Synthesis and Characterization of Benzophenone Based Phenyl Ether Derivatives

Thesis submitted in the partial fulfillment
of the requirements for the degree of
Master of Science In Chemistry

By

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Under the Supervision of

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Akhil Sharma

Akhil Sharma

Candidate's Declaration

I hereby declare that work being presented in this dissertation entitled "**Synthesis and Characterization of Benzophenone Based Phenyl Ether Derivatives**" in partial fulfilment of the requirement for the award of **Master of Science in Chemistry** carried out at School of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala is my own carried out under the supervision of **Dr. Manmohan Chhibber**, Associate Professor, TIET, Patiala during the period **January to June 2018**.

Akhil Sharma

Akhil Sharma
Roll No 301602003

Place : Patiala
Date : 15th June 2018

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

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Certificate

This is to certify that the dissertation entitled "**Synthesis and Characterization of Benzophenone Based Phenyl Ether Derivatives**" being submitted by **Akhil Sharma (Roll No 301602003)** in partial fulfilment of the requirement for the award of degree of **Master of Science in Chemistry** at School of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala is an bona fide work carried out under the supervision of **Dr. Manmohan Chhibber**, Associate Professor, School of Chemistry and Biochemistry, TIET, Patiala and that no part of this thesis has been submitted for the award of any degree.

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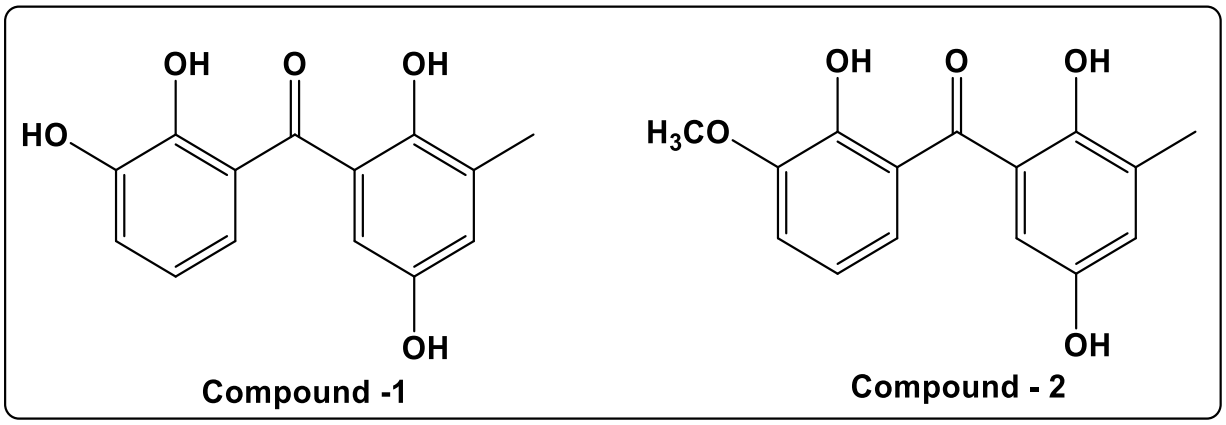
Abstract

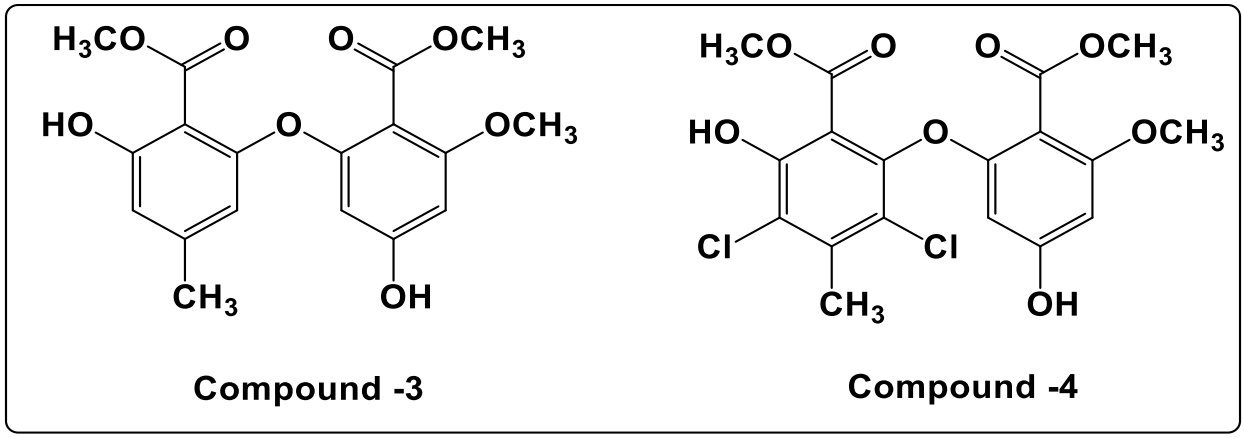
Benzophenone and diphenyl ether derivatives are important compounds because of their biological activities and materialistic applications. Such compounds have also been isolated from a number of natural products. Individually, both these categories of compounds have found numerous applications in medicinal and material world. Therefore, the work presented here describes synthesis of benzophenone derivatives of diphenyl ethers. Three compounds **D**, **E** and **F** were synthesized using same benzophenone precursor, (2-hydroxy-4-methoxyphenyl)(phenyl) methanone, and 2- bromo-5-nitrobenzaldehyde to get 2-(2-benzoyl-5-methoxyphenoxy)-5-nitrobenzaldehyde **(D)**. Using different concentrations of the same reducing agent ($NaBH_4$) two different products were obtained. In one case only aldehyde was reduced **(Compound E)** while in other case both aldehyde and ketone present in the molecule **(Compound F)** were reduced. Characterization was done using ^{1}H and ^{13}C NMR spectroscopy.

Introduction

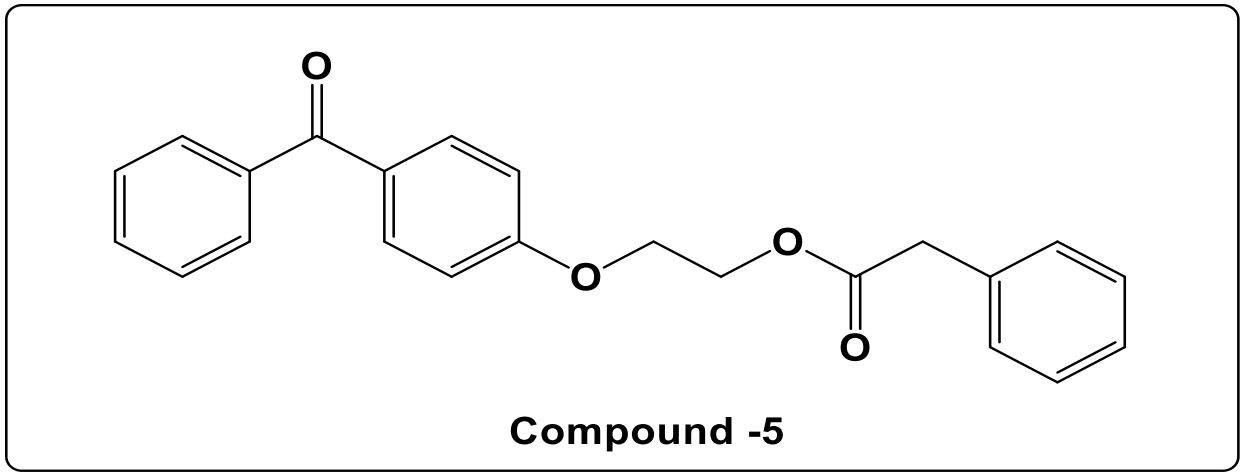
Benzophenone and diphenyl ether derivatives are a series biologically active compounds obtained from nature. Most of these class of compounds are extracted from marine sources like sponges, algae and various marine fungal species. **Compounds -1** and **2** shown below**,** for example, have been isolated from endophytic fungus (*Talaromyces islandicus* EN501) of marine red alga *Laurencia okamurai*. Both these compounds have shown antibacterial activity against human pathogens (*Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*), and aquatic bacteria (*Vibrio alginolyticus, V. harveyi*, and *V. parahaemolyticus*) with minimum inhibitory concentration (MIC) ranging from 4 to 32 µg/m and antioxidant activity with IC_{50} value ranging from 1.23 to 6.92 µg/mL[1].



Similarly **compounds -3** and **4** isolated from the cultures of *Aspergillus sp.* have shown antinematodal activity using *Caenorhabditis elegans* as the nematode model. The LD_{90} of the above two compounds was found to be 75 ppm within 24 hours [2].

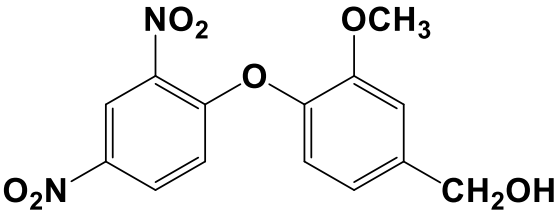


Literature shows that synthetic benzophenone and diphenyl ether derivatives have application in material science as well. For example **compound - 5** is a well known agent in the textile industry that is applicable to polyester materials for the improvement of light fastness with dye providing substantial resistance to its sublimation [3].

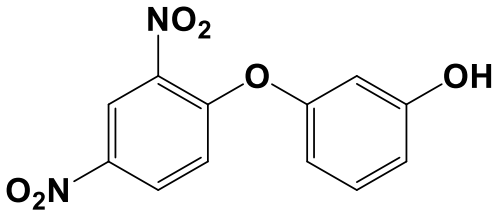


Compound -5

Some of the diphenyl ethers synthesized recently have shown selectivity for various ions. For example, **compound – 6** is selective for Fe^{3+} and **compound – 7** is selective for F^{-}[4][17].



Compound- 6



Compound- 7

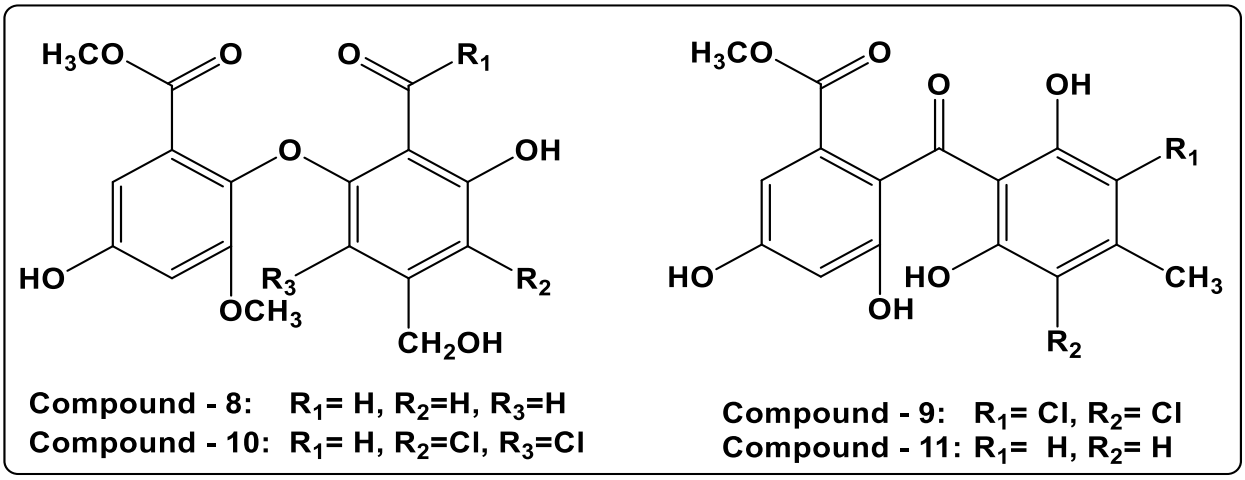
The work hypothesized here is to synthesize benzophenone-ether hybrids to make a new class of molecules that may show enhanced and variable properties. Present thesis describes the synthesis and characterization of few of these molecules.

Literature Review

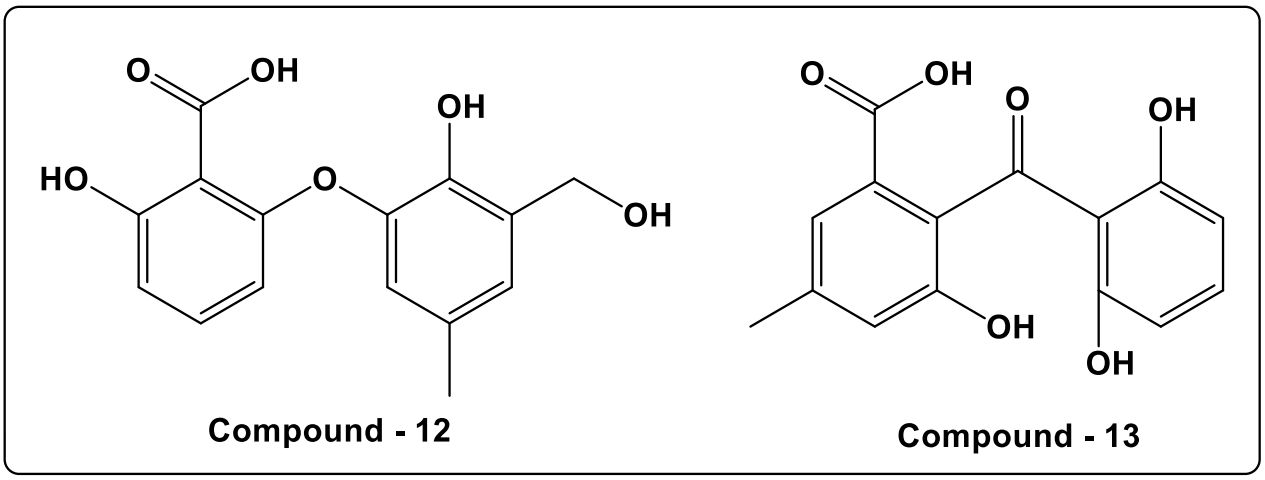
Benzophenone and diphenyl ether derivatives have shown various biological activities like anti-inflammatory[5], antibacterial[1], anti-malarial[6] and antiandrogenic[7] activities. These benzophenone and biphenyl ether derivatives have been found in various marine species. Due to their potential biological activities there are a number of reports for their synthesis using organic chemistry as tool[5][8][9].

Isolation from Natural Sources

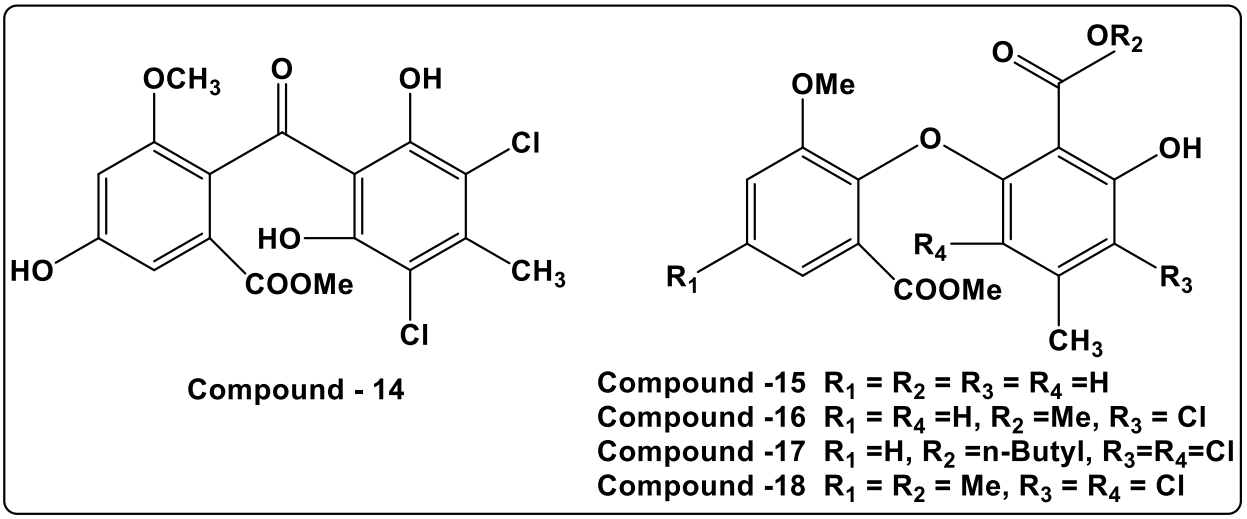
Recently, Zhang et. al isolated two new molecules first a diphenyl ether **(Compound - 8)** and second a benzophenone **(Compound- 9)** from the Chinese wetland fungus *Aspergillus flavipes* PJ03-11 along with many known compounds[10]. Among the isolated compounds one previously reported diphenyl ether **(Compound -11)** and benzophenone **(Compound -12)** gave α-glucosidase inhibitory activity. α-glucosidase inhibitors are considered important for diabetes treatment because of the enzyme's ability to uptake the dietary carbohydrates [11][12].



Another diphenyl ether containing three hydroxyl groups (**Compound–12**)**,** isolated by solvent extraction from *Penicillium albobiverticillium* **(TPU1432)** culture, found in Indonesia, inhibited CD45 with an IC_{50} value of 45µM. CD45 enzyme plays a critical role in lymphocyte signaling and is a potential target for autoimmune diseases[13]. Interestingly, another benzophenone compound **(13)** isolated from the same culture displayed inhibition of protein tyrosine phosphate1B (PTP1B) enzyme having IC_{50} value of 36 µM. PTPIB happens to be one of the potential targets to manage type 2 diabetes mellitus (T2DM) [14].

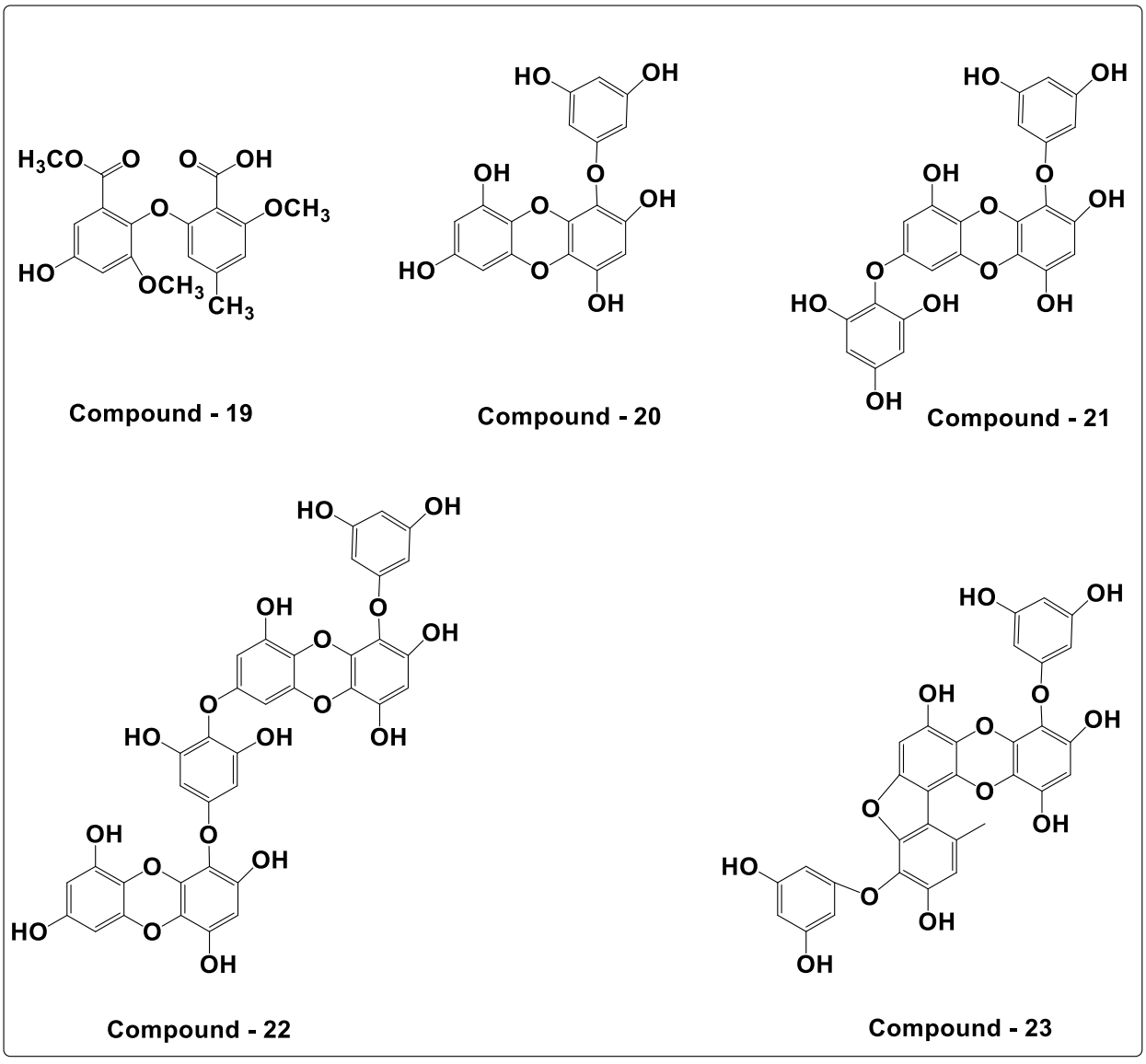


Fungus cultures are a rich source of above mentioned aromatic compounds and have been isolated from many strains. *Aspergillus sp*. F1 fungus strains grown on the seeds of *Trewia nudiflora* yielded diphenyl ether and benzophenone based compounds **(dihydrogeodin, 14)** and diphenyl ethers **(Compounds 15-18)** along with many sesterterpenoids, anthraquinon and lignins[15]. Another novel diphenyl ether compound, circinophoric acid **(Compound 19),** was isolated from from the marine sponge-associated fungus *Sporidesmium circinophorum* KUFA 0043[16].None of the compounds exhibited either antibacterial, anti-quorumsensing, antifungal or anticancer activities when tested against respective strains or cell lines.



A large number of diphenyl ether macromolecules have been reported to be PTP1B inhibitors.

This includes compounds isolated from methanol extract of two brown algae namlely E. bicyclisand E. stolonifera. Four compounds -Phlorotannin (**Compound 20**, IC_{50} 2.64± 0.04 mM), 47-phloroeckol (**Compound 21**, IC_{50} 0.56±0.10 mM), dieckol (**Compound 22**, IC_{50} 1.18±0.02 mM) and phlorofurofucoeckol-A (**Compound 23**, IC_{50} 2.09±0.09 mM), gave an impressive PTP1B inhibition[8].

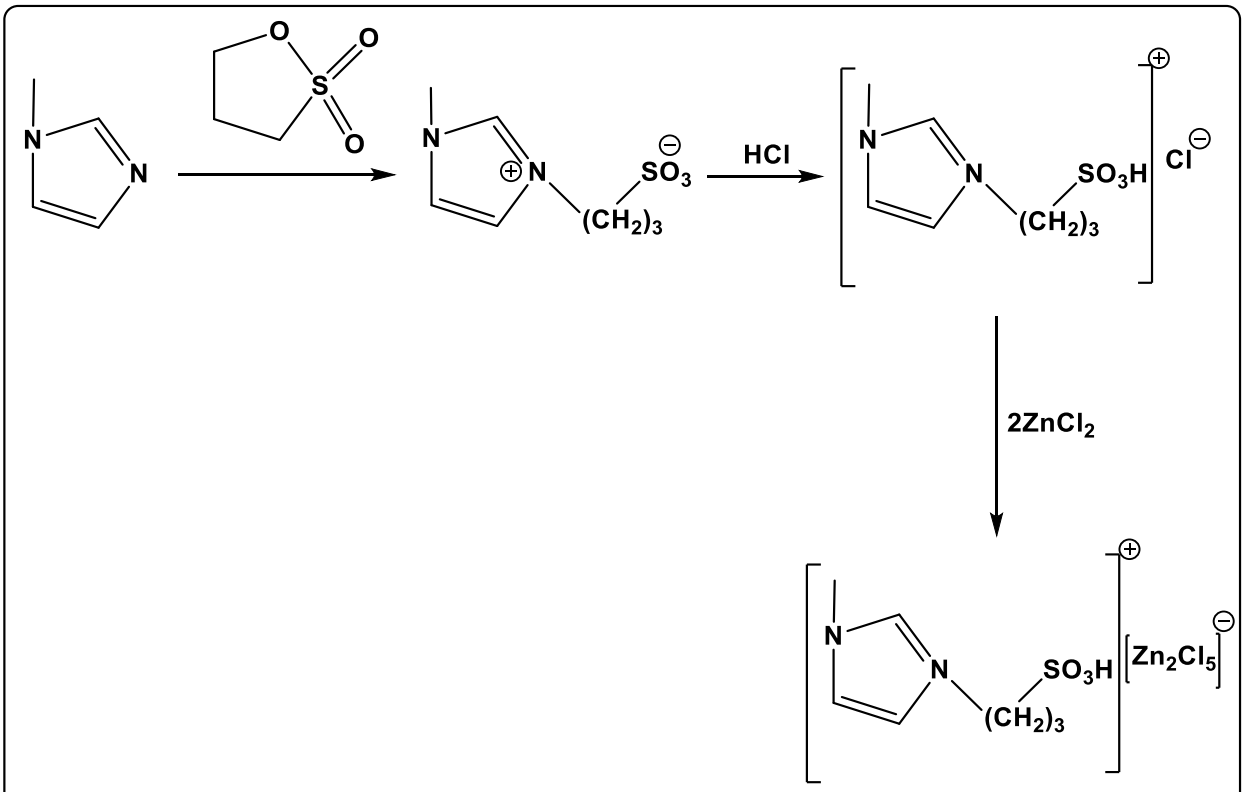


Thus, nature is rich source of both benzophenone and diphenyl ether group of compounds that have been found to be active in many biological applications.

Synthetic Routes

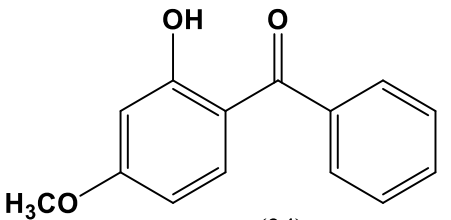
Benzophenone and its derivatives are usually synthesized by Friedel craft acylation of the aro-

-matic compounds in the presence of lewis acids such as BF_3, $TiCl_4$ and $AlCl_3$. Usually the lewis acid has to be taken in a excess due its co-ordination to the product that has to be removed using mineral acids. Besides this, other drawbacks of this methodology are low yield, toxicity of acids, corrosive nature, difficulties in product separation and their reuse. Use of ionic liquids in combination with lewis acids, such as 1-butyl-3-methlyimidazolium chloride- $FeCl_3$ (BmimCl-$FeCl_3$), BmimCl-$ZnCl_2$ has eliminated many of above problems [23]. Synthesis of ionic liquid is carried out as shown below **(Scheme 1)** [20].



Scheme 1. Synthesis of ionic liquid for Freidel Craft Acylation

Following hydroxylated benzophenone derivatives **(Compound 24)** used in commercial sunscreen as skin protecting agent and in plastic packaging as a UV stabilizers[7] have been short listed by EU to use as UV filters[18].



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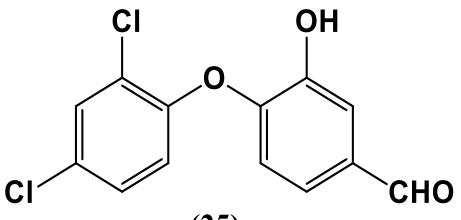
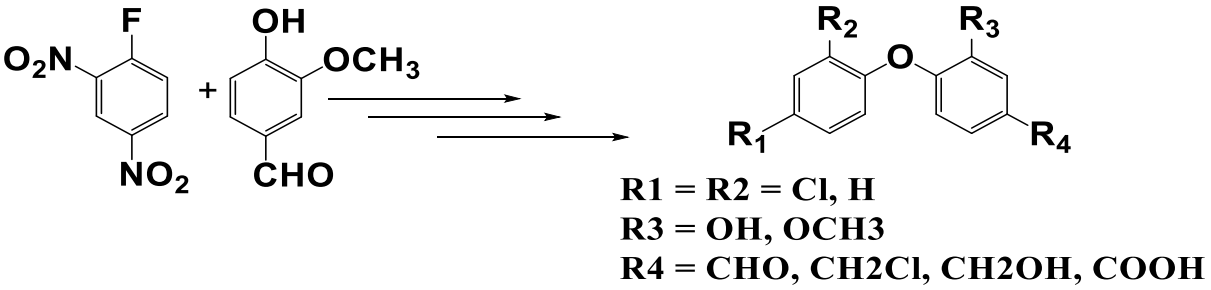


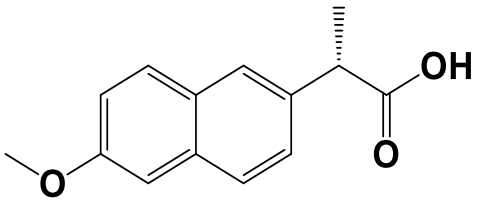
(25)

Chhibber et. al. synthesized a number of diphenyl ethers starting from commercially available Sanger's reagent and vanillin by aromatic nucleophillic substitution **(Scheme 2).** Evaluation of these compounds for antibacterial activity and for the inhibition of enoyl-ACP-reductase gave impressive results. **Compound - 25** gave results that were comparable to the standard compound triclosan.). Enoyl-Acyl carrier protein reductase (ENR) is a potential target for antibacterial and antimalarial drug therapy because of its unique role in fatty acid biosynthesis across many bacterial species [6].

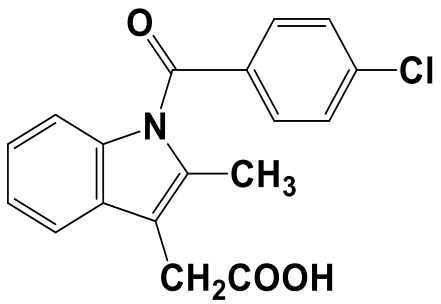


Scheme 2. Syntheis of diphenyl ether

A search of literature revealed many compounds with both benzophenone and diphenyl moieties present in them. The compounds had applications in many important materials and drug molecules. For example benzophenone-based series of compounds, one of which is shown below **(Fig. 1)** is one of the non-nucleoside reverse transcriptase inhibitors (NNRTI) with ability treat HIV infections of AIDS. In fact, this series of compounds have emerged as effective second generation inhibitors with high potency against both resistant and wild-type strains of the virus[9].



Naproxen



Indomethacin

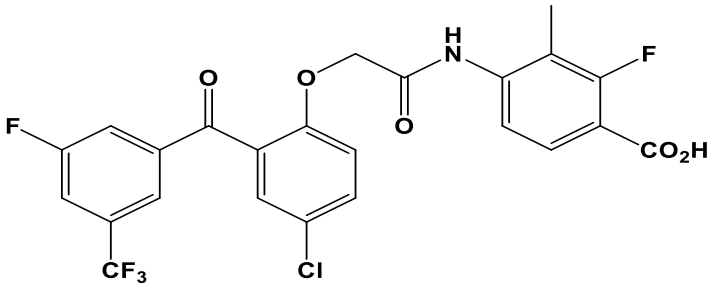
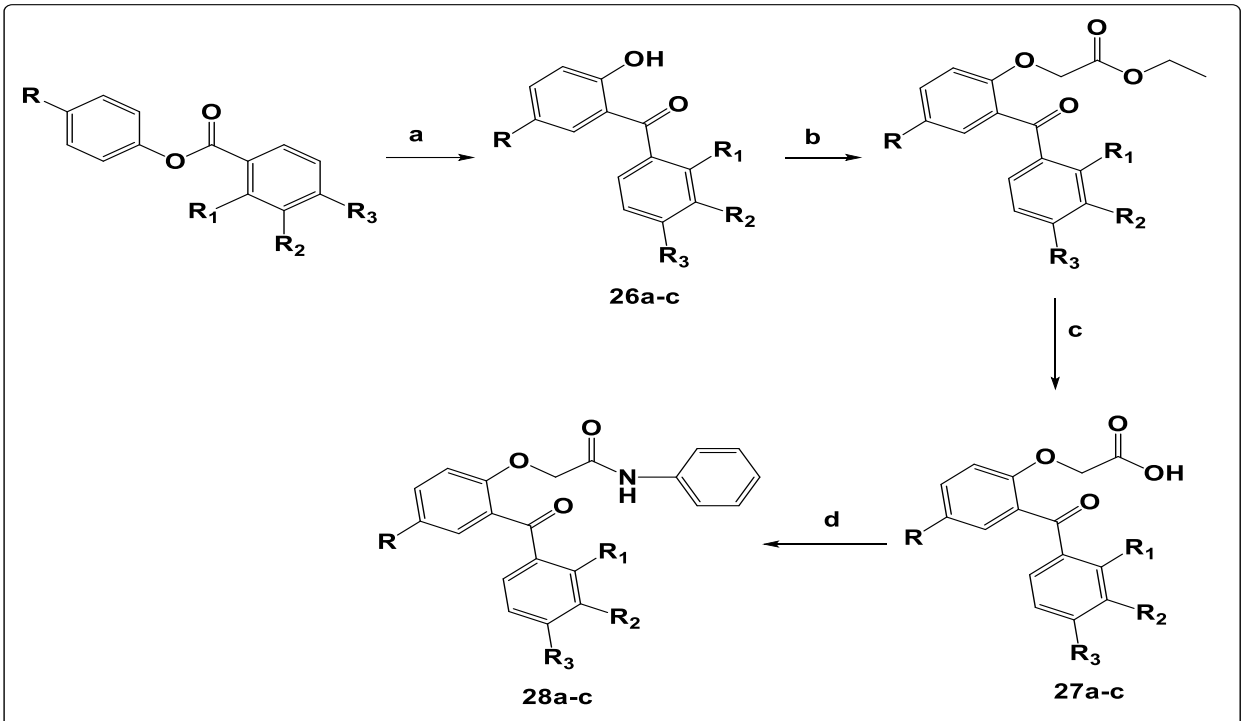


Fig. 1 Benzophenone based NNRTs

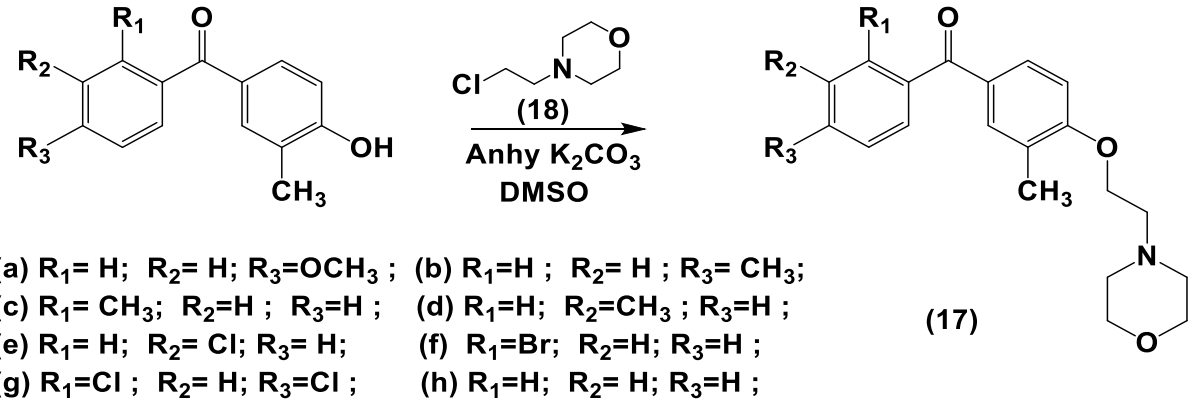
A number of derivatives of this drug have been synthesized in last two decades and evaluated for anti-inflammatory and ulcerogenic activities **(Scheme – 3)**. One of the important aspect is that these compound was that no side effects as seen in non-steroidal anti-inflammatory drugs (NASIDs) was visible as seen in naproxen and indomethacin[19].



(a) $R=CH_3$; R_2= Cl ; R_1= R_3= H;
(b) $R=CH_3$; R_1= Br; R_2= R_3= H;
(c) $R=CH_3$; R_1= R_2= H; R3= OCH_3;

Scheme 3. (a) Anhydrous $AlCl_3$, (b) K_2CO_3, $ClCH_2CO_2Et$, Acetone, (c) NaOH, EtOH, H_2O, (d) BF_3 etherate, $NH_2C_6H_5$, Dry benzene.

Above series of compounds were revisited again for the integration of morpholine in benzophenone framework to revaluate their activities **(Scheme-4)**.

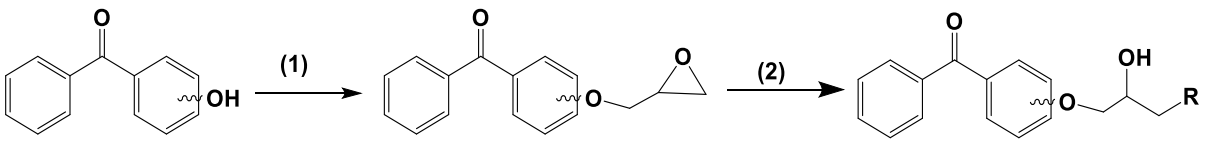


(a) R_1= H; R_2= H; R_3=OCH_3 ; (b) R_1=H ; R_2= H ; R_3= CH_3;
(c) R_1= CH_3; R_2=H ; R_3=H ; (d) R_1=H; R_2=CH_3 ; R_3=H ;
(e) R_1= H; R_2= Cl; R_3= H; (f) R_1=Br; R_2=H; R_3=H ;
(g) R_1=Cl ; R_2= H; R_3=Cl ; (h) R_1=H; R_2= H; R_3=H ;

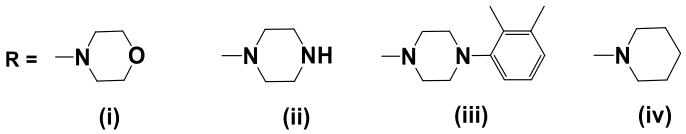
Scheme 4. Integration of Morpholine in benzophenone framework

The compounds displayed high anti-inflammatory activity ranging from 28 to 57.8% at a dose of 40mg/kg. The compounds also exhibited low ulcer production activity as compared to standard drug[5].

A number propafenone analogs that are benzophenone derivatives of ethers have been shown to influence drug efflux pump P-gylcoprotein (P.gp) that promotes the multidrug resistance (MDR) in tumor as well as to influence ADME properties of drug candidate [21]. These benzophenone derivatives have been as shown in **scheme 5** below.



Reagent and condition (a) NaOH, epicholorohydrine, reflux for 24h (b) methanol,repective amine, reflux for 24h



Scheme 5. Synthesis of benzophenone derivative which are structurally analogous to propafenone-type inhibitor

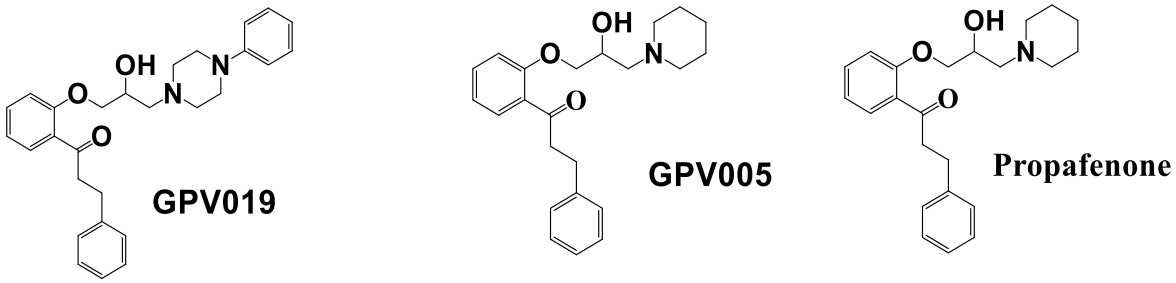


Figure.2 Propafenone Analogues

From the above literature it can be seen that although many ether derivatives of benzophenone compounds are known but aryl ether derivatives of benzophenones are missing as far as their synthesis is concerned. On the other hand from natural resources a number of aryl ether derivatives of benzophenone have been isolated and evaluated for their biological activities with impressive results as shown above. Thus, there is a need to explore this series of compounds and evaluate them for their biological and other material properties. This project, however, concentrates only on the synthesis and characterization of above mentioned compounds.

Materials and Methods

General: All chemicals and solvents were procured from M/s AVRA Chemicals, Hyderabad, India and were of LR grade. Purification of organic compounds was done by column chromatography using silica gel (60-120 mesh) and specified solvents. TLC monitoring was done using silica coated aluminium sheets (60 F254; 0.2mm thickness, Merck, India).

Characterization of all the organic compounds was done using ^{1}H (400 MHz) and ^{13}C (100 MHZ) NMR spectrometer (JEOL, model A1, Sai Labs, Patiala, India).

Synthesis of 2-bromo-5-nitrobenzaldehyde (B): 2-Bromobenzaldehyde (0.400 g, 2.16 mmol) was taken in 100ml round bottom flask. To this was added DCM (7ml) and H_2SO_4 (3ml) in the ratio of 7:3 and then added HNO_3 (0.3ml, 7.2 mmol) and H_2SO_4 (0.9ml, 17 mmol). Reaction mixture was stirred for 2 hours at temperature (10-15^{o} C) in waterbath.TLC was done to monitor the reaction progress **(Fig.3 B)** and after the reaction is complete, the mixture was extracted by using DCM (2×25), washed with water (2×25), and dried over anhydrous sodium sulphate. The solvent was evaporated and the crude product purified by column chromatography using ethyl acetate and hexane as an eluent to obtain white colored solid (363mg). Yield = 72%; Melting Point= 92-95 ^{o}C. ^{1}H NMR (δ; 400 MHz; $CDCl_3$): 7.8 (d, J=8.72Hz, 1H), 8.2 (dd, J=2.72, 9.2Hz, 1H), 8.7 (d, J=2.72Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 124.7, 128.8, 133.1, 134.4, 135.2, 147.6, 189.4.

Synthesis 2-(2-benzoyl-5-methoxyphenoxy)-5-nitrobenzaldehyde (D): Method 1: The compound **(C)** procured commercially (2-hydroxy-4-methoxyphenyl)(phenyl)methanone (0.360 g, 1.5 mmol) was taken in a 100mL round bottom flask to which was added DMF (10ml), K_2CO_3 (0.326 g, 2.3 mmol) and catalytic amount of 18-Crown-6. The contents were stirred in a round bottom flask for 10-15 minutes. To the stirred solution 2-bromo-5-nitrobenzaldehyde **(B)** (0.363 g, 1.5 mmol), synthesized above, was added and further stirred for 12 hours at room temperature. TLC monitoring after 12 hour indicated formation of product that was extracted by using DCM (2×25), washed with water (2×25) and dried over anhydrous sodium sulphate. The solvent was evaporated and the crude product purified by column chromatography using ethyl acetate and hexane as eluent to give a light yellow colored solid (0.406 g). Yield = 55%; Melting Point = 115-119^{o}C.

Method 2: Commercially procured compound **(C)** (2-hydroxy-4-methoxyphenyl) (phenyl) methanone (0.360 g, 1.5 mmol) was taken in a 100 mL round bottom flask to which was added DMF (10 ml), K_2CO_3 (0.326 g, 2.3 mmol) and catalytic amount of 18-Crown-6. The contents of the round bottom flask were stirred for 10-15 minutes. To the stirred solution 2-bromo-5-nitrobenzaldehyde **(B)** (0.363 g, 1.5 mmol), synthesized above, and catalytic amount of CuI was added followed by stirring over night at room temperature. TLC monitoring after 12 hour **(Fig.3 D)** indicated formation of product that was extracted by using DCM (2×25), washed with water (2×25) and dried over anhydrous sodium sulphate. Then solvent was evaporated and the crude product purified by column chromatography using ethyl acetate and hexane as eluent to give a light yellow colored solid (0.406g). Yield = 67%; Melting Point =115-119 ^oC.

^1H NMR (δ; 400MHz; $CDCl_3$): 3.9 (s, 3H), 6.7 (t, 2H), 7.0 (dd, J=2.32, 8.68Hz, 1H), 7.3 (t, 2H), 7.6 (t, 1H), 7.6 (t, 2H), 7.7 (d, J=8.68Hz, 1H), 8.2 (dd, 3.2, 9.16Hz, 1H), 8.5 (d, J=2.76Hz, 1H), 9.9 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 55.9, 108.1, 112.1, 116.0, 124.0, 124.2, 124.8, 128.4, 129.3, 130.0, 133.3, 133.7, 137.9, 142.6, 153.1, 163.9, 164.0, 186.4, 193.5.

Synthesis of (2-(2-(hydroxymethyl)-4-nitrophenoxy)-4-methoxyphenyl)(phenyl)methanone (E): Compound **(D)** obtained above, 2-(2-benzoyl-5-methoxyphenoxy)-5-nitrobenzaldehyde, (0.200 g, 0.53 mmol) was taken in 100ml round bottom flask to which THF (8mL), H_2O (0.1mL) and $NaBH_4$ (0.010g, 0.26mmol) were added. The resulting mixture was stirred magnetically for 5 minutes at room temperature. Reaction progress was monitored by TLC **(Fig.3 E).** After the completion of the reaction, distilled water (3mL) was added to the reaction mixture and solution stirred for another 5 minutes. The mixture was extracted with DCM and dried over anhydrous Na_2SO_4. Solvent evaporated gave crude product that was purified using column chromatography (hexane and ethylacetate) giving yellowish brown solid (.180g). Yield= 89%; Melting Point=109-112 ^oC. ^1H NMR (δ; 400MHz; $CDCl_3$): 3.9 (s, 3H), 4.5 (s, 2H), 6.6 (dd, J= 2.28Hz, 1H), 6.7 (d, J=9.20Hz, 1H), 6.8 (dd, J=2.72, 8.72Hz, 1H), 7.4 (m, 2H), 7.5 (m, 1H), 7.6 (d, J=8.68Hz, 1H), 7.6 (m, 2H), 8.0 (dd, J=2.72, 9.16Hz, 1H), 8.2 (d, 1H). ^{13}C NMR ($CDCl_3$): δ 55.8, 59.9, 107.5, 110.9, 114.6, 122.8, 124.6, 124.8, 128.3, 129.7, 131.6, 133.0, 133.8, 137.9, 142.8, 154.3, 159.7, 163.7, 193.9.

Synthesis of (2-(2-(hydroxymethyl)-4-nitrophenoxy)-4-methoxyphenyl)(phenyl)methanol (F): Compound **(D)**, 2-(2-benzoyl-5-methoxyphenoxy)-5-nitrobenzaldehyde (0.150g, 0.39mmol)

was taken in 100ml round botom flask to which THF (8ml), H_2O (0.1ml) and $NaBH_4$ (0.045 g, 1.1 mmol) was added. The resulting mixture was stirred magnetically for 5 minutes at room temperature. Reaction progress was monitored by TLC **(Fig.3 F)**, after the completion of the reaction, distilled water (3ml) was added and then stirred the reaction mixture for another 5 minutes. Then the mixture was extracted with DCM and dried over anhydrous Na_2SO_4. Solvent evaporated gave crude product that was purified using column chromatography (hexane and ethylacetate) giving light yellow colored solid (.139g). Yield= 91%. ^{1}H NMR (δ; 400MHz; $CDCl_3$): 3.8 (s, 3H), 4.6 (d, J=5.96Hz, 2H), 5.8 (s, 1H), 6.4 (d, J=2.32Hz, 1H), 6.5 (d, J=9.16Hz, 1H), 6.8 (dd, J=2.72, 8.68Hz, 1H), 7.2 (m, 5H), 7.4 (d, J=8.64, 1H), 7.9 (dd, J= 2.72, 9.2Hz, 1H), 8.2 (d, J=2.76Hz, 1H). ^{13}C NMR ($CDCl_3$): 55.6, 60.3, 71.4, 106.5, 110.9, 115.0, 124.6, 124.7, 126.4, 127.5, 127.6, 128.4, 129.7, 135.0, 142.5, 142.5, 152.4, 159.9, 160.4.

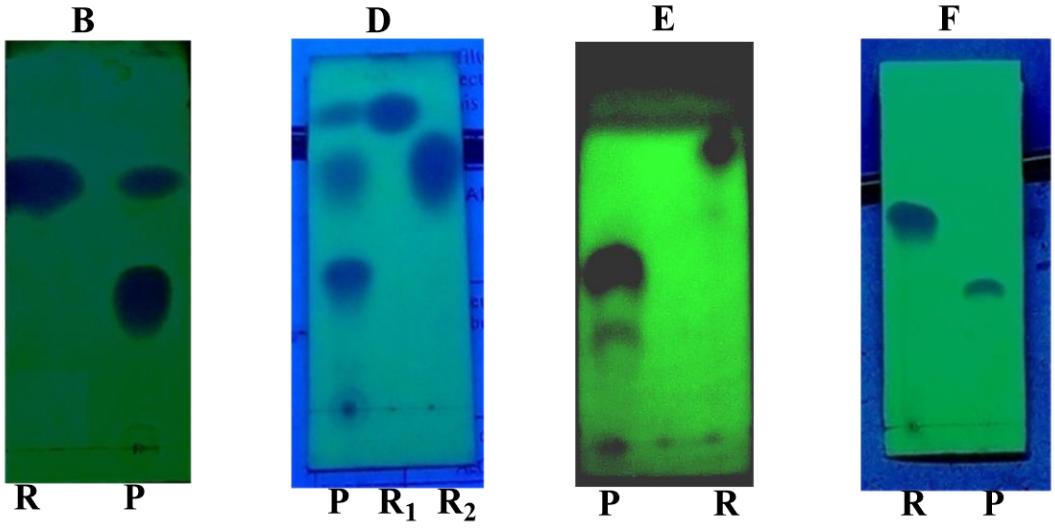
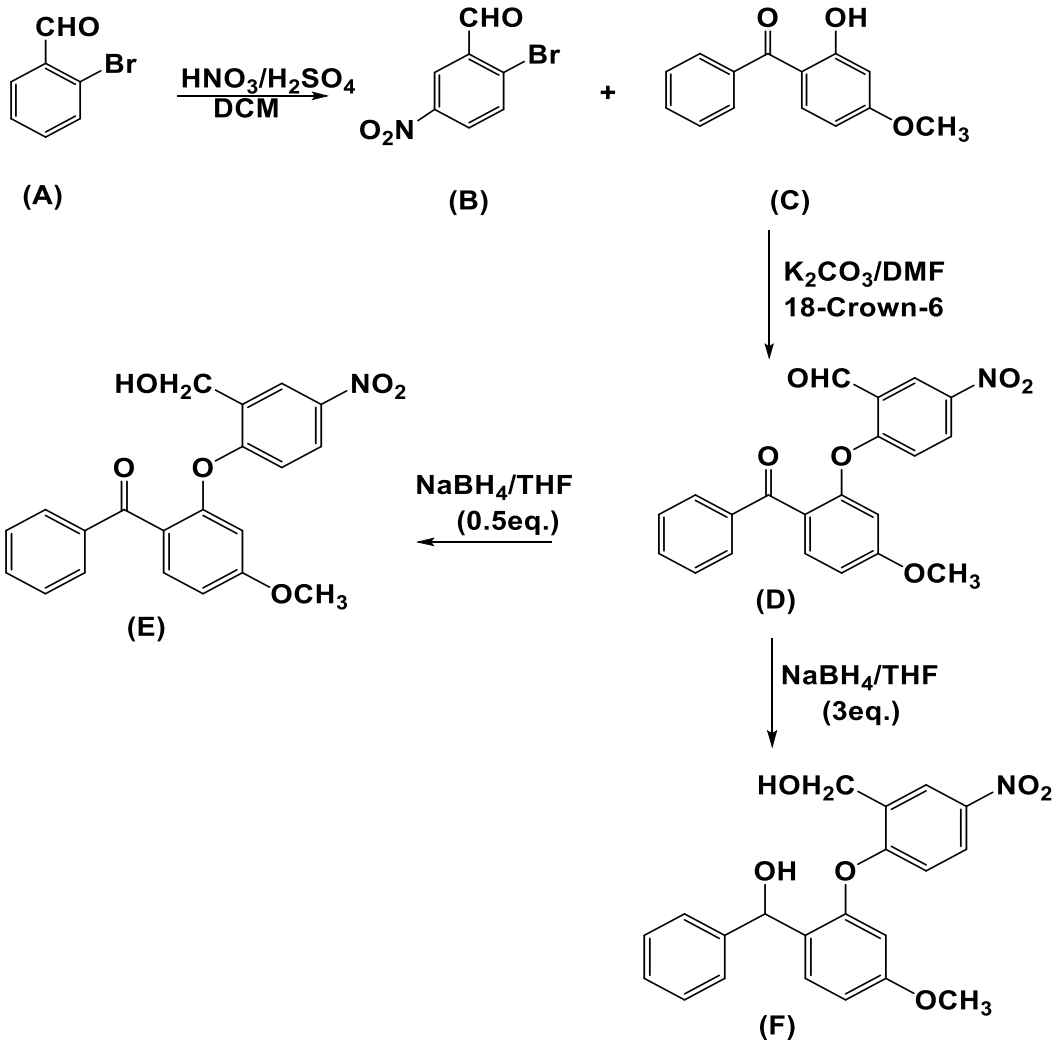


Fig. 3 Reaction monitoring by thin layer chromatography using solvent system ethyl acetate and hexane in the ratio 15:85, 20:80, 30:70, 25:75 for compound B, D, E, F

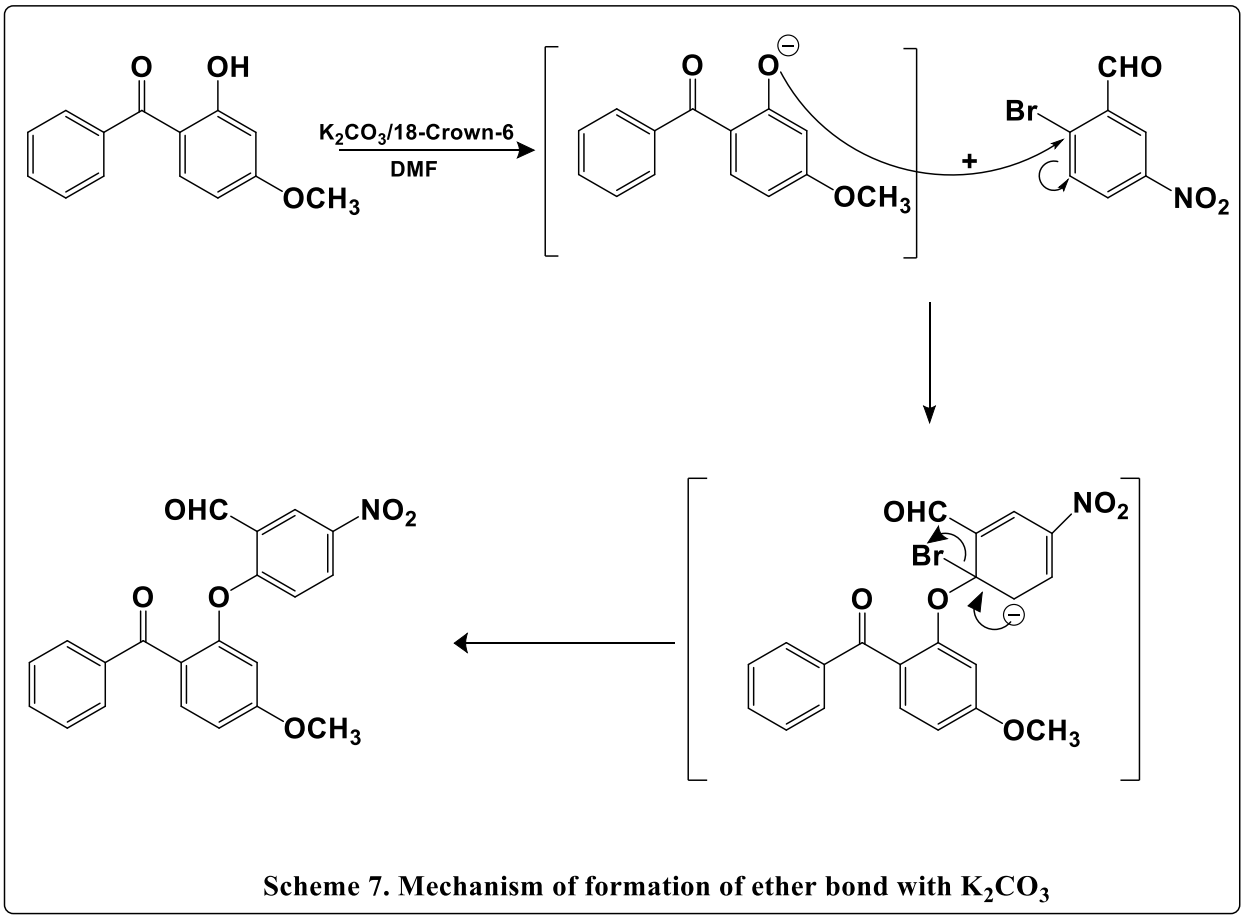
Result and Discussion

Benzophenone based phenyl ether were synthesized as detailed in **scheme 6**. Nitration of 2-bromo benzaldehyde was carried out using concentrated nitric and sulphuric acid in dichloromethane using water bath. The product was obtained in the quantitative amount. Appearance of signals at 7.8 & 8.7ppm towards downfield δ value due to nitro group and decrease of one proton in the aromatic region confirmed the nitration. This was further confirmed by a double doulblet at 8.2ppm having J= 2.7Hz. Absence of double doublets at 7.8 & 7.6 ppm[22] confirmed that nitration has been achieved.



Scheme 6. Synthesis of Benzophenone based phenyl ether

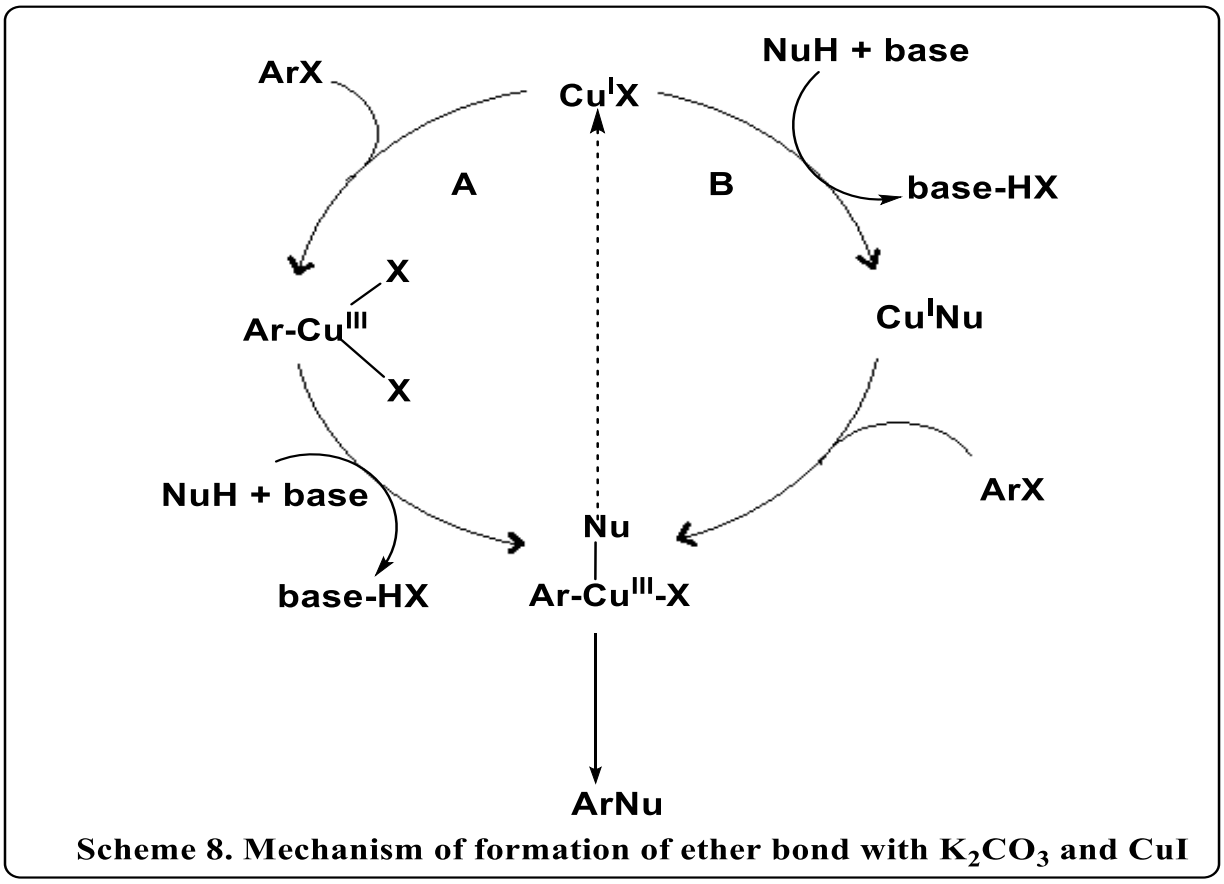
Nitration product **(B)** obtained, was reacted with (2-hydroxy-4-methoxyphenyl)(phenyl)methanone **(C)** via nucleophilic aromatic substitution using mild base (K_2CO_3) in aprotic solvent and phase transfer catalyst (18-Crown-6) to obtain benzophenone based phenyl ether product **(D).** Presence of two carbonyl carbon at 193.5 and 186.4ppm due to ketone and aldehyde groups respectively and methoxy carbon at 55.9ppm confirmed the formation of product **(D)**. In order to improve the product yield, same reaction was carried out in the presence of CuI. An overall improvement of 12% product yield was achieved by later reaction using CuI. **Scheme 7 and 8** briefly describe the mechanism of formation of ether bond by K_2CO_3 and K_2CO_3 with CuI. We envisaged to selectively reduce both the carbonyl groups one by one in the presence of other and total reduction of all the carbonyls.



Scheme 7. Mechanism of formation of ether bond with K_2CO_3

Interestingly products E (Route X, Scheme 8) and F (Route Y, Scheme 8) could be achieved using single reagent, sodium borohydride, by varying molar ratio. It was observed that 0.5 equivalents of $NaBH_4$ reduced only aldehyde group in the presence of ketone giving compound – **E.** While excess of same reagent (3 equivalents) carries out reduction of both aldehyde and

ketone to yield product **F**. Solvent used in both the route X and Y was tetrahydrofuran with drop of water.

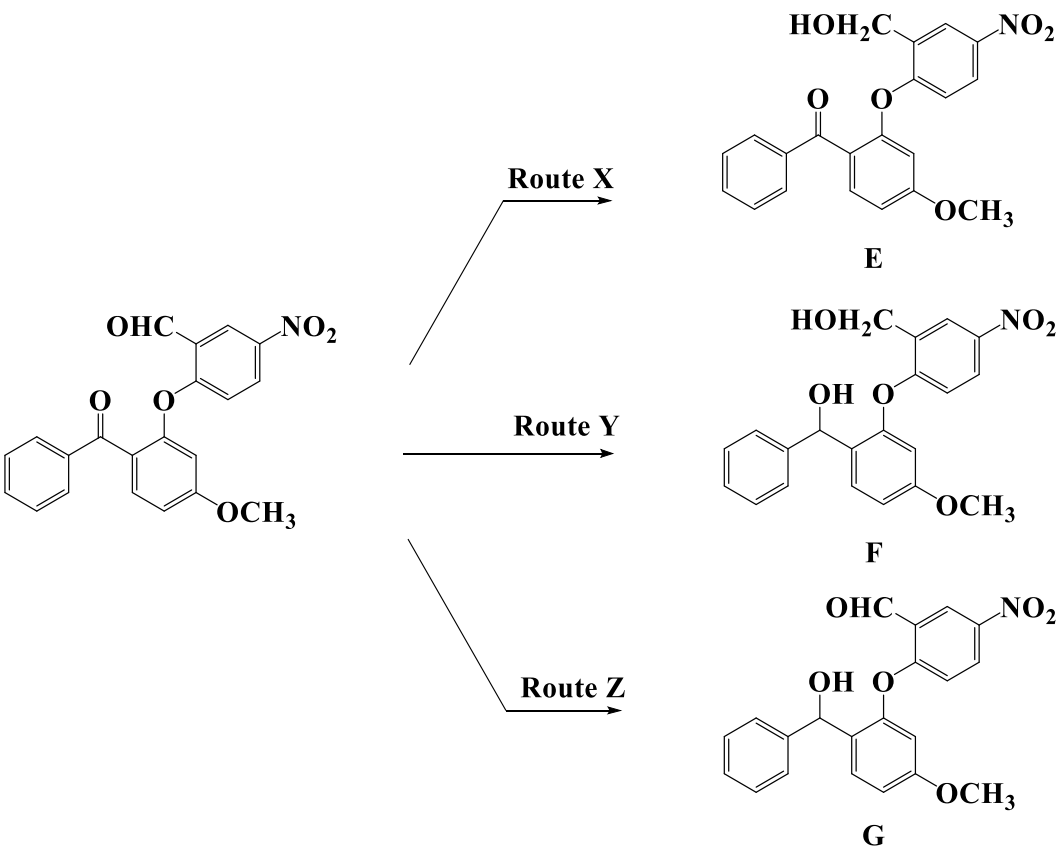


Scheme 8. Mechanism of formation of ether bond with K_2CO_3 and CuI

Absence of proton in ^{1}H NMR at 9.9ppm and appearance of a new methylene proton at 4.5ppm confirmed the reduction of aldehyde to corresponding benzyl alcohol derivatives (**E)**. In ^{13}C NMR also the carbonyl at 186.4ppm due to aldehyde group disappeared with simultaneous appearance of methylene cabron at 59.9ppm. Other carbon at 193.9ppm due to ketone was intact. In aliphatic region of ^{13}C methoxy carbon of the benzophenone moiety appeared at 55.8ppm. Above observation confirmed the synthesis of **compound – E.**

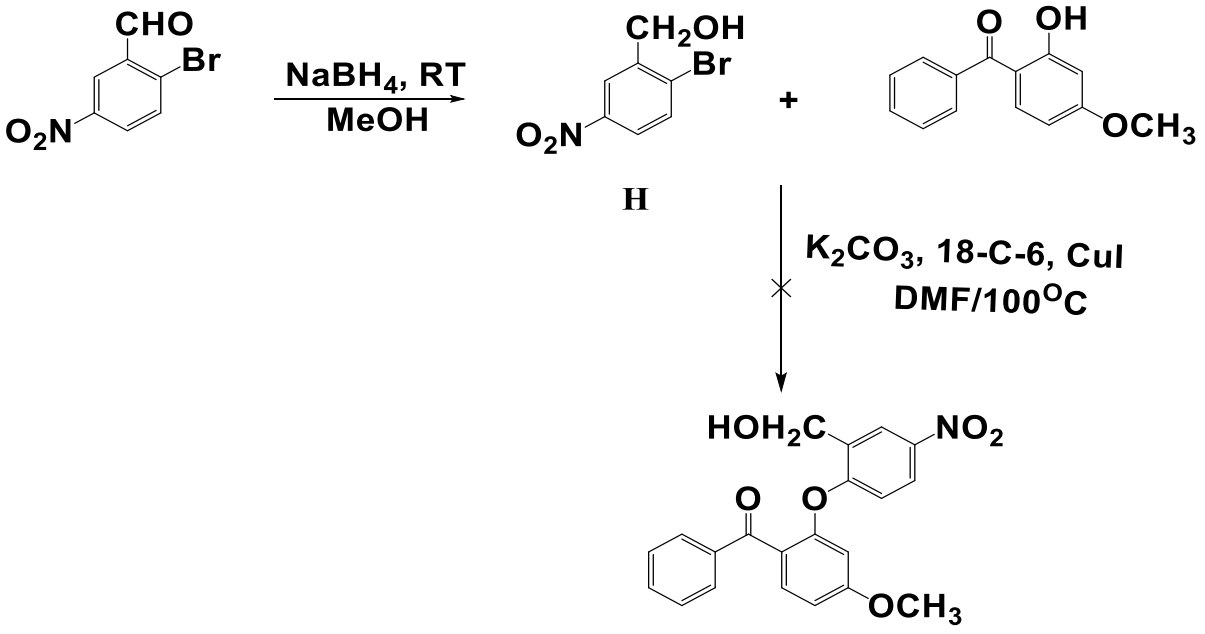
Compound F,that was obtained by 3 equivalents of reducing agent as described above, was also confirmed by ^{1}H and ^{13}C NMR. The disappearance of carbon due to carbonyl ketone from 193.5ppm and simultaneous appearance of alcoholic carbon at 71.3ppm along with methoxy and benzylic carbons at 55.5 and 60.3ppm respectively indicated the reduction of both carbonyl due to aldehyde and ketone together. In ^{1}H NMR also, besides methoxy protons (3.7ppm) the signals

due to methyne proton (5.8ppm) corresponding to one hydrogen and benzylic proton corresponding to two hydrogens (4.6ppm) confirmed the reduction of both the carbonyl groups.



Scheme 9. Routes to synthesis benzophenone based ether derivatives

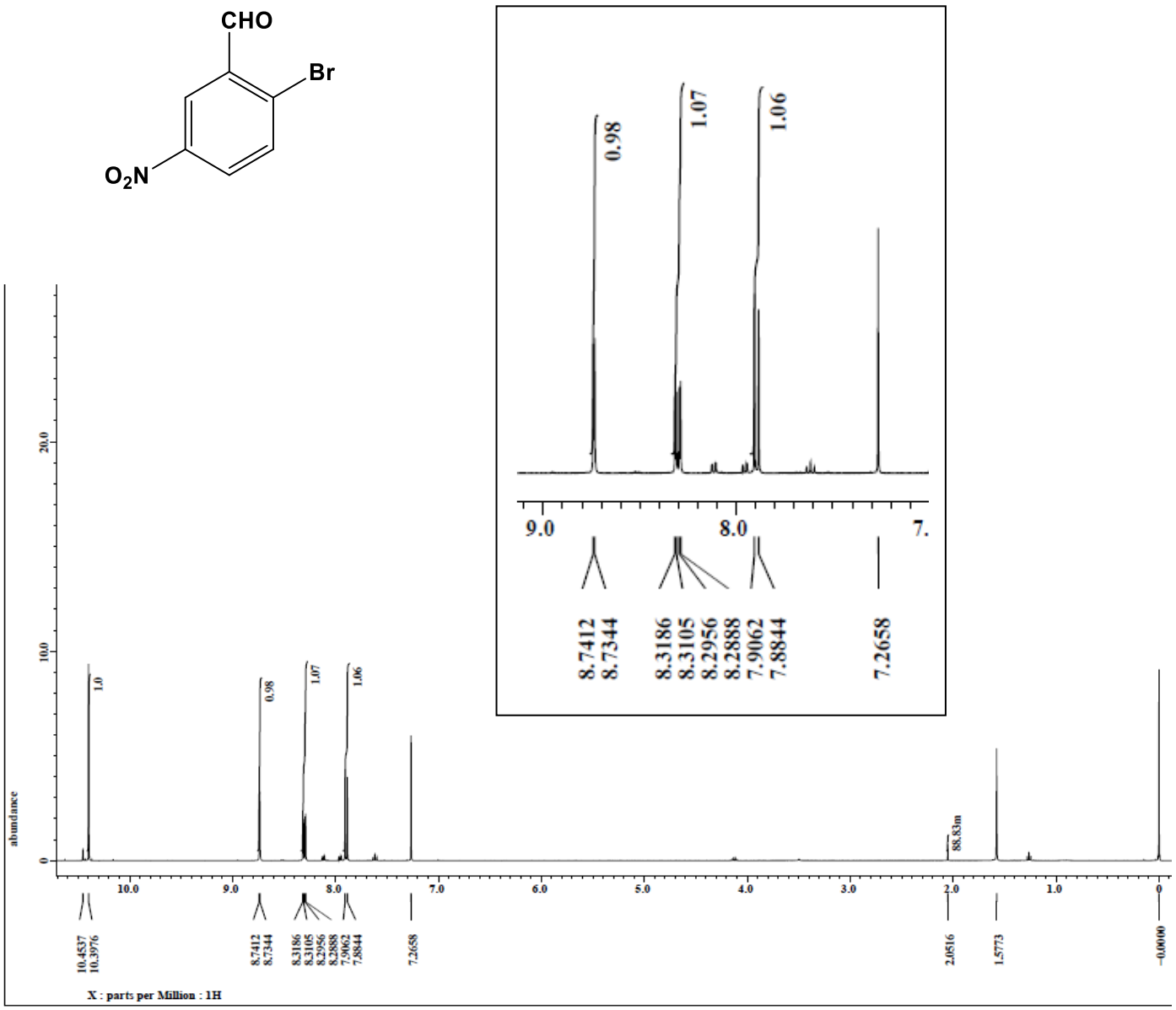
Earlier we attempted the synthesis of **compound - E** using alternative route where aldehyde groups of compound B was 1st converted to corresponding alcohol in the presence of $NaBH_4$ and methanol **(Scheme 10).** The conversion **compound - B** was confirmed by disappearance of aldehyde proton at 9.9ppm and simultaneous appearance of methylene proton of corresponding alcohol at 4.8ppm. Further reaction of **compound** – **H** with **compound** – **C** gave a mixture of multiple products that were inseparable by TLC.



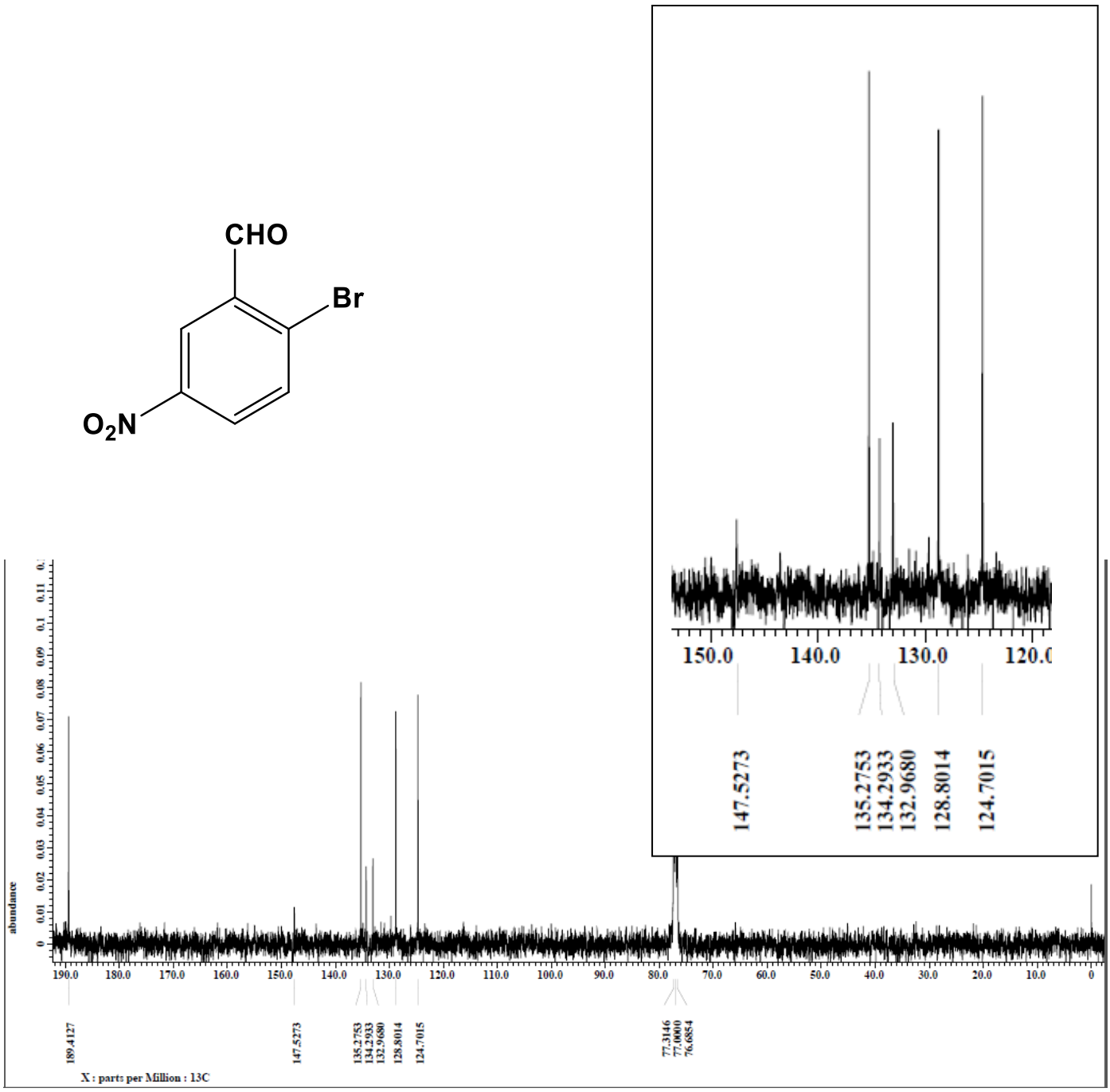
Scheme 10. Alternative route attempted to synthesize compound D

Thus the work described above successfully demonstrates the synthesis and characterization of three **compounds** - **D, E** and **F**. Two of synthesis **compounds - E** and **F** contain a chiral centre also which needs to be resolved before its application in any field.

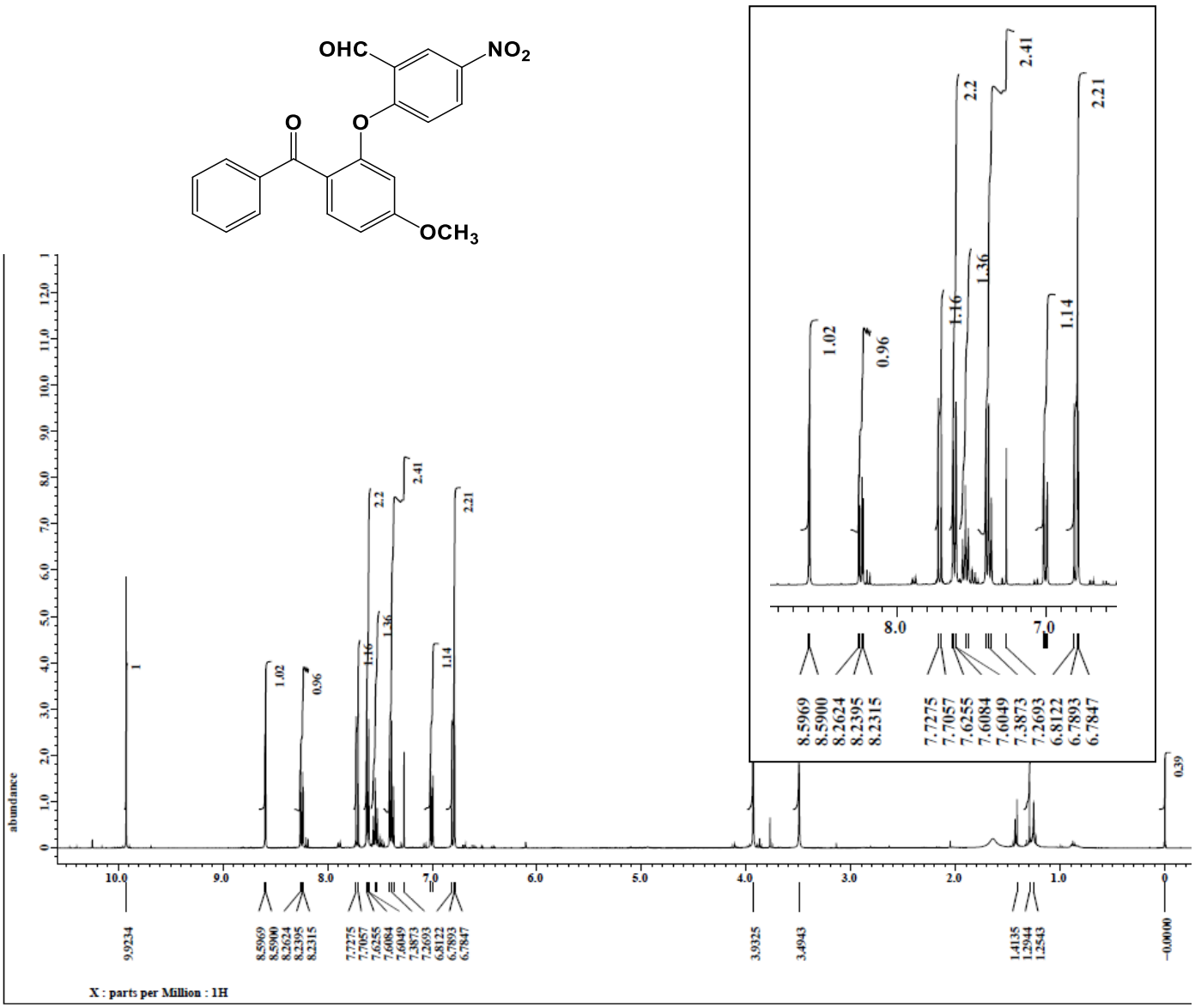
NMR Spectra



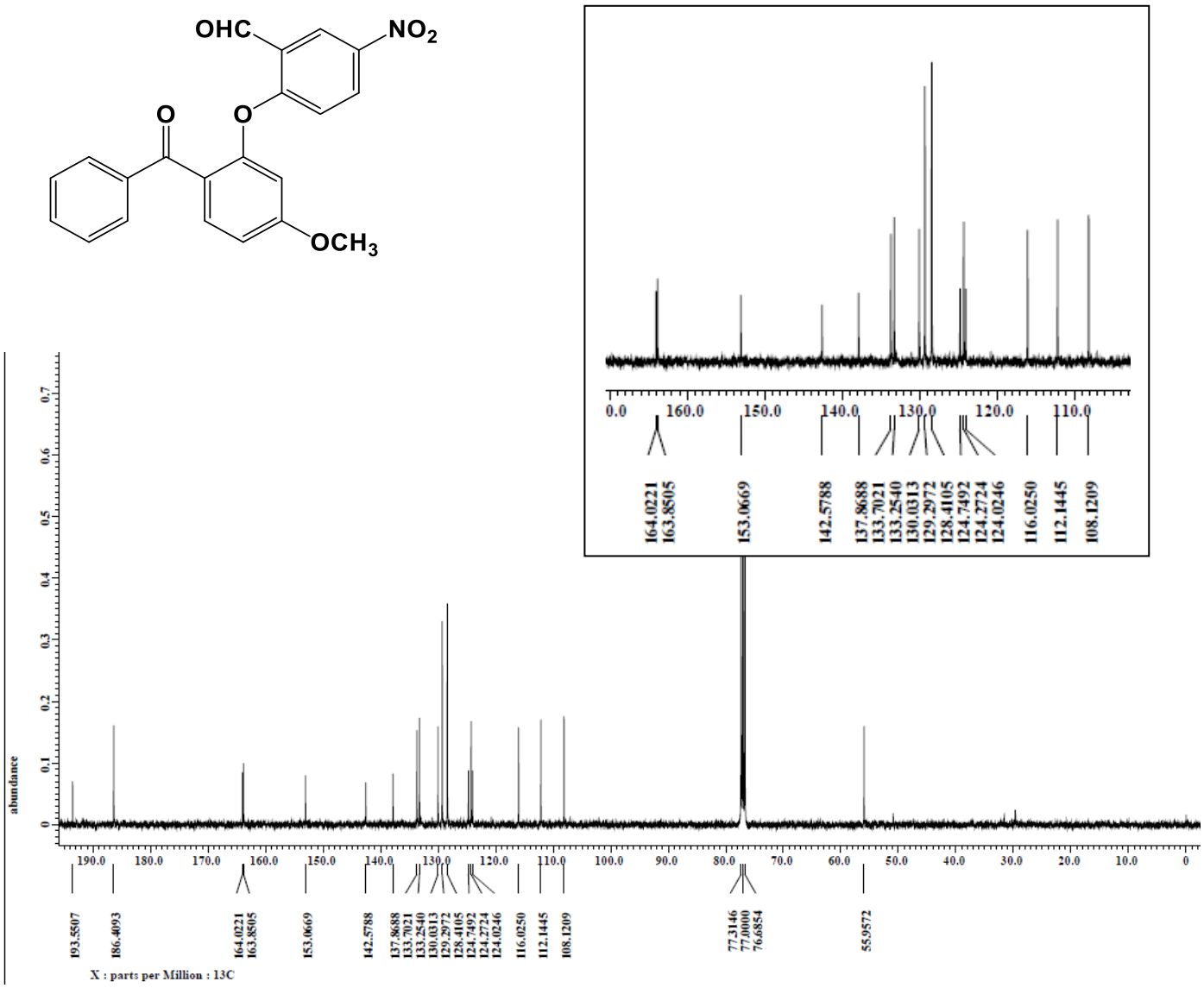
^{1}H NMR Spectra of 2-bromo-5-nitrobenzaldehyde



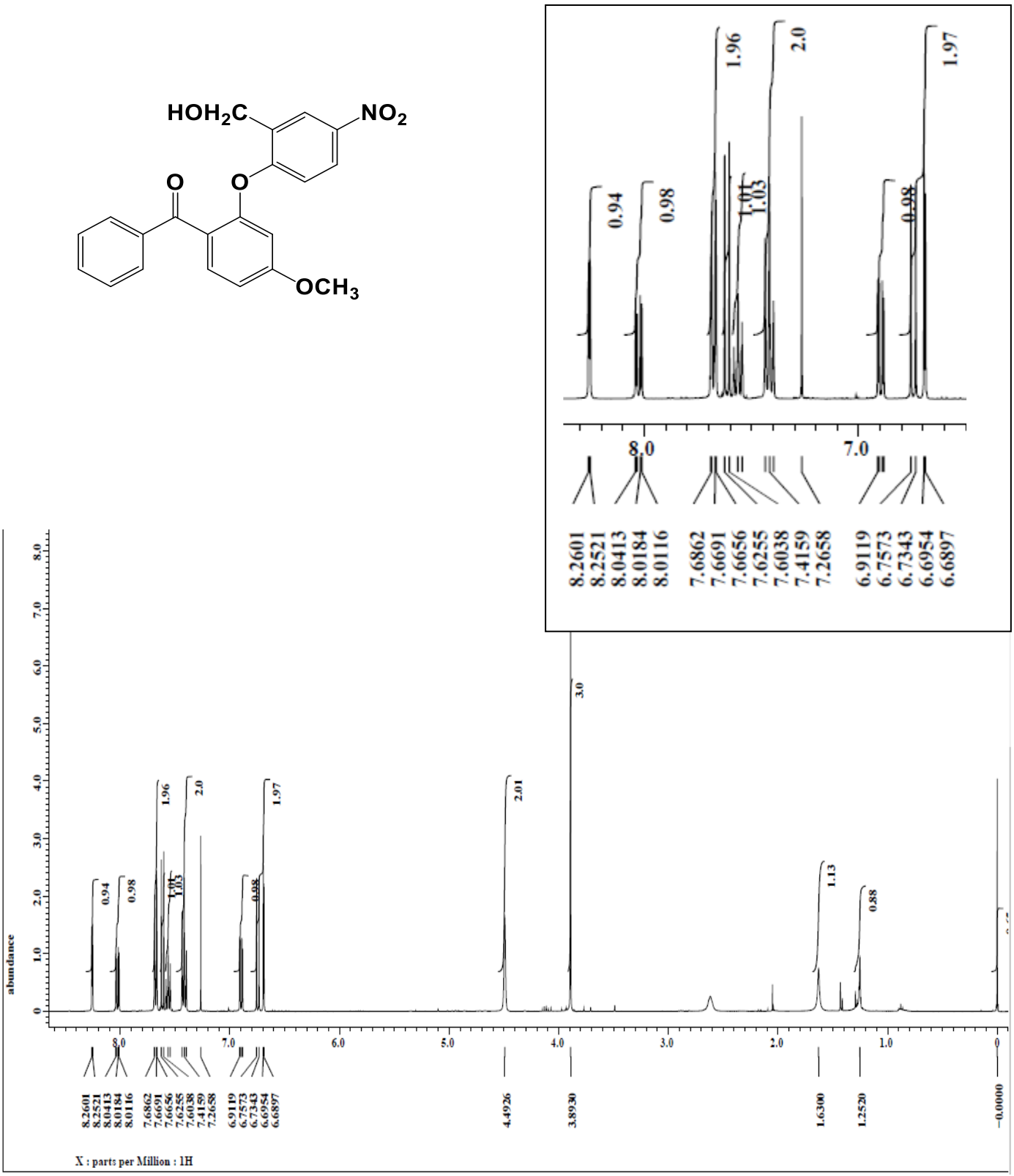
^{13}C NMR Spectra of 2-bromo-5-nitrobenzaldehyde



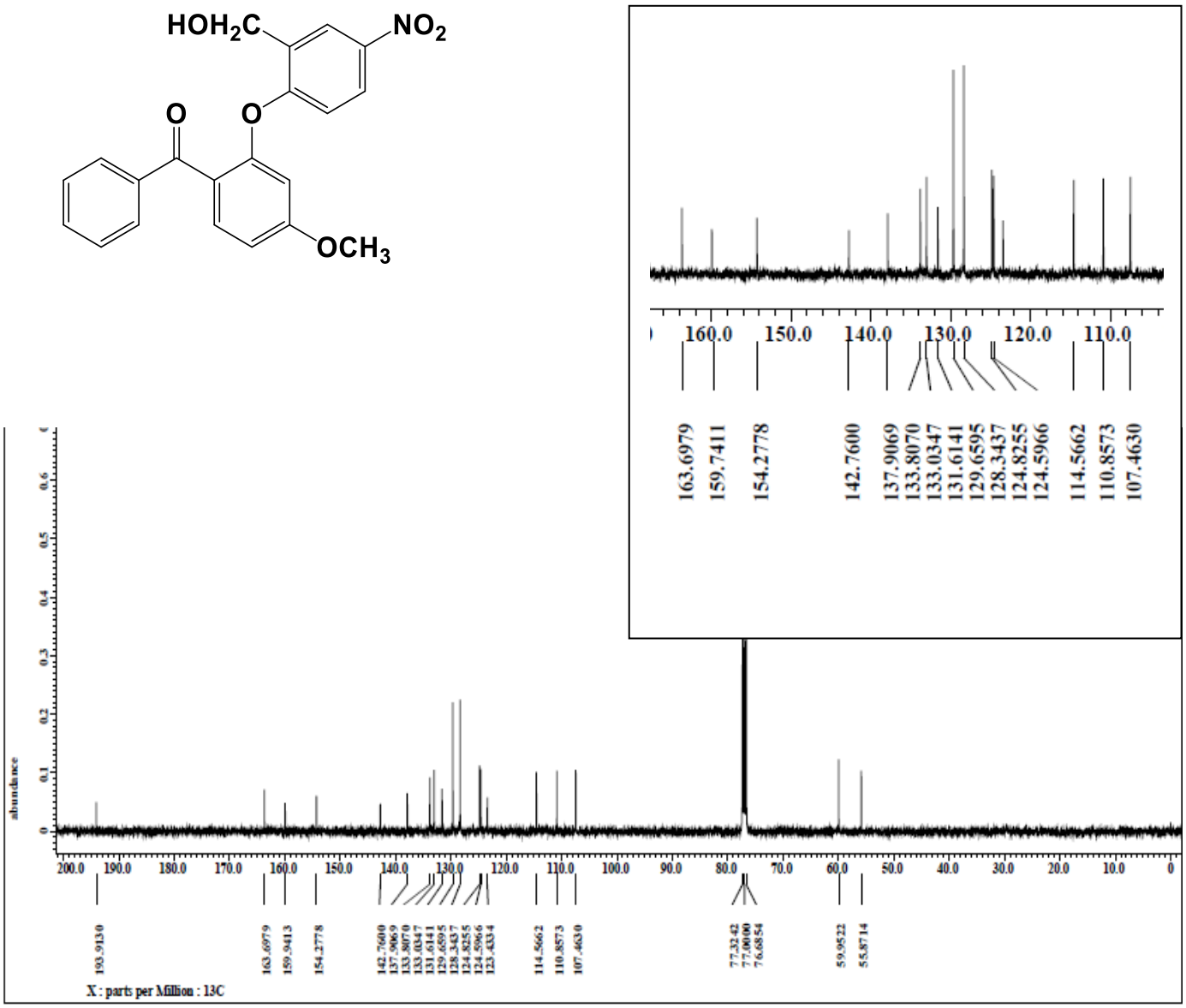
^{1}H NMR Spectra of 2-(2-benzoyl-5-methoxyphenoxy)-5-nitrobenzaldehyde



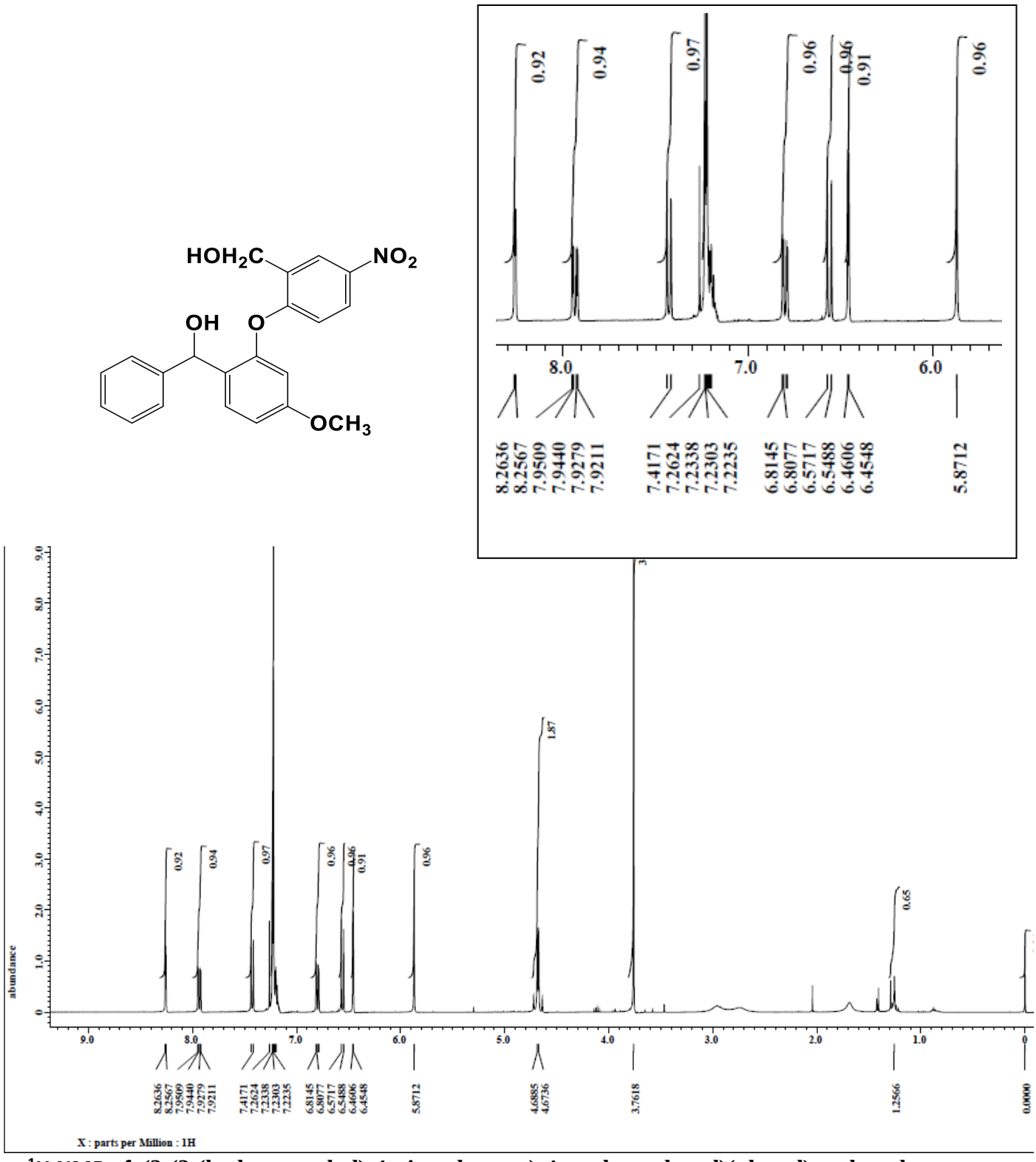
^{13}C NMR Spectra of 2-(2-benzoyl-5-methoxyphenoxy)-5-nitrobenzaldehyde



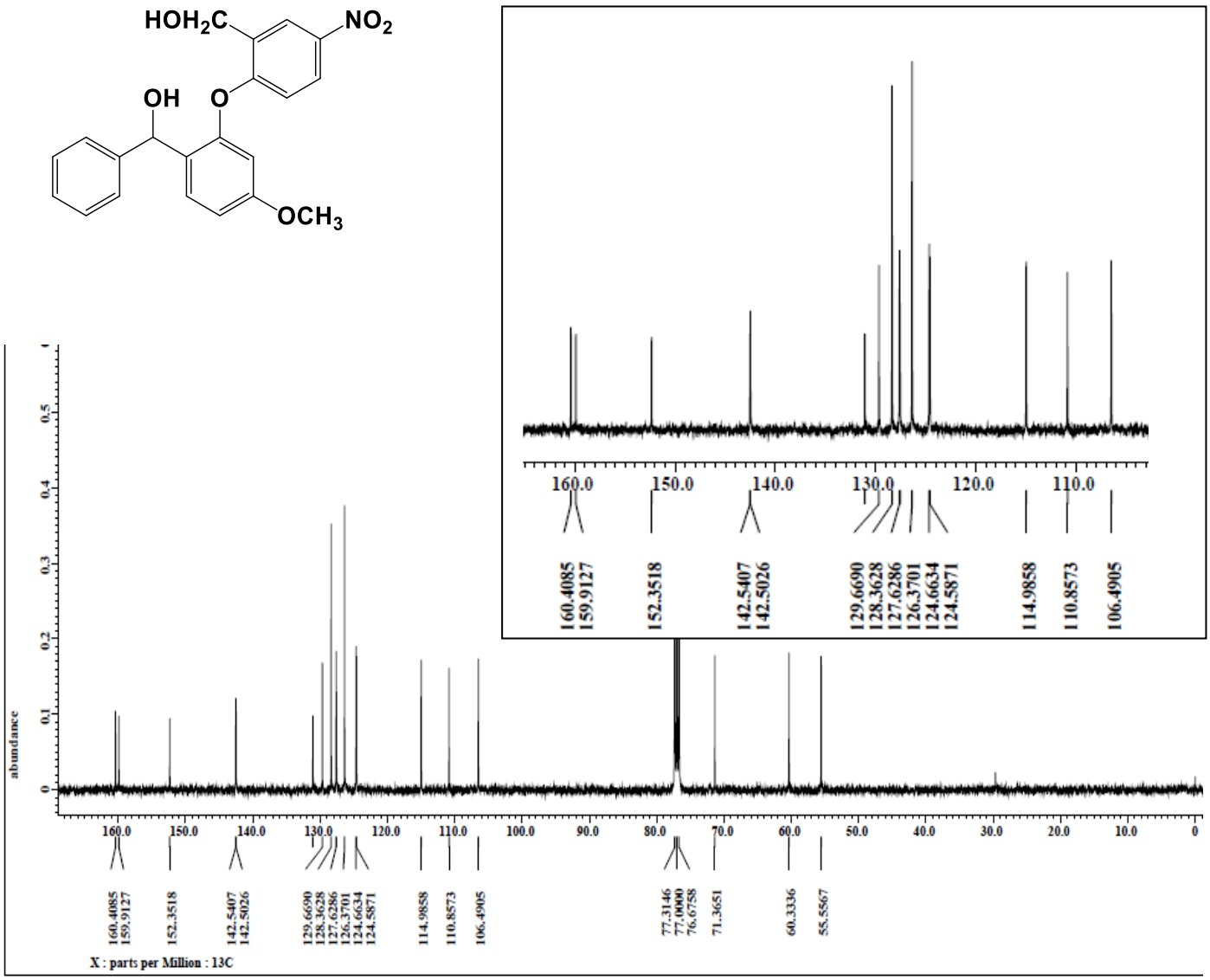
[1]H NMR of (2-(2-(hydroxymethyl)-4-nitrophenoxy)-4-methoxyphenyl)(phenyl)methanone



^{13}C NMR of (2-(2-(hydroxymethyl)-4-nitrophenoxy)-4-methoxyphenyl)(phenyl) methanone



^{1}H NMR of (2-(2-(hydroxymethyl)-4-nitrophenoxy)-4-methoxyphenyl)(phenyl)methanol



^{13}C NMR of (2-(2-(hydroxymethyl)-4-nitrophenoxy)-4-methoxyphenyl)(phenyl)methanol

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