SYNTHESIS AND CHARACTERIZATION OF DIPEHNYL ETHERS BASED AMIDE ESTERS

A

Thesis Submitted

in partial fulfillment of the requirements for the award of the degree of

MASTER OF SCIENCE

IN

CHEMISTRY

BY

TEJASWI BHARDWAJ

Registration No. 301102016

Supervisor

DR. MANMOHAN CHHIBBER

SCHOOL OF CHEMISTRY AND BIOCHEMISTRY

THAPAR UNIVERSITY, PATIALA

JULY, 2013

Certificate

This is to certify that the project entitled **"SYNTHESIS AND CHARACTERIZATION OF DIPEHNYL ETHER BASED AMIDE ESTERS "** being submitted by Tejaswi Bhardwaj, Roll no. 301102016 in partial fulfillment of the requirements for the award of degree of Master of Science in School of Chemistry and Biochemistry, Thapar University, Patiala, is work carried out under my supervision. The work or its part not been submitted for the award of any other degree or certificate in this or any other university.

Dr. Manmohan Chhibber
Assistant Professor
School of Chemistry & Biochemistry
Thapar University, Patiala

Dr. Satnam Singh 15/7/12
Head Of Department
School of Chemistry & Biochemistry
Thapar University, Patiala

Dr. S.K Mahopatra
Dean, Academic Affairs
Thapar University, Patiala

Candidate's Declaration

I hereby declare that the work which is being presented in the dissertation entitled **"SYNTHESIS AND CHARACTERIZATION OF DIPEHNYL ETHER BASED AMIDE ESTERS"** in partial fulfillment of the requirements for the award of the degree of Master of Science in Chemistry, School of Chemistry and Biochemistry, Thapar University, Patiala is an authentic record of my own work carried out during a period of six months from January 2013 to July 2013, under the supervision of Dr. Manmohan Chhibber, Assistant Professor, School of Chemistry and Biochemistry, Thapar University, Patiala. The report has not been submitted for the award of any other degree or certificate in this or any other university.

Tejaswi Bhardwaj

Tejaswi Bhardwaj
301102016

Place : Patiala
Date : 12/07/2013

This is to certify that the above statement given by the candidate is correct and true to the best of our knowledge.

Dr. Manmohan Chhibber
Supervisor
School of Chemistry & Biochemistry
Thapar University, Patiala

Dr. Satnam Singh 15/7/13
Head Of Department
School of Chemistry & Biochemistry
Thapar university, Patiala

Acknowledgement

In pursuit of this academic endeavor, I feel that I have been singularly fortunate because insption, guidance, direction, co-operation, love and care all come in my way in abundance and it seems almost an impossible task for me to acknowledge the same in adequate term.

My wholehearted indebtness goes to my guide, Dr. Manmohan Chhibber, Assistant Professor, School of Chemistry and Biochemistry, Thapar University, Patiala, for his support and patience. Their invaluable assistance and precious guidance helped me in executing this arduous task from its conception to its completion.

I am grateful to Dr. Satnam Singh, Head, School of Chemistry and Biochemistry for approving this project to me

I thank Ms. Ramandeep Kaur, research scholar for her kind cooperation during the project work. Life at Thapar University would be unforgettable for me throughout my life because I was blessed to spend it with my friends. I thank them all for their great company.

I am highly obliged to Chander Sir and other laboratory staff who were very forthcoming and helpful in every possible way.

Words fail me to express my thanks to my family for their selfless sacrifice, encouragement and heart full blessings that continue to enlighten my life.

Above all I thank almighty God for blessing me with strength and wisdom to complete this project successfully.

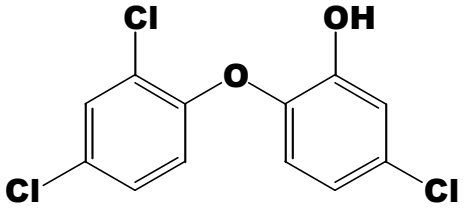
Place:Patiala
Date: 12/07/2013

Tejaswi Bhardwaj
Tejaswi Bhardwaj

SYNTHESIS AND CHARACTERIZATION OF DIPEHNYL ETHERS BASED AMIDE ESTERS

INTRODUCTION

Diphenyl ethers are widely used in many fields including pharmaceutical industry due to their biological properties such as antimicrobial [1], antifungal [2], antimalarial [3] and antituberculosis [4]. Triclosan, a diphenyl ether, is a well–known, broad–spectrum antibacterial that is used in a number of consumer products, such as toothpastes, soaps and plastics. It has been shown to inhibit the growth of *Escherichia coli*[1a, 5] *Pseudomonas aeruginosa*[6] and *Staphylococcus aureus*[7]by lockingenoyl-ACP-reductase enzyme(ENR) in a number of microorganisms which is responsible for fatty acid biosynthesis [8]. ENR is also known as FabI ,InhA in different organisms. Thus, several attempts to develop new triclosan derived antibacterials[1a] have been made. The search for effective broad-spectrum triclosan derivatives is hampered by large variation in the results against different micro-organisms. For example for triclosan itself, IC_{50} value ranges from 70nm to 7.25µm in *Staphylococcus aureus*[7] and *Escherichia coli*[1a, 5]respectively. Therefore, there is need to explore additional triclosan analogs.



Triclosan

A number of diphenyl ethers which are analogs of triclosan with different substituent on both the rings have been either synthesized or isolated from natural resources by different groups [9]. The antimalarial efficacy of small molecule triclosan analogs can be enhanced by incorporating the organic functional group capable of maintaining some of the hydrogen-bonding interactions[10]. Also there is need to develop molecules which could cross cell membrane of the micro-organism to reach their target. The problem with most diphenyl ethers is their poor solubility in water. Present project has been designed with the aim to synthesize and characterize diphenyl ethers having amide and ester group which may impart diphenyl ethers a pro-drug like property besides helping them cross biological membranes.

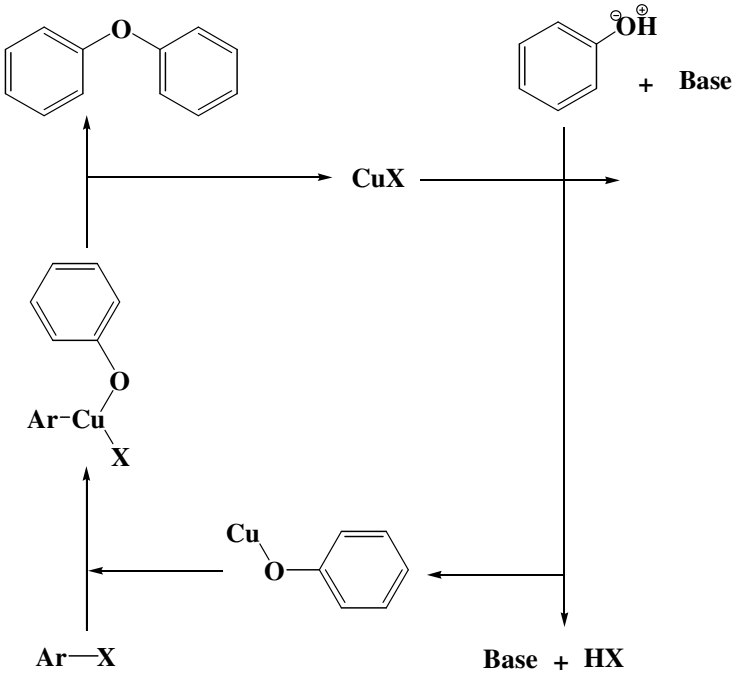
REVIEW OF LITERATURE

Dry distillation of copper benzoate by List et al gave diphenyl ether as early as in 1854 [11]. Later, it was discovered to be a mixture of biphenyls and diphenyl ethers [12]. By 1870, such compounds were prepared, though in poor yields, by reaction of benzenediazonium sulphate and phenols [13]. Kirsch et.al. improved the yields by preparing them with benzene diazonium chloride [14]. Also, a mixture of potassium phenoxide and sodium benzene sulfonate on distillation gave 40-50% yield of diphenyl ether [15]. Diphenyl ether and many of its properties were first reported in 1901[16]. Williamson ether synthesis using S_N^2 mediated reaction of phenol and bromobenzene in the presence of base gave much improved diphenyl ether synthesis over the method of "Ullman type" reaction that utilize copper [17] catalyst and reaction between alkali phenoxides and aryl halides.

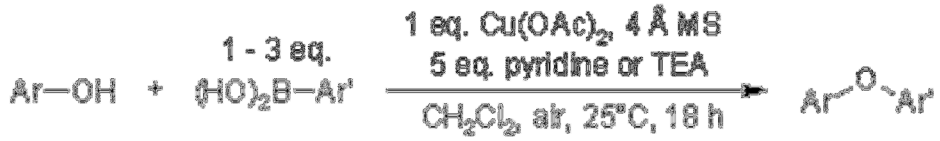
PhONa+PhBr → PhOPh + NaBr

A number of improved synthetic methods have been developed over the years that utilize copper-catalyzednucleophilic aromatic substitution between various substituted phenoxidesand aryl halide. The general mechanism that most of such reactions follow is given below in Scheme-I.

Scheme-I

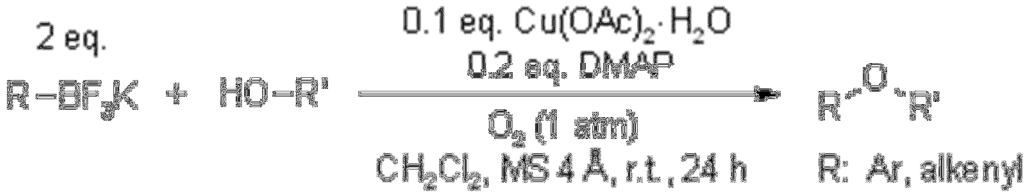


Aryl boronic acids and phenols were used at room temperature through the copper (II)-promoted coupling to give high yield of diaryl ethers. The reaction is tolerant of a wide range of substituents on both coupling partners. The reaction uses mild organic base such as pyridine or triethylamine[18].

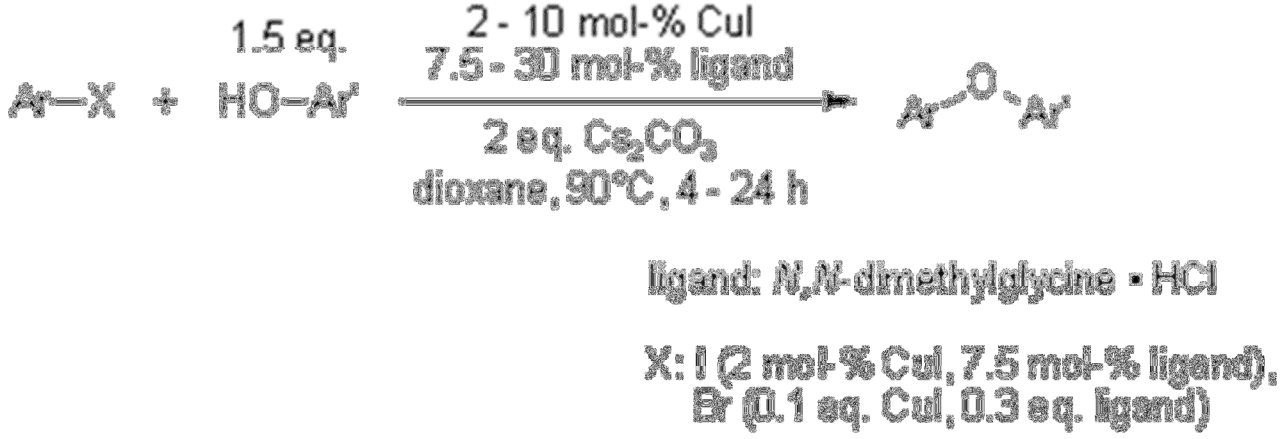


In recent times a number of syntheses have been reported that utilize different ligands to complex with copper to carry out diphenyl ether synthesis.

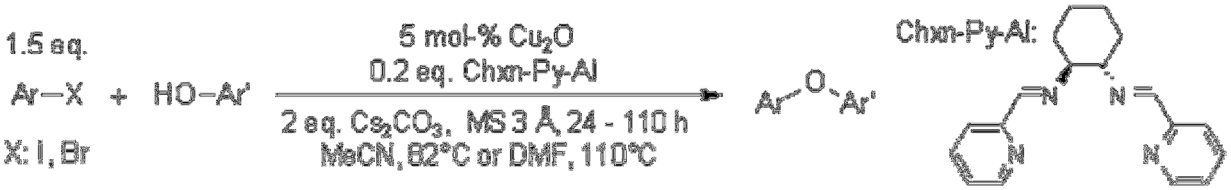
Quach and Batey's protocol utilized copper-(II)-catalyzed etherification of aliphatic alcohols and phenols with potassium alkenyl- and aryltrifluoroborate salts having 4-(dimethylamino)pyridine as ligand.Molecular sieves (4 Å)were also used under an atmosphere of oxygen[19].



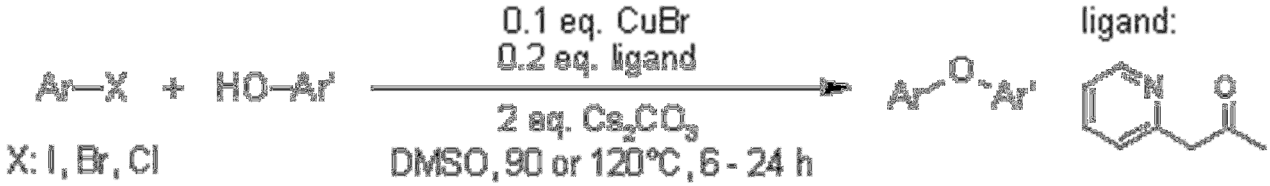
The base used in previous three reactions is cesium carbonate. Similarly Ma et.Al. used hydrochloric salt of N, N-dimethylglycine as ligand to carry out synthesis of diphenyl ethers using aryl iodide and bromides in the presence of Cs_2CO_3 at 90^oC [20].



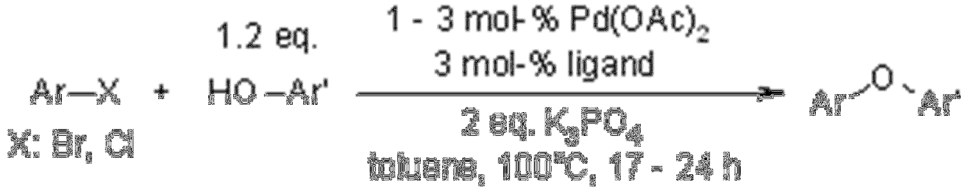
Inexpensive ligands were found to greatly accelerate the Ullmann-type coupling of aryl bromides or iodides with phenols in the presence of Cs_2CO_3 and catalytic copper(I) oxide. The reaction tolerates sterically hindered coupling partners or electron-rich aryl halides [21].

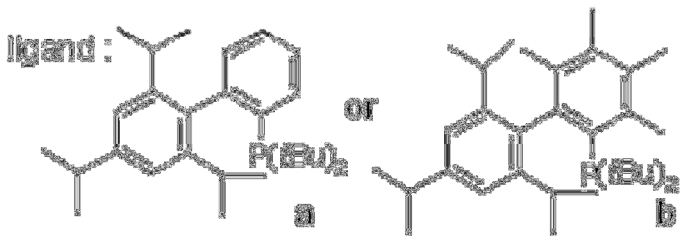


Ding et al reported that copper-catalyzed coupling reactions of aryl halides with various phenols successfully under mild conditions using (2-pyridyl)acetone as ligand in good yields. This reaction displays great functional groups compatibility and excellent selectivity[22].

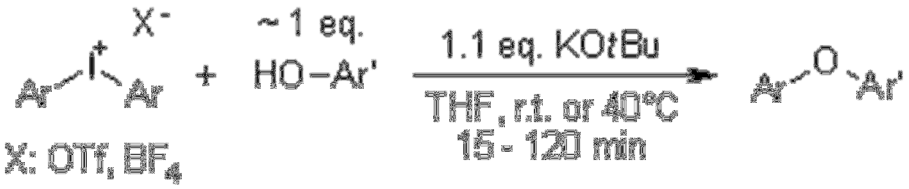


The use of copper catalyst with ligands has been explored extensively and a number of synthetic methods with the ligands have been introduced as discussed above. However, Buchwald-Hartwig cross coupling reactions introduced palladium-catalyzed synthesis of aryl amines and ethers. The methodology gave an alternative to the Ullmann ether synthesis. It gave an improved formation of diaryl ether allowing coupling of electron deficientaryl halides without any restriction [23].





Recently, diphenyl ethers have also been synthesized using metal or ligand free procedures. Heating of phenol with diphenyliodonium salt in the presence of strong base such as potassium tertiary butoxide in THF at room temperature gives diphenyl ether [24].



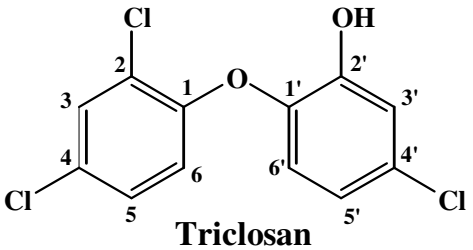
Diphenyl ethers find application in many areas. They have been used as biocide, flame retardents, functional fluida and motifs in many natural products. Among biocides thehave been used as herbicides, antibacterials and also as copolymers.

Present work utilizes a mild synthesis of diphenyl ethers using 18-crown-6 and mild base at room temperature in the presence of aryl halide having electron withdrawing group and vanillin [26]. The synthesized diphenyl ether have been treated with different acid chlorides to convert them into corresponding ester amides

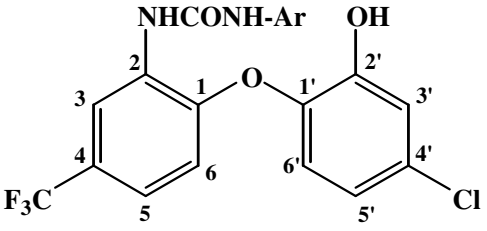
BACKGROUND AND OBJECTIVES

Triclosana diphenyl ether is the lead compound for the antibacterial activity. It has been shown to inhibit an enzyme "enoyl-ACP-reductase" present in most of the pathogenic bacteria, thus rendering its antibacterial properties. A number of diphenyl ether compounds have been reported thus far after this discovery. The difficulty for all new triclosan derivatives is their solubility in water and ability to cross micro-organism's membrane.

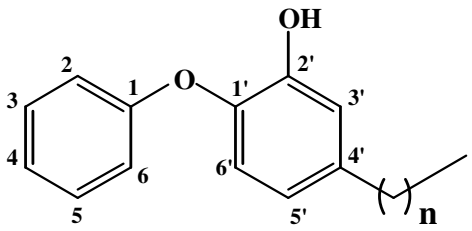
Recently, Freundlichet.al.[25] have shown that incorporation of urea at C-2 position(**Compound-1**) is effective in enhancing their activity in *Plasmodium berghei* mouse model. Similarly Sullivan et al [5]had earlier demonstrated the long carbon chains (C_5-C_{14}) at positionC-4'(**Compound-2**)inhibits drug-sensitive strain *mycobacterium* at low micro molarconcentrations.



Triclosan



Compound-1



n =4 to 13

Compound-2

Present work was initiated with an objective to synthesise and characterize a range of diphenyl ether having long chain amide and ester group together at C-2 and C-4' positions respectively. Thus, formally objectives are as follow:

1) Synthesis of diphenyl etherwith **C-2** and **C-4'** positions available for functionalization.

2)Formation of long chain amide and ester derivatives of the synthesized diphenyl ether.

MATERIALS AND METHODS

All the chemicals and solvents used for synthesis were of LR grade and procured from Aldrich and S.D. Fine Chemicals. ^{1}H NMR and ^{13}C NMR were performed on BRUKER AVANCE II and JOEL 400 MHz spectrometer.

Preparation of *4-(2-nitrophenoxy)-3-methoxybenzaldehyde* (III): To a solution of 1-fluoro-2-nitrobenzene (2.2 ml, 20.9 mmol) in DMF (25 ml) were added K_2CO_3 (11.5 g, 83.9 mmol), 3-methoxy-4-hydroxybenzaldehyde (4.0 g, 26.3 mmol) and 18-crown-6 (50 mg, 0.2 mmol). The mixture was stirred at room temperature for 12 h. After the reaction is complete (TLC monitoring), the reaction mixture was diluted with CH_2Cl_2 (100 ml), washed with water (50 ml), 1 N NaOH (3× 10 ml), water (until neutral to litmus paper), brine and dried over Na_2SO_4. Evaporation of the organic solvent gave crude compound **(III)**. The product obtained was purified using SiO_2 column chromatography and solvent (pet ether/ethyl acetate = 50:50) to afford yellow solid in 80 % yields. (5.7 gms, m.p. 78 ^{o}C). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.9 (s, 3H), 6.9 (dd, J=1.12 Hz, 1H), 7.0 (d, J=8.12 Hz, 1H), 7.2 (t, J=8.76 Hz, 1H), 7.4 (dd, J=7.68 Hz, 1H), 7.5 (m, 2H), 8.0 (dd, J= 8.16 Hz, 1H), 9.9 (s, 1H); **^{13}C NMR**($CDCl_3$): δ 55.98, 76.74, 77.06, 77.37, 111.72, 117.29, 119.68, 122.11, 122.46, 128.69, 138.38, 140.54, 141.03, 151.04, 156.51, 180.04 shown in Figure –I.

Preparation of *4-(2-nitrophenoxy)-3-methoxybenzyl alcohol* (IV): To an ice-cold suspension of compound **(III)** (4.9 g, 18.2 mmol) in methanol (120 ml) was added drop wise a solution of $NaBH_4$ (0.8 g, 21.8 mmol) in methanol (20 ml) over a period of 15 min. After the reaction is complete (TLC monitoring) the solvent was evaporated in vacuo and reaction quenched with water. It was extracted with ethyl acetate (3 x 30 ml) and the combined organic layers were washed with water (2 x 25 ml), brine and dried over Na_2SO_4. Evaporation of the organic solvent gave crude product which was purified using SiO_2 column chromatography and solvent (pet ether/ethyl acetate = 50:50) to afford a yellow solid **(IV)** in 62.0% yield (1.7 g, mp 174-178 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.2 (s, 1H), 3.7 (s, 3H), 4.6 (s, 2H), 6.8 (dd, J = 8.44 Hz, 1H), 6.9 (dd, J=8.08 Hz, 1H), 7.0 (m, 2H), 7.1 (t, J=8.24 Hz, 1H), 7.4 (t, J=7.9 Hz, 1H), 7.9 (dd, J=8.16 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 55.98, 64.74, 111.75, 118.14, 119.48, 121.60, 122.14, 125.67, 134.12, 139.41, 139.91, 142.52, 151.28, 151.67 are shown in Figure-II.

Preparation of *4-(2-aminophenoxy)-3-methoxybenzyl alcohol* (V): To a suspension of compound **(IV)** (2.9 g, 10.6 mmol) in refluxing H_2O (100 ml) were added Fe (5.95 g, 106.2mmol) and $FeSO_4.7H_2O$ (2.9 g, 10.4 mmol). The reaction mixture was refluxed for 8 h. After cooling to room temperature and confirming the completion of reaction (TLC monitoring), it was filtered through celite, washed thoroughly with ethyl acetate (2 x 75 ml). The combined organic layers were dried over Na_2SO_4. Evaporation of the organic solvent gave corresponding amine. This was confirmed by spotting the product on alumina plate which upon dipping in ninhydrin solution (2% in ethanol) and further heating turned black. The compound was isolated and purified using SiO_2 column chromatography and solvent (pet ether/EtOAc = 70:30) to afford a dark brown (mp 143 ^oC) solid in 53% yield. **^{1}H NMR:** (400 MHz, $CDCl_3$): δ 2.0 (br-s, 1H), 3.9 (br-s, 5H), 4.6 (s, 2H), 6.6 (t, J = 7.32 Hz, 1H), 6.7-6.8 (m, 4H), 6.9 (t, J=7.3, 1H), 7.0 (s, 1H); **^{13}C NMR** ($CDCl_3$): δ 55.9, 65.0, 111.2, 116.3, 118.2, 118.5, 118.6, 119.3, 124.2, 136.6, 137.9, 143.9, 145.2, 150.4.

General procedure of preparation amide ester derivatives of 4-(2-aminophenoxy)-3-methoxybenzyl alcohol (VI - XI): To aliphatic carboxylic acid (0.5 mmol) was added PCl_3 (0.5 mmol) and the reaction mixture stirred at 60–70^{o}C. After 45 min, the reaction mixture was poured in-situ to another reaction mixture of compound **(V)** (0.5 mmol), K_2CO_3 (0.3 mmol) and DCM (10 mL) already stirred at 0^{o}C. The reaction mixture was allowed to stir for another 2 hrs. The expected ester amide product was extracted with DCM (3· 60 ml), dried over Na_2SO_4, and concentrated in vacuo. Crude product obtained was purified using SiO_2 column chromatography and solvent (pet ether/ ethyl acetate= 70:30) to afford light brown solids **(VI - XI)**.

***4-(2-Acetamidophenoxy)-3-methoxybenzyl acetate* (VI):** Yield: 66%, melting point: 96^{o}C, **^{1}H NMR:** δ 2.0 (s, 3H), 2.1 (s, 3H), 3.8 (s, 3H), 5.0 (s, 2H), 6.7 (dd, J=8.26 Hz, 1H), 6.9 (m, 4H), 7.0 (t, J=7.56Hz, 1H), 7.9 (s, 1H), 8.4 (dd, J=8.02Hz, 1H); **^{13}C NMR:** δ 20.8, 24.7, 55.6, 65.6, 112.6, 116.0, 120.5, 120.7, 121.1, 123.5, 123.6, 129.2, 132.8, 144.5, 145.9, 150.3, 168.3, 170.8.

***3-Methoxy-4-(2-propionamidophenoxy) benzyl propionate* (VII):** Yield: 58%, melting point: 130^{o}C, **^{1}H NMR:** δ 1.1 (m, 6H), 2.4 (m, 4H), 3.8 (s, 3H), 5.1(s, 2H), 6.7 (dd, J=7.78Hz, 1H), 6.9 (m, 3H), 7.0 (d, J= 1.84Hz, 1H), 7.0 (t, J=7.56Hz, 1H), 7.9(s, 1H), 8.4 (d, J=8.24Hz 1H); **^{13}C**

NMR: δ 9.1, 9.6, 27.6, 30.9, 55.9, 65.8, 112.7, 116.5, 120.6, 120.7, 121.1, 123.5, 123.7, 133.3, 144.6, 146.1, 150.9, 172.1, 174.2 shown in Figure –III.

4-(2-Butyramidophenoxy)-3-methoxybenzyl butyrate **(VIII):** Yield: 69%, melting point: 139^{o}C **^{1}H NMR:** δ 0.9 (q, J=15.56 Hz 6H), 1.7 (m, 4H), 2.3 (t, J=7.36 Hz, 4H), 3.8 (s, 3H), 5.1 (s, 2H), 6.8 (dd, J=8.28, 1H), 6.9 (m, 3H), 7.0 (d, J=1.8 Hz, 1H),7.1(t, J= 7.54 Hz, 1H), 7.9 (s, 1H), 8.4 (dd, J=8.26 Hz, 1H); **^{13}C NMR:** δ 13.6, 13.6, 18.4, 18.9, 36.1, 39.8, 55.9, 65.6, 112.6, 116.4, 120.6, 120.7, 121.0, 123.5, 123.6, 129.2, 123.3, 144.5, 146.0, 150.9, 171.3, 173.5.

3-Methoxy-4-(2-pentanamidophenoxy)benzylpentanoate **(IX):** Yield: 71%, melting point: 145^{o}C **^{1}H NMR:** δ 0.9 (m,6H), 1.4 (m, 4H), 1.6 (m, 4H), 2.4(t, J=7.8 Hz, 4H), 3.8 (s, 3H), 5.1 (s, 2H), 6.8 dd, J=8.2Hz, 1H), 6.9 (m, 4H), 7.0 (t, J=7.78Hz, 1H), 7.9 (s, 1H), 8.4 (dd, J=8.24Hz, 1H); **^{13}C NMR:** δ 13.7, 13.8, 22.2, 22.3, 26.9, 27.6, 34.0, 37.7, 55.9, 65.7, 112.7, 116.5, 120.6, 121.0, 123.5, 123.7, 129.3, 133.3, 144.6, 146.0, 150.9, 171.4, 173.6.

4-(2-(2-Chloroacetamido)phenoxy)-3-methoxybenzyl 2-chloroacetate **(X):** Yield: 78%, melting point : 147^{o}C **^{1}H NMR:** 3.8 (s, 3H), 4.1 (s, 2H), 4.2 (s, 2H), 5.2 (s, 2H), 6.8 (dd, J=8.02Hz, 1H), 6.9 (dd, J=8.26 Hz, 1H), 7.0 (m, 3H), 7.1 (t, J=7.54,1H), 8.4 (dd, J=8.04, 1H), 9.0 (s,1H); **^{13}C NMR:** δ 40.9, 43.0, 55.9, 69.0, 113.0, 116.3, 120.6, 120.9, 121.3, 123.5, 124.7, 132.3, 144.7, 146.7, 151.2, 163.8, 167.1 shown in Figure –IV.

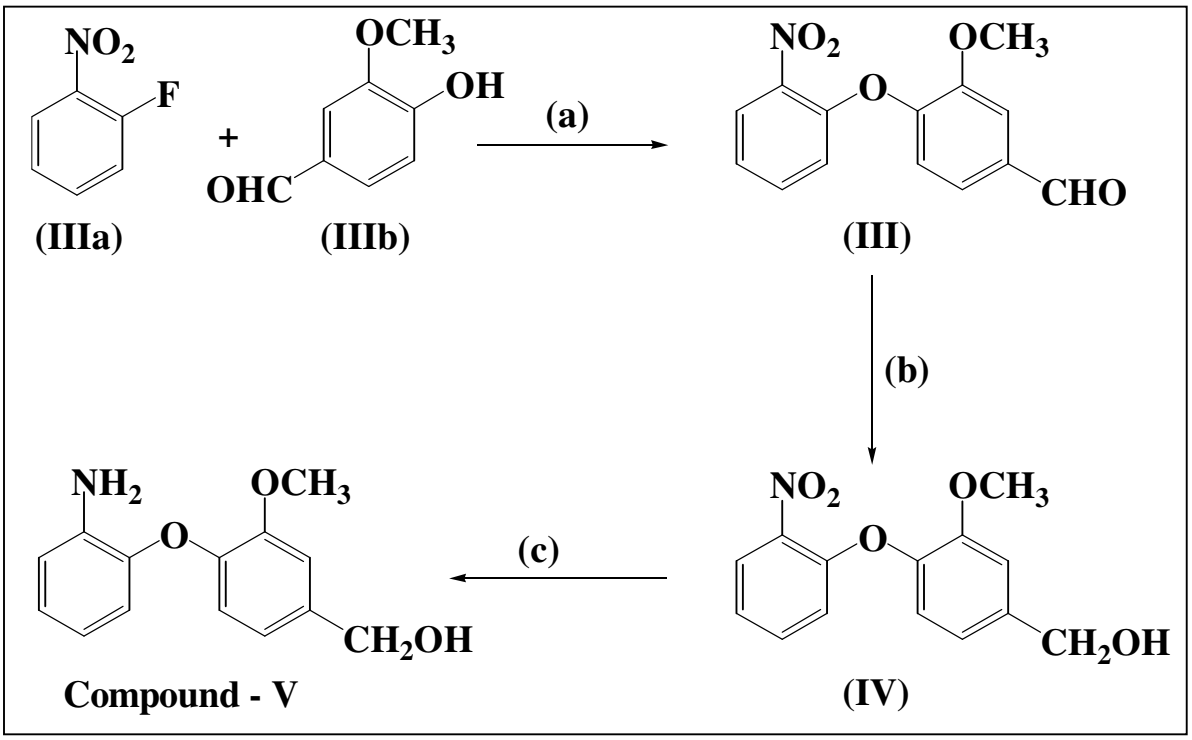
N-(2-(4-(hydroxymethyl)--methoxyphenoxy)phenyl)pivalamide **(XI):** Yield: 81%, melting point: 134^{o}C, **^{1}H NMR:** 1.3(s, 9H) ,3.8(s,3H) ,4.7(s,2H) , 6.7(dd, J= 8.24 Hz, 1H), 6.8 (dd, J= 7.8 Hz, 1H), 6.9 (m, 2H), 7.0 (m, 2H), 8.2 (s,1H), 8.4(dd, J= 8.28, 1H); **^{13}C NMR:** δ 27.4 (intense), 39.3, 55.8, 64.9, 111.3, 116.7, 119.3, 120.2, 120.6, 123.5, 123.7, 129.4, 138.1, 144.2, 146.2, 150.9, 176.7.

RESULT AND DISCUSSION

The objective of the work is to synthesize and **C-2** and **C-4'** position functionalized diphenyl ether [**Compound - V**]and make its long chain amides and ester derivatives in a single step reaction.

Starting diphenyl ether **(III)** was synthesized from commercially available 1-fluoro-2-nitrobenzene**(IIIa)** and vanillin**(IIIb)** using potassium carbonate,18-crown-6 and DMFvianucleophilic aromatic substitution reaction at room temperature [26]. This reaction requires moisture free conditins, an aprotic solvent and a phase transfer catalyst for increased yields. Reduction of aldehyde group, present on starting diphenyl ether **(III),** to corresponding alcohol **(IV)** was done in the presence of reducing agent sodium borohydride in protic solvent, methanol.Reduction of nitro group to corresponding amino could not be achieved under these conditions. This was done in environmental friendly conditions using water as solvent by refluxing in the presence of iron powder and iron sulphate. The amine **(Compound-V)** obtained was confirmed using ninhydrin test on thin layer chromatography.

Scheme-2



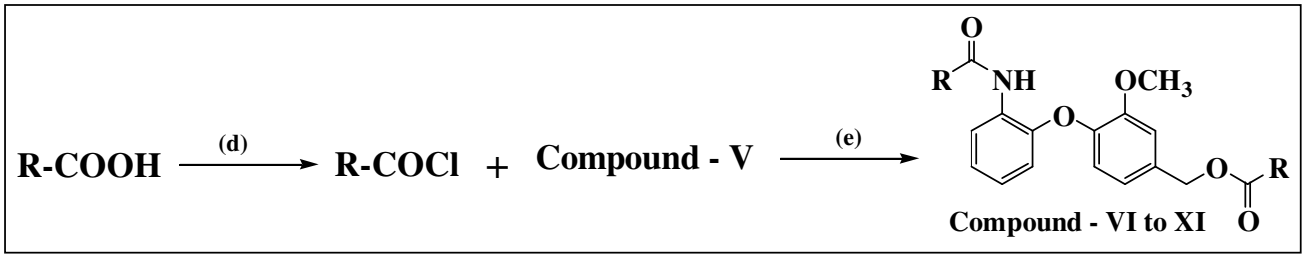
Reagents:(a) K_2CO_3,DMF, 18-Crown-6, **(b)** $NaBH_4$, Methanol **(c)** Fe, $FeSO_4.7H_2O$.

All the products obtained in each of above reaction were purified by silica gel column chromatography and compatible solvent system consisting of petether-ethyl acetate. The melting point of the purified Compound - **V**143^{o}c and it was characterized using ^{1}H and ^{13}CNMR spectroscopy. The yields of the reactions were moderate to good.

The synthesized diphenyl ether **(Compound - V),**having amine at **C-2**position and benzylic alcohol at **C-4'**position were subjected to reaction with acid chlorides of varying chain lengths (C_1 to C_5). The acid chlorides were prepared from corresponding acids using phosphorous trichloride under mild heating conditions. The reaction of acid chlorides with **Compound-V** in the presence of mild base at 0^{o}C gave amide group at C-2 position and ester group at C-4' position in a single step. The acid chlorides used were prepared from acetic acid,propionic acid, butyric acid, pentenoic acid, 2,2-dimethyl propionic acid and chloroacetic acid.

All the products obtained in each of above reaction were purified by silica gel column chromatography and compatible solvent system consisting of petether-ethyl acetate. The melting point of the purified were determined and listed in **Table-1**.Final characterization was done using^{1}H and ^{13}CNMR spectroscopy.

Scheme-3



Reagents:(d) PCl_3**(e)** K_2CO_3, DCM

Table - 1

Compound	R	Yeild	Melting Point
VI	-CH_3	66%	96^{o}C
VII	-CH_2CH_3	58%	130^{o}C
VIII	-$CH_2CH_2CH_3$	69%	139^{o}C
IX	-$CH_2CH_2CH_2CH_3$	71%	145^{o}C
X	-CH_2CH_2Cl	78%	147^{o}C
XI	-$C(CH_3)_3$	81 %	134^{o}C

Analysis of the compounds: Reaction monitoring of all the compounds was done using thin layer chromatography. After column chromatography, all the compounds were analyzed by ^{1}H and ^{13}C NMR and mass spectroscopic techniques. All the compound obtained were in agreement with the proposed structures.

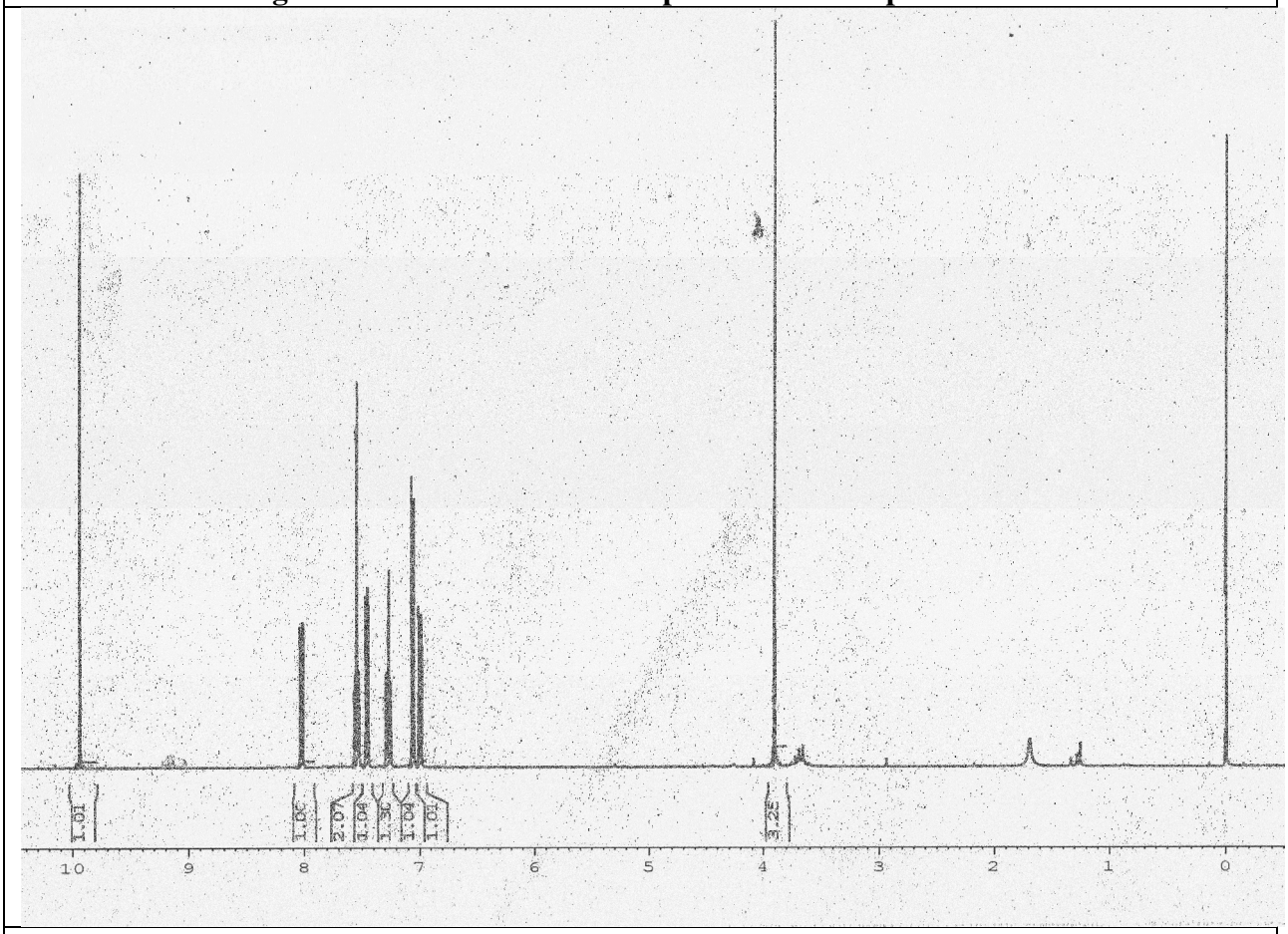
Protons due to methoxy (-OC**H**$_3$) group in all the compounds appeared as singlet between 3.7-3.9 ppm and the corresponding carbon in ^{13}C nmr appeared between 55.6-55.9 ppm. Aldehyde in compounds **III** gave singlet at 9.9 ppm and at 180 ppm in ^{1}H and ^{13}C nmr spectrum respectively. The protons and carbon due to benzylic (-C**H**$_2$-OH) group appeared in the range of 4.6-5.2 ppm and at 64.7 ppm in all the compounds except **III**. One proton of alcohol group (-CH$_2$O**H**) appeared at 2.2 ppm as broad singlet in compound **IV** and **V** respectively. Protons due to amine (-N**H**$_2$) gave board singlet merged with three methoxy protons at 3.9 ppm in diphenyl ether **(III)**.

The two singlets due six methyl protons (-CH$_2$-C**H**$_3$) directly attached to the amide and ester group appear in the range of 1.1 and 2.1 ppm in dipehnyl ether VI and VII. The multiplet due to four protons (-C**H**$_2$-CH$_3$), two each in amide and ester appeared at 2.4 ppm in dipehnyl ether VIII.

Six protons of aliphatic methyl group (-CH$_2$-CH$_2$-C**H**$_3$) gave quartet and multiplet at 0.9 ppm in diphenyl ether VIII and diphenyl ether IX. Methylene protons (-CH$_2$-C**H**$_2$-CH$_3$) gave a multiplet at 1.7 ppm due to coupling with adjacent proton and a triplet coupling with adjacent two proton at 2.3 ppm was appeared due to two aliphatic protons (-C**H**$_2$-CH$_2$-CH$_3$) in diphenyl ether VIII. Two multiplets appeared at 1.4 (-CH$_2$-CH$_2$-C**H**$_2$-CH$_3$) and 1.6 ppm (-CH$_2$-C**H**$_2$-CH$_2$-CH$_3$) and a triplet was appeared at 2.4 ppm due to 2 aliphatic protons (-C**H**$_2$-CH$_2$-CH$_2$-CH$_3$) in diphenyl ether IX.

Two singlets appeared at 4.1 ppm and 4.2 ppm due to –NH-CO-C**H**$_2$-Cl and –O-CO-C**H**$_2$-Cl in diphenyl ether -VIe. All the aromatic protons and carbons appeared in the range of 6.0 -8.9 ppm and 111.2-151.67 ppm respectively. Carbonyl carbons of amide and ester group gave signals 145.2-173.5 ppm. Also carbon of alkyl groups gave peak at 13.6-65.8 ppm.

Figure – I : ^{1}H and ^{13}C NMR Spectrum of Compound - III



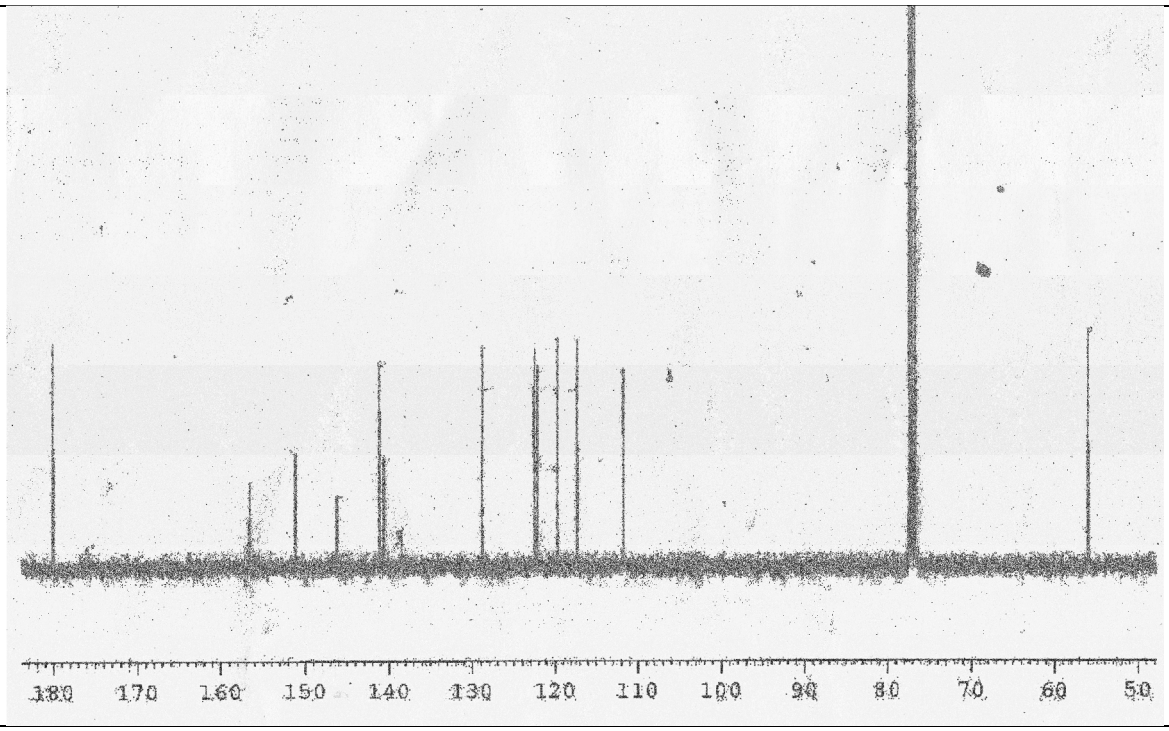
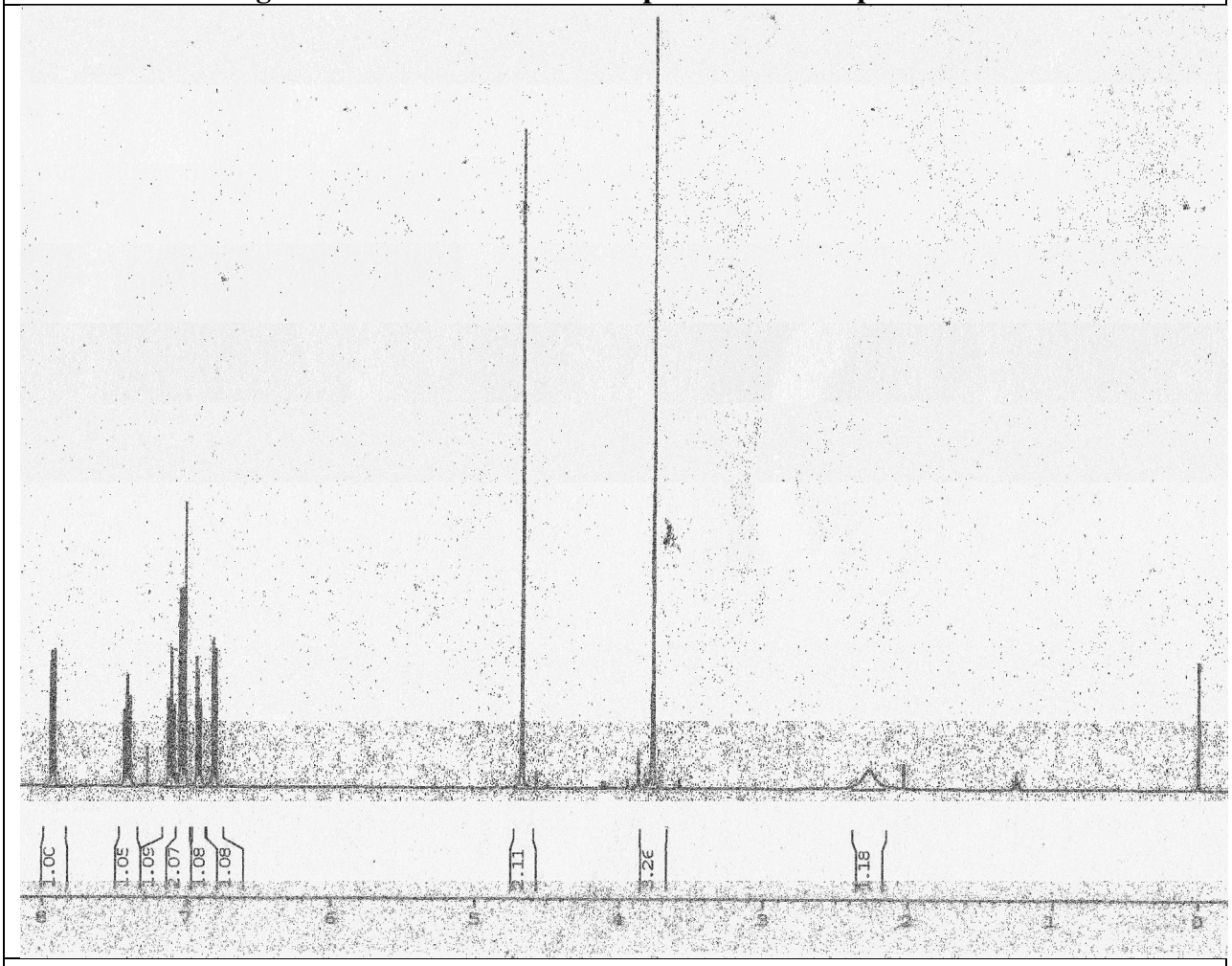


Figure – II : ^{1}H and ^{13}C NMR Spectrum of Compound - IV



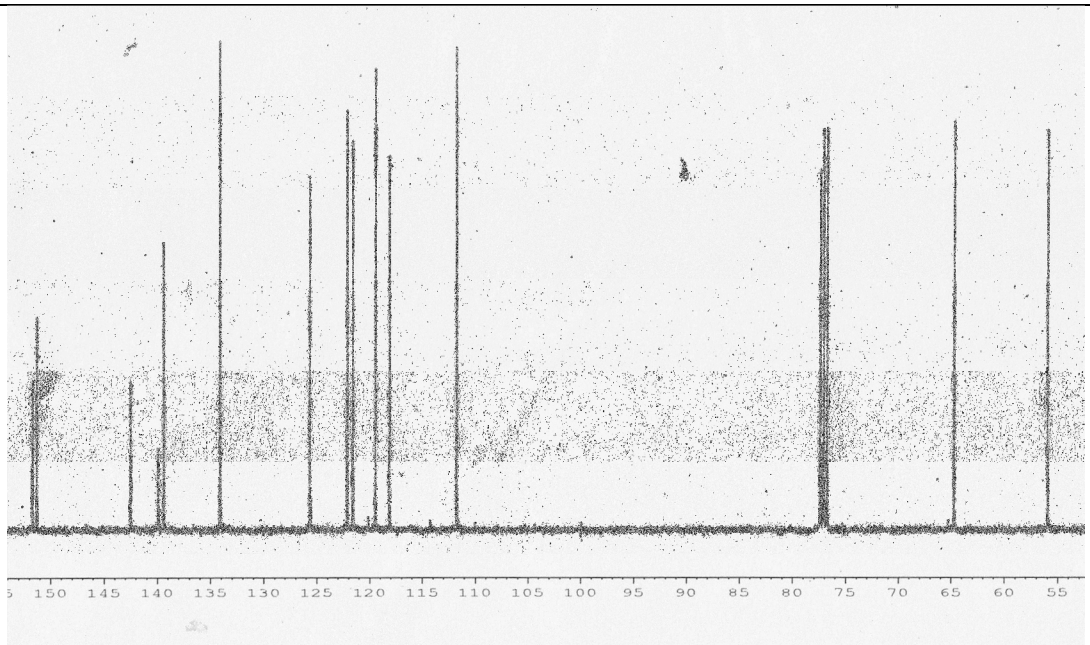
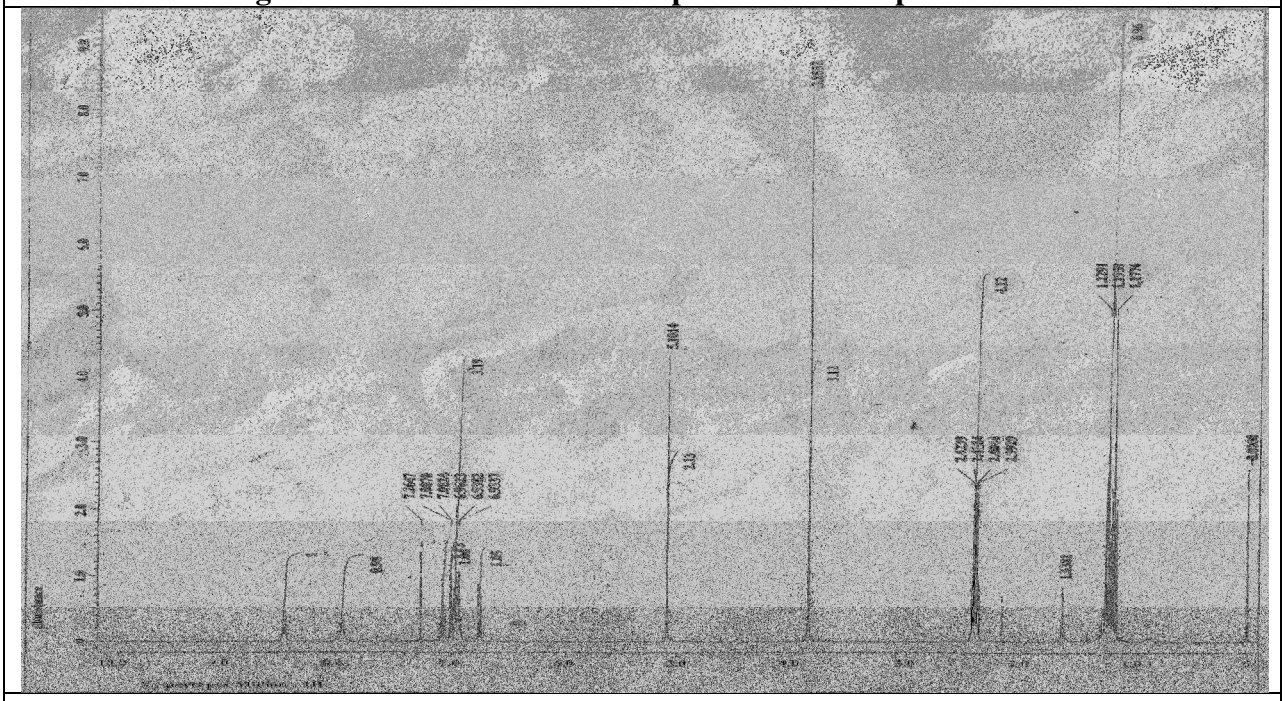


Figure – III : ^{1}H and ^{13}C NMR Spectrum of Compound - VII



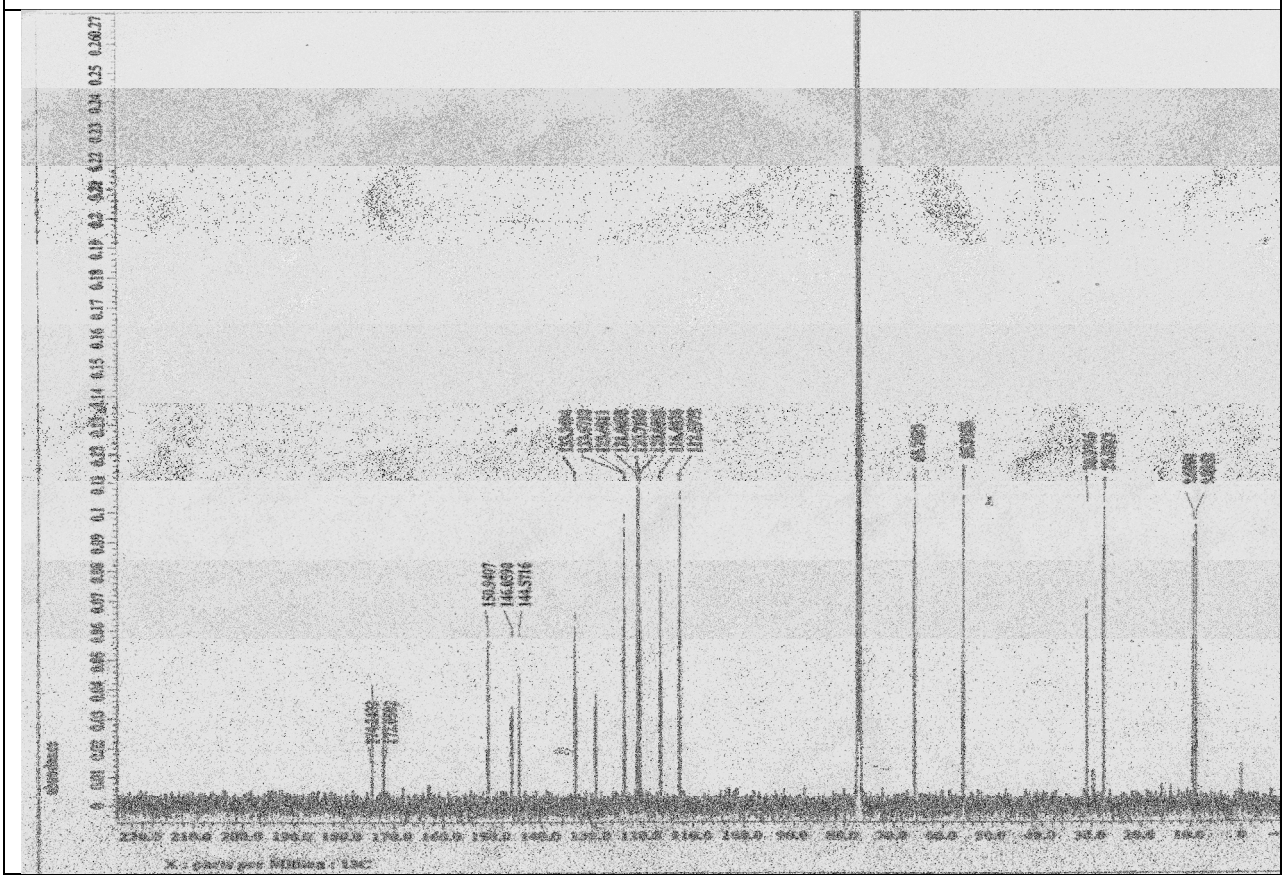
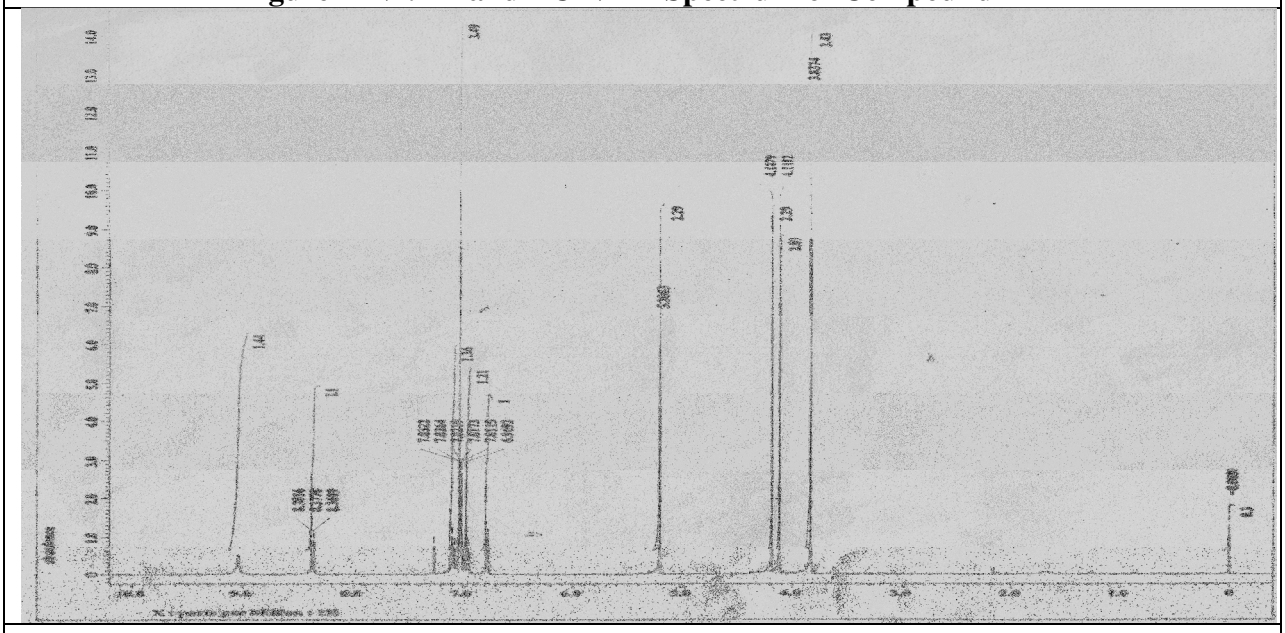
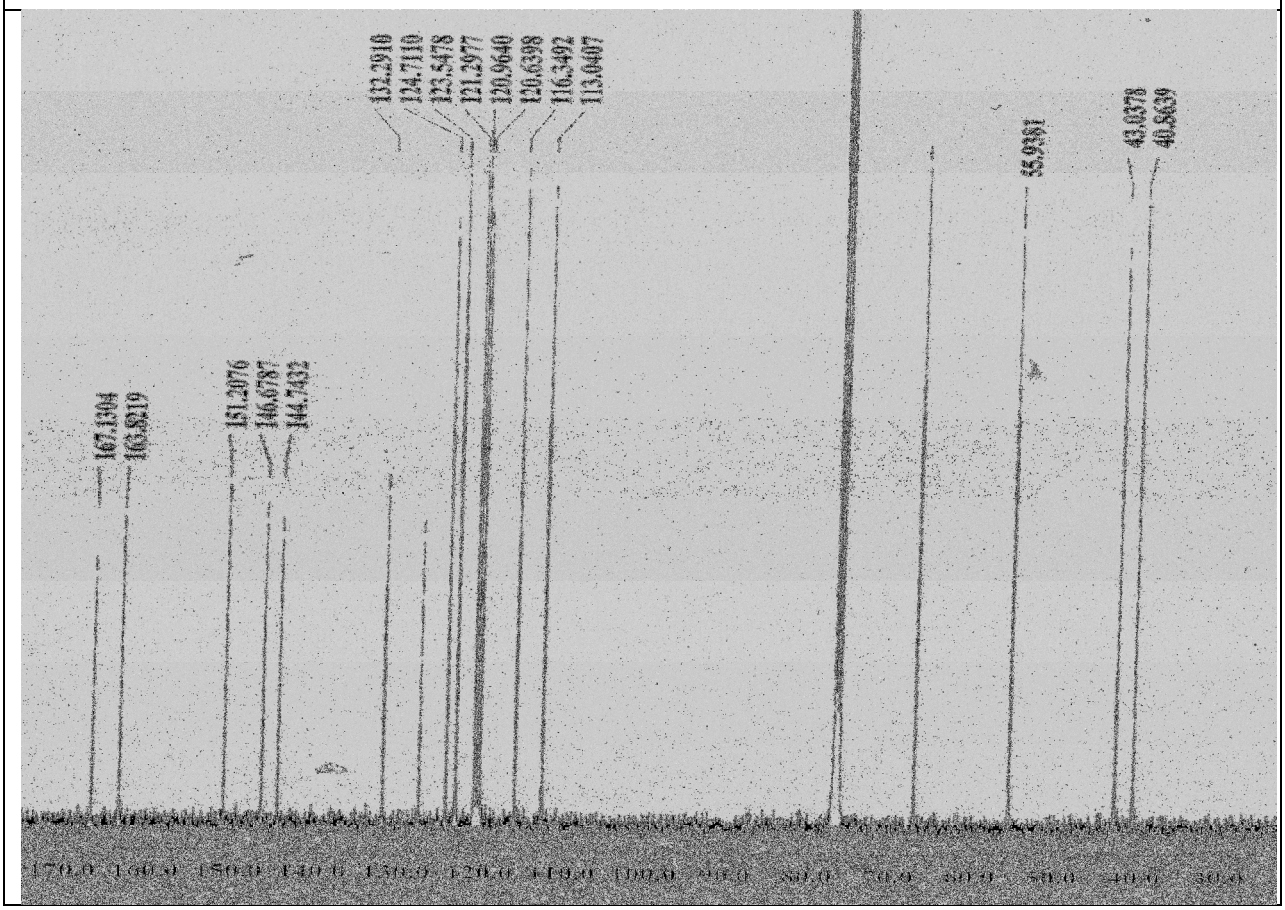


Figure – IV : ^{1}H and ^{13}C NMR Spectrum of Compound - X





REFRENCES:

1: K Suresh, D. Tipparajua, C. M. Debbie,d, M.K. Gary, C. Yufeng, T. Subhasish, H. B. Molly, Y. Shuo, C. Juan, G. Mahmood , D. S. Bernard, L.C. James, M. Johlfsb,A. D. Mesecar, M. E. Johnson, and A. P. Kozikowski, *Chem. Med. Chem.*2008, **3**, 1250. (a)R.J. Heath, Y.T. Yu, .A.M. Shapiro, E. Olson, C.O. Rock, *J.Biol.Chem.*1998, **273**, 30316. (b) H. Lu, P.J. Tonge*, AccChem Res,* 2008, **41**, 11. (c) T.J. Sullivan, J.J. Truglio, M. E. Boyne, P. Novichenok, X. Zhang , C. F. Stratton, H. J. Li, T. Kaur, A. Amin, F. Johnson, R.A. Slayden, C. Kisker, P.J. Tonge. *ACS ChemBiol*, 2006, **1**, 43.

2: G. Giuliana, G. Pizzo, M. E. Milici, G. C. Musotto and R. Giangreco. *J. Periodon.,* 1997, **68**, 729

3: J.S. Freundlich, M. Yu, E. Lucumi, M. Kuo, H.C. Tsai, J.C. Valderramos, L. Karagyozov, W.R. Jr. Jacobs, G.A. Schiehser, D.A. Fidock, D.P. Jacobus, J.C. Sacchettini*, Bioorg. Med. Chem. Lett.*, 2006, **16**, 2163.

4: W. Christopher, A.M Ende, S. E. Knudson, N. Liu, J. Childs, T. J. Sullivan, M. Boyne, H. Xu, Y. Gegina, D. L. Knudson, F. Johnson, C. A. Peloquin, R. A. Slaydend and P. J. Tongea, *Bioorganic & Medicinal Chemistry Letters*, 2008, **18**, 3029.

5: Sivaraman, T. J. Sullivan, F. Johnson, P. Novichenok, G. Cui, C. Simmerling, P. J. Tonge. *J. Med. Chem.*, 2004, **47**, 509.

6: M. G. Escalada, J. L. Harwood, J. Y. Maillard, D. Ochs. *J. Antimicrob. Chemother* 2005, **55**, 879.

7: W. H. Miller, M. A. Seefeld, K. A. Newlander, I. N. Uzinskas, W. J. Burgess, D. A. Heerding, C. C. Yuan, M. S. Head, D. J. Payne, S. F. Rittenhouse, T. D. Moore, S. C. Pearson, V. Berry, W. E. Jr. DeWolf, P. M. Keller, B. J. Polizzi, X. Qiu, C. A. Janson, W. F. Huffman. *J. Med. Chem.*, 2002, **45**, 3246.

8: R.J. Heath, S.W. White and C.O. Rock, *Prog. Lipid Res*., 2001, **40**, 467.

9: H.Liu, M.Namikoshi, S.Meguro, H.Nagai, H.Kobayashi, X.Yao. *J. Nat. Prod.*, 2004, **67**, 472.

10: R. Perozzo, M. Kuo, A. S. Sidhu, J. T. Valiyaveettil, R. Bittman, W. R. Jr. Jacobs, D. A. Fidock, J. C. Sacchettini, *J. Biol. Chem.*, 2002, **277**, 13106

11: K. List, A. Limprichth, *Ann.*, 1854, **90**, 209.

12: W. Hoffmeister, *Ann*., 1871, **169**, 191.

13: W. Hoffmeister, *J. Prakt. Chem.,* 1870, **1**, 143.

14: E. Turnere and B. Sheppardа, *J. Chem. Soc.,* 1925*,* **127**, 544.

15: H. Xollau and C. Danielsl, *J. Am. Chem.,* 1914, **36**, 1585.

16: A. N. Cook, *Journal of the American Chemical Society*, 1901, **23**, 806.

17: E. Westonp and H. Adkiss, *J. Am. Chem. Soc.,* 1928, **60**, 859.

18: D. A. Evans, J. L. Katz, T. R. West, *Tetrahedron Lett.,* 1998, **39**, 2937.

19: T. D. Quach, R. A. Batey, *Org. Lett.,* 2003, **5**, 1381.

20: D. Ma, Q. Cai, *Org. Lett*., 2003, **5**, 3799.

21: H. J. Cristau, P. P. Cellier, S. Hamada, J-F. Spindler and M. Taillefer, *Org. Lett.*, 2004, **6**, 913.

22: Q. Zhang, D. Wang, X. Wang, K. Ding, *J. Org. Chem.,* 2009, **74**, 7187.

23: C. H. Burgos, T. E. Barder, X. Huang, S. L. Buchwald, *Angew. Chem. Int. Ed.,* 2006, **45**, 4321.

24: N. Jalalian, E. E. Ishikawa, L. F. Silwa, Jr., B. Olofsson, *Org. Lett.*, 2011, **13**, 1552.

25: J. W. Anderson, D. Sarantakis, J. Terpinski, T.R. S. Kumar, H-C. Tsai, M. Kuo, A. L. Ager, W. R. Jacobs, G. A. Schiehser, S. Ekins, J. C. Sacchettini, D. P. Jacobus, D. A. Fidock, J. S. Freundlich, *Bioorganic & Medicinal Chemistry Letters* 2013, **23**, 102.

26: M. Chhibber, G. Kumar, P. Parasuraman, TN. Ramya, N. Surolia, A.Surolia. *Bioorg Med Chem*, 2006, **14**, 8086.