Synthesis and Analysis of 2-(2-Formyl-4-nitrophenoxy) phenyl palmitate

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

MASTERS OF SCIENCE
IN
CHEMISTRY

Submitted by
Sanchita
(Roll No. 3021021025)

THAPAR INSTITUTE
OF ENGINEERING & TECHNOLOGY
(Deemed to be University)

Under the Supervision of

Dr. Manmohan Chhibber
Professor, SCBC

Dr. Ranjana Prakash
Professor, SCBC

School of Chemistry and Biochemistry
Thapar Institute of Engineering and Technology
Patiala
July, 2023

CERTIFICATE

This is to certify that the dissertation entitled **Synthesis and Analysis of 2-(2-Formyl-4-nitrophenoxy) phenyl palmitate** being submitted by **Sanchita**(Roll N0. 302102025) to **School of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology**, Patiala in partial fulfillment of the requirements for the award of degree of Master of Science in Chemistry, is an authentic record of the work carried out by the candidate under our guidance and supervision. She has fulfilled the requirements for submitting this dissertation, which has reached the requisite standard to our knowledge.

The results embodied in the dissertation have not been submitted in part or in full to any other university or institute for the award of any other degree or diploma.

Dr. Manmohan Chhibber
Professor
SCBC
TIET, Patiala, Punjab-147004

Ranjana Prakash

Dr. Ranjana Prakash
Professor
SCBC
TIET, Patiala, Punjab-147004

DECLARATION

I, hereby declare that the dissertation entitled **Synthesis and Analysis of 2-(2-Formyl-4-nitrophenoxy) phenyl palmitate** being submitted in the partial fulfilment of the requirements for the award of the degree of Master of Science in Chemistry to **School of Chemistry and Biochemistry**, Thapar Institute of Engineering and Technology, Patiala is a record of my work carried out under the supervision of **Dr Manmohan Chhibber,** Professor, School of Chemistry and Biochemistry(SCBC) and **Dr Ranjana Prakash**, Professor, School of Chemistry and Biochemistry(SCBC), Thapar Institute of Engineering and Technology(TIET), Patiala from January 2023 to July 2023.

Further, the results embodied in the dissertation have not been submitted in part or in full to any other university or institute for the award of any other degree or diploma.

Sanchita

Place: Patiala **Sanchita**

Date:25/7/23 Roll No.302102025

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

Ranjana Prakash

Dr. Manmohan Chhibber
Professor
SCBC
TIET, Patiala, Punjab-147004

Dr. Ranjana Prakash
Professor
SCBC
TIET, Patiala, Punjab-147004

ACKNOWLEDGEMENT

I would like to thank the following individuals for their contributions to the completion of my thesis:

First and foremost, I want to thank my supervisor, **Dr. Manmohan Chhibber, Professor, School of Chemistry and Biochemistry, TIET, Patiala**, for his helpful advice, support, and constant encouragement throughout the whole study process. His knowledge, intelligent input, and determination were invaluable in the completion of this thesis.

I would also like to thank **Dr. Ranjana Prakash,Professor, School Of Chemistry and Biochemistry, TIET, Patiala** for her continuous support in my dissertation. I thank her for her patience and motivation.

I am truly grateful to **Dr. Satnam Singh, Head of Department, School of Chemistry and Biochemistry, TIET, Patiala,** for his perpetual help and support in the completion of my post-graduate program.

Special thanks to all the **Teaching Faculty** of the department for their cooperation and guidance.

I would also like to express my gratitude to **Mr. Ashok** and Ms.**Aashima Mahajan**, research scholars, for their help and valuable suggestion. I express my sincere thanks to my lab matesMs. **Maansi Sharma** and **Ms. Vanshika** for the fun and support. Special thanks to Maansi for helping at the bench and for her excellent company.

I want to thank all my friends for their continuous support and encouragement during this journey. Their faith in me, motivating conversations, and words of support supplied the spark I needed during times of self-doubt.

Finally, I want to thank my wonderful family for their unfailing love, understanding, and constant support during my academic journey. Their support, patience, and sacrifices were the foundation of my success, and I will be always grateful to them. Last but not the least; I thank the almighty for everything that I am blessed with.

Sanchita

Place: Patiala **Sanchita**

Date:25/7/23. Roll No.302102025

CONTENTS

LIST OF FIGURES

LIST OF SCHEMES

Synthesis and Analysis of
2-(2-Formyl-4- nitrophenoxy) phenyl palmitate

ABSTRACT

Diphenyl ethers are essential compounds due to their antibacterial characteristics and materialistic purposes. Many of these have been obtained from natural sources and have various roles in the pharmaceutical and material worlds. Diphenyl ethers with long chain hydrocarbons have wide range of applications in different areas. The work presented here describes the synthesis and analysis of compound 2-(2-formyl-4-nitrophenoxy) phenyl palmitate **(Compound-G)** starting from compound 2-Bromo-5-nitrobenzaldehyde **(Compound-A).** All the synthesized **(compounds A-G)** were characterized by ^{1}H and ^{13}C-NMR spectroscopy. A detailed analysis of both the compounds- **E** and **G** was done using HRMS data.

CHAPTER-1

INTRODUCTION

Diphenyl Ether [$(C_6H_5)_2O$], represents a class of organic compounds consisting of two phenyl (C_6H_5) groups linked by an oxygen atom as shown in **Figure 1**."At room temperature, it is a colorless solid with a pleasant geranium-like aroma[1]. It has unique electronic and physical characteristics because of the two aromatic rings present in the structure.

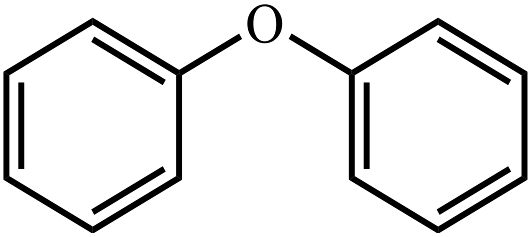
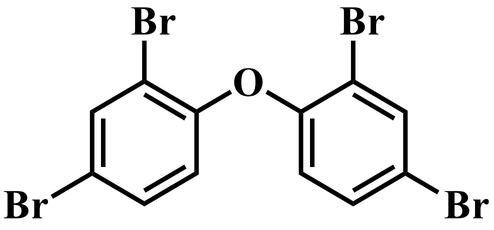


Figure -1: Molecular structure of Diphenyl Ether

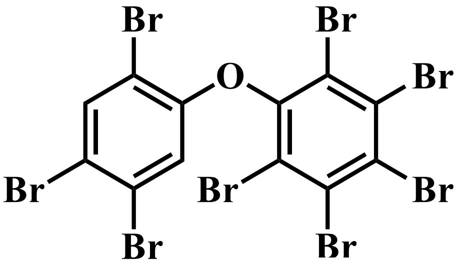
This molecule is highly soluble in lipid-based solvents but is poorly soluble in water. The vapour pressure of diphenyl ether at 20^0C is 6×10^{-2} torr[2]. Due to its beneficial properties, such as its excellent solvating power, low toxicity, and high thermal stability, it has a wide range of uses. This molecule is employed as a heat transfer agent and is frequently referred to as thermal oil due to its low vapour pressure and strong thermal stability. Heat transfer fluid is a eutectic combination of 73.5% diphenyl ether and 26.5% biphenyl, also known as Dowtherm A, Thermex, Diphyl, and VOT[3].

Among other things, the production of polyesters and soap fragrance both employ diphenyl ether. Diphenyl ether is employed as a chemical bridge in the halogenation, acylation, and alkylation of substances as well as the production of surfactants. They have unique properties that make them useful as building blocks in the synthesis of new compounds and materials.

Industrial procedures are used to create synthetic substances called polybrominated diphenyl ethers, which have bromine atoms bonded to the structure of the diphenyl ether molecule. They are serves as flame suppressants[4]. There are 209 congeners - a term given to describe the family of PBDEs - that are possible. **Compounds-1** and **2** are a few examples of polybrominated diphenyl ethers. Some of these are used in variety of polymers as electrical circuits, plastics, textiles, and other products to prevent the spread of fire.

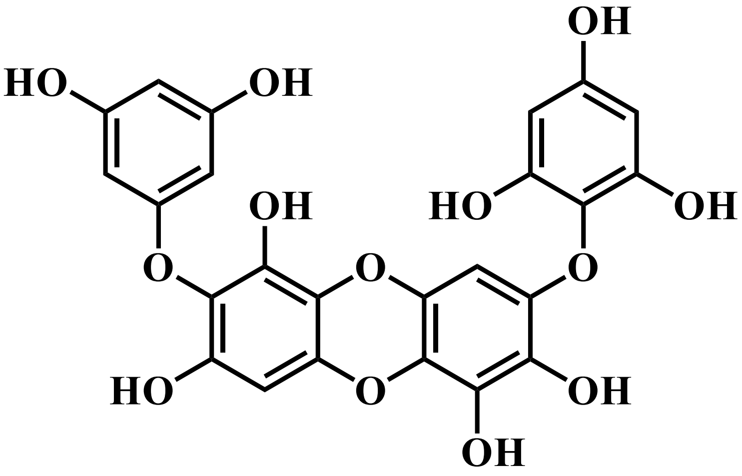


Compound -1



Compound -2

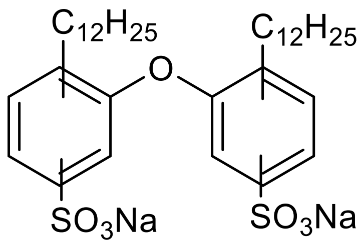
In addition to synthetic ones, there are also naturally occurring diphenyl ethers. Brown algae and other marine organisms include compounds such as diphlorethohydroxycarmalol (DPHC) **[Compound-3]** which is naturally occurring chemicals containing diphenyl ether moiety. The antioxidant DPHC, which was isolated from the brown algae *Ishige okamurae*, lowers reactive oxygen species and has protective effects against high glucose-induced oxidative stress linked to diabetes in humans[5]. DPHC exhibit a preventive effect against UVB-caused damage[6].



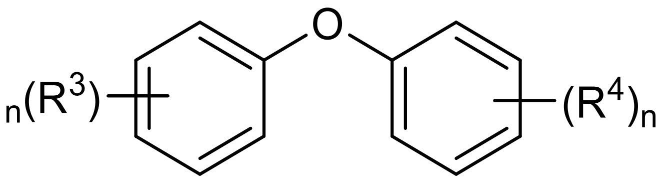
Compound -3

Many diphenyl ethers with long hydrocarbon chains on the phenyl ring have been synthesized and found to have many uses in various fields. Di-tetrapropylene diphenyl ether disulfonate **(Compond-4)** has been discovered to be an anionic gemini surfactant comprised of two tetrapropylene benzene sulfonates joined by an oxygen spacer[7]. Gemini surfactants are dimeric compounds with two hydrophobic chains and two hydrophilic heads connected by a spacer.

These surfactants have the potential to be tens to thousands of times more surface active than ordinary surfactants. **Compound-4** was discovered to have higher surface activity as a gemini surfactant, and the electrical conductivity results suggested that **Compound-4** formed micelles more easily[8].



Compound -4



R^3, **R^4** = Hydrocarbon chain of 10-26 carbons.

Compound -5

Alkyl diphenyl ethers are of interest as lubricants for specialized applications. High temperatures and speeds in bearing lubrication may cause oil film shortages or degradation, causing the lubricant's base oil to evaporate and damage the bearing, reducing the machine's lifetime. Various base oils, such as polyphenyl ether, silicone oil, and fluorinate oil, are used in lubrication. Alkyl diphenyl ether **(Compound-5)** has been identified for its exceptional heat and oxidation stability, with negligible evaporation at high temperatures and little viscosity fluctuation. Because of its unique feature, it has found to be excellent foundation oil for heat-resistant grease. This kind of grease has a broad range of uses, including ball bearings, roller bearings, and vehicle electric auxiliary machinery[9].

As previously stated, diphenyl ethers with long hydrocarbon chains have shown great value in a variety of sectors. This thesis focuses on synthesizing and analyzing 2-(2-Formyl-4-nitrophenoxy) phenyl palmitate , which possesses an ester group with a long hydrocarbon chain. This unique feature presents exciting prospects for future applications and developments.

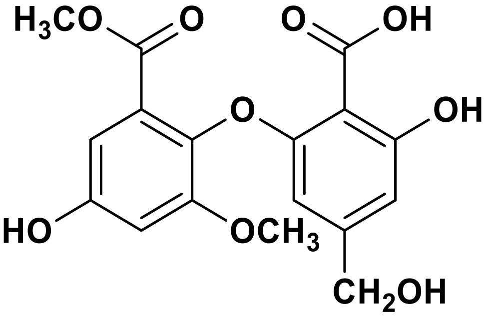
CHAPTER-2

LITERATURE REVIEW

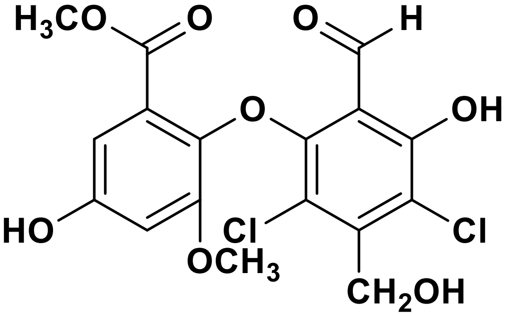
Diphenyl ether derivatives have been demonstrated to have antiinflammatory[10], antimicrobial[11], antimalarial[12], and antiandrogenic properties[13]. These have been found in different kinds of marine organisms. Because of their promising biological effects, numerous publications have emerged regarding the utilization of organic chemistry as a technique for synthesizing these compounds..

Isolation from Natural Products

Diphenyl ether **(Compound-6)**, a polyketide isolated from the marsh fungus *Aspergillus flavipes,* displayed higher inhibitory effects than acarbose[14]. Among the identified compounds, one was a previously reported diphenyl ether **(Compound -7)**, which showed glucosidase inhibitory action. Because of the enzyme's capacity to absorb dietary carbohydrates, α-glucosidase inhibitors are thought to be helpful for diabetes therapy[15].

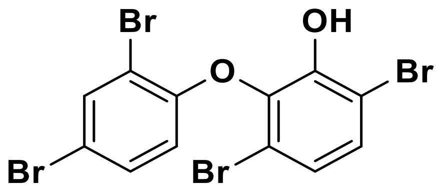


Compound-6

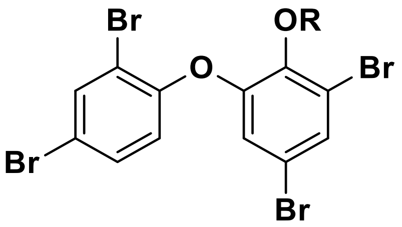


Compound-7

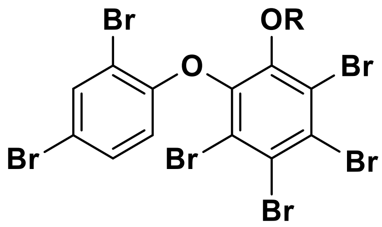
Polybrominated diphenyl ethers are a kind of brominated flame retardant that is used as a constituent in polymers for electronic devices, as well as in textiles[16]. Both hydroxylated and methoxylated PBDEs are recognized natural compounds. Both of them have been found in fish and wildlife from the Baltic Sea. **Compound-8** has been found in plasma of Baltic salmon. Red algae have been identified as the rich source of these compounds. **Compounds-9 and 10** have been isolated from red macroalga *Ceramium tenuicorne*[17]. Another OH-PBDE **(Compound-11)** and MeO-PBDE **(Compound-12)** have been found in Blue mussels (*Mytilus edulis*).



Compound- 8

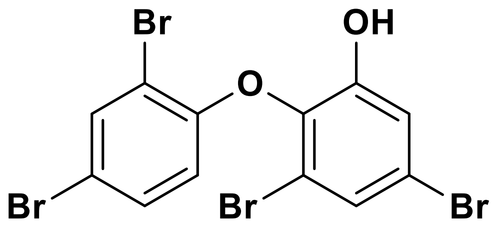


Compound	R
9	H
10	CH_3

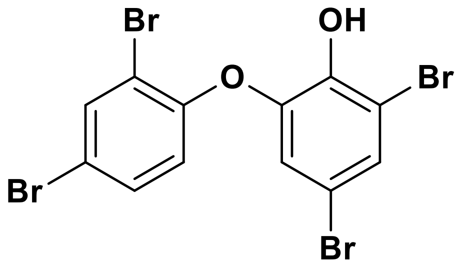


Compound	R
11	H
12	CH_3

Tie2 kinase is an enzyme that promotes angiogenesis, which is required for tumour development and survival. Tie2 kinase was discovered to be inhibited by a crude extract produced from a sponge of the *Dysidea* genus. The crude extract yielded two polybrominated diphenyl ethers **(Compound-13 and 14)** that inhibit Tie2 kinase[18].

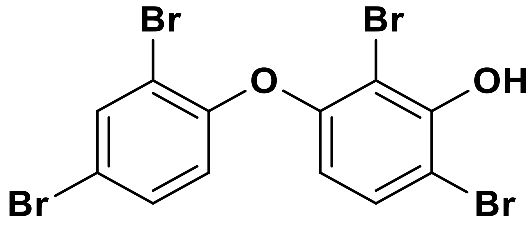


Compound-13

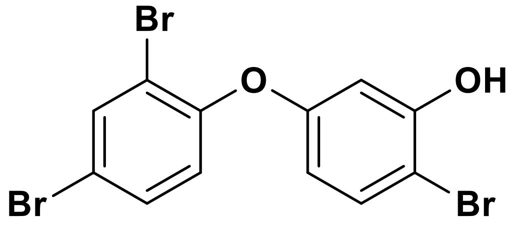


Compound-14

Recently some of the hydroxylated PBDEs have been isolated from rat faeces. Hydroxylated tetrabrominated diphenyl ethers **(Copound-15)** and Hydroxylated tribrominated PBDEs **(Compound-16)** were found in the rat faeces[19].

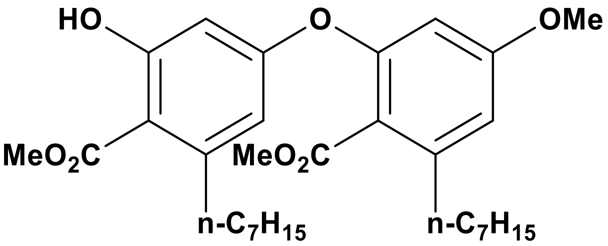


Compound-15

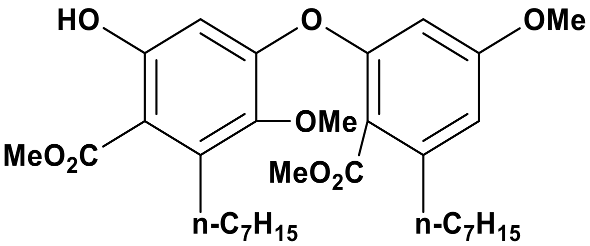


Compound-16

Two diphenyl ethers **(Compounds-17 and 18)** with a long hydrocarbon chain and a methyl ester group on the phenyl ring were discovered and isolated from the lichen *Micavea pvasina* Fr[20].

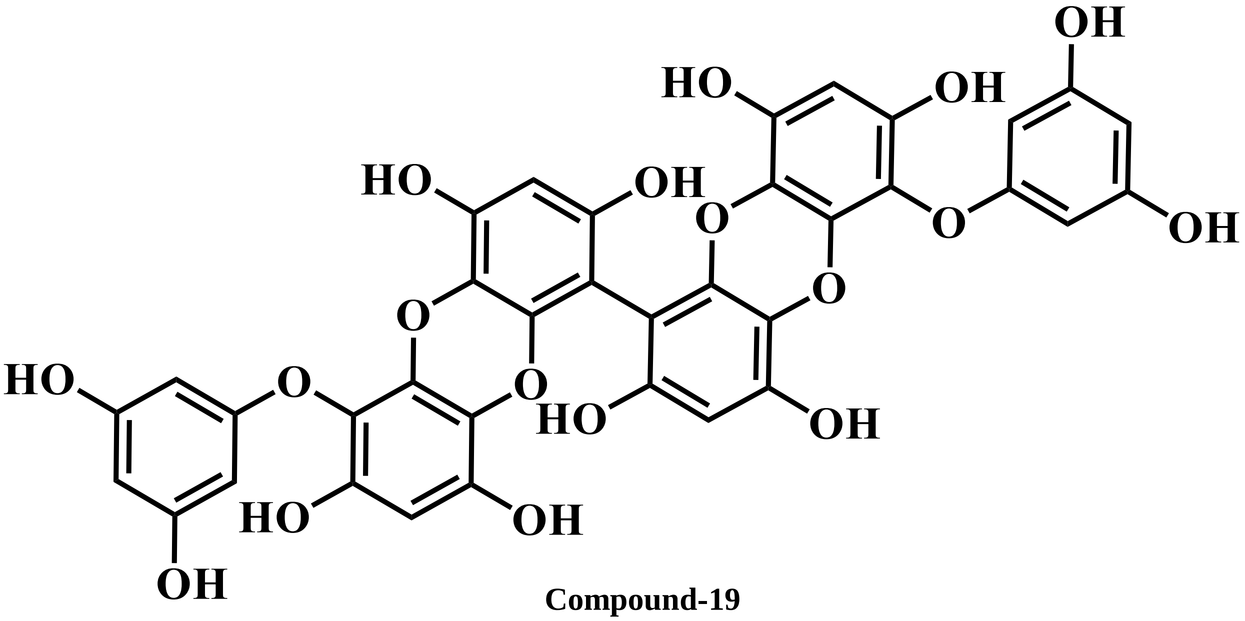


Compounds-17



Compounds-18

Ecklonia cava (brown algae) produced 6, 6'-Bieckol **(Compound-19)**, which has been isolated. It has anti-inflammatory, anti-oxidant, and anti-microbial properties. **Compound-19** was discovered to have an HIV-1 inhibitory mode of action by reducing the activities of HIV-1 RT polymerase and ribonuclease. This compound effectively limit HIV-1 proliferation and reverse transcriptase actions[21]. Additionally, it can be used to treat obesity[22].



Compound-19

As a result, the natural world offers a plentiful supply of diphenyl ether derivatives that have been found effective in a variety of biological applications.

<u>Synthesis of Diphenyl ethers</u>:- Diphenyl ethers have been synthesized since the beginning of the 20th century and their yearly output has grown to several thousand tonnes since 1930s (Kirk and Othmer, 1965)[23].

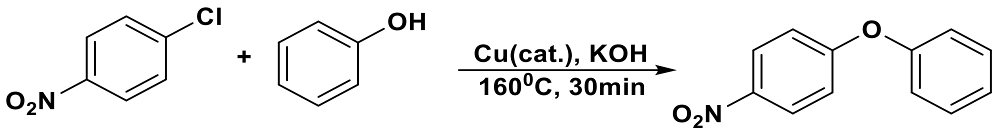
Historical Background: - Synthesis of diphenyl ether has an interesting historical background that can be summarized as follow:

Dr. K. List and H. Limpricht discovered diphenyl ether for the first time in 1854. They were studying the products obtained from distillation of copper benzoate and isolated a substance during fractional distillation they called phenyl oxide. Fittig and Kekule also attempted to create this molecule using different methods, but they were unable to create the necessary phenyl oxide.

In order to confirm its existence, W. Hoffmeister carried out an experiment in 1871[24]. He used steam distillation instead of fractional distillation to isolate this compound from phenyl benzoate and obtained the diphenyl ether in much pure state.

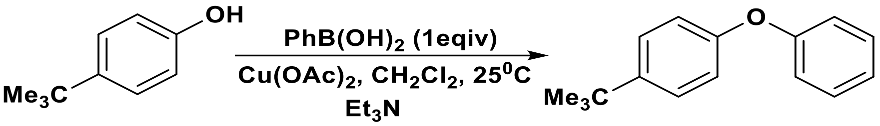
In 1850, Alexander William Williamson postulated the Williamson ether synthesis, an SN^2 mechanism for ether formation involving the interaction of an alkoxide and a haloalkane[25].

In 1904, Ullmann pioneered the development of the copper-mediated arylation method, which involves coupling phenol with aryl halides[26]. This transformational method, known as the Ullmann condensation , which involves the conversion of aryl halides to a variety of compounds such as aryl ethers, thioethers and nitriles. .An illustrative demonstration of this method can be seen in the synthesis of 1-nitro-4-phenoxybenzene through the reaction of 4-chloronitrobenzene with phenol using copper with a base at elevated temperatures **(Scheme-1)**.



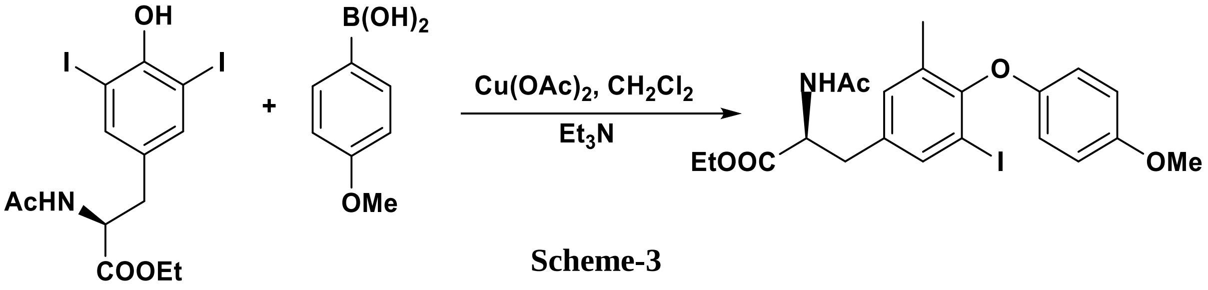
Scheme-1

Ullmann ether synthesis required high temperatures with base and may produce inconsistencies in functionalized systems. Later, Chan and colleagues describe the coupling of arylboronic acids with several nitrogen-containing substrates at room temperature to give the N-arylated compounds[27]. **Scheme-2** depicts the synthesis of desired compound in methylene chloride from 4-tert-butylphenol and phenylboronic acid.



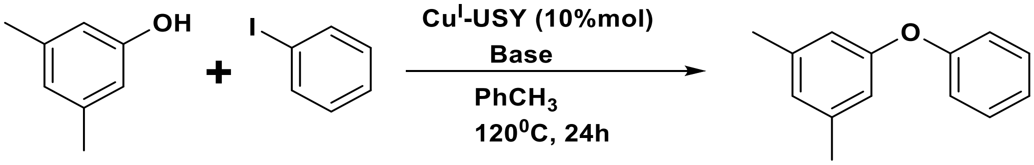
Scheme-2

The reaction, on the other hand, was conducted under ambient conditions, endures a wide range of substituents, providing good yields. Evans used this approach to successfully synthesise diphenyl ether, a critical intermediary in the synthesis of L-thyroxine, by combining phenol and 4-methoxybenzeneboronic acid[28] **(Scheme-3)**.



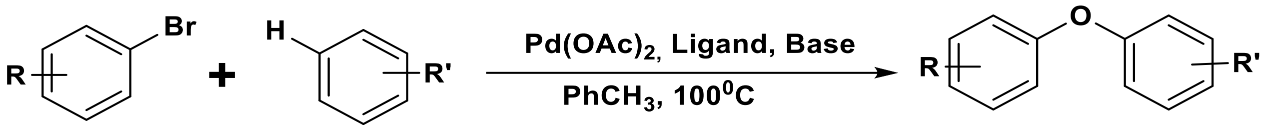
Scheme-3

At 120 °C, using Cu (I)-USY as the catalyst and cesium carbonate as the base, electron-rich phenols like 3,5-dimethylphenol exhibit good reactivity with simple aryl iodides or bromides, resulting in the synthesis of diaryl ether **(Scheme-4)**. Even at greater temperatures, up to 140 °C, the reaction remains efficient. One of the most obvious benefits of employing a copper catalyst is its reduced cost and toxicity when compared to other choices. While typical bases such as potassium phosphate are often used in such couplings, cesium carbonate proved to be the preferable option with Cu (I)-USY as the catalyst, delivering greater conversion rates and yields than potassium phosphate[29].

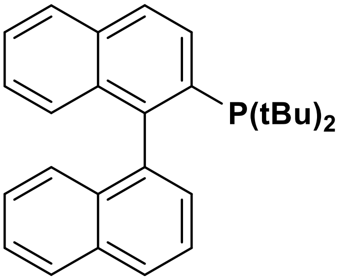


Scheme-4

The use of metal catalysed cross coupling reactions, such as palladium and copper, has become more important in the synthesis of diphenyl ethers. Buchwald synthesised a number of diphenyl ethers (Scheme-5) in 1999 utilising a variety of electron deficient, electron rich, and alkyl halides[29]. In the presence of biphenyl phosphine ligands, the paladium catalysed reaction produced the required product.

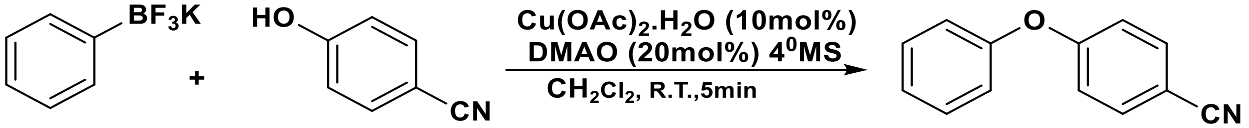


Scheme-5



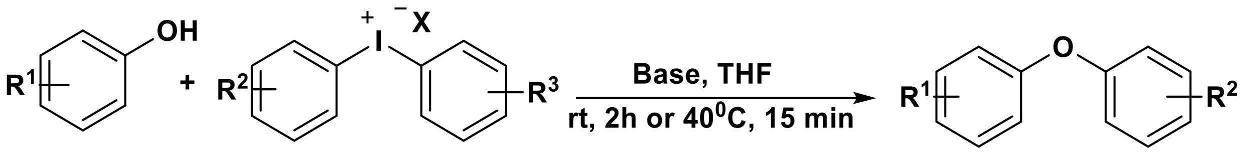
Ligand

Pd-based techniques often need the use of costly catalyst/ligand combinations. Cross coupling reaction between alcohols or phenols and organometalloid reagents has been investigated as an alternate approach for ether production. Quach and Robert A. Batey made an important breakthrough in this field by developing a mild and practically neutral copper (II)-catalyzed etherification approach for aliphatic alcohols **(Scheme-6)**. A catalytic quantity of copper (II) acetate is used in combination with DMAP as a ligand in this method, while the presence of four molecular sieves and an oxygen environment accelerates the reaction further. [30].



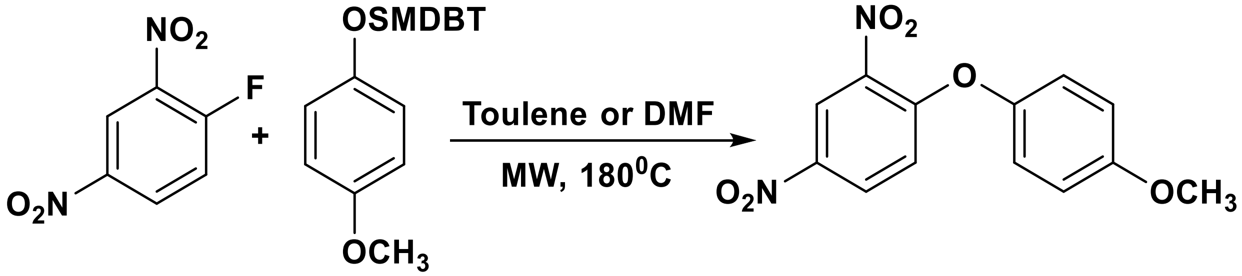
Scheme-6

Berit olofsson discovered a technique for high-yielding diaryl ether synthesis using mild and metal-free conditions **(Scheme-7)**. They produced diphenyl ether without using any ligands or metals by combining phenol with diphenyl iodonium tiflat[30]. This method requires a strong base.



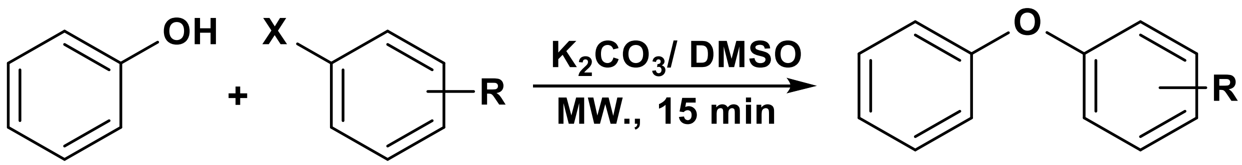
Scheme-7

Verkade's research team successfully synthesised diphenyl ethers using microwave irradiation. The synthesis used electron-deficient aryl fluorides and electron-rich TBDMS-protected phenols, as well as a base in the form of 10% t-Bu-P4[31] **(Scheme-8).**



Scheme-8

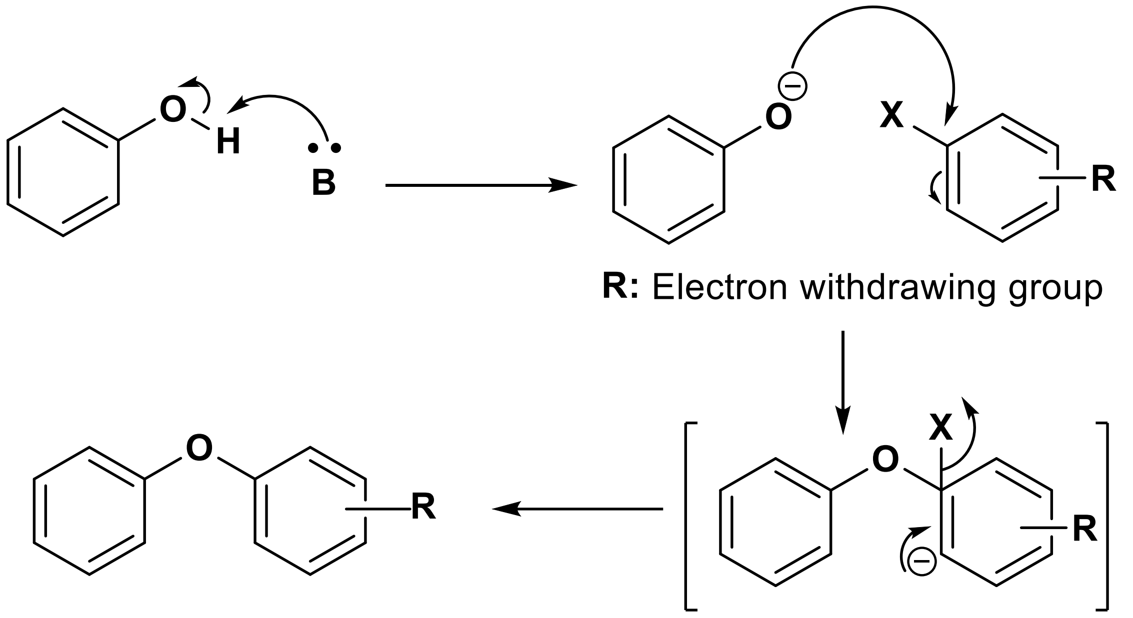
Quanrui Wang found a revolutionary technique for producing high to exceptional yields of diphenyl ethers. This method comprises the direct coupling of phenols with strong electron-withdrawing group with electron-deficient aryl halides in 5-10 minutes through aromatic nucleophilic substitution and microwave irradiation (Scheme-9). Notably, no catalysts are required for this process[32].



Scheme-9

Scheme-10 below shows the proposed mechanism of the nucleophilic aromatic substitution reaction for the formation of diphenyl ethers. The reason for the reaction is the generation of the nucleophilic centre at the halide-containing carbon due to the electron-withdrawing effect of the NO_2 group. The critical step in this mechanism is the formation of intermediate II with sp^3

hybridized carbon when a nucleophile containing phenoxy group attacks the nucleophilic centre. Finally, the halide, a good leaving group, departs to impart aromaticity and the resulting diphenyl ether.



Scheme-10

Many diphenyl ether derivatives are known, as shown by the preceding literature. On the other hand, a number of diphenyl ether derivatives and diphenyl ethers with long hydrocarbon chains have been isolated from natural resources and analysed for their biological activity with excellent findings as shown above. As a result, there is a need to investigate this series of compounds and assess their biological and other material features. This initiative, on the other hand, focuses on synthesising and characterising the 2-(2-Formyl-4-nitrophenoxy) phenyl palmitate.

CHAPTER -3

OBJECTIVES

GAP IN RESEARCH

Several derivatives of diphenyl ether have been synthesized and investigated for their antibacterial activities. However, diphenyl ethers with ester groups although well known need a study to better understand the possible biological activities and other material characteristics with long-chain hydrocarbon. The synthesis and characterization of such a compound is the main objectives of this project. Research on such synthesized diphenyl ethers may shed a new light on antibacterial and material properties of such molecules like involvement of esterase in antibacterial and display of liquid crystals. Also due to their long chain, a unique structural features, may allow them to be used in a wide range of materials, including coatings, polymers and deserve applications. This work involves synthesis and detailed characterization of diphenyl ethers with following objectives.

OBJECTIVES

1. To synthesis of diphenyl ether derivative containing an ester group with a long hydrocarbon chain.
2. To characterize synthesized compounds using spectroscopic techniques.
3. To correlate the analytical data with the structure of synthesized compounds.

CHAPTER-4

MATERIALS AND METHODS

Materials: All of the compounds were bought from various sources and were of purity 98% or above.2-Bromo-5-nitrobanzaldehyde, Catechol and 48%HBr were purchased from Avra Synthesis Pvt. Ltd. Solvents were purchased from AVARICE Laboratories Pvt. Ltd. Organic substances were purified using column chromatography with silica gel having 60-120 mesh size and hexane and ethyl acetate as mobile phase. Aluminium sheets with a silica coating measuring 60 F_{254} and 0.2 mm thick from Merck in India were used for TLC monitoring.

Instrumentation: The characterization of all organic compounds synthesized in this study was performed using advanced instrumentation. NMR spectroscopy was conducted using 400 and 100MHz JEOL model for ^{1}H and ^{13}C-NMR spectrometer respectively at Sai Labs, Patiala, India. Mass analysis of the synthesized compounds was carried out using an XEVO G2 XS mass spectrometer. The ion source utilized a combined ESI and APCI source, enabling both positive and negative ion modes for scanning. The mass analyzer had a wide range, capable of analyzing compounds up to 40000 Daltons. A high-resolution of greater than 40000 FEMH was achieved. Detection of compounds was performed using a PDA detector with a range of 190-800 nm. These advanced analytical techniques ensured accurate and comprehensive characterization of the synthesized compounds.

Methods:

The work described below describes the methods of synthesis of diphenyl ether derivatives, specifically 2-bromo-5-nitrobenzaldehyde **(Compound-B)**, 2-(2-methoxyphenoxy)-5-nitrobenzaldehyde **(Compound-D)**, 2-(2-hydroxyphenoxy)-5-nitrobenzaldehyde **(Compound-E)** (by two different methods 1 and 2), and 2-(2-formyl-4-nitrophenoxy) phenyl palmitate**(Compound-G)**.

Synthesis of Compound-B: 2-Bromo-5-nitrobenzaldehyde **(A)** (0.500g, 1.09mmol) was dissolved in 10ml DCM in a 100 ml RBF and stirred for 10-15 minutes. After 15 minutes, a 7:3 solution of H_2SO_4 (7ml) and HNO_3 (3ml) was added drop by drop to this reaction mixture. The flask was then placed in an ice bath, maintained at 0-10°C and the agitation continued for duration of two hours. Throughout the reaction, TLC was employed to monitor its progress.

After completion, the contents of reaction were poured to a beaker containing ice. To extract the organic compound, DCM (3x25ml) was used, followed by washing the organic layer with water (3x25ml). Any remaining moisture was removed using anhydrous Na_2SO_4. The solvent was evaporated. The solvent was evaporated, leaving the crude product, which was further purified using column chromatography to obtain the desired **compound-B** (0.354gm, Yield: 88.5%). **^{1}H NMR**-(400 MHz; CDCl3): 10.36 (s, 1H), 8.69(d, J=2.8Hz, 1H), 8.29 (dd, J=2.8, 8.72Hz, 1H), 7.87(d, J=8.72Hz, 1H).

Synthesis of compound-D: 2-methoxy phenol**(C)** (0.350g, 2.82mmol) was taken in 100ml RBF. DMF (10ml), K_2CO_3 (0.434g, 3.15mmol) and catalytic amount of 18-crown-6 were added to this RB. This mixture was allowed to stirred at rt. for about 20 min. **Compound-B** (0.648g, 2.82mmol) was added to this RB and further stirred for 12 hours. The course of the reaction was tracked by TLC. The reaction was eventually quenched by adding water to the mixture. To extract the organic compound, DCM (3x25ml) was used, followed by washing the organic layer with water (3x25ml). Any remaining moisture was removed using anhydrous Na_2SO_4. The solvent was evaporated, leaving the crude product, which was further purified using column chromatography to obtain the desired **compound-D** (0.550g, Yield: 71.6%). **^{1}H NMR**-(δ; 400 MHz; CDCl3): 10.64 (s, 1H), 8.76 (d, J=2.88Hz, 1H), 8.24 (dd, J=2.88, 9.2Hz, 1H), 7.31(m, 1H), 7.18(dd, J=1.6, 7.Hz, 1H), 7.05 (m, 2H), 6.73 (d, J=9.2Hz, 1H), 3.75(s, 3H). **^{13}C NMR** (CDCl3):δ 187.6, 164.9, 151.4, 142.6 141.7, 130.1, 127.7, 124.6, 124.5, 122.8, 121.6, 115.8, 113.2, 55.8.

Synthesis of compound-E:

Method 1: The **compound-D** (0.200g, 0.771mmol) and acetic acid (10ml) were taken in 100ml RBF. To this 48% HBr (1ml) was added drop wise and refluxed for 6h. The course of the reaction was tracked by TLC. After the completion, acetic acid was evaporated in vacuo. Water (10ml) was added to dissolve the content. To extract the organic compound, ethyl acetate (3x25ml) was used. Any remaining moisture was removed using anhydrous Na_2SO_4. After evaporating the solvent crude product was purified by column chromatography to obtain solid (0.95mg, 50%).

Method 2: Catechol **(F)** (0.250g, 2.27mmol) was taken in 100ml RBF. DMF (10ml), K_2CO_3 (0.351g, 2.54mmol) and catalytic amount of 18-crown-6 was added to this. At rt. the contents of

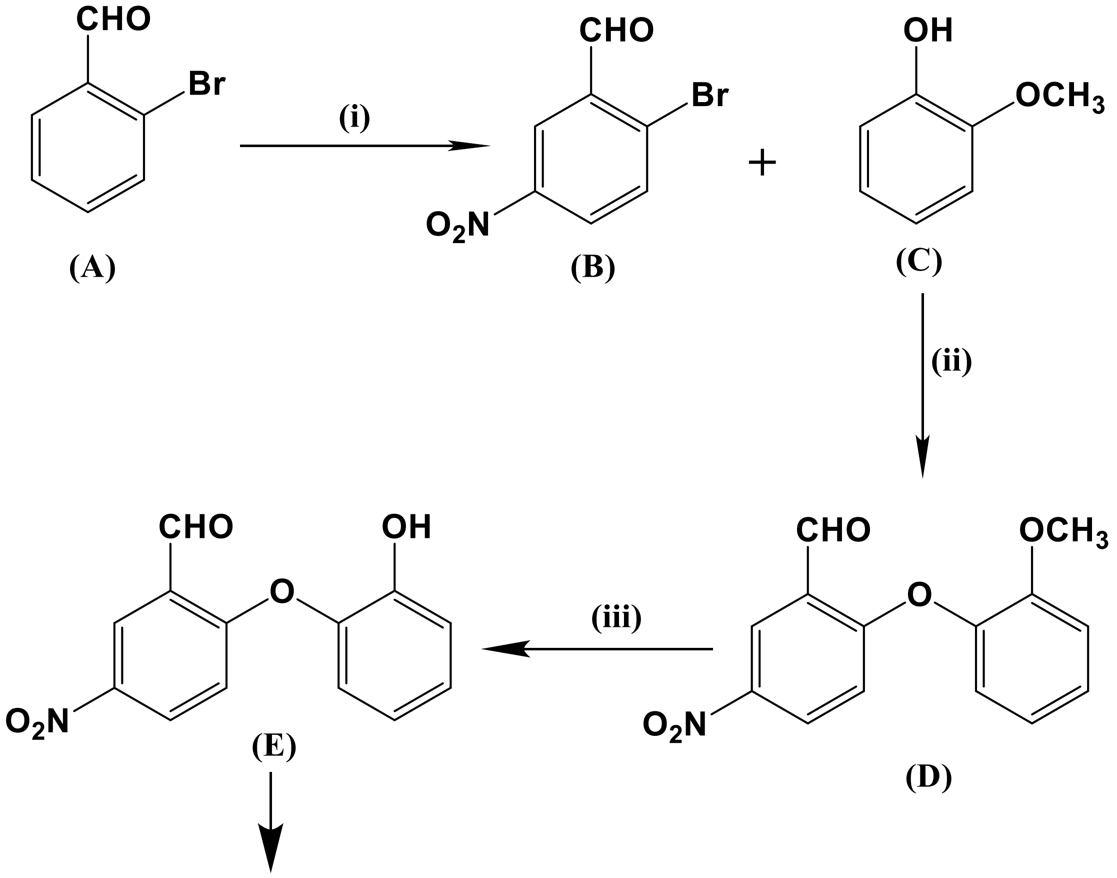
RB were stirred for 20 min. **Compound-B** (0.522g, 2.27mmol) was added to this RB and further stirred for 12 hours at rt. Throughout the reaction, TLC was employed to monitor its progress. The reaction was eventually quenched by adding water to the mixture. To extract the organic compound, DCM (3x25ml) was used, followed by washing the organic layer with water (3x25ml). Any remaining moisture was removed using anhydrous Na_2SO_4. The solvent was evaporated, leaving the crude product, which was further purified using column chromatography to obtain the desired **compound-E** (0.550g, Yield: 71.6%). **^{1}H NMR**-(δ; 400 MHz; CDCl3): 10.56 (s, 1H), 8.72 (d, J=2.84Hz, 1H), 8.24 (dd, J=2.92, 9.2Hz, 1H), 7.21(m, 1H), 7.09(m, 2H), 6.99 (m, 1H), 6.92(d, J=9.2Hz, 1H), 5.88(br s,1H). **^{13}C NMR**-(CDCl3):δ 187.6, 170.9, 163.9, 147.8, 143.0, 140.8, 130.5, 127.7, 125.2, 121.6, 118.0, 116.6. **HR-MS:** m/z= 282 $[M+Na]^+$, 265 $[M+Na-OH]^+$,256 $[M+Na-CHO]^{+\cdot}$,243 $[M-CHO]^{+\cdot}$, 230 $[M-OH]^{+\cdot}$.

Synthesis of compound-G: The **compound-F** (0.300g, 1.16mmol) was taken in 100ml RBF. DMF (10ml), K_2CO_3 (0.239g, 1.73mmol) and catalytic amount of 18-crown-6 were added to RBF. At room temperature, the contents of RBF were stirred for 20min. Palmitic acid (0.222g, 0.866mmol) with phosphorus trichloride (0.119g, 0.866mmol) was taken in another 50ml round bottom flask and refluxed for 15 minutes. After refluxing, the content of RB-2 was transferred drop wise to the RB 1 with DCM (10ml). TLC was employed to monitor its progress. The reaction was eventually quenched by adding water to the mixture. To extract the organic compound, DCM (3x25ml) was used, followed by washing the organic layer with water (3x25ml). Any remaining moisture was removed using anhydrous Na_2SO_4. The solvent was evaporated, leaving the crude product, which was further purified using column chromatography to obtain the desired **compound-G** (0.550g, Yield: 71.6%). **^{1}H NMR**-(δ; 400 MHz; CDCl3): 10.56 (s, 1H), 8.77 (d, J=2.92,Hz, 1H), 8.30 (dd, J=2.84, 9.2Hz, 1H), 7.34(m, 2H), 7.26(m, 1H), 7.19 (m, 1H), 6.93(d, J=9.2Hz, 1H), 2.34(t,2H), 2.03(m, 4H), 1.66(m, 4H), 1.26(m, 18H), 0.88(t, 3H). **^{13}C NMR**-(CDCl3):δ 186.99, 171.41, 163.80, 145.44, 143.12, 142.58, 135.29, 130.35, 127.63, 127.63, 125.10, 124.52, 122.23, 116.99, 37.18, 33.95, 32.28, 32.07, 29.79, 29.68, 29.45, 29.20, 29.01, 27.17, 26.47, 24.87, 23.52, 22.78, 14.22. **HR-MS:** m/z= 303.05, 537.22, 467.27, 287.03,282.03,256.03,144.10,137.05.

CHAPTER-5

RESULT AND DISCUSSION

The work described here details the synthesis and characterization of diphenyl ether derivatives, specifically **Compound-B**, **D**, **E** (by two different methods 1 and 2), and **Compound-G**. **Scheme-11** shows the route to synthesize compounds - **B, D and E.**



Mixture of 6 compounds was obtained
which could not be separated.

Scheme -11: Reagents **(i)** HNO_3 (3ml), H_2SO_4 (7ml), DCM (10ml)**(ii)** K_2CO_3(3.15mmol), 18-Crown -6, DMF (10ml)**(iii)** CH_3COOH (10ml), 48% Aqueous HBr (1ml).

Nitration of **Compound-A** was done using conc. HNO_3 and H_2SO_4 in DCM under stirring in an ice bath at 0-10°C to obtain a yellow-coloured solid in the quantitative yields. After characterization using ^{1}H NMR spectroscopy (Figure-1), the product was conformed to be **Compound-B)** was obtained. As shown in **figure-2**, the appearance of downfield signals at δ

value 7.8 and 8.7ppm due to the NO_2 group and the absence of one peak in the aromatic region corresponding to one proton confirmed the formation of nitration product.

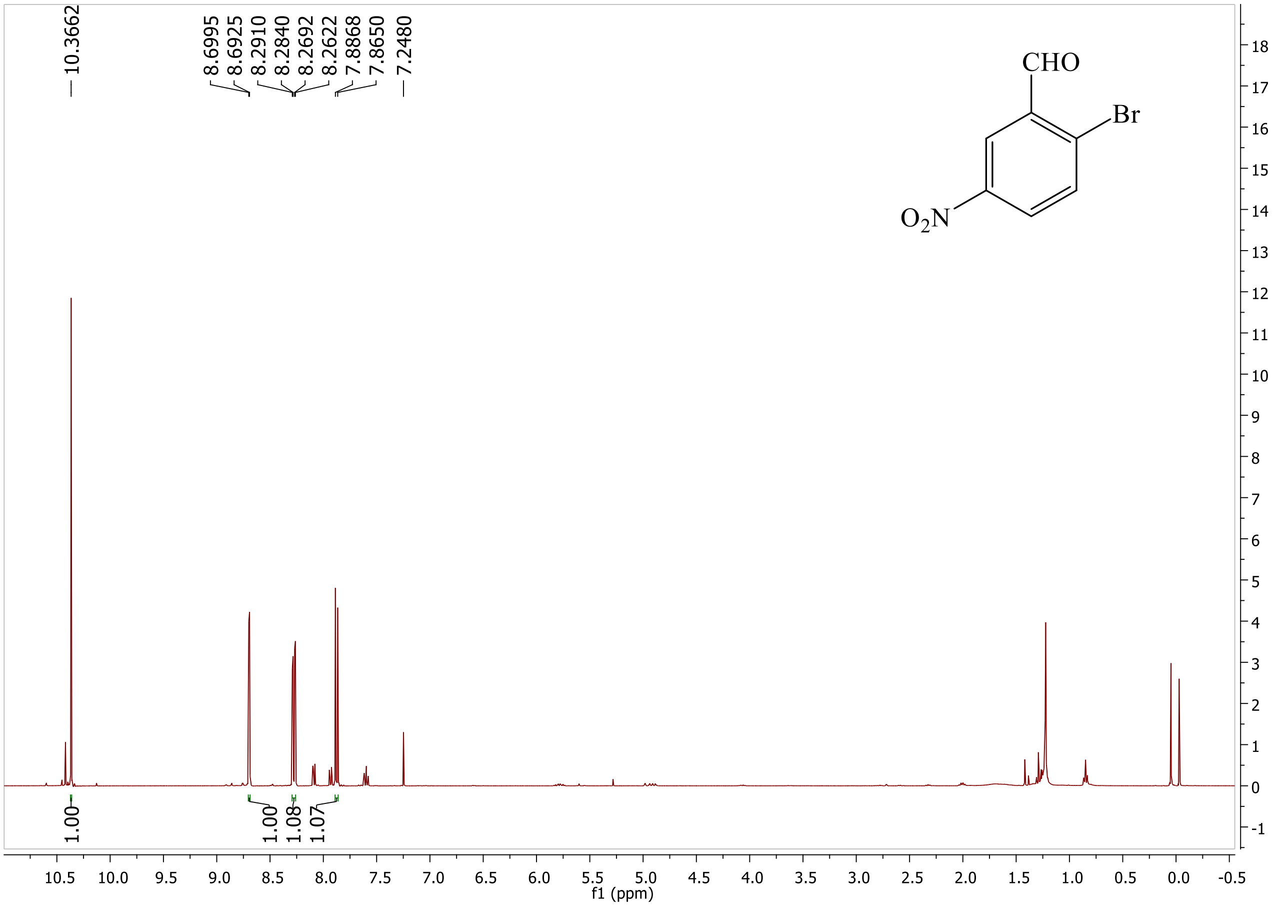


Figure-2: ^{1}H-NMR spectra of **Compound-B.**

Compound- **B** was reacted with **compound-C** through nucleophilic aromatic substitution using a mild base K_2CO_3, in DMF and 18-Crown-6 to obtain **Compound-D.** The formation of the **compound-D** was verified by ^{1}H and ^{13}C-NMR spectroscopy. The presence of a singlet at 3.59 ppm represents 3H corresponding to methoxy group and a singlet at 10.64 ppm due to the proton of the aldehyde group, along with seven protons of the phenyl rings between 6.72-8.75 ppm confirmed the formation of product **(Figure-3).** Similarly, ^{13}C-NMR showed four quaternary carbons at 164.9, 151.4, 142.6 and 130.1 ppm, corresponding to ethereal carbons and the ones attached to methoxy and aldehyde groups. Another quaternary carbon at 141.7 ppm due to carbon attached to the nitro group, methoxy carbon at 55.8 ppm, and carbonyl carbon, way downfield at 187.7 ppm, further confirmed compound-D formation.

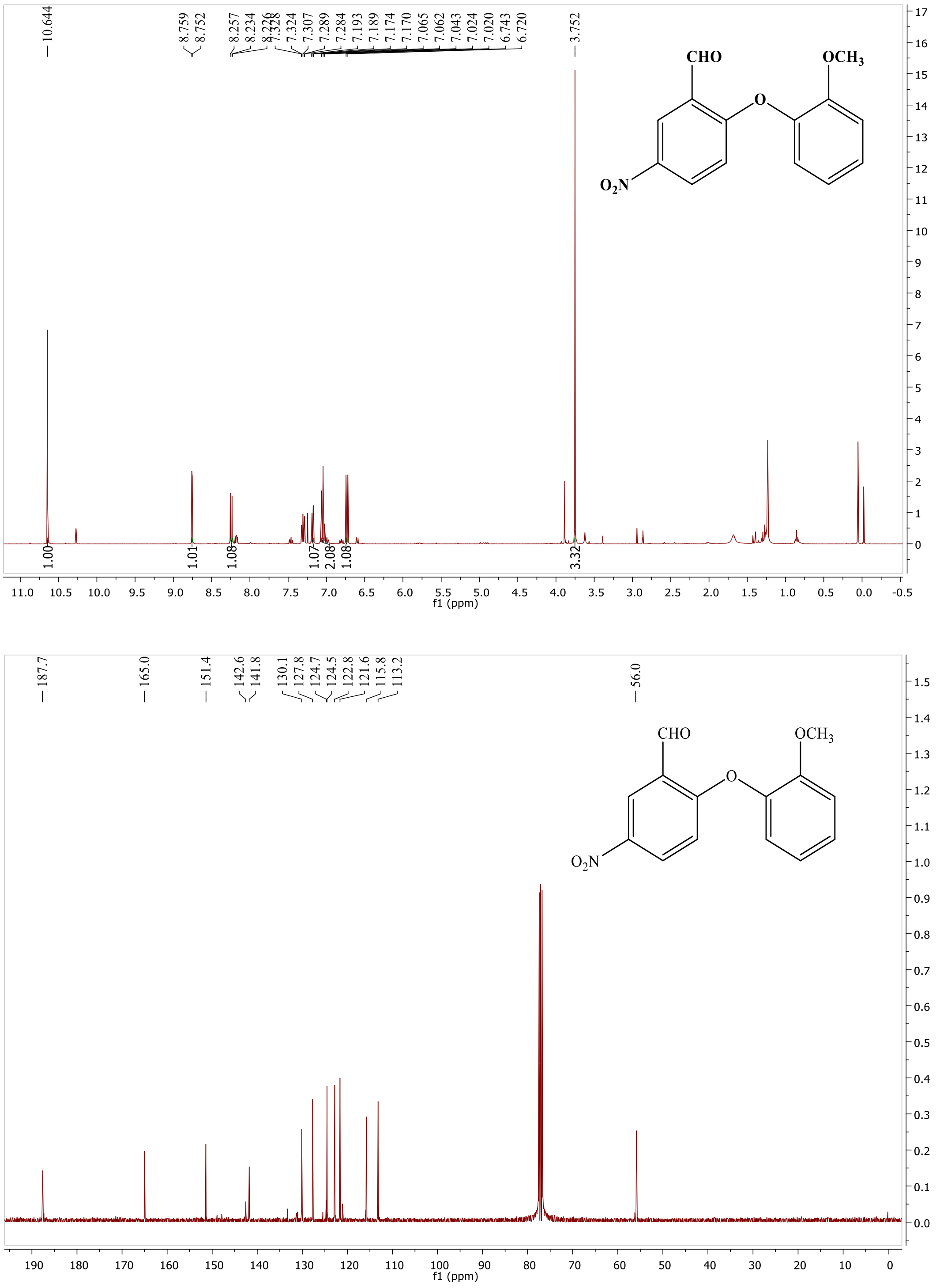
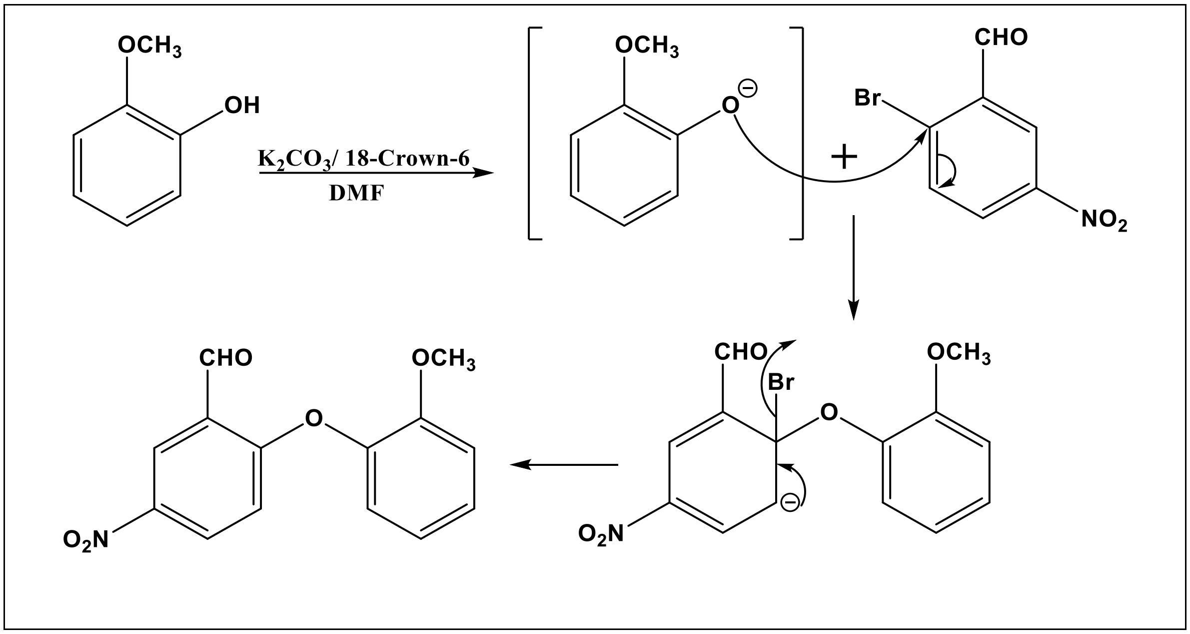


Figure-3a and 3b:^{1}H and ^{13}C-NMR spectra of **compound-D** respectively.

Scheme-12 below shows the nucleophilic aromatic substitution reaction for the formation of diphenyl ethers. The reason for the reaction is the generation of the nucleophilic centre at the halide-containing carbon due to the electron-withdrawing effect of the NO_2 group. The critical step in this mechanism is the formation of intermediate II with sp3 hybridized carbon when a nucleophile containing phenoxy group attacks the nucleophilic centre. Finally, the halide, a good leaving group, departs to impart aromaticity and the resulting diphenyl ether.

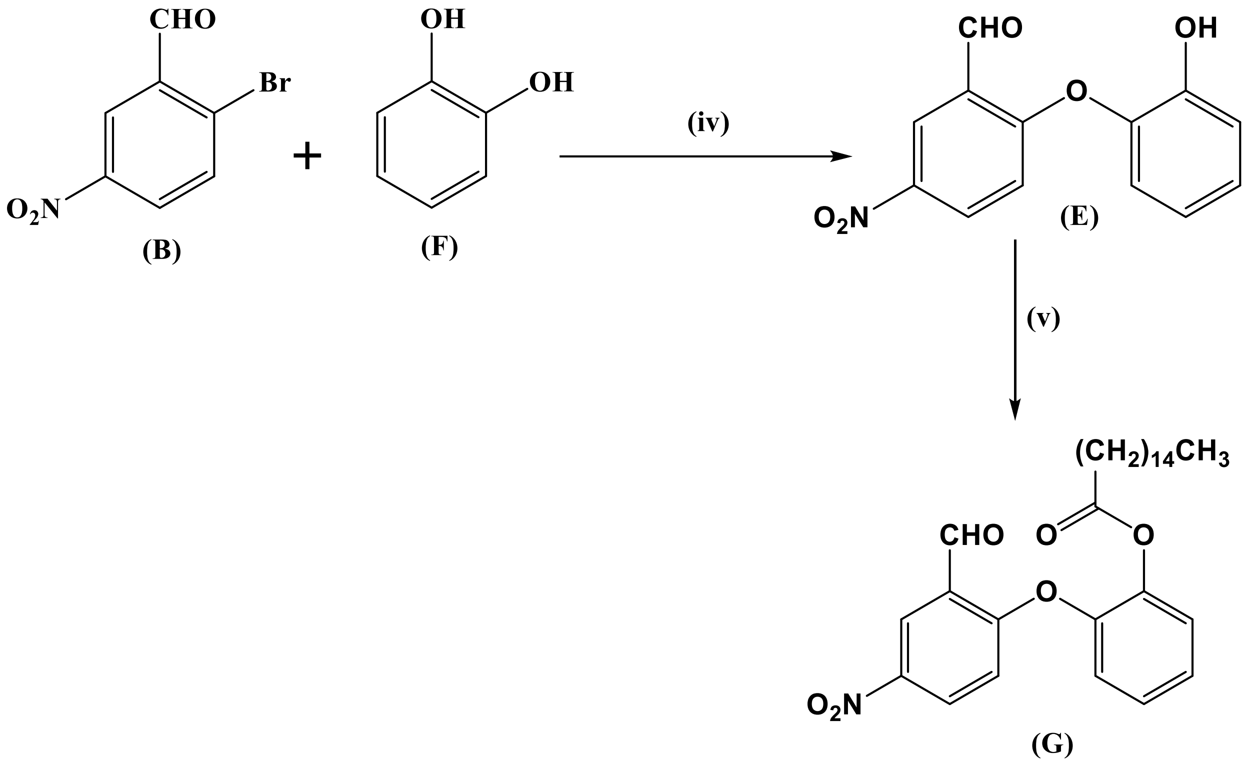


Scheme-12: Mechanism of formation of **compound-D.**

Compound-E was attempted to be synthesized by refluxing **compound-D,** 2-(2-methoxyphenoxy)-5-nitrobenzaldehydein the presence of acetic acid and 48% aqueous HBr. However, using this methodology, a mixture of products was obtained with a lot of decomposed material. Attempts to separate the desired product using column chromatography were unsuccessful

Therefore an alternate approach was adopted, as shown in **Scheme-13.** In this case, **compound-B** obtained above was reacted with Catechol **(Compound-F)** under similar conditions as described for **compound-E** synthesis. Compound **(E)** was thus obtained using this method, a pure product in a 71.6% yield. The care was not to use any excess compound-B to avoid double substitution product. The mechanism of this reaction is the same as that for the synthesis of compound **(E).** The formation of the **compound-E** was verified by ^{1}H and ^{13}C-NMR spectra. In

^{1}H-NMR, a broad peak at 5.88ppm indicated the presence of hydroxyl group, and the loss of singlet from 3.72 ppm stated the absence of the methoxy group.



Scheme-13: Reagents: **(i)** K_2CO_3 (2.54mmol), 18-Crown -6, DMF (10ml) **(ii)** K_2CO_3 (1.73mmol), 18-Crown -6, DMF (10ml), $CH_3(CH_2)_{14}COOH$ (0.866mmol), PCl_3(0.866mmol).

Similarly, ^{13}C-NMR spectra displayed twelve aromatic carbons in the range of 171-116 ppm and a peak at 187.7 ppm due to carbonyl carbon of the aldehyde group. The absence of any peak in the aliphatic region (55.8ppm) was evident due to the choice of a different substrate. **Figures 4a** and **4b** show ^{1}H and ^{13}C-NMR spectra of **compound-E.**

Figure-5 and **6** shows fragmentation pattern and mass spectra of **compound-E.** The mass spectra did not display molecular ion peak corresponding to the compound's molecular weight. However, a peak at m/z = 282 displayed sodiated molecular mass for the compound as shown in **figure-6a**. The loss of carbonyl group and hydroxyl group, respectively, from $[M+Na]^{+}$ corresponded to m/z = 256 **(Figure-6b)** and 265 **(Figure-6c).** Additionally, two peaks at m/z = 230 **(Figure-6d)** and 242 **(Figure-6e)** signifies the removal of aldehyde and hydroxyl groups from the phenyl ring verified the formation of the product.

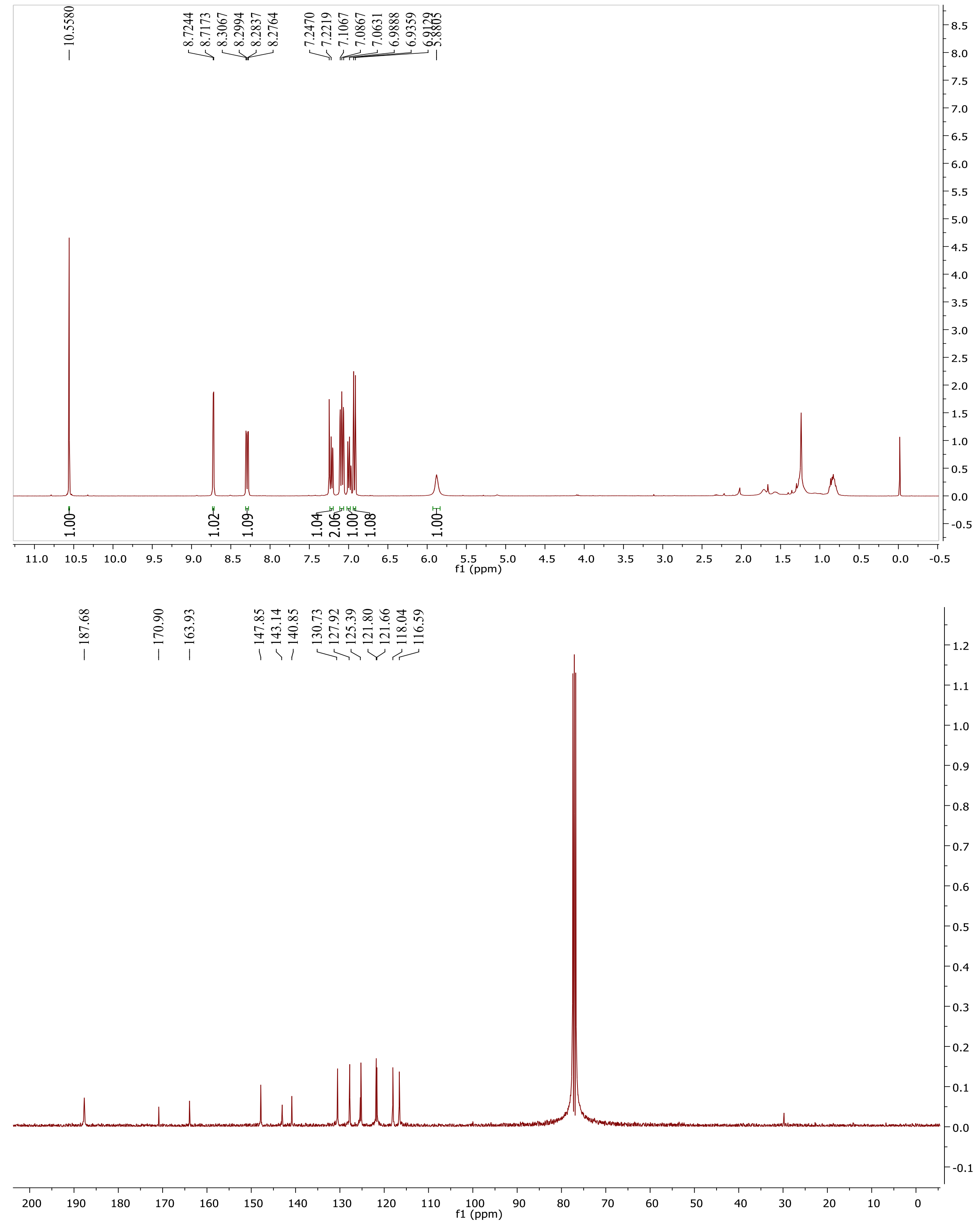
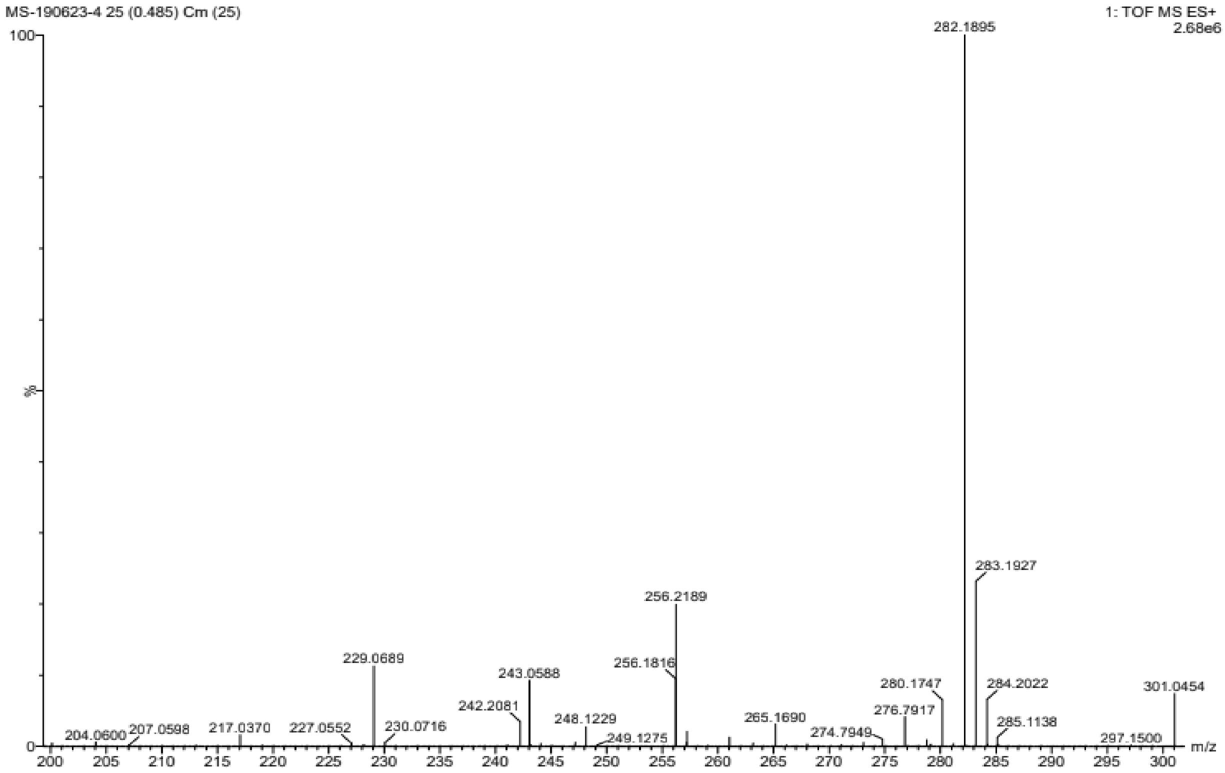


Figure-4a and 4b: ^{1}H and ^{13}C-NMR spectra of compound-**E** respectively.



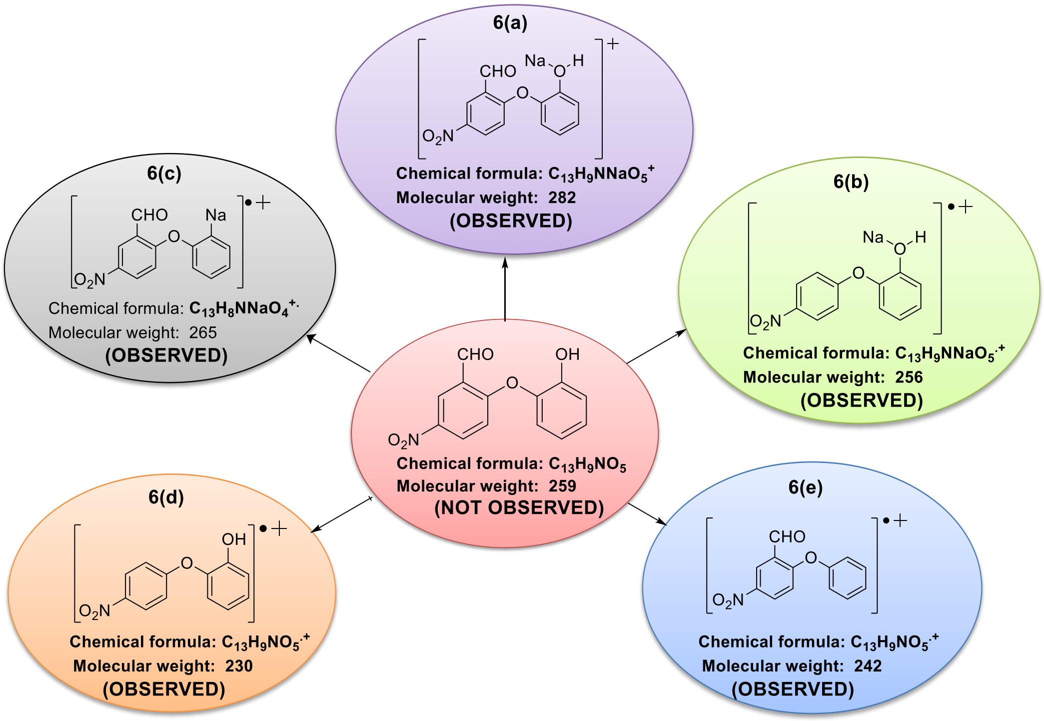


Figure-5 and **6** shows fragmentation pattern and mass spectra of **compound-E**

Finally, to synthesize the long chain ester of the diphenyl ether, **compound -E** was reacted with mild base (K_2CO_3) in DCM with palmityl chloride to give **Compound-G** with 71.6% yield. Before that Palmitic acid and phosphorus trichloride were heated in an oil bath till the evolution of hydrochloric acid gas ceased to afford its corresponding chloride. Conformation of synthesis was done by structure determination using ^{1}H and ^{13}C-NMR **(Figure 7 and 8)**.^{1}H-NMR spectral data displayed the seven aromatic protons in the range of 10.5-6.91ppm and triplet at 2.02ppm due to two protons at carbon adjacent to ester group and presence of fifteen protons in aliphatic region confirmed the formation of compound-**G.** In ^{13}C-NMR spectral data presence of 12 carbons in aromatic region in the range of 163.8-116.9 and peaks at 186.9 and 171.41 due the carbonyl carbon of aldehyde and ester group respectively. Also, the presence of 15 carbons in the aliphatic region verified the formation of **compound-G.**

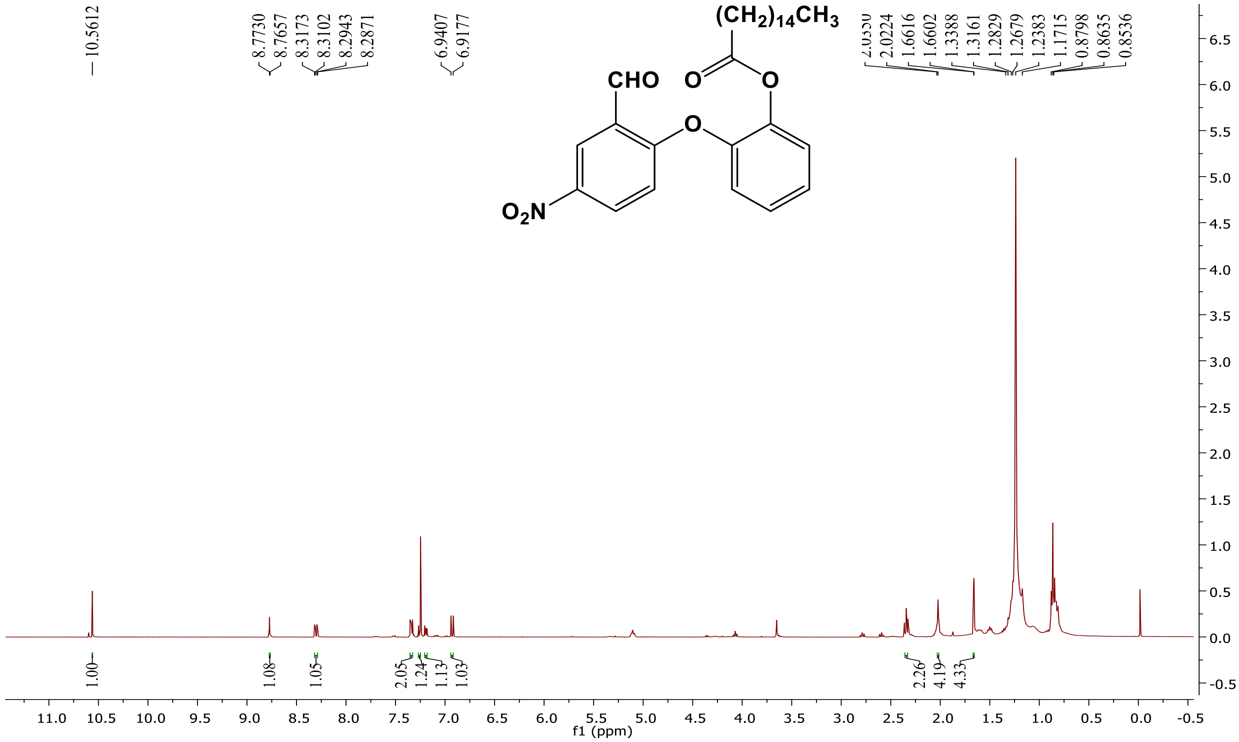


Figure-7:^{1}H-NMR spectra of **compound-G.**

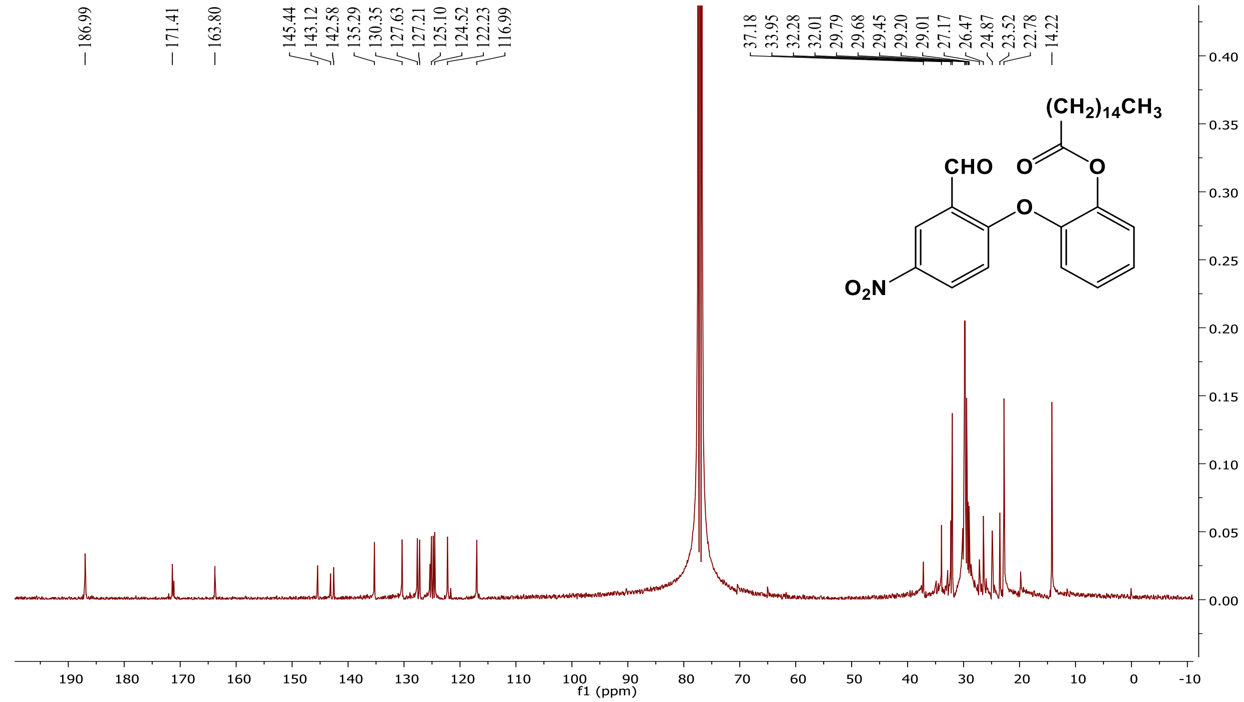
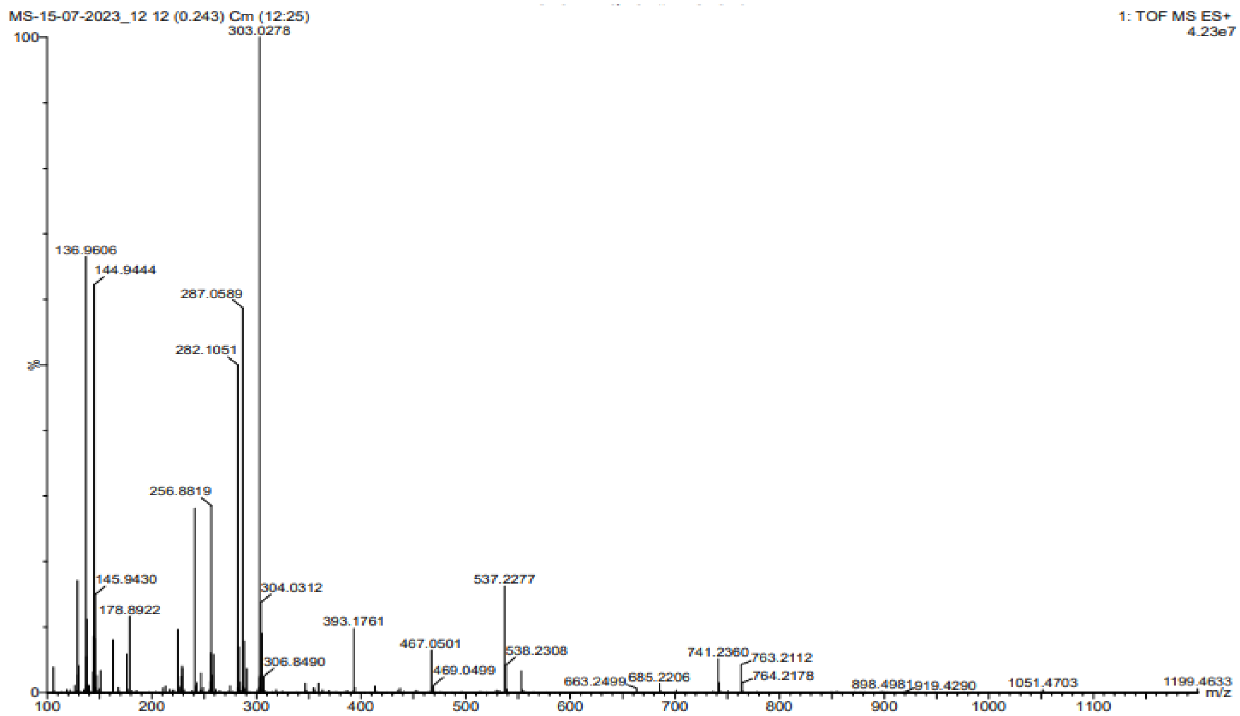


Figure-8:^{13}C-NMR spectra of **compound-G**

Figure-9 and **10** below show mass spectra and the analysis of **Compound-G**. Potassiated peak at m/z= 537.22 [M+K]$^{+}$ **(Figure-10a)**, followed by another one at m/z= 467.05 **(Figure-10b)** signifies the loss of carbonyl group which can be seen in **Figure-9**.The loss of the hydrocarbon chain of palmitic acid, keeping its carbonyl group intact, corresponded to the moiety shown in (**Figure-10c)** peaked at m/z= 287.05.

The peak at m/z= 282.10 signifies the loss of $C_{16}H_{31}O$ radical, and at 256.88 represents the removal of $C_{16}H_{31}O$ and carbonyl group from molecule followed by protonations with sodium matched the peaks as shown by its precursor **(figure-10h**). Thus, the synthesized diphenyl ether motif followed the same fragmentation pattern. The ^{1}H and ^{13}C NMRs did not reveal the presence of any starting material.

Further, the peak at m/z= 144.94 **(Figure-10d)** is due to the fragment arising from the hydrocarbon chain's C_8H_{17} radical and the loss of the phenyl ring. The sodiated segment generated by the loss of the phenyl ring and $C_{10}H_{21}$ radical from the hydrocarbon chain corresponded to a peak at m/z= 136.96 **(figure-10e)**.



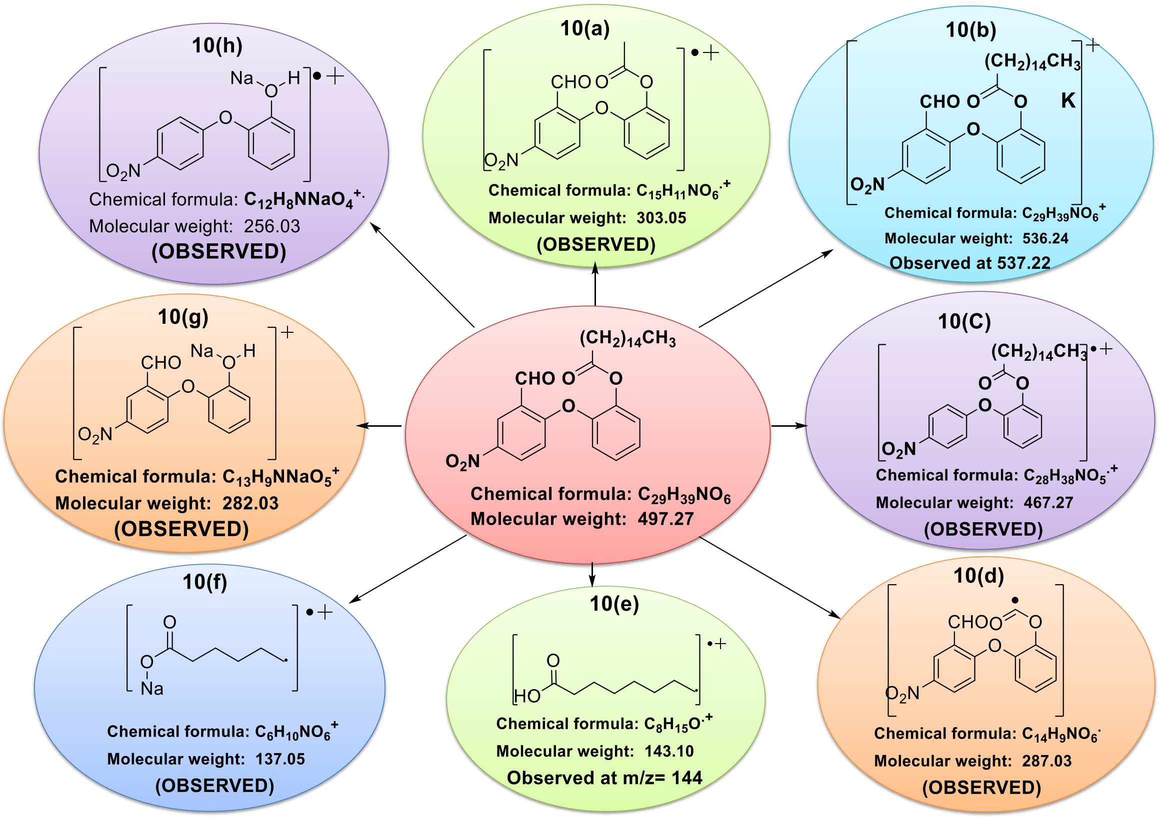
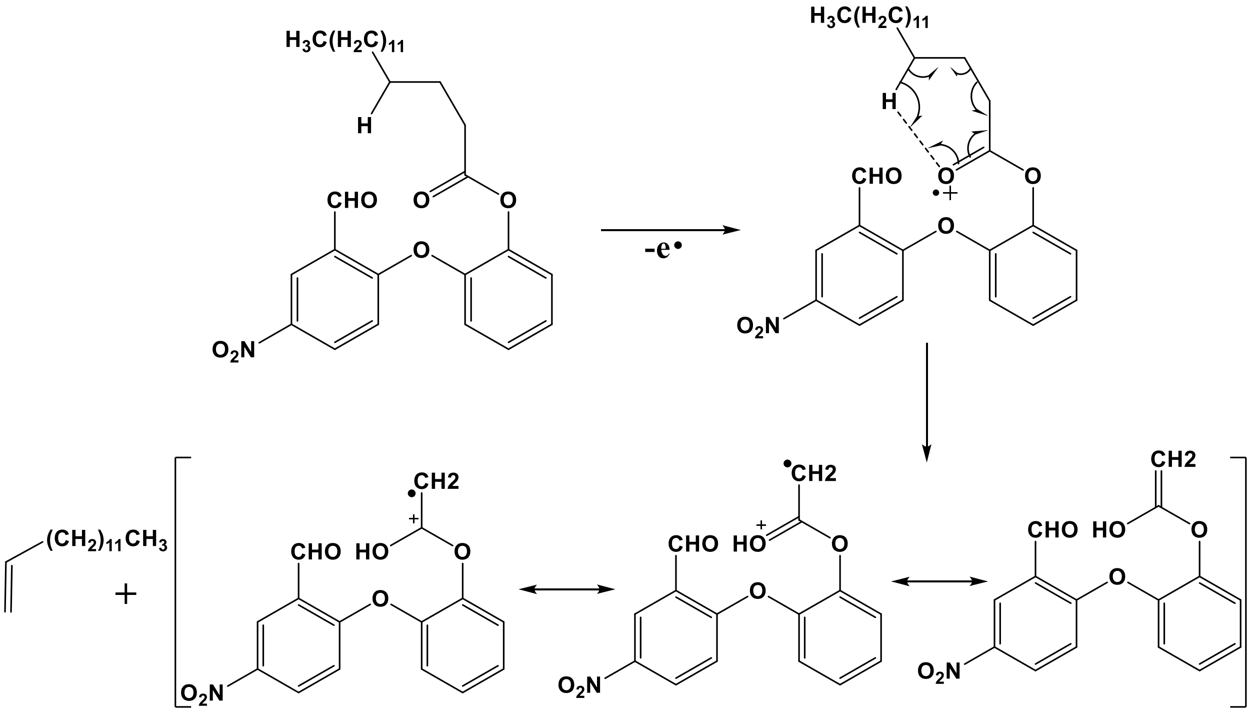


Figure-9 and **10** below show mass spectra and the analysis Compound-**G respectively**.



Scheme-14: Mechanism of McLafferty rearrangement in **Compound-G.**

The long hydrocarbon chains are known to display a classical McLafferty rearrangement. Therefore, in this case, the fragments due to the rearrangement were expected and prominently observed at m/z= 303.02.**Scheme-4** shows the mechanism of McLafferty rearrangements[33] in **(compound-G)** where the γ-hydrogen through a six-membered transition state, gives a terminal alkene (not observed) and a β-carbon-containing carbonyl residue(m/z= 303.02). Also this peak was observed as the base peak in mass spectra which proved the addition of aliphatic chain on diphenyl ether.

Thus the work done above demonstrates the synthesis and characterizations of all four compounds. Based on the spectroscopic results, the synthesis of compounds **B**, **D**, **E**, and **G** starting from compound **A** was successful resulting in the creation of diphenyl ether derivatives with unique structural modifications.

CONCLUSION

In conclusion, antibacterial and material properties make diphenyl ethers useful chemicals. Many diphenyl ethers have been obtained from natural sources and have a wide range of uses in the medical and material sciences. This thesis describes the synthesis and characterisation of Compounds **B**, **D**, **E**, and **G**. Because of their unique structural features, diphenyl ethers with ester groups and lengthy hydrocarbon chains attached to the phenyl ring have been discovered to have a broad variety of uses in many fields. As a result, we synthesised and analysed **Compound-G**, which has an ester group with long hydrocarbon chain. The study of such synthesised diphenyl ethers may provide fresh information on the antibacterial and material characteristics of this molecule, such as the role of esterase in antibacterial and liquid crystal display. ^{1}H and ^{13}C-NMR were used to characterise all of the synthesised substances. A detailed analysis of both the compounds- **E** and **G** was done using HRMS data.

REFRENCES

(1) van der Stelt, T. P.; Casati, E.; Chan, N.; Colonna, P. Technical Equation of State Models for Heat Transfer Fluids Made of Biphenyl and Diphenyl Ether and Their Mixtures. *Fluid Phase Equilib.* **2015**, *393*, 64–77. https://doi.org/10.1016/j.fluid.2015.02.025.

(2) Ziebland, H.; Burton, J. T. A. Transport Properties of Some Organic Heat Transfer Fluids. *J. Chem. Eng. Data* **1961**, *6* (4), 579–583. https://doi.org/10.1021/je60011a029.

(3) Kim, H. J. L. & G. B. An Overview of Polybrominated Diphenyl Ethers (PBDEs) in the Marine Environment. *Ocean Sci. J.* ***2015***, 50(2),119142 https://doi.org/10.1007/s12601-015-0010-8.

(4) Heo, S.-J.; Hwang, J.-Y.; Choi, J.-I.; Lee, S.-H.; Park, P.-J.; Kang, D.-H.; Oh, C.; Kim, D.-W.; Han, J.-S.; Jeon, Y.-J.; Kim, H.-J.; Choi, I.-W. Protective Effect of Diphlorethohydroxycarmalol Isolated from Ishige Okamurae against High Glucose-Induced-Oxidative Stress in Human Umbilical Vein Endothelial Cells. *Food Chem. Toxicol.* **2010**, *48* (6), 1448–1454. https://doi.org/10.1016/j.fct.2010.02.025.

(5) Wang, L.; Kim, H. S.; Oh, J. Y.; Je, J. G.; Jeon, Y.-J.; Ryu, B. Protective Effect of Diphlorethohydroxycarmalol Isolated from Ishige Okamurae against UVB-Induced Damage in Vitro in Human Dermal Fibroblasts and in Vivo in Zebrafish. *Food Chem. Toxicol.* **2020**, *136*, 110963. https://doi.org/10.1016/j.fct.2019.110963.

(6) Artan, M.; Li, Y.; Karadeniz, F.; Lee, S.-H.; Kim, M.-M.; Kim, S.-K. Anti-HIV-1 Activity of Phloroglucinol Derivative, 6,6′-Bieckol, from Ecklonia Cava. *Bioorg. Med. Chem.* **2008**, *16* (17), 7921–7926. https://doi.org/10.1016/j.bmc.2008.07.078.

(7) Bai, L.; Liu, X.; Jiao, T.; Wang, Y.; Huo, Y.; Niu, J. Surface Properties and Thermodynamic Properties of Micellization of Mono- and Di-Tetrapropylene Diphenyl Ether Disulfonates. *J. Mol. Liq.* **2017**, *244*, 433–439. https://doi.org/10.1016/j.molliq.2017.09.033.

(8) Guerrero-Hernández, L.; Meléndez-Ortiz, H. I.; Cortez-Mazatan, G. Y.;

Vaillant-Sánchez, S.; Peralta-Rodríguez, R. D. Gemini and Bicephalous Surfactants: A Review on Their Synthesis, Micelle Formation, and Uses. *Int. J. Mol. Sci.* **2022**, *23* (3), 1798. https://doi.org/10.3390/ijms23031798.

(9) McMurray, J. W.; Frame, B. J.; Voit, S. L. Vaporization Behavior of an Alkyl Diphenyl Ether and a Commercial Lubricant. *Vacuum* **2018**, *155*, 43–48. https://doi.org/10.1016/j.vacuum.2018.05.034.

(10) Zhao, M.; Ruan, Q.; Pan, W.; Tang, Y.; Zhao, Z.; Cui, H. New Polyketides and Diterpenoid Derivatives from the Fungus Penicillium Sclerotiorum GZU-XW03-2 and Their Anti-Inflammatory Activity. *Fitoterapia* **2020**, *143*, 104561. https://doi.org/10.1016/j.fitote.2020.104561.

(11) Hanif, N.; Tanaka, J.; Setiawan, A.; Trianto, A.; de Voogd, N. J.; Murni, A.; Tanaka, C.; Higa, T. Polybrominated Diphenyl Ethers from the Indonesian Sponge Lamellodysidea Herbacea. *J. Nat. Prod.* **2007**, *70* (3), 432–435. https://doi.org/10.1021/np0605081.

(12) Sadorn, K.; Saepua, S.; Bunbamrung, N.; Boonyuen, N.; Komwijit, S.; Rachtawee, P.; Pittayakhajonwut, P. Diphenyl Ethers and Depsidones from the Endophytic Fungus Aspergillus Unguis BCC54176. *Tetrahedron* **2022**, *105*, 132612. https://doi.org/10.1016/j.tet.2021.132612.

(13) Yang, W.; Mu, Y.; Giesy, J. P.; Zhang, A.; Yu, H. Anti-Androgen Activity of Polybrominated Diphenyl Ethers Determined by Comparative Molecular Similarity Indices and Molecular Docking. *Chemosphere* **2009**, *75* (9), 1159–1164. https://doi.org/10.1016/j.chemosphere.2009.02.047.

(14) Zhang, L.-H.; Feng, B.-M.; Zhao, Y.-Q.; Sun, Y.; Liu, B.; Liu, F.; Chen, G.; Bai, J.; Hua, H.-M.; Wang, H.-F.; Pei, Y.-H. Polyketide Butenolide, Diphenyl Ether, and Benzophenone Derivatives from the Fungus Aspergillus Flavipes PJ03-11. *Bioorg. Med. Chem. Lett.* **2016**, *26* (2), 346–350. https://doi.org/10.1016/j.bmcl.2015.12.009.

(15) Du, Z.; Liu, R.; Shao, W.; Mao, X.; Ma, L.; Gu, L.; Huang, Z.; Chan, A. S. C. α-Glucosidase Inhibition of Natural Curcuminoids and Curcumin Analogs. *Eur. J. Med. Chem.* **2006**, *41* (2), 213–218. https://doi.org/10.1016/j.ejmech.2005.10.012.

(16) Marsh, G.; Athanasiadou, M.; Athanassiadis, I.; Sandholm, A. Identification

of Hydroxylated Metabolites in 2,2′,4,4′-Tetrabromodiphenyl Ether Exposed Rats. *Chemosphere* **2006**, *63* (4), 690–697. https://doi.org/10.1016/j.chemosphere.2005.07.072.

(17) Malmvärn, A.; Marsh, G.; Kautsky, L.; Athanasiadou, M.; Bergman, Å.; Asplund, L. Hydroxylated and Methoxylated Brominated Diphenyl Ethers in the Red Algae Ceramium Tenuicorne and Blue Mussels from the Baltic Sea. *Environ. Sci. Technol.* **2005**, *39* (9), 2990–2997. https://doi.org/10.1021/es0482886.

(18) Xu, Y.; Johnson, R. K.; Hecht, S. M. Polybrominated Diphenyl Ethers from a Sponge of the Dysidea Genus That Inhibit Tie2 Kinase. *Bioorg. Med. Chem.* **2005**, *13* (3), 657–659. https://doi.org/10.1016/j.bmc.2004.10.061.

(19) Malmberg, T.; Athanasiadou, M.; Marsh, G.; Brandt, I.; Bergman, A. Identification of Hydroxylated Polybrominated Diphenyl Ether Metabolites in Blood Plasma from Polybrominated Diphenyl Ether Exposed Rats. *Environ. Sci. Technol.* **2005**, *39* (14), 5342–5348. https://doi.org/10.1021/es050574+.

(20) Elix, J. A.; Jones, A. J.; Lajide, L.; Coppins, B. J.; James, P. W. Two New Diphenyl Ethers and a New Depside from the Lichen Micavea Prasina Fr. *Aust. J. Chem.* **1984**, *37* (11), 2349–2364. https://doi.org/10.1071/CH9842349.

(21) Artan, M.; Li, Y.; Karadeniz, F.; Lee, S. H.; Kim, M. M.; Kim, S. K. Anti-HIV-1 Activity of Phloroglucinol Derivative, 6,6′-Bieckol, from Ecklonia Cava. *Bioorganic Med. Chem.* **2008**, *16* (17), 7921–7926. https://doi.org/10.1016/j.bmc.2008.07.078.

(22) Kwon, T. H.; Wu, Y. X.; Kim, J. S.; Woo, J. H.; Park, K. T.; Kwon, O. J.; Seo, H. J.; Kim, T.; Park, N. H. 6,6′-Bieckol Inhibits Adipocyte Differentiation through Downregulation of Adipogenesis and Lipogenesis in 3T3-L1 Cells. *J. Sci. Food Agric.* **2015**, *95* (9), 1830–1837. https://doi.org/10.1002/jsfa.6881.

(23) Addison, R. F. Diphenyl Ether-Another Marine Environmental Contaminant. *Mar. Pollut. Bull.* **1977**, *8* (10), 237–240. https://doi.org/10.1016/0025-326X(77)90433-7.

(24) Cook, A. N. Proceedings of the Iowa Academy of Science Diphenyl Ether Derivatives. **1900**, *8*.

(25) Publication, A. P-NITRODIPHENYL ETHER. *Org. Synth.* **1934**, *14* (September), 66. https://doi.org/10.15227/orgsyn.014.0066.

(26) Cristau, H. J.; Cellier, P. P.; Hamada, S.; Spindler, J. F.; Taillefer, M. A General and Mild Ullmann-Type Synthesis of Diaryl Ethers. *Org. Lett.* **2004**, *6* (6), 913–916. https://doi.org/10.1021/ol036290g.

(27) Evans, D. A.; Katz, J. L.; West, T. R. Synthesis of Diaryl Ethers through the Copper-Promoted Arylation of Phenols with Arylboronic Acids. An Expedient Synthesis of Thyroxine. *Tetrahedron Lett.* **1998**, *39* (19), 2937–2940. https://doi.org/10.1016/S0040-4039(98)00502-4.

(28) Scott Sawyer, J. Recent Advances in Diaryl Ether Synthesis. *Tetrahedron* **2000**, *56* (29), 5045–5065. https://doi.org/10.1016/S0040-4020(00)00257-X.

(29) Magné, V.; Garnier, T.; Danel, M.; Pale, P.; Chassaing, S. CuI-USY as a Ligand-Free and Recyclable Catalytic System for the Ullmann-Type Diaryl Ether Synthesis. *Org. Lett.* **2015**, *17* (18), 4494–4497. https://doi.org/10.1021/acs.orglett.5b02167.

(30) Quach, T. D.; Batey, R. A. Copper(II)-Catalyzed Ether Synthesis from Aliphatic Alcohols and Potassium Organotrifluoroborate Salts. *Org. Lett.* **2003**, *5* (8), 1381–1384. https://doi.org/10.1021/ol034454n.

(31) Ueno, M.; Hori, C.; Suzawa, K.; Ebisawa, M.; Kondo, Y. Catalytic Activation of Silylated Nucleophiles Using TBu-P4 as a Base. *European J. Org. Chem.* **2005**, No. 10, 1965–1968. https://doi.org/10.1002/ejoc.200500087.

(32) Li, F.; Wang, Q.; Ding, Z.; Tao, F. Microwave-Assisted Synthesis of Diaryl Ethers without Catalyst. *Org. Lett.* **2003**, *5* (12), 2169–2171. https://doi.org/10.1021/ol0346436.

(33) Kingston, D. G. I.; Bursey, J. T.; Bursey, M. M. Intramolecular Hydrogen Transfer in Mass Spectra. II. McLafferty Rearrangement and Related Reactions. *Chem. Rev.* **1974**, *74* (2), 215–242. https://doi.org/10.1021/cr60288a004.

M.Sc Thesis after Plag removal — Sanchita (302102025)

ORIGINALITY REPORT

24/7/2023

24/7/2023.

15%	12%	12%	6%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	"Marine Organisms in Cancer Chemoprevention", Marine Biomedicine, 2015. Publication	1%
2	Fabian Schlimpen, Clotilde Plaçais, Eliot Starck, Valérie Bénéteau, Patrick Pale, Stefan Chassaing. " α-Tertiary Propargylamine Synthesis KA -Type Coupling Reactions under Solvent-Free Cu -Zeolite Catalysis ", The Journal of Organic Chemistry, 2021 Publication	1%
3	Lei Wang, Jun-Geon Je, Hye-Won Yang, You-Jin Jeon, Seungheon Lee. "Dieckol, an Algae-Derived Phenolic Compound, Suppresses UVB-Induced Skin Damage in Human Dermal Fibroblasts and Its Underlying Mechanisms", Antioxidants, 2021 Publication	1%
4	patentimages.storage.googleapis.com Internet Source	1%
5	prism.ucalgary.ca	

Sanchita

	Internet Source	1 %
6	benthamscience.com Internet Source	1 %
7	tudr.thapar.edu:8080 Internet Source	1 %
8	es.scribd.com Internet Source	1 %
9	www.freepatentsonline.com Internet Source	1 %
10	A. M. Al Sabagh, Tahany Mahmoud Abdel-Hamid, Fatma H. Abdel-Salam, Mahmoud R. Noor El-Din, Asmaa Mohamed. "Surface activity and thermodynamic properties of some green surfactants from wastes in formation water at reservoir conditions", Journal of Dispersion Science and Technology, 2020 Publication	1 %
11	Yi Wan, Steve Wiseman, Hong Chang, Xiaowei Zhang et al. "Origin of Hydroxylated Brominated Diphenyl Ethers: Natural Compounds or Man-Made Flame Retardants?", Environmental Science & Technology, 2009 Publication	<1 %

12	hdl.handle.net Internet Source	<1 %
13	David A Evans, Jeffrey L Katz, Theodore R West. "Synthesis of diaryl ethers through the copper-promoted arylation of phenols with arylboronic acids. An expedient synthesis of thyroxine", Tetrahedron Letters, 1998 Publication	<1 %
14	Submitted to Chulalongkorn University Student Paper	<1 %
15	Xu, Y.m.. "Polybrominated diphenyl ethers from a sponge of the Dysidea genus that inhibit Tie2 kinase", Bioorganic & Medicinal Chemistry, 20050201 Publication	<1 %
16	repository.mines.edu Internet Source	<1 %
17	Submitted to Aligarh Muslim University, Aligarh Student Paper	<1 %
18	Gwilherm Evano, Nicolas Blanchard, Mathieu Toumi. "Copper-Mediated Coupling Reactions and Their Applications in Natural Products and Designed Biomolecules Synthesis", Chemical Reviews, 2008 Publication	<1 %

19	Scott E. Allen, Ryan R. Walvoord, Rosaura Padilla-Salinas, Marisa C. Kozlowski. "Aerobic Copper-Catalyzed Organic Reactions", Chemical Reviews, 2013 Publication	<1 %
20	"Copper-Oxygen Chemistry", Wiley, 2011 Publication	<1 %
21	Göran Marsh, Maria Athanasiadou, Ioannis Athanassiadis, Anna Sandholm. "Identification of hydroxylated metabolites in 2,2',4,4'-tetrabromodiphenyl ether exposed rats", Chemosphere, 2006 Publication	<1 %
22	Submitted to Widener University Student Paper	<1 %
23	Ziebland, Hans, and J. T. A. Burton. "Transport Properties of Some Organic Heat Transfer Fluids.", Journal of Chemical & Engineering Data, 1961. Publication	<1 %
24	Artan, M.. "Anti-HIV-1 activity of phloroglucinol derivative, 6,6'-bieckol, from Ecklonia cava", Bioorganic & Medicinal Chemistry, 20080901 Publication	<1 %
25	Grognux, J.. "Universal chromogenic substrates for lipases and esterases",	<1 %

	Tetrahedron: Asymmetry, 20040920 Publication	
26	www.thieme-connect.com Internet Source	<1%
27	Hyo Jin Lee, Gi Beum Kim. "An overview of polybrominated diphenyl ethers (PBDEs) in the marine environment", Ocean Science Journal, 2015 Publication	<1%
28	newdrugapprovals.org Internet Source	<1%
29	J.W. McMurray, B.J. Frame, S.L. Voit. "Vaporization behavior of an alkyl diphenyl ether and a commercial lubricant", Vacuum, 2018 Publication	<1%
30	Shuru Li, Xuan Jiao, Hengquan Yang. "Hydrophobic Core/Hydrophilic Shell Structured Mesoporous Silica Nanospheres: Enhanced Adsorption of Organic Compounds from Water", Langmuir, 2013 Publication	<1%
31	link.springer.com Internet Source	<1%
32	www.koreascience.or.kr Internet Source	<1%

33	journals.onaft.edu.ua Internet Source	<1 %
34	www.pubmedcentral.nih.gov Internet Source	<1 %
35	T.P. van der Stelt, E. Casati, N. Chan, P. Colonna. "Technical equation of state models for heat transfer fluids made of biphenyl and diphenyl ether and their mixtures", Fluid Phase Equilibria, 2015 Publication	<1 %
36	drs.nio.org Internet Source	<1 %
37	patents.google.com Internet Source	<1 %
38	J. Scott Sawyer. "Recent Advances in Diaryl Ether Synthesis", Tetrahedron, 2000 Publication	<1 %
39	Long Bai, Xiaochen Liu, Tiliu Jiao, Yueqing Huo, Jinping Niu. "Interfacial tension, wettability, foam and emulsification properties of mono- and di-tetrapropylene diphenyl ether disulfonates", Journal of Dispersion Science and Technology, 2018 Publication	<1 %
40	Wilfried M. A. Niessen, Ricardo A. Correa C.. "Interpretation of MS - MS Mass Spectra of	<1 %

	Drugs and Pesticides", Wiley, 2017 Publication	
41	epub.ub.uni-greifswald.de Internet Source	<1 %
42	nbn-resolving.de Internet Source	<1 %
43	patents.justia.com Internet Source	<1 %
44	patentscope.wipo.int Internet Source	<1 %
45	s3-eu-west-1.amazonaws.com Internet Source	<1 %
46	www.diva-portal.org Internet Source	<1 %
47	www.mdpi.com Internet Source	<1 %

Exclude quotes	On	Exclude matches	< 8 words
Exclude bibliography	On		