An Attempt to Synthesize 2-(2’,4’Dibromophenoxy)anisole

A thesis submitted in the partial fulfilment
of the requirement for the degree of

Masters of Science
in
Chemistry

by

Aanchal
(301502001)

Under the supervision of
Dr. Manmohan Chhibber
Associate Professor

DEPARTMENT OF CHEMISTRY AND BIOCHEMISTRY

THAPAR UNIVERSITY, PATIALA (PUNJAB)-147004

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Candidate’s Declaration

I hereby declare that the work being presented in this dissertation entitled “**An Attempt to Synthesize 2-(2’,4’Dibromophenoxy)anisole**” in the partial fulfillment of the requirements for the award of the degree of Masters in Chemistry, School of Chemistry and Biochemistry, Thapar University, Patiala, is my own work during the period of Janruary 2017 to July 2017, under the supervision of Dr. Manmohan Chhibber. I have not submitted the work embodied in this dissertation for the award of my other degree.

Aanchal

Place: Patiala
Date: ..17/7/2017

Aanchal
301502001

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
(Associate Professor)
School of Chemistry and Biochemistry
Thapar University, Patiala

Acknowledgment

The success and final outcome of this project require a lot of guidance and assistance from many people and I am extremely fortunate to have this all along the completion of my project work. Whatever I have done is only due to such guidance and assistance and I would not forget to thank them.

I respect and thank Dr. **Manmohan Chhibber** for giving me an opportunity to do dissertation project work at School of Chemistry and Biochemistry and providing us all support and guidance which made me complete the work on time. I am extremely grateful to him for providing such a nice support though he had busy schedule managing the institution affairs.

I owe my profound gratitude to research scholar Mr. Ashok kumar, Ms. Shivali gupta who took a keen interest for my work and guided us all along till his completion of the project by providing necessary information for my work.

I wish to express my deep gratitude and sincere thanks for his invaluable guidance, constant encouragement, constructive comments, sympathetic attitude and immense attitude, which has sustained my efforts at all stages of this project. His advice and suggestions for the corrections, modifications, and improvement did enhance the perfection in performing my job well.

I thank my classmates with whom I share numerous memorable moments which made my M.Sc really enjoyable. My heartfelt thanks to Mandeep, Ripanshu, Yadwinder without whom, I could not have imagined life at Thapar University.

I am also thankful for all the facilities that he provided for this work. I sincerely appreciate this magnanimity by taking me into his fold for which I shall remain indebted to him.

Place: Patiala
Date: 17/7/2017.

Aanchal
Regards,
AANCHAL

This thesis is dedicated to my parents

For their endless love, support and encouragement

Table of Contents

Abstract

Poly brominated diphenyl ethers (PBDEs) are used as flame retarding materials in many consumer products. Many other PBDEs that are obtained from marine sources show biological activities like antibacterial, antifungal and antifouling. Most of PBDEs have been isolated from sponges of *Dysidea species.* This work attempts to synthesize a PBDE, 2-(2', 4'-Dibromophenoxy) anisole (1), using three steps. The nucleophilic aromatic substitution of 2,4-dinitroflourobenzene with methoxy phenol (Guaiacol) gave 2-(2',4'-Dinitrophenoxy)anisole (3) which upon reduction with 5% palladium on charcoal gave 2-(2', 4'-Diaminophenoxy) anisole (2). The diazotisation reaction of the synthesized amine (2) using t-butyl nitrite, $CuBr_2$ in anhydrous acetonitrile was expected to yield compound **1**. All the synthesized compounds were purified by column chromatography and analyzed by ^1H and ^{13}C NMR.

Chapter 1 Introduction

Poly-brominated diphenyl ethers (PBDE) **(Figure-1)** are low cost compounds that can act as non-reactive flame retardants additives in furniture, plastics, electronic devices, electrical equipment, textiles and many household products [1, 2]. These compounds have also been found in a variety of environmental matrices, human bodies and biological samples.

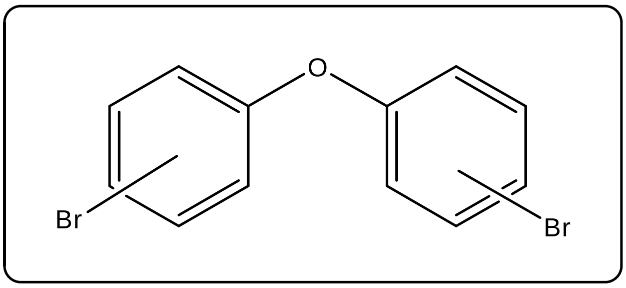


Figure-1: General structure of PBDEs

Traditionally, production of PBDEs started in 1960s and continues till date. The three commercial compounds produced are penta-bromodiphenylether(penta-BDE), octa-bromodiphenyl ether(octa-BDE) and deca-bromodiphenyl ether(deca-BDE) [3]. The formulations of these compounds have different applications.

- Penta-BDE is used in poly urethane resin like foam, furniture, mattresses and automobiles.
- Octa-BDE is used in acrylonitrile butadiene styrene (ABS) resin and electronic devices.
- Deca-BDE is used as flame retardant and in polystyrene(PS), and high impact polystyrene (HIPS) [2].

Different PBDE’s due to their similar structure and difference in substitution are called congeners. Mathematically, PBDE’s can have 209 congeners having general formula of $C_{12}H_{10-x}Br_xO$ (x = 1,2,3…., 10). They can differ in position and number of bromine atoms attached to the structure of diphenyl ether molecule. PBDE congeners having equal number of bromine atoms are called as homologs[1, 2]. These compounds are relatively stable but on exposure to UV radiations they undergo photolytic de-bromination[4, 5]. Due to their insolubility in the water, PBDEs bind to soil, sediment particles and hence their mobility in soil and water is decreased thereby enhancing abundance in the atmosphere [1].

Broadly, PBDEs can be divided into two classes according to the number of bromine atoms present in the molecule **(Figure-2)**.

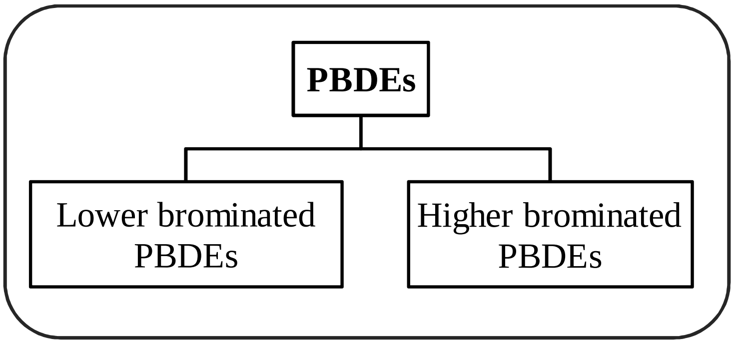


Figure-2: Classification of PBDEs

Lower Brominated PBDEs: These are the species that have an average of 1to 5 bromine atoms in the molecule. These molecules bio-accumulate more efficiently than higher brominated PBDE.

Higher Brominated PBDEs: These species are having an average of 5 to 10 bromine atoms per molecule. Penta-bromodiphenyl ether's commercial mixture contains 50-60% of penta-bromo derivative, 24-38% of tetra bromo, 4-8% of hexa-bromo and 0-1% of tri-bromides.

PBDEs congeners are also extracted from the natural resources like marine sponges, plants, sediments and soil and they have variety of biological activities. Such compounds show antibacterial, antifungal, cytotoxic and enzyme inhibition [6] activities. These compounds also act as anti-tubercular agents [7]. As far as antibacterial activity is concerned, these compounds inhibit both Gram-positive and Gram-negative bacteria. Therefore the synthesis of such PBDEs at low cost for used in shower products, textile, leather products and agriculture is highly recommended. The antibacterial activities are analysed generally in terms of MIC (minimal inhibitory concentration) or IC_{50} (Inhibitory concentration) values. Antifungal activity is also determined with varying concentrations. These compounds have inhibitory activity against various enzymes also with IC_{50}, which is the efficiency of a compound to inhibit an enzyme. Present thesis attempts to synthesize a poly brominated diphenyl ethers namely 2-(2', 4'Dibromophenoxy)anisole.

Poly-brominated diphenyl ethers (PBDEs) are important compounds which occur in nature and synthesized on commercial scale as well. On commercial scale they are used as flame retardant, additives in building materials, paints, textiles, furniture, auto-mobiles and in many electrical gadgets. Besides above applications, due to their flame retardant properties, they are practically used in all types of polymers including polyvinyl chlorides, polycarbonates, polyester resins, ABS – acrylonitrile butadiene styrene, polyamides, poly-olefins and rubber.

Due to their use in vast number of materials and also non-degradable nature, a number of literature reports cite these compounds as pollutants [8-12]. The non-degraded PBDEs have been found in environment (sewage sludge, sediments and indoor air) [8] and biological samples (human blood serum, urine, breast milk and tissues) [9-12].

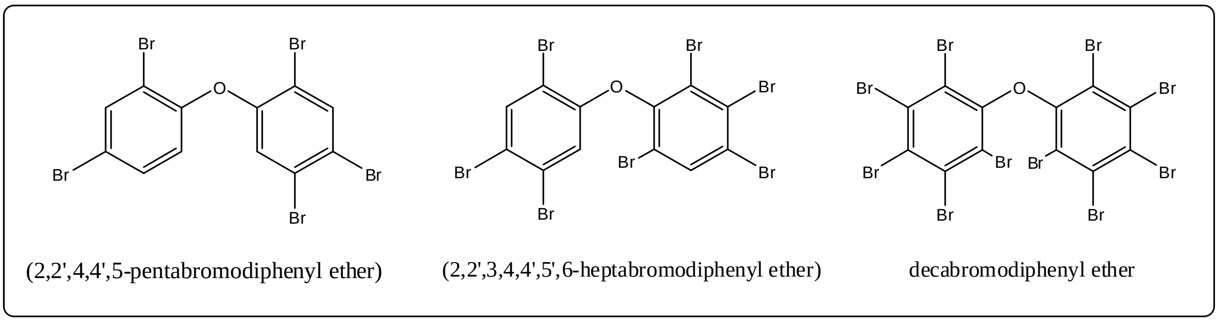


Figure-3: Structures of PBDEs congeners

Figure-3 shows the structure of some commercially available PBDEs. Their use as flame retarding material stems from their ability to release bromine (Br_2) at high temperature which interferes with high energy OH and H radicals released during the combustion process. There are two types of flame retarding materials.

(i) Reactive FRs are bonded through covalent bond in the polymer matrix with certain additives. Tetra bromo bisphenol A is one such additive **(Figure-4a)**.

(ii) Additive FRs do not form any kind of covalent bond with the material, when mixed with the polymer. HCBD (Hexa-bromo-cyclododecane) is another one example [13] **(Figure-4b)**.

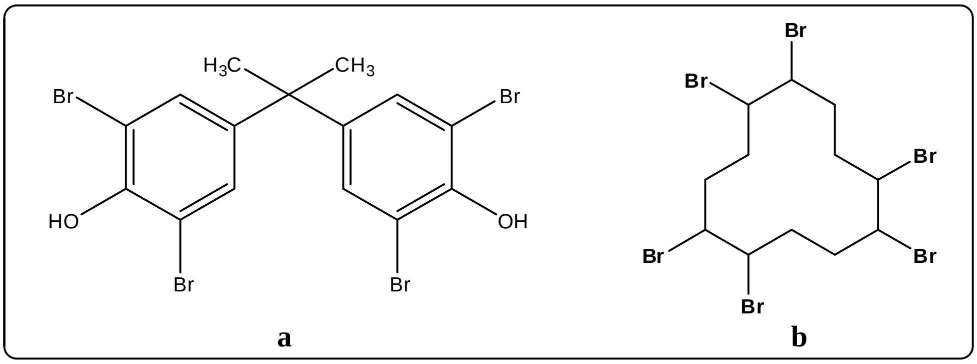


Figure-4: Structure of TBBPA and HCBD

The use of PBDEs in various applications is summarized in **Table-1** [14]

Table-1: List of Polymers where PBDEs are used

Resin / Polymer	**Primary Applications**	**Ultimate/Absolute Product**
Acrylonitrile-butadiene-styrene(ABS)	Molded parts	Computer covering, automotive parts, hair dryers
Epoxy	Protective coating, circuit boards	Ship interiors, electronic parts
Phenolic polymer	Printed circuit boards	Paper laminates
Paints/lacquers	coatings	Industry and marine lacquers for protection of containers
Polyamide	Electrical connections, automotive interior parts	Automotive industry, connectors, transportation
Polyethylene/cross linked polyethylene	Cross-linked wire cable, foam tubing, weather protection	Insulating heating tubes, power cables, marine appliances
Poly-acrylonitrile	Electrical components, panels	Lighting panels, housing of electrical appliances
Polybutylene terephthalate	Connectors, Electrical components	Stereos, switches, fuses
Polypropylene	Electronic devices,	Electro-mechanical parts, underground junction boxes
Polyethylene terephthalate	Electrical components	Coils, bobbins, relays, boxes
Polystyrene/high impact polystyrene	Television cabinets & back covering, housing	Smoke detectors, housing of electrical appliances, office machines,
Rubber	Transportation	Foamed pipes for insulations, conveyor belts
Unsaturated polymers	Circuit boards,	Military/marine applications
Polyurethane	Packing materials	Sound insulation, furniture
Polyvinyl chloride	Cable sheets	Floor mats, wires and cables
Textiles	Coatings	Military safety clothing, automotive seating, tents.

Besides commercial production, a rich source of PBDEs is nature. Sea and sea organisms have been reported to synthesize a vast number of PBDEs for their use and protection. Therefore such PBDEs have been found to possess many biological activities. Following paragraphs describe the sources, structure and biological activity of many PBDEs.

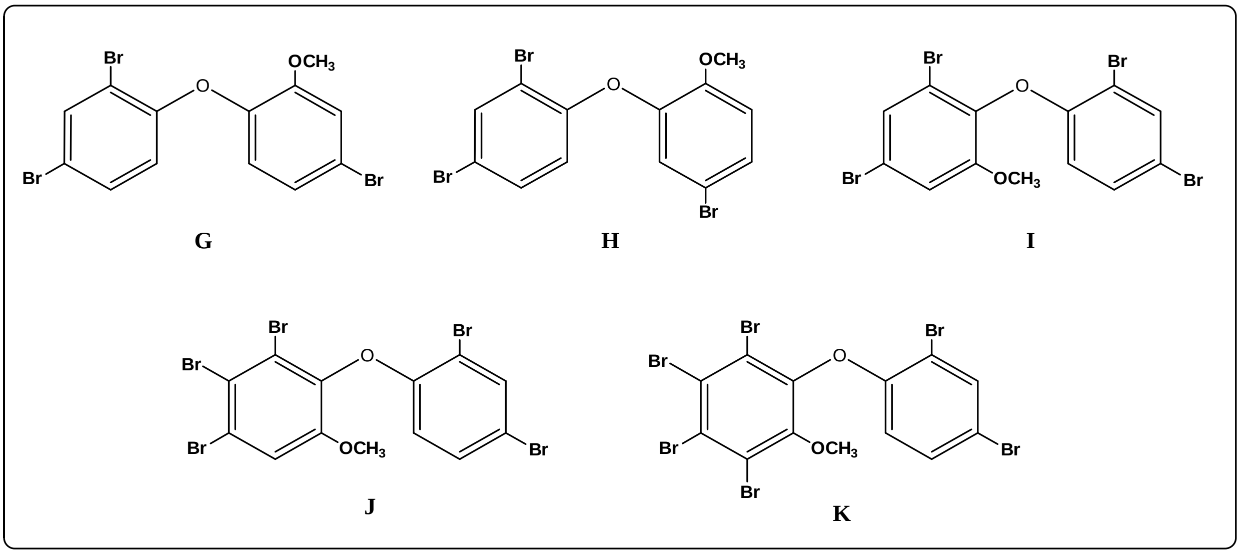


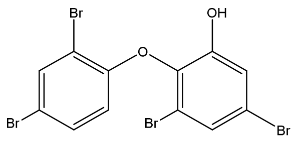
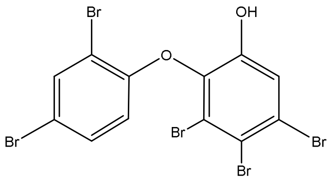
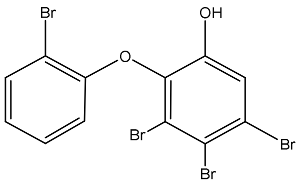
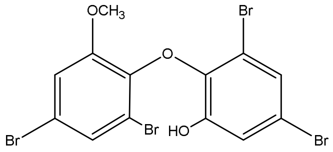
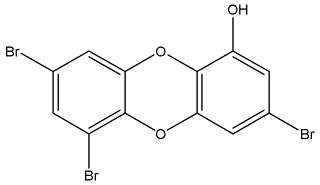
Figure-5: Structure of naturally occurring PBDE

Figure-5 lists the compounds that were identified from marine sponge *Dysidea herbacea* and in their associated bacteria, red algae (*Ceramium tenuicorne)* and brown algae (*Cladophora fascicularis*) [15][16][17]. Compounds H and I were also isolated from true's beaked whale (*Mesoplodon mirus*) in North Atlantic. [18].

It has been proposed that production of PBDEs is the result of symbiotic association of sponges with various bacterial and algal species. Thus, PBDEs play a vital role in the chemical protection for the sponge besides predator and bacterial attack [23], [24].

Following table **(Table-2)** shows some of the PBDEs isolated from marine sponges along with their references.

Table-2: PBDEs and their marine sources.

Compound name	Obtained from	Reference
 3,5-dibromo-2-(2',4'-dibromophenoxy) phenol	 *Callyspongia sp*. (sponge)	19
 3,4,5-tribromo-2-(2,4-dibromophenoxy)phenol	 *Dysidea granulosa* (sponge)	20
 3,4,5-tribromo-2-(2'-bromophenoxy)phenol	 *D.herbacea (sponge)*	20
 3,5-Dibromo-2-(4,6-dibromo-2-hydroxyphenoxy) anisole	 *Phyllospongia dendyi*	21
 3,6,8-tribromodibenzo[*b*,*e*][1,4]dioxin-1-ol	 *Dysidea dendyi*	22

Dysidea herbacea, a marine sponge is known to contain polychlorinated amino acid derivatives and PBDEs. The sponge collected from the shores of the Air Island (Indonesia, West Sumatra) [25] is known to possess PBDEs from *D. herbacea*. The species stays in association with *Oscillatoria spongeliae* (cyanobacterium). It has been noticed that PBDEs derivatives besides antibacterial activity inhibit the enzymes concerned with the tumour development and arteriosclerotic plague, to prove their potential as capable therapeutic agents. [26]

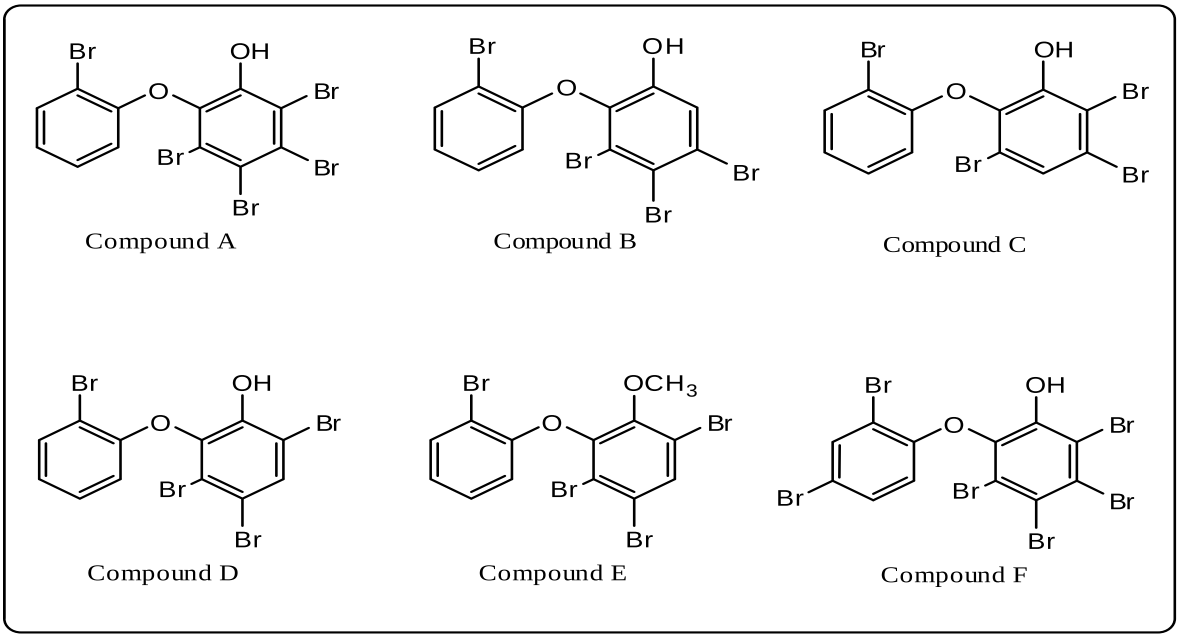
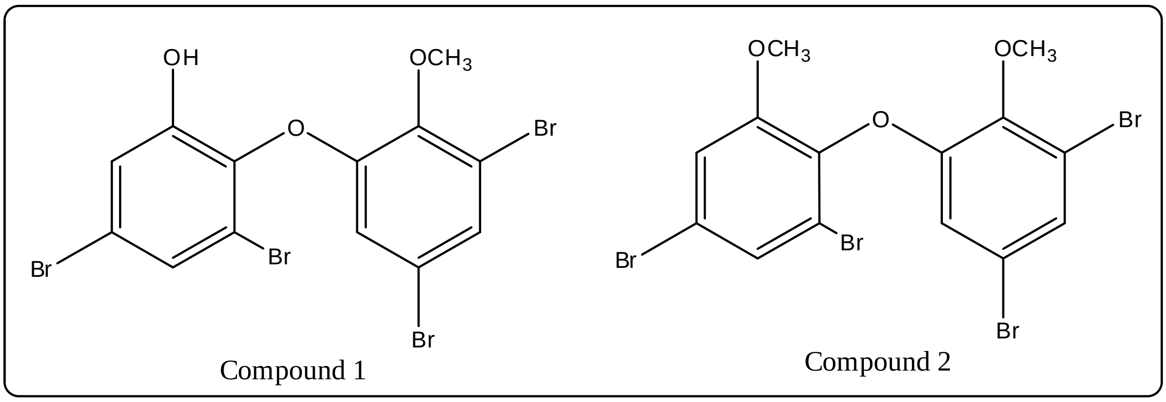


Figure-6: Structure of PBDEs Isolated from *D. Herbacea*

Figure-6 shows six compounds that have been isolated from the species. The compounds A-F were examined for their antifungal, antibacterial and toxicity test (i.e. brine shrimp lethality test). All the compounds as shown in **figure-6** were antibacterial against *Bacillus subtilis* which is a Gram-positive bacterium. However, they did not show any inhibition for *E. coli* which is a Gram-negative bacterium. The minimum inhibitory concentrations (MICs) were comparatively higher for compound A (MIC 0.20μg/mL) than compound C, D and F. Compounds B and E were much less active having MIC value 6.25μg/mL and 104μg/mL respectively. Compound A showed activity identical to that of gentamycin, a standard antibiotic used against *B. subtilis*. These compounds were also showing antifungal activity against *C. cucumerinum*. The concentration is of 50 and 25nmol of compounds C and D were most active against fungus, having effect inhibition region within the diameter of 16 and 8 mm respectively followed by compounds A, B, and F. The toxicity of compound A and F tested against brine shrimp gave an LC_{50} of 0.96 and 0.94 µg/mL [25].

Besides antibacterial and antifungal activity, PBDEs are also known to possess other therapeutic properties. Ethanol extract of a marine sponge *Lamellodysidea herbacea* from Indonesia, exhibits the inhibitory activity of protein tyrosine phosphatase 1B (PTP1B), a targeted enzyme in the treatment of type 2 diabetes mellitus (T2DM)β. An excess of PTP1B is responsible for insulin down-regulation [27-29], causing T2DM.



Compound 1

Compound 2

Figure-7: Structures of Compounds 1 and 2

Compounds **1** and **2 (Figure-7)** purified from above extract have shown inhibition of PTP1B enzyme with IC_{50} value of 0.85μM and 1.7 μM respectively. In fact **compound-1** showed almost similar effect compared with positive control oleanolic acid (1.1 μM), which is used for the treatment of diabetes, cancer and inflammation [30] [31]. As far as cytotoxicity is concerned compound 2 was more active showing none and compound 1 responsible against cancer cell lines.

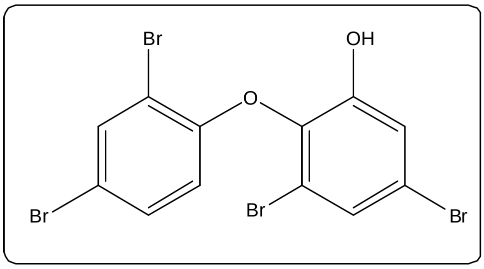
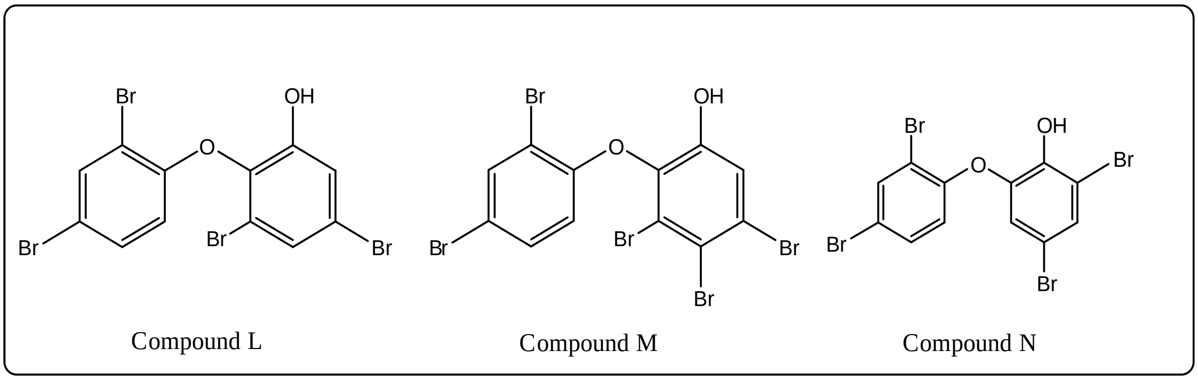


Figure-8: Structure of Compound O

Bio-fouling is a phenomena observed in submerged surfaces where growth of micro-organism, plants animals occurs under the sea [32]. Compound that inhibit this activity are called biofouling agents. PBDEs isolated from certain sponges have shown this activity.

Compound (O), **(Figure-8)** [33] shows strongest anti-fouling having MIC = 0.02-1.52μM and EC_{50s} were 0.66 μM (mussel test), 1.26 μM (barnacle test), 0.24 μM (diatom test).

PBDEs were also showing antimicrobial activity. From *Dysidea granulosa* (marine sponge), two compounds (L and M) were extracted and from *Dysidea* sp., compound N was isolated. These compounds show effective anti-bacterial activity towards various bacteria's such as *Escherichia coli*, *salmonella*, methicillin sensitive *staphylococcus aureus*(MSSA) and methicillin resistant *Staphylococcus aureus* (MRSA).Minimal inhibitory concentration (MIC) was checked against various gram positive and gram negative bacteria. For gram negative bacteria the MIC range comes out to be 0.1-16.0 mg/L and 0.1-4.0 mg/L against gram positive bacteria. Because of the thermal stability of compound they were able to work as anti MRSA, anti-salmonella and anti-E-Coli for drug development [34].



Compound L

Compound M

Compound N

Figure 9: Structure of Antibacterial Compounds L, M, N

Four new PBDEs and their derivatives were extracted from the Palauan sponge *Phyllospongia dendyi*. Their structures were recognized by using mass spectral data and nuclear magnetic resonance. They exhibited anti-microalgal towards *O. amphibia*, *P. micans, S. costatum* and *B. submaria* at concentrations range 0.5–5.0 ppm. and anti-macroalgal activity against *U. conglobata* spores with IC_{50} values between 0.02–0.05 ppm. Among all compounds [21], compound P shows stronger inhibitory activity.

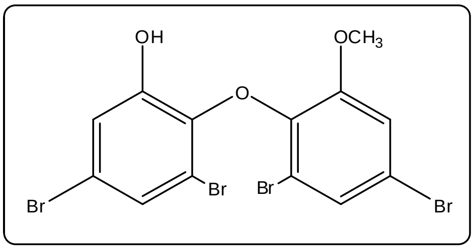
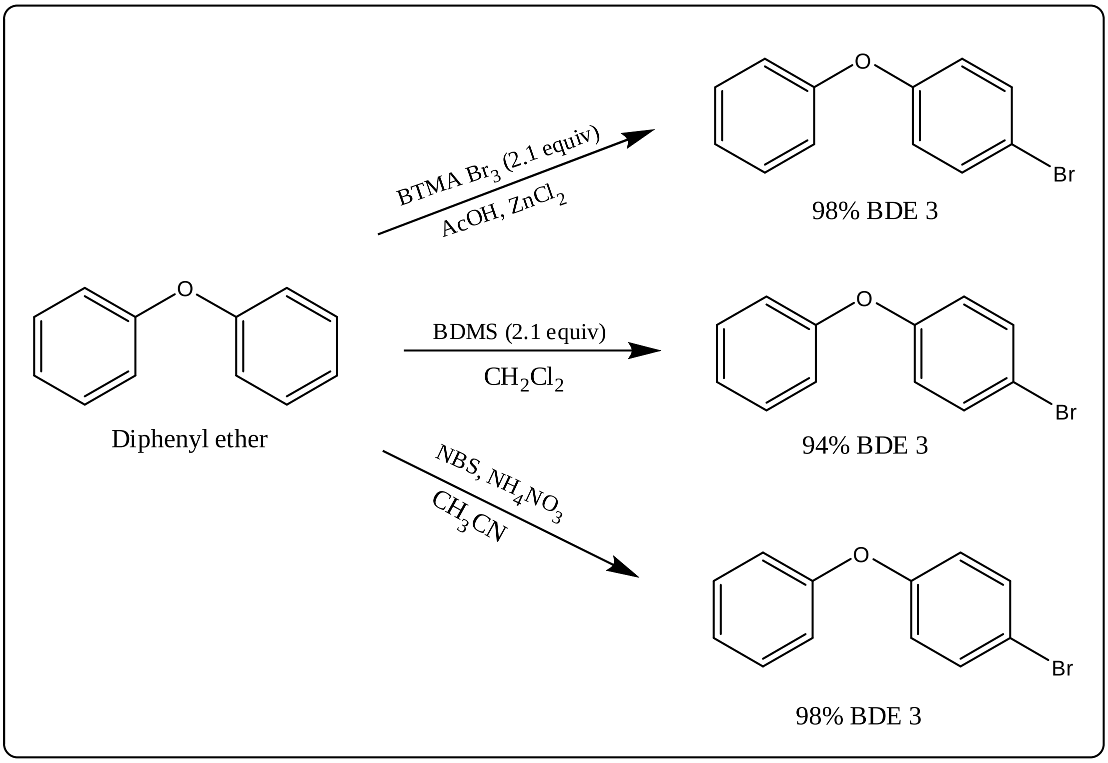


Figure 10: Structure of compound

Synthetic methodologies for PBDEs:

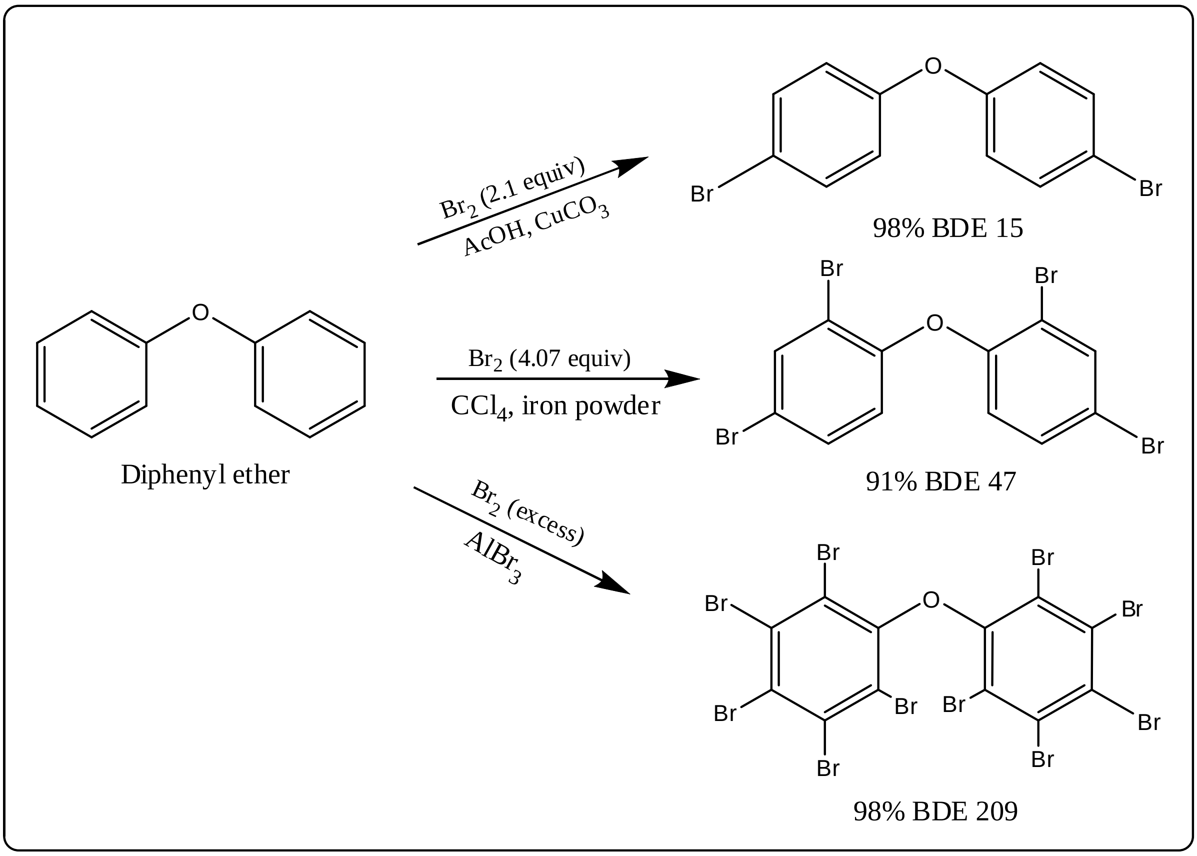
According to the above literature, PBDEs can be obtained from natural resources besides they can also be synthesized by various synthetic procedures. Some are described as following:

Mono brominated diphenyl ether was synthesized from diphenyl ether with reagent benzyl tri methyl ammonium tribromide (BTMA Br_3) in solvent acetic acid (AcOH) and catalyst zinc chloride ($ZnCl_2$) [35], or with reagent N-bromosuccinimide (NBS) in the presence of a weak acid ammonium nitrate (NH_4NO_3) and acetonitrile (CH_3CN) as a solvent [36], or with bromo dimethylsulfonium bromide (BDMS) reagent in the presence of solvent CH_2Cl_2 (dichloromethane) [37], described in **Scheme – 1**.



Scheme - 1

Brominated diphenyl ether was formed from 2.1 equivalents of bromine in solvent AcOH in the presence of catalyst copper carbonate ($CuCO_3$) gave 98% yield of BDE-15 [38], or with bromine (4.1 equivalents) in solvent tetrachloromethane (CCl_4) with iron powder gave 91% yield of BDE-47 [39], and by using excess of bromine with $AlBr_3$ yields 90% BDE- 209 **(Scheme 2)** [40].


Diphenyl ether
Br2 (2.1 equiv)
AcOH, CuCO3
98% BDE 15
Br2 (4.07 equiv)
CCl4, iron powder
91% BDE 47
Br2 (excess)
AlBr3
98% BDE 209
O
Br

Scheme -2

Chapter 3 Materials and method

Reagent grade chemicals and solventsethyl acetate, hexane, di-methylformamide (DMF), petroleum ether, DCM and methanol were purchased from S. D. Fine Chemicals, Mumbai and Merck. TLC analysis was done on silica coated aluminium plates (Aluchrosep Silica Gel) by observing under UV light in a chamber at 254 nm. Column chromatography was carried out in glass column using silica gel (mesh 100-200) as stationary phase. All the NMR analysis was performed using $CDCl_3$ as solvent and terta-methyl silane (TMS) as internal standard.

Synthesis

Synthesis was done by known procedure [41]. Brief details are given below:

2-(2’,4’-Dinitrophenoxy)-anisole (Compound 3)

Guai acol (0.5g, 4.02 mmol) and 2, 4-dinitroflourobenzene (0.20mL, 1.61mmol)were taken in round bottom flask and 6-8 mL DMF was added. To the solution, K_2CO_3 (0.33g, 2.41mmol) and catalytic amount of 18-crown-6 were added and stirred overnight at room temperature.By TLC monitoring progress of the reaction was checked.After completion of reaction, mixture was diluted with CH_2Cl_2 (100mL), washed with 1N NaOH (75mL) and water (100 mL) till neutral to litmus paper to finally dry over anhydrous Na_2SO_4. Organic solvent was evaporated and yellow coloured solid compound was obtained as crude product(1.087g). It was then purified by chromatography using SiO_2, hexane and ethylacetate(75:25, v/v) as solvent. Evaporation of organic solvent gave pure yellow solid product (1.039g). Product obtained was characterised by ^{1}H and ^{13}C NMR and was in line with the proposed structure. ^{1}H NMR (400 MHz,$CDCl_3$): δ3.7 (s, 3H), 6.8 (d, J= 9.16 Hz, 1H), 7.0(d, J = 7.76Hz, 1H), 7.2 (t, J = 8.24, 1.36Hz,1H), 7.3(t, J = 7.8, 1.8Hz, 1H), 8.2(t, J = 9.62, 2.76Hz, 1H), 8.8(d, J = 2.76Hz, 1H); ^{13}C NMR ($CDCl_3$):55.8, 113.2, 117.2, 121.6, 122.0, 122.5, 127.9, 128.6, 141.2, 150.9, 156.4.

2-(2’,4’-Diaminophenoxy)-anisole (Compound 2)

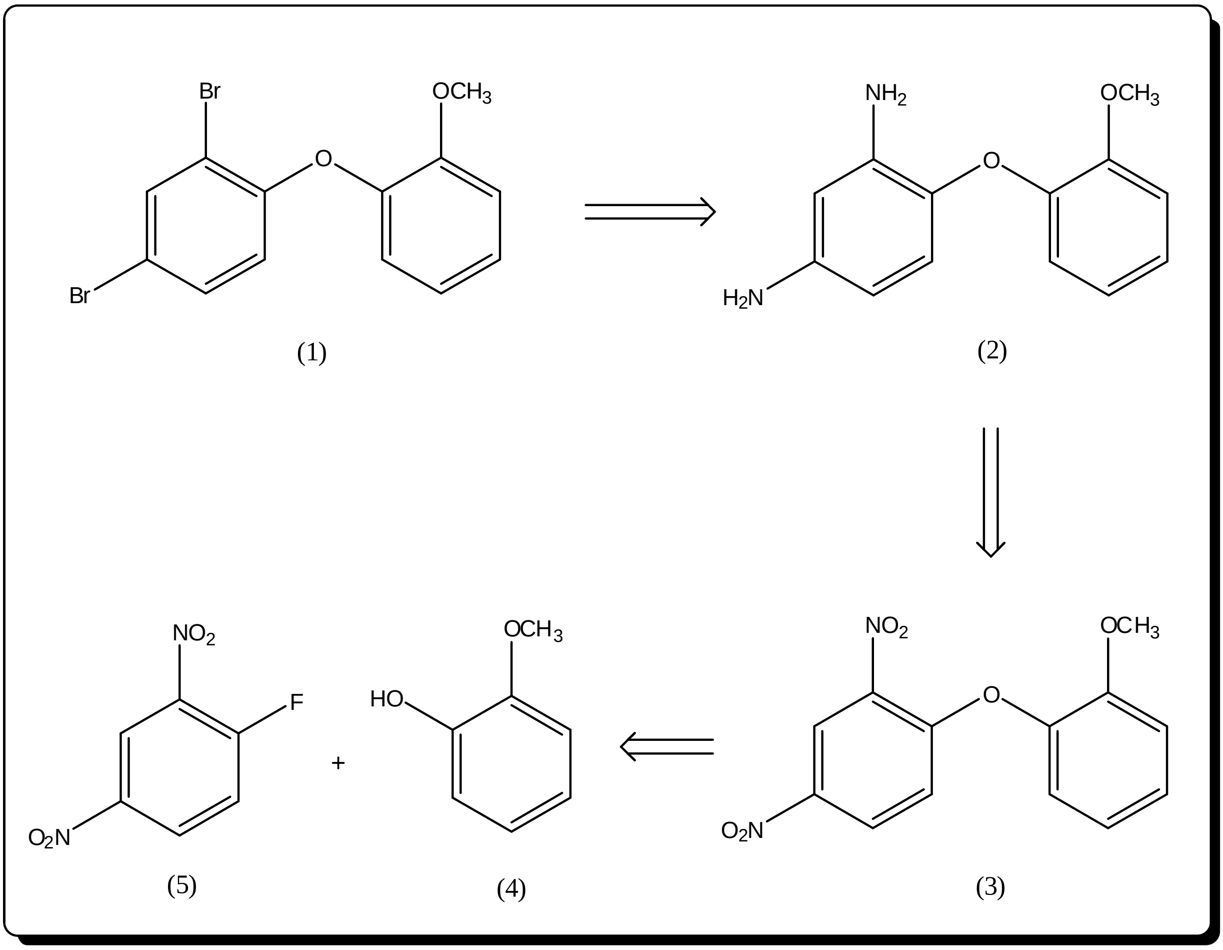
Compound 3 obtained above was dissolved in 50 mL methanol and5% palladium on charcoal (0.18g, 1.69mmol) added.Hydrogen gas balloon with positive pressure was installed and reaction stirred for 14-16 hours. Completion of reaction was analysed by TLC monitoring. After filtration through celite solvent was evaporated that gave crude product which was diluted with ethylacetate and 20% aqueous HCl (v/v) solution (2x30mL), to obtained salt. The salt was separated out and neutralized with 1N NaOH (75 mL). After extraction with solvent it was washed with water (150 mL) till neutral litmus paper and dried with Na_2SO_4. Evaporation of organic solvent gave pure product that was analysed by ^1H and ^{13}C NMR and compared with expected structure. ^1H NMR (400 MHz,$CDCl_3$):δ3.4(s, 4H), 3.8(s, 3H), 6.0(dd, J = 8.2, 2.72Hz, 1H), 6.1(d, J = 2.72, 1H), 6. 69(d, J = 8.27Hz, 1H), 6.73(dd, J = 8.24, 1.48Hz, 1H), 6.78(t, 6.4, 2.28Hz,1H), 6.94(dd, J = 10.52, 2.32Hz, 1H), 6.96(dd, J = 7.76, 1.36Hz, 1H); ^{13}C NMR ($CDCl_3$):55.8, 103.1, 105.6, 112.0, 116.0, 12.8, 121.8, 122.4, 135.6, 139.4, 143.6, 147.3, 149.4.

2-(2’, 4’-Dibromophenoxy)anisole (Compound 1)

In a two necked round bottom flask was added copper bromide (0.23g, 1.04 mmol), under inert conditions and tert-butyl nitrite (0.13g, 1.29 mmol), and anhydrous acetonitrile (3.5 ml). The apparatus equipped with reflux condenser was allowed to heat to 65℃ and inert atmosphere maintained. Amine (compound 2) (0.2g, 0.86 mmol) obtained above dissolved in acetonitrile was added drop wise over a period of 20 minutes and evolution of N_2 gas observed. After the evolution of gas stopped the reaction mixture was poured in hydrochloric acid and extracted with organic solvent. Evaporation of the solvent gave crude product that was optimized for separation by TLC and column chromatography performed.

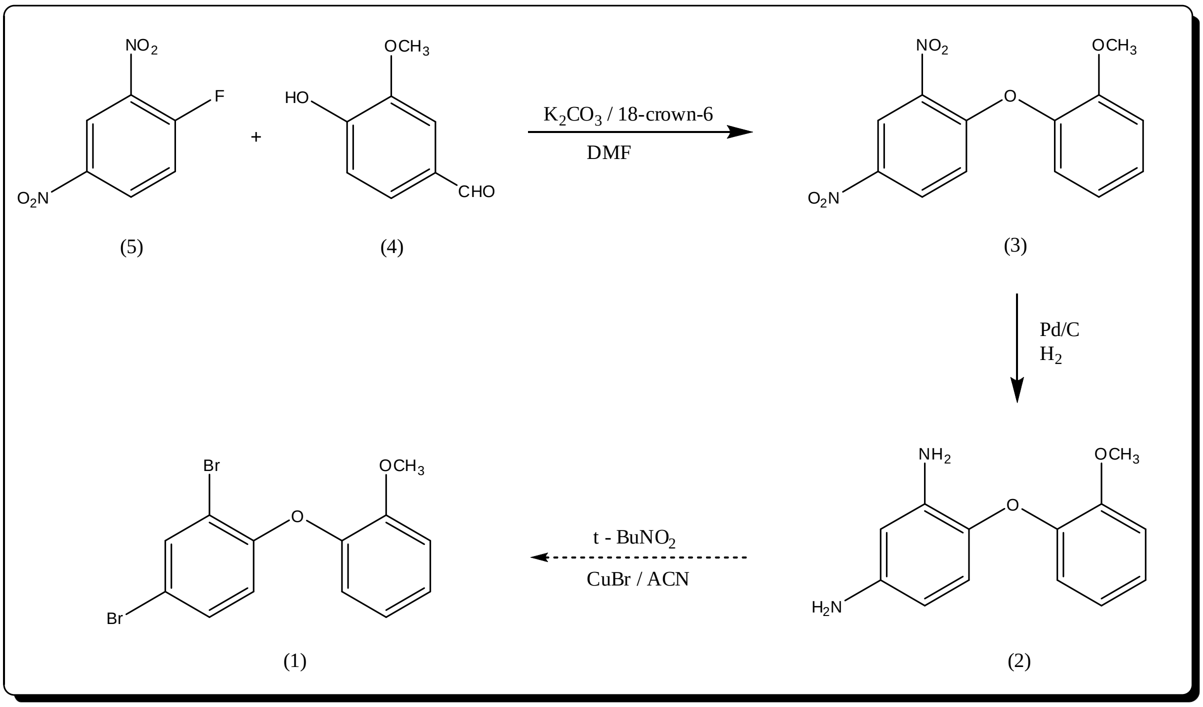
Chapter 4 Result and discussion

Synthesis of Poly brominated diphenyl ethers (PBDEs) has generated interest due to its wide applications like flame retardant materials, antibacterial and antifungal activities. They are used in the ship interiors, smoke detectors, electronic devices and many marine applications. In order to explore other applications and properties different attempts have been made. This work includes an attempt to synthesize a PBDE named 2-(2’, 4’-dibromophenoxy) anisole (1). Scheme – 1 gives the retro synthesis strategy to synthesize the molecule.



Scheme - 3: Retro synthetic strategy to synthesize 2-(2’, 4’-dibromophenoxy) anisole

Final compound (1) can be synthesized by bromination of corresponding amine (2). The amine required for the purpose can be obtained from corresponding nitro compound by its reduction. The nitro diphenyl ether can be synthesized by nucleophilic aromatic substitution of 2, 4-dinitro flourobenzene by corresponding phenol.



Scheme -4: Methodology to synthesize PBDE (1)

Initial diphenyl ether (3) was synthesized from 2, 4-dinitro flourobenzene (5) and 2-methoxy phenol (4) by nucleophilic aromatic substitution. The reaction was carried out at room temperature in the presence of mild base, potassium carbonate, and 18-crown-6 as phase transfer catalyst. The reaction was monitored using TLC and work up followed by purification by column chromatography gave pure compound (3). Melting point is 84-87°C. Mass spectroscopy gives peak at 290.0 m/z which matches with the molecular weight of our compound (3). ^{1}H NMR of compound was in line with its structure having three methoxy protons at 3.7 ppm and seven aromatic protons between 6.8 to 8.7 ppm. ^{13}C NMR of the compound also gave five quaternary and seven primary carbons in aromatic region. The carbon corresponding to methoxy group appeared at 55.3 ppm.

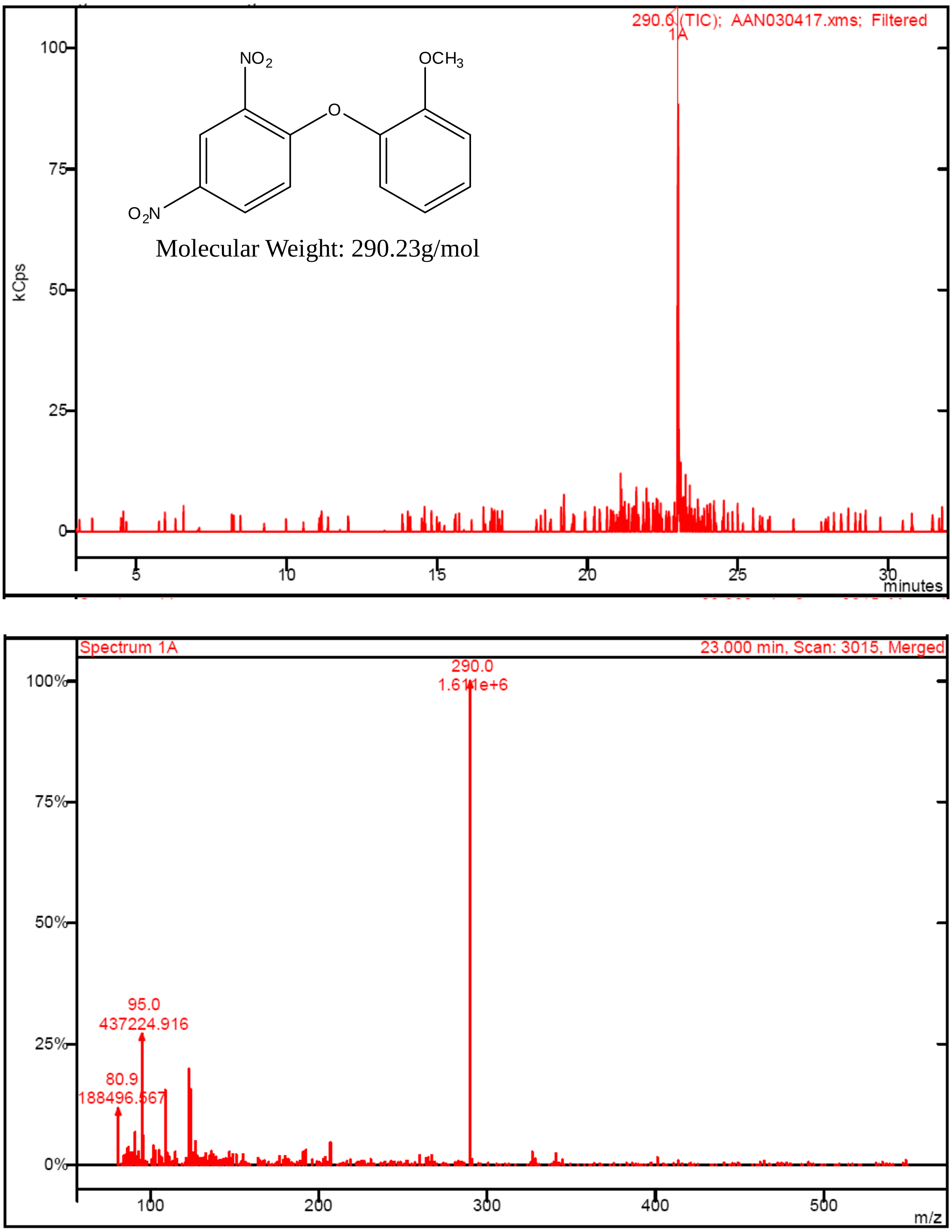


Figure 11: GCMS data of compound (3)

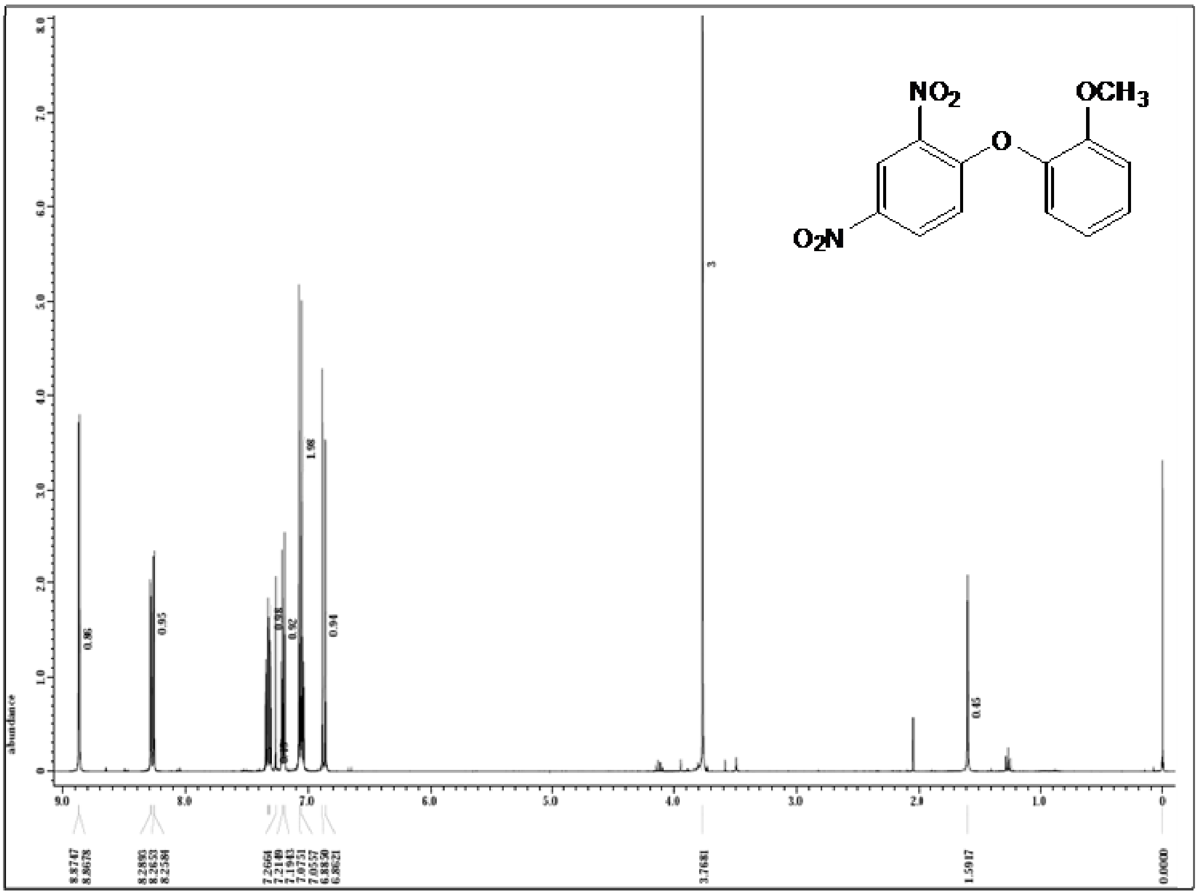


Figure 12: ^{1}H NMR data of compound (3)

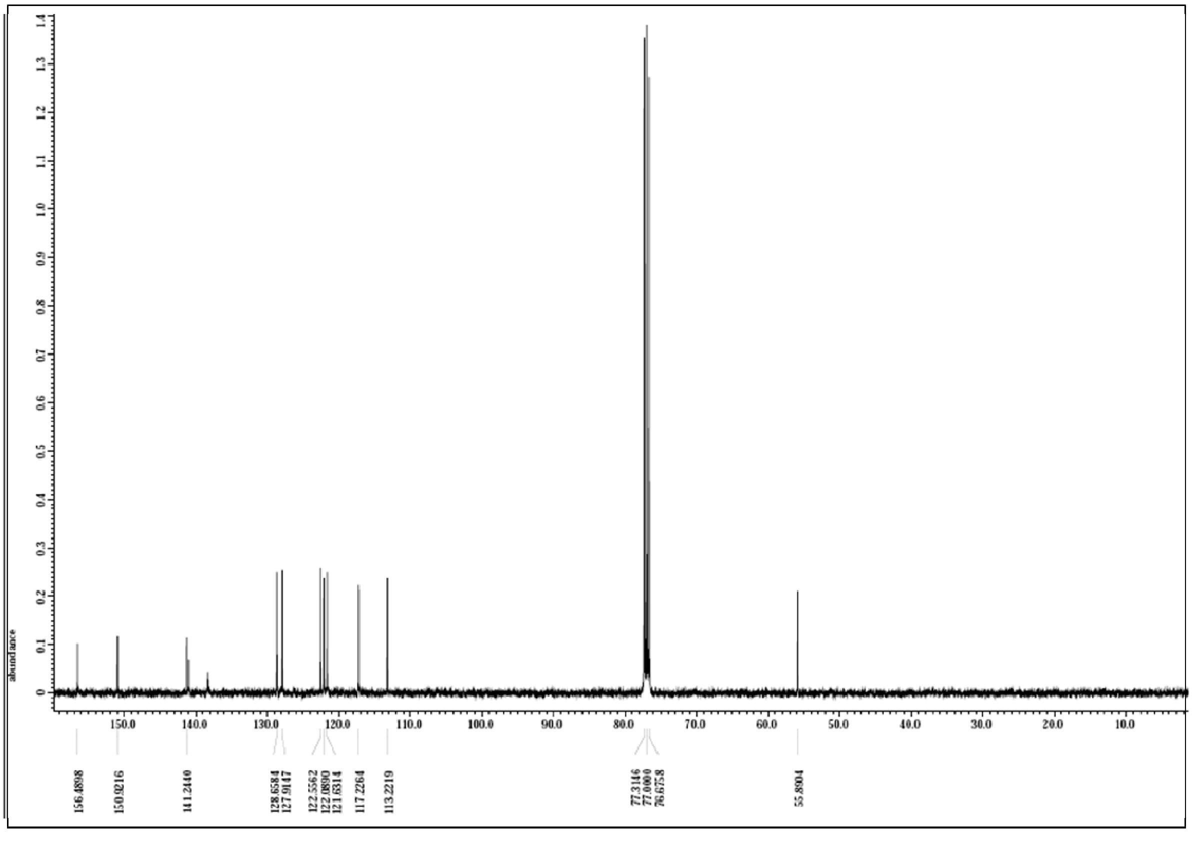


Figure 13: ^{13}C NMR data of compound (3)

Further reduction of compound – 3 was done using hydrogen gas with catalytic amount of 5% Pd over charcoal to offered amine (2). Methanol was used as a solvent in this case. Amine obtained was filtered over celite and solvent evaporated to afford pure product.

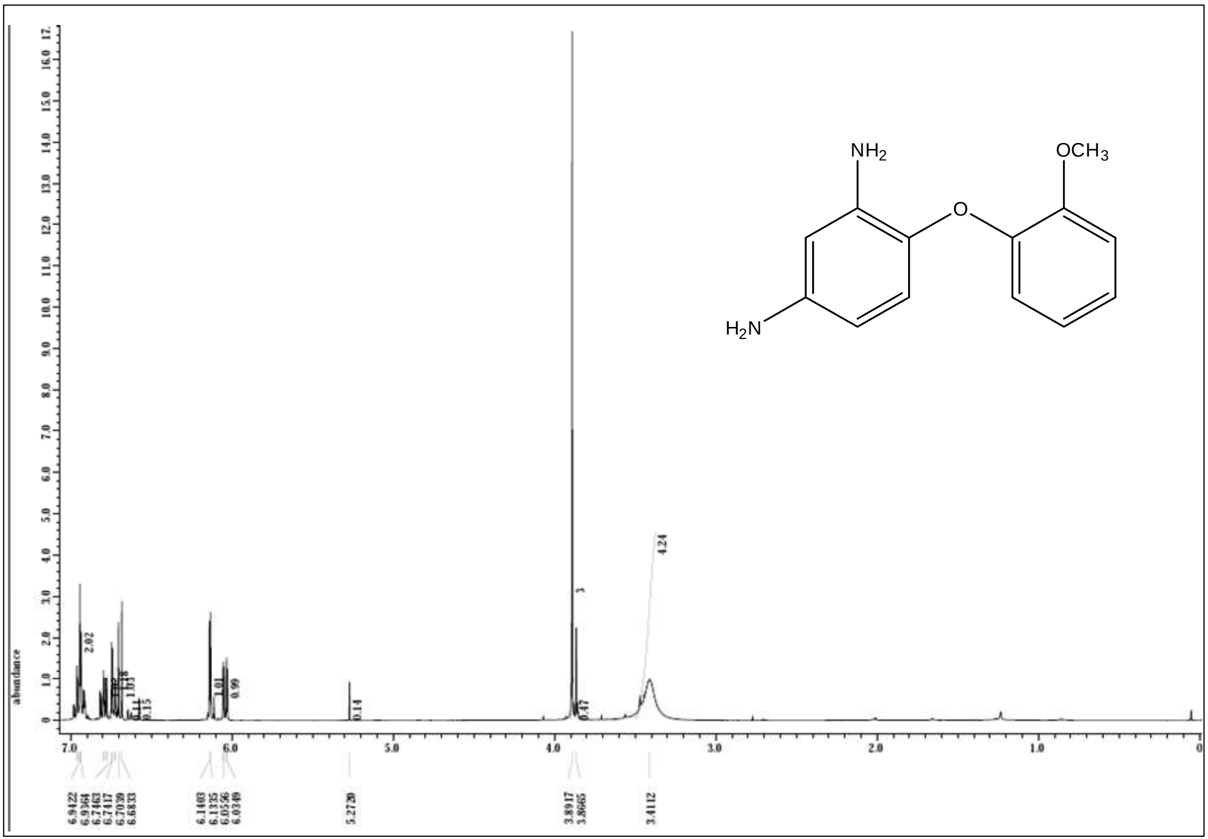


Figure 14: ^{1}H NMR data of compound (2)

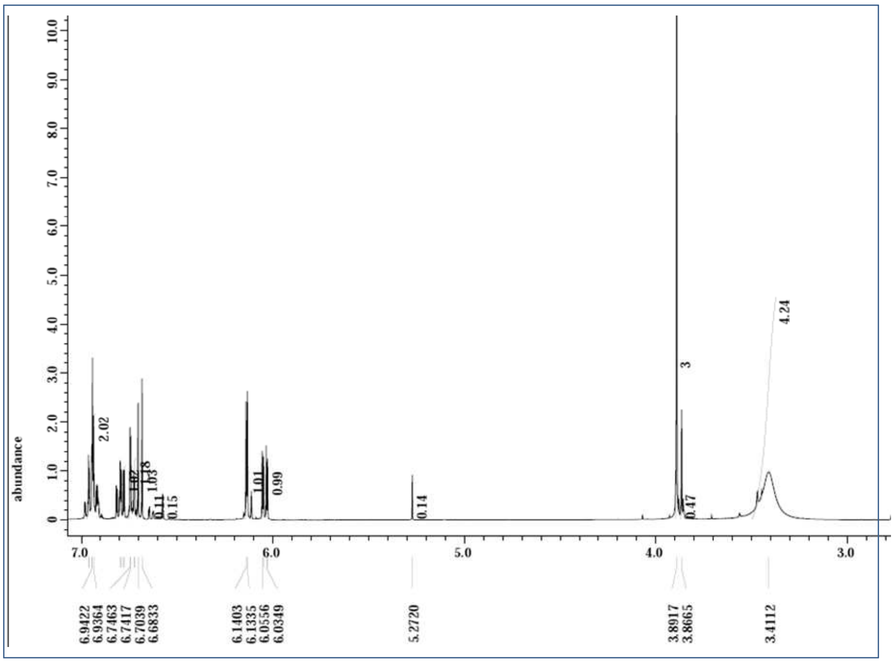


Figure 15: ^{1}H NMR spectra of compound (2) (close view)

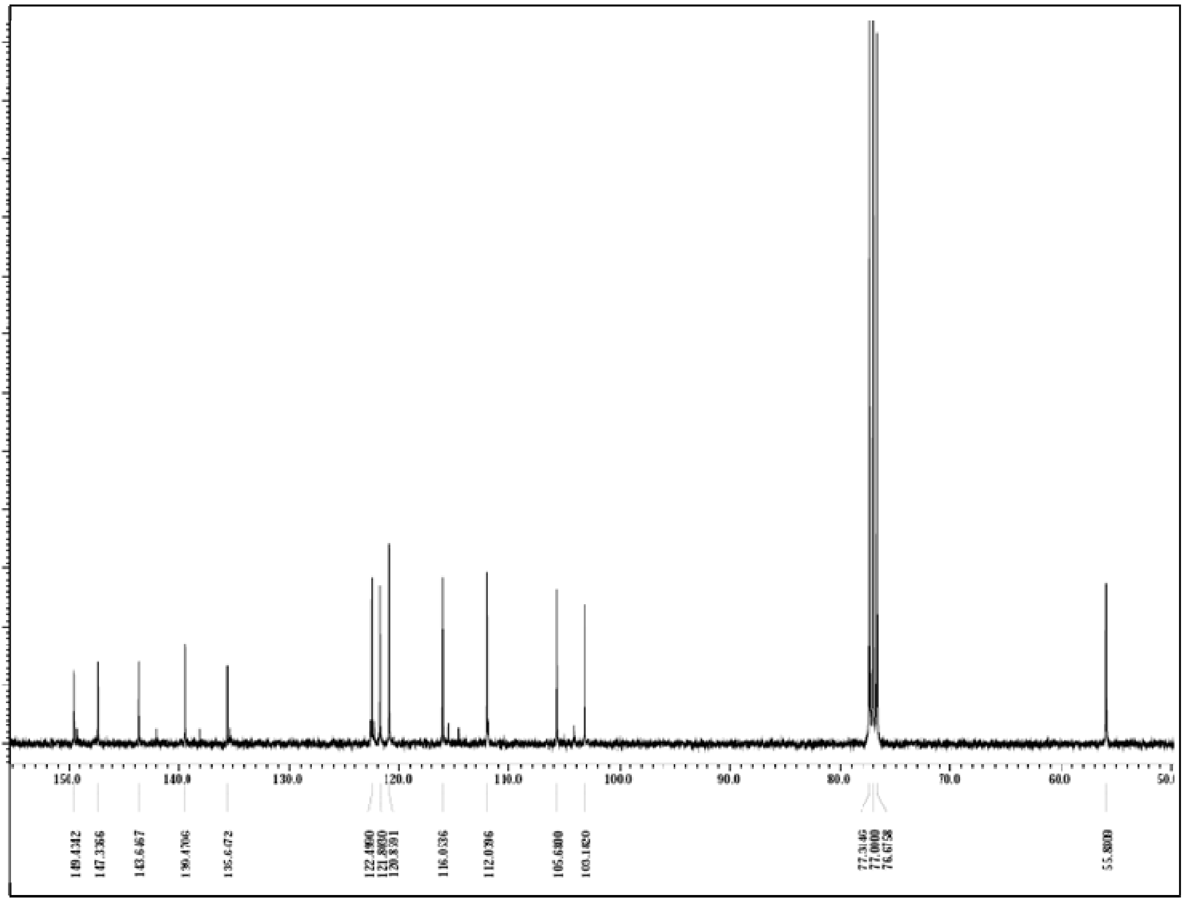


Figure 16: ^{13}C NMR data of compound 2

^{1}H NMR of the compound (2) gave a broad signal corresponding to four protons of NH_2 group at 3.4 ppm. The signal due to methoxy group and aromatic protons appeared at 3.8ppm and 6.0 to 6.9 ppm respectively.^{13}C NMR of the compound gave five quaternary and seven primary carbons in aromatic region and peak appeared at 55.3 ppmcorresponds to the carbon of methoxy group.

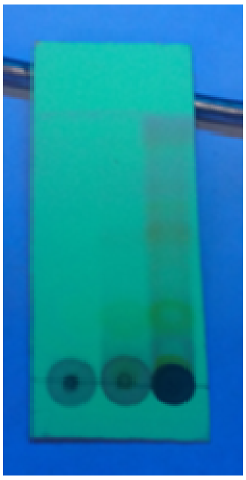


Figure 17: TLC spots of compound 1

Synthesis of final product (1) was attempted using a known procedure [42]. It required diazotisation of synthesized amine (2) using t-butyl nitrite under inert conditions followed by addition of $CuBr_2$ in acetonitrile to give corresponding bromo compound. The reaction was monitored using TLC which gave multiple spots (Figure -17). Purification of reaction mixture using hexane ethyl acetate gave three spots. However, the spot expected to be bromo product did not match with the proposed structure due to absence of any methoxy signal, though aromatic protons appeared between 6.5 and 7.1ppm.

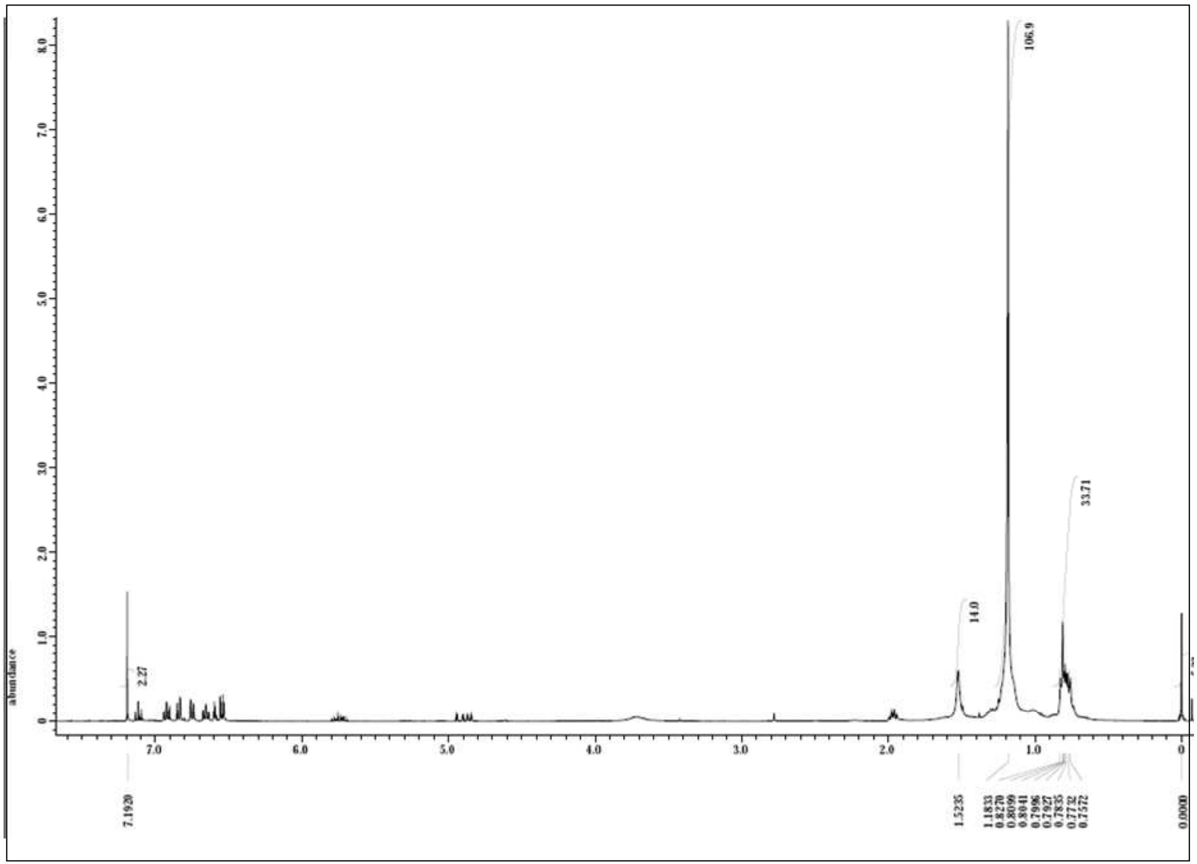


Figure 18: ^{1}H NMR data of 1st spot of PBDE

Thus, an attempt was made to synthesize 2-(2’, 4’-dibromophenoxy) anisole by three steps that included nucleophilic aromatic substitution reductions and bromination.

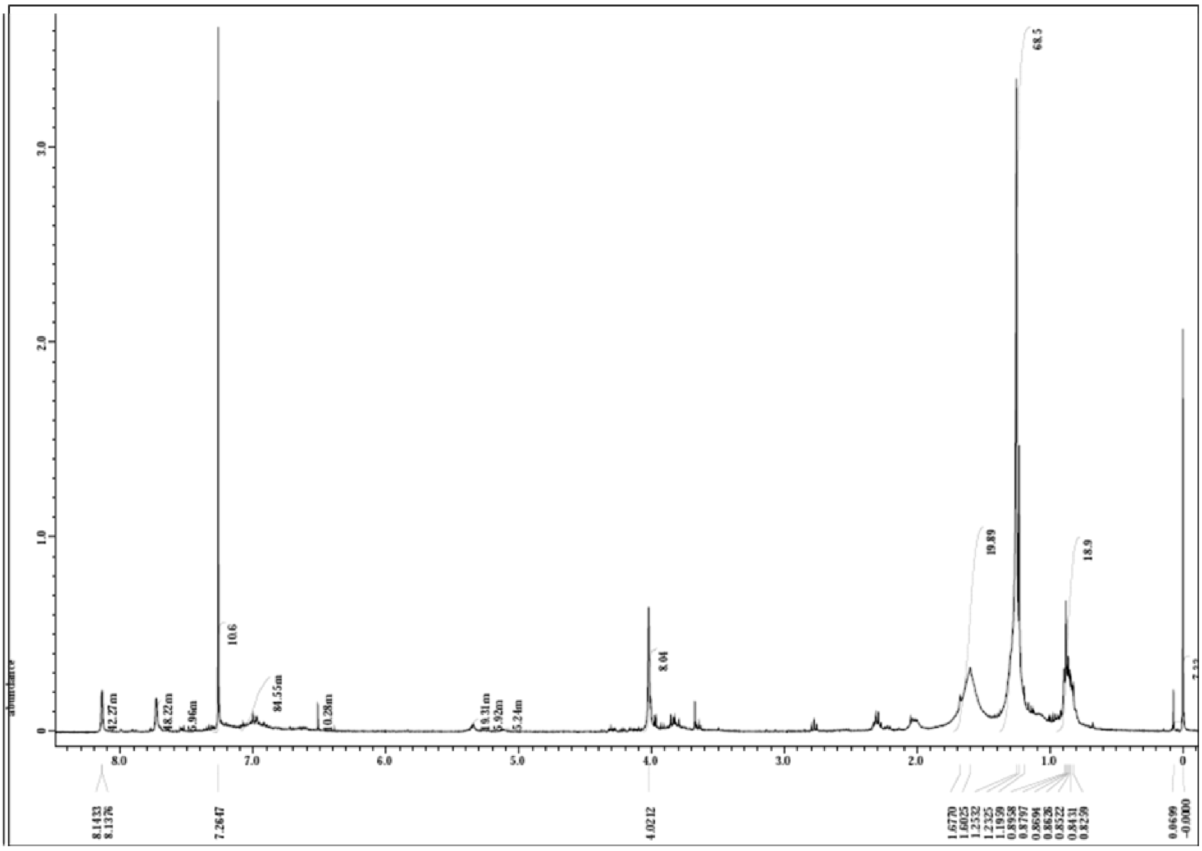


Figure 19:^{1}H NMR data of yellow spot of PBDE

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