

EGE UNIVERSITY INSTITUTE OF NATURAL AND
APPLIED SCIENCES
(DOCTOR OF PHILOSOPHYTHESIS)

**SYNTHESIS OF SOME BENZOFURANS AND
THEIR ACTIVITIES**

Safiye EMİRDAĞ

Chemistry Department

Code of Discipline: 405.02.01

Presentation Date: 21/08/2008

I. Supervisor: Prof. Dr. Hüseyin ANIL

II. Supervisor: Yrd. Doç.Dr. Yurdanur AKGÜL

Bornova-İZMİR

III

Safiye EMİRDAĞ tarafından “**DOKTORA TEZİ**” olarak sunulan “**Synthesis of Some Benzofurans and Their Activities**” adlı bu çalışma, E.Ü. Lisans üstü Eğitim ve Öğretim Yönetmeliği ve E.Ü. Fen Bilimleri Enstitüsü Eğitim ve Öğretim Yönergesi’nin ilgili hükümleri uyarınca tarafımızdan değerlendirilmiş olup/...../2008 tarihinde yapılan tez savunma sınavında aday *oy birliği / oy çokluğu* ile başarılı bulunmuştur.

Jüri Üyeleri

İmza

Jüri Başkanı :

Raportör Üye:

Üye :

ÖZET

BAZI BENZOFURAN BİLEŞİKLERİN KISMİ SENTEZİ VE BİYOLOJİK AKTİVİTELERİN İNCELENMESİ

EMİRDAĞ, Safiye

Doktora Tezi, Kimya Bölümü

I. Tez Yöneticisi: Prof. Dr. Hüseyin ANIL

II. Tez Yöneticisi: Yrd. Doç. Dr. Yurdanur AKGÜL

Ağustos 2008, 172 sayfa

Bu çalışmada, önce *Styrax officinalis* L. tohumlarından egonolün izolasyonu gerçekleşti, ardından egonolden başlayarak sentez çalışmaları yapıldı ve bu yeni benzofuran türevlerinin antimikrobiyal aktiviteleri bazı mikroorganizmalara karşı test edildi.

Egonolden toplam otuz bileşik sentezlenmiştir. Bileşiklerin yapıları IR, UV-vis., ¹H NMR, ¹³C NMR, COSY, HMQC, LCMS teknikleri ile saptandı.

Anahtar Kelimeler: *Styrax*; *Styrax officinalis*, egonol, benzofuran, antimikrobiyal aktivite.

ABSTRACT

SYNTHESIS OF SOME BENZOFURANS AND THEIR ACTIVITIES

EMİRDAĞ, Safiye

Doctor of Philosophy Thesis, Chemistry Department

I. Supervisor: Prof. Dr. Hüseyin ANIL

II. Supervisor: Yrd. Doç.Dr. Yurdanur AKGÜL

August 2008, 172 pages

In this study egonol was isolated from *Styrax Officinalis L.* and then some new benzofuran derivatives were synthesized. The antimicrobial activities of new benzofuran derivatives were tested against some microorganisms.

Totally thirty compounds were synthesised from egonol. Their structures were determined by IR, UV-vis., ^1H NMR, ^{13}C NMR, COSY, HMQC, LCMS techniques.

Keywords: *Styrax*; *Styrax officinalis*, egonol, benzofuran, antimicrobial activity.

IX

ACKNOWLEDGMENT

I would like to present my gratitude to my supervisor, Prof. Dr. Hüseyin ANIL, for his precious suggestions, support, patience and for enlightening me via his deep knowledge, encouragement and understanding for his considerable contribution and supervision.

I would also like to thank Yrd. Doç. Dr. Yurdanur AKGÜL for her support in this study.

I am sincerely grateful to Prof. Dr. Serap ALP who has served on my thesis committee and Doç. Dr. Mustafa Yavuz ERGUN for their valuable suggestions.

I am also grateful to Prof. Dr. Süheyla KIRMIZIGÜL for her continuous support, advice and encouragement in this study.

I am also grateful to Doç. Dr. Stephen ASTLEY for his invaluable assistance and support.

Special thanks go to Prof. Dr. Misir AHMEDZADE who has also been great assistance, support and valuable suggestions.

I wish to express my gratitude to all my colleagues and staff of Ege Un., Fac. Of Sci., Chemistry Dept. for their friendship and help over the years I spent in the faculty.

X

I also thank the Research Grant Office of Ege University for supporting the 2005 FEN 047 numbered project, TUBITAK for supporting the 105T226 numbered project and EBILTEM for supporting the 2007 BİL 036 numbered project.

I am also grateful to my husband Yavuz ÖZTÜRK and my family for their patience, endless encouragement, understanding, devotion and support during my working-times.

I wish to express my gratitude to Aysun ÇAPCI for support especially in the laboratory.

CONTENTS

	<u>Page No</u>
ÖZET.....	V
ABSTRACT	VII
ACKNOWLEDGMENT	IX
LIST OF FIGURES	XVI
LIST OF TABLES	XIX
ABBREVIATIONS.....	XXII
1. INTRODUCTION.....	1
1.1. General Information	1
1.1.1. Natural Benzofuran Derivatives	2
1.1.2. Benzofuran Synthesis	8
1.1.3. Egonol	20
1.2. General Information on <i>Styrax officinalis</i> L.	22
1.2.1. Classification and Botanical description	22
1.2.2. The use of <i>Styrax officinalis</i> L.	23
1.2.3. Chemical studies on <i>Styrax officinalis</i> L.	24
1.2.4. Biological activity studies on <i>Styrax officinalis</i> L.	25
2. MATERIAL AND METHODS	26
2.1. General Information	26
2.2. Plant Materials	28
2.3. Biological Activity Studies	28
2.4. Extraction, Isolation and Purification Processes	29
2.5. Synthesis of new benzofuran derivatives from egonol	29

XII

2.5.1. Compound 1: 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propanal, as an amorphous powder (C ₁₉ H ₁₆ O ₅).	35
2.5.2. Compound 2: 5-(3''-chloropropyl)-7-methoxy-2-(3',4'-methylene dioxyphenyl)benzofuran (C ₁₉ H ₁₇ ClO ₄).	35
2.5.3. Compound 3: 5-(3''-bromopropyl)-7-methoxy-2-(3',4'-methylenedioxyphenyl) benzofuran (C ₁₉ H ₁₇ BrO ₄).	36
2.5.4. Compound 4: 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]propyl chloroacetate (C ₂₁ H ₁₉ ClO ₆).	37
2.5.5. Compound 5: 5-[3''-hydroxypropyl]-6-bromo-7-methoxy-2-(3',4'-methylene dioxyphenyl)benzofuran, (C ₁₉ H ₁₇ BrO ₅).	37
2.5.6. Compound 6: 5-[3''-hydroxypropyl]-3,6-dibromo-7-methoxy-2-(3',4'-methylene dioxyphenyl)benzofuran (C ₁₉ H ₁₆ Br ₂ O ₅).	38
2.5.7. Compound 7: 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propyl hydrogen sulfate (C ₁₉ H ₁₈ O ₈ S).	39
2.5.8. Compound 8: 5-[3''-hydroxypropyl]-7-methoxy-3-nitro-2-(3',4'methylene dioxyphenyl) benzofuran, (C ₁₉ H ₁₇ NO ₇).	40
2.5.9. Compound 9: 5-[3''-hydroxypropyl]-7-methoxy-3,6-dinitro-2-(3',4'methylene dioxyphenyl) benzofuran (C ₁₉ H ₁₆ N ₂ O ₉).	40

XIII

2.5.10. Compound 10: 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propylmethanoat, amorphous solid (C ₂₀ H ₁₈ O ₆).	41
2.5.11. Compound 11: 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propyloleate, oily compound (C ₃₇ H ₅₀ O ₆).	42
2.5.12. Compound 12: 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propylbenzoate , (C ₂₆ H ₂₂ O ₆).	43
2.5.13. Compound 13: 5-[3-(3''-Bromopropoxy)propyl]-7-methoxy-2-(3',4'-methylenedioxyphenyl benzofuran, (C ₂₂ H ₂₃ BrO ₅).	43
2.5.14. Compound 14: 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propyl acetate (C ₂₁ H ₂₀ O ₆).	44
2.5.15. Compound 15: {3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propyl} diethylamine (C ₂₃ H ₂₇ NO ₄).	45
2.5.16. Compound 16: 4-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1benzofuran-5-yl] butanenitrile, amorphous solid (C ₂₀ H ₁₇ NO ₄).	45
2.5.17. Compound 17: 5-(3''-iyodopropyl)-7-methoxy-2-(3',4'methylene dioxyphenyl) benzofuran, amorphous solid (C ₁₉ H ₁₇ IO ₄).	46

XIV

2.5.18. Compound 18 : 5-(3''-chloropropyl)-7-methoxy-3-nitro-2-(3',4'methylene dioxyphenyl) benzofuran (C ₁₉ H ₁₆ ClNO ₆).	47
2.5.19. Compound 19: 4-{3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]propyl}morpholine (C ₂₃ H ₂₅ NO ₅).	47
2.5.20. Compound 20 : 5-[3''-hydroxypropyl]-7-methoxy-3-amino-2-(3',4'methylene dioxyphenyl) benzofuran (C ₁₉ H ₁₉ NO ₅).	48
2.5.21. Compound 21 : 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]propyl morpholin-4-ylacetate (C ₂₅ H ₂₇ NO ₇).	49
2.5.22. Compound 22: 3-[2-(3,4-dimethoxyphenyl)-7-methoxy-1-benzofuran-5-yl]propyl chloroacetate (C ₂₂ H ₂₃ ClO ₆).	49
2.5.23. Compound 23: 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propanoic acid (C ₁₉ H ₁₆ O ₆).	50
2.5.24. Compound 24: 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propanal semicarbazone (C ₂₀ H ₁₉ N ₃ O ₅).	51
2.5.25. Compound 25: 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propanal thiosemicarbazone	51

XV

2.5.26. Compound 26: 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propanal oxime (C ₁₉ H ₁₇ NO ₅).	52
2.5.27. Compound 27: 6-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] hex-3-en-2-one (C ₂₂ H ₂₀ O ₅).....	53
2.5.28. Compound 28: 5-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]-2-{[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]methyl} pent-2-enal (C ₃₈ H ₃₀ O ₉).	53
2.5.29. Compound 29: 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propanal <i>O</i> -benzoyloxime (C ₂₆ H ₂₁ NO ₆).	54
2.5.30. Compound 30: 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propanal <i>O</i> -(2-chloroacetyl)oxime (C ₂₁ H ₁₈ ClNO ₆).	55
3. RESULTS AND DISCUSSION	56
3.1. Conclusion	162
REFERENCES.....	163
CURRICULUM VITAE	172

LIST OF FIGURES

<u>Figure</u>	<u>Page No</u>
1.1. A benzene nucleus with a furan ring	1
1.2. Benzofuran derivatives (2 and 3).....	2
1.3. Benzofuran containing some biological molecules.	4
1.4. Benzofuran derivative (4).....	5
1.5. Benzofuran derivative (5).....	5
1.6. Benzofuran derivatives (6 and 7).....	6
1.7. Benzofuran derivative (8).....	7
1.8. Benzofuran derivative (9).....	7
1.9. Benzofuran derivatives (10-13)	8
1.10. Benzofuran derivatives (14-18).....	9
1.11. Benzofuran derivatives (19-24)	10
1.12. Benzofuran derivative (25).....	11
1.13. Benzofuran derivative (26).....	12
1.14. Benzofuran derivatives (27-30)	13
1.15. Benzofuran derivative (31).....	14
1.16. Benzofuran derivative (32).....	14
1.17. Benzofuran derivative (33).....	15
1.18. Benzofuran derivatives (34-35)	15
1.19. Benzofuran derivatives (36-37)	16
1.20. Benzofuran derivative (38).....	17
1.21. Benzofuran derivatives (39-41)	18
1.22. Benzofuran derivative (42).....	18
1.23. Benzofuran derivatives (43-46)	20

XVII

1.24. Benzofuran derivative (47) (Egonol)	21
1.25. Benzofuran derivatives (48) (trimetoksi egonol)	22
1.26. <i>Styrax Officinalis</i> L. (http://upload.wikimedia.org)	23
2.1. Compounds 1-14	30
2.2. Compounds 15-19	31
2.3. Compounds 8-20	32
2.4. Compounds 4, 21	32
2.5. Compounds 22	32
2.6. Compounds 23-28	33
2.7. Compounds 29-30	34
3.1. The ¹H-NMR Spectrum of Compound 1	70
3.2. The ¹H-NMR Spectrum of Compound 2	72
3.3. The ¹³C-NMR Spectrum of Compound 2	73
3.4. The ¹H-NMR Spectrum of Compound 3	75
3.5. The ¹H-NMR Spectrum of Compound 4	77
3.6. The ¹³C-NMR Spectrum of Compound 4	78
3.7. The ¹H-NMR Spectrum of Compound 5	80
3.8. The ¹³C-NMR Spectrum of Compound 5	81
3.9. The HMQC Spectrum of Compound 5	82
3.10. The ¹H-NMR Spectrum of Compound 6	84
3.11. The ¹³C-NMR Spectrum of Compound 6	85
3.12. The HMQC Spectrum of Compound 6	86
3.13. The ¹H-NMR Spectrum of Compound 7	88
3.14. The ¹³C-NMR Spectrum of Compound 7	89
3.15. The HMQC Spectrum of Compound 7	90
3.16. The ¹H-NMR Spectrum of Compound 8	92

XVIII

3.17. The ^{13}C -NMR Spectrum of Compound 8	93
3.18. The HMQC Spectrum of Compound 8	94
3.19. The ^1H -NMR Spectrum of Compound 9	96
3.20. The ^{13}C -NMR Spectrum of Compound 9	97
3.21. The HMQC Spectrum of Compound 9	98
3.22. The ^1H -NMR Spectrum of Compound 10	100
3.23. The ^{13}C -NMR Spectrum of Compound 10	101
3.24. The ^1H -NMR Spectrum of Compound 11	103
3.25. The ^{13}C -NMR Spectrum of Compound 11	104
3.26. The ^1H -NMR Spectrum of Compound 12	106
3.27. The ^{13}C -NMR Spectrum of Compound 12	107
3.28. The ^1H -NMR Spectrum of Compound 13	109
3.29. The ^{13}C -NMR Spectrum of Compound 13	110

LIST OF TABLES

<u>Table</u>	<u>Page No</u>
3.1. Antimicrobial activity of compound egonol and synthesised compounds (MeOH:CH ₂ Cl ₂)	67
3.2. Antimicrobial activity of compound egonol and synthesised compounds (DMSO)	68
3.3. NMR spectroscopic data of compound 1 in CDCl ₃ (δ ppm)	69
3.4. ¹ H- and ¹³ C-NMR spectroscopic data of compound 2 in CDCl ₃ (δ ppm).....	71
3.5. ¹ H-NMR spectroscopic data of compound 3 in CDCl ₃ (δ ppm)	74
3.6. ¹ H- and ¹³ C-NMR spectroscopic data of compound 4 in CDCl ₃ (δ ppm).....	76
3.7. ¹ H- and ¹³ C-NMR spectroscopic data of compound 5 in CDCl ₃ (δ ppm).....	79
3.8. ¹ H- and ¹³ C-NMR spectroscopic data of compound 6 in CDCl ₃ (δ ppm).....	83
3.9. ¹ H- and ¹³ C-NMR spectroscopic data of compound 7 in CD ₃ OD (δppm).....	87
3.10. ¹ H- and ¹³ C-NMR spectroscopic data of compound 8 in CDCl ₃ (δ ppm).....	91
3.11. ¹ H- and ¹³ C-NMR spectroscopic data of compound 9 in CDCl ₃ (δ ppm).....	95
3.12. ¹ H- and ¹³ C-NMR spectroscopic data of compound 10 in CDCl ₃ (δ ppm).....	99

3.13. ^1H - and ^{13}C -NMR spectroscopic data of compound 11 in CDCl ₃ (δ ppm)	102
3.14. ^1H - and ^{13}C -NMR spectroscopic data of compound 12 in CDCl ₃ (δ ppm)	105
3.15. ^1H - and ^{13}C -NMR spectroscopic data of compound 13 in CDCl ₃ (δ ppm)	108
3.16. ^1H -NMR spectroscopic data of compound 14 in CDCl ₃ (δ ppm)	113
3.17. ^1H - and ^{13}C -NMR spectroscopic data of compound 15 in CDCl ₃ (δ ppm)	115
3.18. ^1H - and ^{13}C -NMR spectroscopic data of compound 16 in CDCl ₃ (δ ppm)	118
3.19. ^1H - and ^{13}C -NMR spectroscopic data of compound 17 in CDCl ₃ (δ ppm)	121
3.20. ^1H - and ^{13}C -NMR spectroscopic data of compound 18 in CDCl ₃ (δ ppm)	124
3.21. ^1H - and ^{13}C -NMR spectroscopic data of compound 19 in CDCl ₃ (δ ppm)	127
3.22. ^1H - and ^{13}C -NMR spectroscopic data of compound 20 in CDCl ₃ (δ ppm)	130
3.23. ^1H - and ^{13}C -NMR spectroscopic data of compound 21 in CDCl ₃ (δ ppm)	133
3.24. ^1H - NMR spectroscopic data of compound 22 in CDCl ₃ (δ ppm)	136
3.25. ^1H - and ^{13}C -NMR spectroscopic data of compound 23 in DMSO (δ ppm)	138

3.26. ^1H - and ^{13}C -NMR spectroscopic data of compound 24 in DMSO (δ ppm).....	141
3.27. ^1H - and ^{13}C -NMR spectroscopic data of compound 25 in CDCl_3 (δ ppm).....	144
3.28. ^1H - and ^{13}C -NMR spectroscopic data of compound 26 in DMSO (δ ppm).....	147
3.29. ^1H - and ^{13}C -NMR spectroscopic data of compound 27 in CDCl_3 (δ ppm).....	150
3.30. ^1H - and ^{13}C -NMR spectroscopic data of compound 28 in CDCl_3 (δ ppm).....	153
3.31. ^1H - and ^{13}C -NMR spectroscopic data of compound 29 in CDCl_3 (δ ppm).....	156
3.32. ^1H - and ^{13}C -NMR spectroscopic data of compound 30 in CDCl_3 (δ ppm).....	159

ABBREVIATIONS

$\nu_{\max}$	: Maximum Frequency
$\lambda_{\max}$	: Maximum Wavelength
$[\alpha]$	: Specific Optical Rotation
^{13}C NMR	: Carbon-13 Nuclear Magnetic Resonance
^1H NMR	: Proton Nuclear Magnetic Resonance
CC	: Open Column Chromatography
CD_3OD	: Methanol- d_4
CDCl_3	: Chloroform- d
CHCl_3	: Chloroform
COSY	: Correlation Spectroscopy
DEPT	: Distortionless Enhanced Polarization Transfer
DMSO	: Dimethylsulfoxide
H_2O	: Water
H_2SO_4	: Sulfuric Acid
HMQC	: Heteronuclear Multiple Quantum Coherence
Hz	: Hertz
IR	: Infrared

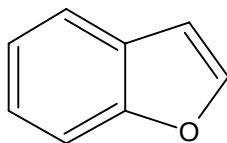
XXIII

m/z	: Mass/Charge
MeOH	: Methanol
MS	: Mass Spectroscopy
NMR	: Nuclear Magnetic Resonance
ppm	: Parts per million
TLC	: Thin Layer Chromatography
UV-Vis	: Ultraviolet-Visible
δ	: Chemical Shift

1. INTRODUCTION

1.1. General Information

Benzofuran, as the name implies, contains a ring system obtained by the fusion of a benzene nucleus with a furan ring in the manner of formula **1**. Another name for this compound is coumarone (Weissberger and Taylor, 1974).



1

Figure 1.1. A benzene nucleus with a furan ring

The benzofuran ring system, although by no means as common as indole, is incorporated into many natural products and into synthetic pharmaceuticals. Some fully unsaturated benzofurans occur naturally, such as the simple 5-methoxy derivative **2**, which has anti-bacterial properties. The majority of natural derivatives have a reduced, or otherwise modified, five-membered ring; an important example is the antifungal antibiotic, griseofulvin, **3** (Gilchrist, 1985).

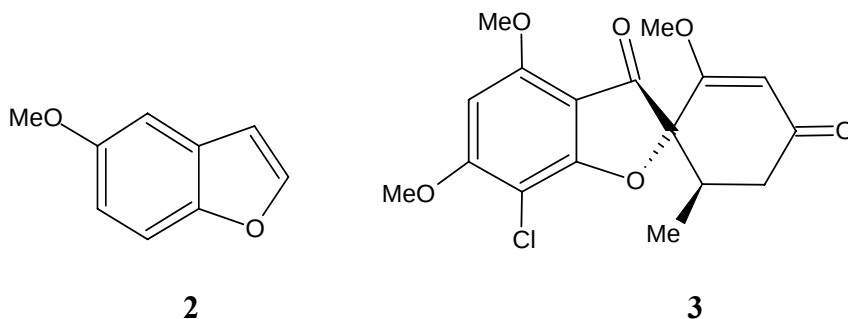


Figure 1.2. Benzofuran derivatives (**2** and **3**)

1.1.1. Natural Benzofuran Derivatives

Benzofuran derivatives are nowadays an important class of organic compounds that occur in a great number of natural products, are used in cosmetics and are used as synthetic pharmaceuticals. Moreover, benzofurans are building blocks for optical brighteners and applied, for example, in combination with benzimidazoles as biphenyl end groups. Many of the natural benzofurans have physiological, pharmacological and toxic properties (Bogdal et al., 2000).

Benzofurans have drawn considerable attention over the last few years due to their profound physiological and chemotherapeutic properties as well as their widespread occurrences in nature. Attempts were made to study the effects of different functional groups on the homocycle and/or the heterocycle for bioactivity. The antimicrobial activity of benzofuran derivatives appears to be dependent on substitution

at the heterocyclic furan ring than the aromatic moiety (Khan et al., 2005).

The most recognized of the benzofurans are *amiodarone*, *angelicin xanthotoxin*, *bergapten*, *nodekenetin* and usnic acid compounds (Fig. 1.3.). The benzofuran ring system is the basic skeleton of numerous compounds possessing cardiovascular activities . *Amiodarone*, an iodinated lipophilic benzofuran derivative (Kirilmis et al., 2008).

It is used in the treatment and prophylaxis of both ventricular and supraventricular arrhythmias , in particular in patients with heart insufficiency , because it has no significant negative inotropic effect. Amiodarone has several adverse effects including corneal deposits, hypo- and hyperthyreosis, pulmonary fibrosis and hepatocellular liver damage . About 1–3% of the patients treated with amiodarone suffer from symptomatic liver disease which may histologically be similar to alcoholic liver lesions (Spaniol et al., 2001).

Benzofuran containing structures have been found among naturally occurring furocoumarins, such as psoralen and methoxalen isolated from the seed of *Ammi majus L.* and used for the treatment of psoriasis and other dermal diseases. Psoralen is structurally related to coumarin by the addition of a fused furan ring, and may be considered as a derivative of umbelliferone. Some important psoralen derivatives are *imperatorin*, *xanthotoxin*, *bergapten* and *nodekenetin*. One of the most important

applications of psoralen is in the field of photo chemotherapy, where psoralens are capable of undergoing photo addition with thymine units present in DNA. Usnic acid is one of the most common and abundant lichen metabolites, well known as an antibiotic (Kirilmis et al., 2008).

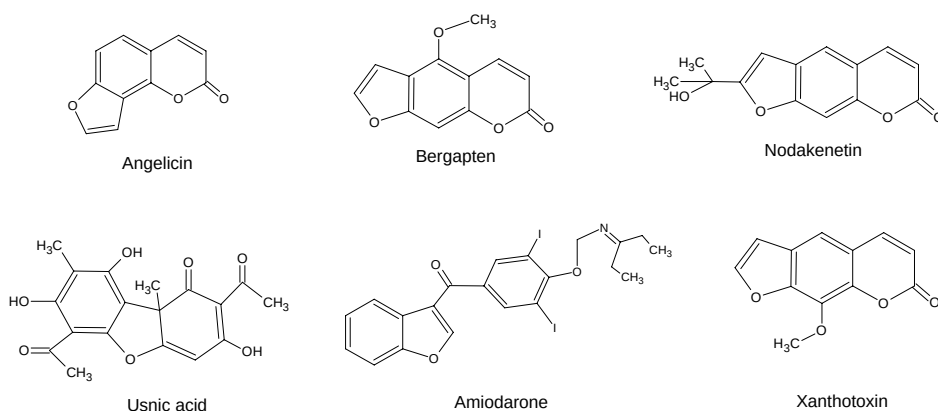
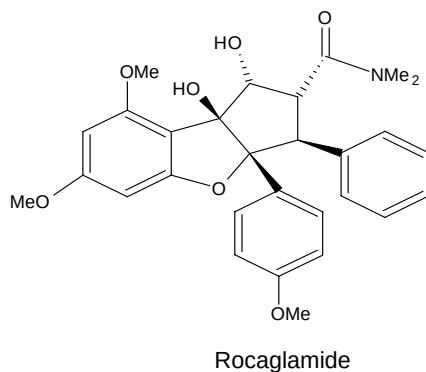


Figure 1.3. Benzofuran containing some biological molecules.

The resin excreted from the plants of the *Styrax spp.* and the oil isolated from *Styrax tonkinensis* were used as antiseptic and analgesic. The plants of this species contain egonol, a natural 2-aryl benzofuran, which is known to be an effective pyrethrum synergist (Yinggang, 2007).

A group of cyclopenta[*b*]benzofurans from the plant genus *Aglaia* has received broad scientific attention as interesting natural product lead compounds with potential anticancer and insecticidal activities. In 1982, the first cyclopenta[*b*]benzofuran-type compound, rocaglamide (**4**), was elucidated by King *et al.* through single-crystal X-ray analysis, thus establishing its relative stereochemistry (Kim et al., 2006).

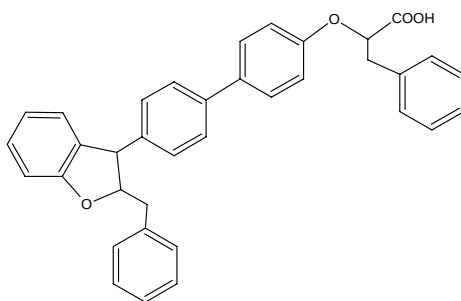


4

Figure 1.4. Benzofuran derivative (4)

PTP-1B inhibitors could potentially ameliorate insulin resistance and normalizes plasma glucose and insulin without inducing hypoglycemia and could be potential pharmacological agents for the treatment of obesity and T2DM.

Malamas et al. reported two novel series of benzofuran/benzothiophene-biphenyl oxo-acetic acids and sulfonyl-salicylic acid as potent inhibitors of PTP-1B with good antihyperglycemic activity (Dixit et al., 2007) (Fig. 1.5.).



5

Figure 1.5. Benzofuran derivative (5)

The endothelins (ETs) are a family of vasoconstrictive peptides originally isolated from endothelial cells. Two distinct receptor subtypes (ET_A and ET_B) have been cloned and expressed. Antagonism of the potent vasoconstrictor endothelin is a potential new approach to the treatment of a variety of human diseases including ischemia, hypertension, congestive heart failure, pulmonary hypertension, and subarachnoid hemorrhage. Two compounds (**6** and **7**) were demonstrated to exhibit ET_A antagonist activity (Kaltenbronn et al., 1996) (Fig. 1.6.).

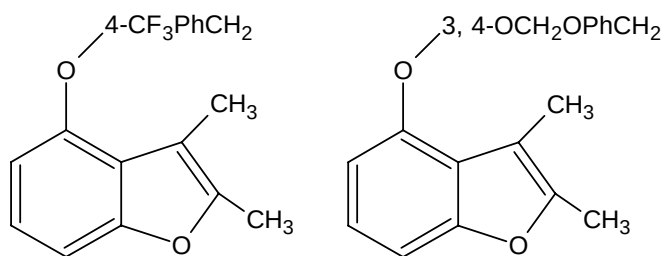


Figure 1.6. Benzofuran derivatives (**6** and **7**)

5-(3-Hydroxypropyl)-7-methoxy-2-(3'-methoxy-4'-hydroxyphenyl)benzo[b]furan-3-carbaldehyde (XH- 14, **8**) was isolated from the plant *Salvia miltorrhiza* Bunge (Danshen), which has been widely used in China for the treatment of coronary heart diseases such as myocardial infarction and angina pectoris. This benzofuran has been reported to bind the A_1 adenosine receptor with high affinity adenosine (Hutchinson et al., 1997).

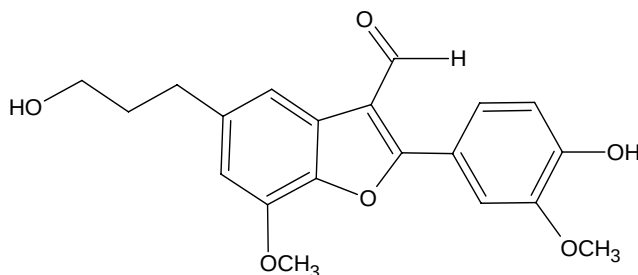


Figure 1.7. Benzofuran derivative (8)

Ailanthoidol (9) and XH-14 (8), are natural products and characteristic members of the neolignan family. Lignans and neolignans are widespread in nature. They have a wide variety of chemical structures and exhibit a broad range of biological activities such as anticancer, antiproliferative, antiviral, immunosuppressive, antiplatelet, antioxidative, insecticidal, anti-inflammatory, antifungal, antifeedant, and cancer preventative. These compounds are also important sources of phytoestrogens. The structures of benzofuran lignans have one common characteristic: they all contain a 2-phenyl-7-methoxy-benzofuran skeleton (Kao et al., 2002).

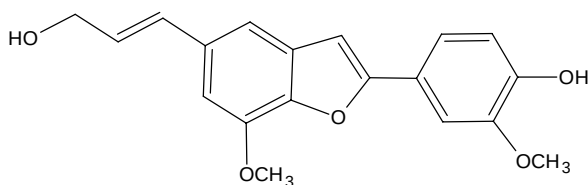


Figure 1.8. Benzofuran derivative (9)

From the leaves of *Styrax ferrugineus*, an endemic species of the Cerrado region, a new 5-[3''-(β-D-glucopyranosyloxy)propyl]-7-

methoxy-2-(3',4'-dimethoxyphenyl) benzofuran (**13**) and the known nor-lignans 5-(3''-hydroxypropyl)-7-methoxy-2-(3',4'-methylenedioxyphenyl) benzofuran (**10**), 5-(3''-hydroxypropyl)-7-methoxy-2-(3',4'-dimethoxyphenyl)benzofuran (**11**), 5-[3''-(β -D-glucopyranosyloxy)propyl]-7-methoxy-2-(3',4'-methylene dioxypheyl)benzofuran (**12**), have been isolated. Compounds **10-13** showed inhibitory properties against the microorganisms, *Candida albicans*, *Cladosporium cladosporioides* and *Staphylococcus aureus*, whereas compounds **10-13** inhibited only *S. aureus* and *C. albicans* (Pauletti et al., 2000).

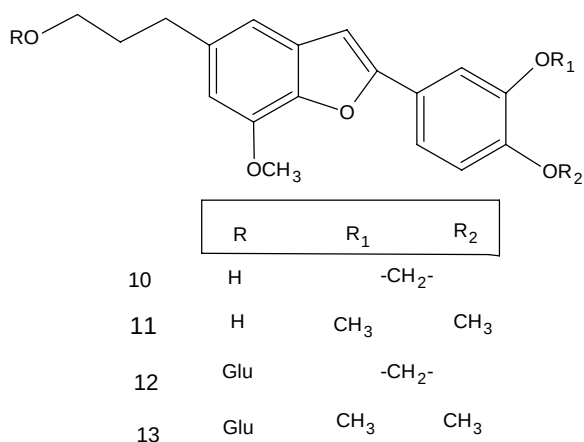


Figure 1.9. Benzofuran derivatives (**10-13**)

1.1.2. Benzofuran Synthesis

(E,Z)-1-(1-Benzofuran-2-yl)-2-mesitylethanoneoxime (**15**) was synthesized from the reaction of the compound (**14**) with hydroxylamine hydrochloride. The derivatives of compound **15**, such as, **16a-d** and

17a-d were obtained in good yields. The compounds were tested for antimicrobial activity against *S. aureus*, *Escherichia coli* and *C. albicans*. Compounds were able to inhibit the growth of the selected microorganisms *in vitro* showing MIC values between 4 and 256 mg/ml. (Kırılmış et al., 2008).

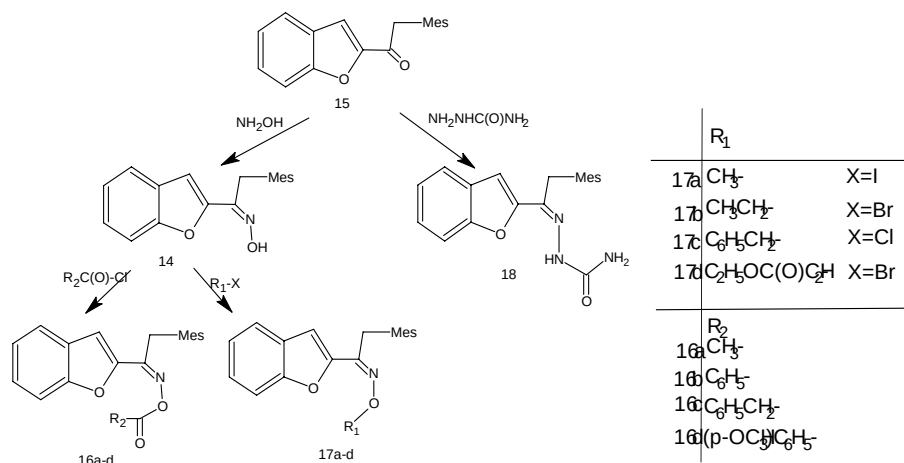
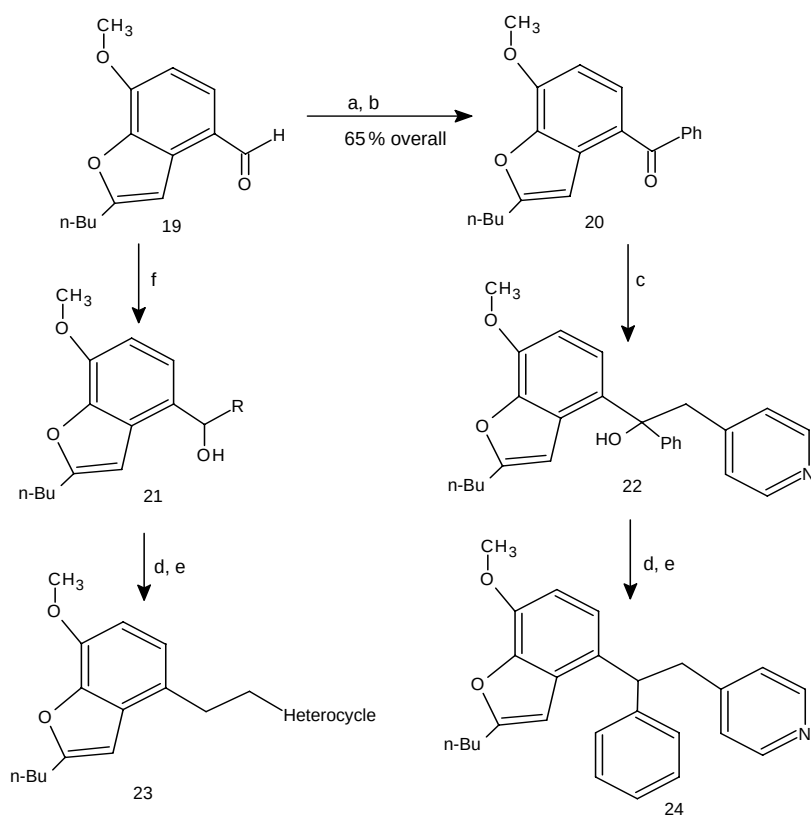


Figure 1.10. Benzofuran derivatives (14-18)

The 1-phenyl-2-pyridyl-ethane derivative. **24** was prepared from **19** as shown in Figure 1.11. The 2-(heteroaromatic)-substituted ethyl derivative **23** was prepared by treatment of **19** with an appropriately protected heteroaromatic-substituted-methyl lithium reagent, to give **21**, followed by dehydration and olefin hydrogenation. Comparison of **24** revealed a significant loss of activity in the benzofuran series. It is speculated that increased steric interactions between the phenyl and benzofuranyl ring systems in **24** could well result in altered conformational preferences in this molecule which, in turn, may disfavor

the bioactive conformer. This idea was subsequently supported by the observation that **23** (in which the phenyl group of **24** has been removed) was highly active. These compounds were evaluated by measuring their ability to inhibit guinea pig macrophage PDE4 (IC₅₀). PDE4 inhibitors for the treatment of various immunological disorders, including asthma and rheumatoid arthritis . (McGarry et al., 1999).



(a) PhMgBr. (b) PCC. (c) LDA/4-methyl-pyridine. (d) TFA. (e) H₂/Pd/C.
(f) LDA/Me-(heterocycle).

Figure 1.11. Benzofuran derivatives (19-24)

Antinociceptive activity of 2-(4-bromobenzoyl)-4,6-dimethoxy-3-methyl-1-benzofuran **25** has recently been reported. This compound, which was prepared from naturally occurring 1-(2-hydroxy-4,6-dimethoxy-phenyl) ethan-1-one (xanthoxyline), represents a new structural type exerting analgesic effect (Rádl et al, 2000, a).

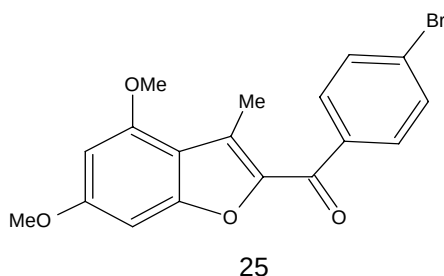


Figure 1.12. Benzofuran derivative (**25**)

For the treatment of Chagas' disease, which places one-quarter (100 million) of the inhabitants of Latin America at risk and results in 16-18 million infected people, the two drugs most frequently used have been nifurtimox (a nitrofurane) and benznidazole (a nitroimidazole). These nitroheterocycles are among a number of nitro compounds having antichagasic properties, but they, as many other nitro species, characteristically have serious side effects. It has been suggested that this toxicity to the host may be inexorably linked to some if not all of the trypanocidal properties of efficacious nitro drugs. (Figure 1.13.) (Kinnamon et al, 1998).

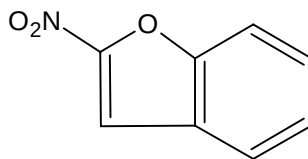
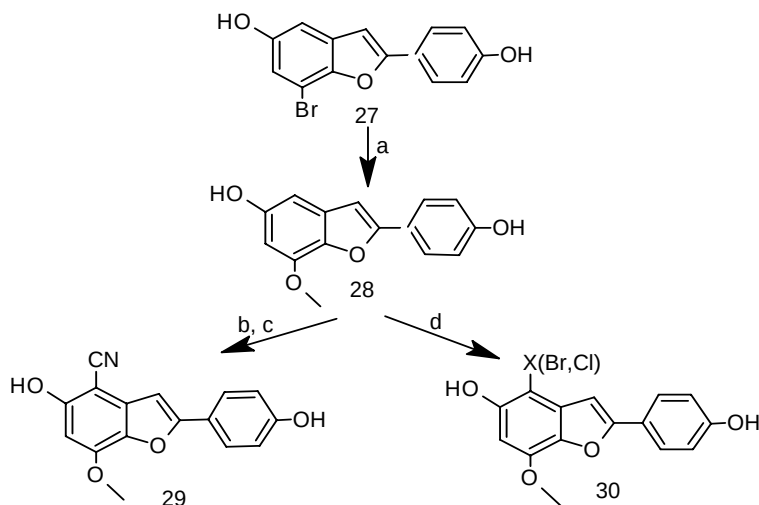


Figure 1.13. Benzofuran derivative (**26**)

The estrogen receptor (ER) is a member of the nuclear receptor family, which functions as a ligand activated transcription factor. Binding of an ER agonist such as 17β -estradiol to the receptor leads to gene regulation in various tissues. Many tissues throughout the body are affected by estrogens, especially mammary gland, bone and uterine tissues. It has been shown that ER α mediates many of the well documented activities associated with estrogens on these tissues. Since the discovery of ER β in 1996, there has been much interest in finding potent and selective ligands for this receptor.

A series of 2-(4-hydroxy-phenyl)-benzofuran-5-ols with relatively lipophilic groups in the 7-position of the benzofuran was prepared and the affinity and selectivity for ER β was measured. Many of the analogues were found to be potent and selective ER β ligands (Collini et al., 2004). (Figure 1.14.)



(a) NaOCH₃, CuBr; (b) POCl₃, DMF; (c) NH₂OH then Burgess reagent;

(d) NBS or NCS, CH₃CN

Figure 1.14. Benzofuran derivatives (**27-30**)

The C-4 side chain modification of lead compound **31** has resulted in the identification of a potent and selective *Candida albicans* N-myristoyltransferase (CaNmt) inhibitor RO-09-4609, which exhibits antifungal activity against *C. albicans* in vitro. Further modification of its C-2 substituent has led to the discovery of RO-09-4879, which exhibits antifungal activity in vivo. The drug design is based on X-ray crystal analysis of a CaNmt complex with benzofuran derivative **32** (Masubuchi et al., 2003).

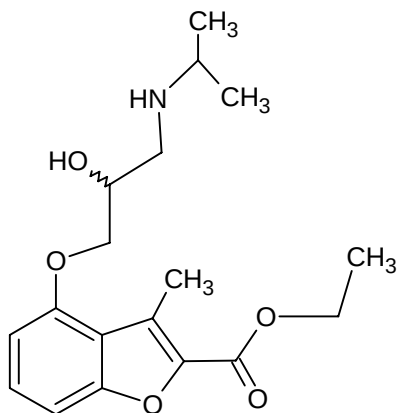
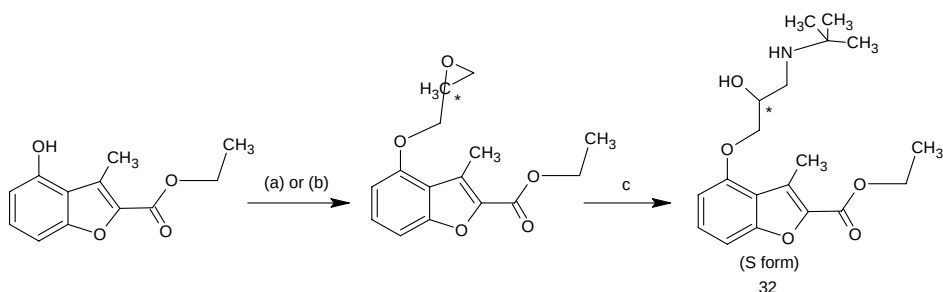


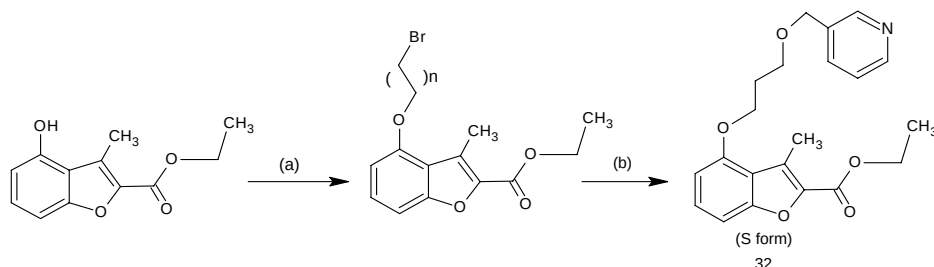
Figure 1.15. Benzofuran derivative (**31**)



(a) (2S)- or (2R)-glycidyl tosylate, NaH, DMF, rt, 76–83%; (b) epichlorohydrin. Cs₂CO₃, CH₃CN, 60 °C, 86%; (c) tert-BuNH₂, EtOH, 60 °C, 74–95%.

Figure 1.16. Benzofuran derivative (**32**)

Pyridin-3-ylmethoxy derivative **13** were devoid of the inhibitory activity, suggesting that the strong basicity of an aliphatic amino group is essential for the inhibitory activity (Masubuchi et al., 2003).



(a) alkylene dibromide, K_2CO_3 , DMF, rt or 100 °C, 1–4 h, 43–88%;

(b) 3-pyridinemethanol, NaH, DMF, rt, 11%;

Figure 1.17. Benzofuran derivative (33)

A number of oximes were synthesised and found to be active against fungi and obtained significant antifungal activity, against *Candida albicans*, from works on aryl benzofuryl ketoxime series. Oxime compounds range between 5–12.5 and 5–25 $\mu\text{g ml}^{-1}$ against *C. glabrata* and *C. albicans*, respectively. In consideration of the results; in regard to the activities of the benzofuryl ketones **34** to benzofuryl ketoximes **35** (Karaburun et al., 2006).

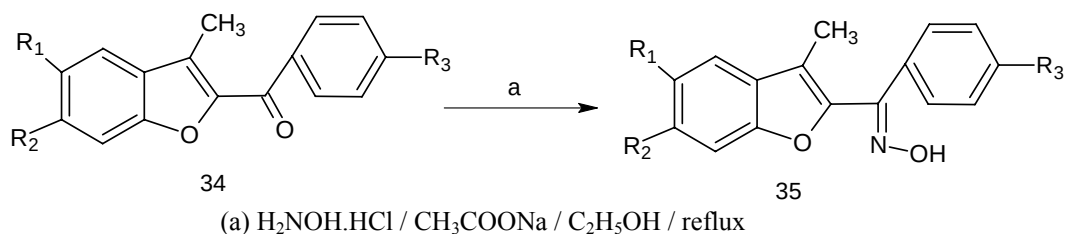


Figure 1.18. Benzofuran derivatives (34-35)

Benign prostatic hyperplasia (BPH) is an ailment afflicting a large proportion of aging men.

Although the etiology of BPH is unclear, dihydrotestosterone (DHT) is recognized as a principal mediator of this disease and its primary role in the hyperplastic growth of the prostate is well established. DHT is derived from a major circulating androgenic hormone testosterone (T) and the conversion of T to DHT is catalyzed by testosterone 5 α -reductase. Recently, several classes of 5 α -reductase inhibitors have been reported, including steroidal inhibitors and nonsteroidal ones, and one of the steroidal inhibitors, finasteride was launched as a medicine for BPH. A series of 2-phenylbenzofuran derivatives with a diphenylmethylecarbonyl group at the 5 or 6 position of the benzofuran ring were evaluated for rat and human testosterone 5 α reductase inhibitory activities *in vitro*. They had inhibitory activities against both enzymes and the 6- carbamoyl derivatives tended to be more potent than the 5-carbamoyl compounds (Ishibashi et al., 1998). (Figure 1.19.)

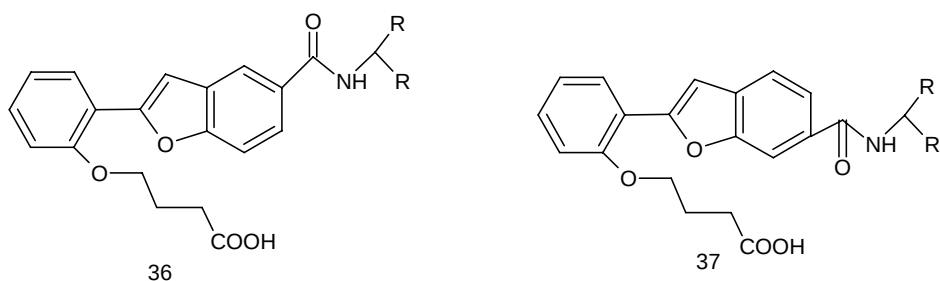


Figure 1.19. Benzofuran derivatives (36-37)

Alzheimer's disease (AD^a) is a progressive neurodegenerative brain disorder that affects millions among the aging population worldwide. AD is characterized by progressive memory loss and severe cognitive decline associated with a degeneration of cholinergic neurons in many areas of the CNS and with a dramatic reduction of the neurotransmitters levels, among which Ach is the most important one. One of the major neuropathological findings in AD is an abnormal extracellular accumulation of β -amyloid peptide ($A\beta$), the main component of the senile plaques that could be responsible for the onset of the disease. Regarding $A\beta$ fibril inhibition, **38** showed a higher potency compared to that of the standart curcumin (IC_{50} = 7 and 10 μ M, respectively) and the highest one among the deries. In other words, **38** is very good inhibitory activity of $A\beta$ aggregation (Rizzo et al., 2008).

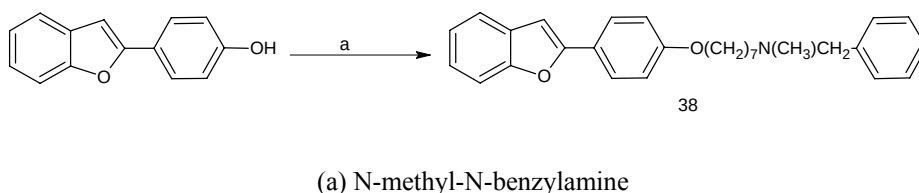


Figure 1.20. Benzofuran derivative (**38**)

In the search for oral agents that could significantly delay preterm birth (the major cause of infant mortality and morbidity), potent and selective non-peptide oxytocin (OT) antagonists have been identified, but none has entered clinical development. A number of oxytocin antagonists were identified, such as the 2-substituted benzofuran derivatives **41** (Wyatt et al., 2002).

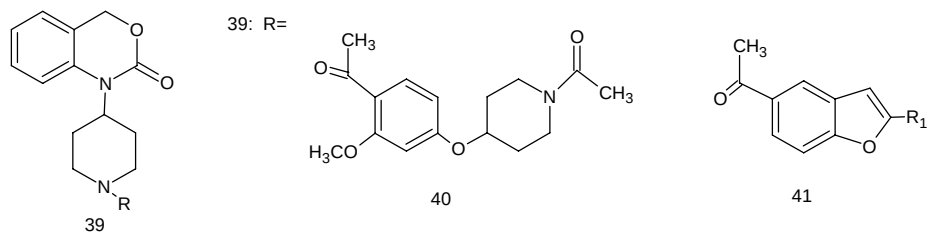
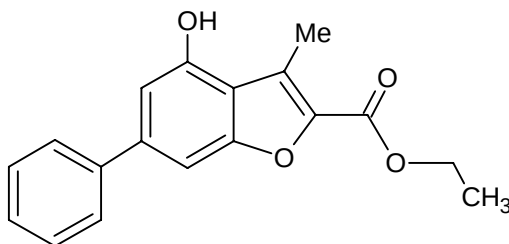


Figure 1.21. Benzofuran derivatives (**39-41**)

Compound **42** showed selective and potent cytotoxicity against a tumorigenic cell line, WI-38 VA-13 subline 2RA (VA-13) (EC_{50} $\frac{1}{40}$ ng/mL), despite no cytotoxicity was observed against the normal parental cell line, WI-38 (EC_{50} >4000 ng/mL) (Hayakawa et al., 2004).



42: EC_{50} = 40ng/mL

Figure 1.22. Benzofuran derivative (**42**)

The performance of catecholaminergic neurons in the brain has been proposed to be controlled according to the physiological need via a catecholaminergic activity enhancer (CAE) mechanism. This novel CAE mechanism can reasonably elucidate the effects of the brain endogenous amines such as phenylethylamine (PEA) and tryptamine which significantly enhance the impulse mediated propagation release of catecholamines from the catecholaminergic neurons. A PEA derivative,

(-)-deprenyl (selegiline), known as a selective inhibitor of B-type monoamine oxidase (MAO-B), is for the time being the only CAE substance in clinical use. The unique effects of (-)-deprenyl such as the prolongation of the life of rats, the neuroprotective effect, the slowing of the functional decline of otherwise untreated subjects with early Parkinson's disease, and the slowing of the progression of Alzheimer's disease, were attributed to the CAE effect of this drug. To furnish a direct evidence that the CAE activity with a small dose of (-)-deprenyl is unrelated to MAO-B inhibition, (-)-1-phenyl-2-propylaminopentane ((-)-PPAP) devoid of MAO-B inhibition was synthesized. BPAP was originally synthesized as follows by starting from 1-(benzofuran-2-yl)-2-nitropene **44** prepared by the condensation of benzofuran-2-caraldehyde and 1-nitrobutane. Reduction of **43** with lithium aluminum hydride gave the corresponding 2-aminopentane **45**, which was treated with propionyl chloride to afford the N-{2-[1-(benzofuran-2-yl)pentyl]} propionamide **46**. The propionamide **45** was reduced with aluminum hydride to give BPAP **43** (Oka et al., 2001).

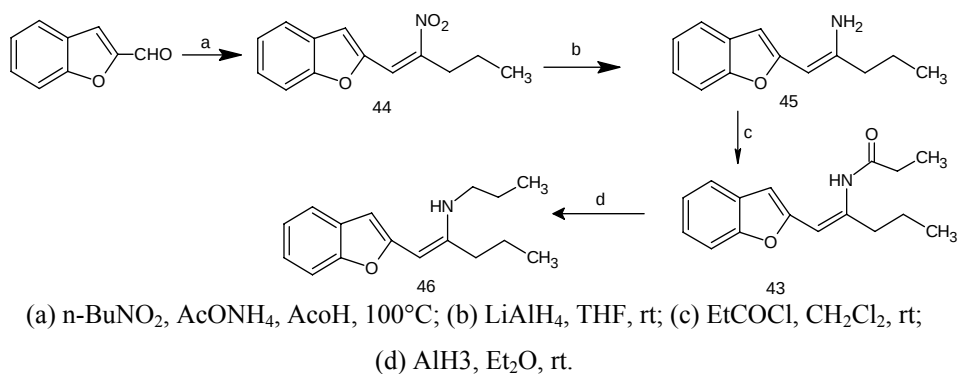


Figure 1.23. Benzofuran derivatives (**43-46**)

The above information demonstrates that the structure of egonol is present in many benzofurans which are of great importance to health. Egonol, ($\text{C}_{19}\text{H}_{18}\text{O}_5$) is an important natural product which can be obtained from many plants. Therefore, it is important to obtain a greater understanding of the chemistry of egonol.

1.1.3. Egonol

Egonol which occurs in a number of *Styrax* species belongs to a small class of natural products containing the simple benzofuran nucleus (Ritchie and Taylor, 1969).

Egonol, which is $\text{C}_{19}\text{H}_{18}\text{O}_5$, was first discovered by Okada in the seed oil of ‘‘egonoki’’ (*Styrax japonicus* Sieb. et Zucc., a plant common to Japan). Other sources are *S. formanosus* Matsum. and *S. obassia* Sieb. et Zucc. According to Kawai, egonol (**47**) is not ketonic, but is a primary alcohol, since it forms an acetate and is also esterified by phthalic anhydride.

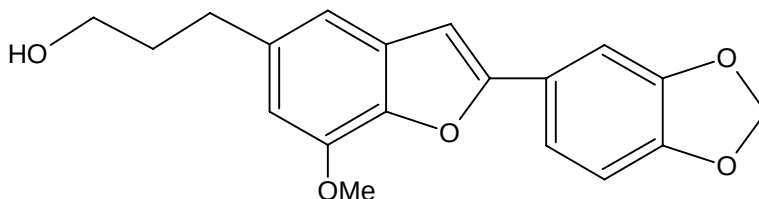


Figure 1.24. Benzofuran derivative (**47**) (Egonol)

Solution of egonol in sulfuric acid are orange-red ; in chloroform containing antimony trichloride, violet ; but in acetic acid with hydrogen peroxide a deep carmine-red color is produced, which forms the basis for spectroscopic estimations of the compound .

Benzofuran derivatives were among the COX-2 inhibitors. In addition, diverse pharmacological properties have been associated with benzofuran derivatives. These include pesticidal, and insecticidal, anti-inflammatory, antihistaminic, antiallergic and antitumor agents. On the other hand, benzotriazole derivatives have shown potential antimycobacterial, antitubercular, antitumor, antiproliferative, anesthetic, and anti-inflammatory activities. Furthermore, pyrazole derivatives were found to possess anti-inflammatory, and antimicrobial, activities. In addition, 1,2,3-thiadiazoles were reported as highly anti-inflammatory, antimicrobial, and anticonvulsant agents.

A series of benzofuran ring system bearing various substituents at the C-2 position is widely distributed in nature and has recently become of interest in biological properties (Kim et al., 2001).

2-(3'-4'-dimethoxyphenyl)-5-(3''-hydroxypropyl)-7-methoxy benzofuran has been isolated as a new benzofuran derivative in addition to egonol from the glycosidic fraction of *S. officinalis* after hydrolysis. This compound was related to egonol and is different only in the substitution pattern in the phenyl ring (Fig.1.25)

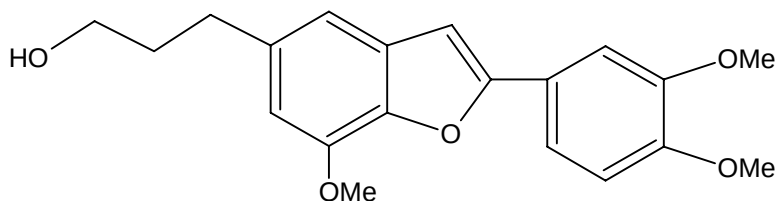


Figure 1.25. Benzofuran derivatives (**48**) (trimetoksi egonol)

1.2.General Information on *Styrax officinalis* L.

In this study describes the isolation from *Styrax officinalis* L. of egonol and then some new synthesis on egonol were derived and antimicrobial activities on new benzofuran derivatives were tested against some microorganisms.

1.2.1. Classification and Botanical description

Styrax officinalis L. is a member of the Styracea family which is constituted of small trees and shrubs. It has been found from in Palestine to Italy. In Turkey, it grows mainly in north, south and western Anatolia (Davis, 1972).

Styrax trees grow to 2-14 m tall, and have alternate, deciduous or evergreen simple ovate leaves 1-18 cm long and 2-10 cm broad. The flowers are pendulous, with a white 5-10-lobed corolla, produced 3-30 together on open or dense panicles 5-25 cm long. The fruit is an oblong dry drupe, smooth and lacking ribs or narrow wings. It is in flower in June, and the seeds ripen in October. The flowers are hermaphrodite (have both male and female organs) The plant prefers light (sandy) and medium (loamy) soils and requires well-drained soil. The plant prefers acid and neutral soils. It can grow in semi-shade (light woodland) or no shade. It requires moist soil and can tolerate drought (Figure 1.26.).

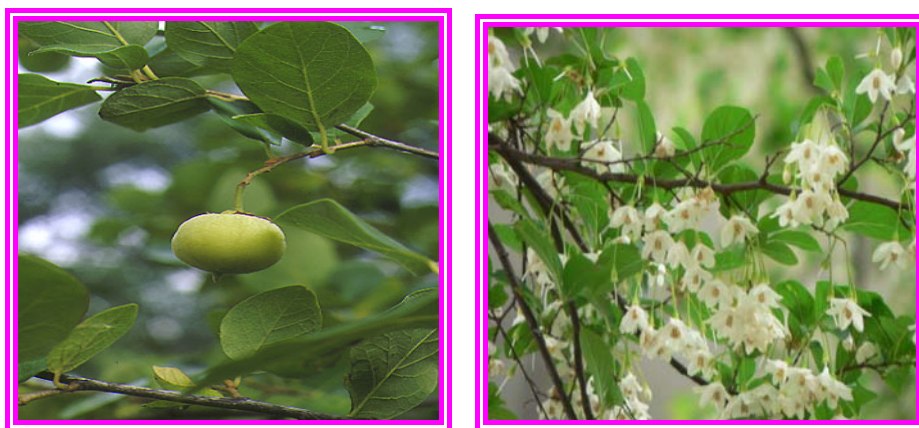


Figure 1.26. *Styrax officinalis* L. (<http://upload.wikimedia.org>)

1.2.2. The use of *Styrax officinalis* L.

Styrax officinalis resin was used by Romans, Egyptians, Phenicians and Ionions to treat a variety of ailments and as an incense (Davis, 1972).

Styrax incense is used in the Middle East and adjacent regions as an air freshener.

Styrax resin, probably from *S. officinalis*, was imported in quantity from the Near East by Phoenician merchants and Herodotus of Halicarnassus in the 5th century BC indicates that different kinds of "storax" were traded. A resin obtained from the stems of the plant is antiseptic and expectorant (Bean, 1981; Chopra et al., 1986). The fragrant resin 'storax' is obtained by wounding the stem (Polunin, 1987). It is used medicinally, in perfumes, incense etc (Bean, 1981; Niebuhr, 1970). The fruits are used as beads in rosaries etc (Thomas, 1992).

Styrax species contain egonol, a natural benzofuran, which is known to be an effective pyrethrum synergist (Takanashi and Takizawa, 1988; Paluetti et al., 2000).

1.2.3. Chemical studies on *Styrax officinalis* L.

Many different chemical compounds are found in *Styrax Officinalis* L. Earlier studies of seeds of *Styrax* species have been reported; egonol mono-, di- and tri-glucosides were subsequently isolated from *Styrax* species (*S.formosanum*, *S. oficinalis* and *S.obassia*). In 1967, Segal et al isolated a dimethoxyphenyl analogue of egenol, named homoegonol from the seeds of *S. officinalis*. The authors isolated 7-demethoxyegonol from *S.obassia* and 7-demethoxyhomoegonol was obtained from *S. japonica* .

In 1988, three new ester derivatives, egonol acetate, egonol 2-methylbutanoate and 7-demethoxyegonol 2-methoxybutanoate were obtained from *S. Obassia*. Two new egonol compounds, egonol 2-methylpropanoate and 7-demethoxyegonol β -gentiobioside and identification of 7-demethoxyegonol acetate from immature seeds of *Styrax japonica* Sieb. et Zucc. (Takanashi and Takizawa, 2002).

1.2.4. Biological activity studies on *Styrax officinalis* L.

Seeds of the fruit of *S. japonicum*, *S. obassia*, *S. formosanum*, *S. suberifolium* and *S. officinalis* are known to contain various egonol derivatives (Luo et al., 2007; Yun et al., Anil 1980). Egonol and its derivatives obtained from the seeds of *Styrax* species has attracted the attention of synthetic organic chemists, as a result of its activity against human leukemic cells in addition to anti-complement activity, cytotoxic activity, and antifungal and antibacterial activity (Pauletti et al, 2000).

To the best of our knowledge, despite the biological activity of species of *Styrax officinalis*, studies on the chemistry of egonol derivatives have not been carried out.

2. MATERIAL AND METHODS

2.1. General Information

In this study, suitable chromatographic techniques, sorbent materials and solvents were used for isolation and purification of all products.

Thin Layer Chromatography (TLC) was carried out using SilicaGel 60 F₂₅₄ (Merck 5554). Bands were visualized under UV light (254 and 366 nm) for UV active components or by heating at 120 °C for 5-10 minutes after spraying with 20 % aqueous sulphuric acid.

Open Column Chromatography (CC) was carried out using SilicaGel 60 (0.063-0.200 mm) (Merck 7734).

Preparative TLC (PTLC) was carried out using SilicaGel 60 (Merck 7747). Preparative TLC (PTLC) has long been a popular method of isolation because of its simplicity and availability to researchers working in natural products chemistry. Separation can be effected rapidly and the amount of material isolated generally falls into the 1 mg to 1 g range, which is certainly sufficient for structure elucidation purposes.

Starting compounds and reagents were obtained from Merck and Carlo Erba; and solvents like dichloromethane, methanol, hexane,

acetone etc. were obtained from industrial grade solvents which were purified by distillation.

Solvents were dried with molecular sieves (type 4 °A). Anhydrous sodium sulfate was used for drying organic solvent extracts. All solvents were removed from solutions of the compounds by evaporation under reduced pressure with a rotary evaporator.

Melting points were recorded with a Gallenkamp electrothermal melting point apparatus.

Structural determination of compounds was performed using modern spectroscopic techniques.

IR spectra were obtained using a Perkin Elmer Spectrum 100 FTIR Spectrometer.

The 1D-NMR and 2D-NMR spectra were measured in CDCl_3 at 400 MHz for ^1H -NMR and 100 MHz for ^{13}C -NMR on a Varian AS-400 spectrometer using TMS as an internal standard. Structures of the compounds were determined according to the results of the following NMR experiments: ^1H , ^{13}C , ^1H - ^1H Correlation (COSY), ^1H - ^{13}C Direct Correlation (HMQC).

Mass spectra (LCMS) of the molecules were recorded on a AGILENT 1100 MSD spectrometer.

Egonol and its derivatives were evaluated for antibacterial activity by the Muller Hilton Broth (MHB) method with *Staphylococcus aureus* ATCC 29213, *Bacillus subtilis* ATCC 6633, *Candida albicans* ATCC 10231 and *Escherichia coli* microorganisms. Stock solution of all compounds were prepared in different solvents (CH_2Cl_2 , MeOH, DMSO).

2.2.Plant Materials

Fruits of *Styrax officinalis* L. (EGE4759) were collected in September-2005 from Ephesus (Selçuk-İZMİR) and were identified by Prof. Dr. Özcan Seçmen, Botanical Garden and Herbarium Research and Application Center, Ege University.

2.3.Biological Activity Studies

Antimicrobial activities of egonol and synthesised compounds were determined by the Broth dilution method. For this method, 10 mg of the substance to be tested were dissolved in 1 mL of MeOH and 0.3 mL CH_2Cl_2 or only 0.5 mL of DMSO. To 40 μl of egonol and their derivatives, 1 mL of Muller Hilton Broth (Mueller Hinton Medium) were added and a series of two-fold dilutions of each agent were prepared in Mueller Hinton Medium (10). 50 μl culture of bacteria was added to 1 mL of the test solution as inoculum. After 24 hours of incubation at 37°C

the results were read. The minimal inhibition concentration (MIC) was the highest concentration of the substance was 800 µg/mL. At the concentration (800 µg/mL) no growth of microorganisms was macroscopically detectable and this was marked with (*).

2.4.Extraction, Isolation and Purification Processes

The shade dried and pulverized seeds (241g) of *S. officinalis L* were exhaustively extracted with a n-hexane at room temperature. After removal of the solvent in vacuo, a crude yellow oily extract (113.72 g) was obtained. The hexane extract was hydrolyzed with 33% KOH at 100 °C for 3 h. The reaction mixture was cooled at room temperature and extracted with CH₂Cl₂. The reaction mixture was purified by CC using silica gel (Merck, 7734) and CH₂Cl₂ as eluent to afford egonol (6g) which was identified by ¹H and ¹³C NMR.

Egonol, 5-[3''-(hydroxy)propyl]-7-metoxy-2-(3',4'-methylenedioxy phenyl)benzofuran as obtained as a white powder (Figure 1.24.).

2.5.Synthesis of new benzofuran derivatives from egonol

Thirty compounds were synthesized from egonol which was isolated from *S.officinalis L.* seeds for the first time.

Fourteen compounds were synthesized using egonol.

Sixteen compounds were synthesized from egonol derivatives(from compound 1, compound 2, compound 4, compound 8, compound 26).

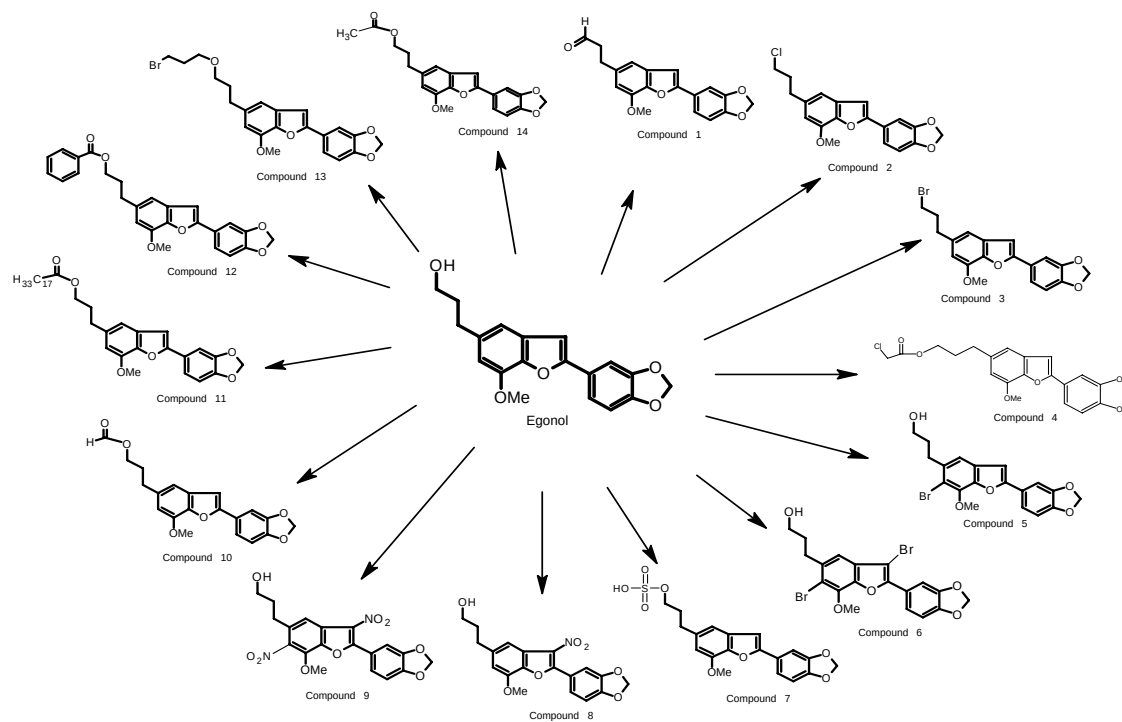


Figure 2.1. Compounds 1-14

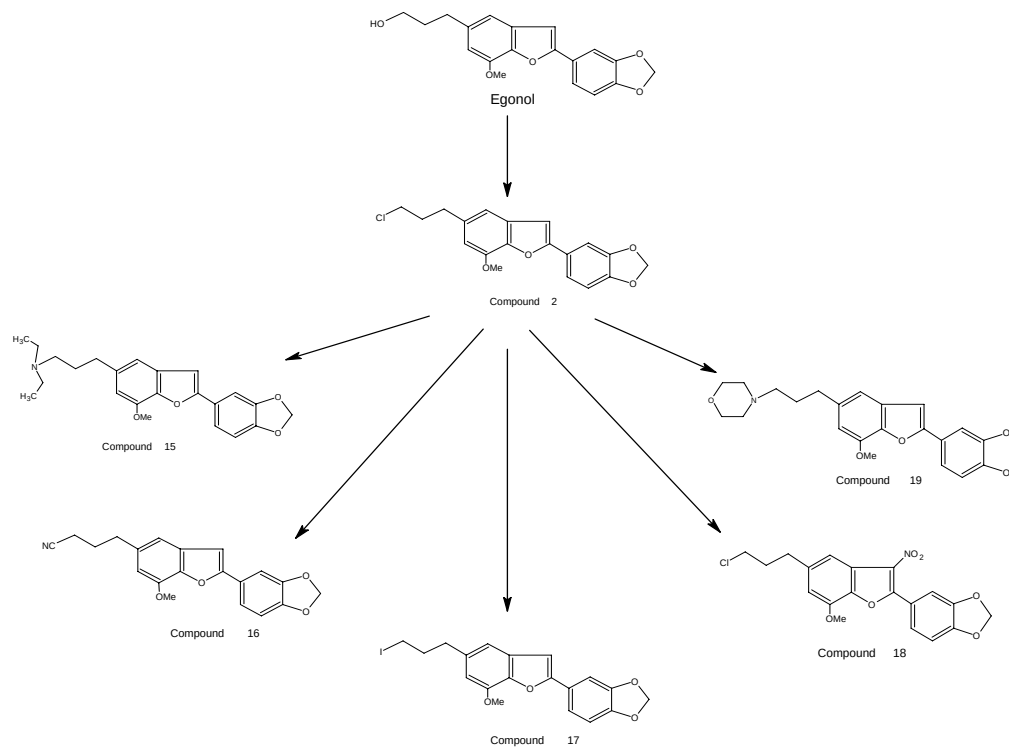


Figure 2.2. Compounds 15-19

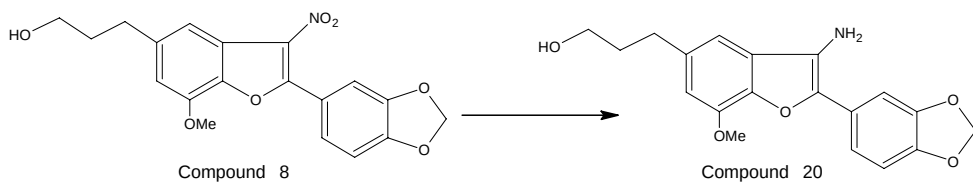


Figure 2.3. Compound 20 from Compound 8

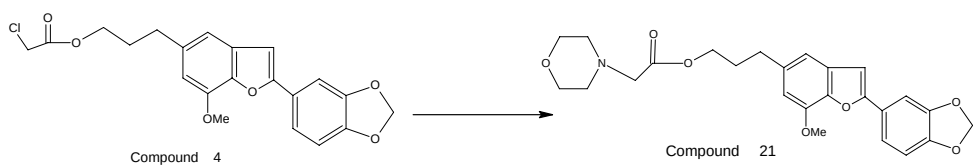


Figure 2.4. Compound 21 from Compound 4

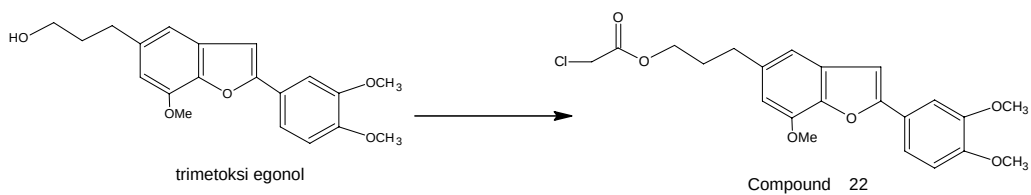


Figure 2.5. Compound 22

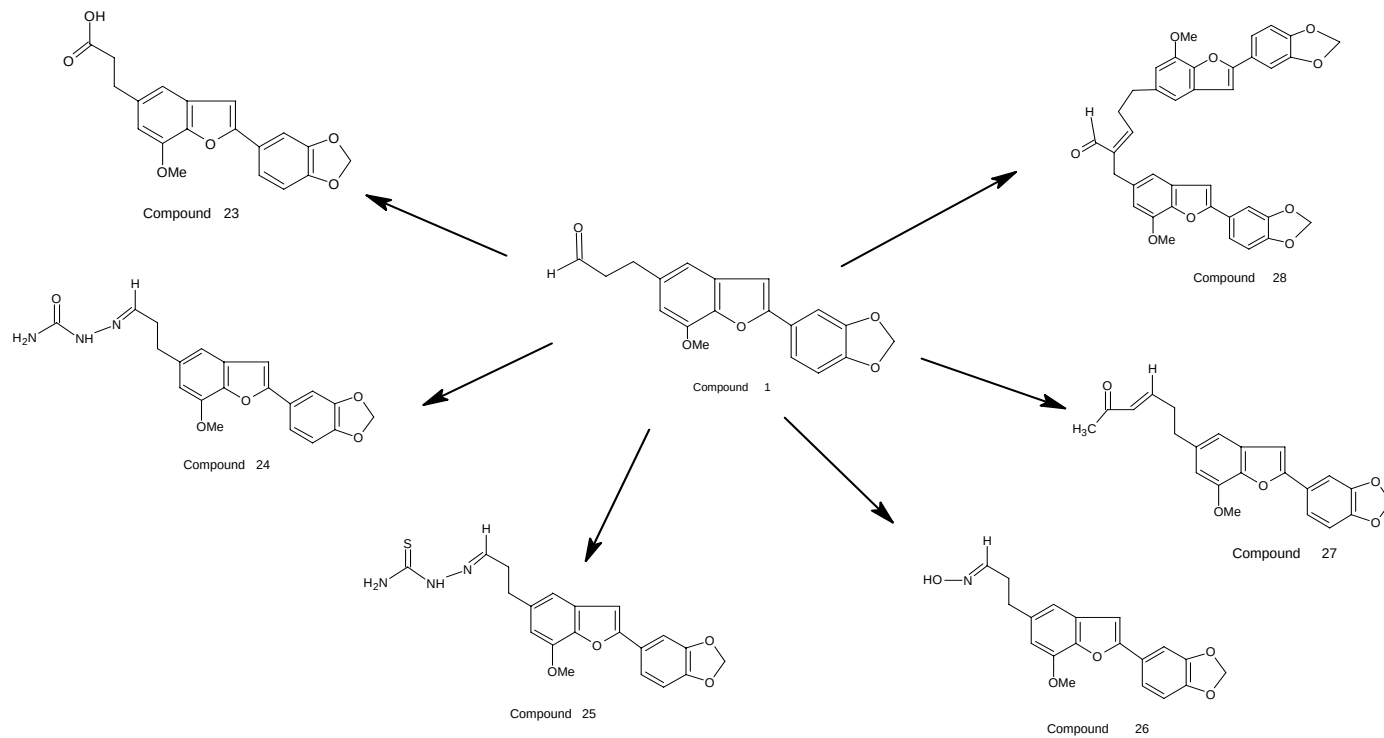


Figure 2.6. Compounds 23-28

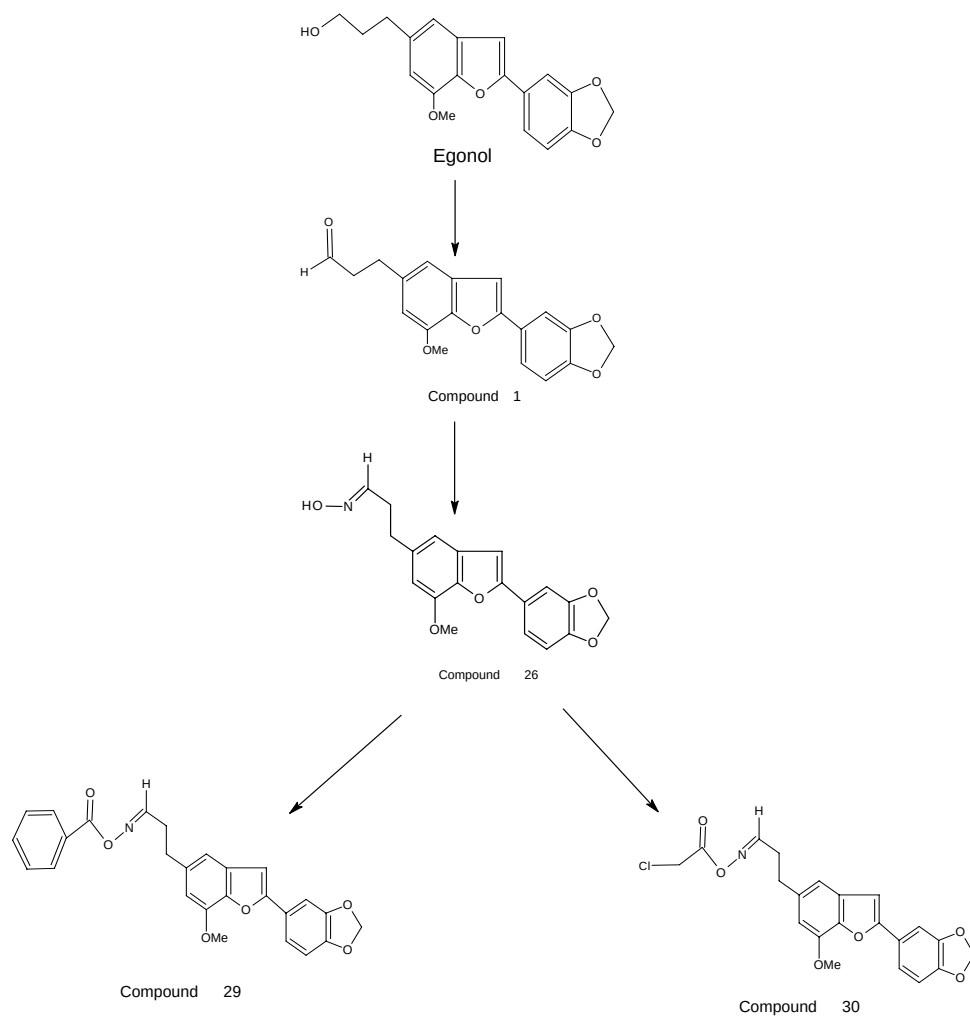


Figure 2.7. Compounds 29-30

2.5.1. Compound 1: 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propanal, as an amorphous powder (C₁₉H₁₆O₅).

A mixture of egonol (50 mg, $1.53 \cdot 10^{-4}$ mol) and acetone : CH₂Cl₂ (3:3 ml) was stirred at room temperature. PCC (146 mg) and molecular sieves (4A, 544 mg) were added in several portions and the mixture was stirred at room temperature for 24 h. Subsequently, the mixture was diluted with water (15 ml) and extracted with CH₂Cl₂ (3x5 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified on silica gel using Hexane/EtOAc/H₂O: 6:4:0,5 as eluent to give the product (12.9 mg, 26.02 %); UV $\lambda_{\max}^{\text{CH}_2\text{Cl}_2}$: 231.0, 318.0 nm. ;IR spectrum $\nu_{\max}^{\text{CH}_2\text{Cl}_2} \text{ cm}^{-1}$: 2921, 2852, 1709, 1473, 1363, 1222, 1033, 927, 749 ; ¹H-NMR (400 MHz, CDCl₃) see Table 3.3. (Öztürk et al., 2008).

2.5.2. Compound 2: 5-(3''-chloropropyl)-7-methoxy-2-(3',4'-methylene dioxyphenyl)benzofuran (C₁₉H₁₇ClO₄).

To a mixture of egonol (472 mg, $1.45 \cdot 10^{-3}$ mol) in pyridine (9 mL) was added p-toluenesulfonylchloride (286 mg, $2.61 \cdot 10^{-3}$ mol) at room temperature and the mixture was stirred for 72h. The reaction mixture was diluted with water (15 ml) and extracted with CH₂Cl₂ (3x5 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by PTLC (CH₂Cl₂) . 33.2 mg compound was obtained. (6.66 %); m.p:120.0-121.7 °C; UV $\lambda_{\max}^{\text{CH}_2\text{Cl}_2}$:

229.0, 318.0 nm.; IR spectrum $\nu_{\max}^{\text{CH}_2\text{Cl}_2} \text{ cm}^{-1}$: 2919, 1615, 1596, 1443, 1229, 1033, 930, 847; LCMS/APCI m/z (rel.int.): 347.1 $[\text{M}]^+$ (5.9), 345.1 $[\text{M}]^+$ (16.4), 282 $[\text{M}-\text{Cl}-\text{CH}_2-\text{CH}_2]^+$ (100), 283 $[\text{M}-(\text{Cl}-\text{CH}_2-\text{CH}_2)+\text{H}]^+$ (24.1); $^1\text{H-NMR}$ (400 MHz, CDCl_3) and $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) see Table 3.4. (Öztürk et al., 2008).

2.5.3. Compound 3: 5-(3''-bromopropyl)-7-mehtoxy-2-(3',4'-methylenedioxyphenyl) benzofuran ($\text{C}_{19}\text{H}_{17}\text{BrO}_4$).

Concentrated H_2SO_4 (1,3 ml) was added slowly to egonol (50 mg, $1.53 \cdot 10^{-4}$ mol) in CH_2Cl_2 (10 ml), followed by a slow addition of NaBr (15.8 mg) in 2 ml water. The mixture was then refluxed for 2h. The reaction mixture was diluted with water (15 ml) and extracted with CH_2Cl_2 (3x5 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The residue was purified by PTLC using CH_2Cl_2 as a solvent. 8.8 mg compound was obtained (12.80 %); UV $\lambda_{\max}^{\text{CH}_2\text{Cl}_2}$: 229.0, 318.0 nm; IR spectrum $\nu_{\max}^{\text{CH}_2\text{Cl}_2} \text{ cm}^{-1}$: 2917, 1596, 1473, 1360, 1229, 1146, 1039, 927, 760, 746; LCMS/APCI m/z (rel.int.): 391.0 $[\text{M}]^+$ (100), 389.0 $[\text{M}]^+$ (97.4), 309 $[\text{M}-\text{Br}]^+$ (22.9); $^1\text{HNMR}$ (400 MHz, CDCl_3) see Table 3.5. (Öztürk et al., 2008).

2.5.4. Compound 4: 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]propyl chloroacetate (C₂₁H₁₉ClO₆).

Egonol (100 mg, $3.06 \cdot 10^{-4}$ mol) in dry diethyl ether (5 ml) and triethylamine (10.5 mg, $1.04 \cdot 10^{-4}$ mol) were placed in a 100 ml two-necked flask. The mixture was stirred for 30 min. at room temperature under argon atmosphere. And then the mixture was stirred for 1 h at 0 °C under argon atmosphere. Chloroacetyl chloride (13.19 mg, $1.16 \cdot 10^{-4}$ mol) in dry diethyl ether (5 ml) was added to the reaction. And then the mixture was stirred 15 min. at 0 °C then 96 h. After addition of 10 ml water with 10% NaHCO₃, the mixture was extracted with diethyl ether (3x10 ml). The diethyl ether was dried with anhydrous sodium sulfate and evaporated to dryness. The residue was purified via column chromatography on silica gel using Hexane/EtOAc: 10:1; 74.2 mg compound was obtained (60.3 %); m.p:111.4 °C; UV $\lambda_{\max}^{\text{CH}_2\text{Cl}_2}$: 230.0, 318.0 nm.; IR spectrum $\nu_{\max}^{\text{CH}_2\text{Cl}_2} \text{ cm}^{-1}$: 3741, 3648, 2934, 2668, 1750, 1643, 1585, 1500, 1412, 1325, 1229, 1122, 1033, 1009, 825, 696; LCMS/APCI m/z (rel.int.): 405.0 [M]⁺ (17.0), 403.0 [M]⁺ (48.5), 327 [M-(Cl-CH₂-C=O)+H]⁺ (11.7); ¹HNMR (400 MHz, CDCl₃) and ¹³C-NMR (100 MHz, CDCl₃) see Table 3.6.

2.5.5. Compound 5: 5-[3''-hydroxypropyl]-6-bromo-7-methoxy-2-(3',4'-methylene dioxyphenyl)benzofuran, (C₁₉H₁₇BrO₅).

A mixture of egonol (100 mg, $3.07 \cdot 10^{-4}$ mol), NBS (48 mg, $2.70 \cdot 10^{-4}$ mmol), 3-chloroperoxybenzoic acid (10 mg, $5.79 \cdot 10^{-5}$ mol) in

CCl_4 (5ml) was refluxed for 1h. The reaction mixture was stirred at room temperature for 15h. After addition of 10 ml water, the mixture was extracted with CH_2Cl_2 (3x5ml). The CH_2Cl_2 was dried with anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by PTLC using dichloromethane/methanol (80:4) as solvent system to give the product as a light brown solid (102 mg, 82.32 %); mp. 137.3-145.0 °C; UV $\lambda_{\text{max}}^{\text{CH}_2\text{Cl}_2}$: 229.0, 322.0 nm; IR spectrum $\nu_{\text{max}}^{\text{CH}_2\text{Cl}_2}$ cm^{-1} : 3296, 2925, 2857, 1733, 1599, 1476, 1363, 1232, 1141, 1039, 930, 749; LCMS/APCI m/z (rel. int.): 405.0 $[\text{M}]^+$ (100), 407.0 $[\text{M}]^+$ (93.7), 326.1 $[\text{M}-\text{Br}]^+$ (46.8), $[(\text{M}-\text{Br})+\text{H}]^+$ 327.1 (32.0); $^1\text{H-NMR}$ (400 MHz, CDCl_3) and $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) see Table 3.7. (Öztürk et al., 2008).

2.5.6. Compound 6: 5-[3''-hydroxypropyl]-3,6-dibromo-7-methoxy-2-(3',4'-methylene dioxyphenyl)benzofuran ($\text{C}_{19}\text{H}_{16}\text{Br}_2\text{O}_5$).

NaBr (64 mg, $6.21 \cdot 10^{-4}$ mol) in H_2O (2ml) was stirred at room temperature. And then egonol (100 mg, $3.07 \cdot 10^{-4}$ mol) in DMSO (5 ml) was added to the mixture. And then H_2SO_4 (1ml) was slowly added to the mixture. And then the reaction mixture was stirred. The reaction was refluxed for 2 h and then stirred for 48 h at room temperature. The reaction mixture was diluted with water (10ml) and extracted with CH_2Cl_2 (3x10 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by PTLC

using Hexane/EtOAc/H₂O: 6:4:0.5. 28.4 mg compound was obtained (19.1%). m.p: 132.5-134.5 °C ; UV $\lambda_{\max}^{\text{CH}_2\text{Cl}_2}$: 230.0, 284.0 nm; IR spectrum $\nu_{\max}^{\text{CH}_2\text{Cl}_2} \text{ cm}^{-1}$: 3703, 3642, 2970, 2862, 1737, 1599, 1451, 1365, 1226, 1215, 1054, 1033, 749; ¹H-NMR (400 MHz, CDCl₃) and ¹³C-NMR (100 MHz, CDCl₃) see Table 3.8.

2.5.7. Compound 7: 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propyl hydrogen sulfate (C₁₉H₁₈O₈S).

A mixture of egonol (150 mg, 4.6.10⁻⁴ mol) and H₂SO₄ (3 ml) were dissolved in 10 ml acetonitrile and 2 ml CH₂Cl₂. The solution was stirred for 2h at 0 °C. And then the mixture was stirred at room temperature for 16h. Acetonitrile was evaporated. After addition of 10 ml water, the mixture was extracted with BuOH (3x10 ml). BuOH phase was extracted 10% NaHCO₃ (10 ml) with CH₂Cl₂ (3x10ml). The organic layer was evaporated to dryness. The residue was purified by column chromatography on silica gel using CH₂Cl₂. 75.7 mg compound was obtained (40.5 %); m.p: 180 °C (dec); UV $\lambda_{\max}^{\text{MeOH}}$: 217.0, 316.0; IR spectrum $\nu_{\max}^{\text{MeOH}} \text{ cm}^{-1}$: 3666, 2966, 2923, 1599, 1473, 1448, 1231, 1214, 1054, 1013, 927; LCMS/APCI *m/z* (rel. int.) : 406.0 [M]⁺ (0.8), 327 [M-(HO-SO₂)+2H]⁺ (9.1), 403 [M-3H]⁺ (50.3); ¹H-NMR (400 MHz, CD₃OD) and ¹³C-NMR (100 MHz, CD₃OD) see Table 3.9.

2.5.8. Compound 8: 5-[3''-hydroxypropyl]-7-methoxy-3-nitro-2-(3',4'methylene dioxyphenyl) benzofuran, (C₁₉H₁₇NO₇).

Powdered KNO₃ (5.05.10³ mg, 0.050 mol) was treated with the appropriate amount of 96% H₂SO₄ (1 ml) and the mixture was stirred for 15 min at room temperature; CH₂Cl₂ (25ml) was added to the homogeneous slurry so obtained and the mixture was cooled at 0°C with vigorous stirring. A solution of egonol (1.63.10⁻³ mg, 0.005 mol) in CH₂Cl₂ was added dropwise and the stirring was continued at room temperature for the required time. The reaction mixture was then poured into 10% aqueous Na₂SO₄ and the separated organic phase was washed with 10% aqueous Na₂SO₄, dried over anhydrous Na₂SO₄, concentrated to dryness to afford the product. The residue was purified by PTLC using Hexane/EtOAc/H₂O: 6:4:0.5 and 66 mg compound was obtained (3.56%); m.p: 140.7-142.7 °C; UV λ_{max}^{CH₂Cl₂}: 228, 268, 384 nm; IR spectrum ν_{max}^{CH₂Cl₂} cm⁻¹: 3379, 2922, 2851, 2483, 2132, 1605, 1473, 1338, 1056, 1033, 765, 743; ¹H-NMR (400 MHz, CDCl₃) and ¹³C-NMR (100 MHz, CDCl₃) see Table 3.10. (Öztürk et al., 2008).

2.5.9. Compound 9: 5-[3''-hydroxypropyl]-7-methoxy-3,6-dinitro-2-(3',4'methylene dioxyphenyl) benzofuran (C₁₉H₁₆N₂O₉).

Powdered KNO₃ (5.05.10³ mg, 0.050 mol) was treated with the appropriate amount of 96% H₂SO₄ (1 ml) and the mixture was stirred for 15 min at room temperature; CH₂Cl₂ (25ml) was added to the homogeneous slurry so obtained and the mixture was cooled at 0°C with

vigorous stirring. A solution of egonol ($1,63 \cdot 10^{-3}$ mg, $0,005$ mol) in CH_2Cl_2 was added dropwise and the stirring was continued at room temperature for the required time. The reaction mixture was then poured into 10% aqueous Na_2SO_4 and the separated organic phase was washed with 10% aqueous Na_2SO_4 , dried over anhydrous Na_2SO_4 , concentrated to dryness to afford the product. The residue was purified by PTLC using Hexane/EtOAc/ H_2O : 6:4:0.5 and 24 mg compound was obtained; m.p: $188.7\text{-}189.0$ $^\circ\text{C}$; UV $\lambda_{\text{max}}^{\text{CH}_2\text{Cl}_2}$: 229.0, 269.0, 384.0 nm; IR spectrum $\nu_{\text{max}}^{\text{CH}_2\text{Cl}_2} \text{ cm}^{-1}$: 3664, 3642, 3354, 3109, 2924, 2853, 2335, 1882, 1736, 1698, 1605, 1543, 1507, 1467, 1439, 1354, 1320, 1277, 1230, 1144, 1099, 1056, 1032, 960, 910, 876, 821, 765, 688, 674; LCMS/APCI m/z (rel. int.): 416.10 $[\text{M}]^+$ (0.2), 403.0 $[\text{M}-(\text{OH})+3\text{H}]^+$ (100), 327.05 $[\text{M}-2\text{x}(\text{NO}_2)+\text{H}]^+$ (15.4); $^1\text{H-NMR}$ (400 MHz, CDCl_3) and $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) see Table 3.11.

2.5.10. Compound 10: 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propylmethanoat, amorphous solid ($\text{C}_{20}\text{H}_{18}\text{O}_6$).

A mixture of egonol (100 mg, $3.07 \cdot 10^{-4}$ mol) and KOH (100 mg) in DMF (5 ml) was refluxed with stirring for 1 h. The reaction mixture was diluted with water (10 ml) and extracted with CH_2Cl_2 (3x5 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by PTLC using CH_2Cl_2 as a solvent to give the product as a white solid (20.6mg, 18.97 %); m.p : $77.8\text{-}78.2$ $^\circ\text{C}$; UV $\lambda_{\text{max}}^{\text{CH}_2\text{Cl}_2}$: 229, 318 nm; IR spectrum $\nu_{\text{max}}^{\text{CH}_2\text{Cl}_2} \text{ cm}^{-1}$: 2929, 2846, 1717, 1615, 1475, 1448, 1274, 1229, 1115, 1034, 921, 749, 710;

LCMS/APCI m/z (rel. int.): 355.1 $[M+H]^+$ (100), 356.1 $[M+2H]^+$ (22.1), 327.1 $[(M+2H)-CHO]^+$ (53.7); ^1H -NMR (400 MHz, $CDCl_3$) and ^{13}C -NMR (100 MHz, $CDCl_3$) see Table 3.12. (Öztürk et al., 2008).

2.5.11. Compound 11: 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propylolate, oily compound ($C_{37}H_{50}O_6$).

To a stirred solution of egonol (472 mg, $1.45 \cdot 10^{-3}$ mol) in pyridine (9 ml) was added oleic acid in CH_2Cl_2 (800 mg, $2.83 \cdot 10^{-3}$ mol). The reaction mixture was refluxed for 8 h and was stirred for a further 72 h at room temperature. The reaction mixture was diluted with water (15ml) and extracted with CH_2Cl_2 (3x5 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by PTLC using CH_2Cl_2 as a solvent. 47.6 mg white solid compound was obtained (5.57 %); UV $\lambda_{max}^{CH_2Cl_2}$: 230, 318 nm; IR spectrum $\nu_{max}^{CH_2Cl_2} cm^{-1}$: 2924, 2846, 1721, 1618, 1600, 1476, 1363, 1232, 1146, 1038, 929, 814, 735; LCMS/APCI m/z (rel.int.): 589.3 $[M-H]^+$ (6.0), 590.4 $[M]^+$ (3.0), 591.3 $[M+H]^+$ (4.5), 282 (100); ^1H -NMR (400 MHz, $CDCl_3$) and ^{13}C -NMR (100 MHz, $CDCl_3$) see Table 3.13. (Öztürk et al., 2008).

2.5.12. Compound 12: 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propylbenzoate , (C₂₆H₂₂O₆).

A mixture of AlCl₃ (30 mg), THF (7 ml) and benzoylchloride (28mg, 1.99.10⁻³ mol) was stirred at ice bath. Egonol (50mg, 1.53.10⁻⁴ mol) in THF was added in several portions and the mixture was stirred at room temperature for 2 h. The mixture was poured into an ice-water mixture and extracted with CH₂Cl₂ (4x5 ml). The extract was dried with anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified via column chromatography on silica gel using Hexane/EtOAc: 15:1 as eluent to afford the product as a white solid (19.5 mg, 29.64 %); mp. 71.9-74.5 °C; UV λ_{max}^{CH₂Cl₂} : 231,318 nm; IR spectrum ν_{max}^{CH₂Cl₂} cm⁻¹ : 2921, 1721, 1476, 1363, 1232, 1054, 1033, 930, 749; ¹H-NMR (400 MHz, CDCl₃) and ¹³C-NMR (100 MHz, CDCl₃) see Table 3.14. (Öztürk et al., 2008).

2.5.13. Compound 13: 5-[3-(3''-Bromopropoxy)propyl]-7-methoxy-2-(3',4'-methylenedioxyphenyl benzofuran, (C₂₂H₂₃BrO₅).

Egonol (100 mg, 3.07.10⁻⁴ mol) was added to a mixture of 1,3-dibromopropane (2 ml) and K₂CO₃ (500 mg) in DMF (5 ml). The mixture was stirred at room temperature for 72h. It was diluted with CH₂Cl₂ (10 ml) and washed with water (3x5 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by PTLC (CH₂Cl₂) and 6.1 mg brown compound

was obtained (4.46 %). mp. 63.7-65.0 °C.; UV $\lambda_{\max}^{\text{CH}_2\text{Cl}_2}$: 229, 318 nm; IR spectrum $\nu_{\max}^{\text{CH}_2\text{Cl}_2} \text{ cm}^{-1}$: 2916, 2846, 1476, 1261, 1229, 1141, 1113, 1039, 950, 749; LCMS/APCI m/z (rel. int.): 449.1 [M]⁺ (100), 447.1 [M]⁺ (96.9), 367.2 [(M-Br)+H]⁺ (16.6), 355 [M-(CH₂-Br)+H]⁺ (9.1), 327 [M-(Br-CH₂-CH₂-CH₂)+H]⁺ (8.7); ¹H-NMR (400 MHz, CDCl₃) and ¹³C-NMR (100 MHz, CDCl₃) see Table 3.15. (Öztürk et al., 2008).

2.5.14. Compound 14: 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propyl acetate (C₂₁H₂₀O₆).

To egonol (50 mg, 1.53.10⁻⁴ mol) in THF (5 ml) was added acetic anhydride (14.5 ml) and then was added AlCl₃ (20 mg, 1.50.10⁻⁴ mol) and stirred for 1h at 0 °C. The mixture was stirred for 48 h at room temperature. After addition of 10 ml water with 1% HCl, the mixture was extracted with CH₂Cl₂ (3x10 ml). And then the CH₂Cl₂ phase was extracted with CH₂Cl₂ and 10 ml water 10% NaHCO₃ (3x10 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. 48.5 mg compound was obtained (86.1 %); mp.85.9-87.0 °C; LCMS/APCI m/z (rel. int.): 368 [M]⁺, 279.0 [M-(CH₃-COO-CH₂-CH₂-2H)⁺ (1.1); UV $\lambda_{\max}^{\text{CH}_2\text{Cl}_2}$: 230.0, 318.0 nm; IR spectrum $\nu_{\max}^{\text{CH}_2\text{Cl}_2} \text{ cm}^{-1}$: 3453, 2923, 2852, 2043, 1736, 1620, 1600, 1503, 1477, 1449, 1386, 1366, 1334, 1233, 1145, 1116, 1039, 995, 962, 930, 871, 819, 742, 722, 696, 649, 605, 512, 459; ¹H-NMR (400 MHz, CDCl₃) see Table 3.16.

2.5.15. Compound 15: {3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propyl} diethylamine (C₂₃H₂₇NO₄).

Compound **2** (40 mg, $1.16 \cdot 10^{-4}$ mol) was added to diethylamine (20 ml) in chloroform (3 ml) at room temperature for 96 h. The reaction mixture was diluted with water (10 ml) and extracted with CH₂Cl₂ (3x7 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by PTLC using Hexane/EtOAc: 9:2; 22 mg compound was obtained (49.7 %); mp. 127.0-128.0 °C; LCMS/APCI m/z (rel. int.): 382.10 [M+H]⁺ (100), 383.10 [M+2H]⁺ (24.3), 354.10 [M-(2xCH₃)+3H]⁺ (4.8), 307 [M-(N(CH₃CH₂)₂)+2H]⁺ (3.5); UV $\lambda_{\max}^{\text{CH}_2\text{Cl}_2}$: 230.0, 319.0 nm; IR spectrum $\nu_{\max}^{\text{CH}_2\text{Cl}_2} \text{ cm}^{-1}$: 3736, 3642, 2928, 2851, 2642, 2318, 2000, 1736, 1662, 1621, 1500, 1470, 1443, 1363, 1273, 1259, 1234, 1209, 1523, 1105, 1034, 927, 814, 762, 749, 691; ¹H-NMR (400 MHz, CDCl₃) and ¹³C-NMR (100 MHz, CDCl₃) see Table 3.17.

2.5.16. Compound 16: 4-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1benzofuran-5-yl] butanenitrile, amorphous solid (C₂₀H₁₇NO₄).

Sodium cyanide (10 mg, $2.09 \cdot 10^{-4}$ mol) was dissolved in anhydrous dimethyl sulfoxide at 90 °C. Then compound **2** (50 mg, $1.39 \cdot 10^{-4}$ mol) in DMSO was added in several portions. The mixture was stirred at room temperature for 1 day. After addition of 15 ml water the mixture was extracted with CH₂Cl₂ (3x15ml). The CH₂Cl₂ was dried with anhydrous sodium sulfate, filtered and concentrated in vacuo. The

residue was purified by PTLC using Hexane/EtOAc/H₂O: 6:4:0.5 as a solvent to give the product as a yellow solid (48 mg, 103.08%); mp. 143.7-144.6 °C; UV $\lambda_{\text{max}}^{\text{CH}_2\text{Cl}_2}$: 229.0, 318.0 nm; IR spectrum $\nu_{\text{max}}^{\text{CH}_2\text{Cl}_2}$ cm⁻¹ : 2935, 2245, 1599, 1448, 1365, 1232, 1144, 1115, 1038, 929, 817, 742;); ¹H-NMR (400 MHz, CDCl₃) and ¹³C-NMR (100 MHz, CDCl₃) see Table 3.18. (Öztürk et al., 2008).

2.5.17. Compound 17: 5-(3''-iodopropyl)-7-methoxy-2-(3',4'methylene dioxyphenyl) benzofuran, amorphous solid (C₁₉H₁₇IO₄).

To a mixture of compound **2** (40 mg, 1,16.10⁻⁴ mol) in acetone (5 mL) was added NaI (81mg) with acetone (20mL) in several portions at room temperature and the mixture was stirred for 120 h. The reaction mixture was diluted with water (15 ml) and extracted with CH₂Cl₂ (3x5 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. 39 mg compound was obtained. (100.36 %); m.p:117.8-118.9 °C ; UV $\lambda_{\text{max}}^{\text{CH}_2\text{Cl}_2}$: 230.0, 319.0 nm; IR spectrum $\nu_{\text{max}}^{\text{CH}_2\text{Cl}_2}$ cm⁻¹ : 2906, 1722, 1622, 1497, 1475, 1363, 1231, 1031, 930, 740;); ¹H-NMR (400 MHz, CDCl₃) and ¹³C-NMR (100 MHz, CDCl₃) see Table 3.19. (Öztürk et al., 2008).

2.5.18. Compound 18 : 5-(3''-chloropropyl)-7-methoxy-3-nitro-2-(3',4'methylene dioxyphenyl) benzofuran (C₁₉H₁₆ClNO₆).

KNO₃ (112 mg, 1.10.10⁻³ mol) and 96% H₂SO₄ (0.3 ml) was stirred at 0°C for 15 min. And then CH₂Cl₂ (7 ml) was added at 0°C. Compound **2** (40 mg, 1.16.10⁻⁴ mol) in CH₂Cl₂ (3 ml) was slowly added to the mixture at 0°C. And then the reaction mixture was stirred for 48 h at room temperature. The reaction mixture was diluted with water (10ml) and extracted with CH₂Cl₂ (3x10 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified via column chromatography on silica gel using Hexane/EtOAc: 9:1. 23 mg compound was obtained. (50.8 %); m.p: 137.3-138.3 °C ; LCMS/APCI m/z (rel. int.): 391.2 [M+H]⁺ (15.3), 392.2 [M]⁺ (5.3), 341.0 [M-(Cl-CH₂)]⁺ (4.5), 327.05 [M-(Cl-CH₂-CH₂)]⁺ (5.6); UV λ_{max}^{CH₂Cl₂} : 228.0, 268.0, 381.0 nm; IR spectrum ν_{max}^{CH₂Cl₂} cm⁻¹ : 3680, 2972, 2512, 2844, 1738, 1473, 1346, 1259, 1215, 1054, 1013, 765, 750; ¹H-NMR (400 MHz, CDCl₃) and ¹³C-NMR (100 MHz, CDCl₃) see Table 3.20.

2.5.19. Compound 19: 4-{3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]propyl}morpholine (C₂₃H₂₅NO₅).

A mixture of compound **2** (40 mg, 1.16.10⁻⁴ mol) in toluene (7 mL) and morpholine (5.11.10⁻³ mg, 5.87.10⁻⁵ mol) was refluxed with stirring for 40 h. The reaction mixture was diluted with water (10 ml) and extracted with CH₂Cl₂ (3x7 ml). The organic was dried over anhydrous sodium sulfate and evaporated to dryness. 38.5 mg compound was

obtained (83.9 %) ; LCMS/APCI m/z (rel. int.): 396.10 $[M+H]^+$ (100), 397.1 $[M+2H]^+$ (23.4), 307.05 $[M-(O-(CH_2CH_2)_2N)-2H]^+$ (2.7); UV $\lambda_{\max}^{CH_2Cl_2}$: 233-318 nm; IR spectrum $\nu_{\max}^{CH_2Cl_2} cm^{-1}$: 2924, 2854, 1620, 1600, 1550, 1503, 1476, 1449, 1365, 1332, 1263, 1232, 1214, 1144, 1116, 1070, 1038, 929, 861, 819, 741, 602, 512, 479, 459; ^1H -NMR (400 MHz, $CDCl_3$) and ^{13}C -NMR (100 MHz, $CDCl_3$) see Table 3.21.

2.5.20. Compound 20 : 5-[3''-hydroxypropyl]-7-methoxy-3-amino-2-(3',4'methylene dioxyphenyl) benzofuran ($C_{19}H_{19}NO_5$).

A solution of compound **8** (29 mg, $7.79 \cdot 10^{-5}$ mol) in EtOH (3 ml) was stirred under Ar atmosphere. Catalyst (2 mg of 10% Pd-C) was added. While the mixture was warmed in water bath at 65 $^{\circ}C$, hydrazine monohydrate (1 ml) in EtOH (3 ml) was slowly added from a dropping funnel in 30 min. The mixture was stirred at room temperature for 24 h under Ar atmosphere. The mixture was filtered to remove Pd-C and the solvent was removed under vacuum. The residue was purified by column chromatography using neutral alumina CH_2Cl_2 :MeOH 10:1. The amine compound **11.7** was obtained (43.9 %) as an amorphous powder; LCMS/APCI m/z (rel. int.): 345.10 $[M+4H]^+$ (37.7), 327.0 $[M-(NH_2)+2H]^+$ (40.2); UV $\lambda_{\max}^{CH_2Cl_2}$: 230.0, 279.0, 311.0 nm; IR spectrum $\nu_{\max}^{CH_2Cl_2} cm^{-1}$: 3478, 3329, 2924, 2857, 2346, 1731, 1676, 1593, 1501, 1443, 1355, 1273, 1259, 1229, 1146, 1075, 1037, 930, 809, 765, 750; ^1H -NMR (400 MHz, $CDCl_3$) and ^{13}C -NMR (100 MHz, $CDCl_3$) see Table 3.22.

2.5.21. Compound 21 : 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]propyl morpholin-4-ylacetate (C₂₅H₂₇NO₇).

A mixture of compound **4** (40 mg, $9.95 \cdot 10^{-5}$ mol) in THF (5 mL) and morpholine ($3.72 \cdot 10^{-3}$ mg, $4.28 \cdot 10^{-5}$ mol) was refluxed with stirring for 10 h. The reaction mixture was diluted with water (10 ml) and extracted with CH₂Cl₂ (3x7 ml). The organic was dried over anhydrous sodium sulfate and evaporated to dryness. 38.25 mg compound was obtained (85 %) as an amorphous powder; LCMS/APCI m/z (rel. int.): 454.10 [M+H]⁺ (100), 455.10 [M+2H]⁺ (27.0), 327.10 [M-(O-(CH₂CH₂)₂N-CH₂-CO)+H]⁺ (19.6); UV $\lambda_{\max}^{\text{CH}_2\text{Cl}_2}$: 231-318 nm; IR spectrum $\nu_{\max}^{\text{CH}_2\text{Cl}_2} \text{ cm}^{-1}$: 2919, 1744, 1599, 1476, 1365, 1232, 1146, 1115, 1036, 929, 868, 820; ¹H-NMR (400 MHz, CDCl₃) and ¹³C-NMR (100 MHz, CDCl₃) see Table 3.23.

2.5.22. Compound 22: 3-[2-(3,4-dimethoxyphenyl)-7-methoxy-1-benzofuran-5-yl]propyl chloroacetate (C₂₂H₂₃ClO₆).

Trimetoksiegonol (100 mg, $3.06 \cdot 10^{-4}$ mol) in dry diethyl ether (5 ml) and triethylamine (10.5 mg, $1.04 \cdot 10^{-4}$ mol) were placed in a 100 ml two-necked flask. The mixture was stirred for 30 min. at room temperature under argon atmosphere. And then the mixture was stirred for 1 h at 0 °C under argon atmosphere. Chloroacetyl chloride (13.19 mg, $1.16 \cdot 10^{-4}$ mol) in dry diethyl ether (5 ml) was added to the reaction. And then the mixture was stirred 15 min. at 0 °C then 96 h. After addition of 10 ml water with 10% NaHCO₃, the mixture was extracted with diethyl

ether (3x10 ml). The diethyl ether was dried with anhydrous sodium sulfate and evaporated to dryness. The residue was purified via column chromatography on silica gel using Hexane/EtOAc: 10:1. 73 mg compound was obtained (60 %); m.p: 63 °C; UV λ_{max} CH₂Cl₂: 230.0, 315.0 nm.; IR spectrum ν_{max} ^{CH}₂ ^{Cl}₂ cm⁻¹ : 3424, 2922, 2851, 1731, 1708, 1598, 1510, 1463, 1250, 1140, 1023, 932, 853, 741; LCMS/APCI m/z (rel.int.): 419.10 [M]⁺ (11.5), 421.10 [M]⁺ (4.1), 369.0 [M-(Cl-CH₂)]⁺ (1.3); ¹HNMR (400 MHz, CDCl₃) and ¹³C-NMR (100 MHz, CDCl₃) see Table 3.24.

2.5.23. Compound 23: 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propanoic acid (C₁₉H₁₆O₆).

30% H₂O₂ (24 ml) and acetone (7 ml) was added to compound **1** (61.5 mg, 1.89.10⁻⁴ mol) in acetone (2 ml). The reaction mixture was stirred for 120h at room temperature. Acetone was evaporated. After addition of 10 ml water, the mixture was extracted with CH₂Cl₂ (3x10 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. 43.5 mg compound was obtained (67.6 %); m.p:148.2-149.0 °C; UV λ_{max} ^{MeOH}: 216.0, 316.0 nm.; IR spectrum ν_{max} ^{MeOH} cm⁻¹ : 3738, 2978, 2862, 1733, 1681, 1454, 1363, 1209, 1054, 1033, 1009; LCMS/APCI m/z (rel.int.): 341.0 [M+H]⁺ (100), 342.0 [M+2H]⁺ (19.0), 323 [M-OH]⁺ (3.5); ¹HNMR (400 MHz, DMSO) and ¹³C-NMR (100 MHz, DMSO) see Table 3.25.

2.5.24. Compound 24: 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propanal semicarbazone (C₂₀H₁₉N₃O₅).

Semicarbazide (32 mg, $4.10 \cdot 10^{-4}$ mol) in water (7 ml) was added to compound **1** (100 mg, $3.08 \cdot 10^{-4}$ mol) in MeOH (7 ml). The mixture was refluxed for 1.5 h and then stirred at room temperature for 24 h. The reaction mixture was diluted with water (10 ml) and extracted with CH₂Cl₂ (3x10 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by column chromatography on silica gel using CH₂Cl₂. 29.4 mg compound was obtained (25.0 %); m.p: 200.2 °C; UV $\lambda_{\max}^{\text{MeOH}}$: 220.0, 316.0 nm.; IR spectrum $\nu_{\max}^{\text{MeOH}}$ cm⁻¹ : 3466, 3196, 2923, 2853, 1698, 1582, 1475, 1439, 1372, 1271, 1232, 1218, 1127, 1040, 929, 766, 743, 633; LCMS/APCI m/z (rel.int.): 380.0 [M+H]⁺, 354.0 [M-(NH₂C)+H]⁺ (8.3), 307 [M-(NH₂CONHN)+H]⁺ (100); ¹HNMR (400 MHz, DMSO) and ¹³C-NMR (100 MHz, DMSO) see Table 3.26.

2.5.25. Compound 25: 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propanal thiosemicarbazone

Thiosemicarbazide (30 mg, $3.29 \cdot 10^{-4}$ mol) in water (7 ml) was added to compound **1** (77 mg, $2.37 \cdot 10^{-4}$ mol) in MeOH (7ml). The mixture was refluxed for 1h and then stirred at room temperature for 48 h. The reaction mixture was diluted with water (10 ml) and extracted with CH₂Cl₂ (3x10 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by

column chromatography on silica gel using CH_2Cl_2 : MeOH (20:1) and 27 mg compound was obtained (28.7 %); m.p: 181.7-182.5 $^{\circ}\text{C}$; UV $\lambda_{\text{max}}^{\text{CH}_2\text{Cl}_2}$: 216.0, 274.0, 316.0 nm.; IR spectrum $\nu_{\text{max}}^{\text{CH}_2\text{Cl}_2} \text{ cm}^{-1}$: 3417, 3263, 3159, 3000, 2923, 2846, 2675, 2318, 2032, 1733, 1593, 1525, 1497, 1478, 1445, 1360, 1262, 1229, 1209, 1144, 1111, 1034, 993, 927, 861, 812, 768, 749, 581; LCMS/APCI m/z (rel.int.): 398.05 $[\text{M}+\text{H}]^+$ (10.3), 307.0 $[\text{M}-(\text{H}_2\text{N-CS-NH-N})-\text{H}]^+$ (57.5), 308.0 $[\text{M}-(\text{H}_2\text{N-CS-NH-N})]^+$ (11.6); ^1H NMR (400 MHz, CDCl_3) and ^{13}C -NMR (100 MHz, CDCl_3) see Table 3.27.

2.5.26. Compound 26: 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propanal oxime ($\text{C}_{19}\text{H}_{17}\text{NO}_5$).

A mixture of the compound **1** (100 mg, $3.08 \cdot 10^{-4}$ mol), hydroxylamine hydrochloride ($\text{NH}_2\text{OH} \cdot \text{HCl}$) (5.5 mg, $7.94 \cdot 10^{-5}$ mol) and sodium acetate (9.6 mg, $1.17 \cdot 10^{-4}$ mol) were dissolved in 6 ml acetonitrile and 2 ml water. The solution was stirred at room temperature for 24 h. Acetonitrile was evaporated. After addition of 10 ml water, the mixture was extracted with CH_2Cl_2 (3x10 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. 100 mg compound was obtained (95.7 %). m.p: 150.0-153.0 $^{\circ}\text{C}$; UV $\lambda_{\text{max}}^{\text{MeOH}}$: 230.0, 319.0 nm.; IR spectrum $\nu_{\text{max}}^{\text{MeOH}} \text{ cm}^{-1}$: 3428 (OH stretching), 2082, 1640, 663; LCMS/APCI m/z (rel.int.): 307.05 $[\text{M}-(\text{OH-N})-\text{H}]^+$ (3.5), 279.0 $[\text{M}-(\text{OH-N}=\text{CH-C})]^+$ (23.0); ^1H NMR (400 MHz, DMSO) and ^{13}C -NMR (100 MHz, DMSO) see Table 3.28.

2.5.27. Compound 27: 6-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] hex-3-en-2-one (C₂₂H₂₀O₅).

A solution of compound **1** (22 mg, 6.79.10⁻⁵ mol) in THF (7 ml) was mixed with PPh₃=CHCOCH₃ (25.5 mg, 8.0.10⁻⁵ mol) and the mixture was refluxed for 10 h. After the reaction mixture was cooled and was hydrolyzed with 10 % HCl solution and then neutralized with a 5 % solution of NaOH. The residue was extracted with CH₂Cl₂ (3x7 ml) and CH₂Cl₂ phase dried with over anhydrous sodium sulfate, filtered and evaporated to dryness. 38 mg compound was obtained as an amorphous powder; UV λ_{max}^{CH₂Cl₂}: 230.0, 319.0 nm.; IR spectrum ν_{max}^{CH₂Cl₂} cm⁻¹: 2960, 1668, 1478, 1433, 1260, 1184, 1118, 1021, 799, 749, 716, 540; LCMS/APCI m/z (rel.int.): 365.0 [M+H]⁺ (1.8), 307.0 [M-(CH₃-CO-C-2H)]⁺ (11.0), 279.0 [M-(CH₃-CO-C=CH-C)-H]⁺ (100.0); ¹HNMR (400 MHz, CDCl₃) and ¹³C-NMR (100 MHz, CDCl₃) see Table 3.29.

2.5.28. Compound 28: 5-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]-2-{{2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl}methyl}pent-2-enal (C₃₈H₃₀O₉).

KOH (20 mg, 3.57.10⁻⁴ mol) in water was added slowly to compound **1** (50 mg, 1.54.10⁻⁴ mol) in THF (5ml). The reaction mixture was stirred at 0°C for 6 h. And then was allowed to stand at 4°C overnight. The reaction mixture was diluted with water (10 ml) and extracted with CH₂Cl₂ (3x7 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was

purified by PTLC using Hexane/EtOAc/H₂O: 6:4:0.5. 16 mg compound was obtained (16.5 %). m.p: 85.0-87.0 °C ; UV $\lambda_{\max}^{\text{CH}_2\text{Cl}_2}$: 230.0, 319.0 nm.; IR spectrum $\nu_{\max}^{\text{CH}_2\text{Cl}_2} \text{ cm}^{-1}$: 3010, 2923, 2846, 2719, 1731, 1681, 1621, 1599, 1502, 1476, 1448, 1364, 1330, 1260, 1232, 1143, 1114, 1038, 987, 929, 871, 815, 751; ¹HNMR (400 MHz, CDCl₃) and ¹³C-NMR (100 MHz, CDCl₃) see Table 3.30.

2.5.29. Compound 29: 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propanal O-benzoyloxime (C₂₆H₂₁NO₆).

The compound **26** (60 mg, 1.76.10⁻⁴ mol) and dry THF (7 ml) were placed in a 50 ml two-necked flask with a reflux condenser. Benzoyl chloride (15.2 mg, 1.09.10⁻⁴ mol) was added. The reaction was refluxed for 15 h at 50 °C under argon atmosphere. After the reaction mixture was cooled. After addition of 10 ml water with 10% NaHCO₃, the mixture was extracted with CH₂Cl₂ (3x10 ml). The CH₂Cl₂ was dried with anhydrous sodium sulfate, concentrated to dryness to afford the product. (77 mg, 98.7 %). m.p: 126.0-128.0 °C; UV $\lambda_{\max}^{\text{CH}_2\text{Cl}_2}$: 230.0, 318.0 nm.; IR spectrum $\nu_{\max}^{\text{CH}_2\text{Cl}_2} \text{ cm}^{-1}$: 3444, 2962, 2245, 1719 (C=O stretching), 1621, 1601, 1475, 1366, 1261, 1233, 1146, 1115, 1038, 929, 870, 802 (N-O stretching), 742, 601, 517; LCMS/APCI m/z (rel.int.): 442 [M-H]⁺ (5.7), 307 [M-(C₆H₅-CO-ON)-H]⁺ (37.1), 279.0 [M-(C₆H₅-COON=CH-CH₂)-2H]⁺ (23.4); ¹HNMR (400 MHz, CDCl₃) and ¹³C-NMR (100 MHz, CDCl₃) see Table 3.31.

2.5.30. Compound 30: 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propanal O-(2-chloroacetyl)oxime (C₂₁H₁₈ClNO₆).

The compound **26** (30 mg, 8.82.10⁻⁵ mol) and dry THF (7 ml) were placed in a 50 ml two-necked flask with a reflux condenser. Chloroacetyl chloride (4.95 mg, 4.38.10⁻⁵ mol) was added. The reaction was refluxed for 13 h at 50 °C under argon atmosphere. After the reaction mixture was cooled, it was neutralized with NH₃ solution. The reaction mixture was diluted with water (10 ml) and extracted with CH₂Cl₂ (3x5 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. 100 mg compound was obtained as an amorphous powder. UV $\lambda_{\text{max}}^{\text{CH}_2\text{Cl}_2}$: 230.0, 318.0 nm; IR spectrum $\nu_{\text{max}}^{\text{CH}_2\text{Cl}_2} \text{ cm}^{-1}$: 3626, 3444, 2098, 1651-1633 (C=O stretching), 1504, 1476, 1365, 1260, 1233, 1146, 1115, 1037, 928, 744 (N-O stretching), 766; LCMS/APCI m/z (rel.int.): 416 [M]⁺ (7.3), 355 [M-(Cl-CH₂-C)+H]⁺ (6.8), 322.0 [M-(Cl-CH₂-CO-O)+H]⁺ (55.9), 307 [M-(Cl-CH₂-COON)+H]⁺ (100); ¹HNMR (400 MHz, CDCl₃) and ¹³C-NMR (100 MHz, CDCl₃) see Table 3.32.

3. RESULTS AND DISCUSSION

The synthetic pathway in the present work is outlined in Figure 2.1.- 2.7. Egonol isolated from the seeds of *S. officinalis* L. was used as the main starting material.

Compound **1** was obtained from an oxidation reaction of egonol using PCC in acetone-CH₂Cl₂. The ¹H NMR spectrum of compound **1** indicated two methylene (δ_H 3.05, 2.85 instead of at δ_H 1.97, 2.85 in egonol), six aromatic methyne (δ_H 6.77, 6.96, 6.82, 7.32, 6.88, 7.41), one methylenedioxy (δ_H 6.00), one methoxy (4.04) and one aldehyde signal (δ_H 9.85). The main difference in the ¹H NMR spectrum of compound **1** with that of egonol the presence of the aldehyde proton signal at δ_H 9.85 (1H,t) and the absence of a signal at δ_H 3.73 (2H,t) in egonol. Therefore, the structure of **1** was established as 3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]propanal.

The major product of the reaction of egonol with p-toluensulphonylchloride in the presence of a small amount of pyridine was 5-[3''-chloropropyl]-7-methoxy-2-(3',4'-methylenedioxyphenyl)benzofuran **2** (Figure 1.27.). Its positive ion-mode LSMS/APCI showed molecular ion peaks at *m/z* 347.1 and 345.1 [M]⁺ consistent with a molecular formula of C₁₉H₁₇ClO₄. The ¹H and ¹³C spectra of compound **2** exhibited peaks at δ 3.57 (H3'') and 44.46 (C3''). The corresponding signals for egonol were at δ 3.73 and 62.70.

Reaction of egonol with NaBr/H₂SO₄ in water:acetone under reflux gave compound **3** (Figure 1.28.), whose LCMS-APCI gave ion peaks at m/z 391.0 and 393.0 [M]⁺ suggesting a molecular formula of C₁₉H₁₇BrO₄. The ¹H NMR spectrum of compound **3** showed an H3" upfield chemical shift at δ_H 3.43 instead of at δ_H 3.73 in egonol. On the basis of the above results, compound **3** was deduced to be *5-(3"-bromopropyl)-7-methoxy-2-(3',4'-methylenedioxyphenyl)benzofuran*.

Compound **4** was obtained from the reaction of egonol with chloroacetyl chloride and triethylamine in diethyl ether (Figure 1.27.). The main difference in the ¹H NMR spectrum of compound **4** with that of egonol is the presence of the H-3'' proton signal at δ 4.25 (2H, t) and the absence of a signal at δ 3.73 (2H,t) in egonol. The ¹³C NMR spectrum of compound **4** showed four methylene carbons (δ_C 65.74, 41.10, 32.51, 30.66) and one carbonyl carbon (167.56).

Compound **5** was obtained from the reaction of egonol with NBS in CCl₄ (Figure 1.27.). The molecular formula of **5** was assigned to be C₁₉H₁₆BrO₅ from the ion peaks at m/z 405.0 [M]⁺, 407.0 [M]⁺ in the LCMS/APCI. The ¹H NMR spectrum of compound **5** exhibited one methylenedioxy (δ_H 6.01), three methylene (δ_H 3.74, 2.88, 2.18), one methoxy (δ_H 4.04) and five aromatic protons (δ_H 7.41, 7.31, 6.85(2H), 6.67), and indicated the disappearance of the H6 signal. The ¹³C NMR spectra showed a total of 19 carbons, which included three methylenes (δ_C 62.39, 33.62, 32.32), one methoxy (δ_C 56.68), five aromatic methynes (δ_C 101.28, 109.15, 105.82, 108.89, 119.71), one

methylenedioxy (δ_C 102.099) and nine quaternary aromatic carbons (δ_C 156.68, 132.79, 136.18, 144.48, 142.13, 124.38, 148.57, 148.37, 105.70). The absence of signals at δ_H 6.66 / δ_C 107.86 (H6 in egonol) and the presence of a signal at δ_C 105.70 (instead at δ_C 100.76 in egonol) confirmed the presence of a C-6 bromo derivative. Thus, compound **5** was identified as *5-[3''-hydroxypropyl]-6-bromo-7-methoxy-2-(3',4'-methylenedioxyphenyl) benzofuran*.

Compound **6** was obtained from the reaction of egonol with NaBr, H₂SO₄ in DMSO. Its structure was confirmed by ¹H, ¹³C, HMQC NMR spectra. The ¹H NMR spectrum of compound **6** exhibited one methylenedioxy (δ_H 5.95), three methylene (δ_H 3.70, 2.80, 1.83), one methoxy (δ_H 3.90) and four aromatic protons (δ_H 7.16, 7.13, 7.07, 6.78), and indicated the disappearance of the H3 and H6 signals.

Compound **7** was obtained from the reaction of egonol with H₂SO₄ in acetonitrile. Its structure was confirmed by ¹H and ¹³C NMR spectra. The ¹H spectrum of compound **7** showed three methyne signals (δ_H 4.06, 2.79, 2.02). The H-3'' proton signal was observed at δ_H 4.06 (2H,t) whereas a signal at δ_H 3.73 (2H,t) in egonol was absent.

Compound **8** was obtained from reaction of egonol with KNO₃. Its structure was established by ¹H, ¹³C, HMQC NMR spectra. The ¹H NMR spectrum of compound **8** exhibited one methylenoxy (δ 6.01), three methylene (δ 3.74, 2.86, 2.00), one methoxy (δ 4.01) and five aromatic protons (7.63, 7.63, 7.56, 7.49, 6.94, 6.77), and indicated the

disappearance of the H-3 signal. The ^{13}C NMR spectra showed a total of 19 carbons, which included three methylenes (δ_{C} 62.32, 34.82, 32.87), one methoxy (δ_{C} 56.43), five aromatic methynes (δ_{C} 125.77, 112.78, 109.68, 110.13, 108.61), one methylenedioxy (δ_{C} 102.099) and nine quaternary aromatic carbons (δ_{C} 156.85, 123.71, 140.39, 141.06, 145.02, 145.02, 121.26, 150.79, 147.93). The absence of the signals at δ_{H} 6.81 / δ_{C} 100.76 (H3 in egonol) and the presence of a signal at δ_{C} 123.71 (instead δ_{C} 100.76 in egonol) confirmed the presence of a C3 nitro derivative. Further, the correlation between δ_{C} 100.76 and δ_{H} 6.81 in the HMQC spectrum of egonol was not observed in the HMQC spectrum of compound **8** and the HMQC spectrum of compound **8** indicated that mononitration occurred at C-3. Therefore, the structure of compound **8** was assigned to be 5-[3"-hydroxypropyl]-7-methoxy-3-nitro-2-(3',4'-methylenedioxyphenyl)benzofuran.

Compound **9** was obtained in the same way as compound **8**. The ^1H NMR spectrum of compound **9** exhibited one methylene dioxy (δ_{H} 6.11), three methylene (δ_{H} 3.71, 2.82, 1.96), one methoxy (δ_{H} 4.30) and four aromatic protons (δ_{H} 7.78, 7.64, 7.47, 7.00), and indicated the disappearance of the H-3 and H-6 signals.

Compound **10** was obtained from the reaction of egonol with KOH in DMF and gave a protonated ion peak at m/z 355.1 $[\text{M}+\text{H}]^+$ by LCMS-APCI which suggested a molecular formula of $\text{C}_{20}\text{H}_{18}\text{O}_6$. The ^1H NMR spectrum of compound **10** showed that the resonance of H-3" (δ_{H} 4.23) was shifted downfield compared to that of H-3" of egonol (δ_{H}

3.73). The ^{13}C NMR spectrum of **10** exhibited 20 carbons instead of 19 carbons which is observed for egonol. The ^{13}C NMR spectrum of compound **10** showed three methylene carbons (63.49, 32.56, 30.82), one methoxy carbon (δ_{C} 56.44), six aromatic methyne carbons (δ_{C} 100.57, 112.61, 107.71, 105.79, 108.84, 119.48), one methylenedioxy carbon (δ_{C} 101.53), eight quaternary carbons (156.43, 148.30, 148.26, 145.10, 142.83, 136.84, 131.38, 124.93), and one carbonyl carbon (161.29). Thus, compound **10** was determined to be *3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]propylmethanoate*.

Compound **11** was obtained from the reaction of oleic acid and egonol. The ^1H NMR spectrum of compound **11** showed that the resonance of H-3" (δ_{H} 4.14) was shifted downfield compared to that of H-3" of egonol (δ_{H} 3.71). LCMS/APCI gave ion peaks at m/z 590.4, 591.3, 589.3 $[\text{M}]^+$. The ^{13}C NMR spectrum exhibited a total of 37 carbons. Comparison of the ^1H and ^{13}C NMR spectral assignments for H-3" and C3" of **7** revealed downfield shifts of +0.41 and 1.11 ppm, respectively, suggesting that C3" had been esterified in compound **11**. Therefore compound **11** was established as *3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]propyleate*.

Compound **12**, which was also isolated from *S. Officinalis* L. as a minor compound, was obtained from the reaction of egonol with benzoylchloride and AlCl_3 in THF.

Compound **13** was obtained from the reaction of egonol with 1,3-dibromopropane and K_2CO_3 in DMF. The molecular formula of **13** was assigned to be $C_{22}H_{23}BrO_5$ from the ion peaks at m/z 449.1 $[M]^+$ and 447.1 $[M]^+$ in the LCMS/APCI. The ^1H NMR spectrum of compound **13** showed a total of 23 proton signals, which included six methylenes (δ_H 3.56, 3.56, 3.48, 2.77, 2.12, 1.97), one methoxy (δ_H 4.03), one methylenedioxy (δ_H 6.00), and six aromatic methylenes (δ_H 7.41, 7.32, 6.96, 6.87, 6.79, 6.62). The ^1H spectrum of compound **13** indicated that H-3" (δ_H 3.48) was shifted upfield compared to that of H-3" (δ_H 3.73) of egonol. This suggested that compound **13** contained an ether bond. The ^{13}C NMR spectrum of **13** indicated a total of 22 carbons instead of 19 carbons which is observed for egonol. Amongst the signals in the ^{13}C NMR spectrum were those for six methylene carbons (δ_C 70.33, 68.28, 32.85, 31.95, 32.16, 30.95), one methoxy carbon (δ_C 56.43), six aromatic methyne carbons (119.44, 112.62, 108.83, 107.83, 105.79, 100.61), one methylenedioxy carbon (δ_C 101.53), and eight quaternary carbons (δ_C 156.29, 148.28, 148.21, 144.99, 142.72, 137.85, 131.25, 125.02). The corresponding carbons bearing the different protons were identified from the HMQC spectrum. In the COSY spectrum, the methylene proton at δ_H 2.12 (δ_C 30.95) showed vicinal coupling with the methylene protons at δ_H 3.56 (2H, m, δ_C 68.28; 2H, m, δ_C 31.95). The protons of another methylene δ_H 1.97 (δ_C 32.16) exhibited coupling with the methylene protons at δ_H 3.48 (2H, t, δ_C 70.33) and δ_H 2.77 (2H, t, δ_C 32.85). Thus, compound **13** was determined to be 5-[3-(3"-bromopropoxy)propyl]-7-methoxy-2-(3',4'-methylenedioxyphenyl)benzofuran.

Compound **14** was obtained from the reaction of egonol with acetic anhydride. The ^1H NMR spectrum of compound **14** exhibited one methylenedioxy (δ_{H} 6.02) and three methylene groups (δ_{H} 4.13, 2.76, 2.03). The presence of a signal at δ_{H} 2.13 ($\text{CH}_3\text{-COO-}$) was also observed.

The reaction of compound **2** and diethylamine in chloroform afforded compound **15**. Its structure was confirmed by ^1H and ^{13}C NMR spectra. In the ^1H spectrum of compound **15** the three methylene groups of the alkyl chain occurred at δ_{H} 2.87, 2.77, 2.14 instead of at δ_{H} 2.16, 3.57, 2.86 in compound **2**. The ^{13}C NMR spectrum showed that the resonances of C3'' occurred at δ_{C} 51.12 instead of at δ_{C} 44.46 in compound **2**.

The reaction of compound **2** and NaCN in DMSO afforded compound **16**. Its structure was confirmed by ^1H and ^{13}C NMR spectra. The ^1H spectrum of compound **16** showed three methylene (δ_{H} 2.83, 2.33, 2.02), one methoxy (δ_{H} 4.03), one methylenedioxy (δ_{H} 5.99) and six aromatic methyne (δ_{H} 7.40, 7.32, 6.95, 6.87, 6.78, 6.60) protons. The ^{13}C NMR spectrum showed a total of 20 carbons, which included three methylene carbons (δ_{C} 34.87, 27.53, 16.54), one methoxy carbon (δ_{C} 56.68), one methylenedioxy carbon (δ_{C} 101.63), six aromatic methyne carbons (δ_{C} 100.51, 112.78, 107.59, 105.82, 108.86, 119.51), and nine quaternary carbons (δ_{C} 156.59, 131.49, 135.60, 145.26, 142.97, 124.80, 148.34, 148.34, 119.81 (CN)). The ^1H and ^{13}C NMR spectra of compound **16** showed that the resonances of H3'' and C3'' (δ 2.83; 16.54)

were shifted upfield compared to that of H3" and C3" (δ 3.57; 46.46) of compound **2**. Therefore, compound **16** was established as *4-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]butanenitrile*.

The product of the reaction of compound **2** with NaI was compound **17**. ^1H and ^{13}C -NMR analysis of compound **17** indicated the H3"/C3" upfield chemical shift at δ_{H} 3.19/ δ_{C} 6.72 instead of at δ_{H} 3.57/ δ_{C} 44.46 in compound **2**. Therefore, the structure of compound **17** was established as *5-(3"-iodopropyl)-7-methoxy-2-(3',4'-methylenedioxyphenyl) benzofuran*.

The product of the reaction of compound **2** with KNO_3 and H_2SO_4 was compound **18** (Figure.1.28.). The ^1H NMR spectrum of compound **18** indicated the disappearance of the H3 signal. The absence of the signals at δ_{H} 6.77/ δ_{C} 100.56 (H3 in compound **2**) and the presence of a signal at δ_{C} 140.48 (instead δ_{C} 100.56 in compound **18**) confirmed the presence of a C3 nitro derivative.

The product of the reaction of compound **2** with morpholine was compound **19**. Comparison of the ^1H and ^{13}C NMR spectra of compound **19** with compound **2** showed that compound **19** is a benzofuran derivative of compound **2**. The ^1H -NMR spectrum of compound **19** displayed methylene signals (δ_{H} 3.66, 2.38, 2.64, 2.33, 1.81).

Compound **20** was prepared from compound **8**, and hydrazine monohydrate in EtOH, and was characterised by its ^1H , ^{13}C NMR

spectra. The ^{13}C NMR spectrum of compound **20** showed a signal for C-3 at δ_{C} 168.00 instead of at δ_{C} 123.71.

The product of the reaction of compound **4** with morpholine was compound **21**. Comparison of the ^1H and ^{13}C NMR spectra of compound **21** with compound **4** showed that compound **21** is a benzofuran derivative of compound **4**. The ^1H -NMR spectrum of compound **21** displayed methylene signals (δ_{H} 4.20, 3.76, 2.75, 2.60, 2.03). The singlet at δ_{H} 3.20 (2H, s) corresponding to $\text{CH}_2\text{COO-}$.

Compound **22** was obtained from the reaction of trimethoxy egonol with chloroacetyl chloride in dry diethyl ether. The main difference in the ^1H -NMR spectrum of compound **22** with that of trimethoxy egonol is the presence of the H-3'' proton signal at δ_{H} 4.26 (2H, t) and the absence of a signal at δ_{H} 3.73 (2H, t) in trimethoxy egonol. In the IR spectra of compound **22** a C=O absorption was observed at 1731 cm^{-1} .

Compound **23** was obtained from the reaction of compound **1** with H_2O_2 in acetone. Its structure was established by comparison of its ^1H and ^{13}C NMR spectra. The ^1H -NMR spectrum of compound **23** indicated the disappearance of the aldehyde proton at δ_{H} 9.85 (1H,t).

The reaction of compound **1** and semicarbazide in MeOH afforded compound **24** (Figure 1.32.). Its structure was confirmed by ^1H and ^{13}C NMR spectra. The ^1H -NMR spectrum of compound **24** showed a resonance of H-3'' at δ_{H} 7.20 (1H, t) compared to that of H-3'' in

compound **1** at δ_H 9.85 (1H, t). In addition, the NH of compound **24** was observed at δ_H 9.8. The ^{13}C NMR spectrum of compound **24** showed one carbonyl carbon and an imine carbon at δ_C 144.94/144.39.

The reaction of compound **1** and thiosemicarbazide in MeOH afforded compound **25** (Figure 1.32.). The ^1H spectrum showed that H-3'' occurred at δ_H 7.45 (1H, t) (instead of δ_H 9.85 in compound **1**). The ^{13}C NMR spectrum showed a thiocarbonyl carbon at δ_C 147.43 and an imine carbon at δ_C 178.3.

The reaction of compound **1** with hydroxylamine hydrochloride ($\text{NH}_2\text{OH}.\text{HCl}$) and sodium acetate in acetonitrile afforded compound **26**. In the IR spectra of compound **26** a broad OH absorption peak was observed between 3428-3419. In ^1H -NMR spectra of compound **26** the $\text{HC}=\text{N}$ - hydrogen was observed as a triplet at 6.69 ppm. In ^{13}C NMR spectra of this compound the $\text{C}=\text{N}$ carbon signal appeared at δ_C 150.42 ppm.

The reaction of compound **1** with the wittig reagent ($\text{PPh}_3=\text{CHCOCH}_3$) in THF afforded compound **27**. The ^1H -NMR spectrum of compound **27** showed three methylene (δ_H 2.77, 2.51 and 2.15) protons. The δ_H 2.15 ppm peak belongs to the CH_3CO . The ^{13}C NMR spectrum showed one carbonyl carbons at δ_C 197.46). Additional peaks seen in the region δ_H 7.62-7.35 ppm may be due to $\text{Ph}_3\text{P}=\text{O}$.

The product of the reaction of compound **1** with KOH in THF was compound **28**. (Figure 1.32.). From the $^1\text{H-NMR}$, it can be seen that dimerisation of **1** has occurred. The observation of only one carbonyl group in the $^{13}\text{C-NMR}$ is evidence that an aldol reaction has occurred.

Compound **29** was obtained from the reaction of compound **1** with benzoyl chloride in dry THF. In the IR spectra of compound **29** two =N-O-C stretching bands appeared. In addition to the C=O absorption of the ester at 1475, 1602, 1719 cm^{-1} , respectively. In the $^{13}\text{C-NMR}$ of compound **29**, C=O signals appeared δ 212 ppm. Also, the H-2'' signal at δ_{H} 2.59 in compound **26** occurred at δ_{H} 3.91, as a triplet instead of a quartet.

Compound **30** was obtained from the reaction of compound **26** with chloroacetyl chloride. In the IR spectra of compound **30**, C=O absorption of the ester occurred at 1476, 1504, 1633, 1651 cm^{-1} . In the $^{13}\text{C-NMR}$ of compound **30**, C=O signals appeared δ_{C} 166.31 ppm. The $^1\text{H-NMR}$ spectrum was similar to that observed for compound **29**.

Table 3.1. Antimicrobial activity of egonol and synthesised compounds
(MeOH:CH₂Cl₂)

Compounds	<i>S. aureus</i> ^a	<i>B. subtilis</i> ^a	<i>C. albicans</i> ^a	<i>E. coli</i> ^a
Egonol	800	800	800	800
1	64	256	128	800
2	256	128	64	256
3	800	400	400	800
5	800	800	800	800
8	*	800	800	*
10	400	400	400	400
11	800	800	800	800
12	800	800	800	800
13	256	256	800	800
16	800	800	*	800
17	800	800	800	800

^a MIC (µg/ml) = minimum inhibition concentration

* = Not active

According to antimicrobial MIC results, compound **1** was found to be the most active compound with the value of 64 µg/mL. Compounds **5**, **11**, **12** and **17** showed similar MIC values to egonol.

Compounds **1**, **2**, **3**, **10** and **13** gave values in between these findings against *Staphylococcus aureus*, *Bacillus subtilis*, *Candida albicans*, *Escherichia coli* microorganisms.

Table 3.2. Antimicrobial activity of egonol and synthesised compounds (DMSO)

Compounds	<i>S. aureus</i> ^a	<i>B. subtilis</i> ^a	<i>C. albicans</i> ^a	<i>E. coli</i> ^a
Egonol	800	800	25	800
4	*	*	100	*
6	800	800	25	*
7	400	400	50	400
9	800	400	400	400
14	*	*	200	*
15	*	*	200	*
18	*	*	25	800
19	200	*	25	*
20	*	*	800	*
21	*	*	*	800
22	400	400	200	*
23	200	800	50	*
24	*	400	25	*
25	*	400	200	*
26	*	*	800	*
27	*	*	200	*
28	25	*	25	*
29	*	400	100	*
30	*	*	25	800
Erytromycin	25	25	*	25
Tetrasiklin	25	25	*	25

^a MIC (µg/ml) = minimum inhibition concentration

* = Not active

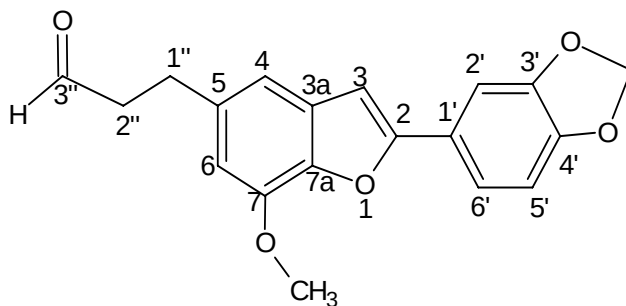
Egonol and synthesised compounds were evaluated for antimicrobial activities against *Staphylococcus aureus*, *Bacillus subtilis*, *Candida albicans*, *Escherichia coli* microorganisms.

Compounds **4**, **14**, **15**, **20**, **26** and **27** showed noticeable activity against *C. albicans*.

Compounds **6**, **18**, **19**, **24**, **28** and **30** were found to be the most active compounds with values of 25µg/mL against *S. aureus* and *C. albicans* microorganisms.

Table 3.3. NMR spectroscopic data of compound **1** in CDCl₃ (δ ppm)

Position	δ ¹ H (Egonol)	δ ¹ H (Compound 1)
2	-	-
3	6.81, s, 1H	6.77, s, 1H
4	6.99, s, 1H	6.96, s, 1H
5	-	-
6	6.66, s, 1H	6.62, d, 1H, $J=1.6$
7	-	-
3a	-	-
7a	-	-
OCH ₂ O	6.02, s, 2H	6.00, s, 2H
1'	-	-
2'	7.34, d, 1H, $J=1.5$	7.32, d, 1 H, $J=4.0$
3'	-	-
4'	-	-
5'	6.90, d, 1H, $J=8.1$	6.88, d, 1H, $J=8.0$
6'	7.43, dd, 1H, $J=1.6, 8.1$	7.41, dd, 1H, $J=1.6, 8.0$
1''	2.81, t, 2H, $J=7.6$	2.85, t, 2H, $J=6.8$
2''	1.97, p, 2H	3.05, t, 2H, $J=7.6$
3''	3.73, t, 2H, $J=6.4$	9.85, t, 1H, $J=1.6$
OMe	4.05, s, 3H	4.04, s, 3H

**Compound 1**

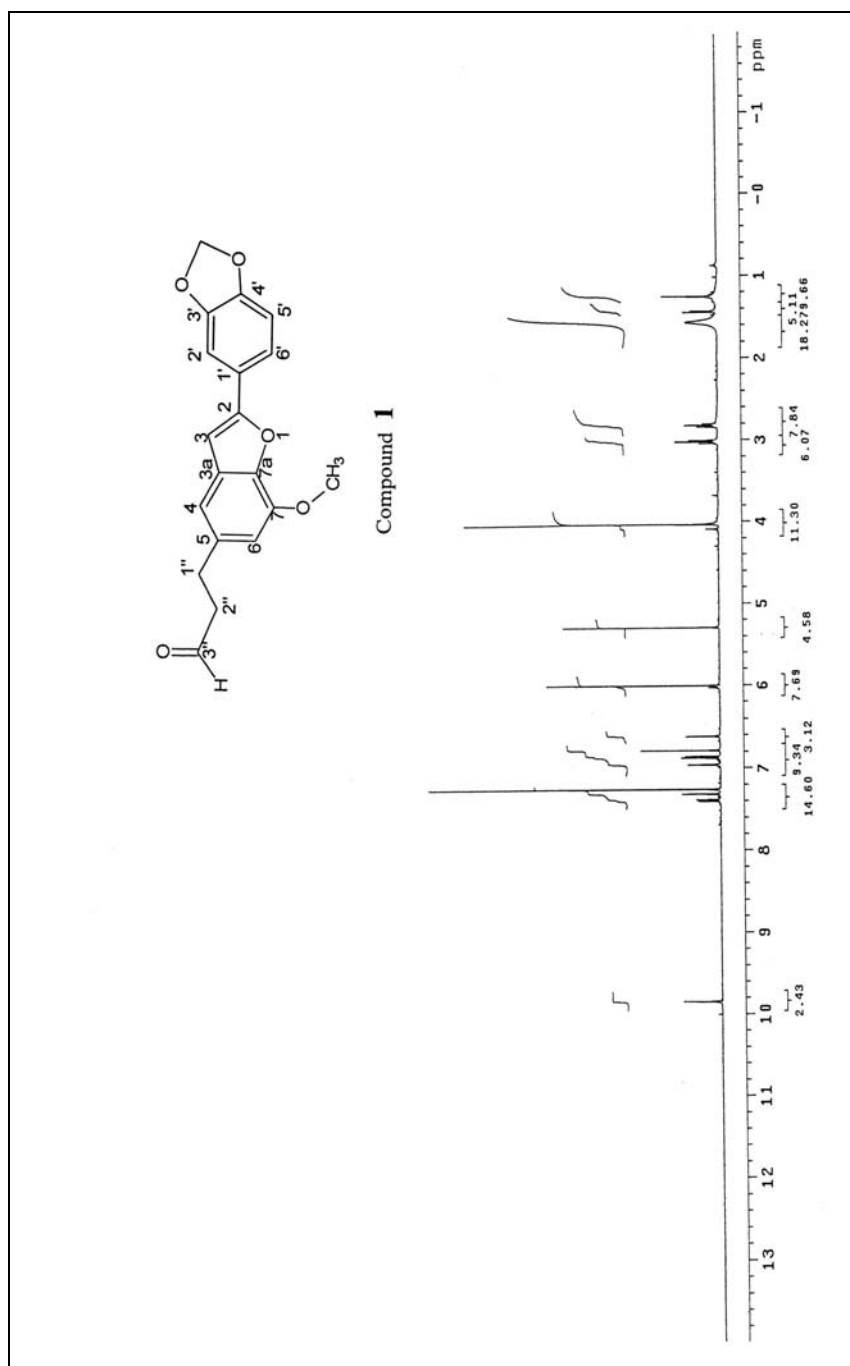
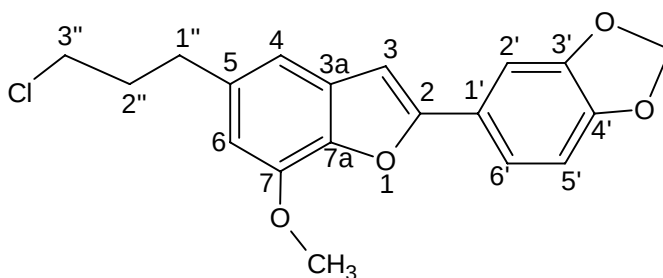


Figure 3.1. The ^1H -NMR Spectrum of Compound **1**

Table 3.4. ^1H - and ^{13}C -NMR spectroscopic data of compound **2** in CDCl_3 (δ ppm)

Position	$\delta^1\text{H}$ (Egonol)	$\delta^1\text{H}$ (Compound 2)	$\delta^{13}\text{C}$ (Egonol)	$\delta^{13}\text{C}$ (Compound 2)
2	-	-	156.51	156.43
3	6.81, s, 1H	6.77, s, 1H	100.76	100.56
3a	-	-	131.46	131.38
4	6.99, s, 1H	6.96, s, 1H	112.72	112.78
5	-	-	137.92	136.58
6	6.66, s, 1H	6.62, s, 1H	107.86	107.82
7	-	-	145.20	145.27
7a	-	-	142.88	142.84
OCH_2O	6.02, s, 2H	6.00, s, 2H	101.71	101.53
1'	-	-	125.12	124.92
2'	7.34, d, 1H, $J=1.5$	7.32, d, 1H, $J=4.0$	105.95	105.78
3'	-	-	148.46	148.32
4'	-	-	148.39	148.27
5'	6.90, d, 1H, $J=8.1$	6.88, d, 1H, $J=8.0$	109.02	108.84
6'	7.43, dd, 1H, $J=1.6, 8.1$	7.41, dd, 1H, $J=8.0, 2.0$	119.62	119.47
1''	2.81, t, 2H, $J=7.6$	2.86, t, 2H, $J=7.2$	32.83	33.27
2''	1.97, p, 2H	2.16, p, 2H	35.08	34.68
3''	3.73, t, 2H, $J=6.4$	3.57, t, 2H, $J=6.6$	62.70	44.46
OMe	4.05, s, 3H	4.04, s, 3H	56.57	56.4

**Compound 2**

Öztürk, S.E.; Akgül, Y. and Anıl, H., 2008, *Bioorganic & Medicinal Chemistry*, 16, 4431-4437.

Figure 3.2. The ^1H -NMR Spectrum of Compound **2**

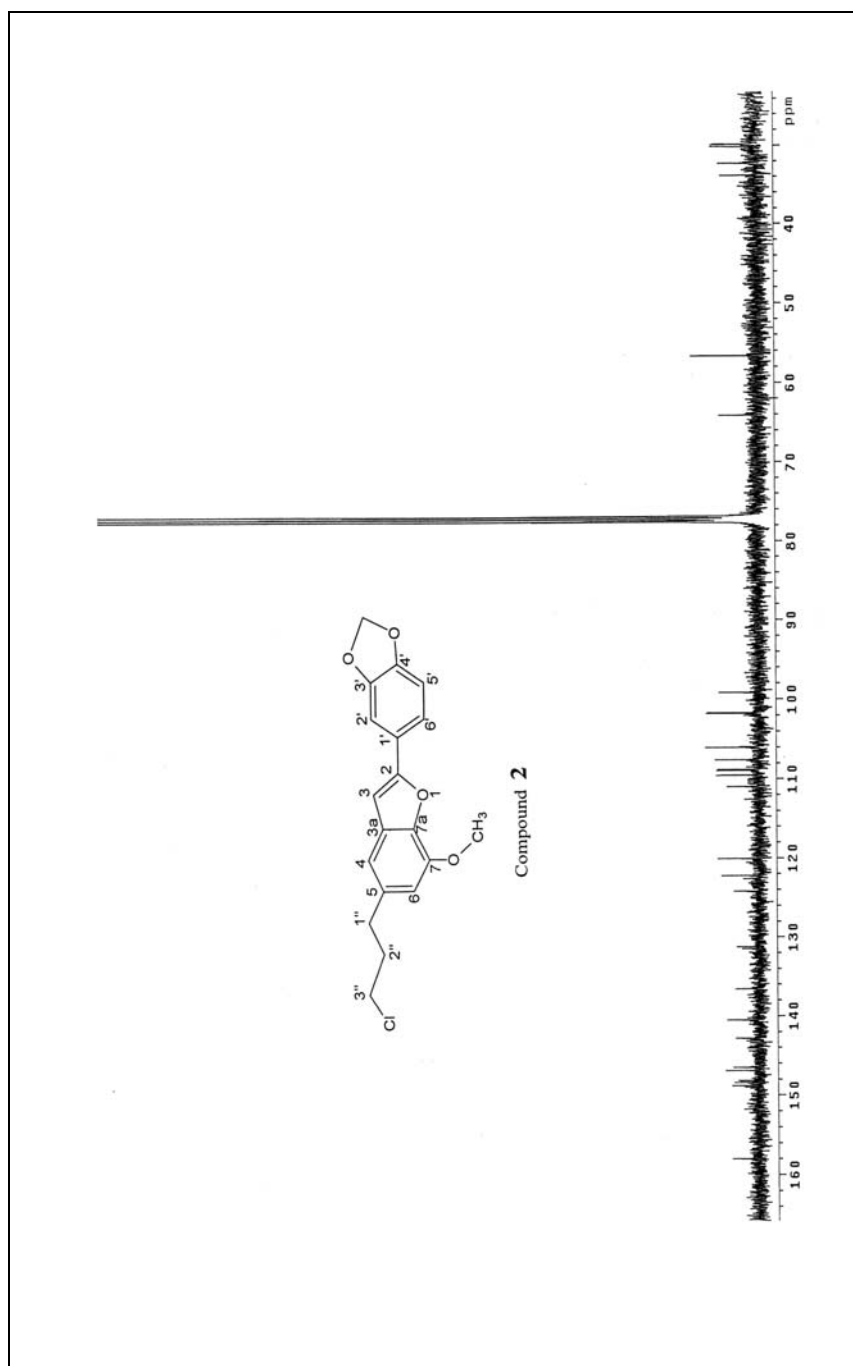
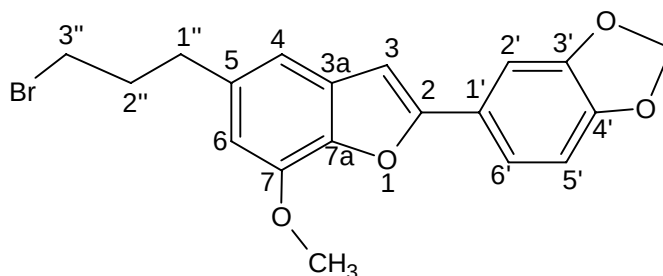


Figure 3.3. The ^{13}C -NMR Spectrum of Compound **2**

Table 3.5. ^1H -NMR spectroscopic data of compound **3** in CDCl_3 (δ ppm)

Position	δ ^1H (Egonol)	δ ^1H (Compound 3)
2	-	-
3	6.81, s, 1H	6.77, s, 1H
4	6.99, s, 1H	6.96, s, 1H
5	-	-
6	6.66, s, 1H	6.62, s, 1H, $J=1.6$
7	-	-
3a	-	-
7a	-	-
OCH_2O	6.02, s, 2H	6.00, s, 2H
1'	-	-
2'	7.34, d, 1H, $J=1.5$	7.32, d, 1 H, $J=4.0$
3'	-	-
4'	-	-
5'	6.90, d, 1H, $J=8.1$	6.88, d, 1H, $J=8.0$
6'	7.43, dd, 1H, $J=1.6, 8.1$	7.41, dd, 1H, $J=1.6, 8.0$
1''	2.81, t, 2H, $J=7.6$	2.86, t, 2H, $J=7.4$
2''	1.97, p, 2H	2.23, p, 2H
3''	3.73, t, 2H, $J=6.4$	3.43, t, 1H, $J=6.4$
OMe	4.05, s, 3H	4.04, s, 3H

**Compound 3**

Öztürk, S.E.; Akgül, Y. and Anıl, H., 2008, *Bioorganic & Medicinal Chemistry*, 16, 4431-4437.

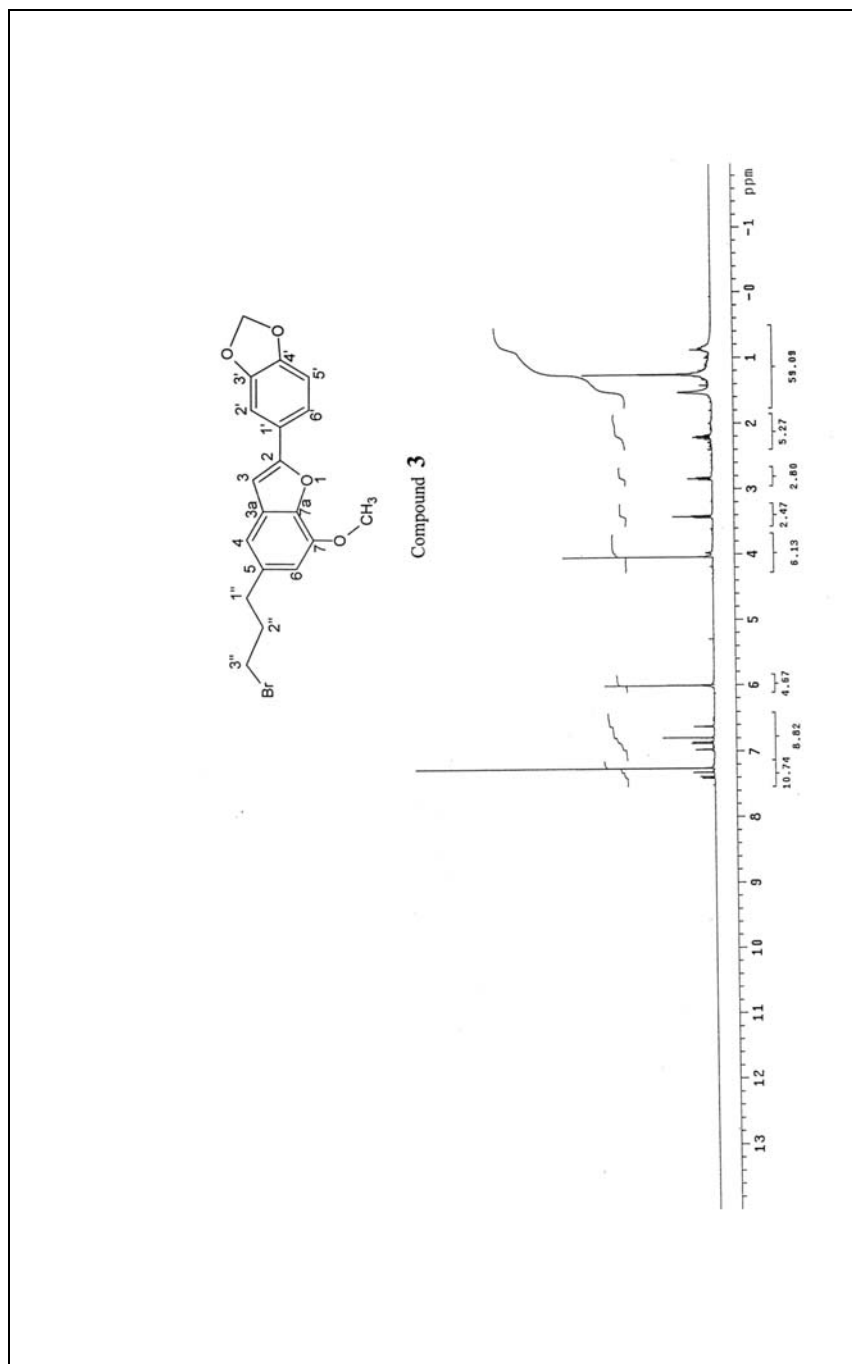
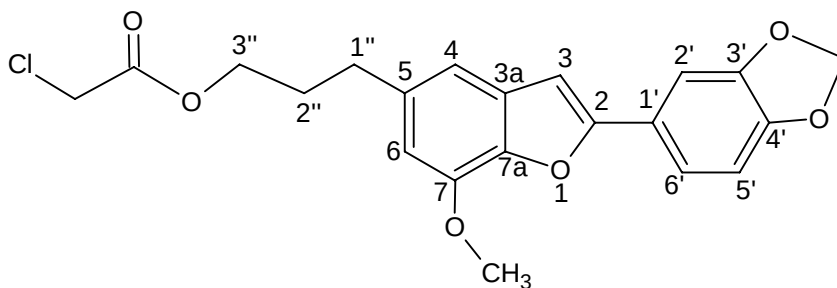


Figure 3.4. The ¹H-NMR Spectrum of Compound **3**

Table 3.6. ^1H - and ^{13}C -NMR spectroscopic data of compound **4** in CDCl_3 (δ ppm)

Position	δ ^1H (Egonol)	δ ^1H (Compound 4)	δ ^{13}C (Egonol)	δ ^{13}C (Compound 4)
2	-	-	156.51	156.45
3	6.81, s, 1H	6.78, s, 1H	100.76	100.55
3a	-	-	131.46	131.38
4	6.99, s, 1H	6.94, s, 1H	112.72	112.60
5	-	-	137.92	136.74
6	6.66, s, 1H	6.59, s, 1H, $J=0.8$	107.86	107.69
7	-	-	145.20	145.11
7a	-	-	142.88	142.82
OCH_2O	6.02, s, 2H	5.99, s, 2H	101.71	101.54
1'	-	-	125.12	124.90
2'	7.34, d, 1H, $J=1.5$	7.31, d, 1H, $J=1.6$	105.95	105.79
3'	-	-	148.46	148.31
4'	-	-	148.39	148.27
5'	6.90, d, 1H, $J=8.1$	6.87, d, 1H, $J=8.4$	109.02	108.84
6'	7.43, dd, 1H, $J=1.6, 8.1$	7.40, dd, 1H, $J=1.2, 1.6$	119.62	119.47
1''	2.81, t, 2H, $J=7.6$	2.78, t, $J=7.6$	32.83	30.66
2''	1.97, p, 2H	2.08, p, 2H	35.08	32.51
3''	3.73, t, 2H, $J=6.4$	4.25, t, 2H, $J=6.4$	62.70	65.74
OMe	4.05, s, 3H	4.03, s, 3H	56.57	56.45
COO	-	-	-	167.56
Cl-CH_2	-	4.05, s, 2H	-	41.10

**Compound 4**

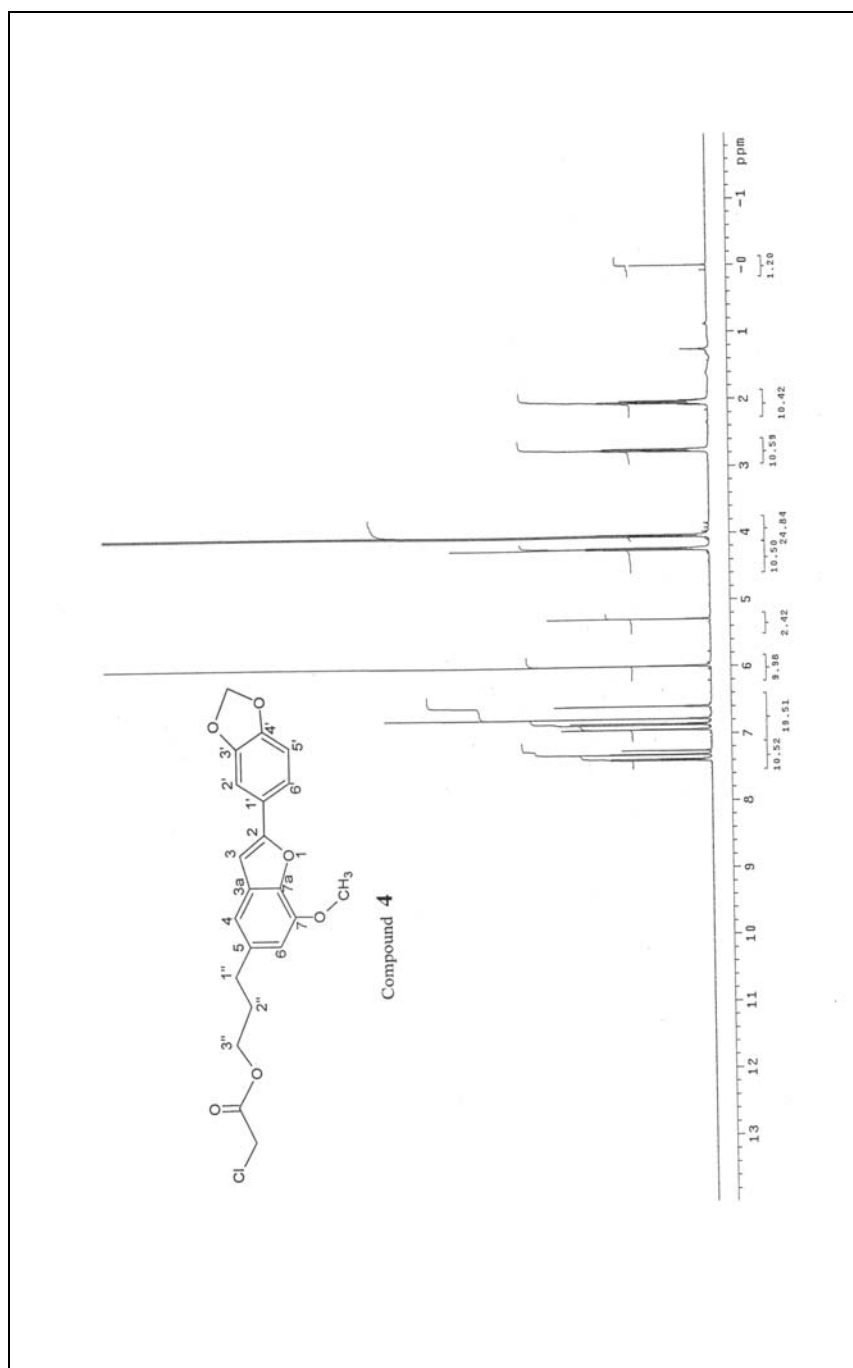


Figure 3.5. The ¹H-NMR Spectrum of Compound 4

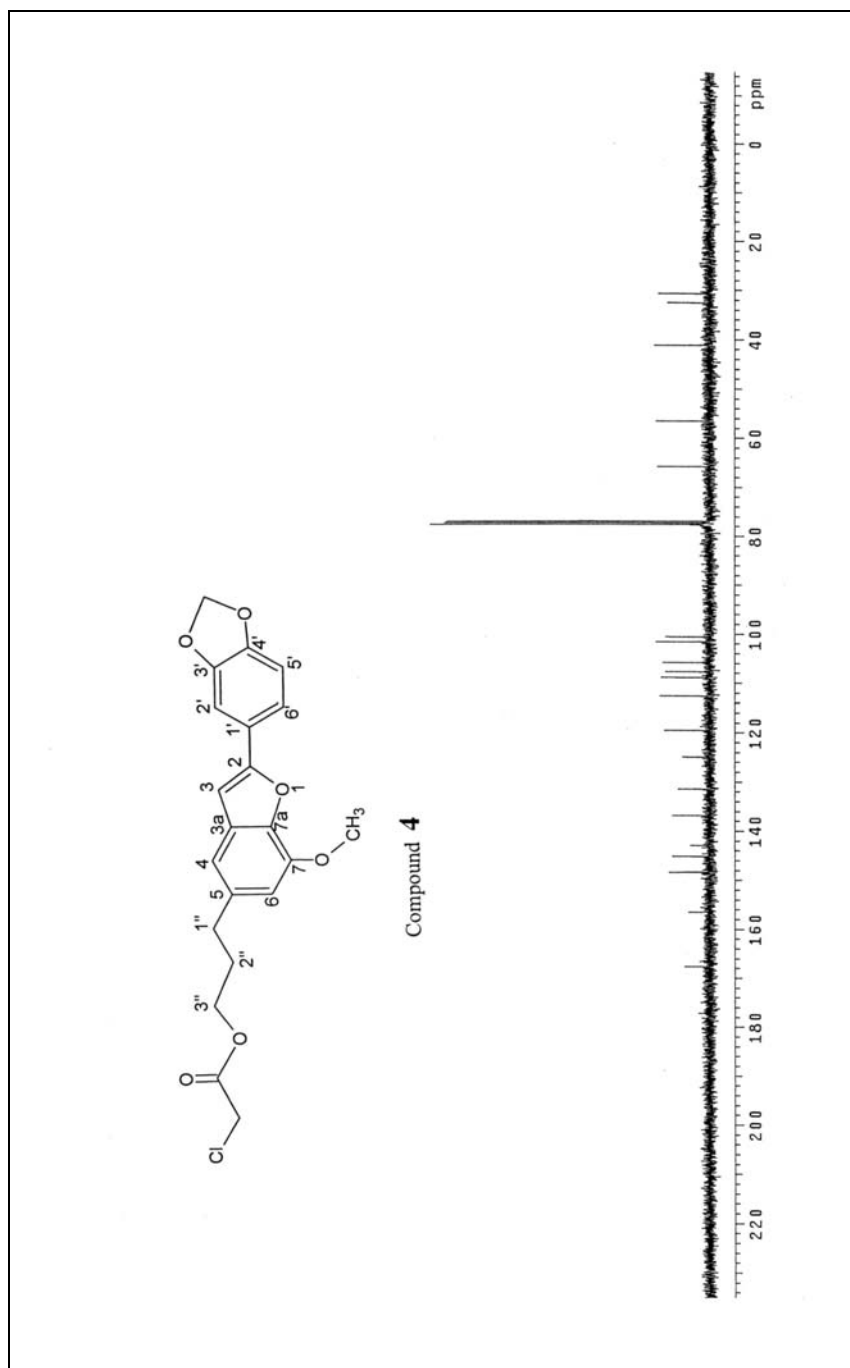
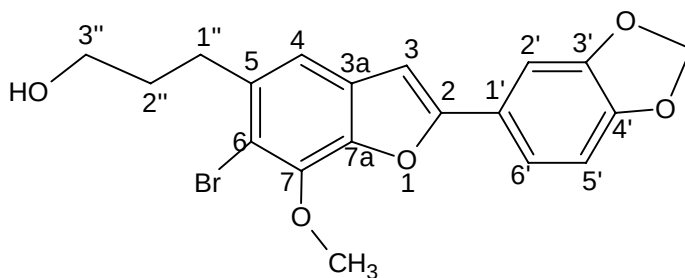


Figure 3.6. The ¹³C-NMR Spectrum of Compound 4

Table 3.7. ^1H - and ^{13}C -NMR spectroscopic data of compound **5** in CDCl_3 (δ ppm)

Position	δ ^1H (Egonol)	δ ^1H (Compound 5)	δ ^{13}C (Egonol)	δ ^{13}C (Compound 5)
2	-	-	156.51	156.68
3	6.81, s, 1H	6.67, s, 1H	100.76	101.28
3a	-	-	131.46	132.79
4	6.99, s, 1H	6.85, s, 1H	112.72	109.15
5	-	-	137.92	136.18
6	6.66, s, 1H	-	107.86	105.70
7	-	-	145.20	144.48
7a	-	-	142.88	142.13
OCH_2O	6.02, s, 2H	6.02, s, 2H	101.71	101.63
1'	-	-	125.12	124.38
2'	7.34, d, 1H, $J=1.5$	7.31, d, 1H, $J=3.8$	105.95	105.82
3'	-	-	148.46	148.57
4'	-	-	148.39	148.37
5'	6.90, d, 1H, $J=8.1$	6.85, d, 1H, $J=8.0$	109.02	108.89
6'	7.43, dd, 1H, $J=1.6, 8.1$	7.41, dd, 1H, $J=1.6, 8.0$	119.62	119.71
1''	2.81, t, 2H, $J=7.6$	2.88, t, 2H, $J=7.6$	32.83	32.32
2''	1.97, p, 2H	2.18, p, 2H	35.08	33.62
3''	3.73, t, 2H, $J=6.4$	3.74, t, 2H, $J=6.4$	62.70	62.39
OMe	4.05, s, 3H	4.04, s, 3H	56.57	56.68

**Compound 5**

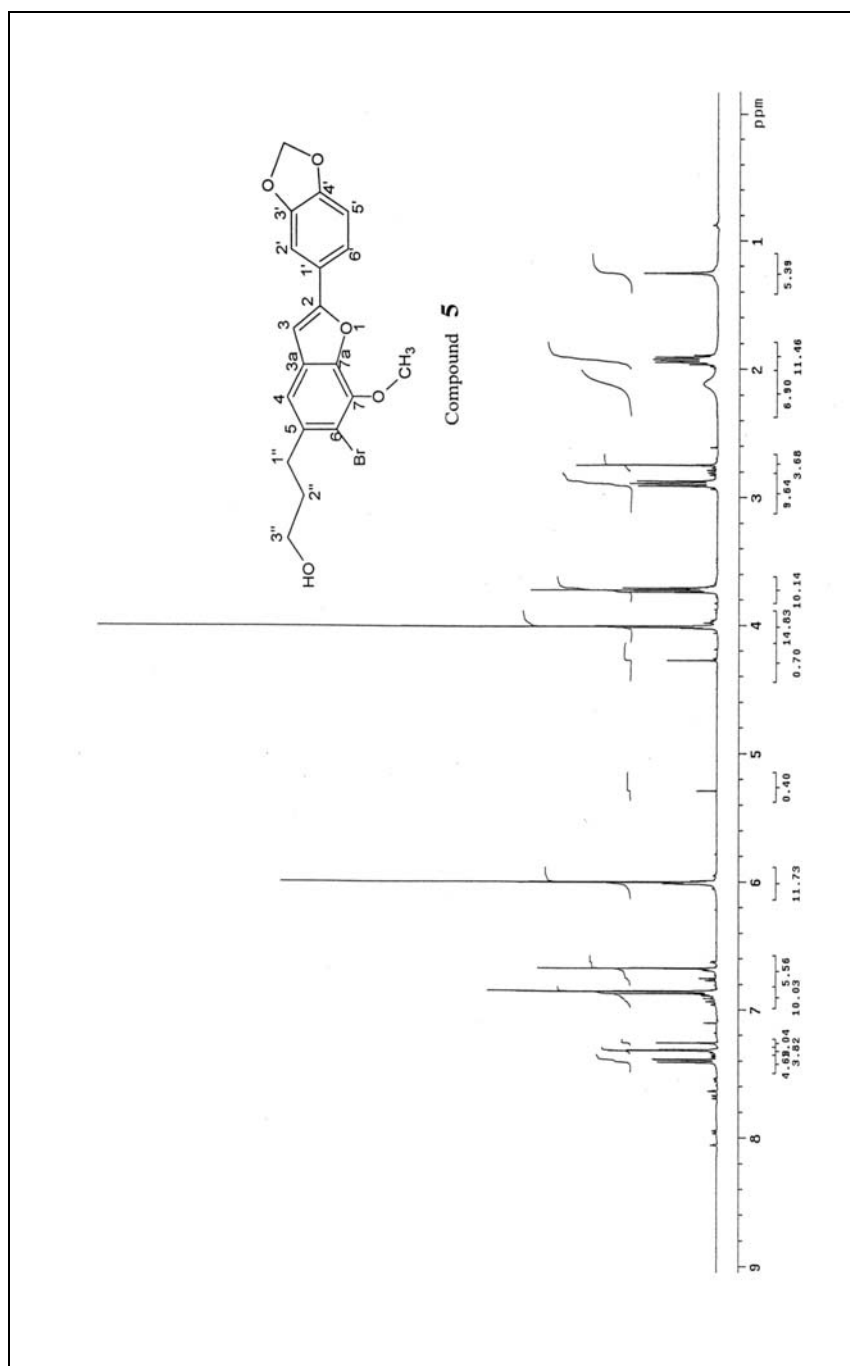


Figure 3.7. The ¹H-NMR Spectrum of Compound 5

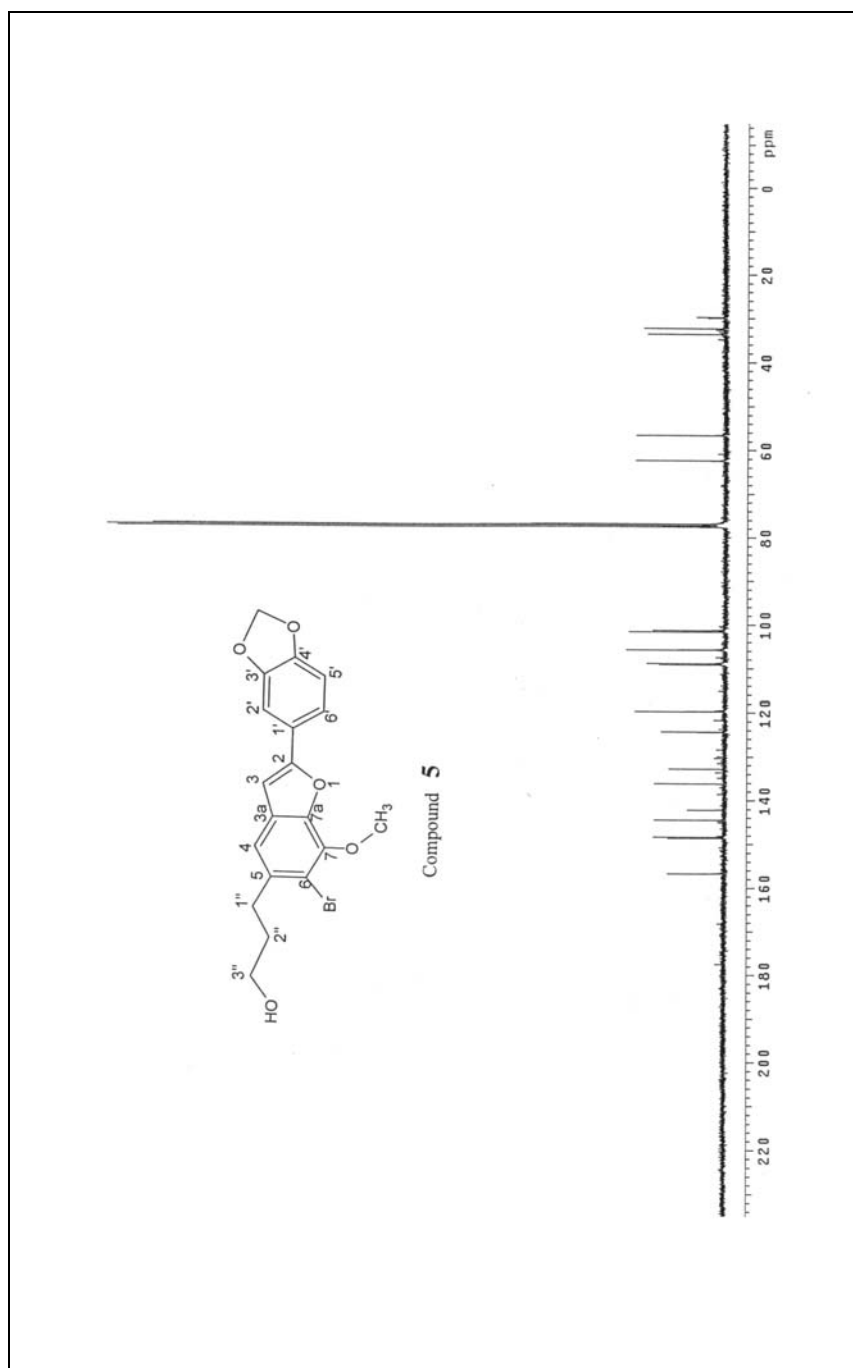


Figure 3.8. The ^{13}C -NMR Spectrum of Compound **5**

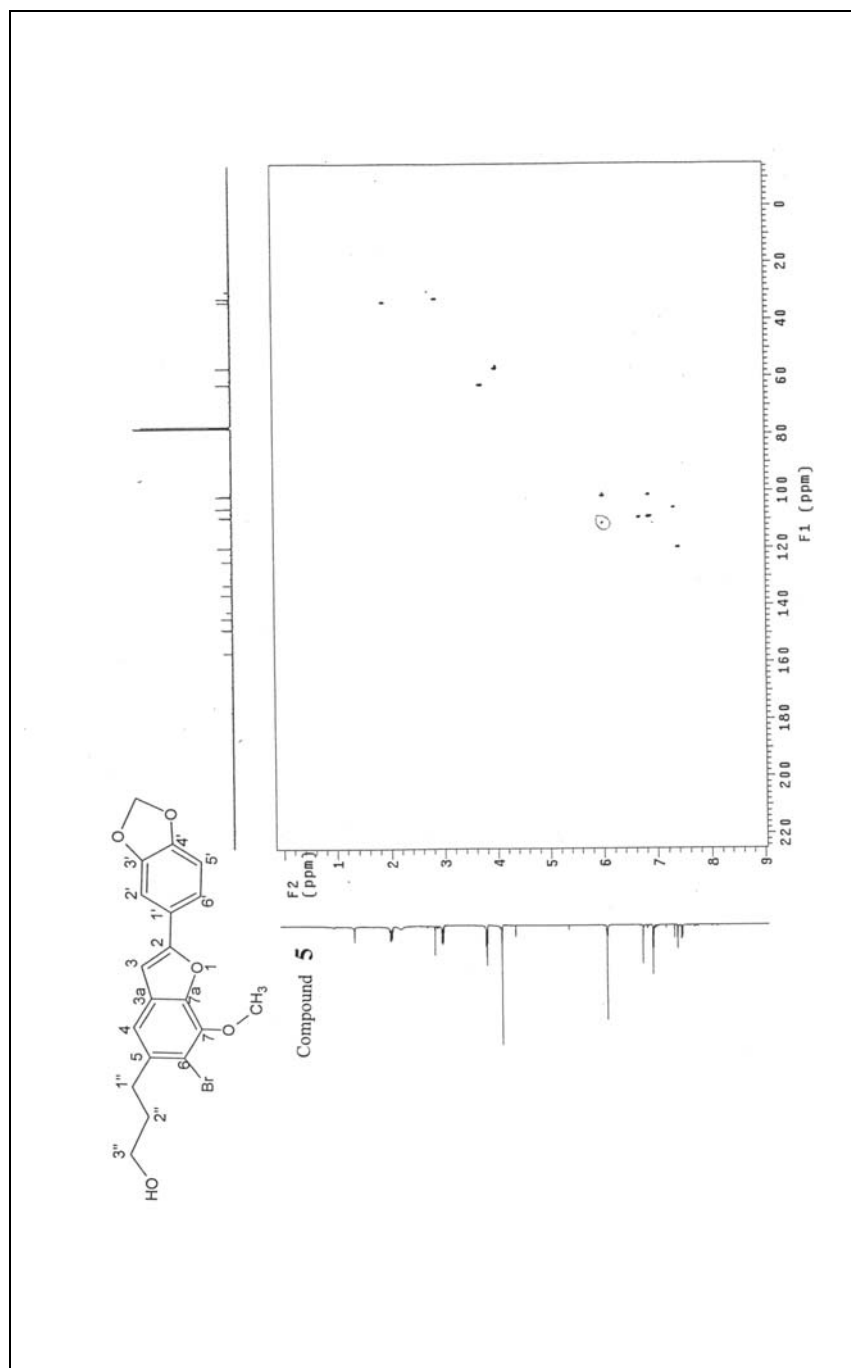
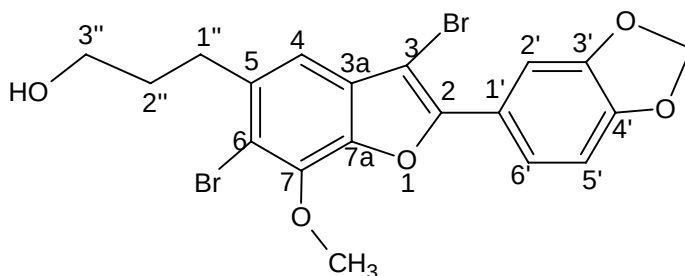


Figure 3.9. The HMQC Spectrum of Compound **5**

Table 3.8. ^1H - and ^{13}C -NMR spectroscopic data of compound **6** in CDCl_3 (δ ppm)

Position	δ ^1H (Egonol)	δ ^1H (Compound 6)	δ ^{13}C (Egonol)	δ ^{13}C (Compound 6)
2	-	-	156.51	160.33
3	6.81, s, 1H	-	100.76	103.96
3a	-	-	131.46	132.69
4	6.99, s, 1H	7.07, s, 1H	112.72	121.88
5	-	-	137.92	136.76
6	6.66, s, 1H	-	107.86	110.53
7	-	-	145.20	145.25
7a	-	-	142.88	145.25
OCH_2O	6.02, s, 2H	5.95	101.71	101.65
1'	-	-	125.12	129.27
2'	7.34, d, 1H, $J=1.5$	7.13, d, 1H, $J=1.6$	105.95	106.98
3'	-	-	148.46	149.20
4'	-	-	148.39	148.22
5'	6.90, d, 1H, $J=8.1$	6.78, d, 1H, $J=8.0$	109.02	108.52
6'	7.43, dd, 1H, $J=1.6, 8.1$	7.16, dd, 1H, $J=1.6, 8.0$	119.62	120.28
1''	2.81, t, 2H, $J=7.6$	2.80	32.83	31.28
2''	1.97, p, 2H	1.83	35.08	32.88
3''	3.73, t, 2H, $J=6.4$	3.70	62.70	62.11
OMe	4.05, s, 3H	3.90	56.57	56.82

Compound **6**

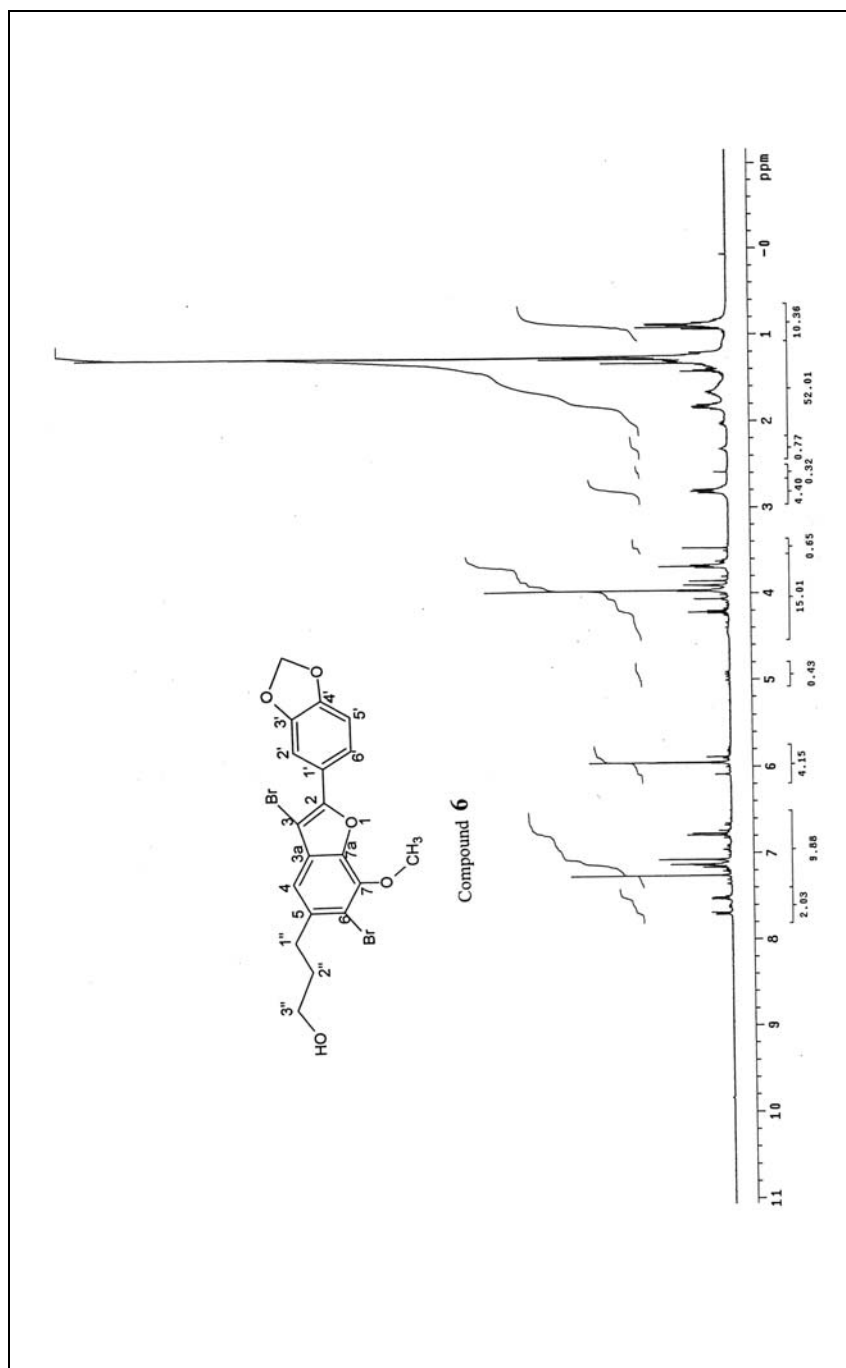


Figure 3.10. The ^1H -NMR Spectrum of Compound 6

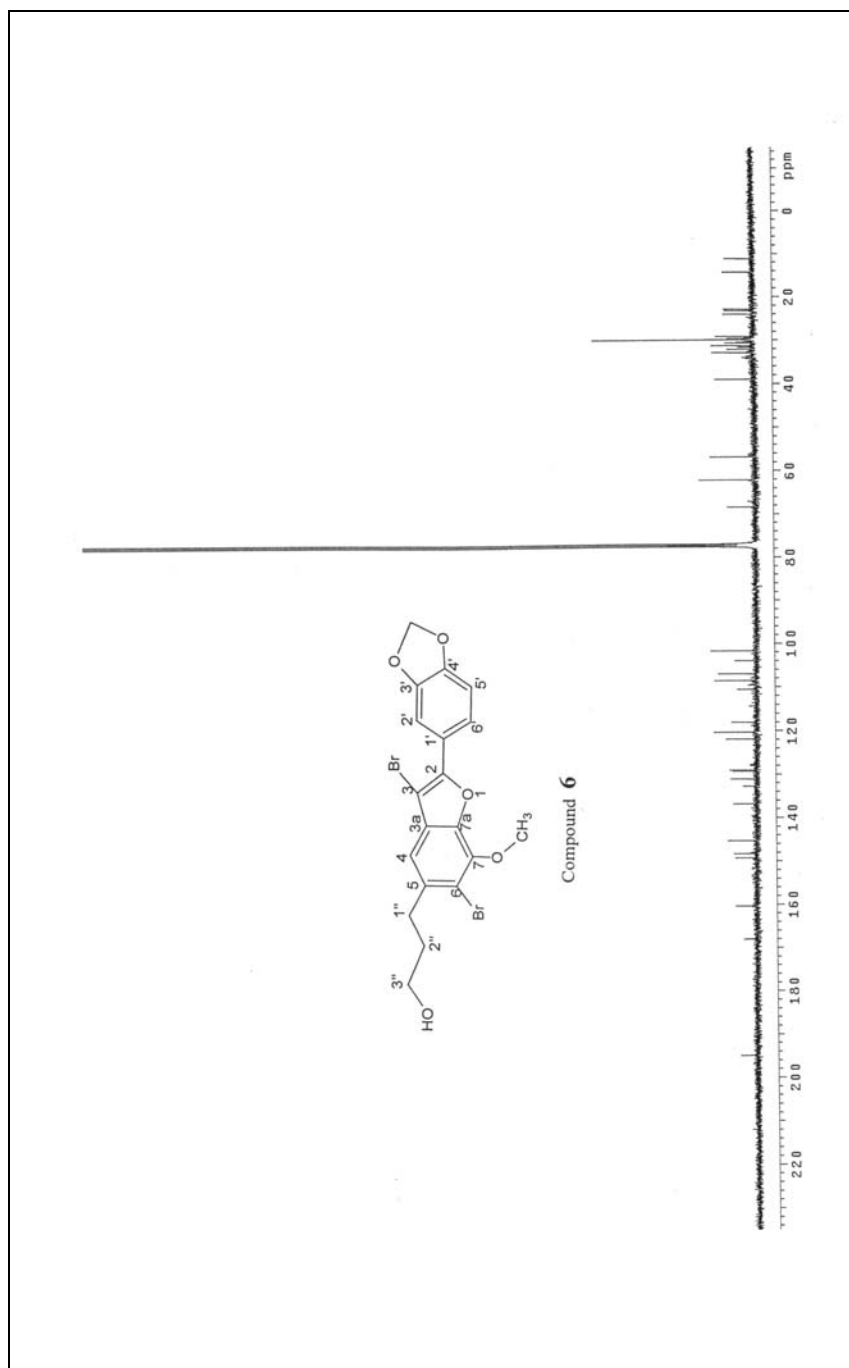


Figure 3.11. The ¹³C-NMR Spectrum of Compound 6

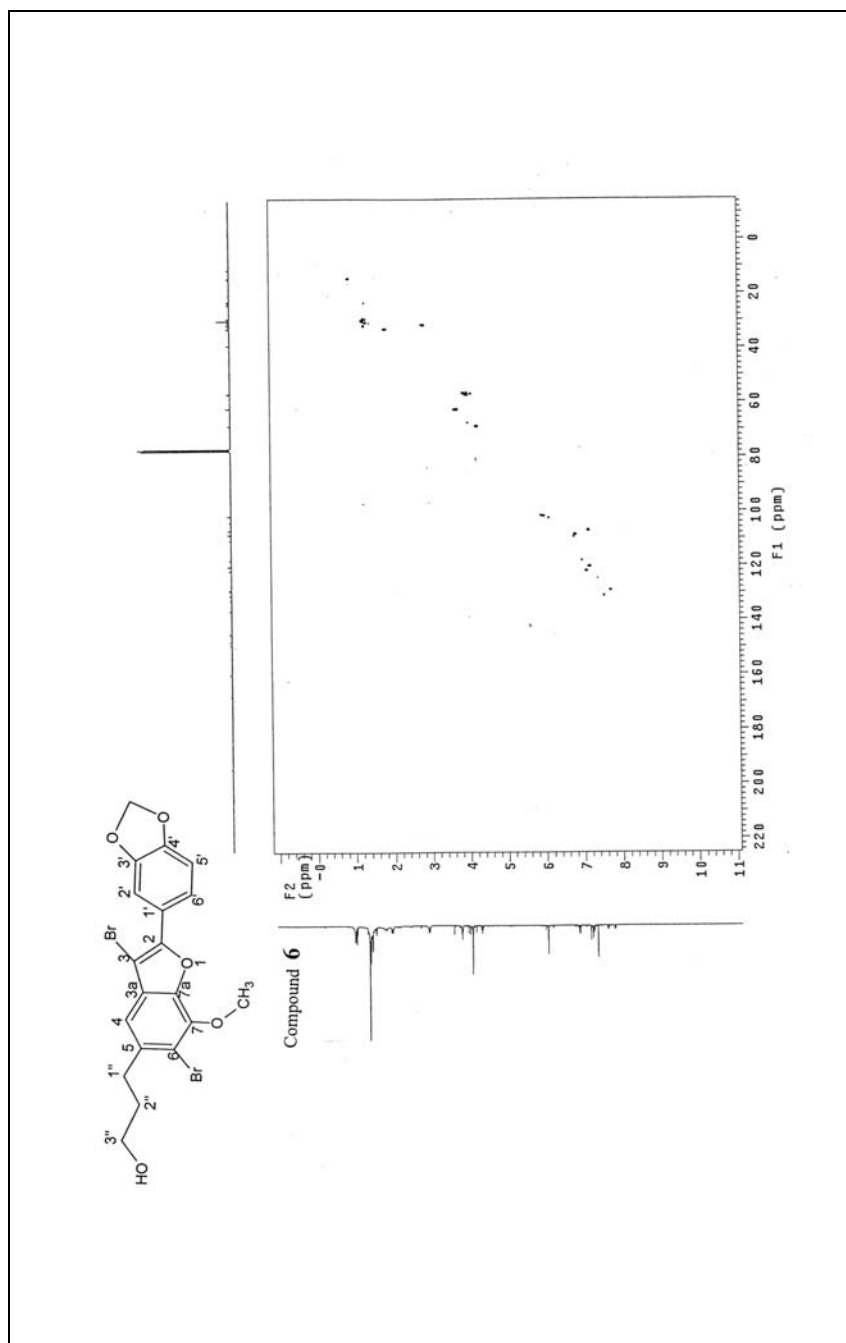
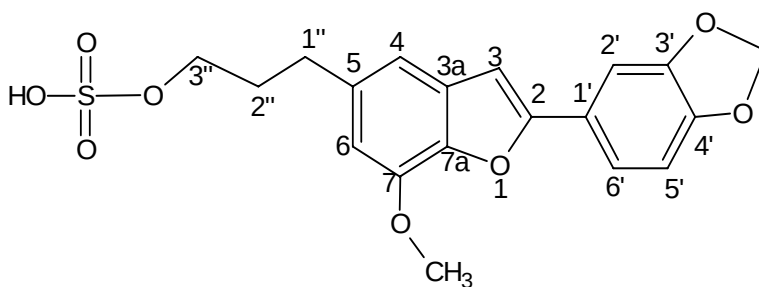


Figure 3.12. The HMQC Spectrum of Compound 6

Table 3.9. ^1H - and ^{13}C -NMR spectroscopic data of compound **7** in CD_3OD (δppm)

Position	$\delta\ ^1\text{H}$ (Egonol)	$\delta\ ^1\text{H}$ (Compound 7)	$\delta\ ^{13}\text{C}$ (Egonol)	$\delta\ ^{13}\text{C}$ (Compound 7)
2	-	-	156.51	155.81
3	6.81, s, 1H	6.89, s, 1H	100.76	102.11
3a	-	-	131.46	131.14
4	6.99, s, 1H	6.94, s, 1H	112.72	112.79
5	-	-	137.92	138.45
6	6.66, s, 1H	6.73, s, 1H	107.86	108.56
7	-	-	145.20	145.01
7a	-	-	142.88	142.32
OCH_2O	6.02, s, 2H	5.99, s, 2H	101.71	101.76
1'	-	-	125.12	124.75
2'	7.34, d, 1H, $J=1.5$	7.30, d, 1H, $J=1.6$	105.95	105.65
3'	-	-	148.46	148.64
4'	-	-	148.39	148.47
5'	6.90, d, 1H, $J=8.1$	6.88, d, 1H, $J=8.4$	109.02	109.50
6'	7.43, dd, 1H, $J=1.6, 8.1$	7.39, dd, 1H, $J=1.6, 1.6$	119.62	119.42
1''	2.81, t, 2H, $J=7.6$	2.79, t, 2H, $J=7.6$	32.83	31.56
2''	1.97, p, 2H	2.02, p, 2H	35.08	32.02
3''	3.73, t, 2H, $J=6.4$	4.06, t, 2H, $J=6.4$	62.70	67.30
OMe	4.05, s, 3H	4.00, s, 3H	56.57	55.48

Compound **7**

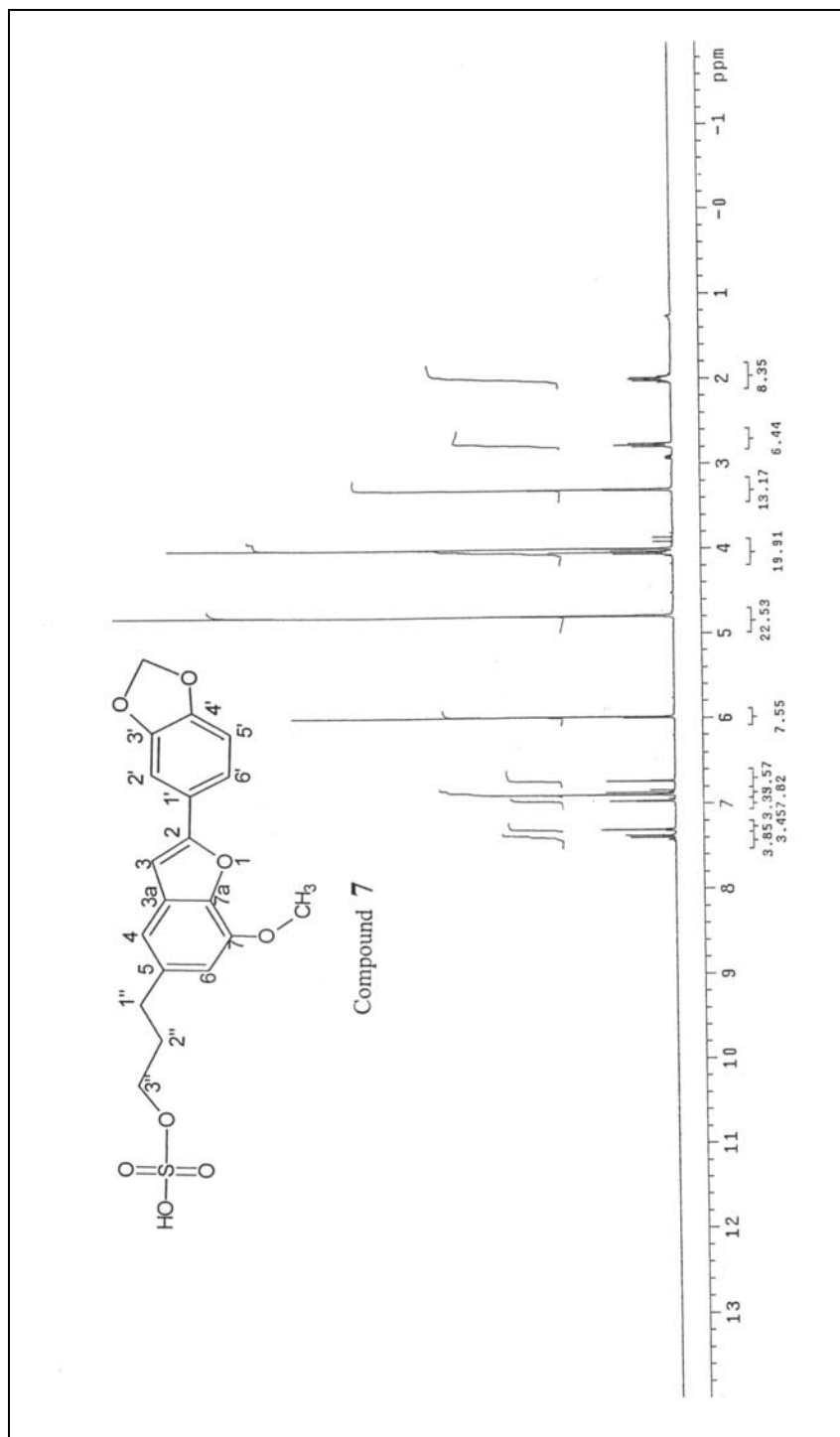


Figure 3.13. The ¹H-NMR Spectrum of Compound 7

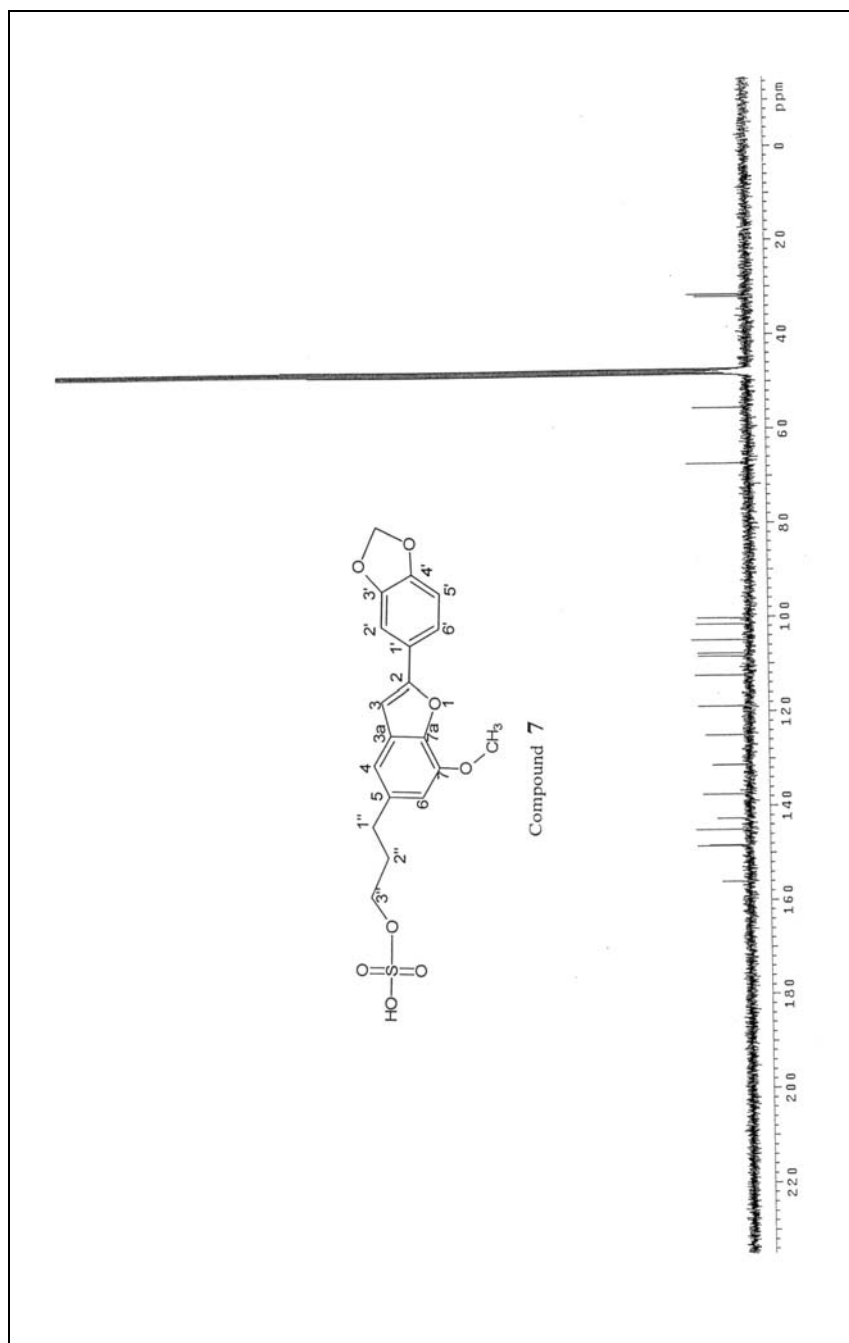


Figure 3.14. The ^{13}C -NMR Spectrum of Compound 7

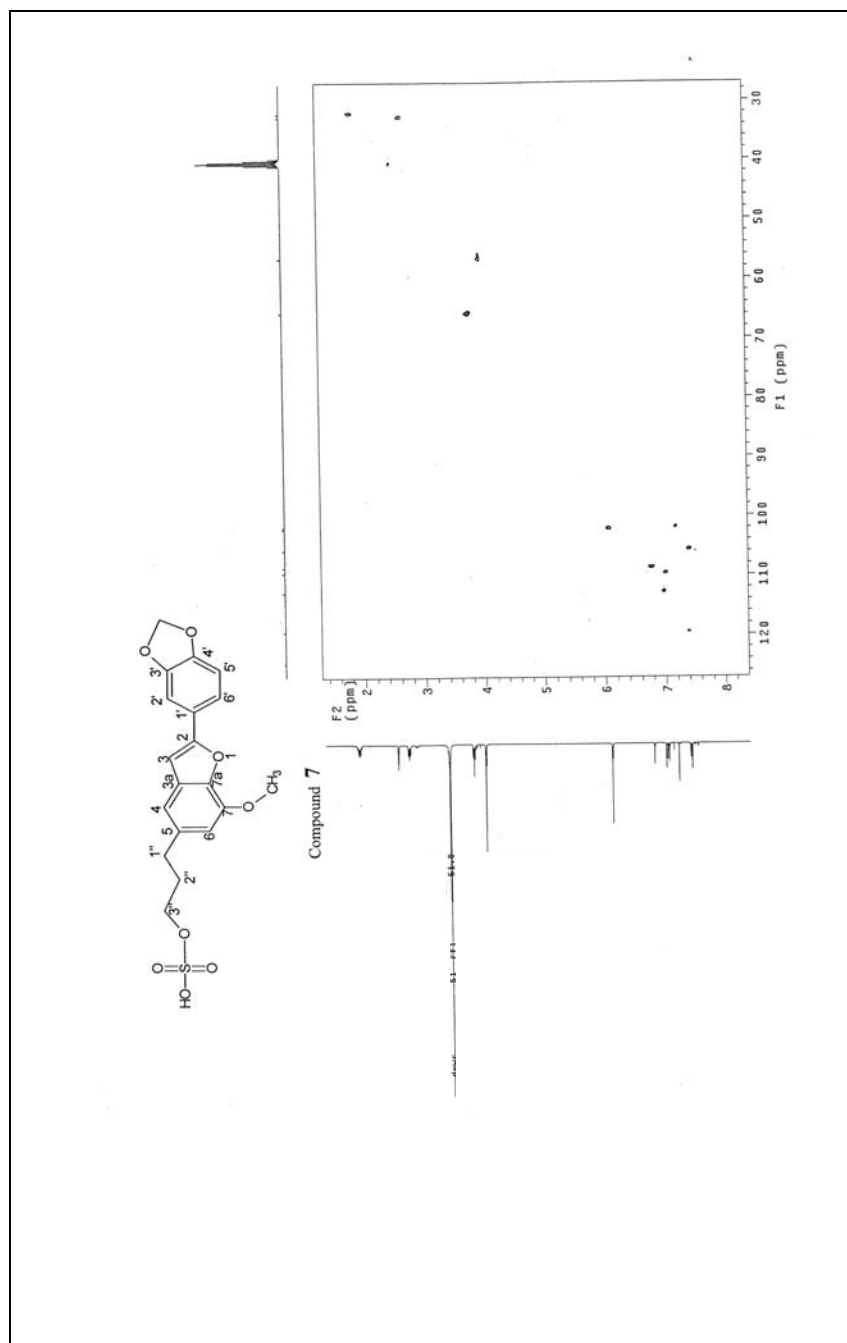
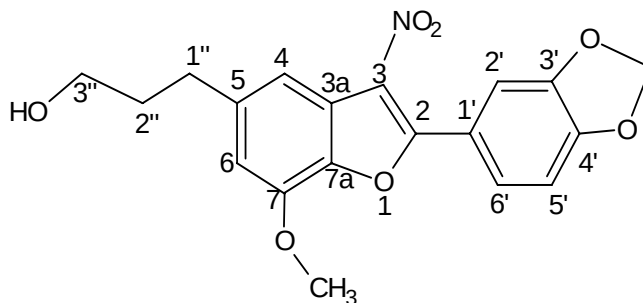


Figure 3.15. The HMQC Spectrum of Compound 7

Table 3.10. ^1H - and ^{13}C -NMR spectroscopic data of compound **8** in CDCl_3 (δ ppm)

Position	δ ^1H (Egonol)	δ ^1H (Compound 8)	δ ^{13}C (Egonol)	δ ^{13}C (Compound 8)
2	-	-	156.51	156.85
3	6.81, s, 1H	-	100.76	123.71
3a	-	-	131.46	140.39
4	6.99, s, 1H	7.56, s, 1H	112.72	112.78
5	-	-	137.92	141.06
6	6.66, s, 1H	6.77, s, 1H	107.86	109.68
7	-	-	145.20	145.02
7a	-	-	142.88	145.02
OCH_2O	6.02, s, 2H	6.01, s, 2H	101.71	102.09
1'	-	-	125.12	121.26
2'	7.34, d, 1H, $J=1.5$	7.49, d, 1H, $J=1.6$	105.95	110.13
3'	-	-	148.46	150.79
4'	-	-	148.39	147.93
5'	6.90, d, 1H, $J=8.1$	6.94, d, 1H, $J=8.4$	109.02	108.61
6'	7.43, dd, 1H, $J=1.6, 8.1$	7.63, d, 1H, $J=1.6, 8.4$	119.62	125.77
1''	2.81, t, 2H, $J=7.6$	2.86, t, 2H, $J=7.8$	32.83	34.82
2''	1.97, p, 2H	2.00, p, 2H	35.08	32.87
3''	3.73, t, 2H, $J=6.4$	3.74, t, 2H, $J=6.4$	62.70	62.32
OMe	4.05, s, 3H	4.01, s, 3H	56.57	56.43

Compound **8**

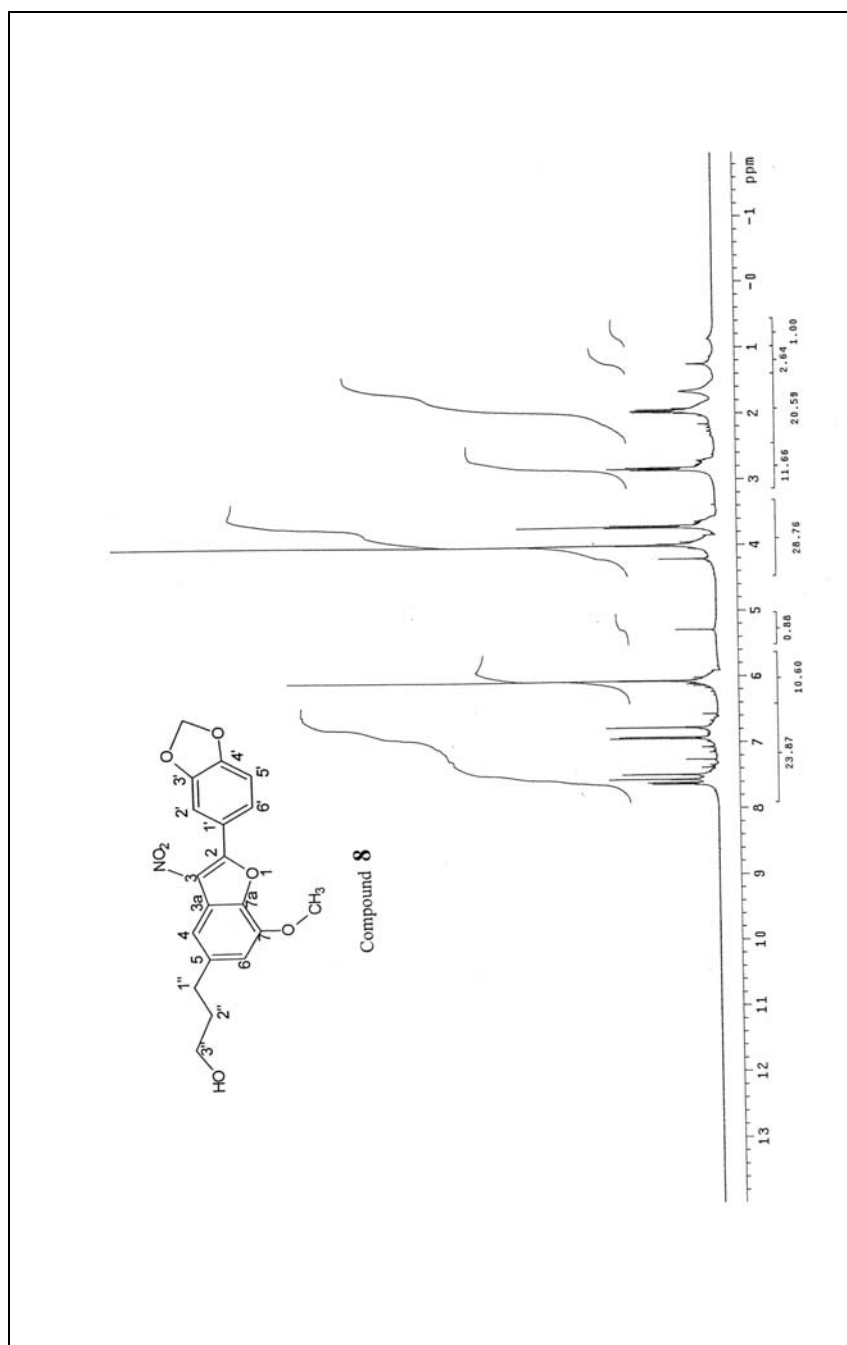


Figure 3.16. The ^1H -NMR Spectrum of Compound 8

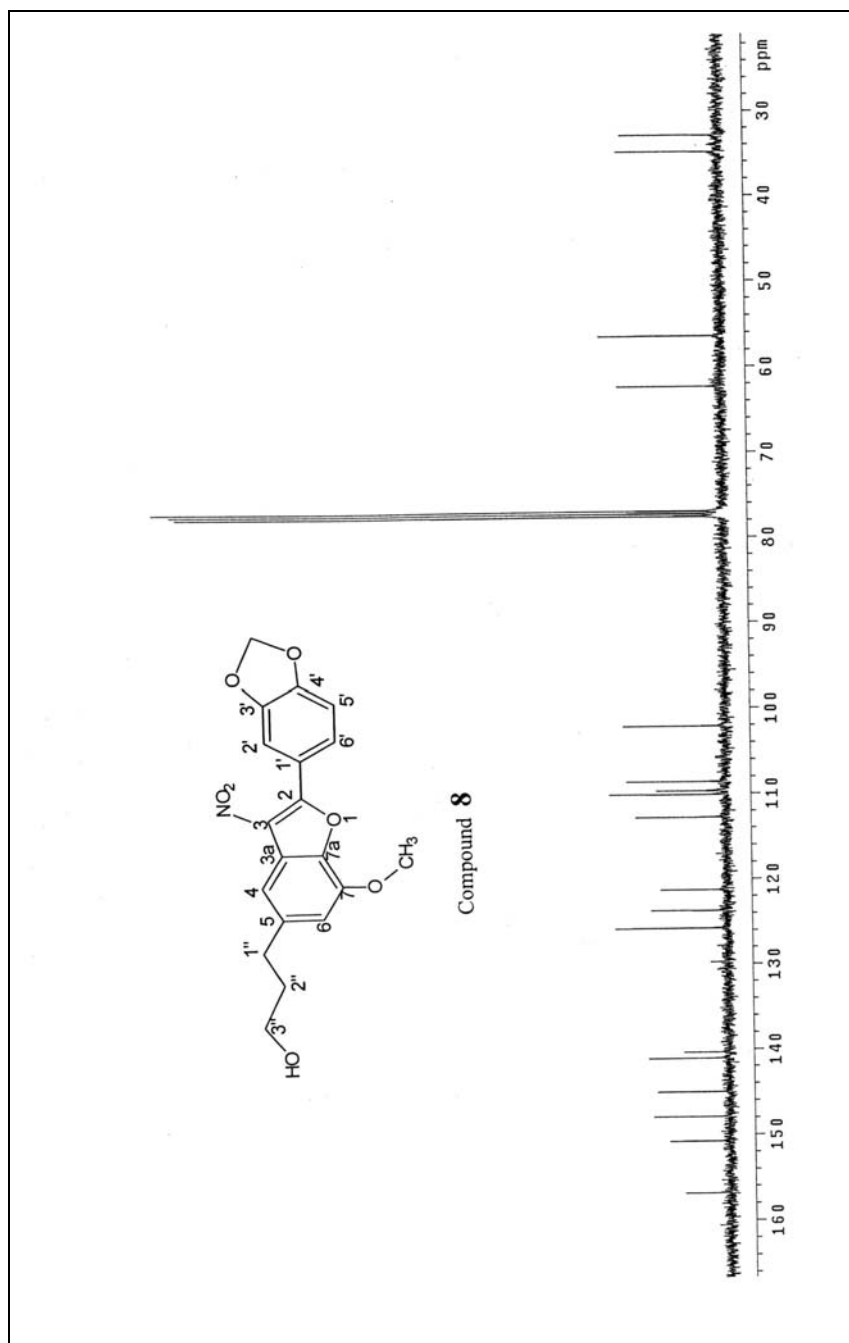


Figure 3.17. The ¹³C-NMR Spectrum of Compound **8**

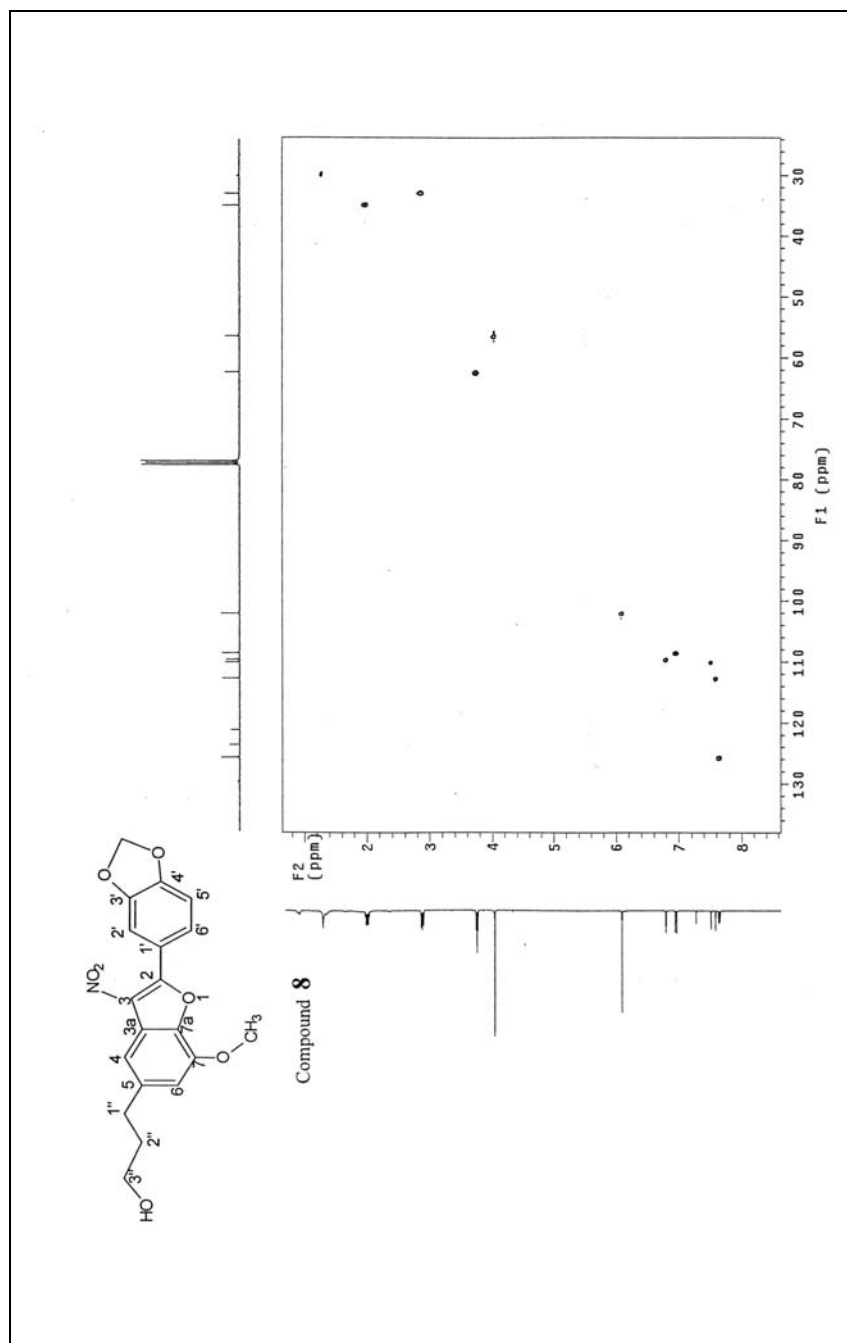
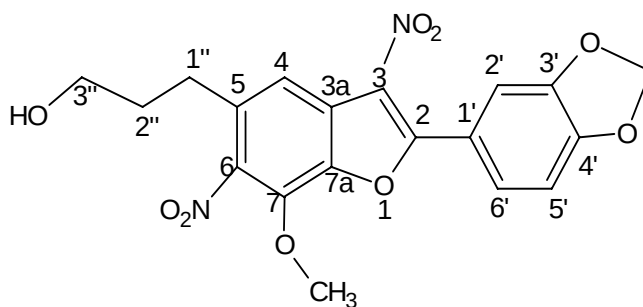


Figure 3.18. The HMQC Spectrum of Compound **8**

Table 3.11. ^1H - and ^{13}C -NMR spectroscopic data of compound **9** in CDCl_3 (δ ppm)

Position	δ ^1H (Egonol)	δ ^1H (Compound 9)	δ ^{13}C (Egonol)	δ ^{13}C (Compound 9)
2	-	-	156.51	156.94
3	6.81, s, 1H	-	100.76	125.51
3a	-	-	131.46	132.80
4	6.99, s, 1H	7.78, s, 1H	112.72	115.58
5	-	-	137.92	132.80
6	6.66, s, 1H	-	107.86	140.38
7	-	-	145.20	142.10
7a	-	-	142.88	137.20
OCH_2O	6.02, s, 2H	6.11, s, 2H	101.71	102.39
1'	-	-	125.12	120.20
2'	7.34, d, 1H, $J=1.5$	7.47, d, 1H, $J=1.6$	105.95	109.91
3'	-	-	148.46	151.62
4'	-	-	148.39	148.28
5'	6.90, d, 1H, $J=8.1$	7.00, d, 1H, $J=8.4$	109.02	108.92
6'	7.43, dd, 1H, $J=1.6, 8.1$	7.64, dd, 1H, $J=1.6, 8.0$	119.62	126.09
1''	2.81, t, 2H, $J=7.6$	2.82, t, 2H, $J=7.8$	32.83	28.13
2''	1.97, p, 2H	1.96, p, 2H	35.08	33.87
3''	3.73, t, 2H, $J=6.4$	3.71, t, 2H, $J=6.2$	62.70	62.04
OMe	4.05, s, 3H	4.30, s, 3H	56.57	61.95

**Compound 9**

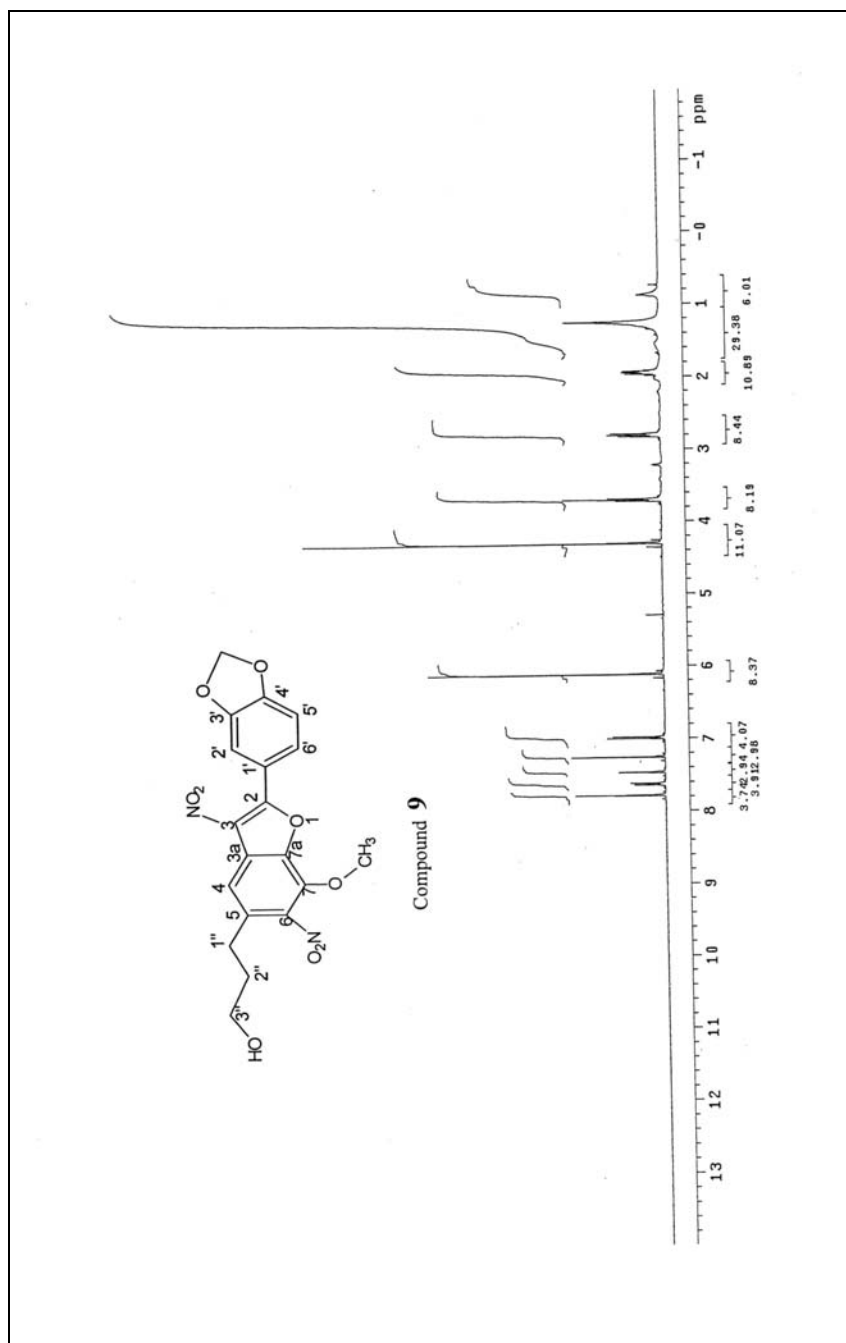


Figure 3.19. The ¹H-NMR Spectrum of Compound 9

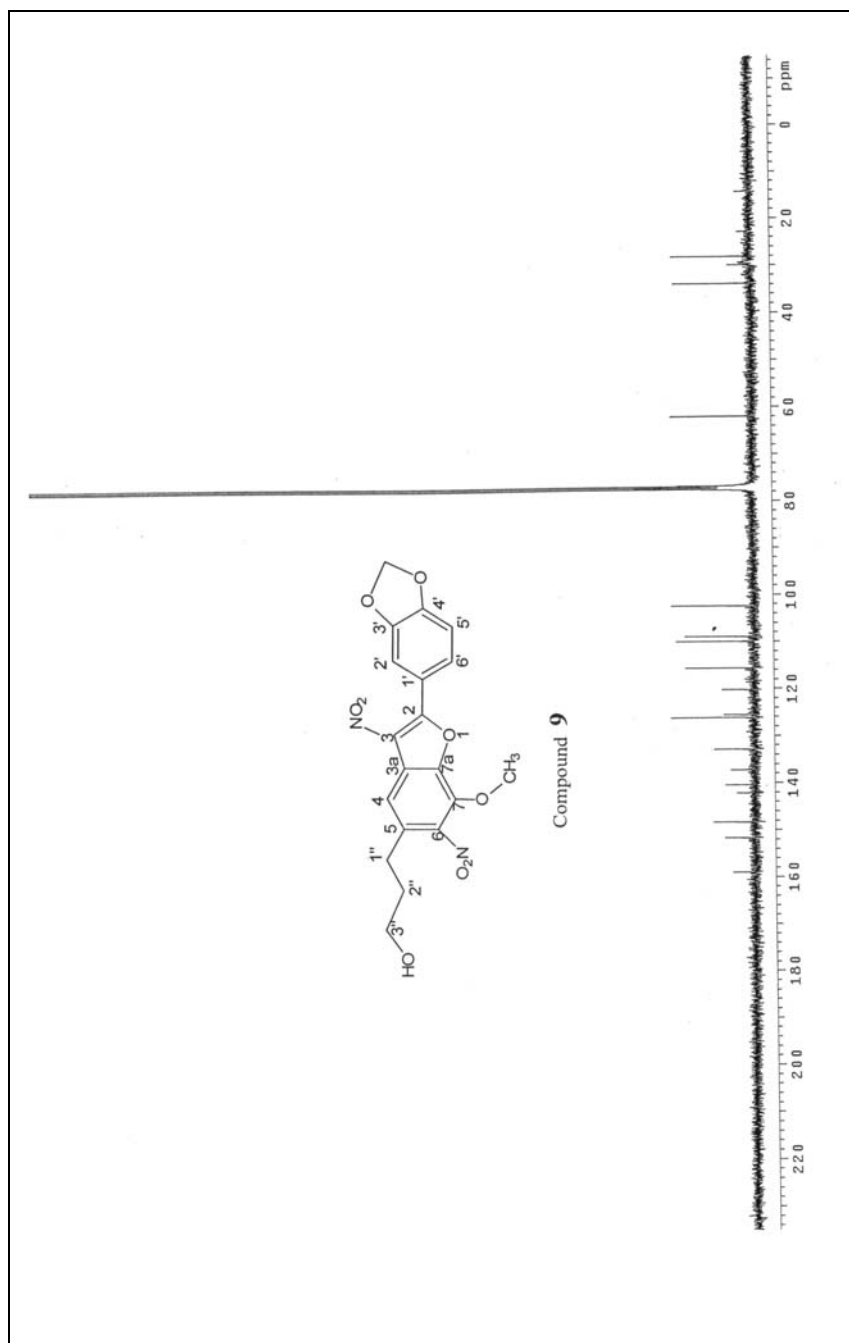


Figure 3.20. The ^{13}C -NMR Spectrum of Compound 9

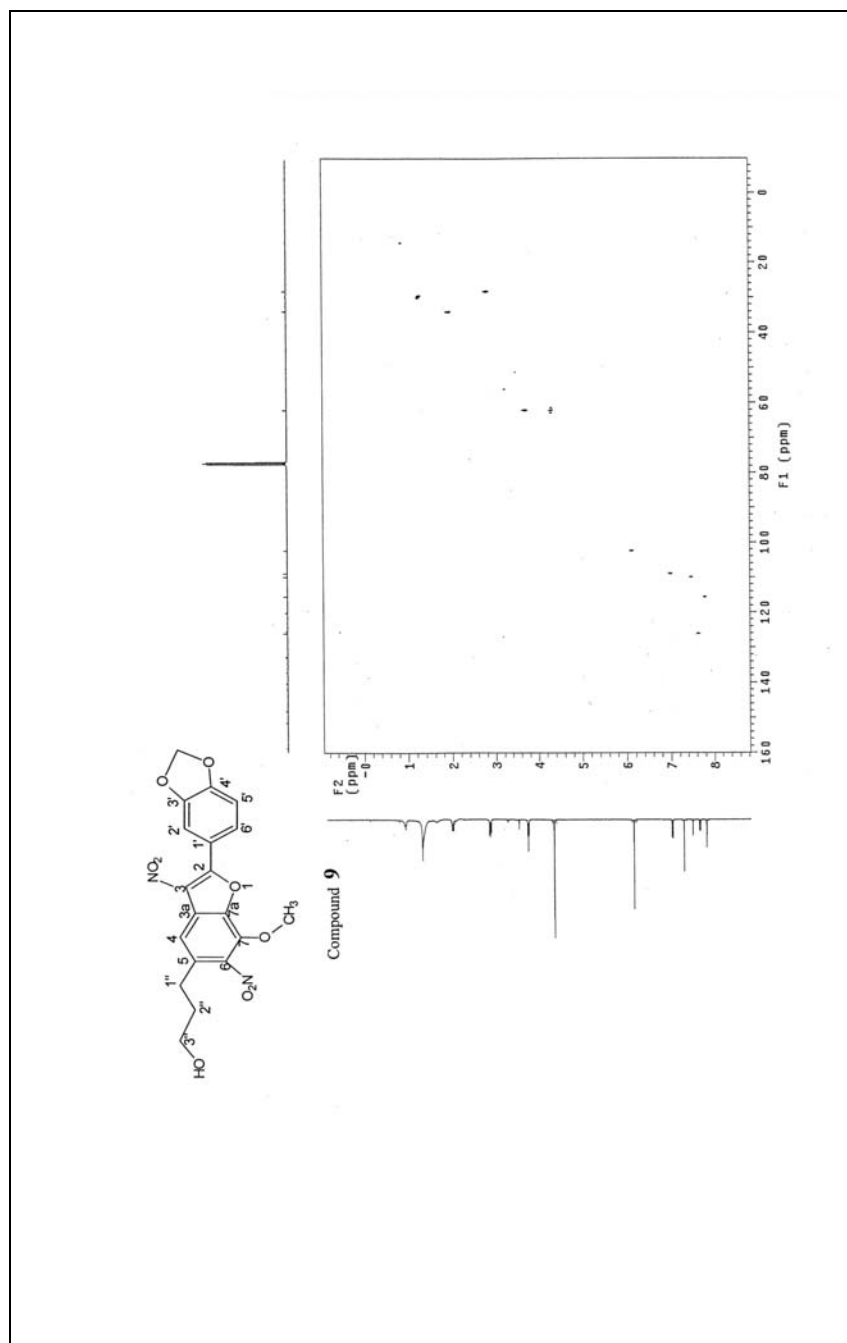
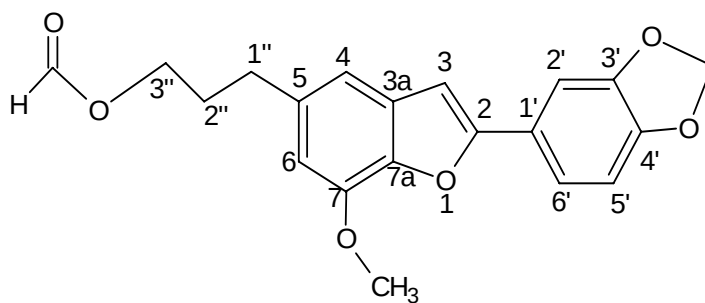


Figure 3.21. The HMQC Spectrum of Compound **9**

Table 3.12. ^1H - and ^{13}C -NMR spectroscopic data of compound **10** in CDCl_3 (δ ppm)

Position	δ ^1H (Egonol)	δ ^1H (Compound 10)	δ ^{13}C (Egonol)	δ ^{13}C (Compound 10)
2	-	-	156.51	156.43
3	6.81, s, 1H	6.78, s, 1H	100.76	100.57
3a	-	-	131.46	131.38
4	6.99, s, 1H	6.95, d, 1H, $J=1.6$ Hz	112.72	112.61
5	-	-	137.92	136.84
6	6.66, s, 1H	6.60, d, 1H, $J=1.2$	107.86	107.71
7	-	-	145.20	145.10
7a	-	-	142.88	142.83
OCH_2O	6.02, s, 2H	6.00, s, 2H	101.71	101.53
1'	-	-	125.12	124.93
2'	7.34, d, 1H, $J=1.5$	7.32, d, 1H, $J=4.0$	105.95	105.79
3'	-	-	148.46	148.30
4'	-	-	148.39	148.26
5'	6.90, d, 1H, $J=8.1$	6.87, d, 1H, $J=8.0$	109.02	108.84
6'	7.43, dd, 1H, $J=1.6, 8.1$	7.40, dd, 1H, $J=1.6, 8.0$	119.62	119.48
1''	2.81, t, 2H, $J=7.6$	2.78, t, 2H, $J=7.6$	32.83	30.82
2''	1.97, p, 2H	2.06, p, 2H	35.08	32.56
3''	3.73, t, 2H, $J=6.4$	4.23, t, 2H, $J=6.4$	62.70	63.49
OMe	4.05, s, 3H	4.03, s, 3H	56.57	56.44
$\text{HCOO}-$	-	8.09, s, 1H	-	-
C=O	-	-	-	161.29

**Compound 10**

Öztürk, S.E.; Akgül, Y. and Anıl, H., 2008, *Bioorganic & Medicinal Chemistry*, 16, 4431-4437.

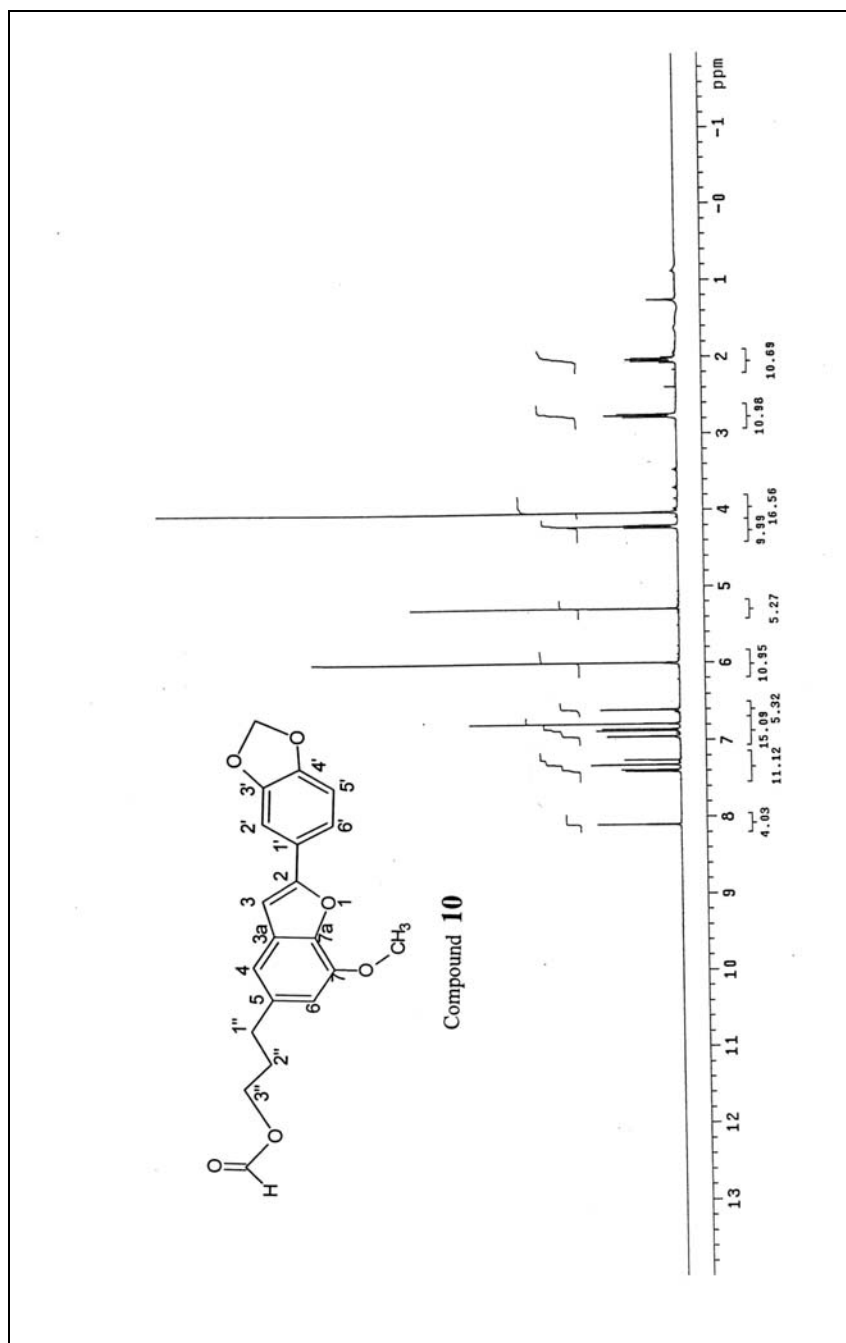


Figure 3.22. The ¹H-NMR Spectrum of Compound **10**

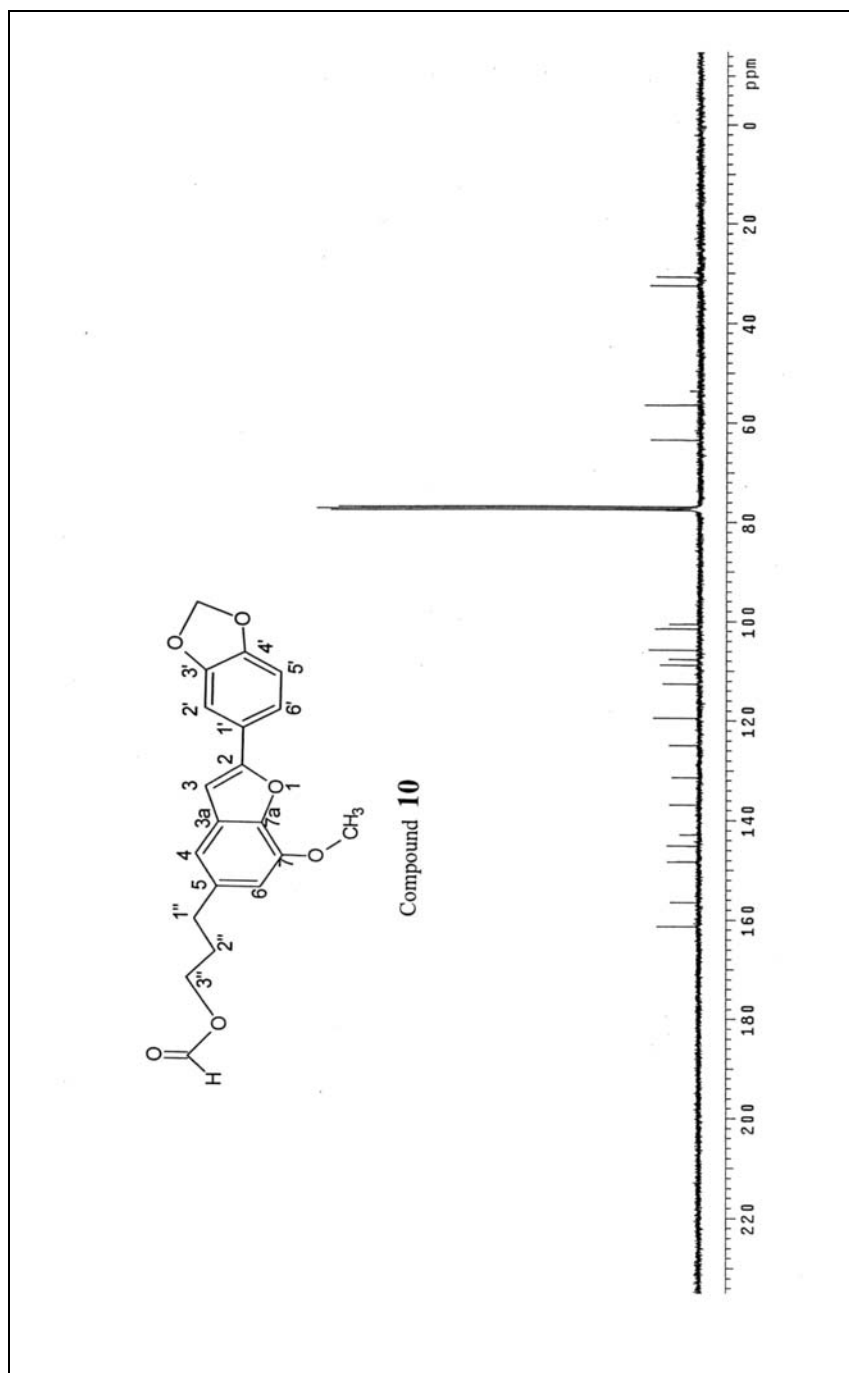


Figure 3.23. The ¹³C-NMR Spectrum of Compound **10**

Chemical structure of compound 1, showing a 17-oxoheptyl ester group attached to a benzofuran core, which is further substituted with a 2-methoxyphenyl group. The structure includes atom numbering: 1-7 for the benzofuran system and 1'-6' for the phenyl ring.

Öztürk, S.E.; Akgül, Y. and Anıl, H., 2008, *Bioorganic & Medicinal Chemistry*, 16, 4431-4437.

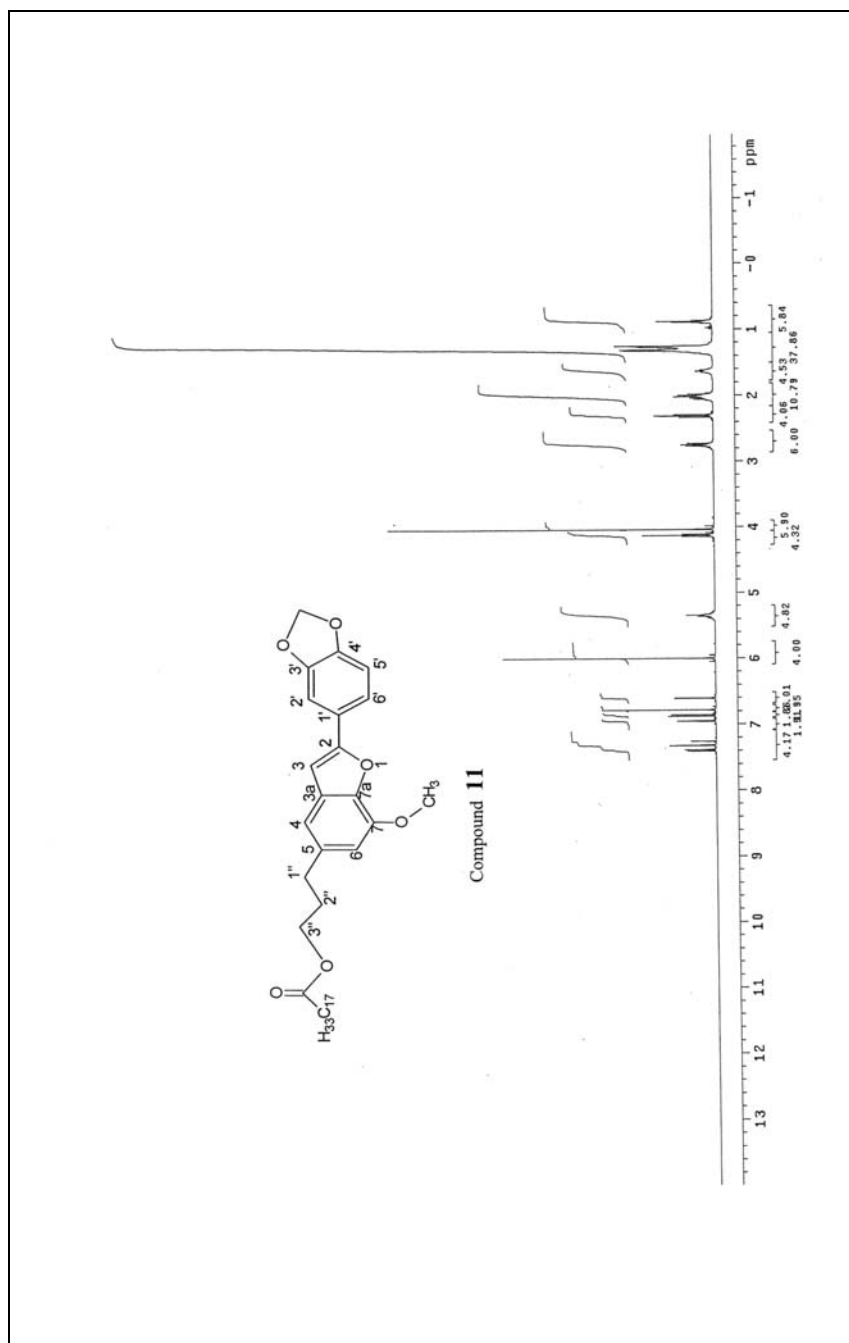


Figure 3.24. The ¹H-NMR Spectrum of Compound **11**

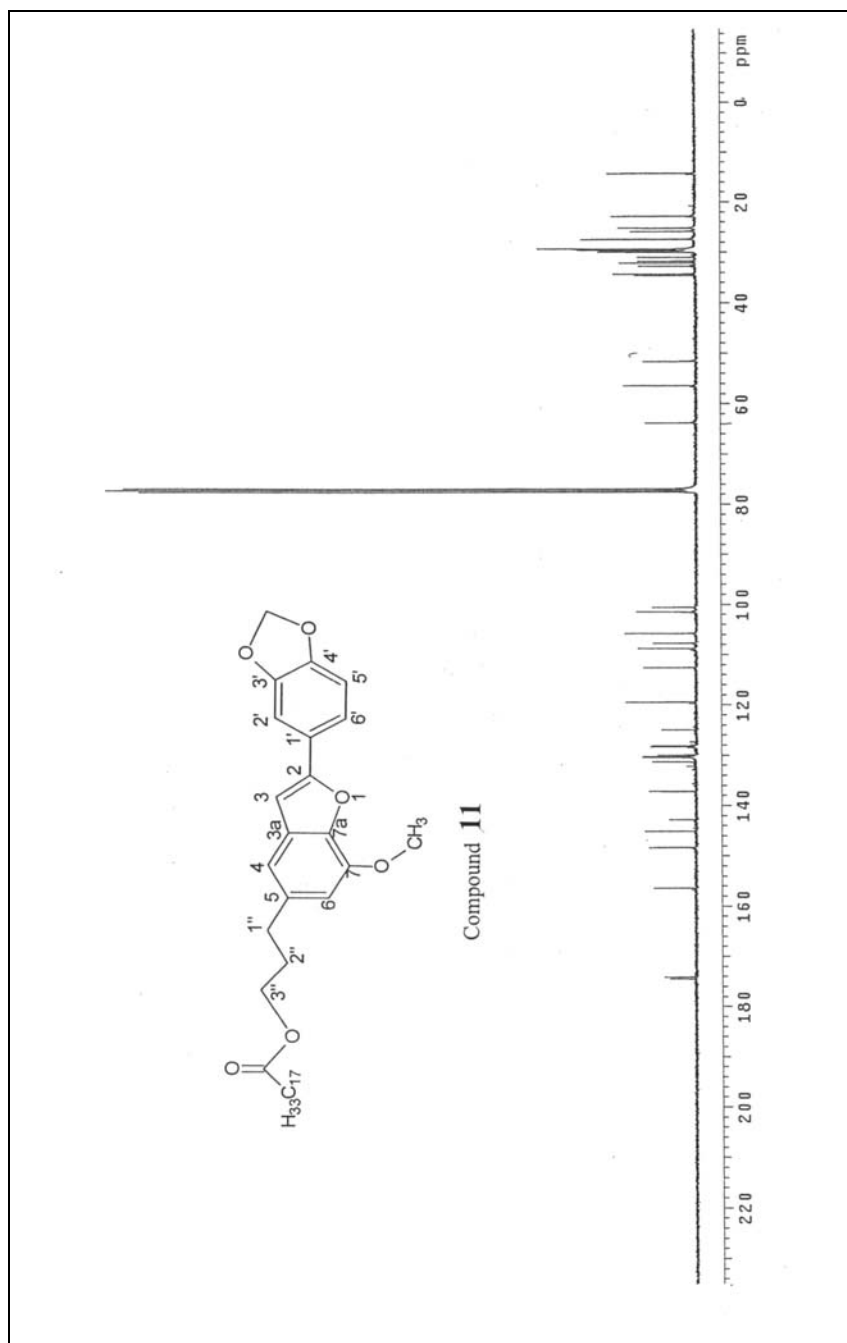


Figure 3.25. The ^{13}C -NMR Spectrum of Compound **11**

Table 3.14. ^1H - and ^{13}C -NMR spectroscopic data of compound **12** in CDCl_3 (δ ppm)

Position	δ ^1H (Egonol)	δ ^1H (Compound 12)	δ ^{13}C (Egonol)	δ ^{13}C (Compound 12)
2	-	-	156.51	156.01
3	6.81, s, 1H	6.64, s, 1H	100.76	100.77
3a	-	-	131.46	131.53
4	6.99, s, 1H	6.99, s, 1H, $J=1.2$	112.72	112.80
5	-	-	137.92	137.31
6	6.66, s, 1H	6.78, s, 1H, $J=0.8$	107.86	107.89
7	-	-	145.20	142.97
7a	-	-	142.88	125.12
OCH_2O	6.02, s, 2H	6.02, s, 2H	101.71	101.71
1'	-	-	125.12	125.12
2'	7.34, d, 1H, $J=1.5$	6.90, d, 1H, $J=0.8$	105.95	109.01
3'	-	-	148.46	148.47
4'	-	-	148.39	148.40
5'	6.90, d, 1H, $J=8.1$	6.87, d, 1H, $J=8.0$	109.02	105.96
6'	7.43, dd, 1H, $J=1.6, 8.1$	7.41, dd, 1H, $J=0.8, 6.4, 1.6$	119.62	119.63
1''	2.81, t, 2H, $J=7.6$	2.88, t, 2H, $J=7.6$	32.83	33.08
2''	1.97, p, 2H	2.18, p, 2H	35.08	31.17
3''	3.73, t, 2H, $J=6.4$	4.41, t, 2H, $J=6.4$	62.70	64.72
OMe	4.05, s, 3H	4.04, s, 3H	56.57	56.58
1'''	-	-	-	130.80
2''' and 6'''	-	7.46, 2H, $J=7.6, 7.8$	-	128.74
3''' and 5'''	-	8.07, 2H, $J=7.2$	-	129.94
4'''	-	7.58, 1H, $J=7.4$	-	133.27
$\text{C}=\text{O}$	-	-	-	167.01

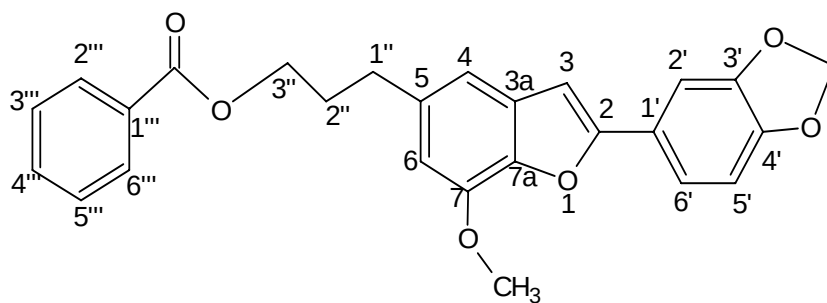
**Compound 12**

Figure 3.26. The ^1H -NMR Spectrum of Compound 12

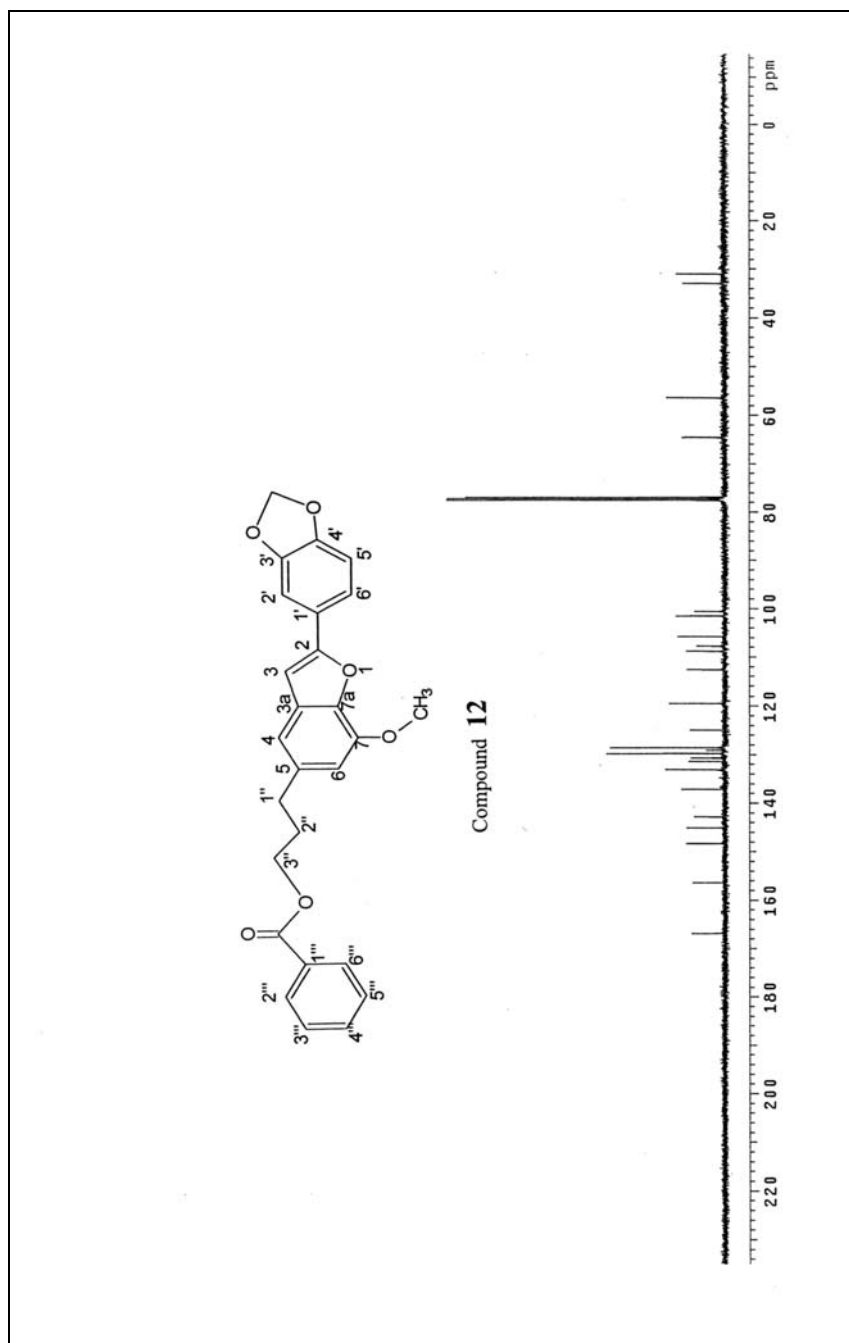
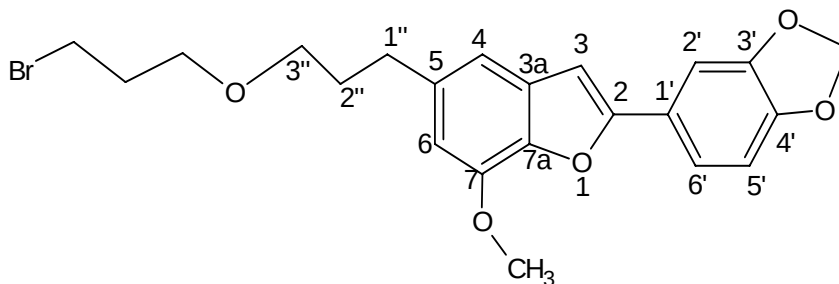


Figure 3.27. The ¹³C-NMR Spectrum of Compound 12

Table 3.15. ^1H - and ^{13}C -NMR spectroscopic data of compound **13** in CDCl_3 (δ ppm)

Position	δ ^1H (Egonol)	δ ^1H (Compound 13)	δ ^{13}C (Egonol)	δ ^{13}C (Compound 13)
2	-	-	156.51	156.29
3	6.81, s, 1H	6.79, s, 1H	100.76	100.61
3a	-	-	131.46	131.25
4	6.99, s, 1H	6.96, s, 1H	112.72	112.62
5	-	-	137.92	137.85
6	6.66, s, 1H	6.62, s, 1H	107.86	107.83
7	-	-	145.20	144.99
7a	-	-	142.88	142.72
OCH_2O	6.02, s, 2H	6.00, s, 2H	101.71	101.54
1'	-	-	125.12	125.02
2'	7.34, d, 1H, $J=1.5$	7.32, d, 1H	105.95	105.79
3'	-	-	148.46	148.28
4'	-	-	148.39	148.21
5'	6.90, d, 1H, $J=8.1$	6.87, d, 1H, $J=8.0$	109.02	108.83
6'	7.43, dd, 1H, $J=1.6, 8.1$	7.41, dd, 1H, $J=1.6, 8.0$	119.62	119.44
1''	2.81, t, 2H, $J=7.6$	2.77, t, 2H, $J=7.6$	32.83	31.95
2''	1.97, p, 2H	1.97, p, 2H	35.08	32.16
3''	3.73, t, 2H, $J=6.4$	3.48, t, 2H, $J=6.4$	62.70	68.28
OMe	4.05, s, 3H	4.03, s, 3H	56.57	56.43
Bromo- propyloxy		3.56, m, 4H; 2.12, p, 2H		70.33, 30.95

Compound **13**

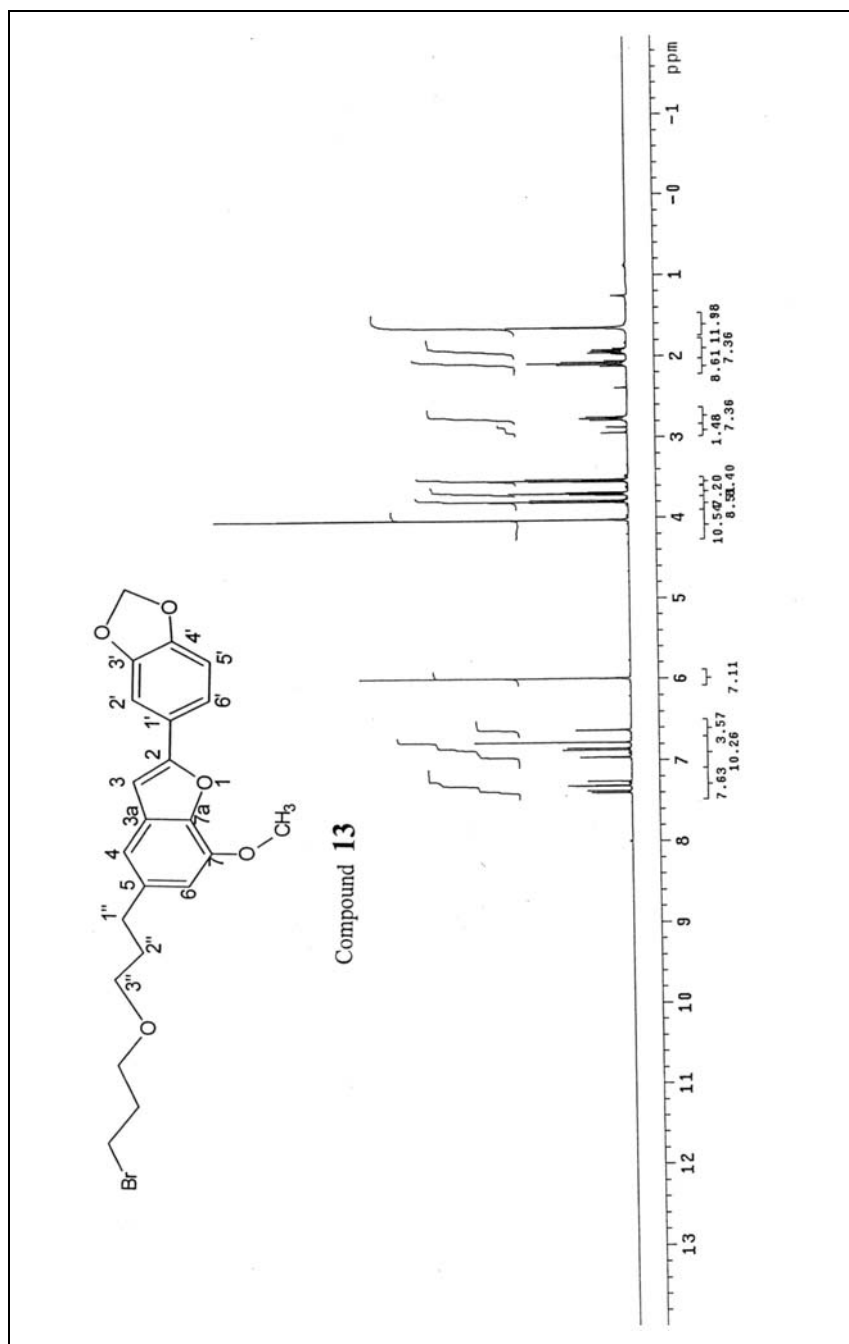


Figure 3.28. The ¹H-NMR Spectrum of Compound **13**

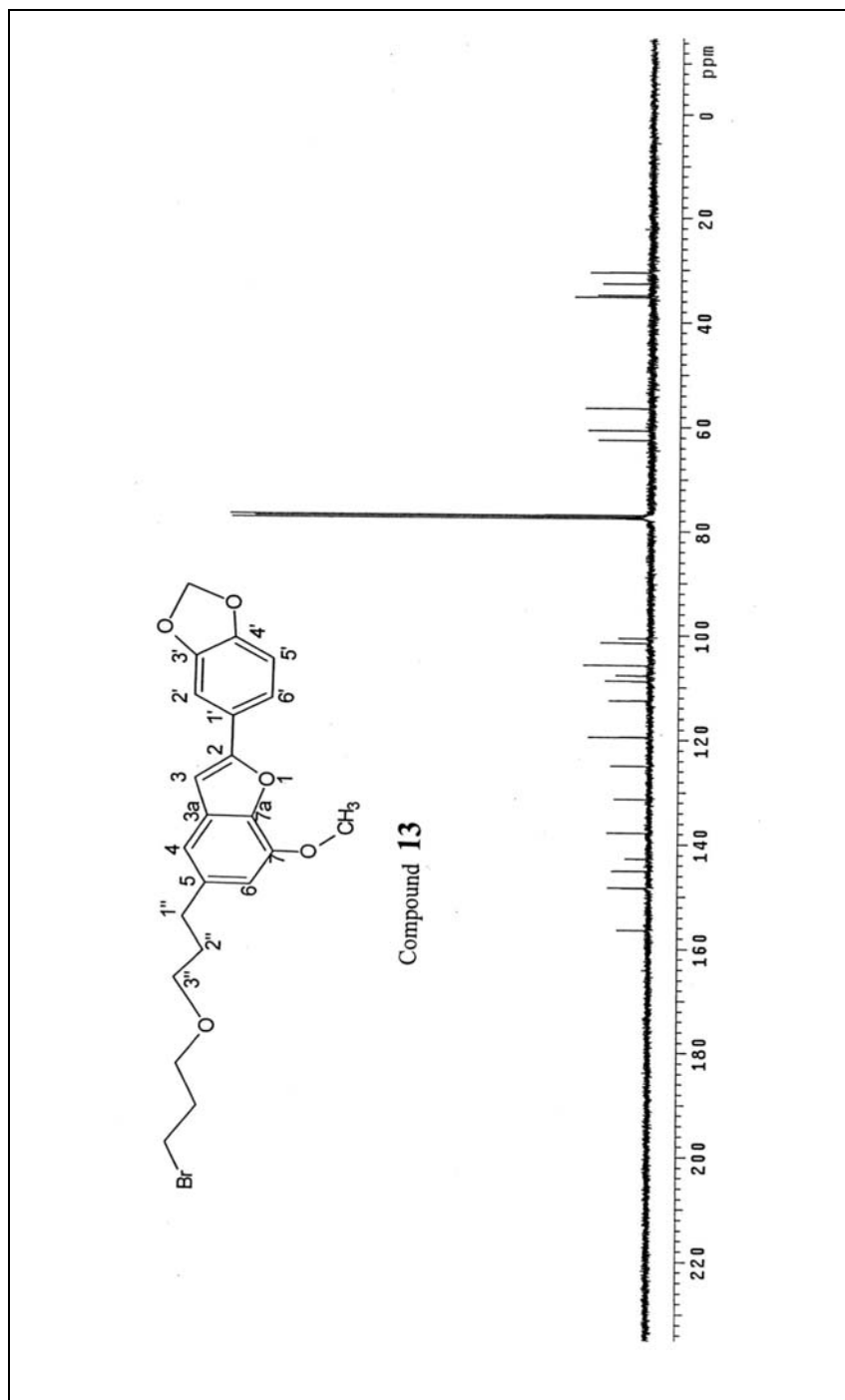


Figure 3.29. The ¹³C-NMR Spectrum of Compound 13

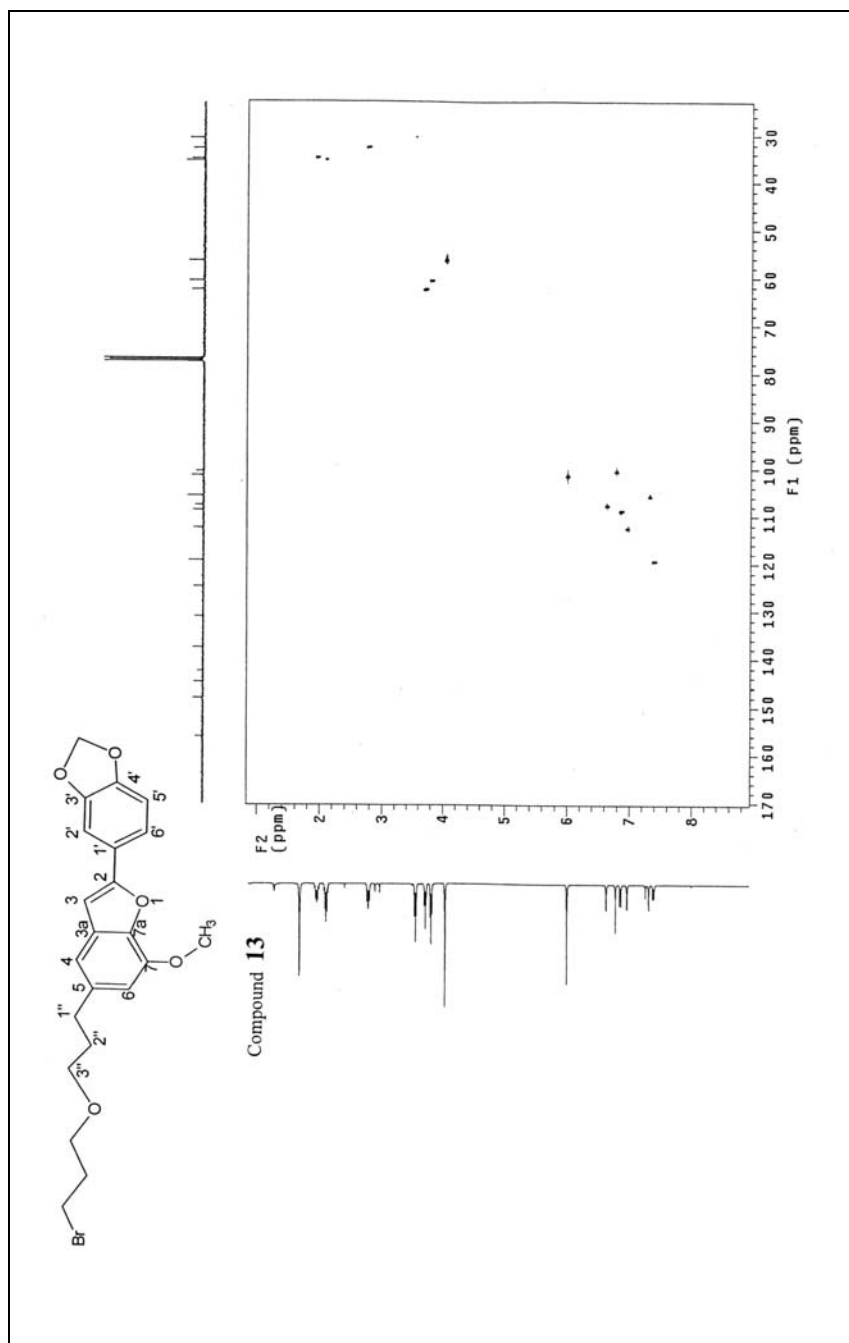


Figure 3.30. The HMQC Spectrum of Compound 13

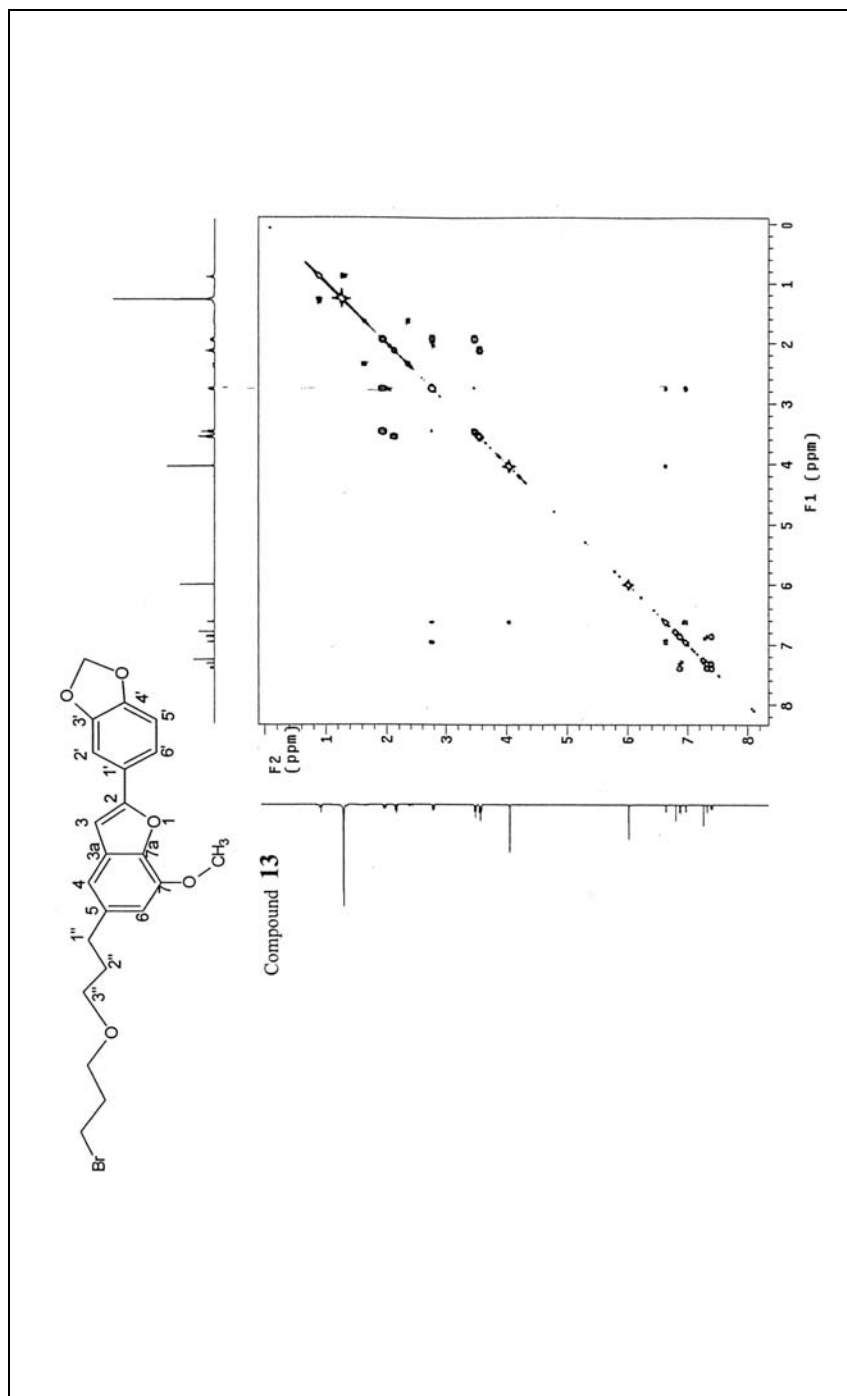
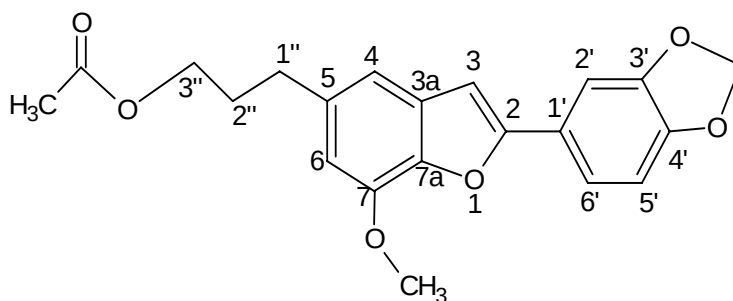


Figure 3.31. The COSY Spectrum of Compound 13

Table 3.16. ^1H -NMR spectroscopic data of compound **14** in CDCl_3 (δ ppm)

Position	δ ^1H (Egonol)	δ ^1H (Compound 14)
2	-	-
3	6.81, s, 1H	6.78, s, 1H
4	6.99, s, 1H	6.95, s, 1H
5	-	-
6	6.66, s, 1H	6.60, s, 1H, $J=1.2$
7	-	-
3a	-	-
7a	-	-
OCH_2O	6.02, s, 2H	5.99, s, 2H
1'	-	-
2'	7.34, d, 1H, $J=1.5$	7.31, d, 1H, $J=1.6$
3'	-	-
4'	-	-
5'	6.90, d, 1H, $J=8.1$	6.87, d, 1H, $J=8.4$
6'	7.43, dd, 1H, $J=1.6, 8.1$	7.40, dd, 1H, $J=1.6, 1.6$
1''	2.81, t, 2H, $J=7.6$	2.76, t, 2H, $J=7.6$
2''	1.97, p, 2H	2.03, p, 2H
3''	3.73, t, 2H, $J=6.4$	4.13, t, 2H, $J=6.4$
OMe	4.05, s, 3H	4.03, s, 3H
$\text{CH}_3\text{-CO}$	-	2.13, s, 3H

Compound **14**

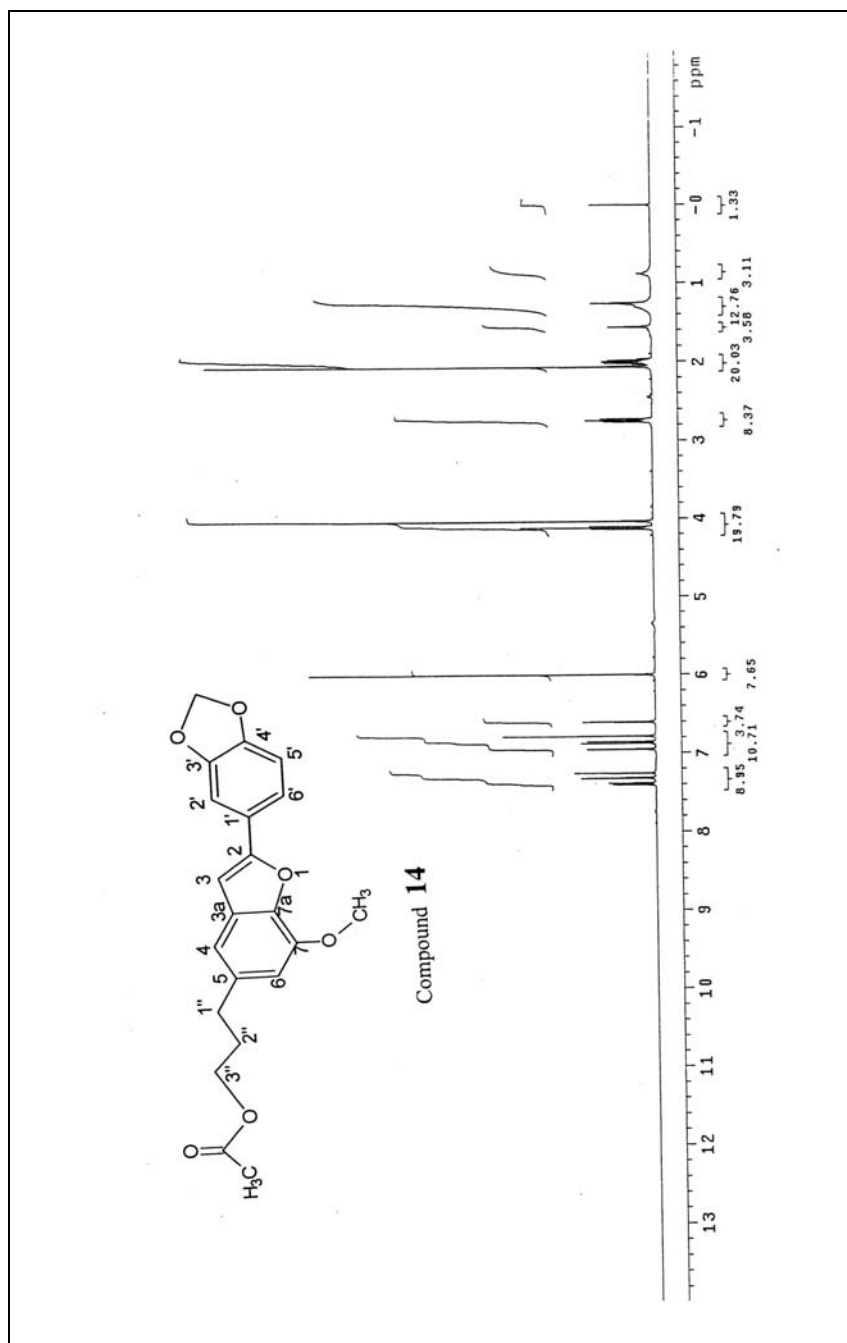
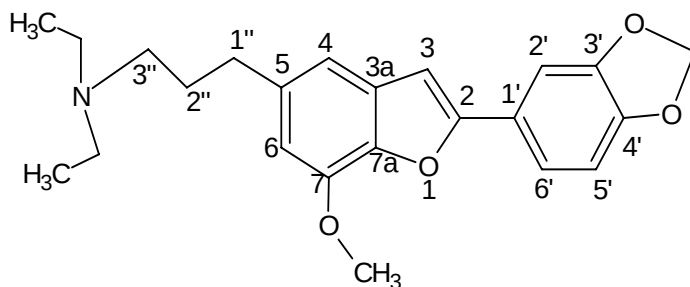


Figure 3.32. The ¹H-NMR Spectrum of Compound **14**

Table 3.17. ^1H - and ^{13}C -NMR spectroscopic data of compound **15** in CDCl_3 (δ ppm)

Position	δ ^1H (Compound 2)	δ ^1H (Compound 15)	δ ^{13}C (Compound 2)	δ ^{13}C (Compound 15)
2	-	-	156.43	156.58
3	6.77, s, 1H	6.77, s, 1H	100.56	100.51
3a	-	-	131.38	131.45
4	6.96, s, 1H	6.94, d, 1H, $J=1.6$ Hz	112.78	112.57
5	-	-	136.58	135.92
6	6.62, s, 1H	6.62, d, 1H, $J=1.2$	107.82	107.48
7	-	-	145.27	145.28
7a	-	-	142.84	142.93
OCH_2O	6.00, s, 2H	5.99, s, 2H	101.53	101.55
1'	-	-	124.92	124.80
2'	7.32, d, 1H, $J=4.0$	7.31, d, 1H, $J=1.6$	105.78	105.79
3'	-	-	148.32	148.33
4'	-	-	148.27	148.33
5'	6.88, d, 1H, $J=8.0$	6.87, d, 1H, $J=8.4$	108.84	108.86
6'	7.41, dd, 1H, $J=8.0, 2.0$	7.40, dd, 1H, $J=1.6, 8.0$	119.47	119.51
1''	2.86, t, 2H, $J=7.2$	2.87, m, 2H, $J=8.0, 8.0$	33.27	33.52
2''	2.16, p, 2H	2.14, 2H	34.68	26.05
3''	3.57, t, 2H, $J=6.6$	2.77, t, 2H, $J=7.2$	44.46	51.12
OMe	4.04, s, 3H	4.03, s, 3H	56.4	56.58
$\text{CH}_3\text{CH}_2\text{N-}$	-	-	-	9.34
$\text{CH}_3\text{CH}_2\text{N-}$	-	-	-	46.75
$\text{CH}_3\text{CH}_2\text{N-}$	-	1.27, 6H, $J=7.2, 2.8$	-	-
$\text{CH}_3\text{CH}_2\text{N-}$	-	2.98, 4H	-	-

**Compound 15**

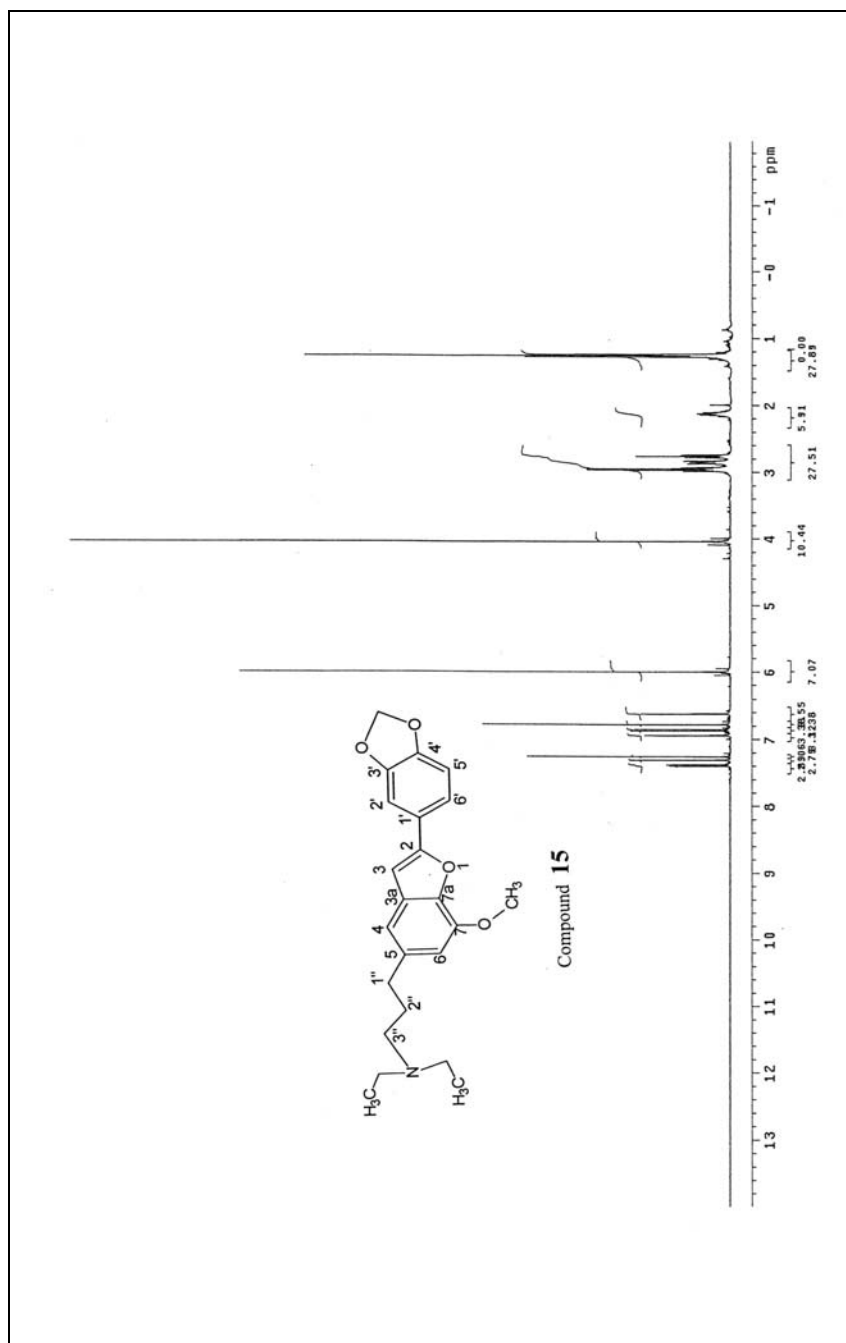


Figure 3.33. The ^1H -NMR Spectrum of Compound **15**

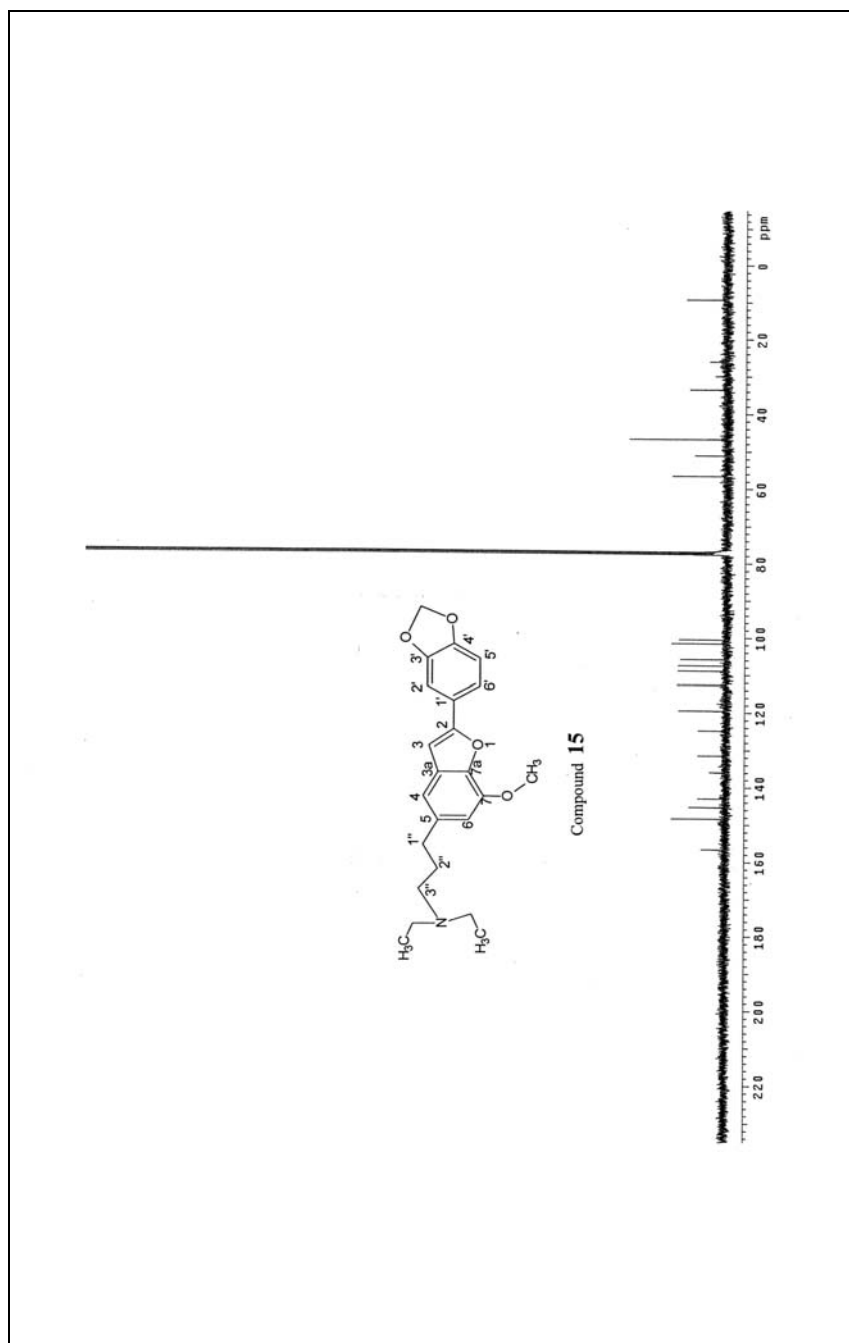
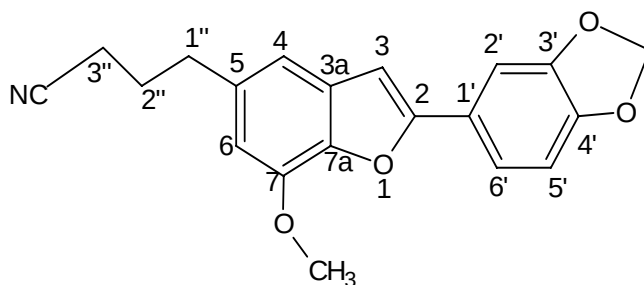


Figure 3.34. The ^{13}C -NMR Spectrum of Compound **15**

Table 3.18. ^1H - and ^{13}C -NMR spectroscopic data of compound **16** in CDCl_3 (δ ppm)

Position	δ ^1H (Compound 2)	δ ^1H (Compound 16)	δ ^{13}C (Compound 2)	δ ^{13}C (Compound 16)
2	-	-	156.43	156.59
3	6.77, s, 1H	6.78, s, 1H	100.56	100.51
3a	-	-	131.38	131.49
4	6.96, s, 1H	6.95, s, 1H	112.78	112.78
5	-	-	136.58	135.60
6	6.62, s, 1H	6.60, s, 1H	107.82	107.59
7	-	-	145.27	145.26
7a	-	-	142.84	142.97
OCH_2O	6.00, s, 2H	5.99, s, 2H	101.53	101.57
1'	-	-	124.92	124.80
2'	7.32, d, 1H, $J=4.0$	7.32, d, 1H, $J=1.2$	105.78	105.82
3'	-	-	148.32	148.34
4'	-	-	148.27	148.34
5'	6.88, d, 1H, $J=8.0$	6.87, d, 1H, $J=8.1$	108.84	108.86
6'	7.41, dd, 1H, $J=8.0, 2.0$	7.40, dd, 1H, $J=1.2, 7.8$	119.47	119.51
1''	2.86, t, 2H, $J=7.2$	2.33, t, 2H, $J=7.2$	33.27	34.87
2''	2.16, p, 2H	2.02, p, 2H	34.68	27.53
3''	3.57, t, 2H, $J=6.6$	2.83, t, 2H, $J=7.4$	44.46	16.54
OMe	4.04, s, 3H	4.03, s, 3H	56.4	56.48
CN	-	-	-	119.81

Compound **16**

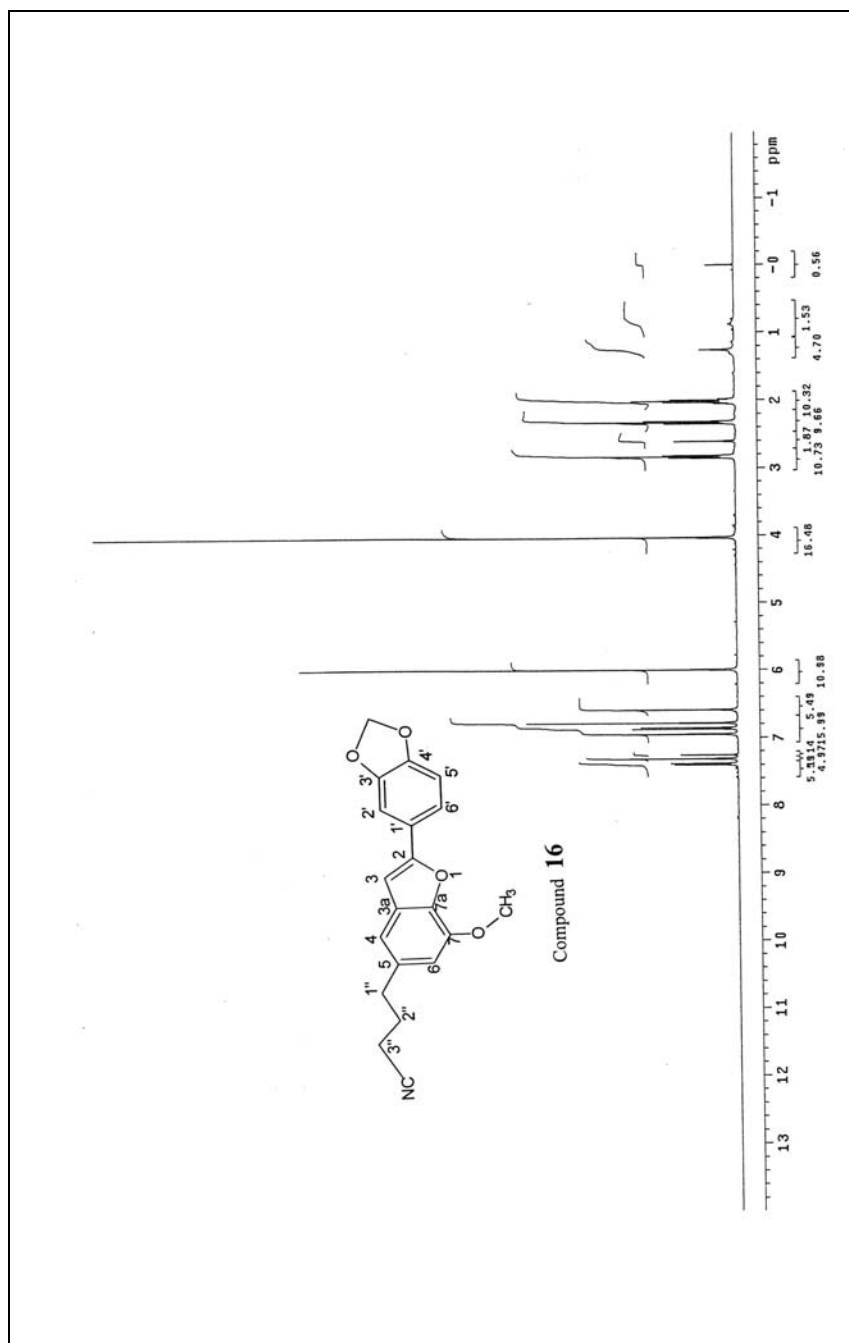


Figure 3.35. The ¹H-NMR Spectrum of Compound 16

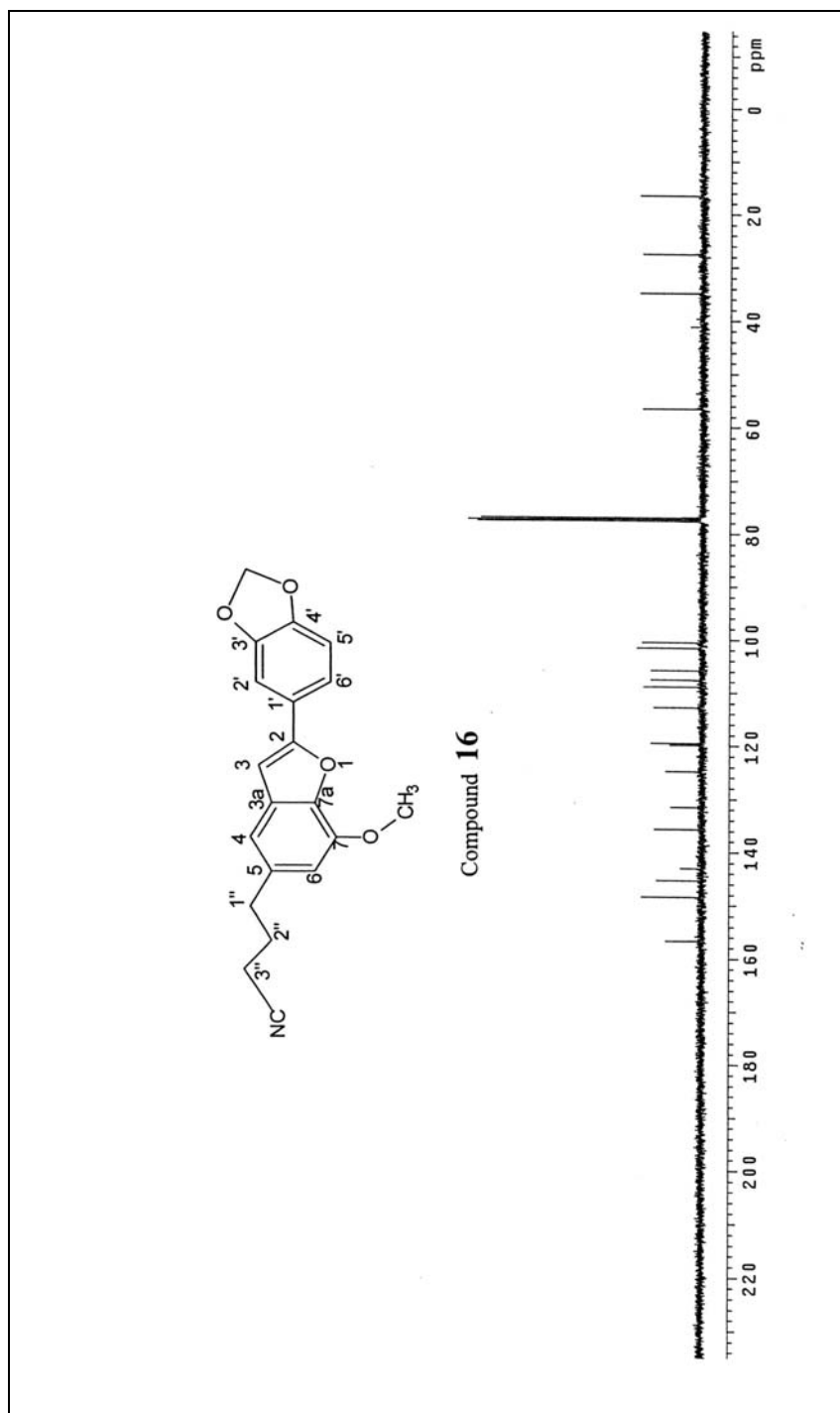
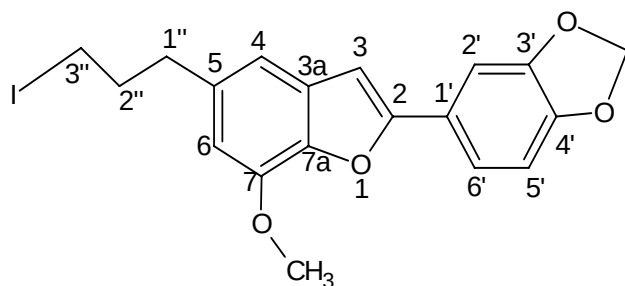


Figure 3.36. The ¹³C-NMR Spectrum of Compound **16**

Table 3.19. ^1H - and ^{13}C -NMR spectroscopic data of compound **17** in CDCl_3 (δ ppm)

Position	δ ^1H (Compound 2)	δ ^1H (Compound 17)	δ ^{13}C (Compound 2)	δ ^{13}C (Compound 17)
2	-	-	156.43	156.44
3	6.77, s, 1H	6.79, s, 1H	100.56	100.56
3a	-	-	131.38	131.37
4	6.96, s, 1H	6.88, s, 1H	112.78	112.79
5	-	-	136.58	136.28
6	6.62, s, 1H	6.62, d, 1H, $J=0.8$	107.82	107.83
7	-	-	145.27	145.10
7a	-	-	142.84	145.10
OCH_2O	6.00, s, 2H	6.00, s, 2H	101.53	101.54
1'	-	-	124.92	124.91
2'	7.32, d, 1H, $J=4.0$	7.32, d, 1H, $J=1.6$	105.78	105.79
3'	-	-	148.32	148.31
4'	-	-	148.27	148.27
5'	6.88, d, 1H, $J=8.0$	6.88, d, 1H, $J=8.4$	108.84	108.85
6'	7.41, dd, 1H, $J=8.0, 2.0$	7.39, dd, 1H, $J=1.2, 7.8$	119.47	119.47
1''	2.86, t, 2H, $J=7.2$	2.79, t, 2H, $J=7.2$	33.27	36.67
2''	2.16, p, 2H	2.17, p, 2H	34.68	35.50
3''	3.57, t, 2H, $J=6.6$	3.19, t, 2H, $J=7.0$	44.46	6.72
OMe	4.04, s, 3H	4.04, s, 3H	56.4	56.45

**Compound 17**

Öztürk, S.E.; Akgül, Y. and Anıl, H., 2008, *Bioorganic & Medicinal Chemistry*, 16, 4431-4437.

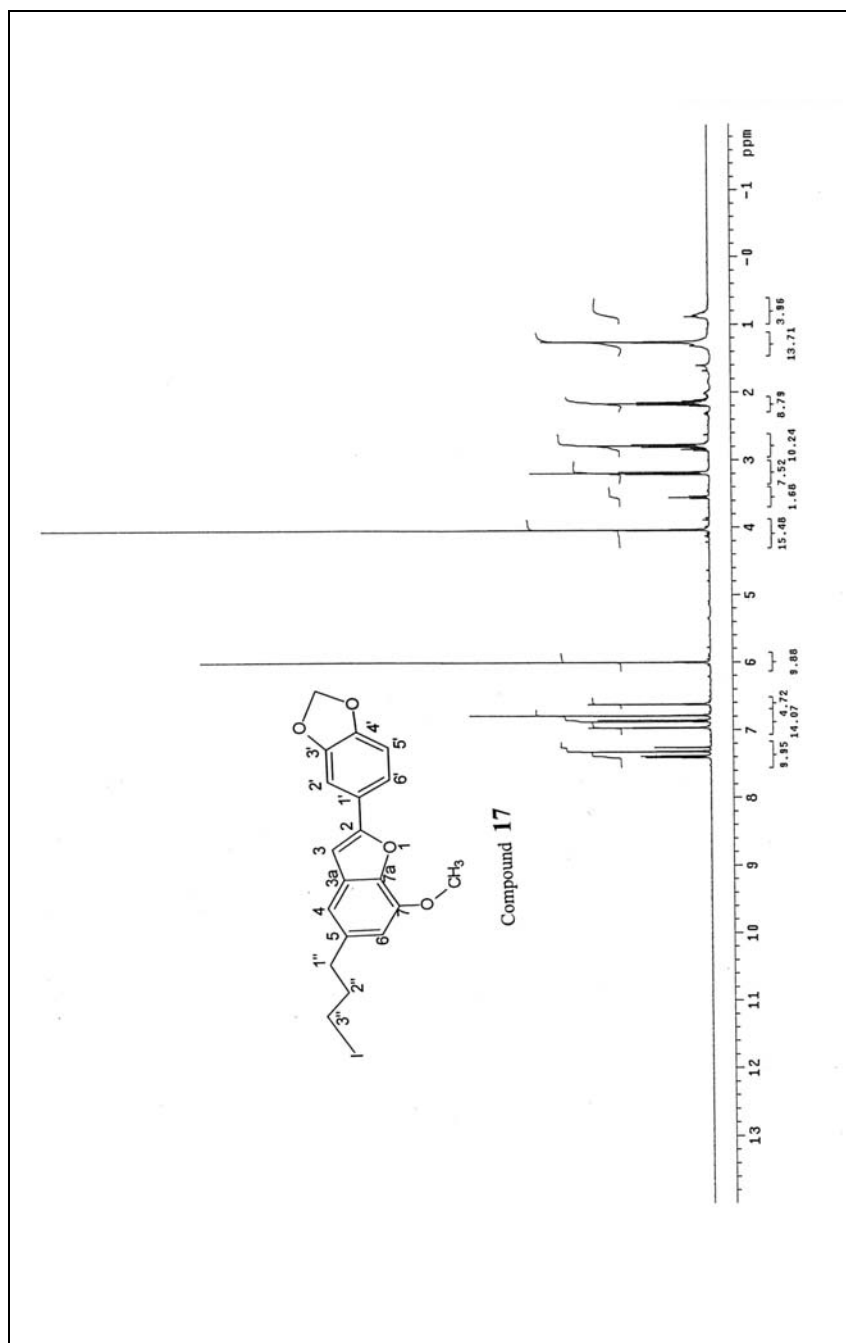


Figure 3.37. The ^1H -NMR Spectrum of Compound 17

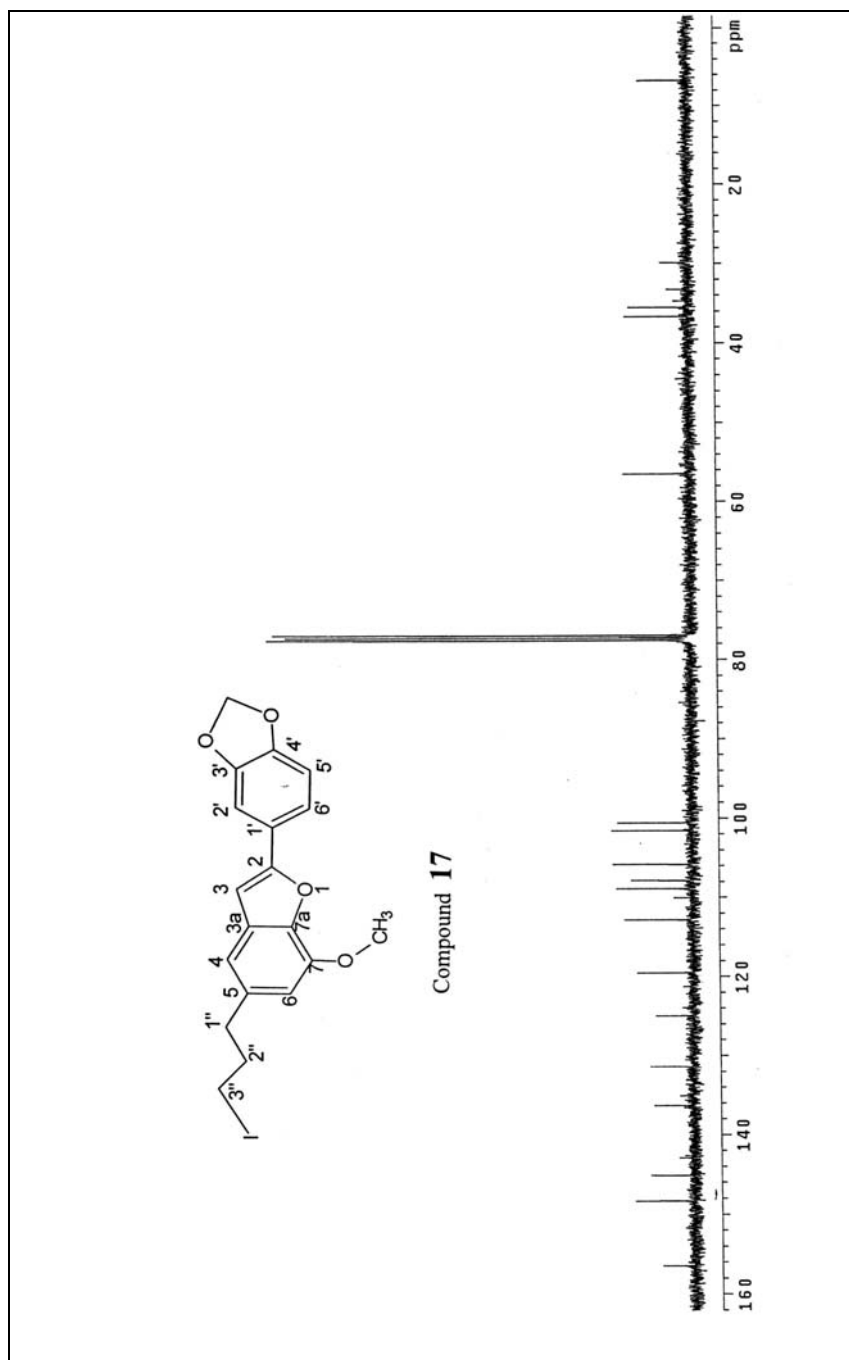
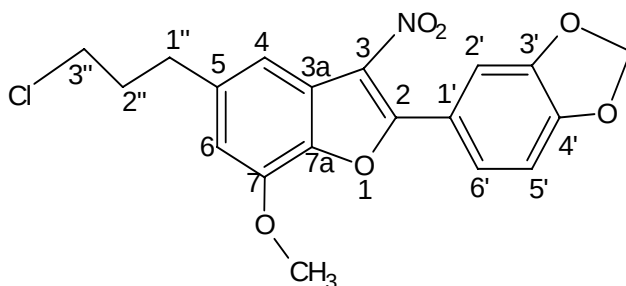


Figure 3.38. The ^{13}C -NMR Spectrum of Compound **17**

Table 3.20. ^1H - and ^{13}C -NMR spectroscopic data of compound **18** in CDCl_3 (δ ppm)

Position	δ ^1H (Compound 2)	δ ^1H (Compound 18)	δ ^{13}C (Compound 2)	δ ^{13}C (Compound 18)
2	-	-	156.43	156.91
3	6.77, s, 1H	-	100.56	140.48
3a	-	-	131.38	139.85
4	6.96, s, 1H	7.57, 1H	112.78	112.92
5	-	-	136.58	123.84
6	6.62, s, 1H	6.77, 1H	107.82	109.74
7	-	-	145.27	147.96
7a	-	-	142.84	145.09
OCH_2O	6.00, s, 2H	6.07, s, 2H	101.53	102.11
1'	-	-	124.92	121.21
2'	7.32, d, 1H, $J=4.0$	7.50, d, 1H, $J=2.0$	105.78	110.12
3'	-	-	148.32	150.83
4'	-	-	148.27	150.83
5'	6.88, d, 1H, $J=8.0$	6.95, d, 1H, $J=8.4$	108.84	108.62
6'	7.41, dd, 1H, $J=8.0, 2.0$	7.64, dd, 1H, $J=1.6, 2.0$	119.47	125.79
1''	2.86, t, 2H, $J=7.2$	2.93, t, 2H, $J=7.6$	33.27	33.54
2''	2.16, p, 2H	2.19, p, 2H	34.68	34.57
3''	3.57, t, 2H, $J=6.6$	3.58, t, 2H, $J=6.4$	44.46	44.31
OMe	4.04, s, 3H	4.02, s, 3H	56.4	56.45

Compound **18**

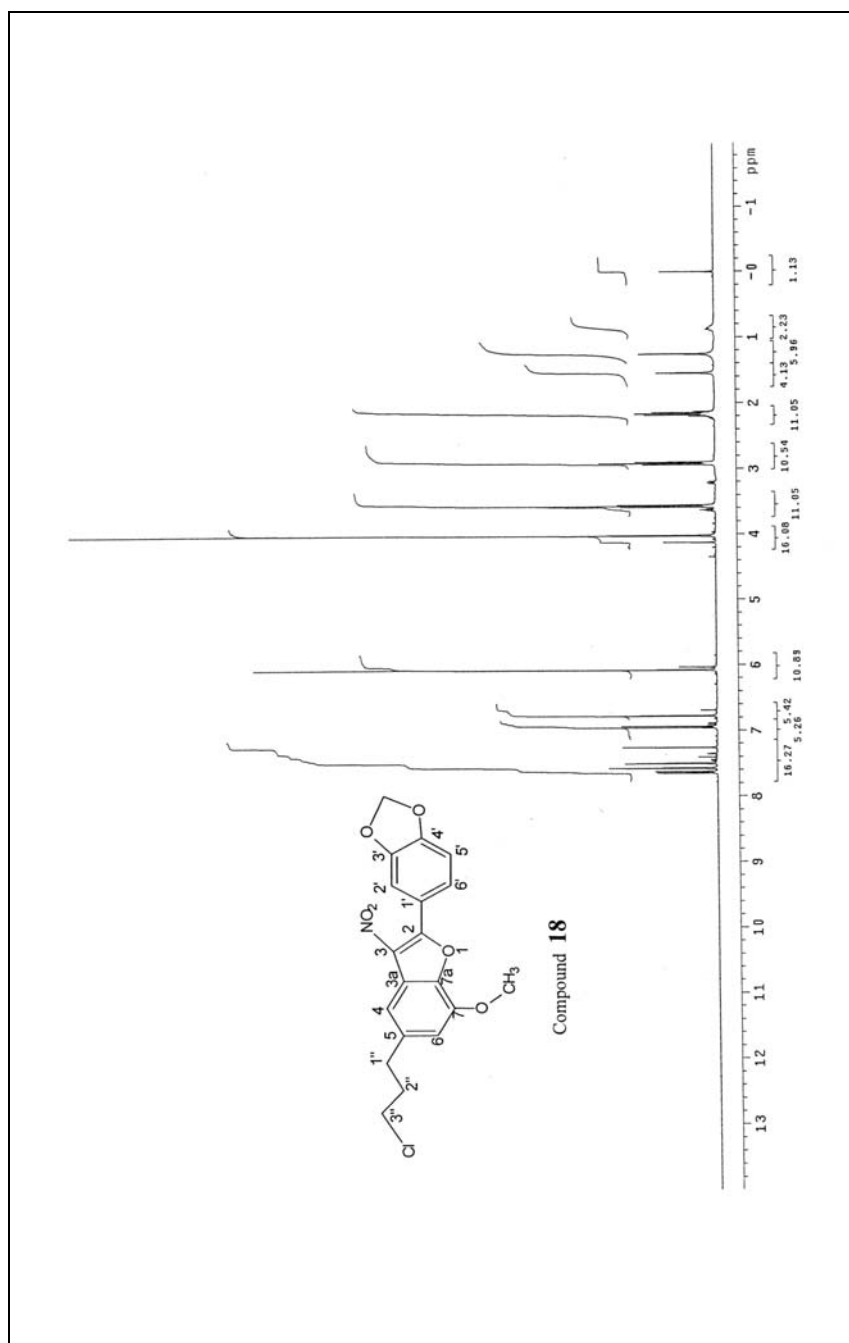


Figure 3.39. The ¹H-NMR Spectrum of Compound **18**

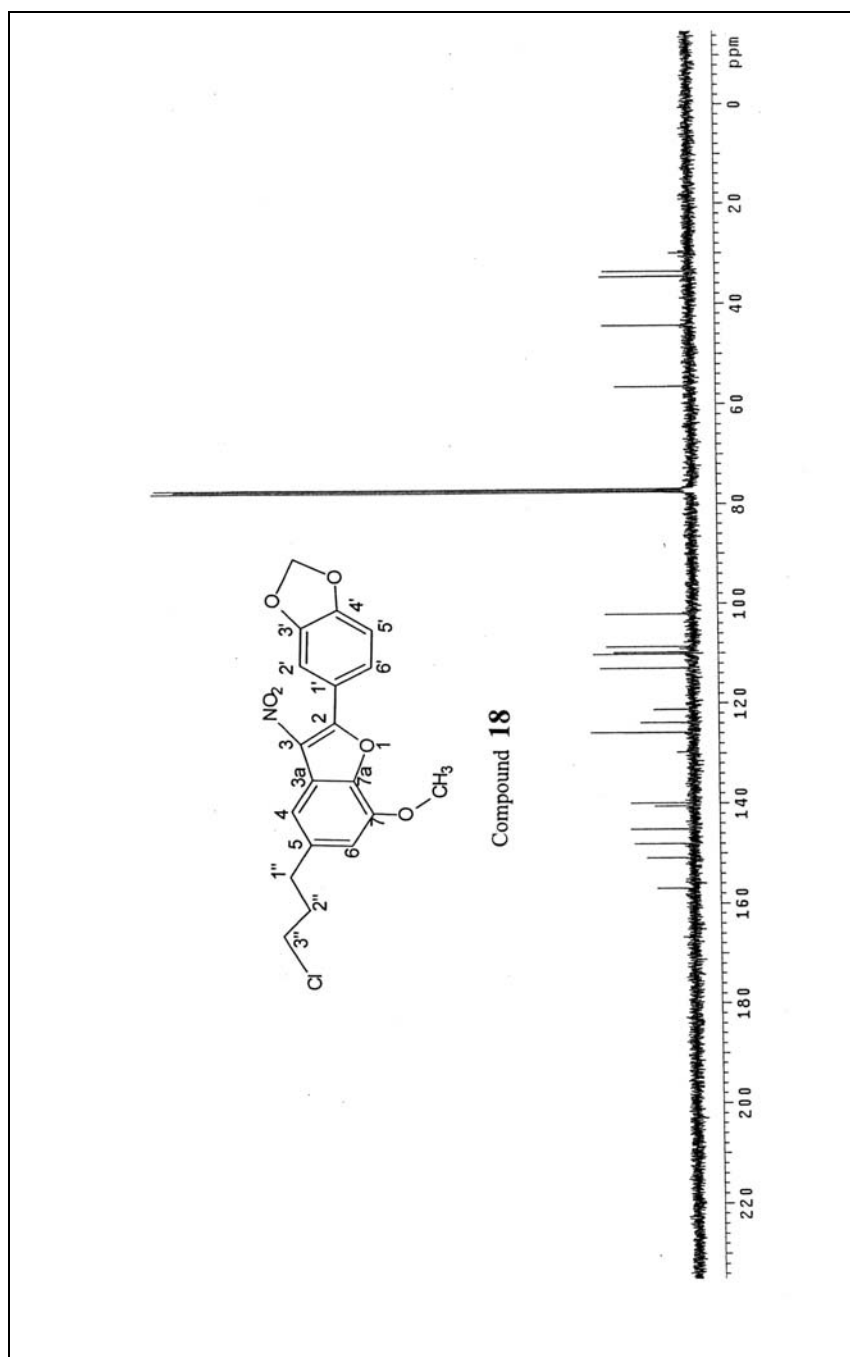
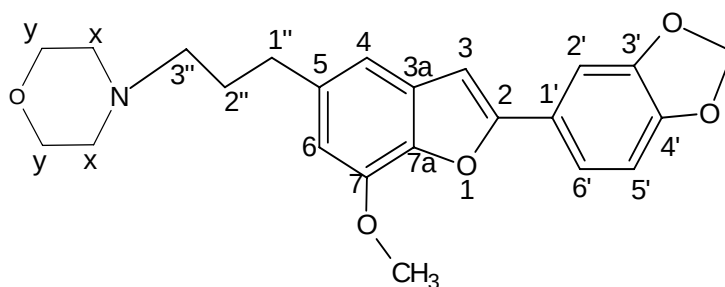


Figure 3.40. The ^{13}C -NMR Spectrum of Compound **18**

Table 3.21. ^1H - and ^{13}C -NMR spectroscopic data of compound **19** in CDCl_3 (δ ppm)

Position	δ ^1H (Compound 2)	δ ^1H (Compound 19)	δ ^{13}C (Compound 2)	δ ^{13}C (Compound 19)
2	-	-	156.43	156.31
3	6.77, s, 1H	6.86, s, 1H	100.56	100.58
3a	-	-	131.38	131.24
4	6.96, s, 1H	7.24, s, 1H	112.78	112.51
5	-	-	136.58	137.94
6	6.62, s, 1H	6.53	107.82	107.78
7	-	-	145.27	144.97
7a	-	-	142.84	142.71
OCH_2O	6.00, s, 2H	5.91, s, 2H	101.53	101.51
1'	-	-	124.92	124.98
2'	7.32, d, 1H, $J=4.0$	6.70, 1H	105.78	105.77
3'	-	-	148.32	148.29
4'	-	-	148.27	148.21
5'	6.88, d, 1H, $J=8.0$	6.79, d, 1H, $J=8.4$	108.84	108.83
6'	7.41, dd, 1H, $J=8.0, 2.0$	7.32, dd, 1H, $J=0.8, 7.2$	119.47	119.43
1''	2.86, t, 2H, $J=7.2$	2.33, t, 2H, $J=7.6$	33.27	29.91
2''	2.16, p, 2H	1.81, p, 2H	34.68	34.14
3''	3.57, t, 2H, $J=6.6$	2.64, t, 2H, $J=6.6$	44.46	56.39
OMe	4.04, s, 3H	3.94, s, 3H	56.4	58.55
x		2.38, 4H		53.93
y		3.66, 4H		67.15

**Compound 19**

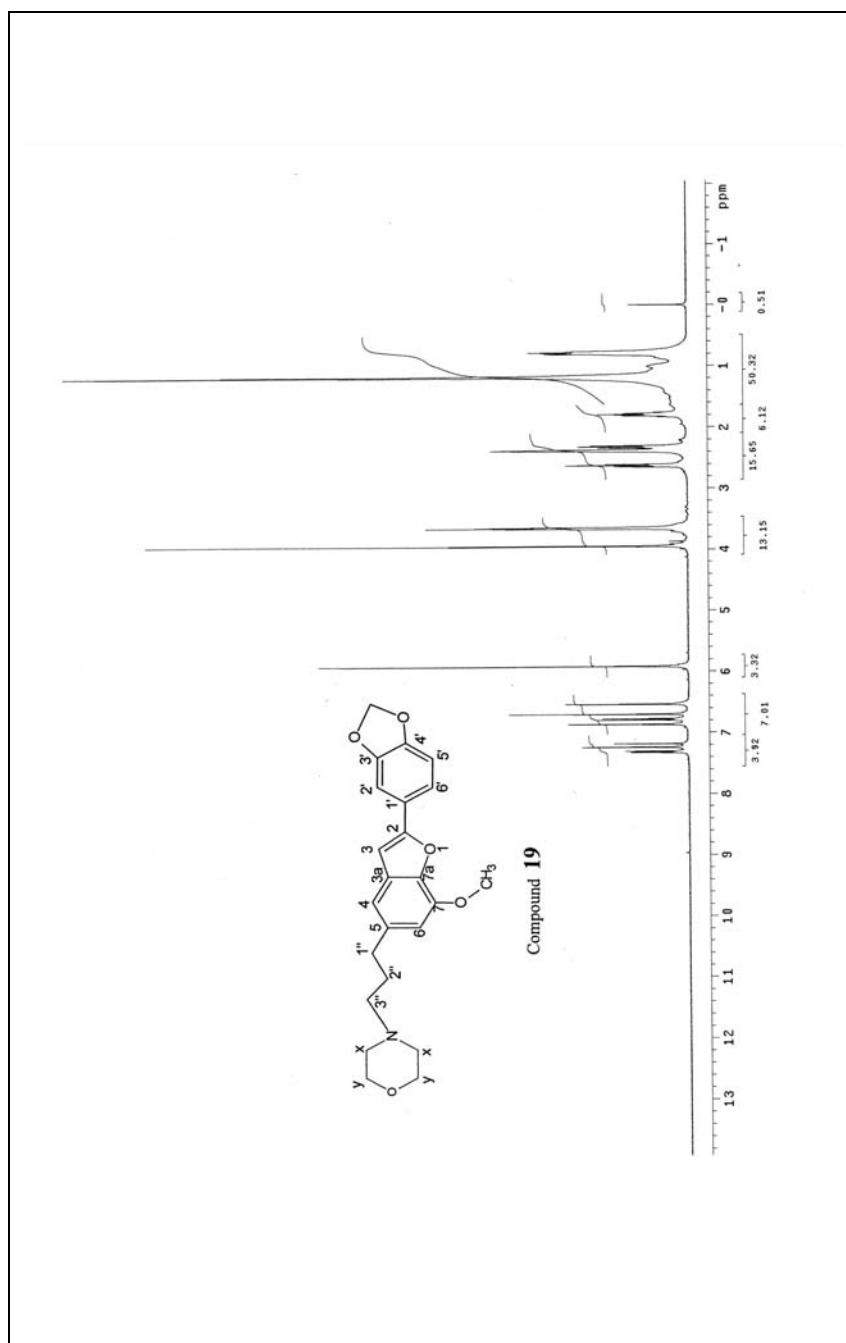


Figure 3.41. The ¹H-NMR Spectrum of Compound 19

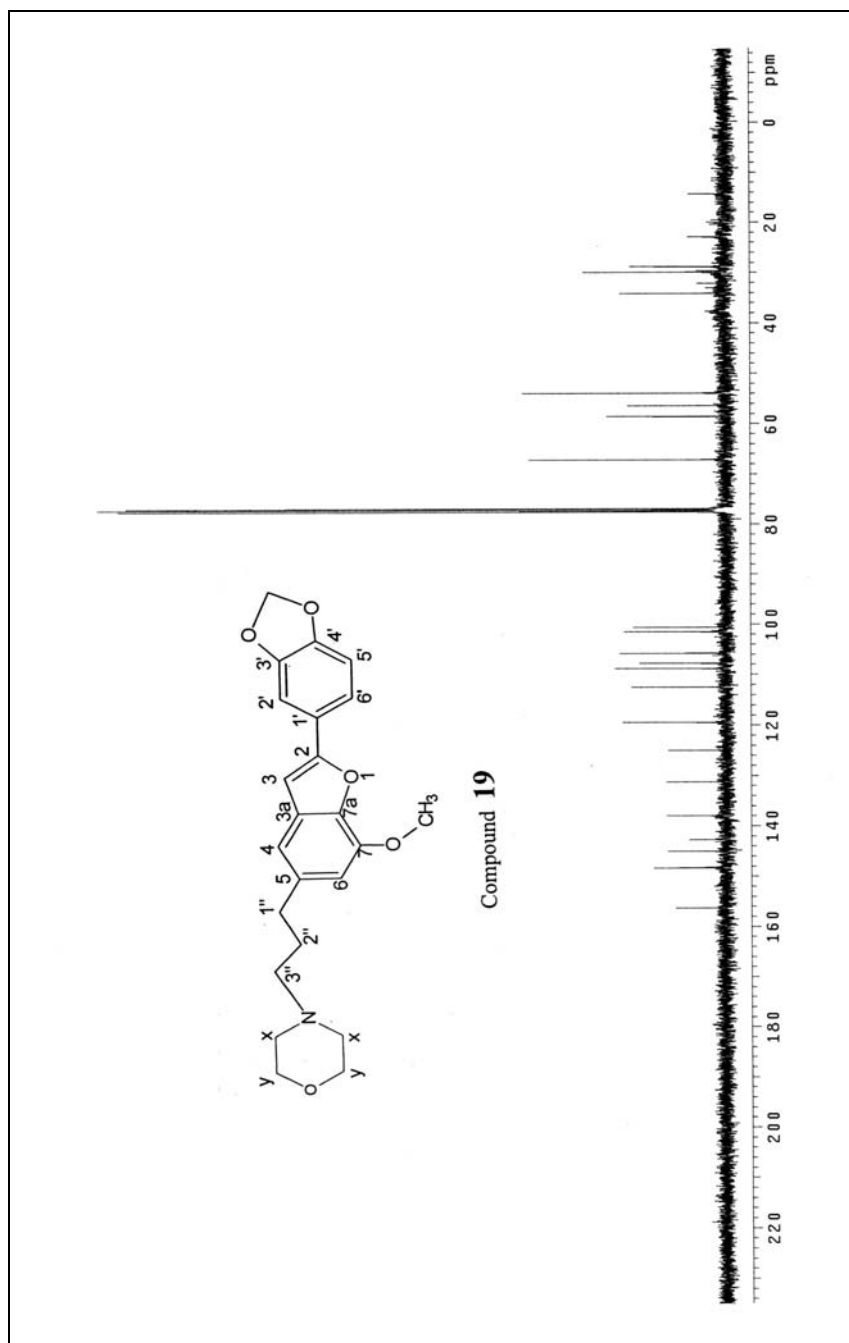
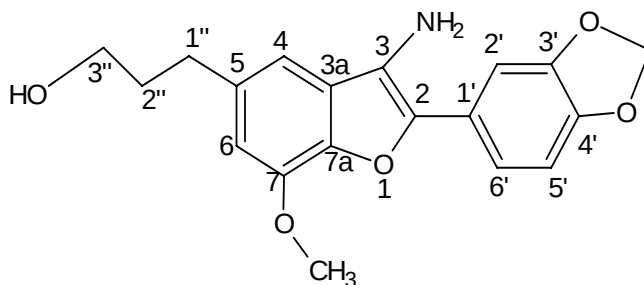


Figure 3.42. The ¹³C-NMR Spectrum of Compound 19

Table 3.22. ^1H - and ^{13}C -NMR spectroscopic data of compound **20** in CDCl_3 (δ ppm)

Position	δ ^1H (Compound 8)	δ ^1H (Compound 20)	δ ^{13}C (Compound 8)	δ ^{13}C (Compound 20)
2	-	-	156.85	163.12
3	-	-	123.71	168.32
3a	-	-	140.39	131.58
4	7.56, s, 1H	7.43, s, 1H	112.78	122.43/122.68/122.92
5	-	-	141.06	132.30
6	6.77, s, 1H	6.51, 1H	109.68	107.97/108.23/110.68
7	-	-	145.02	148.13/148.75/149.59
7a	-	-	145.02	143.64
OCH_2O	6.01, s, 2H	5.97, s, 2H	102.09	101.59
1'	-	-	121.26	122.43/122.68/122.92
2'	7.49, d, 1H, $J=1.6$	6.55, d, 1H, $J=1.6$	110.13	107.97/108.23/110.68
3'	-	-	150.79	148.13/148.75/149.59
4'	-	-	147.93	148.13/148.75/149.59
5'	6.94, d, 1H, $J=8.4$	6.84, d, 1H, $J=8.8$	108.61	107.97/108.23/110.68
6'	7.63, 1H, $J=1.6, 8.4$	7.45, dd, 1H, $J=2.0, 7.6$	125.77	122.43/122.68/122.92
1''	2.86, t, 2H, $J=7.8$	2.55, t, 2H, $J=7.6$	34.82	34.46
2''	2.00, p, 2H	1.78, p, 2H	32.87	31.80
3''	3.74, t, 2H, $J=6.4$	3.57, t, 2H, $J=6.4$	62.32	62.31
OMe	4.01, s, 3H	3.83, s, 3H	56.43	56.09
NH_2		1.58, 2H		-

Compound **20**

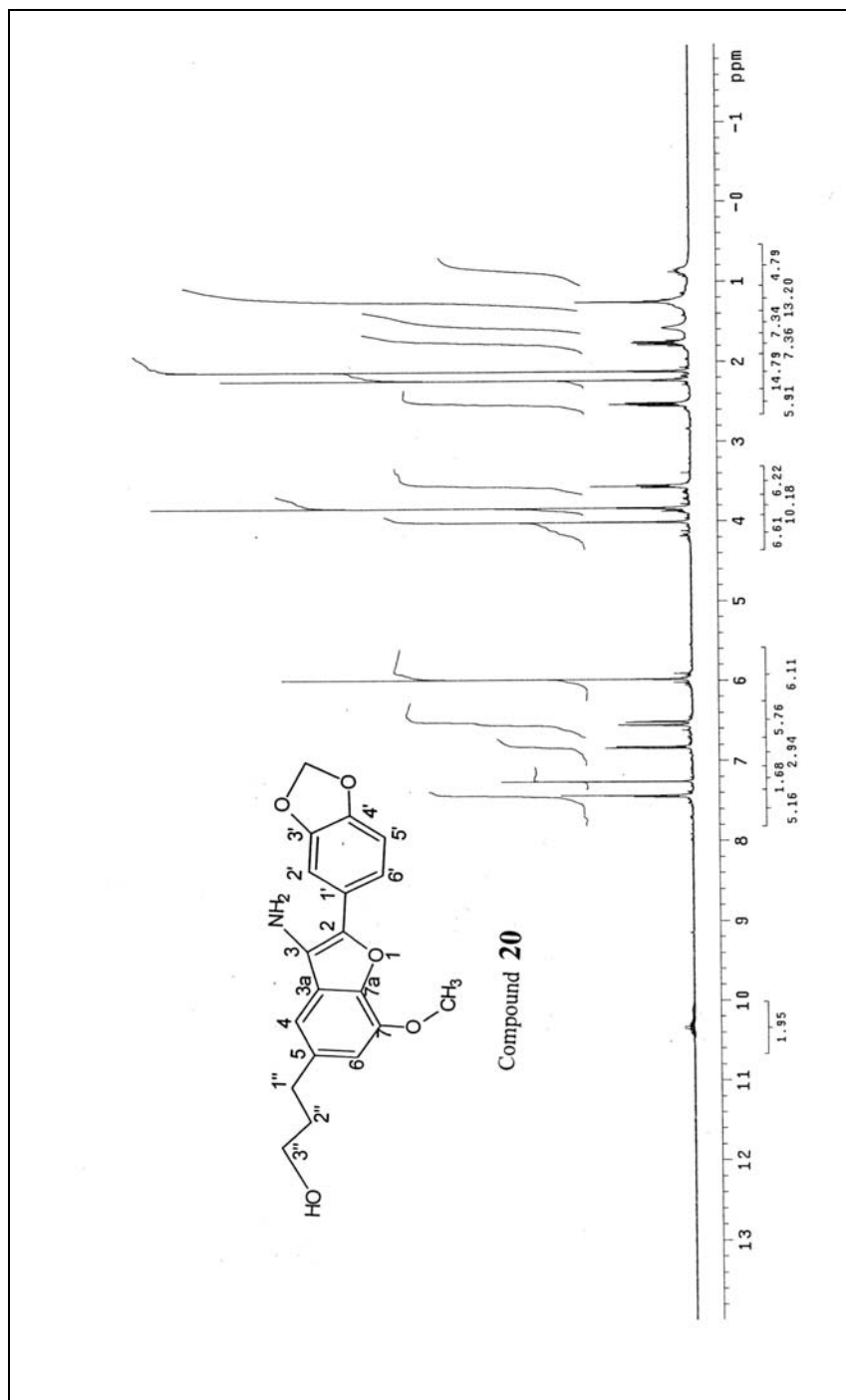


Figure 3.43. The ¹H-NMR Spectrum of Compound **20**

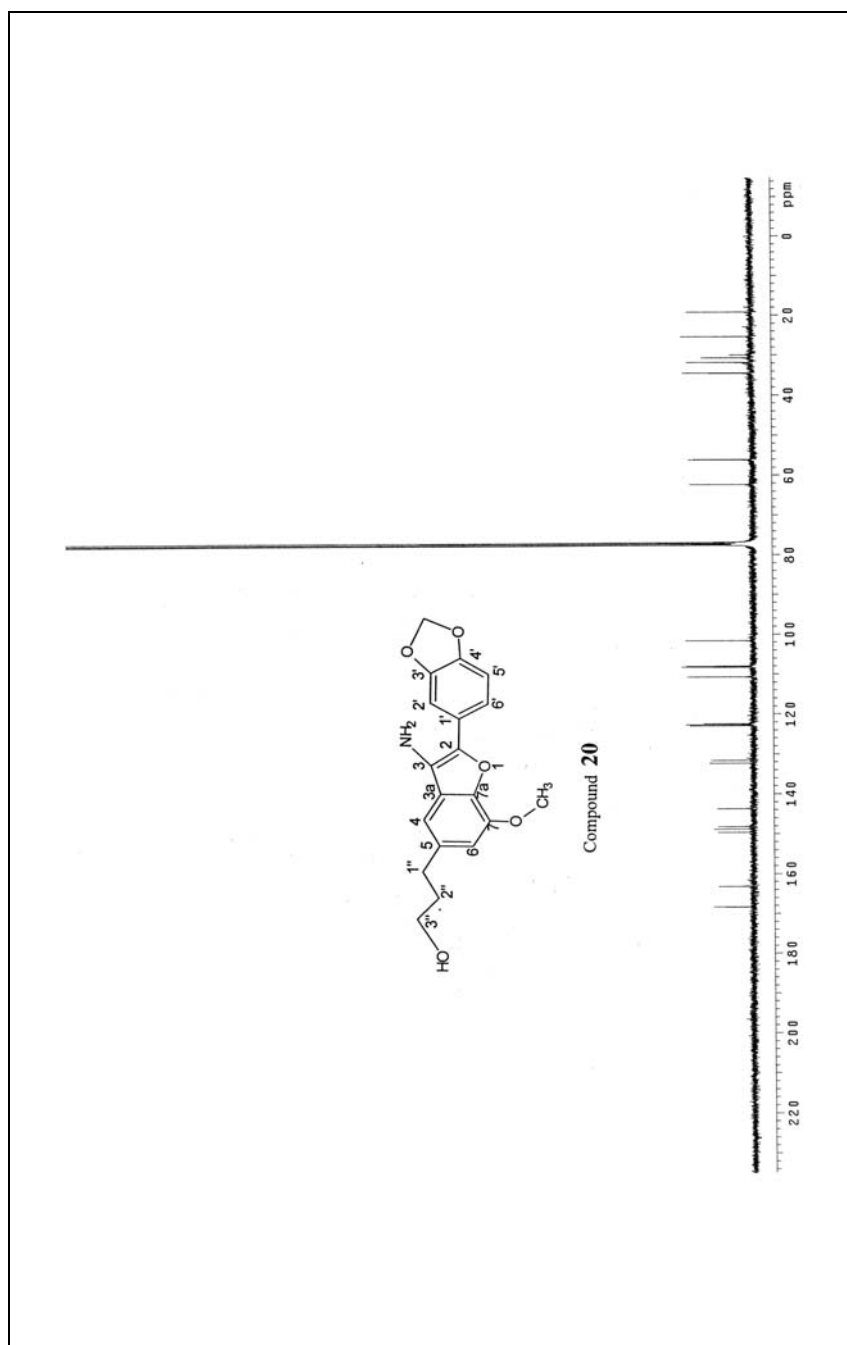
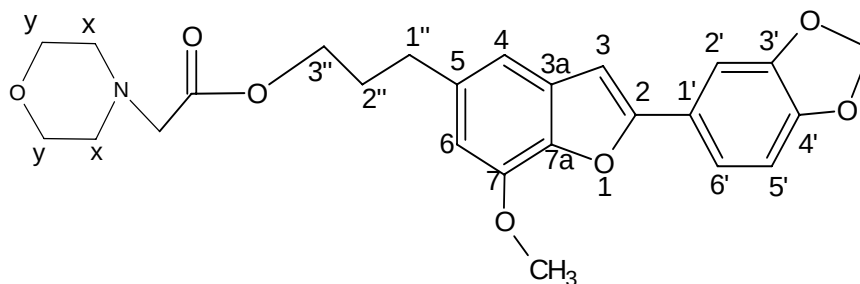


Figure 3.44. The ^{13}C -NMR Spectrum of Compound **20**

Table 3.23. ^1H - and ^{13}C -NMR spectroscopic data of compound **21** in CDCl_3 (δ ppm)

Position	δ ^1H (Compound 4)	δ ^1H (Compound 21)	δ ^{13}C (Compound 4)	δ ^{13}C (Compound 21)
2	-	-	156.45	156.43
3	6.78, s, 1H	6.77, s, 1H	100.55	100.54
3a	-	-	131.38	131.36
4	6.94, s, 1H	6.94, 1H	112.60	112.56
5	-	-	136.74	136.95
6	6.59, s, 1H, $J=0.8$	6.59, d, 1H, $J=1.6$	107.69	107.68
7	-	-	145.11	145.09
7a	-	-	142.82	142.80
OCH_2O	5.99, s, 2H	6.00, s, 2H	101.54	101.53
1'	-	-	124.90	124.90
2'	7.31, d, 1H, $J=1.6$	7.31, d, 1H, $J=1.6$	105.79	105.78
3'	-	-	148.31	148.31
4'	-	-	148.27	148.26
5'	6.87, d, 1H, $J=8.4$	6.87, d, 1H, $J=8.4$	108.84	108.84
6'	7.40, dd, 1H, $J=1.2, 1.6$	7.40, dd, 1H, $J=1.6, 1.6$	119.47	119.46
1''	2.78, t, $J=7.6$	2.75, t, 2H, $J=7.6$	30.66	30.86
2''	2.08, p, 2H	2.03, p, 2H	32.51	32.14
3''	4.25, t, 2H, $J=6.4$	4.20, t, 2H, $J=6.8$	65.74	64.31
OMe	4.03, s, 3H	4.03, s, 3H	56.45	59.87
$\text{C}=\text{O}$	-	-	167.56	170.36
$\text{CH}_2\text{COO}-$	-	-	41.10	56.45
$\text{CH}_2\text{COO}-$	4.05, s, 2H	3.20, s, 2H	-	-
x	-	2.60, t, 4H, $J=4.6$	-	53.53
y	-	3.76, t, 4H, $J=4.8$	-	67.01

Compound **21**

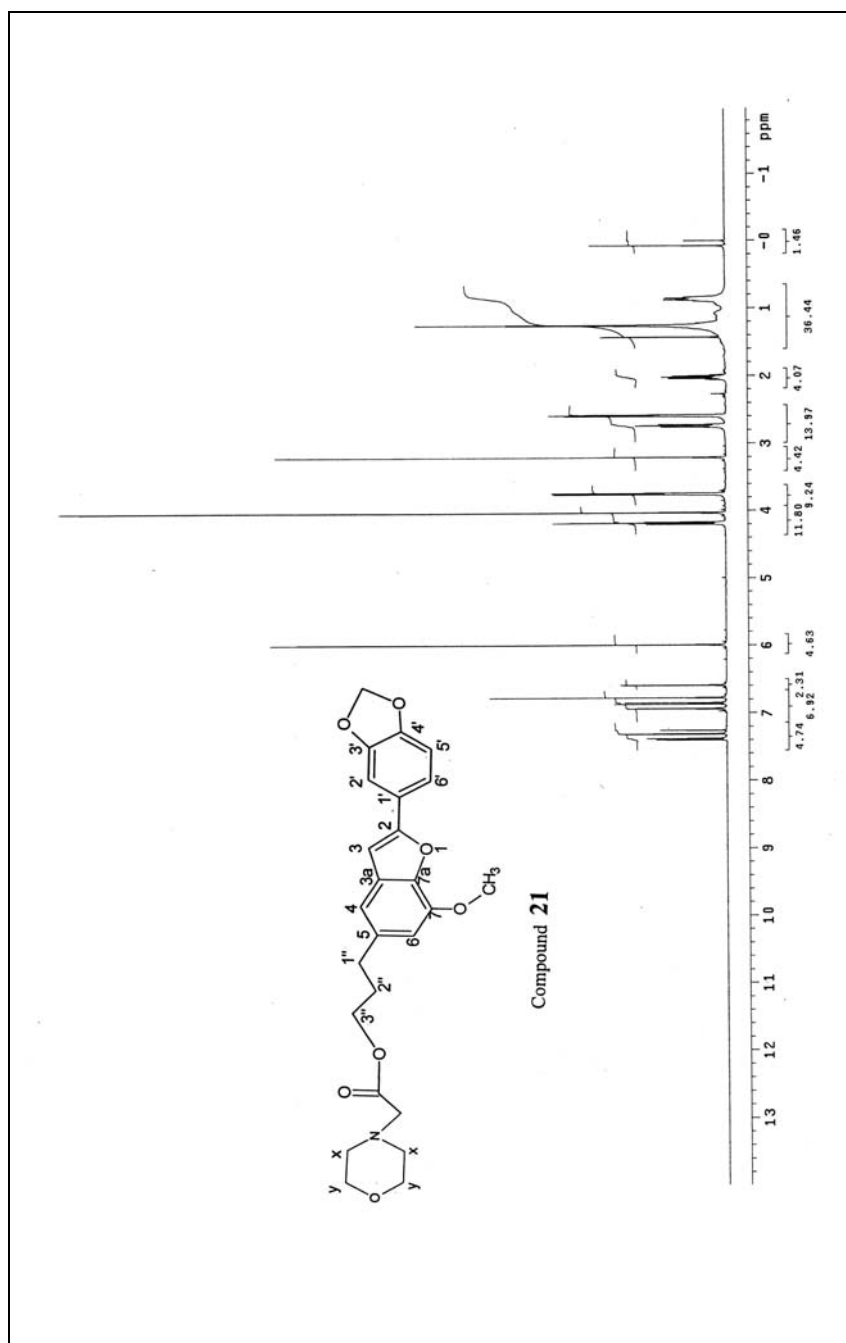


Figure 3.45. The ^1H -NMR Spectrum of Compound **21**

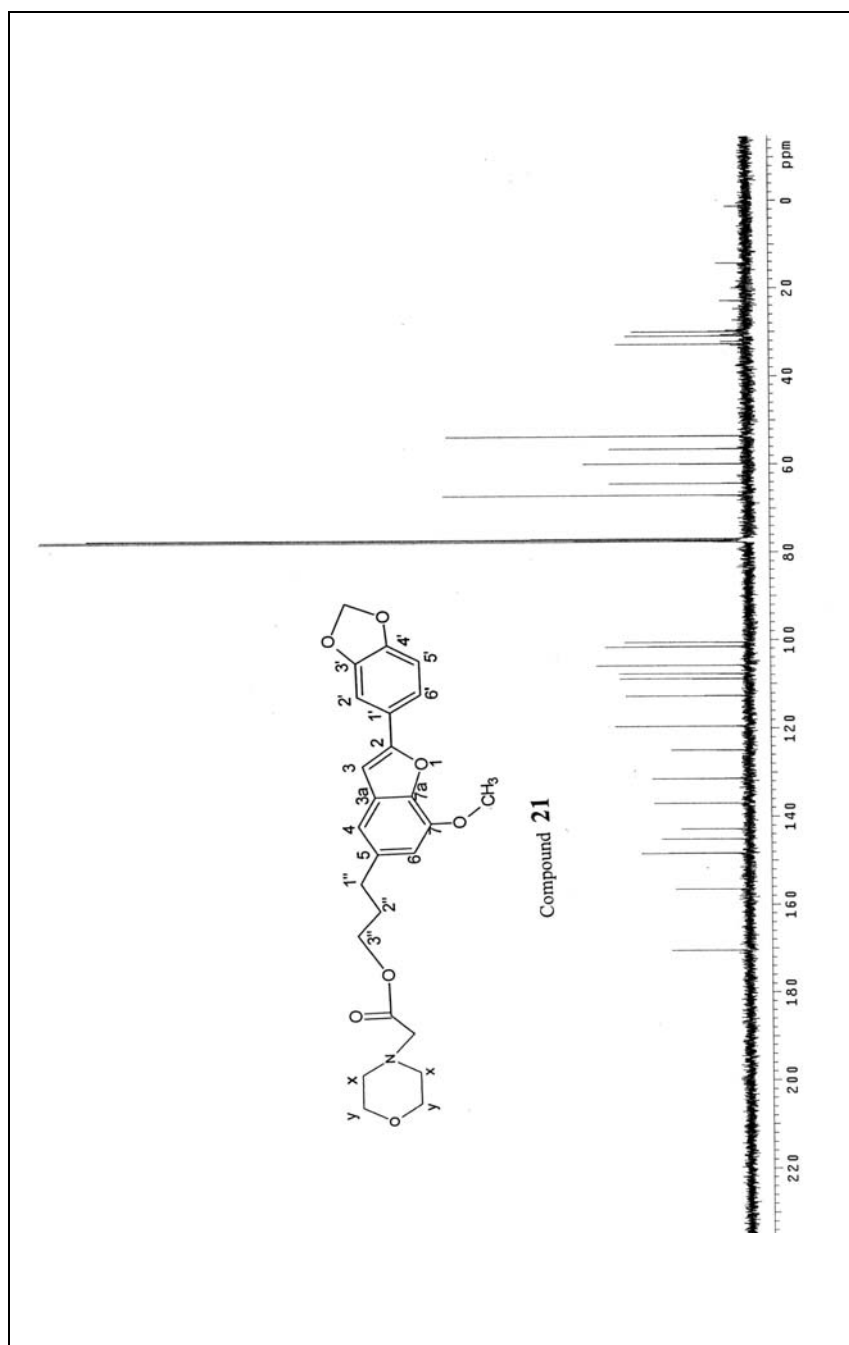
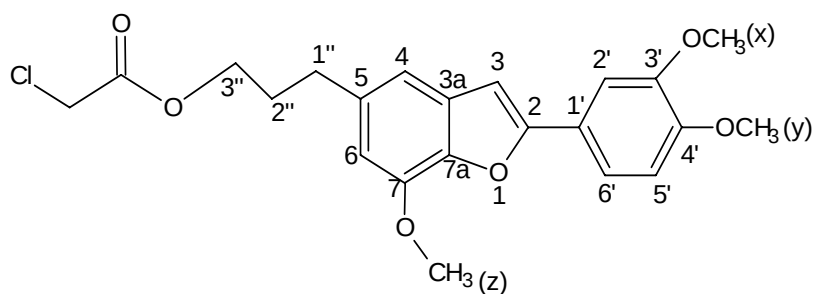


Figure 3.46. The ^{13}C -NMR Spectrum of Compound 21

Table 3.24. ^1H - NMR spectroscopic data of compound **22** in CDCl_3 (δ ppm)

Position	δ 1H (trimethoxy egonol)	δ 1H (Compound 22)
2	-	-
3	6.91, s, 1H	6.60, s, 1H
3a	-	-
4	6.93, s, 1H	6.96, s, 1H
5	-	-
6	6.83, s, 1H	6.83, s, 1H
7	-	-
7a	-	-
1'	-	-
2'	7.36, d, 1H, J=1.6	7.36, d, 1H, J=1.6
3'	-	-
4'	-	-
5'	6.97, d, 1H	6.93, d, 1H, J=8.0
6'	7.46, dd, 1H, J=1.6, 2.4	7.46, dd, 1H, J=1.6, 1.6
1''	2.86, t, 2H, J=7.4	2.79, t, 2H, J=7.6
2''	2.15, p, 2H	2.07, p, 2H
3''	3.57, t, 2H, J=6.4	4.26, t, 2H, J=6.6
OMe (x, y, z)	3.92/3.98/4.04, s, 3H	3.92/3.98/4.04, s, 3H
ClCH_2 -	-	4.05, s, 2H

Compound **22**

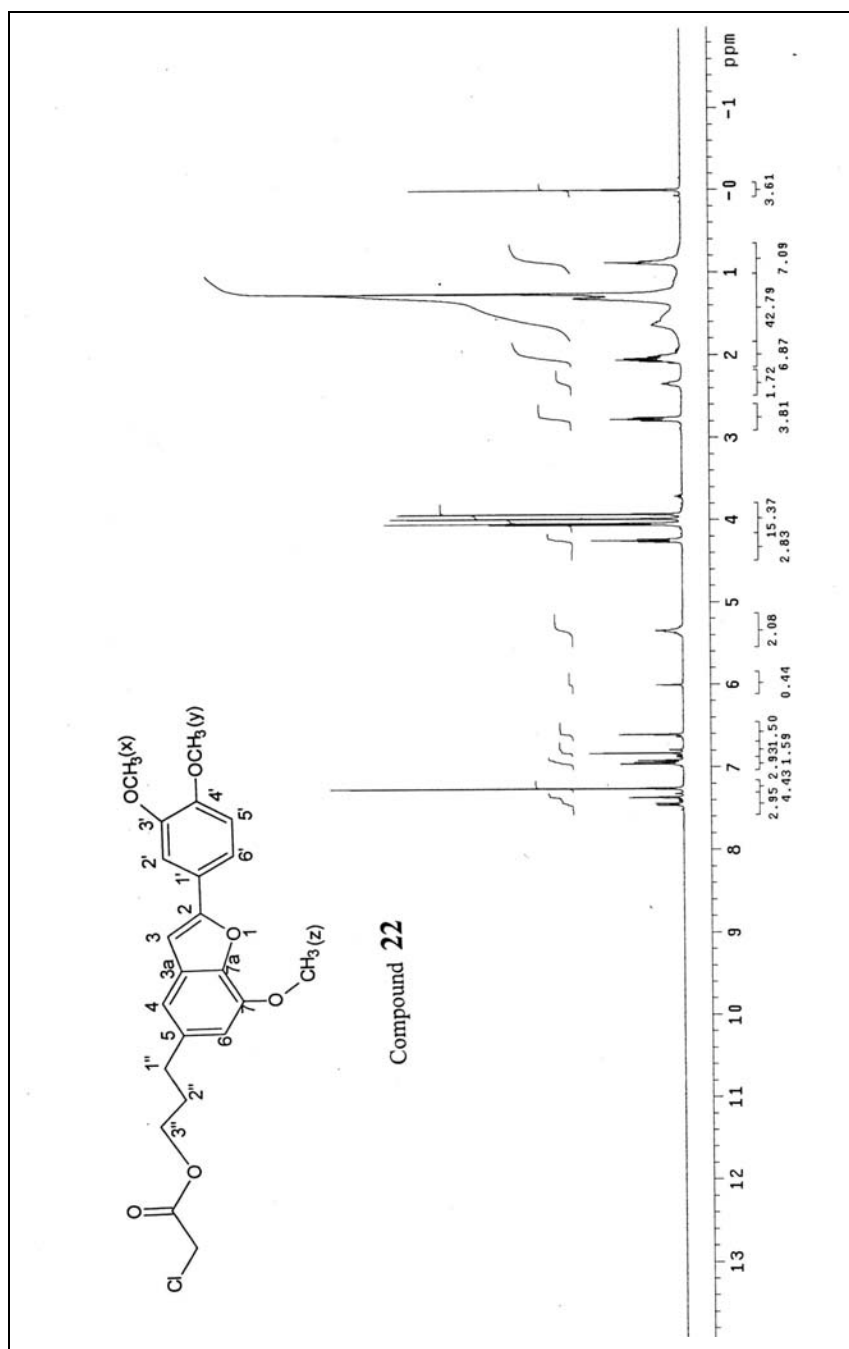


Figure 3.47. The $^1\text{H-NMR}$ Spectrum of Compound 22

Table 3.25. ^1H - and ^{13}C -NMR spectroscopic data of compound **23** in DMSO (δ ppm)

Position	δ ^1H (Compound 1)	δ ^1H (Compound 23)	δ ^{13}C (Compound 23)
2	-	-	155.89
3	6.77, s, 1H	7.17, s, 1H	102.12
3a	-	-	131.14
4	6.96, s, 1H	6.98, d, 1H, $J=1.2$	112.73
5	-	-	137.72
6	6.62, d, 1H, $J=1.6$	6.78, d, 1H, $J=1.2$	108.43
7	-	-	145.01
7a	-	-	142.41
OCH ₂ O	6.00, s, 2H	6.06, s, 2H	101.74
1'	-	-	124.69
2'	7.32, d, 1 H, $J=4.0$	7.37, d, 1H, $J=1.6$	105.66
3'	-	-	148.64
4'	-	-	148.51
5'	6.88, d, 1H, $J=8.0$	7.01, d, 1H, $J=7.6$	109.50
6'	7.41, dd, 1H, $J=1.6, 8.0$	7.40, dd, 1H, $J=1.2, 2.0$	119.43
1''	2.85, t, 2H, $J=6.8$	2.88, t, 2H, $J=7.6$	31.50
2''	3.05, t, 2H, $J=7.6$	2.57, t, 2H, $J=7.8$	36.67
3''	9.85, t, 1H, $J=1.6$	-	-
OMe	4.04, s, 3H	3.93, s, 3H	56.49
COOH	-	-	174.63

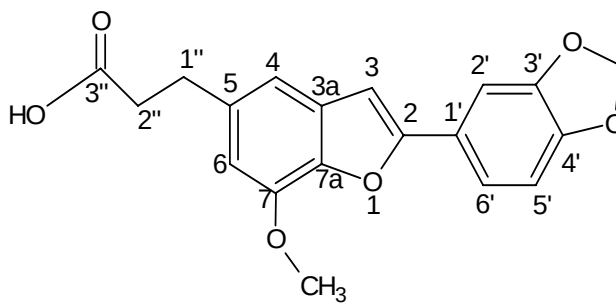
Compound **23**

Figure 3.48. The ^1H -NMR Spectrum of Compound 23

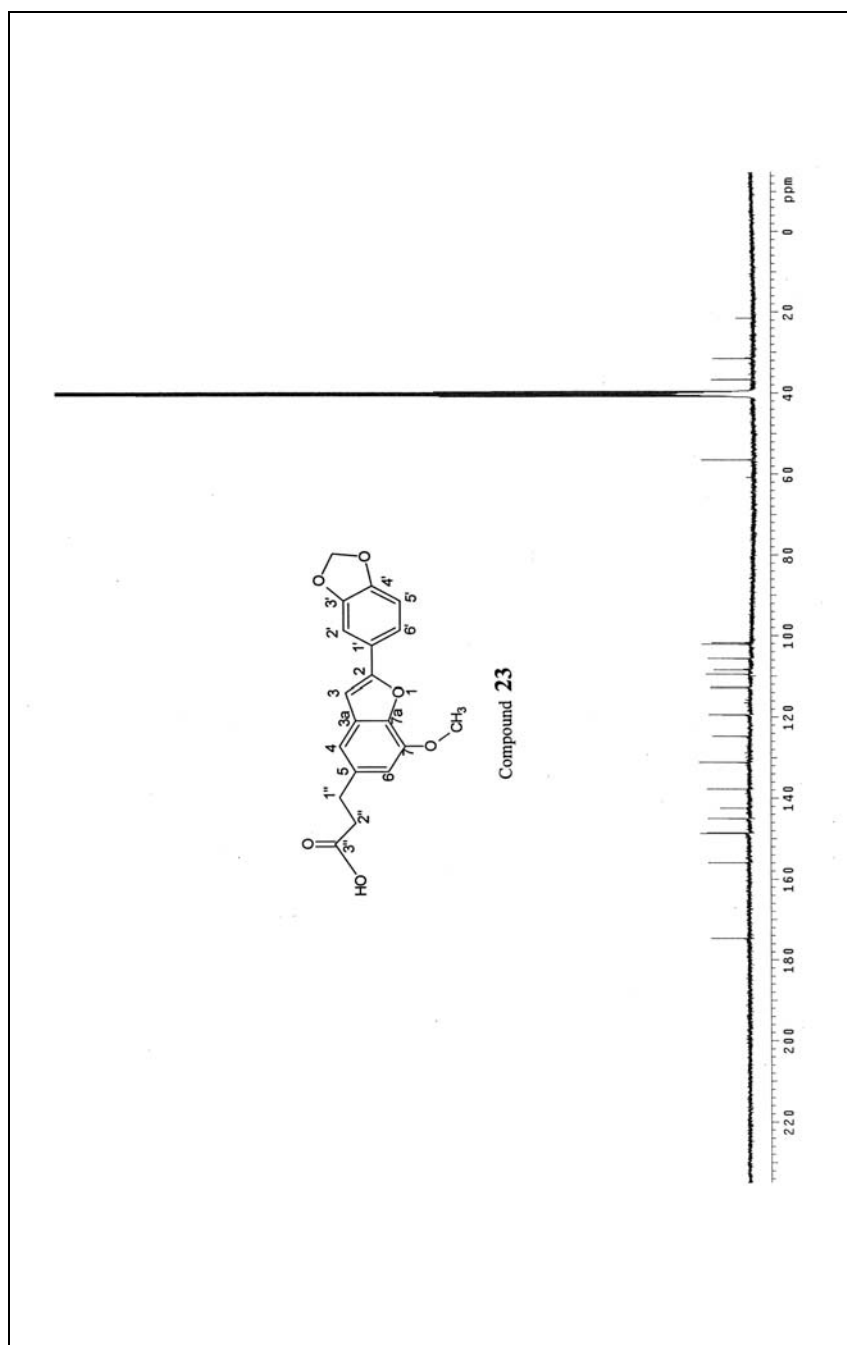
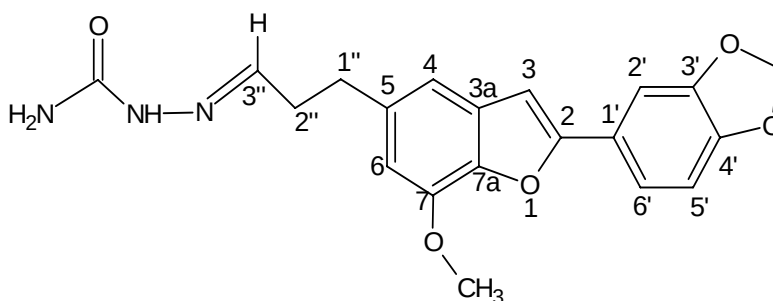


Figure 3.49. The ^{13}C -NMR Spectrum of Compound **23**

Table 3.26. ^1H - and ^{13}C -NMR spectroscopic data of compound **24** in DMSO (δ ppm)

Position	δ ^1H (Compound 1)	δ ^1H (Compound 24)	δ ^{13}C (Compound 24)
2	-	-	155.86
3	6.77, s, 1H	7.00, s, 1H	101.69
3a	-	-	131.15
4	6.96, s, 1H	7.18, s, 1H	112.91
5	-	-	137.90
6	6.62, d, 1H, $J=1.6$	6.76, d, 1H, $J=1.2$	108.48
7	-	-	144.94
7a	-	-	142.31
OCH ₂ O	6.00, s, 2H	6.03, s, 2H	102.09
1'	-	-	124.61
2'	7.32, d, 1 H, $J=4.0$	7.40, d, 1H, $J=1.6$	105.56
3'	-	-	148.59
4'	-	-	148.47
5'	6.88, d, 1H, $J=8.0$	7.07, d, 1H, $J=4.0$	109.56
6'	7.41, dd, 1H, $J=1.6, 8.0$	7.38, dd, 1H, $J=2.0, 2.0$	119.49
1''	2.85, t, 2H, $J=6.8$	2.84, t, 2H, $J=7.6$	32.87
2''	3.05, t, 2H, $J=7.6$	2.53, m, 2H	34.38
3''	9.85, t, 1H, $J=1.6$	7.20, t, 1H, $J=1.6$	-
OMe	4.04, s, 3H	3.94, s, 3H	56.46
NH ₂ C=O		6.07, 2H	-
NH ₂ C=O		-	144.39/144.94
NH ₂ CONH-		9.75, 1H	-
-N=CH-		-	144.39/144.94

**Compound 24**

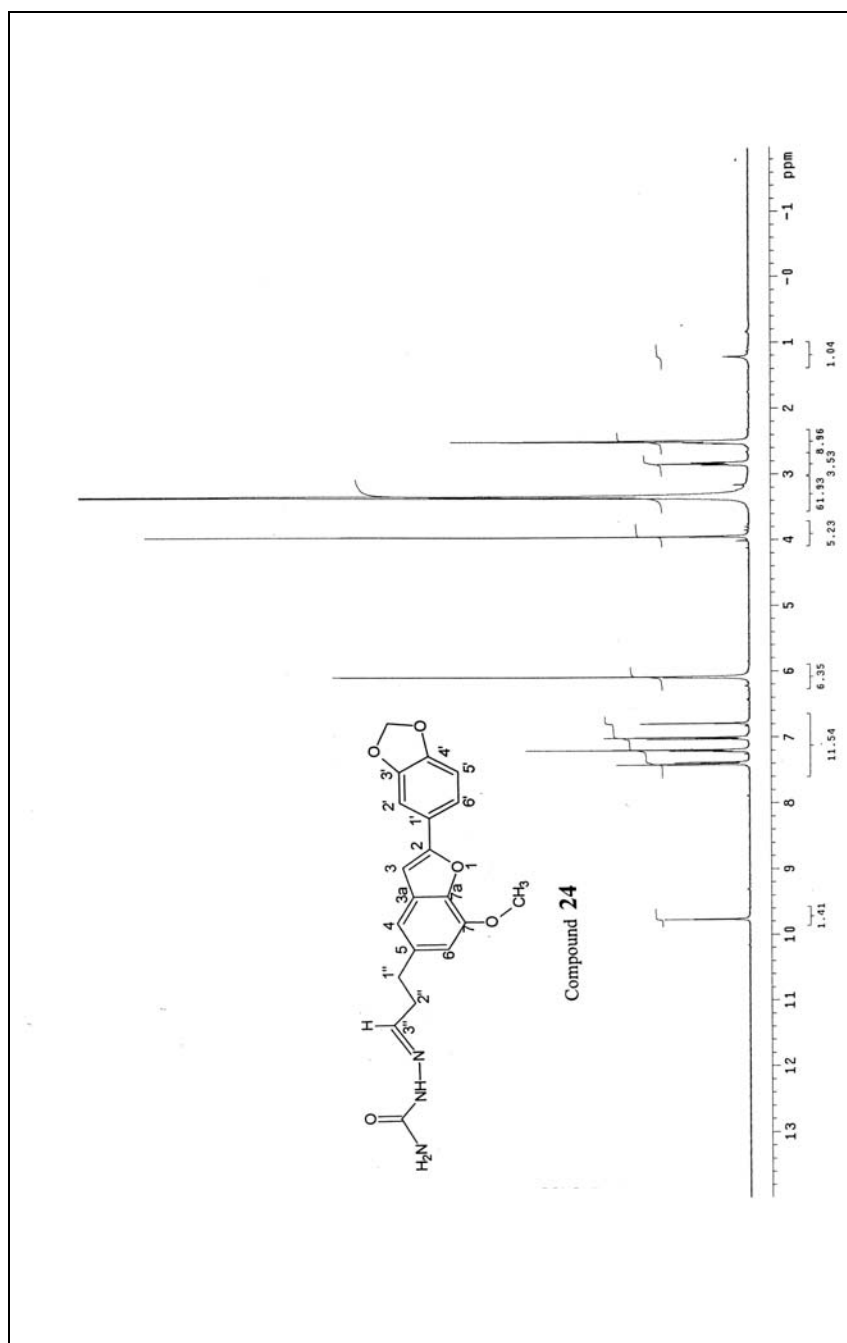


Figure 3.50. The ¹H-NMR Spectrum of Compound **24**

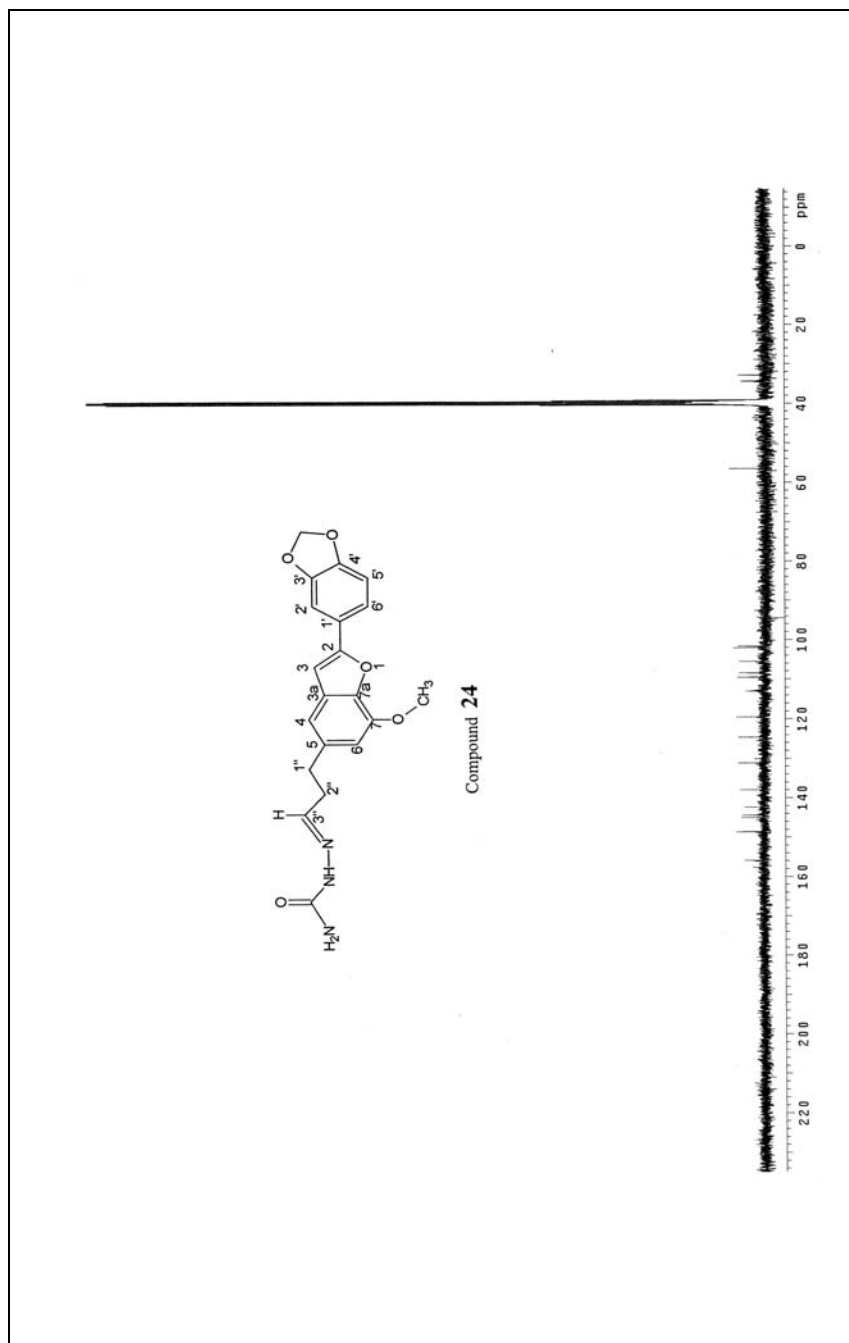
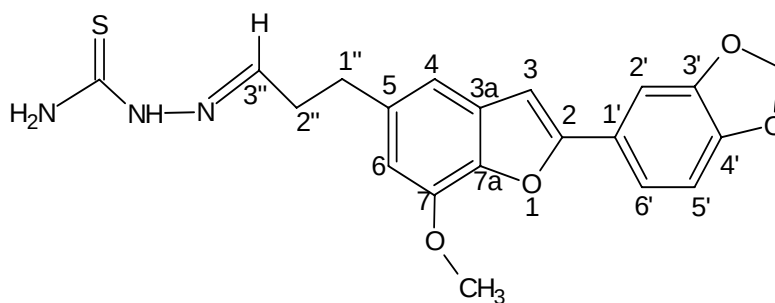


Figure 3.51. The ^{13}C -NMR Spectrum of Compound **24**

Table 3.27. ^1H - and ^{13}C -NMR spectroscopic data of compound **25** in CDCl_3 (δ ppm)

Position	δ ^1H (Compound 1)	δ ^1H (Compound 25)	δ ^{13}C (Compound 25)
2	-	-	155.93
3	6.77, s, 1H	7.00, s, 1H	101.74
3a	-	-	131.19
4	6.96, s, 1H	7.18, s, 1H	112.87
5	-	-	137.77
6	6.62, d, 1H, $J=1.6$	6.78	108.60
7	-	-	145.03
7a	-	-	142.38
OCH_2O	6.00, s, 2H	6.07, s, 2H	102.13
1'	-	-	124.69
2'	7.32, d, 1 H, $J=4.0$	7.40, d, 1H, $J=1.6$	105.68
3'	-	-	148.65
4'	-	-	148.52
5'	6.88, d, 1H, $J=8.0$	7.10, d, 1H, $J=8.0$	109.51
6'	7.41, dd, 1H, $J=1.6, 8.0$	7.38, dd, 1H, $J=8.0, 1.6$	119.45
1''	2.85, t, 2H, $J=6.8$	2.81, t, 2H, $J=7.6$	32.67
2''	3.05, t, 2H, $J=7.6$	2.57, 2H	34.48
3''	9.85, t, 1H, $J=1.6$	7.45, t, 1H	-
OMe	4.04, s, 3H	3.95, s, 3H	56.51
$\text{NH}_2\text{C}=\text{S}$		-	178.33
$\text{NH}_2\text{CSNH}-$		11.03	-
$-\text{N}=\text{CH}-$		-	147.43

Compound **25**

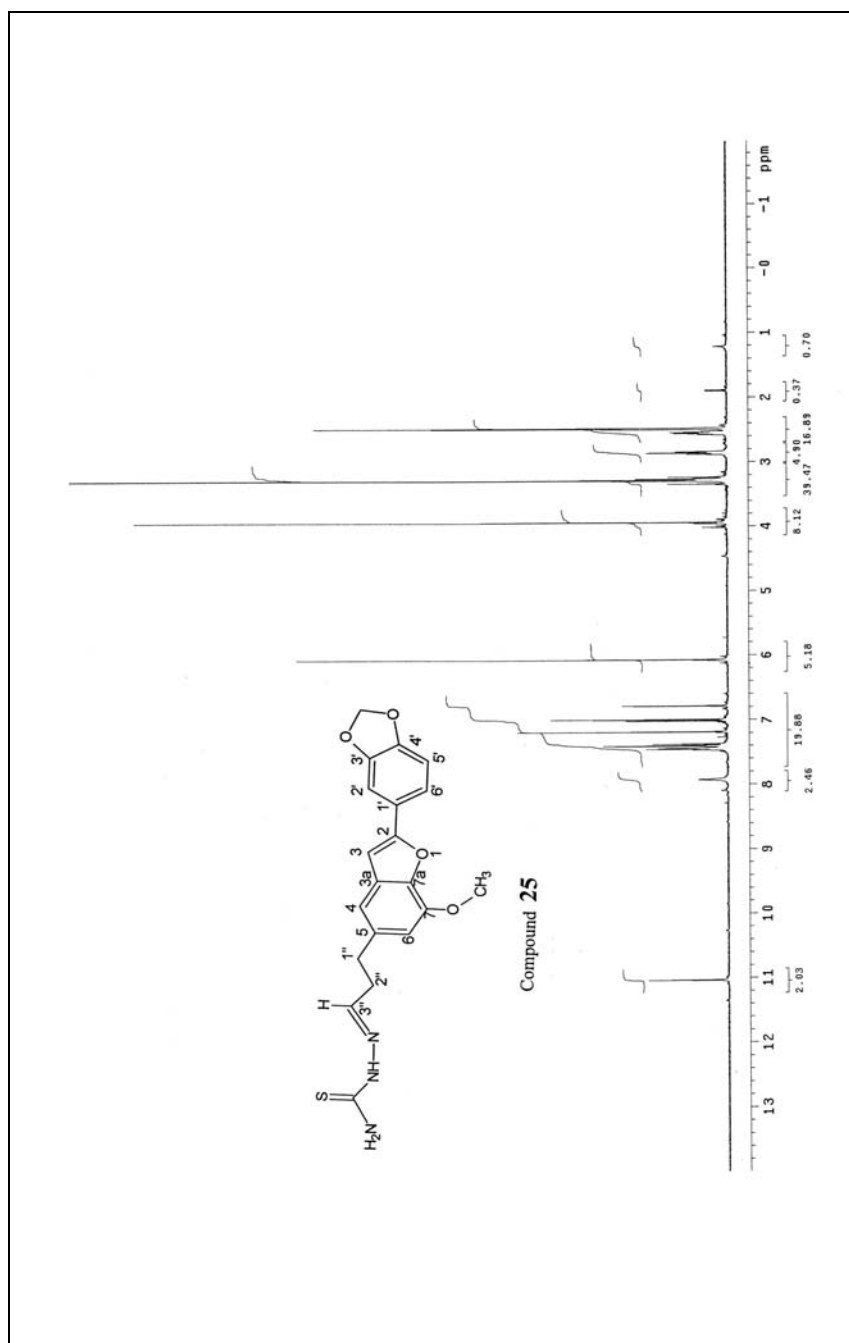


Figure 3.52. The ^1H -NMR Spectrum of Compound 25

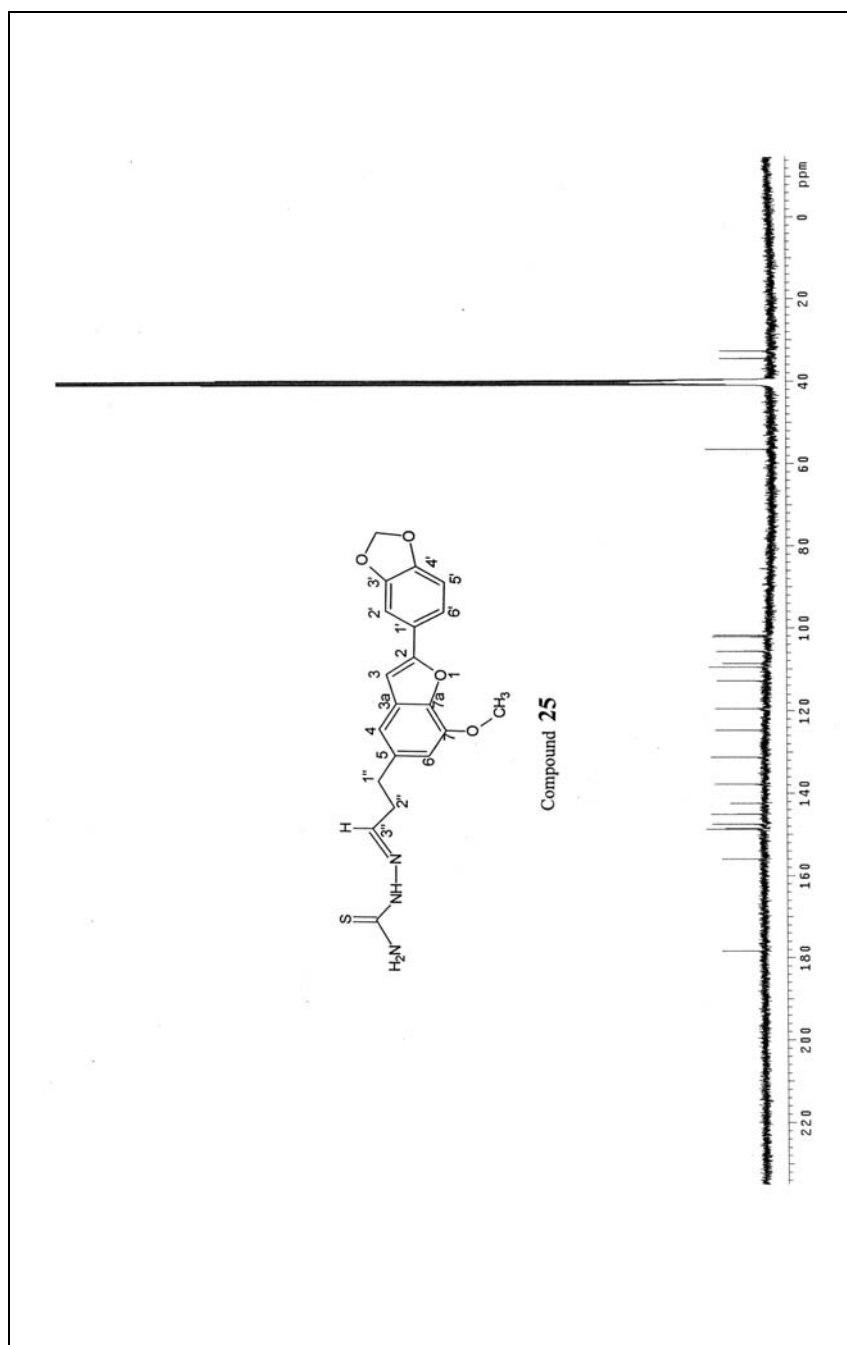
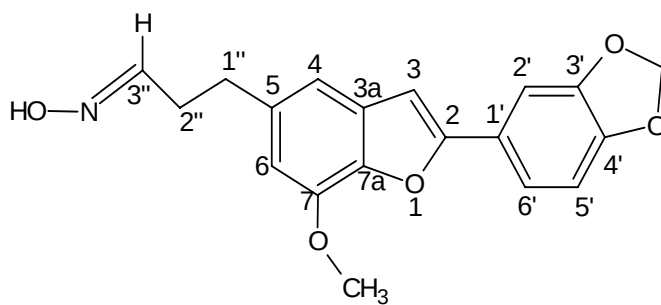


Figure 3.53. The ^{13}C -NMR Spectrum of Compound 25

Table 3.28. ^1H - and ^{13}C -NMR spectroscopic data of compound **26** in DMSO (δ ppm)

Position	δ ^1H (Compound 1)	δ ^1H (Compound 26)	δ ^{13}C (Compound 26)
2	-	-	155.922
3	6.77, s, 1H	7.17, s, 1H	101.74
3a	-	-	131.20
4	6.96, s, 1H	6.99, s, 1H	112.73
5	-	-	137.90
6	6.62, d, 1H, $J=1.6$	6.76, s, 1H	108.34
7	-	-	145.08
7a	-	-	142.42
OCH ₂ O	6.00, s, 2H	6.06, s, 2H	102.12
1'	-	-	124.68
2'	7.32, d, 1 H, $J=4.0$	7.39	105.66
3'	-	-	148.64
4'	-	-	148.51
5'	6.88, d, 1H, $J=8.0$	7.01, d, 1H, $J=8.0$	109.50
6'	7.41, dd, 1H, $J=1.6, 8.0$	7.34, dd, 1H, $J=1.6, 8.0$	119.44
1''	2.85, t, 2H, $J=6.8$	2.80, t, 2H, $J=7.6$	32.40
2''	3.05, t, 2H, $J=7.6$	2.59, 2H	27.29
3''	9.85, t, 1H, $J=1.6$	6.69, t, 1H, $J=5.2$	150.42
OMe	4.04, s, 3H	3.93, s, 3H	56.49
<u>HO-N</u>		10.78	-

Compound **26**

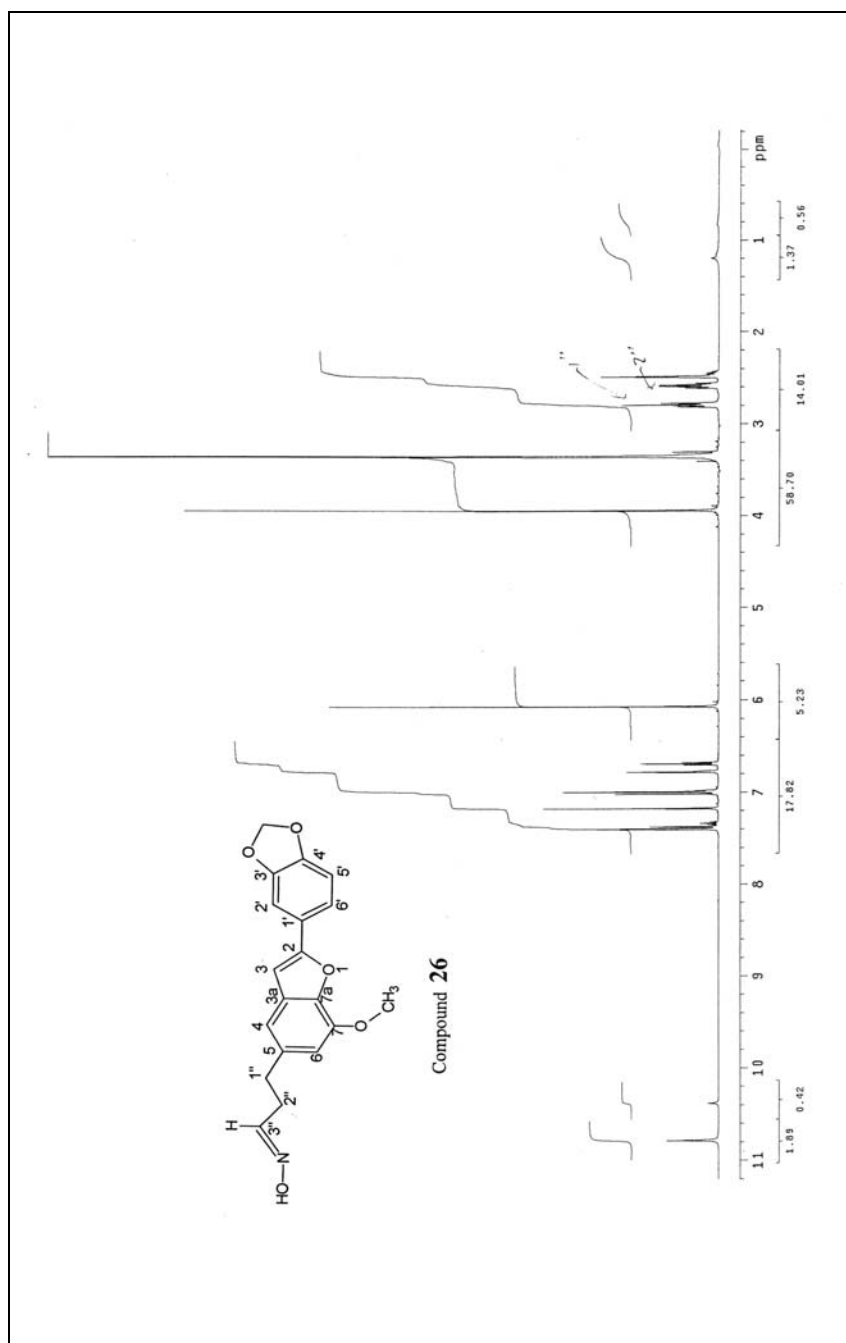


Figure 3.54. The ^1H -NMR Spectrum of Compound 26

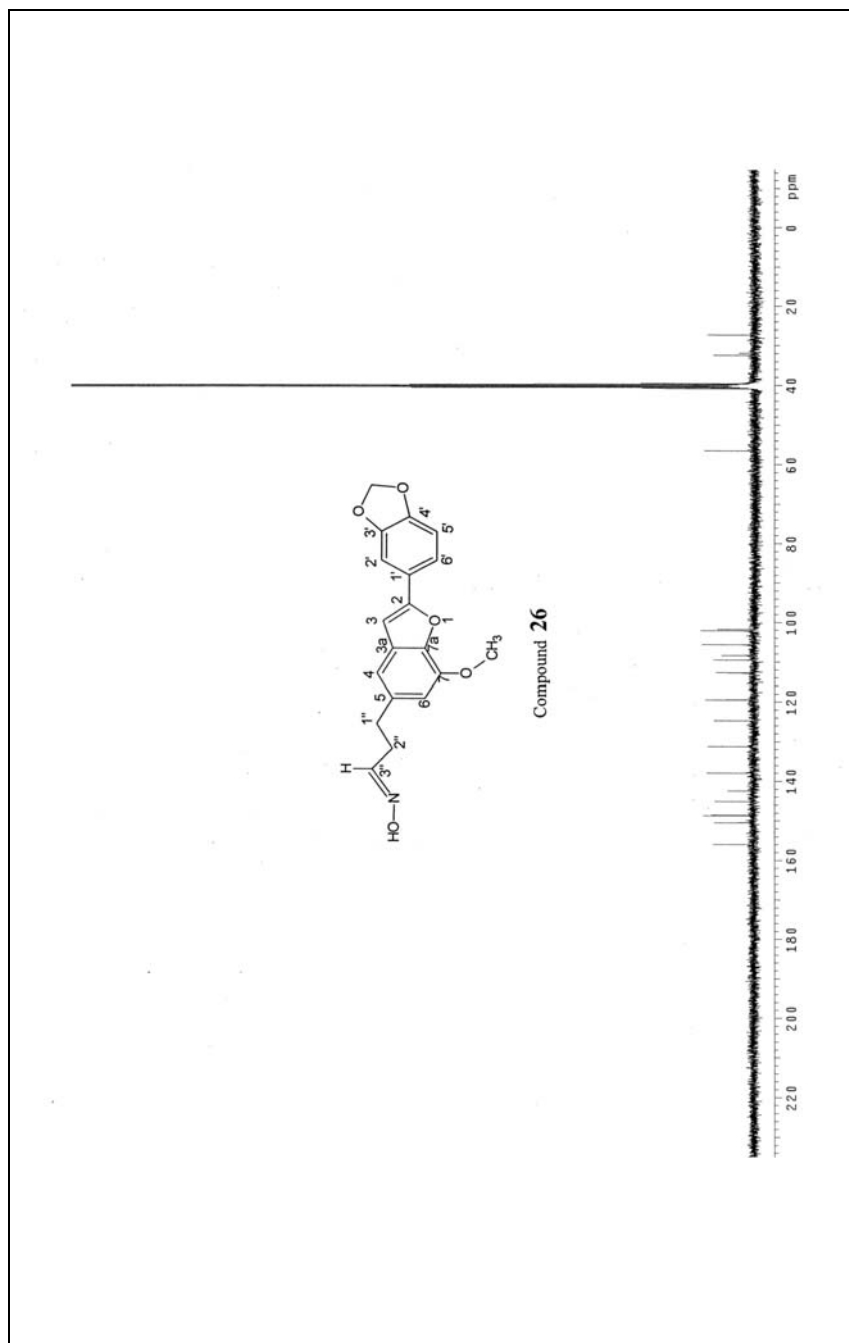
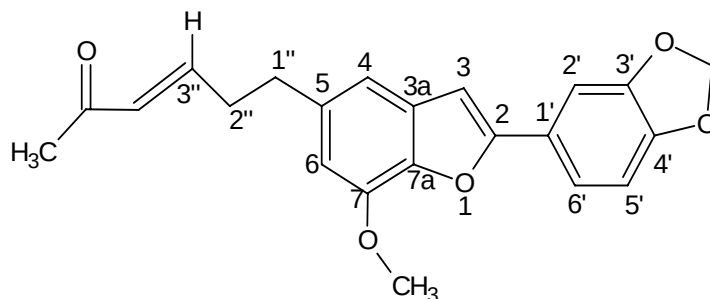


Figure 3.55. The ¹³C-NMR Spectrum of Compound 26

Table 3.29. ^1H - and ^{13}C -NMR spectroscopic data of compound **27** in CDCl_3 (δ ppm)

Position	δ ^1H (Compound 1)	δ ^1H (Compound 27)	δ ^{13}C (Compound 27)
2	-	-	155.25
3	6.77, s, 1H	6.71, s, 1H	99.33
3a	-	-	132.10
4	6.96, s, 1H	6.87, s, 1H	111.29
5	-	-	135.38
6	6.62, d, 1H, $J=1.6$	6.52, d, 1H, $J=1.2$	106.43
7	-	-	143.87
7a	-	-	141.63
OCH_2O	6.00, s, 2H	5.91, s, 2H	100.30
1'	-	-	123.64
2'	7.32, d, 1H, $J=4.0$	7.24, d, 1H, $J=1.6$	104.54
3'	-	-	146.07/ 147.08
4'	-	-	146.07/ 147.08
5'	6.88, d, 1H, $J=8.0$	6.78, d, $J=8.0$	107.62
6'	7.41, dd, 1H, $J=1.6, 8.0$	7.32, dd, $J=8.0, 1.6$	118.25
1''	2.85, t, 2H, $J=6.8$	2.77, t, 2H, $J=8.0$	25.92
2''	3.05, t, 2H, $J=7.6$	2.51, q, 2H, $J=8.0$	33.59/33.79
3''	9.85, t, 1H, $J=1.6$	6.75, 1H	130.18/ 130.91
OMe	4.04, s, 3H	3.95, s, 3H	55.23
$\text{CH}_3\text{-}$		2.15, s, 3H	-
$\text{-CH}_3\text{-}$		-	33.59/33.79
$\text{CH}_3\text{COCH-}$		6.06, d, $J=16$	-
$\text{CH}_3\text{COCH-}$		-	130.18/ 130.91
$\text{CH}_3\text{-COCH-}$		-	197.46

Compound **27**

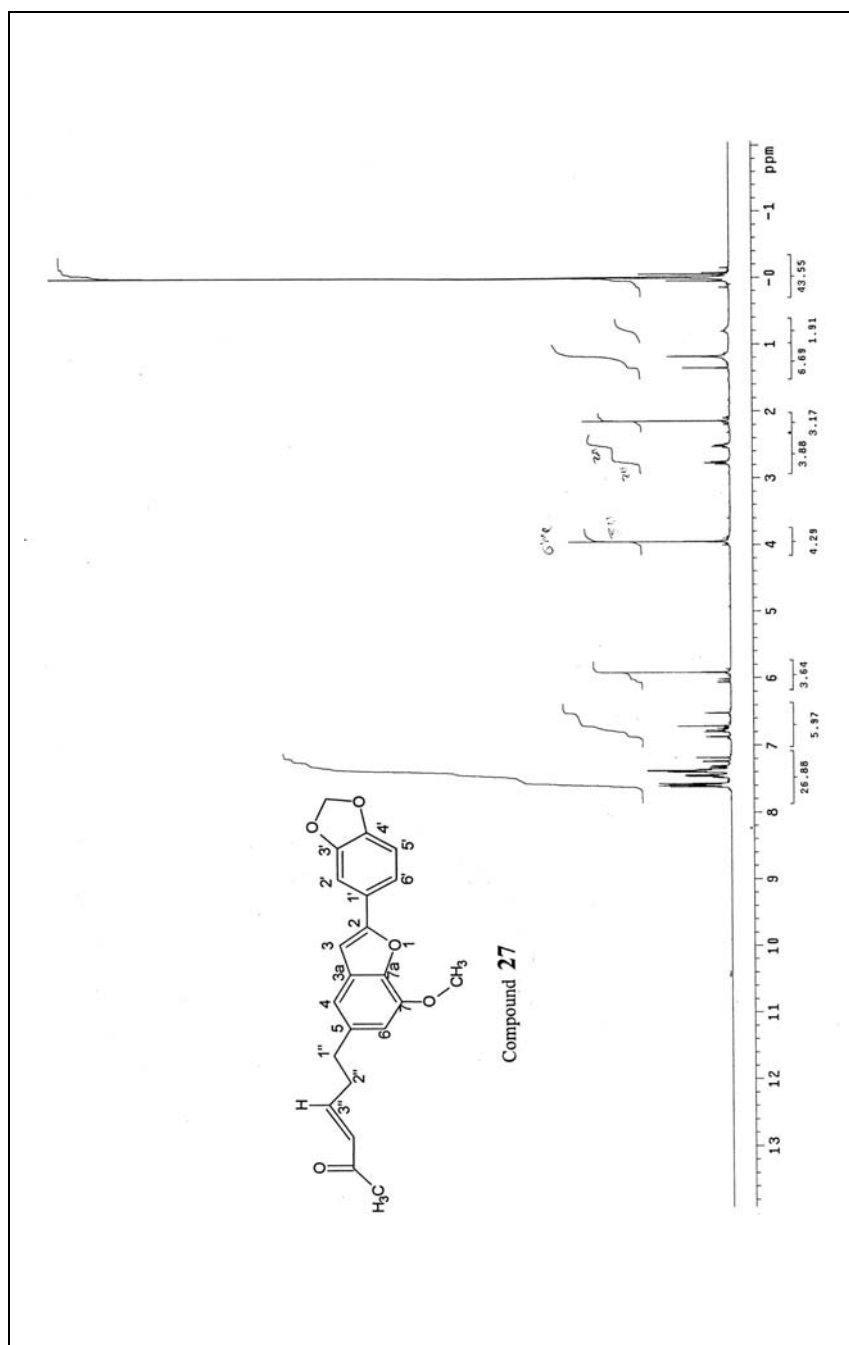
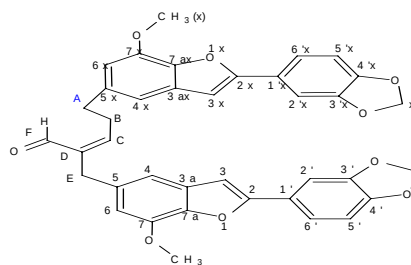


Figure 3.56. The ¹H-NMR Spectrum of Compound **27**

Figure 3.57. The ^{13}C -NMR Spectrum of Compound **27**

Table 3.30. ^1H - and ^{13}C -NMR spectroscopic data of compound **28** in CDCl_3 (δ ppm)

Position	δ ^1H (Compound 1)	δ ^1H (Compound 28)	δ ^{13}C (Compound 28)
2	-	-	156.30
3	6.77, s, 1H	6.57, s, 1H	100.52
3a	-	-	131.20
4	6.96, s, 1H	6.66	112.43
5	-	-	134.95
6	6.62, d, 1H, $J=1.6$	6.43, d, 1H, $J=1.2$	107.62
7	-	-	145.00
7a	-	-	142.76
OCH_2O	6.00, s, 2H	5.92, s, 2H	101.52
1'	-	-	124.80
2'	7.32, d, 1 H, $J=4.0$	7.18, d, 1 H, $J=2.0$	105.73
3'	-	-	148.26
4'	-	-	148.20
5'	6.88, d, 1H, $J=8.0$	6.76, d, 1H, $J=4.0$	108.81
6'	7.41, dd, 1H, $J=1.6, 8.0$	7.27, dd, 1H, $J=1.6, 4.8$	119.42
1''	2.85, t, 2H, $J=6.8$	-	-
2''	3.05, t, 2H, $J=7.6$	-	-
3''	9.85, t, 1H, $J=1.6$	-	-
OMe	4.04, s, 3H	3.88, s, 3H	56.39
2x	-	-	156.48
3x	-	6.63, s, 1H	100.59
3ax	-	-	131.42
4x	-	6.73	112.55
5x	-	-	136.30
6x	-	6.52, d, 1H, $J=1.6$	107.86
7x	-	-	145.10
7ax	-	-	142.86
$\text{OCH}_2\text{O}(x)$	-	5.93, s, 2H	101.54
1'x	-	-	124.89
2'x	-	7.20, d, 1 H, $J=1.2$	105.75
3'x	-	-	148.29
4'x	-	-	148.20
5'x	-	6.78, d, 1H, $J=4.0$	108.84
6'x	-	7.29, dd, 1H, $J=2.0, 2.0$	119.47
OMe(x)	-	3.89, s, 3H	56.42
A	-	2.74, 2H	31.68
B	-	2.74, 2H	30.08
C	-	6.45, 1H	155.35
D	-	-	143.31
E	-	3.58, 2H	35.00
F	-	9.41, 1H	194.92

**Compound 28**

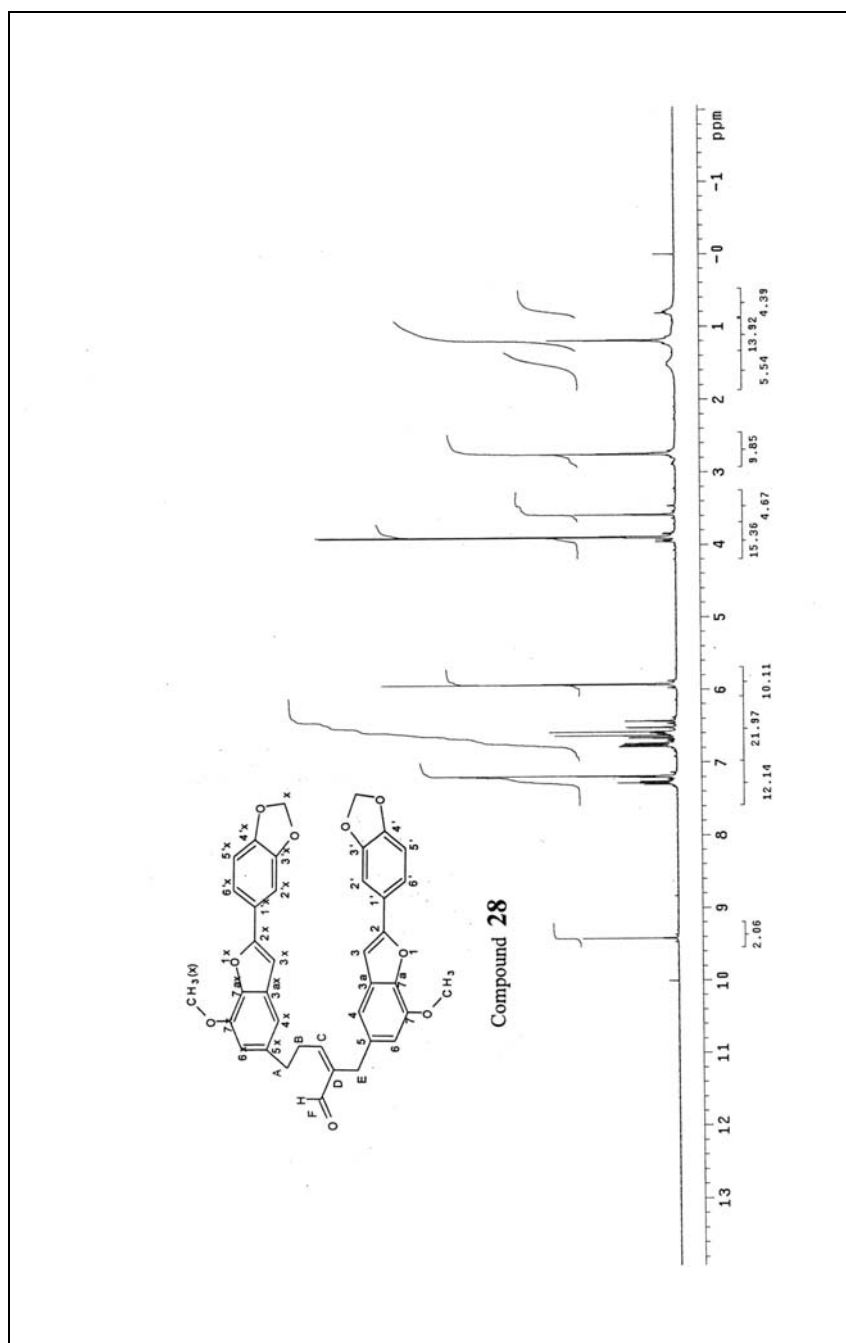


Figure 3.58. The ^1H -NMR Spectrum of Compound 28

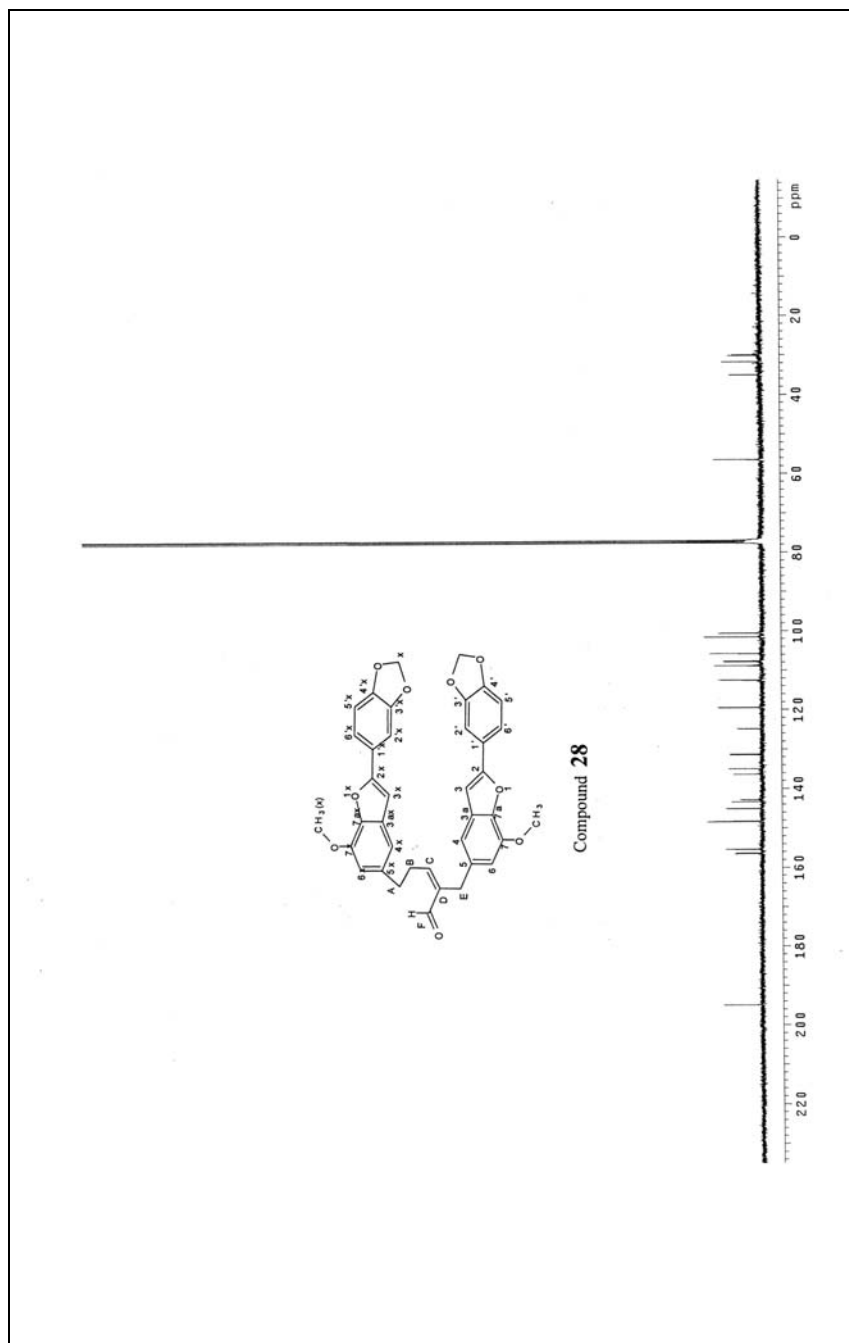
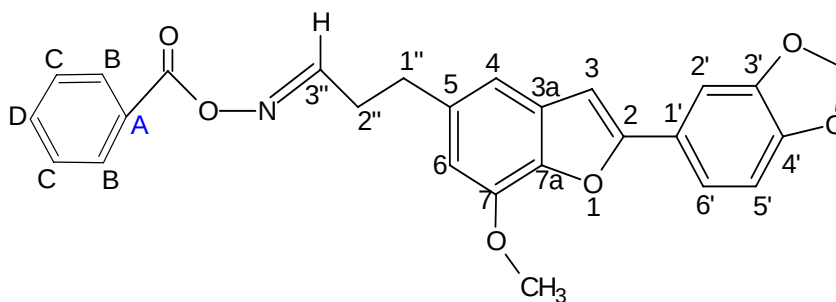


Figure 3.59. The ¹³C-NMR Spectrum of Compound 28

Table 3.31. ^1H - and ^{13}C -NMR spectroscopic data of compound **29** in CDCl_3 (δ ppm)

Position	δ ^1H (Compound 26)	δ ^1H (Compound 29)	δ ^{13}C (Compound 26)	δ ^{13}C (Compound 29)
2	-	-	155.922	155.51
3	7.17, s, 1H	6.69, s, 1H	101.74	100.34
3a	-	-	131.20	131.73
4	6.99, s, 1H	7.21, s, 1H	112.73	111.45
5	-	-	137.90	141.61
6	6.76, s, 1H	6.55, s, 1H	108.34	107.63
7	-	-	145.08	144.10
7a	-	-	142.42	143.91
OCH_2O	6.06, s, 2H	5.95, s, 2H	102.12	104.54
1'	-	-	124.68	127.41
2'	7.39	6.89, d, 1H, $J=15.6$	105.66	106.12
3'	-	-	148.64	147.15
4'	-	-	148.51	147.09
5'	7.01, d, 1H, $J=8.0$	6.78, d, 1H, $J=8.0$	109.50	111.23
6'	7.34, dd, 1H, $J=1.6, 8.0$	7.31, dd, 1H, $J=8.4, 9.6$	119.44	118.31
1''	2.80, t, 2H, $J=7.6$	2.94	32.40	28.67
2''	2.59, 2H	3.91, 2H	27.29	30.93
3''	6.69, t, 1H, $J=5.2$	7.35, t, 1H	150.42	204.02
OMe	3.93, s, 3H	3.95, s, 3H	56.49	55.24
HO-N	10.78	-	-	-
A	-	-	-	200.73
B	-	8.02, d, $J=8.0$	-	123.59
C	-	7.35, t, $J=7.4$	-	130.37
D	-	7.45	-	132.82
C=O	-	-	-	212.47

Compound **29**

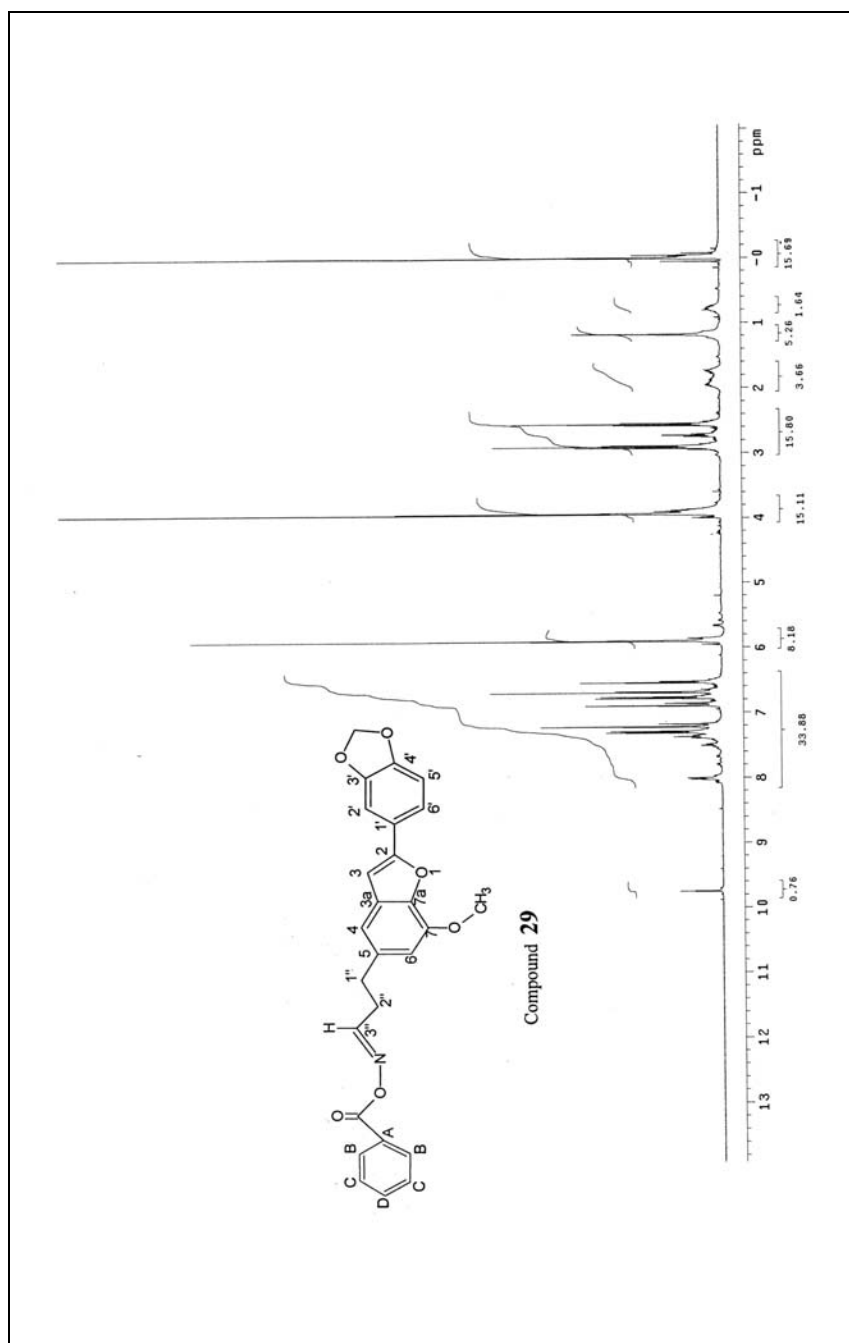


Figure 3.60. The ^1H -NMR Spectrum of Compound 29

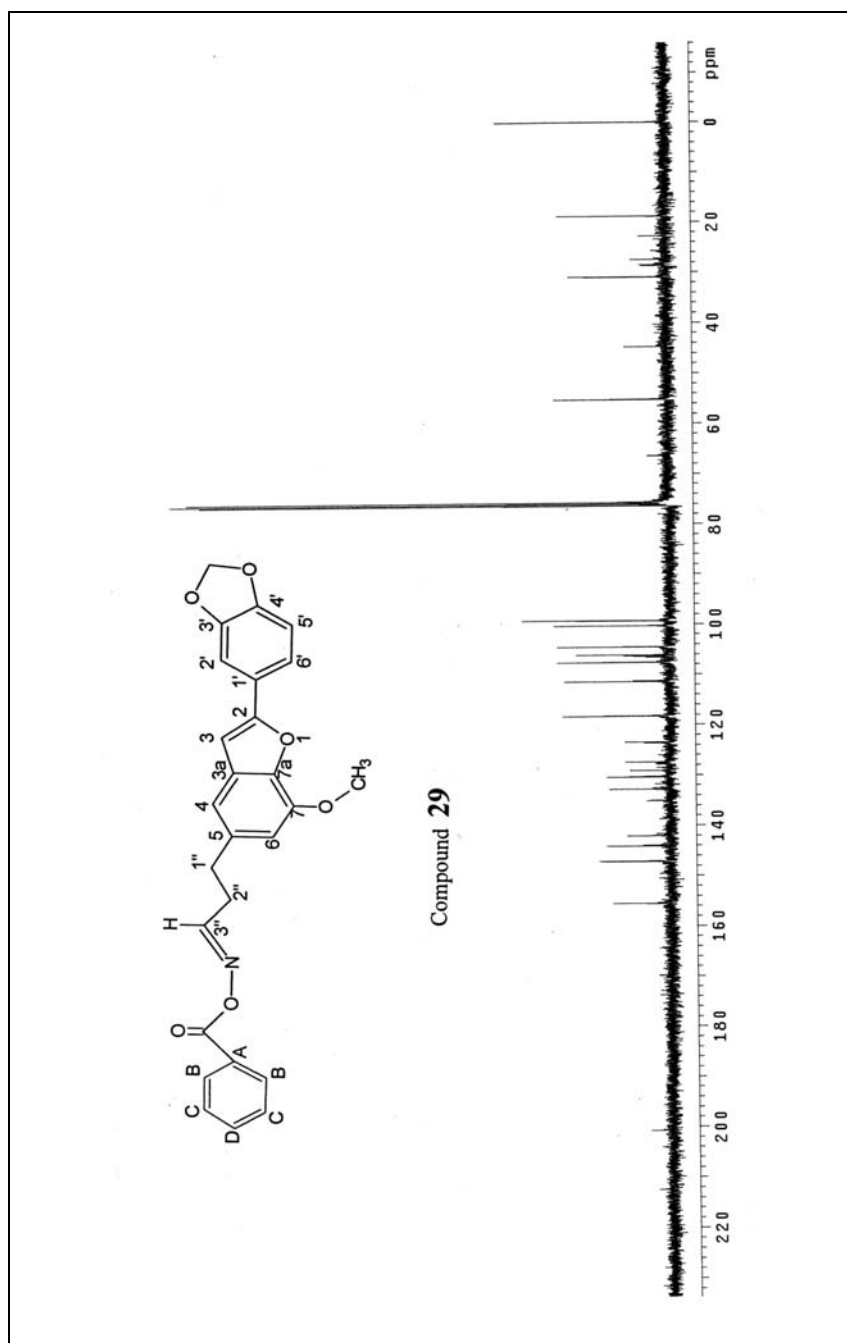
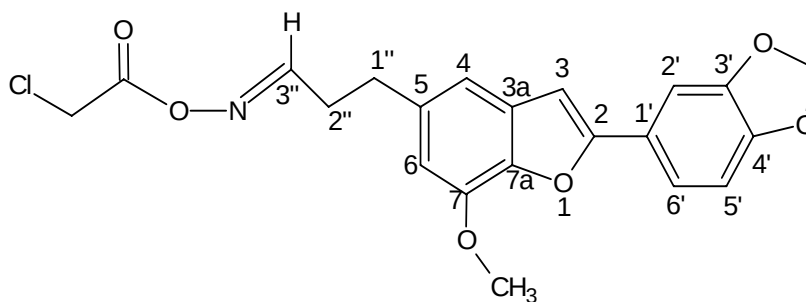


Figure 3.61. The ¹³C-NMR Spectrum of Compound 29

Table 3.32. ^1H - and ^{13}C -NMR spectroscopic data of compound **30** in CDCl_3 (δ ppm)

Position	δ ^1H (Compound 26)	δ ^1H (Compound 30)	δ ^{13}C (Compound 26)	δ ^{13}C (Compound 30)
2	-	-	155.922	155.50
3	7.17, s, 1H	6.73, s, 1H	101.74	99.34
3a	-	-	131.20	130.37
4	6.99, s, 1H	6.93, s, 1H	112.73	111.48
5	-	-	137.90	132.90
6	6.76, s, 1H	6.60, s, 1H	108.34	107.64/ 106.41
7	-	-	145.08	144.12
7a	-	-	142.42	142.03
OCH_2O	6.06, s, 2H	5.93, s, 2H	102.12	100.37
1'	-	-	124.68	123.46
2'	7.39	7.24, d, 1H, $J=1.6$	105.66	106.41
3'	-	-	148.64	147.17
4'	-	-	148.51	147.13
5'	7.01, d, 1H, $J=8.0$	6.80, d, 1H, $J=8.0$	109.50	107.64/ 106.41
6'	7.34, dd, 1H, $J=1.6, 8.0$	7.33, dd, 1H, $J=1.6, 8.0$	119.44	118.32
1''	2.80, t, 2H, $J=7.6$	2.95	32.40	30.95
2''	2.59, 2H	3.51	27.29	39.89
3''	6.69, t, 1H, $J=5.2$	6.73	150.42	166.26
OMe	3.93, s, 3H	3.98, s, 3H	56.49	55.27
C=O	-	-	-	166.31
CH_2Cl	-	-	-	43.96
CH_2Cl	-	4.17	-	-

Compound **30**

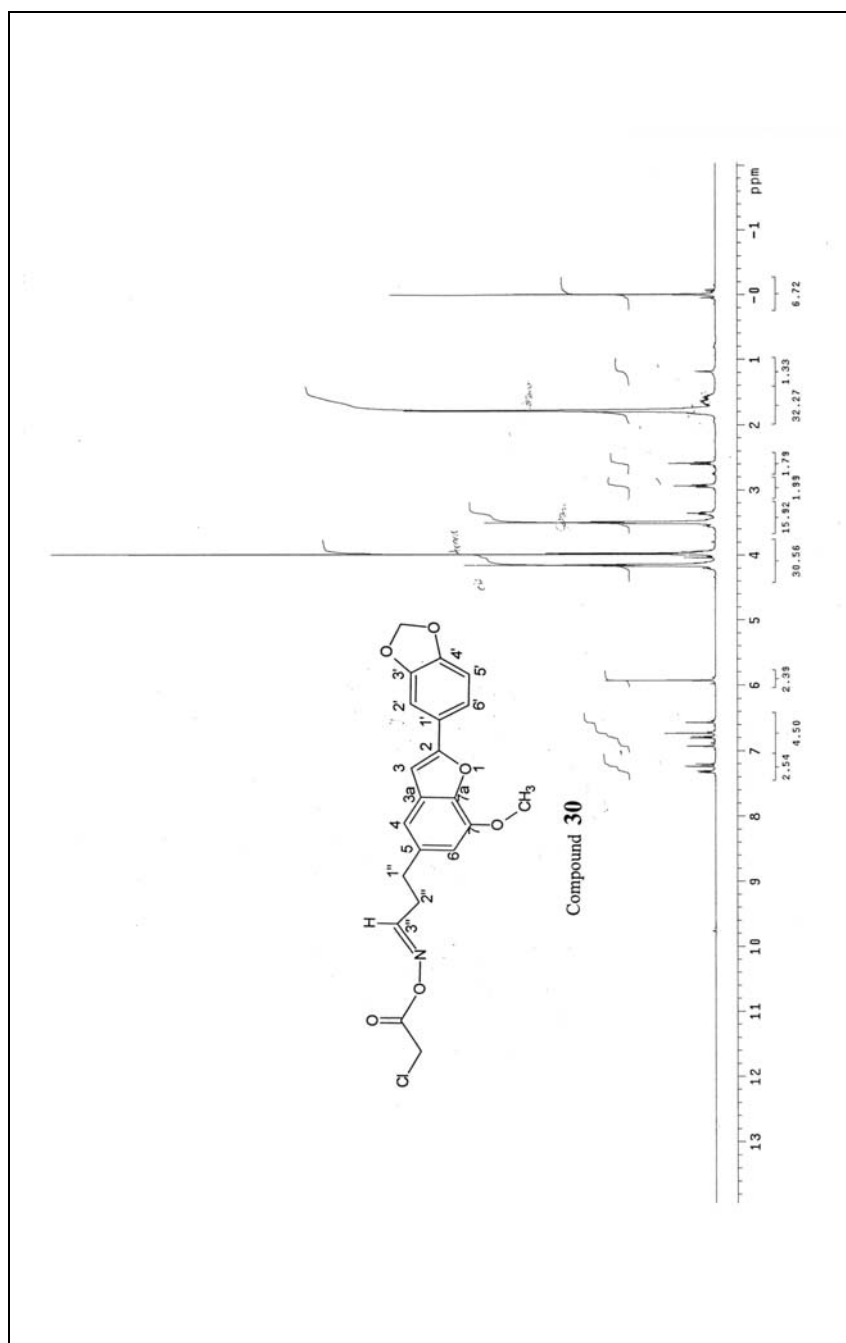


Figure 3.62. The ^1H -NMR Spectrum of Compound 30

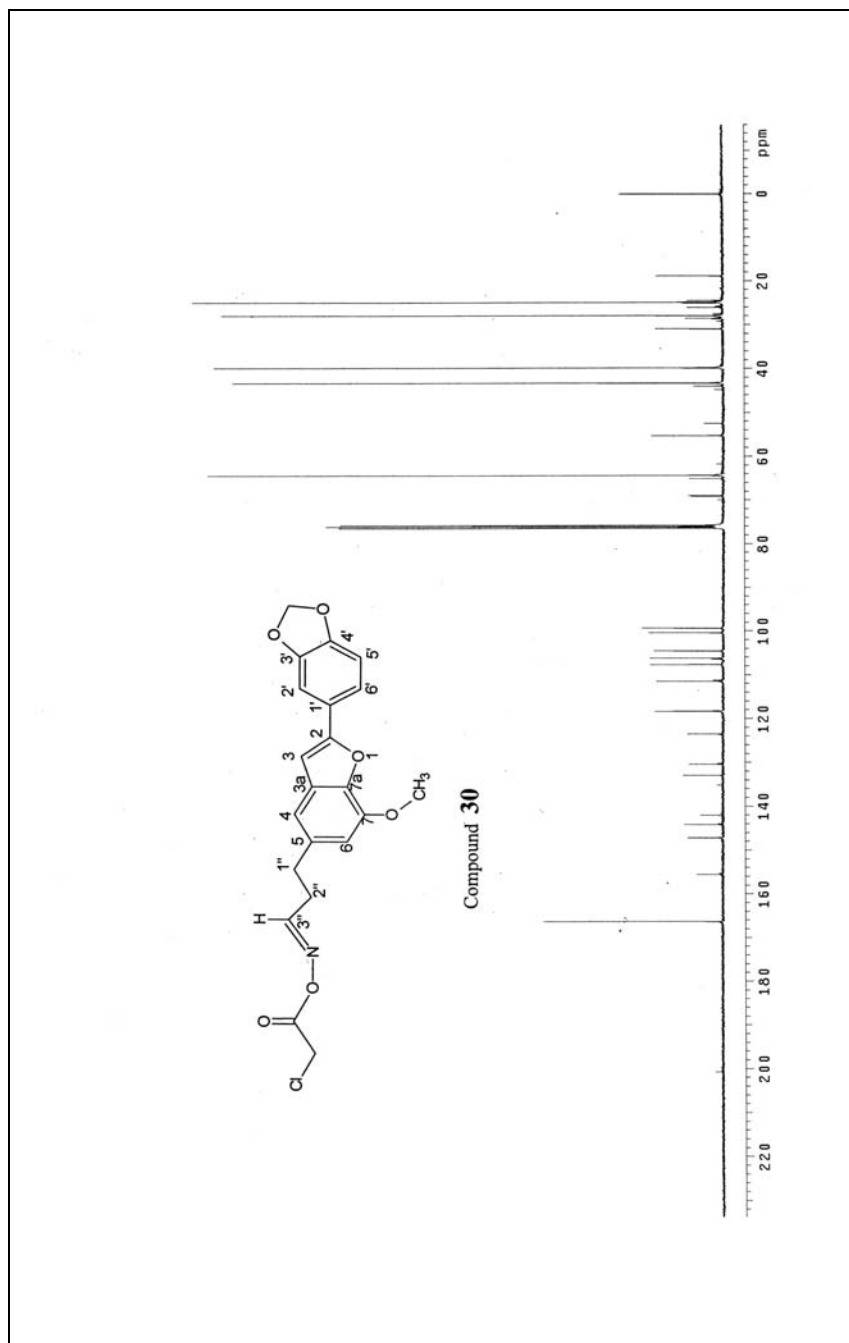


Figure 3.63. The ¹³C-NMR Spectrum of Compound 30

3.1. Conclusion

The shade dried and pulverized seeds of *S. officinalis* L were exhaustively extracted with n-hexane at room temperature. After removal of the solvent in vacuo, a crude yellow oily extract was obtained which was hydrolyzed. After isolation and purification processes, egonol, 5-[3''-(hydroxy)propyl]-7-metoxy-2-(3',4'-methylenedioxy phenyl)benzofuran was obtained. Thirty compounds were synthesized from egonol. Their structures were elucidated by spectral methods including IR, UV, ^1H and ^{13}C NMR, HMQC, COSY and LC-MS. The antimicrobial activities of all compounds were analyzed against different types of microorganisms by the Broth dilution method.

Compounds 5,11,12 and 17 showed similar MIC values to egonol.

Compounds 4, 14, 15, 20, 26 and 27 showed noticeable activity against *C. albicans*. This is an interesting result because the known antibiotics erythromycin and tetracyclin show no activity against this microorganisms.

Compounds **6, 18, 19, 24, 28** and **30** were found to be the most active compounds with values of 25 $\mu\text{g/mL}$ against *S. aureus* and *C. albicans* microorganisms.

REFERENCES

- Baraldi, P.G., Romagnoli, R., Pavani, M.G., Nunez, M.C., Bingham, J.P. and Hartley, J.A.,** 2002, Benzoyl and Cinnamoyl Nitrogen Mustard Derivatives of Benzoheterocyclic Analogues of the Tallimustine: Synthesis and Antitumour Activity, *Bioorganic & Medicinal Chemistry*, 10, 1611-1618.
- Bean, W.,** 1981, *Trees and Shrubs Hardy in Great Britain. Vol 1 - 4 and Supplement.* Murray
- Behrens, C., Nielsen, J.N., Fan, X.J., Doisy, X. Kim, K.H., Praetorius-Ibba, M., Nielsen, P.E. and Ibba, M.,** 2000, Development of Strategies for the Site-Specific In Vivo Incorporation of Photoreactive Amino Acids: p-Azidophenylalanine, p-Acetylphenylalanine and Benzofuranylalanine, *Tetrahedron*, 56, 9443-9449.
- Black, D.S.C. and Rezaie, R.,** 1999, Modified Vilsmeier Reactions of Activated Benzofurans with Indolines: Synthesis of Benzofuran-fused Benzocarbazoles, *Tetrahedron Letters*, 40, 4251-4254.
- Black, D.S.C., Craig, D.C., Kumar, N. and Rezaie, R.,** 2002, Acid-catalysed reactions of activated benzofuranylmethanols: formation of calixbenzofurans, *Tetrahedron*, 58, 5125-5134.
- Bogdal, D. and Warzala, M.,** 2000, Microwave-Assisted Preparation of Benzo [b]furans under Solventless Phase-Transfer Catalytic Conditions, *Tetrahedron*, 56, 8769-8773.
- Bosiak, M.J., Krzemiński, M.P., Jaisankar, P. and Zaidlewicz, M.,** 2008, Asymmetric synthesis of N-1-(heteroaryl)ethyl-N-hydroxyureas, *Tetrahedron: Asymmetry*, 19, 956-963.
- Choi, H.D., Seo, P.J., Son, B.W. and Kang, B.W.,** 2004, Synthesis of 2-(4-Hydroxyphenyl)benzofurans and Their Application to β -Amyloid Aggregation Inhibitor, *Arch Pharm Res.*, 27(1), 19-24.

REFERENCES (Continue)

- Chopra. R. N., Nayar. S. L. and Chopra. I. C.,** 1986, *Glossary of Indian Medicinal Plants (Including the Supplement)*. Council of Scientific and Industrial Research, New Delhi.
- Collini, M.D., Kaufman, D.H., Manas, E.S., Harris, H.A., Henderson, R.A., Xu, Z.B., Unwalla, R.J. and Miller, C.P.,** 2004, 7-Substituted 2-phenyl-benzofurans as ER β selective ligands, *Bioorganic & Medicinal Chemistry Letters*, 14, 4925-4929.
- Dai, W.M. and Lai, K.W.,** 2002, Chemistry of aminophenols. Part 3: First synthesis of nitrobenzo[b]furans via a coupling–cyclization approach, *Tetrahedron Letter*, 43, 9377-9380.
- Davis, P.H.,** 1978, Flora of Turkey, and the East Aegean Islands, 6, 144.
- Demirayak, Ş., Uçucu, Ü., Benkli, K., Karaburun, N.G., Karaburun, A.Ç., Akar, D., Karabacak, M. and Kiraz N.,** 2002, Synthesis and antifungal activities of some aryl(benzofuran-2-yl)ketoximes, *Il Farmaco*, 57, 609-612.
- Dixit, M., Tripathi, B.K., Tamrakar, A.K., Srivastava, A.K., Kumar, B. and Goel, A.,** 2007, Synthesis of benzofuran scaffold-based potential PTP-1B inhibitors, *Bioorganic & Medicinal Chemistry*, 15, 727-734.
- Dupont, R. and Cotelle, P.,** 2001, An expeditious synthesis of polyhydroxylated 2-arylbenzo[b]furans, *Tetrahedron*, 57, 5585-5589.
- Ebiike, H., Masubuchi, M., Liu, P., Kawasaki, K., Morikami, K., Sogabe, S., Hayase, M., Fujii, T., Sakata, K., Shindoh, H., Shiratori, Y., Aoki, Y., Ohtsuka, T. and Shimma, N.,** 2002, Design and Synthesis of Novel Benzofurans as a New Class of Antifungal Agents Targeting Fungal N-Myristoyltransferase. Part 2, *Bioorganic & Medicinal Chemistry Letters*, 12, 607-610.

REFERENCES (Continue)

- Ebiike, H., Masubuchi, M., Liu, P., Kawasaki, K., Morikami, K., Sogabe, S., Hayase, M., Fujii, T., Sakata, K., Shindoh, H., Shiratori, Y., Aoki, Y., Ohtsuka, T. and Shimma, N., 2002,** Design and Synthesis of Novel Benzofurans as a New Class of Antifungal Agents Targeting Fungal N-Myristoyltransferase. Part 2, *Bioorganic & Medicinal Chemistry Letters*, 12, 607-610.
- Fuganti, C. and Serra, S., 1998,** A New Approach to 2-Aryl-7-Alkoxy-Benzofurans: Synthesis of Ailanthoidol, a Natural Neolignan, *Tetrahedron Letters*, 39, 5609-5610.
- Gilchrist, T.L., 1985,** Heterocyclic Chemistry, Longman Group UK Limited, England, 174p.
- Hamilton, C.J., Saravanamuthu, A., Fairlamb, A.H. and Eggleston, I.M., 2003,** Benzofuranyl 3,5-bis-Polyamine Derivatives as Time-Dependent Inhibitors of Trypanothione Reductase, *Bioorganic & Medicinal Chemistry*, 11,3683-3693.
- Hammer, K.A., Carson, C.F. and Riley, T.V., 2000,** In Vitro Activities of Ketoconazole, Econazole, Miconazole, and *Melaleuca alternifolia* (Tea Tree) Oil against *Malassezia* Species, *Antimicrobial Agents and Chemotherapy*, 44(2), 467-469.
- Hayakawa, I., Shioya, R., Agatsuma, T., Furukawa, H. and Sugano, Y., 2004,** Thienopyridine and benzofuran derivatives as potent anti-tumor agents possessing different structure–activity relationships, *Bioorganic & Medicinal Chemistry Letters*, 14, 3411-3414.
- Haywood. V. H.,** *Flowering Plants of the World*. Oxford University Press 0 ISBN 0-19-217674-9
- Hopkins, C. Y., Ewing, D.F. and Chisholm, M.J., 1967,** Egonol spectrometric properties and derivatives, *Canadian Journal of Chemistry*, 45, 1425-1429.

REFERENCES (Continue)

- Howlett, D.R., Perry, A.E., Godfrey, F., Swatton, J.E., Jennings, K.H., Spitzfaden, C., Wadsworth, H., Wood, S. J. and Markwell, R.E., 1999, Inhibition of fibril formation in β -amyloid peptide by a novel series of benzofurans, *Biochemical Society*, 340, 283-289.
- Hutchinson, S.A., Luetjens, H., and Scammells, P.J., 1997, A New Synthesis of The Benzofuran Adenosine Antagonist XH-14, *Bioorganic & Medicinal Chemistry Letters*, 7(24), 3081-3084.
- Ishibashi, K., Nakajima, K., Sugioka, Y., Sugiyama, M., Hamada, T., Horikoshi, H. and Nishi, T., 1998, Synthesis and 5α -Reductase Inhibitory Activities of Benzofuran Derivatives with a Carbamoyl Group, *Bioorganic & Medicinal Chemistry Letters*, 8, 561-566.
- Kaltenbornn, J.S., Quin, J. III, Reisdorph, B.R., Klutchko, S., Reynolds, E.E., Welch, K.M., Flynn, M.A. and Doherty, A.M., 1996, Benzofuran derivatives as ET_A -selective, non-peptide endothelin antagonists, *Eur J. Med Chem*, 32, 425-431.
- Kao, C.L. and Chern, J.W., 2002, A Novel Strategy for the Synthesis of Benzofuran Skeleton Neolignans: Application to Ailanthoidol, XH-14, and Obovaten, *J. Org. Chem.*, 67, 6772-6787.
- Karaburun, N.G., Benkli, K., Tunali, Y., Uçucu, Ü. and Demirayak, Ş., 2006, Synthesis and antifungal activities of some aryl [3-(imidazol-1-yl)triazol-1-ylmethyl] benzofuran-2-yl] ketoximes, *European Journal of Medicinal Chemistry*, 41, 651-656.
- Kawasaki, K., Masubuchi, M., Morikami, K., Sogabe, S., Aoyama, T., Ebüike, H., Niizuma, S., Hayase, M., Fujii, T., Sakata K., Shindoh, H., Shiratori, Y., Aoki, Y., Ohtsuka, T., and Shimma N., 2003, Design and Synthesis of Novel Benzofurans as a New Class of Antifungal Agents Targeting Fungal N-Myristoyltransferase. Part 3, *Bioorganic & Medicinal Chemistry Letters*, 13, 87-91.

REFERENCES (Continue)

- Khan, M.W., Alam, M.J., Rashid, M.A. and Chowdhury, R.,** 2005, A new Structural alternative in benzo [*b*] furans for antimicrobial activity, *Bioorganic & Medicinal Chemistry*, 13, 4796-4805.
- Kim, Y.W., Choi, H.D., Seo, P.J. and Son, B.W.,** 2001, Synthesis of 2-Arylbenzofuran Derivatives Using ω -(Methylsulfinyl)acetophenones, *Journal of the Korean Chemical Society*, 45(4), 391-394.
- Kinnamon, K.E., Poon, B.T., Hanson, W.L. and Waits, V.B.,** 1998, Trypanosoma cruzi: A Novel Chemical Class (Nitrobenzofurans) Active against Infections of Mice (Mus musculus), *Experimental Parasitology*, 89, 251-256.
- Kirilmis, C., Ahmedzade, M., Servi, S., Koca, M., Kizirgil, A. and Kazaz, C.,** 2008, Synthesis and antimicrobial activity of some novel derivatives of benzofuran: Part 2. The synthesis and antimicrobial activity of some novel 1-(1-benzofuran-2-yl)-2-mesitylethanone derivatives, *European Journal of Medicinal Chemistry*, 43, 300-308.
- Koca, M., Ahmedzade, M., Çukurovalı, A. and Kazaz, C.,** 2005, Studies on the Synthesis and Reactivity of Novel Benzofuran-2-yl-[3-Methyl-3-Phenylcyclobutyl] Methanones and their Antimicrobial Activity, *Molecules*, 10, 747-754.
- Koca, M., Servi, S., Kirilmis, C., Ahmedzade, M., Kazaz, C., Özbek, B. and Ötük, G.,** 2005, Synthesis and antimicrobial activity of some novel derivatives of benzofuran: part 1. Synthesis and antimicrobial activity of (benzofuran-2-yl)(3-phenyl-3-methylcyclobutyl) ketoxime derivatives, *European Journal of Medicinal Chemistry*, 40(12), 1351-1358.
- Kyei, A.S., Tchabanenko, K., Baldwin, J.E. and Adlington, R.M.,** 2004, Radical dearomatising spirocyclisations onto the C-2 position of benzofuran and indole, *Tetrahedron Letters*, 45, 8931-8934.

REFERENCES (Continue)

- Li, H., Fu, B., Wang, M.A., Li, N., Liu, W.J., Xie, Z.Q, Ma, Y.Q. and Qin, Z.,** 2008, Total Synthesis and Biological Activity of ($\pm$)-Rocaglamide and Its 2,3-Di-epi Analogue, *Eur. J. Org. Chem.*, 1753-1758.
- Masubuchi, M., Ebiiike, H., Kawasaki, K., Sogabe, S., Morikami, K., Shiratori, Y., Tsujii, S., Fujii, T., Sakata, K., Hayase, M., Shindoh, H., Aoki, Y., Ohtsuka, T. and Shimma, N.,** 2003, Synthesis and Biological Activities of Benzofuran Antifungal Agents Targeting Fungal N-Myristoyltransferase, *Bioorganic & Medicinal Chemistry*, 11, 4463-4478.
- Masubuchi, M., Kawasaki, K., Ebiiike, H., Ikeda, Y., Tsujii, S., Sogabe, S., Fujii, T., Sakata, K., Shiratori, Y., Aoki Y., Ohtsuka, T. and Shimma, N.,** 2001, Design and Synthesis of Novel Benzofurans as a New Class of Antifungal Agents Targeting Fungal N-Myristoyltransferase. Part 1, *Bioorganic & Medicinal Chemistry Letters*, 11, 1833-1837.
- McGarry, D.G., Regan, J.R., Volz, F.A., Hulme, C., Moriarty, K.J., Djuric, S.W., Souness, J.E., Miller, B.E., Travis, J.J. and Sweeney, D.M.,** 1999, Benzofuran Based PDE4 Inhibitors, *Bioorganic & Medicinal Chemistry*, 7, 1131-1139
- Messina, F., Botta, M., Corelli, F. and Mugnaini, C.,** 1999, Chiral Azole Derivatives, 3¹. Synthesis of the Enantiomers of the Potent Aromatase Inhibitor 1-[2-Benzofuranyl(4-chlorophenyl)methyl]-1*H*-imidazole, *Tetrahedron Letters*, 40, 7289-7292
- Miert, S.V., Dyck, S.V., Schmidt, T.J., Brun, R., Vlietinck, A., Lemièrre, G. and Pieters, L.,** 2005, Antileishmanial activity, cytotoxicity and QSAR analysis of synthetic dihydrobenzofuran lignans and related benzofurans, *Bioorganic & Medicinal Chemistry*, 13, 661-669
- Niebuhr. A. D.,** 1970, *Herbs of Greece*. Herb Society of America.

REFERENCES (Continue)

- Oka, T., Yasusa, T., Ando, T., Watanabe, M., Yoneda, F., Ishida, T. and Konll, J.,** 2001, Enantioselective Synthesis and Absolute Configuration of (-)-1-(Benzofuran-2-yl)-2-propylaminopentane, ((-)-BPAP), a Highly Potent and Selective Catecholaminergic Activity Enhancer, *Bioorganic & Medicinal Chemistry Letters*, 9, 1213-1219.
- Ono, M., Kung, M.P., Hou, C. and Kung, H.F.,** 2002, Benzofuran derivatives as A β -aggregate-specific imaging agents for Alzheimer's disease, *Nuclear Medicine and Biology*, 29, 633-642.
- Öztürk, S.E., Akgül, Y. and Anıl, H.,** 2008, Synthesis and antibacterial activity of egonol derivatives, *Bioorganic & Medicinal Chemistry*, 16, 4431-4437.
- Pauletti, P.M., Araújo, A.R., Young, M.C.M., Giesbrecht, A.M. and Bolzani, V.S,** 2000, nor-Lignans from the leaves of *Styrax ferrugineus* (Styracaceae) with antibacterial and antifungal activity, *Phytochemistry*, 55(6), 597-601.
- Polunin, O. and Huxley, A.,** *Flowers of the Mediterranean*. Hogarth Press 1987 ISBN 0-7012-0784-1
- Rádl, S., Hezký, P., Konvička, P., Váchal, P. and Krejčí, I.,** 2000, a, Synthesis and Analgesic Activity of some 1-Benzofurans, 1-Benzothiophenes, *Collect. Czech. Chem. Commun.*, 65, 1093-1108.
- Rádl, S., Hezký, P., Urbánková, J., Váchal, P. and Krejčí, I.,** 2000, b, Synthesis and Analgesic Activity of some 1-Benzofurans, 1-Benzothiophenes and Indoles, *Collect. Czech. Chem. Commun.*, 65, 280-296.
- Ritchie, E. and Taylor, W.C.,** 1969, A new synthesis of egonol, *J. Chem.*, 22, 1329-1330.

REFERENCES (Continue)

- Rizzo, S., Riviere, C., Piazzzi, L., Bisi, A., Gobbi, S., Bartolini, M., Andrisano, V., Morroni, F., Tarozzi, A., Monti, J.P. and Pampa, A.,** 2008, Benzofuran-Based Hybrid Compounds for the Inhibition of Cholinesterase Activity, β Amyloid Aggregation, and A β Neurotoxicity, 51, 2883-2886.
- Sadeghi-Aliabadi, H., Jafarian, A., Fatemi, S.A., Shahidi, G. and Emami, S.A.,** 2007, Evaluation of some Iranian conifers extracts cytotoxicity, using *Sacharomyces cerevisiae*, RS 322N and RS 188N, *Reasearch in Pharmaceutical Sciences*, 2, 66-72.
- Satoh, T., Tsuda, T., Terao, Y., Miura, M. and Nomura, M.,** 1999, Palladium-catalyzed cross-carbonylation of phenolic compounds with aldehydes to give benzofuran-2(3H) -one derivatives, *Journal of Molecular Catalysis A: Chemical*, 143, 203-210.
- Scammells, P.J., Baker, S.P. and Beaglehole, A.R.,** 1998, XH-14 Analogues as Adenosine Antagonists, *Bioorganic & Medicinal Chemistry*, 6, 1517-1524.
- Sogabe, S., Masubuchi, M., Sakata, K., Fukami, T.A., Morikami, K., Shiratori, Y., Ebiike, H., Kawasaki, K., Aoki, Y., Shimma, N., D'Arcy, A., Winkler, F.K., Banne, D.W. And Ohtsuka, T.,** 2002, Crystal Structures of *Candida albicans* N-Myristoyltransferase with Two Distinct Inhibitors, *Chemistry & Biology*, 9, 1119-1128.
- Spaniol, M., Bracher, R., Riem Ha, H., Follath, F., Krähenbühl, S.,** 2001, Toxicity of amiodarone and amiodarone analogues on isolated rat liver mitochondria, *Journal of Hepatology*, 35, 628-636.
- Sun, L.Q., Takaki, K., Chen, J., Iben, L., Knipe, J.O., Pajor, L., Mahle, C.D., Ryan, Elaine. And Xu, C.,** 2004, N-{2-[2-(4-Phenylbutyl)benzofuran-4-yl]cyclopropylmethyl}-acetamide: an orally bioavailable melatonin receptor agonist, *Bioorganic & Medicinal Chemistry*, 14, 5157-5160.

REFERENCES (Continue)

- Takanashi, M. and Takizawa, Y.**, 2002, Isolation of new egonol compounds from seeds of *Styrax japonica* sieb. et zucc., *J. Oleo Sci.*, 51(3), 151-155.
- Tayoub, G., Schwob, I., Bessie`re, J.M., Masotti V., Rabier, J., Ruzzier, M., and Viano, J.**, 2006, Composition of volatile oils of *Styrax* (*Styrax officinalis* L.) leaves at different phenological stages, *Biochemical Systematics and Ecology*, 34, 705-709.
- Tewtrakul, S., Yuenyongsawad, S., Kummee, S. And Atsawajaruwan, L.**, 2005, Chemical components and biological activities of volatile oil of *Kaempferia galanga* Linn., *Songklanakarin J. Sci. Technol*, 27(2), 503-507.
- Thomas, G. S.**, *Ornamental Shrubs, Climbers and Bamboos*. Murray 1992 ISBN 0-7195-5043-2
- Tsai, I.L., Hsien, C.F. and Duh, C.Y.**, 1997, Additional Cytotoxic Neolignans from *Persea Obovatifolia*, *Phytochemistry*, 48(8), 1371-1375.
- Wyatt, P.G., Allen, M.J., Chilcott, J., Gardner, C.J., Livermore, D.G., Mordaunt, J.E., Nerozzi, F., Patel, M., Perren, M.J., Weingarten, G.G., Shabbir, S., Woollard, P.M. and Zhou, P.**, 2002, Identification of Potent and Selective Oxytocin Antagonists Part 2: Further Investigation of Benzofuran Derivatives, *Bioorganic & Medicinal Chemistry Letters*, 12, 1405-1411.
- Yoo, S., Lee, S.H., Kim, S.K. and Lee, S.H.**, 1997, The Conformation and Activity Relationship of Benzofuran Derivatives as Angiotensin II Receptor Antagonists, *Bioorganic & Medicinal Chemistry*, 5(2), 445-459.

CURRICULUM VITAE

PERSONEL KNOWLEDGE

Name Surname : Safiye EMİRDAĞ ÖZTÜRK
Date/ Place of Birth : 22.06.1977/İZMİR
Nationality : Turkish
Home Address : 6001. sok. No:22 D:3 Karşıyaka/İZMİR
Phone Nंबर : (0232) 3641915

EDUCATIONAL BACKGROUND

1995-1999 BSc. In Chemistry, Ege University, Faculty of Art and
Science Graduation Degree: 70/100

1999-2000 Preparation Class (English)
Foreign Languages Department, Ege University

2000-2002 MSc. in Organic Chemistry (In English), Graduate School
of Natural and Applied Sciences, Ege University
Graduation Degree: 97/100

2000-2003 PhD. in Organic Chemistry (In English), Graduate School
of Natural and Applied Sciences, Ege University