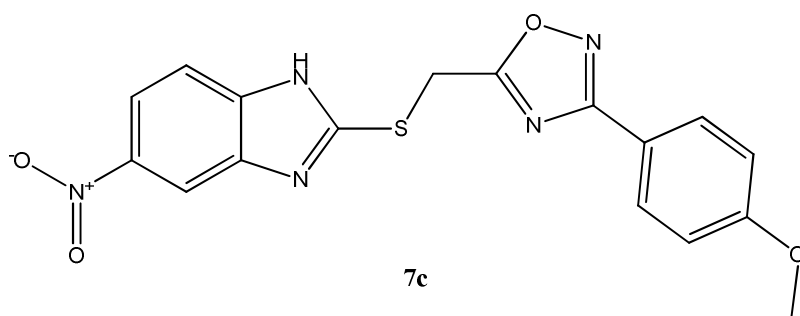
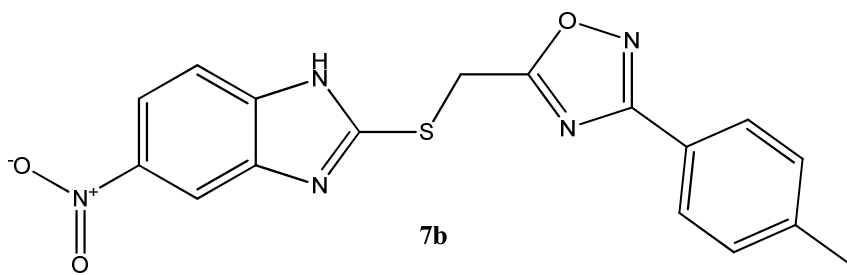
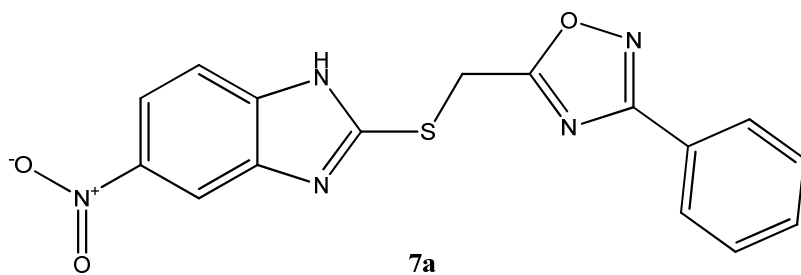


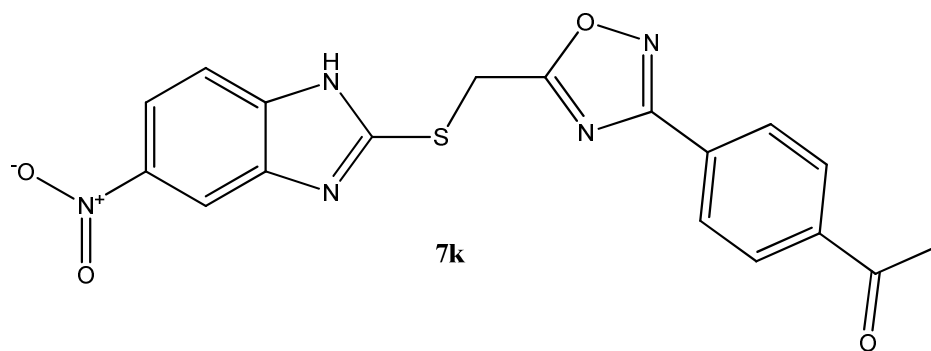
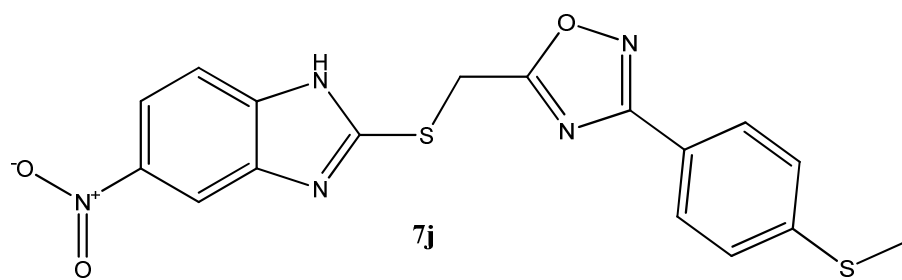
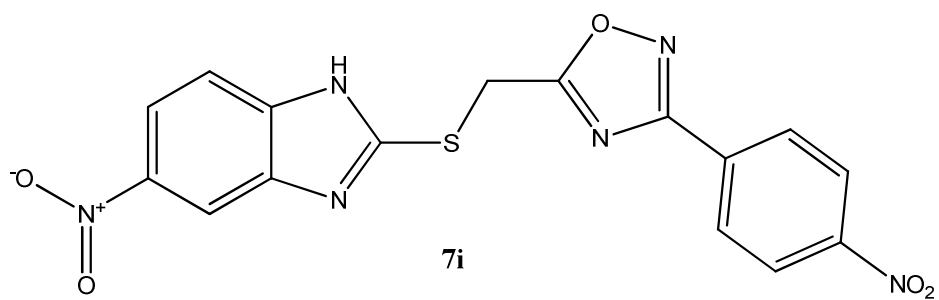
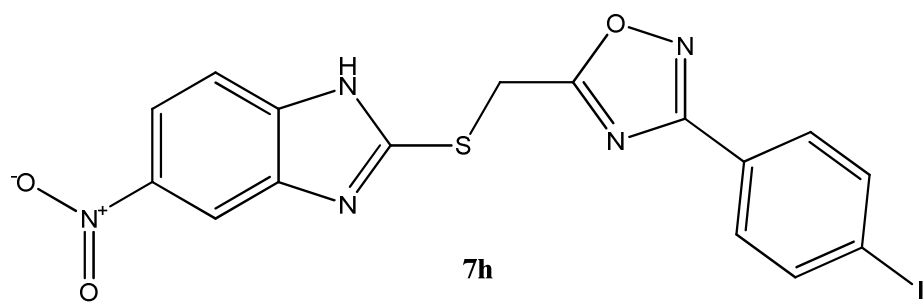
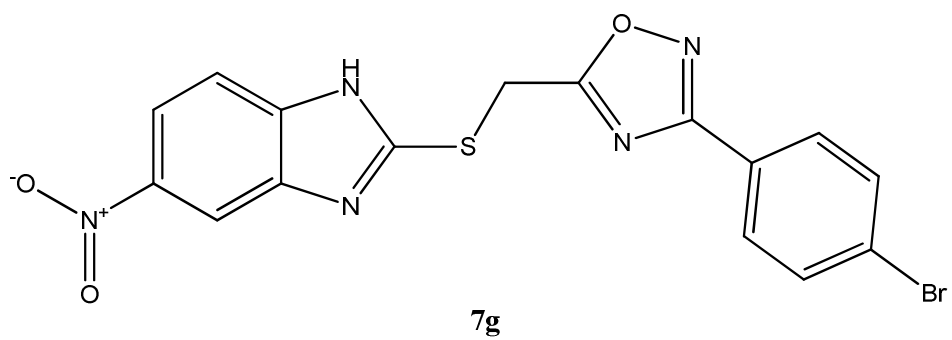












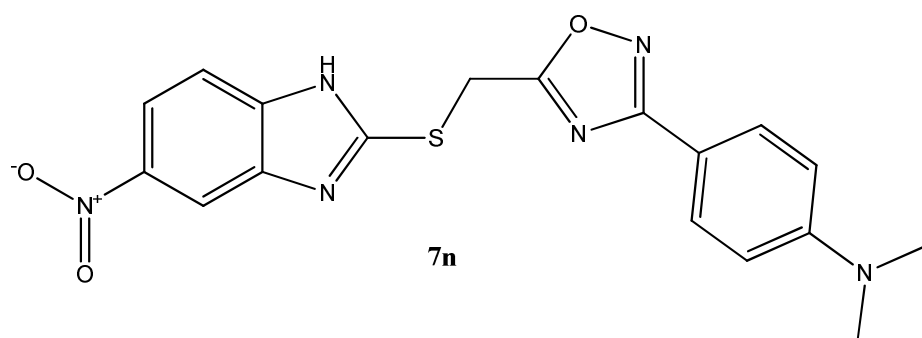
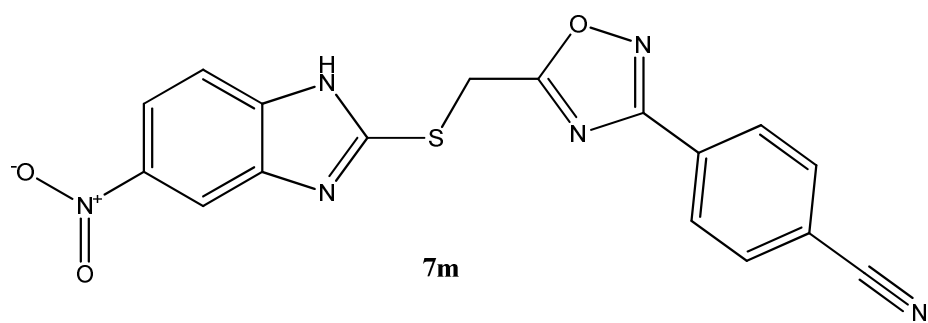
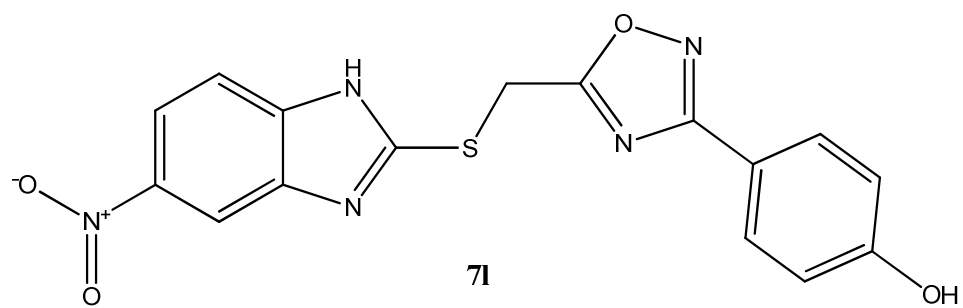


TABLE OF CONTENTS

ABSTRACT	iii
ÖZET	v
ACKNOWLEDGEMENTS	viii
FORMULAE	ix
TABLE OF CONTENTS	xvii
LIST OF SCHEMES	xxiii
LIST OF FIGURES	xxv
ABBREVIATIONS	xxxiii

CHAPTER I	1
1. INTRODUCTION	1
1.1. AMIDOXIMES	1
1.1.1. Synthesis of Amidoximes	2
1.1.1.1. Action of hydroxylamine on nitriles	2
1.1.1.2. Action of hydroxylamine on amides or thioamides ...	3
1.1.1.3. Reduction of nitrosolic and nitrolic acids	4
1.1.1.4. Action of ammonia on hydroxamic acid chlorides (chloroximes)	5
1.1.1.5.Reduction of oxyamidoximes	5
1.1.1.6. Action of hydroxylamine on iminoethers	6
1.1.1.7. Action of ammonia on oxyiminoethers	7
1.1.1.8. Action of hydroxylamine on amidine hydrochlorides	7

1.1.1.9. Reaction of formamidoximes and aromatic aldehydes	8
1.1.2. Reactions of Amidoximes	9
1.1.2.1. Hydrolysis of amidoximes	9
1.1.2.2. Reduction of benzamidoxime with sodium amalgam	9
1.1.2.3. Reduction of amidoxime with Raney nickel	10
1.1.2.4. <i>O</i> -Alkylation of amidoxime	10
1.1.2.5. Reaction of <i>O</i> -alkylated benzamidoxime with HNO ₂	11
1.1.2.6. Action of aniline on amidoximes	11
1.1.2.7. Reaction of amidoximes with isocyanates and isothiocyanates	12
1.1.2.8. Reaction of amidoximes with acyl chlorides (acid chlorides) or acylation of them with acid anhydrides	13
1.1.2.9. Salt Formation	14
1.1.2.10. Organic Complexes	15
1.1.2.11. Thermal Decomposition	15
1.2. OXADIAZOLES	16
1.2.1. 1,2,4- OXADIAZOLES	18
1.2.1.1. Synthesis of 1,2,4-Oxadiazole Compounds	18
1.2.1.1.1 Synthesis of 5-Halomethyl-3-aryl-1,2,4-oxadiazoles from Amidoximes	19
1.2.1.1.2 Synthesis of 3-Aryl-1,2,4-oxadiazol-5-yl-acetic Acids from Amidoximes	20
1.3. HYDANTOINS	20

1.4. BENZIMIDAZOLE AND MERCAPTOBENZIMIDAZOLE DERIVATIVES	21
CHAPTER II	25
2.1. RESULTS AND DISCUSSION	25
2.2. CONCLUSION	34
CHAPTER III	36
EXPERIMENTAL	36
1) Synthesis of Amidoximes	36
Benzamidoxime (2a)	37
4-Methylbenzamidoxime (2b)	38
4-Methoxybenzamidoxime (2c)	38
4-Trifluoromethylbenzamidoxime (2d)	39
4-Bromobenzamidoxime (2g)	39
4-Iodobenzamidoxime (2h)	40
4-Nitrobenzamidoxime (2i)	40
4-Methylthiobenzamidoxime (2j)	41
4-Acetylbenzamidoxime (2k)	41
4-Hydroxybenzamidoxime (2l)	42
4- <i>N,N</i> -Dimethylaminobenzamidoxime (2n)	43
2) Synthesis of 5-(chloromethyl)-3-aryl-1,2,4-oxadiazoles	43
5-(Chloromethyl)-3-phenyl-1,2,4-oxadiazole (3a)	44
5-(Chloromethyl)-3-(<i>p</i> -tolyl)-1,2,4-oxadiazole(3b)	44
5-(Chloromethyl)-3-(4-methoxyphenyl)-1,2,4-oxadiazole (3c)	45
5-(Chloromethyl)-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (3d) ..	45

5-(Chloromethyl)-3-(4-chlorophenyl)-1,2,4-oxadiazole (3f)	46
3-(4-Bromophenyl)-5-(chloromethyl)-1,2,4-oxadiazole (3g)	46
5-(Chloromethyl)-3-(4-iodophenyl)-1,2,4-oxadiazole (3h)	47
5-(Chloromethyl)-3-(4-nitrophenyl)-1,2,4-oxadiazole (3i)	47
5-(Chloromethyl)-3-(4-(methylthio)phenyl)-1,2,4-oxadiazole (3j)	48
3-(4-Acetylphenyl)-5-chloromethyl)-1,2,4-oxadiazole (3k)	49
3-(4-Hydroxyphenyl)-5-(chloromethyl)-1,2,4-oxadiazole (3l)	49
3-(4-Cyanophenyl)-5-(chloromethyl)-1,2,4-oxadiazole (3m)	50
(5-Chloromethyl)-3-(4- <i>N,N</i> -dimethylaminophenyl)-1,2,4-oxadiazole (3n)	50
3) Synthesis of 3-(4-substituted phenyl)-1,2,4-oxadiazolyl-5- methyl)-1-methylimidazolidine-2,4-diones (6a-n)	51
1-Methyl-3-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)imidazolidine- 2,4-dione (6a)	52
1-Methyl-3-((3-(<i>p</i> -tolyl)-1,2,4-oxadiazol-5-yl)methyl)imidazolidine- 2,4-dione (6b)	53
3-((3-(4-Methoxyphenyl)-1,2,4-oxadiazol-5-yl)methyl)-1- methylimidazolidine-2,4-dione (6c)	54
1-Methyl-3-((3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5- yl)methyl)imidazolidine-2,4-dione (6d)	55
3-((3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-1- methylimidazolidine-2,4-dione (6e)	56
3-((3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-1- methylimidazolidine-2,4-dione (6f)	57

3-((3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl)methyl)-1-methylimidazolidine-2,4-dione (6g)	58
3-((3-(4-Iodophenyl)-1,2,4-oxadiazol-5-yl)methyl)-1-methylimidazolidine-2,4-dione (6h)	60
1-Methyl-3-((3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl)methyl)imidazolidine-2,4-dione (6i)	61
1-Methyl-3-((3-(4-(methylthio)phenyl)-1,2,4-oxadiazol-5-yl)methyl)imidazolidine-2,4-dione (6j)	62
3-((3-(4-Acetylphenyl)-1,2,4-oxadiazol-5-yl)methyl)-1-methylimidazolidine-2,4-dione (6k)	63
3-((3-(4-Hydroxyphenyl)-1,2,4-oxadiazol-5-yl)methyl)-1-methylimidazolidine-2,4-dione (6l)	64
3-((3-(4-Cyanophenyl)-1,2,4-oxadiazol-5-yl)methyl)-1-methylimidazolidine-2,4-dione (6m)	65
3-((3-(4-(Dimethylamino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)-1-methylimidazolidine-2,4-dione (6n)	66
4) Synthesis of 5-nitro-2-((3-substituted phenyl-1,2,4-oxadiazol-5-yl)methylthio)-1 <i>H</i> -benzo[<i>d</i>]imidazoles	67
5-(((5-Nitro-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-yl)thio)methyl)-3-phenyl-1,2,4-oxadiazole (7a)	69
5-(((5-Nitro-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-yl)thio)methyl)-3-(<i>p</i> -tolyl)-1,2,4-oxadiazole (7b)	70
3-(4-Methoxyphenyl)-5-(((5-nitro-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-yl)thio)methyl)-1,2,4-oxadiazole (7c)	71

5-(((5-Nitro-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-yl)thio)methyl)-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (7d)	72
3-(4-Chlorophenyl)-5-(((5-nitro-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-yl)thio)methyl)-1,2,4-oxadiazole (7f)	73
3-(4-Bromophenyl)-5-(((5-nitro-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-yl)thio)methyl)-1,2,4-oxadiazole (7g)	74
3-(4-Iodophenyl)-5-(((5-nitro-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-yl)thio)methyl)-1,2,4-oxadiazole (7h)	75
5-(((5-Nitro-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-yl)thio)methyl)-3-(4-nitrophenyl)-1,2,4-oxadiazole (7i)	77
3-(4-(Methylthio)phenyl)-5-(((5-nitro-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-yl)thio)methyl)-1,2,4-oxadiazole (7j)	79
1-(4-(5-(((5-Nitro-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-yl)thio)methyl)-1,2,4-oxadiazol-3-yl)phenyl)ethanone (7k)	80
4-(5-(((5-Nitro-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-yl)thio)methyl)-1,2,4-oxadiazol-3-yl)phenol (7l)	81
4-(5-(((5-Nitro-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-yl)thio)methyl)-1,2,4-oxadiazol-3-yl)benzonitrile (7m)	82
N,N-Dimethyl-4-(5-(((5-nitro-1 <i>H</i> -benzo[<i>d</i>]imidazol-2-yl)thio)methyl)-1,2,4-oxadiazol-3-yl)aniline (7n)	83
REFERENCES	85
APPENDICES	93

LIST OF SCHEMES

Scheme 1.1. Synthesis of mandelamidoxime	2
Scheme 1.2. Action of hydroxylamine on benzonitrile	2
Scheme 1.3. Action of hydroxylamine on nitriles	3
Scheme 1.4. Action of hydroxylamine on amides or thioamides	4
Scheme 1.5. Reduction of nitrosolic acids to amidoximes	4
Scheme 1.6. Reduction of nitrolic acids to amidoximes	4
Scheme 1.7. Preparation of monoamidoximes of dicarboxylic acids	5
Scheme 1.8. Action of ammonia on hydroxamic acid chlorides	5
Scheme 1.9. Action of hydroxylamine on hydroxamic acid chloride	6
Scheme 1.10. Reduction of oxyamidoxime with sulfur dioxide	6
Scheme 1.11. Action of hydroxylamine on ethyl iminobenzoate	6
Scheme 1.12. Action of hydroxylamine on iminoether	7
Scheme 1.13. Action of ammonia on ethyl benzhydroxamic acid	7
Scheme 1.14. Action of ammonia on oxyiminoether	7
Scheme 1.15. Action of hydroxylamine on benzamidine hydrochloride ...	8
Scheme 1.16. Action of hydroxylamine on amidine hydrochloride	8
Scheme 1.17. Reaction of formamidoxime with aromatic aldehydes	8
Scheme 1.18. Reaction of benzaldehyde with formamidoxime	9
Scheme 1.19. Hydrolysis of amidoximes	9
Scheme 1.20. Reduction of benzamidoxime with sodium amalgam	10
Scheme 1.21. Reduction of amidoxime with Raney nickel	10

Scheme 1.22. <i>O</i> -Alkylation of amidoxime	11
Scheme 1.23. Reaction of <i>O</i> -alkylated benzamidoxime with HNO ₂	11
Scheme 1.24. Action of aniline on amidoximes	12
Scheme 1.25. Reaction of amidoximes with isocyanates	12
Scheme 1.26. Reaction of benzamidoxime with phenyl isothiocyanate ...	12
Scheme 1.27. Reaction of benzamidoxime with <i>p</i> -tolyl isothiocyanate ...	13
Scheme 1.28. Reaction of amidoximes with acyl chlorides (acid chlorides) or their acylation with acid anhydrides	14
Scheme 1.29. Thermal decomposition of amidoximes	15
Scheme 1.30. Main routes of chemical transformations of nitrile oxides	18
Scheme 1.31. General synthetic route for 3-Phenyl-1,2,4-oxadiazole-5- methylchlorides from amidoximes	19
Scheme 1.32. Preparation of 3-Aryl-1,2,4-oxadiazol-5-yl-acetic Acids ...	20
Scheme 1.33. Synthesis of 2-mercaptobenzimidazole from <i>o</i> -phenylene daimine	23
Scheme 1.34. Example of conversion of <i>o</i> -aminoarylthioureas into benzimidazolethiones	24
Scheme 2.1. Synthesis of aryl monoamidoximes (2)	26
Scheme 2.2. Synthesis of 3-aryl-5-chloromethyl-1,2,4-oxadiazoles (3) ...	27
Scheme 2.3. Synthesis of <i>N</i> -oxadiazolylmethyl substituted hydantoins 6a-n	28
Scheme 2.4. Synthesis of <i>S</i> -1,2,4-oxadiazolylmethyl substituted 5- nitrobenzimidazoles 7a-n	32

LIST OF FIGURES

Figure 1.1. The structure of isuretin	2
Figure 1.2. The structures of <i>N'</i> -hydroxy-5-phenyl-1,2,4-oxadiazole-3-carboximidamide and 2-amino-2-(hydroxyimino)acetic acid	3
Figure 1.3. Representation of simple oxadiazoles	16
Figure 1.4. Ring - open diazo-ketone tautomer of 1,2,3-oxadiazole	17
Figure 1.5. Structure of sydnone	17
Figure 1.6.. Resonance form of azomethine-imines	18
Figure 1.7. Structures of some hydantoins	21
Figure 1.8. Structures of some benzimidazole derivatives.....	22
Figure 1.9. Structure of thione tautomer of 2-mercaptobenzimidazole ...	23
Figure 2.1. Assignment of hydrogens for the compound 6m	29
Figure 2.2. Assignment of carbons for the compound 6m	30
Figure 2.3. LC-MS spectrum of compound 6m	31
Figure 2.4 . Assignment of protons of the compound 7h	33
Figure 2.5 . Assignment of indicative carbons of the compound 7h	34
Figure 2.6. X-Ray ORTEP view of compound 7h	35
Figure 4.1. The IR spectrum of 2a	93
Figure 4.2. The IR spectrum of 2b	93
Figure 4.3. The IR spectrum of 2c	94
Figure 4.4. The IR spectrum of 2d	94
Figure 4.5. The IR spectrum of 2f	95

Figure 4.6. The IR spectrum of 2g	95
Figure 4.7. The IR spectrum of 2h	96
Figure 4.8. The IR spectrum of 2i	96
Figure 4.9. The IR spectrum of 2j	97
Figure 4.10. The IR spectrum of 2k	97
Figure 4.11. The IR spectrum of 2l	98
Figure 4.12. The IR spectrum of 2m	98
Figure 4.13. The IR spectrum of 2n	99
Figure 4.14. The IR spectrum of 3a	99
Figure 4.15. The IR spectrum of 3b	100
Figure 4.16. The IR spectrum of 3c	100
Figure 4.17. The IR spectrum of 3d	101
Figure 4.18. The IR spectrum of 3e	101
Figure 4.19. The IR spectrum of 3f	102
Figure 4.20. The IR spectrum of 3g	102
Figure 4.21. The IR spectrum of 3h	103
Figure 4.22. The IR spectrum of 3i	103
Figure 4.23. The IR spectrum of 3j	104
Figure 4.24. The IR spectrum of 3k	104
Figure 4.25. The IR spectrum of 3l	105
Figure 4.26. The IR spectrum of 3m	105
Figure 4.27. The IR spectrum of 3n	106
Figure 4.28. The IR spectrum of 4	106
Figure 4.29. The IR spectrum of 5	107
Figure 4.30. The IR spectrum of 6a	107

Figure 4.31. The ^1H NMR spectrum of 6a	108
Figure 4.32. The expanded ^1H NMR spectrum of 6a	108
Figure 4.33. The ^{13}C NMR spectrum of 6a	109
Figure 4.34. LC-MS spectrum of 6a	109
Figure 4.35. The IR spectrum of 6b	110
Figure 4.36. The ^1H NMR spectrum of 6b	110
Figure 4.37. The ^{13}C NMR spectrum of 6b	111
Figure 4.38. LC-MS spectrum of 6b	111
Figure 4.39. The IR spectrum of 6c	112
Figure 4.40. The ^1H NMR spectrum of 6c	112
Figure 4.41. The expanded ^1H NMR spectrum of 6c	113
Figure 4.42. The ^{13}C NMR spectrum of 6c	113
Figure 4.43. LC-MS spectrum of 6c	114
Figure 4.44. The IR spectrum of 6d	114
Figure 4.45. The ^1H NMR spectrum of 6d	115
Figure 4.46. The expanded ^1H NMR spectrum of 6d	115
Figure 4.47. The ^{13}C NMR spectrum of 6d	116
Figure 4.48. LC-MS spectrum of 6d	116
Figure 4.49. The IR spectrum of 6e	117
Figure 4.50. The ^1H NMR spectrum of 6e	117
Figure 4.51. The ^{13}C NMR spectrum of 6e	118
Figure 4.52. LC-MS spectrum of 6e	118
Figure 4.53. The IR spectrum of 6f	119
Figure 4.54. The ^1H NMR spectrum of 6f	119
Figure 4.55. The ^{13}C NMR spectrum of 6f	120

Figure 4.56. LC-MS spectrum of 6f	120
Figure 4.57. The IR spectrum of 6g	121
Figure 4.58. The ^1H NMR spectrum of 6g	121
Figure 4.59. The ^{13}C NMR spectrum of 6g	122
Figure 4.60. LC-MS spectrum of 6g	122
Figure 4.61. The IR spectrum of 6h	123
Figure 4.62. The ^1H NMR spectrum of 6h	123
Figure 4.63. The ^{13}C NMR spectrum of 6h	124
Figure 4.64. LC-MS spectrum of 6h	124
Figure 4.65. The IR spectrum of 6i	125
Figure 4.66. The ^1H NMR spectrum of 6i	125
Figure 4.67. The expanded ^1H NMR spectrum of 6i	126
Figure 4.68. The ^{13}C NMR spectrum of 6i	126
Figure 4.69. The expanded ^{13}C NMR spectrum of 6i	127
Figure 4.70. LC-MS spectrum of 6i	127
Figure 4.71. The IR spectrum of 6j	128
Figure 4.72. The ^1H NMR spectrum of 6j	128
Figure 4.73. The expanded ^1H NMR spectrum of 6j	129
Figure 4.74. The ^{13}C NMR spectrum of 6j	129
Figure 4.75. LC-MS spectrum of 6j	130
Figure 4.76. The IR spectrum of 6k	130
Figure 4.77. The ^1H NMR spectrum of 6k	131
Figure 4.78. The expanded ^1H NMR spectrum of 6k	131
Figure 4.79. The ^{13}C NMR spectrum of 6k	132
Figure 4.80. LC-MS spectrum of 6k	132

Figure 4.81. The IR spectrum of 6l	133
Figure 4.82. The ^1H NMR spectrum of 6l	133
Figure 4.83. The ^{13}C NMR spectrum of 6l	134
Figure 4.84. LC-MS spectrum of 6l	134
Figure 4.85. The IR spectrum of 6m	135
Figure 4.86. The ^1H NMR spectrum of 6m	135
Figure 4.87. The expanded ^1H NMR spectrum of 6m	136
Figure 4.88. The ^{13}C NMR spectrum of 6m	136
Figure 4.89. LC-MS spectrum (ES-) of 6m	137
Figure 4.90. LC-MS spectrum (ES+) of 6m	137
Figure 4.91. The IR spectrum of 6n	138
Figure 4.92. The ^1H NMR spectrum of 6n	138
Figure 4.93. The expanded ^1H NMR spectrum of 6n	139
Figure 4.94. The ^{13}C NMR spectrum of 6n	139
Figure 4.95. LC-MS spectrum of 6a	140
Figure 4.96. The IR spectrum of 7a	140
Figure 4.97. The ^1H NMR spectrum of 7a	141
Figure 4.98. The expanded ^1H NMR spectrum of 7a	141
Figure 4.99. The ^{13}C NMR spectrum of 7a	142
Figure 4.100. LC-MS spectrum of 7a	142
Figure 4.101. The IR spectrum of 7b	143
Figure 4.102. The ^1H NMR spectrum of 7b	143
Figure 4.103. The expanded ^1H NMR spectrum of 7b	144
Figure 4.104. The ^{13}C NMR spectrum of 7b	144
Figure 4.105. LC-MS spectrum of 7b	145

Figure 4.106. The IR spectrum of 7c	145
Figure 4.107. The ^1H NMR spectrum of 7c	146
Figure 4.108. The expanded ^1H NMR spectrum of 7c	146
Figure 4.109. The ^{13}C NMR spectrum of 7c	147
Figure 4.110. LC-MS spectrum of 7c	147
Figure 4.111. The IR spectrum of 7d	148
Figure 4.112. The ^1H NMR spectrum of 7d	148
Figure 4.113. The expanded ^1H NMR spectrum of 7d	149
Figure 4.114. The ^{13}C NMR spectrum of 7d	149
Figure 4.115. LC-MS spectrum of 7d	150
Figure 4.116. The IR spectrum of 7f	150
Figure 4.117. The ^1H NMR spectrum of 7f	151
Figure 4.118. The expanded ^1H NMR spectrum of 7f	151
Figure 4.119. The ^{13}C NMR spectrum of 7f	152
Figure 4.120. The expanded ^{13}C NMR spectrum of 7f	152
Figure 4.121. LC-MS spectrum of 7f	153
Figure 4.122. The IR spectrum of 7g	153
Figure 4.123. The ^1H NMR spectrum of 7g	154
Figure 4.124. The expanded ^1H NMR spectrum of 7g	154
Figure 4.125. The ^{13}C NMR spectrum of 7g	155
Figure 4.126. LC-MS spectrum of 7g	155
Figure 4.127. The IR spectrum of 7h	156
Figure 4.128. The ^1H NMR spectrum of 7h	156
Figure 4.129. The expanded ^1H NMR spectrum of 7h	157
Figure 4.130. The ^{13}C NMR spectrum of 7h	157

Figure 4.131. LC-MS spectrum of 7h	158
Figure 4.132. The X-ray ORTEP view of 7h	158
Figure 4.133. The IR spectrum of 7i	159
Figure 4.134. The ^1H NMR spectrum of 7i	160
Figure 4.135. The expanded ^1H NMR spectrum of 7i	160
Figure 4.136. The ^{13}C NMR spectrum of 7i	161
Figure 4.137. LC-MS spectrum of 7i	161
Figure 4.138. The IR spectrum of 7j	162
Figure 4.139. The ^1H NMR spectrum of 7j	162
Figure 4.140. The expanded ^1H NMR spectrum of 7j	163
Figure 4.141. The ^{13}C NMR spectrum of 7j	163
Figure 4.142. LC-MS spectrum of 7j	164
Figure 4.143. The IR spectrum of 7k	164
Figure 4.144. The ^1H NMR spectrum of 7k	165
Figure 4.145. The expanded ^1H NMR spectrum of 7k	165
Figure 4.146. The ^{13}C NMR spectrum of 7k	166
Figure 4.147. LC-MS spectrum of 7k	166
Figure 4.148. The IR spectrum of 7l	167
Figure 4.149. The ^1H NMR spectrum of 7l	167
Figure 4.150. The expanded ^1H NMR spectrum of 7l	168
Figure 4.151. The ^{13}C NMR spectrum of 7l	168
Figure 4.152. The expanded ^{13}C NMR spectrum of 7l	169
Figure 4.153. LC-MS spectrum of 7l	169
Figure 4.154. The IR spectrum of 7m	170
Figure 4.155. The ^1H NMR spectrum of 7m	170

Figure 4.156. The expanded ^1H NMR spectrum of 7m	171
Figure 4.157. The ^{13}C NMR spectrum of 7m	171
Figure 4.158. LC-MS spectrum of 7m	172
Figure 4.159. The IR spectrum of 7n	172
Figure 4.160. The ^1H NMR spectrum of 7n	173
Figure 4.161. The expanded ^1H NMR spectrum of 7n	173
Figure 4.162. The ^{13}C NMR spectrum of 7n	174
Figure 4.163. LC-MS spectrum of 7n	174

ABBREVIATIONS

NH₂OH.HCl	: Hydroxylamine hydrochloride
KBr	: Potassium bromide
K₂CO₃	: Potassium carbonate
Na₂SO₄	: Sodium sulfate
NaOH	: Sodium hydroxide
Et₃N	: Triethyl amine
DMF	: <i>N,N</i> -Dimethylformamide
PB	: Petroleum Benzine
EtOAc	: Ethyl acetate
EtOH	: Ethanol
DCM	: Dichloromethane
DMSO	: Dimethylsulfoxide
TLC	: Thin Layer Chromatography
MS	: Mass Spectroscopy
IR	: Infra Red
NMR	: Nuclear Magnetic Resonance
LC-MS	: Liquid chromatography–mass spectrometry
R_f	: Retention Factor
M.p.	: Melting Point
RT	: Room Temperature

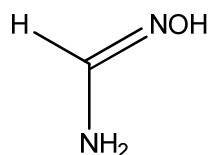
CHAPTER I

1. INTRODUCTION

1.1. AMIDOXIMES:

Amidoximes are compounds bearing both a hydroxyimino and an amino group at the same carbon atom. Due to this property, they are used as building blocks for the synthesis of various heterocycles. Their importance in chemistry along with their rich biology, make amidoximes an attractive target for medicinal chemists, biochemists and biologists. Amidoximes and simple O-substituted derivatives have very important biological activities functioning as antituberculosic, antibacterial, bacteriostatic, insecticidal, elminthocidal, antiviral, herbicidal, fungicidal, antineoplastic, antiarrhythmic, antihypertensive, antihistaminic, anxiolytic-antidepressant, anti-inflammatory/antioxidant, antiaggregatory (NO donors) or plant growth regulatory agents. Several of amidoximes has already been used as drugs, or currently being in clinical trials.[1]

In 1873, Lossen and Schifferdecker [2] prepared the first amidoxime by reacting hydrogen cyanide with hydroxylamine. The compound is called as "isoretin" as shown below (Figure 1.1)

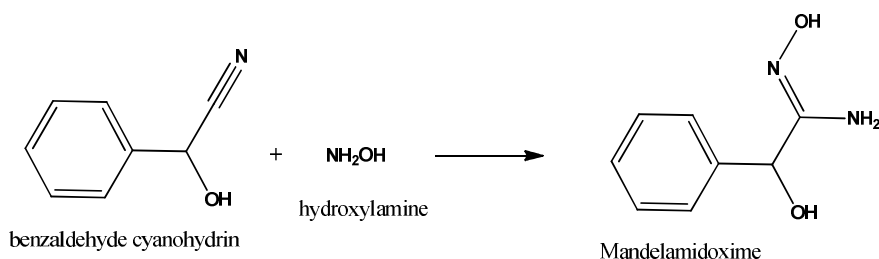


N'-hydroxyformimidamide

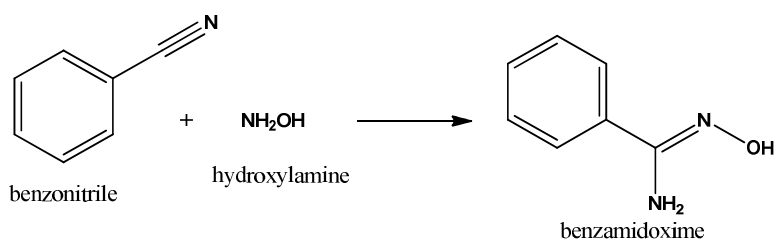
isuretin

Figure 1.1. The structure of isuretin

The name “amidoxime” was first used by Tiemann [3] who prepared two related compounds mandelamidoxime and benzamidoxime in 1884 by addition reaction of hydroxylamine to benzaldehyde cyanohydrin (Scheme 1.1) and to benzonitrile (Scheme 1.2), respectively.



Scheme1.1. Synthesis of mandelamidoxime

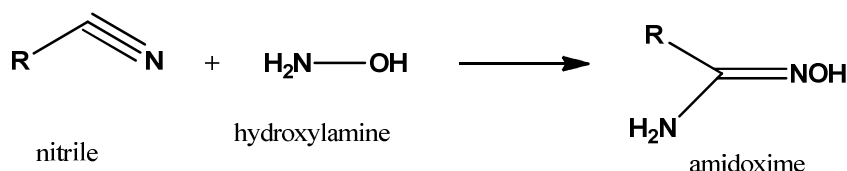


Scheme 1.2. Action of hydroxylamine on benzonitrile

1.1.1. Synthesis of Amidoximes:

1.1.1.1. Action of hydroxylamine on nitriles:

The preparation of amidoximes from nitriles by the action of hydroxylamine was first studied by Tiemann and Krüger (Scheme 1.3) [3].



Scheme 1.3. Action of hydroxylamine on nitriles

After reaction of nitriles with hydroxylamine hydrochloride in alcohol in the presence of a base, Na₂CO₃, amidoximes are produced at 60-80 °C for a few hours. This synthesis method is most commonly used for preparation of simple amidoximes. The aim of using strong base in the reaction liberates hydroxylamine from its hydrochloride form. Instead of sodium carbonate, sodium hydroxide (NaOH) or potassium hydroxide (KOH) or sodium ethoxide or triethylamine also have been used.

1.1.1.2. Action of hydroxylamine on amides or thioamides:

As a rule, hydroxylamine does not react with amides, but this method has only been used [4,5] for preparation of the two amidoximes (Figure 1.2).

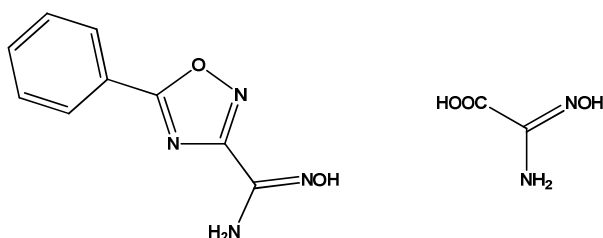
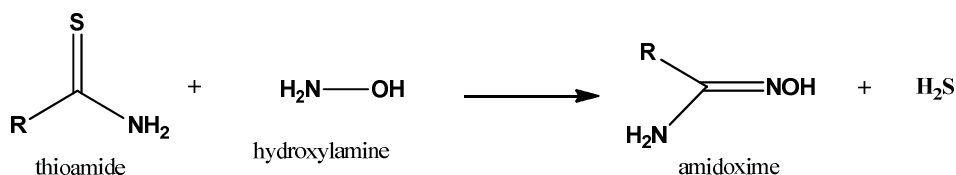


Figure 1.2. The structures of *N'*-hydroxy-5-phenyl-1,2,4-oxadiazole-3-carboximidamide and 2-amino-2-(hydroxyimino)acetic acid

The action of hydroxylamine on thioamides has been reported [6-9] for the preparation of some aromatic amidoximes (Scheme 1.4).

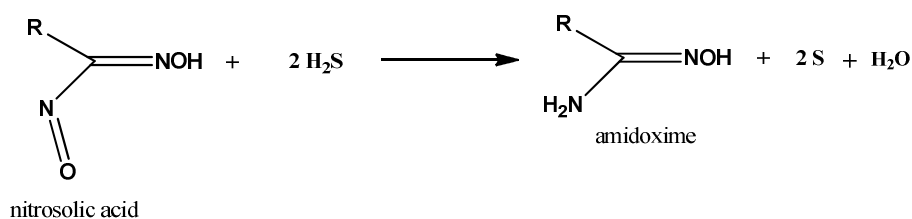


Scheme 1.4. Action of hydroxylamine on amides or thioamides

In this method, an equivalent amount of aqueous sodium carbonate is used to liberate hydroxylamine from its hydrochloride salt. When the thioamide is more easily available than the corresponding nitrile, this procedure is used to prepare the corresponding amidoxime.

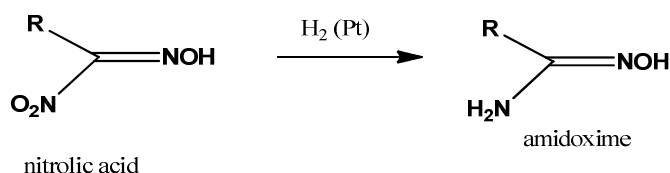
1.1.1.3. Reduction of nitrosolic and nitrolic acids:

Amidoximes can be prepared by the reduction of nitrosolic acids with hydrogen sulfide. Benzamidoxime was prepared by Wieland and Bauer [10] by using this method (Scheme 1.5).



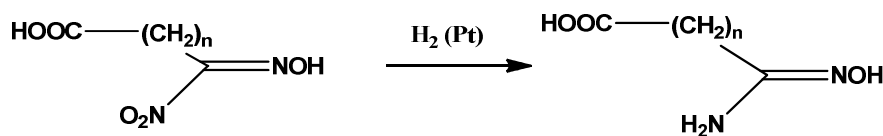
Scheme 1.5. Reduction of nitrosolic acids to amidoximes

The catalytic reduction of nitrolic acids is given as a method for the preparation of monoamidoximes (Scheme 1.6).



Scheme 1.6. Reduction of nitrolic acids to amidoximes

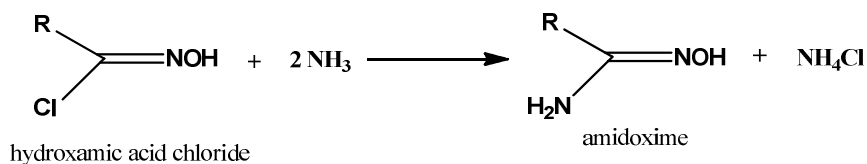
For the preparation of the monoamidoximes of dicarboxylic acids, this catalytic reduction of nitrolic acid was described as a obvious method (Scheme 1.7) [11].



Scheme 1.7. Preparation of monoamidoximes of dicarboxylic acids

1.1.1.4. Action of ammonia on hydroxamic acid chlorides (chloroximes):

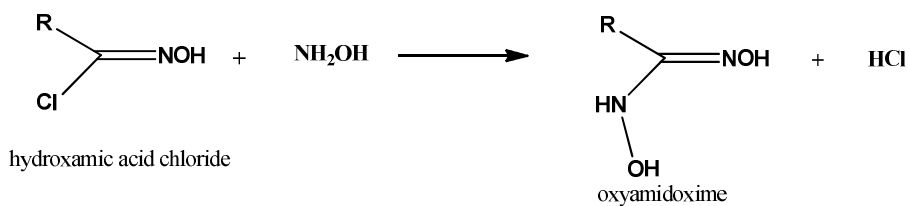
Direct chlorination of aldoximes forms chloroximes (hydroxamic acid chloride). These compounds react with ammonia to produce amidoximes (Scheme 1.8). By using this method, Werner prepared benzamidoxime, *o*-chlorobenzamidoxime [12,13] and terephthalamidoxime [14].



Scheme 1.8. Action of ammonia on hydroxamic acid chlorides

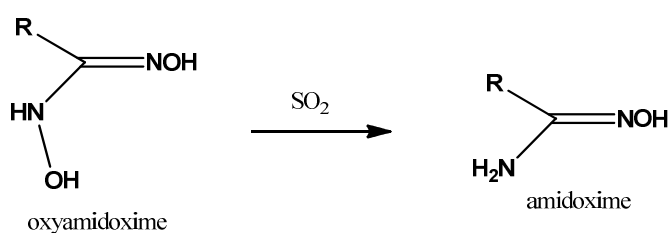
1.1.1.5.Reduction of oxyamidoximes:

Chloroximes react with hydroxylamine to yield oxyamidoximes (Scheme 1.9). This synthesis method was used by Ley and Ulrich [15] to prepare benzoxyamidoxime.



Scheme 1.9. Action of hydroxylamine on hydroxamic acid chloride

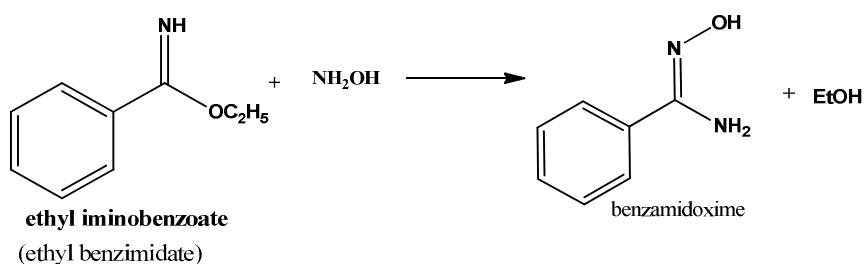
After obtaining the corresponding oxyamidoxime from its chloroxime, this compound is reduced with SO_2 to its amidoxime (Scheme 1.10).



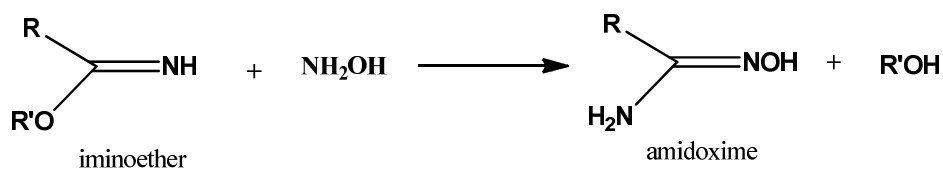
Scheme 1.10. Reduction of oxyamidoxime with sulfur dioxide

1.1.1.6. Action of hydroxylamine on iminoethers:

Pinner [16] and Lossen [17] reported this reaction to obtain benzamidoxime by treating ethyl iminobenzoate with hydroxylamine (Scheme 1.11).



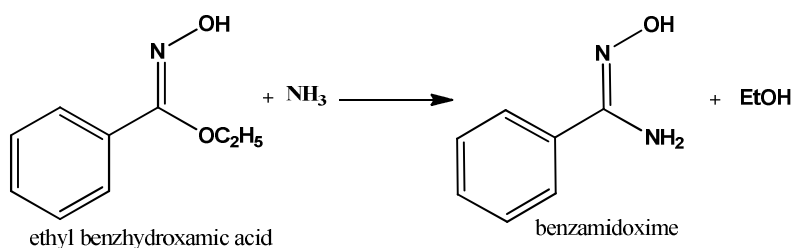
Scheme 1.11. Action of hydroxylamine on ethyl iminobenzoate



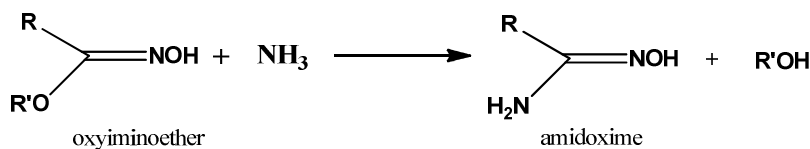
Scheme 1.12. Action of hydroxylamine on iminoether

1.1.1.7. Action of ammonia on oxyiminoethers:

When heated in a pressure bottle for 8 hrs. at 175 °C, an alcoholic solution of ammonia and ethyl benzhydroxamic acid yields benzamidoxime (Scheme 1.13) [18] . This reaction has not found general application.



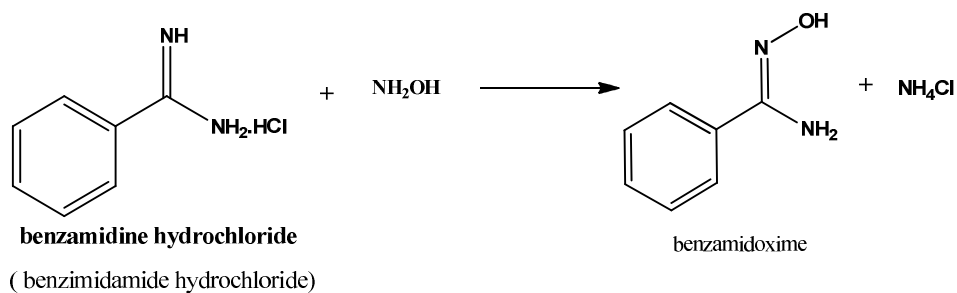
Scheme 1.13. Action of ammonia on ethyl benzhydroxamic acid



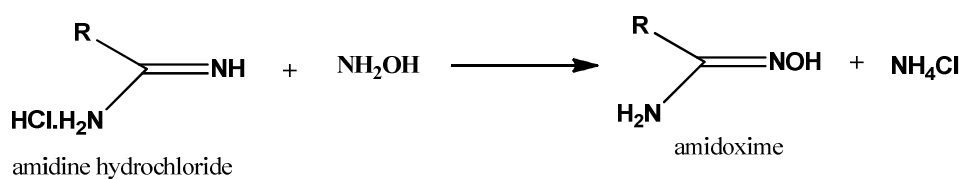
Scheme 1.14. Action of ammonia on oxyiminoether

1.1.1.8. Action of hydroxylamine on amidine hydrochlorides:

Pinner [19] prepared benzamidoxime by treating benzamidine hydrochloride with hydroxylamine (Scheme 1.15) .



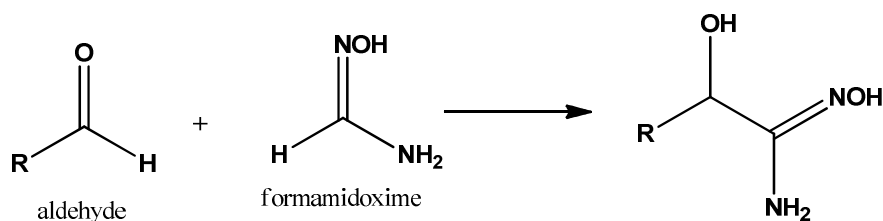
Scheme 1.15. Action of hydroxylamine on benzamidine hydrochloride



Scheme 1.16. Action of hydroxylamine on amidine hydrochloride

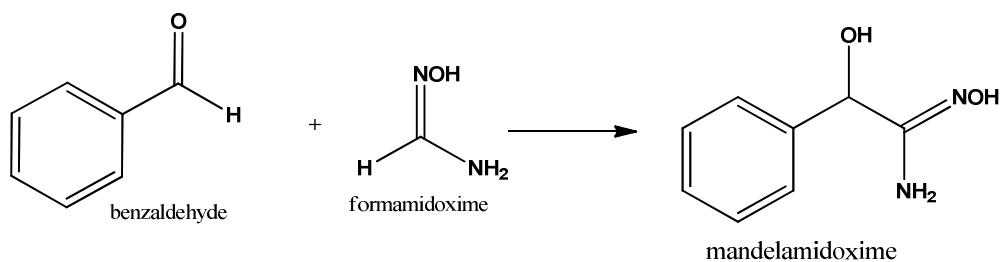
1.1.1.9. Reaction of formamidoximes and aromatic aldehydes:

According to Conduché [16], formamidoxime reacts with aromatic aldehydes, which lead to an aldol condensation (Scheme 1.17).



Scheme 1.17. Reaction of formamidoxime with aromatic aldehydes

Only mandelamidoxime have been produced by this method (Scheme 1.18) .

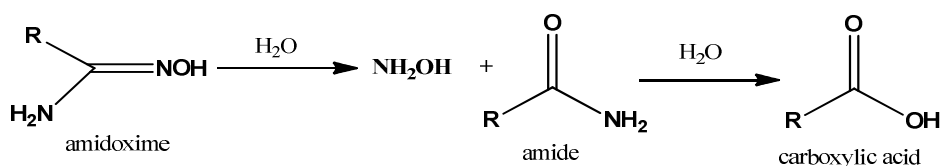


Scheme 1.18. Reaction of benzaldehyde with formamidoxime

1.1.2. Reactions of Amidoximes:

1.1.2.1. Hydrolysis of amidoximes:

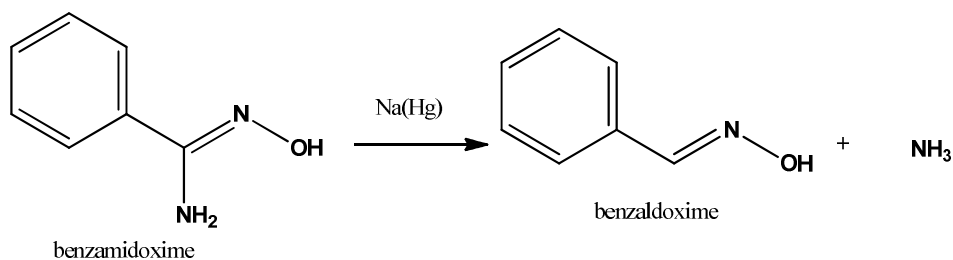
Many amidoximes forming soluble salts with dilute mineral acids and alkalies at room temperature are hydrolyzed completely when heated in the same media [20]. Amides and hydroxylamine are formed and the amides undergo hydrolysis into the corresponding acids under drastic conditions (Scheme 1.19).



Scheme 1.19. Hydrolysis of amidoximes

1.1.2.2. Reduction of benzamidoxime with sodium amalgam:

The reduction of benzamidoxime with sodium amalgam [21,22] produces ammonia and benzaldoxime (Scheme 1.20).

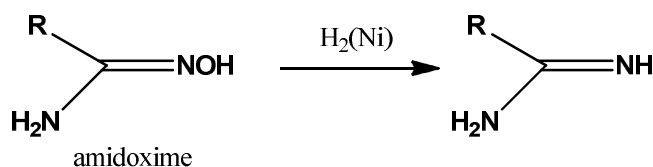


Scheme 1.20. Reduction of benzamidoxime with sodium amalgam

The yield obtained from this reaction is very low. It's around 10-12%. Most of amidoximes does not undergo this reaction.

1.1.2.3. Reduction of amidoxime with Raney nickel:

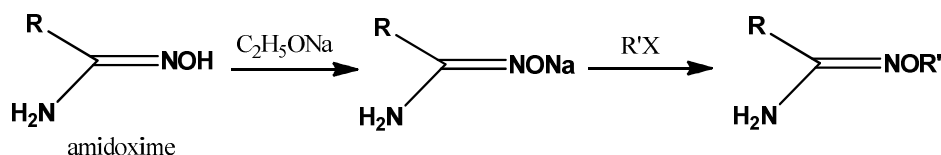
Amidines can be prepared by the reduction of corresponding amidoximes in the presence of Raney nickel [23, 24] at 30 atm and 60-80 °C (Scheme 1.21).



Scheme 1.21. Reduction of amidoxime with Raney nickel

1.1.2.4. O-Alkylation of amidoxime:

Amidoximes and their *N*-substituted derivatives exhibit acidic properties and they form salts with metals. Sodium salts are easily obtained from sodium alcoholate such as sodium ethoxide. These salts produces *O*-alkyl ethers when they are treated with aliphatic halogen compounds (Scheme 1.22) [25-29] .

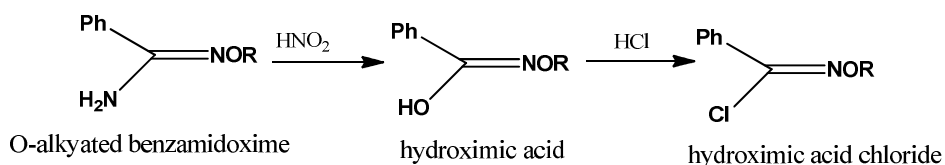


Scheme 1.22 . O-Alkylation of amidoxime

Instead of sodium ethoxide, sodium and potassium hydroxide in aqueous alcoholic solution can be used [30] .

1.1.2.5. Reaction of O-alkylated benzamidoxime with HNO_2 :

When O-alkylated benzamidoxime is treated with nitrous acid, nitrogen gas is evolved, which proves that an amino group exists in the molecule [31] . In this reaction, the hydroxamic acid which formation are expected is not isolated, but in the presence of excess hydrochloric acid, the corresponding hydroxamic acid chloride is formed in high yields (Scheme 1.23) [8, 21, 26, 30, 32-36] .

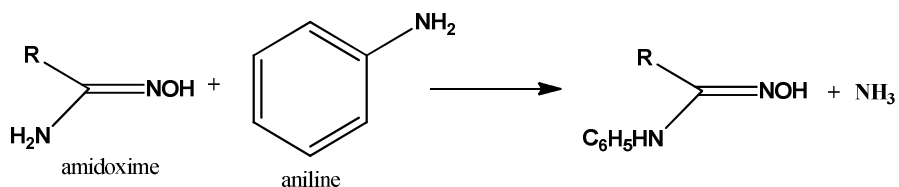


Scheme 1.23. Reaction of O-alkylated benzamidoxime with HNO_2

O-alkyl hydroxamic acid chlorides are very stable oils which can be steam distilled without decomposition and they are soluble in most organic solvents.

1.1.2.6. Action of aniline on amidoximes:

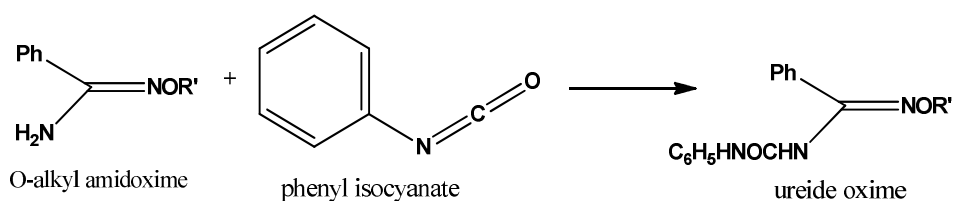
Aniline reacts directly with acetamidoxime and formamidoxime hydrochloride at 80-90°C. Ammonia (NH_3) is evolved with the corresponding N-substituted amidoximes (Scheme 1.24). [31,37]



Scheme 1.24. Action of aniline on amidoximes

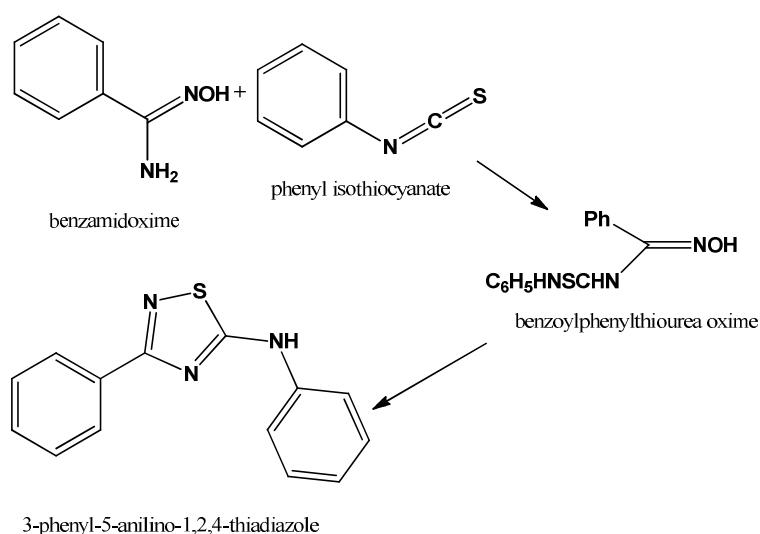
1.1.2.7. Reaction of amidoximes with isocyanates and isothiocyanates:

When *O*-alkyl amidoximes react with isocyanate, ureide oximes are only yielded obviously (Scheme 1.25) [36,38,39].



Scheme 1.25. Reaction of amidoximes with isocyanates

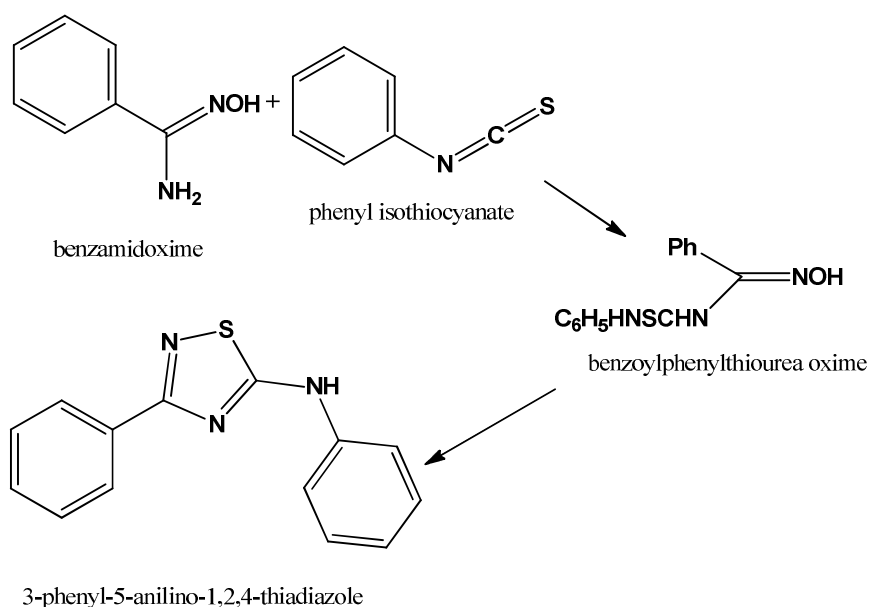
When phenyl isothiocyanate and benzamidoxime react with each other at room temperature in equimolecular amounts, benzoylphenylthiourea oxime is formed [26, 40].



Scheme 1.26. Reaction of benzamidoxime with phenyl isothiocyanate

When the reaction is carried out in boiling chloroform with two moles of isothiocyanate and one mole of benzamidoxime, hydrogen sulfide is evolved and 3-phenyl-5-anilino-1,2,4-thiadiazole is formed (Scheme 1.26).

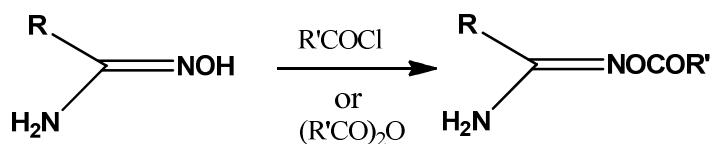
On the contrary, isothiocyanate forms the corresponding thiourea oxime under similar conditions. In this reaction, cyclization of thiourea oxime occurs and 3-phenyl-5-p-toluidino-1,2,4-oxadiazole is produced (Scheme 1.27) [40].



Scheme 1.27. Reaction of benzamidoxime with *p*-tolyl isothiocyanate

1.1.2.8. Reaction of amidoximes with acyl chlorides (acid chlorides) or acylation of them with acid anhydrides:

Amidoximes can be acylated by acyl chlorides or anhydrides at room temperature (Scheme 1.28) [14].



Scheme 1.28. Reaction of amidoximes with acyl chlorides (acid chlorides) or their acylation with acid anhydrides

Instead of acid anhydrides and chlorides, other reagents have been used, such as ketene, mixed carboxylic-carbonic anhydrides, carboxylic acid azides and thioacetic acid [41].

1.1.2.9. Salt Formation

Amidoximes have amphoteric property due to the fact that they are soluble in dilute mineral acids as well as in aqueous alkaline solutions [28].

The group causing basic properties in an amidoxime is the amino group in the molecule. Salts of amidoximes with mineral or organic acids are known; they are crystalized easily and have well defined melting points.

The hydrogen atom of the NOH group in the amidoxime can be substituted by a metal such as sodium and silver. Many sodium and silver salts of them have been described [14] .

In addition to this, amidoximes form colored crystalline compounds with the salts of some metals [20] . Werner [42] prepared a great number of such compounds with different amidoximes and proved that they are internal complexes in which the metal atom is linked to the oxime group as well as the amino group. These amidoximes have been used as analytical reagents for various cations [43,44].

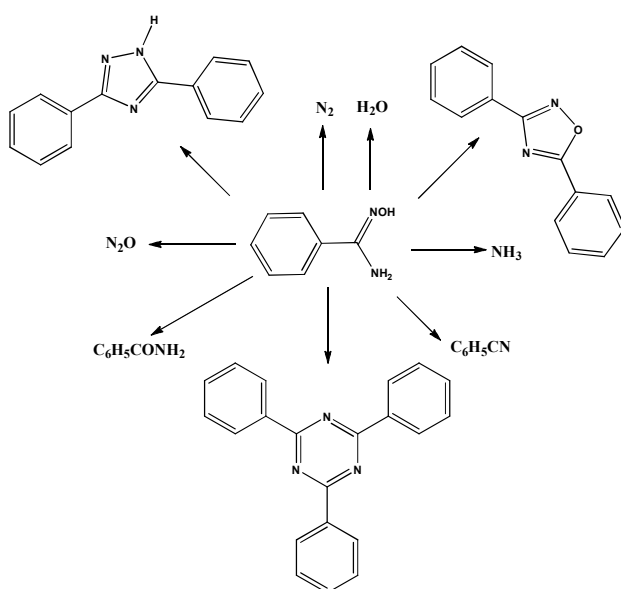
Nicotinamidoxime can be used for the spectrophotometric determination of uranium [45].

1.1.2.10. Organic Complexes

Amidoximes form with chloral bimolecular complexes, which are insoluble in water and organic solvents. They have sharp melting points and may be used for the identification of amidoximes [3,46-48] .

1.1.2.11. Thermal Decomposition

Generally, amidoximes are decomposed when heated in the neighborhood of their melting point. Benzamidoxime is melting at 80°C and stable up to 170°C. At this temperature it decomposes, yielding several products which were identified [49] as nitrogen, nitrous oxide, ammonia, water, benzonitrile, benzamide, diphenyl 1,2,4-oxadiazole, diphenyl-1,2,4-triazole and triphenyl-1,3,5-triazine (Scheme 1.29).



Scheme 1.29. Thermal decomposition of amidoximes

1.2. OXADIAZOLES:

Oxadiazole is a simple five-membered heterocycle which is a versatile lead compound for designing potent bioactive agents. Five-membered heterocyclic compounds show various types of biological activities. One of these biological active compounds is oxadiazoles. The derivatives of oxadiazoles shows various biological activities such as anti-inflammatory [50], antimicrobial, antibacterial [51], antimalarial [52], anticonvulsant [53], antifungal [54], antitubercular, anticancer, hypoglycemic, anti-HIV and genotoxic. Poonam Singh et al. discussed about the oxadiazoles having anticonvulsant activity and the effect of different substituents on the oxadiazole ring on its anticonvulsant activity [55].

A simple oxadiazole having general formula $C_2H_2ON_2$ has two carbons, two nitrogens, one oxygen atom and two double bonds inside of the five-membered ring. Some oxadiazole derivatives are shown below (Figure 1.3) .

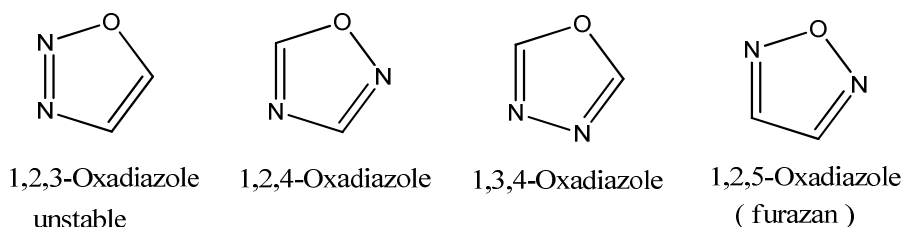


Figure 1.3. Representation of simple oxadiazoles

1,2,4 - Oxadiazoles, [56] 1,3,4 - oxadiazoles [57] and 1,2,5 - oxadiazoles are well known, but the 1,2,3-oxadiazole system, which calculations indicate to be unstable relative to its ring - open diazo-ketone tautomer (Figure 1.4), [58] is known only as a benzo-fused derivative (in solution) and in mesoionic substances, known as ' sydnones ' , [59] which have been well investigated (Figure 1.5) .

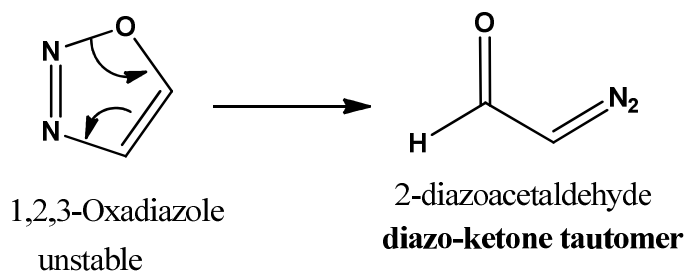


Figure 1.4. Ring - open diazo-ketone tautomer of 1,2,3-oxadiazole

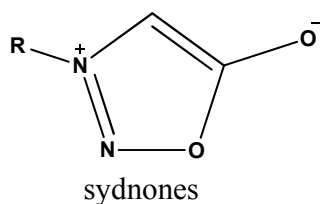


Figure 1.5. Structure of sydnone

Sydnone rings possess not only a mesoionic character but also a labile nature. The charge distribution on the rings can be varied according to their resonance form depending on the nature of substituents on either N(3) or C(4) [60]. In general, N(3) behaves as an electron-withdrawing nature and C(4) acts as an electron-donor character to form the so-called duality effect for the ring. [59a] The rupture of the sydnone rings will cause loss of a carbon dioxide molecule and retain the charges on the fragments. The charges on the fragments after the ring rupture have been proposed as “azomethine-imines” resonance forms, which contain both positive and negative charges for further reactions (Figure 1.6) [61]. Recently, a number of reactions of arylsydnone, acting as azomethine ylides, with either polar conjugate ketones or ring strain systems have been studied [62].

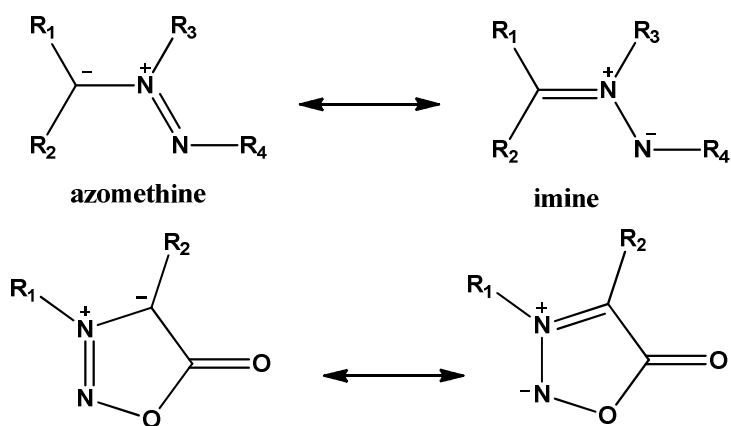
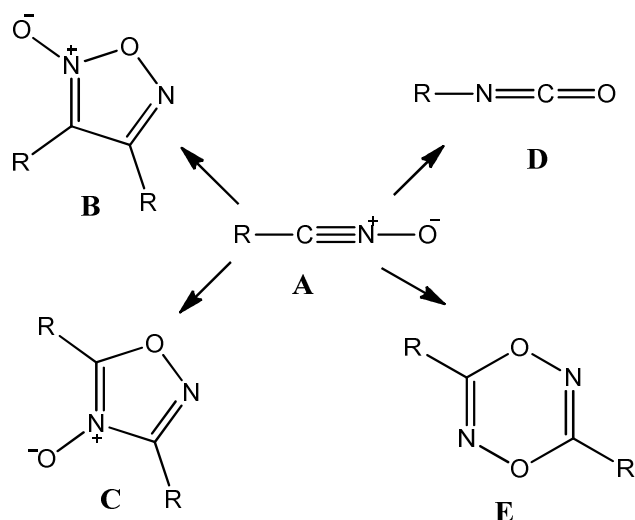


Figure 1.6. Resonance form of azomethine-imines

'Furoxans or furazan oxides', [63] which are formed by the dimerization of nitrile oxides, have also been extensively studied (Scheme 1.30).



A = nitrile oxide, B = furoxans, C = 1,2,4-oxadiazole 4-oxides, D = isocyanates, E = 1,4,2,5-dioxadiazines

Scheme 1.30. Main routes of chemical transformations of nitrile oxides

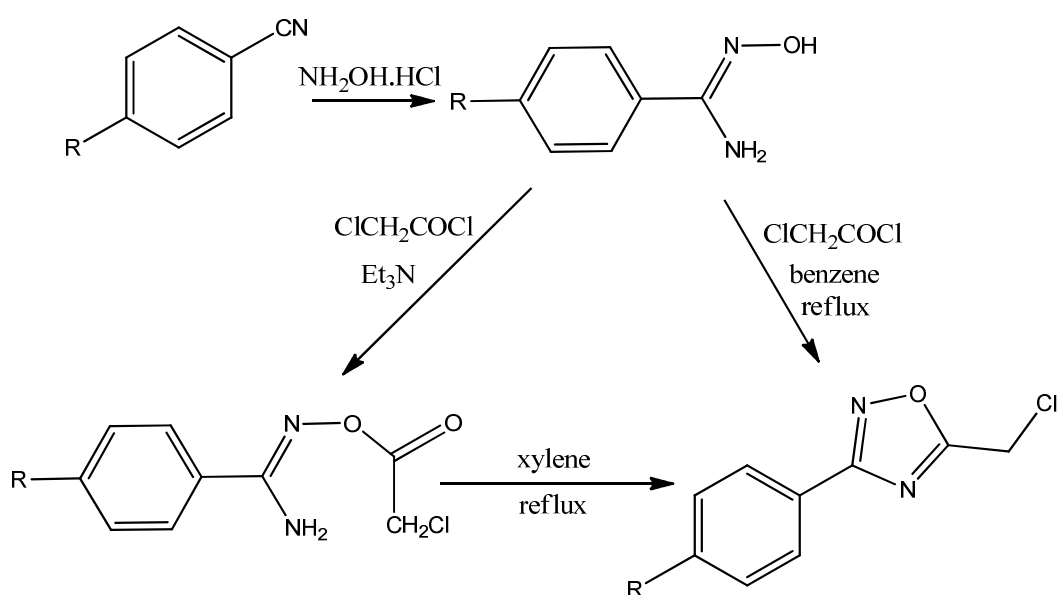
1.2.1. 1,2,4- OXADIAZOLES:

1.2.1.1. Synthesis of 1,2,4-Oxadiazole Compounds:

1,2,4 - Oxadiazoles can be prepared by the reaction of amidoximes with activated acids, [64,65] acid chlorides or anhydrides [66], esters [67] or β -keto-esters [68] .

1.2.1.1.1 Synthesis of 5-Halomethyl-3-aryl-1,2,4-oxadiazoles from Amidoximes:

5-halomethyl-3-aryl-1,2,4-oxadiazoles are prepared as a result of the reactions between arylamidoximes and acylchlorides such as chloroacetyl chloride and bromoacetyl chloride (Scheme 1.31).

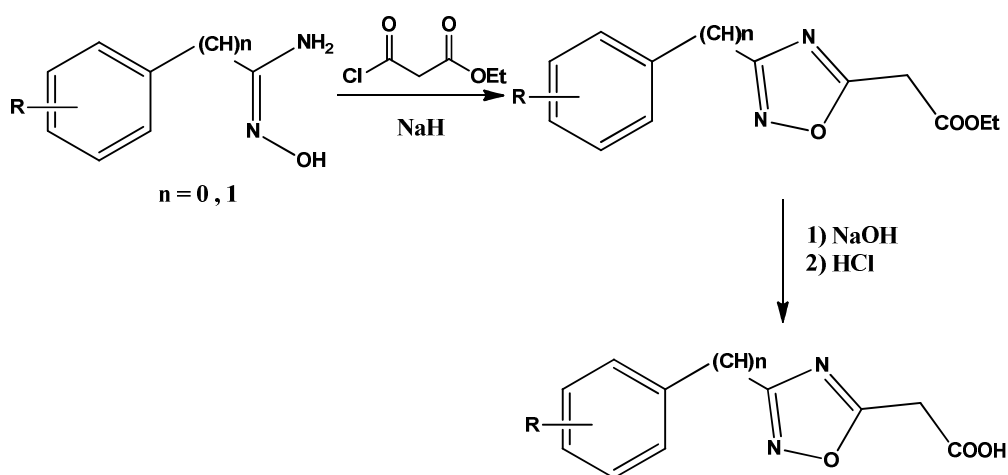


Scheme 1.31. General synthetic route for 3-Phenyl-1,2,4-oxadiazole-5-methylchlorides from amidoximes.

D.M.Cottrell et al. prepared 3-aryl-5-thio-cyanatomethyl-1,2,4-oxadiazoles from corresponding 3-aryl-5-halomethyl oxadiazoles which were synthesized from their amidoximes derivatives [69]. Also, N.P. Rai et al. prepared 5-chloromethyl-3-aryl-1,2,4-oxadiazoles from arylamidoximes used for the preparation {5-chloro-2-[(3-(substitutedphenyl)-1,2,4-oxadiazol-5-yl)-methoxy]-phenyl}-(phenyl)-methanones [70].

1.2.1.1.2 Synthesis of 3-Aryl-1,2,4-oxadiazol-5-yl-acetic Acids from Amidoximes:

Condensation of *N*-hydroxybenzimidamide and *N*-hydroxy-2-phenylacetimidamide intermediates with ethyl 3-chloro-3-oxopropanoate, in the presence of sodium hydride, provided the ethyl esters of corresponding 1,2,4-oxadizoles. After the hydrolysis of these esters with boiling NaOH and acidification, 3-aryl-1,2,4-oxadiazol-5-yl-acetic acids were obtained (Scheme 1.32) [71].



Scheme 1.32. Preparation of 3-Aryl-1,2,4-oxadiazol-5-yl-acetic Acids

1.3. HYDANTOINS:

Hydantoins, the compounds having a reactive urea core, are commonly used for organic synthesis and the most important members of this family are the 5-monosubstituted hydantoins used as precursors for the chemical synthesis of the DL- α -amino acids [72]. For instance, microbial hydantoin transformation was applied to produce optically active amino acids by J. Ogawa and S. Shimizu [73]. In addition to this, hydantoins and thiohydantoins are well known for diverse biological activities and play a key

role as antiarrhythmics [74], anticonvulsants [75], antitumor compounds [76], aldose reductase inhibitors [77], anti-inflammatory compounds [78] and antiandrogens [79]

Hydantoin is known as imidazolidinedione. Imidazolidinedione and thiazolidinedione derivatives are widely studied because of their pharmacological properties [80-82].

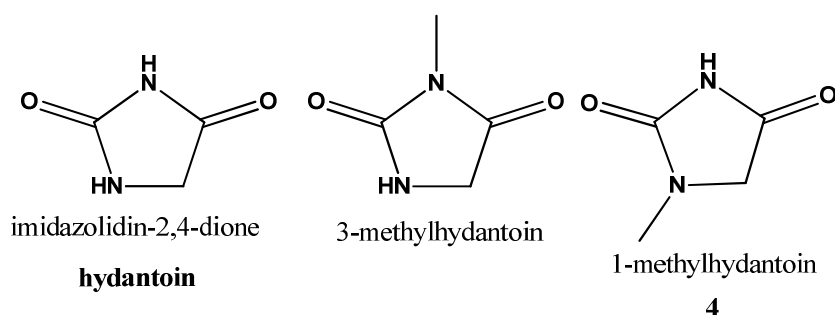


Figure 1.7. Structures of some hydantoin

J.F.C.Albuquerque et al. synthesized new 3-benzyl-4-thioxo-5-arylideneimidazolidine-2-ones and 3-benzyl-5-arylideneimidazolidine-2,4-diones which were synthesized by condensation reaction from aromatic aldehydes and 3-substituted imidazolidine-2,4-diones or 4-thioxoimidazolidine-2-ones. Antimicrobial in vitro activity was determined on some derivatives of these compounds [83].

A series of hydantoin and thiohydantoin were synthesized in water at room temperature from urea (or *N*-methylurea, or thiourea) and simple aldehydes (as glyoxal, and its simple derivatives) in the presence of phosphoric anhydride (P_4O_{10}) [84].

1.4. BENZIMIDAZOLE AND MERCAPTOBENZIMIDAZOLE DERIVATIVES:

Heteroaromatic compounds have attracted considerable attention in the design of biologically active molecules and great interest in synthetic organic

chemistry and medicinal chemistry. There is still interest in the synthesis of benzimidazole derivatives to obtain new biologically active compounds because of their diverse biological activity such as anti-HIV [85], anthelmintic [86], antibacterial [87], antifungal [88], CNS depressant [89], analgesic [90] and antiinflammatory [91] activities.

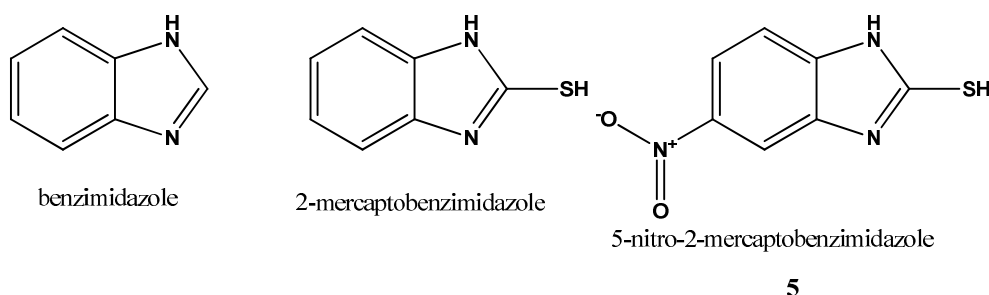
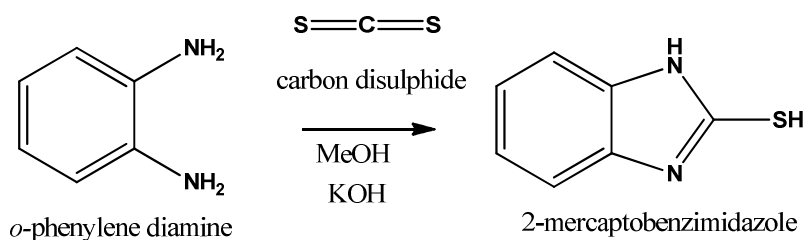


Figure 1.8. Structures of some benzimidazole derivatives

2-mercaptobenzimidazole derivatives, one of the most important derivatives of benzimidazole, exhibited a wide variety of interesting biological activities such as antimicrobial [92], antihistamine [93] and neutropic [94] activities. K. Anandarajagopal et al. synthesized some new 2-mercaptobenzimidazole derivatives by mannich reaction using some selected compounds having secondary amine and formaldehyde and their anti-inflammatory and antimicrobial activities were tested [95] .

Benzimidazole-2-thiones are most commonly made from o-arylenediamines in reaction with thiophosgene, carbon disulfide and other CS sources by direct introduction of sulfur at elevated temperatures to the benzimidazole or by the interaction of alcohols and aryl-1,2-diisothiocyanates.



Scheme 1.33. Synthesis of 2-mercaptobenzimidazole from *o*-phenylene diamine

Imidazole- and benzimidazole-2-thiols usually exist largely as the thione tautomers (Figure 1.9). The thiol (thione) group is susceptible to alkylation (especially in alkaline media), and can be oxidized to sulfide, disulfide and sulfonic acid. This oxidation can often be carried out quite selectively by careful choice of oxidizing agent. The sulfur function can be removed with nitric acid, iron(III) chloride, hydrogen peroxide or, most commonly, Raney nickel. Alkyl- and arylthio groups can be oxidized to sulfoxide or sulfone.

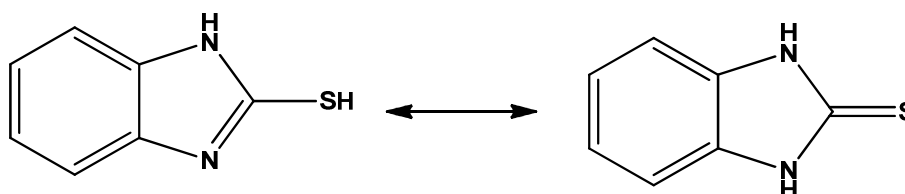
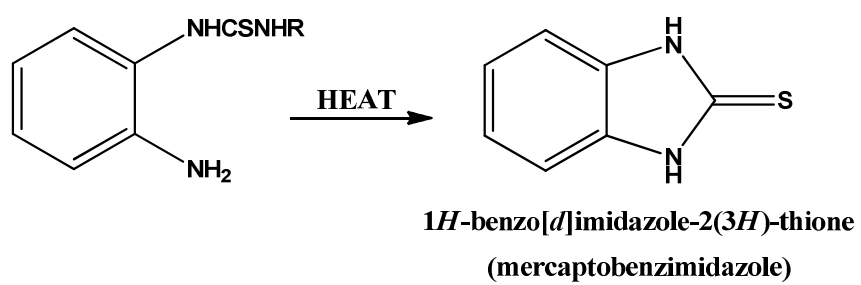


Figure 1.9. Structure of thione tautomer of 2-mercaptobenzimidazole

Another way exists for synthesis of benzimidazolethiones apart from the synthesis of them from *o*-arylenediamines. Conversion of *o*-aminoarylthioureas into benzimidazolethiones is achieved by merely heating them (reactions may go through intermediate isocyanates) (Scheme 1.34) [96].



Scheme 1.34. Example of conversion of *o*-aminoarylthioureas into benzimidazolethiones

CHAPTER II

2.1. RESULTS AND DISCUSSION

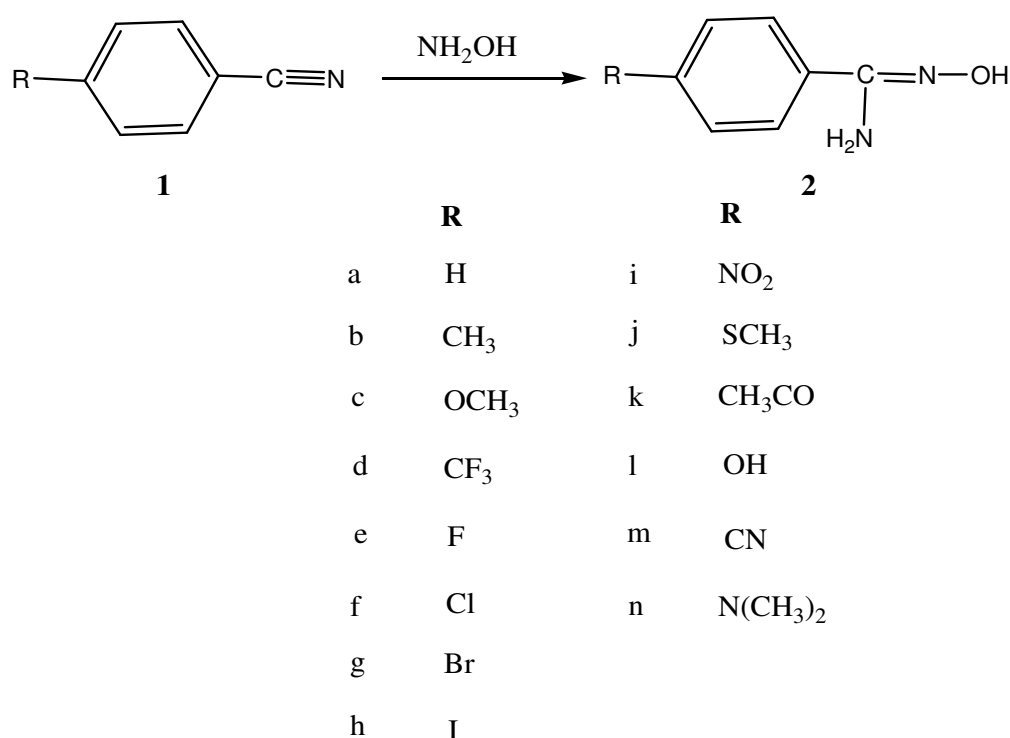
In this study, we attempted to perform *N*-substitution on 1-methyl hydantoin and 5-nitro-2-mercaptobenzimidazole with 5-chloromethyl-3-substituted-phenyl-1,2,4-oxadiazoles. To our best knowledge of literature based on WEB OF KNOWLEDGE, SCI FINDER and REAXYS electronic databases, there is no work related to *N*-substitution of 1-methyl hydantoin (1-methylimidazolidine-2,4-dione) and 5-nitro-2-mercaptobenzimidazole with 5-chloromethyl oxadiazoles. Therefore, increasing importance of these end products carrying oxadiazole, hydantoin and benzimidazole moieties can be considered as to promising valuable potential bioactive molecules. In this regard, we are further getting prepared to examine their bioactivities against various bacteria species and tumor cells in the near future.

The present research work is basically consisted of four parts.

- 1) Synthesis of substituted aryl monoamidoximes (**2**) as primary starting materials,
- 2) Synthesis of aryl substituted 5-(chloromethyl)-1,2,4-oxadiazoles (**3**) as one of the major starting compounds,
- 3) Synthesis of *N*-oxadiazolylmethyl substituted 1-methyl hydantoins (**6**),

4) Synthesis of *S*-1,2,4-oxadiazolymethyl substituted 5-nitro-benzimidazoles (**7**).

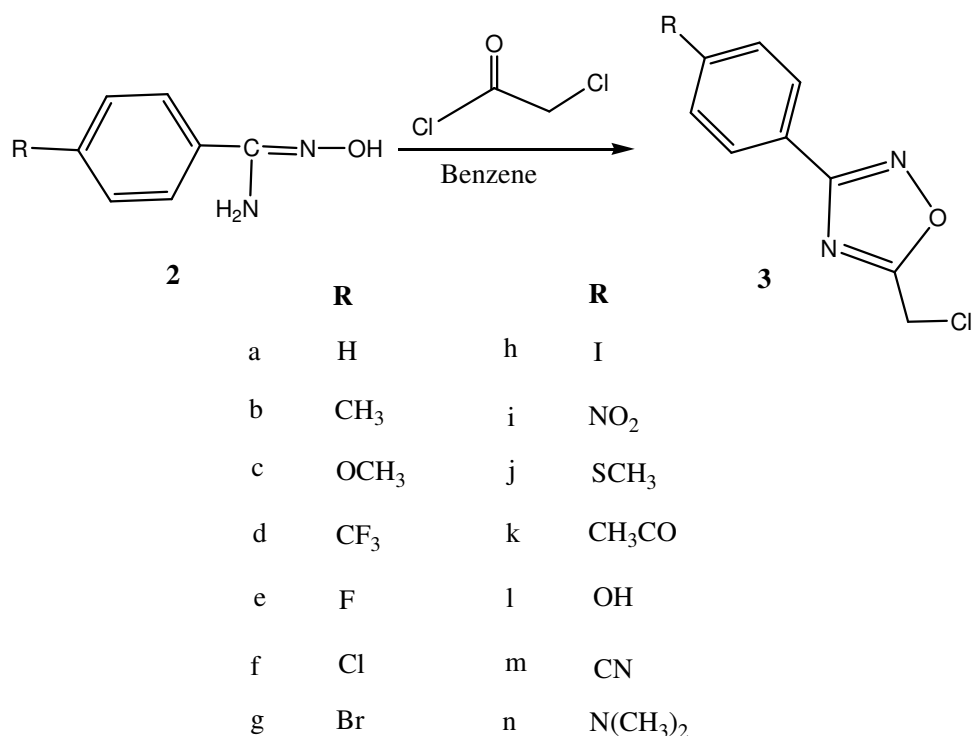
In order to carry out this project, first, aryl monoamidoximes (Scheme 2.1) have been prepared starting from appropriate, basically, *p*-substituted benzonitriles which carry both electron-withdrawing and electron-donating groups. Their physical/spectral data were all evidenced to have confirmed these compounds.



Scheme 2.1. Synthesis of aryl monoamidoximes (**2**)

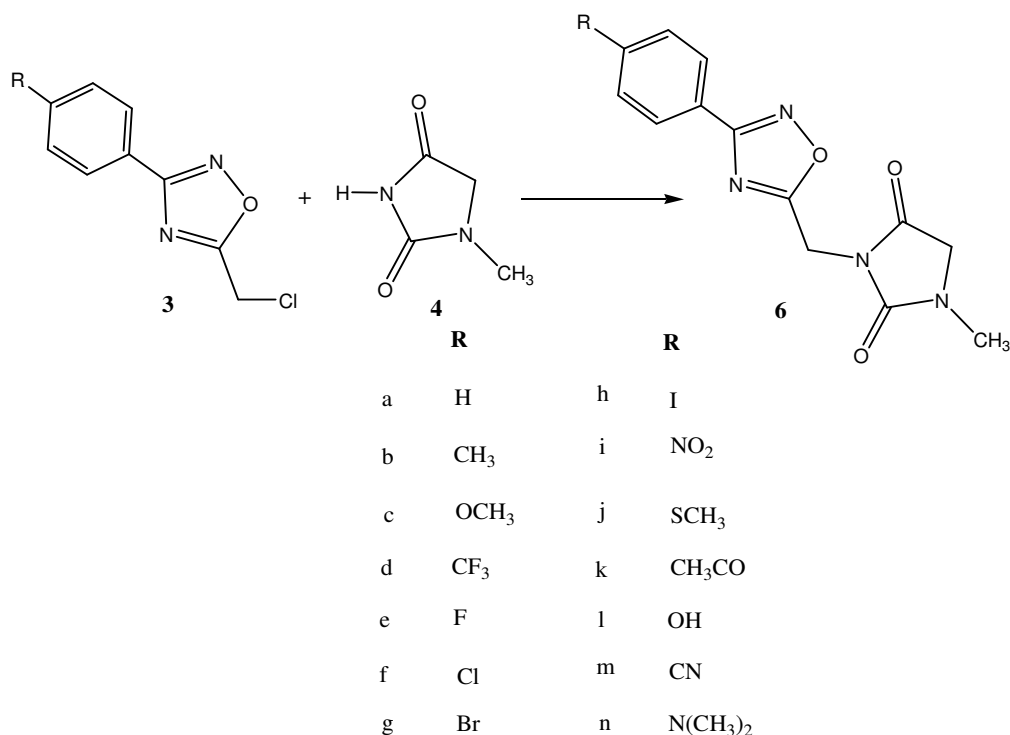
Both electron-releasing and electron-withdrawing groups have been selected. After having prepared mono aryl amidoximes, they were reacted with chloroacetylchloride to yield 3-(4-substituted phenyl)-5-chloromethyl-1,2,4-oxadiazoles (**3**) (Scheme 2.2), which are one of the major components in this

work, according to the literature method described previously. These compounds are found to be similar to those registered in literature.



Scheme 2.2. Synthesis of 3-aryl-5-chloromethyl-1,2,4-oxadiazoles (**3**)

After having prepared the necessary starting compounds, the target molecules were synthesized. First, a series of the *N*-substituted 1-methyl hydantoins were obtained by reacting chloromethyl oxadiazoles and 1-methylimidazolidine-2,4-dione (1-methylhydantoin) (Scheme 2.3).



Scheme 2.3. Synthesis of *N*-oxadiazolymethyl substituted hydantoins **6a-n**.

Hydantoin derivatives are well known for diverse biological activities and play a key role as antiarrhythmics, anticonvulsants, antitumor compounds, aldose reductase inhibitors, anti-inflammatory compounds, and antiandrogens [74-76].

The structures of these novel compounds were determined by their physical (m.p. and *R_f* values) and spectral data, namely, IR, ¹H and ¹³C NMR and mass spectra. Primary indicative evidence of this series is the disappearance of NH absorption in the IR spectra of the compounds. In addition, two carbonyl absorption bands which came out from one of the starting compounds; 1-methyl hydantoin, are observed at around 1710-1770 cm⁻¹. In the proton NMR spectra, typical peaks are observed for the three types of the aliphatic hydrogens which are shown below (Figure 2.1).

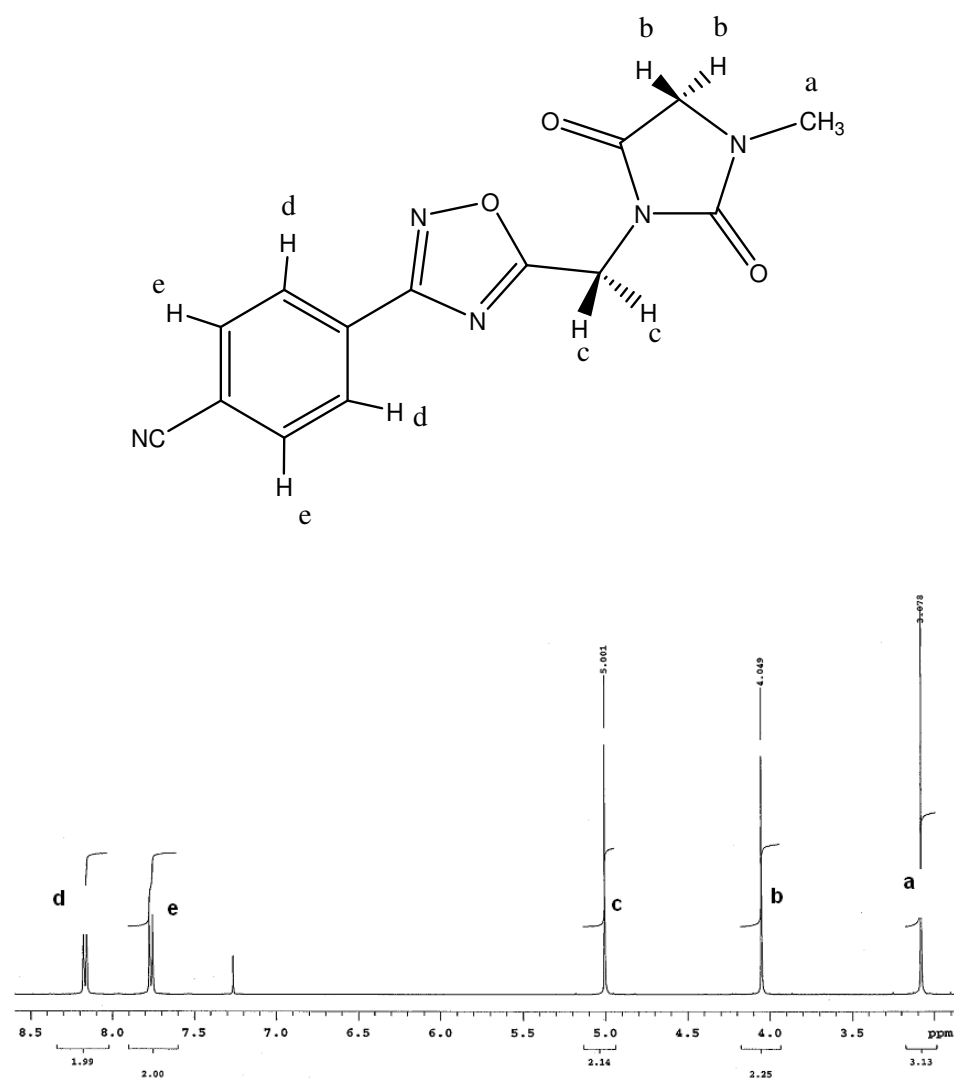


Figure 2.1. Assignment of hydrogens for the compound **6m**.

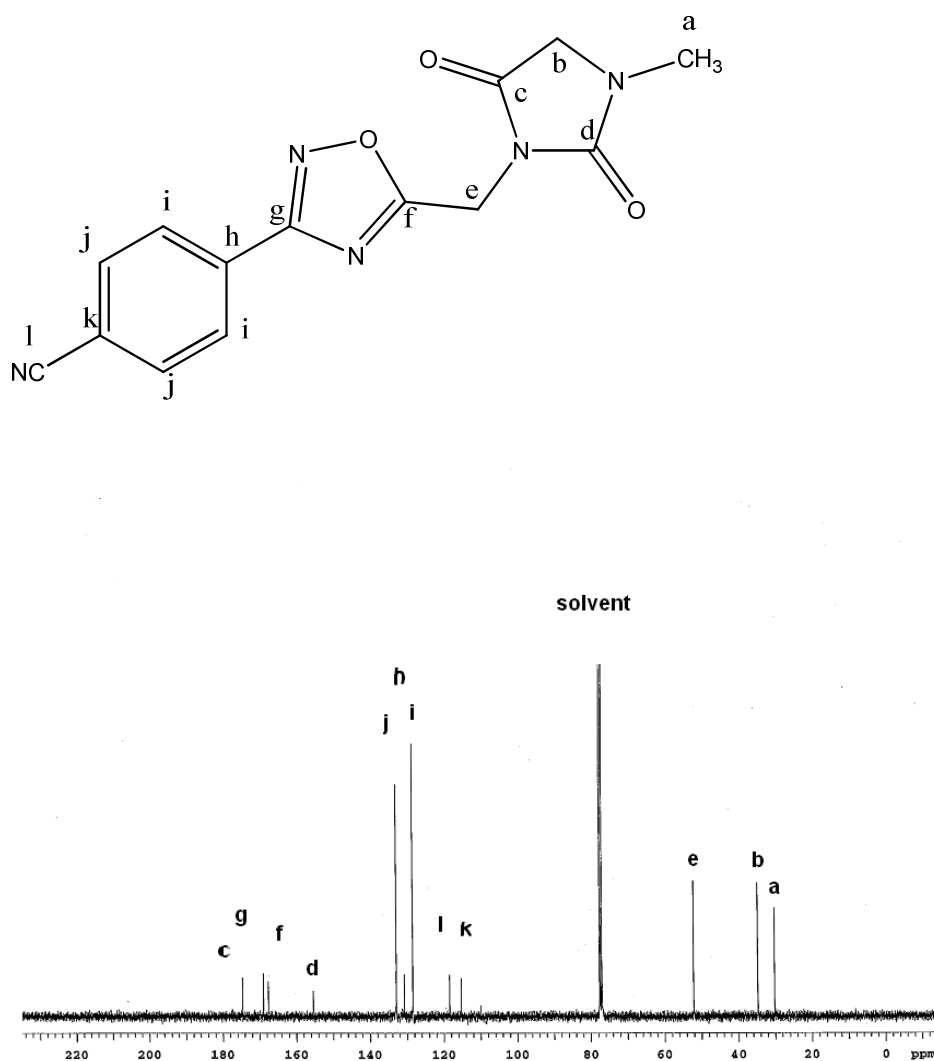


Figure 2.2. Assignment of carbons for the compound **6m**.

Upon examination of the mass spectra of the compounds **6**, we can clearly see the molecular ion+H peaks as base peak. As a representative spectrum, it is illustrated for the compound **6m** below (Figure 2.3).

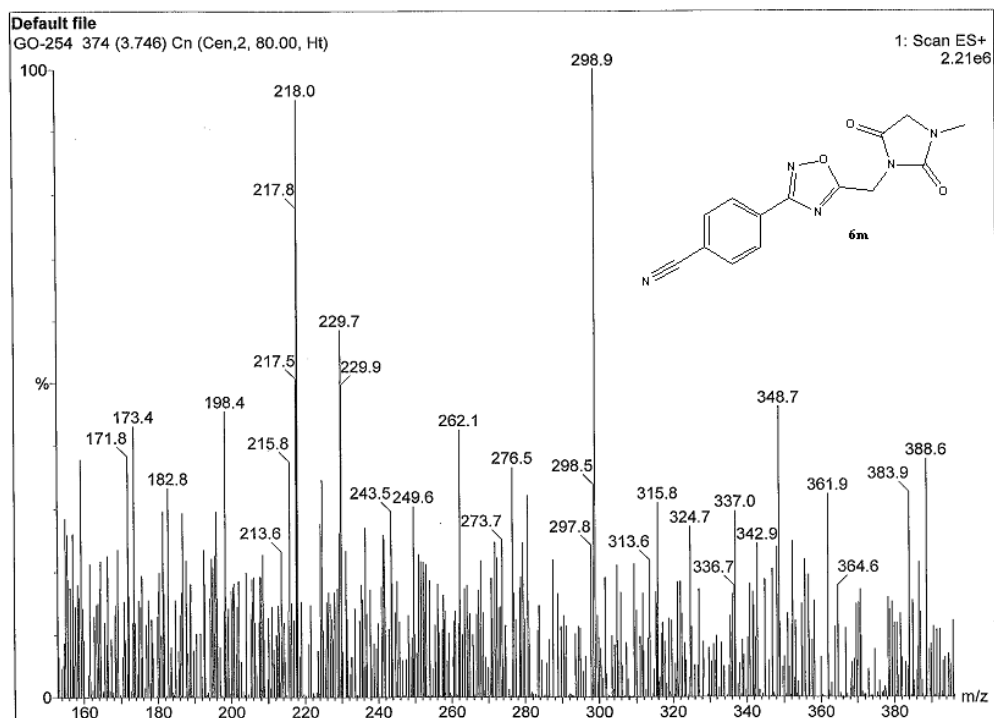
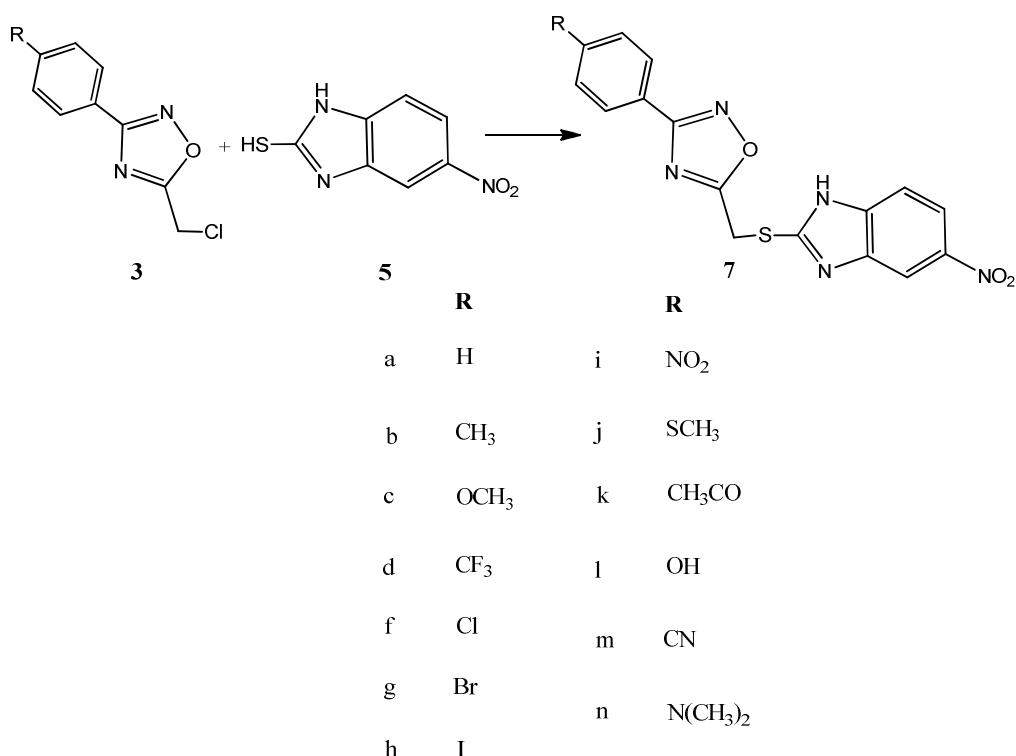


Figure 2.3. LC-MS spectrum of compound **6m**.

In this part of our research, we are focused on *S*-substitution on the 5-nitro-2-mercaptobenzimidazole with a variety of substituted aryl 5-chloromethyl 1,2,4-oxadiazoles (Scheme 2.4). Benzimidazole derivatives are getting much attention recent decade due to their potent bioactivities [97-100].



Scheme 2.4. Synthesis of *S*-1,2,4-oxadiazolymethyl substituted 5-nitrobenzimidazoles **7a-n**

These compounds are quite polar due to the existence of both NH and nitro groups. Therefore, we were just able to record their NMR spectra in DMSO-*d*₆. All of the new benzimidazole derivatives were elucidated by spectral/physical data. Thus, initial evidence for this series was the disappearance of broad absorption around 3400-2900 cm⁻¹ regarding the starting mercapto benzimidazole in the IR spectra. ¹H NMR spectra also showed the protons for the whole compound. Interestingly, NH proton appeared unexpectedly most deshielded at around 13.5 ppm as a broad singlet which can be attributed to the mesomerically electron-withdrawing effect of nitro group and neighboring sp² hybridized imine carbon. However, we noticed that when we recorded ¹H NMR of the samples which have been prepared in dimethylformamide medium, NH protons could not be observed.

Despite the attempts to remove DMF from the reaction mixture, we were unable to do that which could be obviously seen in the DMF signals in ^1H NMR spectra.

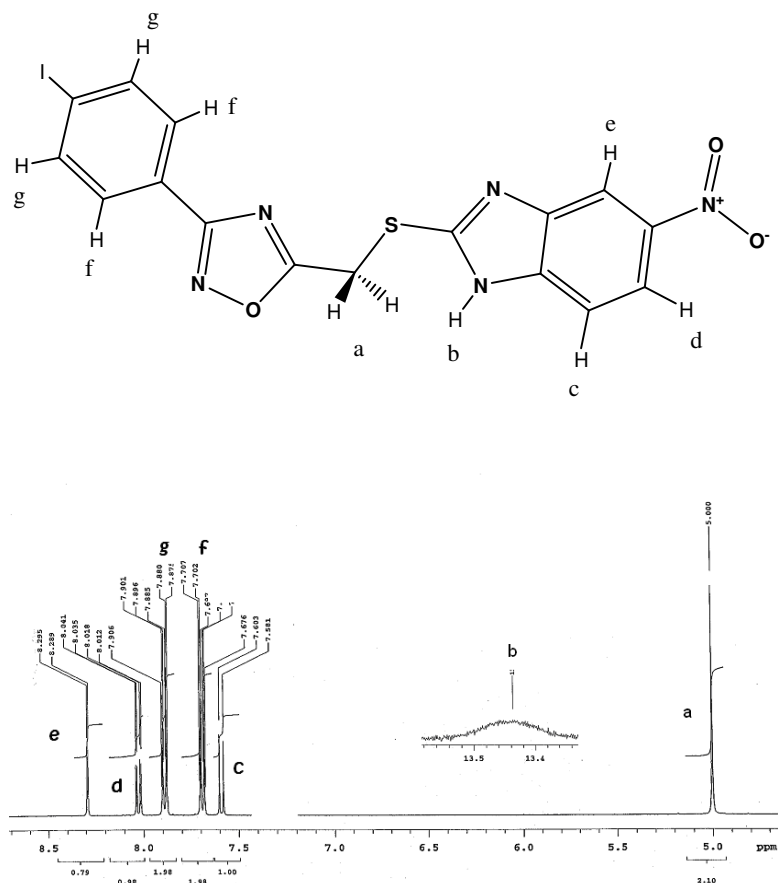


Figure 2.4. Assignment of protons of the compound **7h**.

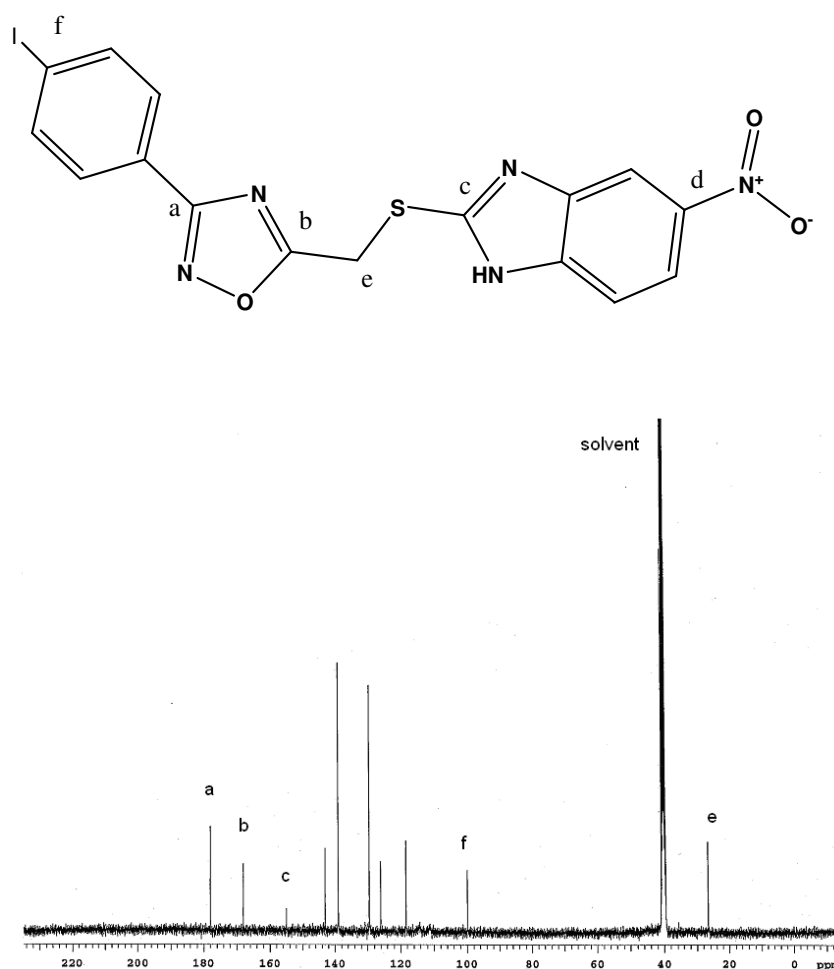


Figure 2.5. Assignment of indicative carbons of the compound **7h**.

2.2. CONCLUSION

In summary, we have introduced a simple and practical method to obtain novel *N*-substituted products of the 1-methylhydantoin and *S*-substitution products of 5-nitro-2-mercaptobenzimidazole. Thus, 14 novel *N*-oxadiazolymethyl-substituted 1-methylhydantoins and 13 novel *S*-1,2,4-oxadiazolymethyl substituted 5-nitrobenzimidazoles have been prepared and their structures were fully determined by using spectral data including single crystal X-Ray diffraction. All of these 27 compounds are novel and we expect they would show bioactivity against various bacteria species and tumor cells. In the near future we will have the preliminary results of this study.

We were also able to obtain X-ray diffraction for the compound **7h**. It was clearly seen that substitution occurred through S atom and there is one mol H₂O inclusion within the molecule (Figure 2.6).

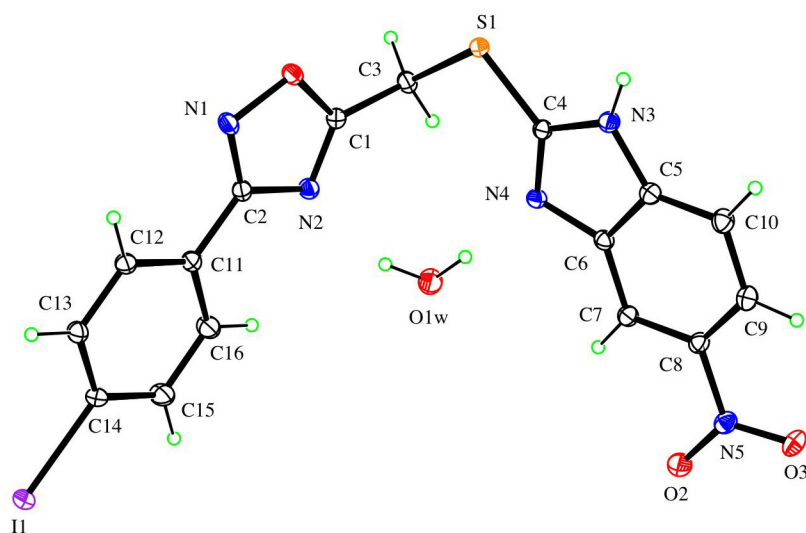


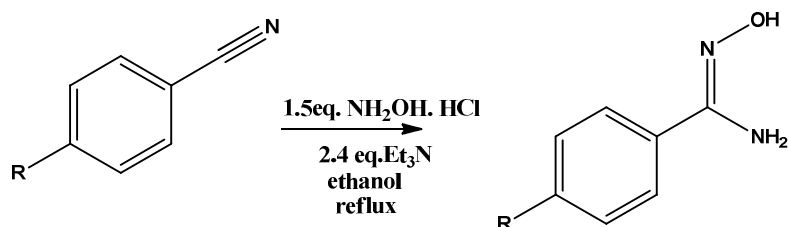
Figure 2.6. X-Ray ORTEP view of compound **7h**.

CHAPTER III

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on Varian Mercury spectrometers (400 and 300 MHz for ^1H ; 100 and 75 MHz for ^{13}C) and IR spectra were recorded on a SHIMADZU FTIR 8400-S instrument (KBr pellet). LC-MS spectra were recorded on Waters 2695 Alliance Micromass ZQ instrument. X-Ray data were obtained from Bruker Kappa APEX-II DUO diffractometer. Melting points were determined on a Meltemp apparatus and uncorrected. Flash column chromatography was performed on Silica Gel (Merck, 230-400 Mesh ASTM). TLC was done using precoated plates with fluorescent indicator (Merck 5735). The stain solutions of permanganate were used for visualization of the TLC spots.

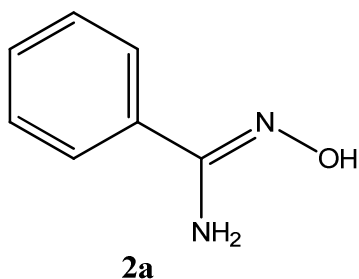
1) Synthesis of Amidoximes [101-104]



General procedure: To a solution of *p*-substituted arynitrile (1 eq.) and triethylamine, Et_3N in ethanol, $\text{NH}_2\text{OH} \cdot \text{HCl}$ (1.5 eq.) was added slowly by

stirring until all of hydroxylamine hydrochloride was dissolved. The mixture was stirred at 80-85 °C for 0.5-24 h. During this time interval, reactions were monitored on TLC plate. When the reaction was finished, the reaction mixture was cooled to RT. When the temperature reduced to RT, white or yellow precipitate form in ethanol mixture. Ethanol was evaporated with a rotary evaporator. Then, water was added to these white or yellow precipitate in remaining ethanol mixture. The resulting precipitate was filtered off and it was washed with a plenty of distilled water. The resulting solid was thoroughly dried under *vacuo*.

Benzamidoxime (2a):



Chemicals used: 3.094 g (30 mmol) benzonitrile (**1a**), 10 ml of triethylamine, 3.132 g (45 mmol) of hydroxylamine hydrochloride (,30 ml of EtOH).

Note: After cooling the reaction mixture to RT, white ppt formation was not observed. After evaporation of most of ethanol from the mixture, white solid was observed, but with addition of water to the remaining part, white solid dissolved. At that time, extraction was done with EtOAc and water only. The organic layer was dried with anhydrous Na₂SO₄.

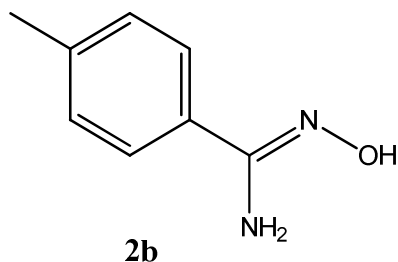
Yield: 2.042 g (50.02%).

M.p. : 74-75 °C.

R_f : 0.425 (2:1 ; EtOAc :n-Hexane).

IR (KBr, v: cm⁻¹): 3454, 3362 (N-H), 1651 (C=N).

4-Methylbenzamidoxime (2b):



Chemicals used: 5.272 g (45 mmol) 4-methylbenzonitrile (**1b**), 15 ml of triethylamine, 4.697 g (67.5mmol) of hydroxylamine hydrochloride, 40 ml of EtOH.

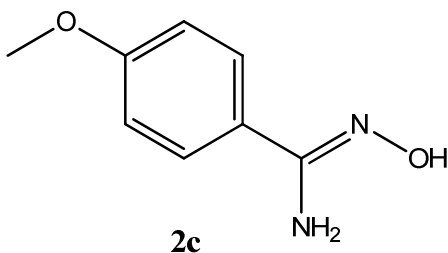
Yield: 5.315 g (78.65%).

M.p. : 145-146 °C.

R_f : 0.325 (1:1 ; EtOAc :n-Hexane).

IR (KBr, v: cm⁻¹): 3500, 3369 (N-H), 1662 (C=N).

4-Methoxybenzamidoxime (2c):



Chemicals used: 3.995 g (30 mmol) 4-methoxybenzonitrile (**1c**), 10 ml of triethylamine, 3.132 g (45 mmol) of hydroxylamine hydrochloride, 30 ml of EtOH.

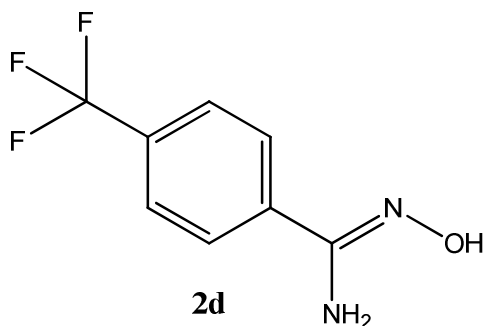
Yield: 3.00 g (60.18%).

M.p. : 118-119 °C.

R_f : 0.125 (1:1 ; EtOAc :n-Hexane).

IR (KBr, ν : cm^{-1}): 3443, 3354 (N–H), 1647 (C=N).

4-Trifluoromethylbenzamidoxime (2d):



Chemicals used: 2.567 g (15 mmol) 4-trifluoromethylbenzonitrile (**1c**), 5 ml of triethylamine, 1.564 g (22.5 mmol) of hydroxylamine hydrochloride, 15 ml of EtOH.

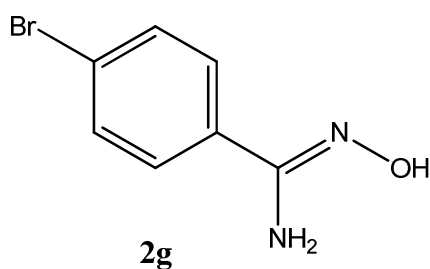
Yield: 2.124g (69.37%).

M.p. : 128-130 °C.

R_f : 0.400 (1:1 ; EtOAc :n-Hexane).

IR (KBr, ν : cm^{-1}): 3489, 3367 (N–H), 1666 (C=N).

4-Bromobenzamidoxime (2g):



Chemicals used: 0.912 g (5 mmol) 4-bromobenzonitrile (**1g**), 1.7 ml of triethylamine, 0.522 g (7.5 mmol) of hydroxylaminehydrochloride, 8 ml of EtOH.

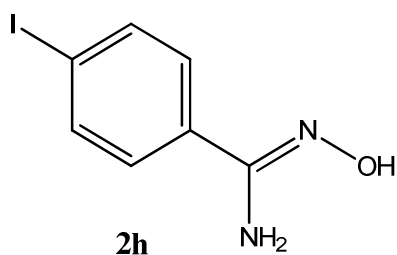
Yield: 0.698 g (64.93%).

M.p. : 139-141 °C.

R_f : 0.450 and 0.200 (1:1 ; EtOAc :n-Hexane).

IR (KBr, v: cm⁻¹): 3473, 3358 (N–H), 1653 (C=N).

4-Iodobenzamidoxime (2h):



Chemicals used: 1.603 g (7 mmol) 4-iodobenzonitrile (**1h**), 2.3 ml of triethylamine, 0.731 g (10.5 mmol) of hydroxylamine hydrochloride, 7 ml of EtOH.

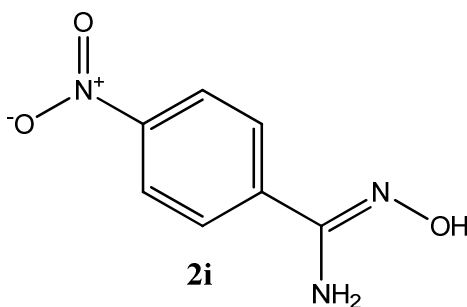
Yield: 1.660g (90.50%).

M.p. : 158-160 °C.

R_f: 0.375 and 0.1875 (1:1 ; EtOAc :n-Hexane)

IR (KBr, v: cm⁻¹): 3483, 3371 (N–H), 1662 (C=N).

4-Nitrobenzamidoxime (2i):



Chemicals used: 4.444 g (30 mmol) 4-nitrobenzonitrile (**1i**), 10 ml of triethylamine, 3.132 g (45 mmol) of hydroxylamine hydrochloride, 30 ml of EtOH.

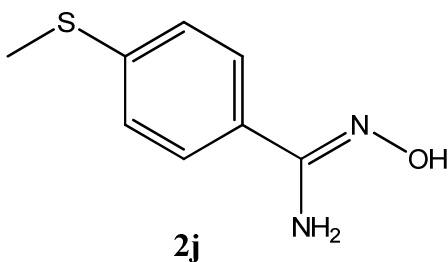
Yield: 4.679g (86.10%)

M.p. : 163-165 °C.

R_f: 0.725 and 0.400 (3:1 ; EtOAc :n-Hexane).

IR (KBr, ν : cm^{-1}): 3462, 3358 (N–H), 1663 (C=N).

4-Methylthiobenzamidoxime (2j):



Chemicals used: 3.730 g (25 mmol) of 4-methylthiobenzonitrile (**1j**), 8.3 ml of triethylamine, 2.610 g (37.5 mmol) of hydroxylamine hydrochloride, 25 ml of EtOH.

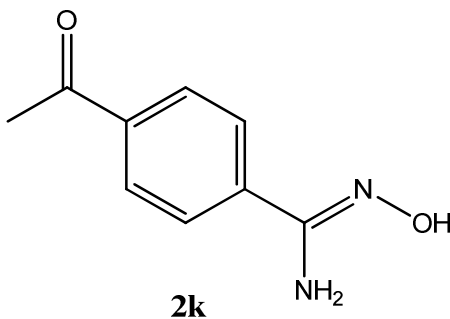
Yield: 4.184 g (91.83%)

M.p. : 125-127 °C

R_f : 0.250 (1:1 ; EtOAc :n-Hexane)

IR (KBr, ν : cm^{-1}): 3476, 3450, 3358(N–H), 1655 (C=N)

4-Acetylbenzamidoxime (2k):



Chemicals used: 1.452 g (10 mmol) 4-acetylbenzonitrile (**1k**), 3.3 ml of triethylamine, 1.044 g (15 mmol) of hydroxylamine hydrochloride, 10 ml of EtOH.

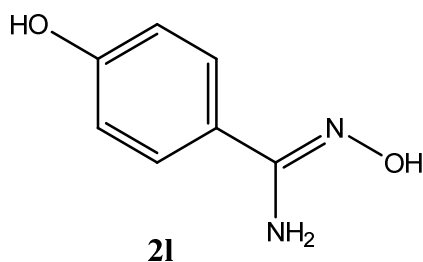
Yield: 1.005 g (50.40%)

M.p. : (197 °C decomposed)

R_f : 0.400 and 0.200 (two spots, possibly, one is the *E* isomer) (3:1; EtOAc:n-Hexane)

IR (KBr, ν : cm⁻¹): 3446, 3365(N-H), 1683 (C=O), 1655 (C=N).

4-Hydroxybenzamidoxime (2l):



Chemicals used: 3.574g (30 mmol) 4-hydroxybenzonitrile (**1l**), 10 ml of triethylamine, 3.132 g (45 mmol) of hydroxylamine hydrochloride, 30 ml of EtOH.

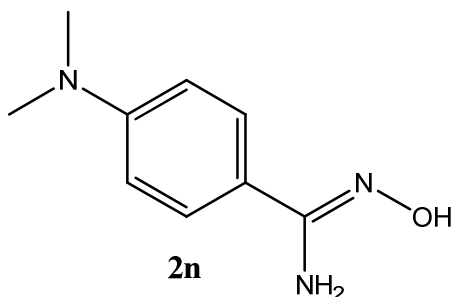
Yield: 1.265g (27.72%)

M.p. : 136-138 °C

R_f : 0.175 (3:1 ; EtOAc :n-Hexane).

IR (KBr, ν : cm⁻¹): 3431, 3365 (N-H), 1643 (C=N).

4-*N,N*-Dimethylaminobenzamidoxime (2n):



Chemicals used: 1.608 g (11.0 mmol) of 4-*N,N*-dimethylaminobenzonitrile (1n), 3.7 ml of triethylamine, 1.147 g (16.5 mmol) of hydroxylamine hydrochloride, 30 ml of EtOH.

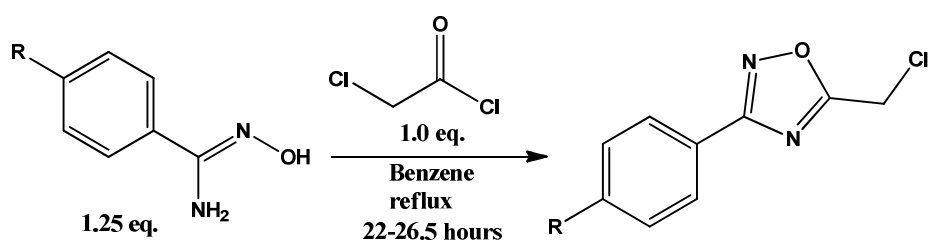
Yield: 0.496 g (25.16%)

M.p. : 127-128°C.

R_f : 0.200 (3:1 ; EtOAc :n-Hexane).

IR (KBr, ν : cm⁻¹): 3505, 3404 (N-H), 3188-2814 (C-H), 1654, 1612(C=N), 1582, 1365.

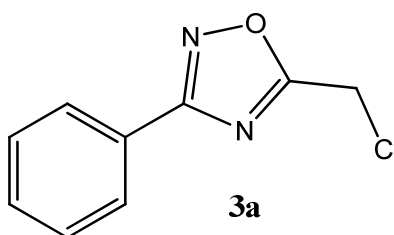
2) Synthesis of 5-(chloromethyl)-3-aryl-1,2,4-oxadiazoles [105]



General procedure: To a solution of 5-(chloromethyl)-3-aryl-1,2,4-oxadiazole (1.25 eq.) in enough benzene, chloroacetyl chloride (1.0 eq.) dissolved in 5 ml of benzene was added slowly by stirring and the mixture was refluxed at 80-85°C. The mixture was stirred for an overnight mixing. After overnight mixing, the temperature was turned off and benzene was

evaporated with a rotary evaporator. The remaining crude was purified with flash column chromatography in silica gel. The final 1,2,4-oxadiazole product was dried under vacuum at the end of purification process. Generally, 5-(chloromethyl)-3-aryl-1,2,4-oxadiazole was obtained as a solid product except for 5-(chloromethyl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (colorless liquid).

5-(Chloromethyl)-3-phenyl-1,2,4-oxadiazole (3a):



Chemicals used: 0.545 g (4.0 mmol) benzamidoxime (**2a**) (136.15 g/mol) in 200ml of benzene, 0.362 g (3.2 mmol) of chloroacetyl chloride in 5 ml of benzene.

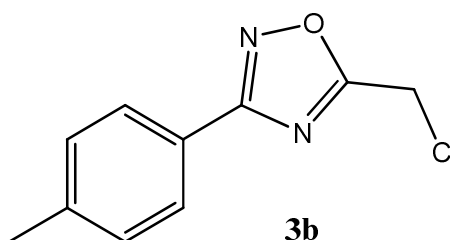
Yield: 529 mg (85.05%).

M.p. : 40-42 °C.

R_f : 0.825 (2:1 ; EtOAc :n-Hexane).

IR (KBr, ν : cm⁻¹): 3069-2967 (C-H), 1597, 1583 (C=N).

5-(Chloromethyl)-3-(*p*-tolyl)-1,2,4-oxadiazole(3b):



Chemicals used: 0.375 g (2.5 mmol) 4-methylbenzamidoxime (**2b**) in 200ml of benzene, 0.226 g (2.0 mmol) of chloroacetyl chloride in 5 ml of benzene.

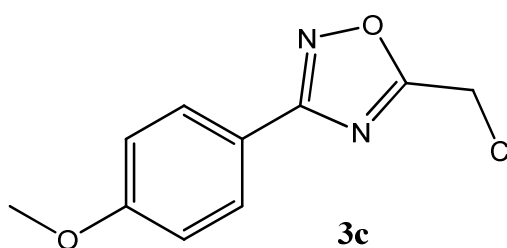
Yield: 298 mg (71.41%)

M.p. : 41-44 °C.

R_f : 0.8125 (1:1 ; EtOAc :n-Hexane).

IR (KBr, ν : cm^{-1}): 3034-2854 (C-H), 1597, 1577 (C=N).

5-(Chloromethyl)-3-(4-methoxyphenyl)-1,2,4-oxadiazole (3c):



Chemicals used: 0.499 g (3 mmol) 4-methoxybenzamidoxime (**2c**) in 115 ml of benzene, 0.271 g (2.4 mmol) of chloroacetyl chloride in 5 ml of benzene.

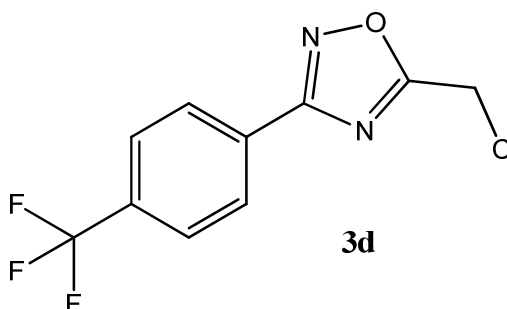
Yield: 448 mg (83.1%).

M.p. : 40-41 °C.

R_f : 0.8125 (1:1 ; EtOAc :n-Hexane).

IR (KBr, ν : cm^{-1}): 3020-2841 (C-H), 1612, 1597, 1573 (C=N).

5-(Chloromethyl)-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (3d):



Chemicals used: 0.510 g (2.5 mmol) of 4-trifluoromethylbenzamidoxime (**2d**) in 90 ml of benzene, 0.226 g (2.0 mmol) of chloroacetyl chloride in 5 ml of benzene.

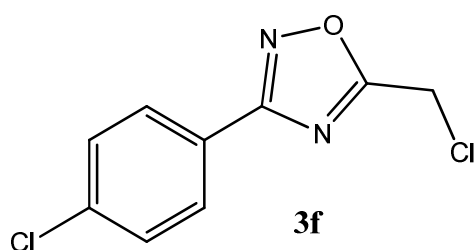
Yield: 380 mg (72.4%).

Nature of product: colorless oil.

R_f: 0.850 (2:1 ; EtOAc : n-Hexane).

IR (KBr, ν : cm^{-1}): 1597, 1577 (C=N).

5-(Chloromethyl)-3-(4-chlorophenyl)-1,2,4-oxadiazole (3f) :



Chemicals used: 0.342 g (2.0 mmol) of 4-chlorobenzamidoxime (**2f**) dissolved in 50 ml of benzene, 0.110 g (0.974 mmol) of chloroacetyl chloride dissolved in 5 ml of benzene.

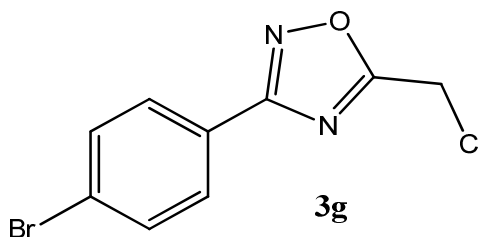
Yield: 194 mg (86.95%)

M.p. : 60-61 °C.

R_f: 0.725 (1:1 ; EtOAc :n-Hexane).

IR (KBr, ν : cm^{-1}): 3020-2972 (C-H), 1591,1568 (C=N).

3-(4-Bromophenyl)-5-(chloromethyl)-1,2,4-oxadiazole (3g):



Chemicals used: 0.538 g (2.5mmol) of 4-bromobenzamidoxime (**2g**) dissolved in 150 ml of benzene, 0.266 g (2.0 mmol) of chloroacetyl chloride dissolved in 5 ml of benzene.

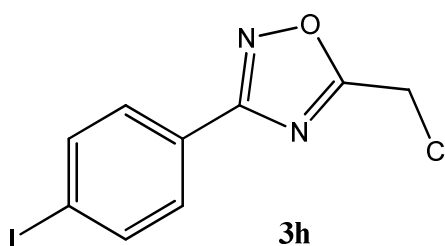
Yield: 545 mg (99.63%)

M.p. : 61-62°C

R_f : 0.800 (1:1 ; EtOAc :n-Hexane)

IR (KBr, v: cm⁻¹): 3020-2970 (C-H), 1600, 1589,1566 (C=N)

5-(Chloromethyl)-3-(4-iodophenyl)-1,2,4-oxadiazole (3h**):**



Chemicals used: 0.524 g (2.0 mmol) of 4-iodobenzamidoxime (**2h**) dissolved in 200 ml of benzene, 0.181 g (1.6 mmol) of chloroacetyl chloride dissolved in 5 ml of benzene.

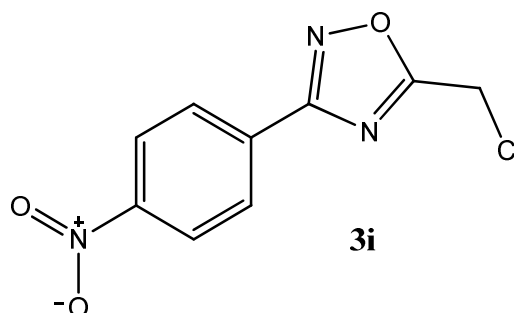
Yield: 510 mg (99.45%).

M.p. : 71-73°C.

R_f : 0.825 (1:1 ; EtOAc :n-Hexane).

IR (KBr, v: cm⁻¹): 3069-2987 (C-H), 1595, 1560 (C=N).

5-(Chloromethyl)-3-(4-nitrophenyl)-1,2,4-oxadiazole (3i**):**



Chemicals used: 0.544 g (3.0 mmol) of 4-nitrobenzaminoxime (**2i**) dissolved in 275 ml of benzene, 0.271 g (2.4 mmol) of chloroacetyl chloride dissolved in 5 ml of benzene.

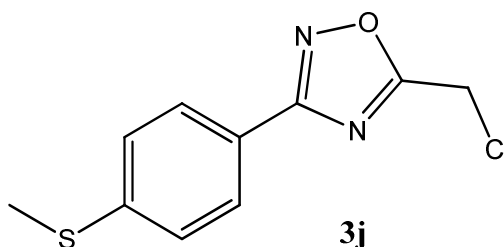
Yield: 356 mg (61.90%).

M.p. : 89-90 °C.

R_f : 0.775 (2:1 ; EtOAc :n-Hexane).

IR (KBr, ν : cm⁻¹): 3099-2960 (C-H), 1612, 1578 (C=N).

5-(Chloromethyl)-3-(4-(methylthio)phenyl)-1,2,4-oxadiazole (3j):



Chemicals used: 0.547 g (3.0 mmol) of 4-methylthiobenzaminoxime (**2i**) dissolved in 225 ml of benzene, 0.271 g (2.4 mmol) of chloroacetyl chloride dissolved in 5 ml of benzene.

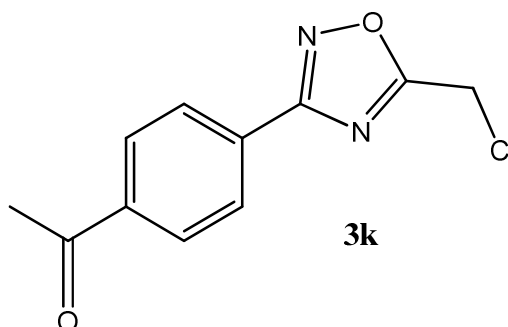
Yield: 412 mg (71.32%).

M.p. : 69-70 °C.

R_f : 0.800 (2:1 ; EtOAc :n-Hexane).

IR (KBr, ν : cm⁻¹): 3020-2918 (C-H), 1595, 1556 (C=N).

3-(4-Acetylphenyl)-5-chloromethyl-1,2,4-oxadiazole (3k):



Chemicals used: 0.535 g (3.0 mmol) of 4-acetylbenzamidoxime (**2k**) dissolved in 215 ml of benzene, 0.271 g (2.4 mmol) of chloroacetyl chloride dissolved in 5 ml of benzene.

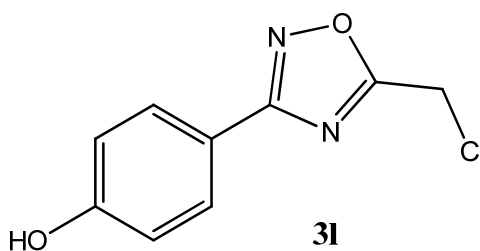
Yield: 370 mg (65.15%).

M.p. : 112-124 °C.

R_f : 0.800 (3:1 ; EtOAc :n-Hexane).

IR (KBr, ν: cm⁻¹): 1680 (C=O), 1595,1566 (C=N).

3-(4-Hydroxyphenyl)-5-(chloromethyl)-1,2,4-oxadiazole (3l):



Chemicals used: 0.457g (3.0mmol) of 4-hydroxylbenzamidoxime (**2l**) dissolved in 300 ml of benzene, 0.271g (2.4 mmol) of chloroacetylchloride dissolved in 5 ml of benzene.

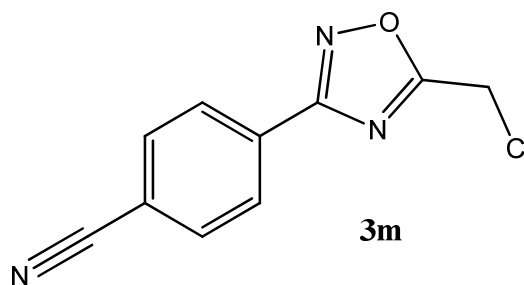
Yield: 244 mg (48.27%).

M.p. : 113-115 °C.

R_f : 0.625 (2:1 ; EtOAc :n-Hexane).

IR (KBr, ν : cm⁻¹): 3281 (O-H, phenol) 3084-2941 (C-H), 1612, 1597,1578 (C=N).

3-(4-Cyanophenyl-5-(chloromethyl)-1,2,4-oxadiazole (3m):



Chemicals used: 0.322 g (2.0 mmol) of 4-cyanobenzamidoxime (**2m**) dissolved in 200 ml of benzene, 0.181g (1.6 mmol) of chloroacetyl chloride dissolved in 5 ml of benzene.

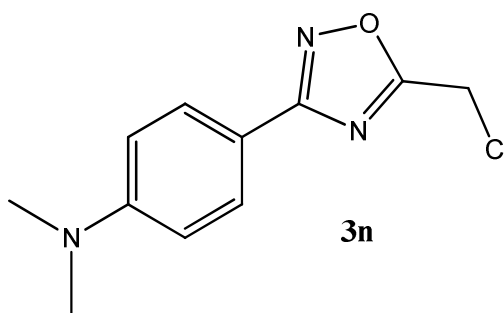
Yield: 53 mg (15.08%)

M.p. : 80-82°C

R_f : 0.775 (1:1 ; EtOAc :n-Hexane)

IR (KBr, ν : cm⁻¹): 3099-2848 (C-H), 2233 (C≡N), 1595,1550 (C=N).

(5-Chloromethyl)-3-(4-*N,N*-dimethylaminophenyl)-1,2,4-oxadiazole (3n):



Chemicals used: 0.448 g (2.50 mmol) of 4-*N,N*-dimethylaminobenzamidoxime (**2n**) dissolved in 225 ml of benzene, 0.226 g (2.0 mmol) of chloroacetylchloride dissolved in 5 ml of benzene.

Yield: 139 mg (29. 24%)

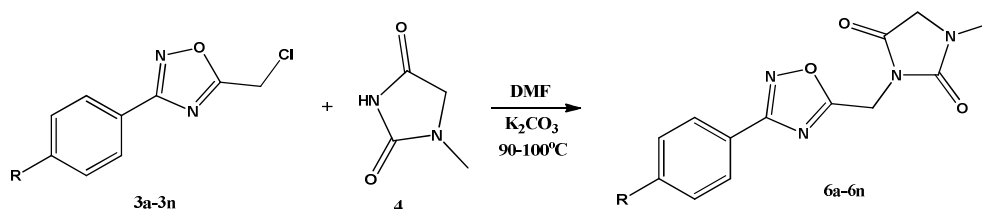
M.p. : 63-66 °C

R_f : 0.775 (2:1 ; EtOAc : n-Hexane)

IR (KBr, ν : cm⁻¹): 3010-2816 (C-H), 1608 (C=N)

Unexpected peak observed in IR at 2212 cm⁻¹ (It is possibly related to trace of starting nitrile used for obtaining amidoxime).

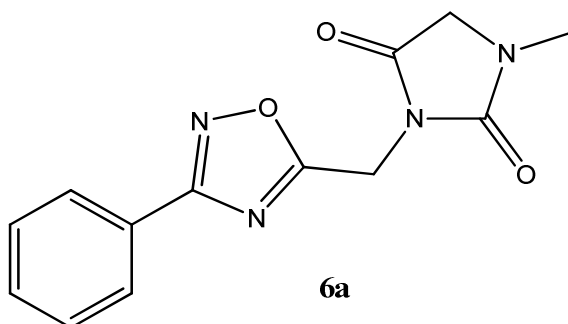
3) Synthesis of 3-(4-substituted phenyl-1,2,4-oxadiazolyl-5-methyl)-1-methylimidazolidine-2,4-diones (6a-n)



General procedure:

1-Methylhydantoin (1-methylimidazolidine-2,4-dione) **4** (1eq.), 5-(chloromethyl)-3-aryl-1,2,4-oxadiazole **3** (1eq.) and K₂CO₃ (1eq.) were mixed at 90-100 °C in DMF for 15-60 min. The reaction was monitored on TLC. After the reaction was ended, the temperature of reaction mixture was reduced to room temperature. In order to remove DMF, water was added to the mixture and it was extracted with DCM. The organic layer was dried over Na₂SO₄. The solvent was removed under reduced pressure and the remaining residue was purified by flash column chromatography (silica gel)

1-Methyl-3-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)imidazolidine-2,4-dione (6a):



Chemicals used: 0.25mmol (49 mg) of 5-(chloromethyl)-3-phenyl-1,2,4-oxadiazole (**3a**), 0,25 mmol (29 mg) of 1-methylhydantoin **4** and 0,25mmol (35 mg) of potassium carbonate (K_2CO_3) in 2 ml of DMF.

Eluent used in column chromatography: 1:2, 1:1, 2:1 (EtOAc: PB).

Yield: 39 mg (57.35%)

M.p. : 97-99 °C

R_f : 0.300 (2:1 ; EtOAc :PB)

Nature of product: white solid

Molecular formula: $C_{13}H_{12}N_4O_3$

Molecular weight: 272.26

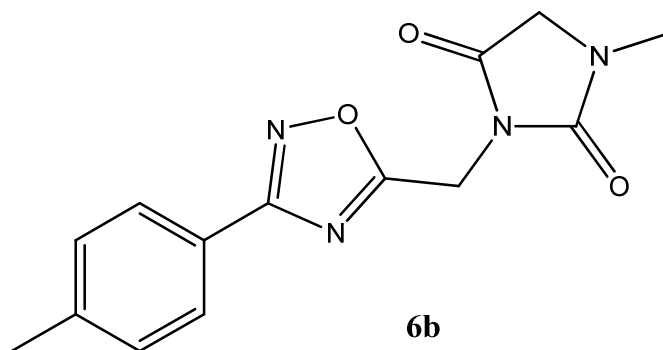
IR (KBr, ν : cm^{-1}): 3076-2852 (C-H stretching), 1780 (C=O), 1724 (C=O), 1595, 1570.

^1H NMR, δ_H ($CDCl_3$, 400 MHz): 8.04-8.01 (2H, dd, J = 7.6, 1.2 Hz), 7.48-7.42 (3H, m), 4.97 (2H, s, oxadiazolylmethyl), 4.00 (2H, s, imidazolidine CH_2), 3.40 (3H, s).

^{13}C NMR, δ_C ($CDCl_3$, 100 MHz): 173.67 (C=O), 168.99 (C=O), 168.84 (C=N), 155.45 (C=N), 131.59, 129.03, 127.79, 126.49, 77.59, 52.06, 34.80, 30.07.

LC-MS (m/z,%): 273.7 (M+H, 100).

1-Methyl-3-((3-(*p*-tolyl)-1,2,4-oxadiazol-5-yl)methyl)imidazolidine-2,4-dione (6b):



Chemicals used: 0.25 mmol (52 mg) of 5-(chloromethyl)-3-(*p*-tolyl)-1,2,4-oxadiazole (**3b**), 0.25 mmol (29 mg) of 1-methylhydantoin **4** and 0.25 mmol (35 mg) of potassium carbonate (K₂CO₃) in 2 ml of DMF.

Eluent used in column chromatography: 1:2, 1:1, 2:1 (EtOAc: PB)

Yield: 64 mg (89.42%)

M.p. : 109-110 °C

R_f : 0.175 (1:1 ; EtOAc :n-Hexane)

Nature of product: white solid

Molecular formula: C₁₄H₁₄N₄O₃

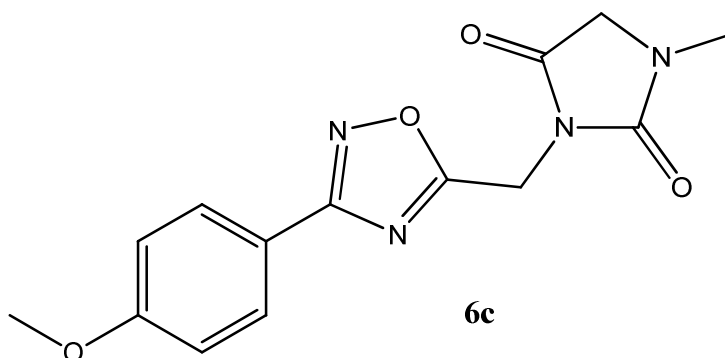
Molecular weight: 286.29

IR (KBr, ν: cm⁻¹): 2962, 2920-2856 (C-H stretching), 1784(C=O), 1709 (C=O), 1601 (C=N).

¹H NMR, δ_H (CDCl₃, 300 MHz): 7.93 (2H,d,*J* = 6.1 Hz), 7.27 (2H,s), 4.97 (2H,s), 4.02 (2H,s), 3.06 (3H,s), 2.40 (3H,s).

^{13}C NMR, δ_{C} (CDCl_3 , 75 MHz): 173.47 (C=O), 169.00 (C=N), 168.85 (C=O), 155.48 (C=N), 141.95, 129.74, 127.73, 123.68, 52.07, 34.82, 30.07, 21.78.
LC-MS (m/z , %): 287.8 ($\text{M}+\text{H}$, 100).

3-((3-(4-Methoxyphenyl)-1,2,4-oxadiazol-5-yl)methyl)-1-methylimidazolidine-2,4-dione (6c):



Chemicals used: 0.25 mmol (56 mg) of 5-(chloromethyl)-3-(4-methoxyphenyl)-1,2,4-oxadiazole (**3c**), 0.25 mmol (29 mg) of 1-methylhydantoin **4** and 0,25 mmol (35 mg) of potassium carbonate (K_2CO_3) in 2 ml of DMF.

Eluent used in column chromatography: 1:1, 2:1 (EtOAc: PB)

Yield: 72 mg (95.30%)

M.p. : 136-137°C

R_f : 0.1875 (2:1 ; EtOAc :PB)

Nature of product: white solid

Molecular formula: $\text{C}_{14}\text{H}_{14}\text{N}_4\text{O}_4$

Molecular weight: 302.29

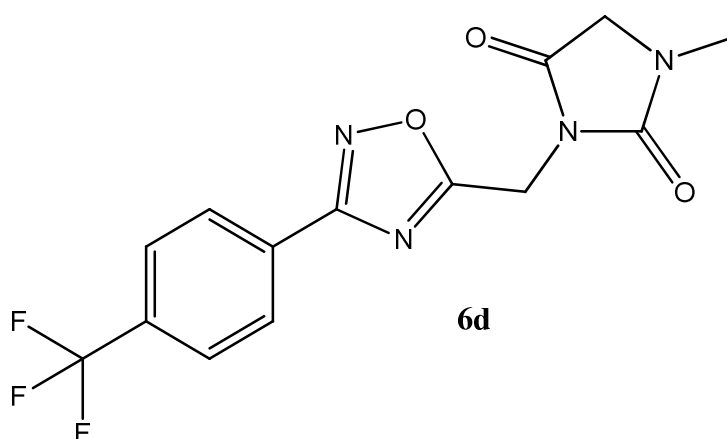
IR (KBr, ν : cm^{-1}): 2962, 2920-2856 (C-H stretching), 1780, 1763 (C=O), 1720, 1713 (C=O), 1612 (C=N), 1595, 1574

^1H NMR, δ_{H} (CDCl_3 , 400 MHz): 7.95 (2H,d, $J = 9.2$ Hz), 6.95 (2H,d, $J = 8.8$ Hz), 4.94 (2H,s), 4.00 (2H,s), 3.83 (3H,s, OCH_3), 3.04 (3H,s, NCH_3).

^{13}C NMR, δ_{C} (CDCl_3 , 100 MHz): 173.34 ($\text{C}=\text{O}$), 169.00 ($\text{C}=\text{N}$), 168.53 ($\text{C}=\text{N}$), 162.25, 155.47 ($\text{C}=\text{O}$), 129.42, 118.94, 114.41, 55.59 (OCH_3), 52.05, 34.80, 30.06.

LC-MS (m/z , %): 303.8 ($\text{M}+\text{H}$, 100).

1-Methyl-3-((3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)methyl)imidazolidine-2,4-dione (6d):



Chemicals used: 0.25 mmol (66 mg) of 5-(chloromethyl)-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (**3d**) 0.25 mmol (29 mg) of 1-methylhydantoin **4** and 0.25 mmol (35 mg) of potassium carbonate (K_2CO_3) in 2 ml of DMF.

Eluent used in column chromatography: 1:2, 1:1, 2:1 (EtOAc: PB)

Yield: 27 mg (31.74%)

M.p. : 105-106 °C

R_f : 0.275 (2:1 ; EtOAc :PB)

Nature of product: white solid

Molecular formula: : C₁₄H₁₁F₃N₄O₃

Molecular weight: 340.26

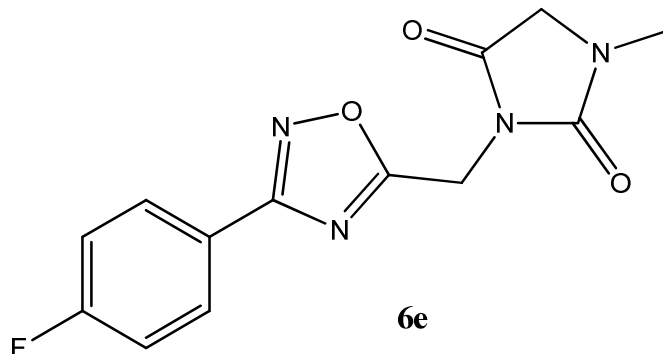
IR (KBr, ν : cm⁻¹): 2970-2854 (C-H stretching), 1782, (C=O), 1736, 1720, 1709 (C=O), 1624 (C=N), 1595, 1574, 1541.

¹H NMR, δ_{H} (CDCl₃, 400 MHz): 8.15 (2H,d, J = 8.0 Hz), 7.70 (2H,d, J = 8.0 Hz), 4.99 (2H,s), 4.03 (2H,s), 3.06 (3H,s).

¹³C NMR, δ_{C} (CDCl₃, 100 MHz): 174.23 (C=O), 168.93 (C=N), 167.86, 155.38 (C=O), 133.78, 133.45, 133.13, 132.80, 129.88, 128.17, 126.09, 126.05, 126.01, 125.97, 125.28, 122.57, 52.07, 34.77, 30.10.

LC-MS (m/z , %): 341.8 (M+H, 100).

3-((3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-1-methylimidazolidine-2,4-dione (6e):



Chemicals used: 0.320 mmol (68 mg) of 5-(chloromethyl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (**3e**), 0.320 mmol (37 mg) of 1-methylhydantoin **4** and 0.320 mmol (44 mg) of potassium carbonate (K₂CO₃) in 2 ml of DMF.

Eluent used in column chromatography: 1:2, 1:1, 2:1 (EtOAc:n-Hexane)

Yield: 83 mg (89.36%)

M.p. : 91-92°C

R_f : 0.125 (1:1 ; EtOAc :n-Hexane)

Nature of product: white solid

Molecular formula: C₁₃H₁₁FN₄O₃

Molecular weight: 290.25

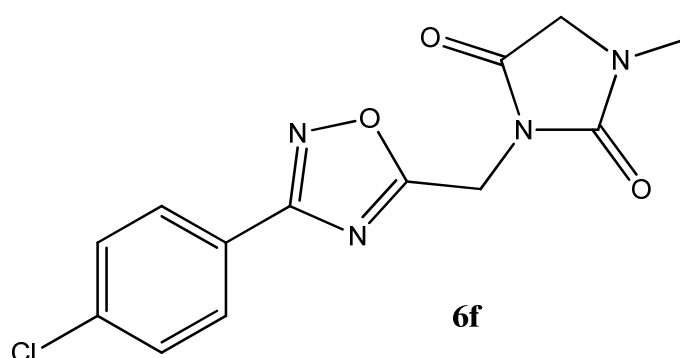
IR (KBr, v: cm⁻¹): 3096-2880 (C-H stretching), 1767(C=O), 1728, 1720, 1709 (C=O), 1607 (C=N), 1586.

¹H NMR, δ_H (CDCl₃, 300 MHz): 8.06-8.02 (2H, m, strong multiplicity due to fluorine), 7.17-7.11(2H,m, strong multiplicity due to fluorine), 4.98 (2H,s), 4.03 (2H,s), 3.07 (3H,s).

¹³C NMR, δ_C (CDCl₃, 75 MHz): 173.81 (C=O), 168.99 (C=N),168.02 (C=N),166.55, 163.21, 155.44 (C=O), 130.06, 129.94, 122.75,122.71, 116.40, 116.11, 52.07, 34.77, 30.08.

LC-MS (m/z,%): 291.8 (M+H, 100).

3-((3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-1-methylimidazolidine-2,4-dione (6f):



Chemicals used: 0.367 mmol (84 mg) of 5-(chloromethyl)-3-(4-chlorophenyl)-1,2,4-oxadiazole (**3f**), 0.367 mmol (42 mg) of 1-

methylhydantoin **4** and 0.367mmol (51 mg) of potassium carbonate (K_2CO_3) in 2 ml of DMF.

Eluent used in column chromatography: 1:1, 2:1 (EtOAc: n-Hexane)

Yield: 95 mg (84.47%)

M.p. : 103-104 °C

R_f : 0.150 (1:1 ; EtOAc : n-Hexane)

Nature of product: white solid

Molecular formula: $C_{13}H_{11}ClN_4O_3$

Molecular weight: 306.70

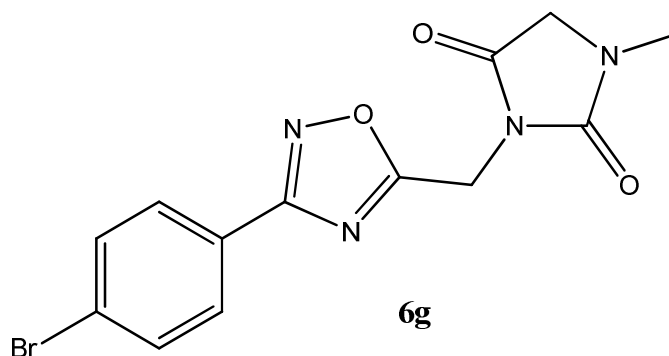
IR (KBr, ν : cm^{-1}): 3086-2922 (C-H stretching), 1784 (C=O), 1711 (C=O), 1597 (C=N), 1569.

^1H NMR, δ_H ($CDCl_3$, 300 MHz): 7.98 (2H,d, J = 6.6 Hz), 7.43 (2H,d, J = 6.6 Hz), 4.98 (2H,s), 4.03 (2H,s), 3.06 (3H,s).

^{13}C NMR, δ_C ($CDCl_3$, 75 MHz): 173.93 (C=O), 168.96 (C=O), 168.06 (C=N), 155.42 (C=O), 137.77, 129.38, 129.12, 124.99, 52.07, 34.77, 30.09.

MS (m/z , %): 307.8 ($M+H$, 100).

3-((3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl)methyl)-1-methylimidazolidine-2,4-dione (6g):



Chemicals used: 0.256mmol (70 mg) of 3-(4-bromophenyl)-5-(chloromethyl)-1,2,4-oxadiazole (**3g**), 0.256 mmol (33 mg) of 1-methylhydantoin **4** and 0.256 mmol (36 mg) of potassium carbonate (K_2CO_3) in 2 ml of DMF.

Eluent used in column chromatography: 1:1, 2:1 (EtOAc: PB)

Yield: 77 mg (85.65%)

M.p. : 107-108 °C

R_f : 0.325 (2:1 ; EtOAc : n-Hexane)

Nature of product: white solid

Molecular formula: $C_{13}H_{11}BrN_4O_3$

Molecular weight: 351,16

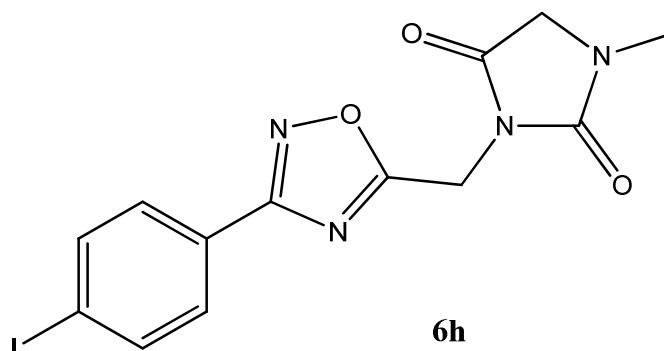
IR (KBr, ν : cm^{-1}): 3078-2852 (C-H stretching), 1784 (C=O), 1705 (C=O), 1595 (C=N), 1568.

^1H NMR, δ_H ($CDCl_3$, 400 MHz): 7.90 (2H, d, J = 8.4 Hz), 7.59-7.57 (2H, d, J = 8.8 Hz), 4.97 (2H, s), 4.02 (2H, s), 3.05 (3H, s).

^{13}C NMR, δ_C ($CDCl_3$, 100 MHz): 173.93, 168.95, 168.15, 155.39, 132.34, 129.29, 126.20, 125.42, 52.06, 34.77, 30.10.

LC-MS (m/z , %): 353.7 ($M+2$, 100), 351.7 (M^+ , 83.03%) 321.8 (24.85%) .

3-((3-(4-Iodophenyl)-1,2,4-oxadiazol-5-yl)methyl)-1-methylimidazolidine-2,4-dione (6h):



Chemicals used: 0.25mmol (80 mg) of 5-(chloromethyl)-3-(4-iodophenyl)-1,2,4-oxadiazole (**3h**), 0,25 mmol (29 mg) of 1-methylhydantoin **4** and 0,25 mmol (35 mg) of potassium carbonate (K_2CO_3) in 2 ml of DMF.

Eluent used in column chromatography: 1:1, 2:1 (EtOAc : PB)

Yield: 92 mg (95.83%)

M.p. : 137-139°C

R_f : 0.350 (2:1 ; EtOAc : n-Hexane)

Nature of product: white solid

Molecular formula: $C_{13}H_{11}IN_4O_3$

Molecular weight: 398.16

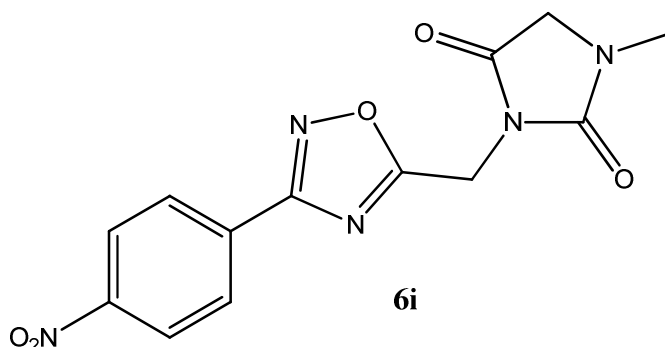
IR (KBr, ν : cm^{-1}): 2953-2853 (C-H stretching), 1788 (C=O), 1720,1712 (C=O), 1593(C=N),1560

^1H NMR, δ_H ($CDCl_3$, 400 MHz): 7.80 (2H,d, J = 8.4 Hz), 7.75 (2H, d, J = 8.4 Hz), 4.97 (2H,s), 4.03 (2H,s), 3.06 (3H,s).

^{13}C NMR, δ_C ($CDCl_3$, 100 MHz): 173.91, 168.95, 155.40, 138.30, 129.29, 125.99, 98.41 (C-I), 52.07, 34.77, 30.11.

LC-MS (m/z ,%): 399.7 ($M+H$, 100).

1-Methyl-3-((3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl)methyl)imidazolidine-2,4-dione (6i):



Chemicals used: 0.25 mmol (60 mg) of 5-(chloromethyl)-3-(4-nitrophenyl)-1,2,4-oxadiazole (**3i**), 0,25 mmol (29 mg) of 1-methylhydantoin **4** and 0.25 mmol (35 mg) of potassium carbonate (K_2CO_3) in 2 ml of DMF.

Eluent used in column chromatography: 1:1, 2:1 (EtOAc : PB)

Yield: 62 mg (78.17%)

M.p. : 140-142 °C

R_f : 0.250 (2:1 ; EtOAc : n-Hexane)

Nature of product: yellow solid

Molecular formula: $C_{13}H_{11}N_5O_5$

Molecular weight: 317.26

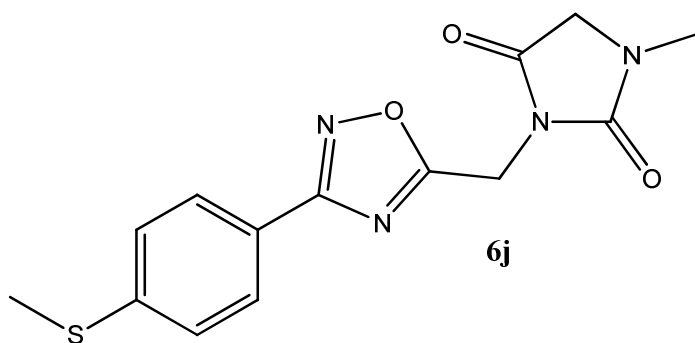
IR (KBr, ν : cm^{-1}): 3099-2854 (C-H stretching), 1776 (C=O), 1708 (C=O), 1610 (C=N, weak), 1580, 1529, 1518.

^1H NMR, δ_H ($CDCl_3$, 400 MHz): 8.32 (2H,d, J = 9.2 Hz), 8.24 (2H,d, J = 9.2 Hz), 5.02 (2H,s), 4.06 (2H,s), 3.09 (3H,s).

^{13}C NMR, δ_C ($CDCl_3$, 100 MHz): 174.64 (C=O), 168.95 (C=N), 167.31 (C=N), 155.34 (C=O), 149.77, 132.33, 128.82, 124.29, 52.09, 34.75, 30.12.

LC-MS (m/z,%): 318.4 (M+H, 100), 183.4 (62.58), 319.9 (53.37), 293.9 (49.69), 192.5 (44.79), 241.9 (42.94).

1-Methyl-3-((3-(4-(methylthio)phenyl)-1,2,4-oxadiazol-5-yl)methyl)imidazolidine-2,4-dione (6j):



Chemicals used: 0.25mmol (60 mg) of 5-(chloromethyl)-3-(4-(methylthio)phenyl)-1,2,4-oxadiazole (**3j**), 0,25 mmol (29 mg) of 1-methylhydantoin **4** and 0.25 mmol (35 mg) of potassium carbonate (K₂CO₃) in 2 ml of DMF.

Eluent used in column chromatography: 1:1, 2:1 (EtOAc : PB)

Yield: 76 mg (%)

M.p. : 126-128°C

R_f : 0.250 (2:1 ; EtOAc : n-Hexane)

Nature of product: white solid

Molecular formula: C₁₄H₁₄N₄O₃S

Molecular weight: 318.35

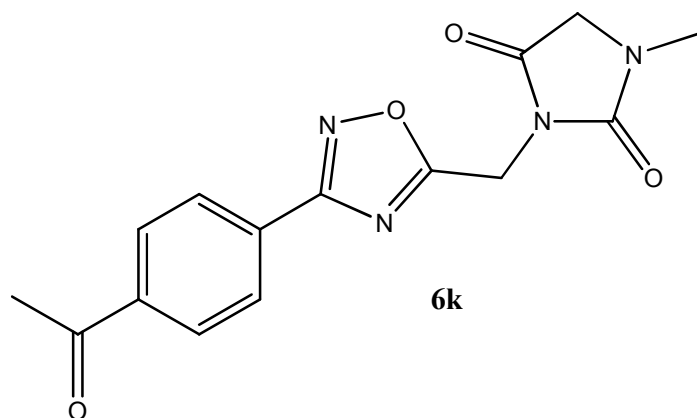
IR (KBr, v: cm⁻¹): 3001-2876 (C-H stretching), 1776 (C=O), 1724, 1712 (C=O), 1593 (C=N), 1557.

^1H NMR, δ_{H} (CDCl_3 , 400 MHz): 7.91 (2H,d, J = 8.4 Hz), 7.26 (2H,d, J = 8.8 Hz), 4.96 (2H,s), 4.01 (2H,s), 3.04 (3H,s, NCH_3), 2.50 (3H,s, SCH_3).

^{13}C NMR, δ_{C} (CDCl_3 , 100 MHz): 173.55 (C=O), 168.99 (C=N), 168.51 (C=N), 155.44 (C=O), 143.40, 128.04, 125.95, 122.73, 52.056, 34.80, 30.08, 15.27.

LC-MS (m/z , %): 319.7 ($\text{M}+\text{H}$, 42.33), 168.6 (16.56), 155.1 (100).

3-((3-(4-Acetylphenyl)-1,2,4-oxadiazol-5-yl)methyl)-1-methylimidazolidine-2,4-dione (6k):



Chemicals used: 0.25 mmol (59 mg) of 1-(4-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)phenyl)ethanone (**3k**), 0,25 mmol (29 mg) of 1-methylhydantoin (**4**) and 0.25 mmol (35 mg) of potassium carbonate (K_2CO_3) in 2 ml of DMF.

Eluent used in column chromatography: 1:1, 2:1 (EtOAc : PB)

Yield: 61 mg (77.63%)

M.p. : 148-150°C

R_f : 0.175 (2:1 ; EtOAc : PB)

Nature of product: white solid

Molecular formula: $\text{C}_{15}\text{H}_{14}\text{N}_4\text{O}_4$

Molecular weight: 314.30

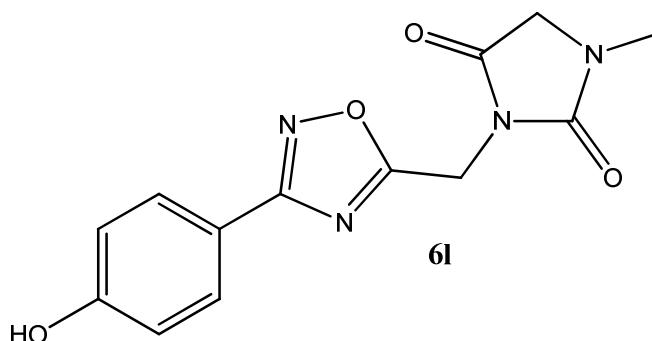
IR (KBr, ν : cm^{-1}): 3010-2854 (C-H stretching, weak), 1784, (C=O), 1724 (C=O), 1681 (C=O, acetyl), 1591 (C=N).

^1H NMR, δ_{H} (CDCl_3 , 400 MHz): 8.12 (2H, d, $J = 8.4$ Hz), 8.01 (2H, d, $J = 8.4$ Hz), 7.70 (1H, d, $J = 8.8$ Hz), 4.98 (2H, s), 4.02 (2H, s), 3.05 (3H, s), 2.62 (2H, s).

^{13}C NMR, δ_{C} (CDCl_3 , 100 MHz): 197.67 (C=O), 174.14 (C=O), 173.77, 169.01, 168.09, 155.46 (C=O), 52.07, 34.78, 30.09, 26.99.

LC-MS (m/z , %): 371.9 (100), 330.8 (80), 371.6 (60), 331.1 (36), 315.6 (8).

3-((3-(4-Hydroxyphenyl)-1,2,4-oxadiazol-5-yl)methyl)-1-methylimidazolidine-2,4-dione (6l):



Chemicals used: 0.25 mmol (53 mg) of 4-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)phenol (**3l**), 0.25 mmol (29 mg) of 1-methylhydantoin (**4**) and 0.25 mmol (35 mg) of potassium carbonate (K_2CO_3) in 2 ml of DMF.

Eluent used in column chromatography: 1:1, 2:1 (EtOAc : PB)

Yield: 33 mg (45.79%)

M.p. : 155-157°C

R_f : 0.150 (2:1 ; EtOAc : n-Hexane)

Nature of product: white solid

Molecular formula: C₁₃H₁₂N₄O₄

Molecular weight: 288.26

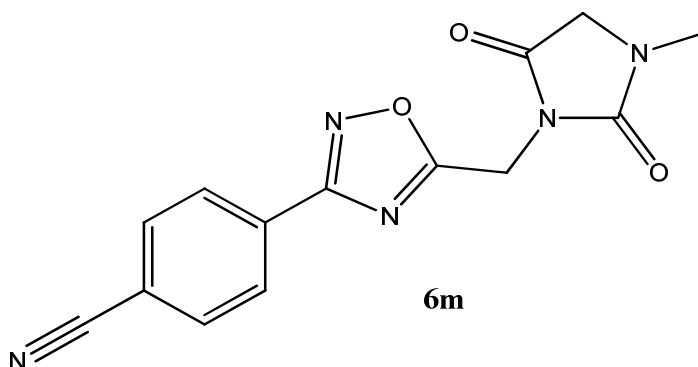
IR (KBr, ν : cm⁻¹): 3315 (O-H), 2955-2924 (C-H stretching, weak), 1784, 1784 (C=O), 1614, 1585 (C=N).

¹H NMR, δ_H (DMSO-*d*₆, 400 MHz): 10.16 (1H, s, OH), 7.97-7.79 (2H, m), 6.93-6.90 (2H, m), 4.95 (2H, s), 4.13 (2H, s), 2.90 (3H, s).

¹³C NMR, δ_C (DMSO-*d*₆, 100 MHz): 174.82 (C=O), 174.76, 174.42, 169.60 (C=N), 167.55, 167.20, 160.39, 159.71, 155.13 (C=O), 128.82, 128.78, 116.26, 115.96, 115.91, 115.47, 51.35, 40.05, 34.08, 29.21.

LC-MS (m/z,%): 289.9 (M+H, 40), 155.3 (100), 155.7 (73).

3-((3-(4-Cyanophenyl)-1,2,4-oxadiazol-5-yl)methyl)-1-methylimidazolidine-2,4-dione (6m):



Chemicals used: 0.15 mmol (33 mg) of 4-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)benzonitrile (**3m**), 0.15 mmol (17 mg) of 1-methylhydantoin (**4**) and 0.15 mmol (20 mg) of potassium carbonate (K₂CO₃) in 1.5 ml of DMF.

Eluent used in column chromatography: 1:1, 2:1 (EtOAc : PB)

Yield: 22 mg (49.34%)

M.p. : 160-161 °C

R_f : 0.250 (2:1 ; EtOAc : n-Hexane)

Nature of product: yellow solid

Molecular formula: C₁₄H₁₁N₅O₃

Molecular weight: 297.27

IR (KBr, ν: cm⁻¹): 2960-2872 (C-H stretching), 2229 (C≡N), 1766,1712 (C=O), 1589 (C=N, weak).

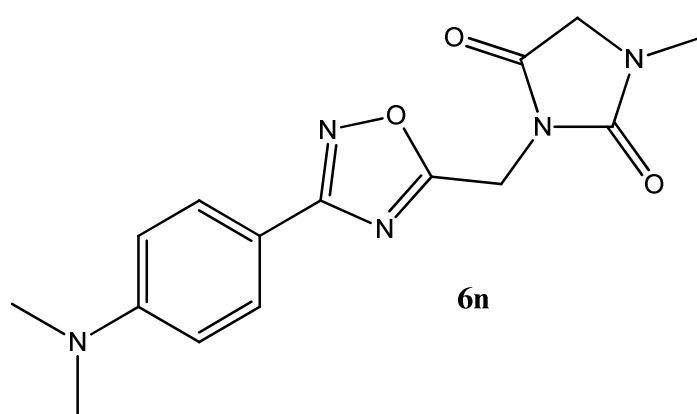
¹H NMR, δ_H (CDCl₃, 400 MHz): 8.17 (2H,d,*J* = 8.4 Hz), 7.76 (2H,d, *J* = 8.0 Hz), 5.00 (2H,s), 4.04 (2H,s), 3.08 (3H,s).

¹³C NMR, δ_C (CDCl₃, 100 MHz): 174.49 (C=O), 168.94 (C=N), 167.56 (C=N), 155.35 (C=O), 132.85, 130.66, 128.38, 118.38, 52.09, 34.77, 30.13.

LC-MS (ES⁻) (m/z,%): 296.9 (M-1, 86), 193.6 (100), 193.8 (63).

LC-MS (ES⁺) (m/z,%): 298.9 (100), 218.0 (95), 217.8 (78), 229.7 (58).

3-((3-(4-(Dimethylamino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)-1-methylimidazolidine-2,4-dione (6n):



Chemicals used: 0.25 mmol (59 mg) of 3-(4-*N,N*-dimethylamino)-5-chloromethyl-1,2,4-oxadiazole (**3n**), 0,25 mmol (29 mg) of 1-methylhydantoin (**4**) and 0.25 mmol (35 mg) of potassium carbonate (K₂CO₃) in 2 ml of DMF.

Eluent used in column chromatography: 2:1, 3:1 (EtOAc : PB)

Yield: 23 mg (29.18%)

M.p. : 158-160 °C

R_f : 0.200 (2:1 ; EtOAc :n-Hexane)

Nature of product: Pale yellow solid.

Molecular formula: C₁₅H₁₇N₅O₃

Molecular weight: 315.33

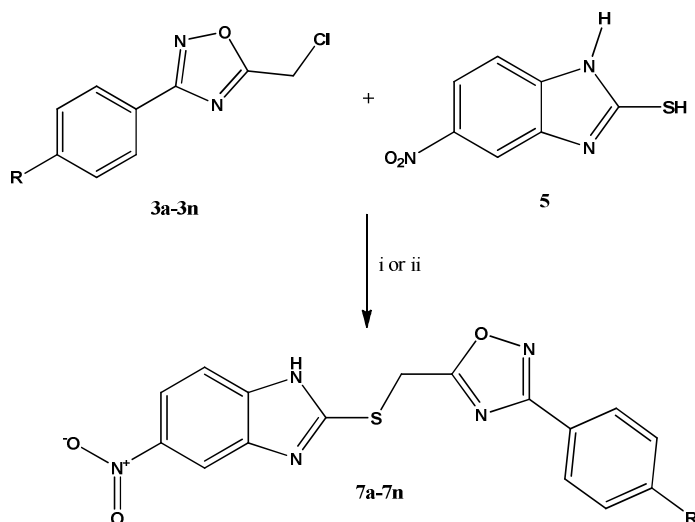
IR (KBr, ν : cm⁻¹): 2926-2816 (C-H stretching), 1776, 1708 (C=O), 1618, 1602 (C=N).

¹H NMR, δ_H (CDCl₃, 400 MHz): 7.88 (2H,d,*J*=8.8 Hz), 6.70 (2H,d, *J* = 9.2 Hz), 4.94 (2H,s), 4.01 (2H,s), 3.05 (3H,s, NCH₃, imidazolidine), 3.02 (6H,s, N(CH₃)₂).

¹³C NMR, δ_C (CDCl₃, 100 MHz): 172.76 (C=O), 169.03 (C=N), 168.97 (C=N), 155.53 (C=O), 129.01, 113.61, 111.79, 52.05, 40.37, 34.87, 30.08.

LC-MS (*m/z*, %): 316.8 (M+H, 96), 357.8 (M+CH₃CN, 100), 317.9 (19).

4) Synthesis of 5-nitro-2-((3-substitutedphenyl-1,2,4-oxadiazol-5-yl)methylthio)-1*H*-benzo[d]imidazoles



General procedure:

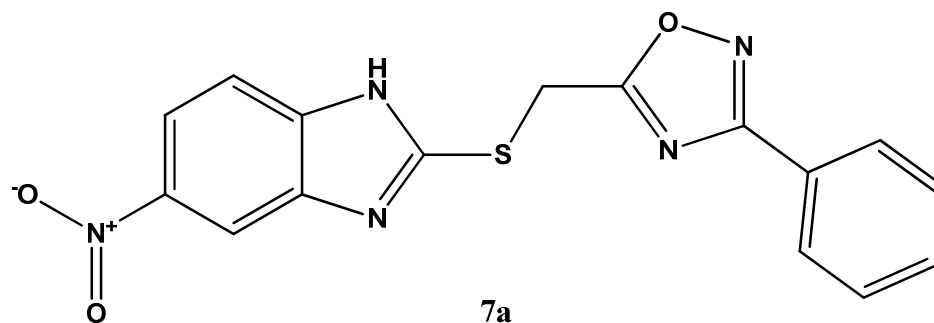
Two different procedures have been applied for the synthesis of these compounds:

i) Method-1: 5-Nitro-2-mercaptobenzimidazole (1eq.), 5-(chloromethyl)-3-aryl-1,2,4-oxadiazole (1 eq.) and K_2CO_3 (1 eq.) were mixed at 90-100°C in DMF for 30-90 min. The progress of the reaction was monitored by TLC. After the reaction was completed, the temperature of reaction mixture was reduced to room temperature. In order to remove DMF, water was added to the mixture and it was extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure and the remaining residue was purified by flash column chromatography (silica gel).

ii) Method-2: 5-Nitro-2-mercaptobenzimidazole (1eq.) was dissolved in 4-10 ml ethanol, 3N NaOH (volume of base solution is given in each section below) was added to the mixture, 5-(chloromethyl)-3-aryl-1,2,4-oxadiazole (1 eq.) was added to mixture, and the mixture was generally stirred at RT overnight, some of them was stirred for 3-4 h. The progress of the reaction was monitored by TLC. Then the solvent was removed under reduced pressure. Water was added to the obtained residue and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the remaining residue was purified by flash column chromatography (silica gel).

5-(((5-Nitro-1*H*-benzo[*d*]imidazol-2-yl)thio)methyl)-3-phenyl-1,2,4-oxadiazole (7a):

Method-1



Chemicals used: 0.25 mmol (49 mg) of 5-(chloromethyl)-3-phenyl-1,2,4-oxadiazole (**3a**), 0,25 mmol (49 mg) of 5-nitro-2-mercaptobenzimidazole (**5**) and 0,25mmol (35 mg) of potassium carbonate (K₂CO₃) in 2 ml of DMF.

Eluent used in column chromatography: 1:3, 1:2, (EtOAc: PB)

Yield: 77 mg (87.16%)

M.p. : 180-181 °C

R_f : 0.125 (1:2 ; EtOAc :n-Hexane)

Nature of product: white solid

Molecular formula: C₁₆H₁₁N₅O₃S

Molecular weight: 353.36

IR (KBr, v: cm⁻¹): 2993-2814(C-H stretching), 1624,1599 (C=N),1533, 1491, 1357,1342.

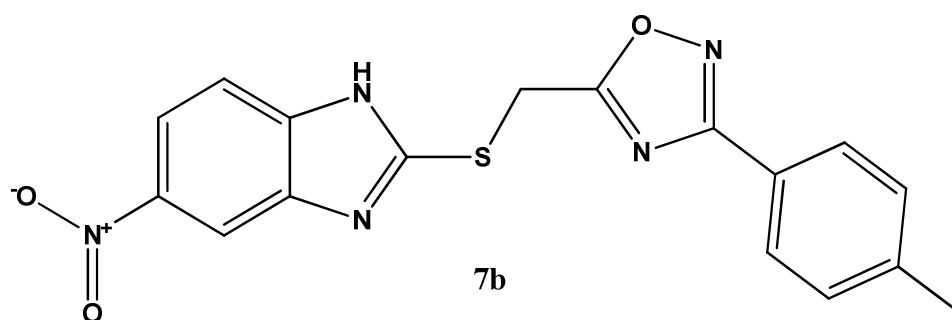
¹H NMR, δ_H (DMSO-*d*₆, 400 MHz): 8.35 (1H, d, *J* = 2.4 Hz), 8.09- 8.06 (1H,dd, *J* = 9.2, 2.4 Hz), 7.66-7.53 (4H,m), 7.98 (2H,d, *J* = 7.6 Hz), 7.65-7.53 (4H, m), 5.07 (2H,s), 3.4 (1H,s).

^{13}C NMR, δ_{C} (DMSO- d_6 , 100 MHz): 177.63, 168.53, 154.86, 143.01, 132.34, 129.94, 127.64, 126.54, 118.34, 26.61.

LC-MS (m/z,%): 354.7 (M+H,100), 355.8 (20), 182.8(16).

5-(((5-Nitro-1*H*-benzo[*d*]imidazol-2-yl)thio)methyl)-3-(*p*-tolyl)-1,2,4-oxadiazole (7b):

Method-2



Chemicals used: 0.25 mmol (52 mg) of 5-(chloromethyl)-3-(*p*-tolyl)-1,2,4-oxadiazole (**3b**), 0.25 mmol (49 mg) of 5-nitro-2-mercaptobenzimidazole (**5**) and 0.25 ml of 3N sodium hydroxide (NaOH) in 5 ml of EtOH.

Eluent used in column chromatography: 1:2, 1:1 (EtOAc: PB)

Yield: 73 mg (79.48%)

M.p. : 154-155 °C

R_f : 0.150 (1:2 ; EtOAc :n-Hexane)

Nature of product: yellow solid.

Molecular formula: $\text{C}_{17}\text{H}_{13}\text{N}_5\text{O}_3\text{S}$

Molecular weight: 367.38

IR (KBr, ν : cm^{-1}): 3076-2816 (C-H stretching), 1624, 1593 (C=N), 1529, 1483, 1338.

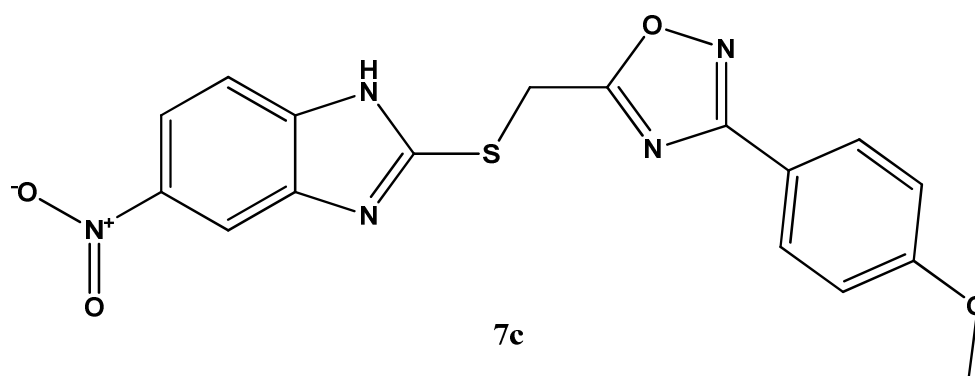
^1H NMR, δ_{H} (DMSO- d_6 , 400 MHz): 8.34 (1H,d, J = 2.0Hz), 8.08 (1H,dd, J = 8.8, 2.0 Hz), 7.86 (2H,d, J = 8.0 Hz), 7.65 (1H,d, J = 8.8 Hz), 7.36 (2H, d, J = 8.0 Hz), 5.04 (2H,s), 2.36 (3H,s).

^{13}C NMR, δ_{C} (DMSO- d_6 , 100 MHz): 177.4,168.50, 143.04,142.33, 130.49, 127.59, 123.77, 118.37, 68.69, 26.60, 21.73.

LC-MS (m/z,%): 368.7 (100), 277.6 (15).

3-(4-Methoxyphenyl)-5-(((5-nitro-1*H*-benzo[*d*]imidazol-2-yl)thio)methyl)-1,2,4-oxadiazole (7c) :

Method-1



Chemicals used: 0.50 mmol (98 mg) of 5-(chloromethyl)-3-(4-methoxyphenyl)-1,2,4-oxadiazole (**3c**), 0.50 mmol (112 mg) of 5-nitro-2-mercaptobenzimidazole (**5**) and 0.50 mmol (69 mg) of potassium carbonate (K_2CO_3) in 4 ml of DMF.

Eluent used in column chromatography: 1:2 (EtOAc: PB)

Yield: 189 mg (98.5%)

M.p. : 176-177°C

R_f : 0.125 (1 :2 ; EtOAc :n-Hexane)

Molecular formula: C₁₇H₁₃N₅O₄S

Molecular weight: 383.38

IR (KBr, ν : cm⁻¹): 1612, 1597 (C=N), 1484, 1425.

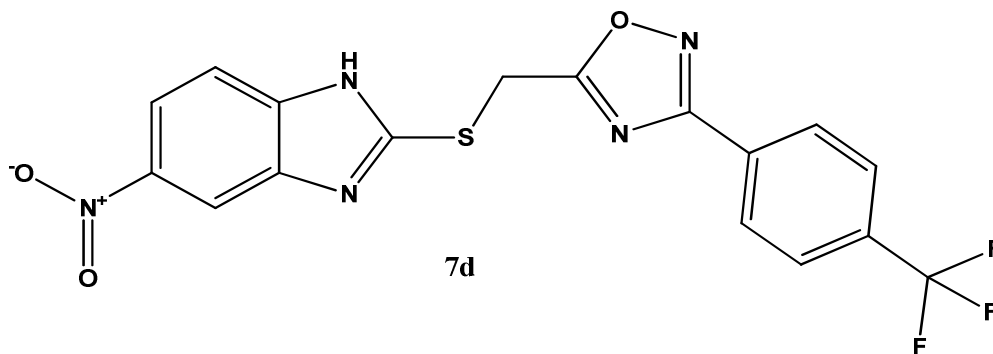
¹H NMR, δ_{H} (DMSO-*d*₆, 400 MHz): 8.34 (1H,d,*J* =2.0 Hz), 8.09-8.06 (1H,dd,*J* = 8.8,2.4 Hz), 7.91 (2H,d,*J* = 8.0 Hz), 7.65 (1H,d,*J* = 8.8 Hz), 7.10 (2H,d,*J* = 9.2 Hz), 5.04 (2H,s), 3.83 (3H,s).

¹³C NMR, δ_{C} (DMSO-*d*₆, 100 MHz): 176.49, 167.51, 162.23, 161.71, 157.15, 142.28, 128.62, 118.06, 117.62, 114.60, 55.52, 25.85.

LC-MS (*m/z*, %): 384.7 (M+H,100), 182.7 (27), 385.8 (23).

5-(((5-Nitro-1*H*-benzo[*d*]imidazol-2-yl)thio)methyl)-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (7d):

Method-1



Chemicals used: 0.50 mmol (130 mg) of 5-(chloromethyl)-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (**3d**), 0.50 mmol (98 mg) of 5-nitro-2-mercaptobenzimidazole (**5**) and 0.50 mmol (69 mg) of potassium carbonate (K₂CO₃) in 4 ml of DMF.

Eluent used in column chromatography: 1:2 (EtOAc: PB)

Yield: 205 mg (97.31%)

M.p. : 102-104 °C

R_f : 0.100 (1:2 ; EtOAc :n-Hexane)

Nature of product: white solid.

Molecular formula: C₁₇H₁₀F₃N₅O₃S

Molecular weight: 421.35

IR (KBr, v: cm⁻¹): 1620, 1595 (C=N), 1570, 1514.

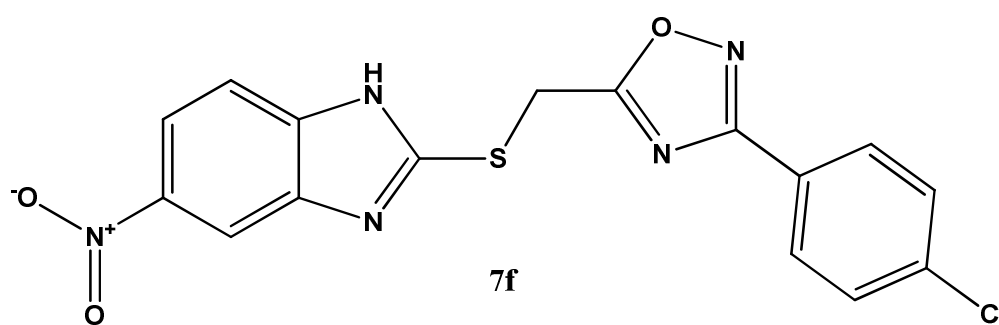
¹H NMR, δ_H (DMSO-*d*₆, 400 MHz): 13.49 (1H, broad s, NH), 8.34 (1H,d,*J* = 2.4 Hz), 8.19 (2H,d, *J* = 8.0 Hz), 7.70 (2H,d, *J* = 8.4 Hz), 7.50 (1H,d, *J* = 9.2 Hz), 5.08 (2H,s).

¹³C NMR, δ_C (DMSO-*d*₆, 100 MHz): 178.29, 167.62, 143.06, 132.32, 132.00, 130.41, 128.57, 126.99, 126.96, 125.83, 123.11, 118.39, 26.66.

LC-MS (m/z,%): 422.7 (M+H,100), 423.7 (35), 423.9 (29), 145.9 (27).

3-(4-Chlorophenyl)-5-(((5-nitro-1*H*-benzo[*d*]imidazol-2-yl)thio)methyl)-1,2,4-oxadiazole (7f):

Method-2



Chemicals used: 0.25 mmol (57 mg) of 5-(chloromethyl)-3-(4-chlorophenyl)-1,2,4-oxadiazole (**3f**), 0.25 mmol (49 mg) of 5-nitro-2-mercaptobenzimidazole (**5**) and 0,25 ml of 3N sodium hydroxide (NaOH) in 5 ml of EtOH.

Eluent used in column chromatography:1:2, 1:1 (EtOAc: PB)

Yield: 49 mg (50.54%)

M.p. : 140-141 °C

R_f : 0.350 (1:1 ; EtOAc :n-Hexane)

Nature of product: yellowish solid

Molecular formula: C₁₆H₁₀ClN₅O₃S

Molecular weight: 387.80

IR (KBr, v: cm⁻¹ : 1589,1566 (C=N),1510,1342.

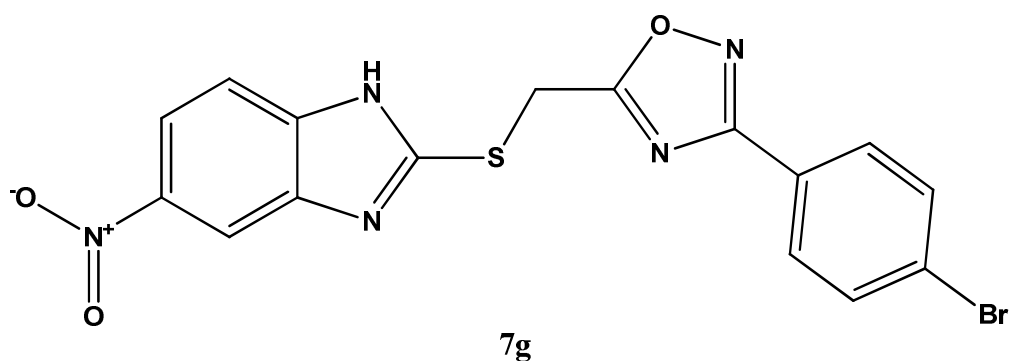
¹H NMR, δ_H (DMSO-*d*₆ , 400 MHz): 8.34 (2H,d,*J* = 2.0 Hz), 8.08-8.06 (2H,dd, *J* = 9.2, 2.4 Hz), 7.97 (2H,d, *J* = 8.4 Hz), 7.65 (3H, t, *J* = 7.6 Hz), 5.05 (2H,s).

¹³C NMR, δ_C (DMSO-*d*₆, 100 MHz): 177.91, 167.76, 143.05, 137.09, 130.13, 129.45, 125.39, 118.37, 26.61.

LC-MS (m/z,%): 386.6 (M+H,100).

3-(4-Bromophenyl)-5-(((5-nitro-1*H*-benzo[*d*]imidazol-2-yl)thio)methyl)-1,2,4-oxadiazole (7g):

Method-2



Chemicals used: 0.25 mmol (68 mg) of 3-(4-bromophenyl)-5-(chloromethyl)-1,2,4-oxadiazole (**3g**) 0.25 mmol (49 mg) of 5-nitro-2-mercaptobenzimidazole (**5**) and 0.25 ml of 3N sodium hydroxide (NaOH) in 5 ml of EtOH.

Eluent used in column chromatography: 1:3 (EtOAc: PB)

Yield: 65 mg (60.15%)

M.p. : 196-198 °C

R_f : 0.150 (1:2 ; EtOAc :n-Hexane)

Nature of product: yellow solid

Molecular formula: C₁₆H₁₀BrN₅O₃S

Molecular weight: 432.25

IR (KBr, ν : cm⁻¹): 1624, 1589 (C=N), 1564, 1525, 1404, 1342.

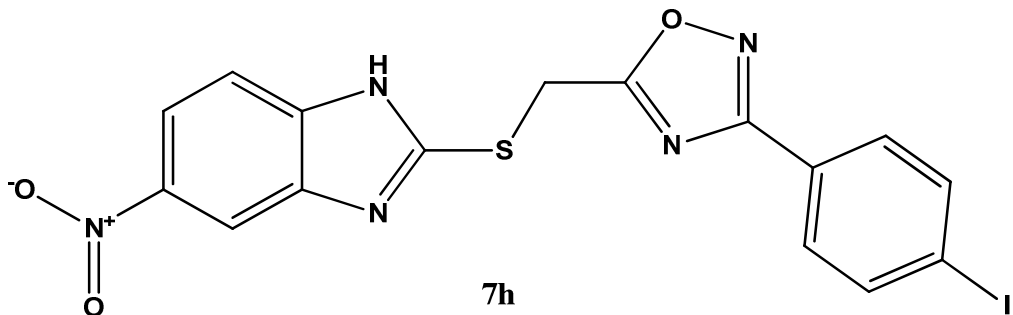
¹H NMR, δ_H (DMSO-*d*₆, 400 MHz): 13.48 (1H, broad s, NH), 8.33 (1H, s), 8.08-8.06 (2H, dd, *J* = 9.2, 2.0 Hz), 7.91-7.88 (2H, d, *J* = 8.0 Hz), 7.76 (2H, d, *J* = 8.0 Hz), 7.63 (1H, d, *J* = 8.4 Hz), 5.04 (2H, s).

¹³C NMR, δ_C (DMSO-*d*₆, 100 MHz): 177.97, 167.89, 143.05, 133.11, 1129.64, 125.98, 125.75, 118.44, 26.62.

LC-MS (*m/z*, %): 434.6 (*M*+H, 100).

3-(4-Iodophenyl)-5-(((5-nitro-1*H*-benzo[*d*]imidazol-2-yl)thio)methyl)-1,2,4-oxadiazole (7h):

Method-1



Chemicals used: 0.25 mmol (80 mg) of 5-(chloromethyl)-3-(4-iodophenyl)-1,2,4-oxadiazole (**3h**), 0,25 mmol (49 mg) of 5-nitro-2-

mercaptobenzimidazole (**5**) and 0.25 mmol (35 mg) of potassium carbonate (K_2CO_3) in 2.5 ml of DMF.

Crystallization: Small amount of **7h** were taken and crystalized from the solvent mixture consisting of 5ml of PB and 6-7 drops of EtOAc.

Eluent used in column chromatography: 1:2 (EtOAc: PB)

Yield: 105 mg (87.6%)

M.p. : 203-204 °C

R_f : 0.125 (1:2 ; EtOAc :n-Hexane)

Nature of product: yellow solid

Molecular formula: $C_{16}H_{10}IN_5O_3S$

Molecular weight: 479.25

IR (KBr, ν : cm^{-1}): 1624, 1587 (C=N), 1560, 1487, 1356.

^1H NMR, δ_H (DMSO- d_6 , 400 MHz): 13.43 (1H, broad s, NH), 8.29 (1H, d, J = 2.4 Hz), 8.04-8.01 (2H,dd, J = 9.2, 2.4 Hz), 7.88 (2H, d, J = 8.4 Hz), 7.68 (2H, d, J = 8.8 Hz), 7.58 (1H, d, J = 8.8 Hz), 5.00 (2H, s).

^{13}C NMR, δ_C (DMSO- d_6 , 100 MHz): 177.91, 168.08, 154.92, 142.99, 138.89, 129.41, 125.98, 118.34, 99.86 (C-I), 26.59.

LC-MS (m/z , %): 480.7 (M+H, 100)

X-Ray diffraction data

Crystal data

$C_{16}H_{10}N_5O_3S \cdot H_2O$
 $M_r = 497.27$
 Triclinic, $P\bar{1}$
 Hall symbol: -P 1
 $a = 7.2417(2) \text{ \AA}$
 $b = 7.2952(2) \text{ \AA}$
 $c = 17.3288(6) \text{ \AA}$
 $\alpha = 88.168(2)^\circ$
 $\beta = 85.458(2)^\circ$
 $\gamma = 72.328(2)^\circ$
 $V = 869.50(5) \text{ \AA}^3$

$Z = 2$
 $F(000) = 488$
 $D_x = 1.899 \text{ Mg m}^{-3}$
 Mo $K\alpha$ radiation, $\lambda = 0.71073 \text{ \AA}$
 Cell parameters from 7881 reflections
 $\theta = 3.1\text{--}33.2^\circ$
 $\mu = 2.00 \text{ mm}^{-1}$
 $T = 90 \text{ K}$
 Plate, Colourless
 $0.34 \times 0.27 \times 0.02 \text{ mm}$

Data collection

Bruker Kappa APEX-II DUO
 diffractometer
 Radiation source: fine-focus sealed tube
 TRIUMPH curved graphite monochromator
 φ and ω scans
 Absorption correction: Multi-scan
 SADABS (Sheldrick, 2004)
 $T_{\min} = 0.550$, $T_{\max} = 0.961$
 10446 measured reflections

6522 independent reflections
 6122 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.016$
 $\theta_{\max} = 33.2^\circ$, $\theta_{\min} = 3.1^\circ$
 $h = -10 \rightarrow 11$
 $k = -11 \rightarrow 11$
 $l = -26 \rightarrow 26$

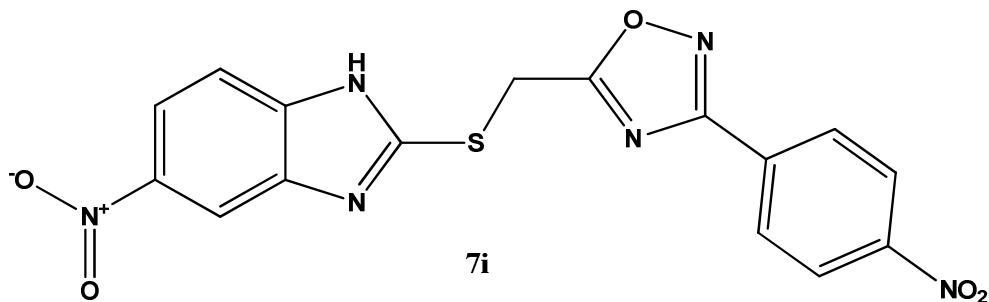
Refinement

Refinement on F^2
 Least-squares matrix: Full
 $R[F^2 > 2\sigma(F^2)] = 0.022$
 $wR(F^2) = 0.057$
 $S = 1.06$
 6522 reflections
 253 parameters
 3 restraints

Primary atom site location: Structure-invariant direct methods
 Secondary atom site location: Difference Fourier map
 Hydrogen site location: Inferred from neighbouring sites
 H atoms treated by a mixture of independent and constrained refinement
 $w = 1/[\sigma^2(F_o^2) + (0.0308P)^2 + 0.3683P]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\max} = 0.001$
 $\Delta\rho_{\max} = 0.89 \text{ e \AA}^{-3}$
 $\Delta\rho_{\min} = -0.82 \text{ e \AA}^{-3}$

5-(((5-Nitro-1*H*-benzo[*d*]imidazol-2-yl)thio)methyl)-3-(4-nitrophenyl)-1,2,4-oxadiazole (7i) :

Method-2



Chemicals used: 0.25 mmol (60 mg) of 5-(chloromethyl)-3-(4-nitrophenyl)-1,2,4-oxadiazole (**3i**) 0.25 mmol (49 mg) of 5-nitro-2-mercaptobenzimidazole (**5**) and 0.25 ml of 3N sodium hydroxide (NaOH) in 5 ml of EtOH.

Eluent used in column chromatography: 1:3, 1:1 (EtOAc : PB)

Yield: 48 mg (48.20%)

M.p. : 106-108 °C

R_f : 0.075 (1:2; EtOAc : n-Hexane)

Nature of product: yellow solid.

Molecular formula: C₁₆H₁₀N₆O₅S

Molecular weight: 398,35

IR (KBr, ν : cm⁻¹): 1624, 1577 (C=N), 1529, 1518, 1342.

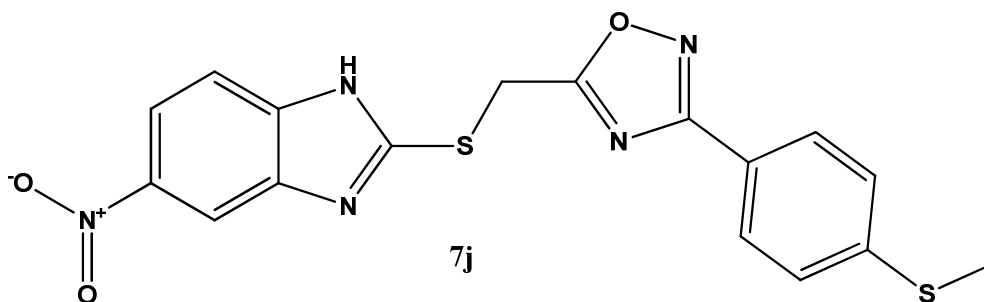
¹H NMR, δ_{H} (DMSO-*d*₆, 400 MHz): 8.33 (2H,d,*J* = 8.8 Hz), 8.27 (1H,s), 8.16 (2H,d,*J* = 8.4 Hz), 8.00 (1H, d, *J* = 8.4 Hz), 7.56 (1H, d, *J* = 8.8 Hz), 5.03 (2H, s).

¹³C NMR, δ_{C} (DMSO-*d*₆, 100 MHz): 178.49, 167.28, 149.88, 143.03, 132.28, 129.08, 125.14, 118.35, 26.63.

LC-MS (m/z,%): 399.8 (M+H, 100).

3-(4-(Methylthio)phenyl)-5-(((5-nitro-1*H*-benzo[*d*]imidazol-2-yl)thio)methyl)-1,2,4-oxadiazole (7j) :

Method-2



Chemicals used: 0.25 mmol (60 mg) of 5-(chloromethyl)-3-(4-(methylthio)phenyl)-1,2,4-oxadiazole (**3j**), 0,25 mmol (49 mg) of 5-nitro-2-mercaptobenzimidazole (**5**) and 0.25 ml of 3N sodium hydroxide (NaOH) in 5 ml of EtOH.

Eluent used in column chromatography: 2:1, 3:1 (EtOAc: PB)

Yield: 56 mg (56.08%)

M.p. : 105-107 °C

R_f : 0.100 (1:2 ; EtOAc :n-Hexane)

Nature of product: Light brown-yellow solid.

Molecular formula: C₁₇H₁₃N₅O₃S₂

Molecular weight: 399.45

IR (KBr, v: cm⁻¹: 1585 (C=N), 1514, 1467, 1408, 1336.

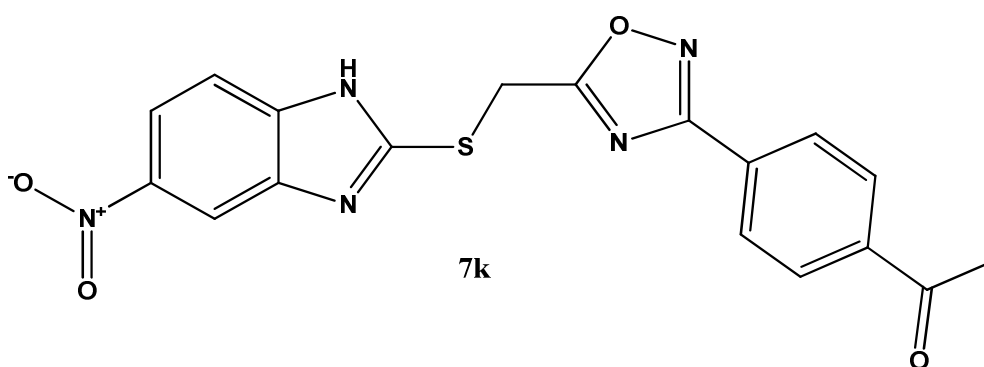
¹H NMR, δ_H (DMSO-*d*₆, 400 MHz): 13.44 (1H, broad s, NH), 8.30 (1H, br s), 8.11-8.02 (2H, m), 7.81 (2H, d, *J* = 8.8 Hz), 7.59 (1H, s), 7.34 (2H, d, *J* = 8.4 Hz), 4.98 (2H,s), 2.46 (3H, s), SCH₃).

^{13}C NMR, δ_{C} (DMSO- d_6 , 100 MHz): 177.46, 168.22, 143.84, 128.41, 127.97, 126.44, 125.27, 122.54, 118.44, 26.60 (CH_2), 14.71 (SCH_3).

LC-MS (m/z , %): 400.7 ($\text{M}+\text{H}$, 100).

1-(4-(5-(((5-Nitro-1*H*-benzo[*d*]imidazol-2-yl)thio)methyl)-1,2,4-oxadiazol-3-yl)phenyl)ethanone (7k):

Method-1



Chemicals used: 0.25 mmol (59 mg) of 1-(4-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)phenyl)ethanone (**3k**), 0.25 mmol (49 mg) of 5-nitro-2-mercaptobenzimidazole (**5**) and 0.25 mmol (35 mg) of potassium carbonate (K_2CO_3) in 2 ml of DMF.

Eluent used in column chromatography: 1:1 (EtOAc : PB)

Yield: 47 mg (47.55%)

M.p. : 219-220 °C

R_f : 0.375 (2:1 ; EtOAc : n-Hexane)

Nature of product: yellow solid

Molecular formula: $\text{C}_{18}\text{H}_{13}\text{N}_5\text{O}_4\text{S}$

Molecular weight: 395.39

IR (KBr, ν : cm^{-1}): 1678 ($\text{C}=\text{O}$), 1622, 1612 ($\text{C}=\text{N}$), 1529, 1487, 1342.

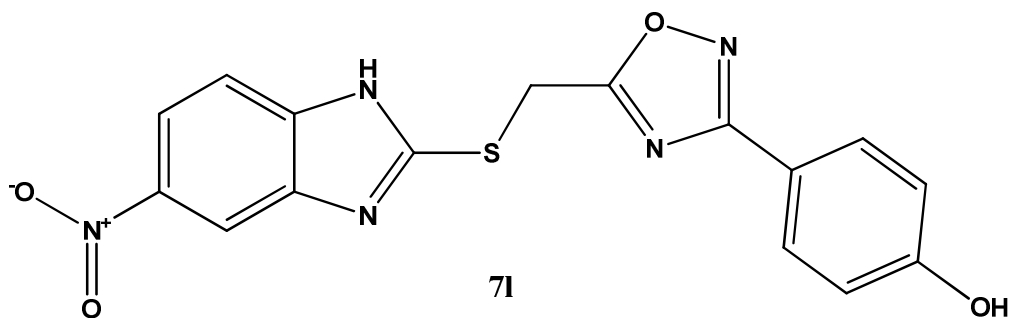
^1H NMR, δ_{H} (DMSO- d_6 , 400 MHz): 13.50 (1H, broad s, NH), 8.33 (1H, d, J = 1.6 Hz), 8.10 (4H, s), 8.08 (1H, d, J = 2.0 Hz), 8.06 (1H, d, J = 1.6 Hz), 7.96 (1H, d, J = 8.4 Hz), 7.81 (1H, d, J = 8.8 Hz), 7.63 (1H, d, J = 8.4 Hz), 5.07 (2H, s), 2.63 (3H, s, CH_3CO).

^{13}C NMR, δ_{C} (DMSO- d_6 , 100 MHz): 198.11 ($\text{CH}_3\text{C}=\text{O}$), 178.10, 167.91, 143.01, 139.55, 130.39, 129.72, 127.96, 127.70, 126.94, 118.36, 27.55, 26.62.

LC-MS (m/z , %): 396.7 (M+H, 100).

4-(5-(((5-Nitro-1*H*-benzo[*d*]imidazol-2-yl)thio)methyl)-1,2,4-oxadiazol-3-yl)phenol (7I):

Method-2



Chemicals used: 0.25 mmol (53 mg) of 4-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)phenol (**3I**), 0.25 mmol (49 mg) of 5-nitro-2-mercaptobenzimidazole (**5**) and 0.25 ml of 3N sodium hydroxide (NaOH) in 5 ml of EtOH.

Eluent used in column chromatography: 1:2, 1:1 (EtOAc: PB)

Yield: 67 mg (72.56%)

M.p. : 214-216°C

R_f : 0.175 (1:1 ; EtOAc :n-Hexane)

Nature of product: yellow solid

Molecular formula: $\text{C}_{16}\text{H}_{11}\text{N}_5\text{O}_4\text{S}$

Molecular weight: 369.35

IR (KBr, ν : cm^{-1}): 3400-2695, 1616, 1593 (C=N), 1521, 1492, 1411, 1340

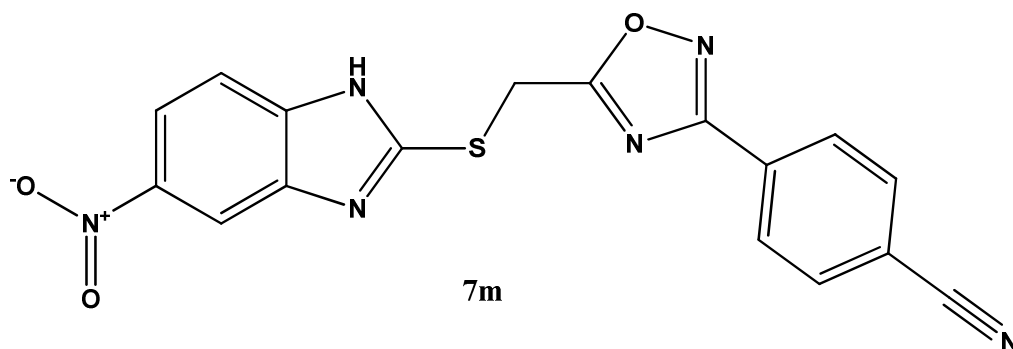
^1H NMR, δ_{H} (CDCl_3 , 400 MHz): 13.44 (1H, broad s, NH), 10.11 (1H, s, OH), 8.31 (1H, s), 8.02 (1H, d, $J = 6.8$ Hz), 7.73 (2H, dd, $J = 6.8, 1.6$ Hz), 7.59 (1H, s), 6.84 (2H, dd, $J = 6.8, 2.0$ Hz), 4.96 (2H, s).

^{13}C NMR, δ_{C} ($\text{DMSO}-d_6$, 100 MHz): 176.98, 168.42, 161.09, 143.14, 129.47, 118.54, 118.12, 117.17, 116.66, 114.01, 26.55.

LC-MS (m/z , %): 370.7 ($\text{M}+\text{H}$, 100).

4-(5-(((5-Nitro-1*H*-benzo[*d*]imidazol-2-yl)thio)methyl)-1,2,4-oxadiazol-3-yl)benzonitrile (7m):

Method-2:



Chemicals used: 0.209 mmol (46 mg) of 4-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)benzonitrile (**3m**), 0.209 mmol (41 mg) of 5-nitro-2-mercaptobenzimidazole **5**, and 0.21 ml of 3N sodium hydroxide (NaOH) in 10 ml of EtOH.

Eluent used in column chromatography: 1: 3, 1: 2 (EtOAc: PB)

Yield: 16 mg (20.23%)

M.p. : 220-223°C

R_f : 0.200 (1:2 ; EtOAc :n-Hexane)

Nature of product: yellow solid.

Molecular formula: C₁₇H₁₀N₆O₃S

Molecular weight: 378.36

IR (KBr, ν : cm⁻¹): 3308, 2245 (C $\equiv$ N), 1618, 1587 (C=N), 1528, 1475, 1420, 1334.

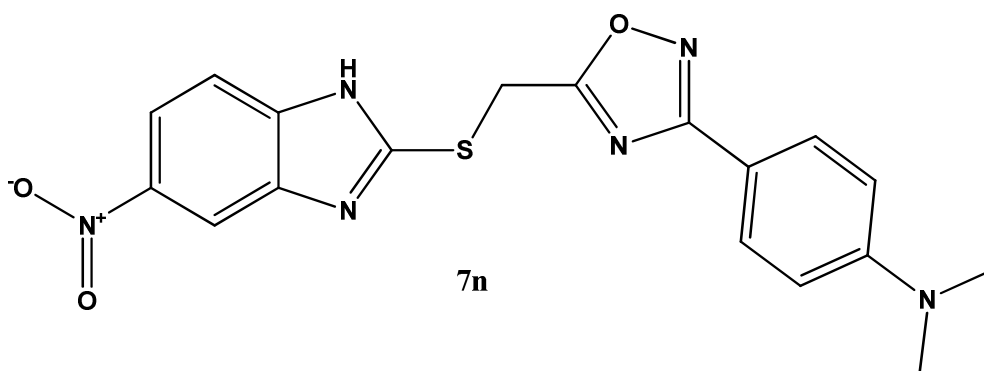
¹H NMR, δ_{H} (DMSO-*d*₆, 400 MHz): 13.49 (1H, broad s, NH), 8.32 (1H, d, *J* = 2.0 Hz), 8.12 (2H, d, *J* = 8.4 Hz), 8.07 (1H, d, *J* = 2.0 Hz), 8.05 (1H, d, *J* = 2.0 Hz), 8.01 (2H, d, *J* = 8.0 Hz), 7.62 (1H, d, *J* = 8.8 Hz), 5.07 (2H, s).

¹³C NMR, δ_{C} (DMSO-*d*₆, 100 MHz): 177.62, 166.74, 142.28, 133.22, 129.94, 127.68, 118.04, 117.60, 113.93, 25.87.

LC-MS (*m/z*, %): 379.6 (M+H, 100).

N,N-Dimethyl-4-(5-(((5-nitro-1*H*-benzo[*d*]imidazol-2-yl)thio)methyl)-1,2,4-oxadiazol-3-yl)aniline (7n):

Method-2



Chemicals used: 0.130 mmol (31 mg) of 3-(4-*N,N*-dimethylaminophenyl)-5-(chloromethyl)-1,2,4-oxadiazole (**3n**), 0.130 mmol (25 mg) of 5-nitro-2-mercaptobenzimidazole (**5**) and 0.130 ml of 3N sodium hydroxide (NaOH) in 4 ml of EtOH.

Eluent used in column chromatography: 1:3, 1:2 (EtOAc: PB)

Yield: 25 mg (48.51%)

M.p. : 181-182°C

R_f : 0.250 (1:1 ; EtOAc :n-Hexane)

Nature of product: Orange brown solid

Molecular Formula: C₁₈H₁₆N₆O₃S

Molecular weight: 396.42

IR (KBr, v: cm⁻¹): 1612, 1589 (C=N), 1492, 1433, 1413, 1332.

¹H NMR, δ_H (DMSO-*d*₆, 400 MHz): 8.33 (1H, d, *J* = 2.0 Hz), 8.08-8.05 (1H, dd, *J* = 8.8 , 2.4 Hz), 7.76-7.73 (2H, dd, *J* = 7.2, 2.0 Hz), 7.62 (1H, d, *J* = 8.8 Hz), 6.77 (2H, d, *J* = 9.2 Hz), 4.97 (2H, s), 2.97 (6H, s, N(CH₃)₂).

¹³C NMR, δ_C (DMSO-*d*₆, 100 MHz): 177.62, 166.74, 142.28, 133.22, 129.94, 127.68, 118.04, 117.60, 113.93, 39.98, 26.87.

LC-MS (m/z,%): 397.7 (M+H, 100).

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APPENDICES

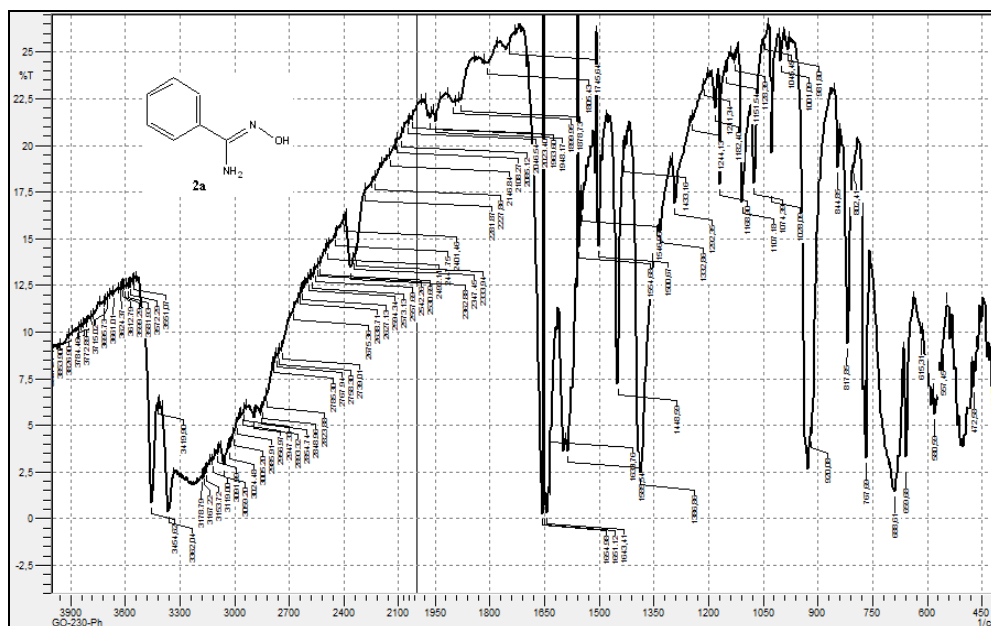


Figure 4.1. The IR spectrum of **2a**

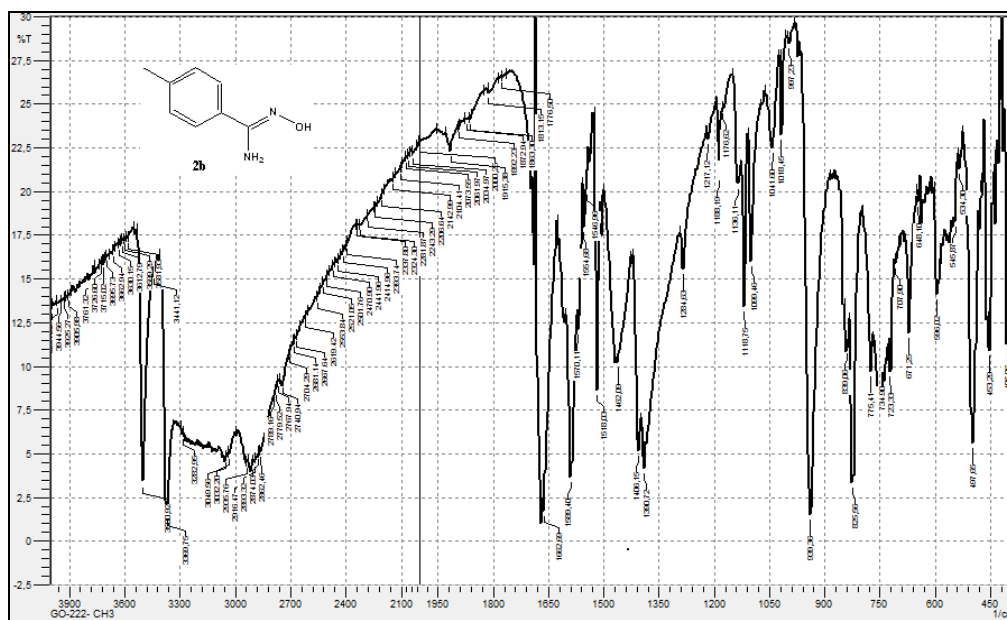


Figure 4.2. The IR spectrum of **2b**

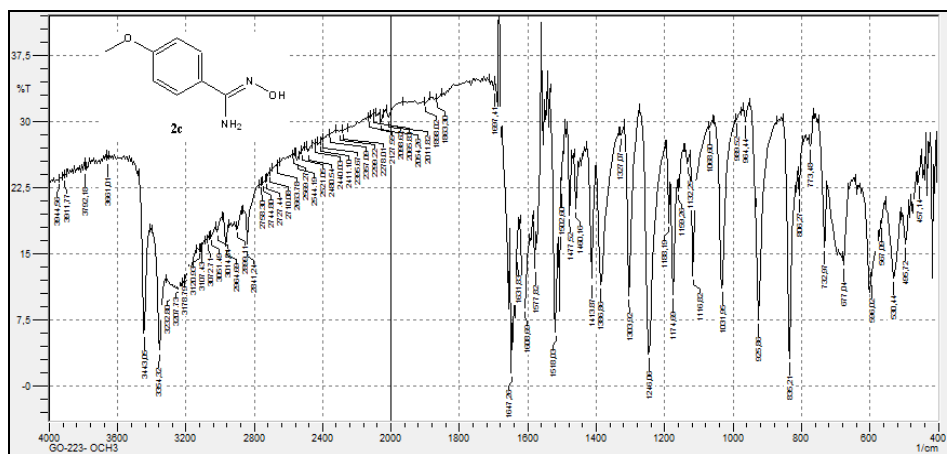


Figure 4.3. The IR spectrum of **2c**

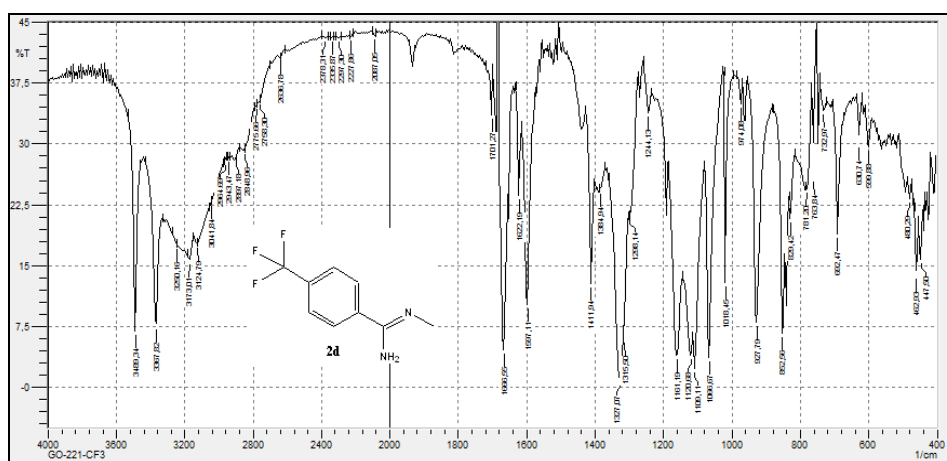


Figure 4.4. The IR spectrum of **2d**

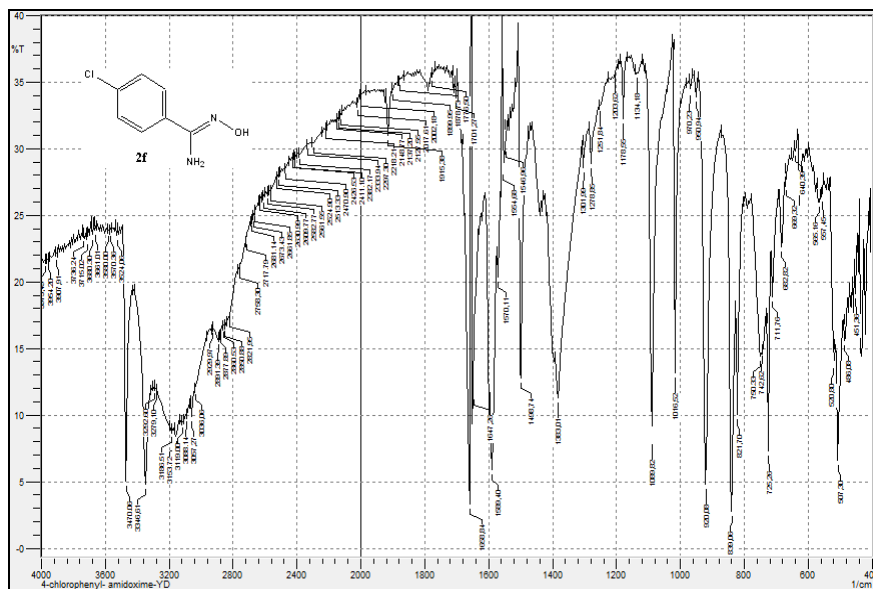


Figure 4.5. The IR spectrum of **2f**

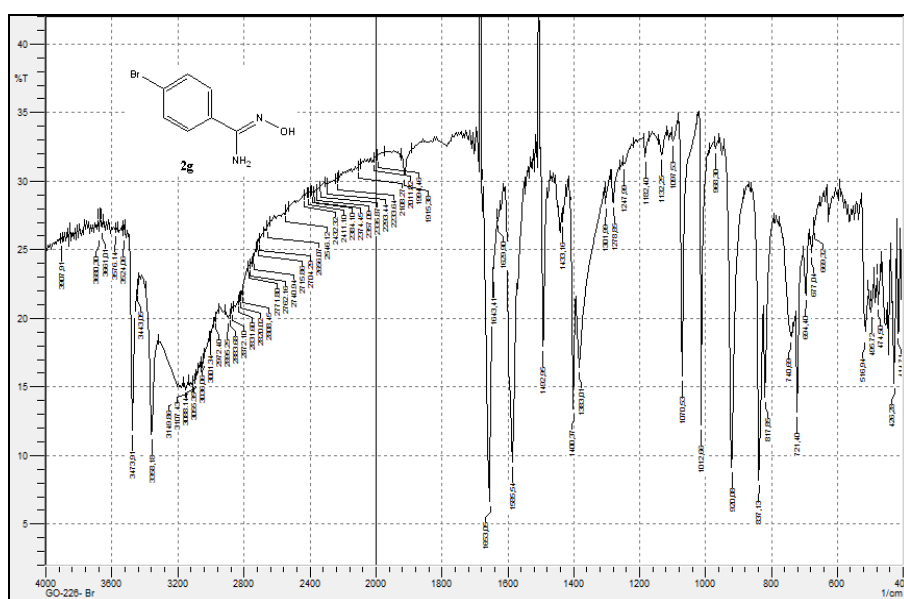


Figure 4.6. The IR spectrum of **2g**

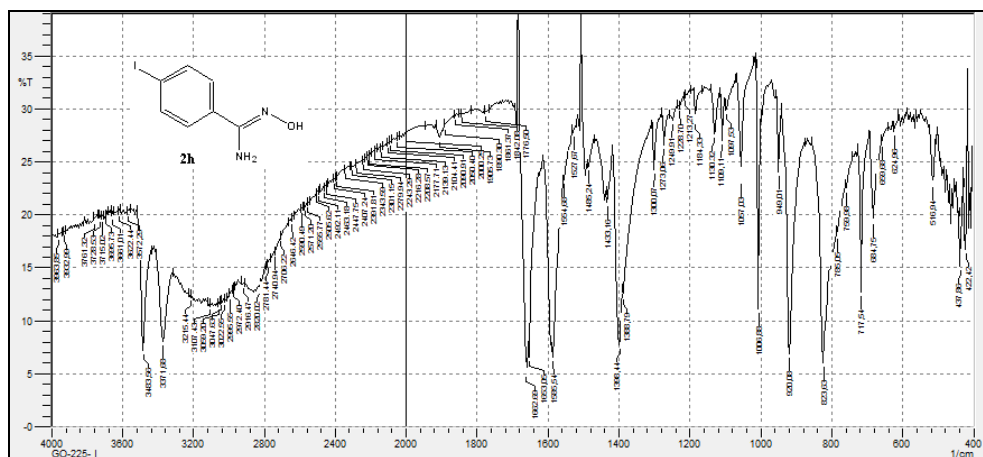


Figure 4.7. The IR spectrum of **2h**

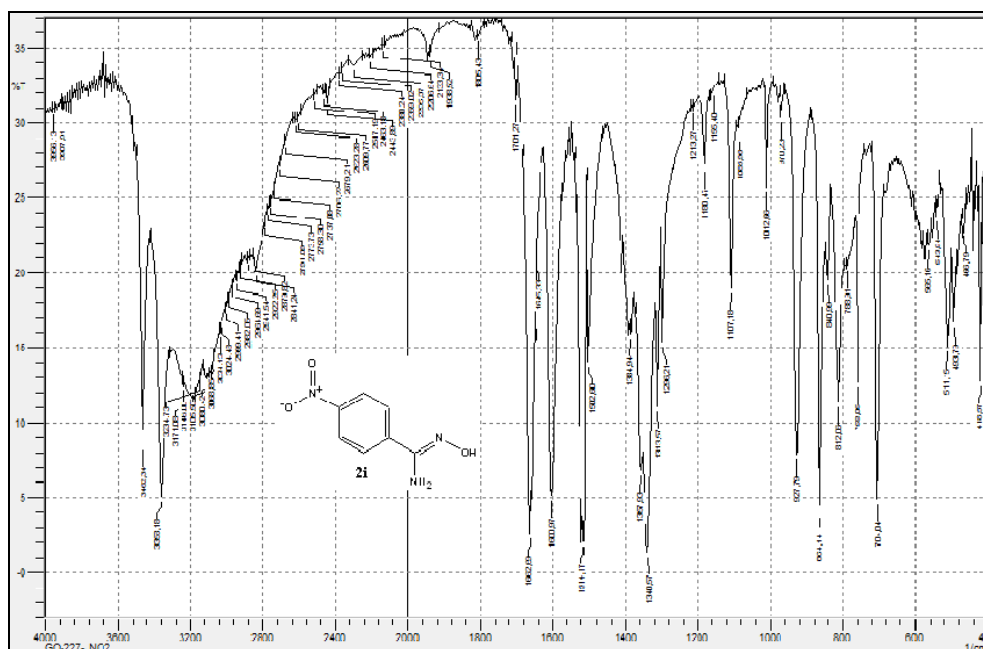


Figure 4.8. The IR spectrum of **2i**

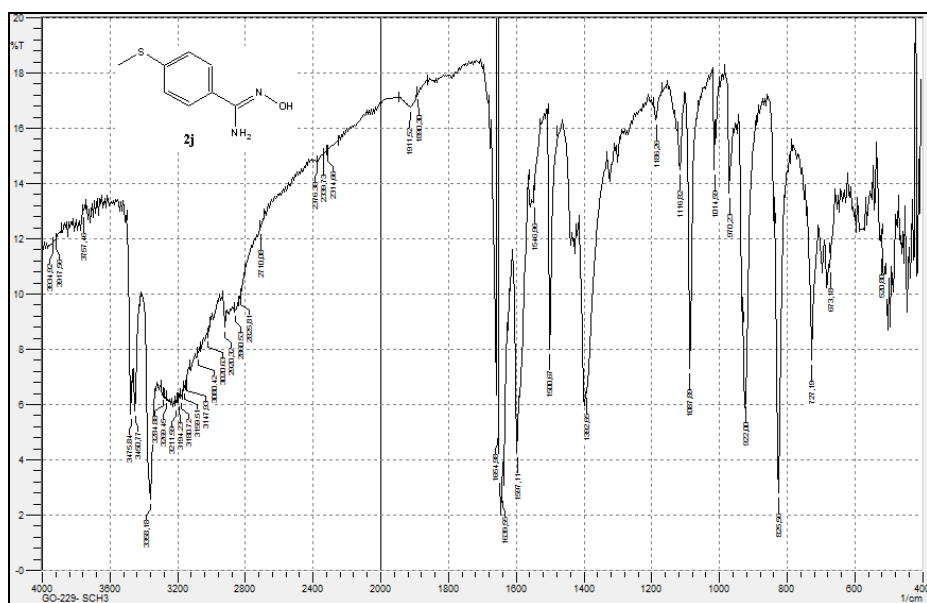


Figure 4.9. The IR spectrum of **2j**

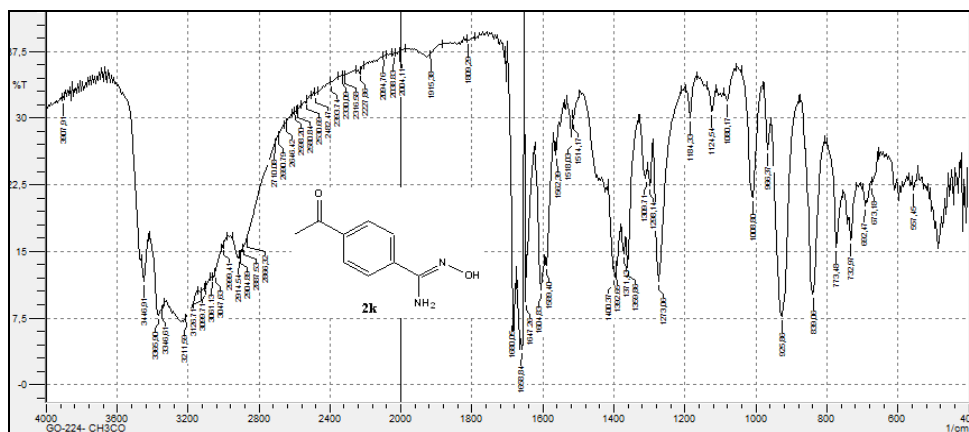


Figure 4.10. The IR spectrum of **2k**

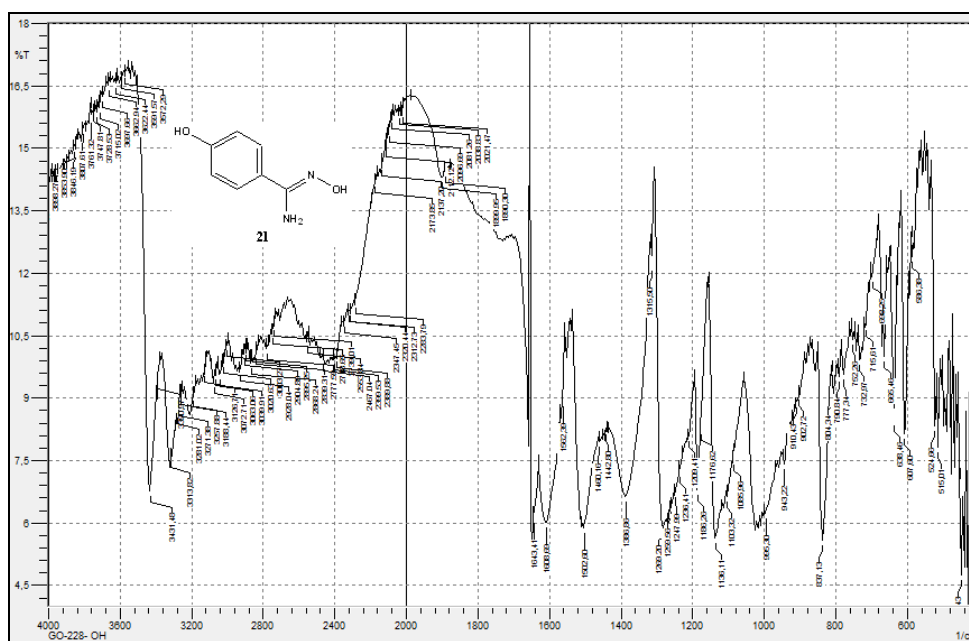


Figure 4.11. The IR spectrum of **2l**

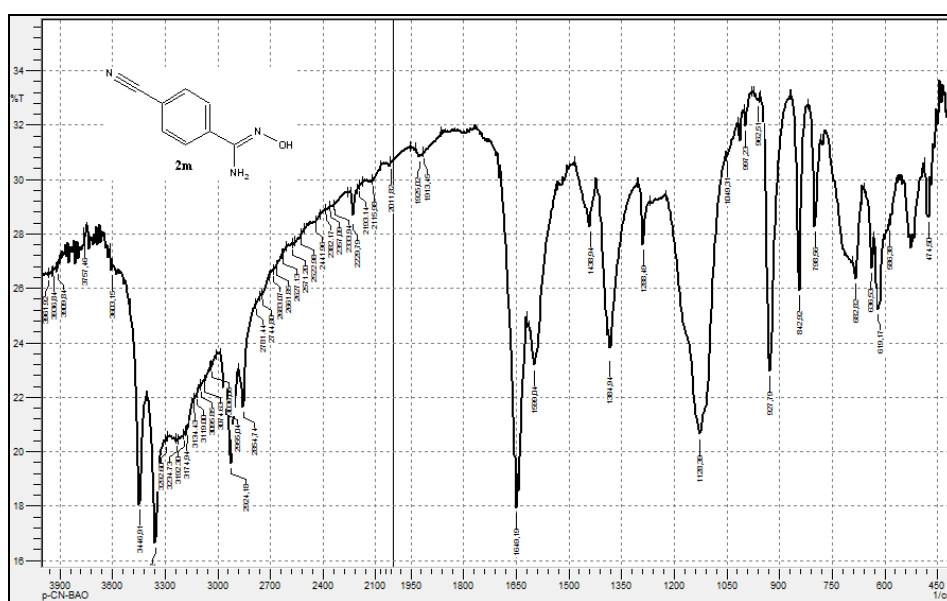


Figure 4.12. The IR spectrum of **2m**

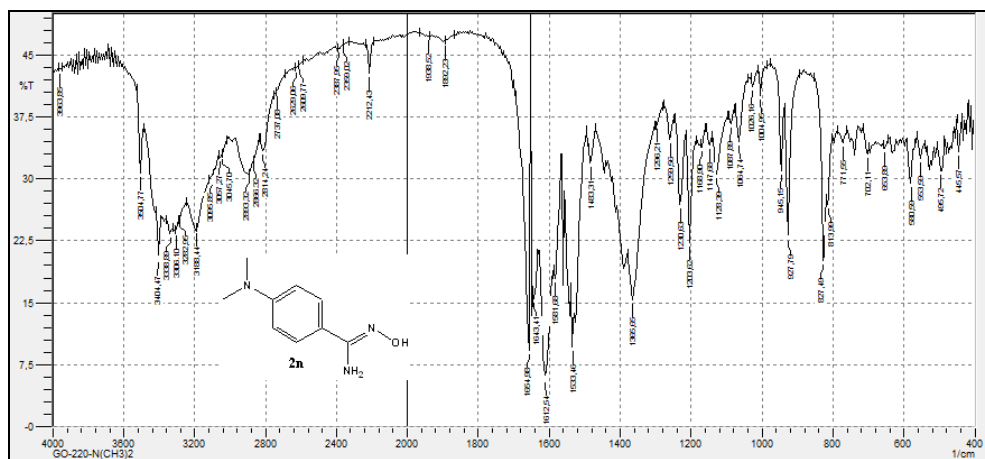


Figure 4.13. The IR spectrum of **2n**

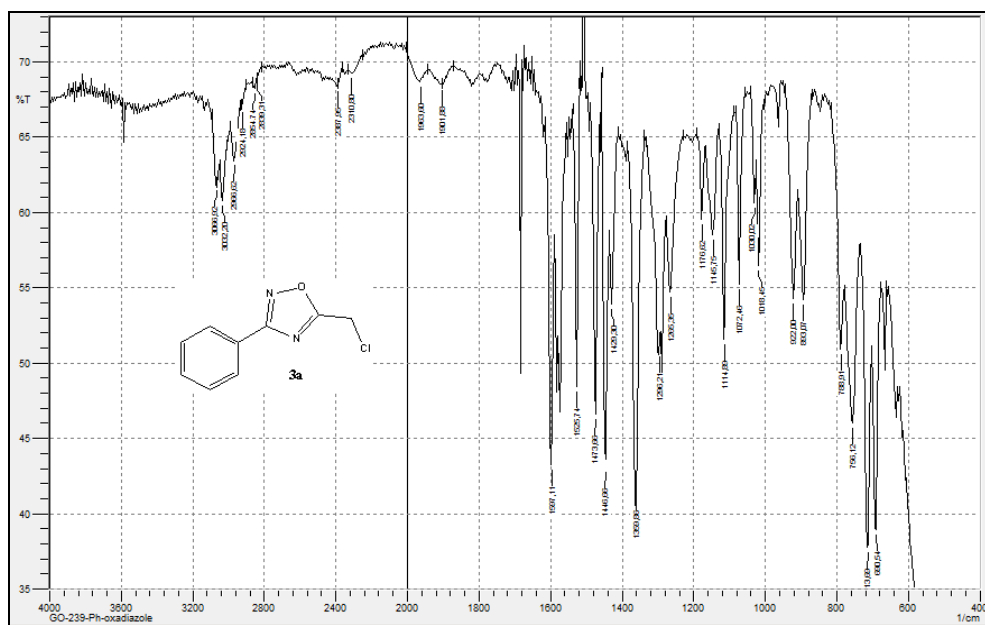


Figure 4.14. The IR spectrum of **3a**

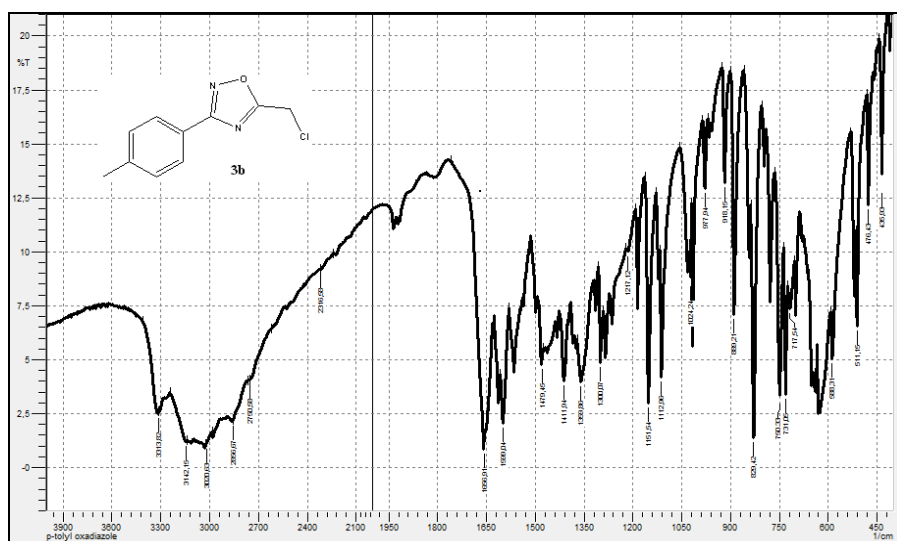


Figure 4.15. The IR spectrum of **3b**

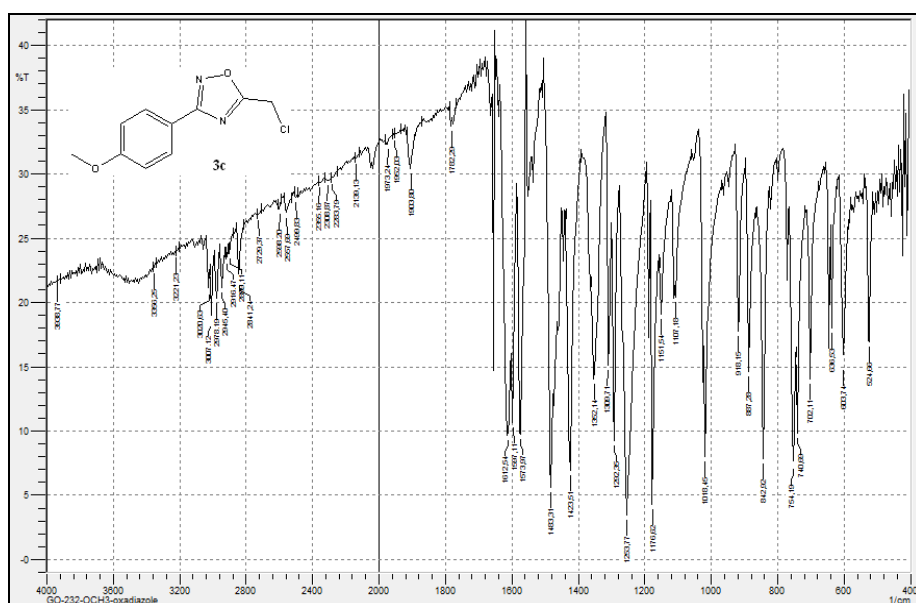


Figure 4.16. The IR spectrum of **3c**

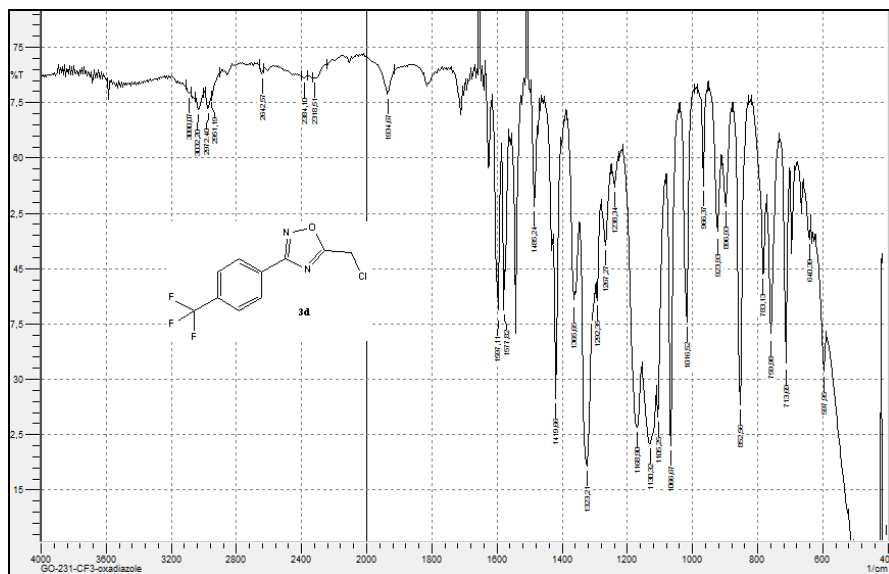


Figure 4.17. The IR spectrum of **3d**

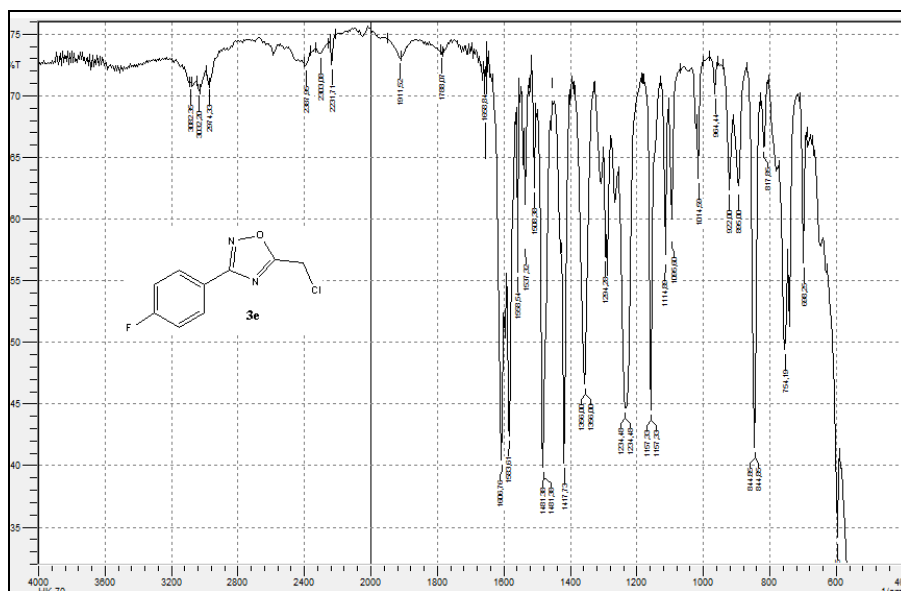


Figure 4.18. The IR spectrum of **3e**

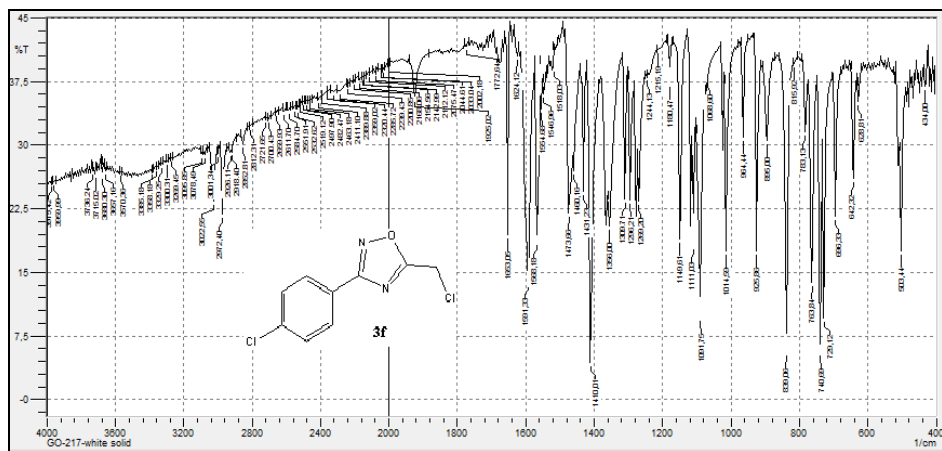


Figure 4.19. The IR spectrum of **3f**

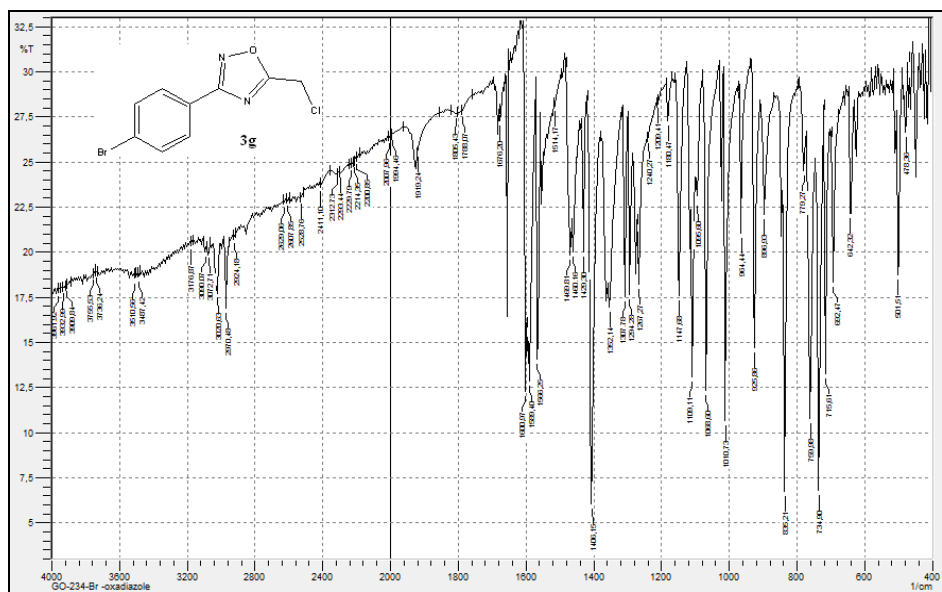


Figure 4.20. The IR spectrum of **3g**

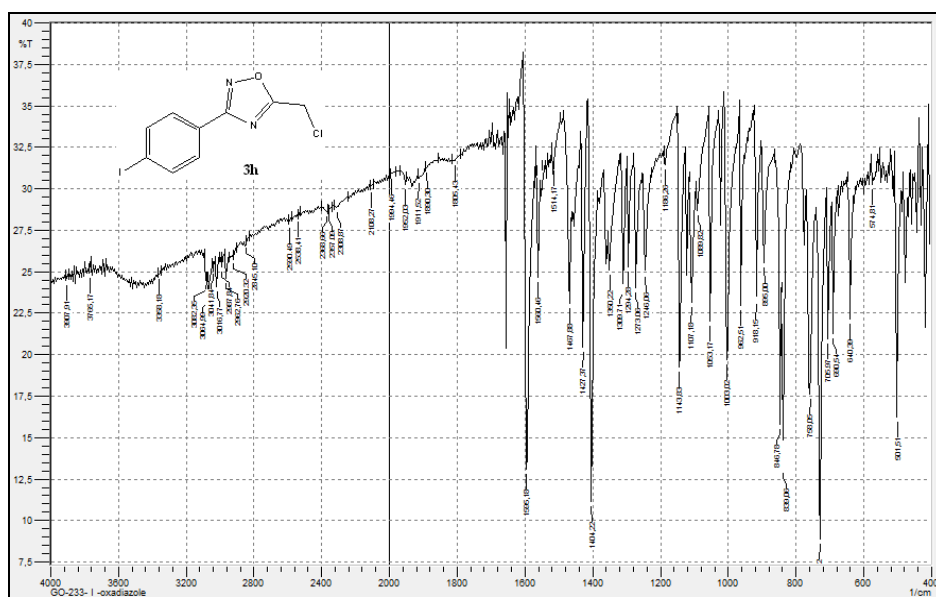


Figure 4.21. The IR spectrum of **3h**

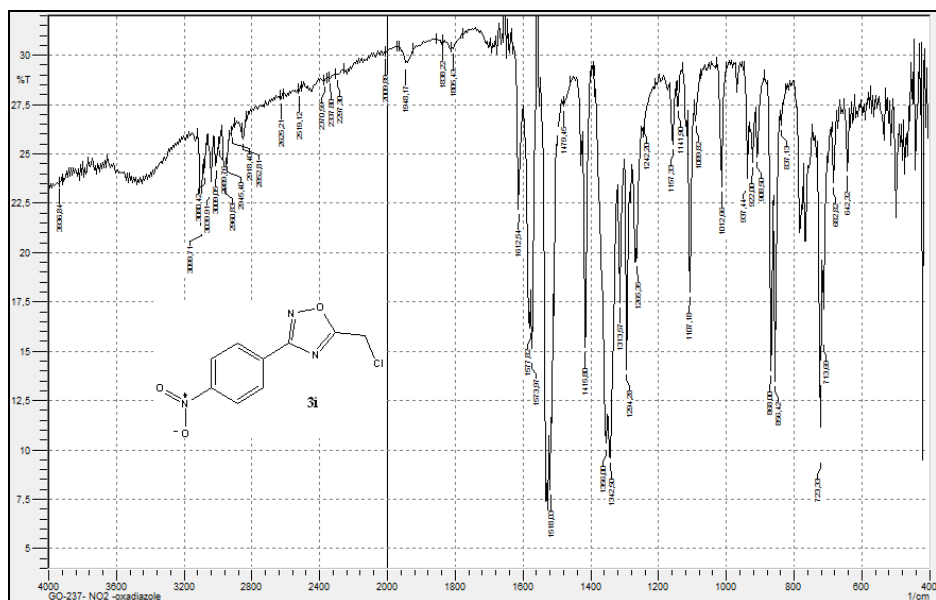


Figure 4.22. The IR spectrum of **3i**

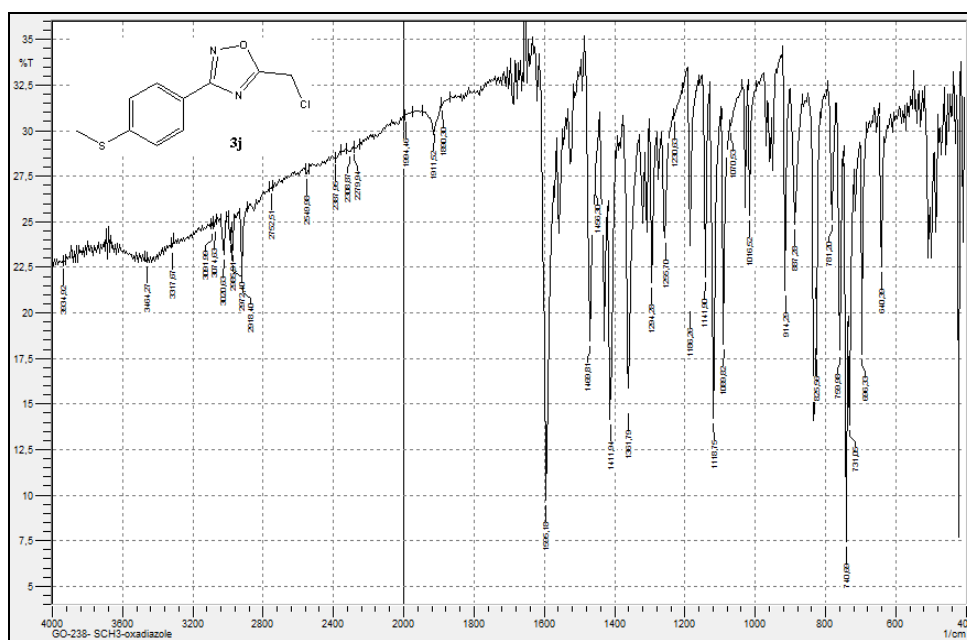


Figure 4.23. The IR spectrum of **3j**

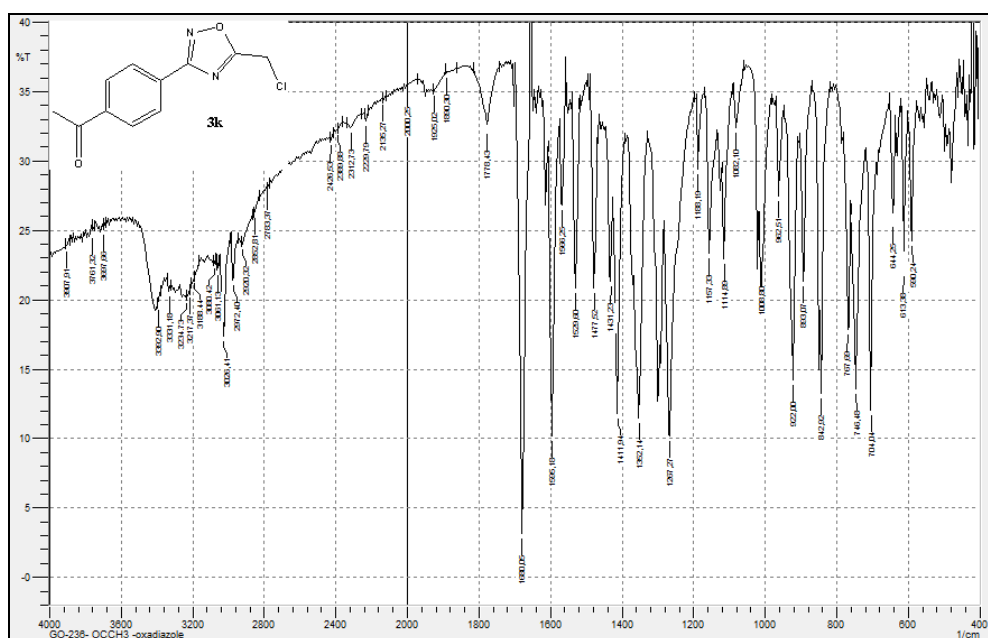


Figure 4.24. The IR spectrum of **3k**

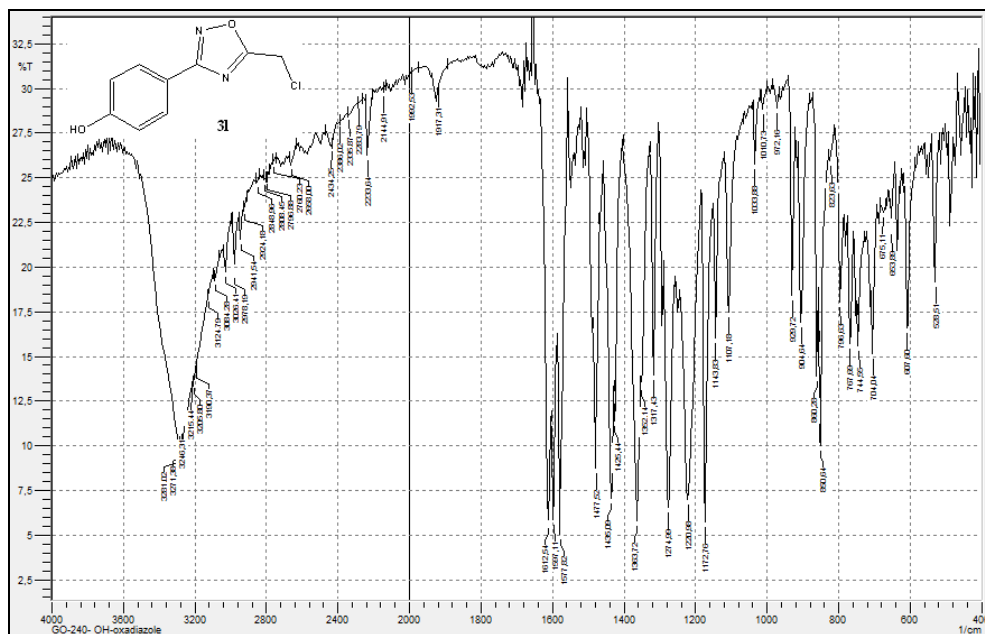


Figure 4.25. The IR spectrum of **3l**

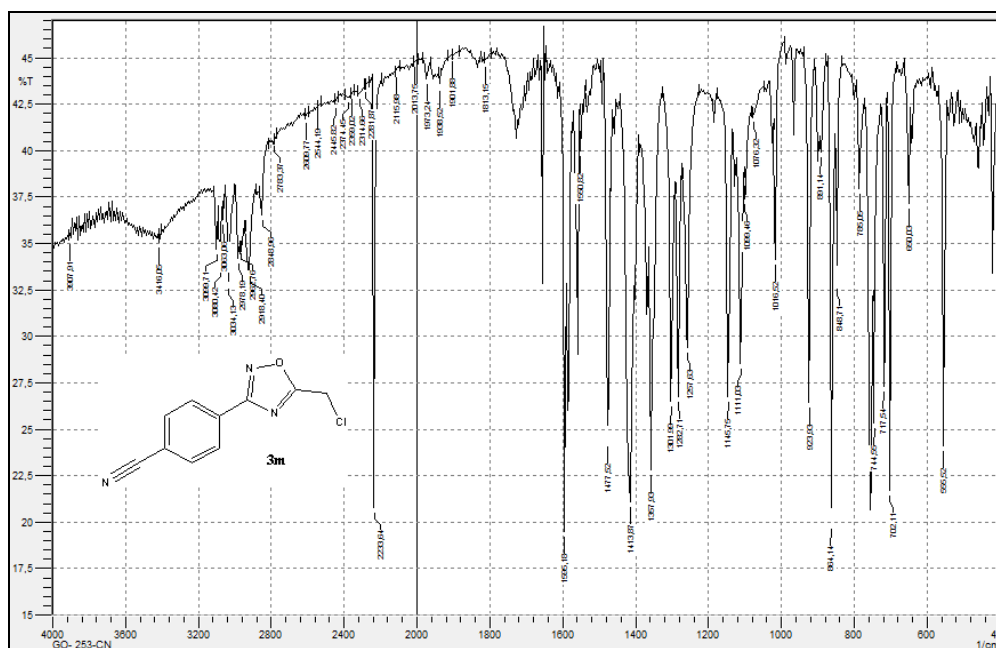


Figure 4.26. The IR spectrum of **3m**

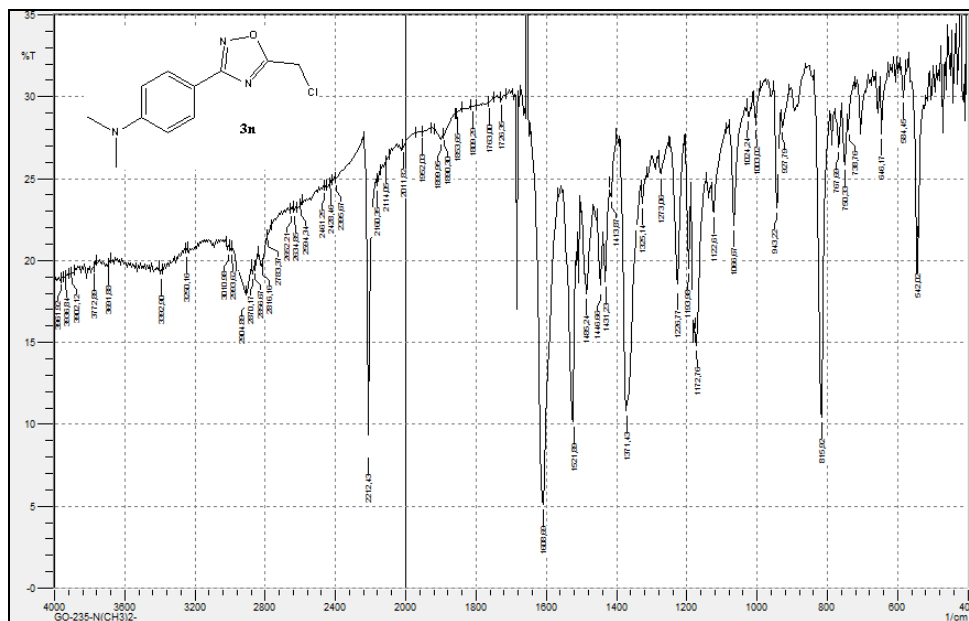


Figure 4.27. The IR spectrum of **3n**

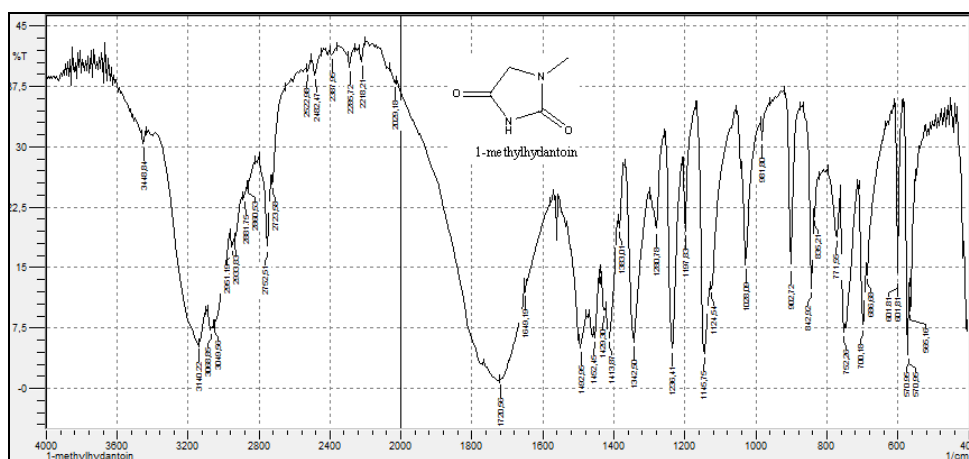


Figure 4.28. The IR spectrum of **4**

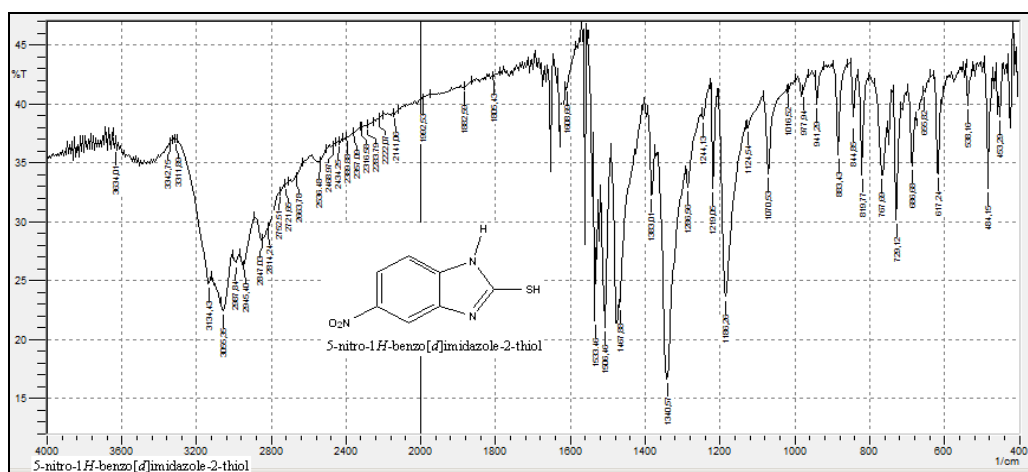


Figure 4.29. The IR spectrum of **5**

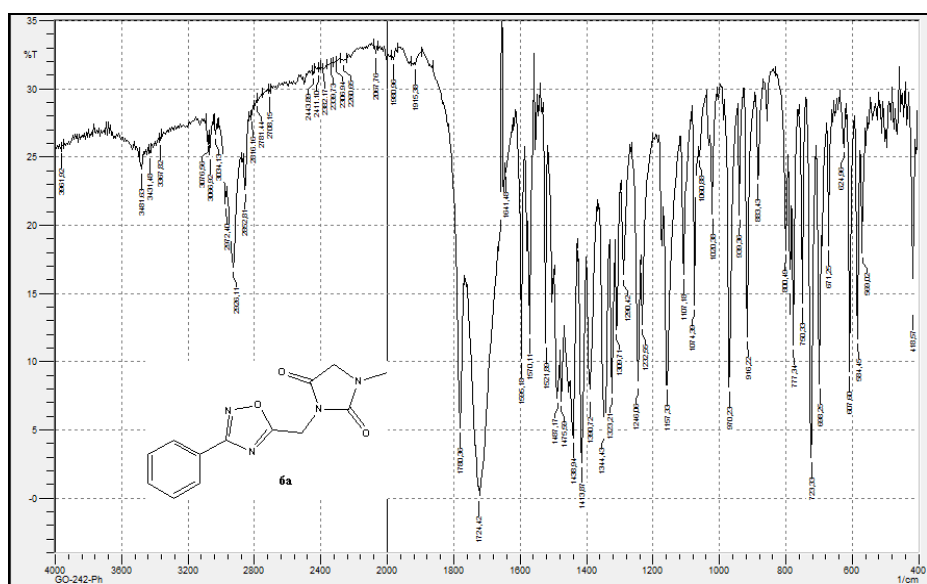


Figure 4.30. The IR spectrum of **6a**

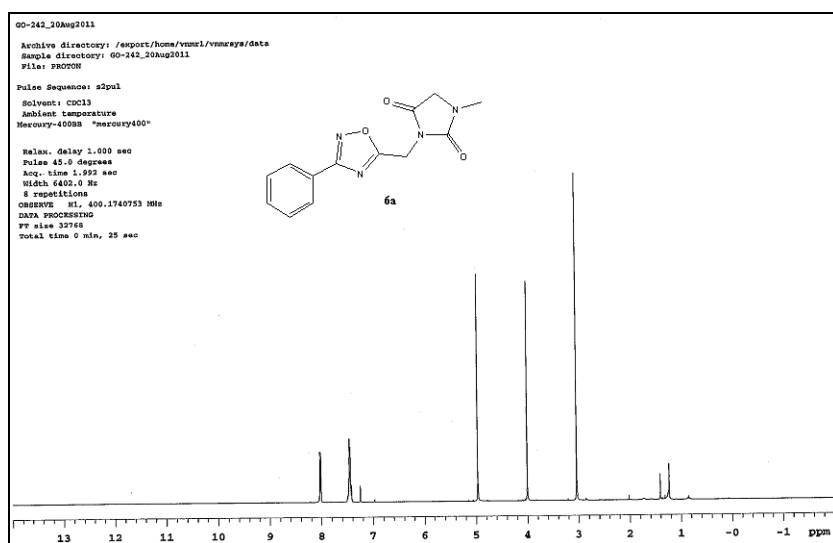


Figure 4.31. The ^1H NMR spectrum of **6a**

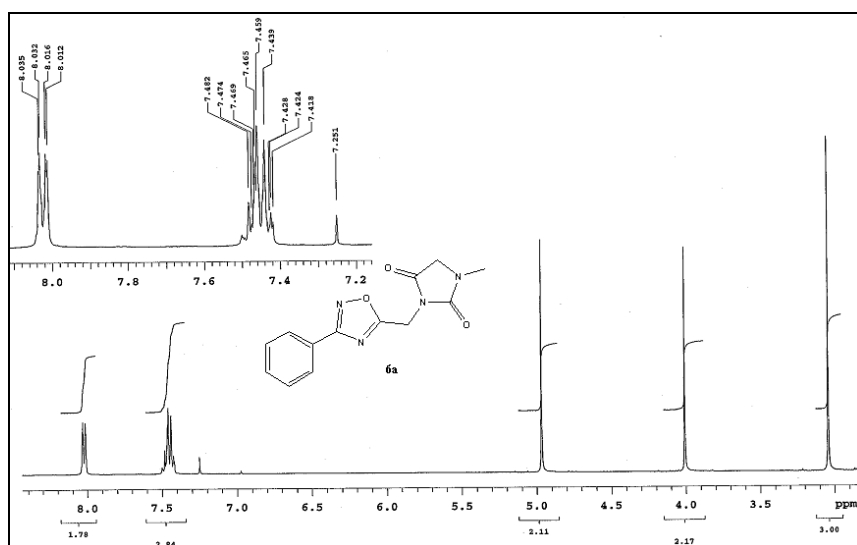


Figure 4.32. The expanded ^1H NMR spectrum of **6a**

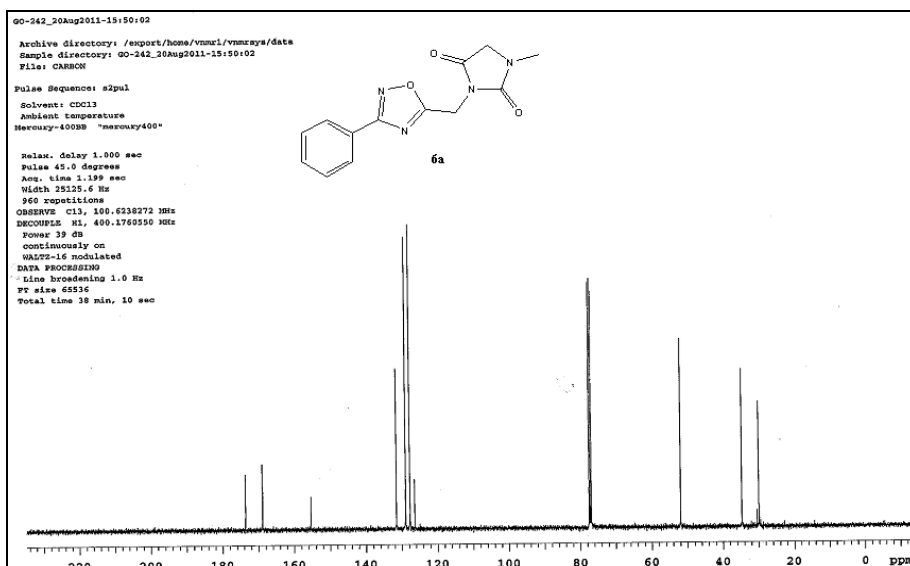


Figure 4.33. The ^{13}C NMR spectrum of 6a

Chemical Formula: $\text{C}_{13}\text{H}_{12}\text{N}_4\text{O}_3$

Molecular Weight: 272.26

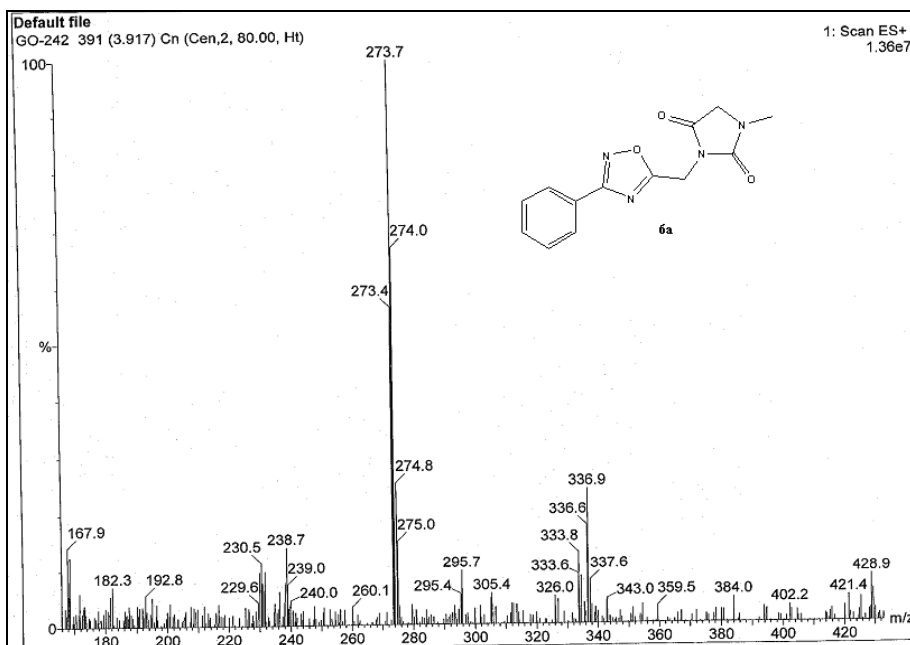


Figure 4.34. LC-MS spectrum of 6a

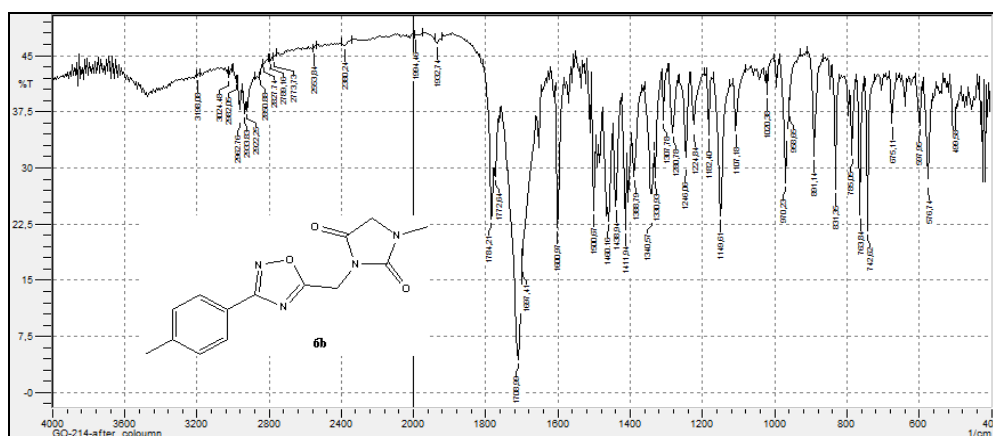


Figure 4.35. The IR spectrum of **6b**

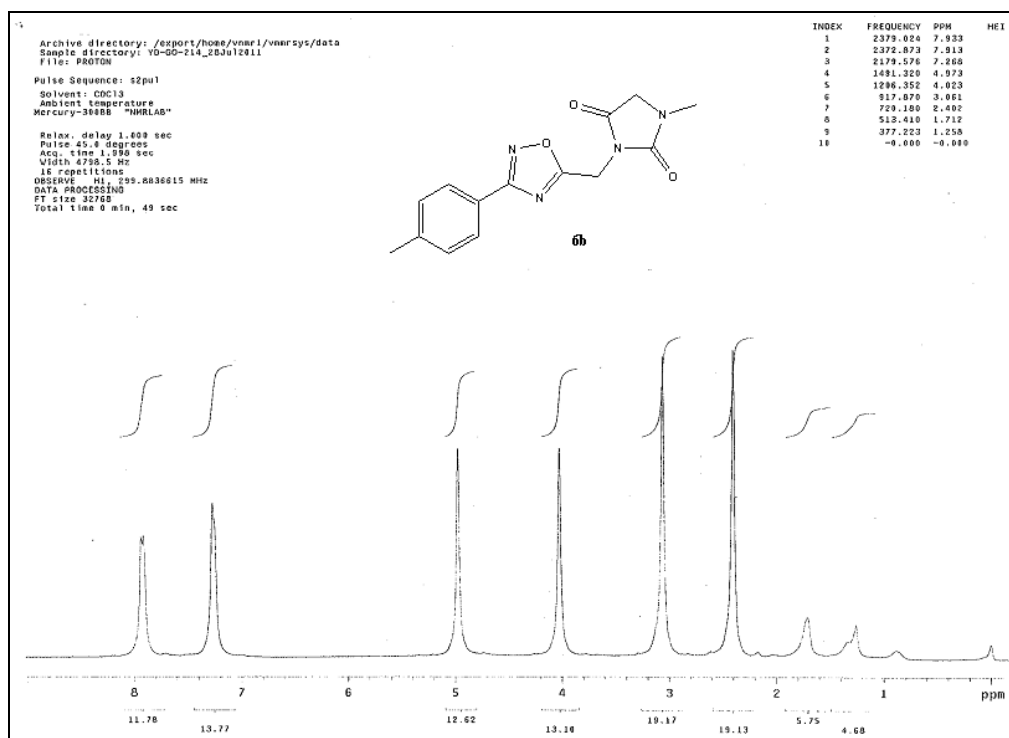


Figure 4.36. The ^1H NMR spectrum of **6b**

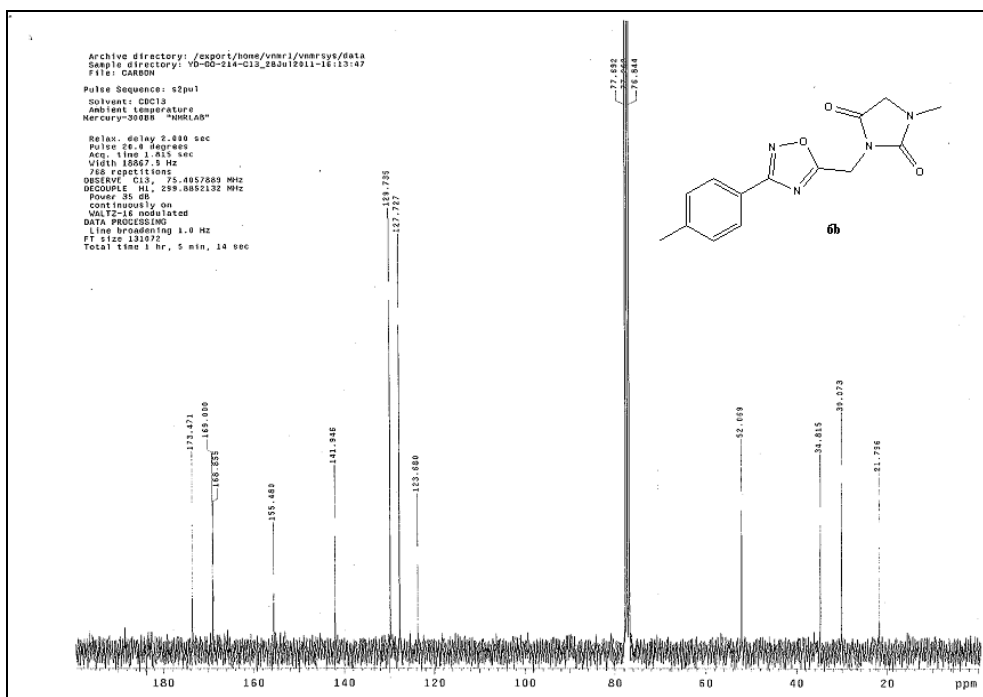


Figure 4.37. The ^{13}C NMR spectrum of **6b**

Chemical Formula: $\text{C}_{14}\text{H}_{14}\text{N}_4\text{O}_3$
Molecular Weight: 286,29

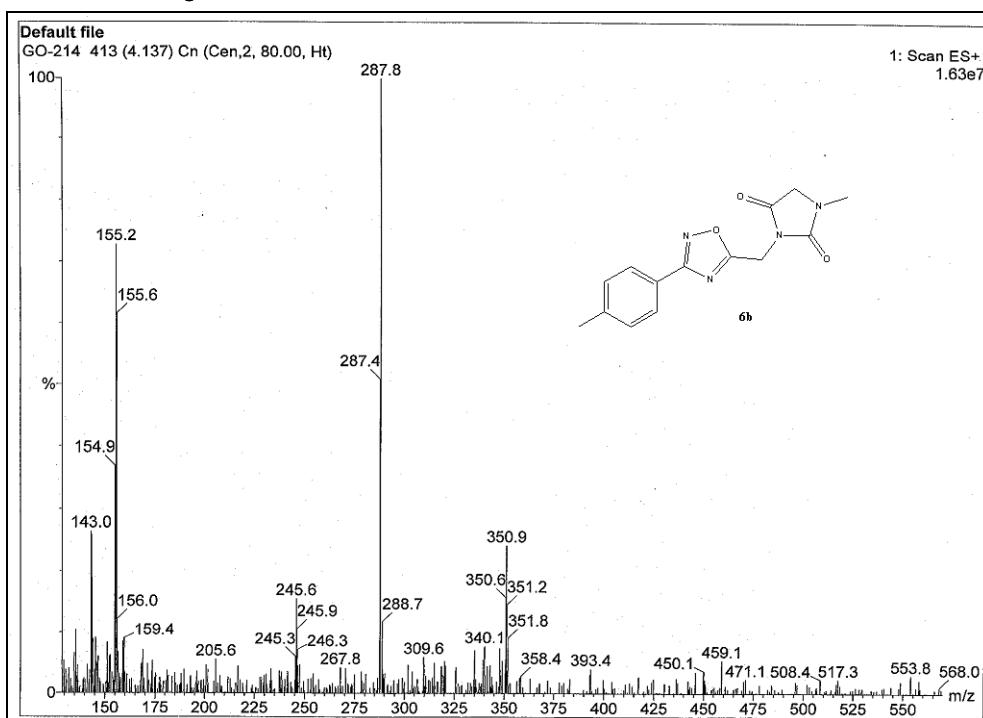
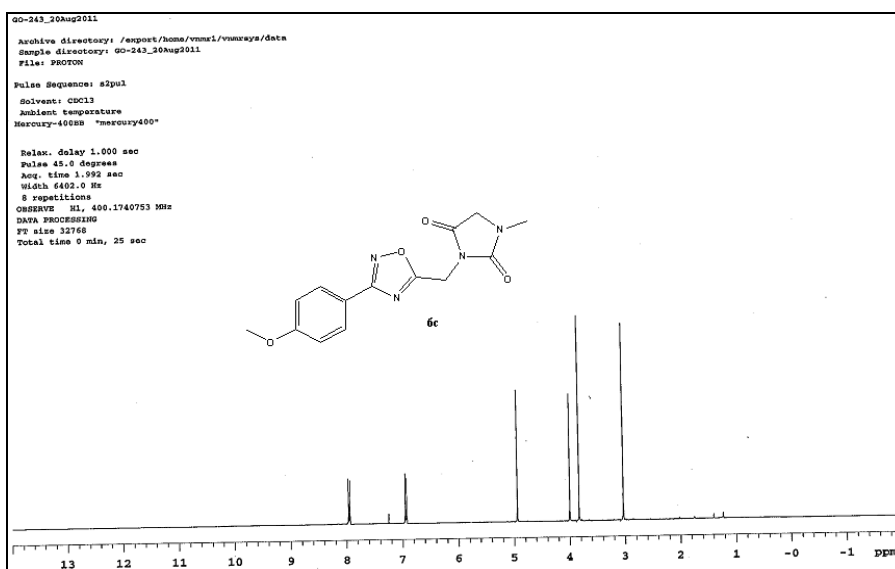
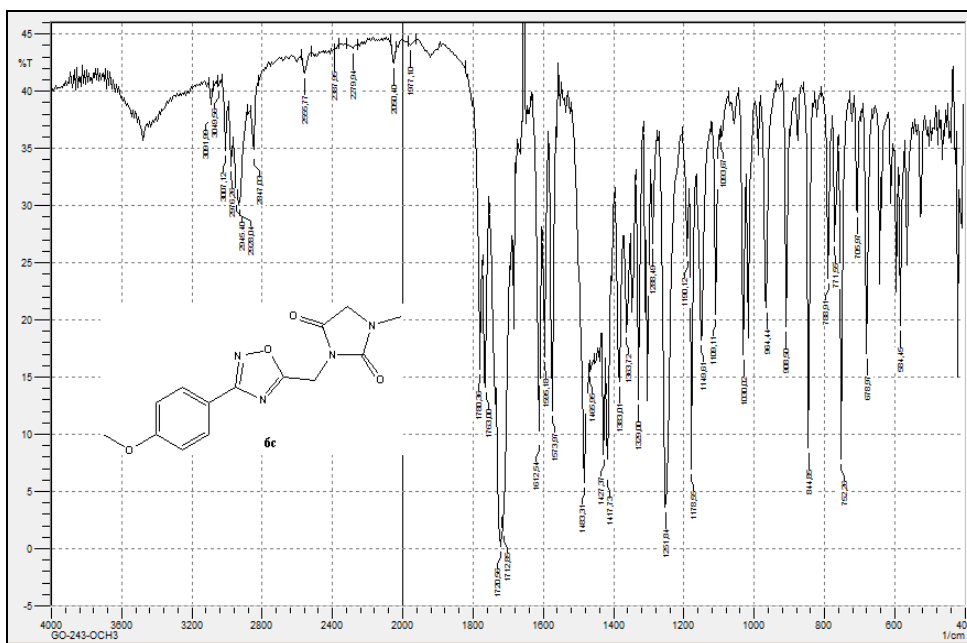


Figure 4.38. LC-MS spectrum of **6b**



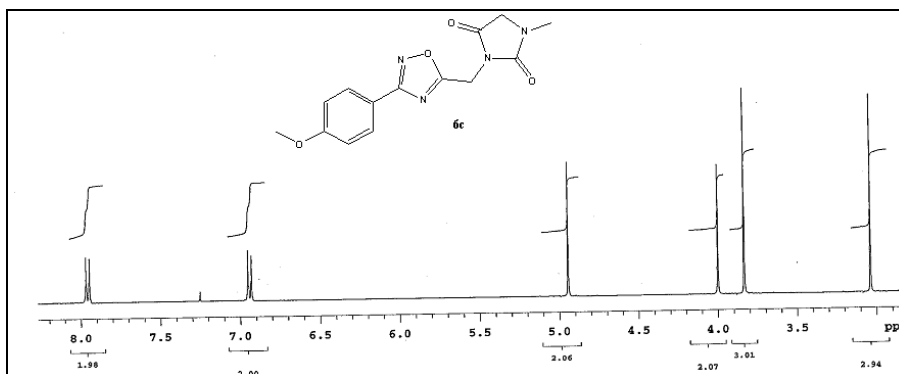


Figure 4.41. The expanded ¹H NMR spectrum of **6c**

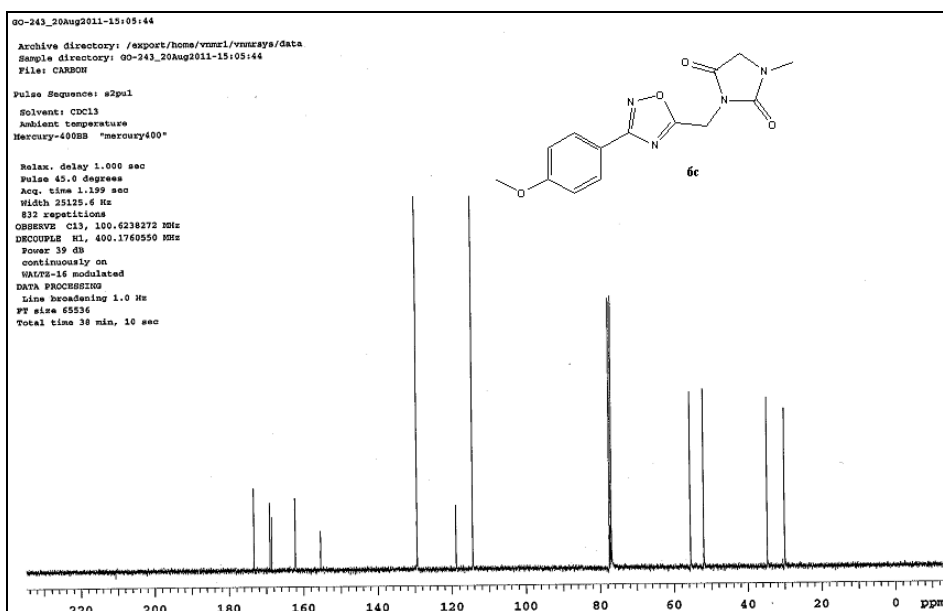


Figure 4.42. The ¹³C NMR spectrum of **6c**

Chemical Formula: $C_{14}H_{14}N_4O_4$
Molecular Weight: 302,29

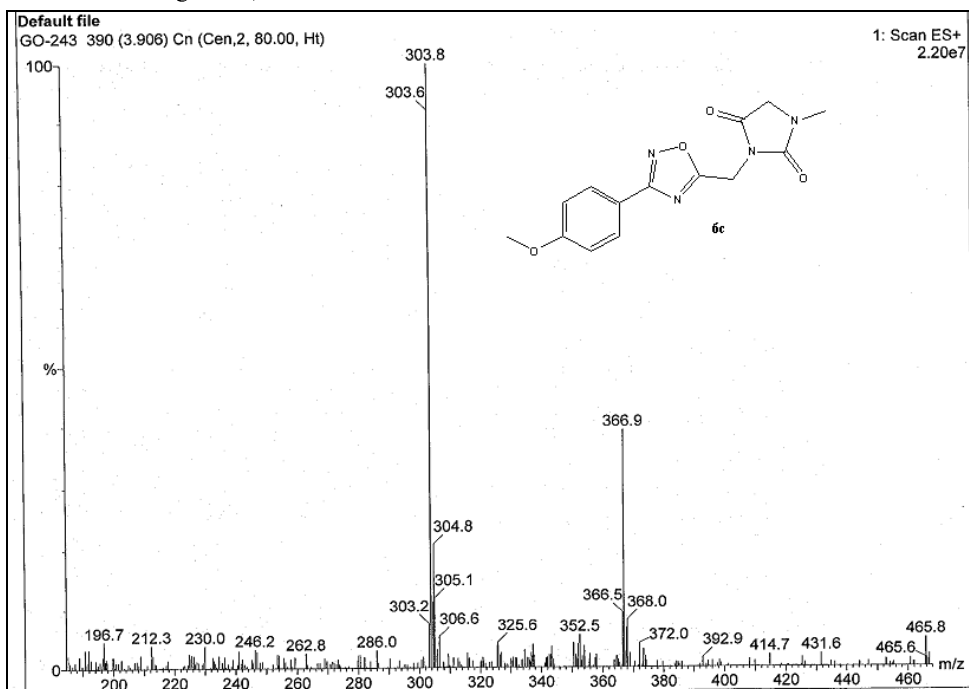


Figure 4.43. LC-MS spectrum of **6c**

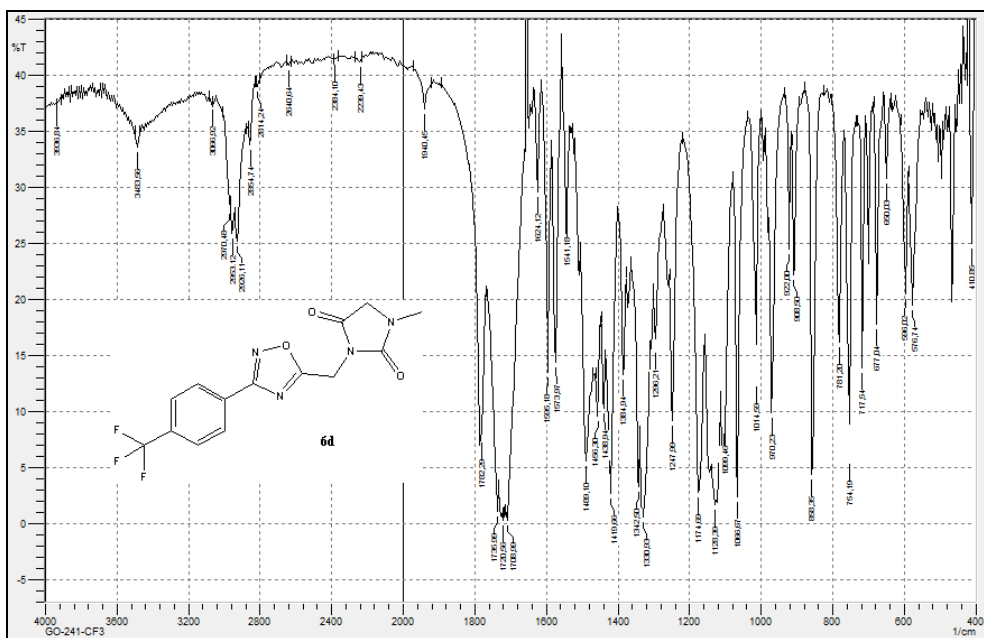


Figure 4.44. The IR spectrum of **6d**

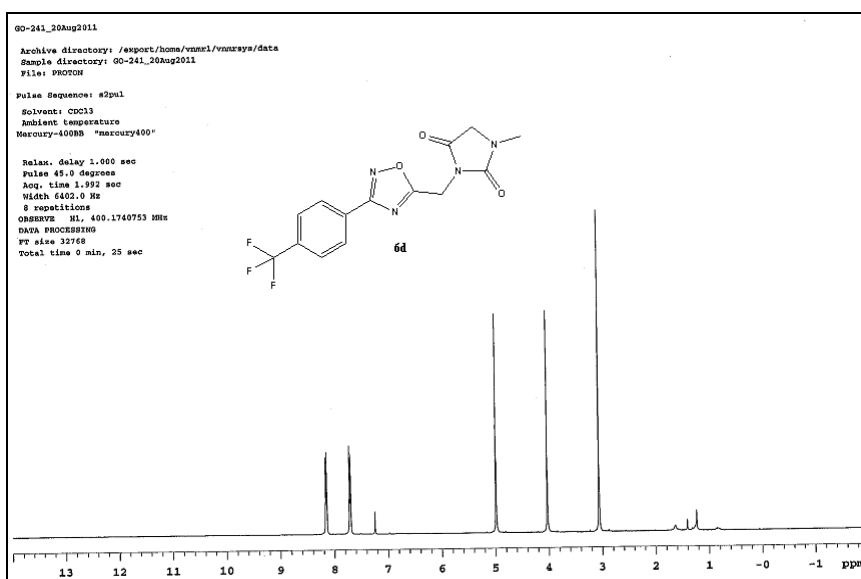


Figure 4.45. The ^1H NMR spectrum of **6d**

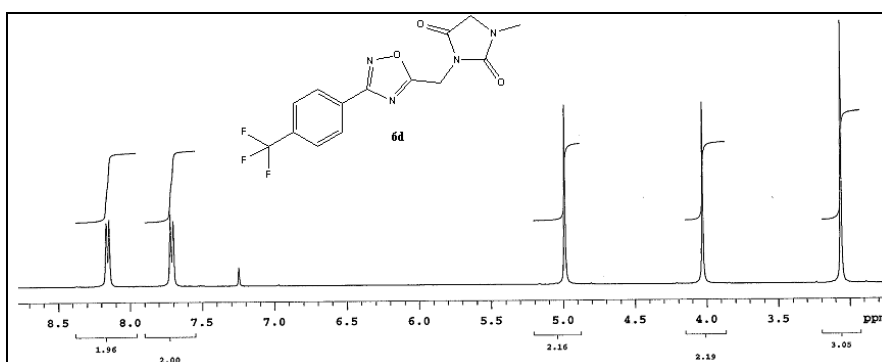


Figure 4.46. The expanded ^1H NMR spectrum of **6d**

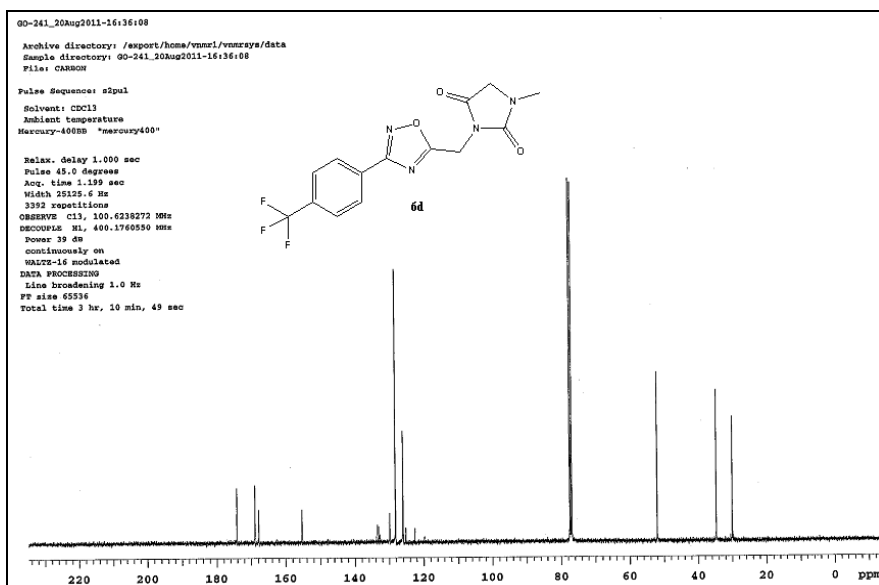


Figure 4.47. The ^{13}C NMR spectrum of **6d**

Chemical Formula: $\text{C}_{14}\text{H}_{11}\text{F}_3\text{N}_4\text{O}_3$
 Molecular Weight: 340.26

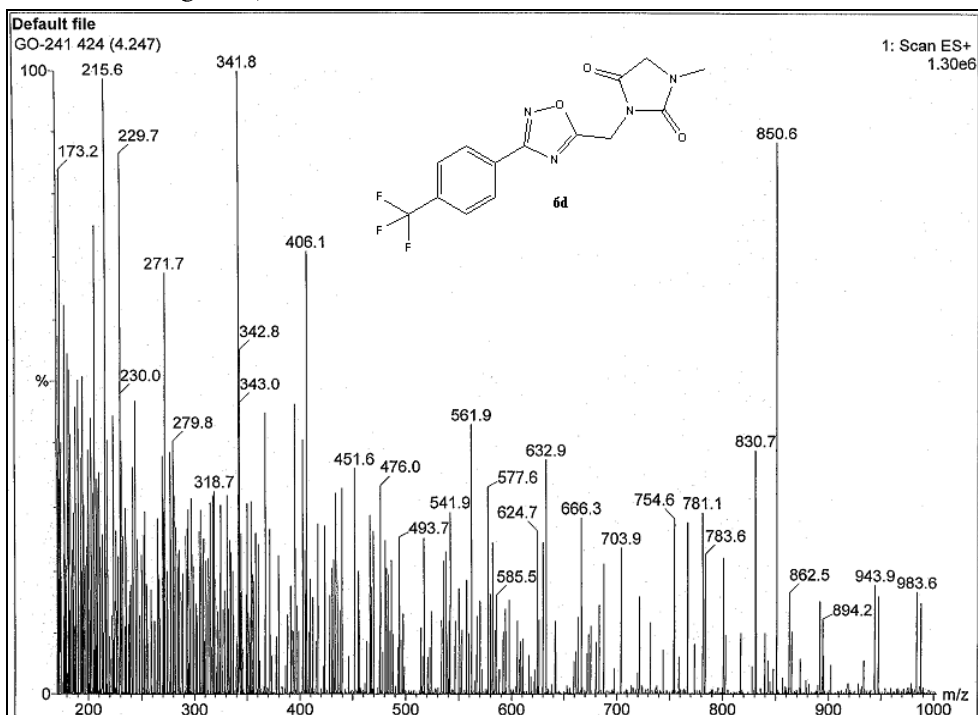


Figure 4.48. LC-MS spectrum of **6d**

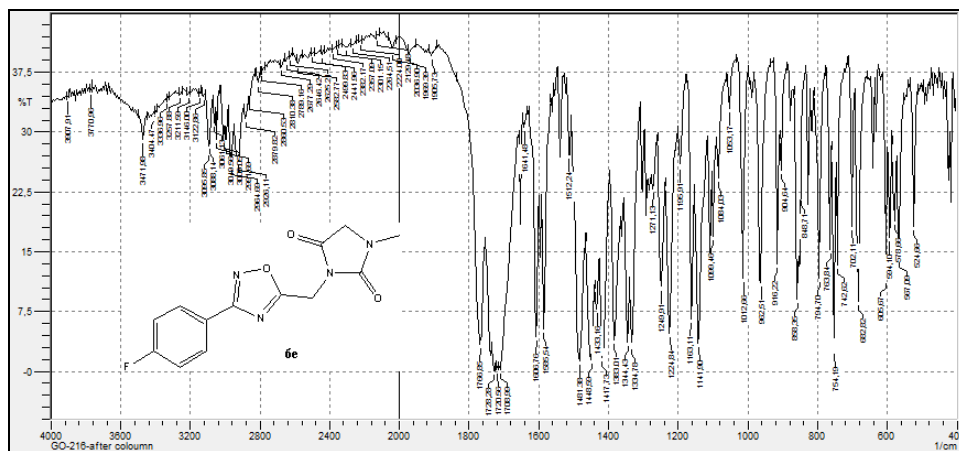


Figure 4.49. The IR spectrum of **6e**

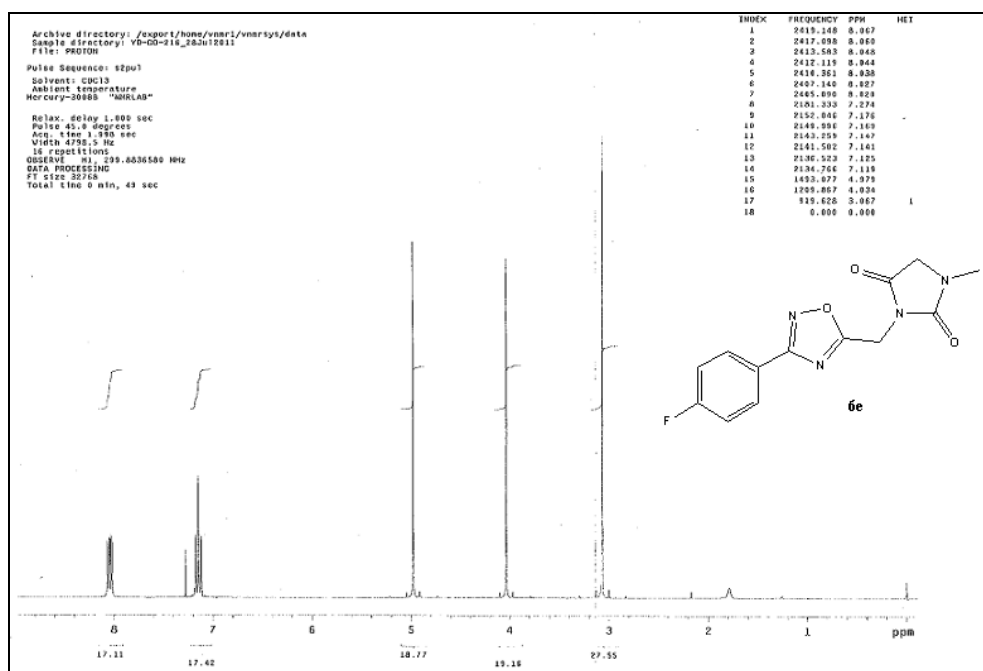


Figure 4.50. The ^1H NMR spectrum of **6e**

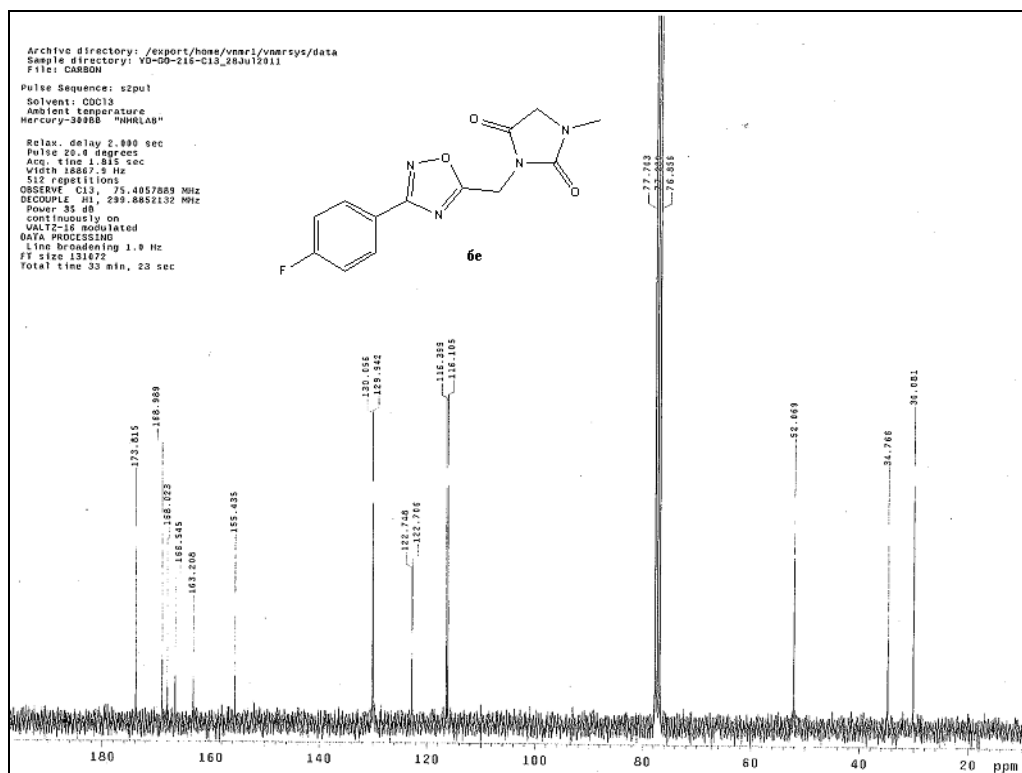


Figure 4.51. The ^{13}C NMR spectrum of **6e**

Chemical Formula: $\text{C}_{13}\text{H}_{11}\text{FN}_4\text{O}_3$
 Molecular Weight: 290,25

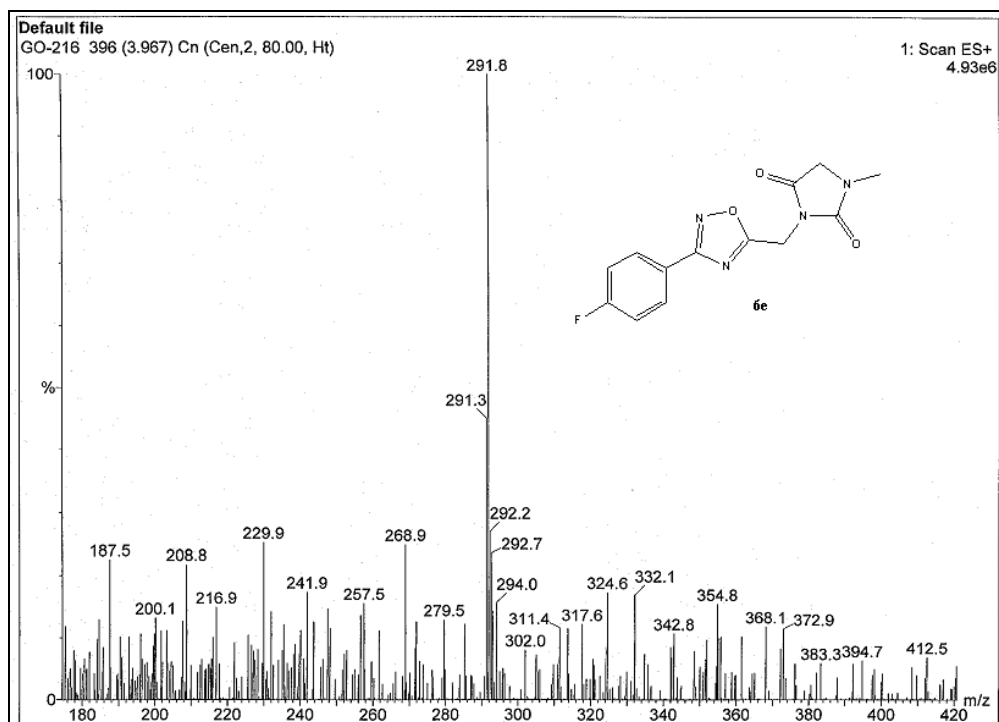


Figure 4.52. LC-MS spectrum of **6e**

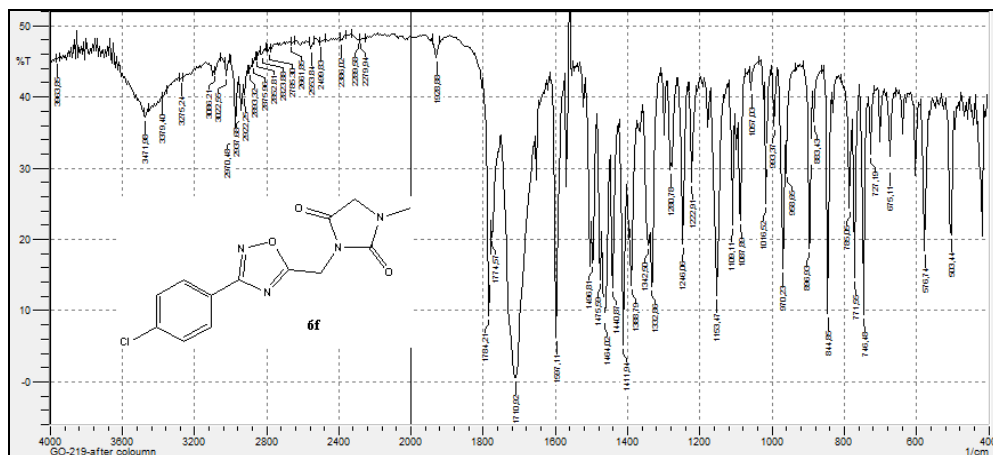


Figure 4.53. The IR spectrum of **6f**

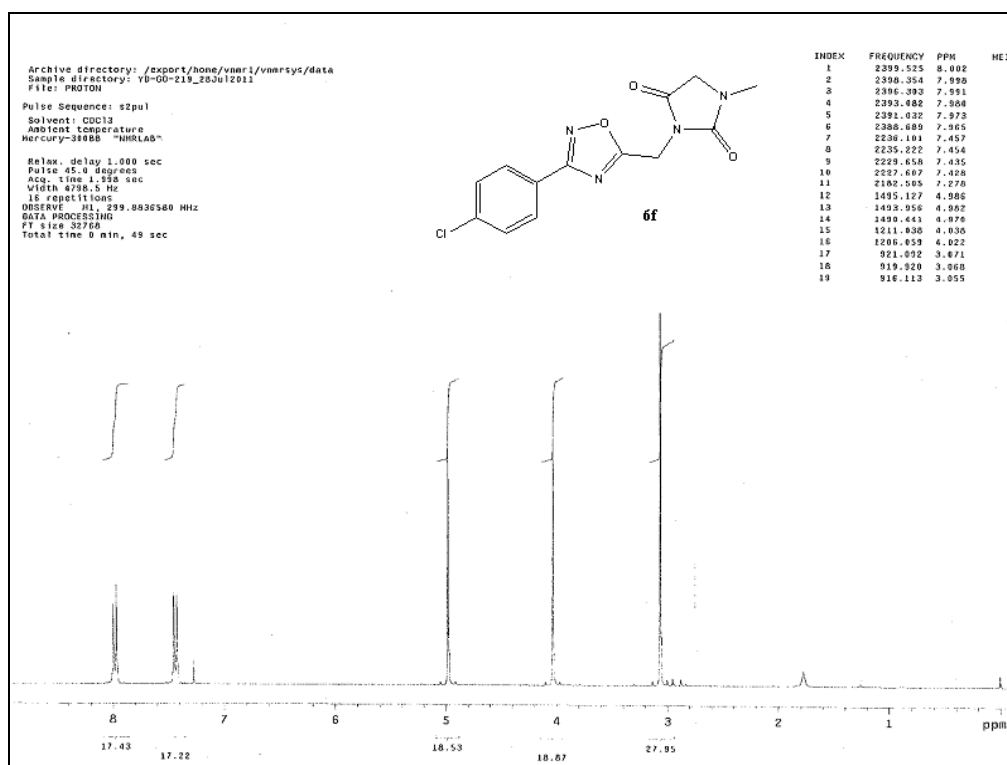


Figure 4.54. The ^1H NMR spectrum of **6f**

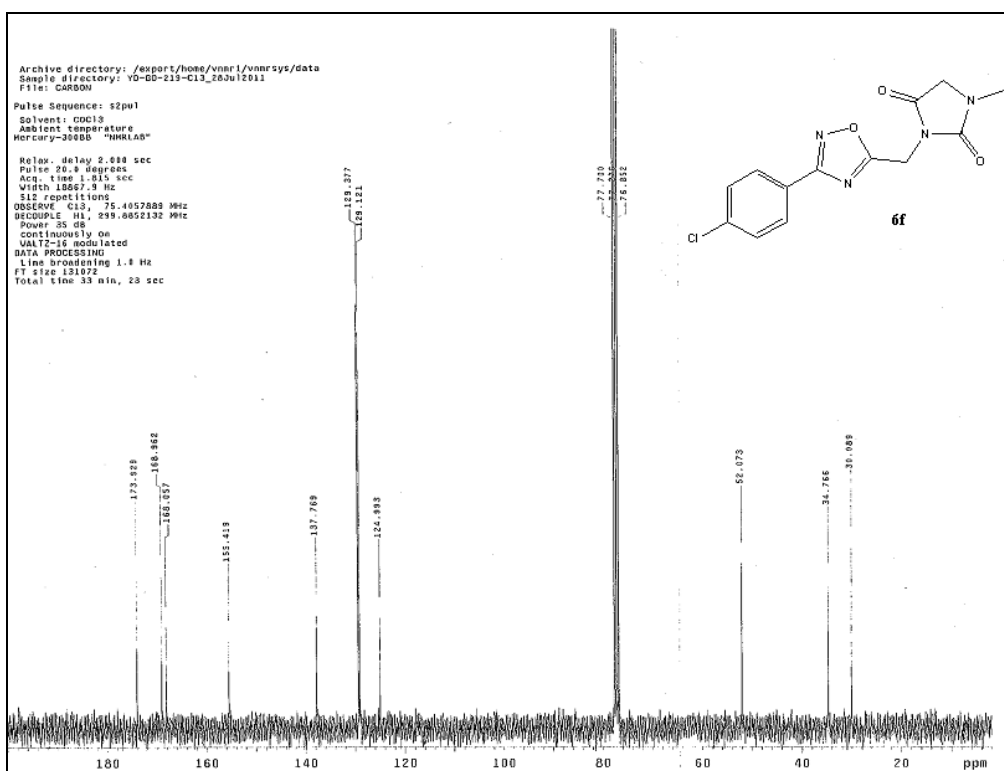


Figure 4.55. The ^{13}C NMR spectrum of **6f**

Chemical Formula: $\text{C}_{13}\text{H}_{11}\text{ClN}_4\text{O}_3$
Molecular Weight: 306.70

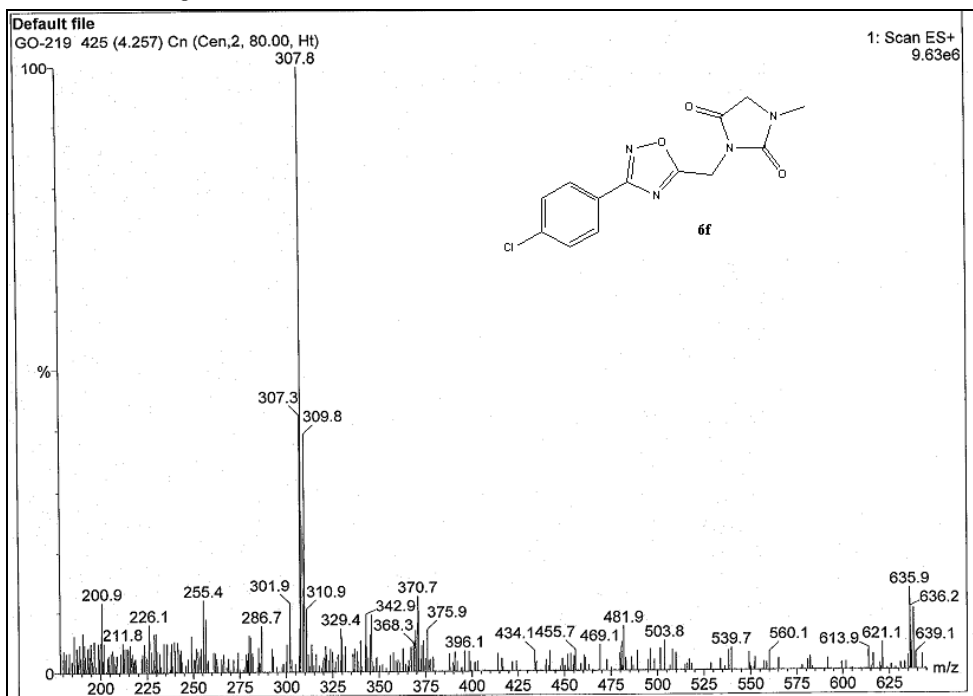


Figure 4.56. LC-MS spectrum of **6f**

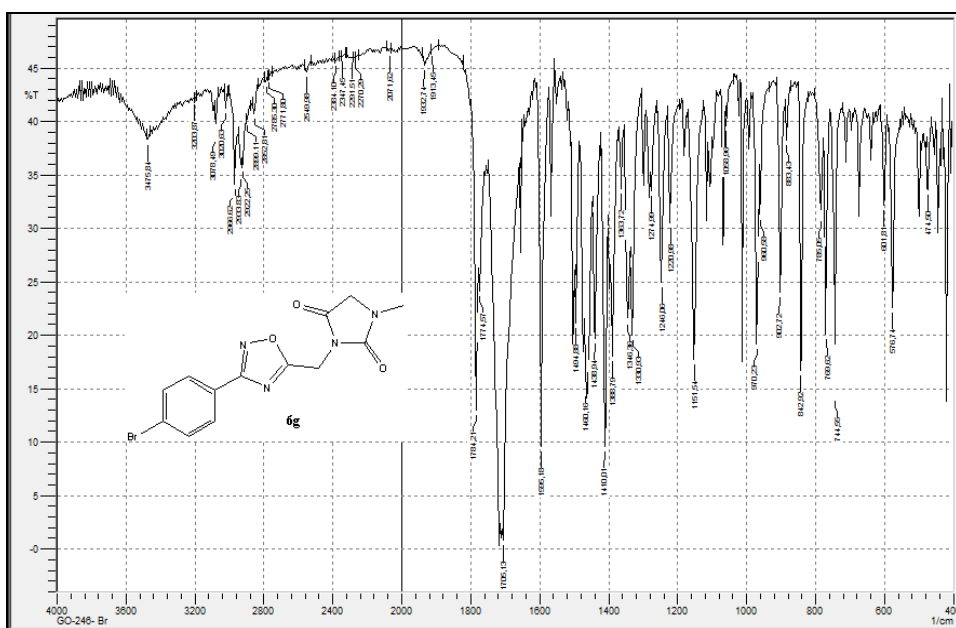


Figure 4.57. The IR spectrum of **6g**

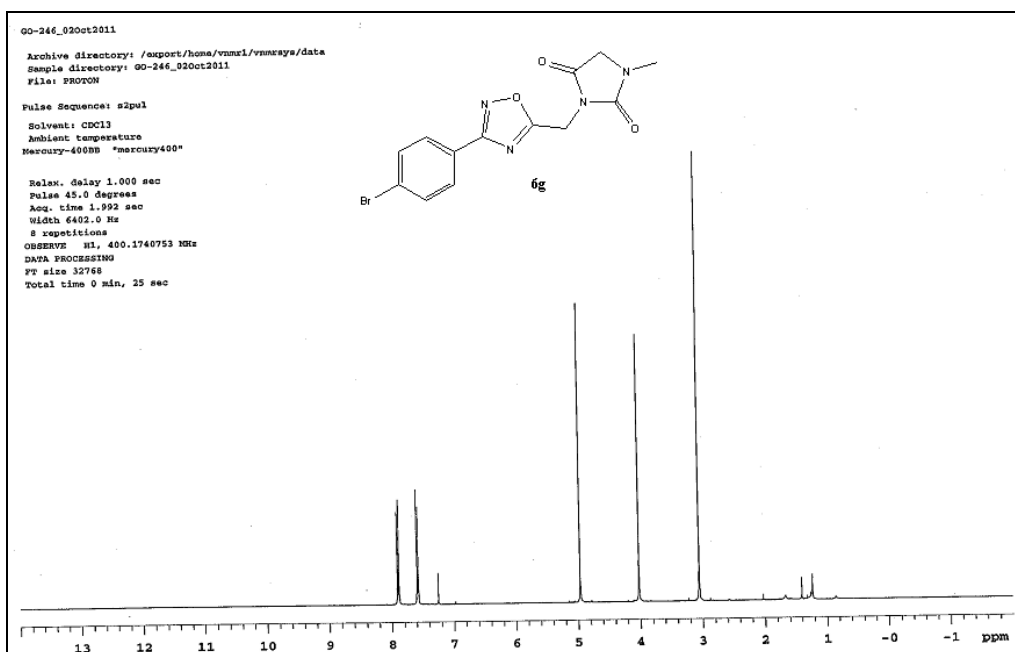


Figure 4.58. The ¹H NMR spectrum of **6g**

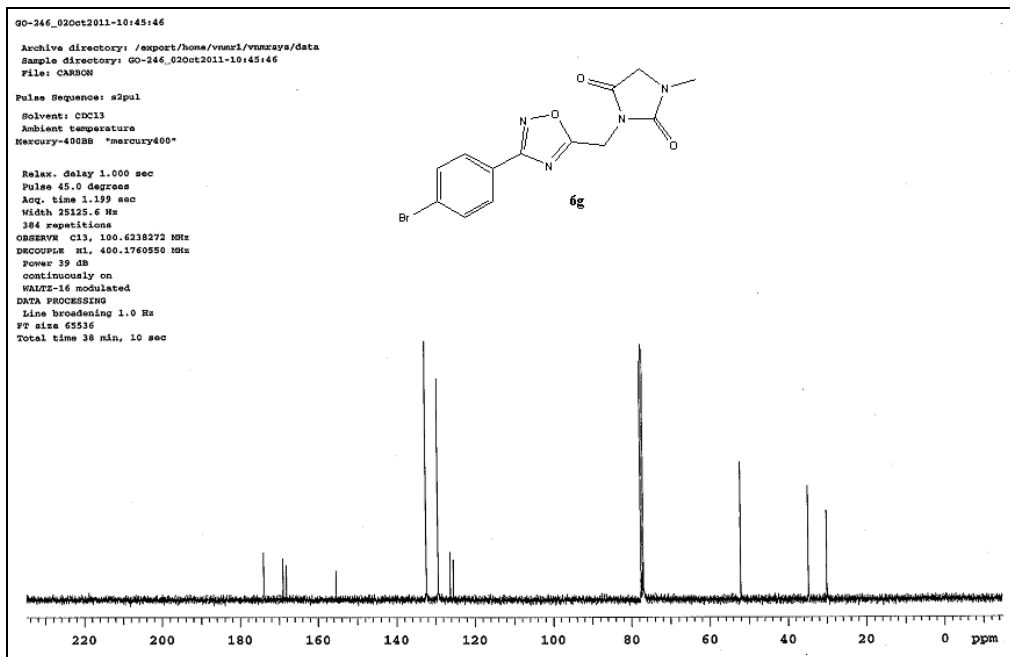


Figure 4.59. The ^{13}C NMR spectrum of **6g**

Chemical Formula: $\text{C}_{13}\text{H}_{11}\text{BrN}_4\text{O}_3$
 Molecular Weight: 351,16

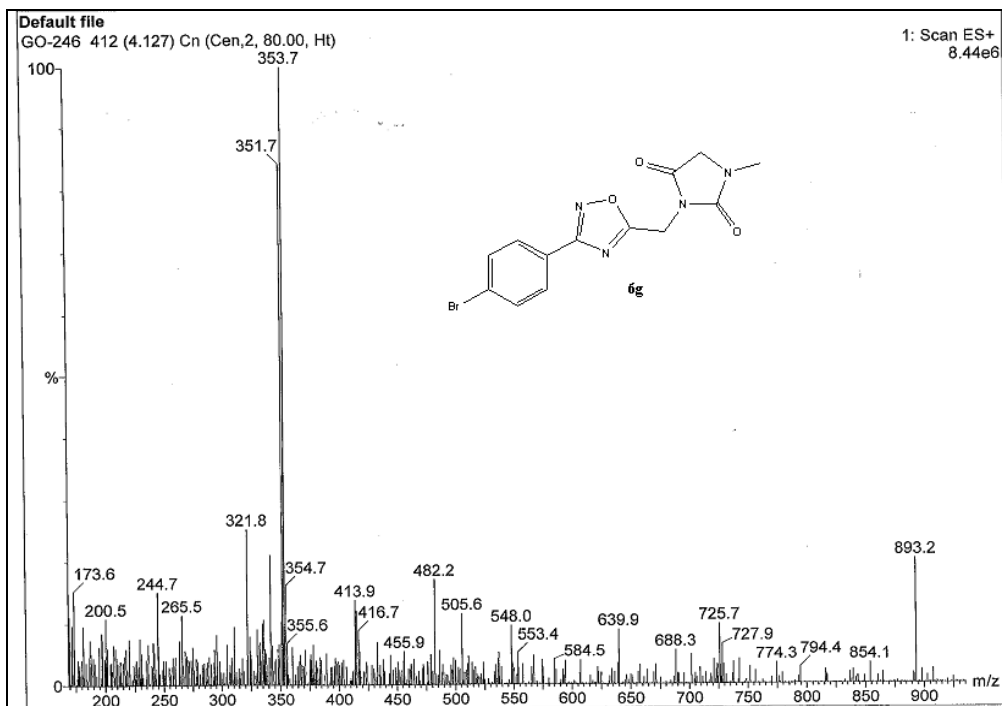


Figure 4.60. LC-MS spectrum of **6g**

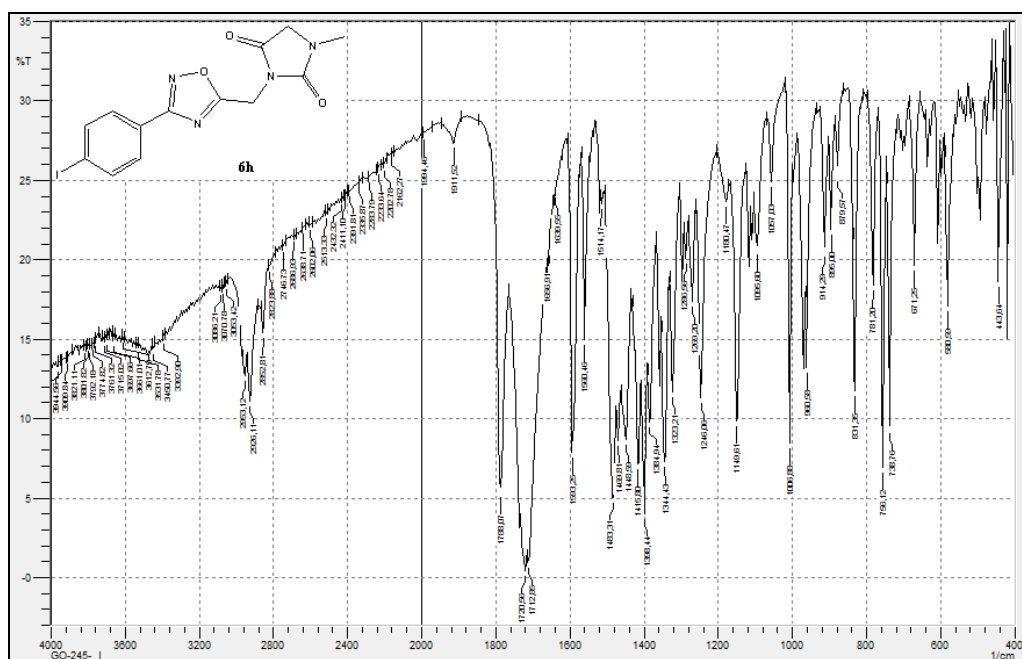


Figure 4.61. The IR spectrum of **6h**

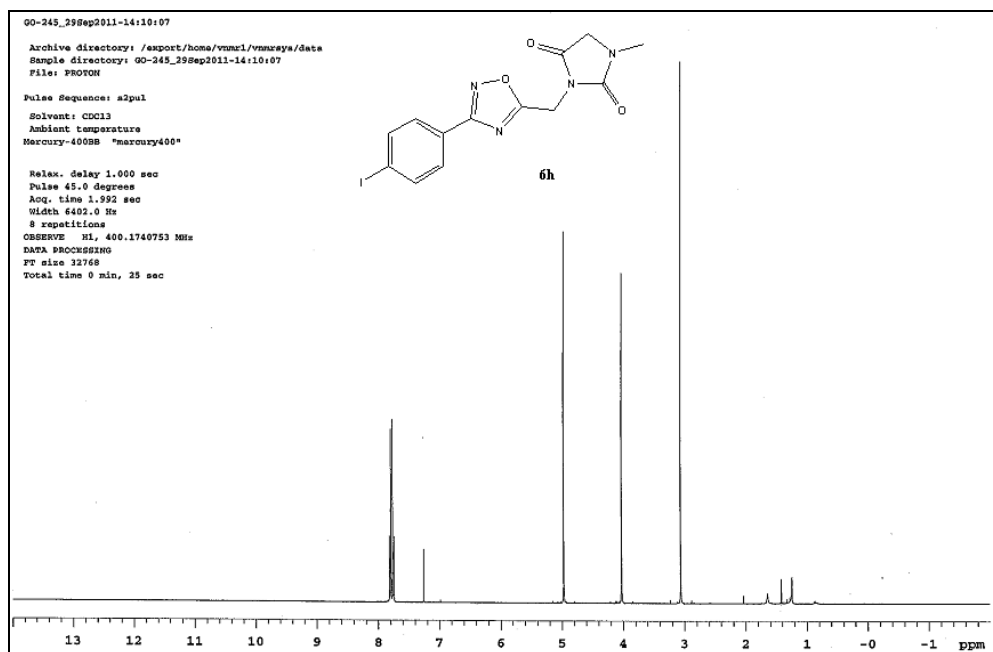


Figure 4.62. The ¹H NMR spectrum of **6h**

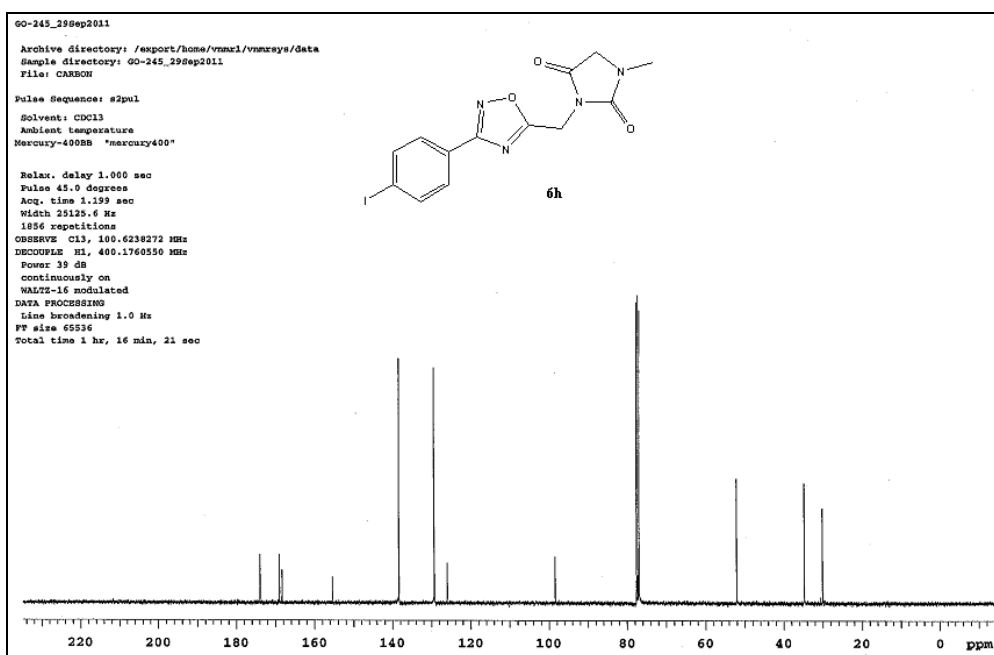


Figure 4.63. The ^{13}C NMR spectrum of **6h**

Chemical Formula: $\text{C}_{13}\text{H}_{11}\text{IN}_4\text{O}_3$
 Molecular Weight: 398,16

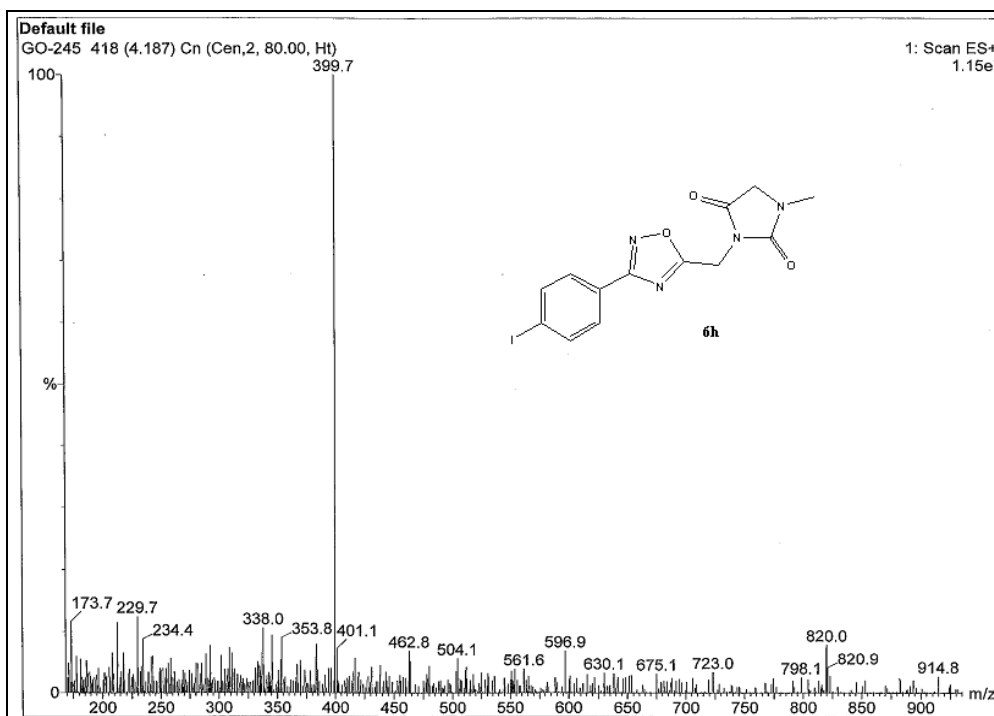


Figure 4.64. LC-MS spectrum of **6h**

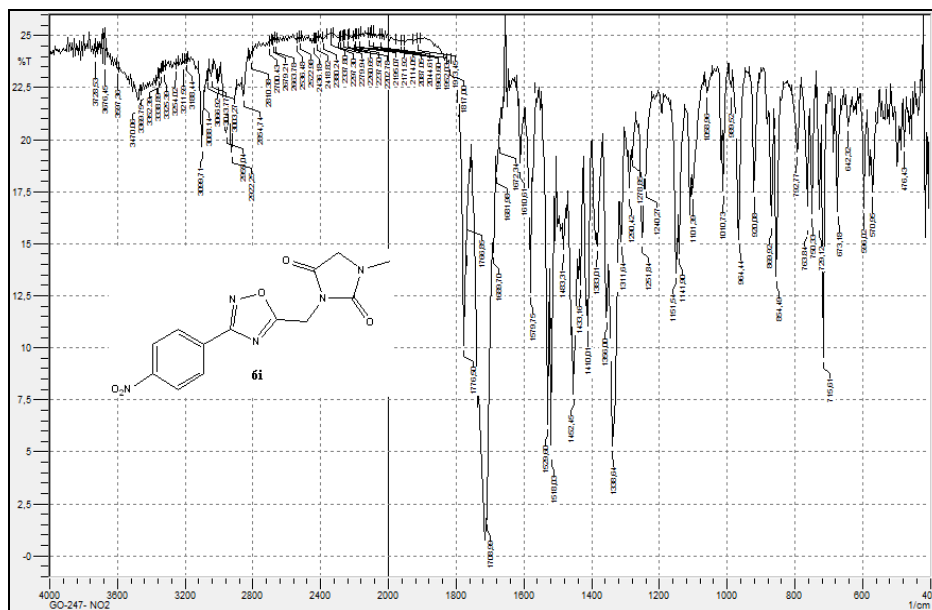


Figure 4.65. The IR spectrum of **6i**

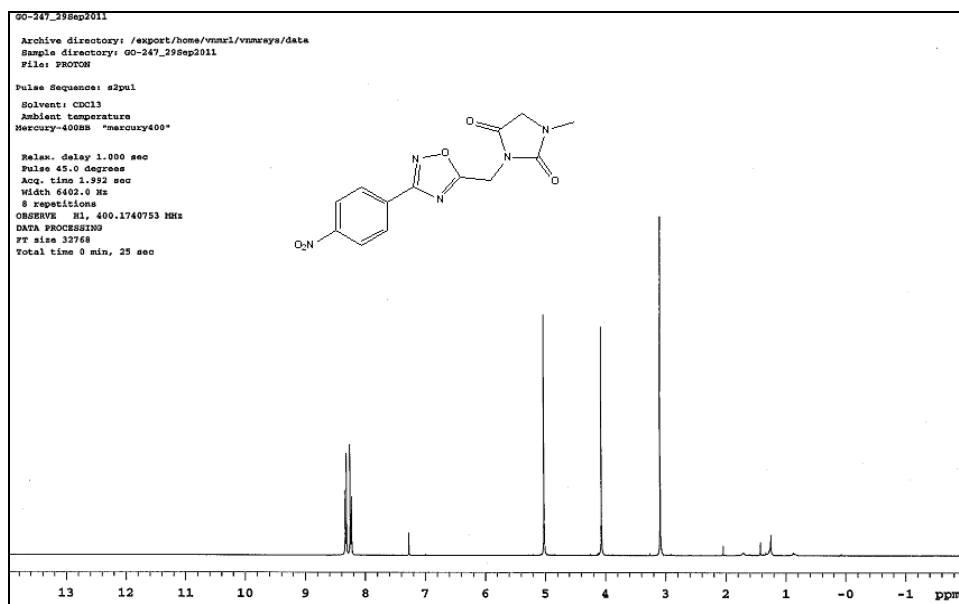


Figure 4.66. The ^1H NMR spectrum of **6i**

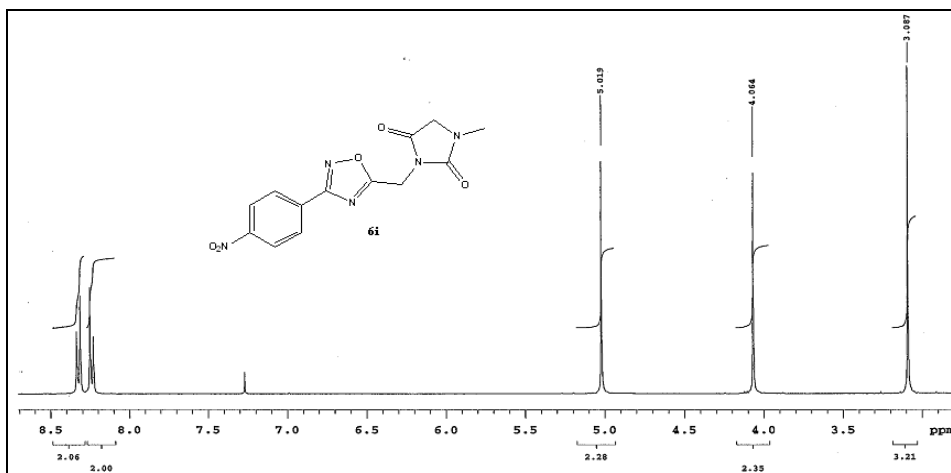


Figure 4.67. The expanded ¹H NMR spectrum of **6i**

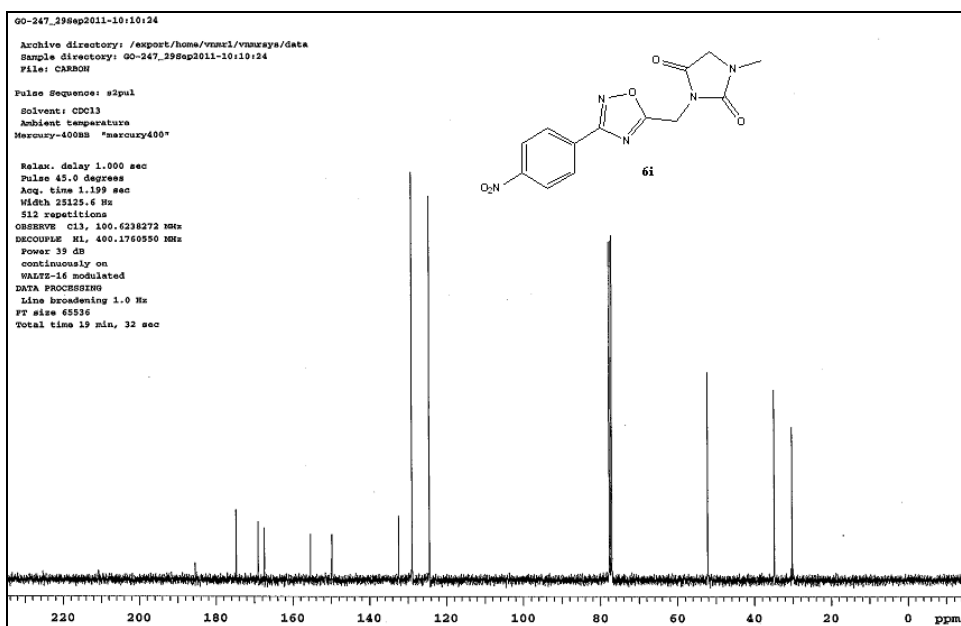


Figure 4.68. The ¹³C NMR spectrum of **6i**

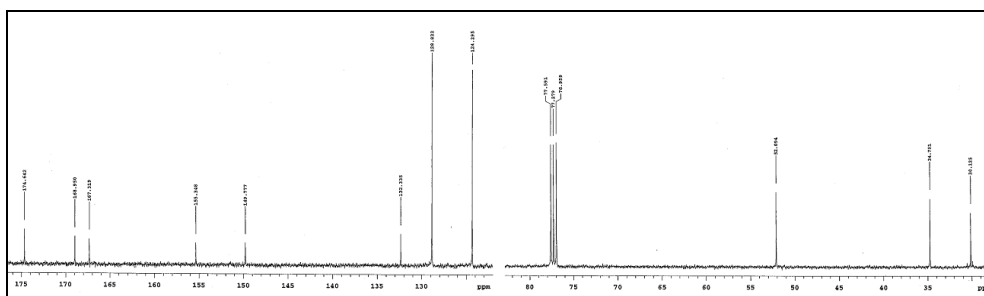


Figure 4.69. The expanded ^{13}C NMR spectrum of **6i**

Chemical Formula: $\text{C}_{13}\text{H}_{11}\text{N}_5\text{O}_5$
Molecular Weight: 317,26

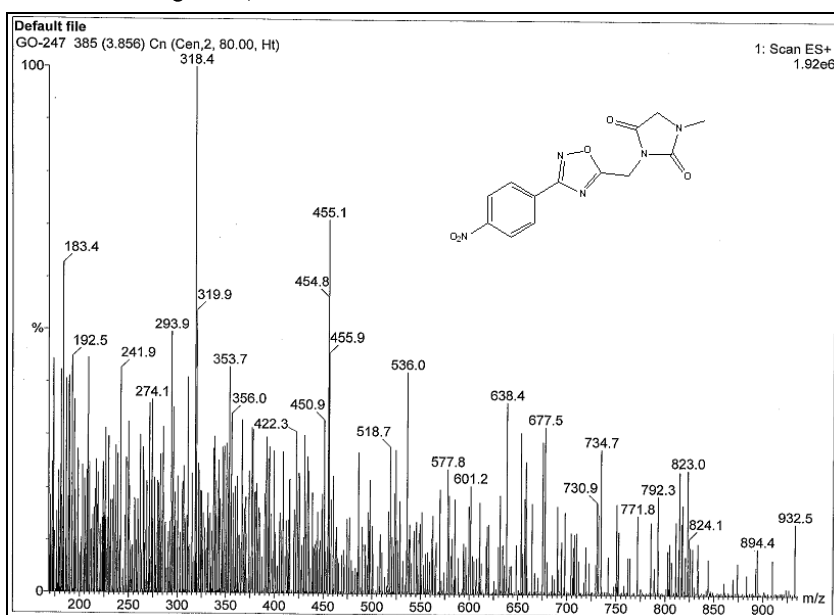


Figure 4.70 . LC-MS spectrum of **6i**

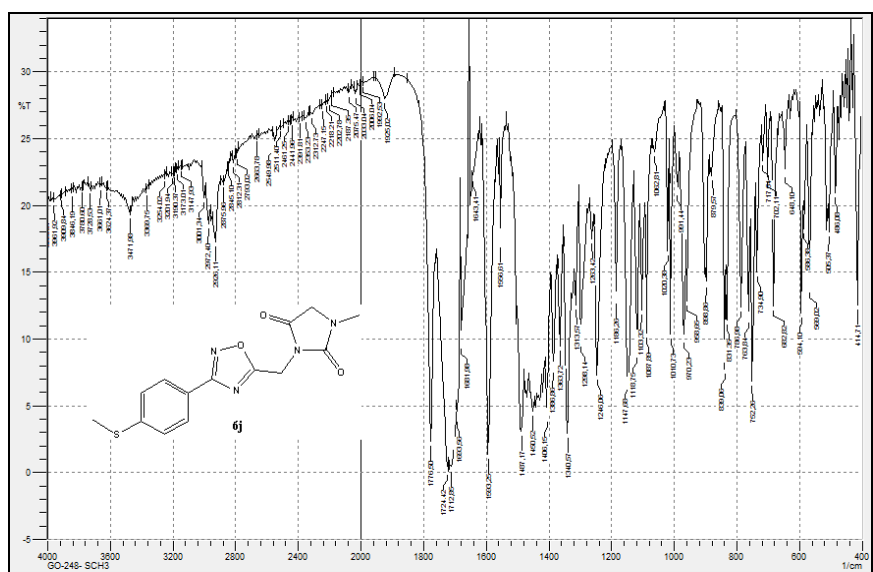


Figure 4.71. The IR spectrum of **6j**

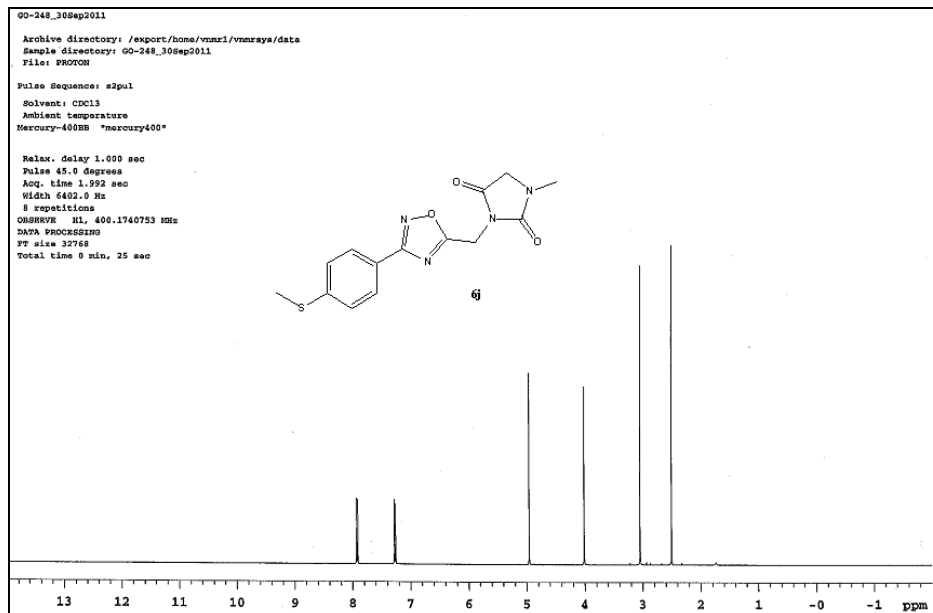


Figure 4.72. The ^1H NMR spectrum of **6j**

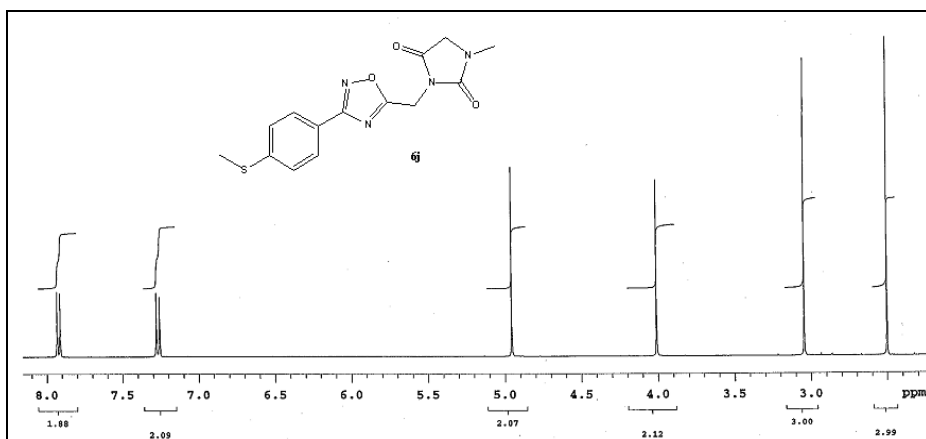


Figure 4.73. The expanded ¹H NMR spectrum of **6j**

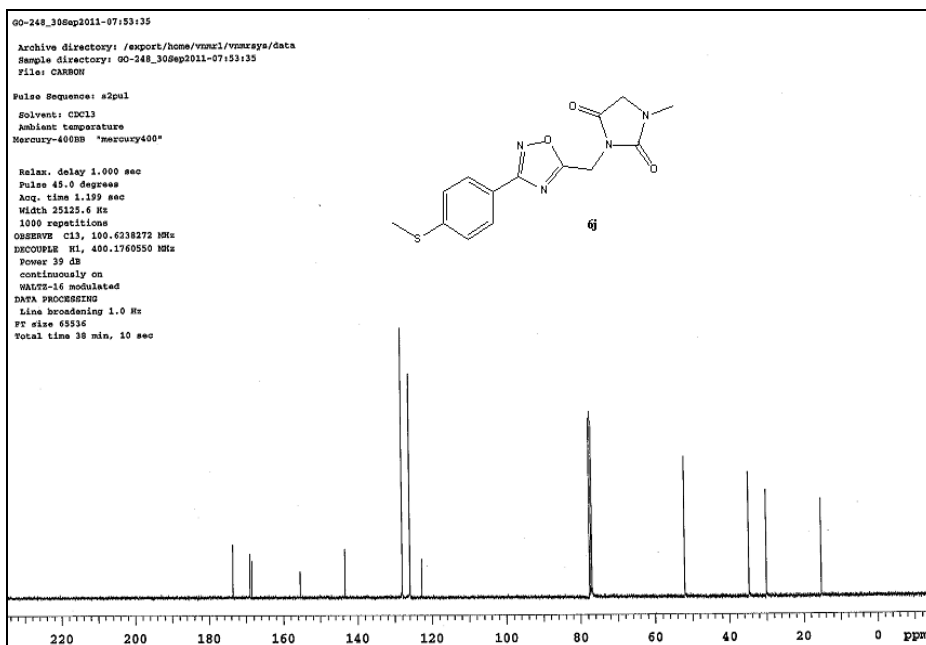


Figure 4.74. The ¹³C NMR spectrum of **6j**

Chemical Formula: $C_{14}H_{14}N_4O_3S$
Molecular Weight: 318,35

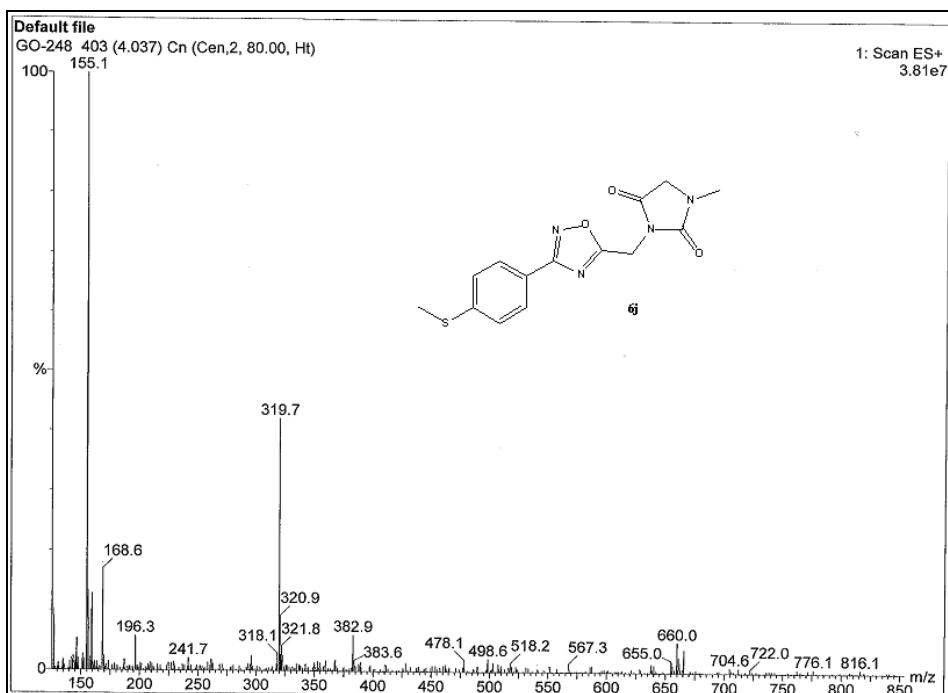


Figure 4.75 . LC-MS spectrum of **6j**

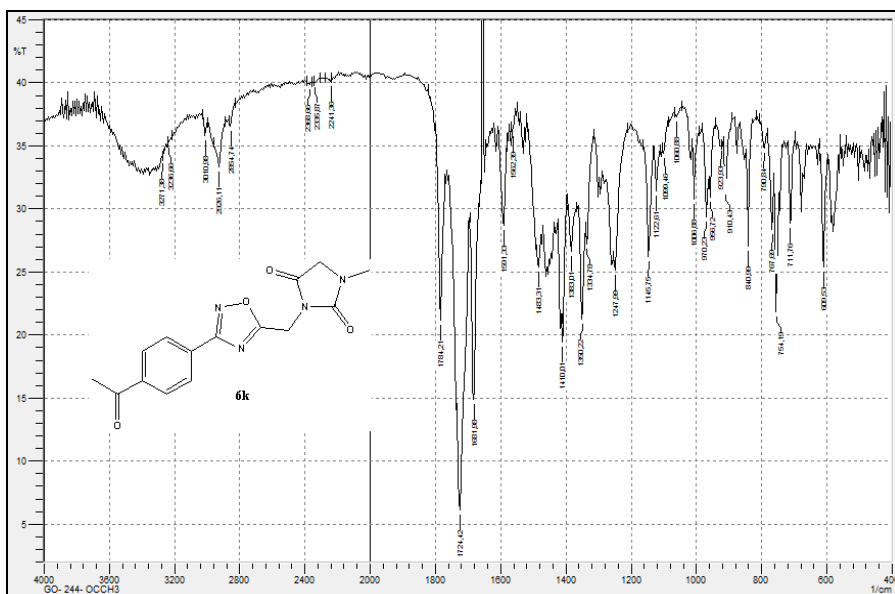


Figure 4.76. The IR spectrum of **6k**

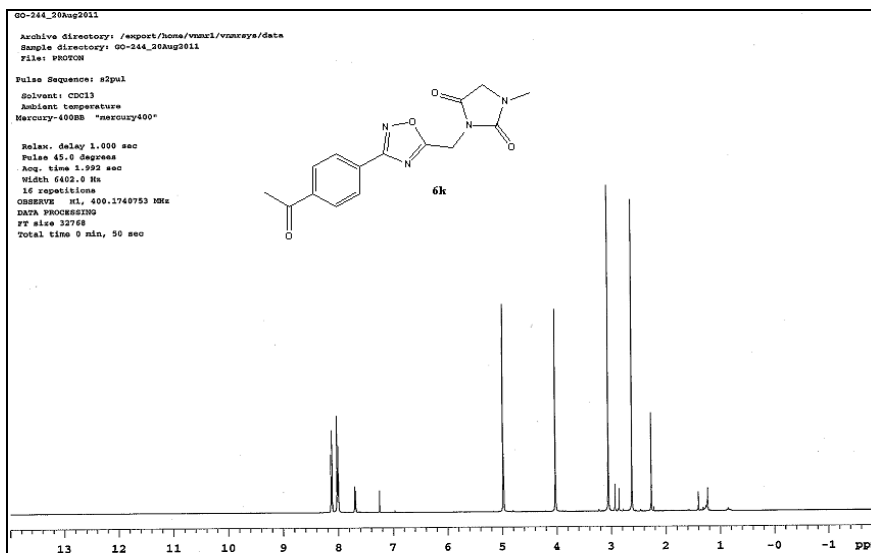


Figure 4.77. The ^1H NMR spectrum of **6k**

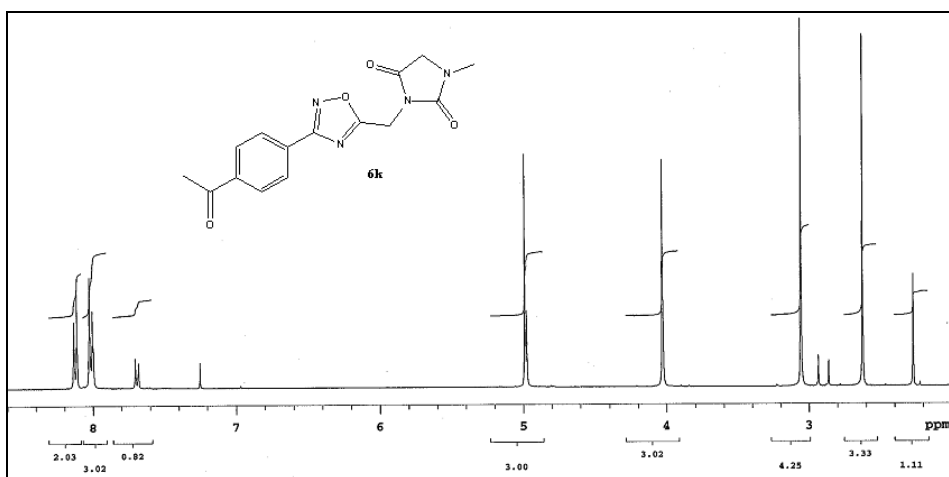


Figure 4.78. The expanded ^1H NMR spectrum of **6k**

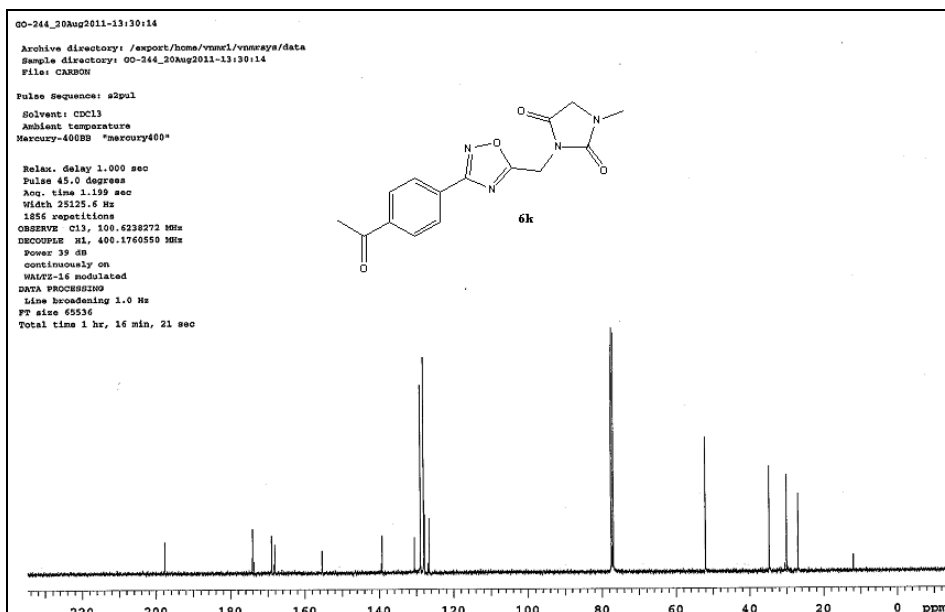


Figure 4.79. The ^{13}C NMR spectrum of 6k

Chemical Formula: $\text{C}_{15}\text{H}_{14}\text{N}_4\text{O}_4$
Molecular Weight: 314,30

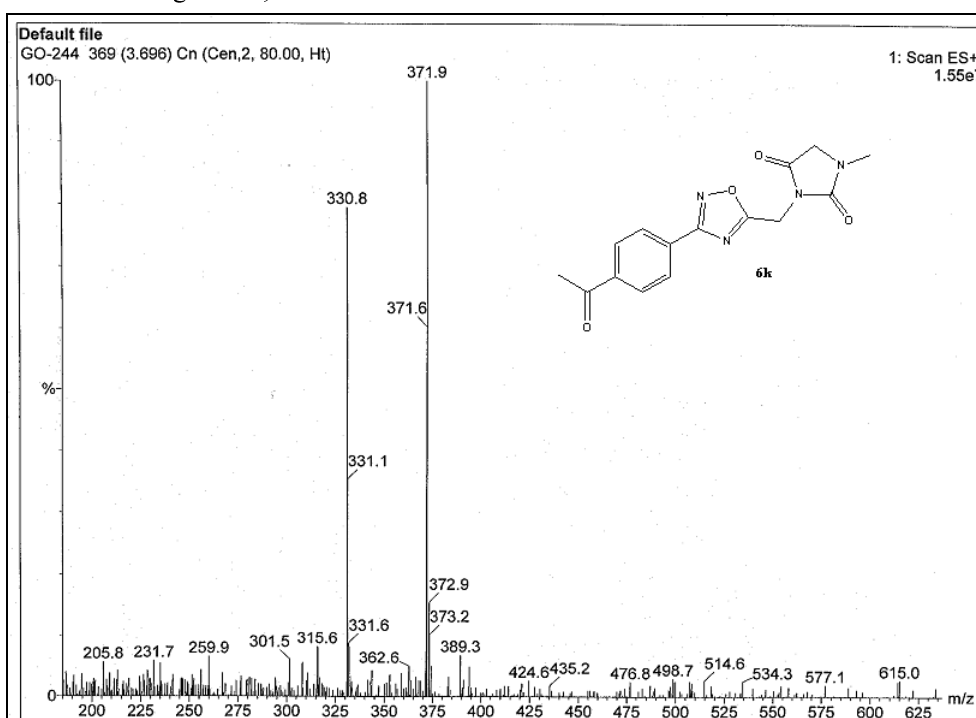


Figure 4.80. LC-MS spectrum of 6k

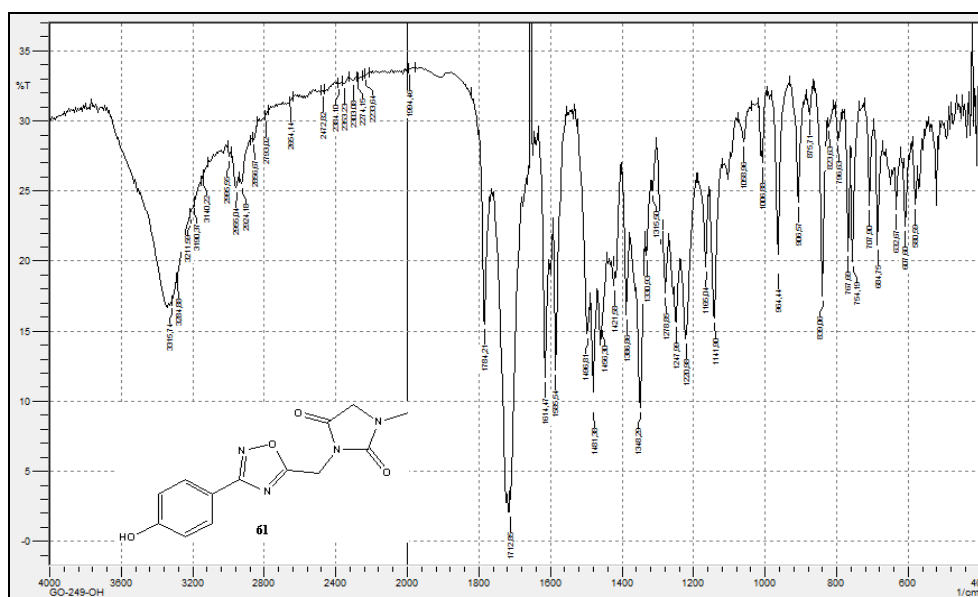


Figure 4.81. The IR spectrum of **6l**

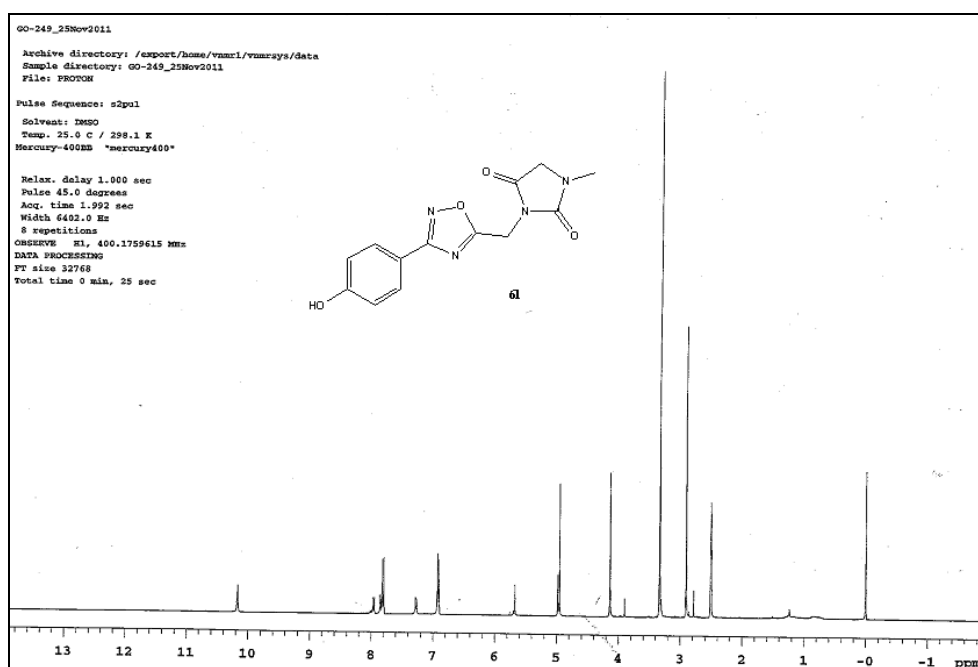


Figure 4.82. The ^1H NMR spectrum of **6l**

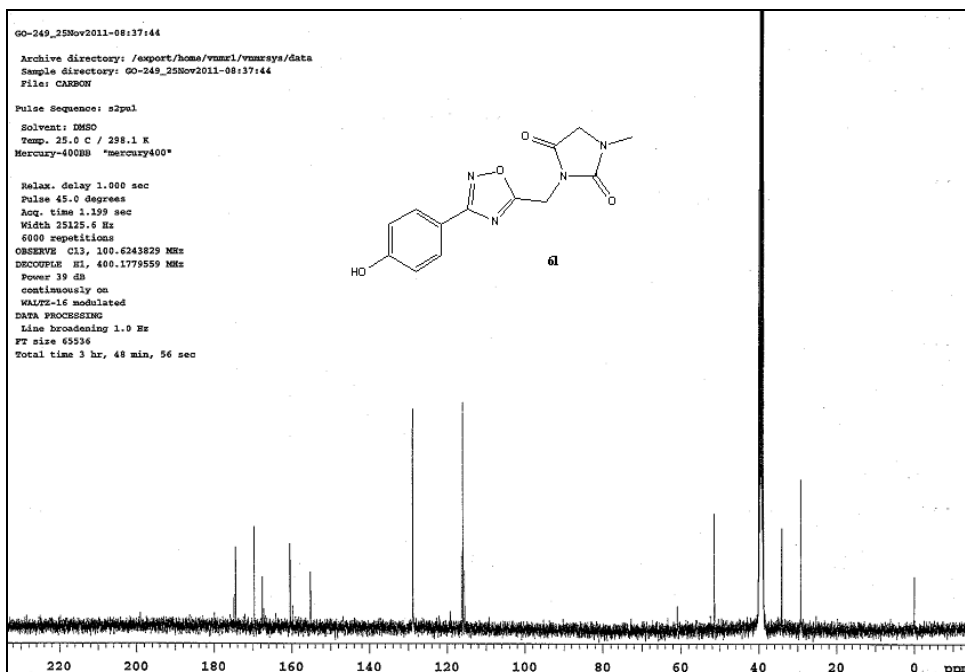


Figure 4.83. The ^{13}C NMR spectrum of 6l

Chemical Formula: $\text{C}_{13}\text{H}_{12}\text{N}_4\text{O}_4$
 Molecular Weight: 288,26

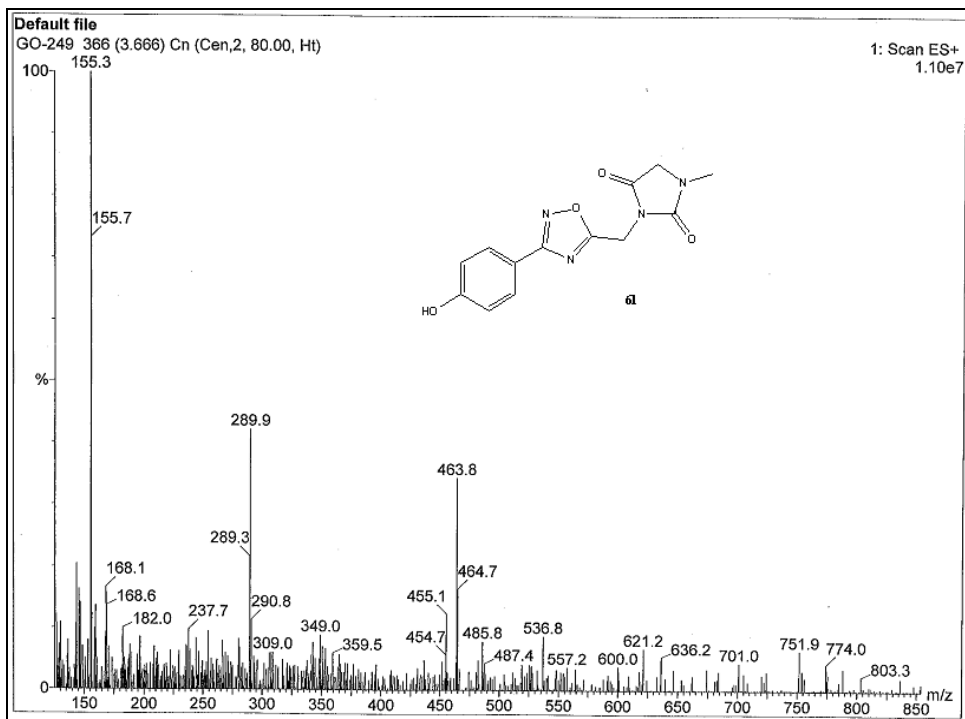


Figure 4.84. LC-MS spectrum of 6l

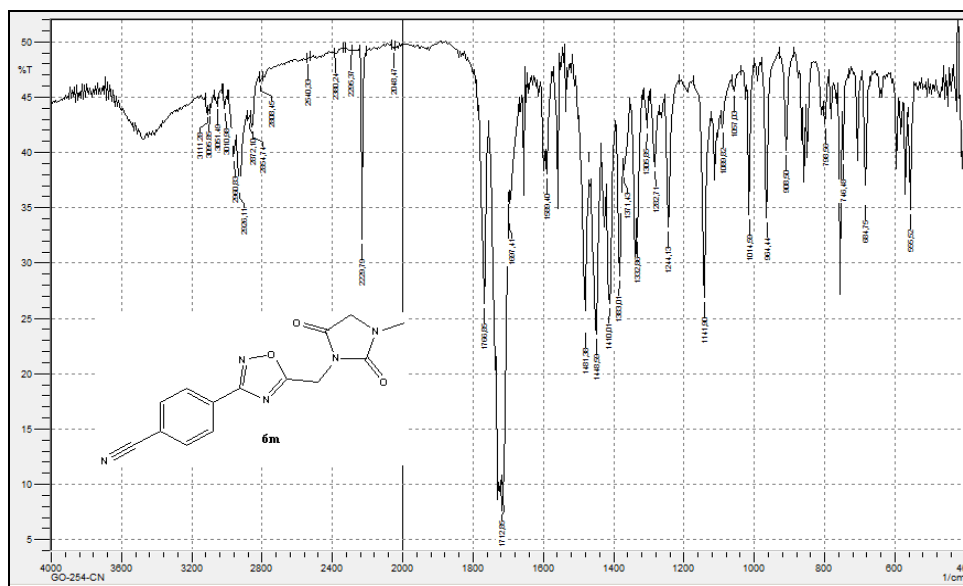


Figure 4.85. The IR spectrum of **6m**

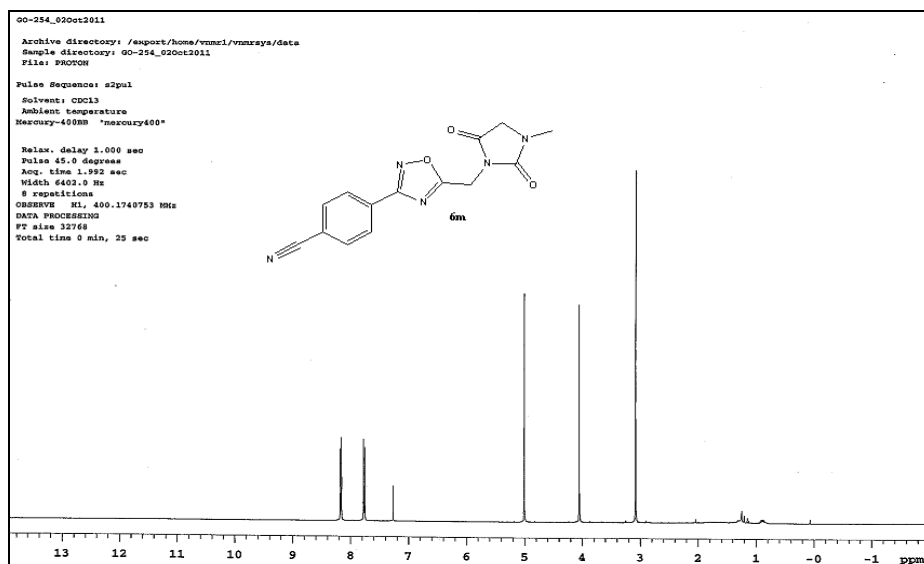


Figure 4.86. The ¹H NMR spectrum of **6m**

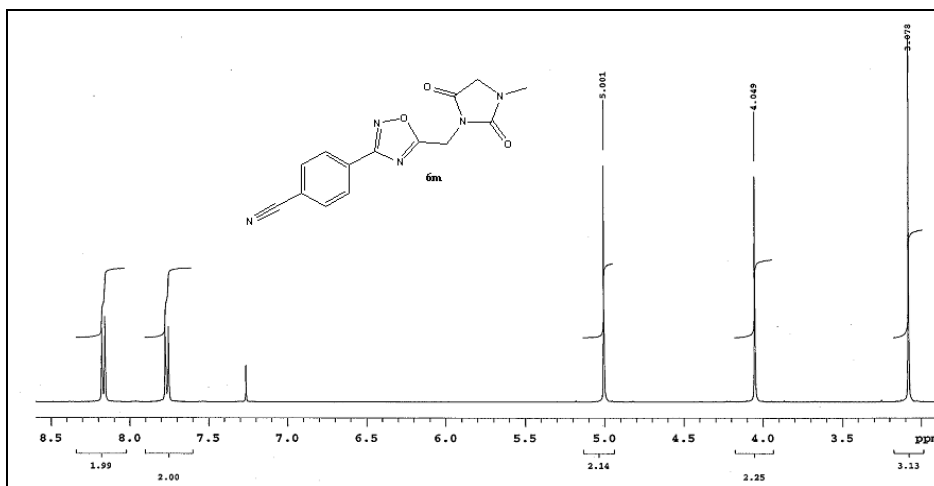


Figure 4.87. The expanded ¹H NMR spectrum of **6m**

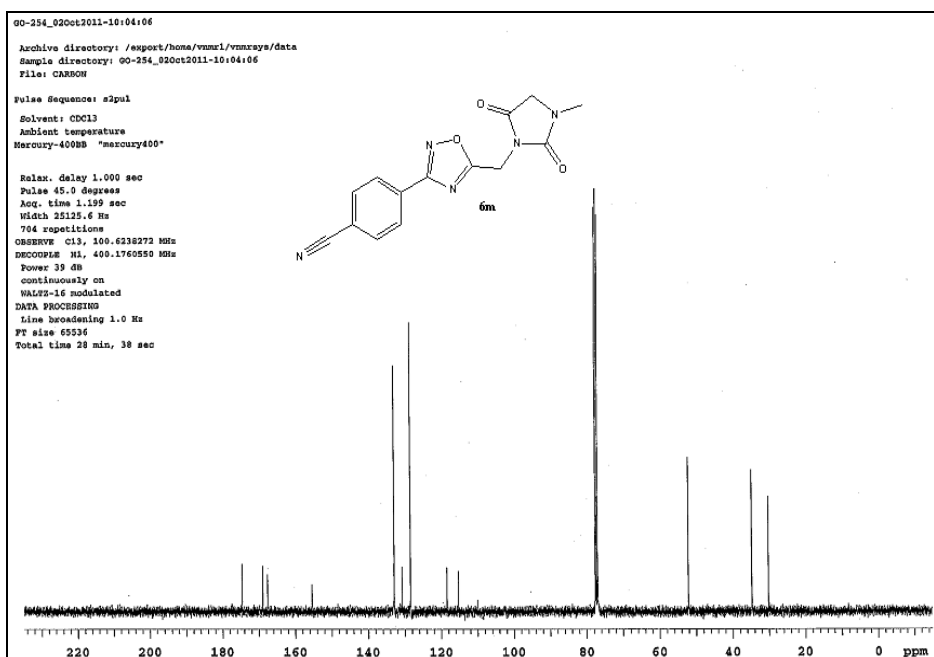
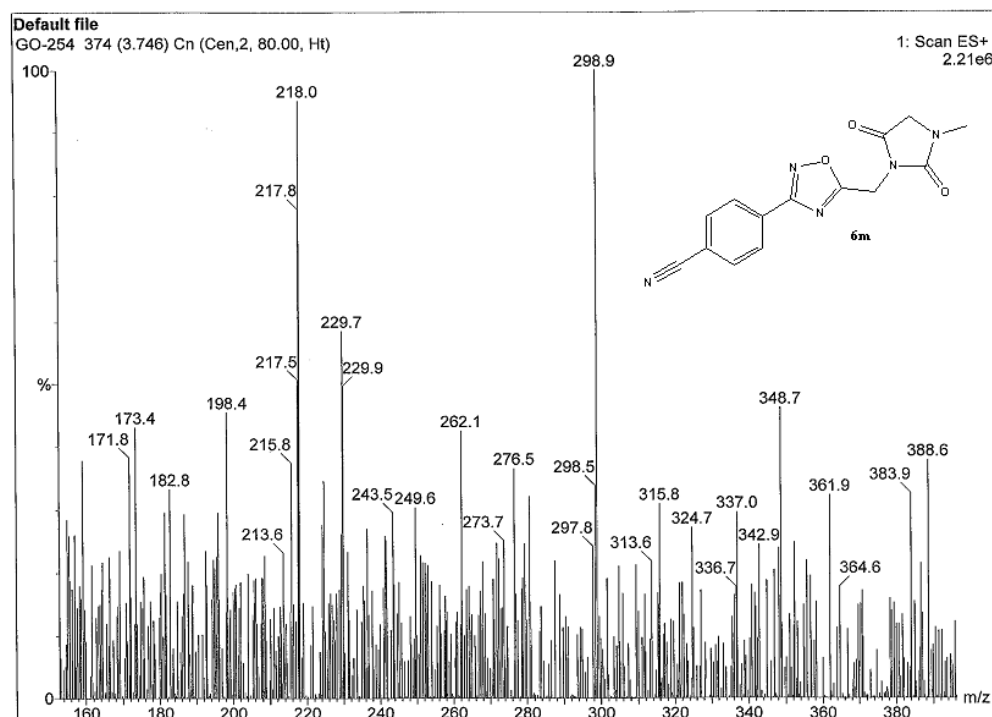
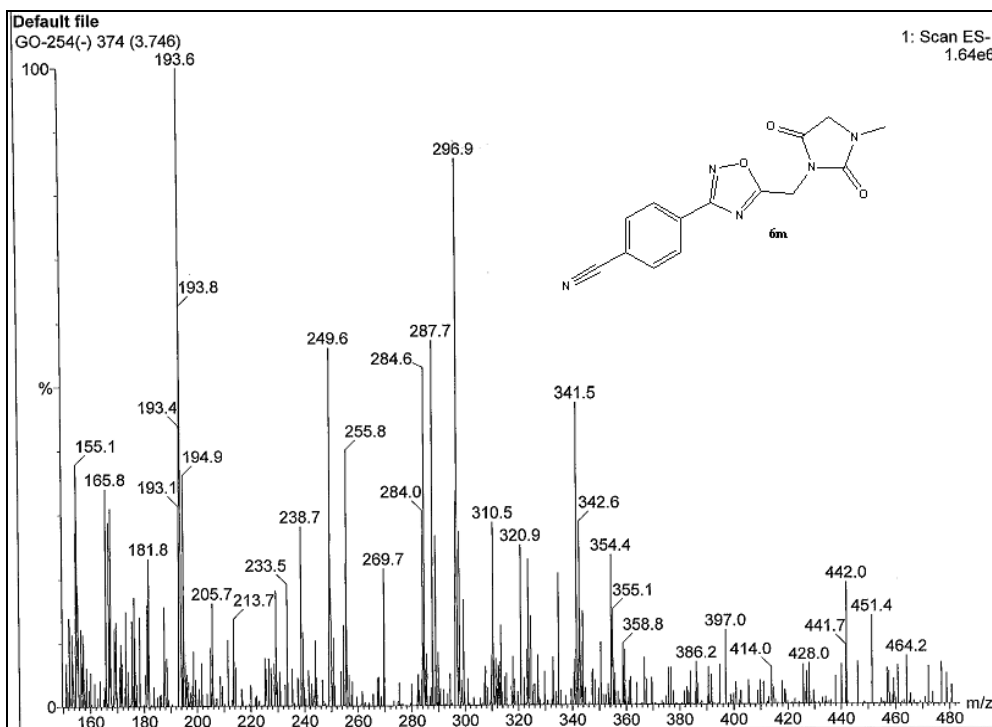
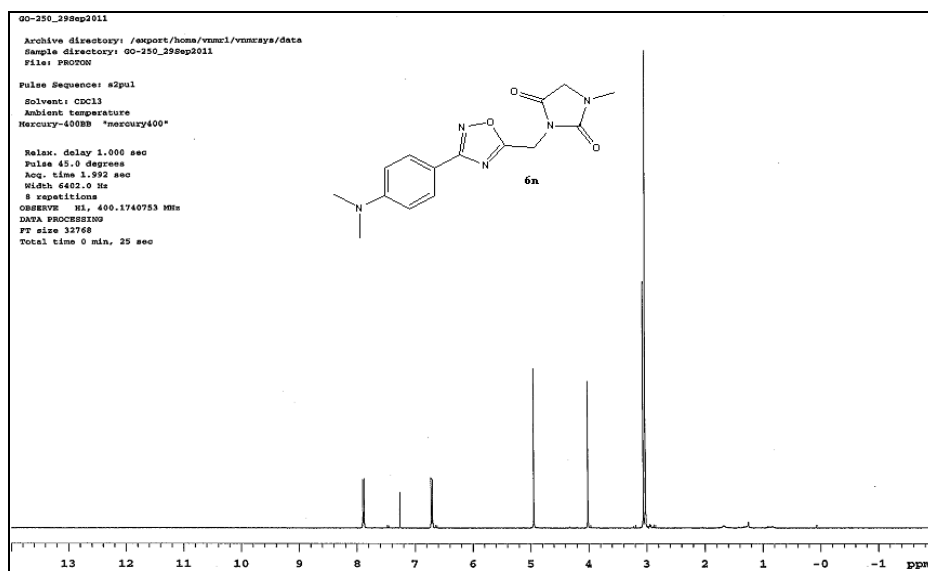
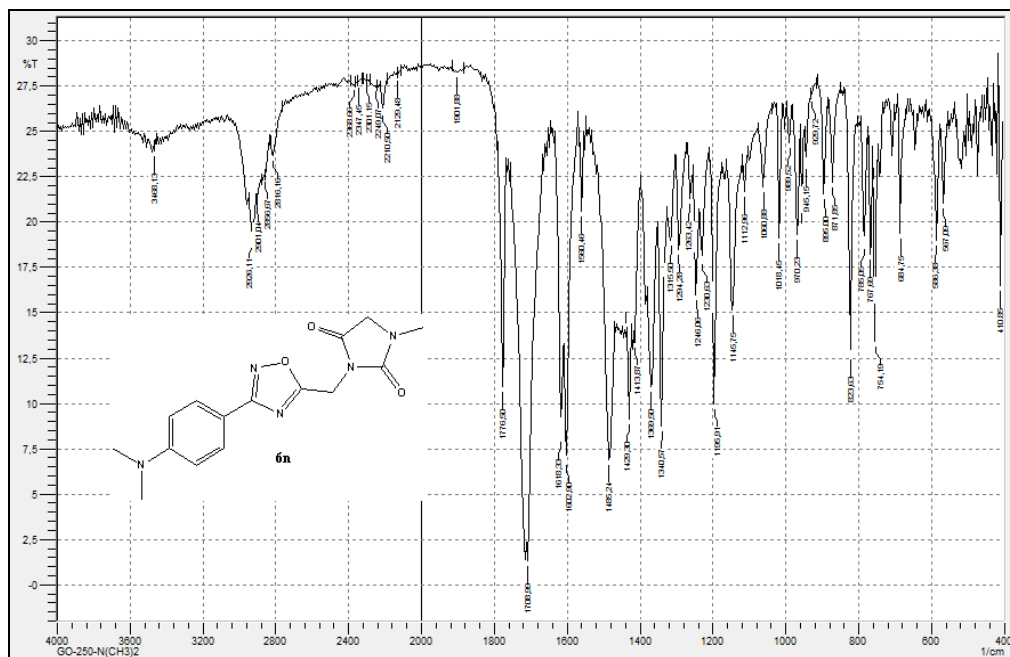


Figure 4.88. The ¹³C NMR spectrum of **6m**

Chemical Formula: $C_{14}H_{11}N_5O_3$

Molecular Weight: 297,27





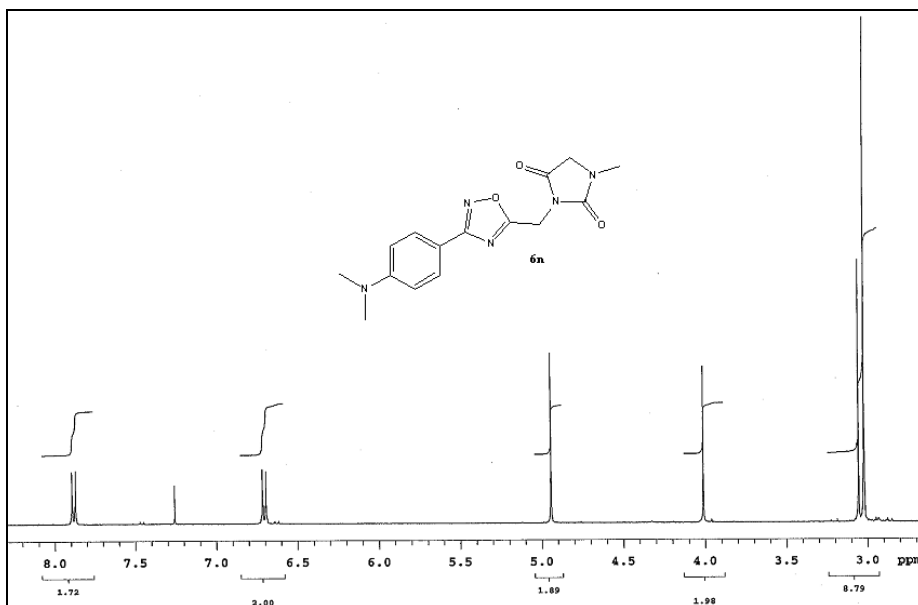


Figure 4.93. The expanded ¹H NMR spectrum of 6n

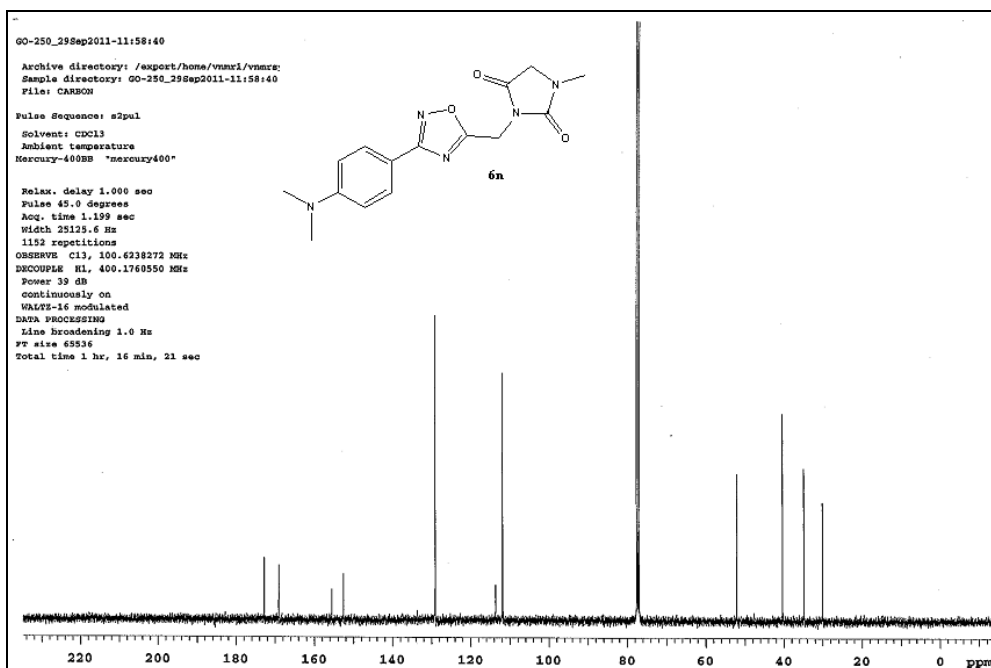


Figure 4.94. The ¹³C NMR spectrum of 6n

Chemical Formula: $C_{15}H_{17}N_5O_3$
Molecular Weight: 315,33

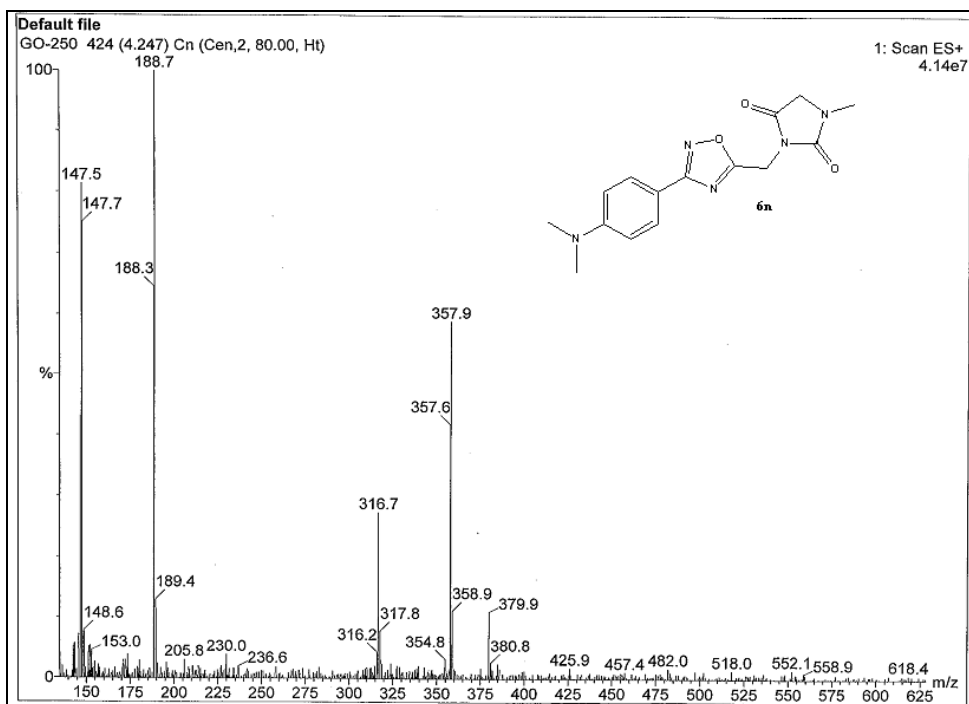


Figure 4.95. LC-MS spectrum of **6a**

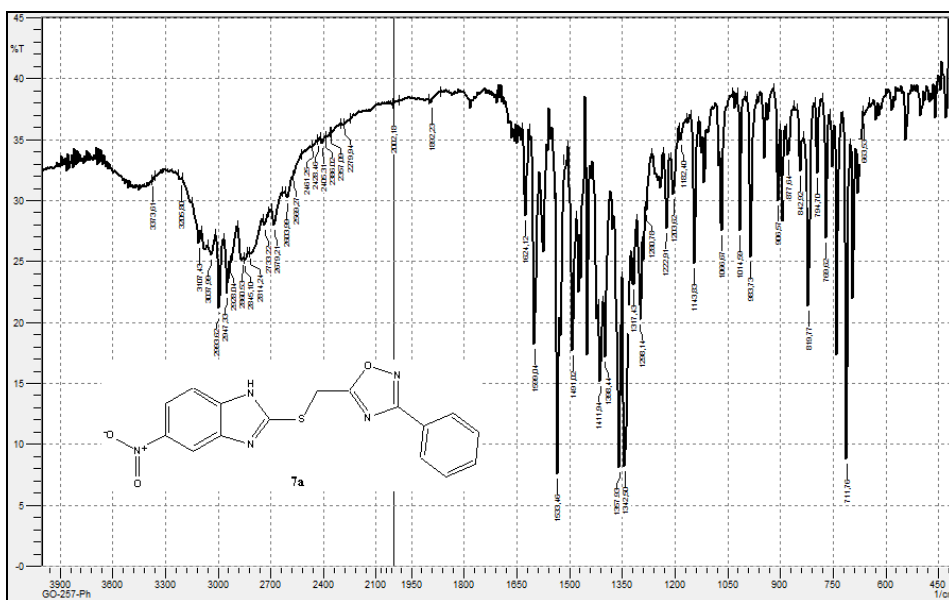


Figure 4.96. The IR spectrum of **7a**

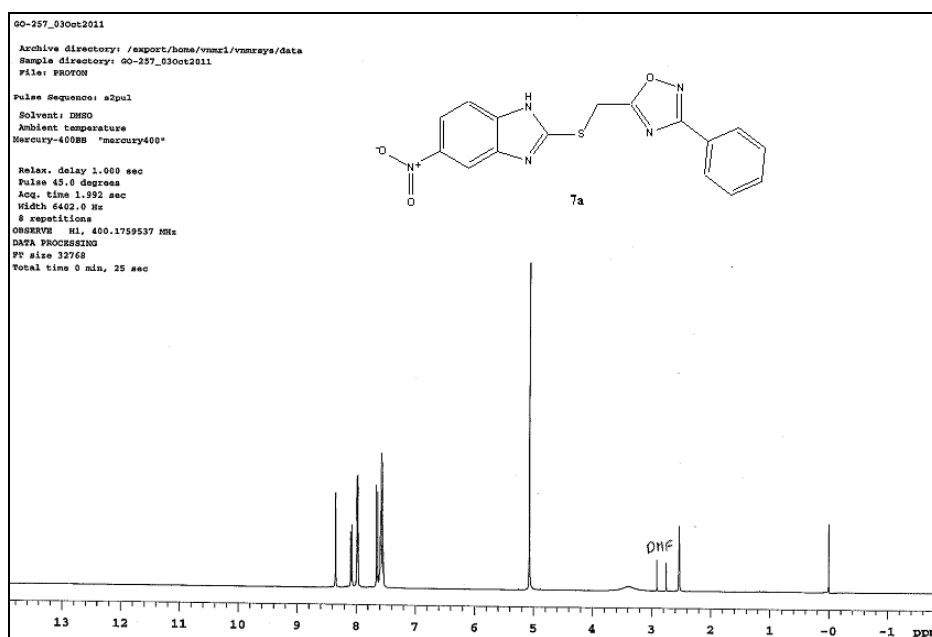


Figure 4.97. The ^1H NMR spectrum of 7a

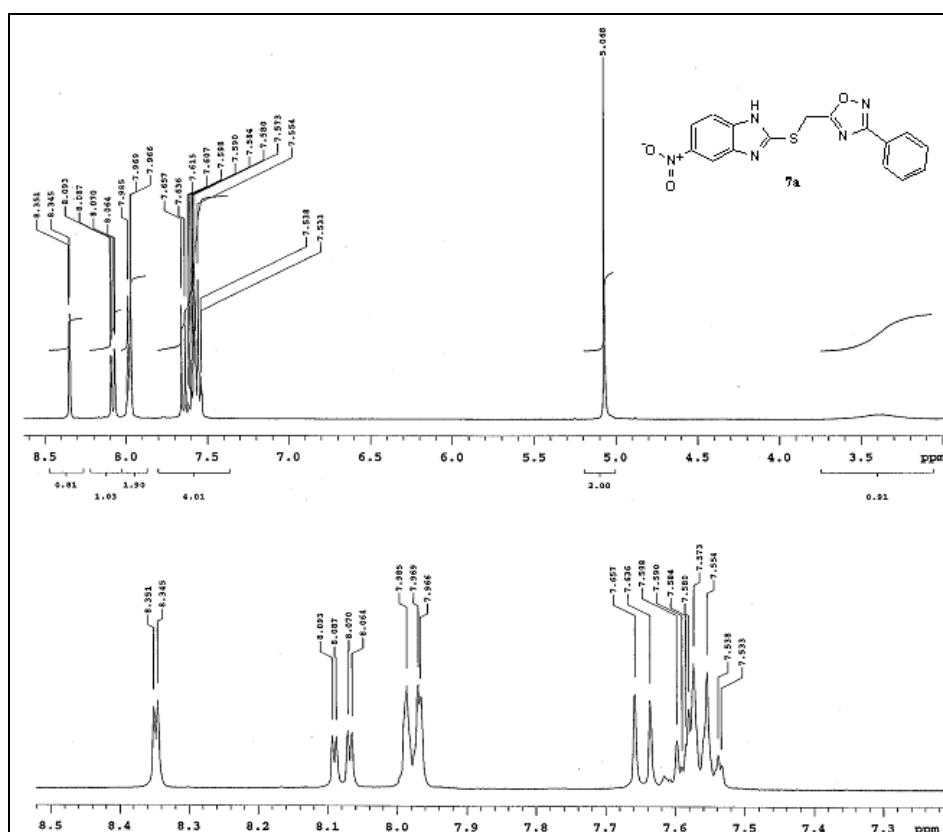


Figure 4.98. The expanded ^1H NMR spectrum of 7a

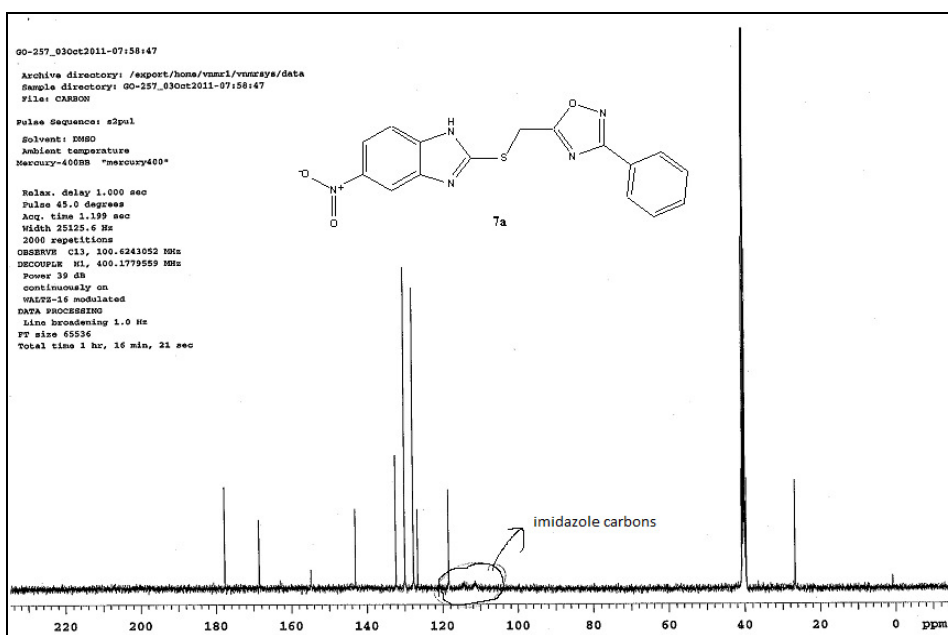


Figure 4.99. The ^{13}C NMR spectrum of 7a

Chemical Formula: $\text{C}_{16}\text{H}_{11}\text{N}_5\text{O}_3\text{S}$
 Molecular Weight: 353,36

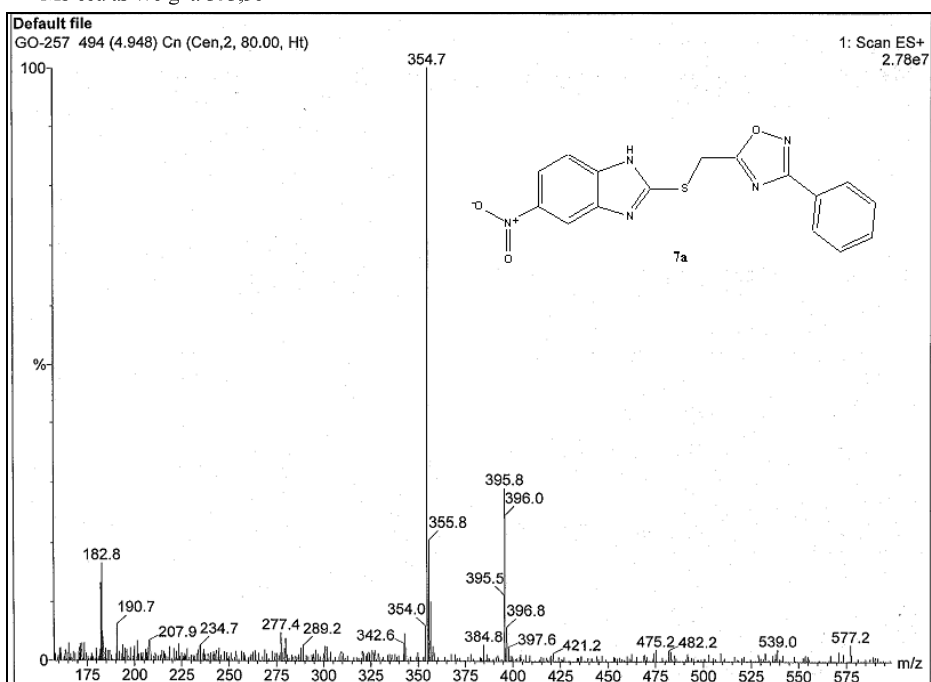


Figure 4.100. LC-MS spectrum of 7a

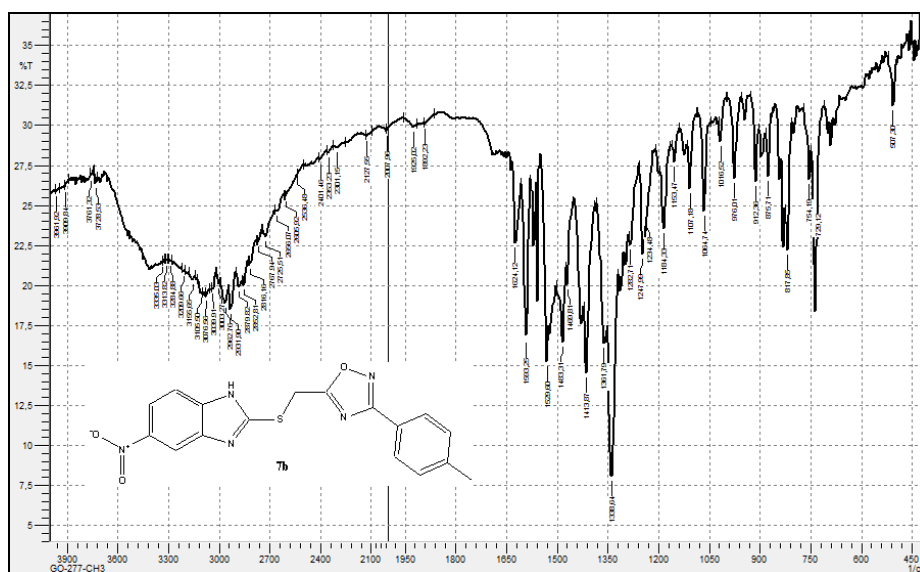


Figure 4.101. The IR spectrum of **7b**

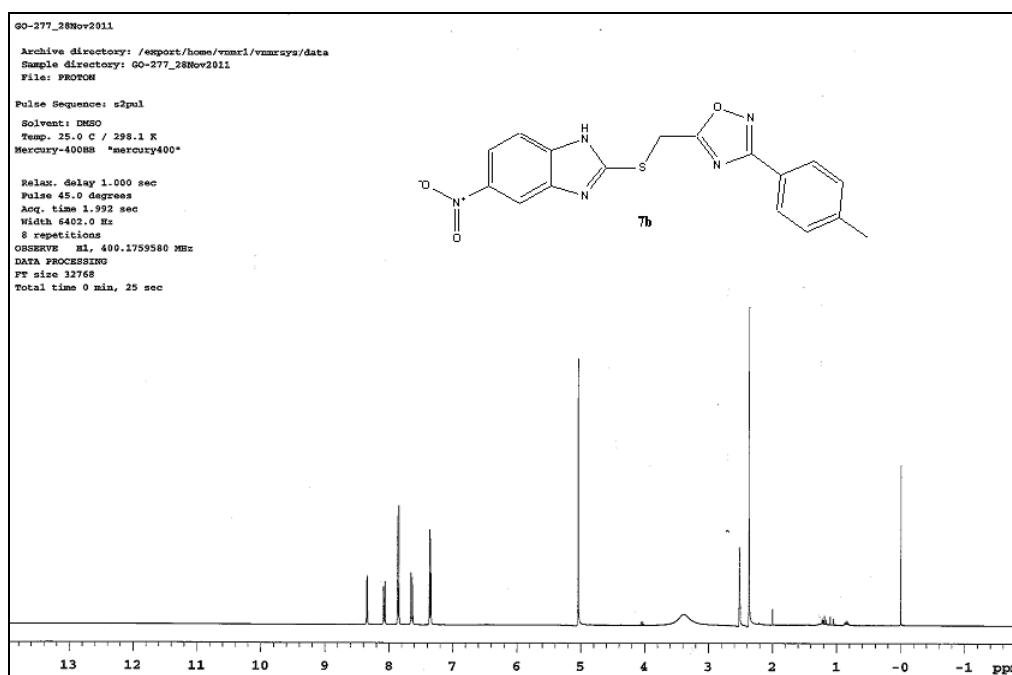


Figure 4.102. The ^1H NMR spectrum of **7b**

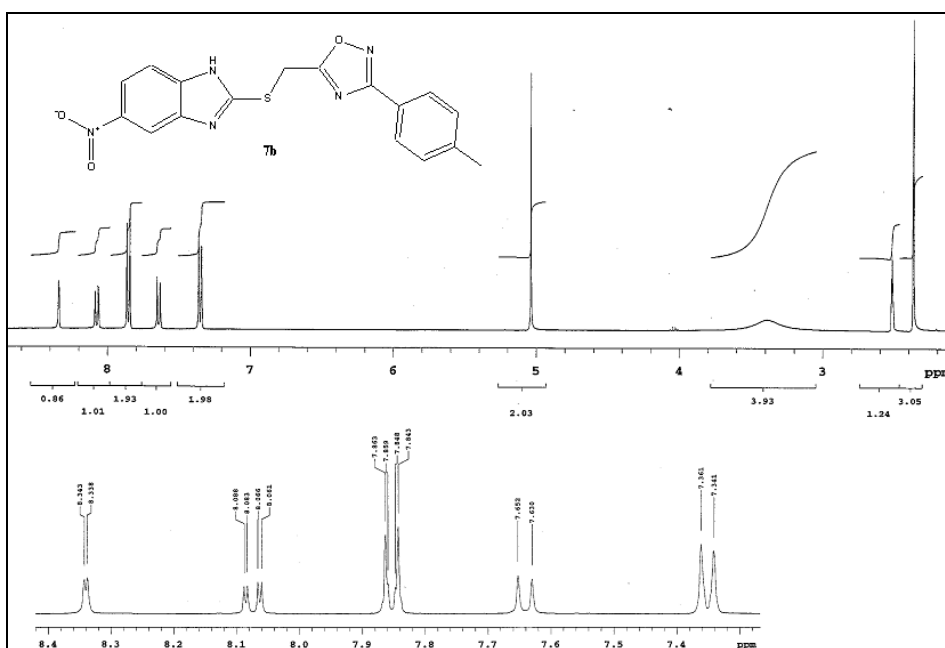


Figure 4.103. The expanded ¹H NMR spectrum of **7b**

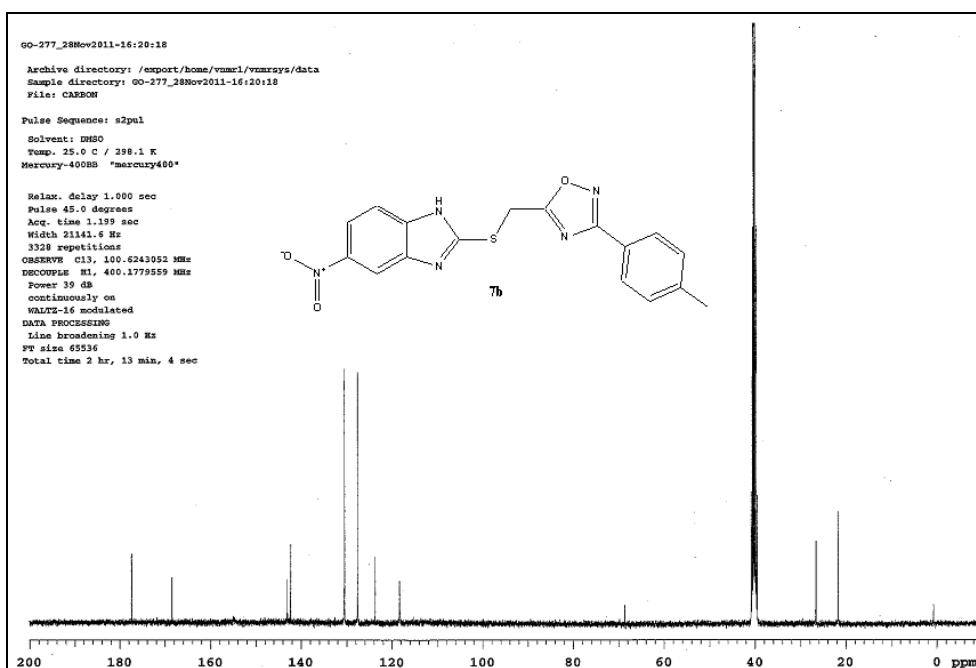


Figure 4.104. The ¹³C NMR spectrum of **7b**

Chemical Formula: $C_{17}H_{13}N_5O_3S$
Molecular Weight: 367,38

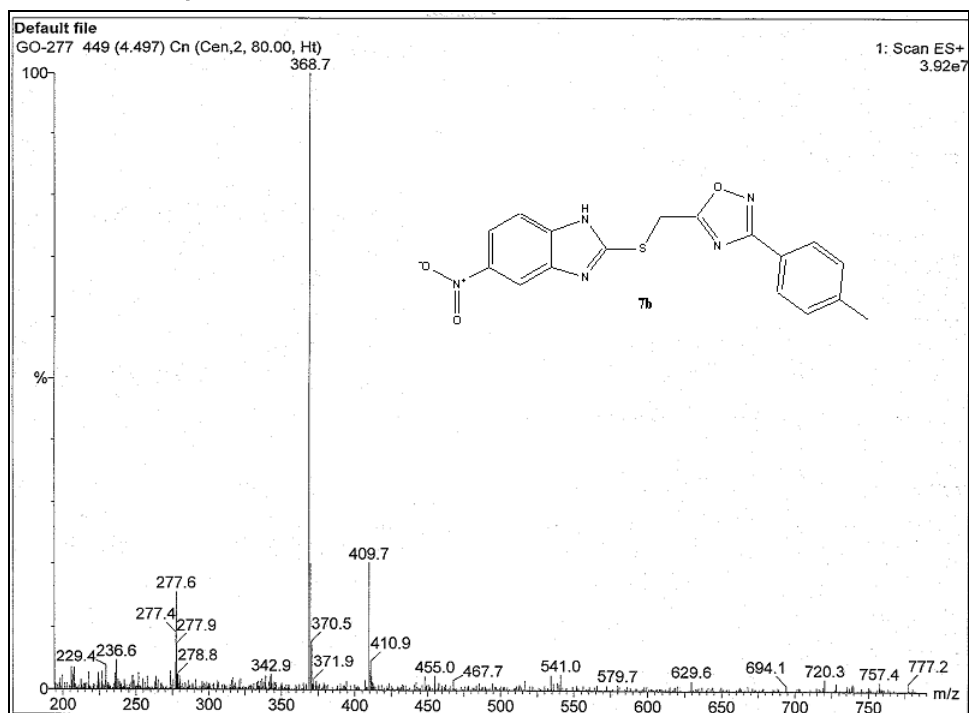


Figure 4.105. LC-MS spectrum of **7b**

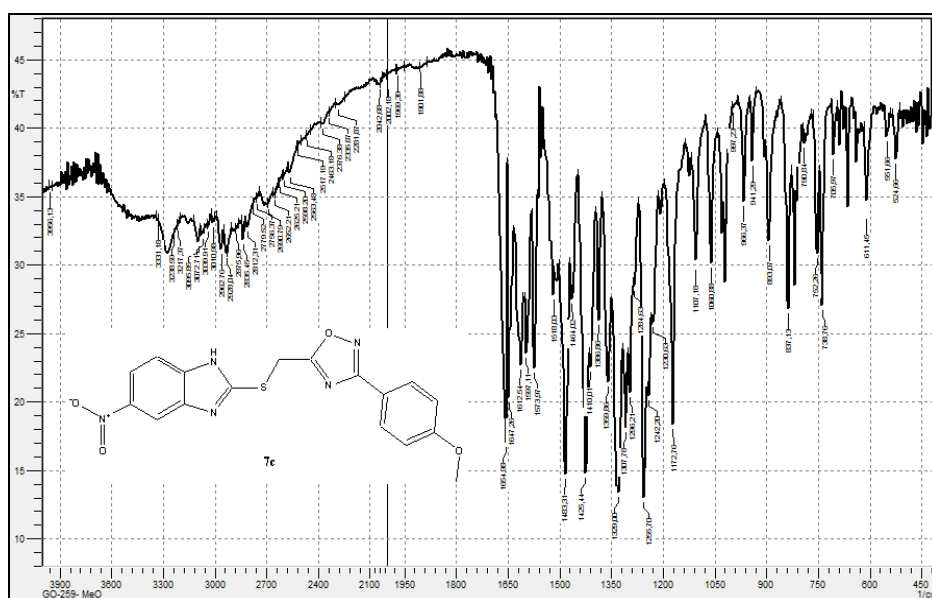


Figure 4.106. The IR spectrum of **7c**

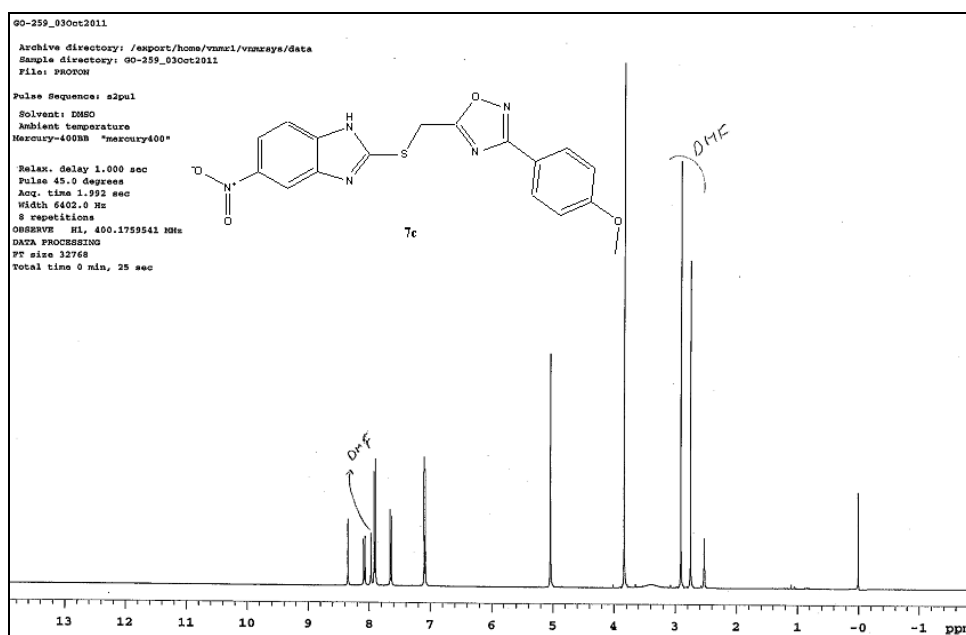


Figure 4.107. The ^1H NMR spectrum of **7c**

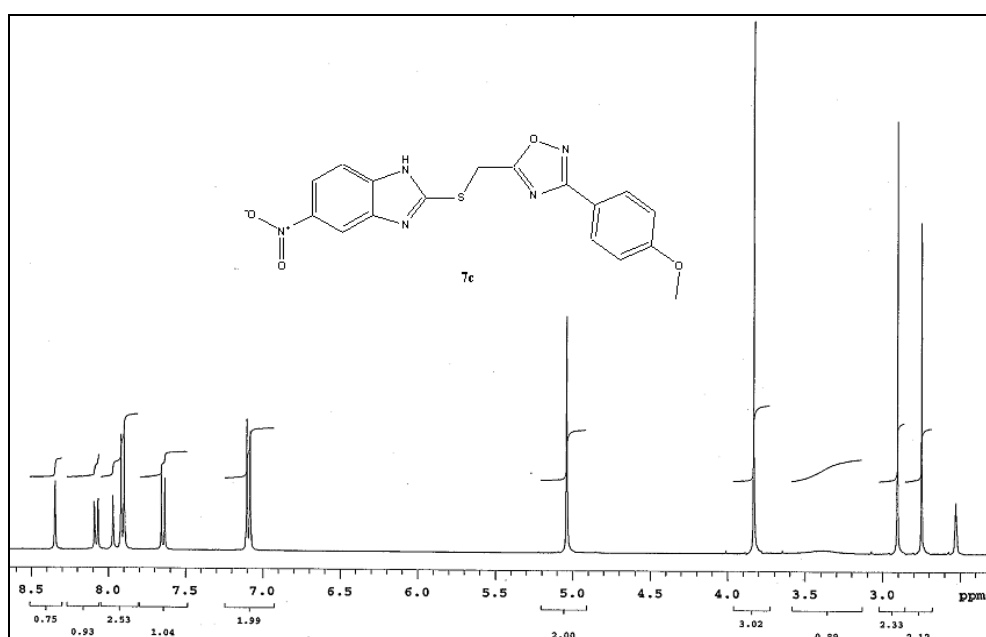


Figure 4.108. The expanded ^1H NMR spectrum of **7c**

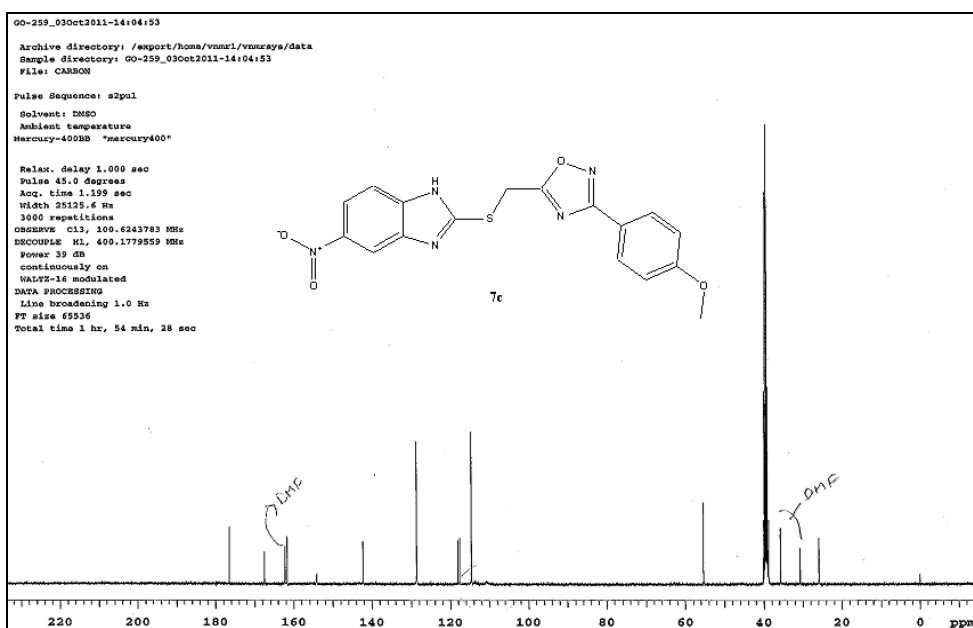


Figure 4.109. The ^{13}C NMR spectrum of **7c**

Chemical Formula: $\text{C}_{17}\text{H}_{13}\text{N}_5\text{O}_4\text{S}$
 Molecular Weight: 383.38

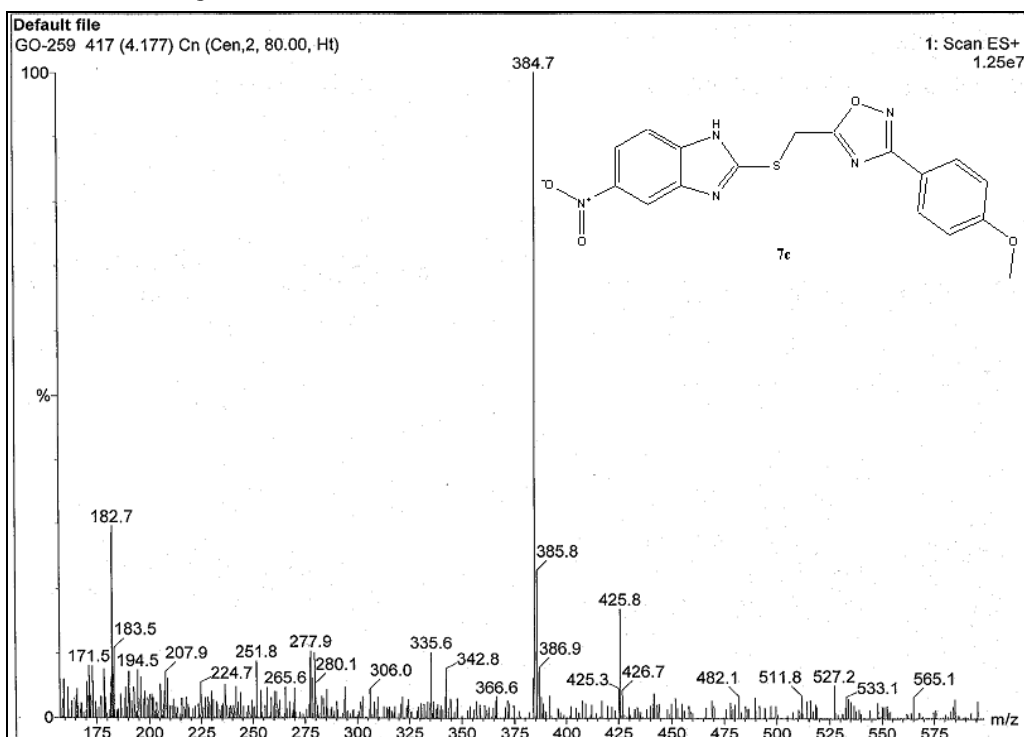


Figure 4.110. LC-MS spectrum of **7c**

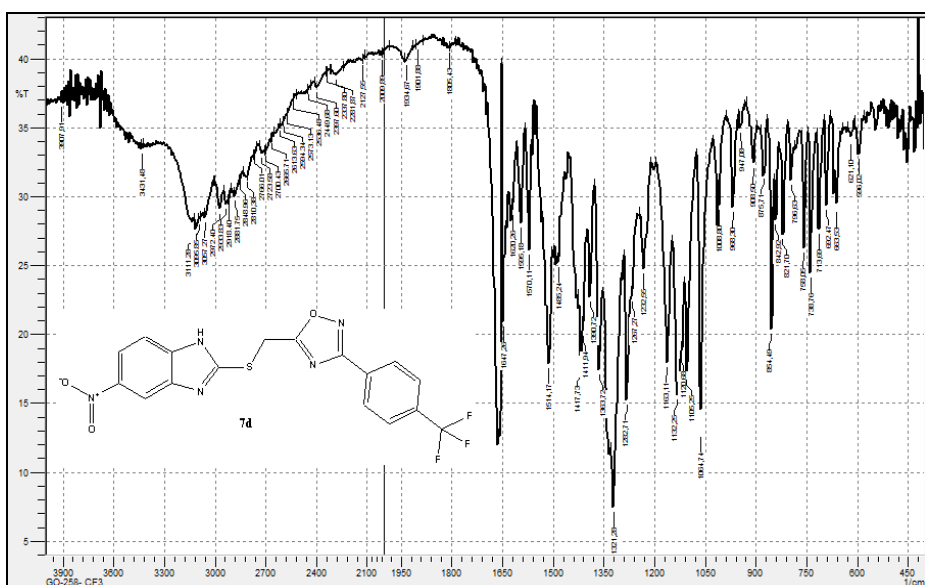


Figure 4.111. The IR spectrum of **7d**

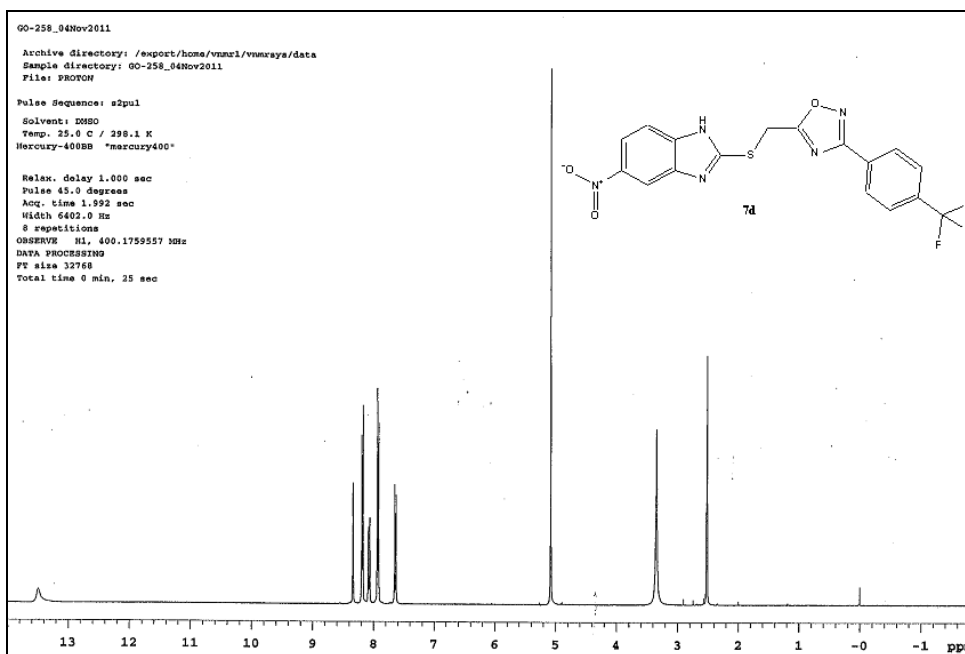


Figure 4.112. The ^1H NMR spectrum of **7d**

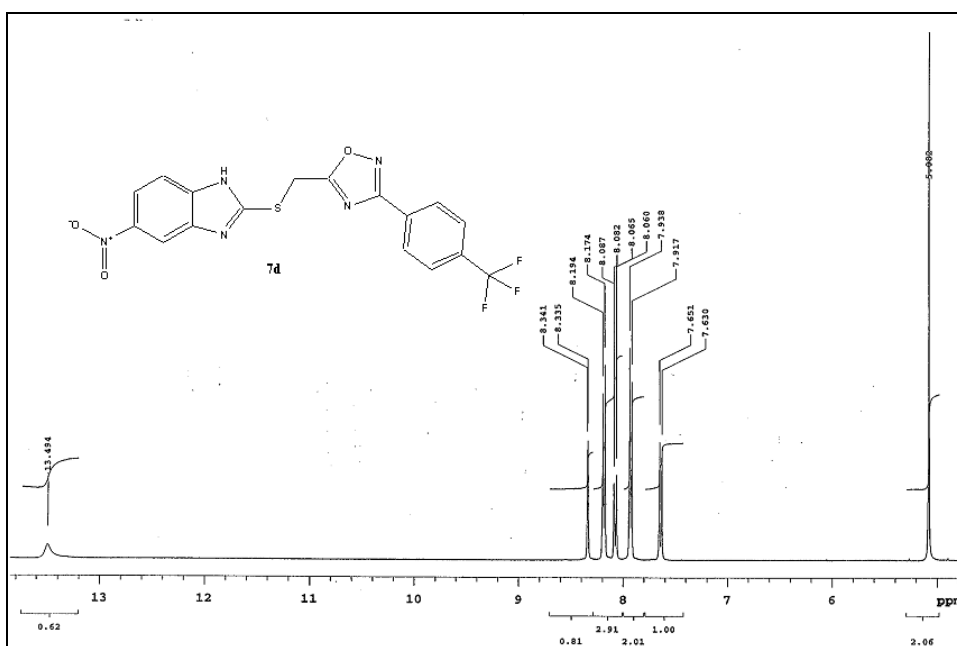


Figure 4.113. The expanded ¹H NMR spectrum of **7d**

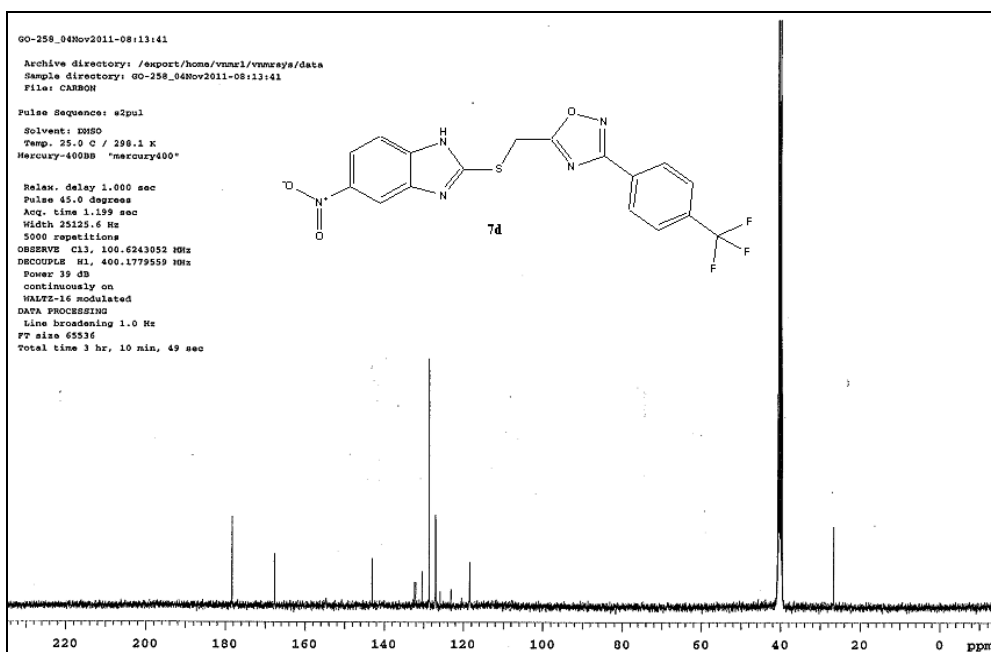


Figure 4.114. The ¹³C NMR spectrum of **7d**

Chemical Formula: $C_{17}H_{10}F_3N_5O_3S$
Molecular Weight: 421,35

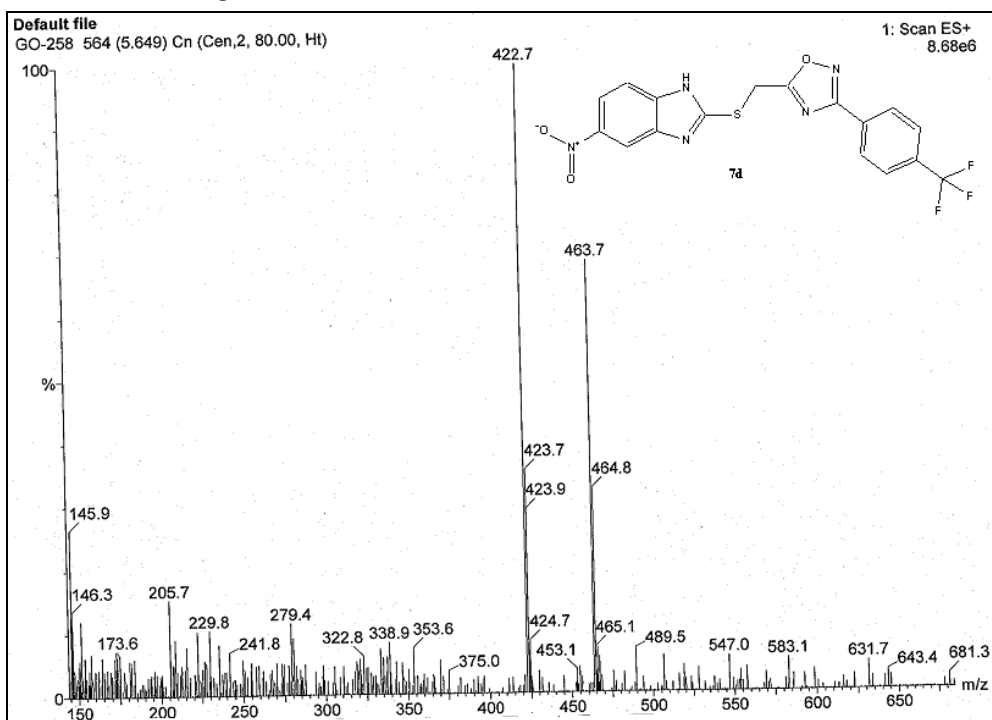


Figure 4.115. LC-MS spectrum of **7d**

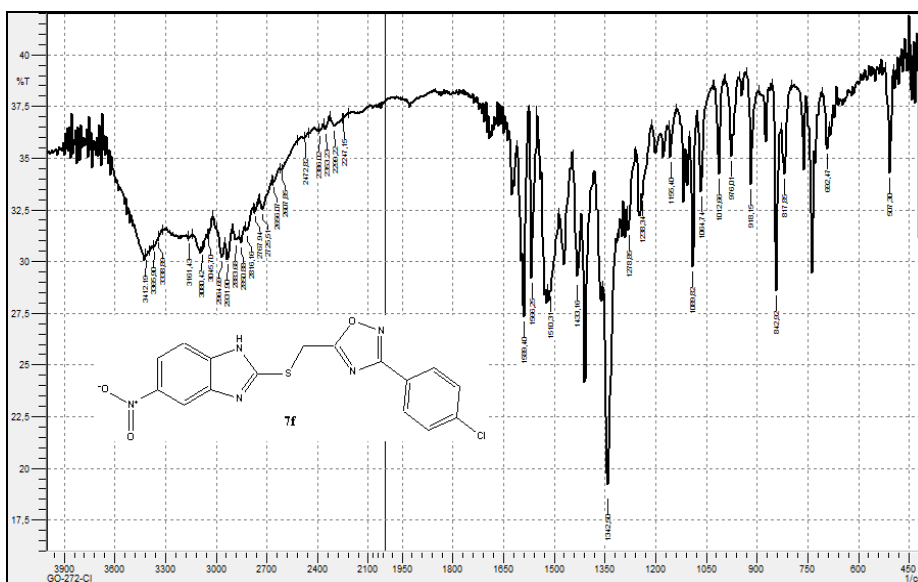


Figure 4.116. The IR spectrum of **7f**

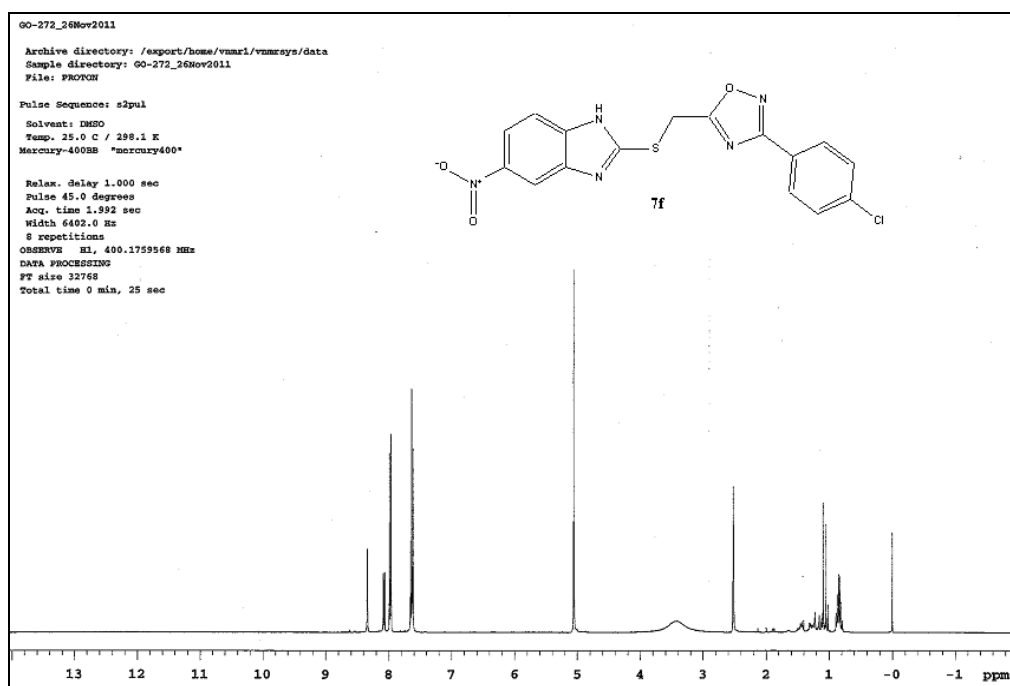


Figure 4.117. The ^1H NMR spectrum of **7f**

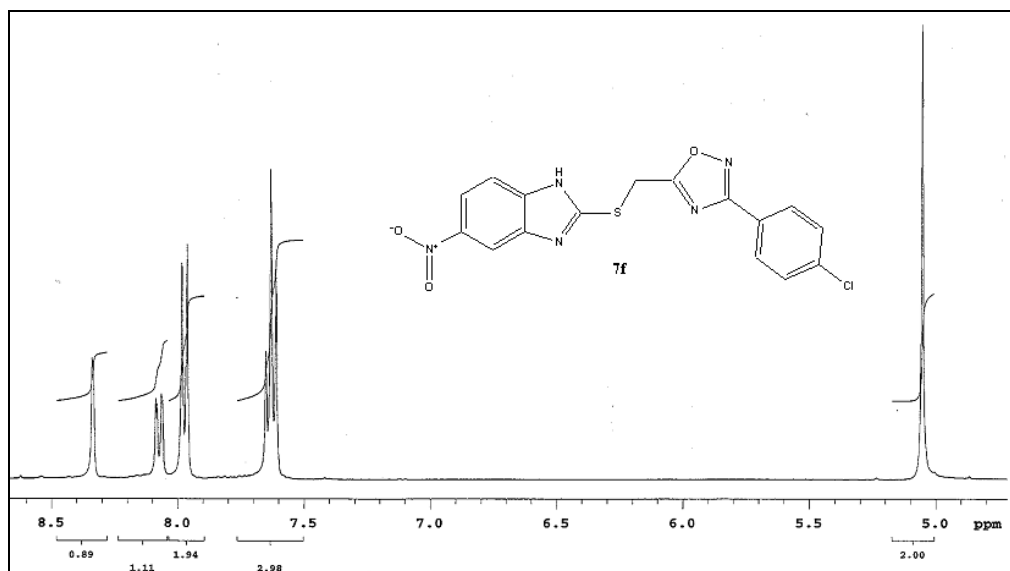
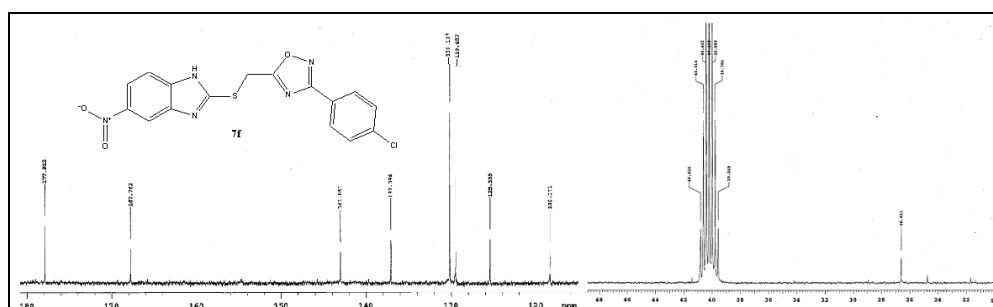
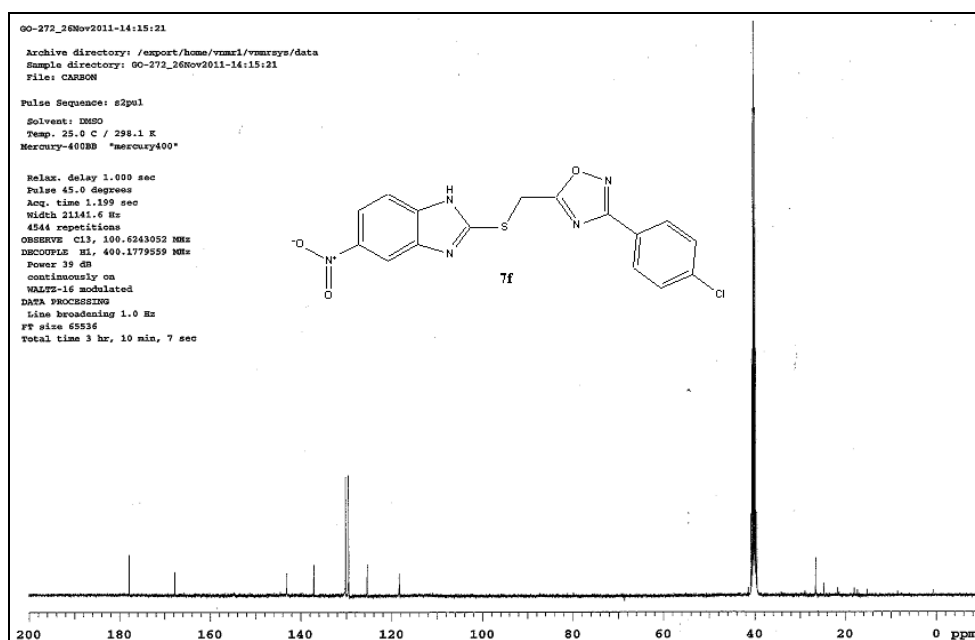


Figure 4.118. The expanded ^1H NMR spectrum of **7f**



Chemical Formula: $C_{16}H_{10}ClN_5O_3S$
Molecular Weight: 387,80

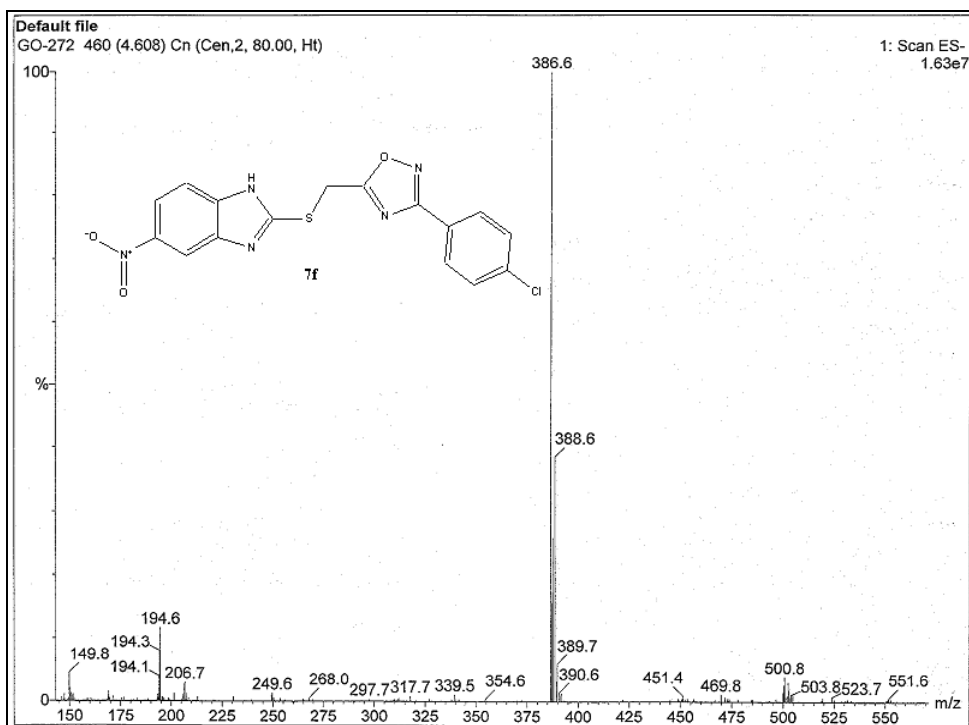


Figure 4.121. LC-MS spectrum of **7f**

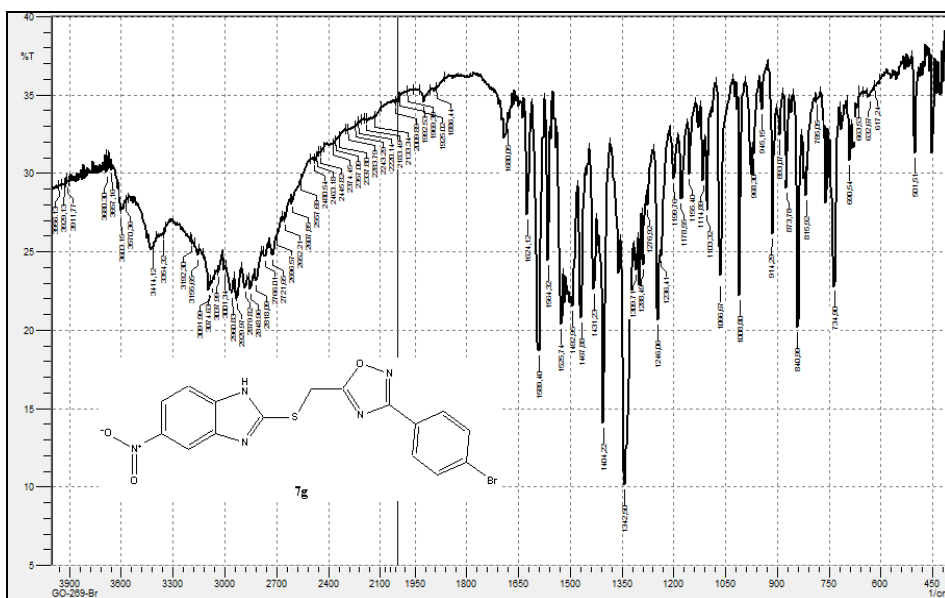


Figure 4.122. The IR spectrum of **7g**

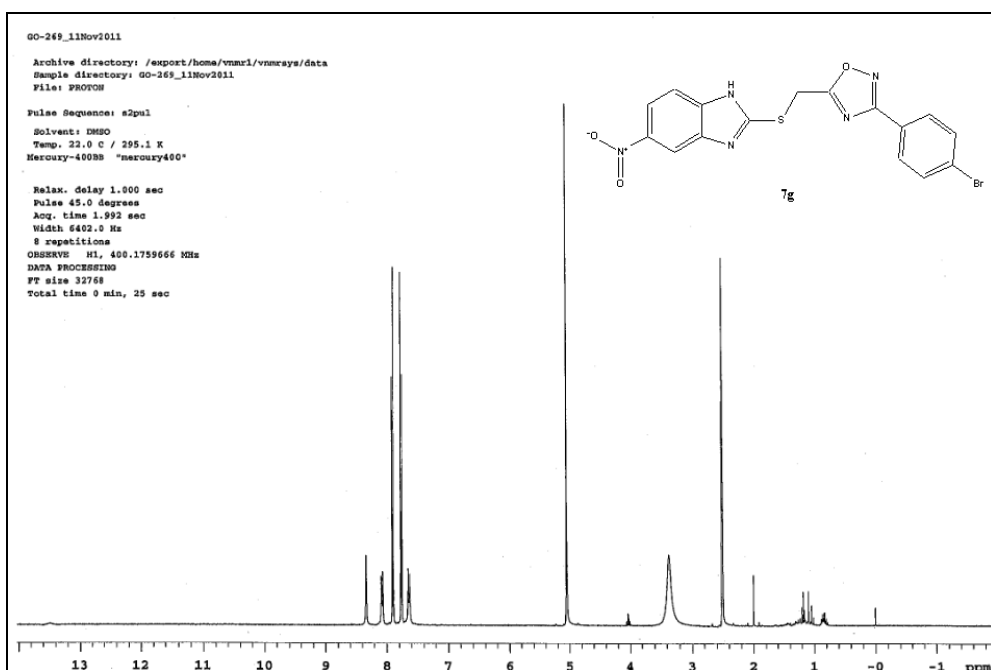


Figure 4.123. The ^1H NMR spectrum of **7g**

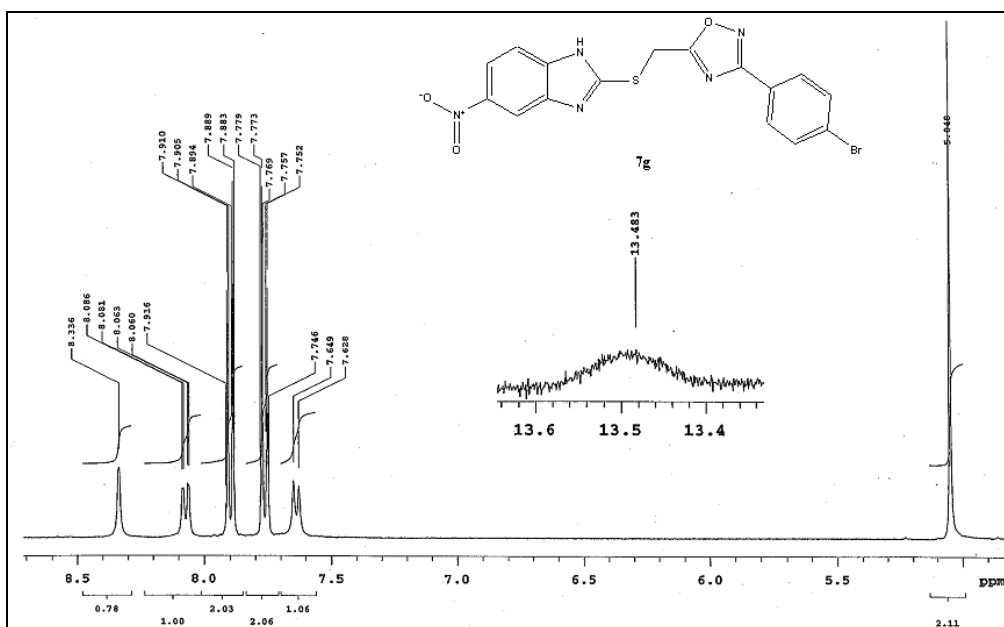


Figure 4.124. The expanded ^1H NMR spectrum of **7g**

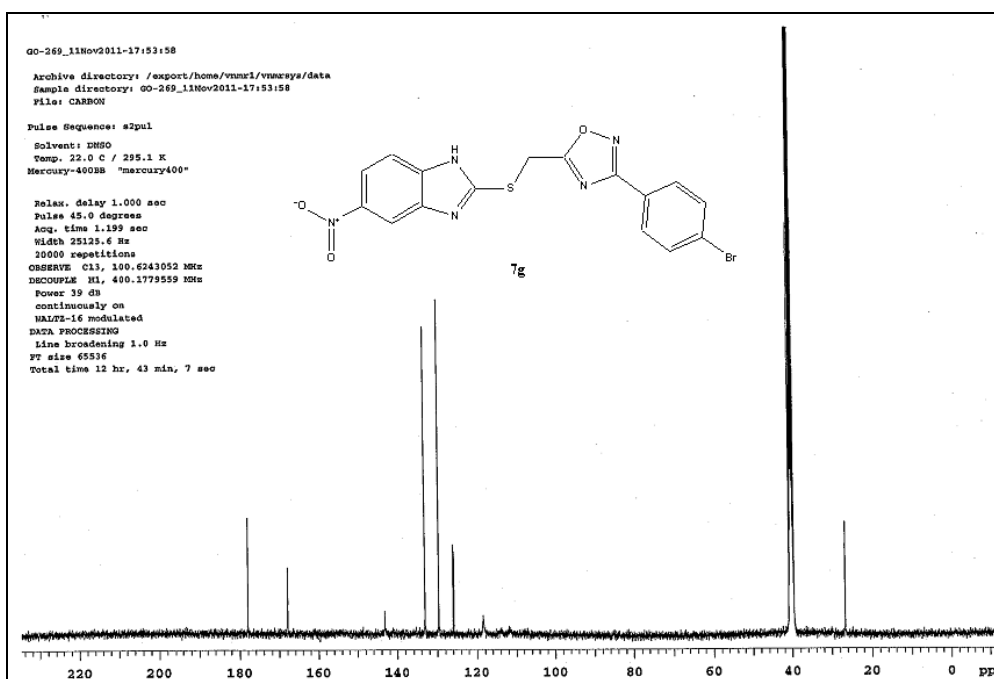


Figure 4.125. The ^{13}C NMR spectrum of **7g**

Chemical Formula: $\text{C}_{16}\text{H}_{10}\text{BrN}_5\text{O}_3\text{S}$

Molecular Weight: 432.25

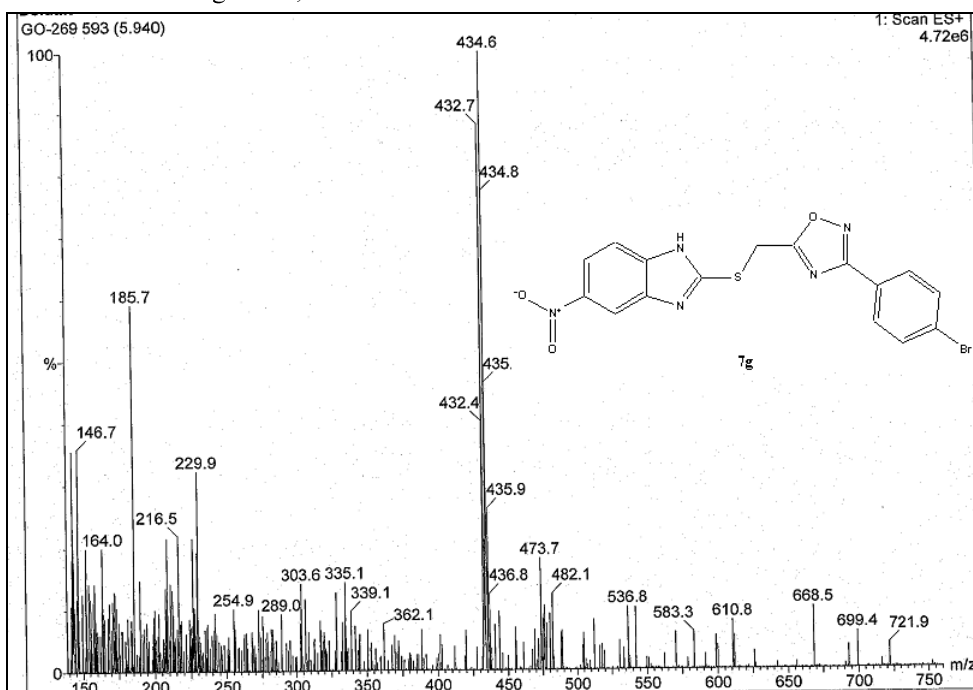


Figure 4.126. LC-MS spectrum of **7g**

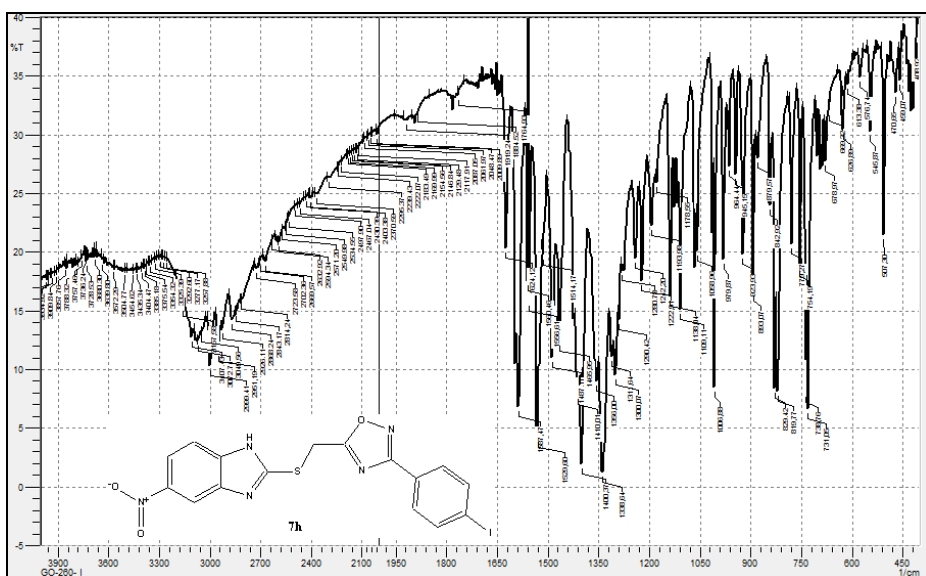


Figure 4.127. The IR spectrum of **7h**

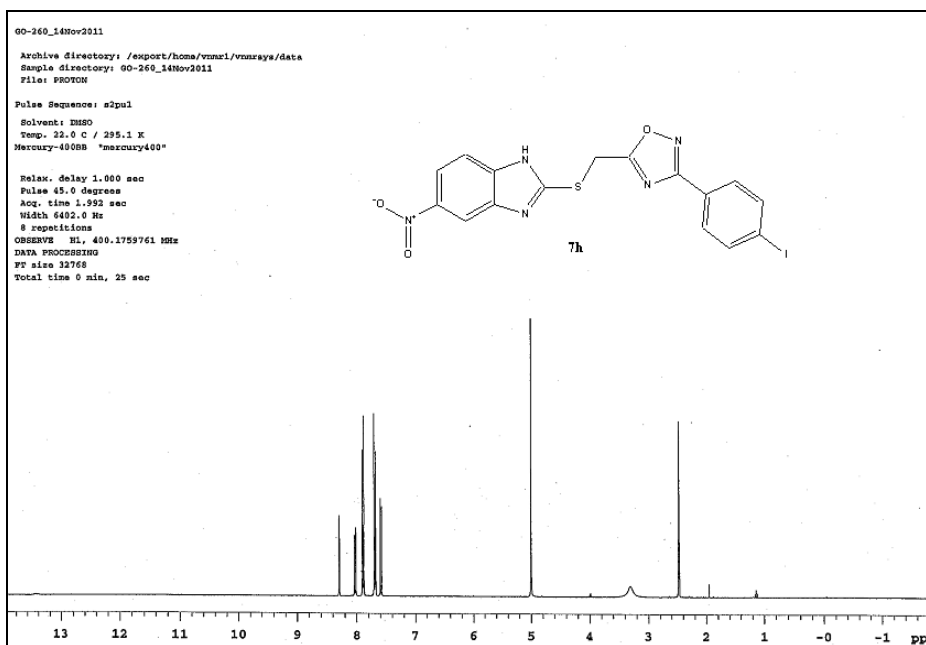


Figure 4.128. The ^1H NMR spectrum of **7h**

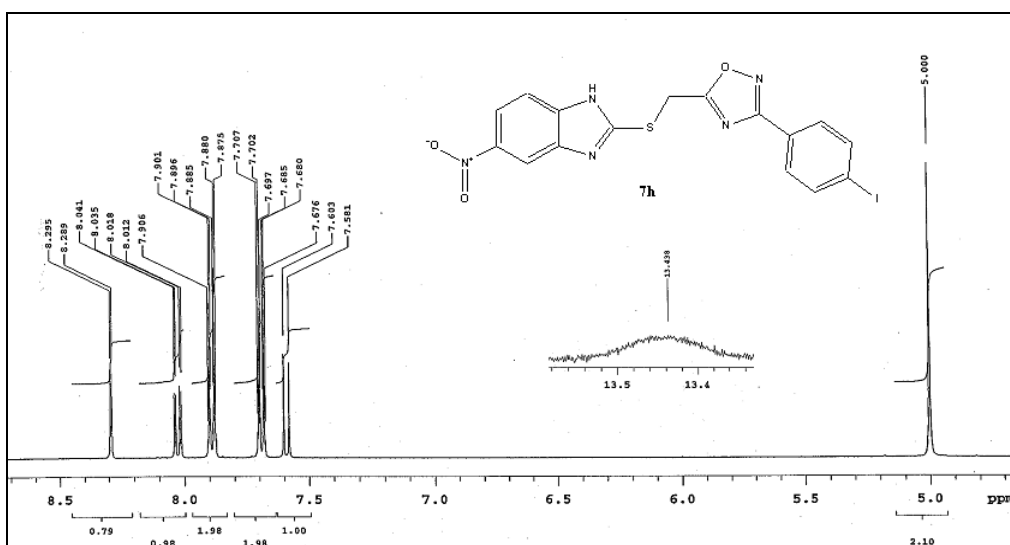


Figure 4.129. The expanded ¹H NMR spectrum of **7h**

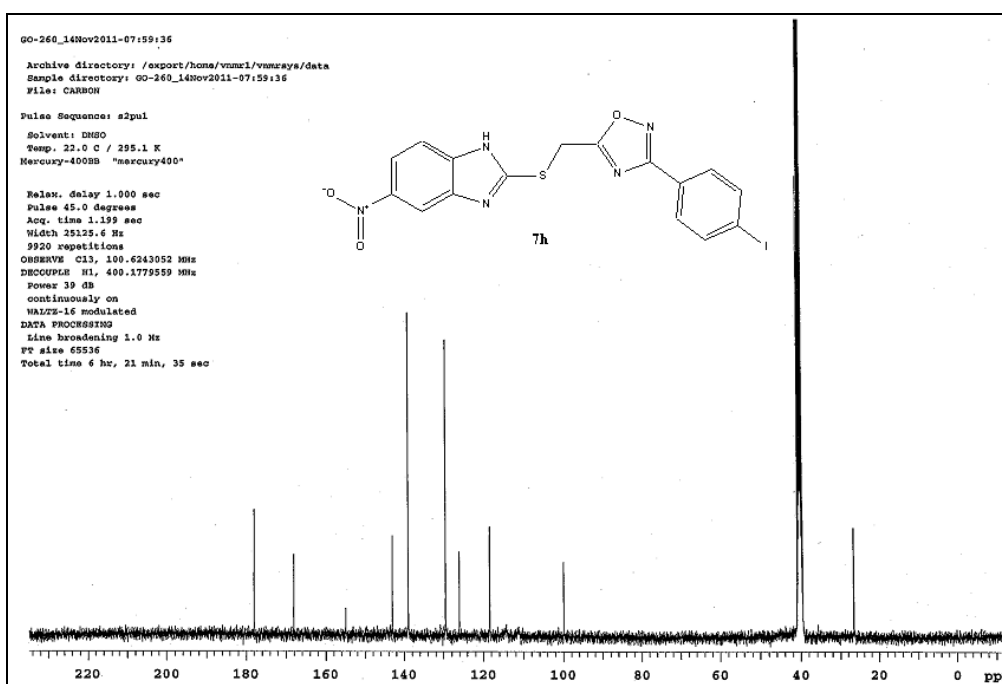


Figure 4.130. The ¹³C NMR spectrum of **7h**

Chemical Formula: $C_{16}H_{10}IN_5O_3S$
Molecular Weight: 479,25

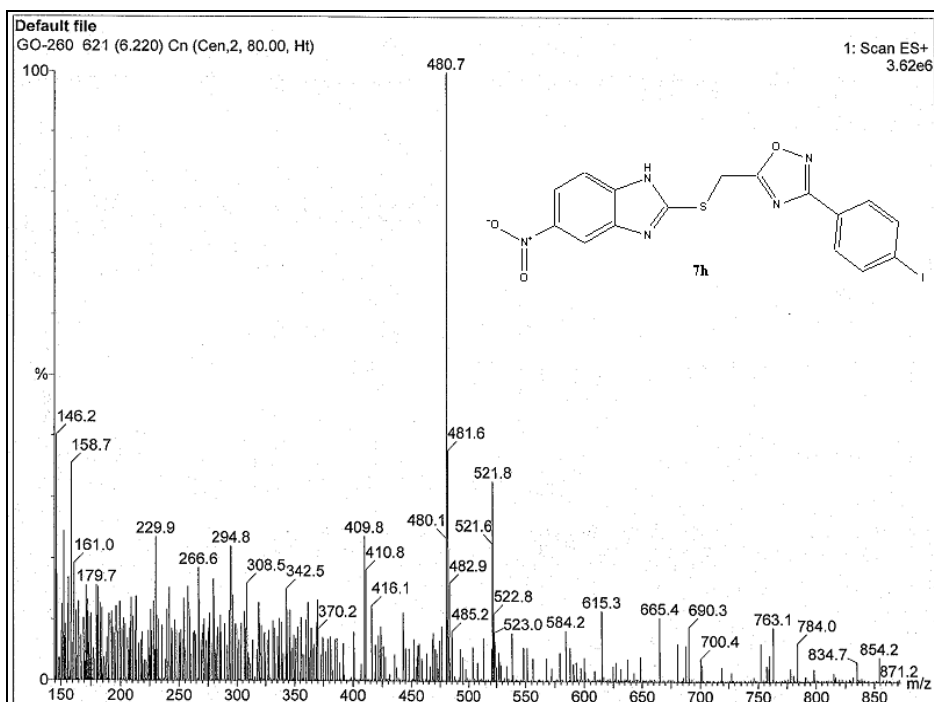


Figure 4.131. LC-MS spectrum of 7h

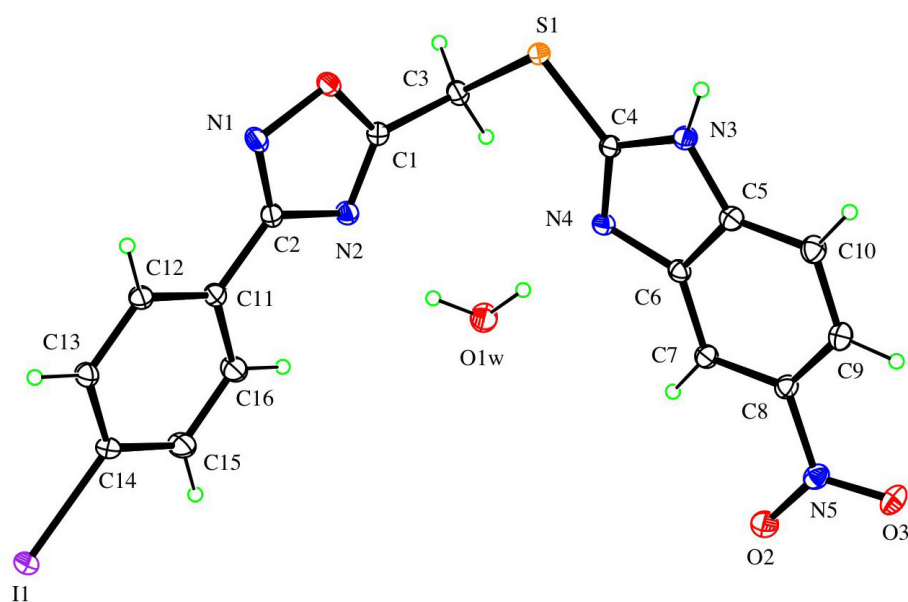


Figure 4.132. The X-ray ORTEP view of 7h

X-Ray diffraction data

Crystal data

$C_{16}H_{10}N_5O_3S \cdot H_2O$

$M_r = 497.27$

Triclinic, $P\bar{1}$

Hall symbol: $-P\ 1$

$a = 7.2417\ (2)\ \text{\AA}$

$b = 7.2952\ (2)\ \text{\AA}$

$c = 17.3288\ (6)\ \text{\AA}$

$\alpha = 88.168\ (2)^\circ$

$\beta = 85.458\ (2)^\circ$

$\gamma = 72.328\ (2)^\circ$

$V = 869.50\ (5)\ \text{\AA}^3$

$Z = 2$

$F(000) = 488$

$D_x = 1.899\ \text{Mg m}^{-3}$

Mo $K\alpha$ radiation, $\lambda = 0.71073\ \text{\AA}$

Cell parameters from 7881 reflections

$\theta = 3.1\text{--}33.2^\circ$

$\mu = 2.00\ \text{mm}^{-1}$

$T = 90\ \text{K}$

Plate, Colourless

$0.34 \times 0.27 \times 0.02\ \text{mm}$

Data collection

Bruker Kappa APEX-II DUO
diffractometer

Radiation source: fine-focus sealed tube

TRIUMPH curved graphite monochromator

φ and θ scans

Absorption correction: Multi-scan

SADABS (Sheldrick, 2004)

$T_{\min} = 0.550$, $T_{\max} = 0.961$

10446 measured reflections

6522 independent reflections

6122 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.016$

$\theta_{\max} = 33.2^\circ$, $\theta_{\min} = 3.1^\circ$

$h = -10 \rightarrow 11$

$k = -11 \rightarrow 11$

$l = -26 \rightarrow 26$

Refinement

Refinement on F^2

Least-squares matrix: Full

$R[F^2 > 2\sigma(F^2)] = 0.022$

$wR(F^2) = 0.057$

$S = 1.06$

6522 reflections

253 parameters

3 restraints

Primary atom site location: Structure-invariant direct methods

Secondary atom site location: Difference Fourier map

Hydrogen site location: Inferred from neighbouring sites

H atoms treated by a mixture of independent and constrained refinement

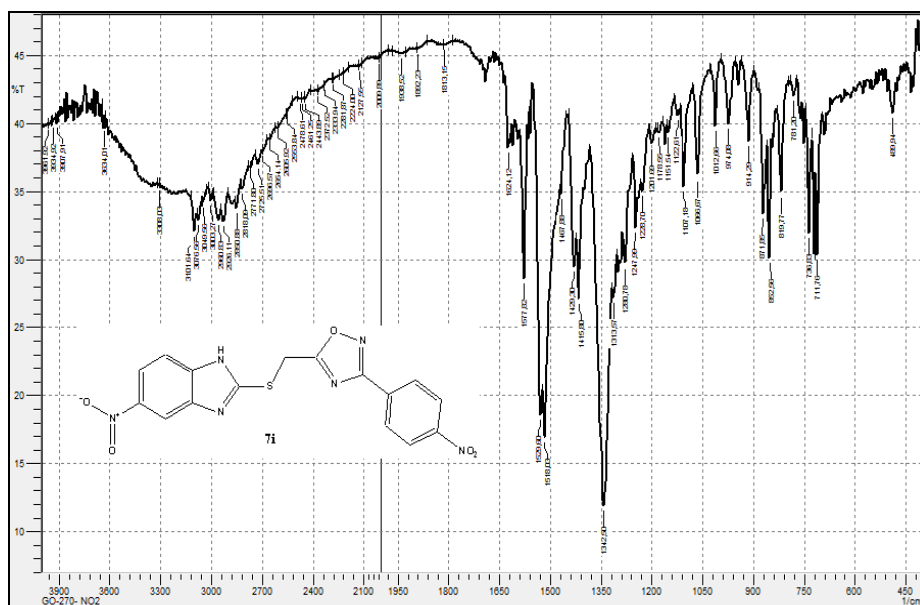
$w = 1/[\sigma^2(F_o^2) + (0.0308P)^2 + 0.3683P]$

where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{\max} = 0.001$

$\Delta\rho_{\max} = 0.89\ \text{e \AA}^{-3}$

$\Delta\rho_{\min} = -0.82\ \text{e \AA}^{-3}$



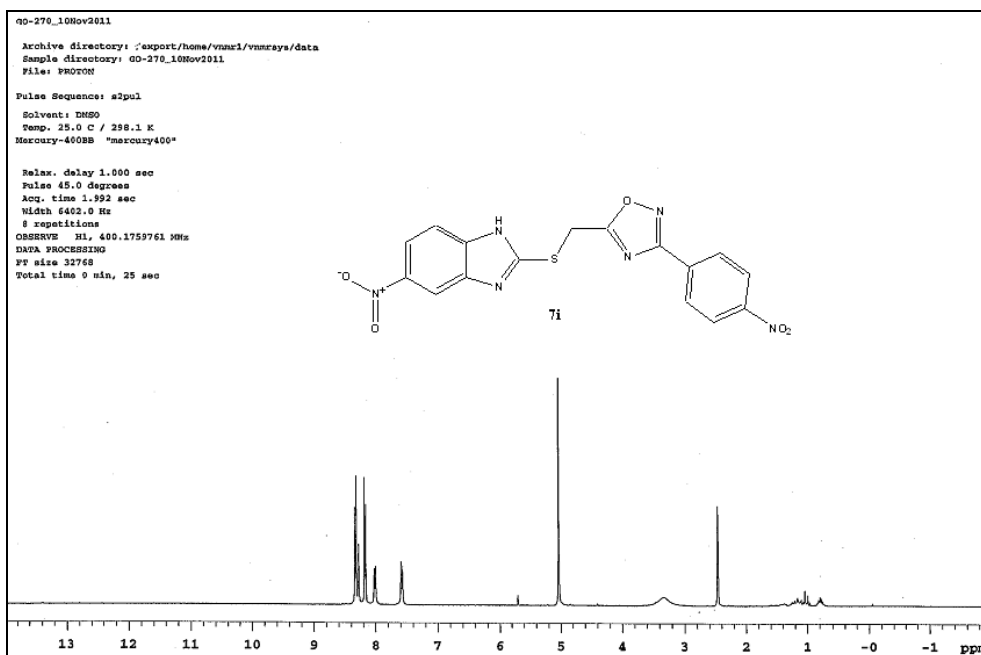


Figure 4.134. The ^1H NMR spectrum of **7i**

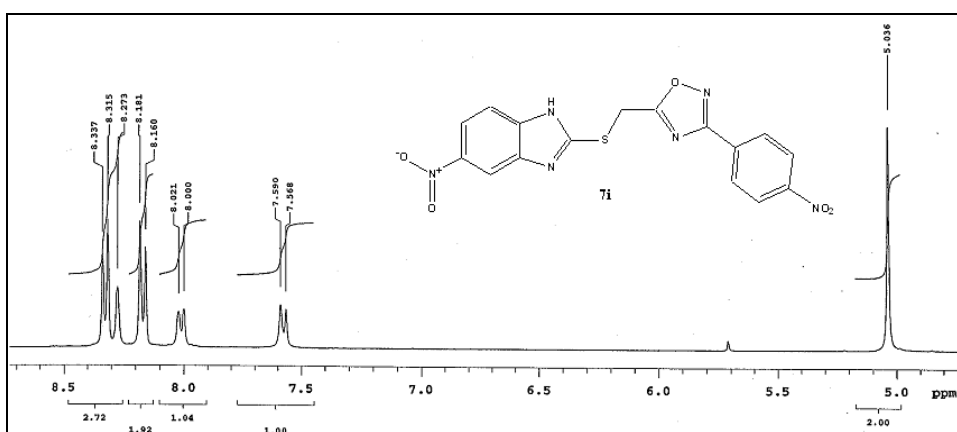


Figure 4.135. The expanded ^1H NMR spectrum of **7i**

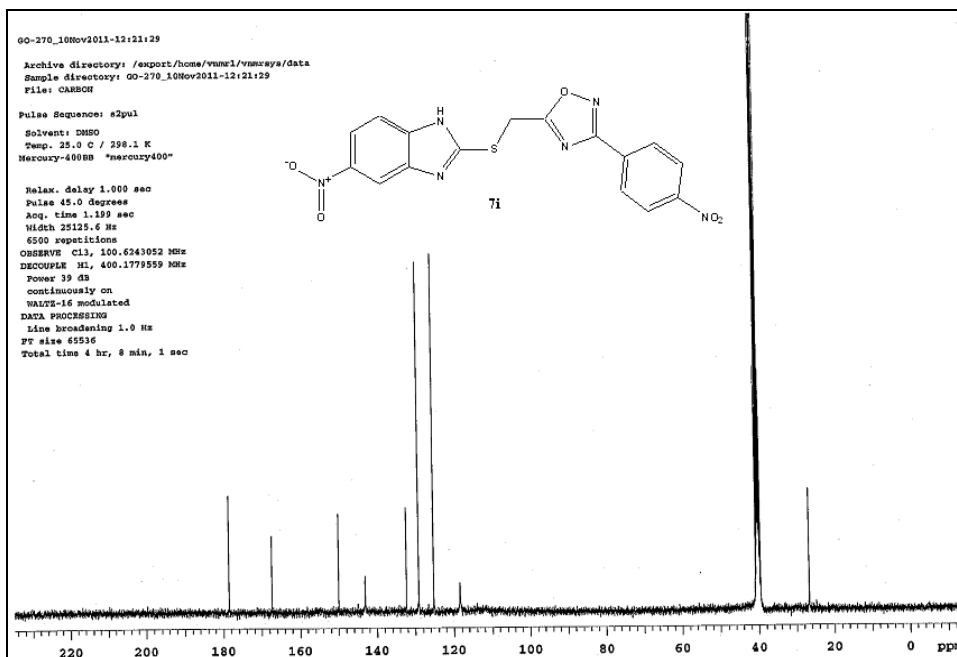


Figure 4.136. The ^{13}C NMR spectrum of 7i

Chemical Formula: $\text{C}_{16}\text{H}_{10}\text{N}_6\text{O}_5\text{S}$
Molecular Weight: 398.35

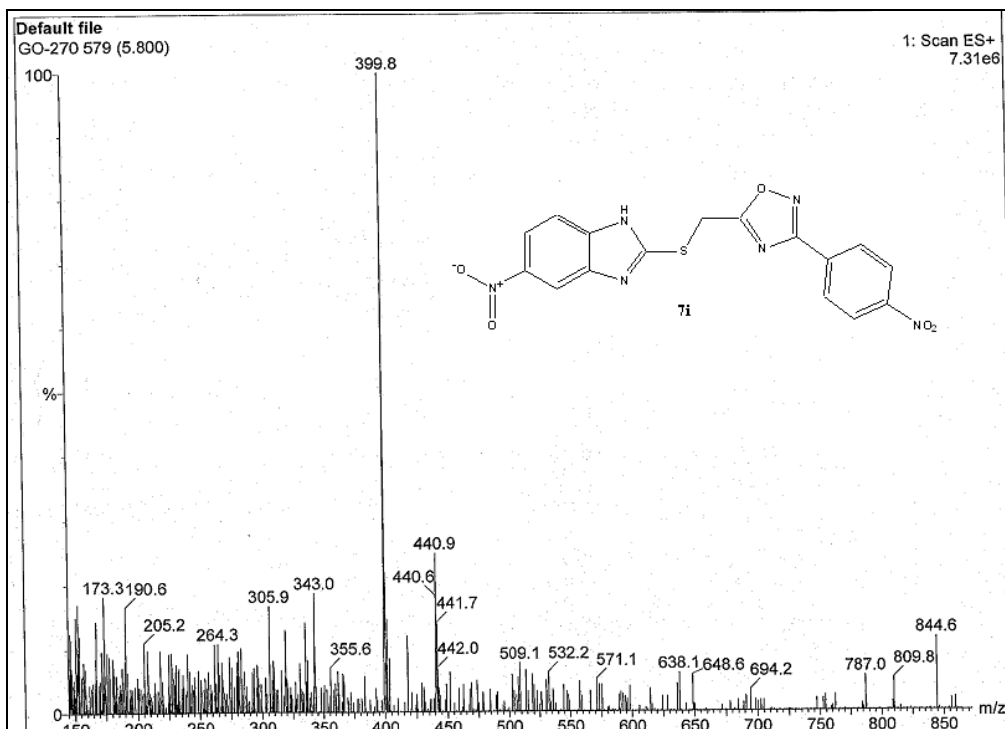
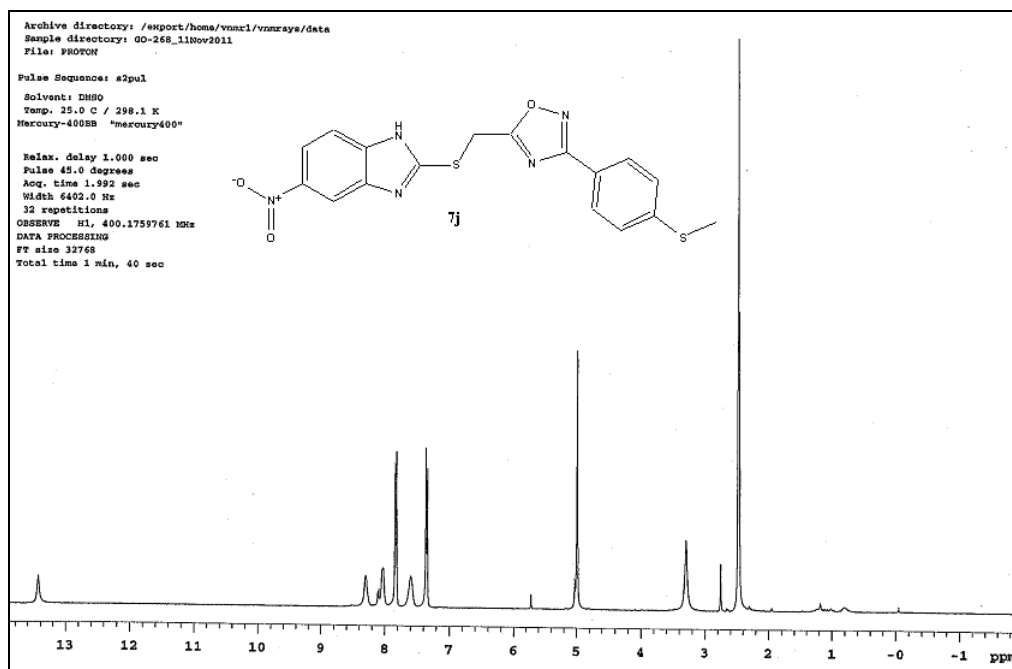
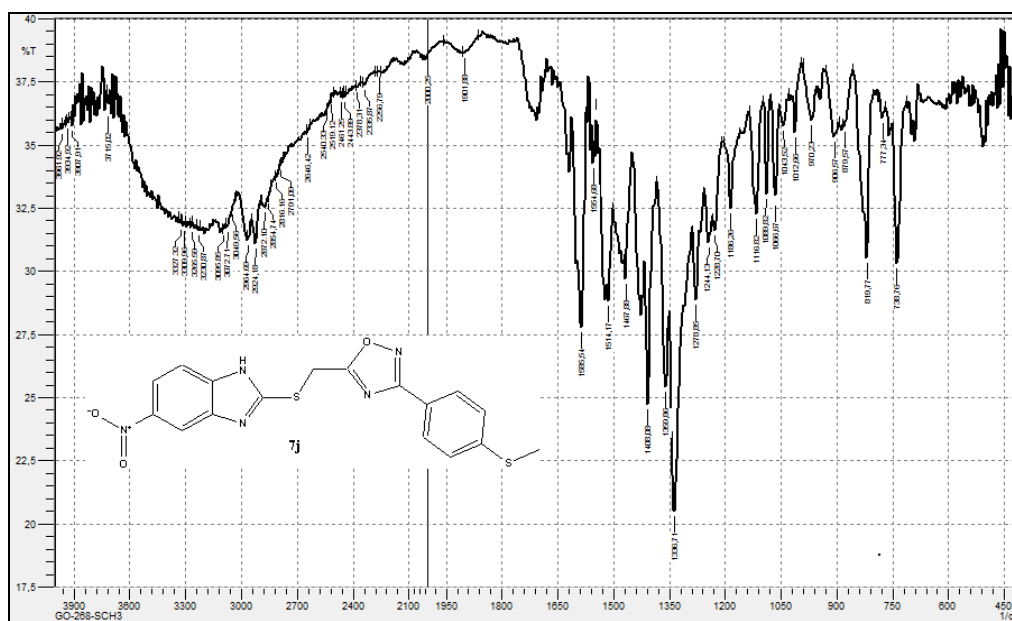


Figure 4.137. LC-MS spectrum of 7i



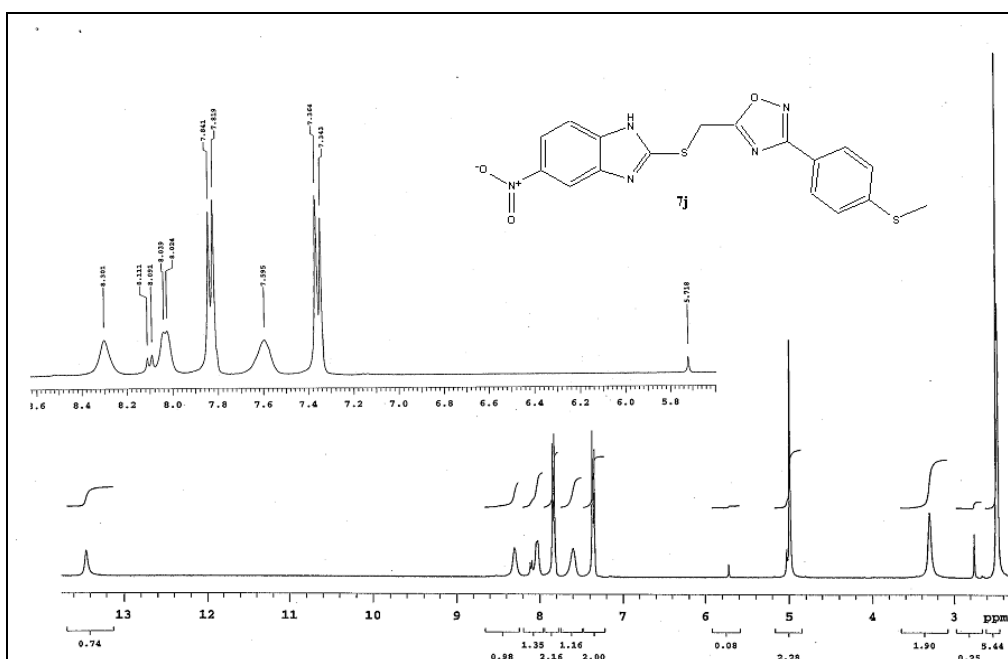


Figure 4.140. The expanded ¹H NMR spectrum of **7j**

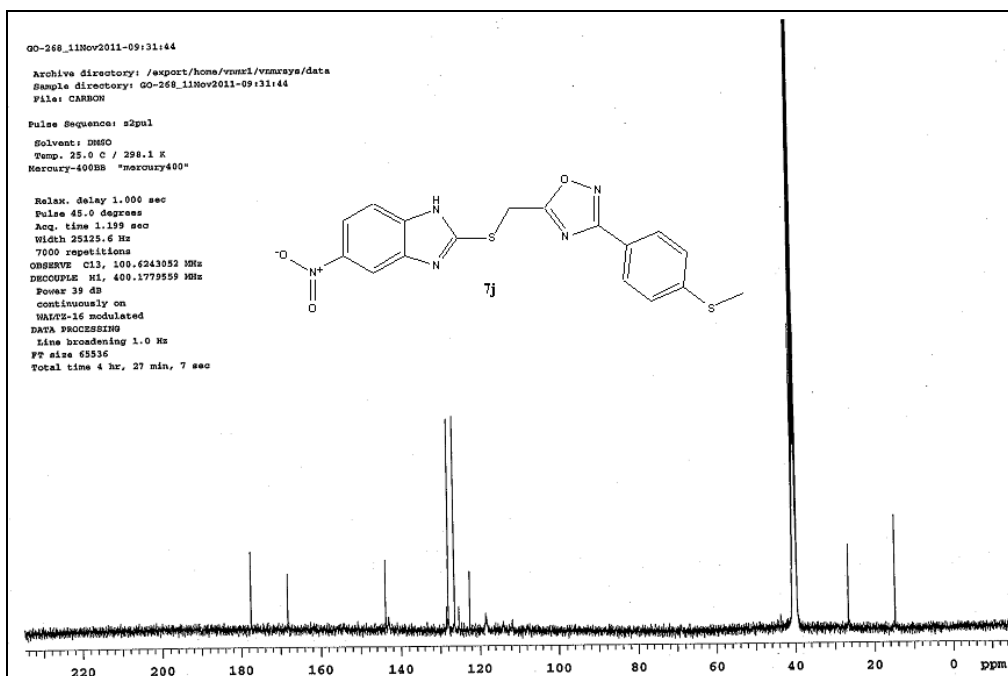


Figure 4.141. The ¹³C NMR spectrum of **7j**

Chemical Formula: $C_{17}H_{13}N_5O_3S_2$
Molecular Weight: 399,45

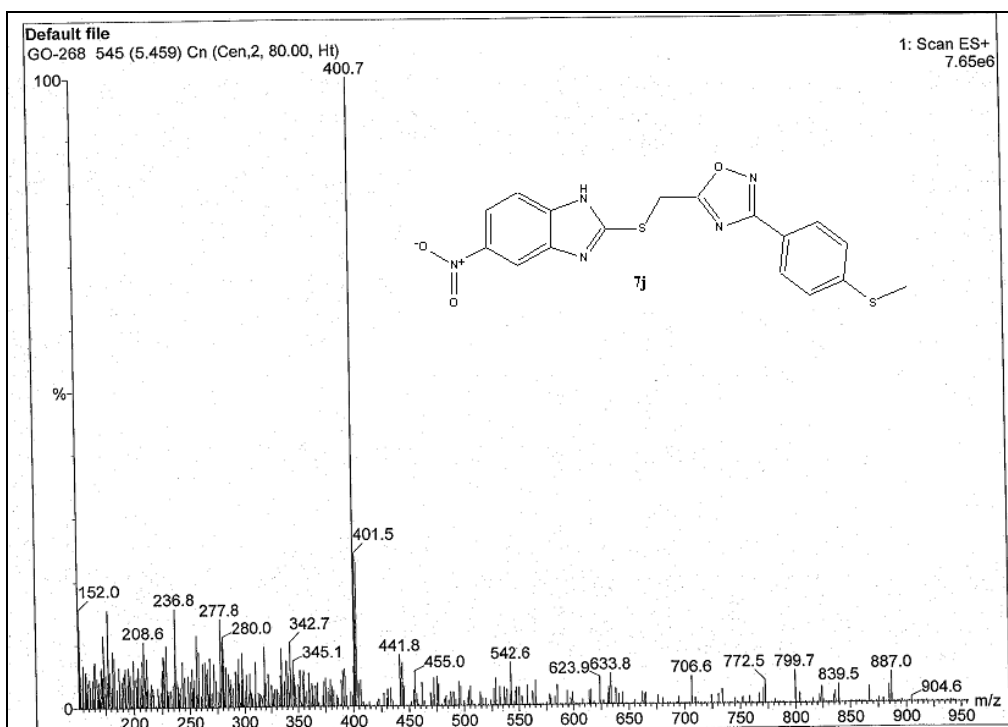


Figure 4.142. LC-MS spectrum of 7j

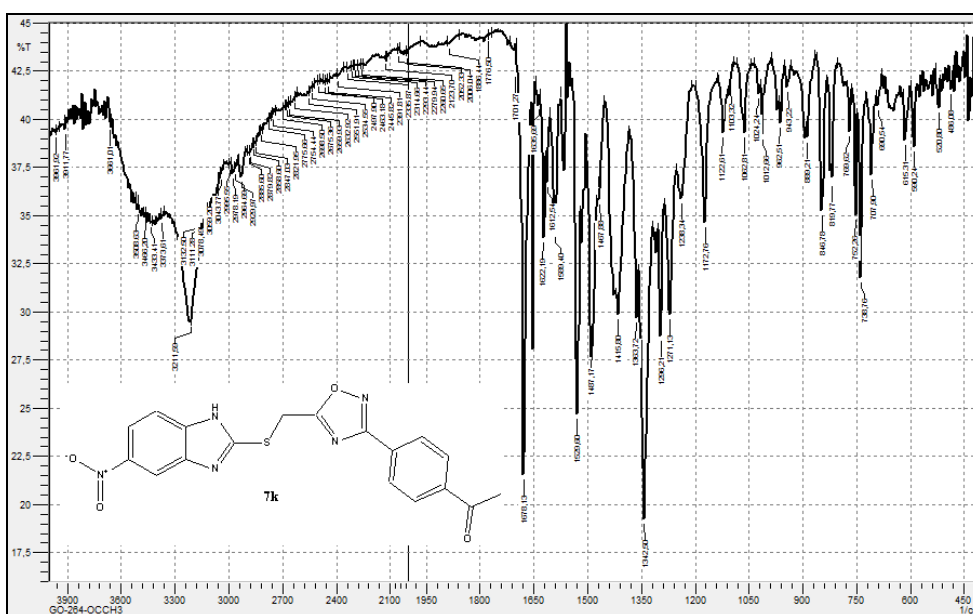


Figure 4.143. The IR spectrum of 7k

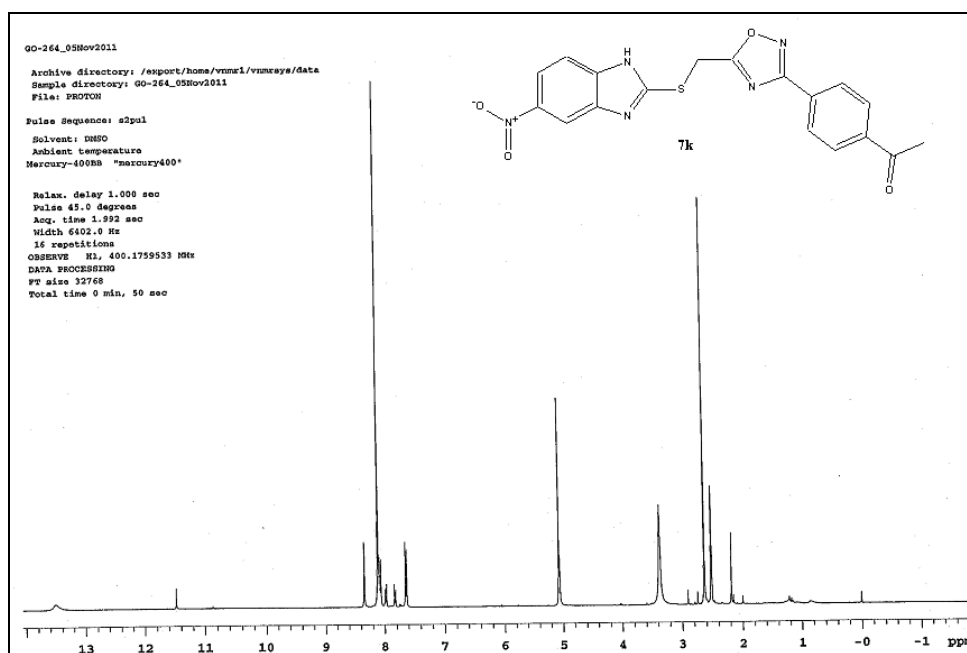


Figure 4.144. The ^1H NMR spectrum of **7k**

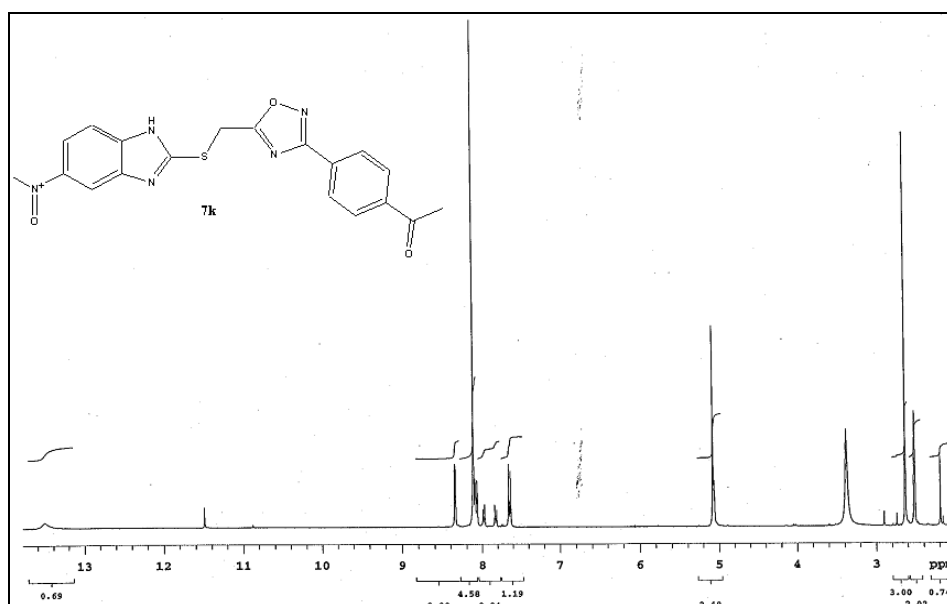


Figure 4.145. The expanded ^1H NMR spectrum of **7k**

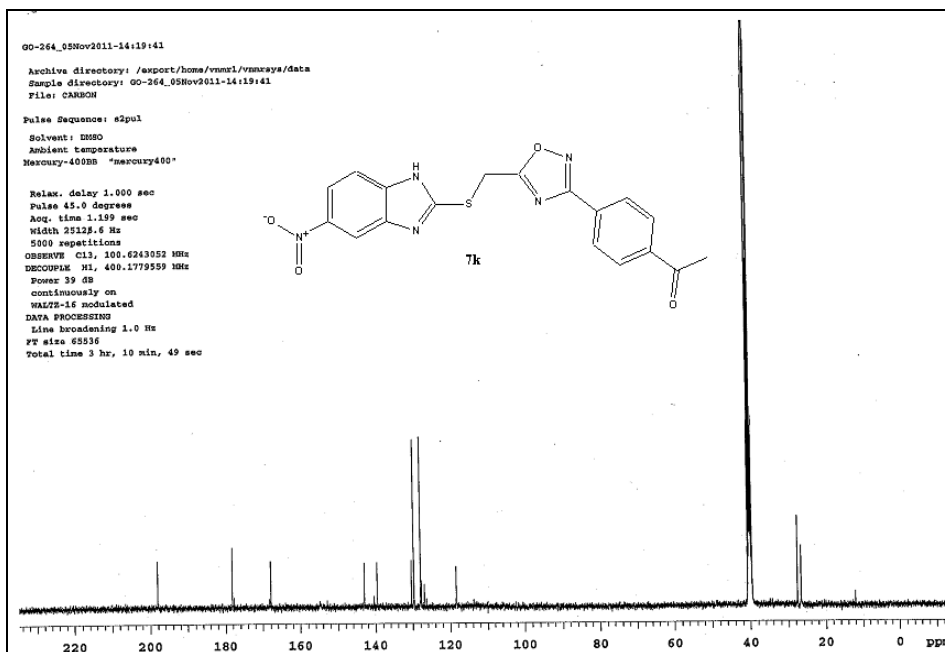


Figure 4.146. The ^{13}C NMR spectrum of **7k**

Chemical Formula: $\text{C}_{18}\text{H}_{13}\text{N}_5\text{O}_4\text{S}$

Molecular Weight: 395.39

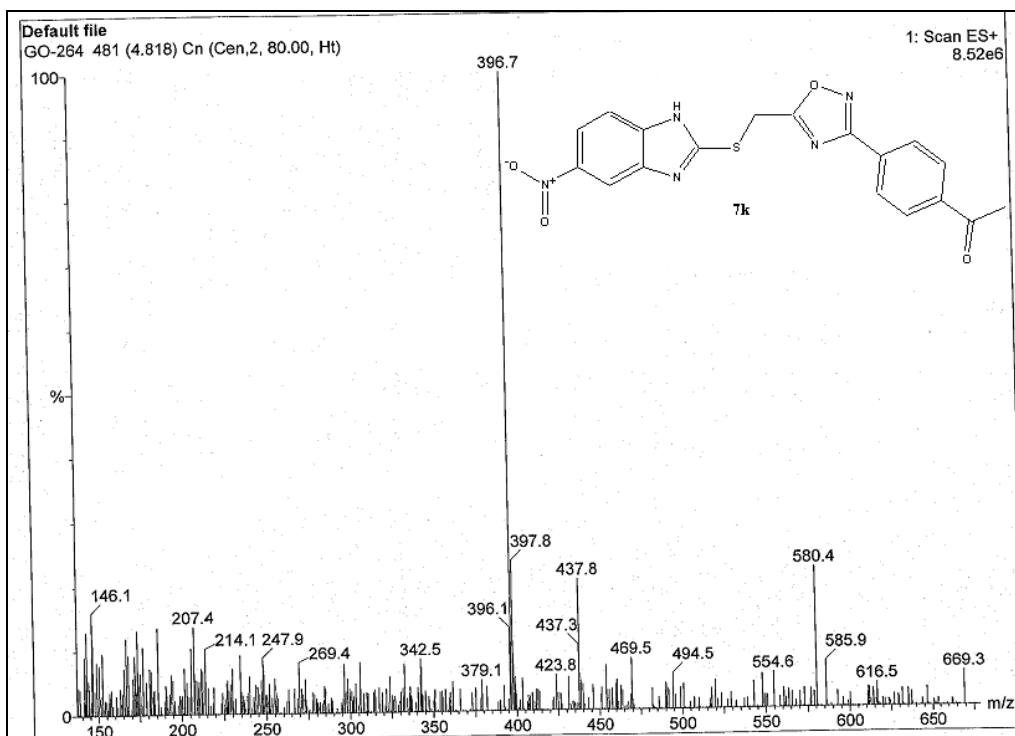


Figure 4.147. LC-MS spectrum of **7k**

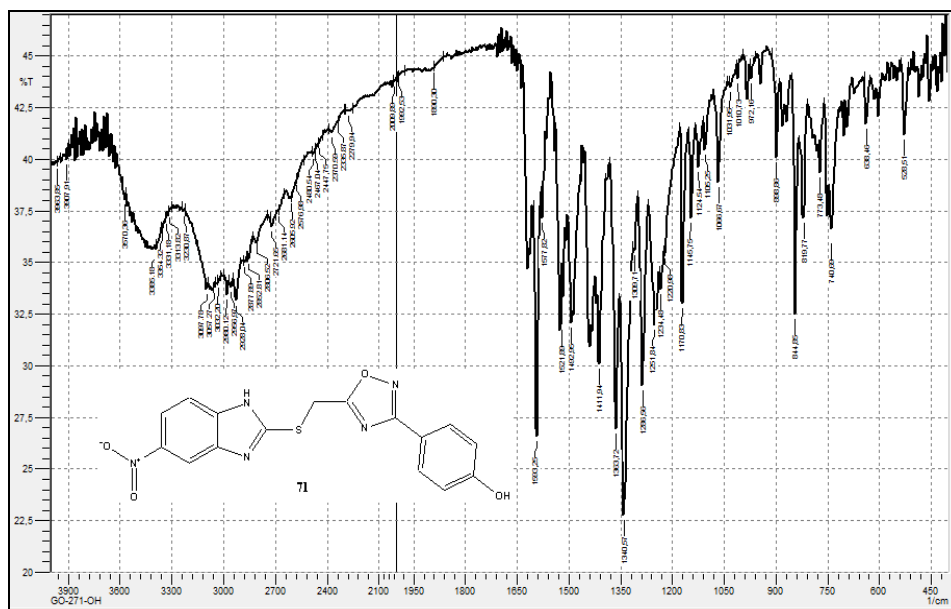


Figure 4.148. The IR spectrum of 71

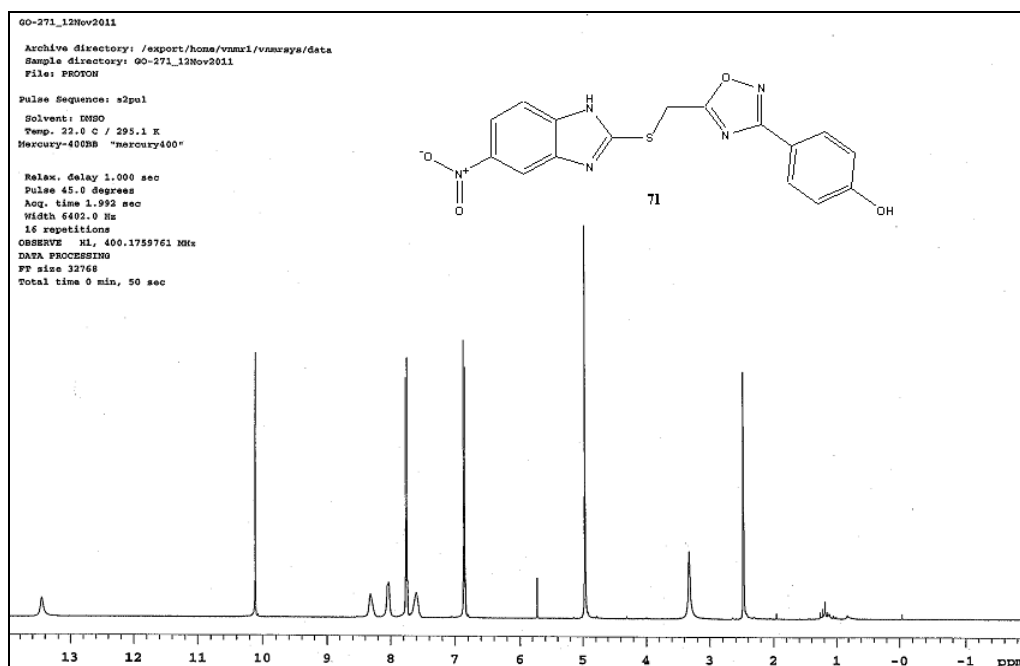


Figure 4.149. The ^1H NMR spectrum of 71

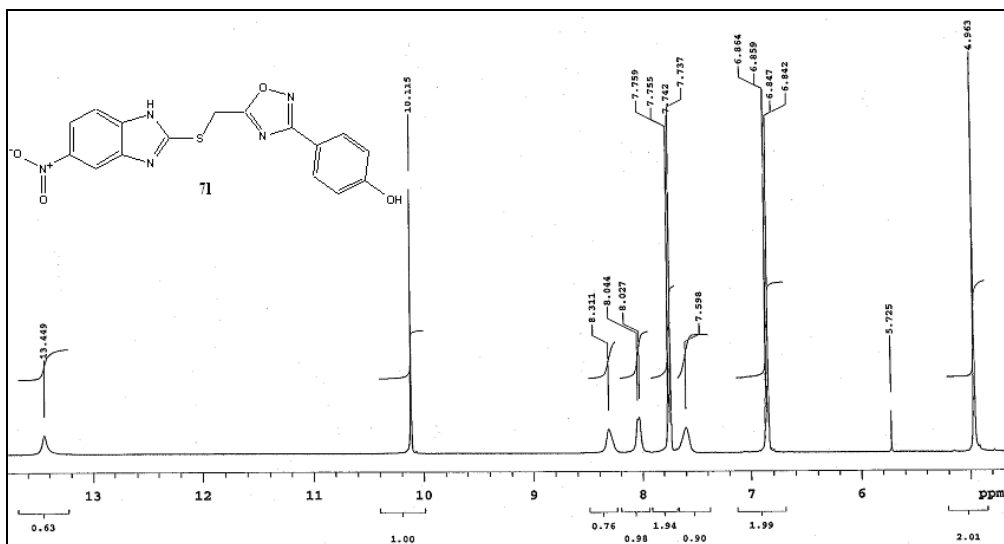


Figure 4.150. The expanded ¹H NMR spectrum of 71

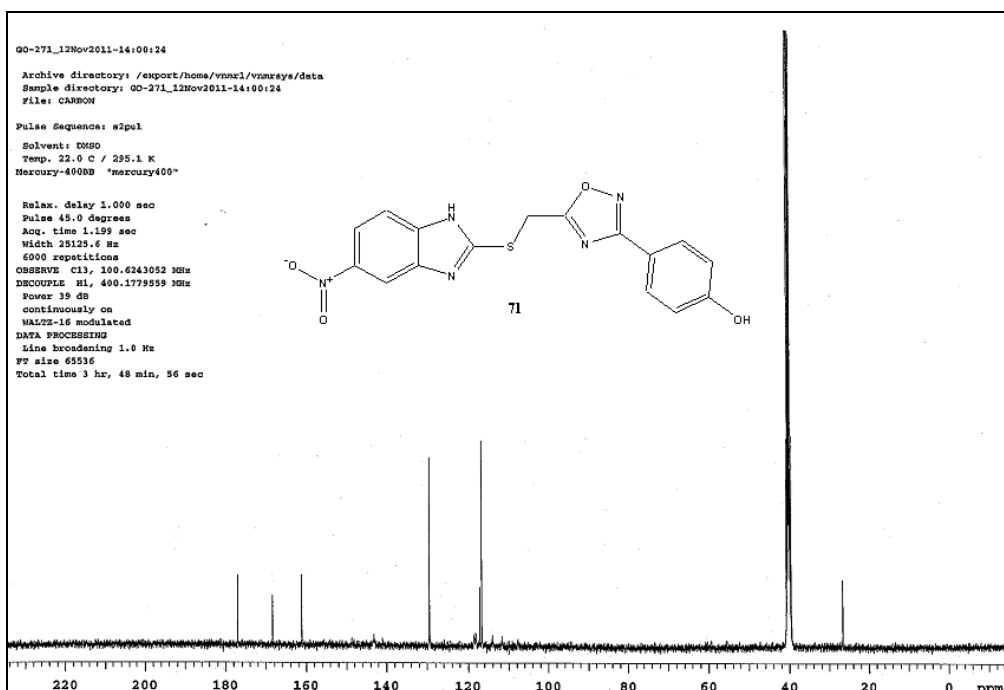


Figure 4.151. The ¹³C NMR spectrum of 71

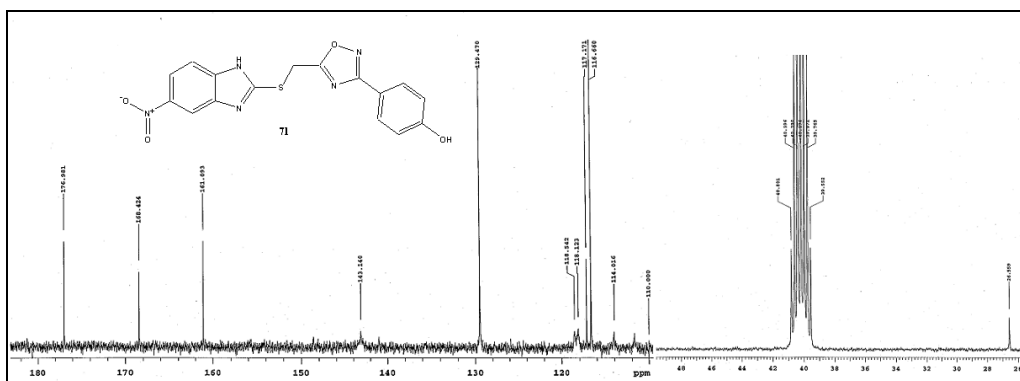


Figure 4.152. The expanded ^{13}C NMR spectrum of **71**

Chemical Formula: $\text{C}_{16}\text{H}_{11}\text{N}_5\text{O}_4\text{S}$
Molecular Weight: 369,35

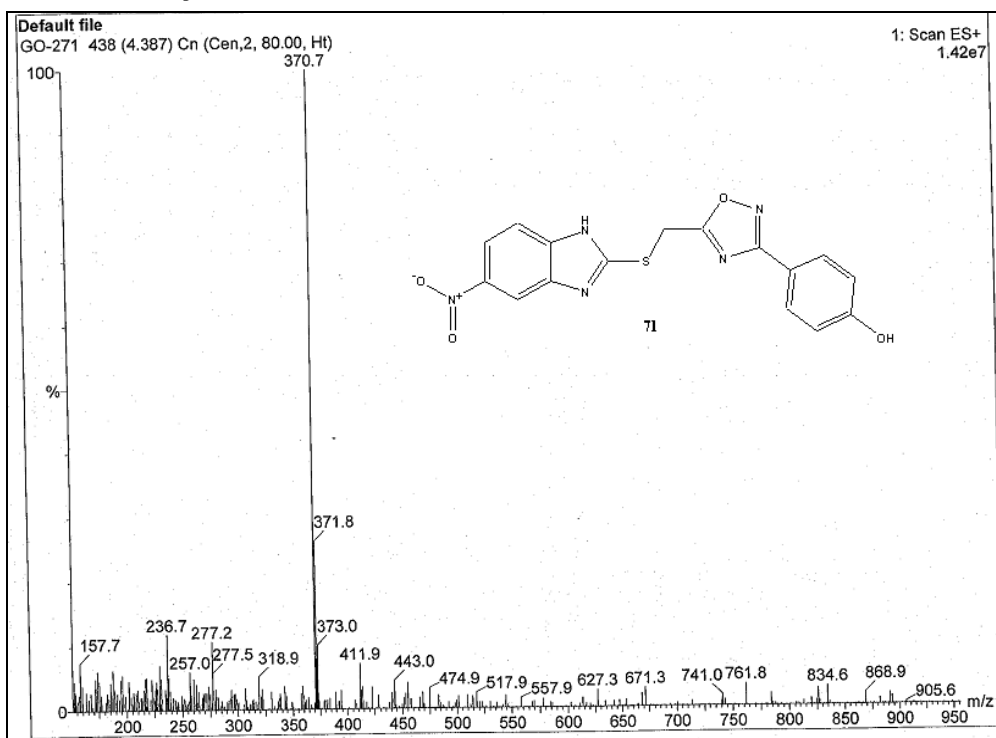


Figure 4.153. LC-MS spectrum of **71**

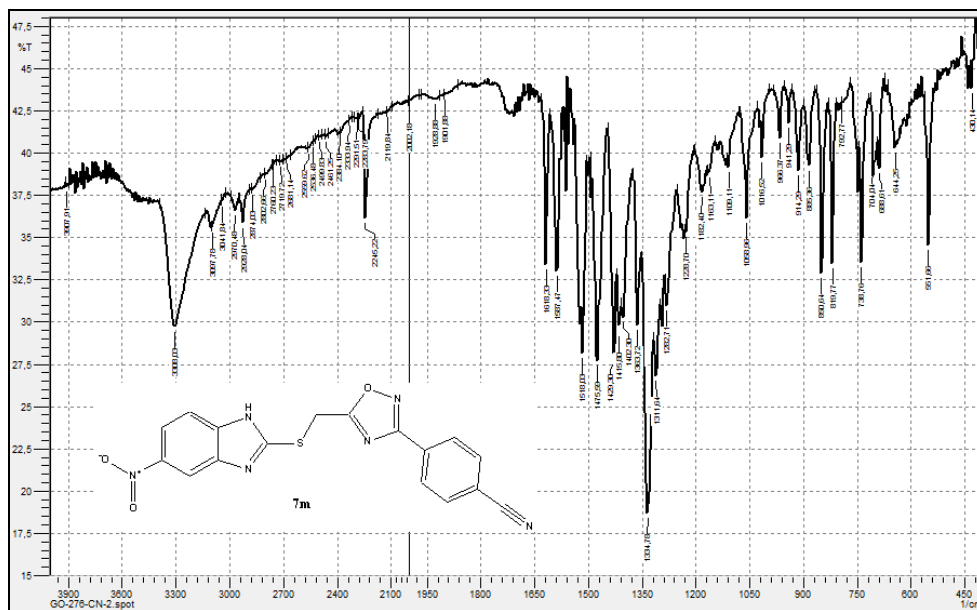


Figure 4.154. The IR spectrum of **7m**

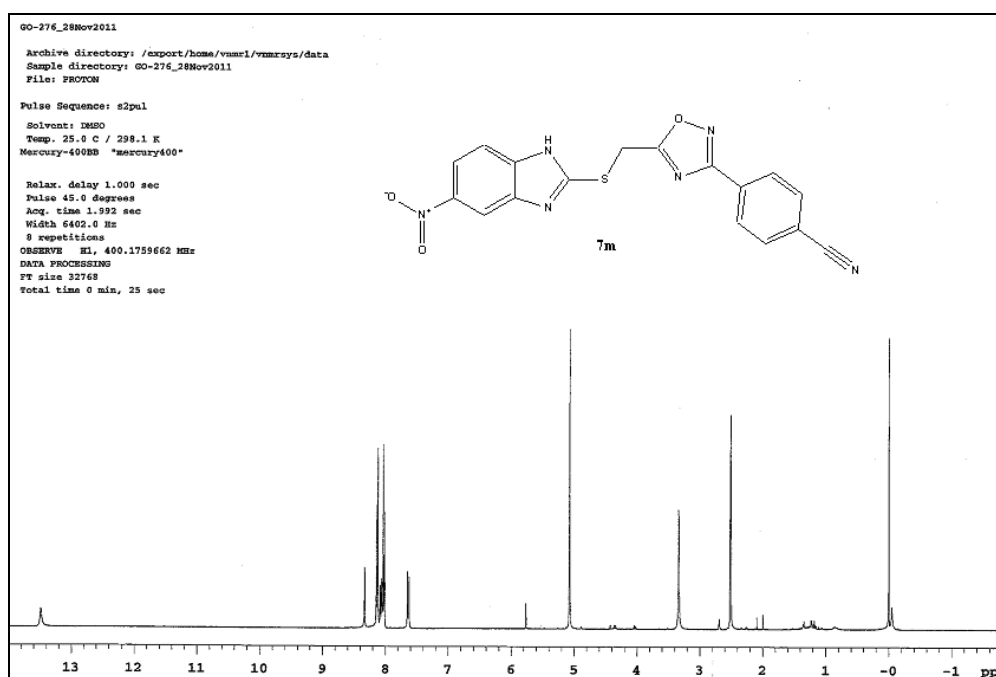


Figure 4.155. The ^1H NMR spectrum of **7m**

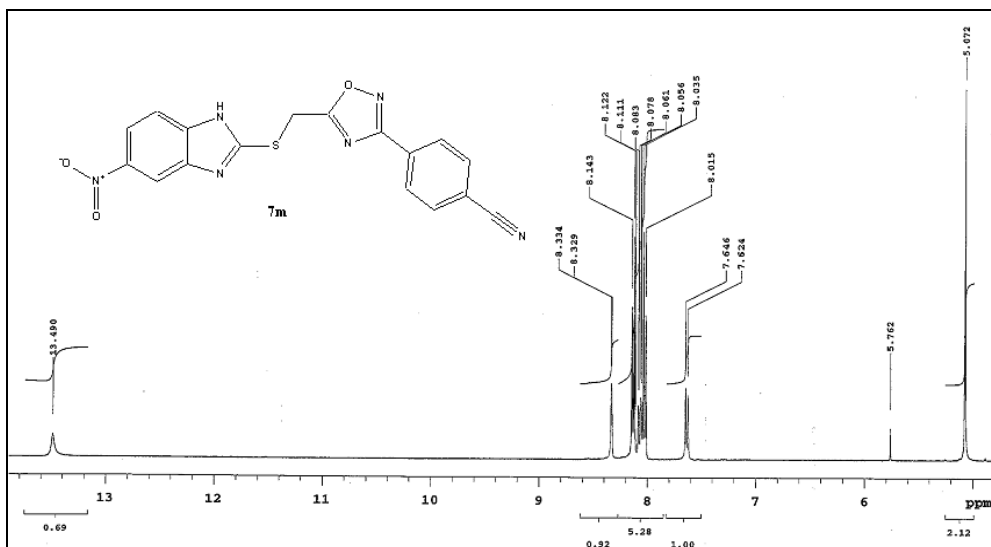


Figure 4.156. The expanded ¹H NMR spectrum of **7m**

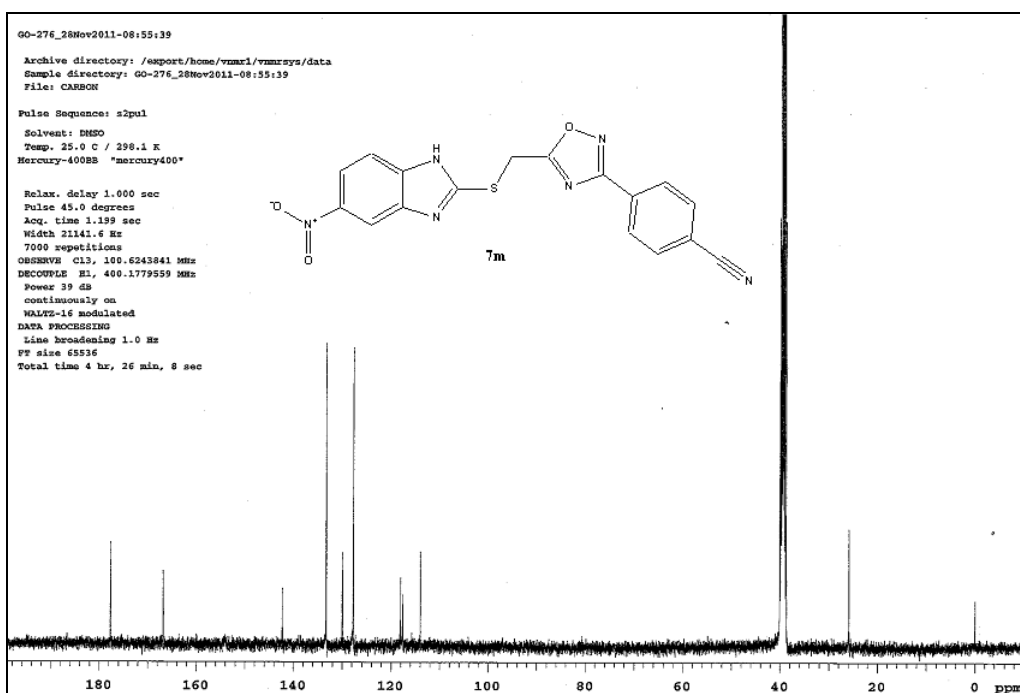


Figure 4.157. The ¹³C NMR spectrum of **7m**

Chemical Formula: C₁₇H₁₀N₆O₃S
Molecular Weight: 378,36

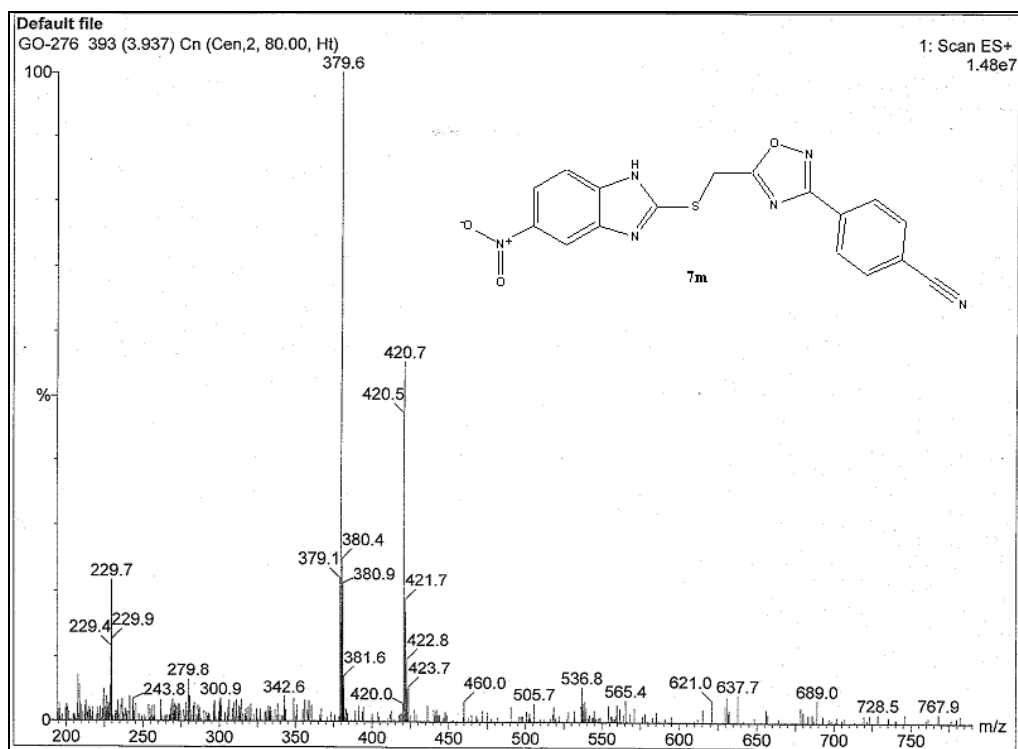


Figure 4.158. LC-MS spectrum of 7m

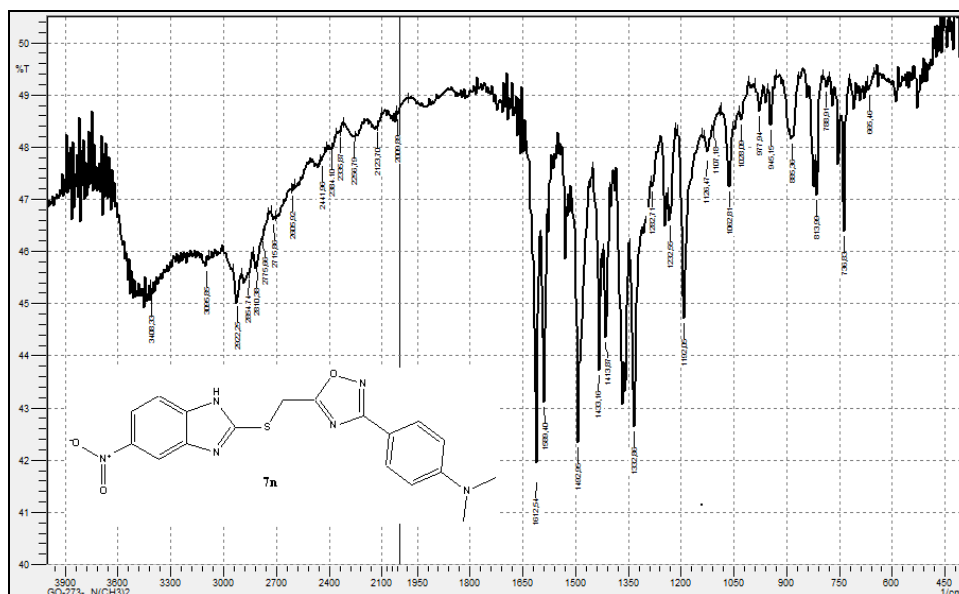


Figure 4.159. The IR spectrum of 7n

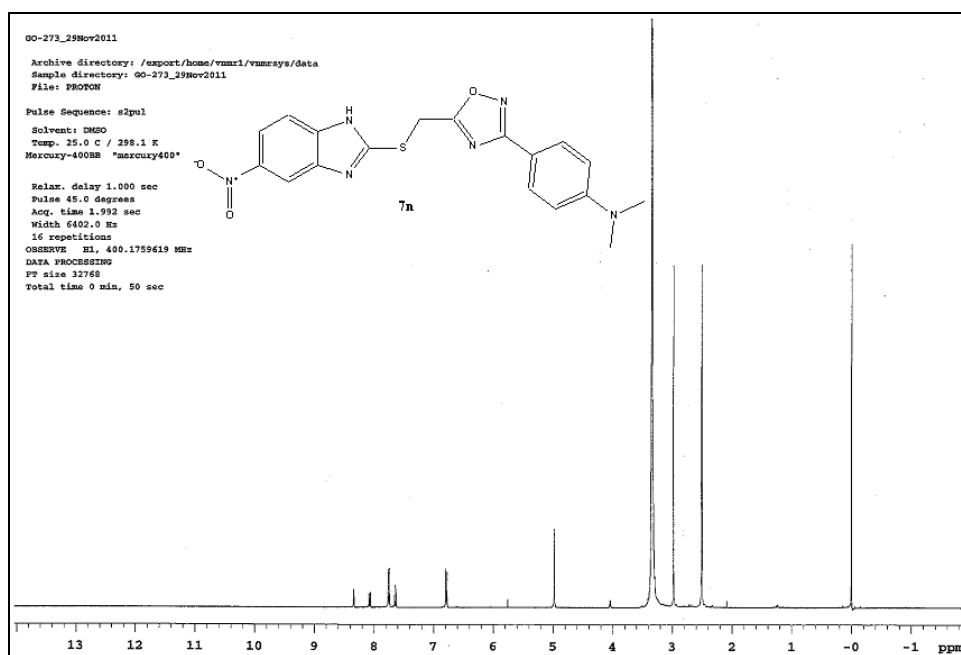


Figure 4.160. The ^1H NMR spectrum of **7n**

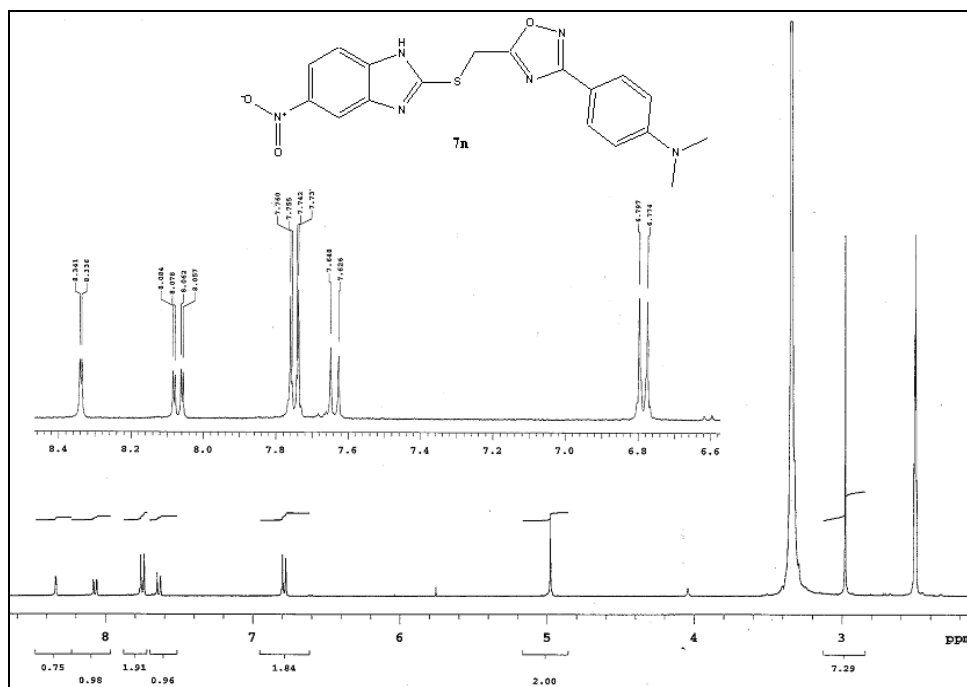


Figure 4.161. The expanded ^1H NMR spectrum of **7n**

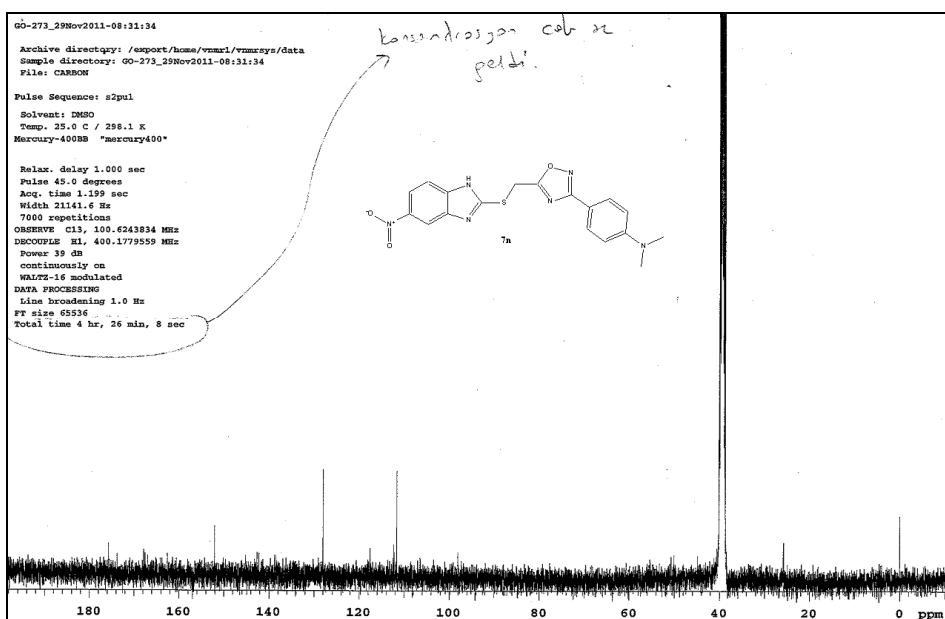


Figure 4.162. The ^{13}C NMR spectrum of 7n

Chemical Formula: $\text{C}_{18}\text{H}_{16}\text{N}_6\text{O}_3\text{S}$
 Molecular Weight: 396.42

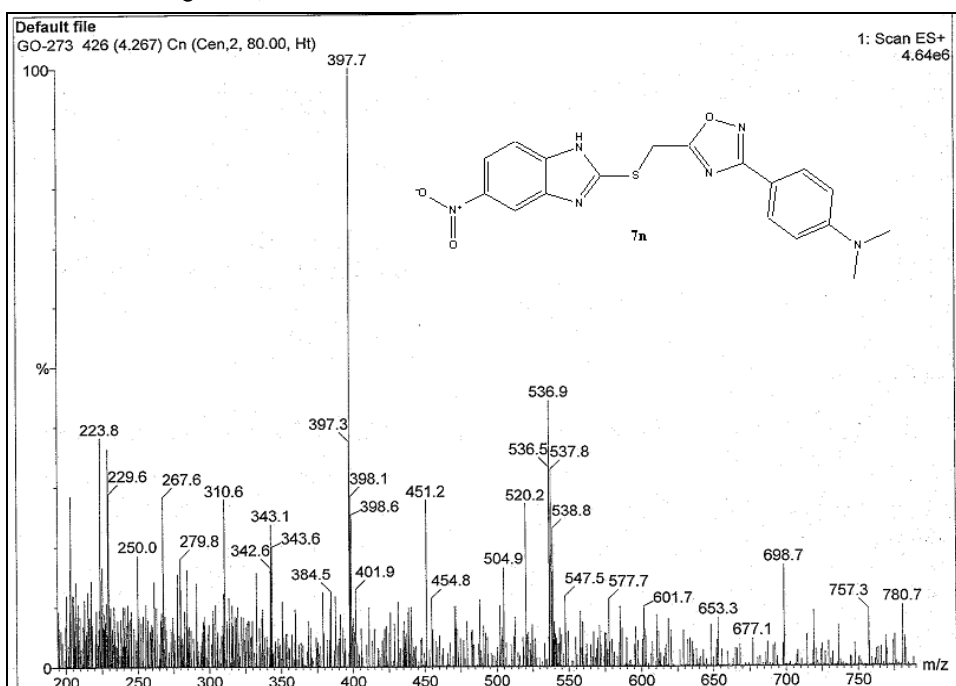


Figure 4.163. LC-MS spectrum of 7n