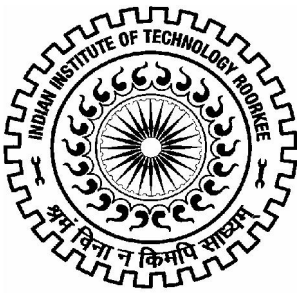
DESIGN, SYNTHESIS AND ESTROGEN RECEPTOR BINDING STUDY OF FLAVONE AND INDANONE BASED LIGANDS

Ph.D. THESIS

by

GULAB KHUSHALRAO PATHE



DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY ROORKEE
ROORKEE – 247667, INDIA
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DESIGN, SYNTHESIS AND ESTROGEN RECEPTOR BINDING STUDY OF FLAVONE AND INDANONE BASED LIGANDS

A THESIS

Submitted in partial fulfilment of the requirements for the award of the degree

of

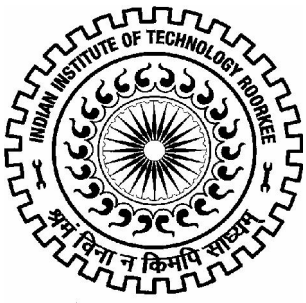
DOCTOR OF PHILOSOPHY

in

CHEMISTRY

by

GULAB KHUSHALRAO PATHE



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CANDIADATE'S DECLARATION

I hereby certify that the work which is being presented in the thesis entitled, **"DESIGN, SYNTHESIS AND ESTROGEN RECEPTOR BINDING STUDY OF FLAVONE AND INDANONE BASED LIGANDS"** in partial fulfilment of the requirements for the award of the Degree of Doctor of Philosophy and submitted in the Department of Chemistry of the Indian Institute of Technology Roorkee, Roorkee is an authentic record of my own work carried out during a period from Jan, 2013 to July, 2015 under the supervision of Dr. Naseem Ahmed, Associate Professor, Department of Chemistry, Indian Institute of Technology Roorkee, Roorkee.

The matter presented in this thesis has not been submitted by me for the award of any other degree of this or any other institute.

(GULAB KHUSHALRAO PATHE)

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

Dated:

(Naseem Ahmed)
Supervisor

ABSTRACT

The thesis entitle **"Design Synthesis and Estrogen Receptor Binding Study of Flavone and Indanone Based Ligands"** is divided into five chapters.

The present work is aimed to synthesize the novel flavone and indanone based ligands and their anti-proliferative evaluation against breast and cervical cancers. The novel methods are developed in the deprotection of hydroxyl groups for alcohols and phenols. Also, novel reagents are explored for the McMurray coupling reaction using different metal catalysts. All synthesized compounds are characterized using standard analytical techniques like IR, ^{1}H-NMR, ^{13}C-NMR, GC-MS, HRMS, etc. The thesis has been divided into five chapters for further transparency and clarity and elaborated as follows:

CHAPTER-1

Introduction

The **first chapter** describes the introduction of flavones, indanone and their biological applications, deprotection methods of hydroxyl groups for alcohols and phenols and reagents in the McMurray coupling reaction. Flavone, a sub-class of flavonoid compounds (polyphenolic phytochemicals), is a secondary metabolite of plants which plays important role in various biological processes. Various natural, semi-synthetic and synthetic derivatives of flavones have been synthesized and evaluated for several therapeutic activities like anti-inflammatory, anti-estrogenic, anti-microbial anti-allergic, anti-oxidant, anti-tumour and anti cytotoxic activities. Indanone, indenone and indane skeletons are important moiety present in different natural products and biologically active compounds. For example, indenone (3-(2,3-dihydrobenzofuran-6-yl)-5,6-dimethoxy-2-methyl-2,3-dihydro-1H-inden-1-one) was isolated from the fruits of virola sebifera, indanone (pterosin C) is a cytotoxic and antibacterial natural products, donepezil**,** a potent acetylcholinessterase inhibitor prescribed for the treatment of Alzheimer's disease, is a marketed drug (Aricept ^{TM}), and indenone (5-(4-chlorophenyl)-3-(methylsulfonyl)-2H-indeno[5,6-d]oxazole-2,7(3H)-dione) is a structural analogue of the selective COX-2 inhibitor nimesulide (**Fig.1**)

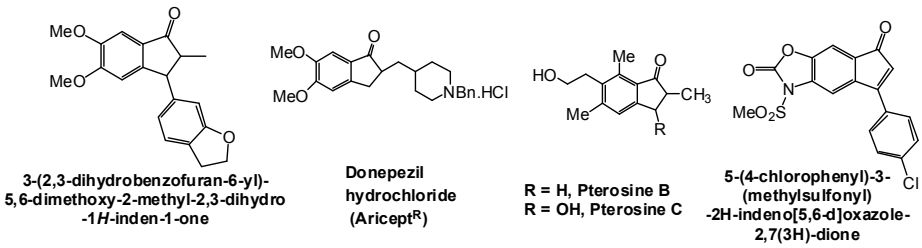


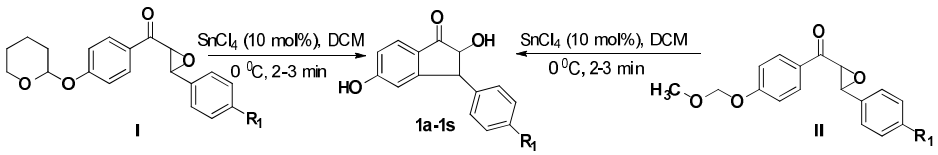
Fig. 1: Bioactive compounds containing indanone and indenone core.

CHAPTER-2

Part-A: Highly efficient deprotection of phenolic tetrahydropyranyl and methoxymethyl ethers and sequel cyclization to indanones using Sn (IV) Cl_4 catalyst

Naseem Ahmed*[a], Gulab Khushalrao Pathe [a] and B. Venkata Babu [a] *Tetrahedron Letters* **2014**, *55*, 3683 – 3687.

In this chapter, we have developed a novel, rapid and efficient deprotection method for the phenolic THP and MOM ethers and sequel intramolecular Friedel-Crafts alkylation reaction of THP and MOM protected chalcone epoxides to indanone by $SnCl_4$ catalyst under mild conditions. The reaction took place in 2-3 min to gave the products **1a-1s** in excellent yield (90-98%) at 0 ^{0}C without affecting the other functional groups (**Scheme 1**). These products were fully characterized on the basis of their spectral analysis ^{1}H-, ^{13}C-NMR and GC-MS.



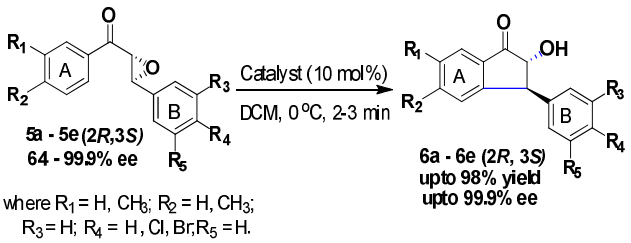
Scheme 1: Detetrahydropyranylation and demethoxymethylation of phenol and sequel cyclization reaction.

Part-B: $SnCl_4$ or $TiCl_4$: Highly efficient catalysts for detetrahydropyranylation and demethoxymethylation of phenolic ethers and sequel one-pot asymmetric synthesis of 3-aryl-2-hydroxy-2, 3-dihydroindan-1-ones from chalcone epoxides

Naseem Ahmed*[a], Gulab Khushalrao Pathe[a] *RSC Advances* **2015,** Accepted.

In this section, we have described the role of novel $SnCl_4$ or $TiCl_4$ catalysts for the deprotection of phenolic THP and MOM ethers and sequel one-pot regioselective synthesis of trans-3-aryl-2-hydroxy-1-indanones (R/S) by intramolecular Friedel-Crafts alkylation of chalcone epoxides with enantiomeric excess up to 99.9% under same conditions. Epoxide ring opening followed

by intramolecular Friedel-Crafts alkylation was performed in the presence of $TiCl_4$ to obtain the diastereoisomerically pure *trans* (2*R*, 3S) indanone derivatives **6a-e** (**Scheme 2**).



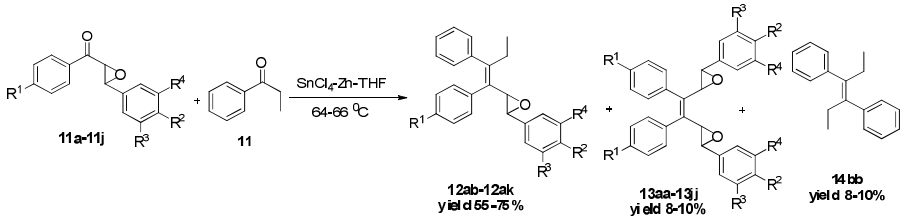
Scheme 2: Synthesis of enantioselective 3-aryl-2-hydroxyindan-1-ones.

CHAPTER- 3

Part-A: Zn-$SnCl_4$: A novel reductive system for deoxygenative coupling of aliphatic, aromatic, chalcone epoxide and indanone carbonyl compounds to olefins

Gulab Khushalrao Pathe and Naseem Ahmed*, *Tetrahedron Letters* **2015**, *56,* 1555-1561.

In this part, $SnCl_4$-Zn complex provided a novel reductive system in the deoxygenative cross-coupling of aliphatic, aromatic, chalcone epoxide and indanone carbonyl compounds to olefins in high yield (55-86%) at reflux temperature in THF. The advantage of this reagent is inexpensive, short reaction time and high yield compare to the reagents used in the McMurry cross-coupling reaction. These products were fully characterized on the basis of their spectral analysis ^{1}H-, ^{13}C-NMR, HRMS and GC-MS.

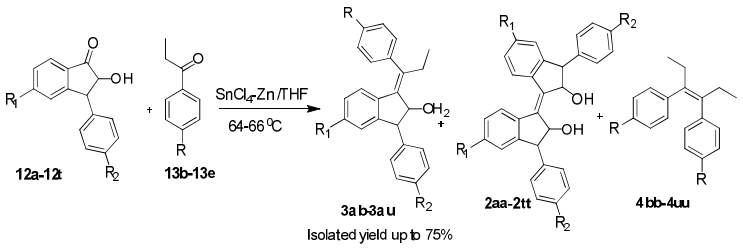


Scheme 3: $SnCl_4$-Zn mediated deoxygenative cross-coupling reaction.

Part-B: Design, Synthesis of McMurry cross-coupled indanophen, analogs of Tamoxifen by novel $SnCl_4$-Zn reagent and Anti-Proliferative Evaluation of Flavone-Estradiol adduct and Indanone based Ligands against Breast Cancer Cell Line

Gulab Khushalrao Pathe, Naveen Konduru, Iram Parveen and Naseem Ahmed*, *European Journal of Medicinal Chemistry* **2015,** Under Review.

In this section, we described the synthesis of McMurry cross-coupled indanophen, analog of tamoxifen using novel $SnCl_4$-Zn reagent and anti-proliferative evaluation of indanone based ligands and flavone-estradiol adduct, against human cervical cancer cell line (HeLa) and human breast cancer cell lines (MCF-7& MDA-MB-231). The compounds **3ac, 3ad, 3ae, 3ao** displayed the best activity having IC_{50} = 2.13 - 3.81μM and rest of the compounds also showed comparable activity to the standard drug doxorubicin having IC_{50} = <28 μM. The flavones-estradiol adduct **6ab, 6ad** showed excellent activity than the standard drug having IC_{50} values in μM 2.85 ± 0.165 & 2.42 ± 0.226 and 3.64 ± 0.276, 2.93 ± 0.137 against MCF-7& MDA-MB-231 and 2.17 ± 0.183, 2.56 ± 0.322 against HeLa respectively. The structure of all the compounds was confirmed by ^{1}H-, ^{13}C-NMR, HRMS, ESI/MS and IR analysis.



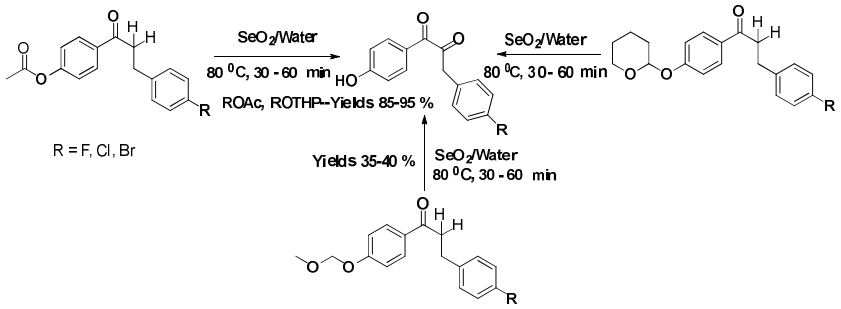
Scheme 4: Synthesis of Tamoxifen Analogs.

CHAPTER-4

SeO_2 in water: A mild and efficient promoter for deprotection of acetyl, methoxymethyl and tetrahydropyranyl ethers and sequel oxidation of carbonyl carbons

Gulab Khushalrao Pathe[a] and Naseem Ahmed*[a], *RSC Advances* **2015,** 5, 59114-59119.

In this chapter, we have reported SeO_2-water system provided an efficient and one-pot green deprotection of acetyl, THP and MOM ethers in alcohols and phenols and sequel oxidation of alpha carbonyl carbons to dicarbonyl functional groups at 80 ^{0}C in 30-60 min. Using substrate: SeO_2 in 1:3 ratio, the reaction gave excellent yield (85-95%) for acetyl and THP deprotections and a moderate yield (30-40%) for MOM deprotection without affecting other functional groups. However, substrate: SeO_2 in 1:1 ratio in 1ml H_2O, got only deprotection product in 85-95% yields for Ac and THP and demethoxymethylation gave moderate yields (30-40%) at 80 ^{0}C in 30-60 min (**Scheme 6**). The products were characterized on the basis of their spectral analysis ^{1}H- and ^{13}C-NMR, GC-MS.



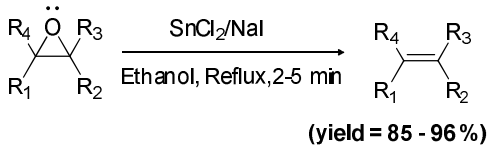
Scheme 6: Deprotection of acetyl, MOM and tetrahydropyranyl ethers and sequel oxidation of active methylene in SeO_2-water promoter.

CHAPTER-5

Part-A: Mild and efficient reductive deoxygenation of epoxides to olefins with $SnCl_2$/NaI as a novel reagent

Gulab Khushalrao Pathe[a] and Naseem Ahmed*[a], Synthesis **2015,** Ahead of print.

In this chapter, we have developed a novel, highly efficient protocol for deoxygenation of aliphatic and aromatic epoxides, chalcone epoxide, nitro styrene epoxide and nitrochromene epoxide to corresponding olefins using $SnCl_2$/NaI in ethanol as a novel reagent, for this conversion with up to 96% yield. This methodology has more importance than the earlier methods such as inexpensive reagents, high yield, short reaction time, environment friendly (**Scheme 7)**. These compounds were further characterised by NMR, IR and GC-MS.

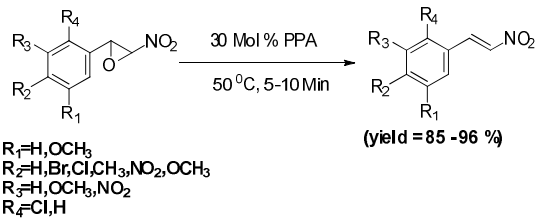


Scheme 7: Deoxygenation of aliphatic and aromatic epoxide by $SnCl_2$/NaI.

Part-B: Efficient and green protocol for the eliminative deoxygenation of aliphatic and aromatic epoxides to olefin with polyphosphoric acid as a novel catalyst

Gulab Khushalrao Pathe[a] and Naseem Ahmed*[a], Helvetica Chemica Acta **2015,** Under Review.

In this part, we have developed a highly efficient and green catalytic deoxygenation of aliphatic and aromatic epoxides, chalcone epoxide, nitro styrene epoxide and nitrochromene epoxide to olefin using 30 mol% of polyphosphoric acid up to 96 % yields. This methodology have more importance than the earlier methods such as inexpensive reagents, high yield, short reaction time, environment friendly and solvent free. These compounds were further characterised by NMR, IR and GC-MS.



Scheme 8: Deoxygenation of nitrostyrene epoxide by polyphosphoric acid catalyst.

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I would like to express my sincere gratitude to my Supervisor Dr. Naseem Ahmed, Department of Chemistry, IIT Roorkee who was always available for discussion, guardian and as a friend. He has contributed a great deal to my understanding in research through valuable discussions, ideas and useful comments, which were a great source of my inspiration.

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I also thank the Coordinator NMR central facility Prof. Ritu Barthwal, Department of Biotechnology for giving me the time to carry out the experiments related to my study whenever required.

I wish to put on record my gratitude to the Editors & Reviewers for their comments/suggestions during publishing manuscripts and conference proceedings.

I would like to take this opportunity to thank Department of Science and Technology (DST), New Delhi for providing me financial assistance during my course of research.

I would like thank my seniors and colleagues Dr. B. Venkata Babu, Dr. Naveen Konduru, Shaily, Nishant, Sumit, Iram, Waheed, Manu, Pushpendra, Ila, Anjali, Varun, Sheela, Pankaj, Balakrishna and Anand for their unflinching helps throughout.

My family deserves special mention for their unflagging love and support in my life. This work simply be impossible without them. I am indebted to my father Khushalrao Pathe and mother Shobha Pathe for their everlasting care and love to me. I also thank to my sister Jayashree and brother Mahesh for their love and encouragement.

Finally, I am thankful to almighty GOD, for his mercy and grace bestowed upon me during my education.

(GULAB KHUSHALRAO PATHE)

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LIST OF ABBREVIATION

ACN	Acetonitrile
AChE	Acetylcholinestearase
CHI	Chalcone isomerase
CHS	Chalcone synthase
CrO_3	Chromium trioxide
CoA	Coenzyme-A
DCM	Dichloromethane
DHP	Dihydropyran
DDQ	**2**,3-Dichloro-5,6-dicyano-1,4-benzoquinon
DMF	N,N-Dimethyl Formamide
DMSO	Dimethyl Sulphoxide
ee	Enantiomeric excess
ER	Estrogen Receptors
FT-IR	Fourier transform infrared spectroscopy
FLS	Flavonol synthase
GC-MS	Gas chromatography mass spectrometry
gm.	Gram
HRMS	High resolution mass spectrometry
HeLa	Human cervical cancer cell line
$InCl_3$	Indium(III)chloride
IPA	Isopropanol
MS	Mass spectrometry
MnO_2	Manganese dioxide
MP	Melting point
MOM	Methoxymethyl

MCF-7	Michigan cancer foundation-7
mg	Milligram
ml	Milliliter
MIC	Minimum inhibitory concentration
NMR	Nuclear magnetic resonance
NaI	Sodium iodide
OsO_4	Osmium tetroxide
Pd	Palladium
PPA	Polyphosphoric acid
Py	Pyridine
PCC	Pyridinium chlorochromate
RT	Room temperature
SeO_2	Selenium dioxide
$SnCl_2$	Tin(II)chloride
$SnCl_4$	Tin Tetrachloride
TBDMSCl	tert-butyl dimethylsylylchloride
THP	Tetrahydropyranyl
THF	Tetrahydrofuran
TMS	Tetra methyl silane
TLC	Thin layer chromatography
$TiCl_4$	Titanium(IV)chloride
TFA	Trifluoro acetic acid
Zn	Zinc metal

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CHAPTER- 1

INTRODUCTION

Introduction

1.1 GENERAL INTRODUCTION OF FLAVONOIDS

First time in 1936 flavonoids are reported by Hungerian scientist Rusznyak and Sent-Gyorgyi, as polyphenolic compounds of plant origin that are the most important compounds in human diet due to their widespread distribution in foods and beverages. In the late 1980s and throughout the 1990s flavonoids were intensely studied concerning their actions as a mutagenic agents, antioxidants and pro-oxidants as their likely roles in biological systems. They can occur both in the free form (aglycones) and as glycosides and differ in their substituent's (types, number and position) and in their in saturation. The most common sub-classes are flavones, flavonols, flavonones, catechins, isoflavones and anthocynidines, which account for around 80 % of flavonoids (**Figure 1**).

All flavonoids share a basic C6-C3-C6 phenyl-benzopyran backbone. The position of the phenyl ring relative to the benzopyran moiety allows a broad separation of these compounds into flavonoids (2-phenyl-benzopyrans) (**Figure 1**).

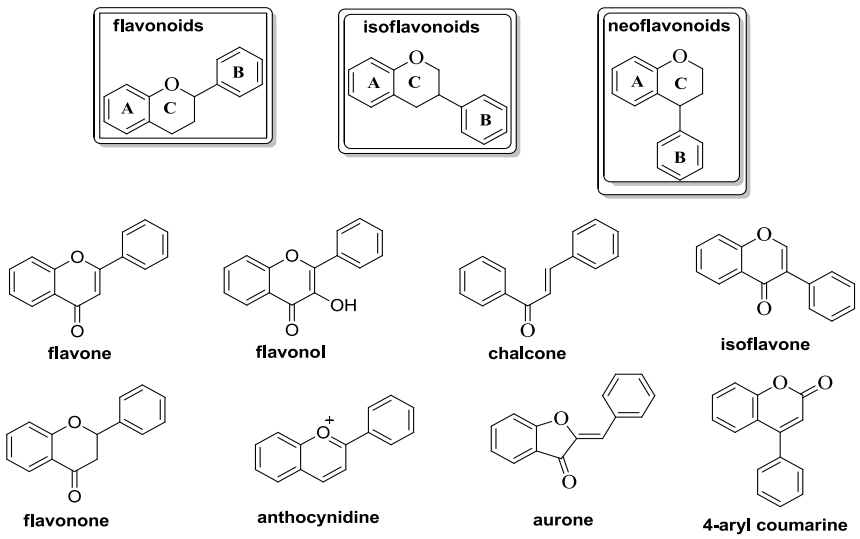


Figure 1: Structure of the structural backbones of the main flavonoid groups (flavan, isoflavan and neoflavan) and of relevant flavonoids classes and classification

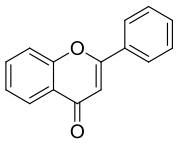
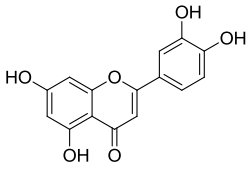
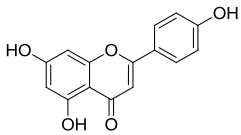
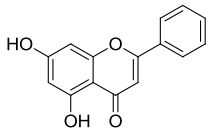
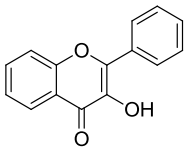
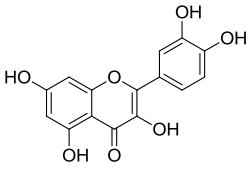
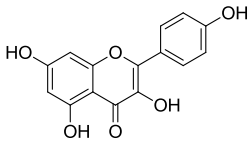
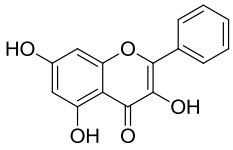
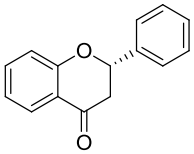
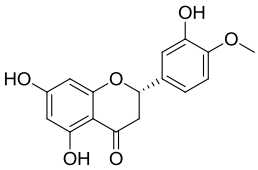
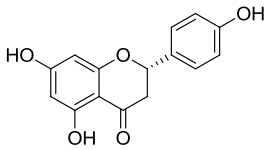
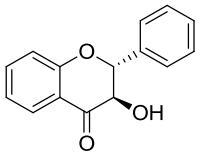
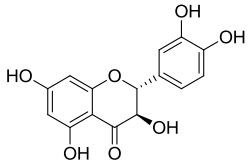
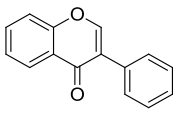
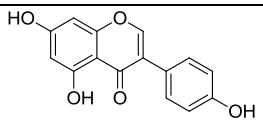
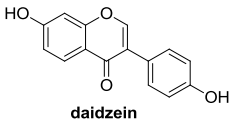
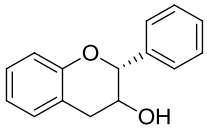
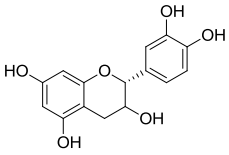
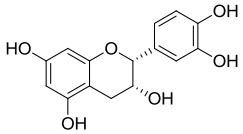
Flavonoids and bioflavonoids are widely distributed in plant kingdom, modulating the human metabolism for prevention of chronic and degenerative diseases. The Hungarian scientist termed flavonoids as citrin or vitamin P to explain the synergy between pure vitamin

C and as yet unidentified co-factors from the peels of lemons.[1] Till now, more than 4000 such molecules have been identified from fruits, vegetables and beverages. They are produced in plants via the flavonoids branch of the phenylpropanoid and acetate-malonate metabolic pathway. These phenolic compounds comprising a general structure of flavan nucleus phenyl benzopyrone skeleton (C-3-C-6-C-3) in all molecules and having a chromene type skeleton having phenyl substituent in C2-C3 position. They have the general structure of a 15-carbon skeleton, which consists of two phenyl rings (A and B) and heterocyclic ring (C). The three cycle or heterocycles in the flavonoid backbone are generally called ring A, B and C. Ring A usually shows a phloroglucinol substitution pattern.[2] The ring A synthesized in polyacetate pathway whereas, B and C rings in shikimic pathway. The different classes of flavonoids have been categorized based on the oxidation status of central ring C. Anthocynidins are produced by oxidation and reduction gives rise to flavon-3-ols and flavan-3, 4-diols. Intermediate compounds such as flavanones, flavonols and flavones produces based on the presence or absence of the double bond between C2-C3 of the molecule.

There are three major classes of flavonoids viz. flavones, isoflavonoids, neoflavonoids. Flavones are derived from 2-phenyl-1,4-benzopyrene derivatives such as quercetin and rutin. Isoflavanoids are derivatives of 3-phenyl-1,4-benzopyrene where being derived from neoflavonoids 4-phenyl-1,4-benzopyrene. Alternative to chemical or synthetic antimicrobials and antioxidants to control the food borne diseases, inhibiting lipid oxidation and thus extending the shelf-life and quality of food products is an increasing trend in food indutry.[3]
The common flavonoids obtained from plants in various classes are shown in Figure 2. All classes of flavonoids exhibit variety of biological activities, but among them, the flavones have been considerably explored. Various natural, semi-synthetic and synthetic derivatives of flavones have been synthesized and evaluated for several therapeutic activities like anti-inflammatory, anti-oestrogenic, anti-microbial, anti-allergic, anti-oxidant, anti-tumor and anti-cytotoxic activities (**Figure 2**).

Figure 2: Structure of flavonoids and their naturally occurring compounds

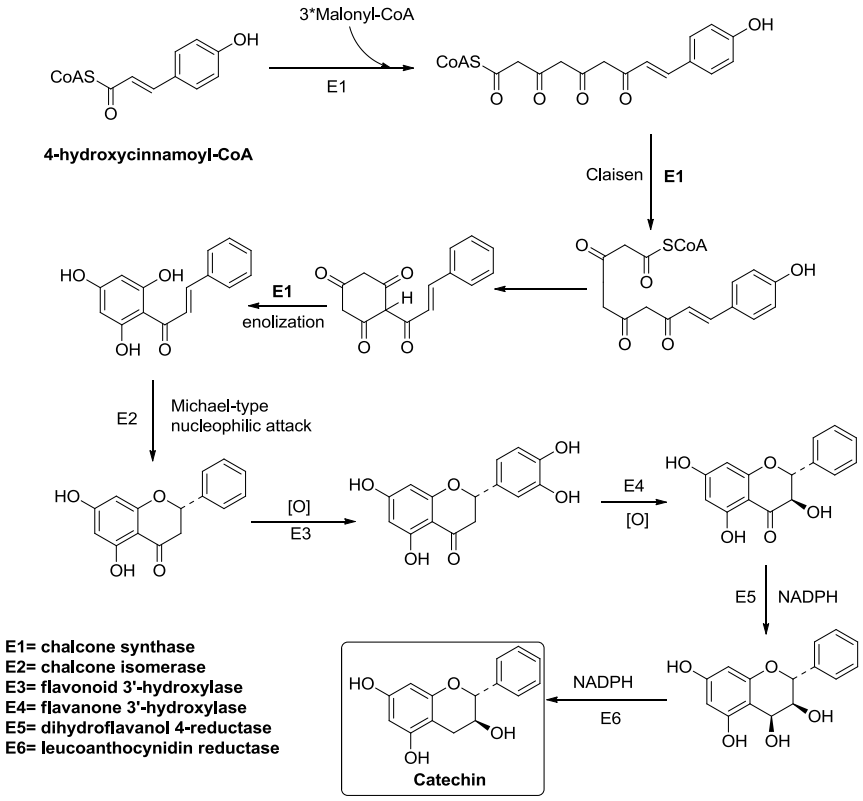
Group of flavonoids	Structure backbones	Examples

Flavone		 Lutiolin	 Apigenin	 Chrycin
Flavonol		 quercitin	 kaempferol	 galangin
Flavanones		 hesperitin	 naringenin	--
Flavanonol		 taxifolin	--	--
Isoflavones		 genistein	 daidzein	--
Flavan-3-ols		 catechin	 epicatechin	--

1.1.1 Biosynthetic pathway for Flavonoids

Flavonoids are synthesized by the phenylpropanoid metabolic pathway in which the amino acid phenylalanine is used to produce 4-coumaroyl-CoA [3]. This can be combined with malonyl-CoA to give the true backbone of flavonoids, a group of compounds called hydroxychalcones. The metabolic pathway continues through a series of enzymatic modifications to yield flavanones →dihydroflavonols → anthocyanins. Along this pathway,

many products can be formed, including the flavonols, flavan-3-ols, pro-anthocyanidins (tannins) and a host of other various polyphenolics (**Scheme 1**).



Scheme 1: Flavonoids biosynthetic pathway

1.2 Chalcone

Chalcone is an aromatic ketone and an enone that forms the central core for a variety of important biological compounds, which are known collectively as chalcones or chalconoids. Benzylidene acetophenone is the parent member of the chalcone series. The alternative name given to chalcone is phenyl styryl ketone, benzalacetophenone, *β*-phenylacrylophenone and *α*-phenyl-*β*-benzoylethylene (**Figure 3)**.

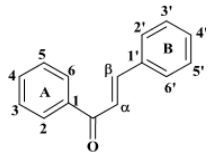


Figure 3: General structure of chalcone (C_6-C_3-C_6)

1.2.1 BIOACTIVITY OF CHALCONES

Chalcone are valuable chemicals because of their well known diverse pharmacological activity. A number of chalcone have demonstrated cytotoxic properties which is an implication of anticancer activity. Dimnock et. al. [4] have studied cytotoxic property of a number of chalcone and their related Mannich base towards murine P388 and L1210 leukemia cell lines, as well as human tumor cell line and are found that compound **1** exhibited the highest activity towards L1210 and human tumor cells. Compounds **2** and **3** are other compound of interest due to its huge differential in cytotoxicity between P388 and L1210 cells, where compound **5** exhibited a high therapeutic index by comparison of the toxicity of P388 cells toward Molt 4/C8 T-lymphocytes. The study showed that in general the Mannich bases were more toxic than the corresponding chalcones.

Attempting to determine the influence of relative direction of the two phenyl rings towards cytotoxic effect, Dimnock et. al. [5] studied the cytotoxic properties of 2-arylideneindanone **4**, 2-arylindenetetralones **5** and 2-arylindenesuberones **6** derivatives against murine P388, L1210, and Molt 4/C8 cancer cell lines and found out that in general the order of cytotoxicity was **6** > **5** > **4**.

Exploration of the mechanism of action as anticancer agent bring us to a better understanding of cancer and can lead us to design better anticancer drug. Licochalcones A **(7)** and Licochalcones E **(8)** are retrochalcone isolated from the root of glycyrrhiza inflate exhibited the DNA topoisomerase inhibitory activity in dose dependent manners and this property might explain the cytotoxic activity of these compounds against some human cancer cell line. (**Figure 4**) [6]

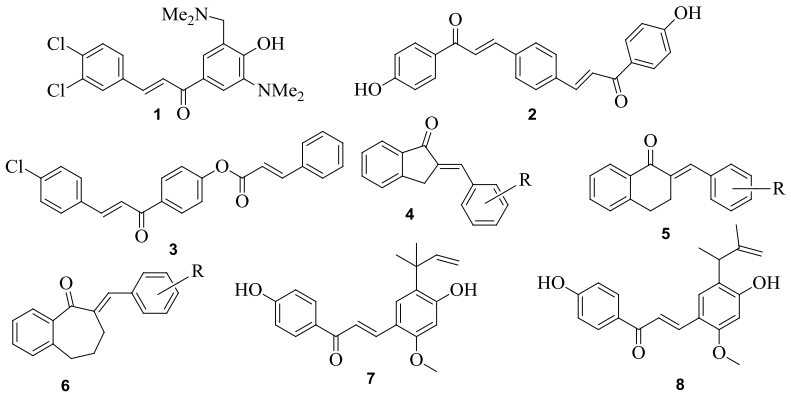
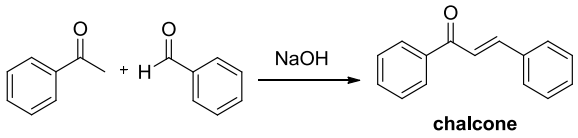


Figure 4: Naturally occurring bioactive chalcone

1.2.2 Methods of Synthesis of chalcone

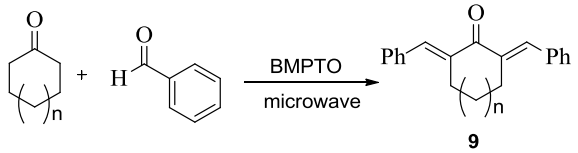
1.2.2.1 Chalcone synthesis

Chalcone and its derivatives are primarily synthesized in the laboratory using Claisen-Schmidt reaction, in which acetophenone and its derivative reacted with benzaldehyde or its derivative using strong base, such as NaOH, KOH, or NaH in polar solvent.[7] Other catalyst is also used, such as sodium phosphate doped sodium nitrite[8] and aluminium-magnesium hydroxide hydrate.[9]



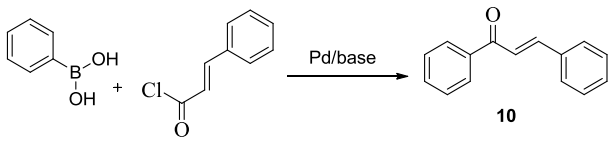
Scheme 2: Synthesis of chalcone by Claisen-Schmidt reaction

Microwave irradiation induced reaction in the chalcone synthesis is another alternative procedure to synthesize chalcone. This reaction method can shorten the reaction time and simplify the purification procedure. Cross aldol condensation by using microwave was used for the synthesis of chalcone analog **9** namely 2, 6-bis (benzyliden)-cyclohexanone employing BMPTO (bis-(4-methoxyphenyl)-telluroxide) as catalyst. [10]



Scheme 3: Synthesis of chalcone by Cross-Aldol Condensation reaction

Chalcone **10** could be synthesized using Suzuki reaction, employing cynnamoyl-chloride and phenyl boronic acids as reagents and Pd-catalyst in base reaction condition. More exotic synthetic protocols have also been developed to pursue high reaction yield and to minimize the side reaction. [11]

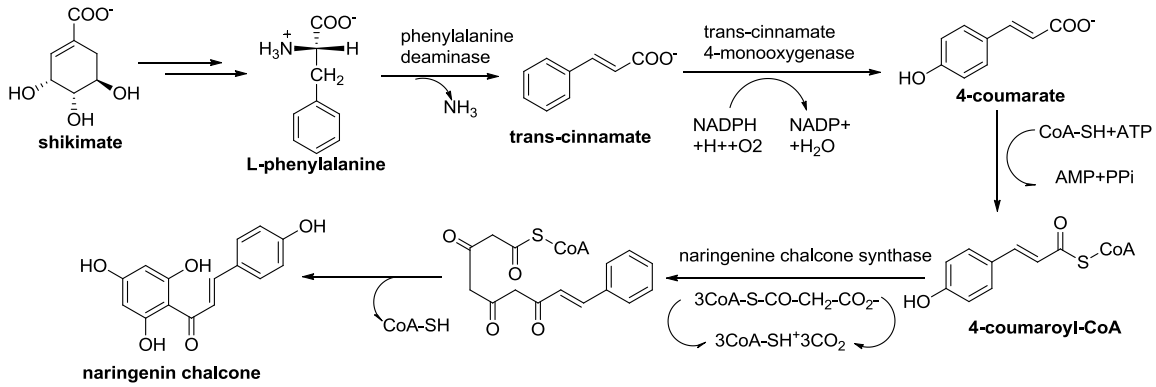


Scheme 4: Synthesis of chalcone by Suzuki reaction

1.2.2.2 Biosynthesis method of chalcone

In biosynthetic pathway, chalcones are synthesized their carbon skeleton from two basic compounds, malonyl-CoA and L-phenylalanine. L-alanine synthesized through the shikimate pathway which is deaminated by phenylalanine deaminase to give trans-cinnamate, and then in the presence of trans-cinnamate 4-monooxygenase generates 4-coumarate which reacts with

coenzyme A to produce 4-coumaroyl-CoA. It reacts with malonyl-CoA in the presence of naringenin chalcone synthase by losing coenzyme A produce naringenin chalcone. (**Scheme 5**) [12, 13]



Scheme 5: Biosynthesis of chalcone

1.3 FLAVONE

Flavones (flavus = yellow), are a class of flavonoids based on the backbone of 2-phenylchromene-4-one apart from flavonoids are isoflavonoids, derived from 3-phenylchromene-4-one structure and neoflavonoids, derived from 4-phenylcoumarine structure. The three flavonoids classes are all ketone-containing compounds, and as such, are anthoxanthins (flavones and flavonols). Flavones are well known for their various biological activities such as anticancer, anti-inflammatory, anti-osteoporotic and anti-diabetic (**Figure 5**).

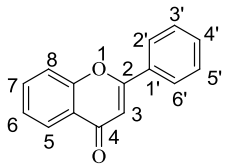


Figure 5: General structure of flavones

1.3.1 BIOACTIVITY OF FLAVONES

The major natural flavones are apigenin (4, 5, 7-trihydroxyflavone), chrysin (5, 7-dihydroxyflavone), 6-hydroxyflavone, baicalein (5, 6, 7-trihydroxyflvone), and wogonin (5, 7-dihydroxy-8-methoxyflavone). They are mainly found in cereals and herbs. Synthetic flavones are diosmin, hindrosmin and flavoxate **(Figure 6).** Flavones intake in the form of dietary supplements and plant extracts has been steadily increasing. Natural dietary flavones, found in parsley, celery and citrus peels. The estimated daily intake of flavones is in the flavones, found in parsley, celery and citrus peels. The estimated daily intake of flavones is in the range 20-50 mg/day. In recent years, scientific and public interest in flavone has grown enormously due to

wide spectrum of biological activities and their putative beneficial effects against atherosclerosis, osteoporosis, diabetes mellitus and certain cancers. Flavones are used to treat urinary bladder spasms, treatment of various disease, neurodegenerative diseases such as Alzheimer's disease, anti-inflammatory and anti-apoptotic activity has been demonstrated in neuronal cells, in vitro. [14]

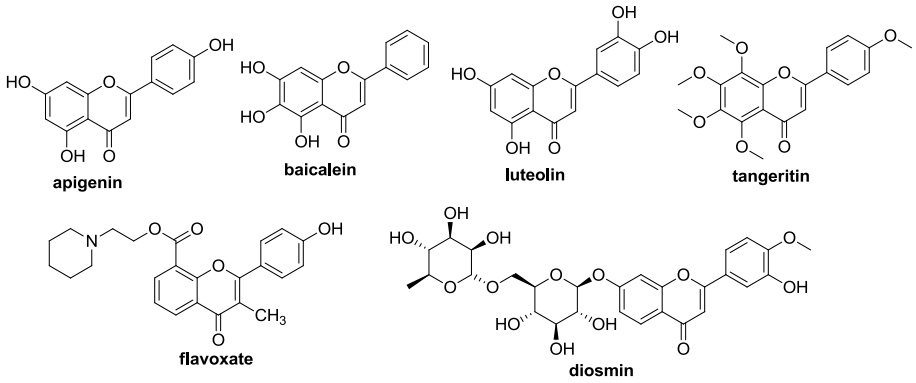
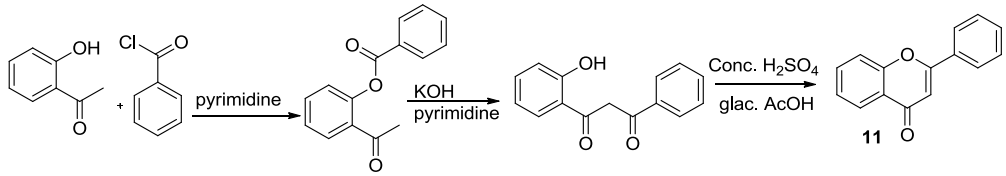


Figure 6: Some examples of natural and synthetic flavones

1.3.2 Methods of Synthesis of flavone

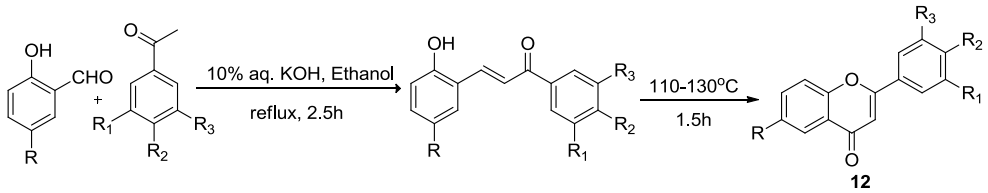
1.3.2.1. Synthesis of flavones

Flavones can be synthesized by various synthetic schemes like Claisen-Schmidt condensation, [15] Baker-Venkataraman-rearrangement, [16] Ionic liquid promoted synthesis, [17] Allan-Robinson, [18] Vilsmeier-Haack reaction, [19] Wittig reaction, Fries rearrangement, [20] and modified Schotten- Baumann reaction. [21] Now a day's most of the flavones are synthesized based on the Baker-Venkataraman method. It involves the conversion of o-hydroxyacetophenone into phenolic esters, which undergoes an intramolecular Claisen condensation in the presence of a base to form beta- diketones, which is cyclized to flavones by an acid catalysed cyclodehydration **(Schemes 6 & 7)**.



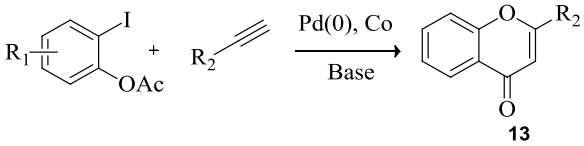
Scheme 6: Synthesis of flavones by via beta diketone intermediate

Aldehyde and ketone using base form a chalcone followed by Claisen-Schmidt condensation at 110-130 ^{0}C to give compound **12**.



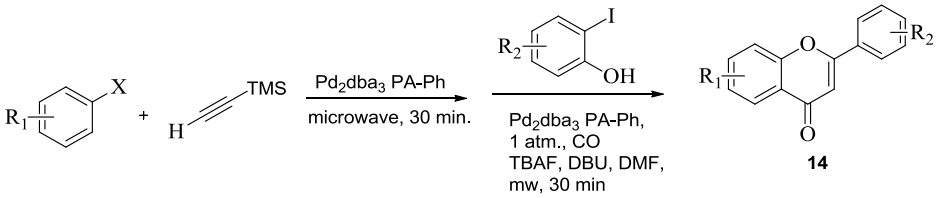
Scheme 7: Synthesis of flavone by Claisen-Schmid condensation reaction

Ferrer, J. L. et. al. synthesized the flavone **13** in excellent yield by reaction of iodo-phenoxy acetate through Sonagashira coupling using palladium catalyst and base. [22]



Scheme 8: Palladium catalysed synthesis is carried out in basic environment by Hua & Yang

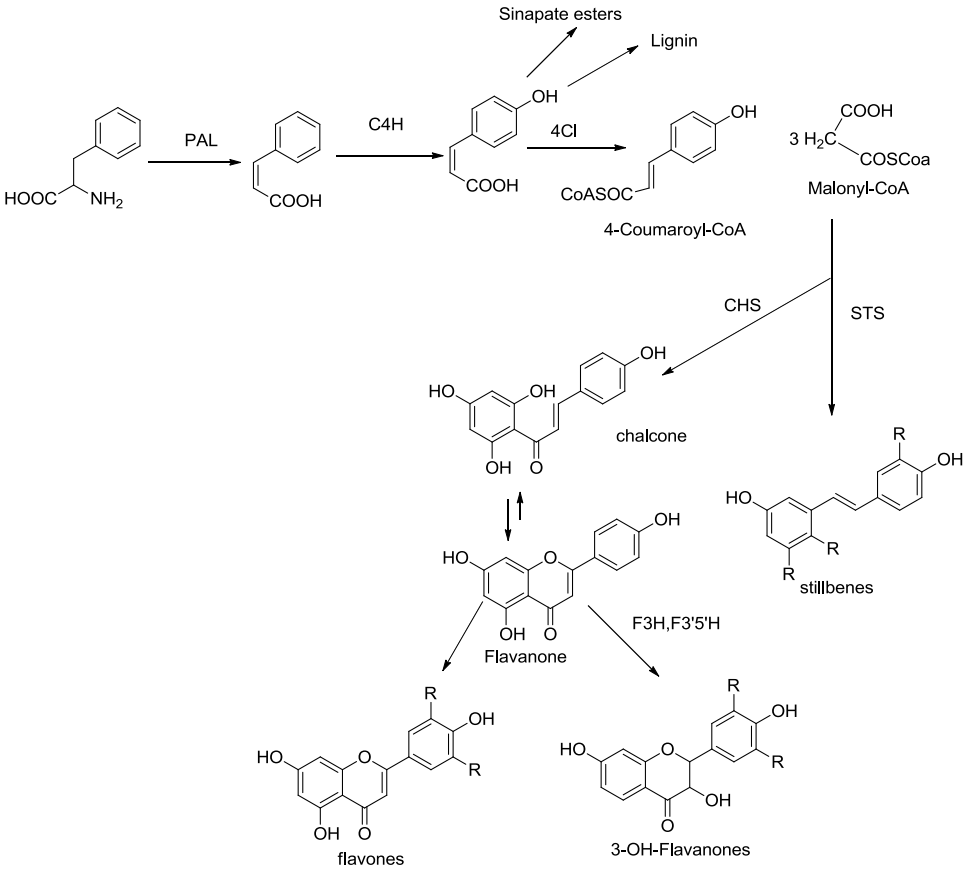
Choi, R. C. Y. et. al. discovered the one-pot micro-assisted synthesis of compound **14** through Sonagashira "carbonylation" annulations in 30 min. using Pd_2dba_3 - catalyst and DBU base. [23]



Scheme 9: Flavones via micro-assisted, one-pot Sonagashira "Carbonylation" Annulations reaction used by E. Awuah & A. Capretta

1.3.2.2 Biosynthesis of flavones

Flavones biosynthesis starts with the condensation of one molecule of 4-coumaroyl-CoA and three molecules of malonyl-CoA yielding neringenin chalcone, carried out by the enzyme chalcone synthase (CHS). The two immediate precursors of the chalcone originate from two different pathways of primary metabolism. Coumaroyl-CoA is synthesized from the amino acid phenylalanine by three enzymatic steps, collectively called the general phenyl propanoid pathway, Malonyl-CoA IS synthesized by carboxylation of acetyl-CoA, a central intermediate in the Krebs tricarboxylic acid cycle. The chalcone is consequently isomerized by the enzyme chalcone flavonone isomerase (CHI) to yield a flavonone. From this central intermediate the pathway diverges into several different classes of flavonoids. [24] **(Scheme 10)**



Scheme 10: Biosynthetic pathway of flavones

1.3.2.3 Flavonoids based ligands

Flavonoids based natural or synthetic compounds have been widely reported to exhibit various biological activities, when incorporate new functional groups (hydroxyl, methoxy, amino, carboxyl, sulphone, prenyl, geranyl, glucose) or biologically active moieties (tetrahydropyran, indole, pyrrole, quinolone, triazole, and admantyl) improves its activity. For example, hydroxyl groups containing chalcone derivative butein extracted from *Rhus verniciflua* which shows good antioxidant activity Flavokawain B found in kava plant it demostrated To possess potent apoptotic abilities, Xanthohumol is, a *prenylated-chalconoid* from hops and beer. Xanthohumol is a free radical scavenger it, has anticancer properties and prevents platelate build-up. Cycloaltilisin extracted from the bud cover of *Artocarpus altilis* showed activity in a cathepsin K inhibition assay and showed IC_{50} value 840 Nm, Flavone-triazole-tetrahydropyran conjugates shows a excellent antiproliferative activity against human cancer cell line. [25] Tetrahydropyran containing flavone derivative calyxin G and epicalyxin G are extracted from the seeds of *A. blepharocalyx* showed significant hepatoprotective activity

against CCl_4 induced hepatotoxicity in rats. Triazole moiety attached isoflavone found inhibitor of estrogen receptor alpha-positive breast cancer.

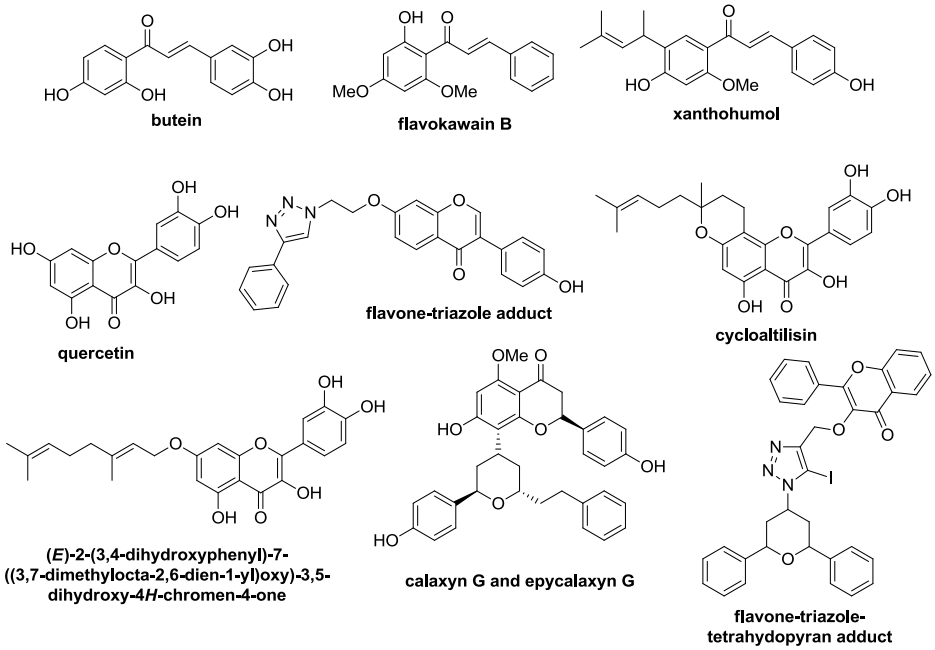


Figure 7: Natural and synthetic biologically active flavonoids conjugates

Based on the literature, we have synthesized novel flavone based ligands as flavone-estradiol adducts and are reported in chapter 2. They were exhibited excellent anti-proliferative activity against human breast cancer cells (MCF-7 and MDA-MB-231) and cervical cancer cells (HeLa). Some derivatives were shown better than the standard drug Doxorubicin.

1.4 DEPROTECTION OF HYDROXYL PROTECTING GROUPS

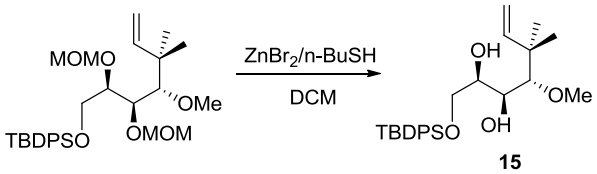
1.4.1 THP deprotection

Tetrahydropyranyl ethers are usually transformed into their parent alcohols or phenols under acid-catalysed conditions. [26] A wide variety of catalysts have been already used for this conversion, including the use of protic acids [27] (acetic acid, toluene-p-sulphonic acids, boric acid), lewis acids [28] (magnesium bromide in diethyl ether, dimethyl alluminium chloride), electrogenerated acids, [29] pyridinium toluene-p-sulphonate, [30] ion-exchange resins, [31] (Amberlyst H-15, Dowex 50W X8, Nafion-117), Bis-(trimethylsylyl)sulphate, [32] distannoxane, [33] organotin phosphate condensates [34] and triphenyl phosphine dibromide (PPh3Br2), [35] more recently, 2, 3-dichloro-5,6-dicyno-p-benzoquinone(DDQ), [36] mesoporous H-MCM-41 molecular sieve, [37] and heteropolyacid, [38] have been applied to this reaction.

1.4.2 MOM-Cl-deprotection

Protection of functional groups in multistep organic synthesis is one of the key factors in the success of the synthesis. The protecting group should selectively react in good yield to give a protected substrate and shoud be selectively removed in good yield by readily available,preferably nontoxic reagents that do not attack the regenerated functional group. [39] one of the most abundant functional groups is the hydroxyl group, which is present in a number of compounds of biological and synthetic interest, including nucleosides, carbohydrates, steroids, macrolides, polyethers, and the side chain of some amino acids or in large number of intermediates in total synthesis of complex natural products. [40] diverse protecting groups have been developed for hydroxyl groups, but it is hard to find an appropriate protecting group for each hydroxyl in the many cases whwre multiple hydroxyl group are present in the molecule. [41]

The methoxymethyl(MOM) group is widely used as a hydroxyl-protecting group because MOM ethers can be easily prepared and are stable under the removal conditions of protecting groups such as silyl, alkoxyacyl, or benzyl derivative, as well as in strongly basic and weakly acidic conditions. [42a] many methods have been developed to cleave MOM ethers using Bronstead acids. [42b] lewis acids, [42c] but synthetic application of these methods has been limited, largely due to the high reactivity combined with long reaction time and low selectivity for MOM in the presence of other protecting groups.



Scheme 11: Selective deprotection of MOM ethers

1.4.3 Deprotection of acetate groups

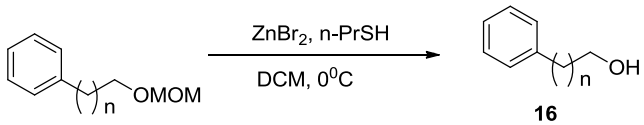
Nucleosides and their analogues have been extensively investigated due to their potential activity as antibiotics, enzyme inhibitors, anticancer and antiviral agents. [43] Consequently, improved and abbreviated synthesis of modified nucleosides from readily available precursors is of considerable interest. [44] However, nucleosides are challenging synthetic substrates as they contain several functionalized groups that must be chemically differentiated for successful transformations. Therefore, multi-step synthesis frequently requires the introduction of protective groups and their subsequent removal. [45-46] Typical methods for the removal of

acetate groups in acetylated nucleosides rely on the use of methanolic ammonia, [47] metal alkoxides, [48] and hydrolytic enzymes, [49] often in good yields. Although all of the above procedures offer certain benefits, they also suffer from drawbacks such as long reaction times, high costs, the use of unstable or noxious reagents, harmful conditions, and the need for special safety precautions, which represent major disadvantages due to environmental concerns. Also, the generation of non-volatile by-products such as acetamide or alkaline salts from the corresponding ammonolysis or alcoholysis of acetates requires additional separation steps for complete product purification. Therefore, the development of a simple catalytic process for the fast and efficient cleavage of acetate groups in acetylated nucleosides, including facilitated workup and purification steps, is highly desirable.

Phenolic hydroxyl groups are frequently observed in various bioactive natural products. The modifications and synthesis of these compounds generally require the protection of this hydroxyl groups. [50] This protection is usually carried out by making the acetates of the compounds as the acetates as the acetate can easily be prepared and again be converted into the parent hydroxyl compounds. [51] However, these deprotection methods may affect several sensitive functional groups present in the molecules. Different methods are also now known for the deprotection of aromatic acetates but the number of process for the selective deprotection of this conversion is limited. Several manipulations can be carried out on the regenerated phenolic hydroxyl groups of a molecule in the presence of alkyl acetate groups and other sensitive functionalities and this method can be utilized in multistep organic transformation and synthesis.

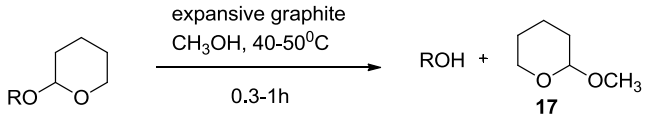
1.4.4 EXAMPLES (deprotection of MOMCl, THP and Acetate)

Hocek, M. & co-workers developed the methodology for the deprotection of mom ethers to alcohol **16** using zinc dibromide as a novel catalyst in DCM at 0^0C. [52]



Scheme 12: Demethoxymethylation with $ZnBr_2$ as a catalyst

Sá, M. M. et. al. used expansive graphite as a catalyst for the detetrahydropyranylation of hydroxyl group in methanol at 40-50 ^{0}C to afford corresponding alcohol **17**.[53]

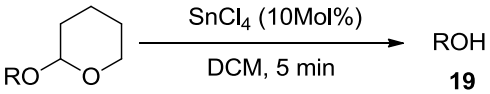


Scheme 13: Detetrahydropyranylation with expansive graphite as a catalyst

Witczak, Z. J. et. al. developed novel methods for the deprotection of THP ethers using bisthmuth triflate as a novel catalyst in 1 mol5 loading to gave alcohol **18**. [54]

Scheme 14: Detetrahydropyranylation with bisthmuth triflate as a catalyst

Ahmed, N. et. al. used expansive zeolite for the detetrahydropyranylation of hydroxyl group in methanol at reflux temperature to afford corresponding alcohol **19**. [55]



Scheme 15: Detetrahydropyranylation with expansive zeolite as a catalyst

Deprotection of THP, MOM and acetate used in total synthesis of Tonkinecin, [56] Solamin, [57] Jimenezin, [58-59] Muricatacin. [60]

We have developed a novel, efficient and green methodology for the deprotection of THP, MOM and acetate groups of alcohol and phenol by using novel catalysts $SnCl_4$, $TiCl_4$ and SeO_2 in water and are reported in chapters 2 and 4. These methods have more advantage than the earlier reported methods like short reaction time, high yields, green reaction condition and easy experimental procedures.

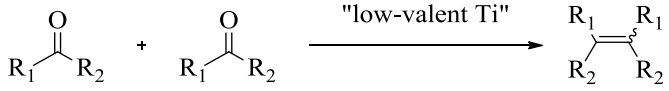
1.5 McMURRY COUPLING

The reaction is discovered by John E. McMurry for the ketones and aldehydes eliminative deoxygenation reaction to alkene using titanium (III) and titanium (IV) as a reductant. [61] The original reaction involved the use of a mixture $TiCl_3$ and $LiAlH_4$, which produces the active reagent(s). Related species have been developed involving the combination of $TiCl_3$ or $TiCl_4$ with various other reducing agents, including potassium, zinc, and magnesium. [62, 63] The coupling is related to the Pinacol coupling reaction which also proceeds by the reductive coupling of carbonyl compounds to diol. This eliminative deoxygenation can be viewed as involving two steps. First is the formation of a pinacolate (1, 2-diolate) complex, a step which is equivalent to the Pinacol coupling reaction. The second step is

the deoxygenation of the pinacolate which yields the alkene. The second step exploits the oxophilicity of titanium.

1.5.1 Introduction

The McMurry coupling is the reaction of two carbonyl functional groups to establish a new double bond between the carbons of the carbonyl groups. The reaction is mediated by low-valent titanium reagents, which may be generated through the combination of titanium chlorides with any of a number of reducing agents. The McMurry coupling is useful for the construction of sterically hindered alkenes, but has limited scope due to a lack of stereo chemical control and statistical mixtures of products in mixed-coupling reactions. [64] The formation of alkenes as minor products in Pinacol couplings of aromatic carbonyl compounds with aluminum amalgam was first reported in 1970. [65] Since then, the reductive coupling of carbonyl compounds to afford alkenes has been developed into a useful synthetic method, most notably by McMurry and colleagues. The modern McMurry coupling employs low-valent titanium generated from a titanium source and a reducing agent (**Scheme 16**), and the scope of the reaction has benefited from the development of several titanium-reductant combinations. Aldehydes and ketones may be coupled in an intra- or intermolecular fashion to afford alkenes that may be difficult to access using other methods. Carboxylic acid derivatives such as esters, amides, and thioesters are amenable to coupling in some cases.



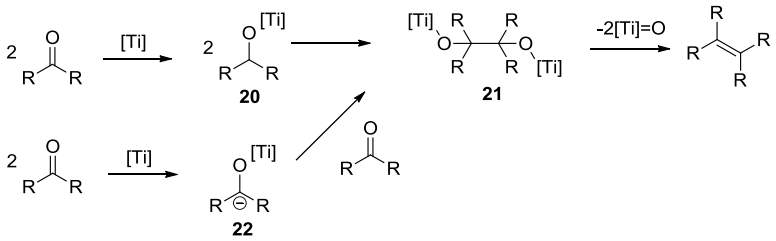
Scheme 16: Reductive coupling of carbonyl compounds to afford alkenes by low-valent Ti

In general, the McMurry coupling has four possibility for the formation of products, homo- and hetero-coupled products and E/Z -isomers, the (*E*)-isomer of product is favored over the (*Z*)-isomer, that depends on the substituent on carbonyl groups. One- and two-electron transfer mechanisms have been postulated for the McMurry coupling and the details of its mechanism remain unknown. When the steric environments and reduction potentials of the carbonyl groups involved are similar, achieving selective mixed coupling (rather than a statistical mixture of homo-coupling and mixed-coupling products) is often difficult. Methods that circumvent this issue have relied on the use of carbonyl equivalents such as thioacetals and geminal dihalides.

1.5.2 Mechanism and Stereochemistry

1.5.2.1 Prevailing Mechanism

The mechanism of the McMurry coupling is unclear at present, and isolated observations have pointed to both one-electron and two-electron mechanisms. One-electron reduction may afford two titanium ketyl radicals **20**, which could subsequently coupled with one another to yield titanium pinacolate **21**. Elimination of two titanium oxo molecules would then occur to afford the product olefin. This mechanism has been supported by electron paramagnetic resonance spectroscopy. [66] More readily reducible aromatic carbonyl compounds undergo two-electron reduction to produce titanium ketyl anion **22**, which leads to the same pinacolate **21** after addition to a second molecule of the carbonyl compound (**Scheme 17**). [67]

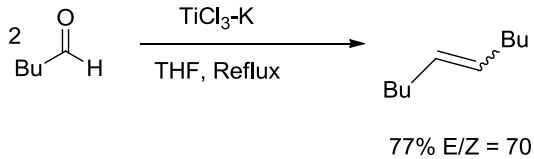


Scheme 17: Plausible mechanism for alkene formation

Several mechanisms have been discussed for this reaction, [68] the nature of low-valent titanium species formed is varied as the products formed by reduction of the precursor titanium halide complex will naturally depend upon both the solvent (most commonly THF or DME) and the reducing agent employed typically, lithium aluminum hydride, zinc-copper couple, zinc dust, magnesium-mercury amalgam, magnesium, or alkali metals. [69]

1.5.2.2 Stereochemistry

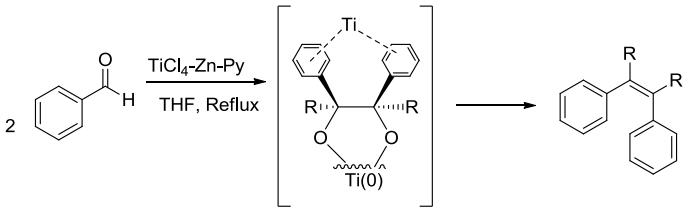
McMurry couplings generally produce mixtures of (*E*)- and (*Z*)-isomers, with the (*E*)-isomer predominating. Increasing the size difference between the substituent's increases the selectivity for the less sterically hindered (*E*)-isomer. [70]



Scheme 18: Formation of mixtures of (*E*)- and (*Z*)-isomers by McMurry couplings

Coupling reactions between monoaryl ketones are an interesting and important exception to this rule. The tendency of these reactions to yield the (*Z*)-isomer as the major product when R

is small has been attributed to coordination of the aryl groups to the titanium center. (**Scheme 19**) [71]

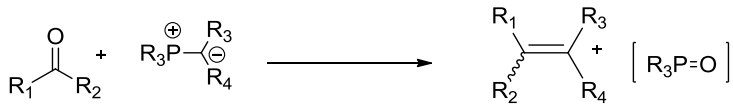


R	Yield (%)	(E)/(Z)
Me	81	26:74
Et	59	27:73
Pr	55	11:89
i-Pr	25	88:12

Scheme 19: Exception to the McMurry couplings gave (*Z*)-isomers as a major product

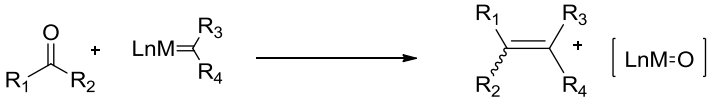
1. 5. 3. Comparison to Other Methods

The McMurry coupling is limited by the formation of *E*/*Z* mixtures and by formation of statistical mixtures of products in many mixed-coupling reactions. A number of alternative olefination methods exist, and these tend to dominate the McMurry coupling in organic synthesis. The Wittig reaction (**Scheme 20**) employs a carbonyl compound in combination with a phosphonium ylide (the latter, in a sense, serving as a carbonyl equivalent). [72]



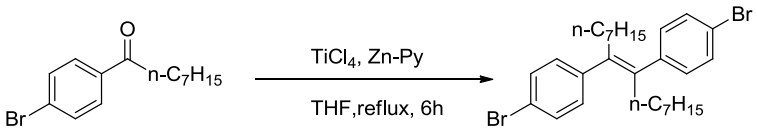
Scheme 20: Comparison of the McMurry coupling with Wittig reaction

Carbonyl olefinating reagents involving pre-formed or intermediate metal carbenes offer another alternative to the McMurry coupling (**Scheme 21**). Schrock carbenes associated with high-valent metals such as niobium and tantalum react with carbonyl compounds to afford the corresponding alkenes. [92] Tebbe's reagent, a titanium methylene complex, is used for the formation of terminal olefins from aldehydes and ketones. [73]



Scheme 21: Alternative to the McMurry coupling (Tebbe's reagent)

The original publication by Mukaiyama demonstrated reductive coupling of ketones using reduced titanium reagents. McMurry and Fleming coupled retinal to give carotene using a mixture of titanium trichloride and lithium aluminium hydride. Other symmetrical alkenes were prepared similarly, e.g. civetone from adamantanone and tetraphenylethylene from benzophenone. [74]

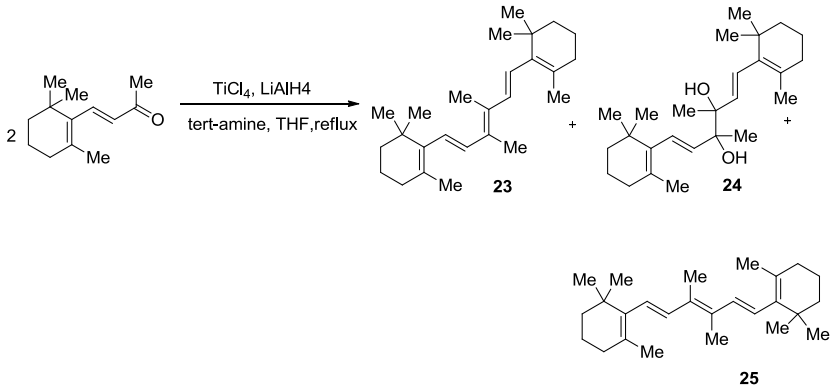


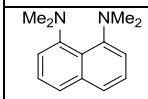
Scheme 22: Alternative to the McMurry coupling

1.5.4 Scope and Limitations

The McMurry coupling employing titanium requires a low-valent species, which is typically generated 'in situ' via treatment of a titanium halide with a reducing agent. A variety of titanium-reductant combinations have been employed for the reaction. Reductants include zinc metal, Zn/Cu, $LiAlH_4$, alkali and alkali earth metals, lithium arenes, and butyllithium. $TiCl_4$ and $TiCl_3$ are the most common titanium sources employed. In general, aliphatic ketones are more difficult to couple than aromatic ketones. For example, aliphatic ketones exclusively form pinacols in the presence of the low-valent titanium reagent generated from $TiCl_4$ and Zn, and are poor substrates for titanium powder. Other metals employed in McMurry couplings include zirconium, vanadium, [75] niobium, [76] molybdenum, [77] tungsten, [78] aluminum, [79] and zinc. [80] The practical utility of some of these metals is limited by their cost and availability, but the scope of the reaction certainly benefits from the large number of metallic reagents that may be used.

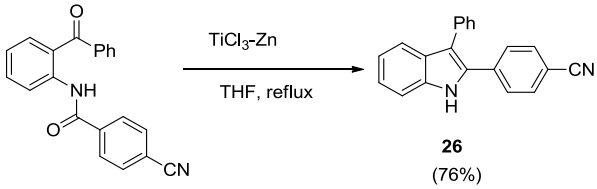
In many cases, additives can have a beneficial effect on McMurry couplings suffering from reduced yields due to pinacol formation and rearrangement. For example, amines suppress the formation of pinacols and rearrangement in the homo-coupling of β-ionone. (**Scheme 23**) [81] Sub-stoichiometric amounts of iodine facilitate the coupling of aliphatic carbonyl compounds by $TiCl_3$–Li at low temperatures and short reaction times. [82]



Tert-amine	68(%)	69 (%)	70 (%)
none	44	8	25
Bu3N	91	0	0
Py	82	0	0
Et3N	82	0	0
	94	0	0
DABCO	72	0	0

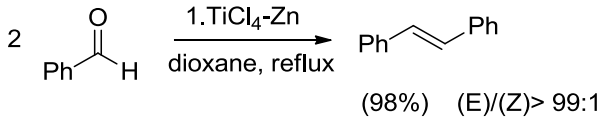
Scheme 23: Effect of additives on McMurry coupling

Amides are relatively versatile substrates, and both inter- and intramolecular homo-coupling reactions of amides have been reported. [83] The intramolecular coupling of amides with ketones has been employed for the synthesis of indole derivatives **26**. (**Scheme 24**) [84]



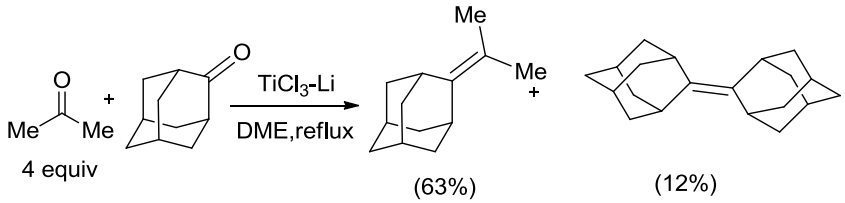
Scheme 24: Intramolecular McMurry coupling with low valent Ti -metal

Homo-coupling reactions are the most straightforward transformations that can be accomplished under the conditions of the McMurry coupling. Aliphatic and aromatic ketones can be converted into the corresponding symmetric alkenes in high yield and stereoselectivity. In reactions that could form diastereomers, selectivity for the (*E*)-isomer is typical. (**Scheme 25**)



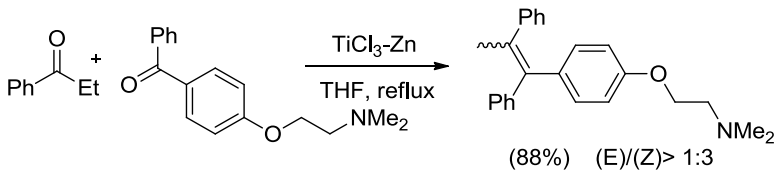
Scheme 25: Selectivity in McMurry coupling

Mixed-coupling reactions between carbonyl substrates with different substitution patterns often afford a statistical mixture of products unless an excess of one of the coupling partners is employed. (**Scheme 26**) The success of a mixed-coupling also depends on the structures of the substrates; in some cases, an excess of one of the coupling partners does not minimize homo-coupling.



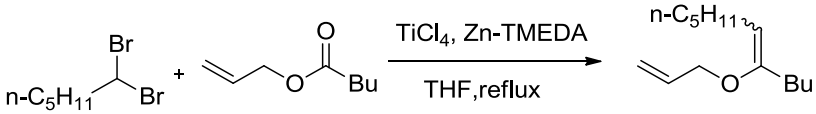
Scheme 26: Application of McMurry coupling in the synthesis of bycyclic products

When the reduction potentials of the two substrates employed are sufficiently different, selective mixed-couplings can be accomplished using equimolar amounts of the two coupling partners. For example, monoaryl and diaryl ketones readily couple with one another in high yield in the presence of $TiCl_3$–Zn. (**Scheme 27**) [85]



Scheme 27: Effect of amount of substrate on formation of mix- coupled products

The McMurry coupling is severely limited by the drawback that mixed coupling between ketones and aldehydes is difficult to achieve. Reactions employing carbonyl equivalents such as *gem*-dihalides and thioacetals are amenable to mixed coupling and nicely complement the traditional McMurry coupling. Essentially, these reactions are an extension of the strategy of using coupling partners with very different reduction potentials. Esters, amides, and thioesters are useful substrates and afford electron-rich olefins. (**Scheme 28**) [86]



Scheme 28: Drawbacks of the McMurry coupling

In chapter 3, we have developed a novel methodology for the deoxygenation of carbonyl compounds to olefin using the novel reagent, $SnCl_4$-Zn (1:1.5) in THF which gave the major cross-coupled products over the homo-coupled products within 1h at 66 ^oC and this methodology extended for the synthesis of E & Z- isomers of Tamoxifen analogs.

1.6 INDANONE

Indanone, indenone and indane skeletons are important moieties present in a variety of natural products and biologically active compounds. For example, indenone (3-(2,3-dihydrobenzofuran-6-yl)-5,6-dimethoxy-2-methyl-2,3-dihydro-1H-inden-1-one) was isolated from the fruits of virola sebifera, [87] indanone (pterosin C) is a cytotoxic and antibacterial natural products, [88] donepezil**,** a potent acetylcholinessterase inhibitor prescribed for the treatment of Alzheimer's disease, [89] is a marketed drug (Aricept ^{TM}), and indenone (5-(4-chlorophenyl)-3-(methylsulfonyl)-2H-indeno[5,6-d]oxazole-2,7(3H)-dione) is a structural analogue of the selective COX-2 inhibitor nimesulide. [90] Indan-1-one and indan-2-one derivatives are important moieties in the core structures of many natural products, agrochemicals and medicines [91-94] including Indacrinone, [95 a-c] indanoyl isoleucine conjugates, [95d] indanocines, [95e] quadranglularin A,[95 f, g] parthenocissin A, [95 h, i] (+)-pauciflorol F, [96] norditerpene taiwaniaquinol B, [97] sulindac, NSAID, [98a-c] NMDA receptor antagonists, [98d] benzodiazepines, [98e] melatonin precursor, [98f] and neoflavonoids [99,100] (Figure 11). They are also reported from higher plants such as *Uvaria afzelii* roots, [101] *Pteridium aquilinum* [102a-c] and *Equisetum arvense* [102d] and screened for various biological activities including cancer and Alzheimer's diseases. 2-(Alkoxycarbonyl) and 2-acetyl-1-indanones are present in cytotoxic natural compound pterosines, a potent and selective COX-2 inhibitor flosulide, and the acetyl cholinesterase inhibitor donepezil hydrochloride. They are approved by US-FDA for the treatment of mild to moderate Alzheimer's disease. Similarly, the enantiomerically pure derivative, 1-amino-2-indanol is a key precursor of the chiral ligand and the chiral auxiliary for asymmetric synthesis of indinavir, a potent inhibitor of the protease of human immunodeficiency virus (HIV) [103] and Detrol LA (tolterodine tartrate), a muscarine receptor antagonist used for the treatment of urinary bladder disorder. [104a] The Indan-1-one bearing carboxylate scaffold is also used a peroxisome proliferator activated receptor γ (PPARγ) agonist in the treatment of type-2 diabetes. [104b]

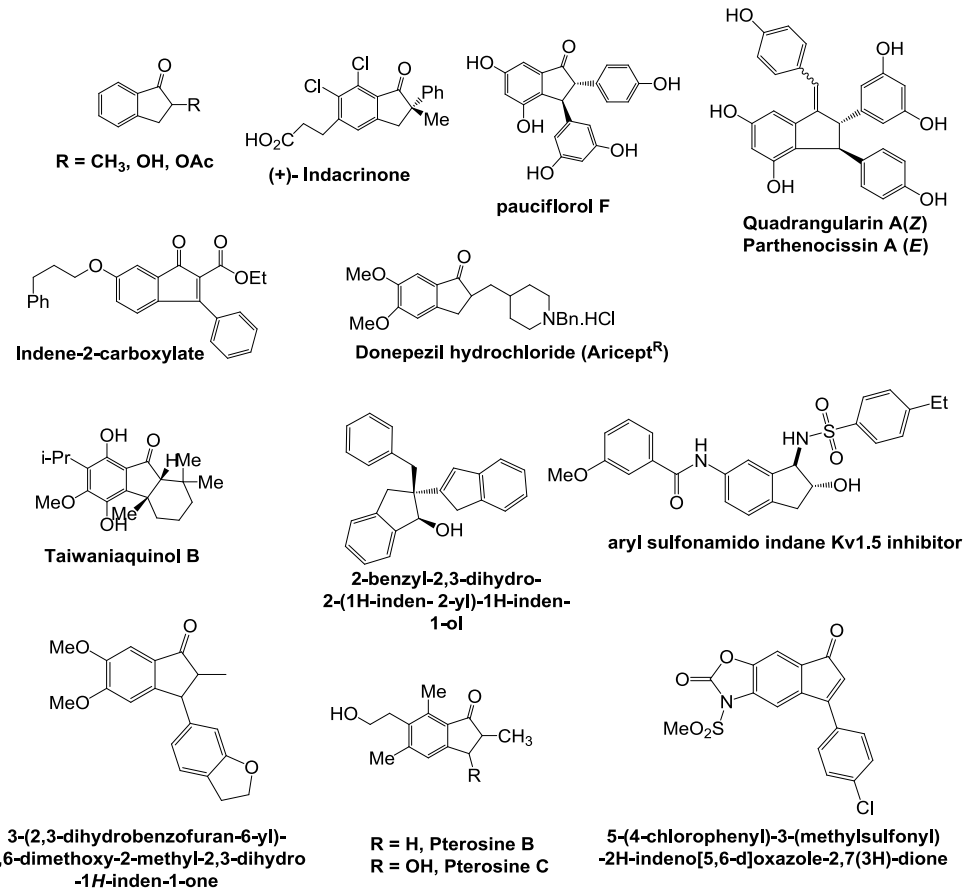
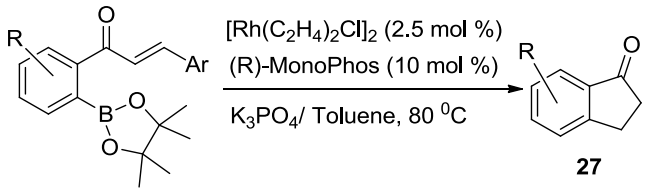


Figure 8: Bioactive compounds containing indanone and indenone cores

Various methods have reported in the literature to access indanones and indenones. Substituted indanones were obtained by using the intramolecular Friedal-Crafts reaction, [105] photochemical reactions, [106] Nazarov cyclization [107] and organometallic-catalysed reactions.[108] Friedel-Crafts alkylation, [109] Nazarov cyclization, [110,111] Tandem Knoevenagel Condensation-cycloalkylation, [112] Heck & Negishi coupling, [113] Larock annulations. [114] Similarly, enantioselective indanones synthesis required multi-step reaction and high catalyst loading for the 3-substituted indanone derivatives. [115] Indanone frameworks are commonly found in a wealth of natural products and biologically active compounds. [116] Among them, 1-indanone bearing a stereogenic center at the 3-position are not only particularly important structural components of many pharmaceutical agents but also versatile intermediates in organic synthesis and medicinal chemistry. [117] As a result, methods that enable convenient access to optically active 3-substituted 1-indanones are of great importance. Surprisingly however, only a limited number of methods for the stereoselective formation of 3-substituted 1-indanones have been developed. [118]

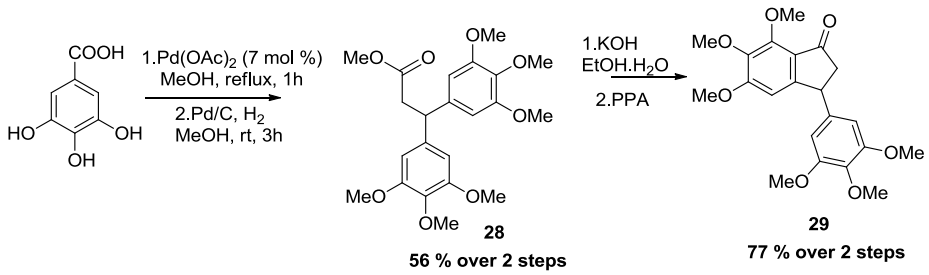
1.6.1 Methods of synthesis of Indanone

Ho, T. et. al. synthesized the indanone **27** by using Rh-catalyst and (R)-Monophos ligand in toluene at 80 ^{0}C in a good yield. [119]



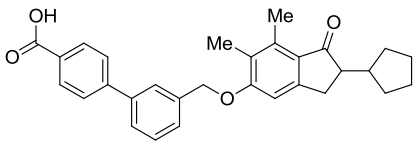
Scheme 29: $[Rh(C_2H_4)Cl]_2$ -catalysed asymmetric intramolecular 1,4-addition

Brunner, et. al. investigated that the target compound could be prepared via a process involving a one pot Pd-catalysed Heck-Matsuda (HM) reaction [120] procedure followed by hydrolysis of the ester **28** to afford the corresponding carboxylic acid. Finally, as the last step, an acid catalyzed cyclization reaction was employed to provide compound **29**. (**Scheme 30**)



Scheme 30: Synthesis of indanone **29** via a Heck-Matsuda (HM) reaction

Galici, R. & co-workers prepared BINA in nine steps from 3-bromotoluene, 2, 3-dimethyl anisole, ethyl 4-iodobenzoate, and cyclopentylacetic acid in 16% overall yield. BINA constitutes a highly selective positive allosteric modulator of mGluR2 with a long duration of action and robust efficacy in several preclinical models used to predict anxiolytic and antipsychotic-like activity. [121]

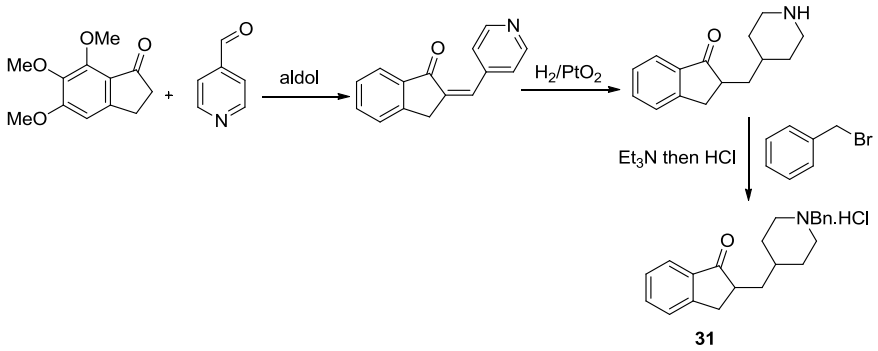


30
biphenylindanone A (BINA)

Scheme 31: Synthesis of BINA

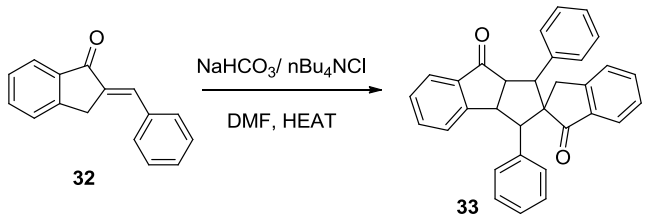
1.6.2 Reactivity of indanone

Vidyadhar, et. al. industrially manufactured the indanone derivative donepezil **31**, which is used for the treatment of mild to moderate Alzheimer's disease, in three steps via aldol condensation of indanone and pyridine aldehyde. [122]



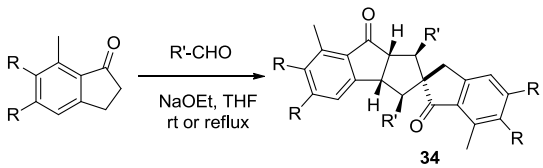
Scheme 32: Industrial manufacture of donepezil via a pyridine derivative

It has been observed that 2-(E)-benzylidine-1-indanone **32** undergoes dimerization under basic conditions. The reaction is highly stereoselective and provides almost exclusively dimer **33** using $NaHCO_3$/DMF, guanidine carbonate/DMF, or Cs_2CO_3/CH_3CN. [123]



Scheme 33: Stereoselective synthesis of dimer of 2-(E)-benzylidine-1-indanone

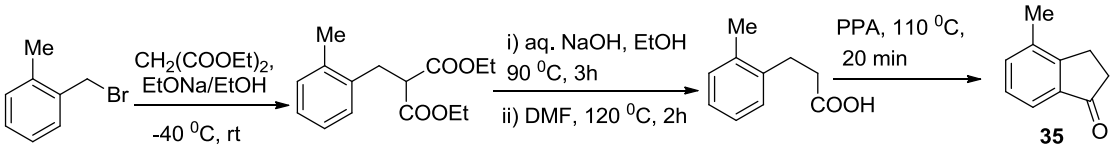
Tretment of 1-indanone with aromatic aldehydes and NaOEt in THF afforded complex spiropolycyclic compounds **34** through a four-component reaction in which two molecules of each starting compounds are combined with formation of four new carbon-carbon bonds, leading to the elaboration of a new five-membered ring that bears five contiguous stereogenic centers with a well defined relative configuration. The reaction seems to take place by cross-aldol condensation, dehydration and dimerization of enones. [124]



R = OMe, H
R' = 4-pyridyl, 2-furyl, 2-thienyl, N-methyl-2-pyrrolyl, phenyl

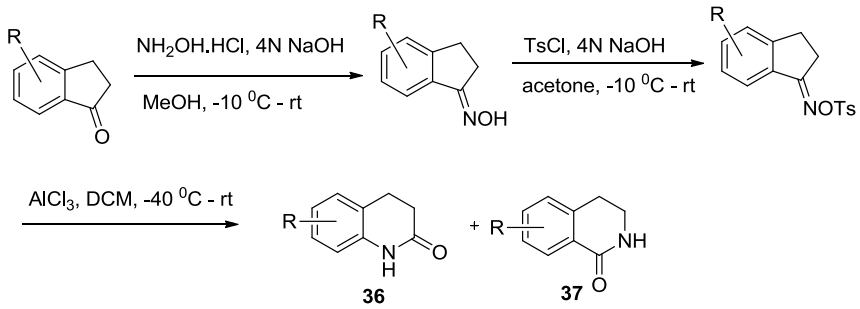
Scheme 34: Synthesis of complex spiropolycyclic compound

2, 2-methyl benzylbromide was reacted with diethyl malonate in alcoholic sodium ethoxide to gave diethyl (2-methylbenzyl)malonate in 75% yield followed by saponification and intramolecular ring formation in PPA to gave compound **35** in 90% yields. [125]



Scheme 35: Synthesis of methyl indanone

Indanone on reaction with hydroxyl amine hydrochloride at -10 ^{0}C followed by tosylation to give a 1-indanone oxime tosylate. Then undergo Beckmann rearrangement in presence of alluminium chloride to obtained isomers **36** & **37**. [126]



Scheme 36: Synthesis of 1-indanone oxime tosylate and their Beckmann rearrangement

We have also synthesized indanone based ligands as tamoxifen analogs via McMurry reaction. A major cross-coupled product was obtained within 1h at 66 ^{0} C. Tamoxifen analogs were exhibited excellent anti-proliferative activity against human breast cancer cells (MCF-7 and MDA-MB-231) and cervical cancer cells (HeLa) are reported in chapter 3, part B.

1.7 References

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CHAPTER- 2

Part-A: Highly efficient deprotection of phenolic tetrahydropyranyl and methoxymethyl ethers and sequel cyclization to indanones using Sn (IV) Cl_4 catalyst

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Part-B: $SnCl_4$ or $TiCl_4$: Highly efficient catalysts for detetrahydropyranylation and demethoxymethylation of phenolic ethers and sequel one-pot asymmetric synthesis of 3-aryl-2-hydroxy-2,3-dihydroindan-1-ones from chalcone epoxides

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Part A: Highly efficient deprotection of phenolic tetrahydropyranyl and methoxymethyl ethers and sequel cyclization to indanones using Sn (IV) Cl_4 catalyst

2.1 INTRODUCTION

Protection-deprotection of the functional groups is the most frequent used strategies in the multi-steps organic syntheses. In particular, the protection and the deprotection of hydroxyl group is extremely important because of its enormous demand for the synthesis of a number of compounds of biological and synthetic interest such as carbohydrates, macrolides, peptides, steroids, nucleotides and polyethers.[1] The protection of hydroxyl groups with 3,4-dihydro-2H-pyran is the most frequent used method due to stability of the resulting 2-tetrahydropyranyl ethers (THPEs) in the presence of strong bases or nucleophiles such as Grignard reagents, organolithium compounds, metal hydrides, catalytic hydrogenation, alkylating and acylating agents.[2] Similarly, methoxymethyl chloride (MOMCl) is an another important reagent for the hydroxyl group protection.[3]

The deprotection of THP and MOM ethers therefore required efficient methods to avoid the decomposition of the products and/or loss of other functional groups in the products under harsh reaction conditions. Therefore, several catalysts have been explored for the detetrahydropyranylation of alcohols and phenols that include protic acids,[4] Lewis acids like BF_3-etherate,[5] LiBr,[6] $LiBF_4$,[7] LiOTf,[8] $LiClO_4$,[9] $Sc(OTf)_3$,[10] $In(OTf)_3$,[11] I_2,[12] $InCl_3$,[13] $ZrCl_4$,[14] $CuCl_2$,[15] and NH_4Cl,[16] expansive graphite,[17] clay materials,[18] silica-supported sulfuric acid,[19] and other miscellaneous catalysts.[20-25] Similarly, many catalysts have been used for the demethoxymethylation of alcohols and phenols such as HCl, BBr_3, pyridinium *p*-toluene sulphonate under strong acidic condition, mild Lewis acids $ZnBr_2$, and $TiCl_4$ in aprotic conditions and BBr_3 derivatives Me_2BBr, and $(i\text{-}PrS)_2BBr$.[26] Most of these methods have different drawbacks such as longer reaction time, low yields, refluxing at high temperature and the tedious workup procedures. Hence, there is still a scope to develop mild and efficient methods in the deprotection of tetrahydropyranyl and methoxymethyl ethers. In continuation of our interest to develop new methods for the synthesis and the acid catalysis reactions, [27] herein, we report an efficient deprotection method of the THP and the MOM ethers and sequel Friedel-Crafts alkylation reaction of the protected THP and MOM chalcone epoxides using $SnCl_4$ catalyst under mild reaction conditions.

2.2 OBJECTIVE

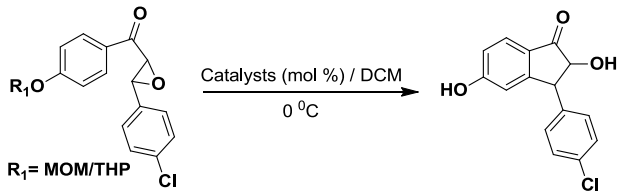
Protection and deprotection of hydroxyl group is very important development, frequently used in organic synthesis of molecule like, carbohydrates, macrolides, peptides, steroids, nucleotides and polyethers. Hence, our intention to developed a highly efficient protocol for the deprotection of hydroxyl group by using metal catalyst, and we used different metal catalyst and found that $SnCl_4$ catalyst provided a rapid and efficient deprotection method for the phenolic THP and MOM ethers and sequel intramolecular Friedel-Crafts alkylation reaction of THP and MOM protected chalcone epoxides under mild conditions. The reaction took 2-3 min to give the products in excellent yield (90-98%) at 0 ^{0}C without affecting the other functional groups.

2.3 Results and Discussion

2.3.1. Optimization reaction conditions by using different catalyst

The catalytic efficiency of different metal halides was screened (Table 1). The metal halides (Table 1, entries 1-5) were shown poor to moderate catalytic activity. $InCl_3$ (Table 1, entry 6) was found to be a better catalyst at 10 mol% catalyst loading, which gave 90% yield of the cyclized products without deprotecting the THP or the MOM ethers. However, the reaction was completed in 4-5 hours. $SnCl_4$ (Table 1, entries 7, 8) at less than 10 mol% catalyst loading gave lower yields in a longer reaction time. $SnCl_4$ (Table 1, entry 9) at 10 mol% catalyst loading was found to be the most efficient catalyst, which gave the optimal yield (98%) with deprotecting the THP and the MOM ethers within 2-3 min. Further, increase in the catalyst loading of $SnCl_4$ (Table 1, entry 10) gave the side-product as 3-(4-chlorophenyl)-2-chloro-2,3-dihydro indan-1-one along with the desider product. We also applied SnI_4 and $SnBr_4$ in 5, 10, and 20 mol% catalysts loading during the deprotection of THP and MOM ethers. However, it gave the desired products only 5-10% yields after stirring for 2-6 h at 0 ^{0}C.

Table 1. Optimization conditions in deprotection of the THP and the MOM ethers and sequel cyclization of phenolic compounds with different catalysts



Entry	Catalyst	Mol %	Time	Yield (%)

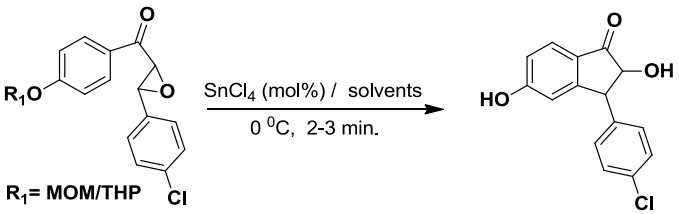
1	$SbCl_3$	10	20-24 h	28[a]
2	SnI_4	10	6 h	7[b]
3	$SbCl_5$	10	20-24 h	20[a]
4	$MgCl_2$	10	18-24 h	18[a]
5	$SnBr_4$	10	6 h	10[b]
6	**$InCl_3$**	**10**	**4-5 h**	**90**[a]
7	$SnCl_4$	1	3 min	75[b]
8	$SnCl_4$	5	2 min	90[b]
9	**$SnCl_4$**	**10**	**3 min**	**98**[b]
10	$SnCl_4$	20	3 min	70+20[c]

[a] Gave only cyclization.[b]Gave both THP and MOM ethers deprotection and sequel cyclization.[c] Other product as 3-(4-chlorophenyl)-2-chloro-2,3-dihydro indan-1-one (20%).

2.3.2. Solvents effect

We observed the solvent effects using different solvents like CH_3COCH_3, $CHCl_3$, CH_2Cl_2 and THF. $CHCl_3$ and CH_2Cl_2 were found to be the desired solvents (Table 2, entries 4, 6).

Table 2. Solvent effects on yields in deprotection of the THP and the MOM ethers and sequel cyclization reaction



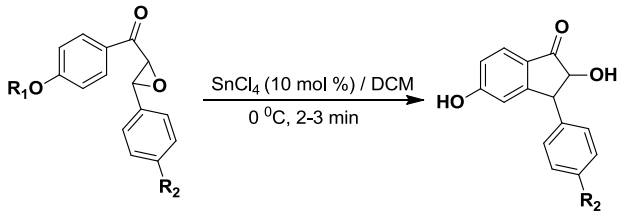
Entry	Mol%	Solvents	Yield (%)
1	1	Acetone	40[a]
2	5	Acetone	45[a]
3	2	DCM	80[b]
4	**10**	**DCM**	**98**[b]
5	2	$CHCl_3$	85[c]
6	**10**	**$CHCl_3$**	**96**[c]
7	5	THF	52[d]
8	10	THF	60[d]

Reaction time: [a] 2h, [b,c] 3 min, [d] 3 h.

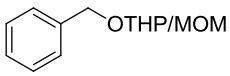
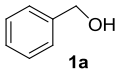
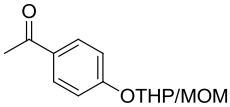
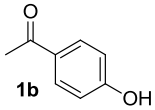
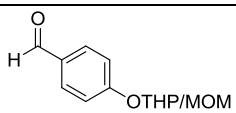
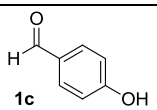
2.3.3. Examples of the THP and MOM ethers deprotection and sequel cyclization reaction

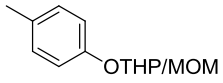
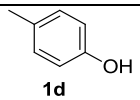
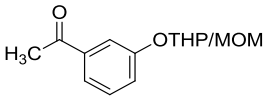
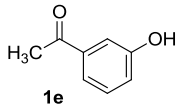
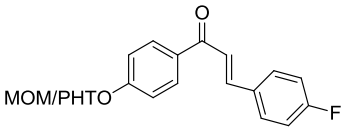
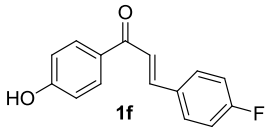
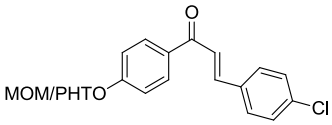
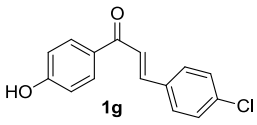
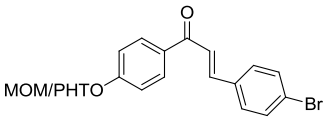
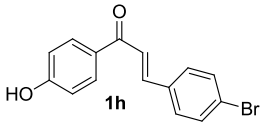
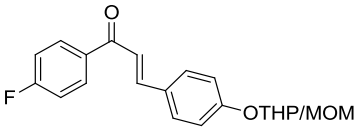
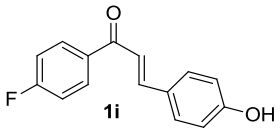
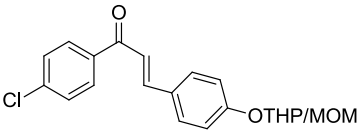
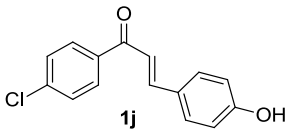
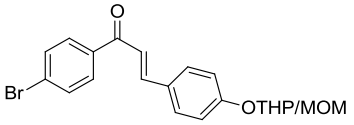
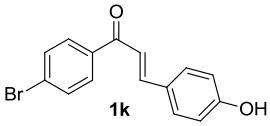
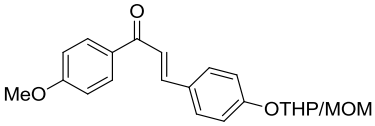
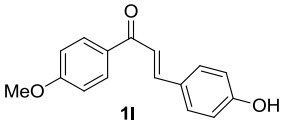
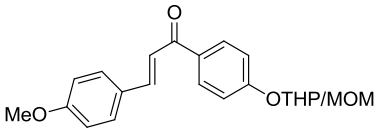
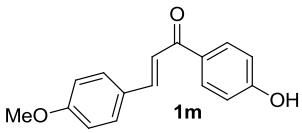
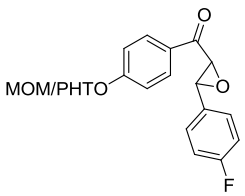
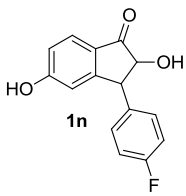
Under optimized reaction conditions, the deprotection of THP and MOM ethers in phenols, chalcone and chalcone epoxides were achieved using 10 mol% of $SnCl_4$ in excellent yields (90-98%) within 2-3 min at 0 ^{0}C in the presence of other functional groups. However, in the case of alcoholic THP and MOM ethers, even 20 mol% of catalyst loading gave less yield 10 and 25% respectively (Table 3, entry 1). In case of chalcone **1f-1m**, only THP and MOM removal was observed without intramolecular Friedel-Crafts alkylation. These products were characterized by comparing their physical and spectral data with the literature values.[22, 28] Interestingly, the THP and MOM removal followed by the Friedel-Crafts alkylation was observed for the chalcone epoxides which gave the corresponding indanones **1n-1s** in excellent yield (90-98%) within 2-3 min at 0 ^{0}C (Table 3). The stereochemistry and the distereomeric excess ratio of the products **1n-1s** were determined by the chiral column separation and determined as 2R, 3S-configuration. These products were fully characterized on the basis of their spectral analysis ^{1}H-, ^{13}C-NMR, GC-MS, Chiral HPLC (Supporting information).

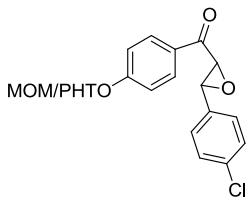
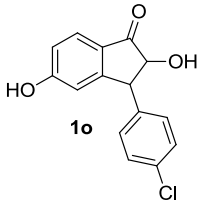
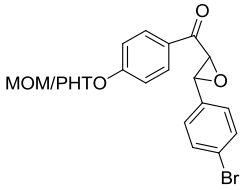
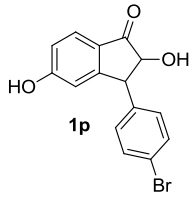
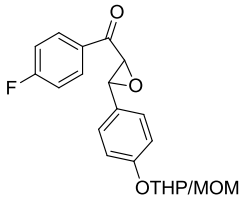
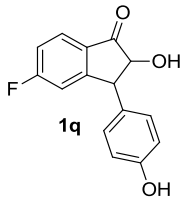
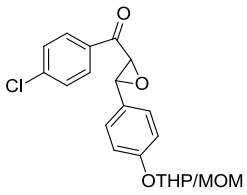
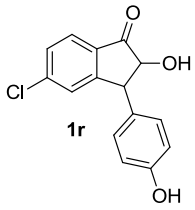
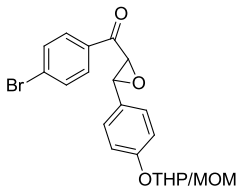
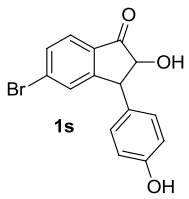
Table 3. Examples of the THP and MOM ethers deprotection and sequel cyclization reaction



R_1= THP/MOM

Entry	ROTHP/MOM	ROH	Time (min)	Yield (%)[a]	Yield (%)[b]
1		 1a	2	10	25
2			2	95	92
3			2	96	95

4		 1d	2	92	95
5		 1e	2	90	92
6		 1f	3	98	94
7		 1g	3	96	98
8		 1h	2	97	94
9		 1i	2	96	93
10		 1j	3	95	92
11		 1k	3	96	95
12		 1l	2	90	92
13		 1m	3	95	95
14		 1n	3	96	93

15			2	98	98
16			2	95	94
17			3	96	93
18			3	95	92
19			2	92	92

[a] yield (**1-19**) from R-OTHP and [b] yield (**1-19**) from R-OMOM ethers deprotection.

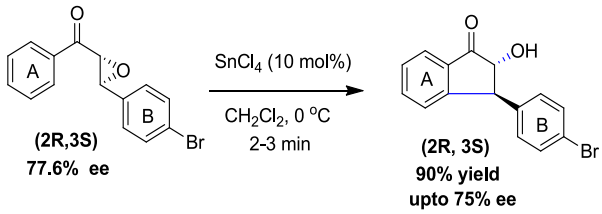
2.3.4. Synthesis of diastereoisomerically pure Trans-3-(4-bromophenyl)-2-hydroxy-2, 3-dihydroindan-1-one.

The stereochemistry and the distereomeric excess ratio of the indanone derivatives **1n-1s** were determined by the chiral column separation of racemic mixture of diastereomers. For example, in the synthesis of racemic indanone 3-(4-bromophenyl)-2-hydroxy-2, 3-dihydroindan-1-one (Scheme 1), the chiral HPLC purification gave peaks at 40.14 (51%) and 56.43 (49%) min. for the diastereomers (See Supporting Information). Then, we synthesized enantiomerically excess (ee) *trans*-chalcone epoxide of 2R, 3S-configuration from chalcone with α, α'-diphenyl-L-prolinol and TBHP in hexane which gave a good yield (58%) with

77.6% ee (scheme 1). Asymmetric epoxides were characterized by comparing with the literature value of ^{1}HNMR and enantiomeric excess was determined by chiral HPLC column and optical rotation in chloroform. [24]

It was observed that during the ring opening of epoxides, the C-2 configuration remained same while the C-3 configuration changed due to S_N1-like mechanism therefore it gave the regio- and stereoselective intramolecular Friedel-Crafts alkylation. The protons at C-2 and C-3 positions are in *trans*-orientation which is confirmed by the coupling constant (J = 2.0 Hz) in ^{1}HNMR spectrum. [24] The absolute configurations at C-2 and C-3 are confirmed as 2*R* and 3*S* respectively. The stereoselectivity and high yields for 1-indanones under acidic condition ($SnCl_4$) might be due to the variable oxidation state and availability of relatively low energy 5d-orbitals on tin. On ligation with epoxide oxygen, the tetrahedron structure of $SnCl_4$ was converted to a trigonal bipyramide/octahedron structure. This geometrical change enhanced the steric hindrance which results in a faster epoxide ring opening from *β*-carbon due to considerable electron deficient character at benzylic carbon. Therefore, the nucleophile attacked at *β*-carbon of carbonyl group.

Scheme 1. Synthesis of diastereoisomerically pure trans-3-(4-bromophenyl)-2-hydroxy-2, 3-dihydroindan-1-one.

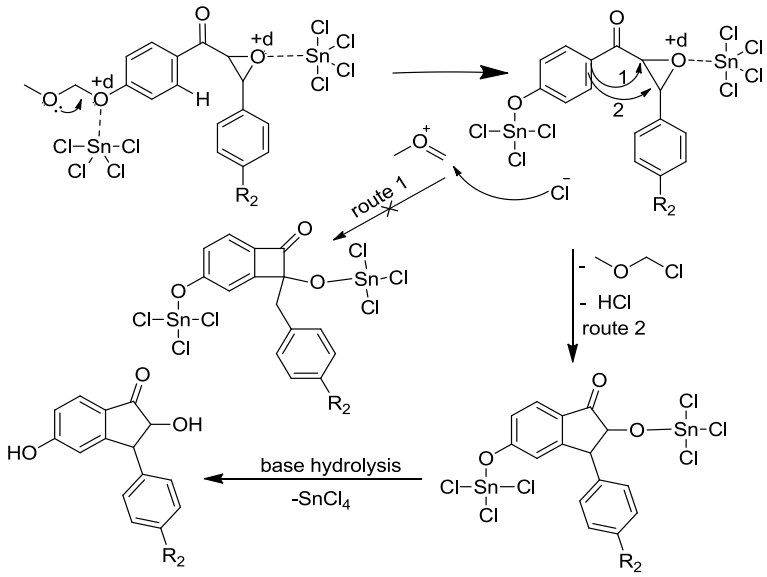


2.4. MECHANISM

A proposed reaction mechanism is shown in the scheme 1 for the MOM ether deprotection and the sequel intramolecular Friedel-Crafts alkylation, where ligation of $SnCl_4$ with MOM oxygen resulted in the removal of the methyl (methylene) oxonium group followed by its reaction with Cl^- generated the MOMCl. [23] Same time, the epoxide oxygen ligation with $SnCl_4$ might change the tetrahedron structure of $SnCl_4$ into trigonal bipyramide/octahedron structure. The geometry changes enhanced the steric hindrance which results in faster epoxide ring opening from *β*-carbon due to considerable electron deficient character at benzylic position not on α-carbon due to a 4-membered cyclobutanone (unstable intermediate). Therefore, the nucleophilic attack took place at *β*-carbon of carbonyl which gave a resonance stabilized

benzyl intermediate. Finally, a base hydrolysis regenerated $SnCl_4$ catalyst which is used in the next catalytic-cycle.

Scheme 2. A propose mechanism for the deprotection of MOM ethers followed by cyclization with $SnCl_4$



2.5. CONCLUSION

In conclusion, we have illustrated an optimized reaction conditions for the rapid and efficient deprotection of the phenolic THP and MOM ethers and sequel intramolecular Friedel-Crafts alkylation reaction of chalcone epoxides. All reactions were completed within 2-3 min and gave excellent yield (90-98%) at 0 ^{0}C for both the THP and the MOM ethers and sequel cyclization reactions without affecting the other functional groups.

2.6. EXPERIMENTAL DETAILS

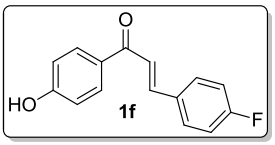
Organic solvents were dried by standard methods, the reagents (chemicals) were purchased from commercial sources, and used without further purification. All reactions were monitored by TLC using precoated silica gel aluminum plates. Visualization of TLC plates was accomplished with an UV lamp. Column chromatography was performed using silica gel 60–120 mesh size (RANKEM Limited) with EtOAc–hexanes as eluent. Melting points were recorded on Perfit apparatus and are uncorrected. All products were characterized by NMR, IR and MS spectra. ^{1}H and ^{13}C NMR spectra were recorded in deuterated chloroform ($CDCl_3$) on a 500 MHz and 125 MHz spectrometer (Bruker), respectively. Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br).

2.6.1. General Procedure for Deprotection of Tetrahydropyranyl and Methoxymethyl Ethers of Alcohols and Phenols:

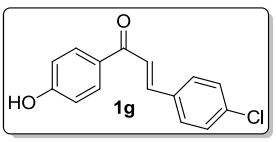
$SnCl_4$ (10 mol %) was added to a stirred solution of THP and MOM ethers (1 mmol) in CH_2Cl_2 (5 mL) at 0 ^{0}C. TLC monitoring, the reaction mixture was poured into 10% aqueous Na_2CO_3 solution and extracted with CH_2Cl_2. The organic layer washed with brine solution, dried with anhyd.Na_2SO_4, and concentrated in *vacuo* to give corresponding alcohol or phenol, which was purified by silica gel column chromatography with hexane-ethyl acetate when required to obtain the products **1** to **19** with excellent yield (90-98%).

2.6.2. Characterization data for selected synthesized compounds

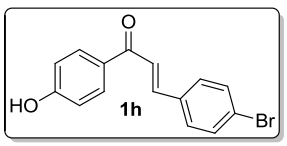
(a) Selected spectral data of THP and MOM deprotected products:



(E)-3-(4-fluorophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (1f): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.99 (d, *J* = 8.5 Hz, 2H), 7.77 (d, *J* = 15.5 Hz, 1H), 7.62 (dd, *J* = 6, 13.5 Hz, 2H), 7.46 (d, *J* = 15.5 Hz, 1H), 7.10 (t, *J* = 8 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 2H), 6.24 (s, 1H, br, D_2O exchangeable); **^{13}C NMR ($CDCl_3$, 125 MHz)** δ ppm 187.50, 164.68, 162.67, 141.94, 132.02, 131.52, 131.45, 129.53, 122.46, 116.42, 116.25. **IR ν_{max} (KBr, cm^{-1})** 3415 (OH str), 2931, 2873 (aromatic C-H str), 1681 (C=O str), 1597 (aromatic, C=C str), 1263, 1081, 860, 737; **GC-MS (m/z)** 242 [$M^{+\cdot}$, $C_{15}H_{11}FO_2$].

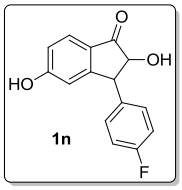


(E)-3-(4-chlorophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (1g): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.99 (d, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 15.5 Hz, 1H), 7.63-7.61 (m, 2H), 7.45 (d, *J* =16 Hz, 1H), 7.10 (t, *J* = 8.5 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 2H), 6.2 (s, 1H, br, D_2O exchangeable); **^{13}C NMR ($CDCl_3$, 125 MHz)** δ ppm 187.20, 162.37, 141.64, 131.72, 131.22, 131.15, 129.23, 122.16, 116.12, 115.95; **IR ν_{max} (KBr, cm^{-1})** 3408 (OH str), 2928, 2876 (aromatic C-H str), 1684 (C=O str), 1598 (aromatic, C=C str), 1268, 1085, 864, 735; **GC-MS (m/z)** 258 [$M^{+\cdot}$, $C_{15}H_{11}ClO_2$].

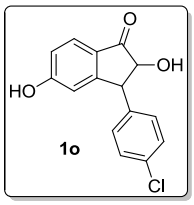


(E)-3-(4-bromophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (1h): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.99 (d, *J* = 8 Hz, 2H), 7.77 (d, *J* = 15.5 Hz, 1H), 7.63 (t, *J* = 8Hz, 2H), 7.46 (d, *J* = 15.5 Hz, 1H), 7.10 (t, *J* = 8.5 Hz, 2H), 6.95 (d, *J* = 8 Hz, 2H); **^{13}C NMR ($CDCl_3$, 125 MHz)** δ ppm 186.88, 162.05, 141.32, 131.41, 130.90, 130.83, 128.92, 121.85, 115.81, 115.21; **IR ν_{max} (KBr, cm^{-1})**

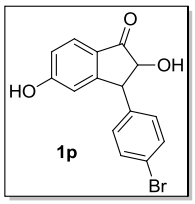
3410 (OH str), 2926, 2875 (aromatic C-H str), 1686 (C=O str), 1599 (aromatic, C=C str), 1265, 1078, 862, 730; **GC-MS (m/z)** 302 [$M^{+\cdot}$, $C_{15}H_{11}BrO_2$], 304 [M+2,].



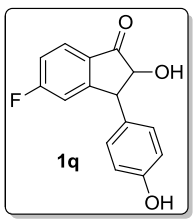
3-(4-fluorophenyl)-2,5-dihydroxy-2,3-dihydroinden-1-one (1n): **^{1}H NMR (CDCl$_3$, 500 MHz)** δ ppm 7.87 (d, *J* = 8.5 Hz, 2H), 7.54 (dd, *J* = 8.5, 14 Hz, 2H), 7.06 (d, *J* = 9 Hz, 2H),6.95 (d, *J* = 9 Hz, 1H), 6.4 (s, 1H) 5.29 (t, *J* = 7 Hz, 1H), 5.22 (d, *J* = 1.5 Hz, 1H); **^{13}C NMR (CDCl$_3$, 125 MHz)** δ ppm 195.55, 161.83, 137.36, 131.82, 131.42, 129.79, 125.99, 123.01, 116.23, 75.01, 63.53; **IR ν_{max} (KBr, cm^{-1})** 3405 (OH str), 2922, 2875 (aromatic C-H str), 1688 (C=O str), 1595 (aromatic, C=C str), 1266, 1089, 858, 731; **GC-MS (m/z)** 258 [$M^{+\cdot}$,$C_{15}H_{11}FO_3$].



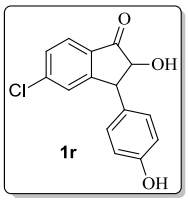
3-(4-chlorophenyl)-2,5-dihydroxy-2,3-dihydroinden-1-one (1o): ^{1}H NMR (CDCl$_3$, 500 MHz) δ ppm 7.88 (d, *J* = 8.5 Hz , 2H), 7.56-7.53 (m, 1H), 7.07 (t, *J* = 7 Hz, 2H), 6.96 (d, *J* = 9 Hz, 2H), 6.45 (s, 1H), 5.30 (t, *J* =7 Hz,1H), 5.23 (d, *J* = 1.5 Hz,1H); **^{13}C NMR (CDCl$_3$, 125 MHz)** δ ppm 195.72, 162.00, 137.53, 131.99, 131.59, 129.96, 126.16, 123.18, 116.40, 76.23, 63.70; **IR ν_{max} (KBr,cm^{-1})** 3415 (OH str), 2931, 2873 (aromatic C-H str), 1681 (C=O str), 1597 (aromatic, C=C str), 1263, 1081, 860, 737; **GC-MS (m/z)** 274 [$M^{+\cdot}$, $C_{15}H_{11}ClO_3$].



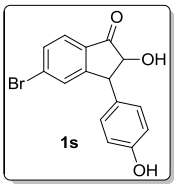
3-(4-bromophenyl)-2,5-dihydroxy-2,3-dihydroinden-1-one (1p): ^{1}H NMR (CDCl$_3$, 500 MHz) δ ppm 7.86 (d, *J* = 8.5 Hz, 2H), 7.54-7.52 (m, 1H), 7.05 (t, *J* = 7 Hz, 2H), 6.95 (d, *J* = 9 Hz, 2H), 6.42 (s, 1H), 5.29 (t, *J* = 7 Hz, 1H), 5.22 (d, *J* = 1.5 Hz,1H); **^{13}C NMR (CDCl$_3$, 125 MHz)** δ ppm 195.57, 161.85, 137.38, 131.84, 131.45, 129.81, 126.01, 123.04, 116.25, 75.40, 63.55; **IR ν_{max} (KBr, cm^{-1})** 3425 (OH str), 2935, 2877 (aromatic C-H str), 1687 (C=O str), 1585 (aromatic, C=C str), 1266, 1088, 862, 733; **GC-MS (m/z)** 318 [$M^{+\cdot}$, $C_{15}H_{11}BrO_3$], 320 [M+2].



5-fluoro-2-hydroxy-3-(4-hydroxyphenyl)-2,3-dihydroinden-1-one (1q): ^{1}H NMR (CDCl$_3$, 500 MHz) δ ppm 7.86 (d, *J* = 8.5 Hz , 2H), 7.53 (dd, *J* = 8.5, 14 Hz, 2H), 7.06 (t, *J* = 7 Hz, 2H), 6.95 (d, *J* = 9 Hz, 1H), 6.44 (s, 1H, br, D_2O exchangeable), 5.30 (t, *J* =7 Hz, 1H), 5.22 (d, *J* = 1.5 Hz, 1H); **^{13}C NMR (CDCl$_3$, 125 MHz)** δ ppm 195.53, 161.81, 137.34, 131.79, 131.40, 129.76, 125.96, 122.99, 116.21, 75.36, 63.51; **IR ν_{max} (KBr, cm^{-1})** 3428 (OH str), 2933, 2877 (aromatic C-H str), 1687 (C=O str), 1599 (aromatic, C=C str), 1265, 1088, 858, 725; **GC-MS (m/z)** 258 [$M^{+\cdot}$, $C_{15}H_{11}FO_3$].



5-chloro-2-hydroxy-3-(4-hydroxyphenyl)-2,3-dihydroinden-1-one (1r): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.87 (d, *J* = 8.5 Hz, 2H), 7.54-7.52 (m, 1H), 7.06 (t, *J* = 7 Hz, 2H), 6.95 (d, *J* = 9 Hz, 2H), 6.45(s, 1H, br, D_2O exchangeable), 5.30 (t, *J* =7 Hz,1H), 5.22(d, *J* = 1.5 Hz, 1H); **^{13}C NMR ($CDCl_3$, 125 MHz)** δ ppm 195.82, 162.10, 137.63, 132.09, 131.69, 130.06, 126.26, 123.28, 116.50, 75.65, 63.80; **IR ν_{max} (KBr, cm^{-1})** 3415 (OH str), 2931, 2873 (aromatic C-H str), 1681 (C=O str), 1597 (aromatic, C=C str), 1263, 1081, 860, 737; **GC-MS (m/z)** 274 [$M^{+\cdot}$, $C_{15}H_{11}ClO_3$].



5-bromo-2-hydroxy-3-(4-hydroxyphenyl)-2,3-dihydroinden-1-one (1s): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.86 (d, *J* = 8.5 Hz , 2H), 7.54-7.52 (m, 1H), 7.06 (t, *J* = 7 Hz, 2H), 6.95 (d, *J* = 9 Hz, 2H), 6.44 (s, 1H, br, D_2O exchangeable), 5.30 (t, *J* =7 Hz, 1H), 5.22 (d, *J* = 1.5 Hz, 1H); **^{13}C NMR ($CDCl_3$, 125 MHz)** δ ppm 195.54, 161.82, 137.35, 131.80, 131.41, 129.78, 125.97, 123.00, 116.22, 75.37, 63.52; **IR ν_{max} (KBr, cm^{-1})** 3427 (OH str), 2937, 2875 (aromatic C-H str), 1685 (C=O str), 1593 (aromatic, C=C str), 1266, 1083, 864, 727; **GC-MS (m/z)** 318 [$M^{+\cdot}$, $C_{15}H_{11}BrO_3$], 320 [M+2].

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Part B*: $SnCl_4$ or $TiCl_4$: Highly efficient catalysts for detetrahydropyranylation and demethoxymethylation of phenolic ethers and sequel one-pot asymmetric synthesis of 3-aryl-2-hydroxy-2, 3-dihydroindan-1-ones from chalcone epoxides*

3.1. INTRODUCTION

Protection and deprotection of functional groups are the most frequently used strategies in the multi-step organic syntheses. In particular, the protection and deprotection of the hydroxyl group is extremely important because of its enormous demand for the synthesis of a number of compounds of biological and synthetic interest such as carbohydrates, macrolides, peptides, steroids, nucleotides and polyethers.[1] Protection of the hydroxyl group with 3,4-dihydro-2*H*-pyran (DHP) and methoxymethyl chloride (MOMCl) is the most frequently used method due to the stability of the resulting 2-tetrahydropyranyl ethers (THPEs) and the methoxymethyl ethers (MOMEs) respectively in the presence of strong bases or nucleophiles such as Grignard reagents, organolithium compounds, metal hydrides, catalytic hydrogenation, alkylating and acylating agents.[2,3]

Conversely, the deprotection of THP and MOM ethers required efficient methods to avoid decomposition and/or loss of other functional groups in the product under harsh reaction conditions. Therefore, many catalysts are explored for the detetrahydropyranylation of alcohols and phenols include protic acids,[4] Lewis acids such as BF_3-etherate,[5] LiBr,[6] $LiBF_4$,[7] LiOTf,[8] $LiClO_4$,[9] $Sc(OTf)_3$,[10] $In(OTf)_3$,[11] I_2,[12] $InCl_3$,[13] $ZrCl_4$,[14] $CuCl_2$,[15] and salt NH_4Cl, [16] expansive graphite,[17] clay materials,[18] silica-supported sulfuric acid,[19] and other miscellaneous catalysts.[20-26] Similarly, many catalysts are used for the demethoxymethylation of alcohols and phenols; these catalysts include HCl, BBr_3, pyridinium *p*-toluene sulphonate under strong acidic condition, mild Lewis acids $ZnBr_2$, and $TiCl_4$ in aprotic conditions and BBr_3 derivatives like Me_2BBr, and $(i\text{-PrS})_2BBr$.[27] Most of these methods have different drawbacks such as long reaction time, low yields, reflux at high temperature and tedious workup procedures. Hence, there is still scope to develop more straightforward and efficient methods in the deprotection of tetrahydropyranyl and methoxymethyl ethers.

Indan-1-one and indan-2-one derivatives are important moieties in the core structures of many natural products, agrochemicals and medicines [28] including indacrinone,[28a-c]

indanoyl isoleucine conjugates,[28d] indanocines,[28e] quadranglularin A,[28 f,g] parthenocissin A,[28 h,i] (+)-pauciflorol F,[29] norditerpene taiwaniaquinol B,[30] sulindac, NSAID,[31a-c] NMDA receptor antagonists,[31d] benzodiazepines,[31e] melatonin precursor,[31f] and neoflavonoids[32,33] (Figure 1). They are also reported from higher plants such as *Uvaria afzelii* roots,[34] *Pteridium aquilinum* [34c] and *Equisetum arvense* [34d] and screened for various biological activities including cancer and Alzheimer's diseases. 2-(Alkoxycarbonyl)- and 2-acetyl-1-indanones are present in cytotoxic natural compound pterosines,[28,29] a potent and selective COX-2 inhibitor flosulide,[30,32] and the acetylcholinesterase inhibitor donepezil hydrochloride.[30] They are approved by US-FDA for the treatment of mild to moderate Alzheimer's disease.[29] Similarly, the enantiomerically pure derivative, 1-amino-2-indanol is a key precursor of the chiral ligand and the chiral auxiliary for asymmetric synthesis of indinavir, a potent inhibitor of the protease of human immunodeficiency virus (HIV)[35] and Detrol LA (tolterodine tartrate), a muscarine receptor antagonist used for the treatment of urinary bladder disorder.[36a] The Indan-1-one bearing carboxylate scaffold is also used a peroxisome proliferator activated receptor γ (PPARγ) agonist in the treatment of type-2 diabetes.[36b]

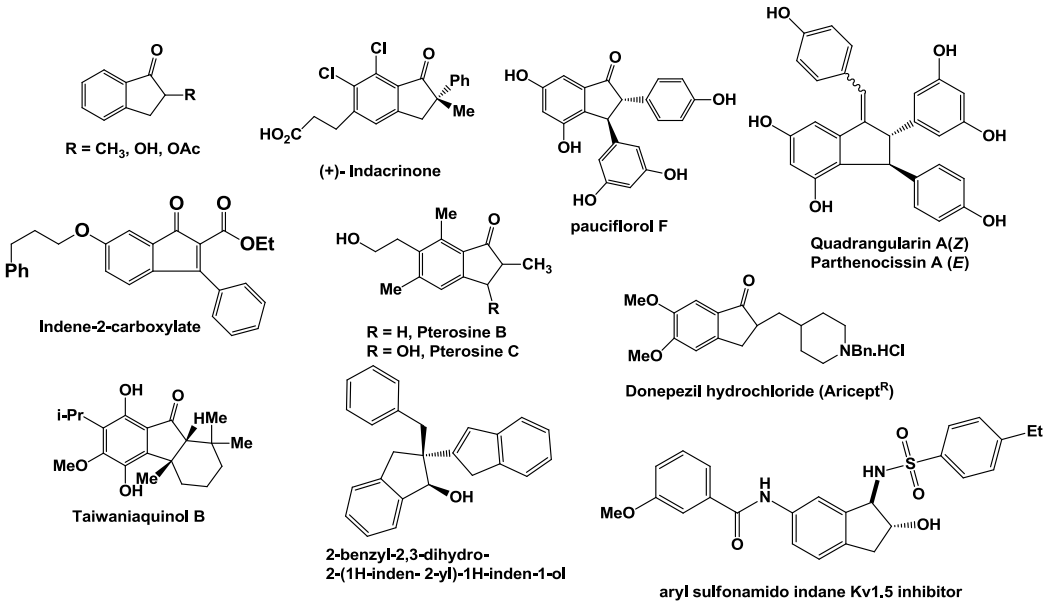


Figure 1. Bioactive indan-1-one derivatives.

Therefore, a number of synthetic methods have been reported that include intramolecular Friedel-Crafts alkylation, [37] Nazarov cyclization, [38,39] tandem Knoevenagel

condensation-cycloalkylation,[40] Heck & Negishi coupling,[41] Larock annulations [42] and ring-closing metathesis[43] reactions under different Lewis acids such as SbF_5,[44a] $AlCl_3$,[44b] and $TiCl_4$.[45-51] The Friedel-Crafts reactions were carried out at high temperature and in strong acidic conditions. Similarly, enantioselective indanones synthesis required multi-step reaction and high catalyst loading for the 3-substituted indanone derivatives.[32] In continuation of our interest in Lewis acid catalysis[52] and metal halides were used as inexpensive, easily available and stable catalysts during epoxide ring opening.[53] Herein, we report an efficient deprotection method of THP and MOM ethers and sequel Friedel-Crafts alkylation reaction in the stereoselective synthesis of functionalized 3-aryl 2-hydroxy-1-indanone derivatives catalyzed by a highly efficient $TiCl_4$ catalyst at 0 ^{0}C (Scheme 1, Table 1). In comparison with other methods, our protocol gave high yields (76-98%) with excellent regioselective products (up to 99.9% ee) in short reaction time (2-3 min).

3.2. OBJECTIVE

Metal catalysed organic transformation are the very important tool for inter and intra-molecular reaction in Stereoselective synthesis under mild condition. Now a day's people are trying to synthesize the cheap, inexpensive, commercial favorable methods for the one pot conversion in organic synthesis. Hence, our goal is to synthesize the commercially favorable methodology by using catalyst and we used different metal catalyst and $SnCl_4$ or $TiCl_4$ was found to be the versatile catalyst for the opening of chalcone epoxide and deprotection of hydroxyl group in a single step. Stereoselective syntheses of 3-aryl-2-hydroxy-1-indanones were also reported using $TiCl_4$ as a catalyst. Our protocol gave regio-selective products in excellent yield (76-98%) and enantiomeric excess up to 99.9% under same conditions.

3.3. RESULTS AND DISSCUSSION

3.3.1. Optimization reaction conditions by using different catalyst

The catalytic efficiency of different metal halides was screened (Table 1). Metal halides (Table 1, entries 1-6) exhibited poor to moderate catalytic activity. $InCl_3$ (Table 1, entry 7) was found to be a better catalyst at 10 mol% catalyst loading, which gave 90% yield of cyclized product without deprotecting of THP or MOM ethers. However, $TiCl_4$ (Table 1, entry 10,12) was found to be the most efficient catalyst at 10 mol% catalyst loading, which gave the optimal yield (98%) with deprotecting of THP and MOM ethers. We also used SnI_4 and $SnBr_4$ in 5, 10, and 20 mol% during the deprotection of THP and MOM ethers which gave the desired product

in a 5-10% yield after stirring for 2-6 h at 0 ^{0}C temperature. However, $TiCl_4$ gave excellent yield of 90-98% within 2-3 min. under the same conditions (Table 1, entry 10, 12).

To optimize the catalysts ($InCl_3$ and $TiCl_4$) loading, the reactions were carried out in 2, 5, 10 and 20 mol% (Table 1, entries 8-12) in dichloromethane and the efficiency of the catalyst loading was determined from the amount of time needed for the complete conversion of epoxides (Figure 2). $TiCl_4$ at 2 & 5 mol% loading, proceeded the reaction slowly, whereas at 20 mol% the loading reaction gave the side product as *3-(4-Chlorophenyl)-2-chloro-2,3-dihydroindan-1-one* (20%), which was isolated and characterized by GC-MS.

Scheme 1. Synthesis of indanone derivative in one-pot deprotection and cyclization.

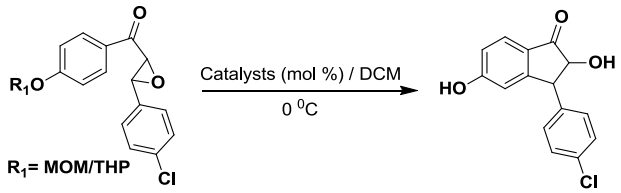
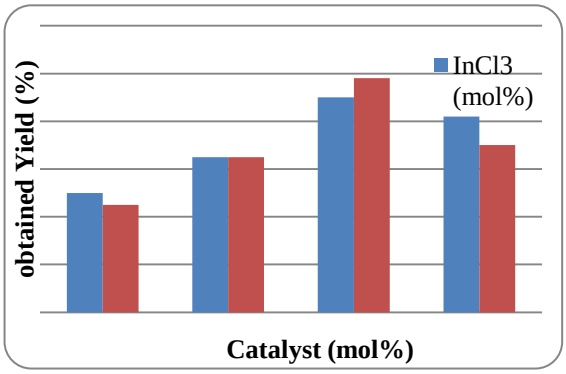


Table 1. Optimization of catalysts for Scheme 1

Entry	Catalyst	Loading (mol%)	Rxn.Time	Yield (%)
1	$SbCl_3$	10	20-24 h	28 [a]
2	$SbCl_5$	10	20-24 h	20 [a]
3	$MgCl_2$	10	18-24 h	18 [a]
4	$ZrCl_4$	10	10-15 h	10 [a]
5	$SnBr_4$	10	6 h	10 [b]
6	SnI_4	10	6 h	7 [b]
7	$InCl_3$	10	4-5 h	90 [a]
8	$SnCl_4$	2	30 min	45 [b]
9	$SnCl_4$	5	15 min	65 [b]
10	$SnCl_4$	10	2 min	98 [b]
11	$InCl_3/SnCl_4$	20	1 min	70+20 [c]
12	$TiCl_4$	10	2 min	98 [d]

[a]Gave only cyclization.[b,d] Gave both THP and MOM ethers deprotection and sequel cyclization other product as 3-(4-chlorophenyl)-2-chloro-2,3-dihydro indan-1-one(20%).

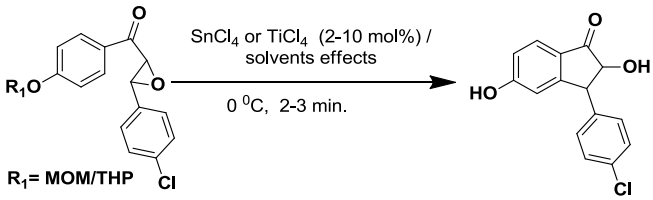
Figure 2. Comparison of $InCl_3$ and $TiCl_4$ catalysts loading only for cyclization reaction



3.3.2. Solvent effect by catalyst $SnCl_4$ or $TiCl_4$

We also observed the solvent effects using acetone, chloroform, dichloromethane and tetrahydrofuran where chloroform and dichloromethane were found to be desired solvents (Table 2, entries 4, 6).

Table 2. Solvent effects on yields in the deprotection of THP and MOM ethers

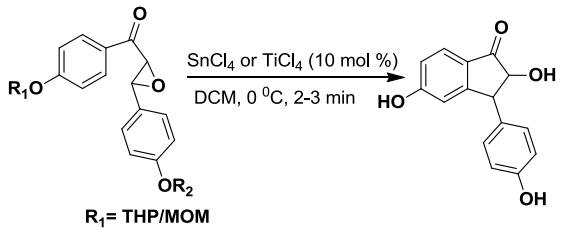


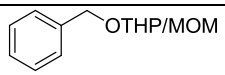
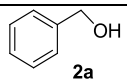
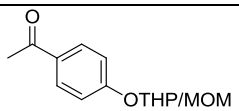
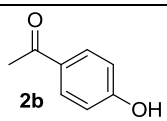
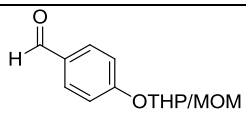
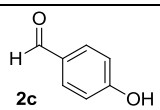
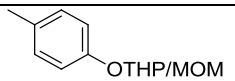
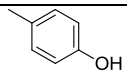
Entry	Mol%	Solvents	Yield (%)
1	2	Acetone	40[a]
2	5	Acetone	45[a]
3	5	DCM	80[b]
4	10	DCM	98[b]
5	5	$CHCl_3$	85[c]
6	10	$CHCl_3$	96[c]
7	5	THF	52[d]
8	10	THF	60[d]

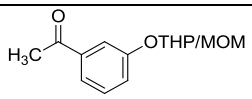
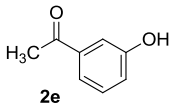
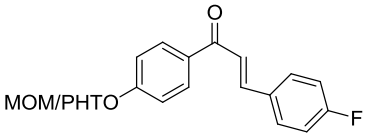
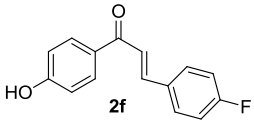
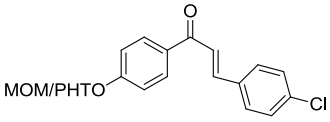
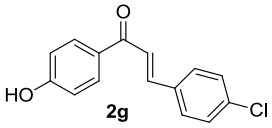
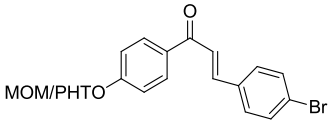
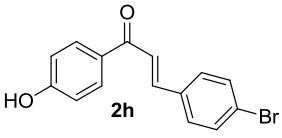
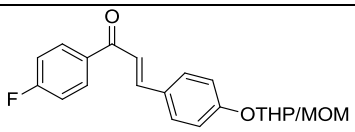
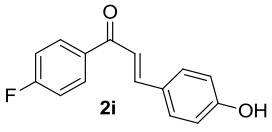
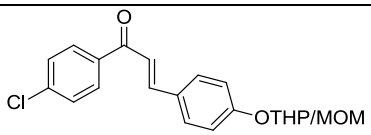
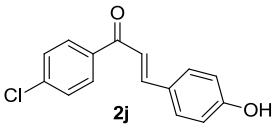
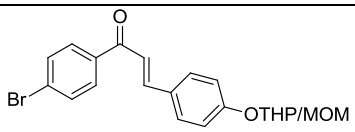
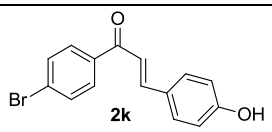
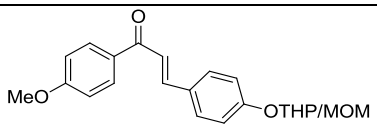
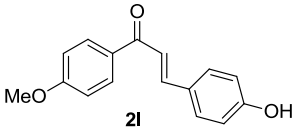
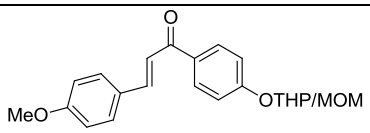
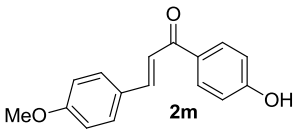
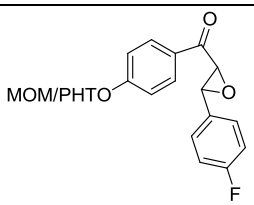
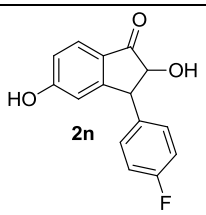
3.3.3. Examples of the THP and MOM ethers deprotection and sequel cyclization reaction by catalyst $SnCl_4$ or $TiCl_4$

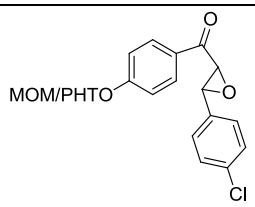
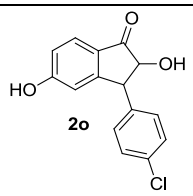
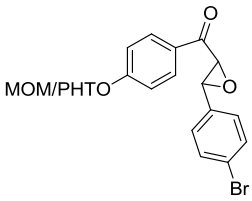
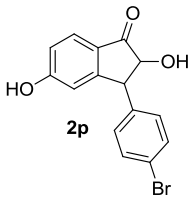
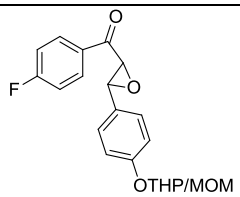
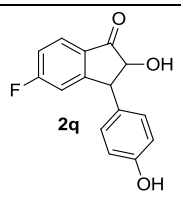
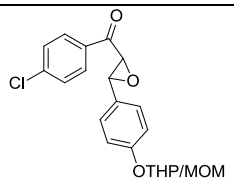
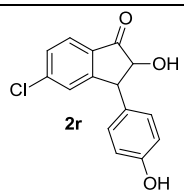
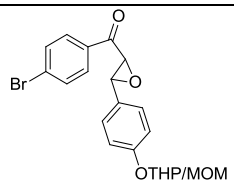
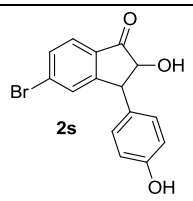
Under optimized reaction conditions, the deprotection of THP and MOM ethers in phenols, chalcone and chalcone epoxides were achieved using 10 mol% of $SnCl_4$ or $TiCl_4$ $TiCl_4$ in excellent yields (90-98%) within 2-3 min at 0 ^{0}C in the presence of other functional groups. However, in the case of alcoholic THP and MOM ethers, even 20 mol% of catalyst loading gave less yield 10 and 25% respectively (Table 3, entry 1). In case of chalcone **2f-2m**, only THP and MOM removal was observed without intramolecular Friedel-Crafts alkylation. These products were characterized by comparing their physical and spectral data with the literature values.[22,28] Interestingly, the THP and MOM removal followed by the Friedel-Crafts alkylation was observed for the chalcone epoxides which gave the corresponding indanones **2n-2s** in excellent yield (90-98%) within 2-3 min at 0 ^{0}C (Table 3). The stereochemistry and the distereomeric excess ratio of the products **2n-2s** were determined by the chiral column separation and determined as 2R, 3S-configuration. These products were fully characterized on the basis of their spectral analysis ^{1}H-, ^{13}C-NMR, GC-MS, Chiral HPLC

Table 3. Examples of the THP and MOM ethers deprotection and sequel cyclization reaction



Entry	ROTHP/MOM	ROH	Time (min)	Yield (%)[a]	Yield (%)[b]
1		 **2a**	2	10	25
2		 **2b**	2	95	92
3		 **2c**	2	96	95
4		 **2d**	2	92	95

5		 **2e**	2	90	92
6		 **2f**	3	98	94
7		 **2g**	3	96	98
8		 **2h**	2	97	94
9		 **2i**	2	96	93
10		 **2j**	3	95	92
11		 **2k**	3	96	95
12		 **2l**	2	90	92
13		 **2m**	3	95	95
14		 **2n**	3	96	93

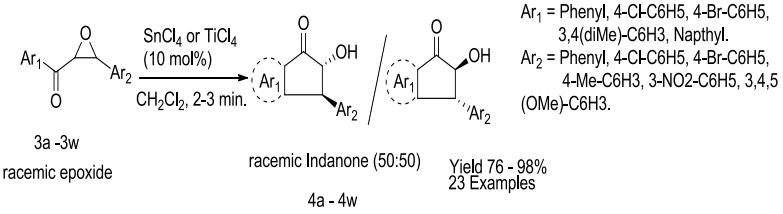
15			2	98	98
16			2	95	94
17			3	96	93
18			3	95	92
19			2	92	92

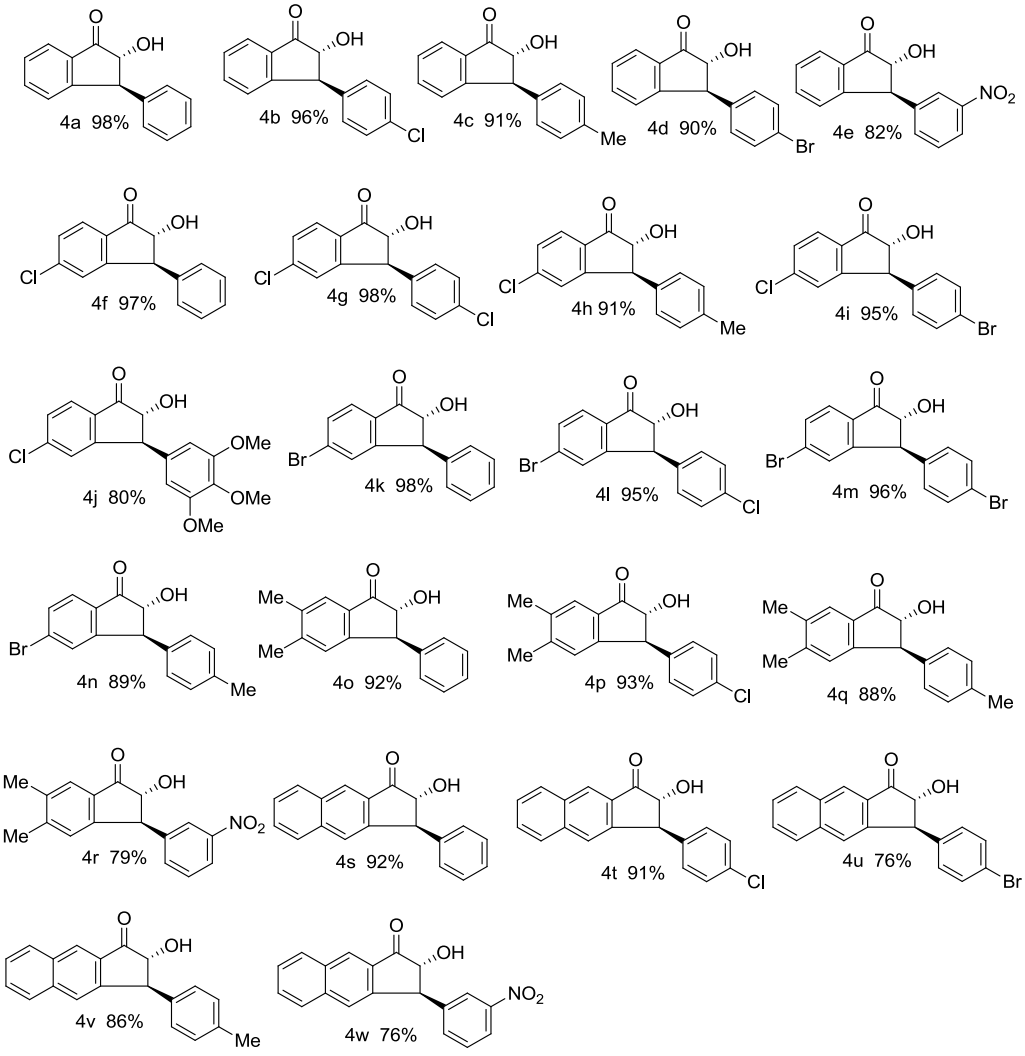
[a] yield (**1-19**) from R-OTHP and [b] yield (**1-19**) from R-OMOM ethers deprotection.

3.3.4. Asymmetric synthesis

In asymmetric synthesis, following a simple experimental procedure (given in the experimental section), chalcone epoxides **3a-3w** was dissolved in dichloromethane by stirring, $SnCl_4$ or $TiCl_4$ was added in proportion and stirred at 0 ^{0}C temperature for 2-3 min. After the usual work up, the 3-aryl-2-hydroxy-2, 3-dihydroindan-1-ones **4a-4w** were obtained in 76-98% yields (Table 4).

Table 4. Synthesis of racemic 3-aryl-2-hydroxy-1-indanones from racemic chalcone epoxides[a, b, c]





[a]Epoxides and 2-hydroxyindan-1-ones are racemic compounds and are shown as a single enantiomeric derivative (*trans*-configuration). [b] Reaction of **4e**, **4j**, **4r**, **4w** were carried out at -20 °C and others are at 0 ^{0}C using 10 mol % of $SnCl_4$. [c] Isolated yield of racemic 2-hydroxy indan-1-ones.

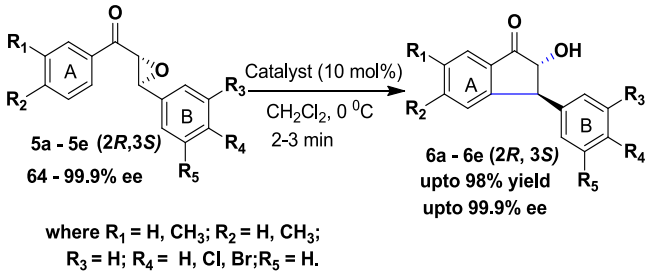
For example, in the synthesis of racemic indanone **4b** (table 4) HPLC purification gave peaks at 26.9 (50%) and 35.4 (50%) min. for enantiomers (see experimental section). The assigned structures of chalcone epoxides **3a-3w** and products **4a-4w** were confirmed on the basis of their spectral analysis (IR, ^{1}H and ^{13}C-NMR, and GC–MS/EI MS) and also when compared with reported data in the literature.[32] The *trans*-stereochemistry of epoxides **3a-3w** was confirmed by the coupling constants of the α- & β-protons. For example, **(***4-chlorophenyl)*-

3-(4-bromophenyl) oxiran-2-yl-methanone **(3i)**, the ^{1}H NMR (500 MHz) δ (ppm): 4.07 (d, *J* = 2.0 Hz, β-*H*, 1H), 4.21 (d, *J* =2.0 Hz, α-*H*, 1H), in which the *J*-values (2.0 Hz) indicate a *trans*-substituted epoxide. Similarly, the *trans*-configuration of 2-hydroxy-2, 3-dihydro indan-1-ones **4a-4w** was confirmed by the coupling constants of the α- & β-protons. For example, *trans 3-(4-bromophenyl)-5-chloro-2-hydroxy-2,3-dihydroindan-1-one* **(4i)**, the ^{1}H NMR (500 MHz) δ (ppm) at 5.15 (d, *J* = 2.0 Hz, β-*H*, 1H), 5.31 (d, *J* = 2.0 Hz, α-*H*, 1H), in which the *J*-values (2.0 Hz) indicate a *trans*-configuration.[42] The stereoselectivity and high yields for 1-indanones under acidic condition ($SnCl_4$) might be due to the variable oxidation state and availability of relatively low energy 5d-orbitals on tin. On ligation with epoxide oxygen, the tetrahedron structure of $SnCl_4$ was converted to a trigonal bipyramide/octahedron structure. This geometrical change enhanced the steric hindrance which results in a faster epoxide ring opening from *β*-carbon due to considerable electron deficient character at benzylic position therefore, nucleophile attack takes place at *β*-carbon of carbonyl. In the case of electron donating (Table 4, entry **4j**) and electron withdrawing groups on ring-Ar_2 (Table 4, entries **4e**, **4r**, **4w**) the reaction at 0 ^{0}C temperature gave decomposed products. Therefore, reactions were carried out by lowering the temperature (-20 ^{0}C) to obtain the desired product.

3.3.5. Synthesis of enantioselective 3-aryl-2-hydroxyindan-1-ones.

During enantioselective synthesis of indanones, first we synthesized diastereoisomerically pure *trans*-(2*R*, 3S)-chalcone epoxides (**5a-e)** from corresponding chalcones with α, α'-diphenyl-L-prolinol and TBHP in hexane which gave a good yield (58%) with 64-99.9% enantiomeric excess. Epoxides were characterized by comparing with literature values and enantiomeric excess was determined by chiral HPLC column and optical rotation in chloroform (see in experimental section).[54] Epoxide ring opening followed by intramolecular Friedel-Crafts alkylation was performed in the presence of $SnCl_4$ to obtain the diastereoisomerically pure *trans* (2*R*,3*S*) indanone derivatives **6a-e** (Scheme 2). The enantiomeric excess of indanones was again determined by chiral HPLC column and optical rotation in chloroform (see in experimental section). In general, indanones were obtained in 90-98% yields and 64-99.9% ee (table 6). It was observed that with the ring opening of epoxide in the presence of metal halides, the configuration at C-2 position is retained while C-3 position is changed due to S_N1-like mechanism to obtain regio- and stereoselective intramolecular Friedel-Crafts alkylation. Therefore, protons at C-2 and C-3 positions are in *trans*-oriented which was

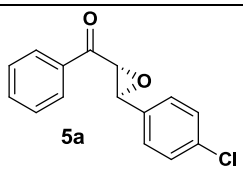
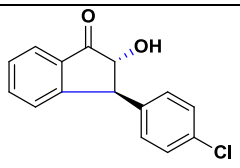
confirmed by the coupling constant (J = 2.0 Hz) in ^{1}HNMR spectrum.[42] Therefore, the absolute configurations at C-2 and C-3 were confirmed as 2*R*, and 3*S* respectively.

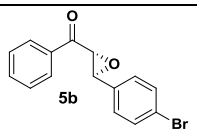
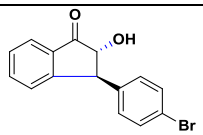
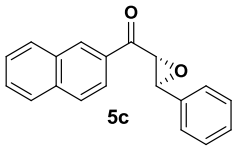
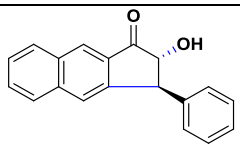
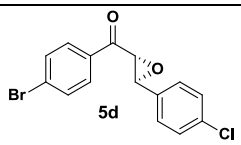
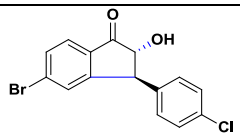
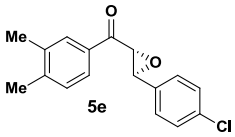
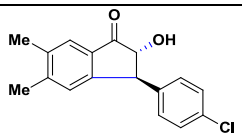


Scheme 2. Synthesis of enantioselective 3-aryl-2-hydroxyindan-1-ones.

The assigned structures of diastereoisomerically pure *trans* chalcone epoxides **5a-5e** and products **6a-6e** were confirmed on the basis of their spectral analysis (^{1}H- & ^{13}C-NMR and chiral HPLC) and also when compared with those reported data.[32] For example, *trans-3-(4-chlorophenyl)-2-hydroxy-2,3-dihydroindan-1-one* **(6a)**, the ^{1}H NMR (500 MHz) δ (ppm) at 5.36 (d, J = 2.0 Hz, 1H, -CO-C*H*-), and 5.21 (d, J = 2.0 Hz, -C*H*-Ar-,1H), in which the J-values indicate a *trans*-configuration.[15] The ^{13}C NMR spectrum gave peaks at δ 197.49 ppm for the characteristic carbonyl carbon, 62.95 ppm for Ar-*CH*-CH, and 75.89 ppm for Ar-CH-*CH*-CO- of indanone ring carbon. Since enantioselective epoxide **5a** gave peaks at 54.7 min (13%) and 58.7 min (87%), the major peak correlated with retention time of reported literature.[54] Therefore, the configuration is confirmed as 2*R* and 3*S*. We also took enantioselective indanone **6a** (table 5) which gave peaks at 27.9 min (13.9%) and 36.9 min (86.1%) (See HPLC chromatogram in supporting information). These retention time match those of racemic indanone (**4b**). Similarly, all other compounds **6b** to **6e** were confirmed on the basis of analytical data.

Table 5. Synthesis of Enantioselective 3-aryl-2-hydroxy-1-indanones. [a,b,c]

Entry	Epoxide	Indanone	Yield (%)[b]	ee(%)[a] Configuration
1	 **74% ee; (2*R*,3*S*)**	 **6a**	**98**	**72.2% (2*R*,3*S*)**

2	 **77.6% ee; (2*R*,3*S*)**	 **6b**	**90**	**75% (2*R*,3*S*)**
3	 **64.8% ee; (2*R*,3*S*)**	 **6c**	**92**	**64.8% (2*R*,3*S*)**
4	 **>99.9% ee; (2*R*,3*S*)**	 **6d**	**95**	**>99.9% (2*R*,3*S*)**
5	 **66.8% ee; (2*R*,3*S*)**	 **6e**	**93**	**66.8% (2*R*,3*S*)**

[a]Enantiomeric excess was determined by chiral HPLC column and found to be equivalent to literature data, [b]isolated yields. [c]all reactions are carried out at 0 ^{0}C for 2-3 min.HPLC conditions and retention times of racemic and enantiomeric excess of the epoxide and indanonone derivatives given in Tables 6 and 7.

Table 6. HPLC conditions and retention times of racemic and enantiomeric excess of the epoxide derivatives.[a]

S.No	Indanone[a]	Chiral Column	Eluent (hexane:Isopropanol)	Flow rate (ml/min)	Retention time (min) & Area (%)	ee (config)[a]
1	**5a**	Chiralcel-OD-H	55/1	0.5	54.7(13) 58.7 (87)	**74% (2*R*,3*S*)**
2	**5b**	Chiralcel-OD-H	95/5	0.8	22.4(11.2) 22.4(88.8)	**77.6% (2*R*,3*S*)**
3	**5c**	Chiralpak-AD-H	95/5	1	20.8(17.6) 23.5(82.4)	**64.8% (2*R*,3*S*)**
4	**5d**	Chiralpak-AD-H	95/5	0.5	54.0(>99.9)	**>99.9% (2*R*,3*S*)**
5	**5e**	Chiralcel-AD-H	95/5	0.8	20.5 16.6) 22.9(83.4)	**66.8% (2*R*,3*S*)**

[a-]Detection at 254 nm. Configuration determined ased on HPLC data analysis.

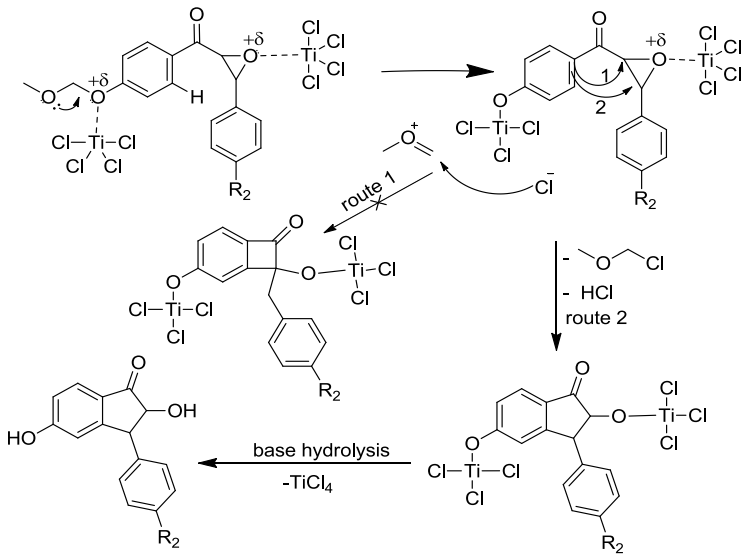
Table 7. HPLC conditions and retention times of racemic and enantiomeric excess of the indanone derivatives.[a]

S. No	Indanone [a]	Chiral Column	Eluent (hexane:Isopropanol)	Flow rate (ml/min)	Retention time (min) & Area (%)	ee [a] (config)[a]
1	**6a**	Chiralcel-OD-H	97.5/2.5	0.5	26.9(13.9) 36.9(86.1)	**72.2%** **(2*R*,3*S*)**
2	**6b**	Chiralcel-OD-H	92.5/7.5	0.8	38.8(12.5) 53.1(87.5)	**75%** **(2*R*,3*S*)**
3	**6c**	Chiralpak-AD-H	92.5/7.5	1	28.6 82.4) 32.5(17.6)	**64.8%** **(2*R*,3*S*)**
4	**6d**	Chiralpak-AD-H	92.5/7.5	1	5.3(>99.9)	**>99.9%** **(2*R*,3*S*)**
5	**6e**	Chiralcel-AD-H	92.5/7.5	0.5	28.8(16.5) 42.5(83.5)	**66.8%** **(2*R*,3*S*)**

[a-]Detection at 254 nm. Configuration determined based on HPLC data analysis.

3.4. MECHANISM

Proposed mechanism is shown in Scheme 3, where ligation of $TiCl_4$ with MOM oxygen resulted in the removal of the methyl(methylene)oxonium group followed by its reaction with Cl^- generated the MOMCl.[24] Similarly, epoxide oxygen ligation might change the tetrahedron structure of $TiCl_4$ into trigonal bipyramide/octahedron structure. The geometry changes enhanced the steric hindrance which results in faster epoxide ring opening from β-carbon due to considerable electron deficient character at benzylic position. Therefore, the nucleophilic attack takes place at β-carbon of carbonyl. Finally, base hydrolysis produces $TiCl_4$ which is used as a Lewis acid in the next catalytic-cycle.



Scheme 3: Propose mechanism for the deprotection of MOM ethers followed by cyclization with $TiCl_4$

3.5. CONCLUSION

In conclusion, we have developed a novel and highly efficient catalytic protocol for the deprotection of phenolic THP and MOM ethers and stereoselective synthesis of 2-hydroxy-3-aryl-1-indanone derivatives by sequential ring opening of chalcone epoxides and intramolecular Friedel-Crafts alkylation in the presence of $SnCl_4$ or $TiCl_4$. This method has advantages such as (i) mild protocol (ii) excellent yield (up to 98%) with high regio and enantioselectivity (up to 99.9% ee) (iii) short reaction time (2-3 min) and (iv) easy work-up procedure. To the best of our knowledge, $SnCl_4$ and $TiCl_4$ has not been studied in this capacity before and therefore represents a novel subject for investigation.

3.6. EXPERIMENTAL DETAILS

3.6.1. GENERAL PROCEDURES

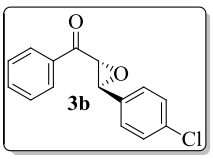
Synthesis of chalcones epoxides: Aqueous NaOH (5M, 10 ml) was added drop wise to a stirred solution of chalcones (18 mmol) in aq. THF (30 ml, H_2O: THF, 1:2 ratio) and further stirred for 10 min. Then, H_2O_2 (15 ml, 30% wt.%) was added drop wise and further stirred for 6-7 h at room temperature. TLC monitoring, the reaction mixture was poured in water. The resulting precipitate was filtered, washed with water and dried under reduced pressure. The product was recrystallized in EtOH or silica gel column chromatography in petroleum ether: CH_2Cl_2 (8:2) as eluent gave 80-90% yields.

Synthesis of 3-aryl-2-hydroxy-2, 3-dihydroindan-1-one (**6a-6e**)**:** Chlacone epoxides (1.0 mmol) were dissolved in dichloromethane (5 mL) by stirring, $SnCl_4$ or $TiCl_4$ (10 mol%) was added drop wise and stirred for 2-3 min. at 0 ^{0}C. The reaction mixture was extracted with CH_2Cl_2 by adding water. The organic layer was dried (anhyd. Na_2SO_4), filtered and evaporated under reduced pressure to obtain the pure product or purified by flash column chromatography on silica gel using hexane: CH_2Cl_2 (8:2) as eluent to afford the products in 76-98% yields and 64-99.9% enantiomeric excess.

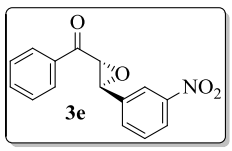
Synthesis of Enantioselective chalcones epoxides: To a solution of (-)(*s*) α,α'-diphenyl-L-prolinol (23.0 mg, 0.090 mmol) and trans-chalcone (77.5 mg, 0.30 mmol) in distilled hexane (3.0 mL) (hexane of HPLC grade furnished comparable results) was added TBHP (5-6 M decane solution, 75µL, 0.40 mmol) at room temperature and stirring was maintained for the indicated time. The crude reaction mixture was then purified by flash chromatography on silica gel (petroleum ether/ diethyl ether 99/1) to provide the epoxy ketone.

3.6.2. Spectral data of deprotected chalcone, 2-hydroxy- indanone, epoxy chalcones and 2-hydroxy-indanone derivatives

a) Spectral data of chalcone epoxides derivatives

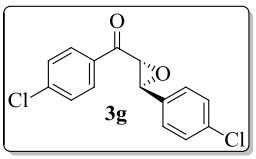


3-(4-Chlorophenyl)oxiran-2-yl-phenyl methanone (3b): White crystalline solid, Yield: 88%, m.p. = 120-123 ^{0}C; **^{1}HNMR ($CDCl_3$, 500 MHz):** δ ppm: 8.00 (dd, J_1=7.5Hz, J_2=1.5Hz, Ar-H, 2H), 7.63-7.48 (m, Ar-H, 5H), 7.40-7.30 (m, Ar-H, 4H), 4.25 (d, J=1.5 Hz, -CO-CH- 1H), 4.06 (d, J= 2.0 Hz, -CH-Ar- 1H); **^{13}C-NMR ($CDCl_3$, 125MHz):** δ ppm 192.8, 135.4, 134.9, 134.2, 129.7, 129.3, 129.0, 128.7, 128.4, 127.2, 60.9, 58.7; **IR ν_{max} (KBr, cm^{-1}):** CO $\nu_{stretch}$ 1685.55, 1592.37, 1438.03, 1391.67, 1232.43, 1089.53, 1010.26, 888.63, 808, 700.79, 527.01; **MS (EI, 70eV): m/z (%)** 258 [$M^{+\cdot}$, $C_{15}H_{11}O_2Cl$], 242, 207, 165, 125, 105(100), 91, 77, 65.

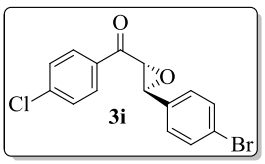


Phenyl-3-(3-nitrophenyl) oxiran-2-yl-methanone (3e): Yellow solid; yield: 86%; m.p = 125–129 ^{0}C; **IR ν_{max} (KBr, cm^{-1}):** 1689 (C=O str), 1589 (arom C=C str), 1525 (N–O str),1405, 1344 (N–O bending), 1232, 1081, 1009, 891, 812, 691, 601; **^{1}H-NMR (500 MHz, CDCl3):** 8.25–8.24 (m, 2 H, H_{Ar}), 8.03–8.01 (m, 2 H, H_{Ar}), 7.73 (d, *J* = 6.5 Hz, 1 H, H_{Ar}), 7.67–7.59 (m, 2 H, HAr), 7.53–7.50 (dd, *J* = 8.0, 1.5 Hz, 2 H, H_{Ar}), 4.31 (d, *J* = 2.0 Hz, 1 H, C(O)CH], 4.22 (d, *J* = 1.5 Hz, 1 H, Ar-CH(-O-)CH);**^{13}C-NMR ($CDCl_3$,125 MHz,):** δ (ppm) 192.2 (C=O), 148.6, 137.9, 135.2, 134.7, 133.4,

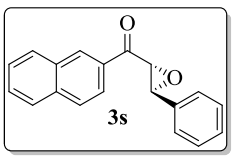
131.9, 129.9, 129.4, 128.7, 128.4, 123.9, 120.8, 60.9 (C(O)-CH), 58.7 (Ar-CH-O); **MS (EI, 70 eV):** m/z (%) 269 (24) [M+. $C_{15}H_{11}NO_4$], 253 (23), 105 (100), 91 (68).



(4-Chlorophenyl)-3-(4-chlorophenyl)oxiran-2-yl- methanone (3g): White crystalline solid; Yield = 85%; m.p = 121-123 ^{0}C; **IR ν_{max} (KBr, cm^{-1}):** 3095, 3043 (aromatic C-H str), 1675 (C=O str), 1587 (aromatic, C=C str), 1485, 1399, 1235, 1177, 1090, 817 (C-Cl, str); **^{1}H-NMR ($CDCl_3$, 500 MHz):** δ (ppm): 7.97 (dd, *J* = 9.0Hz, 2.0Hz, 2 H, H_{Ar}), 7.48 (dd, *J* = 9.0 Hz, 2.0 Hz, 2 H, H_{Ar}), 7.39 (d, *J* = 8.5 Hz, 2 H, H_{Ar}), 7.31 (m, 2 H, H_{Ar}), 4.20 (d, *J* = 1.5 Hz,1 H, C(O)CH), 4.07 (d, *J* = 1.5 Hz,1 H, Ar-CH(-O-)CH); **^{13}C-NMR ($CDCl_3$, 125 MHz):** δ (ppm) 191.7 (C=O), 60.9 (C(O)CH), 58.6 (Ar-CH-O-), 140.7, 135.1, 133.7, 130.0, 129.7, 129.3, 129.1, 127.1; **MS (EI, 70eV):** m/z (%) 292 [$M^{+\cdot}$, $C_{15}H_{10}Cl_2O_2$]: 292, 139 (100).

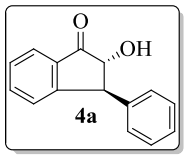


(4-Chlorophenyl)-3-(4-bromophenyl)oxiran-2-yl-methanone (3i): White crystalline solid; Yield = 89%; m.p =127-129 ^{0}C; **IR ν_{max} (KBr, cm^{-1}):** 3039 (aromatic C-H str), 1675 (C=O str), 1587 (aromatic, C=C str), 1430, 1400, 1236, 1177, 1092, 1011, 735 (C-Cl, str); **^{1}H-NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.99 (dd, *J* = 7.0, 2.0 Hz, 2 H, H_{Ar}), 7.54 (m, 4 H, H_{Ar}), 7.27 (dd, *J* = 7.0, 2.0 Hz, 2 H, H_{Ar}), 4.21 (d, *J* = 2.0 Hz, 1 H, C(O)CH), 4.07 (d, *J* = 2.0 Hz, 1 H, Ar-CH(-O-)CH); **^{13}C-NMR ($CDCl_3$, 125 MHz):** δ (ppm) 191.7 (C=O), 60.9 (C(O)CH), 58.7 (Ar-CH-O-), 140.7, 134.4, 133.6, 132.0, 129.8, 129.3, 127.4, 123.2; **MS (EI, 70eV):** m/z (%) = 336 [$M^{+\cdot}$, $C_{15}H_{10}ClBrO_2$]: 336, 139 (100).

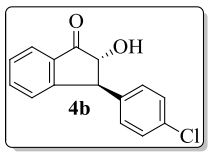


Naphthalen-2-yl-3-phenyloxiran-2-ylmethanone (3s): White crystalline solid; Yield = 88%; m.p = 90-92 ^{0}C; **IR ν_{max} (KBr, cm^{-1}):** 2928, 2891 (aromatic C-H str), 1695 (C=O str), 1595 (aromatic, C=C str), 1460, 1396, 1230, 1127, 1011, 820 (C-Cl, str); **^{1}H-NMR ($CDCl_3$, 500 MHz):** δ (ppm) 8.54 (s, 1 H, H_{Ar}), 8.03 (dd, *J* = 8.5, 1.5 Hz, H_{Ar}), 7.93-7.85 (m, 3 H, H_{Ar}), 7.61 (t, *J* = 8.0 Hz, 1H, H_{Ar}), 7.54 (t, *J* = 8.0 Hz, 1H, H_{Ar}), 7.43-7.38 (m, 5 H, H_{Ar}), 4.43 (d, *J* = 1.5 Hz,1 H, C(O)CH), 4.14 (d, *J* = 1.5 Hz, 1 H, Ar-CH(-O-)CH); **^{13}C-NMR ($CDCl_3$, 125 MHz):** δ (ppm) 193.0 (C=O), 61.1 (C(O)CH), 59.6 (Ar-CH-O-), 135.9, 135.6, 132.8, 132.4, 130.5, 130.2, 129.7, 129.1, 129.1, 128.9, 128.8, 128.4, 127.1, 125.9, 123.7; **MS (EI, 70eV):** m/z (%) = 274 [$M^{+\cdot}$, $C_{19}H_{14}O_2$]: 257 (12), 155 (100), 91 (25).

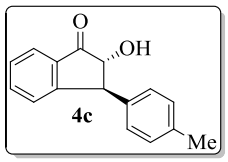
(c) Spectral data of indanone derivatives



3-Phenyl-2-hydroxy-2, 3-dihydroindan-1-one (4a): Light yellow solid; m.p = 178-180 ^{0}C; Yield = 98%; **IR ν_{max} (KBr, cm^{-1}):** 3452 (OH str), 2963 (aromatic C-H str), 1686 (C=O str), 1599 (aromatic, C=C str), 1451, 1419, 1262, 1021, 933, 868, 799 and 704; **^{1}H-NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.89 (m, 2 H, H_{Ar}), 7.66 (m, 1 H, H_{Ar}), 7.54 (m, 3 H, H_{Ar}), 7.37-7.30 (m, 3 H, H_{Ar}), 5.39 (d, *J* = 2.0 Hz, 1 H, H2), 5.24 (d, *J* = 2.0 Hz, 1 H, H3), 4.05 (s, br, D_2O exchangeable, 1 H); **^{13}C-NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 197.8 (C=O), 138.1, 134.3, 133.6, 129.2, 128.8, 128.6, 127.9, 76.1 (C2), 63.8 (C3); **MS (EI, 70eV):** m/z (%) 224(35) [M^+, $C_{15}H_{12}O_2$], 207(25), 195(29), 178(37), 165(40), 152(33), 121(64), 105(100), 91(62), 77(74) and 51(69).



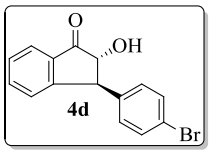
3-(4-Chlorophenyl) -2-hydroxy-2, 3-dihydroindan-1-one (4b): Light yellow solid; m.p = 188-190 ^{0}C; Yield = 98%; **IR ν_{max} (KBr, cm^{-1}):** 3408 (OH str), 2917 (aromatic C-H str), 1689 (C=O str), 1589 (aromatic, C=C str), 1489, 1415, 1288, 1177, 1091, 1014, 929 and 701; **^{1}H-NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.83 (d, *J* = 7.5 Hz, 2 H, H_{Ar}), 7.59 (t, *J* = 7.0 Hz, 1 H, H_{Ar}), 7.48-7.45 (m, 2 H, H_{Ar}), 7.40 (dd, J=6.0, 2.0Hz, 2 H, H_{Ar}), 7.25 (m, 1 H, H_{Ar}), 5.27 (d, *J* = 2.0 Hz, 1 H, H2), 5.12 (d, *J* = 2.0 Hz, 1 H, H3), 4.02 (s, br, D_2O exchangeable, 1 H); **^{13}C-NMR ($CDCl_3$, 125 MHz):** δ (ppm) 197.4 (C=O), 136.6, 134.8, 134.4, 133.5, 129.4, 129.2, 128.7, 128.5, 75.9 (C2), 62.9 (C3); **MS (EI, 70eV):** m/z (%) 258(17) [M^+, $C_{15}H_{11}ClO_2$], 242(28), 207(36), 179(43), 165(32), 135(57), 130(61), 105(100), 89(49), 77(61), 75(55) and 51(62).



2-Hydroxy-3-p-tolyl-2,3-dihydroinden-1-one (4c): Light yellow solid; m.p = 144-146 ^{0}C; Yield = 91%; **IR ν_{max} (KBr, cm^{-1}):** 3391 (OH str), 2951 (aromatic C-H str), 1693 (C=O str), 1577 (aromatic, C=C str), 1468, 1401, 1271, 1152, 1084, 1002, 910 and 725; **^{1}H-NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.81 (d, *J* = 5.5 Hz, 2 H, H_{Ar}), 7.55 (m, 1 H, H_{Ar}), 7.44 (m, 1 H, H_{Ar}), 7.34 (d, *J* = 6.0 Hz, 2 H, H_{Ar}), 7.07(d, *J* = 5.0 Hz, 2 H, H_{Ar}), 5.28 (d, *J* = 2.0 Hz, 1 H, H2), 5.14 (d, *J* = 2.0 Hz, 1 H, H3), 4.05 (s, br, D_2O exchangeable, 1 H), 2.24 (s, 3 H); **^{13}C-NMR ($CDCl_3$, 125 MHz):** δ (ppm) 197.9 (C=O),138.7, 135.2, 134.3, 133.7, 129.2, 129.2, 128.6, 127.9, 76.2 (C2), 63.8 (C3), 21.2; **MS (EI, 70eV):** m/z (%) 238(21) [M^+, $C_{16}H_{14}O_2$], 212(28), 203(16), 159(43), 145(32), 125(57), 105(100), 79(49), and 55(42).

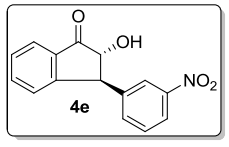
3-(4-Bromophenyl)-2-hydroxy-2,3-dihydroindan-1-one (4d): Light yellow solid; m.p = 183-185 ^{0}C; Yield = 90%; **IR ν_{max} (KBr, cm^{-1}):** 3434 (OH str), 2924 (aromatic C-H str), 1670 (C=O

str), 1588 (aromatic, C=C str), 1485, 1413, 1288, 1177, 1071, 930, 703 and 545; **^{1}H-NMR (CDCl$_3$, 500 MHz) :** δ (ppm) 7.82 (d, *J* = 7.5 Hz, 2 H, H$_{Ar}$), 7.57 (t, *J* = 7.0 Hz, 1 H, H$_{Ar}$), 7.46-7.43 (m, 2 H, H$_{Ar}$), 7.38 (dd, *J* = 6.0, 2.0 Hz, 2 H, H$_{Ar}$), 7.24 (m, 1 H, H$_{Ar}$), 5.30 (d, *J* = 2.0 Hz, 1 H, H2), 5.21 (d, *J* = 2.0 Hz, 1 H, H3), 4.11 (s, br, D$_2$O exchangeable, 1 H); **^{13}C-NMR (CDCl$_3$, 125 MHz):** δ(ppm) 197.3 (C=O), 136.6, 134.6, 134.2, 133.4, 129.3, 129.3, 128.6, 128.4, 76.0 (C2), 62.5 (C3); **MS (EI, 70eV):** m/z (%) 302(16) [M$^+$, $C_{15}H_{11}BrO_2$], 196(55), 169(45), 139(73), 105(100), 89(47), 77(54), 63(49) and 51(66).



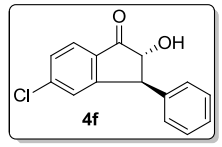
4d

3-(3-Nitrophenyl)-2-hydroxy-2,3-dihydroindan-1-one (4e): Light yellow solid; m.p = 196-198 ^{0}C; Yield = 82%; **IR ν$_{max}$ (KBr, cm^{-1}):** 3369 (OH str), 2923 (aromatic C-H str), 1680 (C=O str), 1613 (aromatic, C=C str), 1528 (N─O str), 1393, 1348 (N─O bending), 1259, 1094, 986, 911, 840, 728, 687; **^{1}H-NMR (CDCl$_3$, 500 MHz):** δ (ppm): 8.14 (d, *J* = 7.5 Hz, I H, H$_{Ar}$), 7.99 (m, 1 H, H$_{Ar}$), 7.86 (m, 2 H, H$_{Ar}$), 7.70 (t, *J* = 7.5 Hz, 1 H, H$_{Ar}$), 7.61-7.58 (m, 2 H, H$_{Ar}$), 7.45 (m, 1 H, H$_{Ar}$), 5.57 (d, J = 2.0 Hz, 1 H, H2), 5.32 (d, *J* = 2.0 Hz, 1 H, H3), 3.82 (s, br, D$_2$O exchangeable, 1 H); **^{13}C-NMR (CDCl$_3$, 125 MHz):** δ (ppm) 197.4 (C=O), 147.8, 137.7, 134.9, 134.2, 129.4, 129.2, 128.7, 123.8, 123.2, 76.5 (C2), 61.75 (C3); **MS (EI, 70eV):** m/z (%) 269(13) [M$^+$, $C_{15}H_{11}NO_4$], 241(21), 196(61), 176(32), 165(48), 136(43), 105(100), 89(64), 77(44), 63(39) and 51(60).



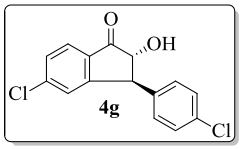
4e

3-Phenyl-5-chloro-2-hydroxy-2,3-dihydroinden-1-one (4f): Light yellow solid; m.p = 180-182 ^{0}C; Yield = 97%; **IR ν$_{max}$ (KBr, cm^{-1}):** 3449 (OH str), 2950 (aromatic C-H str), 1682 (C=O str), 1582 (aromatic, C=C str), 1389, 1275, 1059, 854, 723 (C-Cl, str); **^{1}H-NMR (CDCl$_3$, 500 MHz):** δ (ppm) 7.92 (d, *J* = 8.5 Hz,2 H, H$_{Ar}$), 7.78 (d, *J* = 8.5 Hz, 2 H, H$_{Ar}$), 7.45 (m, 2 H, H$_{Ar}$), 7.17 (m, 2 H, H$_{Ar}$), 5.23 (d, *J* = 4.0 Hz, 1 H, H2), 5.10 (d, *J* = 4.0 Hz, 1 H, H3), 3.92 (s, br, D$_2$O exchangeable, 1 H); **^{13}C-NMR (CDCl$_3$, 125 MHz):** δ (ppm) 196.7 (C=O), 140.8, 137.7, 132.0, 130.0, 129.5, 128.9, 128.6, 127.9, 76.1 (C2), 63.7 (C3); **MS (EI, 70eV):** m/z (%) 258(35) [M$^{+\cdot}$, $C_{15}H_{11}ClO_2$], 139 (100).



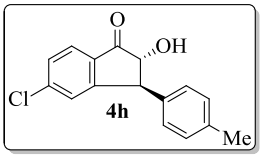
4f

3-(4-Chlorophenyl)-5-chloro-2-hydroxy-2,3-dihydro-indan-1-one (4g): Light yellow solid; m.p = 202-204 ^{0}C; Yield = 98%; **IR ν$_{max}$ (KBr, cm^{-1}):** 3438 (OH str), 2922 (aromatic C-H str), 1674 (C=O str), 1591 (aromatic, C=C str), 1396, 1282, 1173, 1091, 756 (C-Cl, str); **^{1}H-NMR (CDCl$_3$, 500**

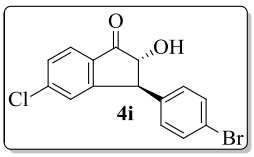


4g

MHz): δ (ppm) 8.06 (d, *J* = 8.5 Hz, 1 H, H_{Ar}), 7.89 (m, 1 H, H_{Ar}), 7.53 (d, *J* = 8.5 Hz, 1 H, H_{Ar}), 7.47 (d, *J* = 8.5 Hz, 1 H, H_{Ar}), 7.28 (m, 2 H, H_{Ar}), 7.16 (d, *J* = 8.5 Hz, 1 H, H_{Ar}), 5.48 (d, *J* = 3.5 Hz, 1 H, H2), 5.21 (d, *J* = 3.5 Hz, 1 H, H3), 3.72 (s, br, D_2O exchangeable, 1 H); **^{13}C-NMR ($CDCl_3$, 125MHz):** δ (ppm) 196.4 (C=O), 141.0, 136.3, 134.3, 131.8, 131.6, 129.9, 129.6, 129.4, 128.9, 128.8, 75.9 (C2), 62.8 (C3); **MS (EI, 70eV):** m/z (%) 292(10) [$M^{+\cdot}$, $C_{15}H_{10}Cl_2O_2$], 245(25), 139(100).

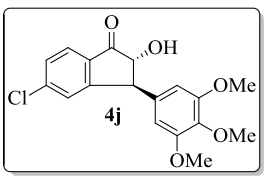


5-Chloro-2-hydroxy-3-p-tolyl-2,3-dihydroindan-1-one (4h): Light yellow solid; m.p = 182-184 ^{0}C; Yield = 91%; **IR ν_{max} (KBr, cm^{-1}):** 3439 (OH str), 2922 (aromatic C-H str), 1670 (C=O str), 1594 (aromatic, C=C str), 1491, 1399, 1296, 1095, 760 (C-Cl, str); **^{1}H-NMR ($CDCl_3$, 500 MHz):** δ (ppm) 8.01 (dd, *J* = 8.0, 2.0 Hz,2 H, H_{Ar}), 7.74 (m,1 H, H_{Ar}), 7.54 (m, 2 H, H_{Ar}), 7.21 (m, 2 H, H_{Ar}), 5.02 (d, *J* = 3.0 Hz, 1 H, H2), 4.95 (d, *J* = 3.0 Hz, 1 H, H3), 3.68 (s, br, D_2O exchangeable, 1 H), 2.49 (s, 3H); **^{13}C-NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 193.4 (C=O), 146.5, 141.5, 131.4, 131.2, 130.3, 130.1, 129.8, 129.4, 128.9, 76.2 (C2), 62.3 (C3), 22.3; **MS (EI, 70eV):** m/z (%) 272(25) [$M^{+\cdot}$, $C_{16}H_{13}ClO_2$], 160(55), 141(72), 139(100), 111(62), 105(73).

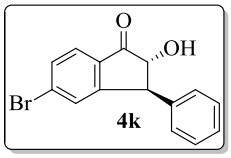


3-(4-Bromophenyl)-5-chloro-2-hydroxy-2,3-dihydro indan-1-one (4i): Light yellow solid; m.p = 210-212 ^{0}C; Yield = 95%; **IR ν_{max} (KBr, cm^{-1}):** 3426 (OH str), 2923 (aromatic C-H str), 1678 (C=O str), 1591 (aromatic, C=C str), 1417, 1395, 1282, 1170, 1092, 757 (C-Cl, str); **^{1}H-NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.88 (m, 2 H, H_{Ar}), 7.55-7.49 (m, 3 H, H_{Ar}), 7.40 (m, 2 H, H_{Ar}), 5.31 (d, *J* = 2.5 Hz, 1 H, H2), 5.15, (d, *J* = 2.5 Hz, 1 H, H3), 4.05 (s, br, D_2O exchangeable, 1 H); **^{13}C-NMR ($CDCl_3$, 125 MHz):** δ(ppm) 196.3 (C=O), 141.1, 136.8, 131.8, 131.8, 129.9, 129.6, 129.6, 123.1 75.8 (C2), 62.8 (C3); MS (EI, 70eV): m/z (%) = 336(18) [$M^{+\cdot}$, $C_{15}H_{10}ClBrO_2$], 139 (100), 111(53).

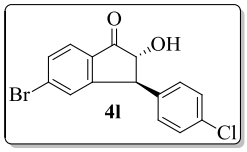
3-(3, 4, 5-Trimethoxyphenyl)-5-chloro-2-hydroxy-2,3-dihydroindan-1-one (4j): Light yellow solid; m.p = 220-222 ^{0}C; Yield = 80%; **IR ν_{max} (KBr, cm^{-1}):** 3440 (OH str), 2920 (aromatic C-H str), 1666 (C=O str), 1592 (aromatic, C=C str), 1406, 1336, 1233, 1125(C-O-C, str), 1091, 771 (C-Cl, str); **^{1}H-NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.84 (d, *J* = 6.5 Hz, 2 H, H_{Ar}), 7.51 (d, *J* = 7.0 Hz, 1 H, H_{Ar}), 6.74 (s, 2 H, H_{Ar}), 5.35 (d, *J* = 2.5 Hz, 1 H, H2), 5.10 (d, *J* = 2.5 Hz, 1 H, H3), 4.10 (s, br, D_2O exchangeable, 1 H), 3.87 (s, OMe, 9H) ; ^{13}C-NMR ($CDCl_3$, 125 MHz)



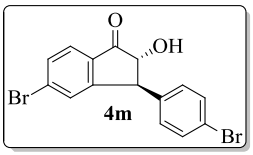
δ (ppm): 191.2 (C=O), 153.6, 132.3, 131.6, 131.5, 129.8, 129.3, 128.9, 127.6, 107.4, 75.2(C2), 61.0(C3), 60.8, 56.3; **MS (EI, 70eV):** m/z (%) 348(29) [$M^{+\cdot}$, $C_{18}H_{17}ClO_5$], 181(69), 139 (100), 111(59).



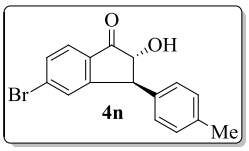
3-Phenyl-5-bromo-2-hydroxy-2,3-dihydroindan-1-one (4k): Light yellow solid; m.p = 192-194 ^{0}C; Yield = 98%; **IR ν_{max} (KBr, cm^{-1}):** 3466 (OH str), 2920 (aromatic C-H str), 1678 (C=O str), 1593 (aromatic, C=C str), 1398, 1281, 1095, 843, 713 (C-Br, str); **^{1}H-NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.99 (dd, *J* = 8.5 Hz, 1.5 Hz, 1 H, H_{Ar}), 7.87 (dd, *J* = 8.5 Hz, 1.5 Hz, 2 H, H_{Ar}), 7.69 (m, 3 H, H_{Ar}), 7.54 (m, 2 H, H_{Ar}), 5.48 (d, *J* = 2.5 Hz, 1 H, H2), 5.15 (d, *J* = 2.5 Hz, 1 H, H3), 3.51 (s, br, D_2O exchangeable, 1 H); **^{13}C-NMR ($CDCl_3$, 125 MHz):** δ (ppm) 196.9 (C=O), 137.7, 132.5, 132.4, 131.7, 130.6, 130.4, 129.6, 128.9, 128.6, 128.6, 127.9, 76.1 (C2), 63.7 (C3); **MS (EI, 70eV):** m/z (%) 302(18) [$M^{+\cdot}$, $C_{15}H_{11}BrO_2$], 185(69), 183(53), 91(100).



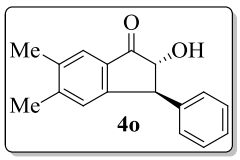
3-(4-Chlorophenyl)-5-bromo-2-hydroxy-2,3-dihydro indan-1-one (4l): Light yellow solid; m.p = 205-207 ^{0}C; Yield = 95%; **IR ν_{max} (KBr, cm^{-1}):** 3422 (OH str), 3087 (aromatic C-H str), 1678 (C=O str), 1583 (aromatic, C=C str), 1404, 1278, 1169, 1091, 830, 752 (C-Br, str); **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.78 (m, 1 H, H_{Ar}), 7.70 (m, 2 H, H_{Ar}), 7.47 (m, 2 H, H_{Ar}), 7.35 (m, 2 H, H_{Ar}), 5.30 (d, *J* = 2.0 Hz, 1 H, H2), 5.16 (d, *J* = 2.0 Hz, 1 H, H3), 3.62 (s, br, D_2O exchangeable, 1 H); **^{13}C-NMR ($CDCl_3$, 125 MHz) δ (ppm):** 196.6 (C=O), 136.3, 134.9, 132.6, 132.3, 129.8, 129.4, 128.8, 75.9 (C2), 62.8 (C3); **MS (EI, 70eV): m/z (%)** 336(30) [$M^{+\cdot}$, $C_{15}H_{10}ClBrO_2$], 185(79), 183 (100), 125(49).



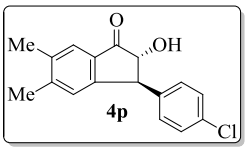
3-(4-Bromophenyl)-5-bromo-2-hydroxy-2,3-dihydro indan-1-one (4m): Light yellow solid; m.p = 198-200 ^{0}C; Yield = 96%; **IR ν_{max} (KBr, cm^{-1}):** 3441 (OH str), 2921, 2853 (aromatic C-H str), 1676 (C=O str), 1588 (aromatic, C=C str), 1276, 1066, 820, 746 (C-Br, str);**^{1}H-NMR ($CDCl_3$, 500MHz):** δ (ppm) 7.79 (d, *J* = 8.5 Hz, 1 H, H_{Ar}), 7.71 (d, *J* = 7.0 Hz, 2 H, H_{Ar}), 7.50 (d, *J* = 7.0 Hz, 2 H, H_{Ar}), 7.40 (m, 2 H, H_{Ar}), 5.30 (d, *J* = 4.5 Hz, 1 H, H2), 5.15 (d, *J* = 4.5 Hz, 1 H, H3), 4.05 (s, br, D_2O exchangeable, 1 H); **^{13}C-NMR ($CDCl_3$, 125 MHz):** δ (ppm) 196.5 (C=O), 136.8, 132.6, 132.2, 131.8, 130.0, 129.8, 129.6, 123.1, 75.9 (C2), 62.8 (C3); **MS (EI, 70eV):** m/z (%) 380(32) [$M^{+\cdot}$, $C_{15}H_{10}Br_2O_2$], 185(75), 183 (100).



3-p-Tolyl-5-bromo-2-hydroxy-2,3-dihydroindan-1-one (4n): Light yellow solid; m.p = 181-183 ^{0}C; Yield = 89%; **IR ν_{max} (KBr, cm^{-1}):** 3464 (OH str), 2917, 2849 (aromatic C-H str), 1685 (C=O str), 1586 (aromatic, C=C str), 1279, 1071, 815, 757 (C-Br, str); **^{1}H-NMR (CDCl$_3$, 500 MHz):** δ (ppm) 7.69 (m, 2 H, H_{Ar}), 7.69 (m, 1 H, H_{Ar}), 7.32 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.10 (m, 2 H, H_{Ar}), 5.23 (d, *J* = 2.5 Hz, 1 H, H2), 5.10 (d, *J* = 2.5 Hz, 1 H, H3), 3.98 (s, br, D_2O exchangeable, 1 H), 2.26 (s, 3 H); **^{13}C-NMR (CDCl$_3$, 125 MHz):** δ (ppm) 195.99 (C=O), 137.84, 133.76, 131.41, 129.00, 128.24, 126.79, 75.23 (C2), 62.68 (C3), 20.12; **MS (EI, 70eV):** m/z (%) 316(14) [$M^{+\cdot}$, $C_{16}H_{13}BrO_2$], 219(59), 185 (100), 183(82).



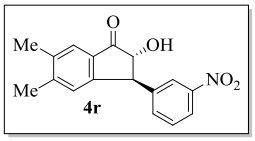
2-Hydroxy-5,6-dimethyl-3-phenyl-2,3-dihydroinden-1-one (4o): Light yellow solid; m.p = 112-114 ^{0}C; Yield = 92%; **IR ν_{max} (KBr, cm^{-1}):** 3420 (OH str), 2959, 2869 (aromatic C-H str), 1688 (C=O str), 1583 (aromatic, C=C str), 1253, 1063, 835; **^{1}H-NMR (CDCl$_3$, 500 MHz):** δ (ppm) 7.71 (m, 1 H, H_{Ar}), 7.63 (dd, *J* = 7.0, 1.5 Hz, 1 H, H_{Ar}), 7.54 (d, *J* = 7.5 Hz, 2 H, H_{Ar}), 7.36 (t, *J* = 7.0 Hz, 1 H, H_{Ar}), 7.32 (d, *J* = 7.0 Hz, 1 H, H_{Ar}), 7.27 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 5.35 (d, *J* = 2.5 Hz, 1 H, H2), 5.25 (d, *J* = 2.5 Hz, 1 H, H3), 3.95 (s, br, D_2O exchangeable, 1 H), 2.34 (s, 3 H), 2.33 (s, 3 H); **^{13}C-NMR (CDCl$_3$, 125 MHz):** δ (ppm) 197.4 (C=O), 144.2, 138.4, 137.8, 131.3, 130.3, 129.8, 128.7, 128.5, 127.9, 126.2, 75.8 (C2), 64.1 (C3), 20.2, 19.8; **MS (EI, 70eV):** m/z (%) = 252(07) [$M^{+\cdot}$, $C_{17}H_{16}O_2$], 234(15),105 (25), 88(100).



3-(4-Chlorophenyl)-2-hydroxy-5,6-dimethyl-2,3-dihydro inden-1-one (4p): Light yellow solid; m.p =116-118 ^{0}C; Yield = 93%; **IR ν_{max} (KBr, cm^{-1}):** 3412 (OH str), 2952, 2847 (aromatic C-H str), 1675 (C=O str), 1609 (aromatic, C=C str), 1225, 1091, 842, 762; **^{1}H-NMR (CDCl$_3$, 500 MHz):** δ (ppm) 7.70 (m, 1 H, H_{Ar}), 7.62 (d, *J* = 7.5 Hz, 1 H, H_{Ar}), 7.49 (m, 2 H, H_{Ar}), 7.34 (m, 1 H, H_{Ar}),7.29 (d, *J* = 7.5 Hz, 1 H, H_{Ar}), 5.32 (d, *J* = 2.5 Hz, 1 H, H2), 5.21 (d, *J* = 2.5 Hz, 1 H, H3), 4.12 (s, br, D_2O exchangeable, 1 H), 2.36(s, 3H), 2.35 (s, 3H); **^{13}C-NMR (CDCl$_3$, 125 MHz):** δ (ppm) 197.1 (C=O), 144.4, 137.9, 136.9, 134.6, 131.1, 130.3, 129.7, 129.4, 128.7, 126.1, 75.6 (C2), 63.2 (C3), 20.2, 19.9; **MS (EI, 70eV):** m/z (%) = 286(10) [$M^{+\cdot}$, $C_{17}H_{15}ClO_2$], 268 (20), 122 (100).

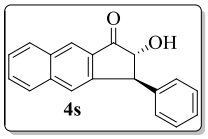
2-Hydroxy-5,6-dimethyl-3-(3-nitrophenyl)-2,3-dihydro inden-1-one (4r): Light yellow solid; m.p = 142-144 ^{0}C; Yield = 79%; **IR ν_{max} (KBr, cm^{-1}):** 3381 (OH str), 2943 (aromatic C-H str), 1674 (C=O str), 1620 (aromatic, C=C str), 1504 (N─O str), 1371, 1353 (N─O bending),

1241, 1061, 916, 832, 783, 675; **^{1}H-NMR ($CDCl_3$, 500 MHz):** δ (ppm) 8.14 (m, 1 H, H_{Ar}),



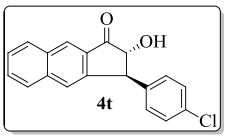
4r

7.94 (m, 1 H, H_{Ar}), 7.59 (m, 2 H, H_{Ar}), 7.44 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 7.29 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 5.54 (d, *J* = 4.0 Hz, 1 H, H2), 5.34 (d, *J* = 4.0 Hz, 1 H, H3), 3.82 (s, br, D_2O exchangeable, 1 H), 2.35(s, 3 H), 2.30 (s, 3 H); **^{13}C-NMR ($CDCl_3$, 125 MHz):** δ (ppm) 196.9(C=O), 147.7, 145.1, 138.1, 137.7, 134.3, 131.7, 130.5, 129.6, 129.1, 126.4, 123.7, 123.2, 76.5 (C2), 62.0 (C3), 20.2, 19.8; **MS (EI, 70eV):** m/z (%) = 297(14) [$M^{+\cdot}$, $C_{17}H_{15}NO_4$], 280 (10), 133 (100).



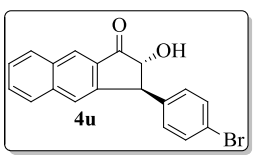
4s

2-Hydroxy-3-phenyl-2,3-dihydrocyclopenta[b]naphth- alen-1-one (4s): Light yellow solid; m.p = 114-116 ^{0}C; Yield = 92%; **IR ν_{max} (KBr, cm^{-1}):** 3395 (OH str), 2951, 2848 (aromatic C-H str), 1677 (C=O str), 1580 (aromatic, C=C str), 1247, 1092, 842; **^{1}H-NMR ($CDCl_3$, 500 MHz):** δ (ppm) 8.41 (m, 1H, H_{Ar}), 7.95 (m, 2 H, H_{Ar}), 7.85 (m, 1 H, H_{Ar}), 7. 63 (t, *J* = 7.0 Hz, 1 H, H_{Ar}), 7.58 (m, 3H, H_{Ar}), 7.38-7.30 (m, 3 H, H_{Ar}), 5.53 (d, *J* = 2.0 Hz, 1H, H2), 5.31 (d, *J* = 2.0 Hz, 1H, H3), 4.21 (s, br, D_2O exchangeable, 1 H); **^{13}C-NMR ($CDCl_3$, 125 MHz):** δ (ppm) 197.7 (C=O), 138.2, 136.0,132.4, 130.9, 130.5, 129.7, 129.3, 129.2, 128.8, 128.6, 128.0, 127.9, 127.3, 123.9, 76.2 (C2), 64.1 (C3); **MS (EI, 70eV):** m/z (%) = 274 (12) [$M^{+\cdot}$, $C_{19}H_{14}O_2$], 256 (15), 110 (100).



4t

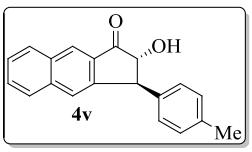
3-(4-Chlorophenyl)-2-hydroxy-2,3-dihydrocyclopenta[b] naphthalen-1-one (4t): Light yellow solid; m.p = 108-110 ^{0}C; Yield = 91%; **IR ν_{max} (KBr, cm^{-1}):** 3415 (OH str), 2931, 2873 (aromatic C-H str), 1681 (C=O str), 1597 (aromatic, C=C str), 1263, 1081, 860, 737; **^{1}H-NMR ($CDCl_3$, 500 MHz):** δ (ppm) 8.41 (m, 1H, H_{Ar}), 7.97 (t, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.92 (t, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.62 (dd, *J* = 2.0, 7.5 Hz, 2 H, H_{Ar}), 7.50 (d, *J* = 7.0 Hz, 2 H, H_{Ar}), 7.33 (d, *J* = 7.5 Hz, 1H, H_{Ar}), 5. 49 (d, *J* = 2.0 Hz, 1H, H2), 5.27 (d, *J* = 2.0 Hz, 1H, H3), 4.15 (s, br, D_2O exchangeable, 1 H); **^{13}C-NMR ($CDCl_3$, 125 MHz):** δ (ppm) 197.4 (C=O), 136.7, 136.0, 134.8, 132.4, 130.8, 130.5, 129.7, 129.4, 129.3, 129.3, 128.8, 128.0, 127.4, 123.8, 75.9 (C2), 63.1 (C3); **MS (EI, 70eV):** m/z (%) 308 (11) [$M^{+\cdot}$, $C_{19}H_{13}ClO_2$], 290 (23), 144 (100), 65 (45).



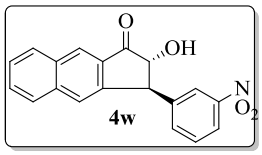
4u

3-(4-Bromophenyl)-2-hydroxy-2,3-dihydrocyclopenta[b] naphthalen-1-one (4u): Light yellow solid; m.p = 112-114 ^{0}C; Yield = 92%; **IR ν_{max} (KBr, cm^{-1}):** 3409 (OH str), 2925, 2870 (aromatic C-H str), 1685 (C=O str), 1590 (aromatic, C=C str), 1258, 1080, 865, 730; **^{1}H-NMR ($CDCl_3$, 500 MHz):** δ (ppm) 8.42 (m, 1 H, H_{Ar}), 7.98 (t, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.93

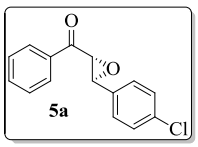
(t, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.65 (dd, *J* = 2.0, 7.5 Hz, 2 H, H_{Ar}), 7.50 (d, *J* = 7.0 Hz, 2 H, H_{Ar}), 7.43 (d, *J* = 7.5 Hz, 1 H, H_{Ar}), 5. 50 (d, *J* = 2.0 Hz, 1 H, H2), 5.27 (d, *J* = 2.0 Hz, 1 H, H3), 4.20 (s, br, D_2O exchangeable, 1 H); **^{13}C-NMR ($CDCl_3$, 125 MHz):** δ (ppm) 197.3 (C=O), 137.2, 136.0, 132.4, 131.7, 130.8, 130.5, 129.7, 129.7, 129.3, 129.3, 128.0, 127.4, 123.7, 123.0, 75.9 (C2), 63.2 (C3); **MS (EI, 70eV):** m/z (%) = 352 (09), 354 (09) [$M^{+\cdot}$, $C_{19}H_{13}BrO_2$], 155 (100).



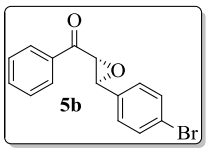
2-Hydroxy-3-p-tolyl-2,3-dihydrocyclopenta[b]naphth-alen-1-one (4v): Light yellow solid; m.p = 125-127 ^{0}C; Yield = 86%; IR ν_{max} (KBr, cm^{-1}): 3429 (OH str), 2951, 2880 (aromatic C-H str), 1692 (C=O str), 1607 (aromatic, C=C str), 1271, 1107, 843, 729; **^{1}H-NMR ($CDCl_3$, 500 MHz):** δ (ppm) 8.41 (m, 1 H, H_{Ar}), 7.98-7.87 (m, 3 H, H_{Ar}), 7.63 (m, 2 H, H_{Ar}), 7.45 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.17 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 5. 52 (d, *J* = 2.0 Hz, 1 H, H2), 5.29 (d, *J* = 2.0 Hz, 1 H, H3), 4.09 (s, br, D_2O exchangeable, 1 H), 2.32 (s, 3H); **^{13}C-NMR ($CDCl_3$, 125 MHz):** δ (ppm) 197.8 (C=O), 138.8, 136.0, 135.3, 132.4, 130.9, 130.5, 129.7, 129.3, 129.2, 128.6, 128.3, 127.9, 127.3, 123.9, 76.3 (C2), 64.0 (C3), 21.2; **MS (EI, 70eV):** m/z (%) 288 (08) [$M^{+\cdot}$, $C_{20}H_{16}O_2$], 270 (28), 133 (100).



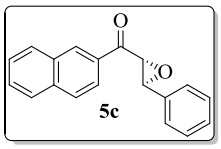
2-Hydroxy-3-(3-nitrophenyl)-2,3-dihydrocyclopenta[b] naphthalen-1-one (4w): Light yellow solid; m.p =138-140 ^{0}C; Yield = 76%; **IR ν_{max} (KBr, cm^{-1}):** 3382 (OH str), 2992, 2886 (aromatic C-H str), 1695 (C=O str), 1620 (aromatic, C=C str), 1262, 1095, 860, 743; **^{1}H-NMR ($CDCl_3$, 500 MHz):** δ (ppm) 8.54 (m, 1 H, H_{Ar}), 8.14 (m, 1 H, H_{Ar}), 7.97-7.87 (m, 3 H, H_{Ar}), 7.70 (m, 1 H, H_{Ar}), 7.62 (m, 1 H, H_{Ar}), 7.59 (m, 1 H, H_{Ar}), 7.43 (m, 1 H, H_{Ar}), 7.25 (m, 1 H, H_{Ar}), 5.72 (d, *J* = 2.0 Hz, 1 H, H2), 5.40 (d, *J* = 2.0 Hz, 1 H, H3), 3.84 (s, br, D_2O exchangeable, 1 H); **^{13}C-NMR ($CDCl_3$, 125 MHz):** δ (ppm) 197.2 (C=O), 137.8, 136.2, 134.2, 132.3, 131.2, 130.9, 129.8, 129.7, 129.5, 129.2, 128.0, 127.6, 123.8, 123.6, 123.2, 76.6 (C2), 61.9 (C3); **MS (EI, 70eV):** m/z (%) 319 (09) [$M^{+\cdot}$, $C_{19}H_{13}NO_4$], 302 (12), 189 (20), 155 (100), 127 (50).



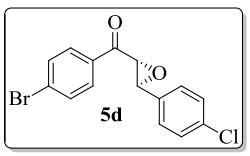
trans-(2R,3S)-3-(4-Chlorophenyl)oxiran-2-yl)(phenyl)methanone (5a): ^{1}HNMR ($CDCl_3$, 500 MHz): δ ppm 8.00 (dd, J_1=7.5Hz, J_2=1.5Hz, Ar-H, 2H), 7.63-7.48 (m, Ar-H, 5H), 7.40-7.30 (m, Ar-H, 4H), 4.25 (d, J=2.0 Hz, -CO-CH- 1H), 4.06 (d, J= 2.0 Hz, -CH-Ar- 1H). The absolute configuration was determined by comparison with the optical rotation reported in the $[\alpha]_D^{25}$ = -171.9 (c 0.53, $CHCl_3$) and chiral HPLC using Chiralcel OD-H columns and compared with the literature data.



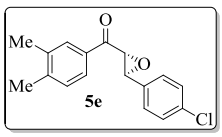
trans-(2R,3S)-3-(4-Bromophenyl)oxiran-2-yl)(phenyl)methanone (5b): **^{1}HNMR (CDCl$_3$, 500MHz):** δ ppm 8.02-7.98 (m, Ar-H, 2H), 7.63-7.59 (m, Ar-H, 1H), 7.56 7.48 (m, Ar-H, 4H), 7.26-7.24 (m, Ar-H, 1H), 4.25 (d, J=2.0 Hz, -CH-Ar, 1H), 4.05 (d, J= 1.5 Hz,-CO-CH-, 1H). The absolute configuration was determined by comparison with the optical rotation reported in the $[\alpha]_D^{25}$ = -118.4 (c 0.27, $CHCl_3$) [lit. for (2R,3S)-epoxy-3-phenyl-1-(4-bromophenyl)-propan-1-one: $[\alpha]_D^{25}$ = -162.1 (c 0.46, $CHCl_3$) for 74% ee and chiral HPLC using Chiralcel OD-H column and compared with the literature data.



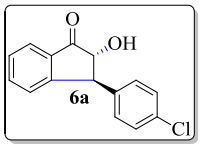
trans-(2R,3S)-Naphthalen-2-yl(3-phenyloxiran-2-yl)met -hanone (5c): **^{1}H-NMR (CDCl$_3$, 500 MHz):** δ (ppm) 8.54 (s, 1 H, H_{Ar}), 8.03 (dd, *J* = 8.5, 1.5 Hz, H_{Ar}), 7.93-7.85 (m, 3 H, H_{Ar}), 7.61 (t, *J* = 8.0 Hz, 1H, H_{Ar}), 7.54 (t, *J* = 8.0 Hz, 1H, H_{Ar}), 7.43-7.38 (m, 5 H, H_{Ar}), 4.43 (d, *J* = 1.5 Hz,1 H, C(O)CH), 4.14 (d, *J* = 1.5 Hz, 1 H, Ar-CH(-O-)CH). The absolute configuration was determined by comparison with the optical rotation reported in the $[\alpha]_D^{25}$ = -89.7 (c 1.0, $CHCl_3$) [lit.[28] for (2R,3S)-epoxy-3-phenyl-1-(2-naphthyl)-propan-1-one: $[\alpha]_D^{25}$ = -90.1 (c 1.0, CH_2Cl_2) for 64% ee] and chiral HPLC using Chiralpak AD-H column and compared with the literature data.



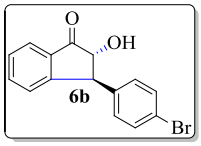
trans-(2R,3S)-(4-Bromophenyl)(3-(4-chlorophenyl)oxi -ran-2-yl)methanone (5d): ^{1}H-NMR (CDCl$_3$, 500 MHz): δ (ppm) 7.98 (dd, *J* = 7.0, 2.0 Hz, 2 H, H_{Ar}), 7.53 (m, 4 H, H_{Ar}), 7.28 (dd, *J* = 7.0, 2.0 Hz, 2 H, H_{Ar}), 4.22 (d, *J* = 2.0 Hz, 1 H, C(O)CH), 4.08 [d, *J* = 2.0 Hz, 1 H, Ar-CH(-O-)CH]. The absolute configuration was determined by comparison with the optical rotation reported in the $[\alpha]_D^{25}$ = -108.5 (c 0.31, $CHCl_3$) and chiral HPLC using Chiralpak AD-H column.



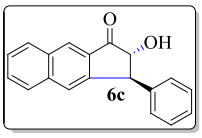
trans-(2R,3S)-(-3-(4-Chlorophenyl)oxiran-2-yl)(3,4-di-methylphenyl)methanone (5e): **^{1}H-NMR (CDCl$_3$, 500 MHz):** δ (ppm) 7.85 (m, 1H, H_{Ar}), 7.72 (dd, *J* = 7.0, 2.0 Hz, 2 H, H_{Ar}), 7.61(m, 2 H, H_{Ar}), 7.30 (dd, *J* = 7.0, 2.0 Hz, 2 H, H_{Ar}), 4.27 [d, *J* = 2.0 Hz, 1 H, C(O)CH], 4.05 [d, *J* = 2.0 Hz, 1 H, Ar-CH(-O-)CH], 2.36(s, 3H), 2.35 (s, 3H). The absolute configuration was determined by comparison with the optical rotation reported in the $[\alpha]_D^{25}$ = -134.3 (c 0.28, $CHCl_3$) and chiral HPLC using Chiralpak AD-H column.



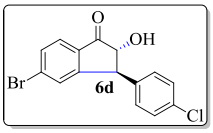
trans-(2R,3S)-3-(4-Chlorophenyl)-2-hydroxy-2,3-dihyd-roindan-1-one (6a): ^{1}H-NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.92 (d, *J* = 7.5 Hz, 2 H, H_{Ar}), 7.69 (d, *J* = 7.0 Hz, 1 H, H_{Ar}), 7.56 (t, *J* = 7.0 Hz, 2 H, H_{Ar}), 7.49 (d, *J*=7.5 Hz, 2 H, H_{Ar}), 7.35 (d, *J* = 7.0 Hz, 1 H, H_{Ar}), 5.36 (d, *J* = 2.0 Hz, 1 H, H2), 5.21 (d, *J* = 2.0 Hz, 1 H, H3), 4.13 (s, br, D_2O exchangeable, 1 H); The absolute configuration was determined by comparison with the optical rotation reported in the $[\alpha]_D^{25}$ = -16.4 (c 1.0, $CHCl_3$) and chiral HPLC using Chiralcel OD-H column.



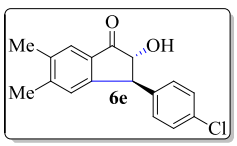
trans-(2R,3S)-3-(4-Bromophenyl)-2-hydroxy-2,3-dihyd-roindan-1-one (6b): ^{1}H-NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.91 (d, *J* = 7.5 Hz, 2 H, H_{Ar}), 7.57 (t, *J* = 7.0 Hz, 1 H, H_{Ar}), 7.50 (d, *J* = 7.0 Hz, 2 H, H_{Ar}), 7.43 (d, *J* = 7.0, 2.0 Hz, 2 H, H_{Ar}), 7.24 (m, 1 H, H_{Ar}), 5.35 (d, *J* = 2.0 Hz, 1 H, H2), 5.19 (d, *J* = 2.0 Hz, 1 H, H3), 4.13 (s, br, D_2O exchangeable, 1 H); The absolute configuration was determined by comparison with the optical rotation reported in the $[\alpha]_D^{25}$ = -8.8 (c 1.2, $CHCl_3$) and chiral HPLC using Chiralcel OD-H column.



trans-(2R,3S)-2-Hydroxy-3-phenyl-2,3-dihydrocyclo penta[b]naphthalen-1-one (6c): ^{1}H-NMR ($CDCl_3$, 500 MHz): δ(ppm) 8.45 (m, 1 H, H_{Ar}), 7.99 (m, 2 H, H_{Ar}), 7.85 (m, 1 H, H_{Ar}), 7. 65 (t, *J* = 7.0 Hz, 1 H, H_{Ar}), 7.60 (m, 3 H, H_{Ar}), 7.39-7.34 (m, 3 H, H_{Ar}), 5.57 (d, *J* = 2.0 Hz, 1 H, H2), 5.32 (d, *J* = 2.0 Hz, 1 H, H3), 4.19 (s, br, D_2O Exchange-able, 1H); The absolute configuration was determined by comparison with the optical rotation reported in the $[\alpha]_D^{25}$ = -3.5 (c 0.12, $CHCl_3$) and chiral HPLC using Chiralcel AD-H column.



trans-(2R,3S)-3-(4-Chlorophenyl)-5-bromo-2-hydroxy-2,3-dihydroindan-1-one (6d): ^{1}H-NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.89 (m, 2 H, H_{Ar}), 7.56-7.50 (m, 3 H, H_{Ar}), 7.41 (m, 2 H, H_{Ar}), 5.31 (d, *J* = 2.0 Hz, 1 H, H2), 5.16, (d, *J* = 2.0 Hz, 1 H, H3), 4.04 (s, br, D_2O exchangeable, 1 H). The absolute configuration was determined by comparison with the optical rotation reported in the $[\alpha]_D^{25}$ = -10.1 (c 0.26, $CHCl_3$) &chiral HPLC using Chiralcel AD-H column.



trans-(2R,3S)-3-(4-Chlorophenyl)-2-hydroxy-5,6-dimet-hyl-2,3-dihydroinden-1-one (6e): ^{1}H-NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.71 (m, 1 H, H_{Ar}), 7.61 (d, *J* = 7.5 Hz, 1 H, H_{Ar}), 7.50 (m, 2 H, H_{Ar}), 7.33 (m, 1 H, H_{Ar}),7.28 (d, *J* = 7.5 Hz, 1 H, H_{Ar}), 5.25 (d, *J* = 2.0 Hz, 1 H, H2), 5.14 (d, *J* = 2.0 Hz, 1 H,

H3), 4.10 (s, br, D_2O exchangeable, 1 H), 2.36(s, 3H), 2.35 (s, 3H); The absolute configuration was determined by comparison with the optical rotation reported in the $[\alpha]_D^{25}$ = -9.5 (c 0.57, $CHCl_3$) and chiral HPLC using Chiralcel AD-H column.

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CHAPTER- 3

Part-A: Zn-$SnCl_4$: A novel reductive system for deoxygenative coupling of aliphatic, aromatic, chalcone epoxide and indanone carbonyl compounds to olefins

Gulab Khushalrao Pathe and Naseem Ahmed*, *Tetrahedron Letters* ***2015***, *56,* 1555-1561.

Part-B: Design, Synthesis of McMurry cross-coupled indanophen, analogs of Tamoxifen by novel $SnCl_4$-Zn reagent and Anti-Proliferative Evaluation of Flavone-Estradiol adduct and Indanone based Ligands against Breast Cancer Cell Line

Gulab Khushalrao Pathe, Naveen Konduru, Iram Parveen and Naseem Ahmed*, *European Journal of Medicinal Chemistry* ***2015****,* Under Review**.**

Part A: $SnCl_4$ - Zn: A novel reductive system for deoxygenative coupling of aliphatic, aromatic, chalcone epoxide and indanone carbonyl compounds to olefins

4.1. INTRODUCTION

In the carbon- carbon bonds formation, the McMurry reaction plays an important role to obtain homo and cross-coupled alkenes from aliphatic and aromatic aldehydes and ketones in the presence of *in situ* generated low valent titanium (LVT) reagents at reflux temperature.[1] However, the reaction gave a moderate yield due to homo and cross-coupled products formation. To enhance the yield of cross-coupled products under mild reaction conditions, different reagents are explored for the McMurry reaction. For example, magnesium-mercury couple, $NbCl_5/NaAlH_4$,[2] zinc-copper couple,[3] $LiAlH_4$,[4] dicyclopentadienyl titaniumdichloride,[5] trimethyl aluminium.[6] Although, these procedures have drawbacks like costly reagents, low yield, longer reaction time and/or less fuctional group tolerance. In recent years, tin tetrahalides (SnX_4, X=Cl, Br) have been widely used as Lewis acids in numerous organic syntheses.[7] In many cases, these metal halides have been reported as efficient catalysts and easy to handle as compare to other metal halides such as TiX_4 AlX_3, ZnX_2 and ZrX_4.[8]

Generally, metal alloy is used as reductive deoxygenating agent in the organic synthesis for coupling reactions. For example, zinc alloy is prepared by mixing of zinc and SnCl4 in 2:1 ratio following the Rieck method.[9] Where metals like Zn involves reduction of an oxidized metal species by enhancing the reactivity of zinc at the surface of the alloy. The reductive deoxygenating reagents may also be generated in situ by reaction of two equivalent of zinc dust with one equivalent metal chloride under refluxing temperature in ether or hydrocarbon solvents. In the case of McMurry reaction reagent Ti (IV) reduced to Ti (II) with reducing agent Zn in THF, which generate a complex $TiCl_4$ -Zn-$(THF)_2$ in situ.[10, 11] which is responsible for the coupling of aldehyde or ketone to pinacolate, followed by removal of TiO_2 gave olefins.[12] Likewise, it might be taking place in $SnCl_4$-Zn and THF to form a complex $SnCl_4$-Zn-$(THF)_2$ for the coupling of aldehydes or ketones. Initially Sn(IV) converted into Sn(II) by reduction of tin halide with Zn, Sn(II) converted carbonyl oxygen to pinacolate, followed by removal of SnO_2 gave olefins.

Therefore, in continuation of our interest to develop new methods in the organic synthesis and the acid catalysis reactions.[13] Herein, we report a novel and efficient reagent, $SnCl_4$-Zn

system for the McMurry cross-coupling reaction in the conversion of aliphatic and aromatic ketones, aldehydes, chalcone epoxides and indanones into olefins and also useful in the synthesis of molecules like tamoxifen analogs in good yield within 4-4.5 h at reflux temperature.

4.2. OBJECTIVE

The McMurry reaction plays an important role in the carbon- carbon bonds formation, in which aliphatic and aromatic aldehydes and ketones undergo eliminative deoxygenation to gave homo and cross-coupled alkenes by using low valent titanium (LVT) reagents at reflux temperature. Several reagents explored for the McMurry reaction to enhance the cross-coupled products formation over the homo-coupled. Therefore, in continuation of our interest to develop new methods in the organic synthesis and the acid catalysis reactions. Hence, our aim is to find a novel and efficient reagent for McMurry reaction, we observed that $SnCl_4$-Zn system for the McMurry cross-coupling reaction in the conversion of aliphatic and aromatic ketones, aldehydes, chalcone epoxides and indanones into olefins and also useful in the synthesis of molecules like tamoxifen analogs in good yield within 4-4.5 h at reflux temperature.

4.3. RESULTS AND DISCUSSION

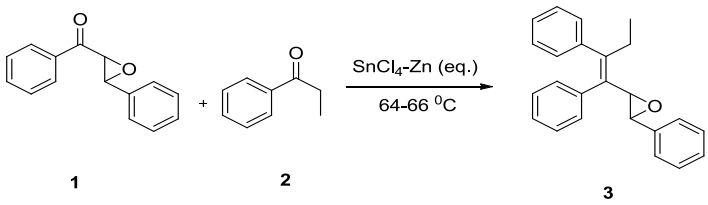
4.3.1. Optimized reaction condition

Initially, we optimized the cross-coupling reaction conditions in the reaction of chalcone epoxide **1** and propiophenone **2** used in 1:1.5 ratio and varying the equivalents of $SnCl_4$-Zn (prepared in 1:2 ratio). We obtained the cross-coupled product in 50% and 55% yields in 4h using 1 and 2 equivalent of $SnCl_4$-Zn respectively (Table1, entries 1 & 2). When $SnCl_4$-Zn was used in 3 equivalents, the yield was serendipitously improved up to 75% in 4h (Table1, entry 3). Further, increase in $SnCl_4$-Zn equivalent decreased the yields of the cross-coupled product and increased the homo-coupled products (Table 1, entries 4 & 5).

We optimized the reaction time, by using optimized condition of table 1, we checked the progress of reaction from 1h-3h to get only 20 to 60% of conversion at reflux temperature (Table 2, entries 1-3).Further increasing time from 3h to 4h gave a very good yield up to 75% (Table 2, entry 4). And further increase in time from 4 to 5h decreased in product yield to 35% (Table 2, entry 5). After separating the homo-coupled products, we also determined the formation of E and Z isomers in the cross-coupled product where E-isomer and Z- isomer were

found as major and minor products respectively. Due to the closed R_f -values of Z- isomers with byproducts, we were unable to separate the Z- isomers by the column chromatography However, the yields of Z- isomers were confirmed by GC analysis which is ranging between 2-5%.

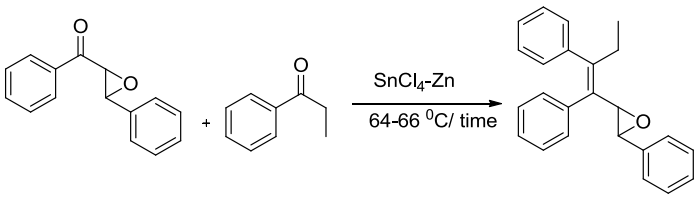
Table 1. Optimized condition for cross-coupling reaction by using different equivalent of $SnCl_4$-Zn



Entry	$SnCl_4$ –Zn	Time (h)	Yield (%)[a]
1	$SnCl_4$-Zn (1 equiv.)	4	50
2	$SnCl_4$-Zn (2 equiv.)	4	55
3	$SnCl_4$-Zn (3 equiv.)	4	75
4	$SnCl_4$-Zn (3.5 equiv.)	4	60
5	$SnCl_4$-Zn (4 equiv.)	4	35

[a]Isolated yield of cross-product

Table 2. Optimized condition for cross-coupling reaction by varying reaction time



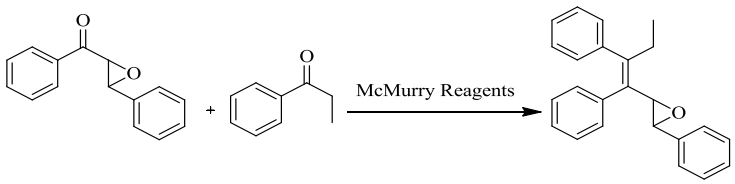
Entry	$SnCl_4$ –Zn	Time (h)	Yield (%)[a]
1	$SnCl_4$-Zn (3equiv.)	1	20
2	$SnCl_4$-Zn (3 equiv.)	2	35
3	$SnCl_4$-Zn (3 equiv.)	3	60
4	$SnCl_4$-Zn (3 equiv.)	4	75
5	$SnCl_4$-Zn (3 equiv.)	5	65

[a]Isolated yield of cross-product

Under optimal reaction conditions, the efficiency of different McMurry reagents was compared (Table 3). Aluminium and Indium complexes gave poor products yield (20%) at

reflux in 14 h (Table 3, entries 1, 2). However, the titanium complex ($TiCl_4$-Zn-THF**)** gave the yield (40%) at reflux temperature in 6 h (Table 3, entry 3), while the tin complex ($SnCl_4$-Zn-THF**)** gave the optimal yield (75%) at reflux temperature within 4 h (Table 3, entry 4). Other reagents gave poor yield (traces to 20-25 %) in acetonitrile solvent (Table 3, entries 5, 6, 7 & 8).

Table 3. Comparison of McMurry reagents and solvents in McMurry cross- coupling of chalcone epoxide and propiophenone



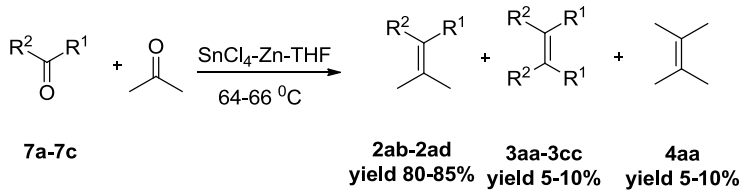
Entry	McMurry reagents	Time (h)	Yield (%)[a]
1[b]	$AlCl_3$-Zn (3 equiv.)	14	20
2[b]	$InCl_3$-Zn (3 equiv.)	14	20
3[b]	$TiCl_4$-Zn (3 equiv.)	6	60
4[b]	$SnCl_4$-Zn (3 equiv.)	4	75
5[C]	$AlCl_3$-Zn (3 equiv.)	14	trace
6[C]	$InCl_3$-Zn (3 equiv.)	14	trace
7[C]	$TiCl_4$-Zn (3 equiv.)	14	20
8[C]	$SnCl_4$-Zn (3 equiv.)	14	25

[a] Isolated yield of cross-product at 64-66 ^{0}C.
[b]reaction performed in THF
[c]reaction performed in Acetonitrile

4.3.2. Deoxygenative cross-coupling of aromatic ketone and aldehyde with acetone

In the case of aromatic aldehydes or aromatic ketones **7a-7c** with acetone (1:1.5 ratio) and $SnCl_4$- Zn (1:2 ratio) gave the corresponding cross-coupled olefin **2ab-2ad** in excellent yield 80-85% along with minor homo-coupled product **3aa-3cc** and **4aa** in yield 8-10% at reflux temperature within 1 h (Scheme 1). The reaction of aromatic aldehydes or aromatic ketones **8a-8g** with $SnCl_4$- Zn (1:2 ratio) gave the homo-coupled olefins **8a-8g** in excellent yield 70-86% at reflux temperature within 1 hour. Products **9a-9g** was characterized on the basis of their spectral data IR, ^{1}H NMR and melting point and comparing it with those of authentic samples.

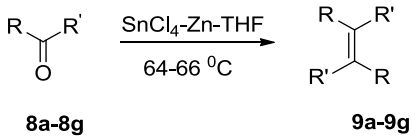
Scheme 1. Under optimized conditions, $SnCl_4$-Zn mediated deoxygenative cross-coupling of aromatic ketone and aldehyde with acetone



Entry	R^1	R^2	Time (h)	Yield (%)[a]
1	PH	H	1	85**(2ab)**
2	PH	CH_3	1	82**(2ac)**
3	PH	PH	1	80**(2ad)**

[a]Isolated yield.

Scheme 2: Deoxygenation of simple carbonyl compound to olefin by using $SnCl_4$-Zn

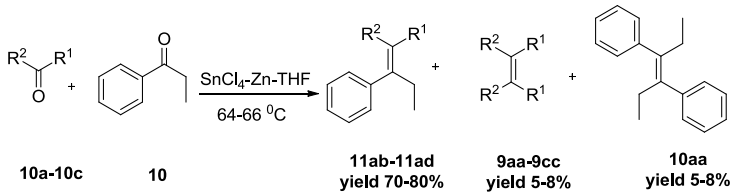


Entry	Product	R	R'	Yield(%)[a]
1	**9a**	Me	Me	85
2	**9b**	Ph	Ph	82
3	**9c**	Ph	H	85
4	**9d**	4-FC_6H_4	H	83
5	**9e**	4-Cl C_6H_4	H	80
6	**9f**	4-Me C_6H_4	H	70
7	**9g**	4-OMe C_6H_4	H	86

[a]Isolated product yield.

Further, the reaction of aromatic aldehyde or aromatic ketone **10a-10c** with propiophenone **10** (1:1.5 ratio) and $SnCl_4$- Zn (1:2 ratio) gave the cross-coupled olefins **11ab**, **11ac**, **11ad** in 80, 77, 70 % yields respectively along with homo-coupled products **9aa-9cc** and **10aa** in 5-8 % yields at reflux temperature in 2 h (Scheme 3).

Scheme 3. Under optimized conditions, $SnCl_4$-Zn mediated deoxygenative cross-coupling of aromatic ketone with propiophenone



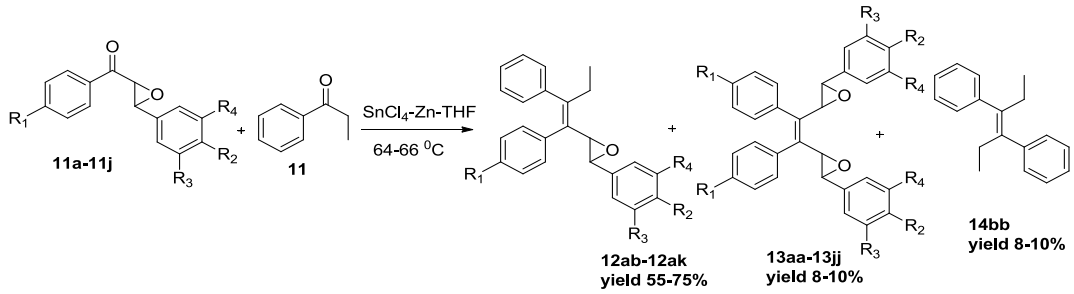
Entry	R^1	R^2	Time (h)	Yield (%)[a]
1	PH	H	2	80**(11ab)**
2	PH	CH_3	2	77**(11ac)**
3	PH	PH	2	70**(11ad)**

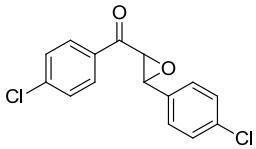
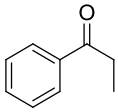
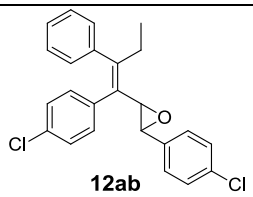
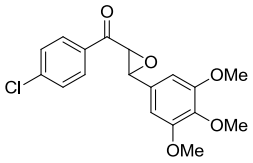
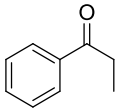
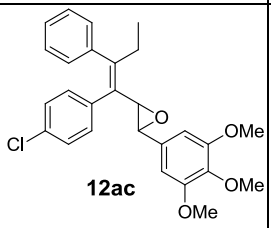
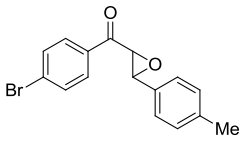
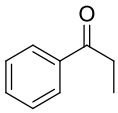
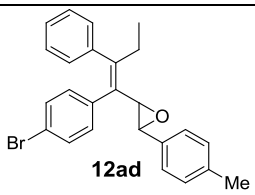
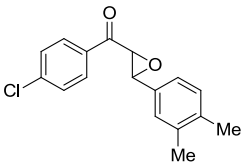
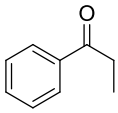
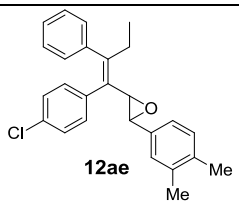
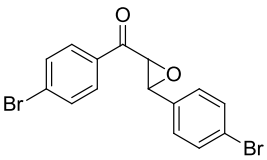
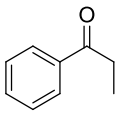
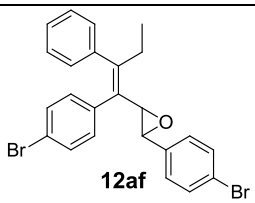
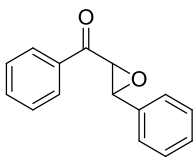
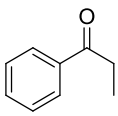
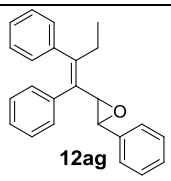
[a]Isolated product yield.

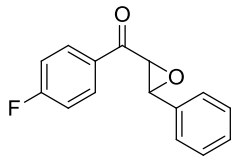
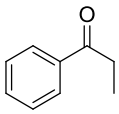
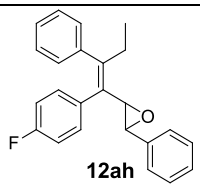
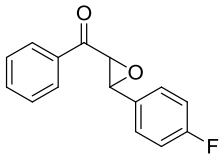
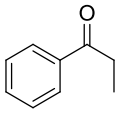
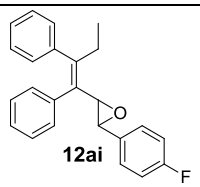
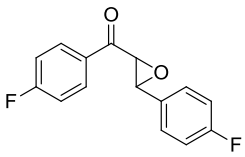
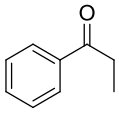
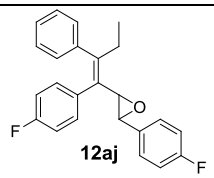
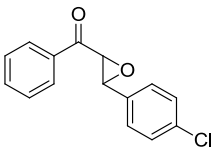
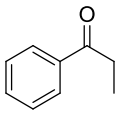
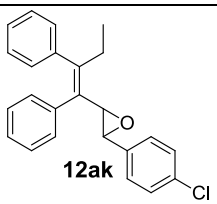
4.3.3. Deoxygenative cross-coupling of chalcone epoxides with propiophenone

The tin reagent ($SnCl_4$-Zn**)** was further applied as an alternate reagent in the McMurry reaction for the synthesis of various classes of carbonyl compounds. For example, the cross-coupled products **12ab-12ak** was obtained in good yield (55-75%) from different chalcone epoxides **11a-11j** and propiophenone **11** under optimized reaction conditions (table 4). Along with major cross-coupled product some minor homo-coupled products **13aa-13jj** and **14bb** were obtained in 8-10% yields. These homo-coupled products were isolated and the yields of product were written as isolated yields. The products were characterized on the basis of their spectral data. In ^{1}H NMR spectra, the characteristic doublet signal appeared for **12ab-12ak** in the range of δ 3.85-3.20 ppm, whereas for the compounds **11a-11j** was obtained in the range of δ 4.30-4.20 ppm, the characteristic quartet and triplet signal of $–CH_2CH_3$ appeared in between δ 0.80-2.5 ppm, indicates the cross-coupling reactions (Experimental section).

Table 4. $SnCl_4$-Zn mediated deoxygenative cross-coupling of chalcone epoxides with propiophenone



Entry	**11a-11j**	**11**	Cross-coupled products (**12ab-12ak**)	Homo-coupled products		Time (h)	Yield (%)[a]
				13aa-13jj	**14bb**		
1			 **12ab**	8	10	4	66
2			 **12ac**	9	8	4	60
3			 **12ad**	10	9	4	64
4			 **12ae**	8	8	4.5	58
5			 **12af**	10	10	4.5	55
6			 **12ag**	9	8	4	75

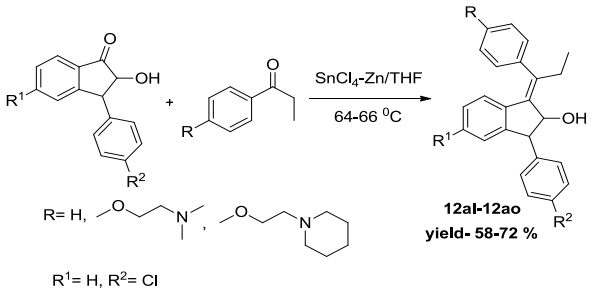
7			 12ah	10	9	4	72
8			 12ai	9	9	4	70
9			 12aj	10	10	4.5	68
10			 12ak	10	9	4.5	67

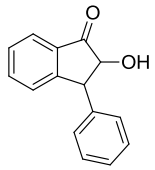
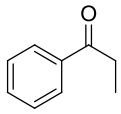
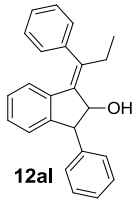
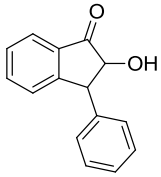
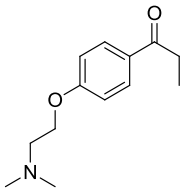
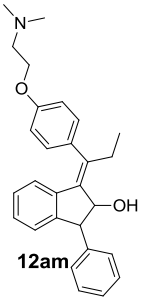
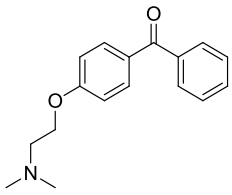
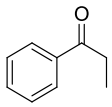
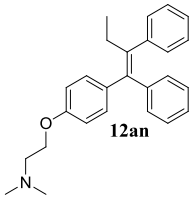
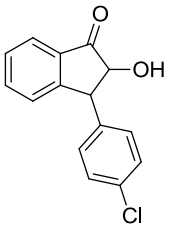
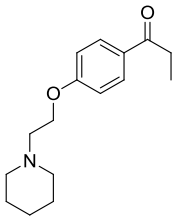
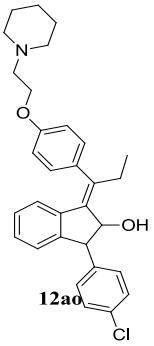
[a] Isolated yield of cross-product at 64-66 ^{0}C.

4.3.4. Synthesis of Tamoxifen analogs

The tin reagent ($SnCl_4$-Zn**)** was also successfully used in the synthesis of tamoxifen and tamoxifen analogs (Table 5). Products **12al-12ao** were synthesized in good yield 58- 72% at reflux temperature in 4-5 h using $SnCl_4$: Zn (1:2 equiv.) and the products were confirmed on the basis of their spectral data (supporting information). For example, product **12al**, the ^{1}H NMR spectra showed the characteristic double doublet peaks at δ 4.70- 4.60 ppm for C*H*-C*H*- which shifted from δ 5.30- 5.23 ppm in the indanone molecule and the characteristic quartet and triplet peaks of –CH_2CH_3 protons appeared at δ 0.90- 2.30 ppm, indicated the cross-coupling product.[14] The structures of all other compounds were further confirmed by IR and HRMS.

Table 5. Synthesis of Tamoxifen analogs (E isomers) of indanone using novel $SnCl_4$-Zn reagent



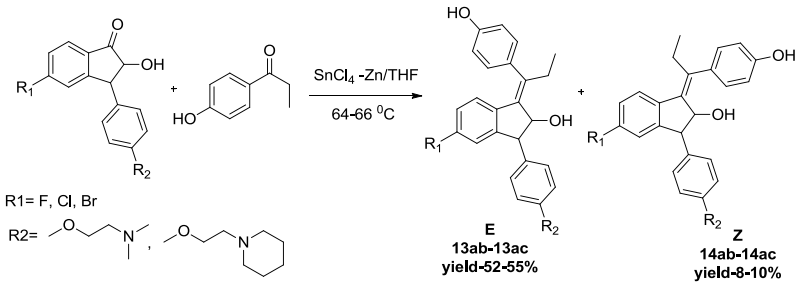
Entry	Indanone/Ketone	Propiophenone derivatives	Tamoxifen analog (**12al-12ao**)	Time (h)	Yield (%)[a]
1			 **12al**	4	72
2			 **12am**	4	65
3			 **12an**	4	71
4			 **12ao**	4	58

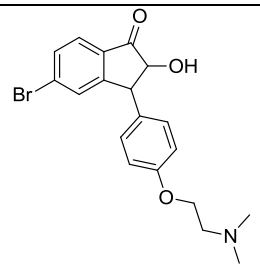
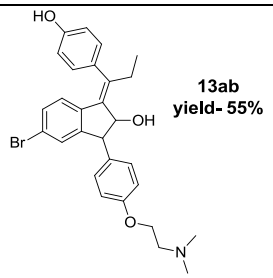
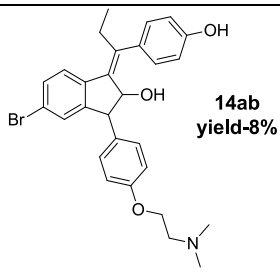
[a] Isolated yield of cross-product at 64-66 ^{0}C.

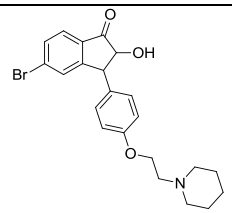
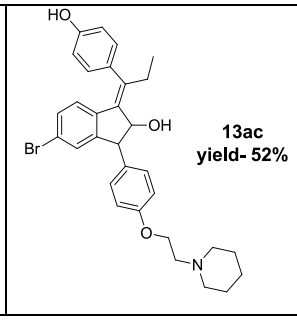
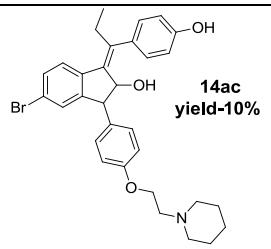
4.3.5. Determination of E and Z-Tamoxifen analogs

Compounds **4ab-4ac** and **5ab-5ac** were synthesized as a mixture of E and Z isomers which can be separated by using column chromatography and by comparing their spectral values in the literature. We observed that the E isomer is the major isomer with 52-55% yields and Z isomer is the minor product with 8-10% yields in 5 h, using $SnCl_4$: Zn (1:2 equiv.) in indanone and propiophenone (1: 1.5 equiv.). The ^{1}HNMR chemical shift (δ) 1.0-1.3 ppm for -CH_3 and 2.0-2.3 ppm for -CH_2 indicated the **E** isomer of products **13ab-13ac** and δ 0.6-0.7 ppm for -CH_3 and 1.6-1.9 ppm for -CH_2 gave the **Z** isomer for products **14ab-14ac**. Similarly, ^{13}CNMR chemical shift (δ)13-15 ppm for -CH_3 and 27-28 ppm for -CH_2 indicated the **E** isomer for products **13ab-13ac** and δ 10-12 ppm for -CH_3 and 23-25 ppm for -CH_2 gave the **Z** isomer in **14ab-14ac**.[15] Similarly, products **12ab-12ao** was characterized as E-isomer. The NMR chemical shift (δ) values of –CH_2CH_3 in products **12ab-12ao** is matches with the **13ab-13ac** (E-isomer) and not with **14ab-14ac** (Z-isomer). We were unable to isolate the Z-isomer due to close R_f values with other byproducts. However, the yields of Z-isomers were confirmed by GC analysis which is ranging between 2-5%.

Table 6. Determination of E and Z-Tamoxifen analogs by using novel $SnCl_4$-Zn reagent



Entry	Indanone	E-Analog[a]	Z-Analog[a]	Time (h)
1		 13ab yield- 55%	 14ab yield-8%	5

2		 13ac yield- 52%	 14ac yield-10%	5

[a]Isolated yield of E and Z isomers.

4.4. CONCLUSION

In conclusion, we have reported a novel, efficient and economical tin-reagent for the reductive cross-coupling reaction of carbonyl compounds, known as McMurry coupling with aliphatic and aromatic ketones, aldehydes, chalcone epoxides and indanones in high yield with minor homo-coupling products. To our knowledge, no studies exploiting this reagent for such conversion have previously been reported.

4.5. EXPERIMENTAL DETAILS

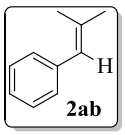
Materials and methods. All the required chemicals were purchased from Merck and Aldrich Chemical Company**.** Pre-coated aluminium sheets (silica gel 60 F_{254}, Merck) were used for thin-layer chromatography (TLC) and spots were visualized under UV light.IR spectra were recorded with KBr on Thermo Nicolet FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded respectively on Bruker Spectrospin DPX 500 MHz and Bruker Spectrospin DPX 125 MHz spectrometer using $CDCl_3$ as a solvent and trimethylsilane (TMS) as an internal standard. Splitting patterns are designated as follows; s, singlet; d, doublet; m, multiplet. Chemical shift values are given in ppm.

4.5.1. General procedure for the synthesis compounds 2ab-2ad/9a-9g/11ab-11ad/12ab-12ao/13ab-13ac & 14ab-14ac:

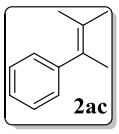
Under N_2 atmosphere, a three neck flask equipped with magnetic stirrer was charged with Zn-powder (1.5gm, 12 mmol) and 50 mL THF solvent. The mixture was cooled at 0 ^{0}C and $SnCl_4$ (2.3mL, 6 mmol) was added drop wise at 0 ^{0}C. The suspension was warmed to room temperature and stirred for 15 min and then heated at 64-66 ^{0}C for 1.5 h. The solution of aromatic aldehyde or ketone **10a-10c /**chalcone epoxide **11a-11j/** indanone and propiophenone derivatives (1:1.5 molar ratio, 2 mmol) dissolved in THF (30 mL) was added slowly at same temperature. TLC monitoring, the reaction mixture was stirred at same temperature until the carbonyl compound was consumed in the reaction. Then, the reaction mixture was cooled and

quenched with 10% aqueous $NaHCO_3$ solution and extracted in EtOAc. The organic layer was washed with brine solution, dried with anhydrous Na_2SO_4 and concentrated in *vacuo.* The crude material was purified by column chromatography to give the desired products**2ab-2ad/9a-9g/11ab-11ad/12ab-12ao/13ab-13ac** & **14ab-14ac** in 55-86 % yields.

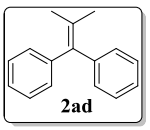
4.5.2. SPECTRAL DATA OF SYNTHESIZED COMPOUNDS



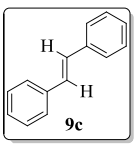
(2-methylprop-1-en-1-yl)benzene (2ab): White solid; Yield: (111 mg, 85%); **IR ν_{max} (KBr, cm^{-1}):** 3083 (aliphatic, =C-H str), 2946 (aromatic C-H str), 1655 (aliphatic, C=C str), 1582 (aromatic, C=C str), 1391, 1280, 1062, 864; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.91 (t, *J* = 7.0 Hz, 2H), 7.52 (dd, *J* = 1.5,8.0 Hz, 2H), 7.41(dd, *J* = 1.5,8.0 Hz, 2H), 1.91 (s, 3H); **^{13}C- NMR ($CDCl_3$, 125 MHz) δ (ppm):**138.82, 135.76, 129.03, 128.97, 128.68, 127.65, 25.66, 19.65; **HRMS (ES-TOF) calcd** for $C_{10}H_{12}$ 132.0939, found 132.0941.



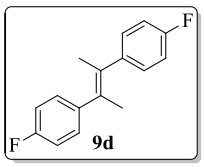
(3-methylbut-2-en-2-yl)benzene (2ac): White solid; Yield: (119 mg, 82%); %); **IR ν_{max} (KBr, cm^{-1}):** 2975 (aromatic C-H str), 1680 (aliphatic, C=C str), 1578 (aromatic, C=C str), 1392, 1270, 1072, 845; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.31 (t, *J* = 7.0 Hz, 1H), 7.12 (t, *J* = 6.5 Hz, 2H), 6.81 (dd, *J* = 1.5,8.0 Hz, 2H), 2.56 (s, 3H), 1.95 (s, 6H); **^{13}C- NMR ($CDCl_3$, 125 MHz) δ (ppm):**145.54, 139.76, 129.65, 128.97, 128.68, 127.03, 22.90, 12.77; **HRMS (ES-TOF) calcd** for $C_{11}H_{14}$ 146.1096, found 146.1098.



(2-methylprop-1-ene-1,1-diyl)dibenzene (2ad): White solid;; Yield: (165 mg, 80%); **IR ν_{max} (KBr, cm^{-1}):** 2962 (aromatic C-H str), 1667 (aliphatic, C=C str), 1568 (aromatic, C=C str), 1390, 1284, 1065, 835;**^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.52 (t, *J* = 8.0 Hz, 4H), 7.31 (t, *J* = 7.0 Hz, 4H), 7.11 (dd, *J* = 1.5,6.5 Hz, 2H), 1.92 (s, 6H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm):**141.76, 138.77, 128.97, 128.65, 127.66, 19.65; **HRMS (ES-TOF) calcd** for $C_{16}H_{16}$ 208.1252, found 208.1250.

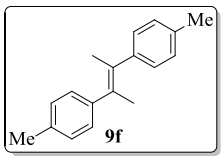


1,2-diphenylethene (9c): White solid; Yield: (153 mg, 85%); **IR ν_{max} (KBr, cm^{-1}):** 3083 (aliphatic, =C-H str), 2948 (aromatic C-H str), 1648 (aliphatic, C=C str), 1580 (aromatic, C=C str), 1393, 1280, 1062, 864; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.82 (t, *J* = 8.0 Hz, 4H), 7.62 (dd, *J* = 1.0, 7.0 Hz, 2H), 7.50(t, *J* = 7.5Hz, 4H), 7.00 (s, 2H); **^{13}C- NMR ($CDCl_3$, 125 MHz) δ (ppm):**162.68, 133.58, 130.68, 127.35, 115.78; **HRMS (ES-TOF) calcd** for $C_{14}H_{12}$ 180.0939, found 180.0940.

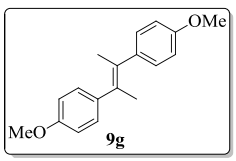


4,4'-(but-2-ene-2,3-diyl)bis(fluorobenzene) (9d): White solid; Yield: (174 mg, 83%); %); **IR ν_{max} (KBr, cm^{-1}):** 2955 (aromatic C-H str), 1674 (aliphatic, C=C str), 1574 (aromatic, C=C str), 1396, 1277, 1074, 855; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.87-7.84 (m, 4H), 7.16 (t, *J* = 8.5 Hz, 4H), 6.94 (s, 2H); **^{13}C- NMR ($CDCl_3$, 125 MHz) δ (ppm):**137.65, 129.97, 129.68, 128.66, 127.97; **HRMS (ES-TOF) calcd** for $C_{16}H_{14}F_2$ 244.1064, found 244.1064.

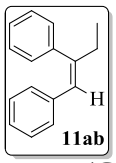
4,4'-(but-2-ene-2,3-diyl)bis(chlorobenzene) (9e): White solid;; Yield: (193 mg, 80%); **IR ν_{max} (KBr, cm^{-1}):** 2958 (aromatic C-H str), 1665 (aliphatic, C=C str), 1568 (aromatic, C=C str), 1399, 1288, 1062, 830;**^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.95 (t, *J* = 7.0 Hz, 4H), 7.56 (dd, *J* = 1.0,7.5 Hz, 4H), 6.95 (s, 2H); **^{13}C- NMR ($CDCl_3$, 125 MHz) δ (ppm):**135.65, 133.58, 129.67, 128.68, 127.77; **HRMS (ES-TOF) calcd** for $C_{16}H_{14}Cl_2$ 276.0473, found 276.0473.



4,4'-(but-2-ene-2,3-diyl)bis(methylbenzene) (9f): White solid; Yield: (165 mg, 70%); %); IR ν_{max} (KBr, cm^{-1}): 2960 (aromatic C-H str), 1665 (aliphatic, C=C str), 1570 (aromatic, C=C str), 1397, 1278, 1072, 852; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.75 (t, *J* = 7.0 Hz, 4H), 7.25 (dd, *J* = 1.5,8.0 Hz, 4H), 6.96 (s, 2H), 2.39 (s, 6H); **^{13}C- NMR ($CDCl_3$, 125 MHz) δ (ppm):**137.65, 135.53, 129.67, 128.68, 127.77, 21.65; **HRMS (ES-TOF) calcd** for $C_{18}H_{20}$ 236.1565, found 236.1566.

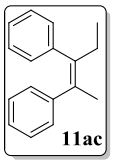


4,4'-(but-2-ene-2,3-diyl)bis(methoxybenzene) (9g): White solid; Yield: (231 mg, 86%); **IR ν_{max} (KBr, cm^{-1}):** 2957 (aromatic C-H str), 1668 (aliphatic, C=C str), 1568 (aromatic, C=C str), 1395, 1283, 1065, 833;**^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.55 (t, *J* = 7.0 Hz, 4H), 7.05 (dd, *J* = 1.5,8.0 Hz, 4H), 6.90 (s, 2H), 3.19 (s, 6H); **^{13}C- NMR ($CDCl_3$, 125 MHz) δ (ppm):**162.42, 133.92, 130.66, 127.51, 115.78, 55.78; **HRMS (ES-TOF) calcd** for $C_{18}H_{20}O_2$ 268.1463, found 268.1463.

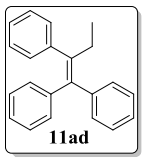


but-1-ene-1,2-diyldibenzene (11ab): Light yellow semi solid; Yield: (155 mg, 80%); **IR ν_{max} (KBr, cm^{-1}):** 3080 (aliphatic, =C-H str), 2950 (aromatic C-H str), 1644 (aliphatic, C=C str), 1582 (aromatic, C=C str), 1391, 1278, 1062, 860; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.78 (t, *J* = 7.5 Hz, 2H), 7.49 (dd, *J* = 1.5, 7.0 Hz, 2H), 7.39(t, *J* = 7.0 Hz, 2H), 7.08 (t, *J* = 7.0 Hz, 2H), 6.96 (t, *J* = 7.0 Hz, 2H), 6.46 (s, 1H), 2.07 (q, *J*

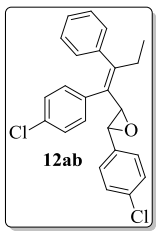
=2.0 , 8.0 Hz, 2H), 1.18 (t, *J* = 7.0 Hz, 3H), **^{13}C- NMR ($CDCl_3$, 125 MHz) δ (ppm):**142.32, 138.46, 137.44, 128.95, 127.97, 126.66, 28.35, 12.97; **MS (EI, 70eV):** m/z (%) = 195$[M]^{+\cdot}$, for $C_{15}H_{15}$; **HRMS (ES-TOF) calcd** for $C_{15}H_{15}$ 195.1174, found 195.1172.



pent-2-ene-2,3-diyldibenzene (11ac): Light brown semi solid; Yield: (171 mg, 77%); %); **IR ν_{max} (KBr, cm^{-1}):** 2958 (aromatic C-H str), 1678 (aliphatic, C=C str), 1572 (aromatic, C=C str), 1395, 1278, 1072, 850; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.49 (dd, *J* = 1.5, 7.0 Hz, 2H), 7.39(t, *J* = 7.5 Hz, 4H), 6.96 (t, *J* = 8.0 Hz, 4H), 2.44(s, 3H), 2.12 (q, *J* =2.0 , 7.5 Hz, 2H), 1.17 (t, *J* = 7.0 Hz, 3H), **^{13}C- NMR ($CDCl_3$, 125 MHz) δ (ppm):**146.54, 144.47, 142.32, 129.68, 128.66, 127.97, 126.95, 28.35, 14.28, 12.95; **MS (EI, 70eV):** m/z (%) = 222$[M]^{+\cdot}$, for $C_{17}H_{18}$; **HRMS (ES-TOF) calcd** for $C_{17}H_{18}$ 222.1409, found 222.1411.



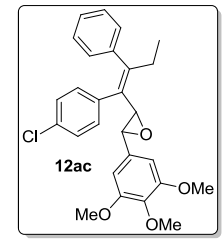
But-1-ene-1,1,2-triyltribenzene (11ad): Yellow semi solid; Yield: (198 mg, 70%); **IR ν_{max} (KBr, cm^{-1}):** 2958 (aromatic C-H str), 1665 (aliphatic, C=C str), 1568 (aromatic, C=C str), 1399, 1288, 1062, 830; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.88 (dd, *J* = 2.5, 7.5 Hz, 4H), 7.78 (t, *J* = 8.5Hz, 4H), 7.48(t, *J* = 7.5 Hz, 2H), 7.34(t, *J* = 8.0 Hz, 2H), 6.80(t, *J* = 8.0 Hz, 2H), 2.10 (q, *J* =2.5 , 8.0 Hz, 2H), 0.98(t, *J* = 7.0 Hz, 3H); **^{13}C- NMR ($CDCl_3$, 125 MHz) δ (ppm):** 140.51, 139.41, 129.12, 128.68, 128.36, 128.12, 127.85, 127.78, 126.28, 26.66, 13.68; **MS (EI, 70eV):** m/z (%) = 284$[M]^{+\cdot}$, for $C_{22}H_{20}$; **HRMS (ES-TOF) calcd** for $C_{22}H_{20}$ 284.1565, found 284.1563.

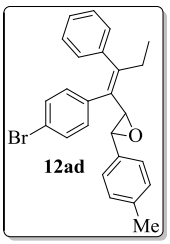


2-(4-chlorophenyl)-3-(1-(4-chlorophenyl)-2-phenylbut-1-en-1-yl) oxirane (12ab): Light brown semi Solid; Yield: (260 mg, 66 %); **IR ν_{max} (KBr, cm^{-1}):** 2937, 2878 (aromatic C-H str), 1588 (aromatic, C=C str), 1268, 1090, 868, 735; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 8.18-8.06 (m, 3H), 7.87(t, *J* = 8.0 Hz, 2H), 7.48 (dd, *J* = 1.5, 8.5 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.30 (m, 2H), 6.88-6.85 (m, 2H), 3.60 (d, *J* = 1.5 Hz, 1H), 3.47 (d, *J* = 1.5 Hz, 1H), 2.19 (q, *J* = 2.5, 8.0 Hz, 2H), 1.07 (t, *J* = 7.0 Hz, 3H);**^{13}C- NMR ($CDCl_3$, 125 MHz) δ (ppm):**144.35, 143.27, 137.95, 132.55, 132.49, 131.65, 130.49, 130.47, 130.05, 129.65, 128.97, 128.77, 128.66, 127.66, 67.72, 61.05, 27.05, 12.95; **MS (EI, 70eV):** m/z (%) = 394$[M]^{+\cdot}$, for $C_{24}H_{20}Cl_2O$, 396$[M+2H]^+$; **HRMS (ES-TOF) calcd** for $C_{24}H_{20}Cl_2O$ 394.0891, found 394.0893.

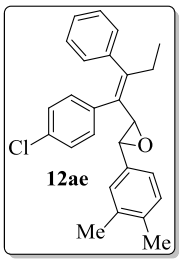
2-(1-(4-chlorophenyl)-2-phenylbut-1-en-1-yl)-3-(3,4,5-trimethoxyphenyl)oxirane (12ac): Light yellow semi solid; Yield: (269 mg, 60 %); **IR ν_{max} (KBr, cm^{-1}):** 2952 (aromatic C-H str),

1582 (aromatic, C=C str), 1393, 1277, 1060, 856; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 8.00 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 8.5 Hz, 1H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.80 (t, *J* = 9 Hz, 1H), 6.76 (d, *J* = 7.5 Hz, 1H), 6.49 (dd, *J* = 2, 7 Hz, 1H), 3.91(s, 6H), 3.89 (s, 3H), 3.62 (d, *J* = 2 Hz, 1H), 3.46 (d, *J* = 2 Hz, 1H), 2.10 (q, *J* = 2, 7.5 Hz, 2H), 1.17 (t, *J* = 7 Hz, 3H) **^{13}C-NMR ($CDCl_3$, 125 MHz) δ (ppm):**156.27, 141.54, 137.76, 132.54, 132.47, 131.77, 130.65, 130.49, 130.05, 129.65, 128.97, 128.68, 128.66, 127.03, 100.06, 67.82, 64.13, 60.33, 54.52, 28.95, 14.05; **MS (EI, 70eV):** m/z (%) = 450$[M]^{+\cdot}$, for $C_{27}H_{27}ClO_4$; **HRMS (ES-TOF) calcd** for $C_{27}H_{27}ClO_4$ 450.1598, found 450.1596.





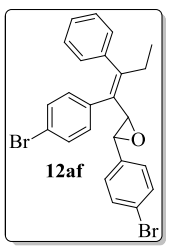
2-(1-(4-bromophenyl)-2-phenylbut-1-en-1-yl)-3-(p-tolyl) oxirane (12ad): Light yellow semi solid; Yield: (267 mg, 64 %); **IR ν_{max} (KBr, cm^{-1}):** 2922 (aromatic C-H str), 1594 (aromatic, C=C str), 1491, 1399, 1296, 1095; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.92-7.90 (m, 2H), 7.66 (dd, *J* = 1.5, 6.5 Hz, 2H), 7.29-7.23 (m, 4H), 6.91-6.86 (m, 3H), 6.47 (t, *J* = 7.5 Hz, 2H), 3.84 (d, *J* = 2Hz, 1H), 3.66 (d, *J* = 2 Hz, 1H), 2.41 (s, 3H), 2.09 (q, *J* = 2.0, 7.0 Hz, 2H), 1.19 (t, *J* = 6.5 Hz, 3H);**^{13}C- NMR ($CDCl_3$, 125 MHz) δ (ppm):**143.45, 143.05, 134.31, 129.74, 129.52, 128.65, 127.93, 127.69, 127.65, 126.76, 125.75, 125.48, 125.18, 124.07, 68.56, 62.95, 28.01, 21.54, 13.47; **MS (EI, 70eV):** m/z (%) = 418$[M]^{+\cdot}$, for $C_{25}H_{23}BrO$, 420 $[M+2H]^+$; **HRMS (ES-TOF) calcd** for $C_{25}H_{23}BrO$ 418.0932, found 418.0929.

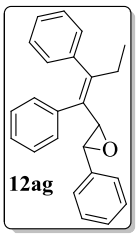


2-(1-(4-chlorophenyl)-2-phenylbut-1-en-1-yl)-3-(3,4-dimethylphenyl)oxirane (12ae): Light yellow semi solid; Yield: (223 mg, 58 %); **IR ν_{max} (KBr, cm^{-1}):** 2925 (aromatic C-H str), 1594 (aromatic, C=C str), 1399, 1289, 1091, 845;**^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.70-7.62 (m, 3H), 7.50-7.47 (m, 2H), 7.36-7.29 (m, 3H), 6.88-6.75 (m, 3H), 3.65 (d, *J* = 3.5 Hz, 1H), 3.51 (d, *J* = 3.5 Hz, 1H), 2.66 (s, 3H), 2.65(s, 3H), 2.10 (q, *J* = 1.5, 7.5 Hz, 2H), 0.98 (t, *J* = 7 Hz, 3H); **^{13}C- NMR ($CDCl_3$, 125 MHz) δ (ppm):**146.05, 145.79, 144.93, 137.47, 132.74, 132.57, 131.65, 130.93, 130.68, 130.66, 129.79, 128.79, 128.45, 128.16, 127.05, 68.78, 64.05, 27.87, 21.15, 19.35, 14.43; **MS (EI, 70eV):** m/z (%) = 388$[M]^{+\cdot}$, for $C_{26}H_{25}ClO$, 390 $[M+2H]^+$; **HRMS (ES-TOF) calcd** for $C_{26}H_{25}ClO$ 388.1594, found 388.1590.

2-(4-bromophenyl)-3-(1-(4-bromophenyl)-2-phenylbut-1-en-1-yl) oxirane (12af): Light brown semi solid; Yield: (263 mg, 55 %); **IR ν_{max} (KBr, cm^{-1}):** 2923 (aromatic C-H str), 1591

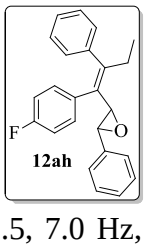
(aromatic, C=C str), 1417, 1395, 1282, 1170, 1092, 757 (C-Br, str); **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.92-7.89 (m, 2H), 7.68-7.66 (m, 2H), 7.58-7.56 (m, 2H), 7.29-7.26 (m, 3H), 6.67-6.55 (m, 4H), 3.78 (d, *J* = 3.5 Hz, 1H), 3.62 (d, *J* = 3.5 Hz, 1H), 2.12 (q, *J* = 2.5, 7.5 Hz, 2H), 0.88 (t, *J* = 7.0 Hz, 3H); **^{13}C- NMR ($CDCl_3$, 125 MHz) δ (ppm):**142.65, 141.32, 138.52, 131.66, 130.97, 130.68, 129.97, 129.58, 128.68, 127.97, 126.68, 121.97, 121.68, 116.66, 115.32, 70.68, 64.08, 26.12, 13.03; **MS (EI, 70eV):** m/z = 482$[M+2H]^+$, 484$[M+4H]^+$, for $C_{24}H_{20}Br_2O$; **HRMS (ES-TOF) calcd** for $C_{24}H_{20}Br_2O$ 481.9881, found 481.9884.

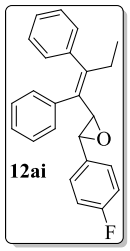




2-(1,2-diphenylbut-1-en-1-yl)-3-phenyloxirane (12ag): Light brown semi solid; Yield: (243 mg, 75 %); **IR ν_{max} (KBr, cm^{-1}):** 2935, 2877 (aromatic C-H str), 1585 (aromatic, C=C str), 1266, 1088, 862, 733; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.91-7.63 (m, 5H), 7.54-7.51 (m, 4H), 7.37-7.33 (m, 3H), 7.32-7.29 (m, 3H), 3.88 (d, *J* = 3.0 Hz, 1H), 3.62 (d, *J* = 3.0 Hz, 1H), 2.32 (q, *J* = 1.5, 8.5 Hz, 2H), 1.18 (t, *J* = 8.0 Hz, 3H);**^{13}C- NMR ($CDCl_3$, 125 MHz) δ (ppm):**142.51, 141.28, 138.58, 131.52, 130.97, 130.68, 129.97, 129.68, 128.68, 127.78, 126.35, 121.97, 121.68, 68.03, 66.51, 26.68, 13.66; **MS (EI, 70eV):** m/z (%) = 326$[M]^{+\cdot}$, for $C_{24}H_{22}O$; **HRMS (ES-TOF) calcd** for $C_{24}H_{22}O$ 326.1671, found 326.1673.

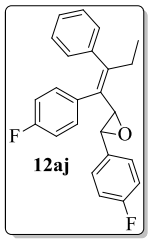
2-(1-(4-fluorophenyl)-2-phenylbut-1-en-1-yl)-3-phenyloxirane (12ah): Light yellow semi solid; Yield: (247 mg, 72 %); **IR ν_{max} (KBr, cm^{-1}):** 2950 (aromatic C-H str), 1582 (aromatic, C=C str), 1389, 1275, 1059, 854; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.88-7.85 (m, 4H), 7.55-7.49 (m, 4H), 7.41-7.39 (m, 3H), 6.88-6.85 (t, *J* = 7.5 Hz, 3H), 3.78 (d, *J* = 3.5 Hz, 1H), 2.37 (d, *J* = 3.5 Hz, 1H), 2.37 (q, *J* = 2.5, 7.0 Hz, 2H), 1.38 (t, *J* = 7.5 Hz, 3H);**^{13}C- NMR ($CDCl_3$, 125 MHz) δ (ppm):160**.54, 142.32, 141.58, 138.65, 130.97, 130.68, 129.97, 129.68, 128.66, 127.97, 126.68, 125.65, 116.66, 115.05, 67.65, 64.08, 27.35, 13.12; **MS (EI, 70eV):** m/z (%) = 344$[M]^{+\cdot}$, for $C_{24}H_{21}FO$; **HRMS (ES-TOF) calcd** for $C_{24}H_{21}FO$ 344.1576, found 344.1574



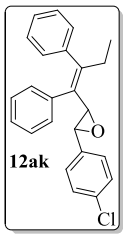


2-(1,2-diphenylbut-1-en-1-yl)-3-(4-fluorophenyl) oxirane (12ai): Light yellow semi solid; Yield: (240 mg, 70 %); **IR ν_{max} (KBr, cm^{-1}):** 2922 (aromatic C-H str), 1592 (aromatic, C=C str), 1495, 1397, 1298, 1093; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.88-7.86 (m, 4H), 7.56-7.50 (m, 4H), 7.41-7.40 (m, 3H), 6.88 (t, *J* = 7.5 Hz, 3H), 3.92 (d, *J* = 3.0 Hz, 1H), 3.71 (d, *J* = 3.0 Hz, 1H), 2.37 (q, *J* = 2.0,

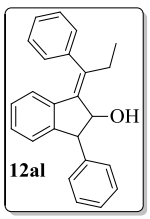
7.5 Hz, 2H), 1.38 (t, *J* = 7.0 Hz, 3H);**^{13}C- NMR ($CDCl_3$, 125 MHz) δ (ppm):**160.55, 142.32, 141.65, 138.58, 130.97, 130.66, 129.97, 129.68, 128.68, 127.97, 126.68, 125.65, 116.66, 115.08, 67.67, 64.15,27.35, 13.08; **MS (EI, 70eV):** m/z (%) = 344$[M]^{+\cdot}$, for $C_{24}H_{21}FO$; **HRMS (ES-TOF) calcd** for $C_{24}H_{21}FO$ 344.1576, found 344.1574.



2-(4-fluorophenyl)-3-(1-(4-fluorophenyl)-2-phenylbut-1-en-1-yl) oxirane (12aj): Light yellow semi solid; Yield: (246 mg, 68 %); **IR ν_{max} (KBr, cm^{-1}):** 2920 (aromatic C-H str), 1597 (aromatic, C=C str), 1399, 1285, 1092, 845; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 8.10-8.06 (m, 2H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.5 Hz, 2H), 6.89 (dd, J = 2.0, 8.0 Hz, 2H), 3.85(d, *J* = 4.5 Hz, 1H), 3.51 (d, *J* = 4.5 Hz, 1H), 2.19 (q, *J* = 2, 8 Hz, 2H), 1.09(t, *J* = 8 Hz, 3H); **^{13}C- NMR ($CDCl_3$, 125 MHz) δ (ppm):**160.58, 160.32, 135.54, 134.47, 130.97, 130.68, 129.97, 129.68, 128.66, 127.97, 126.95, 116.66, 115.05, 68.52, 63.66, 28.35, 14.95; **MS (EI, 70eV):** m/z (%) = 362$[M]^{+\cdot}$, for $C_{24}H_{20}F_2O$; **HRMS (ES-TOF) calcd** for $C_{24}H_{20}F_2O$ 362.1482, found 362.1482.

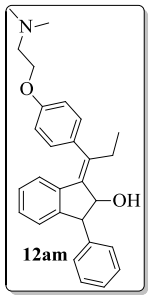


2-(4-chlorophenyl)-3-(1,2-diphenylbut-1-en-1-yl) oxirane (12ak): Light brown semi solid; Yield: (240 mg, 67 %); **IR ν_{max} (KBr, cm^{-1}):** 2928 (aromatic C-H str), 1591 (aromatic, C=C str), 1419, 1397, 1278, 1172, 1097, 755 (C-Cl, str); **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.98 (t, *J* = 7.5 Hz, 2H), 7.79-7.77 (m, 2H),7.69 (dd, *J* = 2.0, 8.0 Hz, 2H), 7.48-7.45 (m, 2H), 7.36-7.33 (m, 3H), 6.86 (dd, *J* = 2.5, 7.5 Hz, 3H), 3.86 (d, *J* = 2.0 Hz, 1H), 3.73 (d, *J* = 2.0 Hz, 1H), 2.29 (q, *J* = 2.0, 7.0 Hz, 2H), 1.28 (t, *J* = 7.0 Hz, 3H);**^{13}C- NMR ($CDCl_3$, 125 MHz) δ (ppm):**142.32, 141.58, 138.65, 131.52, 130.97,130.68, 129.68, 128.68, 127.78, 126.35, 125.65, 116.66, 115.32, 66.65, 63.12, 26.68, 13.66; **MS (EI, 70eV):** m/z 360$[M]^{+\cdot}$, for $C_{24}H_{21}ClO$, 362$[M+2H]^+$; **HRMS (ES-TOF) calcd** for $C_{24}H_{21}ClO$ 360.1281, found 360.1283.

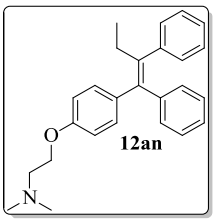


1-phenyl-3-(1-phenylpropylidene)-2,3-dihydro-1H-inden-2-ol (12al): Light brown semi solid; Yield: (259 mg, 72 %); **IR ν_{max} (KBr, cm^{-1}):** 3425 (OH str), 2935, 2877 (aromatic C-H str), 1585 (aromatic, C=C str), 1266, 1088, 862, 733; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.91-7.66 (m, 4H), 7.6-7.54 (m, 1H), 7.54-7.50 (m, 4H), 7.37-7.34 (m, 2H), 7.33-7.32 (m, 1H), 7.31-23 (m, 2H), 4.72 (d, *J* = 2.0 Hz, 1H), 4.18 (d, *J* = 2.0 Hz, 1H), 2.31 (q, *J* = 1.0, 7.5 Hz, 2H), 1.17 (t, *J* = 7.0 Hz, 3H), 3.30 (s, br, D_2O exchangeable, 1H); **^{13}C- NMR ($CDCl_3$, 125 MHz) δ (ppm):**157.60,

142.65, 141.32, 138.58, 131.52, 130.97, 130.68, 129.97, 129.68, 128.68, 127.78, 126.35, 121.97, 121.68, 116.66, 115.32, 71.12, 51.03, 26.66, 13.68; **MS (EI, 70eV):** m/z (%) 326[M]$^{+\cdot}$for $C_{24}H_{22}O$; **HRMS (ES-TOF) calcd** for $C_{24}H_{22}O$ 326.1671, found 326.1673.



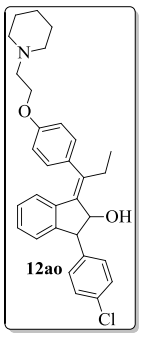
1-(1-(4-(2-(dimethylamino)ethoxy)phenyl)propylidene)-3-phenyl-2,3-dihydro-1H-inden-2-ol (12am): Light yellow semi solid; Yield: (268 mg, 65 %); **IR ν_{max} (KBr, cm^{-1}):** 3452 (OH str), 2963 (aromatic C-H str), 1599 (aromatic, C=C str), 1451, 1419, 1262, 1021, 933, 868, 799 and 704; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.92 (d, *J* = 8 Hz, 2H), 7.83 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 7 Hz, 1H), 7.49-7.45 (m, 2H), 7.41 (dd, *J* = 7.5, 2.5 Hz, 2H), 7.27-7.25 (m, 2H), 6.92 (d, J = 7.5 Hz, 2H) 4.73 (d, *J* = 3.5 Hz, 1H), 4.62 (d, *J* = 3.5 Hz, 1H), 4.15 (t, J = 1.5 Hz, 2H), 2.90 (s, 6H), 2.61 (t, J = 1.5 Hz, 2H), 2.25 (q, *J* = 8.0, 2.0 Hz, 2H), 1.18 (t, *J* = 7 Hz, 3H), 3.60 (s, br, D_2O exchangeable, 1 H); **^{13}C-NMR ($CDCl_3$, 125 MHz) δ (ppm):** 160.25, 157.05, 137.76, 132.57, 132.42, 131.77, 130.65, 130.49, 130.33, 129.65, 128.97, 128.68, 128.66, 127.05, 116.56, 116.32, 114.65, 71.65, 67.73, 61.35, 52.65, 48.35, 28.27, 14.03; **MS (EI, 70eV):** m/z = 413 [M]$^{+\cdot}$for $C_{28}H_{31}NO_2$; **HRMS (ES-TOF) calcd** for $C_{28}H_{31}NO_2$ 413.2355, found 413.2354.

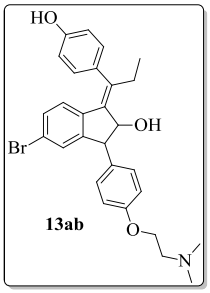


2-(4-(1,2-diphenylbut-1-en-1-yl)phenoxy)-N,N-dimethylethanamine (12an): White solid; Yield: (264 mg, 71%); **IR ν_{max} (KBr, cm^{-1}):** 2920 (aromatic C-H str),1670 (C=C str for alkene), 1592 (aromatic, C=C str), 1406, 1336, 1233, 1125(C-O-C, str), 1091; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.89-7.85 (m, 4H), 7.55-7.49 (m, 4H), 7.41-7.39 (m, 2H), 6.86 (t, *J* = 7.5 Hz, 2H), 4.15(t, *J* = 2.5 Hz, 2H), 2.9 (s, 6H), 2.62 (t, *J* = 2.5 Hz, 2H), 2.25 (q, *J* = 2.5, 7.0 Hz, 2H), 1.18 (t, *J* = 2.0 Hz, 3H); **^{13}C- NMR ($CDCl_3$, 125 MHz) δ (ppm):** 158.66, 139.97, 138.77, 131.65, 130.49, 130.47, 130.05, 129.65, 128.97, 128.77, 128.68, 127.66, 114.05, 67.72, 61.05, 47.11, 26.05, 12.95; **MS (EI, 70eV):** m/z (%) = 371[M]$^{+\cdot}$for $C_{26}H_{29}NO$; **HRMS (ES-TOF) calcd** for $C_{26}H_{29}NO$ 371.2249, found 371.2251.

1-(4-chlorophenyl)-3-(1-(4-(2-(piperidin-1-yl)ethoxy)phenyl)propylidene)-2,3-dihydro-1H-inden-2-ol (12ao): Light yellow semi solid; Yield: (281 mg, 58 %); **IR ν_{max} (KBr, cm^{-1}):** 3440 (OH str), 2920 (aromatic C-H str), 1592 (aromatic, C=C str), 1406, 1336, 1233, 1125(C-O-C, str), 1091, 771 (C-Cl, str); **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.92 (d, *J* = 7.0 Hz, 2H), 7.83 (d, *J* = 7.5 Hz, 2H), 7.59 (d, *J* = 7.0 Hz, 1H), 7.48-7.45 (m, 1H), 7.41(dd, *J* = 7.0, 2.5 Hz,

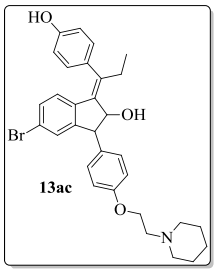
1H), 7.27-7.25 (m, 2H), 6.91 (d, *J* = 7.5 Hz, 1H), 5.27 (d, *J* = 2.0 Hz, 1H), 5.12 (d, *J* = 3.0 Hz, 1H), 4.14 (t, *J* = 3.0 Hz, 2H), 2.94-2.90 (m, 2H), 2.77 (t, *J*=6.0 Hz, 2H), 2.49-2.47 (m, 4H), 1.59 (q, *J* = 7.0, 2.0 Hz, 2H), 1.44 (t, *J* = 6.0 Hz, 4H), 1.19 (t, *J* = 7.0 Hz, 3H), 3.70 (s, br, D_2O exchangeable, 1H); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):** 157.78, 153.62, 137.74, 132.57, 132.47, 131.79, 130.65, 130.45, 130.05, 129.63, 128.79, 128.68, 128.66, 127.05, 118.96, 117.65, 117.05, 115.66, 76.13, 74.32, 64.73, 58.90, 56.75, 27.95, 26.79, 25.45, 14.35; **MS (EI, 70eV):** m/z (%) = 487[M]$^{+\cdot}$, $C_{31}H_{34}ClNO_2$], 488[M+H]$^{+\cdot}$, for $C_{31}H_{35}ClNO_2$, 489[M+2H]$^{+}$; **HRMS (ES-TOF) calcd** for $C_{31}H_{34}ClNO_2$ 487.2278, found 487.2276.



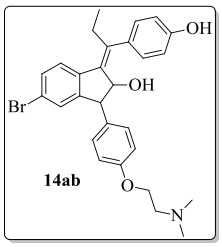


(E)-5-bromo-3-(4-(2-(dimethylamino)ethoxy)phenyl)-1-(1-(4-hydroxyphenyl)propylidene)-2,3-dihydro-1H-inden-2-ol (13ab): Light brown semi solid; Yield: (265mg, 55 %); **IR ν_{max} (KBr, cm^{-1}):** 3451 (OH str), 2952 (aromatic C-H str), 1588 (aromatic, C=C str), 1389, 1277, 1060, 854; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.88 (dd, *J* = 8.0, 2.5 Hz, 2H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.69-7.59 (m, 4H), 7.35-7.32 (m, 1H), 6.95(d, *J* = 9 Hz, 3 H), 5.34 (s, 1H), 4.87 (d, *J* = 2.0 Hz, 1H), 4.48 (d, *J* = 2.0 Hz, 1H), 4.26 (t, *J* = 2.5 Hz, 2H), 3.52 (s, 1H), 2.74 (s, 6H), 2.58 (t, *J* = 2.5 Hz, 2H), 2.12 (q, *J* = 7.5, 1.5 Hz, 2H,), 1.04 (t, *J* = 7.0 Hz, 3H); **^{13}C- NMR ($CDCl_3$, 125 MHz) δ (ppm):** 163.14, 161.127, 159.41, 157.88, 156.62, 140.112, 139.53, 136.28, 133.63, 131.54, 130.78, 129.62, 129.30, 124.37, 123.13, 116.12, 115.11, 73.13, 68.13, 62.15, 52.12, 47.45, 27.45, 14.10; **HRMS (ES-TOF) calcd** for $C_{28}H_{30}BrNO_3$ 507.1409, found 507.1407.

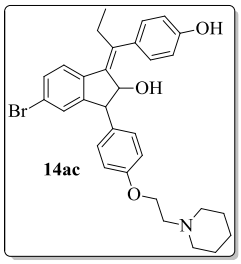
(E)-5-bromo-1-(1-(4-hydroxyphenyl)propylidene)-3-(4-(2-(piperidin-1-yl)ethoxy)phenyl)-2,3-dihydro-1H-inden-2-ol (13ac): Light yellow semi solid; Yield: (275mg, 52 %); **IR ν_{max} (KBr, cm^{-1}):** 3355 (OH str), 2955 (aromatic C-H str), 1570 (aromatic, C=C str), 1458, 1410, 1277, 1154, 1088, 1012, 915 and 730; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 8.03 (d, *J* = 8.0 Hz, 3H), 7.82 (d, *J* = 7.0 Hz, 2H), 7.76 (dd, *J* = 2.0, 7.0 Hz, 4H), 7.49 (d, *J* = 9.0 Hz, 1H),7.12 (t, *J* = 7.5 Hz, 3H), 5.56 (s, 1H), 4.75 (d, *J* = 2.0 Hz, 1H), 4.36 (d, *J* = 2.0 Hz, 1H), 4.14 (t, *J* = 2.5 Hz, 2H), 3.75 (s, 1H), 3.05(t, *J* = 2.5, 2H), 2.65(t, *J* = 3.0 Hz, 4H), 2.33 (q, *J* = 1.5, 9.0 Hz, 2H), 1.64-1.61 (m, 2 H), 1.51 (t, , *J* = 2.5 Hz, 2H), 1.02 (t, , *J* = 8.0 Hz, 3H); **^{13}C- NMR ($CDCl_3$, 125 MHz) δ (ppm):** 161.13, 157.13, 156.41, 142.62,



140.10, 139.54, 136.27, 133.63, 131.54, 130.78, 129.62, 129.30, 122.37, 122.13, 116.19, 115.19, 73.13, 69.15, 58.10, 57.45, 52.81, 29.17, 25.14, 23.10, 12.56; **HRMS (ES-TOF) calcd** for $C_{31}H_{34}BrNO_3$ 547.1722, found 547.1724.



(Z)-5-bromo-3-(4-(2-(dimethylamino)ethoxy)phenyl)-1-(1-(4-hydroxyphenyl)propylidene)-2,3-dihydro-1H-inden-2-ol (14ab): Light brown semi solid; Yield: (45mg, 8 %); **IR ν_{max} (KBr, cm^{-1}):** 3415 (OH str), 2934, 2875 (aromatic C-H str), 1599 (aromatic, C=C str), 1265, 1081, 865, 735; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.89-7.69 (m, 4H), 7.55-7.48 (m, 2H), 6.97-6.81(m, 5H), 4.69 (d, *J* = 2.5 Hz, 2H), 4.28 (d, *J* = 2.5 Hz, 2H), 4.27 (t, *J* = 2.5 Hz, 2H), 2.93 (s, 6H), 2.87 (t, *J* = 2.5 Hz, 2H), 1.78 (q, *J* = 8.0, 2.5 Hz, 2H), 0.67 (t, *J* = 7 Hz, 3H); **^{13}C- NMR ($CDCl_3$, 125 MHz) δ (ppm):** 163.14, 161.22, 159.42, 157.87, 156.62, 140.12, 139.53, 136.27, 133.63, 132.54, 130.77, 129.62, 129.30, 124.37, 123.13, 116.12, 115.10, 71.14, 66.13, 60.13, 50.17, 46.45, 25.45, 12.20; **HRMS (ES-TOF) calcd** for $C_{28}H_{30}BrNO_3$ 507.1409, found 507.1407.



(Z)-5-bromo-1-(1-(4-hydroxyphenyl)propylidene)-3-(4-(2-(piperidin-1-yl)ethoxy)phenyl)-2,3-dihydro-1H-inden-2-ol (14ac): Light yellow semi solid; Yield: (55mg, 10 %); **IR ν_{max} (KBr, cm^{-1}):** 3444 (OH str), 2922 (aromatic C-H str), 1595 (aromatic, C=C str), 1412, 1333, 1235, 1126(C-O-C, str), 1091; **^{1}HNMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.91-7.86 (m, 3H), 7.71-7.51 (m, 1H), 7.49-7.26 (t, *J* = 8.0 Hz, 4H), 7.12-6.85 (m, 4H), 5.59(s, 1H), 4.59 (d, *J* = 2.0 Hz, 1H), 4.18 (d, *J* = 2.0 Hz, 1H), 2.98 (t, *J* = 2.5 Hz, 2H), 2.87(t, *J* = 2.5 Hz, 4H), 4.02 (t, *J* = 2.5 Hz, 2H), 1.87 (q, *J* = 1.5, 8.0 Hz, 2H), 1.34 (t, *J* = 2.5 Hz, 2H), 1.26 (t, *J* = 2.5 Hz, 4H), 0.78 (t, *J* = 7.0 Hz, 3H)); **^{13}CNMR ($CDCl_3$, 125 MHz) δ (ppm):** 161.124, 157.13, 156.41, 142.63, 140.10, 139.54, 136.27, 133.63, 131.54, 130.77, 129.62, 129.30, 122.36, 122.12, 116.19, 115.19, 73.11, 69.15, 58.48, 57.55, 52.81, 25.25, 23.14, 21.30, 10.77; **HRMS (ES-TOF) calcd** for $C_{31}H_{34}BrNO_3$ 547.1722, found 547.1724.

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Part-B: Design, Synthesis of McMurry cross-coupled indanophen, analogs of Tamoxifen by novel $SnCl_4$-Zn reagent and Anti-Proliferative Evaluation of Flavone-Estradiol adduct and Indanone based Ligands against Breast Cancer Cell Line

5.1. INTRODUCTION

Breast cancer remains a major cause of death for women in the western world (2-10 times higher than for oriental women) with the global incidence estimated at 1.15 million in 2002.[1] It is the second leading cause of cancer related deaths. More than 18000 women are diagnosed with breast cancer each year. Although breast cancer mainly affects women, data shows that men can also be affected as well; each year more than 1000 men are diagnosed with breast cancer.[2] Approximately 80% of breast cancer cases occurs in post-menopausal women whose ovarian estrogen production has ceased with remaining estrogens originating in extra-glandular tissues. Estrogen is a harmone that promotes the growth of breast cancer cells. As an antiestrogen drug, Tamoxifen was designed to slow and stop the growth of the cancer cells that are constantly being produced in every breast cancer patient. Estrogen receptors α and β (ERα AND ERβ) are transcription Factors that bind to specific hormone response elements located near their target genes and regulate their expression in a ligand-dependent manner . Genistein and other flavonoids are phytoestrogens, i.e. they function as selective estrogen receptor modulators (SERMs).[3] It is hypothesized that these flavonoids modulate the endogenous activities of estrogen receptors to slow down or prevent the developments of breast and overian cancers.[4] The estrogen mimetic effects of dietary compounds are currently being explored to prevent the symptoms associated to estrogen deficiency in women during menopause.[5,6] The molecular basis of flavonoids estrogenicity is particularly difficult to elucidate, principally because of the 17β- estradiol (E2) mechanism of action which occurs via multiple pathways upon E2 binding to estrogen receptor α and β (ERα and ERβ) The estrogen receptor complex can dimerize and interact directly with the DNA at the estrogen response element (ERE), or in the activated protein pathway (AP1), the monomer can interact with two proteins (c-Jun and c-Fos proto-oncogenes) to form a complex that binds to DNA.[7]

Many naturally occurring steroid harmones [8] and non-steroidal [9] derivatives are recognized by steroid hormone receptors (SHRs) either as agonists or antagonists depending on their interaction with the SHR. Both agonists or antagonists are used for the treatment of hormone-dependent breast cancers (HDBCSs).[10,11] Acquired resistance to TAM or other

selective ER modulator (SERMs) is unique in that the growth of resistant tumours is dependent on SERMs.[12,13] Acquired TAM resistance during the treatment of metastatic breast cancer occurs within one or two years. Prolong adjuvant treatment with endocrine therapy markedly reduces the likelihood of breast cancer recurrence. Five years of tamoxifen, for example, reduces the risk of recurrence by 41% [14] However, the regimen duration and the various side effects combined with the prophylactic, and hence delayed, efficacy are likely to decrease adherence. Indeed, despite the efficacy of endocrine therapy, nonadherence and premature discontinuation by up to 30% of women have been reported.[15-17] The clinical application of the laboratory strategy of long-term adjuvent antihormone therapy for the treatment of breast cancer has significantly improved breast cancer survival.[18] Selection of patients whose tumours express the oestrone receptor (ER) are more likely to respond to long-term adjuvent tamoxifen (TAM).[19] or aromatase inhibitors (AIs)[20] than those without ER. The evolution of acquired resistance to TAM treatment was discovered using MCF-7 tumours transplanted in athymic mice to mimic years of adjuvant treatment in patients.[21] The activity of TAM in the breasts has been illuminated by recent developments in the complex endocrinology of breast cancer.[22] A second estrogen receptor, ERβ, was discovered in 1996.[23] Tumors which had been classified as ER-negative due to the lack of ERα have been shown to contain ERβ, which may be important in the proliferation of tamoxifen resistant tumors, although the role of this receptor is still poorly understood.[24]

Tamoxifen (TAM) and its congeners are widely used as a supplementary therapy to control cancers of the breast that test positive for the oestradiol receptor [25](ER). This series of molecules has a number of advantages in increasing the survival rate of patients, especially because they are relatively well tolerated over time. However, in the long run patients develop resistance to treatment with TAM. And in fact the development of certain tumours of the breast is eventually stimulated by TAM Research efforts aimed at finding new and effective anti-estrogens, without the disadvantage of TAM of clearly of great interest today, with this goal in mind, the company ICI has modified the 7 alpha position oestradiol, [26] Rousel-Uclaf, [27] (RU) has concentrated on 11beta position.

In the carbon- carbon bonds formation, the McMurry reaction plays an important role to obtain homo and cross-coupled alkenes from aliphatic and aromatic aldehydes and ketones in the presence of *in situ* generated low valent titanium (LVT) reagents at reflux temperature.[28]

However, the reaction gave a moderate yield due to homo and cross-coupled products formation. To enhance the yield of cross-coupled products under mild reaction conditions, different reagents are explored for the McMurry reaction. For example, magnesium-mercury couple, $NbCl_5/NaAlH_4$, [29] zinc-copper couple,[30] $LiAlH_4$,[31] dicyclopentadienyl titaniumdichloride,[32] trimethyl aluminium.[33] Although, these procedures have drawbacks like costly reagents, low yield, longer reaction time and/or less fuctional group tolerance. In recent years, tin tetrahalides (SnX_4, X=Cl, Br) have been widely used as Lewis acids in numerous organic syntheses.[34] In many cases, these metal halides have been reported as efficient catalysts and easy to handle as compare to other metal halides such as TiX_4 AlX_3, ZnX_2 and ZrX_4.[35]

Generally, metal alloy is used as reductive deoxygenating agent in the organic synthesis for coupling reactions. For example, zinc alloy is prepared by mixing of zinc and SnCl4 in 2:1 ratio following the Rieck method.[36] where metals like Zn involves reduction of an oxidized metal species by enhancing the reactivity of zinc at the surface of the alloy. The reductive deoxygenating reagents may also be generated in situ by reaction of two equivalent of zinc dust with one equivalent metal chloride under refluxing temperature in ether or hydrocarbon solvents. In the case of McMurry reaction reagent Ti (IV) reduced to Ti (II) with reducing agent Zn in THF, which generate a complex $TiCl_4$ -Zn-$(THF)_2$ in situ.[37,38] which is responsible for the coupling of aldehyde or ketone to pinacolate, followed by removal of TiO_2 gave olefins.[39] Likewise, it might be taking place in $SnCl_4$-Zn and THF to form a complex $SnCl_4$-Zn-$(THF)_2$ for the coupling of aldehydes or ketones. Initially Sn(IV) converted into Sn(II) by reduction of tin halide with Zn, Sn(II) converted carbonyl oxygen to pinacolate, followed by removal of SnO_2 gave olefins.

Therefore, in continuation of our interest to develop new methods in the organic synthesis and the acid catalysis reactions.[40] Herein, we report a novel and efficient reagent, $SnCl_4$-Zn system for a selective cross McMurry coupling between various indanone derivative and propiophenone derivative was achieved. We now disclosed a novel one- step synthetic strategy for tamoxifen analog using selective cross McMurry coupling between two aromatic ketone in good yield within 4-4.5 h at reflux temperature.

5.2. OBJECTIVE

Breast cancer is a second most common cancer and second leading cause of death for women. In the western world (2-10 times higher than for oriental women) with the global incidence estimated at 1.15 million in 2002. Breast cancer is always caused by genetic abnormality. About 90% of breast cancers are due to genetic abnormalities and 5-10 % of cancers are due to abnormality inherited form mother or father. Hence our intention to synthesized the drug used for the treatment of breast cancer and we have synthesized some indanophen analog of Tamoxifen by novel $SnCl_4$-Zn reagent and Flavone-Estradiol which shows Anti-Proliferative activity against Human cervical cancer cell line (HeLa) and Human Breast cancer cell lines (MCF-7& MDA-MB-231) .

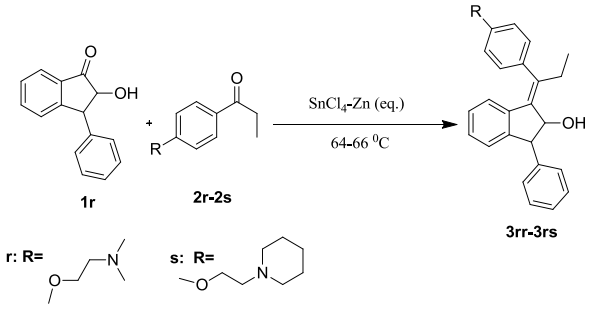
5.3. RESULTS AND DISCUSSION

Initially, we performed the McMurry coupling of indanone **1r** with propiophenone **2r,** used in 1:1.5 ratio and varying the equivalents of $SnCl_4$-Zn (prepared in 1:2 ratio). We obtained the cross-coupled product 3rr in 41% and 50% yields in 4h using 1 and 2 equivalent of $SnCl_4$-Zn respectively (Table1, entries 1 & 2). When $SnCl_4$-Zn was used in 3 equivalents, the yield was serendipitously improved up to 65% in 4h (Table1, entry 3). Further, increase in $SnCl_4$-Zn equivalent decreased the yields of the cross-coupled product 3rr and increased the homo-coupled products (Table 1, entries 4 & 5). Similarly, we optimized the reaction condition by reaction of 1r with 2s. We observed that the cross-coupled product 3rs gave 43-60 % yield. When $SnCl_4$-Zn was used in 1, 2, 3.5 & 4 (Table1, entries 6, 7, 9 & 10). The yield was serendipitously improved up to 70% in 4h when we used 3 equivalents, (Table1, entry 8).

We optimized the reaction time, by using optimized condition of table 1, we checked the progress of reaction from 1h-3h to get only 15 to 55 % of conversion at reflux temperature (Table 2, entries 1-3).Further increasing time from 3h to 4h gave a very good yield up to 65 % (Table 2, entry 4). And further increase in time from 4 to 5h decreased in product yield to 45 % (Table 2, entry 5). We also determined the formation of E and Z isomers in the cross-coupled product where E-isomer and Z- isomer were found as major and minor products respectively. Due to the closed R_f -values of Z- isomers with byproducts, we were unable to separate the Z-isomers by the column chromatography However, the yields of Z- isomers were confirmed by GC analysis which is ranging between 2-5%.

Here, the optimal condition for cross McMurry couplings of substituted indanone **1r** with propiophenone **2r-2s** employed 3 equivalent of $SnCl_4$-Zn with a 1:1.5 mol ratio of **1r** to **2r-2s** to give 3rr-3rs in very good yield in 4h.

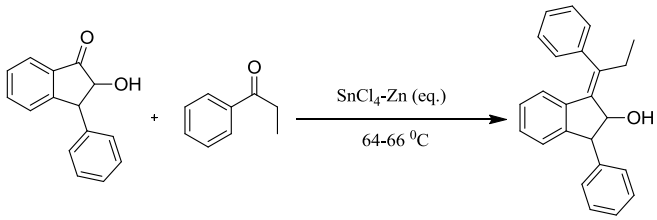
Table 1. Optimized condition for cross-coupling reaction by using different equivalent of $SnCl_4$-Zn.



Entry	Ketones[a]	$SnCl_4$-Zn	Time(h)	Yield(%)[b]
1	1r+2r	$SnCl_4$-Zn (1 equiv.)	4	**3rr** (41)
2	1r+2r	$SnCl_4$-Zn (2 equiv.)	4	**3rr** (50)
3	1r+2r	$SnCl_4$-Zn (3 equiv.)	4	**3rr** (65)
4	1r+2r	$SnCl_4$-Zn (3.5 equiv.)	4	**3rr** (59)
5	1r+2r	$SnCl_4$-Zn (4 equiv.)	4	**3rr** (55)
6	1r+2s	$SnCl_4$-Zn (1 equiv.)	4	**3rs** (43)
7	1r+2s	$SnCl_4$-Zn (2 equiv.)	4	**3rs** (52)
8	1r+2s	$SnCl_4$-Zn (3 equiv.)	4	**3rs** (70)
9	1r+2s	$SnCl_4$-Zn (3.5 equiv.)	4	**3rs** (60)
10	1r+2s	$SnCl_4$-Zn (4 equiv.)	4	**3rs** (50)

[a]The mole ratios of 1r to 2r,2s were 1:1.5, [b]Yield of isolated product

Table 2. Optimized condition for cross-coupling reaction by varying reaction time.



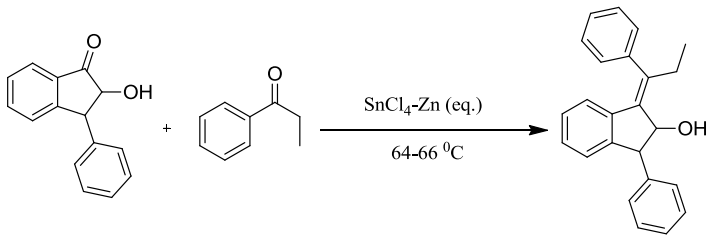
Entry	$SnCl_4$ –Zn	Time (h)	Yield (%)[a]
1	$SnCl_4$-Zn (3 equiv.)	1	15
2	$SnCl_4$-Zn (3 equiv.)	2	40

3	$SnCl_4$-Zn (3 equiv.)	3	55
4	$SnCl_4$-Zn (3equiv.)	4	65
5	$SnCl_4$-Zn (3 equiv.)	5	45

[a]Isolated yield of cross-product

Under optimal reaction conditions, the efficiency of different McMurry reagents was compared (Table 3). Aluminium and Indium complexes gave poor products yield (15 %) at reflux in 14 h (Table 3, entries 1, 2). However, the titanium complex ($TiCl_4$-Zn-THF**)** gave the yield (55 %) at reflux temperature in 6 h (Table 3, entry 3), while the tin complex ($SnCl_4$-Zn-THF**)** gave the optimal yield (70%) at reflux temperature within 4 h (Table 3, entry 4).

Table 3. Comparison of McMurry reagents and solvents in McMurry cross- coupling of Indanone and propiophenone.



Entry	McMurry reagents	Time (h)	Yield (%)[a]
1	$AlCl_3$-Zn (3 equiv.)	14	15
2	$InCl_3$-Zn (3 equiv.)	14	15
3	$TiCl_4$-Zn (3 equiv.)	6	55
4	$SnCl_4$-Zn (3 equiv.)	4	70

[a] Isolated yield of cross-product at 64-66 ^{0}C.

5.3.1. Synthesis of Tamoxifen Analogs by Cross -McMurry coupling reaction between indanone derivatives and propiophenone derivatives.

To examine the scope and generality of the cross mcmurry coupling reaction we examine the reaction of substituted indanone**12a-12u** with substituted propiophenone **13b-13e** (table 4) under optimized reaction condition describe in entry **4 & 9** of table 1, pleasingly all of these reaction proceeded as anticipated to give the corresponding cross mcmurry coupled **3ab-3au** tamoxifen analog as well as homo coupled product **2aa-2tt** and **4bb-4uu**, but the cross mcmurry product **3ab-3au** with **52- 74%** yields dominant over homo-coupled products **2aa-2tt** and **4bb-4uu**, with **8-15%** yields. (Table 4)

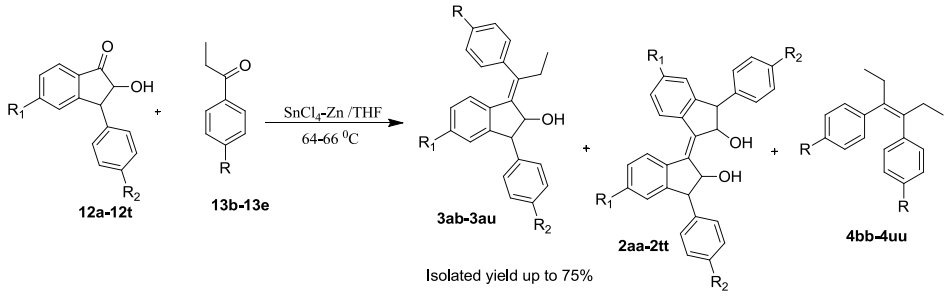
Table 3 reveals that the reaction of substrate **12a-12e** with 1-(4-(2-(dimethylamino)ethoxy)phenyl)propan-1-one in molar ratio 1:1.5 respectively, by using 6 equivalent of low valent titanium and 12 equivalent of Zn was heated at reflux in THF under nitrogen atmosphere, the reaction takes 6h to completion to yield dominant cross-coupling product **3ab-3af** with 55-66% yields along with minor homo-coupled products **2aa-2ee** and **4bb-4ff** with 8-12% yields.

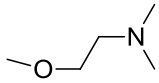
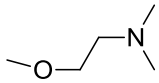
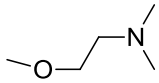
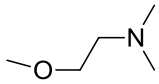
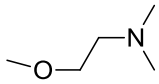
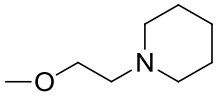
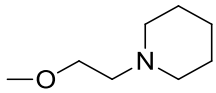
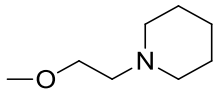
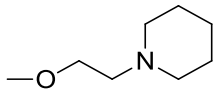
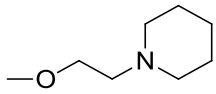
Similarly, the reaction of substrate **12f-12j** with 1-(4-(2-(piperidin-1-yl)ethoxy)phenyl)propan-1-one under same reaction condition as above to gave dominant cross-coupling product **3ag-3ak** with 52-59% yields along with minor homo-coupled products **2ff-2ll** and **4gg-4kk** with 8-14% yields, also the reaction of **12k-12o** with 4-hydroxy propiophenone to gave **3al-3ap** with 67-72% yields along with minor homo-coupled products **2mm-2qq** and **4ll-4pp** with 8-14% and reaction of **12p-12t** with propiophenone to gave **3aq-3au** with 65-74% yields along with minor homo-coupled products **2nn-2tt** and **4mm-4uu** with 8-14% yields respectively (Table 4). we observed that the reaction of **12k** to **12t** with unsubstituted propiophenone gave good yield and reaction completed in a short time as compared to reaction of **12a-12j** with 1-(4-(2-(dimethylamino)ethoxy)phenyl)propan-1-one and 1-(4-(2-(piperidin-1-yl)ethoxy)phenyl)propan-1-one.

The synthesized compounds were confirmed on the basis of their spectral data. In ^{1}H NMR spectra, the characteristic doublet signal for –CH-CH- from indanone appeared for tamoxifen analog **3ab-3au** in the range of δ 4.12- 5.12 ppm, whereas for compound **12a-12t** in the range of δ 5.33- 5.20, also the characteristic quartet and triplet signal of $–CH_2CH_3$ appeared in between δ 0.90- 2.30 ppm, indicates the coupling of two molecule took place and products were formed. The structures of all the compounds were further confirmed by HRMS, ESI/MS and IR analysis.

The geometrical isomer is easily ascertained by the H^{1}NMR spectra. In the more mobile Z-isomer, indanone ring proton is significantly up field (0.3 ppm) relative to the corresponding resonance in the E-isomer.[17] We observed that for E-isomer nmr signal for characteristic quartet and triplet signal of $–CH_2CH_3$ appeared downfield at 2.25 (q, J = 7.0, 2.5 Hz, 2H CH_3CH_2), 1.19 (t, J = 7 Hz, 3H CH_3CH_2) than the minor Z-isomer 2.00 (q, J = 7.0, 2.5 Hz, 2H CH_3CH_2), 0.80 (t, J = 7 Hz, 3H CH_3CH_2), also for -OCH_2 at 4.14-4.10 δ indicates the formation of E-isomer as the major product.

Table 4. Synthesis of Tamoxifen Analogs by Cross -McMurry coupling reaction between indanone derivatives and propiophenone derivatives.



Entry	Indanone[a]		Propiophenone[a]	Ti	Time	Yield (%)[b]		
	R_1	R_2	R	(Eq.)	(h)	2aa-2tt	**3ab-3au**[c]	4bb-4uu
1	H	H		3	6	10	**3ab** (66)	9
2	F	H		3	6	12	**3ac** (60)	8
3	H	F		3	6	8	**3ad** (64)	12
4	F	F		3	8	12	**3ae** (58)	9
5	H	Cl		3	8	12	**3af** (55)	8
6	H	H		3	9	12	**3ag** (58)	9
7	F	H		3	9	12	**3ah** (59)	9
8	H	F		3	9	10	**3ai** (58)	8
9	F	F		3	11	14	**3aj** (55)	9
10	H	Cl		3	11	14	**3ak** (52)	9
11	H	H	OH	3	4	12	**3al** (70)	9

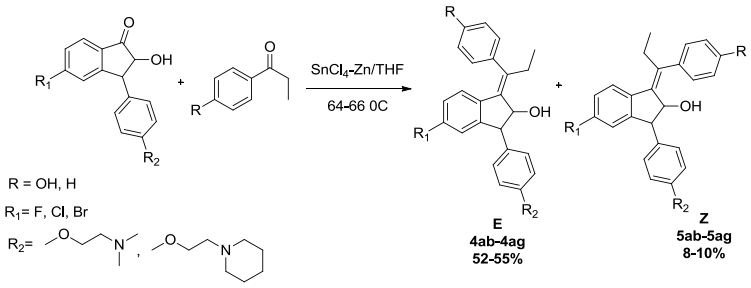
12	F	H	OH	3	4	8	**3am** (72)	8
13	H	F	OH	3	4	14	**3an** (70)	10
14	F	F	OH	3	5	10	**3ao** (68)	8
15	H	Cl	OH	3	5	10	**3ap** (67)	9
16	H	H	H	3	3	14	**3aq** (72)	12
17	F	H	H	3	3	9	**3ar** (74)	10
18	H	F	H	3	3	12	**3as** (70)	9
19	F	F	H	3	4	8	**3at** (68)	8
20	H	Cl	H	3	4	9	**3au** (65)	10

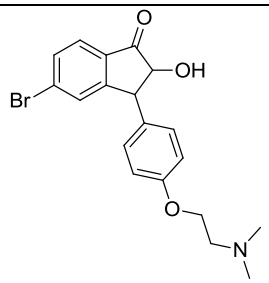
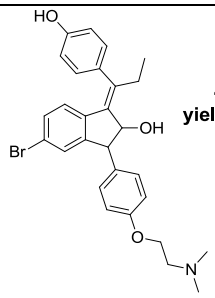
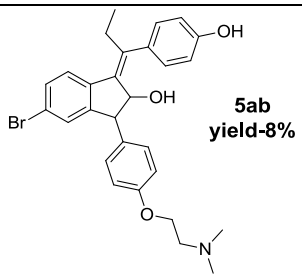
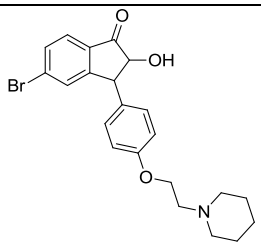
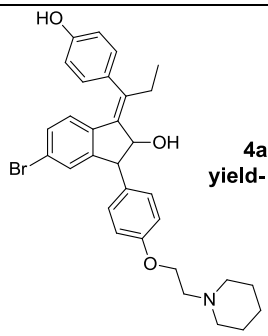
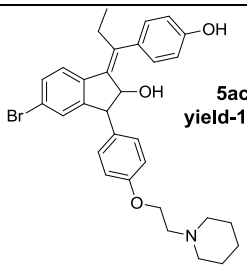
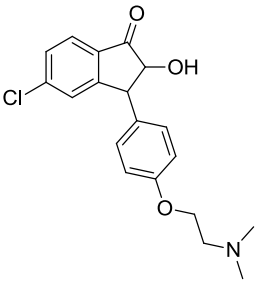
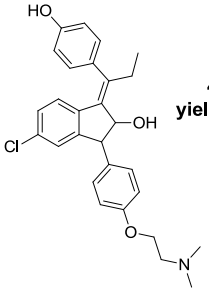
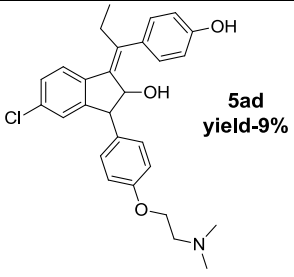
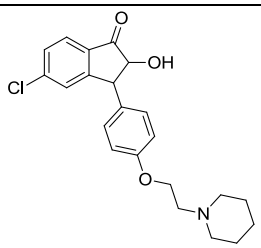
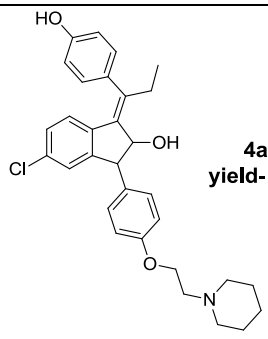
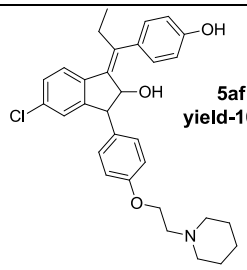
[a]The mole ratio of **12a-12s** and propiophenone derivative **13b-13e** were 1:1.5. [b]Isolated yield. [c]E-isomer was confirmed by using H^1 NMR .

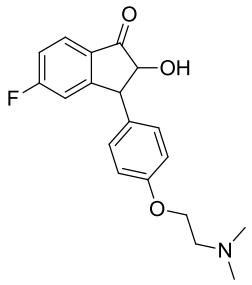
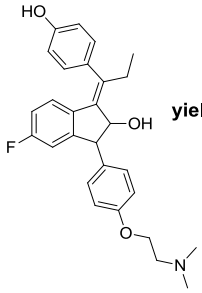
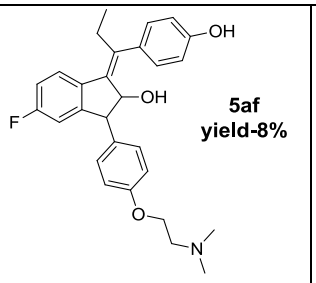
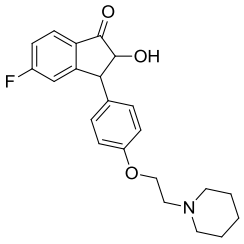
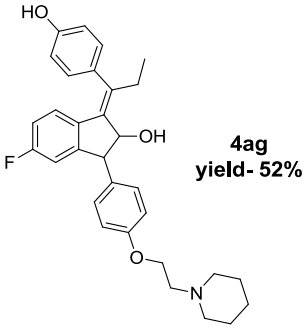
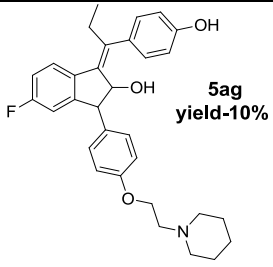
5.3.2. Synthesis of E and Z Tamoxifen analogs of indanone.

In table 5 compounds **4ab-4ag** and **5ab-5ag** were synthesized as a mixture of E and Z isomers which can be separated by using column chromatography and by comparing their spectral values in the literature. We observed that the E isomer is the major isomer with 52-55% yields and Z isomer is the minor product with 8-10% yields in 5 h, using $SnCl_4$: Zn (1:2 equiv.) in indanone and propiophenone (1: 1.5 equiv.). The ^{1}HNMR chemical shift (δ) 1.0-1.3 ppm for -CH_3 and 2.0-2.3 ppm for -CH_2 indicated the **E** isomer of products **4ab-4ag** and δ 0.6-0.7 ppm for -CH_3 and 1.6-1.9 ppm for -CH_2 gave the **Z** isomer for products **5ab-5ag**. Similarly, ^{13}CNMR chemical shift (δ)13-15 ppm for -CH_3 and 27-28 ppm for -CH_2 indicated the **E** isomer for products **4ab-4ag** and δ 10-12 ppm for -CH_3 and 23-25 ppm for -CH_2 gave the **Z** isomer in **5ab-5ag**. Similarly, products **3ab-3au** was characterized as E-isomer. The NMR chemical shift (δ) values of –CH_2CH_3 in products **3ab-3ao** is matches with the **4ab-4ac** (E-isomer) and not with **5ab-5ac** (Z-isomer). We were unable to isolate the Z-isomer due to close R_f values with other byproducts. However, the yields of Z-isomers were confirmed by GC analysis which is ranging between 2-5%.

Table 5. Synthesis of E and Z-Tamoxifen analogs of indanone.



Entry	Indanone	E-Analog	Z-Analog	Time (h)
1		 **4ab yield- 55%**	 **5ab yield-8%**	5
2		 **4ac yield- 52%**	 **5ac yield-10%**	5
3		 **4ad yield- 52%**	 **5ad yield-9%**	5
4		 **4ae yield- 55%**	 **5af yield-10%**	5

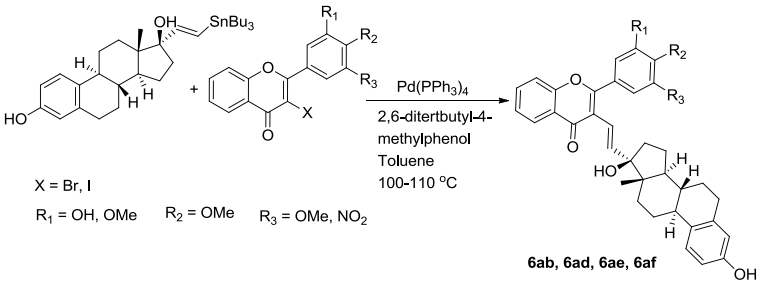
5		 **4af yield- 55%**	 **5af yield-8%**	5
6		 **4ag yield- 52%**	 **5ag yield-10%**	5

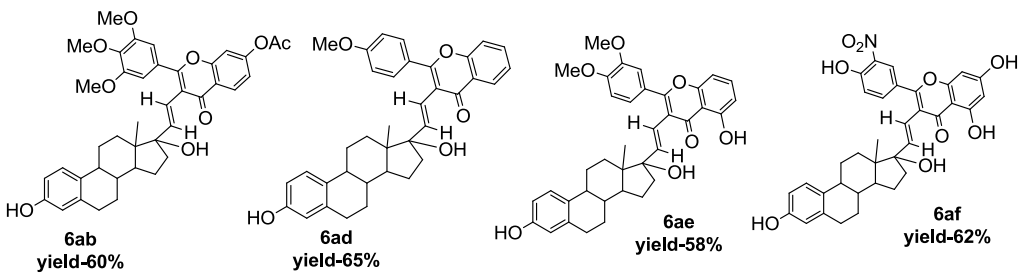
Mole ratio of indanone and propiophenone (1:1.5) and $SnCl_4$-Zn (1:2)

5.3.3. Synthesis of Flavone-Estradiols adduct

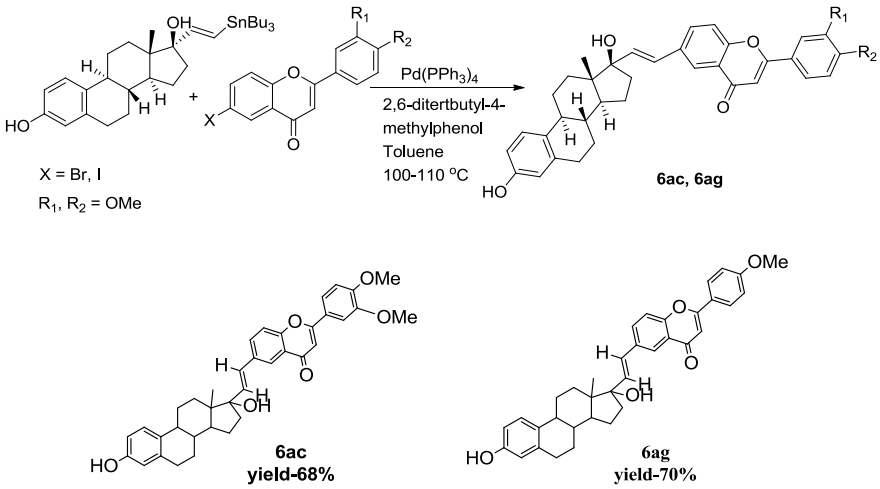
Scheme **1** and scheme **2** to shows that the Flavones-estradiol were synthesized by stile coupling between tin Estradiol derivatives with flavones derivatives in presence of palladium catalyst and 3 crystals of 2,6-dirtetbutyl-4-methyl phenol in toluene at 100-110 ^{0}C to gave products **6ab** to **6ag** in good yield up to 70% and reaction takes 2 days for completion.

Scheme 1. Synthesis of Flavone-Estradiols adduct by coupling at alpha to the carbonyl





Scheme 2. Synthesis of flavone-Estradiols adduct by coupling at benzene ring



5.3.4. Pharmacology

Anticancer evaluation

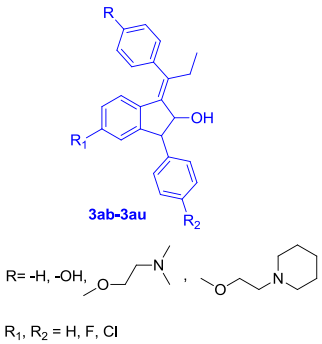
The antiproliferative activities of all synthesized conjugate were determined against the human cervical cancer cell line HeLa and estrogen-responsive breast cancer cell lines MCF-7, as well as the estrogen-independent breast cancer cell line MDA-MB-231, using the MTT assay and the corresponding inhibitory concentration 50% (IC_{50s}) value are enlisted in **Table 6**. As evident from **Table 6** and **Figure 1,** For a preliminary SAR evaluation, the series of synthesized compounds (3ab to 3ao) was first evaluated against HeLa and MCF-7 & MDA-MB-231 to investigate the effect of halogen, hydroxyl substituent on indanone moiety and side chain 2-methoxy-N,N-dimethylethanamine and 1-(2-methoxyethyl)piperidine on propiophenone moiety. The IC_{50} (half maximal inhibitory concentration) values of these compounds were determine as a measure of their respective cytotoxicity and are tabulated in Table 6. The compounds **3ac, 3ad, 3ae, 3ao** having R_1, R_2 = fluoro substituent and the R= 2-methoxy-N,N-dimethylethanamine and hydroxyl group shows high activity as standard drug doxorubicin against Human cervical cancer cell line (HeLa) and Human Breast cancer cell lines (MCF-7 & MDA-MB-231).

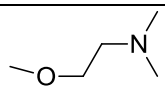
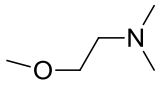
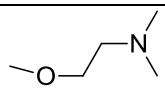
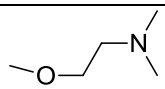
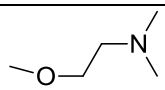
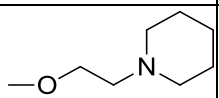
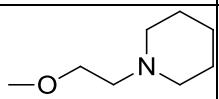
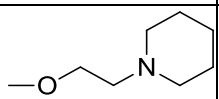
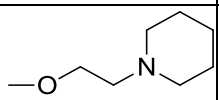
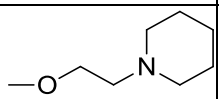
Among this series the compound **3ab** with R_1, R_2 = H and R= 2-methoxy-N, N-dimethylethanamine shows weak activity comparable to standard drug but by introducing the fluoro substituent on indanone moiety and 2-methoxy-N, N-dimethylethanamine on propiophenone moiety in compounds 3ac, showed the highest antiproliferative potency with IC_{50} values of 02.56 ± 0.028μM, 03.62 ± 0.219μM & 02.94 ± 0.084μM against HELA, MCF-7

& MDA-MB-231 cell line, respectively than the drug doxorubicin. Similarly in compounds 3ad & 3ae showed equally antiproliferative activity to standard drug having IC_{50} values of 02.56 ± 0.028 µm, 03.57 ± 0.014µm, 03.62 ± 0.219µm, 3.26 ± 0.120µm and 02.94 ± 0.084µm, 03.05 ± 0.215µm respectively. In compounds 3af having chloro substituent and 2-methoxy-N,N-dimethylethanamine side chain showed comparable antiproliferative potency to drug doxorubicin with IC_{50} values 06.65 ± 0.197µm, 08.81 ± 0.176µm, 07.48 ± 0.283µm against HELA, MCF-7 & MDA-MB-231 respectively. Also the conjugate **3ao** with R=OH and R_1, R_2 = F showed most antiproliferative potency having IC_{50} values 02.88 ± 0.021µm, 02.24 ± 0.176µm**, 02.13 ± 0.134** µm respectively.

By introducing the chain from R = 2-methoxy-n, n-dimethylethanamine to R = 1-(2-methoxyethyl) piperidine in compounds **3ag-3ak** seemed to have comparable activity displayed IC_{50s} in the range 4.09- 13.05µm, 8.05-14.28µm, 5.68-12.08µm against HELA, MCF-7 and MDA-MB-231 respectively. If we change R=OH then the compounds **3al-3ap** shows moderate activity displayed IC_{50s} in the range 5.05-10.75µm against HELA, 6.47-9.72µm against MCF-7 and 5.64-8.94µm against MDA-MB-231; by replacing R = H in compounds **3aq-3au** shows weak activity comparable to standard drug displayed IC_{50s} in the range 9.95-27.65µm against HELA, 13.06-26.60µm against MCF-7 and 8.46-24.00µm against MDA-MB-231. from **Table 6** it reveals that the compounds **3ao** most potent with r=OH among all the synthesized compounds displayed IC_{50s} 2.88µm against HELA, 2.24µm against MCF-7 and 2.13µm and **3ac-3ae** shows equally potent as that of standard drug doxorubicin displayed IC_{50s} in the range 2.56-3.81µm against HELA, 2.87-3.62µm against MCF-7 and 2.94-3.26 µm against MDA-MB-231.

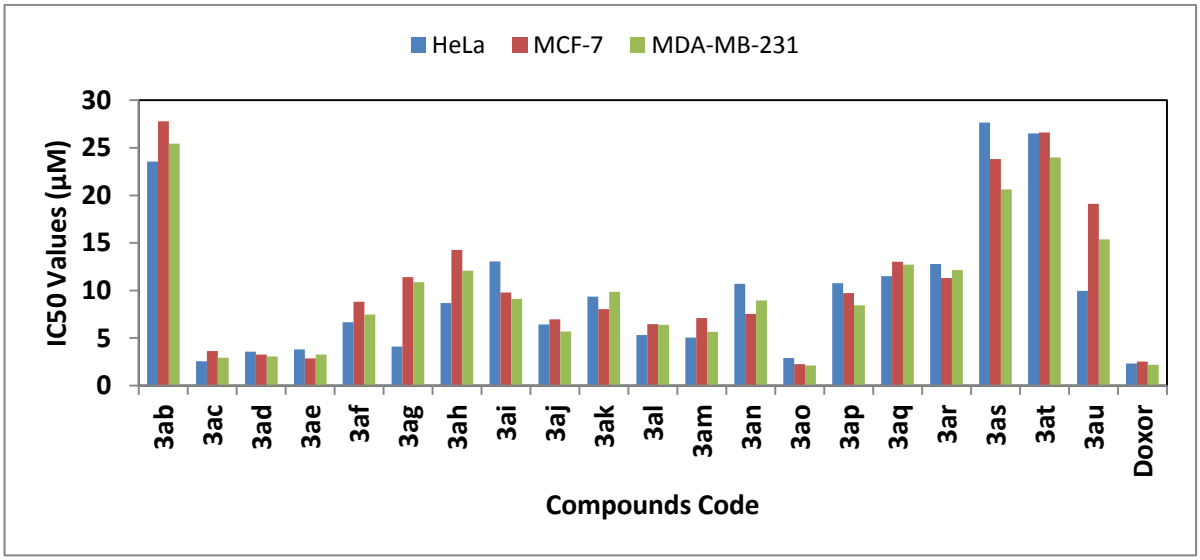
Table 6. Showing anti-proliferative data (IC_{50} Values in µM) of all the synthesized tamoxifen analog drugs and standard drug against Human cervical cancer cell line (HeLa) and Human Breast cancer cell lines (MCF-7& MDA-MB-231).



Entry	DRUG	R_1	R_2	R	HeLa	MCF-7	MDA-MB-231
1	**3ab**	H	H		23.55± 0.070	27.80 ± 1.272	25.43 ± 0.985
2	**3ac**	F	H		**02.56 ± 0.028**	**03.62 ± 0.219**	**02.94 ± 0.084**
3	**3ad**	H	F		**03.57 ± 0.014**	**03.26 ± 0.120**	**03.05 ± 0.215**
4	**3ae**	F	F		**03.81 ± 0.049**	**02.87 ± 0.127**	**03.26 ± 0.321**
5	**3af**	H	Cl		**06.65 ± 0.197**	**08.81 ± 0.176**	**07.48 ± 0.283**
6	**3ag**	H	H		**04.09 ± 0.431**	11.40 ± 0.332	10.85 ± 0.535
7	**3ah**	F	H		08.69 ± 0.233	14.28 ± 0.296	12.08 ± 0.372
8	**3ai**	H	F		13.05 ± 0.070	09.78 ± 0.431	09.12 ± 0.288
9	**3aj**	F	F		**06.44 ± 0.395**	**06.95 ± 0.342**	**05.68 ± 0.431**
10	**3ak**	H	Cl		09.35 ± 0.827	08.05 ± 0.521	09.85 ± 0.635
11	**3al**	H	H	OH	**05.31 ± 0.134**	**06.47 ± 0.134**	**06.38 ± 0.512**
12	**3am**	F	H	OH	**05.05 ± 0.007**	**07.09 ± 0.339**	**05.64 ± 0.186**
13	**3an**	H	F	OH	10.70 ± 0.141	**07.53 ± 0.509**	08.94 ± 0.543
14	**3ao**	F	F	OH	**02.88 ± 0.021**	**02.24 ± 0.176**	**02.13 ± 0.134**
15	**3ap**	H	Cl	OH	10.75 ± 0.212	09.72 ± 0.360	08.46 ± 0.482
16	**3aq**	H	H	H	11.50 ± 0.141	13.03 ± 0.381	12.73 ± 0.736

17	**3ar**	F	H	H	12.80 ± 0.141	11.32 ± 0.346	12.16± 0. 538
18	**3as**	H	F	H	27.65 ± 0.355	23.82 ± 0.459	20.63 ± 0.689
19	**3at**	F	F	H	26.50 ± 0.420	26.60 ± 0.989	24.00 ± 1.290
20	**3au**	H	Cl	H	09.95 ± 0.205	19.12 ± 0.459	15.39 ± 0.984
	Doxorubicin*				02.33 ± 0.035	02.51 ± 0.183	02.18 ± 0.127

Figure 1. In vitro anti- cancer activity of a compounds 3ab-3au against Human cervical cancer cell line (HeLa) and Human Breast cancer cell lines (MCF-7& MDA-MB-231)

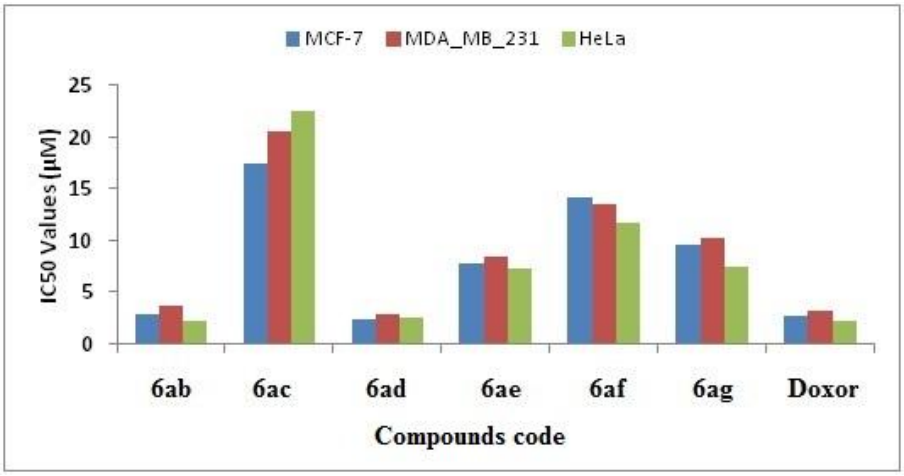


As evident from **Table 7** and **Figure 2,** the antiproliferative activities of Flavone-Estradiol adduct 6ab to 6ag were determined against the human cervical cancer cell line HeLa and estrogen-responsive breast cancer cell lines MCF-7, as well as the estrogen-independent breast cancer cell line MDA-MB-231. In Flavone-Estradiol adduct **6ad,** the coupling reaction took place at 2-position of flavones with 4'- methoxy substituent on the flavones moiety, showed greater antiproliferative activity than the standard drug doxorubicin having IC_{50} Values 02.42 ± 0.226µM, 02.93 ± 0.137µM, 02.56 ± 0.322µM against MCF-7, MDA-MB-231 and HeLa, respectively. Also compound **6ab** with 3', 4' 5' - trimethoxy substituent on flavone was equally potent as that of doxorubicin with IC_{50} 02.85 ± 0.165µM, 03.64 ± 0.276µM, 02.17 ± 0.183µM against MCF-7, MDA-MB-231 & HeLa resp. and the compound **6ae** and **6ag** were moderately active with IC_{50} in between 07.27 ± 0.815µM to 08.42 ± 0.563µM, rest of the compounds **6ac** and **6af** shows poor activity having IC_{50} more than 10.28± 0.736µM.

Table 7. Showing anti-proliferative data (IC_{50S} Values in μM) of all the synthesized Flavone-Estradiol adduct and standard drug against Human Breast cancer cell lines (MCF-7& MDA-MB-231) and Human Cervical cancer cell line (HeLa).

S. No.	Compounds code	MCF-7	MDA-MB-231	HeLa
1	**6ab**	**02.85 ± 0.165**	**03.64 ± 0.276**	**02.17 ± 0.183**
2	**6ac**	17.38± 1.212	20.52± 1.388	22.44± 1.436
3	**6ad**	**02.42 ± 0.226**	**02.93 ± 0.137**	**02.56 ± 0.322**
4	**6ae**	**07.72 ± 0.628**	**08.42 ± 0.563**	**07.27 ± 0.815**
5	**6af**	14.15± 0.825	13.54± 1.023	11.62± 0.794
6	**6ag**	09.61± 1.019	10.28± 0.736	**07.40 ± 0.655**
	Doxorubicin*	02.70 ± 0.185	03.14 ± 0.126	02.25 ± 0.095

Figure 2. In vitro anti- cancer activity of a compounds 6ab-6ag against Human cervical cancer cell line (HeLa) and Human Breast cancer cell lines (MCF-7& MDA-MB-231).



5.4. CONCLUSION

In conclusion, we have developed a facile one-step synthetic strategy for tamoxifen analog. It involves selective cross McMurry coupling between a substituted indanone and substituted propiophenone. These compounds were screened for their anti proliferative activity against human cancer cell line. (Hela, MCF-7 & MDA-MB-231). The compounds 3ac, 3ad, 3ae,3ao with an optimal combination of side chain at Para position of propiophenone and fluoro substituent on indanone moiety displayed the best activity among the test compounds having IC_{50} = 2.13 - 3.81μm of 3ac, 3ad, 3ae & 3ao and rest of the compounds also shows

comparable activity to the standard drug doxorubicin having IC_{50} < 28μm. The flavones-Estradiol adduct 6ab and 6ad shows excellent activity having IC_{50} Values in μM 02.85 ± 0.165 & 02.42 ± 0.226 and 03.64 ± 0.276, 02.93 ± 0.137 against Human Breast cancer cell lines (MCF-7& MDA-MB-231) and 02.17 ± 0.183, 02.56 ± 0.322 against Human cervical cancer cell line (HeLa) respectively and rest of the compounds also shows moderate activity to the standard drug doxorubicin having IC_{50} < 10μm.

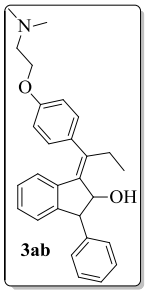
5.5. EXPERIMENTAL DETAILS

5.5.1. General procedure for the synthesis of tamoxifen analog 3ab-3au/4ab-4ac & 5ab-5ac:

Under N_2 atmosphere, a three neck flask equipped with magnetic stirrer was charged with Zn-powder (1.5gm, 12 mmol) and 50 mL THF solvent. The mixture was cooled at 0 ^{0}C and $SnCl_4$ (2.3mL, 6 mmol) was added drop wise at 0 ^{0}C. The suspension was warmed to room temperature and stirred for 15 min and then heated at 64-66 ^{0}C for 1.5 h. The solution of solution of indanone derivative **1a-1t** and propiophenone derivative **2b-2e** (1:1.5 molar ratio, 2 mmol) dissolved in THF (30 mL) was added slowly at same temperature. TLC monitoring, the reaction mixture was stirred at same temperature until the carbonyl compound was consumed in the reaction. Then, the reaction mixture was cooled and quenched with 10% aqueous $NaHCO_3$ solution and extracted in EtOAc. The organic layer was washed with brine solution, dried with anhydrous Na_2SO_4 and concentrated in *vacuo.* The crude material was purified by column chromatography to give the desired products **3ab-3au/4ab-4ac** & **5ab-5ac** in 52-72% % yields.

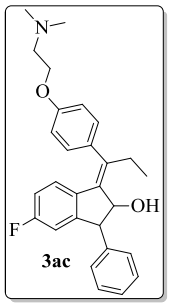
General procedure for the synthesis of Flavone-Estradiol adducts analog 6ab-6ag: Under N_2- atmosphere, a four necked flask equipped with magnetic stirrer was charged with 0.11 mmol tin derivative and 0.1 mmol flavones derivative and three crystals of 2,6-ditert butyl-4-methylphenol dissolve in dry toluene (2 ml), flushed the reaction mixture for 10 min under nitrogen atmosphere. Added 6 mg of palladium catalyst again flush with N_2 gas for 5 min. Then, the reaction mixture was stirred for 2 days at 100-110 ^{0}C. After completion of reaction, the solvent was evaporated under reduced pressure and washed with hexane to remove excess tin derivative. The reaction mixture was purified using silica gel column chromatography in 20:80 ethyl acetate/hexane to obtain flavones-estradiol adduct with 60-70% yields.

5.5.2 Spectral data of indanofen derivatives



3ab

(E)-1-(1-(4-(2-(dimethylamino)ethoxy)phenyl)propylidene)-3-phenyl-2,3-dihydro-1H-inden-2-ol (3ab): Light yellow semi solid; Yield: 66 %; **IR ν_{max} (KBr, cm^{-1}):** 3452 (OH str), 2963 (aromatic C-H str), 1599 (aromatic, C=C str), 1451, 1419, 1262, 1021, 933, 868, 799 and 704; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.92 (d, *J* = 8 Hz, 2H), 7.83 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 7 Hz, 1H), 7.49-7.45 (m, 2H), 7.41 (dd, *J* = 7.5, 2.5 Hz, 2H), 7.27-7.25 (m, 2H), 6.92 (d, J = 7.5 Hz, 2H) 4.73 (d, *J* = 3.5 Hz, 1H), 4.62 (d, *J* = 3.5 Hz, 1H), 4.15 (t, J = 1.5 Hz, 2H), 2.90 (s, 6H), 2.61 (t, J = 1.5 Hz, 2H), 2.25 (q, *J* = 8.0, 2.0 Hz, 2H), 1.18 (t, *J* = 7 Hz, 3H) 3.60 (s, br, D_2O exchangeable, 1 H); **^{13}C-NMR ($CDCl_3$, 125 MHz) δ (ppm):** 160.25, 157.05, 137.76, 132.57, 132.42, 131.77, 130.65, 130.49, 130.33, 129.65, 128.97, 128.68, 128.66, 127.05, 116.56, 116.32, 114.65, 71.65, 67.73, 61.35, 52.65, 48.35, 28.27, 14.03; **MS (EI, 70eV):** m/z = 413 [$M^{+\cdot}$, $C_{28}H_{31}NO_2$]; **HRMS (ES-TOF) calcd** for $C_{28}H_{31}NO_2$ 413.2355, found 413.2354.

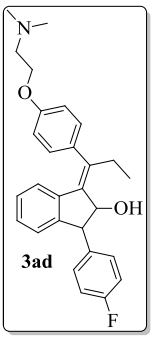


3ac

(E)-1-(1-(4-(2-(dimethylamino)ethoxy)phenyl)propylidene)-5-fluoro-3-phenyl-2,3-dihydro-1H-inden-2-ol (3ac): Light yellow semi solid; Yield: 60 %; **IR ν_{max} (KBr, cm^{-1}):** 3408 (OH str), 2917 (aromatic C-H str), 1589 (aromatic, C=C str), 1489, 1415, 1288, 1177, 1091, 1014, 929 and 701; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.88 (t, *J* = 8 Hz, 2H), 7.85 (t, *J* = 8 Hz, 2H), 7.55-7.49 (m, 5H), 7.41-7.39 (m, 1H), 6.86 (t, *J* = 7.5 Hz, 2H), 4.58 (d, *J* = 4.0 Hz, 1H), 4.41 (d, *J* = 4.5 Hz, 1H), 4.15 (t, *J* = 2.0 Hz, 2H), 2.90 (s, 6H), 2.62 (t, *J* = 2.0 Hz, 2H), 2.25 (q, *J* = 7.0, 2.5 Hz, 2H) 1.18 (t, *J* = 7.0 Hz, 3H), 3.42 (s, br, D_2O exchangeable, 1H); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):** 159.68, 158.55, 157.11, 137.93, 132.55, 132.49, 131.65, 130.97, 130.77, 130.68, 129.65, 128.49, 128.47, 128.05, 127.66, 116.05, 114.11, 71.75, 67.72, 61.55, 52.11, 47.32, 26.05, 12.98; **MS (EI, 70eV):** m/z (%) = 431[$M^{+\cdot}$, $C_{28}H_{30}FNO_2$]; **HRMS (ES-TOF) calcd** for $C_{28}H_{30}FNO_2$ 431.2261, found 431.2259

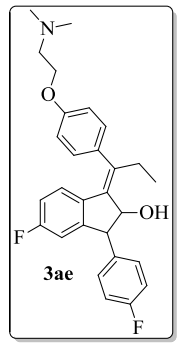
(E)-1-(1-(4-(2-(dimethylamino)ethoxy)phenyl)propylidene)-3-(4-fluorophenyl)-2,3-dihydro-1H-inden-2-ol (3ad): Light yellow semi solid; Yield: 64 %; **IR ν_{max} (KBr, cm^{-1}):** 3391 (OH str), 2951 (aromatic C-H str), 1577 (aromatic, C=C str), 1468, 1401, 1271, 1152, 1084, 1002, 910 and 725; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.87 (t, *J* = 7.5Hz, 2H), 7.85 (t, *J* = 7.5Hz, 2H), 7.55-7.49 (m, 5H), 7.41-7.39 (m, 1H), 6.86 (t, *J* = 7.5 Hz, 2H), 4.58 (d, *J* = 4.0 Hz, 1H), 4.41 (d, *J* = 4.0 Hz, 1H), 4.14 (d, *J* = 3.5 Hz, 1H), 2.90 (s, 6H), 2.62 (t, *J*

= 2.5, 2H), 2.25(q, *J* = 7.0, 2.5 Hz, 2H), 1.18 (t, *J* = 8.0, Hz, 3H), 3.40 (s, br, D_2O exchangeable, 1 H); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):** 159.54, 158.66, 137.95, 132.55, 132.49, 131.65, 130.49, 130.47, 130.05, 129.65, 128.97, 128.77, 128.68, 127.66, 116.03, 114.05, 71.73, 67.72, 61.05, 52.32, 47.11, 26.05, 12.95; **MS (EI, 70eV):** m/z (%) = 431[$M^{+\cdot}$, $C_{28}H_{30}FNO_2$]; **HRMS (ES-TOF) calcd** for $C_{28}H_{30}FNO_2$ 431.2261, found 431.2259



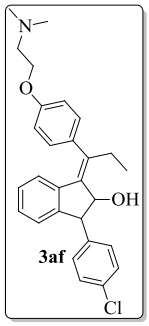
3ad

(E)-1-(1-(4-(2-(dimethylamino)ethoxy)phenyl)propylidene)-5-fluoro-3-(4-fluorophenyl)-2,3-dihydro-1H-inden-2-ol (3ae): Light brown semi solid; Yield: 58 %; **IR ν_{max} (KBr, cm^{-1}):** 3426 (OH str), 2923 (aromatic C-H str), 1591 (aromatic, C=C str), 1417, 1395, 1282, 1170, 1092; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.98 (t, *J* = 8.5 Hz, 2H), 7.79-7.76 (m, 2H), 7.70 (dd, *J* = 7.5, 1.5 Hz, 2H), 7.47 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.25-7.36 (m, 2 H), 6.86 (dd, *J* = 8.0, 3.0 Hz, 2H), 4.52 (d, *J* = 3.0, Hz, 1H), 4.44 (d, *J* = 3.0 Hz, 1H), 4.15 (t, *J* = 2.0 Hz, 2H), 2.98 (s, 6H), 2.72 (t, *J* = 2.0 Hz, 2H), 2.25 (q, *J* = 7.0, 2.5 Hz, 2H), 1.19 (t, *J* = 7 Hz, 3H), 3.52 (s, br, D_2O exchangeable, 1 H); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):** 161.27, 160.55, 159.47, 158.77, 138.76, 138.54, 130.68, 130.49, 130.05, 129.65, 128.97, 128.65, 127.66, 117.97, 117.66, 114.76, 70.72, 66.73, 61.35, 52.32, 48.05, 26.95, 13.32; **MS (EI, 70eV):** m/z = 449 [$M^{+\cdot}$, $C_{28}H_{29}F_2NO_2$]; **HRMS (ES-TOF) calcd** for $C_{28}H_{29}F_2NO_2$ 449.2166, found 449.2168



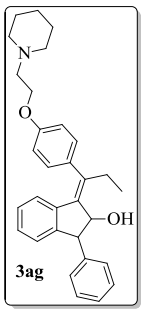
3ae

(E)-1-(4-chlorophenyl)-3-(1-(4-(2-(dimethylamino)ethoxy)phenyl) propylidene) -2,3-dihydro-1H-inden-2-ol (3af): Light brown semi solid; Yield: 55 %; **IR ν_{max} (KBr, cm^{-1}):** 3449 (OH str), 2950 (aromatic C-H str), 1582 (aromatic, C=C str), 1389, 1275, 1059, 854, 723 (C-Cl, str); **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 8.08 (dd, *J* = 7.0, 2.0 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.83 (d, *J* = 8.5, Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.47(d, *J* = 8.5 Hz, 1 H), 7.27 (t, *J* = 7.0 Hz, 2H), 7.16 (d, *J* = 8.5 Hz, 1H), 6.89 (dd, *J* = 8.0, 2.5 Hz, 2H), 4.67 (d, *J* = 3.0 Hz, 1H), 4.32 (d, *J* = 3.0 Hz, 1H), 3.94 (d, *J* = 2.5 Hz, 2H), 3.00 (s, 6H), 2.81(t, *J* = 3.0 Hz, 2H), 2.26 (q, *J* = 8.0, 3.0 Hz, 2H,), 1.08 (t, *J* = 8.0 Hz, 3H), 3.41 (s, br, D_2O exchangeable, 1 H); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):** 159.55, 157.27, 137.76, 132.54, 132.47, 131.77, 130.65, 130.49, 130.05, 129.65, 128.97, 128.68, 128.66, 127.03, 117.95, 115.76, 71.72, 67.73, 61.35, 52.32, 48.97,

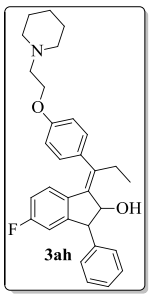


3af

28.95, 14.05; **MS (EI, 70eV):** m/z (%) = 447[$M^{+\cdot}$, $C_{28}H_{30}ClNO_2$], 449[M^{+2}]; **HRMS (ES-TOF) calcd** for $C_{28}H_{30}ClNO_2$ 447.1965, found 447.1967.



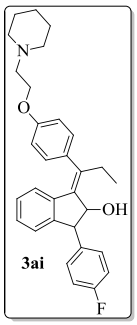
(E)-1-phenyl-3-(1-(4-(2-(piperidin-1-yl)ethoxy)phenyl)propylidene)-2,3-dihydro-1H-inden-2-ol (3ag): Light yellow semi solid; Yield: 58 %; **IR ν_{max} (KBr, cm^{-1}):** 3420 (OH str), 2959, 2869 (aromatic C-H str), 1583 (aromatic, C=C str), 1253, 1063, 835; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.91(d, *J* = 8.0 Hz, 2H), 7.83 (d, *J* = 8.5 Hz, 2H), 7.59 (t, *J* = 8.5 Hz, 1H), 7.48-7.45 (m, 2H), 7.42-7.39 (m, 2H), 7.27-7.25 (m, 2H), 6.91 (d, *J* = 8.0 Hz, 2H), 5.27 (d, *J* = 2.0 Hz, 1 H), 5.12 (d, *J* = 2.0 Hz, 1H), 4.14 (t, *J* = 2.5 Hz, 2H), 2.92 (m, 2H), 2.76 (t, *J* = 6.0 Hz, 2H), 2.49 (s, 4H), 1.59 (q, *J* = 7.5, 3.0 Hz, 2H), 1.44 (t, *J* = 6.0 Hz, 2H), 1.18 (t, *J* = 8.0 Hz, 3H), 3.85 (s, br, D_2O exchangeable, 1 H), **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):** 158.27, 153.65, 137.77, 132.54, 132.47, 131.77, 130.65, 130.49, 130.05, 129.65, 128.97, 128.68, 128.66, 127.03, 118.95, 117.66, 117.05, 115.65, 76.16, 74.32, 63.73, 58.79, 56.95, 28.15, 26.97, 25.04, 13.05; **MS (EI, 70eV):** m/z = 453[$M^{+\cdot}$, $C_{31}H_{35}NO_2$]; **HRMS (ES-TOF) calcd** for $C_{32}H_{35}NO_2$ 453.2668, found 453.2666.



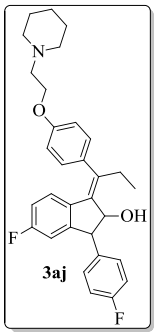
(E)-5-fluoro-3-phenyl-1-(1-(4-(2-(piperidin-1-yl)ethoxy)phenyl)propylidene)-2,3-dihydro-1H-inden-2-ol (3ah): Light brown semi solid; Yield: 59 %; **IR ν_{max} (KBr, cm^{-1}):** 3415 (OH str), 2931, 2873 (aromatic C-H str), 1597 (aromatic, C=C str), 1263, 1081, 860, 737; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.88-7.84 (m, 4H), 7.55-7.49 (m, 4H), 7.42-7.26 (m, 2H), 6.87 (t, *J* = 7.5 Hz, 2H), 4.68 (d, *J* = 3.5 Hz, 1H), 4.51 (d, *J* = 3.0 Hz, 1H), 3.83 (d, *J* = 3.0 Hz, 2H), 3.84-3.80 (m, 2 H), 2.77 (t, *J* = 4.0 Hz, 2H), 2.39-2.36 (m, 4H), 1.49 (q, *J* = 7.5, 1.5 Hz, 2H), 1.14 (t, *J* = 6 Hz, 4H), 0.97 (t, *J* = 7.5 Hz, 3H), 3.83(s, br, D_2O exchangeable, 1H), **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):** 161.15, 157.78, 153.62, 137.47, 132.74, 132.57, 131.65, 130.79, 130.45, 130.05, 129.79, 128.93, 128.68, 128.66, 127.05, 117.00, 116.65, 116.08, 76.32, 74.16, 64.75, 58.93, 56.70, 27.79, 26.95, 25.43, 14.55; **MS (EI, 70eV):** m/z (%) = 471[$M^{+\cdot}$, $C_{31}H_{34}FNO_2$]; **HRMS (ES-TOF) calcd** for $C_{31}H_{34}FNO_2$ 471.2574, found 471.2571.

(E)-1-(4-fluorophenyl)-3-(1-(4-(2-(piperidin-1-yl)ethoxy)phenyl)propylidene)-2,3-dihydro-1H-inden-2-ol (3ai): Light yellow semi solid; Yield: 58 %; **IR ν_{max} (KBr, cm^{-1}):** 3429 (OH str), 2951, 2880 (aromatic C-H str), 1607 (aromatic, C=C str), 1271, 1107, 843, 729; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.89-7.85 (m, 4H), 7.56-7.50 (m, 4H), 7.41-7.39 (m, 2H), 6.87

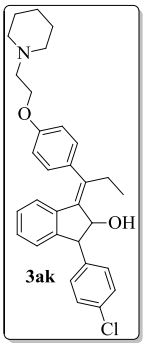
(t, *J* = 7.5 Hz, 2H), 4.67 (d, *J* = 3.5 Hz, 1H), 4.50 (d, *J* = 4.0 Hz, H), 3.74 (t, *J* = 6.5 Hz, 2H), 3.85-3.80 (m, 2 H), 2.76 (t, *J* = 6.0 Hz, 2H), 2.40-2.39 (m, 4H), 1.48 (q, *J* = 8.0, 2.5 Hz, 2H), 1.14(t, *J* = 6.0 Hz, 4H), 0.97(t, *J* = 7.5 Hz, 3H), 3.45 (s, br, D_2O exchangeable, 1H); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):** 161.15, 157.62, 153.78,137.47, 132.74, 132.57, 131.65, 130.93, 130.68, 130.66, 129.79, 128.45, 128.16, 127.05, 117.00, 116.65, 116.05, 76.32, 74.08, 64.75, 58.93, 56.70, 27.87, 26.95, 25.79, 14.43; **MS (EI, 70eV):** m/z (%) = 471[$M^{+\cdot}$, $C_{31}H_{34}FNO_2$]; **HRMS (ES-TOF) calcd** for $C_{31}H_{34}FNO_2$ 471.2574, found 471.2571.



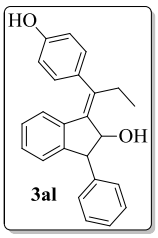
(E)-5-fluoro-3-(4-fluorophenyl)-1-(1-(4-(2-(piperidin-1-yl)ethoxy) phenyl) propylidene)-2,3-dihydro-1H-inden-2-ol (3aj): Light yellow semi solid; Yield: 55%; **IR ν_{max} (KBr, cm^{-1}):** 3382 (OH str), 2992, 2886 (aromatic C-H str), 1620 (aromatic, C=C str), 1262, 1095, 860, 743; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 8.05 (d, *J* = 8.5 Hz, 2H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.47(d, *J* = 8.5 Hz, 2H), 7.28 (t, *J* = 8.5 Hz, 2H), 7.16 (d, *J* = 8.5 Hz, 1H), 6.94 (d, *J* = 8.5 Hz, 2H), 4.98 (d, *J* = 3.5 Hz, 1H), 4.71 (d, *J* = 4.0 Hz, 1H), 3.94 (t, *J* = 6.0 Hz, 1H), 3.04-3.00 (m, 2H), 2.96 (t, *J* = 6.0 Hz, 2H), 2.49-2.48 (m, 2H), 1.69 (q, *J* = 1.0, 7.5 Hz, 4H), 1.44 (t, *J* = 8.5 Hz, 3H), 4.42 (s, br, D_2O exchangeable, 1 H); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):**161.25, 160.57, 159.44, 158.76, 138.77, 138.57, 130.68, 130.49, 130.25, 129.65, 128.97, 128.65, 127.66, 117.97, 117.67, 114.76, 73.32, 70.72, 66.73, 61.35, 51.32, 30.09, 27.15, 26.09, 13.05; MS (EI, 70eV): m/z (%) = 489[$M^{+\cdot}$, $C_{31}H_{33}F_2NO_2$]; **HRMS (ES-TOF) calcd** for $C_{31}H_{33}F_2NO_2$ 489.2479, found 489.2477.



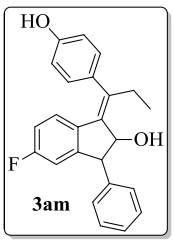
(E)-1-(4-chlorophenyl)-3-(1-(4-(2-(piperidin-1-yl)ethoxy)phenyl)propylidene)-2,3-dihydro-1H-inden-2-ol (3ak): Light yellow semi solid; Yield: 52 %; **IR ν_{max} (KBr, cm^{-1}):** 3440 (OH str), 2920 (aromatic C-H str), 1592 (aromatic, C=C str), 1406, 1336, 1233, 1125(C-O-C, str), 1091, 771 (C-Cl, str); **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.92 (d, *J* = 7.0 Hz, 2H), 7.83 (d, *J* = 7.5 Hz, 2H), 7.59 (d, *J* = 7.0 Hz, 1H), 7.48-7.45 (m, 1H), 7.41(dd, *J* = 7.0, 2.5 Hz, 1H), 7.27-7.25 (m, 2H), 6.91 (d, *J* = 7.5 Hz, 1H), 5.27 (d, *J* = 2.0 Hz, 1H), 5.12 (d, *J* = 3.0 Hz, 1H), 4.14 (t, *J* = 3.0 Hz, 2H), 2.94-2.90 (m, 2H), 2.77 (t, *J*=6.0 Hz, 2H), 2.49-2.47 (m, 4H), 1.59 (q, *J* = 7.0, 2.0 Hz, 2H), 1.44 (t, *J* = 6.0 Hz, 4H), 1.19 (t, *J* = 7.0 Hz, 3H), 3.70 (s, br, D_2O exchangeable, 1H); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):** 157.78, 153.62, 137.74, 132.57, 132.47,



131.79, 130.65, 130.45, 130.05, 129.63, 128.79, 128.68, 128.66, 127.05, 118.96, 117.65, 117.05, 115.66, 76.13, 74.32, 64.73, 58.90, 56.75, 27.95, 26.79, 25.45, 14.35; **MS (EI, 70eV):** m/z (%) = 487[$M^{+\cdot}$, $C_{31}H_{34}ClNO_2$], 489[M^{+2}]; **HRMS (ES-TOF) calcd** for $C_{24}H_{20}F_2O$ 487.2278, found 487.2276.



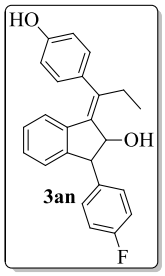
(E)-1-(1-(4-hydroxyphenyl) propylidene)-3-phenyl-2,3-dihydro-1H-inden-2-ol (3al): Light brown semi solid; Yield: 70%; **IR ν_{max} (KBr, cm^{-1}):** 3429 (OH str), 2951, 2880 (aromatic C-H str), 1607 (aromatic, C=C str), 1271, 1107, 843, 729; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 8.11(dd, *J* = 8.5, 2.0 Hz, 2H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.47(d, *J* = 8.5 Hz, 1H), 7.27 (t, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.5 Hz, 2H), 6.88 (dd, *J* = 8.0, 2.0 Hz, 2H), 4.67 (d, *J* = 4.0 Hz, 1H), 4.20 (d, *J* = 4.0 Hz, 1H), 2.19 (q, *J* = 2.0, 8.0 Hz, 2H), 1.10 (t, *J* = 8.0 Hz, 3H), 3.68 (s, br, D_2O exchangeable, 1H); 1.56 (s, br, D_2O exchangeable, 1H) ; **^{13}C-($CDCl_3$, 125 MHz) δ (ppm):**159.60, 155.65, 142.65, 141.32, 138.52, 131.66, 130.97, 130.68, 129.97, 129.58, 128.68, 127.97, 126.68, 121.97, 121.68, 116.66, 115.32, 71.08, 51.68, 26.12, 13.03; **MS (EI, 70eV):** m/z (%) = 342[$M^{+\cdot}$, $C_{24}H_{22}O_2$]; **HRMS (ES-TOF) calcd** for $C_{24}H_{22}O_2$ 342.1620 $[M+H]^+$, found 342.1617.



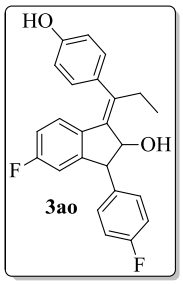
(E)-5-fluoro-1-(1-(4-hydroxyphenyl)propylidene)-3-phenyl-2,3-dihydro-1H-inden-2-ol (3am): Light brown semi solid; Yield: 72%; **IR ν_{max} (KBr, cm^{-1}):** 3415 (OH str), 2931, 2873 (aromatic C-H str), 1597 (aromatic, C=C str), 1263, 1081, 860, 737; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.99-7.86 (m, 2H), 7.79-7.76 (m, 2H), 7.71 (dd, *J* = 1.5, 8.0 Hz, 2H), 7.49-7.44 (m, 2H), 7.34(dd, *J* = 2.0, 8.0 Hz, 2H), 6.88 (dd, *J* = 2.0, 7.0 Hz, 2H), 4.49 (t, *J* = 3.0 Hz, 1H), 4.46 (d, *J* = 3.0 Hz, 1H), 2.29 (q, *J* = 2.0, 8.0 Hz, 2H), 1.28 (t, *J* = 8.0 Hz, 3H), 6.17 (s, br, D_2O exchangeable, 1H), 3.70 (s, br, D_2O exchangeable, 1H); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):**165.58, 158.32, 142.54, 141.47, 138.35, 130.97, 130.66, 129.97, 129.68, 128.97, 127.97, 126.95, 116.66, 115.05, 113.65, 73.05, 52.12, 28.03, 14.03; **MS (EI, 70eV):** m/z = 360[$M^{+\cdot}$, $C_{24}H_{21}FO_2$]; **HRMS (ES-TOF) calcd** for $C_{24}H_{21}FO_2$ 360.1526, found 360.1529.

(E)-1-(4-fluorophenyl)-3-(1-(4-hydroxyphenyl)propylidene)-2,3-dihydro-1H-inden-2-ol (3an): Light yellow semi solid; Yield:70%; **IR ν_{max} (KBr, cm^{-1}):** 3382 (OH str), 2992, 2886 (aromatic C-H str), 1620 (aromatic, C=C str), 1262, 1095, 860, 743; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.88-7.84 (m, 4H), 7.55-7.50 (m, 4H), 7.42-7.39 (m, 2H), 6.87 (t, *J* = 8.0 Hz,

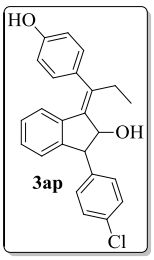
2H), 4.88 (d, *J* = 3.5 Hz, 1H), 4.61 (d, *J* = 3.5 Hz, 1H), 2.38 (q, *J* = 2.0, 7.5 Hz, 2H), 1.37 (t, *J* = 7.0 Hz, 3H), 3.65 (s, br, D_2O exchangeable, 1H), 1.62 (s, br, D_2O exchangeable, 1H), **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):**162.32, 156.54, 142.47, 141.58, 138.65, 130.97, 130.68, 129.97, 129.68, 128.68, 127.96, 126.67, 116.65, 115.05, 113.66, 71.12, 55.08, 26.35, 14.35; **MS (EI, 70eV):** m/z (%) = 360[$M^{+\cdot}$, $C_{24}H_{21}FO_2$]; **HRMS (ES-TOF) calcd** for $C_{24}H_{21}FO_2$ 360.1526, found 360.1528.

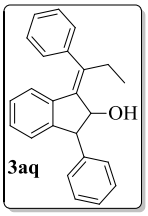


(E)-5-fluoro-3-(4-fluorophenyl)-1-(1-(4-hydroxyphenyl)propylidene)-2,3-dihydro-1H-inden-2-ol (3ao): Light brown semi solid; Yield: 68%; **IR ν_{max} (KBr, cm^{-1}):** 3405 (OH str), 2922, 2875 (aromatic C-H str), 1595 (aromatic, C=C str), 1266, 1089, 858, 731; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 8.00-7.85 (m, 2H), 7.80-7.77 (m, 2H), 7.76-7.69 (m, 2H), 7.47 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.36 (dd, *J* = 2.0, 7.0 Hz, 2H), 6.89 (dd, *J* = 2.0, 8.0 Hz, 2H), 4.50 (d, *J* = 4.0 Hz, 1H), 4.46 (d, *J* = 3.5 Hz, 1H), 2.29 (q, *J* = 2.0, 8.0 Hz, 2H), 1.28 (t, *J* = 8.0 Hz, 3 H), 6.10 (s, br, D_2O exchangeable, 1H), 1.72 (s, br, D_2O exchangeable, 1H); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):**163.58, 158.32, 142.65, 141.47, 138.54, 130.97, 130.68, 129.97, 129.68, 128.97, 127.68, 126.66, 116.65, 115.05, 113.66, 73.05, 52.12, 28.35, 14.59; **MS (EI, 70eV):** m/z (%) = 378[$M^{+\cdot}$, $C_{24}H_{20}F_2O_2$]; **HRMS (ES-TOF) calcd** for $C_{24}H_{20}F_2O_2$ 378.1431, found 378.1434.



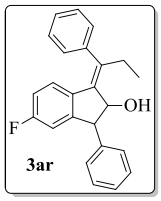
(E)-1-(4-chlorophenyl)-3-(1-(4-hydroxyphenyl)propylidene)-2,3-dihydro-1H-inden-2-ol (3ap): Light brown semi solid; Yield: 67%; **IR ν_{max} (KBr, cm^{-1}):** 3440 (OH str), 2920 (aromatic C-H str), 1592 (aromatic, C=C str), 1406, 1336, 1233, 1091, 771 (C-Cl, str); **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 8.09 (dd, *J* = 2.0, 7.5 Hz, 2H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.27 (t, *J* = 8.5 Hz, 1H), 7.16 (d, *J* = 8.5Hz, 1H), 6.89 (dd, *J* = 2.0, 8.0 Hz, 1H), 4.68 (d, *J* = 3.5 Hz, 1H), 4.21 (d, *J* = 4.5 Hz, 1H), 2.19(q, *J* = 2.0, 7.0 Hz, 2H), 1.19 (t, *J* = 8.0 Hz, 3H), 3.67 (s, br, D_2O exchangeable, 1H), 1.65 (s, br, D_2O exchangeable, 1H); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):**163.35, 142.68, 141.52, 138.75, 131.52, 130.97, 130.68, 129.98, 129.65, 128.68, 127.78, 126.36, 116.62115.35, 113.66, 70.13, 51.12, 26.66, 51.68, 15.68; **MS (EI, 70eV):** m/z (%) = 376[$M^{+\cdot}$, $C_{24}H_{21}ClO_2$], 378[M^{+2}]; **HRMS (ES-TOF) calcd** for $C_{24}H_{21}ClO_2$ 376.1230, found 376.1233.



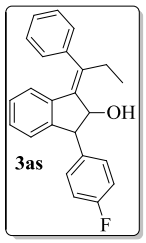


(E)-1-phenyl-3-(1-phenylpropylidene)-2,3-dihydro-1H-inden-2-ol (3aq): Light brown semi solid; Yield: 72%; **IR ν_{max} (KBr, cm^{-1}):** 3425 (OH str), 2935, 2877 (aromatic C-H str), 1585 (aromatic, C=C str), 1266, 1088, 862, 733; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.91-7.66 (m, 4H), 7.6-7.54 (m, 1H), 7.54-7.50 (m, 4H), 7.37-7.34 (m, 2H), 7.33-7.32 (m, 1H), 7.31-23 (m, 2H), 4.72 (d, *J* = 2.0 Hz, 1H), 4.18 (d, *J* = 2.0 Hz, 1H), 2.31 (q, *J* = 1.0, 7.5 Hz, 2H), 1.17 (t, *J* = 7.0 Hz, 3H), 3.30 (s, br, D_2O exchangeable, 1H); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):**157.60, 142.65, 141.32, 138.58, 131.52, 130.97, 130.68, 129.97, 129.68, 128.68, 127.78, 126.35, 121.97, 121.68, 116.66, 115.32, 71.12, 51.03, 26.66, 13.68; **MS (EI, 70eV):** m/z (%) = 326[$M^{+\cdot}$, $C_{24}H_{22}O$]; **HRMS (ES-TOF) calcd** for $C_{24}H_{22}O$ 326.1671, found 326.1673.

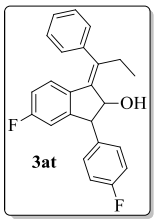
(E)-5-fluoro-3-phenyl-1-(1-phenylpropylidene)-2,3-dihydro-1H-inden-2-ol (3ar): Light yellow semi solid; Yield: 74%; **IR ν_{max} (KBr, cm^{-1}):** 3449 (OH str), 2950 (aromatic C-H str), 1682 (C=O str), 1582 (aromatic, C=C str), 1389, 1275, 1059, 854; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.87-7.85 (m, 4H), 7.55-7.49 (m, 4H), 7.41-7.39 (m, 2H), 6.87 (t, *J* = 7.5 Hz, 2H), 4.58 (d, *J* = 3.5 Hz, 1H), 4.31 (d, *J* = 4.0 Hz, 1H), 2.37 (q, *J* = 2.5, 7.5 Hz, 2H), 1.38 (t, *J* = 7.5 Hz, 3H), 1.88 (s, br, D_2O exchangeable, 1H); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):**160.54, 156.47, 142.32, 141.58, 138.65, 130.97, 130.68, 129.97, 129.68, 128.66, 127.97, 126.68, 116.06, 115.05, 113.65, 71.12, 51.08, 26.35, 13.95; **MS (EI, 70eV):** m/z (%) = 344[$M^{+\cdot}$, $C_{24}H_{21}FO$]; **HRMS (ES-TOF) calcd** for $C_{24}H_{21}F_2O$ 344.1576, found 344.1574



(E)-1-(4-fluorophenyl)-3-(1-phenylpropylidene)-2,3-dihydro-1H-inden-2-ol (3as): Light yellow semi solid; Yield: 70 %; **IR ν_{max} (KBr, cm^{-1}):** 3439 (OH str), 2922 (aromatic C-H str), 1670 (C=O str), 1594 (aromatic, C=C str), 1491, 1399, 1296, 1095; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.88-7.85 (m, 4H), 7.56-7.50 (m, 4H), 7.42-7.39 (m, 2H), 6.87 (t, *J* = 7.0 Hz, 2H), 4.88 (d, *J* = 3.5 Hz, 1H), 4.60 (d, *J* = 3.5 Hz, 1H), 2.38 (q, *J* = 2, 7.5 Hz, 2H), 1.38 (t, *J* = 6.5 Hz, 3H), 1.70 (s, br, D_2O exchangeable, 1 H); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):**160.52, 156.44, 142.32, 141.58, 138.65, 130.97, 130.68, 129.78, 129.68, 128.68, 127.97, 126.68, 116.66, 115.05, 113.65, 71.08, 51.12, 26.35, 13.66; **MS (EI, 70eV):** m/z (%) = 344[$M^{+\cdot}$, $C_{24}H_{21}FO$]; **HRMS (ES-TOF) calcd** for $C_{24}H_{21}F_2O$ 344.1576, found 344.1574.

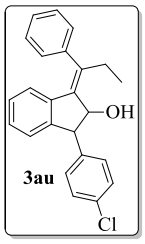


(E)-5-fluoro-3-(4-fluorophenyl)-1-(1-phenylpropylidene)-2,3-dihydro-1H-inden-2-ol (3at):



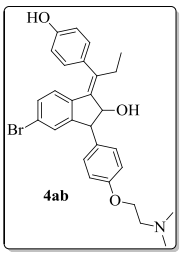
Light yellow semi solid; Yield: 68 %; **IR ν_{max} (KBr, cm^{-1}):** 3466 (OH str), 2920 (aromatic C-H str), 1593 (aromatic, C=C str), 1398, 1281, 1095, 843; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.99-7.86 (m, 2H), 7.80-7.76 (m, 2H), 7.71 (dd, *J* = 2.5, 8.5 Hz, 2H), 7.47 (dd, *J* = 2, 7.5 Hz, 2H), 7.37-7.34 (m, 2H), 6.89 (dd, J = 2.5, 7.5 Hz, 2H), 4.50 (d, *J* = 4.5 Hz, 1H), 4.46 (d, *J* = 4.5 Hz, 1 H), 2.29 (q, *J* = 2, 8 Hz, 2H), 1.28(t, *J* = 8 Hz, 3H), 3.52 (s, br, D_2O exchangeable, 1 H); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):**164.58, 160.32, 142.54, 141.47, 138.65, 130.97, 130.68, 129.97, 129.68, 128.66, 127.97, 126.95, 116.66, 115.05, 113.65, 73.12, 52.05, 28.35, 14.95; **MS (EI, 70eV):** m/z (%) = 362[$M^{+\cdot}$, $C_{24}H_{20}F_2O$]; **HRMS (ES-TOF) calcd** for $C_{24}H_{20}F_2O$ 362.1482, found 362.1482.

(E)-1-(4-chlorophenyl)-3-(1-phenylpropylidene)-2,3-dihydro-1H-inden-2-ol (3au): Light



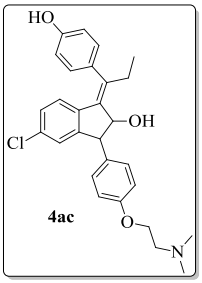
brown semi solid; Yield: 65 %; **IR ν_{max} (KBr, cm^{-1}):** 3426 (OH str), 2923 (aromatic C-H str), 1591 (aromatic, C=C str), 1417, 1395, 1282, 1170, 1092, 757 (C-Cl, str); **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 8.08 (dd, *J* = 2, 8 Hz, 2H), 7.94 (d, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 7.5 Hz, 1H), 7.53 (d, J = 7.5 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.27(t, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 1H), 6.87 (dd, *J* = 2.0, 7.5 Hz, 2H), 4.68 (d, *J* = 3.5 Hz, 1H), 4.21 (d, *J* = 3.5 Hz, 1H), 2.19 (q, *J* = 2, 8 Hz, 2H), 1.10 (t, *J* = 8.5 Hz, 3H), 1.60 (s, br, D_2O exchangeable, 1H); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):**156.60, 142.32, 141.58, 138.65, 131.52, 130.97, 130.68, 129.97, 129.68, 128.68, 127.7, 126.35, 116.66, 115.32, 113.65, 71.03, 51.12, 26.68, 13.66; **MS (EI, 70eV):** m/z = 360[$M^{+\cdot}$, $C_{24}H_{21}ClO$], 362[M^{+2}]; **HRMS (ES-TOF) calcd** for $C_{24}H_{21}ClO$ 360.1281, found 360.1283.

(E)-5-bromo-3-(4-(2-(dimethylamino)ethoxy)phenyl)-1-(1-(4-hydroxy phenyl)propylidene)-2,3-dihydro-1H-inden-2-ol (4ab):

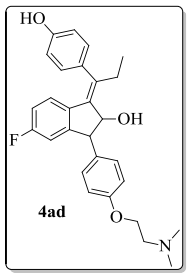


Yellow semi solid; Yield: 55%; **IR ν_{max} (KBr, cm^{-1}):** 3453 (OH str), 2957 (aromatic C-H str), 1587 (aromatic, C=C str), 1385, 1274, 1064, 851; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.88 (dd, *J* = 8.0, 2.5 Hz, 2H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.69-7.59 (m, 4H), 7.35-7.32 (m, 1H), 6.95(d, *J* = 9 Hz, 3 H), 5.34 (s, 1H), 4.87 (d, *J* = 2.0 Hz, 1H), 4.48 (d, *J* = 2.0 Hz, 1H), 4.26 (t, *J* = 2.5 Hz, 2H), 3.52 (s, 1H), 2.74 (s, 6H), 2.58 (t, *J* = 2.5 Hz, 2H), 2.12 (q, *J* = 7.5, 1.5 Hz, 2H,), 1.04 (t, *J* = 7.0 Hz, 3H); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):** 163.14, 161.127, 159.41, 157.88, 156.62, 140.112, 139.53,

136.28, 133.63, 131.54, 130.78, 129.62, 129.30, 124.37, 123.13, 116.12, 115.11, 73.13, 68.13, 62.15, 52.12, 47.45, 27.45, 14.10; **HRMS (ES-TOF) calcd** for $C_{28}H_{30}BrNO_3$ 507.1409, found 507.1407.



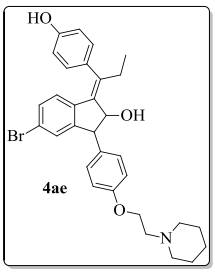
(E)-5-chloro-3-(4-(2-(dimethylamino)ethoxy)phenyl)-1-(1-(4-hydroxy phenyl)propylidene)-2,3-dihydro-1H-inden-2-ol (4ac): Yellow semi solid; Yield: 52%; **IR ν_{max} (KBr, cm^{-1}):** 3408 (OH str), 2917 (aromatic C-H str), 1589 (aromatic, C=C str), 1489, 1415, 1288, 1177, 1091, 1014, 929 and 701; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.88 (t, *J* = 8 Hz, 2H), 7.85 (t, *J* = 8 Hz, 2H), 7.88 -7.81 (m, 3H), 7.79 – 7.61 (m, 4H), 7.59 – 7.32 (m, 1H), 6.94 (d, *J* = 8.0 Hz, 3H), 5.34 (s, 1H), 4.87 (d, *J* = 2.0 Hz, 1H), 4.48 (d, *J* = 2.0 Hz, 1H), 4.26 (t, *J* = 2.5 Hz, 2H), 3.52 (s, 1H), 2.74 (s, 6H), 2.58 (t, *J* = 2.5 Hz, 2H), 2.12 (q, *J* = 7.5, 1.5 Hz, 1H), 1.04 (t, *J* = 7.0 Hz, 3H); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):** 160.07, 159.62, 144.00, 143.57, 137.30, 136.65, 133.00, 130.92, 129.62, 129.29, 128.66, 128.07, 122.30, 117.13, 116.93, 73.13, 66.26, 61.16, 51.79, 46.79, 31.19, 14.92; **HRMS (ES-TOF) calcd** for $C_{28}H_{30}ClNO_3$ 463.1914, found 463.1915.



(E)-3-(4-(2-(dimethylamino)ethoxy)phenyl)-5-fluoro-1-(1-(4-hydroxy phenyl) propylidene)-2,3-dihydro-1H-inden-2-ol (4ad): Light yellow semi solid; Yield:52%; **IR ν_{max} (KBr, cm^{-1}):** 3393 (OH str), 2953 (aromatic C-H str), 1575 (aromatic, C=C str), 1464, 1403, 1275, 1152, 1081, 1002, 911 and 725; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.91 – 7.64 (m, 3H), 7.63 - 7.51 (m, 3H), 7.37 – 7.33 (m, 2H), 7.32 – 7.21 (m, 3H), 5.75 (s, 1H), 4.79 (d, *J* = 2.0 Hz, 1H), 4.18 (d, *J* = 2.0 Hz, 1H), 4.07 (d, *J* = 2.5 Hz, 2H), 3.6 (s, 1H), 3.12 (s, 6H), 2.50 (t, *J* = 2.5 Hz, 2H), 2.32(q, *J* = 8.5, 1.5 Hz, 2H), 1.17 (t, *J* = 7.0, Hz, 3H); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):** 163.14, 161.12, 159.41, 157.87, 156.62, 140.11, 139.52, 136.27, 133.62, 131.54, 130.77, 129.62, 129.30, 124.36, 123.12, 116.12, 115.10, 73.13, 68.12, 62.14, 52.81, 47.45, 27.45, 14.10; **HRMS (ES-TOF) calcd** for $C_{28}H_{30}FNO_3$ 447.2210, found 447.2209.

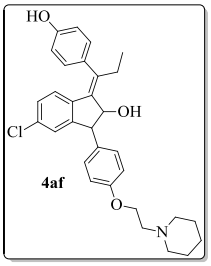
(E)-5-bromo-1-(1-(4-hydroxyphenyl)propylidene)-3-(4-(2-(piperidin-1-yl)ethoxy)phenyl)-2,3-dihydro-1H-inden-2-ol (4ae): Yellow semi solid; Yield: 55%; **IR ν_{max} (KBr, cm^{-1}):** 3359 (OH str), 2957 (aromatic C-H str), 1572 (aromatic, C=C str), 1458, 1412, 1278, 1156, 1088, 1013, 915 and 732; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 8.03 (d, *J* = 8.0 Hz, 3H), 7.82 (d, *J* = 7.0 Hz, 2H), 7.76 (dd, *J* = 2.0, 7.0 Hz, 4H), 7.49 (d, *J* = 9.0 Hz, 1H),7.12 (t, *J* = 7.5 Hz,

3H), 5.56 (s, 1H), 4.75 (d, *J* = 2.0 Hz, 1H), 4.36 (d, *J* = 2.0 Hz, 1H), 4.14 (t, *J* = 2.5 Hz, 2H),

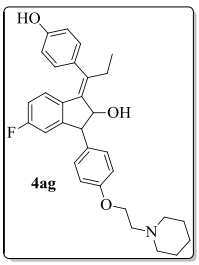


3.75 (s, 1H), 3.05(t, *J* = 2.5, 2H), 2.65(t, *J* = 3.0 Hz, 4H), 2.33 (q, *J* = 1.5, 9.0 Hz, 2H), 1.64-1.61 (m, 2 H), 1.51 (t, , *J* = 2.5 Hz, 2H), 1.02 (t, , *J* = 8.0 Hz, 3H); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):** 161.13, 157.13, 156.41, 142.62, 140.10, 139.54, 136.27, 133.63, 131.54, 130.78, 129.62, 129.30, 122.37, 122.13, 116.19, 115.19, 73.13, 69.15, 58.10, 57.45, 52.81, 29.17, 25.14, 23.10, 12.56; **HRMS (ES-TOF) calcd** for $C_{31}H_{34}BrNO_3$ 547.1722, found 547.1724.

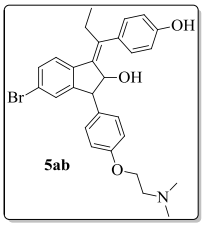
(E)-5-chloro-1-(1-(4-hydroxyphenyl)propylidene)-3-(4-(2-(piperidin-1-yl)ethoxy)phenyl)-



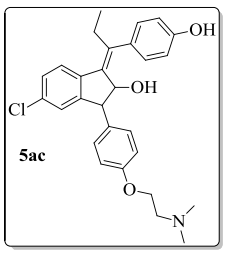
2,3-dihydro-1H-inden-2-ol (4af): Brown semi solid; Yield: 55%; **IR ν_{max} (KBr, cm^{-1}):** 3419 (OH str), 2933, 2879 (aromatic C-H str), 1598 (aromatic, C=C str), 1262, 1083, 862, 739; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.96 (t, *J* = 9.0 Hz, 2H), 7.55-7.47 (m, 4H), 7.45-7.39 (m, 3H), 6.99-6.97 (m, 2H), 5.77 (s, 1H), 4.64 (d, *J* = 2.0 Hz, 1H), 4.21 (d, *J* = 2.0 Hz, 1H), 4.04 (t, *J* = 2.5 Hz, 2H), 3.75 (s, 1 H), 2.95 (t, *J* = 2.5 Hz, 2H), 2.58 (t, *J* = 2.5 Hz, 4H), 2.35 (q, *J* = 7.0, 1.5 Hz, 2H), 1.48 (t, *J* = 2.5 Hz, 4H), 1.01 (t, *J* = 7.5 Hz, 3H); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm): 160**.12, 158.41, 144.87, 144.62, 140.10, 139.54, 136.27, 133.63, 131.54, 130.78, 129.62, 124.37, 124.13, 117.69, 117.19, 73.15, 69.13, 58.10, 57.45, 52.81, 27.17, 25.14, 23.10, 13.13; **HRMS (ES-TOF) calcd** for $C_{31}H_{34}ClNO_3$ 503.2227, found 503.2227.



(E)-5-fluoro-1-(1-(4-hydroxyphenyl)propylidene)-3-(4-(2-(piperidin-1-yl)ethoxy)phenyl)-2,3-dihydro-1H-inden-2-ol (4ag): Yellow semi solid; Yield: 52%; **IR ν_{max} (KBr, cm^{-1}):** 3438 (OH str), 2953, 2882 (aromatic C-H str), 1609 (aromatic, C=C str), 1271, 1107, 846, 729; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 8.02 (d, *J* = 8.0 Hz, 2H), 7.77 (t, *J* = 7.0 Hz, 2H), 7.61 (t, *J* = 7.0 Hz, 3H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.13 (t, *J* = 8.0 Hz, 3H), 5.55 (s, 1H), 4.74 (d, *J* = 2.0 Hz, 1H), 4.36 (d, *J* = 2.0 Hz, 1H), 4.14 (t, *J* = 2.5 Hz, 2H), 3.75 (s, 1H), 3.048 (t, *J* = 2.5 Hz, 2H), 2.65 (t, *J* = 2.5 Hz, 4H), 2.33 (q, *J* = 2.5, 7.5 Hz, 2H), 1.65 – 161 (m, 2H), 1.51 (t, *J* = 2.5 Hz, 4H), 1.02 (t, *J* = 8.0 Hz, 3H); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):** 161.12, 157.12, 156.41, 142.62, 140.10, 139.54, 136.27, 133.63, 131.54, 130.78, 129.62, 129.30, 122.37, 122.13, 116.19, 115.19, 73.13, 69.15, 58.10, 57.45, 52.81,27.17, 25.14, 23.10, 12.55; **HRMS (ES-TOF) calcd** for $C_{31}H_{34}FNO_3$ 487.2523, found 487.2524.

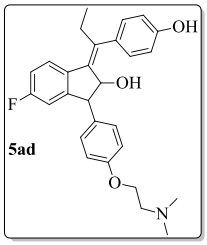


(Z)-5-bromo-3-(4-(2-(dimethylamino)ethoxy)phenyl)-1-(1-(4-hydroxyphenyl)propylidene)-2,3-dihydro-1H-inden-2-ol (5ab): Brown semi solid; Yield: 8%; **IR ν_{max} (KBr, cm^{-1}):** 3415 (OH str), 2934, 2875 (aromatic C-H str), 1599 (aromatic, C=C str), 1267, 1085, 865, 635**; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.89-7.69 (m, 4H), 7.55-7.48 (m, 2H), 6.97-6.81(m, 5H), 4.69 (d, *J* = 2.5 Hz, 2H), 4.28 (d, *J* = 2.5 Hz, 2H), 4.27 (t, *J* = 2.5 Hz, 2H), 2.93 (s, 6H), 2.87 (t, *J* = 2.5 Hz, 2H), 1.78 (q, *J* = 8.0, 2.5 Hz, 2H), 0.67 (t, *J* = 7 Hz, 3H); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):** 163.14, 161.22, 159.42, 157.87, 156.62, 140.12, 139.53, 136.27, 133.63, 132.54, 130.77, 129.62, 129.30, 124.37, 123.13, 116.12, 115.10, 71.14, 66.13, 60.13, 50.17, 46.45, 25.45, 12.20; **HRMS (ES-TOF) calcd** for $C_{28}H_{30}BrNO_3$ 507.1409, found 507.1407.

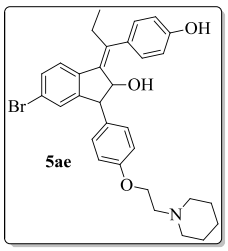


(Z)-5-chloro-3-(4-(2-(dimethylamino)ethoxy)phenyl)-1-(1-(4-hydroxyphenyl)propylidene)-2,3-dihydro-1H-inden-2-ol (5ac): Brown semi solid; Yield: 10%; **IR ν_{max} (KBr, cm^{-1}):** 3451 (OH str), 2955 (aromatic C-H str), 1584 (aromatic, C=C str), 1387, 1275, 1062, 855, 725 (C-Cl, str); **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.90 -7.85 (m, 2H), 7.54 – 7.59 (m, 2H), 7.10 – 7.03 (m, 3H), 7.00- 6.93 (m, 4H), 5.52 (s, 1H), 4.52 (d, *J* = 2.0 Hz, 1H), 4.18 (d, *J* = 2.0 Hz, 1H), 4.06 (t, *J* = 2.5 Hz, 2H), 3.50 (s, 1H), 2.86 (s, 6H), 2.63 (t, *J* = 2.5 Hz, 2 H), 1.67 (q, *J* = 1.5, 7.5 Hz, 2H), 0.67 (t, *J* = 6.5 Hz, 3H); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):** 160.12, 159.62, 159.29, 144.01, 143.62, 137.12, 136.65, 133.09, 130.92, 129.87, 129.29, 128.66, 128.07, 122.30, 117.29, 116.93, 72.33, 65.26, 61.17, 51.76, 45.69, 26.31, 11.92; **HRMS (ES-TOF) calcd** for $C_{28}H_{30}ClNO_3$ 463.1914, found 463.1912.

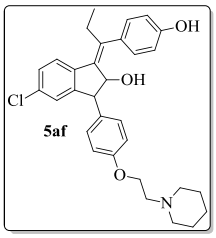
(Z)-3-(4-(2-(dimethylamino)ethoxy)phenyl)-5-fluoro-1-(1-(4-hydroxyphenyl)propylidene)-2,3-dihydro-1H-inden-2-ol (5ad): Brown semi solid; Yield: 9%; **IR ν_{max} (KBr, cm^{-1}):** 3382 (OH str), 2992, 2886 (aromatic C-H str), 1620 (aromatic, C=C str), 1262, 1095, 860, 743; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.91 – 7.71 (m, 4H), 7.70-7.42 (m, 4H), 6.96 (t, *J* = 8.5 Hz, 1H), 6.86 (t, *J* = 8.5 Hz, 2H), 5.29 (s, 1H), 4.50 (d, *J* = 2.0 Hz, 1H), 4.18 (d, *J* = 2.0 Hz, 1H), 4.03 (t, *J* = 2.5 Hz, 2H), 3.39 (s, 1H), 2.78 (s, 6H), 2.66 (t, *J* = 2.5 Hz, 2H), 1.78 (q, *J* = 2.5, 6.0 Hz, 2H), 0.68 (t, *J* = 6.5 Hz, 3H); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):**163.14, 161.12, 159.41, 157.87, 156.62, 140.11, 139.52, 136.27, 133.62, 131.54,



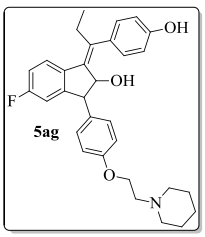
130.77, 129.62, 129.30, 124.36, 123.12, 116.17, 115.10, 71.13, 66.12, 60.13, 50.17, 46.45, 25.45, 12.10; **HRMS (ES-TOF) calcd** for $C_{28}H_{30}FNO_3$ 447.2210, found 447.2209..



(Z)-5-bromo-1-(1-(4-hydroxyphenyl)propylidene)-3-(4-(2-(piperidin-1-yl)ethoxy)phenyl)-2,3-dihydro-1H-inden-2-ol (5ae): Light yellow semi solid; Yield:10 %; **IR ν_{max} (KBr, cm^{-1}):** 3444 (OH str), 2922 (aromatic C-H str), 1595 (aromatic, C=C str), 1418, 1328, 1235, 1129(C-O-C, str), 1091; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.91-7.86 (m, 3H), 7.71-7.51 (m, 1H), 7.49-7.26 (t, *J* = 8.0 Hz, 4H), 7.12-6.85 (m, 4H), 5.59(s, 1H), 4.59 (d, *J* = 2.0 Hz, 1H), 4.18 (d, *J* = 2.0 Hz, 1H), 2.98 (t, *J* = 2.5 Hz, 2H), 2.87(t, *J* = 2.5 Hz, 4H), 4.02 (t, *J* = 2.5 Hz, 2H), 1.87 (q, *J* = 1.5, 8.0 Hz, 2H), 1.34 (t, *J* = 2.5 Hz, 2H), 1.26 (t, *J* = 2.5 Hz, 4H), 0.78 (t, *J* = 7.0 Hz, 3H)); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):** 161.124, 157.13, 156.41, 142.63, 140.10, 139.54, 136.27, 133.63, 131.54, 130.77, 129.62, 129.30, 122.36, 122.12, 116.19, 115.19, 73.11, 69.15, 58.48, 57.55, 52.81, 25.25, 23.14, 21.30, 10.77; **HRMS (ES-TOF) calcd** for $C_{31}H_{34}BrNO_3$ 547.1722, found 547.1724.

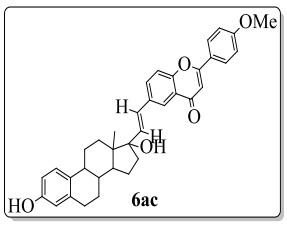


(Z)-5-chloro-1-(1-(4-hydroxyphenyl)propylidene)-3-(4-(2-(piperidin-1-yl)ethoxy)phenyl)-2,3-dihydro-1H-inden-2-ol (5af): Light yellow semi solid; Yield: 8%; **IR ν_{max} (KBr, cm^{-1}):** 3431 (OH str), 2951, 2880 (aromatic C-H str), 1608 (aromatic, C=C str), 1271, 1109, 843, 729; **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.87 (t, *J* = 8.0 Hz, 3H), 7.52-7.11 (m, 3H), 7.01-6.92 (m, 5H), 5.61 (s, 1H), 4.67 (d, *J* = 2.0 Hz, 1H), 4.23 (d, *J* = 2.0 Hz, 1H), 4.11 (t, *J* = 2.5 Hz, 2H), 2.67-2.52 (m, 6 H), 1.86 (q, *J* = 8.5, 1.5 Hz, 2H), 1.49-1.25 (m, 6H), 0.68 (t, *J* = 7.0 Hz, 3H); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):** 160.12, 158.41, 144.87, 144.67, 140.10, 139.54, 136.22, 133.62, 131.50, 130.77, 129.64, 129.32, 124.36, 123.12, 117.69, 117.10, 73.19, 69.13, 58.10, 57.44, 52.85, 25.67, 23.83, 21.14, 11.10; **HRMS (ES-TOF) calcd** for $C_{31}H_{34}ClNO_3$ 503.2227, found 503.2228.

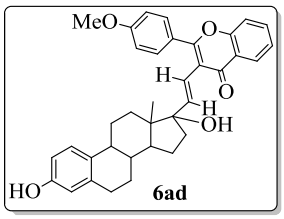


(Z)-5-fluoro-1-(1-(4-hydroxyphenyl)propylidene)-3-(4-(2-(piperidin-1-yl)ethoxy)phenyl)-2,3-dihydro-1H-inden-2-ol (5ag): Light yellow semi solid; Yield: 10%; **IR ν_{max} (KBr, cm^{-1}):** 3440 (OH str), 2920 (aromatic C-H str), 1592 (aromatic, C=C str), 1408, 1338, 1231, 1125(C-O-C, str), 1091, 650 (C-F, str); **^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm):** 7.91-7.18 (m, 3H), 7.70-7.42 (m, 4H), 6.96 (t, *J* = 8 Hz, 1H), 6.86 (t, *J* = 8.0 Hz, 3H), 5.59 (s, 1H), 4.59 (d, *J* = 2

Hz, 1H), 4.18 (d, *J* = 2.0 Hz, 1H), 4.03 (t, *J* = 2.5 Hz, 3H), 3.45 (s, 1H), 2.98 (t, *J*=2.5 Hz, 2H), 2.87 (t, *J* = 2.5 Hz , 4H), 1.87 (q, *J* = 8.0, 1.0 Hz, 2H), 1.34 (t, *J* = 2.5 Hz, 4H), 1.26 (t, *J* = 2.5 Hz, 4H), 0.78 (t, *J* = 7.0 Hz, 3H); **^{13}C- ($CDCl_3$, 125 MHz) δ (ppm):** 161.12, 157.13, 156.41, 142.62, 140.10, 139.54, 136.27, 133.62, 131.55, 130.77, 129.62, 129.30, 122.36, 122.12, 116.19, 115.19, 73.10, 69.14, 58.45, 57.55, 52.81, 25.25, 23.14, 21.30, 10.77; **HRMS (ES-TOF) calcd** for $C_{31}H_{34}FNO_3$ 487.2523, found 487.2525.



(E)-6-(2-(3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)vinyl)-2-(4-methoxyphenyl)-4H-chromen-4-one (6ac): Cream color solid, yield: 70%, **^{1}H NMR($CDCl_3$, 500 MHz):** 8.26 (s, 1H), 7.87 (d, J = 7Hz, 2H), 7.70 (d, J= 8.5Hz, 1H), 7.50 (d, J = 8.5Hz, 2H), 7.08 (d, J = 8.5Hz, 1H), 7.01 (d, J = 8.5Hz, 2H), 6.76 (s, 1H), 6.69-6.59 (m, 3H), 3.88 (s, 3H), 3.70 (s, br, D2O exchangeable, 1H, OH), 2.83-2.80 (m, 2H), 2.24-1.54 (m, 13H), 1.01 (s, 3H); **HRMS (ES-TOF) calcd** for $C_{36}H_{36}NaO_5$ (M+Na) 571.2460, found 571.2481.



(E)-3-(2-(3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)vinyl)-2-(4-methoxyphenyl)-4H-chromen-4-one (6ad): Cream color solid, yield: 65%, **^{1}H NMR($CDCl_3$, 500 MHz):** 8.26 (s, 1H), 7.87 (d, J = 7Hz, 2H), 7.70 (d, J= 8.5Hz, 1H), 7.50 (d, J = 8.5Hz, 2H), 7.08 (d, J = 8.5Hz, 1H), 7.01 (d, J = 8.5Hz, 2H), 6.76 (s, 1H), 6.69-6.59 (m, 3H), 3.88 (s, 3H), 3.70 (s, br, D2O exchangeable, 1H, OH), 2.83-2.80 (m, 2H), 2.24-1.54 (m, 13H), 1.01 (s, 3H). **IR ν_{max} (KBr, cm^{-1}):** 3650, 3501, 1682, 1400, 1215, 1034; **HRMS (ES-TOF) calcd** for $C_{36}H_{36}NaO_5$ (M+Na) 571.2460, found 571.2481.

5.6. REFERENCES

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CHAPTER-4

SeO_2 in water: A mild and efficient promoter for deprotection of acetyl, methoxymethyl and tetrahydropyranyl ethers and sequel oxidation of carbonyl carbons

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SeO_2 in water: A mild and efficient promoter for deprotection of acetyl, methoxymethyl and tetrahydropyranyl ethers and sequel oxidation of carbonyl carbons

6.1. INTRODUCTION

Protection and deprotection of the functional groups is the most frequent used strategies in the multi-steps organic syntheses. In particular, the protection and the deprotection of hydroxyl and phenolic groups is extremely important because of its presence of a number of compounds of natural products, biological and synthetic compounds such as carbohydrates, macrolides, peptides, steroids, nucleotides and polyethers.[1] The protection of hydroxyl groups with 3,4-dihydro-2H-pyran (DHP) is the most common method because of the stability of the product, 2-tetrahydropyranyl ethers (THPEs) in the strong basic conditions such as Grignard reagents, organolithium, metal hydrides, catalytic hydrogenation, alkylating and acylating conditions.[2] Similarly, methoxymethyl chloride (MOMCl) and acetyl chloride/acetic anhydride (CH_3COCl/Ac_2O) reagents are used for the hydroxyl and phenolic groups protection.[3]

Deprotection of these groups (Acetyl, THP and MOM ethers) therefore required efficient methods to avoid the product decomposition and/or loss of other functional groups in the molecules. Several catalytic methods have been explored for the selective deacetylation of alcohols and phenols under acidic and basic conditions. For example, the deprotection of acetates such as NaOMe,[4a] micelles,[4b] Zn-MeOH,[4c] Cyclodextrins,[4d] enzymes,[4e] mettallo-enzyme,[4f] metal complexes,[4g] and antibodies,[4h] montmorillonite k-10,[4i] I_2,[4j] $NaBO_3$,[4k] and $HCOONH_4$-SiO_2,[4l] for the detetrahydropyranylation include protic acids,[5a-d] Lewis acids like BF_3-etherate,[5e] LiBr,[5f] $LiBF_4$,[5g] LiOTf,[5h] $LiClO_4$,[5i] $Sc(OTf)_3$,[5j] $In(OTf)_3$,[5k] I_2,[5l] $InCl_3$,[5m] $ZrCl_4$,[5n] $CuCl_2$,[5o] NH_4Cl,[5p] graphite,[5q] clay materials,[5r] silica-supported sulfuric acid,[5s] electrogenerated acids,[5t] bis(trimethylsylyl)sulphate,[5u] Distannoxane,[5v] triphenylphosphine dibromide,[5w] DDQ,[5x] and heteropoly acids.[5y] Similarly, for the demethoxymethylation include HCl,[6a] BBr_3,[6b] pyridinium *p*-toluene sulphonate under strong acidic condition,[6c] $ZnBr_2$ and $TiCl_4$ in aprotic solvents,[6d] Me_2BBr[6e] and $(i\text{-}PrS)_2BBr$.[6f] Most of these methods have one or other drawbacks such as long reaction time, low yields, reflux at high temperature and tedious workup procedures.[7] Hence, there is still scope to develop mild and efficient methods in the deacetylation, detetrahydropyranylation and demethoxymethylation of hydroxyl of alcoholic and phenolic groups.

In the alpha carbonyl carbon (active methyl and methylene) oxidation to dicarbonyl molecule, various reagents and reaction conditions have been explored that include ammonium chlorochromate,[8a] I_2,[8b] CrO_3-NH_4Cl,[8c] HBr,[8d] MeSSMe-$CuCl_2$-CuO,[8e] $Cu(OAc)_2.H_2O$,[8f] P-Me-sulphonic acid,[8g] SeO_2-DMSO,[8h] KI+O_2-t-$BuNH_2$.[8i] However, SeO_2 is not reported for one-pot deprotection and alpha carbonyl carbons oxidation in eco-friendly environment. In continuation of our interest [9] to develop new methods for the organic synthesis, herein, we report an efficient green protocol of deprotection of acetyl, tetrahydropyranyl and methoxymethyl ethers and sequel oxidation of alpha carbonyl carbons to dicarbonyl group using SeO_2 in water as a novel reagent.

6.2. OBJECTIVE

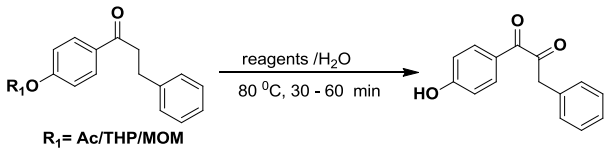
Protection and deprotection is a most common conversion in multi step organic synthesis. The MOM, THP ethers and esters of hydroxyl group is a very frequently used strategy. These methods are attractive because they are easy to deprotect and stable enough in basic media and reaction involving acylating agent like Grignard, lithium alkyl. As a part of ongoing research program to developed the methods for the deprotection, our goal is to developed cheap, inexpensive, green protocol for the deprotection of hydroxyl group and we observed that the SeO_2-water system provided an efficient one-pot green protocol for the deprotection of Acetyl, THP and MOM ethers in alcohols and phenols and sequel oxidation of alpha carbonyl carbons to dicarbonyl compound at 80 ^{0}C within 30-60 min.

6.3. RESULTS AND DISSCUSSION

6.3.1. Optimization reaction conditions by using different oxidizing agents

We screened different oxidizing agents in water for the deprotection and sequel oxidation, where CrO_3, DDQ and PCC in H_2O failed to give the product **(Table 1, entries 1, 3** & **6**), OsO_4 and MnO_2 gave a poor yield (5-10%) at 80 ^{0}C after 6h **(Table 1, entry 2** & **7)**,while, substrate:SeO_2 (1:3 ratio) in 1ml H_2O gave the optimal yield (85-95%) in the one-pot deacetylation, detetrahydropyranylation and sequel oxidation of alpha carbonyl carbons to dicarbonyl group at 80 ^{0}C within 1h **(Table 1, entry 5**). When, we used substrate:SeO_2 (1:1ratio) in 1ml H_2O gave only deprotection product in 95 % yields in 1h-3h **(Table 1, entry 4)**. The novel method also used for the one-pot demethoxymethylation and sequel oxidation of alpha carbon but gave moderate product yields (40%) at 80 ^{0}C in 1h. Therefore, substrate:SeO_2 (1:3 ratio) in 1ml H_2O was selected as an optimized condition.

Table 1. Optimization of deprotection conditions for Ac, THP and MOM groups and sequel oxidation of alpha carbonyl carbon

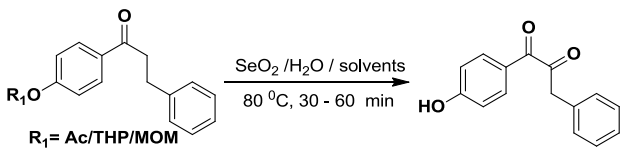


Entry	Substrate.:Reagent (equiv.)	Time (h)	Yield[a] (%) (deacetylation)	Yield[b] (%) (detetrahydropyranylation)
1	Sub.:CrO_3(1:1)	24 h	No reaction	No reaction
2	Sub.:OsO_4(1:1)	6 h	8	5
3	Sub.:DDQ(1:1)	24 h	No reaction	No reaction
4	Sub.:SeO_2(1:1)	1h-3h	Only deprotection	Only deprotection
5	Sub.:SeO_2(1:3)	1 h	95	94
6	Sub.:PCC(1:1)	6 h	No reaction	No reaction
7	Sub.:MnO_2(1:1)	6h	10	10

6.3.2. Solvent effect

In the case of low soluble or insoluble compounds, even under optimized conditions, the reaction gave moderate yield (35%). Therefore, 3-4 drops of organic solvents (THF, dioxane, DMF, DEE, ethanol, methanol, $CHCl_3$ and DMSO) were used to improve the solubility, in which THF and dioxane gave maximum 60% and 94% yields respectively (**Table 2, entries 1-10**). However, the SeO_2 in organic solvents without H_2O failed to give the product **(Table 2, entry 2)**.

Table 2. Solvents effects in deprotection of Ac, THP and MOM groups and sequel oxidation of alpha carbons.



Entry	H_2O(1ml):Solvents	Yield[a]	Yield[b]

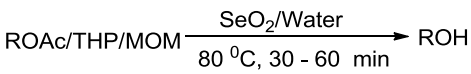
	(3-4 drops)	(%)	(%)
1	H_2O	30	35
2	Organic solvents*	0	0
3	H_2O:THF	65	60
4	H_2O:Dioxane	95	94
5	H_2O:DMF	50	40
6	H_2O:DEE	25	20
7	H_2O:Ethanol	0	0
8	H_2O:methanol	0	0
9	H_2O:$CHCl_3$	0	0
10	H_2O:DMSO	50	40

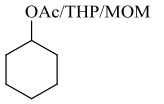
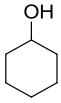
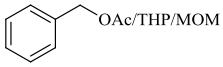
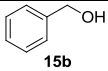
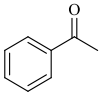
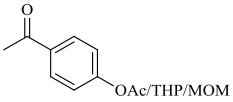
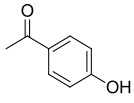
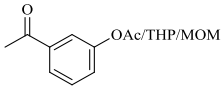
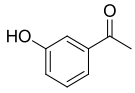
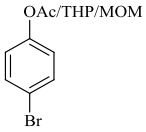
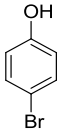
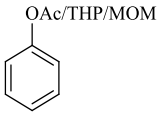
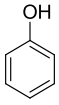
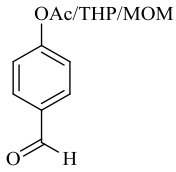
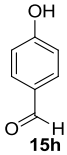
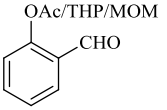
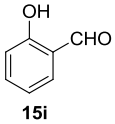
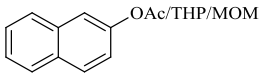
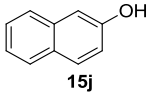
[a] Yields of deacetylation,[b] Yields of detetrahydropyranylation, *DMSO, Dioxane, THF, DMF

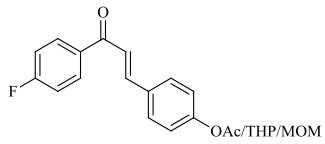
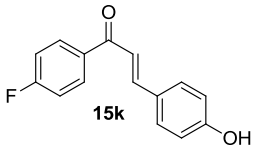
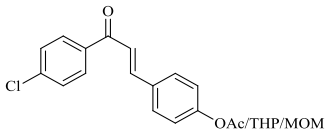
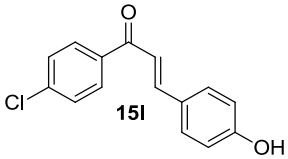
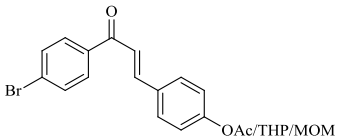
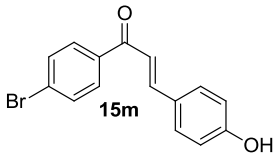
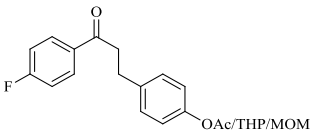
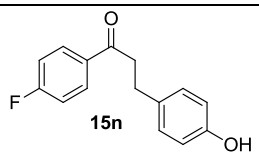
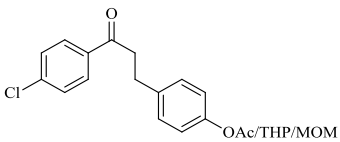
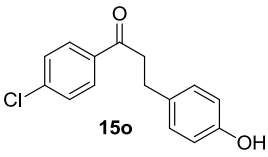
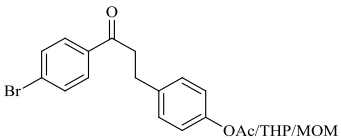
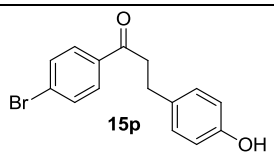
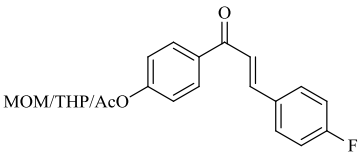
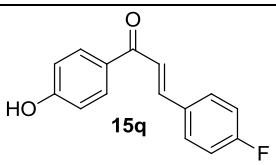
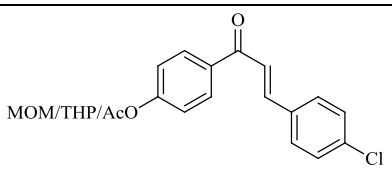
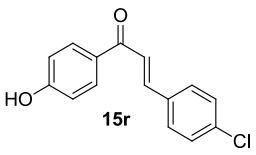
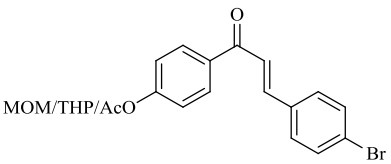
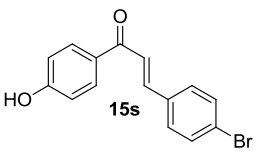
6.3.3. Examples of the deprotection of acetyl, THP and MOM ethers

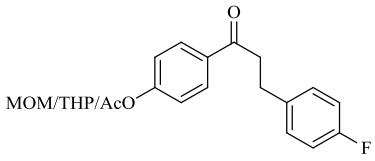
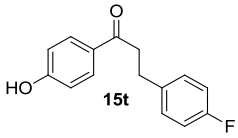
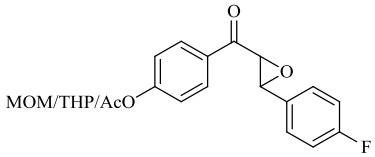
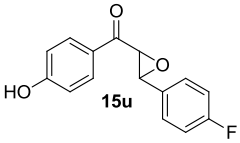
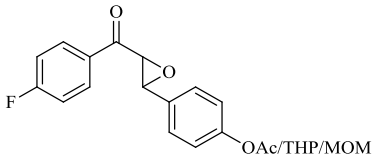
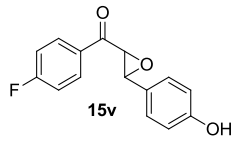
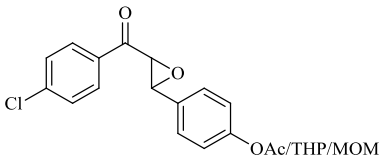
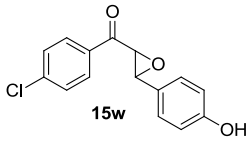
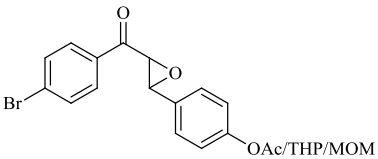
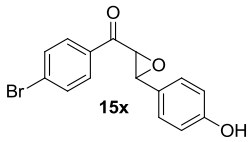
Only deacetylation, detetrahydropyranylation and demethoxymethylation products were afforded using substrate:SeO_2 (1:1ratio) in 1ml H_2O at 80 ^{0}C (Table 3, entries 1-10). In the case of entry **11- 24** of chalcone, dihydrochalcone, epoxide only acetyl, THP and MOM removal were observed without sequel oxidation of alpha carbonyl carbon due to used of substrate:SeO_2 (1:1 ratio) in H_2O system. The products were confirmed on the basis of their spectral data (supporting information). For example, product **15q,** the ^{1}H-NMR spectra showed the characteristic two triplet peak at δ 2.80 & 2.73 ppm, J= 6.0 - 6.5 Hz for -CH_2-CH_2- protons and broad peak at δ 5.45 ppm for hydroxyl group. IR value at 3425 cm^{-1} for –OH groups indicates only deprotection without oxidation of alpha carbonyl carbon. In ^{13}CNMR spectra, the characteristic peak at δ 199.12 ppm for one –CO- groups and peak at 45.81 & 30.17 of -CH_2-CH_2- groups indicates only deprotection.

Table 3. Examples of deprotection of Ac, THP and MOM groups in alcohols and phenols.



Entry	ROAc/THP/MOM	ROH	Time (min)	Yield[a] (%)	Yield[b] (%)	Yield[c] (%)
1		 **15a**	30	92	89	40
2		 **15b**	30	92	88	40
3		 **15c**	60	--	--	--
4		 **15d**	30	95	85	35
5		 **15e**	30	94	90	32
6		 **15f**	30	95	92	35
7		 **15g**	30	90	93	40
8		 **15h**	30	94	92	35
9		 **15i**	30	93	95	40
10		 **15j**	30	95	95	32

11			30	96	95	35
12			30	97	96	40
13			30	93	94	32
14			30	90	85	30
15			30	92	85	30
16			30	90	87	35
17			30	93	95	38
18			30	96	94	40
19			30	94	94	35

20			30	92	90	32
21			30	95	90	35
22			30	94	95	35
23			30	95	96	40
24			30	90	96	35

Yields **(15a-15x)** from [a] ROAc, [b] ROTHP and [c] ROMOM respectively.

6.3.4. Examples of the deprotection of acetyl, THP and MOM ethers and sequel oxidation of alpha carbonyl carbon

Under optimized reaction conditions using substrate:SeO_2,1:3 ratio, the reaction gave the deprotection and sequel oxidation of methylene carbon alpha carbonyl carbon to carbonyl groups in excellent yield (85-95%) for the deacetylation, detetrahydropyranylation and moderate yield 30-40% for demethoxymethylation (Table 4, entries 3-10) within 30-60 min at 80 ^{0}C. Interestingly, acetyl and THP removal and sequel oxidation of methylene carbon alpha carbonyl carbon to carbonyl groups were observed in the protected hydroxyl acetophenone and dihydrochalcones to give the corresponding hydroxy dicarbonyl derivatives **16e-16j** in excellent yield (85-95%).

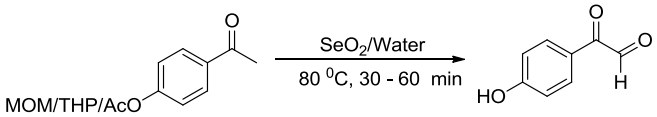
We used excess of substrate:SeO_2, in1:4, 1:5 & 1:6 ratios, also altering the reaction time from 60-120 minutes to checked for the oxidation of another alpha carbon, but no further oxidation was observed, (Table 4, entries 11), also under optimized condition we took

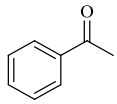
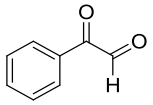
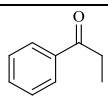
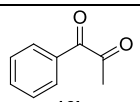
dicarbonyl compounds for further alpha carbon oxidation, but no change was observed. (Table 4, entries 12)

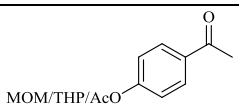
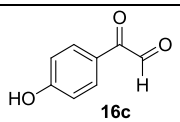
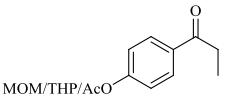
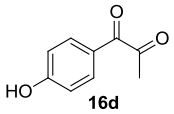
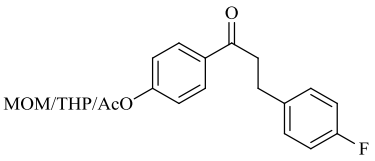
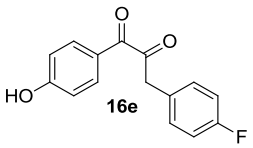
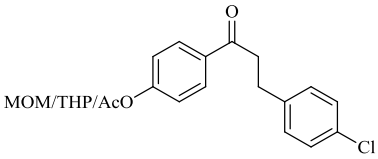
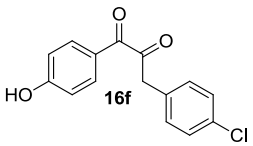
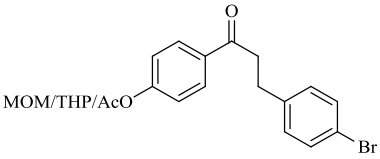
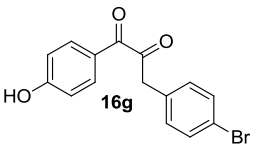
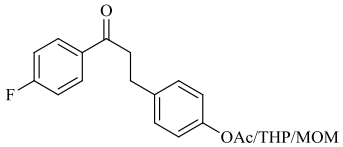
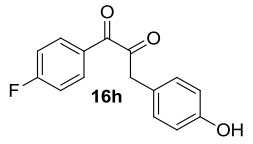
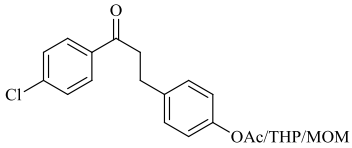
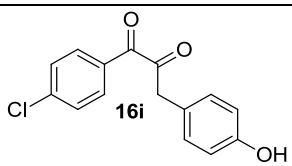
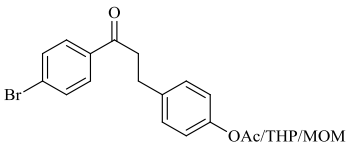
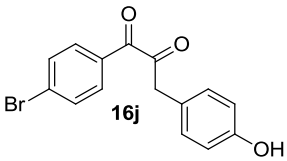
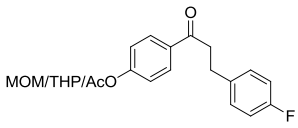
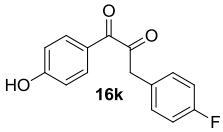
The reagent is also useful for the deprotection of methoxymethyl ether (MOM) of phenolic compounds like, chalcone and chalcone epoxides but the yield of the product was moderate 30-40% (Table 4, entries 3-12). In demethoxymethylation we performed reaction for 1h-3h, but no further conversion were observed, reaction gave only 30-40 % product, and remaining starting material was recovered by column chromatography.

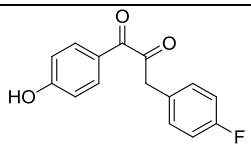
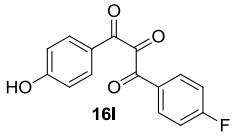
The products were characterized on the basis of their spectral analysis ^{1}H- and ^{13}C-NMR, GC-MS (supporting information). For example, product **16e**, the ^{1}H-NMR spectra showed the characteristic singlet peak at δ 3.99 ppm for $–CH_2$ and disappear the charecteristic two triplet peak at δ 2.80 and 2.72 ppm (J = 5.5 - 6.5 Hz) of $-CH_2-CH_2-$ and broad peak at δ 5.19 ppm for hydroxyl group, indicates oxidation of alpha carbonyl carbon. In ^{13}C-NMR spectra, the characteristic peak at δ 197.12 and 191.10 ppm for two carbonyl (–CO-CO-) groups and peak at δ 50.89 ppm for $–CH_2$ confirms the oxidation of alpha carbonyl carbon, this confirmation also support by the disappearance of peak at 46.35 and 30.51 ppm of $-CH_2-CH_2-$ groups in dihydrochalcone. IR value at 3415 cm^{-1} for –OH groups, 1705 and 1715 cm^{-1} for dicarbonyl indicates the deprotection and sequel oxidation of alpha carbonyl carbon. The structures of all other compounds were further confirmed by GCMS (supporting information).

Table 4. Deprotection of Ac, THP and MOM groups and sequel oxidation of alpha carbonyl carbon.



Entry	Active methylene compounds	Dicarbonyl	Time (min)	Yield[a] (%)	Yield[b] (%)	Yield[c] (%)
1		 **16a**	60	92	95	32
2		 **16b**	60	90	88	32

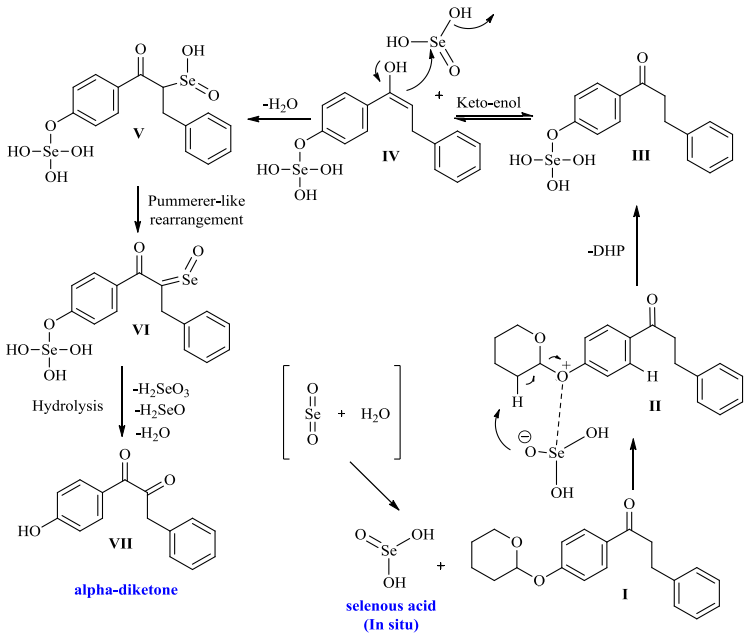
3			60	93	95	40
4			30	94	94	35
5			60	91	85	40
6			60	93	88	40
7			60	90	87	30
8			60	95	85	35
9			60	94	82	35
10			60	95	80	30
11[d]			>120	-	-	-

12[e]		 16l	>60	-	-	-

[a]Yields of deacetylation, [b]Yields of detetrahydropyranylation, [c]Yields of demethoxymethylation, Used substrate:SeO_2, in1:4,1:5 & 1:6 ratios, also altering the reaction time but no further oxidation was observed, [e]Under optimized condition we took dicarbonyl compounds for further alpha carbon oxidation, but no change was observed.

6.4. PLAUSIBLE MECHANISM

A plausible mechanism was proposed (Scheme 1). First, selenium dioxide and water reacts to form the selenous acid in *situ* which reacted with tetrahydropyranyl dihydrochalcone **I** to make complex **II.** Selenous acid ligated with oxygen of tetrahydropyranyl dihydochalcone **II** , followed by removal of DHP via intramolecular abstraction of proton with seloxide ion to give compound **III.** Further, complex **III** undergoes keto-enol tautomerization to get compound **IV**. The key step is the beta-ketoseleninic acid **V** formation by the attack of selenous acid electrophile on enol **IV** of dihydrochalcone and Pummerer like [10] reaction to obtained compound **VI.** Then, hydrolysis gave the deprotected alpha-diketone **VII** of THP dihydochalcone.



Scheme 1. Propose mechanism for the deprotection of THP Ethers and oxidation of active methylene in SeO_2: Water.

6.5. CONCLUSION

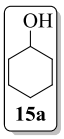
In conclusion, we have developed an efficient one-pot green protocol for the deprotection of alcoholic and phenolic acetyl, tetrahydropyranyl and methoxymethyl ethers and sequel oxidation of active alpha carbonyl carbons to dicarbonyl group using substrate: SeO_2 (1:3 ratio) in H_2O. The reaction gave excellent yield (85-95%) for acetyl and THP ethers and moderate yield (30-40%) at 80 ^{0}C within 30-60 min. However, using substrate: SeO_2 (1:1 ratio) in H_2O, selectively afforded only deprotection of alcoholic and phenolic acetyl, tetrahydropyranyl and methoxymethyl ethers. This methodology has advantages such as versatility of reagent, short reaction time, high yields, inexpensive reagents, environment friendly green protocol and easy workup procedures.

6.6. EXPERIMENTAL DETAILS

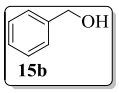
6.6.1. General Procedure for Deprotection of Acetyl esters, Tetrahydropyranyl and methoxymethyl ethers of Alcohol and Phenol: SeO_2 (1 mmol) was added to a stirred solution of Esters and ethers (1 mmol) in a water (1ml) and 3-4 drops of dioxane, suspension obtained, applied heating to 80 ^{0}C. After TLC monitoring, the resulting reaction mixture was poured in cold water and extracted with EtOAc. The organic layer was washed with brine, dried with anhyd.Na_2SO_4, and concentrated in *vacuo* to give the corresponding product which was purified by silica gel column chromatography with hexane- EtOAc eluent to obtain the products **15a to 15x** (table 3) in excellent yield 85-95% and 30-40% for deacetylation, detetrahydropyranylation and demethoxymethylation respectively. Similarly,

General Procedure for Deprotection of Acetyl esters, Tetrahydropyranyl ethers and methoxymethyl ethers of Alcohols and Phenols and sequel oxidation of alpha carbonyl carbon: SeO_2 (3 mmol) was added to a stirred solution of Esters and ethers (1mmol) in a water (1ml) and 3 to 4 drops of dioxane, suspension obtained, applied heating to 80 ^{0}C, gave products **16a to 16j** (table 4) in excellent yield 85-95% and 30-40% for deacetylation, detetrahydropyranylation and demethoxymethylation followed by sequel oxidation of alpha carbonyl carbon respectively.

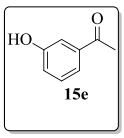
6.6.2. Characterization data for selected synthesized compounds.



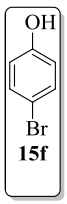
Cyclohexanol (15a): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm: 3.75 (s,1H), 3.08-3.04 (m, 1H), 2.32 (t, *J* = 6 Hz, 1H), 1.64-1.61 (m, 4H), 1.51 (t, *J* = 6 Hz, 2H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm:** 69.148, 36.270, 25.144, 23.100; **GC-MS (m/z):** 100 [$M^{+\cdot}$, $C_6H_{12}O$].



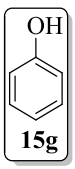
Phenylmethanol (15b): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.46-7.41 (m,2H), 7.37 (d, *J* = 8 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 2H) 4.79 (s, 1H), **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 142.62, 131.54, 130.71, 129.62, 69.13; **GC-MS (m/z):** 108 [$M^{+\cdot}$, C_7H_8O].



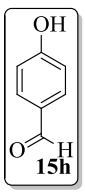
1-(3-hydroxyphenyl)ethanone (15e): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.53-7.51 (m,2H), 7.35 (t, *J* = 10 Hz, 1H), 7.12-7.09 (m, 1H) 6.10 (s, 1H), **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 130.02, 121.23, 120.87, 114.75, 26.89; **GC-MS (m/z):** 136 [$M^{+\cdot}$, $C_8H_8O_2$].



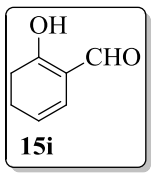
4-bromophenol (15f): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.44 (d, *J* = 9 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 5.31 (s, 1H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 157.12, 133.61, 122.37, 115.19; **GC-MS (m/z):** 172 $[M]^{+\cdot}$, 174 [m+2] for C_6H_5BrO].



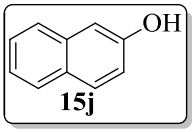
Phenol (15g): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.30-7.26 (m, 2H), 6.98 (dd, *J* = 9, 1 Hz, 2H), 6.90-6.88 (m, 2H), 6.11 (s, 1H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 155.51, 129.85, 120.91, 115.51; **GC-MS (m/z):** 94 $[M]^{+\cdot}$ for C_6H_6O].



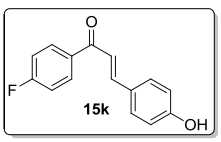
4-Hydroxy benzaldehyde (15h): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 9.86 (s, 1H), 7.84-7.81 (m, 2H), 6.98 (t, *J* = 7 Hz, 2H), 6.25 (s, 1H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 191.34, 161.60, 132.61, 129.94, 116.08; **GC-MS (m/z):** 122 $[M]^{+\cdot}$ for $C_7H_6O_2$].



2-Hydroxy benzaldehyde (15i): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 11.01 (s, 1H), 9.88 (t, *J* = 4.5 Hz, 1H)), .52 (dd, *J* = 8.5 Hz, 2H), 6.98 (t, *J* = 10 Hz, 2H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 194.36, 162.15, 136.27, 131.54, 122.37, 122.13, 117.69; **GC-MS (m/z):** 124 $[M]^{+\cdot}$ for $C_7H_8O_2$].

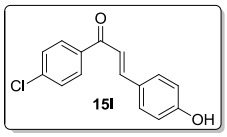


2-Naphthol (15j): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.76 (t, *J* = 8 Hz, 2H)), 7.68 (d, *J* = 10 Hz, 1H),7.44 (d, *J* = 9 Hz, 1H), 7.34 (d, *J* = 9 Hz, 1H),7.10-7.15 (m, 2H), 5.02 (s, *1H*); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 153.36, 134.65, 129.98, 129.03, 127.87, 126.65, 126.46, 123.75, 117.80, 109.58; **GC-MS (m/z):** 144 $[M]^{+\cdot}$ for $C_{10}H_8O$].

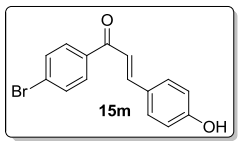


(E)-1-(4-fluorophenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (15k): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 8.02(d, *J* = 8.5 Hz, 2H), 7.74 (d, *J* = 15.5 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 16 Hz, 1H), 7.39 (t, *J* = 8.5

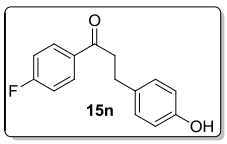
Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 6.24 (s, 1H, br, D_2O exchangeable); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 187.50, 164.68, 162.67, 141.94, 132.02, 131.52, 131.45, 129.53, 122.46, 116.42, 116.25. **IR ν_{max} (KBr, cm^{-1}):** 3415 (OH str), 2931, 2873 (aromatic C-H str), 1681 (C=O str), 1597 (aromatic, C=C str), 1263, 1081, 860, 737; **GC-MS (m/z):** 242 [$M^{+\cdot}$, $C_{15}H_{11}FO_2$].



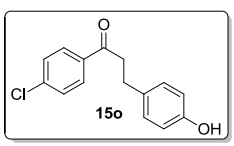
(E)-1-(4-chlorophenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (15l): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 8.02 (d, *J* = 9 Hz, 2H), 7.76 (d, *J* = 15.5 Hz, 1H), 7.64-7.61 (m, 2H), 7.46 (d, *J* =15.5 Hz, 1H), 7.14-7.09 (m, 4H), 5.54 (s, 1H, br, D_2O exchangeable);**^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 187.24, 162.41, 141.68, 131.76, 131.26, 131.19, 129.27, 122.20, 116.16, 115.99; **IR ν_{max} (KBr, cm^{-1}):** 3408 (OH str), 2928, 2876 (aromatic C-H str), 1684 (C=O str), 1598 (aromatic, C=C str), 1268, 1085, 864, 735; **GC-MS (m/z):** 258 [$M^{+\cdot}$, $C_{15}H_{11}ClO_2$].



(E)-1-(4-bromophenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (16c): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 8.01 (t, *J* = 8.5 Hz, 2H), 7.73 (d, *J* = 15.5 Hz, 1H), 7.55-7.44 (m, 3H), 7.47 (d, *J* = 15.5 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 2H); ^{13}C **NMR ($CDCl_3$, 125 MHz) δ ppm** 186.98, 162.15, 141.42, 131.51,131.00, 130.93, 129.02, 121.95, 115.91, 115.74, 115.31; **IR ν_{max} (KBr, cm^{-1}):** 3410 (OH str), 2926, 2875 (aromatic C-H str), 1686 (C=O str), 1599 (aromatic, C=C str), 1265, 1078, 862, 730; **GC-MS (m/z):** 302 [$M^{+\cdot}$, $C_{15}H_{11}BrO_2$], 304 [M+2,].

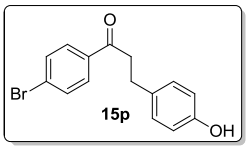


1-(4-fluorophenyl)-3-(4-hydroxyphenyl)propan-1-one (16d): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 8.01 (d, *J* = 9 Hz, 2H), 7.75 (d, *J* = 8 Hz, 1H), 7.63 (dd, *J* = 8, 3 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 1H) .7.14-7.09 (m, 3H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 200.12, 165.89, 157.59, 133.27, 131.65, 131.57, 130.77, 117.41, 116.20, 47.15, 30.49; **IR ν_{max} (KBr, cm^{-1}):** 3419 (OH str), 2933, 2875 (aromatic C-H str), 1684 (C=O str), 1587 (aromatic, C=C str), 1266, 1087, 865, 739; **GC-MS (m/z):** 244 [$M^{+\cdot}$, $C_{15}H_{13}FO_2$].

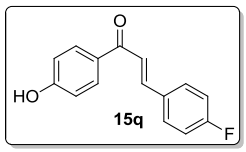


1-(4-chlorophenyl)-3-(4-hydroxyphenyl)propan-1-one (15o): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.73 (d, *J* = 9 Hz, 1H), 7.57 (d, *J* = 8 Hz, 2H), 7.52 (d, *J* = 8, 3 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 2H) , 6.98 (d, *J* = 8.5 Hz, 2H), 5.54 (s, 1H), 2.80 (t, *J* = 6.0 Hz, 2H), 2.73 (t, *J* = 7.0 Hz, 2H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 201.14, 157.88, 139.58, 136.23, 133.63, 131.54, 130.78, 129.62, 116.12, 115.10,

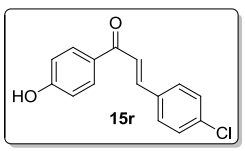
46.46, 31.17; **IR ν_{max} (KBr, cm^{-1}):** 3406 (OH str), 2930, 2877 (aromatic C-H str), 1685 (C=O str), 1598 (aromatic, C=C str), 1269, 1087, 865, 733; **GC-MS (m/z):** 260 [$M^{+\cdot}$, $C_{15}H_{13}ClO_2$].



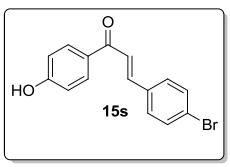
1-(4-bromophenyl)-3-(4-hydroxyphenyl)propan-1-one (15p): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 8.02 (d, *J* = 7.5 Hz, 2H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H) , 7.39 (d, *J* = 8.5 Hz, 2H), 5.45 (s, 1H), 2.80 (t, *J* = 6.5 Hz, 2H), 2.73 (t, *J* = 6.0 Hz, 2H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 199.12, 157.13, 136.27, 133.63, 131.54, 130.78, 129.62, 129.30, 115.19, 45.81, 30.17; **IR ν_{max} (KBr, cm^{-1}):** 3425 (OH str), 2928, 2885 (aromatic C-H str), 1687 (C=O str), 1599 (aromatic, C=C str), 1265, 1079, 862, 725; **GC-MS (m/z):** 304, 306 [$M^{+\cdot}$, $C_{15}H_{13}BrO_2$].



(E)-3-(4-fluorophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (15q): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 8.00 (d, *J* = 8.0 Hz, 2H), 7.76 (d, *J* = 15.5 Hz, 1H), 7.62 (dd, *J* = 6, 13.5 Hz, 2H), 7.46 (d, *J* = 14.5 Hz, 1H), 7.10 (t, *J* = 8.5 Hz, 2H), 6.95 (d, *J* = 8.0 Hz, 2H), 6.24 (s, 1H, br, D_2O exchangeable); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 187.50, 164.68, 162.67, 141.94, 132.02, 131.52, 131.45, 129.53, 122.46, 116.42, 116.25**; IR ν_{max} (KBr, cm^{-1}):** 3419 (OH str), 2935, 2877 (aromatic C-H str), 1684 (C=O str), 1599 (aromatic, C=C str), 1268, 1087, 866, 731; **GC-MS (m/z):** 243 [$M^{+\cdot}$, $C_{15}H_{11}FO_2$].

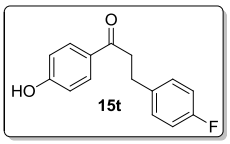


(E)-3-(4-chlorophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (15r): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.87 (d, *J* = 8.5 Hz, 2H), 7.54 (dd, *J* = 8.5, 5 Hz, 2H), 7.05 (d, *J* = 8.5 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 2H), 6.42 (s, 1H, br, D_2O exchangeable); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 187.20, 162.37, 141.64, 131.72, 131.22, 131.15, 129.23, 122.16, 116.12, 115.95; **IR ν_{max} (KBr, cm^{-1}):** 3411 (OH str), 2930, 2881 (aromatic C-H str), 1688 (C=O str), 1594 (aromatic, C=C str), 1270, 1089, 868, 729; **GC-MS (m/z):** 258 [$M^{+\cdot}$, $C_{15}H_{11}ClO_2$].

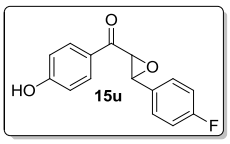


(E)-3-(4-bromophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (15s): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 8.00 (d, *J* = 8.5 Hz, 2H), 7.77 (d, *J* = 15.5 Hz, 1H), 7.63 (t, *J* = 8Hz, 2H), 7.46 (d, *J* = 15.5 Hz, 1H), 7.09 (t, *J* = 8.5 Hz, 2H), 6.94 (d, *J* = 8 Hz, 2H), 6.24 (s, 1H); **^{13}C NMR ($CDCl_3$, 125**

MHz) δ ppm 186.88, 162.05, 141.32, 131.41, 130.90, 130.83, 128.92, 121.85, 115.81, 115.64, 115.21; **IR ν_{max} (KBr, cm^{-1}):** 3409 (OH str), 2929, 2873 (aromatic C-H str), 1688 (C=O str), 1591 (aromatic, C=C str), 1259, 1075, 865, 733; **GC-MS (m/z):** 302, 304 [$M^{+\cdot}$, $C_{15}H_{11}BrO_2$].

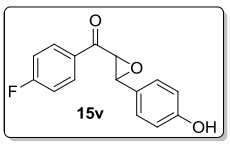


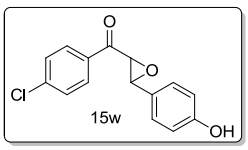
3-(4-fluorophenyl)-1-(4-hydroxyphenyl)propan-1-one(15t): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.88 (d, *J* = 8.5 Hz, 2H), 7.55 (dd, *J* = 8.5, 5 Hz, 2H), 7.06 (t, *J* = 8.5 Hz, 2H) , 6.96 (d, *J* = 9.0 Hz, 2H), 5.90 (s, 1H), 2.80 (t, *J* = 5.0 Hz, 2H), 2.72 (t, *J* = 5.5 Hz, 2H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 199.68, 166.54, 156.47, 132.65, 130.97, 130.68, 129.97, 128.66, 116.66, 115.05, 46.35, 30.51; **IR ν_{max} (KBr, cm^{-1}):** 3421 (OH str), 2937, 2879 (aromatic C-H str), 1686 (C=O str), 1587 (aromatic, C=C str), 1262, 1089, 870, 727; **GC-MS (m/z):** 244 [$M^{+\cdot}$, $C_{15}H_{13}FO_2$].



(3-(4-fluorophenyl)oxiran-2-yl)(4-hydroxyphenyl)methanone (15u): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 8.02(d, *J* = 8.5 Hz, 2H), 7.73 (dd, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 8.5 Hz, 2H) , 7.52 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 2H), 5.62 (s, 1H), 4.22 (d, *J* = 2.0 Hz, 1H), 4.17 (d, *J* = 2.0 Hz, 1H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 197.32, 156.54, 138.65, 130.97, 130.68, 129.97, 129.68, 128.68, 127.96, 126.67, 116.65, 71.12, 59.35; **IR ν_{max} (KBr, cm^{-1}):** 3421 (OH str), 2937, 2879 (aromatic C-H str), 1686 (C=O str), 1596 (aromatic, C=C str), 1267, 1088, 867, 733; **GC-MS (m/z):** 258 [$M^{+\cdot}$, $C_{15}H_{11}FO_3$].

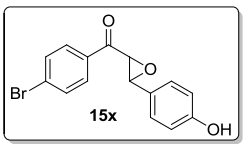
(4-fluorophenyl)(3-(4-hydroxyphenyl)oxiran-2-yl)methanone (15v): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 8.01(d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 2H) , 7.13 (d, *J* = 8.5 Hz, 1H), 5.59 (s, 1H), 4.42 (d, *J* = 1.5 Hz, 1H), 4.26 (d, *J* = 2.0 Hz, 1H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 197.41, 167.14, 157.88, 131.54, 130.78, 129.62, 124.36, 116.12, 115.10, 72.13, 58.10; **IR ν_{max} (KBr, cm^{-1}):** 3417 (OH str), 2939, 2881 (aromatic C-H str), 1687 (C=O str), 1589 (aromatic, C=C str), 1263, 1091, 871, 729; **GC-MS (m/z):** 258 [$M^{+\cdot}$, $C_{15}H_{11}FO_3$].



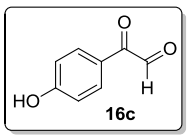


(4-chlorophenyl)(3-(4-hydroxyphenyl)oxiran-2-yl)methanone (15w): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.87 (d, *J* = 8.5 Hz, 2H), 7.54 (dd, *J* = 8.5, 5 Hz, 1H), 7.06 (t, *J* = 8.5 Hz, 2H) , 6.96 (d, *J* = 9.0 Hz, 1H), 5.65 (s, 1H), 4.30 (d, *J* = 1.5 Hz, 1H), 4.23 (d, *J* = 2.0 Hz, 1H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 198.20, 157.12, 139.53, 133.63,131.54, 130.78, 129.62, 124.42, 115.10, 71.46, 59.17; **IR**

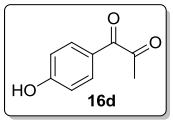
ν_{max} (KBr, cm^{-1}): 3411 (OH str), 2930, 2881 (aromatic C-H str), 1688 (C=O str), 1594 (aromatic, C=C str), 1270, 1089, 868, 729; **GC-MS (m/z):** 274 [$M^{+\cdot}$, $C_{15}H_{11}ClO_3$].



(4-bromophenyl)(3-(4-hydroxyphenyl)oxiran-2-yl)methanone (15x): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 8.01(d, *J* = 9.0 Hz, 2H), 7.75 (d, *J* = 8.0Hz, 1H), 7.63 (dd, *J* = 8.5, 5 Hz, 2H), 7.45 (d, *J* = 9.5 Hz, 1H) , 7.13 (d, *J* = 9.0 Hz, 2H), 5.40 (s, 1H), 4.39 (d, *J* = 2.5 Hz, 1H), 4.28 (d, *J* = 2.5 Hz, 1H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 198.01, 159.07, 133.01, 130.92, 129.62, 129.29, 128.66, 128.07, 117.13, 73.13, 60.17; **IR ν_{max} (KBr, cm^{-1}):** 3411 (OH str), 2933, 2879 (aromatic C-H str), 1689 (C=O str), 1595 (aromatic, C=C str), 1275, 1079, 869, 725; **GC-MS (m/z):** 318, 320 [$M^{+\cdot}$, C15H11BrO_3].

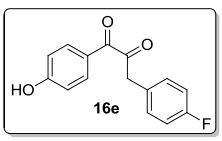


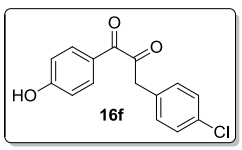
2-(4-hydroxyphenyl)-2-oxoacetaldehyde (16c): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 9.50(s, 1H), 7.88-7.86 (m, 2H), 6.89-6.87 (m, 2H), 5.58 (s, 1H, br, D_2O exchangeable); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 190.69, 187.73, 163.98, 132.91, 130.67, 116.55; **GC-MS (m/z):** 150 $[M]^{+\cdot}$ for $C_8H_6O_3$].



1-(4-hydroxyphenyl)propane-1,2-dione (16d): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.93-7.90 (m, 2H), 6.92-6.89 (m, 2H), 6.55 (s, 1H), 2.18 (s, 3H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 197.85, 192.83, 164.85, 131.44, 124.80, 117.22, 23.05; ***GC-MS (m/z):*** 164 [$M^{+\cdot}$, $C_9H_8O_3$].

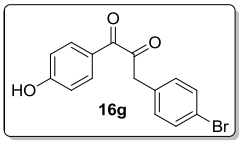
3-(4-fluorophenyl)-1-(4-hydroxyphenyl)propane-1,2-dione (16e): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.73(d, *J* = 9.0 Hz, 1H), 7.57 (d, *J* = 7.5 Hz, 2H), 7.53 (d, *J* = 9.0 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 2H) , 6.98 (d, *J* = 8.5 Hz, 2H), 5.19 (s, 1H), 3.99 (s, 2H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 197.12, 191.10, 166.42, 163.17, 131.54, 130.71, 129.62, 129.30, 122.38, 117.19, 116.11, 50.89; GC-MS (m/z): ; **IR ν_{max} (KBr, cm^{-1}):** 3415 (OH str), 2935, 2879 (aromatic C-H str), 1685 (C=O str), 1593 (aromatic, C=C str), 1268, 1087, 865, 731; **GC-MS (m/z):** 258 [$M^{+\cdot}$, C15H11FO_3].



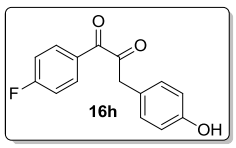


3-(4-chlorophenyl)-1-(4-hydroxyphenyl)propane-1,2-dione(16f): ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 8.02 (d, *J* = 8.5 Hz, 2H), 7.73 (d, *J* = 9.0 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 1H) , 7.38 (d, *J* = 8.5 Hz, 2H), 5.45 (s, 1H), 3.79 (s, 2H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 197.41, 190.12, 157.13, 140.10, 133.63, 131.54, 130.78, 129.62, 129.30, 116.19, 50.81; **IR ν_{max} (KBr,**

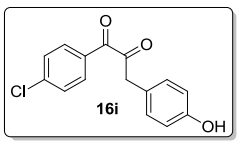
cm^{-1}): 3407 (OH str), 2933, 2875 (aromatic C-H str), 1689 (C=O str), 1594 (aromatic, C=C str), 1270, 1090, 870, 729; **GC-MS (m/z):** 274 [$M^{+\cdot}$, $C_{15}H_{11}ClO_3$].



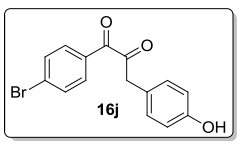
3-(4-bromophenyl)-1-(4-hydroxyphenyl)propane-1,2-dione(16g): ^{1}H NMR (CDCl$_3$, 500 MHz) δ ppm 7.86 (d, *J* = 8.5 Hz, 2H), 7.54-7.52 (m, 2H), 7.05 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 2H), 6.42 (s, 1H), 3.85 (s, 2H); **^{13}C NMR (CDCl$_3$, 125 MHz) δ ppm** 196.62, 191.12, 157.29, 133.01, 130.92, 129.87, 129.29, 128.66, 128.07, 116.93, 51.77; **IR ν_{max} (KBr, cm^{-1}):** 3425 (OH str), 2928, 2885 (aromatic C-H str), 1687 (C=O str), 1599 (aromatic, C=C str), 1265, 1079, 862, 725; **GC-MS (m/z):** 318, 320 [$M^{+\cdot}$, $C_{15}H_{11}BrO_3$].



1-(4-fluorophenyl)-3-(4-hydroxyphenyl)propane-1,2-dione (16h): ^{1}H NMR (CDCl$_3$, 500 MHz) δ ppm 78.03-7.99 (m, 2H), 7.58 (d, *J* = 7.5 Hz, 2H), 7.53-7.50 (m, 3H), 7.33 (t, *J* = 8.5 Hz, 1H) , 7.13 (d, *J* = 8.5 Hz, 2H), 5.31 (s, 1H), 2.79 (s, 2H); **^{13}C NMR (CDCl$_3$, 125 MHz) δ ppm** 197.65, 190.05, 168.52, 156.60, 130.68, 129.97, 128.68, 127.78, 116.66, 115.32, 51.12; **IR ν_{max} (KBr, cm^{-1}):** 3417 (OH str), 2935, 2871 (aromatic C-H str), 1679 (C=O str), 1581 (aromatic, C=C str), 1267, 1088, 867, 741; **GC-MS (m/z):** 258 [$M^{+\cdot}$, $C_{15}H_{11}FO_3$].



1-(4-chlorophenyl)-3-(4-hydroxyphenyl)propane-1,2-dione (16i): ^{1}H NMR (CDCl$_3$, 500 MHz) δ ppm 7.97-7.94 (m, 3H), 7.55-7.43 (m, 3H), 7.47 (t, *J* = 9.0 Hz, 1H) , 6.98 (dd, *J* = 8.5, 2.0 Hz, 1H), 5.31 (s, 1H), 2.73 (s, 2H); **^{13}C NMR (CDCl$_3$, 125 MHz) δ ppm** 197.27, 191.55, 157.77, 131.68, 130.49, 130.05, 129.65, 128.97, 128.65, 127.66, 117.54, 48.52; **IR ν_{max} (KBr, cm^{-1}):** 3401 (OH str), 2931, 28851 (aromatic C-H str), 1688 (C=O str), 1594 (aromatic, C=C str), 1275, 1091, 867, 729; **GC-MS (m/z):** 274 [$M^{+\cdot}$, $C_{15}H_{11}ClO_3$].



1-(4-bromophenyl)-3-(4-hydroxyphenyl)propane-1,2-dione (16j): ^{1}H NMR (CDCl$_3$, 500 MHz) δ ppm 7.88-7.79 (m, 3H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.64-7.59 (m, 3H), 7.33 (t, *J* = 8.5 Hz, 1H) , 6.94 (d, *J* = 8.5 Hz, 3H), 5.34 (s, 1H), 2.71 (s, 2H); **^{13}C NMR (CDCl$_3$, 125 MHz) δ ppm** 196.68, 190.25, 157.05, 141.35, 131.77, 130.65, 130.49, 129.65, 128.97, 116.56, 49.85; **IR ν_{max} (KBr, cm^{-1}):** 3405 (OH str), 2930, 2871 (aromatic C-H str), 1675 (C=O str), 1591 (aromatic, C=C str), 1259, 1071, 865, 733; **GC-MS (m/z):** 318, 320 [$M^{+\cdot}$, $C_{15}H_{11}BrO_3$].

6.7. REFERENCES

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CHAPTER- 5

Part-A: Mild and efficient reductive deoxygenation of epoxides to olefins with $SnCl_2$/NaI as a novel reagent

Gulab Khushalrao Pathe[a] and Naseem Ahmed*[a], Synthesis **2015, Ahead of print.**

Part-B: Efficient and green protocol for the eliminative deoxygenation of aliphatic and aromatic epoxides to olefin with polyphosphoric acid as a novel catalyst

Gulab Khushalrao Pathe[a] and Naseem Ahmed*[a], Helvetica Chemica Acta **2015,** Under Review**.**

Part A: Mild and efficient reductive deoxygenation of epoxides to olefins with $SnCl_2$/NaI as a novel reagent

7.1. INTRODUCTION

Epoxidation of organic compounds is well-known in organic and pharmaceutical syntheses to obtain a number of oxygen-containing intermediates.[1] In contrast, the reverse reaction (reductive deoxygenation) of epoxide to alkene is little-known with NaOH/n-BuNBr,[2] $[Fe_4S_4(SC_6H_5)_4]^{2-}$,[3] $CpTiCl_2$/Mg,[4] PPh_3,[5] Na/Hgb[6] and $NaBH_4$.[7] However, these catalysts have some drawbacks such as low activity, low atom efficiency, tedious work up and moisture sensitive reaction conditions.

The $SnCl_2$ is used as a non-toxic, inexpensive and mild lewis acid catalyst in diverse organic synthesis. It was mainly used for the functional groups reduction such as nitrile and nitro groups and as a catalyst in ring cyclization reactions to yield heterocycles: benzoxzzoles, qinoxalines, benzimidazoles and allylation of carbonyl compounds.[8] It was also used as a Lewis acid catalyst for the C-C bond formation, Sonn-Muller reaction, Stephen reduction,[9] polymerization of L-lactide and trans-esterification reactions. Recent deoxygenation reactions of epoxides to olefins was reported using $Co(salane)_2$/NaHg,[10] $(EtO)_2P(O)TeNa$,[11] LiI/Amberlyst-15,[12] $LReO_3/PPh_3$,[13] $MoO(Et_2dtc)_2$[14] reagents but these methods have drawbacks like less functional group tolerance, less versatility, low yields, long reaction time and tedious workup. Therefore, the development of simple and efficient reductive deoxygenation methods is of high interest.

In continuation of our interest in Lewis acid/base catalysis [15] and the importance of inexpensive, easily available, and stable catalysts in epoxide ring opening. Herein, we report a facile and eco-friendly protocol in the reductive deoxygenation of aliphatic and aromatic epoxides to olefins in the presence of $SnCl_2$/NaI combination as a highly efficient catalyst to afford alkenes in excellent yields (96%) within 2-10 min. at reflux in ethanol.

7.2. OBJECTIVE

Deoxygenation of epoxide into alkene is well-known in organic synthesis and pharmaceutical industry. Several methods have been applied for this conversion but these methods have a drawback like tedious work-up, moisture sensetive reaction etc. In our continious efforts to obtain a facile and environment-friendly protocol in the eleminitive deoxygenation of aliphatic and aromatic epoxides to olefins. A highly efficient green protocol

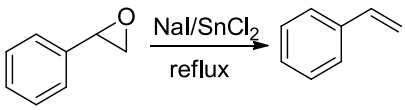
was reported for the eliminative deoxygenation of organic epoxides to olefins using $SnCl_2$/NaI as a novel reagent. The reaction gave an excellent yield (85-96%) at reflux in ethanol within 2-10 mins without affecting other functional groups.

7.3. RESULTS AND DISSCUSSION

7.3.1. Optimization reaction conditions for deoxygenation of styrene epoxide by $SnCl_2$/NaI

We optimized the deoxygenation reaction conditions in the reaction of styrene oxide (1equiv.) with novel $SnCl_2$/NaI reagent by varying molar ratios and different solvents (Table1). The product was obtained in excellent yield (96%) in ethanol at reflux using $SnCl_2$ (2 equiv.) and NaI (3 equiv.) within 5 min (Table1, entry 5). When, we increased or decreased molar ratios of $SnCl_2$/NaI reagent and solvents, the reaction gave lower yields (Table 1).

Table1. Optimization of deoxygenation reaction in styrene oxide with $SnCl_2$/NaI.



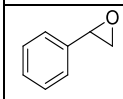
Entry	NaI(eq.)	$SnCl_2$ (eq.)	Solvent	Time (min)	Temp	Yields (%)[a]
1	3	2	DMF	5	Reflux	25
2	3	2	THF	5	Reflux	10
3	1	2	Ethanol	5	Reflux	50
4	2	2	Ethanol	5	Reflux	60
5	**3**	**2**	**Ethanol**	**5**	**Reflux**	**96**
6	4	2	Ethanol	5	Reflux	70
7	3	2	NMP	5	Reflux	20
8	3	2	DMSO	5	Reflux	20

[a]Yields of isolated products

7.3.2. Comparison of the $SnCl_2$/NaI reagent and recent reported methods of deoxygenation of epoxides to corresponding olefins

Our method is expanded to overcome the drawbacks of the previous reported methods. In order to show the advantages of the method, we have compaired with other methods in the deoxygenation of epoxides to the corresponding olefins (Table 2).

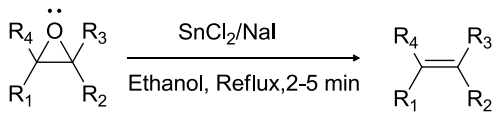
Table 2. Comparison of the $SnCl_2$/NaI reagent and recent reported methods of deoxygenation of epoxides to corresponding olefins

Sub.	**$SnCl_2$/NaI** min.[yields%]	Co(salane)$_2$/ NaHg h[yields%]	$(EtO)_2P(O)$ TeNa h[yields%]	LiI/Ambe-rlyst 15 h[yields%]	$LReO_3$/ PPh_3 h[yields%]	MoO $(Et_2dtc)_2$ h[yields%]
	2-5 [95]	6 [95]	42 [88]	-	-	36 [92]
	2-5 [95]	1 [95]	-	3[85]	2 [32]	-

7.3.3. Examples of the deoxygenation of aliphatic and aromatic epoxides by $SnCl_2$/NaI

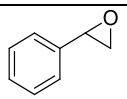
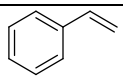
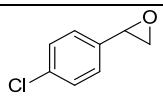
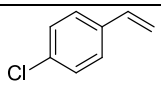
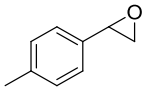
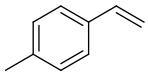
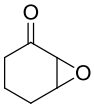
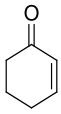
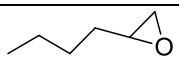
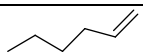
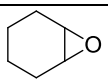
Under optimal condition, $SnCl_2$/NaI reagent was explored for various aliphatic and aromatic epoxides (Table 3). As depicted in table 3, the $SnCl_2$/NaI reagent surprisingly gave the products **17a -17l** in excellent yield (85-96%) (Table 3, entries 1-12) within 2-5 minutes at reflux temperature. Various aromatic epoxides (Table 3, entries 1-3 & 9-11), alicyclic (Table 3, entry 4, 6 & 12) and aliphatic (Table 3, entries 5,7 & 8) were transformed to alkenes in excellent yield. The carbonyl, nitro, hydroxyl, esters and and ketones groups in the deoxygenation of alicyclic epoxides (Table 3, entries 4 & 12) and ether linkage in the aromatic and aliphatic epoxides (Table 3, entries 8 & 9) remained unaffected during the reaction. Our method is also highly stereospecific in nature. For example, deoxygenation of cis-stilbene oxide gave cis-stilbene and trans-stilbene oxide to trans-stilbene (Table 3, entry 10 & 11) and the chemoselectivity between epoxide ring and hydroxyl group (Table 3, entry 12). All products were characterized by comparing their physical and chemical properties with authentic samples.[16]

Table 3. Deoxygenation of aliphatic and aromatic epoxide by $SnCl_2$/NaI



1-12 **17a-17l (yield = 85 - 96 %)**

Entry	Epoxides	Product	Time (min)[a]	Yield (%)[a]

1		 17a	2	96*
2		 17b	4	92
3		 17c	5	90
4		 17d	5	88
5		 17e	2	85
6		 17f	3	85
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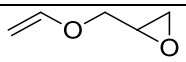
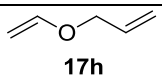
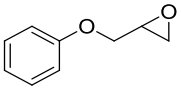
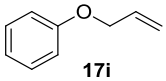
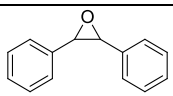
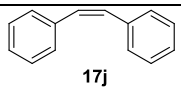
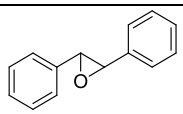
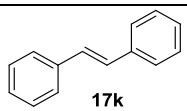
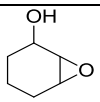
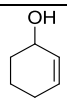
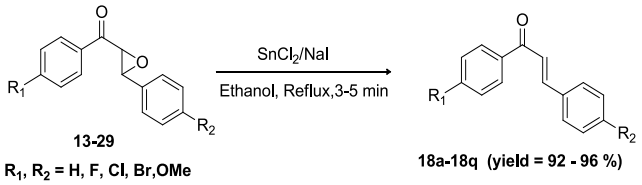
8		 17h	3	86
9		 17i	5	90
10		 17j	5	85
11		 17k	2	95
12		 17l	3	88

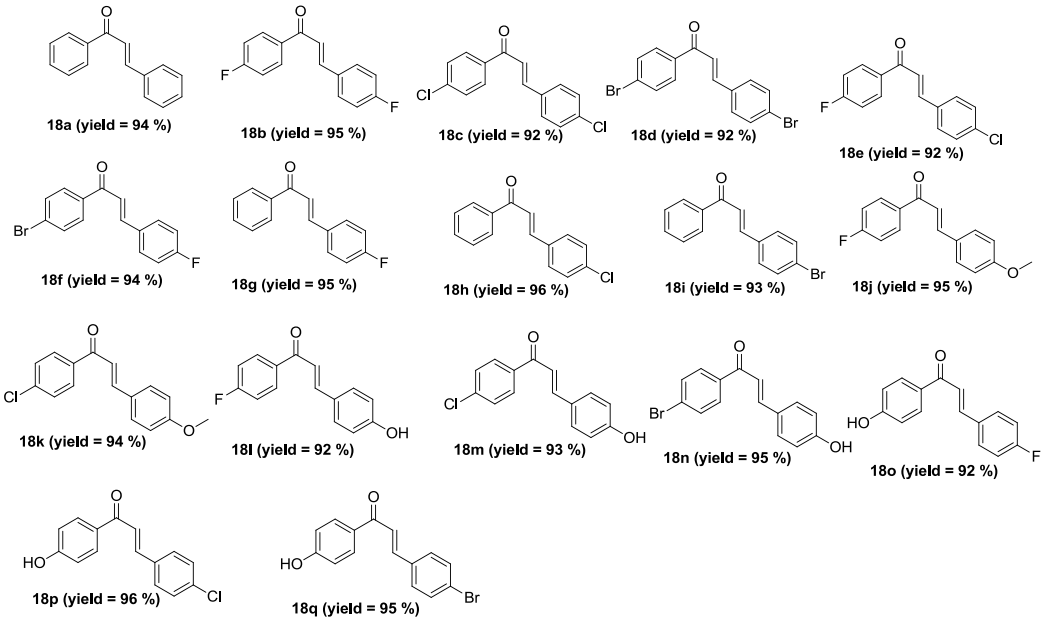
[a]Yields of Isolated products, all these product are characterized by comparing their physical and chemical properties with authentic samples [16]. *Volatile compounds isolated by fractional distilation (supporting information)

7.3.4. Examples of the deoxygenation of chalcone epoxide by $SnCl_2$/NaI

Under optimal condition, we have converted various chalcone epoxides to chalcone **18a-18q** with novel reagent $SnCl_2$/NaI in excellent yields (92-96%) within 5 minutes at reflux temperature in ethanol without affecting carbonyl, hydroxyl and halogen groups (Scheme 1). For example, product **18h,** the ^{1}H-NMR spectra showed two characteristic doublet peaks at δ 4.25 & 4.06 ppm (J =1.5-2 Hz) of the corresponding epoxide (–CHOCH-) dissapeared and two protons peak of –CH=CH- appeared downfield in aromatic proton region between δ 6.5-8.0 ppm. ^{13}C-NMR spectra, the disappearance of characteristic peak at δ 61.03 & 58.81 ppm of (–CHOCH-) groups and that two protons peaks appeared in downfield region at δ 122.41 & 116.20 ppm and carbonyl peak somewhat shifted downfield compaired to corresponding epoxide, indicated deoxygenation of chalcone epoxide to chalcone. These compounds were further characterised by IR and GC-MS.

Scheme 1. Deoxygenation of chalcone epoxide by $SnCl_2$/NaI

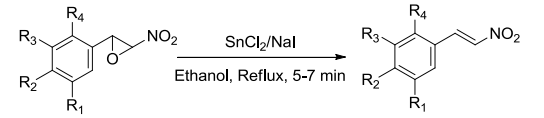


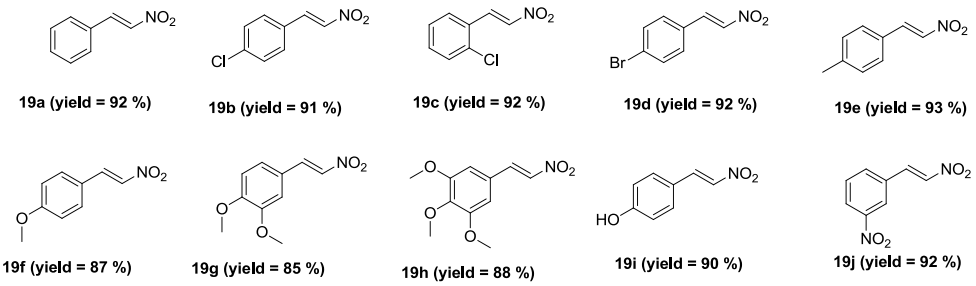


7.3.5. Examples of the deoxygenation of styrene epoxide by $SnCl_2$/NaI

In Scheme 2, we performed deoxygenation of various nitro styrene epoxides with novel reagent $SnCl_2$/NaI in ethanol to afford products **19a-19j** in excellent yields 85-93% within 5-7 minutes at reflux temperature (Scheme 2). The products were characterized on the basis of their spectral analysis. For example, product **19b,** ^{1}H-NMR spectra showed absence of two characteristic doublet peaks at δ 5.41 & 3.87 ppm of –CHOCH-N- (J = 2.5 Hz) and appearance of –CH=CH-N in aromatic region. Similarlly, ^{13}C-NMR spectra, the absence of two characteristic peaks at δ 100.18 & 89.26 ppm of –COC-N- carbon nitrostyrene epoxide, indicated deoxygenation of nitrostyrene epoxide to nitrostyrene. These compounds were further characterised by IR and GC-MS.

Scheme 2. Deoxygenation of nitro styrene epoxide by $SnCl_2$/NaI.

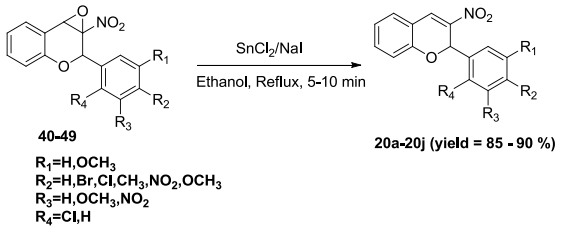


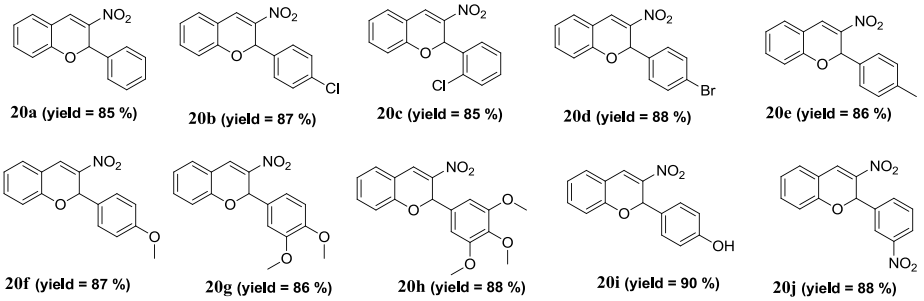


7.3.6. Examples of the deoxygenation of nitrochromene epoxide by $SnCl_2$/NaI

We also carried out deoxygenation of hindered chromene epoxides with novel reagent $SnCl_2$/NaI in ethanol (Scheme 3). It gave deoxygenation products **20a -20j** in excellent yield (85-90%) within 5-10 minutes at reflux temperature. Spectral analysis for example, compound **20b,** ^{1}H-NMR spectra showed the characteristic singlet peak at δ 6.86 ppm of –CH=CH-N- and absence of peak at δ 3.82 ppm of nitrochromene epoxide indicated deoxygenation product. Similarlly, in ^{13}C-NMR spectra, the characteristic peaks at δ 60.67 & 116.94 ppm of –C=C-N- carbon indicated the deoxygenation to nitrochromene. These compounds were further characterised by IR and GC-MS.

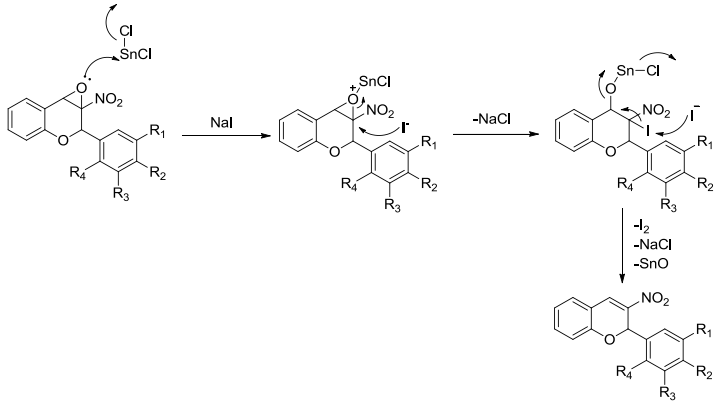
Scheme 3. Deoxygenation of nitrochromene epoxide by $SnCl_2$/NaI





7.4. Plausible mechanism for the deoxygenation epoxide to olefin by $SnCl_2$/NaI.

In the deoxygenation reactions consistently brown color was observed due to the generation of molecular iodine, by taking into account this observation, we gave the plausible reaction mechanism, where a nucleophile attack of oxygen lone pair electrons of epoxide on tin dichloride liberates the chloride ion followed by epoxide ring opening by iodide ion and removal of the molecular iodine to give the corresponding olefins (Scheme 4).



Scheme 4. Plausible mechanism for the deoxygenation epoxide to olefin by $SnCl_2$/NaI.

7.5. CONCLUSION

In conclusion, we have reported $SnCl_2$/NaI in ethanol as an efficient reagent during eliminative deoxygenation reaction for epoxides to olefins in excellent yield (85-96%) within 2-10 mins. This method has advantages as inexpensive reagent, high yield, short reaction time, eco-friendly, green reaction and high functional group tolerance.

7.6. EXPERIMENTAL DETAILS

Organic solvents were dried by standard methods; the reagents (chemicals) were purchased from commercial sources, and used without further purification. All reactions were monitored by TLC using precoated silica gel aluminum plates. Visualization of TLC plates was accomplished with an UV lamp. Column chromatography was performed using silica gel 60–120 mesh size (RANKEM Limited) with EtOAc–hexanes as eluent. Melting points were recorded on Perfit apparatus and are uncorrected. All products were characterized by NMR, IR and MS spectra. 1H and 13C NMR spectra were recorded in deuterated chloroform (CDCl3) on a 500 MHz and 125 MHz spectrometer (Bruker), respectively. Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br).

7.6.1. General procedure for the synthesis of chromene epoxides (39-49): Aqueous NaOH (5M, 10 ml) was added drop wise to a stirred solution of chromines (18 mmol) in aq. THF (30 ml, H_2O: THF, 1:2 ratio) and further stirred for 10 min. Then, H_2O_2 (15 ml, 30% wt.%) was added drop wise and further stirred for 2 days at room temperature. TLC monitoring, the reaction mixture was poured in water. The resulting precipitate was filtered, washed with water and dried under reduced pressure. The product was recrystallized in EtOH or silica gel column chromatography in petroleum ether: CH_2Cl_2 (8:2) as eluent gave chromine epoxide **(39-49)** in 60-70% yields.

General procedure for Deoxygenation of aliphatic and aromatic epoxide, chalcone epoxide, nitro styrene epoxide and nitrochromene epoxide by novel $SnCl_2$/ NaI reagent: To a solution epoxide (1mmol) and NaI (3mmol) in absolute alcohol (5ml), $SnCl_2$ (2mmol) was added in a several portions. The mixture was stirred at reflux temperature and the progress of reaction was monitored by TLC. within 2-10 min the reaction mixture is poured in ice-water, precipitation obtained, stirred for 10 min and filtered the solid, dried to obtained pure products **17a-17l/ 18a-18q/19a-19j and 20a- 20j** with 85-96% yield. *2-(2-cholorophenyl)-3-nitro-2H-chromene (20c):* Yellow solid; Yield: 243 mg (85%); melting point-90-92°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 8.15(s, 1H), 7.48 (dd, *J* = 1Hz, 9.5Hz, 1H), 7.34(dd, *J*= 2Hz, 8Hz, 1H), 7.32-7.27 (m, 2H), 7.192 (dd, J = 2Hz, 8Hz, 1H), 7.07 (s, 1H), 7.0 (dt, *J*=1Hz, 1H), 6.82 (d, *J*=8Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 153.61, 146.74, 144.99, 139.94, 134.77, 129.92, 128.99, 128.72, 128.59, 127.21, 122.34, 121.94, 116.91, 114.47, 79.59.

I R (vmax, cm-1): 3069, 2923, 1644, 1511, 1327, 1107;GCMS (m/z) 287 [M^+. $C_{15}H_{10}$ $ClNO_3$] 289, 287, 270, 257, 241, 205, 176, 146 (100%), 89, 76, 63.

Note: Examples are same for the both sections therefore experimental section given in Part: B for all spectral data of synthesized compounds.

7.7. REFERENCES

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Part-B: Efficient and green protocol for the eliminative deoxygenation of aliphatic and aromatic epoxides to olefin with polyphosphoric acid as a novel catalyst

8.1. INTRODUCTION

Epoxidation of organic compounds is well-known in organic and pharmaceutical syntheses to obtain a number of oxygen-containing intermediates.[1] In contrast, the reverse reaction (reductive deoxygenation) of epoxides to alkenes is little-known with NaOH/n-BuNBr,[2] $[Fe_4S_4(SC_6H_5)_4]^{2-}$,[3] $CpTICl_2$/Mg,[4] PPh_3,[5] indium- metal, Na/Hg [6] and $NaBH_4$.[7] However, these catalysts have some drawbacks such as low activity, low atom-economy, tedious work up and moisture sensitive reaction conditions.

Polyphosphoric acid (PPA) has been used extensively in organic syntheses.[8] for example, in acylation, alkylation, cyclization, acid catalyzed reactions like dehydration, rearrangements and synthesis of polymer and N-containing heterocycles.[9-11] Epoxides are being potential precursors for a variety of molecules, recently, some methods for deoxygenation of epoxides to olefins were studied using LiI/Amberlyst-15,[12] $LReO_3/PPh_3$,[13] $Co(salane)_2$/Na-Hg,[14] $(EtO)_2P(O)$-TeNa,[15] $MoO(Et_2dtc)_2$[16] but these reagents have drawbacks as less tolerance of functional groups, low yields, long reaction time and tedious workup with moisture sensitive reaction conditions. Therefore, the development of simple and efficient catalytic deoxygenation methods is of high interest.

In continuation of our interest in Lewis acid/base catalysis [17] and the importance of inexpensive, easily available, and stable catalysts in epoxide ring opening. Herein, we report a facile and eco-friendly protocol in the eleminative deoxygenation of aliphatic and aromatic epoxides to olefins in the presence of PPA (30 mol% loading) as a highly efficient catalyst to afford alkenes in excellent yields (85-96%) within 5-15 min. at 50 ^{0}C under neat condition.

8.2. OBJECTIVE

Deoxygenation of epoxide into alkene is well-known in organic synthesis and pharmaceutical industry. Several methods have been applied for this conversion but these methods have a drawback like tedious work-up, moisture sensetive reaction etc. In our continious efforts to obtain a facile and environment-friendly protocol in the eleminitive deoxygenation of aliphatic and aromatic epoxides to olefins, herein, we demonstrate that phosphoric acid act as a highly efficient catalyst in 30 mol % loading to afford the alkenes in

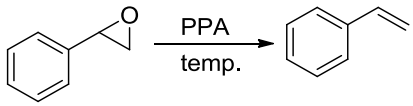
excellent yields (85-96%) within 5-15 min. at 50 ^{0}C. This methodology is very good alternative to the known methods of deoxygenation of epoxides.

8.3. RESULTS AND DISSCUSSION

8.3.1. Optimization reaction conditions for deoxygenation of styrene epoxide by PPA

We optimized the deoxygenation reaction conditions in the reaction of styrene oxide (1 equiv.) with PPA by varying mol% and solvents (**Table1**). The product was obtained in excellent yield (95%) at 50 ^{0}C using PPA (30 mol%) within 5-10 min under neat condition (**Table 1, entry 6**). However, further increase or decrease in mol% of PPA and use of other organic solvents, gave lower yields **(Table 1)**.

Table 1. Optimized condition for the deoxygenation of styrene oxide by polyphosphoric acid



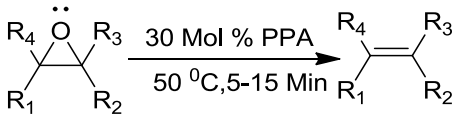
Entry	Mol % of PPA	Solvent	Time (min)	Temp (^{0}C)	Yields[a] (%)
1	30	DMF	15	Reflux	15
2	30	ACN	15	Reflux	20
2	30	Ethanol	15	Reflux	30
4	10	-	15	50	20
5	20	-	15	50	50
6	30	-	5-10	50	95
7	40	-	10	50	85
8	30	NMP	15	Reflux	15
9	30	DMSO	10	Reflux	15

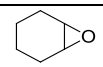
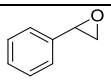
[a]Yield of isolated product

8.3.2. Comparison of polyphosphoric acid system with erlier methods

In order to show the advantages of our method, we have also compared the existing methods in the case of eliminative deoxygenation of epoxides to olefins (**Table 2**).

Table 2. Comparison of the green PPA system with formerly reported systems for deoxygenation of epoxides to alkenes

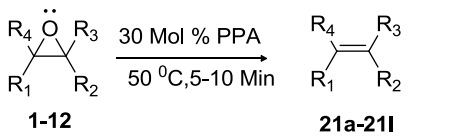


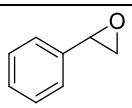
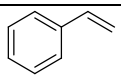
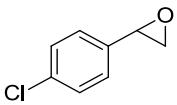
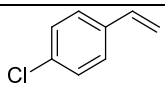
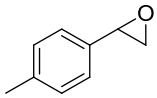
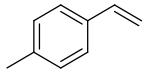
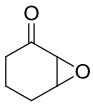
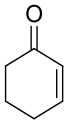
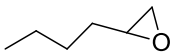
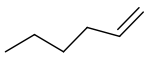
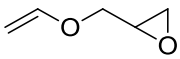
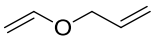
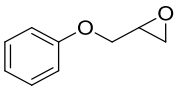
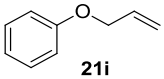
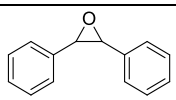
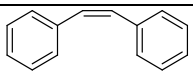
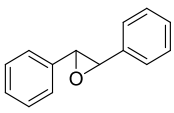
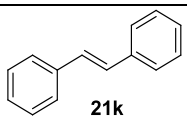
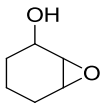
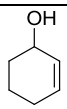
Substrate	30 mol % PPA min.[yields%]	LiI/ Amberlyst 15 h[yields%]	$LReO_3$/ PPh_3 h[yields%]	$Co(salane)_2$/ NaHg h[yields%]	$(EtO)_2P(O)$-TeNa h [yields%]	Mo $(Et_2dtc)_2$ h[yields%]
	< 10 [96]	-	-	6 [95]	42 [88]	36 [92]
	< 10 [96]	3[85]	2 [32]	1 [95]	-	-
With or without Solvent	**Without Solvent**	With Solvent	With Solvent	With Solvent	With Solvent	With Solvent

8.3.3. Examples of the deoxygenation of aliphatic and aromatic epoxide by PPA

Under optimal conditions, PPA catalyst was explored for various aliphatic and aromatic epoxides (**Table 3**) to afford alkenes **21a**-**21l** in excellent yields 85-96% at 50 ^{0}C under neat condition (**Table 3, entries 1-12**) within 5-10 minutes. Like, aromatic (**Table 3, entries 1-3 & 9-11**), alicyclic (**Table 3, entry 4, 6 & 12**), aliphatic (**Table 3, entries 5,7 & 8**) epoxides were transformed to alkenes in excellent yields. The carbonyl, nitro, hydroxyl, esters and ketone groups in the deoxygenation of alicyclic epoxides (**Table 3, entries 4 & 12**) and ether linkage in the aromatic and aliphatic epoxides (**Table 3, entries 8 & 9**) remained unaffected during the reaction. Our method is also highly stereospecific in nature. For example, deoxygenation of Z-stilbene oxide gave Z-stilbene and E-stilbene oxide to E-stilbene (**Table 3, entry 10 & 11**) and the chemoselectivity between epoxide ring and hydroxyl group (**Table 3, entry 12**). All products were characterized by comparing with their physical and chemical properties of authentic samples. [18]

Table 3. Deoxygenation of aliphatic and aromatic epoxide by polyphosphoric acid



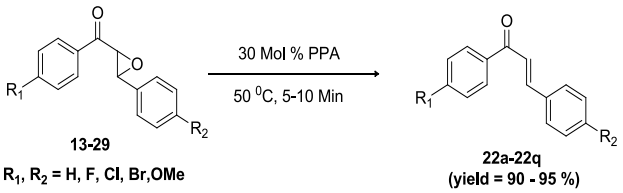
Entry	Epoxides	Product	Time (min)	Yield (%)[a]
1		 **21a**	5	95
2		 **21b**	5	92
3		 **21c**	5	90
4		 **21d**	5	88
5		 **21e**	6	93
6		 **21f**	5	88
7		 **21g**	5	85
8		 **21h**	6	85
9		 **21i**	6	88
10		 **21j**	10	86
11		 **21k**	5	96
12		 **21l**	5	95

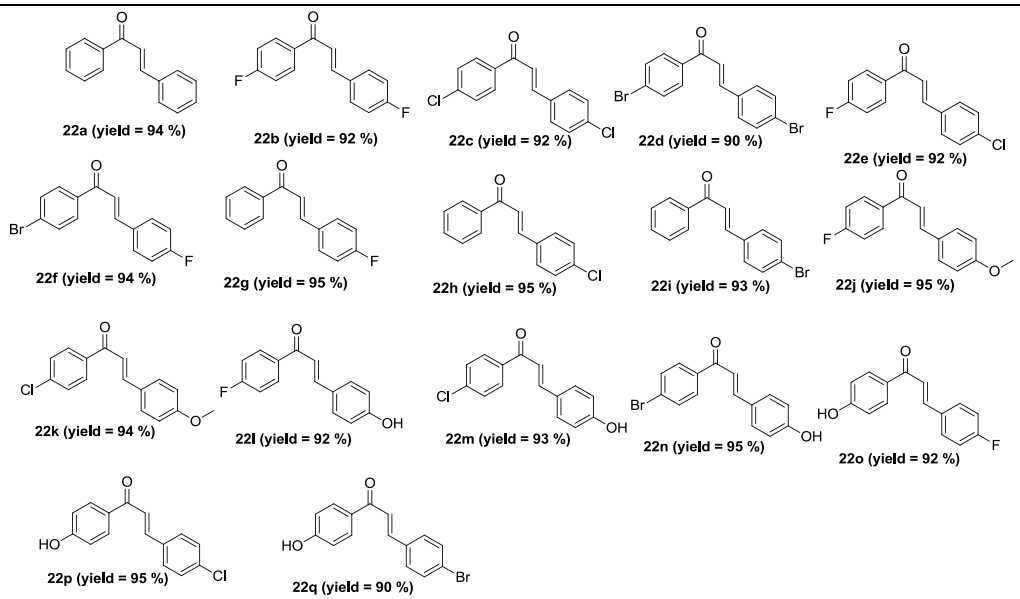
[a] Yields of Isolated product, all these product are characterized by comparing their physical and chemical properties with authentic samples.[18]

8.3.4. Examples of the deoxygenation of chalcone epoxide by PPA

Under optimal condition, we have converted various chalcone epoxides to chalcone **22a-22q** with novel PPA catalyst in excellent yield (90-95%) within 5-10 minutes at 50 ^{0}C (Scheme 1). As depicted in Scheme 1, PPA has transformed various chalcone epoxides into corresponding chalcones in excellent yield without affecting carbonyl, hydroxyl and halogen groups (Scheme 1). The products were characterized on the basis of their spectral analysis ^{1}H- and ^{13}C-NMR, GC-MS (see, supporting information). For example, product **22h,** the ^{1}H-NMR spectra showed two characteristic doublet peaks at δ 4.25 & 4.06 ppm (*J* =1.5-2 Hz) of corresponding epoxide (–CHOCH-) dissapeared and two protons peak of –CH=CH- appeared downfield in aromatic proton region between δ 6.5-8.0 ppm. ^{13}C-NMR spectra, the disappearance of characteristic peaks at δ 61.03 & 58.81 ppm of (–CHOCH-) groups and the two protons peak appeared in downfield region at δ 122.41 & 116.20 ppm and carbonyl peak somewhat shifted downfield compaired to the corresponding epoxide, indicated deoxygenation of chalcone epoxide to chalcone. These compounds were further characterised by IR and GC-MS.

Scheme 1. Deoxygenation of chalcone epoxide by polyphosphoric acid

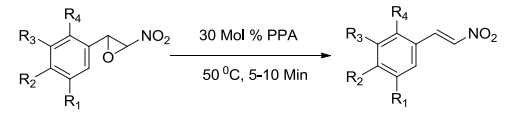




8.3.5. Examples of the deoxygenation of styrene epoxide by PPA

We also performed deoxygenation of various nitro styrene epoxides with PPA catalyst at 50 ^{0}C under neat condition to afford products **23a-23j** in excellent yields 85-92 % within 5-10 min. (Scheme 2). The products were characterized on the basis of their spectroscopic analysis. For example, product **23b,** ^{1}H-NMR spectra showed absence of two characteristic doublet peaks at δ 5.41 & 3.87 ppm of –CHOCH-N- (J = 2.5 Hz) and appearance of –CH=CH-N in aromatic region. Similarlly, ^{13}C-NMR spectra, the absence of two characteristic peaks at δ 100.18 & 89.26 ppm of –COC-N- carbon nitrostyrene epoxide indicated deoxygenation of nitrostyrene epoxide to nitrostyrene. These compounds were further characterised by IR and GC-MS.

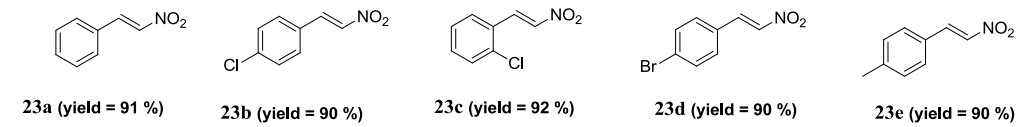
Scheme 2. Deoxygenation of nitro styrene epoxide by polyphosphoric acid



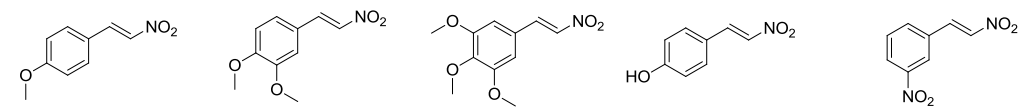
30-39

23a-23j (yield = 85 - 92 %)

R_1=H,OCH_3
R_2=H,Br,Cl,CH_3,NO_2,OCH_3
R_3=H,OCH_3,NO_2
R_4=Cl,H



23a (yield = 91 %) **23b (yield = 90 %)** **23c (yield = 92 %)** **23d (yield = 90 %)** **23e (yield = 90 %)**

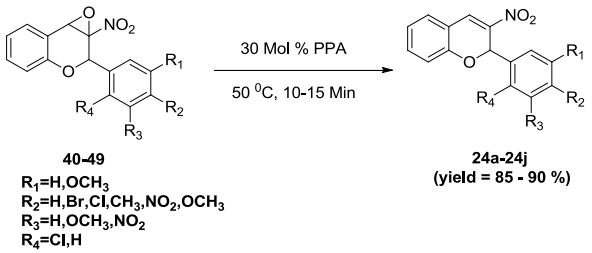


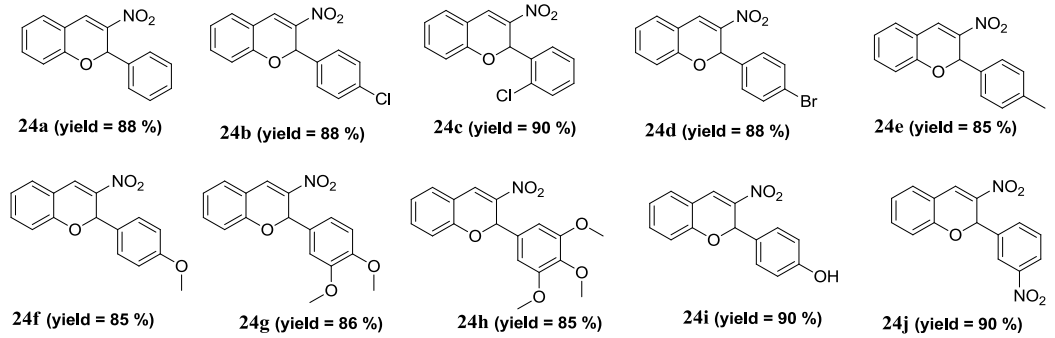
23f (yield = 87 %) **23g (yield = 88 %)** **23h (yield = 87 %)** **23i (yield = 90 %)** **23j (yield = 92 %)**

8.3.6. Examples of the deoxygenation of styrene epoxide by PPA

We also carried out deoxygenation of hindered chromene epoxides with catalyst PPA (Scheme 3). It gave deoxygenation products **24a -24j** in excellent yield (85-90%) within 10-15 minutes at 50 ^{0}C under neat condition. Spectral analysis for example, compound **24b,** ^{1}H-NMR spectra showed the characteristic singlet peak at δ 6.86 ppm of –CH=CH-N- and absence of peak at δ 3.82 ppm of nitrochromene epoxide indicated the deoxygenation product. Similarlly, in ^{13}C-NMR spectra, the characteristic peaks at δ 60.67 & 116.94 ppm of –C=C-N- carbon indicated the deoxygenation to nitrochromene. These compounds were further characterised by IR and GC-MS.

Scheme 3. Deoxygenation of nitrochromene epoxide by polyphosphoric acid

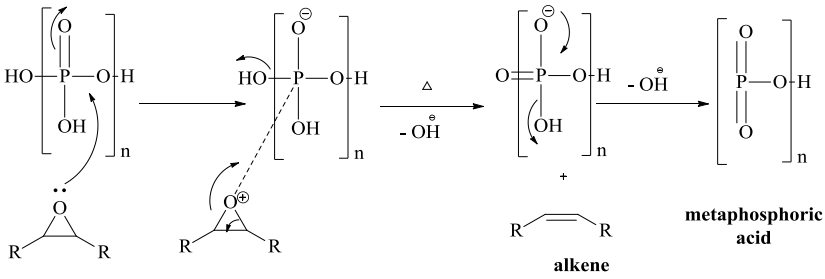




8.4. MECHANISM

In scheme 4, we suggested a plausible reaction mechanism as S_N2 nucleophilic attack of oxygen lone pair of epoxide on phosphorous of PPA (like Wittig and Horner- Wadsworth-Emmons reactions) followed by the reaction like [2+2] chelotropic pericyclic reaction gave the corresponding alkenes with removal of meta-phosphoric acid [19] (Scheme 4).

Scheme 4. Plausible mechanism for the deoxygenation of epoxides to alkenes



8.5. CONCLUSION

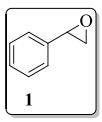
In conclusion, we have reported polyphosphoric acid as an efficient catalyst in the eliminative deoxygenation reaction for epoxides to give olefins in excellent yield (85-96%) under neat condition. This method has advantages as inexpensive reagent, high yield, short reaction time, eco-friendly and green reaction.

8.6. EXPERIMENTAL DETAILS

8.6.1. General procedure for the synthesis of chromene epoxides (39-49): Aqueous NaOH (5M, 10 ml) was added drop wise to a stirred solution of chromines (18 mmol) in aq. THF (30 ml, H_2O: THF, 1:2 ratio) and further stirred for 10 min. Then, H_2O_2 (15 ml, 30% wt.%) was added drop wise and further stirred for 2 days at room temperature. TLC monitoring, the reaction mixture was poured in water. The resulting precipitate was filtered, washed with water and dried under reduced pressure. The product was recrystallized in EtOH or silica gel column chromatography in petroleum ether: CH_2Cl_2 (8:2) as eluent gave chromene epoxide **(39-49) in** 60-70% yields.

General procedure for the Deoxygenation of aliphatic and aromatic epoxide, chalcone epoxide, nitro styrene epoxide and nitrochromene epoxide by novel Catalyst polyphosphoric acid: The PPA (30 mol%) was added to a epoxide (1mmole) and the mixture was heated under neat condition for 15 min at 50 ^{0}C, and the progress of reaction was monitored by TLC. After 15 min the reaction mixture was poured in ice-water, precipitation obtained, stirred for 10 min and filtered the solid, dried to gave pure products **21a-21l/ 22a-22q/23a-23j and 24a- 24j** with 85-96% yield. 2-(2-cholorophenyl)-3-nitro-2H-chromene (3d): Yellow solid; Yield: 258 mg (90%); melting point-90-92 ^{0}C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 8.15(s, 1H), 7.48 (dd, *J* = 1Hz, 9.5Hz, 1H), 7.34(dd, *J*= 2Hz, 8Hz, 1H), 7.32-7.27 (m, 2H), 7.192 (dd, J = 2Hz, 8Hz, 1H), 7.07 (s, 1H), 7.0 (dt, *J*=1Hz, 1H), 6.82 (d, *J*=8Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 153.61, 146.74, 144.99, 139.94, 134.77, 129.92, 128.99, 128.72, 128.59, 127.21, 122.34, 121.94, 116.91, 114.47, 79.59; I R (vmax, cm-1): 3069, 2923, 1644, 1511, 1327, 1107;GCMS (m/z) 287 [M^+. $C_{15}H_{10}$ $ClNO_3$] 289, 287, 270, 257, 241, 205, 176, 146 (100%), 89, 76, 63.

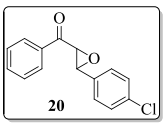
8.6.2. Characterization data for selected synthesized compounds

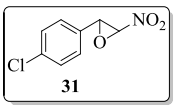


2-phenyloxirane (1): Colorless oily liquid; Yield: 115 mg (96%); boiling point-145 ^{0}C;**^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 7.34-7.24 (m, 5H), 3.83 (t, *J* = 4.0 Hz , 1H), 3.12 (t, *J* = 5.0 Hz , 1H), 2.77 (dd, *J* = 7.0, 3.5 Hz , 1H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 137.68, 128.61, 128.29, 125.59, 52.48, 51.35; **IR νmax (KBr, cm^{-1}):** 2994, 2888 (aromatic C-H str), 1622 (aromatic, C=C str), 1263, 1096, 860, 745; **GC-MS (m/z):** 120 [M^+., C_8H_8O].

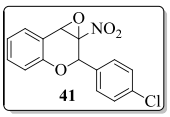
(3-(4-chlorophenyl)oxiran-2-yl)(phenyl)methanone (20): White solid; Yield: 247 mg (96%); melting point-155 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 8.01 (d, *J* = 8.5,1.5 Hz, 2H), 7.62

(d, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 8.5 Hz, 2H), 7.37(t, *J* = 7.0 Hz, 2H), 7.30 (dd, *J* = 8.5, 2.5 Hz, 2H), 4.25 (d, *J* = 1.5 Hz, 2H), 4.06 (d, *J* = 1.5 Hz, 2H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 192.83, 135.44, 134.23, 134.11, 129.13, 129.04, 128.45, 127.22, 61.03, 58.81; **IR νmax (KBr, cm^{-1}):** 2933, 2877 (aromatic C-H str), 1598 (aromatic, C=C str), 1266, 1085, 866, 731; **GC-MS (m/z):** 258 [M^+., $C_{15}H_{11}ClO_2$].

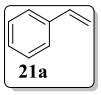




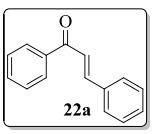
2-(4-chlorophenyl)-3-nitrooxirane (31): Yellow oily liquid; Yield: 189 mg, (95%); boiling point-150-152 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 7.44 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 5.41 (s, 1H), 3.87 (s, 1H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 136.00, 132.98, 128.93, 127.36, 100.18, 89.26; **IR (vmax, cm^{-1}):** 3118, 3057, 1516, 1339; **GCMS (m/z):** 199 [M^+.$C_8H_6ClNO_3$] .



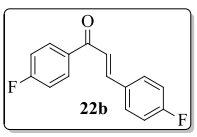
2-(4-chlorophenyl)-1a-nitro-2,7b-dihydro-1aH-oxireno[2,3-c]chromene (41): Brown oily liquid; Yield: 196 mg (65%); boiling point-160-163 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 7.36 (dd, *J* = 7.0, 2.0 Hz, 2H), 7.21 (t, *J*= 7.5 Hz, 1H), 7.11-6.97 (m, 3H), 6.94 (dd, *J*=6.5, 2.0 Hz, 1H), 5.29 (s, 1H), 3.82 (s, 1H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 153.61, 134.77, 129.92, 128.99, 128.72, 128.59, 127.21, 122.34, 121.94, 116.91, 111.47, 89.87, 60.67; **I R (vmax, cm-1):** 3070, 2925, 1642, 1513, 1329, 1108; **GCMS (m/z):** 303 [M^+. $C_{15}H_{10}$ $ClNO_4$].



styrene (21a): Colorless oily liquid; Yield: 99 mg (95%); boiling point-145 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 7.43-7.41 (m, 2H), 7.35-7.31 (m,2H), 7.27-7.24 (m, 1H), 7.15-7.13 (m, 1H,), 6.73 (m,1H), 5.78 (d, *J* = 1.5, 1H), 5.26 (d, *J* = 1.5, 1H) ; **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 137.63, 136.95, 128.61, 127.89, 126.29, 125.58, 113.91; IR (vmax, cm-1):3106, 2908, 2839, 1498, 1309; **GCMS (m/z):** 104 [M^+.C_8H_8].

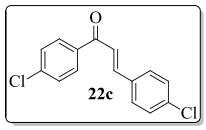


(E)-chalcone (22a): Yellow solid; Yield: 192 mg (94%); melting point-55-57 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 7.99 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 4H), 7.30 (d, *J* = 8.5 Hz, 4H), 7.12 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 190.70, 144.98, 138.28, 134.96, 132.91, 130.67, 129.07, 128.73, 128.61, 128.56, 122.15; **IR νmax (KBr, cm^{-1}):** 2935, 2877 (aromatic C-H str), 1585 (aromatic, C=C str), 1266, 1088, 862, 733; **GC-MS (m/z):** 208 [M^+., $C_{15}H_{12}O$].

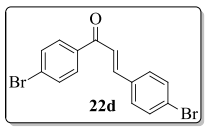


(E)-1,3-bis(4-fluorophenyl)prop-2-en-1-one (22b): Yellow solid; Yield: 224mg (92%); melting point-56-58 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 8.01 (d, *J* = 8.5 Hz, 2H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.58-7.49 (m, 2H), 7.39

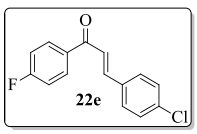
(d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 190.47, 165.40, 162.90, 143.65, 138.18, 132.98, 130.50, 130.41, 128.75, 128.57, 128.20, 121.82, 116.35, 116.13; ; **IR νmax (KBr, cm^{-1}):** 2922, 2875 (aromatic C-H str), 1595 (aromatic, C=C str), 1266, 1089, 858, 731; **GC-MS (m/z):** 244[M^+., $C_{15}H_{10}F_2O$].



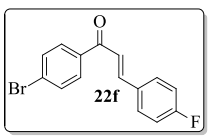
(E)-1,3-bis(4-chlorophenyl)prop-2-en-1-one (22c): Yellow solid; Yield: 255 mg (92%); melting point-56-57 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 8.01 (d, *J* = 8.5 Hz, 2H), 7.77-7.61 (m, 3H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.14-7.09 (m, 2H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 188.66, 142.59, 136.27, 133.66, 131.56, 130.77, 129.60, 129.29,122.41, 118.60, 118.19; **IR νmax (KBr, cm^{-1}):** 2920 (aromatic C-H str), 1592 (aromatic, C=C str), 1406, 1336, 1233, 1091, 771 (C-Cl, str); **GC-MS (m/z):** 276[M^+., $C^{15}H_{10}Cl_2O$], 278 [M^{+2}]



(E)-1,3-bis(4-bromophenyl)prop-2-en-1-one (22d): Yellow solid; Yield: 334mg (90%); melting point-55-59 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 8.00 (d, *J* = 9.0 Hz, 2H), 7.75-7.61 (m, 3H), 7.45 (d, *J* = 9.0 Hz, 1H), 7.14-7.08 (m, 4H) ; **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 190.69, 144.98, 138.29, 134.96, 132.91, 130.67, 129.07, 128.74, 128.61, 128.56, 122.16; **IR νmax (KBr, cm^{-1}):** 2992, 2886 (aromatic C-H str), 1620 (aromatic, C=C str), 1262, 1095, 860, 743; **GC-MS (m/z):** 364[M^+., $C_{15}H_{10}Br_2O$], 366 [M^{+2}].

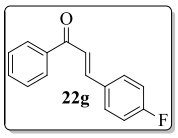


(E)-3-(4-chlorophenyl)-1-(4-fluorophenyl)prop-2-en-1-one (22e): Yellow solid; Yield: 239 mg (92%); melting point-58-59 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 8.01 (d, *J* = 7.5 Hz, 2H), 7.74 (d, *J* = 15.5 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.51(d, *J* = 16.0 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 188.69, 161.14, 142.67, 134.07, 132.24, 131.54, 130.78, 130.44, 129.82, 124.64, 122.49, 116.20; **IR νmax (KBr, cm^{-1}):** 2931, 2873 (aromatic C-H str), 1597 (aromatic, C=C str), 1263, 1081, 860, 737; **GC-MS (m/z):** 260 [M^+., $C_{15}H_{10}ClFO$].

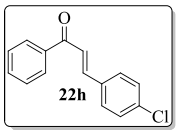


(E)-1-(4-bromophenyl)-3-(4-fluorophenyl)prop-2-en-1-one (22f): Yellow solid; Yield: 285mg (94%); melting point-60-62 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 8.02 (d, *J* = 8.5 Hz, 2H), 7.93-7.75 (m, 1H), 7.74 (d, *J* = 15.5 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.39-7.30 (m, 2H), 6.98 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 190.70, 160.07, 144.98, 138.28, 134.96, 132.91, 130.67, 129.07,

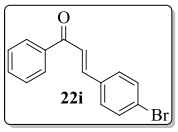
128.73, 128.61, 122.16; **IR νmax (KBr, cm^{-1}):** 2951, 2880 (aromatic C-H str), 1607 (aromatic, C=C str), 1271, 1107, 843, 729; **GC-MS (m/z):** 304 [M^+., $C_{15}H_{10}BrFO$], 306 [M^{+2}].



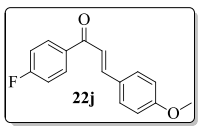
(E)-3-(4-fluorophenyl)-1-phenylprop-2-en-1-one (22g): Yellow solid; Yield: 214mg (95%); melting point-60-62 ^{0}C;**^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 8.01 (d, *J* = 7.0 Hz, 2H), 7.72 (d, *J* = 15.5 Hz, 1H), 7.55-7.49 (m, 5H), 7.26 (d, J = 7.0 Hz, 1H), 6.98 (d, *J* = 7.0 Hz, 2H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 188.66, 161.13, 142.59, 136.27, 133.65, 131.56, 130.76, 129.60, 129.29, 122.40, 116.20; **IR νmax (KBr, cm^{-1}):** 2920 (aromatic C-H str), 1592 (aromatic, C=C str), 1406, 1336, 1233, 1125(C-O-C, str), 1091, 771 (C-Cl, str); **GC-MS (m/z):** 226[M^+., $C_{15}H_{11}FO$].



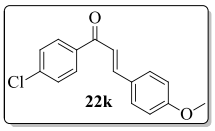
(E)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (22h): Yellow solid; Yield: 229 mg (95%); melting point-56-57 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 8.01 (d, *J* = 9.0 Hz , 2H), 7.78-7.56 (m, 4H), 7.53-7.51 (m, 3H), 7.48-7.26 (m, 2H);**^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 188.66, 142.59, 136.27, 133.65, 131.57, 130.77, 129.60, 129.29, 122.41, 116.20; **IR νmax (KBr, cm^{-1}):** 2992, 2886 (aromatic C-H str), 1620 (aromatic, C=C str), 1262, 1095, 860, 743; **GC-MS (m/z):** 242 [M^+., $C_{15}H_{11}ClO$].



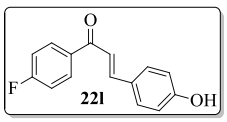
(E)-3-(4-bromophenyl)-1-phenylprop-2-en-1-one (22i): Yellow solid; Yield: 265 mg (93%); melting point-55-57 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 8.02 (t, *J* = 8 Hz , 2H), 7.72 (d, *J* = 8 Hz, 2H), 7.56-7.50 (m, 3H), 7.27 (d, *J* = 7.5 Hz, 1H),6.99 (d, *J* = 7 Hz,2 H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 190.00, 143.45, 138.09, 133.45, 133.05, 129.69, 129.35, 128.77, 128.59, 122.52, 120.35; **IR νmax (KBr, cm^{-1}):** 2951, 2880 (aromatic C-H str), 1607 (aromatic, C=C str), 1271, 1107, 843, 729; **GC-MS (m/z):** 286[M^+., $C_{15}H_{11}BrO$], 288 [M^{+2}].



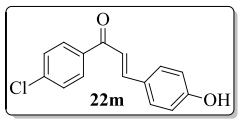
(E)-1-(4-fluorophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (22j): Yellow solid; Yield: 243 mg (95%); melting point-59-61 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 8.01 (d, *J* = 8.5 Hz , 2H), 7.74 (d, *J* =15.5 Hz,1H), 7.58-7.49 (m, 3H), 7.38 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.5 Hz,2H), 3.88 (m,3H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 190.47, 165.40, 162.90, 143.65, 138.18, 132.98, 131.18, 130.50, 130.41, 128.75, 128.57, 128.20, 121.82, 116.35, 116.33, 55.47; **IR νmax (KBr, cm-1):** 2931, 2873 (aromatic C-H str), 1597 (aromatic, C=C str), 1263, 1081, 860, 737; **GC-MS (m/z):** 256[M^+., $C_{16}H_{13}FO_2$].



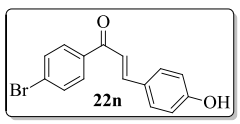
(E)-1-(4-chlorophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (22k): Yellow solid; Yield: 255mg (94%); melting point-58-60 ^{0}C; **^{1}H NMR (CDCl$_3$, 500 MHz) δ ppm** 8.02 (d, *J* = 9.0 Hz , 2H), 7.73 (d, *J* = 9 Hz , 1H) 7.57 (d, *J* = 8.5 Hz, 3H), 7.50 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 3.83 (s,3H); **^{13}C NMR (CDCl3, 125 MHz) δ ppm** 189.52, 161.94, 145.41, 137.29, 131.95, 130.46, 130.06, 127.72, 127.45, 119.15, 114.55, 55.55; **IR νmax (KBr, cm^{-1}):** 2950 (aromatic C-H str), 1582 (aromatic, C=C str), 1389, 1275, 1059, 854, 723 (C-Cl, str); **GC-MS (m/z):** 272[M$^+$., $C_{16}H_{13}ClO_2$].



(E)-1-(4-bromophenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (22l): Yellow solid; Yield: 222 mg (92%); melting point-60-62 ^{0}C; **^{1}H NMR (CDCl$_3$, 500 MHz) δ ppm** 8.001 (d, *J* = 8 Hz, 2H), 7.775 (d, *J* = 15.5 Hz, 1H), 7.633 (t, 2H), 7.471 (d, *J* =16 Hz, 1H), 7.11 (t, *J* = 8.5 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 1H); **^{13}C NMR (CDCl$_3$, 125 MHz) δ ppm** 187.50, 164.68, 162.67, 141.94, 132.02, 131.52, 131.45, 129.53, 122.46, 116.42, 116.25; **IR νmax (KBr, cm-1):** 3426 (OH str), 2923 (aromatic C-H str), 1591 (aromatic, C=C str), 1417, 1395, 1282, 1170, 1092; **GC-MS (m/z):** 242[M$^+$., $C_{15}H_{11}FO_3$].

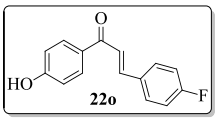


(E)-1-(4-chlorophenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (22m): Yellow solid; Yield: 239 mg (93%); melting point-58-62 ^{0}C; **^{1}H NMR (CDCl$_3$, 500 MHz) δ ppm** 7.992 (d, *J* = 8.5 Hz, 2H), 7.766 (d, *J* = 15.5 Hz, 1H), 7.636- 7.583 (m, 2H), 7.462 (d, *J* = 15.5 Hz, 1H), 7.102 (t, *J* = 8.5 Hz, 2H), 6.946 (d, *J* = 8.5 Hz, 1H); **^{13}C NMR (CDCl3, 125 MHz) δ ppm** 187.24, 162.41, 141.68, 131.76, 131.26, 131.19, 129.27, 122.20, 116.16, 115.99; **IR νmax (KBr, cm-1):** 3452 (OH str), 2963 (aromatic C-H str), 1599 (aromatic, C=C str), 1451, 1419, 1262, 1021, 933, 868, 799 and 704; **GC-MS (m/z):** 258 [M+., $C_{15}H_{11}ClO_3$].

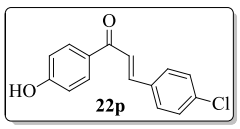


(E)-1-(4-bromophenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (22n): Yellow solid; Yield: 286mg (95%); melting point-60-63 ^{0}C;**^{1}H NMR (CDCl$_3$, 500 MHz) δ ppm** 7.992 (d, *J* = 8.5 Hz, 2H), 7.767 (d, *J* = 15.5 Hz, 1H), 7.625 (m, 2H), 7.462 (d, *J* = 15.5 Hz, 1H), 7.102 (t, *J* = 8.5 Hz, 2H), 6.946 (d, *J* = 8.5 Hz, 1H); **^{13}C NMR (CDCl$_3$, 125 MHz) δ ppm** 186.98, 162.15, 141.42, 131.51, 131.00, 130.93, 129.02, 121.95, 115.91, 115.74, 115.31; **IR νmax (KBr, cm-1):** 3408 (OH str), 2917

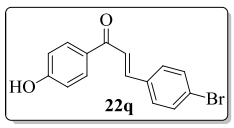
(aromatic C-H str), 1589 (aromatic, C=C str), 1489, 1415, 1288, 1177, 1091, 1014, 929 and 701; **GC-MS (m/z):** 302[M^+., $C_{15}H_{11}BrO_2$], 304 [M^{+2}].



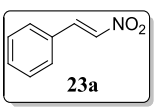
(E)-3-(4-fluorophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (22o): Yellow solid; Yield: 222 mg (92%); melting point-60-62 ^{0}C; **^{1}H NMR (CDCl$_3$, 500 MHz) δ ppm** 7.99(d, *J* = 8.5 Hz, 2H), 7.77 (d, *J* = 15.5 Hz, 1H), 7.62 (dd, *J* = 6, 13.5 Hz, 2H), 7.46 (d, *J* = 15.5 Hz, 1H), 7.10 (t, *J* = 8 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 2H), 6.24 (s, 1H, br, D2O exchangeable); **^{13}C NMR (CDCl$_3$, 125 MHz) δ ppm** 187.50, 164.68, 162.67, 141.94, 132.02, 131.52, 131.45, 129.53, 122.46, 116.42, 116.25; **IR νmax (KBr, cm^{-1}):** 3415 (OH str), 2931, 2873 (aromatic C-H str), 1681 (C=O str), 1597 (aromatic, C=C str), 1263, 1081, 860, 737; **GC-MS (m/z):** 242 [M^+., $C_{15}H_{11}FO_2$].



(E)-3-(4-chlorophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (22p): Yellow solid; Yield: 245 mg (95%); melting point-61-64 ^{0}C; **^{1}H NMR (CDCl$_3$, 500 MHz) δ ppm** 7.99 (d, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 15.5 Hz, 1H), 7.63-7.61 (m, 2H), 7.45 (d, *J* =16 Hz, 1H), 7.10 (t, *J* = 8.5 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 2H), 6.2 (s, 1H, br, D2O exchangeable); **^{13}C NMR (CDCl$_3$, 125 MHz) δ ppm** 187.20, 162.37, 141.64, 131.72, 131.22, 131.15, 129.23, 122.16, 116.12, 115.95; **IR νmax (KBr, cm^{-1}):** 3408 (OH str), 2928, 2876 (aromatic C-H str), 1684 (C=O str), 1598 (aromatic, C=C str), 1268, 1085, 864, 735; **GC-MS (m/z):** 258 [M^+., $C_{15}H_{11}ClO_2$].

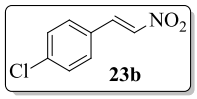


(E)-3-(4-bromophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (22q): Yellow solid; Yield: 289 mg (90%); melting point-61-63 ^{0}C;**^{1}H NMR (CDCl$_3$, 500 MHz) δ ppm** 7.99 (d, *J* = 8 Hz, 2H), 7.77 (d, *J* = 15.5 Hz, 1H), 7.63 (t, *J* = 8Hz, 2H), 7.46 (d, *J* = 15.5 Hz, 1H), 7.10 (t, *J* = 8.5 Hz, 2H), 6.95 (d, *J* = 8 Hz, 2H); **^{13}C NMR (CDCl$_3$, 125 MHz) δ ppm** 186.88, 162.05, 141.32, 131.41, 130.90, 130.83, 128.92, 121.85, 115.81, 115.21; **IR νmax (KBr, cm^{-1}):** 3410 (OH str), 2926, 2875 (aromatic C-H str), 1686 (C=O str), 1599 (aromatic, C=C str), 1265, 1078, 862, 730; **GC-MS (m/z):** 302 [M^+., $C_{15}H_{11}BrO_2$], 304 [M^{+2}].



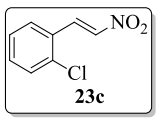
(E)-1-(2-nitrovinyl) benzene (23a): Yellow Solid; Yield: 135 mg (91%); melting point - 55-57 ^{0}C;**^{1}H NMR (CDCl$_3$, 500 MHz) δ ppm** 8.02 (d, *J* = 14Hz, 1H), 7.59 (d, *J* =14Hz, 1H), 7.57-7.53 (m, 2H), 7.52-7.48 (m, 1H), 7.32-

7.43 (m, 2H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 139.54, 136.27, 131.54, 130.77, 129.62, 124.36; **IR (vmax, cm-1):** 3106, 3042, 1508, 1341. **GCMS (m/z):** 149 [M^+.$C_8H_7NO_2$] 150, 149(100%), 148, 132, 125, 104, 92, 74, 60.



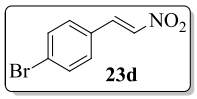
23b

(E)-1-choloro-4-(2-nitrovinyl) benzene (23b): Yellow solid; Yield: 170 mg (90%); melting point-115-116 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 7.99 (d, *J* = 13.5 Hz, 1H), 7.58 (d, *J* = 13.5Hz, 1H), 7.52-7.51(m, 2H), 7.47-7.45(m, 2H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 137.30, 136.65, 133.00, 130.92, 129.62, 129.29; **IR(vmax, cm^{-1}):** 3099, 3025, 1590, 1398; **GCMS (m/z):** 183 [M^+.$C_8H_6ClNO_2$] 185, 183, 149, 148, 136, 125, 102(100%), 74, 73.



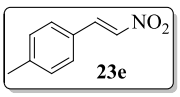
23c

(E)-1-choloro-2-(2-nitrovinyl) benzene (23c): Brown solid; Yield: 168 mg (92%); melting point-40-42 ^{0}C;**^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 7.96 (d, *J* = 13.6 Hz, 1H), 7.51 (d, *J* = 13.6Hz, 1H), 7.47-7.45 (m, 2H), 6.91-6.89 (m, 2H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 139.52, 136.27, 133.62, 131.54, 130.77, 129.62, 129.30, 124.36; **IR (vmax, cm^{-1}):** 3116, 3056, 1516, 1338; **GCMS (m/z):** 183 [M^+.$C_8H_6ClNO_2$] 185, 183, 149, 148, 136, 125, 102(100%), 74, 73.



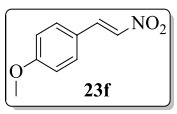
23d

(E)-1-bromo-4-(2-nitrovinyl) benzene (23d): Light yellow solid; Yield: 204 mg (90%); melting point-148-150 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 7.94 (d, *J* = 14 Hz, 1H), 7.60-7.58 (m, 2H), 7.57(d, *J* = 14 Hz),7.42-7.40 (m, 2H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 139.54, 136.27, 133.61, 131.54, 130.71, 129.62, 122.37; **IR (vmax,cm^{-1}):** 3102, 3052, 1507, 1331; **GCMS (m/z):** 227 [M^+.$C_8H_6ClNO_2$] 227, 229, 226, 228, 180, 182(100%), 178, 175.



23e

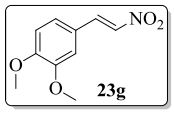
(E)-1-methyl-4-(2-nitrovinyl) benzene (23e): Yellow solid; Yield: 146 mg (90%); melting point-100-102 ^{0}C;**^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 7.99 (d, *J* = 13.5Hz, 1H), 7.57(d, *J* = 13.5Hz, 1H), 7.45-7.43 (m, 2H), 7.26-7.25 (m, 2H), 2.41(s, 3H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 140.10, 139.54, 136.27, 133.62, 131.54, 130.77, 129.62, 23.10; **IR (vmax, cm^{-1}):** 3110, 3056, 2916, 1496, 1336; **GCMS (m/z):** 163 [M^+. $C_9H_9NO_2$] 168, 163, 146, 114, 102, 80 (100%).



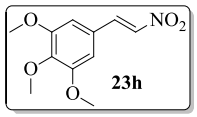
23f

(E)-1-methoxy-4-(2-nitrovinyl) benzene (23f) : Yellow solid; Yield: 155 mg (87%); melting-point-86-88 ^{0}C;**^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 7.97 (d, *J* = 13.5Hz, 1H), 7.57(d, *J* = 13.5 Hz, 1H), 7.38-7.35 (m, 1H), 7.15-7.13 (m, 1H,), 7.05-7.03(m, 2H), 3.853 (s, 3H) ; **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 157.12, 139.54,

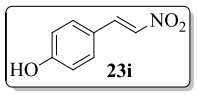
136.27, 130.77, 122.36, 115.19, 57.45; **IR (vmax, cm-1):** 3104, 2904, 2838, 1495, 1307; **GCMS (m/z):** 179 [M^+.$C_9H_9NO_3$] 179, 132, 118, 103, 89(100%).



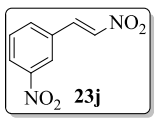
(E)-1,2-dimethoxy-4-(2-nitrovinyl)benzene (23g): Yellow solid; Yield: 183 mg (88%); melting point-138-140 ^{0}C;**^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 7.96 (d, *J* = 13.5Hz, 1H), 7.53(d, *J* = 13.5Hz, 1H), 7.18-7.16 (m, 1H), 7.00-6.91 (m, 2H), 3.947 (s, 3H), 3.901(s, 3H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 149.87, 149.10, 138.54, 135.27, 122.36, 121.12, 115.89, 115.06, 57.87; **IR (vmax, cm^{-1}):** 3128, 2958, 2923, 1500, 1334; **GCMS (m/z):** 209[M^+.$C_{10}H_{11}NO_4$] 209, 163, 162,147, 119, 77(100%).



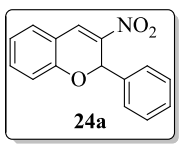
(E)-1,2,3-trimethoxy-5-(2-nitrovinyl)benzene (23h): Yellow Solid; Yield: 207 mg (87%); melting point-115-116 ^{0}C;**^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 7.93 (d, *J* = 13.6Hz, 1H), 7.53(d, *J* = 13.6Hz, 1H), 6.75(s, 2H), 3.91(s, 3H), 3.90(s, 6H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 155.12, 143.62, 137.12, 136.65,129.87, 106.00, 61.17, 55.76; **IR (vmax, cm^{-1}):** 3104, 2935, 2832, 1503, 1323; **GCMS (m/z):** 239 [M^+. $C_{11}H_{13}NO_5$] 239, 191, 176, 149, 120, 63, (100%), 53.



(E)-4-(2-nitrovinyl) phenol (23i): Yellow solid; Yield: 148 mg (90%); melting point-162-164 ^{0}C;**^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 7.96 (d, *J* = 13.6Hz, 1H), 7.51 (d, *J* = 13.6Hz, 1H), 7.47-7.45(m, 2H), 6.91-6.89 (m, 2H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 157.87, 140.11, 139.52, 130.77, 123.12, 115.10; **IR (vmax, cm^{-1}):** 3370, 3108, 1483, 1339; **GCMS (m/z):** 165 [M^+. C $_8H_7NO_3$] 166, 165, 148, 118(100%), 91, 65.

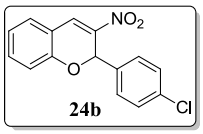


(E)-1-nitro-3-(2-nitrovinyl) benzene (23j): Light Brown solid; Yield: 178 mg, (92%); melting point-120-122 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 7.96 (d, *J* = 13.7Hz, 1H), 7.56 (d, *J* = 13.7 Hz, 1H), 7.50-7.48 (m, 2H), 7.44-7.43 (m, 2H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 148.13, 140.10, 139.54, 136.27, 133.61, 130.71, 122.35, 122.12; **IR (vmax, cm-1):** 3100, 2832, 1522, 1349; **GCMS (m/z):** 194 [M^+. $C_8H_6N_2O_4$] 194, 147, 108, 102 (100%), 89, 76, 63.

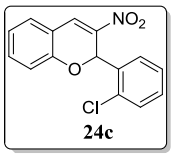


3-nitro-2-phenyl-2H-chromene (24a): Yellow solid; Yield: 222 mg (88%); melting point-98-100 ^{0}C;**^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 8.05 (s, 1H), 7.38-7.36 (m, 2H), 7.33-7.30 (m, 5H), 7.01-6.98 (m, 1H), 6.87-6.85 (m, 1H), 6.58 (s, 1H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 153.61, 146.47, 141.96, 141.35, 134.47, 130.03, 129.03, 128.85, 127.34, 127.12, 122.96, 122.60, 117.43, 107.37, 79.79; **IR (vmax, cm$^-$**

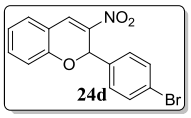
1): 3071, 1646, 1507, 1328, 1215; **GCMS (m/z):** 253 [M^+. $C_{15}H_{11}NO_3$] 253, 236, 207, 178(100%), 152, 89, 77, 63.



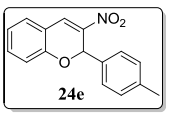
2-(4-cholorophenyl)-3-nitro-2H-chromene (24b): Yellow solid; Yield: 252 mg (88%); melting point-150 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 8.05 (s, 1H), 7.35-7.27 (m, 6H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.86(d, *J* = 8Hz, 1H), 6.57 (s, 1H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 156.96, 147.43, 145.11, 139.90,128.84, 128.80, 127.33, 126.58, 122.91, 122.55, 117.43, 115.91, 79.47; **IR (vmax, cm^{-1}):** 3076, 2923, 1639, 1495, 1323, 1214; **GCMS (m/z):** 287 [M^+. $C_{15}H_{10}$ $ClNO_3$] 287, 270, 257, 241(100%), 205, 178, 89, 77, 63.



2-(2-cholorophenyl)-3-nitro-2H-chromene (24c): Yellow solid; Yield: 258 mg (90%); melting point-90-92 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 8.15(s, 1H), 7.48 (dd, *J* = 1Hz, 9.5Hz, 1H), 7.34(dd, *J*= 2Hz, 8Hz, 1H), 7.32-7.27 (m, 2H), 7.192 (dd, J = 2Hz, 8Hz, 1H), 7.07 (s, 1H), 7.0 (dt, *J*=1Hz, 1H), 6.82 (d, *J*=8Hz, 1H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 153.61, 146.74, 144.99, 139.94, 134.77, 129.92, 128.99, 128.72, 128.59, 127.21, 122.34, 121.94, 116.91, 114.47, 79.59; **IR (vmax, cm-1):** 3069, 2923, 1644, 1511, 1327, 1107; **GCMS (m/z):** 287 [M^+. $C_{15}H_{10}$ $ClNO_3$] 289, 287, 270, 257, 241, 205, 176, 146 (100%), 89, 76, 63.



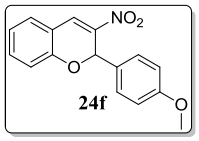
2-(4-bromophenyl)-3-nitro-2H-chromene (24d): Yellow solid; Yield: 291 mg (88%); melting point-162 ^{0}C;**^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 8.23 (s, 1H), 8.19 (d, *J* = 8.5Hz, 1H), 8.13 (s, 1H), 7.71(d, *J* = 8Hz, 1H), 7.52(t, *J* = 8 Hz, 1H), 7.36 (t, *J* = 7.5 Hz), 7.05 (t, *J* = 7.5Hz), 6.90 (d, *J* = 8.5Hz, 1H), 6.66 (s, 1H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 153.36, 146.74, 144.02, 141.16, 133.48, 132.27, 128.94, 128.72, 127.36, 124.24, 123.16, 122.48, 117.41, 79.11; **IR (vmax, cm^{-1}):** 3078, 2923, 1639, 1496, 1323, 1065; **GCMS (m/z):** 331 [M^+. $C_{15}H_{10}$ Br NO_3] 333, 331, 287, 285, 205 (100%), 176, 146, 89, 76, 63.

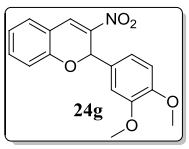


3-nitro-2-p-tolyl-2H-chromene (24e): Yellow solid; Yield: 226 mg (85%); meltingpoint-136-138 ^{0}C;**^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 8.04 (s, 1H), 7.32-7.28 (m, 2H), 7.25-7.24 (m, 2H),7.11(d, *J* = 8 Hz), 6.98 (dt, *J* = 1Hz, 1H), 6.84 (dd, J = 1Hz, 7.5Hz), 6.54 (s, 1H),2.304 (s, 3H); **^{13}C NMR (CDCl3, 125 MHz) δ ppm** 153.68, 148.83, 145.95, 140.06, 131.42, 129.70, 128.80, 127.32, 127.05, 122.86, 122.59,

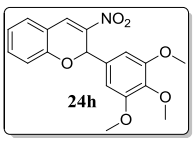
117.42, 79.71; **IR (vmax, cm^{-1}):** 3078, 2924, 1646, 1506, 1321, 1114; **GCMS (m/z):** 267 [M^{+}. $C_{16}H_{13}NO_3$] 267, 250, 237, 221(100%), 178, 146, 91, 77, 65.

2-(4-methoxyphenyl)-3-nitro-2H-chromene (24f): Yellow solid; Yield: 240 mg (85%); melting point-158-160 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 8.03 (s, 1H), 7.31 (d, *J* = 7.5Hz, 2H), 7.30-7.28 (s, 2H), 7.02-6.96 (m, 1H), 6.85-6.80 (m, 3H), 6.52 (s, 1H), 3.75 (s, 3H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 160.78, 153.74, 146.82, 143.94, 128.81, 128.55, 127.34, 126.41, 122.87, 122.62, 117.43, 114.42, 107.42, 79.54; **IR (vmax, cm^{-1}):** 2945, 1645 , 1507, 1326, 1179; **GCMS (m/z):** 283 [M^{+}. $C_{16}H_{13}NO_4$] 283, 266, 253, 237, (100%), 222, 194, 165, 91, 89, 69.

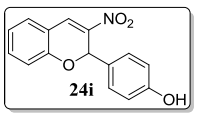




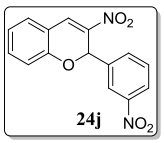
2-(3,4-dimethoxyphenyl)-3-nitro-2H-chromene (24g): Yellow solid; Yield: 269 mg (86%); melting point-86-88 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 8.05 (s, 1H), 7.33-7.29 (m, 2H), 7.01-6.98 (m, 1H), 6.92 (d, *J* = 2.05 Hz, 1H), 6.87-6.84 (m, 2H), 6.74 (d, *J* = 8.5Hz), 6.51 (s, 1H), 3.82 (s, 6H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 153.67, 150.27, 149.31, 144.79, 141.99, 128.84, 127.35, 126.69, 122.95, 122.61, 119.97, 117.47, 111.20, 109.78, 107.35, 79.77; **IR (vmax, cm^{-1}):** 2931, 1645, 1517, 1334, 1145; **GCMS (m/z):** 313 [M^{+}. $C_{17}H_{15}NO_5$] 314, 313, 267 (100%), 251, 223, 177, 122, 91, 77, 63.



3-nitro-2-(3,4,5-trimethoxyphenyl)-2H-chromene (24h): Yellow solid; Yield: 291 mg (85%); melting point-130-132 ^{0}C;**^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 8.05 (s, 1H), 7.34 (t, *J* = 7.5Hz, 1H), 7.01 (t, *J* = 7.5Hz, 1H), 6.89 (d, *J* = 8 Hz, 1H), 6.56 (s, 2H), 6.51 (s, 1H), 3.79 (s, 6H), 3.75 (s, 3H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 153.59, 147.49, 145.59, 139.13, 129.75, 128.87, 127.33, 123.05, 122.55, 117.46, 107.20, 104.11, 79.93; **IR (vmax, cm^{-1}):** 2941, 2832, 1576, 1507, 1329, 1128; **GCMS (m/z):** 343 [M^{+}. $C_{18}H_{17}NO_6$] 344, 343, 313, 297, 207 (100%), 191, 168, 91, 77, 63.



4-(3-nitro-2H-chromene-2-yl) phenol (24i): Yellow solid; Yield: 242 mg (90%); melting point-144-146 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 7.66 (s, 1H), 7.64 (s, 1H), 7.60-7.57 (m, 2H), 7.34-7.32 (m, 2H), 7.29-7.26 (m, 2H), 7.11-7.09 (m, 2H), 6.90-6.87 (m, 1H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 153.38, 147.18, 144.74, 142.09, 136.00, 132.98, 129.31, 128.93, 128.46, 127.36, 123.14, 122.49, 117.40, 79.06; **IR (vmax, cm^{-1}):** 3069, 2954, 1650, 1515, 1391, 1187; **GCMS (m/z):** 269 [M^{+}. $C_{15}H_{11}NO_4$] 269, 252, 236, 223(100%), 165, 131, 89, 77, 65.



3-nitro-2-(3-nitrophenyl)-2H-chromene (24j): Yellow solid; Yield: 268 mg (90%); melting point-160-162 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm** 8.42-8.41 (m, 1H), 8.35-8.33 (m, 1H), 8.31 (s, 1H), 8.21 (dd, *J* = 1Hz, 8Hz, 1H), 8.06-8.03 (m, 1H), 8.42-8.41(m, 1H), 7.88(d, *J* = 8Hz, 1Hz, 1H), 7.77 (d, *J* = 8Hz, 1H), 7.70-7.66 (m, 2H), 7.61 (t, *J* = 8Hz), 6.90-6.87 (m, 1H); **^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm** 153.00, 148.59, 144.68, 142.16, 136.67, 133.14, 130.15, 129.12, 127.40,124.89, 123.49, 122.34, 122.13, 117.44, 78.56; **IR (vmax, cm^{-1}):** 3074, 1649, 1520, 1395, 1070. **GCMS (m/z)** 298 [M^+. $C_{15}H_{10}N_2O_5$] 299, 298, 283, 252, 205(100%), 176, 130, 102, 76, 63.

8.7. References

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NMR SPECTRA'S

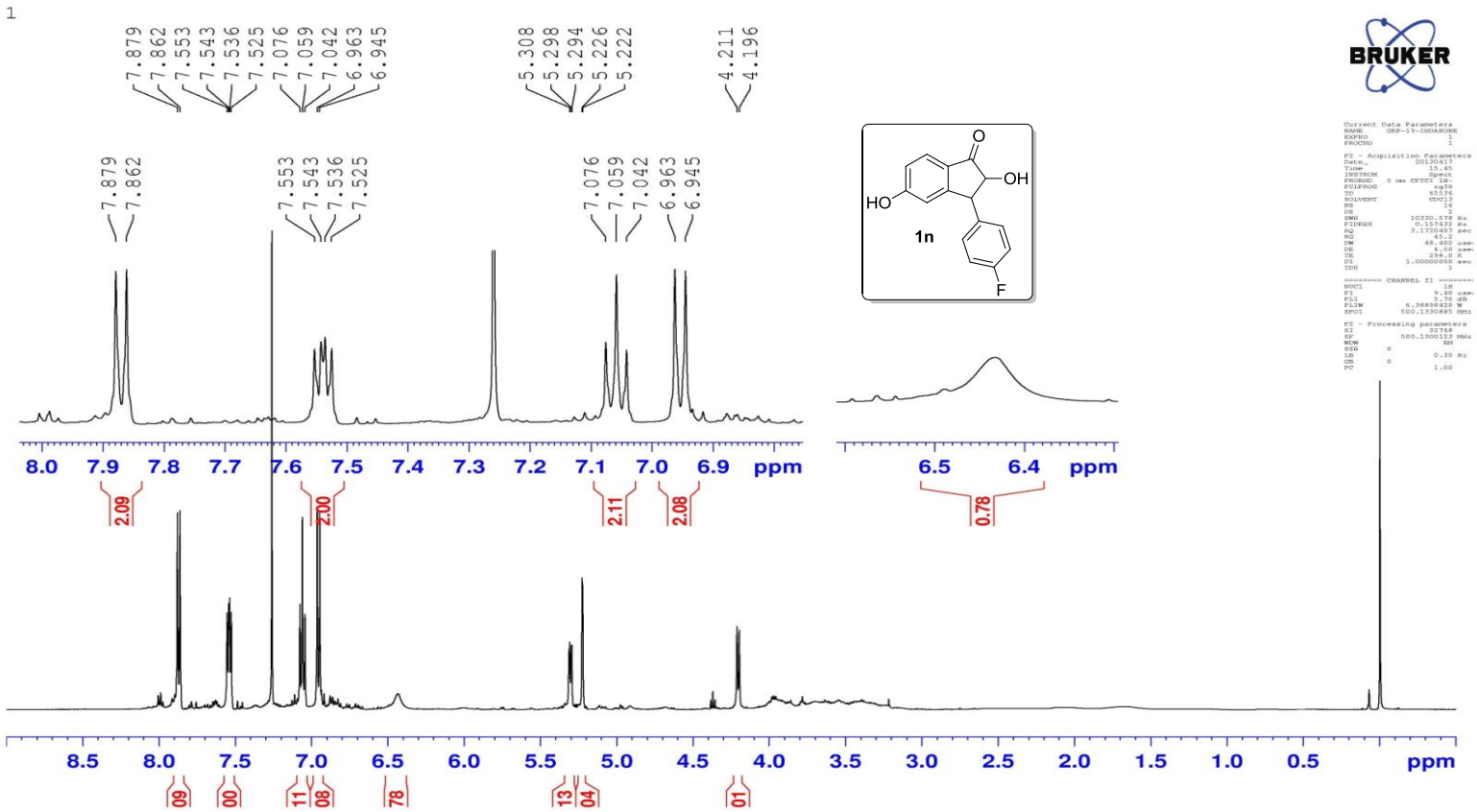


Figure S-1: ^{1}H NMR Spectrum of compound 1n

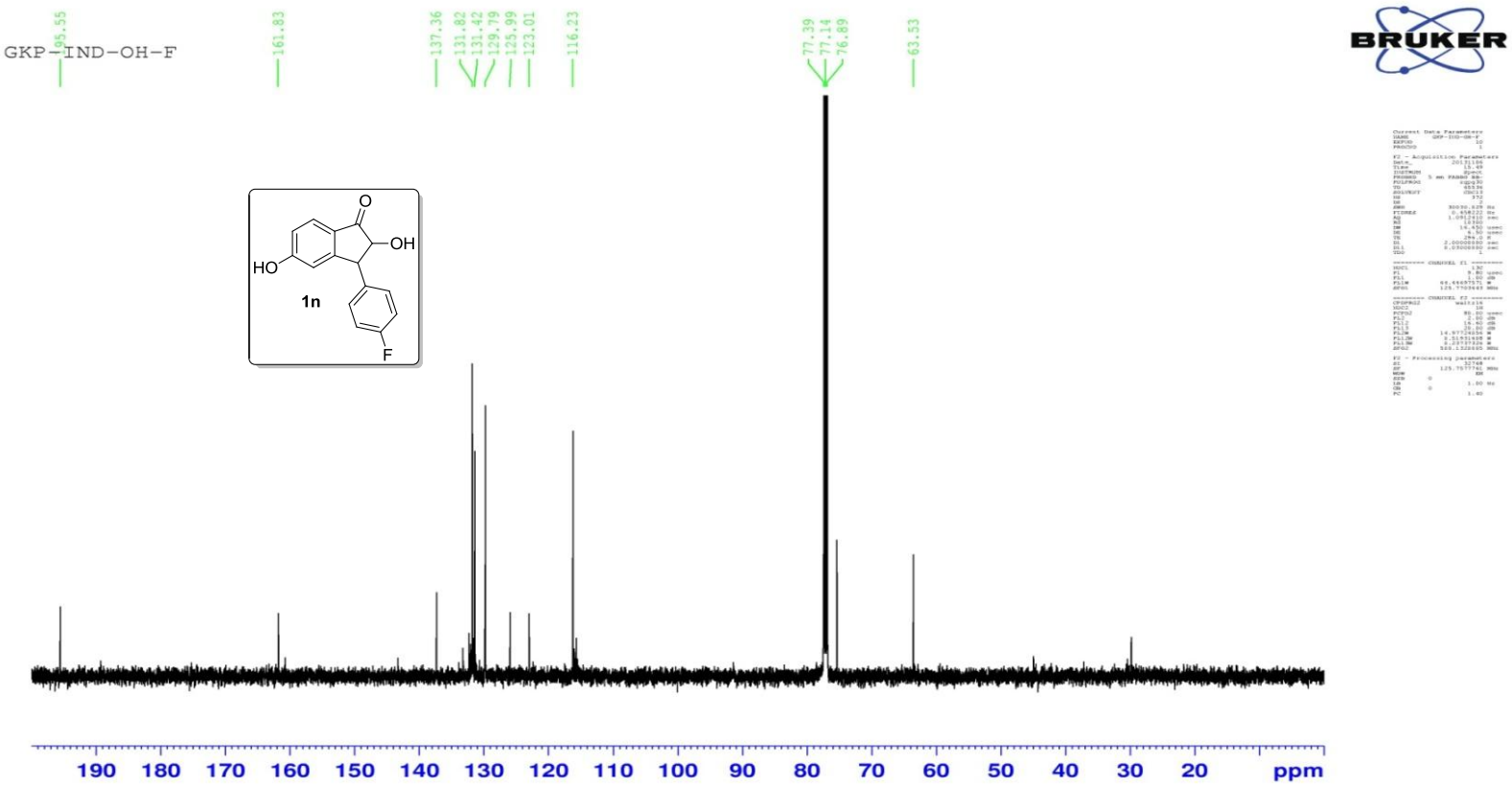


Figure S-2: ^{13}C NMR Spectrum of compound 1n

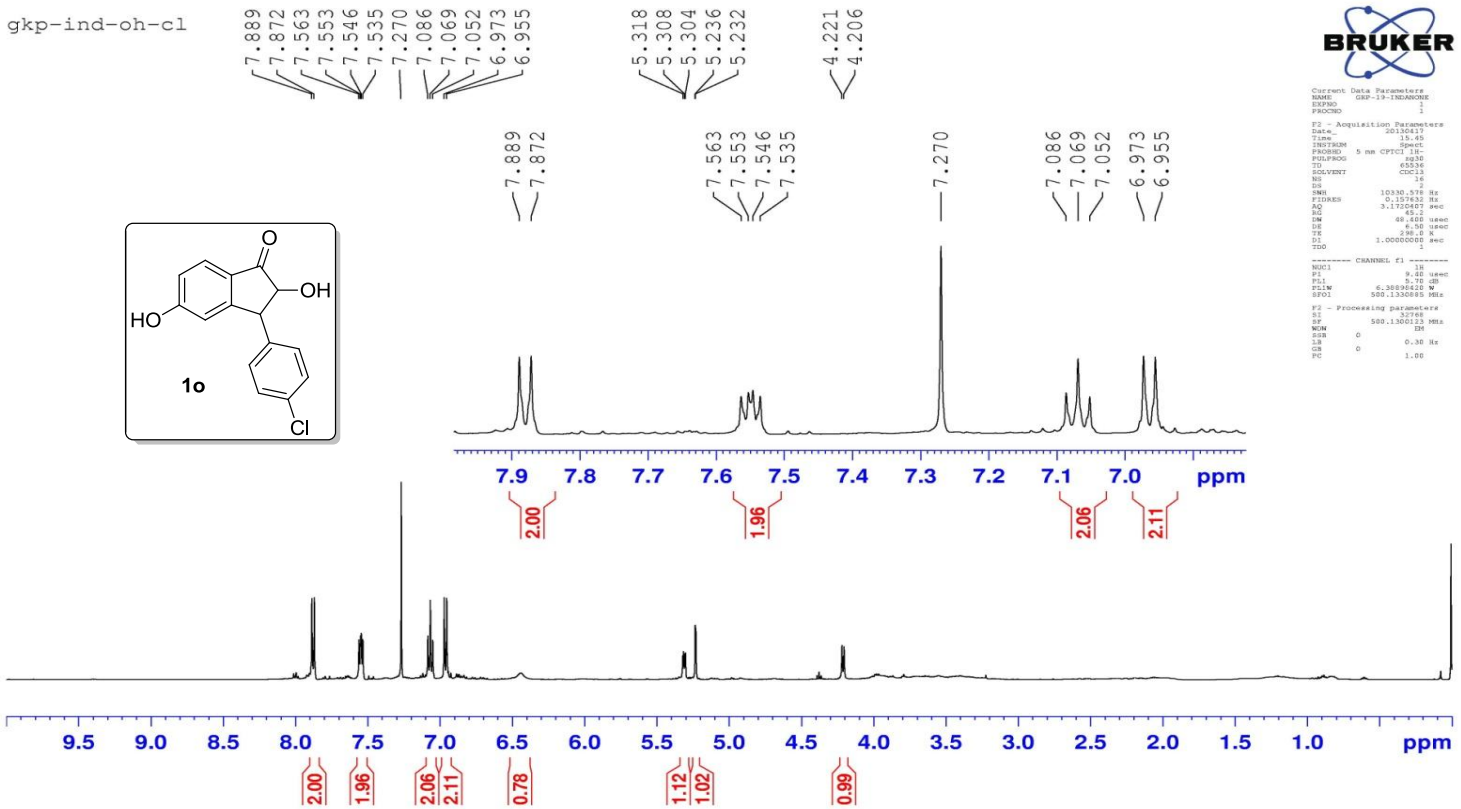


Figure S-3: ^{1}H NMR Spectrum of compound 1o

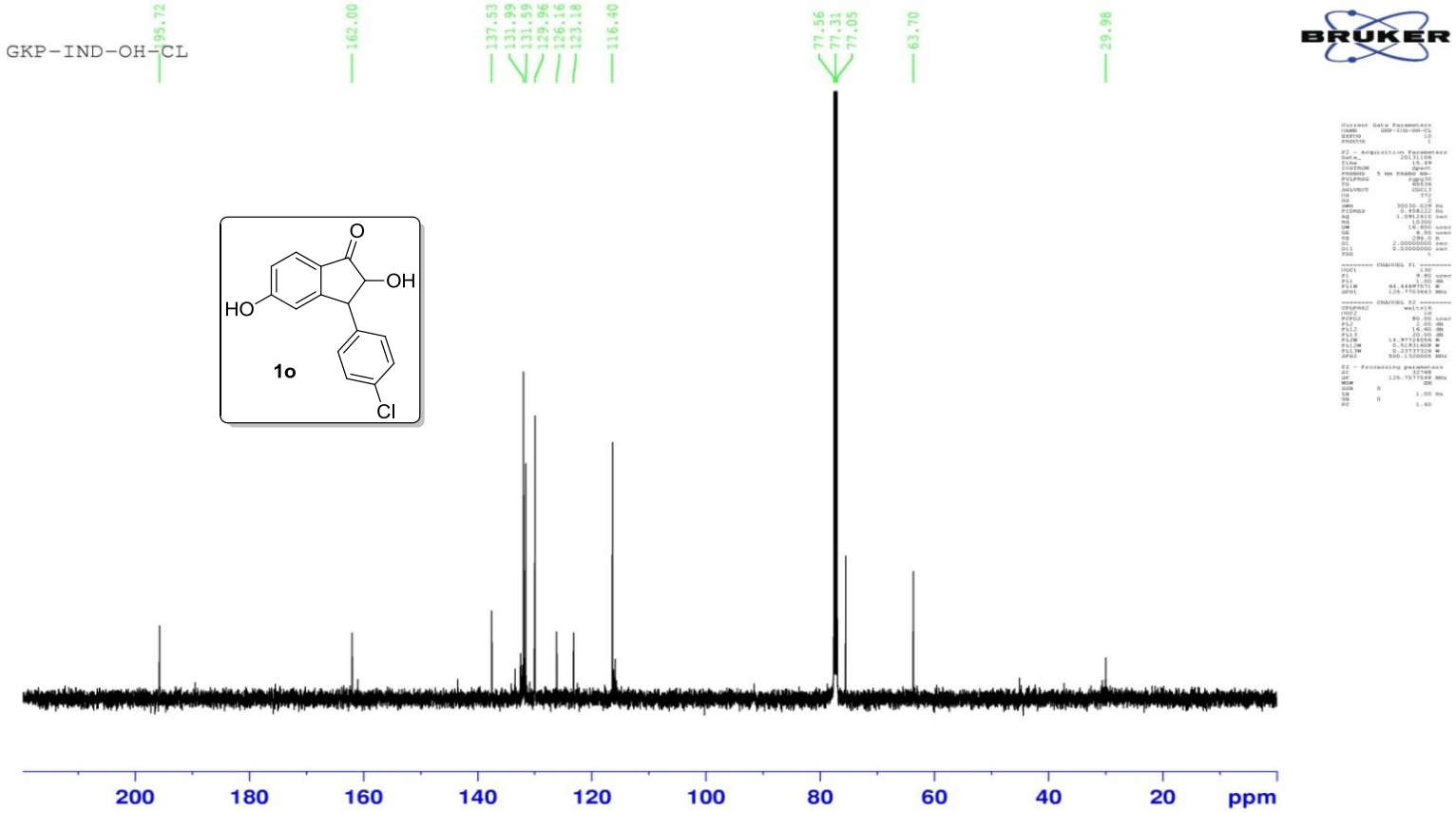


Figure S-4: ^{13}C NMR Spectrum of compound 1o

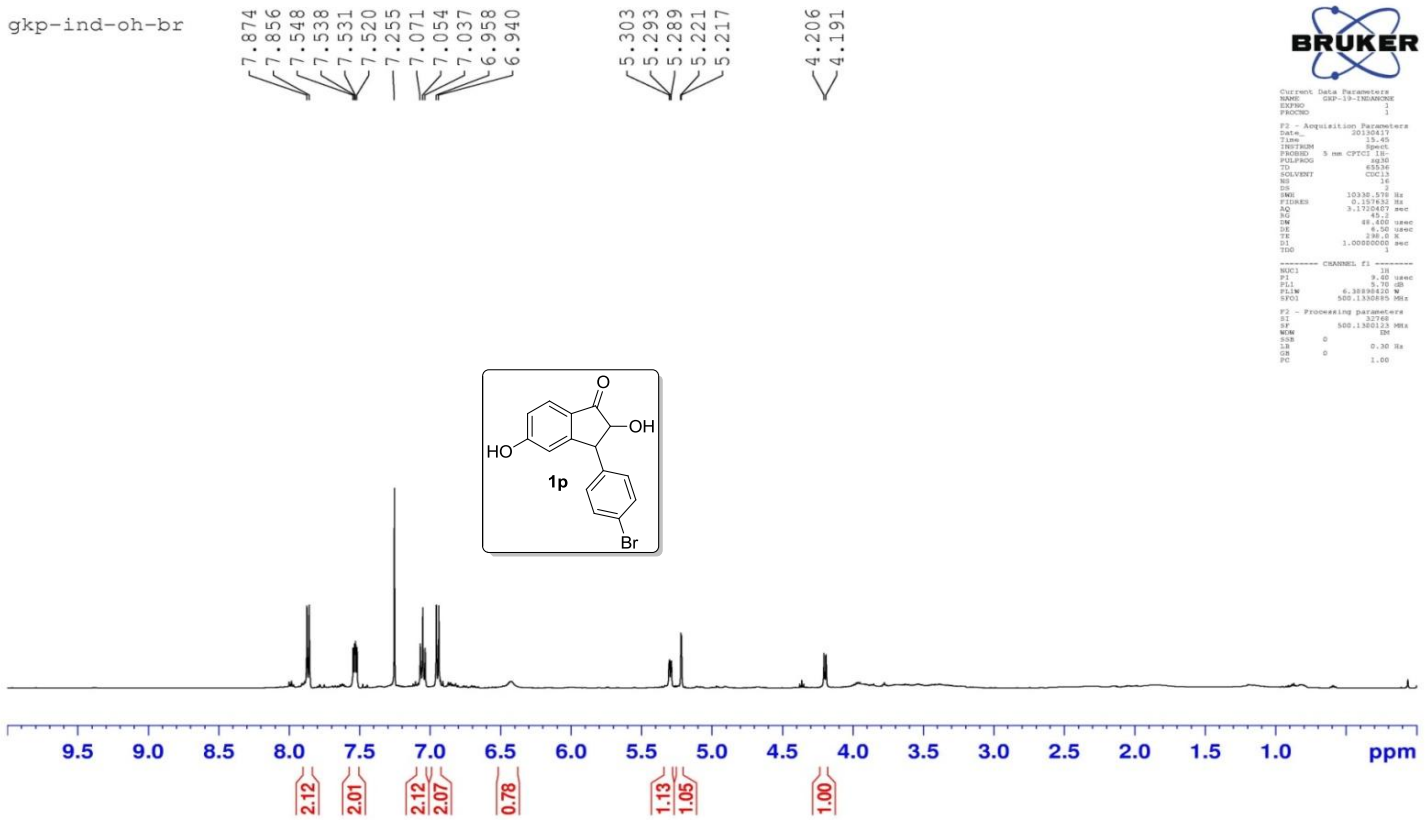


Figure S-5: ^{1}H NMR Spectrum of compound 1p

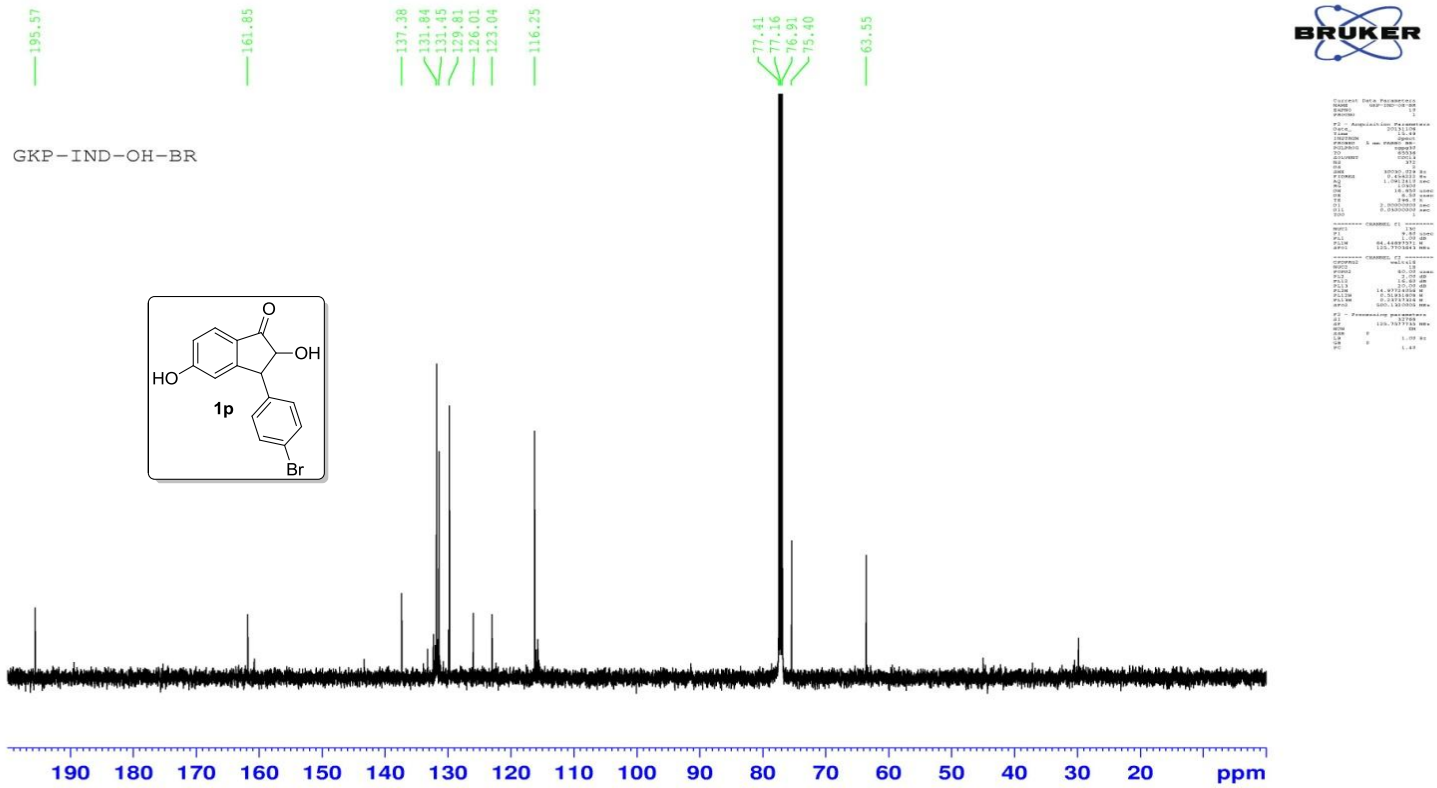


Figure S-6: ^{13}C NMR Spectrum of compound 1p

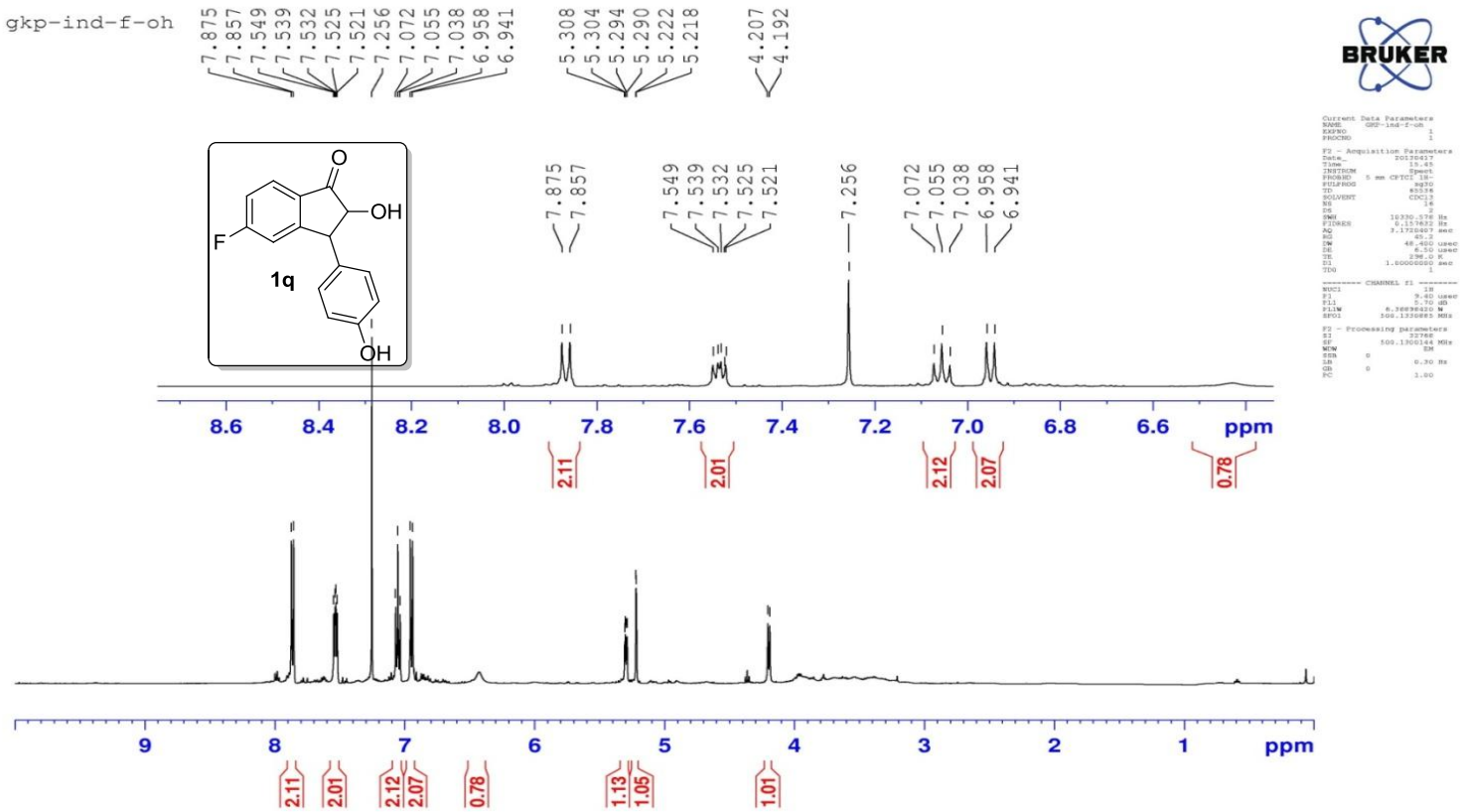


Figure S-7: ^{1}H NMR Spectrum of compound 1q

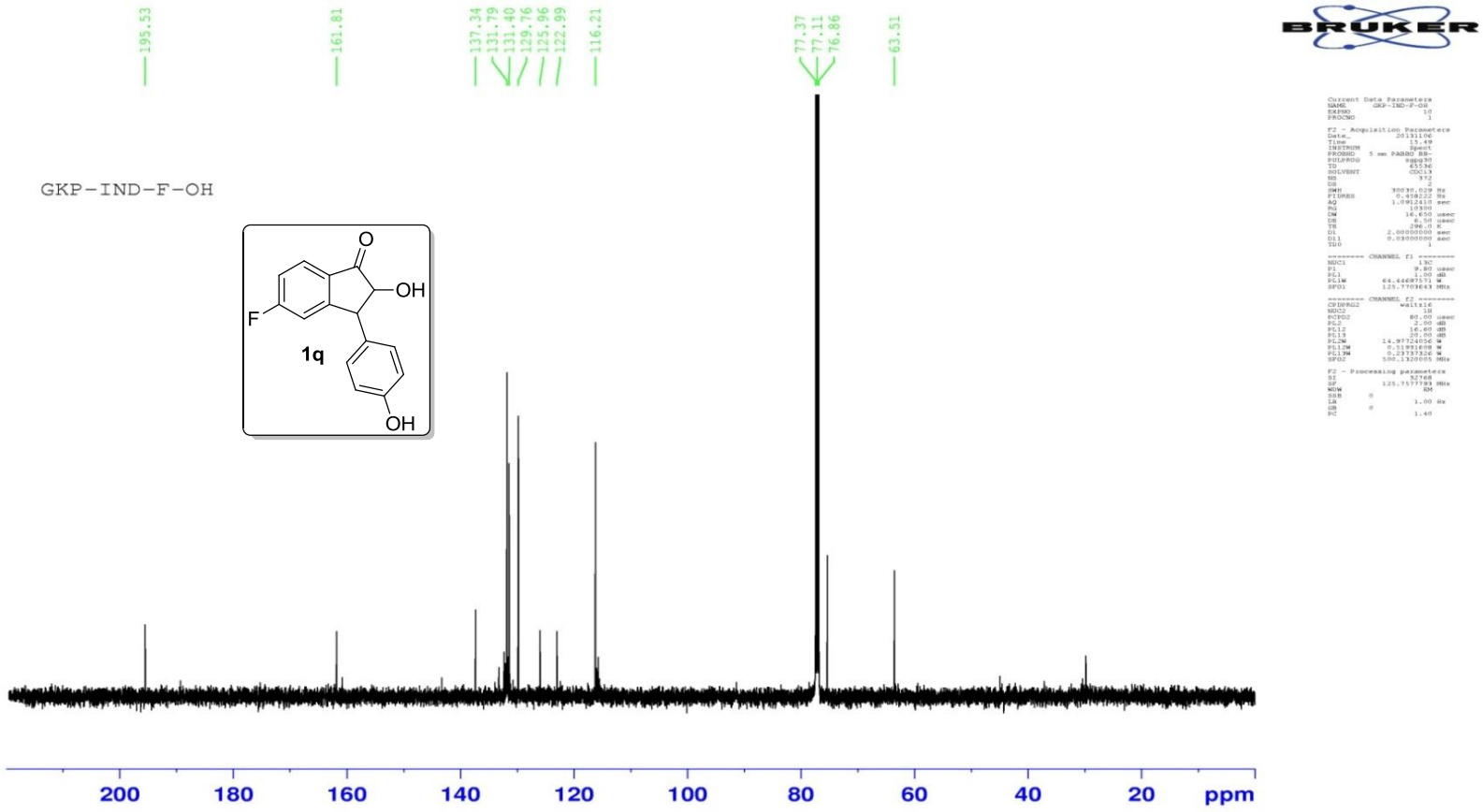


Figure S-8: ^{13}C NMR Spectrum of compound 1q

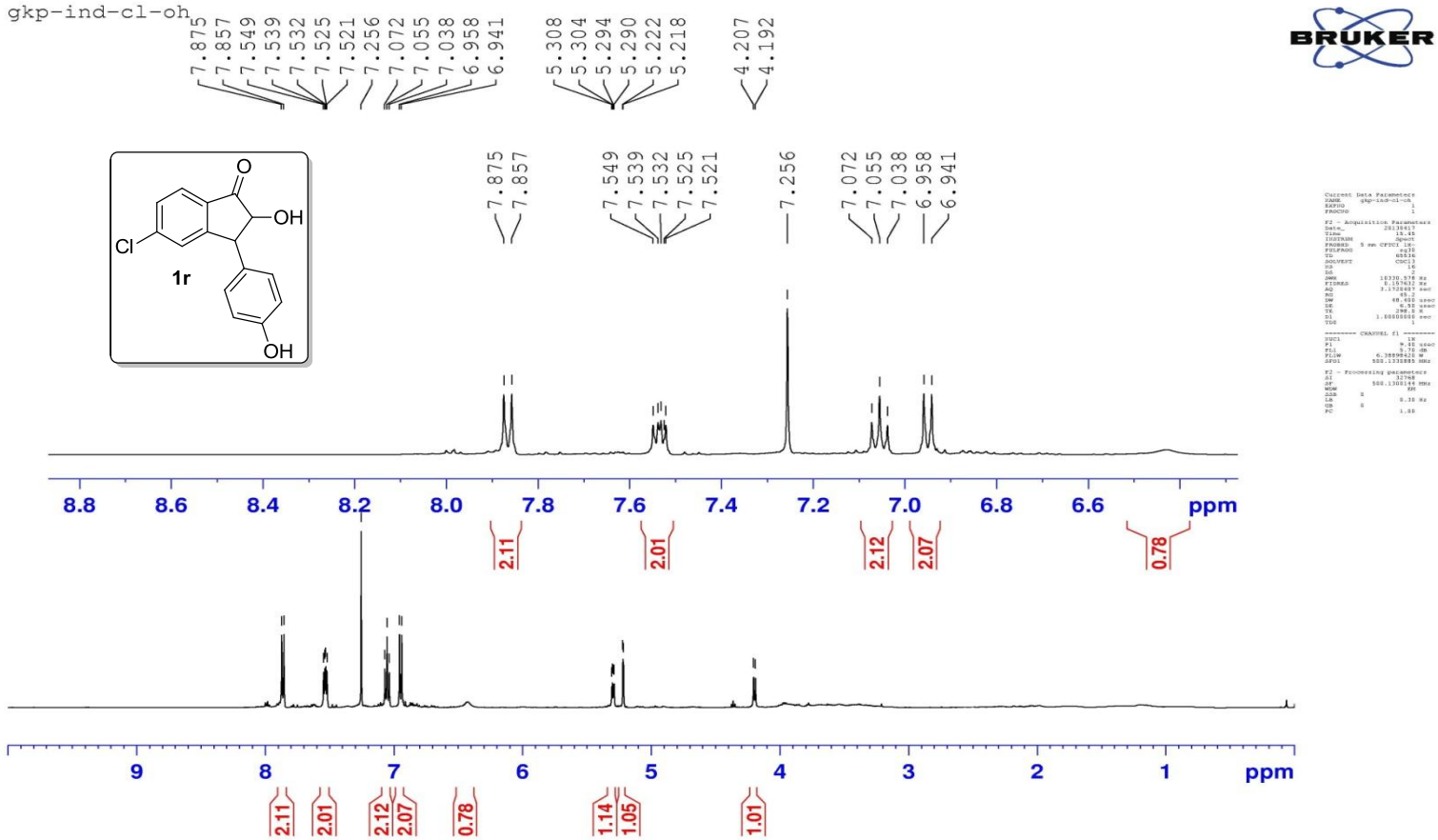


Figure S-9: ^{1}H NMR Spectrum of compound 1r

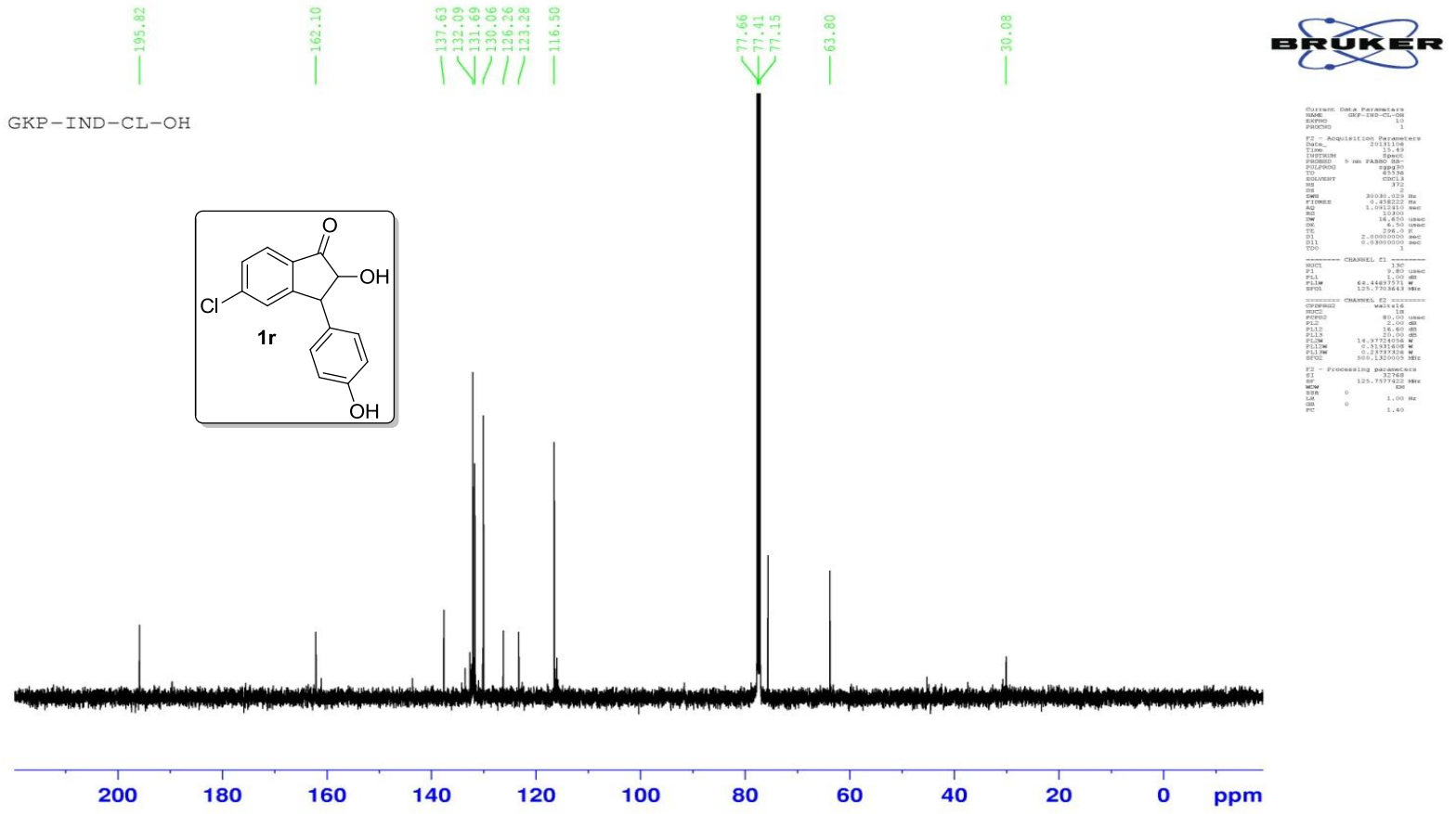


Figure S-10: ^{13}C NMR Spectrum of compound 1r

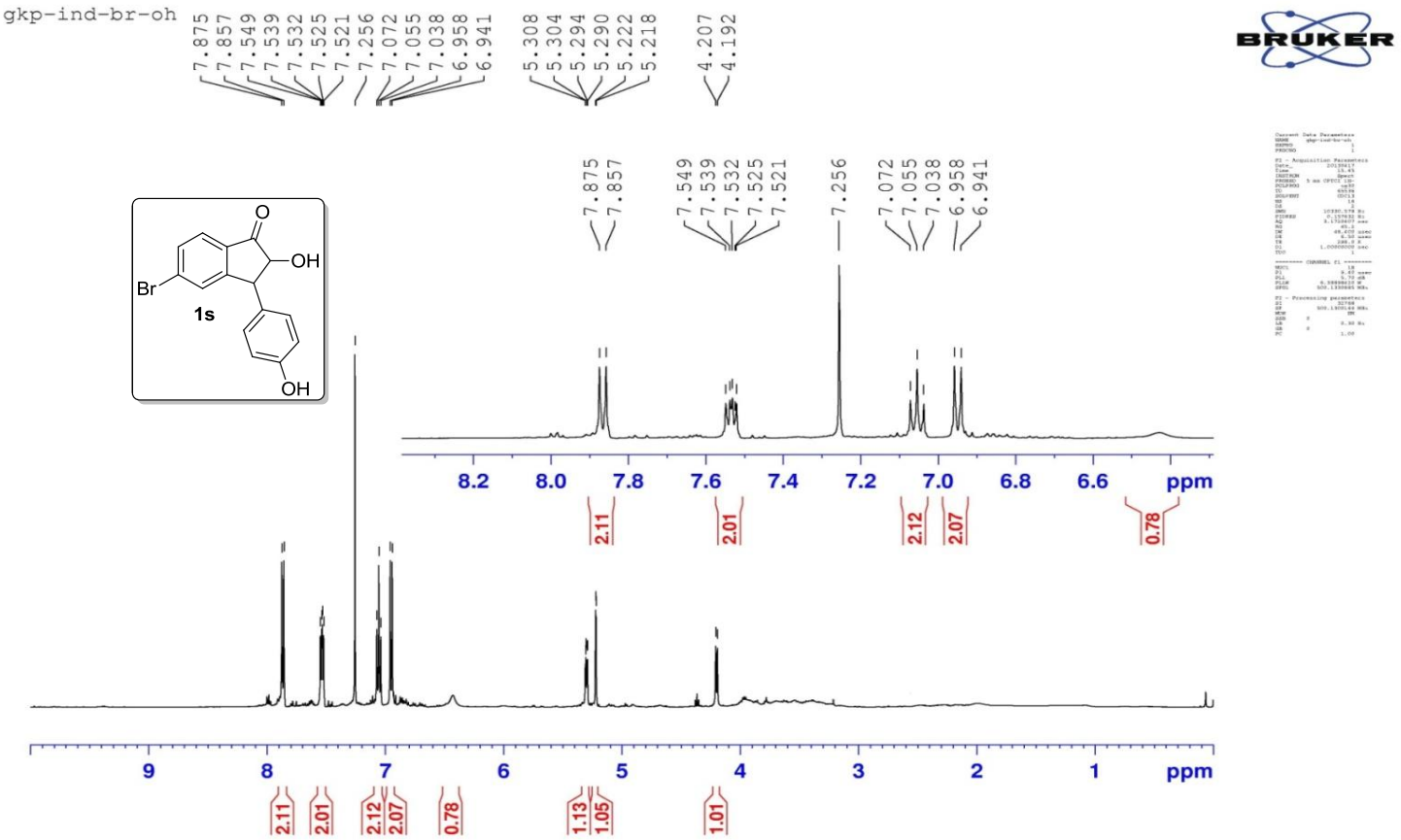


Figure S-11: ^{1}H NMR Spectrum of compound 1s

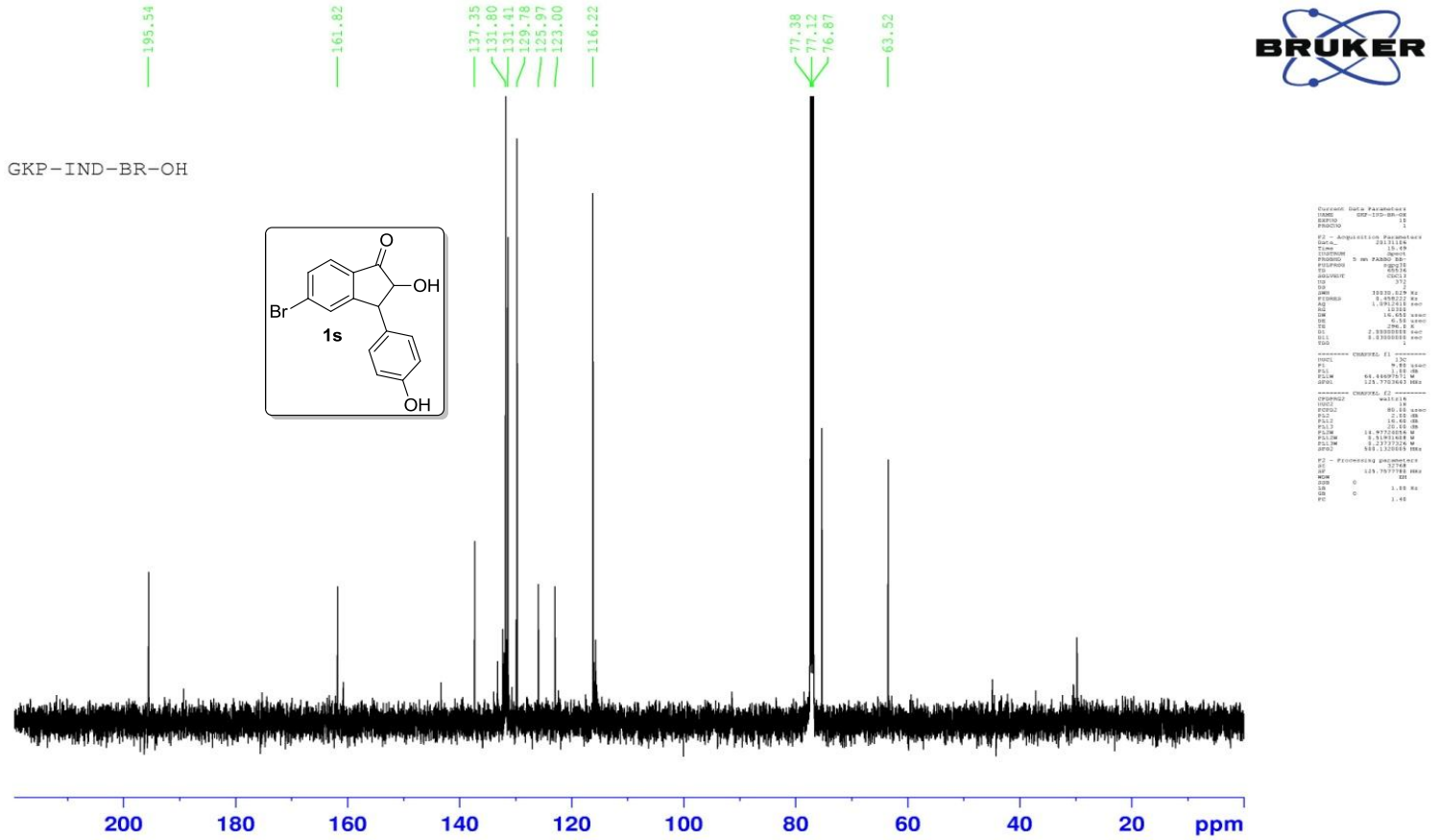


Figure S-12: ^{13}C NMR Spectrum of compound 1s

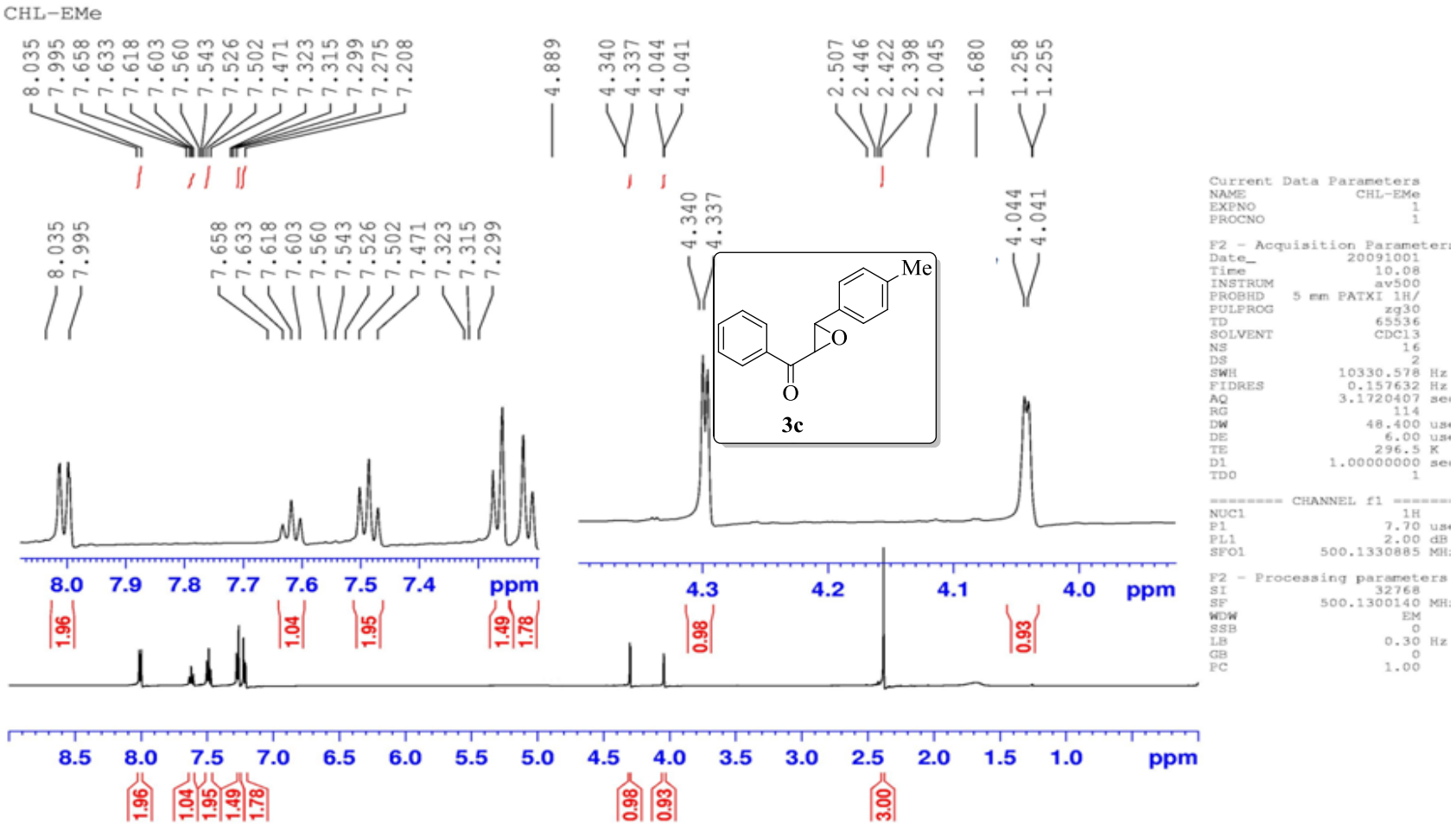


Figure S-13: ^{1}H NMR Spectrum of compound 3c

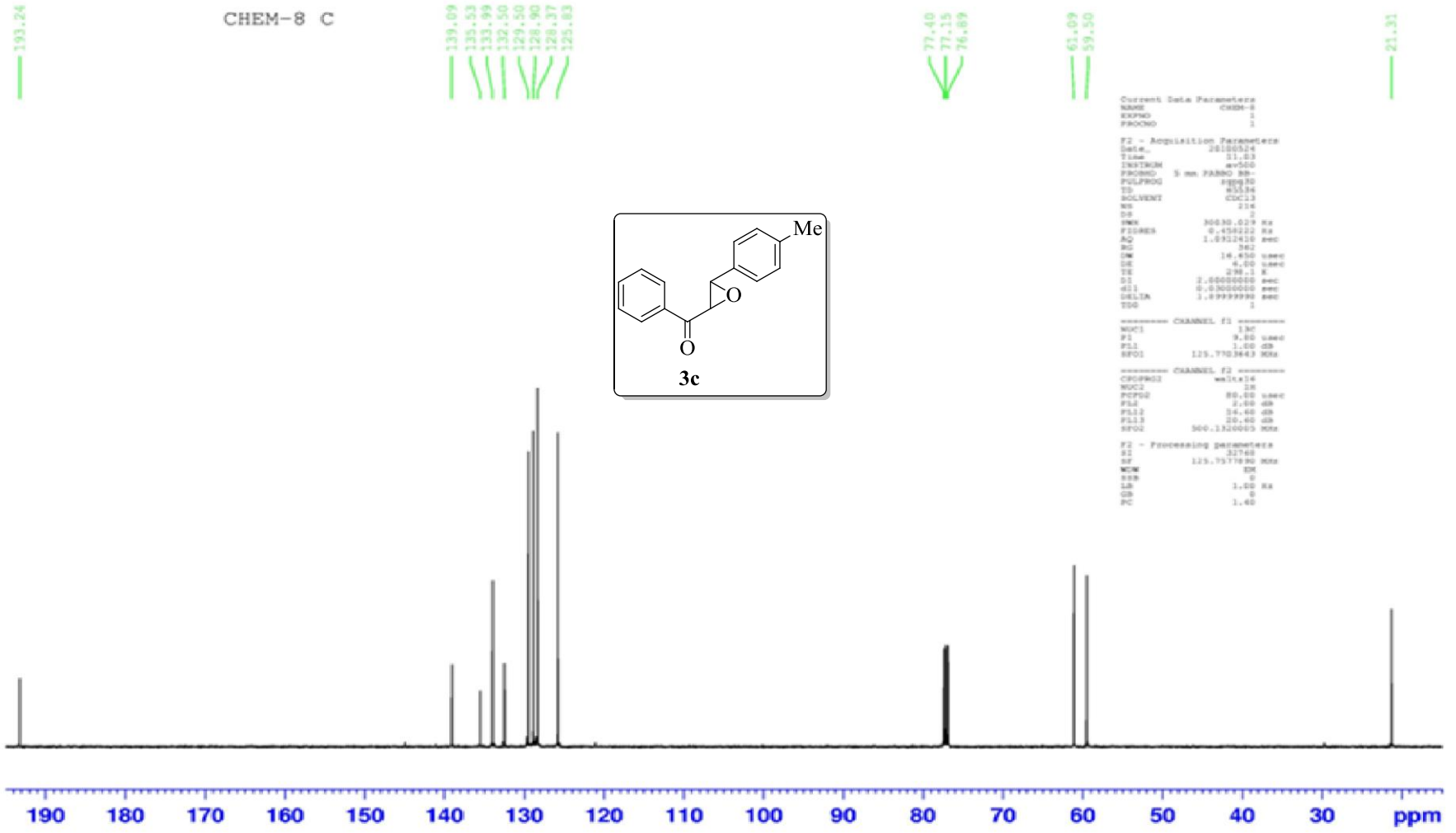


Figure S-14: ^{13}C NMR Spectrum of compound 3c

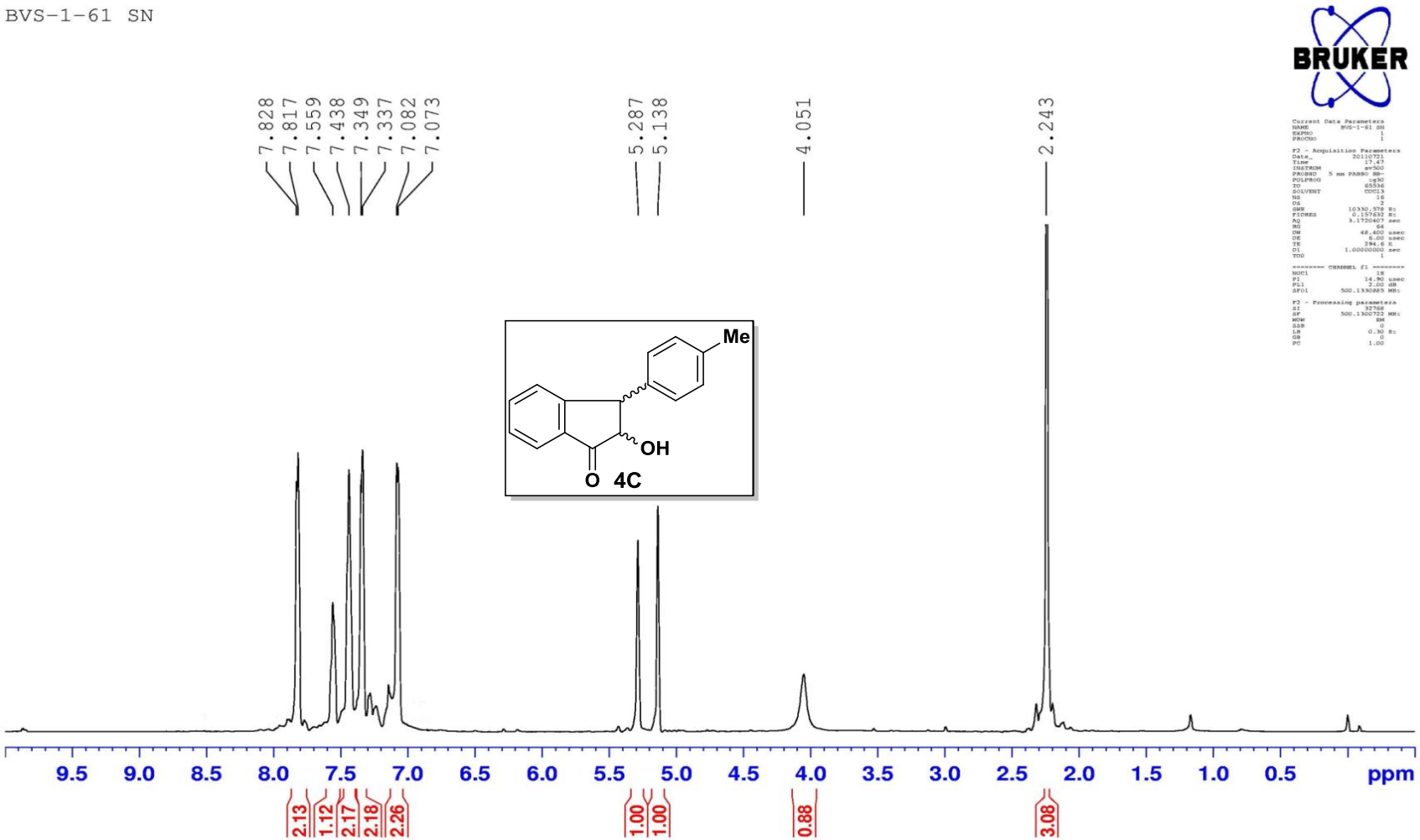


Figure S-15: ^{1}H NMR Spectrum of compound 4c

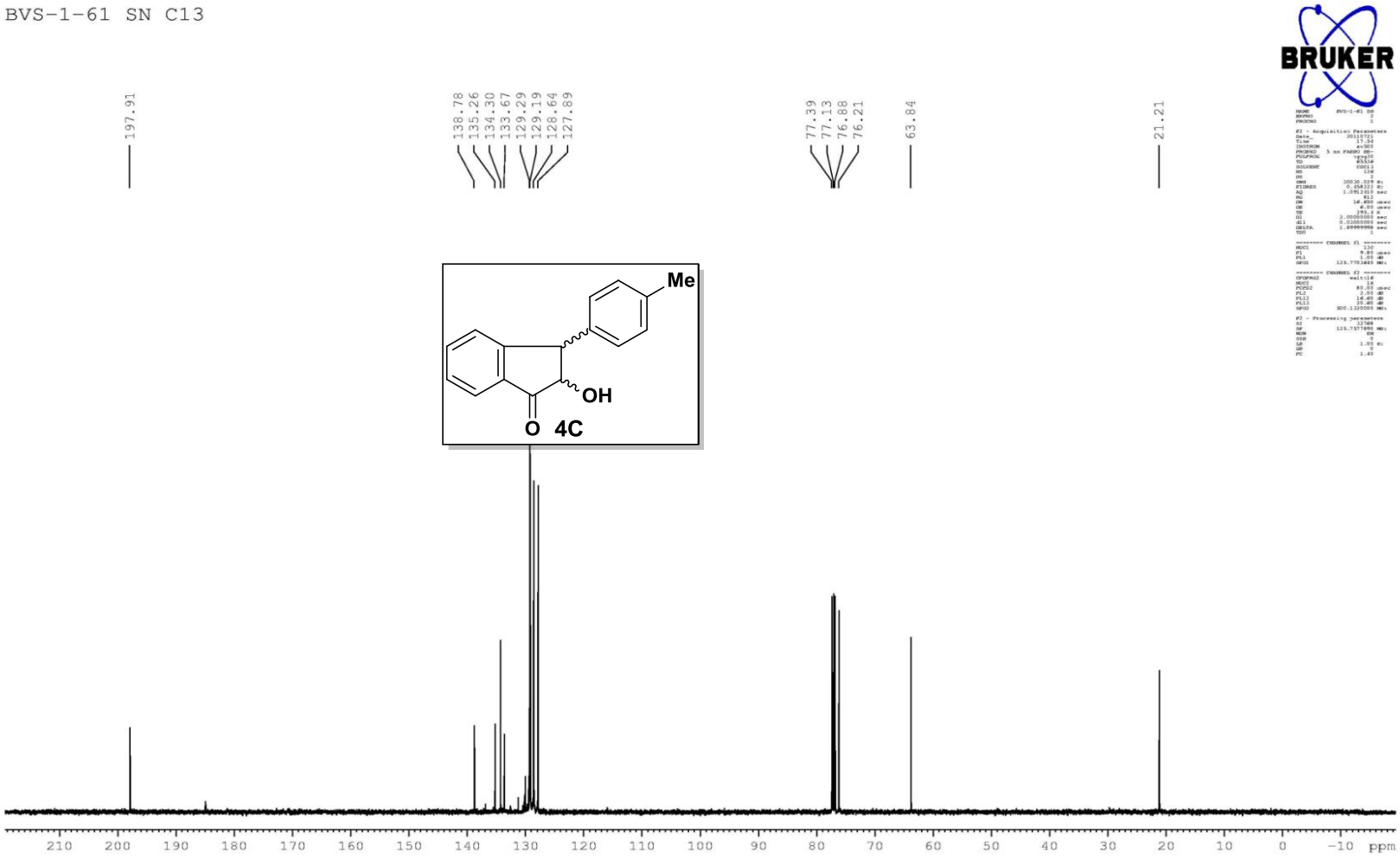


Figure S-16: ^{13}C NMR Spectrum of compound 4c

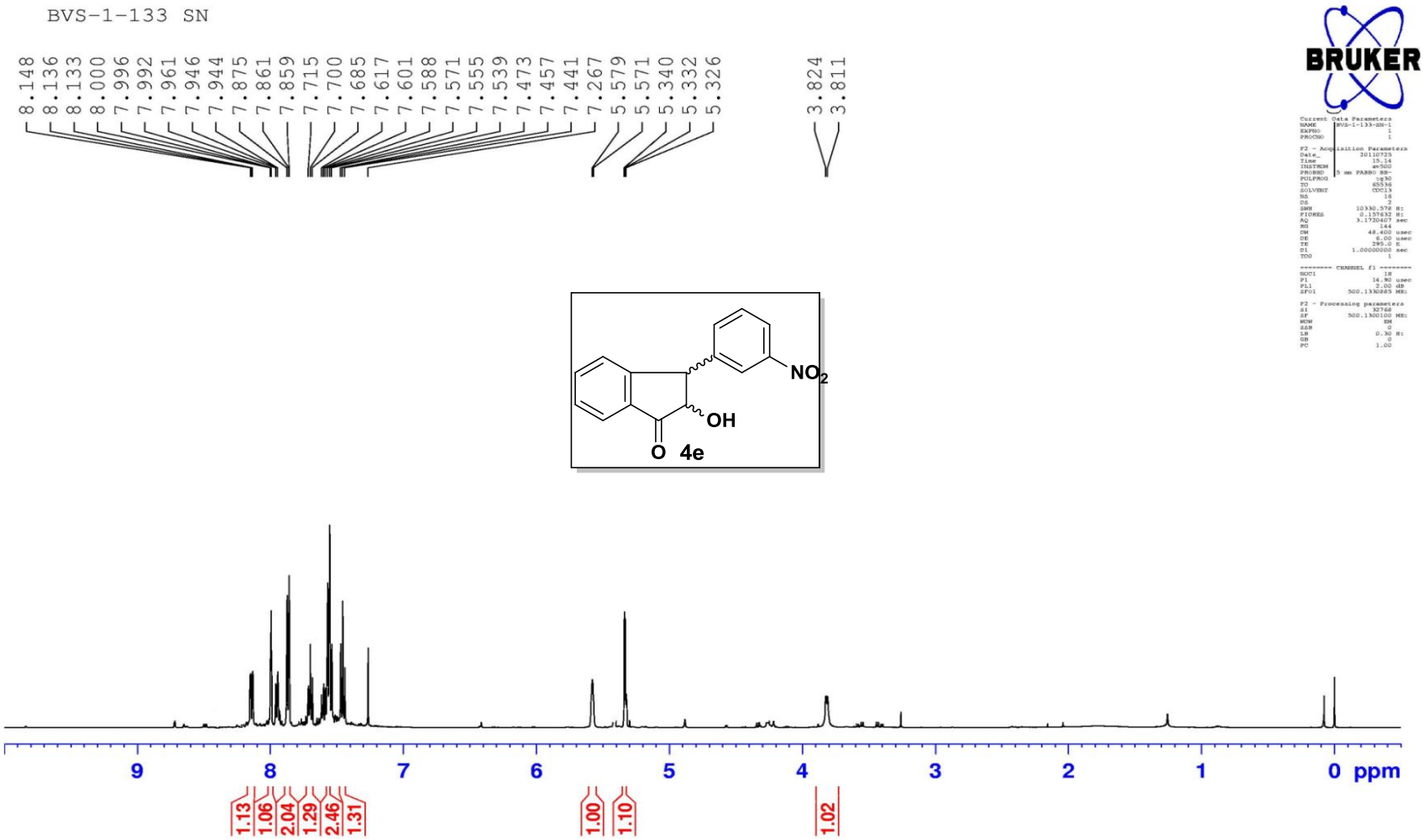


Figure S-17: ^{1}H NMR Spectrum of compound 4e

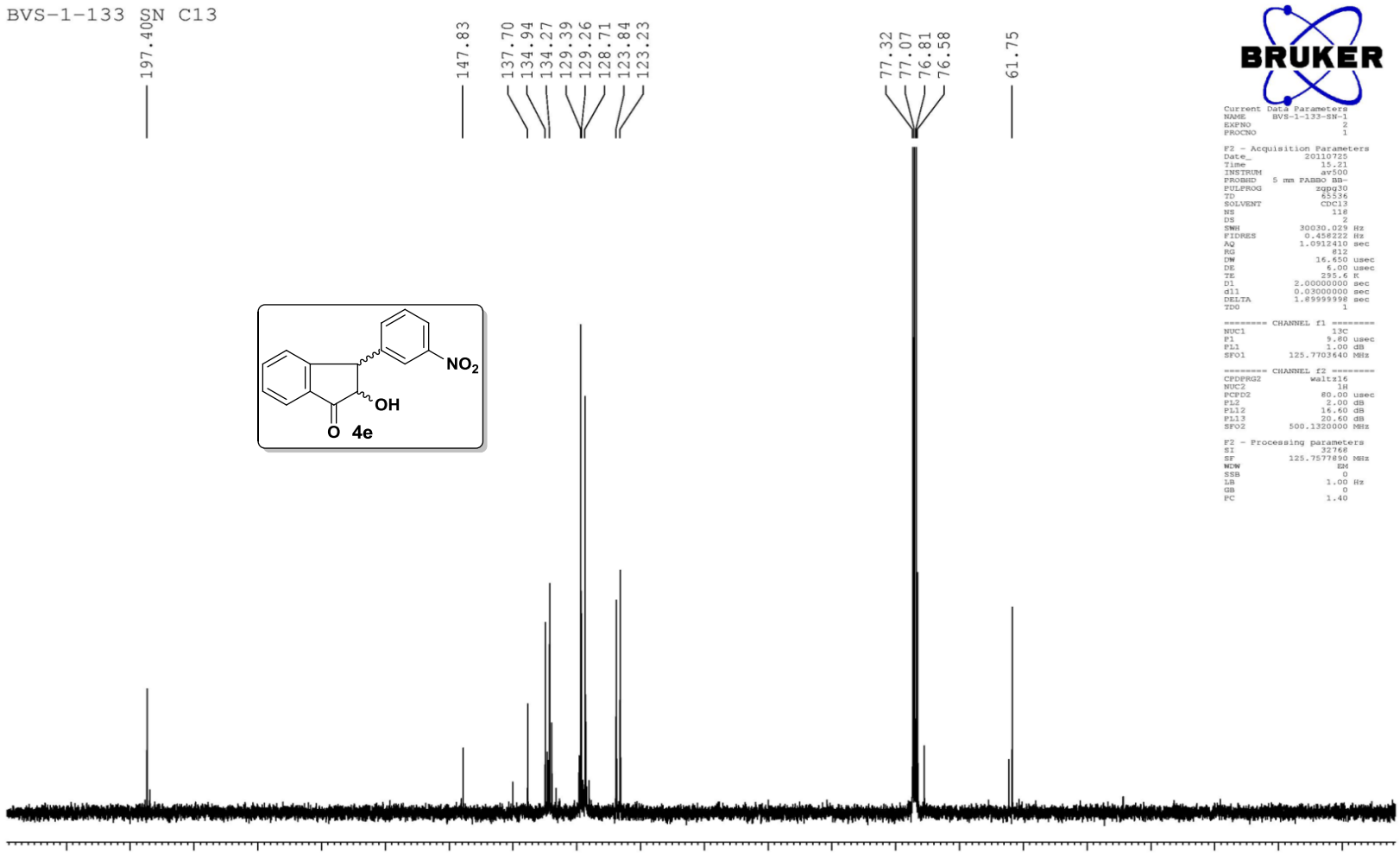


Figure S-18: ^{13}C NMR Spectrum of compound 4e

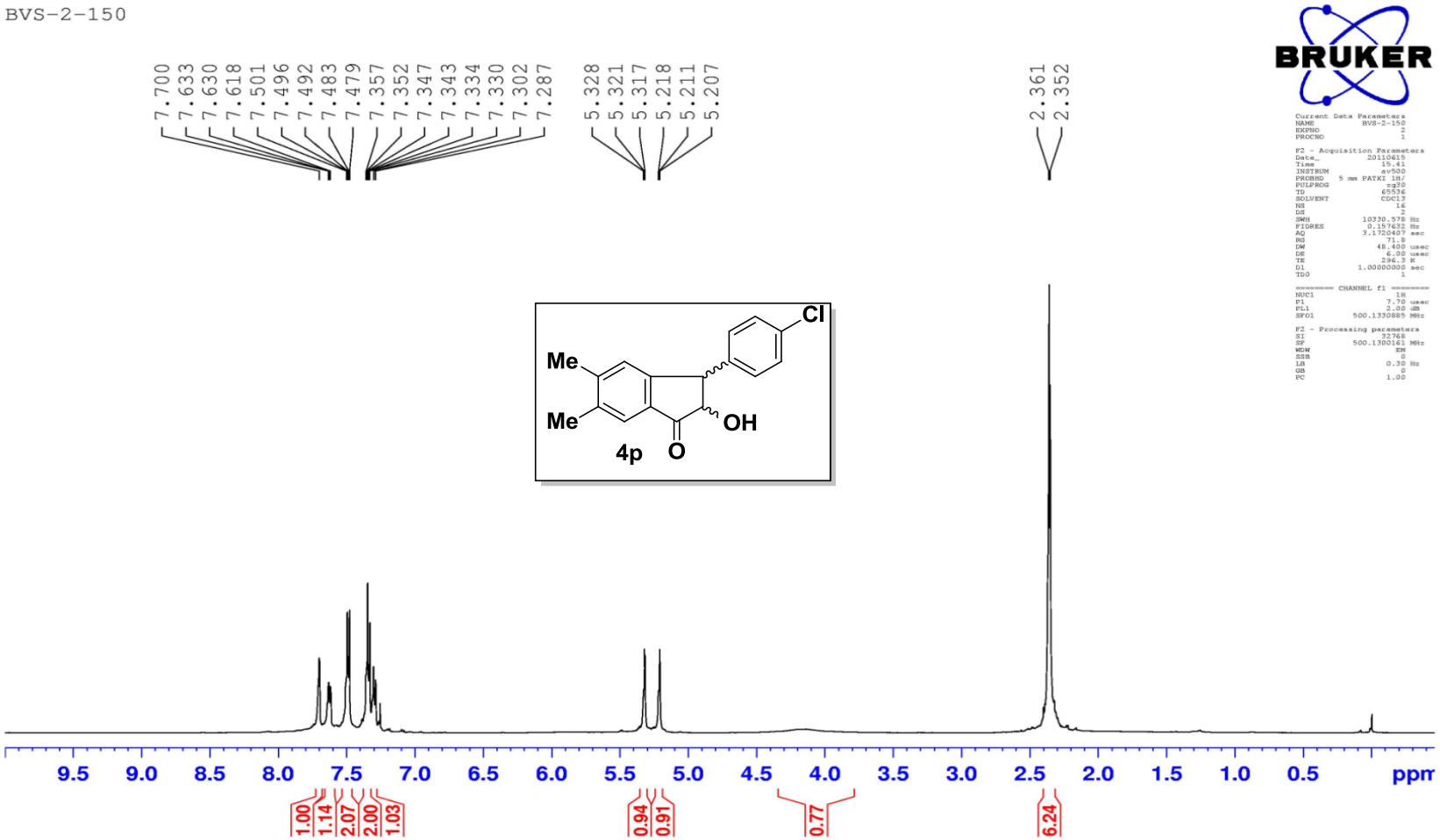


Figure S-19: ^{1}H NMR Spectrum of compound 4p

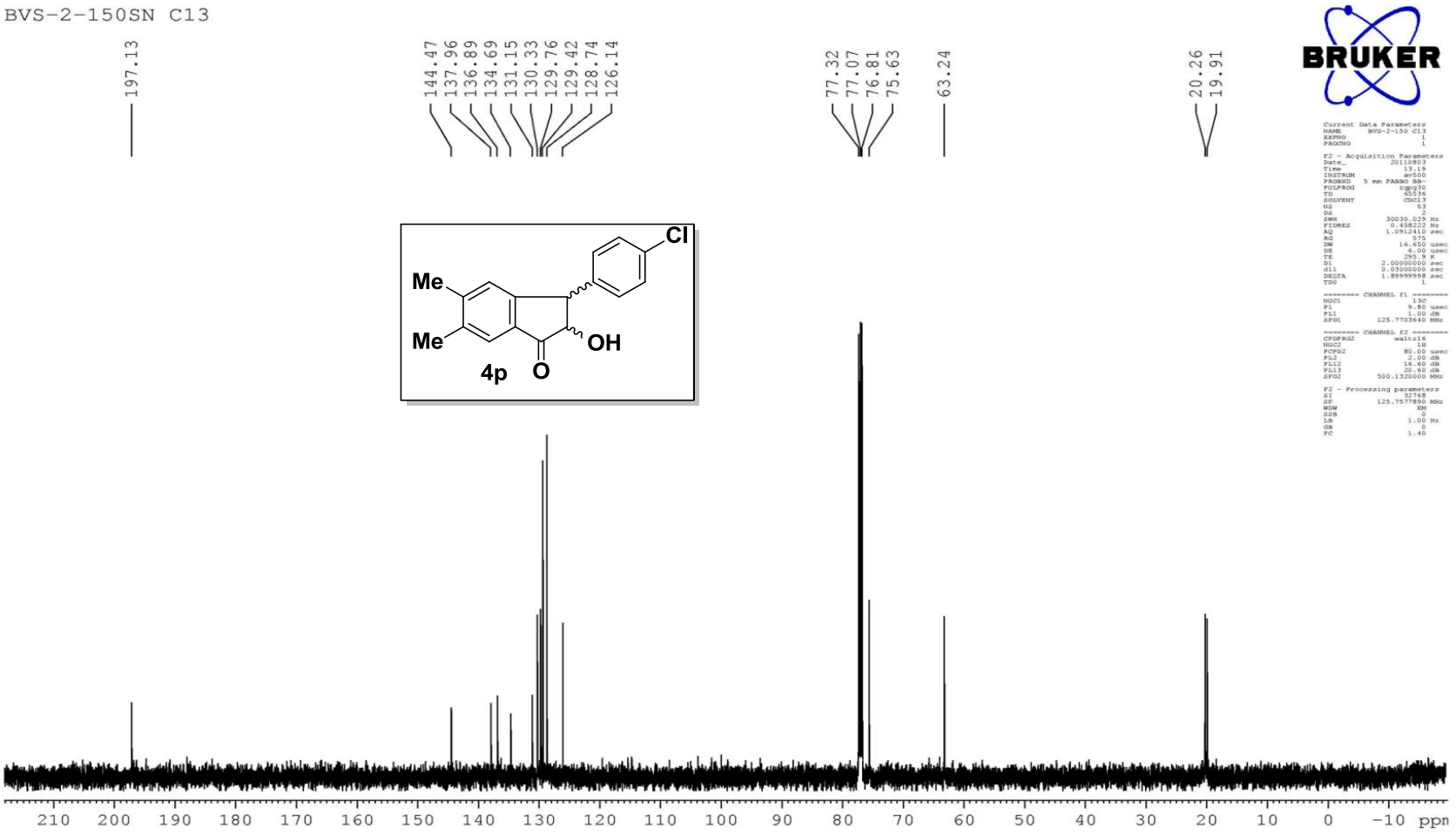


Figure S-20: ^{13}C NMR Spectrum of compound 4p

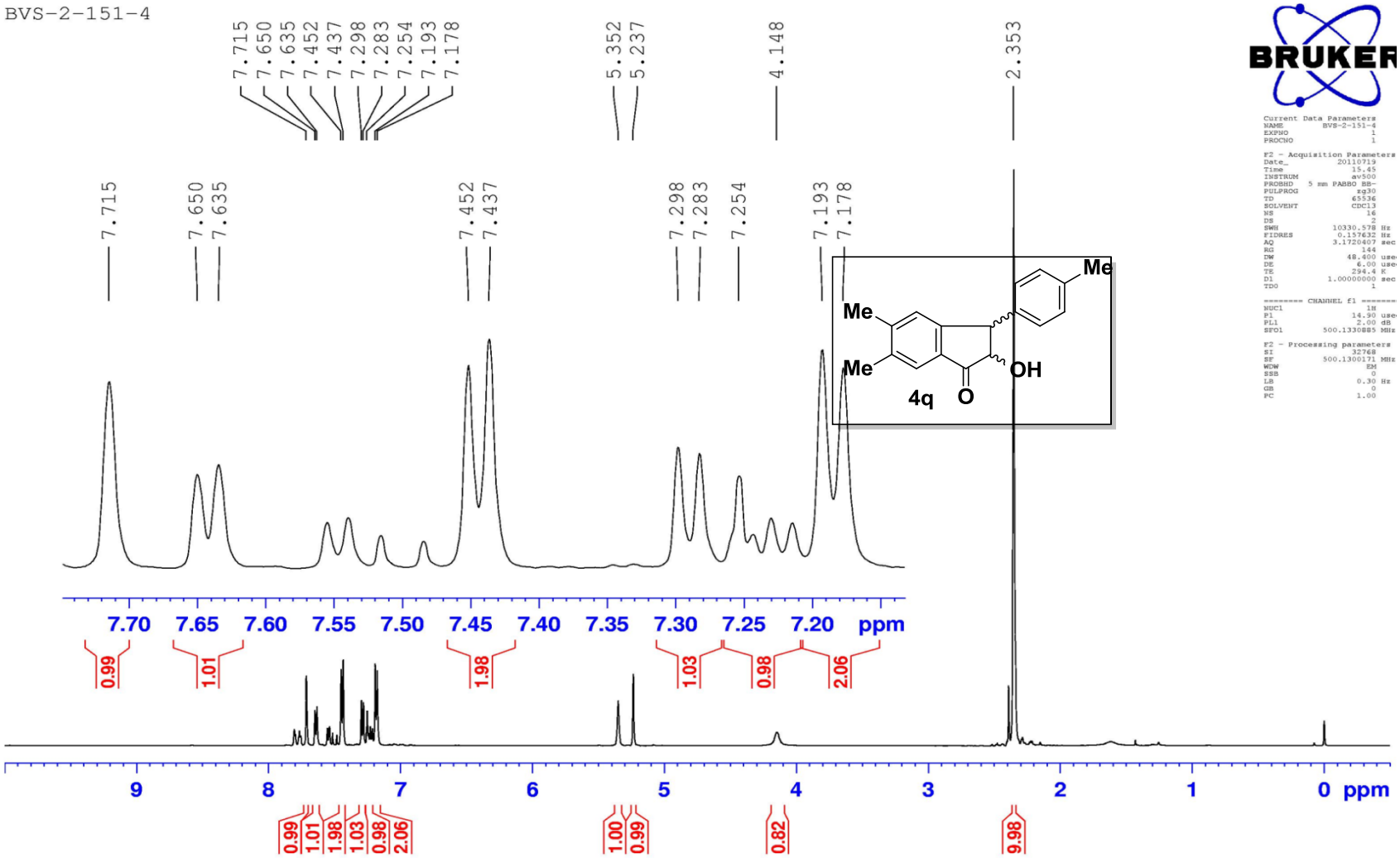


Figure S-21: ^{1}H NMR Spectrum of compound 4q

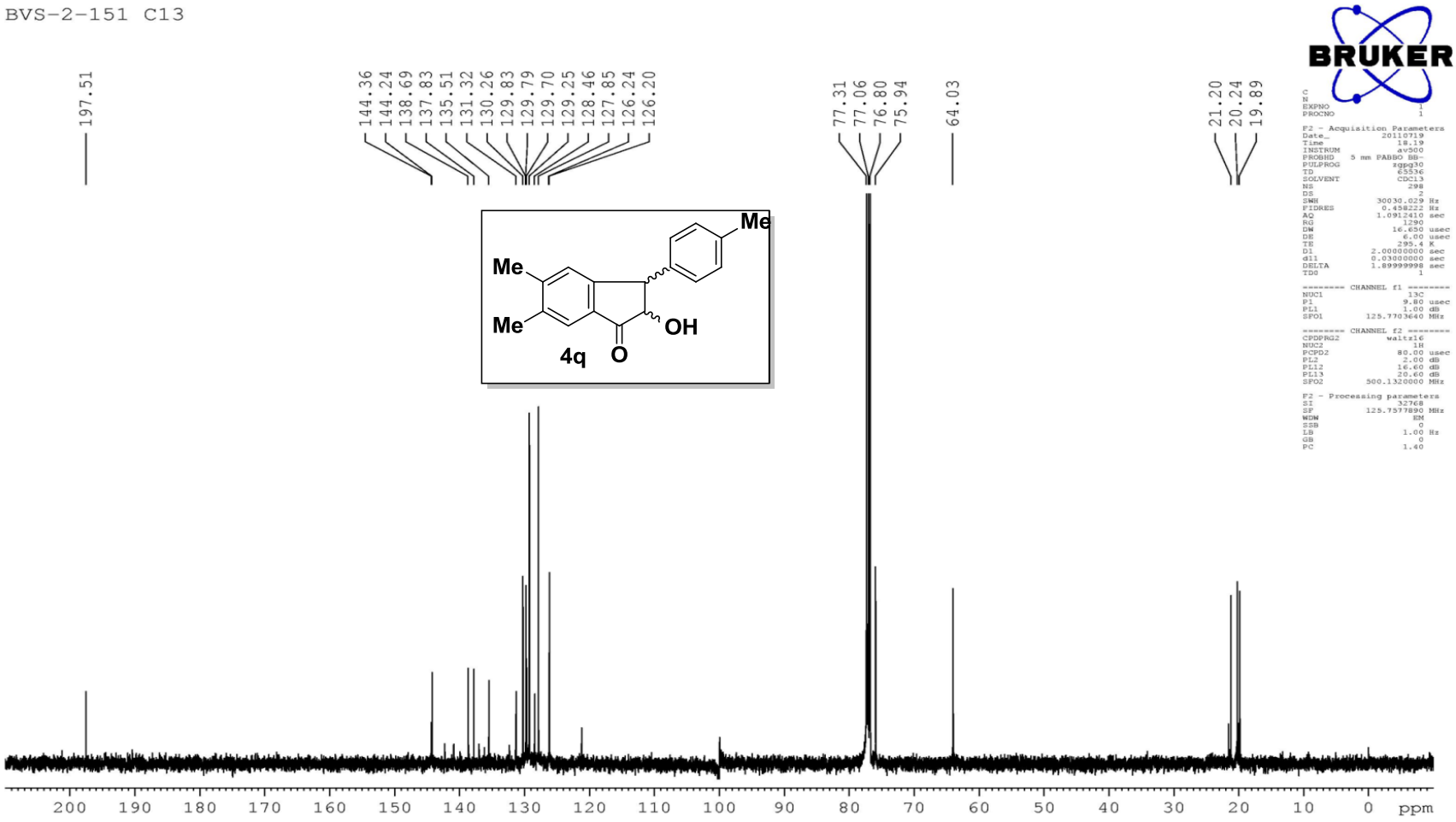


Figure S-22: ^{13}C NMR Spectrum of compound 4q

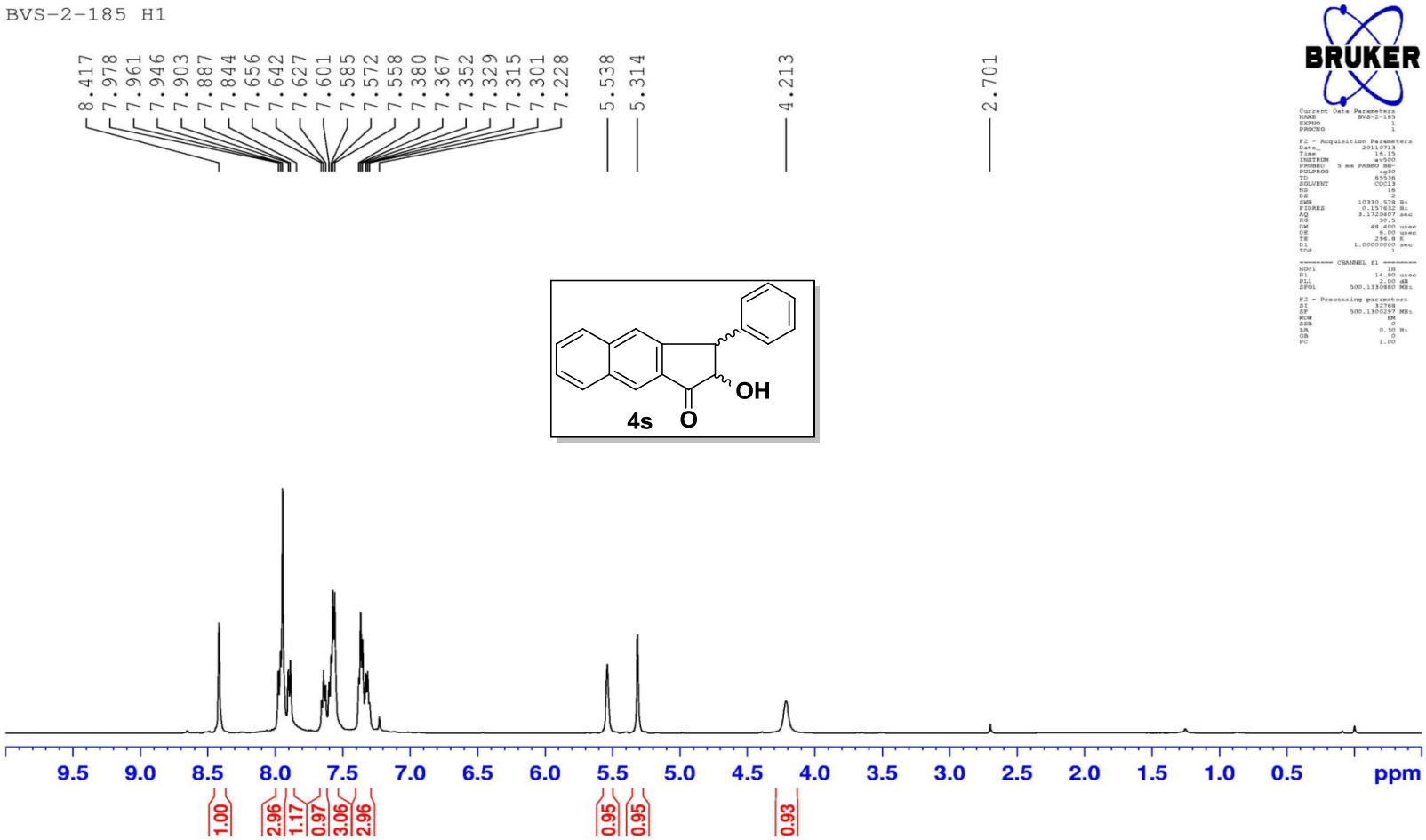


Figure S-23: ^{1}H NMR Spectrum of compound 4s

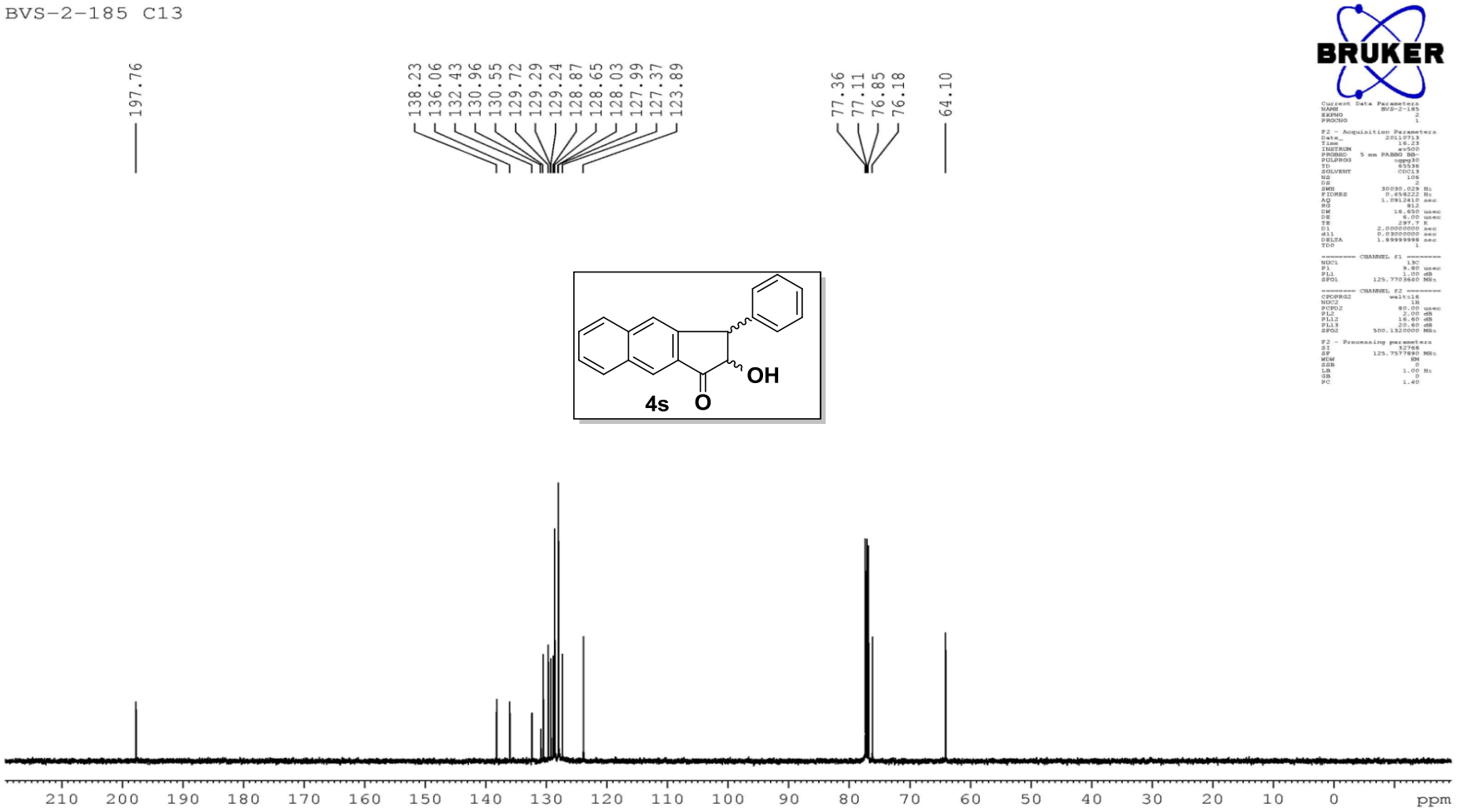


Figure S-24: ^{13}C NMR Spectrum of compound 4s

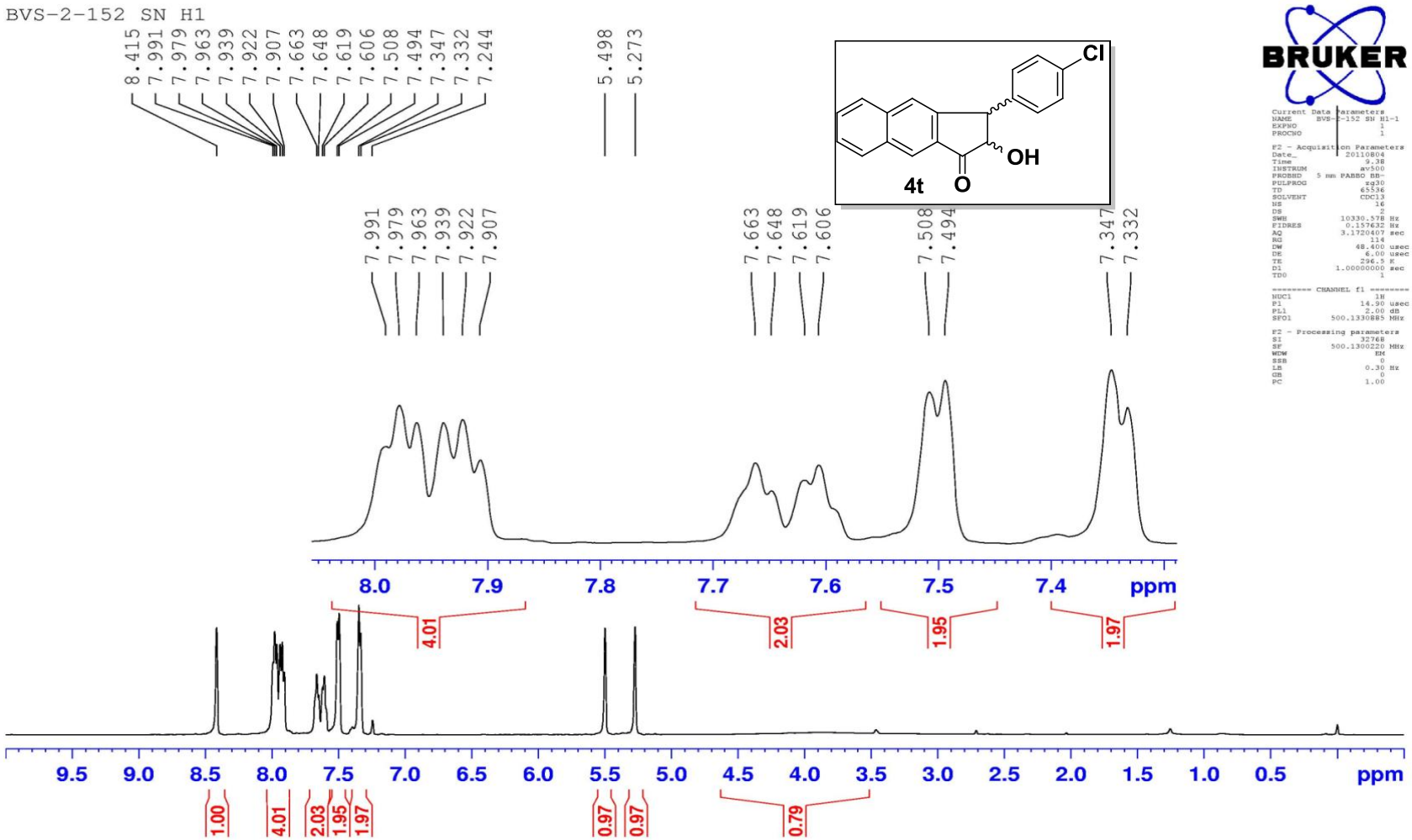


Figure S-25: ^{1}H NMR Spectrum of compound 4t

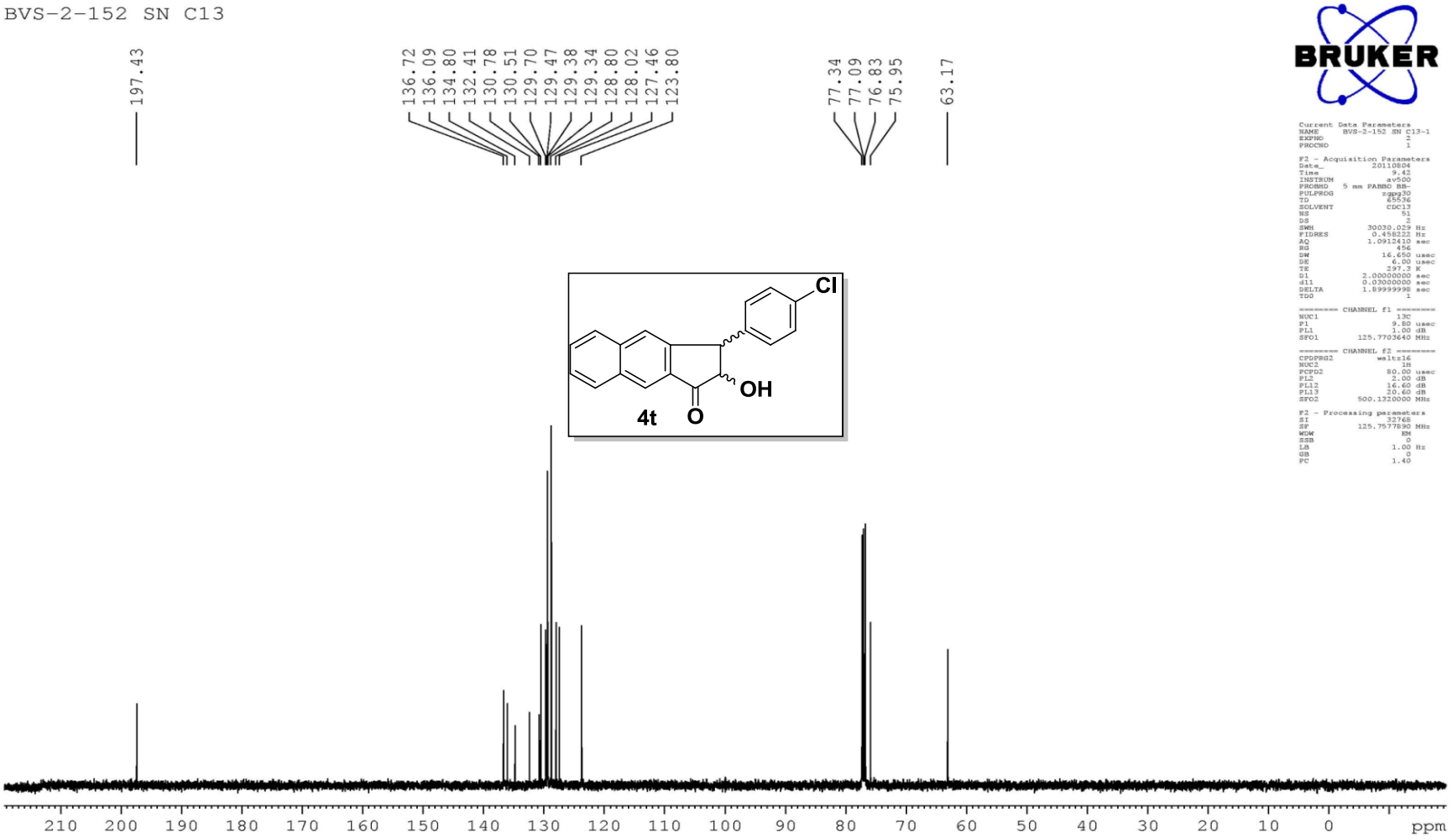


Figure S-26: ^{13}C NMR Spectrum of compound 4t

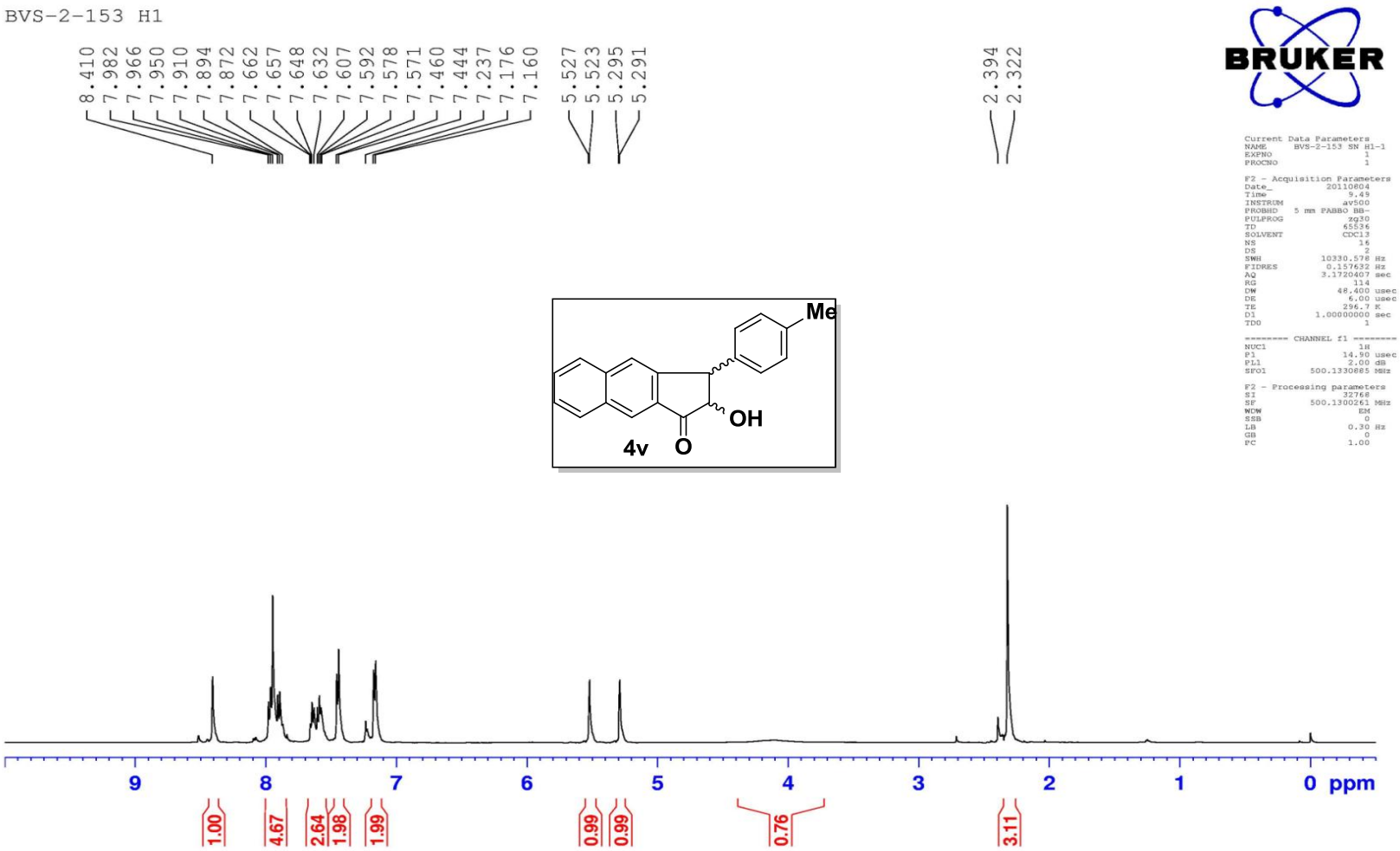


Figure S-27: ^{1}H NMR Spectrum of compound 4v

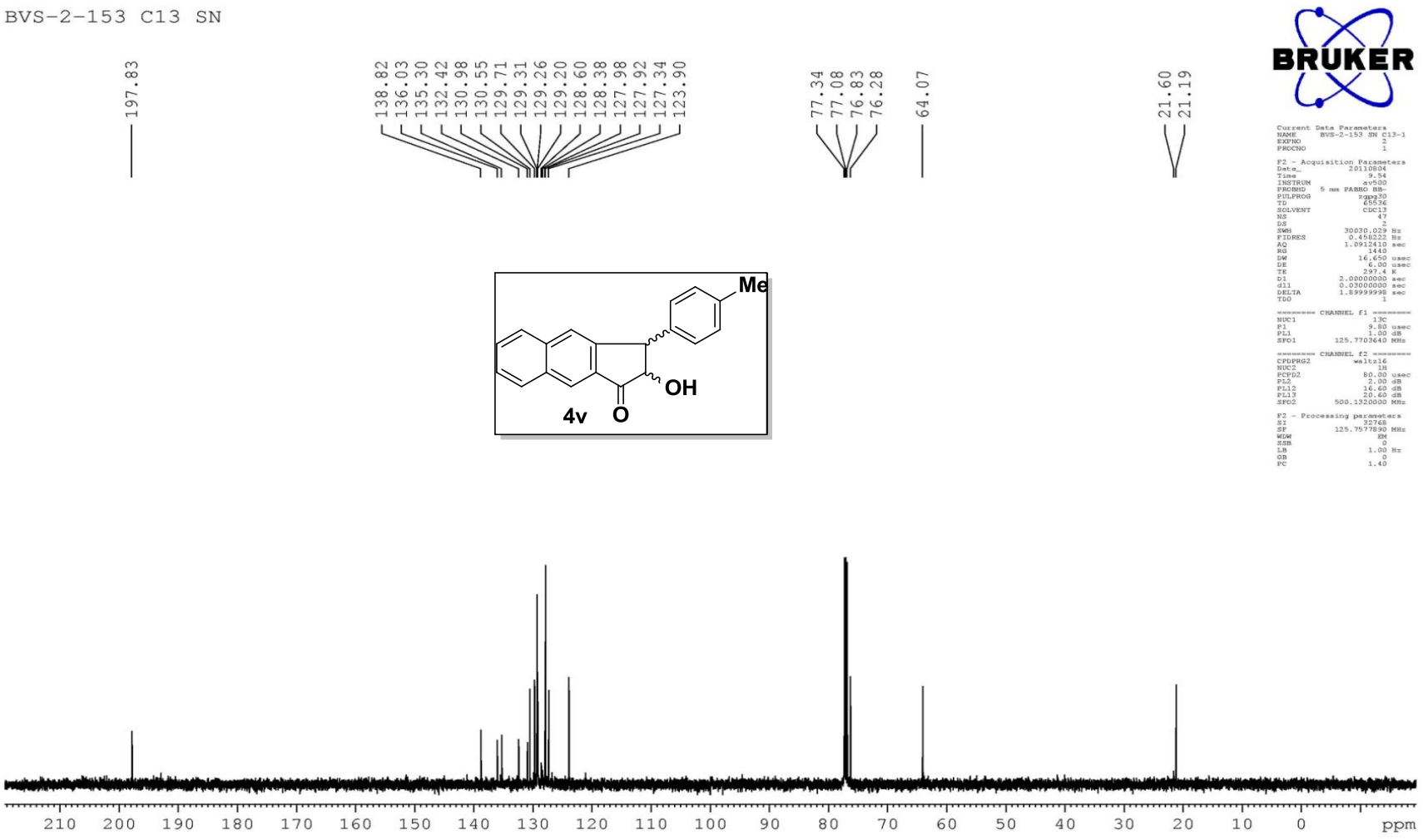


Figure S-28: ^{13}C NMR Spectrum of compound 4v

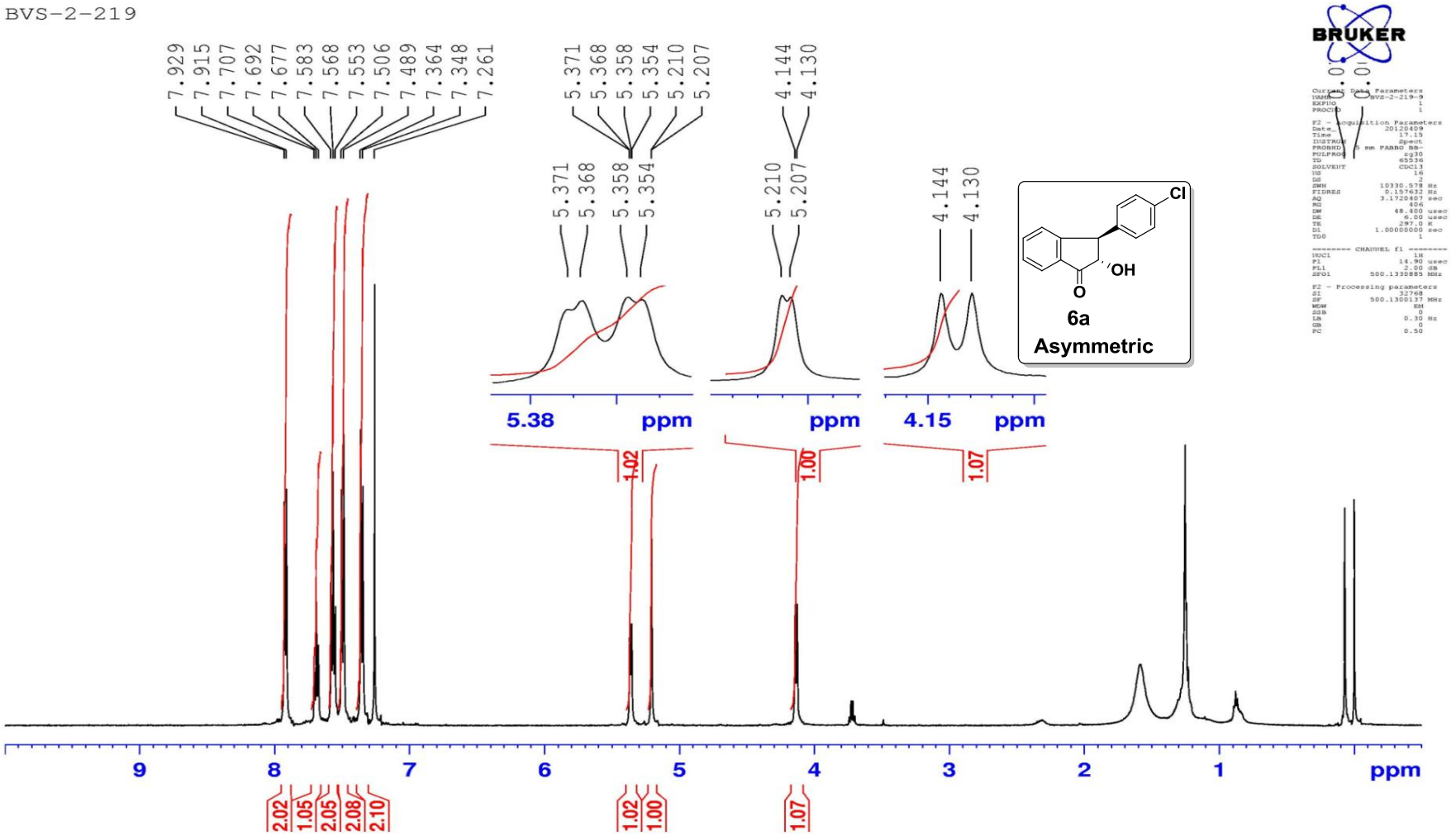


Figure S-29: ^{1}H NMR Spectrum of compound 6a

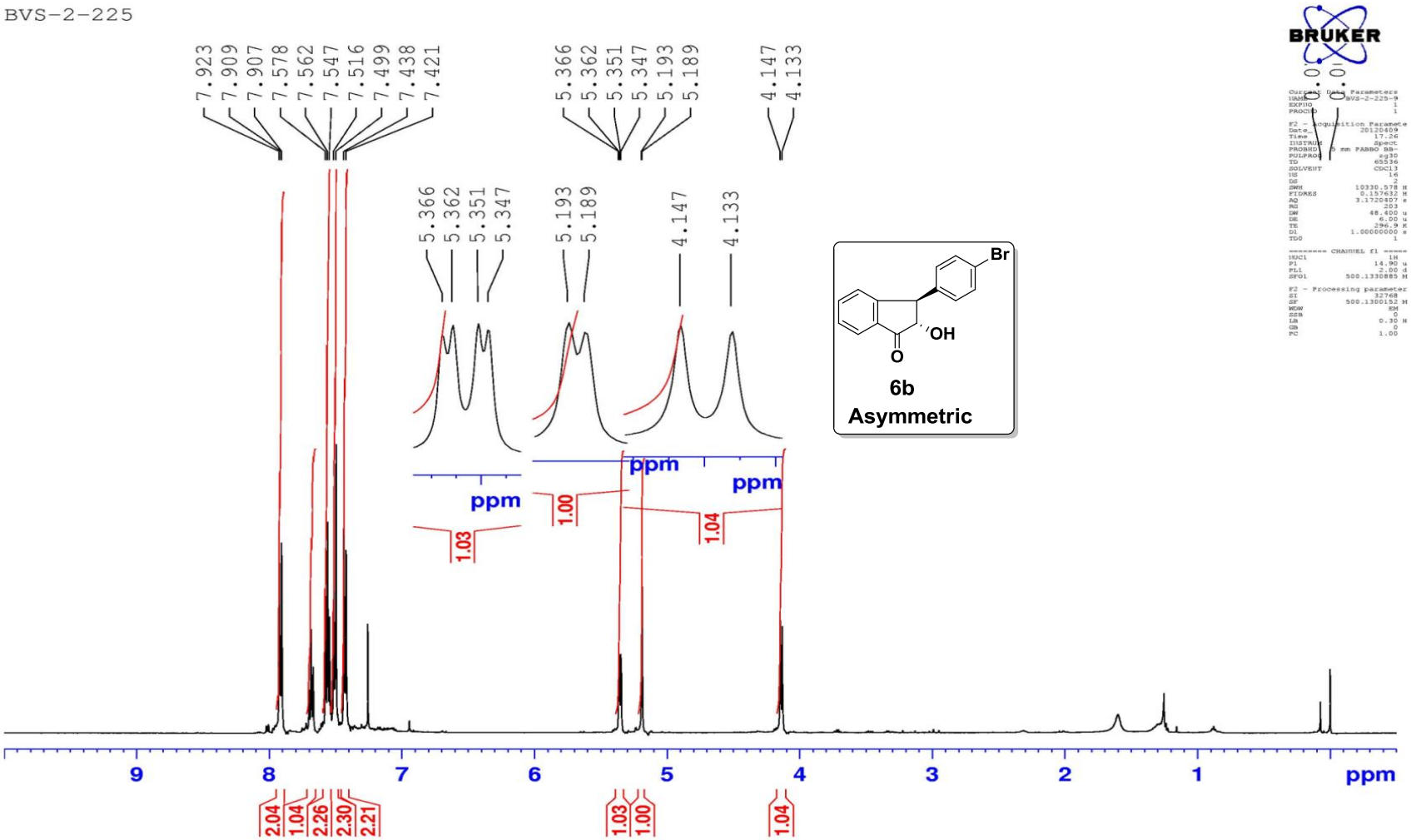


Figure S-30: ^{1}H NMR Spectrum of compound 6a

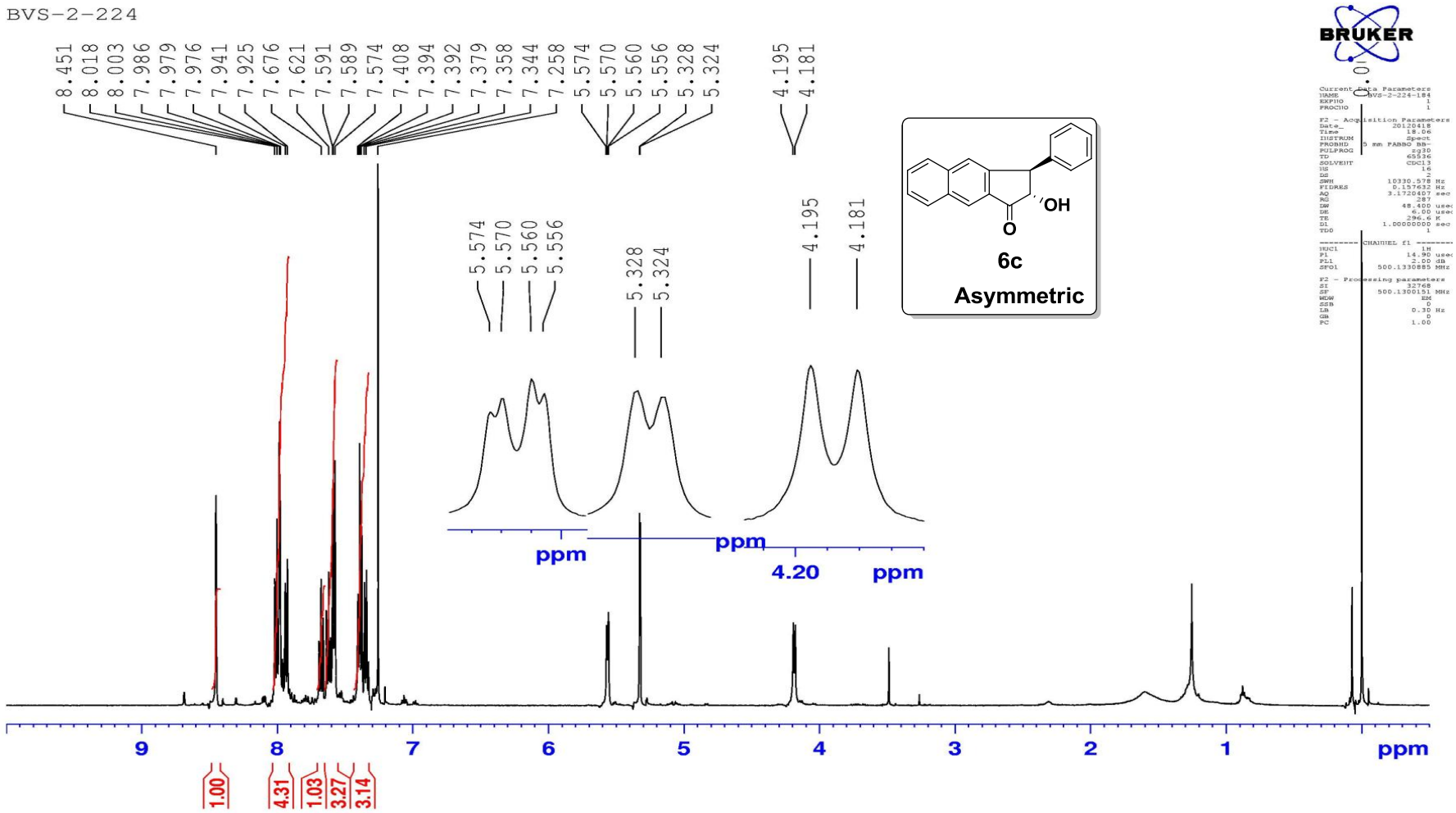


Figure S-31: ^{1}H NMR Spectrum of compound 6c

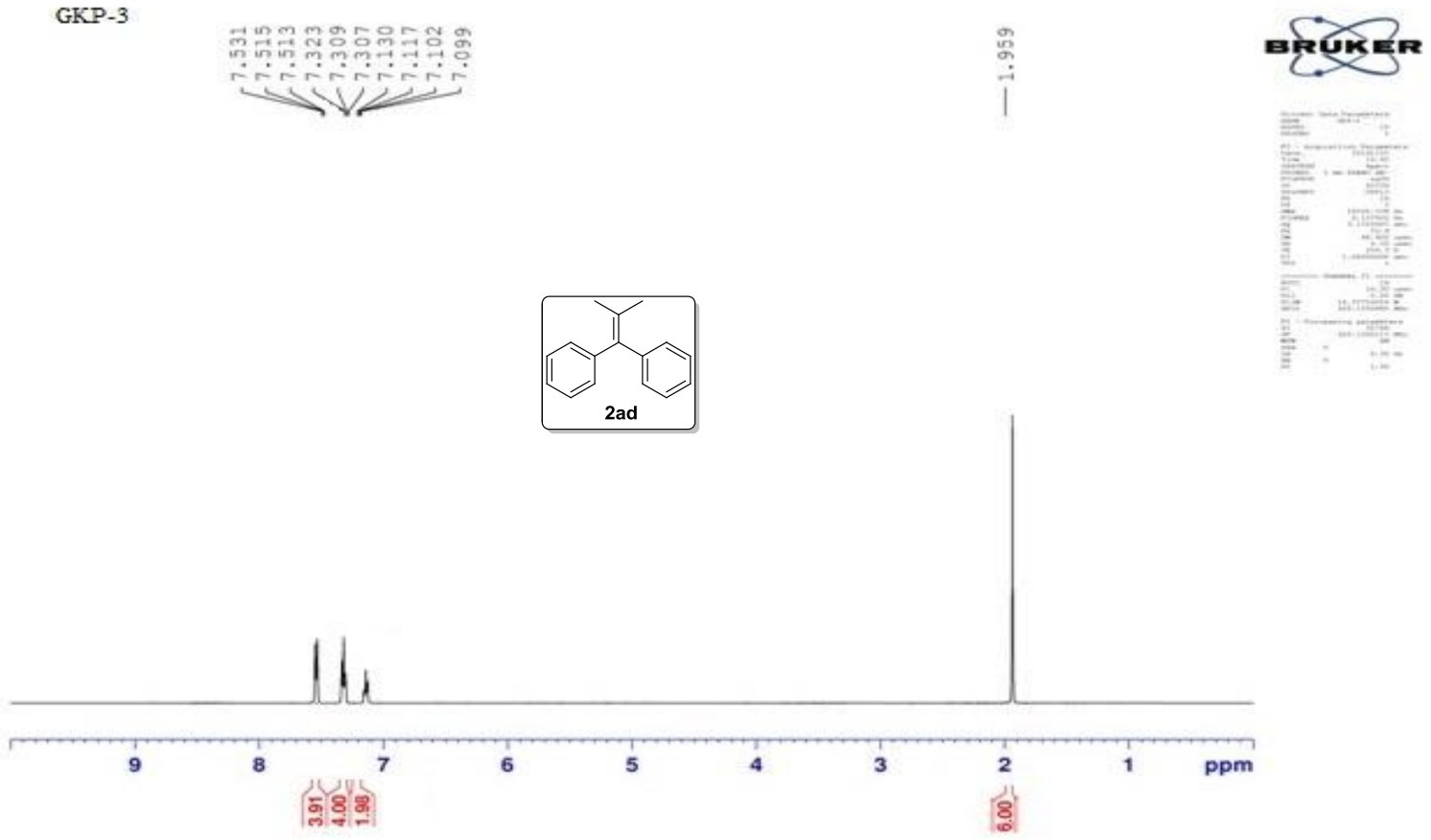


Figure S-32: ^{1}H NMR Spectrum of compound 6c

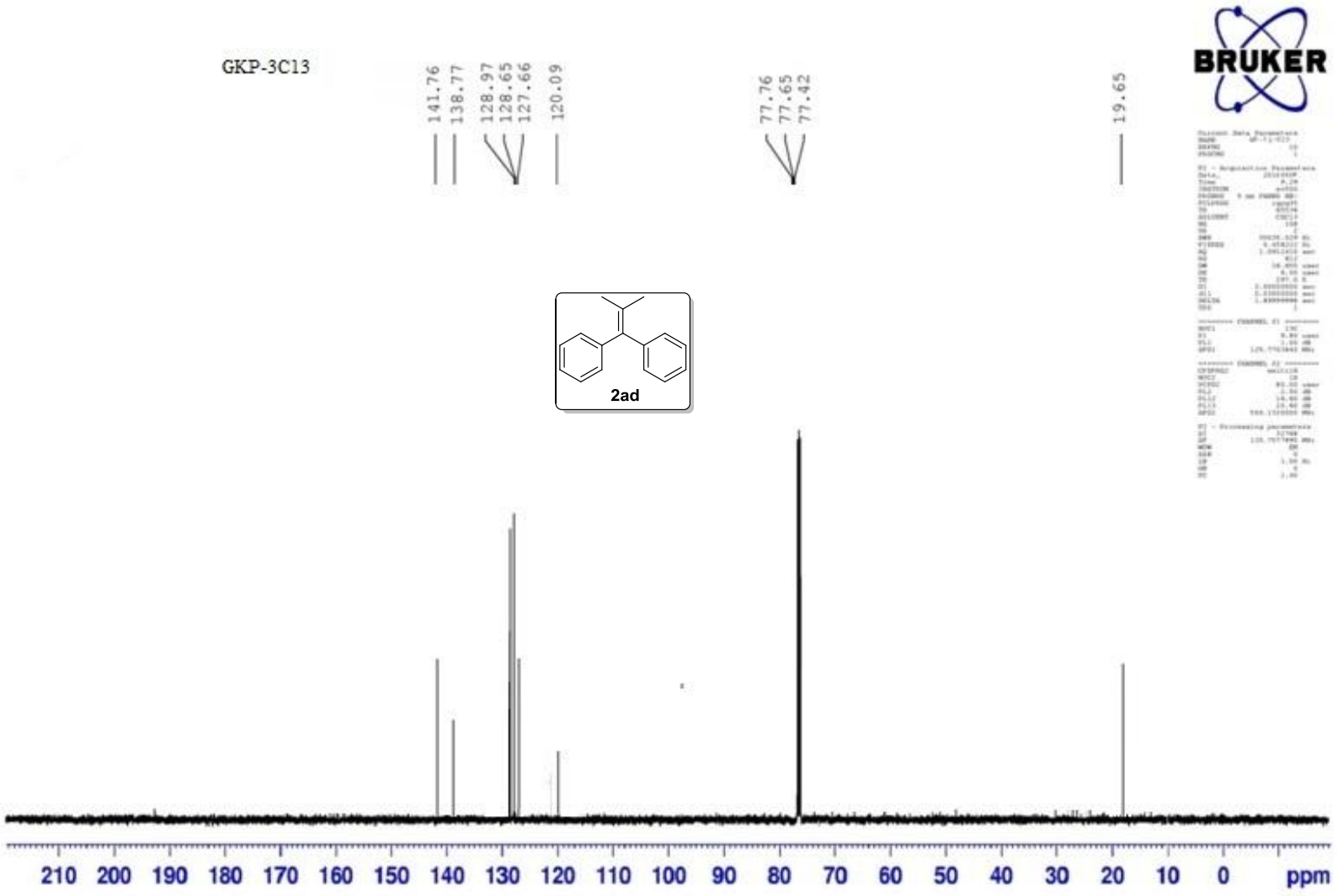


Figure S-33: ^{13}C NMR Spectrum of compound 2ad

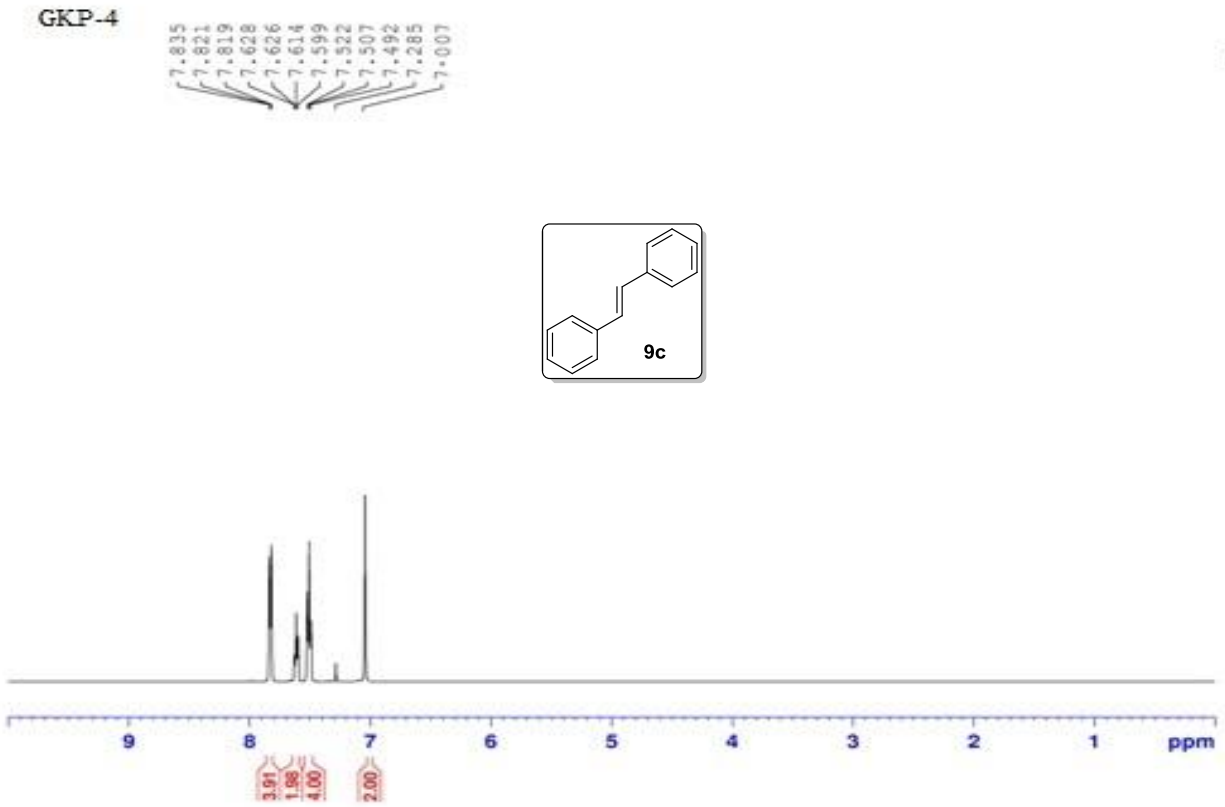


Figure S-34: ^{1}H NMR Spectrum of compound 2ad

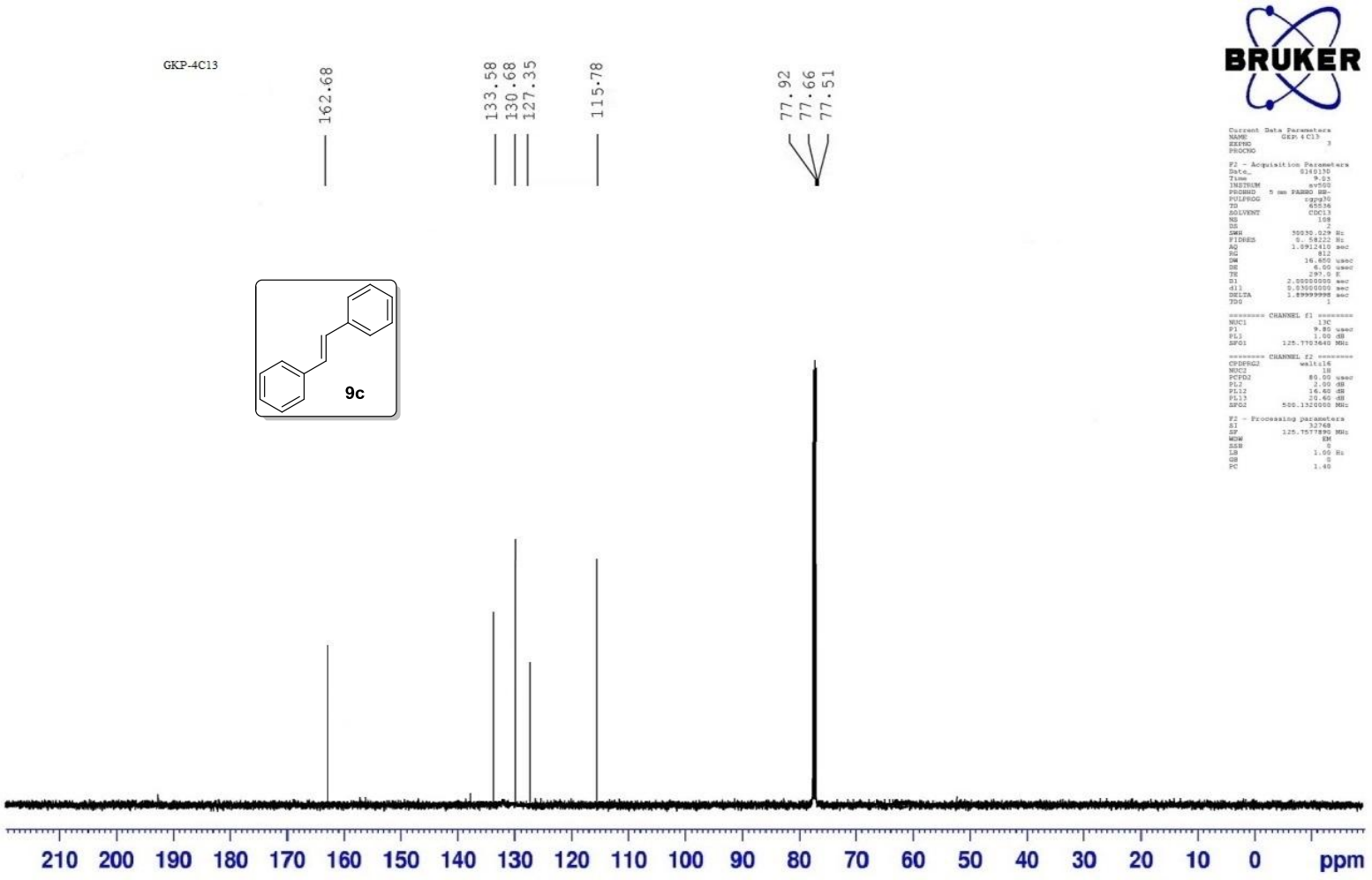


Figure S-35: ^{13}C NMR Spectrum of compound 9c

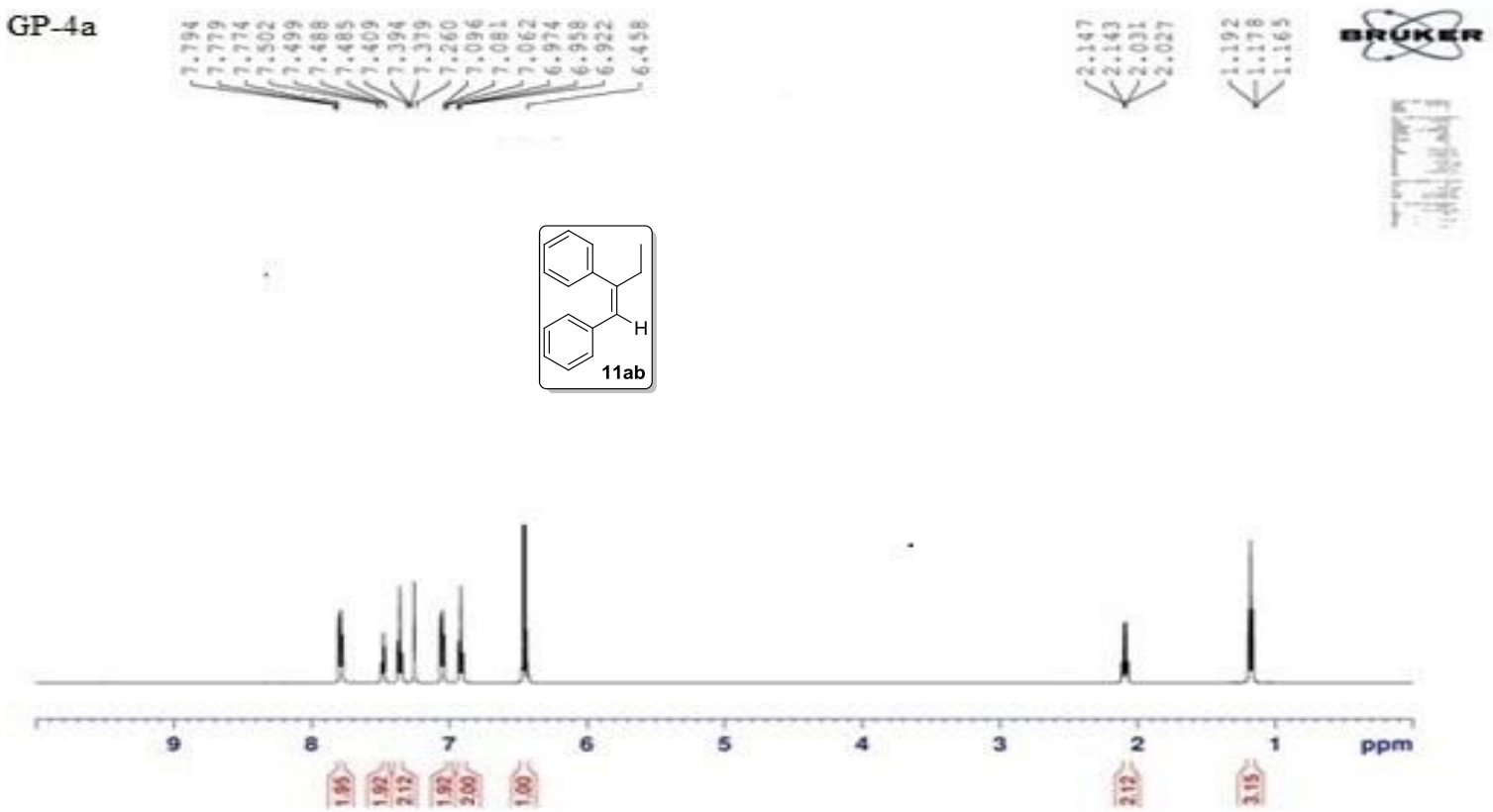


Figure S-36: ^{1}H NMR Spectrum of compound 9c

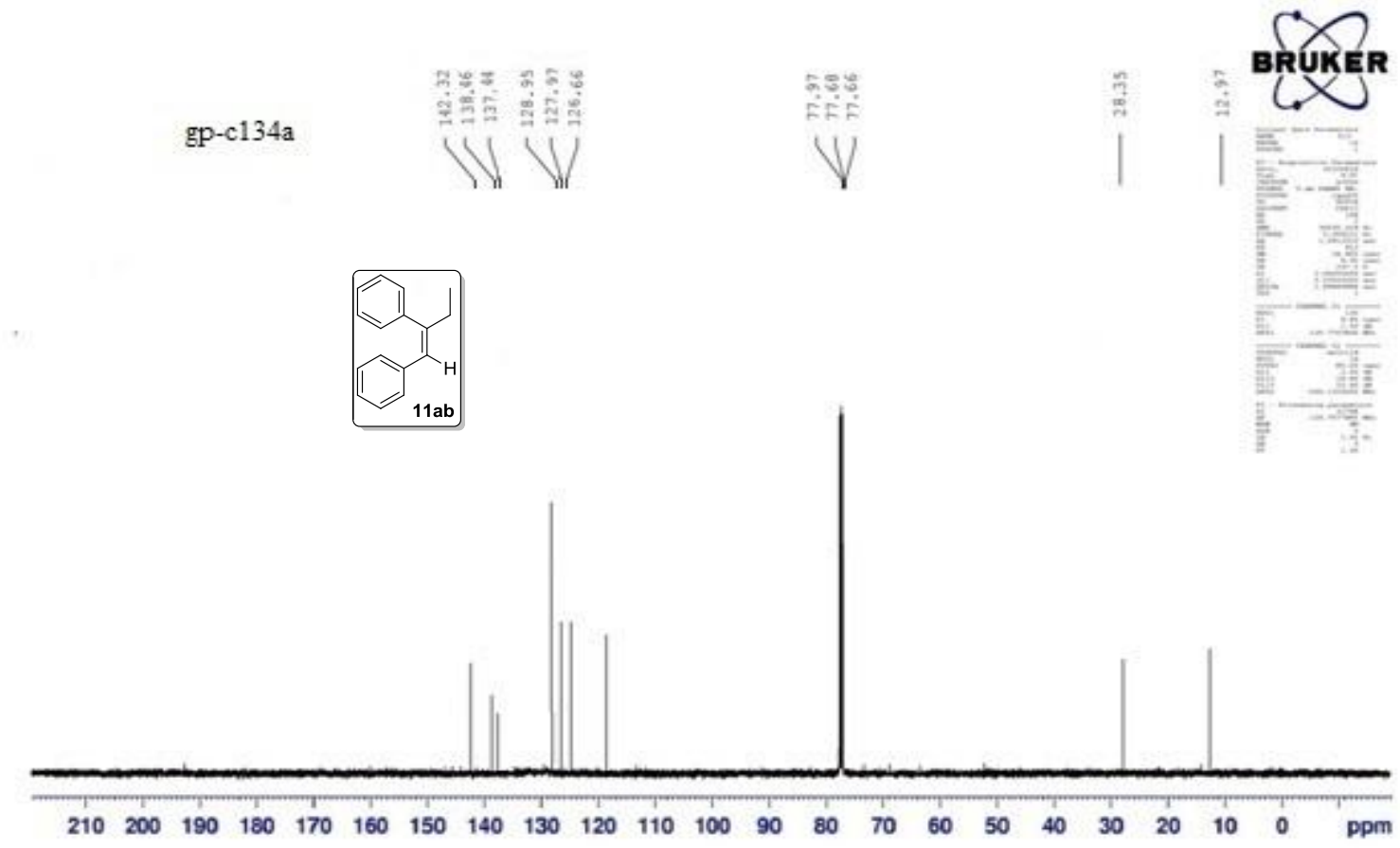


Figure S-37: ^{13}C NMR Spectrum of compound 11ab

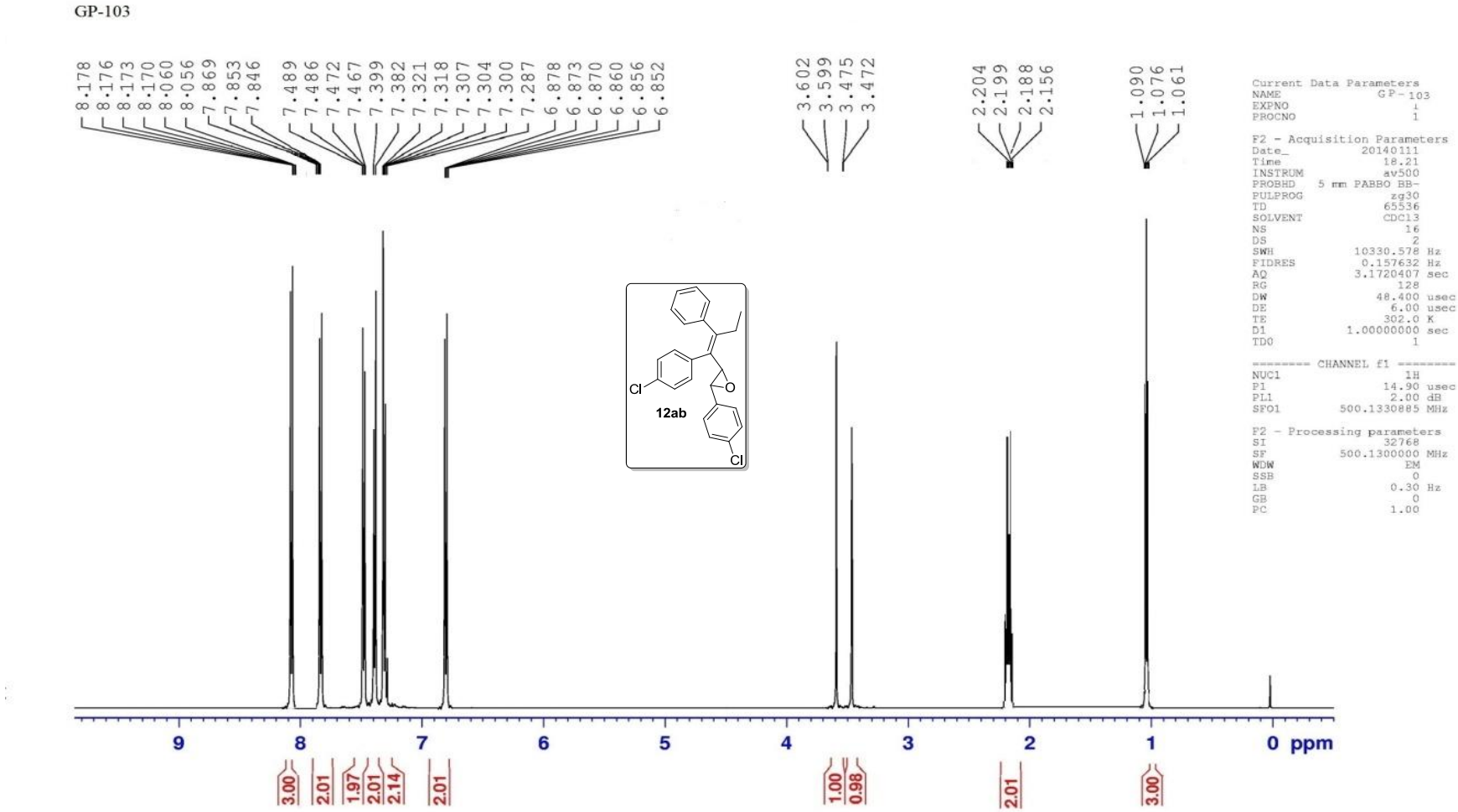


Figure S-38: ^{1}H NMR Spectrum of compound 12ab

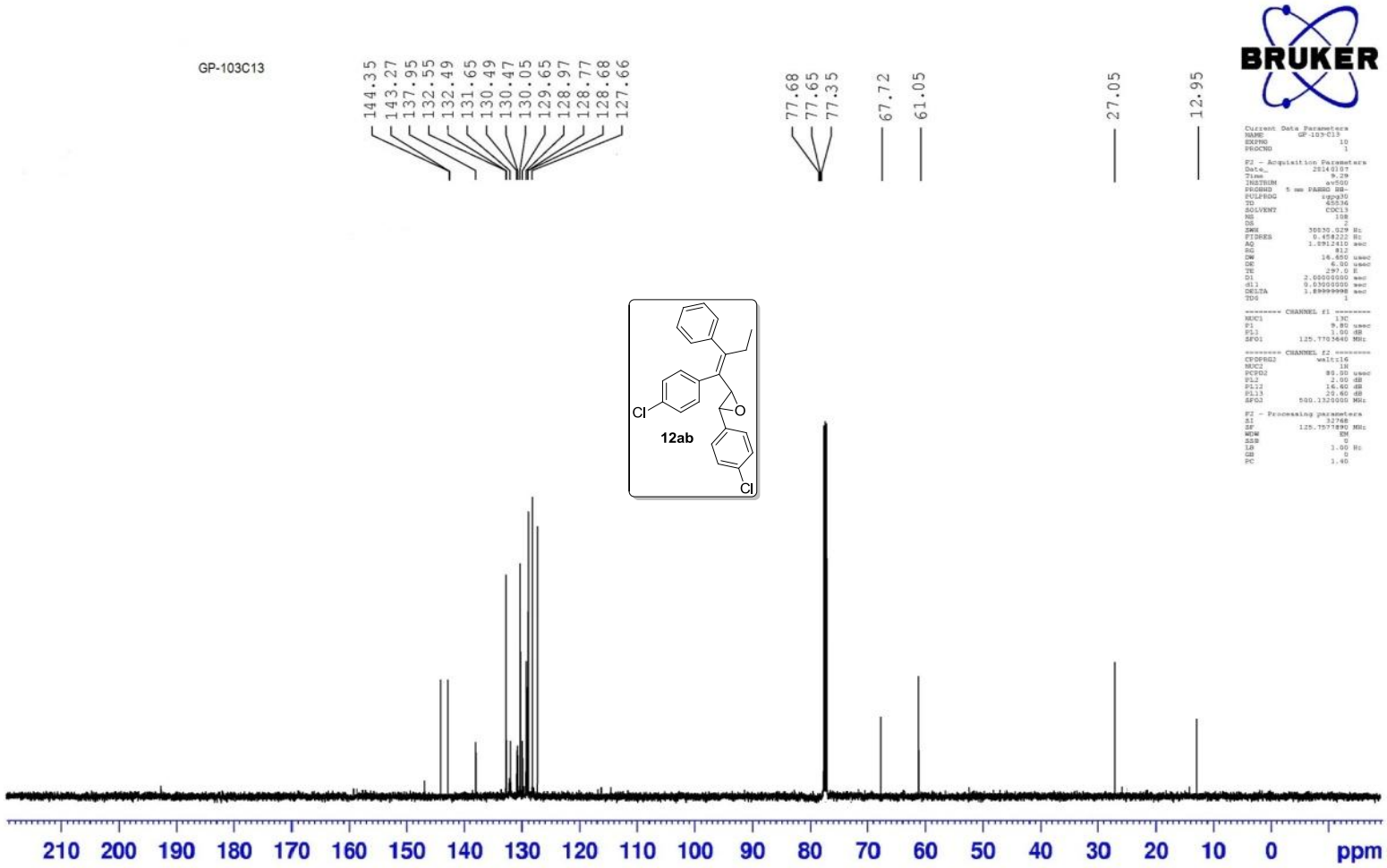


Figure S-39: ^{13}C NMR Spectrum of compound 12ab

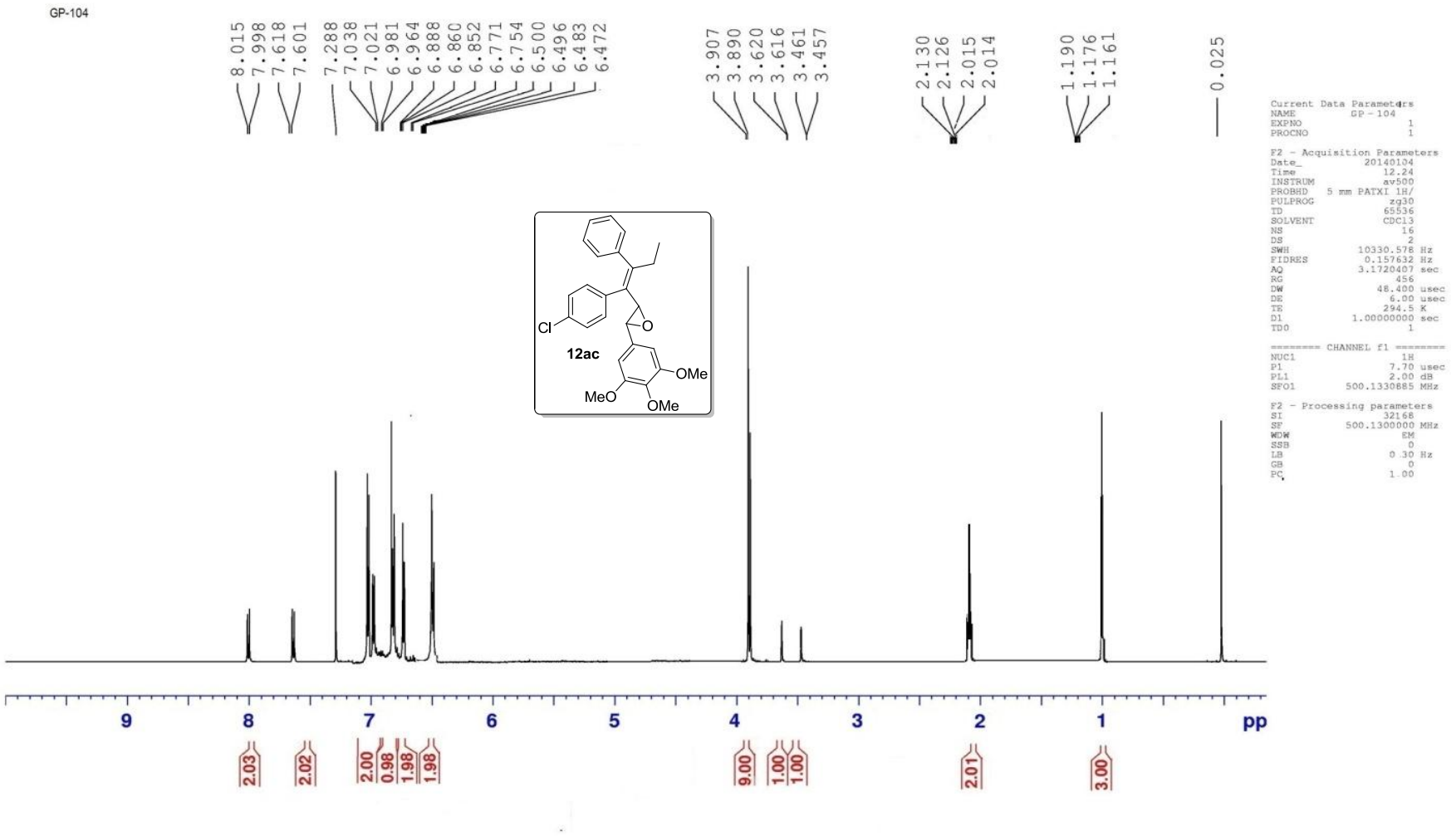


Figure S-40: ^{1}H NMR Spectrum of compound 12ac

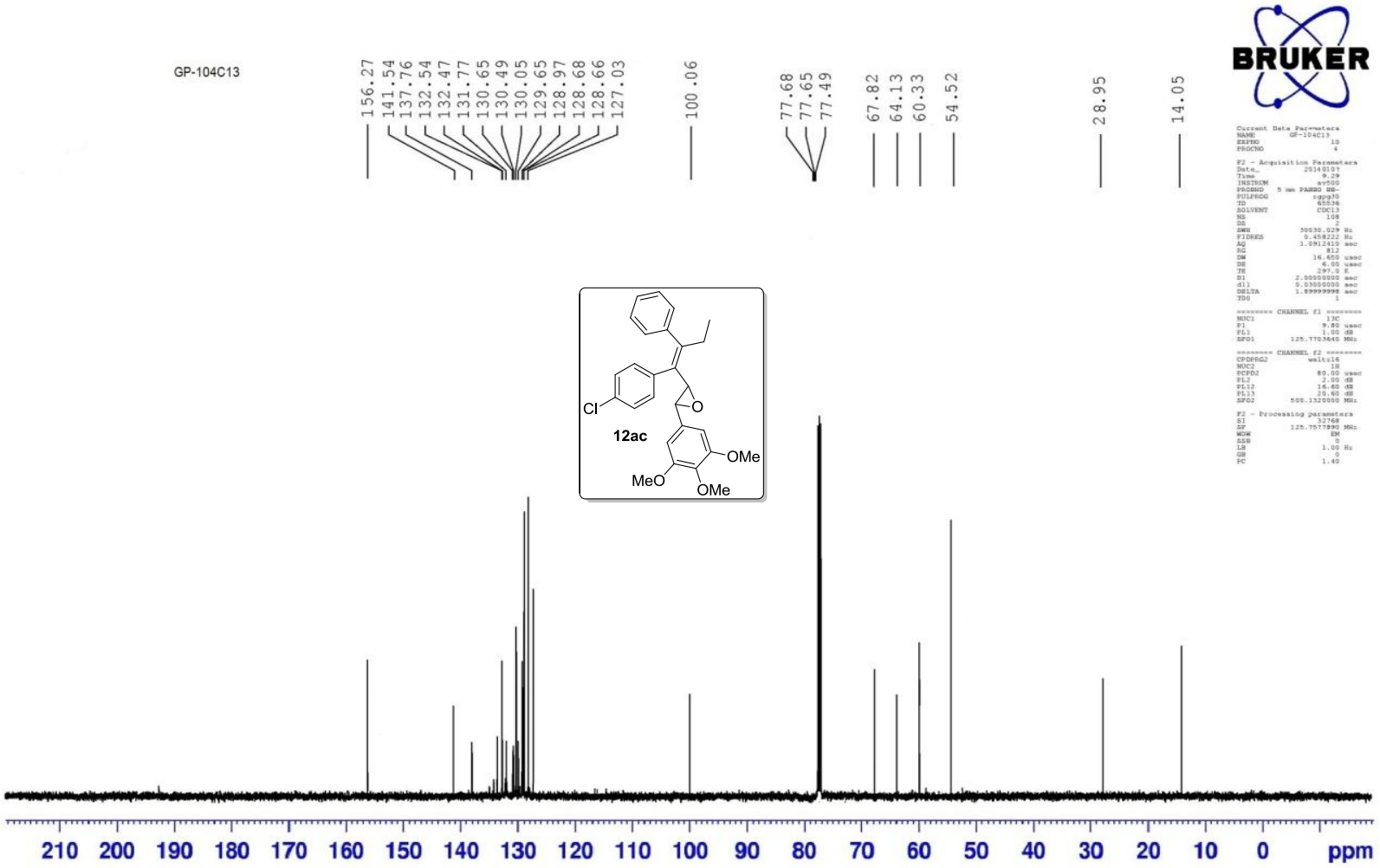


Figure S-41: ^{13}C NMR Spectrum of compound 12ac

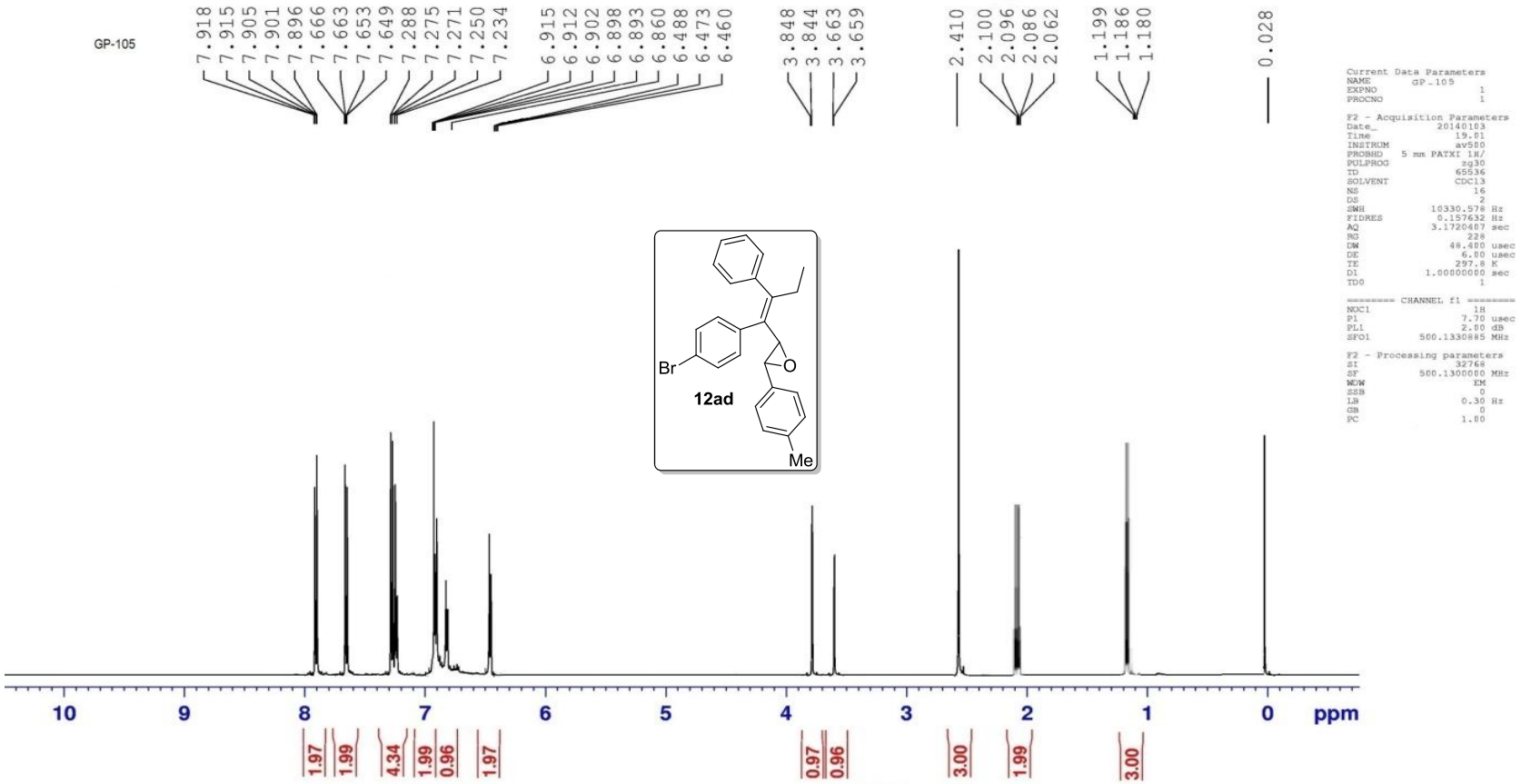


Figure S-42: ^{1}H NMR Spectrum of compound 12ad

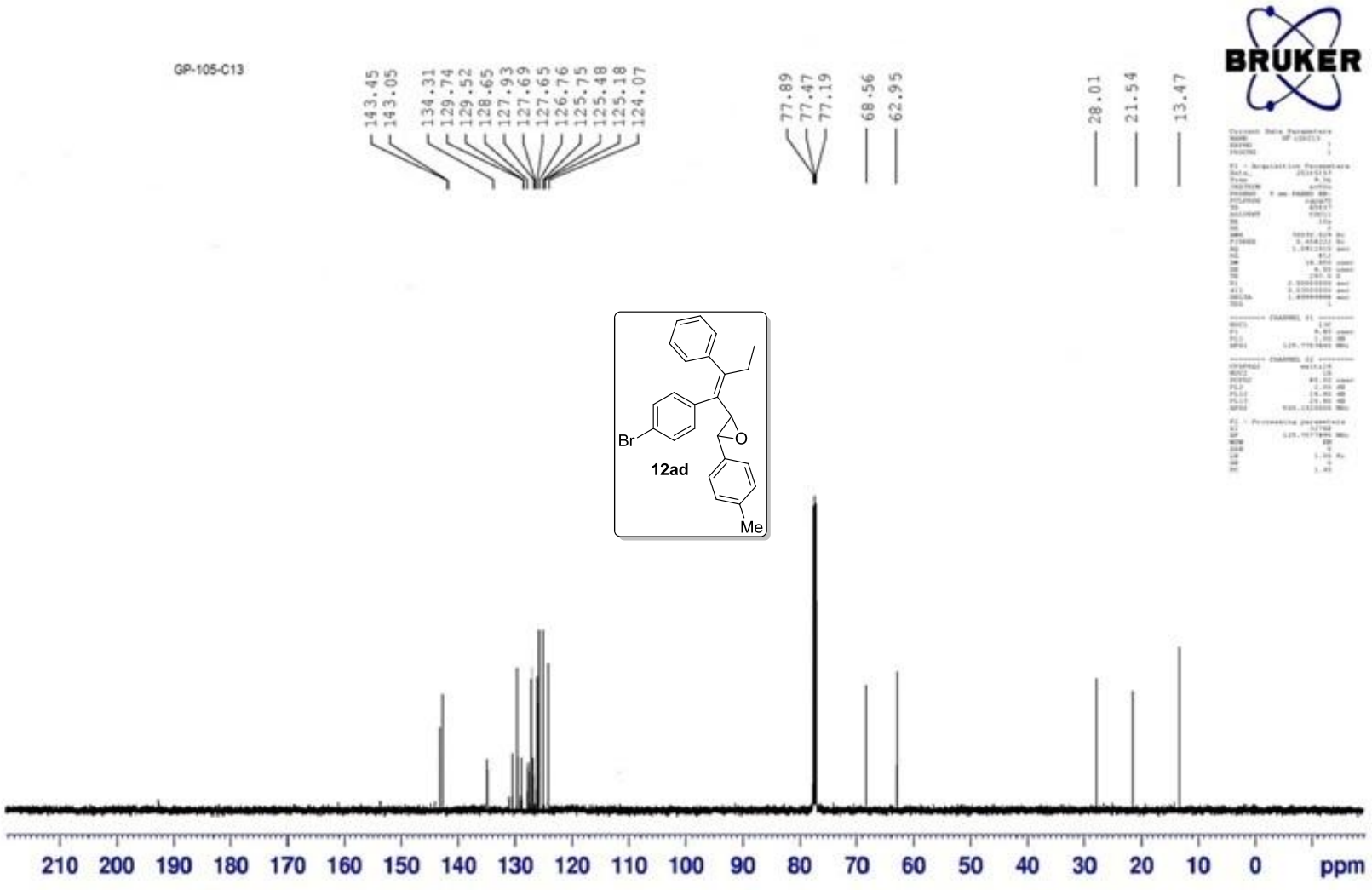


Figure S-43: ^{13}C NMR Spectrum of compound 12ad

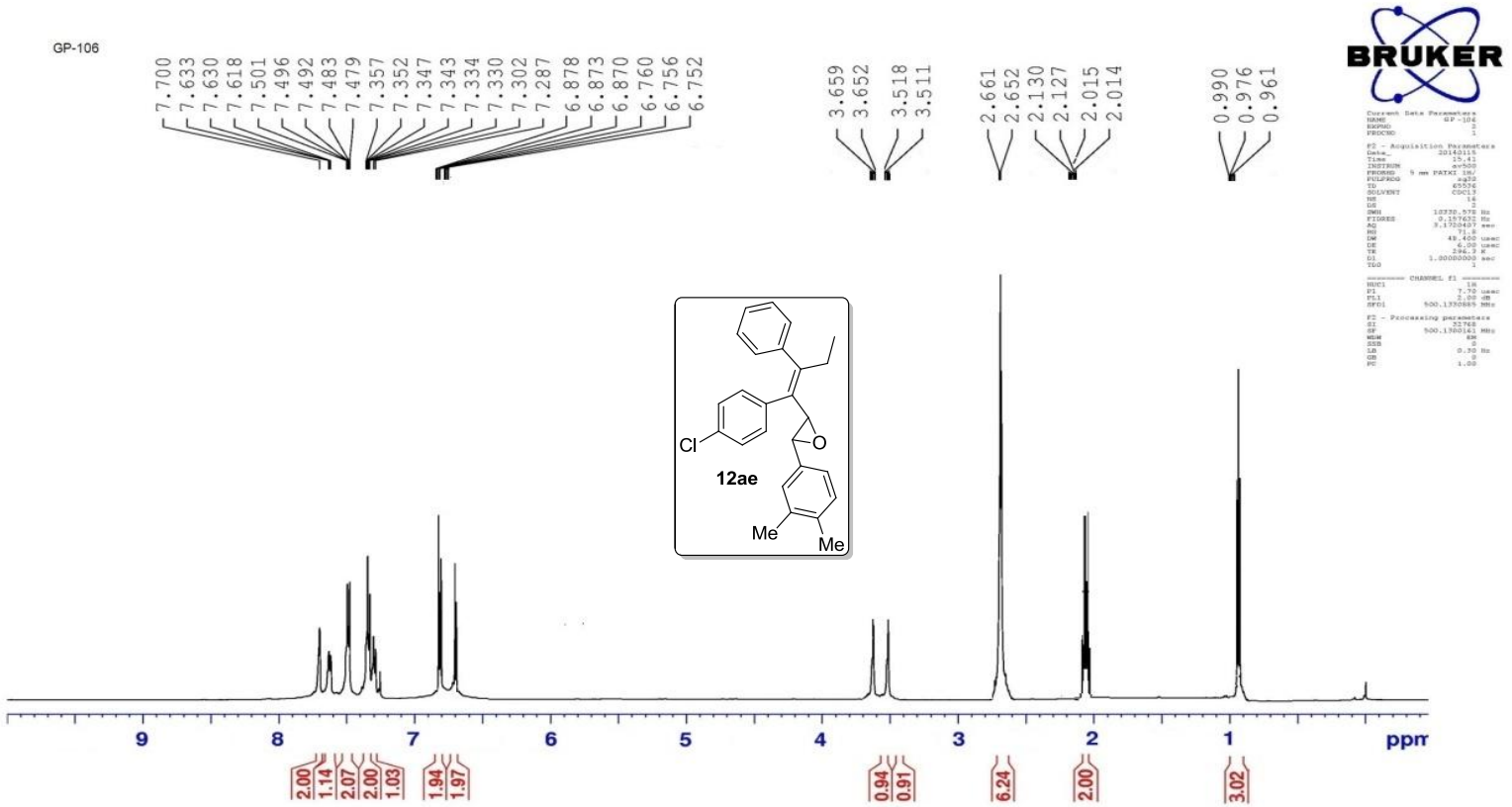


Figure S-44: ^{1}H NMR Spectrum of compound 12ae

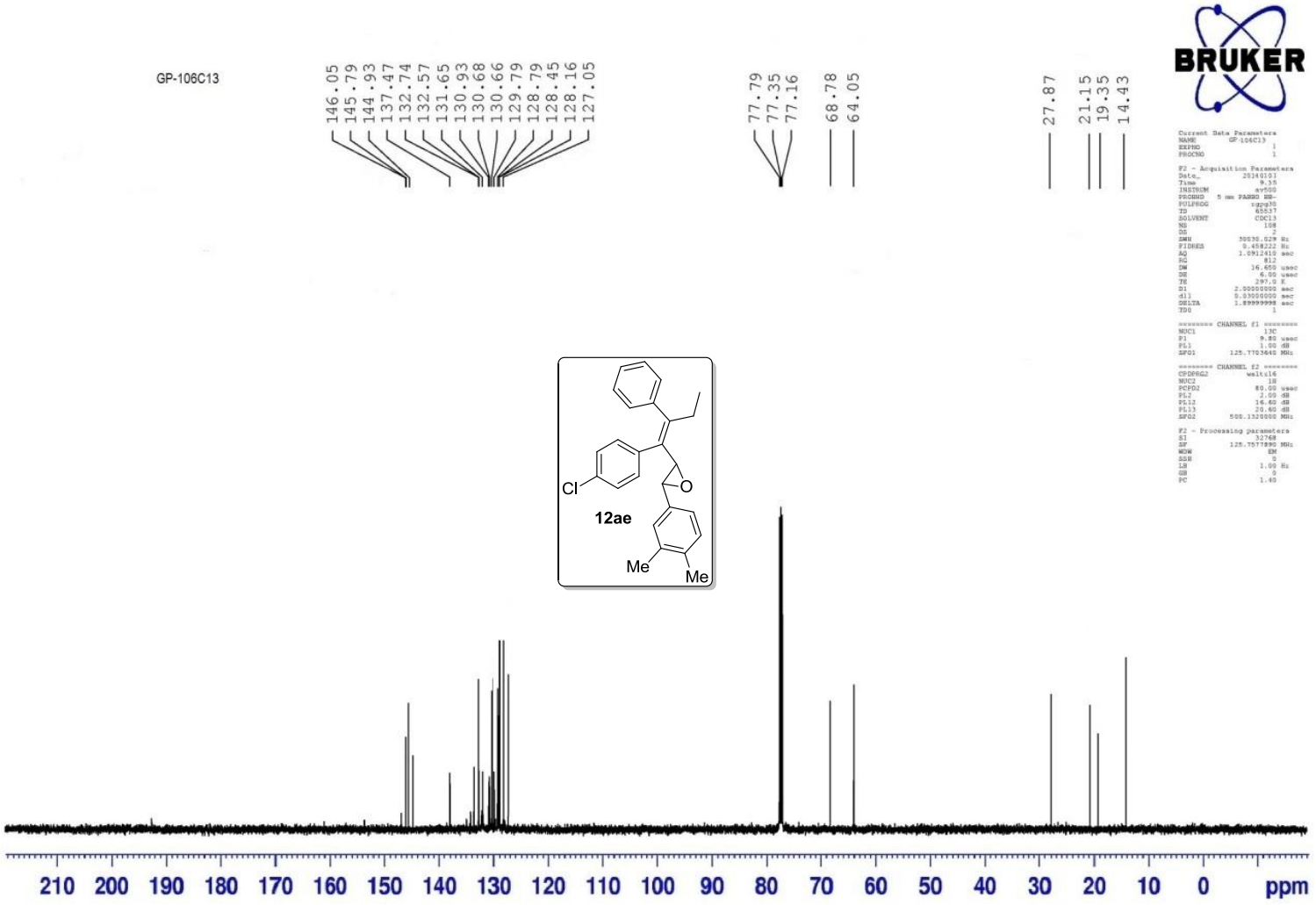


Figure S-45: ^{13}C NMR Spectrum of compound12ae

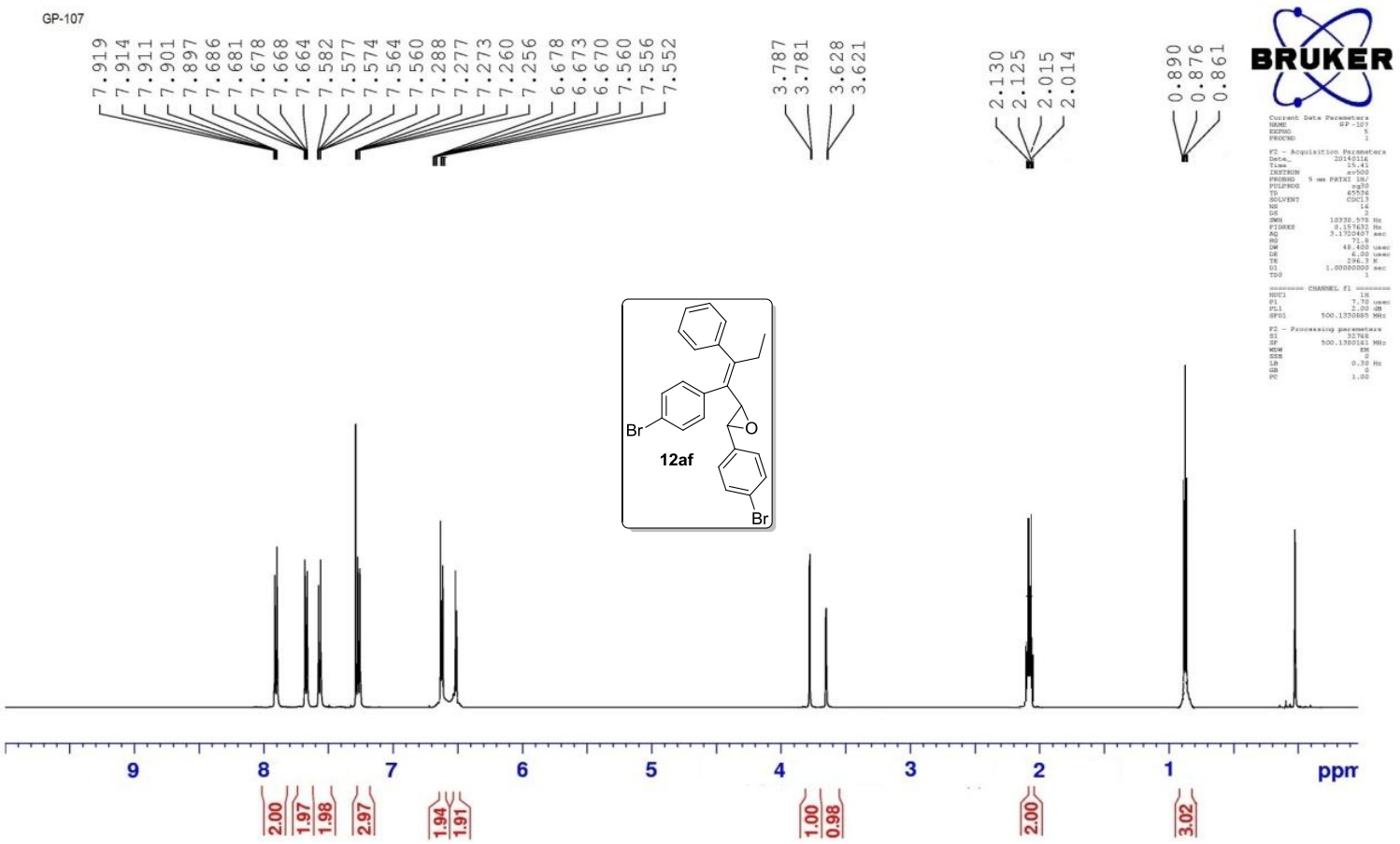


Figure S-46: ^{1}H NMR Spectrum of compound 12af

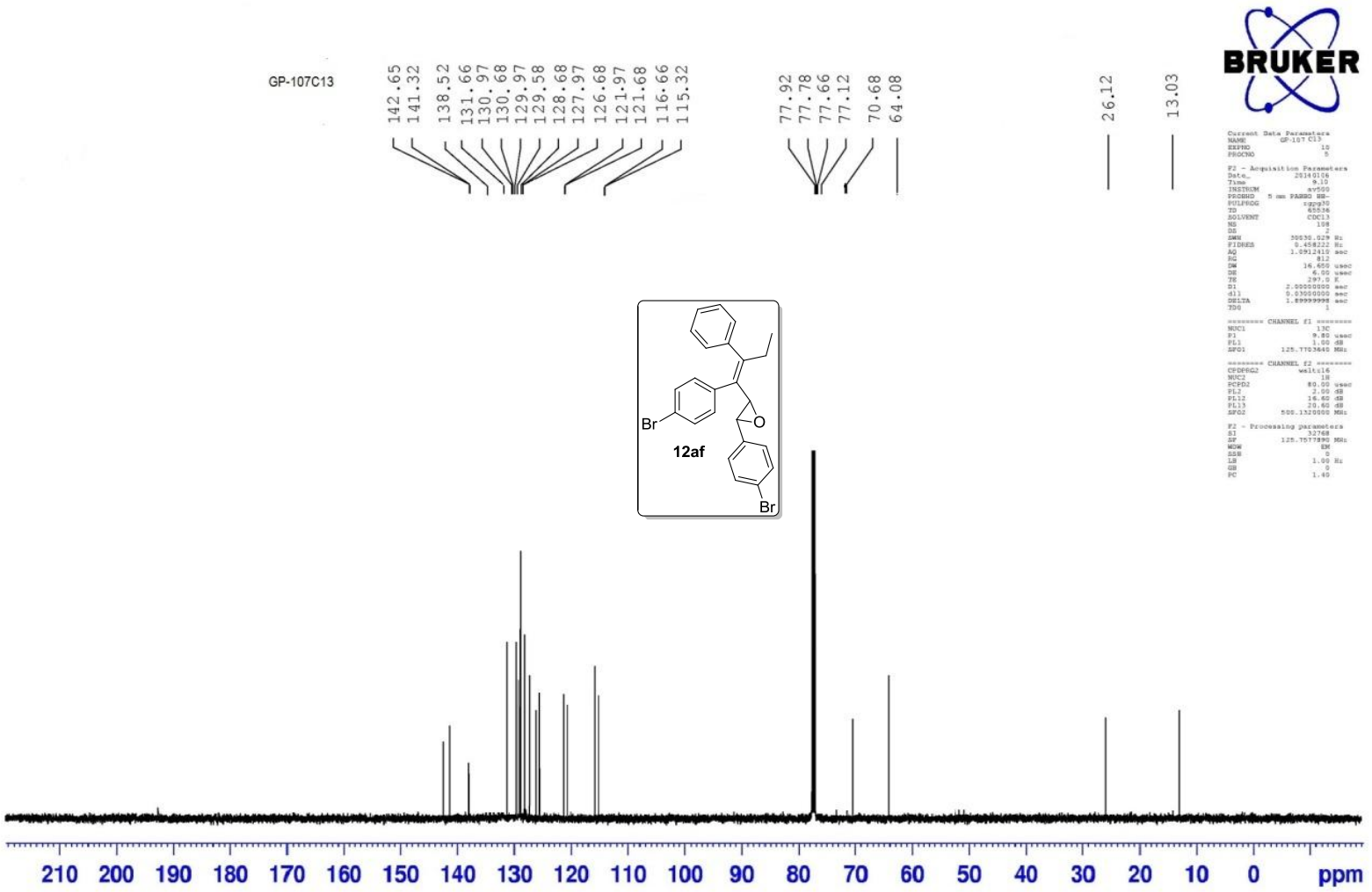


Figure S-47: ^{13}C NMR Spectrum of compound 12af

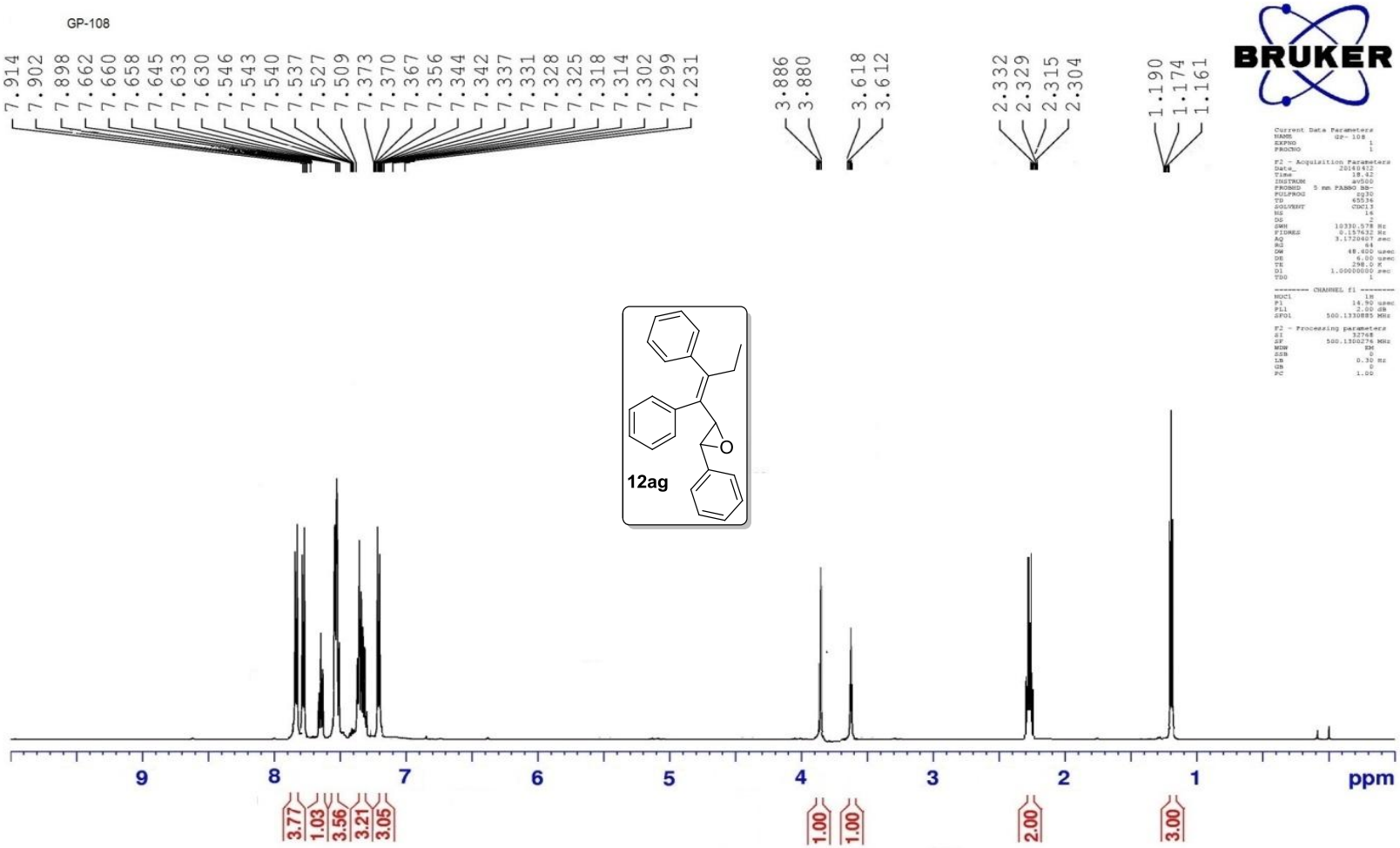


Figure S-48: ^{1}H NMR Spectrum of compound 12ag

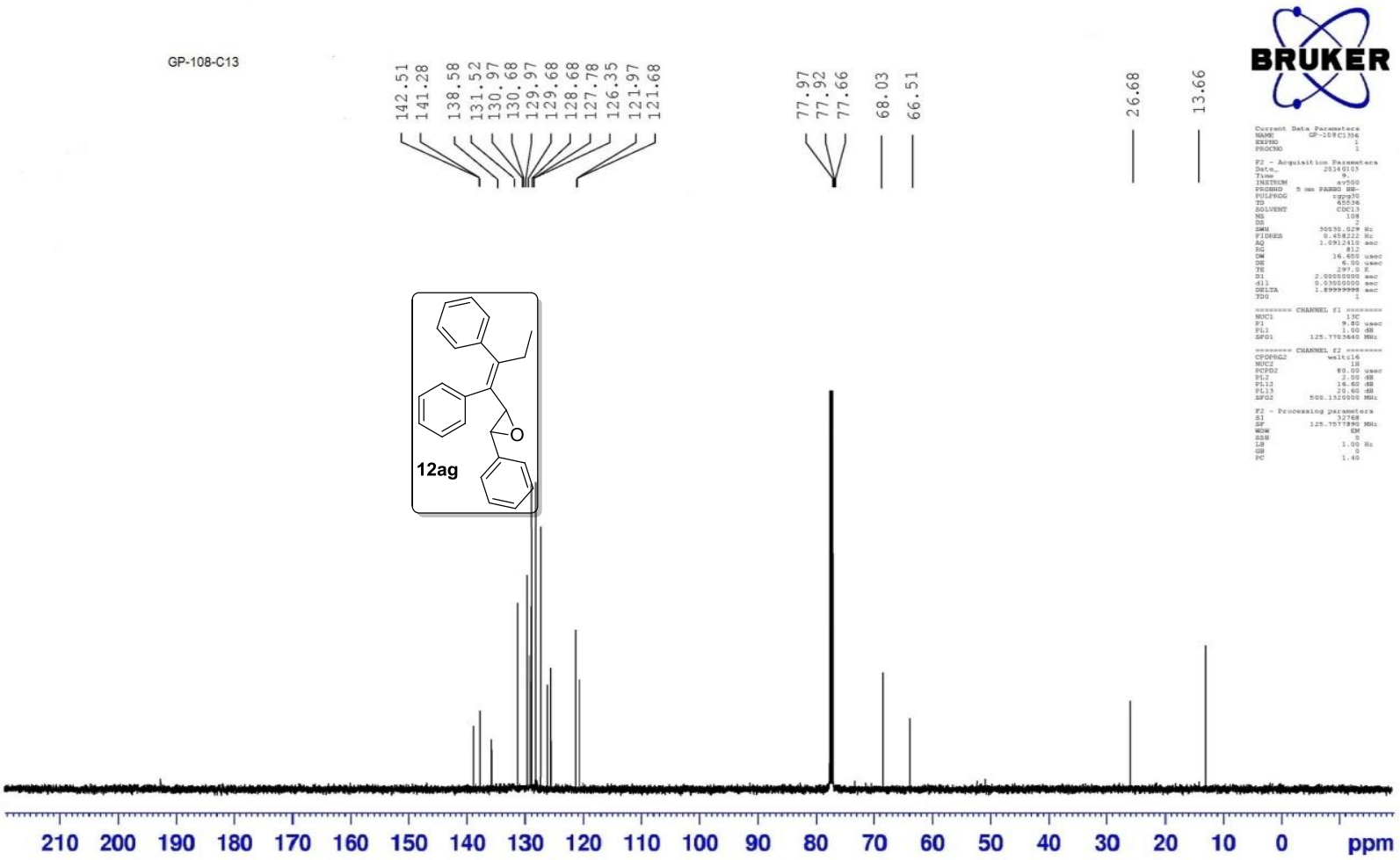


Figure S-49: ^{13}C NMR Spectrum of compound 12ag

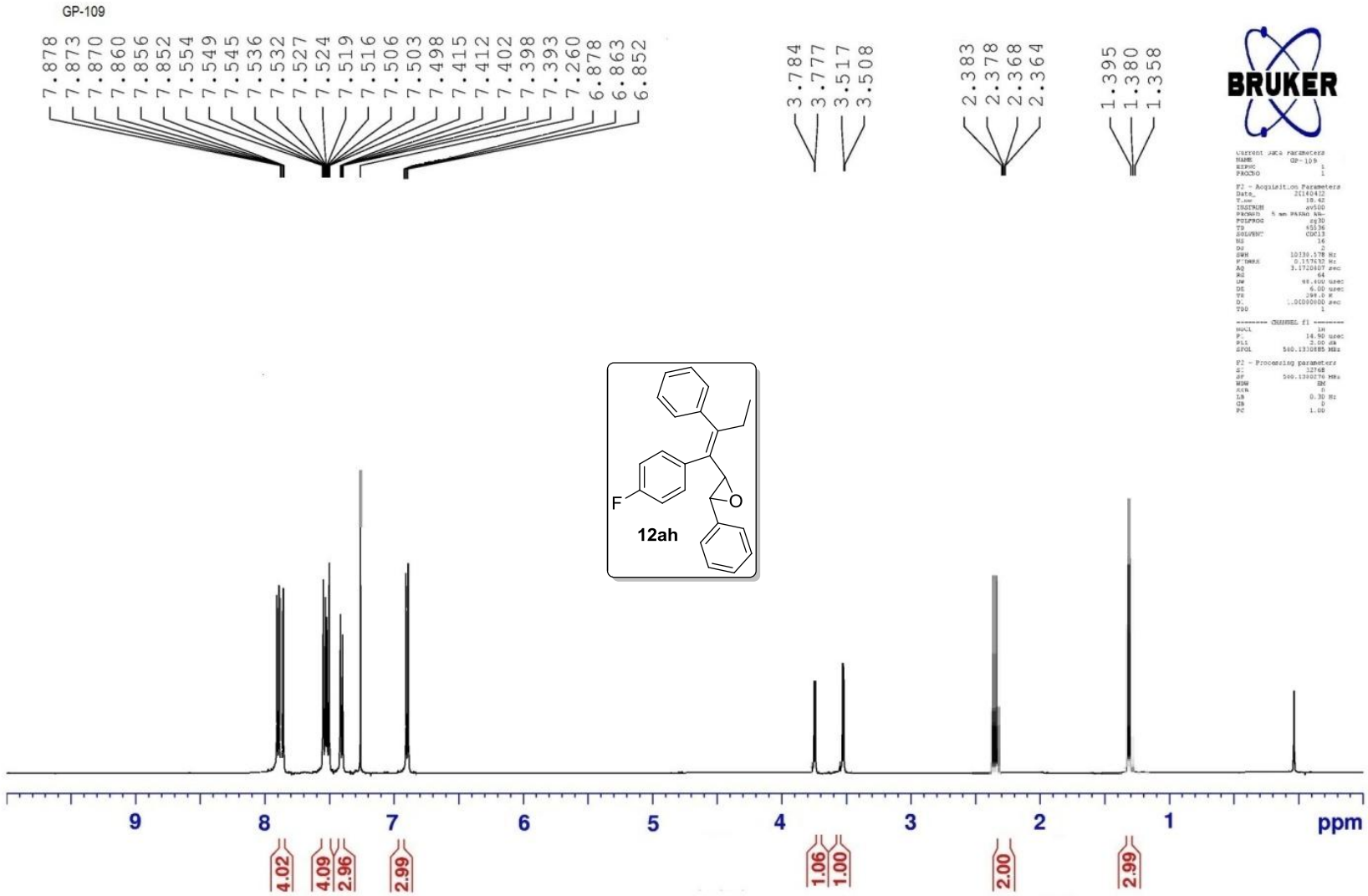


Figure S-50: ^{1}H NMR Spectrum of compound 12ah

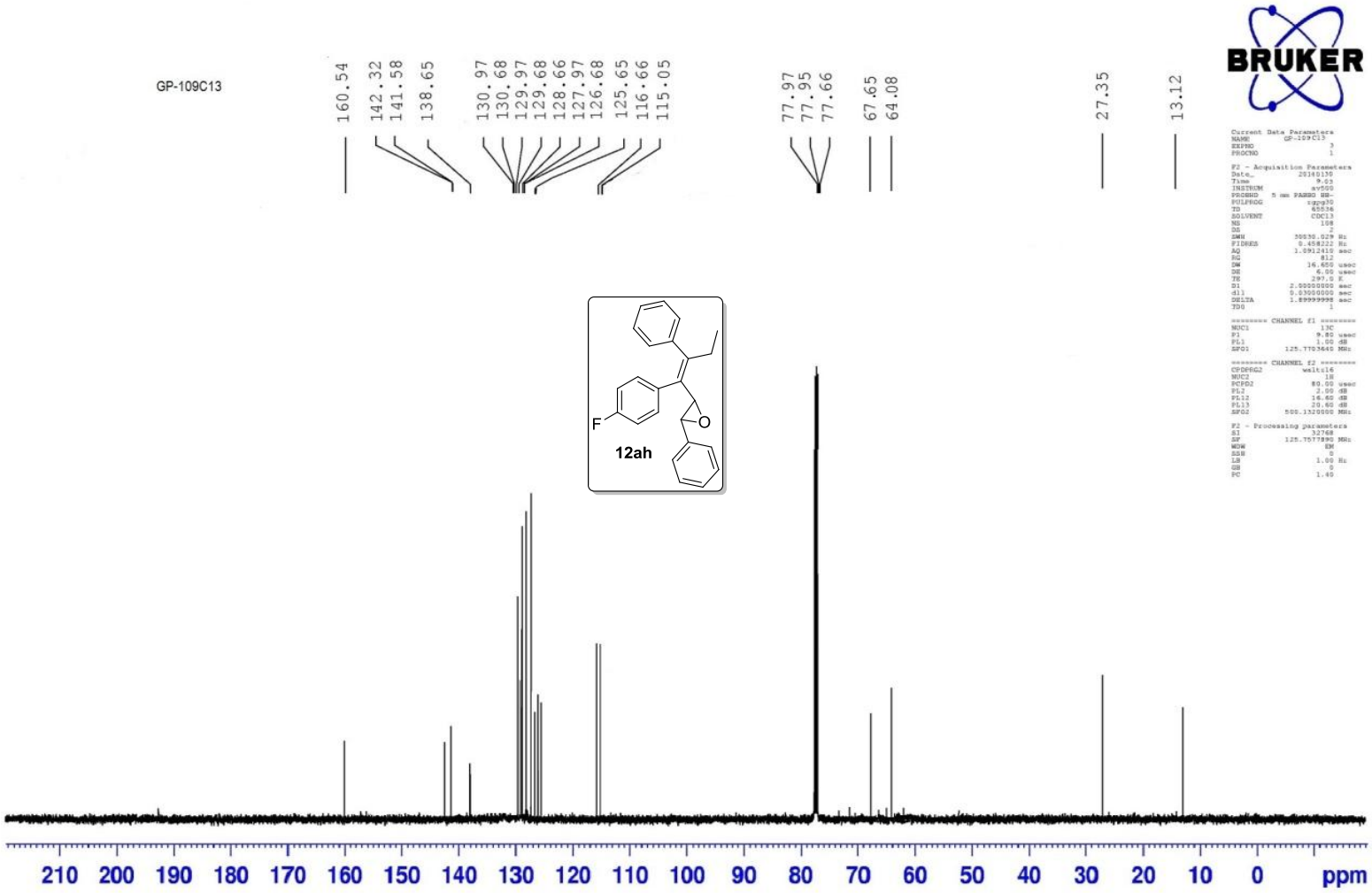


Figure S-51: ^{13}C NMR Spectrum of compound 12ah

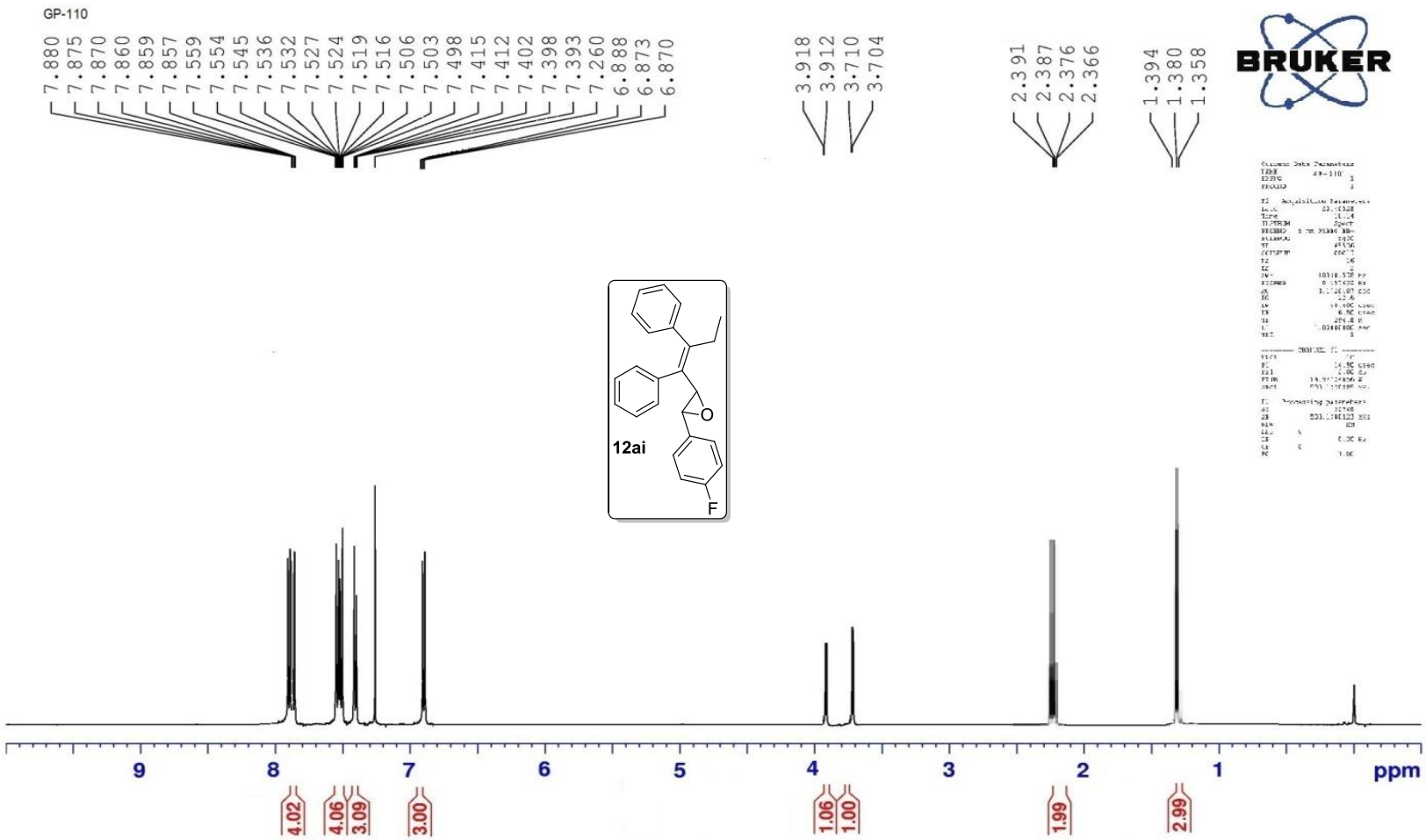


Figure S-52: ^{1}H NMR Spectrum of compound 12ai

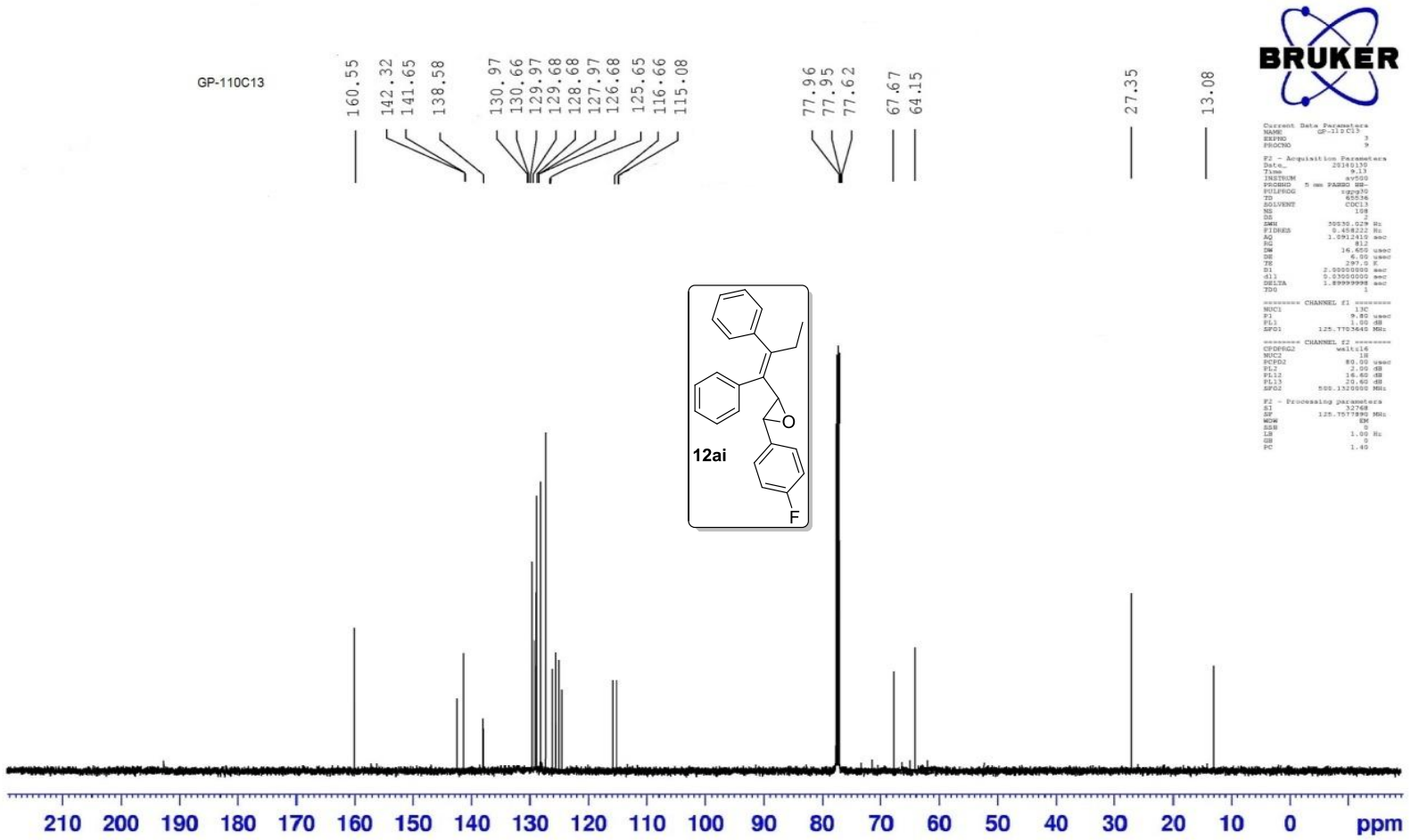


Figure S-53: ^{13}C NMR Spectrum of compound 12ai

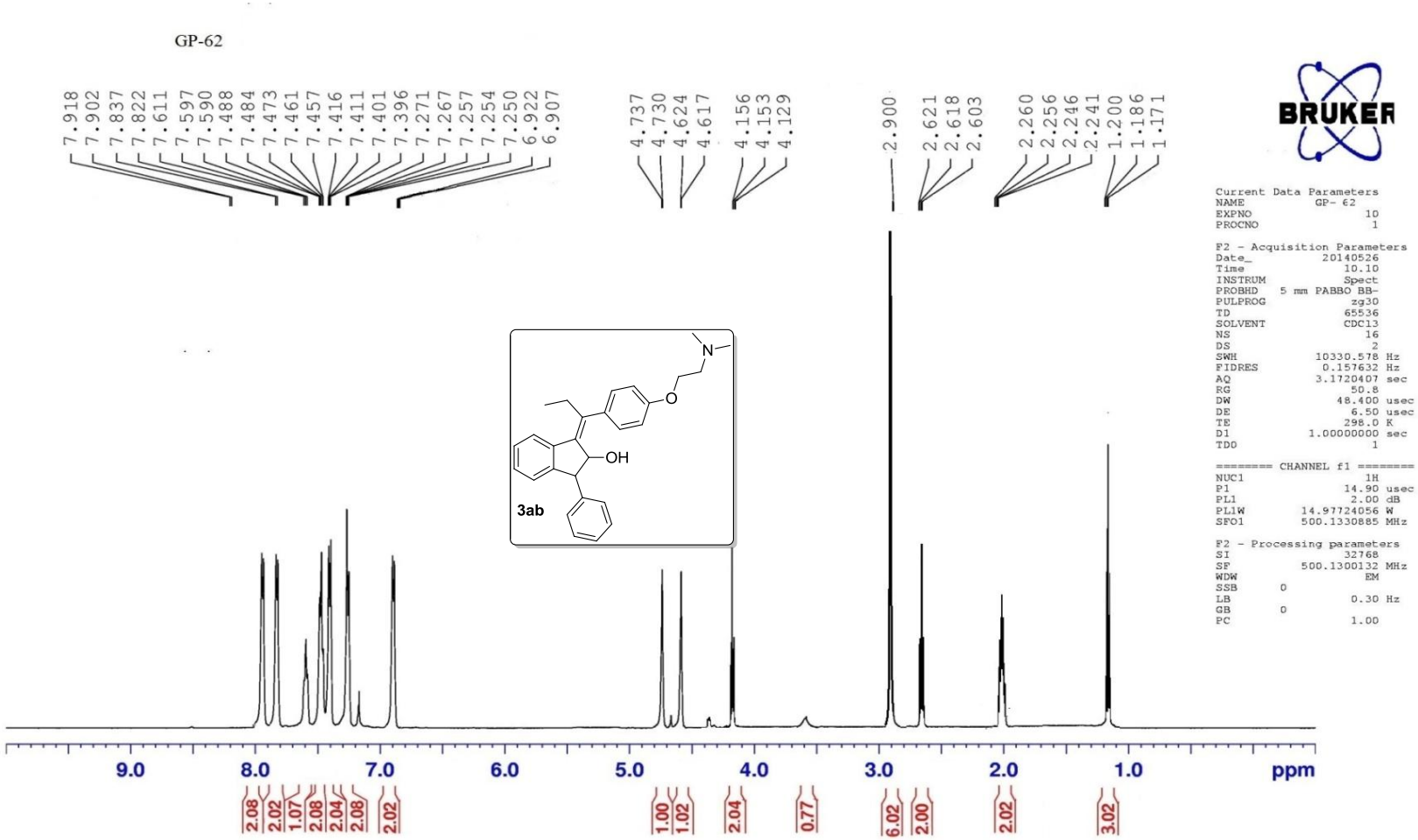


Figure S-54: ^{1}H NMR Spectrum of compound 3ab

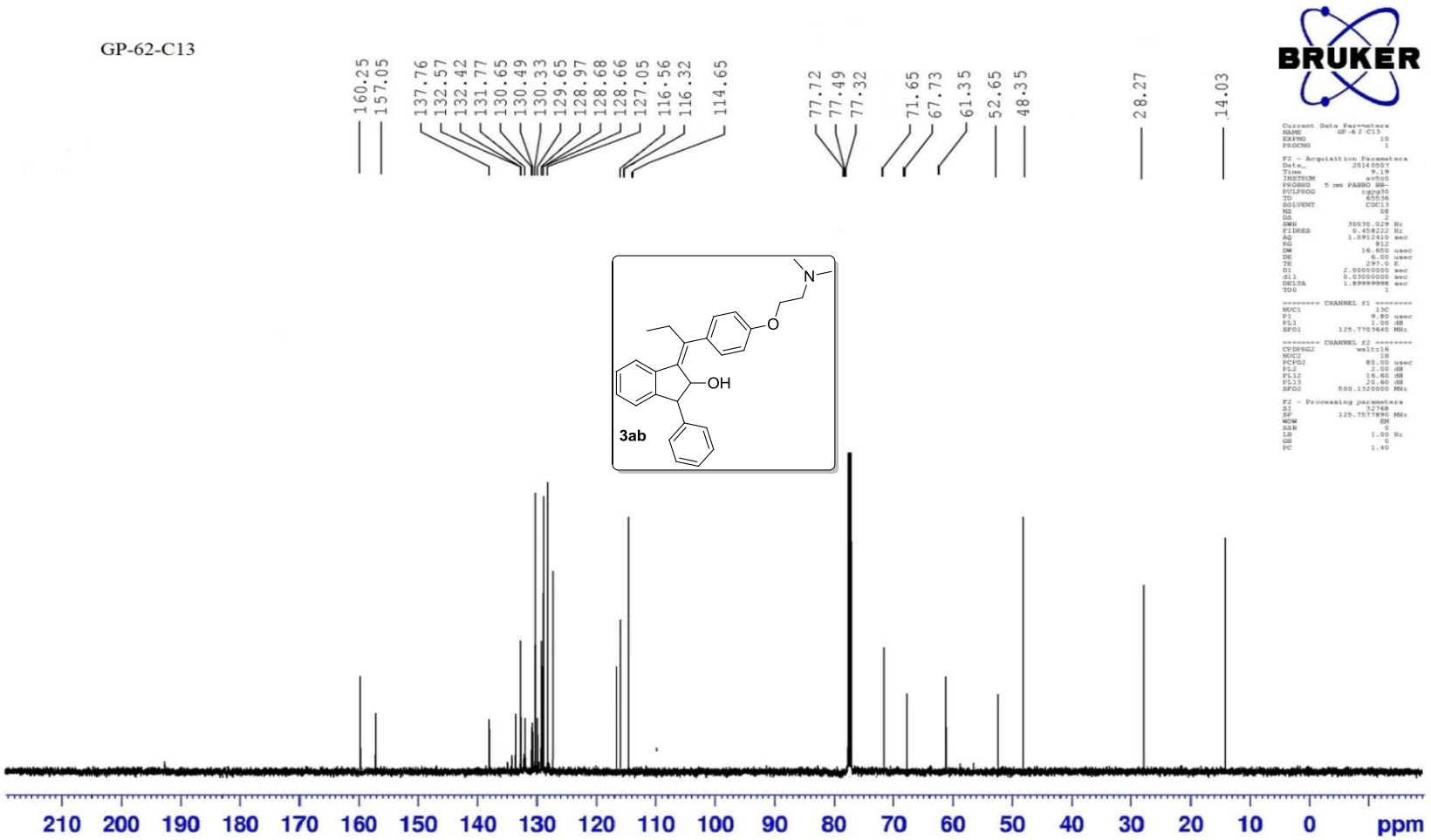


Figure S-55: ^{13}C NMR Spectrum of compound 3ab

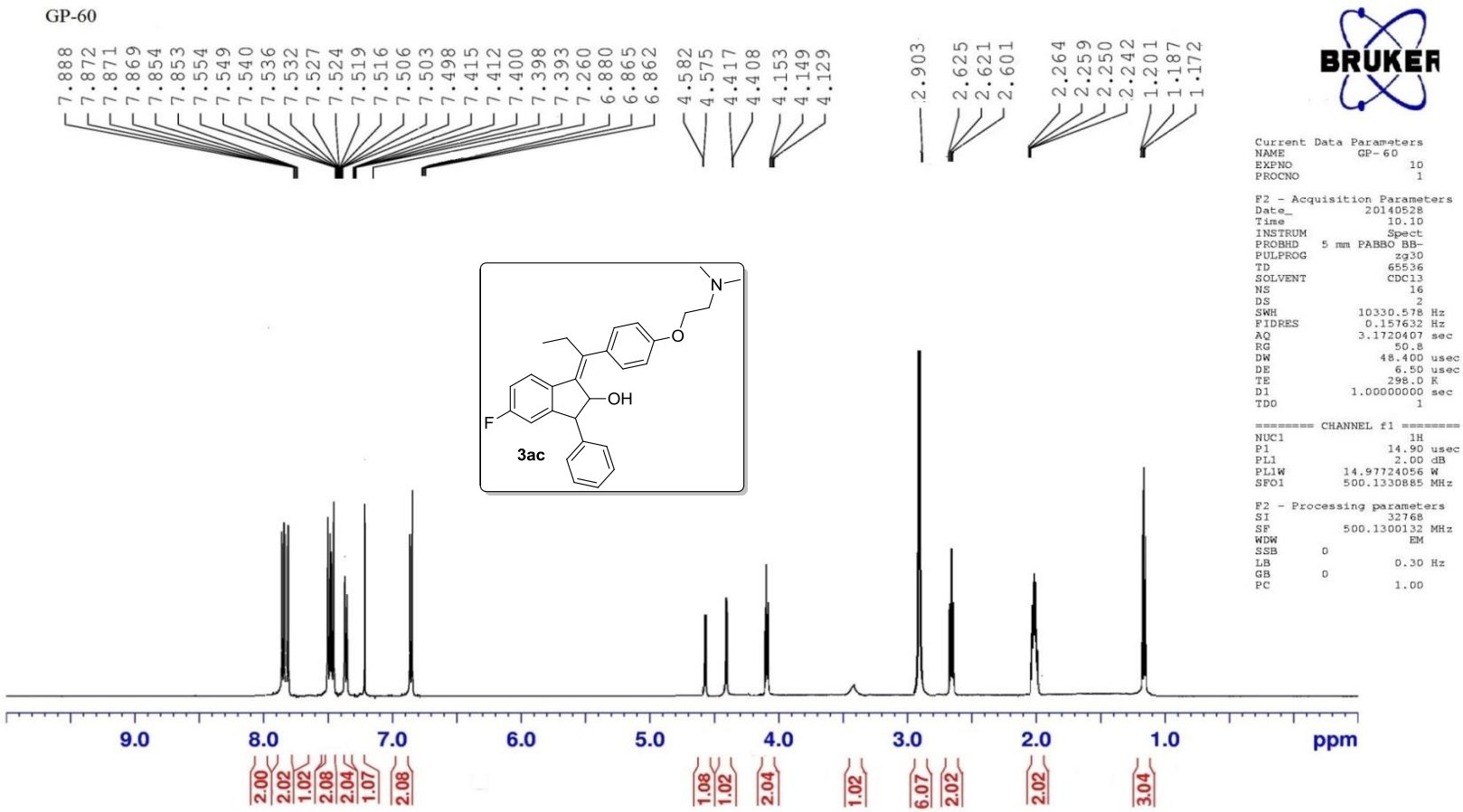


Figure S-56: ^{1}H NMR Spectrum of compound 3ac

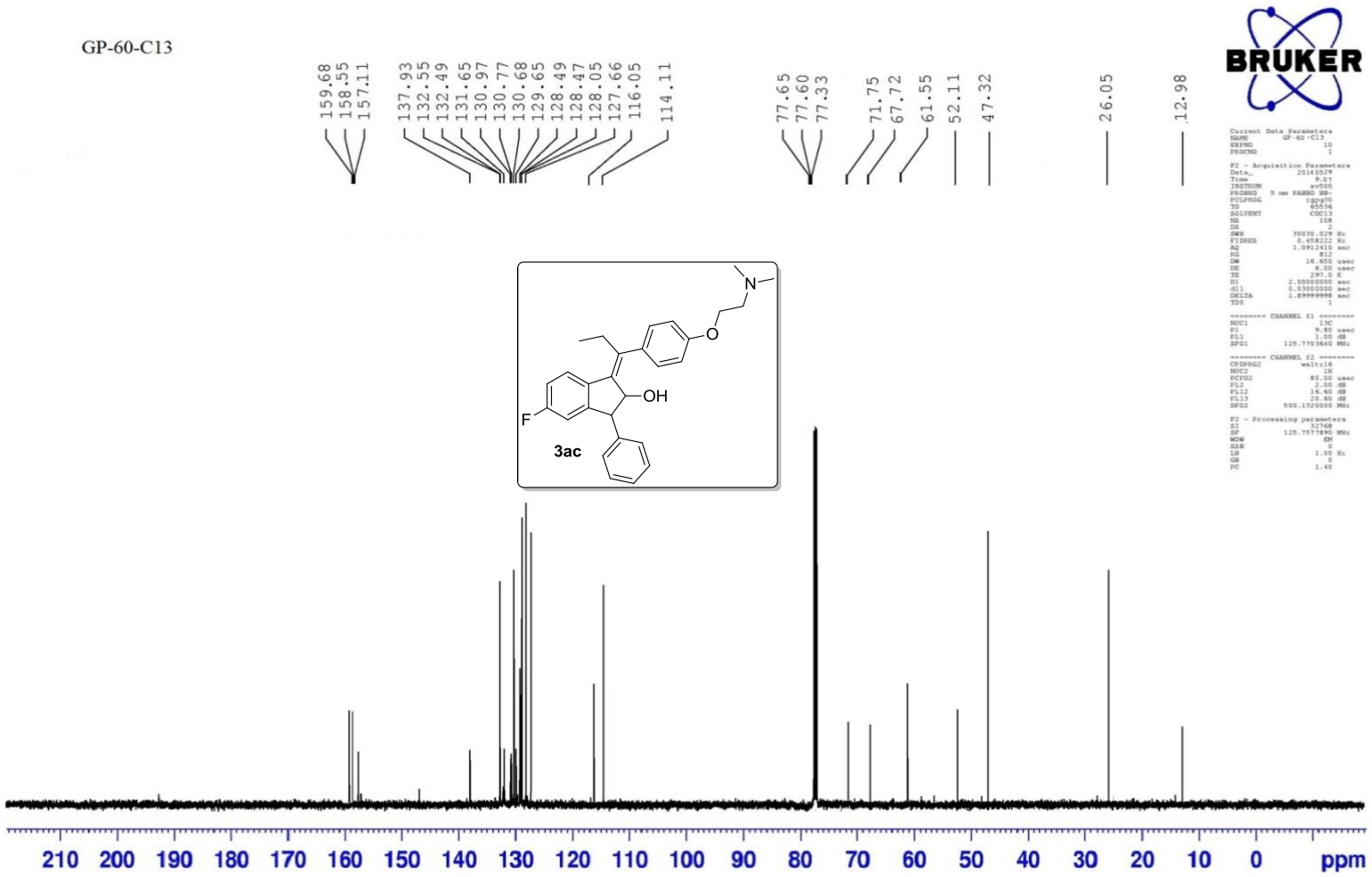


Figure S-57: ^{13}C NMR Spectrum of compound 3ac

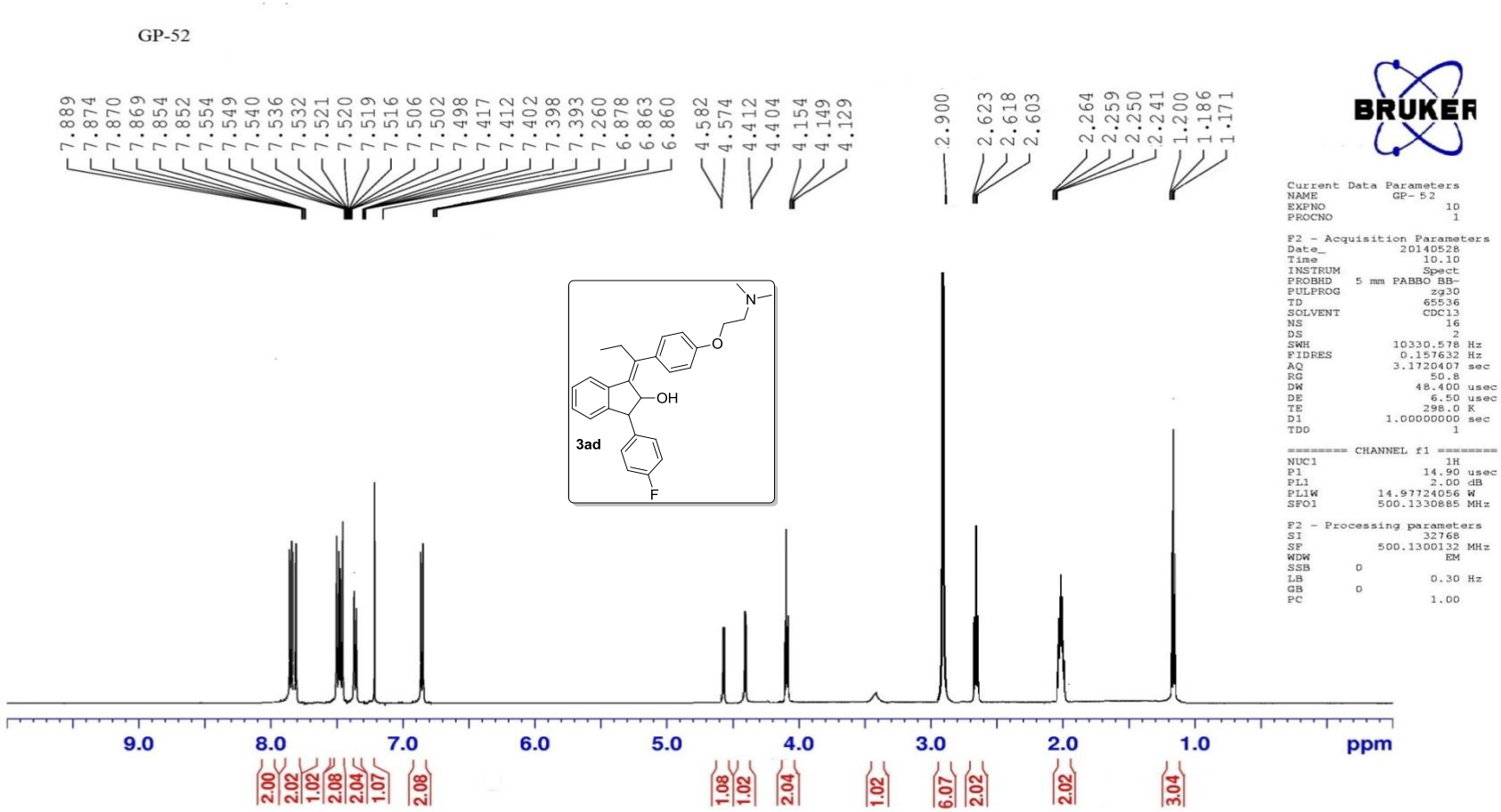


Figure S-58: ^{1}H NMR Spectrum of compound 3ad

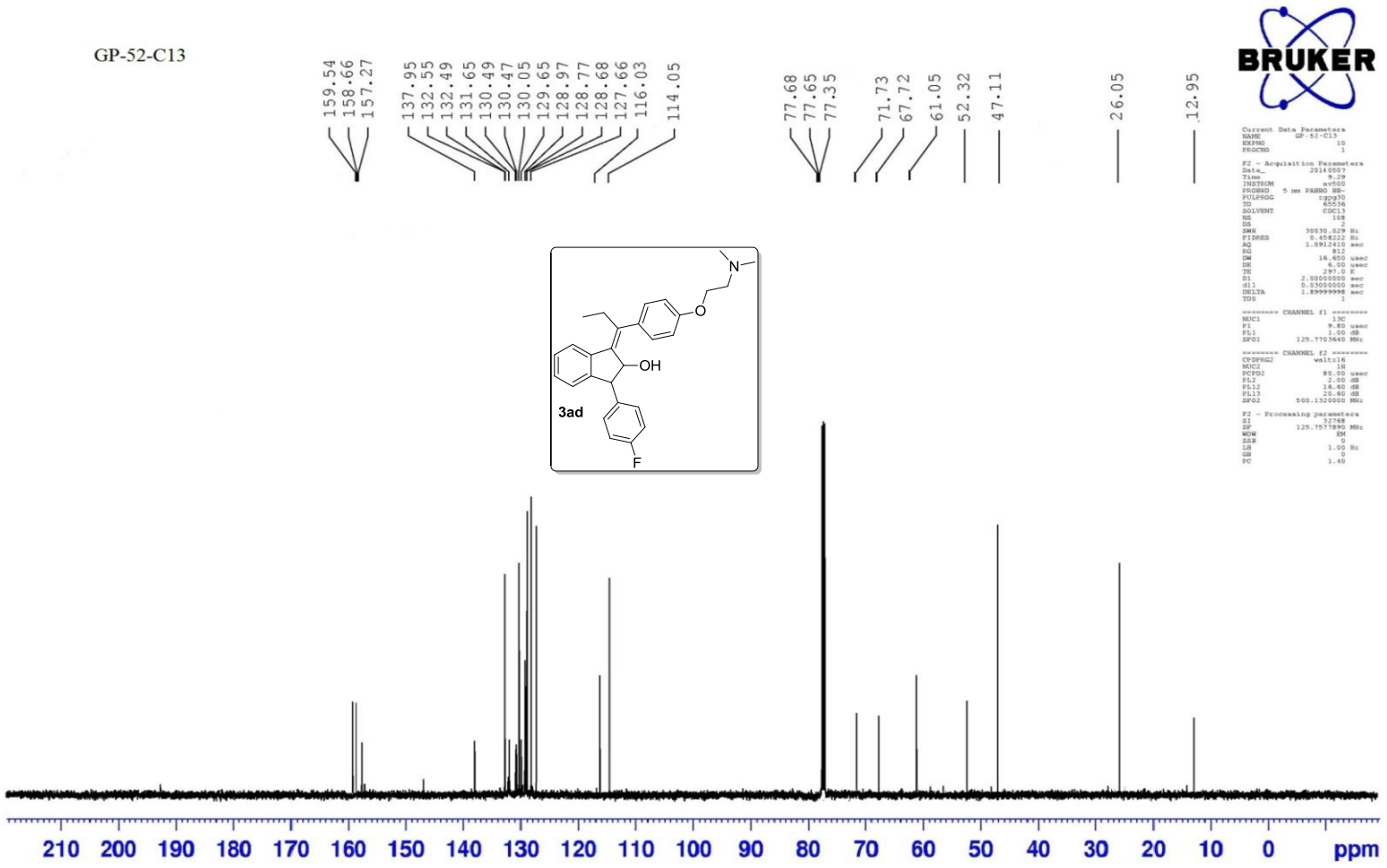


Figure S-59: ^{13}C NMR Spectrum of compound 3ad

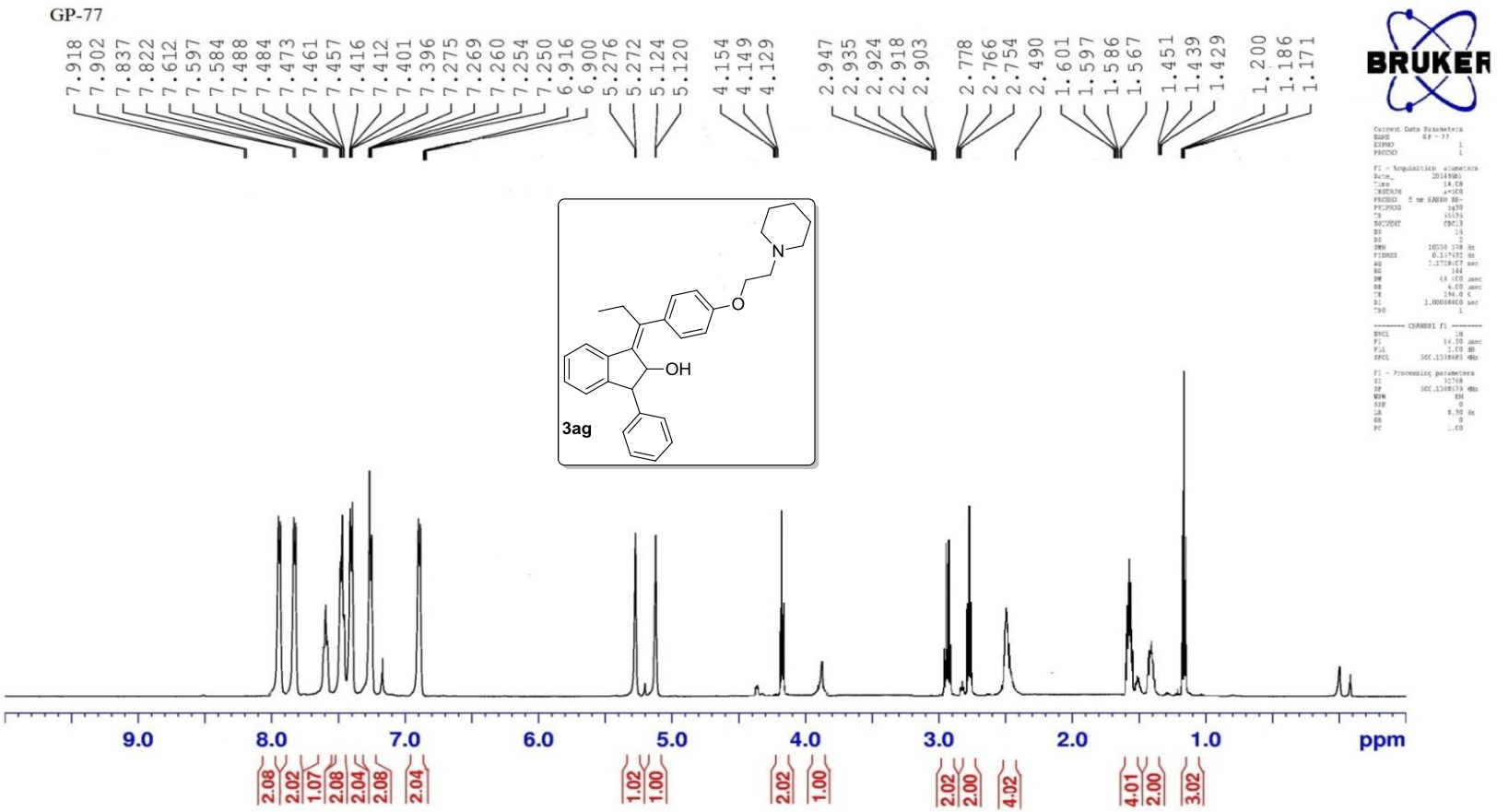


Figure S-60: ^{1}H NMR Spectrum of compound 3ag

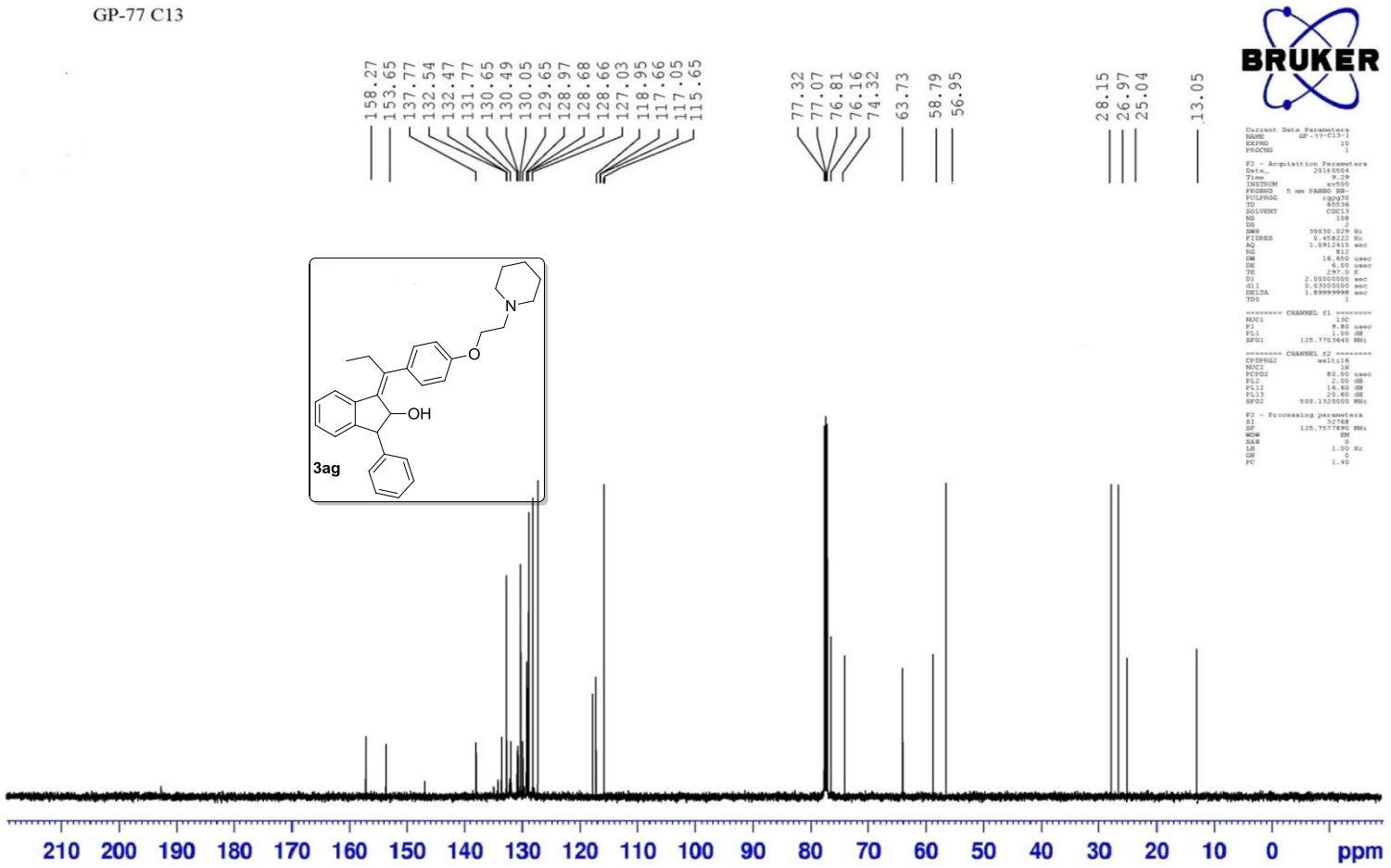


Figure S-61: ^{13}C NMR Spectrum of compound 3ag

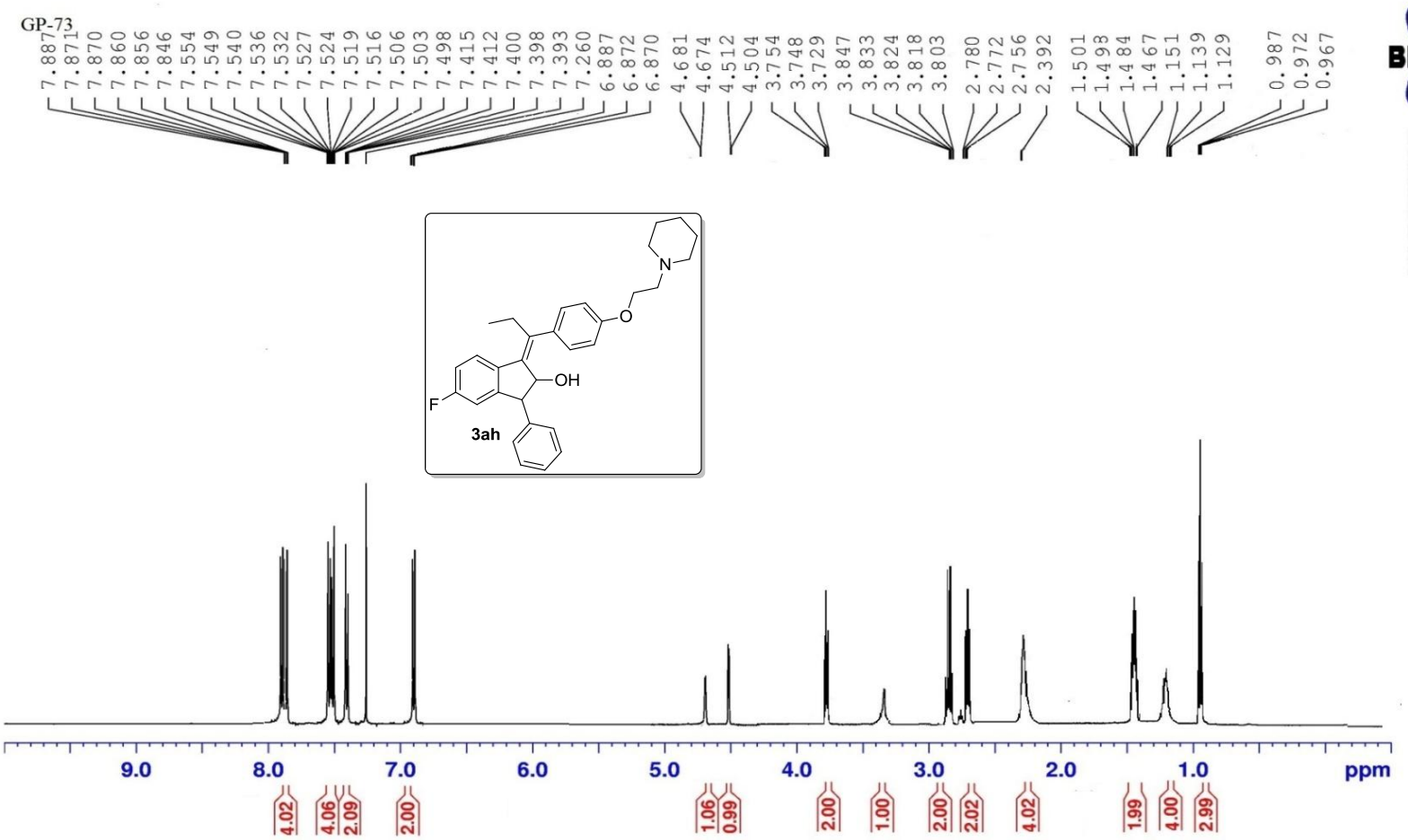


Figure S-62: ^{1}H NMR Spectrum of compound 3ah

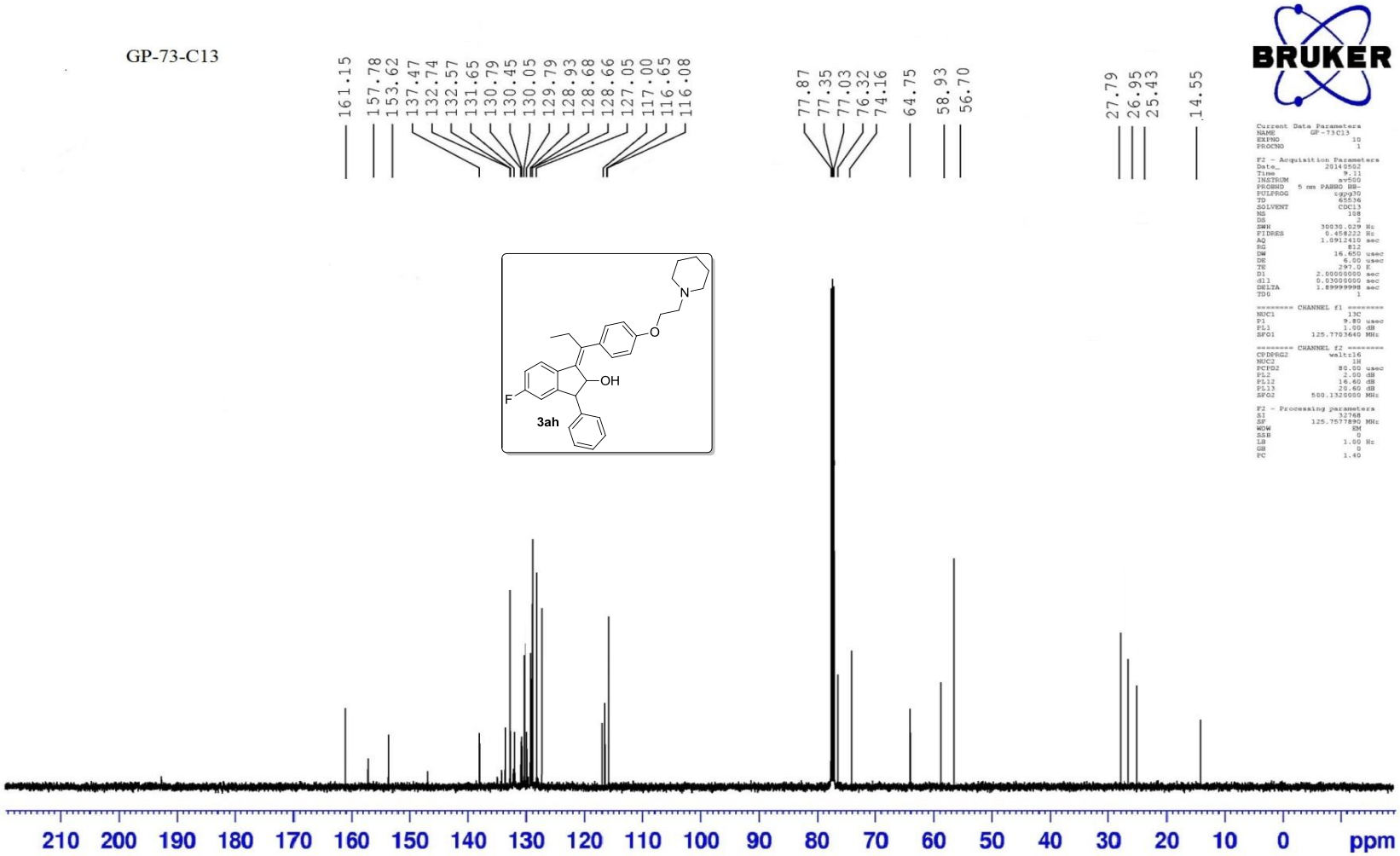


Figure S-63: ^{13}C NMR Spectrum of compound 3ah

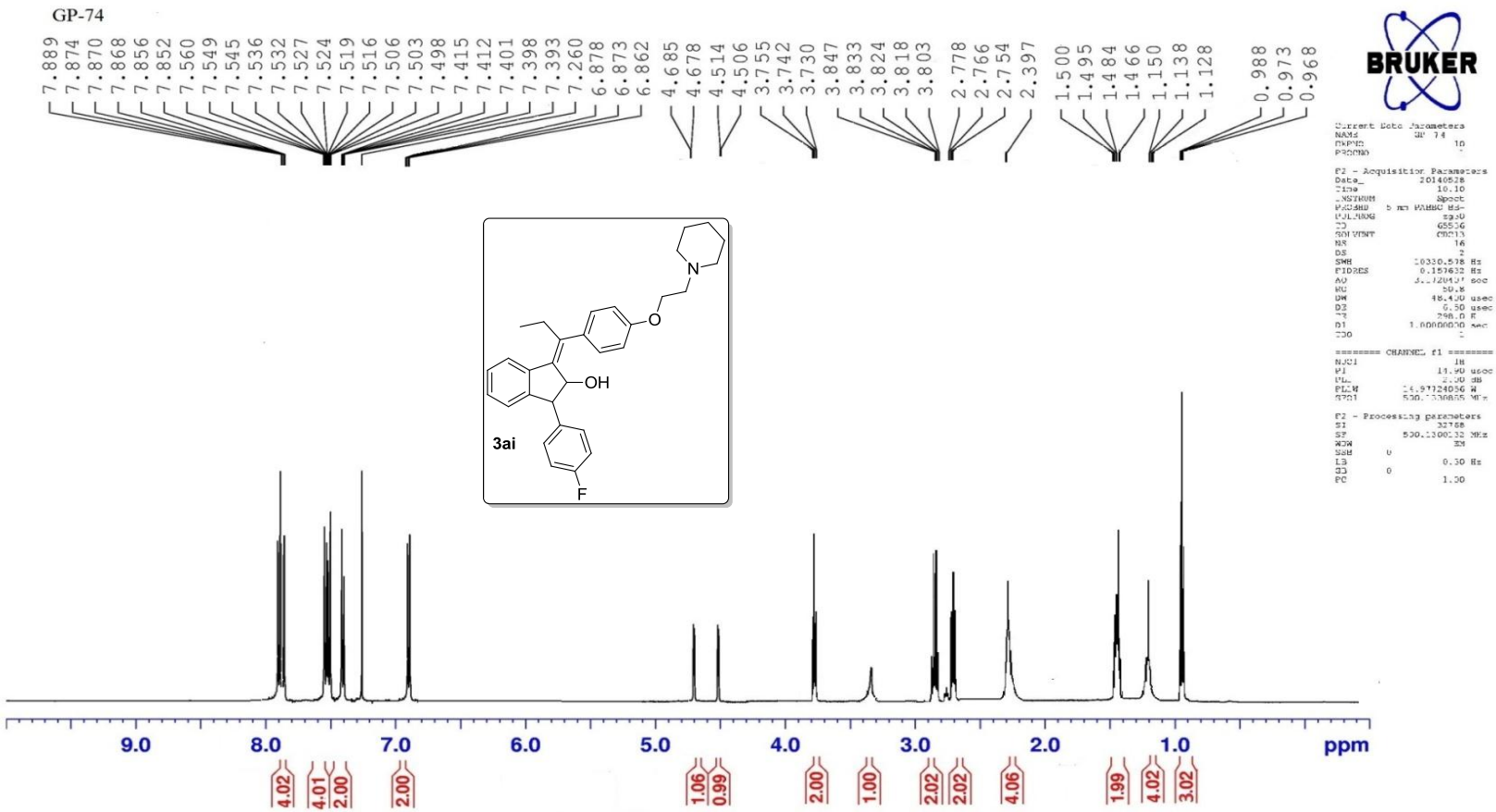


Figure S-64: ^{1}H NMR Spectrum of compound 3ai

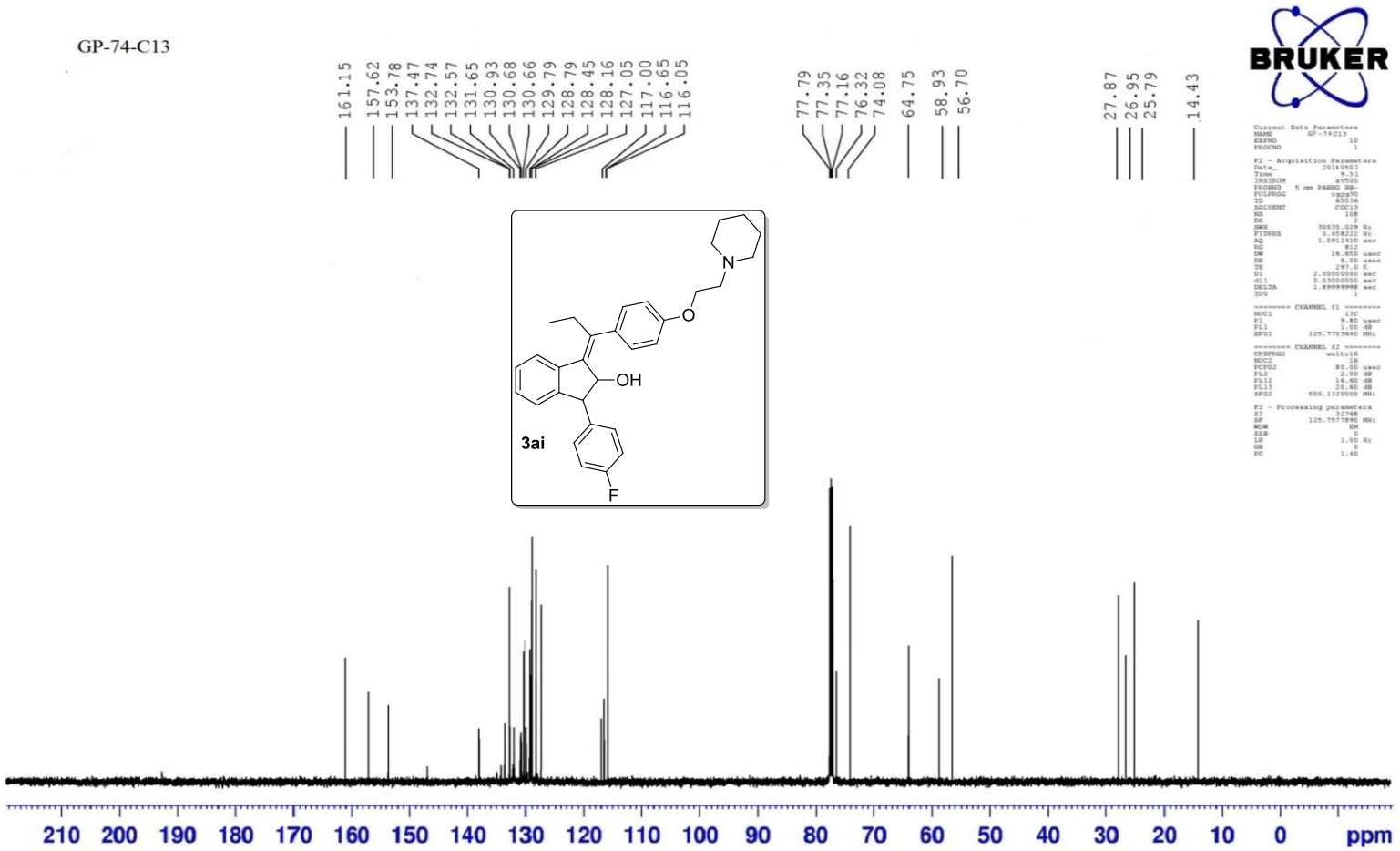


Figure S-65: ^{13}C NMR Spectrum of compound 3ai

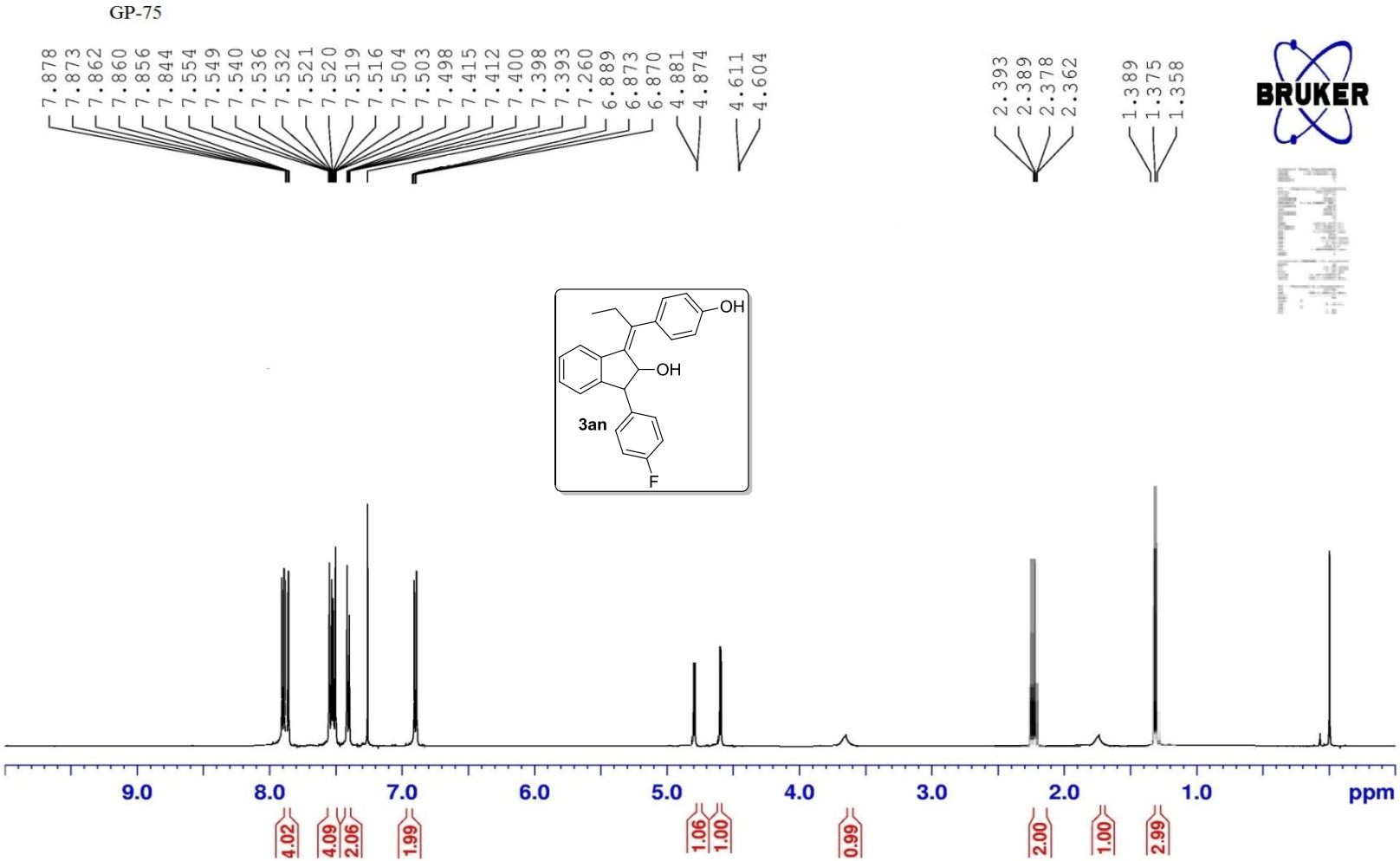


Figure S-66: ^{1}H NMR Spectrum of compound 3an

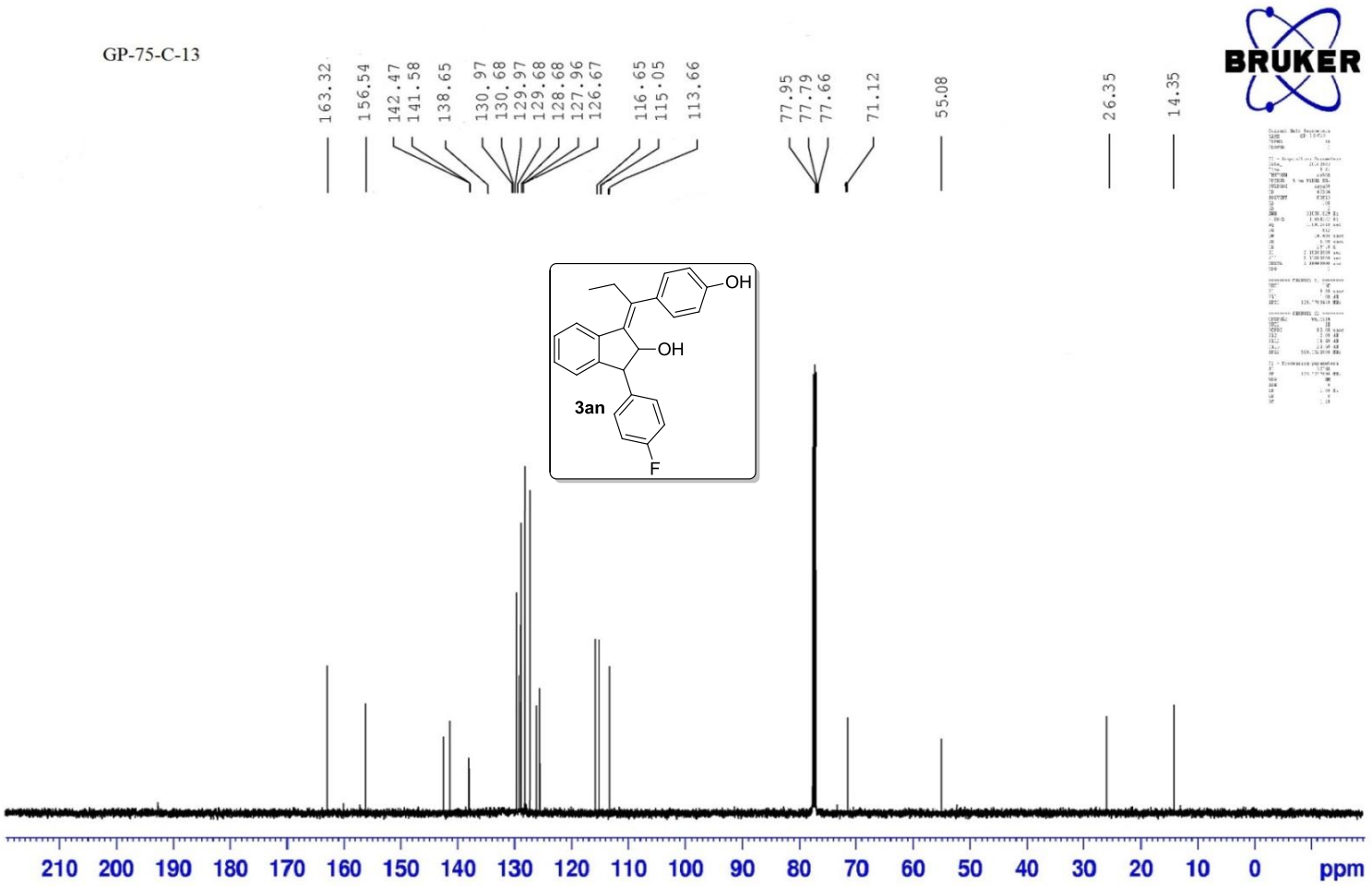


Figure S-67: ^{13}C NMR Spectrum of compound 3an

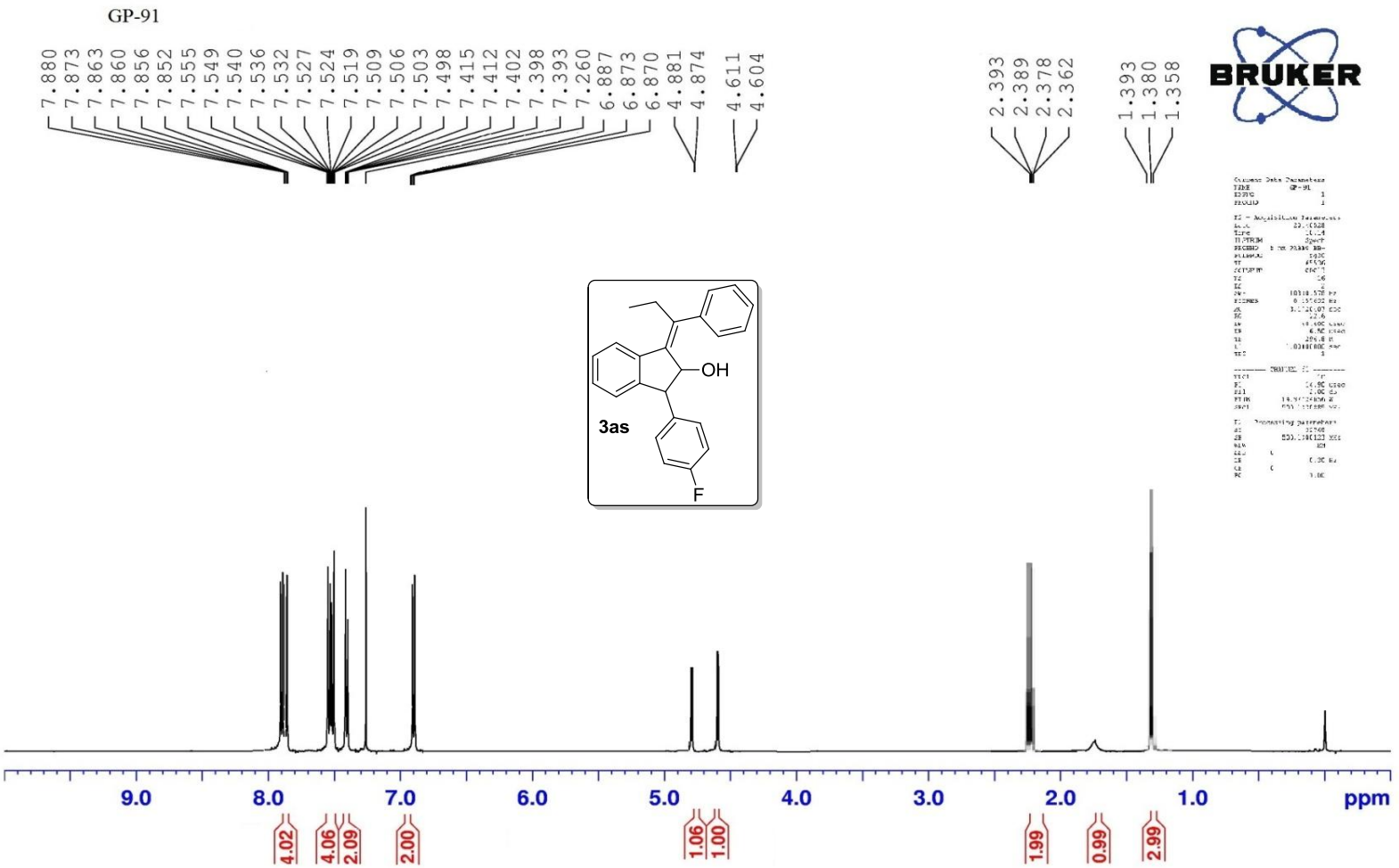


Figure S-68: ^{1}H NMR Spectrum of compound 3as

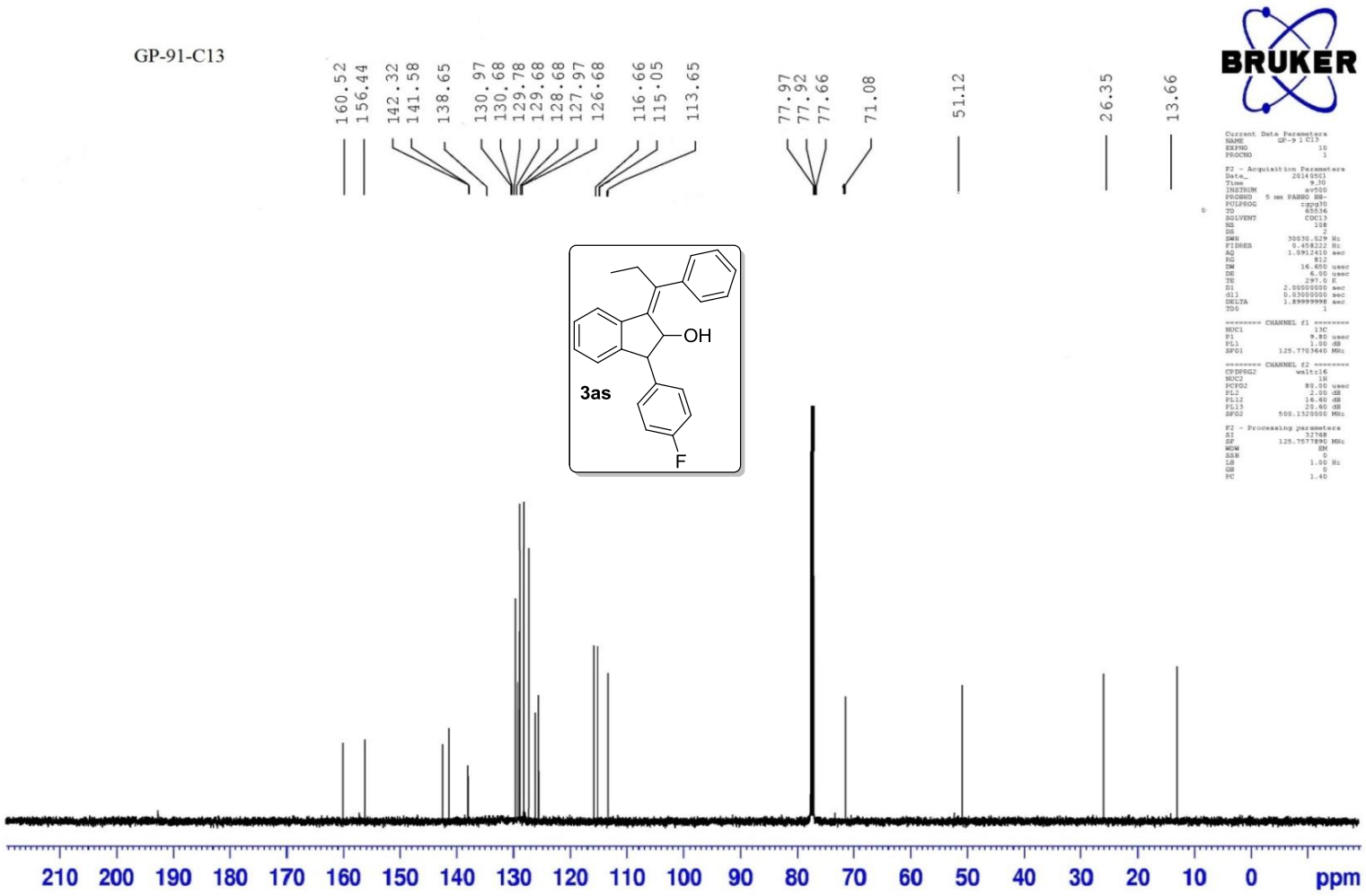


Figure S-69: ^{13}C NMR Spectrum of compound 3as

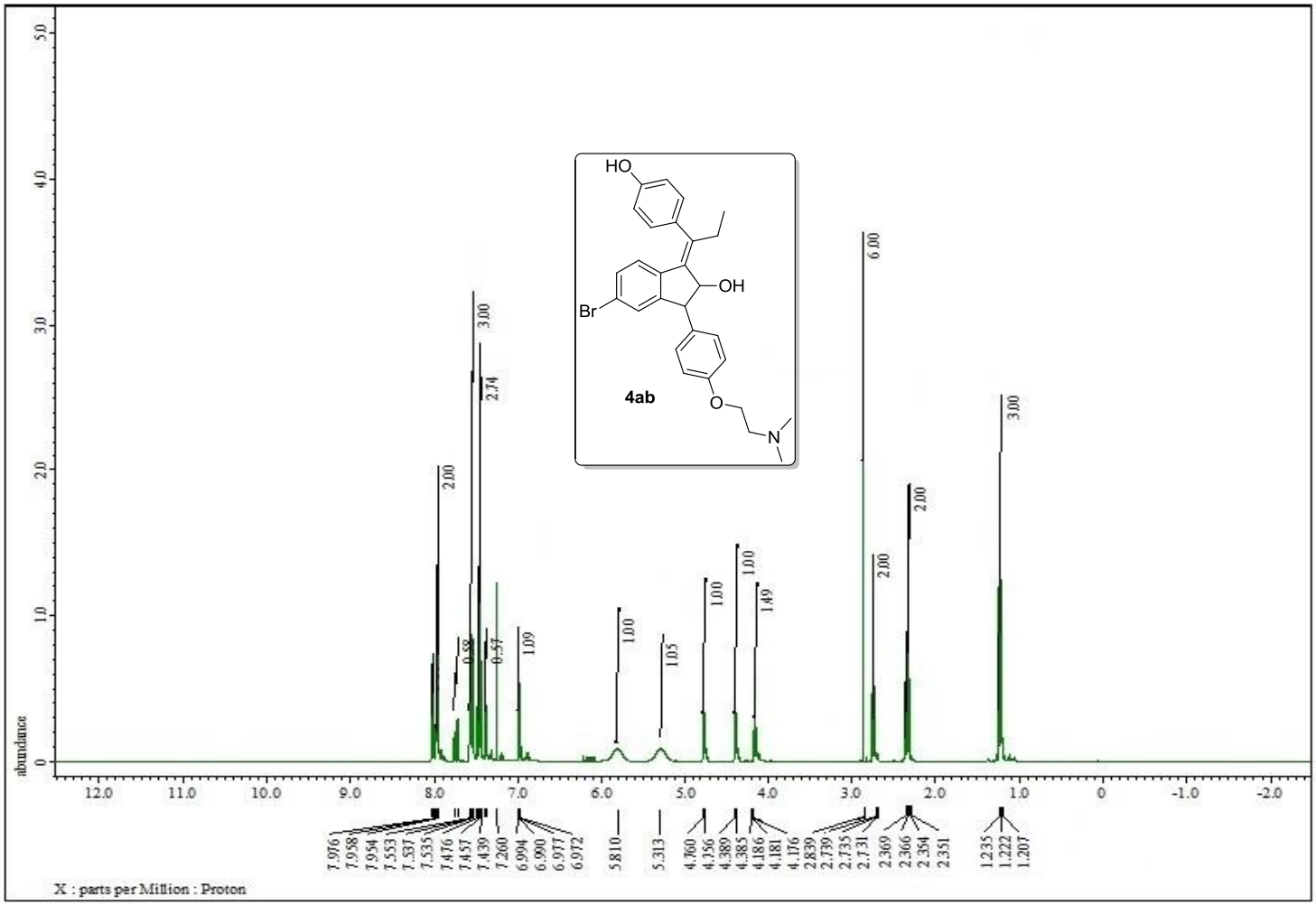


Figure S-70: ^{1}H NMR Spectrum of compound 4ab

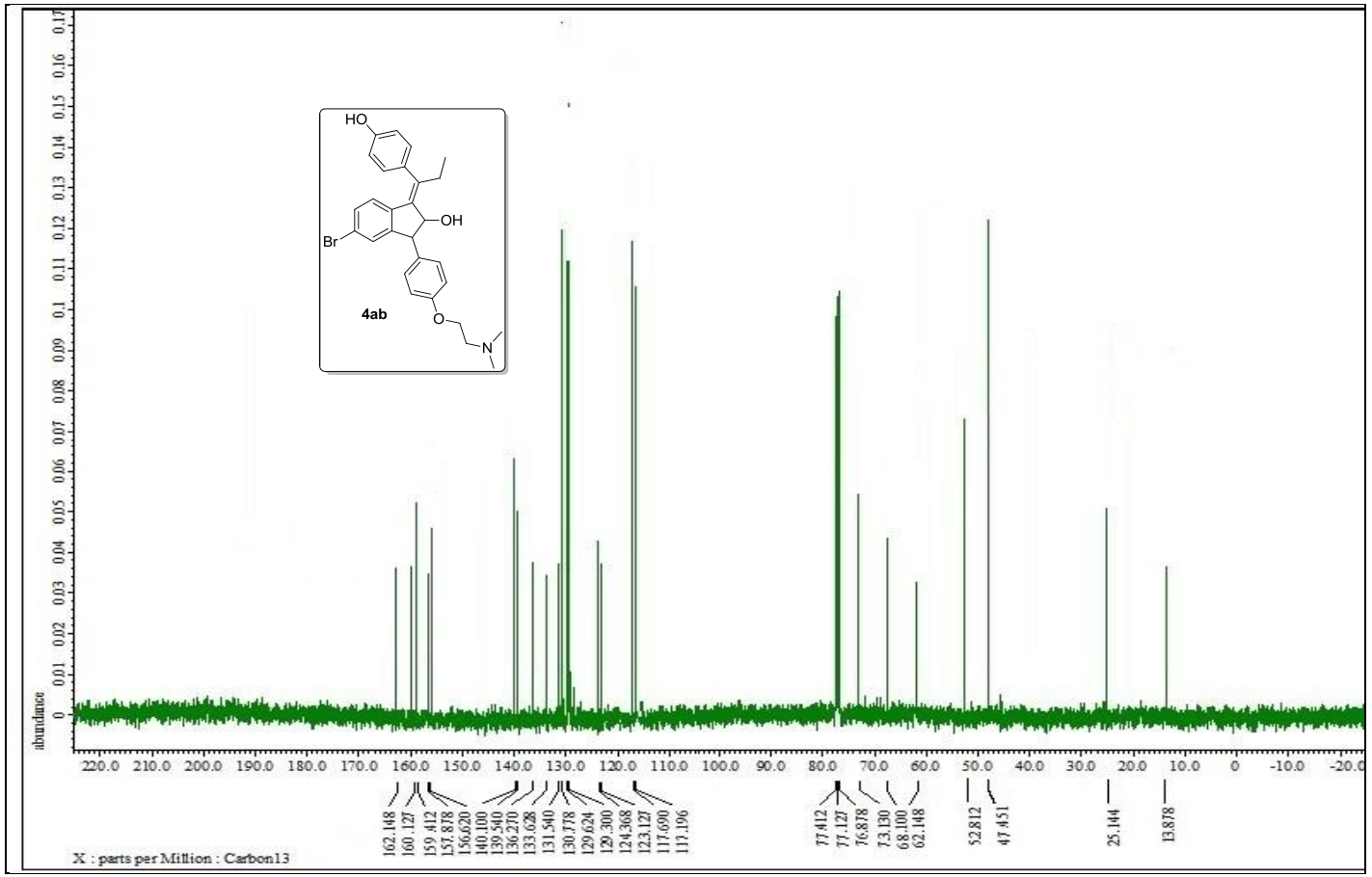


Figure S-71: ^{13}C NMR Spectrum of compound 4ab

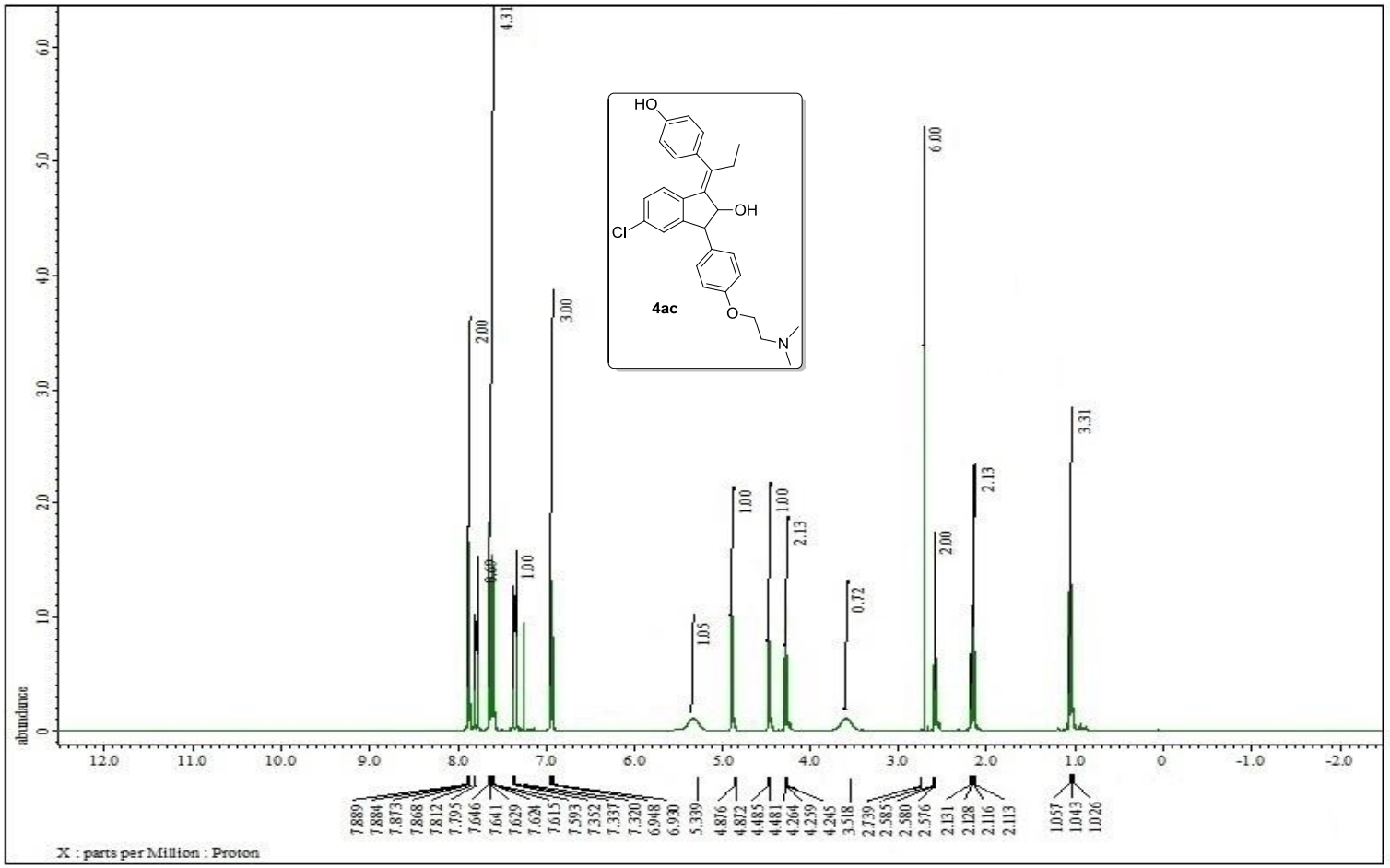


Figure S-72: ^{1}H NMR Spectrum of compound 4ac

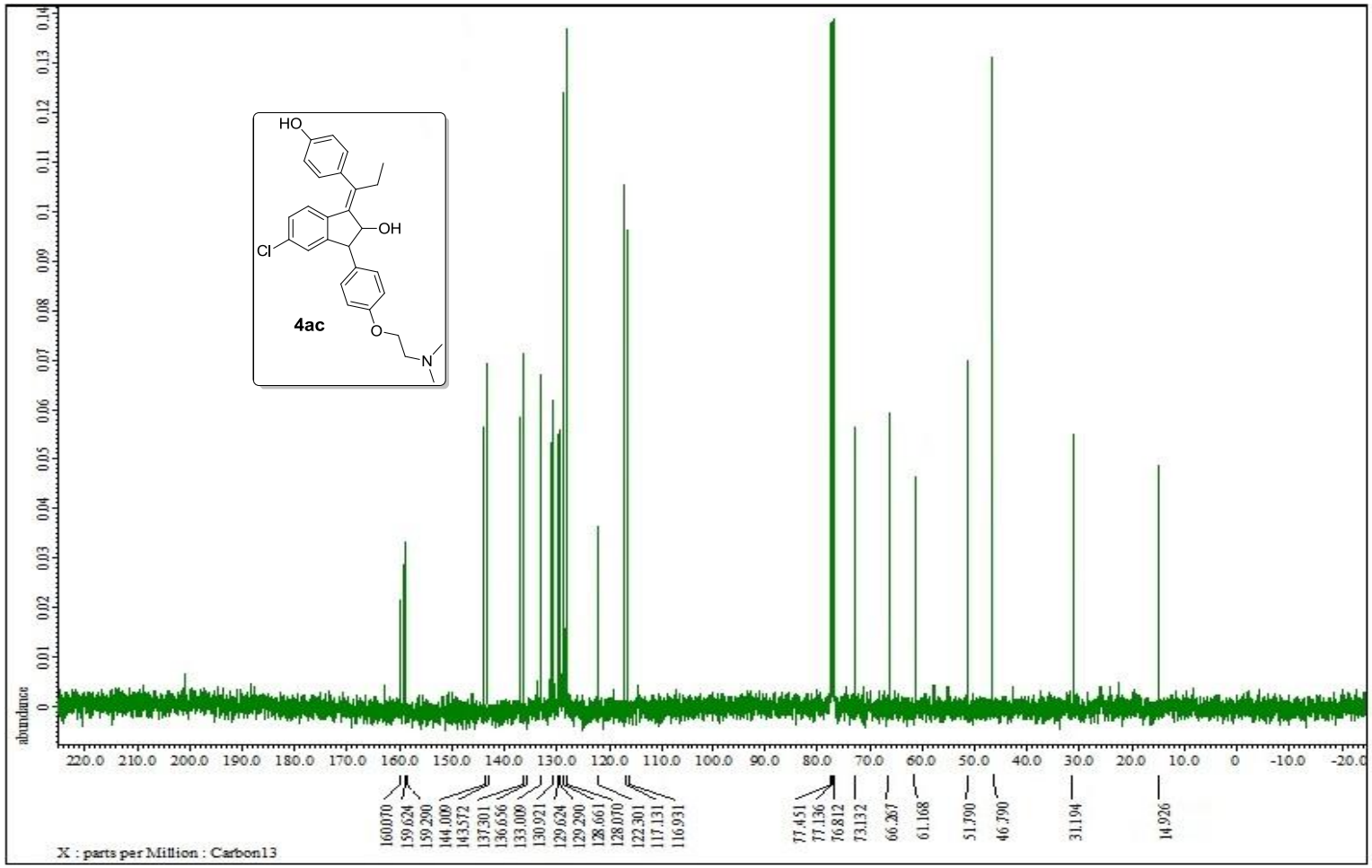


Figure S-73: ^{13}C NMR Spectrum of compound 4ac

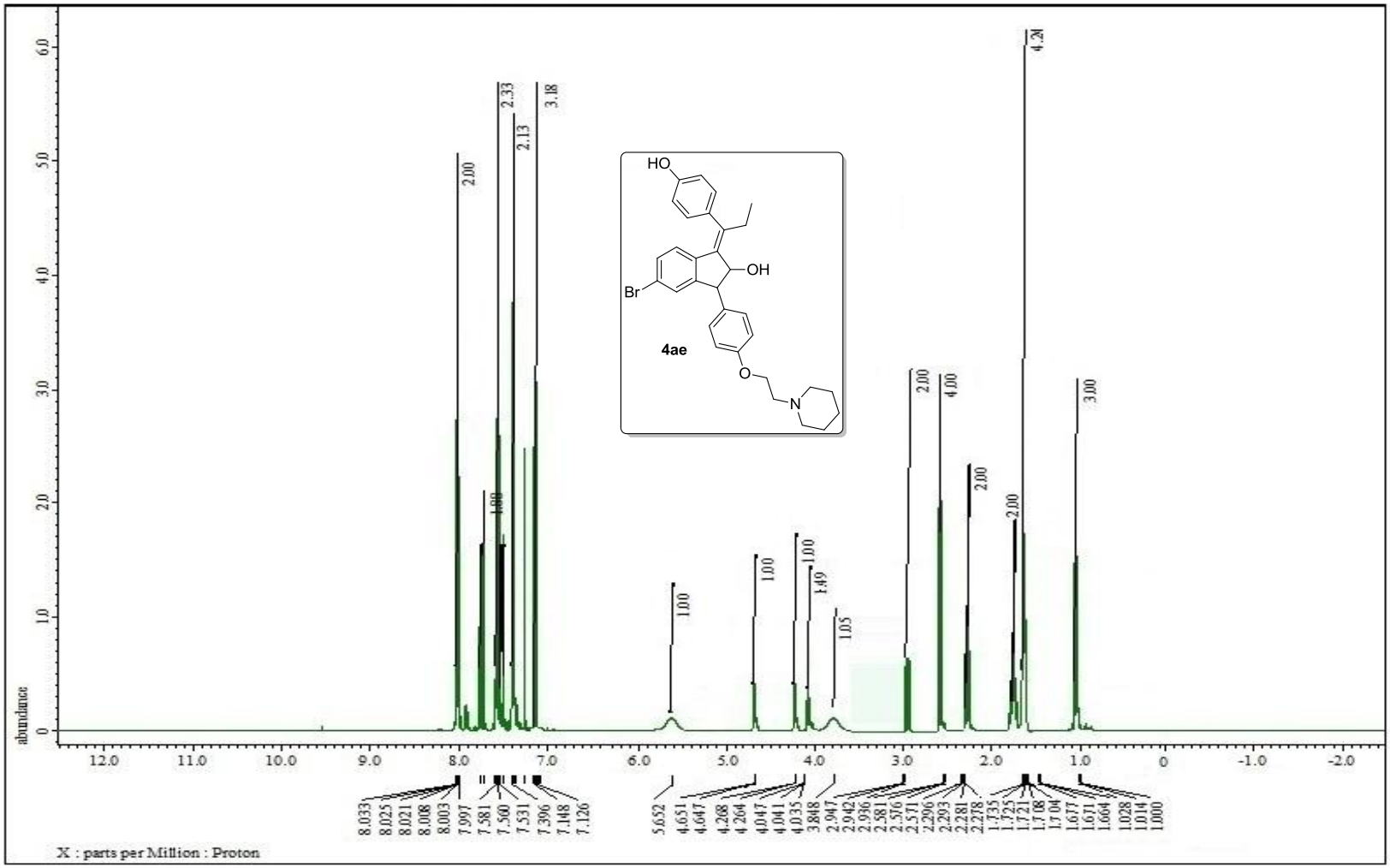


Figure S-74: ^{1}H NMR Spectrum of compound 4ae

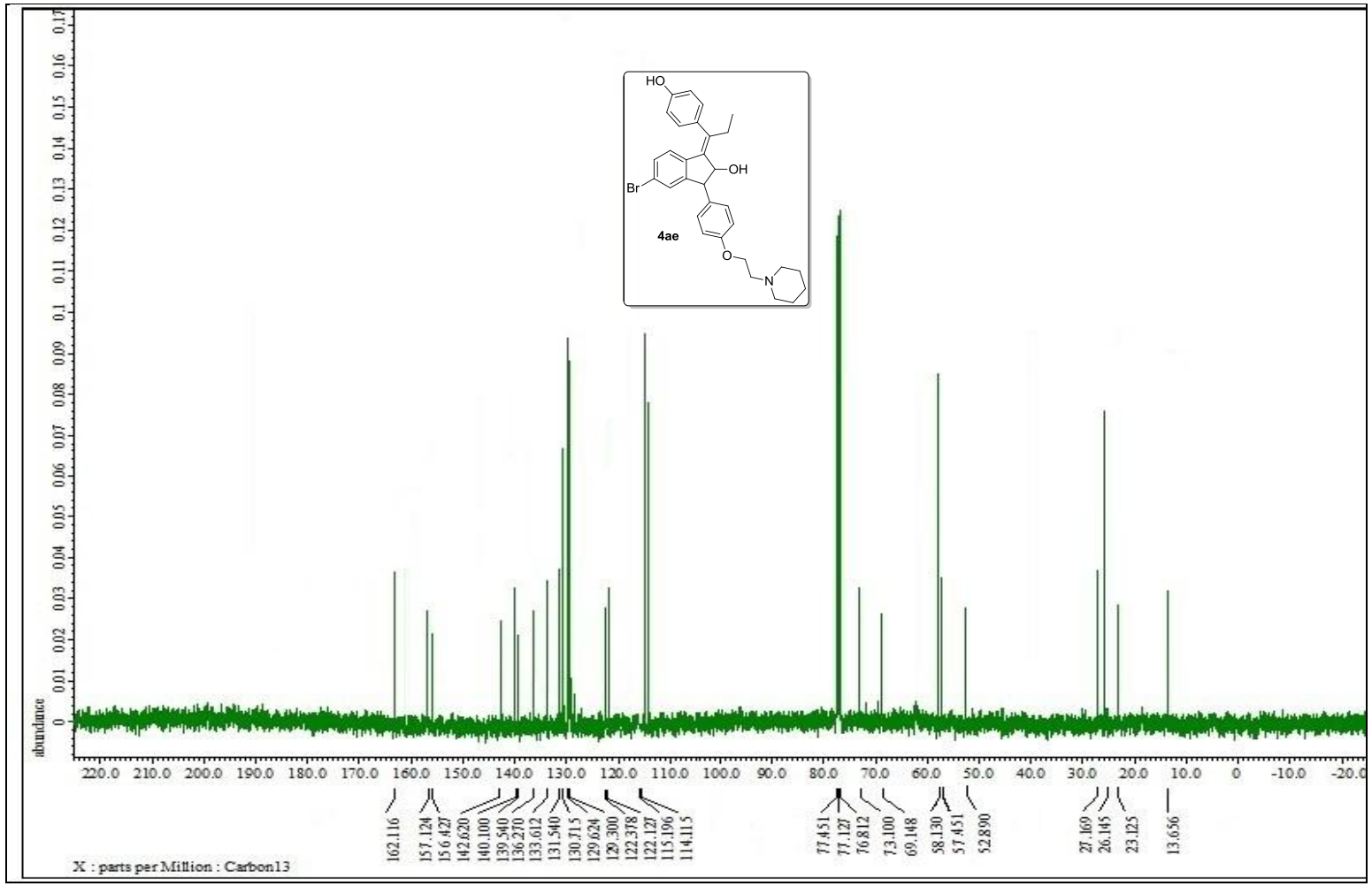


Figure S-75: ^{13}C NMR Spectrum of compound 4ae

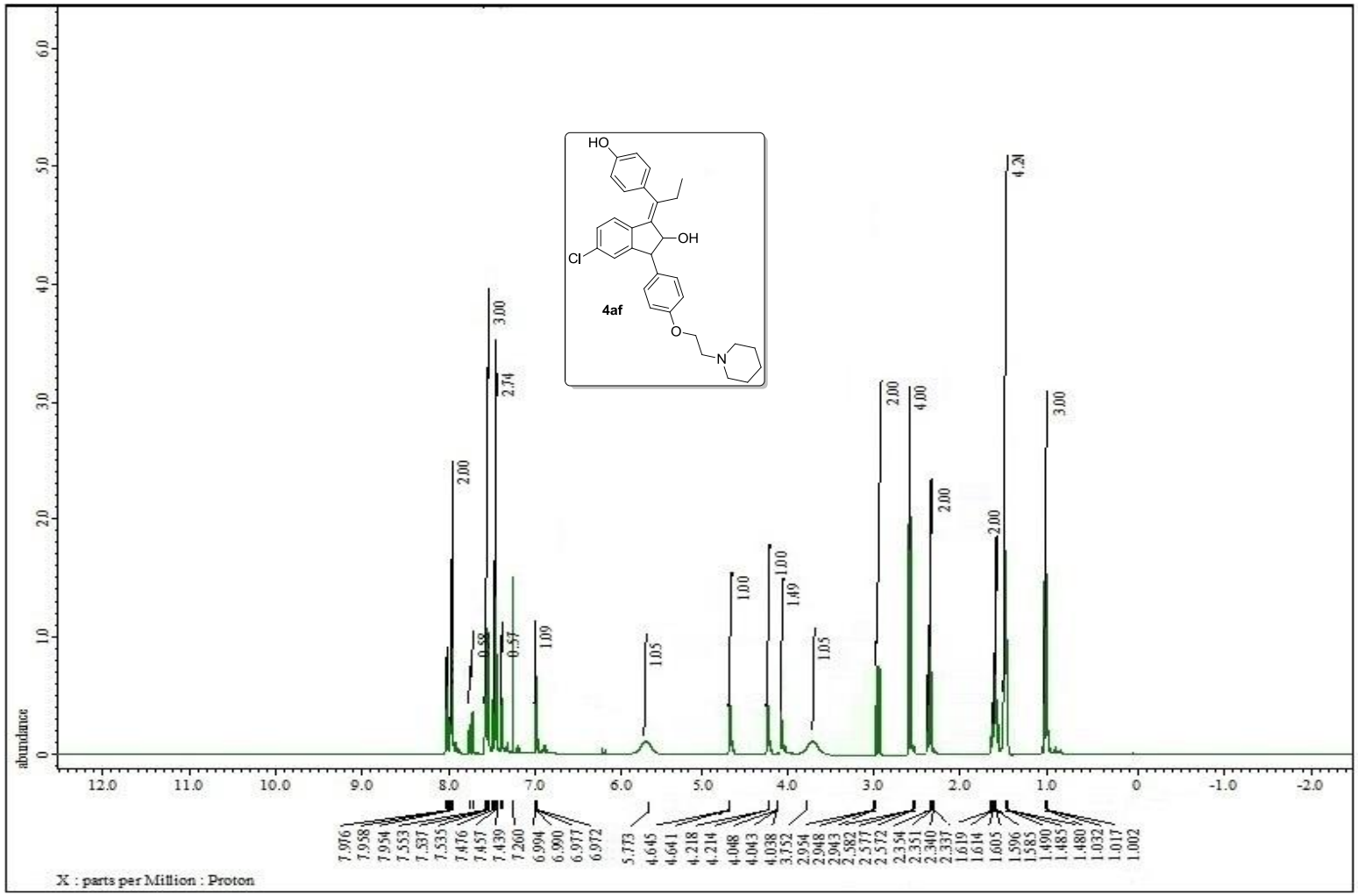


Figure S-76: ^{1}H NMR Spectrum of compound 4af

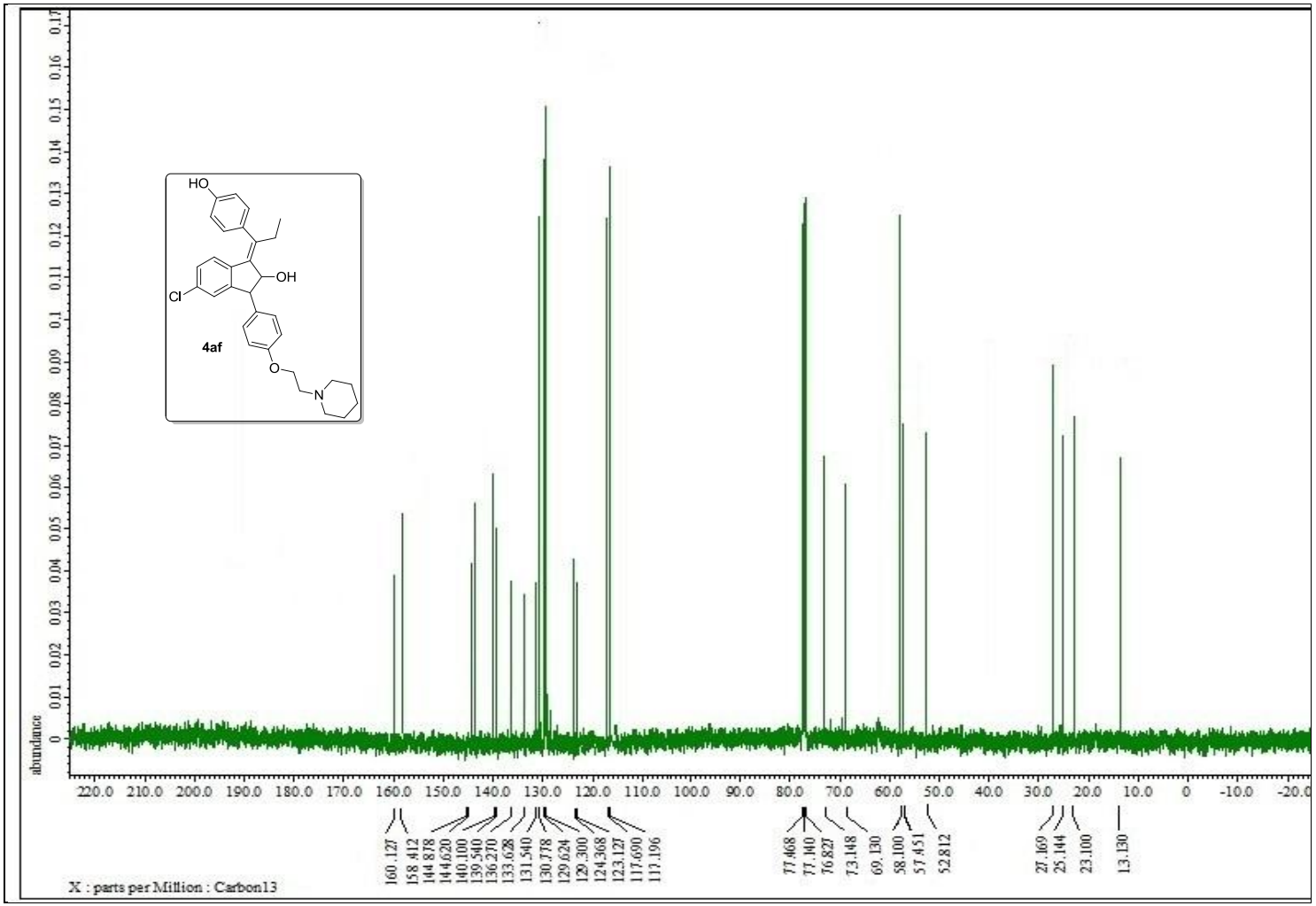


Figure S-77: ^{13}C NMR Spectrum of compound 4af

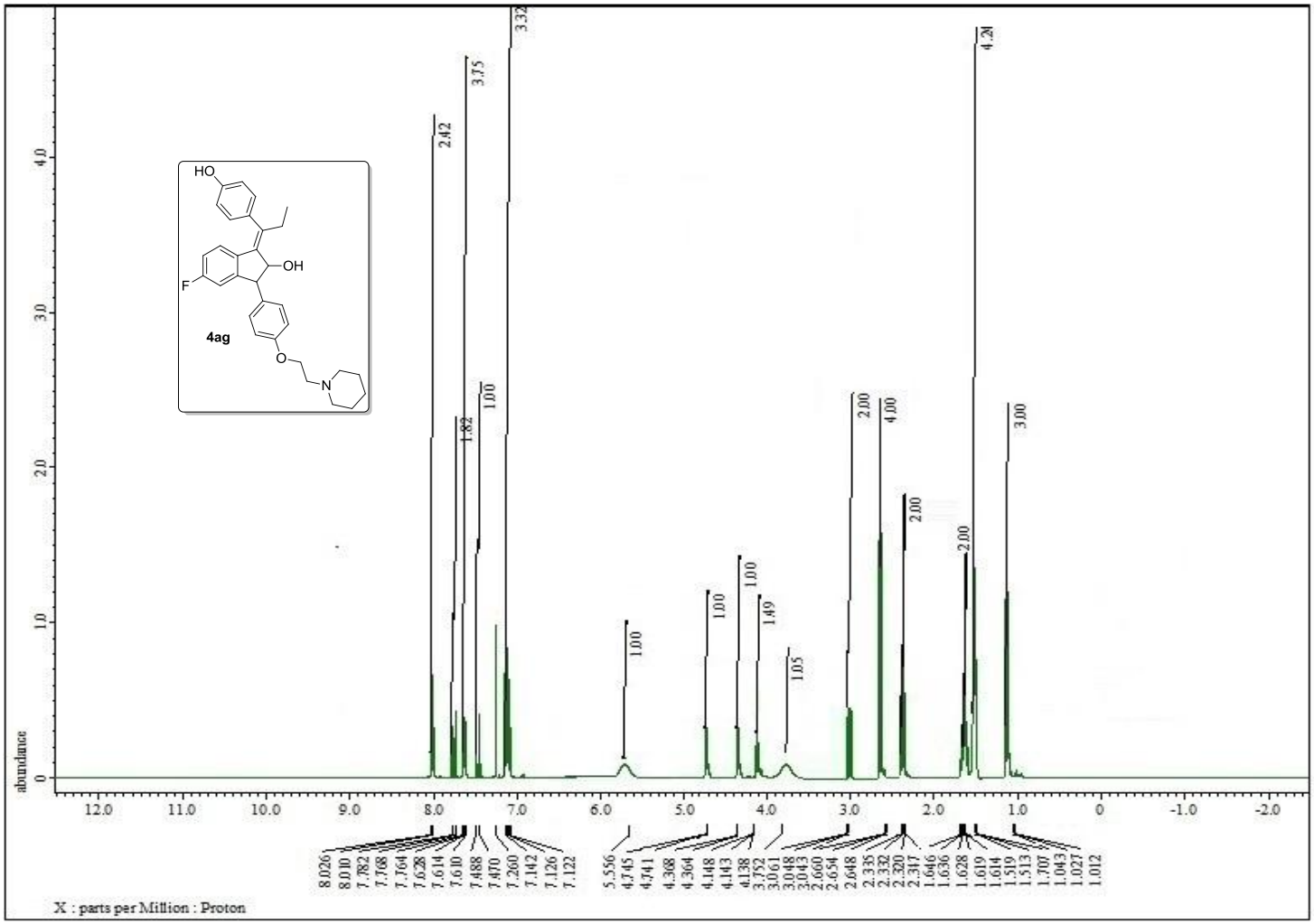


Figure S-78: ^{1}H NMR Spectrum of compound 4ag

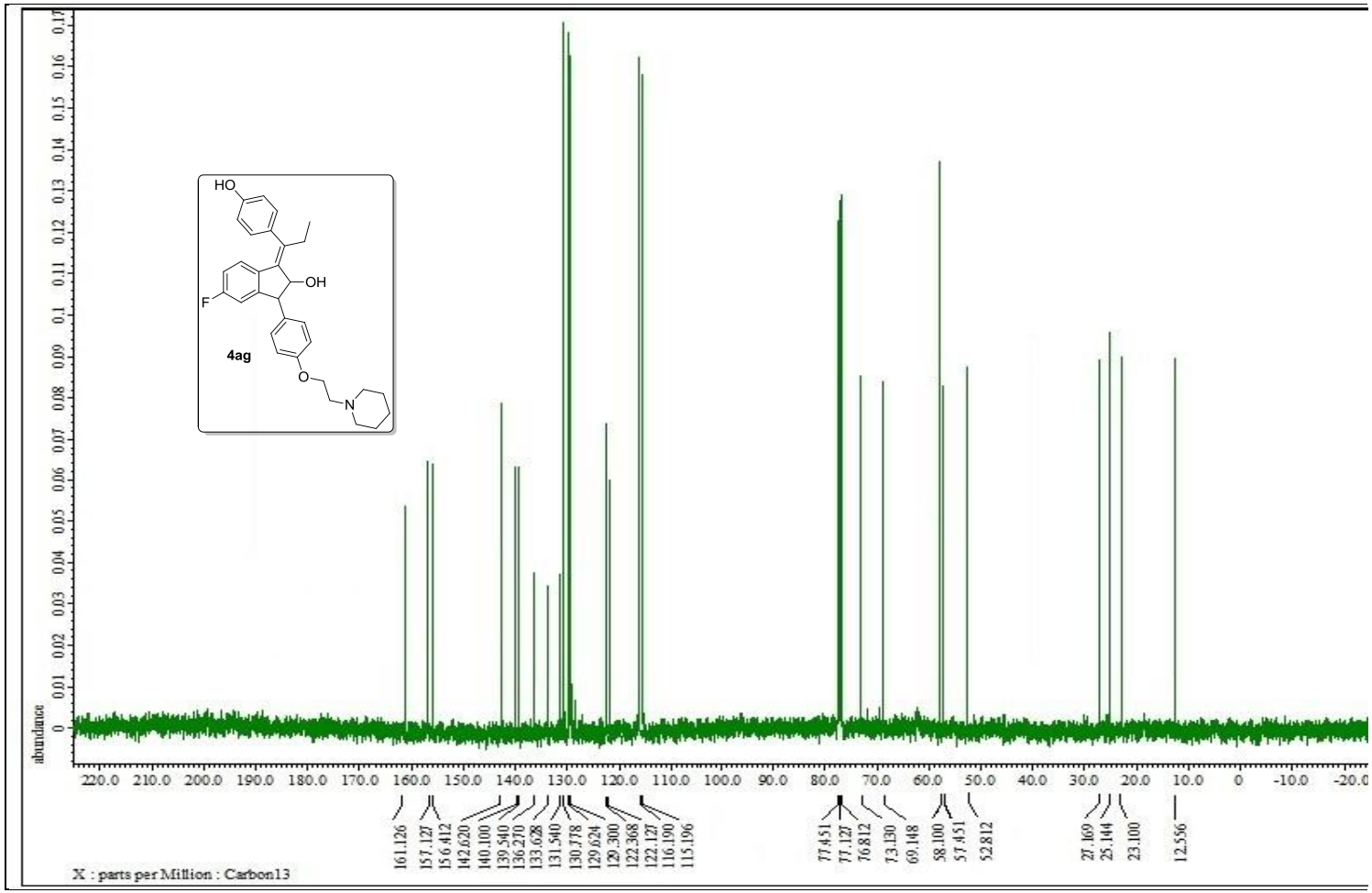


Figure S-79: ^{13}C NMR Spectrum of compound 4ag

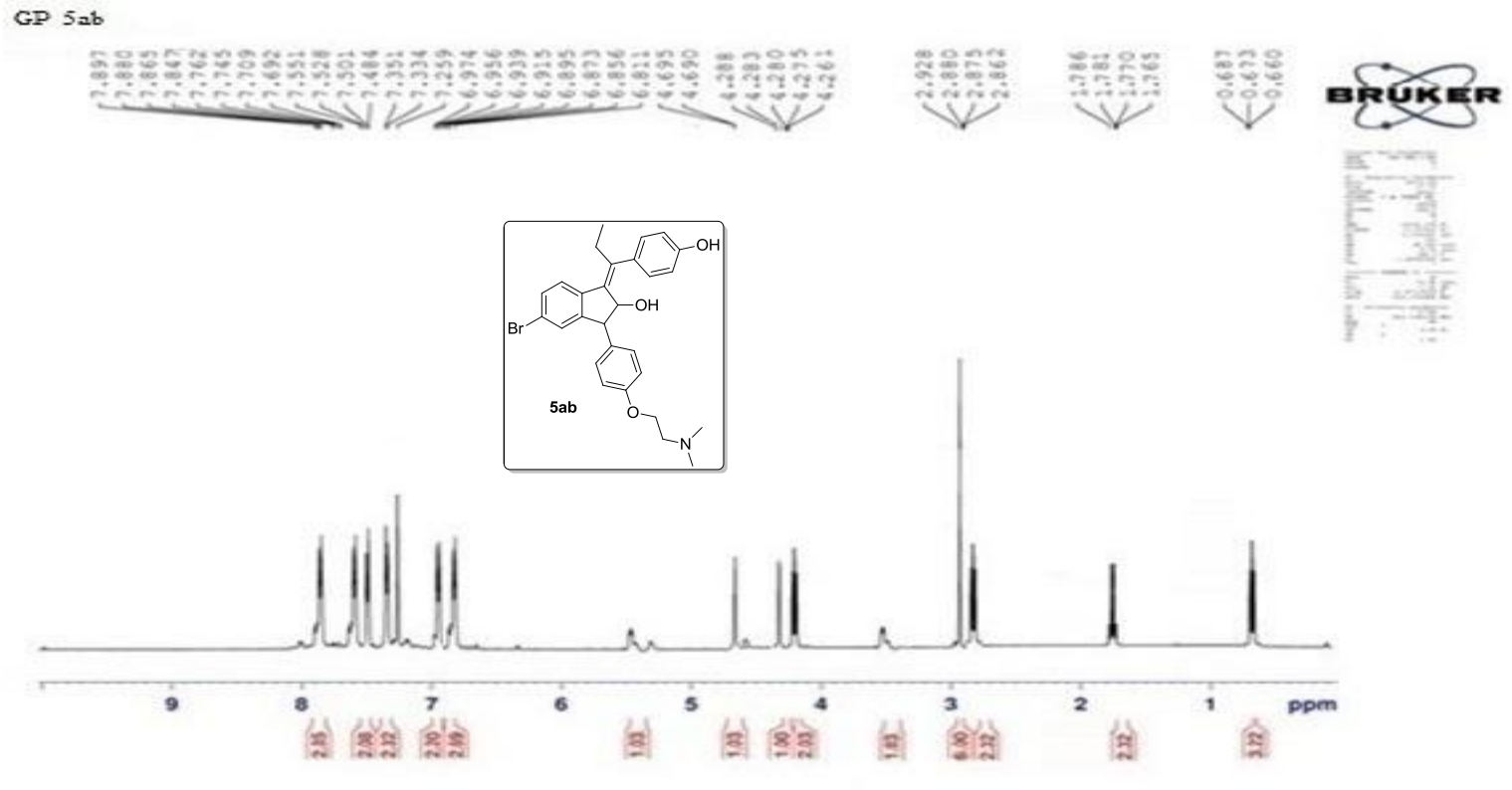


Figure S-80: ^{1}H NMR Spectrum of compound 5ab

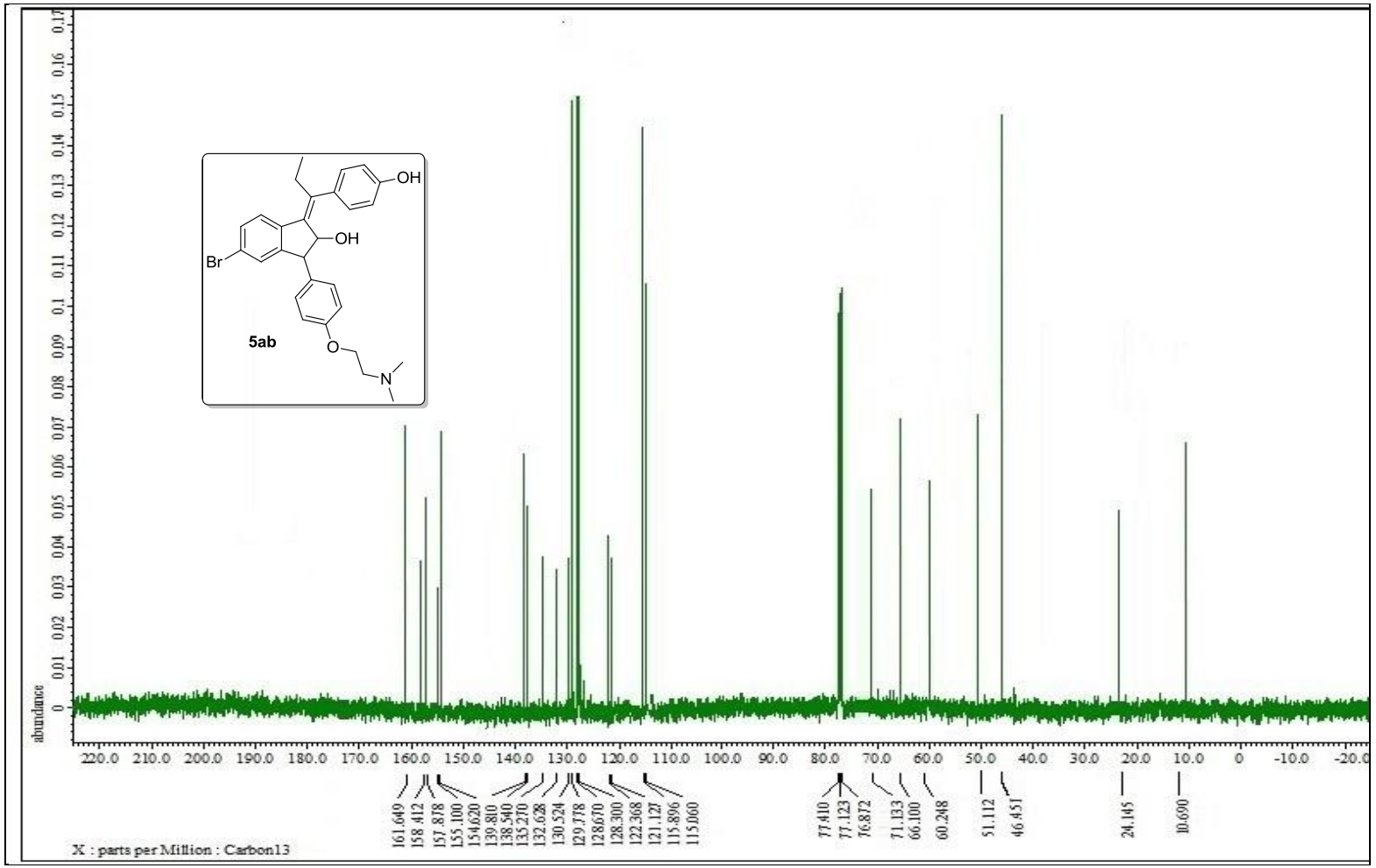


Figure S-81: ^{13}C NMR Spectrum of compound 5ab

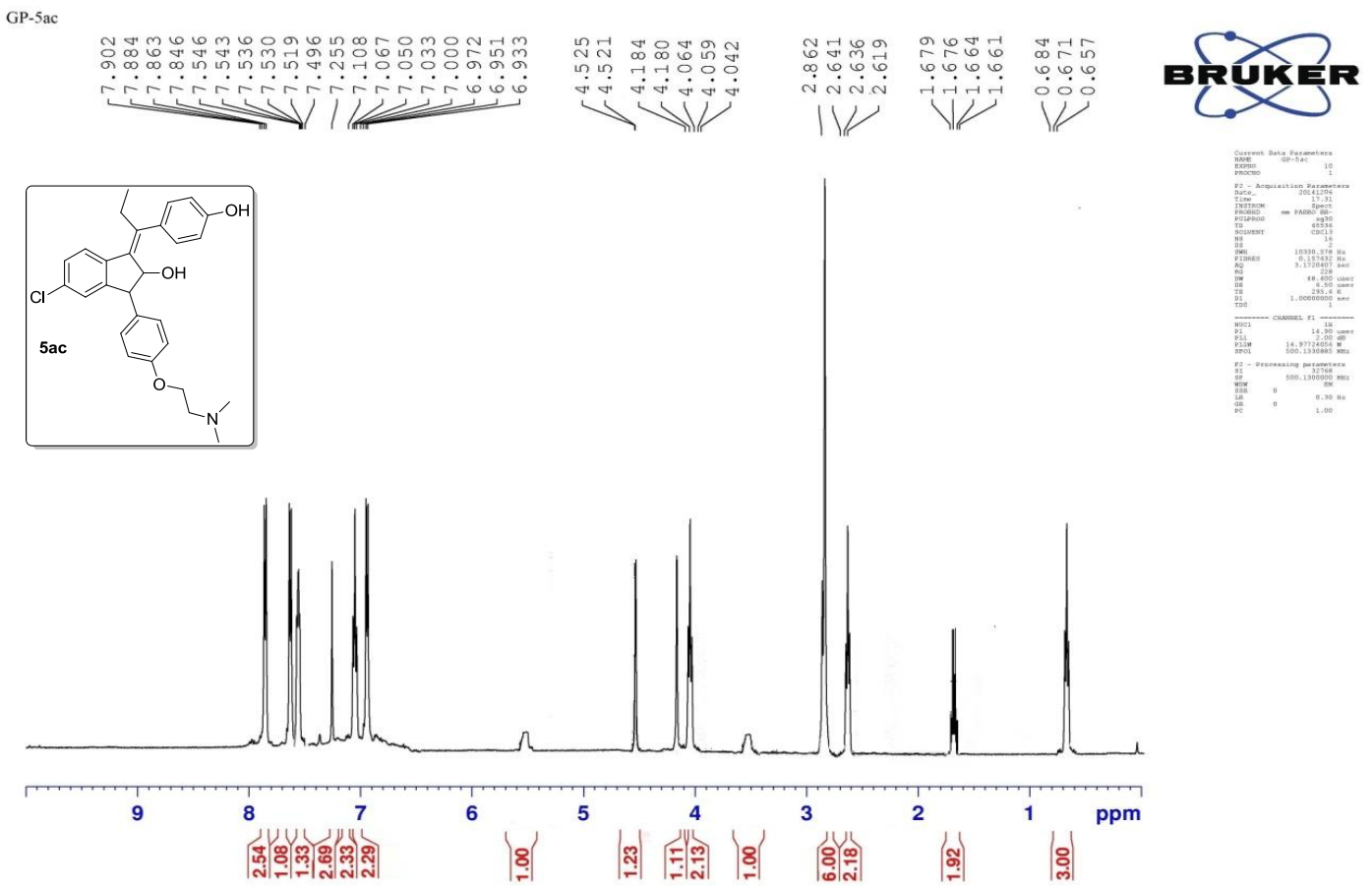


Figure S-82: ^{1}H NMR Spectrum of compound 5ac

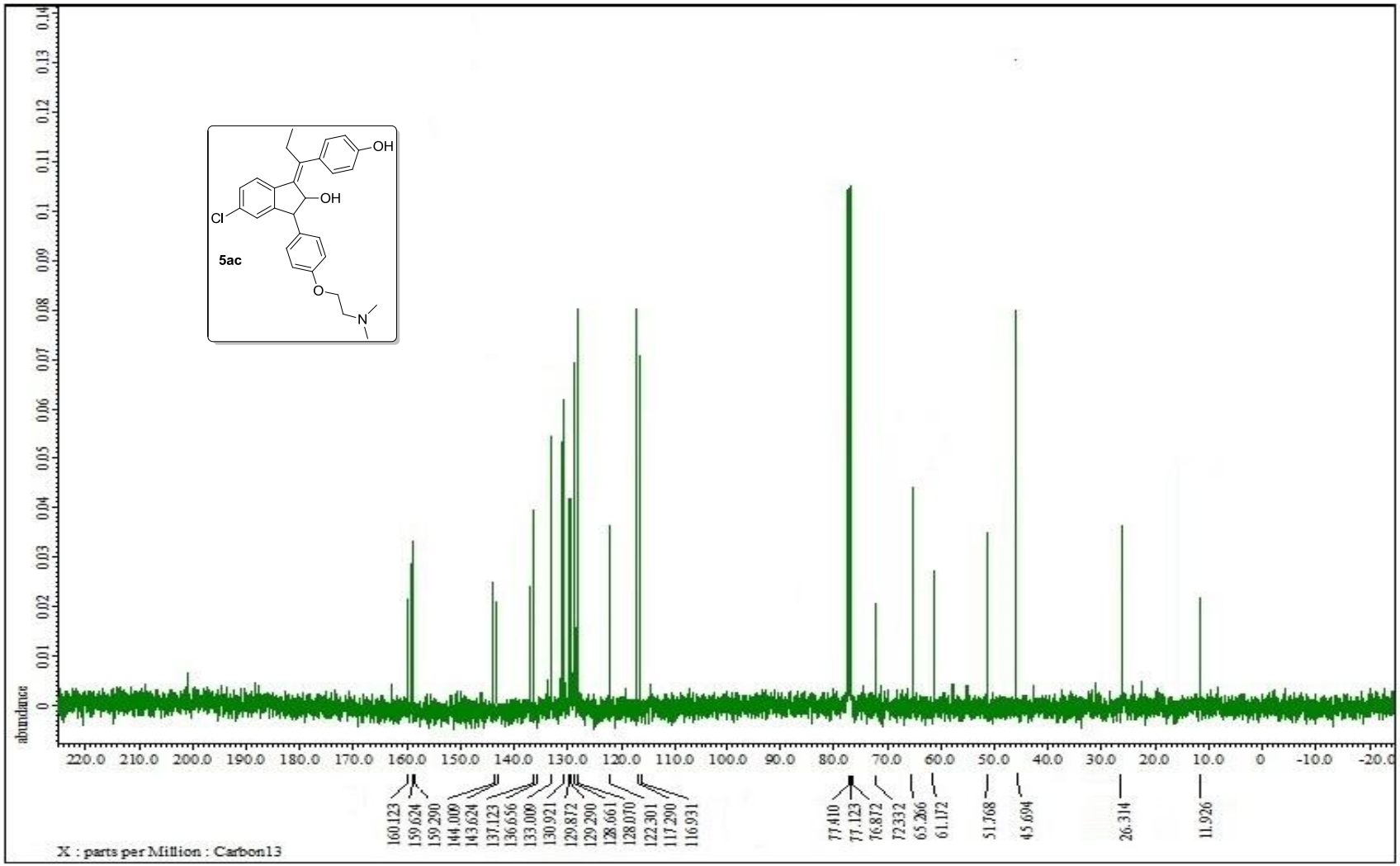


Figure S-83: ^{13}C NMR Spectrum of compound 5ac

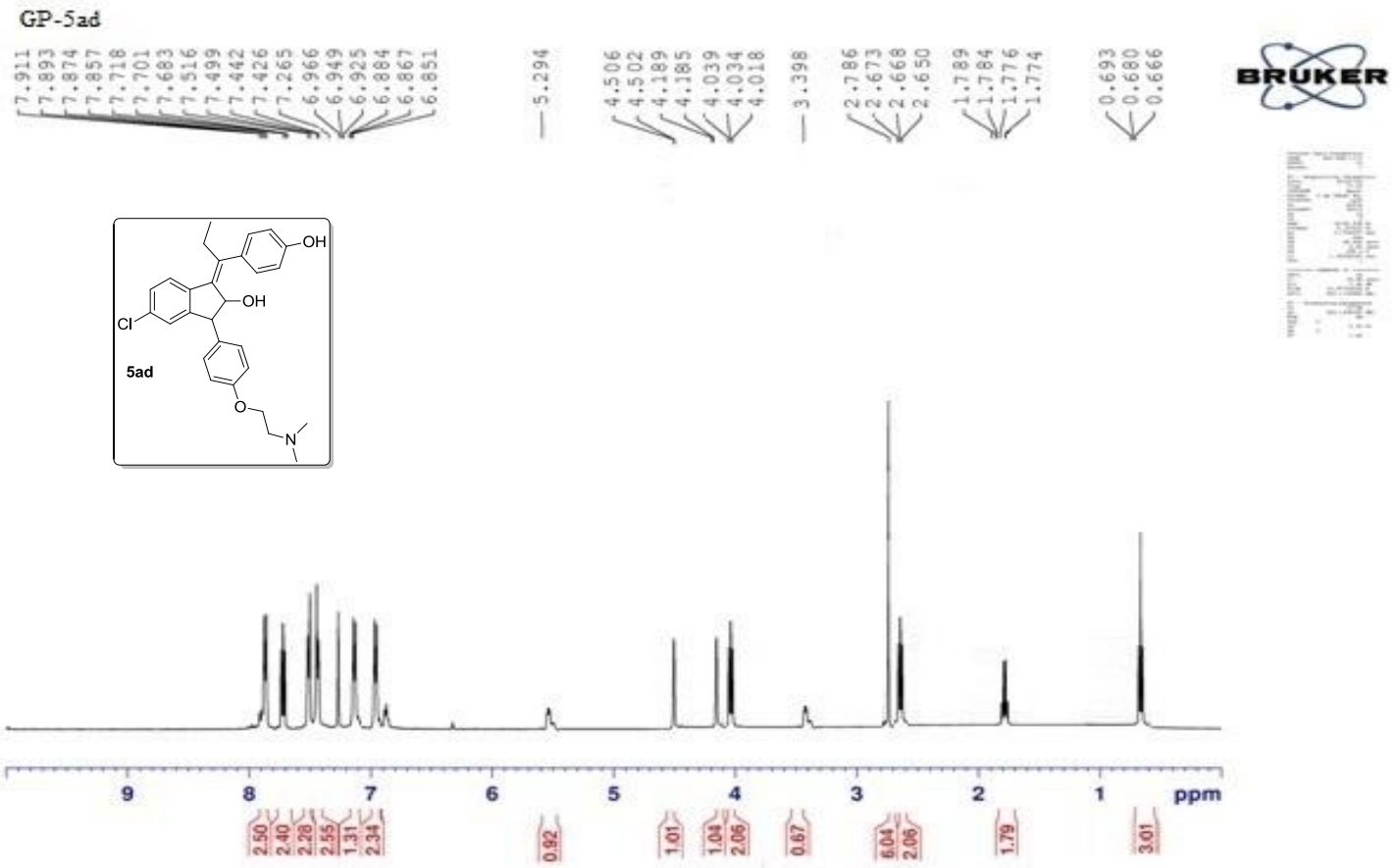


Figure S-84: ^{1}H NMR Spectrum of compound 5ad

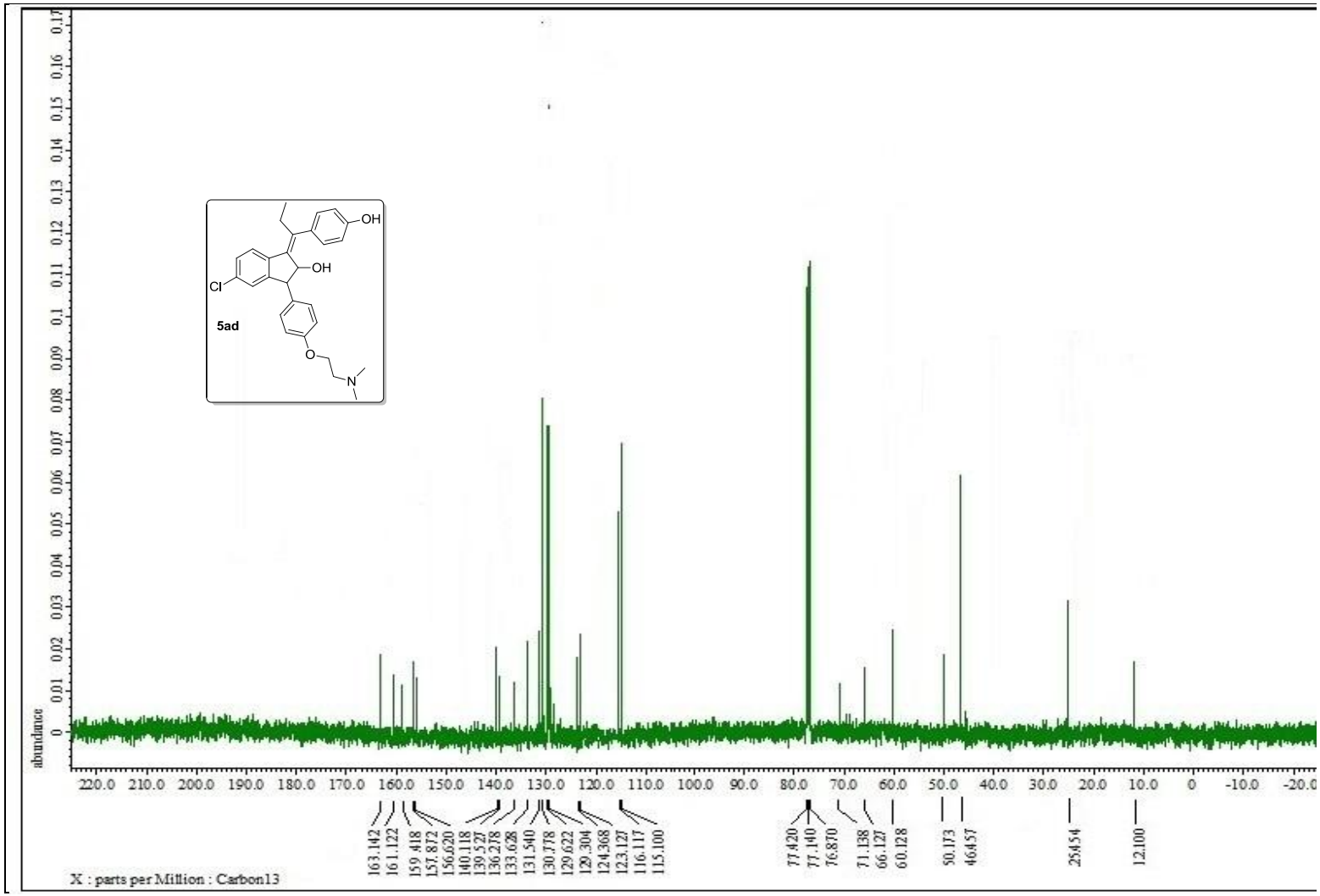


Figure S-85: ^{13}C NMR Spectrum of compound 5ad

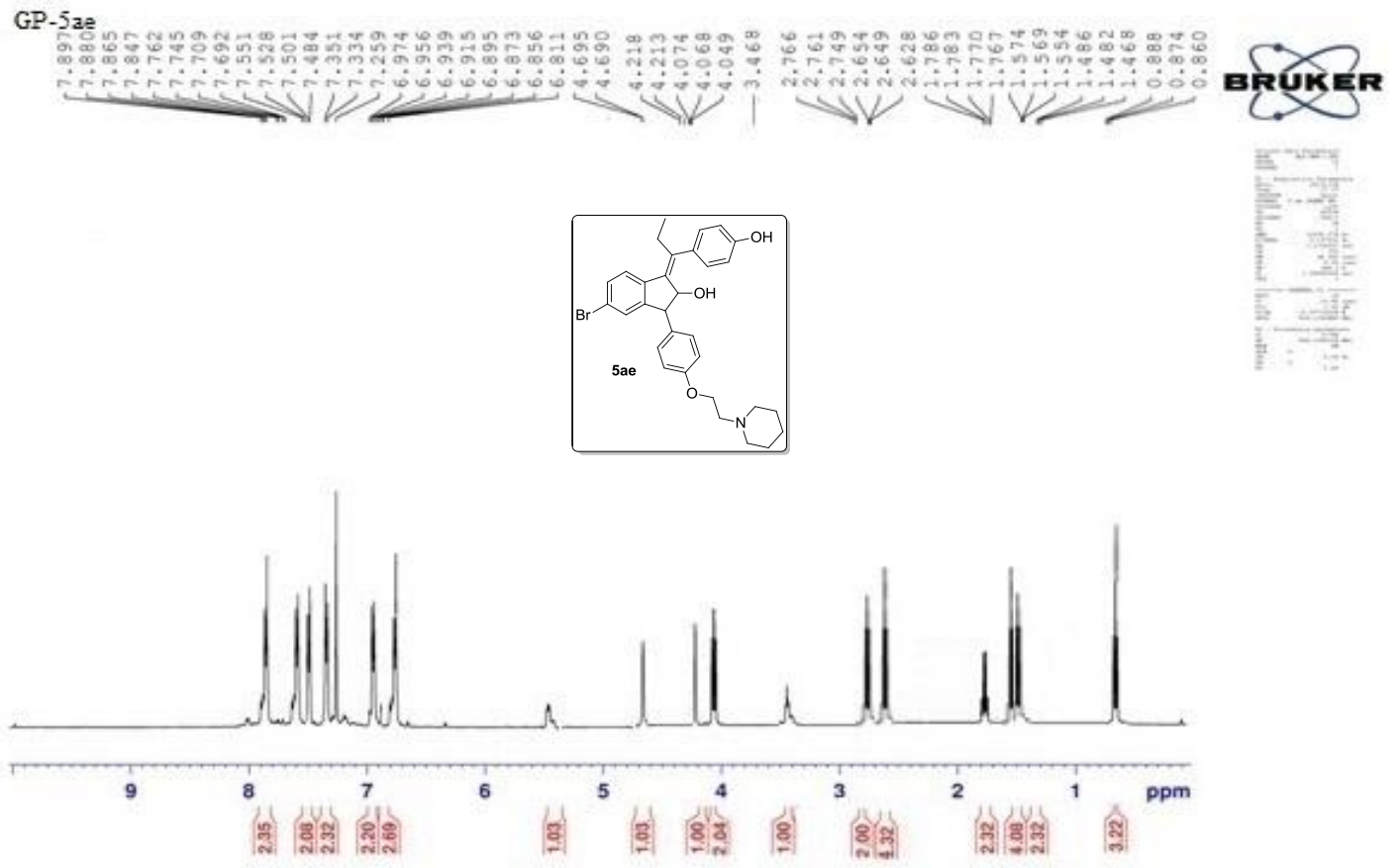


Figure S-86: ^{1}H NMR Spectrum of compound 5ae

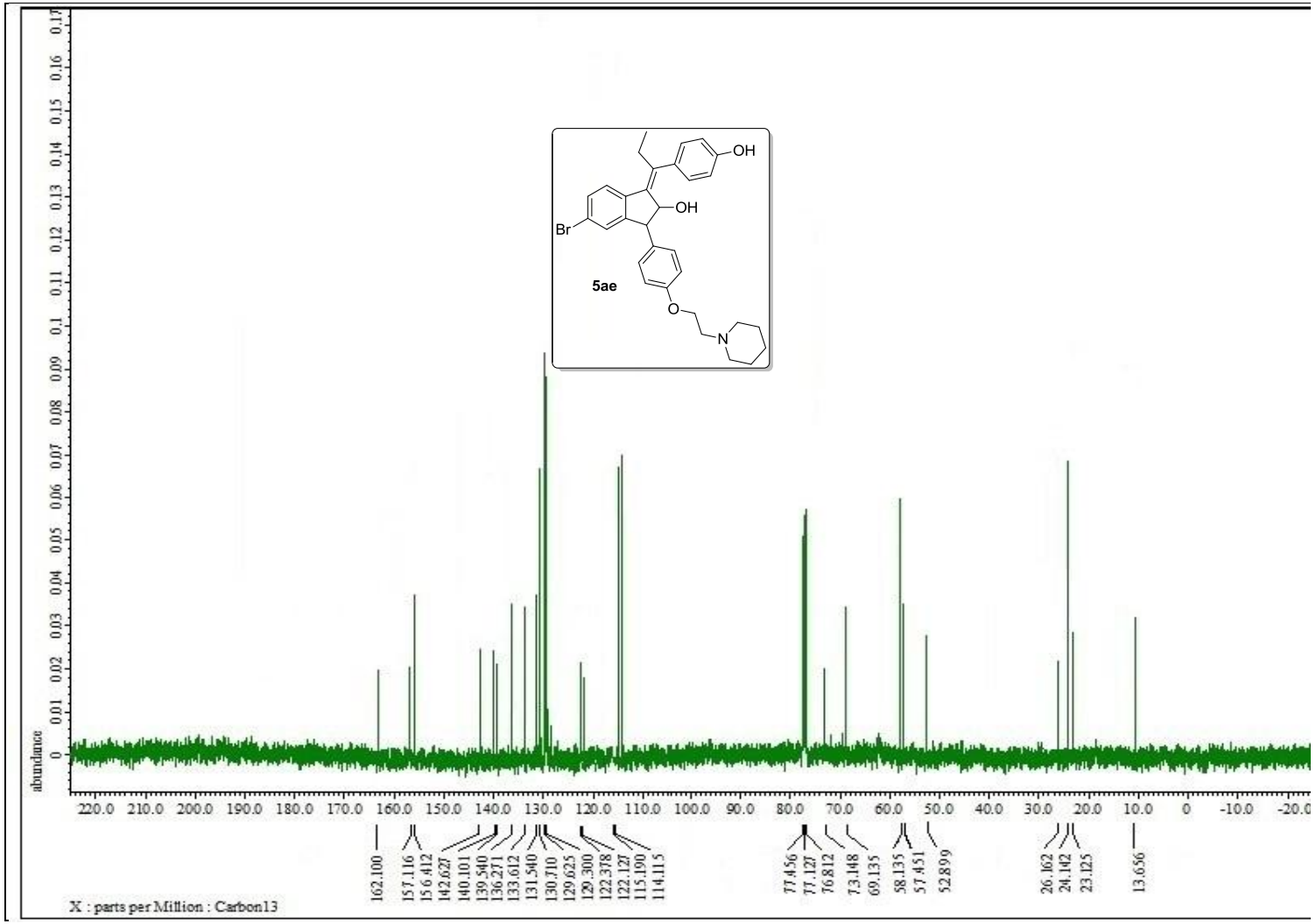


Figure S-87: ^{13}C NMR Spectrum of compound 5ae

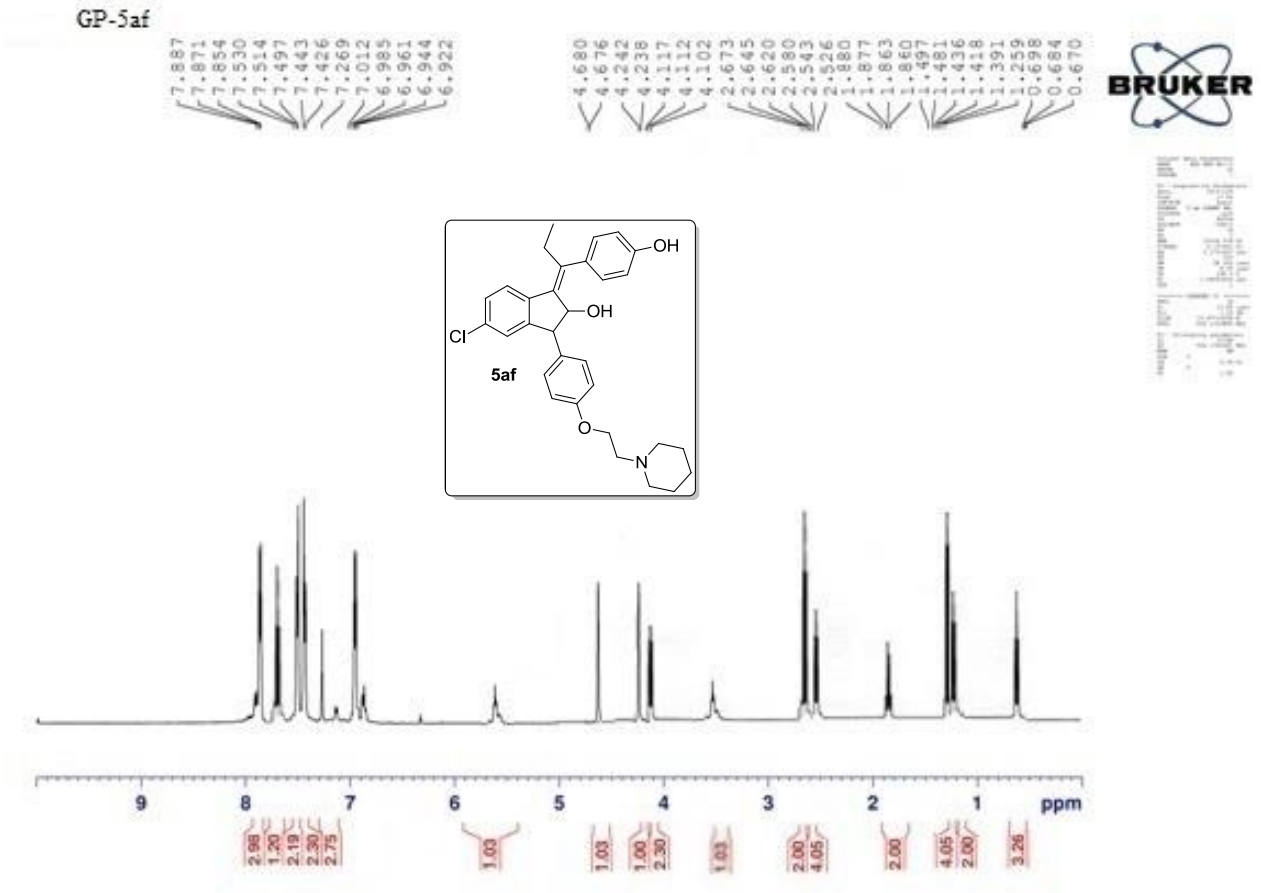


Figure S-88: ^{1}H NMR Spectrum of compound 5af

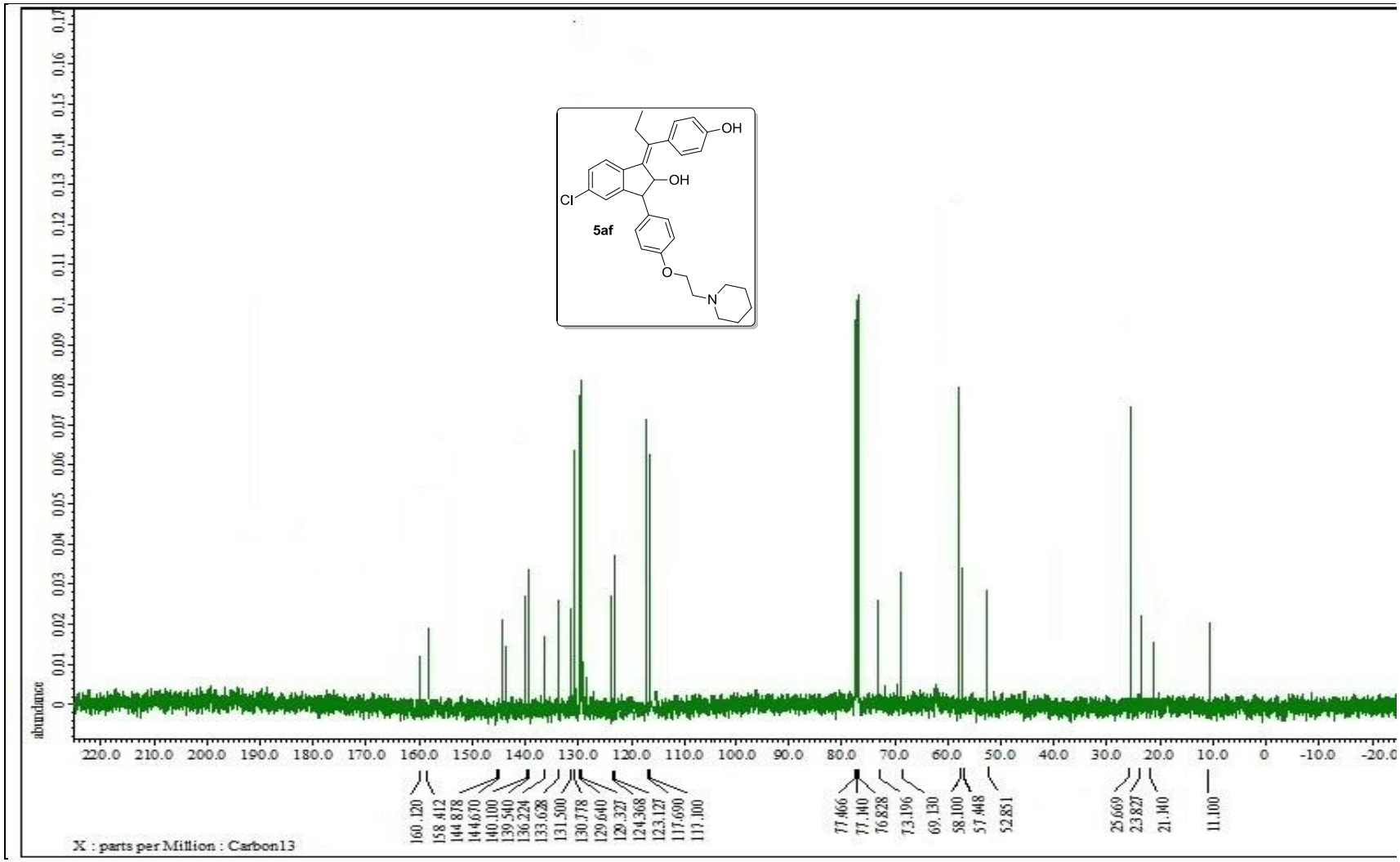


Figure S-89: ^{13}C NMR Spectrum of compound 5af

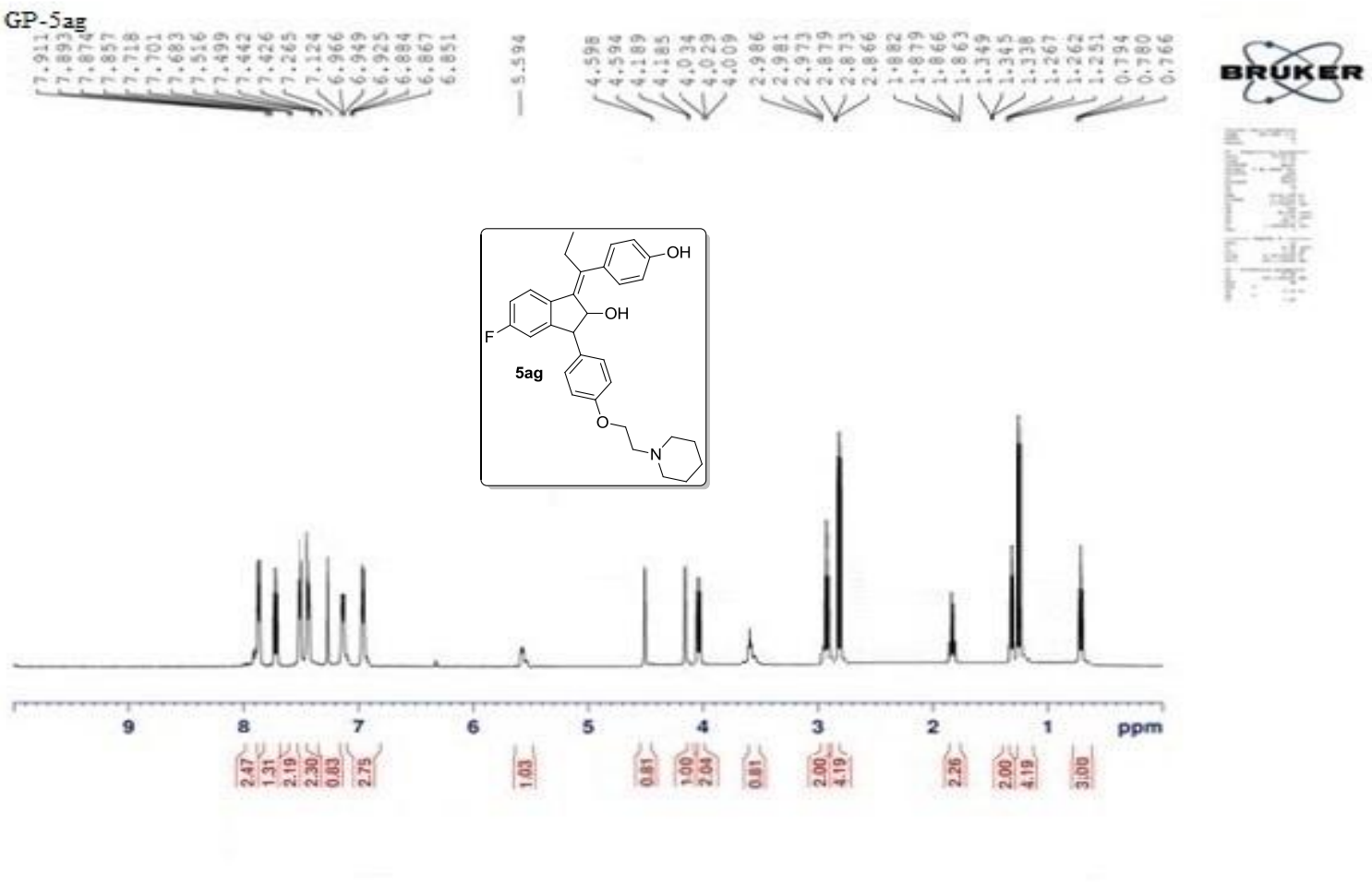


Figure S-90: ^{1}H NMR Spectrum of compound 5ag

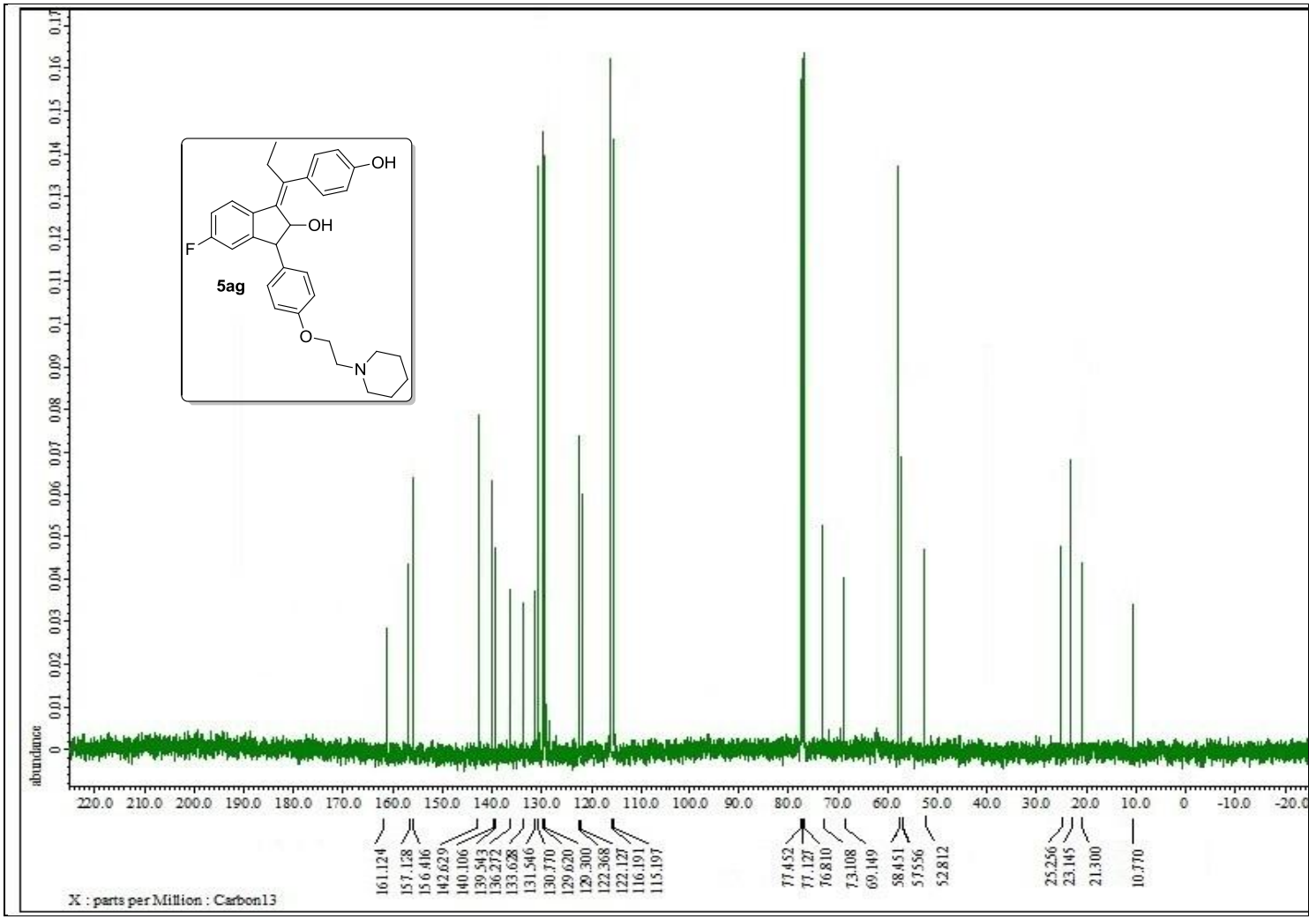


Figure S-91: ^{13}C NMR Spectrum of compound 5ag

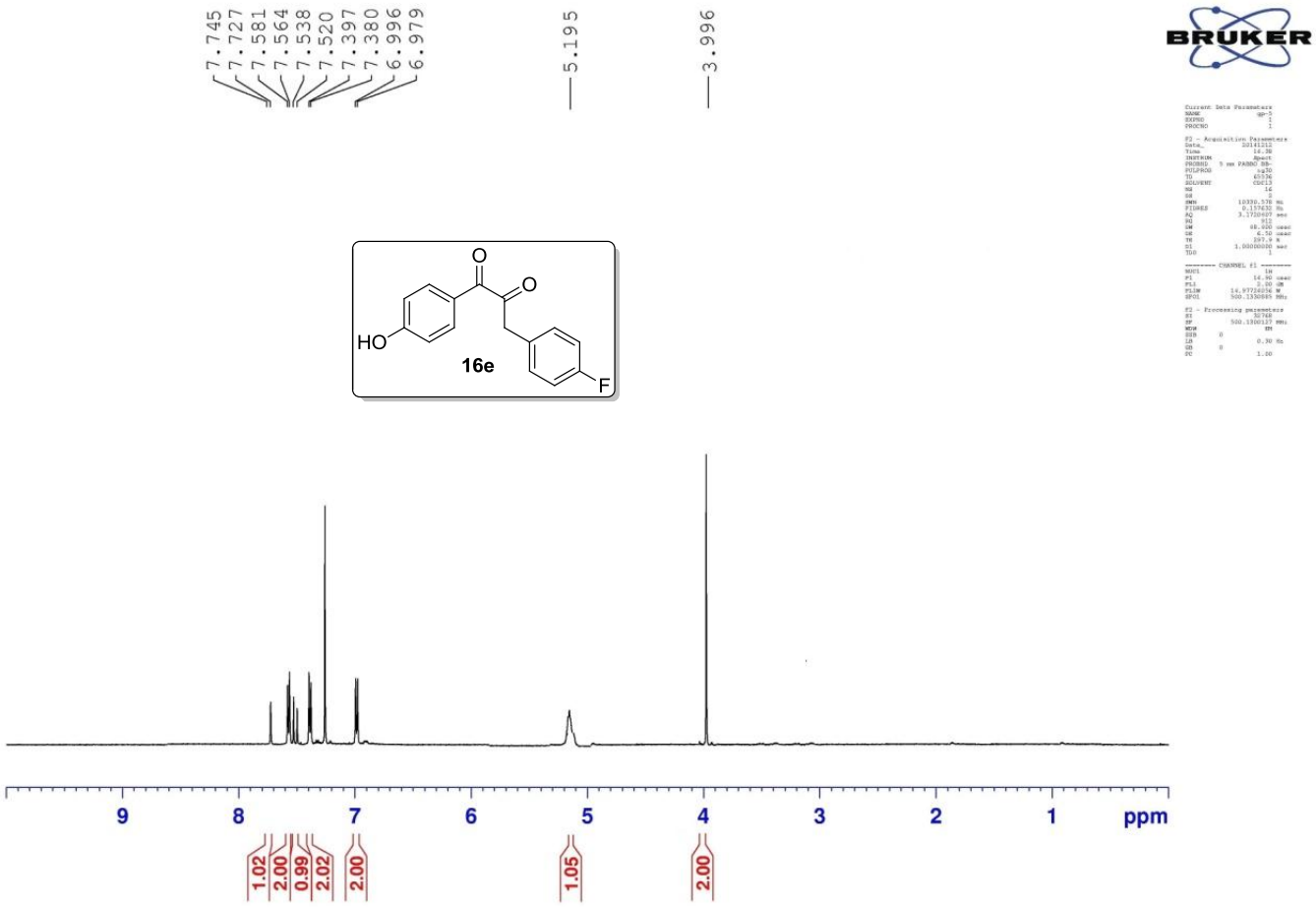


Figure S-92: ^{1}H NMR Spectrum of compound 16e

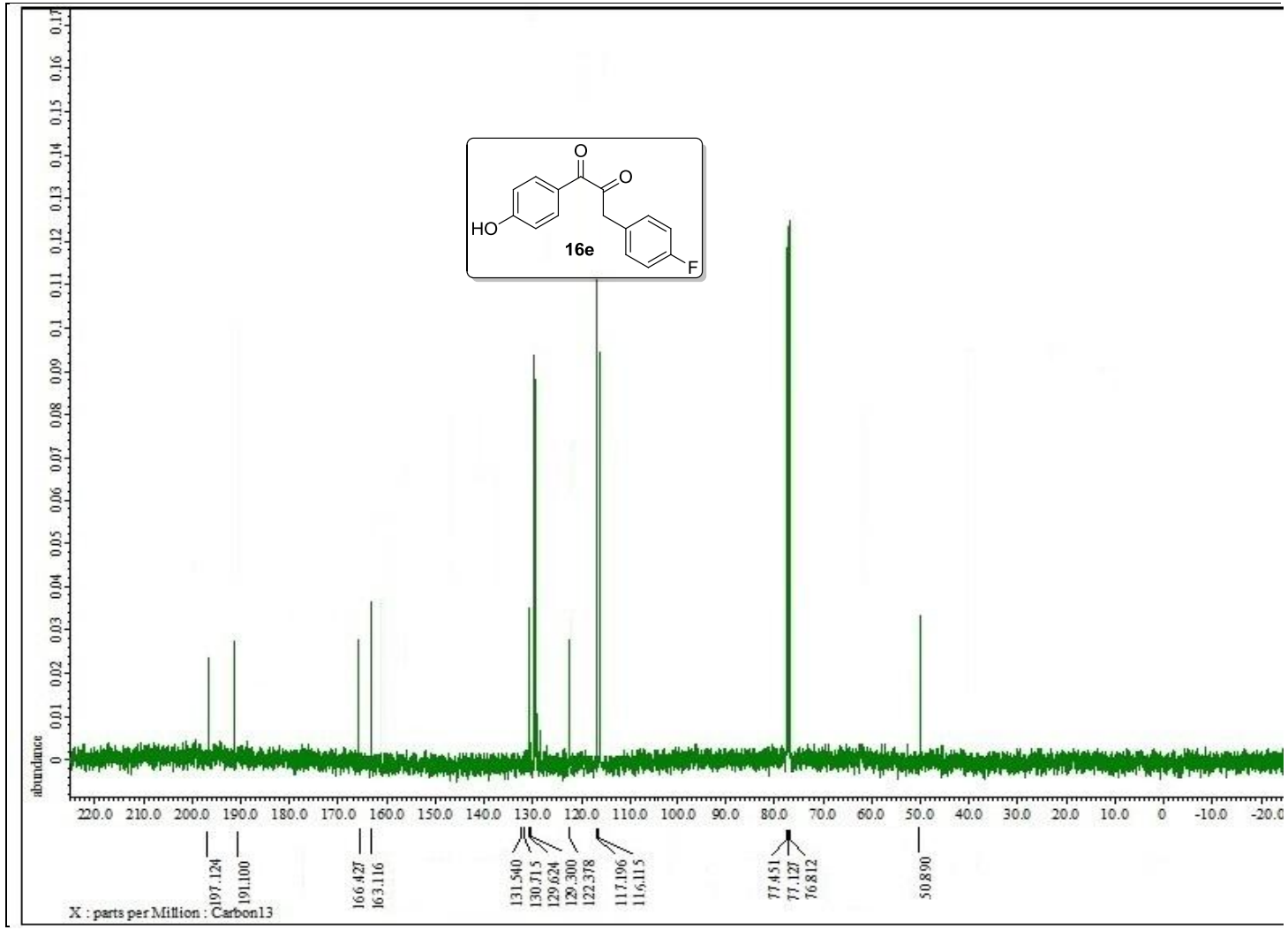


Figure S-93: ^{13}C NMR Spectrum of compound 16e

Figure S-94: ^{1}H NMR Spectrum of compound 16f

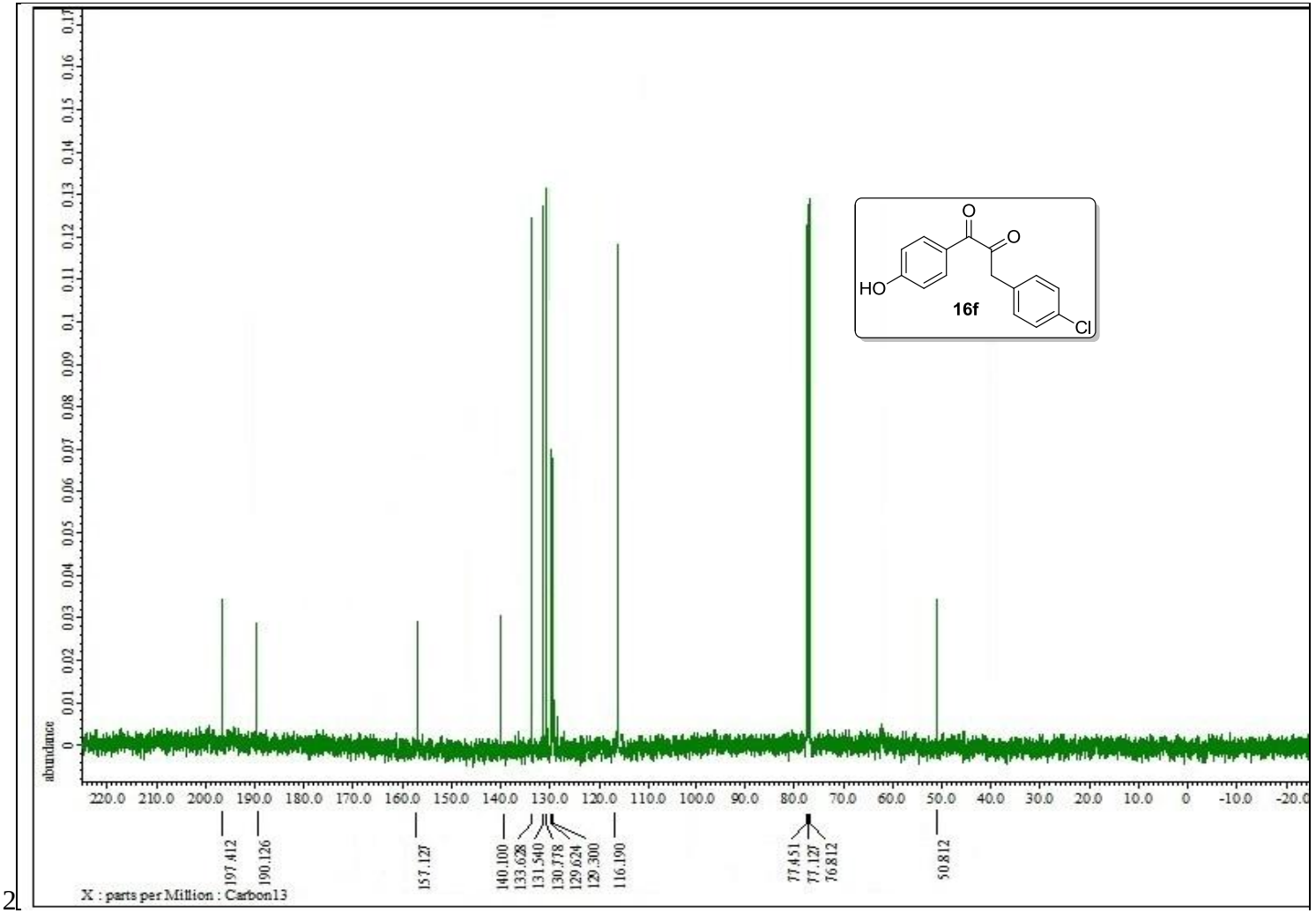


Figure S-95: ^{13}C NMR Spectrum of compound 16f

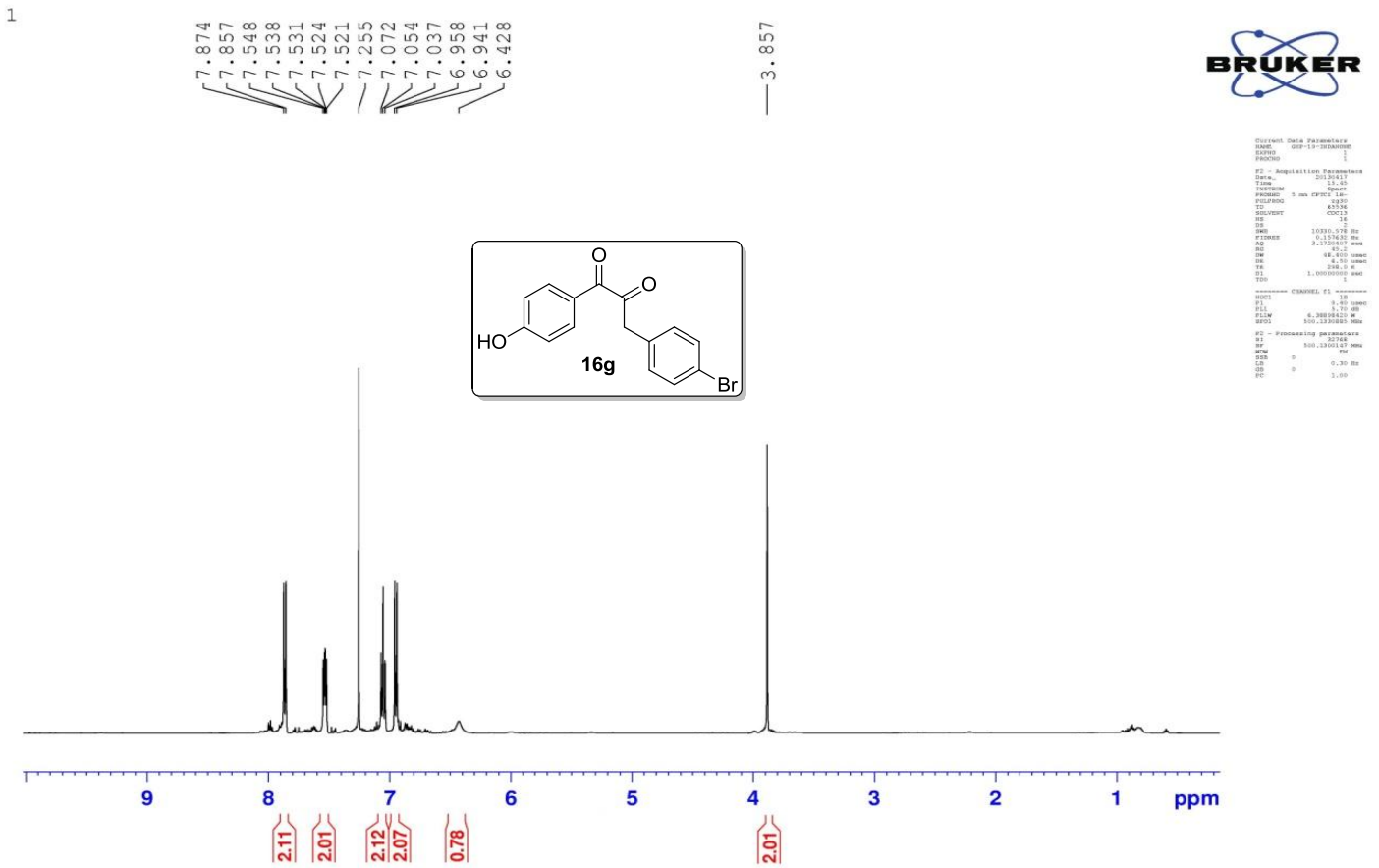


Figure S-96: ^{1}H NMR Spectrum of compound 16g

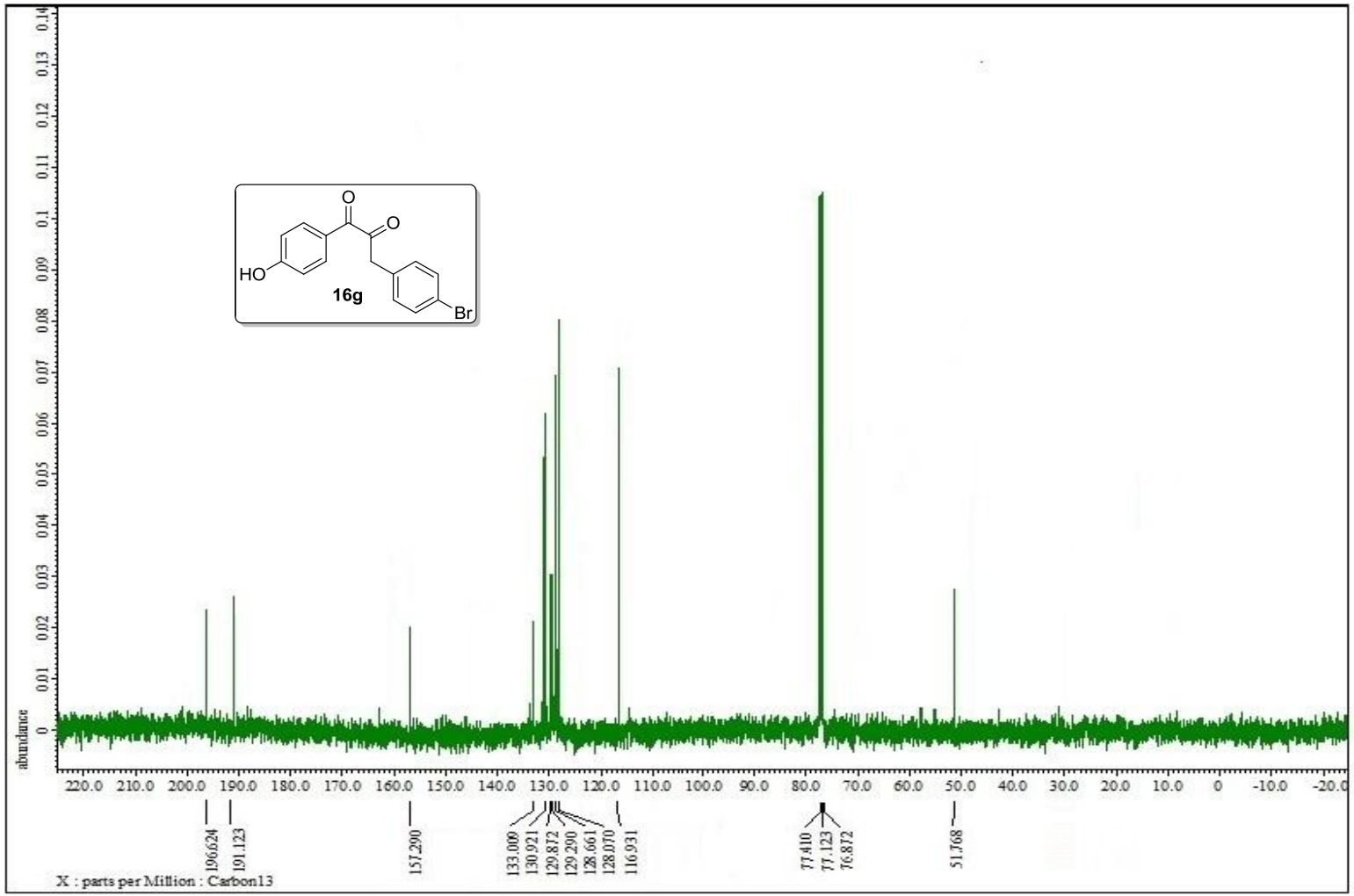


Figure S-97: ^{13}C NMR Spectrum of compound 16g

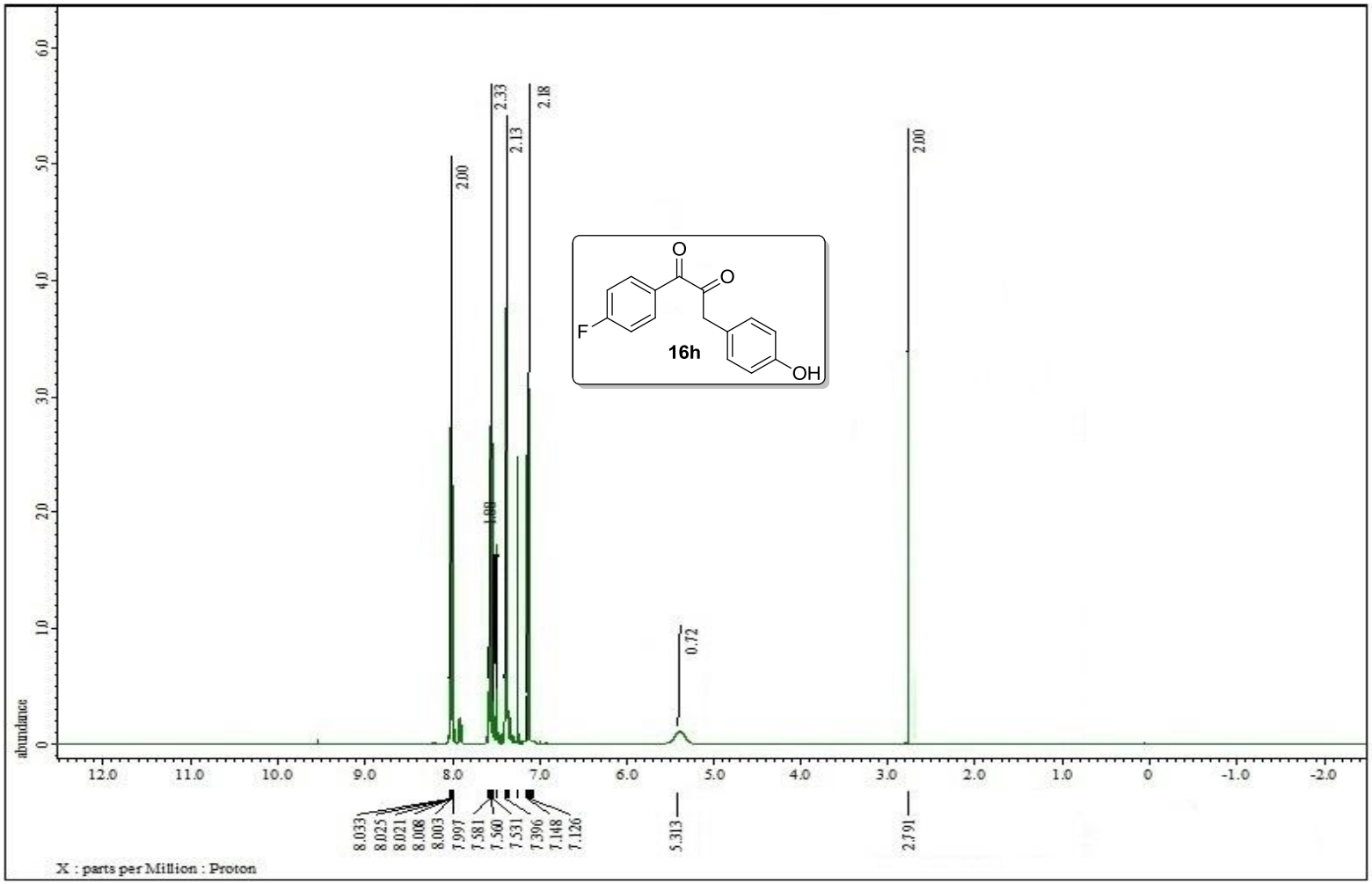


Figure S-98: ^{1}H NMR Spectrum of compound 16h

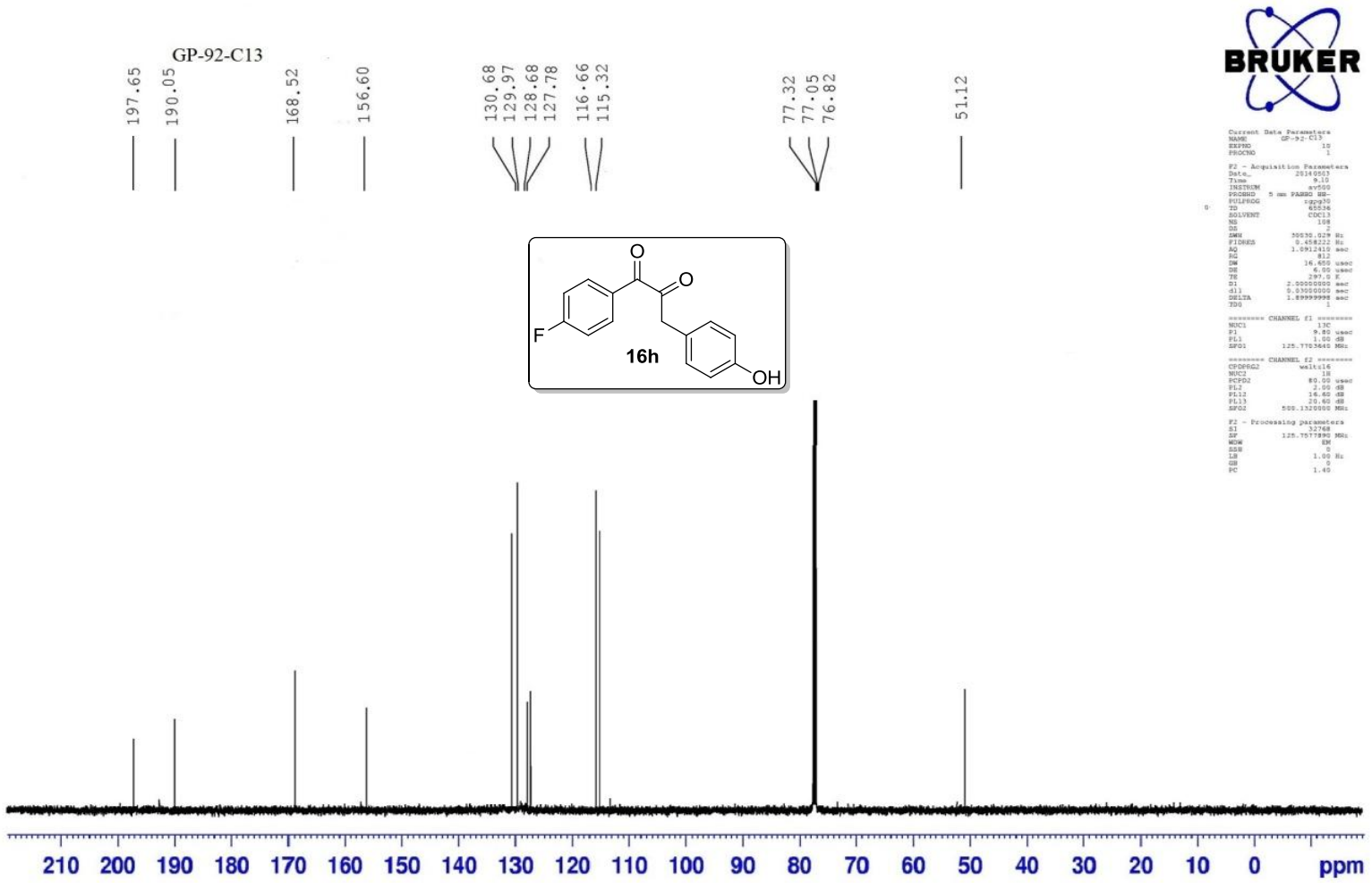


Figure S-99: ^{13}C NMR Spectrum of compound 16h

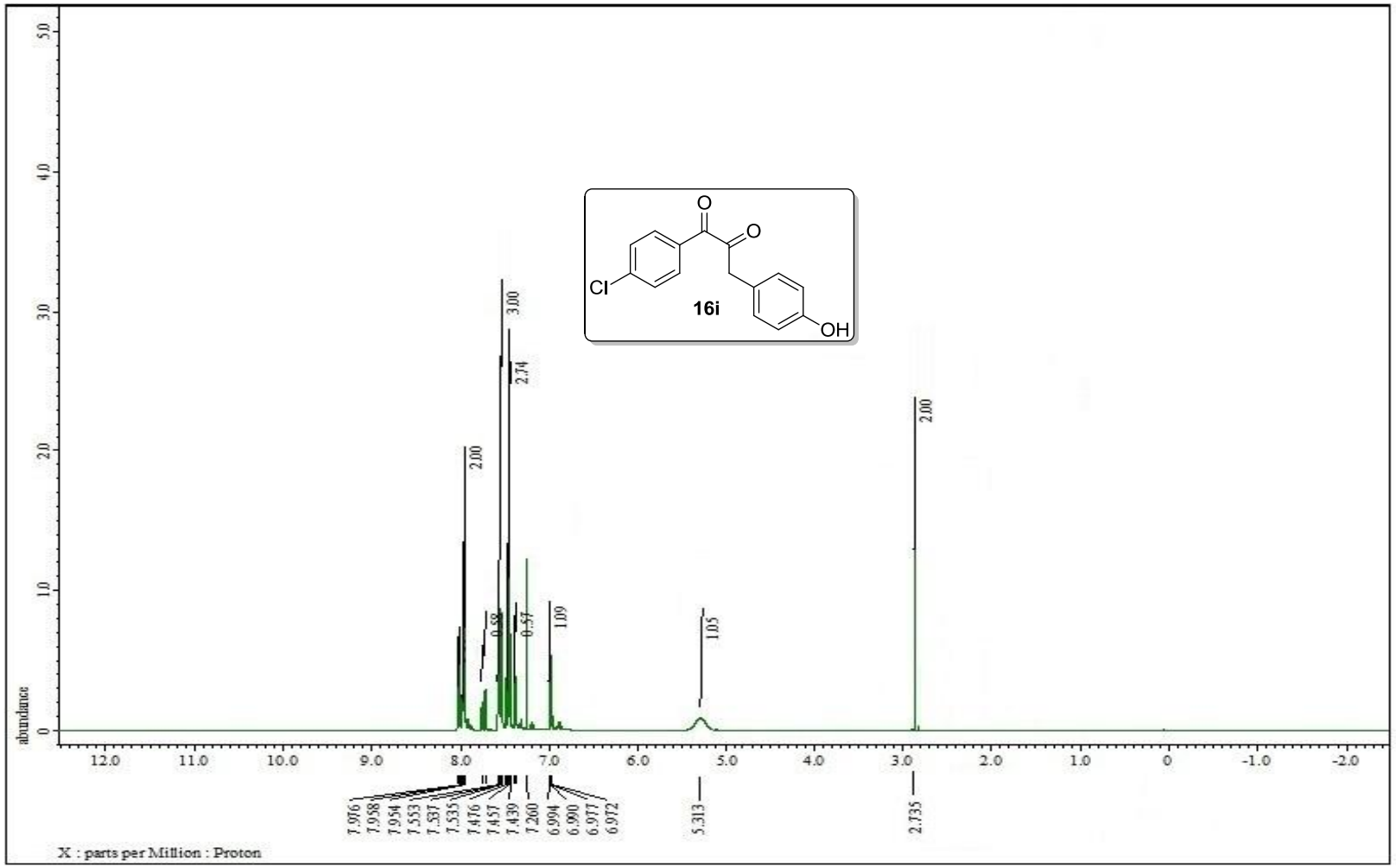


Figure S-100: ^{1}H NMR Spectrum of compound 16i

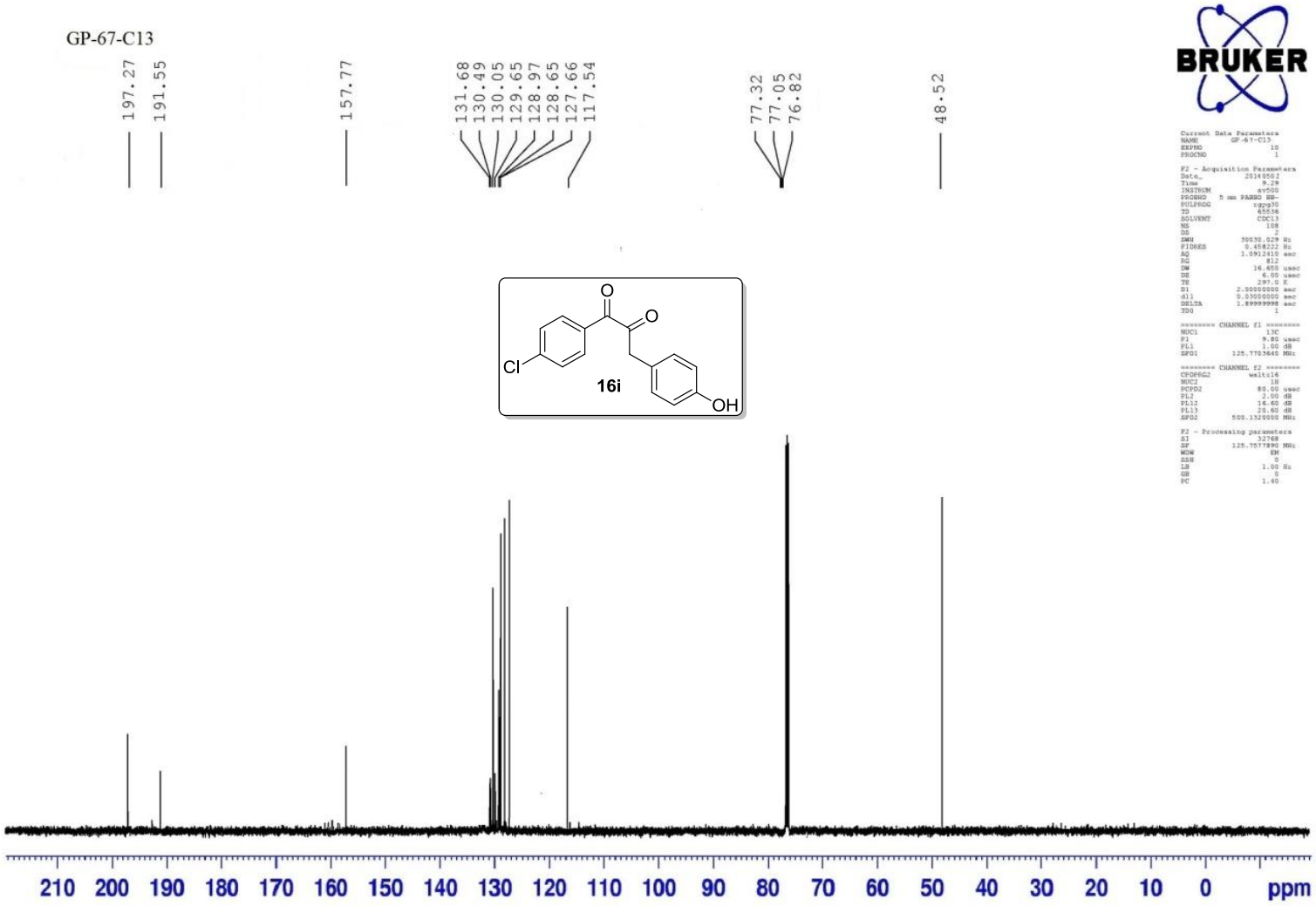


Figure S-101: ^{13}C NMR Spectrum of compound 16i

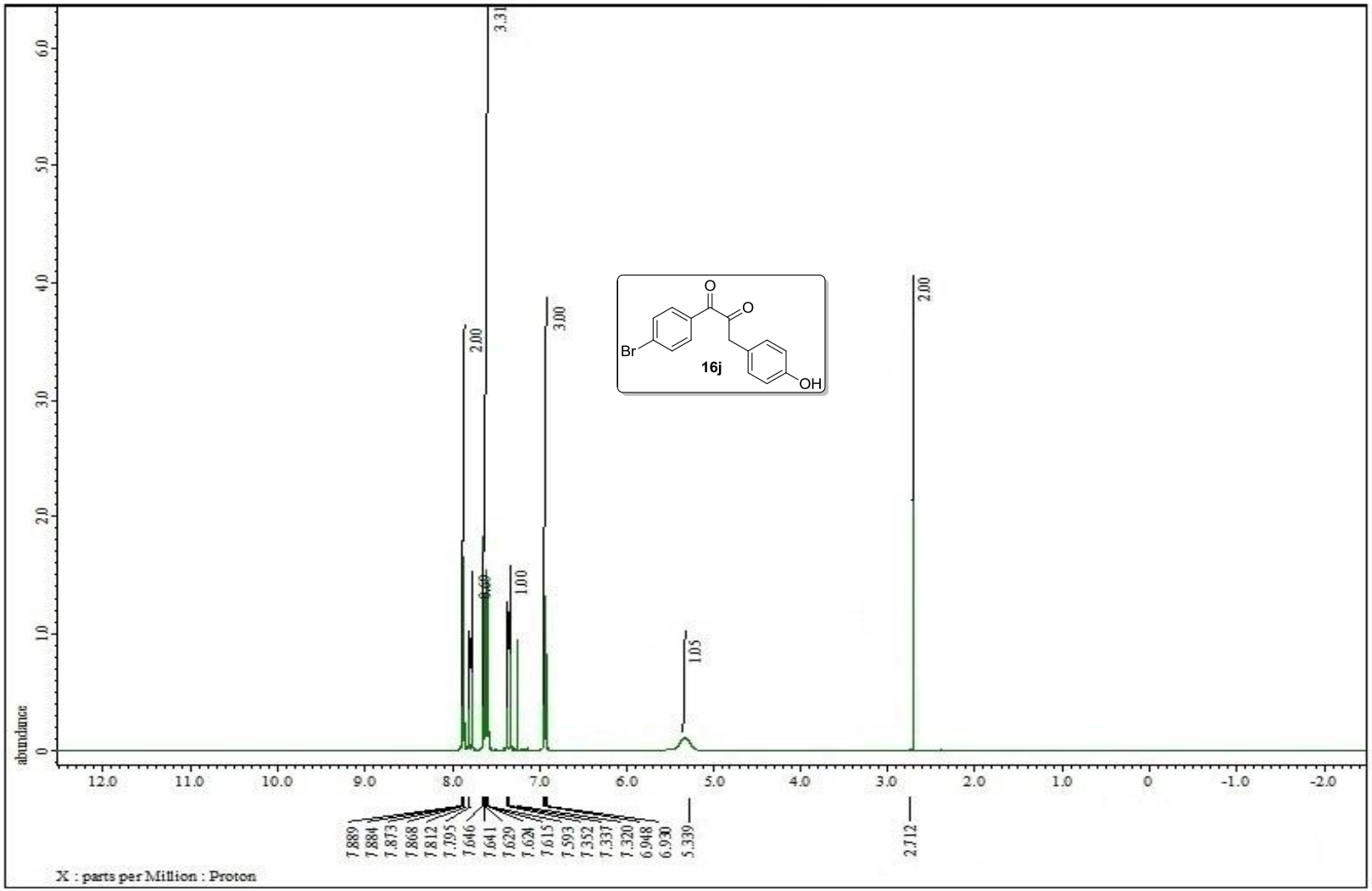


Figure S-102: ^{1}H NMR Spectrum of compound 16j

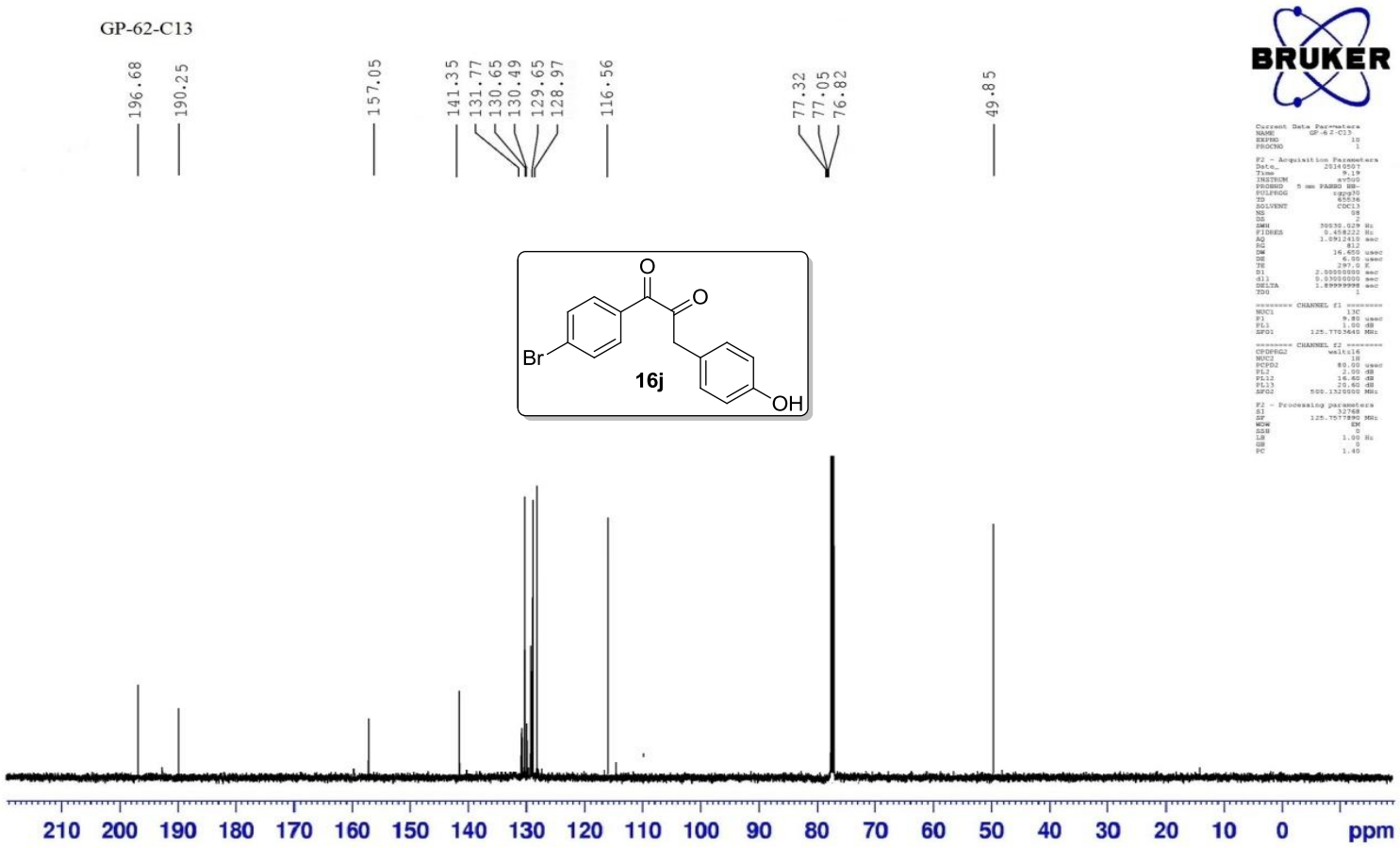


Figure S-103: ^{13}C NMR Spectrum of compound 16j

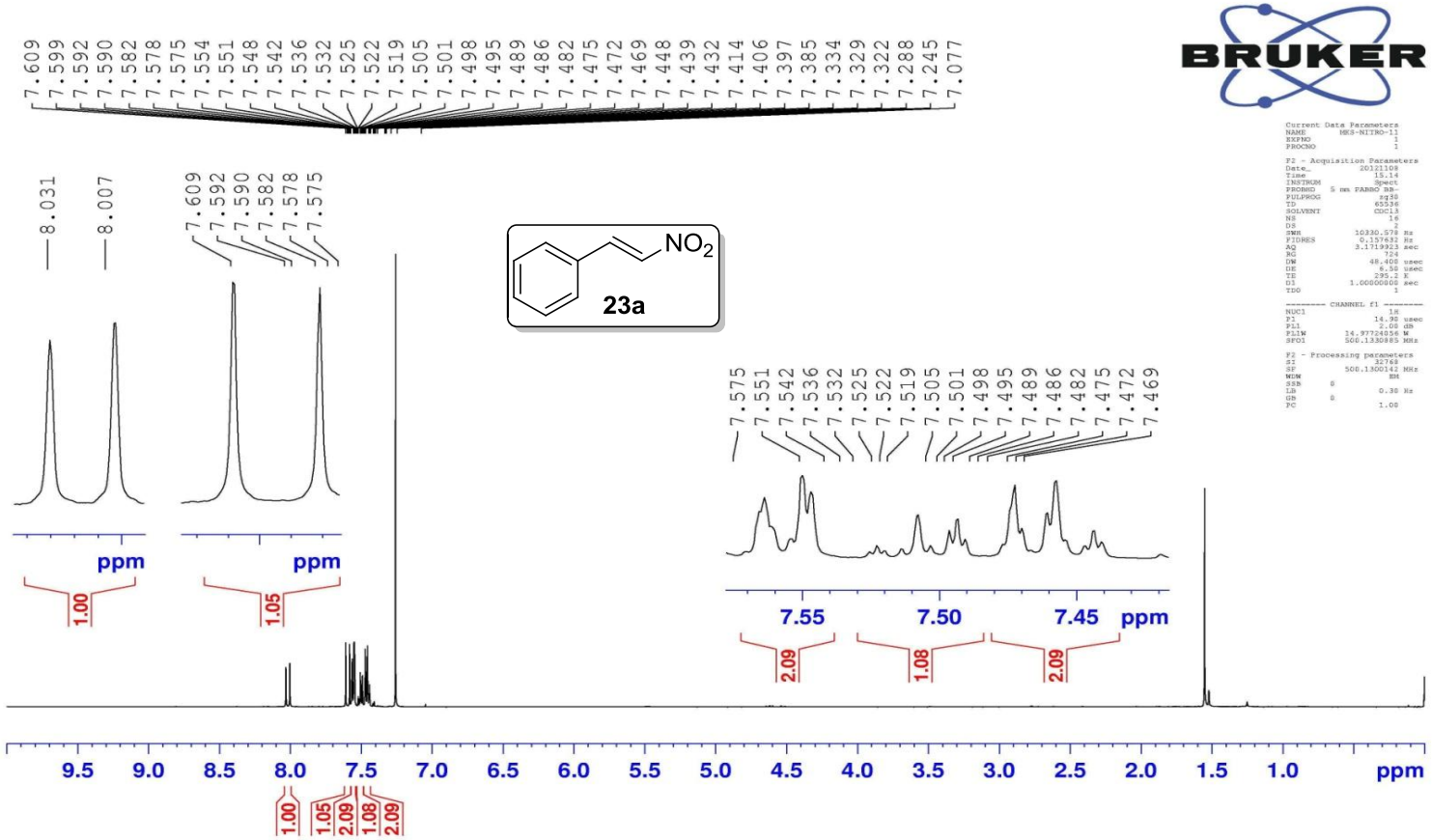


Figure S-104: ^{1}H NMR Spectrum of compound 23a

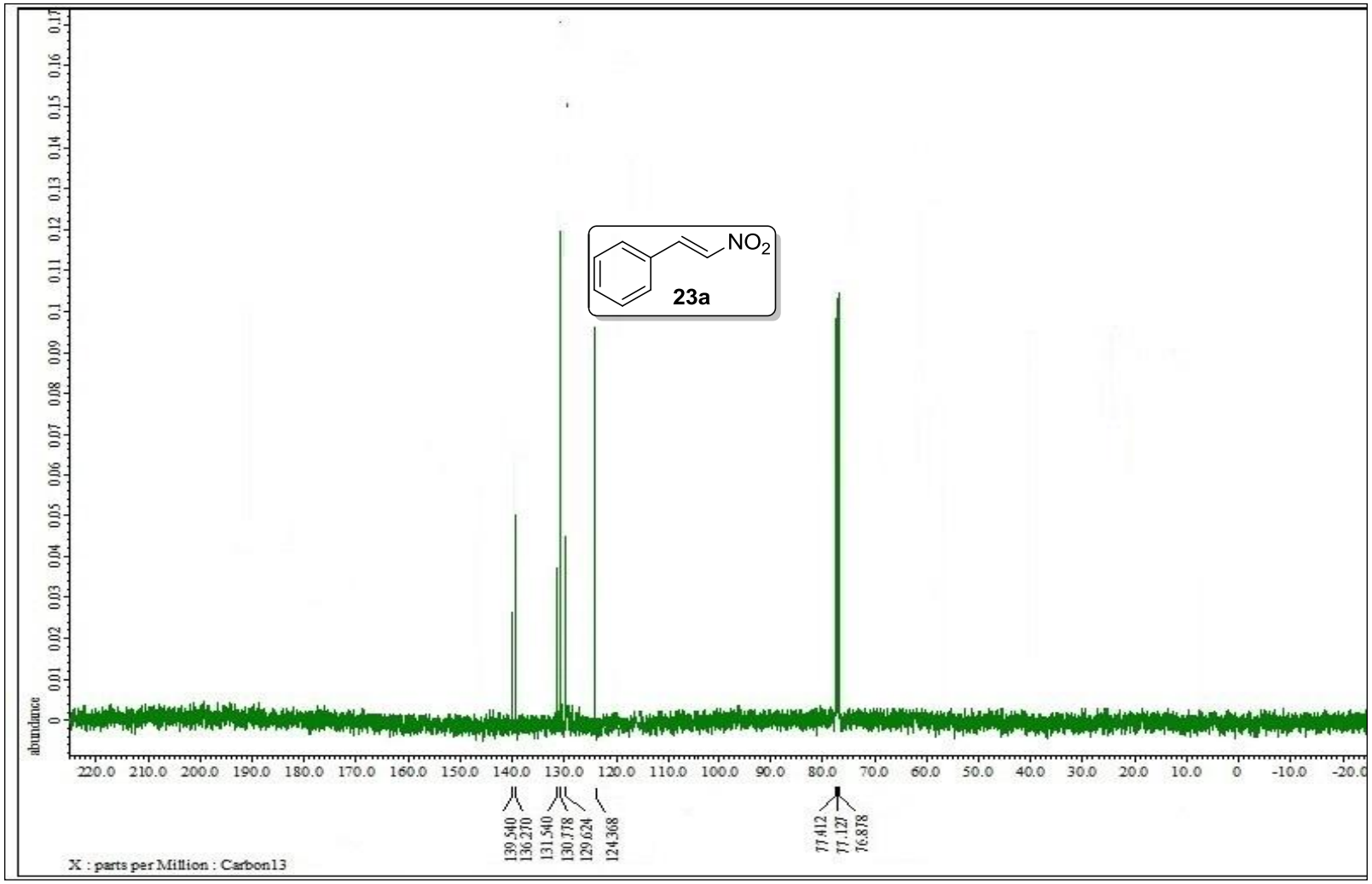


Figure S-105: ^{13}C NMR Spectrum of compound 23a

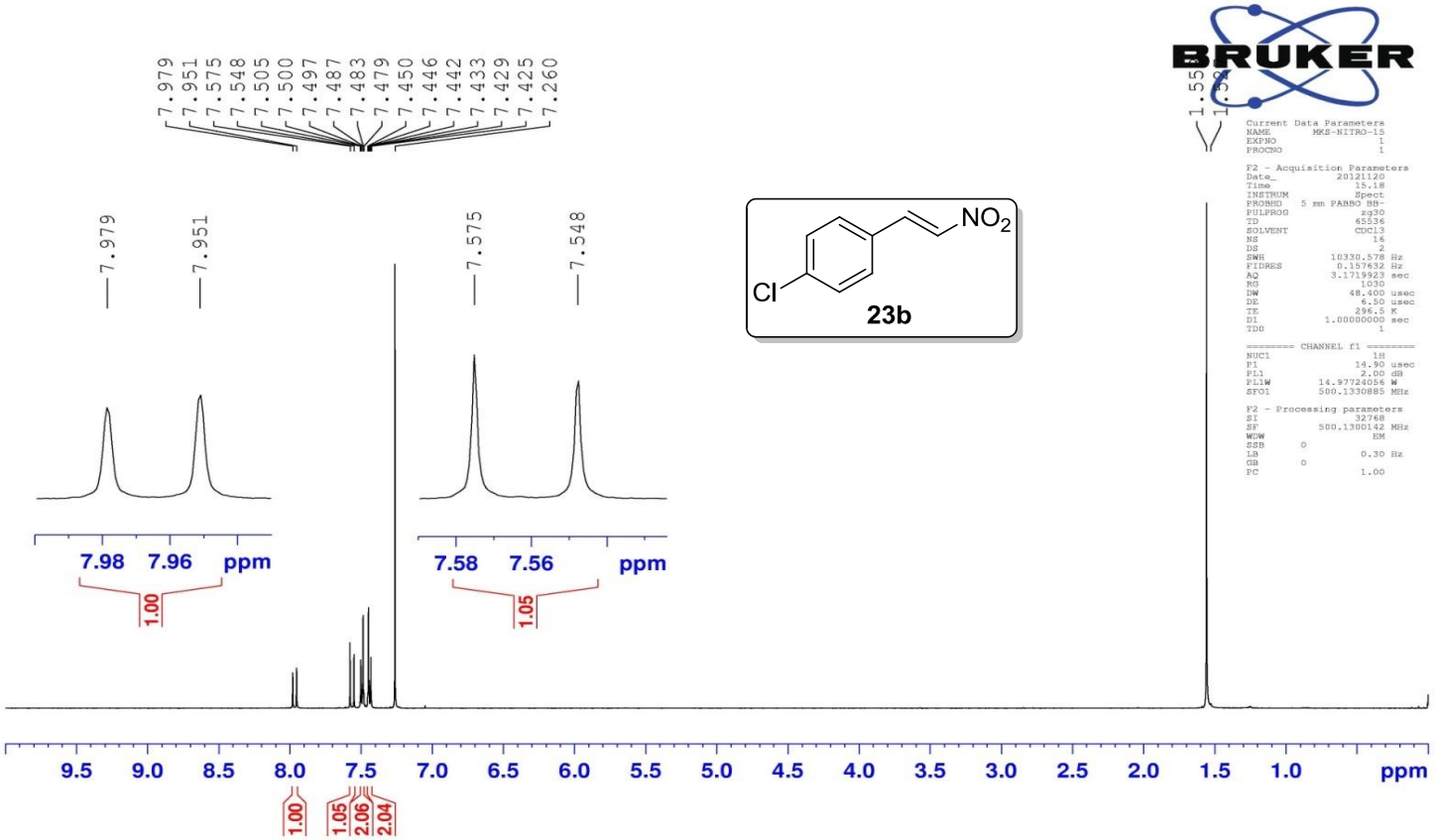


Figure S-106: ^{1}H NMR Spectrum of compound 23b

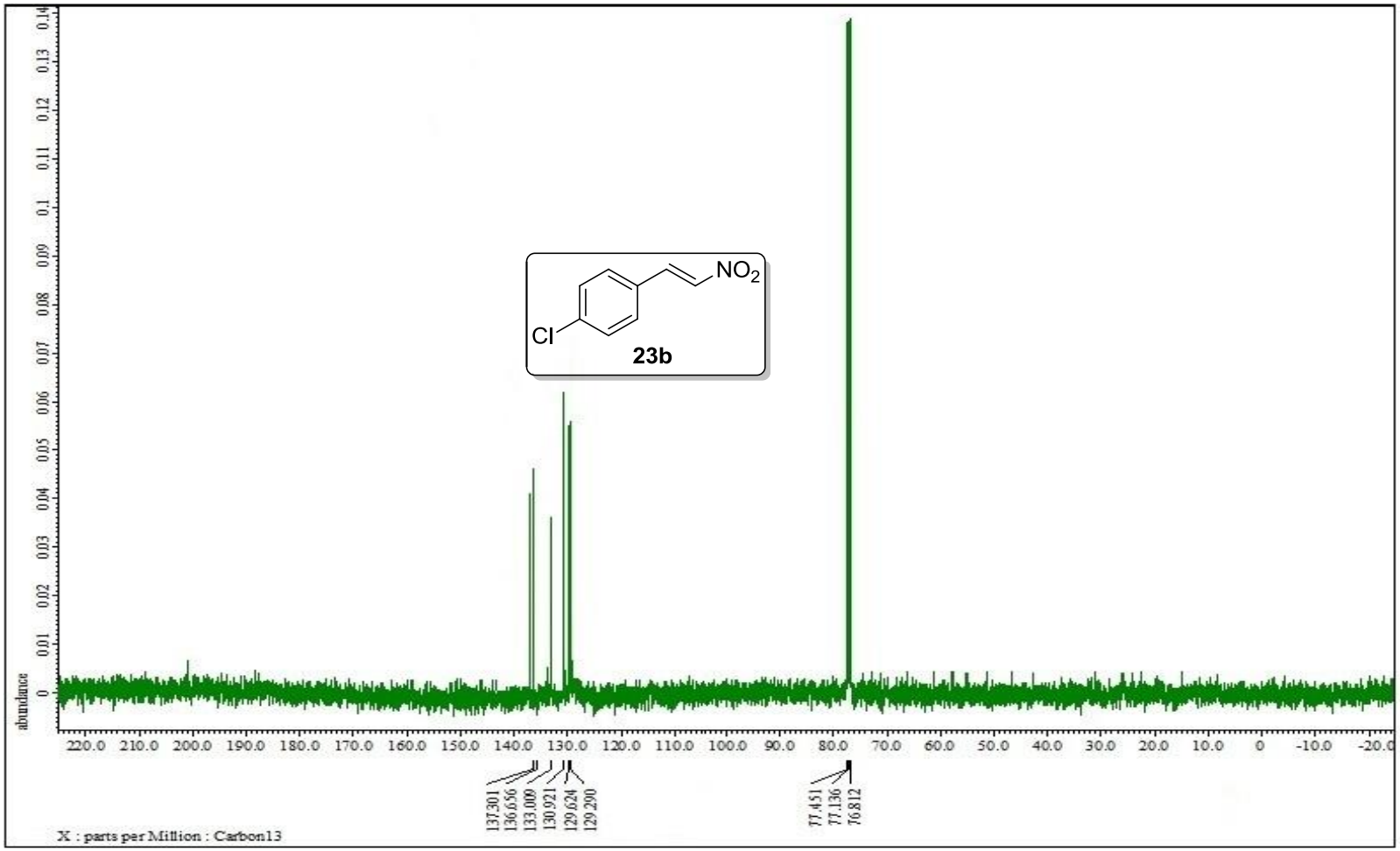


Figure S-107: ^{13}C NMR Spectrum of compound 23b

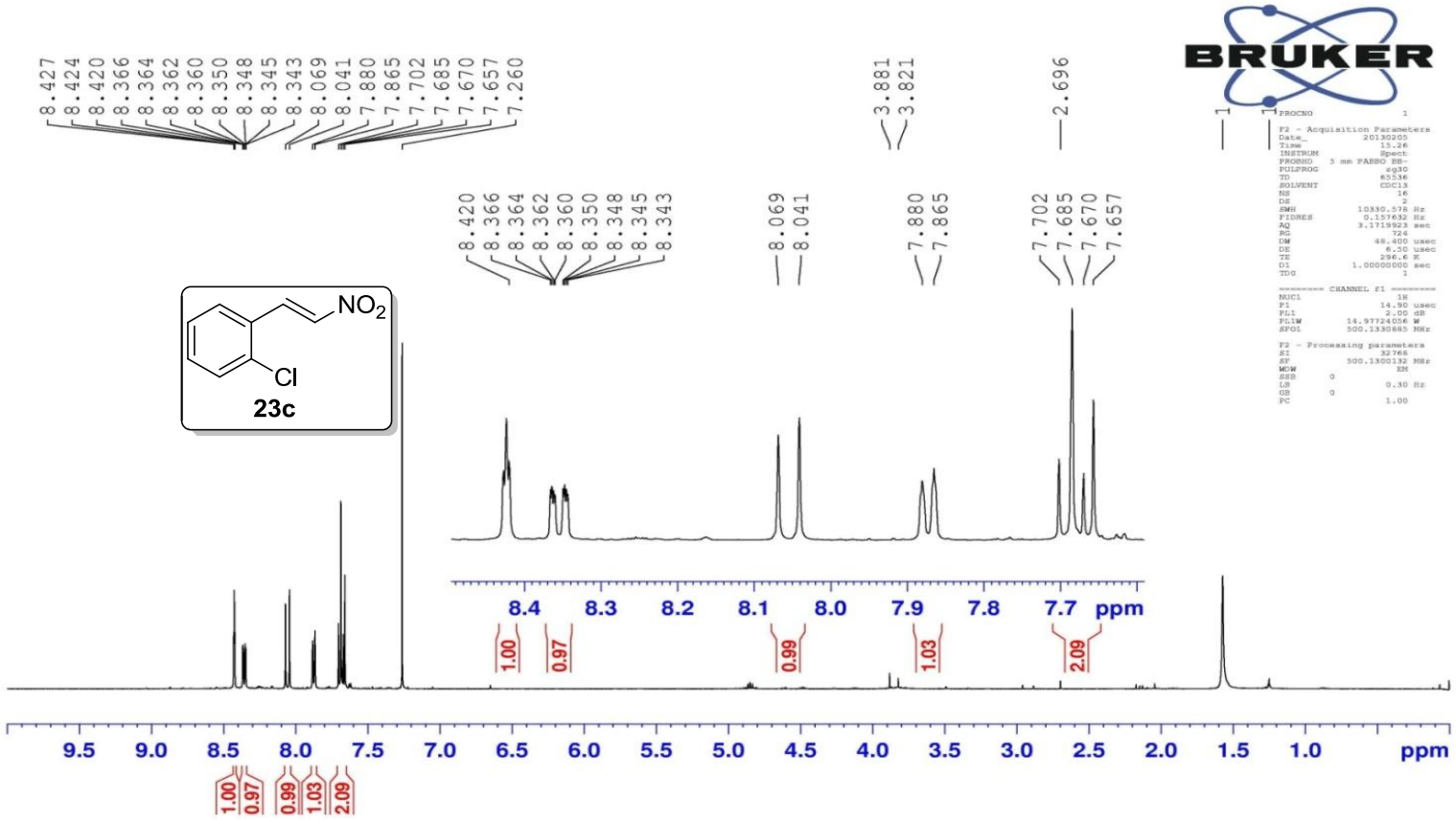


Figure S-108: ^{1}H NMR Spectrum of compound 23c

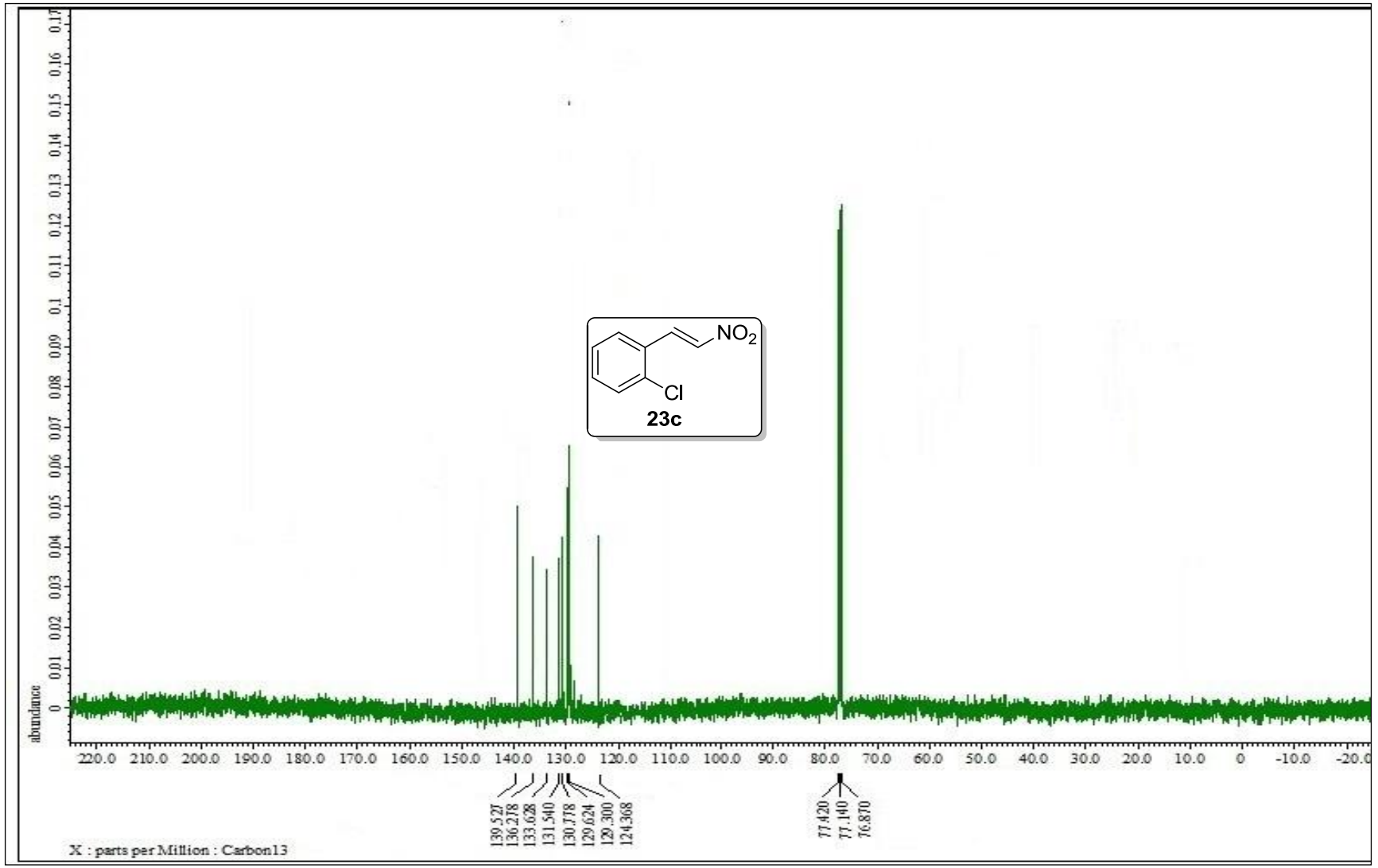


Figure S-109: ^{13}C NMR Spectrum of compound 23c

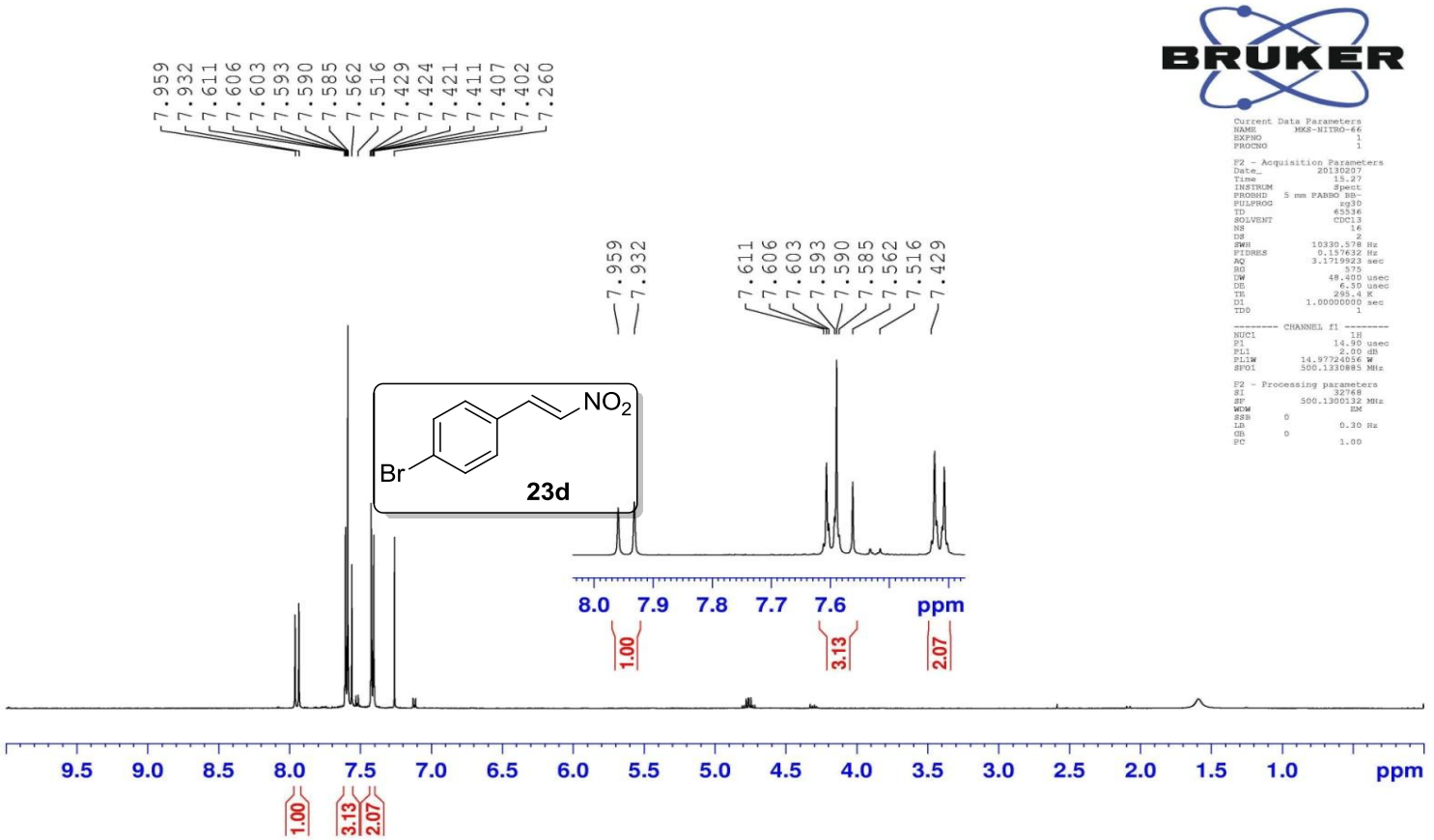


Figure S-110: ^{1}H NMR Spectrum of compound 23d

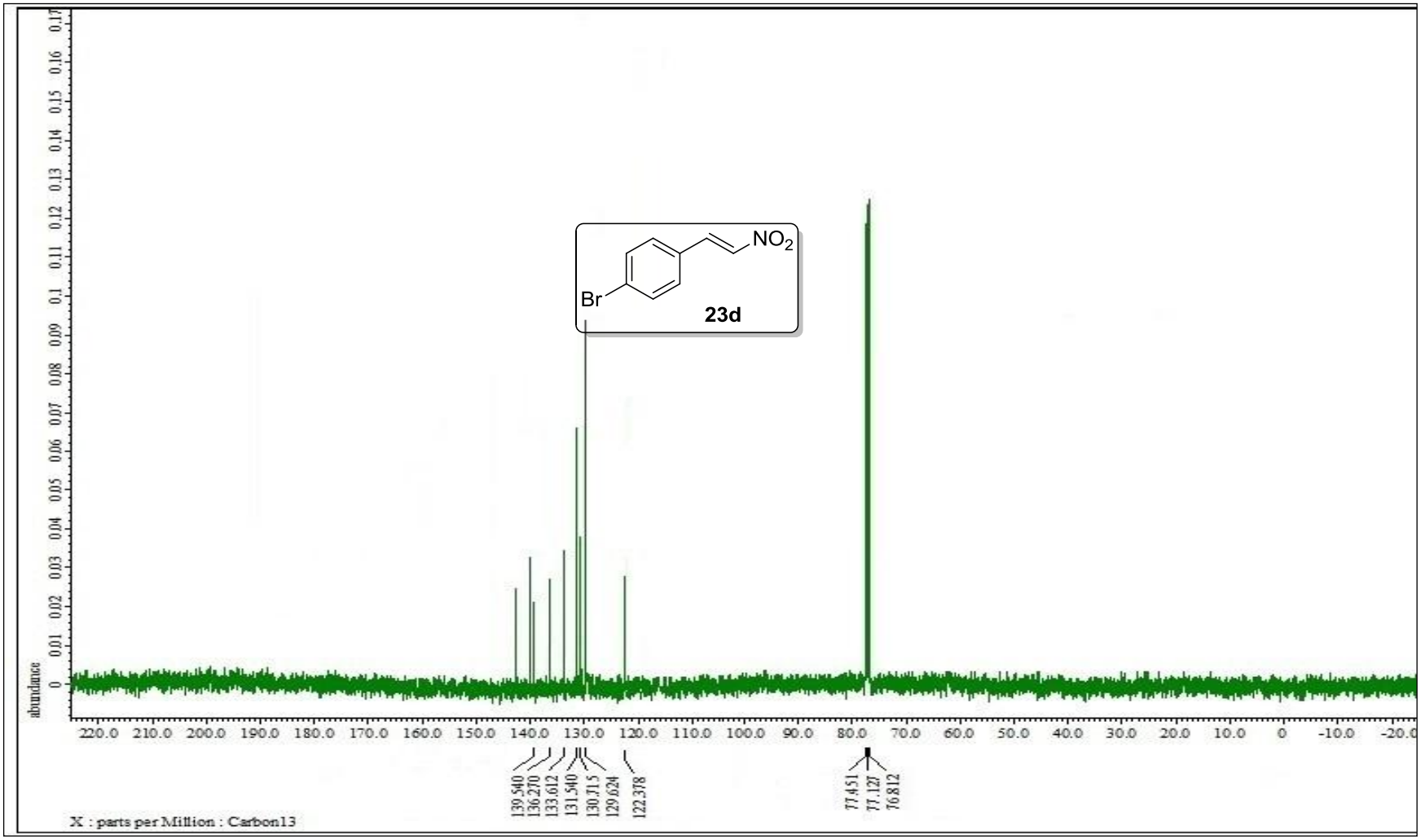


Figure S-111: ^{13}C NMR Spectrum of compound 23d

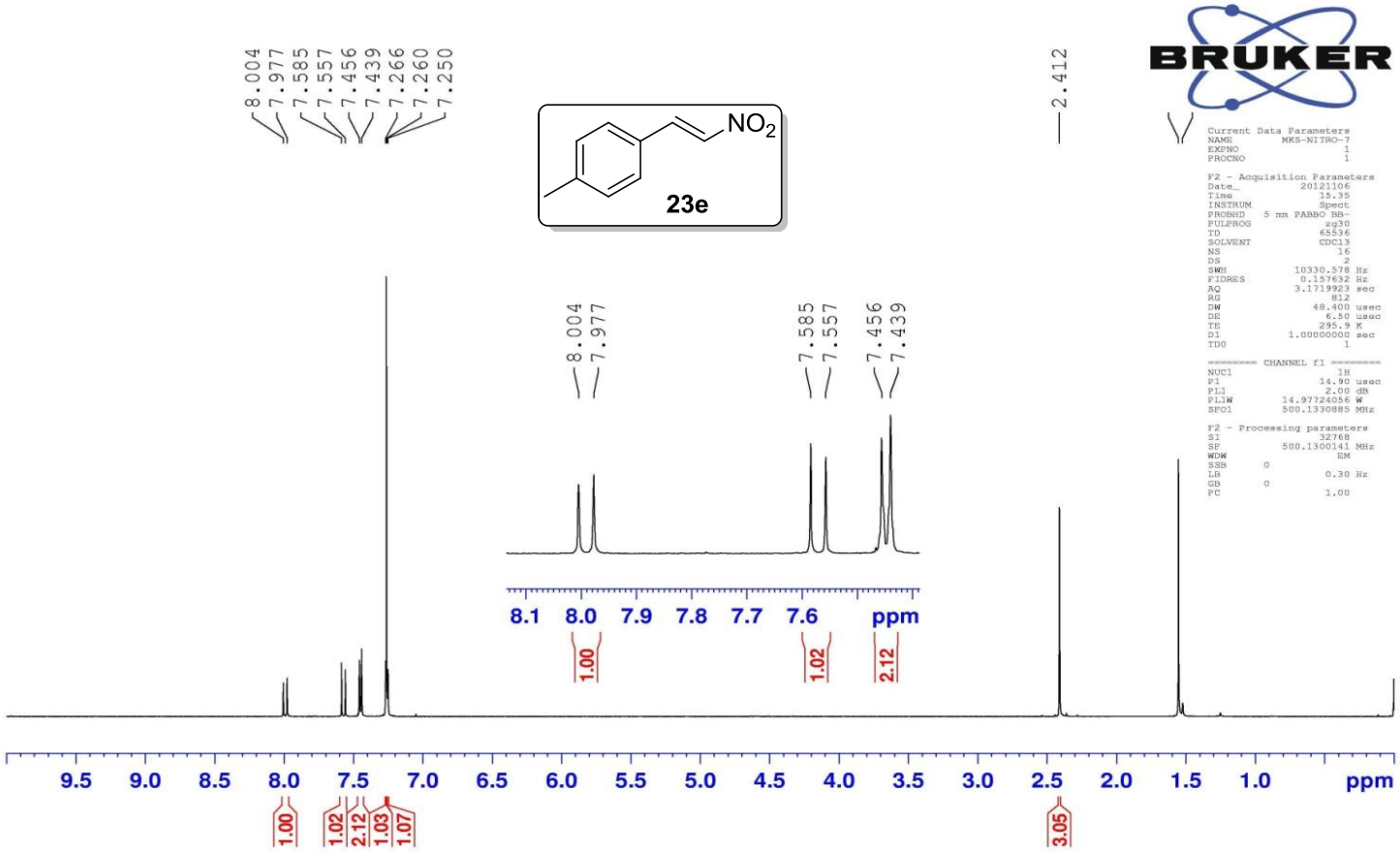


Figure S-112: ^{1}H NMR Spectrum of compound 23e

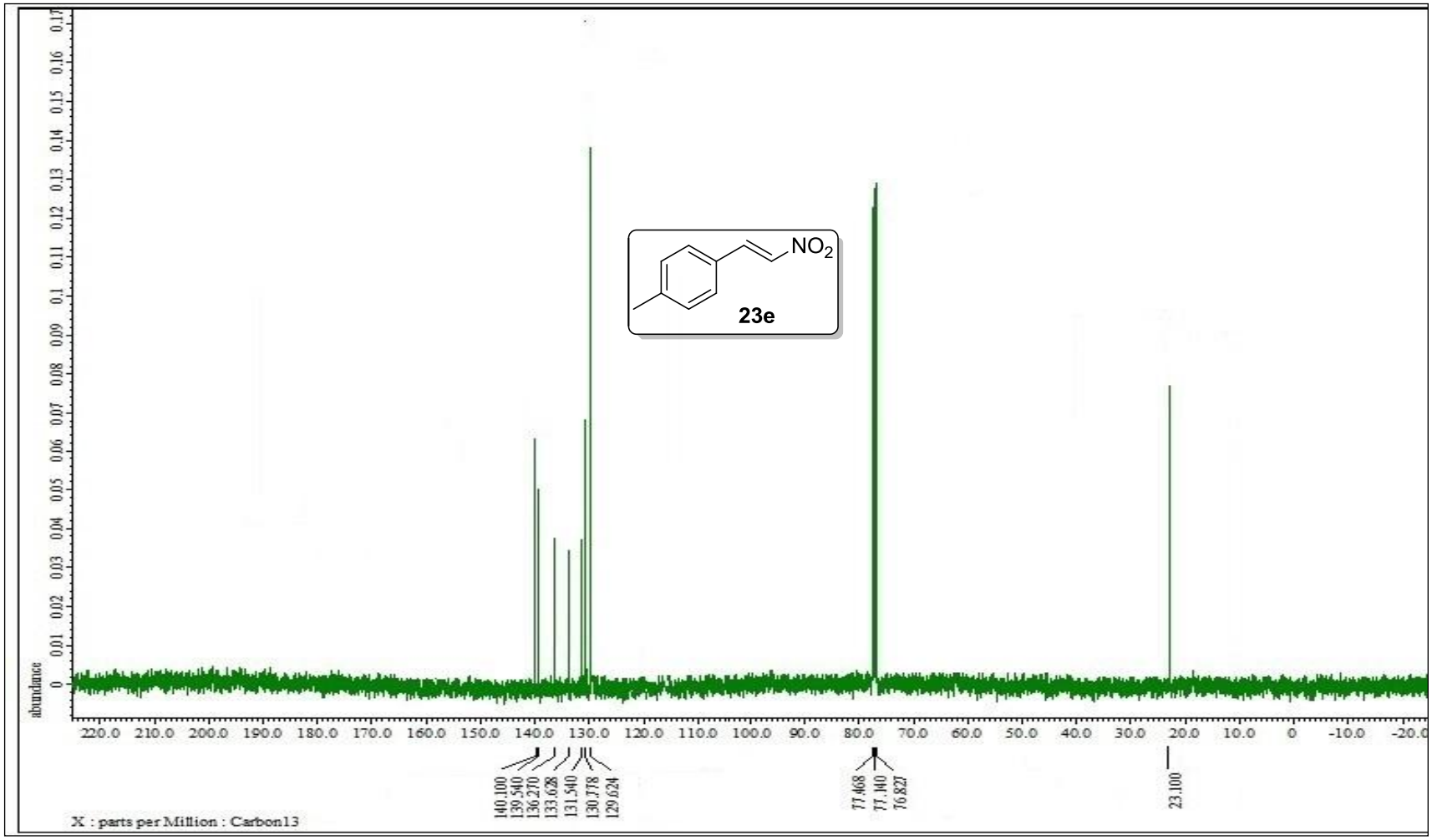


Figure S-113: ^{13}C NMR Spectrum of compound 23e

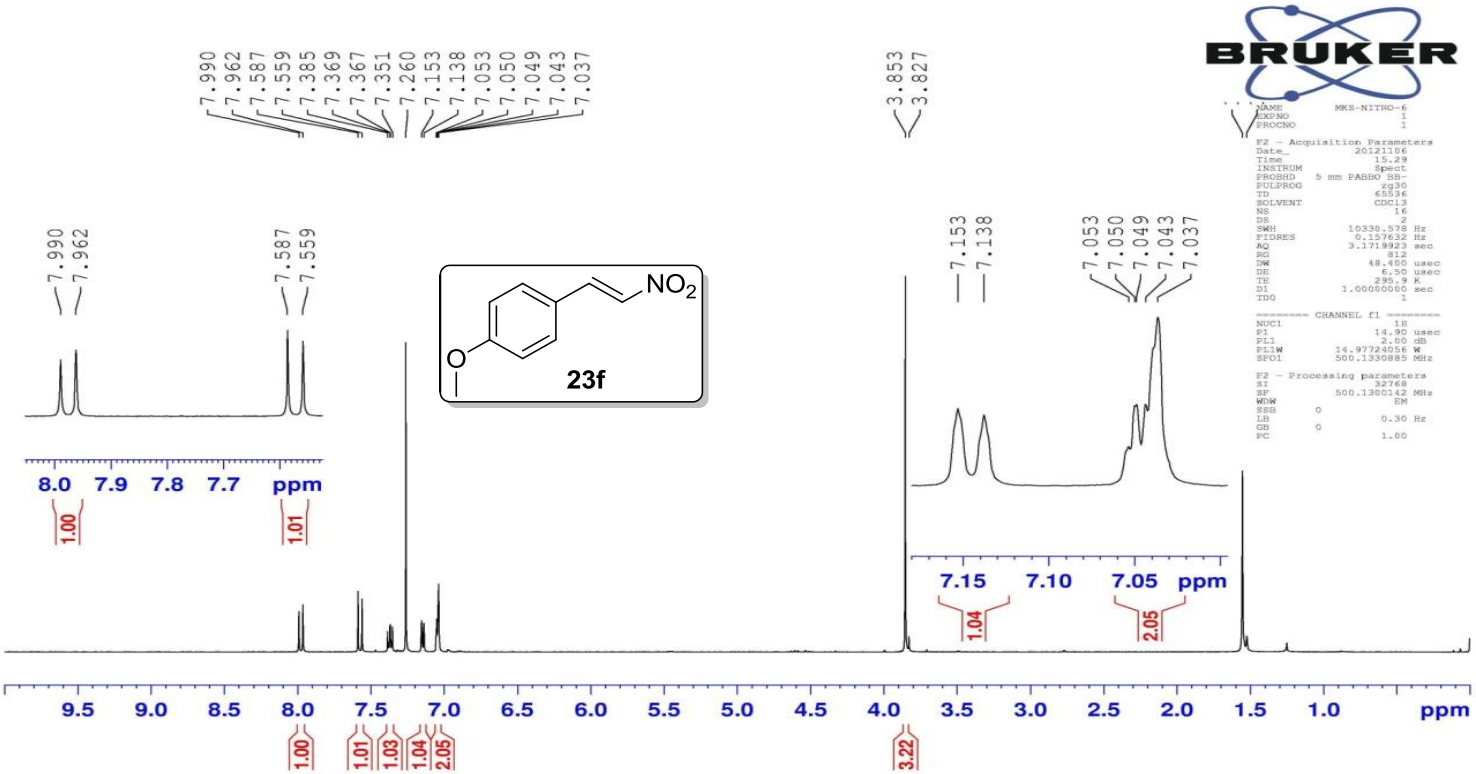


Figure S-114: ^{1}H NMR Spectrum of compound 23f

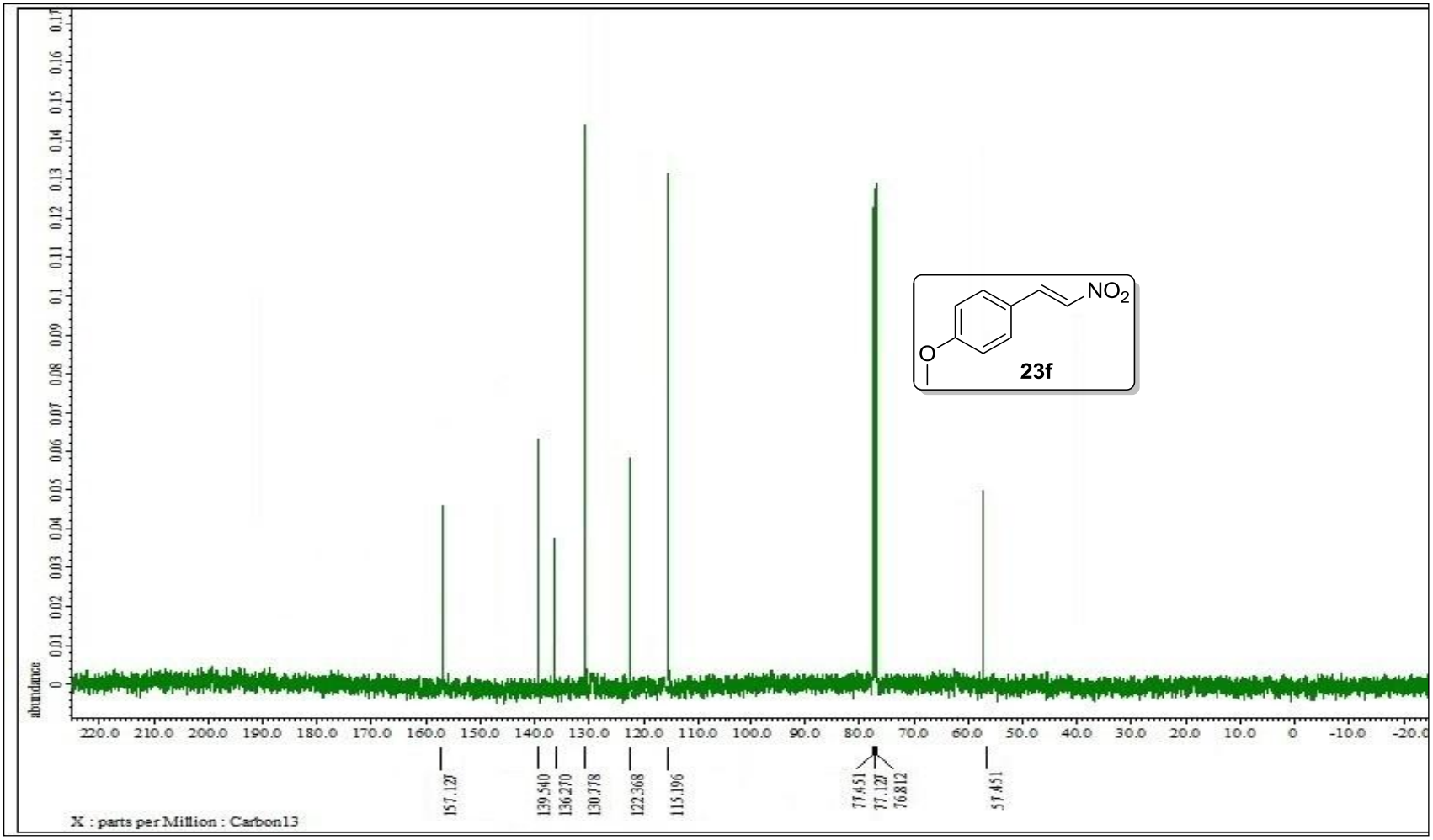


Figure S-115: ^{13}C NMR Spectrum of compound 23f

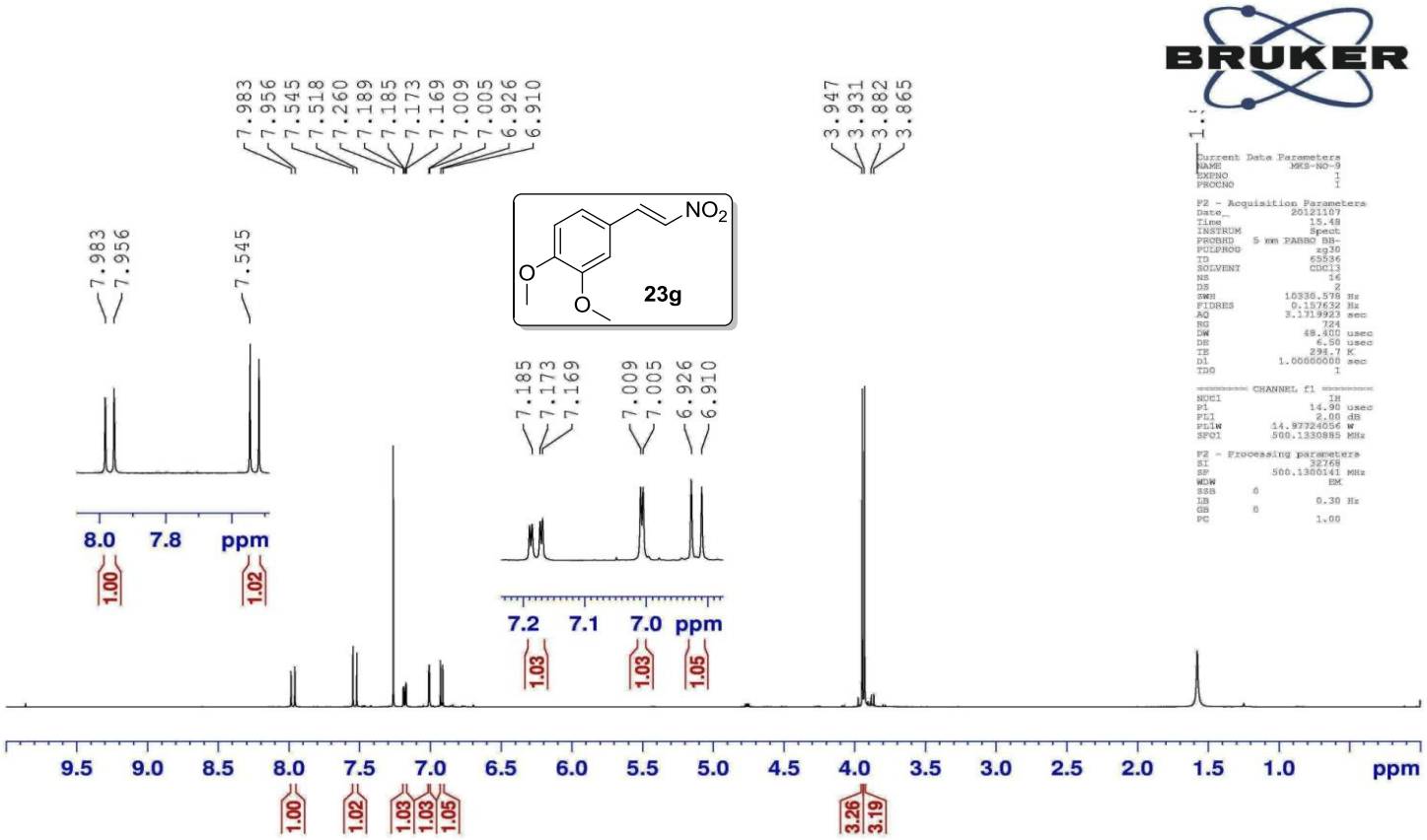


Figure S-116: ^{1}H NMR Spectrum of compound 23g

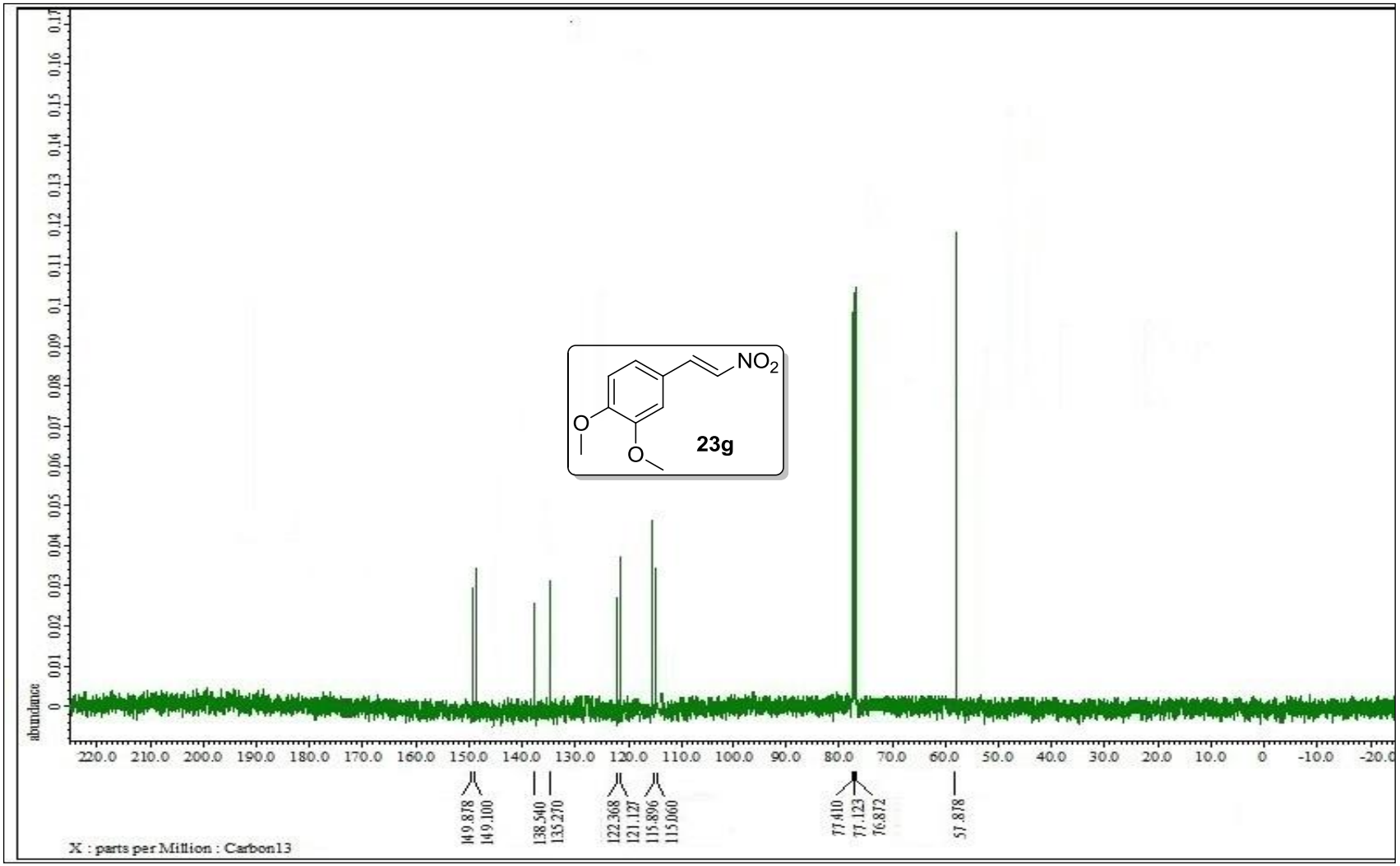


Figure S-117: ^{13}C NMR Spectrum of compound 23g

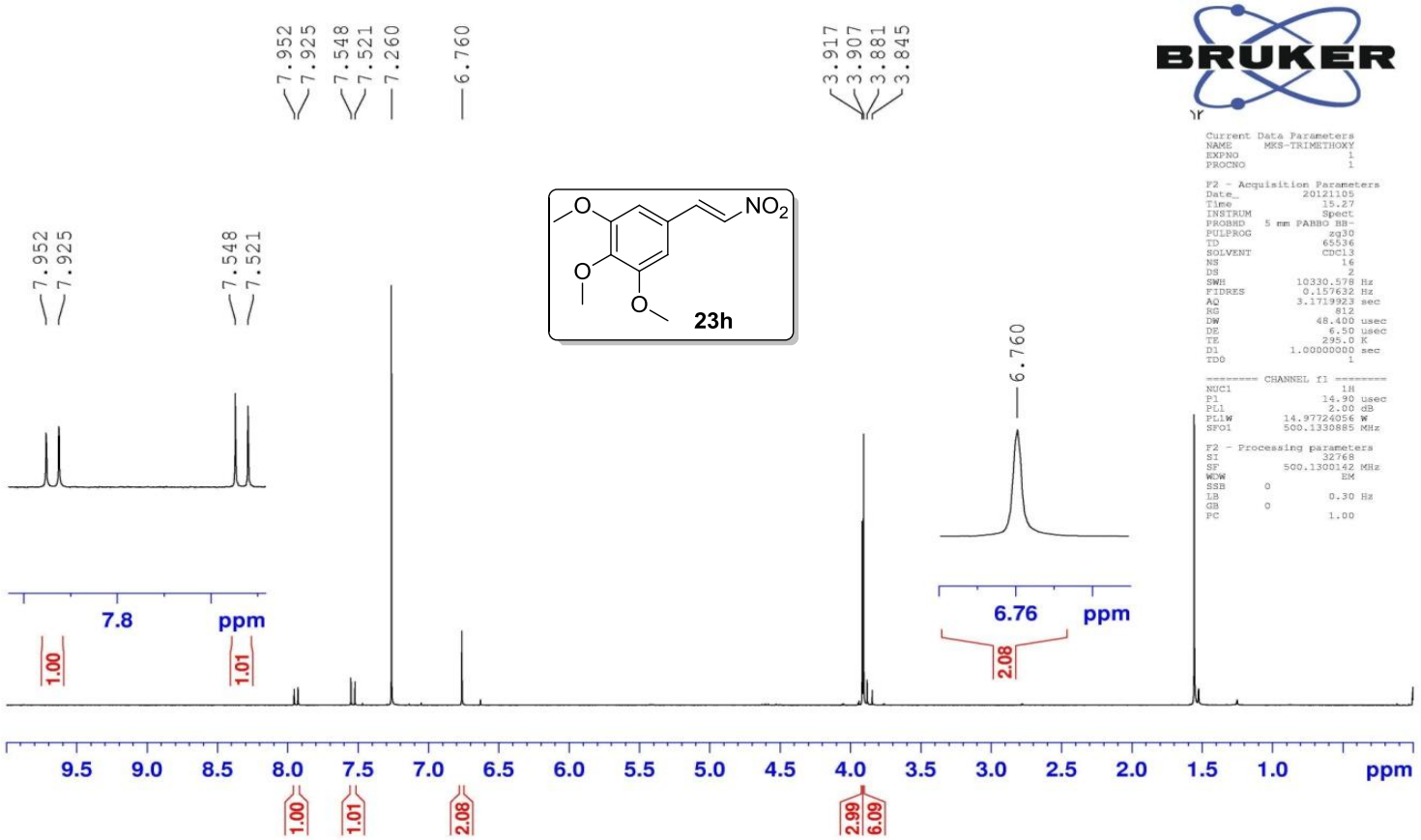


Figure S-118: ^{1}H NMR Spectrum of compound 23h

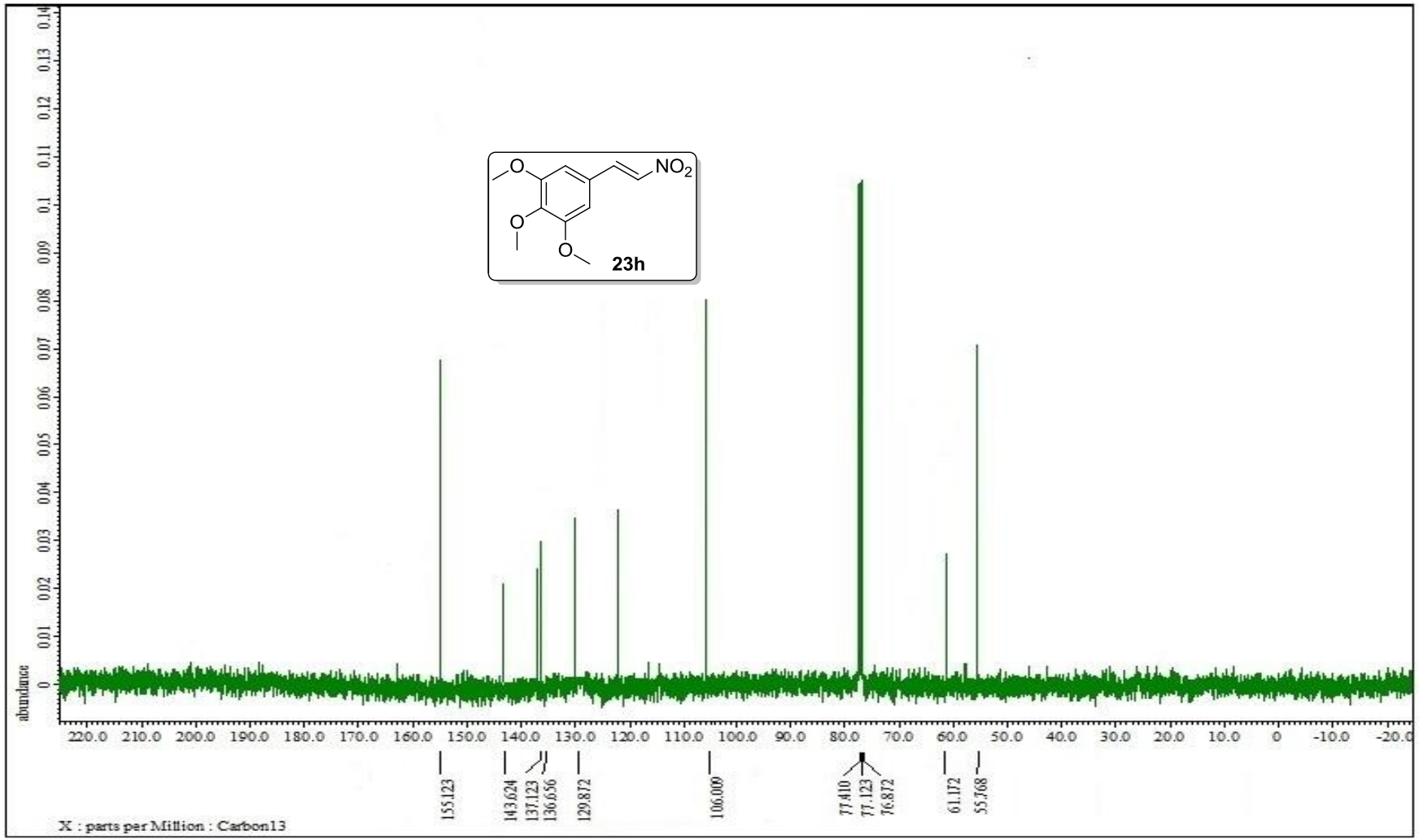


Figure S-119: ^{13}C NMR Spectrum of compound 23h

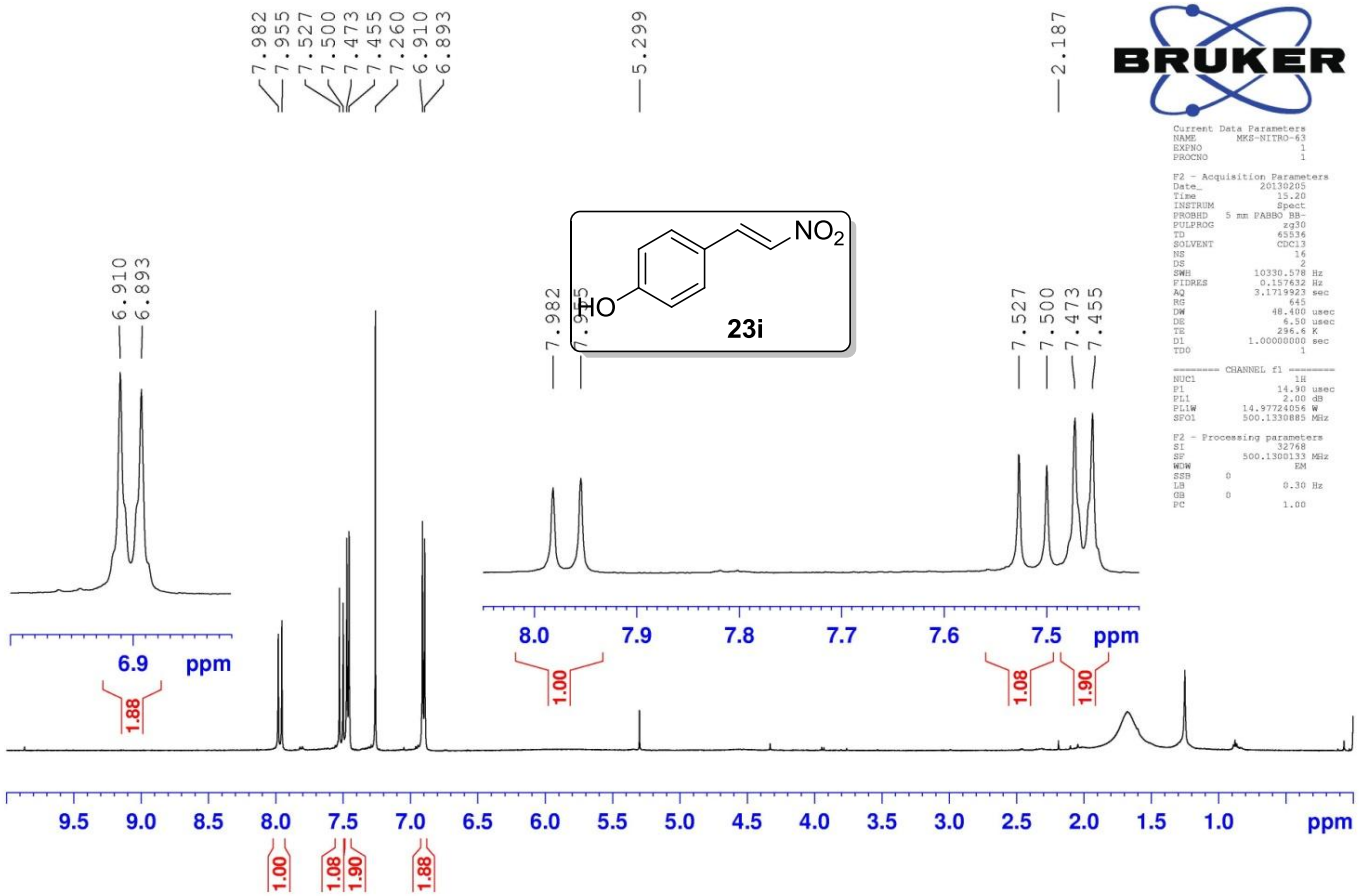


Figure S-120: ^{1}H NMR Spectrum of compound 23i

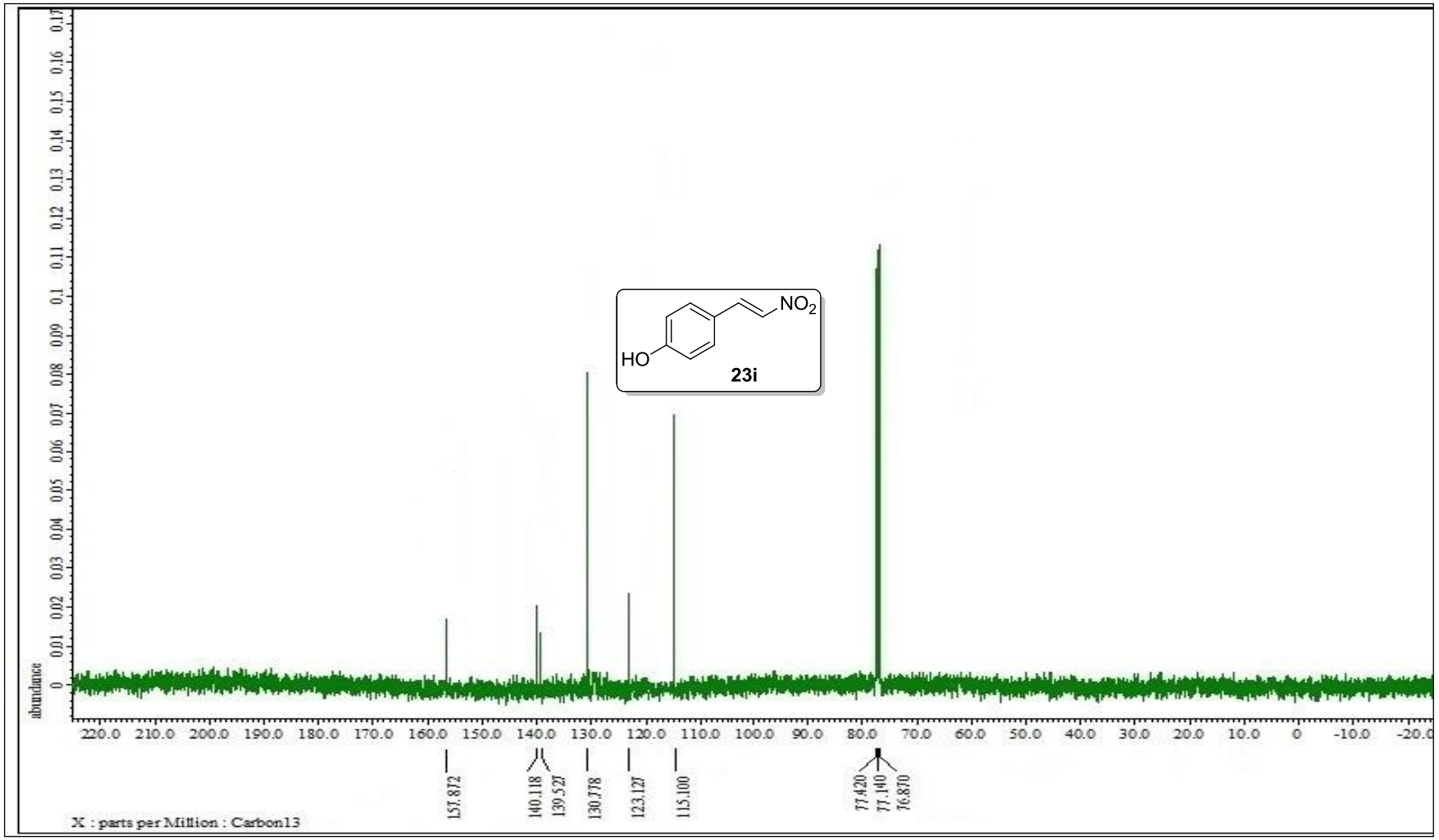


Figure S-121: ^{13}C NMR Spectrum of compound 23i

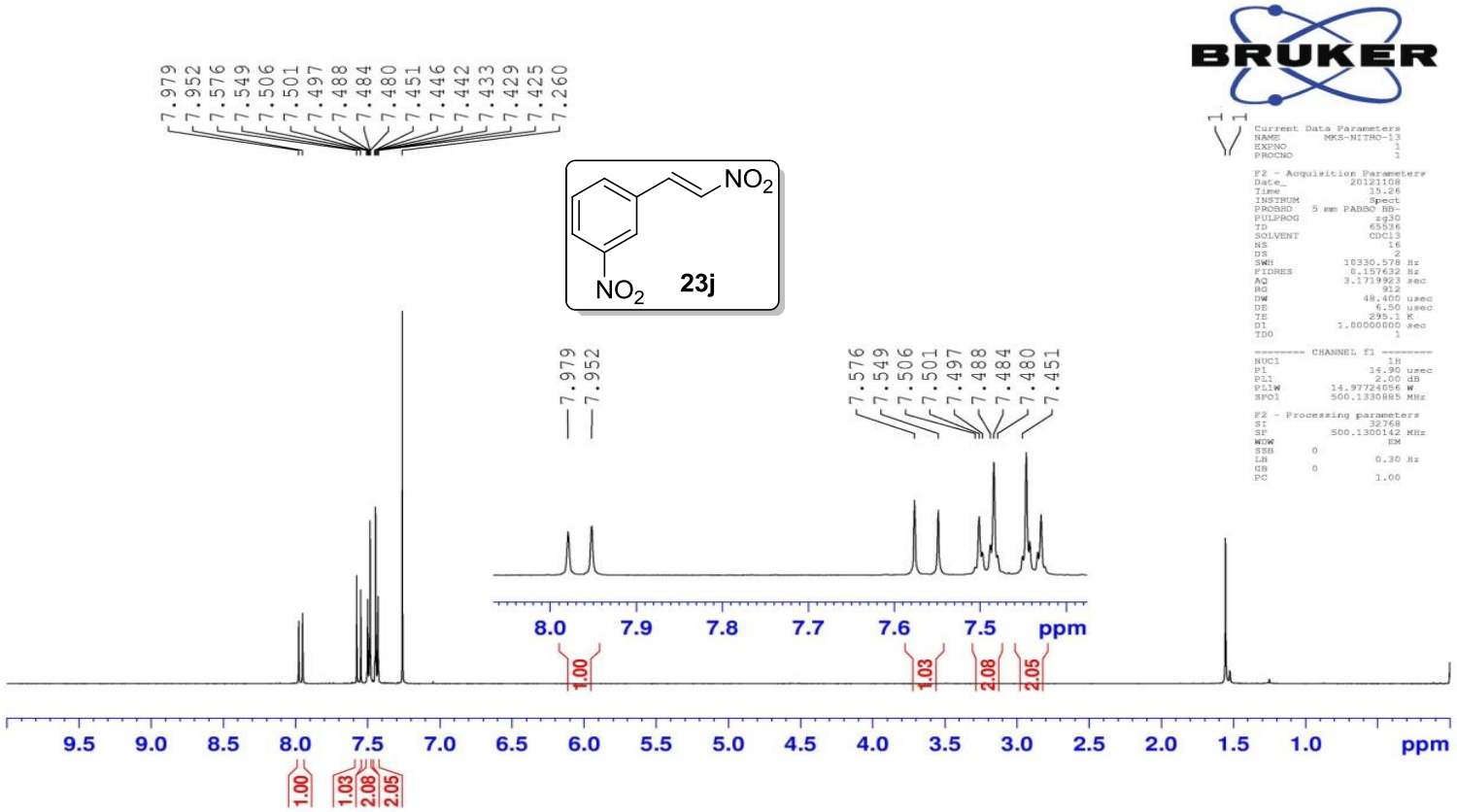


Figure S-122: ^{1}H NMR Spectrum of compound 23j

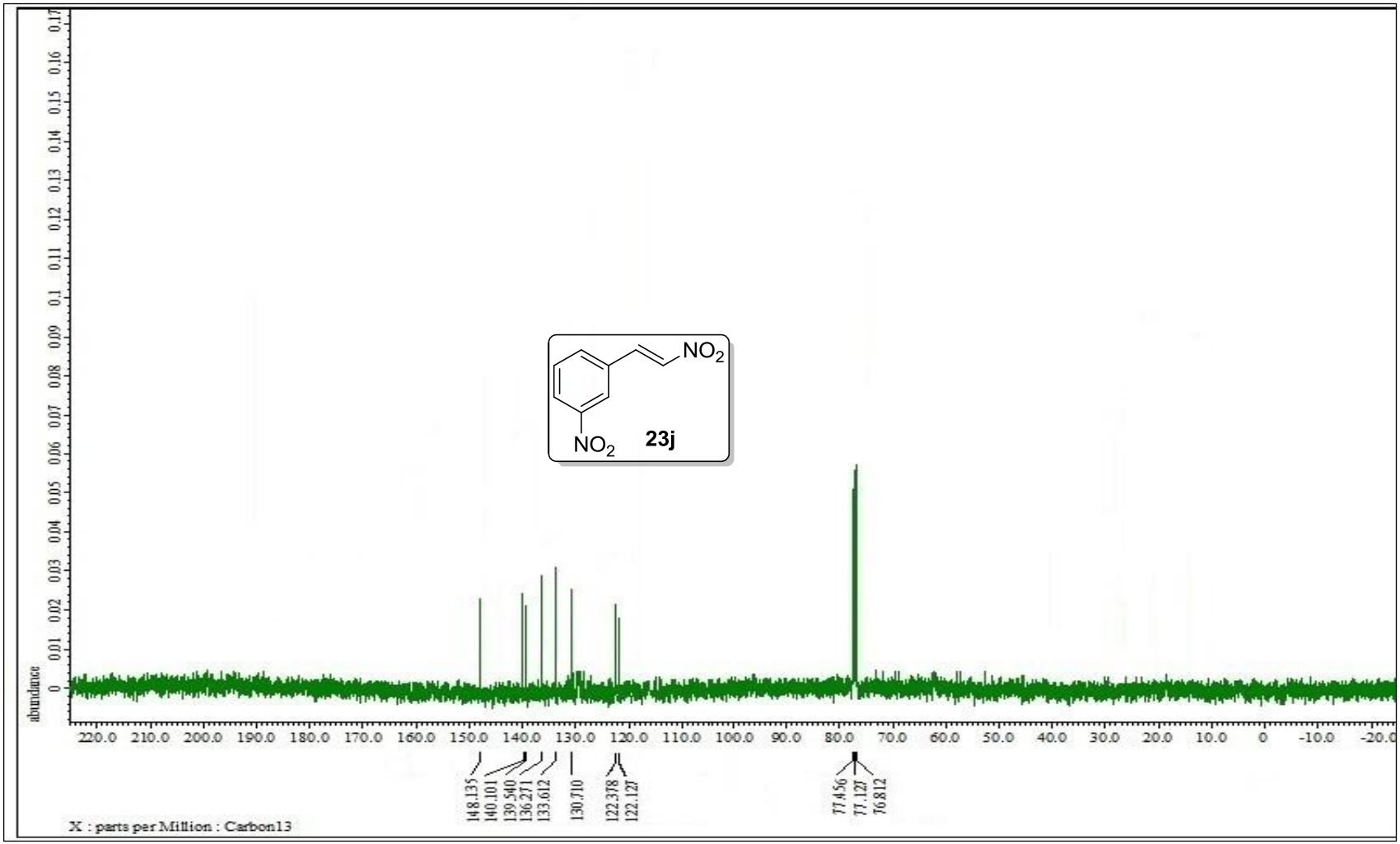


Figure S-123: ^{13}C NMR Spectrum of compound 23j

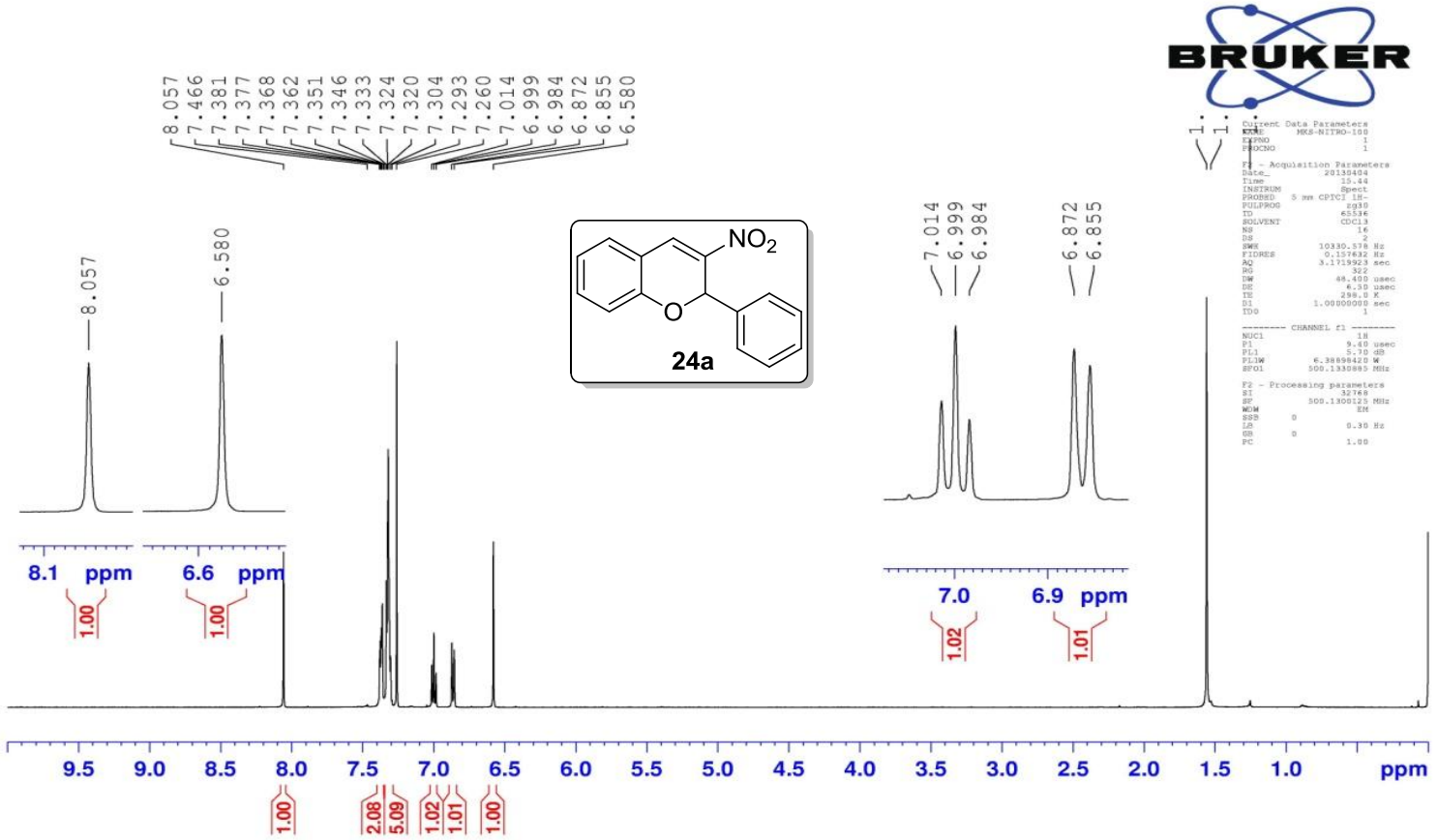


Figure S-124: ^{1}H NMR Spectrum of compound 24a

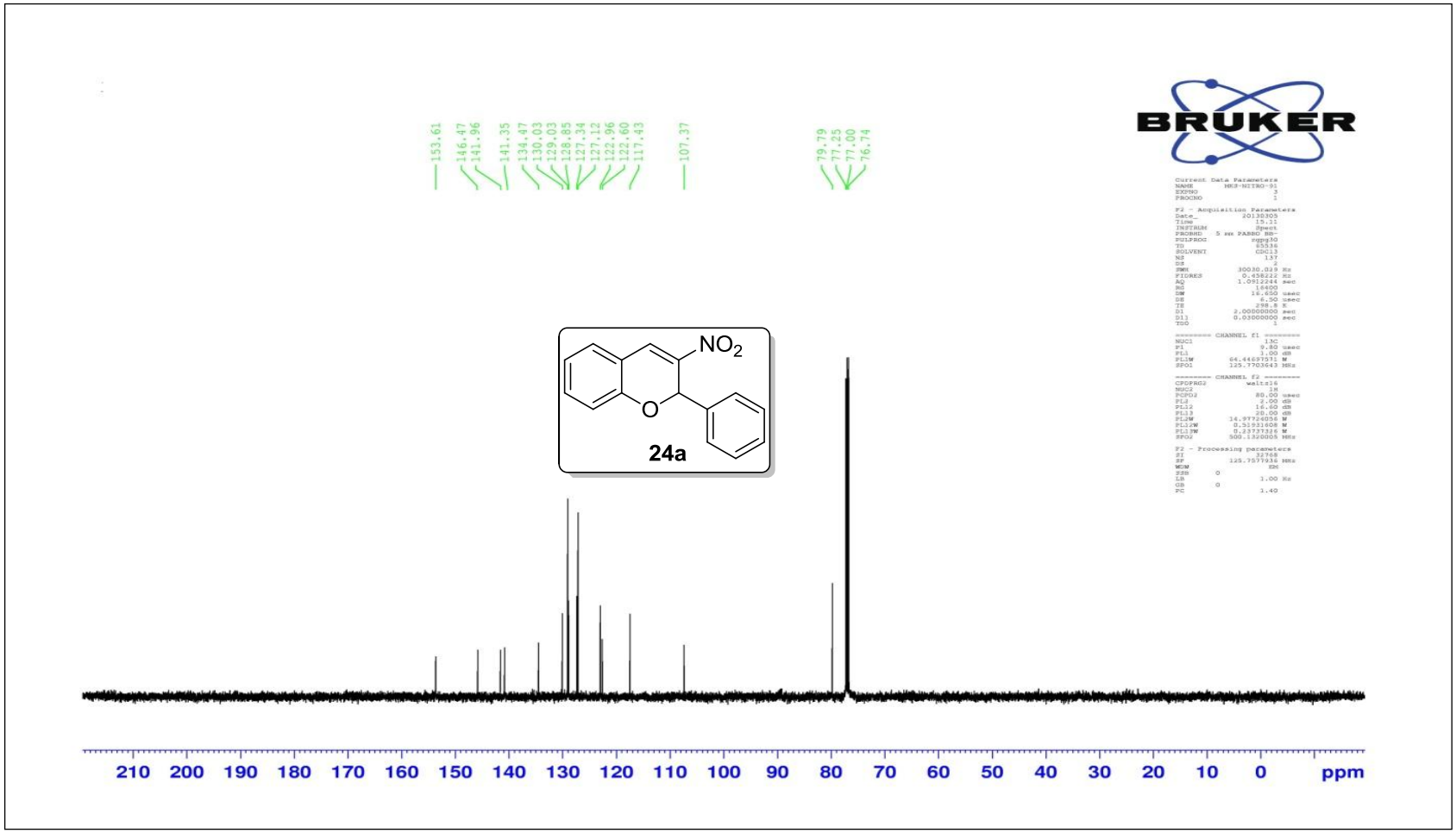


Figure S-125: ^{13}C NMR Spectrum of compound 24a

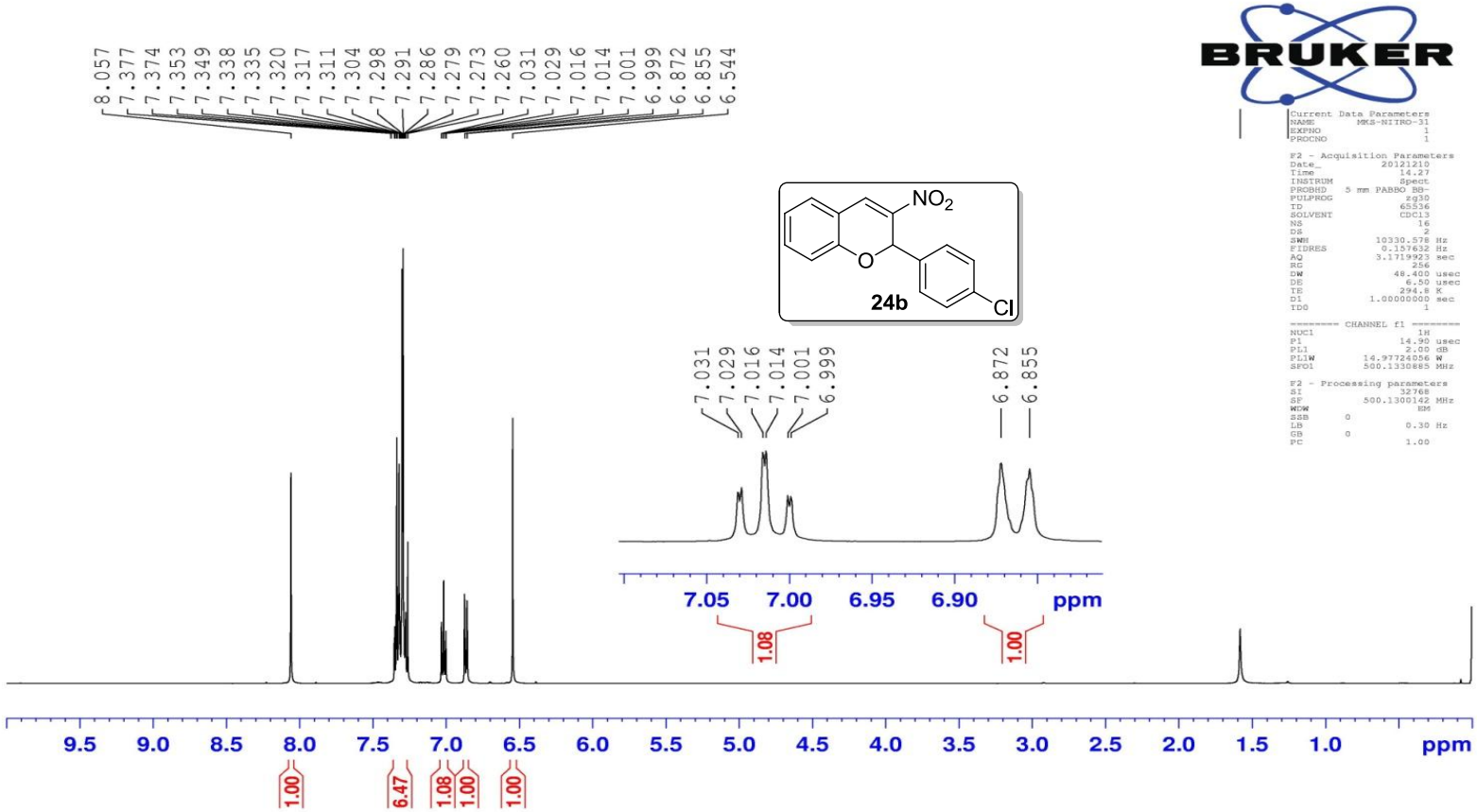


Figure S-126: ^{1}H NMR Spectrum of compound 24b

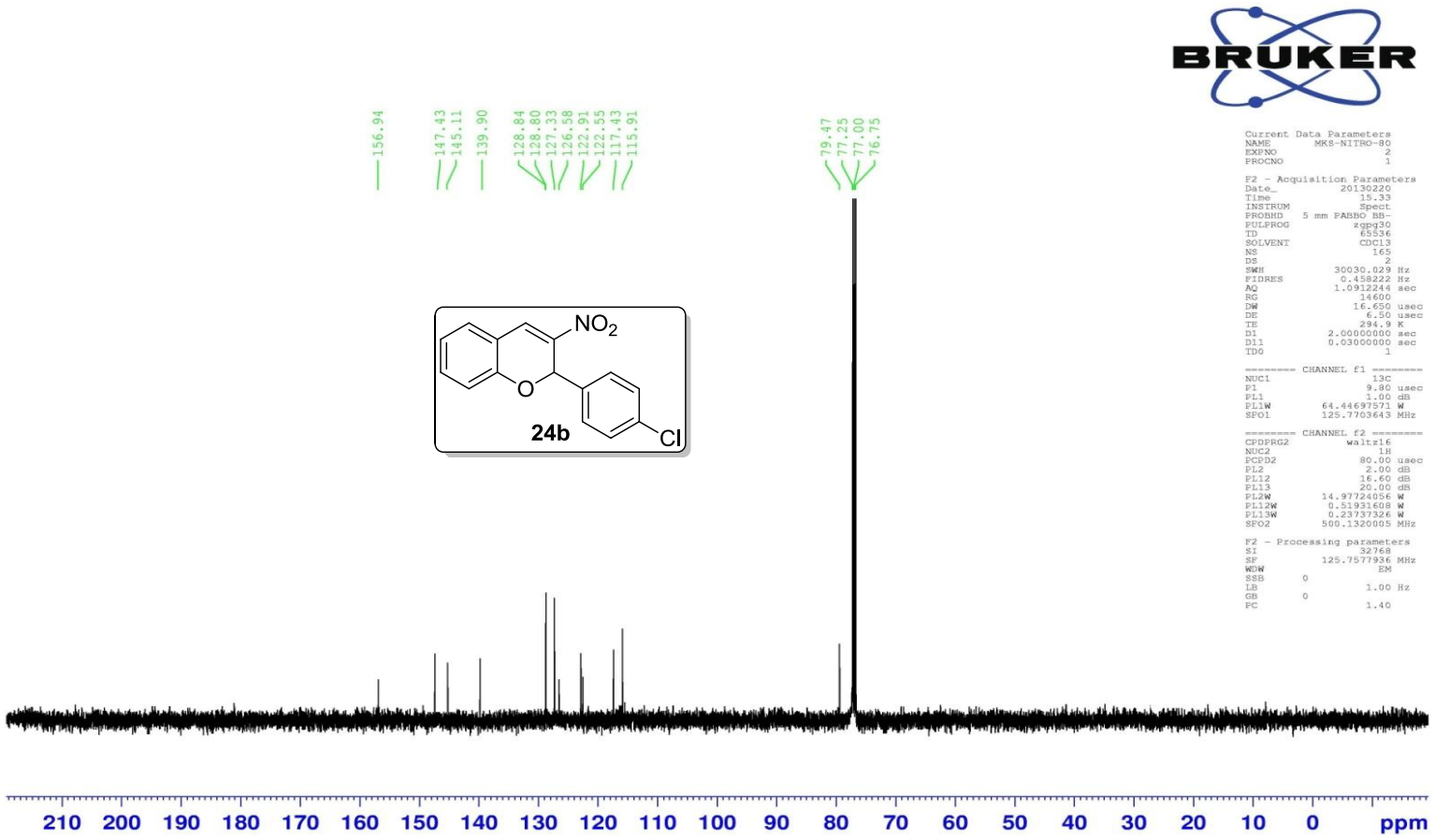


Figure S-127: ^{13}C NMR Spectrum of compound 24b

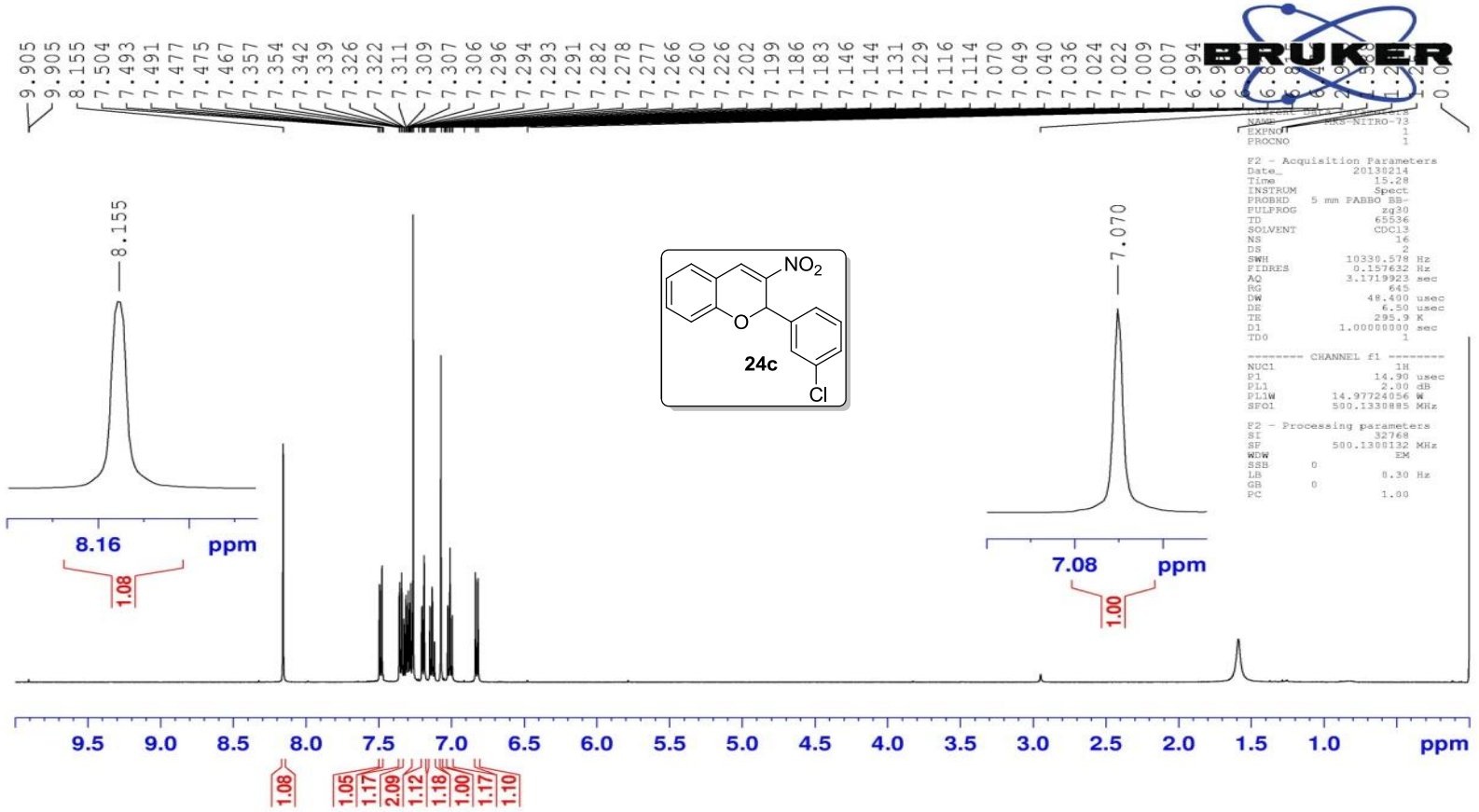


Figure S-128: ^{1}H NMR Spectrum of compound 24c

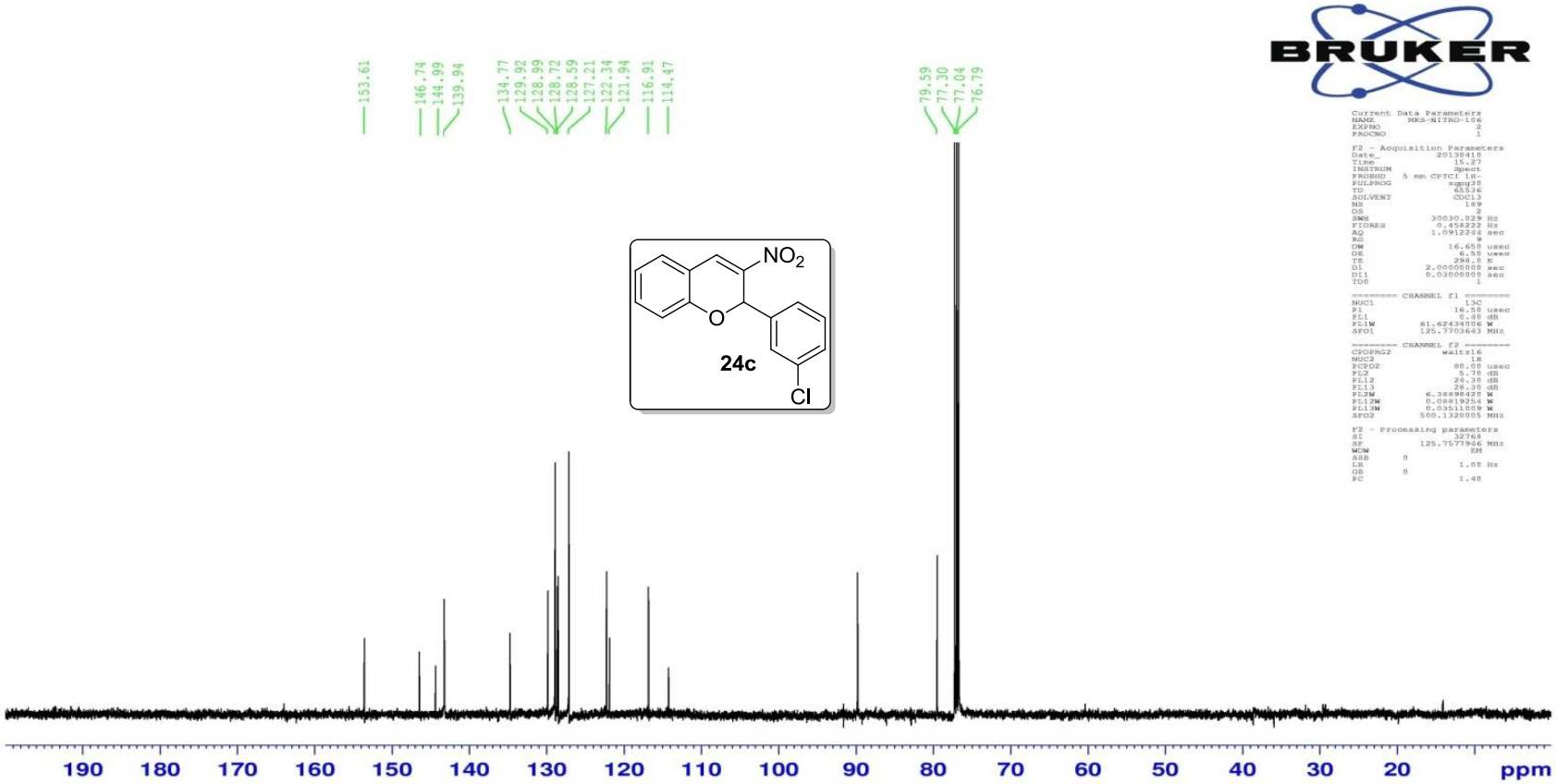


Figure S-129: ^{13}C NMR Spectrum of compound 24c

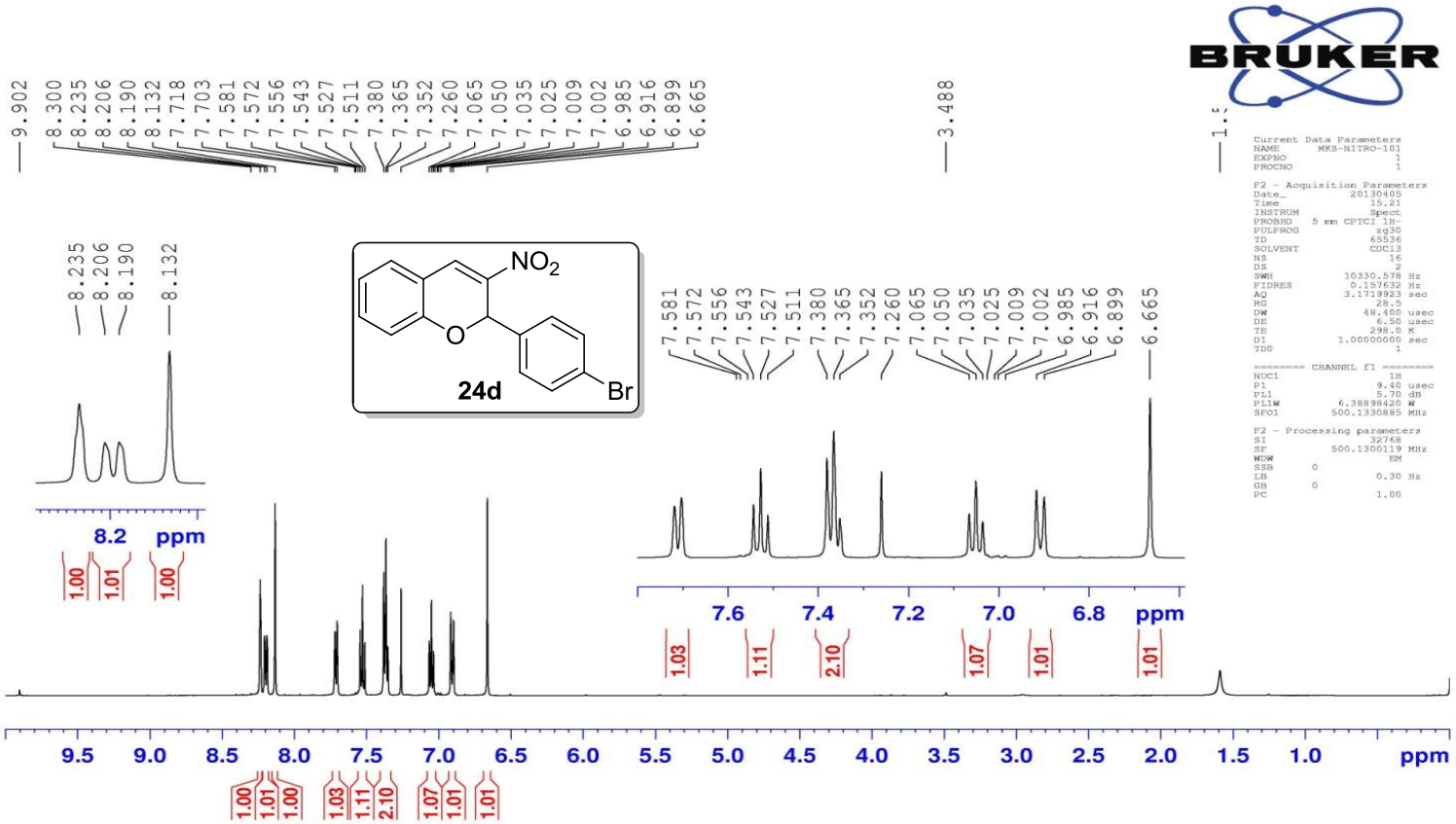


Figure S-130: ^{1}H NMR Spectrum of compound 24d

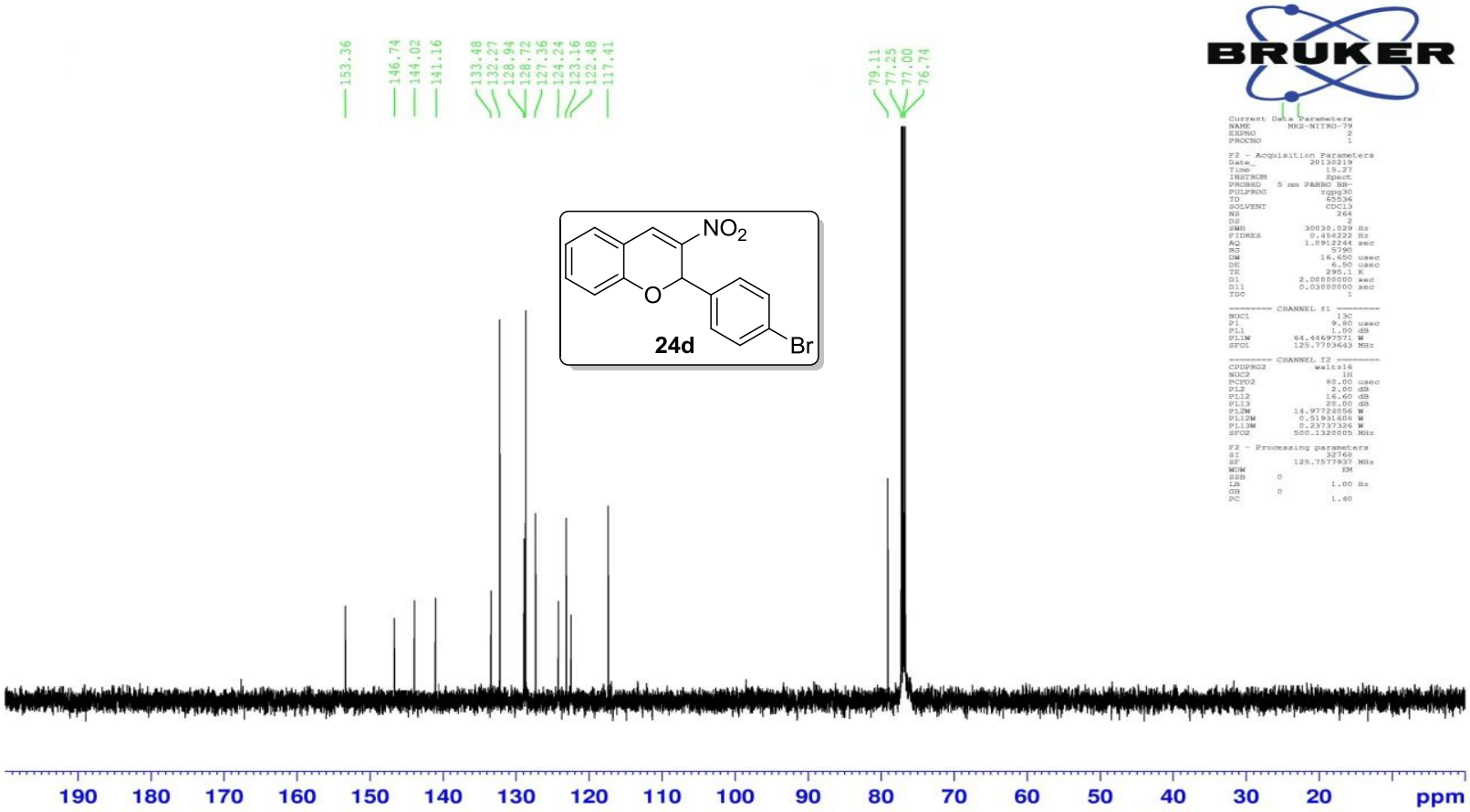


Figure S-131: ^{13}C NMR Spectrum of compound 24d

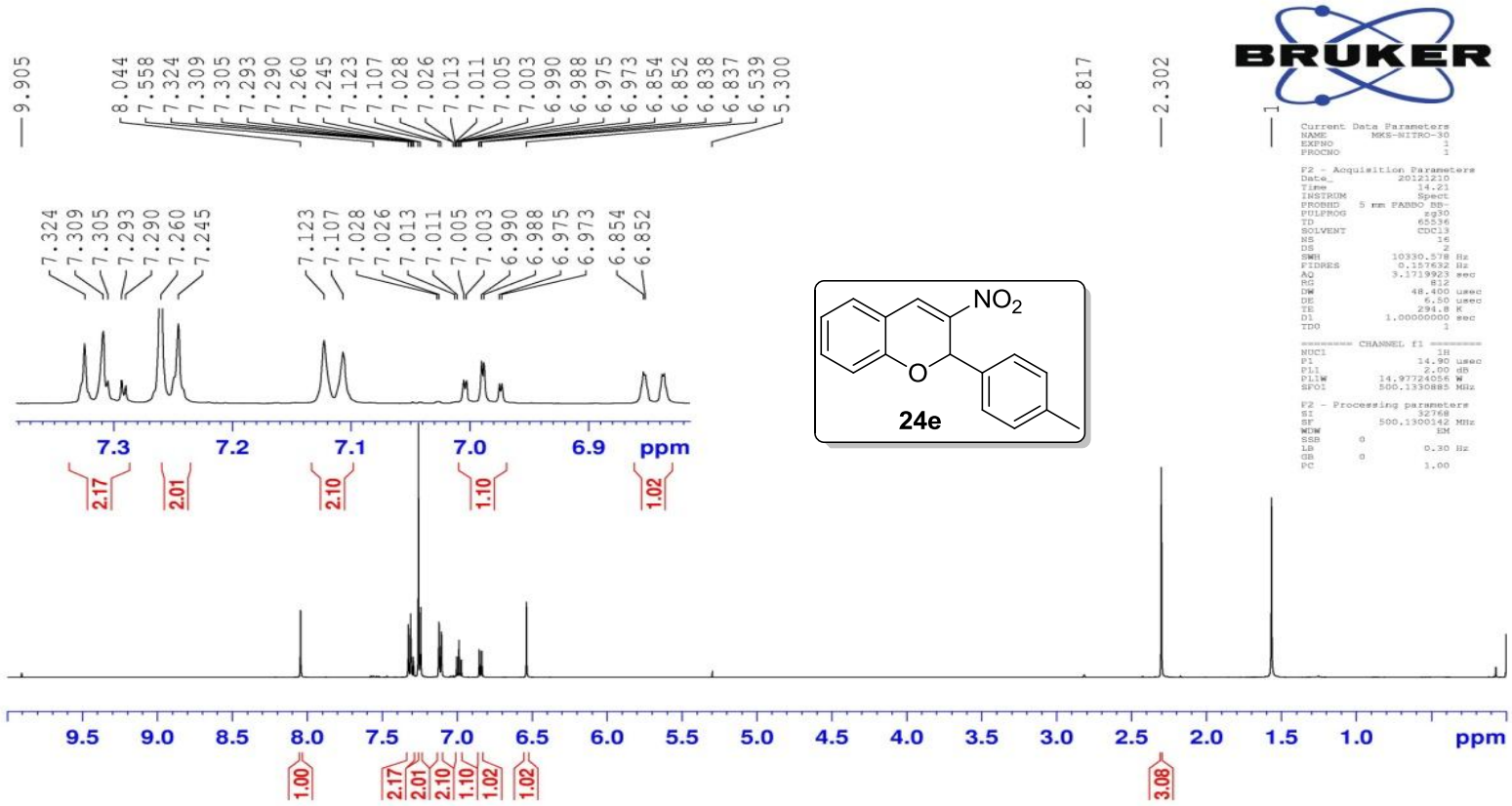


Figure S-132: ^{1}H NMR Spectrum of compound 24e

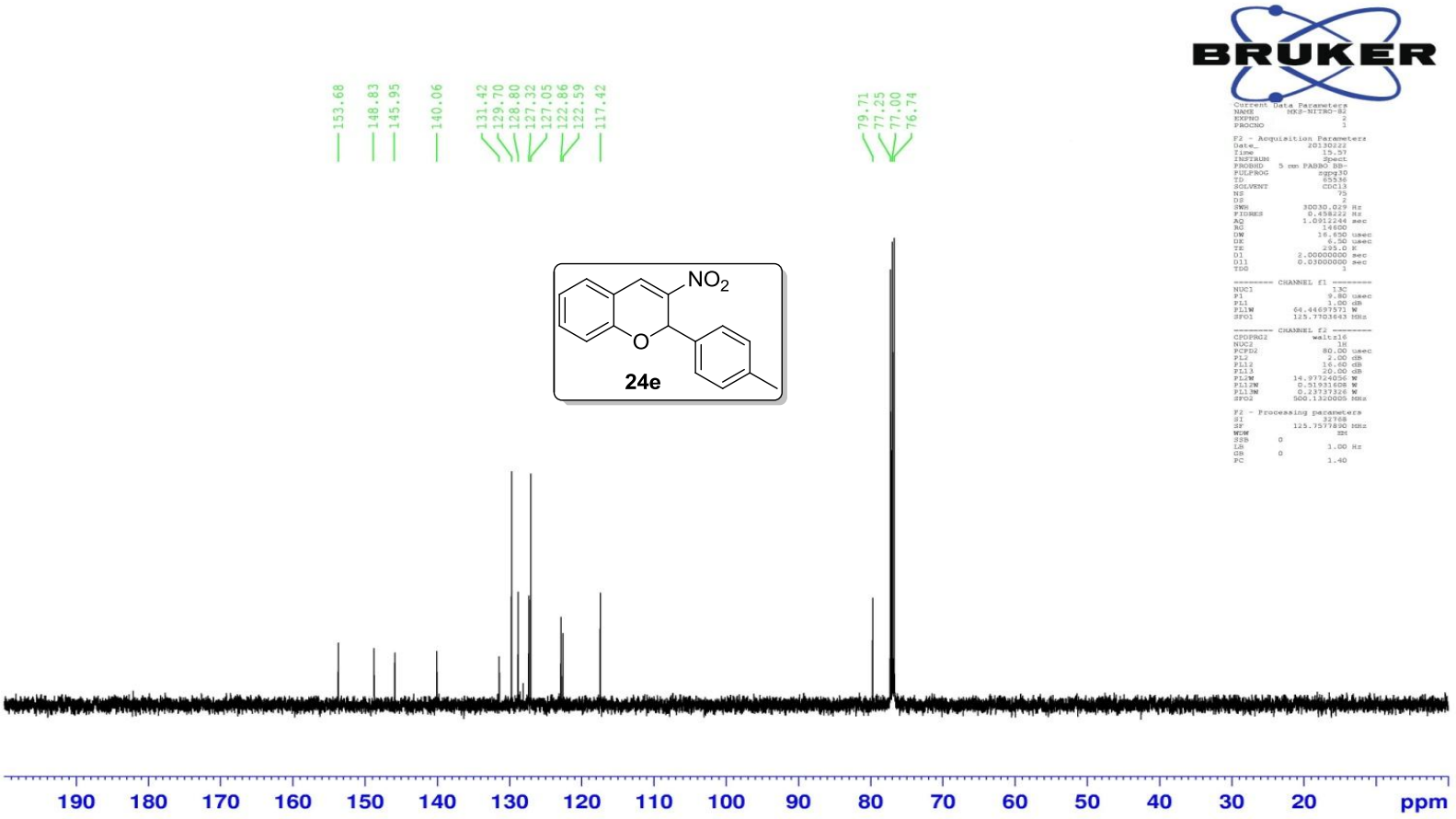


Figure S-133: ^{13}C NMR Spectrum of compound 24e

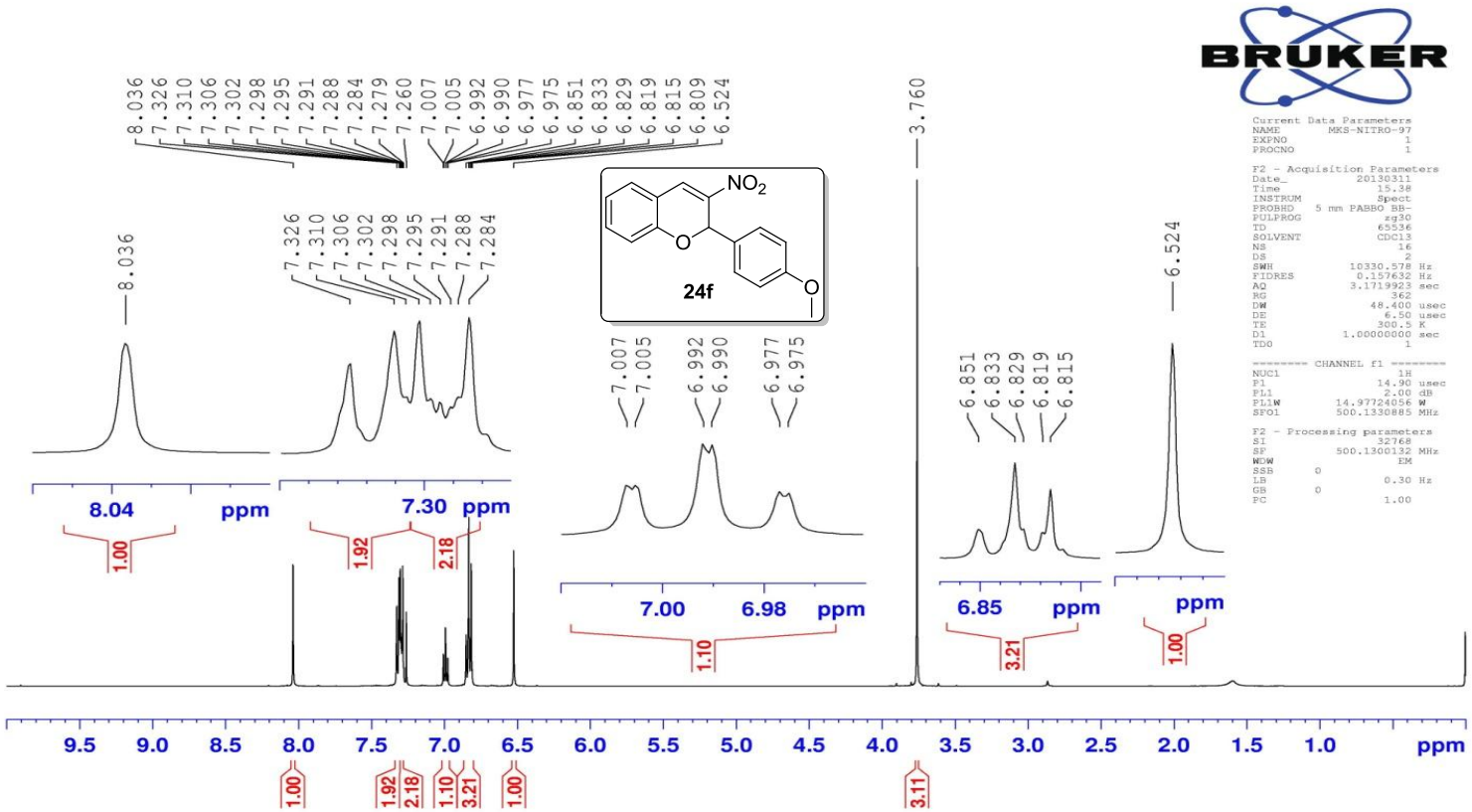


Figure S-134: ^{1}H NMR Spectrum of compound 24f

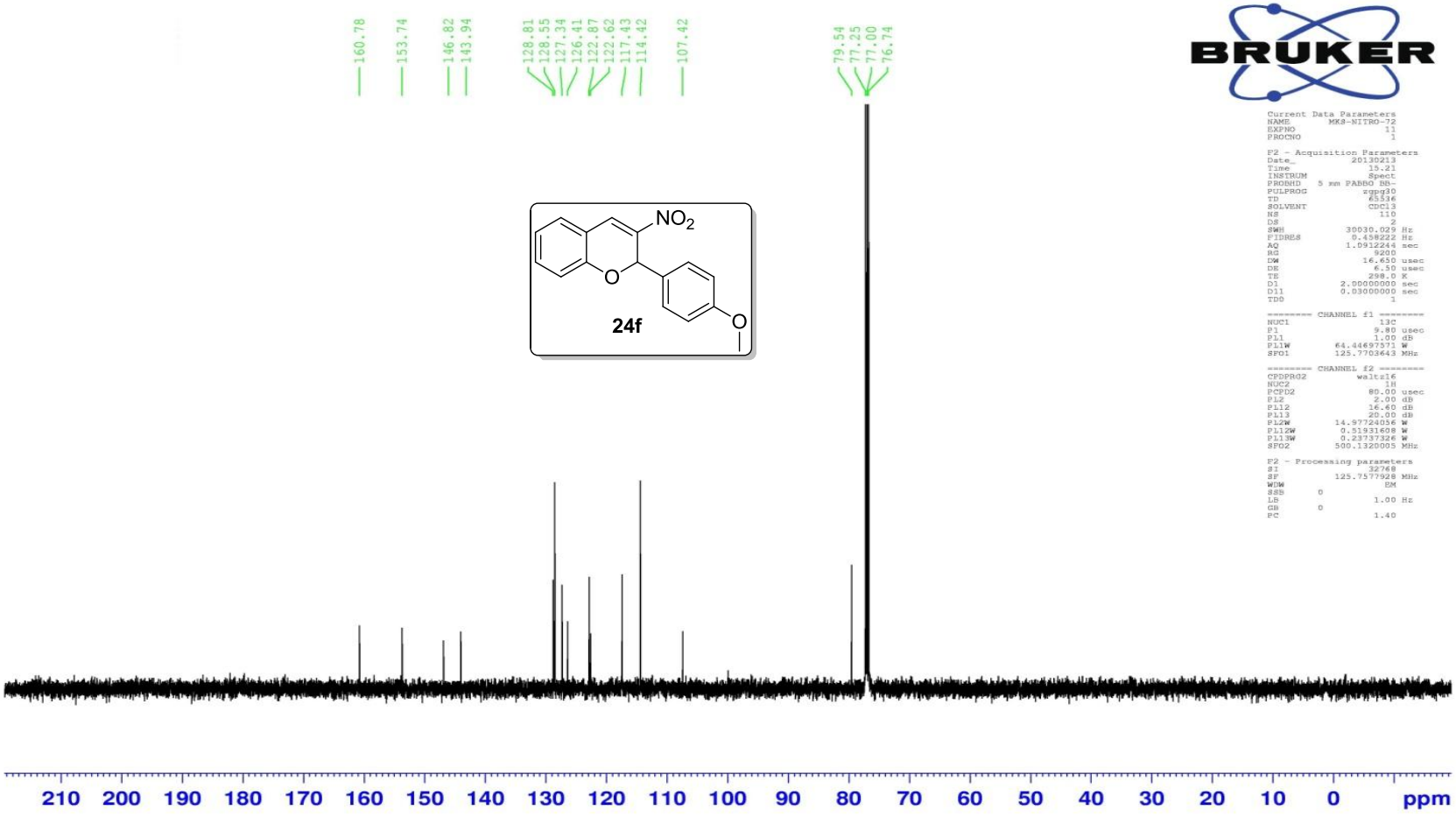


Figure S-135: ^{13}C NMR Spectrum of compound 24f

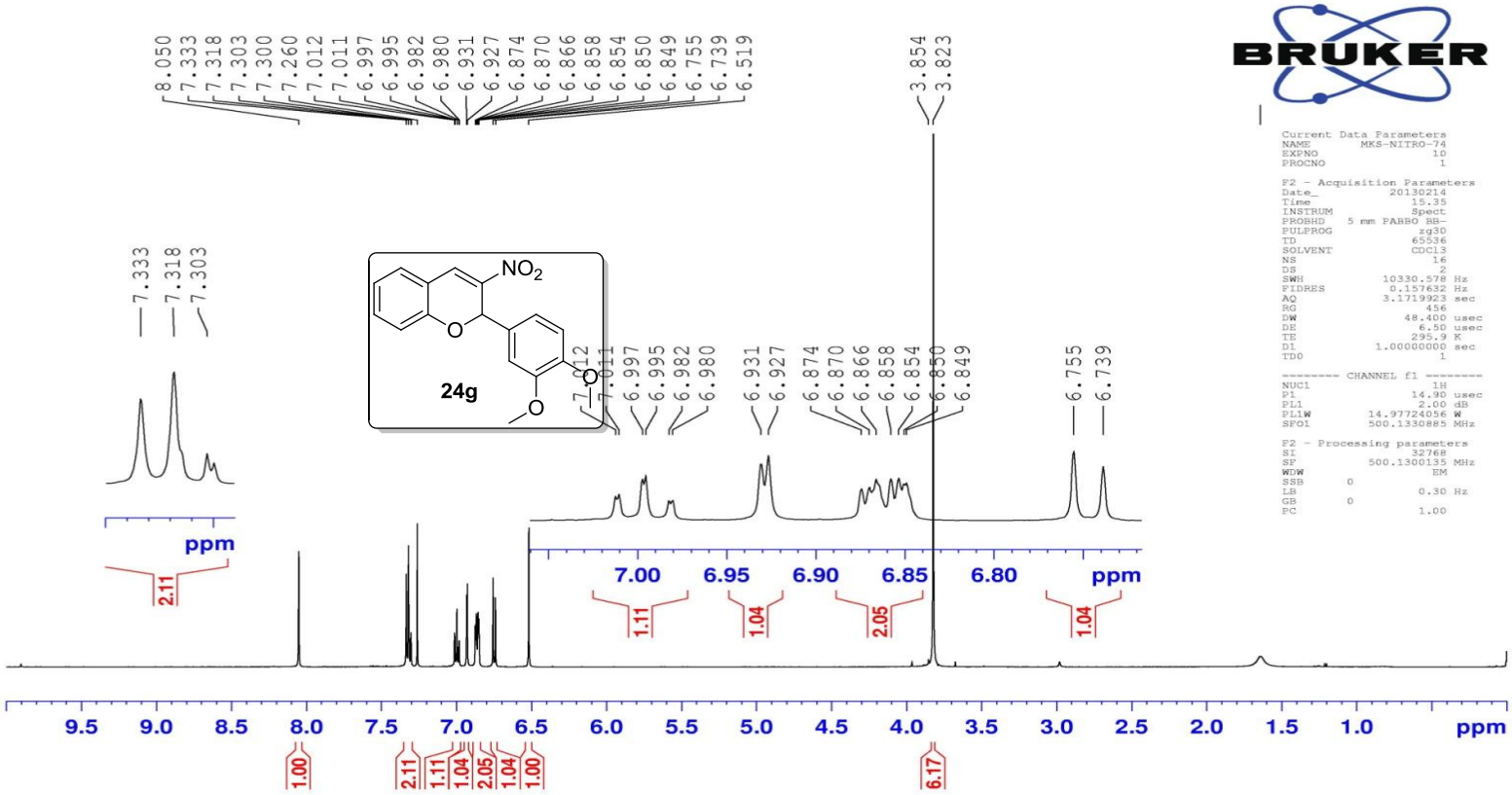


Figure S-136: ^{1}H NMR Spectrum of compound 24g

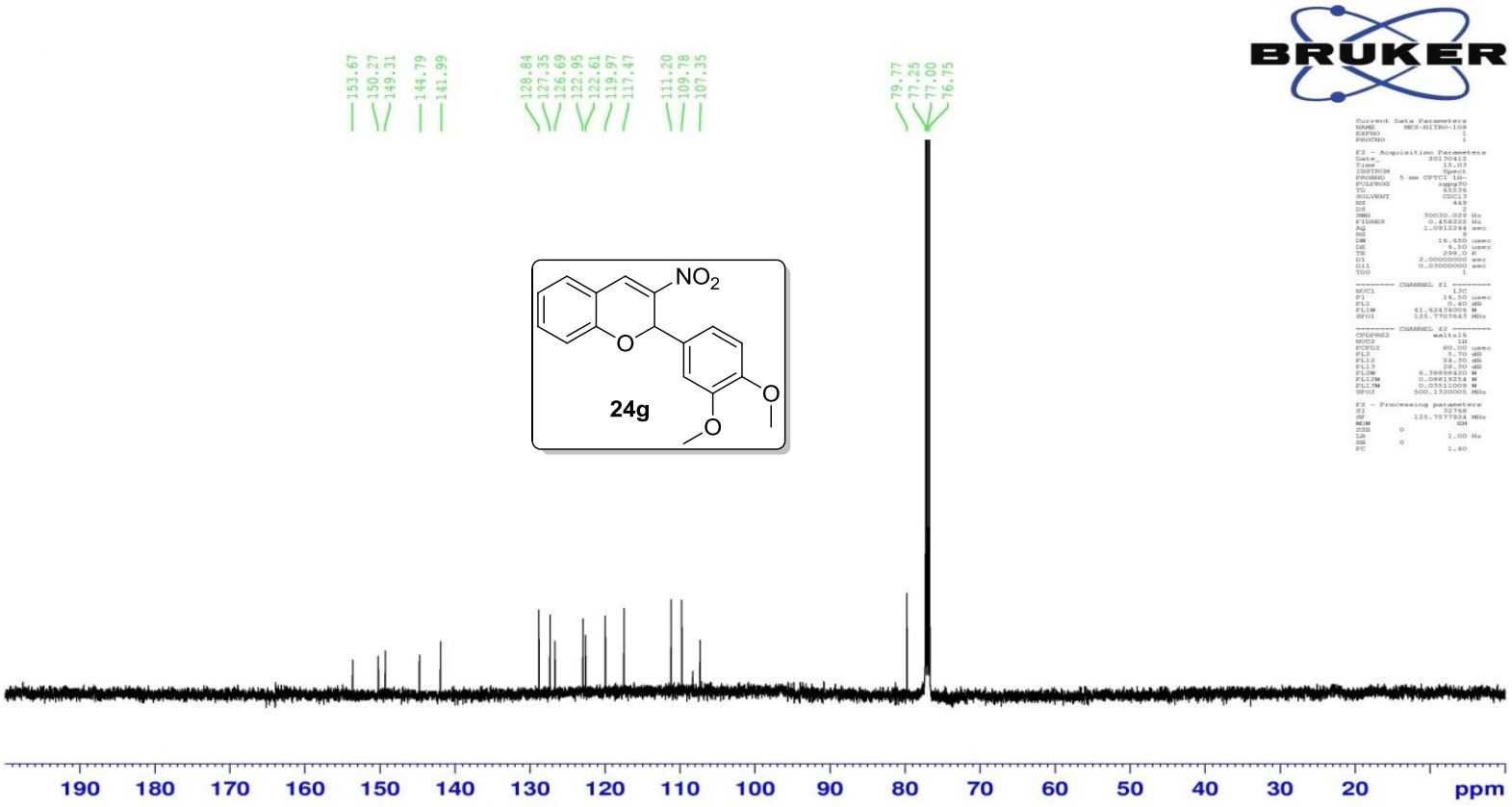


Figure S-137: ^{13}C NMR Spectrum of compound 24g

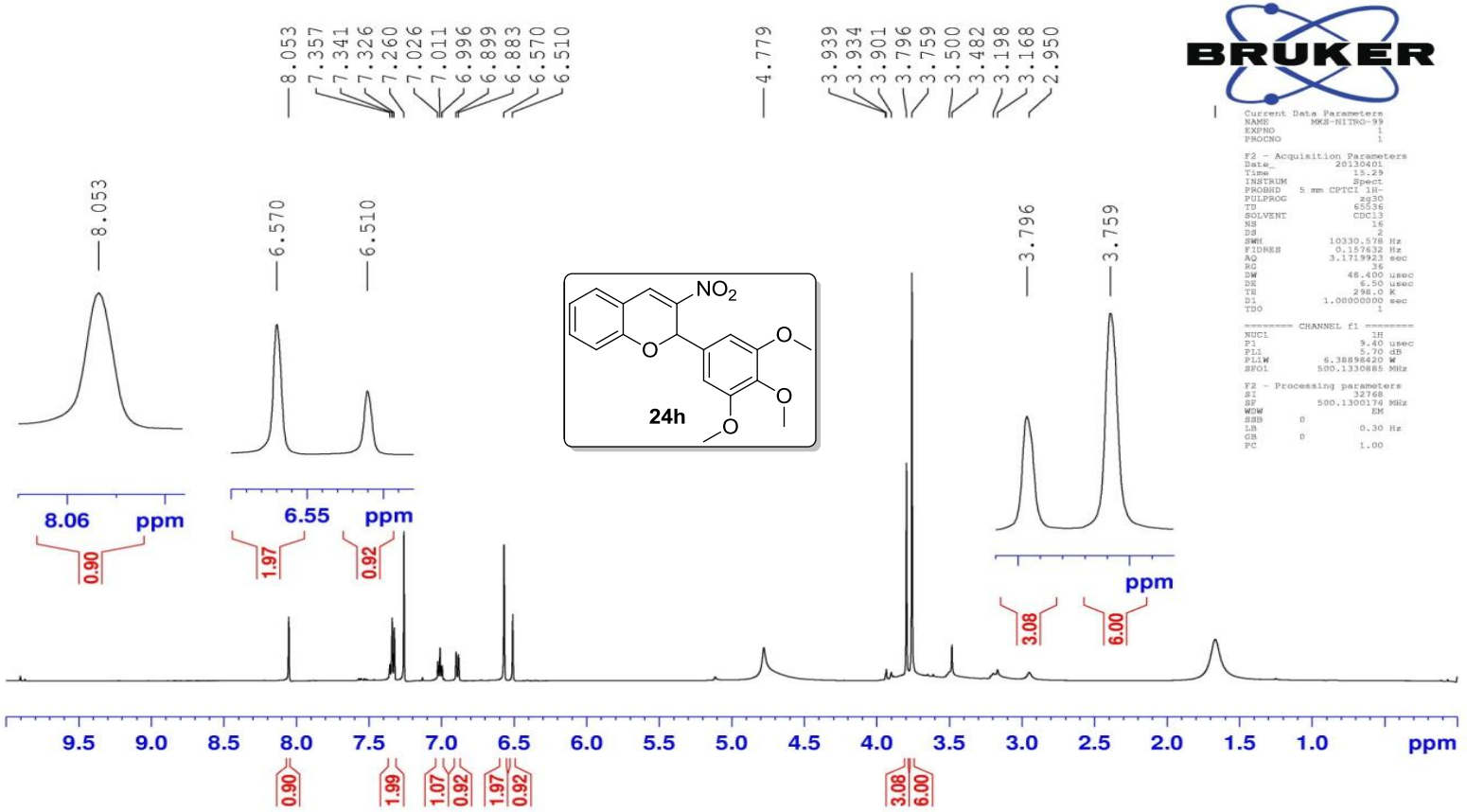


Figure S-138: ^{1}H NMR Spectrum of compound 24h

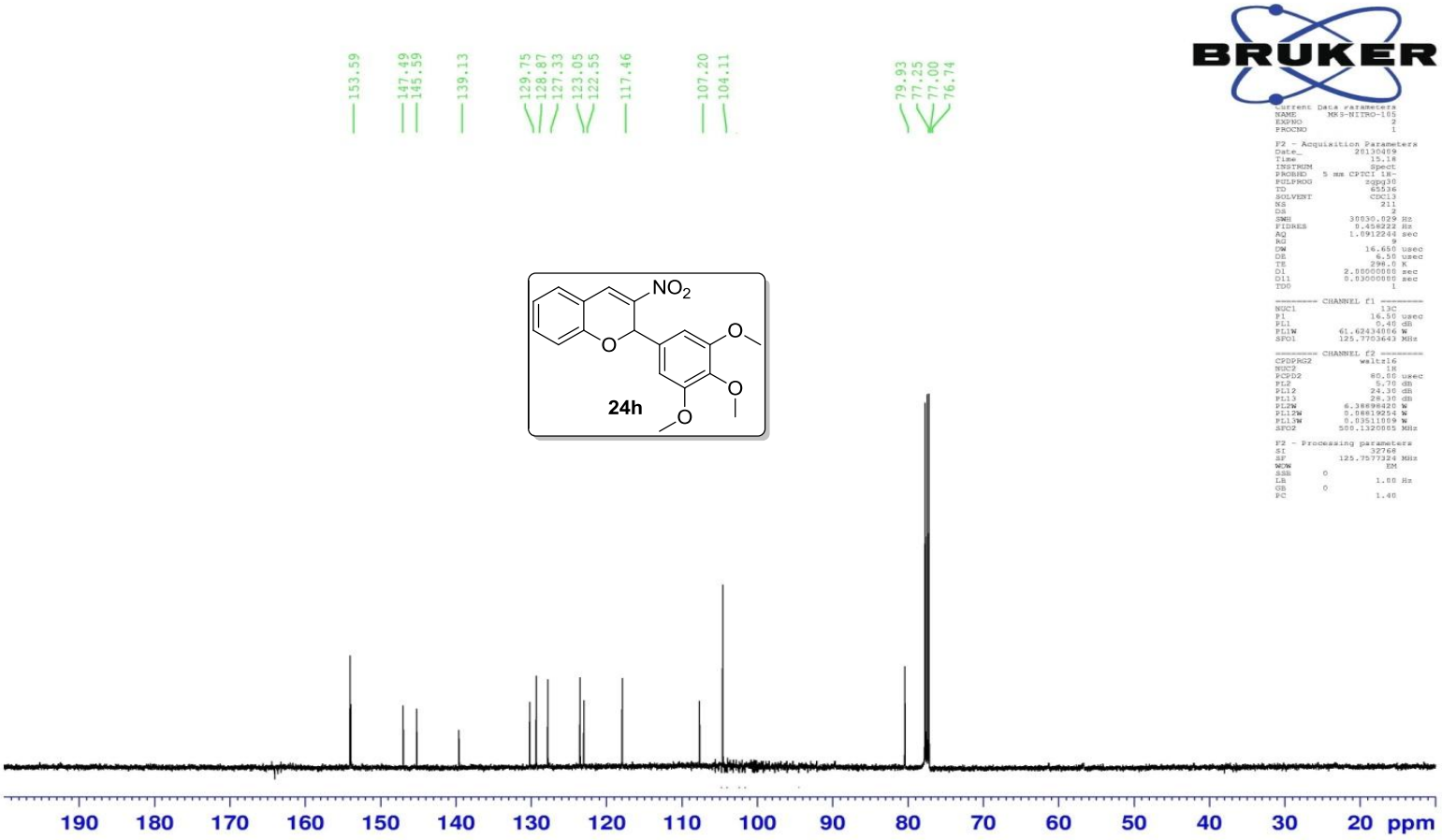


Figure S-139: ^{13}C NMR Spectrum of compound 24h

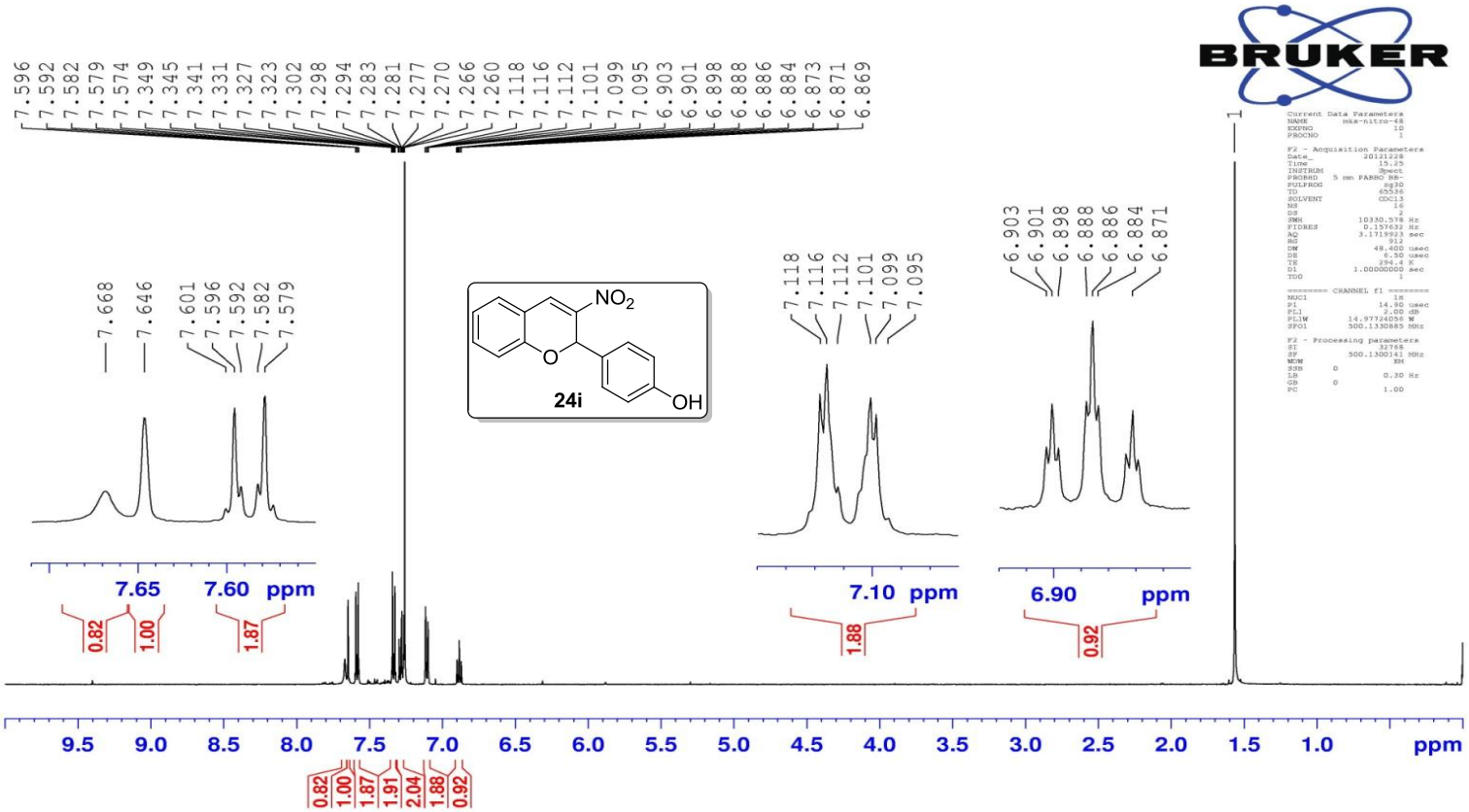


Figure S-140: ^{1}H NMR Spectrum of compound 24i

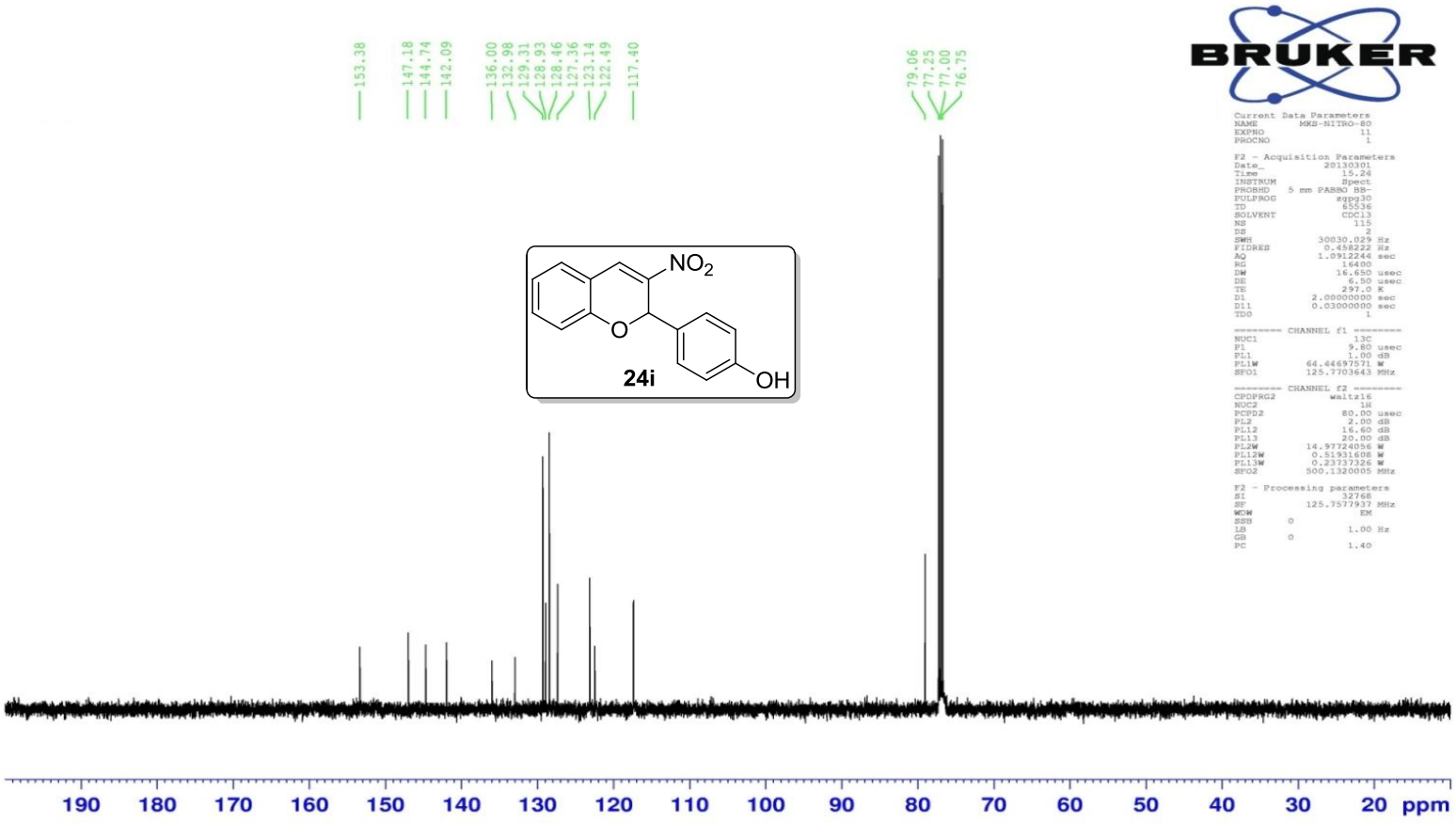


Figure S-141: ^{13}C NMR Spectrum of compound 24i

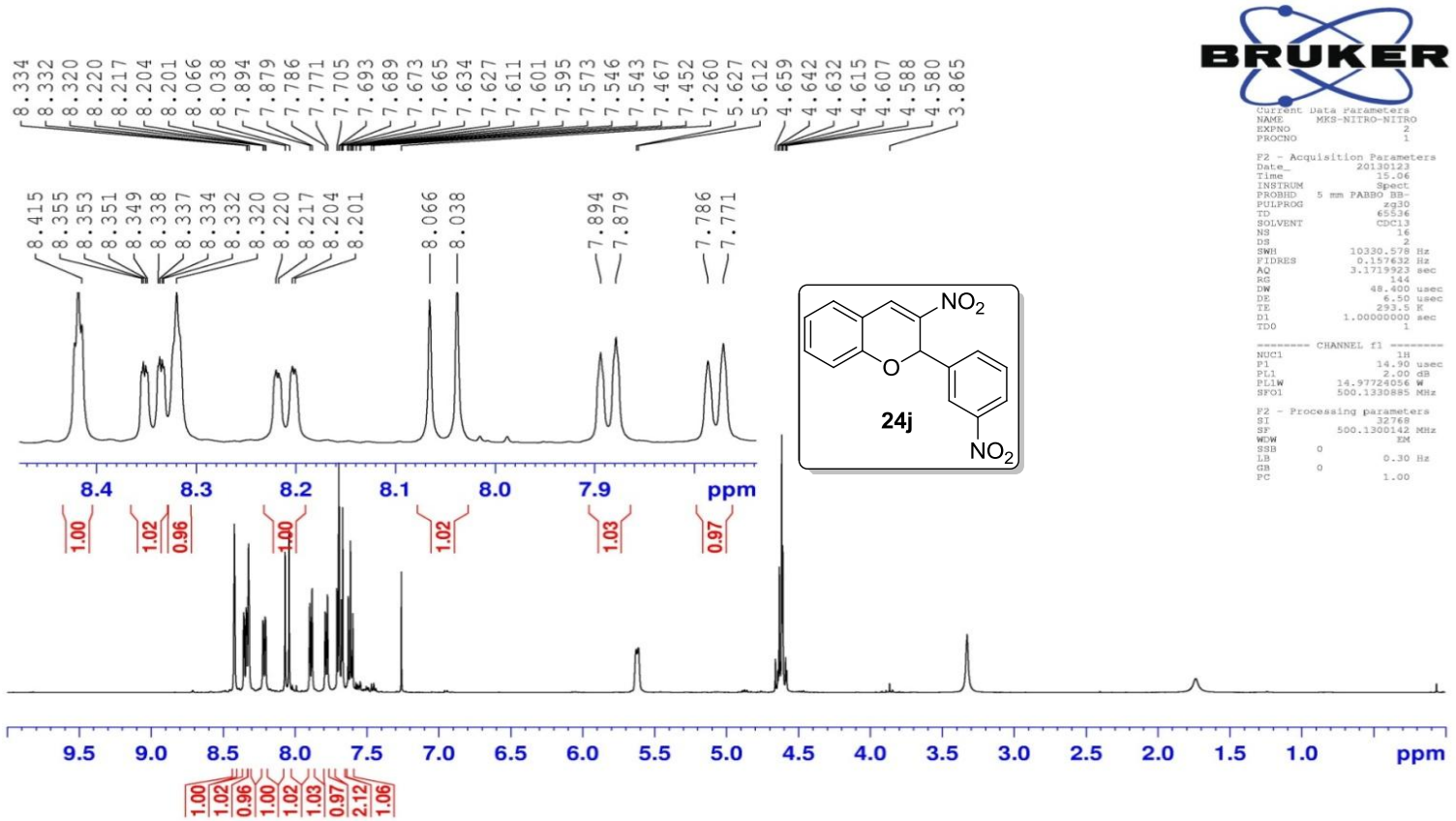


Figure S-142: ^{1}H NMR Spectrum of compound 24j

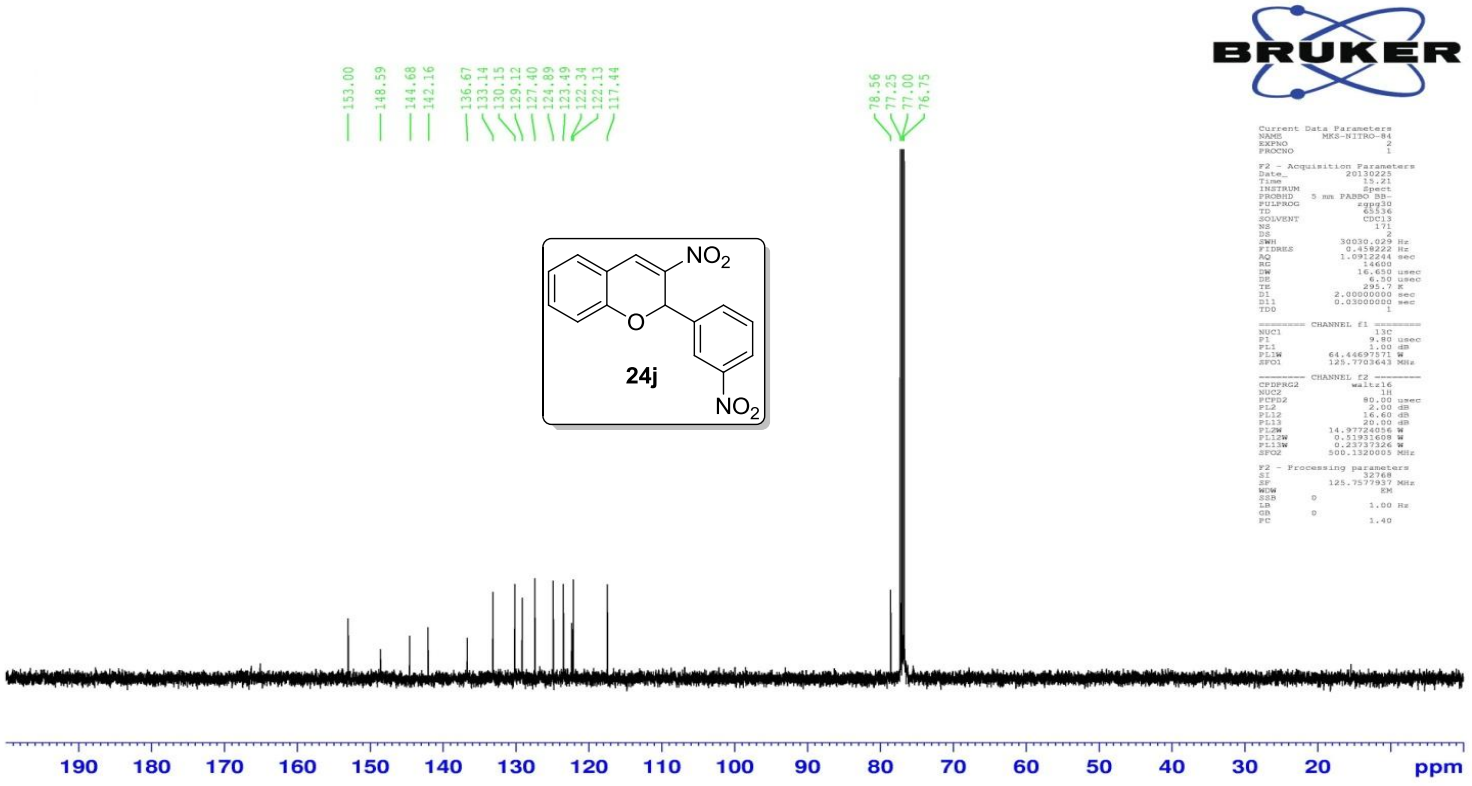
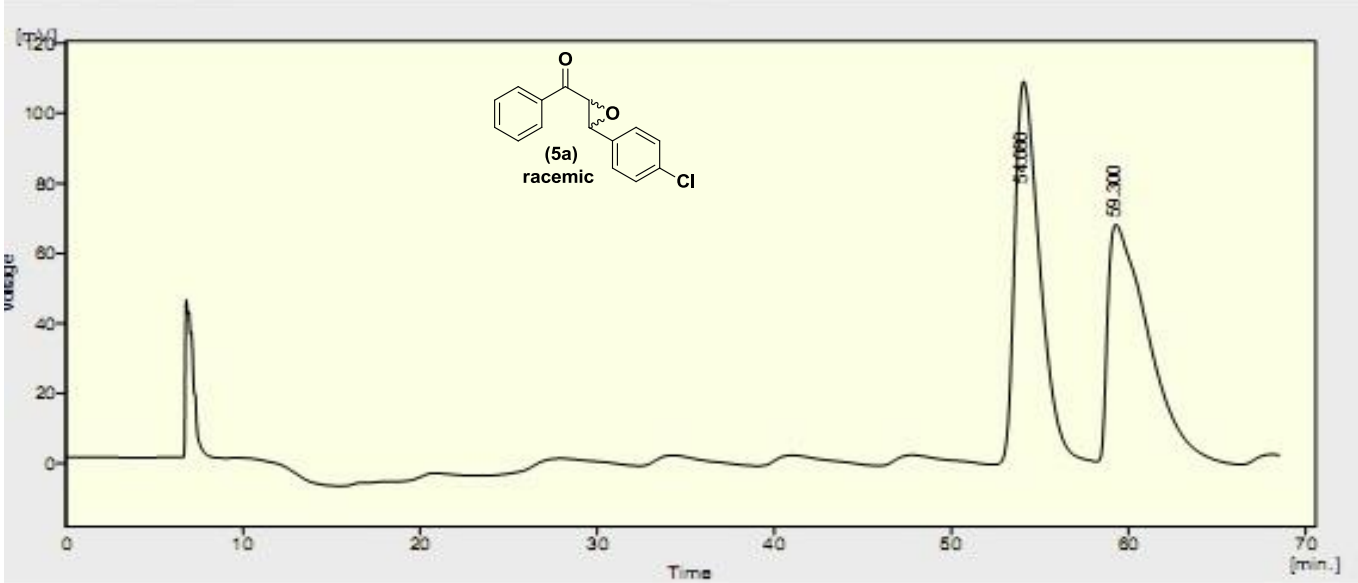


Figure S-143: ^{13}C NMR Spectrum of compound 24j

DEPT. OF CHEMISTRY
IIT ROORKEE

Sample Info:

Sample ID	: BVS-2-221 RACEMIC	Amount	: 0
Sample	: BVS-2-221 RACEMIC	ISTD Amount	: 0
Inj. Volume [ml]	: 0	Dilution	: 1



Result Table (Uncal - F:\Shrinivasvenkat.b\BVS-2-221 RACEMIC)

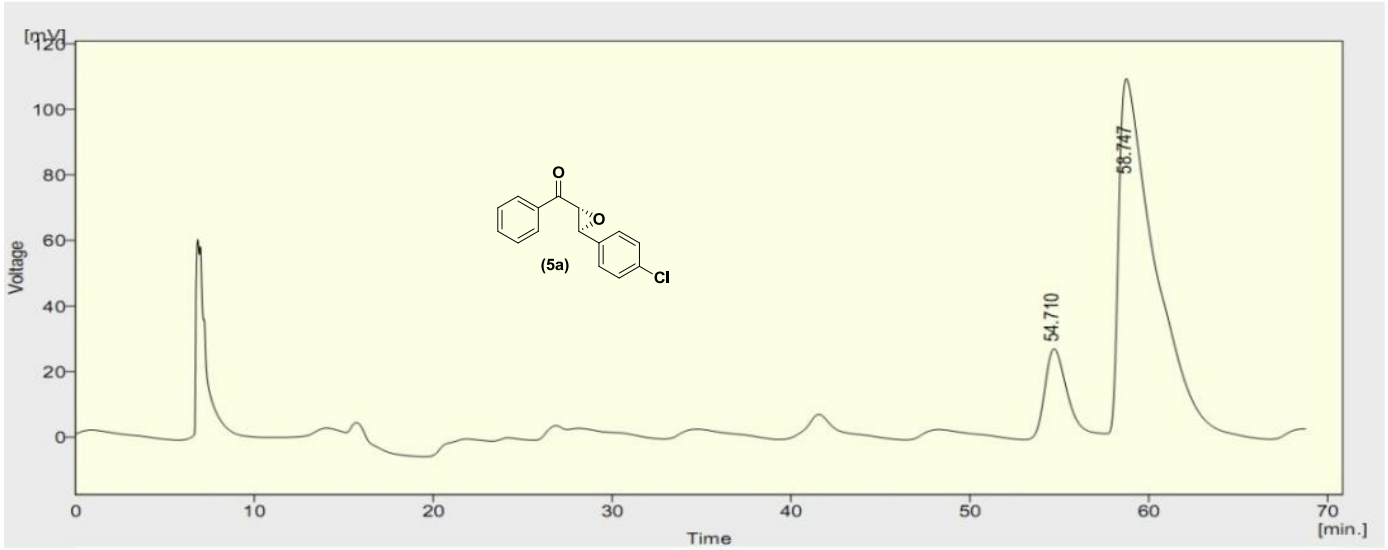
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	54.060	10830.192	109.358	49.6	61.5	1.51
2	59.300	11013.546	68.494	50.4	38.5	2.49
	Total	21843.738	177.853	100.0	100.0	

Chromatogram of **5a** (racemic).

DEPT. OF CHEMISTRY
IIT ROORKEE

Sample Info:

Sample ID	: BVS-2-221 chairal-1	Amount	: 0
Sample	: BVS-2-221 chairal-1	ISTD Amount	: 0
Inj. Volume [ml]	: 0	Dilution	: 1



Result Table (Uncal - F:\Shrinivas\venkat.b\BVS-2-221 chairal-1)

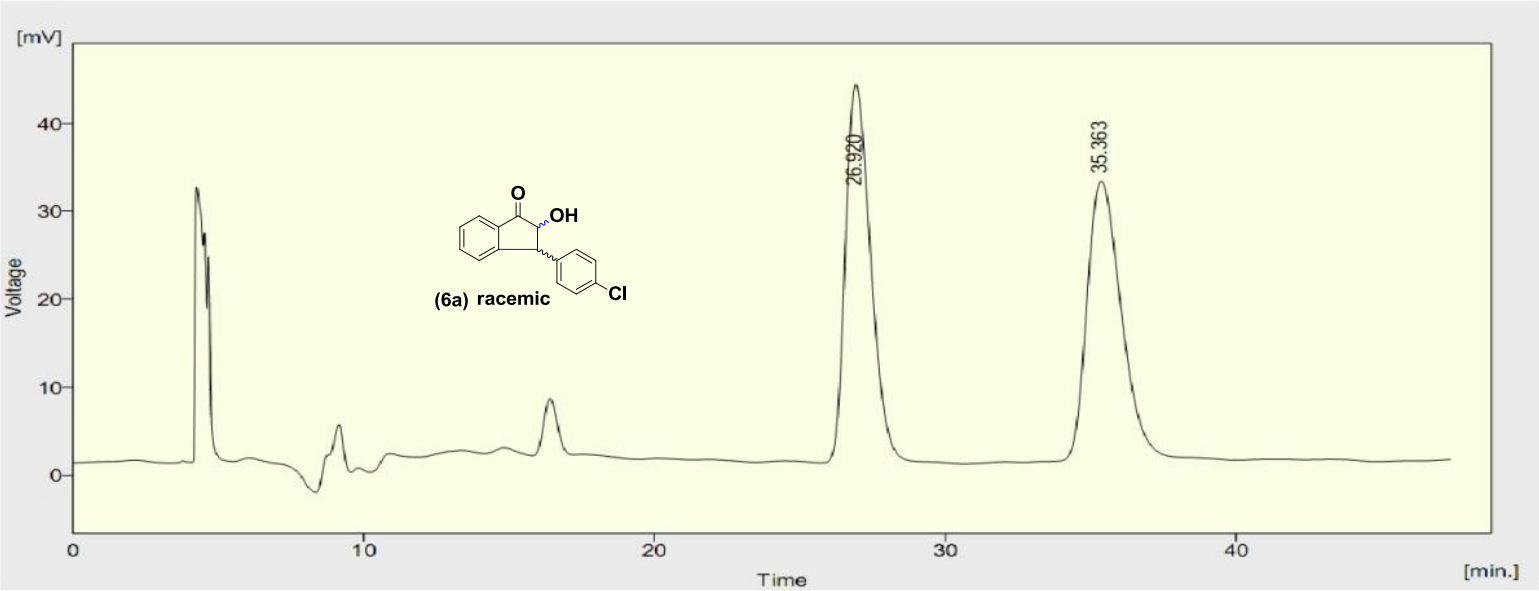
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	54.710	2269.937	26.611	13.0	19.6	1.29
2	58.747	15224.951	109.040	87.0	80.4	2.00
	Total	17494.889	135.651	100.0	100.0	

Chromatogram of **5a** (asymmetric).

DEPT. OF CHEMISTRY
IIT ROORKEE

Sample Info:

Sample ID	: BVS-2-214 Racemic	Amount	: 0
Sample	: BVS-2-214 Racemic	ISTD Amount	: 0
Inj. Volume [ml]	: 0	Dilution	: 1



Result Table (Uncal - F:\Shrinivas\venkat.b\BVS-2-214 Racemic)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	26.920	2576.361	42.957	50.0	57.5	0.94
2	35.363	2580.839	31.704	50.0	42.5	1.27
	Total	5157.201	74.661	100.0	100.0	

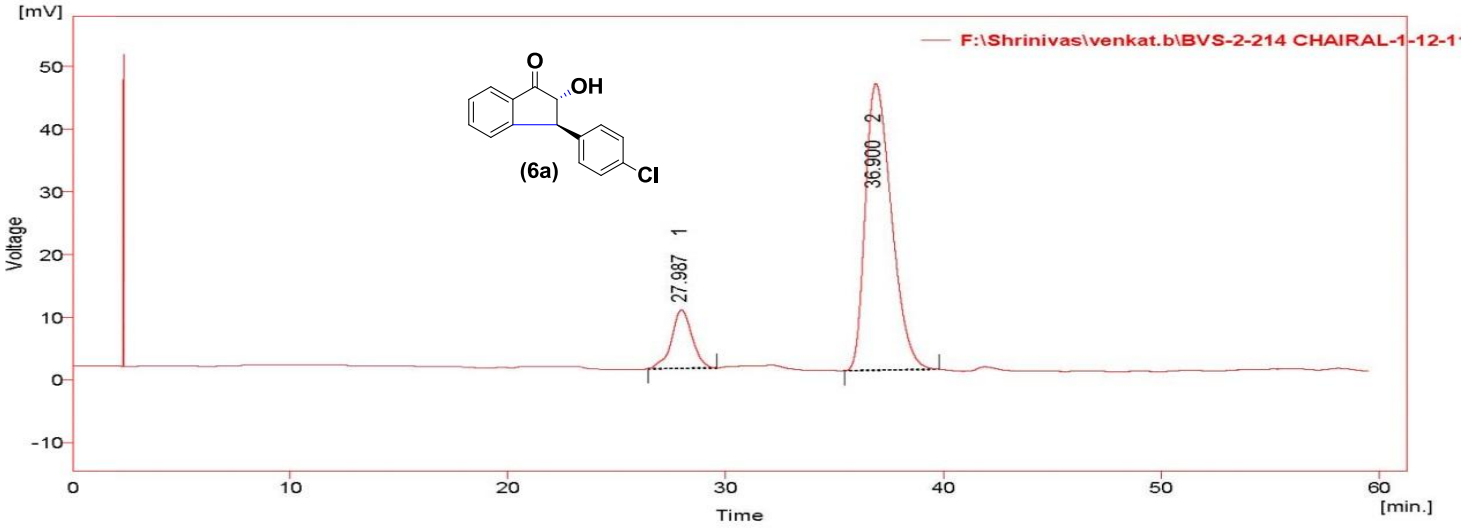
Chromatogram of **6a** (racemic).

DEPT. OF CHEMISTRY

IIT ROORKEE

Sample Info:

Sample ID	: BVS-2-214 CHAIRAL-1	Amount	: 0
Sample	: BVS-2-214 CHAIRAL-1	ISTD Amount	: 0
Inj. Volume [ml]	: 0	Dilution	: 1



Result Table (Uncal - F:\Shrinivas\venkat.b\BVS-2-214 CHAIRAL-1-12-11)

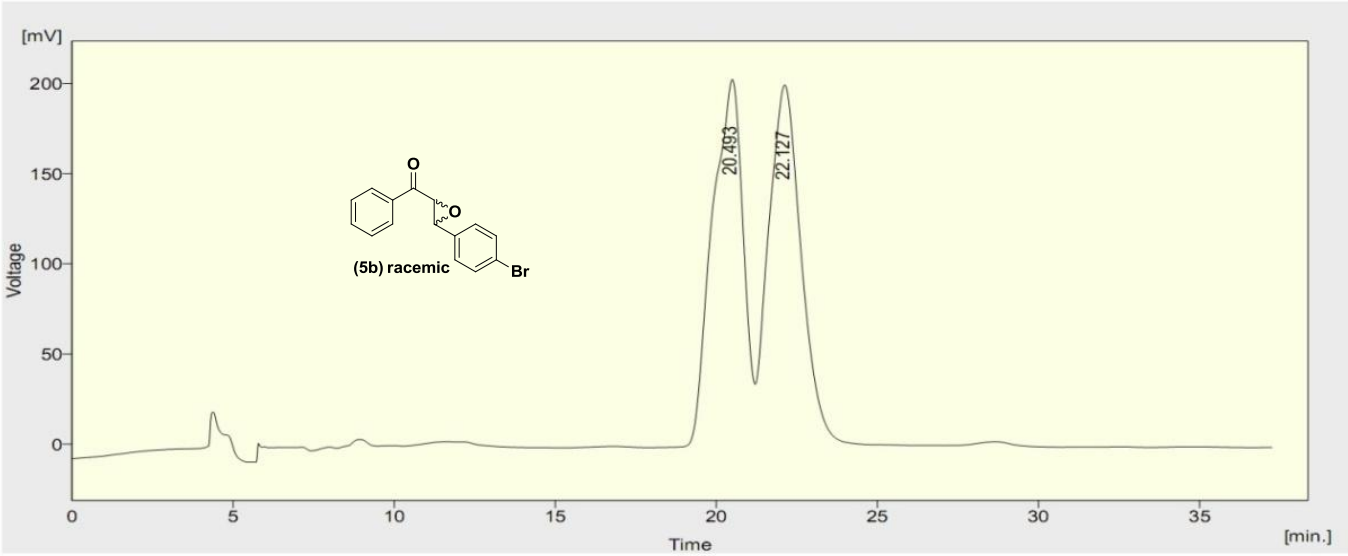
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	27.987	615.855	9.368	13.9	17.0	0.98
2	36.900	3829.838	45.782	86.1	83.0	1.31
	Total	4445.692	55.150	100.0	100.0	

Chromatogram of **6a** (asymmetric).

DEPT. OF CHEMISTRY
IIT ROORKEE

Sample Info:

Sample ID	: BVS-2- 221 (RACEMIC EPOXIDE SINGLE BROMO)	Amount	: 0
Sample	: BVS-2- 221 (RACEMIC EPOXIDE SINGLE BROMO)	ISTD Amount	: 0
Inj. Volume [ml]	: 0	Dilution	: 1



Result Table (Uncal - F:\Shrinivas\venkat.b\BVS-2- 221 (RACEMIC EPOXIDE SINGLE BROMO))

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	20.493	11127.669	178.922	49.9	50.3	1.06
2	22.127	11182.367	176.941	50.1	49.7	1.03
	Total	22310.036	355.863	100.0	100.0	

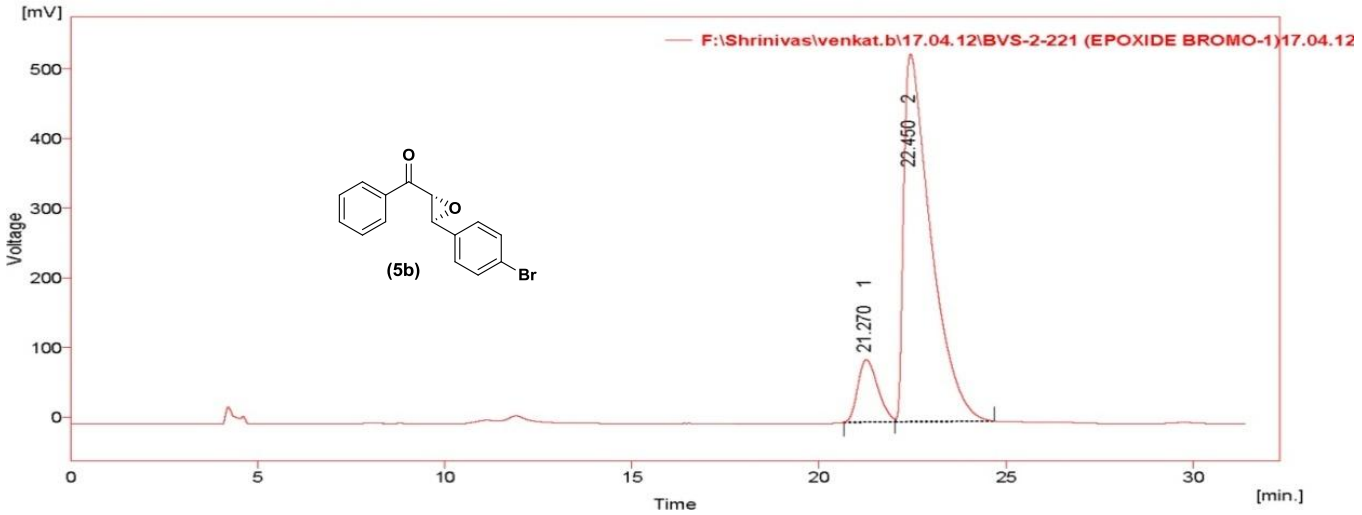
Chromatogram of **5b** (racemic).

DEPT. OF CHEMISTRY

IIT ROORKEE

Sample Info:

Sample ID	: BVS-2-221 (EPOXIDE BROMO-1)17.04.12.	Amount	: 0
Sample	: BVS-2-221 (EPOXIDE BROMO-1)17.04.12.	ISTD Amount	: 0
Inj. Volume [ml]	: 0	Dilution	: 1



Result Table (Uncal - F:\Shrinivas\venkat.b\17.04.12\BVS-2-221 (EPOXIDE BROMO-1)17.04.12.)

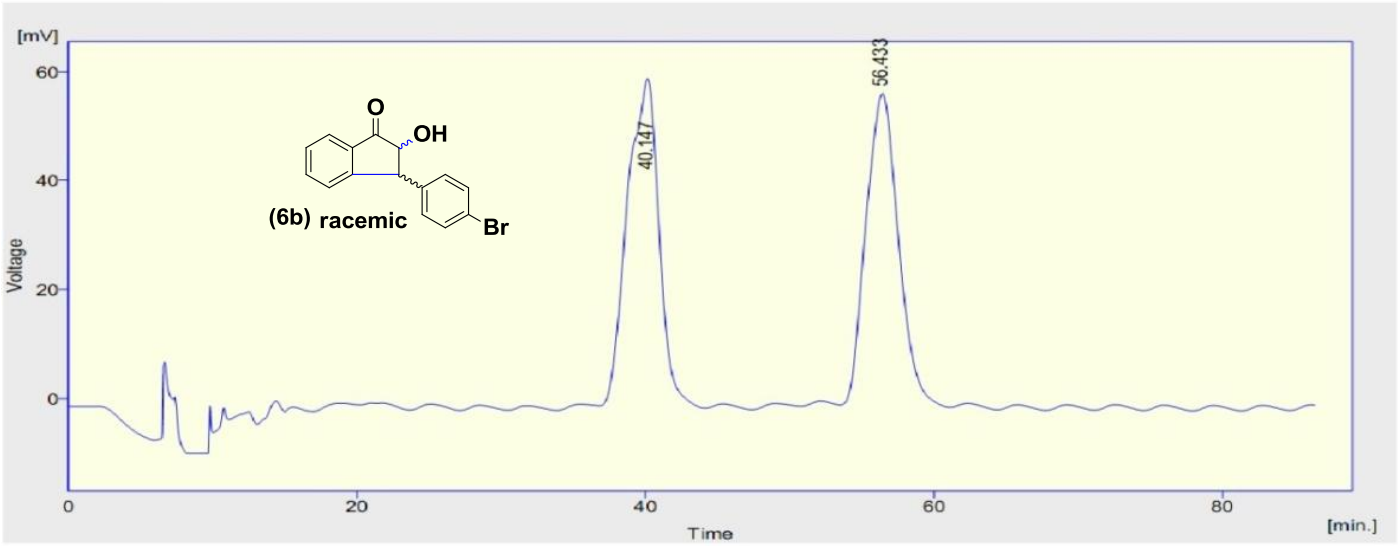
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	21.270	3345.229	89.675	11.2	14.5	0.59
2	22.450	26653.670	527.569	88.8	85.5	0.76
	Total	29998.898	617.244	100.0	100.0	

Chromatogram of **5b** (asymmetric).

DEPT. OF CHEMISTRY
IIT ROORKEE

Sample Info:

Sample ID	: BVS-2-225 (RACEMIC SINGLEBROMO -2)	Amount	: 0
Sample	: BVS-2-225 (RACEMIC SINGLEBROMO -2)	ISTD Amount	: 0
Inj. Volume [ml]	: 0	Dilution	: 1



Result Table (Uncal - F:\Shrinivas\venkat.b\17.04.12\BVS-2-225 (RACEMIC SINGLEBROMO -2))

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	40.147	8771.229	59.125	50.1	51.0	2.46
2	56.433	8744.352	56.862	49.9	49.0	2.46
	Total	17515.581	115.988	100.0	100.0	

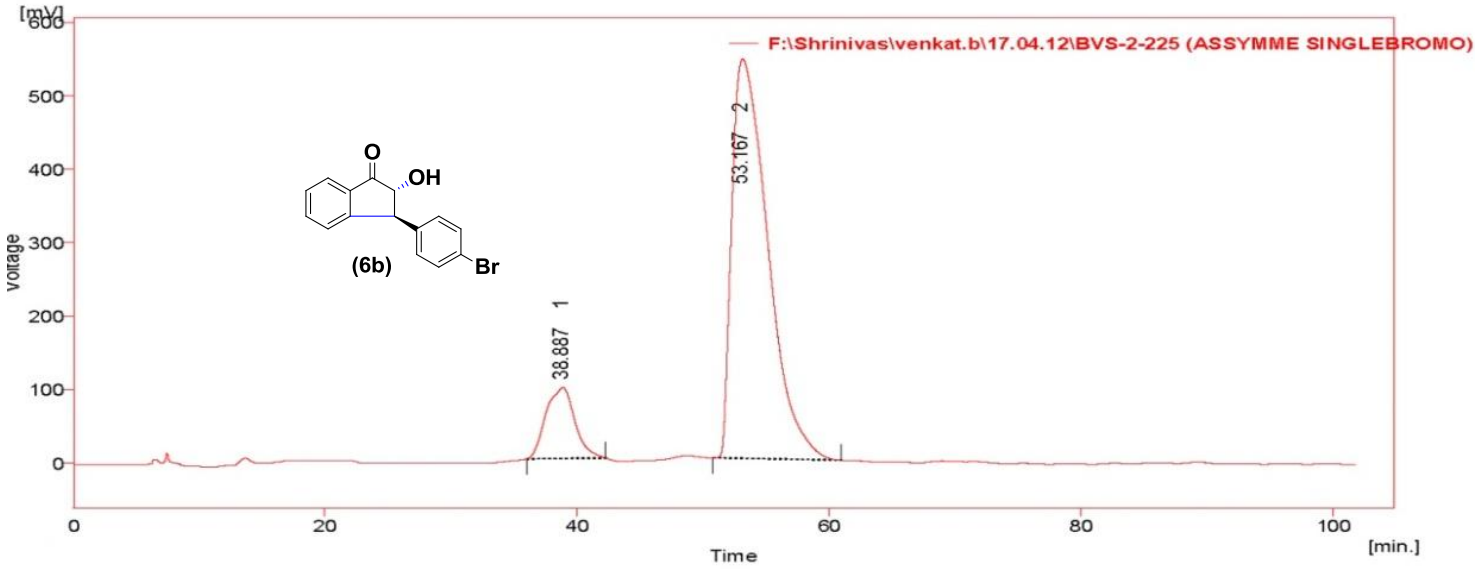
Chromatogram of 6b (racemic).

DEPT. OF CHEMISTRY

IIT ROORKEE

Sample Info:

Sample ID	: BVS-2-225 (ASSYMME SINGLEBROMO)	Amount	: 0
Sample	: BVS-2-225 (ASSYMME SINGLEBROMO)	ISTD Amount	: 0
Inj. Volume [ml]	: 0	Dilution	: 1



Result Table (Uncal - F:\Shrinivas\venkat.b\17.04.12\BVS-2-225 (ASSYMME SINGLEBROMO))

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	38.887	15400.980	96.525	12.5	15.1	2.55
2	53.167	107678.977	543.640	87.5	84.9	3.10
	Total	123079.957	640.165	100.0	100.0	

Chromatogram of **6b** (asymmetric).

LIST OF PUBLICATIONS

1. Naseem Ahmed, Gulab Khushalrao Pathe and B. Venkata Babu "Highly efficient deprotection of phenolic tetrahydropyranyl and methoxymethyl ethers and sequel cyclization to indanones using Sn(IV)Cl_4 catalyst" *Tetrahedron Letters* **2014**, 55, 3683 – 3687.
2. Naseem Ahmed, Gulab Khushalrao Pathe and B. Venkata Babu "$SnCl_4$ or $TiCl_4$: Highly efficient catalysts for deprotection of phenolic THP and MOM ethers and sequel one-pot Asymmetric synthesis of 3-aryl-2-hydroxy-2,3-dihydroindan-1-one from chalcone epoxides" RSC Advance, **2015,** Ahead of print.
3. Gulab Khushalrao Pathe and Naseem Ahmed'' $SnCl_4$: Zn- A novel reductive system for deoxygenative coupling of aliphatic, aromatic, chalcone epoxide and indanone carbonyl compounds to olefins" *Tetrahedron Letters* **2015**, 56, 1555-1561.
4. Gulab Khushalrao Pathe, Naveen Konduru, Iram Parveen and Naseem Ahmed'' Design, Synthesis of McMurry cross-coupled indanophen analogs of Tamoxifen by novel $SnCl_4$-Zn reagent and Anti-Proliferative Evaluation of Flavone-Estradiol adduct and Indanone based Ligands against Breast Cancer Cell Line, *European Journal of Medicinal Chemistry,* **2015**, Under Review
5. Gulab Khushalrao Pathe and Naseem Ahmed "SeO_2-water: an efficient catalyst for deprotection of acetyl, methoxymethyl and tetrahydropyranyl ethers and sequel oxidation of carbonyl carbons" *RSC Advance,* **2015**, Ahead of print.
6. Gulab Khushalrao Pathe and Naseem Ahmed "Mild and efficient reductive deoxygenation of epoxides to olefins with $SnCl_2$/NaI as a novel reagen'*Synthesis,* **2015**, Ahead of print.
7. Gulab Khushalrao Pathe and Naseem Ahmed "Solvent free green protocol for the eliminative deoxygenation of aliphatic and aromatic epoxides, to olefin by novel, efficient polyphosphoric acid as catalyst" *Helvetica chemical acta,* **2015**, Under Review.