Synthesis of Some Amidoalkyl naphthol and Benzoxanthene Derivatives by Zinc Oxide Nanoparticles as a Catalyst under Solvent-Free Condition and Evaluation of their Antimicrobial and Antioxidant Activities

By: Demirew Abera

A Thesis Submitted to the Department of Applied Chemistry Program

School of Applied Natural Science

In Partial Fulfillment of the Requirements for the Degree of

Master of Science in Chemistry (Synthetic Organic Chemistry)

Office of Graduate Studies

Adama Science and Technology University

December, 2018

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Approval Sheet

Submitted by

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As a thesis research advisor/s, We hereby certify that we have read and evaluated this thesis prepared under our guidance by Demirew Abera. We recommended the paper to be submitted as fulfilling the requirements for the Degree of Master of Science in Chemistry (Synthetic Organic Chemistry).

Advisor	Signature	Date

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DECLARATION

I hereby declare that the thesis entitled "Synthesis of Some Amidoalkyl naphthol and Benzoxanthene Derivatives by Zinc Oxide Nanoparticles Catalyst under Solvent-Free Condition and Evaluation of their Antimicrobial and Antioxidant Activities." has been carried out by me under the supervision of Dr. H/mikael Tesso, during the year 2017/2018 as part of Master of Science Program in Synthetic Organic Chemistry Chemistry. I further declare that this work has not been submitted to any other Universities or institutions for the award of any degree. All quotations and their sources are specifically acknowledged by means of references.

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Date of Submission _____

DEDICATION

This M.Sc. thesis is dedicated to my beloved families, especially to my Brother Sisay Abera and Kebede abera, my Father Abera Ketema and my sisters (Aster Abera and Emebet Abera), whose advice, support, prayers and love helped me all along the right way and made me who I am today. They will always be in my heart forever.

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ABSTRACT

Synthesis of amidoalkyl naphthol and benzoxanthene is significant, because they have important pharmaceutical applications. They exhibit wide range of biological activities such as antimalarial, anticancer, antibacterial, antifungal, antiviral, anti-inflammatory, analgesic, antirheumatic and antianginal. In this research, some of amidoalkyl naphthol and benzoxanthene derivatives were synthesized by one-pot condensation reaction of aromatic aldehydes,beta-naphthol and amide using zinc oxide nanoparticles (ZnO NPs). The structures of the synthesized compounds were characterized by spectroscopic techniques (FT-IR spectra and NMR spectra). The synthesized compounds have been screened for their biological activities such as antibacterial activities against gram positive bacterial strains (*S.aureus ATCC 25923,* B. subtilis ATCC 6623), gram negative bacterial strains (*E. coli ATCC 25922, P.aeroginosa ATCC 7553*) using tetracycline as positive control*,* antifungal activities against *C. albicunas* using fluconazole as positive control. Antioxidant activities of synthesized compounds were determined by using 2, 2-diphenyl-1-picryl-hydrazyl (DPPH) assay method and ascorbic acid as a standard. The corresponding synthesized amidoalkyl naphthols **27**, **28** (89.8-90.4%) and benzoxanthenes **29**, 3**0** and **31** (89.4-93.5%) were found higher yield than other reported methods. Antibacterial activity results of synthesized benzoxanthenes **30 and 31** showed activities with zone of inhibition (mm) against all gram negative strains (9-15mm) and gram positive bacterial strains (9-13mm) tested where as benzoxanthene 29 was active against *B. subtilis* (8,9,10mm), (10,11,12mm) for both *B. subtilis and E.coli*. Amidoalkyl naphthol **27** showed activity against *B. subtilis* (10, 11, 12mm) *only* and amidoalkyl naphthol **28** was active against both *B. subtilis* (9, 10,12mm) *and E.coli* (10, 11,15mm). Amongst all, the benzoxanthene **29** has only shown antifungal activity against *C. albicuna* (12, 14,16 mm zone of inhibition) even stronger than the standard fluconazole and amidoalkyl naphthol **28**, **27** and benzoxanthenes **30**, **31** were inactive against *C. albicuna*. Except benzoxanthene **31**, All the remaining synthesized compounds have shown promising antioxidant activities with an IC_{50} values of 24.45, 17.65, 22.6 and 47.56 µg/ml for amidoalkyl naphthol 27, **28** and benxoxanthene **29**, compared to standard ascorbic acid (9.28µg/ml)respectively.

Keywords: Antibacterial, Antifungal, Antioxidant, Amidoalkyl naphthols, Benzoxanthenes.

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LIST OF ABBREVIATIONS

AA	Ascorbic Acid
CA-SiO_2	Caro's Acid Silica gel
CSA	(±) –Camphor -10-Sulfonic Acid
DMSO	Dimethyl Sulfoxide
DPPH	1, 1, diphenyl -2-picrylhydrazyl radical
MCRs	Multi-component Reactions
MHA	Mueller Hinton Agar
NPs	Nanoparticles
O-QMs	Ortho-quinone methides
PEG-400	Poly (4-ethylene glycol)
SESA	[2-(sulfooxy) ethyl] Sulfamic Acid
TCS	Tetrachlorosilane
TEA	Triethanol amine
TMS	Tetramethylsilane
TSA	Tryptose Soya Agar
VSA	Vanadate Sulfonic Acid

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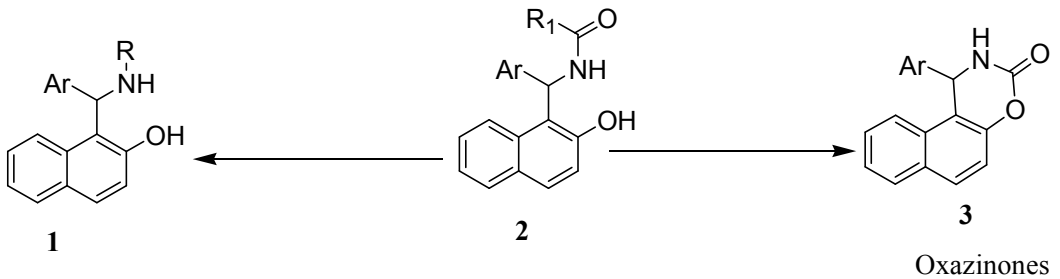
1. INTRODUCTION

1.1. Background

The naphthalene and its derivatives play important roles in the chemical and pharmaceutical industries [1]. They have shown a wide spectrum of biological activities. Naphthols are one of the naphthalene derivatives. Literature survey reveals that extensive research has been done on β-naphthol as an excellent lead moiety for designing a synthetic derivative, which possess good biologically activity [2-6].

Amidoalkyl naphthols and Benzoxanthenes are the class of organic compounds which are derived from naphthols and have vital roles in pharmaceutical applications. Synthesis of 1-amidoalkyl-2-naphthols is among one of the naphthol derivatives which have attracted strong interest due to their biological, medicinal and pharmacological activities [7]. It has been noted that 1-amidoalkyl-2-naphthols can be converted to hypotensive and bradycardia causing 1-aminomethyl-2- naphthol derivatives **1** by amide hydrolysis reaction [8] (**scheme 1**). Besides to this, amidoalkyl naphthols can be converted to derivatives of 1,3-oxazines as an exclusive class of bioactive compounds that present in many biologically important natural products and drug candidates [9, 10], which exhibit broad ranges of biological activities such as antihypertensive [11],analgesic [12], antirheumatic [13], antianginal [14],antibacterial, and antiviral [15] and antimalarial [16]. Moreover, 1-amidoalkyl-2-naphthols can also be transformed to another biological significant class of heterocyclic compound such as oxazinone derivatives. Oxazinones **3** shows a variety of biological activities such as antibacterial [17], anti-ulcers [18], HIV-1 reverse transcriptase inhibitors [19], human cytomegalovirus protease inhibitor [20], neuropeptide Y5 antagonist [21] Apart from these, napthoxazinone derivative in particular, exhibit therapeutic potential in the treatment of Parkinson's disease [22].



1

Aminoalkyl naphthols
(Possess hypotensive and bradycardiac effects

2

Amidoalkyl naphthols

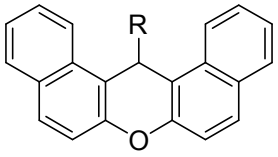
3

Oxazinones
(Used in treatment of parkinson's disease)

R=CH_3, R_1= CH_3, ph, NH_2, Ar= aryls (aryl groups)

Scheme 1: Conversion of amidoalkyl naphthols to aminoalkyl naphthols and oxazinones

The synthesis of xanthenes and their derivatives, especially benzoxanthenes **4** have attracted considerable interest due to their various pharmacological activities, such as antibacterial[23], antifungal [24], analgesic [25], anti-inflammatory [26], anti-viral [27,28], antioxidant [29], anti-cancer [30,31], cytotoxic [32], antiproliferative properties [33]. These compounds have also been employed as sensitisers in photodynamic therapy [34-36], in the food industry as additives [37-40], in laser technologies [41, 42] and as fluorescent materials for the visualization of biomolecules [43-45]. In addition, xanthenes and their derivatives can be used as sensitisers in dye-sensitised solar cells (DSSCs) [46-49] and as hole-transporting materials in organic light emitting devices (OLEDs) [50] (**scheme 2**).



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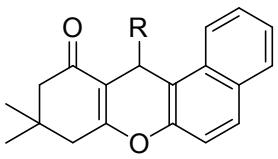

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R=alkyl, aryl groups

Scheme 2: Some of the examples of xanthene derivatives

1.2. Statement of the problem

Numerous methods of synthesis of amidoalkyl naphthols and benzoxanthenes have been reported. The preparation of 1-amidoalkyl-2-naphthols can be carried out by multi-component condensation of aldehydes, 2-naphthol and urea or amide in the presence of Lewis or Brønsted acid catalysts such as montmorillonite K10-clay [51], silica-sodium hydrogen sulphate [52], Iodine [53], PentafluorophenylammoniumTriflate (PFPAT) [54], copper perchlorate hexahydrate [Cu(ClO4)2.6H2O][53], phosphorus pentoxide (P_2O_5)[54], nanosilica phosphoric acid (H3PO4-SiO2)[55], oxalic acid [56], biodegradable ionic liquid [DDPA][HSO4][57], silica-supported perchloric acid (HClO4-SiO2)[58], ultrasonic irradiation [59] or use of microwave [60]. On the other hand, different catalytic systems such as ionic liquid [61, 62], hetero polyacid [63], Amberlyst-15 [64], Montmorillonite K10 [65], sulfuric acid [66], I_2 [67], sulfamic acid [68] have been used to synthesize xanthenes and benzoxanthenes.

However, the majority of them suffer from several limitations such as prolonged reaction time, side products, use of toxic solvents, highly acidic and expensive catalysts, and use of non-re-usable catalysts, unsatisfactory yield and high temperature. In view of these problems and due to ever-strengthening environmental regulations and safety concerns, it is essential to use a rapid, efficient and practical method for the synthesis of 1-amidoalkyl-2-naphthols and benzoxanthenes under eco-friendly conditions without those disadvantages.

The recent literature reveals that zinc oxide nanoparticles (ZnO NPs) find application as heterogeneous catalysts and have received considerable attention because they are recyclable, high yield, reduce side products, short reaction time, inexpensive, nontoxic, easy to handle, nonvolatile and eco-friendly which can be used in many organic transformations. Synthesis of amidoalkyl naphthol and benzoxanthene derivatives are among one of the application of ZnO NPs. Therefore, in this project, 1-amidoalkyl-2-naphthol derivatives and benzoxanthene derivatives were synthesized by using solvent free, zinc oxide nanoparticles (ZnO NPs) catalyst. Besides to this antimicrobial and antioxidant activities of synthesized amidoalkyl naphthol and benzoxanthene derivatives were evaluated.

1.3. Objectives of the study

1.3.1. General Objective

- ✓ To synthesize some amidoalkyl naphthol and benzoxanthene derivatives using zinc oxide nanoparticles as a catalyst under solvent free condition and also to evaluation of their antimicrobial and antioxidant activities.

1.3.2. Specific Objective/s

- ✓ To synthesize [(2-Hydroxy-naphthalen-1-yl)-phenyl-methyl]-urea and [(2-hydroxy-naphthalen-1-yl)-(4-methoxy-phenyl)-methyl]-urea from β-naphthol by the reaction with benzaldehyde and p-methoxybenzaldehyde with urea respectively using ZnO NPs as a catalyst.
- ✓ To synthesize 14-Phenyl-14H-Dibenzo[a, j] xanthene, 14-(4-Methoxy-Phenyl) -14H-dibenzo [a, j] xanthene and 14-(4-Nitro-Phenyl)-14H-dibenzo [a, j] xanthene from β-naphthol by the reaction with benzaldehyde, p-methoxybenzaldehyde and p-nitro benzaldehyde respectively using ZnO NPs as a catalyst.
- ✓ To characterize the synthesized [(2-Hydroxy-naphthalen-1-yl)-phenyl-methyl]-urea and [(2-hydroxy-naphthalen-1-yl)-(4-methoxy-phenyl)-methyl]-urea using FT-IR, ^{1}H NMR, ^{13}C NMR and DEPT-135 NMR.
- ✓ To characterize the synthesized 14-Phenyl-14H-Dibenzo[a, j] xanthene,14-(4-Methoxy-Phenyl)-14H-dibenzo [a, j] xanthenes and 14-(4-Nitro-Phenyl)-14H -dibenzo [a, j] xanthene using FT-IR, ^{1}H NMR, ^{13}C NMR and DEPT-135 NMR.
- ✓ To screen antibacterial activity of synthesized [(2-Hydroxy-naphthalen-1-yl)-phenyl-methyl]-urea and [(2-hydroxy-naphthalen-1-yl)-(4-methoxy-phenyl)-methyl]-urea.
- ✓ To screen antifungal activity of synthesized [(2-Hydroxy-naphthalen-1-yl)-phenyl-methyl]-urea and [(2-hydroxy-naphthalen-1-yl)-(4-methoxy-phenyl)-methyl]-urea

- ✓ To screen antioxidant activity of synthesized [(2-Hydroxy-naphthalen-1-yl)-phenyl-methyl]-urea and [(2-hydroxy-naphthalen-1-yl)-(4-methoxy-phenyl)-methyl]-urea.
- ✓ To screen antibacterial activity of synthesized 14-Phenyl-14H-Dibenzo [a, j] xanthene, 14-(4- Methoxy - Phenyl) -14H-dibenzo [a, j] xanthene and 14-(4-Nitro-Phenyl) - 14H - dibenzo [a, j] xanthene.
- ✓ To screen antifungal activity of synthesized 14-Phenyl-14H-Dibenzo [a, j] xanthene, 14- (4-Methoxy - Phenyl) -14H-dibenzo [a, j] xanthene and 14-(4-Nitro-Phenyl) - 14H - dibenzo [a, j] xanthene.
- ✓ To screen antioxidant activity of synthesized 14-Phenyl-14H-Dibenzo [a, j] xanthene, 14- (4-Methoxy - Phenyl) -14H-dibenzo [a, j] xanthene and 14-(4-Nitro-Phenyl) - 14H – dibenzo [a, j] xanthene.

1.4. Significance of the study

The study was follow environmentally sound and ecofriendly synthesis protocol that avoided the use of toxic catalysts or reagents. This synthesis protocol has advantages over the other reported synthesis methods such as inexpensive and easily available solid base catalyst, shorter reaction time, high yield, easy work up procedure and avoids use of toxic reagents. Therefore, in this study, it was significant to synthesize bioactive 1-amidoalkyl-2-naphthol derivatives and benzoxanthene derivatives by using this method of synthesis.

2. LITERTURE REVIEW

2.1. Zinc Oxide nanoparticles

From the viewpoint of green chemistry, the use of transition metal nanoparticles (NPs) in catalysis can play a vital role as they mimic metal surface activation and catalysis at the nanoscale and thereby bring selectivity and efficiency to heterogeneous catalysis [69]. Among transition metal nanoparticles (NPs), Zinc Oxide nanoparticles (ZnO NPs) have been of considerable interest because of the role of zinc oxide in solar cells, catalysis, antibacterial materials, gas sensors, luminescent materials and photocatalysis [70, 71]. Zinc Oxide (ZnO) is a unique material with a direct band gap (3.37eV) and large exciton binding energy of 60meV [72, 73]. The recent literature reveals that zinc oxide nanoparticles (ZnO NPs) find application as heterogeneous catalysts and have received considerable attention because they are recyclable, high yield, reduce side products, short reaction time, inexpensive, nontoxic, easy to handle, nonvolatile and eco-friendly which can be used in many organic transformations. Among other advantages of zinc oxide nanoparticles (ZnO NPs), mention can be made of the very simple separation of the product and very low wastage during the separation [74-77].

2.2. Amidoalkyl naphthols and Benzoxanthenes

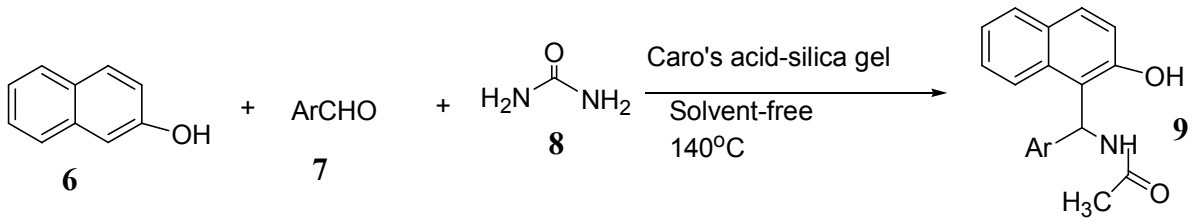
Amidoalkylnaphthols (1-Amidoalkyl-2-naphthols) are the vital synthetic building blocks and used as intermediates for the synthesis of many important derivatives such as 1, 3-oxazine derivatives and 1-aminomethyl-2-naphthol derivatives which are widely used class of bioactive compounds due to their remarkable biological and many pharmacological properties [78]. Xanthenes and its derivatives, especially benzoxanthenes are another important oxygenated heterocyclic compounds which have wide range of biological and therapeutic properties such as antibacterial, antiviral and anti-inflammatory actions as good as in Photodynamic therapy. Furthermore, due to their useful spectroscopic properties, they were used as dyes in laser technologies and in fluorescent materials for visualization of bio molecules [79-86]. Due to the biological and industrial applicability of the amidoalkyl naphthols and benzoxanthenes, several synthetic protocols have been reported and noted in the literatures.

2.3. Methods of Synthesis of Amidoalkylnaphthols and Benzoxanthenes

2.3.1. Methods of synthesis of amidoalkylnaphthols

2.3.1.1. Using caro's acid- silica gel (CA-SiO2) under solvent free condition

Montazeri *et al.,* [87] have reported an efficiently synthesis of amidoalkyl naphthol derivatives **9** by the reaction of appropriated aromatic aldehydes **7**, 2-naphthol **6** and an amide **8** in the presence of Caro's acid- silica gel (CA-SiO2) as an effective solid acid catalyst under solvent-free conditions. The significant features of this procedure are high yields of the products, shorter reaction times, and simple procedure with an easy work- up (**Scheme 3**).



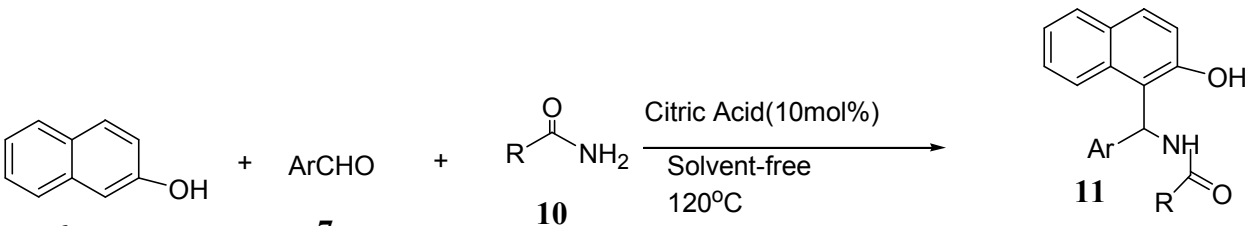
6 **7** **8** **9**

Ar=3-$NO_2C_6H_4$,C_6H_4, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 4-$CH_3C_6H_4$, 2-$CH_3C_6H_4$, 2-ClC_6H_4,4-$OCH_3C_6H_4$.

Scheme 3: Synthesis of midoalkyl naphthol derivatives using caro's acid- silica gel (CA-SiO2)

2.3.1.2. Citric Acid as a biodegradable catalyst

Kabeer *et al*., [88] reported an efficient synthesis of amidoalkyl naphthols **11** using Citric acid as a biodegradable catalyst by the three-component reaction of 2-naphthol **6**, aldehydes **7** and amides/urea **10** under thermal solvent-free conditions (**Scheme 4**).



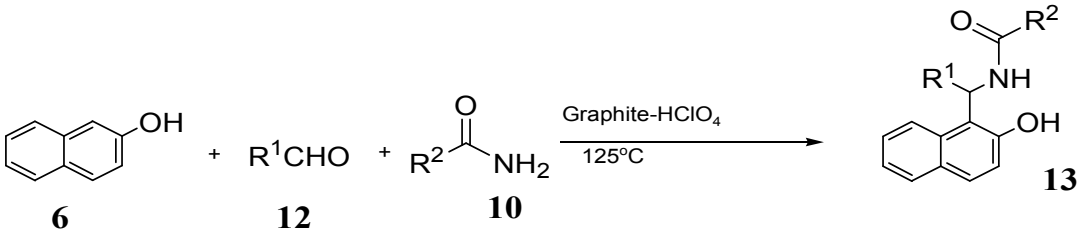
6 **7** **10** **11**

Ar= 4-ClC_6H_4,3-$OCH_3C_6H_4$,2-$NO_2C_6H_4$,4-$NO_2C_6H_4$,2-ClC_6H_4, 4-$CH_3C_6H_4$, C_6H_5, R=CH_3,NH_2,C_6H_5.

Scheme 4: Citric acid catalyzed synthesis of 1-amidoalkyl-2-naphthols.

2.3.1.3. Using Graphite-Supported Perchloric Acid (HClO4-C)

Zhen-Kai *et al.*,[89] reported an efficient and direct protocol for the preparation of amidoalkylnaphthols**13** employing a multi-component, one-pot condensation reaction of 2-naphthol **6**, aromatic aldehydes **12** and acetamide or benzamide**10** in the presence of graphite supported perchloric acid under solvent-free conditions. The thermal solvent-free procedure offers advantages such as simple work-up, shorter reaction times and higher product yields, and the catalyst exhibited remarkable reactivity and can be recycled (**Scheme 5**).

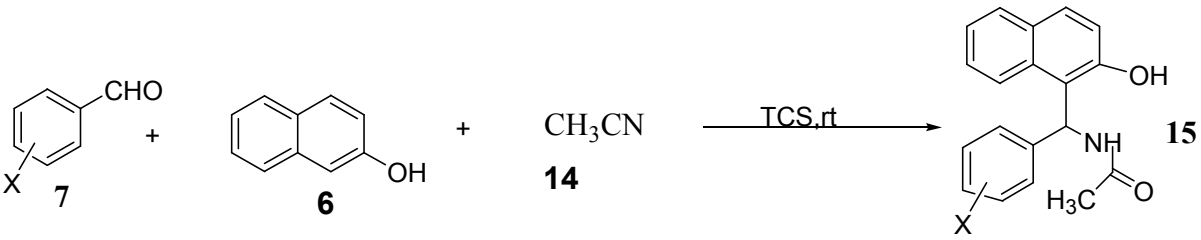


R_1=C_6H_5,4-$CH_3C_6H_4$,3-ClC_6H_4,4-ClC_6H_4, 3-FC_6H_4,4-$OCH_3C_6H_4$,3-$OCH_3C_6H_4$,2-4-$(Cl)_2C_6H_3$, ,4-OHC_6H_4,3-$NO_2C_6H_4$.

Scheme 5: The synthesis of 1-amidoalkyl-2-naphthol derivatives catalyzed by HClO4-C

2.3.1.4. Using Tetrachlorosilane

Samy *et al*.,[90] reportedan efficient and direct procedure for the synthesis of amidoalkyl naphthol derivatives **15** employing a multi-component and one-pot condensation reaction of 2-naphthol **6**, aromatic aldehyde **7** and acetonitrile **14** in the presence of tetrachlorosilane (TCS) (**Scheme 6**). A binary reagent from (TCS)/ZnCl2 was used upon applying benzonitrile.



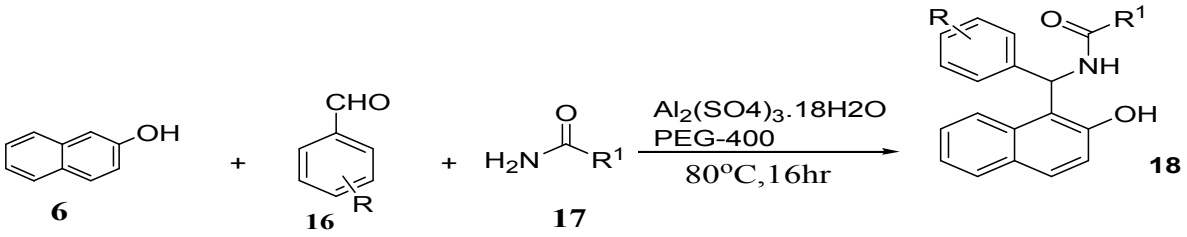
X=H,4-Cl,4-CH_3,4-$(CH_3)_2N$,4-OCH_3,2-Br,3-Br,3-NO_2

Scheme 6: Synthesis of amidoalkyl naphthol in the presence of tetrachlorosilane (TCS)

2.3.1.5. Using Aluminium sulphate in PEG

Bhata et al [91] reported Aluminium sulphate as a catalyst in PEG as a reaction solvent is found to be an attractive, environmentally benign and highly efficient catalytic system for the one-pot multicomponent reaction of aromatic aldehyde **16**, β-naphthol **6** and amide **17** to form the

corresponding amidoalkyl naphthol **18** (**Scheme 7**). The procedure is simple, rapid and high yielding. Moreover, the catalyst exhibited a remarkable reactivity and is reusable in PEG-400 as a solvent.



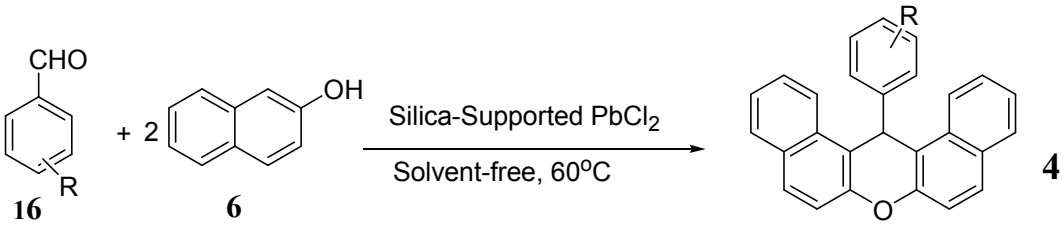
R= H, 2-Cl, 4-Cl,4-OCH_3,4-CH_3,3-NO_2,4-NO_2 R_1= CH_3,C_6H_5

Scheme 7: Synthesis of 1-amidoalkyl-2-naphthols using Aluminium sulphate in PEG

2.3.2. Methods of synthesis of Benzoxanthenes

2.3.2.1. Using Solid Supported PbCl2

Vishvanath [92**]** reported synthesis of Benzoxanthenes **4** by the reaction of aromatic aldehyde **16** and two mole of β-naphthol **6** using simple method in the presence of Silica supported anhydrous $PbCl_2$ (**Scheme 8**). The prepared catalyst was found to be thermally stable up to 220^0C. It was found to be heterogeneous and recyclable catalyst.

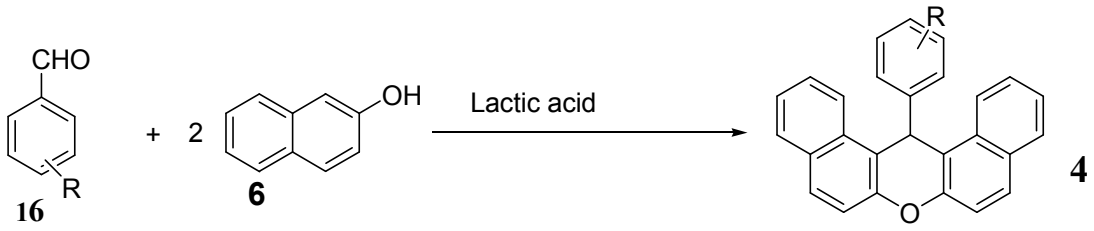


R= H, 4-Cl,2-Cl, 4-CH_3,4-OCH_3, 2-OCH_3, 4-NO_2 , 3-NO_2,4-OH

Scheme 8: synthesis of Benzoxanthenes in presence of silica supported anhydrous $PbCl_2$

2.3.2.2. Using Lactic Acid

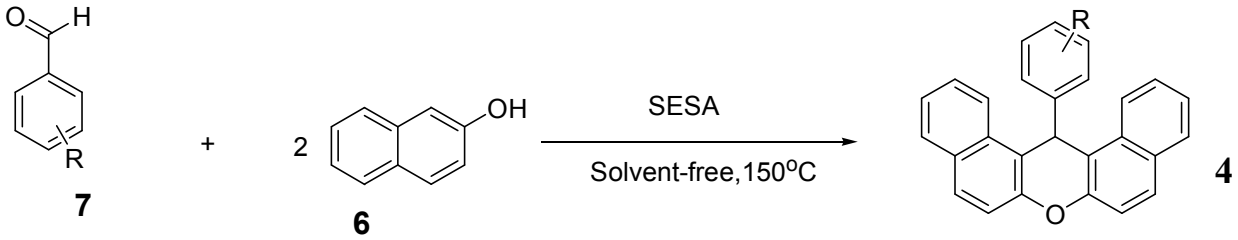
Fatemeh *et al*., [93]reported synthesis of some biologically important xanthenes**4**, by efficient and convenient approach for one-pot condensation reaction of aldehydes **16** and dimedone or *β*-naphthol **6** in the presence of lactic acid as an efficient, inexpensive and environmental friendliness catalyst under solvent-free conditions (**Scheme 9**). The merits of this reaction are higher product yields in shorter reaction time and environmentally benign reaction conditions.



Scheme 9: Synthesis of 14-aryl-14*H*-dibenzo [*a, j*] xanthenes using lactic acid as catalyst

2.3.2.3. Using Silica Supported [2-(Sulfooxy) ethyl] sulfamic Acid

SAMI et al., [94]have reported an efficient and simple method for the synthesis of xanthenes derivatives **4** via one-pot condensation of various aldehydes **7** and 2-naphthol **6** using [2-(sulfooxy)ethyl]sulfamic acid (SESA) as a novel catalyst (**Scheme 10**). Different types of aromatic aldehydes **7** were used in the reaction and in all cases the products synthesized successfully Use of easily available catalyst, time minimizing, excellent yields, simplicity of the reaction, heterogeneous system, a cleaner reaction and easy workup are the advantages of the present method.

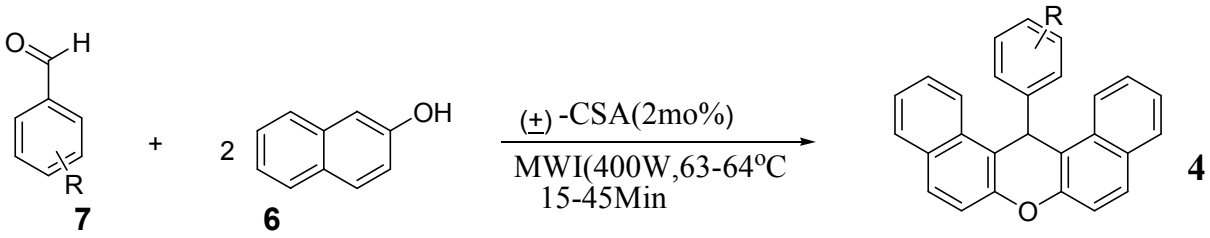


R= H,4-Br,3-Br, 4-F,4-Cl,2-Cl, 4-CH_3,4-OCH_3, 2-OCH_3, 4-NO_2 , 3-NO_2,3-OH

Scheme 10: Synthesis of xanthenes using SESA

2.3.2.4. Using Camphor-10-sulfonic acid

KSHAMA and SANDIP [95] have reported (±)-camphor-10-sulfonic acid (CSA) catalyzed condensation of 2-naphthol **6** with both aliphatic/aromatic aldehydes **7** for the preparation of alkyl/ /aryldibenzoxanthenes**4** as the sole products in high yields (**Scheme 11).** .Moreover, the condensation of 2-naphthol with aromatic/aliphatic aldehydes with low catalyst loading (2 mol %) was greatly accelerated under microwave irradiation to afford the corresponding aryl/alkyl dibenzoxanthenes as the sole products in high yields.

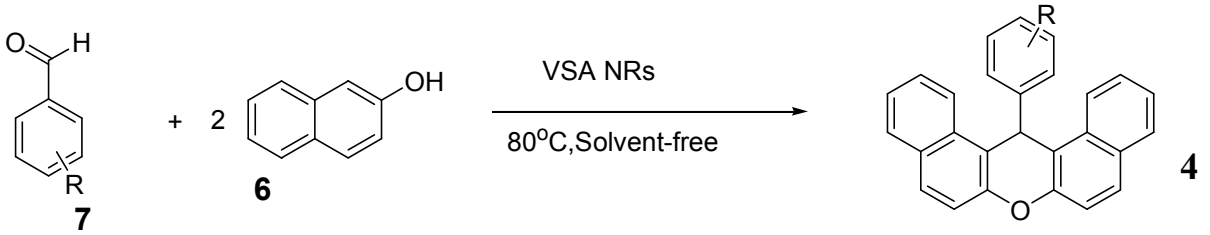


R= H,4-Br,4-OCH_3, 2-OCH_3,3-OCH_3, 4-NO_2 ,4-$NHCOCH_3$,4-F,3-OH,4-CO_2H,4-CN

Scheme 11: Synthesis of benzoxanthenes using (±)-camphor-10-sulfonic acid (CSA)

2.3.2.5. Using vanadate sulfuric acid

Masoud and Tooba [96] reported Vanadate sulfuric acid (VSA) as a recyclable and eco-benign catalyst for the preparation of biologically active 14-aryl-14-*H*-dibenzo [*a, j*]xanthenes**4** by a one-pot condensation reaction of 2-naphthol **6** and aldehydes **7** under solvent-free conditions in high to excellent yields (80–93%) and in short reaction times (10-45 min) (**Scheme 12**). The present method offers several advantages such as simple procedure, short reaction time, high yields, simple workup, and reusability of the catalyst and simple purification of the products.



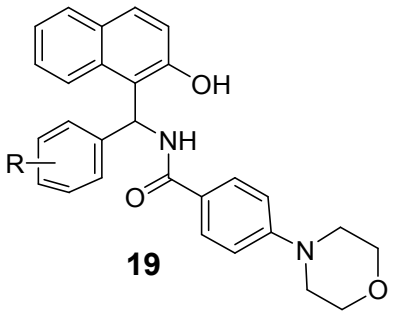
R= H,4-Br, 2-Cl, 2,4-$(Cl)_2$, 4-OCH_3, 2-OCH_3,4-CH_3, 4-NO_2,3-NO_2, 2-NO_2,,4-OH,2-OH,2,4-$(OH)_2$, 2,4-$(CH_3)_2$

Scheme 12: Synthesis of benzoxanthenes using vanadate sulfuric acid

2.3.3. Therapeutic potential of naphthols/ amidoalkylnaphthols

2.3.3.1. Antimicrobial Activity

Anna *et al*., [97] have tested antimicrobial (anti-bacterial and anti-mycobacterial) activity of N-((2-hydroxynaphthalen-1-yl) (substituted phenyl) methyl)-4-morpholino benzamide derivatives **19** (3a-h) (**Figure 1)**.



19

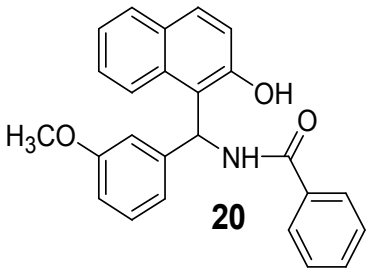
R=4-OCH_3, 4-OH, 2-SH, 2-OH, 4-Cl, 2,4-$(Cl)_2$, 4-F

Figure 1: Antimicrobial activity of N-((2-hydroxynaphthalen-1-yl) (substituted phenyl) methyl)-4-morpholino benzamide derivatives

Some of the synthesized compounds like 3**b** (R= 4-Hydroxy) has shown comparable activity against *S. aureus* and *B. subtilis*, 3**g** (R= 4-Chloro) and 3**k** (R= 4-Fluoro) have shown excellent activity against *S. aureus* and *B. subtilis* when compared with standard Linezolid. Compound **3h** (R= 2, 4-Dichloro) has shown excellent antitubercular activity. Compound 3**f** (R= 2-hydroxy) has shown significant antitubercular activity. Compound 3**i** (R= 4-Nitro) have shown comparable antitubercular activity. All other compounds have shown satisfactory antitubercular activity when compared with the results obtained from standard (Rifampicin). The correlation of activity with the structure of synthesized derivatives, it has been observed that electron donating groups like 4-Chloro **(3g)**, 2, 4-Dichloro **(3h)**, 4-Fluoro **(3k)**, attached to the phenyl ring increases antimicrobial activity. When the substituent R has electron donating groups such as 4-Hydroxy **(3b)**, 2-Hydroxy (3**f)** showed moderate antimicrobial activity. The structure-activity relationship study showed that the morpholine ring is essential for antibacterial activity.

2.3.3.2. Antibacterial Activity

Afinisha and Jyothi [98] have reported the synthesis of vanillin based aminoalkyl and amidoalkyl naphthols **20** (**Figure 2**) for their antibacterial activity against *Bacillus subtilis* and found that they shows very little effect on the inhibition against bacterial growth rate. Many factors such as structure of compound, concentration of compounds applied, PH conditions of the culture medium, bacterial growth concentration, size of the petri-plate, storage conditions etc may affect the inhibition rate.

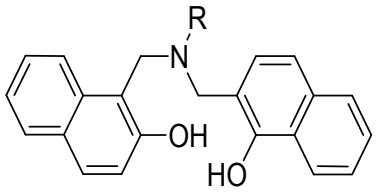


20

Figure 2: Antibacterial activity of 1-[(4-hydroxy-3-methoxyphenyl) (phenylamido)] methyl naphthalene-2-ol.

2.3.3.3. Antimicrobial and anti-inflammatory activity

Huang *et al*., [99] evaluated the antimicrobial potential of 18 synthetic naphthalene derivatives and tested for their anti-inflammatory activity **21** (**Figure 3**).They prepared naphthalene derivative prepared according to the Mannich reaction.

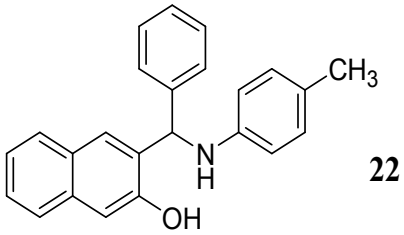


21

Figure 3: Synthetic naphthalene derivatives

2.3.3.4. Antimicrobial and antioxidant activity

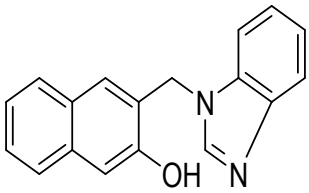
Chakkaravarthi *et al*., [100] have tested the antimicrobial and antioxidant activities of two mannich bases derived from beta-naphthol. The two synthesized compounds: 3-(phenyl (ptolylamino) methyl) naphthalene-2-ol (**TNPTB**) **22** and 3-((1H-benzo[d]imidazole-1-yl) methyl) naphthalene-2-ol (**TNBIF**) **23** showed moderate antimicrobial and anti-oxidant activities (**Figure 4 and 5**). The antimicrobial study specifically focused on the skin inflectional microbes and got the good results. The results of anti-bacterial, anti-fungal and anti-oxidant assay concludes the TNBIF shows the good and significant activities compared to the TNPTB. Findings show the biological activity of TNBIF may be due to the presence of two hetero atoms in the benzimidazole. The antioxidant activities of derived mannich bases due to presence of electron releasing OH group. For further in vivo investigation in these findings can have good effect on Mannich base compounds can be used as a potential drug for anti-skin inflectional drug.



22

3-(Phenyl-*p*-tolylamino-methyl)-naphthalen-2-ol

Figure 4: Structure of TNPTB



23

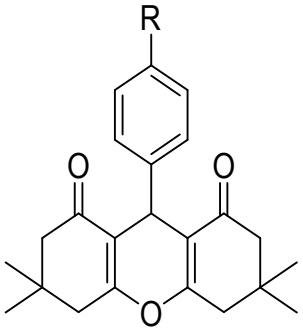
3-Benzoimidazol-1-ylmethyl-naphthalen-2-ol

Figure 5: Structure of TNBIF

2.3.4. Therapeutic potential of xanthenes/benzoxanthenes

2.3.4.1. Antimicrobial (antibacterial and antifungal) activity

Muharrem kaya *et al*., [101] have tested antibacterial and antifungal activities of xanthene sulfonamide and carboxamide derivatives **26** (**Figure 6**).



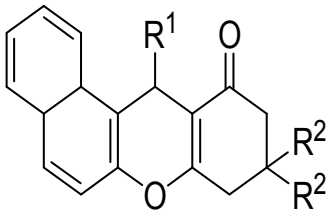
26

R= $-NO_2$,$-NH_2$,$-NHSO_2R$,-NHCOR' R'= C_6H_5,P-$NO_2C_6H_5$,3,5-$(NO_2)C_6H_5$,CH_3

Figure 6: Biologically active xanthenes

2.3.4.2. Antibacterial Activity

Ali and Asghar [102] reported antibacterial activity tetrahydrobenzo [*a*] xanthenes-11-one derivatives **24** (**Figure 7**) against *Pseudomonas syringae*, *Xanthomonasciti* and *Pectobacterium carotovorum.*



24

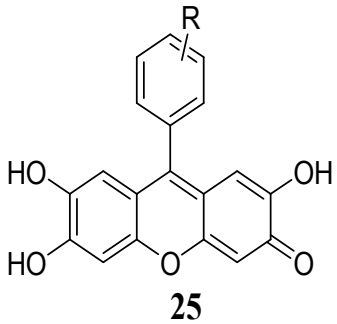
R_1= 3- BrC_6H_4, 4-CH $(CH_3)_2C_6H$, 2, 3-OHC_6H_3…, R_2= Me, H

Figure 7: Antibacterial activity of benzoxanthenes

The increase of the antibacterial activity with increasing numbers of hydroxyl groups in the molecule was observed. Compounds containing 2, 3-OHC_6H_3 substituent and 4-OHC_6H_4 substituent which bear 1-hydroxyl groups and Chloro group, showed only moderate activity. The increase of the antibacterial activity with increasing numbers of another group in the molecule was not observed.

2.3.4.3. Antioxidant activity

Elma *et al*., [103] have tested antioxidant activity of 9-Aryl Substituted hydroxylated xanthen-3-ones **25** (**Figure 8**).



25

R=4-$MeOCH_3$,4-Cl,2-Cl, 2-F,4-F

Figure 8: Antioxidant activity of benzoxanthenes

It was deduced that the substitution of hydrogen at the phenyl ring with an electron-donating group affected the reducing power of the compounds by lowering the biological oxidation potential. Additional *in vivo* antioxidant assays are needed to confirm the potential use of these derivatives in disease prevention and/or treatment. Since it has been proven that antioxidant potency may correlate with antitumor activity, synthesized xanthene-3-one derivatives with good antioxidative potential will be further biologically evaluated as potential anti-proliferative agents [104].

3. MATERIALS AND METHODS

3.1. Reagents and Chemicals

Ethyl acetate (99%), *n*-hexane(99%), zinc oxide nanoparticles (ZnO NPs), methanol (99.8%), ,ethanol (95%), distilled water, silica gel, Urea, beta naphthol (99%), benzaldehyde, vanillin (m-methoxy, p-hydroxybenzaldehyde), *P*-nitrobenzaldyde, *P*-methoxybenzaldehyde. All reagents and chemicals used in the synthesis were obtained from Sigma-Aldrich Co., St. Louis, MO, USA, and all solvents were purchased from Fine Chemical General Trading PLC, Addis Ababa, Ethiopia.

3.2. Apparatus and Instruments

Reactions were monitored by TLC using silica gel-G (Merck grade) as the adsorbent and the solvent systems are indicated at appropriate places. Silica gel (100-200 mesh, Merck grade) has been used for column chromatography. The column was subjected to gradient elution using n-hexane, mixtures of hexane and ethyl acetate (5%, 10%, 15 %, 25%, 50% and 75% hexane in ethyl acetate). Fractions each of 100 ml were collected. The separation of the compounds was checked on TLC under UV lamp. All the melting points were determined in open capillaries, using digital melting point apparatus, expressed in ^{o}C. Infrared spectra (FT-IR) were recorded on Perkin Elmer – 337 Infrared Spectrophotometer. Samples were screened in Potassium bromide (KBr) pellets and the values are expresses in cm^{-1}. The ^{1}H and ^{13}C NMR spectra of the compounds were recorded on Bruker avance 400 MHz NMR spectrophotometer using TMS as an internal standard and the values are expressed in δ ppm.

3.3.1. Synthetic procedure for Synthesis of Amidoalkyl naphthol derivatives using ZnO NPs

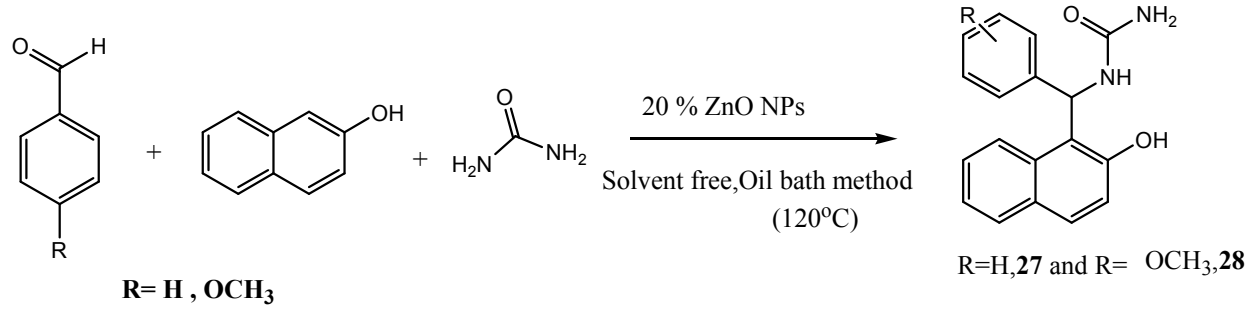
The preparation procedure for both syntheses of amidoalkyl naphthol and benzoxanthene derivatives was according to literature procedure [105].

Synthesis of [(2-Hydroxy-naphthalen-1-yl)-phenyl-methyl]-urea **27** and [(2-hydroxy-naphthalen-1-yl)-(4-methoxy-phenyl)-methyl]-urea **28**

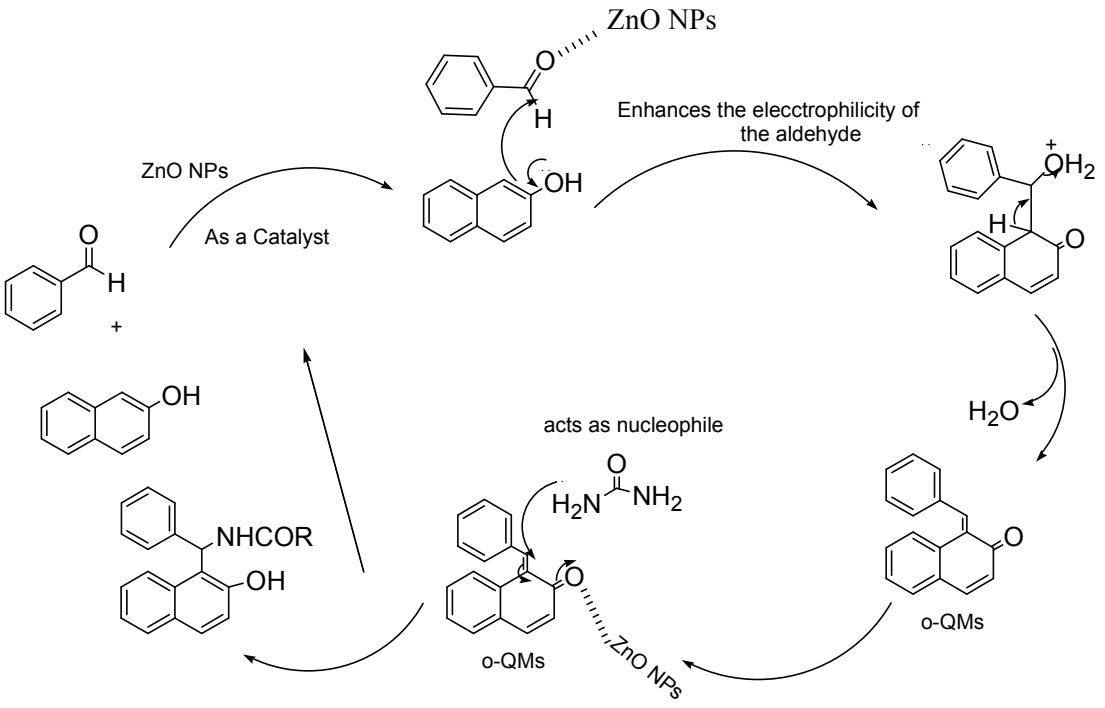
A mixture of benzaldehyde (1mmol,0.102ml) ,β-naphthol (1 mmol,0,144 g), and urea (1.2 mmol,0.072 g) and catalytic amount of ZnO NPs (20 mol%,0.2mmol) were taken in 100ml conical flask and heated in an oil bath at 120ºC for 42 minutes to synthesize compound **27** and 48 minutes to synthesize compound **28** with regular stirring . The progress of the reaction was

monitored through TLC (ethyl acetate: n-hexane, 2:8) using precoated silica aluminium plates. The spots were visualized by ultraviolet light irradiation at 254 nm. After completion, the reaction mixture was cooled to room temperature and ethyl acetate was added. The catalyst was separated from the reaction mixture by simple filtration. The filtrate was collected and dried. The obtained product (residue) was checked by TLC and purified using silica gelcolumn chromatography (230-400 mesh, Merck), with increasing gradient of ethyl acetate in n-hexane as the mobile phase. Finally the product yield was recorded. By adopting the above synthetic procedure, compounds **27** and **28** were also synthesized.

The reaction involving the formation of amidoalkyl naphthols and the proposed mechanism is indicated below (**Scheme 13 and 14**).



Scheme 13: Reaction involving reaction of amidoalkyl naphthols



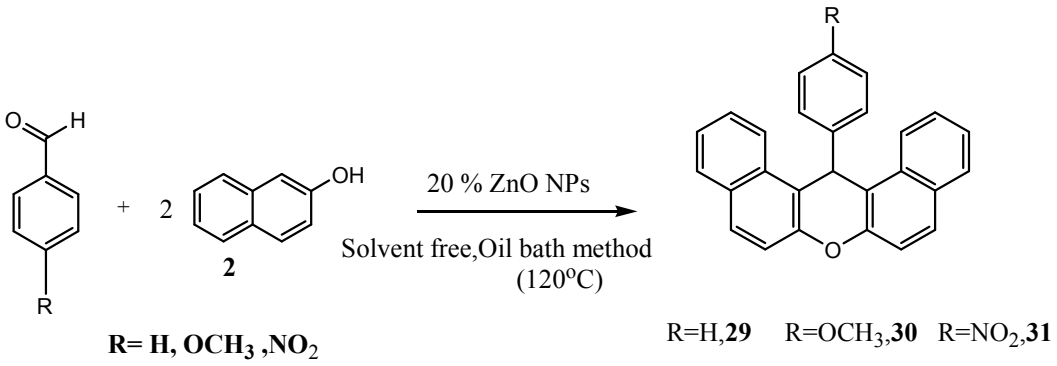
Scheme 14: Plausible mechanism of ZnO NPs promoted synthesis of Amidoalkylnaphthols

3.3.2. Synthetic procedure for synthesis of benzoxanthene derivatives using ZnO NPs

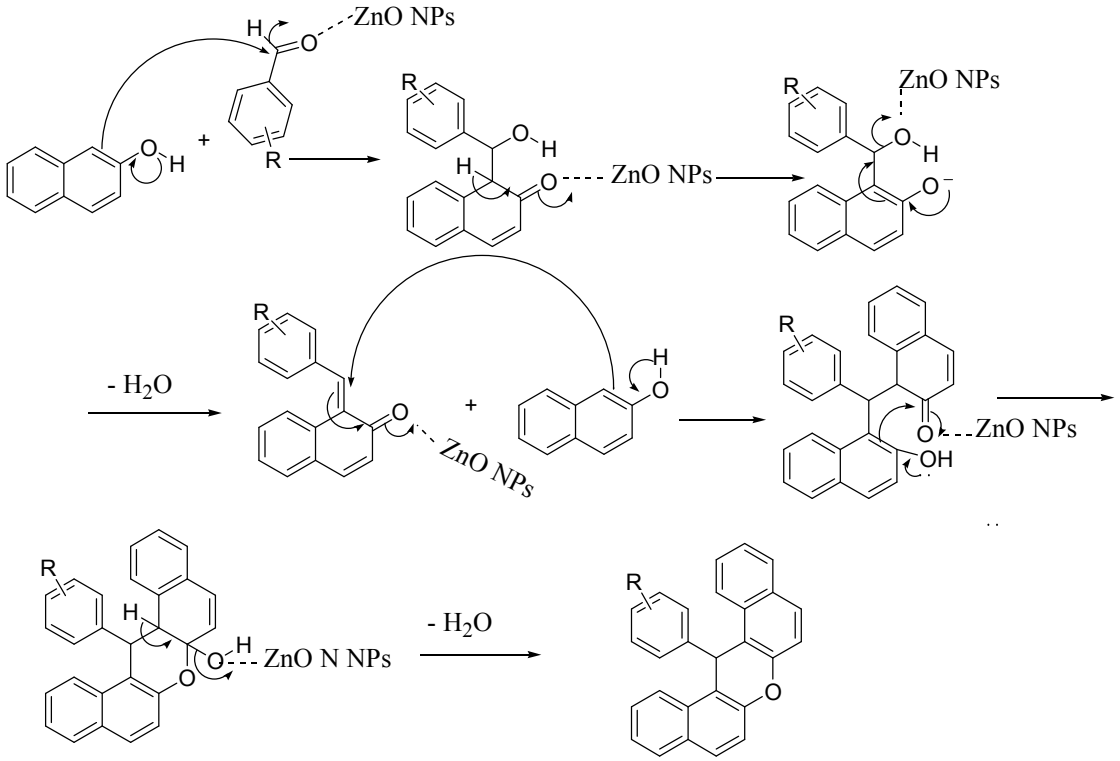
Synthesis of 14-Phenyl-14H-Dibenzo [a, j] xanthene **29**, 14- (4- Methoxy - Phenyl) -14H-dibenzo [a, j] xanthene **30** and 14-(4-Nitro-Phenyl) - 14H - dibenzo [a, j] xanthene **31**

A mixture of benzaldehyde (1mmol, 0.102 ml), β-naphthol (2 mmol,0.288 g) and catalytic amount of ZnO NPs (20 mol%,0.2mmol) were taken in 100ml conical flask and heated in an oil bath at 120ºC for 53 minutes,59 minutes and 55 minutes to synthesize compound **29**, **30** and **31** with regular stirring respectively. The progress of the reaction was monitored through TLC (ethyl acetate: n-hexane, 2:8) using precoated silica aluminium plates. The spots were visualized by ultraviolet light irradiation at 254 nm. After completion, the reaction mixture was cooled to room temperature and ethyl acetate was added. The catalyst was separated from the reaction mixture by simple filtration. The filtrate was collected and dried. The obtained product (residue) was checked by TLC and purified using silica gel column chromatography (230-400 mesh, Merck), with increasing gradient of ethyl acetate in n-hexane as the mobile phase. Finally the product yield was recorded. The reaction involving the formation of benzoxanthenes and the

proposed mechanism is indicated below (**Scheme 13 and 14**). By adopting the above synthetic procedure, compounds **29, 30** and **31** were also synthesized.



Scheme 15: Reaction involving reaction of Benzoxanthenes



Scheme 16: Plausible mechanism of ZnO NPs promoted synthesis of benzoxanthenes

3.4. Spectroscopic techniques

Characterizations of the synthesized compounds were carried out by spectroscopic techniques. NMR spectra were recorded on a Bruker Advance 400 NMR spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C at room temperature using DMSO-d_6 and $CDCl_3$. A region from 0 to 12 ppm for ^{1}H and 0 to 205 ppm for ^{13}C was employed for scanning. Signals were referred to an internal standard tetra methyl silane (TMS). Chemical shifts are reported in δ ppm units and

coupling constants (*J*) in Hz. Multiplicities of ^{1}H NMR signals are indicated as *s* (singlet), *d* (doublet), *dd* (doublet of doublets), *t* (triplet), and *m* (multiplate). IR spectra were recorded between 400-4000 cm^{-1} in KBr pellets.

3.5. Evaluation of antibacterial and antifungal activities

Antibacterial and antifungal activities of test samples were evaluated using disc diffusion method against the test strains .The plates were allowed to solidify for 5min and 0.1% inoculums suspension of tested organisms were swabbed uniformly and the inoculums were allowed to dry for 5min. 5mg of synthesized compounds were loaded on 6 mm sterile individual paper discs (HiMedia) and thoroughly dried in air draft to remove traces of the solvent. Negative control was prepared using respective solvent which is DMSO. Tetracycline was used as reference standard for antibacterial activity and fluconazole for fungal activity for comparing the results. Nutrient broth was used for the preparation of inoculum of the bacteria and nutrient agar was used for the screening method. The test organisms were sub cultured using nutrient agar medium. The tubes containing sterilized medium were inoculated with the respective bacterial strain. After incubation at 37ºC ±1ºC for 24 hours for bacteria and 48 hours for fungi, they were stored in a refrigerator. The nutrient agar medium was sterilized by autoclaving at 121ºC (15 lb/sq.inch) for 15 min. The petriplates tubes and flasks plugged with cotton were sterilized in hot-air oven at 160ºC, for an hour. Into each sterilized petriplate (20cm diameter), was poured about 125mL of molten nutrient agar medium which was already inoculated with the respective strain of bacteria and fungi (5 ml of inoculum to 250 mL of nutrient agar medium) aseptically. The plates were left at room temperature aseptically to allow the solidification. After solidification, the cups of each of 6 mm diameter were made by scooping out medium with a sterilized cork borer from a petridish and labeled accordingly. Each test compound (5 mg) was dissolved in dimethyl sulfoxide (5mL Analatical grade) to give a concentration of 1000µg/mL. Tetracycline solution was also prepared to give a concentration of 1000 µg/ml in sterilized distilled water. The pH of all the test solutions and control was maintained in between 2 to 3 by using concentrated HCl. All the compounds were tested at dose levels of 50 µg (0.05mL), 100µg (0.1 ml), 200 µg (0.2ml) and DMSO used as a control. The solutions of each test compound, control and reference standard (0.05 ml, 0.1 ml and 0.2ml) were added separately in the cups and the plates were kept undisturbed for at least 2 hours in a refrigerator to allow diffusion of the solution properly into

nutrient agar medium. Petri dishes were subsequently incubated at 37±1 ^{0}C for 24 hr for bacteria and 48 hr for fungi. After incubation, the diameter of zone of inhibition was measured [106].

3.6. Evaluation of antioxidant activity

Antioxidant activity of the synthesized compounds was assessed according reported procedure [107] by the DPPH radical scavenging method (1, 1-Diphenyl-2-2picrylhydrazyl).The nitrogen centered stable free radical 1, 1-diphenyl-2-picrylhydrazyl (DPPH) has often been used to characterize antioxidants. It is reversibly reduced and the odd electron in the DPPH free radical gives a strong absorption maximum at 517 nm using spectrophotometer, which is purple in color. This property makes it suitable for spectrophotometer studies. A radical scavenging antioxidant reacts with DPPH stable free radical and converts it into 1, 1-diphenyl-2-picrylhydrazine. The resulting decolorization is stoichiometric with respect to the number of electrons captured. The change in the absorbance produced in this reaction used to measure antioxidant properties. The hydrogen atom or electron donation ability of the compounds was measured from the bleaching of the purple colored methanol solution of DPPH radical. To 4 ml of 0.004% (w/v) methanol solution of DPPH, 2 ml of various concentrations of the test compounds (12.5,25,50,100,200 and 400 μg/ml) in methanol were added. After a 30 min incubation period at room temperature, the absorbance was measured against blank at λ 517 nm [108]. Ascorbic acid was used as the standard. The activity was expressed as IC_{50}, which is the concentration of the test compound required to give a 50% decrease of the absorbance from that of the control solution. The inhibition curves were prepared and IC_{50} values were obtained. The percent of inhibition (I %) of free radical production from DPPH was calculated by the following equation:

$$\% \text{ of } I = [(A_{control} - A_{sample}) / A_{control}] \times 100$$

Where $A_{control}$ is the absorbance of the control reaction, A_{sample} is the absorbance of the test compound.

4. RESULTS AND DISCUSSION

4.1. Comparison of 20 % of ZnO NPs (present work) with reported catalysts in the synthesis of amidoalkyl naphthols and benzoxanthenes

In order to show the merit of the present work in comparison with reported results in the literature, we compared the reactions of ZnO NPs with Montmorillonite K10 clay [108], $K_5CoW_{12}O_{40}.3H_2O$ [109], *p*-TSA [110] and $Ce(SO_4)_2$ [111] in the synthesis of 1-amidomethyl-2-naphthol derivatives (Table 2). Zinc oxide nanoparticles (ZnO NPs) was an efficient catalyst in the formation of compound **27** and **28** with high yields and shorter reaction times (Table 1).

The results obtained in this work for the synthesis of benzoxanthenes **29**, **30** and **31** were compared with other studies detailed in the literature with Camphor-10-sulfonic acid((±)-CSA) [95], p-TSA [113],4-Dodecylbenzenesulfonic acid (DBSA**) [**114]and Vanadate Sulfuric Acid NRs(O_2V-OSO_3H) [96] (Table 4). Zinc oxide nanoparticles (ZnO NPs) proved to be the only one capable of promoting this one-pot reaction with high yield and shorter reaction time (Table 3). The electronic effect and the nature of substituents have a strong effect on the yield of the products. Benzaldehyde and other aromatic aldehydes having electron withdrawing and electron donating group were used and reacted to give the corresponding benzoxanthene derivatives. Electron-withdrawing groups were strongly more effective than electron-donating group. That is why nitro group was found to be higher yield compared to the others groups.

Table 1: Physical characterization data of synthesized amidoalkyl naphthols

Compound	R	Color	Time (min)	Melting point	Yield obtained
27	H	White solid	42	177-179	90.4
28	OCH_3	White solid	48	169-171	89.8

Table 2: Comparison of 20 % of ZnO NPs with reported catalysts in the synthesis ofamidoalkyl naphthols (1-amidoalkyl-2-naphthols)

Catalyst	Mol%/[g]/conditions/T/^{o} C	Time/min	Yield/%	Reference
Montmorillonite K10 clay	(0.1g);Solvent free,125 ^{o} C	90	78	108
$K_5CoW_{12}O_{40}.3H_2O$	(1mol%); Solvent free,125 ^{o} C	120	80	109

p-TSA	(10mol%);Solvent free,125 ^{o} C	360	86	110
$Ce(SO_4)_2$	(1 mmol), CH_3CN, Reflux	2160	72	111

Table 3: Physical characterization data of synthesized benzoxanthenes

Compound	R	Color	Time(min)	Melting point (^{o}C)	Yield obtained (%)
29	H	White solid	53	183-185	89.4
30	OCH_3	Yellow solid	59	204-205	92.0
31	NO_2	Yellow solid	55	314-315	93.5

Table 4: Comparison of 20 % of ZnO NPs with reported catalysts in the synthesis of benzoxanthenes (14-aryl-14H-dibenzo [a, j] xanthenes)

Catalyst	Mol%/[g]/conditions/T/^{o} C	Time/min	Yield/%	Reference
Camphor-10-sulfonic acid((±)-CSA)	(20mo%);Solvent free, 25 ^{o} C	930	21	95
p-TSA	(0.1g); H_2O, reflux,	600	88	112
4-Dodecylbenzenesulfonic acid (DBSA)	(15mol%);toluene,60 ^{o} C	120	50	113
Vanadate Sulfuric Acid NRs(O_2V-OSO_3H)	Chloroform, 80 ºC	600	60	96

4.2. Characterization of Synthesized compounds

4.2.1. Characterization of compound 27

Compound **27** was obtained as white solid with melting point of 177-179^{o}C and its percent yield was 90.4 %.

The IR (KBr pellet) spectrum showed (v in cm^{-1}, Appendix 1A) broad absorption at 3462 cm^{-1} attributed to O-H stretching and 3223 cm^{-1} to N-H stretching. The intense absorption bands at 1666 cm^{-1} and at 1437 cm^{-1} showed the presence of carbonyl carbon and aromatic C-C double bond respectively.

The ^{1}H NMR spectrum (DMSO-d6, 400 MHz, Appendix 1B) showed a single peak at δ 5.85 (1H, s) corresponding to a hydroxyl group on the aromatic ring and a single peak at δ 6.95 (1H, s) showed the presence of methine proton at C-2. The peaks from δ 7.21-7.12 (2H, m) showed the presence of aromatic protons at C-16, C-14, C-14' respectively. The peaks at δ 7.24 (1H, d, J=7.2) at C-5, from δ 7.34-7.26 (2H,m) at C-15,C-15', from δ 7.39-7.38 (1H,m) at C-11, from δ 7.45-7.41 (1H,m) at C-10 , δ 7.49 (1H,d,J=8.8Hz) at C-6 , at δ 7.77 (1H,d, J=7.2 Hz) at C-12 and at δ 7.83 (1H,d,J=8HZ) at C-9 showed the presence of aromatic protons. The peak at δ 8.32 as singlet indicated the presence of 1H for NH and 2H for NH_2 (Table 3).

The ^{13}C NMR spectrum revealed peak resonating at δ 159.0 at C-1 attributed to carbonyl carbon (Appendix 1C).The peaks observed at δ 129.4 at C-15 and C-15', and at δ 129.0 at C-14 and C-14' showed that the presence of sp^2 carbon on the benzene ring whereas the peak observed at δ153.4 indicated the presence of oxygenated quaternary carbon at C-4. On the other hand the peaks at δ 132.7 at C-8 and δ 128.3 at C-7, and at δ 48.6 at C-2 showed that the presence of non-oxygenated quaternary carbon and methine carbon respectively (Table 3).Thus, on the basis of ^{1} H-NMR, ^{13}C NMR and IR spectra data, the structure of compound **27** was established as Amidoalkyl naphthol: [(2-Hydroxy-naphthalen-1-yl)-phenyl-methyl]-urea (**Figure 9**).

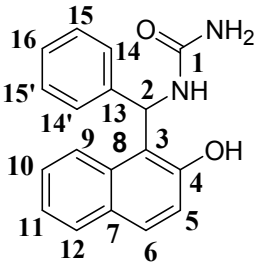


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Figure 9: structure of [(2-Hydroxy-naphthalen-1-yl)-phenyl-methyl]-urea

Position	^{1}H NMR (δ in ppm)	^{13}C NMR(δ in ppm)	DEPT-135 NMR(δ in ppm)	P osition	^{1}H NMR(δ in ppm)	^{13}C NMR(δ in ppm)	DEPT-135 NMR(δ in ppm)
1	-	159.0	-	11	7.39-7.38 (1H,m)	122.9	122.9
2	6.95 (1H,s)	48.6	48.6	12	7.77 (1H,d, J=7.2 Hz)	128.3	128.3
3	-	114.5	-	13	-	144.8	-
4	-	153.4	-	14,14’	7.15-7.12 (1H,m)	129.0	129.0
5	7.24 (1H,d,J=7.2)	119.0	119.0	15,15’	7.34-7.26 (1H,m)	129.4	129.4
6	7.49 (1H,d,J= 7.2 Hz)	128.3	128.3	16	7.21-7.17 (1H,m)	126.9	126.9
7	-	128.3	-	NH	8.32 (1H,s)	-	-
8	-	132.7	-	NH_2	8.32 (2H,s)	-	-
9	7.83 (1H,d,J=8HZ)	122.9	122.9	OH	5.85 (1H,br,s)	-	-
10	7.45-7.41(1H,m)	126.3	126.3				

Table 5: ^{1}H- NMR, ^{13}C-NMR and DEPT-135 NMR spectral data of Compound 27

4.2.2. Characterization of compound 28

Compound **28** was obtained as white solid with melting 169-171^{o}C and its percent yield was 89.8%.

From IR (KBr pellet) spectrum showed (v in cm^{-1}, Appendix 2A) broad absorption band at 3430 cm^{-1} and at 3267 cm^{-1} attributed to O-H and N-H stretching respectively. The intense absorption bands at 1736 cm^{-1} and at 1178 cm^{-1} showed the presence of carbonyl carbon and O-C stretching for methoxy group respectively.

The ^{1}H NMR spectrum (Appendix 2B) showed a single peak at δ 6.06 (1H, s) corresponding to a hydroxy group on the aromatic ring and a single peak at δ 6.49 (1H, s) showed the presence of methine proton at C-2. A single peak at δ 3.76 (3H, s) at C-16 and at δ 6.07 (1H,-NH) and (2H,-$CONH_2$) showed the presence of methoxy group on the benzene ring and, amine and amide protons respectively. The peaks at δ 6.85 (1H, d, J=8.4 Hz) at C-15 and C-15’, at δ 7.22 (1H, d,

J=8.8 Hz) at C-14 and C-14' showed the presence of aromatic protons. The peaks at δ 7.36 (1H, d J=9.2) at C-5, δ 7.89 (1H, d, J=8.8Hz) at C-9, from δ 7.89-7.41 (4H, m) indicated the aromatic protons on ring (Table 4).

From ^{13}C NMR spectrum, the peaks at δ 159.7 at C-1 and δ 55.6 at C-2 showed that the presence of carbonyl carbon and methoxy group respectively (Appendix 2C). The peaks observed at δ 114.7 is due to C-15 and C-15' , and at δ 130.5 at C-14 and C-14' showed that the presence of sp^2 carbon on the benzene ring A whereas the peak observed at δ 150.3 and δ 147.5 indicated the presence of oxygenated quaternary carbon at C-17 and C-4 respectively. Besides to this the peaks at δ 131.0 at C-8 and δ 129.4 at C-7 showed that the presence of non-oxygenated quaternary carbon (Table 4). Thus, on the basis of ^{1}H-NMR, ^{13}C-NMR and IR spectra data, the structure of compound **28** was established as amidoalkyl naphthol: [(2-hydroxy-naphthalen-1-yl)-(4-methoxy-phenyl)-methyl]-urea (**Figure 10**) **.**

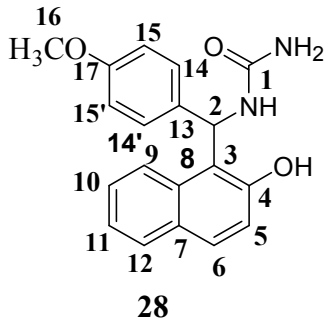

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Figure 10 : Structure of [(2-hydroxy-naphthalen-1-yl)-(4-methoxy-phenyl)-methyl]-urea

Table 6:^{1}H-NMR, ^{13}C-NMR and DEPT-135 NMR spectral data of Compound 28

Position	^{1}H NMR	^{13}C NMR	DEPT-135 NMR	position	^{1}H NMR	^{13}C NMR	DEPT-135 NMR
1	-	159.7	-	11	7.42-41(1H,m)	122.9	122.9
2	6.49(1H,s)	55.3	55.3	12	7.86-7.83 (1H,m)	128.3	128.3
3	-	112.7	-	13	-	134.0	-
4	-	147.5	-	14,14'	7.22 (1H,d,J=8.8 Hz)	130.5	130.5
5	7.36 (1H,d,J=9.2)	117.1	117.1	15,15'	6.85 (1H,d,J=8.4 Hz)	114.7	114.7
6	7.45 - 7.43(1H,m)	127.4	127.4	16	-	150.3	-

7	-	129.4	-	OCH_3	3.76 (1H,s)	55.6	55.6
8	-	131.0	-	16	6.07 (1H,bs,s)	-	-
9	7.89(1H,d,J=8.8 Hz)	128.8	128.8	NH	6.07(1H,bs,s)	-	-
10	7.59-7.56 (1H,m)	125.2	125.2	NH_2	6.06 (1H,bs,s)	-	-
				OH			

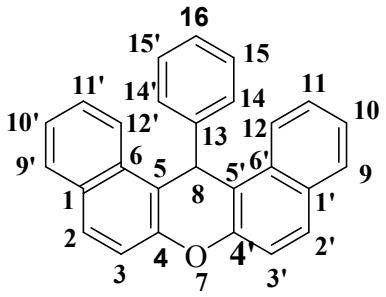
4.2.3. Characterization of compound 29

Compound **29** was obtained as white solid with melting point of 184-186^{o}C and its percent yield was 89.4 %.

From IR (KBr pellet) spectrum (v in cm^{-1}, Appendix 3A), absorption band at 1593 cm^{-1} and at 1431 cm^{-1} indicated the presence of aromatic C-C double bond .The intense absorption bands at 1254 cm^{-1} showed -C-O-C stretching.

The ^{1}H NMR spectrum (Appendix 3B) of **29** exhibited a doublet for the aromatic protons at δ 8.44 (1H, d ,J=8.4 Hz) at C-12and C-12', at δ 7.86 (1H,d,J=8.0 Hz) at C-9 and C-9', at δ 7.83 (1H,d,J=8.8 Hz) at C-2 and C-2', at δ 7.53 (1H,d,J=8.8 Hz) at C-3 and C-3', and a multiplet for the 4 aromatic protons at δ 7.46 -7.16 ppm and 4 aromatic protons at δ 7.63-7.55 ppm. The peak at δ6.52 (1H, C-H, s) at C-8 showed a single peak for the presence of methine proton (Table 5).

From ^{13}C NMR spectrum, the peak observed at δ 148.8 at C-4 and C-4', and δ 145.0 at C-13 showed the presence of oxygenated quaternary carbon and non-oxygenated quaternary carbon on the benzene ring respectively (Appendix 3C). The peaks observed at δ 131.5 at C-6 and C-6', and at δ 131.1 at C-1 and C-1' showed that the presence of non-oxygenated carbon whereas the peak observed at δ 128.8 for C-14, C-14', C-15, C-15', and δ 128.4 for C-9 and C-9', δ 128.3 for C-2 and C-2' indicated the presence of sp^2 of aromatic carbon. The peak at δ 38.1 at C-8 indicated the presence of methine carbon (Table 5). Thus, on the basis of ^{1}H NMR, ^{13}C NMR and IR spectra data, the structure of compound **29** was established as benzoxanthene: 14-Phenyl-14H-Dibenzo [a, j] xanthene **(Figure 11).**



29

Figure 11: Structure of 14-Phenyl-14H-Dibenzo [a, j] xanthene

Table 7: ^{1}H-NMR, ^{13}C-NMR and DEPT-135 NMR spectral data of Compound 29

Position	^{1}H NMR	^{13}C NMR	DEPT-135 NMR	position	^{1}H NMR	^{13}C NMR	DEPT-135 NMR
1,1’	-	131.1	-	9,9’	7.86 (1H,d,J=8.0 Hz)	128.4	128.4
2,2’	7.83 (2H,d,J=8.8 Hz)	128.3	128.3	10,10’	7.59-7.55 (1H,m)	122.7	122.7
3,3’	7.53 (2H,d,J=8.8 Hz)	118.0	118.0	11,11’	7.63-7.61(1H,m)	124.2	124.2
4,4’	-	148.8	-	12,12’	8.44 (1H,d,J=8.4 Hz)	122.7	122.7
5,5’	-	117.4	-	13	-	145.0	-
6,6’	-	131.5		14,14’	7.04-7.00 (1H,m)	128.8	128.8
7	-	-	-	15,15’	7.46-7.42 (1H,m)	128.8	128.8
8	6.52 (1H,s)	38.1	38.1	16	7.2-7.16 (1H,m)	126	126

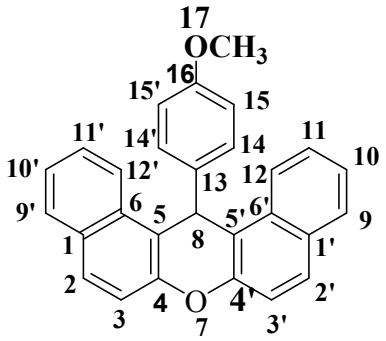
4.2.4. Characterization of compound 30

Compound **30** was obtained as yellowish solid with melting point of 203-205^{o}C and its percent yield was 92 %.

From IR (KBr pellet) spectrum (v in cm^{-1}, Appendix 4A), absorption band at 1602 cm^{-1} and at 1514 cm^{-1} showed the presence of aromatic c-c double bond stretching .The intense absorption bands at 1218 cm^{-1} and 1163 indicated -C-O-C and -O-CH_3 stretching respectively.

The ^{1}H NMR spectrum (Appendix 4B) of **30** exhibited a doublet for the aromatic protons at δ 7.71 (1H, d, J=8) at C-2 and C-2', at δ 7.05 (1H, d, J=8.8Hz) at C-3 and C-3', and a multiplet for the 4 aromatic protons at δ 7.48 -7.34 ppm and 4 aromatic protons at δ 7.91-7.77 ppm. The peak at δ5.56 (1H, C-H, s) at C-8 and at δ3.92 at C-17 showed a single peak for the presence of methine proton and methoxy group respectively (Table 6).

From ^{13}C NMR spectrum, the peak observed at δ 164.9 at C-16, δ 153.5 at C-4 and C-4', and at δ 134.6 at C-13 showed the presence of oxygenated quaternary carbon and non-oxygenated quaternary carbon on the benzene ring respectively (Appendix 4C). The peaks observed at δ 132.3 at C-6 and C-6', and at δ 128.5 at C-1 and C-1' showed that the presence of non-oxygenated carbon whereas the peak observed at δ 129.9 for C-14 and C-14', and δ 109.5 for C-15 and C-15', δ 127.8 for C-2 and C-2' indicated the presence of sp^2 of aromatic carbon (Table 6). Thus, on the basis of ^{1} H NMR, ^{13}C NMR and IR spectra data, the structure of compound **30** was established as benzoxanthene:14-(4-Methoxy -Phenyl) -14H-dibenzo [a, j] xanthene (**Figure 12**).



30

Figure 12: Structure of 14-(4-Methoxy -Phenyl) -14H-dibenzo [a,j] xanthene

Table 8: ^{1}H-NMR, ^{13}C-NMR and DEPT-135 NMR spectral data of Compound 30

Position	^{1} H NMR	^{13} C NMR	DEPT-135 NMR	position	^{1} H NMR	^{13} C NMR	DEPT-135 NMR
1	-	128.5	128.5	10,10'	7.38-7.34 (1H,m)	126.4	126.4
2,2'	7.71 (1H,d,J=8)	127.8	127.8	11,11'	7.48-7.44(1H,m)	126.5	126.5
3,3'	7.05 (1H,d,J=8.8)	117.8	117.8	12,12'	7.91-7.88 (1H,m)	123.6	123.6

4,4’	-	153.5	-	13	-	134.6	-
5,5’	-	114.4	-	14,14’	7.19-7.16(1H,m)	129.9	129.9
6,6’	-	132.3	-	15,15’	7.15-7.13 (1H,m)	109.5	109.5
7	-	-	-	16	-	164.9	-
8	5.56 (1H,s)			17	3.92	55.6	55.6
9,9’	7.87- 7.77 (1H,m)	127.8	127.8	-	-	-	-

4.2.5. Characterization of compound 31

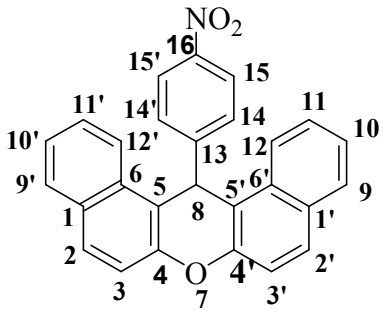
Compound **31** was obtained as yellow solid with melting point of 314-215^{o}C and its percent yield was 93.5 %.

From IR (KBr pellet) spectrum (v in cm^{-1}, Appendix 5A), the intense peak observed at 1592 cm^{-1} and at 1415 cm^{-1} showed the presence of aromatic c-c double bond stretching whereas the intense absorption bands at 1341 cm^{-1} and 1240 cm^{-1} indicated -C-O-C stretching and NO_2 attached to aromatic system respectively.

The ^{1}H NMR spectrum (Appendix 5B) of **31** exhibited a doublet for the aromatic protons at δ 8.04 (1H, d, J= 8.8 Hz) for C-12, C-12’ ,C-9 and C-9’, at δ 8.32 (1H, d, J=9.6) for C-15 and C-15’, and at δ 7.72 (1H, d, J= 8.8 Hz) for C-14 and C-14’, δ 7.87(1H,d,J=8.8Hz) for C-2 and C-2’,at δ 7.54 (1H,d,J=8.8Hz) for C-3 and C-3’. The peak at δ 7.49-7.45 (1H, m) for C-10 and C-10’, and δ7.65-7.60 (1H, m) for C-11 and C-11’) showed multiple spectra for the 4 aromatic protons respectively. The peak at δ 6.63 (1H, C-H, s) at C-8 showed a single peak for the presence of methine proton of sp^3 carbon (Table 7).

From ^{13}C NMR spectrum, the peak observed at δ 152.0 at C-4 and C-4’, at δ 148.8 at C-13 and δ 146.3 at C-16 showed the presence of oxygenated quaternary carbon, non-oxygenated quaternary carbon and quaternary carbon attached with NO_2 on the benzene ring respectively. (Appendix 5C). The peaks observed at δ 131.1 at C-6 and C-6’, and at δ 129.1 at C-1 and C-1’ showed that the presence of non-oxygenated carbon whereas the peak observed at δ 129.6 for C-14 and C-14’, and δ 124.6 for C-15 and C-15’, δ 128.9 for C-2 and C-2’ indicated the presence of sp^2 of aromatic carbon. The peak at δ 37.9 at C-8 indicated the presence of methine carbon. (Table7). Thus, on the basis of ^{1} H NMR, ^{13}C NMR and IR spectra data, the structure of

compound **31** was established as benzoxanthene: 14-(4-Nitro-Phenyl) - 14H - dibenzo [a,j] xanthene (**Figure 13**).



31

Figure 13: Structure of 14-(4-Nitro-Phenyl) - 14H - dibenzo [a, j] xanthene

Table 9: ^{1}H-NMR, ^{13}C-NMR and DEPT-135 NMR spectral data of Compound 31

Position	^{1}H -NMR	^{13}C-NMR	DEPT-135 NMR	Position	^{1}H- NMR	^{13}C-NMR	DEPT-135 NMR
1,1’	-	129.1	-		9,9’	8.04 (1H,d,J=8.8 Hz)	128.9
2,2’	7.87(1H,d,J=8.8Hz)	128.9		10,10’	7.49-7.45 (1H,m)	123.9	123.9
3,3’	7.54 (1H,d,J=8.8Hz)	118.1		11,11’	7.65-7.60(1H,m)	127.2	127.2
4,4’	-	152.0	-	12,12’	8.04 (1H,d,J= 8.8 Hz)	122.0	122.0
5,5’	-	115.8	-	13	-	148.8	148.8
6,6’	-	131.1	-	14,14’	7.72 (1H,d,J= 8.8 Hz)	129.6	129.6
7	-	-	-	15,15’	8.32 (1H,d,J=9.6)	124.6	124.6
8	6.63 (1H,s)	37.9	37.9	16	-	146.3	-

4.3. Antibacterial Activity

The antibacterial activities of the synthesized compounds were tested *against Escherichia coli ATCC 25922* and *Pseudomonas Aeruginosa ATCC 7553* (Gram-negative bacteria), *Bacillus subtilis ATCC 6633* and *Staphylococcus aureus ATCC 25923* (Gram-positive bacteria) using Mueller Hinton agar (MHA) as a medium by disk diffusion method. The results have been compared with antibacterial agent tetracyclinas standard drug. The results of the antibacterial

activities of the synthesized compounds were determined by measuring the zone of inhibition in millimeter.

The compound **27** was active against *Bacillus Subtilis* (Gram-positive bacteria) at all concentrations tested and inactive against *Strophylococcus Aureus* (Gram-positive bacteria) *Escherichia Coli* and *Pseudomonas Aeruginosa* (Gram-negative bacteria). The compound **28** did not show any activity against Gram-positive bacteria (*Strophylococcus Aureus*) and Gram – negative bacteria (*Pseudomonas Aeruginosa)* at all three concentrations (50,100 and 200µg/ml) and showed activity against Gram-positive bacteria (*Bacillus Subtilis*) and Gram-negative bacteria (*Escherichia Coli*) at all three concentrations tested where as compound **29** showed activity against Gram-positive bacteria (*Bacillus Subtilis*),*Escherichia Coli* and *Pseudomonas Aeruginosa* (Gram-negative bacteria) and did not show any activity against *Strophylococcus Aureus*(Gram-positive bacteria). The compound **30** and **31** were active and showed activity, at all concentrations tested, against both Gram-positive and Gram-negative organisms (**Table 10**).

Table 10: Antibacterial activities of the synthesized compounds

Compound	Zone of inhibition(mm)											
	Gram positive Bacteria						Gram negative Bacteria					
	StrophylococcusAureus			*Bacillus Subtilis*			*Escherichia Coli*			*Pseudomonas Aeruginosa*		
	Concentration (µg/ml)			Concentration (µg/ml)			Concentration (µg/ml)			Concentration (µg/ml)		
	50	100	200	50	100	200	50	100	200	50	100	200
27	6mm	6mm	6mm	10mm	11mm	12mm	6mm	6mm	6mm	6mm	6mm	6mm
28	6mm	6mm	6mm	9mm	10mm	12mm	10mm	11mm	15mm	6mm	6mm	6mm
29	6mm	6mm	6mm	8mm	9mm	10mm	10mm	11mm	12mm	10mm	11mm	12mm
30	9mm	10mm	13mm	8mm	9mm	10mm	9mm	10mm	15mm	8mm	9mm	10mm
31	10mm	11mm	12mm	9mm	10mm	12mm	9mm	10mm	12mm	10mm	11mm	12mm
Tetracycline	10mm	12mm	14mm	7mm	8mm	10mm	12mm	14mm	17mm	9mm	10mm	11mm
DMSO	6mm	6mm	6mm	6mm	6mm	6mm	6mm	6mm	6mm	6mm	6mm	6mm

4.4. Antifungal Activity

All synthesized compounds were evaluated for their antifungal activities against *Candidia Albicunas* using TSA (tryptose soya agar) as medium by disk diffusion method. The results of this evaluation were compared with fluconazole as reference standard. From the results obtained, compound **29** showed better antifungal activity even than standard fluconazole at all concentration tested. On the other hand compound **27**, **28**, **30** and **31** were inactive at all concentration tested (**Table** 11).

Table 11: Antifungal activities of the synthesized compounds

Compound	Zone of inhibition(mm)		
	CandidiaAlbicunas		
	Concentration (µg/ml)		
	50	100	200
27	6mm	6mm	6mm
28	6mm	6mm	6mm
29	12mm	14mm	16mm
30	6mm	6mm	6mm
31	6mm	6mm	6mm
Fluconazole	8mm	9mm	10mm
DMSO	6mm	6mm	6mm

4.5. Antioxidant Activity

The antioxidant activity of the synthesized compounds was analyzed using 2,2-diphenyl-1-picryl-hydrazyl (DPPH) according to [107]. According to Phongpaichit, *et al*. [114], extracts which possess IC_{50} values ranging from 50 to 100 µg / mL is considered to exhibit intermediate antioxidant activity and extracts with IC_{50} greater than 100µg /mL is considered to possess weak antioxidant activity. Meanwhile, extracts with IC_{50} value ranging between 10 to 50 µg /mL is considered to possess strong antioxidant acitivity.

Based on the experiment done on antioxidant activity from % inhibition, all synthesized compounds (**27, 28, 29, 30, 31**) have shown promising antioxidant activities as compared with

standard ascorbic acid starting from 29.8 to 94.4 percentage of inhibition at the tested concentrations (12.5,25,50,100,200,400 µg/ml) of the compounds respectively (**Table 12**).

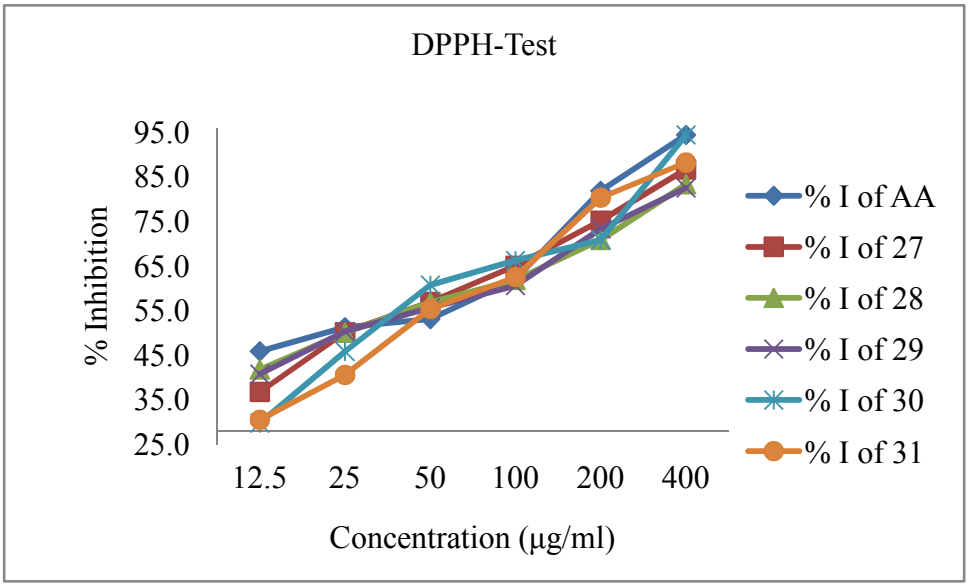
Synthesized amidoalkyl naphthol 27,28 showed strong radical scavenging ability with an IC_{50} value of 24.45µg /mL and 17.65µg /mL respectively. Synthesized benzoxanthene 29,30 also exhibited strong radical scavenging ability with an IC_{50} value of 22.6 µg /mL and 47.56 µg /ml respectively where as benzoxanthene 31 showed weak antioxidant activity with an IC_{50} value of 60.3 µg /mL.

Table 12: % inhibition of inhibition of the compounds compared to standard ascorbic acid

Concentration (µg/ml)	% Inhibition					
	Standard	Synthesized Compounds				
	AA	27	28	29	30	31
12.5	45.9	36.8	41.8	40.7	29.8	30.5
25	51.3	50.1	50.0	50.3	45.8	40.6
50	53.1	57.0	56.9	55.6	60.8	55.4
100	62.0	65.0	61.9	60.6	66.3	62.5
200	81.8	75.2	70.9	73.3	70.9	80.3
400	94.4	86.7	83.3	82.6	94.4	88.2

Table 13: IC_{50} of the synthesized compounds compared to standard ascorbic acid

Synthesized Compounds	IC50 (µg/ml)
27	24.45
28	17.65
29	22.6
30	47.56
31	60.30
Ascorbic acid	9.28


DPPH-Test
95.0
85.0
75.0
65.0
55.0
45.0
35.0
25.0
% Inhibition
12.5
25
50
100
200
400
Concentration (µg/ml)
% I of AA
% I of 27
% I of 28
% I of 29
% I of 30
% I of 31

5. CONCLUSSION AND RECOMMENDATION

5.1. CONCLUSSION

From this study, zinc oxide nanoparticles (ZnO NPs) was found to be an efficient, facile and environmentally green protocol to synthesis both amidoalkylnaphthols and benzoxanthenesas biologically interesting compounds. This synthetic protocol offers several advantages including inexpensive, easily available, avoidance of harmful organic solvents, high yield, short reaction time, simple work-up procedure and ease of separation compared to conventional reported methods. On the hand the biological activities results showed that benzoxanthene **29, 30 and 31** showed antibacterial activities against all gram negative and gram positive bacterial strains tested where as amidoalkyl naphthol **27** showed activity against *B. Subtilis*only and amidoalkyl naphthol **28** was active against both *B. subtilis and E.coli.* Amongst all, the benzoxanthene **29** has only shown antifungal activity even than standard fluconazole. Except compound 31, All the remaining synthesized compounds have shown promising antioxidant activities with an IC_{50} values of 24.45, 17.65, 22.6 and 47.56 µg/ml for amidoalkyl naphthol 27, 28 and benxoxanthene 29,29 compared to standard ascorbic acid(9.28µg/ml)respectively.

5.2. RECOMMENDATION

From this present research work it is recommended to synthesize additional series of amidoalkyl naphthol derivatives from benzaldehyde and its derivatives, beta-naphthol and urea or thiourea, and synthesis of benzoxanthene derivatives from benzaldehyde and its derivatives and beta-naphthol by introducing different functional groups and conduct their structure-activity relationship (SAR) analysis to explore their potency of biological activities. It is also recommended to determine potential application of the compounds to be synthesized against wide range of human pathogens.

6. REFERENCE

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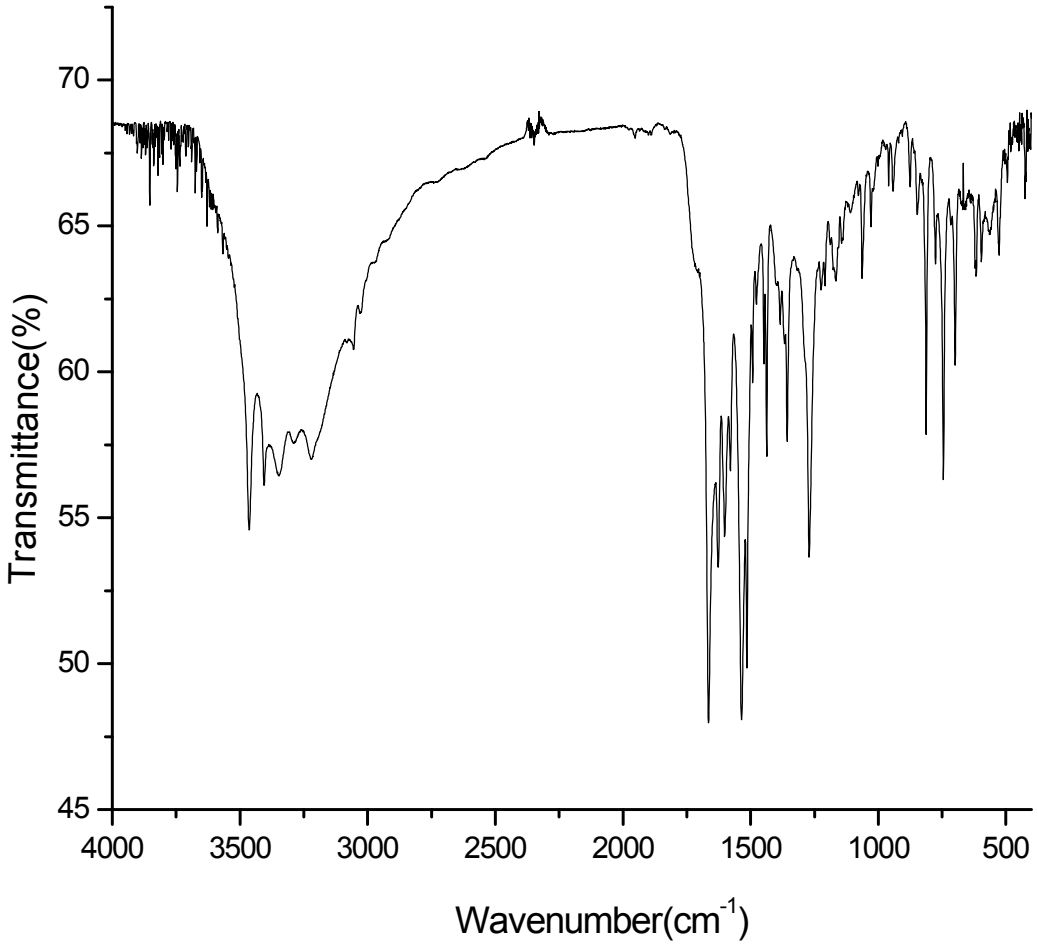
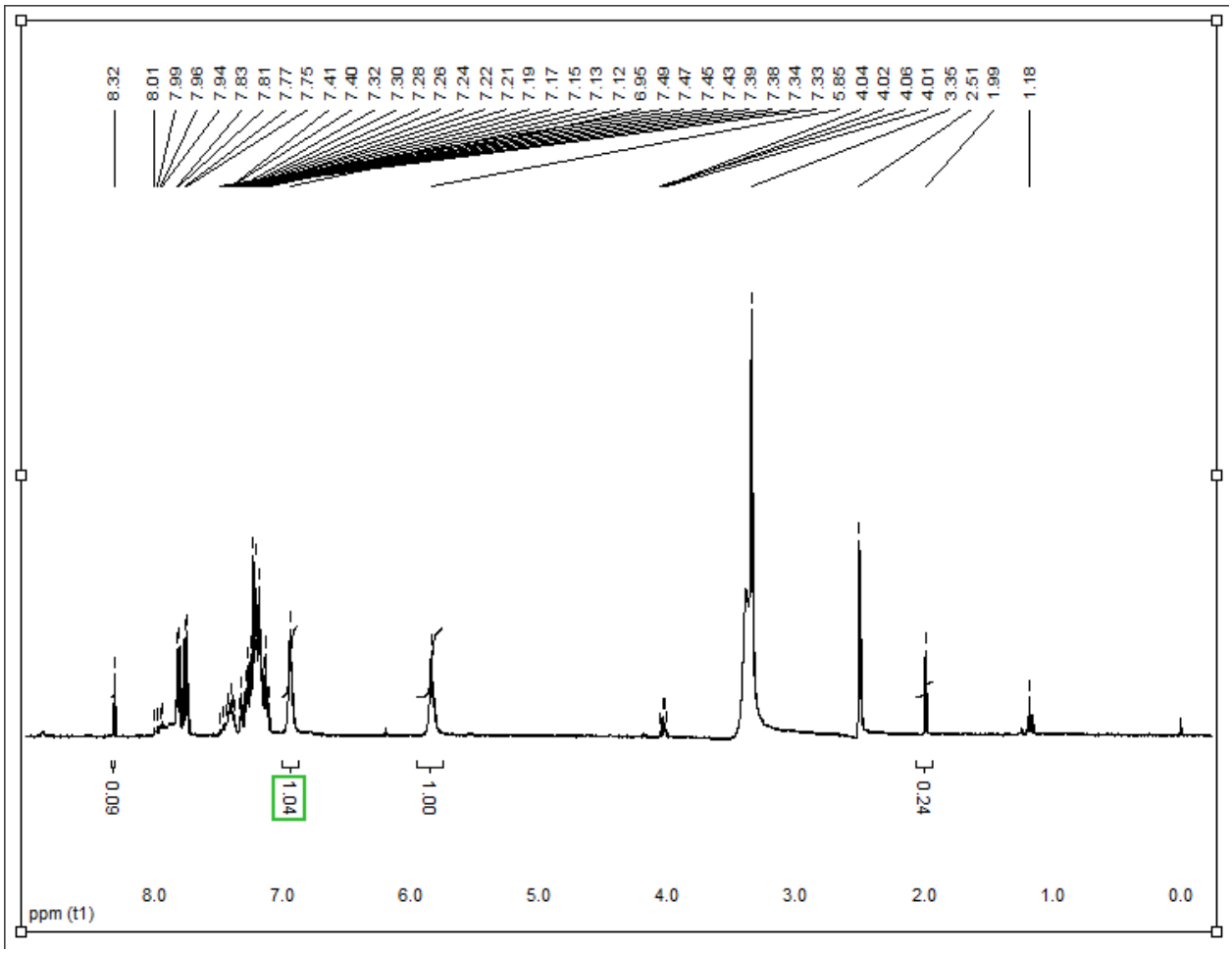
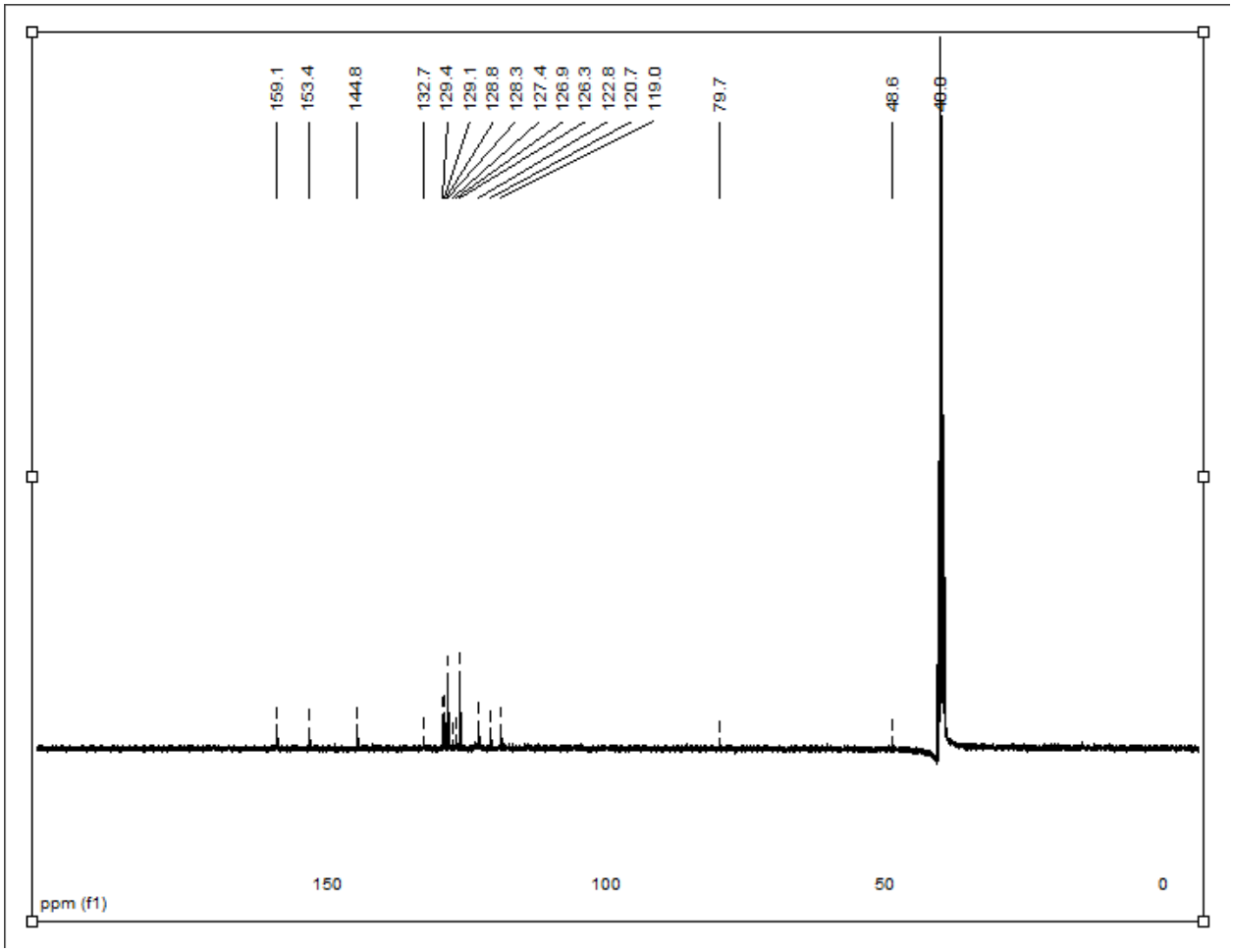
Appendix 1A: FT-IR spectrum of Compound 27



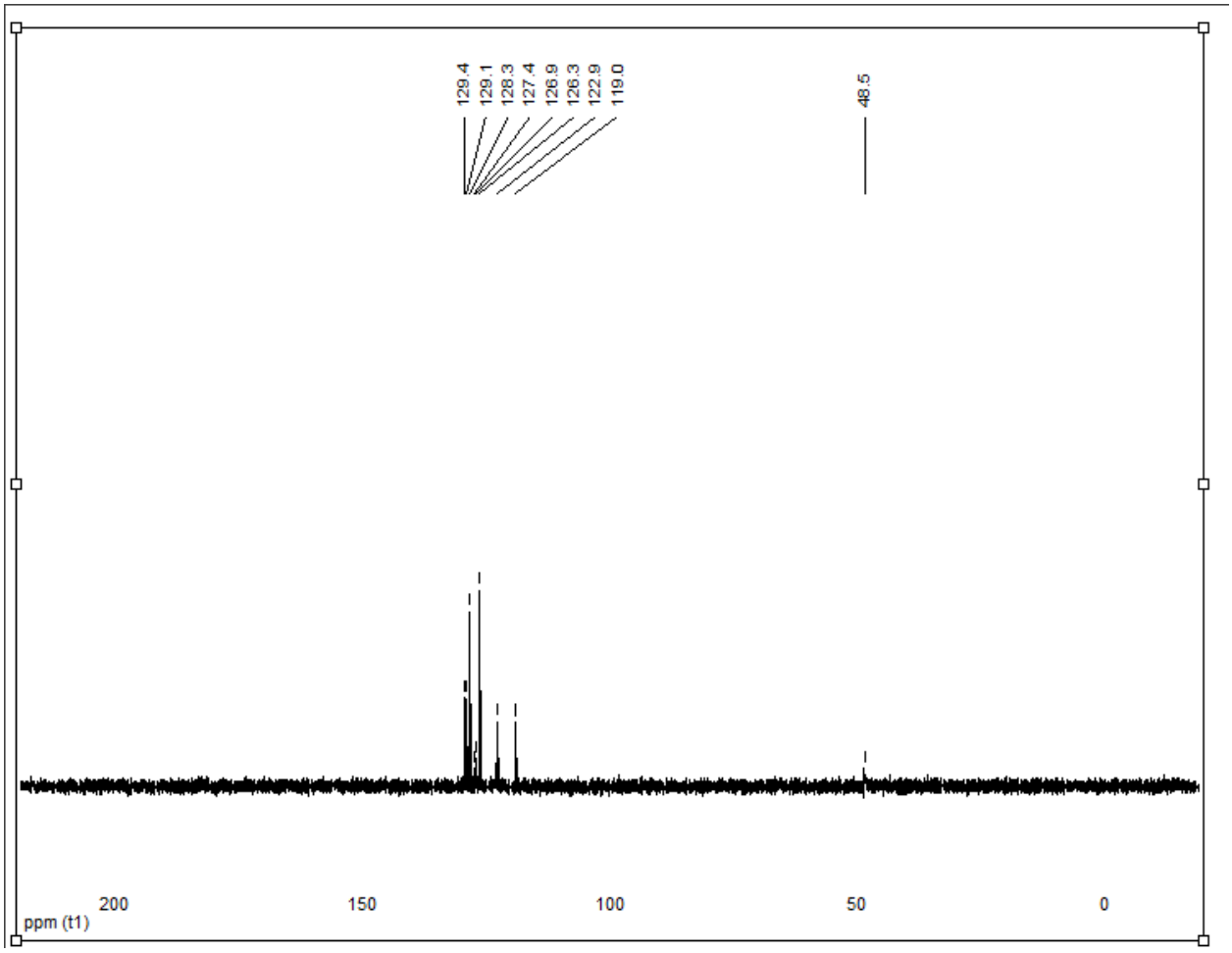
Appendix 1B: ^{1}H-NMR spectrum of Compound 27



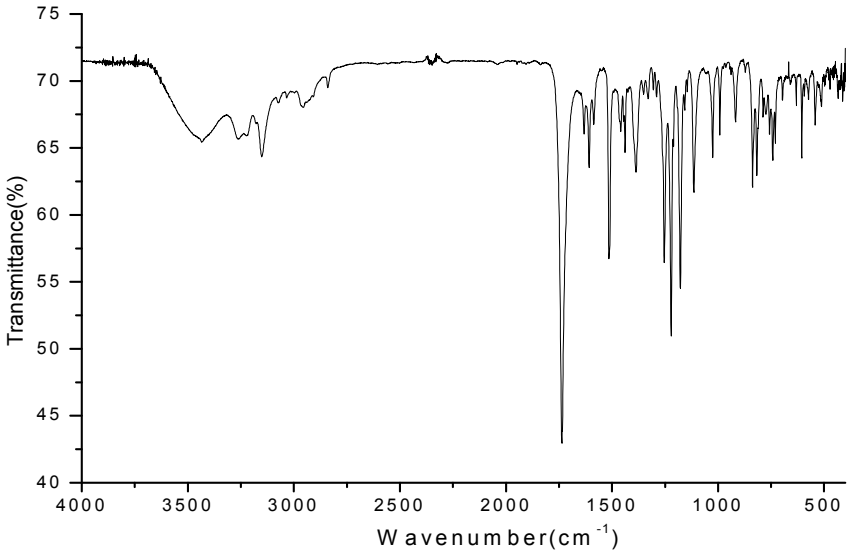
Appendix 1C: ^{13}C- NMR spectrum of compound 27



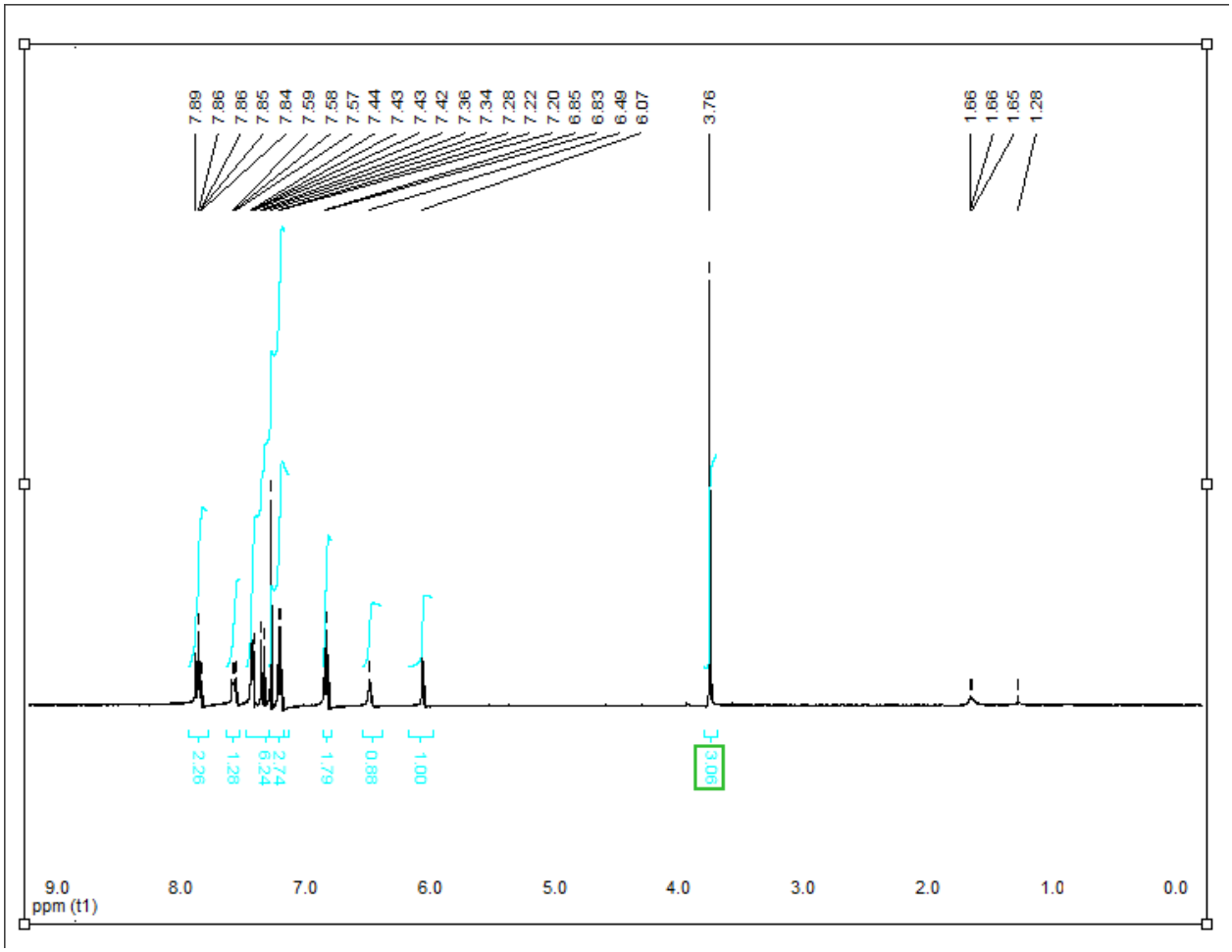
Appendix 1D: DEPT- 135 NMR spectrum of compound 27



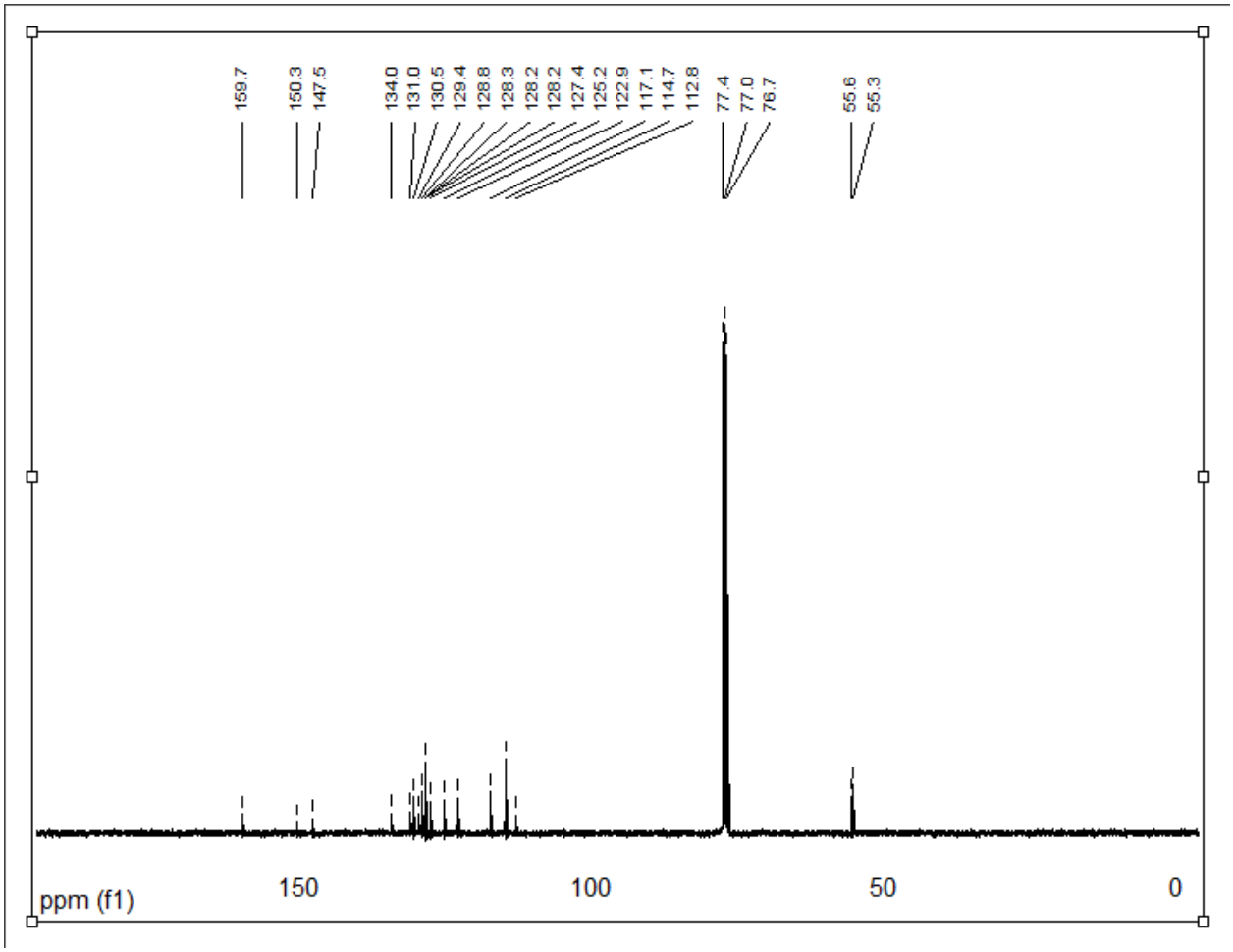
Appendix 2A: FT-IR spectrum of compound 28



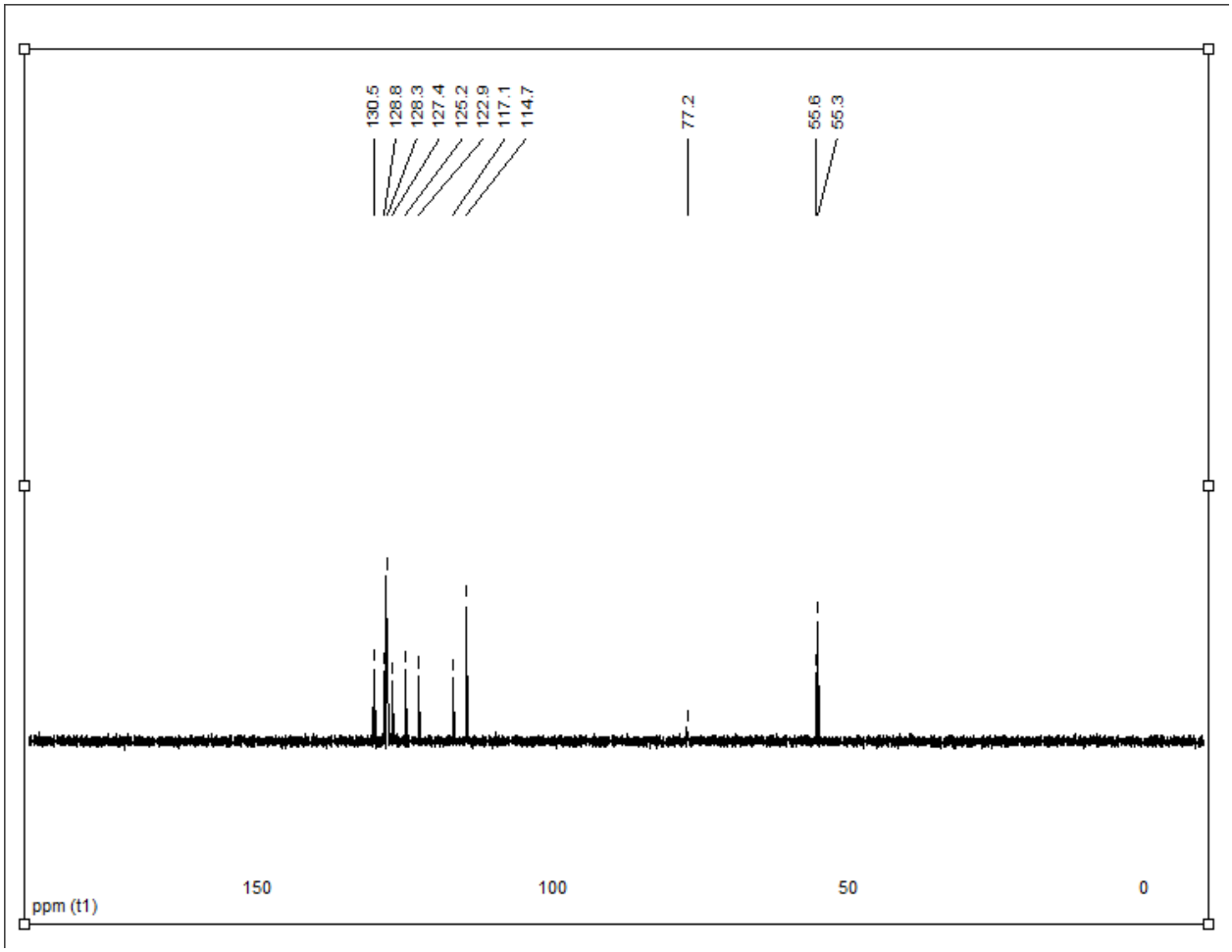
Appendix 2B: ^{1}H-NMR spectrum of compound 28



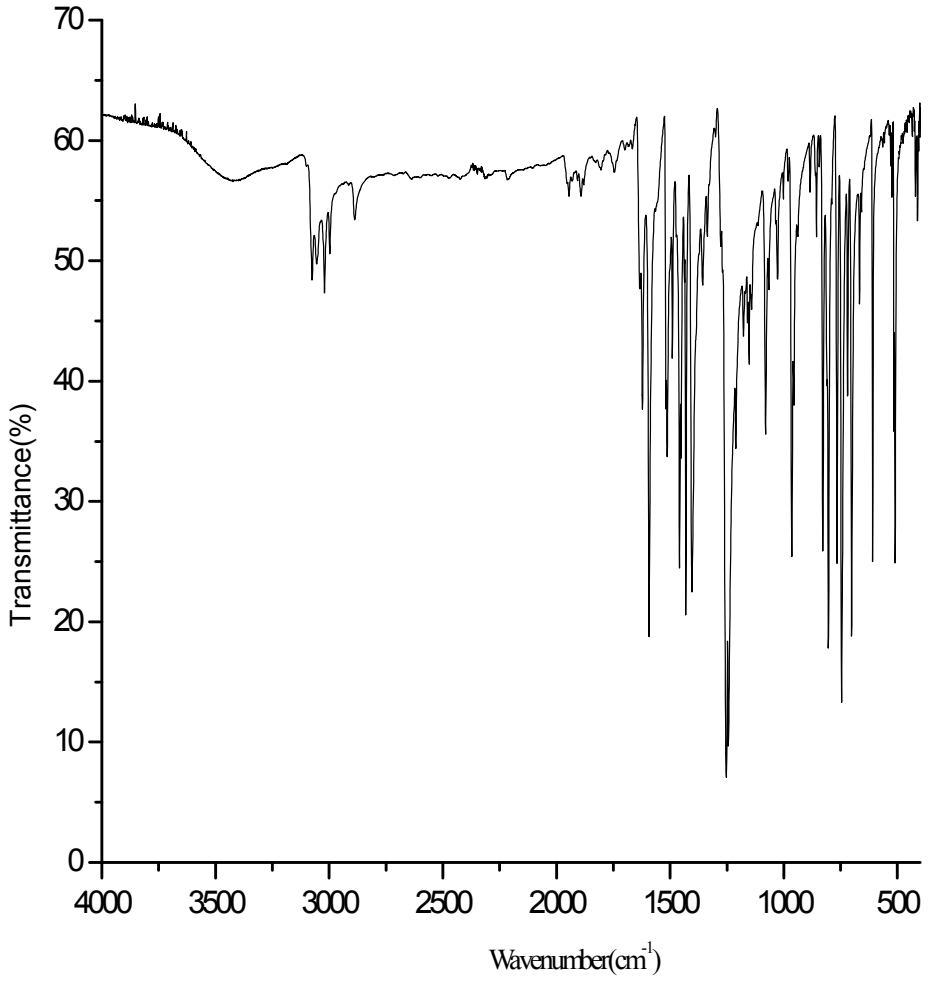
Appendix 2C: ^{13}C-NMR spectrum of compound 28



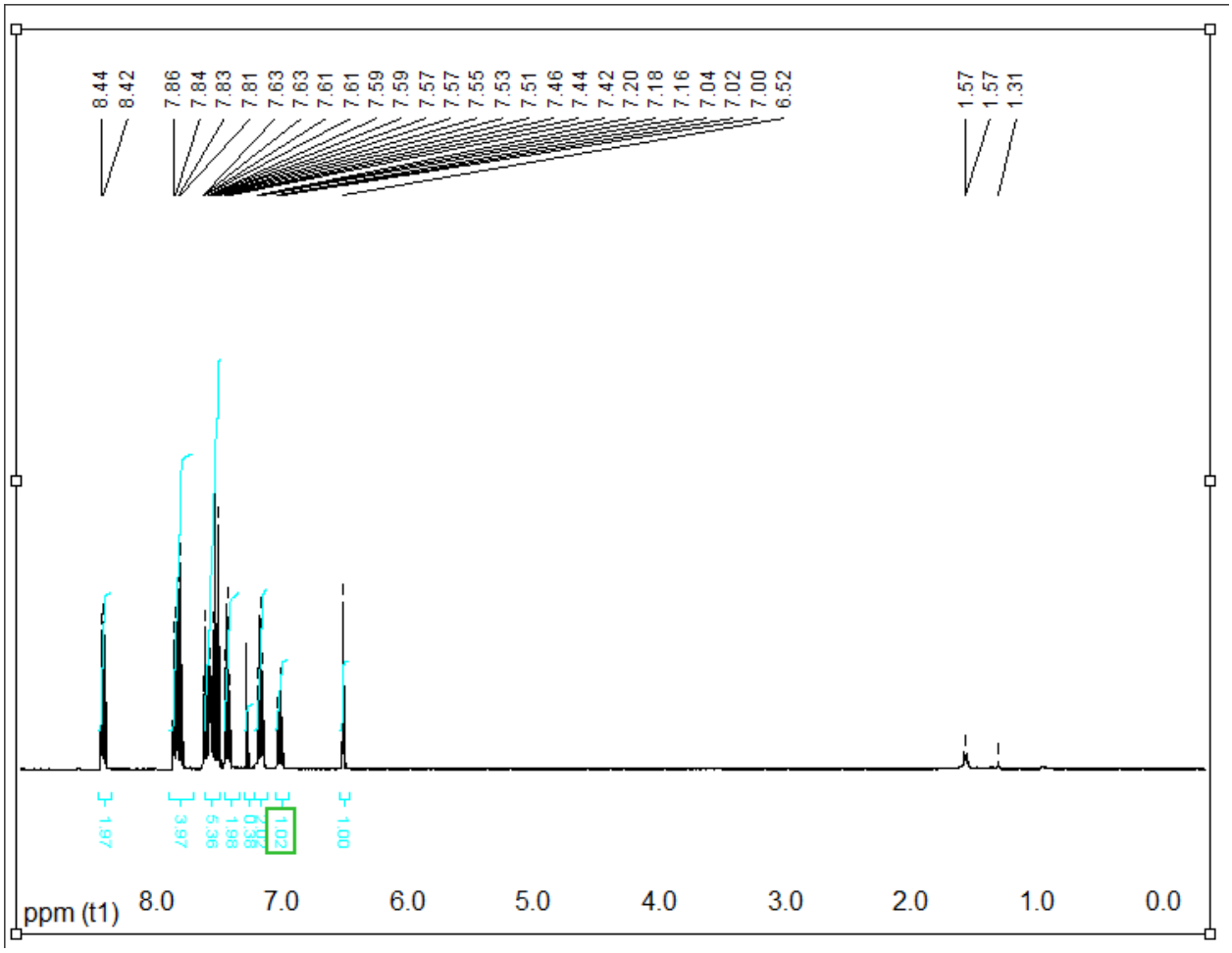
Appendix 2D: DEPT- 135 NMR spectrum of compound 28



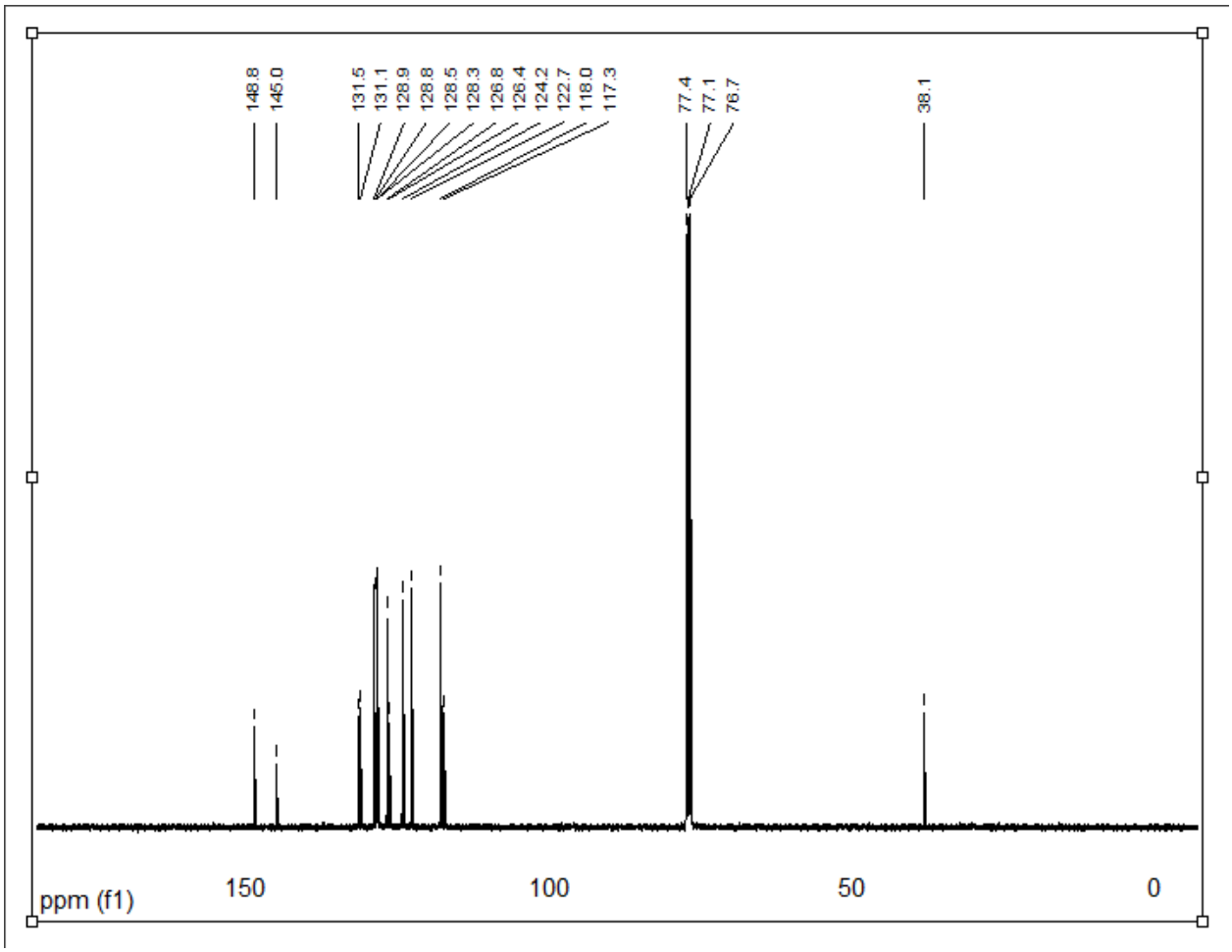
Appendix 3A: FT-IR spectrum of compound 29



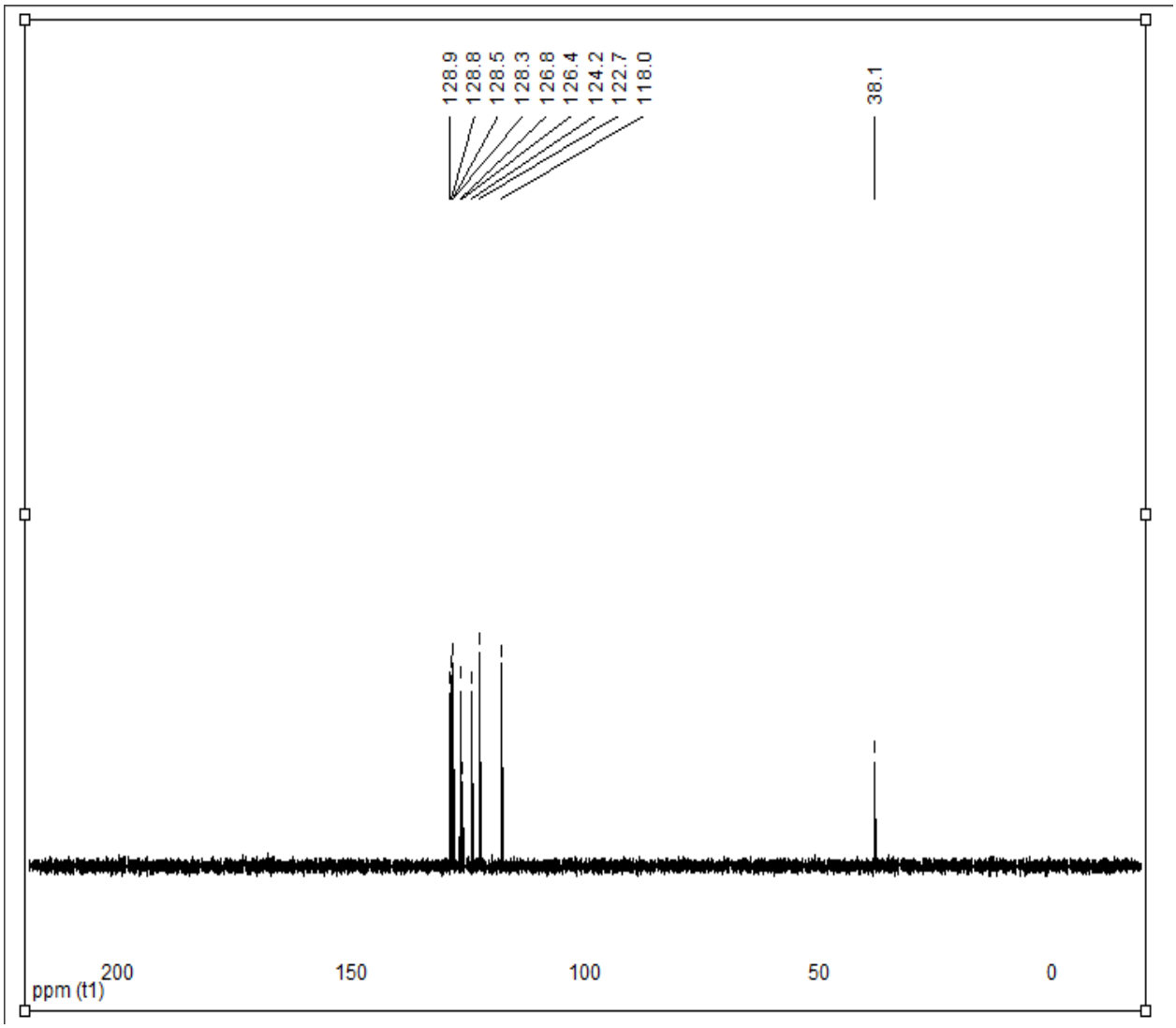
Appendix 3B: [1]H-NMR spectrum of compound 29



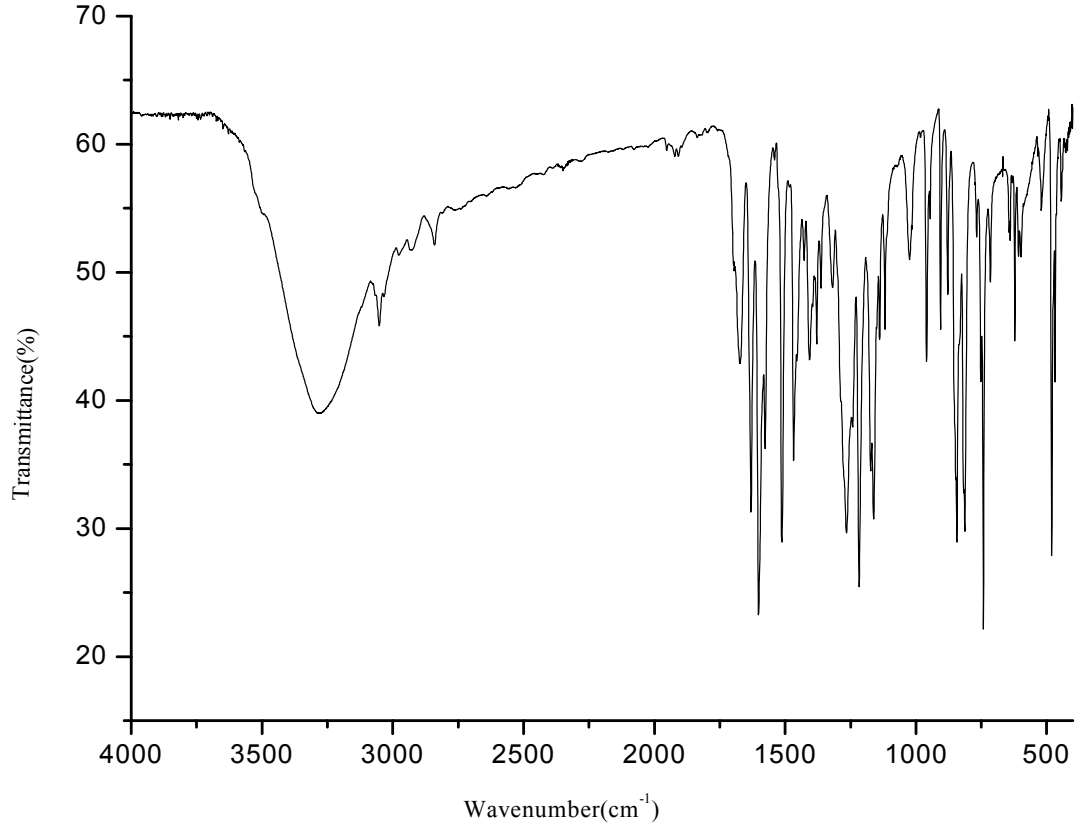
Appendix 2: ^{13}C-NMR spectrum of compound 29



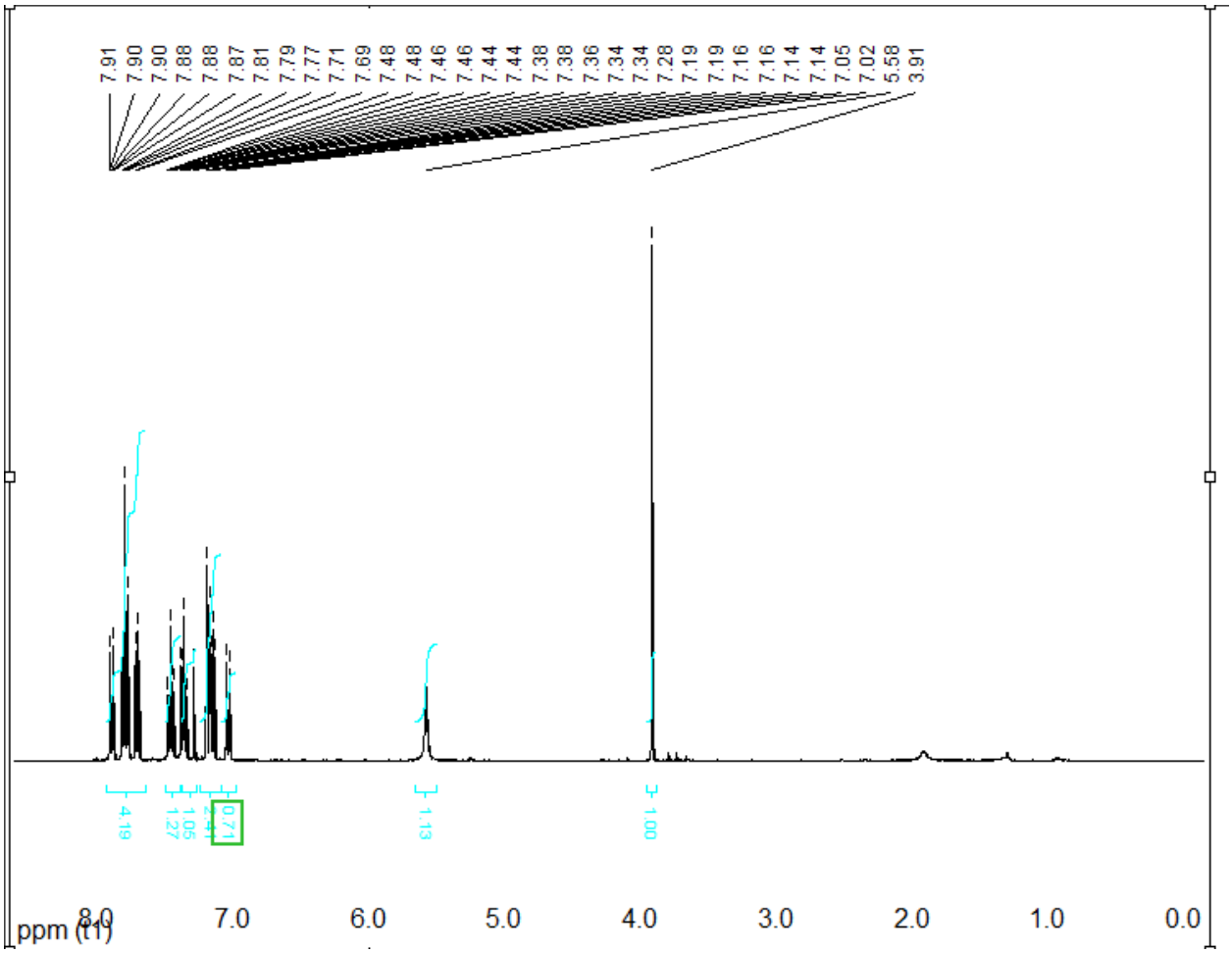
Appendix 3D: DEPT- 135 NMR spectrum of compound 29



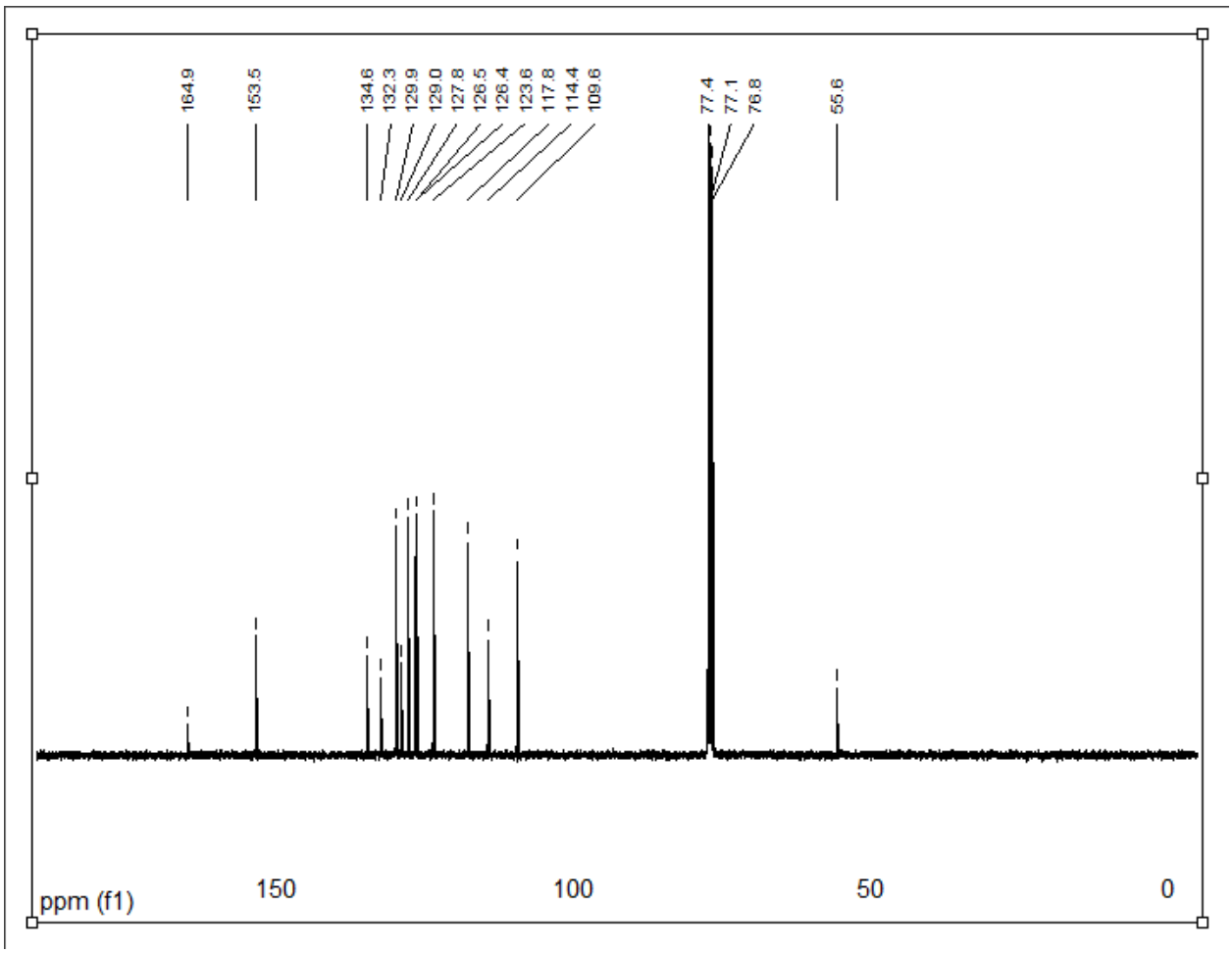
Appendix 4A: FT-IR spectrum of compound 30



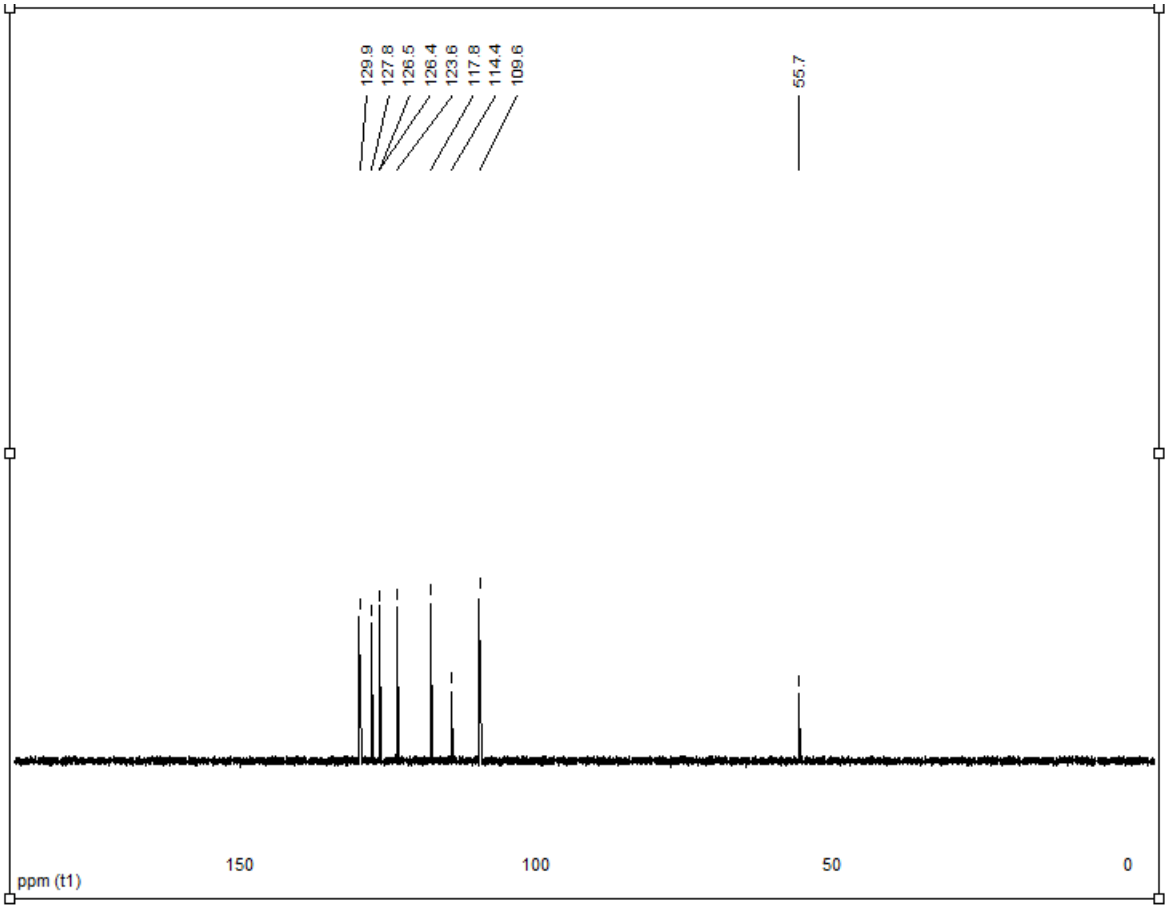
Appendix 3B: ^{1}H-NMR spectrum of compound 30



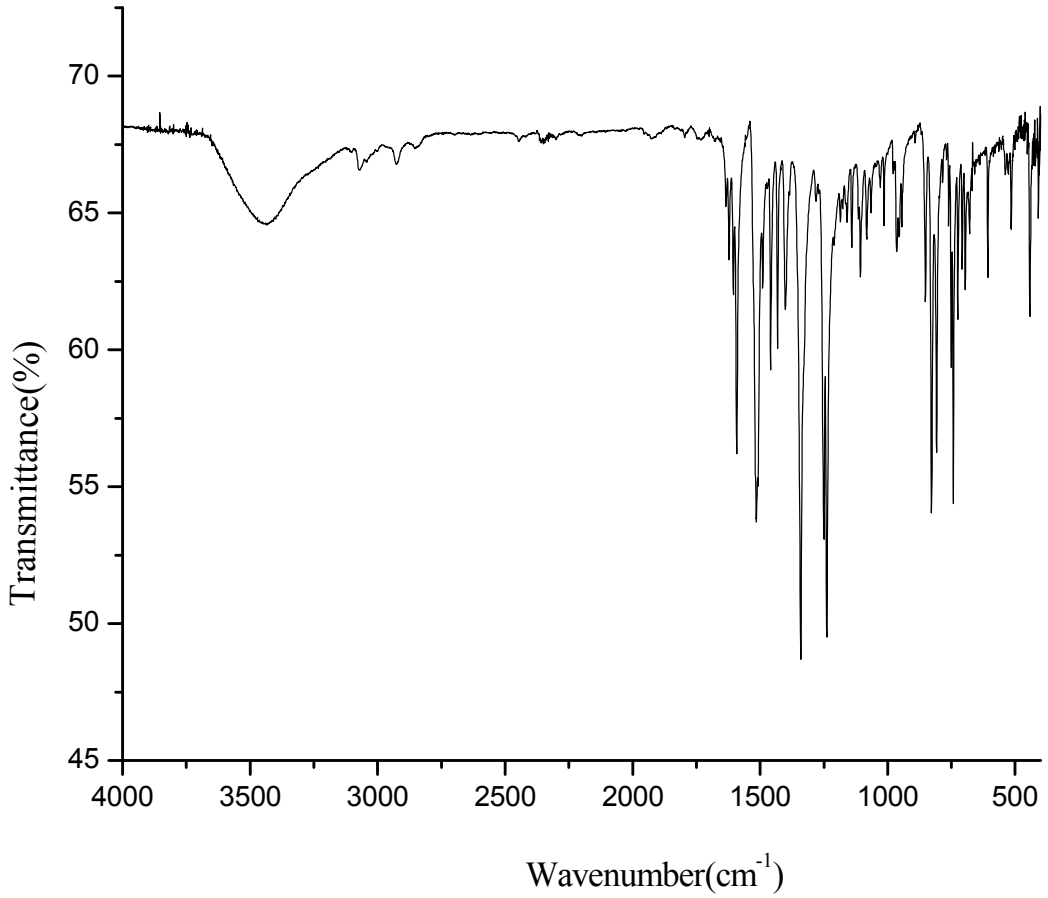
Appendix 4: ^{13}C-NMRspectrum of compound 30



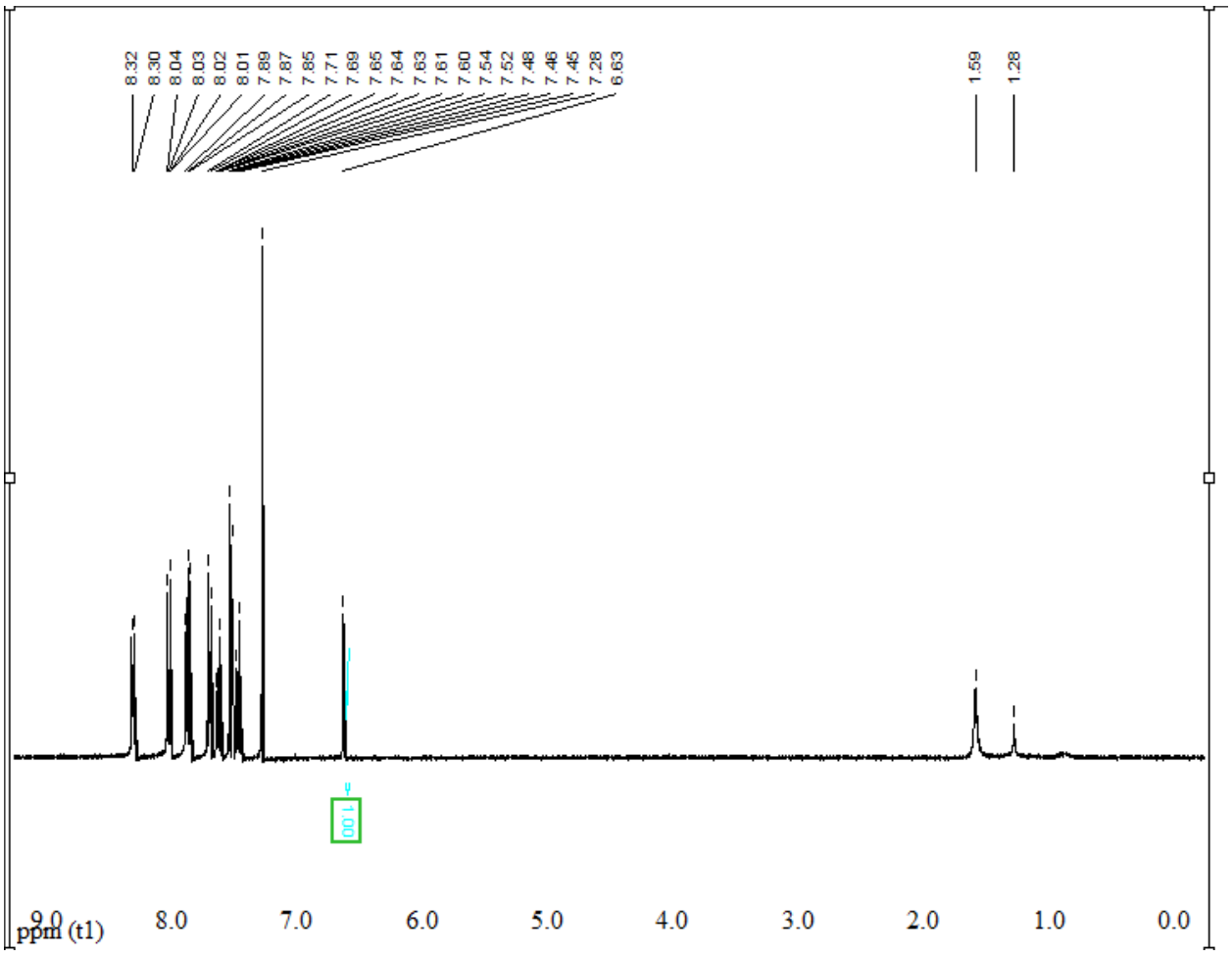
Appendix 4D: DEPT-135 NMR spectrum of compound 30



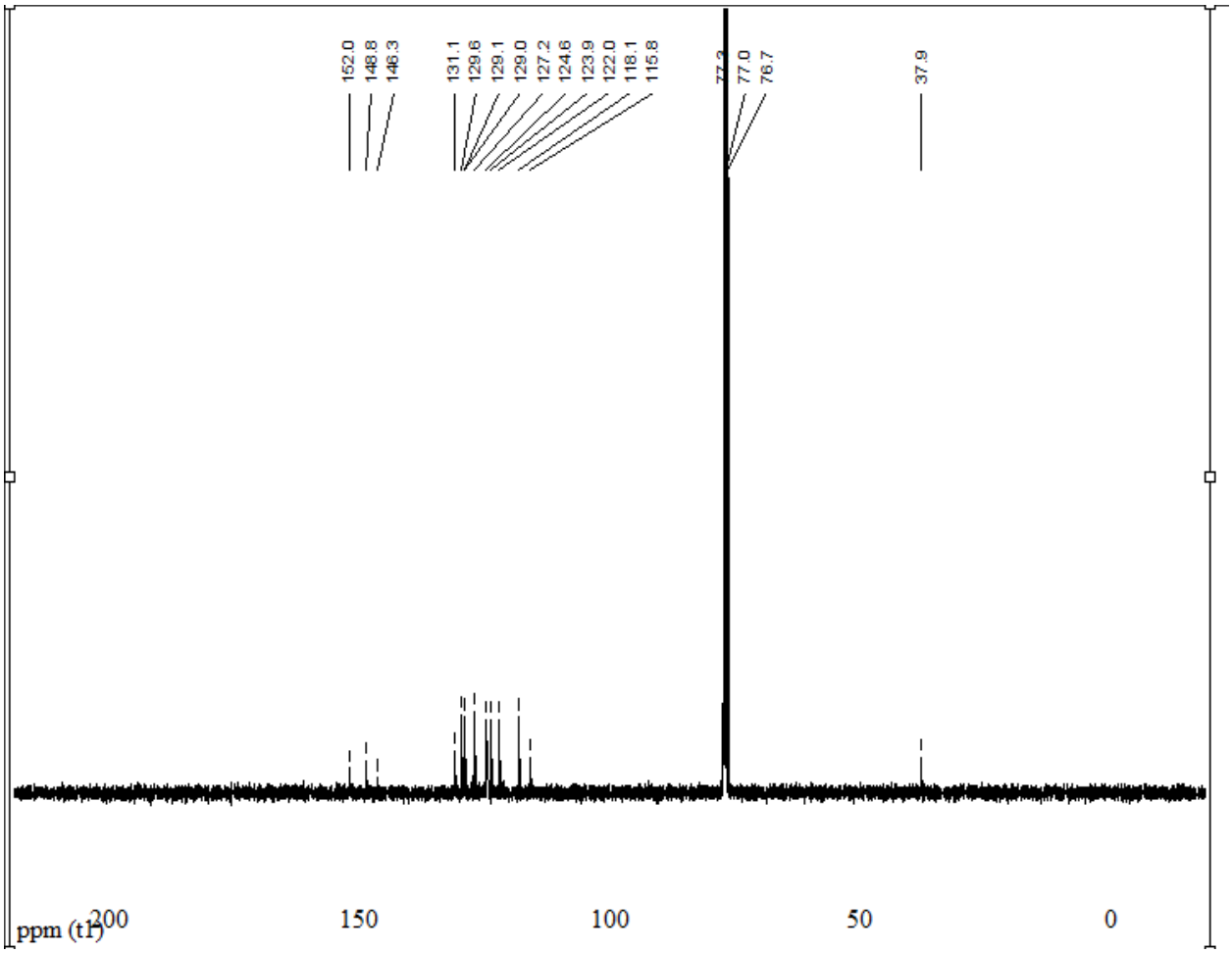
Appendix 5A: FT-IR spectrum of compound 31



Appendix 5B: ^{1}H-NMR spectrum of compound 31



Appendix 5C: ^{13}C-NMR spectrum of compound 31



Appendix 5D: DEPT- 135 NMR spectrum of compound 31