SYNTHESIS AND CHARACTERIZATION OF DIPHENYL ETHERS

A

Thesis Submitted

in partial fulfillments of requirements for the

Degree of

Master of Science in Chemistry

Submitted By

Dipti Bansal

(Reg. no. 30702002)

Under the supervision of

Dr. Manmohan Chhibber

Lecturer

School of Chemistry and Biochemistry

Thapar University

Patiala 147004

June 2009

DEDICATED TO MY PARENTS

Acknowledgements

It's said that life is a carnival of experiences and a journey with various goals. So in my journey where I experienced this project I want to thank the supreme almighty for his presence in my soul and in my mind.

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Patiala

Date: 16 June 2009

Dipti.

Dipti Bansal

Candidate's Declaration

I hereby declare that the work being presented in the dissertation entitled **"Synthesis and characterization of diphenyl ethers"**, in partial fulfillment of the requirements for the award of the degree of Masters in Chemistry, School of Chemistry and Biochemistry (SCB), Thapar University, Patiala, is my own work during the period of Jan 2009 to May 2009, under the supervision of Dr. Manmohan Chhibber, Lecturer, School of Chemistry and Biochemistry, Thapar University, Patiala. I have not submitted the matter embodied in this dissertation for the award of any other degree.

Patiala

Date: 16 June 2009

Dipti

Dipti Bansal

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

Dr. Manmohan Chhibber
Project Supervisor,
Lecturer (SCB),
Thapar University

Susheel Mittal 16/6/09

Dr. Susheel Mittal
Head, SCB
Thapar University

Certificate

This is to certify that the project entitled **"Synthesis and characterization of diphenyl ethers"**, being submitted by Ms. Dipti Bansal in partial fulfillment of the requirement for the award of degree of Master of Science in the School of Chemistry and Biochemistry, Thapar University, Patiala, is a bonifide work carried out under the supervision of Dr. Manmohan Chhibber and that no part of this project has been submitted for the award of any other degree.

Dr. Manmohan Chhibber,
Lecturer,
Thapar University

Head, 16/6/09
(Dr. Susheel Mittal)
School of Chemistry and Biochemistry,
Thapar University

Dean, Academic Affairs, 22/6/09
(Dr. R.K. Sharma)
Thapar University

Abbreviations

ACP	Acyl carrier protein
AcDP	2,4,4'-trichloro-2'-acryloyloxydiphenyl ether
CNP	Chloronitrofen
CPP	5-chloro-2- phenoxyphenol
d	Doublet
DCM	Dichloro methane
dd	Double doublet
DPE	Diphenyl ethers
EPP	5-ethyl-2-phenoxyphenol
HEMA	2-hydroxymethylacrylate
m	Multiplet
MS	Mass spectroscopy
NMR	Nuclear magnetic resonance
PBDE	Polybrominated diphenyl ethers
s	Singlet
S_NAr	Aromatic nucleophilic substitution reaction
t	Triplet
TLC	Thin layer chromatography

List of contents

Introduction

Diphenyl ether was prepared in 1854 by List and Lmpricht[1] by dry distillation of copper benzoate. The product was shown to be a mixture of diphenyl ether and diphenyl by Hoffmeister[2], who was the first to isolate the pure substance by separating this mixture. The ether was also prepared by the reaction of benzenediazonium sulfate with phenol[3]. The yields were poor in either case. Improved yields of diphenyl ether from benzenediazonium chloride were claimed by Kirsch[4]. Diphenyl ether is obtained among other products from the distillation of calcium phenyl salicylate. It is formed in good yield (40-50 per cent) when a mixture of sodium benzenesulfonate and potassium phenoxide is distilled[5]. The best laboratory method for the preparation of diphenyl ether is due to Ullmann and Stein**,** who discovered in 1905 that copper[6] catalyzes the reaction between alkali phenoxides and aryl halides.

Recentely, diphenyl ethers have also been synthesised by heating phenol with symmetrical diphenyliodonium salt[7] in presence of sodium tertiary butyl dioxane and water **(Figure-1)** The preparation of the iodonium salts is done by oxidation of iodine to iodyl sufate ($(IO)_2SO_4$) with the help of nitric and sulphuric acid at about 75^0 C which is then reacted with a benzene to obtain the iodonium salt.

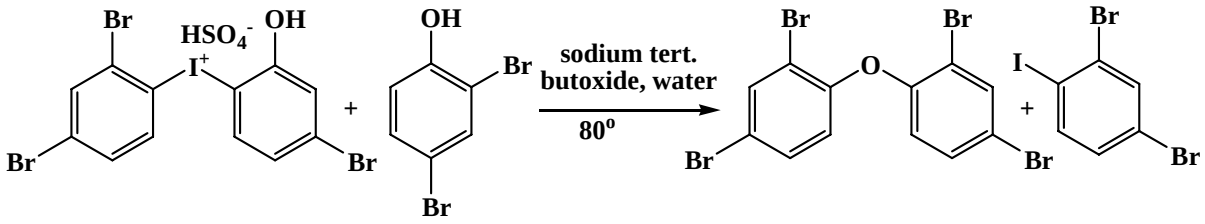


Figure-1

Another method for the preparation of diphenyl ethers is via Suzuki coupling[8] which involves the synthesis of biphenyls through palladium-catalyzed cross coupling between organoboronic acid and halides **(Figure-2).**

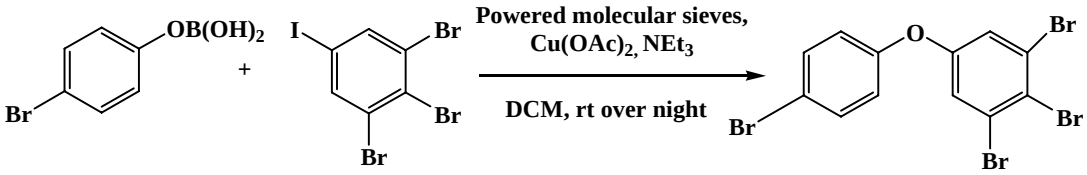
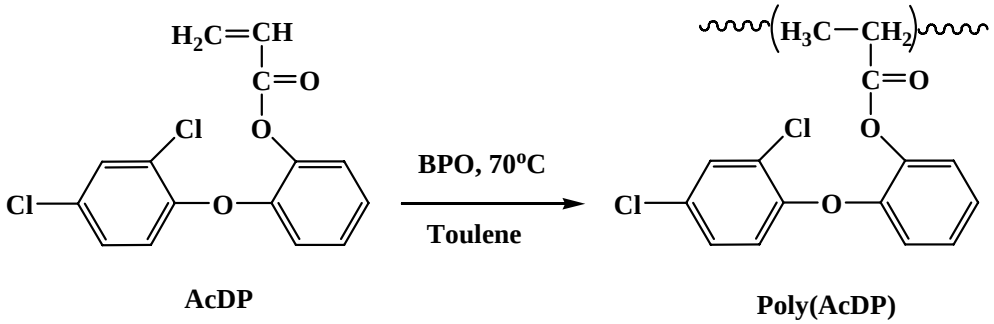


Figure-2

One of the very convenient and mild methods for the synthesis of diphenyl ethers is aromatic nucleophilic substitution reaction[9] (S_NAr based reaction). This method utilizes potassium carbonate, a halogenated benzene ring with electron withdrawing group and phenol. The electron withdrawing group activates the halogenated carbon for nucleophilic attack by the phenol. We have made use of this method for the synthesis of diphenyl ethers in this work.

Diphenyl ethers find applications in many areas. They have been used as biocides, flame retardents, functional fluids and motifs in many natural products. Among biocides they have been used as herbicides, antibacterials, and also as copolymers.

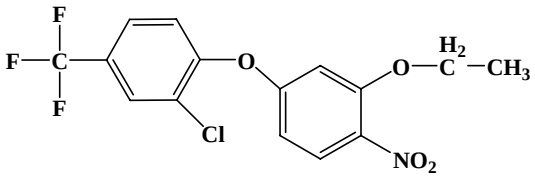
Cho et. Al.[10] used antibacterial monomer 2,4.4'-trichloro-2'-acryloyloxydiphenyl ether as copolymer with 2-hydroxymethylacrylate (HEMA) and evaluated its antibacterial activity against *Staphylococcus aureus*. **(Figure-3)** The copolymerized materials showed excellent activities as compared to their noncopolymerized counterparts. Polymeric bacteriocides can significantly reduce losses associated with volatilization, photolytic decomposition, dissolution, and transport. Moreover, increases efficiency, selectivity and handling safety are additional benefits which may be realized.



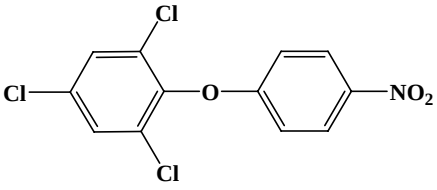
AcDP **Poly(AcDP)**

Figure- 3

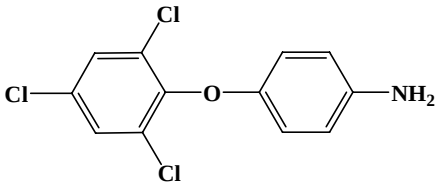
Many diphenyl ethers posses herbicidal properties. Oxyfluorfen[11], and Chlornitrofen[12] that are used as herbicides **(Figure-4)** have a very peculiar action. They kill plants only in the light by inducing peroxidative degradation of cellular constituents, especially membrane lipids leading to cell lysis.



Oxyfluorfen



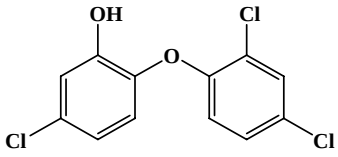
CNP



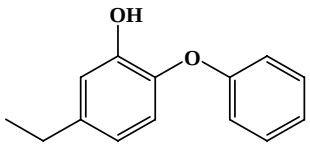
CNP-amino

Figure-4

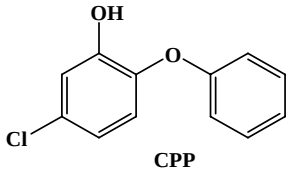
Recently, triclosan[13] and many of its diphenyl ether analogs for eg 5-ethyl-2-phenoxyphenol (EPP) and 5-chloro-2-phenoxyphenol (CPP) have been shown to be potent antibacterial[13]. **(Figure-5)** It has been shown that antibacterial activity of these compounds is due to their ability to inhibit an enzyme, enoyl-ACP-reductase, that is responsible for the fatty acid biosynthesis in these organisms.



Triclosan



EPP



CPP

Figure-5

Many natural products contain diphenyl ethers motifs in them that has great significance. For example Vancomycin[14]**(Figure-6)**, the last resort antibacterial and K-13[15]**(Figure-7)** both contain diphenyl ether moiety. Similarly OF4949I-IV, is a family of competitive inhibitors of aminopeptidase B that. contain the biaryl ether diamino diacid, isodityrosine, as their basic structural subunit.

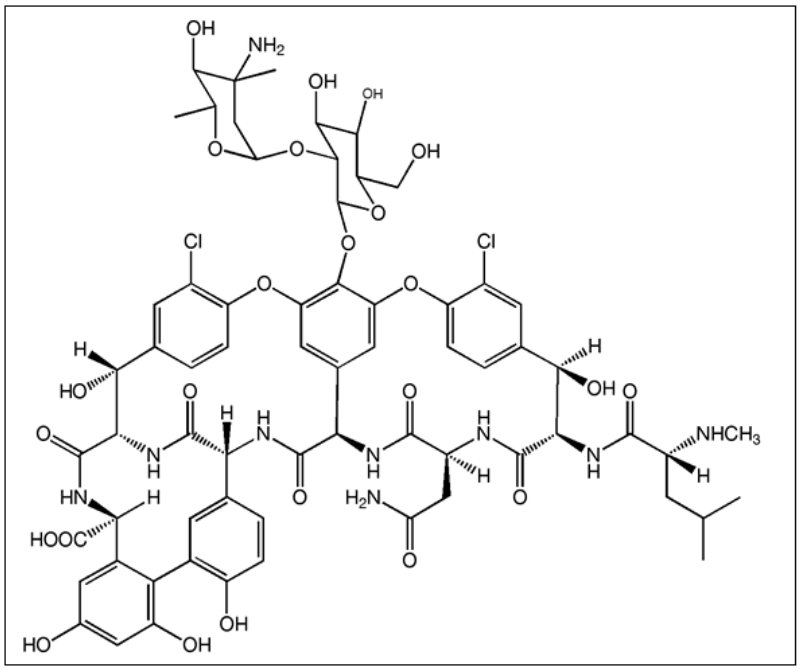
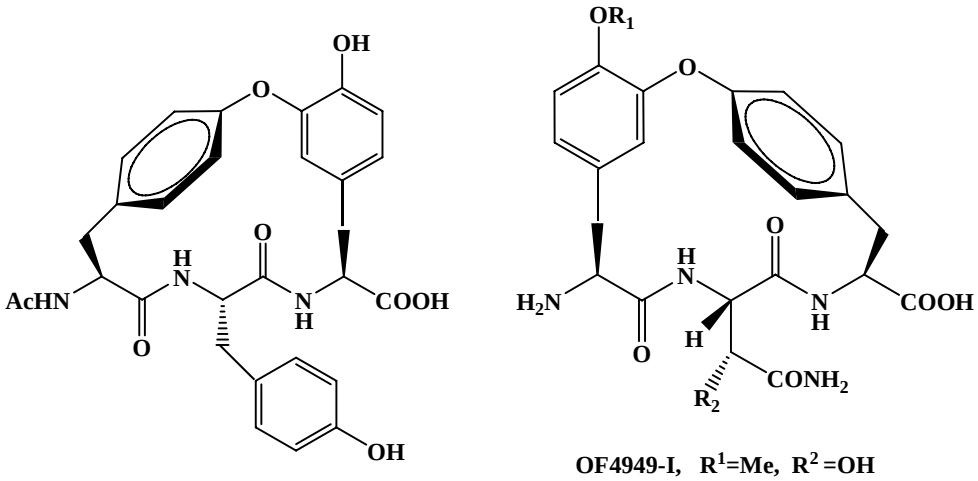


Figure-6: Vancomycin

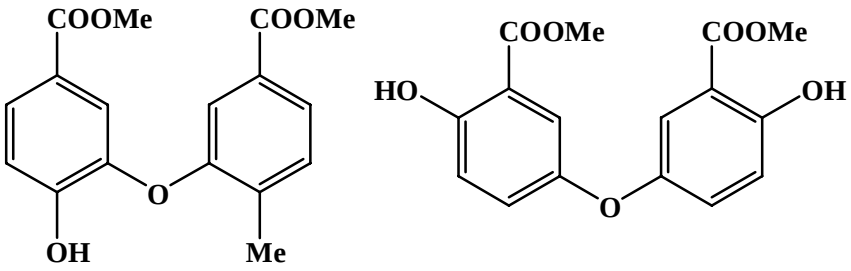


K-13

OF4949-I, R^1=Me, R^2=OH
OF4949-II, R^1=H, R^2=OH
OF4949-III, R^1=Me, R^2=H
OF4949-IV, R^1=H, R^2=H

Figure-7

Similarly, Cylindol A[16] is an example of naturally occurring novel biphenyl ether with a related compound from *Imperata Cylindrica*.**(Figure-8)** These compounds may be useful as anti-inflammatory drugs in therapeutic applications.

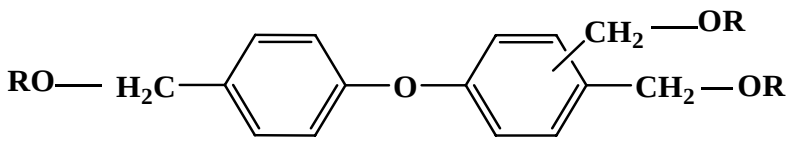


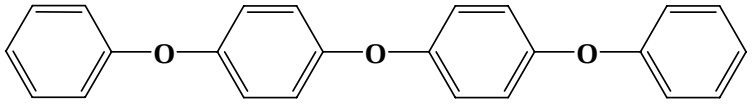
Cylindol A Cylindol B

Figure-8

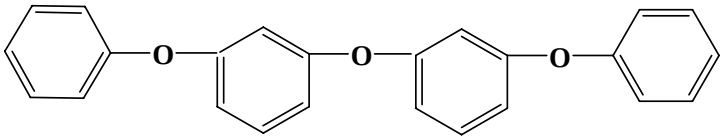
Besides being used as biocides, diphenyl ethers also find applications in materials. They have long been used as flame retardants. Flame retardants are materials that inhibit or resist the spread of fire.

Polyphenyl ethers[17,19]**(Figure-9)** possess many properties desirable for functional fluids. Many diphenyl ethers could also be used as lubricants. This is because aromatic compounds are much more resistant to radiation than aliphatic compounds**.** The properties of polyphenyl ethers properties such as viscosity, temperature coefficients and oxidation, thermal, and radiation stabilities, as well as lubrication characteristics, were investigated in detail and it was found that these could be used as lubricants. Such lubricants[18] must possess good oxidation, radiation, and thermal stability and at the same time be capable of lubricating high-speed bearings and moderately-loaded gear trains. Furthermore, physical properties must permit operation over a wide temperature range.

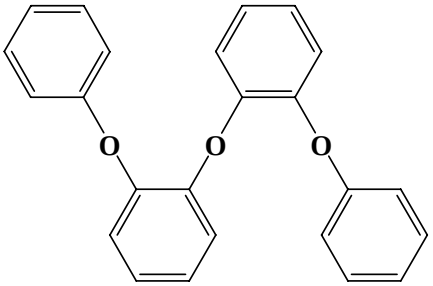




Bis (m-phenoxy phenyl) ethr

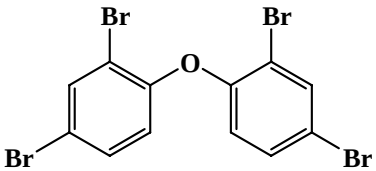


Bis (p-phenoxyphenyl) ether

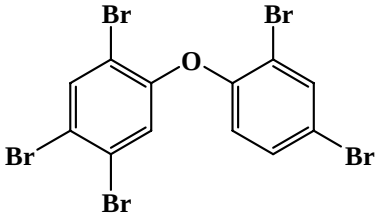


Bis-(o-phenoxyphenyl) ether

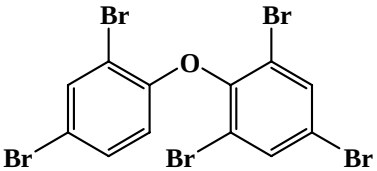
Figure-9



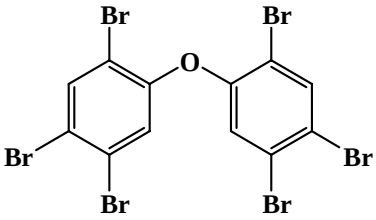
2,2',4,4'-tetraBDE (PBDE-47)



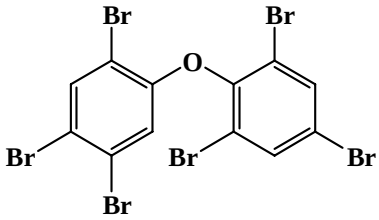
2,2',4,4',5-pentaBDE (PBDE-99)



2,2',4,4',6-pentaBDE (PBDE-100)



2,2',4,4',5',5-hexaBDE (PBDE-153)



2,2',4,4',5,6'-hexaBDE (PBDE-154)

Figure-10

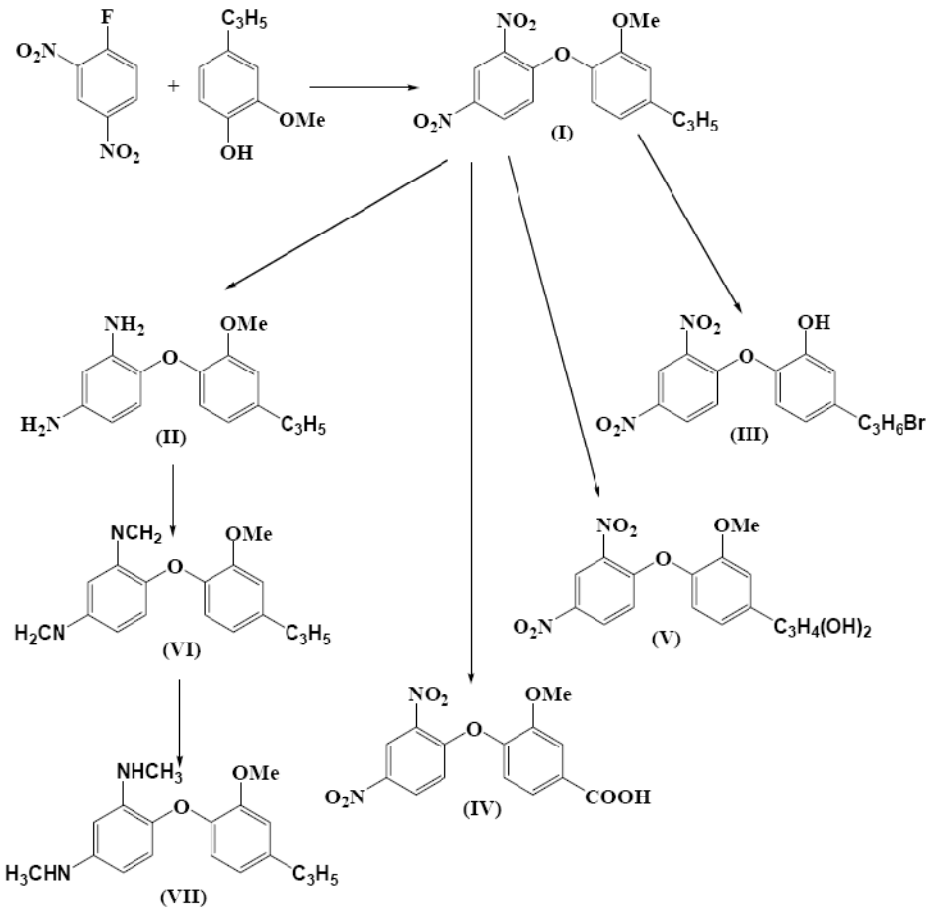
Diphenyl ethers have also been used as flame retardants. A flame retardant[20] is a material that inhibits or resist the spread of fire. Some examples of compounds that could be used as flame retardants are shown in **Figure-10**.

For all the compounds presented in this work reaction monitoring was done using TLC. Purification from the crude mixture was mostly done using column chromatography. Confirmation of the structure was done using ^{1}H , ^{13}C NMR and mass spectroscopy.

From this discussion we found that the field of diphenyl ethers has been explored to great extend but due to its properties and great usage still there is lot of scope to explore this field more. Our aim was to synthesize and characterize various diphenyl ethers so that their activity could be tested for possible use as antimicrobials and for other materialistic properties.

Aim and Objective

Sullivan et. al.[21] have shown that a long carbon chain (C5 to C14) at position 4 inhibits drug-sensitive strain of *mycobacterium* at low micromolar concentrations. As per our knowledge, there are no reports of any study with an allyl group the same position. Present work was initiated with an objective to synthesize and characterize a range of diphenyl ethers having allyl group at position 4. The usefulness of these compounds as antimicrobials and for other material properties will be further taken up.



Scheme 1

Schemetic representation of synthesis of various diphenyl ethers

We first plan to prepare a diphenyl ether (I) with 2,4-dinitrofluorobenzene and eugenol using S_NAr reaction.. The nitro groups of this diphenyl ether will be converted into corresponding amino groups (II), which will be further explored to form Schiff base (VI) that upon reduction with $NaBH_4$ will give corresponding methyl amines (VII).

We also plan further to investigate the chemistry of allyl group by doing its carboxylation , hydroxylation and halohydrogenation to get corresponding carboxylic acid (IV) diol (V) and halohydrin (III) respectively. Scheme I below shows the schematic representation of the reactions planned.

Experimental Section

All the chemicals and solvents used for synthesis were of LR grade and procured from S.D.Fine-chem Limited, Mumbai, India. Eugenol was extracted from cloves and also purchased from S.D.Fine-chem Limited, Mumbai, India. ^{1}H and ^{13}C NMR spectral analysis were performed on BRUKER AVANCE II 400 MHz spectrometer and mass analysis was done on LC-MS instrument using turbo spray.

Preparation of eugenol

Place 10 g of freshly ground cloves in a 250 mL two necked roundbottom flask, add 150 mL of water and boiling chips. Assemble the apparatus for a simple distillation and use a 100 mL Erlenmeyer flask for collection. As the distillation proceeds collect 20-25 ml of distillate in conical flask. Distillation is done until distillate drop is transparent. Extract it with DCM. Then give it NaOH treatment. Then add HCl until it becomes acidic. Again extract it with DCM and dried over Na_2SO_4. Evaporation of organic solvent gave eugenol in 82% yield. TLC of eugenol prepared in laboratory as well as purchased from company gave spot at same place.

Preparation of 4-(2',4'-Dinitrophenoxy)-3-methoxyallylbenzene[22] (I)

To a solution of 1-fluoro-2,4-dinitrobenzene (0.607ml) in DMF (10ml) were added K_2CO_3 (2.69gm) , 3-methoxy-4-hydroxyallylbenzene i.e Eugenol (0.937ml) and 18-crown-6 (pinch). The mixture was stirred at room temperature for 12 hours. After the reaction is complete (TLC monitoring), the reaction mixture was diluted with CH_2Cl_2 (100ml), washed with water (50ml), 1N NaOH(3x10ml), water (until neutral to litmus paper), brine, and dried over Na_2SO_4 . Evaporation of organic solvent gave yellow solid (1) in 80% (1.74gms, mp 87-90^{o} C) yield. It was purified by colum in 80:20 ethyl acetate: pet ether. It gave yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$):δ 3.4 (d, J=2.8 Hz, 2H), 3.7 (s, 3H), 5.1 (dd, J=1.6 Hz, 2H), 6.0 (m, 1H), 6.8 (d, J=8.4 Hz, 1H), 6.9 (d, J=9.6 Hz, 1H), 7.1 (d, J=1.6 Hz, 1H), 7.2 (d, 8.0 Hz, 1H), 8.2 (dd, J=9.6 Hz, 1H), 8.8 (d, J=2.8 Hz, 1H); ^{13} C NMR ($CDCl_3$): δ 40.05, 55.92, 113.56, 116.62, 117.30, 128.64, 136.62, 138.36, 139.59, 140.35, 140.94, 150.77, 156.69; MS: m/z 330.4 $[M]^{+}$

Preparation of 4-(2',4'-diaminophenoxy)-3-methoxyallylbenzene[22](II)

To a suspension of 4-(2',4'-dinitrophenoxy)-3-methoxyallylbenzene (500mg)in refluxing water (15 ml) were added Fe (0.875 gm) and $FeSO_4$.$7H_2O$ (0.426 gm). The reaction mixture was refluxed for 8 h. After cooling to and confirming the completion of reaction (TLC monitoring), it was filtered through celite, washed thoroughly with CH_2Cl_2 (2x75 ml). The combined organic layers were dried over Na_2S0_4, and concentrated in vacuo. Crude product obtained was purified using column chromatography. Its column was done in 90:10 chloroform: methanol in 51% (0.45 gms) yield. ^{1}H NMR (400 MHz, $CDCl_3$):δ 3.7 (s, 3H), 4.6 (s, 2H), 4.4 (s, 2H), 3.2 (d, J=6.4 Hz, 2H), 5.7 (dd, J=8.4 Hz, 1H), 5.9 (m, 1H), 5.99 (d, J=2.4 Hz, 1H), 6.4 (d, 8.4 Hz, 1H), 6.5 (d, J=8.4 Hz, 1H), 6.6 (dd, J=8.0 Hz, 1H), 6.8 (d, J=1.6 Hz, d); ^{13} C NMR ($CDCl_3$): δ 40.32, 55.82, 101.52, 103.16, 113.17, 115.78, 116.27, 120.41, 120.73, 133.72, 133.97, 138.04, 140.45, 145.87, 146.00, 149.41; MS: m/z=271.5 $[M+1]^+$, m/z=272.6 $[M+2]^+$, m/z=273.7 $[M+3]^+$

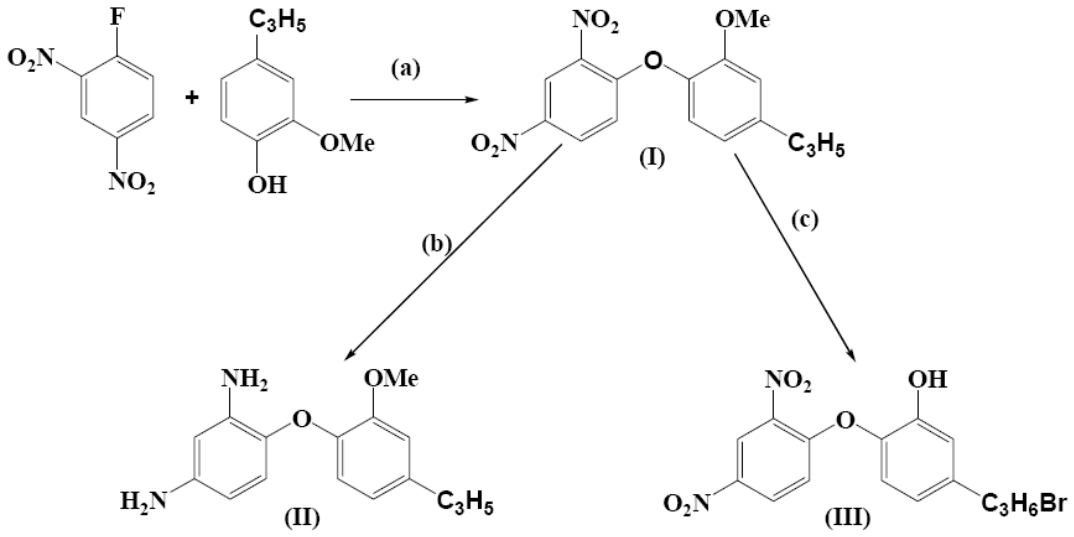
Preaparation of 5-(2-bromopropyl)-2-nitrophenoxy)phenol[22] (III)

To 4-(2',4'-dinitrophenoxy)-3-methoxyallylbenzene (400 mg) in acetic acid (20 ml) was added 48% HBr (2 ml) and heated under reflux for 2 hours. After cooling to room temperature and confirming completion of reaction (TLC monitoring), acetic acid was evaporated in vaccuo. Water (10 ml) was added to dissolve the contents and the aqueous layer extracted with ethyl acetate (3x10 ml). The combined organic layer was dried over Na_2SO_4 . Evaporation of the organic solvent gave product which was purified using SiO_2 column chromatography and the solvent (100% toluene) to afford a solid in 27% (0.10gms) yield. NMR of this compound showed that it was mixture of compounds. ^{1}H NMR (400 MHz, $CDCl_3$):δ 1.2 (s, 1H), 1.6 (d, J=2.8 Hz, 3H), 3.0 (m, 1H), 3.7 (s, 1H), 4.4 (m, 1H), 6.9 (m, 2H), 7.1 (d, J=8.4 Hz, 1H), 7.2 (m, 1H), 7.3 (d, J=8.0 Hz, 1H), 7.3 (d, J=1.6 Hz, 1H), 8.4 (m, 1H), 8.8 (m, 1H), 10.0 (d, J=6.4 Hz, 1H); MS: m/z=397.1 [M^+ for $C_{15}H_{13}N_2O_6Br^+$], 316.1[M^+ for $C_{15}H_{14}N_2O_6^+$]

Result and discussion

Allyl group containing aromatic ring of eugenol for the desired diphenylethers (I) can utilized for the purpose. Eugenol, commonly known as oil of cloves, was isolated from finely grounded cloves using steam distillation. Lignin and other polyphenols were separated from distillate to get pure eugenol by chemical method using sodium hydroxide and hydrochloric acid. The starting diphenyl ether **(I)** was prepared from commercially available Sanger's reagent (2,4-dinitrofluorobenzene) and eugenol using potassium carbonate, 18-Crown-6 and DMF via nucleophilic aromatic substitution. Reduction of dinitro diphenyl ether **(I)** was done by refluxing in presence of Fe and $FeSO_4 .7H_2O$ using water as solvent to afford corresponding amine **(II)**. Progress of the reaction was monitored using TLC.

Treatment of compound **(I)** with 48 % aqueous HBr in acetic acid afforded an inseparable mixture of compounds that contained a halohydrogenated **(IV)** and demethylated halo hydrogenated product **(III)**. This was apparent as HBr not only demethylated the methyl ether but also underwent addition at the terminal alkene. Scheme-2 below depicts the above mentioned reactions.



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

Scheme-2

In addition to above mentioned reactions the allyl group of (1) was attempted to convert into corresponding carboxylic acid by treating with $KMnO_4$ in acetic acid and then with sodium sulphite. As an alternative method refluxing with $KMnO_4$ was also tried. All the methods gave low yields and mixture of products. Similarly an attempt was made to prepare diol from alkene of the allylic group using hydrogen peroxide-formic acid hydroxylation reaction. However, in this case crude yield was so less that it was difficult to perform further purification, Schiff base of the diamine compound **(II)** with formaldehyde and simultaneous reduction by $NaBH_4$ was also attempted. However, ^1H NMR of the crude product was not in agreement with proposed structure.

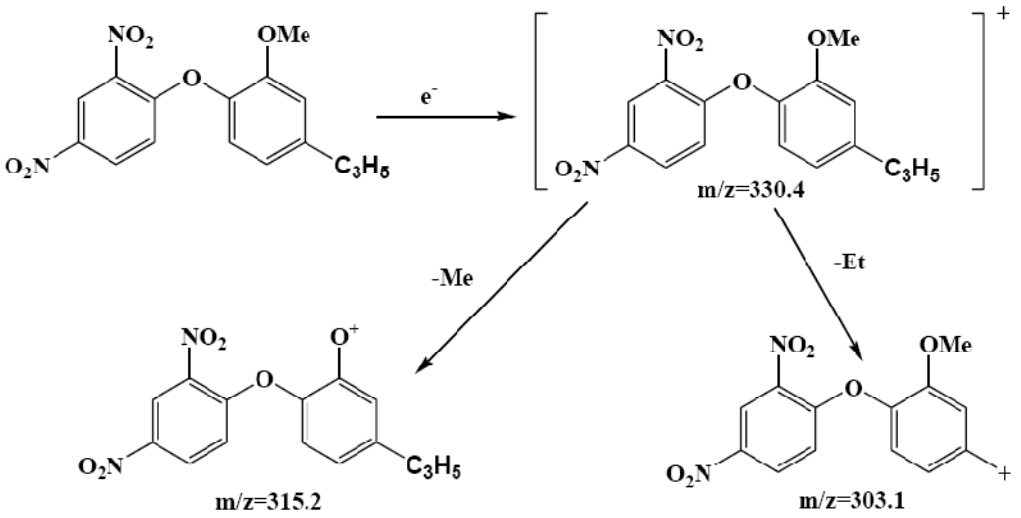
Analysis of the compounds:

All the compounds were analyzed by ^1H NMR, ^{13}C NMR and mass spectroscopic techniques **(Appendix-1)**. For the compounds obtained in scheme-1 values obtained were in agreement with the proposed structures.

Methoxy (OCH_3) group in all the these compounds gave expected singlet at 3.7 ppm. Terminal alkene of the allyl group ($=CH_2$) gave 2 separate signals at 5.0 ppm to 5.5 ppm due to their nonequivalent environment. Other olefinic proton (-CH=) gave multiplet at 5.7-6.0 ppm due to coupling with 4 protons on adjacent carbons. Allylic protons ($-CH_2-$) directly attached to the aromatic ring gave a doublet at 3.2-3.5ppm due to coupling with adjacent proton. The aromatic hydrogens appeared in the range of 6.0 ppm to 8.9 ppm. Protons due to amine and hydroxyl gave singlet at 4.4 to 4.6 ppm **(Appendix-1, Figure-14)** and 10.0 ppm **(Appendix-1, Figure-17).**

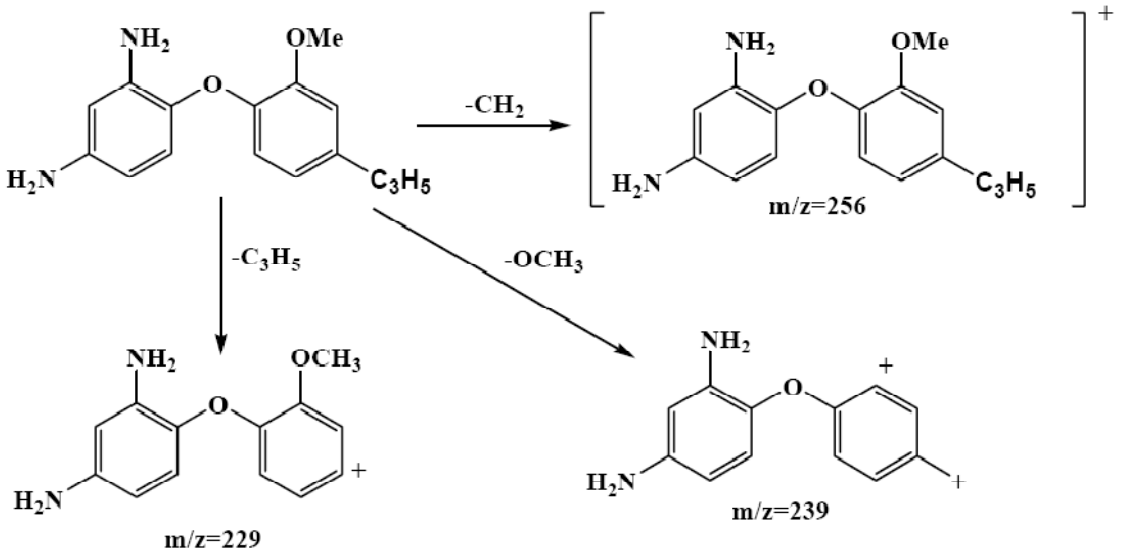
The results of ^{13}C NMR **(Appendix-1)** were also consistent with anticipated structures. Methoxy carbon (OCH_3) in compounds appeared at 55.5- 56.0 ppm. The terminal olefinic carbon of allyl group gave peak at 116-118 ppm. Allylic carbon directly attached to the carbon of aromatic ring gave signal 40.0- 40.2 ppm. All aromatic carbons appeared at 133-136 ppm.

Mass spectra of compound **(I) (Scheme-3, Appendix-1, Figure13)** gave molecular ion peak at m/z=330.4. The other two prominent peaks appeared at m/z 315.2 and at 303.1 due to loss of methyl and C_2H_3 group containing double bond respectively. it gave $C_{15}H_{11}N_2O_6^+$ peak at and the loss of gave $C_{13}H_{11}N_2O_6^+$ peak at.



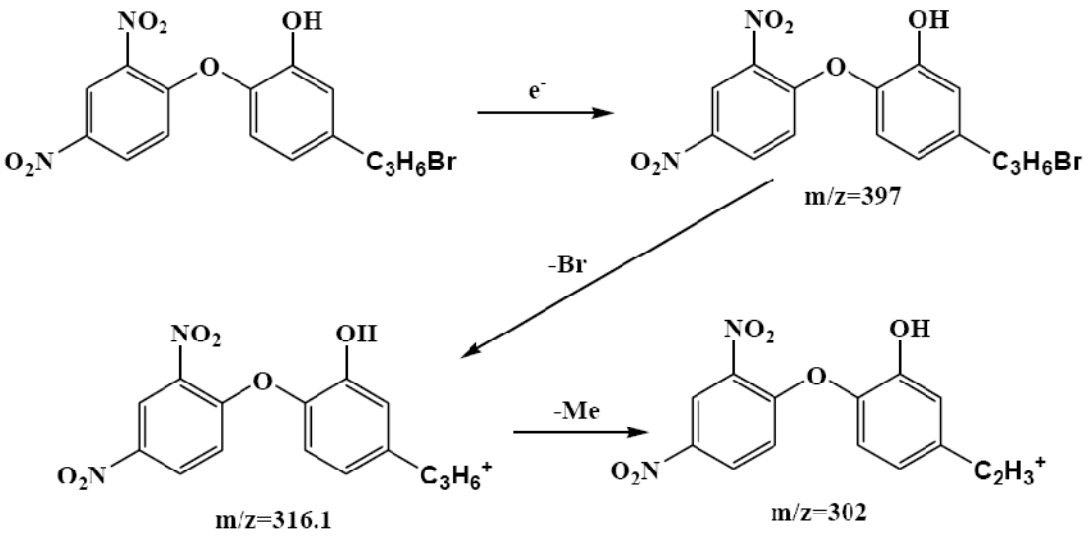
Scheme-3

Mass spectra of compound **(II) (Scheme-4, Appendix-1, Figure-16)** gave $[M+1]^+$ $[M+2]^+$ and $[M+3]^+$ peaks at m/z=271.5, 272.6 and273.7 . Loss of CH_2, C_3H_5 and methoxy group gave peak at m/z=256, 229 and at 239.



Scheme-4

Bromohydrin **(III) (Scheme-5, Appendix-1, Figure-18)** product after treatment with HBr gave molecular ion peak at 397.1 which upon loss of bromide ion gave peak at 316.1.Simaltenous loss bromide and methyl from OCH_3 of compound **III** gave m/z value of 302.



Scheme-5

Conclusion

From the work done we can conclude that we were able to prepare 4-(2',4'-dinitrophenoxy)-3-methoxyallylbenzene from eugenol and then we were able to prepare 4-(2',4'-diaminophenoxy)-3-methoxyallylbenzene and 5-(2-bromopropyl)-2 nitrophenoxy)phenol from the 4-(2',4'-dinitrophenoxy)-3-methoxyallylbenzene.

Appendix-1

Figure11: ^{1}H NMR of 4-(2',4'-dinitrophenoxy)-3-methoxyallylbenzene (I)

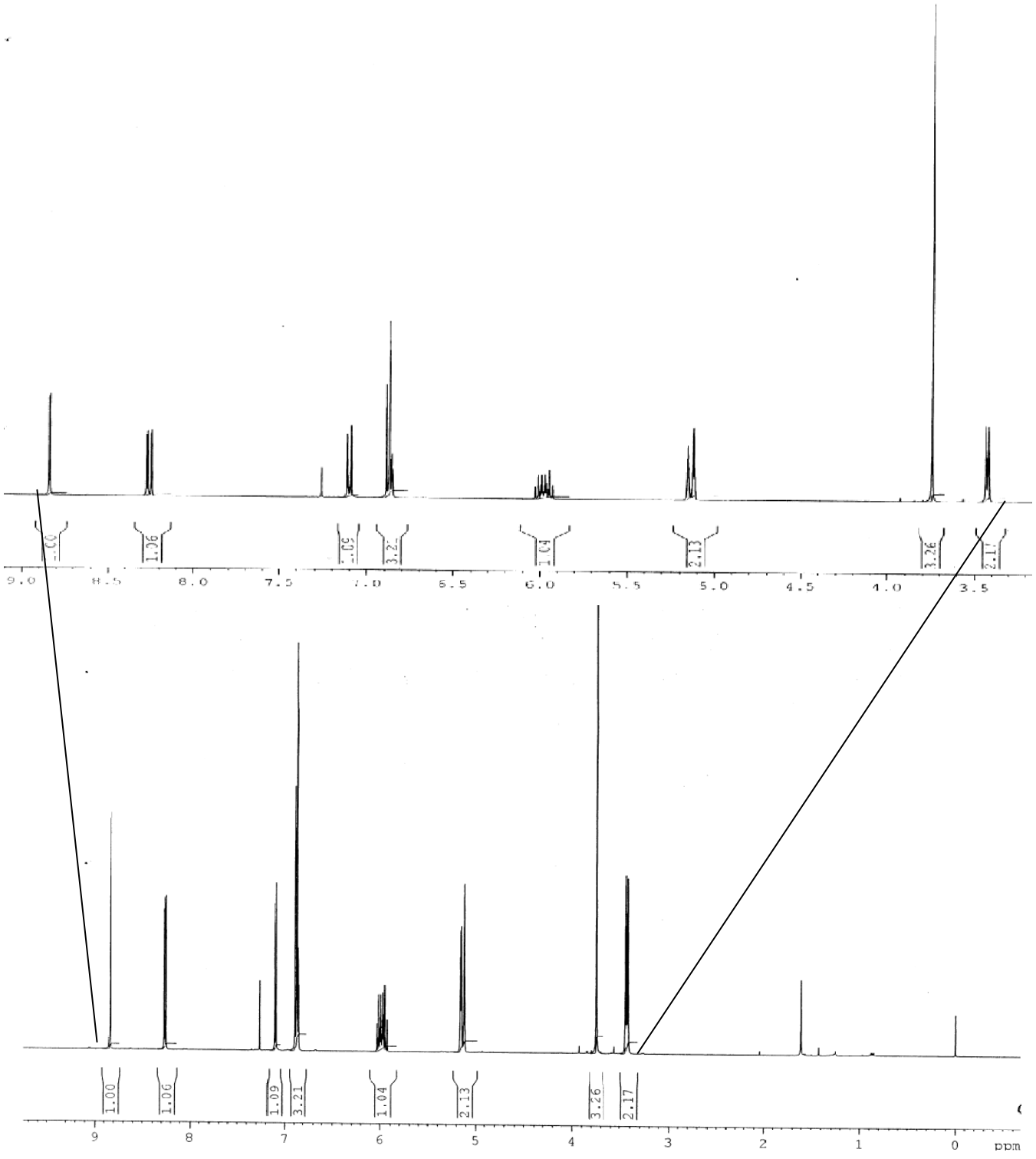
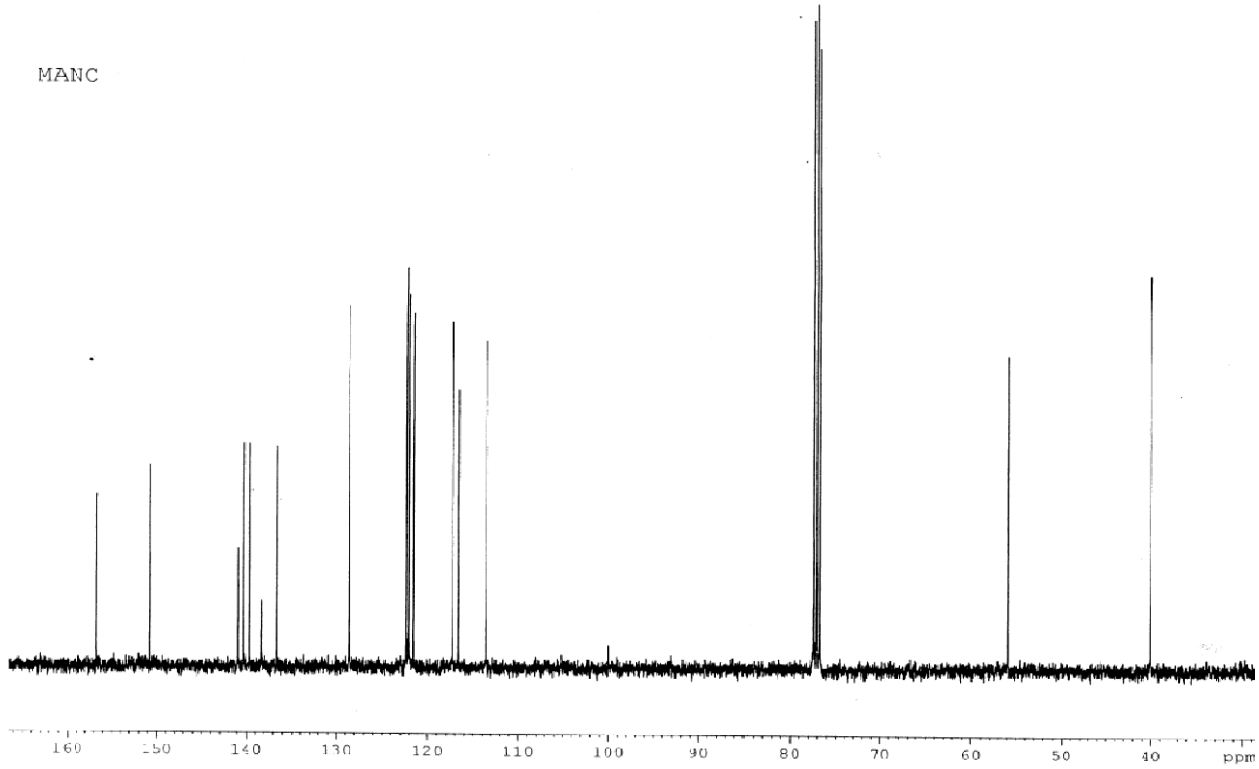


Figure 12: ^{13}C NMR of 4-(2',4'-dinitrophenoxy)-3-methoxyallylbenzene (I)



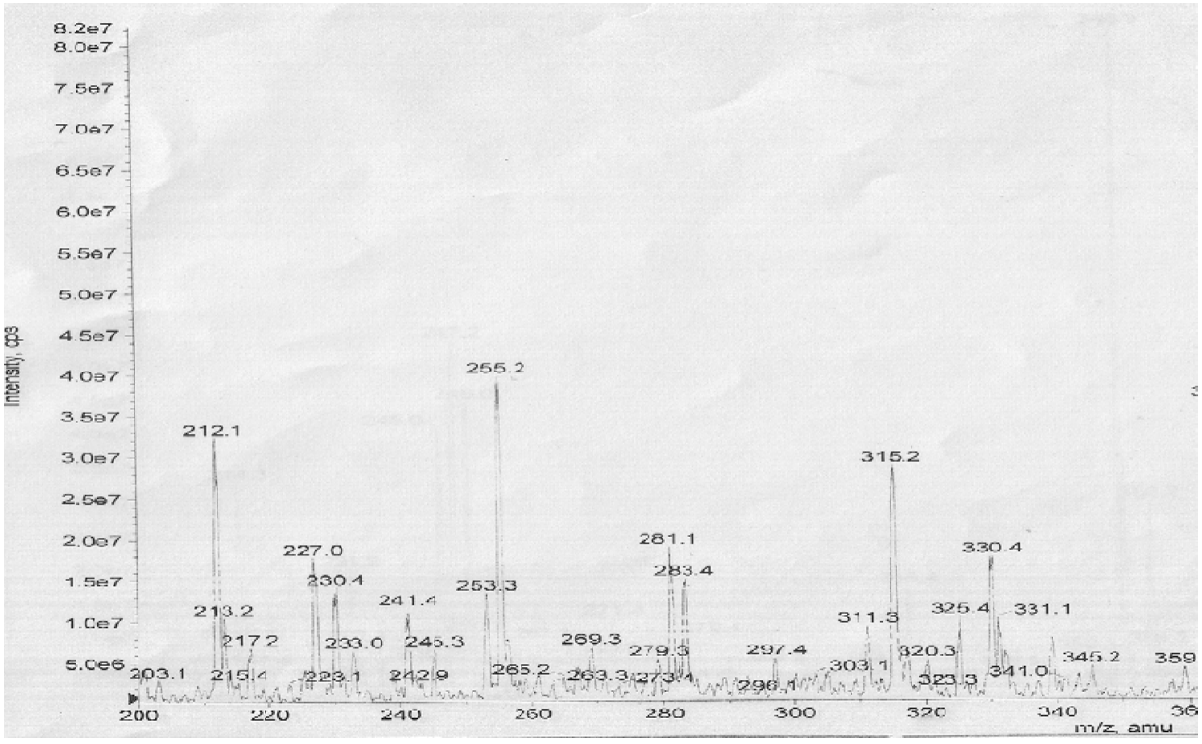


Figure 13: Mass spectra of of 4-(2',4'-dinitrophenoxy)-3-methoxyallylbenzene (I)

Figure 14: ^{1}H NMR of 4-(2',4'-diaminophenoxy)-3-methoxyallylbenzene (II)

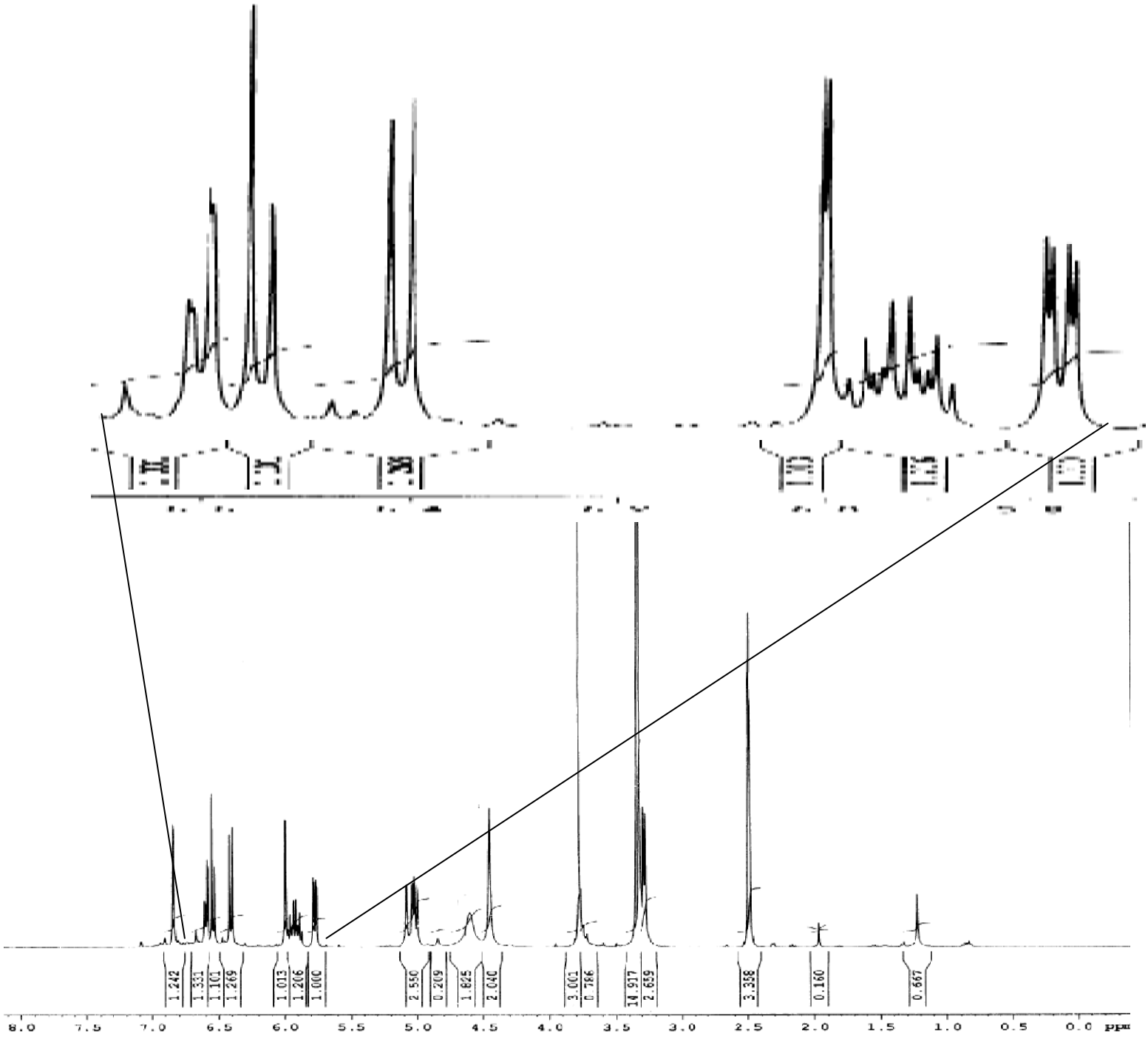
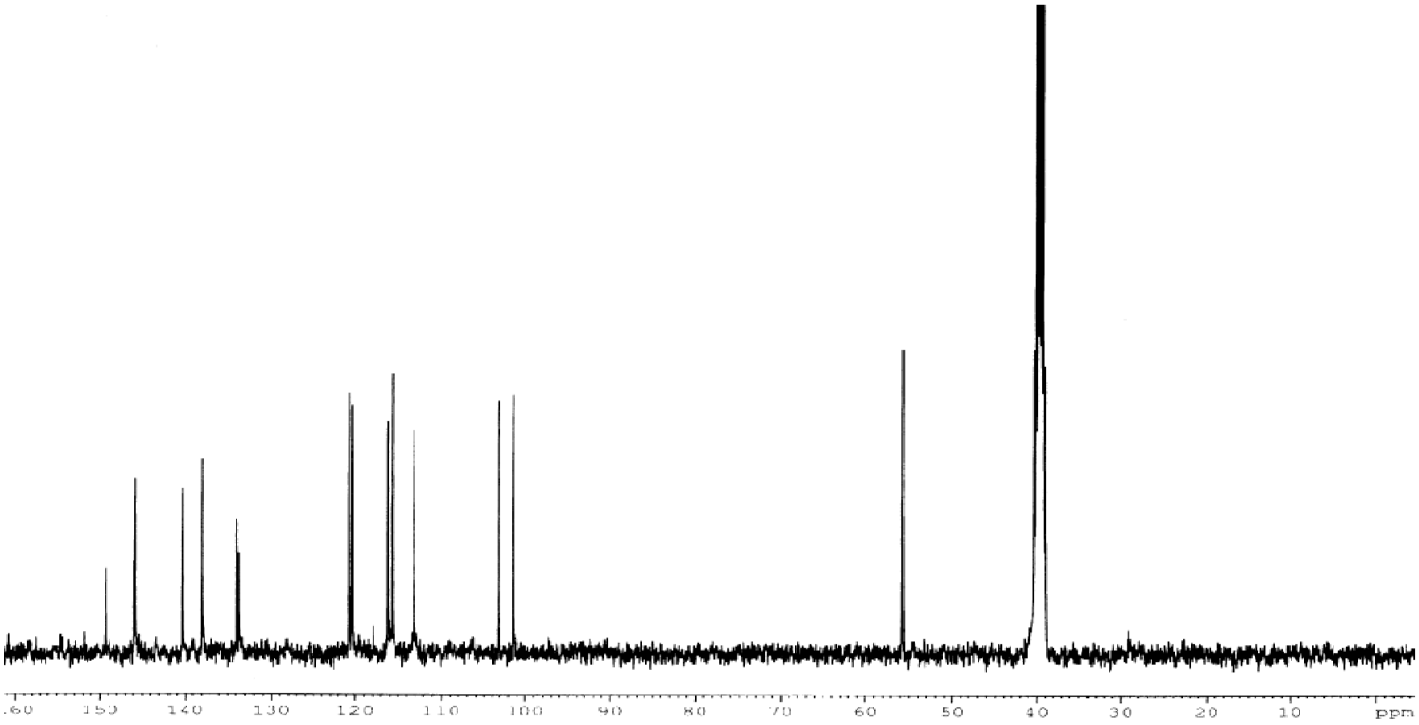


Figure 15: ^{13}C NMR of 4-(2',4'-diaminophenoxy)-3-methoxyallylbenzene (II)



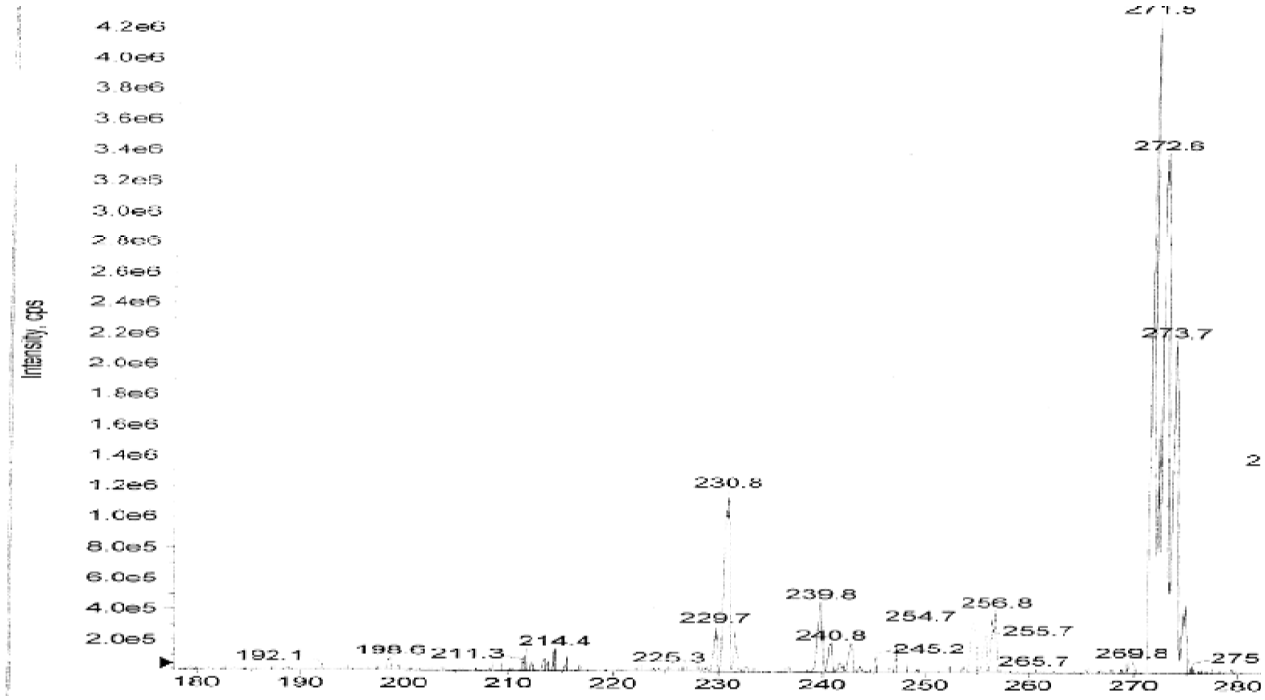


Figure 16: Mass spectra of 4-(2',4'-diaminophenoxy)-3-methoxyallylbenzene (II)

Figure 17: ^{1}H NMR of 5-(2-bromopropyl)-2-nitrophenoxy)phenol (III)

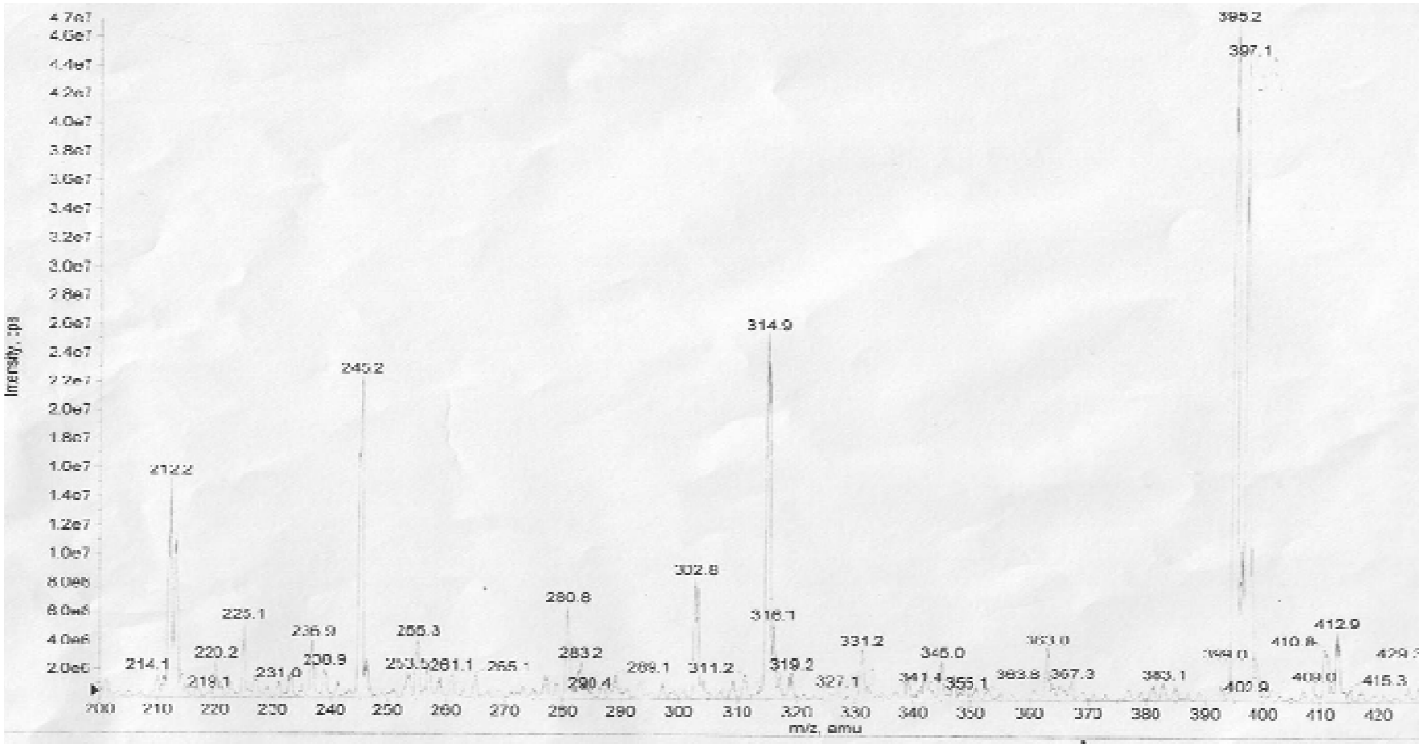


Figure 18: Mass spectra of 5-(2-bromopropyl)-2-nitrophenoxy)phenol (III)

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