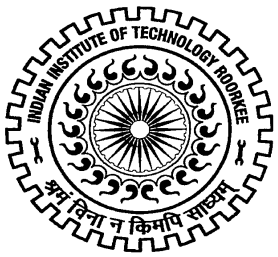
DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF FUNCTIONALIZED FLAVONOIDS DERIVATIVES

Ph.D. THESIS

by

NAVEEN KUMAR K.



DEPARTMENT OF CHECHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY ROORKEE
ROORKEE – 247667 (INDIA)
JANUARY, 2014

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A THESIS

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

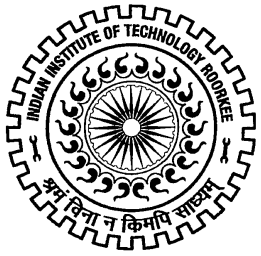
DOCTOR OF PHILOSOPHY

in

CHEMISTRY

by

NAVEEN KUMAR K.



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CANDIDATE'S DECLARATION

I hereby certify that the work which is being presented in the thesis entitled **"DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF FUNCTIONALIZED FLAVONOIDS DERIVATIVES"** 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 December, 2009 to January, 2014 under the supervision of Dr. Naseem Ahmed, Assistant 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 in this or any other Institute.

(NAVEEN KUMAR K.)

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

(Naseem Ahmed)
Supervisor

Date:

The Ph.D Viva-Voice Examination of **Mr. NAVEEN KUMAR K.**, Research Scholar, has been held on _____

Supervisor Chairman, SRC External Examiner

Head of the Department/Chairman, ODC

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NAVEEN KUMAR K.

LIST OF CONTENTS

LIST OF ABBREVIATIONS

AChE	Acetylcholinesterase
ACN	Acetonitrile
AIDS	Acquired Immunodeficiency Syndrome
BACE1	β-Secretase 1
CHS	Chalcone Synthase
CHI	Chalcone Isomerase
CoA	Coenzyme A
CNS	Central Nervous System
COX	Cyclooxygenase
CAI	Carboxyamido Triazole
COSY	Correlated Spectroscopy
DMSO	Dimethyl Sulfoxide
DNA	Deoxyribonucleic Acid
DCM	Dichloromethane
DHP	Dihydropyran
DDQ	2,3-Dichloro-5,6-Dicyano-1,4-benzoquinone
DMF	*N*,*N*-Dimethylformamide
DIPEA	Diisopropylethylamine
ER	Estrogen Receptor
FLS	Flavonol Synthase
GC-MS	Gas Chromatography Mass Spectrometry
HRMS	High Resolution Mass Spectrometry
HMTA	Hexamethylenetetraamine
HMBC	Heteronuclear Multiple Bond Correlation
HIV	Human Immunodeficiency Virus
IR	Infrared
LDA	Lithium Diisopropylamide
LDL	Low-Density Lipoprotein

MIC	Minimum Inhibitory Concentration
MS	Molecular Sieves
MCF-7	Michigan Cancer Foundation-7
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
MP	Melting Point
m-CPBA	*meta*-Chloroperbenzoic acid
µg	Microgram
ml	Milliliter
µM	Micro Molar
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Spectrodcopy
NLO	Non-Linear Optical
NSAID	Non-Steroidal Anti-Inflammatory Drug
NBS	*N*-Bromosuccinamide
PDE	Phosphodiesterase
PFT	Protein Farnesyl Transfer
PTSA	*p*-Toluenesulfonic acid
RT	Room Temperature
SAR	Structure Activity Relationship
TBTA	Tris((1 -benzyl-1H-1,2,3-triazolyl)-methyl)amine
TTTA	Tris((1-tert-butyl-1H-1,2,3-triazolyl)-methyl) amine
TEA	Triethylamine
TFA	Trifluoroacetic Acid
TBDMSCl	*tert*-Butyldimethylsilyl chloride
THP	Tetrahydropyran
TLC	Thin Layer Chromatography
TSAO	*tert*-Butyldimethylsilyl Spiro Amino Oxathioledioxide
THF	Tetrahydrofuran

ABSTRACT

The thesis entitled **"Design, Synthesis and Biological Evaluation of Functionalized Flavonoids Derivatives"** is reported in five chapters.

The present work is aimed to design and synthesis of novel flavonoids based derivatives involving C-C, C-O, C-N, C-S bonds formation using different reactions like Prins cyclization, thia-Michael addition, and click reaction. Novel synthesized compounds were characterized using different analytical techniques such as ^{1}H NMR, ^{13}C NMR, 2D NMR, IR, mass, CHNS and X-ray diffraction and their biological evaluations were reported as antimicrobials and anti-proliferative applications. The thesis has been divided into five chapters for the sake of convenience and clarity, and organized as follows:

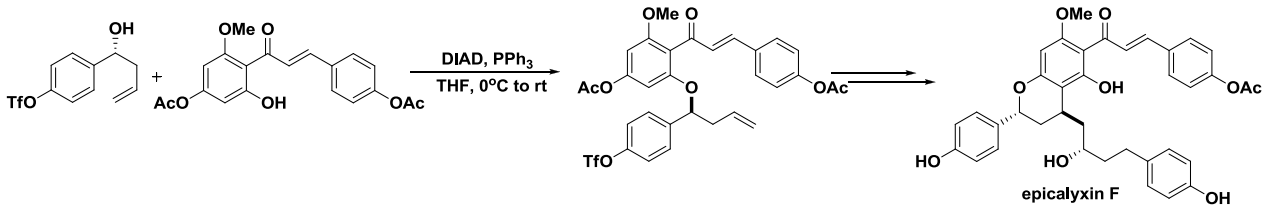
Chapter 1: Introduction

Flavonoids are found in most of the higher plants as secondary metabolites and are water soluble due to polyphenolic nature. These naturally occurring compounds are widely distributed in plants like vegetables, tea, soya bean, berries and other citrus fruits as dietary sources. They have exhibited antioxidant and chelating properties so have many health promoting effects. Some of the activities attributed to flavonoids include anti-allergic, anti-cancer, antioxidant, anti-inflammatory and anti-viral. Flavonoids as central core containing compounds are used as drugs such as xanthokeismins A-C, and dimefine for the treatment of bronchial asthma.

This chapter describes classification of flavonoids and a brief literature review of flavonoids biosynthesis and different synthetic methods that include Baker-Venkataraman rearrangement, Claisen-Schmidt condensation, Friedel-Crafts acylation, Microwave assisted synthesis, Algar–Flynn–Oyamada reaction, Auwers synthesis, Allan–Robinson reaction, and Suzuki-Miyaura reaction. Flavonoids are central core structures in natural and synthetic compounds such as xanthohumol, rhuschalcone, amentoflavone, robustaflavone, ochnaflavone their synthesis and applications such as anti-cancer, antioxidant, anti-inflammatory and anti-microbial were discussed. Similarly, the effects of different substituents on biological activity such as prenyl, geranyl, hydroxyl, amino, methoxy, methyl and hydroxyl on flavonoids were discussed.

Functionalized tetrahydropyrans (THPs) are key structural motifs in many natural products such as (+)-neopeltolide, phorboxazole A & B, and pheromones. They have shown many promising biological applications including *in vivo* antinociceptive activity, *in vitro* anti-cancer, anti-

hypertensive, anti-bacterial and anti-fungal activities. Flavonoid based THPs are also precursors of drugs like tetrahydrocannabinol, dimethylheptylpyran, etc. Therefore, various reaction strategies have been explored for the stereoselective synthesis with proper functionalization such as hetero-Diels-Alder method, oxidative C−H bond activation, Prins cyclization, etc. Among them, Prins cyclization is found the best method for the pyran ring construction in high yields under mild reaction conditions. Applications of Prins cyclization strategy in total synthesis of natural products such as neopeltolide, and epicalyxin F, were discussed.



Scheme 1: Total synthesis of epicalyxin F *via* Prins cyclization.

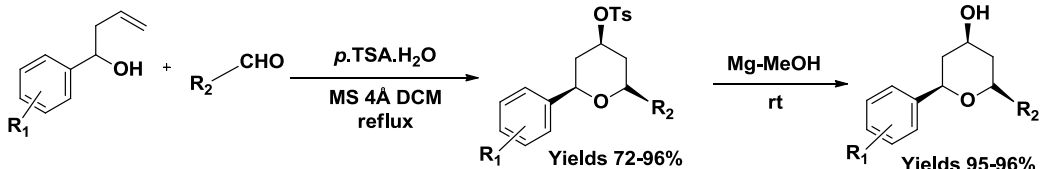
Chapter 2: Synthesis of 2,6-Disubstituted-4-Tosyloxytetrahydropyrans *via* Prins cyclization

Part-A:

Efficient, Highly Diastereoselective MS 4 Å-Promoted One-pot, Three-Component Synthesis of 2,6-Disubstituted-4-Tosyloxytetrahydropyrans *via* Prins cyclization

Naseem Ahmed* and Naveen Kumar Konduru, *Beilstein J. Org. Chem*. 8 (2012) 177–185

In this part, a novel synthetic method is demonstrated for the synthesis of 2,6-disubstituted-4-tosyloxytetrahydropyrans *via* Prins cyclization using aromatic homoallylic alcohols, aldehydes, *p*-toluenesulfonic acid and MS 4 Å under optimized reaction conditions. This methodology proved to be versatile enough to provide an array of symmetrical and unsymmetrical tetrahydropyran derivatives with moderate to excellent yields (72–96%) within 20–90 min. under mild reaction condition. Further, deprotection of 4-tosyl group with Mg–MeOH afforded 4-hydroxytetrahydropyrans. All products were fully characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, CHNS and stereochemistry of products determined by ^{1}H NMR and NOESY techniques.



R_1 = H, 4-Cl, 4-Br, 4-Me, 4-OMe, 3,4-diOMe, 3,4,5-TriOMe;
R_2 = Ph, 4-ClPh, 4-BrPh, 4-MePh, 4-OMePh, 3,4-diOMePh, 3,4,5-TriOMePh, Pyrrolyl, Furanyl, Methyl

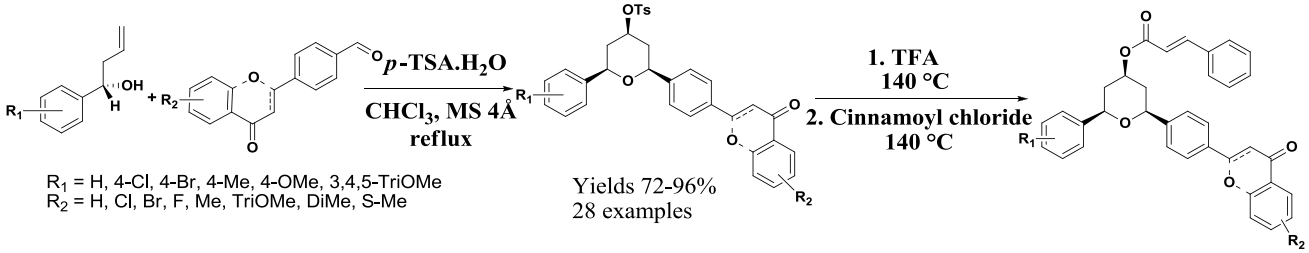
Scheme 2: Synthesis of 4-tosyloxy and 4-hydroxy tetrahydropyrans.

Part B:

Synthesis of Flavonoids based Novel Tetrahydropyran Conjugates (Prins Products) and Their Antiproliferative Activity Against Human Cancer Cell Lines

Naseem Ahmed,[a]* Naveen Kumar Konduru,[a] Sarfaraz Ahmad,[b] Mohammad Owais,[b] *Eur. J. Med. Chem.2013 Accepted with minor review.*

In this part, the synthesis and characterization of novel flavonoid-tetrahydropyran conjugates and their anti-proliferative activity against human cancer cell lines were reported. Here products were synthesized in moderate to excellent yields (72–96%) and high diastereoselectivity under optimized reaction condition using aromatic homoallylic alcohol, flavonoid based aldehyde, *p*-toluenesulfonic acid and MS 4 Å in $CHCl_3$. Deprotection of tosyl group and the reaction with cinnamoyl chloride resulted in 4-cinnamate tetrahydropyrans. Products were fully characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, HRMS and stereochemistry of products were determined by ^{1}H NMR, COSY, HMBC and NOESY techniques and compounds were evaluated for their anti-proliferative activity *in vitro* against 3 human cancer cell lines (Hep3β, MCF-7 and Hela), most of the compounds showed good anti-proliferative activities.



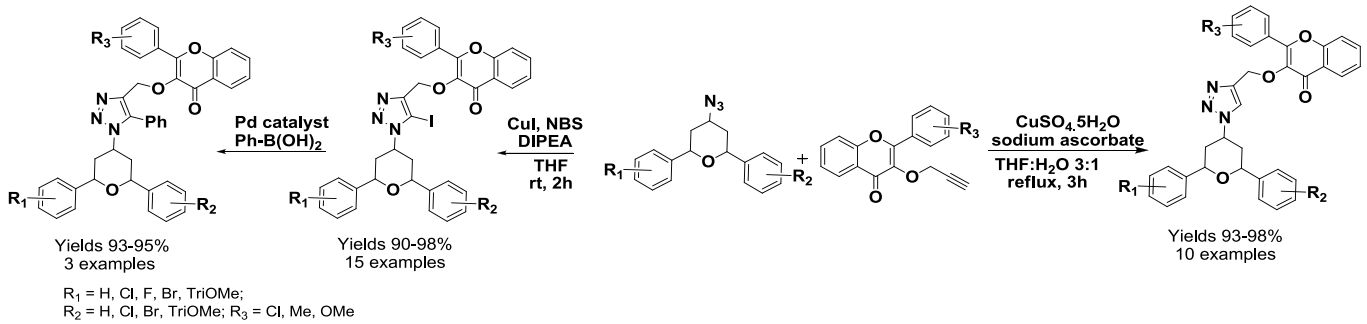
Scheme 3: Synthesis of flavonoid based 4-tosyloxy, 4-hydroxy and 4-cinnamate tetrahydropyrans.

Chapter 3: Design and Efficient Synthesis of Functionalized Flavone-Triazole-Tetrahydropyran Conjugates *via* Click Chemistry

Manuscript under preparation.

In this chapter, a mild and efficient synthesis of functionalized flavone-triazole-tetrahydropyran conjugates was reported *via* click reaction. We performed reaction between 4-azidotetrahydropyran and flavone based alkynes under optimized Cu-catalyzed 1,3-dipolar cycloaddition reaction condition. The products 5-iodo and 5-*H*-1-(tetrahydropyran)-1,2,3-triazol-4-(3-methoxylflavone) derivatives were obtained in excellent yields (90-98%) within 1-3 h. Pd-

catalyzed Suzuki cross-coupling reaction of 5-iodo-1,2,3-triazoles with phenylboronic acids were performed to afford 5-phenyl-1-(tetrahydropyran)-1,2,3-triazol-4-(3-methoxylflavone) derivatives in high yields (93-95%) within 4–5h.



Scheme 4: Synthesis of 5-*H*, 5-*I* and 5-phenyl triazole derivatives.

All products were fully characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, HRMS and stereochemistry of products determined by ^{1}H NMR, NOESY and single crystal X-ray analysis.

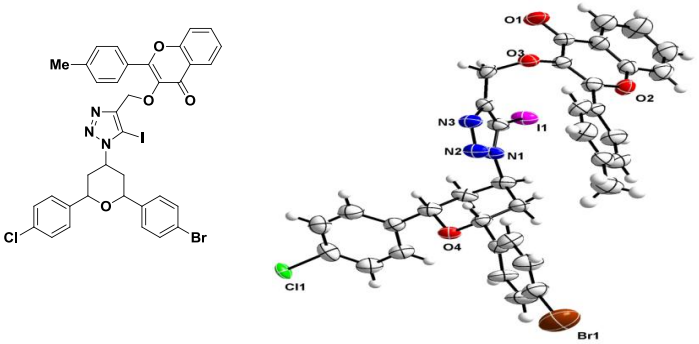


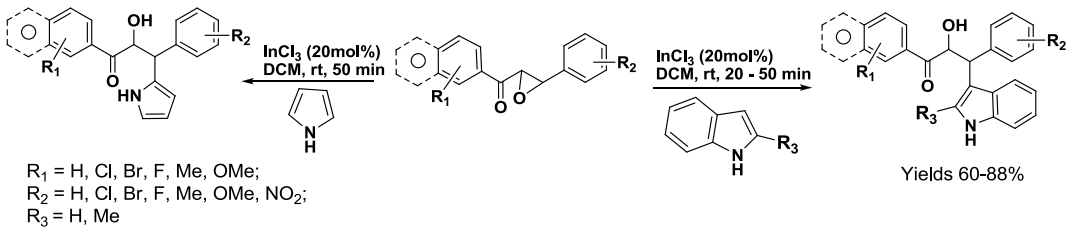
Figure 1: ORTEP diagram of 3-((1-((2S,4S,6R)-2-(4-bromophenyl)-6-(4-chlorophenyl)tetrahydro-2*H*-pyran-4-yl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2-*p*-tolyl-4*H*-chromen-4-one.

Chapter 4: Regioselective Opening of Chalcone Epoxides with Nitrogen Heterocycles using Indium(III) Chloride as an Efficient Catalyst

Naveen Kumar Konduru and Naseem Ahmed,* *Synth. Commun.* 43 (2013) 2008-2018.

In this chapter, the synthesis and characterization of chalcone based nitrogen heterocycles were reported by opening of chalcone epoxides with different nitrogen heterocycles (indole, 2-methyl indole, pyrrole) in the presence of suitable Lewis acid catalyst. Optimization of reaction conditions and screening of Lewis acids gave Indium(III) chloride at 20 mol% the best catalyst and dichloromethane as suitable solvent for the regioselective epoxide ring opening which gave

products in good yields (60-88%). All products were fully characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, GC-MS and HRMS.



Scheme 5: Regioselective opening of chalcone epoxides with nitrogen heterocycles.

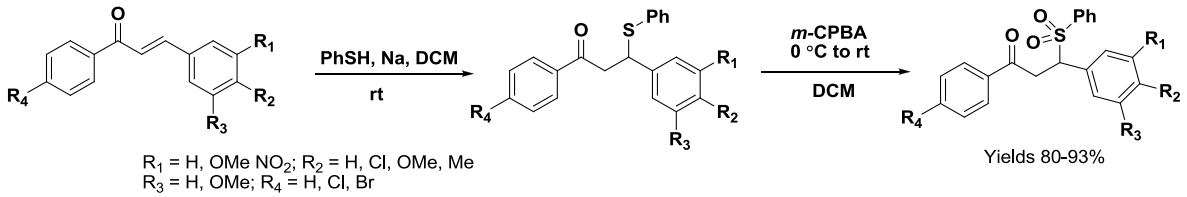
Chapter 5: Synthesis of Chalcone based Sulfones and Bisulfones and their Antimicrobial Evaluation

Part-A:

Synthesis, Antibacterial and Antifungal Evaluation of some Chalcone based Sulfones and Bisulfones

Published in: Naveen Kumar Konduru,[a] Sunita Dey,[a] Mohammad Sajid,[b] Mohammad Owais,[b] Naseem Ahmed,[a]* *Eur. J. Med. Chem.* 59 (2013) 23-30.

In this part, the synthesis and characterization of chalcone based sulfone and bisulfone derivatives and evaluation of their antimicrobial activity were reported. Chalcone sulfides and bisulfides were synthesized using chalcone, thiophenol and sodium metal at room temperature, followed by oxidation of chalcone sulfides with *m*-CPBA under optimal conditions affords chalcone sulfones and bisulfones. All synthesized compounds were fully characterized using analytical techniques such as FT-IR, ^{1}H NMR, ^{13}C NMR, and CHNS. Synthesized chalcone sulfones and bisulfones were evaluated for their antimicrobial activities against yeast (*A. niger*, *C. albicans*), Gram (+) bacteria (*B. subtilis*, *S. aureus*) and Gram (−) bacteria (*P. aeruginosa*,, *S. typhimurium*). All compounds have shown moderate to high antimicrobial activity.



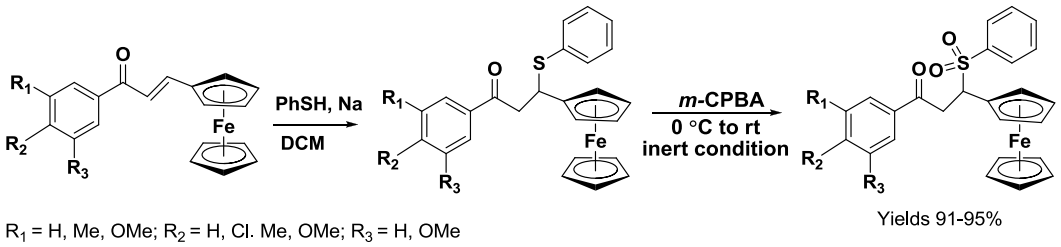
Scheme 6: Synthesis of chalcone based sulfones and bisulfone.

Part-B:

Design, Synthesis and Antimicrobial Activities of Novel Ferrocenyl and Organic Chalcone based Sulfones and bis-Sulfones

Communicated in: Naveen Kumar Konduru,[a] Sarfaraz Ahmad,[b] Mohammad Owais,[b] Naseem Ahmed[a]* J. Heterocycle Chemistry, Under Review.

In this part, the synthesis and characterization of a series of novel ferrocenyl, organic chalcone based sulfone derivatives and evaluation of their antimicrobial activities against important pathogens were reported. The products were afforded with excellent yields (91-95%). All synthesized compounds were fully characterized using analytical techniques such as FT-IR, ^{1}H NMR, ^{13}C NMR, and HRMS. Synthesized compounds were tested for antimicrobial activity [*A. niger, C. albicans, A. fumigatus, C. neoformans, C. parapsilosis* and *C. tropicalis* (yeast), *B. subtilis, S. aureus* and *L. monocytogenes* (Gram (+) bacteria) and *P. aeruginosa, K. pneumonia, E. coli, and P. vulgaris* (Gram (-) bacteria) strains]. Majority of the synthesized compounds have shown good activity.



R_1 = H, Me, OMe; R_2 = H, Cl. Me, OMe; R_3 = H, OMe

Scheme 7: Synthesis of ferrocenylchalcone based sulfones.

APPENDIX-1

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Chapter-1

INTRODUCTION

INTRODUCTION

1.1. GENERAL INTRODUCTION OF FLAVONOIDS

Flavonoid originated from the Latin word "*flavus*" means yellow and first time reported by Hungarian scientist Albert Szent-Gyorgyi in 1938. They are found in the plants as secondary metabolites and are water soluble due to polyphenolic nature. Over 5,000 flavonoids have been identified from fruits, vegetables, flowers, leaves, stem, root and seeds which are responsible for their vibrant color. Flavonoids also play vital role in protecting the plants from microbes and insects attack [1]. These compounds have antioxidant and chelating properties therefore they have many health promoting effects [2]. Some other properties attributed to flavonoids include: anti-allergic, anti-cancer, antiprotozoal activity, anti-oxidant, anti-inflammatory, anti-viral, reduced risk of cancer, heart disease, asthma, and stroke [3]. For example, quercetin is known for its ability to relieve hay fever, ecszema, sinusitis, heart related diseases and asthma by preventing the oxidation of low-density lipoprotein (LDL) thereby reducing the risk for the development of atherosclerosis [4]. Red wine contains high levels of quercetin and rutin flavonoids. The high intake of red wine (hence flavonoids) by the French people might be the reason for less suffering from coronary heart disease than other Europeans, although their consumption of cholesterol rich foods is higher (French paradox). Similarly, green tea contains 25% flavonoids reduces the oxidation of low-density lipoprotein, lowers the blood levels of cholesterol and triglycerides. Soy flavonoids (mainly isoflavones) also reduce blood cholesterol, prevent osteoporosis and ease menopausal symptoms. Therefore, there is no exaggeration in the statement that plants have sustained and are sustaining human life on this planet [5].

Flavonoids are good for health but may also have adverse effects, such as anti-nutritional effects, thyroid toxicity, carcinogenic development effects and drug interaction [5]. However, many foods are rich in flavonoids and are generally recognized as safe. Very high intakes of flavonoids have been associated with reduced intake of glucose and minerals. But the slower absorption of glucose may protect against diabetes mellitus. Some flavonoids have an effect on the thyroid function: they inhibit thyroid peroxidase and interfere with the production of the thyroid hormone. The effects of tea and red wine (flavonoids) on cardiovascular diseases have been studied intensively. It is estimated that the extra daily consumption of 3 cups of tea reduces the risk of cardiovascular risk by more than 10%.

The plant chemistry (also known as natural products chemistry) is vital for understanding the natural products isolation and their pharmaceutical importance. Similarly, synthetic organic chemistry is another dynamic field which concerned with the design and synthesis of organic compounds or modifications in natural products (alkaloids, amino acids, flavonoids, terpenoids, fatty acids, steroids, etc.) using different conventional methods, microwave method, green concept of synthesis and solid phase reactions. Among them, flavonoids are one of the most fascinating areas of the plant chemistry and organic synthesis has many challenges in the transformation of these molecules to obtain higher level of complexity for enhanced medicinal values as compared to natural flavonoids and bi-flavonoids. Isolation and identification of unknown natural products are a big task. Therefore, organic synthesis specifically becomes center of attraction for many organic chemists because of the ability to produce beneficial products such as natural products, pharmaceuticals, medicinal/drugs, agricultural and materials during the organic modification of flavonoids. Special interest has been shown on the synthesis of chalcone based derivatives due to their biodynamic activity, importance in plant chemistry and human life.

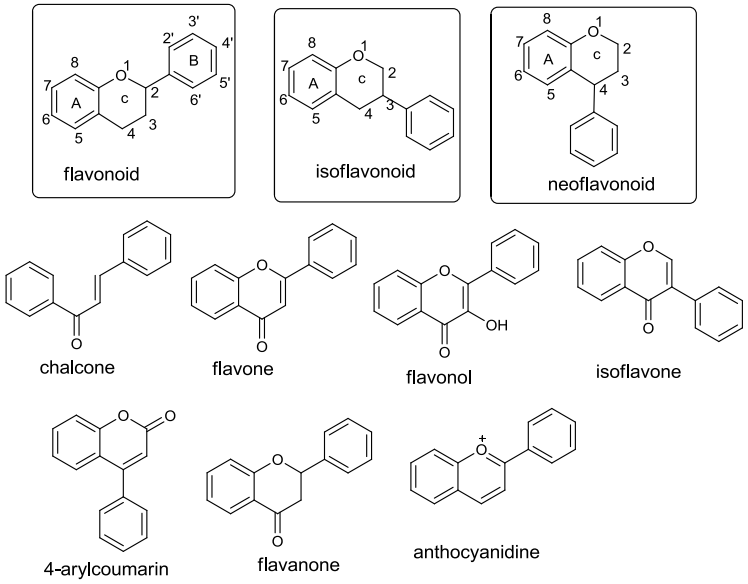


Fig. 1: Structural backbones of the main flavonoid groups and of relevant flavonoid classes.

All flavonoids share a basic C_6-C_3-C_6 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), isoflavonoids (3-phenyl-benzopyrans) and neoflavonoids (4-phenyl-benzopyrans) (Fig. 1). Chalcone, a biogenetic precursor to flavonoids are often classified as flavonoids. Division into further groups is made on the basis of the central ring oxidation and on the

presence of specific hydroxyl groups. Most common flavonoids are flavones (with a C2-C3 double bond and a C4-oxo function), flavonols (flavones with a 3-OH group) and flavanones (flavone analogues but with a C2-C3 single bond), and abundant isoflavonoids include isoflavones (the analogue of flavones). 4-arylcoumarin (a neoflavonoid with a C3-C4 double bond) and its reduced form, 3,4-dihydro-4-arylcoumarin are the major neoflavonoids (Fig. 1) [6].

Flavonoid based natural or synthetic compounds have been widely reported to exhibit various biological activities, when incorporate new functional groups (hydroxyl, methoxy, amino, carboxyl, sulfone, prenyl, geranyl, glucose) or biologically active moieties (tetrahydropyran, indole, pyrrole, quinolone, triazole, adamantyl) improves its activity. For example, hydroxyl groups containing chalcone derivative butein extracted from *Rhus verniciflua* which shows good antioxidant activity [7], flavokawain B found in kava plant it demonstrated to possess potent apoptotic abilities [8], xanthohu-

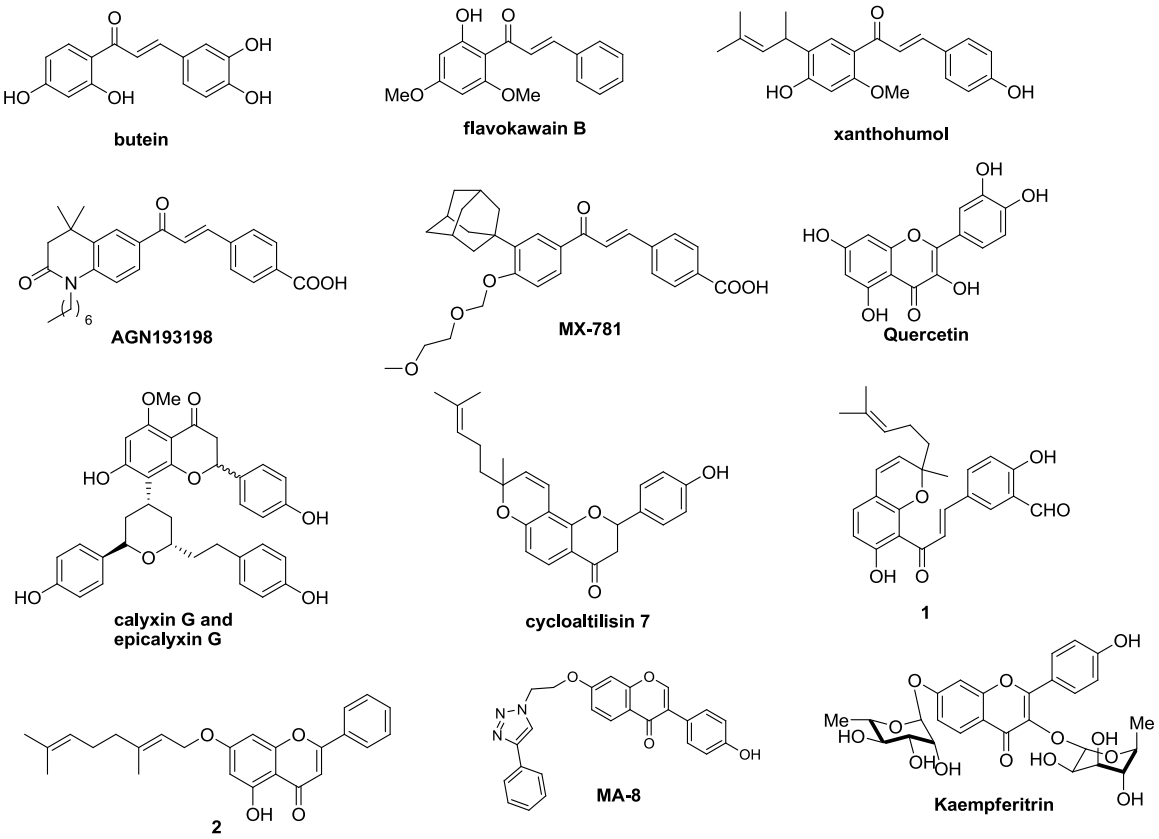


Fig. 2: Natural, synthetic biologically active flavonoid derivatives.

-mol is, a prenylated-chalconoid from hops and beer. Xanthohumol is a free radical scavenger, it has anticancer properties and prevents platelet build-up. Carboxyl, adamantyl group bearing chalcones AGN193198, MX781 showed NF-κB inhibitory activity. Cycloaltilisin 7 extracted from the bud

covers of *Artocarpus altilis* showed activity in a cathepsin K inhibition assay and showed IC_{50} value 840 nM [9]. Tetrahydropyran containing chalcone derivatives calyxin G and epicalyxin G are extracted from the seeds of *A. blepharocalyx* showed significant hepatoprotective activity against CCl_4 induced hepatotoxicity in rats. Prenyl, dihydropyran containing chalcone **1** exhibited good *in vitro* antimalarial activity against *P. falciparum* strains 3D7 and K1 with low cytotoxicity. Triazole moiety attached isoflavone MA-8 found inhibitor of estrogen receptor alpha-positive breast cancer, kaempferitrin extracted from the leaves of *Hedyotis verticillata* it showed good biological activity (Fig. 2) [10].

1.2. CHALCONE

The name of chalcone (1,3-diaryl-2-propen-1-ones) was first given by Kostanecki and Tambor [11]. Chemically, chalcone is defined as open-chain flavonoid in which the two aromatic rings (ring A and B) having various substituents. Rings are inter-connected by a highly electrophilic three carbon α,β-unsaturated carbonyl (–CO–CH=CH-) system that assumes linear or nearly planar structure [12]. They possess conjugated double bonds and a completely delocalized-π-electron system on both benzene rings (Fig. 3) [13].

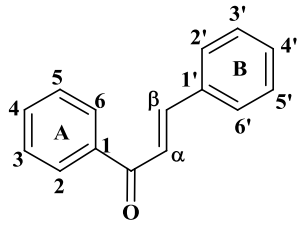


Fig.3: General structure of chalcone (C_6 - C_3 - C_6 system).

They are both intermediates and end products in flavonoids biosynthesis, act as self-protective compounds, participate in plant-insects interactions and contribute to the medicinal value of herbs. Some of chalcone derivatives from plant extraction have shown in fig. 4 which has shown excellent biological activities. In laboratories, chalcones are used as precursors in the synthesis of biologically important molecules and intermediates such as chalcone containing pyrans, benzopyrans [14], pyrazolines [15], chalcone epoxides [16], chalcone sulfones and flavones [17]. Naturally occurring chalcones and their synthetic analogs display a wide spectrum of biological activities including anti-inflammatory [18], antifungal [19], antioxidant [20], cytotoxic [21] and anticancer [22]. Some other chalcone derivatives are reported to inhibit the polymerization of tubulin to form microtubules and are

therefore anti-mitotic agents which can be used as anti-gout agents. They are also known to inhibit the annihilation of myelin sheath in the central nervous system (CNS) of multiple sclerosis patients and are thus useful in controlling the progressive nature of the disease [23]. Some of the chalcone derivatives have been found to inhibit several important enzymes in cellular systems such as xanthine oxidase and protein tyrosine kinase. Apart from being biologically important, chalcone derivatives have also shown non-linear optical (NLO) properties with excellent blue light transmittance and good crystallizability [24]. They provide a necessary configuration to show NLO property with two planar rings connected through conjugated double bond. For this reason they are an object of continuously growing interest amongst the scientists. Attention is mainly drawn to the common skeleton and possibilities for its modifications guided by mechanistic and structure-activity relationship (SAR) studies.

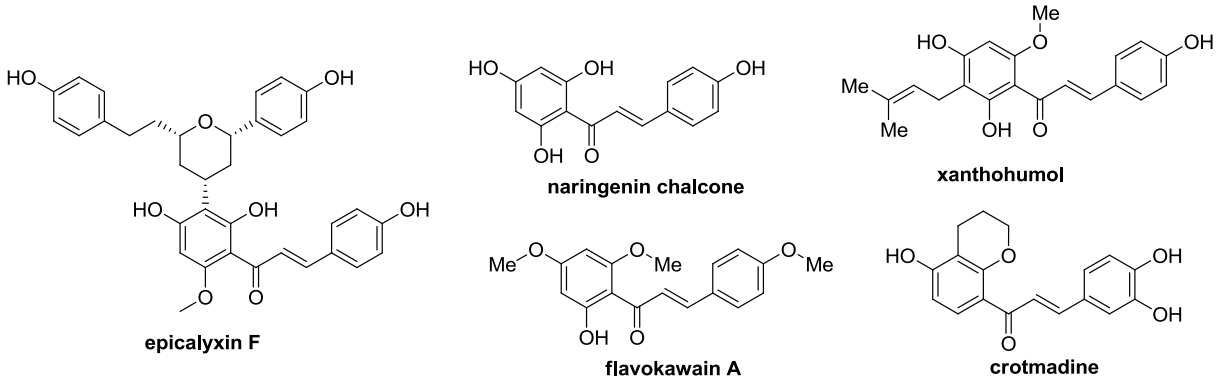
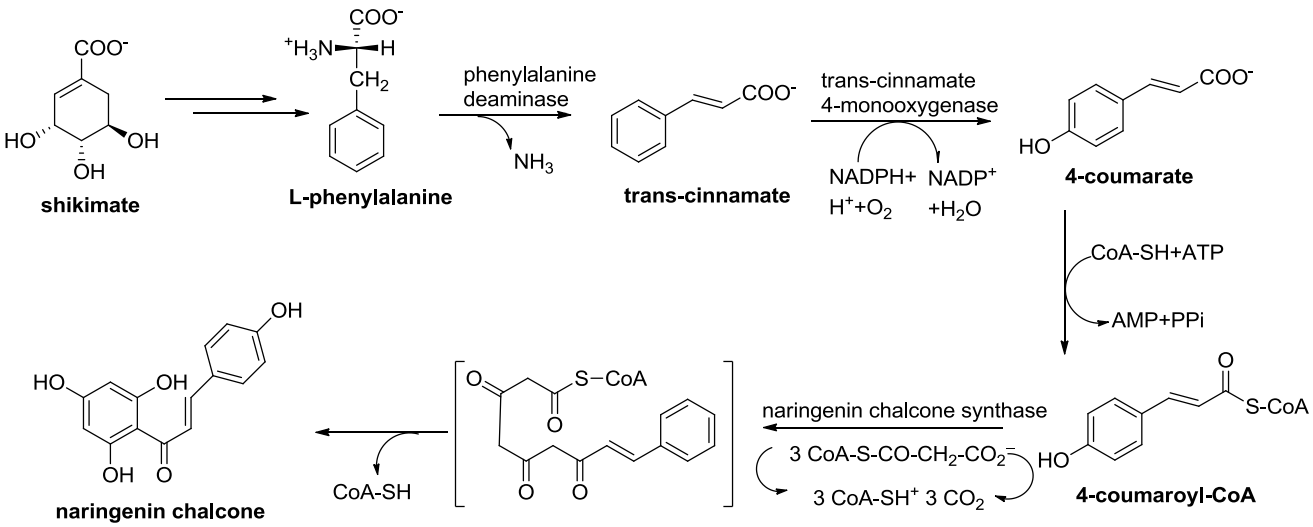


Fig. 4: Some naturally occurring chalcone derivatives.

1.2.1. Methods of chalcone synthesis

1.2.1.1. Biosynthesis method of chalcone

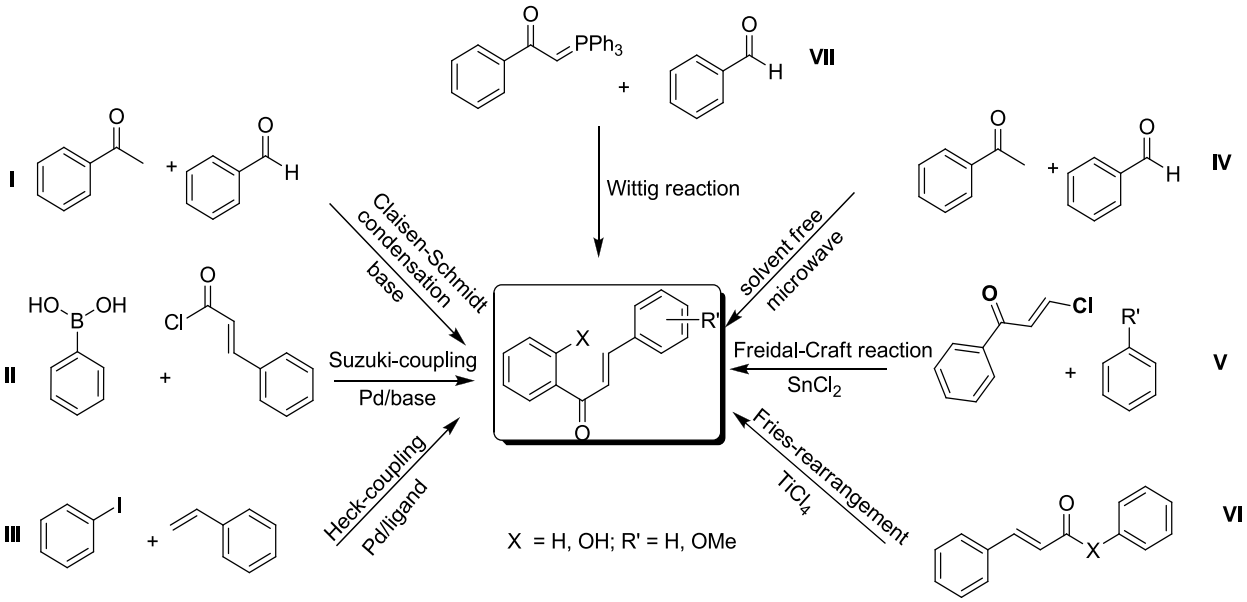
In biosynthesis, chalcones are synthesized their carbon skeleton from two basic compounds, L-phenylalanine, and malonyl CoA. L-phenylalanine synthesized *via* the shikimate pathway which is deaminated by *phenylalanine deaminase* to give trans-cinnamate, then in the presence of *trans-cinnamate 4-monooxygenase* generates 4-coumarate which reacts with coenzyme A to produce 4-coumaroyl-CoA. It reacts with malonyl-CoA in presence of *naringenin chalcone synthase* by losing coenzyme A produce naringenin chalcone (scheme 1) [25,26].



Scheme 1: Biosynthesis pathway of chalcone.

1.2.1.2. Synthetic methods

Chalcone extraction and purification from plants is expensive and time consuming processes. Therefore synthetic chemists in laboratory to synthesize these in a cheap, easy way and in short time various methods developed. Chalcones usually synthesized from acetophenones and benzaldehydes *via* the Claisen-Schmidt condensation, using acids and bases such as potassium hydroxide (KOH),



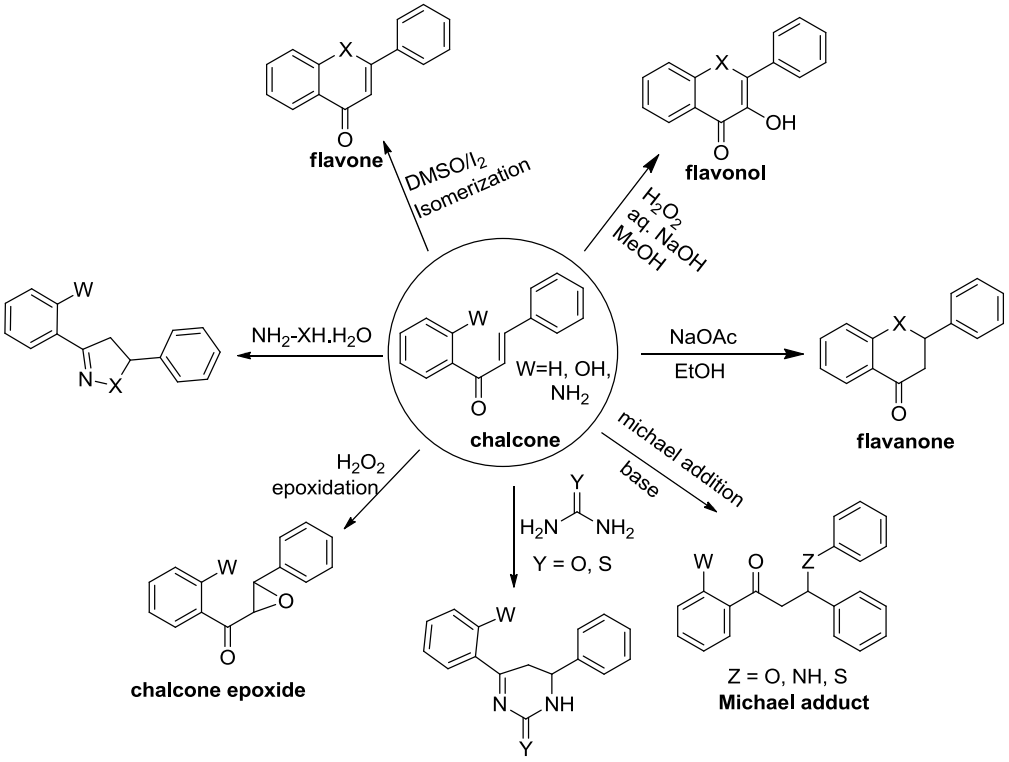
Scheme 2: Synthetic routes towards chalcone preparation.

barium hydroxide ($Ba(OH)_2$), lithium hydroxide ($LiOH.H_2O$) and sodium hydroxide (NaOH), whereas dry HCl, Boron trifluoride (BF_3), aluminium chloride ($AlCl_3$), titanium chloride ($TiCl_3$) and ruthenium

chloride ($RuCl_3$) are used as acids in polar solvents. In addition, more exotic synthetic protocols have been reported, such as the palladium-mediated Suzuki coupling between cinnamoyl chloride and phenyl boronic acids, the carbonylative Heck coupling with aryl halides, styrenes in the presence of carbon monoxide [27], Wittig reaction of α-carbonylated ylide with aldehydes [28], Fries-rearrangement, Friedel-Crafts acylation [29], and solvent free microwave irradiation [30] (Scheme 2).

1.2.2. Reactivity of chalcone

Chalcones are highly electrophilic α,β-unsaturated carbonyl system which makes chalcone very prone to undergo various transformations and different reactions with bidentate nucleophiles to give five, six and seven-membered heterocyclic compounds. Chalcone is a key intermediate in the formation of major flavonoid classes in biosynthesis and synthetic methods. The reaction of 2'-hydroxychalcone, in presence of iodine in DMSO (dimethyl sulfoxide) which gave flavone [31], with sodium acetate in ethanol to obtain flavanone [32], likewise, reaction with hydrogen peroxide in alkali methanol gave flavonol [33]. Similarly, the reaction with hydrazine hydrate, hydroxylamine, urea, thiourea gave pyrazole [34], isooxazole, pyrimido incorporated derivatives respectively [35]. Due to highly reactiveness of α,β-unsaturated double bond it can undergo oxa, aza and thia Michael addition reactions and gave Michael adducts (scheme 3) [36].



Scheme 3: Various derivatives from chalcone as starting material.

1.3. FLAVONE

Flavones are a class of flavonoids based on the backbone of 2-phenylchromen-4-one (2-phenyl-1-benzopyran-4-one), which are also widely distributed in plant kingdom (Fig. 5).

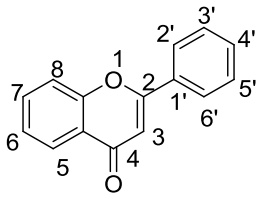


Fig. 5: General structure of flavone.

They are mainly found in cereals and herbs. The major natural flavones are apigenin (4',5,7-trihydroxyflavone), luteolin (3',4',5,7-tetrahydroxyflavone), tangeritin (4',5,6,7,8-pentamethoxyflavone), chrysin (5,7-dihydroxyflavone), 6-hydroxyflavone, baicalein (5,6,7-trihydroxyflavone), scutellarein (5,6,7,4'-tetrahydroxyflavone) and wogonin (5,7-dihydroxy-8-methoxy flavone). Synthetic flavones are diosmin, hidrosmin and flavoxate (Fig. 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 range 20–50 mg per day. In recent years, scientific and public interest in flavones 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 venous disease, neurodegenerative diseases such as alzheimer's disease, anti-inflammatory and anti-apoptotic activity has been demonstrated in neuronal cells, *in vitro* [37].

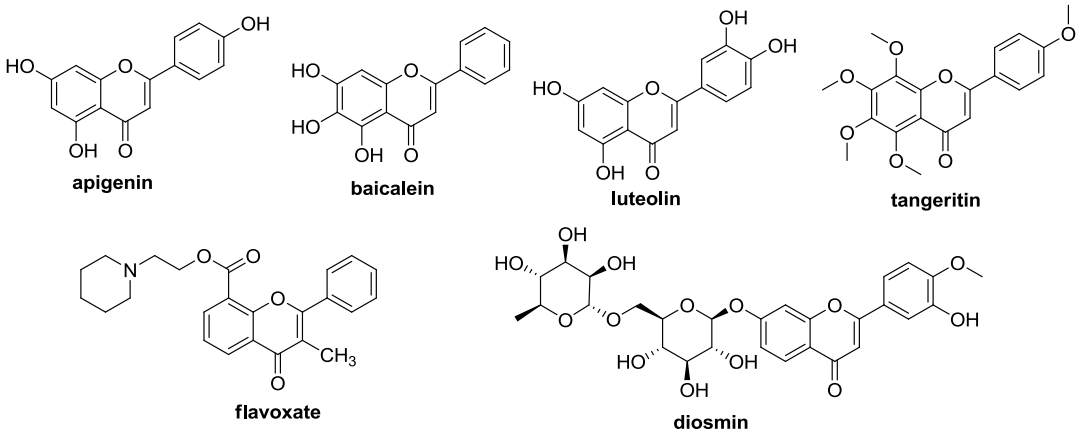
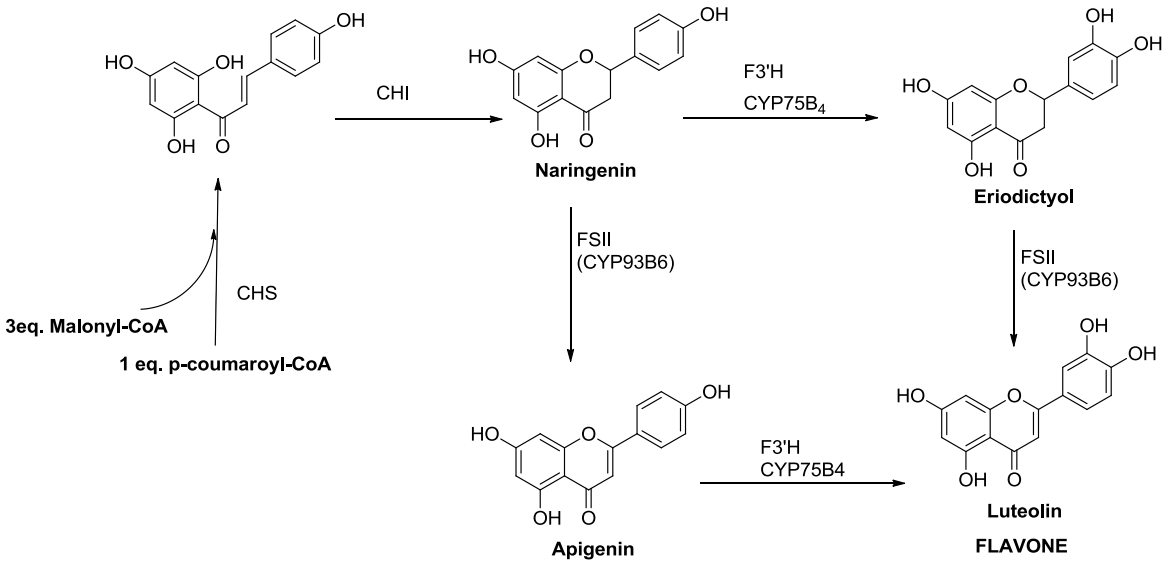


Fig. 6: Some examples of natural and synthetic flavones.

1.3.1. Methods for flavone synthesis

1.3.1.1. Biosynthesis method

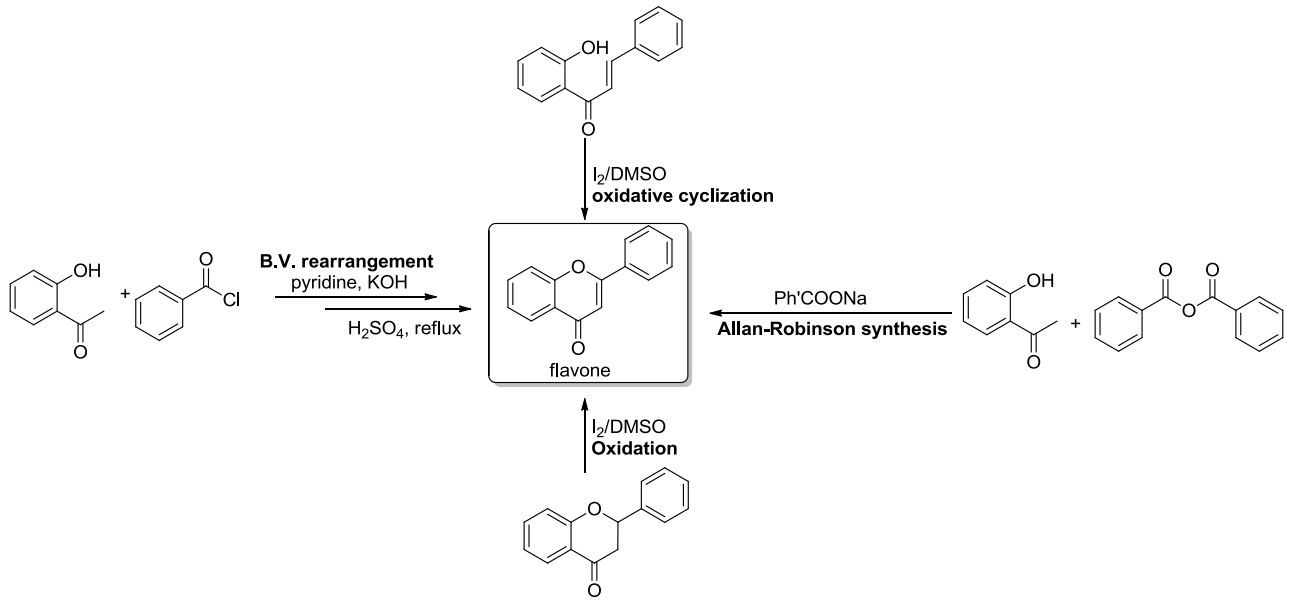


Scheme 4: Biosynthesis pathway of flavone.

Flavones are occurs in nature as C-glycosides, O-glycosides, N-glycosides. In biosynthesis method, the main frame of flavone constructed by 3eq. malonyl-CoA and 1 eq. *p*-coumaroyl-CoA in presence of *chalcone synthase* enzyme forms chalcone (naringenin chalcone), it undergoes cyclization in presence of *chalcone isomerase* enzyme to give flavanone (naringenine), and after dehydration in presence of *flavone synthase* affords flavone (apigenine). In presence of *flavone 3'-hydroxylase* (F3'H) hydroxylation on apigenine taking place to give luteolin [2].

1.3.1.2. Synthetic methods

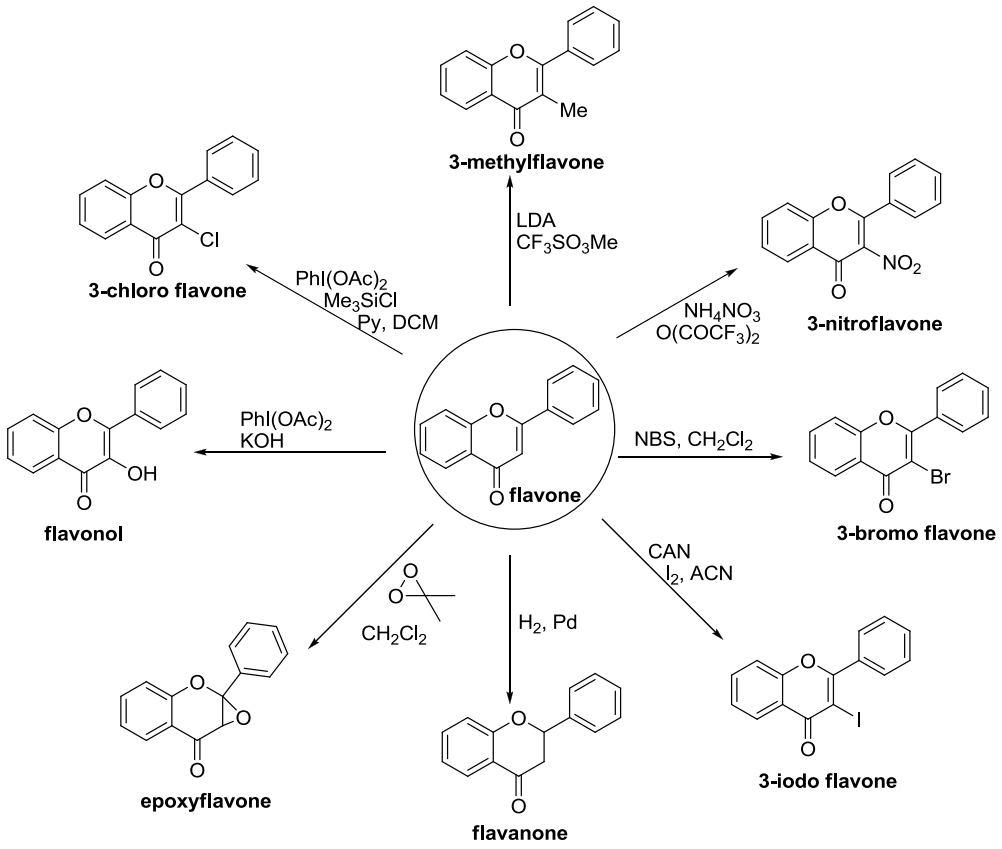
Synthesize flavones in the laboratory, many methods have developed such as Allan-Robinson method in which 2'-hydroxyacetophenone and benzoic anhydride reacts in presence of sodium salt of acid to give flavone [38]. Baker-Venkataraman rearrangement in which 2'-hydroxy acetophenone and benzoyl chloride reacts in presence of base in pyridine forms 1,3-diketone which in presence of acidic medium cyclizes to afford flavone [39]. Oxidative cyclization of 2'-hydroxy chalcone in presence of iodine catalyst gave flavone [40]. Similarly, oxidation of flavanone in presence of I_2/DMSO affords flavone [41].



Scheme 5: Synthetic routes towards flavones synthesis.

1.3.2. Reactivity of flavone

In flavones, the reactive centers are 3rd position and α,β-unsaturated double bond therefore enough reactions performed at those centers such as bromination using N-bromosuccinimide to afford 3-bromoflavone [42], Regioselective monobromination using bromodimethylsulfonium bromide to synthesize 8-bromoflavones [43], chlorination using trimethylsilyl chloride to afford 3-chloroflavone [44], iodination using I_2, ceric ammonium nitrate to afford 3-iodoflavone [45], methylation using lithium diisopropylamide (LDA), CF_3SO_3Me to afford 3-methylflavone [46], nitration using ammonium nitrate and trifluoroacetic anhydride to afford 3-nitroflavone [47], hydroxylation using (diacetoxyiodo)benzene and KOH to afford 3-hydroxy flavone [48], reduction of α,β-unsaturated double bond performed using $NiCl_2.6H_2O$ catalyst and $NaBH_4$ as reducing agents in methanol treated to afford flavanone [49], similarly epoxidation of α,β-unsaturated double bond occurred using dimethyldioxirane [50].



Scheme 6: Various derivatives from flavone as starting material.

1.4. FLAVONOL

Flavonols are a class of flavonoids that have the 3-hydroxyflavone backbone (3-hydroxy-2-phenylchromen-4-one) (Fig. 7).

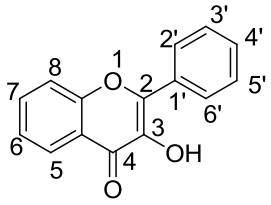


Fig.7: General structure of flavonol.

Their diversity stems from the different positions of the phenolic-OH groups. Good sources of flavonols in the diet are onion, tomato, apple, grape, berries, kale, broccoli, lettuce, tea and red wine. The greener the leaf is, the more it contains flavonols. The major dietary flavonols are quercetin, kaempferol, myricetin, rutin and isorhamnetin (Fig. 8).

Flavonols provide numerous health benefits. For example, increased intake of flavonols is associated with reduced risk of cardiovascular diseases [51]. This can be attributed to their anti-

oxidant properties which helps improve endothelial function and reduce platelet activity. Furthermore, antioxidant properties of flavonols also help prevent oxidative damage to cells, lipids and DNA. The antioxidant properties of flavonols stem from the presence of aromatic rings of the flavonoid molecule, which allow the donation and acceptance of electrons from free radical species. This helps quench free radicals. In addition, intake of flavonols is associated with reduced risk of cancer and stroke. Furthermore, some flavonols promote bone health, prevent osteoporosis and have anti-inflammatory properties. Flavonols also promote healthy brain, as they possess neuroprotective properties. Hence, consumption of food rich in flavonols is associated with long-term health benefits.

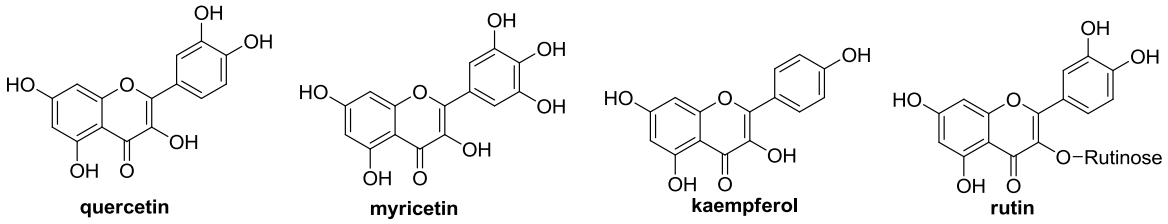
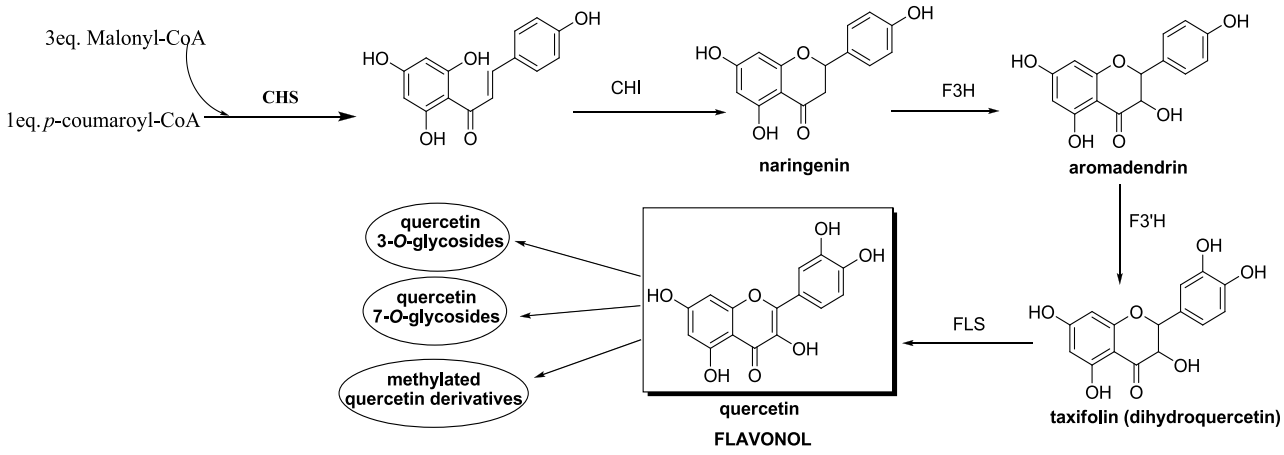


Fig.8: Some important derivatives of flavonol.

1.4.1. Methods for flavonol synthesis

1.4.1.1. Biosynthesis method



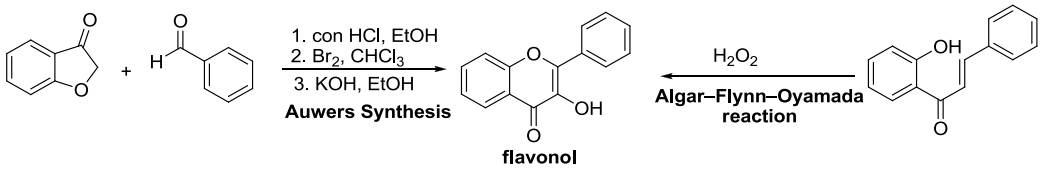
Scheme 7: Biosynthesis pathway of flavonol.

The main frame of flavonol in biosynthesis method constructs by reacting 3 eq. malonyl-CoA and 1eq. *p*-coumaroyl-CoA in presence of *chalcone synthase enzyme* (CHS) to form chalcone (naringenin chalcone), which in the presence of *chalcone isomerase enzyme* (CHI) cyclization takes place and gave flavanone (naringenin) while in the presence of *flavone 3-hydroxylase (F3H), flavone 3'-hydroxylase (F3'H)* hydroxylation takes place and gave aromadendrin, taxifoline respectively.

Taxifolin in presence of *flavonol synthase* (FLS) gave flavonol and further undergoes various transformations to give glycosides.

1.4.1.2. Synthetic methods

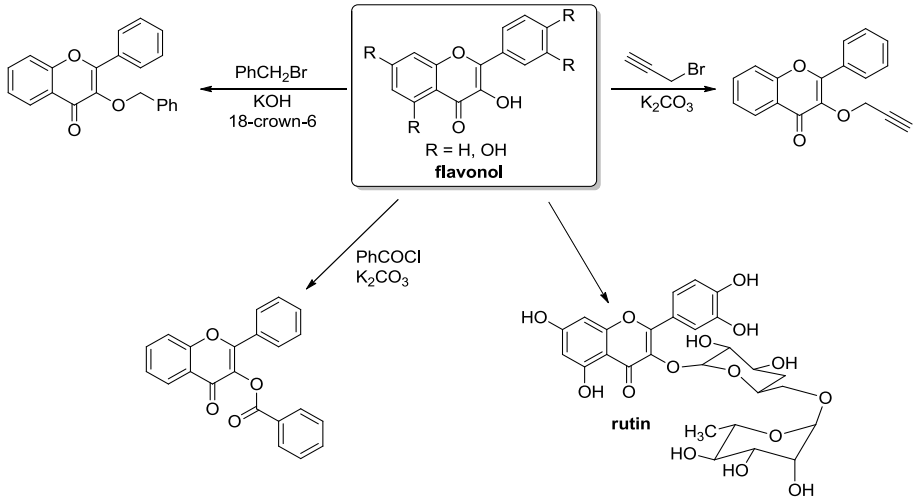
Synthesize of flavonols in the laboratory, many synthetic procedures developed such as Auwers synthesis [52] in which 3-benzofuranone reacts with aldehyde in acidic medium followed by bromination and then rearrangement to give flavonol, Alger-Flynn-Oyamada reaction in which the reaction of chalcone with hydrogen peroxide gave chalcone oxiranes which undergo cyclization to give flavonol [53].



Scheme 8: Synthetic routes towards flavonol synthesis.

1.4.2. Reactivity of flavonol

In flavonol, the reactive site is 3-hydroxy group which undergoes various chemical transformations to give ethers and esters. Propargylation, benzylation and benzoylation of flavonol can obtain by reaction with propargyl bromide, benzyl bromide, benzoyl chloride respectively [54].

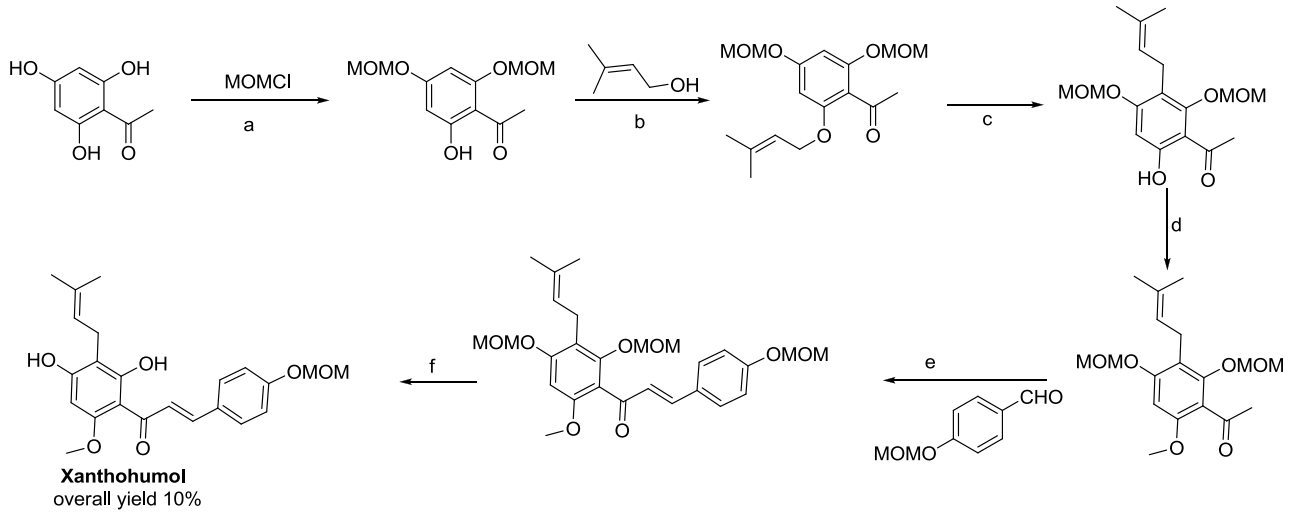


Scheme 9: Synthetic transformations of flavonol.

1.5. SOME NATURALLY OCCURRING/BIOLOGICALLY ACTIVE SYNTHETIC FLAVONOIDS: THEIR SYNTHESIS AND BIOLOGICAL ACTIVITY

Prenyl, geranyl, coumaroyl, pyrano, pyrimidinyl and triazolyl flavonoids are an abundant sub-class of flavonoids that are widely distributed in nature [55]. These are associated with a wide variety of biological activities such as anti-malarial, anti-diabetic, anti-fungal, anti-bacterial, antitumor, anti-metastatic, anti-oxidative, anti-inflammatory and NF-κB inhibitory activities [56].

Xanthohumol is prenylated chalcone present in female inflorescences of the hop plant *Humulus lupulus L*. It showed antioxidant activity and inhibition of HIV-1 as well as anticancer and cancer prevention agent (applicable to both breast and prostate cancers). Khupse *et al.* synthesized xanthohumol in six steps overall 10% yield (Scheme 10) [57].

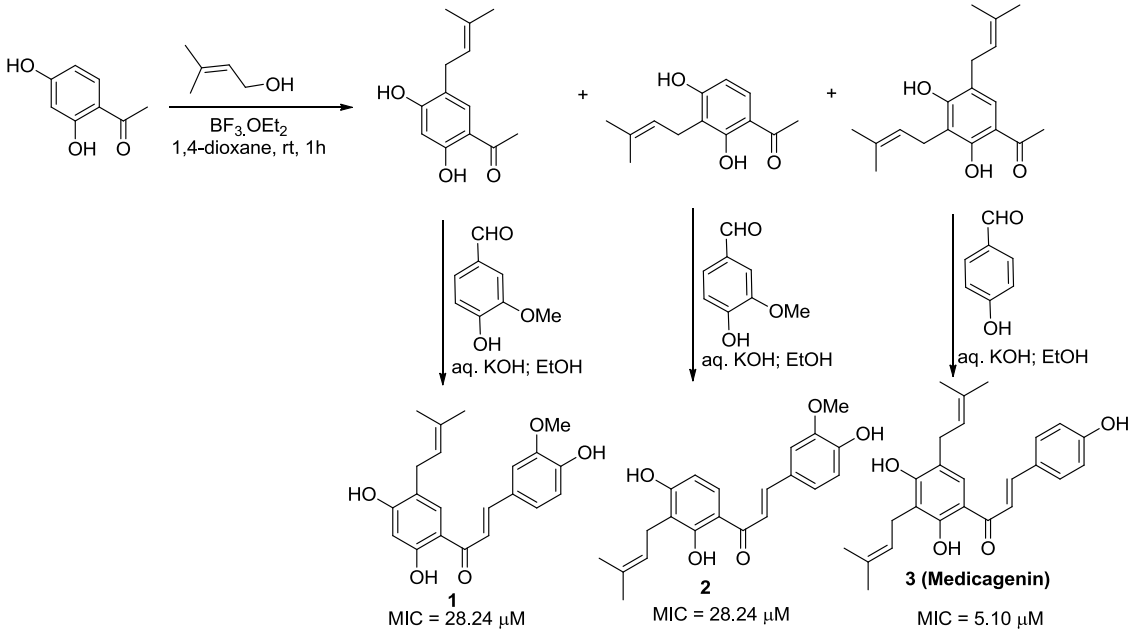


Reagents and conditions: (a) MOMCl (3 equiv.), diisopropyl ethyl amine (3 equiv.), CH_2Cl_2, RT (60%); (b) 3-Methyl-2-butene-1-ol (1.5 equiv.), diethylazodicarboxylate (1.6 equiv.), PPh_3 (1.2 equiv.), toluene/THF, RT (80%); (c) *N*,*N*-dimethylaniline, reflux, 200 ^{0}C (64%); (d) $(CH_3O)_2SO_2$ (2 equiv.), K_2CO_3 (2 equiv.), acetone, reflux (82%); (e) Aqueous NaOH, MeOH, reflux (60%); (f) Conc. HCl (pH 1), MeOH/H_2O, RT (72%).

Scheme 10: Total synthesis of xanthohumol.

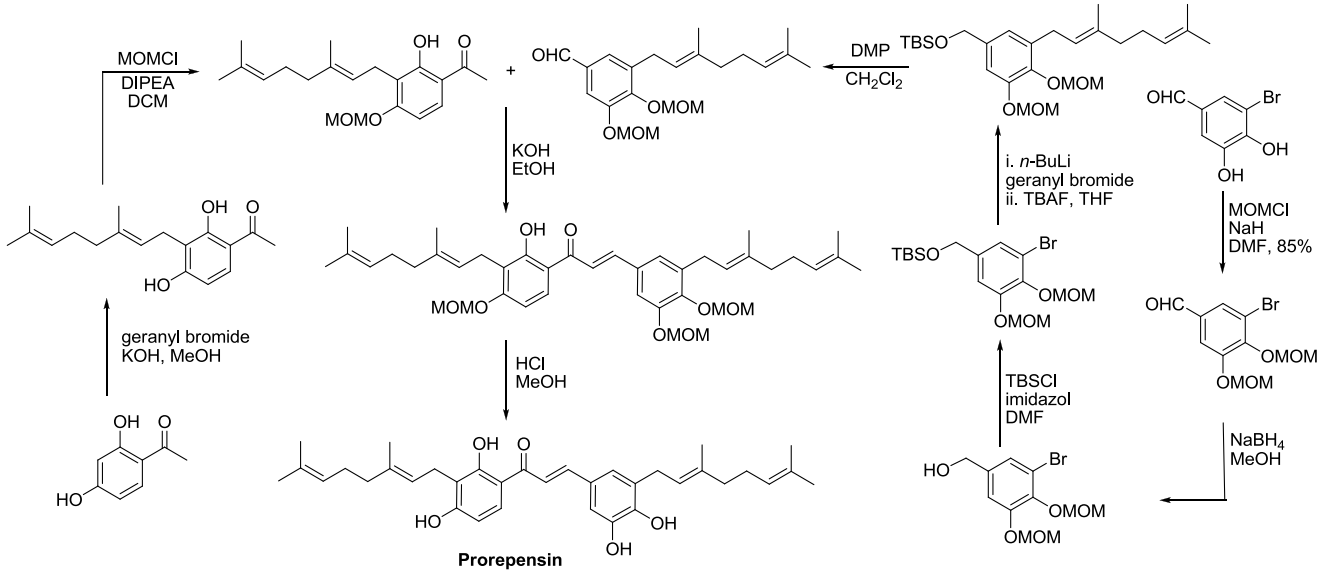
Tadigoppula *et al.* isolated medicagenin (**3**) from *Crotalaria medicagenia*, which exhibited antimalarial activity against *Plasmodium falciparum* and synthesized following synthetic path. Prenylation of 2,4-dihydroxyacetophenone with 2-methyl-but-3-en-2-ol in the presence of $BF_3{\cdot}OEt_2$ in dry dioxane resulted 2,4-dihydroxy-5-C-prenylacetophenone, 2,4-dihydroxy-3-C-prenylacetophenone, and 2,4-dihydroxy-3,5-C-diprenylacetophenone. The prenylacetophenone and substituted benzaldehydes were subjected to Claisen−Schmidt condensation using aqueous KOH in ethanol to afford **1**, **2** and medicagenin **3** (Scheme 11). Among them diprenylated chalcone **3** shown

excellent activity (MIC: 5.10 μM) than monoprenylated chalcone (MIC: 28.24 μM) and the position of prenyl group didn't show any effect [58].



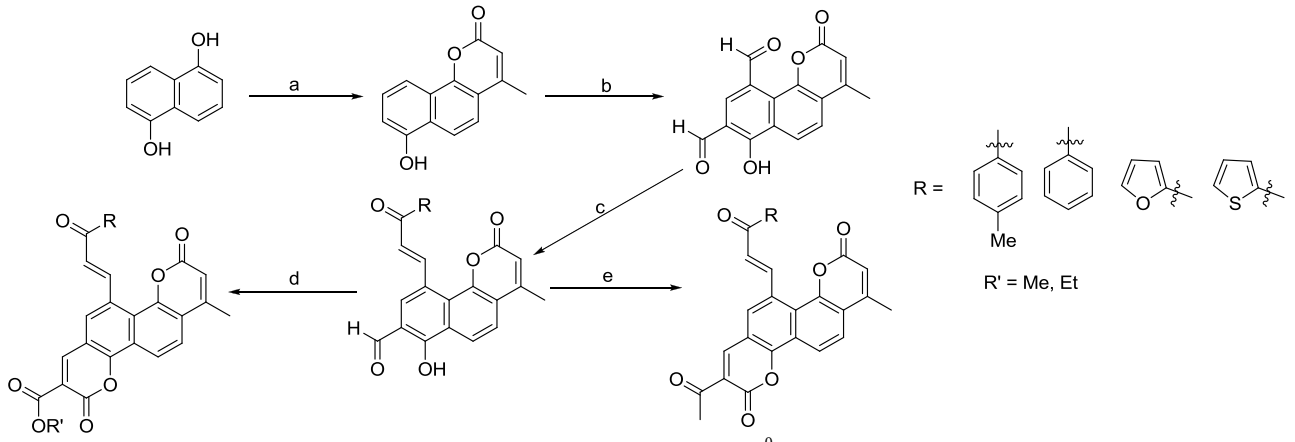
Scheme 11: Synthesis of prenylated chalcone.

Prorepensin isolated from *Dorstenia prorepens* and *D. picta*. Jung *et al.* first time reported total synthesis of prorepensin in which Claisen-Schmidt condensation of MOM protected geranylated aldehyde and MOM protected geranylated ketone reacts in presence of alkali KOH gave MOM protected bis-geranyl chalcone which on deprotection with HCl in MeOH gave prorepensin. Prorepensin showed *in vitro* antimicrobial activity against β-lactam-resistant bacteria [59].



Scheme12: Synthetic pathway of prorepensin.

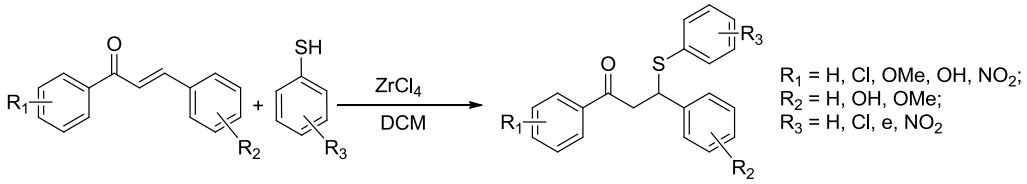
Sashidhara *et al*. synthesized novel biscoumarin–chalcone hybrids, the Pechmann reaction of 1,5-dihydroxynaphthalene with ethylacetoacetate followed by Duff formylation in the presence of hexamethylenetetraamine (HMTA) and TFA at 120 ^{0}C gave dicarbaldehyde, which on condensation with different acetophenones in the presence of a catalytic amount of conc. HCl afforded regioselective *para* condensed chalcones in good yields. These chalcone derivatives on subsequent Knoevenagel type condensation with different active methylene compounds furnished biscoumarin–chalcone hybrids. Biscoumarin–chalcone hybrids were showed anti-inflammatory and antioxidant activity (Scheme 13) [60].



Reagents and conditions: (a) Ethyl acetoacetate, *p*-toluene sulphonic acid, 75 ^{0}C, 8h; (b) (i) Hexamethylenetetramine, trifluoroacetic acid, 120 ^{0}C, 4 h; (ii) aq H_2SO_4, 100 ^{0}C, 1 h; (c) R-$COCH_3$, Conc. HCl, dioxane, reflux, 5 h; (d) $CH_2(COOR')_2$, piperidine, EtOH, reflux, 30 min.; (e) Ethyl acetoacetate, piperidine, EtOH, reflux, 30 min.

Scheme 13: Synthesis of novel biscoumarin–chalcone hybrids.

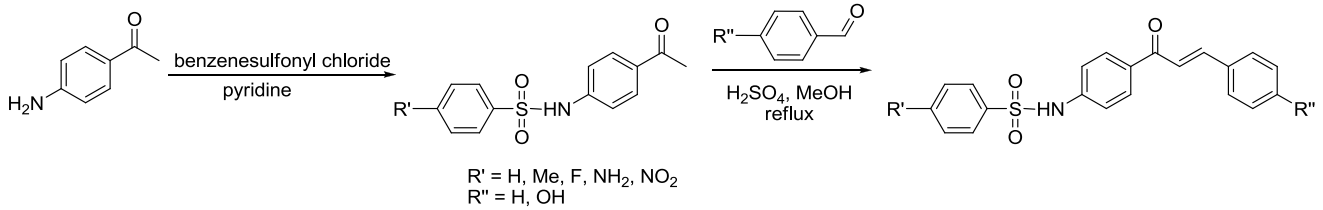
1,3-biarylsulfanyl derivatives act as anti-breast cancer agents which are synthesized by reaction of chalcone with mercaptans in the presence of a catalytic amount of zirconium (IV) chlorides in dichloromethane to affords Michael adducts (scheme 14) [61].



Scheme 14: Synthesis of 1,3-biarylsulfanyl derivatives.

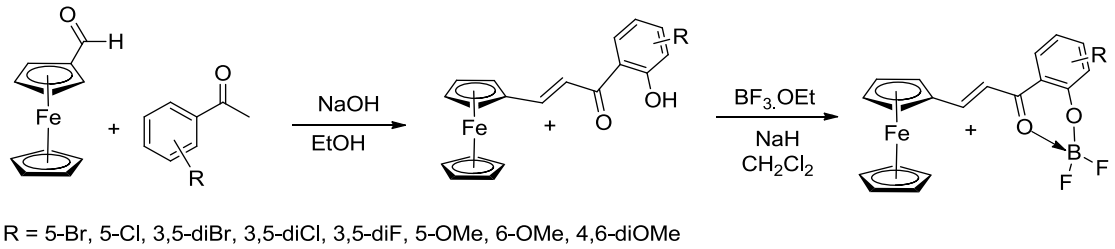
Kang *et al*. synthesized sulfonamide derivatives and evaluated inhibitory effects of compounds on BACE1 (β-secretase 1) activities. Here treatment of aminoacetophenone with the appropriate benzenesulfonyl chloride in pyridine gave N-sulfonyl aminoacetophenone which on Claisen-Schmit

condensation with appropriate benzaldehyde in presence of a catalytic amount of H_2SO_4 obtained sulfonamide chalcones (Scheme 15).



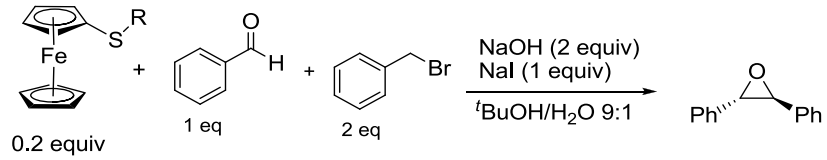
Scheme 15: Synthesis of sulfonamide chalcone.

Ferrocenylchalcones were synthesized by treatment of ferrocenyl aldehydes with substituted acetophenones in basic medium. Ferrocenylchalcones were showed *in vitro* antimalarial activity against a chloroquine resistant strain of *plasmodium falciparum* and their difluoridoborates inhibit HIV-1 integrase and display low activity towards cancer and endothelial cells (Scheme 16) [62].



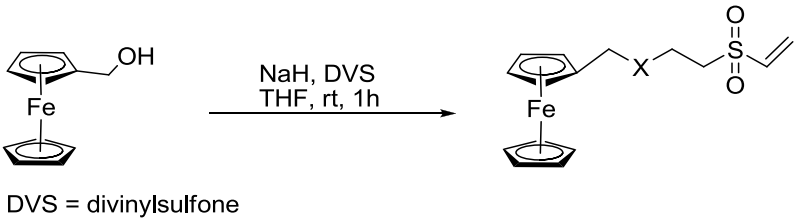
Scheme 16: Synthesis of ferrocenyl chalcone difluoridoborates.

Ferrocenyl sulfides acts as catalysts for the asymmetric epoxidation of stilbenes *via* formation of sulfonium ylides, obtained stilbene oxide in good yields with enantiomeric excess up to 53% (Scheme 17) [63].



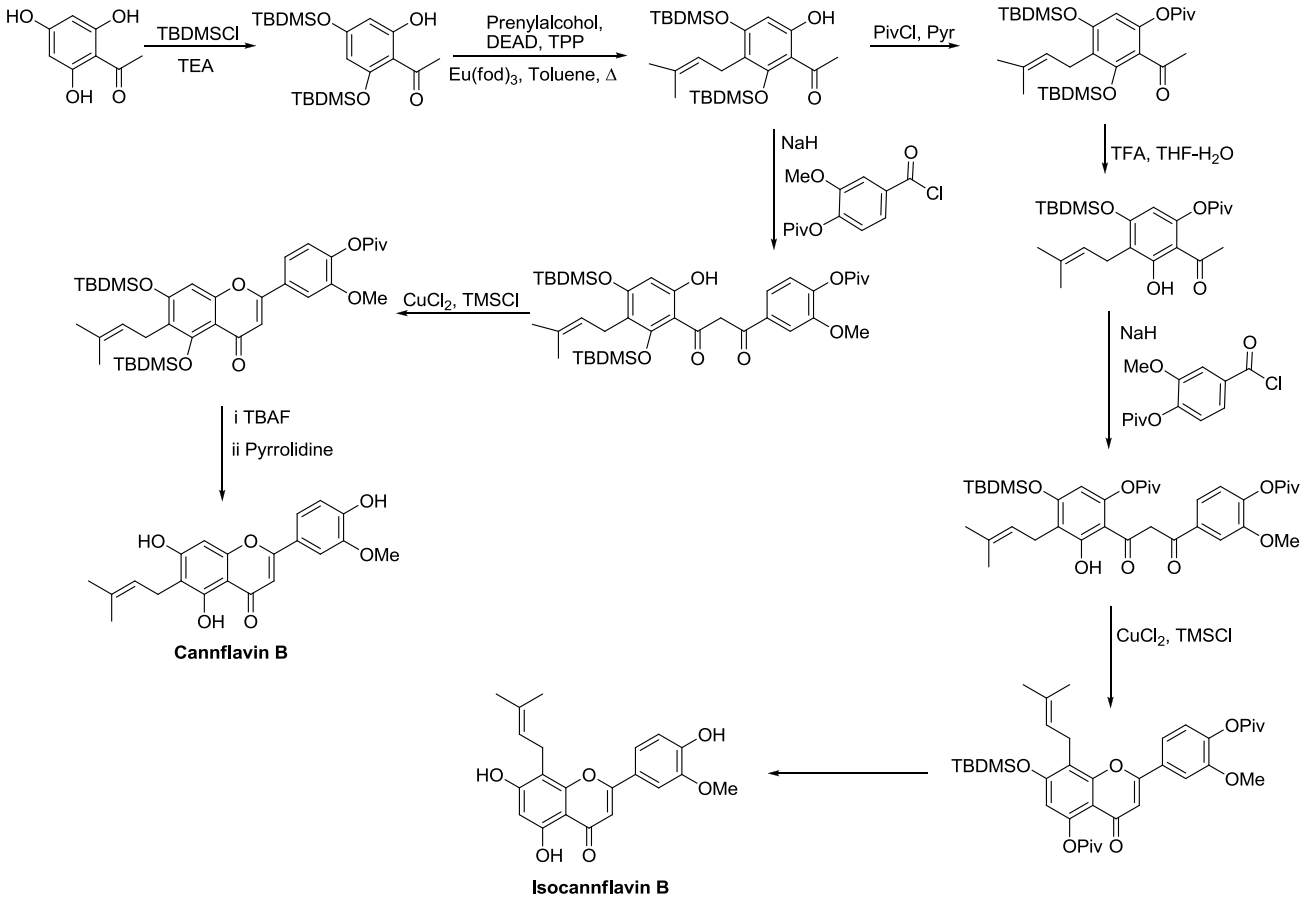
Scheme 17: Asymmetric epoxidation using ferrocenyl sulfides as catalysts.

Fernandez *et al*. synthesized vinyl sulfone ferrocenylation reagents which are applicable in conjugation and bioconjugation process (Scheme 18) [64].



Scheme 18: Synthesis of vinyl sulfone ferrocenylation reagents.

C-prenylated flavonoids such as cannflavin B and isocannflavin B have been demonstrated number of bioactivities including estrogen receptors (ERs), heat-shock proteins (Hsp-90), cyclooxygenases (COXs), P-glycoproteins (PgPs), and phosphodiesterases (PDEs). The key C-prenyldisilylated intermediate was synthesized as follows. The 2,4,6-trihydroxy acetophenone protected with *tert*-butyldimethylsilyl chloride (TBDMSCl) next pivaloylated and then by mild acidolysis with TFA in THF/water chemoselectively *ortho*-desilylated followed by reaction with pivaloyl-protected vanilloyl chloride under NaH promotion obtained 1,3-diketone which on rearrangement and deprotection obtained C-6 and C-8 prenylated flavones (Scheme 19) [65].



Scheme 19: Synthesis of cannflavin B and isocannflavin B.

Hosek *et al*. recently reported prenylated and geranylated flavonoids such as cudraflavone B, pomiferin, osajin and diplacone were tested for their antioxidant and anti-inflammatory effects to identify potential relationships between chemical structure and antioxidant or anti-inflammatory properties. The most potent antioxidant activities in cell-free models were observed for diplacone,

whereas cudraflavone B and osajin showed a pro-oxidant effect in J774.A1 cells. All flavonoids were able to inhibit IκB α-degradation, but only diplacone down-regulated COX-2 expression (Fig. 9) [66].

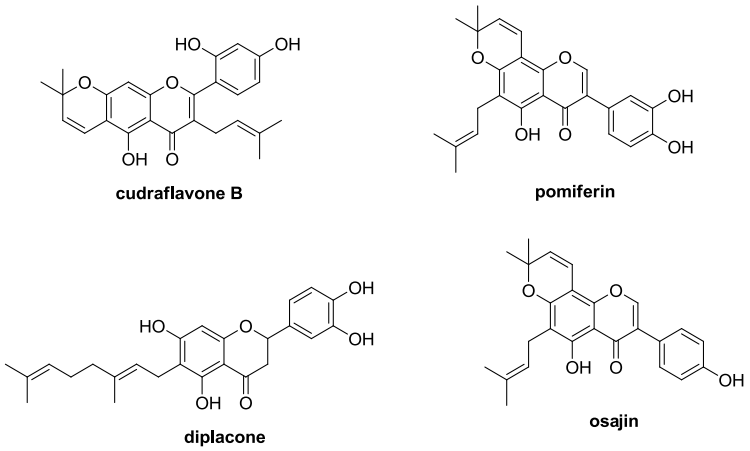
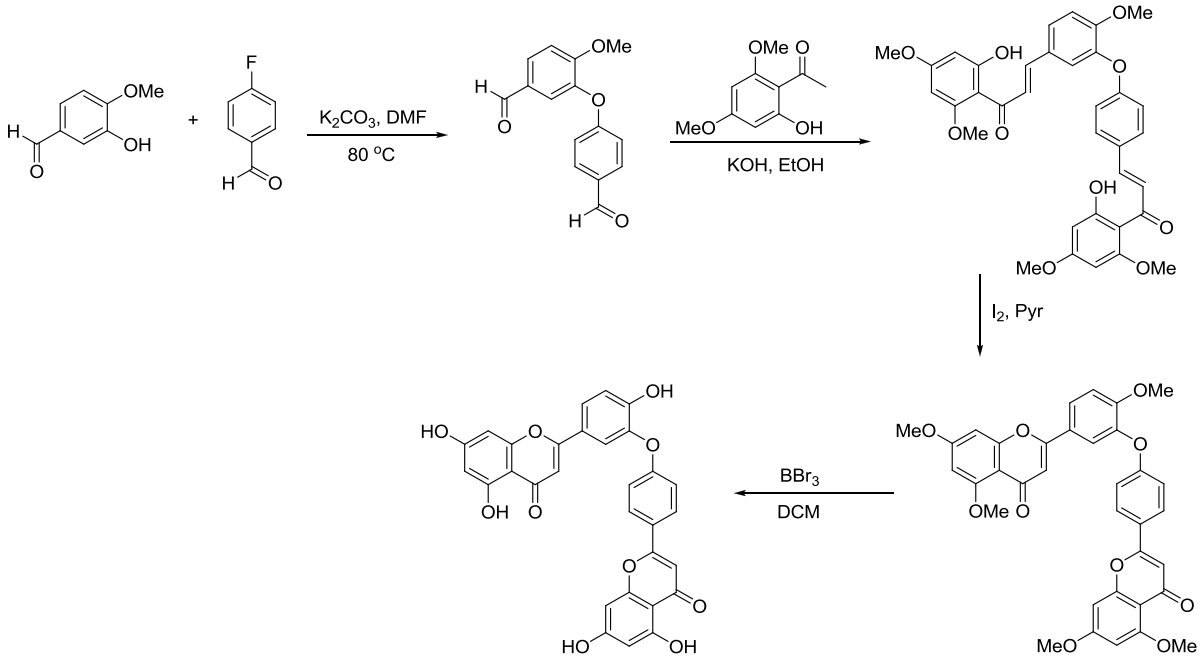


Fig.9: Prenylated and geranylated flavonoids.

Ndoile *et al*. synthesized ochnaflavone, it is an asymmetric biflavone consisting of apigenin and luteolin moieties. This biflavone showed anti-inflammatory, antileishmanial, antiplasmodial, antiviral and β-secretase inhibitory activity (Scheme 20) [67].



Scheme 20: Synthesis of ochnaflavone.

Nine flavonoids were isolated from the root bark of *Morus lhou L*. displayed cholinesterase inhibitory activity. The isolated compounds were identified as 5'-geranyl-4'-methoxy-5,7,2'-trihydroxyflavone, 5'-geranyl-5,7,2',4'-tetrahydroxyflavone, kuwanon U, kuwanon E, morusin,

morusinol, cyclomorusin, neocyclomorusin, and kuwanon C. All compounds apart from compounds inhibited cholinesterase enzyme in a dose-dependent manner with K_i values ranging between 3.1-37.5μM and between 1.7-19.1μM against acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes respectively (Fig. 10) [68].

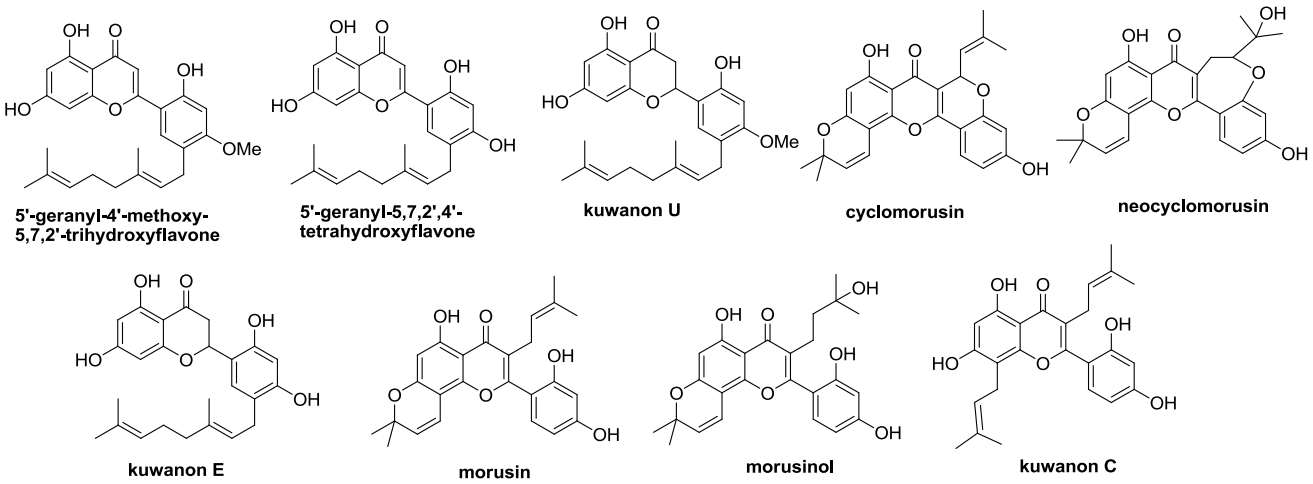
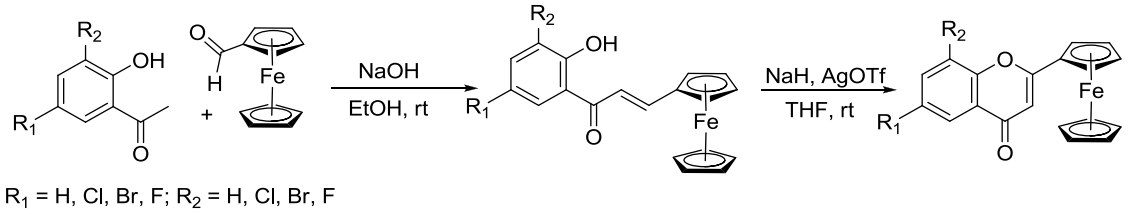


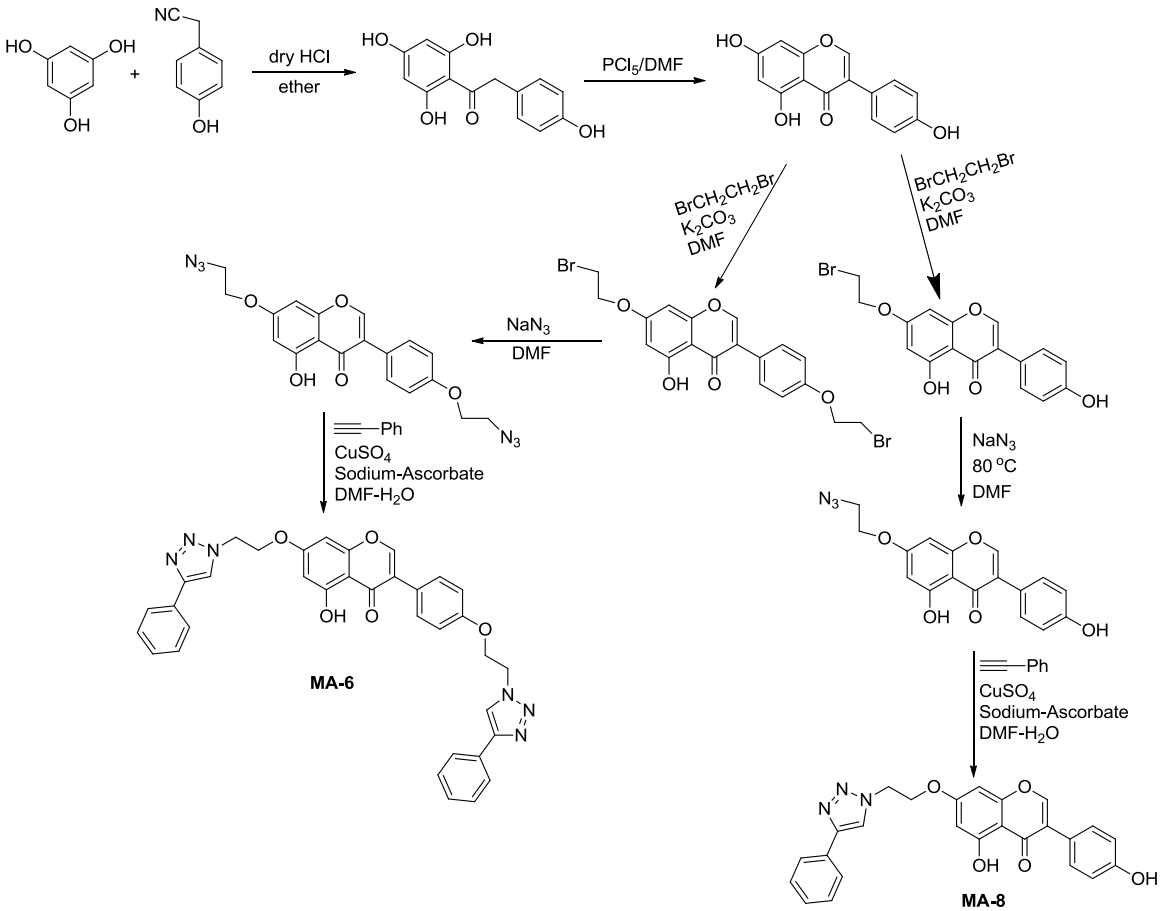
Fig. 10: Flavonoids isolated from *Morus lhou.*

Ferrocene chalcone was synthesized by combining an equimolar proportion of ferrocene carboxaldehyde and the 2'-hydroxyacetophenone in the presence of 3 eq. NaOH in EtOH. Followed by oxidative cyclization of the chalcone was achieved using NaH and silver triflate in THF at room temperature. The ferrocenyl chalcones and flavones showed cytotoxicity against the murine B16 melanoma cancer cell line. Ferrocenyl flavones significantly more cytotoxic than their organic analogs against B16 melanoma cells, Ferrocenyl flavones having IC_{50} values in micromolar range (Scheme 21) [69].



Scheme 21: Synthesis of ferrocenyl flavone.

Triazole containing flavonoids were synthesized *via* copper catalyzed click chemistry in DMF-H_2O. These acts as inhibitors of estrogen receptors, alpha-positive breast cancer (Scheme 22) [70].



Scheme 22: Synthesis of inhibitors of estrogen receptors.

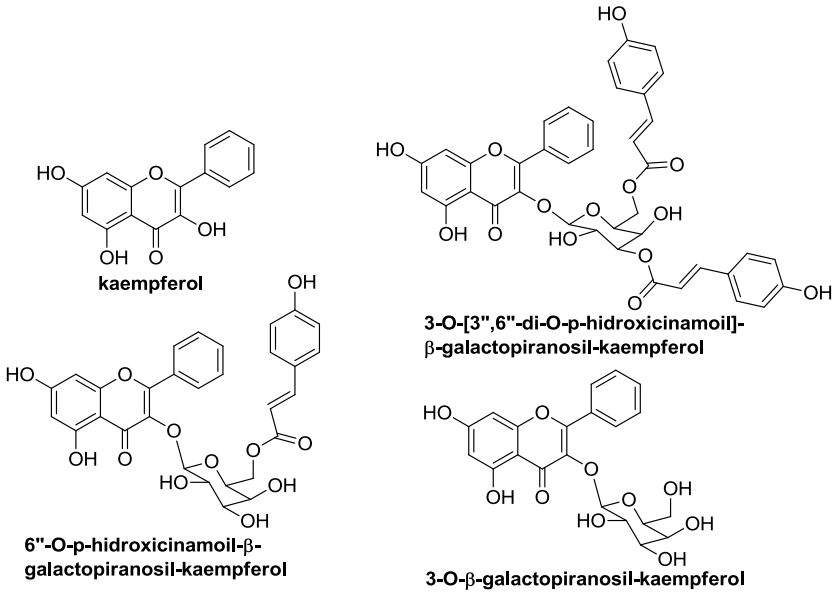


Fig. 11: Flavonoids isolated from *Annona dioica* leaves methanol extract.

Vega *et al*. extracted four kaempferol derivatives from leaves of *Annona dioica.* identified as kaempferol, 3-*O*-[3",6"-di-*O*-p-hydroxycinnamoyl]-β-galactopyranosyl-kaempferol, 6"-*O*-*p*-hydroxycinnamoyl-β-galactopyranosyl-kaempferol and 3-O-β-galactopyranosyl-kaempferol and evaluated for anti-proliferative activity which showed better than quercetin (Fig. 11) [71].

1.6. TETRAHYDROPYRAN

Functionalized tetrahydropyrans (THPs) ring systems are important structural motifs feature in a vast array of natural products such as phorboxazoles (A and B) [72], (−)-centrolobine [73], GEX1A/herboxidiene [74], tetrahydrocannabinol, bryostatins [75], pheromones [76], neopeltolide, altohyrtin A, and miyakolide (Fig.12). They are also used as materials in photographic films [77] and host–guest chemistry [78]. Among available THPs, 2,4,6-trisubstituted THPs are one of the most abundant classes in natural products and have tremendous applications in pharmaceuticals and are widely present in biologically active core structures such as 4-oxygenated, 4-halogenated, 4-sulfonyl- and 4-azido/amido THPs therefore, attracted considerable interest [79].

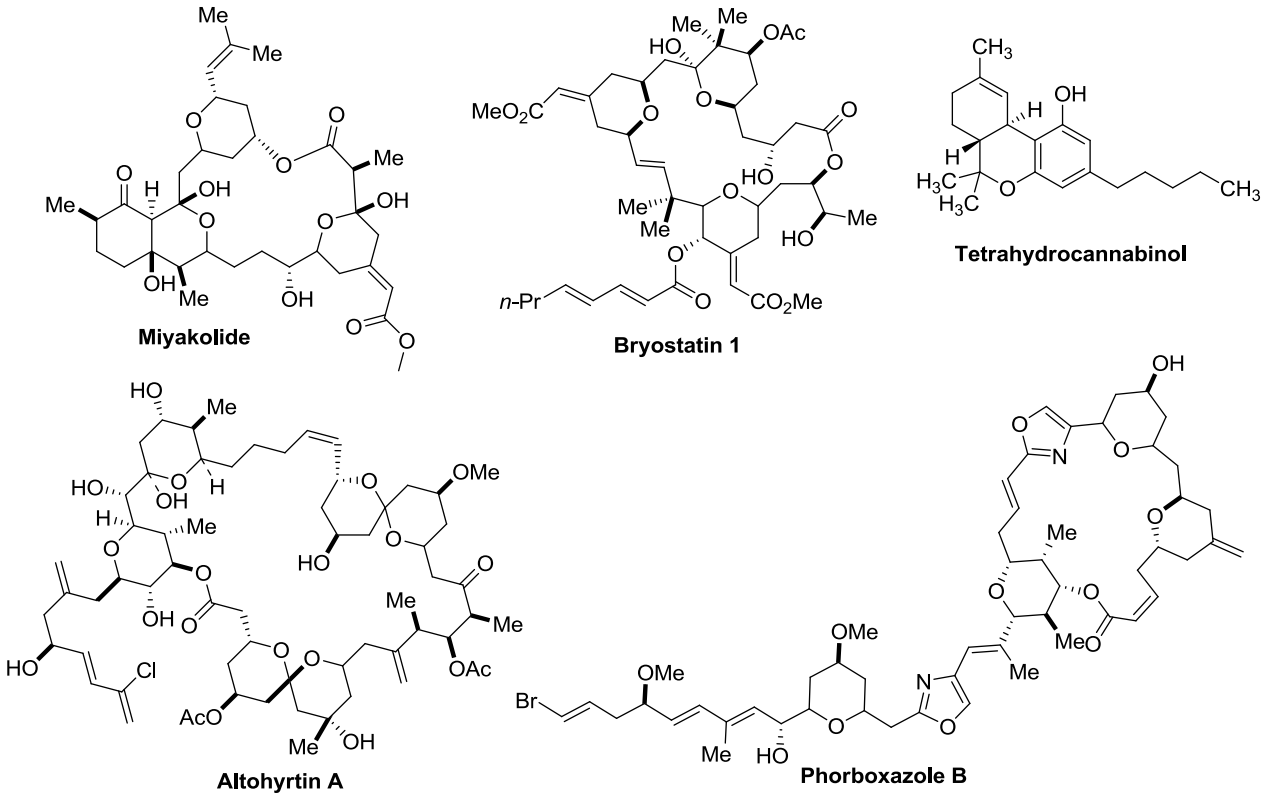


Fig. 12: Natural products containing 2,4,6-trisubstituted tetrahydropyran ring system as central core.

Substituted THPs have shown many promising biological applications including *in vivo* antinociceptive activity, *in vitro* anti-cancer, anti-hypertensive, anti-bacterial and anti-fungal activities, anti-inflammatory [80], cytokinin activity in bio-assays and also cyclooxygenase-2, tumor growth inhibitors [81].

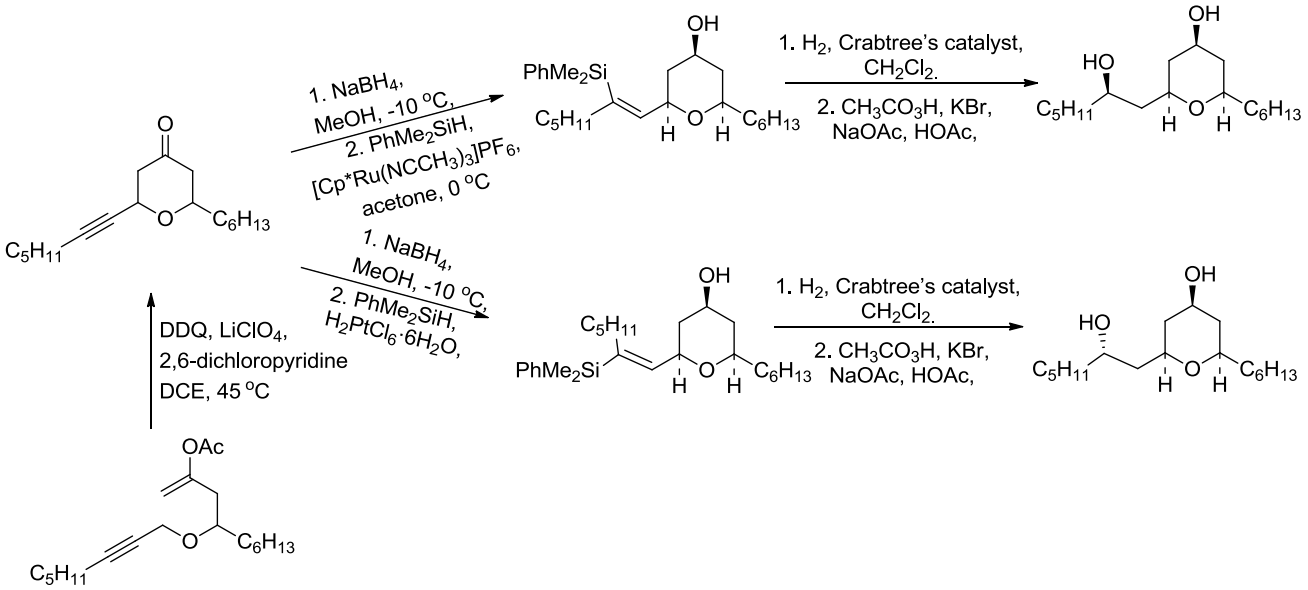
1.6.1. Synthetic routes for pyran derivatives:

The structural diversity of the pyran core presence in the above moieties prompted synthetic chemists for their design and synthesis. Therefore, various strategies have been explored in the stereoselective synthesis with proper functionalization includes hetero-Diels-Alder method, oxidative C−H bond activation, reductive cyclization of organohalides, intramolecular hydroalkoxylation, reductive cyclization of organohalides, intramolecular allylation, Prins cyclization etc.

1.6.1.1. Synthesis of tetrahydropyran *via* C−H bond activation approach:

C-H bond activation is a prologue to C-C bond formation which utilizes THPs synthesis. This approach is both step and atom economical, because the substrate preparation and reactive intermediate generation employ unreactive C-H bonds, rather than conventional leaving groups.

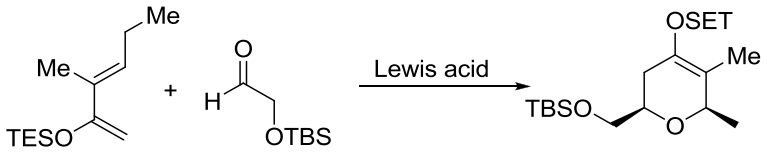
Liu *et al*. synthesized THPs using propargylic ethers as substrates in which DDQ-mediated cyclization of alkyne gave tetrahydropyranone. The reductions were achieved with $NaBH_4$. The 'E' vinylsilylated tetrahydropyran were then formed by hydrosilylation using $PhMe_2SiH$ and [Cp*Ru-$(CH_3CN)_3PF_6$], and the 'Z' vinylsilylated tetrahydropyran were formed by hydrosilylation using a H_2PtCl_6 catalyst (Scheme 23) [82].



Scheme 23: Synthesis of a stereochemically diverse tetrahydropyrans.

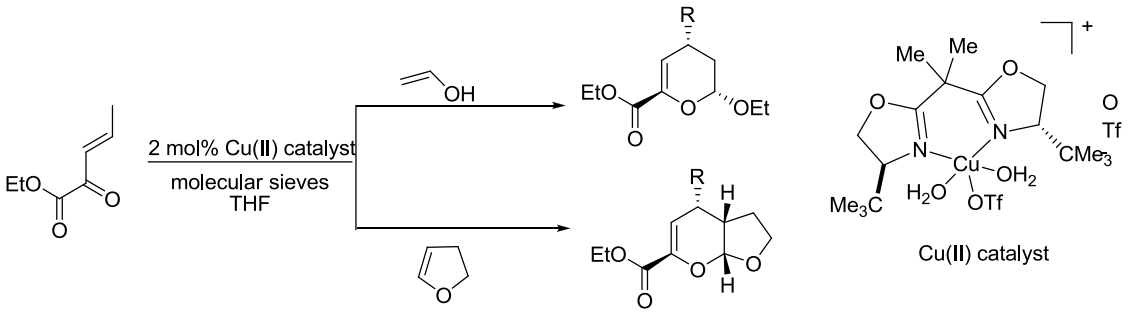
1.6.1.2. Hetero Diels-Alder reaction approach

Pyran derivatives are synthesized *via* hetero Diels-Alder approach. In this approach [4+2] cyclo-addition of butadiene and carbonyl in presence of Lewis acid medium gives dihydropyran (DHP) derivatives (Scheme 24) [83].



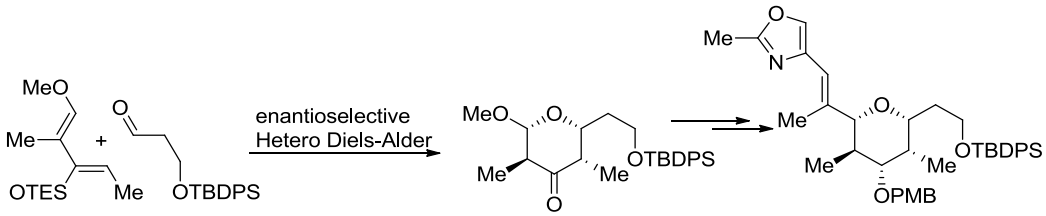
Scheme 24: Hetero-Diels-Alder reaction.

Evans *et al*. synthesized asymmetric pyrans using Cu(II) catalyzed enantioselective hetero-Diels-Alder reaction (Scheme 25) [84].



Scheme 25: Cycloaddition of heterodiene and enol ethers catalyzed by Cu(II) catalyst.

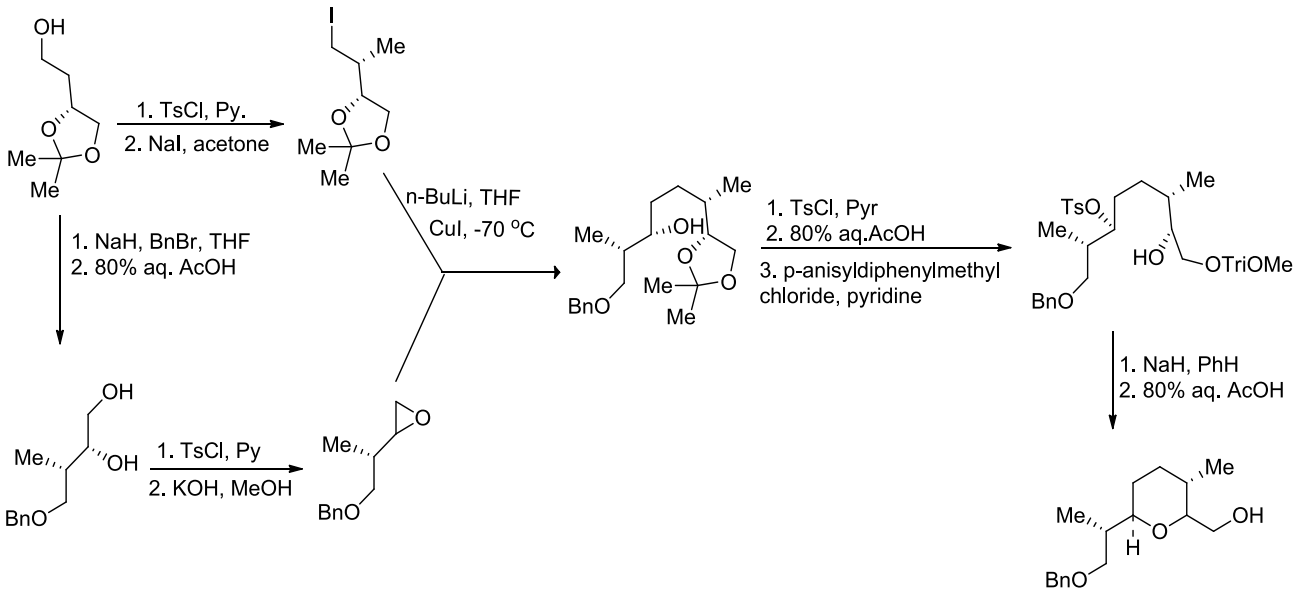
Burke *et al*. synthesized C20-C32 segment of phorboxazole, which is synthesized by hetero Diels-Alder approach (Scheme 26) [85].



Scheme 26: Catalytic enantioselective hetero Diels-Alder approach to the C20-C32 segment of the phorboxazoles.

1.6.1.3. Intramolecular diol cyclization method

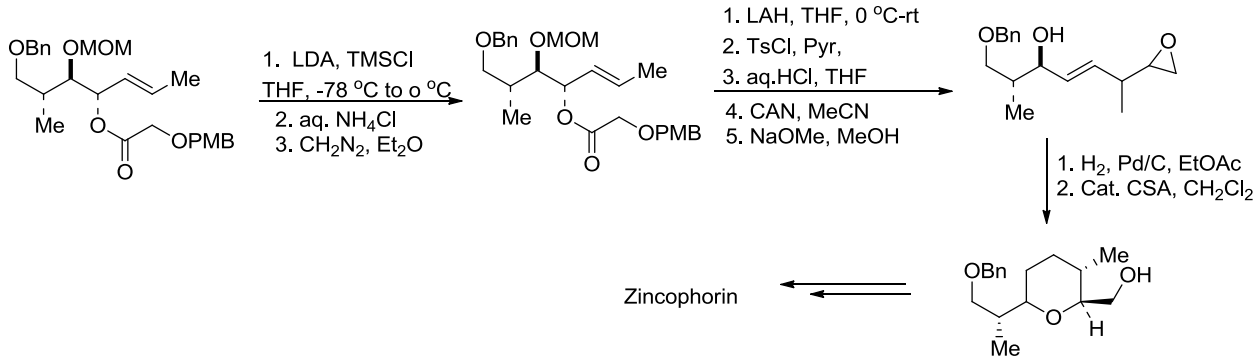
Ho synthesized THPs *via* intramolecular diol cyclization, this methodology applied to synthesize natural product antibiotic X-14547A (Scheme 27) [86].



Scheme 27: Synthesis of tetrahydropyran *via* intramolecular diol cyclization.

1.6.1.4. Intramolecular epoxide opening approach

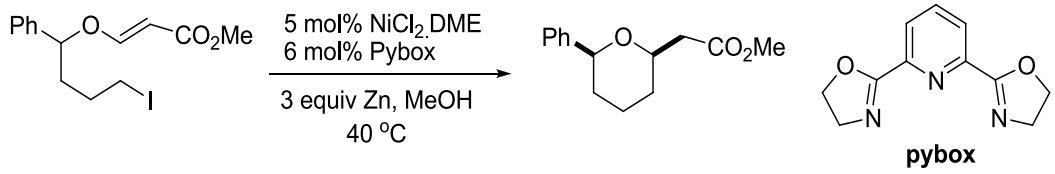
THPs can synthesize by intramolecular epoxide opening. Kallmerten applied intramolecular epoxide opening methodology to synthesize 'zincophorin' (Scheme 28) [87]**.**



Scheme 28: Synthesis of zincophorin.

1.6.1.5. Reductive cyclization of organohalides approach

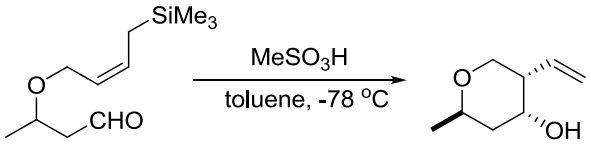
Catalyst $NiCl_2$.DME/Pybox and zinc powder in methanol efficiently promotes the reductive cyclization of various unsaturated alkyl halides to give THP derivatives as products in high yields. This method proceeds *via* free-radical cyclization (Scheme 29) [88].



Scheme 29: Reductive cyclization of organohalides.

1.6.1.6. Intramolecular allylation method

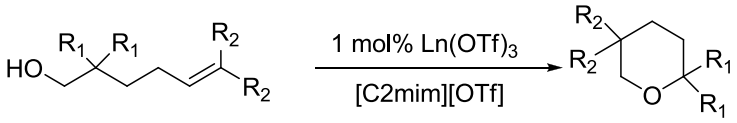
An intramolecular allylation of a (Z)-allylsilane onto an aldehyde under Brønsted acid obtained highly stereoselective 4-hydroxytetrahydropyrans (Scheme 30).



Scheme 30: Stereoselective synthesis of 4-hydroxytetrahydropyrans.

1.6.1.7. Intramolecular hydroalkoxylation

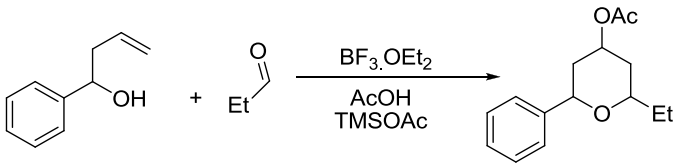
THPs can synthesize using intramolecular hydroalkoxylation. Lanthanide triflates ($Ln(OTf)_3$) serve as efficient catalysts for the intramolecular hydroalkoxylation cyclization of primary/secondary and aliphatic/aromatic hydroxyl alkenes in room temperature ionic liquids (RTILs) (Scheme 31).



Scheme 31: Synthesis of tetrahydropyrans using Lanthanide triflate.

1.6.1.8. Prins cyclization approach

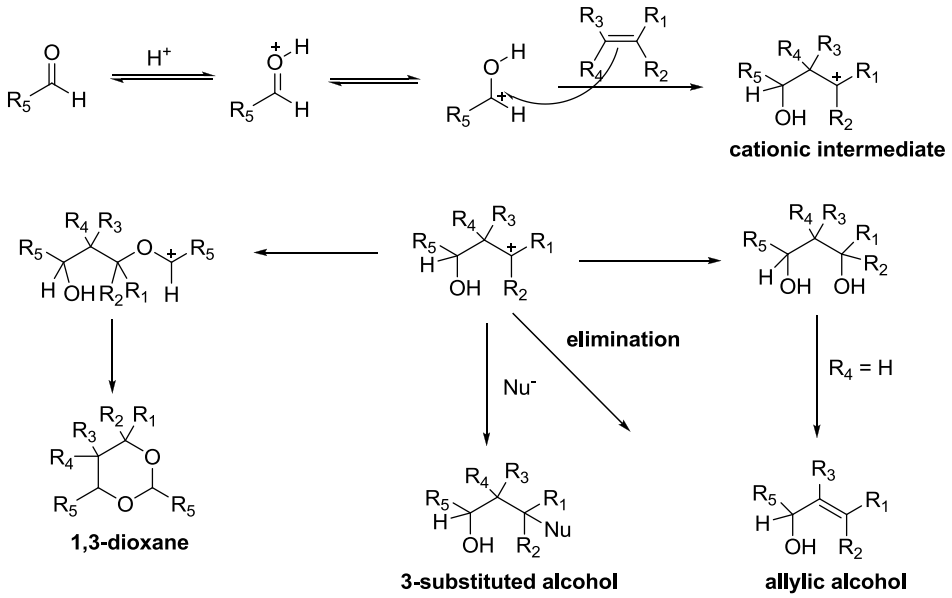
In Prins cyclization homoallylic alcohol and aldehyde in presence of acidic medium cyclization takes place to give functionalized pyran derivatives (Scheme 32) [89].



Scheme 32: Synthesis of 2,4,6-trisubstituted tetrahydropyran.

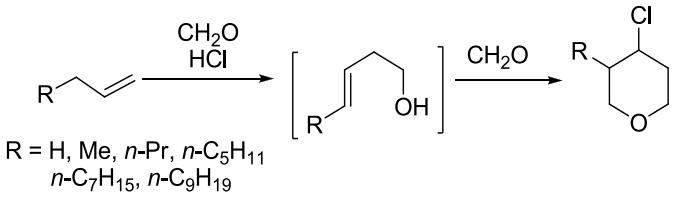
Of the range of permutations that is available for substituted THPs, the 2,6/2,3,6-substitution pattern has been the most widely studied; excellent methods now exist for its construction. Indeed, we need to study to the synthesis of 2,4,6-trisubstitution. Among available methods Prins cyclization is found best method for 2,6/2,4/2,4,6-substitution.

In 1919 H. J. Prins first time reported the electrophilic addition of an aldehyde or ketone to alkene or alkyne in presence of an acid medium to generate homoallylic alcohol/diol/1,3-dioxane here, product formation depends on reaction conditions. The scope of this process called Prins reaction these reactions proceeds *via* an oxocarbenium ion intermediate formation (Scheme 33) [90].



Scheme 33: Pathway for different products formation dependent on reaction conditions in Prins reaction.

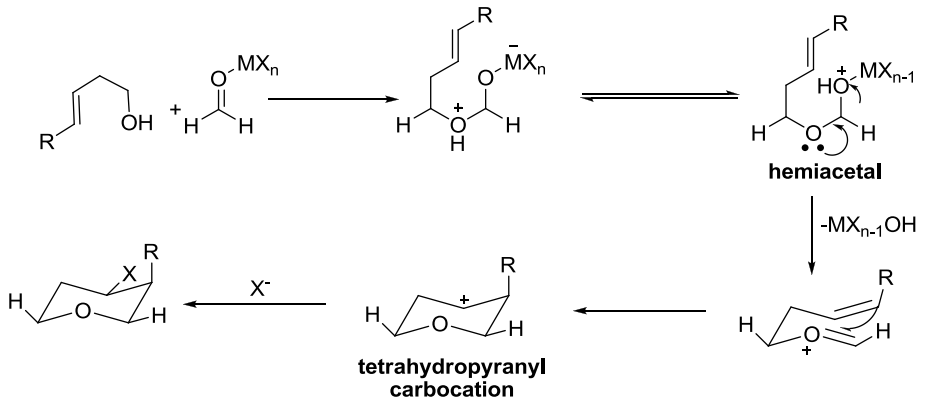
Many modifications on the Prins reaction undertaken, in 1955 Hanschke and Gendorf, was the first to report the selective synthesis of 3-alkyl-4-chloro-tetrahydropyrans through by combining 3-buten-1-ol with a variety of aldehydes or ketones in the presence of acid (Scheme 34) [91]. The demonstration that homoallylic alcohols were intermediates on the reaction pathway has induced the development of 'Prins cyclization', which provides a powerful access to THP derivatives.



Scheme 34: Prins cyclization reaction.

1.6.2. General mechanism

A general mechanism is shown in Scheme 35. The reaction involves a homoallylic alcohol, an aldehyde and a Lewis acid. The key intermediate, *i.e.*, an oxocarbenium ion is generated from a hemi-acetal and undergoes 6-*endo* cyclization to give selectively a secondary tetrahydropyranyl carbocation that can be trapped by various nucleophiles.

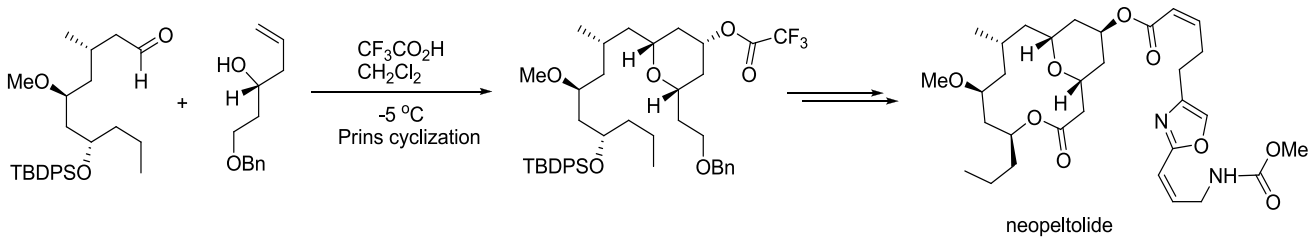


Scheme 35: General mechanism of Prins cyclization.

1.7. APPLICATION OF PRINS CYCLIZATION IN SYNTHESIS OF TETRAHYDROPYRAN CONTAINING NATURAL PRODUCTS

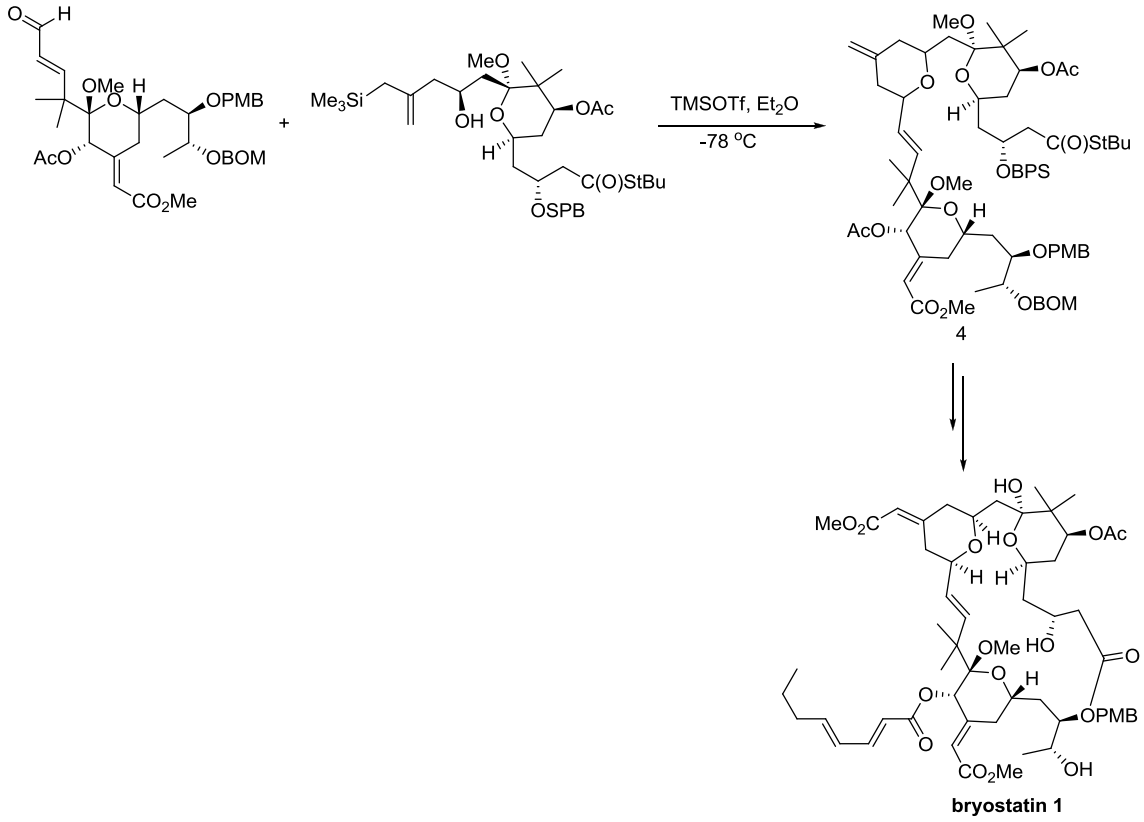
The Prins reaction is often a key step in the synthesis of various heterocyclic rings that are important structural components of many classes of biologically active compounds and natural products [91]. The Prins reaction is one of the fundamental methods for C–C bond formation. The ubiquitous presence of pyran heterocycle in natural products and other biologically relevant compounds has led to numerous applications of Prins cyclization to the syntheses of complex molecules.

In 2007 neopeltolide was isolated from a deep-water sponge of the family neopeltidae by Wright and co-workers. Bioactivity studies revealed that neopeltolide showed *in vitro* cytotoxicity toward several different cancer cell lines, including A-549, NCI-ADR-RES, and P388 with IC_{50}values 1.2, 5.1, and 0.56 nM respectively. Neopeltolide also inhibited the growth of the fungal pathogen *Candida albicans*. Neopeltolide showed strong inhibition of cell proliferation at nanomolar concentrations. Maier *et al*. reported total synthesis of the neopeltolide in which 2,4,6-trisubstituted THP fragment synthesized *via* Prins cyclization strategy by condensation of aldehyde with homoallylic alcohol in the presence of CF_3CO_2H (Scheme 36) [92].



Scheme 36: Synthesis of neopeltolide.

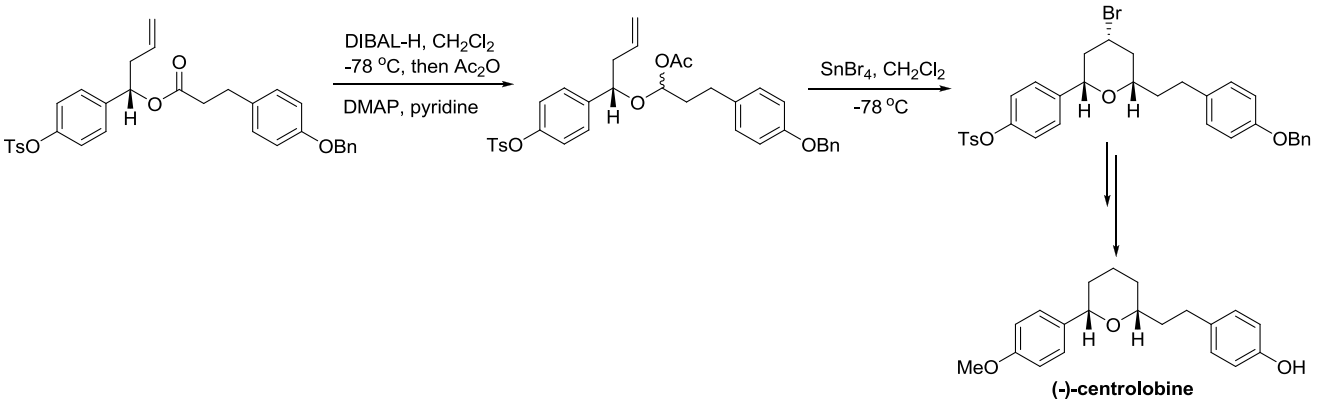
Bryostatin 1 isolated from the marine organism *bugula neritina* by Pettit *et al*. Bryostatin 1 active against a range of cancers and has also shown synergism with established oncolytic agents such as taxol. In addition, bryostatin 1 has shown promising activities including diabetes, stroke, and alzheimer's disease. The Keck group reported total synthesis of bryostatin 1 in which B ring synthesized *via* Prins cyclization strategy by the coupling of aldehyde with allylsilane containing alcohol in the presence of TMSOTf obtained methylene tetrahydropyran **4** in 61% yield (Scheme 37) [93].



Scheme 37: Synthesis of bryostatin 1.

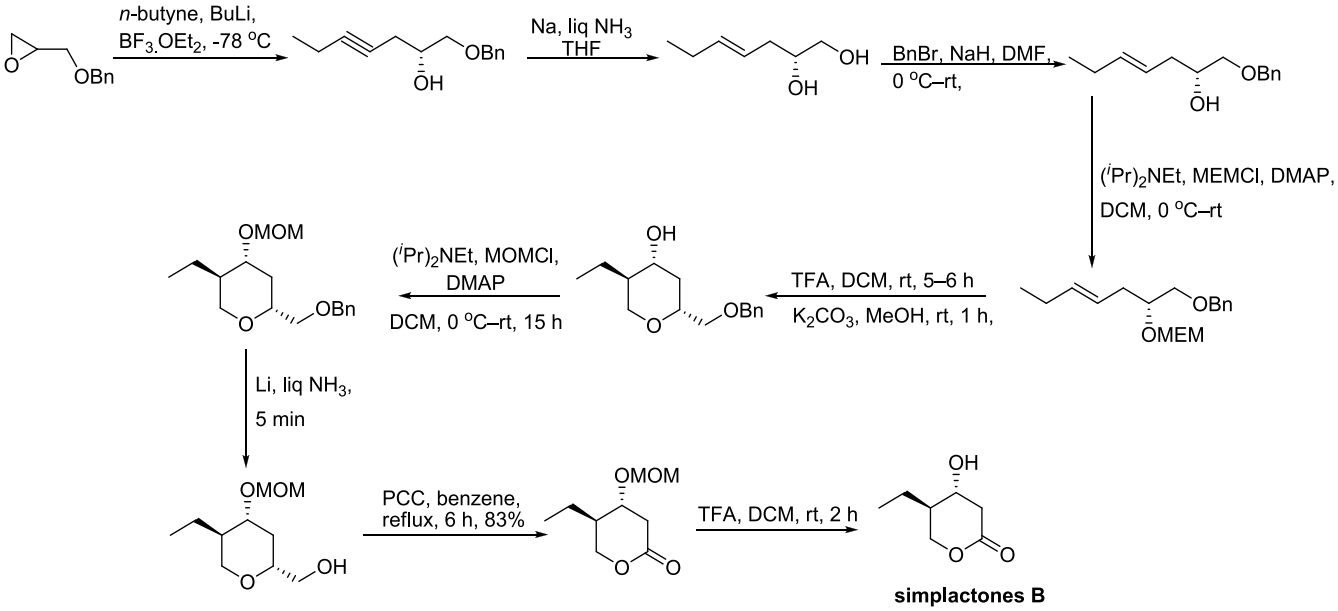
(-)-Centrolobine, isolated from the heartwood of *Centrolobium robustum* and from the stem of *Brosimum potabile* in the amazon forest. The basic structure was elucidated in 1964 but its absolute configuration has established by Carreno *et al*. (-)-centrolobine shown antibiotic and anti-fungal activity, it exhibits activity against *Leishmania amazonensis* promastigotes, a parasite associated with leishmaniasis. The Rychnovsky *et al.* synthesized absolute configuration of (-)-centrolobine *via* Prins-type cyclization in their synthesis α-acetoxy ether used as precursor. Prins cyclization of α-

acetoxyether in presence of $SnBr_4$ provided 4-bromotetrahydropyran in 84% yield with no racemization through oxonia-Cope processes (Scheme 38) [94].



Scheme 38: Synthesis of (-)-centrolobine.

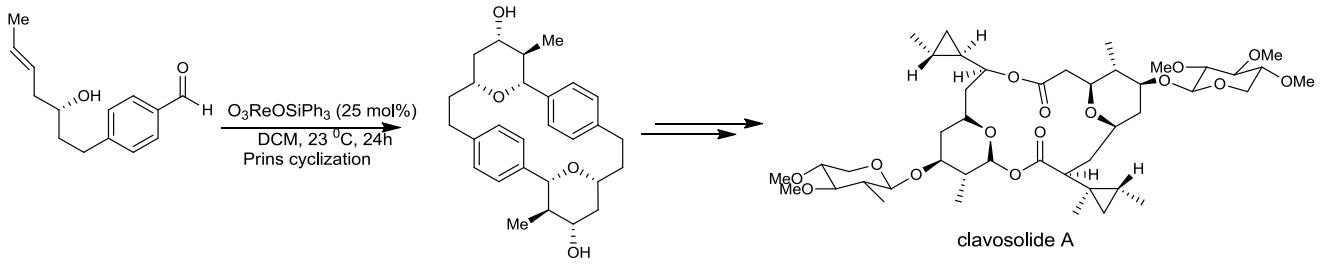
Simplactones B isolated from the *Caribbean sponge*, and *Plakortis simplex*, it showed interesting cytotoxic activities. Rao *et al*. synthesized stereoselective simplactones B in nine steps in this key intermediate THP synthesized *via* Prins cyclization approach (Scheme 39).



Scheme 39: Synthesis of simplactones B.

Oxacyclic macrodimers constitute an important class of natural products that possess a wide range of structural complexity and bioactivity, and are popular targets for synthetic chemists. Rychnovsky and co-workers using $O_3ReOSiPh_3$ introduced a new sequential dimerization–

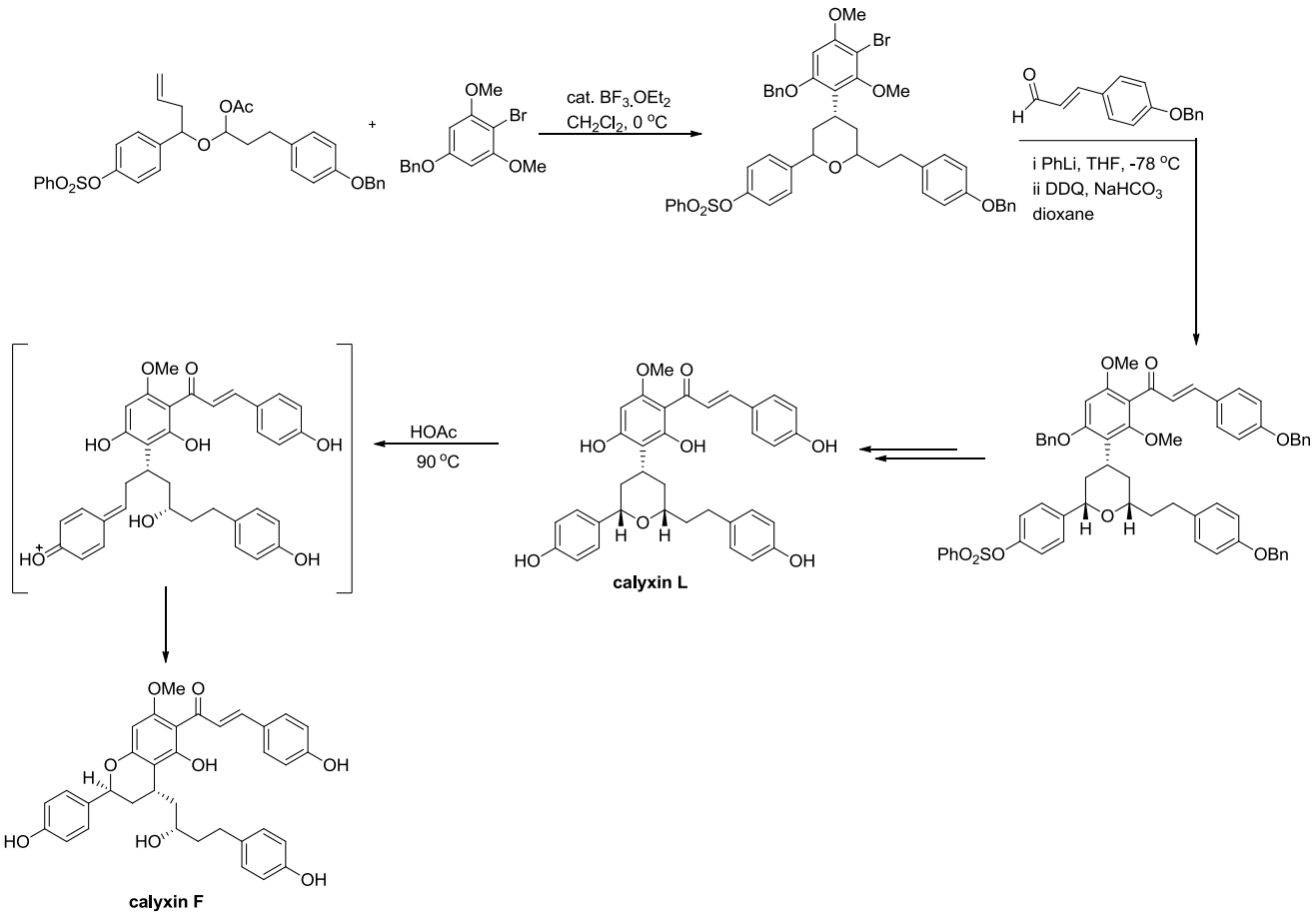
macrocyclization based on Prins cyclization for forming symmetrical macrocycles. The usefulness of this strategy was demonstrated in a successful synthesis of a model for clavosolide A, a marine sponge metabolite [95].



Scheme 40: Synthesis of clavosolide A *via* Prins-cyclization strategy.

Molecular hybridization approach is a powerful medicinal chemistry tool for design and synthesis of hybrid compounds, molecules encompassing in a single scaffold with two pharmacophores from known entities end owed with well-established biological activities. Flavonoids are ubiquitous in nature and showed various biological applications, similarly, pyran derivatives also present in many natural products they showed promising biological applications. The hybrid molecules of flavonoids and pyrans have been isolated from the seeds of *Alpinia blepharocalyx Sp* including epicalyxin F, calyxin F, epicalyxin G, calyxin G, epicalyxin K, calyxin K, calyxin L, calyxin I. These hybrid molecules have shown interesting hepatoprotective and anti-proliferative activity against cancer cell lines.

Rychnovsky *et al*. synthesized calyxin L and calyxin F natural products using Prins-Friedel-Crafts cyclization strategy. In which α-acetoxy ether with brominated phloroglucinol in the presence of $BF_3 \cdot OEt_2$ Prins-Friedel-Crafts cyclization takes place to give 4-aryltetrahydropyran. Then it metallated with PhLi, followed by addition of aldehyde gave the allylic alcohol, which was oxidized with DDQ to produce 4-chalcone substituted THP obtained. After several-steps sequence calyxin L and calyxin F was obtained (Scheme 40) [96].



Scheme 41: Synthesis of calyxin L and calyxin F through a Prins-Friedel-Crafts cyclization strategy.

1.8. REFERENCES

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Chapter-2

SYNTHESIS OF 2,6-DISUBSTITUTED-4-TOSYLOXYTETRAHYDROPYRANS VIA PRINS CYCLIZATION

PART-A

EFFICIENT, HIGHLY DIASTEREOSELECTIVE MS 4 Å-PROMOTED ONE-POT, THREE-COMPONENT SYNTHESIS OF 2,6-DISUBSTITUTED-4-TOSYLOXYTETRAHYDRO-PYRANS VIA PRINS CYCLIZATION

Beilstein J. Org. Chem. **2012**, *8,* 177–185

PART-B

SYNTHESIS OF FLAVONOIDS BASED NOVEL TETRAHYDROPYRAN CONJUGATES (PRINS PRODUCTS) AND THEIR ANTIPROLIFERATIVE ACTIVITY AGAINST HUMAN CANCER CELL LINES

Eur. J. Med. Chem. Accepted with minor review

SYNTHESIS OF 2,6-DISUBSTITUTED-4-TOSYLOXYTETRAHYDROPYRANS VIA PRINS CYCLIZATION

2.1. INTRODUCTION

Substituted tetrahydropyrans (THPs) are common structural motifs in numerous biological molecules and core units in natural products that include avermectins, cromakalim, calanolide A, centchroman, aplysiatoxins, oscillatoxins, latrunculins, talaromycins, acutiphycins [1], (−)-centrolobine [2], GEX1A/herboxidiene [3], and pheromones [4] (Fig. 1). They have shown a large pharmacological profile such as potent S-phase cytostatic activity against cancer cell lines [5], potent antitumor agents, inhibiting the proliferation of various cell lines including A-549 human lung adenocarcinoma, NCI-ADR-RES human ovarian sarcoma, and P388 murine leukemia cell lines in the low nano-molar range, inhibited the growth of the fungal pathogen *Candida albicans* [6], *in vivo* antinociceptive activity [7], HIV protease inhibitors, sialidase inhibitors related to zanamivir [8]. Apart pharmacology THPs are also used as materials in photographic films [9] and host–guest chemistry [10]. In particular, 2,4,6-trisubstituted THPs have special interest they have shown tremendous applications in pharmaceuticals and are widely present in natural products and biologically active core structures such as lasonolide A, phorboxazoles (A and B) [11], bryostatins [12], Miyakolide [13], 17-Deoxyroflamycoin (Fig. 1) [14].

Similarly, flavonoids occur naturally and are widely distributed in plants available in vegetables, tea, soya bean, berries and other fruits as dietary sources. They have exhibited antioxidant and chelating properties and so have many health promoting effects. Some other activities attributed to flavonoids include anti-allergic, anti-cancer, antioxidant, anti-inflammatory and anti-viral [15].

A new family of natural products flavonoid based pyran derivatives have previously been isolated from the *Alpinia blepharocalyx* seeds that include epicalyxin F, calyxin F, epicalyxin G, calyxin G, epicalyxin K, calyxin K, calyxin L, calyxin I (Fig. 1) [16]. The isolated compounds have an interesting structure *i.e.* a chalcone or a flavanone moiety attached to a pyran skeleton. These plants are widely distributed in south-western China and their seeds are commonly used in traditional medicine for the treatment of various stomach disorders [17]. Many of these natural products have shown interesting hepatoprotective and anti-proliferative activity against cancer cell lines. For example, epicalyxin F is the most potent member of this class and used as anti-cancer activity

(approx.1 μM) against human HT-1080 fibrosarcoma and murine 26-L5 carcinoma [18]. A high potency of epicalyxin F is hypothesized due to flavonoid and pyran natural moieties are accommodated in a single molecule.

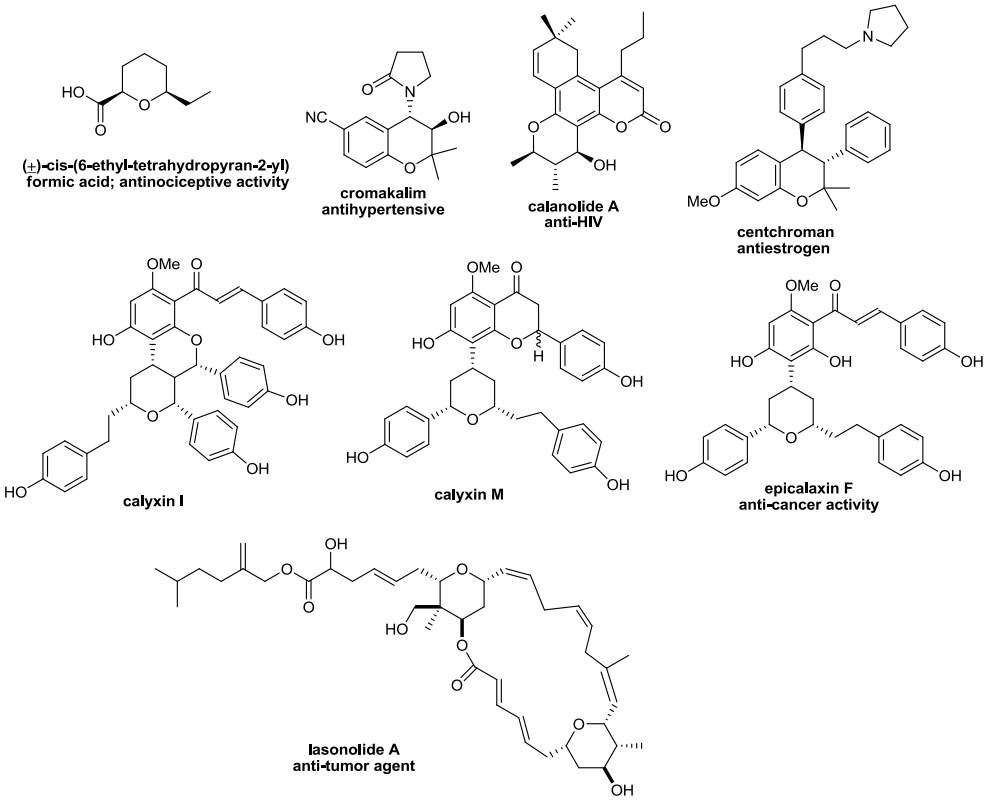
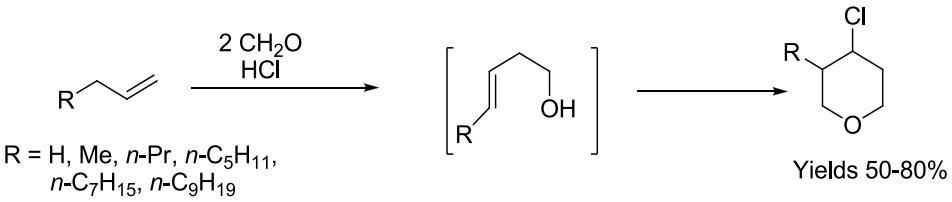


Fig. 1: Biologically active natural and synthetic flavonoids, tetrahydropyran derivatives.

The conspicuous prevalence of 2,4,6-trisubstituted THPs in these natural products encouraged to the development of many elegant methods such as hetero Diels-Alder [19], manipulation of carbohydrates [20], intramolecular Michael reactions [21], cyclization of diols and δ-hydroxyketones, iodolactonization, seleno-etherification of unsaturated alcohols, through the epoxide opening, the Prins-cyclization reaction and others [7,22] for the stereoselective synthesis of appropriately substituted THPs such as 4-oxygenated, 4-halogenated, 4-sulfonyl, 4-triazolyl, and 4-azido/amido THPs [23]. However, many of these classical methods often involve the use of expensive reagents and extended reaction times, and also generate mixtures of products, sometimes failed to give desired substituted THPs but among available methods Prins cyclization has been considered to be the best approach to introduce the desired substituents and stereochemistry at the 2,4,6-positions of the THP ring.

The Prins cyclization has been widely recognized as a powerful tool to generate multi-substituted THPs. To make it as efficient, powerful tool some variation and modification have been undertaken towards this transformation illustrated as follows.

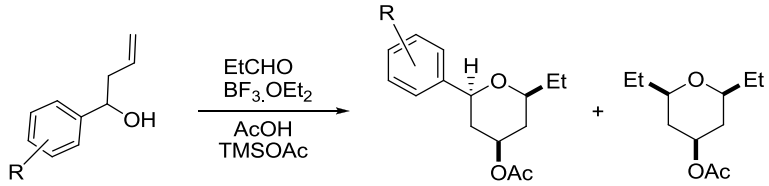
First time Hanschke and Gendorf [24], and Stapp [25] performed reactions between 3-alkyl propanes with formaldehyde in presence of HCl obtained racemic mixture of 3-alkyl-4-chloro-THPs with low yield (Scheme 1).



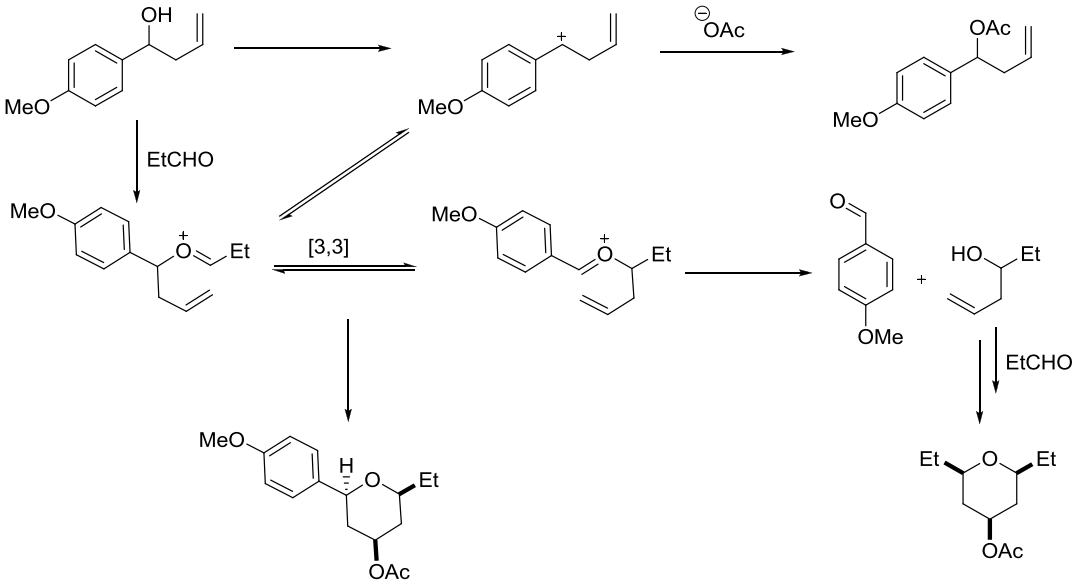
Scheme 1: First synthesis of tetrahydropyran derivatives *via* Prins cyclization

To improve yields of THPs reactions has conducted in presence of different Brønsted acid catalysts namely TFA [26], AcOH, $MeSO_3H$ [27], $Sc(OTf)_3$ [28], $O_3ReOSiPh_3$ [29], or in presence of Lewis acid catalysts such as $AlCl_3$ [30], $InCl_3$ [31], $TiCl_4$, $InBr_3$ [32], Fe(III) compounds [33], $BF_3{\cdot}OEt_2$ [34], $BiCl_3$ [35].

Willis *et al.* performed reactions between substituted aromatic homoallylic alcohols and propanal using $BF_3.OEt_2$ in the presence of AcOH and TMSOAc in cyclohexane at room temperature to give 2,4,6-trisubstituted THP (Scheme 2). It was observed that, the desired product along with some other side products, desired product obtain low yield due to the oxonia-Cope rearrangement. Electron-rich aromatic rings favor an oxonia-Cope rearrangement yielding a symmetrical tetrahydropyran as the major product *via* a side-chain exchange process. In contrast, with electron-deficient aromatic rings the expected 2,4,6-trisubstituted tetrahydropyran is major [36]. Path way for side product formation also explained (Scheme 3).

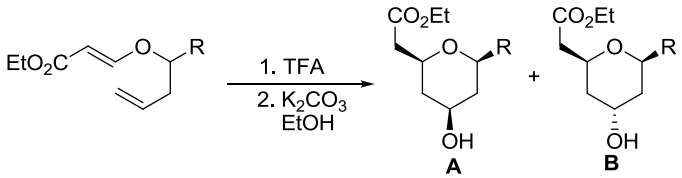


Scheme 2: Synthesis of 2,4,6-trisubstituted tetrahydropyran *via* Prins cyclization.



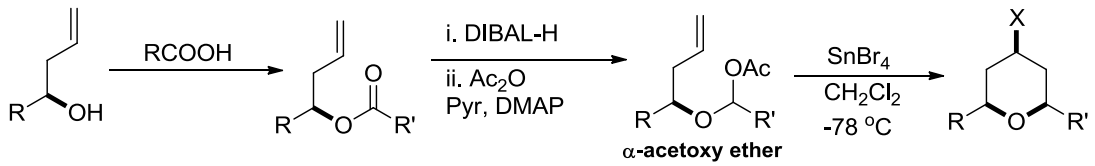
Scheme 3: Proposed mechanism for the products formation.

To avoid above allyl transfer process both catalyst and precursor got modified. Hart *et al.* synthesized THPs **A** and **B** using trifluoroacetic acid as catalyst to cyclize enol ethers *via* Prins cyclization. THPs are isolated with combined yields of 42−85% and stereoselectivity from 95:5 to 50:50 (Scheme 4) [26].



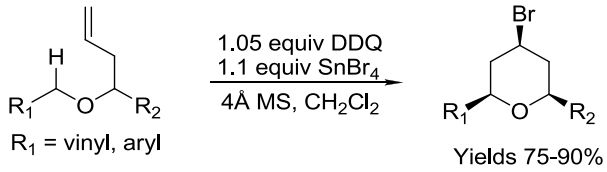
Scheme 4: Synthesis of tetrahydropyrans using enol ethers as precursors.

Therefore, the segment-coupling Prins cyclization developed by Rychnovsky [37] is considered as an elegant supplement in that it could avoid the side-chain exchange and the partial racemization. In which key cyclization precursor is α-acetoxy ether, in presence of $SnBr_4$ it cyclizes to afford desired product in good yields (Scheme 5). This methodology is applicable to synthesize biologically active natural product (−)–centrolobine [38].



Scheme 5: Segment-coupling Prins cyclization.

In the segment-coupling Prins cyclization, the cyclization precursor is α-acetoxy ether, which is prepared by reductive acetylation of a homoallylic ester [5]. However, aryl ester and α,β-unsaturated ester failed to undergo reduction and in situ acetylation of esters and further incomplete the Prins cyclization. To overcome this limitation, She et al. developed a step-economic method to construct the tetrahydropyran ring, involving sequential benzylic/allylic C-H bond activation *via* DDQ oxidation and nucleophilic attack of an un-activated olefin, is described (Scheme 6) [39].



Scheme 6: Strategy for Prins cyclization through benzylic/allylic C-H activation.

Above methods require precursors such as α-acetoxy ethers, vinyl ethers and benzylic or allylic ethers. Preparation of these precursors requires expensive reagents and time taking processes. Therefore, there is urgent need for an efficient method to overcome these limitations using readily available starting materials, simple, cheap and environmentally benign conditions to give high yield and stereoselectivity. *p*-Toluenesulfonic acid (PTSA) is reported as a versatile Brønsted acid catalyst in various organic transformations [40]. Additionally, tosylate group having good leaving nature it facilitates for many functional group transformations such as azides [41], alcohols [42], alkene, etc. [43]. In continuation of our interest in acid catalysis herein, we report an efficient methodology to synthesize 2,4,6-trisubstituted THPs using readily available homoallylic alcohols, aldehydes and cheaper catalyst *p*-toluenesulfonic acid, in the presence of molecular sieves (MS 4Å). In comparison with other methods our method gave better yields (72–96%) in short reaction times (20–90 min.) with high diastereoselectivity.

2.2. OBJECTIVE

From past few decades the battle against cancer is one of the biggest social problems encountered worldwide, because cancer is one of the most dreadful diseases, and the second leading cause of death throughout the world. The world health organization (WHO) reported that cancer accounted for 7.6 million deaths (around 13% of all deaths) in 2008, and 13.1 million deaths is estimated for 2030. The discovery and development of new drugs that can be used in the treatment of cancer remains one of the biggest challenges for the scientific community and the pharmaceutical industry. Thus, search for new natural molecules, semi-synthetic and synthetic compounds which display specific activity against cancer is of great interest. To synthesize those compounds need to

develop good methodologies considering cost-effective, environmentally benign catalytic systems, time saving, high yielding and also good stereoselectivity is one of the main themes of contemporary organic synthesis.

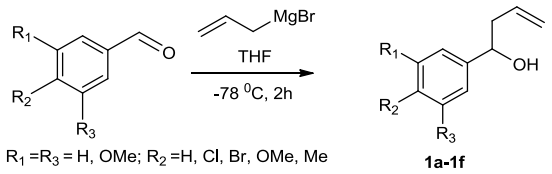
The Prins cyclization has emerged as a powerful tool for C-O and C-C bond forming technique in the synthesis of THPs with various substitutions. It has applications towards the synthesis of bioactive macrocycles, and natural products which are showed anti-proliferative activity against various cancer cell lines. Thereby will continue, firmly to establish it as a powerful method considering yield, time, catalyst, selectivity aspects a great task to organic chemists. Therefore, considering above requirements herein, we developed a new and efficient method for one pot synthesis of THPs using aromatic homoallylic alcohols, aldehyde, and cheaper catalyst *p*-toluenesulfonic acid in presence of MS 4Å in good yields (72-96%) within short reaction time (20-90 min.) with high diastereoselectivity. This methodology applied to synthesize flavonoid based 2,4,6-trisubstituted THPs also, the synthesized compounds tested for *in vitro* anti-proliferative activity.

2.3. RESULTS AND DISCUSSION

2.3.1. Part A: Efficient, highly diastereoselective MS 4Å-promoted one-pot, three-component synthesis of 2,6-disubstituted-4-tosyloxytetrahydropyrans *via* Prins cyclization.

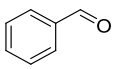
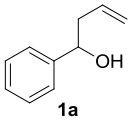
2.3.1.1. Synthesis of homoallylic alcohols

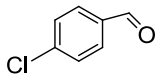
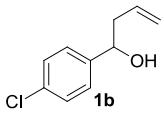
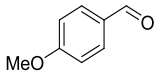
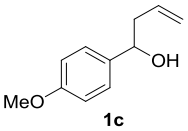
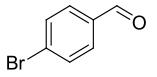
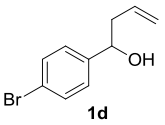
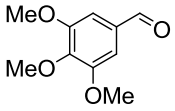
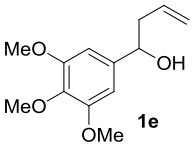
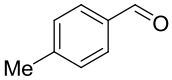
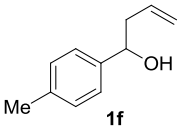
The starting materials, aromatic homoallylic alcohols were readily prepared by treatment of aromatic aldehydes with allylic Grignard reagents under a nitrogen atmosphere at −78 ^{0}C for 2 h (Scheme 7, Table 1) [44].



Scheme 7: Synthesis of homoallylic alcohols from aldehydes.

Table 1: Construction of homoallylic alcohols.

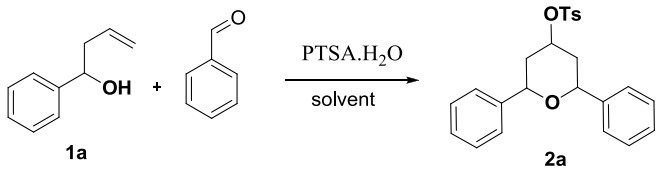
Entry	Aldehyde	Homoallylic alcohol	Product yield (%)
1.		 1a	86

2.		 **1b**	88
3.		 **1c**	85
4.		 **1d**	88
5.		 **1e**	82
6.		 **1f**	85

2.3.1.2. Synthesis of 2,6-diaryl-4-tosyloxytetrahydropyran derivatives

Initially, we carried out the reaction with homoallylic alcohol **1a**, benzaldehyde and PTSA at room temperature to afford 2,4,6-trisubstituted tetrahydropyran **2a**. After 22 h stirring, yielded side products than the desired product. To optimize the reaction yield, we varied the reaction conditions such as enhancing the catalytic loading (1.2 equiv to 1.4 equiv), varying solvents and temperature, rearranging the order of reagent addition and adding MS 4Å as drying agent (Table 2). Among different solvents (toluene, THF, DCM, DCE and diethyl ether) that were used, DCM was found as the solvent of choice at reflux temperature (Table 2, entries 5, 6, 8–10). Similarly, various acids like trifluoroacetic acid (TFA), benzoic acid, acetic acid, and benzylphosphonic acid, PTSA were tried as catalysts but all of them failed to give the desired product in good yields. We expected that the order of reagent addition would have significant influence on the yield. For example, the addition of PTSA (1.4 equiv.) to a stirred solution of homoallylic alcohol and benzaldehyde in dichloromethane (DCM) at room temperature gave the product in 35% yield (Table 2, entry 6). Compared to that, the addition of homoallylic alcohol to a stirred mixture of PTSA (1.4 equiv) and aromatic aldehyde in DCM improved the yield (45%) at the same temperature (Table 2, entry 8). Following the later addition order at reflux (40 ^{0}C) in DCM (Table 2, entry 9), the yield was enhanced upto 75% within 20 min. Furthermore, the addition of molecular sieves (MS 4Å) to the above mentioned reaction mixture

within 20 min resulted in serendipitous improvement of the yield (94%, Table 2, entry 10). In the presence of MS 4Å, the yield was unexpectedly enhanced from 75% to 94% under the same reaction conditions (Table 2, entry 9 *vs* entry 10). The significant improvements in product yields, reaction time and/or diastereoselectivity might be due to the regulate of the [3,3] sigmatropic rearrangement along with the dehydrating activity of MS 4Å. In addition, we studied the stoichiometric ratio of MS 4Å with respect to the substrate and found that 30 mg/mmol of MS 4Å are necessary to receive optimal yields.



Scheme 8: Synthesis of tetrahydropyran using homoallylic alcohol and aldehyde.

Table 2: Optimization of reaction conditions.

Entry[a]	Brønsted acid	Solvent	Temp (^{0}C)	Time	Yield (%)[b]
1	PTSA (1.2equiv)	Toluene	rt	20h	25
2	PTSA (1.2equiv)	EtOAc	rt	20h	22
3	PTSA (1.2equiv)	THF	rt	28h	26
4	PTSA (1.2equiv)	DCE	rt	18h	25
5	PTSA (1.2equiv)	DCM	rt	22h	30
6	PTSA (1.4equiv)	DCM	rt	20h	35
7	PTSA (1.4 equiv)	THF	66	22h	28
8	PTSA (1.4equiv)	DCM	rt	40min	45
9	PTSA (1.4equiv)	DCM	40	20min	75
[c]**10**	**PTSA (1.4equiv)**	DCM	40	20min	**94**

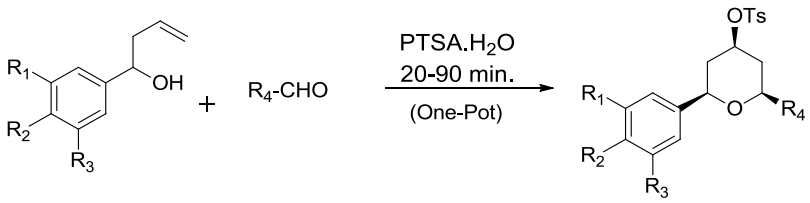
[a]All reactions were carried out at homoallylic alcohol (1 equiv.), aldehyde (1 equiv.) and PTSA. [b]isolated yield.

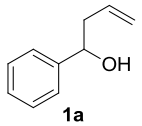
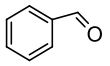
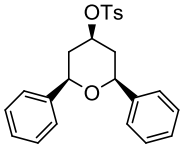
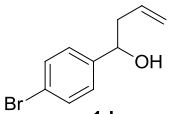
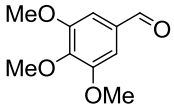
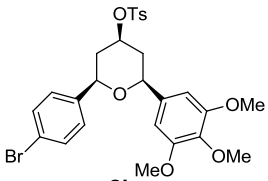
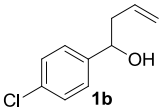
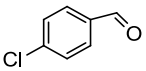
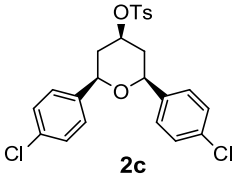
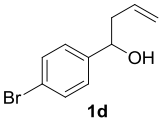
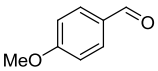
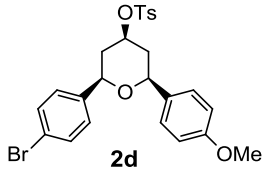
[c]MS 4Å (30 mg/equiv.) was used.

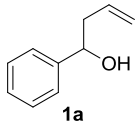
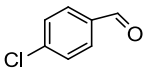
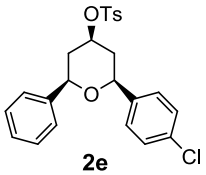
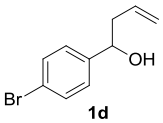
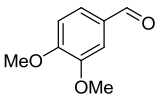
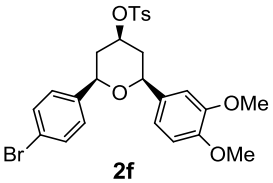
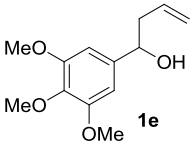
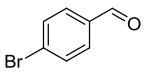
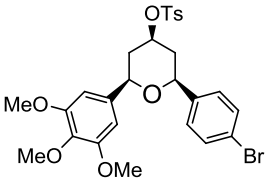
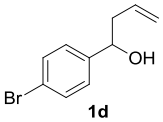
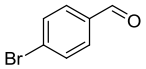
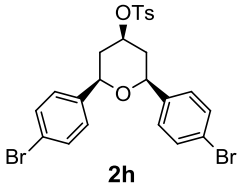
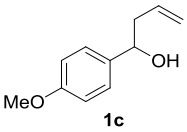
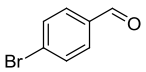
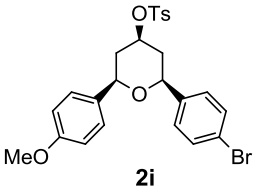
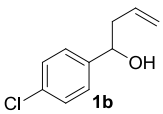
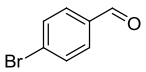
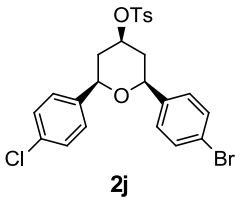
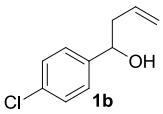
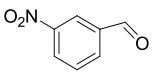
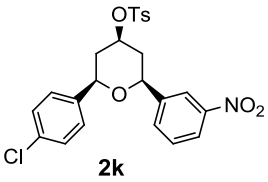
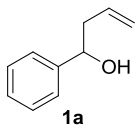
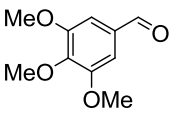
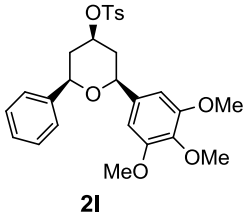
Under optimal reaction conditions we treated a wide selection of aromatic homoallylic alcohols and aldehydes. The experimental results are summarized in Table 3. In all cases, the corresponding THPs were obtained in high diastereoselectivity and excellent yields without side products (Table 3). A high degree of diastereoselectivity was determined from the ^{1}H NMR spectra without purification (crude product). We observed that substituents on the aromatic rings influenced the reaction rates and yields. For example, strong electron-donating groups such as methoxy or

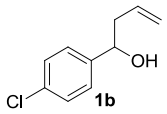
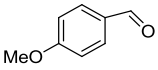
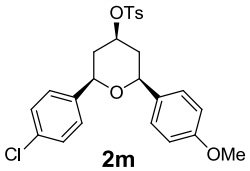
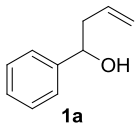
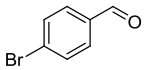
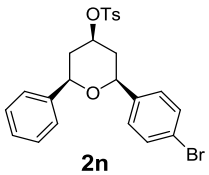
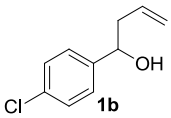
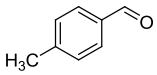
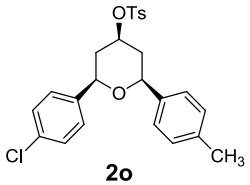
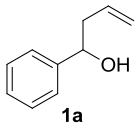
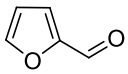
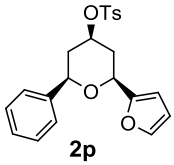
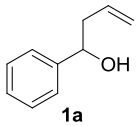
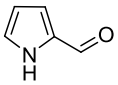
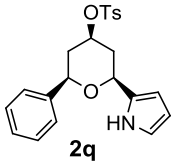
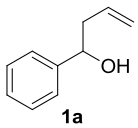
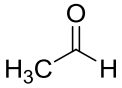
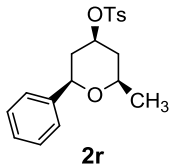
trimethoxy at homoallylic alcohols afforded the corresponding THPs in lower yields (72–75%) but in a faster rate (Table 3, entries 7 and 9). Similarly, the presence of electron-withdrawing substituents such as chlorine or bromine atoms at homoallylic alcohols gave the corresponding THPs in high yields (85–96%) but the reaction times were longer (Table 3, entries 2–4, 6, 8, 10). However, substituents on aldehydes have no significant effect on the reaction time or yields (Table 3, entries 2, 4, 6, 12–15). We further extended our method to aliphatic aldehydes (e.g., acetaldehyde) and hetero aromatic aldehydes (e.g., pyrrole aldehyde, furfural). Under optimal reaction conditions they reacted smoothly with homoallylic alcohols to afford the corresponding THP derivatives which show almost the same distereoselectivity and product yields (83–89%, Table 3, entries 16–18).

Table 3: Construction of tetrahydropyrans from aromatic homoallylic alcohols, aldehydes and PTSA.H_2O.



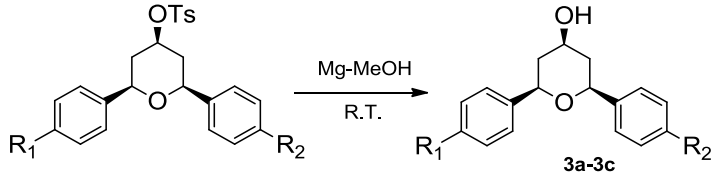
Entry	Homoallylic alcohol	Aldehyde	Product	Reaction time (min)	Yield (%)
1.	 **1a**		 **2a**	90	94
2.	 **1d**		 **2b**	20	82
3.	 **1b**		 **2c**	90	92
4.	 **1d**		 **2d**	25	88

5.	 **1a**		 **2e**	90	90
6.	 **1d**		 **2f**	35	85
7.	 **1e**		 **2g**	23	72
8.	 **1d**		 **2h**	90	95
9.	 **1c**		 **2i**	25	75
10.	 **1b**		 **2j**	90	95
11.	 **1b**		 **2k**	90	96
12.	 **1a**		 **2l**	20	83

13.	 1b		 2m	30	88
14.	 1a		 2n	90	95
15.	 1b		 2o	60	93
16.	 1a		 2p	50	83
17.	 1a		 2q	50	86
18.	 1a		 2r	75	89

2.3.1.3. Synthesis of 2,6-disubstituted-4-hydroxytetrahydropyrans

The tosyl group at C-4 easily deprotected at room temperature with Mg–MeOH (Scheme 9) [45] to afford 2,6-disubstituted-4-hydroxy THPs with retention of the stereochemistry in quantitative yield (Table 4).



Scheme 9: Deprotection of tosyl group.

Table 4: Construction of 2,6- disubstituted-4-hydroxytetrahydropyran.

Entry	4-Tosyloxy tetrahydropyran (R_1, R_2)	4-Hydroxy tetrahydropyran (R_1, R_2)	Yield (%)
1.	Cl, Cl	Cl, Cl	**3a** (96)
2.	H, H	H, H	**3b** (95)
3.	Br, Br	Br, Br	**3c** (95)

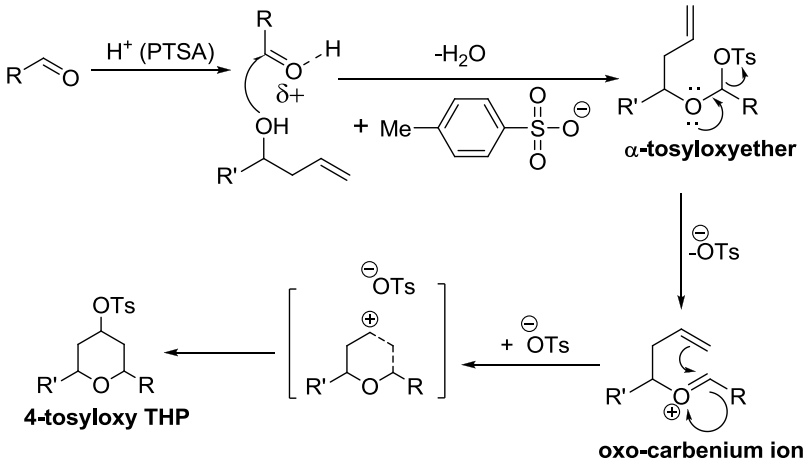
2.3.1.4. STRUCTURE DETERMINATION

All structures of homoallylic alcohols (**1a-f**) were established by their IR, GC–MS, ^{1}H, and ^{13}C NMR spectral data. For example, homoallylic alcohol **1a** obtained as a color less oil, the IR spectrum of **1a** showed absorptions at 3450, 1417, 1260 cm^{-1} for OH, C=C and C-O-C bonds *asymmetric stretching* respectively. In the ^{1}H NMR spectrum of **1a** peak at δ_H 7.3-7.18 (m, 5H) indicates phenyl group present, peaks at δ_H 5.76-5.67 (m, 1H), 5.08-5.03 (m, 2H), are corresponds to ethylenic (-$\underline{H}C=CH_2$, -$HC=C\underline{H_2}$ respectively) protons. Further, GC-MS (*m/z*) showed molecular ion peak at 148 [M^+], indicates product formation. Similarly remaining compounds (**1b-f**) were conformed by their analytical data (experimental section). Similarly, 2,6-disubstituted-4-tosyloxytetrahydropyran derivative compound **2c** obtained as a yellow solid. CHNS data supported a molecular composition of $C_{24}H_{22}Cl_2O_4S$. The IR spectrum of **2c** showed absorptions at 1634, 1353, 1171 cm^{-1} for C=C, $–SO_2–$ bonds *asymmetric* and *symmetric stretching* respectively. In the ^{1}H and ^{13}C NMR spectra of **2c**, methyl group resonating at δ_H 2.44 and δ_C 21.7. In ^{1}H NMR spectrum oxymethine (Ph-C$\underline{H}$-O), methine (-C$\underline{H}$-OTs) protons resonating at δ_H 4.50, 4.93 ppm and two asymmetric methylene protons (-CH_2-) resonating at δ_H 2.27, 1.75 ppm suggested that the presence of a THP ring. The stereochemistry of **2c** established using NOE experiment. In NOESY spectrum of **2c**, the correlation of H-4 observed with H-2 and H-6 indicated that they were located on the same side of the ring with diaxial orientation. Similarly, the structures of other products (**2a-b, 2d-r)** were confirmed on their spectral data (experimental section).

2.3.1.5. MECHANISM

The possible reaction mechanism for regioselective pyran ring construction is illustrated in Scheme 10. The first step is protonation of aldehyde carbonyl group with PTSA (Brønsted acid catalyst). Then its reaction with homoallylic alcohol followed by intermolecular nucleophilic addition of tosylate group and loss of a water molecule, afforded intermediate α-tosyloxyether. The delocalization of oxygen lone-pair electrons in α-tosyloxyether generates oxo-carbenium ion

intermediate after removal of tosylate group. Further, the nucleophilic addition of *in situ* generated tosylate group on tetrahydropyranyl cation resulted in the formation of substituted 2-aryl-6-flavonoid-4-tosyloxy THPs (Scheme 10).



Scheme 10: Plausible reaction mechanism for Prins cyclization.

2.3.1.6. CONCLUSION

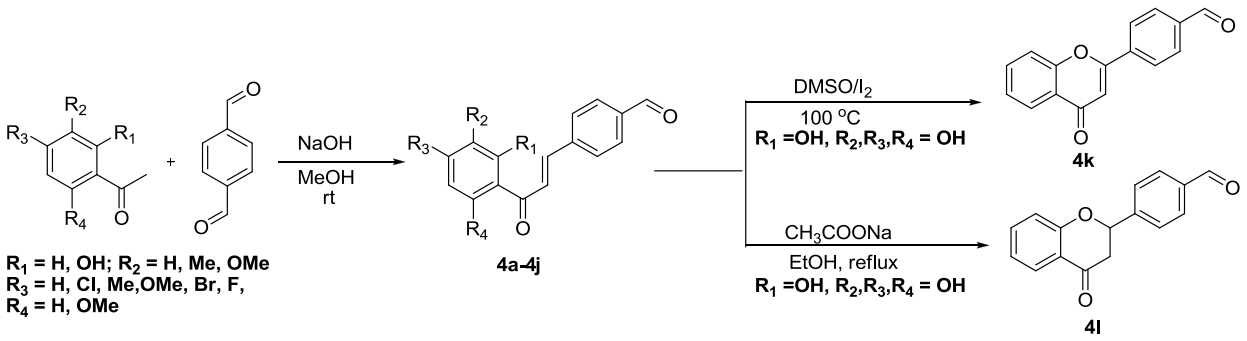
In conclusion, we have developed a simple and efficient method for one-pot three-component synthesis of highly diastereoselective and functionalized 2,6-disubstituted-4-tosyloxy THPs *via* Prins cyclization. An aromatic homoallylic alcohol, an aromatic/aliphatic aldehyde, and *p*-toluenesulfonic acid (catalyst and reagent) are reacted in the presence of MS 4Å in dichloromethane at reflux to afford 2,6-disubstituted-4-tosyloxytetrahydropyrans in excellent yields (72–96%) within short reaction times (20–90 min). This methodology proved to be versatile enough to provide an array of symmetrical and unsymmetrical THP derivatives in an economical manner. Furthermore, cleavage of the 4-tosyl group under mild conditions afforded 4-hydroxy THPs in excellent yields (95–96%) with retained stereochemistry.

2.4. Part B: Synthesis of flavonoids based novel tetrahydropyran conjugates (Prins products) and their antiproliferative activity against human cancer cell lines

2.4.1. Synthesis of flavonoid aldehydes

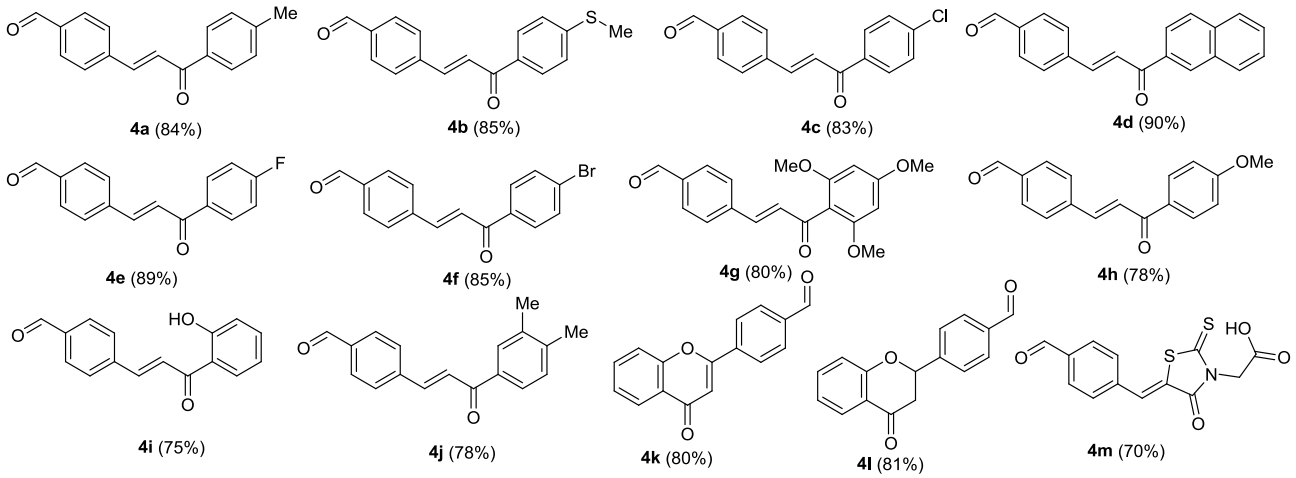
Starting materials such as chalcone aldehydes (**4a-j**), flavone aldehyde **4k**, flavanone aldehydes **4l** were synthesized as follows. Treatment of different acetophenones with terephthaladehyde in alkali methanol at room temperature afforded chalcones [46], 2'-

hydroxychalcone **4i** in DMSO/I_2 at 110 ^{0}C gave flavone aldehyde **4k**. Similarly, 2'-hydroxychalcone **4i** treating with sodium acetate in ethanol gave flavanone aldehyde **4l** (Scheme 11).

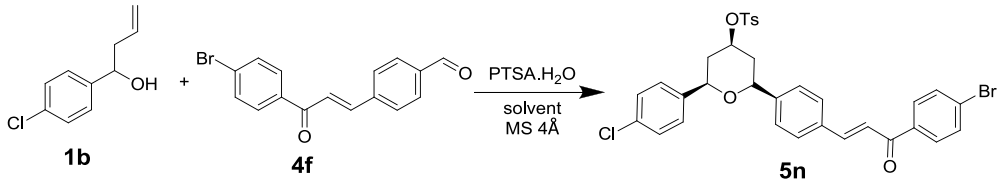


Scheme 11: Synthesis of flavonoid aldehydes.

Table 5: Derivatives of flavonoid based aldehydes.



2.4.2. Synthesis of flavonoid based 4-tosyloxy tetrahydropyran derivatives



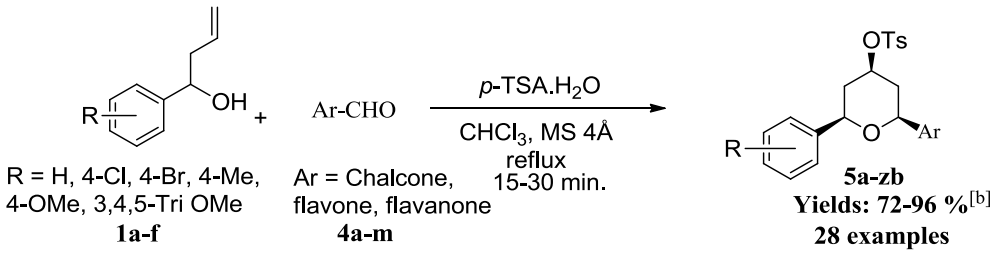
Scheme 12: Synthesis of chalcone based 2,4,6-trisubstituted tetrahydropyran.

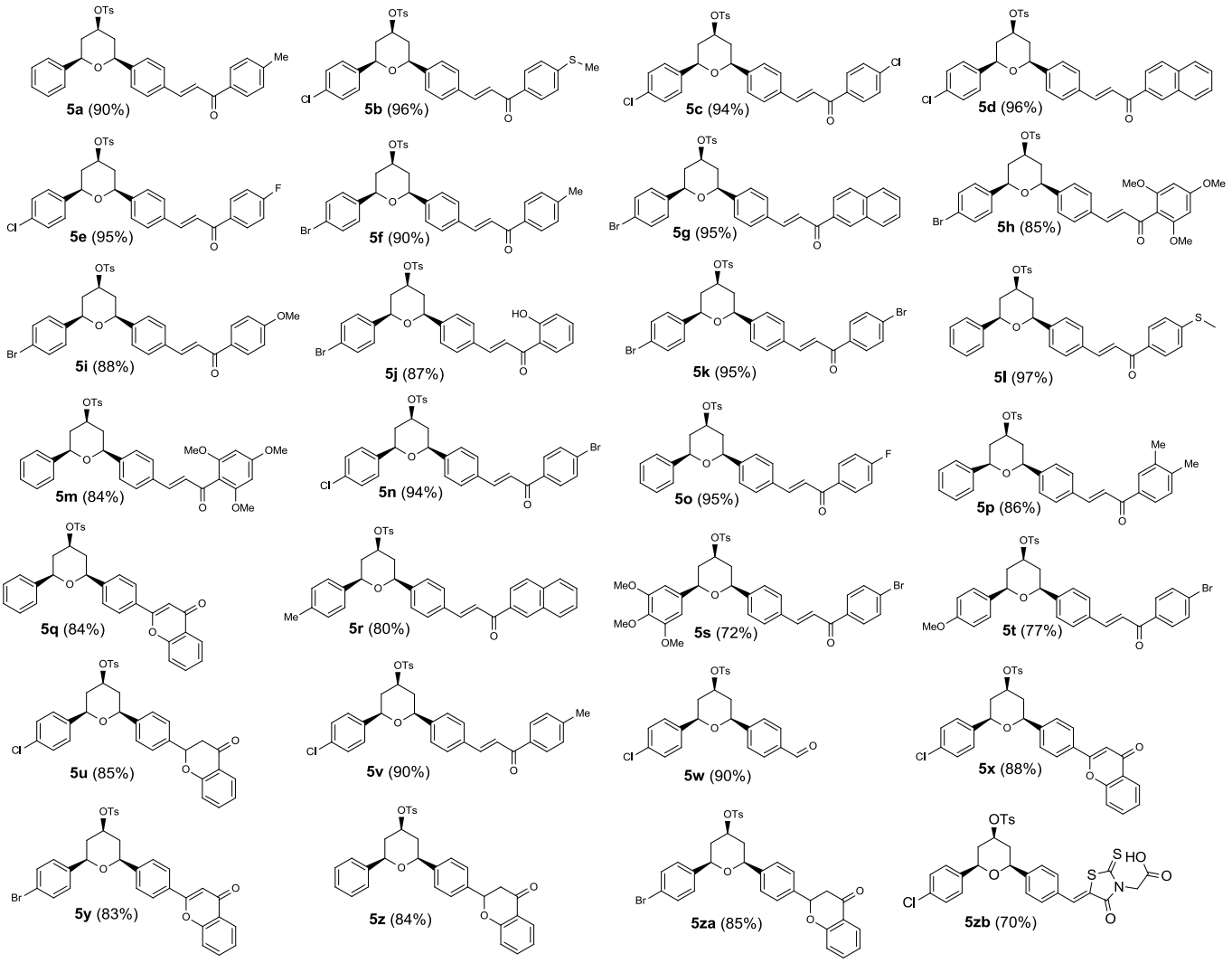
Initially 4-tosyloxy THPs were attempted to synthesize using homoallylic alcohol **1b**, chalcone aldehyde **4f**, *p*-TSA.H_2O and MS 4Å in DCM following reported procedure [42]. However, due to poor solubility of chalcone aldehyde in DCM, the product obtained in low yield even after prolonging the reaction time. To improve the solubility of aldehydes **4**, the reaction performed in different solvents. Among the solvents (THF, DCM, ACN, $CHCl_3$ and EtOAc) used, $CHCl_3$ was found to be

the best option for our synthetic needs, the 4-tosyloxy THP **5n** was obtained in excellent yield (95%) within 25 min (Scheme 12).

To affirm the general applicability of this reaction, a variety of flavonoid aldehydes (chalcone, flavone and flavanone aldehydes) were investigated to obtain THPs (**5a-zb)** in high diastereoselectivity and yields (Table 6).

Table 6: Construction of flavonoid based 4-tosyloxy THPs.[a]

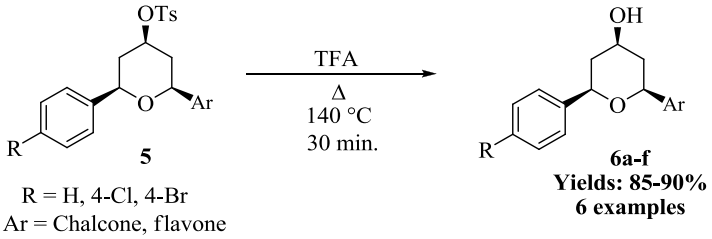




[a]All reactions were carried out with 1 mmol of flavonoid aldehyde, 1 mmol of homoallylic alcohol, 1.4 mmol of *p*-TSA.H_2O and 30 mg MS 4Å.
[b]Yields refer to isolated products.

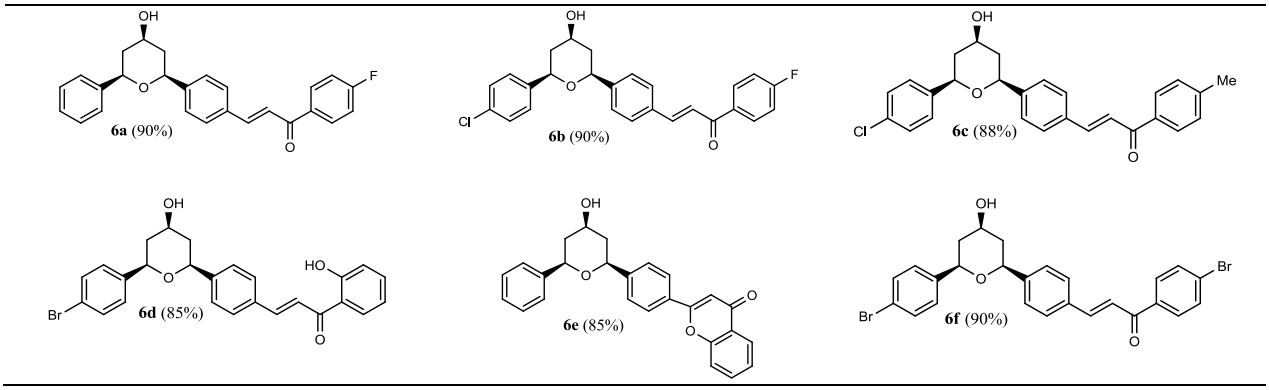
2.4.3. Synthesis of flavonoid based 4-hydroxy THPs

For the synthesis of 4-cinnamate THPs (Scheme 13), we tried to deprotect tosyl group at C-4 in compound **5** following a reported method with Mg–MeOH at room temperature [42] but, failed to give 4-hydroxy THPs. Therefore, we further investigated different reaction conditions by varying temperature, solvents (MeOH, acetone, THF) and acids (conc. H_2SO_4, TFA). The best reaction efficiency in terms of yields (85-90%) and reaction time (30 min.) was obtained with TFA at 140 ^{0}C (Scheme 13, Table 7).



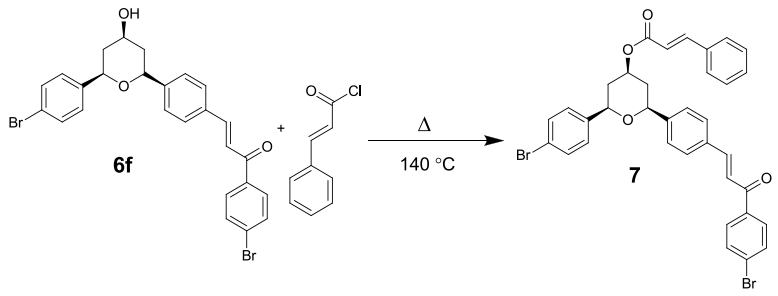
Scheme 13: Deprotection of tosyl group.

Table 7: Preparation of flavonoid based 4-hydroxy pyran derivatives.



2.4.4. Synthesis of 4-cinnamate THPs.

The reaction of **6f** with cinnamoyl chloride was performed at 140 ^{0}C under neat condition afforded 4-cinnamate THP **7 (**Scheme 14**)**.



Scheme 14: Synthesis of 4-cinnamate THPs.

2.4.5. STRUCTURE DETERMINATION

All structures of aldehydes (**4a-m**) were established by their IR, HRMS, ^{1}H, and ^{13}C NMR spectral data. For example, compound (E)-4-(3-(4-bromophenyl)-3-oxopropenyl) benzaldehyde **4f** obtained light yellow solid, the IR spectrum of **4f** showed absorptions at 1711, 1654 cm^{-1} for aldehyde, ketone carbonyl bond *asymmetric stretching* respectively. The HRMS of **4f** supported a molecular composition of $C_{16}H_{11}BrNaO_2$ $(M+Na)^+$. In the ^{1}H NMR spectrum of **4f** peak at δ_H 10.05 corresponds to aldehyde proton, and in ^{13}C NMR spectrum of **4f** peaks at δ_C 188.99, 191.60 corresponds to ketone and aldehyde carbonyl carbons respectively. In the ^{1}H NMR spectrum peaks at δ_H 7.58 (d, *J* = 15.5Hz, 1H), 7.83 (d, *J* = 15.5Hz, 1H) corresponds to ethylenic protons, in which the coupling constant *J* = 15.5Hz indicates protons coupled trans to each other. All these findings suggested that product formation and remaining compounds (**4a-e**, **4g-m**) also characterized using their analytical data (experimental). Similarly, the assigned structures of new products (**5a-zb**) were established from their spectroscopic data (IR, HRMS, ^{1}H, ^{13}C and 2D-NMR). For example, compound **5f** was obtained as a yellow solid. The IR spectrum of **5f** showed absorptions at 1657, 1360, 1201, and 1181cm^{-1} for carbonyl, C-O-C and $–SO_2–$ bonds *asymmetric* and *symmetric stretching* respectively. The HRMS of **5f** supported a molecular composition of $C_{34}H_{31}BrNaO_5S$ $(M+Na)^+$, representing 19 degrees of unsaturation. In the ^{1}H and ^{13}C NMR spectra of **5f**, two methyl signals resonating at δ_H 2.4, and 2.42 and δ_C 21.56 were assigned to C-11, and C-12, respectively. Two oxymethine groups at δ_H 4.56 and 4.51 and two asymmetrical methylene group resonating at δ_H 1.78, and 2.30 assigned to H-2, H-6, H-3a/H-5a, H-3e/H-5e, respectively, suggested the presence of a THP ring [47]. The relative downfield shift of H-3e/H-5e at δ_H 2.30 and upfield shift of H-3a/H-5a at δ_H 1.78 suggested that H-3a and H-5a are in axial and H-3e and H-5e in equatorial orientations. The substituents (at 2,4, and 6 positions) orientation and stereochemistry on THP moiety in **5f** was supported by coupling constants and 2D-NMR correlations (Fig. 2). In ^{1}H NMR spectrum, H-3a axial proton showed doublet of triplets at δ 1.78 (^{3}J = 11.5, 10.5Hz, 2H). The coupling constant (11.5 Hz) indicates that H-3a coupled with H-2 and H-4 axial protons. Similarly, in H,H-COSY spectrum H-3a/H-5a axial protons showed correlation to H-2/H-6 (δ_H 4.56) and H-4 (δ_H 4.95) axial protons. In ^{1}H NMR spectrum, H-3e/H-5e equatorial protons showed triplet of triplets at δ 2.30 (^{2}J = 11.5 Hz, ^{3}J = 2 Hz, 2H) in which the coupling constant (11.5 Hz) indicates the geminal coupling with H-3a/H-5a and vicinal coupling constant (2 Hz) indicates coupled with H-2/H-6 and H-4 axial protons. In H,H-COSY spectrum, H-3e/H-5e equatorial protons showed correlation to H-2 and H-4 axial protons. In HMBC, H-3 protons

showed correlations to C-2 (δ_C 76.92), C-4 (δ_C 77.51), C-5 (δ_C 39.66) and C-4" (δ_C 143.00) suggested that C-3 and C-5 adjacent carbons are C-2, C-4 and C-4, C-6, respectively. The H-2 proton in ^{1}H NMR spectrum gave doublet of doublets at δ 4.56 (J = 10.5, 1.0 Hz, 1H), and in H,H-COSY spectrum showed correlation to H-3 proton. Further, in HMBC correlations to C-3 (δ_C 39.73), C-4" (δ_C 139.83), C-3" (δ_C 126.39) suggested that chalcone moiety is located at C-2. The H-6 proton showed HMBC correlations to C-1' (δ_C 143.00) and C-2' and C-6' (δ_C 127.45) suggested that *para*-bromophenyl moiety is located at C-6. In the ^{1}H NMR spectrum, H-4 proton showed triplet of triplets at δ 4.95 (^3J = 11.5 Hz, 5.0 Hz, 1H) in which the coupling constants 11.5 Hz (trans) and 5 Hz (cis) indicate coupled with H-3a/H-5a and H-3e/H-5e adjacent protons, suggested that H-4 proton is oriented in axial position. In ^{1}H-^{1}H COSY, H-4 proton showed interaction with H-3 and H-5 protons and HMBC correlations to C-2, C-3, C-5 and C-6 suggested that C-4 present between C-3 and C-5. In ^{13}C NMR spectrum, a peak at δ 189.18 corresponds to carbonyl carbon (Fig. 2). The relative configurations of asymmetric carbons were established by analysing the coupling constants and the NOESY spectrum (Fig. 2). In NOESY spectrum, the correlation of H-4 (δ_H 4.95) with H-2 and H-6 indicated that they were located on the same side of the ring with diaxial orientation. In ^{1}H NMR, the chemical shift at δ_H 1.78 for H-3a/H-5a protons, at δ_H 2.30 for H-3e/H-5e protons showed axial and equatorial orientation, respectively. The coupling constants $J_{H\text{-}2/H\text{-}3a}$ = 11.5Hz for H-2 and H-3a and $J_{H\text{-}3a/H\text{-}4}$ = 11.5 Hz for H-3a and H-4 indicate trans orientation to each other. It is confirmed that protons H-3a and H-5a are in axial orientation therefore H-2, H-4 and H-6 protons are also axially orientated. It means that the pyran ring exists in chair conformation with substituents at C-2, C-4 and C-6 are in equatorial position (Fig. 2). All of these assignments led to the structure of **5f** as (2R,4S,6S)-2-(4-bromophenyl)-6-(4-((E)-3-oxo-3-p-tolylpropenyl)phenyl)-4-tosyloxy tetrahydropyran. Similarly, the structures of other products (**5a-za, 5zb)** were confirmed on their spectral data (experimental section).

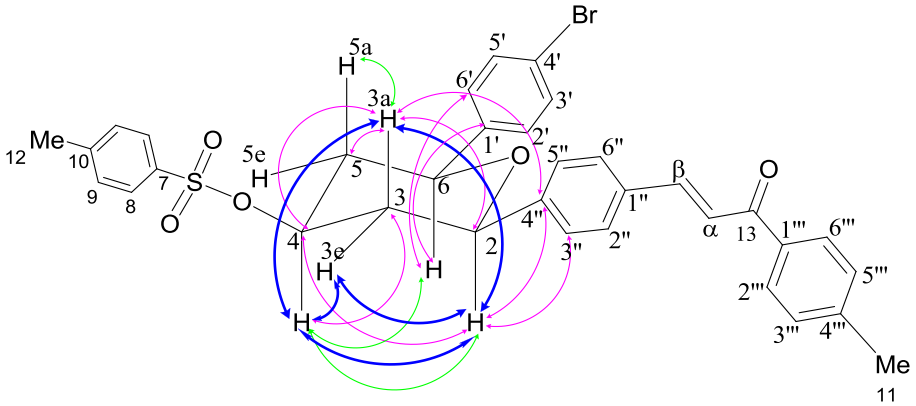


Fig. 2: Selected ^{1}H-^{1}H COSY (blue arrows), HMBC (pink arrows), NOE (green arrows) correlations for compound **5f**.

The assigned structures of 4-hydroxy THPs (**6a-f**) were established from their spectroscopic data (IR, HRMS, ^{1}H, ^{13}C and 2D-NMR). For example, (2R,4S,6S)-2-(4-chlorophenyl)-6-(4-((E)-3-(4-fluorophenyl)-3-oxopropenyl)phenyl)-4-hydroxytetrahydropyran **6b** obtained as a yellow semi-solid. The IR spectrum of **6b** showed absorptions at 3434 (br), and 1734 cm^{-1} for hydroxyl and carbonyl bonds *asymmetric stretching* respectively. The HRMS of **6b** supported a molecular composition of $C_{26}H_{22}ClFNaO_3$ $(M+Na)^+$, representing 15 degrees of unsaturation. In ^{1}H NMR spectrum, peak at δ_H 2.05 (s, br, D_2O exchangeable, 1H) confirms the presence of hydroxy group. In the ^{1}H NMR spectrum of **6b**, two oxymethine groups resonating at δ_H 4.66, 4.14 and two asymmetrical methylene group resonating at δ_H 1.78, and 2.30 assigned to H-2/H-6, H-4, H-3a/H-5a, H-3e/H-5e, respectively, suggested the presence of a THP ring. The relative downfield shift of H-3e/H-5e at δ_H 2.30 and up field shift of H-3a/H-5a at δ_H 1.78 suggested that H-3a and H-5a are in axial and H-3e and H-5e in equatorial orientation. The substituents (at 2,4, and 6 positions) orientation and stereochemistry on THP moiety in **6b** was supported by coupling constants and 2D-NMR correlations (Fig. 3). In ^{1}H NMR spectrum, H-3a axial proton showed triplet of triplets at δ 1.78 (^{3}J = 11.5, 2Hz, 2H). The coupling constant (11.5 Hz) indicates that H-3a coupled with H-2 and H-4 axial protons. Similarly, in H,H-COSY spectrum H-3a/H-5a axial protons showed correlation to H-2/H-6 (δ_H 4.66) and H-4 (δ_H 4.14) axial protons. In ^{1}H NMR spectrum, H-3e/H-5e equatorial protons showed triplet of triplets at δ 2.30 (^{2}J = 11.5 Hz, ^{3}J = 2 Hz, 2H) in which the coupling constant (11.5 Hz) indicates the geminal coupling with H-3a/H-5a and vicinal coupling constant (2 Hz) indicates coupling with H-2/H-6 and H-4 axial protons. In H, H-COSY spectrum, H-3e/H-5e equatorial protons showed correlation to H-2/H-6 and H-4 axial protons. In HMBC, H-3 protons showed correlations to C-2 (δ_C 77.70), C-4 (δ_C 69.46), C-5 (δ_C 40.05) and C-4" (δ_C 143.77) suggested that C-3 and C-5 adjacent carbons are C-2, C-4 and C-4, C-6, respectively. The H-2 proton in ^{1}H NMR spectrum gave triplet at δ 4.66 (J = 6.5 Hz, 1 H), and in H,H-COSY spectrum showed correlation to H-3 proton. Further, in HMBC correlations to C-3 (δ_C 40.05), C-4" (δ_C 143.77), C-3" (δ_C 126.55) suggested that chalcone moiety is located at C-2. The H-6 proton showed HMBC correlations to C-1' (δ_C 143.89) and C-2' and C-6' (δ_C 127.71) suggested that *para*-chlorophenyl moiety is located at C-6. In ^{1}H NMR spectrum, H-4 proton showed triplet of triplets at δ 4.14 (^{3}J = 11.5 Hz, 3.0 Hz, 1H) in which the coupling constants 11.5 Hz (trans) and 3 Hz (cis) indicate coupled with H-3a/H-5a and H-3e/H-5e adjacent protons, suggested that H-4 proton is oriented in axial position. In H, H-COSY, H-4 proton showed interaction with H-3 and H-5

protons and HMBC correlations to C-2, C-3, C-5 and C-6 suggested that C-4 present between C-3 and C-5. In ^{13}C NMR spectrum, a peak at δ 188.84 corresponds to carbonyl carbon (Fig. 3). The relative configurations of asymmetric carbons were established by analyzing the coupling constants and the NOESY spectrum (Fig. 3). In NOESY spectrum, the correlation of H-4 (δ_H 4.14) with H-2 and H-6 indicated that they were located on the same side of the ring with diaxial orientation. In ^1H NMR, the chemical shift at δ_H 1.78 for H-3a/H-5a protons, at δ_H 2.30 for H-3e/H-5e protons showed axial and equatorial orientation respectively. The coupling constants $J_{H\text{-}2/H\text{-}3a}$ = 11.5Hz for H-2 and H-3a, $J_{H\text{-}3a/H\text{-}4}$ = 11.5 Hz for H-3a and H-4 indicate trans-orientation to each other. It is confirmed that protons H-3a and H-5a are in axial orientation therefore H-2, H-4 and H-6 protons are also axially orientated, meaning that the pyran ring exists in chair conformation with substituents at C-2, C-4 and C-6 is in equatorial position (Fig. 3). All of these assignments led to the structure of **6b** as (2R,4S,6S)-2-(4-chlorophenyl)-6-(4-((E)-3-(4-fluorophenyl)-3-oxopropenyl)phenyl)-4-hydroxytetrahydropyran.

Similarly, the structure of other products (**6a, 6c-f**) was confirmed on their spectral data (experimental section).

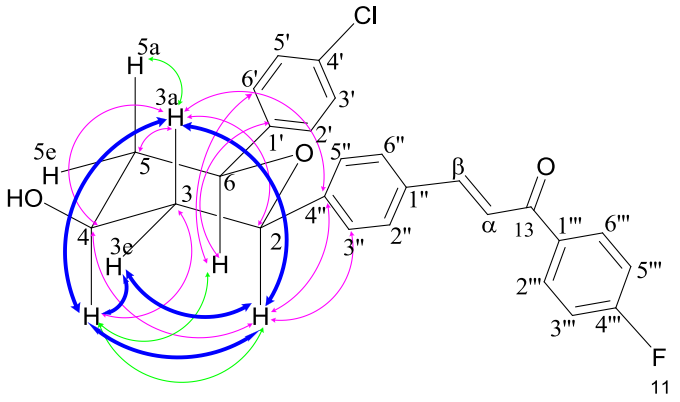
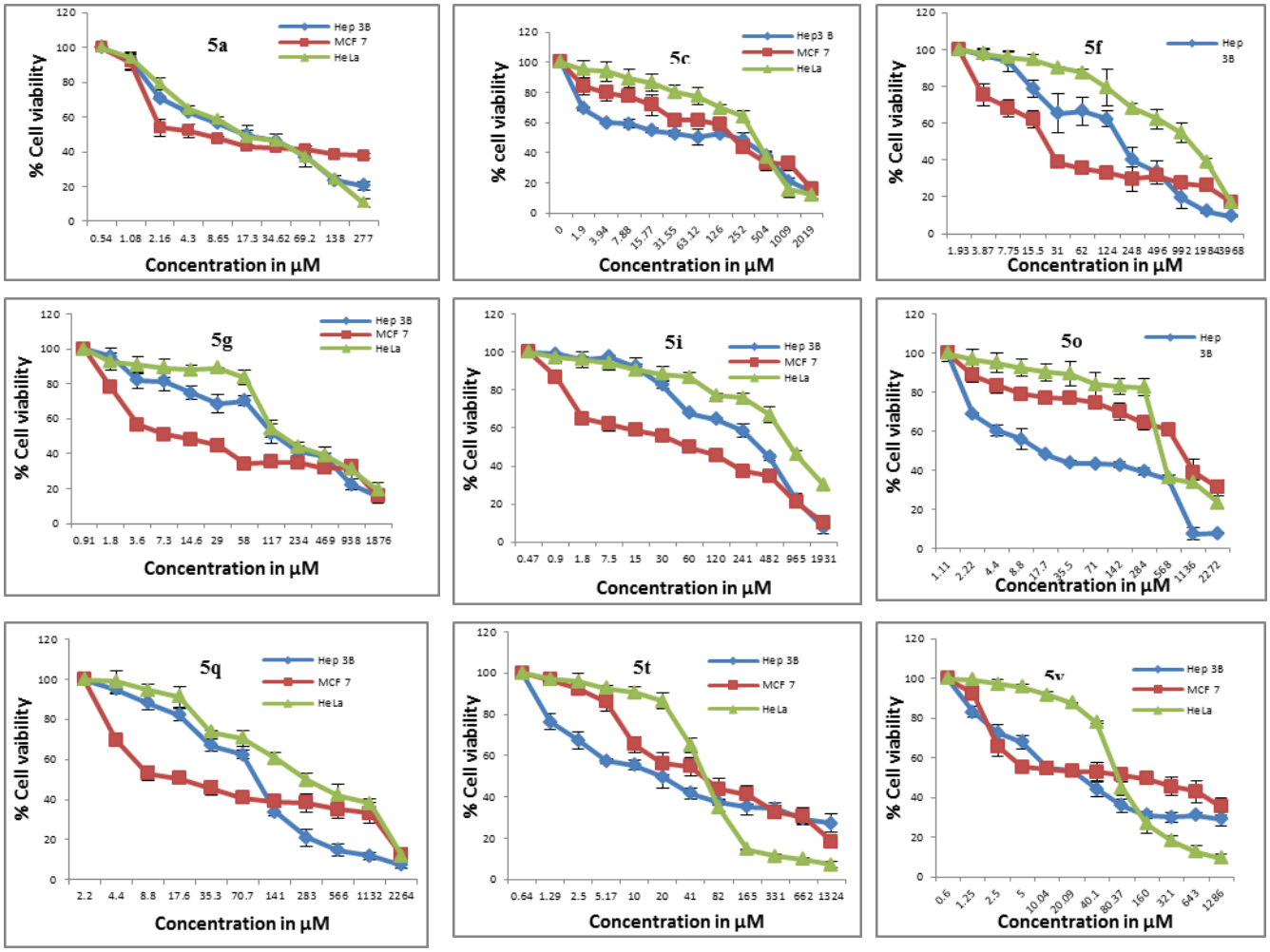


Fig. 3: Selected ^1H-^1H COSY (blue arrows), HMBC (pink arrows), NOE (green arrows) correlations for compound **6b.**

2.4.6. ANTI-PROLIFERATIVE ACTIVITY

All synthesized Prins products (**5a-zb**, **6a-f**, **7**) were evaluated for their *in vitro* anti-proliferative activity against three human cancer cell lines namely; human hepatocellular carcinoma (Hep3β), human breast adenocarcinoma (MCF-7) and human cervical carcinoma (HeLa) following the standard procedure of MTT ((3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay. Each compound was tested in concentration (dose) - % cell viability (response) experiments; with varying the concentration by dilution to define potency. In MTT (colorimetric) assay, the

cytotoxicity of potential drugs and other toxic compounds were measured by the reduction of cellular growth that reduces the tetrazolium yellow dye (MTT) to its insoluble formazan (purple color) by mitochondrial dehydrogenases of living cells. IC_{50} (concentration required to achieve 50% inhibition of tumour growth) values of tested compounds are reported in μM against above cell lines and summarized in Table 8. The insoluble purple formazan product was dissolved in a colored solution by the addition of a suitable solvent and the absorbance of the colored solution was measured. Each experiment was performed in triplicate and the data are reported as average value in Fig. 4. The potency of the drugs (compounds **5a-zb**, **6a-f**, **7**) in causing cell death was obtained through the production of dose-response curves when the amount of purple formazan produced by untreated control cells. Experiments revealed that there was substantial increase in cytotoxicity in cells with increasing exposure to drug concentration (Fig. 4).



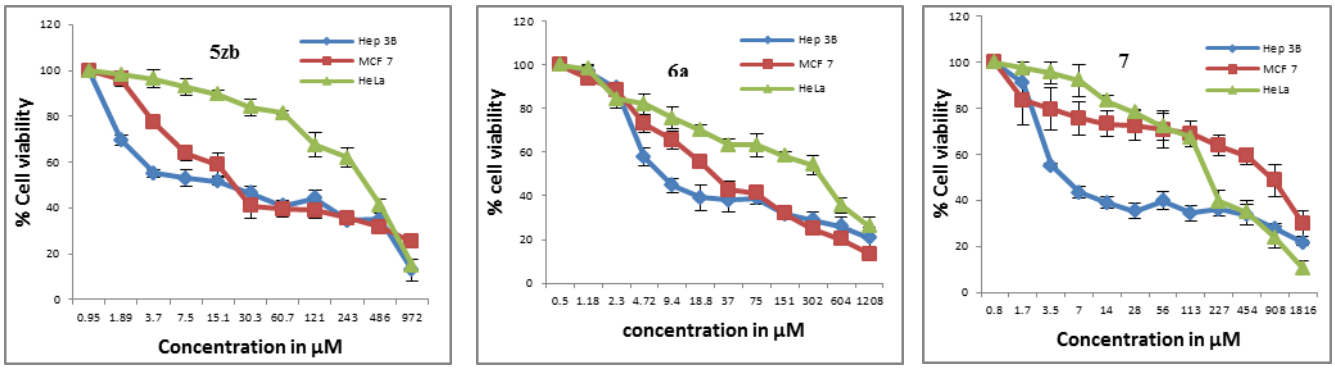


Fig. 4: MTT assay graph of selected compounds.

The results revealed that all synthesized compounds have anti-proliferative activities by inhibiting cell growth with IC_{50} values varying 4.48-56 µM against all tested cell lines. In the Hep3β cell line, some compounds exhibited IC_{50} values upto 46 µM, but the majority of the reported compounds inhibited IC_{50} values below 20 µM. Compound **5zb** was found the most potent with high cytotoxicity (IC_{50} 4.48±2.1 µM) similar to the reference drug Doxorubicin (IC_{50} 4.1±1.1 µM) against the Hep3β cell line. Compounds **5c**, **5o, 5p**, **5q** and **7** showed moderate cytotoxicity against the Hep3β cell line with IC_{50} values 10.40±1.1, 11.1±1.1, 14.1±1.3, 12.9±1.7 and 11.3±1.0 µM, respectively. Against the MCF-7 cell line, some compounds exhibited IC_{50} values upto 56 µM, but the majority of the reported compounds inhibited IC_{50} value below 15µM. Compounds **5q** and **5zb** were found the most potent which exhibited similar cytotoxicity (IC_{50} 6.6±1.4, 6.9±1.0 µM, respectively) to the reference drug doxorubicin (IC_{50} 7.6±0.9 µM) against the MCF-7 cell line. Compounds **5f, 5g, 5i,** and **5s** exhibited moderate cytotoxicity (IC_{50} <11 µM) against the MCF-7 cell line. Against the HeLa cell line, some compounds exhibited IC_{50} values upto 36 µM, but the majority of the reported compounds inhibited IC_{50} values below 20 µM. Compound **5c** was found the most potent with IC_{50} value 12.5±1.7µM against the HeLa cells. Compounds **5q** and **5v** demonstrated better cytotoxicity with IC_{50} values 14.4±1.9 and 15.1±2.8 µM, respectively against the HeLa cells.

On the basis of cytotoxicity results obtained, the flavonoids (chalcone, flavone and flavonone) based pyrans envisaged remarkable anti-proliferative activity against the Hep3β and the MCF-7 cell lines as compared to the HeLa cell line. The *p*-chlorophenyl substituted at C-6 of pyran derivatives (**5b-e**, **5n**, **5u**, **5v**, **5x**, **5zb),** compound **5zb** a rhodanine-3-acetic acid chalcone containing pyran derivative showed excellent cytotoxicity against the Hep3β and the MCF-7 cell lines (IC_{50} ≤6.9±1.0µM). It was also observed that chloro-substituents on chalcone (e.g., **5c**) enhanced cytotoxicity against the Hep3β and the HeLa cell lines (IC_{50} ≤12.5±1.7 µM) and methyl-substitutents

on chalcone (e.g., **5v**) enhanced cytotoxicity against the MCF-7 and the HeLa cell lines (IC_{50} ≤15.1±2.8 μM). Other substituents (F, Br and SMe) showed moderate cytotoxicity against these cancer lines (IC_{50} ≤17.8-34.8 μM). Among *p*-bromophenyl substituted at C-6 of pyran derivatives (**5f-k**, **5y** and **5za**), naphthalene chalcone **5g** at C-2 of pyran ring demonstrated good cytotoxicity (IC_{50} ≤8.85±1.8μM) against MCF-7 cells. Similarly, *p*-methylphenyl **5f** and *p*-methoxyphenyl **5i** substituted chalcones showed better cytotoxicity against MCF-7 cells (IC_{50} ≤11.2±1.2 μM). However, 2-hydroxyphenyl substituted **5j**, 2,4,6-trimethoxyphenyl substituted **5h** chalcones decreased cytotoxicity (IC_{50} ≤37.0±1.6 μM) against MCF-7 cells. In compounds having no substitution on phenyl ring at C-6 of pyran derivatives (**5a**, **5l-m**, **5o-q, 5z)**, compound **5q** showed the maximum cytotoxicity (IC_{50} 6.6-14.4 μM) against these cell lines. Whereas flavanone substituted compound **5z** decreased the cytotoxicity (IC_{50} 45.7±1.3 μM). Further, *p*-methylphenyl substituted **5a** and 3,4-dimethylphenyl substituted **5p** chalcones enhanced cytotoxicity (IC_{50} ≤10.6-16.4 μM) against all the cancer cell lines and *p*-fluorophenyl substituted chalcone **5o** also increased cytotoxicity (IC_{50} 11.1±1.1 μM) against Hep3β cells. Similarly, *p*-methylmercaptophenyl substituted chalcone **5l** enhanced cytotoxicity (IC_{50} 15.3±1.5 μM) against the MCF-7 cells. However, 2,4,6-trimethoxyphenyl substituted chalcone **5m** decreased cytotoxicity against these cancer cell lines (Table 8). But, 3,4,5-trimethoxyphenyl substituted at C-6 compound **5s** showed excellent cytotoxicity (IC_{50} 9.43±2.1 μM) against the MCF-7 cells. In total, cytotoxicity of C-2 substituted chalcones and flavones on pyran ring have shown better activity against tested cancer cell lines. We also observed that at C-4 substituted hydroxyl group on pyran ring decreased cytotoxicity than the tosyl group. However, introduction of cinnamoyl group at C-4 showed high cytotoxicity against the Hep3β cells (IC_{50} value 11.3±1.0 μM). Overall, the substituent effects of different C-4 substituted THPs were observed as 4-tosyloxy THPs > 4-cinnamate THPs > 4-Hydroxy THPs for cytotoxicity.

Table 8: IC_{50} values of flavonoid based THPs on the growth of human cancer cell lines.[a]

Entry	Drug	Hep3β	MCF-7	HeLa
1	**5a**	**14.7±1.5**	**10.6±1.7**	**16.4±2.1**
2	**5b**	31.8±1.6	56.4±3.2	34.8±1.2
3	**5c**	**10.40 ±1.1**	26.0±1.2	**12.5±1.7**
4	**5d**	19.4±1.2	41.4±1.3	26.6±3.1
5	**5e**	24.8±1.9	20.8±1.3	34.6±2.1
6	**5f**	19.4±1.1	**10.9±2.3**	30.4±2.1

7	**5g**	22.2±1.1	**8.85±1.8**	27.8±3.1
8	**5h**	24.6±0.8	24.62±0.7	25.3±1.2
9	**5i**	15.1±1.1	**11.2±1.2**	23.23±2.1
10	**5j**	45.9±3.1	37.0±1.6	35.2±1.9
11	**5k**	35.6±1.1	30.5±2.1	21.5±2.1
12	**5l**	46.1±1.9	15.3±1.5	23.8±.9
13	**5m**	24.5±2.5	19.7±1.1	25.2±.9
14	**5n**	26.3±1.1	17.8±2.1	23.4±4.1
15	**5o**	**11.1±1.1**	27.7±1.1	29.1±2.3
16	**5p**	**14.1±1.3**	**15.3±1.3**	**16.12±0.8**
17	**5q**	**12.9±1.7**	**6.6±1.4**	**14.4±1.9**
18	**5r**	26.3±1.1	17.8±2.1	23.4±4.1
19	**5s**	17.0±.8	**9.43±2.1**	43.1±1.9
20	**5t**	14.7±3.2	28.7±2.7	24.2±1.8
21	**5u**	31.3±1.6	27.9±1.9	36.2±3.2
22	**5v**	18.1±1.7	**14.6±1.8**	**15.1±2.8**
23	**5w**	37.7±1.1	43.2±1.6	32.3±2.5
24	**5x**	35.6±1.1	30.5±2.1	21.5±2.1
25	**5y**	29.8±1.5	37.1±4.1	33±1.3
26	**5z**	38.9±5.0	34.4±3.1	41.1±1.1
27	**5za**	36.9±1.2	42.5±3.2	45.7±1.3
28	**5zb**	**4.48±2.1**	**6.9±1.0**	33.6±3.1
29	**6a**	14.9±.9	23.4±5.1	19.1±4.1
30	**6b**	15.6±3.7	24.4±3.8	22.1±1.9
31	**6c**	16.5±1.8	20.1±.90	20.7±1.9
32	**6d**	37.5±1.5	38.2±2.1	24.32±1.5
33	**6e**	33.5±.5	26.8±5	33.2±1.1
34	**6f**	29.8±1.5	37.1±4.1	33±1.3
35	**7**	**11.3±1.0**	27.9±3.2	23.3±1.4
	Doxorubicin	4.1±1.1	7.6±0.9	5.3±1.2

[a]Values were means of three experiments, each done in duplicate. IC_{50}values are expressed in μm. Hep3β, MCF-7 and Hela cells IC_{50}values are expressed in μm.

2.4.7. CONCLUSIONS

In conclusion, we have reported a new strategy for the synthesis of highly diastereoselective and functionalized 2-flavonoid-6-aryl-4-tosyloxy THPs *via* Prins cyclization in excellent yields (72–96%) within 20-90 min. Deprotection of tosyl group in 4-tosyloxy THPs with TFA and then reaction with cinnamoyl chloride gave 4-cinnamate THPs under neat condition. Novel products show good anti-proliferative activities against human cancer cell lines (Hep3β, MCF-7 and HeLa). Compounds **5q** and **5zb** have shown similar potency IC_{50} 6.6±1.4, 6.9±1.0 μM respectively against the MCF-7 cells compared to the reference drug doxorubicin. Compound **5zb** showed equal cytotoxicity (IC_{50} 4.48±2.1 μM) against the Hep3β cells compared to the reference drug doxorubicin. Compounds **5c, 5o** and **7** showed moderate cytotoxicity (IC_{50} 10.40±1.1, 11.1±1.1, 11.3±1.0 μM, respectively) against the Hep3β cells. Compounds **5a**, **5f**, **5g**, **5i**, and **5s** showed moderate cytotoxicity (IC_{50} 10.6±1.7, 10.9±2.3, 8.85±1.8, 11.2±1.2, 9.43±2.1 μM, respectively) against the MCF-7 cells and compounds **5c** and **5q** showed moderate cytotoxicity (IC_{50} 10.40 ±1.1, 12.9±1.7 μM, respectively) against the HeLa cells. The present work provides strong incentive for future development of flavonoids based THPs as potential antitumor agents.

2.5. EXPERIMENTAL

2.5.1. General methods

Organic solvents were dried by standard methods when necessary. Commercially available reagents were used without further purification unless mentioned. All reactions were monitored by TLC using pre-coated silica gel aluminum plates. Visualization of TLC plates was accomplished with UV lamp or in iodine chamber. The column chromatography was performed using silica gel 100–200 mesh size (SD Fine-Chem Limited) with ethyl acetate/hexane mixture as eluent. Melting points were recorded on perfit apparatus and are uncorrected. The IR spectrum was recorded with KBr on a Thermo Nicolet FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ on a Bruker Spectrospin-500/125 MHz spectrometer using TMS as internal standard. Chemical shifts of ^{1}H NMR spectra were given in parts per million with respect to TMS, and the coupling constant *J* was measured in Hz. Datas are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets). HRMS were recorded on Bruker instrument.

2.5.2. General procedures

Synthesis of aromatic homoallylic alcohols (1a-f):

To a cooled (–78 ºC) solution of aromatic aldehyde (5 mmol) in THF (30 mL) was added allylmagnesium bromide solution (10 mL, 1.0 M in THF, 10 mmol). After stirred for 2h at the same temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in *vacuo* to afford homoallylic alcohol.

Synthesis of 4-tosyloxy THP (2a-r):

Aldehyde (1 mmol) and PTSA (1.4 mmol) were dissolved in DCM (2 mL) and stirred for 5 min at 40 ^{0}C. Then, aromatic homoallylic alcohol (1 mmol, dissolved in 2 mL DCM) followed by MS 4Å were added to the stirred reaction mixture. Further, the reaction mixture was stirred at same temperature for a specified time (table 2). TLC monitoring, the reaction mixture was cooled and added aq. $NaHCO_3$ solution. The product was extracted with dichloromethane (3 x 10 mL). The combined organic layer was washed with brine (5 mL) and water (5 mL) followed by dried on anhyd. Na_2SO_4. Evaporation of solvent under *vacuo*, pure product was obtained. In some cases, purified by silica gel column chromatography using hexane: EtOAc as eluent.

Synthesis of 4-hydroxy tetrahydropyrans (3a-c):

4-Tosyloxy THP (0.5 mmol) and magnesium (120 mg, 5 mmol) in dry methanol (5 mL) in a round bottom flask fitted with condenser and calcium chloride guard tube, stirred at room temperature keeping flask in a water bath for 6h. When the reaction was complete, the reaction mixture was neutralized with chilled 5% HCl and extracted with diethyl ether (3x 8 mL) and the combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4 and concentrated. Crystallization from ethanol yielded pure tetrahydropyran-4-ol.

Synthesis of chalcone based aldehyde (4a-l):

Substituted ketone (5 mmol) and NaOH (0.2 g, 5 mmol) were dissolved in ethanol (20 mL) in Erlenmeyer flask and stirred at room temperature for 10 min. The aldehyde (3 mmol, 5 mL) was added and the mixture was stirred at room temperature. The reaction was monitored by TLC. After completion of reaction, by adding cold aq. 2M HCl neutralized to pH = 7. In most cases, the product

was obtained as a pale yellow precipitate after neutralization followed by filtered the precipitate and recrystallized from ethanol.

Synthesis of flavone based aldehyde (4m):

To a solution of the 2'-hydroxychalcone aldehyde **4i** (1 equiv) in DMSO (5.0 mL/mmol) was added I_2 (0.01 equiv). The mixture was heated at 110 ^{0}C for 1 h. Then reaction mixture was cooled to room temperature then poured into ice cold water to precipitate, precipitate washed with aqueous sodium thiosulphate solution to remove excess I_2, then washed with water and dried to get pure flavone based aldehyde.

Synthesis of flavanone based aldehyde (4n):

2'-Hydroxychalcone aldehyde **4i** (1 mmol) and sodium acetate (10 mmol) were heated in refluxing ethanol (10 mL) for 24h. The mixture was then allowed to cool to r.t. and poured into ice-water (30 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and then concentrated *in vacuo*. The residue was column chromatographed on silica gel, eluting with mixture of ethyl acetate/hexane 1:4, to afford flavanone aldehyde.

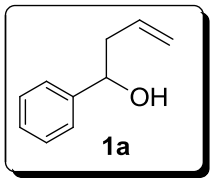
Synthesis of flavonoid based 4-tosyloxy THP (5a-zb):

To a stirred solution of aldehyde (1 mmol), MS 4Å and *p*-toluenesulfonic acid (1.4 mmol) at 62 ^{0}C in chloroform (5 mL) was added aromatic homoallylic alcohol (1 mmol, dissolved in 2 mL $CHCl_3$) drop wise. Further, the reaction mixture was stirred at same temperature. TLC monitoring, after completion of reaction the reaction mixture was cooled and added aq. $NaHCO_3$ solution. The product was extracted with chloroform (3 x 10 mL). The combined organic layer was washed with brine (5 mL) and water (5 mL) followed by dried on anhyd. Na_2SO_4. Evaporation of solvent under *vacuo*, pure product was obtained. In some cases, purification was performed by silica gel column chromatography using hexane: EtOAc as eluent.

Synthesis of flavonoid based 4-hydroxy THPs (6a-f):

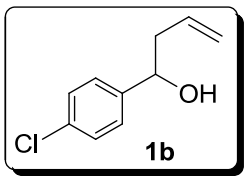
In a flame dried round bottom flask flavonoid based 4-tosyloxy THP (0.5 mmol) dissolved in trifluoroacetic acid (0.5 ml) under inert atmosphere (N_2) heated to 140 ^{0}C. At the same temperature reaction continued 30 min, then poured in ice cold water washed with water and brine, extracted with ethyl acetate (3 x 10 mL). Combined ethyl acetate layer dried over anhyd. Na_2SO_4 and solvent evaporated in *vacuo* which gave pure flavonoid based 4-hydroxy THPs.

2.5.3. SPECTROSCOPIC DATA



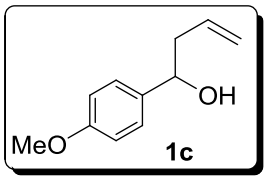
1-Phenyl-but-3-en-1-ol (1a):

Yield: 86%; color less oil. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.3-7.25 (m, 4H), 7.22-7.18 (m, 1H), 5.76-5.67 (m, 1H), 5.08-5.03 (m, 2H), 4.60 (t, *J* = 5Hz, 1H), 3.2 (s, br, D_2O exchangeable, 1H, OH), 2.42 (t, *J* = 7.5Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 143.8, 134.4, 128.4, 127.6, 125.8, 118.5, 73.3, 43.9. **IR (KBr, cm^{-1})**: 3450, 3070, 2935, 2917, 1639, 1491, 1417, 1260, 1099, 835. **GC-MS**: (m/z) 148 (M^+).



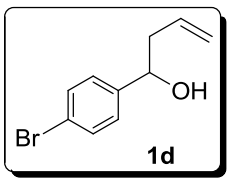
1-(4-Chlorophenyl) but-3-en-1-ol (1b):

Yield: 88%; pale yellow oil. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.3 (d, *J* = 4Hz, 2H), 7.2 (d, *J* = 4Hz, 2H), 5.7 (m, 1H), 5.0 (m, 1H), 4.6 (t, *J* = 5Hz, 1H), 2.4 (m, 2H), 2.3 (s, br, D_2O exchangeable, 1H, OH). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 143.8, 134.5, 128.4, 127.6, 125.8, 118.5, 73.3, 43.9. **IR (KBr, cm^{-1})**: 3425, 3072, 2923, 1638, 1443, 1262, 1030, 804, 701. **GC-MS**: (m/z) 182 (M^+).



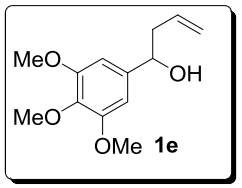
1-(4-Methoxyphenyl) but-3-en-1-ol (1c):

Yield: 85%; pale yellow oil; **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.28 (d, *J* = $9H_Z$, 2H), 6.88 (d, *J* = $8.5H_Z$, 2H), 5.82 (m, 2H), 4.68 (t, *J* = 6.5Hz, 1H), 3.80 (s, 3H), 2.49 (t, *J* = 7Hz, 2H), 2.1 (s, br, D_2O exchangeable, 1H, OH). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 158.2, 135.4, 133.9, 126.3, 117.0, 113.2, 72.0, 54.0, 42.0. **IR (KBr, cm^{-1})**: 3421.5, 3073.7, 2998.0, 1617, 1508, 1299, 1178, 1039. **GC-MS**: (m/z) 178 (M^+).



1-(4-Bromophenyl) but-3-en-1-ol (1d):

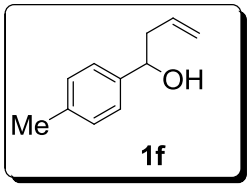
Yield: 88%; pale yellow oil. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.4 (d, *J* = $7H_Z$, 2H), 7.1 (d, *J* = $10.5H_Z$, 2H), 5.7 (m, 1H), 5.1(m, 2H), 4.6 (td, *J* = 6.5, 17Hz, 1H), 2.49 (m, 2H), 2.49 (s, br, D_2O exchangeable, 1H, OH). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 143.8, 134.4, 128.4, 127.6, 125.8, 125.8, 118.5, 73.3, 43.9. **IR (KBr, cm^{-1})**: 3406.2, 3077.4, 2978.2, 2928.6, 1640.3, 1591.3, 1405, 1068.6, 1008.6, 910, 825.7, 735.9, 649.27, 535.1. **GC-MS**: (m/z) 226 (M^+).



1-(3,4,5-Trimethoxyphenyl) but-3-en-1-ol (1e):

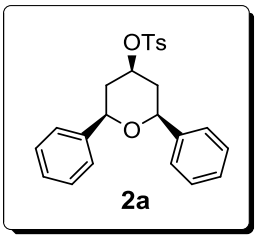
Yield: 82%; pale yellow oil. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 6.57 (s, 2H, Ar-H), 5.8 (m, 1H), 5.16 (m, 2H), 4.64 (m, 1H), 3.85 (s, 6H), 3.82 (s, 3H), 2.49 (m, 2H), 2.2 (s, broad-OH, D_2O exchangeable, 1H). **^{13}C NMR (125 MHz,**

$CDCl_3$): δ (ppm) 153.0, 140.0, 136.9, 134.6, 118.0, 102.6, 73.5, 60.7, 56.0, 43.9. **IR (KBr, cm^{-1})**: 3442, 3100, 2934.8, 2847.83, 1637.1, 1593.9, 1460.3, 1421.7, 1330.4, 1233.9, 1126.2, 1060.9, 1004.35, 913.04, 834.8, 669.57 cm^{-1}. **GC-MS**: (m/z) 238 (M^+).



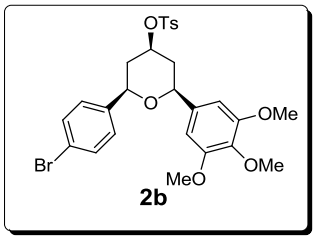
1-(4-Methylphenyl) but-3-en-1-ol (1f):

Yield: 85%; pale yellow oil. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.28 (d, *J* = $9H_Z$, 2H), 6.88 (d, *J* = $8.5H_Z$, 2H), 5.82 (m, 2H), 4.68 (t, *J* = 6.5Hz, 1H), 2.49 (t, *J* = 7Hz, 2H), 2.23 (s, 3H), 2.1 (s, br, D_2O exchangeable, 1H, OH). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 158.2, 135.4, 133.9, 126.3, 117.0, 113.2, 72.0, 54.0, 42.0. **IR (KBr, cm^{-1})**: 3421.5, 3073.7, 2998.0, 2925.9, 1617, 1508, 1447, 1299, 1247, 1178, 1039, 926, 830, 739. **GC-MS**: (m/z): 162 (M^+).



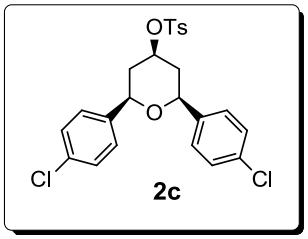
(2R,4S,6S)-2,6-Diphenyl-4-tosyloxy tetrahydropyran (2a):

Yield: 92%; yellow solid; mp 100-102 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.88 (d, *J* = 8Hz, 2H), 7.43-7.37 (m, 10H), 7.34-7.31 (m, 2H), 5.03 (tt, *J* = 4.5, 11.5Hz, 1H), 4.59 (d, *J* = 11.5Hz, 2H), 2.48 (s, 3H), 2.34 (dd, *J* = 4.5, 12.5Hz, 2H), 1.88 (q, *J* = 12.5Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 144.7, 140.9, 134.2, 129.8, 128.3, 127.7, 127.5, 125. 78.18, 77.4, 61.2, 39.94, 21.56. **IR (KBr, cm^{-1})**: 3056, 3039, 2923, 2852, 2373, 1717, 1629, 1454, 1379, 1178, 1065, 945, 903, 757, 699. **CHNS**: Anal. calcd for $C_{24}H_{24}O_4S$: C, 70.56; H, 5.92; S, 7.85; found: C, 70.49; H, 5.91; S, 7.68.

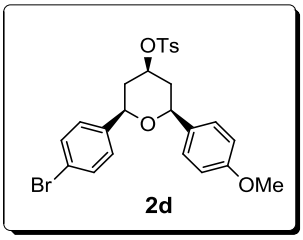


(2R,4R,6S)-2-(4-Bromophenyl)-6-(3,4,5 trimethoxy-phenyl)-4-tosyloxy tetrahydropyran (2b):

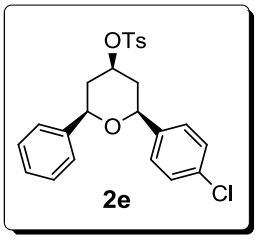
Yield: 82%; yellow semisolid. **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.81 (d, *J* = 8.5Hz, 2H), 7.45 (d, *J* = 8.5Hz, 2H), 7.34 (d, *J* = 8.5Hz, 2H), 7.22 (d, *J* = 8.5Hz, 2H), 6.56 (s, 2H), 4.94 (tt, *J* = 5.0, 11.0Hz, 1H), 4.46 (m, 2H), 3.85 (s, 6H), 3.81 (s, 3H), 2.44 (s, 3H), 2.35 (m, 2H), 1.85 (q, J = 11.5Hz, 1H), 1.79 (q, J = 11.5Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ (ppm) 153.3, 145.0, 139.8, 137.7, 136.3, 134.2, 131.6, 129.9, 127.6, 121.8, 103.1, 77. 9, 77.7, 71.8, 60.8, 56.5, 39.8, 21.7. **IR (KBr, cm^{-1})**: 2960, 2925, 2843, 1726, 1594, 1461, 1382, 1175, 1126, 1010, 953, 904, 817. **CHNS**: Anal. calcd for $C_{27}H_{29}BrO_7S$: C, 56.16; H, 5.06; S, 5.55; found: C, 56. 03; H, 5.49; S, 5.65.



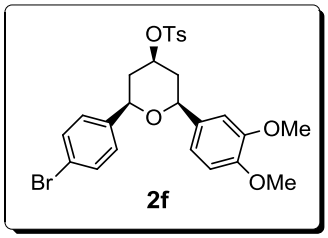
(2R,4S,6S)-2,6-Bis(4-chlorophenyl)-4-tosyloxy tetrahydropyran (2c): Yield: 92%; yellow solid; mp 106-108 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.80 (d, *J* = 8Hz, 2H), 7.35-7.27 (m, 10H), 4.93 (tt, *J* = 4.5, 11Hz, 1H), 4.50 (dd, *J* = 1.5 and 11.5Hz, 2H), 2.44 (s, 3H), 2.268 (dd, *J* = 4.5 and 11.5Hz, 2H), 1.75 (q, *J* = 11.5Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 145.0, 139.3, 134.2, 133.7, 130.0, 128.7, 127.6, 127.2, 77.6, 76.8, 39.9, 21.7. **IR (KBr, cm^{-1})**: 3051, 2956, 2924, 2853, 1721, 1634, 1596, 1491, 1353, 1293, 1171, 1089, 1014, 950, 908, 859, 828, 665. **CHNS**: Anal. calcd for $C_{24}H_{22}Cl_2O_4S$: C, 60.38; H, 4.64; S, 6.72; found: C, 60.45; H, 4. 65; S, 6.55.



(2R,4S,6S)-2-(4-Bromophenyl)-6-(4-methoxyphenyl)-4-tosyloxy tetrahydropyran (2d): Yield: 88%; yellow semisolid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.81 (d, *J* = 8.5Hz, 2H), 7.45 (d, *J* = 8.5Hz, 2H), 7.34 (d, *J* = 8.5Hz, 2H), 7.27 (d, *J* = 9Hz, 2H), 7.22 (d, *J* = 8.5Hz, 2H), 6.87 (d, *J* = 9Hz, 2H), 4.92 (tt, *J* = 4.5, 11Hz, 1H), 4.48 (t, *J* = 10Hz, 2H), 3.792 (s, 3H), 2.45(s, 3H), 2.29-2.22 (m, 2H), 1.83 (q, *J* = 11.5Hz, 1H), 1.76 (q, *J* = 11.5Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm) 158.2, 143.8, 139.0, 133.2, 131.8, 130.5, 128.9, 126.5, 126.2, 120.6, 112.8, 76.9, 75.7, 54.2, 38.9, 38.7, 20.6. **IR (KBr, cm^{-1})**: 2920, 2850, 1631, 1499, 1383, 1299, 1248, 1175, 1073, 904, 813, 730, 721, 669. **CHNS**: Anal. calcd for $C_{25}H_{25}BrO_5S$: C, 58.03; H, 4.87; S, 6.20; found: C, 58.11; H, 4.90; S, 6.28.

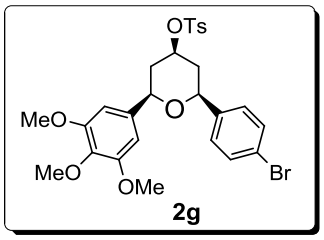


(2S,4R,6R)-2-(4-Chlorophenyl)-6-phenyl-4-tosyloxy tetrahydropyran (2e): Yield: 90%; yellow solid; mp 95-97 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm) 7.82.(dd, *J* = 2, 8.5Hz, 3H), 7.38-7.261 (m, 10H), 4.99-4.91 (tt, *J* = 4.5, 11Hz, 1H), 4.55-4.50 (m, 2H), 2.48 (s, 3H), 2.30 (dd, *J* = 4.5, 12.5Hz, 2H), 1.85 (q, *J* = 11.5Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 144.0, 140.0, 134, 133, 129, 128, 127.8, 127.6, 127.2, 125.9, 125.8, 78, 77.0, 40.0, 39.0, 21. **IR (KBr, cm^{-1})**: 3056, 2962, 1600, 1149, 1356, 1261, 1172, 1095, 1022, 802, 560. **CHNS**: Anal. calcd for $C_{24}H_{23}ClO_4S$ (442.95): C, 65.08; H, 5.23; S, 7.24; found: C, 64.18; H, 5.25; S, 7.30.



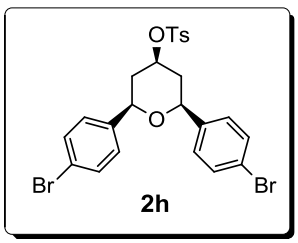
(2R,4R,6S)-2-(4-Bromophenyl)-6-(3,4-dimethoxyphenyl)-4-tosyloxytetrahydropyran (2f):

Yield: 85%; yellow solid; mp 111-113 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.81 (d, *J* = 8Hz, 2H), 7.45 (d, *J* = 8Hz, 2H), 7.34 (d, *J* = 8Hz, 2H), 7.22 (d, *J* = 8.5Hz, 2H), 6.90-6.82 (m, 3H), 4.93 (tt, *J* = 4.5, 11Hz, 1H), 4.48 (t, *J* = 10Hz, 2H), 2.45 (s, 3H), 2.265 (dd, *J* = 4.5, 2.5Hz, 2H), 1.86 (q, *J* = 11.5Hz, 1H), 1.76 (q, *J* = 11.5Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm) 149.2, 145.1, 140.2, 133.5, 131.7, 130.1, 127.8, 118.5, 111.3, 109.6, 78.1, 77.7, 77.0, 56.1, 40.1, 39.9, 21.9. **IR (KBr, cm^{-1})**: 3010, 2965, 2924, 2852, 1734, 1630, 1516, 1460, 1361, 1265, 1174, 1070, 1028, 949, 904, 846, 813.7, 668.37. **CHNS**: Anal. calcd for $C_{26}H_{27}BrO_6S$: C, 57.04; H, 4.97; S, 5.86; found: C, 56. 98; H, 4.95; S, 5.75.



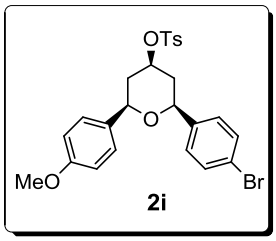
(2S,4S,6R)-2-(4-Bromophenyl)-6-(3,4,5-trimethoxyphenyl)-4-tosyloxytetrahydropyran (2g):

Yield: 72%; yellow semisolid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.82 (d, *J* = 8Hz, 2H), 7.46 (d, *J* = 8.5Hz, 2H), 7.35 (d, *J* = 8Hz, 2H), 7.23 (m, 2H), 6.57 (s, 2H), 4.95 (tt, *J* = 6.5, 11.5Hz, 1H), 4.47 (m, 2H), 3.86 (s, 6H), 3.82 (s, 3H), 2.45 (s, 3H), 2.29 (m, 2H), 1.84 (q, *J* = 12Hz, 1H), 1.79 (q, *J* = 11.5Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 154.2, 145.8, 140.7, 138.6, 137.2, 135.0, 132.5, 130.8, 129.0, 128.5, 122.6, 104.0, 78.8, 78.7, 72.7, 61.7, 57.0, 40.7, 22.6. **IR (KBr, cm^{-1})**: 2960, 2925, 2843, 1726, 1594, 1461, 1382, 1175, 1126, 1010, 953, 904, 817. **CHNS**: Anal. calcd for $C_{27}H_{29}BrO_7S$: C, 56.16; H, 5.06; S, 5.55; found: C, 56.20; H, 5.03; S, 5.42.



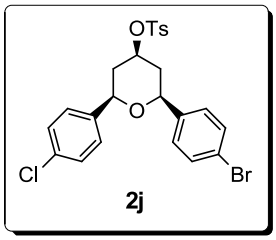
(2R,4S,6S)-2,6-Bis(4-bromophenyl)- 4-tosyloxy tetrahydropyran (2h):

Yield: 95%; pale yellow solid; mp 110-112 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.73 (d, *J* = 8Hz, 2H), 7.38 (d, *J* = 13Hz, 4H), 7.26 (d, *J* = 8Hz, 2H), 7.13 (d, *J* = 8.5Hz, 4H), 4.88-4.82 (tt, *J* = 4.5, 11Hz, 1H), 4.40 (d, *J* = 10Hz, 2H), 2.37 (s, 3H), 2.18 (dd, *J* = 4.5, 12.5Hz, 2H), 1.68 (q, *J* = 12Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 145.0, 139.8, 134.2, 131.6, 130.0, 127.6, 121.8, 77.5, 76.8, 39.8, 21.7. **IR (KBr, cm^{-1})**: 3100, 2960, 2908, 2843, 1895, 1726, 1595, 1489, 1353, 1172, 1073, 1011, 950, 908, 811, 682, 664 cm^{-1}. **CHNS**: Anal. calcd for $C_{24}H_{22}Br_2O_4S$: C, 50.90; H, 3.92; S, 5.66; found: C, 50.82; H, 3.94; S, 5.55.



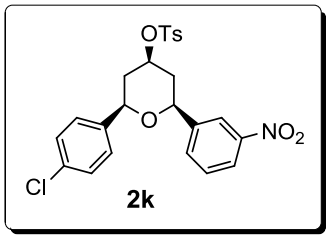
(2S,4R,6R)-2-(4-Bromophenyl)-6-(4-methoxyphenyl)-4-tosyloxy tetrahydropyran (2i):

Yield: 75%; yellow semisolid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.74 (d, *J* = 8.5Hz, 2H), 7.38 (dd, *J* = 2, 7Hz, 2H), 7.27 (d, *J* = 8.5Hz, 2H), 7.21-7.14 (m, 4H), 6.80 (dd, *J* = 2, 6.5Hz, 2H), 4.84 (tt, *J* = 4.5, 11Hz, 1H), 4.41 (t, *J* = 10Hz, 2H), 3.72 (s, 3H), 2.38 (s, 3H), 2.22-2.15 (m, 2H), 1.77 (q, *J* = 12Hz, 1H), 1.73 (q, *J* = 12Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 156.1, 141.7, 137.0, 131.1, 129.7, 128.4, 124.4, 124.1, 118.5, 110.7, 74.8, 73.6, 52.1, 36.8, 28.5, 21.0. **IR (KBr, cm^{-1})**: 2920, 2850, 1631, 1499, 1383, 1299, 1248, 1175, 1073, 904, 813, 730, 721, 669. **CHNS**: Anal. calcd for $C_{25}H_{25}BrO_5S$: C, 58.03; H, 4.87; S, 6.20; found: C, 58.10; H, 4.85; S, 6.10.



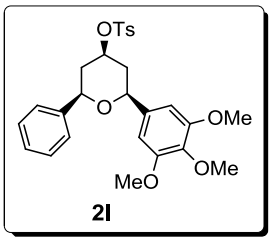
(2S,4R,6R)-2-(4-Bromophenyl)-6-(4-chlorophenyl)-4-tosyloxy tetrahydropyran (2j):

Yield: 95%; pale yellow solid; mp 110-112 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.78 (d, *J* = 8Hz, 2H), 7.42 (d, *J* = 8.5Hz, 2H), 7.31 (d, *J* = 8Hz, 2H), 7.28-7.23 (m, 4H), 7.18 (d, *J* = 8.5Hz, 2H), 4.9 (tt, *J* = 4.5, 11Hz, 1H), 4.46 (t, *J* = 10Hz, 2H), 2.40 (s, 3H), 2.22 (dd, *J* = 3, 12.5Hz, 2H), 1.72 (q, *J* = 11.5Hz, 2H). **^{13}C NMR (125MHz, $CDCl_3$)**: δ (ppm) 144.9, 139.7, 139.2, 134.1, 133.5, 131.5, 129.9, 128.5, 127.5, 127.1, 121.7, 77.5, 76.7, 39.7, 39.7, 21.6. **IR (KBr, cm^{-1})**: 3078, 2965, 2921, 2856, 1908, 1708, 1630, 1591, 1489, 1354, 1171, 1081, 948, 908, 831, 669. **CHNS**: Anal. calcd for $C_{24}H_{22}BrClO_4S$: C, 55.24; H, 4.25; S, 6.14; found: C, 55.16; H, 4.20; S, 6.22.



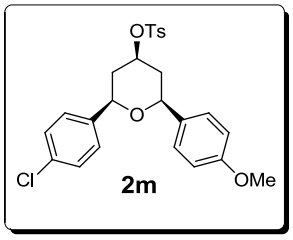
(2R,4R,6S)-2-(4-Chlorophenyl)-6-(3-nitrophenyl)- 4-tosyloxy tetrahydropyran (2k):

Yield: 96%; yellow solid; mp 118-120 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 8.62 (s, 1H), 8.4 (dd, *J* = 3, 8Hz, 1H), 8.14 (d, *J* = 7.5Hz, 1H), 7.72 (d, *J* = 8.5Hz, 2H), 7.67 (t, *J* = 8Hz, 1H), 7.26 (d, *J* = 8Hz, 2H), 7.229-7.186 (m, 4H), 4.85 (tt, *J* = 4.5, 11Hz, 1H), 4.43 (dd, *J* = 1, 11.5Hz, 2H), 2.36 (s, 3H), 2.18 (dd, *J* = 4.5, 12.5Hz, 2H), 1.68 (q, *J* = 11.5Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 148.5, 144.9, 139.0, 137.1, 134.6, 133.7, 133.4, 130.3, 129.8, 128.5, 127.4, 127.1, 124.4, 77.4, 76.7, 39.7, 21.6. **IR (KBr, cm^{-1})**: 3069.6, 2960.87, 2926.1, 1703.7, 1596, 1533, 1352, 1171, 1090, 970.9, 908.8, 841, 700, 666. **CHNS**: Anal. calcd for $C_{24}H_{22}ClNO_6S$: C, 59.07; H, 4.54; N, 2.87; S, 6.57; found: C, 58.93; H, 4.58; N, 2.82; S, 6.40.



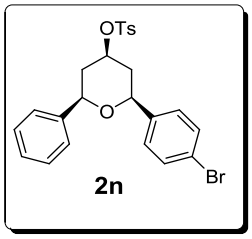
(2R,4R,6S)-2-Phenyl-6-(3,4,5-trimethoxyphenyl) 4-tosyloxy tetrahydropyran (2l):

Yield: 83%; dark yellow solid; mp 116-118 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm) 7.85 (d, *J* = 8Hz, 2H), 7.37 (m, 7H), 6.61 (s, 2H), 4.99 (tt, *J* = 5, 11Hz, 1H), 4.52 (ddd, *J* = 2, 11.5Hz, 2H), 3.88(s, 6H), 3.84 (s, 3H), 2.47 (s, 3H), 2.34-2.29 (m, 2H), 1.93-1.84 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 152.3, 143.8, 143.1, 139.8, 136.5, 135.4, 128.9, 127.5, 126.9, 126.6, 124.9, 102.2, 77.1, 76.8, 59.8, 55.1, 39.0, 20.6. **IR (KBr, cm^{-1})**: 2962, 2926, 2852, 1634, 1595, 1456, 1417, 1261, 1178, 1096, 1023, 803, 873, 708. **CHNS**: Anal. calcd for $C_{27}H_{30}O_7S$: C, 65.05; H, 6.06; S, 6.43; found: C, 65.10; H, 6.08; S, 6.38.



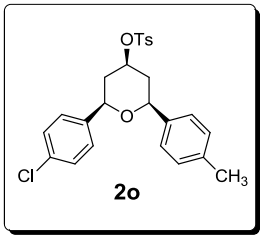
(2R,4S,6S)-2-(4-Chlorophenyl)-6-(4-methoxyphenyl)-4-tosyloxy tetrahydropyran (2m):

Yield: 88%; yellow semisolid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm) 7.74 (d, *J* = 8.5Hz, 2H), 7.28-7.19 (m, 8H), 6.8 (d, *J* = 9Hz, 2H), 4.85 (tt, *J* = 4.5, 11.5Hz, 1H), 4.45-4.39 (ddd, *J* = 1.5, 11.5Hz, 2H), 3.72 (s, 3H), 2.38 (s, 3H), 2.22-2.15 (m, 2H), 1.74(q, *J* = 11.5Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 159.3, 144.9, 144.5, 132.5, 131.3, 129.8, 128.5, 127.5, 127.1, 126.1, 121.5, 113.7, 77.9, 55.2, 39.9, 39.6, 21.6. **IR (KBr, cm^{-1})**: 3010, 2956, 2921, 2847, 1721, 1633, 1508, 1456, 1386, 1252, 1178, 1082, 1026, 904, 813. **CHNS**: Anal. calcd for $C_{25}H_{25}ClO_5S$: C, 63.48; H, 5.33; S, 6.78; found: C, 63.45; H, 5.36; S, 6.69.

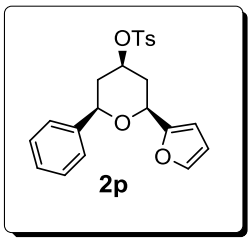


(2S,4R,6R)-2-(4-Bromophenyl)-6-phenyl-4-tosyloxy tetrahydropyran (2n):

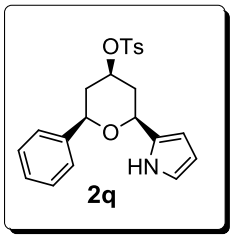
Yield: 95%; Pale yellow solid; mp 104-106 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.83 (d, *J* = 1.5Hz, 2H), 7.46 (dd, *J* = 2 and 8.5Hz, 2H), 7.39-7.22 (m, 9H), 4.95 (tt, *J* = 4.5, 11.5Hz, 1H), 4.56-4.48 (m, 2H), 2.45 (s, 3H), 2.30-2.27 (m, 2H), 1.89-1.74 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: **δ** (ppm) 143.9, 139.9, 139.0, 133.2, 130.5, 128.9, 127.4, 126.9, 126.5, 124.8, 120.7, 77.2, 76.8, 38.9, 20.6. **IR (KBr, cm^{-1})**: 2921.7, 1630, 1486, 1352, 1182, 1065, 1008, 900, 817, 756. **CHNS**: Anal. calcd for $C_{24}H_{23}BrO_4S$: C, 59.14; H, 4.76; S, 6.58; found: C, 59.12; H, 4.79; S, 6.49.



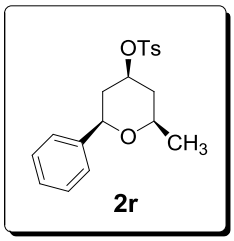
(2R,4S,6S)-2-(4-Chlorophenyl)-6-*p*-tolyl-4-tosyloxy tetrahydropyran (2o): Yield: 93%; yellow solid; mp 104-106 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm) 7.81 (d, *J* = 8Hz, 2H), 7.34 (d, *J* = 8.5Hz, 2H), 7.30- 7.22 (m, 6H), 7.146 (d, *J* = 7.5Hz, 2H), 4.92 (tt, *J* = 11Hz, 4.5Hz, 1H), 4.49 (td, *J* = 2, 11.5Hz, 2H), 2.45 (s, 3H), 2.33 (s, 3H), 2.29-2.26 (m, 2H), 1.84-1.76 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm) 144.9, 139.5, 137.7, 134.2, 133.5, 129.9, 129.2, 128.5, 127.6, 127.2, 125.8, 78.8, 78.0, 40.4, 39.8, 21.7, 21.1. **IR (KBr, cm^{-1})**: 3047, 2982, 2916, 2843, 2373, 1639, 1369, 1265, 1169, 1117, 738. **CHNS**: Anal. calcd for $C_{25}H_{25}ClO_4S$: C, 65.71; H, 5.51; S, 7.02; found: C, 65.76; H, 5.49; S, 7.15.



(2S,4R,6R)-2-(Furan-2-yl)-6-phenyl-4-tosyloxy tetrahydropyran (2p): Yield: 83%; yellow solid; mp 123-125 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.82 (d, *J* = 7.5Hz, 2H), 7. 41 (d, *J* = 7.5Hz, 2H), 7.31 (m, 1H), 7.21 (m, 5H), 6.43-6.25 (m, 2H), 5.15 (t, 12Hz, 1H), 4.95 (tt, *J* = 11Hz, 4.5Hz, 1H), 4.53 (td, *J* = 2, 11.5Hz, 1H, Ar-CH-O), 2.45 (s, 3H), 2.25-2.21 (m, 2H, C-CH_{eq}-C), 1.90-1.86 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 153.2, 144.5, 142.2, 139.8, 138.4, 132.7, 130.9, 128.6, 128.5, 127.0, 112.4, 111.6, 78.0, 75.2, 40.7, 39.9, 22.5. **IR (KBr, cm^{-1})**: 3021, 2986, 2355, 1696, 1432. **CHNS**: Anal. calcd for $C_{22}H_{22}O_5S$: C, 66.31; H, 5.56; S, 8.05; found: C, 66.24; H, 5.52; S, 8.20.

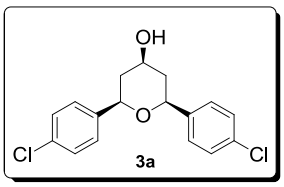


(2S,4R,6R)-2-Phenyl-6-(1*H*-pyrrol-2-yl)-4-tosyloxy tetrahydropyran (2q): Yield: 86%; yellow semi solid; **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm) 8.21 (s, br, D_2O exchangeable, 1H, NH), 7.81 (d, *J* = 7.5Hz, 2H), 7. 44 (d, *J* = 7.5Hz, 2H), 7.19 (m, 5H), 6.43 (m, 1H), 5.95-5.7 (m, 2H), 4.93 (tt, *J* = 12Hz, 4.5Hz, 1H), 4.87 (td, *J* = 2, 11.5Hz, 2H), 2.41 (s, 3H), 2.25-2.21 (m, 2H), 1.90-1.86 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 144.3, 140.3, 139.1, 133.6, 130.8, 128.9, 128.2, 127.2, 118.5, 108.6, 107.4, 77.6, 72.1, 59.8, 41.4, 40.2, 23.9. **IR (KBr, cm^{-1})**: 3451, 3069.6, 2960.87, 1703.7, 1596, 1533, 1352. **CHNS**: Anal. calcd for $C_{22}H_{23}NO_4S$: C, 66.48; H, 5.83; N, 3.52; S, 8.07; found: C, 66.40; H, 5.81; N, 3.60; S, 8.20.



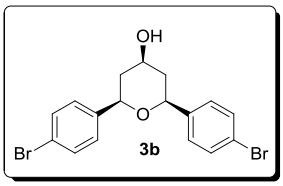
(2R,4S,6S)-2-Methyl-6-phenyl-4-tosyloxy tetrahydropyran (2r):

Yield: 89%; yellow solid; mp 92-94 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.88 (d, *J* = 8Hz, 2H), 7.34-7.31 (d, *J* = 8Hz, 2H), 7.22 (m, 5H), 5.03 (tt, *J* = 4.5, 11.5Hz, 1H), 4.59 (t, *J* = 11.5Hz, 1H), 3.92 (m, 1H), 2.48 (s, 3H), 2.33-2.37 (dd, *J* = 4.5, 12.5Hz, 2H), 1.88 (q, *J* = 7.5Hz, 2H). 1.56 (m, 3H). **^{13}CNMR (125 MHz, $CDCl_3$)**: δ (ppm) 144.7, 140.9, 134.2, 129.8, 128.3, 127.7, 127.5, 125. 82, 77.4, 68.21, 61.2, 39.9, 24.3, 21.6. **IR (KBr, cm^{-1})**: 3056, 2923, 2852, 1717, 1629, 1454, 1379. **CHNS**: Anal. Calcd for $C_{19}H_{22}O_4S$ (346.12): C, 65.87; H, 6.40; S, 9.26; found: C, 65.85; H, 6.36; S, 9.20.



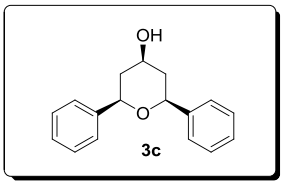
(2R,4S,6S)-2,6-Bis(4-chlorophenyl)-tetrahydropyran-4-ol (3a):

Yield: 92%; yellow solid; mp 110-112 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.29-7.24 (m, 8H), 4.47 (d, *J* = 11.5Hz, 2H), 4.06 (tt, *J* = 4.5, 11.5Hz, 1H), 2.19 (dd, *J* = 4, 11.5Hz, 2H), 1.48 (q, *J* = 11.5Hz, 2H). **^{13}C NMR (125 MHz, CDCl3)**: δ (ppm) 139.2, 132.3, 127.5, 126.2, 77.8, 67.4, 41.9. **IR (KBr, cm^{-1})**: 3447.1, 2960.87, 2886, 1652, 1543, 1088, 804. **GC-MS**: (m/z) 323 (M^+).



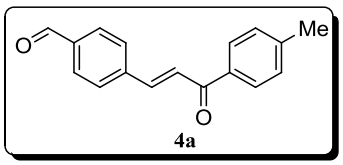
(2R,4S,6S)-2,6-Diphenyl-tetrahydropyran-4-ol (3b):

Yield: 95%; yellow solid; mp 102-103 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.42 (d, *J* = 7Hz, 4H), 7.35 (t, *J* = 7.5Hz, 4H), 7.28 (m, 2H), 4.57 (d, *J* = 11.5Hz, 2H), 4.16 (tt, *J* = 4.5, 11.5Hz, 1H), 2.29 (dd, *J* = 2, 10Hz, 2H), 2.23 (s, br, D_2O exchangeable, 1H, OH), 1.60 (q, *J* = 11.5Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm) 141.8, 128.2, 127.4, 125.7, 77.8, 68.6, 42.96. **IR (KBr, cm^{-1})**: 3434, 3010, 2922, 2843, 1734, 1626, 1456, 1386, 1256, 1069, 808.8. **GC-MS**: (m/z) 254 (M^+).



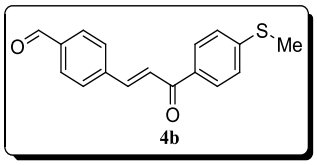
(2R,4S,6S)-2,6-Bis(4-bromophenyl)-tetrahydropyran-4-ol (3c):

Yield: 94%; yellow solid; mp 122-123 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.19-7.41 (m, 8H), 4.51-4.43 (m, 2H), 4.07 (tt, *J* = 4.5, 11.5Hz, 1H), 2.28 (s, br, D_2O exchangeable, 1H, OH), 2.21 (dd, *J* = 4, 11.5Hz, 2H), 1.53 (q, *J* = 11.5Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 131.4, 128.3, 127.5, 125.8, 77.8, 68.6, 43.0, 42.8. **IR (KBr, cm^{-1})**: 3433.8, 2965.2, 2921.7, 2852.1, 1634.8, 1452.1, 1382.6, 1265.2, 1156.5, 1065.2, 900.0, 760.87, 700. **GC-MS**: (m/z) 410 (M^+).



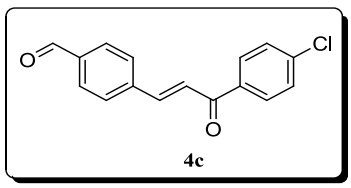
(E)-4-(3-Oxo-3-p-tolylpropenyl)benzaldehyde (4a):

Yield 84%; light yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 2.45 (s, 3H), 7.32 (d, *J* = 7.5Hz, 2H), 7.57-7.69 (m, 2H), 7.79 (d, *J* = 8Hz, 2H), 7.94 (d, *J* = 8.5Hz, 4H), 10.05 (s, 1H). **IR (KBr, cm^{-1})**: 3014, 2961, 2878, 1708, 1641, 1421. **HRMS (ESIMS)**: Anal. calcd for $C_{17}H_{14}NaO_2$ $(M+Na)^+$ 273.0891; found 273.0883.



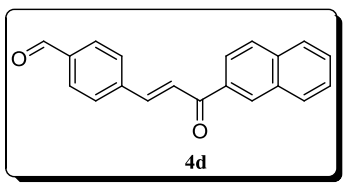
(E)-4-(3-(4-Methylmercaptophenyl)-3-oxopropenyl)benzaldehyde (4b):

Yield 85%; light yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 2.56 (s, 3H), 7.33 (d, *J* = 8.5Hz, 2H), 7.63 (d, *J* = 16Hz, 1H), 7.79 (d, *J* = 8Hz, 2H), 7.83 (d, *J* = 16Hz, 1H), 7.94 (d, *J* = 8.5Hz, 2H), 7.97 (d, *J* = 8.5Hz, 2H), 10.05 (s, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 14.93, 124.65, 12.26, 128.98, 129.18, 130.38, 134.09, 137.38, 140.83, 142.65, 146.52, 188.74, 191.64. **IR (KBr, cm^{-1})**: 3021, 2945, 2882, 1712, 1646, 1402, 1205. **HRMS (ESIMS)**: Anal. calcd for $C_{17}H_{14}NaO_2S$ $(M+Na)^+$ 305.0612; found 305.0604.



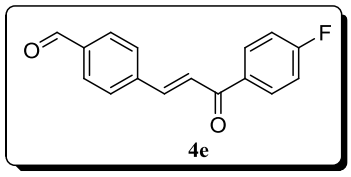
(E)-4-(3-(4-Chlorophenyl)-3-oxopropenyl)benzaldehyde (4c):

Yield 83%; light yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.50 (d, *J* = 8.5Hz, 2H), 7.70 (d, *J* = 11Hz, 1H), 7.81 (t, *J* = 8.5Hz, 3H), 7.94 (d, *J* = 8Hz, 2H), 7.98 (d, *J* = 8.5Hz, 2H), 10.06 (s, 1H). **IR (KBr, cm^{-1})**: 3020, 2985, 2881, 1711, 1654, 1426. **HRMS (ESIMS)**: Anal. calcd for $C_{16}H_{11}ClNaO_2$ $(M+Na)^+$ 293.0345; found 293.0388.



(E)-4-(3-(Naphthalen-2-yl)-3-oxopropenyl)benzaldehyde (4d):

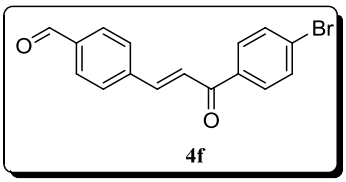
Yield 90%; light yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.60 (td, *J* = 1.5Hz, 8.5Hz, 1H), 7.64 (td, *J* = 1.5Hz, 8Hz, 1H), 7.79 (d, *J* = 12Hz, 1H), 7.84 (d, *J* = 7Hz, 1H), 7.88 (d, *J* = 13Hz, 2H), 7.92 (m, 1H), 7.96-7.98 (m, 2H), 8.02 (d, *J* = 9.5Hz, 1H), 8.12 (dd, *J* = 2Hz, 9Hz, 1H), 10.07 (s, 1H). **IR (KBr, cm^{-1})**: 3021, 2945, 2882, 1712, 1646, 1402. **HRMS (ESIMS)**: Anal. calcd for $C_{20}H_{14}NaO_2$ $(M+Na)^+$ 309.0891; found 309.0880.



(E)-4-(3-(4-Fluorophenyl)-3-oxopropenyl)benzaldehyde (4e):

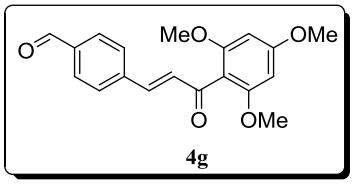
Yield 89%; light yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.18 (d, *J* = 8.5Hz, 2H), 7.58-7.61 (m, 1H), 7.68 (m, 1H), 7.79-7.85 (m, 2H), 7.94 (d, *J* = 8Hz, 2H), 8.07-8.10 (m, 2H), 10.04 (s, 1H). **^{13}C NMR ($CDCl_3$, 125MHz):** δ 115.58, 115.67, 115.76, 115.86, 124.11, 128.69, 128.84, 130.07, 131.01,

131.08, 137.17, 142.87, 191.26. **IR (KBr, cm^{-1})**: 3027, 2991, 2801, 1743, 1656, 1414. **HRMS (ESIMS):** Anal. calcd for $C_{16}H_{11}FNaO_2$ $(M+Na)^+$ 277.0641; found 277.0630.



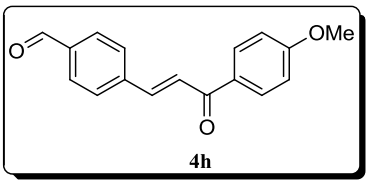
4f

(E)-4-(3-(4-Bromophenyl)-3-oxopropenyl)benzaldehyde (4f): Yield 85%; light yellow solid. **^{1}H NMR (500 MHz, CDCl$_3$)**: δ (ppm) 7.58 (d, *J* = 15.5Hz, 1H), 7.66 (dd, *J* = 6.5Hz, 1.5Hz, 2H), 7.79 (d, *J* = 8Hz, 2H), 7.83 (d, *J* = 15.5Hz, 1H), 7.90 (dd, *J* = 7Hz, 2Hz, 2H), 7.93 (d, *J* = 8Hz, 2H), 10.05 (s, 1H). **^{13}C NMR (125 MHz, CDCl$_3$)**: δ 124.30, 128.58, 129.09, 130.24, 130.41, 132.26, 136.62, 137.57, 140.49, 143.55, 188.99, 191.60. **IR (KBr, cm^{-1})**: 3020, 2985, 2881, 1711, 1654, 1426. **HRMS (ESIMS)**: Anal. calcd for $C_{16}H_{11}BrNaO_2$ $(M+Na)^+$ 336.9840; found 336.9834.



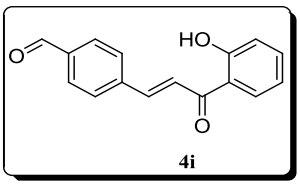
4g

(E)-4-(3-Oxo-3-(2,4,6-trimethoxyphenyl)propenyl)benzaldehyde (4g): Yield 80%; light yellow solid. **^{1}H NMR (500 MHz, CDCl$_3$)**: δ (ppm) 3.95 (s, 3H), 3.96 (s, 6H), 7.29 (s, 2H), 7.52-7.60 (m, 1H), 7.71 (s, 1H), 7.79-7.82 (m, 2H), 7.84- (d, *J* = 5.5Hz, 1H), 7.94 (d, *J* = 8Hz, 1H). **IR (KBr, cm^{-1})**: 3033, 2955, 2888, 1717, 1636, 1413, 1253. **HRMS (ESIMS)**: Anal. calcd for $C_{19}H_{18}NaO_5$ $(M+Na)^+$ 349.1052; found 349.1055.



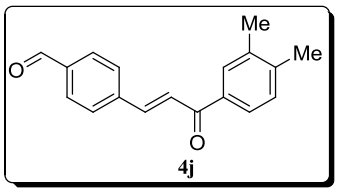
4h

(E)-4-(3-(4-Methoxyphenyl)-3-oxopropenyl)benzaldehyde (4h): Yield 78%; light yellow solid. **^{1}H NMR (500 MHz, CDCl$_3$)**: δ (ppm) 3.92 (s, 3H), 7.01 (d, *J* = 9Hz, 2H), 7.60-7.70 (m, 2H), 7.80 (d, *J* = 8Hz, 2H), 7.95 (d, *J* = 8Hz, 2H), 8.07 (d, *J* = 8.5Hz, 2H), 10.06 (s, 1H). **^{13}C NMR (125 MHz, CDCl$_3$)**: δ (ppm) 55.71, 114.15, 124.81, 128.92, 130.36, 131.11, 137.28, 140.98, 142.14, 142.94, 163.90, 188.25, 191.67. **IR (KBr, cm^{-1})**: 3027, 2991, 2801, 1743, 1656, 1414. **HRMS (ESIMS):** Anal. calcd for $C_{17}H_{14}NaO_3$ $(M+Na)^+$ 289.0841; found 289.0816.



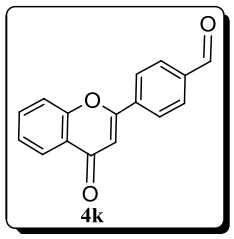
4i

(E)-4-(3-(2-Hydroxyphenyl)-3-oxopropenyl)benzaldehyde (4i): Yield 75%; light yellow solid. **^{1}H NMR (500 MHz, CDCl$_3$)**: δ (ppm) 6.97 (t, *J* = 7.5Hz, 1H), 7.05 (d, *J* = 8.5Hz, 1H), 7.53 (d, *J* = 7.5Hz, 2H), 7.82 (d, *J* = 7.5Hz, 2H), 7.92-7.96 (m, 4H), 10.06 (s, 1H), 12.66 (s, D_2O exchangeable, 1H). **^{13}C NMR (CDCl$_3$, 125MHz)**: δ (ppm) 118.80, 119.05, 119.87, 123.08, 129.06, 129.70, 130.28, 136.87, 137.49, 140.22, 143.45, 163.71, 191.43, 193.28. **IR (KBr, cm^{-1})**: 3021, 2945, 2882, 1712, 1646, 1402, 1205. **HRMS (ESIMS)**: Anal. calcd for $C_{16}H_{12}NaO_3(M+Na)^+$ 275.0684; found 275.0687.



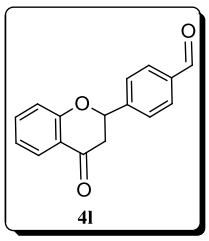
(E)-4-(3-(3,4-Dimethylphenyl)-3-oxopropenyl)benzaldehyde (4j):

Yield 78%; light yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 2.35 (s, 6H), 7.63-7.69 (m, 2H), 7.78-7.79 (m, 5H), 7.92 (m, 2H), 10.05 (s, 1H). **^{13}C NMR ($CDCl_3$, 125MHz):** δ (ppm) 20.01, 20.28, 123.26, 125.11, 126.51, 128.97, 129.07, 129.89, 130.13, 130.37, 137.32, 137.41, 140.96, 142.39, 143.11, 190.01, 191.67. **IR (KBr, cm^{-1})**: 2943, 2814, 1701, 1606, 1401, 1256, 1069, 801. **HRMS (ESIMS)**: Anal. calcd for $C_{18}H_{16}NaO_2$ $(M+Na)^+$ 287.1048; found 287.1032.



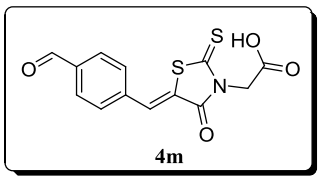
4-(4-Oxo-4H-chromenyl)benzaldehyde (4k):

Yield 80%; light yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 6.90 (s, 1H), 7.44 (t, *J* = 7.5Hz, 1H), 7.59 (d, *J* = 9Hz, 1H), 7.73 (td, *J* = 8.5Hz, 1Hz, 1H), 8.03 (d, *J* = 8.5Hz, 2H), 8.09 (d, *J* = 8.5Hz, 2H), 8.22 (d, *J* = 7Hz, 1H). **^{13}C NMR ($CDCl_3$, 125MHz):** δ (ppm) 109.13, 118.17, 123.93, 125.63, 125.82, 126.90, 130.17, 134.23, 137.08, 138.09, 156.23, 161.70, 178.27, 191.33. **IR (KBr, cm^{-1})**: 3021, 2945, 2882, 1712, 1646, 1402, 1205. **HRMS (ESIMS)**: Anal. calcd for $C_{16}H_{10}NaO_3$ $(M+Na)^+$ 273.0528; found 273.0514.



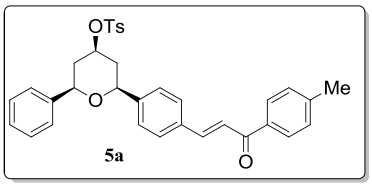
4-(4-Oxochromanyl)benzaldehyde (4l):

Yield 81%; light yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 2.92-3.07 (m, 2H), 5.57 (dd, *J* = 13.5Hz, 3.5Hz, 1H), 7.07-7.10 (m, 2H), 7.54 (td, *J* = 7Hz, 1.5Hz, 1H), 7.67 (d, *J* = 8Hz, 2H), 7.93-7.97 (m, 3H), 10.05 (s, 1H). **IR (KBr, cm^{-1})**: 3100, 2934, 2847, 1731, 1623, 1460, 1421, 1330, 12339, 1060, 834. **HRMS (ESIMS)**: Anal. calcd for $C_{16}H_{12}NaO_3$ $(M+Na)^+$ 275.0684; found 275.0664.



(E)-2-(5-(4-Formylbenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (4m):

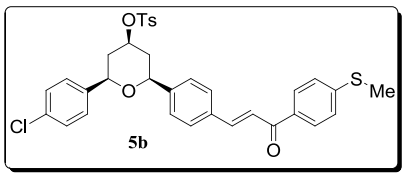
Yield 70%; light yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 4.75 (s, 2H), 7.88-7.90 (m, 2H), 7.94-7.97 (m, 1H), 8.03-8.07 (m, 2H), 10.07 (s, 1H). **IR (KBr, cm^{-1})**: 3475, 3072, 2923, 2852, 1701, 1443, 1262, 1094, 1030, 804, 781. **HRMS (ESIMS)**: Anal. calcd for $C_{13}H_9NNaO_4S_2$ $(M+Na)^+$ 329.9871; found 329.9888.



(2R,4R,6S)-2-Phenyl-6-(4-((E)-3-oxo-3-p-tolylpropenyl)phenyl)-4-tosyloxytetrahydropyran (5a):

Yield 90%; yellow solid, mp 80 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 1.84 (dq, *J* = 12Hz, 2H), 2.30 (m, 2H), 2.43 (s, 3H), 2.45 (s, 3H), 4.55 (dd, *J* = 11.5Hz, 1Hz, 1H), 4.58 (dd, *J* = 12Hz, 1Hz, 1H), 4.98 (tt, *J* = 11Hz, 4.5Hz, 1H),

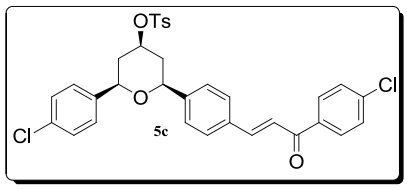
7.30 (d, *J* = 8Hz, 3H), 7.34-7.38 (m, 4H), 7.42 (d, *J* = 8Hz, 2H), 7.52 (d, *J* = 15.5Hz, 1H), 7.62 (d, *J* = 8Hz, 2H), 7.69 (s, 1H), 7.78 (d, *J* = 15.5Hz, 1H), 7.83 (d, *J* = 8.5Hz, 2H), 7.93 (d, *J* = 8Hz, 2H), 7.96 (d, *J* = 8.5Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 21.58, 39.83, 76.96, 77.49, 77.87, 122.05, 125.76, 126.30, 127.51, 127.86, 128.42, 128.56, 128.82, 129.25, 129.84, 134.17, 134.46, 135.50, 140.70, 143.28, 143.57, 143.78, 144.79, 189.86. **IR (KBr, cm^{-1})**: 3024, 2953, 2841, 1683, 1612, 1345, 1201, 1131, 853. **HRMS (ESIMS):** Anal. calcd for $C_{34}H_{32}NaO_5S$ $(M+Na)^+$ 575.1868; found 575.1856.



5b

(2R,4S,6S)-2-(4-Chlorophenyl)-6-(4-((E)-3-(4-methylmercaptophenyl)-3-oxopropenyl)phenyl)-4-tosyloxytetrahydropyran (5b):

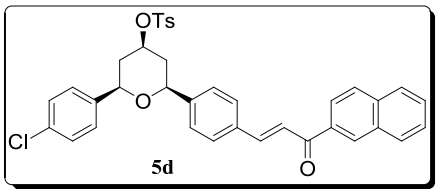
Yield 96%; yellow semisolid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 1.75 (m, 2H), 2.26-2.34 (m, 2H), 2.44 (s, 3H), 2.51 (s, 3H), 4.54 (ddd, *J* = 20Hz, 11.5Hz, 1Hz, 2H), 4.96 (tt, *J* = 11Hz, 5Hz, 1H), 7.29-7.32 (m, 5H), 7.34 (d, *J* = 8Hz, 2H), 7.40 (d, *J* = 8Hz, 2H), 7.50 (d, *J* = 15.5Hz, 1H), 7.61 (d, *J* = 16Hz, 2H), 7.76-7.83 (m, 3H), 7.94-7.96 (m, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 14.82, 21.71, 39.81, 39.90, 76.84, 77.35, 77.63, 121.90, 125.11, 126.40, 127.24, 127.63, 128.61, 128.67, 128.98, 129.98, 133.67, 134.21, 134.37, 134.64, 139.33, 143.18, 143.90, 144.99, 145.79, 189.10. **IR (KBr, cm^{-1})**: 3024, 2953, 2841, 1683, 1612, 1345, 1201, 1131, 853. **HRMS (ESIMS)**: Anal. calcd for $C_{34}H_{31}ClNaO_5S_2$ $(M+Na)^+$ 641.1199; found 641.1184.



5c

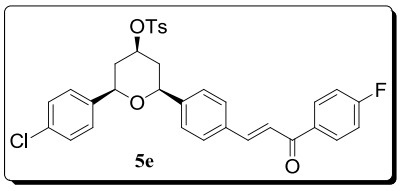
(2R,4S,6S)-2-(4-Chlorophenyl)-6-(4-((E)-3-(4-chlorophenyl)-3-oxopropenyl)phenyl)-4-tosyloxytetrahydropyran (5c):

Yield 94%; yellow semisolid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 1.84 (qd, *J* = 24Hz, 12Hz, 2H), 2.34 (dd, 12.5Hz, 4Hz, 2H), 2.45 (s, 3H), 4.55 (ddd, *J* = 23.5Hz, 11.5Hz, 1.5Hz, 2H), 4.99 (tt, *J* = 5Hz, 1H), 7.29-7.31 (m 4H), 7.35 (d, *J* = 8Hz, 2H), 7.41 (d, *J* = 8Hz, 2H), 7.45-7.48 (m, 3H), 7.61 (d, *J* = 8Hz, 2H), 7.77-7.83 (m, 3H), 7.95 (d, *J* = 8.5Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm) 21.70, 39.83, 39.88, 76.92, 77.17, 77.58, 121.63, 126.45, 127.24, 127.63, 128.68, 128.71, 128.98, 129.94, 129.98, 133.71, 134.19, 134.37, 136.46, 139.29, 143.48, 144.76, 145.00, 189.12. **IR (KBr, cm^{-1})**: 3001, 2946, 1678, 1614, 1350, 1200, 1114, 862. **HRMS (ESIMS)** Anal. calcd for $C_{33}H_{28}Cl_2NaO_5S$ $(M+Na)^+$ 629.0932; found 629.0921.



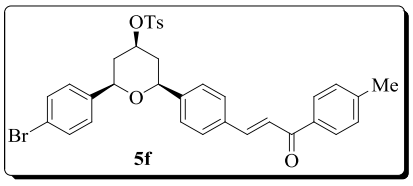
(2R,4S,6S)-2-(4-Chlorophenyl)-6-(4-((E)-3-(naphthalen-2-yl)-3-oxopropenyl)phenyl)-4-tosyloxytetrahydropyran (5d):

Yield 96%; yellow semisolid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 1.77 (q, *J* = 12Hz, 2H), 2.30 (td, *J* = 16.5Hz, 2Hz, 2H), 2.43 (s, 3H), 4.53 (dd, *J* = 27.5Hz, 10.5Hz, 2H), 4.97 (tt, *J* = 11Hz, 3Hz, 1H), 7.28-7.34 (m, 4H), 7.39-7.41 (d, *J* = 8Hz, 2H), 7.54-7.68 (m, 6H), 7.81-7.91 (m, 6H), 7.97 (d, *J* = 8Hz, 1H), 8.08 (d, *J* = 8.5Hz, 1H), 8.52 (s, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 21.79, 39.92, 40.01, 76.95, 77.26, 77.74, 122.33, 124.58, 126.52, 126.94, 127.34, 127.72, 127.96, 128.55, 128.77, 129.66, 130.08, 132.68, 133.76, 134.35, 134.73, 135.61, 139.45, 143.38, 144.27, 144.27, 145.07, 190.27. **IR (KBr, cm^{-1})**: 3013, 2942, 1681, 1604, 1331, 1241, 1126, 880. **HRMS (ESIMS)**: Anal. calcd for $C_{37}H_{31}ClNaO_5S$ $(M+Na)^+$ 645.1478; found 645.1481.



(2R,4S,6S)-2-(4-Chlorophenyl)-6-(4-((E)-3-(4-fluorophenyl)-3-oxopropenyl)phenyl)-4-tosyloxytetrahydropyran (5e):

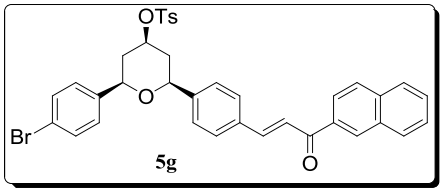
Yield 95%; yellow semisolid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 1.76-1.83 (m, 2H), 2.25-2.33 (m, 2H), 2.43 (s, 3H), 4.54 (dddd, *J* = 33.5Hz, 22Hz, 12Hz, 2Hz, 2H), 4.96 (tt, *J* = 11Hz, 4.5Hz, 1H), 7.33 (d, *J* = 8Hz, 2H), 7.39 (dd, *J* = 8.5Hz, 3Hz, 3H), 7.47 (d, *J* = 15.5Hz, 2H), 7.60 (dd, *J* = 8Hz, 2.5Hz, 4H), 7.75 (d, *J* = 5Hz, 1H), 7.78 (d, *J* = 5Hz, 1H), 7.81 (d, *J* = 8.5Hz, 1H), 8.02-8.05 (m, 4H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm) 21.79, 39.80, 39.86, 76.90, 77.36, 77.65, 121.28, 126.49, 127.26, 127.62, 128.62, 128.68, 130.00, 131.10, 131.17, 133.65, 133.89, 134.10, 134.38, 139.32, 143.42, 144.80, 146.92, 164.60, 188.85. **IR (KBr, cm^{-1})**: 3000, 2945, 1678, 1614, 1354, 1208, 1130, 865. **HRMS (ESIMS)**: Anal. calcd for $C_{33}H_{28}ClFNaO_5S$ $(M+Na)^+$ 613.1228; found 613.1220.



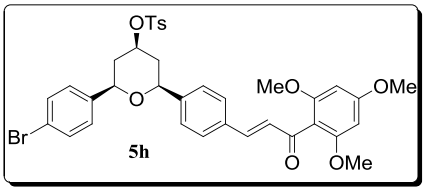
(2R,4S,6S)-2-(4-Bromophenyl)-6-(4-((E)-3-oxo-3-*p*-tolylpropenyl)phenyl)-4-tosyloxytetrahydropyran (5f):

Yield 90%; yellow solid; mp 75 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 1.78 (dt, *J* = 11.5, 10.5Hz 2H), 2.30 (tt, *J* = 11.5, 2Hz, 2H), 2.4 (s, 3H), 2.42 (s, 3H), 4.51 (dd, *J* = 10.5Hz, 1Hz, 1H), 4.56 (dd, *J* = 10.5, 1Hz, 1H) 4.95 (tt, *J* = 11.5, 5Hz, 1H), 7.22-7.39 (m, 8H), 7.44-7.53 (m, 3H), 7.56-7.60 (m, 2H), 7.75-7.82 (m, 3H), 7.92 (d, *J* = 8Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 21.56, 39.66, 39.73, 76.74, 76.99, 77.51, 121.64, 122.13, 126.25, 127.45, 127.49, 128.45, 128.55, 128.81, 129.25, 129.86, 131.47, 134.12, 134.54, 135.47, 139.76, 143.00, 143.65, 144.85, 189.77. **IR (KBr, cm^{-1})**: 2960, 2917, 2848, 1657,

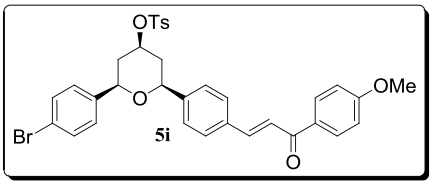
1602, 1360, 1201, 1181, 818. **HRMS (ESIMS):** Anal. calcd for $C_{34}H_{31}BrNaO_5S$ $(M+Na)^+$ 653.0973; found 653.0962.



(2R,4S,6S)-2-(4-Bromophenyl)-6-(4-((E)-3-(naphthalen-2-yl)-3-oxopropenyl)phenyl)-4-tosyloxytetrahydropyran (5g): Yield 95%; yellow semisolid. **^{1}H NMR (500MHz, $CDCl_3$)**: δ (ppm) 1.70 (q, *J* = 12Hz, 2H), 2.22 (dd, *J* = 19Hz, 12Hz, 2H), 2.35 (s, 3H), 4.44 (dd, *J* = 29.5Hz, 11Hz, 2H), 4.88 (tt, *J* = 5Hz, 1Hz, 1H), 7.15 (d, *J* = 8Hz, 2H), 7.25 (d, *J* = 8Hz, 2H), 7.35 (dd, *J* = 27Hz, 7.5Hz, 4H), 7.48 (d, *J* = 7Hz, 1H), 7.51 (d, *J* = 7Hz, 1H), 7.54-7.60 (m, 3H), 7.73-7.91 (m, 6H), 8.00 (d, *J* = 7.5Hz, 1H), 8.44 (s, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 21.57, 39.71, 76.70, 76.96, 77.50, 121.69, 122.18, 124.38, 126.31, 126.72, 127.45, 127.52, 127.75, 128.34, 128.56, 129.44, 129.86, 131.52, 132.48, 133.95, 134.17, 134.56, 135.42, 139.75, 143.14, 144.06, 144.86, 190.11. **IR (KBr, cm^{-1})**: 3000, 2945, 1678, 1625, 1350, 1205, 1121, 868. **HRMS (ESIMS)**: Anal. calcd for $C_{37}H_{31}BrNaO_5S$ $(M+Na)^+$ 689.0973; found 689.0978.

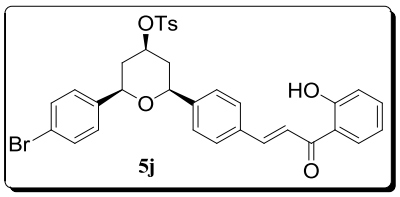


(2R,4S,6S)-2-(4-Bromophenyl)-6-(4-((E)-3-oxo-3-(2,4,6-trimethoxyphenyl)propenyl)phenyl)-4-tosyloxytetrahydropyran (5h): Yield 85%; yellow semisolid. **^{1}H NMR (500MHz, $CDCl_3$)**: δ (ppm) 1.76-1.83 (m, 2H), 2.25-2.33 (m, 2H), 2.44 (s, 3H), 3.93 (s, 9H), 4.53 (dd, *J* = 30Hz, 10Hz, 2H), 4.96 (tt, *J* = 11Hz, 3Hz, 1H), 7.23 (d, *J* = 8Hz, 2H), 7.27-7.28 (m, 2H), 7.34 (d, *J* = 8Hz, 2H), 7.40 (d, , *J* = 8Hz, 2H), 7.44-7.46 (m, 2H), 7.50 (s, 1H), 7.62-7.63 (m, 2H), 7.77 (d, *J* = 8Hz, 1H), 7.81(d, *J* = 8.5Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 21.73, 39.86, 56.45, 61.03, 72.90, 77.19, 77.64, 106.20, 121.97, 126.45, 127.61, 127.64, 128.68, 130.03, 131.64, 133.48, 134.23, 134.60, 139.91, 142.61, 143.33, 144.18, 144.48, 145.03, 1553.21, 189.18. **IR (KBr, cm^{-1})**: 2921, 2847, 1660, 1605, 1421, 1326, 1213, 1173, 817. **HRMS (ESIMS)**: Anal. calcd for $C_{36}H_{35}BrNaO_8S$ $(M+Na)^+$ 729.1134; found 729.1108.



(2R,4S,6S)-2-(4-Bromophenyl)-6-(4-((E)-3-(4-methoxyphenyl)-3-oxopropenyl)phenyl)-4-tosyloxytetrahydropyran (5i): Yield 88%; yellow semisolid. **^{1}H NMR (500MHz, $CDCl_3$)**: δ (ppm) 1.80 (q, *J* = 11.5Hz, 2H), 2.29 (t, *J* = 12Hz, 2H), 2.44 (s, 3H), 3.88 (s, 3H), 4.50 (d, *J* = 12Hz, 1H), 4.55 (d, *J* = 11.5Hz, 1H), 4.95 (m, 1H), 6.97 (m, 3H), 7.23 (d, *J* = 7Hz, 1H), 7.34 (d, *J* = 8Hz, 2H), 7.39 (d, *J* = 7Hz, 2H), 7.46 (d, *J* = 6.5Hz, 2H), 7.53 (d, *J* = 15.5Hz, 1H), 7.57-7.60 (m, 2H), 7.76 (d, *J* = 15Hz, 1H), 7.81 (d, *J* = 6.5Hz, 1H), 8.02-8.05 (m, 3H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm) 21.81, 39.89, 39.96, 55.63, 77.02, 77.29, 77.74, 122.13,

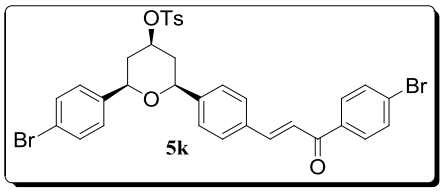
126.48, 127.68, 127.73, 128.65, 129.00, 130.09, 130.96, 131.72, 134.30, 134.86, 139.97, 142.91, 143.10, 143.48, 145.10, 163.60, 188.75. **IR (KBr, cm^{-1})**: 2960, 2921, 2850, 1661, 1600, 1355, 1172, 818. **HRMS (ESIMS)**: Anal. calcd for $C_{34}H_{31}BrNaO_6S$ $(M+Na)^+$ 669.0922; found 669.0900.



5j

(2R,4S,6S)-2-(4-Bromophenyl)-6-(4-((E)-3-(2-hydroxyphenyl)-3-oxopropenyl)phenyl)-4-tosyloxytetrahydropyran (5j):

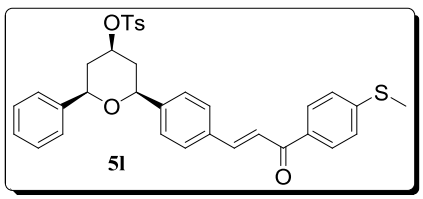
Yield 87%; yellow semisolid. **^{1}H NMR (500MHz, CDCl$_3$)**: δ (ppm) 1.81 (q, *J* = 11.5Hz, 2H), 2.32 (dd, *J* = 26.5Hz, 8Hz, 2H), 2.46 (s, 3H), 4.52 (d, *J* = 11.5Hz, 1H), 4.92-5.01 (m, 1H), 4.58 (d, *J* = 11Hz, 1H), 6.96 (t, *J* = 7.5Hz, 1H), 7.03 (d, *J* = 8.5Hz, 1H), 7.25 (dd, *J* = 9Hz, 1Hz, 1H), 7.36 (d, *J* = 7.5Hz, 2H), 7.43 (d, *J* = 7Hz, 2H), 7.48 (d, *J* = 8.5Hz, 2H), 7.52 (d, *J* = 8Hz, 1H), 7.65 (d, *J* = 8.5Hz, 3H), 7.73 (d, *J* = 13Hz, 1H), 7.82 (*J* = 6.5Hz, 2H), 7.89-7.93 (m, 2H), 11.59 (s, br, D_2O exchangeable, 1H). **^{13}C NMR (125 MHz, CDCl$_3$)**: δ (ppm) 21.86, 39.97, 77.12, 77.32, 77.68, 118.83, 119.06, 120.43, 122.00, 126.62, 127.72, 127.79, 129.01, 129.41, 129.82, 130.13, 131.80, 134.33, 134.43, 136.65, 139.92, 143.80, 145.04, 145.16, 163.77, 193.83. **IR (KBr, cm^{-1})**: 3045, 2926, 2852, 1695, 1655, 1600, 1324, 1179 1121, 850. **HRMS (ESIMS)**: Anal. calcd for $C_{33}H_{29}BrNaO_6S$ $(M+Na)^+$ 655.0766; found 655.0753.



5k

(2R,4S,6S)-2-(4-Bromophenyl)-6-(4-((E)-3-(4-bromophenyl)-3-oxopropenyl)phenyl)-4-tosyloxytetrahydropyran (5k):

Yield 95%; yellow semisolid. **^{1}H NMR (500MHz, CDCl$_3$)**: δ (ppm) 1.77 (q, *J* = 11Hz, 2H), 2.29 (dd, *J* = 24Hz, 12.5Hz, 2H), 2.43 (s, 3H), 4.52 (dd, *J* = 28Hz, 10Hz, 2H), 4.95 (tt, *J* = 6.5Hz, 3Hz, 1H), 7.22 (d, *J* = 8.5Hz, 1H), 7.33 (d, *J* = 8Hz, 1H), 7.39-7.46 (m, 6H), 7.60 (dd, *J* = 10.5Hz, 8.5Hz, 6H), 7.86 (dd, *J* = 8.5Hz, 2Hz, 4H). **^{13}C NMR (125 MHz, CDCl$_3$)**: δ (ppm) 21.55, 39.65, 72.70, 76.73, 77.43, 118.61, 121.03, 126.33, 127.42, 127.46, 128.50, 129.90, 131.46, 131.78, 133.67, 133.91, 136.75, 139.67, 143.35, 146.84, 189.18. **IR (KBr, cm^{-1})**: 3000, 2945, 1678, 1614, 1347, 1234, 1128, 840. **HRMS (ESIMS)**: Anal. calcd for $C_{33}H_{28}Br_2NaO_5S$ $(M+Na)^+$ 716.9922; found 716.9900.

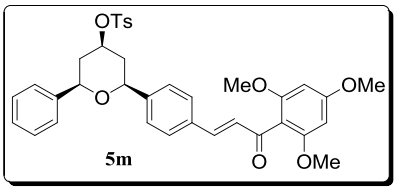


5l

(2R,4R,6S)-2-Phenyl-6(4-((E)-3-(4-methylmercaptophenyl)-3-oxopropenyl)phenyl)-4-tosyloxytetrahydropyran (5l):

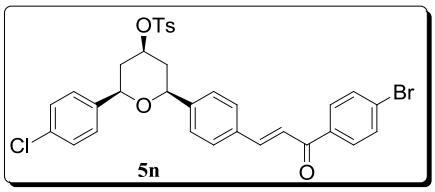
Yield 97%; yellow semisolid. **^{1}H NMR (500MHz, CDCl$_3$)**: δ (ppm) 1.79-1.89 (m, 2H), 2.29-2.35 (m, 2H), 2.45 (s, 3H), 2.53 (s, 3H), 4.56 (td, *J* = 9Hz, 4Hz, 2H), 4.98 (tt, *J* = 5Hz, 1H), 7.28-7.36 (m, 8H), 7.42 (d, *J* = 8Hz, 2H), 7.50 (dd, *J* = 15.5Hz, 3Hz, 1H), 7.61 (d, *J* = 8Hz, 2H), 7.77-7.83 (m, 3H), 7.95 (d, *J* = 8.5Hz, 3H). **^{13}C NMR (125 MHz, CDCl$_3$)**: δ (ppm) 14.71, 21.55, 39.83, 76.91, 77.16, 77.83, 121.73, 125.01, 125.74,

126.29, 127.50, 127.86, 128.38, 128.43, 128.84, 129.81, 134.18, 134.31, 134.43, 140.67, 143.31, 143.87, 144.77, 145.59, 189.04. **IR (KBr, cm^{-1})**: 3024, 2953, 2841, 1683, 1612, 1345, 1201, 1131, 853. **HRMS (ESIMS):** Anal. calcd for $C_{34}H_{32}NaO_5S_2(M+Na)^+$ 607.1589; found 607.1569.



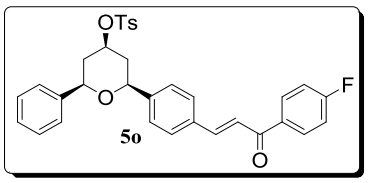
(2R,4R,6S)-2-Phenyl-6-(4-((E)-3-oxo-3-(2,4,6-trimethoxyphenyl)-propenyl)phenyl)-4-tosyloxytetrahydropyran (5m):

Yield 84%; yellow semisolid. **^{1}H NMR (500MHz, CDCl$_3$)**: δ (ppm) 1.76 (q, *J* = 11.5Hz, 2H), 2.22 (dd, *J* = 12.5Hz, 4.5Hz, 2H), 2.37 (s, 3H), 3.88 (s, 3H), 3.89 (s, 6H), 4.23 (t, *J* = 6.5Hz, 1H), 4.46 (d, *J* = 10.5Hz, 1H), 4.86-4.93 (m. 1H), 7.19-7.30 (m, 10H), 7.52 (d, *J* = 15.5Hz, 1H), 7.65 (d, *J* = 3Hz, 1H), 7.72-7.78 (m, 4H), 7.86-7.88 (d, *J* = 8.5Hz, 1H). **^{13}C NMR (125 MHz, CDCl$_3$)**: δ (ppm) 22.86, 40.19, 56.61, 61.19, 77.72, 78.42, 106.38, 124.60, 126.03, 127.76, 128.02, 128.60, 129.03, 130.08, 130.39, 131.09, 132.85, 133.17, 137.42, 140.74, 141.12, 142.95, 144.99, 153.40, 191.64. **IR (KBr, cm^{-1})**: 2954, 2912, 2850, 1653, 1599, 1345, 1172, 830. **HRMS (ESIMS):** Anal. calcd for $C_{36}H_{36}NaO_8S$ $(M+Na)^+$ 651.2029; found 651.2041.



(2R,4S,6S)-2-(4-Chlorophenyl)-6-(4-((E)-3-(4-bromophenyl)-3-oxopropenyl)phenyl)-4-tosyloxytetrahydropyran (5n):

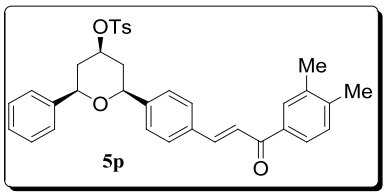
Yield 94%; yellow semisolid. **^{1}H NMR (500MHz, CDCl$_3$)**: δ (ppm) 1.84 (q, *J* = 12Hz, 2H), 2.34 (dd, *J* = 11.5Hz, 7Hz, 2H), 2.46 (s, 3H), 4.60 (d, *J* = 11Hz, 2H), 4.99 (tt, *J* = 4.5Hz, 1H), 7.36 (d, *J* = 8Hz. 2H), 7.43-7.48 (m, 5H), 7.62-7.66 (m, 5H), 7.78-7.82 (m, 3H), 7.88 (dd, *J* = 7Hz, 2Hz, 3H). **^{13}C NMR (125 MHz, CDCl$_3$):** δ (ppm) 21.60, 39.72 39.77, 76.73, 77.24, 77.48, 121.49, 126.34, 127.14, 127.52, 128.57, 128.60, 128.76, 129.88, 129.94, 131.86, 133.59, 134.09, 134.24, 136.77, 139.19, 143.40, 144.71, 144.89, 189.18. **IR (KBr, cm^{-1})**: 3045, 2926, 2852, 1695, 1655, 1600, 1324, 1221, 1179 850. **HRMS (ESIMS):** for $C_{33}H_{28}BrClNaO_5S$ $(M+Na)^+$ Anal. calcd. 673.0427; found 673.0400.



(2R,4R,6S)-2-Phenyl-6-(4-((E)-3-(4-fluorophenyl)-3-oxopropenyl)-phenyl)-4-tosyloxytetrahydropyran (5o):

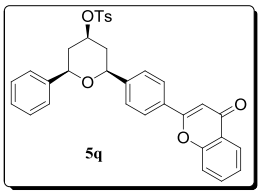
Yield 95%; yellow semisolid. **^{1}H NMR (500MHz, CDCl$_3$):** δ (ppm) 1.81 (q, *J* = 11.5Hz, 2H), 2.30 (dd, *J* = 24.5Hz, 14.5Hz, 2H), 2.43 (s, 3H), 4.50-4.58 (m, 2H), 4.96 (t, *J* = 5Hz, 1H), 7.15 (d, *J* = 8Hz, 3H), 7.23-7.41 (m, 8H), 7.59 (t, *J* = 8Hz, 2H), 7.76-7.82 (m, 3H), 8.03-8.04 (m, 3H). **^{13}C NMR (125 MHz, CDCl$_3$)**: δ (ppm) 21.77, 39.80, 40.05, 77.41, 77.70, 78.05, 115.77, 121.68, 125.97, 126.55, 127.71, 128.08, 128.61, 128.72, 130.06, 131.18, 131.25, 134.39, 134.59, 140.89, 143.77, 144.64, 145.02, 166.72, 188.84. **IR (KBr, cm^{-1})**:

2921, 2847, 1660, 1605, 1421, 1326, 1213, 1173, 817. **HRMS (ESIMS)**: Anal. calcd for $C_{33}H_{29}FNaO_5S$ $(M+Na)^+$ 579.1617; found 579.1613.



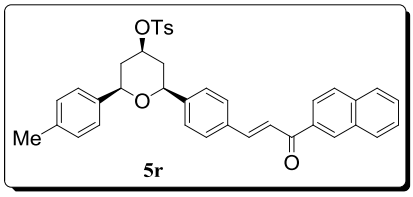
2R,4R,6S)-2-Phenyl-6-(4-((E)-3-(3,4-dimethylphenyl)-3-oxopropenyl)phenyl)-4-tosyloxytetrahydropyran (5p):

Yield 86%; yellow semisolid. **^{1}H NMR (500MHz, $CDCl_3$):** δ (ppm) 1.83 (q, *J* = 11.5Hz, 2H), 2.32 (m, 9H), 2.35 (m, 2H), 2.42 (d, *J* = 9Hz, 2H), 4.53-4.57 (m, 2H), 4.95-4.98 (m, 1H), 7.24 (d, *J* = 7.5Hz, 2H), 7.31-7.35 (m, 3H), 7.40-7.42 (m, 3H), 7.48-7.53 (m, 1H), 7.60-7.61 (m, 2H), 7.66 (d, *J* = 9Hz. 1H), 7.75-7.80 (m, 6H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm) 19.94, 20.18, 21.77, 40.03, 77.20, 77.68, 78.09, 122.35, 125.95, 126.37, 126.49, 127.70, 128.06, 128.60, 129.79, 129.95, 130.06, 134.34, 134.70, 136.09, 137.16, 140.92, 142.56, 143.45, 143.82, 145.00, 190.27. **IR (KBr, cm^{-1})**: 3056, 2920, 2847, 1698, 1660, 1601, 1324, 1179, 815. **HRMS (ESIMS)**: Anal. calcd for $C_{35}H_{34}KO_5S$ $(M+K)^+$ 605.1764; found 605.1775.



(2R,4R,6S)-2-Phenyl-6-(4-(4-oxo-2-chromenyl)phenyl)-4-tosyloxytetrahydropyran (5q):

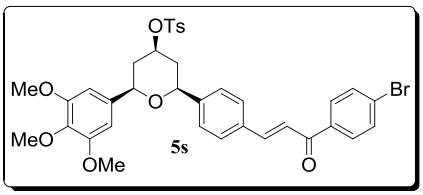
Yield 84%; yellow semisolid. ^{1}H NMR (500MHz, $CDCl_3$): δ (ppm) 1.80 (q, *J* = 11Hz, 2H), 2.30 (t, *J* = 13Hz, 2H), 2.44 (s 3H), 4.51-4.57 (m, 2H), 4.95 (tt, *J* = 4.5Hz, 3Hz, 1H), 6.90 (s, 1H), 7.25-7.31 (m, 4H), 7.34 (d, *J* = 8Hz, 2H), 7.39 (d, *J* = 8.5Hz, 2H), 7.50 (d, *J* = 16Hz, 1H), 7.61 (d, *J* = 8Hz, 2H), 7.77 (d, *J* = 16Hz, 1H), 7.81 (d, *J* = 8.5Hz, 2H), 7.91-7.97 (m, 3H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm) 21.77, 40.05, 77.41, 77.70, 78.05, 100.24, 115.94, 121.68, 125.97, 126.55, 127.71, 128.08, 128.61, 128.72, 130.06, 131.18, 131.25, 134.39, 134.59, 144.64, 145.02, 157.02, 164.69, 188.84. **IR (KBr, cm^{-1})**: 2999, 2852, 1654, 1602, 1418, 1324, 1201, 1163, 821. **HRMS (ESIMS):** Anal. calcd for $C_{33}H_{28}NaO_6S$ $(M+Na)^+$ 575.1504; found 575.1531.



(2R,4R,6S)-2-*p*-Tolyl-6-(4-((E)-3-(naphthalen-2-yl)-3-oxopropenyl)phenyl)-4-tosyloxytetrahydropyran (5r):

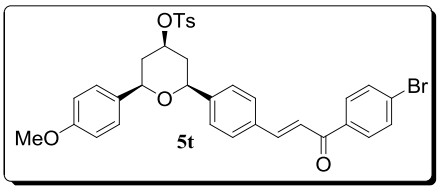
Yield 80%; yellow semisolid. ^{1}H NMR (500MHz, $CDCl_3$): δ (ppm) 1.69 (q, *J* = 24.5Hz, 14Hz, 2H), 2.22 (dd, *J* = 19Hz, 11Hz, 2H), 2.35 (s, 6H), 4.45 (dd, *J* = 29.5Hz, 11H, 2H), 4.88 (m, 1H), 7.15 (d, *J* = 8Hz, 2H), 7.25 (d, *J* = 8Hz, 2H), 7.32 (d, *J* = 7Hz, 2H), 7.38 (d, *J* = 7Hz, 2H), 7.47-7.56 (m, 5H), 7.72-7.91 (m, 6H), 8.00 (d, *J* = 7.5Hz, 1H), 8.44 (s, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm) 21.31, 21.38, 39.95, 77.06, 77.32, 77.74, 121.94, 122.42, 124.62, 126.55, 126.97, 127.69, 127.76, 127.99, 128.55, 128.81, 129.68, 130.10, 131.76, 132.72, 134.19, 134.41, 134.80, 135.67, 139.99, 143.38, 144.31, 145.10, 190.35. **IR**

(KBr, cm^{-1}): 3056, 2920, 2847, 1698, 1660, 1601, 1324, 1179 1125, 857. **HRMS (ESIMS)**: Anal. calcd for $C_{38}H_{34}NaO_5S$ $(M+Na)^+$ 625.2025; found 625.2031.



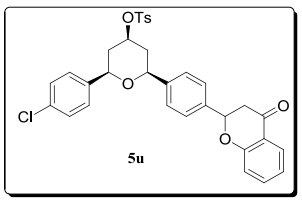
(2R,4S,6S)-2-(3,4,5-Trimethoxyphenyl)-6-(4-((E)-3-(4-bromophenyl)-3-oxopropenyl)phenyl)-4-tosyloxytetrahydropyran (5s):

Yield 72%; yellow semisolid. **^{1}H NMR (500MHz, $CDCl_3$)**: δ (ppm) 1.76-1.83 (m, 2H), 2.25-2.33 (m, 2H), 2.44 (s, 3H), 3.93 (s, 9H),4.53 (dd, *J* = 30Hz, 10Hz, 2H), 4.96 (tt, *J* = 11Hz, 3Hz, 1H), 7.23 (d, *J* = 8Hz, 2H), 7.27-7.28 (m, 2H), 7.34 (d, *J* = 8Hz, 2H), 7.40 (d, , *J* = 8Hz, 2H), 7.44-7.46 (m, 2H), 7.50 (s, 1H), 7.62-7.63 (m, 2H), 7.77 (d, *J* = 8Hz, 1H), 7.80–7.82 (m, 2H).**^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 21.73, 39.86, 56.45, 61.03, 72.90, 77.19, 77.64, 106.20, 121.97, 126.45, 127.61, 127.64, 128.68, 130.03, 131.64, 133.48, 134.23, 134.60, 139.91, 142.61, 143.33, 144.18, 144.48, 145.03, 153.21, 189.78. **IR (KBr, cm^{-1})**: 3001, 2851, 1666, 1601, 1432, 1325, 1200, 1121, 825. **HRMS (ESIMS)**: Anal. calcd for $C_{36}H_{35}BrNaO_8S$ $(M+Na)^+$ 729.1134; found 729.1139.



(2R,4S,6S)-2-(4-Methoxyphenyl)-6-(4-((E)-3-(4-bromophenyl)-3-oxopropenyl)phenyl)-4-tosyloxytetrahydropyran (5t):

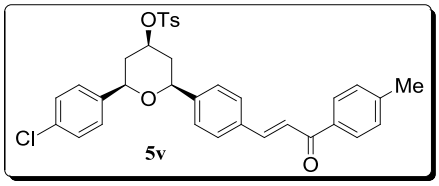
Yield 77%; yellow semisolid. **^{1}H NMR (500MHz, $CDCl_3$)**: δ (ppm) 1.80 (q, *J* = 11.5Hz, 2H), 2.29 (t, *J* = 12Hz, 2H), 2.44 (s, 3H), 3.88 (s, 3H), 4.50 (d, *J* = 12Hz, 1H), 4.55 (d, *J* = 11.5Hz, 1H), 4.95 (m, 1H), 7.23 (d, *J* = 7Hz, 1H), 7.34 (d, *J* = 8Hz, 2H), 7.39 (d, *J* = 7Hz, 2H), 7.40 (m, 3H), 7.46 (d, *J* = 6.5Hz, 2H), 7.53 (d, *J* = 15.5Hz, 1H), 7.57-7.60 (m, 2H), 7.76 (d, *J* = 15Hz, 1H), 7.81 (d, *J* = 6.5Hz, 1H), 8.02-8.05 (m, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 21.81, 39.89, 39.96, 55.63, 77.02, 77.29, 77.74, 122.13, 126.48, 127.68, 127.73, 128.65, 129.00, 130.09, 130.96, 131.72, 134.30, 134.86, 139.97, 142.91, 143.10, 143.48, 145.10, 163.60, 188.75. **IR (KBr, cm^{-1})**: 3012, 2952, 1654, 1602, 1418, 1324, 1201, 1163, 821. **HRMS (ESIMS):** Anal. calcd for $C_{34}H_{31}BrNaO_6S$ $(M+Na)^+$ 669.0922; found 669.0912.



(2R,4S,6S)-2-(4-Chlorophenyl)-6-(4-(4-oxochromanyl)phenyl)-4-tosyloxytetrahydropyran (5u):

Yield 85 %; yellow semisolid. **^{1}H NMR (500MHz, $CDCl_3$)**: δ (ppm) 1.80 (q, *J* = 11Hz, 2H), 2.30 (t, *J* = 13Hz, 2H), 2.44 (s 3H), 2.89-3.12 (m, 2H), 4.51-4.57 (m, 2H), 4.95 (tt, *J* = 4.5Hz, 3Hz, 1H), 5.55-5.65 (m, 1H), 7.25-7.31 (m, 4H), 7.34 (d, *J* = 8Hz, 2H), 7.39 (d, *J* = 8.5Hz, 2H), 7.50 (d, *J* = 16Hz, 1H), 7.61 (d, *J* = 8Hz, 2H), 7.77 (d, *J* = 16Hz,

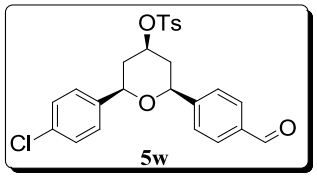
1H), 7.81 (d, *J* = 8.5Hz, 2H), 7.91-7.97 (m, 2H). **^{13}C NMR (125 MHz, CDCl3)**: δ (ppm) 21.45, 39.95, 44.5, 77.40, 77.70, 78.05, 85.01, 116.34, 125.68, 125.97, 126.54, 127.91, 128.08, 128.77, 129.71, 130.06, 131.18, 131.25, 135.39, 136.59, 144.88, 145.02, 164.69, 188.84. **IR (KBr, cm^{-1})**: 3021, 2960, 1678, 1602, 1421, 1346, 1201, 1154, 845. **HRMS (ESIMS):** Anal. calcd for $C_{33}H_{29}ClNaO_6S$ $(M+Na)^+$ 611.1271; found 611.1261.



5v

(2R,4S,6S)-2-(4-Chlorophenyl)-6-(4-((E)-3-oxo-3-p-tolylpropenyl)phenyl)-4-tosyloxytetrahydropyran (5v):

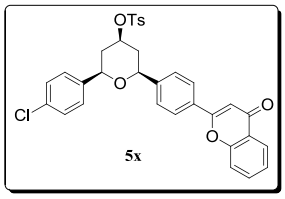
Yield 90 %; yellow semisolid. **^{1}H NMR (500MHz, CDCl$_3$)**: δ (ppm) 1.83 (q, *J* = 12Hz, 2H), 2.33 (dd, *J* = 12Hz, 3Hz, 2H), 2.43 (s, 3H), 2.45 (s, 3H), 4.58 (d, *J* = 11Hz, 2H), 5.00 (tt, *J* = 11Hz, 5Hz, 1H), 7.30 (d, *J* = 8Hz, 3H), 7.35 (d, *J* = 8Hz, 1H), 7.42 (d, *J* = 8.5Hz, 2H), 7.53 (d, *J* = 15.5Hz, 2H), 7.62 (d, *J* = 8.5Hz, 3H), 7.68 (s, 1H), 7.77 (s, 1H), 7.80 (t, *J* = 9Hz, 1H), 7.83 (d, *J* = 8Hz, 1H), 7.93 (d, *J* = 8.5Hz, 3H). **^{13}C NMR (125 MHz, CDCl$_3$):** δ (ppm) 21.64, 21.66, 39.74, 39.85, 76.72, 77.03, 77.68, 118.41, 121.66, 122.08, 127.23, 127.57, 128.65, 129.34, 129.97, 133.52, 134.14, 134.23, 134.54, 135.49, 139.38, 143.17, 143.70, 143.79, 144.11, 144.95, 189.83. **IR (KBr, cm^{-1})**: 2921, 2847, 1660, 1605, 1421, 1326, 1213, 1173, 817. **HRMS (ESIMS):** Anal. calcd for $C_{34}H_{31}ClNaO_5S$ $(M+Na)^+$ 609.1478; found 609.1501.



5w

(2R,4S,6S)-2-(4-Chlorophenyl)-6-(4-formylphenyl)-4-tosyloxytetrahydropyran (5w):

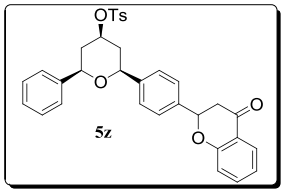
Yield 90%; yellow semisolid. **^{1}H NMR (CDCl3, 500MHz)**: δ (ppm) 1.96 (q, *J* = 11.5Hz, 2H), 2.41 (dd, *J* = 3Hz, 2Hz, 2H), 2.57 (s, 3H), 4.66 (d, *J* = 10Hz, 2H), 5.08 (tt, *J* = 11.5Hz, 6.5Hz, 1H), 7.40-7.41 (m, 2H), 7.43-7.50 (m, 8H), 7.94 (d, *J* = 8Hz, 2H), 10.00 (s, 1H). **IR (KBr, cm^{-1})**: 3010, 2990, 2885, 1701, 1405, 1325, 1205, 1125, 843. **HRMS (ESIMS):** Anal. calcd for $C_{25}H_{23}ClNaO_5S$ $(M+Na)^+$ 493.0852; found 493.0810.



5x

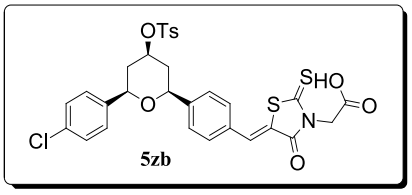
(2R,4S,6S)-2-(4-Chlorophenyl)-6-(4-(4-oxo-2-chromenyl)phenyl)-4-tosyloxytetrahydropyran (5x):

Yield 88%; yellow semisolid. **^{1}H NMR (500MHz, CDCl$_3$)**: δ (ppm) 1.87 (q, *J* = 11Hz, 2H), 2.32 (t, *J* = 13Hz, 2H), 2.47 (s 3H), 4.57 (d, *J* = 11.5Hz, 2H), 4.99 (tt, *J* = 4.5Hz, 3Hz, 1H), 7.25-7.41 (m, 16H), 7.85 (d, *J* = 8Hz, 1H). **^{13}C NMR (125 MHz, CDCl$_3$)**: δ (ppm) 21.64, 40.00, 77.24, 77.97, 78.05, 100.45, 116.64, 123.68, 125.70, 126.55, 127.75, 128.85, 128.91, 129.72, 130.06, 131.14, 131.25, 134.39, 135.61, 144.71, 14602, 157.02, 164.69, 188.84. **IR (KBr, cm^{-1})**: 3011, 2995, 2872, 1701, 1614, 1415, 1365, 1212, 1163. **HRMS (ESIMS)**: Anal. calcd for $C_{33}H_{27}ClNaO_6S$ $(M+Na)^+$ 609.1115; found 609.1132.



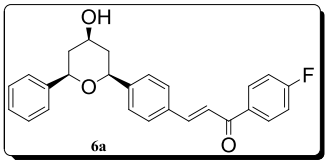
(2R,4R,6S)-2-Phenyl-6-(4-(4-oxochromanyl)phenyl)-4-tosyloxytetrahydropyran (5z):

Yield 84%; yellow semisolid. **^{1}H NMR (500MHz, $CDCl_3$)**: δ (ppm) 1.81 (q, *J* = 11Hz, 2H), 2.28 (t, *J* = 13Hz, 2H), 2.35 (s, 3H), 2.90-3.15 (m, 2H), 4.49-4.54 (m, 2H), 4.93 (tt, *J* = 4.5Hz, 3Hz, 1H), 5.55-5.65 (m, 1H), 7.25-7.35 (m, 4H), 7.37 (d, *J* = 8Hz, 2H), 7.41 (d, *J* = 8.5Hz, 2H), 7.50 (d, *J* = 16Hz, 1H), 7.61 (m, 2H), 7.77 (d, *J*= 16Hz, 1H), 7.85 (d, *J* = 8.5Hz, 2H), 7.91-7.97 (m, 2H). **^{13}C NMR (125 MHz, CDCl3)**: δ (ppm) 21.41, 39.74, 39.85, 43.51, 76.72, 77.03, 77.68, 84.31, 116.34, 121.94, 122.42, 124.62, 126.55, 126.97, 127.69, 128.81, 129.68, 130.10, 131.76, 132.72, 134.19, 144.88, 146.02, 165.32, 189.21. **IR (KBr, cm^{-1})**: 3026, 2965, 1679, 1612, 1436, 1356, 1200, 1145. **HRMS (ESIMS)**: Anal. calcd for $C_{33}H_{30}O_6NaS$ $(M+Na)^+$ 577.1661; found 577.1673.



2-((E)-5-(4-((2S,4S,6R)-6-(4-Chlorophenyl)-4-tosyloxytetrahydropyran-2-yl)benzylidene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (5zb):

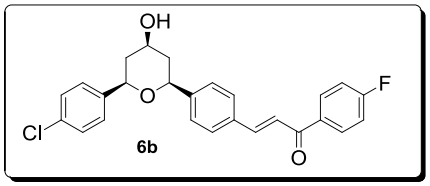
Yield 70 %; yellow semisolid. **^{1}H NMR (500MHz, *d*-DMSO)**: δ (ppm) 1.81 (q, *J* = 11Hz, 2H), 2.30 (dd, *J* = 25Hz, 15Hz, 2H), 2.41 (s, 3H), 4.51-4.56 (m, 2H), 4.77 (s, 2H), 4.95-4.97 (m, 1H), 7.15 (d, *J* = 8Hz, 2H), 7.19-7.41 (m, 6H), 7.66 (d, *J* = 10.5Hz, 1H), 7.76-7.82 (m, 2H), 8.03-8.04 (m, 2H). **^{13}C NMR (125MHz, $CDCl_3$)**: δ (ppm) 21.81, 39.89, 39.96, 46.63, 77.01, 77.46, 77.74, 114.00, 127.68, 127.73, 128.65, 129.00, 130.09, 130.96, 131.72, 134.30, 134.86, 139.97, 142.91, 143.10, 143.48, 145.10, 165.60, 168.75, 193.97. **IR (KBr, cm^{-1})**: 2921, 2847, 1660, 1605, 1421, 1326, 1213, 1173, 817. **HRMS (ESIMS):** Anal. calcd for $C_{30}H_{26}ClNNaO_7S_3$ $(M+Na)^+$ 666.0458; found 666.0442.



(2R,4R,6S)-2-Phenyl-6-(4-((E)-3-(4-fluorophenyl)-3-oxopropenyl) phenyl)-4-hydroxytetrahydropyran (6a):

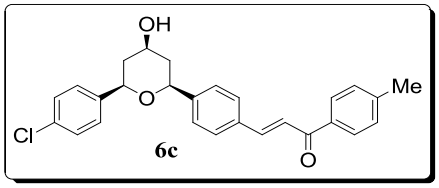
Yield 90 %; yellow semisolid. **^{1}H NMR (500MHz, $CDCl_3$)**: δ (ppm)1.60 (q, *J* = 11.5Hz, 2H), 2.22 (s, br, D_2O exchangeable, 1H), 2.29 (dt, *J* = 12Hz, 2Hz, 2H), 3.97 (tt, *J* = 4.5Hz, 11Hz, 1H), 4.52 (dd, *J* = 26Hz, 7Hz, 2H), 7.23 (d, *J* = 7Hz, 1H), 7.34 (d, *J* = 8Hz, 2H), 7.39 (d, *J* = 7Hz, 2H), 7.46 (d, *J* = 6.5Hz, 2H), 7.53 (d, *J* = 15.5Hz, 1H), 7.57-7.60 (m, 3H), 7.75-7.82 (m, 3H), 8.03 (d, *J* = 8.5Hz, 1H). **^{13}C NMR (125MHz, $CDCl_3$)**: δ (ppm) 39.71, 68.01, 76.70, 77.50, 124.38, 127.75, 128.34, 128.56, 129.44, 129.86, 131.52, 132.48, 134.17, 143.14, 144.06, 144.86, 168.56, 190.11. **IR (KBr, cm^{-1})**: 3433.8, 2965.2, 2921.7, 2852.1, 1634.8,

1452.1, 1265.2, 1156.5, 1065.2, 900.0, 760.87, 700. **HRMS (ESIMS)**: Anal. calcd for $C_{26}H_{23}FNaO_3$ $(M+Na)^+$ 425.1529; found 425.1545.



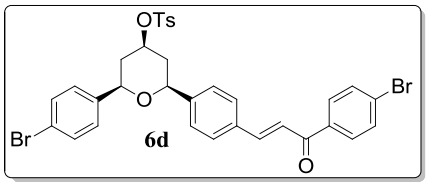
6b

(2R,4S,6S)-2-(4-Chlorophenyl)-6-(4-((E)-3-(4-fluorophenyl)-3-oxo-propenyl)phenyl)-4-hydroxytetrahydropyran (6b):
Yield 90%; yellow semisolid. **^{1}H NMR (500MHz, $CDCl_3$)**: δ (ppm) 1.73-1.84 (m, 2H), 2.046 (s, br, D_2O exchangeable, 1H), 2.22-2.85 (m, 2H), 4.14 (tt, *J* = 11Hz, 3Hz, 1H), 4.66 (t, *J* = 3Hz, 2H), 7.01 (d, *J* = 9Hz, 2H), 7.36 (d, *J* = 8.5Hz, 2H), 7.41 (d, *J* = 9Hz, 2H), 7.48 (d, *J* = 8Hz, 2H), 7.59 (d, *J* = 9Hz, 3H), 7.95 (d, *J* = 8Hz, 2H), 8.18 (d, *J* = 8Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 40.05, 69.46, 77.70, 78.05, 115.94, 121.68, 125.97, 126.55, 127.71, 128.72, 130.06, 131.25, 134.39, 134.59, 140.89, 143.77, 144.64, 164.69, 166.72, 188.84. **IR (KBr, cm^{-1})**: 3434, 3010, 2922, 2843, 1734, 1626, 1456, 1256, 1069, 808.8 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{26}H_{22}ClFNaO_3$ $(M+Na)^+$ 459.1139; found 459.1150.



6c

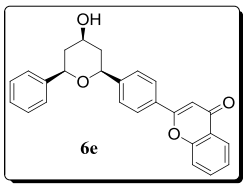
(2R,4S,6S)-2-(4-Chlorophenyl)-6-(4-((E)-3-oxo-3-p-tolylpropenyl)phenyl)-4-hydroxytetrahydropyran (6c):
Yield 88 %; yellow semisolid. **^{1}H NMR (500MHz, $CDCl_3$)**: δ (ppm) 1.63-1.72 (m, 2H), 2.12-2.25 (dd, *J* = 12.5Hz, 4Hz, 2H), 2.35 (s, 3H), 3.91 (tt, *J* = 10.5Hz, 3Hz, 1H), 4.45 (d, *J* = 32Hz, 11.5Hz, 2H), 7.11-7.15 (m. 2H), 7.16-7.19 (m, 2H), 7.23 (d, *J* = 8Hz, 2H), 7.28-7.32 (m, 2H), 7.33-7.36 (m, 2H), 7.52 (d, *J* = 8Hz, 2H), 7.71 (d, *J* = 8Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 21.57, 40.07, 69.24, 76.94, 78.10, 125.99, 126.53, 128.09, 128.65, 128.79, 129.06, 129.48, 130.08, 134.41, 134.69, 135.73, 143.51, 143.81, 145.03, 190.10. **IR (KBr, cm^{-1})**: 3447.1, 2960.87, 2886, 1652, 1543, 1088, 804. **HRMS (ESIMS)**: Anal. calcd for $C_{27}H_{25}ClNaO_3$ $(M+Na)^+$ 455.1390; found 455.1392.



6d

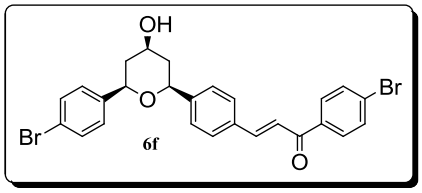
(2R,4S,6S)-2-(4-Bromophenyl)-6-(4-((E)-3-(2-hydroxyphenyl)-3-oxoprop-1-enyl)phenyl)-4-hydroxytetrahydropyran (6d):
Yield 85%; yellow semisolid, **^{1}H NMR (500MHz, $CDCl_3$)**: δ (ppm) 1.79 (q, *J* = 11.5Hz, 2H), 2.19 (s, br, D_2O exchangeable, 1H), 2.40 (dd, *J* = 11Hz, 2H), 4.02 (tt, *J* = 15.5Hz, 8.5Hz, 1H), 4.55 (dd, *J* = 32Hz, 11.5Hz, 2H), 6.94-7.04 (m, 1H), 7.03 (d, *J* = 8.5Hz, 1H), 7.35 (d, *J* = 7.5Hz, 2H), 7.42-7.52 (m, 4H), 7.64 (t, *J* = 8.5Hz, 3H), 7.74-7.79 (m, 1H), 7.81-7.89 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 40.08, 68.56, 77.22, 77.42, 118.93, 120.26, 120.53, 121.66, 122.10, 126.72, 127.82, 127.89, 129.12, 129.92, 130.23, 131.90, 136.75, 143.90, 145.14, 163.88, 193.93. **IR (KBr, cm^{-1})**: 3440, 2943, 2814, 1701, 1606, 1401,

1256, 1069, 801. **HRMS (ESIMS):** Anal. calcd for $C_{26}H_{23}BrNaO_4(M+Na)^+$ 501.0677; found 501.0683.



(2R,4R,6S)-2-Phenyl-6-(4-(4-oxo-4H-chromenyl)phenyl)-4-hydroxytetrahydropyran (6e):

Yield 85%; yellow semisolid. **^{1}H NMR (500MHz, $CDCl_3$)**: δ (ppm) 1.68-1.77 (m, 2H), 2.15-2.22 (m, 2H), 3.90 (tt, *J* = 11Hz, 3Hz, 1H), 4.40 (t, *J* = 11.5Hz, 2H), 6.79 (dd, *J* = 6.5Hz, 3Hz, 2H), 6.92 (s, 1H), 7.15 (d, *J* = 8.5Hz, 2H), 7.17-7.21 (m, 3H), 7.27 (d, *J* = 8.5Hz, 2H), 7.37 (dd, *J* = 6Hz, 3Hz, 2H), 7.74 (d, *J* = 8Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm) 39.78, 39.85, 65.07, 76.92, 77.19, 121.80, 122.23, 126.39, 127.57, 127.63, 128.60, 128.69, 129.38, 129.99, 131.62, 134.16, 135.56, 139.83, 156.09, 163.07, 190.04. **IR (KBr, cm^{-1})**: 3446, 2971, 2880, 1652, 1513, 1208, 799. **HRMS (ESIMS):** Anal. calcd for $C_{26}H_{21}NaO_4$ $(M+Na)^+$ 421.1416; found 421.1441.



(2R,4S,6S)-2-(4-Bromophenyl)-6-(4-((E)-3-(4-bromophenyl)-3-oxopropenyl)phenyl)-4-hydroxytetrahydropyran (6f):

Yield 90%; yellow semisolid. **^{1}H NMR (500MHz, $CDCl_3$)**: δ (ppm) 1.77-1.86 (m, 2H), 2.20 (s, br, D2O exchangeable, 1H), 2.30-2.35 (m, 2H), 4.07 (tt, *J* = 10.5Hz, 3Hz, 1H), 4.45 (d, *J* = 32Hz, 11.5Hz, 2H), 7.31-7.32 (m, 2H), 7.35 (d, *J* = 8Hz, 2H), 7.47 (s, 1H), 7.61-7.66 (m, 4H), 7.78 (s, 1H), 7.82 (d, *J* = 8.5Hz, 2H), 7.88 (d, *J* = 8Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 39.83, 67.21, 77.49, 77.87, 122.05, 125.75, 126.29, 127.50, 127.86, 128.41, 128.55, 129.24, 129.84, 134.17, 134.45, 135.49, 140.70, 143.77, 189.86. **IR (KBr, cm^{-1})**: 3454, 2961, 2878, 1651, 1541, 1091, 801. **HRMS (ESIMS):** Anal. calcd for $C_{26}H_{22}Br_2NaO_3$ $(M+Na)^+$ 562.9833; found 562.9853.

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Chapter-3

DESIGN AND EFFICIENT SYNTHESIS OF FUNCTIONALIZED FLAVONE-TRIAZOLE-TETRAHYDROPYRAN CONJUGATES VIA CLICK CHEMISTRY

[*Manuscript under preparation*]

DESIGN AND EFFICIENT SYNTHESIS OF FUNCTIONALIZED FLAVONE-TRIAZOLE-TETRAHYDROPYRAN CONJUGATES VIA CLICK CHEMISTRY

3.1. INTRODUCTION

Heterocycles are of enormous chemical and biological interest in our life [1a]. For example, 1,2,3-triazoles are belonging to an important class of *N*-heterocycle compounds. Due to their wide range of applications in biological [1b-d], pharmaceutical and agrochemical products [2], they capture the synthetic organic chemists attention. They are used in corrosion inhibition [3] and a number of biological applications such as anti-fungal, anti-bacterial [4], anti-allergic [5], anti-HIV [6], anti-tubercular [7], anti-inflammatory agents [8], selective β_3-adrenergic receptor agonist [9], herbicidal, antitumor, tyrosinase inhibitor and glycosidase inhibitors [10]. They are also present as central core in drugs such as carboxyamido triazole (CAI) [11], antibiotic tazobactam [12], and cefatrizine [13]. The nucleoside derivative non-nucloside reverse transcriptase inhibitor *tert*-butyldimethylsilyl spiro amino oxathioledioxide (TSAO) [14] are now available in the market as anti-cancer drugs. 1,2,3-Triazoles are quite stable under basic and acidic hydrolysis and reductive and oxidative conditions due to high aromatic nature [15]. They have high dipole moment and so capable of hydrogen bonding with bio-moleculars [16].

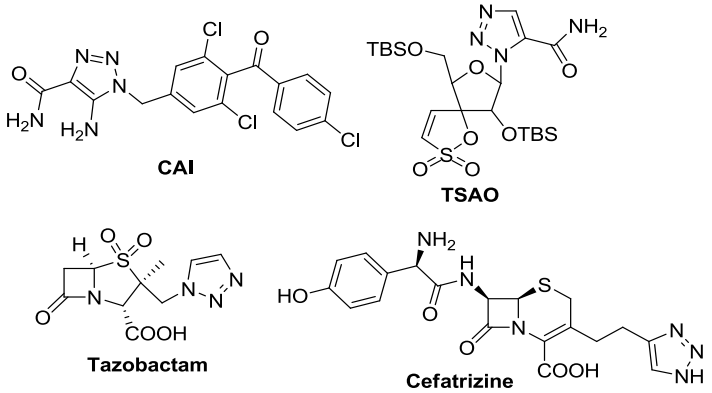


Fig.1: Some potential pharmaceuticals based on 1,2,3-triazoles.

Therefore, different methods are explored for their convenient synthesis such as transition-metal-free catalytic synthesis [17], Palladium-catalyzed one-pot synthesis [18], Ruthenium-catalyzed azide-alkyne cycloaddition [19], thermal Huisgen 1,3-dipolar cycloaddition. Among them, the most

attractive is the thermal Huisgen 1,3-dipolar cycloaddition of azides with alkynes. The synthesis of 1,2,3-triazoles *via* Huisgen 1,3-dipolar cycloaddition got developed in modern synthetic concept by Sharpless and co-workers and has become a paradigm of click chemistry [20]. In this concept, the copper (I) catalyzed azide–alkyne cycloaddition (CuAAC) [21] reaction is a key step in the design of novel products. The experimental simplicity and high selectivity of this process have been exploited in many applications in synthetic and medicinal chemistry, bio-conjugations, materials development, and the design of new catalysts in biotechnology [22].

Molecular hybridization is a new concept in the drug design and development based on the combination of pharmacophores of different bioactive substances to produce a new hybrid compound with improved affinity and efficacy, when compared to the parent drugs [23]. Recent studies have shown that triazole based chalcone-pyrrolo[2,1-c] [1,4] benzodiazepine (PBD) hybrids (**W**) resulted in G1 cell-cycle arrest and exhibited inhibitory effect on NF-kβ, Bcl-XL proteins which are vital for breast cancer cell proliferation [24] and 1,2,3-triazole tethered β-lactam-chalcone bifunctional hybrids (**Y**) resulted as potent anticancer agents [25]. 1,2,3-triazole-bearing podophyllotoxins proven to be more potent than etoposide in selected human cancer cell lines [26]. 1,2,3-triazole analogs of combretastatin A-4 displayed potent cytotoxic activity against several cancer cell lines with IC_{50} values in the nanomolar range [27]. Arylamide-1,2,3-triazole conjugates were reported as important scaffold for potential antitumor agents, and exhibited IC_{50} 46 nM against the MCF-7 cancer cell line [28]. 1,2,3-triazole-dithiocarbamate hybrids (**Z**) acts as potential anticancer agents [29]. Natural product hybrids for example, thiolactone-triazole-chalcone scaffolds were found active against W2 strain *Plasmodium falciparum* with IC_{50} ranging from 0.68 to 6.08μm [30].

Flavonoids itself shown many biological applications [31] when conjugated with new biologically active molecule enhanced their activity [32] for example, flavonylazole derivative (**X**) has shown antifungal and antibacterial activities [33], compounds MA-6, MA-8 and MA-21 were found inhibitors of estrogen receptor alpha-positive breast cancer. N-methyl-1,2,3-triazole derivatives of 2-cyanochromones have shown anti-inflammatory, psychotropic and anti-allergic effects [34]. Flavone based triazoles are useful for the treatment of inflammation, immune disease and cancer [35] (Fig.2).

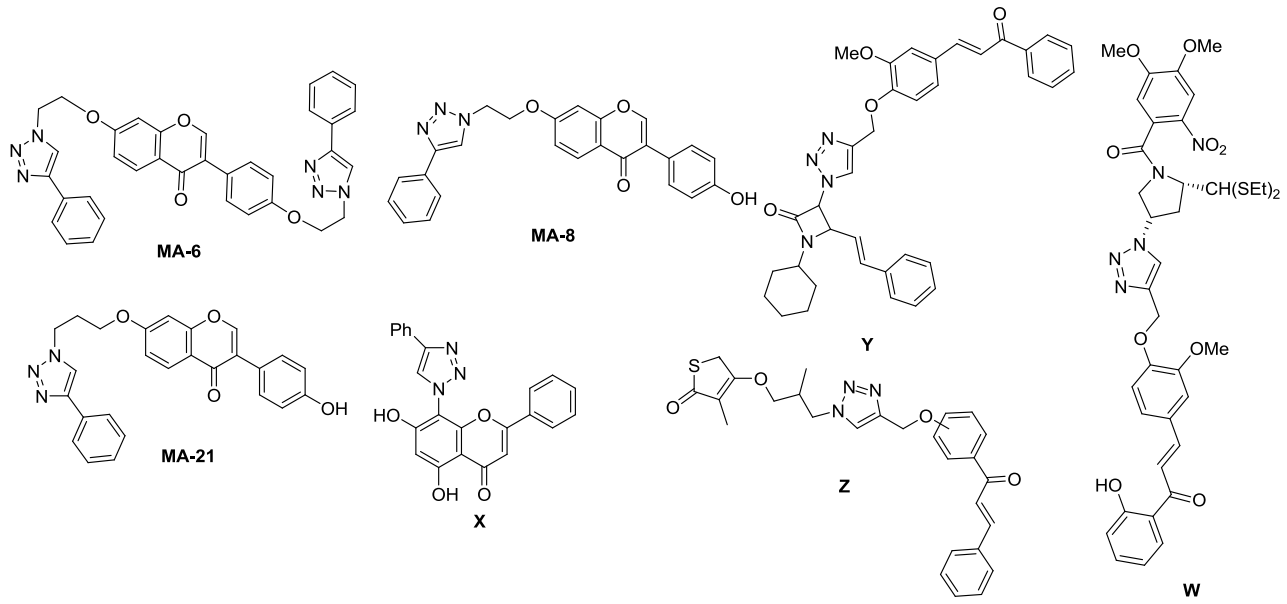
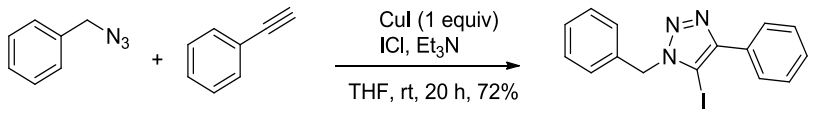


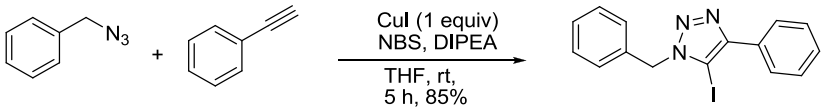
Fig.2: Flavonoid-triazole containing scaffolds as potential drug entities.

Therefore, Wu *et al.* first time reported a regiospecific synthesis of 5-iodo-1,4-disubstituted-1,2,3-triazole in which ICl is the iodinating agent (scheme 1) [36]. However, iodinating agent ICl is corrosive in nature and products obtained in moderate yield after longer reaction time.



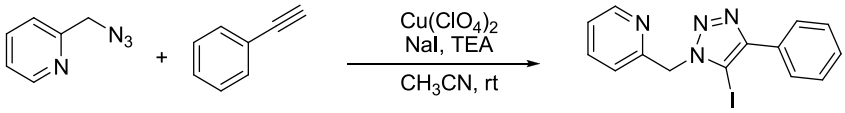
Scheme 1: Synthesis of 5-iodotriazole using ICl as iodinating agent.

Zhang *et al.* synthesized 5-iodo-1,4-disubstituted-1,2,3-triazoles using NBS and CuI as iodinating agent (scheme 2) [37].



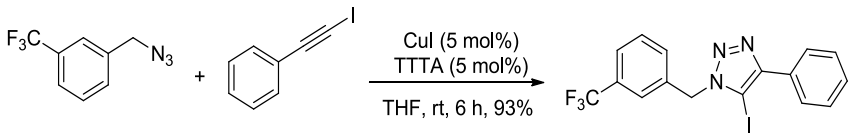
Scheme 2: Synthesis of 5-iodotriazoles using CuI as iodinating agent.

Zhu *et al.* synthesized 5-iodo triazoles using copper(II) perchlorate and NaI (Scheme 3) [38].



Scheme 3: Synthesis of 5-iodotriazoles using NaI as iodinating agent.

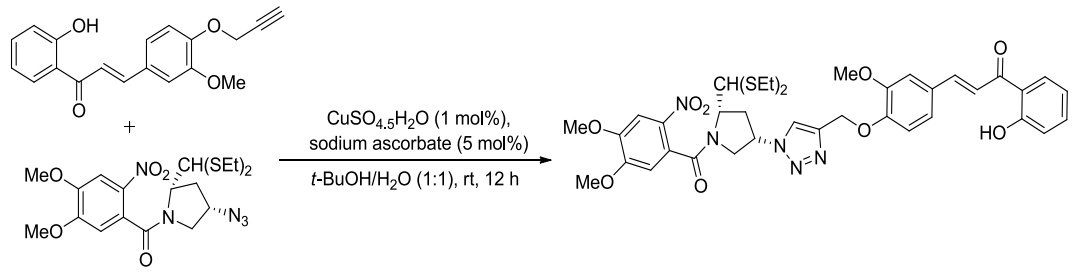
Similarly, Hein *et al.* reported the synthesis of 5-iodotriazole using CuI-catalyzed cycloaddition of 1-iodoalkyne and organic azide in the presence of an assisting ligand such as tris((1-benzyl-1*H*-1,2,3-triazolyl)-methyl)amine (TBTA) and tris((1-tert-butyl-1*H*-1,2,3-triazolyl)-methyl) amine (TTTA) (Scheme 4) [39]. However, the starting material 1-iodoalkyne is unstable therefore difficulty in handling and requires expensive ligands.



Scheme 4: Synthesis of 5-iodotriazoles using CuI as iodinating agent.

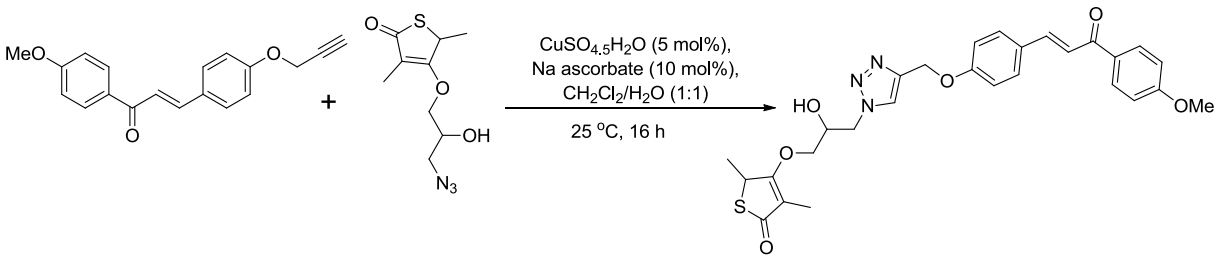
Indeed, we need to develop an efficient and high yielding methodology considering environmental benign conditions.

Kamal *et al.* synthesized chalcone-pyrrolobenzodiazepine conjugates linked *via* 1,2,3-triazole ring. Synthesized compounds showed good anticancer activity (scheme 5) [40].



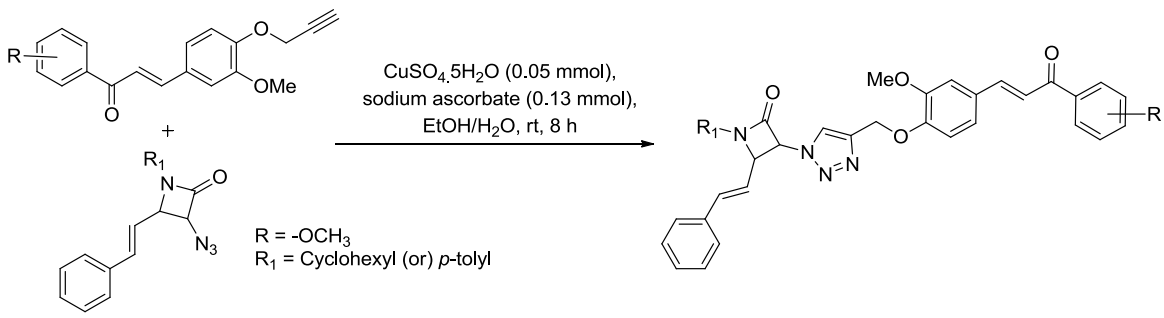
Scheme 5: Synthesis of chalcone-triazole-pyrrolobenzodiazepine hybrids.

Hans *et al.* synthesized β-amino alcohol thiolactone-chalcone hybrids and tested antiplasmodial and falcipain-2 inhibitory activity (Scheme 6) [30].



Scheme 6: Synthesis of β-amino alcohol thiolactone-chalcone hybrids.

Kumar *et al.* synthesized 1,2,3-triazole tethered β-lactam-Chalcone bifunctional hybrids and evaluated for anticancer activity (scheme 7) [25].



Scheme7: Synthesis of 1,2,3-Triazole tethered β-lactam-chalcone bifunctional hybrids.

Due to above significance applications and also our research interest on flavonoids and tetrahydropyrans [31b,32, 41]. We selected these pharmacophores for hybridization and to make one entity, i.e. flavone-triazole-tetrahydropyran conjugates *via* click reaction. Herein, we report two different triazole derivatives (i) 5-*I*-1-(tetrahydropyran)-1,2,3-triazol-4-(3-methoxylflavone)and (ii) 5-*H*-1-(tetrahydropyran)-1,2,3-triazol-4-(3-methoxylflavone) using 4-azido tetrahydropyran and 3-(2-propynyloxy) flavone derivatives under two different copper-catalyzed reaction conditions.

3.2. OBJECTIVE

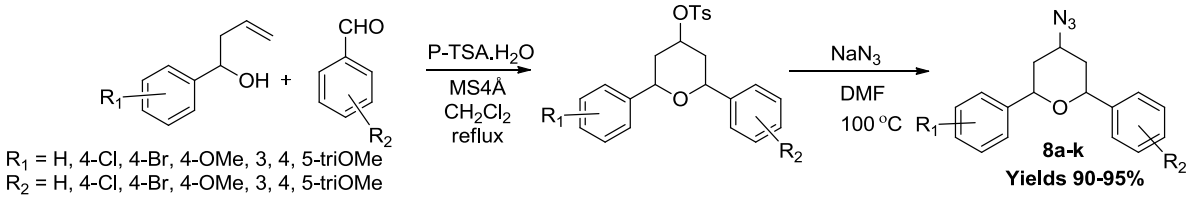
One-pot multicomponent synthetic pathway give highly functionalized hetero and non-hetero derivatives in a single step reaction. This will overcome problems of multi-step synthesis such as long reaction time and wastage since the amount of solvents, reagents and energy would be dramatically decreased. These reactions are increased synthetic efficiency and diversity, with bio-relevance, molecular complexity impressive region- and stereoselectivity of objectives offered by natural products and facilitate the generation of high quality for drug discovery. Molecular hybridization is vital for the synthesis of analogous natural products with high efficiency. Click reaction is the best reaction to combine two or more reactants in one step without side products in short reaction time and high yield. Hence, we utilized click reaction strategy in molecular hybridization of flavonoids and tetrahydropyrans to give flavonoid-triazole-tetrahydropyran hybrids.

3.3. RESULTS AND DISCUSSION

3.3.1. Synthesis of 4-azido tetrahydropyrans.

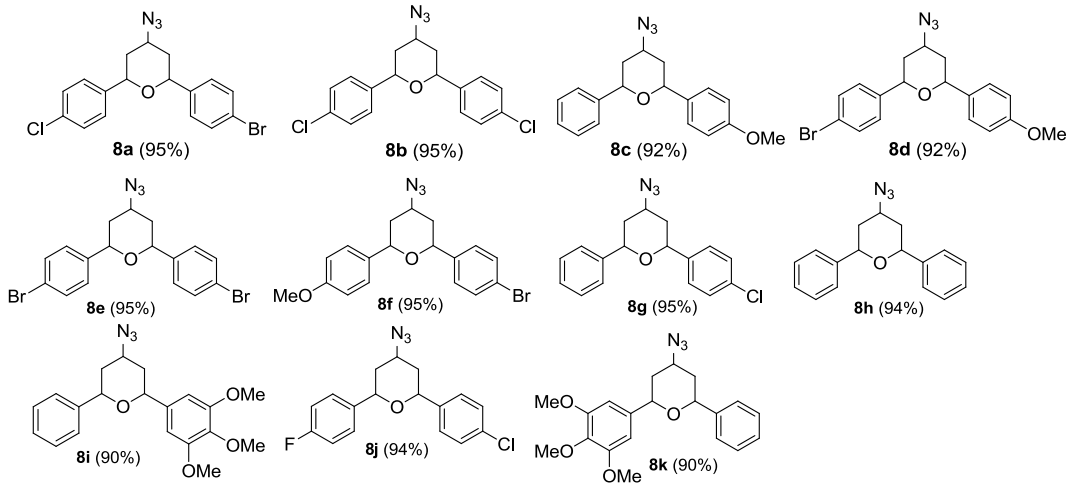
Reaction intermediates 4-tosyloxy THPs synthesized using homoallylic alcohols, aldehydes and *p*-TSA.H_2O in presence of MS 4Å *via* Prins cyclization [41a] followed by reaction of 4-tosyloxy

THPs with sodium azide in DMF at 100 ^{0}C for 1 hour obtained 4-azido THPs (scheme 8, **8a-k**) in good yield (Table 1, 90-95%).



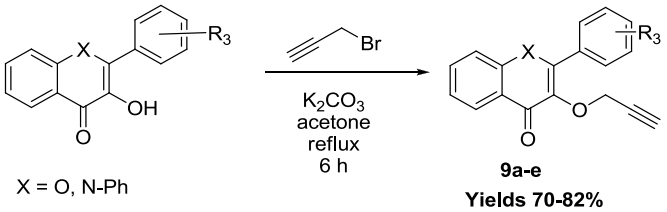
Scheme 8: Synthesis of 4-azido tetrahydropyran.

Table 1: Synthesis of 4-azido tetrahydropyrans *via* Prins cyclization.



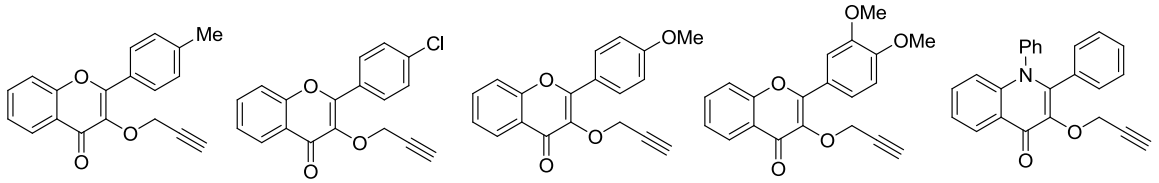
3.3.2. Synthesis of 3-(2-propynyloxy) flavone derivatives

Terminal alkynes 3-(2-propynyloxy) flavone derivatives were synthesized following the literature [42] followed by the reaction of 3-flavonol or N-phenyl amino flavon-3-ol with propargyl bromide (80% in toluene) at 66 ^{0}C for 6 h (Scheme 9) gave the products in good to excellent yields (Table 2).



Scheme 9: Synthesis of 3-(2-propynyloxy) flavones.

Table 2: List of 3-(2-propynyloxy) flavone derivatives.

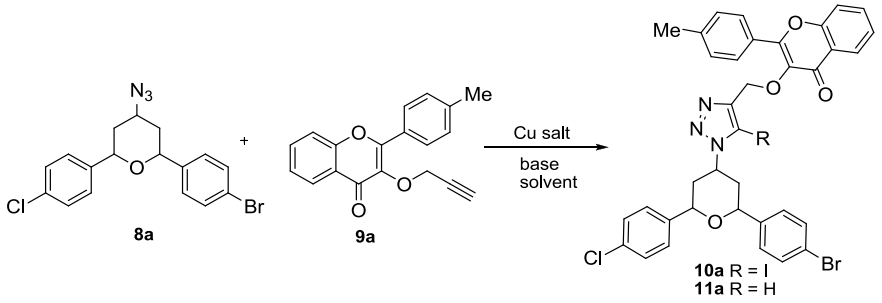


9a (75%) **9b** (78%) **9c** (82%) **9d** (80%) **9e** (70%)

3.3.3. Synthesis of 5-iodo 1,2,3-triazole derivatives

Initially, the reaction was performed without using base of 4-azido tetrahydropyran **8a** and alkyne (**9a**) in the presence of copper(I) iodide (1 equiv.) and *N*-bromosuccinamide (NBS, 1.1 equiv.). The reactants were remained intact after prolonging reaction time. However, addition of DIPEA (diisopropylethylamine, 0.5 equiv.) gave 5-iodo-1,2,3-triazole **10a** along with 5-prototriazoles **11a** in 10:1 ratio and overall 75% yield (Table 3, entry 9). In search of better base, we screened other bases such as TEA, DIPEA, 2,6-lutidine, DBU, DABCO, Na_2CO_3 and 1,10-phenanthroline in the same reaction condition using 0.5 equiv. base. Among them, DIPEA was found the most suitable base in the reaction (Table 3). We gradually increased the quantity of DIPEA from 0.5 to 2.5 equiv. It was observed that at 2.5 equiv. DIPEA gave maximum yield of 5-iodo substituted triazole as a single product (Table 3, entry 13). Further, increase in base quantity of DIPEA has no effect on product yield or reaction time.

Table 3: Optimization of reaction conditions for synthesis of 5-iodo triazole derivatives.



Entry	Cu (I) salt (equiv)	Base	Equiv.	Time (h)	Triazole 10a:11a	Yield (%)
1	1	2,6-lutidine	0.5	8	4:1	60
2	1	DBU	0.5	5	8:1	58
3	1	DABCO	0.5	5	7:1	55
4	1	Na_2CO_3	0.5	6	7.5:1	45
5	1	1,10-phenanthroline	0.5	6	4:1	45

6	1	TEA	0.5	6	10:1	65
7	1	TEA	2	5	12:1	68
8	1.2	TEA	2	5	12:1	72
9	1	DIPEA	0.5	4	10:1	75
10	1.2	DIPEA	1	3	15:1	78
11	1.2	DIPEA	1.5	1	20:1	80
12	1.2	DIPEA	2	1	1:0	85
13	**1.2**	**DIPEA**	**2.5**	**1**	**1:0**	**90**

Furthermore, we saw the solvent effects using ACN, MeOH, THF, THF:H_2O, EtOAc, acetone, toluene, DMF, water, ACN:H_2O. Among the solvents, THF was found as suitable solvent. These solvents have no effects on products **10a**:**11a** ratio but gave major effects on the reaction rate and product yields (Table 4).

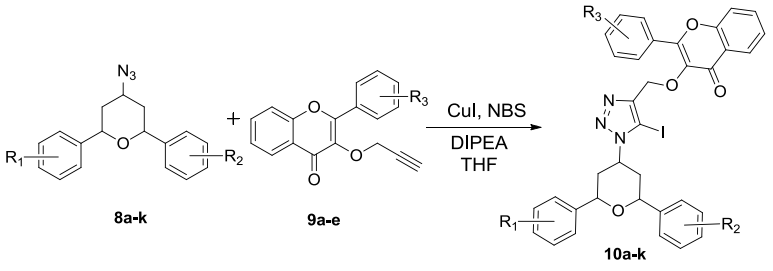
Table 4: Solvent effects on triazole yields.

Entry	Solvent	Time (h)	Yield (%)
1	ACN	3	68
2	MeOH	5	60
3	**THF**	**1**	**95**
4	THF:H_2O	4	73
5	EtOAc	6	65
6	Toluene	6	60
7	DMF	6	60
8	Water	nr	nr
9	ACN:H_2O	4	70
10	acetone	3	72

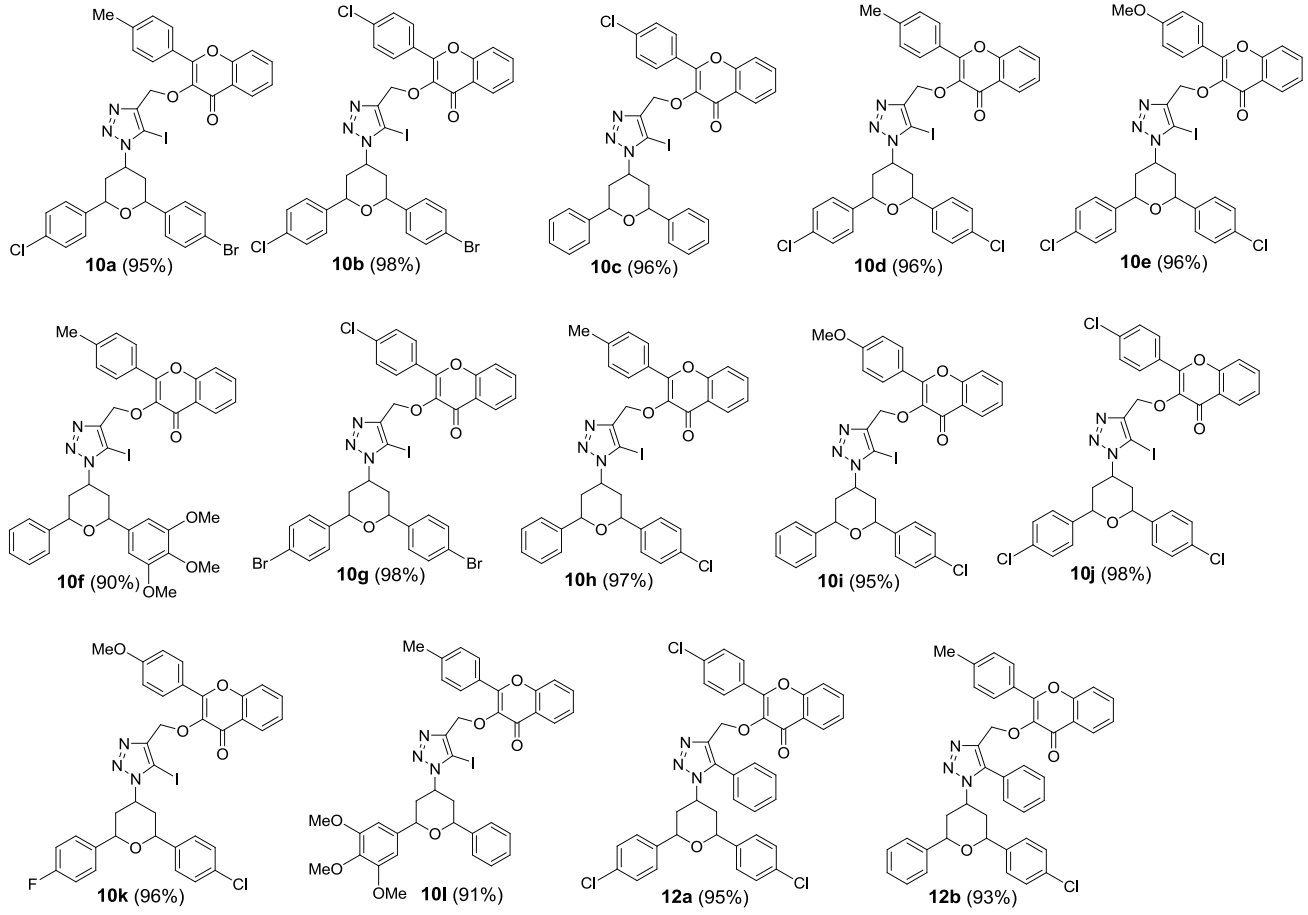
To prove its general applicability, a number of flavones based terminal alkynes and 4-azido tetrahydropyrans were subjected to the optimized reaction conditions as CuI (1.2 equiv. as copper source), DIPEA (2.5 equiv. as base), NBS (1.1 equiv) and THF as the solvent (Table 5). The reaction proceeded smoothly in all cases, where 5-iodo-1,2,3-triazoles **3** were obtained as the exclusive product. There is no substituent effect on products yields and reaction rate. Both sterically and functionally demanding (Table 5, e.g., **10f** and **10l**) substrates were utilized as reactants.

The sequence extended for the synthesis of 5-phenyl-1-(tetrahydropyran)-1,2,3-triazol-4-(3-methoxylflavone) derivatives (**12a**-**b**) by Pd-catalyzed Suzuki cross coupling reaction of 5-iodo triazole derivative with phenylboronic acid which gave an excellent yield (Table 5) [21c].

Table 5: Synthesis of 5-iodotriazoles from 4-azido tetrahydropyrans and flavone based alkynes.



8a-k 9a-e 10a-k 12a-b

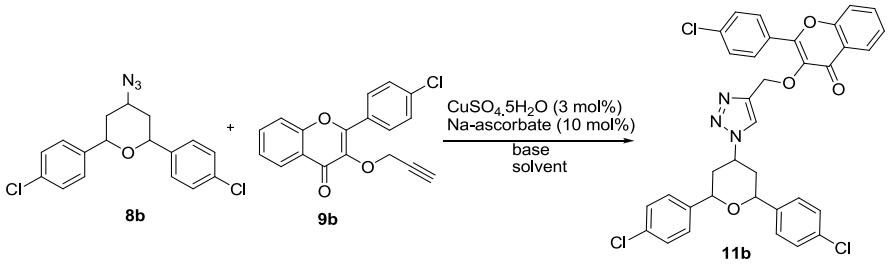


3.3.4. Synthesis of 5-*H*- 1,2,3-triazol derivatives

Many reports are available in the literature for copper-catalyzed [3+2] azide-alkyne cycloaddition (CuAAC) for the synthesis of 1,4-disubstituted-1,2,3-triazole derivatives [43].

Surprisingly, there were no report available to conjugate flavone and tetrahydropyran through 1,2,3-triazole linker. Therefore, during the synthesis of 1-tetrahydropyran-1,2,3-triazolyl-4-(3-methoxylflavone) derivatives we initially performed a model reaction as 4-azido tetrahydropyran **8b** treated with 3-(2-propynyloxy) flavone **9b** following available methods such as Cu(I) catalyzed, Cu(II) catalyzed, catalyst free [44], and clay supported [45]. In these methods, the desired product 1,2,3-triazole **11** was obtained in moderate to low yield even prolonging the reaction time and reaction temperature.

Table 6: Optimization conditions for synthesis of 1,4-disubstituted 1,2,3-triazole derivatives.

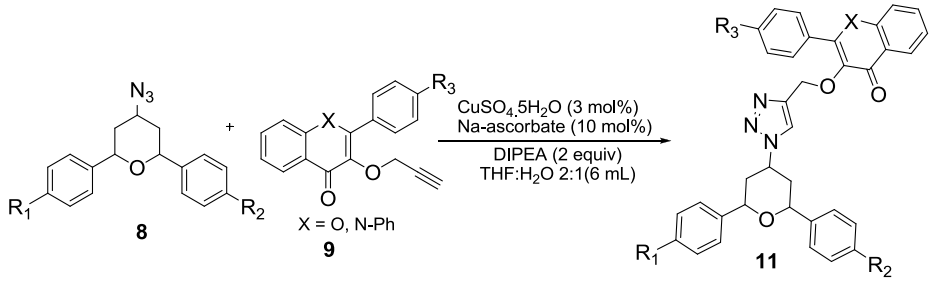


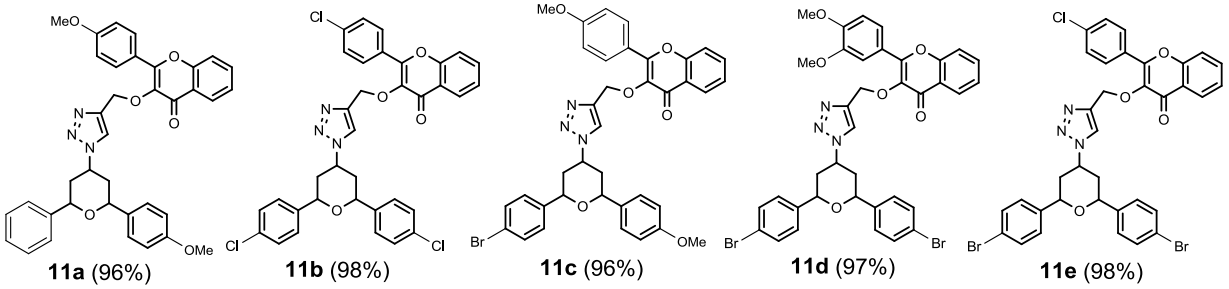
Entry	Base	Equiv	Solvent	Temp	Time (h)	Yield (%)
1	DIPEA	1	THF	Rt	10	55
2	DABCO	1	ACN	Rt	14	50
3	DBU	1	DCM	Rt	16	50
4	TEA	1	DMF	Rt	15	46
5	DIPEA	1	THF	Reflux	8	55
6	DIPEA	1.5	THF:H_2O (1:1)	Rt	18	35
7	DIPEA	1.5	THF:H_2O (1:1)	Reflux	6	75
8	DIPEA	2	THF:H_2O (1:1)	Reflux	6	85
9	DIPEA	2	^{t}BuOH:H_2O (1:1)	Reflux	6	65
10	DIPEA	2	MeOH:H_2O (1:1)	Reflux	7	65
11	DIPEA	2	CAN : H_2O (1:1)	Reflux	6	60
12	DIPEA	2	THF:^{t}BuOH:H_2O (1:1:1)	reflux	5	75

13	**DIPEA**	**2**	**THF:H_2O (2:1)**	**reflux**	**3**	**98**

To optimize reaction conditions, we examined a broad array of copper(I) salts (CuI, CuCl, CuBr), copper(II) salts ($Cu(OAc)_2.H_2O$, $CuSO_4.5H_2O$, $CuBr_2$, $CuCl_2$), solvents, bases and mole ratio of reactants **8b**:**9b** at different temperature (Table 6). We found $CuSO_4.5H_2O$ (3 mol%) an efficient catalyst. Therefore, using $CuSO_4.5H_2O$ (3 mol%) as catalyst and sodium ascorbate (10 mol%), azide : alkyne at 1.15:1 ratio, gave optimal yield (98%). Similarly, a mixture of solvents (THF: H_2O, 2:1 ratio) and base DIPEA (2 equiv.) was found optimal condition at reflux temperature (Table 6, entry **13**). In the optimal conditions, one-pot CuAAC was investigated for various 4-azido tetrahydropyrans and 3-(2-propynyloxy) flavones (Table 7). Further, it was noticed that no substituent effects as electron releasing or withdrawing and steric effects was observed. In all cases, the products (**11a-j**) were formed in excellent yields (Table 7).

Table 7: Synthesis of 1,4-disubstituted 1,2,3-triazole derivatives.





3.4. STRUCTURE DETERMINATION

All structures of new products (**10a-l, 11a-j, 12a-b**) were established by their spectral analysis (IR, ^{1}H, ^{13}C-NMR and HRMS) and reported compounds (**8a-k**, **9a-e**) were compared with literature data [42,46]. For example, compound **10a** was obtained as light yellow solid. The IR spectrum of **10a** showed absorptions at 1628, 1617, and 1233 cm^{-1} for carbonyl, N=N, C−O−C bonds *asymmetric stretching* respectively. The HRMS of **10a** supported a molecular composition of $C_{36}H_{28}BrClIN_3NaO_4$ $(M+Na)^+$ representing 23 degrees of unsaturation. In the ^{1}H and ^{13}C NMR spectra of **10a**, methyl signal resonating at δ_H 2.32, and δ_C 21.68 were assigned to C-10. Two oxymethine protons at δ_H 5.28, two asymmetrical methylene protons resonating at δ_H 2.17, and 2.10 were assigned to H-2, H-6, H-3e/H-5e, H-3a/H-5a respectively, one methylyne proton at δ_H 4.85 suggested the presence of a THP ring. The substituents (at 2,4, and 6 positions) orientation and stereochemistry on THP moiety in **10a** was established by coupling constants, NOESY experiment and finally single crystal X-ray analysis. The relative downfield shift of H-3e/H-5e at δ_H 2.17 and upfield shift of H-3a/H-5a at δ_H 2.10 suggested that H-3a and H-5a are in axial and H-3e and H-5e are in equatorial orientations. The ^{1}H NMR spectrum, H-3e equatorial proton showed doublet of doublets at δ_H 2.17 (dd, J = 4, 14.5Hz, 2H) in which the coupling constant (^{3}J = 4 Hz) indicates that H-3e coupled with H-5e and H-4, and coupling constant (^{2}J = 14.5 Hz) indicates geminal coupling of H-3e/H-5e with H-3a/H-5a. In ^{13}C NMR spectrum of **10a** peaks at δ_C 36.92, 36.96 are corresponding to C-3, C-5 carbons of THP ring. Similarly, peaks at δ_C 82.69, 73.94 are corresponding to C-2, C-4 carbons of THP ring respectively. In the ^{1}H and ^{13}C NMR spectra of **10a**, oxymethylene signals resonating at δ_H 5.29, and δ_C 64.39 were assigned to H-7 and C-7 respectively. Peak at δ_C 131.72 corresponds to C-9 (Fig-3). Peak at δ_C 175.19 corresponds to carbonyl carbon C-4'. The stereo-chemical assignment of the triazole was established by NOESY experiment, in which no correlation observed between H-2 and H-4 or H-4 and H-6 therefore, H-4 not in same direction of H-2 and H-6 suggested that the triazole group exist in axial orientation. These data confirmed that the assigned product formation and the pyran ring exist in chair conformation with substituents at C-2, C-6 are in equatorial orientation and substituent at C-4 is in axial orientation (Fig. 3). It was well supported by single crystal x-ray analysis (Fig. 4). Similarly, structural assignment of other derivatives **10b-l** was confirmed on their spectral analysis (experimental). Similarly, 5-*H* 1,2,3-triazole derivative compound **11b** was obtained as light yellow solid. The IR spectrum of **11b** showed absorptions at 1644, 1622, 1211 cm^{-1} for C=O, N=N, C−O−C bonds *asymmetric stretching* respectively. The

HRMS of **11b** supported a molecular composition of $C_{35}H_{26}Cl_3N_3NaO_4$ $(M+Na)^+$ representing 23 degrees of unsaturation. In the ^1H and ^{13}C NMR spectra of **11b**, oxymethylene group resonating at δ_H 5.38, and δ_C 65.17 were assigned to H-7 and C-7 respectivly (Fig. 3). Two oxymethine protons at δ_H 4.93, two asymmetrical methylene protons resonating at δ_H 2.53, and 2.16 were assigned to H-2, H-6, H-3e/H-5e, H-3a/H-5a respectively, one methine proton at δ_H 4.90 suggested the presence of a THP ring. The substituents (at 2,4, and 6 positions) orientation and stereochemistry on THP moiety in **11b** was established by coupling constants, NOESY experiment. The relative downfield shift of H-3e/H-5e at δ_H 2.53 and upfield shift of H-3a/H-5a at δ_H 2.17 suggested that H-3a and H-5a are in axial and H-3e and H-5e are in equatorial orientations. The ^1H NMR spectrum contained peak at δ_H 2.53 (dd, J = 4, 14Hz, 2H) in which coupling constant ^2J = 14 Hz indicates geminal coupling of H-3e/H-5ewith H-3a/H-5a, and coupling constant ^3J = 4 Hz indicates that the cis coupling of H-3e/H-5e with H-2/H-6 or H-4. ^{13}C NMR spectrum gave peaks at δ_C 37.07 are corresponds to C-3, C-5 carbons of THP ring. Similarly, peaks at δ_C 73.89, 54.62 ppm are corresponding to C-2, C-4 carbons of THP ring respectively, peak at δ 175.08 ppm corresponds to carbonyl carbon. In the NOESY experiment, there is no correlation observed between H-4 and H-2 or H-4 and H-6 therefore, H-4 not in same direction of H-2/H-6 suggested that the triazole group exist in axial orientation. These data confirmed that the assigned product formation and the pyran ring exist in chair conformation with substituents at C-2, C-6 are in equatorial orientation and substituent at C-4 is in axial orientation (Fig. 3). Similarly, structural assignment of other derivatives **11a, 11c-j** was confirmed on their spectral analysis (experimental).

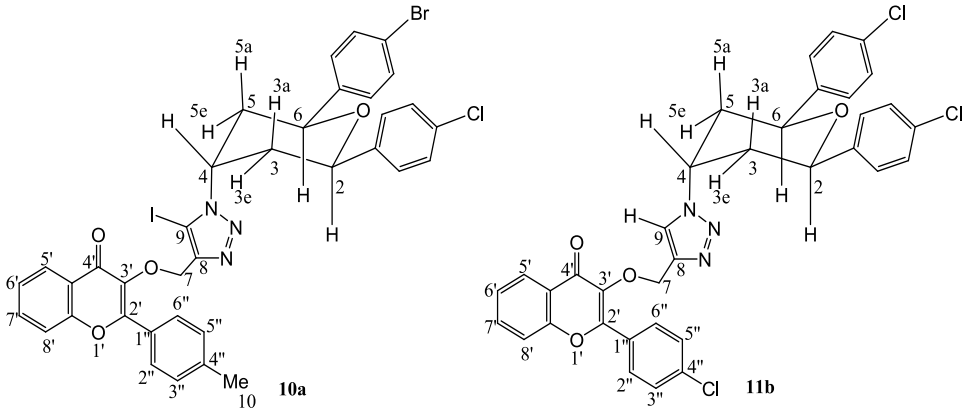


Fig. 3: Stereochemical alignment of compound **10a** and compound **11b**.

3.5. SINGLE CRYSTAL X-RAY ANALYSIS

Single-crystal x-ray diffraction analysis reveals that compound **10a** is crystallized in the

monoclinic space group P 21/n and crystal data are presented in Table 8. Crystal packing shows that two organic molecules are hydrogen bonded with each other via C11-H11---Cl1, 3.186 Å; and with solvent *via* C38-H38A---I1, 3.124 Å. Also, the 3-dimensional packing of **10a** showed 1D channel along b-axis lining up the solvent molecules in it [47] (Fig. 4).

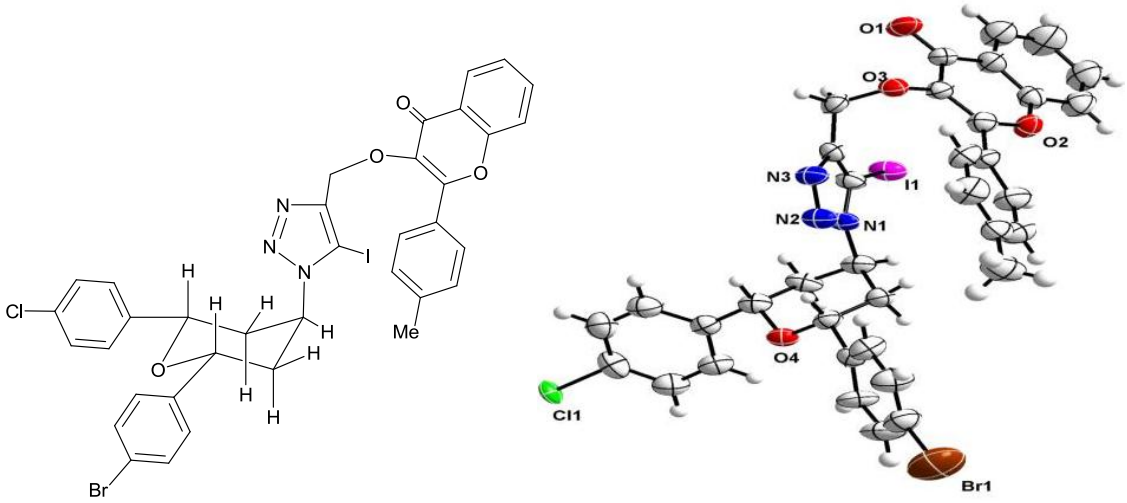


Fig. 4: ORTEP diagram of compound **10a**. C(white), N (blue), O (red), Cl (green), Br (brown), I (pink).

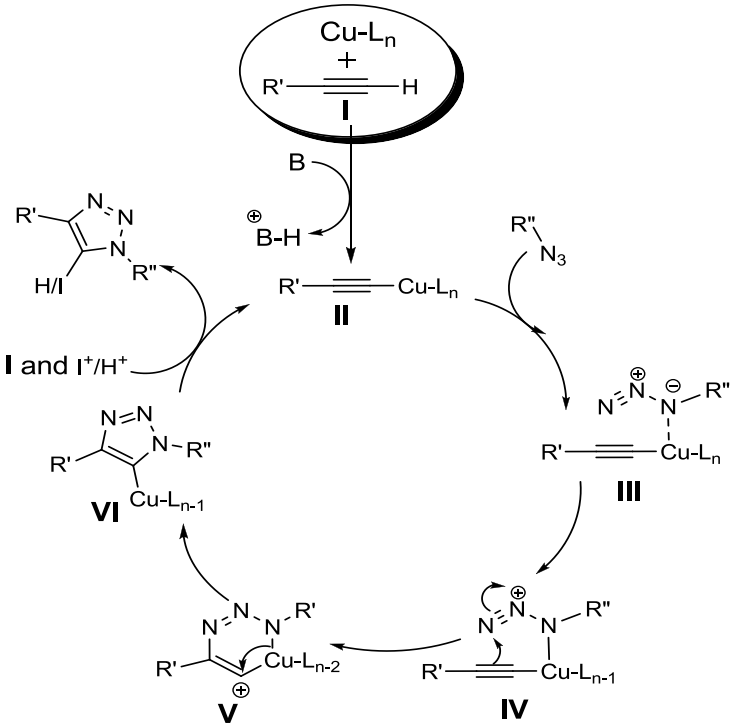
Table 8: Crystallographical and experimental data for compound **10a**.

Data	**Compound 10a**
Moiety formula	$C_{36}H_{28}BrClIN_3O_4$, C_4H_8, C_2H_4, O
Formula weight	909.02
Temperature	296 K
Crystal system	monoclinic
space group	P 21/n
a	16.4169 (10)
b	9.8127 (6)
c	24.3844 (15)
Alpha (α)	90
Beta (β)	102.992 (3)
Gamma (γ)	90
Dx, gcm-3	1.577
F (000)	1832.0

Theta (max)	25.000
Volume	3827.6 (4)
Hall group	2yn
h,k,l max	19,11,28
R (reflections)	0.0878 (4508)
wR2 (reflections)	0.2792 (6696)
Goodness-of-fit (S)	1.032

3.6. MECHANISM

Based on the literature of the click reaction mechanisms [37,39], we proposed a plausible mechanism depicted in Scheme 10. In the first step, deprotonation of alkyne by a base (DIPEA), followed by the formation of the σ-acetylide (**II**) complex as the first key intermediate. Coordination of the azide through the proximal nitrogen center and subsequent cyclization to yield the six membered cuprated triazoles (**V**) which undergoes a reductive ring contraction to reach the copper(I) triazolide (**VI**). An electrophilic I^+ (in situ generates from CuI+NBS) or H^+ (from protonated base +BH) captures the copper (I) triazolide (**VI**) to afford 5-I/5-H triazole (Scheme 10).



Scheme 10: Plausible mechanism for synthesis of 5-I/5-H 1,2,3-triazoles.

ANTI-PROLIFERATIVE ACTIVITY (Data obtained after finishing Thesis writing)

All synthesized compounds flavone-triazole-tetrahydropyran conjugates (**10a-l**, **11a-j**) were evaluated for their *in vitro* anti-proliferative activity against three human cancer cell lines namely; human breast cancer cell line (MDA-MB-231), human lymphoblastoid cancer cell line (KCL22) and human cervical carcinoma (HeLa) following the standard procedure of MTT ((3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay. Each compound was tested in concentration (dose) - % cell viability (response) experiments; with varying the concentration by dilution to define potency.

MTT assay

The MDA-MB-231/KCL22/HeLa cell lines was maintained in RPMI 1640 culture medium supplemented with 10% heat-inactivated fetal-calf serum and antibiotic antimycotic solution (Sigma Aldrich). The cells were plated at a density of 5×10^3 cells per well in a 96-well plate, and cultured for 24 hours at 37°C. The cells were subsequently exposed to drugs. The plates were incubated for 48 hours, and cell proliferation was measured by adding 20 µL of MTT dye (5 mg/mL in phosphate-buffered saline) per well. The plates were incubated for a further 4 hours at 37°C in a humidified chamber containing 5% CO_2. Formazan crystals formed due to reduction of dye by viable cells in each well were dissolved in 150 µL dimethyl sulfoxide, and absorbance was read at 570 nm. The absorption values were expressed as the cell viability (%), according to the control group as 100%. The concentration required for 50% inhibition of cell viability (IC_{50}) was calculated using the software ‘‘Prism 3.0’’.

The results revealed that all synthesized compounds have shown anti-proliferative activities by inhibiting cell growth with IC_{50} values varying 0.75-5.4 µM against all tested cell lines. In the MDA-MB-231 cell line, some compounds exhibited IC_{50} values upto 4.42 µM, but the majority of the reported compounds inhibited IC_{50} values below 1.5 µM. Compounds **10c**, **10g**, **10j**, **11a**, **11c**, **11e**, **11h** were found more potent ($IC_{50} \leq 1.34 \pm 2.6$ µM) compared to the reference drugs doxorubicin (IC_{50} 1.36±1.0 µM), and FU (IC_{50} 2.45±2.7µM), compounds **10a**, **10b**, **10e**, **10f**, **10i**, **10k**, **10l**, **11a**, **11d** were found more potent ($IC_{50} \leq 2.15 \pm 2.4$ µM) than reference drug FU (IC_{50} 2.45±2.7µM) against the MDA-MB-231 cell line. Remaining compounds showed moderate antiproliferative activity against the MDA-MB-231 cell line. In the KCL-22 cell line, some compounds exhibited IC_{50} values upto 4.51 µM, but the majority of the reported compounds inhibited IC_{50} values below 1.5 µM. Compounds **10c**, **10f-j**, **10l**, **11a**, **11c-f**, **11h** were found more potent ($IC_{50} \leq 1.68 \pm 2.8$ µM) compared to the reference drugs doxorubicin (IC_{50} 1.8±3.1 µM), and FU (IC_{50} 3.52±2.1 µM), compounds **10b**, **10d**, **10e**, **10k**, **11b**, **11i, 11j** were found more potent

($IC_{50} \leq 2.73\pm2.1$ µM) than reference drug FU (IC_{50} 3. 52±2.1 µM) against the KCL22 cell line. In the HeLa cell line, some compounds exhibited IC_{50} values upto 5.4 µM, but the majority of the reported compounds inhibited IC_{50} values below 1.2 µM. Compounds **10a**, **10c-g**, **10i-l**, **11c-d**, **11g**, **11h** were found more potent ($IC_{50} \leq 1.33\pm1.8$ µM) compared to the reference drugs Doxorubicin (IC_{50} 1.5±1.7 µM), and FU (IC_{50} 2.78±1.9 µM), compounds **10b**, **10d**, **10e**, **10k**, **11b**, **11i, 11j** were found more potent ($IC_{50} \leq 2.23\pm1.6$ µM) than reference drug FU (IC_{50} 2.78±1.9 µM) against the HeLa cell line.

Table 9: IC_{50} values of flavone-triazole-tetrahydropyran conjugates on the growth of human cancer cell lines.

Entry	Drug	MDA-MB-231	KCL22	HeLa
1	10a	2.03±1.6	3.74±1.6	**1.28±1.3**
2	10b	2.1±1.7	2.1±2.6	2.23±1.6
3	10c	**1.34±2.6**	**0.96±1.4**	**1.13±1.9**
4	10d	2.53±1.7	2.55±2.5	**1.54±1.4**
5	10e	1.99±1.3	2.1±0.8	**0.9±1.5**
6	10f	2.04±1.2	**1.3±2.8**	**1.1±1.3**
7	10g	**0.77±2.5**	**0.96±.2.7**	**0.91±2.4**
8	10h	3.94±1.8	**1.49±2.6**	3.43±2.5
9	10i	**1.36±1.6**	**1.68±2.8**	**1.15±2.13**
10	10j	**1.05±2.3**	**0.61±1.3**	**1.52±2.4**
11	10k	2.03±0.9	1.67±0.8	**0.84±1.2**
12	10l	2.04±1.2	**1.3±2.8**	**1.1±1.3**
13	11a	**1.0±1.4**	**1.45±2.5**	1.74±2.4
14	11b	1.44±1.2	2.56±0.9	3.27±1.3
15	11c	**1.03±0.8**	**1.46±2.3**	**1.2±1.3**
16	11d	2.15±2.4	**0.75±1.5**	**0.65±2.3**
17	11e	**0.70±1.8**	**1.02±2.6**	2.96±4.1
18	11f	3.39±1.3	**0.82±1.9**	2.43±2.8
19	11g	2.99±1.6	4.51±2.3	**1.33±1.8**
20	11h	**1.03±0.8**	**1.46±2.3**	**1.2±1.3**
21	11i	4.42±1.2	2.73±2.1	5.4±2.4
22	11j	3.12±2.1	2.13±1.3	3.5±0.9
	Doxorubicin	1.36±1.6	1.8±3.1	1.5±1.7
	FU	2.45±2.7	3.52±2.1	2.78±1.9

3.7. CONCLUSIONS

In conclusion, we have developed a mild and efficient one pot synthesis for functionalized 5-iodo and 5-*H*-1,2,3-triazole-tetrahydropyran-flavone derivatives *via* Prins cyclization followed by click reaction in excellent yields (90-98%). And Pd-catalyzed Suzuki cross-coupling reaction of 5-iodo-1,2,3-triazole with phenylboronic acid gave 5-phenyl-1,2,3-triazole derivative in excellent yield. Our new method gave a synthetic route for combining more than two different natural products *via* click chemistry.

3.8. EXPERIMENTAL

3.8.1. General Procedures:

General Procedure for synthesis of 4-azido THPs (8a-k):

4-Tosyloxy THP (1 mmol) was dissolved in 3 mL of *N*,*N*-dimethylformamide then sodium azide (3 mmol) was added the resulting solution was stirred at 100 ^{0}C for 1h. TLC monitoring, after completion of reaction was added excess ice cold water and stirred for 30 min. In most of the cases precipitate formed if not extract with chloroform, and wash with brine solution dried over anhydrous Na_2SO_4, concentrate in *vacuo* to obtain pure 4-azido THPs. This azide can use without purification in further reactions.

Synthesis of 3-(2-propynyloxy)-flavone derivatives (9a-e):

3-Flavonol (1 mmol) was dissolved in 20mL of dry acetone and 1mL of 3-bromo-1-propyne was added. The resulting mixture was stirred at room temperature for 15 min, followed by addition of potassium carbonate (3 mmol). The mixture was stirred at 65 ℃ for 12 h. Then, 20mL of CH_2Cl_2 was added into the reaction mixture and washed with brine and water, then dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. This alkyne we used without purification in further reactions.

General Procedure for synthesis of 5-iodo-1,2,3-triazoles (10a-l):

A mixture of azide (1 mmol), alkyne (1 mmol), CuI (1.2 mmol), DIPEA (2.5 mmol) in 10 mL of THF was stirred at room temperature for 10 min. followed by added NBS (1.1 mmol) the resulting solution stirred for 1 h. after completion of reaction the solvent was evaporated, and diluted with chloroform and washed with brine and water then extracted with chloroform (3x15mL). The

combined organic layers dried over anhydrous Na_2SO_4, and solvent evaporated in *vacuo* and purified using silicagel column chromatography.

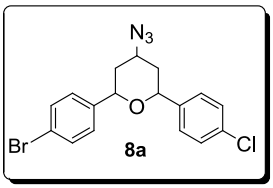
General Procedure for synthesis of 5-*H*-1,2,3-triazoles (11a-j):

A mixture of azide (1.15 mmol), alkyne (1 mmol), DIPEA (2.5 mmol) was dissolved in 4 mL of THF. Then added a mixture of $CuSO_4.5H_2O$ (3 mol%) and sodium ascorbate (10 mol%) in 2mL of water. The resulting solution stirred at 66 ^{0}C for 3h. TLC monitoring, after completion of reaction solvent evaporated and compound became precipitated, wash with water and dry to obtain pure products.

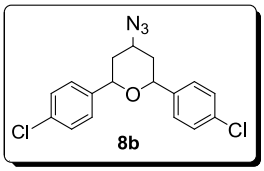
General Procedure for synthesis of 5-phenyl-1,2,3-triazoles 12a-b:

In a flame dried round bottom flask was taken 5-iodo-1,2,3-triazole (0.1 mmol) in THF (3 mL) and purge with nitrogen gas for 5min. then added phenylboronic acid (0.15 mmol) and $PdCl_2(PPh_3)_2$ (4 mol%) again purge with nitrogen gas for 2 min. The resulting mixture stirred at 70 °C for 4–5 h. After completion of reaction solvent evaporated, the crude was diluted with chloroform and washed with brine solution and extracted with chloroform (3x5mL). The combined organic layer dried over anhydrous Na_2SO_4. Product was purified on a silica gel column chromatography with hexane : EtOAc 7:3 as eluent.

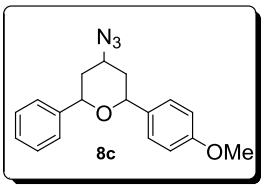
3.8.2. SPECTROSCOPIC DATA



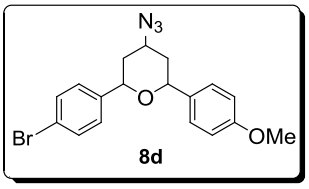
4-Azido-2-(4-bromophenyl)-6-(4-chlorophenyl)tetrahydropyran (8a):
Yield 95%; light yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.48 (dd, *J* = 1.5, 6.5Hz, 2H), 7.33 (d, *J* = 2.5Hz, 4H), 7.28 (d, *J* = 8.5Hz, 2H), 4.87 (t, *J* = 9.5Hz, 2H), 4.24 (m, 1H), 2.02 (d, *J* = 12.5Hz, 2H), 1.86-1.80 (m, 2H). **IR (KBr, cm^{-1})**: 3010, 2922, 2114, 1426, 1025. **HRMS (ESIMS)**: Anal. calcd for $C_{17}H_{15}BrClN_3NaO$ $(M+Na)^+$ 413.9985; found 413.9999.



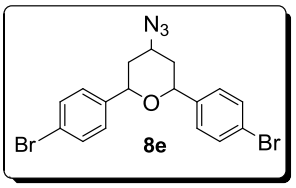
4-Azido-2,6-bis(4-chlorophenyl)tetrahydropyran (8b):
Yield 95%; light yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.34 (s, 8H), 4.54 (dd, *J* = 2, 12Hz, 2H), 4.29 (tt, *J* = 3, 12Hz, 1H), 2.44 (m, 2H), 1.88 (q, *J* = 12Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm) 141.40, 128.53, 127.86, 125.93, 79.04, 55.73, 44.36. **IR (KBr, cm^{-1})**: 3032, 2915, 2121, 1413, 1023. **HRMS (ESIMS):** Anal. calcd for $C_{17}H_{15}Cl_2N_3NaO$ $(M+Na)^+$ 370.0490; found 370.0478.



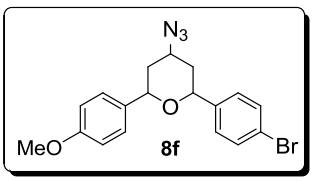
4-Azido-2-(4-methoxyphenyl)-6-(4-chlorophenyl)tetrahydropyran (8c): Yield 92%; light yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.37-7.33 (m, 7H), 6.92 (d, *J* = 8.5Hz, 2H), 4.89 (td, *J* = 1.5, 11.5Hz, 2H), 4.23 (t, *J* = 3Hz, 1H), 3.81 (s, 3H), 2.05-2.0 (m, 2H), 1.90 (dddd, *J* = 3.5, 12, 15, 26Hz, 1H), 1.82 (dddd, *J* = 3.5, 12, 15, 26Hz, 1H). **IR (KBr, cm^{-1})**: 3021, 2923, 2106, 1440, 1022. **HRMS (ESIMS)**: Anal. calcd for $C_{18}H_{19}N_3NaO_2$ $(M+Na)^+$ 332.1375; found 332.1389.



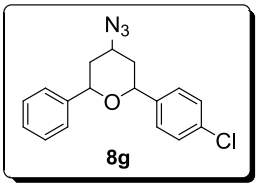
4-Azido-2-(4-bromophenyl)-6-(4-methoxyphenyl)tetrahydropyran (8d): Yield 92%; light yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.70 (s, 4H), 7.18 (s, 2H), 7.06-7.02 (m, 2H), 4.56 (m, 2H), 4.23 (m, 1H), 3.50 (s, 3H), 1.95 (s, 2H), 1.72-1.51 (m, 2H). **IR (KBr, cm^{-1})**: 3031, 2933, 2116, 1420, 1032. **HRMS (ESIMS)**: Anal. calcd for $C_{18}H_{18}BrN_3NaO_2$ $(M+Na)^+$ 410.0480; found 410.0491.



4-azido-2,6-bis(4-bromophenyl)tetrahydropyran (8e): Yield 95%; light yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.51 (d, *J* = 7Hz, 4H), 7.32 (d, *J* = 6.5Hz, 4H), 4.89 (d, *J* = 1.5Hz, 2H), 4.22 (s, 1H), 2.03 (d, *J* = 14Hz, 2H), 1.82 (t, *J* = 3.5, 12Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 140.91, 131.40, 127.40, 121.28, 73.74, 55.82, 36.98. **IR (KBr, cm^{-1})**: 3033, 2934, 2115, 1421, 1033. **HRMS (ESIMS):**Anal. calcd for $C_{17}H_{15}Br_2N_3NaO$ $(M+Na)^+$ 457.9480; found 457.9471.

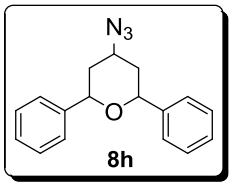


4-azido-2-(4-methoxyphenyl)-6-(4-bromophenyl)tetrahydropyran (8f): Yield 95%; light yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm) 7.70 (s, 4H), 7.18 (s, 2H), 7.06-7.02 (m, 2H), 4.56 (m, 2H), 4.23 (m, 1H), 3.50 (s, 3H), 1.95 (s, 2H), 1.72-1.51 (m, 2H). **IR (KBr, cm^{-1})**: 3036, 2936, 2116, 1425, 1036. **HRMS (ESIMS):**Anal. calcd for $C_{18}H_{18}BrN_3NaO_2$ $(M+Na)^+$ 410.0480; found 410.0492.



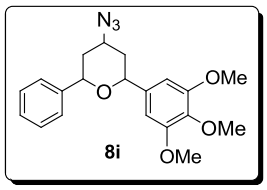
4-azido-2-phenyl-6-(4-chlorophenyl)tetrahydropyran (8g): Yield 95%; light yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.51 (td, *J* = 1.5, 9.5Hz, 2H), 7.45 (td, *J* = 3.5, 7.5, 3H), 7.42-7.40 (m, 3H), 7.40-7.36 (m, 1H), 5.01-4.92 (m, 2H), 4.22 (m, 1H), 2.11-2.03 (m, 2H), 1.93-1.82 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 142.12, 128.38, 128.31, 128.26, 127.41, 127.06, 125.68,

125.65, 74.37, 73.65, 55.94, 43.69. **IR (KBr, cm^{-1})**: 3026, 2926, 2106, 1435, 1046. **HRMS (ESIMS)**: Anal. calcd for $C_{17}H_{16}ClN_3NaO$ $(M+Na)^+$ 336.0880; found 336.0882.



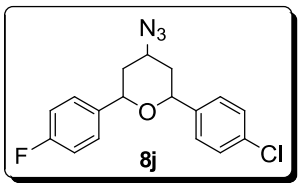
4-azido-2,6-bis(phenyl)tetrahydropyran (8h):

Yield 94%; light yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.47 (d, *J* = 7.5Hz, 4H), 7.40 (t, *J* = 8Hz, 4H), 7.33-7.30 (m, 2H), 4.95 (d, *J* = 11.5Hz, 2H), 4.26 (t, *J* = 3Hz, 1H), 2.08 (dd, *J* = 2, 14.5Hz, 2H), 1.92 (td, *J* = 3, 11.5Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 142.21, 128.43, 127.60, 125.87, 125.84, 74.56, 56.27, 37.34. **IR (KBr, cm^{-1})**: 3021, 2921, 2101, 1431, 1041. **HRMS (ESIMS)**: Anal. calcd for $C_{17}H_{17}N_3NaO$ $(M+Na)^+$ 302.1269; found 302.1261.



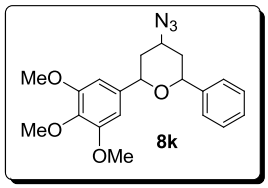
4-azido-2-phenyl-6-(3,4,5-trimethoxyphenyl)tetrahydropyran (8i):

Yield 90%; light yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.41 (d, *J* = 7.5Hz, 2H), 7.35 (d, *J* = 7.5Hz, 2H), 7.25-7.27 (m, 1H), 6.65 (s, 2H), 4.90 (dd, *J* = 2, 11.5, 1H), 4.83 (dd, *J* = 2, 11.5Hz, 1H), 4.26 (t, *J* = 3Hz, 1H), 3.87 (s, 6H), 3.82 (s, 3H), 2.06-2.01 (m, 4H). **IR (KBr, cm^{-1})**: 3031, 2931, 2111, 1432, 1031. **HRMS (ESIMS)**: Anal. calcd for $C_{20}H_{23}N_3NaO_4$ $(M+Na)^+$ 392.1586; found 392.1578.



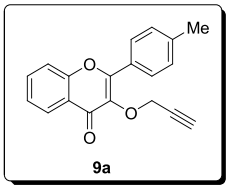
4-azido-2-(4-fluorophenyl)-6-(4-chlorophenyl)tetrahydropyran 8j:

Yield 94%; light yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.39-7.32 (m, 6H), 7.04 (t, *J* = 9Hz, 2H), 4.88 (d, *J* = 11.5Hz, 2H), 4.25 (m, 1H), 2.03 (dd, *J* = 6.5Hz, 2H), 1.87 (q, *J* = 11.5Hz, 2H). **IR (KBr, cm^{-1})**: 3026, 2926, 2106, 1435, 1046. **HRMS (ESIMS)**: Anal. calcd for $C_{17}H_{15}ClFN_3NaO$ $(M+Na)^+$ 354.0785; found 354.0798.



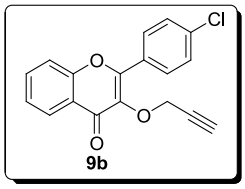
4-azido-2-(3,4,5-trimethoxyphenyl)-6-phenyl tetrahydropyran 8k:

Yield 90%; light yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 7.41 (d, *J* = 7.5Hz, 2H), 7.35 (d, *J* = 7.5Hz, 2H), 7.25-7.27 (m, 1H), 6.65 (s, 2H), 4.90 (dd, *J* = 2, 11.5, 1H), 4.83 (dd, *J* = 2, 11.5Hz, 1H), 4.26 (t, J = 3Hz, 1H), 3.87 (s, 6H), 3.82 (s, 3H), 2.06-2.01 (m, 4H). **IR (KBr, cm^{-1})**: 2996, 2912, 2108, 1423, 1078. **HRMS (ESIMS)**: Anal. calcd for $C_{20}H_{23}N_3NaO$ $(M+Na)^+$ 392.1586; found 392.1595.



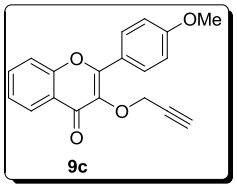
3-(2-propynyloxy)-2-p-tolyl-4*H*-chromen-4-one (9a):

Yield 75%; light yellow solid. **^{1}H NMR (500 MHz, CDCl3)**: δ (ppm) 8.25 (dd, *J* = 1.5, 8Hz, 1H), 8.04 (d, *J* = 8Hz, 2H), 7.68 (td, *J* = 1.5, 7Hz, 1H), 7.54 (d, *J* = 8.5Hz, 1H), 7.40 (t, *J* = 8Hz, 1H), 7.31(d, *J* = 8.5Hz, 3H), 4.97 (d, *J* = 2.5Hz, 2H), 2.44 (s, 3H), 2.33 (t, *J* = 2.5Hz, 1H). **HRMS (ESIMS)**: Anal. calcd. for $C_{19}H_{14}NaO_3$ $(M+Na)^+$ 313.0841; found 313.0864.



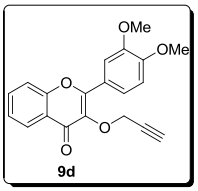
3-(2-propynyloxy)-2-(4-chlorophenyl)-4*H*-chromen-4-one (9b):

Yield 78%; light yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 8.26 (dd, *J* = 1.5, 8Hz, 1H), 8.12 (d, *J* = 8.5Hz, 2H), 7.71 (td, *J* = 1.5,7Hz, 1H), 7.55 (d, *J* = 8.5Hz, 1H), 7.49 (d, *J* = 8.5Hz, 2H), 7.43 (td, *J* = 1, 7.5Hz, 1H), 5.00 (d, *J* = 2Hz, 2H), 2.32 (t, *J* = 2.5Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 174.8, 155.54, 138.69, 136.95, 133.79, 130.31, 129.41, 128.72, 125.85, 124.99, 123.98, 118.05, 78.51, 76.42, 59.23. **HRMS (ESIMS)**: Anal. calcd. for $C_{18}H_{11}ClNaO_3$ $(M+Na)^+$ 333.0294; found 333.0282.



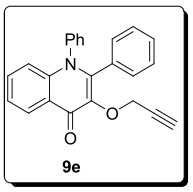
3-(2-propynyloxy)-2-(4-methoxyphenyl)-4*H*-chromen-4-one (9c):

Yield 82%; light yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 8.28 (dd, *J* = 1.5, 8.5Hz, 1H), 8.19 (d, *J* = 2, 7Hz, 2H), 7.71 (td, *J* = 2, 7Hz, 1H), 7.57 (dd, *J* = 0.5, 8.5Hz, 1H), 7.43 (td, *J* = 1, 7Hz, 1H), 7.05 (d, *J* = 9Hz, 2H), 5.01 (d, *J* = 2.5Hz, 2H), 3.93 (s, 3H), 2.36 (t, *J* = 2.5Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 173.65, 163.18, 161.36, 155.90, 154.65, 137.28, 134.14, 130.48, 125.21, 124.90, 123.25, 122.58, 118.44, 114.08, 79.24, 78.83, 58.54, 55.49. **HRMS (ESIMS)**: Anal. calcd for $C_{19}H_{14}NaO_4$ $(M+Na)^+$ 329.0790; found 329.0782.



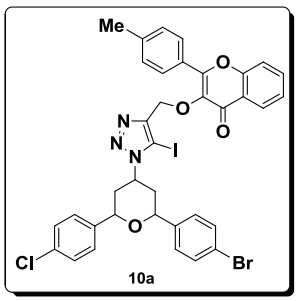
3-(2-propynyloxy)-2-(3,4-dimethoxyphenyl)-4*H*-chromen-4-one (9d):

Yield 80%; light yellow solid. **^{1}H NMR (500 MHz, $(CD_3)_2SO$)**: δ (ppm) 8.11 (d, *J* = 8Hz, 1H), 7.85-7.78 (m, 4H), 7.52 (t, *J* = 7Hz, 1H), 7.18 (d, *J* = 8.5Hz, 1H), 4.99 (s, 2H), 3.89 (s, 6H), 3.55 (s, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm) 174.62, 156.22, 155.02, 151.16, 148.42, 138.11, 133.36, 125.61, 124.66, 123.86, 123.22, 122.30, 117.86, 111.92, 110.57, 78.79, 76.01, 59.08, 56.02, 55.89. **HRMS (ESIMS)**: Anal. calcd. for $C_{20}H_{16}NaO_5$ $(M+Na)^+$ 359.0895; found 359.0888.



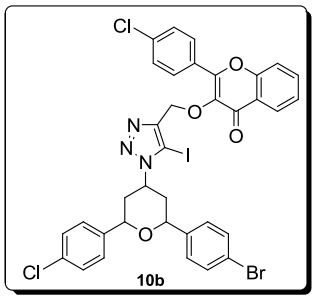
3-(2-propynyloxy)-2-phenyl-4*H*-chromen-4-one (9e):

Yield 70%; light yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm) 8.57 (d, *J* = 8Hz, 1H), 7.45 (t, *J* = 8.5Hz, 1H), 7.36 (t, *J* = 7.5Hz, 1H), 7.33-7.28 (m, 3H), 7.18 (s, 5H), 7.12 (d, *J* = 7.5Hz, 2H), 6.84 (d, *J* = 8.5Hz, 1H), 4.94 (s, 2H), 2.31 (s, 1H). **HRMS (ESIMS)**: Anal. calcd. for $C_{24}H_{17}NNaO_2$ $(M+Na)^+$ 374.1157; found 374.1180.



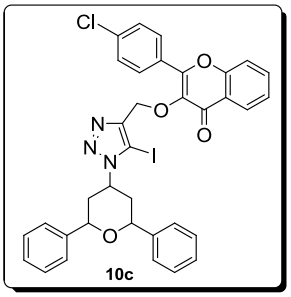
3-((1-(2-(4-bromophenyl)-6-(4-chlorophenyl)-4-tetrahydropyranyl)-5-iodo-1*H*-1,2,3-triazol)-4-methoxyl)-2-(p-tolyl)-4*H*-chromen-4-one (10a):

Yield 95%; light yellow solid; mp 175-176 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm) 8.29 (dd, *J* = 1.5, 8Hz, 1Hz), 7.92 (d, *J* = 8Hz, 2H), 7.68 (td, *J* = 1.5, 7Hz, 1H), 7.54 (d, *J* = 8.5Hz, 1H), 7.47 (d, *J* = 8.5Hz, 2H), 7.40 (td, *J* = 1, 8Hz, 1H), 7.32 (s, 4H), 7.27 (d, *J* = 7Hz, 2H), 7.20 (d, *J* = 8Hz, 2H), 5.29 (s, 2H), 5.29-5.25 (m, 2H), 4.85 (m, 1H), 2.32 (s, 3H), 2.17 (dd, *J* = 4, 14.5Hz, 2H), 2.12-2.07 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm) 175.19, 157.09, 155.50, 147.41, 141.14, 141.05, 140.53, 138.99, 133.70, 133.58, 131.72, 129.23, 128.86, 128.77, 128.09, 127.77, 127.43, 126.00, 124.96, 124.37, 121.70, 118.23, 82.69, 73.94, 64.39, 55.16, 36.96, 36.92, 21.68. **IR (KBr, cm^{-1})**: 2953, 2921, 1628, 1617, 1554, 1467, 1233, 1067, 820. **HRMS (ESIMS)**: Anal. calcd for $C_{36}H_{28}BrClIN_3NaO_4$ $(M+Na)^+$ 829.9894; found 829.9837.



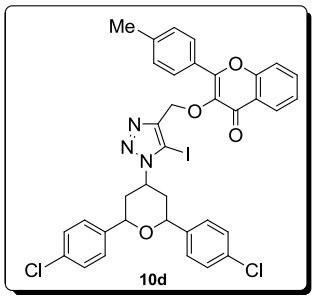
3-((1-(2-(4-bromophenyl)-6-(4-chlorophenyl)-4-tetrahydropyranyl)-5-iodo-1*H*-1,2,3-triazol)-4-methoxyl)-2-(4-chlorophenyl)-4*H*-chromen-4-one (10b):

Yield 98%; light yellow solid; mp 160-162 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 8.30 (dd, *J* = 1.5, 8Hz, 1H), 7.96 (dd, *J* = 1.5, 7Hz, 2H), 7.71 (td, *J* = 1.5, 7Hz, 1H), 7.53 (d, *J* = 8.5Hz, 1H), 7.48 (d, *J* = 8.5Hz, 2H) 7.43 (td, *J* = 1, 8Hz, 1H), 7.37 (d, *J* = 9Hz, 2H), 7.33 (s, 4H), 7.27 (d, *J* = 8Hz, 2H), 5.31 (s, 2H), 5.27-5.24 (m, 2H), 4.85 (m, 1H), 2.19-2.10 (m, 4H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 174.88, 155.45, 155.22, 147.05, 140.74, 140.21, 139.07, 136.54, 133.75, 133.37, 131.51, 130.07, 129.13, 128.56, 128.56, 128.50, 127.54, 127.20, 125.85, 124.96, 124.10, 121.50, 118.00, 82.47, 73.71, 64.34, 55.04, 36.71, 36.67. **IR (KBr, cm^{-1})**: 2965, 2928, 1625, 1611, 1565, 1482, 1213, 1082, 831. **HRMS (ESIMS)**: Anal. calcd for $C_{35}H_{25}BrCl_2IN_3NaO_4$ $(M+Na)^+$ 849.9347; found 849.9295.



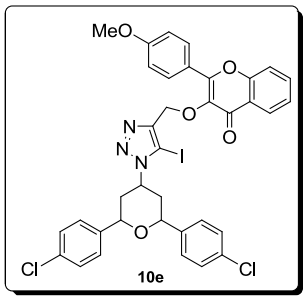
3-((1-(2,6-diphenyl-4-tetrahydropyranyl)-5-iodo-1H-1,2,3-triazol)-4-methoxyl)-2-(4-chlorophenyl)-4*H*-chromen-4-one (10c):

Yield 96%; light yellow solid; mp 149-150 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 8.31 (dd, *J* = 1.5, 8Hz, 1H), 7.94 (d, *J* = 9Hz, 2H), 7.71 (td, *J* = 1.5, 7Hz, 1H), 7.53 (d, *J* = 8.5Hz, 1H), 7.42-7.40 (m, 5H), 7.37-7.22 (m, 6H), 7.29-7.28 (m, 2H), 5.32 (s, 2H), 5.29-5.25 (m, 2H), 4.85-4.84 (m, 1H), 2.21 (d, *J* = 3.5Hz, 2H), 2.18 (d, *J* = 5H). **IR (KBr, cm^{-1})**: 2943, 2918, 1635, 1602, 1542, 1490, 1234, 1090, 846. **HRMS (ESIMS)**: Anal. calcd for $C_{35}H_{27}ClIN_3NaO_4$ $(M+Na)^+$ 738.0632; found 738.0637.



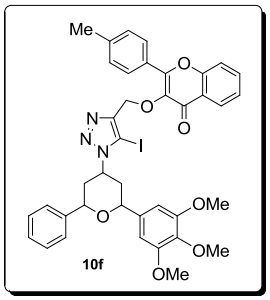
3-((1-(2,6-bis(4-chlorophenyl)-4-tetrahydropyranyl)-5-iodo-1H-1,2,3-triazol)-4-methoxyl)-2-(4-chlorophenyl)-4*H*-chromen-4-one (10d):

Yield 96%; light yellow solid; mp 125-126 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm) 8.29 (dd, *J* = 1, 8Hz, 1H), 7.93 (d, *J* = 8.5Hz, 2H), 7.71-7.67 (m, 1H), 7.53 (d, *J* = 5.5Hz, 1H), 7.41 (t, *J* = 7H), 7.33 (s, 8H), 7.20 (d, *J* = 8Hz, 2H), 5.29 (s, 2H), 5.27 (dd, *J* = 2, 8Hz, 2H), 4.86 (m, 1H), 2.32 (s, 3H), 2.18 (d, *J* = 14.5Hz, 2H), 2.12 (dd, *J* = 5, 11.5Hz, 2H).**^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm) 175.24, 157.17, 155.52, 147.41, 141.17, 140.55, 139.01, 133.73, 133.59, 129.24, 128.88, 128.78, 128.09, 127.44, 126.01, 124.99, 124.36, 118.24, 82.69, 73.93, 64.41, 55.21, 37.11, 21.67. **IR (KBr, cm^{-1}) *v*:** 2954, 2911, 1622, 1612, 1565, 1456, 1211, 1087, 835. **HRMS (ESIMS)**: Anal. calcd for $C_{36}H_{28}Cl_2IN_3NaO_4$ $(M+Na)^+$ 786.0399; found 738.0381.



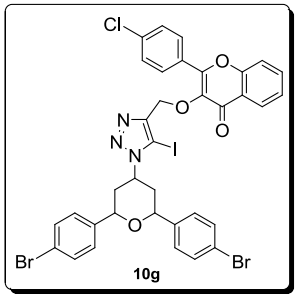
3-((1-(2,6-bis(4-chlorophenyl)-4-tetrahydropyranyl)-5-iodo-1H-1,2,3-triazol)-4-methoxyl)-2-(4-methoxyphenyl)-4*H*-chromen-4-one (10e):

Yield 95%; light yellow solid; mp 169-170 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm) 8.25 (d, *J* = 7.5Hz, 1H), 8.01 (d, *J* = 8Hz, 2H), 7.65 (t, *J* = 8Hz,1H), 7.50 (d, *J* = 8Hz, 1H), 7.37 (t, *J* = 7Hz, 2H), 7.29 (m, 8H), 6.88 (d, *J* = 8Hz, 2H), 5.26 (t, *J* = 11Hz, 4H), 4.84 (m, 1H), 3.74 (s, 3H), 2.11 (d, *J* = 14Hz, 2H), 2.08 (d, *J* = 11Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 177.82, 174.89, 161.29, 156.71, 155.18, 140.37, 138.41, 133.31, 130.52, 128.54, 127.25, 125.74, 124.75, 124.09, 122.96, 118.00, 113.77, 113.69, 73.69, 64.12, 55.02, 36.72. **IR (KBr, cm^{-1})**: 2966, 2902, 1654, 1623, 1555, 1445, 1213, 1086, 826. **HRMS (ESIMS):** Anal. calcd for $C_{36}H_{28}Cl_2IN_3NaO_5$ $(M+Na)^+$ 802.0348; found 802.0330.



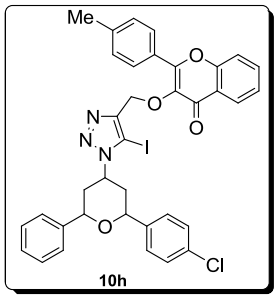
3-((1-(2-phenyl-6-(3,4,5-trimethoxyphenyl)-4-tetrahydropyranyl)-5-iodo-1H-1,2,3-triazol)-4-methoxyl)-2-(*p*-tolyl)-4*H*-chromen-4-one (10f):

Yield 90%; light yellow solid; mp 133-135 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 8.30 (dd, *J* = 1.5, 8Hz, 1H), 7.91 (d, *J* = 8Hz, 2H), 7.68 (td, *J* = 2, 7.5Hz, 1H), 7.54 (d, *J* = 8.5Hz, 1H), 7.39 (d, *J* = 8.5Hz, 3H), 7.35 (t, *J* = 7.5Hz, 2H), 7.28 (dd, *J* = 1.5, 8.5Hz, 1H), 7.19 (d, *J* = 8.5Hz, 2H), 6.66 (s, 2H), 5.31-5.23 (m, 4H), 4.87-4.86 (m, 1H), 3.87 (s, 6H), 3.81 (s, 3H), 2.30 (s, 3H), 2.22-2.18 (m, 4H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 175.07, 157.07, 155.37, 153.28, 147.16, 141.90, 141.01, 138.85, 137.80, 137.48, 133.55, 129.09, 128.70, 128.44, 127.91, 127.73, 125.97, 125.85, 124.81, 124.21, 118.08, 103.24, 82.55, 74.44, 64.31, 60.83, 56.23, 55.38, 36.86, 21.48. **IR (KBr, cm^{-1})**: 2974, 2931, 1646, 1632, 1565, 1454, 1231, 1068, 862. **HRMS (ESIMS)**: Anal. calcd for $C_{39}H_{36}IN_3NaO_7$ $(M+Na)^+$ 808.1496; found 808.1470.



3-((1-(2,6-bis(4-bromophenyl)-4-tetrahydropyranyl)-5-iodo-1*H*-1,2,3-triazol)-4-methoxyl)-2-(4-chlorophenyl)-4*H*-chromen-4-one (10g):

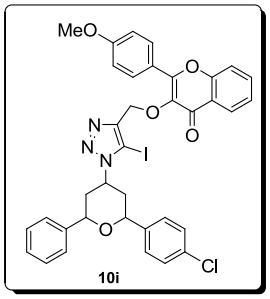
Yield 98%; light yellow solid; mp 174-176 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 8.29 (dd, *J* = 1.5, 8Hz, 1H), 7.96 (d, *J* = 9Hz, 2H), 7.70 (ddd, *J* = 1.5, 7, 8.5Hz, 1H), 7.52 (d, *J* = 8Hz, 1H), 7.50 (d, *J* = 8.5Hz, 1H), 7.48 (d, *J* = 8.5Hz, 4H), 7.42 (td, *J* = 1, 8.5Hz, 1H), 7.37 (d, *J* = 9Hz, 2H), 7.32 (d, *J* = 8Hz, 1H), 7.27 (d, *J* = 8Hz, 2H), 5.31 (s, 2H), 5.24 (d, *J* = 2.0, 11Hz, 2H), 4.86-4.84 (m, 1H), 2.20-2.11 (m, 2H), 2.12 (dd, *J* = 4.5, 11.5Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 175.12, 155.70, 155.47, 147.30, 140.98, 139.33, 136.79, 133.97, 131.87, 131.74, 130.31, 129.37, 128.73, 127.76, 126.09, 125.19, 124.34, 121.74, 118.22, 82.64, 73.94, 64.58, 55.29, 36.90. **IR (KBr, cm^{-1})**: 2922, 2844, 1628, 1614, 1488, 1407, 1194, 1070, 1018, 817, 756. **HRMS (ESIMS)**: Anal. calcd for $C_{35}H_{25}Br_2ClIN_3NaO_4$ $(M+Na)^+$ 893.8843; found 893.8810.



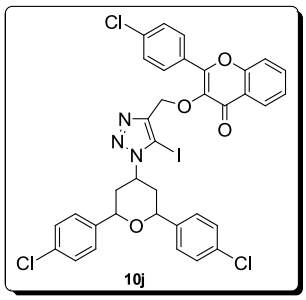
3-((1-(2-phenyl-6-(4-chlorophenyl)-4-tetrahydropyranyl)-5-iodo-1*H*-1,2,3-triazol)-4-methoxyl)-2-(*p*-tolyl)-4*H*-chromen-4-one (10h):

Yield 97%; light yellow solid; mp 145-146 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 8.33-8.31 (m, 1H), 7.94 (d, *J* = 8.5Hz, 1H), 7.72-7.69 (m, 2H), 7.55 (d, *J* = 8Hz, 1H), 7.43 (d, *J* = 8Hz, 2H), 7.42 (d, *J* = 9Hz, 2H), 7.39 (d, *J* = 2Hz, 1H), 7.38-7.37 (m, 3H), 7.35 (s, 2H), 7.23-7.21 (m, 2H), 5.33-5.26 (m, 4H), 4.6 (m, 1H), 2.37-2.32 (m, 5H), 2.22-2.19 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm)

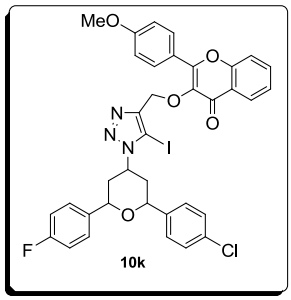
175.20, 157.15, 155.48, 147.32, 142.25, 141.97, 141.11, 140.80, 140.52, 138.97, 133.67, 129.19, 128.84, 128.73, 128.68, 128.59, 128.54, 128.04, 127.43, 127.41, 126.15, 126.04, 124.92, 118.20, 82.63, 74.47, 64.39, 55.35, 36.98, 21.61. **IR (KBr, cm^{-1})**: 2954, 2913, 1635, 1619, 1522, 1441, 1202, 1091, 815. **HRMS (ESIMS)**: Anal. calcd for $C_{36}H_{29}ClIN_3NaO_4$ $(M+Na)^+$ 752.0789; found 752.0770.



3-((1-(2-phenyl-6-(4-chlorophenyl)-4-tetrahydropyranyl)-5-iodo-1*H*-1,2,3-triazol)-4-methoxyl)-2-(4-methoxyphenyl)-4*H*-chromen-4-one (10i): Yield 95%; light yellow solid; mp 165-166 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 8.29-8.27 (m, 1H), 8.03-8.01 (m, 1H), 7.51 (d, *J* = 8.5Hz, 1H), 7.36-7.32 (m, 4H), 7.32 (s, 2H), 7.30-7.26 (m, 1H), 6.91 (d, *J* = 8.5Hz, 2H), 5.30 (s, 2H), 5.28 (s, 2H), 4.86 (m, 1H), 3.75 (s, 3H), 2.20-2.10 (m, 4H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 175.03, 161.43, 156.86, 155.35, 142.22, 141.94, 140.77, 140.49, 138.56, 133.53, 133.34, 130.63, 128.62, 128.53, 128.48, 127.83, 127.71, 127.37, 125.99, 124.83, 123.14, 118.06, 113.86, 74.41, 73.82, 64.27, 55.41, 53.54, 37.04, 36.96. **IR (KBr, cm^{-1})**: 2945, 2931, 1653, 1639, 1522, 1414, 1220, 1067, 821. **HRMS (ESIMS)**: Anal. calcd for $C_{36}H_{29}ClIN_3NaO_5$ $(M+Na)^+$ 768.0738; found 768.0738.

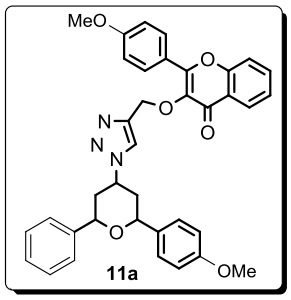


3-((1-(2,6-bis(4-chlorophenyl)-4-tetrahydropyranyl)-5-iodo-1*H*-1,2,3-triazol)-4-methoxyl)-2-(4-chlorophenyl)-4*H*-chromen-4-one (10j): Yield 98%; light yellow solid; mp 155-156 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 8.30 (dd, *J* = 1, 7.5Hz, 1H), 7.99 (d, *J* = 8.5Hz, 2H), 7.72 (t, *J* = Hz, 1H), 7.54 (d, *J* = 8.5Hz, 1H), 7.44 (t, *J* = 7.5Hz, 1H), 7.38 (d, *J* = 8.5Hz, 3H), 7.34 (s, 9H), 5.33 (s, 2H), 5.27 (dd, *J* = 2, 11Hz, 2H), 4.87 (m, 1H), 2.21-2.13 (m, 4H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 174.97, 163.61, 155.54, 155.29, 147.10, 140.42, 140.31, 140.16, 139.13, 136.62, 133.43, 133.25, 129.18, 128.63, 128.59, 128.56, 127.29, 127.19, 125.97, 125.83, 125.10, 125.01, 124.15, 82.65, 73.81, 64.41, 55.20, 36.38. **IR (KBr, cm^{-1})**: 2955, 2941, 1663, 1629, 1532, 1424, 1210, 1057, 813. **HRMS (ESIMS)**: Anal. calcd for $C_{35}H_{25}Cl_3IN_3NaO_4$ $(M+Na)^+$ 805.9853; found 805.9828.



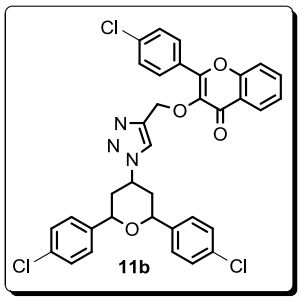
3-((1-(2-(4-fluorophenyl)-6-(4-chlorophenyl)-4-tetrahydropyranyl)-5-iodo-1*H*-1,2,3-triazol)-4-methoxyl)-2-(4-methoxyphenyl)-4*H*-chromen-4-one (10k):

Yield 96%; light yellow solid; mp 159-160 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 8.29 (d, *J* = 7.5 Hz, 1H), 8.05 (d, *J* = 8.5Hz, 2H), 7.68 (t, *J* = 7.5Hz, 1H), 7.53 (d, *J* = 8.5Hz, 1H), 7.42-7.33 (m, 3H), 7.34 (s, 4H), 7.05 (t, *J* = 8.5Hz, 2H), 6.92 (d, *J* = 8.5Hz, 2H), 5.31 (s, 2H), 5.30-5.27 (m, 2H), 4.88 (m, 1H), 3.77 (s, 3H), 2.20-2.06 (m, 4H), **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 174.92, 161.33. 156.72, 155.24, 147.29, 140.48, 138.46, 137.70, 133.37, 130.56, 128.59, 127.66, 127.28, 125.78, 124.76, 124.16, 123.04, 118.03, 115.35, 115.18, 113.72, 82.64, 73.80, 64.16, 55.10, 36.81. **IR (KBr, cm^{-1}):** 2955, 2931, 1653, 1649, 1522, 1414, 1250, 1067, 873. **HRMS (ESIMS)**: Anal. calcd for $C_{36}H_{28}FClIN_3NaO_5$ $(M+Na)^+$ 786.0644; found 786.0631.



3-((1-(2-(4-methoxyphenyl)-6-phenyl-4-tetrahydropyranyl)-1*H*-1,2,3-triazol)-4-methoxyl)-2-(4-methoxyphenyl)-4*H*-chromen-4-one (11a):

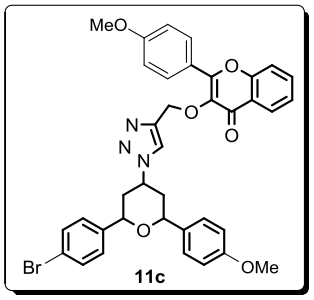
Yield 96%; light yellow solid; mp 125-126 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 8.2 -8.12 (m, 2H), 8.2-7.95 (m, 1H), 7.65-7.50 (m, 2H), 7.40-7.30 (m, 7H), 6.96-6.87 (m, 4H), 5.36 (m, 1H), 4.86 (m, 2H), 3.66 (s, 3H), 3.76 (s, 3H), 1.86 (m, 2H), 2.24 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 174.93, 161.60, 159.14, 156.39, 155.14, 140.49, 138.86, 133.79, 133.45, 133.16, 130.48, 128.48, 127.16, 127.11, 125.59, 124.76, 122.91, 117.99, 113.93, 113.80, 74.08, 73.80, 65.01, 55.31, 54.73, 37.03. **IR (KBr, cm^{-1})**: 2935, 2921, 1656, 1626, 1523, 1442, 1201, 1075, 831. **HRMS (ESIMS)**: Anal. calcd for $C_{37}H_{33}N_3NaO_6$ $(M+Na)^+$ 638.2267; found 638.2261.



3-((1-(2,6-bis(4-chlorophenyl)-4-tetrahydropyranyl)-1*H*-1,2,3-triazol)-4-methoxyl)-2-(4-chlorophenyl)-4*H*-chromen-4-one (11b):

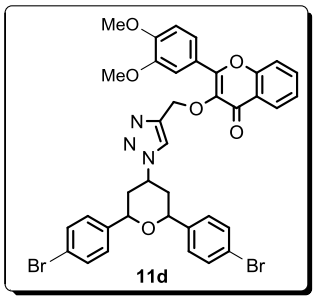
Yield 98%; light yellow solid; mp 145-146 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 8.25 (d, *J* = 5.5Hz, 1H), 8.09 (d, *J* = 6Hz, 2H), 8.00 (s, 1H), 7.70 (m, 1H), 7.53 (d, *J* = 7.5Hz, 1H), 7.45 (d, *J* = 7Hz, 2H), 7.41 (s, 1H), 7.33 (s, 7H), 5.38 (s, 2H), 4.93 (d, *J* = 8.5, 2H), 4.90 (m, 1H), 2.53 (dd, *J* = 4, 14Hz, 2H), 2.16-2.09 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 175.08, 164.00, 155.20, 140.16, 139.68, 137.06, 133.87, 133.40, 130.08, 129.13, 128.83, 128.62, 127.17, 125.70, 125.06, 124.00, 118.11, 73.89, 65.17, 54.62, 37.07. **IR (KBr, cm^{-1})**: 2944, 2911, 1644, 1622, 1533, 1422,

1211, 1066, 822. **HRMS (ESIMS)**: Anal. calcd for $C_{35}H_{26}Cl_3N_3NaO_4$ $(M+Na)^+$ 680.0887; found 680.0862.



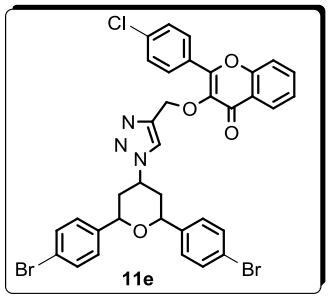
3-((1-(2-(4-chlorophenyl)-6-(4-methoxyphenyl)-4-tetrahydropyranyl)-1*H*-1,2,3-triazol)-4-methoxyl)-2-(4-methoxyphenyl)-4*H*-chromen-4-one (11c):

Yield 96%; light yellow solid; mp 152-154 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 8.25 (d, *J* = 7.5Hz, 1H), 8.12 (d, *J* = 9Hz, 2H), 7.93 (s, 1H), 7.68 (t, 7Hz, 1H), 7.52 (d, *J* = 8.5Hz, 1H), 7.48 (d, *J* = 8Hz, 2H), 7.40 (t, *J* = 7.5Hz,1H), 7.31 (d, *J* = 8.5Hz, 2H), 7.27 (d, *J* = 9.5Hz, 1H), 6.97 (d, *J* = 9Hz, 2H), 6.88 (d, *J* = 8.5Hz, 2H), 5.36 (s, 2H), 4.88-4.81 (m, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 2.56 (m, 2H), 2.26-2.10 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 175.07, 163.24, 161.69, 159.21, 156.52, 155.23, 141.07, 133.85, 131.50, 130.56, 127.57, 127.17, 125.70, 124.84, 123.01, 121.39, 118.05, 114.01, 113.87, 74.14, 73.91, 55.40, 55.35, 37.08, 29.74, 1.07. **IR (KBr, cm^{-1})**: 2975, 2921, 1673, 1639, 1552, 1414, 1230, 1077, 812. **HRMS (ESIMS)**: Anal. calcd for $C_{37}H_{32}BrN_3NaO_6$ $(M+Na)^+$ 716.1372; found 716.1351.



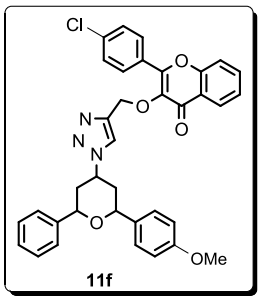
3-((1-(2,6-bis(4-bromophenyl)-4-tetrahydropyranyl)-1*H*-1,2,3-triazol)-4-methoxyl)-2-(3,4-dimethoxyphenyl)-4*H*-chromen-4-one (11d):

Yield 97%; light yellow solid; mp 160-161 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm) 8.26 (d, *J* = 6.5Hz, 1H), 7.97 (s, 1H), 7.80 (m, 2H), 7.70 (m, 1H), 7.56-7.42 (m, 6H), 7.28 (s, 3H), 6.95 (d, *J* = 7.5Hz, 1H), 5.38 (s, 2H), 4.86 (d, *J* = 11Hz, 3H), 3.97 (s, 3H), 3.89 (s, 3H), 2.56 (d, *J* = 14Hz, 2H), 2.17-2.12 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 175.01, 162.42, 156.25, 155.15, 151.36, 148.68, 140.68, 139.03, 133.56, 131.56, 127.47, 125.65, 124.87, 124.00, 123.06, 122.25, 121.53, 118.02, 111.68, 110.73, 73.87, 65.05, 56.17, 55.92, 54.47, 37.05. **IR (KBr, cm^{-1}):** 2976, 2922, 1674, 1638, 1562, 1424, 1250, 1078, 811. **HRMS (ESIMS)**: Anal. calcd for $C_{37}H_{31}Br_2N_3NaO_6$ $(M+Na)^+$ 794.0477; found 794.0457.



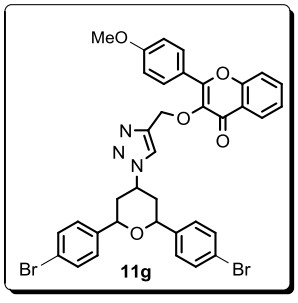
3-((1-(2,6-bis(4-bromophenyl)-4-tetrahydropyranyl)-1*H*-1,2,3-triazol)-4-methoxyl)-2-(4-chlorophenyl)-4*H*-chromen-4-one (11e):

Yield 98%; light yellow solid; mp 170-172 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 8.24 (dd, *J* = 1.5, 8Hz, 1H), 8.08 (d, *J* = 9Hz, 2H), 7.93 (s, 1H), 7.70 (ddd, *J* = 1.5, 7.5, 10Hz, 1H), 7.53 (d, *J* = 8.5Hz, 1H), 7.48 (d, *J* = 8.5Hz, 4H), 7.46 (d, *J* = 9.5Hz, 2H), 7.41 (t, *J* = 7.5Hz, 1H), 7.27 (d, *J* = 9.5Hz, 4H), 5.35 (s, 2H), 4.92 (d, *J* = 11Hz, 2H), 4.89 (m, 1H), 2.53 (d, *J* = 13.5Hz, 2H), 2.18-2.12 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 175.11, 155.23, 140.67, 139.69, 137.10, 133.86, 131.58, 130.08, 129.16, 128.84, 127.49, 125.73, 125.07, 124.03, 121.56, 118.10, 73.93, 67.97, 65.19, 54.55, 37.06. **IR (KBr, cm^{-1})**: 2967, 2932, 1664, 1608, 1552, 1404, 1210, 1048, 831. **HRMS (ESIMS)**: Anal. calcd for $C_{35}H_{26}Br_2ClN_3NaO_4$ $(M+Na)^+$ 767.9876; found 767.9866.



3-((1-(2-(4-methoxyphenyl)-6-phenyl-4-tetrahydropyranyl)-1*H*-1,2,3-triazol)-4-methoxyl)-2-(4-chlorophenyl)-4*H*-chromen-4-one (11f):

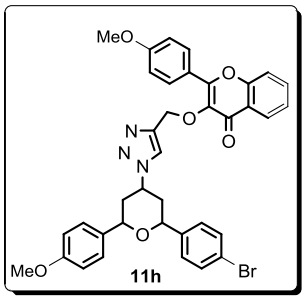
Yield 96%; light yellow solid; mp 120-121 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 8.26 (d, *J* = 7.5Hz, 1H), 8.09 (d, *J* = 8Hz, 1H), 7.91 (s, 1H), 7.70 (t, *J* = 7.5Hz, 1H), 7.53 (d, *J* = 8.5Hz, 1H), 7.45 (d, *J* = 8Hz, 2H), 7.42 (t, *J* = 7.5Hz, 1H), 7.35-7.28 (m, 6H), 6.90 (d, *J* = 8.5Hz, 2H), 5.40 (s, 2H), 4.94-4.86 (m, 3H), 3.81 (s, 3H), 2.57 (d, *J* = 14.5Hz, 1H)2.50 (d, *J* = 14.5Hz, 2H), 2.25-2.14 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 175.06, 159.22, 155.20, 155.14, 140.50, 139.65, 137.02, 133.81, 133.24, 130.09, 129.18, 128.80, 128.61, 128.53, 127.21, 127.15, 125.73, 125.02, 124.03, 123.76, 118.09, 113.87, 74.16, 73.90, 65.14, 55.31, 54.75, 37.06. **IR (KBr, cm^{-1})**: 2966, 2901, 1634, 1600, 1512, 1431, 1219, 1031, 801. **HRMS (ESIMS)**: Anal. calcd for $C_{36}H_{30}ClN_3NaO_5$ $(M+Na)^+$ 642.1772; found 642.1756.



3-((1-(2,6-bis(4-bromophenyl)-4-tetrahydropyranyl)-1*H*-1,2,3-triazol)-4-methoxyl)-2-(4-methoxyphenyl)-4*H*-chromen-4-one (11g):

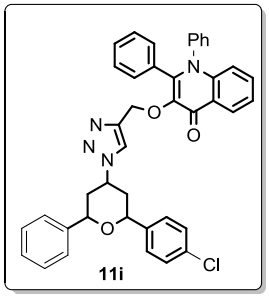
Yield 96%; light yellow solid; mp 180-181 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm) 8.15 (d, *J* = 7.5Hz, 1H), 8.04 (d, *J* = 8.5Hz, 2H), 7.07 (s, 1H), 7.59 (t, *J* = 7.5Hz, 1H), 7.43 (d, *J* = 8Hz, 1H), 7.39 (d, *J* = 8.5Hz, 4H), 7.31 (t, *J* = 7.1Hz, 1H), 7.18 (dd, *J* = 4, 8.5Hz, 4H), 6.89 (d, *J* = 9Hz, 2H), 5.27 (s, 2H), 4.79 (d, *J* = 10.5Hz, 3H), 3.71 (s, 3H), 2.45 (d, *J* = 14.5Hz, 2H), 2.08-2.04 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm) 175.03, 161.66, 156.46, 155.18, 140.74, 138.93, 137.02, 133.53,

131.55, 130.51, 128.59, 127.49, 125.64, 124.83, 124.02, 122.95, 121.51, 118.02, 113.98, 73.87, 65.04, 55.37, 54.44, 37.05. **IR (KBr, cm^{-1})**: 2966, 2910, 1643, 1610, 1521, 1413, 1261, 1015, 850. **HRMS (ESIMS)**: Anal. calcd for $C_{36}H_{29}Br_2N_3NaO_5$ $(M+Na)^+$ 764.0372; found 764.0368.



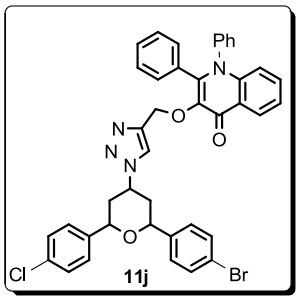
3-((1-(2-(4-methoxyphenyl)-6-(4-bromophenyl)-4-tetrahydropyranyl)-1*H*-1,2,3-triazol)-4-methoxyl)-2-(4-methoxyphenyl)-4*H*-chromen-4-one (11h):

Yield 95%; light yellow solid; mp 141-143 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 8.25 (d, *J* = 7.5Hz, 1H), 8.12 (d, *J* = 9Hz, 2H), 7.93 (s, 1H), 7.68 (t, 7Hz, 1H), 7.52 (d, *J* = 8.5Hz, 1H), 7.48 (d, *J* = 8Hz, 2H), 7.40 (t, *J* = 7.5Hz,1H), 7.31 (d, *J* = 8.5Hz, 2H), 7.27 (d, *J* = 9.5Hz, 1H), 6.97 (d, *J* = 9Hz, 2H), 6.88 (d, *J* = 8.5Hz, 2H), 5.36 (s, 2H), 4.88-4.81 (m, 2H), 4.50 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 2.56 (m, 2H), 2.26-2.10 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 175.07, 163.24, 161.69, 159.21, 156.52, 155.23, 141.07, 133.85, 131.50, 130.56, 127.57, 127.17, 125.70, 124.84, 123.01, 121.39, 118.05, 114.01, 113.87, 74.14, 73.91, 55.40, 55.35, 37.08, 29.74, 1.07. **IR (KBr, cm^{-1})**: 2963, 2911, 1642, 1613, 1524, 1416, 1265, 1019, 827. **HRMS (ESIMS)**: Anal. calcd for $C_{37}H_{32}BrN_3NaO_6$ $(M+Na)^+$ 716.1372; found 716.1351.



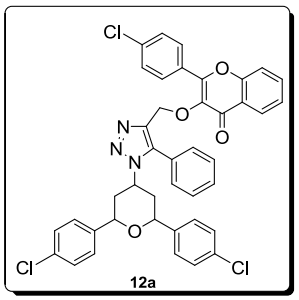
3-((1-(2-(4-chlorophenyl)-6-phenyl-4-tetrahydropyranyl)-1*H*-1,2,3-triazol)-4-methoxyl)-1,2-diphenylquinolin-4(1*H*)-one (11i):

Yield 93%; light yellow solid; mp 142-143 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 8.60 (d, *J* = 7.5Hz, 1H), 7.75 (t, *J* = 7.5Hz, 1H), 7.69-7.64 (m, 2H), 7.47 (m, 1H), 7.36-7.26 (m, 16H), 5.80 (s, 2H), 5.10-5.02 (m, 2H), 4.85 (m, 1H), 2.45 (dddd, *J* = 1.5, 14.5, 31.5, 46Hz, 2H), 2.23-2.09 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 173.41, 163.57, 146.89, 141.94, 141.71, 141.06, 140.52, 140.28, 130.85, 133.28, 133.16, 131.96, 129.94, 129.50, 128.92, 128.53, 128.47, 128.40, 128.35, 127.68, 127.56, 127.19, 125.80, 123.40, 74.45, 73.84, 60.36, 54.32, 36.33. **IR (KBr, cm^{-1})**: 2973, 2921, 1632, 1603, 1544, 1426, 1255, 1029, 798. **HRMS (ESIMS)**: Anal. calcd for $C_{41}H_{33}ClN_4NaO_3$ $(M+Na)+$ 687.2139; found 687.2114.



3-((1-(2-(4-chlorophenyl)-6-(4-bromophenyl)-4-tetrahydropyranyl)-1*H*-1,2,3-triazol)-4-methoxyl)-1,2-diphenylquinolin-4(1H)-one (11j):

Yield 93%; light yellow solid; mp 148-150 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 8.20 (d, *J* = 8Hz, 2H), 7.42 (t, *J* = 7Hz, 2H), 7.33 (d, *J* = 9Hz, 2H), 6.99-6.96 (m, 12H), 5.46 (s, 2H), 4.77 (d, *J* = 11.5, 2H), 4.56 (m, 1H), 2.15 (d, *J* = 14.5Hz, 2H), 1.84-1.78 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 177.94, 143.72, 141.91, 140.06, 134.28, 133.48, 128.64, 127.98, 122.62, 122.04, 121.85, 114.76, 74.03, 54.94, 43.04, 37.16. **IR (KBr, cm^{-1})**: 2965, 2931, 1663, 1614, 1534, 1414, 1266, 1024, 828. **HRMS (ESIMS)**: Anal. calcd for $C_{41}H_{32}Cl_2N_4NaO_3$ $(M+Na)^+$ 721.1749; found 721.1721.



3-((1-(2,6-bis(4-chlorophenyl)-4-tetrahydropyranyl)-5-phenyl-1*H*-1,2,3-triazol)-4-methoxyl)-2-(4-chlorophenyl)-4*H*-chromen-4-one (12a):

Yield 95%; light yellow semisolid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm) 8.25 (dd, *J* = 1, 8Hz, 1H), 8.08 (d, *J* = 9Hz, 2H), 7.92 (s, 1H), 7.72-7.56 (m, 7H), 7.56-7.53 (m, 4H), 7.33 (m, 7H), 5.36 (s, 2H), 4.93 (d, *J* = 11Hz, 2H), 4.89 (m, 1H), 2.53 (d, *J* = 14Hz, 2H), 2.19-2.13 (td, *J* = 4, 12Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 175.22, 155.29, 143.94, 140.20, 139.73, 137.17, 133.97, 133.50, 132.82, 132.21, 132.13, 132.06, 130.16, 128.92, 128.71, 128.65, 128.56, 127.24, 125.80, 125.16, 123.90, 118.19, 73.99, 65.22, 54.61, 37.19. **IR (KBr, cm^{-1})**: 2945, 2922, 1666, 1622, 1524, 1441, 1211, 1085, 811. **HRMS (ESIMS)**: Anal. calcd for $C_{41}H_{30}Cl_3N_3NaO_4$ $(M+Na)^+$ 756.1200; found 733.1221.

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Chapter-4

REGIOSELECTIVE OPENING OF CHALCONE EPOXIDES WITH NITROGEN HETEROCYCLES USING INDIUM (III) CHLORIDE AS AN EFFICIENT CATALYST

Synth. Commun. **2013**, *43*, 2008-2018.

REGIOSELECTIVE OPENING OF CHALCONE EPOXIDES WITH NITROGEN HETEROCYCLES USING INDIUM(III) CHLORIDE AS AN EFFICIENT CATALYST

4.1. INTRODUCTION

Functionalized indole and pyrrole derivatives have a wide range of biological and pharmaceutical importance [1]. In particular, 3-substituted indole derivatives are found in various natural products and medicines [2]. For example, soraphinol A [3], actinopolymorphol B [4], and kurasoin B [5] a protein farnesyl transferase (PFTase) inhibitor therefore have anticancer property [6]. Sattazoline and its derivatives have expressed antiviral activity against herpes simplex viruses type 1 and 2 and selectively inhibited the protein synthesis in herpes virus–infected cells [7]. Similarly, compounds **1** and **2** isolated from *Xenorhabdus nematophilus,* balasubramide isolated from *Clausena indica* have shown good antibacterial activity [8] (Fig. 1). These compounds have indole a basic moiety. Similarly, natural products containing pyrrole moiety are also present in different organic functional materials, drugs, pigments, and pharmaceuticals, for example, solsodomine A, chlorophyllone A, porphyrin, and bile pigments [9]. Particularly, chalcone or chromone fused pyrrole natural products have shown very interesting biological activities. For example, pyranigrin D isolated from sponge fungus *Aspergillus niger* [10], polycitone B isolated from *Marine ascidian, Polycitor africanus* which showed excellent antitumor activity [11]. Similarly, rigidin isolated from *Cystodytes sp.* which is active against cancer cell lines [12].

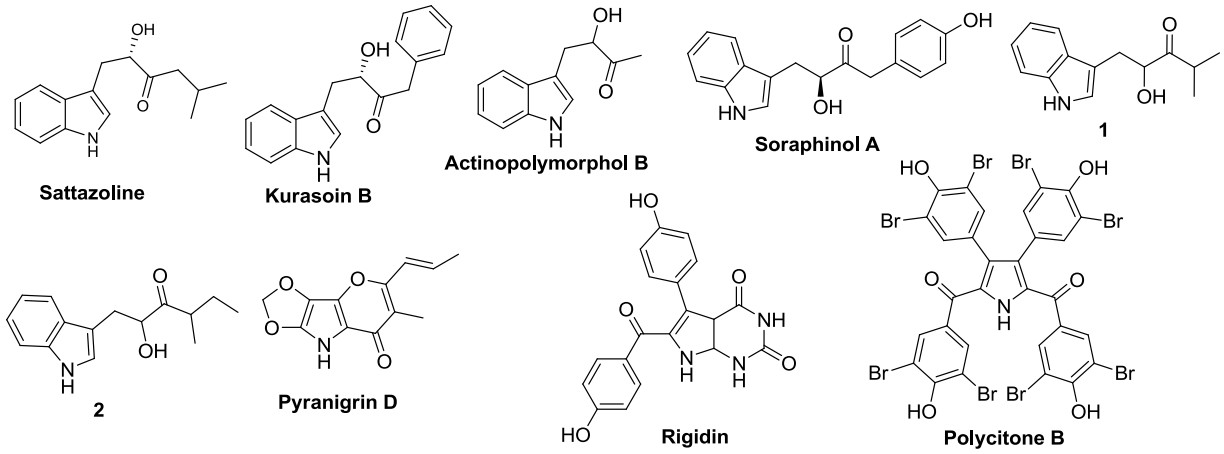


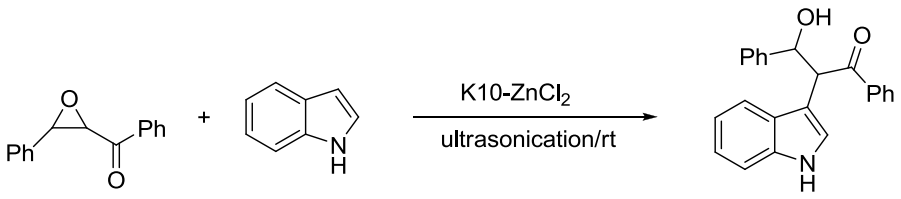
Figure 1: Indole/pyrrole containing biologically active compounds and natural products.

The central core α-hydroxy ketone (acyloin) unit is found in many natural products of pharmacological significance, such as kurasoin A, kurasoin B, kurasoin C, cytochalasian, sesquiterpene, secokotomolide, steroidal glycosides [4]. These moieties are used as synthons in various organic syntheses of complex and biologically active molecules. The presence of the hydroxy group at α-position of carbonyl enriches the chemical behavior of the indolyl/pyrrolyl ketones, for these reason β-indolyl/pyrrolyl ketones are used as versatile building blocks for the construction of biologically and medicinally important compounds [13].

Chalcone and chalcone epoxide are natural products found as secondary products in higher plants. Epoxides have been recognized among the most versatile compounds in organic synthesis, not only as final products but as key intermediate for further manipulations. They are used as substrate in organic syntheses having biological and pharmaceutical importance [14]. Ring-opening of epoxides is an atom economical reaction. Because of ring strain in epoxides, they undergo easy intramolecular and intermolecular nucleophilic addition reactions [15] under mild catalytic conditions and gives β-hydroxy derivatives [16]. Under controlled reaction conditions, epoxide ring opening had a highly regioselective synthetic strategy in carbon–carbon bond formation [17].

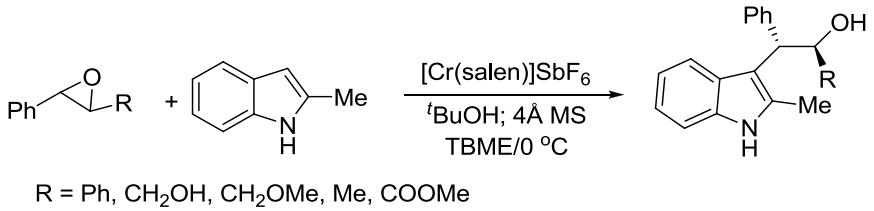
Different procedures have been reported for the ring opening of terminal epoxides with nitrogen heterocycles (nucleophile) under high pressure [18] and in the presence of catalysts such as SiO_2 [19], lanthanide triflate [20], chromium salen complexes [21], sulfated zirconia [22], antimony trichloride/montmorillonite K-10 [23], and $InBr_3$ [24]. Opening of terminal epoxides with nitrogen/other nucleophiles studied enough but, internal epoxides opening with N-heterocycles very less studied, straightly opening of chalcone epoxide with N-heterocycles only two reports are available.

Li *et al.* reported chalcone epoxide ring-opening reaction using indole in the presence of $ZnCl_2$, K-10, and ultra-sonication (Scheme 1). In contrast to our finding, in the later reaction procedure indole attacked at the α-position of the carbonyl group, which afforded 3-aryl-3-hydroxy-2-(1*H*-indol-3-yl)-1-phenyl-1-propanone [25].



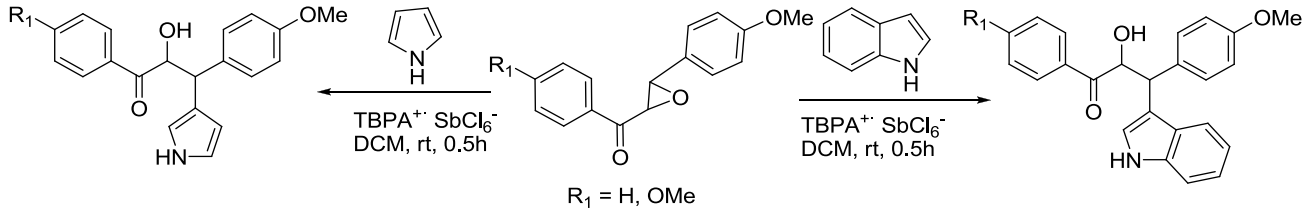
Scheme 1: Opening of chalcone epoxide with indole by using $ZnCl_2$/K-10 in ultra-sonication.

Cozzi *et al.* reported opening of epoxides with 2-methyl indole using metal salen complexes in *tert*-butyl methyl ether at 0 ^{0}C (Scheme 2) [26]. However, an expensive reagents and long reaction time are required.



Scheme 2: Cr salen complexes catalyzed opening of epoxides.

Huo *et al.* recently reported opening of chalcone epoxides with N-heterocycles using $TBPA^{+\cdot}$ $SbCl_6^-$. This methodology applicable only electron releasing substituents containing chalcone epoxides, are failed to open electron withdrawing group containing chalcone epoxides (Scheme 3) [27].



Scheme 3: Opening of chalcone epoxides with N-heterocycles induces by $TBPA^{+\cdot}$ $SbCl_6^-$.

Indeed, we need an efficient method as mild reaction conditions, in short reaction time, to give high yield. In continuation of our interest in Lewis acid catalysis [28] and the importance of metal halides as inexpensive, easily available, and stable catalysts in epoxide ring opening, herein we report an efficient method for regioselective ring opening of chalcone epoxides with nitrogen heterocycles in the presence of indium(III) chloride as catalyst. In our method, indole nucleophile attacks regioselectively at the β-position of the carbonyl group to afford 1,3-bis(4-chlorophenyl)-2-hydroxy-3-(1*H*-indol-3-yl)propan-1-ones in significant yields (88%) within 20–50 min.

4.2. OBJECTIVE

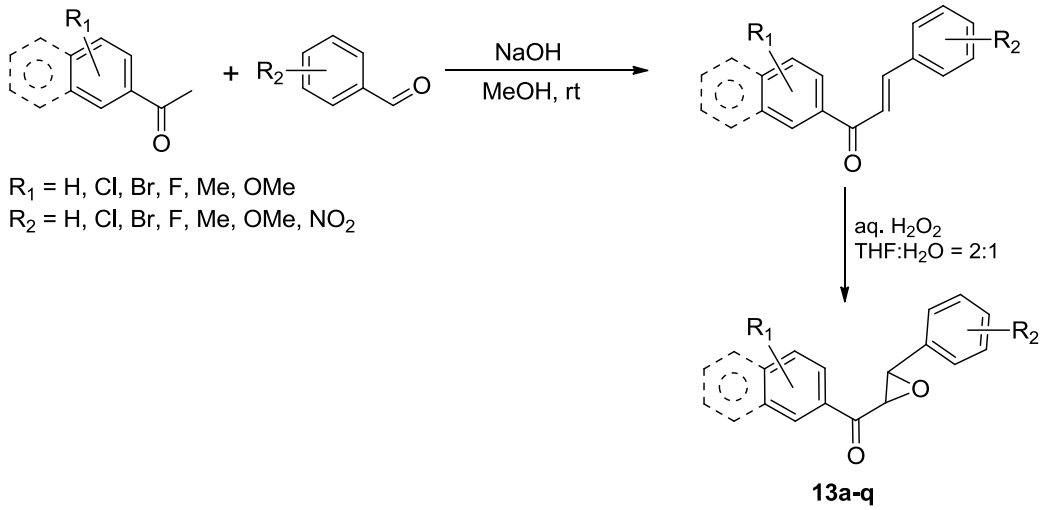
Metal catalyzed organic transformations are powerful method for inter- and intra- molecular reactions in stereo- and regioselective manner under mild reaction condition. Due to electron deficient nature, cheap and readily commercial availability metal halides are used as Lewis acid catalyst in various organic syntheses like alkylation, acylation, C-C, C-N, C-O bonds formation, rearrangements

and cyclization reactions. Hence we have applied chalcone epoxide opening followed by intermolecular Friedel-Craft reaction with N-heterocycles to synthesize 1,3-diaryl-2-hydroxy-3-(1*H*-3-indolyl/2-pyrrolyl)propan-1-one using different metal halides. We found $InCl_3$ is the most efficient catalyst in epoxides opening.

4.3. RESULTS AND DISCUSSION

4.3.1. Synthesis of chalcone epoxides

Various chalcones were prepared by the condensation of aromatic acetophenones and aromatic aldehydes in alkaline methanol at room temperature [28]. Epoxidation of chalcones was carried out using aqueous sodium hydroxide and hydrogen peroxide in tetrahydrofuran (THF) to give the corresponding epoxides **13a**–**q** in good yields (80–90%).



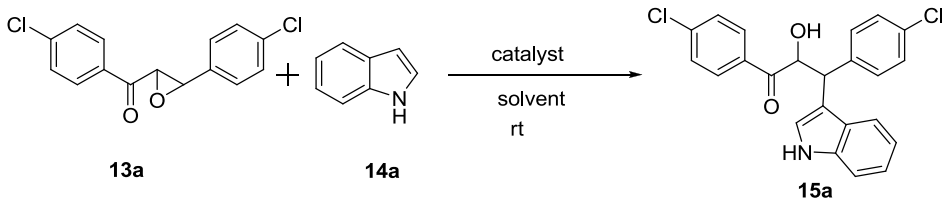
Scheme 4: Synthesis of chalcone epoxides.

4.3.2. Synthesis of 1,3-diaryl-2-hydroxy-3-(1*H*-3-indolyl)propan-1-one

Initially, we examined epoxide ring opening with indole nucleophile under neat grinding and silica gel-supported grinding at room temperature. These reactions failed to give the products; however, in later case at elevated temperature (140 ^{0}C) afforded the product in 20% yield. Further, different Lewis acids ($SnCl_4$, $TaCl_5$, $SnCl_2.2H_2O$, $AlCl_3$, $ZnCl_2$, ZnO, $CuBr_2$, $LaCl_3$, $BiCl_3$, LiBr, $InCl_3$, $TiCl_4$, and $FeCl_3$) and solvents (toluene, THF, DCM, CHCl3, EtOAc, and diethyl ether) were used to optimize the product yields. Among the solvents and catalysts used, DCM and indium(III) chloride (Table 1, entry 6) were found the best solvent and the most efficient catalyst (20 mol%

catalyst loading) respectively. The epoxide opening with indole gave the optimal yield (85–88%) within 20–50 min. in DCM and 20 mol% catalyst loading. The other catalyst, $BiCl_3$ gave good yields (75%) in 2h, but showed moderate catalytic activity (Table 1, entry 8). Similarly, $TaCl_5$ and $SnCl_2.2H_2O$ gave poor yields (20–48%) after 28–38h because of poor catalytic activity, and other catalysts failed to give the product.

Table 1: Optimization of reaction conditions.



13a **14a** **15a**

Entry	Lewis Acid[a]	Yield (%)	Solvent	Reaction Time
1.	$SnCl_4$	<5	$CHCl_3$	4 min
2.	$SnCl_4$	<5	CH_2Cl_2	4 min
3.	$SnCl_2.2H_2O$	45	CH_2Cl_2	35 hr
4.	$SnCl_2.2H_2O$	45	$CHCl_3$	38 hr
5.	$AlCl_3$	trace	CH_2Cl_2	3 days
6.	**$InCl_3$**	**85**	**CH_2Cl_2**	**40 min**
7.	$InCl_3$	76	EtOAc	1 hr
8.	$BiCl_3$	75	CH_2Cl_2	2 hr
9.	ZnO	trace	CH_2Cl_2	3 days

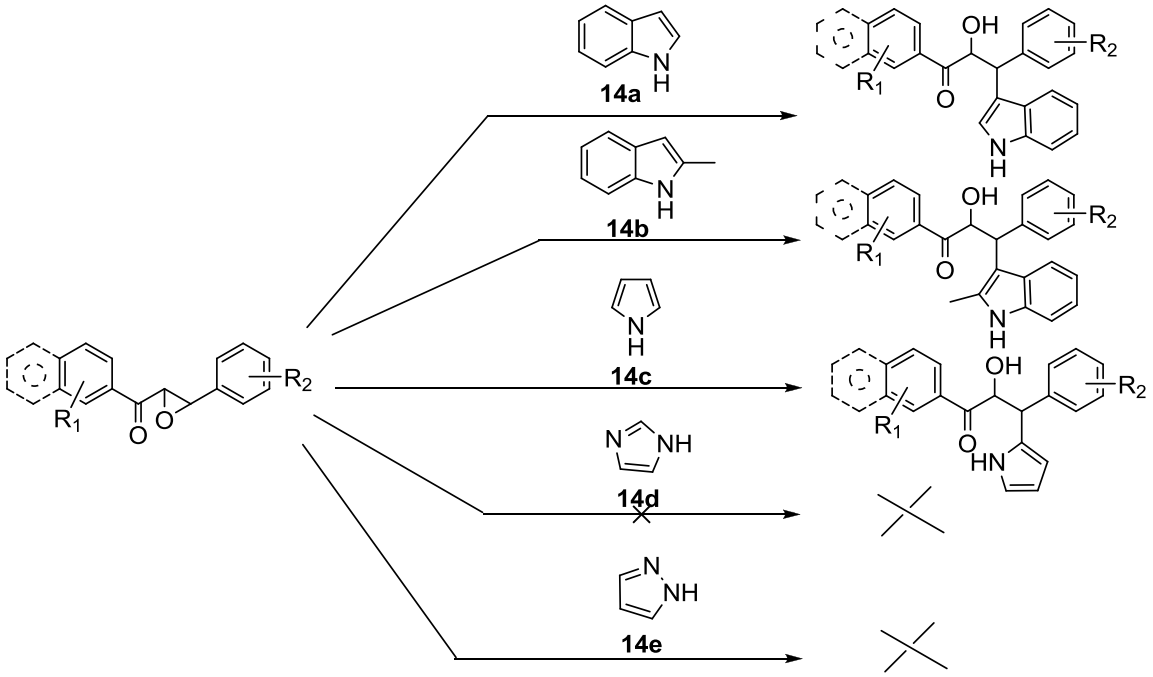
Catalytic loading has also influenced the rate of the reaction. To optimize the catalytic loading, the reactions were carried out with 5, 10, 20, and 25 mol% catalyst in DCM, and the efficiency of the catalyst loading was determined from the time needed for the complete conversion of the epoxide **13a**. $InCl_3$ at 5 mol% loading gave the complete conversion of epoxide **13a** to **15a** in 2h. At increased catalytic loading (10 mol%) the reaction time decreased to 1h. Further, increase in catalytic loading to 20 mol% serendipitously reduced the reaction time to 40 min., and further increase in catalytic loading from 20 to 25 mol% (Table 2), there was no increase in the rate of the reaction. As a result, catalytic loading has influence on the rate of reaction but not on product yields.

Table 2: Optimization of catalyst loading.

Entry[a]	Lewis Acid	Solvent	Reaction Time	Yield (%)[b]
1.	$BiCl_3$[c]	CH_2Cl_2	4 hr	75
2.	$BiCl_3$[d]	CH_2Cl_2	2 hr	75
3.	$InCl_3$[c]	CH_2Cl_2	1 hr	85
4.	**$InCl_3$**[d]	**CH_2Cl_2**	**40 min**	**85**
5.	$InCl_3$[e]	CH_2Cl_2	40 min	85

[a]1 equiv. of epoxide and 1 equiv. indole were used, [b] isolated yield, [c] catalyst 10 mol % used, [d] catalyst 20 mol % used, [e]catalyst 25mol % used.

Under optimal reaction condition, we carried out reactions using a variety of chalcone epoxides and nitrogen heterocycles such as indole (**14a**), 2-methyl indole (**14b**), pyrrole (**14c**), imidazole (**14d**), and pyrazole (**14e**) using $InCl_3$ catalyst in DCM (Scheme 5). N-heterocycles **14a**, **14b**, and **14c** have successfully opened chalcone epoxide (Table 3); however, **14d** and **14e** failed in epoxide ring opening, which might be due to poor nucleophilicity.

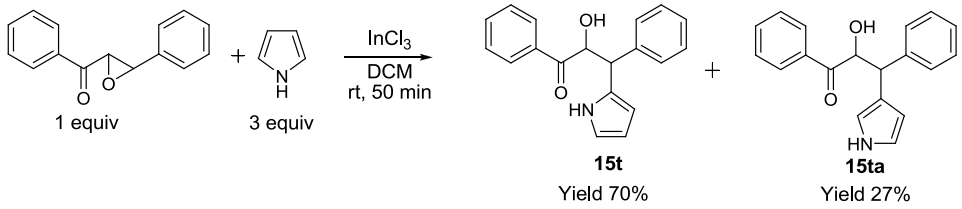


Scheme 5: Opening of chalcone epoxide with different nitrogen hetero-nucleophiles.

We observed that the substituents on the aromatic rings have influence on the reaction rate and product yields. For example, electron-donating groups such as methoxy and methyl groups on B ring afforded the product in poor yields in a faster rate (Table 3, products **15c**, **15i**, **15p**, **15q**). Similarly,

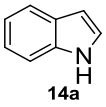
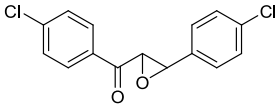
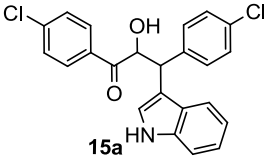
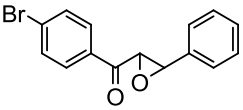
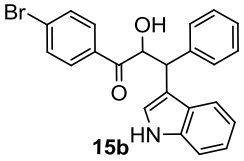
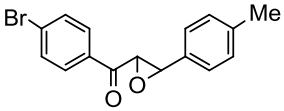
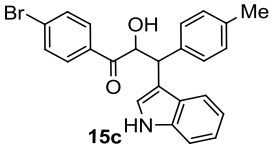
electron-withdrawing groups such as chloro, bromo, and nitro on B ring gave products in good yields but took longer reaction time (Table 3, products **15a**, **15e**, **15f**, **15h**, **15k**, **15o**). However, substituent effect on A-ring has no significant influence on the rate of the reaction and the product yields (Table 3, products **15f**, **15g**, **15l**, **15m**). Treatment of chalcone epoxides with 2-methyl indole afforded 1,3-diaryl-2-hydroxy-3-(2-methyl-1*H*-indol-3-yl)propan-1-ones in poor yields (Table 3, products **15r**, **15s**) because of steric hindrance of the methyl group.

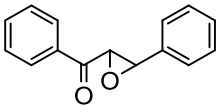
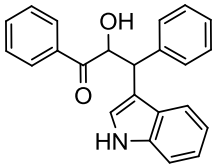
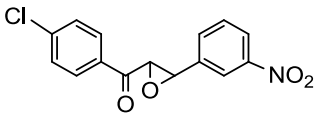
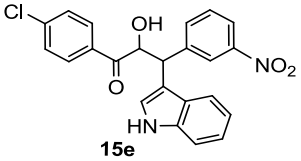
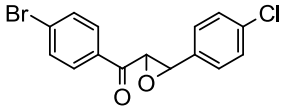
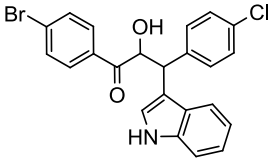
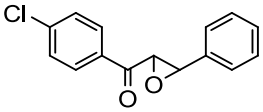
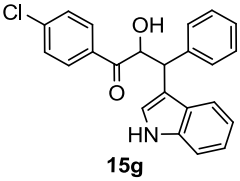
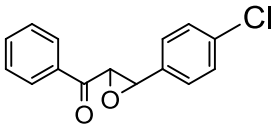
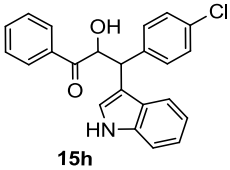
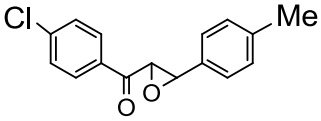
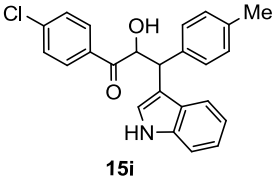
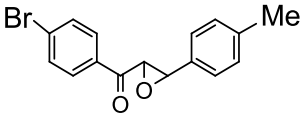
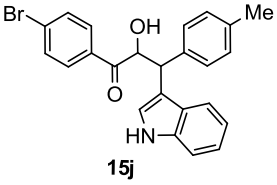
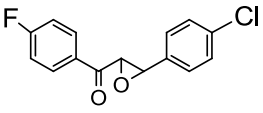
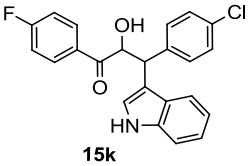
The reaction of pyrrole with chalcone epoxide might need to be performed under controlled conditions, because a mixture of products was obtained using 1 to 2 equiv. pyrrole in the reaction. To avoid this, we used 3 equiv. of pyrrole and got 2-sustituted and 3-sustituted products in 70% and 27% yields respectively (Scheme 6).

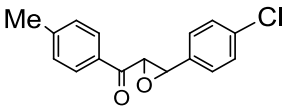
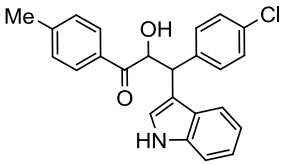
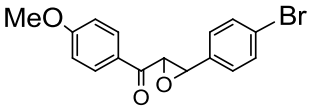
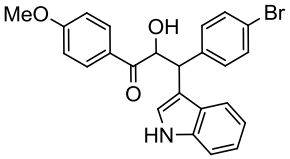
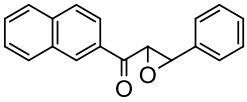
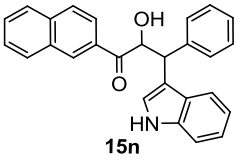
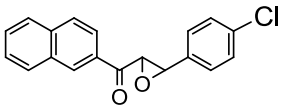
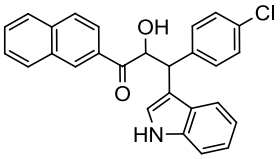
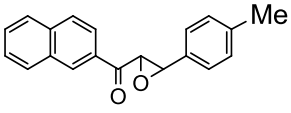
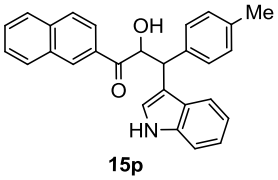
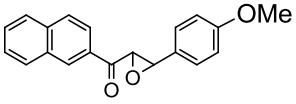
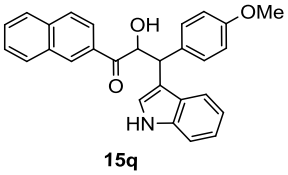
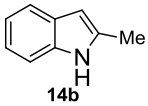
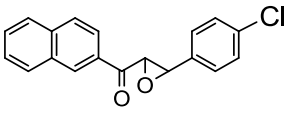
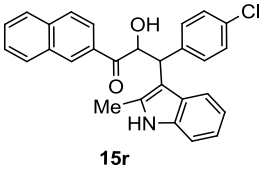
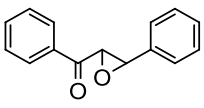
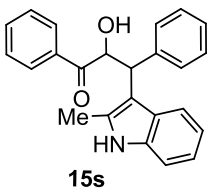


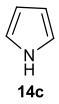
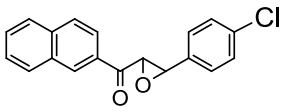
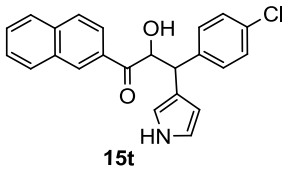
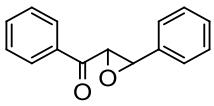
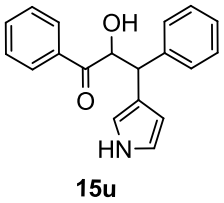
Scheme 6: Opening of chalcone epoxide with pyrrole.

Table 3: Synthesis of 1,3-diaryl-2-hydroxy-3-(1*H*-3-indolyl/2-pyrrolyl)propan-1-one.

Entry	Nucleophile	Reactant	Product	Reaction time (min)	Yield (%)
1	 14a	 13a	 15a	35	85
2	14a	 13b	 15b	40	82
3	14a	 13c	 15c	25	72

4	14a	 **13d**	 **15d**	40	81
5	14a	 **13e**	 **15e**	50	86
6	14a	 **13f**	 **15f**	40	86
7	14a	 **13g**	 **15g**	40	82
8	14a	 **13h**	 **15h**	40	85
9	14a	 **13i**	 **15i**	30	72
10	14a	 **13j**	 **15j**	30	71
11	14a	 **13k**	 **15k**	45	85

12	14a	 13l	 15l	40	82
13	14a	 13m	 15m	35	80
14	14a	 13n	 15n	40	88
15	14a	 13o	 15o	40	86
16	14a	 13p	 15p	30	73
17	14a	 13q	 15q	20	60
18	 14b	 13o	 15r	40	74
19	14b	 13d	 15s	40	75

20	 14c	 13o	 15t	50	70
21	14c	 13d	 15u	50	70

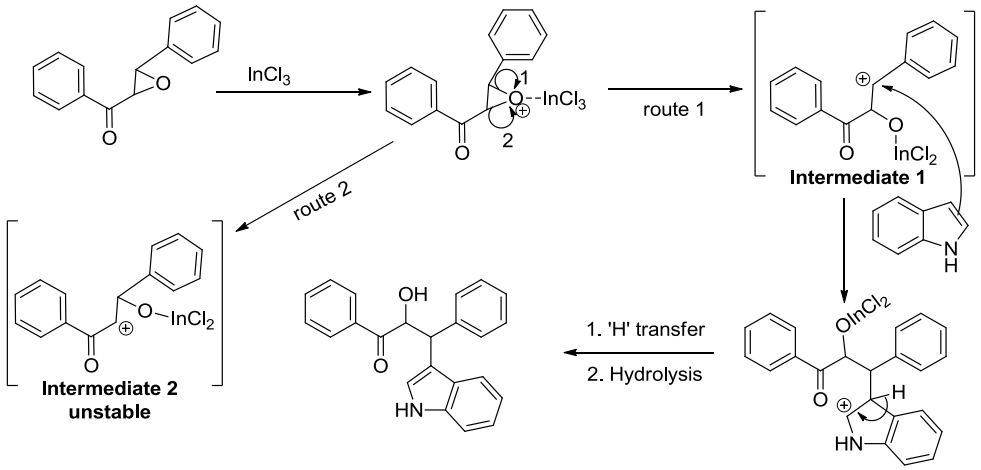
4.4. STRUCTURE DETERMINATION

The assigned structures of new products (**15a–u)** were established by their spectral analysis (IR, ^{1}H, ^{13}C-NMR and HRMS) and reported compounds (**13a**-**q**) compared with reported data in the literature [14,19]. For example, compound (4-chlorophenyl)-3-(4-chlorophenyl)-oxiran-2-yl-methanone **13a** was obtained as a white crystalline solid. The IR spectrum of **13a** showed absorption at 1675, 1400, 1236 cm^{-1} for carbonyl, C=C and C-O-C bonds *asymmetric stretching* respectively. The GC-MS of **13a** gave molecular ion peak at 292 supported a molecular composition of $C_{15}H_{10}Cl_2O_2$ $[M^+]$, representing 10 degrees of unsaturation. In the ^{1}H NMR spectrum of **13a** peaks at δ_H 4.06 (d, *J* = 2Hz, 1H), and 4.18 (d, *J* = 2Hz, 1H) in which the coupling constant (2 Hz) indicates hydrogens are coupled trans to each other. These data confirmed that the product formation. Similarly, other chalcone epoxides **13b**-**q** confirmed on their spectral data (experimental section). Chalcone based 2-hydroxy-3-indolyl derivatives for example, compound 1-(4-chlorophenyl)-2-hydroxy-3-(1*H*-indol-3-yl)-3-phenylpropan-1-one **15g** obtained as yellow semisolid. The IR spectrum of **15g** showed absorptions at 3420, 3376, 1679 1400 cm^{-1} for NH, OH, C=O, and C=C bonds *asymmetric stretching* respectively. The HRMS of **15g** gave peak at 398.1000 supported a molecular composition of $C_{23}H_{18}ClNNaO_2$ $(M+Na)^+$, representing 14 degrees of unsaturation. In the ^{1}H NMR spectrum, peaks at δ_H 4.75 (d, *J* = 7.5Hz, 1H, H3) and 5.81ppm (d, *J* = 7.5Hz, 1H, H2), in which the coupling constant (*J* = 7.5Hz) indicated a vicinal trans-coupling of H-2 with H-3. The ^{13}C NMR spectrum gave peaks at δ_C 47.2 (C-indole), 76.17 (C-OH), and 199.36 (C=O) suggested that product formation and hydroxy and indole groups are trans to each other. Similarly, the structures of other compounds (**15a**–**f** and **15h**–**s**) confirmed on their spectral data (experimental section). Similarly, chalcone based 2-hydroxy-3-pyrrolyl derivatives for example, compound 3-(4-chlorophenyl)-2-hydroxy-1-(naphthalen-2-yl)-3-(1H-pyrrol-2-yl)propan-1-one **15t** was obtained light yellow semisolid. The IR spectrum of **15t**

showed absorptions at 3422, 3365 and 1680 cm^{-1} for NH, OH, and C=O bonds *asymmetric stretching* respectively. The HRMS of **15g** gave peak at 375.1053 supported a molecular composition of $C_{23}H_{18}ClNO_2$ $[M]^+$, representing 15 degrees of unsaturation. In the ^1H NMR spectrum, peaks at δ_H 4.79 (d, 1H, *J* = 7.5 Hz), and 5.87 (dd, 1H, *J*= 7.5, 1.5 Hz) in which the coupling constant *J* = 7.5Hz indicates a vicinal trans-coupling of H-2 with H-3 proton. In the ^1H and ^{13}C NMR spectrum peaks at δ_H 6.02 (dd, 1H, *J* = 5.5, 3.5Hz), 6.13 (dd, 1H, *J* = 5.5, 2.5Hz), and 6.71 (dd, 1H, *J* = 3.5, 2.5Hz) and peaks at δ_C 106.0, 108.4, 118, and 132.1 corresponds to pyrrole ring and indicating that the formation of 2-substituted pyrrole derivative. Similarly, compound **15u** also confirmed on their spectral data (experimental section).

4.5. MECHANISM

The proposed mechanism for the opening of chalcone epoxide with nitrogen heterocycles is presented in Scheme 7. Ligation of $InCl_3$ catalyst with oxygen of chalcone epoxide followed by nucleophilic attack led to the cleavage of the C-O bond. It might cleave in two different ways, but route 2 will be preferred than route 1 because of stable carbocation formation. The nucleophilic attack of indole on carbocation and subsequent hydrogen transfer produced the title compounds with concurrent liberation of $InCl_3$ for the next catalytic cycle. The mechanism for pyrrole derivatives also can illuminate as above.



Scheme 7: Mechanism of opening of chalcones epoxide with indole.

4.6. CONCLUSIONS

In conclusion, we have developed a mild and efficient procedure for regioselective ring opening of chalcone epoxide with nitrogen heterocycles such as indole, 2-methyl indole, and pyrrole

using indium(III) chloride as a catalyst to afford 1,3-diaryl-2-hydroxy-3-(1*H*-3-indolyl/2-pyrrolyl)propan-1-ones in good to excellent yield (60–88%), under short reaction time (20–50 min), and mild reaction conditions.

4.7. EXPERIMENTAL

4.7.1. General Procedures

General procedure for preparation of chalcone epoxides (13a-q):

5 M aq. NaOH solution (3 mL) was added dropwise to a stirred solution of chalcone (1 mmol) in THF–H_2O (2:1, 6 mL) at 0 ^{0}C and stirred at same temperature for 10 min. Then, added H_2O_2 (3 mL, 30 wt%) dropwise and the resulting mixture was stirred at r.t. for 6–7 h (TLC monitoring). The mixture was poured into cold water and the resulting precipitate was filtered and washed with H_2O. The product was recrystallized from EtOH.

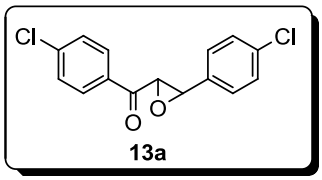
General procedure for synthesis of 1,3-diaryl -2-hydroxy-3-(1*H*-3-indolyl)propan-1-one (15a-s):

To a stirred mixture of chalcone epoxides (1 mmol) and indium(III) chloride (4.43 mg, 20 mol%) in dichloromethane was added indole or 2-methyl indole (1 mmol). The resulting reaction mixture was stirred at room temperature for appropriate time (20-50 min). TLC monitoring, after completion of the reaction, diluted with DCM (3 x 15 mL) and washed with brine and water then extracted with DCM. The combined organic layer dried over anhydrous Na_2SO_4 and evaporated solvent under reduced pressure to give the crude product. Further purification by silica gel column chromatography gave 1,3-diaryl-2-hydroxy-3-(1*H*-3-indolyl)propan-1-one.

General procedure for synthesis of 1,3-diaryl -2-hydroxy-3-(1*H*-2-pyrrolyl)propan-1-one(15t-u):

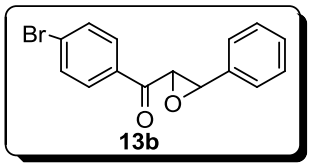
To a stirred mixture of chalcone epoxides (1 mmol) and indium(III) chloride (4.43 mg, 20 mol%) in dichloromethane was added pyrrole (201.3 mg, 3 mmol). The resulting reaction mixture was stirred at room temperature for 50 min. TLC monitoring, after completion of the reaction, diluted with DCM (3 x 15 mL) and washed with brine and water then extracted with DCM. The combined organic layer dried over anhydrous Na_2SO_4 and evaporated solvent under reduced pressure to give the crude product. Further purification by silica gel column chromatography gave 1,3-diaryl-2-hydroxy-3-(1H-2-pyrrolyl)propan-1-one.

4.7.2. SPECTROSCOPIC DATA



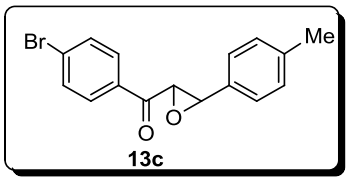
13a

(4-Chlorophenyl)-3-(4-chlorophenyl)-oxiran-2-yl-methanone (13a): Yield: 89%; white crystalline solid; mp 112–118 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 4.06 (d, *J* = 2Hz, 1H), 4.18 (d, *J* = 2Hz, 1H), 7.30 (d, *J* = 11Hz, 2H), 7.40 (d, *J* = 11Hz, 2H), 7.47 (d, *J* = 8.5Hz, 2H), 7.96 (d, *J* = 8.5Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 191.69, 140.76, 134.37, 133.62, 132.04, 129.82, 129.31, 127.40, 123.21, 60.91, 58.81. **IR (KBr, cm^{-1})**: 3039, 1675, 1587, 1400, 1236 cm^{-1}. **GC-MS**: (m/z) 292.



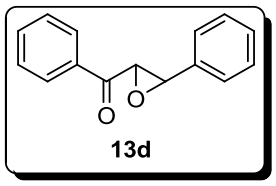
13b

(4-Bromophenyl)-3-phenyl-oxiran-2-yl-methanone (13b): Yield: 76%; white crystalline solid; mp 65-66 ^{0}C. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm) 4.07 (d, *J* = 1.5Hz, 1H), 4.27 (d, *J* = 1.5Hz, 1H), 7.26-7.38 (m, 4H), 7.51-7.53 (m, 2H), 7.65 (m, 1H), 8.01 (dd, *J* = 7.8, 1.2Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm): 191.91, 134.36, 134.01, 132.31, 132.04, 129.87, 129.54, 127.40, 123.22, 60.94, 58.72. **IR (KBr, cm^{-1})**: 3050, 1680, 1452, 1258.



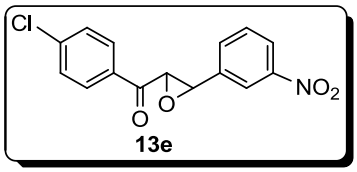
13c

(4-Bromophenyl)-3-(p-tolyl)-oxiran-2-yl-methanone (13c): Yield: 88%; white crystalline solid; mp 100-101 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 2.25 (s, 3H), 4.12 (d, *J* = 1.6Hz, 1H), 4.32 (d, *J* = 1.6Hz, 1H), 7.7– 7.17 (m, 6H), 8.25–8.08 (m, 2H), **IR (KBr, cm^{-1})**: 1400, 1600, 1677.



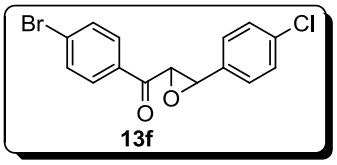
13d

Phenyl-3-phenyl-oxiran-2-yl-methanone (13d): Yield: 86%; white crystalline solid; mp 84-85 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 4.01 (d, *J* = 1.5Hz, 1H), 4.23 (d, *J* = 1.5Hz, 1H), 7.22-7.45 (m, 8H), 7.94 (d, *J* = 7.5 Hz, 2H). **IR (KBr, cm^{-1})**: 3040, 1660, 1404, 1221.

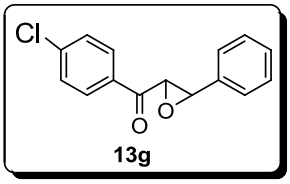


13e

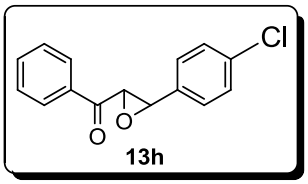
(4-Chlorophenyl)-3-(3-nitrophenyl)-oxiran-2-yl-methanone (13e): Yield: 87%; white crystalline solid; mp 64-65 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 4.24 (d, *J* = 1.5Hz, 1H), 4.27 (d, *J* = 1.5Hz, 1H), 7.52 (m, 2H), 7.63 (m, 1H), 7.74 (d, *J* = 7.5Hz, 1H), 8.01 (dd, *J* = 7.0, 1.5Hz, 2H), 8.27 (d, *J* = 8.5Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 191.18, 148.74, 141.02, 137.70, 133.49, 131.75, 129.98, 129.89, 129.40, 124.00, 120.80, 60.76, 57.96. **IR (KBr, cm^{-1})**: 3091, 1665, 1537, 1358, 1212.



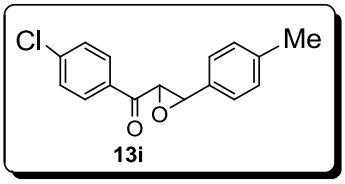
(4-Bromophenyl)-3-(4-chlorophenyl)-oxiran-2-yl-methanone (13f): Yield: 89%; White crystalline solid; mp 65-66 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 4.07 (d, *J* = 2Hz, 1H), 4.21 (d, *J* = 2Hz, 1H), 7.27 (dd, *J* = 7.0, 2Hz, 2H), 7.54 (m, 4H), 7.99 (dd, *J* = 7.0, 2Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 191.69, 60.96, 58.71, 140.76, 134.37, 133.62, 132.04, 129.82, 129.31, 127.40, 123.21. **IR (KBr, cm^{-1})**: 3039, 1675, 1587, 1430, 1400, 1236, 1092.



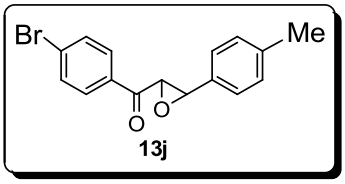
(4-Chlorophenyl)-3-phenyl-oxiran-2-yl-methanone (13g): Yield: 85%; white crystalline solid; mp 63-64 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 4.07 (d, *J* = 2Hz, 1H), 4.23 (d, *J* = 2Hz, 1H), 7.35-7.41 (m, 5H), 7.45-7.47 (m, 2H), 7.96-7.98 (m, 2H). **^{13}C NMR(125 MHz, $CDCl_3$)**: 192.04, 140.59, 135.23, 133.68, 129.79, 129.23, 129.14, 128.79, 125.75, 61.06, 59.34. **IR (KBr, cm^{-1})**: 3040, 1680, 1566, 1421, 1206.



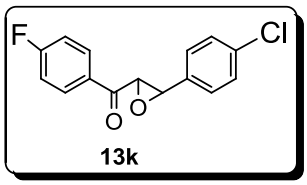
Phenyl-3-(4-chlorophenyl)-oxiran-2-yl-methanone (13h): Yield: 83%; white crystalline solid; mp 50-51 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 4.06 (d, *J* = 1.6Hz, 1H), 4.25 (d, *J* = 1.6Hz, 1H), 7.30-7.32 (m, 2H), 7.37-7.39 (m, 2H), 7.48-7.52 (m, 2H), 7.61-7.65 (m, 1H), 7.99-8.01 (m, 2H). **IR (KBr, cm^{-1})**: 3010, 1660, 1546, 1411, 1201.



***p*-Tolyl-3-(4-chlorophenyl)-oxiran-2-yl-methanone (13i):** Yield: 87%; white crystalline solid; mp 110-115 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 2.37 (s, 3H), 4.04 (d, *J* = 2Hz, 1H), 4.24 (d, *J* = 2Hz, 1H), 7.21-7.27 (m, 4H), 7.46 (dd, *J* = 7.0, 2Hz, 2H), 7.96 (dd, *J* = 6.6, 2Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 191.89, 153.79, 140.65, 138.74, 133.72, 130.84, 129.83, 129.26, 112.57, 60.97, 59.54, 21.27. **IR (KBr, cm^{-1})**: 3011, 1686, 1560, 1403, 1207.



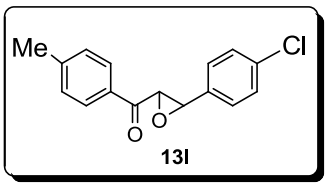
***p*-Tolyl-3-(4-bromophenyl)-oxiran-2-yl-methanone (13j):** Yield: 90%; White crystalline solid; mp 85-86 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 2.29 (s, 3H), 4.07(d, *J* = 2Hz, 1H), 4.20 (d, *J* = 2Hz, 1H), 7.11-7.19 (m, 4H), 7.38-7.41 (m, 2H), 7.91-8.03 (m, 2H). **IR (KBr, cm^{-1})**: 3010, 1664, 1421, 1223, 1021.



13k

(4-Florophenyl)-3-(chlorophenyl)-oxiran-2-yl-methanone (13k):

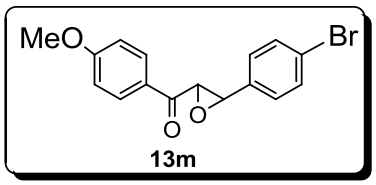
Yield: 88%; white crystalline solid; mp 66-67 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 4.07 (d, *J* = 2Hz, 1H), 4.26 (d, *J* = 2Hz, 1H), 7.07-7.11 (m, 2H), 7.33-7.37 (m, 2H), 7.48-7.51 (m, 2H), 7.99-8.02 (m, 2H). **IR (KBr, cm^{-1})**: 3011, 1683, 1400, 1243, 1018.



13l

***p*-Tolyl-3-(4-chlorophenyl)-oxiran-2-yl-methanone (13l):**

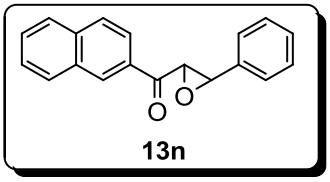
Yield: 84%; white crystalline solid; mp 54 –56 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 2.25 (s, 3H), 4.12 (d, *J* = 1.6Hz, 1H), 4.31 (d, *J* = 1.6Hz, 1H), 7.6-7.2 (m, 6H), 8.05–7.99 (m, 2H). **IR (KBr, cm^{-1})**: 3050, 1677, 1600, 1400, 1280, 1240, 1180, 1120.



13m

(4-Methoxylphenyl)-3-(4-chlorophenyl)-oxiran-2-yl-methanone (13m):

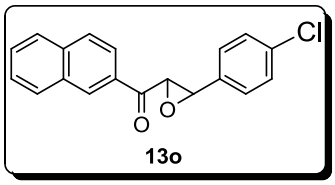
Yield: 81%; white crystalline solid; **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 3.88 (s, 3H), 4.05 (d, *J* = 2Hz, 1H), 4.21 (d, *J* = 2Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 2H); 7.29-7.39 (m, 4H), 8.00 (d, *J* = 7.5 Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ (ppm) 191.89, 153.79, 140.65, 138.74, 133.72, 130.84, 129.83, 129.26, 112.57, 60.97, 59.54, 56.22. **IR (KBr, cm^{-1})**: 3045, 1634, 1421, 1232, 1064.



13n

Naphthalen-2-yl-3-phenyl-oxiran-2-yl-methanone (13n):

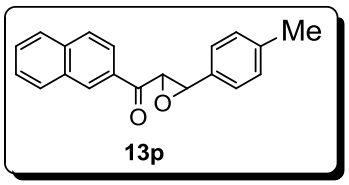
Yield: 91%; light yellow solid; mp 80-81 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 4.16 (d, *J* = 2Hz, 1H), 4.44 (d, *J* = 1.6Hz, 1H), 7.40−7.45 (m, 5H), 7.55−7.59 (m, 1H), 7.62−7.64 (m, 1H), 7.88–7.97 (m, 3H), 8.05−8.07 (m, 1H), 8.58 (s, 1H). **IR (KBr, cm^{-1})**: 3010, 1664, 1421, 1223, 1021.



13o

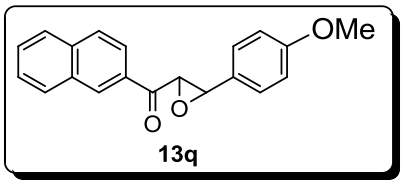
Naphthalen-2-yl-3-(4-chlorophenyl)-oxiran-2-yl-methanone (13o):

Yield: 90%; light yellow solid; mp 81-82 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 4.12 (d, *J* = 2Hz, 1H), 4.31 (d, *J* = 2Hz, 1H), 7.47 (d, *J* = 8.5Hz, 2H), 7.55−7.59 (m, 1H), 7.62−7.64 (m, 1H), 7.88–7.97 (m, 3H), 7.96 (d, 2H, *J* = 8.5Hz), 8.05−8.07, (m, 1H), 8.58 (s, 1H). **IR (KBr, cm^{-1})**: 3039, 1675, 1587, 1430, 1400, 1236, 1092.



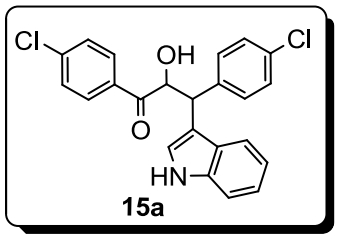
Naphthalen-2-yl-3-(p-tolyl)-oxiran-2-yl-methanone (13p):

Yield: 87%; light yellow solid; mp 74-75 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 2.13 (s, 3H), 4.07 (d, *J* = 2Hz, 1H), 4.20 (d, *J* = 2Hz, 1H), 7.40 (d, *J* = 8.5Hz, 2H), 7.55−7.59 (m, 1H), 7.62−7.64 (m, 1H), 7.71 (d, *J* = 8.5Hz, 2H), 7.88–7.97 (m, 3H), 8.05−8.07 (m, 1H), 8.58 (s, 1H). **IR (KBr, cm^{-1})**: 3040, 1660, 1404, 1221.



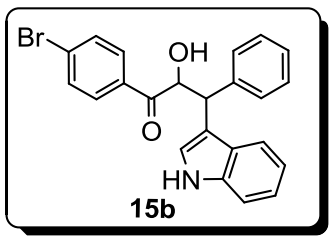
Naphthalen-2-yl-3-(4-methoxyphenyl)-oxiran-2-yl-methanone (13q):

Yield: 85%; light yellow solid; mp 81-82 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 3.88 (s, 3H), 4.05 (d, *J* = 2Hz, 1H), 4.21 (d, *J* = 2Hz,, 1H), 8.58 (s, 1H), 8.05 − 8.07 (m, 1H), 7.88 – 7.97 (m, 3H), 7.72-7.76 (d, *J* = 8.5Hz, 2H), 7.62 − 7.64 (m, 1H), 7.55 − 7.59 (m, 1H),. 6.96 (d, *J* = 9.2Hz, 2H). **IR (KBr, cm^{-1})**: 3040, 1660, 1404, 1221.



1,3-bis(4-Chlorophenyl)-2-hydroxy-3-(1*H*-indol-3-yl)propan-1-one (15a):

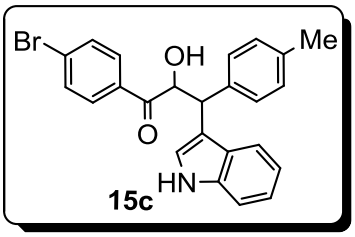
Yield: 85%; yellow semisolid; **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 3.71 (br, 1H, D_2O exchangeable, OH), 4.71 (d, 1H, *J* = 7Hz), 5.82 (d, 1H, *J* = 7Hz), 6.91 (d, 2H, *J* = 8.5Hz), 6.96 (t, 1H, *J* = 7.5Hz), 7.12-7.13 (m, 3H), 7.37 (d, 2H, *J* = 8.5Hz), 7.51 (dd, 2H, *J* = 8.5, 2Hz), 7.67 (m, 1H), 7.87 (d, 2H, *J* = 8.5Hz), 8.19 (br, 1H, D_2O exchangeable, NH). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 46.6, 75.89, 111.26, 111.16, 118.76, 119.36, 119.65, 112.36, 123.12, 126.68, 128.19, 129.55, 130.03, 130.53, 132.33, 133.01, 136.25, 140.79, 199.16. **IR (KBr, cm^{-1})**: 3420 3376, 3133, 2917, 1679, 1584, 1400, 1099, 1063, 742 cm^{-1}. **HRMS (ESIMS)**: for $C_{23}H_{17}Cl_2NNaO_2$ $(M+Na)^+$ Anal. calcd for 432.0534; found 432.0546.



1-(4-Bromophenyl)-2-hydroxy-3-(1*H*-indol-3-yl)-3-phenylpropan-1-one (15b):

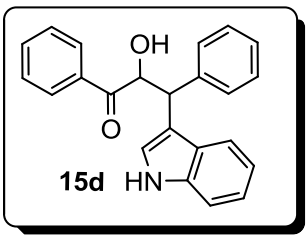
Yield: 82%; yellow semisolid. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 3.65 (br, 1H, D_2O exchangeable, OH), 4.73 (d, 1H, *J* = 7.5Hz), 5.81 (d, 1H, *J* = 7.5Hz), 6.97-7.02 (m, 2H), 7.15-7.18 (m, 4H), 7.36 (d, 2H, *J* = 8Hz), 7.66-7.69 (m, 3H), 7.79 (d, 2H, *J* = 8Hz), 8.16 (br, 1H, D_2O exchangeable, NH). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm): 46.11, 75.11, 98.96, 110.09, 115.55, 117.88, 118.50, 121.18, 122.01,

125.83, 126.15, 126.97, 128.16, 129.06, 131.40, 131.96, 134.98, 136.54, 198.49. **IR (KBr, cm^{-1})**: 3416, 3363 (OH), 3134, 2962, 2923, 2847, 1680, 1585, 1400, 1261, 1098, 1022, 803 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{23}H_{18}BrNNaO_2$ $(M+Na)^+$ 442.0418; found 442.0419.



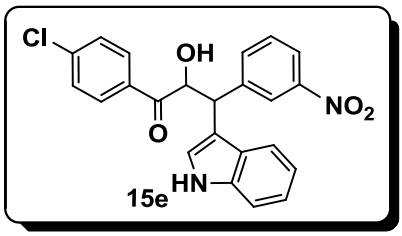
1-(4-Bromophenyl)-2-hydroxy-3-(1*H*-indol-3-yl)-3-*p*-tolylpropan-1-one (15c):

Yield: 72%; yellow solid; mp 137-139 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 2.25 (s, 3H), 3.61 (br, 1H, D_2O-exchangeable, OH), 4.70 (d, 1H, *J* = 7.5Hz), 5.79 (d, 1H, *J* = 7.5Hz), 6.86 (dd, 2H, *J* = 8, 1.5Hz), 6.95 (d, 2H, *J* = 4.5Hz), 7.14 (t, 2H, *J* = 7.5Hz), 7.18 (d, 1H, *J* = 8.5Hz), 7.35 (d, 1H, *J* = 8Hz), 7.65-7.67 (m, 2H), 7.78-7.84 (m, 3H), 8.14 (br, 1H, D_2O-exchangeable, NH). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 21.02, 46.71, 76.21, 111.06, 116.71, 118.71, 119.44, 122.11, 122.92, 126.85, 128.71, 129.99, 130.05, 132.35, 133.02, 134.45, 135.99, 136.62, 199.57. **IR (KBr, cm^{-1})**: 3456, 3392, 3133, 2917, 1679, 1584, 1400, 1099, 1063, 742 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{24}H_{20}BrNNaO_2$ $(M+Na)^+$ 456.0575; found 456.0528.



2-Hydroxy-3-(1*H*-indol-3-yl)-1,3-diphenylpropan-1-one (15d):

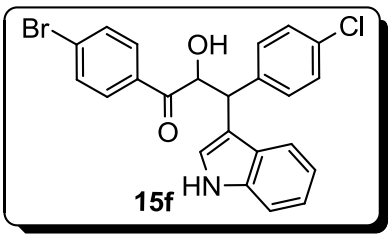
Yield: 81%; yellow semisolid. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 3.72 (br, 1H, D_2O-exchangeable, OH), 4.79 (d, 1H, *J* = 7.5Hz), 5.87 (d, 1H, *J* = 7.5Hz), 6.43-6.46 (m, 1H), 7.12-7.20 (m, 5H), 7.93-7.95 (m, 2H), 7.54 (t, 2H, *J* = 7.5Hz), 7.62-7.71 (m, 3H), 7.94 (d, 2H, *J* = 7.5Hz), 8.19 (br, 1H, D_2O-exchangeable, NH). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 47.12, 76.15, 100.89, 107.68, 111.13, 116.82, 118.98, 112.12, 123.12, 126.97, 127.90, 128.70, 129.31, 132.33, 134.01, 136.08, 137.74, 165.31, 200.44. **IR (KBr, cm^{-1})**: 3412, 3124, 2923, 1680, 1626, 1452, 1258, 1106, 744, 697 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{23}H_{19}NNaO_2$ $(M+Na)^+$ 364.1313; found 364.1322.



1-(4-Chlorophenyl)-2-hydroxy-3-(1*H*-indol-3-yl)-3-(3-nitrophenyl)propan-1-one (15e):

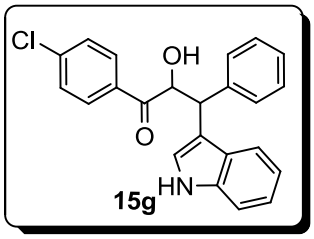
Yield: 86%; yellow semisolid. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 3.80 (1H, D_2O-exchangeable, OH), 4.79 (d, 1H, *J* = 7Hz), 5.90 (d, 1H, *J* = 7Hz), 7.02 (t, 2H, *J* = 7.5Hz), 7.18 (t, 2H, *J* = 8Hz), 7.34-7.38 (m, 5H), 7.45 (t, 2H, *J* = 8Hz), 7.69 (d, 1H, *J* = 7.5Hz), 8.01 (br, 1H, D_2O-exchangeable, NH), 8.21 (s, 1H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 48.05, 76.21, 101.03, 107.53, 111.15, 116.92, 119.05, 122.32, 123.45, 126.84, 127.80, 127.94, 128.72, 129.32, 130.32, 132.34, 134.21, 136.10, 137.98, 139.88, 148.32. **IR (KBr, cm^{-1})**: 3407, 3141, 2921, 2847, 1677, 1590, 1527, 1400,

1348, 1093, 738 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{23}H_{17}ClN_2NaO_4$ $(M+Na)^+$ 443.0877; found 443.0886.



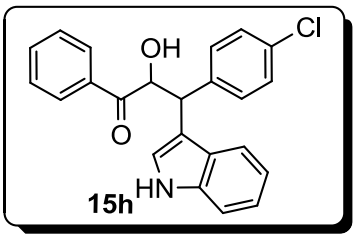
1-(4-Bromophenyl)-3-(4-chlorophenyl)-2-hydroxy-3-(1*H*-indol-3-yl)propan-1-one (15f):

Yield: 86%; yellow semisolid. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 3.69 (br, 1H, D_2O-exchangeable, OH), 4.70 (d, 1H, *J* = 7Hz), 5.82 (d, 1H, *J* = 7Hz), 6.91 (d, 2H, *J* = 8.5Hz), 6.94 (t, 2H, *J* = 7.5Hz), 7.11-7.19 (m, 4H), 7.34 (d, 2H, *J* = 8.5Hz), 7.46 (m, 1H), 7.55 (dd, 2H, *J* = 7.5, 2Hz), 8.18 (br, 1H, D_2O exchangeable, NH). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 46.8, 75.88, 111.27, 111.18, 118.78, 119.26, 119.55, 112.38, 123.15, 126.70, 128.21, 129.58, 130.03, 130.53, 132.33, 133.01, 136.25, 140.79 and 199.16. **IR (KBr, cm^{-1})**: 3412, 3124, 2923, 1680, 1626, 1452, 1258, 1106, 744, 697 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{23}H_{17}BrClNNaO_2$ $(M+Na)^+$ 477.7436; found 477.7449.



1-(4-Chlorophenyl)-2-hydroxy-3-(1*H*-indol-3-yl)-3-phenylpropan-1-one (15g):

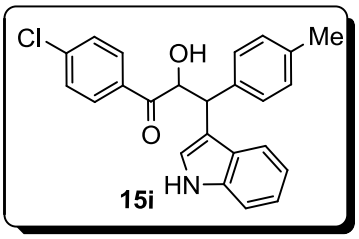
Yield: 82%; yellow semisolid. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 3.65 (br, 1H, D_2O-exchangeable, OH), 4.73 (d, 1H, *J* = 7.5Hz), 5.81 (dd, 1H, *J* = 7.5, 2Hz), 6.94-6.99 (m, 3H), 7.12-7.18 (m, 5H), 7.34 (d, 1H, *J* = 8.5Hz), 7.67-7.78 (m, 3H), 7.86 (d, 2H, *J* = 8.5Hz), 8.16 (br, 1H, D_2O-exchangeable, NH). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 47.20, 76.17, 111.17, 116.56, 118.93, 119.54, 122.22, 123.10, 126.89, 127.20, 128.02, 129.23, 129.45, 130.05, 132.62, 136.05, 137.65, 140.53, 199.36**. IR (KBr, cm^{-1})**: 3414, 3328, 3058, 2923, 1680, 1589, 1400, 1262, 1093, 742, 704 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{23}H_{18}ClNNaO_2$ $(M+Na)^+$ 398.1026; found 398.1000.



3-(4-Chlorophenyl)-2-hydroxy-3-(1*H*-indol-3-yl)-1-phenylpropan-1-one (15h):

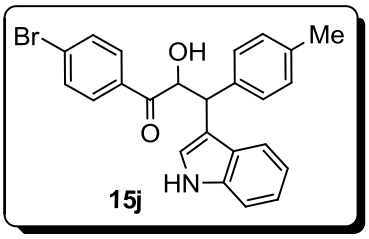
Yield: 85%; yellow solid; mp 94-96 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 3.80 (br, 1H, D_2O-exchangeable, OH), 4.74 (d, 1H, *J* = 7Hz), 5.85 (d, 1H, *J* = 7Hz), 6.88 (dd, 2H, *J* = 8.5, 2Hz), 6.93 (td, 1H, *J* = 7, 1Hz), 7.08-7.14 (m, 4H), 7.29 (d, 1H, *J* = 8.5Hz), 7.49 (t, 2H, *J* = 7.5Hz), 7.62-7.65 (m, 2H), 7.90 (dd, 2H, *J* = 3.5, 1Hz), 8.22 (br, 1H, D_2O-exchangeable, NH). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 46.58, 75.92, 111.31, 116.33, 118.86, 119.57, 122.30, 123.23, 126.78, 128.15, 128.74, 129.24, 130.69,

132.92, 134.05, 134.29, 136.13, 136.44, 200.37. **IR (KBr, cm^{-1})**: 3419, 3353, 3050, 2900, 1672, 1488, 1403, 1264, 1090, 982, 778, 740, 690. **HRMS (ESIMS)**: Anal. calcd for $C_{23}H_{18}ClNNaO_2$ $(M+Na)^+$ 398.1026; found 398.1011.



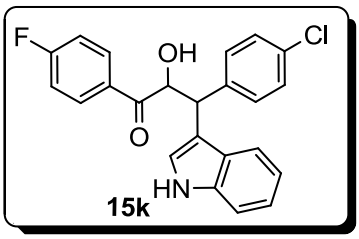
1-(4-Chlorophenyl)-2-hydroxy-3-(1*H*-indol-3-yl)-3-*p*-tolylpropan-1-one (15i):

Yield: 72%; yellow solid; mp 123-125 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 2.22 (s, 3H), 3.67 (br, 1H, D_2O-exchangeable, OH), 4.68 (d, 1H, *J* = 7.5Hz), 5.76 (dd, 1H, *J* = 7.5, 1.5Hz), 6.85 (d, 2H, *J* = 8Hz), 6.94 (d, 3H, 8Hz), 7.09-7.12 (m, 1H), 7.17 (d, 1H, *J* = 7.5Hz), 7.26 (d, 1H, *J* = 8Hz), 7.43 (d, 2H, *J* = 8.5Hz), 7.57 (s, 1H), 7.81 (d, 2H, *J* = 8.5Hz), 8.15 (br, 1H, D_2O-exchangeable, NH). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 21.15, 46.82, 76.24, 111.25, 116.68, 118.89, 119.51, 122.18, 123.11, 124.5, 126.92, 128.84, 129.11, 129.47, 130.10, 132.63, 134.58, 136.74, 140.52, 199.53. **IR (KBr, cm^{-1})**: 3446, 3389, 3050, 2920, 1680, 1589, 1455, 1399, 1262, 1093, 991, 742 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{24}H_{20}ClNNaO_2$ $(M+Na)^+$ 412.1183; found 412.1196.



1-(*p*-Tolyl)-2-hydroxy-3-(1*H*-indol-3-yl)-3-(4-bromophenyl)-propan-1-one (15j):

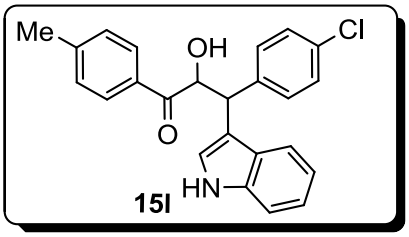
Yield: 71%; yellow semisolid. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 2.24 (s, 3H), 3.63 (br, 1H, D_2O-exchangeable, OH), 4.69 (d, 1H, *J* = 7.5Hz), 5.78 (dd, 1H, *J* = 7.5, 2Hz), 6.85 (d, 2H, *J* = 8Hz), 6.94-6.96 (m, 2H), 7.13 (t, 2H, *J* = 8Hz), 7.17 (d, 1H, *J* = 7.5Hz), 7.33 (d, 1H, *J* = 8Hz), 7.64-7.66 (m, 3H), 7.78 (dd, 2H, *J* = 6.5, 1.5Hz), 8.15 (br, 1H, D_2O-exchangeable, NH). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 21.15, 46.82, 76.24, 111.25, 116.68, 118.99, 119.51, 122.18, 123.11, 126.92, 128.84, 129.11, 129.47, 130.10, 132.63, 134.58, 136.08, 136.74, 140.52, 199.53. **IR (KBr, cm^{-1})**: 3416, 3133, 2922, 1680, 1584, 1399, 1262, 1100, 990, 745 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{24}H_{20}BrNNaO_2$ $(M+Na)^+$ 456.0677; found 456.0680.



3-(4-Chlorophenyl)-1-(4-fluorophenyl)-2-hydroxy-3-(1*H*-indol-3-yl)propan-1-one (15k):

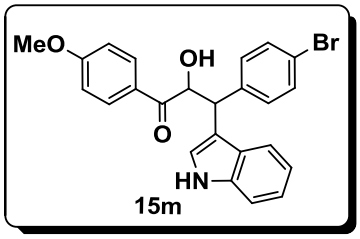
Yield: 85%; yellow semisolid. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 3.76 (br, 1H, D_2O-exchangeable, OH), 4.69 (d, 1H, *J* = 7Hz), 5.79 (d, 1H, *J* = 7Hz), 6.89 (d, 2H, *J* = 2Hz), 6.95 (t, 1H, *J* = 7Hz), 7.09-7.18 (m, 6H), 7.29 (d, 1H, *J* = 3Hz), 7.61 (m, 1H), 7.91-7.93 (m, 2H), 8.23 (br, 1H, D_2O-exchangeable,

NH). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 46.53, 75.65, 111.20, 116.03, 116.29, 116.47, 118.67, 119.50, 122.23, 123.06, 126.56, 128.07, 130.46, 131.34, 132.85, 135.94, 136.18, 167.20, 198.63. **IR (KBr, cm^{-1})**: 3415, 3124, 2924, 1679, 1597, 1457, 1238, 1093, 842, 744 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{23}H_{17}ClFNNaO_2$ $(M+Na)^+$ 416.0932; found 416.0946.



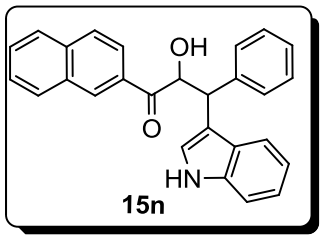
3-(4-Chlorophenyl)-2-hydroxy-3-(1*H*-indol-3-yl)-1-*p*-tolylpropan-1-one (15l):

Yield: 82%; yellow semisolid. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 2.22 (s, 3H), 3.62 (br, 1H, D_2O-exchangeable, OH), 4.62 (d, 1H, *J* = 7.6Hz), 5.80 (dd, 1H, *J* = 7.6, 2.5Hz), 6.80 (d, 2H, *J* = 7.5Hz), 6.91-6.94 (m, 3H), 7.14 (t, 2H, *J*= 7.5Hz), 7.20 (d, 1H, *J* = 8Hz), 7.35 (d, 1H, *J* = 8Hz), 7.66-7.69 (m, 2H), 7.78 (dd, 2H, *J* = 6.5, 1.5Hz), 8.17 (br, 1H, D_2O-exchangeable, NH). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 21.19, 46.78, 76.85, 112.12, 116.68, 119.09, 119.51, 122.81, 123.41, 126.29, 129.04, 129.15, 129.47, 130.10, 132.36, 134.57, 136.08, 136.74, 139.66, 200.13. **IR (KBr, cm^{-1})**: 3410, 3130, 2924, 1678, 1581, 1400, 1262 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{24}H_{20}ClNNaO_2$ $(M+Na)^+$ 412.1183; found 412.1186.



3-(4-Bromophenyl)-2-hydroxy-3-(1*H*-indol-3-yl)-1-(4-methoxyphenyl)propan-1-one (15m):

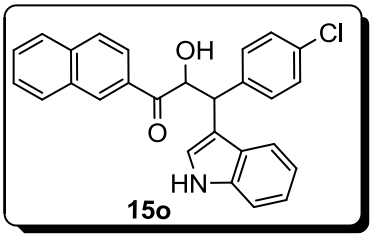
Yield: 80%; yellow semisolid. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 3.68 (br, 1H, D_2O-exchangeable, OH), 3.89 (s, 3H), 4.66 (d, 1H, *J* = 7.6Hz), 5.88 (dd, 1H, *J* = 7.6, 2.5Hz), 6.85 (d, 2H, *J* = 7.5Hz), 7.14 (t, 2H, *J* = 7.5Hz), 7.20 (d, 1H, *J* = 8Hz), 7.35 (d, 1H, *J* = 8Hz), 7.66-7.71 (m, 3H), 7.78 (dd, 2H, *J* = 6.5, 1.5Hz), 7.80 (d, 2H, *J* = 7.5Hz), 8.17 (br, 1H, D_2O-exchangeable, NH). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 46.78, 55.45, 76.85, 112.12, 116.68, 119.09, 119.51, 122.81, 123.41, 126.29, 129.04, 129.15, 129.47, 130.10, 132.36, 134.57, 136.08, 136.74, 139.66, 200.13. **IR (KBr, cm^{-1})**: 3410, 1678, 1554, 1412, 1256 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{24}H_{20}BrNNaO_3$ $(M+Na)^+$ 472.0627; found 472.0631.



2-Hydroxy-3-(1*H*-indol-3-yl)-1-(naphthalen-2-yl)-3-phenylpropan-1-one (15n):

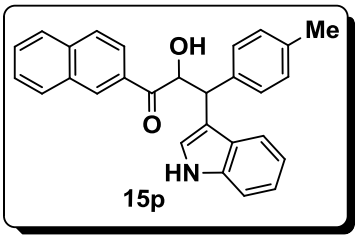
Yield: 88%; yellow solid; mp 122-124 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 3.82 (br, 1H, D_2O-exchangeable, OH), 4.88 (d, 1H, *J* = 7.5Hz),6.02 (dd, 1H, *J* = 7.5, 2Hz), 6.92 (t, 1H, *J* = 7.5Hz), 6.98 (d, 2H, *J* = 6.5Hz),

7.11-7.16 (m, 5H), 7.33 (d, 1H, *J* = 8Hz), 7.57 (t, 1H, 7Hz), 7.64 (t, 1H, *J* = 7Hz), 7.34 (s, 1H), 7.91-7.95 (m, 4H), 8.21 (br, 1H, D_2O-exchangeable, NH), 8.47 (s, 1H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 47.40, 76.24, 111.17, 116.84, 119.48, 122.15, 123.22, 124.16, 127.00, 127.12, 127.96, 129.11, 129.16, 129.36, 129.84, 130.46, 131.55, 132.54, 136.03, 136.07, 137.81, 140.21, 200.41. **IR (KBr, cm^{-1})**: 3442, 3133, 3058, 2922, 1670, 1402, 1277, 1093, 749 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{27}H_{21}NNaO_2$ $(M+Na)^+$ 414.1572; found 414.1586.



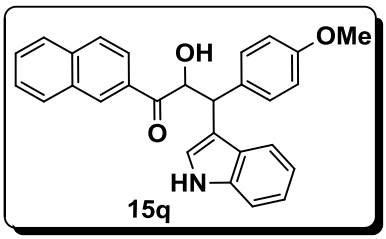
3-(4-Chlorophenyl)-2-hydroxy-3-(1*H*-indol-3-yl)-1-(naphthalen-2-yl)propan-1-one (15o):

Yield: 86%; yellow semisolid. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 3.85 (br, 1H, D_2O-exchangeable, OH), 4.85 (d, 1H, 7.5Hz), 6.02 (dd, 1H, *J* = 7.5, 1.5Hz), 6.89-6.95 (m, 3H), 7.10-7.16 (m, 4H), 7.37 (d, 1H, *J* = 9.5Hz), 7.59 (t, 1H, *J* = 7Hz), 7.67 (t, 1H, *J* 7.5Hz), 7.75 (s, 1H), 7.93-7.99 (m, 5H), 8.22 (br, 1H, D_2O-exchangeable, NH). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 46.81, 75.97, 111.24, 116.46, 118.90, 119.60, 122.31, 123.22, 124.04, 126.79, 127.31, 127.98, 128.13, 129.24, 129.27, 129.83, 130.50, 130.66, 131.28, 132.52, 132.91, 136.07, 136.09, 136.43, 200.21. **IR (KBr, cm^{-1})**: 3411, 3055, 2920, 1673, 1486, 1408, 1272, 1093, 1015, 742 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{27}H_{20}ClNNaO_2$ $(M+Na)^+$ 448.1183; found 448.1200.



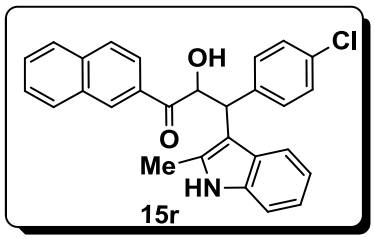
2-Hydroxy-3-(1*H*-indol-3-yl)-1-(naphthalen-2-yl)-3-*p*-tolylpropan-1-one (15p):

Yield: 73%; yellow semisolid. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 2.14 (s, 3H), 3.73 (br, 1H, D_2O-exchangeable, OH), 4.76 (d, 1H, *J* = 7.5Hz),5.90 (dd, 1H, *J* = 7.5, 1.6Hz), 6.77-6.85 (m, 5H), 7.01 (t, 1H, *J* = 8Hz), 7.07 (d, 1H, *J* = 8Hz), 7.20 (d, 1H, *J* = 8Hz), 7.45 (t, 1H, *J* = 7Hz), 7.53 (t, 1H, *J* = 7Hz), 7.60 (s, 1H), 7.79-7.85 (m, 4H), 8.13 (br, 1H, D_2O-exchangeable, OH), 8.36 (s, 1H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 21.15, 47.04, 76.33, 111.20, 116.99, 119.12, 119.45, 122.12, 123.19, 124.20, 127.05, 127.19, 127.97, 128.75, 129.10, 129.14, 129.23, 129.85, 130.49, 131.62, 132.56, 134.76, 136.03, 136.11, 136.58, 200.56. **IR (KBr, cm^{-1})**: 3500, 3406, 3051, 2920, 1674, 1456, 1412, 1277, 1096, 749 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{28}H_{23}NNaO_2$ $(M+Na)^+$ 428.1729; found 428.1705.



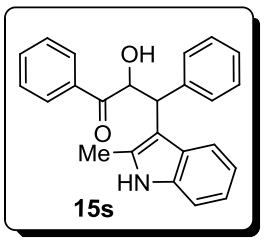
2-Hydroxy-3-(1*H*-indol-3-yl)-3-(4-methoxyphenyl)-1-(naphthalene-2-yl)propan-1-one (15q) :

Yield: 60%; yellow semisolid. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 3.67 (s, 3H), 4.12 (br, 1H, D_2O-exchangeable, OH), 4.69 (d, 1H, *J* = 7Hz), 5.89 (dd, 1H, *J* = 7, 1.5Hz), 6.77 (dd, 2H, *J* = 6.6, 2Hz), 6.95 (t, 1H, *J* = 8Hz), 7.01-7.04 (m, 2H), 7.05-7.11 (m, 1H), 7.16-7.18 (m, 1H), 7.30-7.38 (m, 3H), 7.51 (t, 1H, *J* = 8Hz), 7.57 (t, 2H, *J* = 5.5Hz), 7.77-7.82 (m, 2H), 8.12-8.22 (m, 2H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 48.2, 55.3, 76.1, 102.03, 110.88, 114.17, 119.53, 120.23, 121.59, 124.00, 127.22, 127.75, 127.95, 129.01, 129.11, 129.41, 129.71, 130.39, 131.36, 131.85, 132.39, 135.93, 136.01, 136.39, 200.33. **IR (KBr, cm^{-1})**: 3412, 3129, 2924, 2854, 1675, 1510, 1457, 1403, 1250, 1179, 1029, 744 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{28}H_{23}NNaO_3$ $(M+Na)^+$ 444.1678; found 444.1681.



3-(4-Chlorophenyl)-2-hydroxy-3-(2-methyl-1*H*-indol-3-yl)-1-(naphthalen-2-yl)propan-1-one (15r):

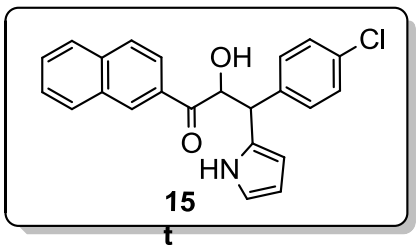
Yield: 74%; yellow semisolid; **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 2.17 (s, 3H), 3.72 (br, 1H, D_2O-exchangeable, OH), 4.60 (d, 1H, *J* = 7Hz), 6.02 (d, 1H, *J* = 7Hz), 6.89-6.95 (m, 3H), 7.12-7.19 (m, 3H), 7.33 (d, 1H, *J* = 9.5Hz), 7.51 (t, 1H, *J* = 7Hz), 7.67 (t, 1H, *J* = 7.5Hz), 7.79 (s, 1H), 7.96-8.03 (m, 5H), 8.21 (br, 1H, D_2O-exchangeable, NH). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 11.94, 47.18, 73.59, 99.95, 110.24, 111.23, 119.16, 119.55, 119.85, 120.72, 121.38, 123.23, 126.66, 127.51, 128.14, 128.79, 129.64, 130.44, 131.10, 131.89, 131.91, 132.13, 135.29, 135.53, 138.69, 202.17. **IR (KBr, cm^{-1})**: 3522, 3421, 3075, 2931, 1686, 1492, 1434, 1299, 1093, 1017 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{28}H_{22}ClNNaO_2$ $(M+Na)^+$ 462.1399; found 462.1376.



2-Hydroxy-3-(2-methyl-1*H*-indol-3-yl)-1,3-diphenylpropan-1-one (15s):

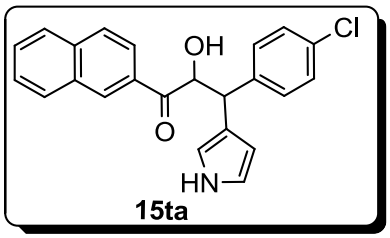
Yield: 75%; yellow semisolid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 2.11 (s, 3H), 3.81 (br, 1H, D_2O-exchangeable, OH), 4.79 (d, 1H, *J* = 7.5Hz), 5.87 (dd, 1H, *J* = 7.5, 1.5Hz), 6.43-6.46 (m, 1H), 7.12-7.17 (m, 2H), 7.12-7.17 (m, 3H), 7.93-7.95 (m, 2H), 7.54 (t, 2H, *J* = 7.5Hz), 7.62-7.71 (m, 2H), 7.94 (d, 2H, *J* = 7.5Hz), 8.19 (br, 1H, D_2O-exchangeable, NH). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 22.01, 47.12, 76.15, 100.89, 107.68, 111.13, 116.82, 118.98, 112.12, 123.12, 126.97, 127.90, 128.70, 129.31, 132.33, 134.01, 136.08, 137.74, 165.31, 200.44. **IR (KBr, cm^{-1})**: 3421, 3131, 2973, 1675, 1630, 1464,

1274, 1123, 764, 667 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{24}H_{21}NO_2$ $(M+Na)^+$ 378.1472; found 378.1508.



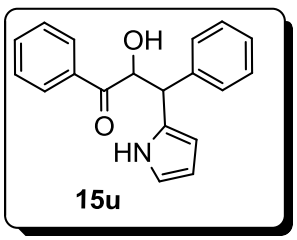
3-(4-Chlorophenyl)-2-hydroxy-1-(naphthalen-2-yl)-3-(1*H*-pyrrol-2-yl)propan-1-one (15t):

Yield: 70%; light yellow semisolid. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 3.79 (br, 1H, D_2O-exchangeable, OH), 4.79 (d, 1H, *J* = 7.5Hz), 5.87 (dd, 1H, *J* = 7.5, 1.5Hz), 6.02 (dd, 1H, *J* = 5.4, 3.6Hz), 6.13 (dd, 1H, *J* = 5.4, 2.5Hz), 6.4-6.54 (m, 1H), 6.71 (dd, 1H, *J* = 3.6, 2.5Hz), 6.77 (dd, 2H, *J* = 6.6, 2Hz), 6.95 (t, 1H, *J* = 8Hz), 7.01-7.04 (m, 2H), 7.05-7.11 (m, 1H), 7.16-7.18 (m, 1H), 7.30-7.38 (m, 2H), 7.51 (t, 1H, *J* = 8Hz), 8.19 (br, 1H, D_2O-exchangeable, NH). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 47.12, 76.15, 100.89, 106.0, 108.4, 116.82, 118.0, 112.12, 123.12, 126.97, 127.90, 128.70, 129.31, 131.91, 132.1, 134.01, 136.08, 137.74, 165.31, 200.44. **IR (KBr, cm^{-1})**: 3412, 3124, 2923, 1680, 1626, 1452, 1258, 1106, 744, 697 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{23}H_{18}ClNO_2$ $(M)^+$ 375.1026; found 375.1053.



3-(4-Chlorophenyl)-2-hydroxy-1-(naphthalen-2-yl)-3-(1H-pyrrol-3-yl)propan-1-one (15ta):

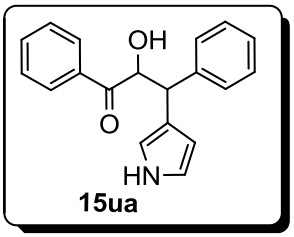
Yield: 27%; light yellow semisolid. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 4. 09 (br, 1H, D_2O-exchangeable, OH), 4.67 (d, 1H, *J* = 7.5Hz), 5.89 (dd, 1H, *J* = 7.5, 1.5Hz), 6.11 (dd, 1H, *J* = 3.5, 2.5Hz), 6.22 (dd, 1H, *J* = 3.5, 2Hz), 6.76 (dd, 2H, *J* = 2.5, 2Hz), 6.82 (dd, 1H, *J* = 6.5, 2Hz), 7.10 (dd, 2H, *J* = 8, 2Hz), 7.61-7.64 (m, 1H), 7.67-7.70 (m, 1H), 7.90-7.95 (m, 2H), 7.98-8.01 (m, 2H), 8.46 (s, 1H), 9.35 (br, 1H, D2O-exchangeable, NH). **^{13}C NMR (CDCl3, 125 MHz)**: δ (ppm) 47.11, 76.15, 101.09, 106.3, 107.4, 114.12, 119.01, 122.13, 125.02, 127.03, 127.92, 128.72, 129.34, 132.01, 133.12, 134.01, 136.08, 137.74, 164.11, 198.96. **IR (KBr, cm^{-1})**: 3422, 3132, 2925, 1676 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $(M)^+$ $C_{23}H_{18}ClNO_2$ 375.1026; found 375.1053.



2-Hydroxy-1,3-diphenyl-3-(1H-pyrrol-2-yl)propan-1-one (15u):

Yield: 70%; light yellow semisolid; **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 3.77 (br, 1H, D_2O-exchangeable, OH), 4.75 (d, 1H, *J* = 7.5Hz), 5.89 (dd, 1H, *J* = 7.5, 1.5Hz), 6.15 (dd, 1H, *J* = 5.4, 3.6Hz), 6.18 (dd, 1H, *J* = 5.4, 2.5Hz), 6.66 (dd, 1H, *J* = 3.6, 2.5Hz), 7.11-7.45 (m, 10H), 8.19 (br, 1H, D_2O-exchangeable, NH). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 43.54, 86.75, 106.16, 108.44,

118.63, 126.08, 126.46, 127.21, 128.00, 129.10, 129.78, 130.03, 132.33, 136.20, 200.44. **IR (KBr, cm^{-1})**: 3412, 3124, 2923, 1680, 1636, 1443, 1270, 1122, 765 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $(M)^+$ $C_{19}H_{17}NO_2$ 291.1259; found 291.1304.



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2-Hydroxy-1,3-diphenyl-3-(1H-pyrrol-3-yl)propan-1-one (16ta): Yield: 27%; light yellow semisolid. **^{1}H NMR (CDCl3, 500 MHz)**: δ (ppm) 3.79 (br, 1H, D2O-exchangeable, OH), 4.76 (d, 1H, *J* = 7.5Hz), 5.86 (dd, 1H, *J* = 7.5, 1.5Hz), 6.22 (dd, 1H, *J* = 3.5, 2.5Hz), 6.65 (dd, 1H, *J* = 3.5, 2Hz), 6.78 (dd, 1H, *J* = 2.5, 2Hz), 7.10-7.53 (m, 10H), 8.16 (br, 1H, D_2O-exchangeable, NH). **^{13}C NMR (CDCl3, 125 MHz)**: δ (ppm) 43.54, 86.75, 108.26, 116.83, 119.05, 120.24, 125.96, 127.19, 128.12, 129.21, 129.66, 130.63 131.52, 135.73, 200.37. **IR (KBr, cm^{-1})**: 3446, 3389, 3126, 2943, 1676 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{19}H_{17}NO_2$ $(M)^+$ 291.1259; found 291.1304.

4.8. REFERENCES

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Chapter-5

SYNTHESIS OF CHALCONE BASED SULFONES AND BISULFONES AND THEIR ANTIMICROBIAL EVALUATION

PART-A

SYNTHESIS, ANTIBACTERIAL AND ANTIFUNGAL EVALUATION OF SOME CHALCONE BASED SULFONES AND BISULFONES

Eur. J. Med. Chem. **2013**, *59,* 23-30.

PART-B

DESIGN, SYNTHESIS AND ANTIMICROBIAL ACTIVITIES OF NOVEL FERROCENYL AND ORGANIC CHALCONE BASED SULFONES AND BIS-SULFONES

[Communicated….]

SYNTHESIS OF CHALCONE BASED SULFONES AND BISULFONES AND THEIR ANTIMICROBIAL EVALUATION

5.1. INTRODUCTION

Micro-organisms are present everywhere on earth from geothermal vents to the coldest Arctic ice. They play both beneficial and harmful roles in our life. For example, the beneficial roles include production of oxygen *via* photosynthesis, circulation of carbon by decomposition of dead organic matter, nitrogen fixation, formation of crude oil, and helping animals to digest their food. And also used for making bread, beer, cheese, and antibiotics. Some of the harmful effects are caused by the virulence of pathogenic micro-organisms, for example, infection causing bacteria such as *Staphylococcus aureus* (*S. aureus*), *Escherichia coli* (*E. coli*), and *Enterococcus faecalis* (*E. faecalis*) etc. [1].

Over the past several decades, the considerable growth of bacterial, mycobacterial, viral and associated fungal infections can be noticed. This correlates in part with the increasing number of patients being admitted to intensive care units, HIV-positive individuals, AIDS patients, organ transplant recipients and individuals who are hospitalized for long periods and subjected to antibiotic therapy, application of corticosteroids, parenteral nutrition and invasive medical procedures in intensive care [2]. In the latter half of the 19^{th} century, micro-organisms were found to be responsible for a variety of infectious diseases that had been afflicting humanity from ancient days. Accordingly, chemotherapy aimed at the causative organisms was developed as the main therapeutic strategy. The first antimicrobial agent in the world was salvarsan, a remedy for syphilis that was synthesized by Ehrlich in 1910. In 1935, sulfonamides were developed by Domagk and other researchers. These drugs had limitations in terms of safety and efficacy [3]. Therefore many antimicrobial compounds used for the prevention or treatment of infections have been rendered less effective through evolved bacterial drug resistance. This has underlines the importance of searching for new, fast-acting, broad spectrum antimicrobial agents with reduced potential for inducing resistance.

Despite advances in the multimodal management of a wide spectrum of human microbial infections, it remains life-threatening along with the drug-resistant bacterial and fungal strains globally, highlighting the need for the development of new drugs. Interestingly, the nature has proven to be one of the best sources of molecules that can help in the prevention or treatment [4]. Therefore, the search for new natural molecules, semi-synthetic and synthetic molecules that display fast-acting

and broad spectrum antimicrobial activity against bacteria and fungi are of great interest for the scientific community and the pharmaceutical industry.

Chalcone, bis-chalcone, sulfones and its analogous have entertained a special status as versatile building blocks in the synthesis of biologically active compounds, fine chemicals and chiral auxiliaries [5]. Many of these derivatives have been exploited in synthetic organic and medicinal chemistry [6]. Chalcone, bis-chalcone, sulfones containing molecules widely used as antimicrobial, antinociceptive and anti-inflammatory drugs [7]. Chemically sulfonyl group is well-established as activating moiety in a number of intermediates for the construction of C-C and C-heteroatoms bond formation during organic transformations [8]. Recently, they have been used in the total syntheses and in the generation of database of functionalized compounds. Also, these moieties have potential to stabilize carbanions and radicals and act as cationic reagents [9]. Similarly, sulfone groups facilitate conjugate addition by activation of the olefins with Lewis acids [10]. Moreover, the removal of sulfonyl groups might be possible by a reductive process or *via* a base promoted β-elimination route [11]. Therefore, sulfone becames quite popular functional group for organic chemistry in the generation of database of functionalized compounds. Also, the chemistry of sulfur containing ferrocene and their derivatives remained an important research area [12] in the development of novel materials [13], catalysts for asymmetric transformation of aldehydes into epoxides [14]. Ferrocenyl compounds displayed important biological, pharmaceutical activities like antitumor, antimalarial, anti-fungal and DNA cleaving properties [15].

Penicillin derivatives such as pencillin G, methicillin, ampicillin, piperacillin and sulfanilamide, tolnaftate acts as good antimicrobial drugs which contain sulphide and sulfone groups [2]. Tolnaftate is a known antifungal agent which has sulfur in an organically combined form *e.g. Allium sativum* (garlic) which is also known to inhibit *Candida albicans* [16]. In market, it is available as cream, powder, spray, and liquid aerosol. Moreover, these compounds possess a *para*-SO_2Me substitution on the phenyl ring have been reported to inhibit COX activity [17]. For example, compounds 1,3-diphenylprop-2-yn-1-one and etorocoxib exhibit selective COX-2 inhibitory activity [18]. Rofecoxib, a non-steroidal anti-inflammatory drug (NSAID), is used in treatment of arthritis and other similar conditions causing chronic or acute pain. Sulindac sulfone has been used for antitumor properties. Besides that sulindac sulfone is also used in the treatment of HCA-7 cells, led to inhibition of prostaglandin E_2 production (Fig. 1) [19].

Synthesis of sulfones is mainly reported *via* oxidation of the corresponding sulfides, which is typically achieved using stoichiometric or catalytic amounts of inorganic reagents [20]. However,

oxidation of sulfides using these reagents is slow and gives a mixture of compounds due to their rapid decomposition [21]. Therefore, extensive studies have been undertaken to develop new catalysts for such reactions. Previously, formation of chalcone based sulfones was reported in the literature although they have limitations due to poor yields, longer reaction time and need of catalysts or additives for better yield [9]. In the present study, *m*-CPBA has been used as oxidant first time at room temperature which converted quantitatively chalcone based sulfides to chalcone based sulfones under simple reaction condition.

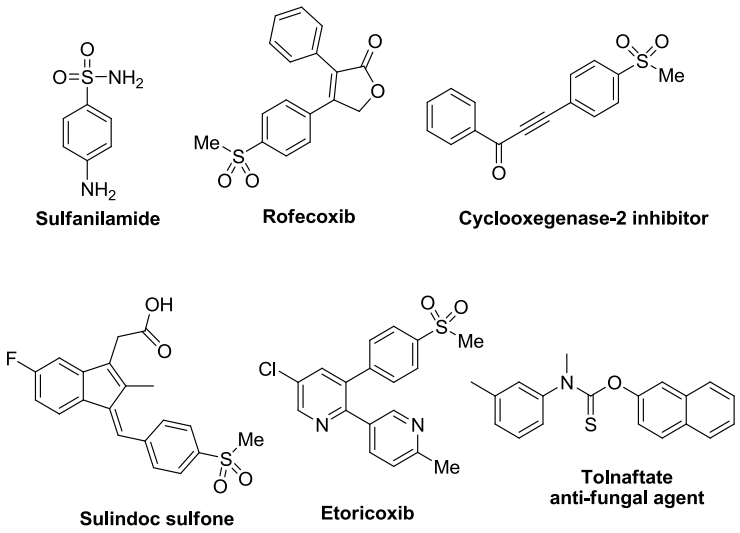
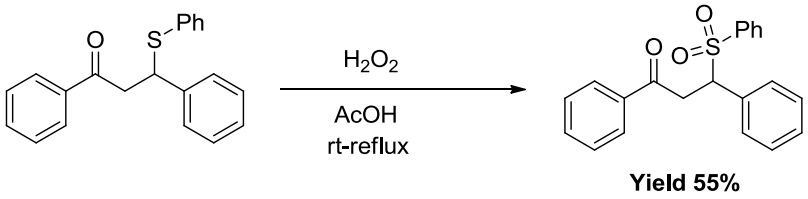


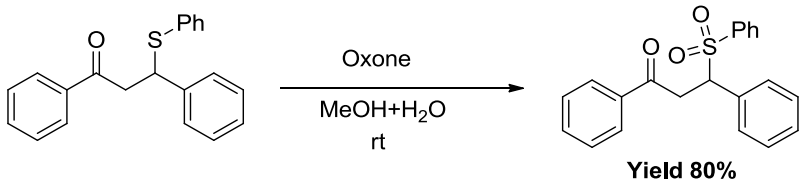
Fig. 1: Natural and biologically active sulfone derivatives.

Lakkakula *et al.* synthesized chalcone based sulfones using hydrogen peroxide in acetic acid at reflux temperature and evaluated for their antimicrobial activity [22]. However, the products obtained low yield due to decompose the oxidizing agent.



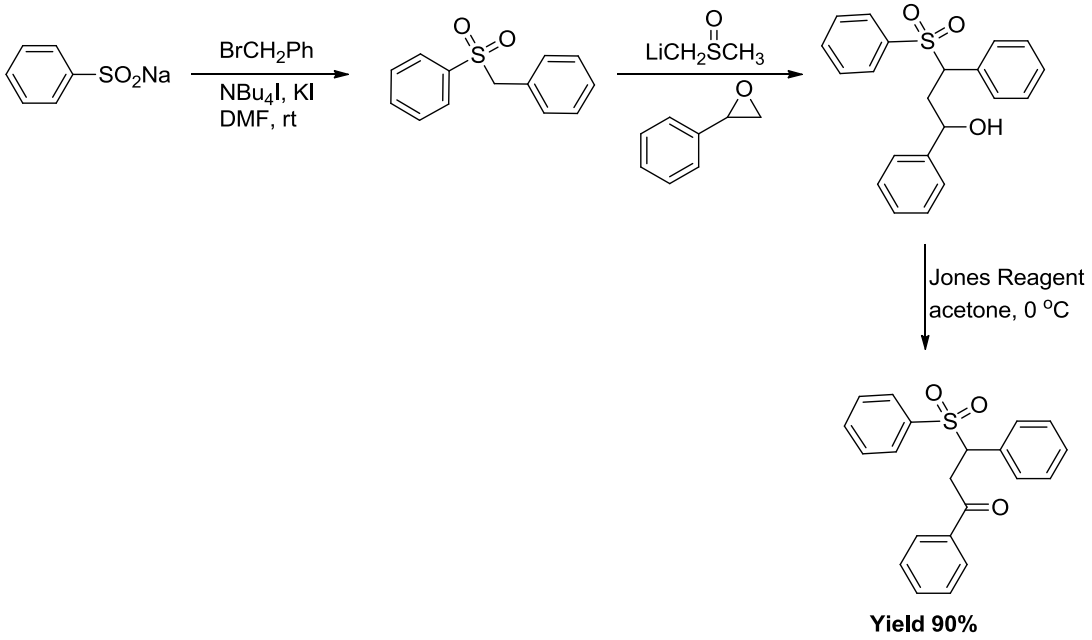
Scheme 1: Synthesis of chalcone based sulfones using hydrogen peroxide as oxidizing agent.

Skarzewski *et al.* synthesized chalcone based sulfones using oxone as oxidizing agent in methanol at room temperature [23]. However, the products obtained in low yields with expensive reagents.



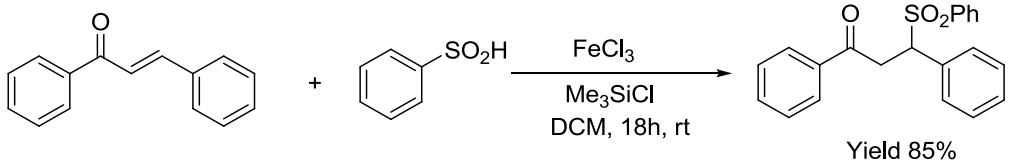
Scheme 2: Synthesis of chalcone based sulfones using oxone as oxidizing agent.

Lam *et al.* synthesized chalcone based sulfones by opening styrene oxide with [(phenylsulfonyl)methyl]benzene, followed by Jones oxidation [24]. It is multi step and expensive process, obtained overall low yield and handling of lithium reagents difficult.



Scheme 3: Synthesis of chalcone based sulfones *via* opening of epoxides.

Similarly, Sreedhar *et al.* reported chalcone based sulfones by treating chalcones with benzenesulfonic acid in presence of ferric chloride in DCM at room temperature [25]. However, it took long reaction time and given moderate yield.



Scheme 4: Synthesis of chalcone based sulfones using ferric chloride as catalyst.

Indeed, we need to develop an efficient method to synthesize flavonoid based sulfones using stable oxidizing agent in mild conditions with high yield. Therefore, in the present study, *m*-CPBA has been used as oxidant at room temperature which converted quantitatively sulfides to sulfones under simple reaction conditions. *m*-CPBA is a stable oxidizing agent, cheap, readily available, less toxic and used for various organic transformations such as epoxidation of alkenes, ketones to esters in Bayer-Villiger oxidation, silyl enol ethers to silyl α-hydroxy ketones in Rubottom oxidation, and oxidation of amines to amine oxides.

5.2. OBJECTIVE

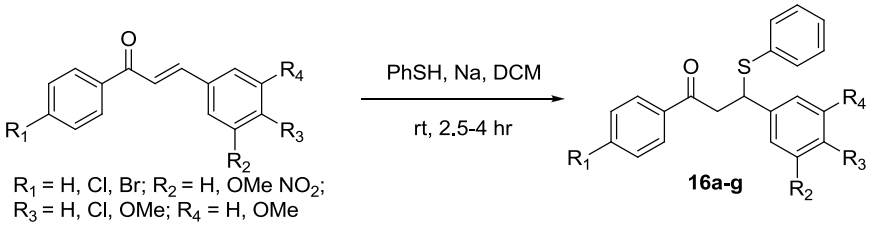
Globally each year at least 20 million people acquire serious infections with microbes. At least 23,000 people die each year as a direct result of these microbial infections. Many more die from other conditions that were complicated by a microbial infection. In addition, almost 250,000 people each year require hospital care for *Pseudomonas aeruginosa* infections. In the most of these infections, the use of antibiotics was a major contributing factor leading to the illness. At least 14,000 people die each year in India from *Staphylococcus aureus* infections. Many of these infections could have been prevented. The use of antimicrobials is the single most important factor leading to antimicrobial resistance around the world. Antimicrobials are also commonly used in food animals to prevent, control, and treat disease, and to promote the growth of food-producing animals. Therefore, we search for new antimicrobial agents herein, we report an efficient method for synthesis of chalcone based sulfones and bis-sulfone derivatives and their evaluation against some selected bacterial and fungal pathogens.

5.3. RESULTS AND DISCUSSION

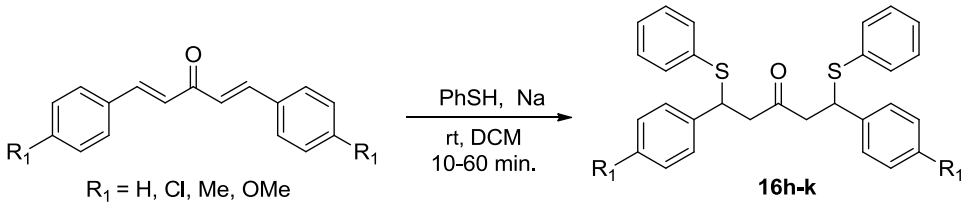
5.3.1. Part-A: Synthesis, antibacterial and antifungal evaluation of some chalcone based sulfones and bisulfones

5.3.1.1. Synthesis of chalcone based sulfide derivatives

The chalcone based sulfides were synthesized by the reaction of chalcones, thiophenol and sodium metal in DCM at room temperature *via* thia-Michael addition reaction (Schemes 5, 6).



Scheme 5: Synthesis of chalcone based sulfides.

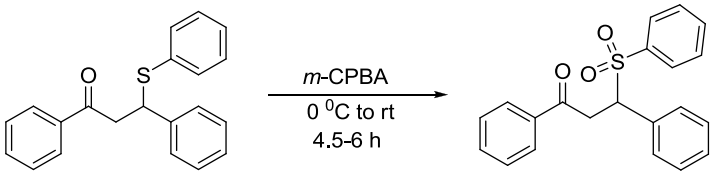


Scheme 6: Synthesis of chalcone based bisulfides.

5.3.1.2. Synthesis of chalcone based sulfones and bisulfones

Initially, we used hydrogen peroxide as an oxidant under different reaction conditions like 0 ^{0}C, room temperature and at reflux with varying solvents (AcOH, THF, ACN) which gave mixture of sulfoxide and sulfone along with about 50% reactant. Further, changes in hydrogen peroxide concentrations have unfavorable effects in the reaction due to rapid decomposition of hydrogen peroxide. Then *m*-CPBA is used as oxidant which easily converted sulfides to sulfones under an optimized reaction condition (Table 1).

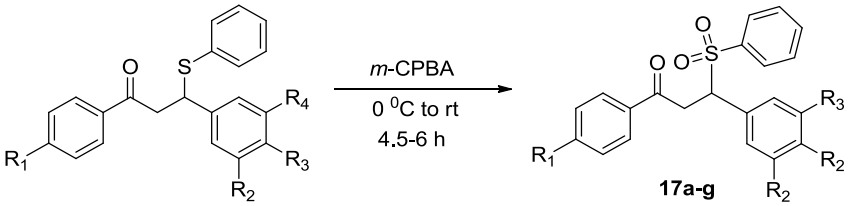
Table 1: Optimization of reaction conditions.



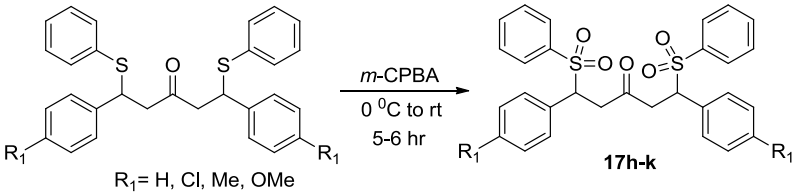
Entry	Sulfide (mmol)	*m*-CPBA (mmol)	Yield (%)	Sulfoxide : sulfone
1.	1	1	50	80:20
2.	1	1.5	60	30:70
3.	1	2	80	20:80
4.	1	2.2	95	0:100

Using above protocol, we have prepared sulfones **17a-g** and bisulfones **17h-k**. Compounds **17a-g** were prepared using sulfide and *m*-CPBA in 1:2.2 mmol ratio and compounds **17h-k** (Scheme 2) using sulfide and *m*-CPBA in 1:4.5 mmol ratio due to two-SO_2-groups which gave good yields

without further purification. No significant substituent effects were observed in sulfone formation and excellent yields obtained in all cases (Tables 2).

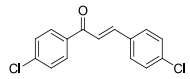
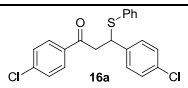
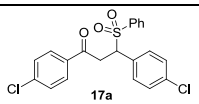
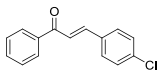
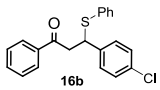
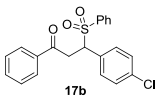
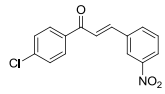
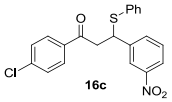
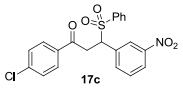
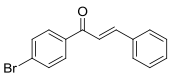
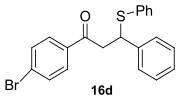
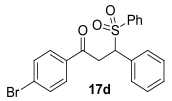
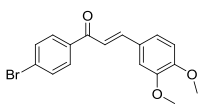
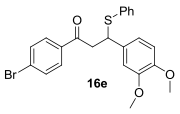
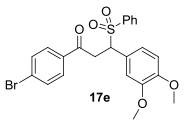
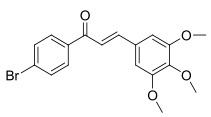
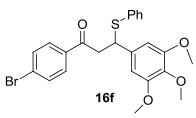
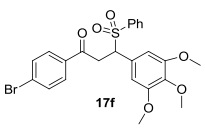


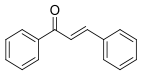
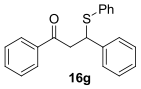
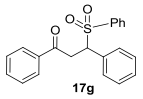
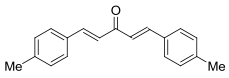
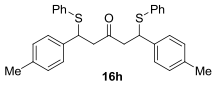
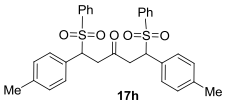
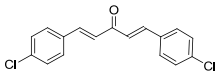
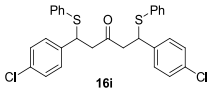
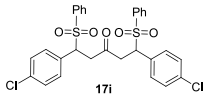
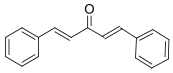
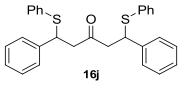
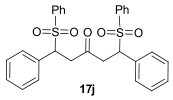
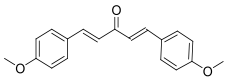
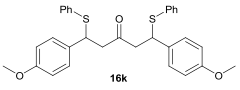
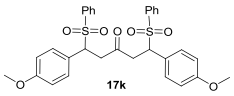
Scheme 7: Synthesis of chalcone based sulfones.



Scheme 8: Synthesis of chalcone based bisulfones.

Table 2: Synthesis of sulfones and bisulfones from chalcones.

S.No.	Chalcone	Reaction Time	Yield (%)	Michal adduct	Reaction time	Yield (%)	Sulfone
1.		4 h	90	 16a	5 h	89	 17a
2.		3 h	90	 16b	4.5 h	90	 17b
3.		3 h	92	 16c	4.5 h	88	 17c
4.		3 h	95	 16d	5 h	92	 17d
5.		3 h	95	 16e	5 h	86	 17e
6.		3 h	89	 16f	6 h	80	 17f

7.		2.5 h	95	 **16g**	4.5 h	93	 **17g**
8.		10 min	92	 **16h**	5 h	90	 **17h**
9.		10 min	90	 **16i**	5.5 h	88	 **17i**
10.		10 min	90	 **16j**	5 h	89	 **17j**
11.		60 min	89	 **16k**	6 h	80	 **17k**

5.3.1.3. STRUCTURE DETERMINATION

The assigned structures of intermediates (**16a-k**) and the new products (**17a-k**) were established by their spectral analysis (^{1}H, ^{13}C, IR and elemental analysis) and also comparison with reported values in the literature [20]. For example, compound 1-(4-chlorophenyl)-3-(4-chlorophenyl)-3-phenylsulfenylpropane-1-one **16a** obtained as a white solid. The IR spectrum of **16a** showed absorptions at 1679, 1217 cm^{-1} for carbonyl, C-S bond *asymmetric stretching* respectively. The GC-MS of **16a** showed molecular ion peak at 387 and elemental analysis data given molecular composition of $C_{21}H_{16}Cl_2OS$ supported a molecular composition of $C_{21}H_{16}Cl_2OS$ $[M]^+$. In ^{1}H NMR spectrum peak at δ_H 4.57, 3.59-3.49 corresponds to H-3, H-2 protons respectively (Fig. 2). In ^{13}C NMR spectrum peak at δ_C 195.5 corresponds to carbonyl carbon (C-1), peaks at δ_C 47.6, 44.5 corresponds to C-3, C-2 carbons respectively, confirms the product formation. The corresponding sulfone, was confirmed on the basis of their analytical data (^{1}H, ^{13}C, IR and elemental analysis). For example, compound 1,3-bis(4-chlorophenyl)-3-(phenylsulfonyl)propan-1-one **17a** obtained as a white solid. The IR spectrum of **17a** showed absorptions at 1687, 1304, 1142 cm^{-1} for carbonyl *asymmetric stretching*, -SO_2- *asymmetric* and *symmetric stretching* respectively. In the ^{1}H NMR spectrum of **17a** peak at δ_H 4.96 corresponds to H-3, peak at δ_H 4.12, 3.84 corresponds to geminal protons of H-2a, H2b. In the ^{13}C NMR spectrum of **17a** peaks at δ_C 65.74, 36.85 correspond to C-3, C-2 respectively (Fig. 2). Further, comparison with sulfide **16a** shift of H-3 proton from δ_H 4.57 to 4.96, shift of C-3 carbon from δ_C 47.6 to 65.74 in sulfone **17a** indicates sulfide conversion to sulfone. Similarly other

chalcone based sulfides (**16b-g**), and sulfones (**17b-g**) were characterized using their analytical data (experimental section). Similarly, chalcone based bisulfides and bisulfones also characterized from their analytical data. For example, compound 1,5-di(4-methylphenyl)-1,5-bis(phenylsulfenyl)pentan-3-one **16h** was obtained as a white solid. The IR spectrum of **16h** showed absorptions at 1715, 1375 cm^{-1} for carbonyl, C-S bond *asymmetric stretching* respectively. The GC-MS showed molecular ion peak at 483 and elemental analysis data given molecular composition of $C_{31}H_{30}OS_2$ $[M]^+$. In ^1H and ^{13}C NMR spectra of **16h** peaks resonating at δ_H 2.35 (s, 6H), δ_C 21.12 suggests that methyl group presence and peaks at δ_H 2.95, 4.32 corresponds to H-2, H-3 respectively (Fig. 2). In ^{13}C NMR spectrum of **16h** peak at δ_C 204.9 corresponds to carbonyl carbon (C-1), peaks at δ_C 47.42, 49.51 corresponds to C-2, C-3 carbons respectively. All of these assignments led to the confirms the product **16h** formation. The corresponding sulfone 1,5-di(4-methylphenyl)-1,5-bis(phenylsulfonyl)pentan-3-one **17h** was confirmed on the basis of their analytical data (^1H, ^{13}C, IR and elemental analysis). The product obtained as white crystalline solid. The IR spectrum of **17h** showed absorptions at 1769, 1302, 1145 cm^{-1} for carbonyl bond *asymmetric stretching*, $-SO_2-$ bond *asymmetric* and *symmetric stretching* respectively. In ^1H NMR spectrum contained peak at δ_H 4.95 corresponds to H-3, peak at δ_H 3.64, 3.17 corresponds to geminal protons H-2a, H2b. In the ^{13}C NMR spectrum of **17h** peaks at δ_C 60.55, 39.66 correspond to C-3, C-2 respectively. Further, comparison with sulfide **16h** shift of H-3 from δ_H 4.32 to 4.95, shift of carbon C-3 from δ_C 49.51 to 60.55 in sulfone **17h** indicates sulfide conversion to sulfone. Similarly the structures of other chalcone based sulfides (**16b-g**, **16i-k**), and sulfones (**17b-g**, **17i-k**) were confirmed on their analytical data (experimental section).

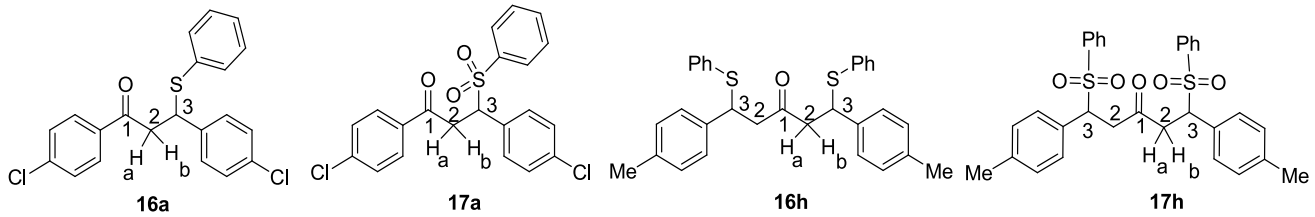


Fig. 2: Numbering of structures **16a**, **17a**, **16h** and **17h**.

5.3.1.4. ANTIMICROBIAL ACTIVITY

5.3.1.4.1. Microdilution assay

Minimum inhibitory concentration (MIC) is the lowest concentration of an antimicrobial compound that inhibits the visible growth of a microorganism. MIC values of the compounds against bacterial and fungal isolates were determined on the basis of micro-well dilution method following

NCCLS recommendations [26]. In this method we made stock of chemically synthesized compounds at a concentration of 10 mg/ml in DMSO, which was further converted to working solution of concentration 1 mg/ml solution in methanol. Using a micropipette, 100 µl of media into all wells of pre-sterilized microtiter plate was dispensed (experiment was done in triplicate). Two fold serial dilutions were carried out from the well 1 to the well 10 and excess media (100 µl) was discarded from the last well (No.10). Liquid culture of test organism was grown to a suitable phase in corresponding medium (Yeast, Peptone, and D-Glucose for fungal growth and Luria Bertani Broth, Nutrient Broth for bacterial growth) for 12-18 hr at 37 ^{0}C. Then optical density of liquid culture was determined at 600 nm and diluted in such a way that each well received 10^4cfu/100 µl of fungal suspension and 10^7cfu/100 µl of bacterial culture. Appropriate positive and negative control was also included in the study. Positive control contained only microbial cells whereas negative control contained only standard drug solution (Amphotericin-B, Nystatin for fungus and Ampicillin, Kanamycin for bacteria). All experimental procedures were performed under sterile condition using bio-safety hood and microtiter plates were incubated at 37 ^{0}C for 12-18 hr.

Synthesized compounds (**17a**-**k**) were screened for their anti-microbial activity. Two yeast (*Aspergillusniger* and *Candida albicans*), two gram positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*) and two gram negative bacteria (*Pseudomonas aeruginosa* and *Salmonella typhimurium)* were selected to evaluate the effectiveness of the test compounds.

5.3.1.4.2. Antibacterial activity

Compounds **17a**-**k** was subjected to MIC (minimum inhibitory concentration) determination by micro dilution method [27] and the results are given in Table 3. Reference drugs Ampicillin and Kanamycin were chosen as positive control in antibacterial activity assay.

As seen in the Table 3, compounds **17e**, **17g**, **17h**, **17j** (MIC: 62.50 µg/ml) have shown better antimicrobial activity than positive control against *S. aureus*. In case of *B. subtilis*, all compounds have shown lower activity than positive control (Kanamycin) while compound **17a** (MIC: 15.62 µg/ml) has shown better antibacterial activity against *B. subtilis*. Moreover, compounds **17f**, **17g**, **17i**, **17k (**MIC: 31.25 µg/ml) and compounds **17b**, **17c**, **17d**, **17e**, **17h** (MIC: 62.50 µg/ml) have demonstrated sound activity against *B. subtilis* than Ampicillin drug. Compounds **17b**, **17c**, **17d**, **17e**, **17h**, **17j** (MIC: 62.50 µg/ml) have shown better activity than positive controls against *P. aeruginosa* while others have shown lower activity (MIC ≥ 125 µg/ml). Compounds **17e**, **17f**, **17g** have shown admirable antibacterial activity (MIC: 1.95 µg/ml) against *S. typhimurium* while **17i** (MIC: 15.62

μg/ml), **17h** (MIC: 31.25 μg/ml) and **17c**, **17k** (MIC: 62.50 μg/ml) have shown comparable antibacterial activity against *S. typhimurium* as compare to positive control Ampicillin. Thus, both electron releasing groups (OMe or Me) and without substitution containing sulfones have shown excellent (MIC 1.95 μg/ml) to good (MIC: 31.25 μg/ml) antibacterial activity against *S. typhimurium* (compounds **17e**, **17f**, **17g** and **17h**). Sulfones having electron withdrawing groups (Cl, Br, NO_2) on aromatic ring have shown less antibacterial activity (MIC: 250 μg/ml to 62.50 μg/ml) against *S. typhimurium* (compounds **17a**, **17b**, **17c**, **17d**, **17k**). Against *S. aureus* also either electron releasing groups (OMe or Me) or without substitution on aromatic ring containing compounds **17e**, **17g**, **17h**, **17j** have shown good (MIC: 62.50 μg/ml) antibacterial activity. Against *B. subtilis,* all compounds have shown low activity compare to standard drug Kanamycin without depending on functional groups on aromatic ring. While, compare to standard drug Ampicillin against *B. subtilis,* trimethoxy group containing compounds **17f**, **17k** have shown good antibacterial activity (MIC: 31.25μg/ml). Against *P. aeruginosa* compare to standadards (Kanamycin, Ampicillin) electron withdrawing groups containing compounds **17b**, **17c**, **17d** have shown good activity. Comparative analysis of antibacterial activity (Gram positive and negative bacteria) of novel compounds in respect to reference drugs is shown in Fig. 3 and 4.

Table 3: Minimum inhibitory concentration (MIC) in μg/ml of chalcone derivatives against bacterial strains evaluated by microdilution method

Entry	Drug	Gram positive		Gram negative	
		B. subtilis (μg/ml)	*S. aureus* (μg/ml)	*S. typhimurium* (μg/ml)	*P. aeruginosa* (μg/ml)
1	Ampicillin	250	500	125	125
2	Kanamycin	7.81	500	15.62	250
3	17a	15.62	250	125	125
4	17b	62.50	125	125	62.50
5	17c	62.50	125	62.50	62.50
6	17d	62.50	125	250	62.50
7	**17e**	62.50	62.50	**1.95**	62.50
8	**17f**	31.25	125	**1.95**	125
9	**17g**	31.25	62.50	**1.95**	125
10	17h	62.50	62.50	31.25	62.50

11	17i	31.25	250	15.62	250
12	17j	125	62.50	250	62.50
13	17k	31.25	250	62.50	125

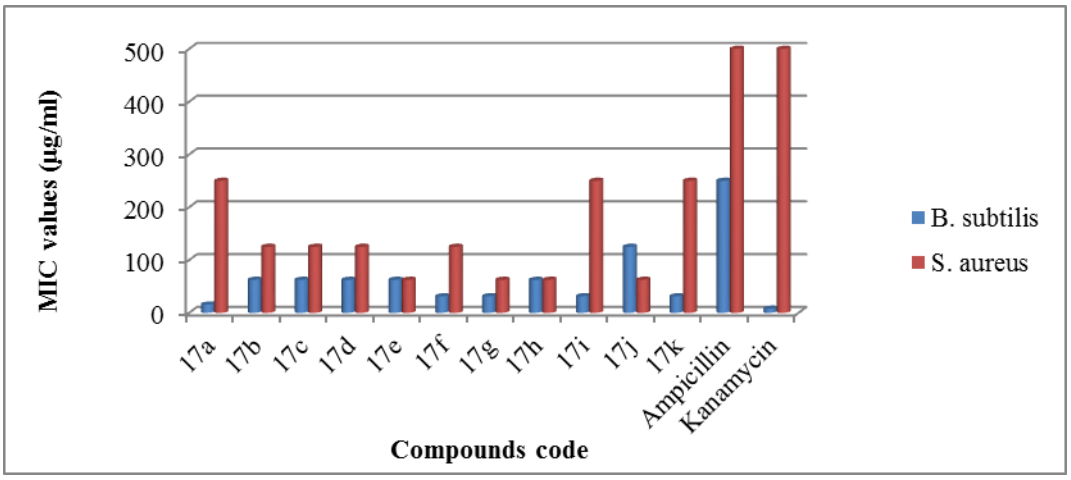


Fig. 3: Gram (+) bacterial activity of the synthesized compounds and their comparison to standard drugs Ampicillin and Kanamycin.

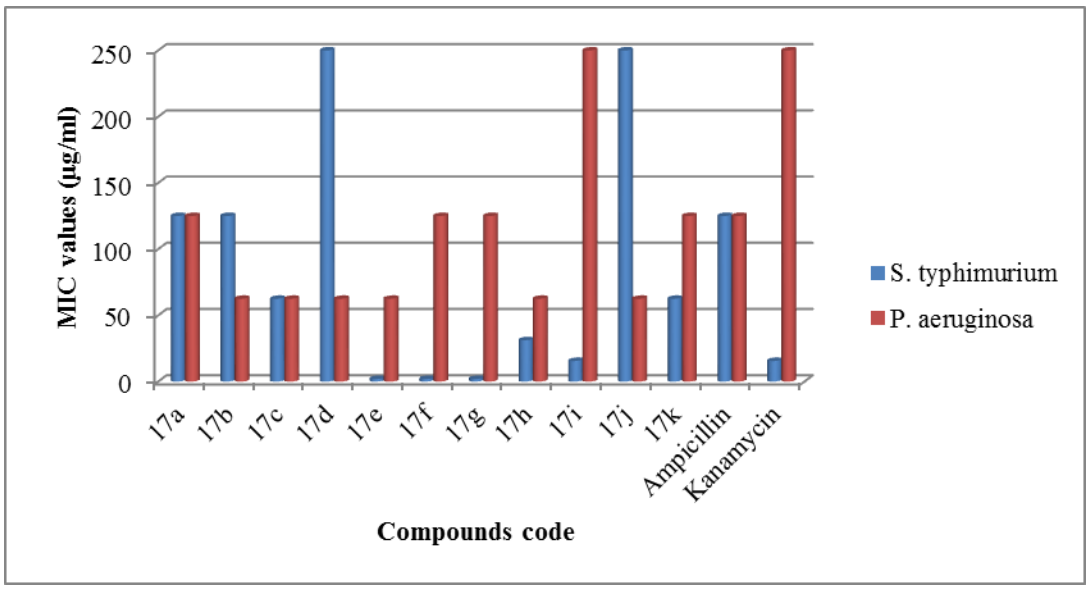


Fig. 4: Gram (-) bacterial activity of the synthesized compounds and their comparison to standard drugs Ampicillin and Kanamycin.

5.3.1.4.3. Antifungal activity

Compounds **17a-k** was subjected to MIC (minimum inhibitory concentration) determination by micro dilution method [26] and the results are given in Table 4. Reference drugs Amphotericin-B and Nystatin were selected as positive control in antifungal activity assay.

Compounds **17b**, **17c**, **17h** and **17i** have shown excellent antifungal activity (MIC: 1.95 μg/ml) against *Candida albicans.* Compounds **17f**, **17c** have shown better antifungal activity (MIC: 3.90 μg/ml), **5c** has shown the activity (MIC: 15.62 μg/ml) same as Amphotericin-B against *C. albicans* while others have lower activity (MIC ≥ 125-62.50 μg/ml). Compounds **17f**, **17g** have shown better antifungal activity (MIC: 7.81 μg/ml) against *Aspergillus niger.* Compounds **17a**, **17e** have shown sensible antifungal activity (MIC: 15.62 μg/ml) and **17h** (MIC: 31.25 μg/ml), **17c**, **17d** (MIC: 62.50 μg/ml) have shown good antifungal activity against *A. niger* as compare to Amphotericin-B. Highly electron releasing groups (triOMe) or without substitutions on aromatic ring containing compounds **17f**, **17g** have shown equal activity compare to standard drug Nystatin against *A. niger.* Against *C. albicans* electron withdrawing groups containing compounds **17b**, **17c**, **17i** have shown excellent antifungal activity (MIC: 1.95 μg/ml) compare to standards drugs Amphotericin-B and Nystatin. Comparative analysis of antifungal activity of novel synthesized compounds in respect to reference drugs is shown in Fig. 5.

Table 4: Minimum inhibitory concentration (MIC) in μg/ml of chalcone derivatives against fungus evaluated by microdilution method.

Entry	Drug	*Aspergillusniger (μg/ml)*	*Candida albicans (μg/ml)*
1	Amphotericin-B	500	15.62
2	Nystatin	7.81	7.81
3	17a	15.62	31.25
4	**17b**	125	**1.95**
5	**17c**	62.50	**1.95**
6	17d	62.50	125
7	17e	15.62	15.62
8	**17f**	**7.81**	**3.90**
9	**17g**	**7.81**	**3.90**
10	**17h**	31.25	**1.95**

11	**17i**	125	**1.95**
12	17j	125	250
13	17k	125	125

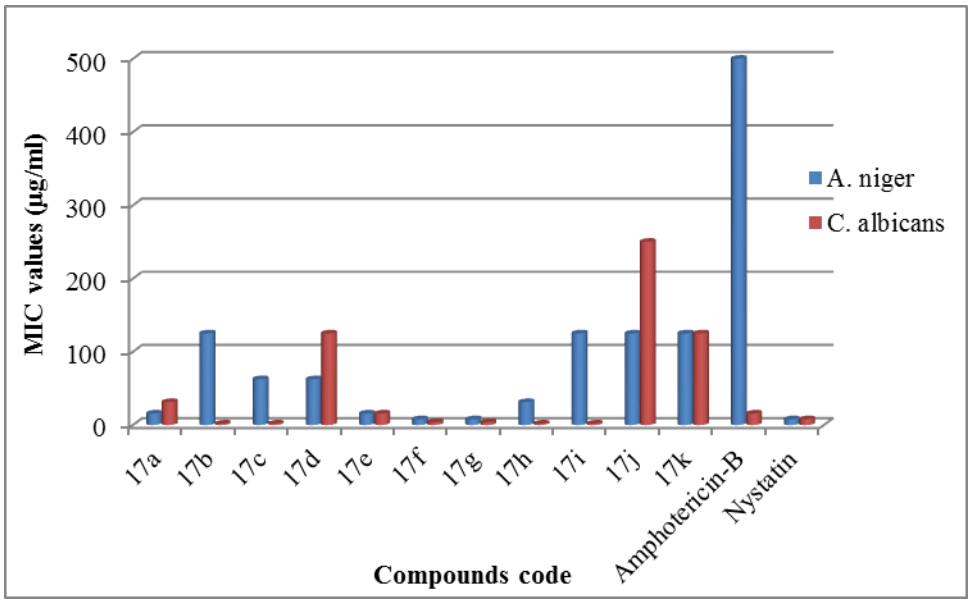


Fig. 5: Anti-fungal activity of the synthesized compounds and their comparison to standard drugs Nystatin and Amphotericin B.

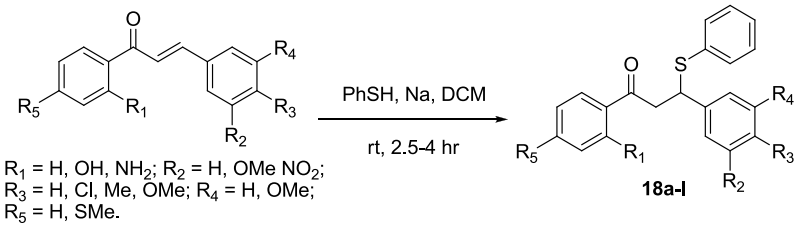
5.3.1.5. CONCLUSIONS

In conclusion, we have developed an efficient route for the synthesis of chalcone based sulfones and bisulfones using *m*-CPBA as an oxidizing agent. Both sulfones and bisulfones were evaluated for their antimicrobial activities against *A. niger* and *C. albicans* (yeast), *B. subtilis* and *S. aureus* (Gram (+) bacteria) and *P. aeruginosa* and *S. typhimurium* (Gram (-) bacteria) strains. They were evaluated for their antibacterial and antifungal activities. Compounds **17b**, **17c**, **17f**, **17g**, **17h** and **17i** were demonstrated high antifungal activity against *C. albicans* compare to reference drugs *viz.* Amphotericin-B and Nystatin. Compound **17a** have shown better antibacterial activity against *B. subtilis*. Compounds **17e**, **17f**, **17g** have shown admirable antibacterial activity against *S. typhimurium* compare to reference drugs Ampicillin and Kanamycin. Other sulfone derivatives have shown fair to medium antibacterial and antifungal activities.

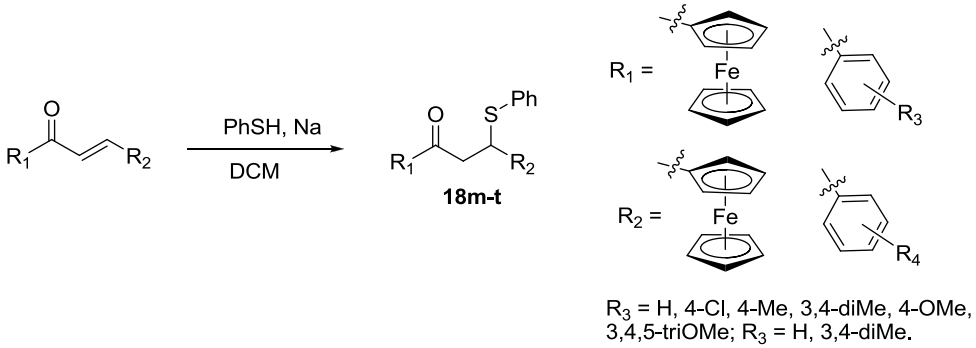
5.3.2. Part-B: <u>Design, synthesis and antimicrobial activities of novel ferrocenyl and organic chalcone based sulfones and bis-sulfones</u>

5.3.2.1. Synthesis of chalcone based sulfide derivatives

The organic chalcone based sulfides, ferrocenyl chalcone based sulfides were synthesized by the reaction of chalcones, thiophenol and sodium metal in DCM at room temperature *via* thia-Michael addition reaction following according literature procedure (Schemes 9, 10) [28].



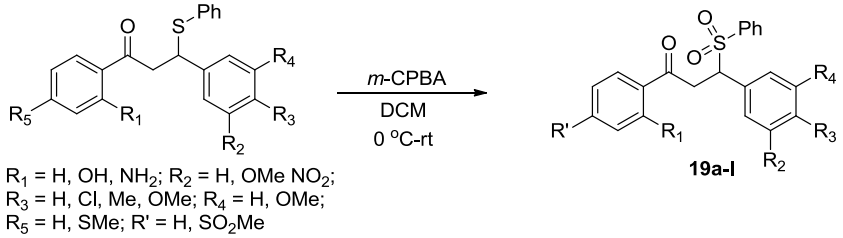
Scheme 9: Synthesis of organic chalcone based sulfides.



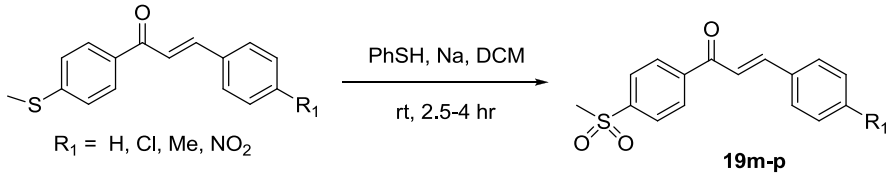
Scheme 10: Synthesis of ferrocenyl chalcone based sulfides.

5.3.2.2. Synthesis of chalcone based sulfones and bis-sulfones

The organic chalcone based sulfones synthesized following literature procedure [26]. The sulfides were oxidized to sulfones using *m*-CPBA as oxidizing reagent in DCM at 0 ^{0}C to room temperature products obtained in good yields (Schemes 11&12).

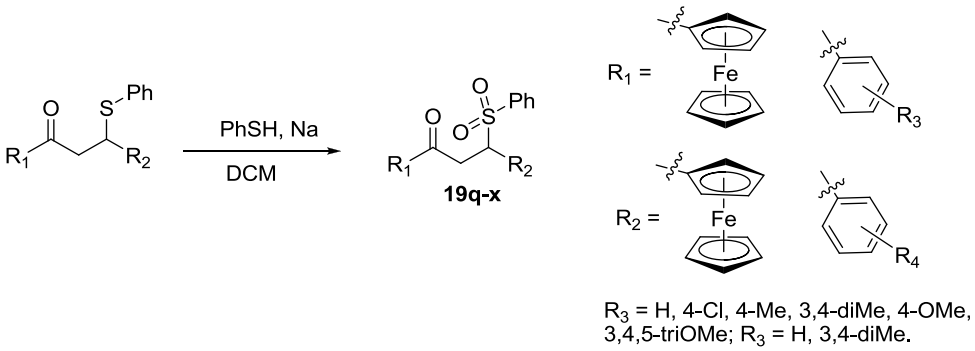


Scheme 11: Synthesis of organic chalcone based sulfones.



Scheme 12: Synthesis of (E)-3-aryl-1-(4-(methylsulfonyl)phenyl)prop-2-en-1-one.

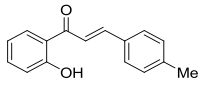
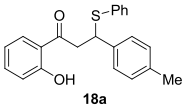
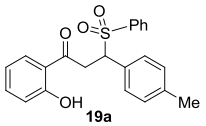
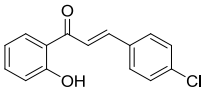
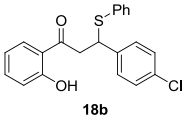
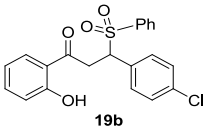
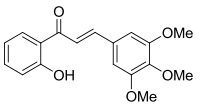
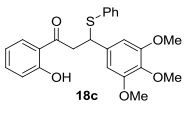
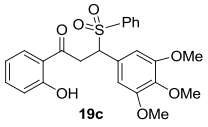
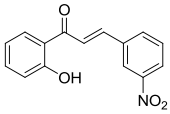
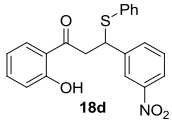
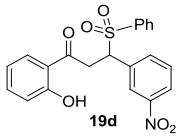
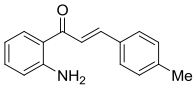
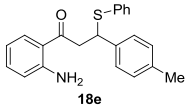
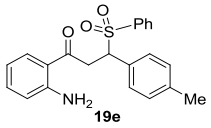
Ferrocenyl chalcone based sulfones were synthesized following the literature [27] but failed to give the product. However, after using inert atmosphere gave the product in excellent yields (Scheme 13).



Scheme 13: Synthesis of ferrocenyl chalcone based sulfones.

Here, we have reported five different type of chalcone based sulfone derivatives such as **19a-d** (2'-hydroxychalcone sulfones), **19e-h** (2'-aminochalcone sulfones), **19i-l** (bis-sulfones), **19m-p** and **19q-x** (ferrocenyl sulfones). Mono-sulfone products (**19a-d, 19e-h, 19m-p** and **19q-x**) were synthesized using corresponding sulfide and *m*-CPBA in 1: 2.2 mol ratio and bis-sulfone products (**19i-l**) were synthesized using corresponding sulfide and *m*-CPBA in 1: 4.5 mol ratio.

Table 5: Synthesis of 2'-hydroxy- and 2'-aminochalcone based sulfides and sulfones

Entry	Chalcone	Reaction time	Yield (%)	Sulfide	Reaction time	Yield (%)	Amino/hydroxy sulfone
1		1.5 h	90	 **18a**	3 h	90	 **19a**
2		1.5 h	92	 **18b**	4 h	95	 **19b**
3		2 h	90	 **18c**	3.5 h	91	 **19c**
4		2 h	93	 **18d**	3 h	92	 **19d**
5		2.5 h	90	 **18e**	2.5 h	94	 **19e**

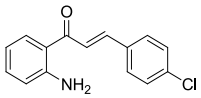
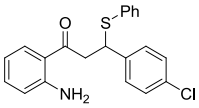
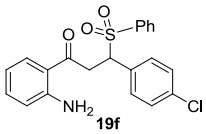
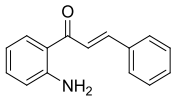
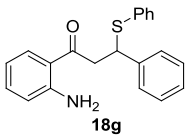
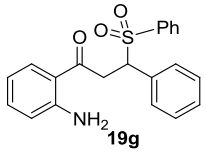
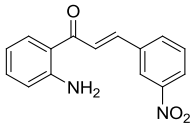
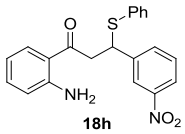
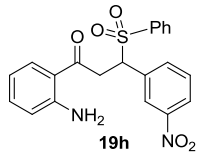
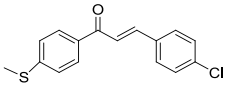
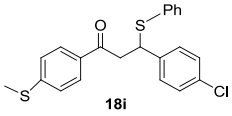
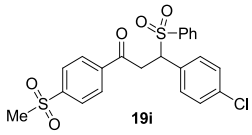
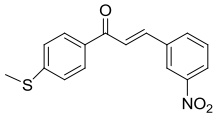
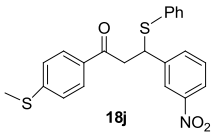
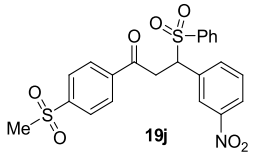
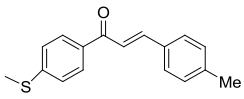
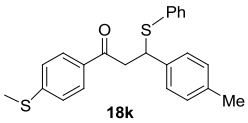
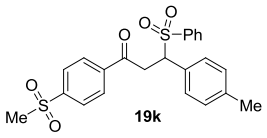
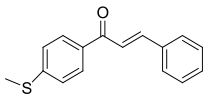
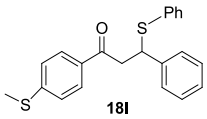
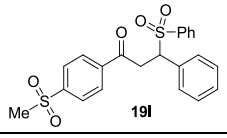
6		3 h	95	 **18f**	3 h	95	 **19f**
7		3 h	91	 **18g**	3.5 h	93	 **19g**
8		2 h	92	 **18h**	3 h	91	 **19h**
9		20 min	95	 **18i**	20 min	95	 **19i**
10		20 min	96	 **18j**	20 min	96	 **19j**
11		20 min	94	 **18k**	20 min	91	 **19k**
12		20 min	95	 **18l**	20 min	92	 **19l**

Table 6: Synthesis of (E)-3-aryl-1-(4-(methylsulfonyl)phenyl)prop-2-en-1-one.

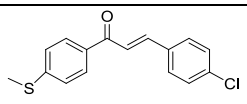
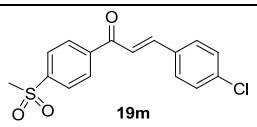
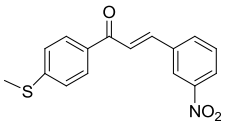
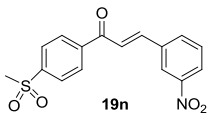
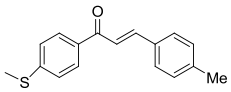
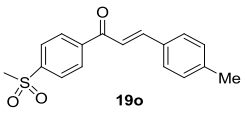
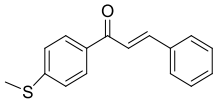
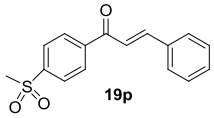
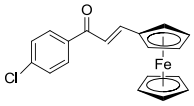
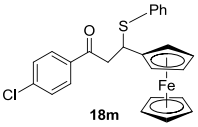
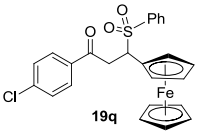
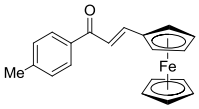
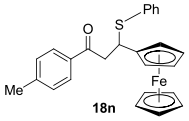
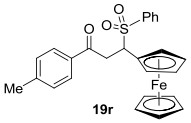
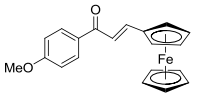
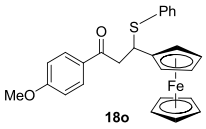
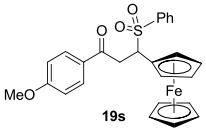
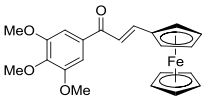
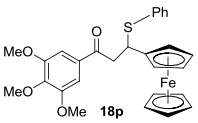
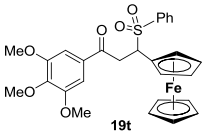
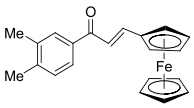
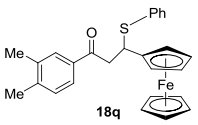
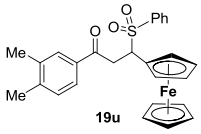
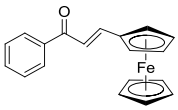
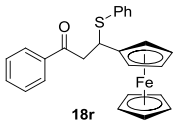
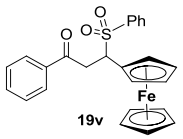
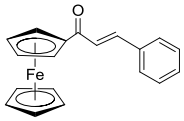
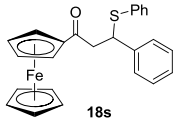
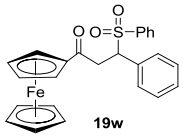
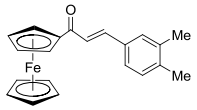
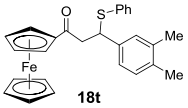
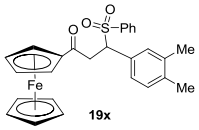
Entry	Chalcone	Reaction time (h)	Sulfone	Yield (%)
14		**3**	 **19m**	**96**
15		**3**	 **19n**	**95**
16		**3.5**	 **19o**	**96**
17		**3**	 **19p**	**98**

Table 7: Synthesis of ferrocenyl chalcone based sulfone derivatives

Entry	Chalcone	Reaction time (h)	Yield (%)	Sulfide	Reaction time (h)	Yield (%)	Sulfone
1		1.5	92	 **18m**	4	92	 **19q**
2		2	91	 **18n**	4	92	 **19r**
3		2.5	93	 **18o**	4	94	 **19s**
4		1	89	 **18p**	4	92	 **19t**
5		1.5	94	 **18q**	4	94	 **19u**
6		2	96	 **18r**	4	94	 **19v**
7		2	96	 **18s**	4.5	95	 **19w**

8		*2*	*95*	 **18t**	*4*	*93*	 **19x**

5.3.2.3. STRUCTURE DETERMINATION

The assigned structures of new products (**19a**-**h**) were established from their spectroscopic data (IR, HRMS, ^{1}Hand ^{13}C-NMR). For example, compound **19a** was obtained as a white solid. The IR spectrum of **19a** showed absorptions at 3450, 1707, 1315, 1154 cm^{-1} for OH, C=O *asymmetric* and –SO_2– bond *asymmetric* and *symmetric* stretching respectively. The HRMS of **19a** supported a molecular composition of $C_{22}H_{21}O_4S$ $(M+H)^+$, representing 12 degrees of unsaturation. In the ^{1}H and ^{13}C NMR spectra, peaks resonating at δ_H 2.3 (s, 3H) and δ_C 21.28 indicates methyl group present. In the ^{1}H NMR spectrum of **19a** peaks at δ_H 4.90 (dd, J = 9.5 Hz, 3.5Hz, 1H), δ_C 62.94 corresponds to methine group (–C<u>H</u>–SO_2) in which coupling constants ^{3}J = 9.5 Hz, and 3.5Hz indicates methine proton coupled with adjacent protons trans and cis coupling respectively. Peaks at δ_H 4.13 (dd, J = 16Hz, 3.5Hz, 1H), 3.97-3.92 (m, 1H) corresponds to -C<u>H_2</u>–CH–SO_2, in which coupling constant J = 16Hz indicates geminal coupling of methylene protons and J = 3.5Hz indicates vicinal coupling of δ_H 4.13 with 4.90 protons, which confirms the product formation. Further, shift in δ_H value of proton (–C<u>H</u>–SO_2) from 4.56 to 4.90 indicates sulfide **18a** conversion to sulfone **19a** (Table 5). Compound **19i** was obtained as a white solid. The IR spectrum of **19i** showed absorptions at 1653, 1589, 1303, 1057 cm^{-1} for carbonyl *asymmetric* and –SO_2– *asymmetric* and *symmetric* stretching respectively. The HRMS of **19i** supported a molecular composition of $C_{22}H_{19}ClNaO_5S_2$ $(M+Na)^+$representing 13 degrees of unsaturation. In the ^{1}H and ^{13}C NMR spectra of **19i**, peaks resonating at δ_H 3.01 (s, 3H) and δ_C 44.25 suggested that methyl group attached with -SO_2- group. Peaks at δ_H 4.99 (dd, J = 8.5Hz, 6Hz, 1H) corresponds to –CH_2–C<u>H</u>–SO_2 in which coupling constants ^{3}J = 8.5 Hz, and 6 Hz indicates trans and cis coupling of methine proton (–CH_2–C<u>H</u>–SO_2) with adjacent methene protons (–C<u>H_2</u>-CH-SO_2) respectively. Peaks at δ_H 3.63-3.61 (m, 1H), and 3.59-3.56 (m, 1H) corresponds to methene protons (–C<u>H_2</u>–CH–SO_2), which confirms the product formation and shift in δ_H value of methene proton (C<u>H</u>-SO_2) from 4.58 to 4.99, shift in δ_H value of methyl proton (C<u>H_3</u>–SO_2) from 2.5 to 3.01 in sulfone indicates bis-sulfide **18i** conversion to bis-sulfone **19i** (Table 5). Compound **19m** was obtained as a white solid. The IR spectrum of **19m** showed absorptions at 1726, 1298, 1143 cm^{-1} for carbonyl *asymmetric*,–SO_2– *asymmetric*, and *symmetric* stretching respectively. The HRMS of **19m**

supported a molecular composition of $C_{16}H_{13}ClO_3NaS$ $(M+Na)^+$ representing 10 degrees of unsaturation. In the ^1H and ^{13}C NMR spectra of **19m**, peaks resonating at δ_H 3.03 (s, 3H) and δ_C 44.36 indicates $-SO_2-CH_3$ group present (Table 6).

Compound **19q** was obtained as orange red solid. The IR spectrum of **19q** showed absorptions at 3021, 1108, 1463, 1401 cm^{-1} for ferrocene characteristic stretching, and 1702, 1298, 1156 cm^{-1} for carbonyl *asymmetric* and $–SO_2–$ *asymmetric*, and *symmetric* stretching respectively. The HRMS of **19q** supported a molecular composition of $C_{25}H_{22}ClFeO_3S$ $(M+H)^+$ representing 15 degrees of unsaturation. In the ^1H NMR spectrum peaks at δ_H 4.19-4.10 (m, 4H), 4.09 (s, 5H) suggested that mono-substituted ferrocene moiety present. In the ^1H and ^{13}C NMR spectrum peaks at δ_H 4.98 (t, J = 6.5Hz, 1H), δ_C 66.9, corresponds to methine group ($–\underline{CH}–SO_2$) in which coupling constant ^3J = 6.5 Hz indicates methine proton cis coupling with adjacent methylene protons ($–C\underline{H_2}–CH–SO_2$). Peaks at δ_H 3.85, 3.58 corresponds to methylene protons ($–C\underline{H_2}–CH–SO_2$), which confirms the product formation. Further, shift in δ_H-value from 4.50 to 4.98 and δ_C-value from 44.5 to 66.9 of methene group ($–C\underline{H}–SO_2$) in sulfone indicates ferrocenyl sulfide **18m** conversion to ferrocenyl sulfone **19q** (Table 7).

5.3.2.4. ANTIMICROBIAL ACTIVITY

The synthesized compounds (**19a-x**) were screened for their antimicrobial activity. Yeasts (*Aspergillus niger, Candida albicans, Aspergillus fumigatus, Cryptococcus neoformans, Candida parapsilosis* and *Candida tropicalis*), gram positive bacteria (*Bacillus subtilis, Staphylococcus aureus* and *Listeria monocytogenes*) and gram negative bacteria (*Pseudomonas aeruginosa, Klebseilla pneumonia, Escherichia coli, Proteus vulgaris*) strains were evaluated against the synthesized compounds. The novel compounds showed interesting biological activity against these strains; particularly the compounds **19a**, **19f**, **19t** and **19x** were found better than the standard drugs.

5.3.2.4.1. Anti-bacterial activity

Among various synthesized compounds, the novel sulfone (**19a-x)** series were evaluated for their anti-bacterial activity against three gram positive bacterial strains such as *B. subtilis, S. aureus* and *L. monocytogenes* and four gram negative bacterial strains such as *P. aeruginosa, K. pneumonia, E. coli, P. vulgaris*. The activities expressed as minimum inhibitory concentrations (MIC, μg/mL). The MIC (minimum inhibitory concentration) was determined by micro dilution method [26] and the

results are shown in Table 8. Ampicillin and Kanamycin were chosen as standard drugs in antibacterial activity assay.

Here, five types of sulfones such as **19a-d**, **19e-h**, **19i-l**, **19m-p** and **19q-x** were screened for their antimicrobial activity. As seen in the Table 8 against *B. subtilis*, all compounds exhibited MIC values in range 3.90-250 μg/mL. All compounds (**19a-x**) showed higher antibacterial activity compared to reference drug Ampicillin (MIC: 250 μg/mL) against *B. subtilis.* Compounds **19f** (MIC: 3.90 μg/mL) and **19t** (MIC: 3.90 μg/mL) showed higher and compound **19x** (MIC: 7.81 μg/mL) showed equal antibacterial activity compared to positive control Kanamycin (MIC: 7.81 μg/mL), while remaining compounds showed moderate to low antibacterial activity against *B. subtilis*. Against *S. aureus,* all compounds exhibited MIC values in range 1.95-250 μg/mL. All compounds showed higher antibacterial activity compared to reference drugs Ampicillin (MIC: 500μg/mL) and Kanamycin (MIC: 500 μg/mL) against *S. aureus.* Compounds **19d** (MIC: 7.81 μg/mL), **19f** (MIC: 1.95 μg/mL), **19t** (MIC: 3.90 μg/mL) showed highest antibacterial activity, compounds **19h**, **19j**, **19q**, **19s**, **19u**, **19w**, **19x** (MIC: 62.50 μg/mL) showed good antibacterial activity and remaining compounds moderate to low antibacterial activity against *S. aureus*. Against *L. monocytogenes,* all compounds exhibited MIC values in range MIC: 7-200 μg/mL. All compounds showed higher antibacterial activity compared to standard drug Ampicillin (MIC: 250 μg/mL) but most of the compounds showed lower activity than reference drug Kanamycin (MIC: 100 μg/mL). Compounds **19f** (MIC: 7.81 μg/mL), **19t** (MIC: 15 μg/mL) showed highest antibacterial activity, remaining compounds showed moderate to low antibacterial activity against *L. monocytogenes.* Against *P. aeruginosa,* all compounds exhibited MIC values in range MIC: 1.95-250 μg/mL. Compounds **19x** (MIC: 1.95 μg/mL), and **19u** (MIC: 15.62 μg/mL) showed highest antibacterial activity, compounds **19c**, **19f, 19k**, **19o** (MIC: 31.25 μg/mL) showed good antibacterial activity, compounds **19a**, **19h**, **19l**, **19m**, **19p**, **19w** (MIC: 62.50 μg/mL) showed better antibacterial activity while others showed moderate antibacterial activity (MIC ≥125 μg/mL) compare to standard drugs (Ampicillin (MIC: 125 μg/mL), Kanamycin (MIC: 250 μg/mL)) against *P. aeruginosa.* Against *K. pneumonia,* all compounds exhibited MIC values in range MIC: 1.95-250 μg/mL. Most of the tested compounds showed better antibacterial activity (MIC: <150 μg/mL) compared to standard drug Ampicillin (MIC: 200 μg/mL). Compound **19t** (MIC: 1.95 μg/mL) showed highest antibacterial activity, compounds **19f** (MIC: 25.5 μg/mL), **19w**, **19x** (MIC: 31.5 μg/mL) showed good antibacterial activity, compounds **19k**, **19m** (MIC: <50 μg/mL) showed moderate antibacterial activity compared to standard drugs (Ampicillin (MIC: 200 μg/mL), Kanamycin (MIC: 80μg/mL)) against *K. pneumonia.* Against *E. coli*,

all compounds exhibited MIC values in range MIC: 3.90-250 μg/mL. Most of the tested compounds showed better antibacterial activity (MIC: ≤100 μg/mL) compared to reference drugs (Ampicillin (MIC: 150 μg/mL), Kanamycin (MIC: 100 μg/mL)). Compounds **19t** (MIC: 10.00 μg/mL), **19x** (MIC: 3.90 μg/mL) showed highest antibacterial activity, compounds **19d**, **19f** (MIC: 25.50 μg/mL), showed good antibacterial activity **19u**, **19w** (MIC: 50.0 μg/mL), **19c** (MIC: 55.5 μg/mL) showed moderate antibacterial activity compared to standard drugs against *E. coli*. Against *P. vulgaris*, all compounds exhibited MIC values in range MIC: 25-250 μg/mL. Most of the tested compounds showed equal to higher antibacterial activity compared to reference drugs (Ampicillin (MIC: 200 μg/mL), Kanamycin (MIC: 125 μg/mL)). Compounds **19t, 19x** (MIC: 25.00 μg/mL), **19f**, **19o** (MIC: 30.50 μg/mL) showed highest antibacterial activity, compounds **19p, 19u** (MIC: 70.00 μg/mL), **19h**, **19w** (MIC: 80.00 μg/mL) showed moderate antibacterial activity, remaining compounds showed lower activity compared to reference drugs against *P. vulgaris*. Compounds **19f** and **19t** expressed the highest antibacterial activity against almost all tested bacterial strains (Table 8).

We further investigated the influence of the various substituents on sulfone nucleus for antibacterial activity, in 2'-hydroxychalcone based sulfones (**19a-d**) on B ring incorporating 3-NO_2 group (compound **19d**) antibacterial activity effectively increases against *S. aureus* than 4-methyl, 4-chloro, 3,4,5-trimethoxy groups containing compounds. In 2'-aminochalcone based sulfones (**19e-h**) in B ring incorporating 4-Cl group (compound **19f**) antibacterial activity effectively increases against all tested stains than 4-Me, 3-NO_2 groups and no substitution containing compounds. In bis-sulfones (**19i-l**) in B ring incorporating 4-Me group (compound **19k**) antibacterial activity increases against *P. aruginosa* than 4-Cl, 3-NO_2 groups and no substitution containing compounds. In ferrocenyl chalcone based sulfones (**19q-x**) in A ring incorporating 3,4,5-trimethoxy group (compound **19t**), in B ring incorporating 3,4-dimethyl group (compound **19x**) antibacterial activity effectively increases against all tested stains. Comparative analysis of antibacterial activity (Gram positive and negative bacteria) of novel compounds in respect to reference drugs is shown in Fig. 6 and 7.

Table 8: Minimum inhibitory concentration (MIC) in μg/mL of chalcone based sulfone derivatives against bacterial strains evaluated by microdilution method.

Entry	Drug	Gram positive bacteria			Gram negative bacteria			
		B. subtilis (μg/mL)	*S. aureus* (μg/mL)	*L. monocytogenes* (μg/mL)	*P. aeruginosa* (μg/mL)	*K. pneumonia* (μg/mL)	*E. coli* (μg/mL)	*P. vulgaris* (μg/mL)
1	Ampicillin	250	500	250	125	200	150	200
2	Kanamycin	7.81	500	100	250	50	100	125

3	19a	62.50	125	150	**62.50**	80.0	100	150
4	19b	125	125	150	250	100	125	200
5	19c	125	125	150	**31.25**	125	**55.5**	150
6	**19d**	62.50	**7.81**	150	**62.50**	80.0	**25.5**	150
7	19e	125	250	200	250	250	200	250
8	**19f**	**3.90**	**1.95**	**7.81**	**31.25**	**25.5**	**25.5**	**30.50**
9	19g	250	250	200	250	150	200	150
10	19h	125	**62.50**	**100**	**62.50**	150	80.0	**80.0**
11	19i	125	125	150	125	150	200	150
12	19j	62.50	**62.50**	125	250	80.0	100	125
13	19k	62.50	125	**100**	**31.25**	**50.0**	70.0	100
14	19l	125	125	200	**62.50**	100	125	150
15	19m	62.50	125	**100**	**62.50**	**48.5**	80.0	100
16	19n	62.50	125	150	125	100	150	150
17	**19o**	125	250	**100**	**31.25**	125	250	**30.50**
18	19p	125	125	**100**	**62.50**	100	100	**70.0**
19	19q	125	**62.50**	**100**	125	150	150	150
20	19r	125	250	250	250	150	200	200
21	19s	62.50	**62.50**	200	125	80.0	80.0	100
22	**19t**	**3.90**	**3.90**	**15.0**	250	**1.95**	**10.0**	**25.0**
23	**19u**	125	**62.50**	125	**15.62**	100	**50.0**	**70.0**
24	19v	125	125	150	125	150	125	125
25	**19w**	125	**62.50**	**100**	**62.50**	**31.5**	**50.0**	**80.0**
26	**19x**	**7.81**	**62.50**	150	**1.95**	**31.5**	**3.90**	**25.0**

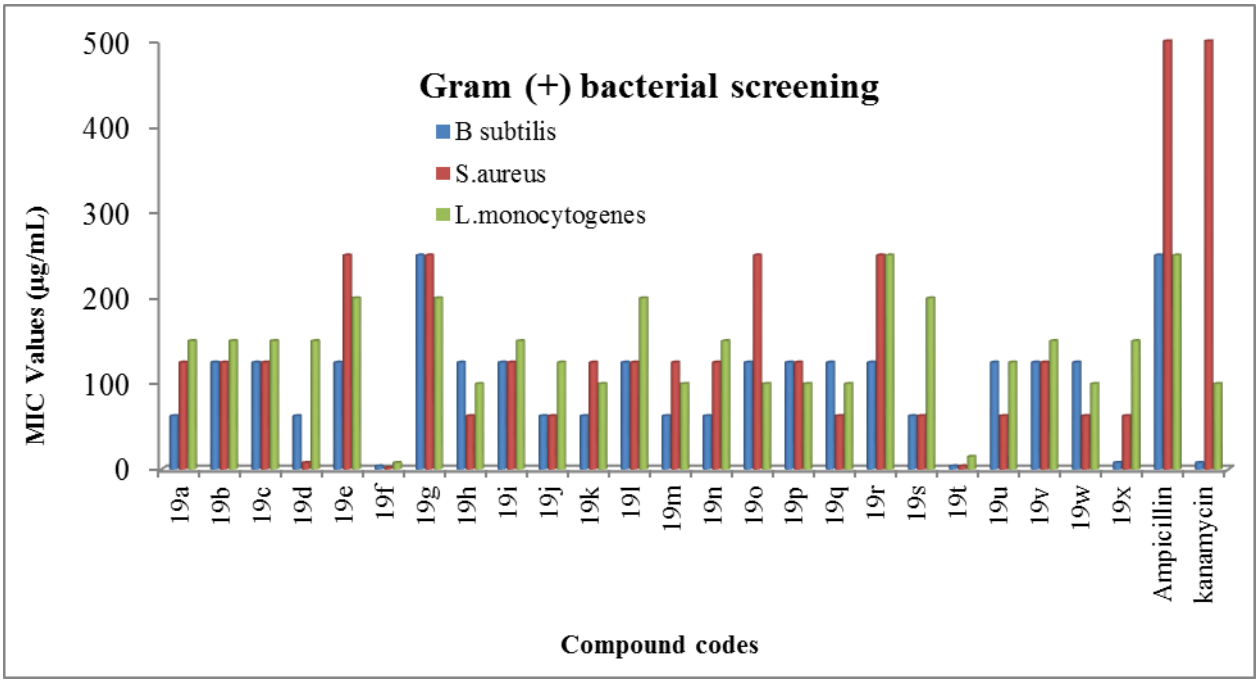


Fig. 6: Gram (+) bacterial activity of the synthesized compounds and their comparison to standard drugs Ampicillin and Kanamycin.

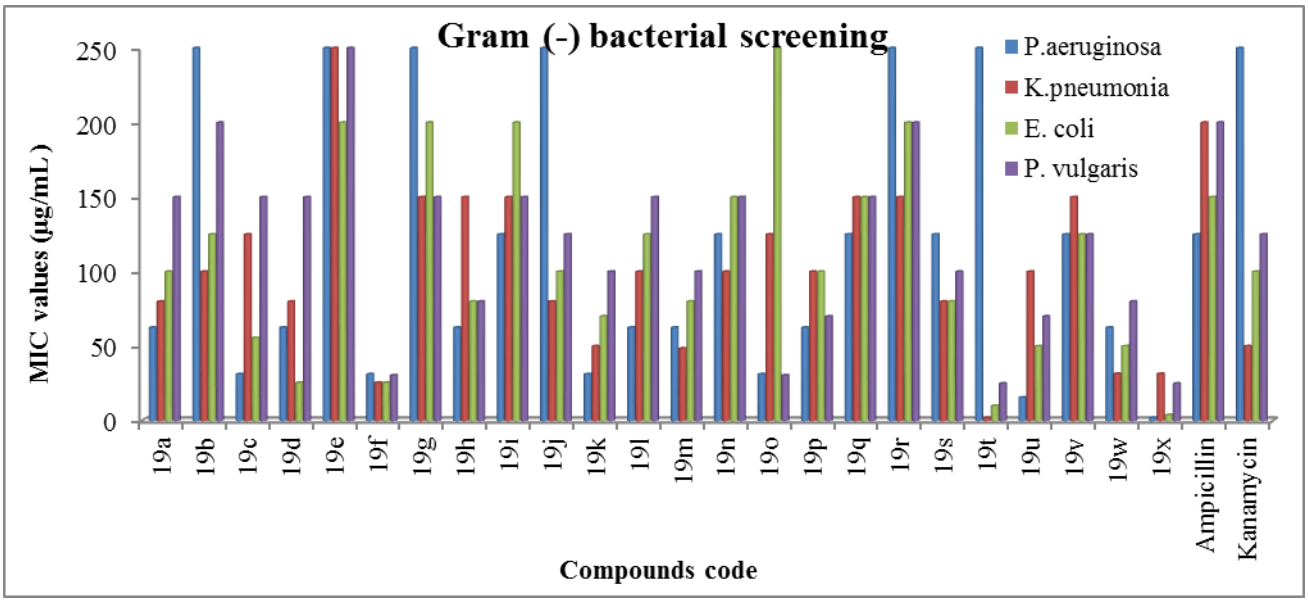


Fig. 7: Gram (-) bacterial activity of the synthesized compounds and their comparison to standard drugs Ampicillin and Kanamycin.

5.3.2.4.2. Antifungal activity

The synthesized compounds (**19a-x)** were evaluated for their anti-fungal activity against test pathogens. The antifungal activities expressed as minimum inhibitory concentrations (MIC, µg/mL).

The MIC (minimum inhibitory concentration) was determined by micro dilution method [26] and the results are given in Table 9. Amphotericin-B and Nystatin were selected as positive control in antifungal activity assay. Against *A. niger,* all compounds (**19a-x)** exhibited MIC values in range MIC: 3.90-125 μg/mL. All tested compounds showed higher antifungal activity compared to reference drug Nystatin (MIC: 500 μg/mL), most of the compounds showed lower antifungal activity than reference drug amphotericin B (MIC: 7.81 μg/mL). Among them, compound **19x** (MIC: 3.90 μg/mL) showed highest antifungal activity, compound **19b** (MIC: 31.25 μg/mL) good antifungal activity, compounds **19a**, **19d-f**, **19j**, **19s** (MIC: 62.5 μg/mL) showed moderate antifungal activity while remaining compounds showed lower activity against *A. niger*. Against *C. albicans,* all compounds exhibited MIC values in range MIC: 7.81-250 μg/mL. Most of the tested compounds showed moderate antifungal activity compared to reference drugs Nystatin (MIC: 15.62 μg/mL) and Amphotericin B (MIC: 7.81 μg/mL). Compound **19x** (MIC: 7.81 μg/mL) showed highest antifungal activity, compound **19f** (MIC: 31.25 μg/mL) showed good antifungal activity and remaining compounds showed lower antifungal activity compared to reference drugs against *C. albicans.* Against *A. fumigatus,* all compounds exhibited MIC values in range MIC: 10.5-100 μg/mL. All tested compounds showed higher antifungal activity compared to reference drug Nystatin (MIC: 500 μg/mL), but all compounds showed lower antifungal activity than reference drug Amphotericin B (MIC: 5.65 μg/mL). Compound **19x** (MIC: 10.5 μg/mL) showed highest antifungal activity, compound **19b** (MIC: 30.5 μg/mL), **19f** (MIC: 25.5 μg/mL), **19g** (MIC: 31.5 μg/mL) showed good antifungal activity, remaining compounds showed moderate to low antifungal activity compared to reference drugs against *A. fumigatus*. Against *C. neoformans*, all compounds exhibited MIC values in range MIC: 3.90-200 μg/mL. All tested compounds showed better antifungal activity compared to reference drug Nystatin (MIC: 200 μg/mL), but most of the compounds showed lower antifungal activity compared to reference drug amphotericin B (MIC: 5.75 μg/mL). Compound **19x** (MIC: 3.90 μg/mL) showed highest antifungal activity, compounds **19b (**MIC: 40.5 μg/mL**)**, **19c (**MIC: 50.0 μg/mL**)**, **19d (**MIC: 45.5 μg/mL**)**, **19f (**MIC: 35.5 μg/mL**)**, **19g (**MIC: 50.0 μg/mL**)** showed good antifungal activity while all other compounds showed moderate to low antifungal activity compared to reference drugs against *C. neoformans.* Against *C. parapsilosis,* all compounds exhibited MIC values in range MIC: 7.81-80 μg/mL. Most of the tested compounds showed moderate antifungal activity compared to reference drugs Nystatin (MIC: 25.0 μg/mL) and Amphotericin B (MIC: 4.5 μg/mL). Compound **19x** (MIC: 7.81 μg/mL) showed good antifungal activity compared to reference drugs against *C. parapsilosis.* Against *C. tropicalis,* all compounds exhibited MIC values in range

MIC: 15.5-200 μg/mL. Most of the tested compounds showed low antifungal activity compared to reference drugs Nystatin (MIC: 10.0 μg/mL) and Amphotericin B (MIC: 8.5 μg/mL). Compounds **19c**, **19x** (MIC: 15.5 μg/mL) showed good antifungal activity, compounds **19b**, 1**9s** (MIC: 25.5 μg/mL), **19g** (MIC: 25 μg/mL) also showed moderate antifungal activity against *C. tropicalis.* Compound **19x** expressed the highest antifungal activity against almost all tested fungal strains (Table 9). We further investigated the influence of the various substituents in the chalcone based sulfone nucleus on antifungal activity, in 2'-hydroxy chalcone based sulfones (**19a-d**) on B ring 4-Cl group containing compound (compound **2c**) showed better antifungal activity against tested all fungal pathogens than 4-methyl, 3-NO_2 3,4,5-trimethoxy groups containing compounds. In 2'-aminochalcone based sulfones (**19e-h**) in B ring incorporating 4-Cl group containing compound (compound **19f**) showed better antifungal activity against *A. niger, C. albicans, A. fumigatus, C. neofarmans,* and no substitution containing compound (compound **19g**) showed better antifungal activity against *C. neofarmans, C. parapsilosis, C. tropicalis.* In ferrocenyl chalcone based sulfones (**19q-x**) in B ring 3,4-dimethyl group containing compound (compound **19x**) showed good antifungal activity against almost tested stains. Comparative analysis of antifungal activity of novel synthesized compounds in respect to reference drugs is shown in Fig. 8.

Table 9: Minimum Inhibitory Concentration (MIC) in μg/mL of Chalcone based sulfone derivatives against fungus evaluated by micro-dilution method.

Entry	Drug	*A. niger* (μg/mL)	*C. albicans* (μg/mL)	*A. fumigatus* (μg/mL)	*C. neoformans* (μg/mL)	*C. parapsilosis* (μg/mL)	*C. tropicalis* (μg/mL)
1	Nystatin	500	15.62	500	200	25.0	10.0
2	Amphotericin B	7.81	7.81	5.65	5.75	4.5	8.50
3	19a	**62.50**	62.50	67.25	75.5	80.0	80.0
4	**19b**	**31.25**	62.50	**30.50**	**40.5**	**35.5**	**25.5**
5	19c	125	62.50	95.0	**50.0**	75.5	**15.5**
6	19d	**62.50**	62.50	100.0	**45.5**	45.5	70.0
7	19e	**62.50**	250	100	75.0	75.0	75.0
8	**19f**	**62.50**	**31.25**	**25.5**	**35.5**	65.5	80.0
9	**19g**	125	62.50	**31.5**	**50.0**	**25**	**25**
10	19h	125	62.50	100	65	50	40
11	19i	125	62.50	70	70	80	**25.5**
12	19j	**62.50**	125	100	70	80	100
13	19k	125	250	125	200	150	150
14	19l	125	125	125	200	200	100

15	19m	250	62.50	100	80.0	100	150
16	19n	125	62.50	100	125	125	100
17	19o	125	125	200	125	125	100
18	19p	125	125	200	125	125	100
19	19q	125	250	200	150	100	150
20	19r	250	250	150	150	200	200
21	19s	**62.50**	62.50	70.0	70.0	50.0	45.5
22	19t	125	250	125	100	100	150
23	19u	125	125	125	150	100	100
24	19v	125	125	125	100	100	125
25	19w	125	250	150	125	100	100
26	**19x**	**3.90**	**7.81**	**10.5**	**3.90**	**7.81**	**15.5**

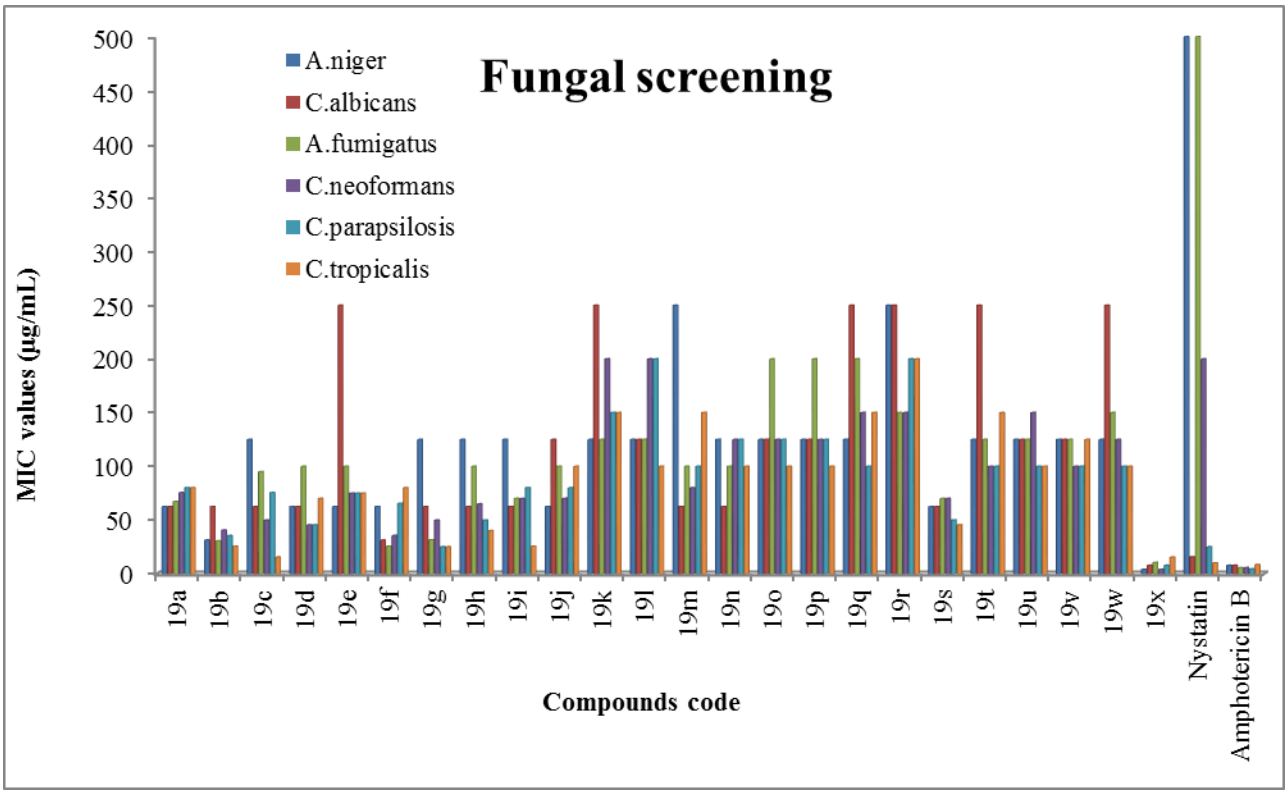


Fig. 8: Anti-fungal activity of the synthesized compounds and their comparison to standard drugs Nystatin and Amphotericin B.

5.3.2.5. CONCLUSIONS

In conclusion, we have synthesized new class of ferrocenyl and organic chalcone based sulfone and bis-sulfone derivatives and evaluated their antibacterial and antifungal activities. We found that the majority of these compounds have higher inhibitory activity against bacteria than the

fungi. In case of anti-bacterial activity, Compounds **19f**, **19t** and **19x** active against *B. subtilis*, compounds **19d**, **19f** and **19t** active against *S. aureus* than positive control, compounds **19f**, and **19t** active against *L. monocytogenes*, compound **19x** active against *P. aeruginosa*. Compound **19t** showed highest antibacterial activity, compounds **19f**, **19w** and **19x** active against *K. pneumonia*, compounds **20c** and **19x** active against *E. coli*. In case of antifungal activity, compound **19x** demonstrated good antifungal activity against tested pathogens and against *A. niger*, *C. parapsilosis* is better than the reference drugs. Other sulfone derivatives showed fair to medium antibacterial and antifungal activities. 3-NO_2 group on 2'-hydroxychalcone sulfones, 4-Cl group on 2'-aminochalcone sulfones, 3,4,5-trimethoxy, 3,4-dimethyl groups on ferrocenyl chalcone sulfones are suitable substituents, which showed excellent antimicrobial activity. The order of tested compounds antimicrobial activity: ferrocenyl chalcone sulfones > 2'-hydroxychalcone sulfones > 2'-aminochalcone sulfones > bis sulfones.

5.3.2.6. EXPERIENTAL

5.3.2.6.1. Gereneral Procedures

General procedure for synthesis of chalcone based sulfides (16a-k, 18a-t):

To a stirred solution of α, β-unsaturated carbonyl compound (1 mmol) in DCM was added thiophenol (1.2 mmol, 132 mg), followed by sodium metal (1.2 mmol, 27.6 mg) at room temperature. The reaction mixture was stirred for appropriate time given in Table 2. TLC monitoring, after completion of reaction filtered excess amount of sodium then the reaction mixture was quenched with water and extracted with DCM (3 x 8 mL), washed with brine solutions (10mL). The combined organic layers dried over anhydrous Na_2SO_4 and the solvent evaporated *in vacuo*. Pure sulfide was obtained by recrystallization from methanol.

General procedure for synthesis of chalcone based mono-sulfones (17a-g, 19a-h, 19m-p):

To a stirred solution of chalcone sulfide (1 mmol) in DCM was added *m*-CPBA (2.2 mmol, 379.5 mg) at 0 ^{0}C portion wise for 15 min, reaction mixture stirred at this temperature for 30 min then warmed to room temperature and stirred for appropriate time in Table 2. TLC monitoring, After completion of reaction, the reaction was diluted with DCM (8 mL) and washed with 5% aqueous K_2CO_3 (3 x 8 mL) and 5% $NaHCO_3$ (10 mL) solution for removing excess *m*-CPBA, then aqueous layer extracted with DCM (3 x 10mL), the combined organic layers dried over anhydrous Na_2SO_4, and solvent evaporated in *vacuo*. Pure sulfone was obtained by recrystallization from methanol.

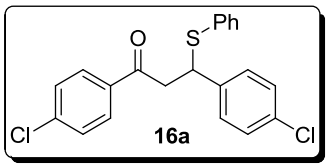
General procedure for synthesis of chalcone based bis-sulfones (17h-k, 19i-l):

To a stirred solution of chalcone sulfide (1 mmol) in DCM was added *m*-CPBA (4.5mmol, 776.5 mg) at 0 ^{0}C portion wise for 25 min, reaction mixture stirred at this temperature for 30 min. then warmed to room temperature and stirred appropriate time in Table 3. TLC monitoring, After completion of reaction, the reaction was diluted with DCM (8 mL) and washed with 5% aqueous K_2CO_3 (3 x 8 mL) and $NaHCO_3$ (10 mL) solution for removing excess *m*-CPBA, then aqueous layer extracted with DCM (3 x 10mL), the combined organic layers dried over anhydrous Na_2SO_4, and solvent evaporated in *vacuo.* Pure sulfone was obtained by recrystallization from methanol.

General procedure for synthesis of ferrocenyl chalcone based sulfones (19q-x):

In a flame dried round bottom flask was taken ferrocenyl chalcone sulfide (1 mmol) and dissolved in dry dichloromethane and flush with N_2 gas for 6 min. Then *m*-CPBA (2.2 mmol, 379.5 mg) in dichloromethane was added at 0 ^{0}C drop wise for 15 min, the reaction mixture stirred at this temperature for 30 min. then warmed to room temperature and stirred for appropriate time in Table 5. TLC monitoring, the reaction was diluted with dichloromethane (8 mL) and washed with 5% aqueous K_2CO_3 (3 x 8 mL) and 5% $NaHCO_3$ (10 mL) solution for removing excess *m*-CPBA, then aqueous layer extracted with dichloromethane (3 x 10mL), the combined organic layers dried over anhydrous Na_2SO_4 and solvent evaporated in *vacuo.* Pure ferrocenyl sulfone was obtained by recrystallization from methanol.

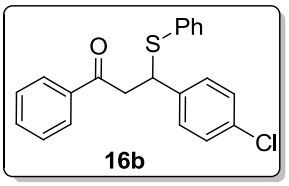
5.3.2.6.2. SPECTROSCOPIC DATA



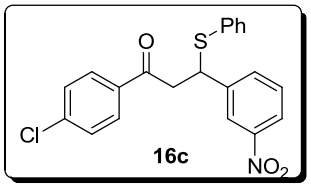
16a

1-(4-Chlorophenyl)-3-(4-chlorophenyl)-3-phenylsulfenylpropane-1-one (16a):

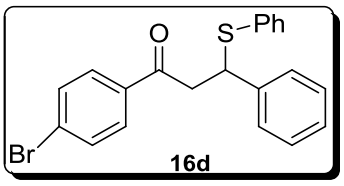
Yield 90%; white solid; mp 115-116 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 7.81 (d, *J* = 8.5Hz, 2H), 7.41 (d, *J* = 8.5Hz, 2H), 7.31-7.29 (m, 2H), 7.26-7.18 (m, 7H), 4.57 (t, *J* = 7.5Hz, 1H), 3.59-3.49 (m, 2H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 195.5, 139.95, 139.69, 134.86, 137.57, 133.57, 133.06, 130.73, 129.48, 129.16, 129.03, 128.65, 127.94, 47.6, 44.5. **IR (KBr, cm^{-1})**: 3070, 2913, 1679, 1588, 1217. **GC-MS**: (m/z) 387 $[M+H]^+$. **CHNS**: Anal. calcd for $C_{21}H_{16}Cl_2OS$: C, 65.12; H, 4.16; S, 8.28; found: C, 64.01; H, 4.13; S, 8.52.



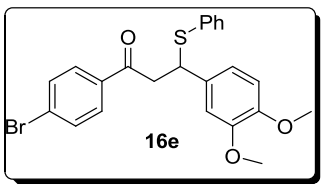
1-Phenyl-3-(4-chlorophenyl)-3-phenylsulfenylpropane-1-one (16b): Yield 90%; white solid; mp 84-86 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 7.83 (d, *J* = 16Hz, 2H), 7.46 (d, *J* = 6.5Hz, 1H), 7.39-7.15 (m, 11H), 4.51 (m, 1H), 3.59-3.51 (m, 2H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 194.6, 141.04, 139.96, 134.68, 137.75, 134.57, 133.60, 130.37, 129.48, 129.26, 129.03, 128.76, 127.94, 47.6, 44.6. **IR (KBr, cm^{-1})**: 3057, 2926, 2890, 1679, 1489, 1325. **GC-MS**: (m/z) 353 $[M+H]^+$. **CHNS**: Anal. calcd for $C_{21}H_{17}ClOS$: C, 71.48; H, 4.86; S, 9.09; found: C, 71.41; H, 4.85; S, 8.89.



1-(4-Chlorophenyl)-3-(3-nitrophenyl)-3-phenylsulfenylpropane-1-one (16c): Yield 92%; white solid; mp 124-126 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 8.16 (s, 1H), 8.0 (dd, *J* = 8, 1.5Hz, 1H), 7.82 (d, *J* = 7.5Hz, 2H), 7.6 (d, *J* = 7.5Hz, 1H), 7.47-7.29 (m, 3H), 7.28-7.2 (m, 5H), 4.67 (t, *J* = 7Hz, 1H), 3.65-3.59 (m, 2H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 194.97, 148.22, 143.56, 140.17, 134.55, 134.20, 133.48, 132.67, 129.44, 129.04, 128.37, 127.48, 127.13, 122.58, 122.39, 47.69, 44.07. **IR (KBr, cm^{-1})**: 3078, 3056, 2917, 1683, 1535, 1223. **GC-MS**: **(**m/z) 398 $[M+H]^+$. **CHNS**: Anal. calcd for $C_{21}H_{16}ClNO_3S$: C, 63.39; H, 4.05; N, 3.52; S, 8.06; found: C, 63.51; H, 4.09; N, 3.70; S, 8.21.

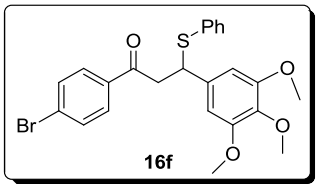


1-(4-Bromophenyl)-3-phenyl-3-phenylsulfenylpropane-1-one (16d): Yield 95%; white solid; mp 114-116 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 7.72 (dd, *J* = 5Hz, 1.5Hz, 2H), 7.58-7.54 (m, 2H), 7.32-7.22 (m, 10H), 4.45-4.52 (m, 1H), 3.62-3.50 (m, 2H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 196.1, 141.0, 135.4, 134.59, 133.65, 132.8, 131.96, 129.62, 128.93, 128.54, 127.79, 127.67, 127.57, 48.27, 44.67. **IR (KBr,cm^{-1})**: 3067, 3023, 2019, 1684, 1577, 1222. **GC-MS**: (m/z) 397 $[M+H]^+$. **CHNS**: Anal. calcd for $C_{21}H_{17}BrOS$: C, 63.48; H, 4.31; S, 8.07; found: C, 63.49; H, 4.28; S, 8.11.



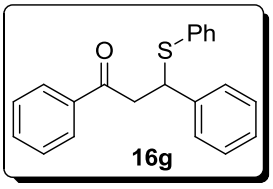
1-(4-Bromophenyl)-3-(3,4-dimethoxyphenyl)-3-phenylsulfenylpropane-1-one (16e): Yield 95%; white solid; mp 131-133 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 7.61 (d, *J* = 8.5Hz, 2H), 7.43 (d, *J* = 8.5Hz, 2H), 7.38 (d, *J* = 8Hz, 1H), 7.2-7.25 (m, 2H), 7.2 (t, *J* = 7Hz, 1H), 7.16-7.08 (m, 2H), 6.73 (t, *J* = 6.5Hz, 2H), 4.40-4.38 (m, 1H), 3.70 (s, 6H), 3.51-3.33 (m, 2H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 189.44, 151.62, 149.27, 147.83, 145.60, 137.18, 134.56, 131.85, 129.96, 127.64, 127.60, 123.33, 119.41, 111.12, 110.10, 56.0, 55.97, 47.61, 43.97. **IR (KBr, cm^{-1})**: 3073, 3009, 2925, 1681, 1581, 1253. **GC-MS**: (m/z) 457

$[M+H]^+$. **CHNS**: Anal. calcd for $C_{23}H_{21}BrO_3S$: C, 60.40; H, 4.63; S, 7.01; found: C, 60.32; H, 4.71; S, 7.06.



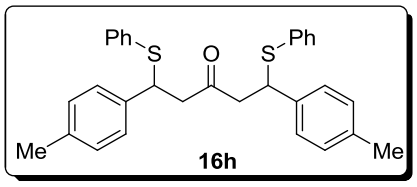
1-(4-Bromophenyl)-3-(3,4,5-trimethoxyphenyl)-3-phenylsulfenylpropa- ne-1-one (16f):

Yield 89%; white solid; mp 140-142 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 7.88 (d, *J* = 8.5Hz, 2H), 7.74 (m, 3H), 7.58 (d, *J* = 7.5Hz, 2H), 7.27-7.24 (m, 2H), 6.50 (s, 2H), 4.45 (t, *J* = 8.5Hz, 1H), 3.78 (s, 6H), 3.75 (s, 3H), 3.6-3.48 (m, 2H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 196.12, 153.09, 137.22, 136.54, 135.46, 134.01, 133.06, 131.99, 129.60, 128.96, 128.59, 127.81, 104.77, 56.11, 55.21, 48.77, 44.71. **IR (KBr, cm^{-1})**: 3065, 2939, 2830, 1683, 1586, 1131. **GC-MS**: (m/z) 487 $[M+H]^+$. **CHNS**: Anal. calcd for $C_{24}H_{23}BrO_4S$: C, 59.14; H, 4.76; S, 6.58; found:C, 59.24; H, 4.76; S, 6.66.



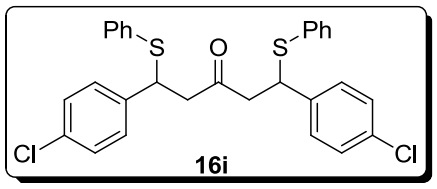
1-Phenyl-3-phenyl- 3-phenylsulfenylpropane-1-one (16g):

Yield 95%; white solid; mp 117-119 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 7.87 (d, *J* = 7.5Hz, 2H), 7.54 (t, *J* = 8Hz, 1H), 7.43 (t, *J* = 7.5Hz, 2H), 7.34-7.32 (m, 4H), 7.27-7.17 (m, 6H), 4.57-4.54 (m, 1H), 3.7-3.5 (m, 2H). **^{13}C NMR ($CDCl_3$, 125 MHz)** : δ (ppm) 197.04, 141.21, 136.72, 134.33, 133.29, 132.8, 128.9, 128.62, 128.51, 128.13, 127.84, 127.62, 127.47, 48.23, 44.72. **IR (KBr, cm^{-1})**: 3057, 2900, 1673, 1446, 1331, 1584. **GC-MS**: (m/z) 319 $[M+H]^+$. **CHNS**: Anal. calcd for $C_{21}H_{18}OS$: C, 79.21; H, 5.70; S, 10.07; found: C, 79.11; H, 5.73; S, 10.18.



1,5-Di(4-methylphenyl)-1,5-bis(phenylsulfenyl)pentan-3-one (16h):

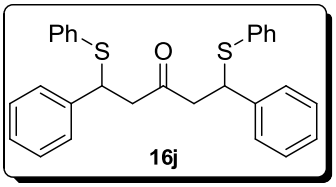
Yield 92%; white solid; mp 125-126 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 7.36 (d, *J* = 7.5Hz, 2H), 7.23-7.04 (m, 16H), 4.32-4.28 (m, 2H), 2.95-2.77 (m, 4H), 2.35 (s, 6H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 204.9, 137.6, 137.0, 134.2, 132.6, 128.85, 126.91, 125.15, 127.42, 49.51, 47.42, 21.12. **IR (KBr, cm^{-1})**: 3030, 2921, 2878, 1715, 1375. **GC-MS**: (m/z) 483 $[M+H]^+$. **CHNS**: Anal. calcd for $C_{31}H_{30}OS_2$: C, 77.14; H, 6.26; S, 13.29; found: C, 77.21; H, 6.28; S, 13.38.



1,5-Di(4-chlorophenyl)-1,5-bis(phenylsulfenyl)pentan-3-one (16i):

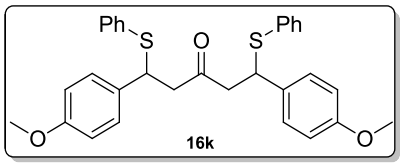
Yield 90%; white solid; mp 143-145 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 7.48 (d, *J* = 1.5Hz, 1H), 7.28-7.25 (m, 11H), 7.14

(d, *J* = 7Hz, 2H), 7.07 (d, *J* = 7Hz, 2H), 6.99 (d, *J* = 7Hz, 2H), 4.56-4.52 (m, 2H), 3.0-2.79 (m, 4H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 204.5, 140.5, 133.88, 132.91, 128.6, 128.5, 127.68, 127.40, 126.84, 49.2, 47.6. **IR (KBr, cm^{-1})**: 3056, 2917, 1709, 1483, 1090. **GC-MS**: (m/z) 523 $[M+H]^+$. **CHNS**: Anal. calcd for $C_{29}H_{24}Cl_2OS_2$: C, 66.53; H, 4.62; S, 12.25; found: C, 66.63; H, 4.61; S, 12.42.



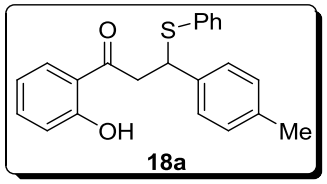
1,5-Diphenyl-1,5-bis(phenylsulfenyl)pentan-3-one (16j):

Yield 90%; white solid; mp 100-102 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 7.25-7.10 (m, 20H), 4.45-4.4.50 (m, 2H), 3.08-2.78 (m, 4H).**^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 204.6, 140.68, 133.9, 132.86, 128.87, 128.49, 127.66, 127.47, 126.84, 49.39, 47.76. **IR (KBr, cm^{-1})**: 3056, 3021, 2886, 1716, 1321. **GC-MS**: (m/z) 455 $[M+H]^+$. **CHNS**: Anal. calcd for $C_{29}H_{26}OS_2$: C, 76.61; H, 5.76; S, 14.11; found: C, 76.70; H, 5.81; S, 14.25.



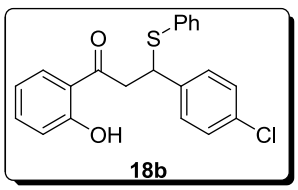
1,5-Di(4-methoxyphenyl)-1,5-bis(phenylsulfenyl)pentan-3-one (16k):

Yield 89%; white solid; mp 135-137 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 7.36 (d, *J* = 6.5Hz, 2H), 7.30 (d, *J* = 6.5Hz, 2H), 7. 28 (dd, *J* = 8, 7.5, 4H), 6.91 (d, *J* = 8.5Hz, 2H), 6.81 (d, *J* = 8.5Hz, 2H), 6.66 (d, *J* = 8.5Hz, 2H), 6.62 (d, *J* = 8.5Hz, 2H), 4.55 (m, 2H), 3.71 (s, 6H), 3.44 (m, 2H), 3.36-3.31 (m, 2H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 199.10, 135.56, 134.02, 131.83, 129.64, 129.01, 128.81, 128.64, 126.65, 55.06, 49.01, 42.45. **IR (KBr, cm^{-1})**: 3062, 2954, 2842, 1713, 1509, 1248, 741. **GC-MS**: (m/z) 515 $[M+H]^+$. **CHNS**: Anal. calcd for $C_{31}H_{30}O_3S_2$: C, 72.34; H, 5.87; S, 12.46; found: C, 72.36; H, 5.91; S, 12.14.



1-(2-Hydroxyphenyl)-3-(4-methylphenyl)-3-(phenylsufenyl)propan-1-one (18a):

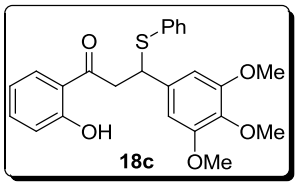
Yield 90%; white solid; mp 114-115 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 12.0 (s, br, D_2O exchangeable, 1H), 7.8 (d, *J* = 8Hz, 2H), 7.56-7.16 (m, 7H), 7.04 (d, *J* = 8Hz, 2H), 6.90 (d, *J* = 3.5Hz, 1H), 6.82 (t, *J* = 10, 3Hz, 1H), 4.56-4.49 (m, 1H), 3.56 (dddd, *J* = 58.5, 43, 17, 5.5Hz, 2H), 2.25 (s, 3H). **IR (KBr, cm^{-1})**: 3445, 3011, 2998, 1723, 1356, 1208, 750. **HRMS (ESIMS)**: Anal. calcd for $C_{22}H_{21}O_2S$ $(M+H)^+$ 349.1262; found 349.1259.



1-(2-Hydroxyphenyl)-3-(4-chlorophenyl)-3-(phenylsufenyl)propan-1-one (18b):

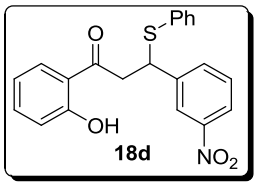
Yield 92%; white solid; mp 126-128 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 11.90 (s, br, D_2O exchangeable, 1H), 7.55 (d, *J* = 8Hz, 1H), 7.31 (dd, *J* = 8.5, 1Hz, 2H), 7.22-7.09 (m, 8H), 6.82 (d, *J* = 8.5Hz, 1H), 6.75 (t, *J* = 8Hz, 1H), 4.55 (t, *J* =

7.5Hz, 1H), 3.49 (d, *J* = 7.5Hz, 2H). **IR (KBr, cm^{-1})**: 3425, 3017, 2985, 1728, 1301, 741. **HRMS (ESIMS)**: Anal. calcd for $C_{21}H_{17}ClNaO_2S$ $(M+Na)^+$ 391.0535; found 391.0531.



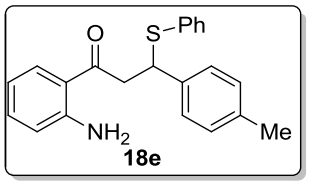
1-(2-Hydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)-3-(phenylsufenyl)propan-1-one(18c):

Yield 90%; white solid; mp 88-89 ^{0}C. **^{1}H NMR (CDCl$_3$, 500 MHz)** δ (ppm) 12.08 (s, br, D_2O exchangeable, 1H), 7.69 (dd, *J* = 8, 1Hz, 1H), 7.50-7.41 (m, 2H), 7.36-7.22 (m, 3H), 6.95 (d, *J* = 8.5Hz, 1H), 6.87 (t, *J* = 7.5Hz, 1H), 6.51 (s, 2H), 4.56-4.53 (m, 1H), 3.79 (s, 3H), 3.78 (s, 6H), 3.66-3.54 (m, 2H). **IR (KBr, cm^{-1})**: 3435, 3100, 2996, 1695, 1256, 755. **HRMS (ESIMS)**: Anal. calcd for $C_{24}H_{24}NaO_5S$ $(M+Na)^+$ 447.1242; found 447.1252.



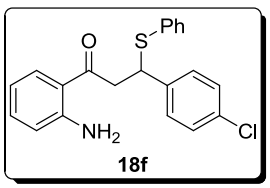
1-(2-Hydroxyphenyl)-3-(3-nitrophenyl)-3-(phenylsufenyl)propan-1-one (18d):

Yield 93%; white solid; mp 184-185 ^{0}C. **^{1}H NMR (CDCl$_3$, 500 MHz)** δ (ppm) 12.01 (s, br, D_2O exchangeable, 1H), 8.17 (s, 1H), 8.05 (d, *J* = 8Hz, 1H), 7.71 (d, *J* = 8Hz, 1H), 7.60 (d, *J* = 7.5Hz, 1H), 7.47 (d, *J* = 9.5Hz, 1H), 7.45-7.4 (m, 3H), 7.32-7.23 (m, 3H), 6.95-6.88 (m, 2H), 4.57 (t, *J* = 6.5Hz, 1H), 3.74-3.27 (m, 2H). **IR (KBr, cm^{-1})**: 3408, 3070, 2985, 2852, 1674, 1533, 1144, 750. **HRMS (ESIMS)**: Anal. calcd for $C_{21}H_{17}NNaO_4S$ $(M+Na)^+$ 402.0776; found 402.0769.



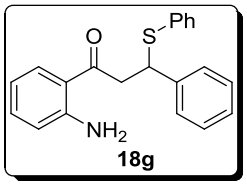
1-(2-Aminophenyl)-3-(4-methylphenyl)-3-(phenylsufenyl)propan-1-one (18e):

Yield 90%; white solid; mp 120-122 ^{0}C. **^{1}H NMR (CDCl$_3$, 500 MHz)** δ (ppm) 7.59 (d, *J* = 8Hz, 1H), 7.38-7.0 (m, 12 H), 6.47 (d, *J* = 8Hz, 1H), 6.3 (s, br, D_2O exchangeable, 2H), 4.62-4.56 (m, 1H), 3.53 (dddd, *J* = 64.5, 47.5, 17, 6Hz, 2H), 2.21 (s, 3H). **IR (KBr, cm^{-1})**: 3416, 3308, 3070, 2925, 2852, 1724, 1647, 1612, 1141, 746. **HRMS (ESIMS)**: Anal. calcd for $C_{22}H_{21}NNaOS$ $(M+Na)^+$ 370.1242; found 370.1236.

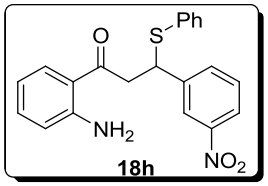


1-(2-Aminophenyl)-3-(4-chlorophenyl)-3-(phenylsufenyl)propan-1-one (18f):

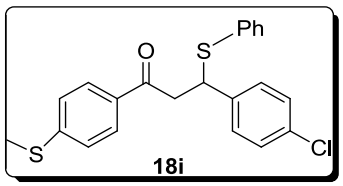
Yield 95%; white solid; mp 136-137 ^{0}C. **^{1}H NMR (CDCl$_3$, 500 MHz)** δ (ppm) 7.81 (dd, *J* = 8Hz, 1H), 7.64-7.2 (m, 11Hz), 6.69-6.17 (m, 1H), 6.3 (s, br, D_2O exchangeable, 2H), 4.55-4.46 (m, 1H), 3.58-3.54 (m, 2H). **IR (KBr, cm^{-1})**: 3415, 3317, 3015, 2984, 1688, 1267, 743. **IR (KBr, cm^{-1})**: 3426, 3318, 3075, 2995, 2872, 1699, 1647, 1176, 748. **HRMS (ESIMS)**: Anal. calcd for $C_{21}H_{18}ClNNaOS$ $(M+Na)^+$ 390.0695; found 390.0672.



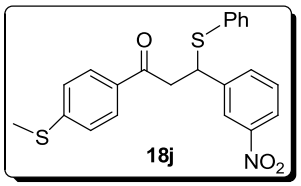
1-(2-Aminophenyl)-3-phenyl-3-(phenylsufenyl)propan-1-one (18g):
Yield 91%; white solid; mp 110-111 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 7.63 (d, *J* = 8Hz, 1H), 7.41-7.39 (m, 3H), 7.33-7.18 (m, 8H), 6.56-6.53 (m, 1H), 6.19 (s, br, D_2O exchangeable, 2H), 4.57 (t, *J* = 6.5Hz, 1H), 3.57 (dddd, 55, 35, 17, 3.5Hz, 2H). **IR (KBr, cm^{-1})**: 3416, 3318, 3175, 2985, 2872, 1679, 1647, 1176, 748. **HRMS (ESIMS)**: Anal. calcd for $C_{21}H_{19}NNaOS$ $(M+Na)^+$ 356.1085; found 356.1081.



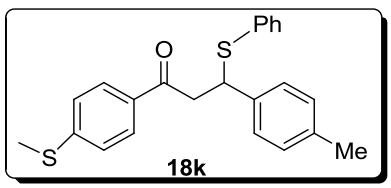
1-(2-Aminophenyl)-3-(3-nitrophenyl)-3-(phenylsufenyl)propan-1-one (18h):
Yield 92%; white solid; mp 173-174 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 8.15 (s, 1H), 7.96 (d, *J* = 8Hz, 1H), 7.63 (d, *J* = 8.5Hz, 1H), 7.58 (d, *J* = 8Hz, 1H), 7.39 (d, *J* = 7.5Hz, 1H), 7.33-7.16 (m, 6H), 6.61-6.15 (m, 2H), 4.97 (t, *J* = 7Hz, 1H), 3.61 (m, 2H). **IR (KBr, cm^{-1})**: 3426, 3318, 3075, 2995, 2872, 1699, 1647, 1176, 748. **HRMS (ESIMS)**: Anal. calcd for $C_{21}H_{19}N_2O_3S$ $(M+H)^+$ 379.1116; found 379.1126.



1-[4-(Methylmercapto)phenyl]-3(4-chlorophenyl)-3-(phenylsulfenyl)propan-1-one (18i):
Yield 95%; white solid; mp 121-123 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 7.77 (d, *J* = 8.5Hz, 2H), 7.42 (dd, *J* = 8.5Hz, 1.5Hz, 3H), 7.31-7.29 (m, 3H), 7.25-7.21 (m, 5H), 4.58 (dd, *J* = 8Hz, 6.5Hz, 1H), 3.53 (m, 2H), 2.5 (s, 3H). **IR (KBr, cm^{-1})**: 3066, 2921, 2888, 1670, 1585, 1089, 744.5. **HRMS (ESIMS)**: Anal. calcd for $C_{22}H_{19}ClNaOS_2$ $(M+Na)^+$ 421.0464; found 421.0472.

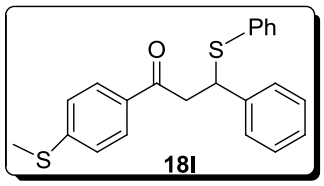


1-[4-(Methylmercapto)phenyl]-3(3-nitrophenyl)-3-(phenylsulfenyl)propan-1-one (18j):
Yield 96%; white solid; mp 87-88 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 8.16 (s, 1H), 8.02 (d, *J* = 8Hz, 1H), 7.80 (dd, *J* = 7, 2Hz, 2H), 7.43-7.41 (m, 2H), 7.32-7.28 (m, 3H), 7.26-7.22 (m, 4H), 4.5 (t, *J* = 6.5Hz, 1H), 3.6 (m, 2H), 2.51 (s, 3H). **IR (KBr, cm^{-1})**: 3046, 2917, 1669, 1583, 1343, 1088, 739. **HRMS (ESIMS)**: Anal. calcd for $C_{22}H_{19}NNaO_3S_2$ $(M+Na)^+$ 432.0704; found 432.0698.



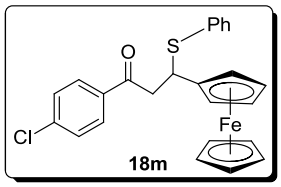
1-[4-(Methylmercapto)phenyl]-3(4-methylphenyl)-3-(phenylsulfenyl)propan-1-one (18k):
Yield 94%; white solid; mp 112-113 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 7.77 (d, *J* = 8.5Hz, 2H), 7.42 (dd, *J* = 9, 1.5Hz, 3H), 7.34-7.30 (m, 4H), 7.25-7.21 (m, 2H), 7.05 (d, *J* = 8Hz, 2H), 4.51 (dd, *J* = 8, 6Hz, 1H), 3.54 (dddd,

83, 49, 17, 6Hz, 2H), 2.41 (s, 3H), 2.3 (s, 3H). **IR (KBr, cm^{-1})**: 3050, 2913, 2855, 1665, 1584, 1401, 1089, 735. **HRMS (ESIMS)**: Anal. calcd for $C_{23}H_{23}OS_2(M+H)^+$ 379.1190; found 379.1187.



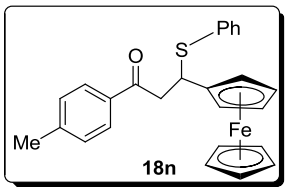
1-[4-(Methylmercapto)phenyl]-3-phenyl-3-(phenylsulfenyl)propan-1-one (18l):

Yield 95%; white solid; mp 111-112 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 7.78 (dd, *J* = 8.5, 1.5Hz, 2H), 7.42 (dd, *J* = 8, 1.5Hz, 2H), 7.33-7.21 (m, 10H), 4.54 (t, *J* = 6.5Hz, 1H), 3.55 (dddd, *J* = 62.5, 35.1, 17, 2Hz, 2H), 2.5 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 195.94, 146.17, 141.12, 132.66, 130.65, 128.97, 128.81, 128.44, 127.74, 127.33, 127.10, 124.86, 99.91, 48.24, 44.32, 14.62. **IR (KBr, cm^{-1})**: 3066, 2917, 2851, 1673, 1587, 1401, 1089, 741.9. **HRMS (ESIMS)**: Anal. calcd for $C_{22}H_{21}OS_2(M+H)^+$ 365.1034; found 365.1030.



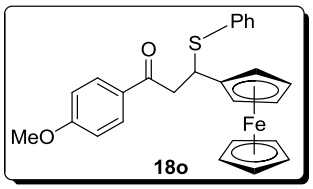
1-(4-Chlorophenyl)-3-ferrocenyl-3-phenylsulfenylpropan-1-one (18m):

Yield 92%; orange red solid; mp 102-103 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 7.86 (d, *J* = 9Hz, 2H), 7.43 (dd, *J* = 9, 2.5Hz, 2H), 7.34-7.31 (m, 2H), 7.26-7.21 (m, 3H), 4.5 (t, *J* = 6.5Hz, 1H), 4.13-4.07 (m, 9H), 3.51 (m, *J* = 6.5Hz, 2H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 196.5, 139.6, 135.2, 134.0, 133.5, 130.6, 129.5, 129.0, 128.9, 128.8, 127.6, 127.4, 89.7, 68.8, 67.9, 67.7, 66.9, 44.5, 43.5. **IR (KBr, cm^{-1})**: 3093, 2923, 2888, 1683, 1583, 1399. **HRMS (ESIMS)**: Anal. calcd for $C_{25}H_{22}ClFeOS$ $(M+H)^+$ 461.0429; found 461.0436.



1-(4-Methylphenyl)-3-ferrocenyl-3-phenylsulfenylpropan-1-one (18n):

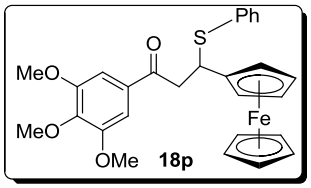
Yield 91 %; orange red solid; mp 87-88 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 7.78 (d, *J* = 3.5Hz, 2H), 7.42-7.114 (m, 7H), 4.56 (t, *J* = 6.5Hz, 1H), 4.06-3.99 (m, 9H), 3.48-3.45 (m, 2H), 2.3 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 197.3, 144.2, 134.6, 134.4, 133.5, 129.4, 128.8, 127.5, 127.2, 68.8, 67.9, 67.7, 67.0, 44.5, 44.6, 21.9. **IR (KBr, cm^{-1})**: 3092, 2925, 1672, 1448. **HRMS (ESIMS)**: Anal. calcd for $C_{26}H_{24}FeNaOS$ $(M+Na)^+$ 463.0795; found 463.0781.



1-(4-Methoxylphenyl)-3-ferrocenyl-3-phenylsulfenylpropan-1-one (18o):

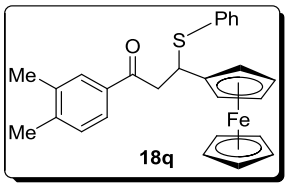
Yield 93%; orange red solid; mp 131-133 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 7.94 (dd, *J* = 7, 2Hz, 2H), 7.35-7.33 (m, 2H), 7.25-7.23 (m, 3H), 6.94 (dd, *J* = 7, 2Hz, 2H), 4.63 (t, *J* = 6Hz, 1H), 4.10-4.07 (m, 9H), 4.06 (s, 3H), 3.51 (dd, *J* = 7Hz, 3.5Hz, 2H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 195.11, 162.61, 132.3, 132.35, 129.5, 129.1,

127.7, 126.5, 112.8, 89.0, 67.78, 66.8, 66.6, 65.9, 54.5, 43.0. **IR (KBr, cm^{-1})**: 3091, 2961, 1669, 1596. **HRMS (ESIMS)**: Anal. calcd for $C_{26}H_{24}FeNaO_2S$ $(M+Na)^+$ 479.0744; found 479.0760.



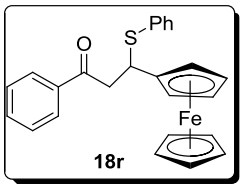
1-(3,4,5-Trimethoxylphenyl)-3-ferrocenyl-3-phenylsulfenylpropan-1-one (18p):

Yield 89%; orange red solid; mp 100-101 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 7.23-7.12 (m, 5H), 7.1 (s, 2H), 4.55 (t, *J* = 6.5Hz, 1H), 4.1-3.92 (m, 9H), 3.84 (s, 3H), 3.82 (s, 6H), 3.41 (d, *J* = 6.5Hz, 2H). ^{13}C **NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 196.7, 153.1, 142.8, 134.35, 132.32, 130.8, 129.1, 127.5, 127.2, 125.6, 105.8, 90.0, 68.9, 68.02, 67.73, 67.1, 61, 56.4, 44.3. **IR (KBr, cm^{-1})**: 3011, 2924, 2850, 1670, 1490, 1300, 1110, 1000, 851. **HRMS (ESIMS)**: Anal. calcd for $C_{28}H_{29}FeO_4S$ $(M+H)^+$ 517.1136; found 517.1148.



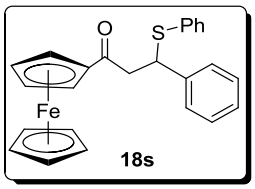
1-(3,4-Dimethylphenyl)-3-ferrocenyl-3-phenylsulfenylpropan-1-one (18q):

Yield 94 %; orange red solid; mp 102-104 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 7.64 (d, *J* = 1.5Hz, 1H), 7.60 (dd, *J* = 7.5, 1.5Hz, 1H), 7.36-7.34 (m, 1H), 7.28-7.14 (m, 8H), 4.57 (t, *J* = 6.5Hz, 1H), 4.27 (s, 1H), 4.1-4.02 (m, 9H), 3.45 (dd, *J* = 7, 3Hz, 2H), 2.25 (s, 6H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 197.6, 142.9, 137.1, 135.0, 134.4, 133.4, 130.7, 129.9, 129.4, 129.0, 128.8, 127.5, 127.2, 125.9, 90.1, 68.8, 67.0, 44.3, 40.61, 20.1, 19.9. **IR (KBr, cm^{-1})**: 3102, 2935, 1670, 1465, 1376, 1131, 1010, 865. **HRMS (ESIMS)**: Anal. calcd for $C_{27}H_{26}FeNaOS$ $(M+Na)^+$ 477.0951; found 477.0937.



1-Phenyl-3-ferrocenyl-3-(phenylsulfenyl)propan-1-one (18r):

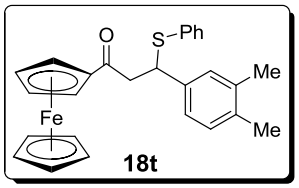
Yield 96%; orange red solid; mp 89-90 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 7.94-7.90 (m, 2H), 7.59-7.46 (m, 3H), 7.34-7.23 (m, 5H), 4.63(t, *J* = 6.5Hz, 1H), 4.16-4.08 (m, 9H), 3.6-3.56 (m, 2H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 197.70, 137.0, 134.3, 133.5, 133.3, 128.8, 128.7, 128.2, 127.6, 90.0, 68.84, 67.9, 67.8, 67.7, 66.9, 44.5, 43.9. **IR (KBr, cm^{-1})**: 3102, 2935, 1709, 1425. **HRMS (ESIMS)**: Anal. calcd for $C_{25}H_{23}FeOS$ $(M+H)^+$ 427.0819; found 427.0830.



1-Ferrocenyl-3 phenyl-3-(phenylsulfenyl)propan-1-one (18s):

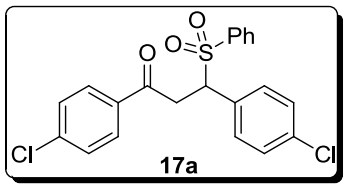
Yield 96%; orange red solid; 116-117 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 7.43 (d, *J* = 7.5Hz, 2H), 7.36 (d, *J* = 7Hz, 2H), 7.28 (t, *J* = 8Hz, 2H), 7.24-7.18 (m, 4H), 5.0 (dd, *J* = 9, 5Hz, 1H), 4.70 (d, *J* = 12.5Hz, 2H), 4.44 (s, 2H), 3.94 (s, 5H), 3.42-3.36 (m, 1H), 3.23 (dd, *J* = 17, 4.5Hz, 1H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 200.7, 141.6, 134.8, 132.2, 129.1, 128.9, 127.6, 127.5, 127.2, 78.7, 77.4, 77.1, 76.9, 72.4, 69.8, 69.3,

69.1, 47.6, 46.2. **IR (KBr, cm^{-1})**: 3112, 2925, 1659, 1455. **HRMS (ESIMS)**: Anal. calcd for $C_{25}H_{23}FeOS$ $(M+H)^+$ 427.0819; found 427.0824.



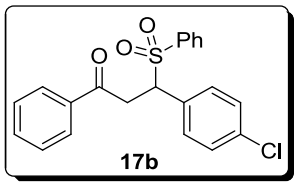
1-Ferrocenyl-3(3,4-dimethylphenyl)-3-(phenylsulfenyl)propan-1-one (18t):

Yield 95%; orange red solid; 138-139 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 7.32 (d, *J* = 8Hz, 2H), 7.24-7.06 (m, 5H), 6.97 (d, *J* = 8Hz, 1H), 4.59-4.56 (m, 1H), 4.48-4.44 (m, 2H), 4.38-4.37 (m, 2H), 3.92-3.85 (m, 5H), 3.36-3.30 (m, 1H), 3.13 (dd, *J* = 17, 4.5Hz, 1H), 2.18 (s, 3H), 2.15 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 201.10, 138.65, 136.71, 135.90, 135.21, 131.81, 129.77, 129.10, 127.52, 127.18, 125.38, 78.74, 72.28, 70.12, 69.73, 69.31, 69.10, 47.20, 46.25, 19.89, 19.48. **IR (KBr, cm^{-1})**: 3010, 2934, 1637, 1593. **HRMS (ESIMS)**: Anal. calcd for $C_{27}H_{27}FeOS$ $(M+H)^+$ 455.1132; found 455.1143.



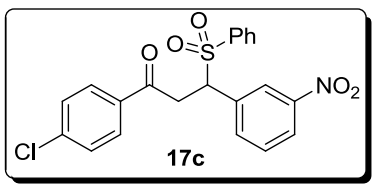
1,3-Bis(4-chlorophenyl)-3-(phenylsulfonyl)propan-1-one (17a):

Yield 89%; white solid; mp 175-177 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 7.86 (dd, *J* = 8.5, 1.5Hz, 2H), 7.62-7.56 (m, 3H), 7.46-7.42 (m, 4H), 7.18 (d, *J* = 8.5Hz, 2H), 7.12 (d, *J* = 8.5Hz, 2H), 4.96 (dd, *J* = 9.5, 3Hz, 1H), 4.12 (dd, *J* = 18, 3.5Hz, 1H), 3.86-3.80 (m, 1H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 193.59, 140.40, 136.60, 135.01, 134.25, 134.00, 133.25, 131.02, 130.93, 129.51, 129.37, 129.15, 128.77, 65.74, 36.85. **IR (KBr, cm^{-1})**: 3060, 2919, 2843, 1687, 1304,1142. **CHNS**: Anal. calcd for $C_{21}H_{16}Cl_2O_3S$ (418.02): C, 60.15; H, 3.85; S, 7.65; found: C, 60.26; H, 3.87; S, 7.25.



1-Phenyl-3-(4-chlorophenyl)-3-(phenylsulfonyl)propane-1-one (17b):

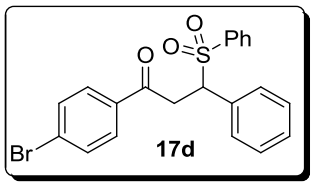
Yield 90%; white solid; mp 140-141 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 7.93 (d, *J* = 7.5Hz, 2H), 7.62-7.57 (m, 4H), 7.5-7.42 (m, 4H), 7.18 (d, *J* = 8.5Hz, 2H), 7.13 (d, *J* = 8.5Hz, 2H), 4.9 (dd, *J* = 5, 3.5Hz, 1H), 4.12 (dd, *J* = 17.5, 3Hz, 1H), 3.89 (m, 1H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 194.69, 136.74, 135.97, 134.96, 133.98, 133.87, 131.15, 131.02, 128.99, 128.95, 128.83, 128.76, 128.13, 65.85, 36.92. **IR (KBr, cm^{-1})**: 3104, 2940, 1687, 1302,1147. **CHNS**: Anal. calcd for $C_{21}H_{17}ClO_3S$ (384.06): C, 65.53; H, 4.45; S, 8.33; found: C, 65.43; H, 4.49; S, 8.13.



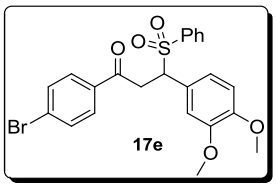
1-(4-Chlorophenyl)-3-(3-nitrophenyl)-3-phenylsulfonylpropane-1-one (17c):

Yield 88%; white solid; mp 168-170 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 8.13 (dd, *J* = 7, 1.5Hz, 1H), 8.022 (m, 1H), 7.88 (dd, *J* = 7, 2Hz, 2H), 7.64-7.58 (m, 4H), 7.47-7.43 (m, 5H), 5.0 (dd, *J* = 10, 3.5Hz, 1H), 4.16 (dd, *J* = 18,

3.5Hz, 1H), 3.93-3.88 (m, 1H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 201.13, 138.79, 136.71, 135.17, 134.53, 133.77, 130.29, 129.81, 129.36, 129.17, 129.05, 128.69, 128.60, 127.93, 127.08, 65.65, 41.53. **IR (KBr, cm^{-1})**: 3075, 2962, 1684, 1533. **CHNS**: Anal. calcd for $C_{21}H_{16}ClNO_5S$ (429.04): C, 58.67; H, 3.75; N, 3.26; S, 7.46; found: C, 59.00; H, 3.81; N, 3.16; S, 7.34.

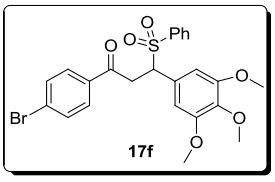


1-(4-Bromophenyl)-3-phenyl-3-(phenylsulfonyl) propane-1-one (17d): Yield 92%; white solid; mp 173-174 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 7.94 (dd, *J* = 7, 1.5Hz, 1H), 7.81 (d, *J* = 8.5Hz, 2H), 7.62 (d, *J* = 8.5Hz, 2H), 7.56-7.52 (m, 3H), 7.38 (t, *J* = 8.5Hz, 2H), 7.2-7.16 (m, 4H), 4.9 (dd, *J* = 9.5, 3.5Hz, 1H), 4.1 (dd, *J* = 16, 3.5Hz, 1H), 3.91-3.87 (m, 1H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 193.98, 145.45, 136.94, 134.86, 133.79, 132.42, 131.96, 130.79, 130.05, 129.71, 129.03, 128.77, 128.54, 66.44, 36.85. **IR (KBr, cm^{-1})**: 3070, 2917, 2847, 1684, 1585, 1299. **CHNS**: Anal. calcd for $C_{21}H_{17}BrO_3S$ (428.01): C, 58.75; H, 3.99; S, 7.47; found: C, 58.66; H, 3.96; S, 7.27.



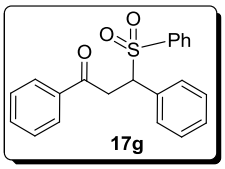
1-(4-Bromophenyl)-3-(3,4-dimethoxyphenyl)-3-(phenylsulfonyl)propane-1-one (17e):

Yield 86%; white solid; mp 160-161 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 7.82 (d, *J* = 8.5Hz, 2H), 7.62 (d, *J* = 8Hz, 2H), 7.57-7.55 (m, 2H), 7.41 (t, *J* =7.5Hz, 2H), 6.75 (dd, *J* = 8.5, 2Hz, 1H), 6.69 (d, *J* = 13.5Hz, 1H), 6.58 (s, 2H), 4.84 (dd, *J* = 9.5, 3Hz, 1H), 4.08 (dd, *J* = 18, 3.5Hz, 1H), 3.87-3.83 (m, 1H), 3.81 (s, 3H), 3.69 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 194.13, 149.44, 148.69, 136.92, 134.89, 133.73, 132.13, 129.66, 129.08, 128.81, 126.55, 124.48, 122.08, 112.69, 110.87, 66.18, 55.82, 53.35, 36.73. **IR (KBr,cm^{-1})**: 3090, 2933, 1690, 1517. **CHNS**: Anal. calcd for $C_{23}H_{21}BrO_5S$ (488.03): C, 56.45; H, 4.33; S, 6.55; found: C, 56.55; H, 4.30; S, 6.25.



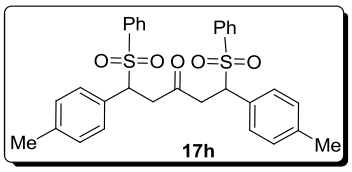
1-(4-Bromophenyl)-3-(3,4,5-trimethoxyphenyl)-3-(phenylsulfonyl)propane-1-one (17f):

Yield 80%; white solid; mp 200-201 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 7.84 (d, *J* = 8Hz, 2H), 7.63 (d, *J* = 17Hz, 2H), 7.60 (d, *J* = 6Hz, 3H), 7.43-7.37 (m, 2H), 6.33 (s, 2H), 4.83 (d, *J* = 9.5 Hz, 1H), 4.08 (d, *J* = 18Hz, 1H), 3.93-3.71 (m, 1H), 3.78 (s, 3H), 3.65 (s, 6H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 194.5, 153.06, 136.82, 133.77, 132.18, 131.58, 129.67, 129.14, 128.80, 127.68, 106.85, 100.00, 66.66, 56.12, 53.45, 36.64. **IR (KBr,cm^{-1})**: 3065, 2921, 2847, 1693, 1587, 1134. **CHNS**: Anal. calcd for $C_{24}H_{23}BrO_6S$ (518.04): C, 55.50; H, 4.46; S, 6.17; found: C, 55.60; H, 4.50; S, 6.30.



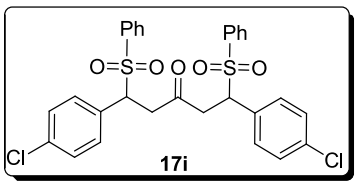
1-Phenyl-3-phenyl- 3-phenylsulfonylpropane-1-one (17g):

Yield 93%; white solid; mp 138-140 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 7.94 (dd, *J* = 5, 1Hz, 2H), 7.57-7.37 (m, 8H), 7.26-7.19 (m, 5H), 4.95-4.93 (m, 1H), 4.13 (dd, *J* = 18, 3.5Hz, 1H), 3.98-3.91 (m, 1H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 194.88, 136.93, 136.1, 133.74, 133.7, 132.5, 129.8, 129.03, 128.83, 128.78, 128.76, 128.5, 128.15, 66.51, 36.9. **IR (KBr, cm^{-1})**: 3065, 2926, 1687, 1306, 1142. **CHNS**: Anal. calcd for $C_{21}H_{18}O_3S$ (350.09): C, 71.98; H, 5.18; S, 9.15; found: C, 72.06; H, 5.20; S, 9.31.



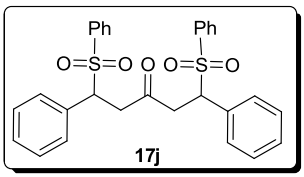
1,5-Di(4-methylphenyl)-1,5-bis(phenylsulfonyl)pentan-3-one (17h):

Yield 90%; white solid; mp 158-160 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 8.05 (d, *J* = 2Hz, 1H), 7.57-7.49 (m, 6H), 7.40-7.37 (m, 4H), 6.92 (d, *J* = 16Hz, 4H), 6.81 (d, *J* = 8Hz, 3H), 4.95 (dd, *J*= 9, 4.5Hz, 2H), 3.64 (dd, *J* = 17.5, 4.5Hz, 2H), 3.17-3.12 (m, 2H), 2.14 (s, 6H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 193.51, 140.71, 136.20, 135.65, 134.81, 134.35, 129.53, 128.90, 124.55, 60.55, 39.66, 20.92. **IR (KBr, cm^{-1})**: 3065, 2923, 1769, 1302, 1145 cm^{-1}. **CHNS**: Anal. calcd for $C_{31}H_{30}O_5S_2$ (546.15): C, 68.11; H, 5.53; S, 11.73; found: C, 68.23; H, 5.57;S, 11.90.



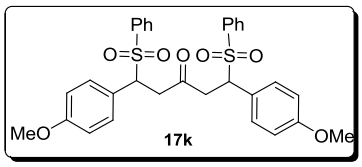
1,5-Di(4-chlorophenyl)-1,5-bis(phenylsulfonyl)pentan-3-one (17i):

Yield 88 %; white solid; mp 184-185 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 8.07 (d, *J* = 3Hz, 1H), 7.96 (d, *J* = 3Hz, 1H), 7.56 (q, 3H), 7.51-7.37 (m, 8H), 7.19 (d, *J* = 8.5Hz, 1H), 7.09 (d, *J* = 8.5Hz, 1H), 6.96 (d, *J* = 8.5Hz, 1H), 6.85 (d, *J* = 8.5Hz, 2H), 4.98-4.93 (dd, *J*= 9, 4.5Hz, 2H), 3.56 (dddd, *J* = 35, 17.5, 4.5Hz, 2H), 3.33 (m, 1H), 3.15 (m, 1H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 196.12, 136.35, 135.23, 134.09, 130.79, 130.61, 130.33, 128.99, 128.74, 65.31, 41.51. **IR (KBr, cm^{-1})**: 3065, 2920, 2847, 1724,1301. **CHNS**: Anal. calcd for $C_{29}H_{24}Cl_2O_5S_2$ (586.04): C, 59.28; H, 4.12; S, 10.92; found: C, 59.37; H, 4.09; S, 10.68.



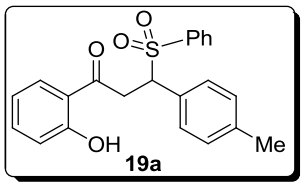
1,5-Di(phenyl)-1,5-bis(phenylsulfonyl)pentan-3-one (17j):

Yield 89%; white solid; mp 161-162 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 7.54-7.46 (m, 5H), 7.41 (d, *J* = 8Hz, 1H), 7.36-7.29 (m, 5H), 7.18 (t, *J* = 6.5Hz, 3H), 7.09 (t, *J* = 7Hz, 3H), 7.02 (d, *J* = 7.5Hz, 1H), 6.92 (d, *J* = 7.5Hz, 2H), 4.92 (m, 2H), 3.62 (dd, *J* = 17.5, 4.5Hz, 1H), 3.53 (dd, *J* = 18, 4.5Hz, 1H), 3.41 (m, 1H), 3.21 (m, 1H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 201.1, 136.53, 133.92, 131. 83, 129.54, 129.01, 128.81, 128.54, 126.55, 66.01, 41.42. **IR (KBr, cm^{-1})**: 3066, 2924, 1723, 1304, 1143, 691. **CHNS**: Anal. calcd for $C_{29}H_{26}O_5S_2$ (518.12): C, 67.16; H, 5.05; S, 12.36; found: C, 67.06; H, 5.10; S, 12.56.



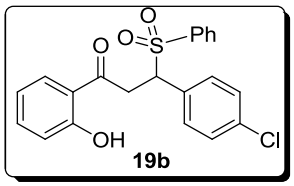
1,5-Di(4-methoxyphenyl)-1,5-bis(phenylsulfonyl)pentan-3-one(17k):

Yield 80%; white solid; mp 188-190 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 7.49 (d, *J* = 6.5Hz, 2H), 7.43 (d, *J* = 6.5Hz, 4H), 7.37 (dd, *J* = 8, 7.5Hz, 4H), 6.92 (d, *J* = 8.5Hz, 2H), 6.84 (d, *J* = 8.5Hz, 2H), 6.71 (d, *J* = 8.5Hz, 2H), 6.62 (d, *J* = 8.5Hz, 2H), 4.95 (m, 2H), 3.75 (s, 6H), 3.50 (dddd, *J* = 50.5, 28, 18, 9.5Hz, 2H), 3.36-3.31 (m, 1H), 3.18-3.12 (m, 1H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 200.10, 137.56, 135.12, 132.86, 130.64, 129.10, 128.91, 128.70, 124.97, 65.01, 58.06, 42.45. **IR (KBr, cm^{-1})**: 3019, 2995, 1707, 1356, 1155. **CHNS**: Anal. calcd for $C_{31}H_{30}O_7S_2$ (578.14): C, 64.34; H, 5.23; S, 11.08; found: C, 64.55; H, 5.19; S, 11.21.



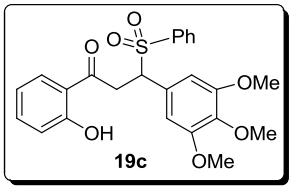
1-(2-Hydroxyphenyl)-3-(4-methylphenyl)-3-(phenylsufonyl)propan-1-one (19a):

Yield 90%; white solid; mp 155-157 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 11.61 (s, br, D_2O exchangeable, 1H), 7.93-7.83 (m, 2H), 7.64-7.47 (m, 4H), 7.26-7.23 (m, 2H), 7.06-7.02 (m, 3H), 6.95-6.92 (m,2H), 4.90 (dd, *J* = 9.5, 3.5Hz, 1H), 4.13 (dd, *J* = 16, 3.5Hz, 1H), 3.97-3.92 (m, 1H), 2.30 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 198.63, 161.38, 139.83, 136.25, 135.48, 132.02, 129.92, 129.64, 129.27, 128.81, 128.29, 127.93, 127.63, 126.21, 116.22, 62.94, 37.22, 21.28. **IR (KBr, cm^{-1})**: 3438, 3067, 2997, 2952, 1707, 1543, 1315, 1154, 761 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{22}H_{21}O_4S$ $(M+H)^+$ 381.1161; found 381.1169.



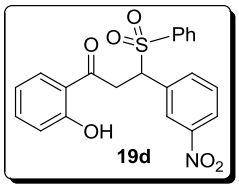
1-(2-Hydroxyphenyl)-3-(4-chlorophenyl)-3-(phenylsufonyl)propan-1-one (19b):

Yield 95%; white solid; mp 165-167 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 11.63 (s, br, D_2O exchangeable, 1H), 7.96 (d, *J* = 8Hz, 1H), 7.83 (d, *J* = 8Hz, 1H), 7.60-7.57 (m, 3H), 7.43-7.4 (m, 3H), 7.16 (dd, *J* = 13, 8Hz, 3H), 6.96-6.93 (m, 2H), 4.89 (dd, *J* = 18, 3Hz, 1H), 4.16 (dd, *J* = 18, 3Hz, 1H), 3.94-3.89 (m, 1H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 199.24, 160.54, 138.74, 136.14, 133.14, 131.35, 130.14, 129.81, 129.07, 128.64, 128.05, 127.99, 127.43, 125.74, 115.98, 64.43, 37.22. **IR (KBr, cm^{-1})**: 3438, 3067, 2997, 2952, 1707, 1543, 1154, 761cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{21}H_{18}ClO_4S$ $(M+H)^+$ 401.0614; found 401.0625.



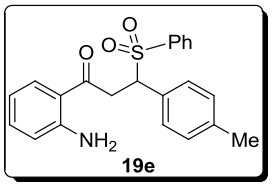
1-(2-Hydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)-3-(phenylsufonyl)propan-1-one (19c):

Yield 91%; white solid; mp 121-122 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 12.10 (s, br, D_2O exchangeable, 1H), 7.70 (dd, *J* = 8, 1.5Hz, 1H), 7.42-7.38 (m, 2H), 7.26-7.23 (m, 3H), 6.95 (d, *J* = 8.5Hz, 1H), 6.9 (t, *J* = 7.5Hz, 1H), 6.6 (s, 2H), 5.0 (dd, *J* = 16, 3Hz, 1H), 3.8 (s, 3H), 3.78 (s, 6H), 3.7 (m, 1H), 3.68 (m, 1H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 200.01, 161.64, 151.43, 139.84, 136.76, 135.47, 134.28, 131.54, 130.58, 129.67, 128.53, 122.58, 116.29, 105.94, 65.47, 56.64, 56.13, 38.24. **IR (KBr, cm^{-1})**: 3412, 3019, 2967, 1701, 1355, 1206. **HRMS (ESIMS)**: Anal. calcd for $C_{24}H_{25}O_7S$ $(M+H)^+$ 457.1321; found 457.1336.



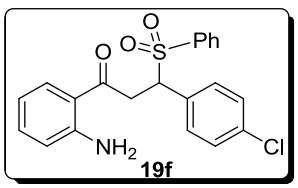
1-(2-Hydroxyphenyl)-3-(3-nitrophenyl)-3-(phenylsufonyl)propan-1-one (19d):

Yield 92%; white solid; mp 121-123 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 12.10 (s, br, D_2O exchangeable, 1H), 8.2 (s, 1H), 7.66-7.43 (m, 6H), 7.4-7.01 (m, 4H), 6.72 (d, *J* = 8Hz, 1H), 5.05 (m, 1H), 3.82-3.78 (m, 1H), 3.76-3.72 (m, 1H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 200.11, 160.54, 149.84, 140.24, 138.76, 135.64, 133.84, 132.24, 130.54, 129.21, 129.01, 128.75, 128.60, 128.10, 122.68, 119.64, 116.58, 63.54, 36.95. **IR (KBr, cm^{-1})**: 3412, 3019, 2967, 1701, 1355, 1206. **HRMS (ESIMS)**: Anal. calcd for $C_{21}H_{17}NNaO_6S$ $(M+Na)^+$ 434.0674; found 434.0665.



1-(2-Aminophenyl)-3-(4-methylphenyl)-3-(phenylsufonyl)propan-1-one (19e):

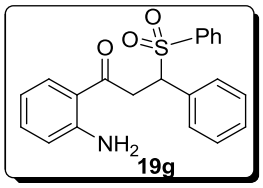
Yield 94%; white solid; mp 152-153 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 7.82 (d, *J* = 8Hz, 1H), 7.44-7.30 (m, 1H), 6.52 (d, *J* = 8Hz, 1H), 6.5 (s, br, D_2O exchangeable, 2H), 5.04-498 (m, 1H), 3.72-3.69 (m, 1H), 3.68 (m, 1H), 2.3 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 199.01, 150.67, 138.55, 137.01, 134.58, 132.51, 13.02, 130.73, 129.35, 129.26, 129.04, 127.88, 125.46, 117.54, 115.84, 65.24, 37.96, 21.32. **IR (KBr, cm^{-1})**: 3416, 3318, 3175, 2985, 2872, 1679, 1647, 1176, 748. **HRMS (ESIMS)**: Anal. calcd for $C_{22}H_{22}NO_3S$ $(M+H)^+$ 380.1320; found 380.1327.



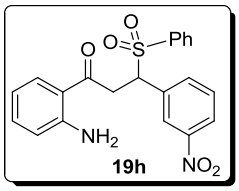
1-(2-Aminophenyl)-3-(4-chlorophenyl)-3-(phenylsufonyl)propan-1-one (19f):

Yield 95%; white solid; mp 163-165 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 7.84 (dd, *J* = 8, 2Hz, 1H), 7.66-7.3 (m, 11Hz), 6.69-6.17 (m, 1H), 6.3 (s, br, D_2O exchangeable, 2H), 4.95-4.86 (m, 1H), 3.68-3.64 (m, 2H). **^{13}C NMR ($CDCl_3$, 125 MHz)**:

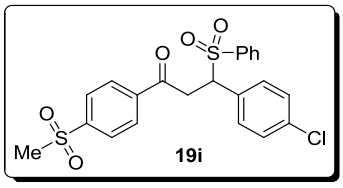
δ (ppm) 198.46, 150.73, 140.43, 135.31, 134.27, 132.98, 130.99, 130.72, 129.27, 129.18, 127.87, 127.28, 117.69, 115.95, 68.65, 40.46. **IR (KBr, cm^{-1})**: 3415, 3317, 3015, 2984, 1686, 1175, 1267, 741. **HRMS (ESIMS)**: Anal. calcd for $C_{21}H_{19}ClNO_3S$ $(M+H)^+$ 400.0774; found 400.0770.



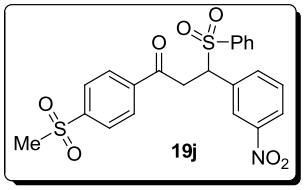
1-(2-Aminophenyl)-3-phenyl-3-(phenylsufonyl)propan-1-one (19g):
Yield 93%; white solid; mp 135-136 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: δ (ppm) 7.65 (d, *J* = 8Hz, 1H), 7.45-7.40 (m, 3H), 7.33-7.18 (m, 8H), 6.58-6.5 (m, 1H), 6.40 (s, br, D_2O exchangeable, 2H), 4.97 (m, 1H), 3.59-3.56 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 198.36, 150.27, 140.98, 135.99, 134.73, 132.46, 130.31, 130.65, 129.95, 129.28, 127.87, 127.18, 117.69, 115.27, 68.72, 40.43. **IR (KBr, cm^{-1})**: 3418, 3328, 3075, 2978, 2872, 1679, 1648, 1206, 756. **HRMS (ESIMS)**: Anal. calcd for $C_{21}H_{19}NNaO_3S$ $(M+Na)^+$ 388.0983; found 388.0994.



1-(2-Aminophenyl)-3-(3-nitrophenyl)-3-(phenylsufonyl)propan-1-one (19h):
Yield 91%; white solid; mp 220-222 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 8.02 (s, 1H), 7.79-7.71 (m, 4H), 7.67-7.51 (m, 3H), 7.45-7.42 (m, 2H), 6.69-6.59 (m, 2H), 6.12 (s, br, D_2O exchangeable, 2H), 5.0 (m, 1H), 4.13 (m, 1H), 3.9 (m, 1H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 200.11, 150.64, 149.32, 140.15, 139.67, 135.21, 135.02, 134.54, 134.22, 130.21, 129.52, 129.10, 128.67, 124.88, 119.81, 119.00, 116.54, 63.41, 38.01. **IR (KBr, cm^{-1})**: 3416, 3308, 3070, 2925, 2852, 1724, 1647, 1612, 1533, 1141, 746. **HRMS (ESIMS)**: Anal. calcd for $C_{21}H_{19}N_2O_5S$ $(M+H)^+$ 411.1015; found 411.1032.

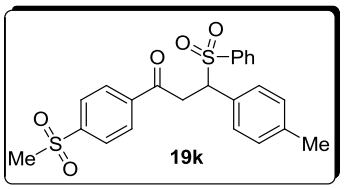


1-[4-(Methylsulfonyl)phenyl]-3(4-chlorophenyl)-3-(phenylsulfonyl)propan-1-one (19i):
Yield 95%; white solid; mp 124-126 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 7.86 (d, *J* = 8.5Hz, 2H), 7.54 (dd, *J* = 8, 2Hz, 3H), 7.42-7.38 (m, 3H), 7.28-7.22 (m, 5H), 4.99 (dd, *J* = 8.5, 6Hz, 1H), 3.63-3.61 (m, 1H), 3.59-3.56 (m, 1H), 3.01 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 195.66, 146.49, 139.88, 133.73, 132.98, 132.84, 129.18, 128.97, 128.60, 128.47, 127.82, 124.98, 99.99, 63.84, 44.25, 37.68. **IR (KBr, cm^{-1})**: 3131, 2979, 2921, 1653, 1589, 1401, 1303, 1057, 740**. HRMS (ESIMS)**: Anal. calcd for $C_{22}H_{19}ClNaO_5S_2$ $(M+Na)^+$ 485.0260; found 485.0257.



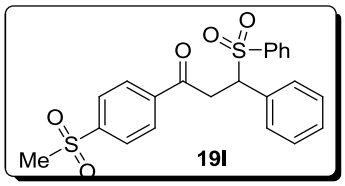
1-[4-(Methylsulfonyl)phenyl]-3(3-nitrophenyl)-3-(phenylsulfonyl)propan-1-one (19j):

Yield 96%; white solid; mp 152-153 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 8.18 (s, 1H), 8.10 (d, *J* = 8Hz, 1H), 7.9-7.85 (m, 2H), 7.68 (dd, *J* = 15, 4Hz, 2H), 7.55-7.51 (m, 4H), 7.28-7.23 (m, 3H), 4.98 (dd, *J* = 17.5, 4.5Hz, 1H), 3.56-3.53 (m, 1H), 3.45-3.42 (m, 1H), 3.01 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 195.15, 146.87, 143.76, 134.31, 133.46, 132.83, 132.50, 130.73, 129.26, 128.47, 128.32, 127.17, 125.00, 122.64, 99.99, 63.54, 44.65, 38.52. **IR (KBr, cm^{-1})**: 3418, 3328, 3075, 2978, 2872, 1679, 1648, 1206 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{22}H_{19}NNaO_3S_2$ $(M+Na)^+$ 432.0704; found 432.0698.



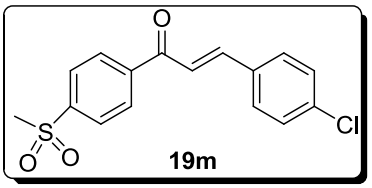
1-[4-(Methylsulfonyl)phenyl]-3(4-methylphenyl)-3-(phenylsulfonyl)propan-1-one (19k):

Yield 91%; white solid; mp 162-163 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 8.12 (dd, *J* = 8.5, 2Hz, 1H), 8.06-8.02 (m, 2H), 7.97 (dd, *J* = 8.5, 1Hz, 2H), 7.75-7.72(m, 3H), 7.42-7.39 (m, 2H), 7.03 (q, 3H), 4.88 (dd, *J* = 9.5, 4Hz, 1H), 4.40-4.30 (m, 1H), 4.18 (dd, *J* = 18, 4Hz, 1H), 3.89-3.83 (m, 1H), 3.10 (s, 3H), 2.27 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 196.13, 146.16, 138.11, 137.04, 132.94, 132.52, 130.74, 129.20, 129.04, 28.88, 128.52, 127.65, 127.41, 127.17, 124.92, 63.51, 44.34, 38.00, 21.14. **IR (KBr, cm^{-1})**: 3064, 2942, 2831, 1663, 1584, 1342, 1111, 781 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{23}H_{22}NaO_5S_2$ $(M+Na)^+$ 465.0806; found 465.0811.



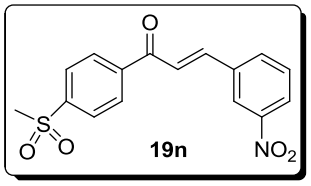
1-(4-(Methylsulfonyl)phenyl)-3-phenyl-3-(phenylsulfonyl)propan-1-one (19l):

Yield 92%; white solid; mp 143-144 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 8.10 (dd, *J* = 8Hz, 1.5Hz, 1H), 8.05-8.03 (m, 2H), 7.95 (dd, *J* = 8Hz, 1.5Hz, 2H), 7.62-7.59 (m, 3H), 7.41-7.38 (m, 2H), 7.0-6.56 (m, 3H), 4.96 (dd, *J* = 8.5Hz, 3Hz, 1H), 4.34-4.30 (m, 1H), 4.20-4.18 (m, 1H), 3.90-3.88 (m, 1H), 3.05 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 195.82, 147.32, 141.83, 131.92, 130.74, 130.02, 129.21, 128.69, 127.63, 127.14, 126.26, 124.74, 122.53, 65.52, 38.53, 44.65. **IR (KBr, cm^{-1})**: 3054, 2929, 2851, 1660, 1599, 1302, 1146, 756. **HRMS (ESIMS)**: Anal. calcd for $C_{22}H_{20}NaO_5S_2$ $(M+Na)^+$ 451.0650; found 451.0661.



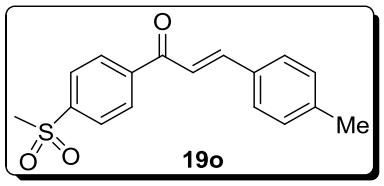
(E)-3-(4-Chlorophenyl)-1-(4-(methylsulfonyl)phenyl)prop-2-en-1-one (19m)

Yield 96%; white solid; mp 199-200 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 8.09 (d, *J* = 8.5Hz, 2H), 8.02 (d, *J* = 8.5Hz, 2H), 7.72 (d, *J* = 15.5Hz, 2H), 7.52 (d, *J* = 8.5Hz, 2H), 7.41-7.34 (m, 3H), 3.03 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 189.13, 145.15, 143.81, 142.30, 137.15, 132.78, 129.81, 129.41, 129.26, 127.83, 121.76, 44.36. **IR (KBr, cm^{-1})**: 3021, 2926, 1726, 1298, 1143. **HRMS (ESIMS)**: Anal. calcd for $C_{16}H_{13}ClO_3NaS$ $(M+Na)^+$ 343.0172; found 343.0152.



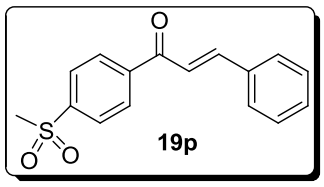
(E)-3-(3-Nitrophenyl)-1-(4-(methylsulfonyl)phenyl)prop-2-en-1-one (19n):

Yield 95%; white solid; mp 243-244 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 8.55 (s, 1H), 8.31-8.29 (m, 1H), 8.21-8.2 (dd, *J* = 6.5, 2Hz, 2H), 8.13 (dd, *J* = 7, 2Hz, 2H), 7.95-7.9 (m, 2H), 7.67-7.6 (m, 2H), 3.12 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 189.65, 149.58, 146.83, 139.46, 138.53, 136.84, 134.93, 134.23, 132.02, 129.60, 122.84, 121.04, 44.75. **IR (KBr, cm^{-1})**: 3011, 2985, 1698, 1534, 1443, 1268. **HRMS (ESIMS)**: Anal. calcd for $C_{16}H_{14}NO_5S$ $(M+H)^+$ 332.0593; found 332.0600.



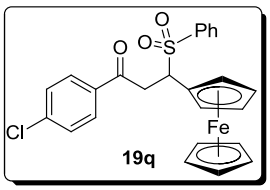
(E)-3-(4-Methylphenyl)-1-(4-(methylsulfonyl)phenyl)prop-2-en-1-one (19o):

Yield 96%; white solid; mp 160-162 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 8.07 (d, *J* = 3.5Hz, 2H), 8.0 (d, *J* = 3.5Hz, 2H),. 7.74 (d, *J* = 15.5Hz, 1H), 7.48 (d, *J* = 5Hz, 2H), 7.36 (d, *J* = 16Hz, 1H), 7.21-7.16 (m, 2H), 3.13 (s, 3H), 2.21 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 189.50, 146.81, 143.51, 142.66, 141.88, 131.55, 129.81, 129.19, 128.70, 127.70, 120.36, 44.33, 21.56. **IR (KBr, cm^{-1})**: 3017, 2921, 1660, 1597. **HRMS (ESIMS)**: Anal. calcd for $C_{17}H_{17}O_3S$ $(M+H)^+$ 301.0898; found 301.0904.

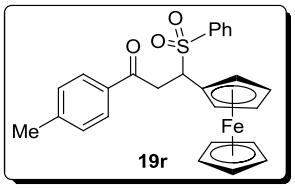


(E)-3-Phenyl-1-(4-(methylsulfonyl)phenyl)prop-2-en-1-one (19p):

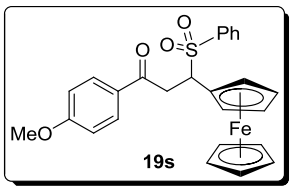
Yield 98 %; white solid; mp 168-170 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 8.08 (d, *J* = 8Hz, 2H), 7.80 (d, *J* = 8Hz, 2H), 7.75 (d, *J* = 16Hz, 1H), 7.41-7.36 (m, 4H), 3.03 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 188.12, 145.76, 143.54, 142.45, 141.62, 134.15, 130.42, 129.49, 128.27, 126.41, 120.36, 45.10. **IR (KBr, cm^{-1})**: 3024, 2921, 1633, 1307, 1149. **HRMS (ESIMS)**: Anal. calcd for $C_{16}H_{14}NaO_3S$ $(M+Na)^+$ 309.0561; found 309.0554.



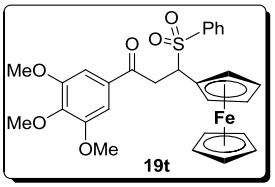
1-(4-Chlorophenyl)-3-ferrocenyl-3-phenylsulfonylpropan-1-one (19q): Yield 92 %; orange red solid; mp 147-148 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 7.81 (d, *J* = 9Hz, 2H), 7.45 (dd, *J* = 9, 2.5Hz, 2H), 7.32-7.30 (m, 2H), 7.25-7.20 (m, 3H), 4.98 (t, *J* = 6.5Hz, 1H), 4.19-4.10 (m, 4H), 4.09 (s, 5H), 3.85-3.84 (m, 1H), 3.58 (dd, 18, 4Hz, 1H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 197.25, 138.14, 135.41, 134.24, 133.84, 131.54, 130.68, 129.38, 128.56, 81.21, 71.12, 70.15, 68.8, 67.9, 67.7, 66.9, 37.81. **IR (KBr, cm^{-1})**: 3021, 2954, 1702, 1463, 1401, 1298, 1108, 1156. **HRMS (ESIMS)**: Anal. calcd for $C_{25}H_{22}ClFeO_3S$ $(M+H)^+$ 493.0328; found 493.0321.



1-(4-Methylphenyl)-3-ferrocenyl-3-phenylsulfonylpropan-1-one (19r): Yield 91 %; orange red solid; mp 152-153 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 7.86 (d, *J* = 3.5Hz, 2H), 7.42-7.40 (m, 2H), 7.30-7.24 (m, 5H), 5.06 (t, *J* = 7.5Hz, 1H), 4.06-3.99 (m, 9H), 3.48-3.45 (m, 2H), 2.3 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 196.53, 145.28, 135.26, 134.21, 133.54, 130.41, 129.51, 128.82, 127.58, 70.15, 68.8, 68.4, 67.9, 67.7, 67.5, 67.0, 36.16, 20.91. **IR (KBr, cm^{-1})**: 3102, 2935, 1670, 1465, 1376 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{26}H_{24}FeNaO_3S$ $(M+Na)^+$ 495.0693; found 495.0690.

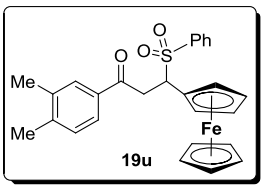


1-(4-Methoxylphenyl)-3-ferrocenyl-3-phenylsulfonylpropan-1-one (19s): Yield 94 %; orange red solid; mp 165-166 ^{0}C; **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 7.92 (dd, *J* = 7, 2Hz, 2H), 7.34-7.31 (m, 2H), 7.22-7.18 (m, 3H), 6.95 (dd, *J* = 7, 2Hz, 2H), 5.06 (t, *J* = 7.5Hz, 1H), 4.15-4.06 (m, 9H), 3.99 (s, 3H), 3.48-3.45 (m, 2H).**^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 199.54, 163.64, 134.31, 131.94, 130.51, 129.14, 128.37, 126.66, 114.17, 89.0, 67.78, 66.8, 66.6, 65.9, 63.51, 37.41. **IR (KBr, cm^{-1})**: 3060, 2919, 2843, 1679, 1489, 1404, 1325, 1142, 1010, 865 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{26}H_{25}FeO_4S$ $(M+H)^+$ 489.0823; found 489.0812.

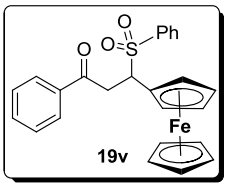


1-(3,4,5-Trimethoxylphenyl)-3-ferrocenyl-3-phenylsulfonylpropan-1-one (19t): Yield 92 %; orange red solid; mp 182-183 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 7.26-7.15 (m, 5H), 6.92 (s, 2H), 4.95 (t, *J* = 6.5Hz, 1H), 4.06 (s, 5H), 4.02-4.01 (m, 4H), 3.86 (s, 3H), 3.84 (s, 6H), 3.46 (d, *J* = 6.5Hz, 2H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 196.91, 154.21, 143.54, 134.35, 132.32, 130.8, 129.1, 127.5, 105.8, 69.84, 68.9, 68.02, 67.73, 67.1, 66.47, 61.0, 56.4, 56.12, 37.64. **IR (KBr, cm^{-1})**: 3096, 2927, 2843, 1659, 1489,

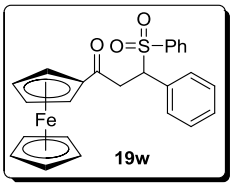
1404,1325,1131,1010, 865 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{28}H_{29}FeO_6S$ $(M+H)^+$ 549.1034; found 549.1039.



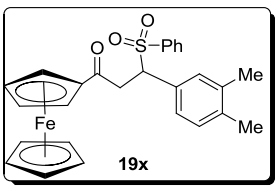
1-(3,4-Dimethylphenyl)-3-ferrocenyl-3-phenylsulfonylpropan-1-one (19u): Yield 94%; orange red solid; mp 152-154 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 7.84-7.80 (m, 2H), 7.59-7.55 (m, 3H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 8 Hz, 1H), 5.03-5.01 (m, 1H), 4.19-4.10 (m, 4H), 4.09 (s, 5H), 3.85-3.84 (m, 1H), 3.56 (dd, *J* = 18, 4Hz, 1H), 2.37 (s, 3H), 2.36 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 194.90, 143.42, 137.27, 136.80, 134.13, 133.55, 130.07, 129.47, 129.44, 128.59, 126.05, 81.19, 71.11, 69.18, 68.85, 68.45, 67.32, 61.65, 37.46, 20.14, 19.88. **IR (KBr, cm^{-1})**: 3021, 2910, 2852, 1671, 1441, 1417, 1311, 1142, 1051, 893 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{27}H_{26}FeNaO_3S$ $(M+Na)^+$ 509.0850; found 509.0862.



1-Phenyl-3-ferrocenyl-3-(phenylsulfonyl)propan-1-one (19v): Yield 94%; orange red solid; mp 133-135 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 7.52-7.50 (m, 2H), 7.32 (t, *J* = 8Hz, 2H), 7.22-7.16 (m, 6H), 4.86 (m, 1H), 4.72-4.70 (m, 2H), 4.45-4.43 (m, 1H), 4.15 (s, 1H), 3.91 (s, 5H), 3.73-3.59 (m, 2H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 195.54, 144.43, 135.67, 131.73, 130.24, 129.9, 127.64, 127.35, 126.05, 90.05, 68.92, 67.95, 67.46, 67.12, 66.43, 61.3, 37.86. **IR (KBr, cm^{-1})**: 3096, 2927, 2843, 1659, 1489, 1404,1325,1131,1010, 865 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{25}H_{23}FeO_3S$ $(M+H)^+$ 459.0717; found 459.0699.



1-Ferrocenyl-3-phenyl-3-(phenylsulfonyl)propan-1-one (19w): Yield 95 %; orange red solid; mp 143-144 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 7.43-7.40 (m, 2H), 7.34 (t, *J* = 8Hz, 2H), 7.21-7.16 (m, 6H), 4.85 (m, 1H), 4.75-4.72 (m, 2H), 4.46-4.44 (m, 1H), 4.15 (s, 1H), 3.94 (s, 5H), 3.66-3.60 (m, 2H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 200.69, 141.67, 135.64, 133.15, 130.41, 129.45, 128.61, 127.64, 127.35, 78.87, 78.01, 77.4, 76.98, 73.44, 72.38, 69.76, 69.42, 69.31, 60.59, 38.83. **IR (KBr, cm^{-1})**: 3096, 2927, 2843, 1659, 1489, 1404,1325,1131,1010, 865 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{25}H_{23}FeO_3S$ $(M+H)^+$ 459.0717; found 459.0725.



1-Ferrocenyl-3-(3,4dimethylphenyl)-3-(phenylsulfonyl)propan-1-one (19x)

Yield 93%; orange red solid; mp 170-172 ^{0}C. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ (ppm) 7.62 (d, *J* = 8Hz, 2H), 7.56 (t, *J* = 7.5Hz, 1H), 7.41 (t, *J* = 8Hz, 2H), 7.03 (s, 1H), 7.0-6.96 (m, 2H), 4.86-4.83 (m, 1H), 4.78-4.76 (m, 2H), 4.51-4.50 (m, 2H), 3.99 (s,

5H), 3.67 (m, 2H), 2.17 (s, 3H), 2.16 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz)**: δ (ppm) 198.73, 137.42, 137.32, 136.66, 133.46, 130.88, 129.65, 128.93, 128.60, 127.27, 78.13, 72.50, 69.72, 69.35, 69.05, 65.78, 37.97, 19.65, 19.43. **IR (KBr, cm^{-1})**: 3021, 2921, 2852, 1652, 1443, 1400,1361,1131,1038, 881 cm^{-1}. **HRMS (ESIMS)**: Anal. calcd for $C_{27}H_{26}FeNaO_3S$ $(M+Na)^+$ 509.0850; found 509.0858.

5.3.2.7. REFERENCES

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NMR SPECTRA OF SELECTED COMPUNDS

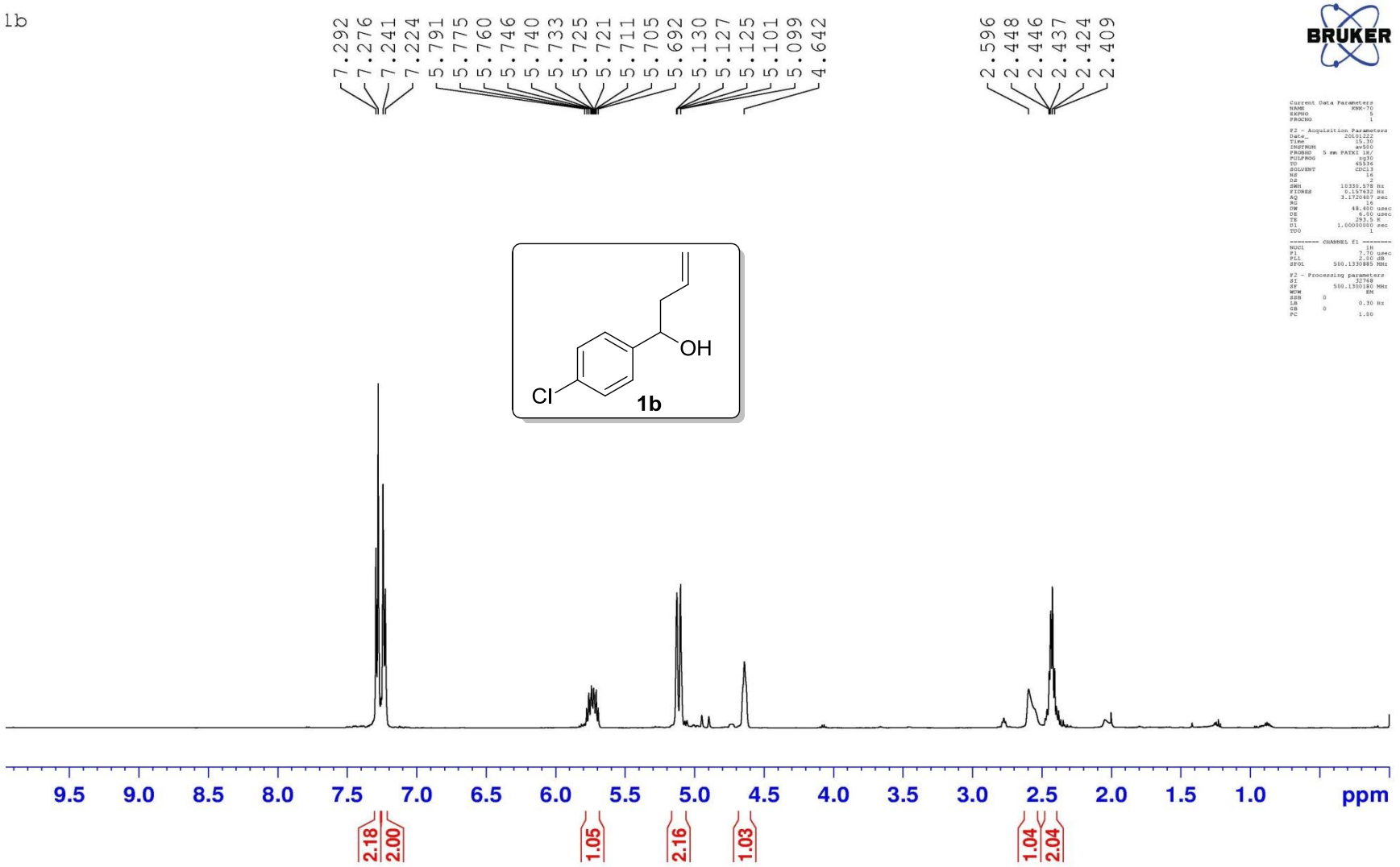


Figure S-1: ^{1}H NMR spectrum of compound 1b

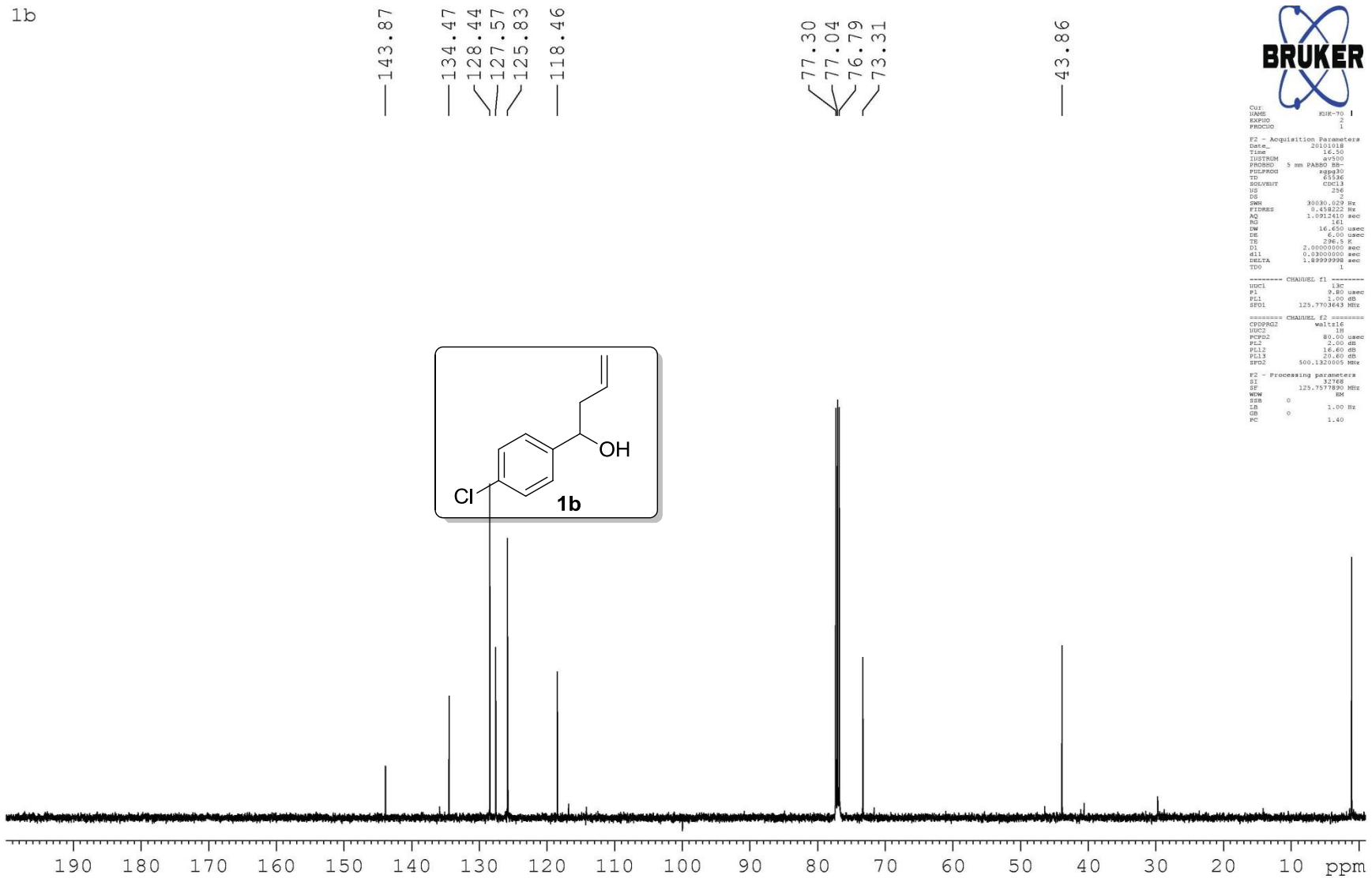


Figure S-2: ^{13}C NMR spectrum of compound 1b

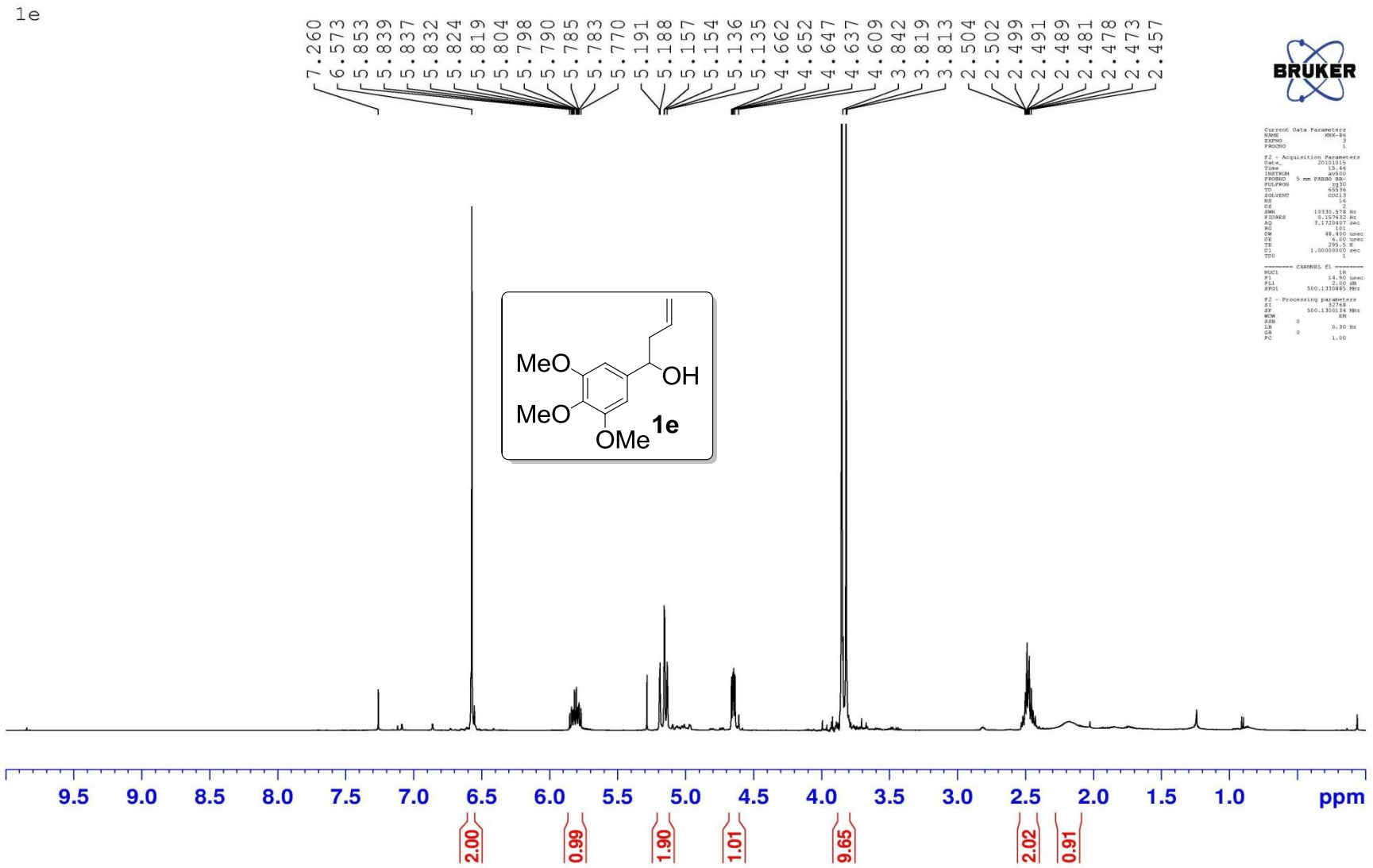


Figure S-3: ^{1}H NMR spectrum of compound 1e

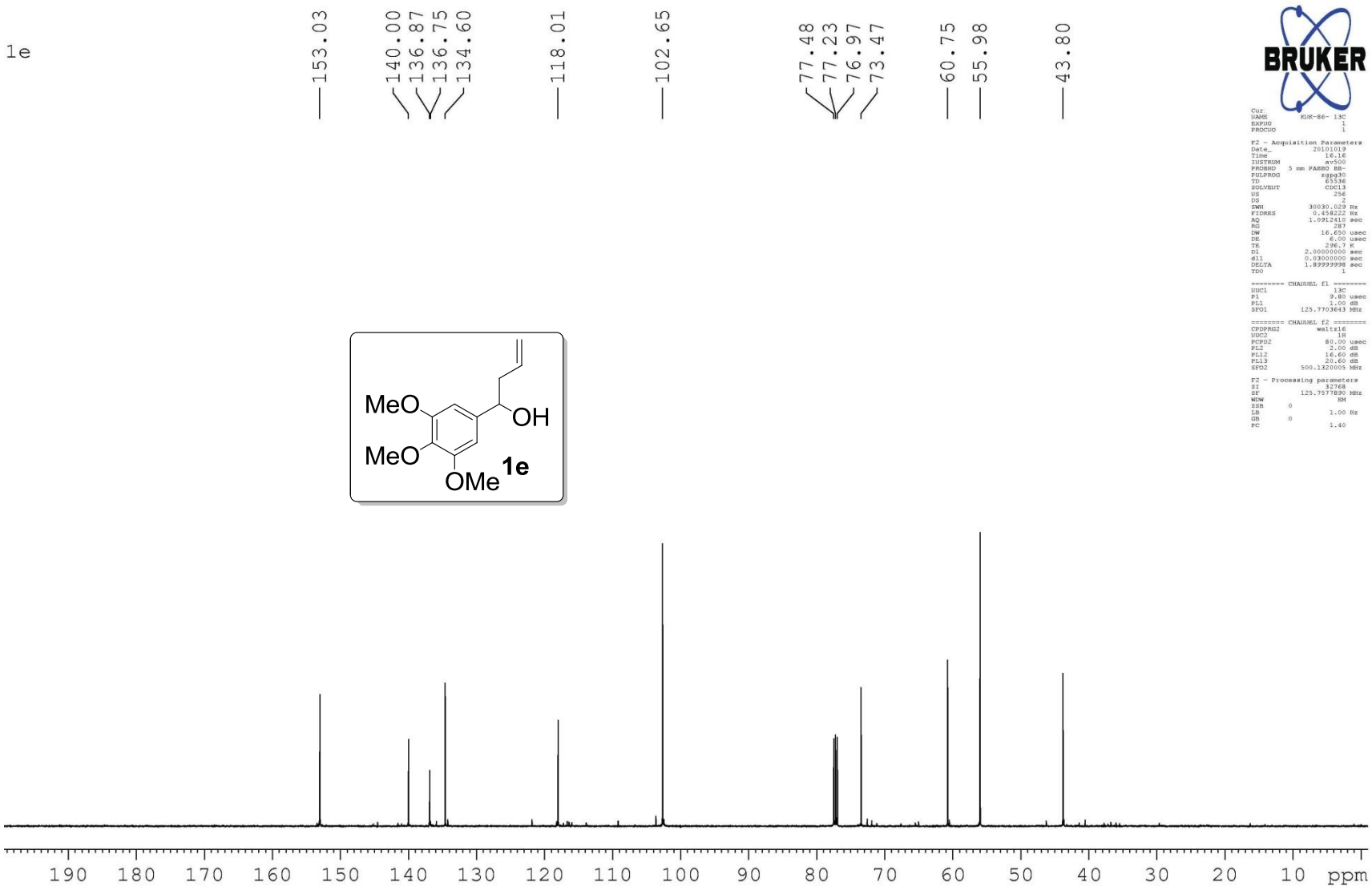


Figure S-4: ^{13}C NMR spectrum of compound 1e

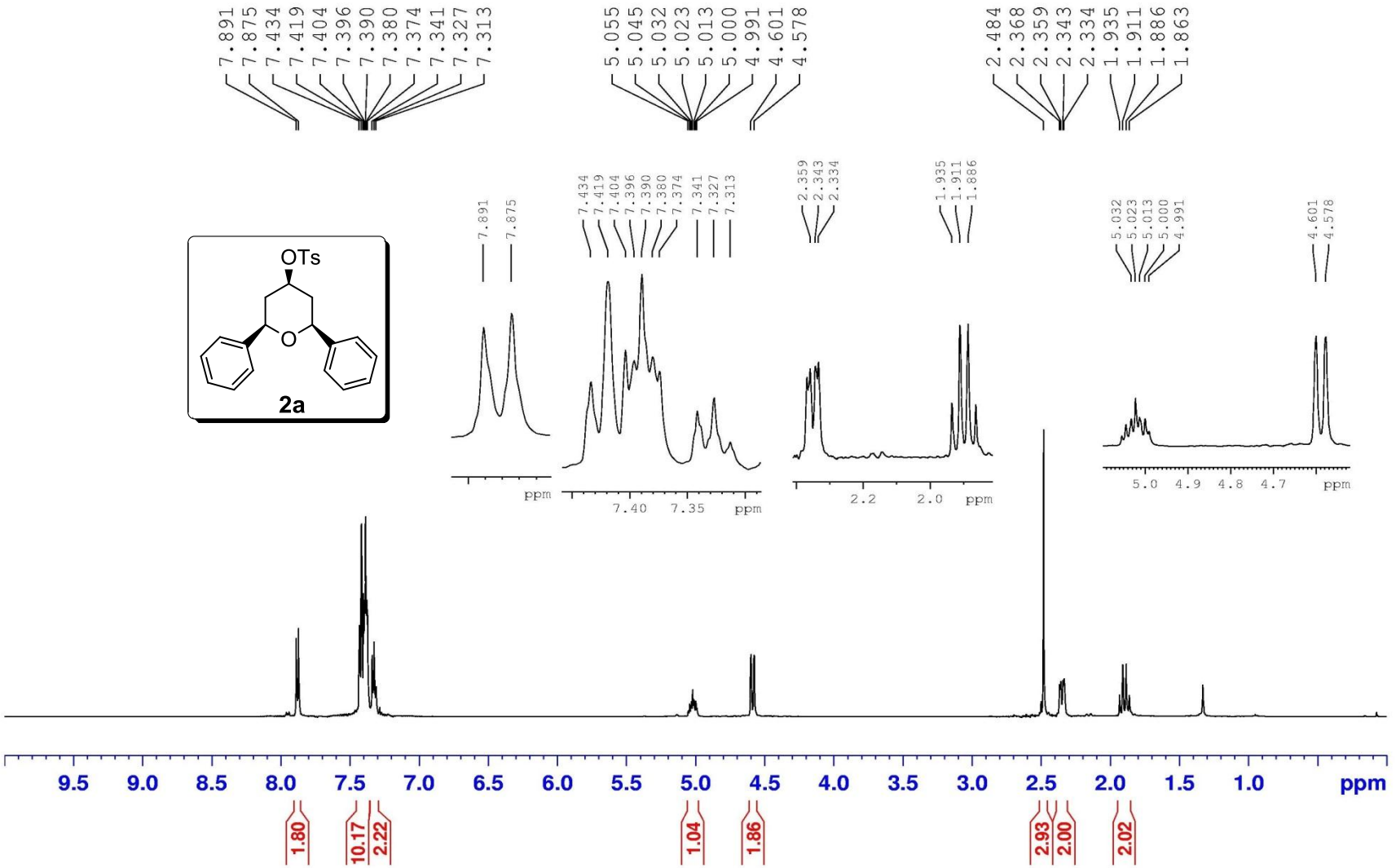


Figure S-5: ^{1}H NMR spectrum of compound 2a

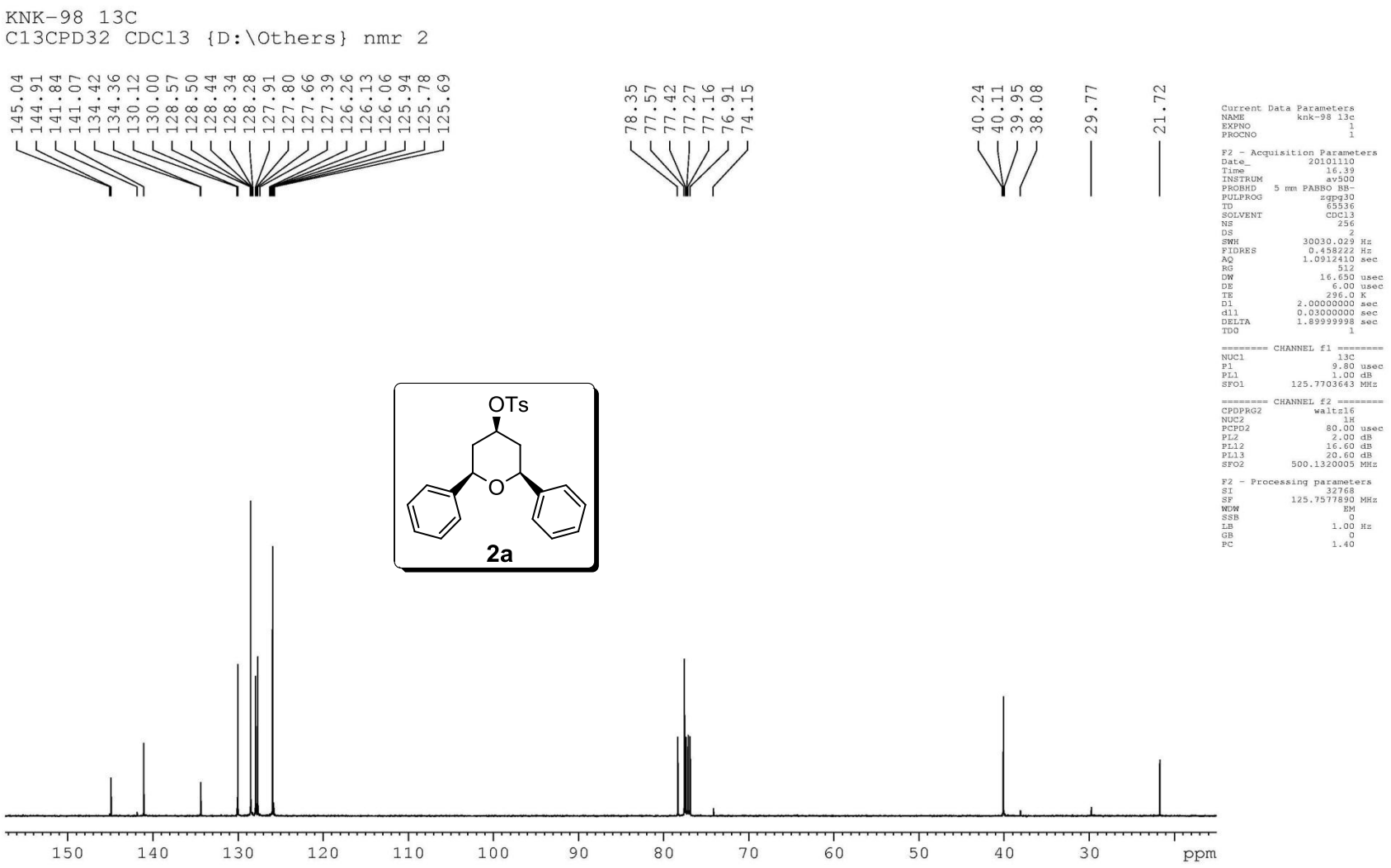


Figure S-6: ^{13}C NMR spectrum of compound 2a

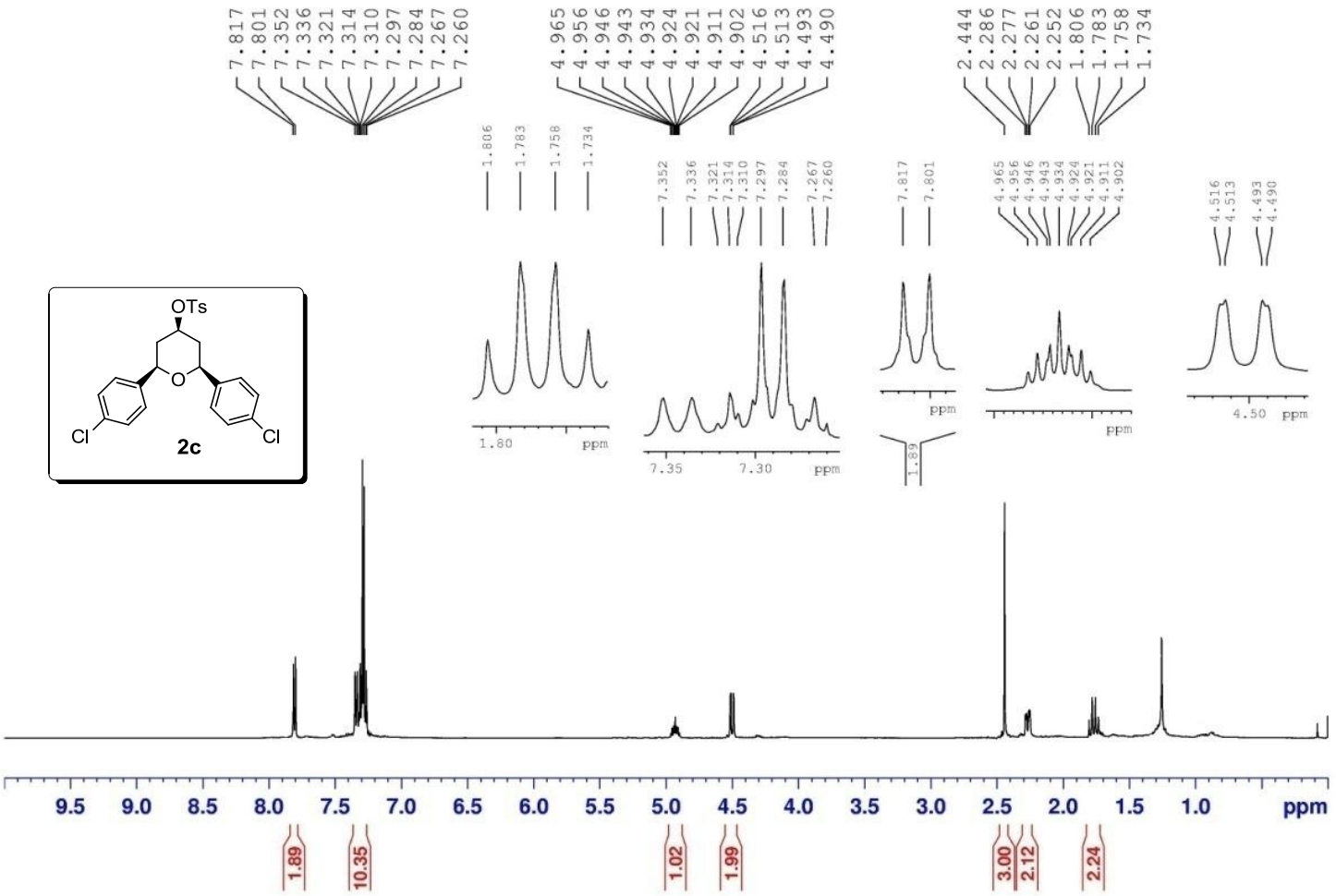


Figure S-7: ^{1}H NMR spectrum of compound 2c

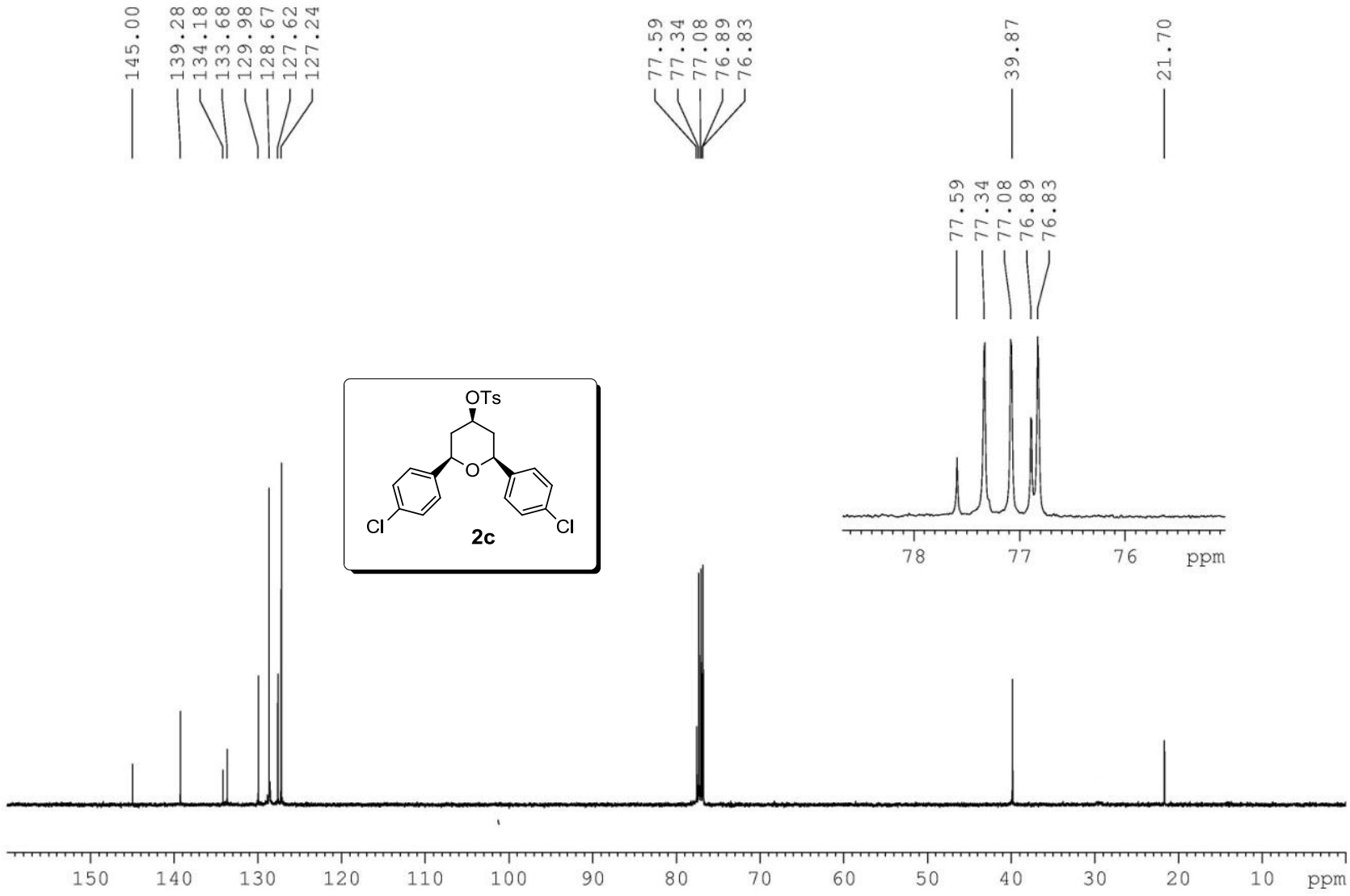


Figure S-8: ^{13}C NMR spectrum of compound 2c

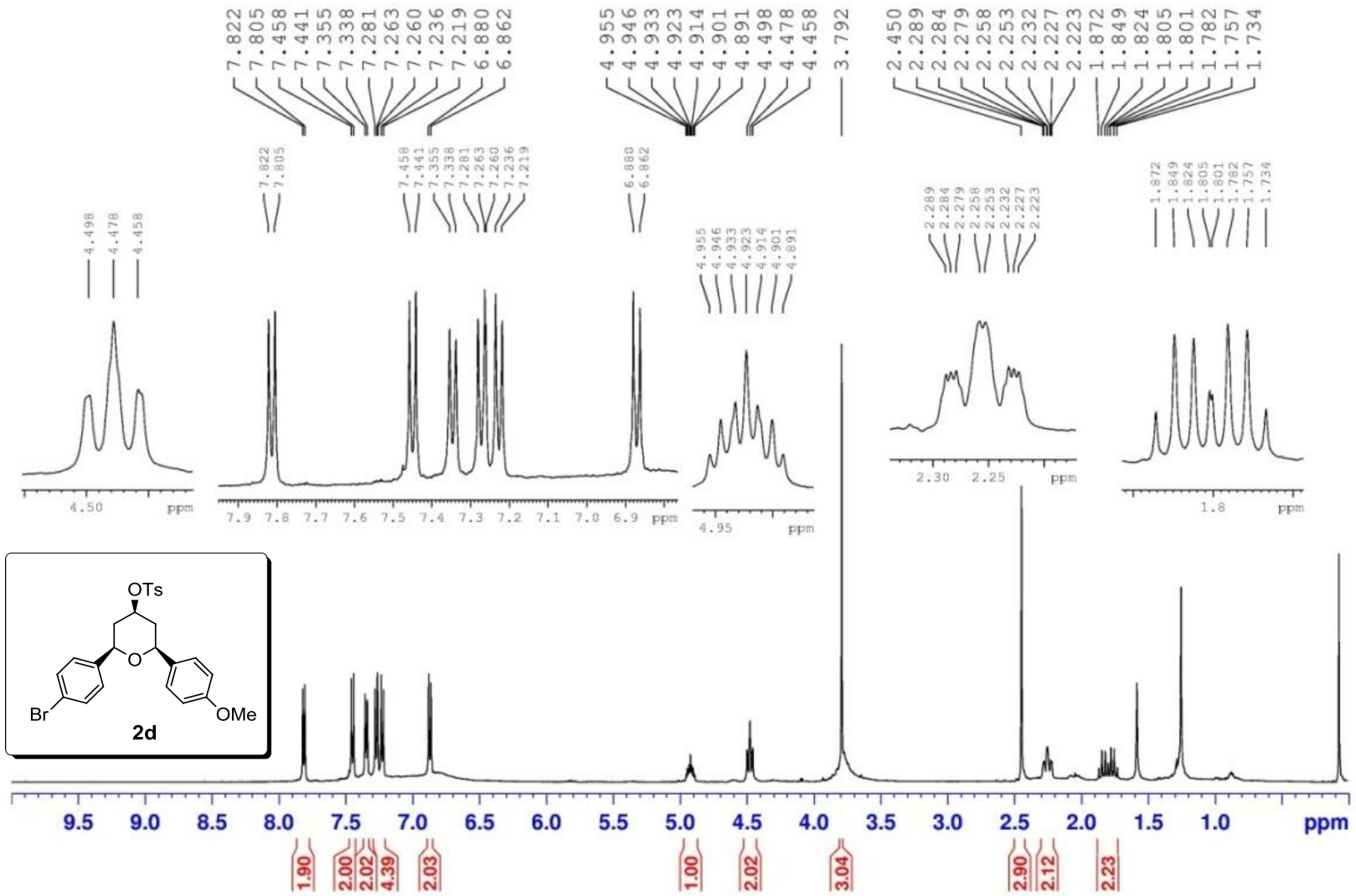


Figure S-9: ^{1}H NMR spectrum of compound 2d

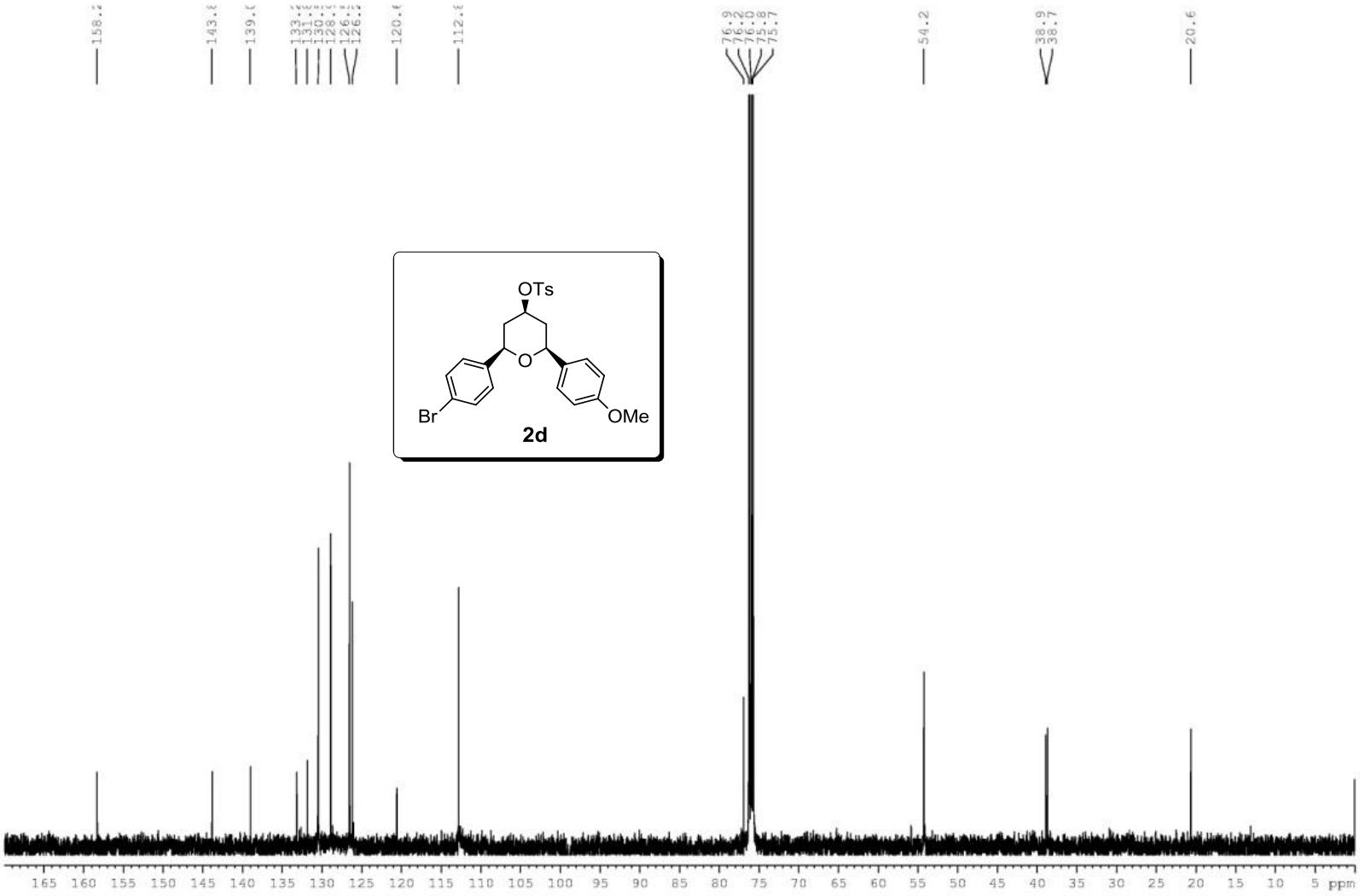


Figure S-10: ^{13}C NMR spectrum of compound 2d

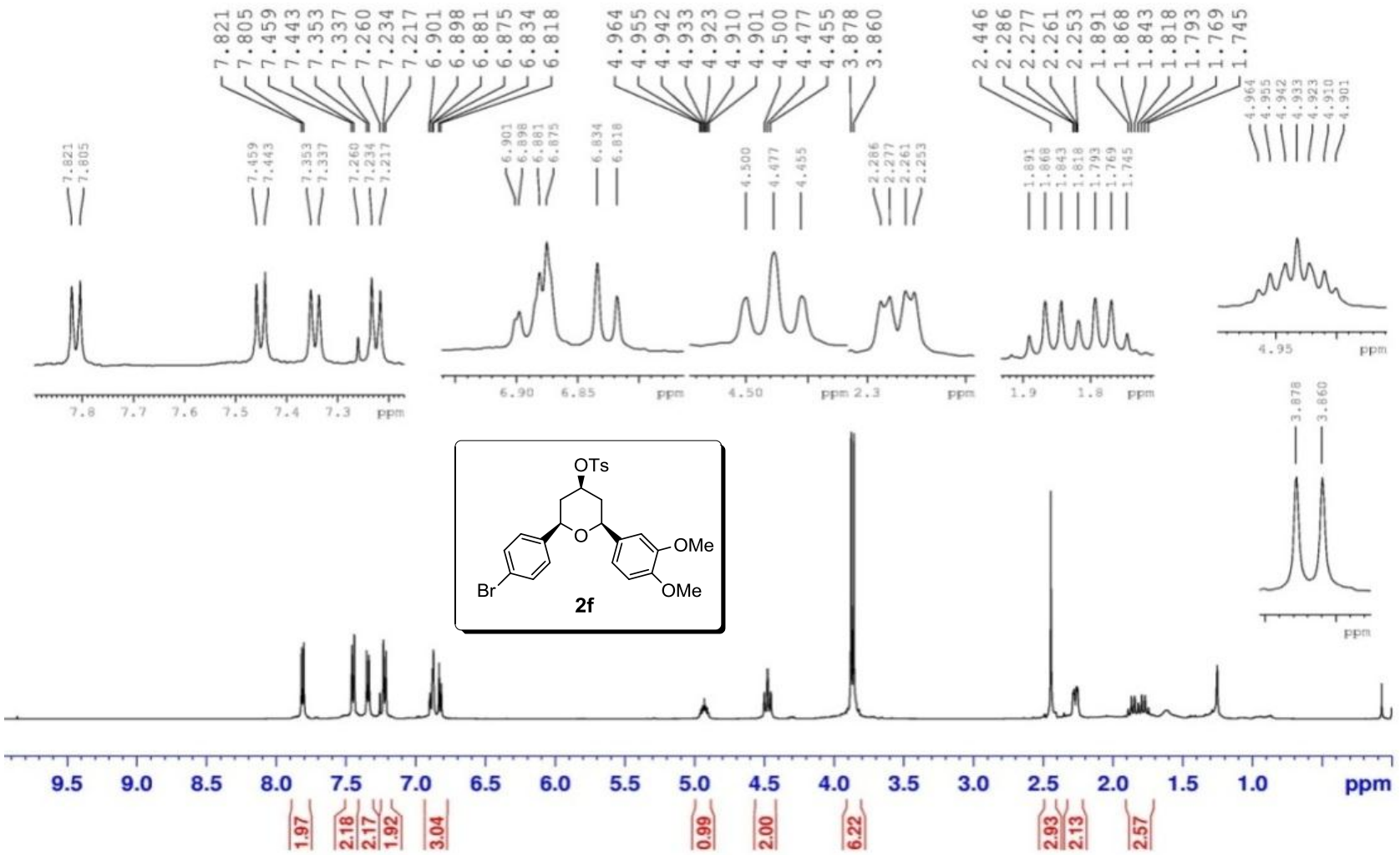


Figure S-11: ^{1}H NMR spectrum of compound 2f

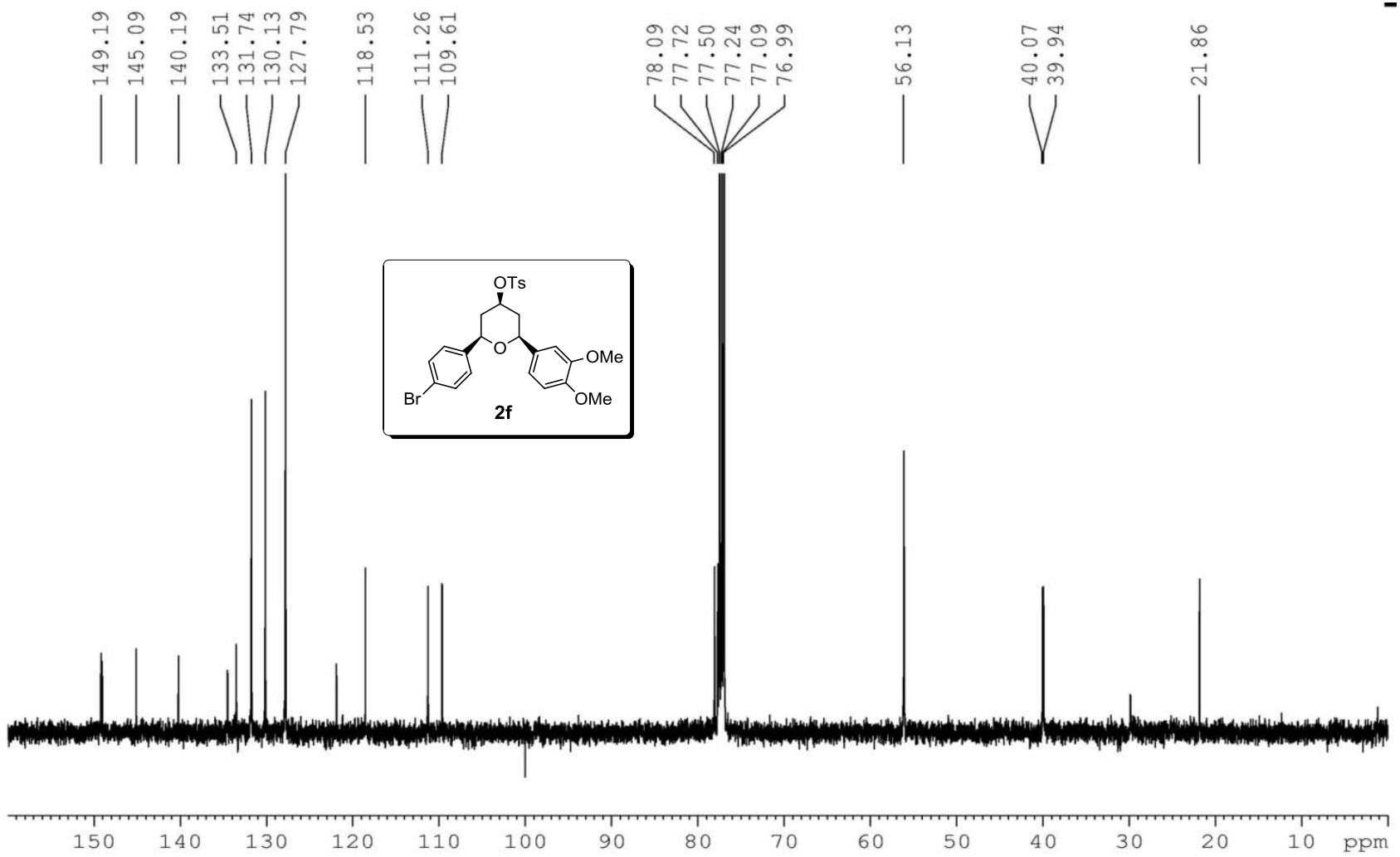


Figure S-12: ^{13}C NMR spectrum of compound 2f

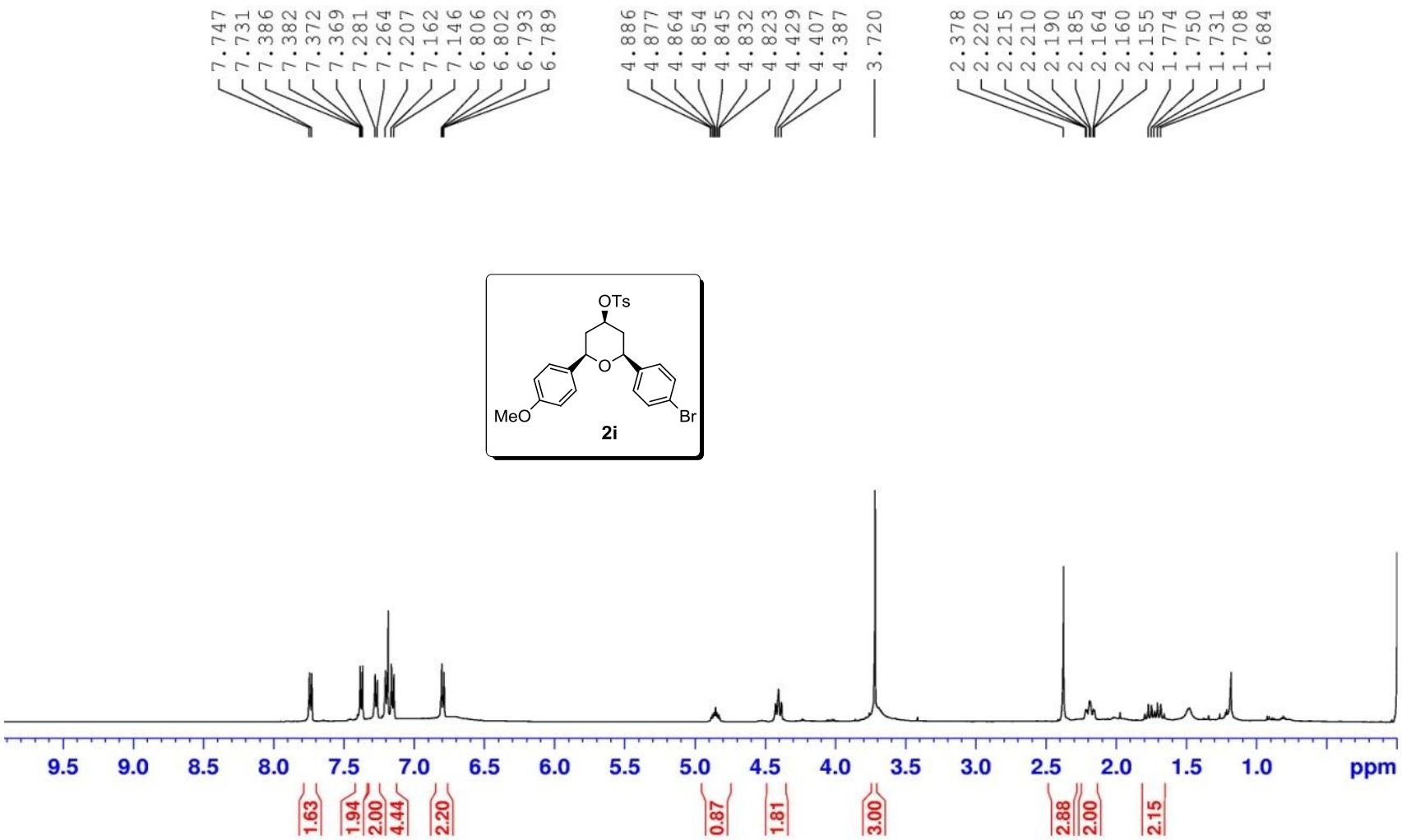


Figure S-13: ^{1}H NMR spectrum of compound 2i

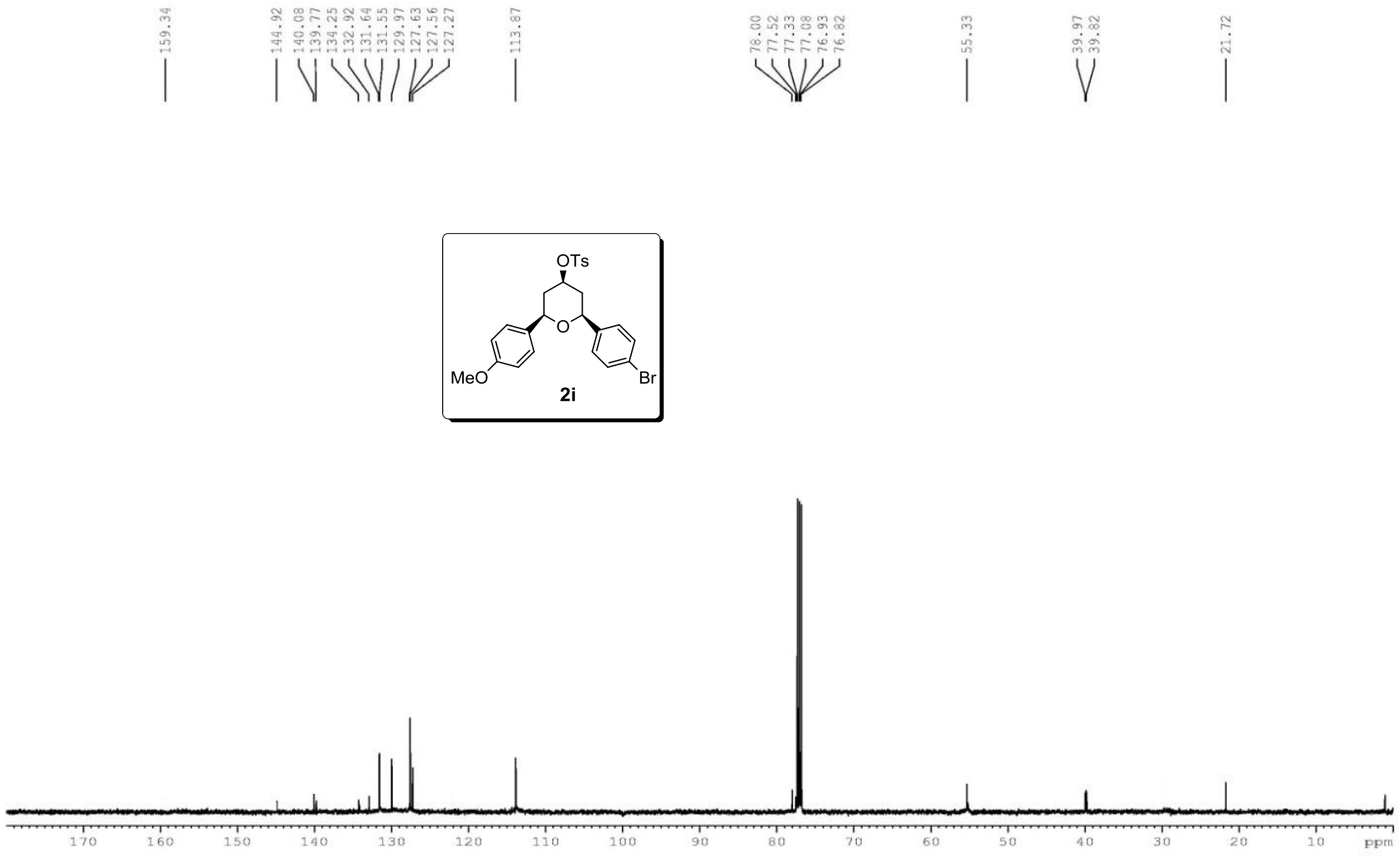


Figure S-14: ^{13}C NMR spectrum of compound 2i

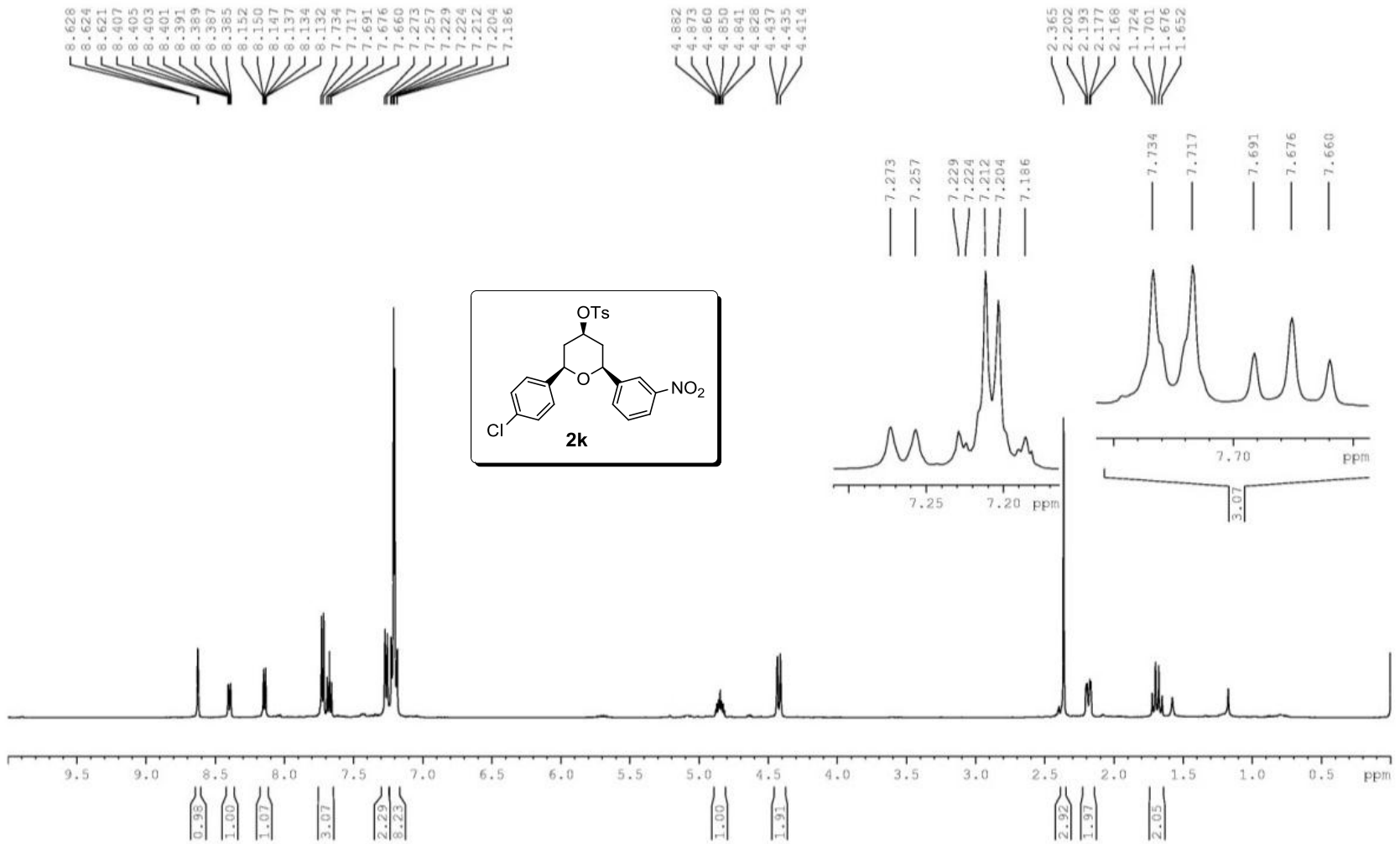


Figure S-15: ^{1}H NMR spectrum of compound 2k

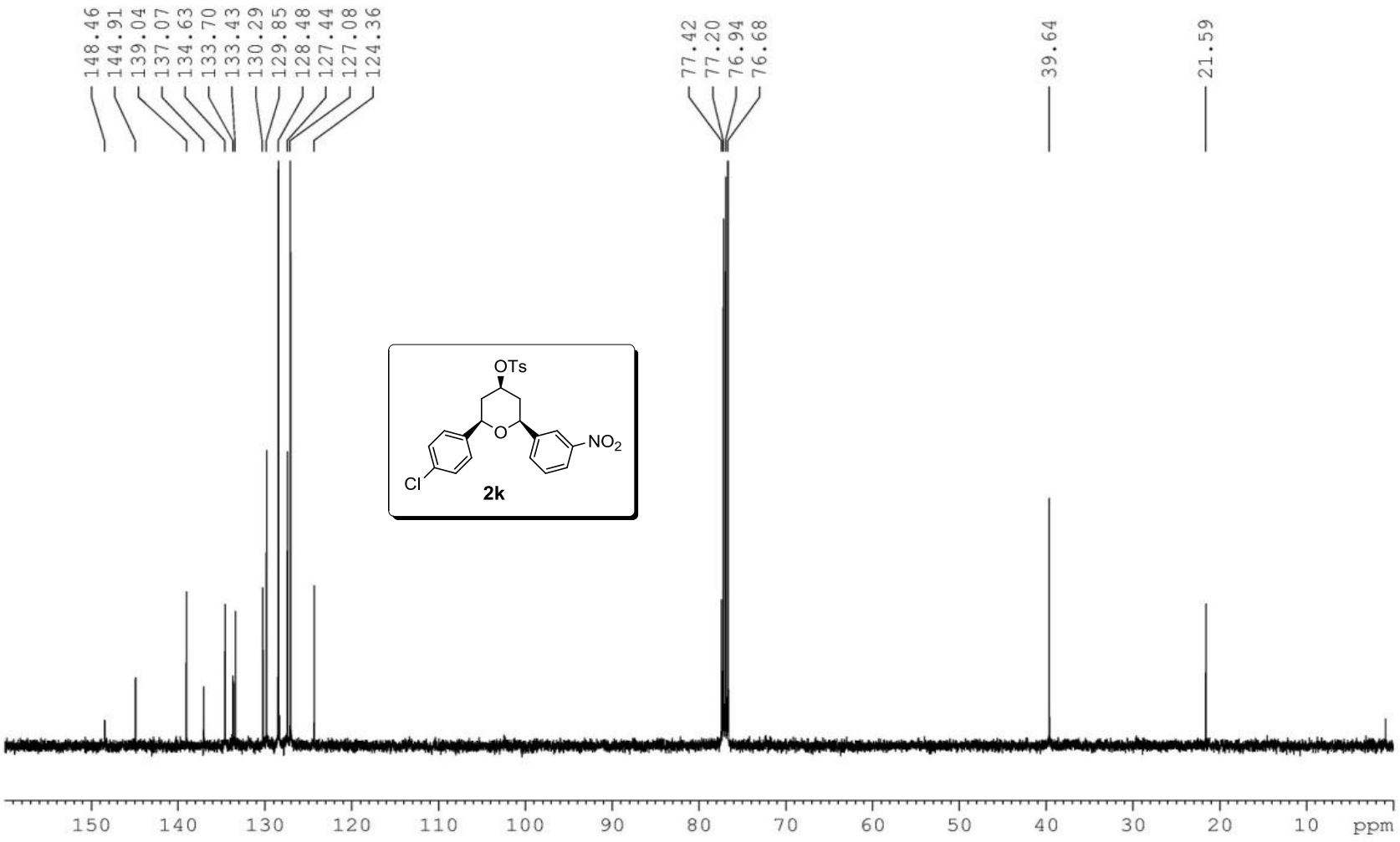


Figure S-16: ^{13}C NMR spectrum of compound 2k

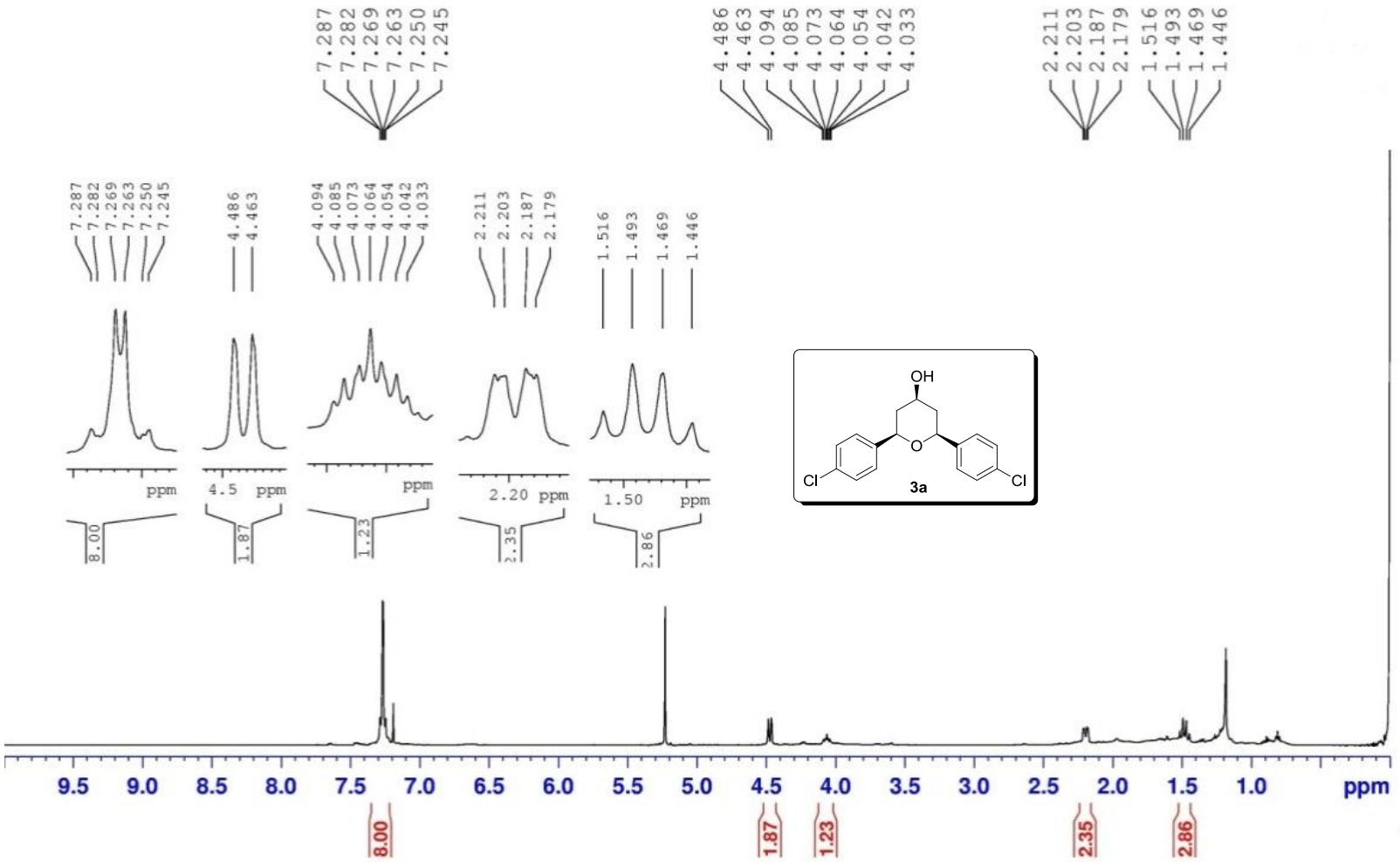


Figure S-17: ^{1}H NMR spectrum of compound 3a

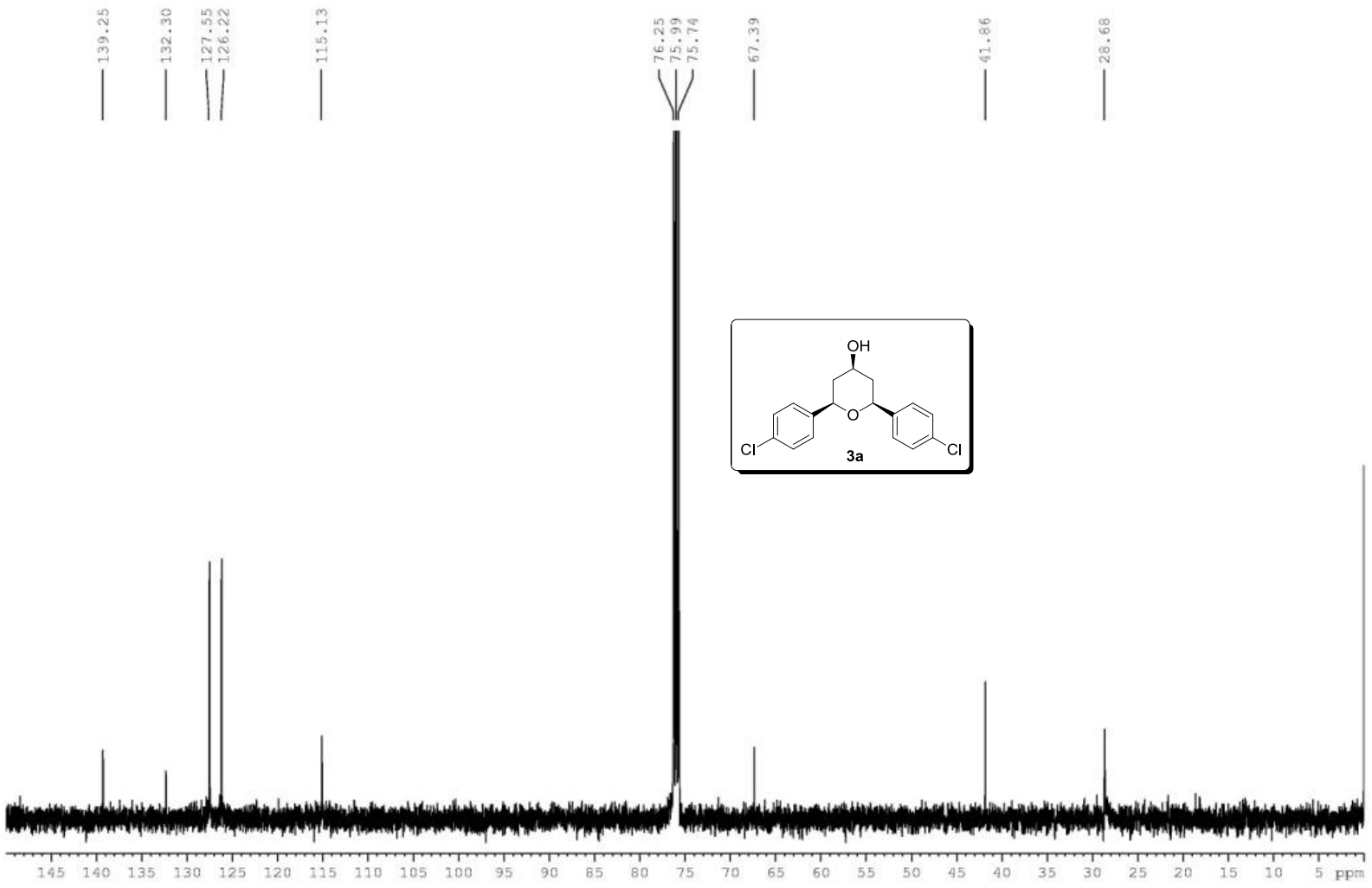


Figure S-18: ^{13}C NMR spectrum of compound 3a

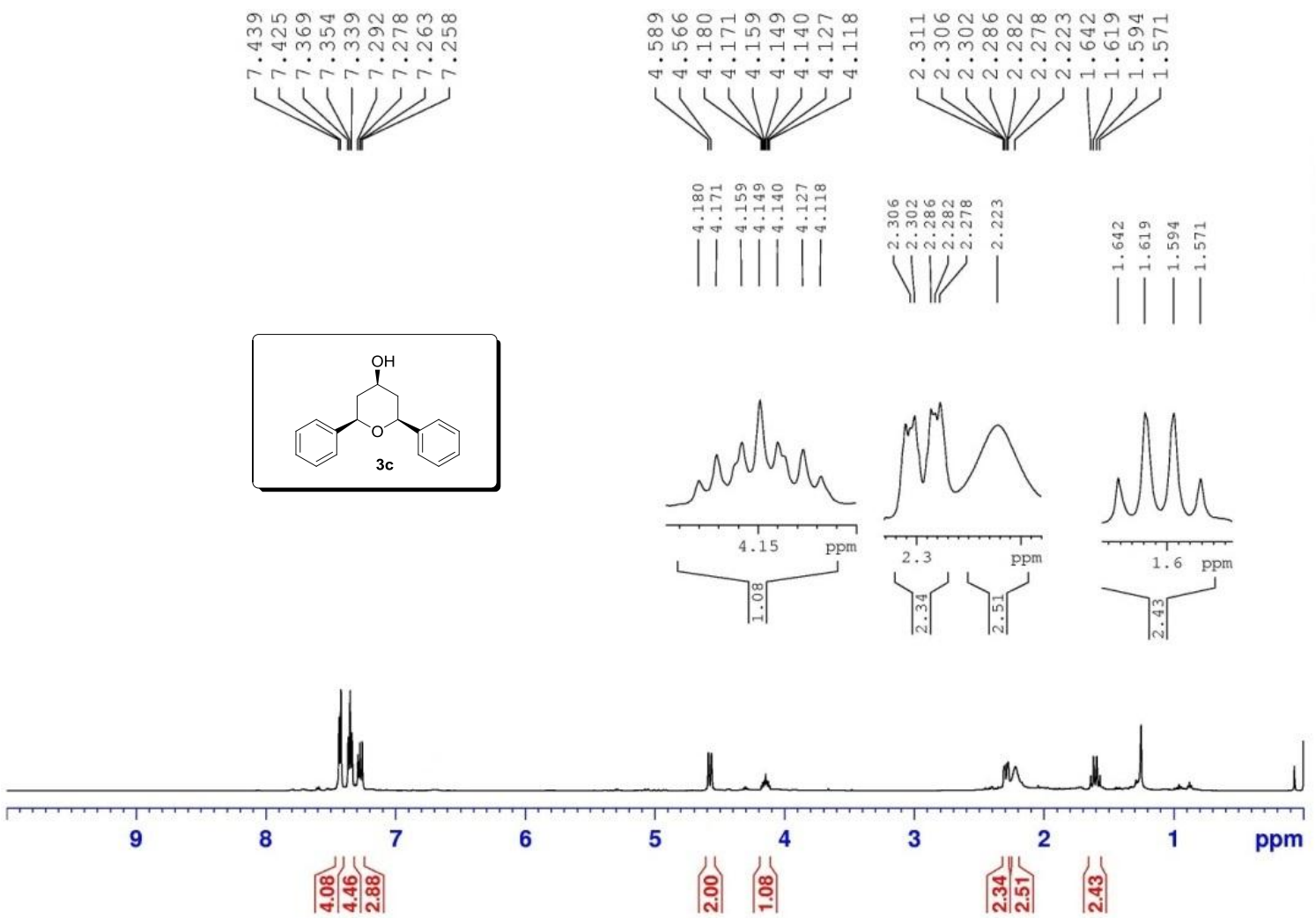


Figure S-19: ^{1}H NMR spectrum of compound 3c

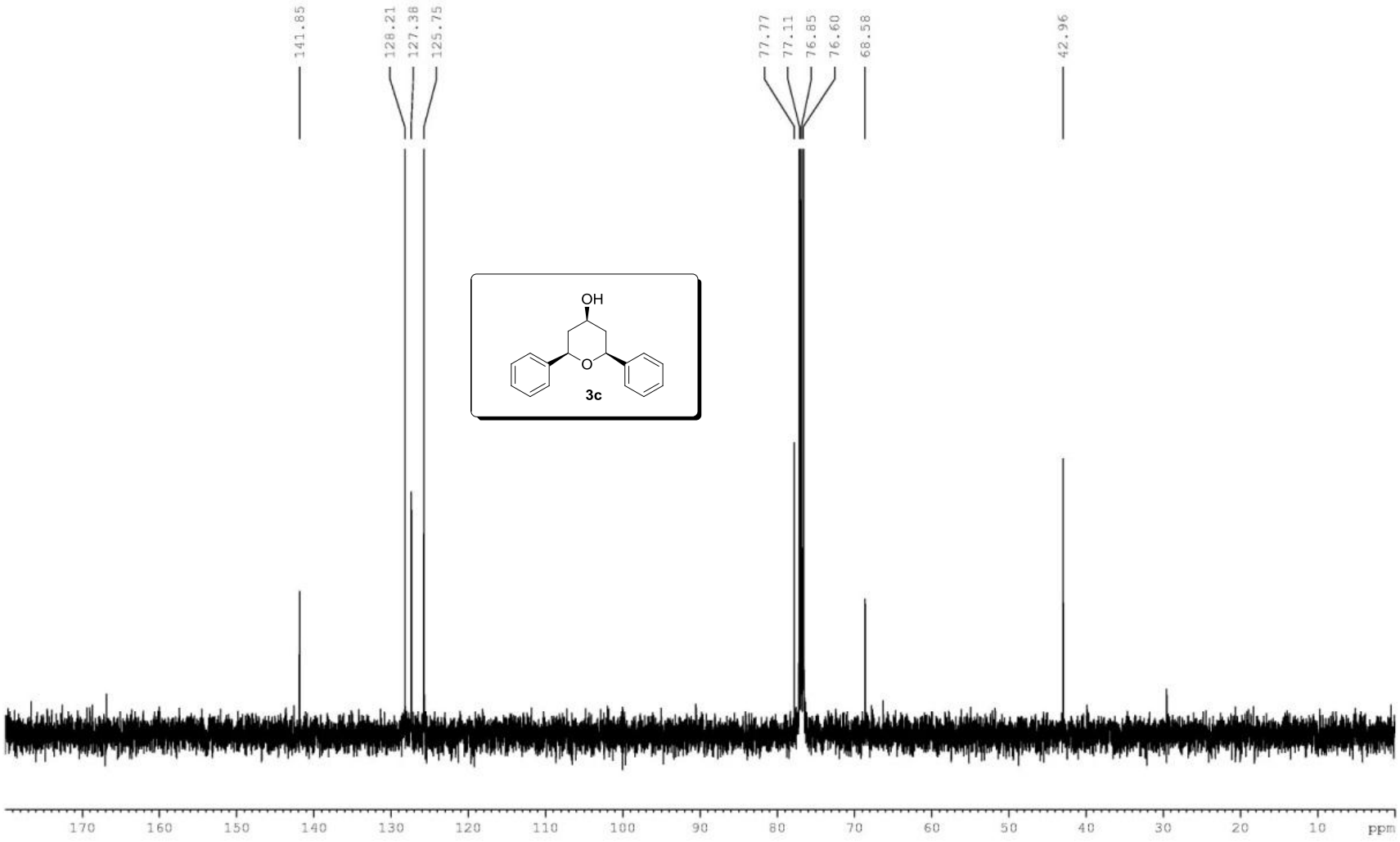


Figure S-20: ^{13}C NMR spectrum of compound 3c

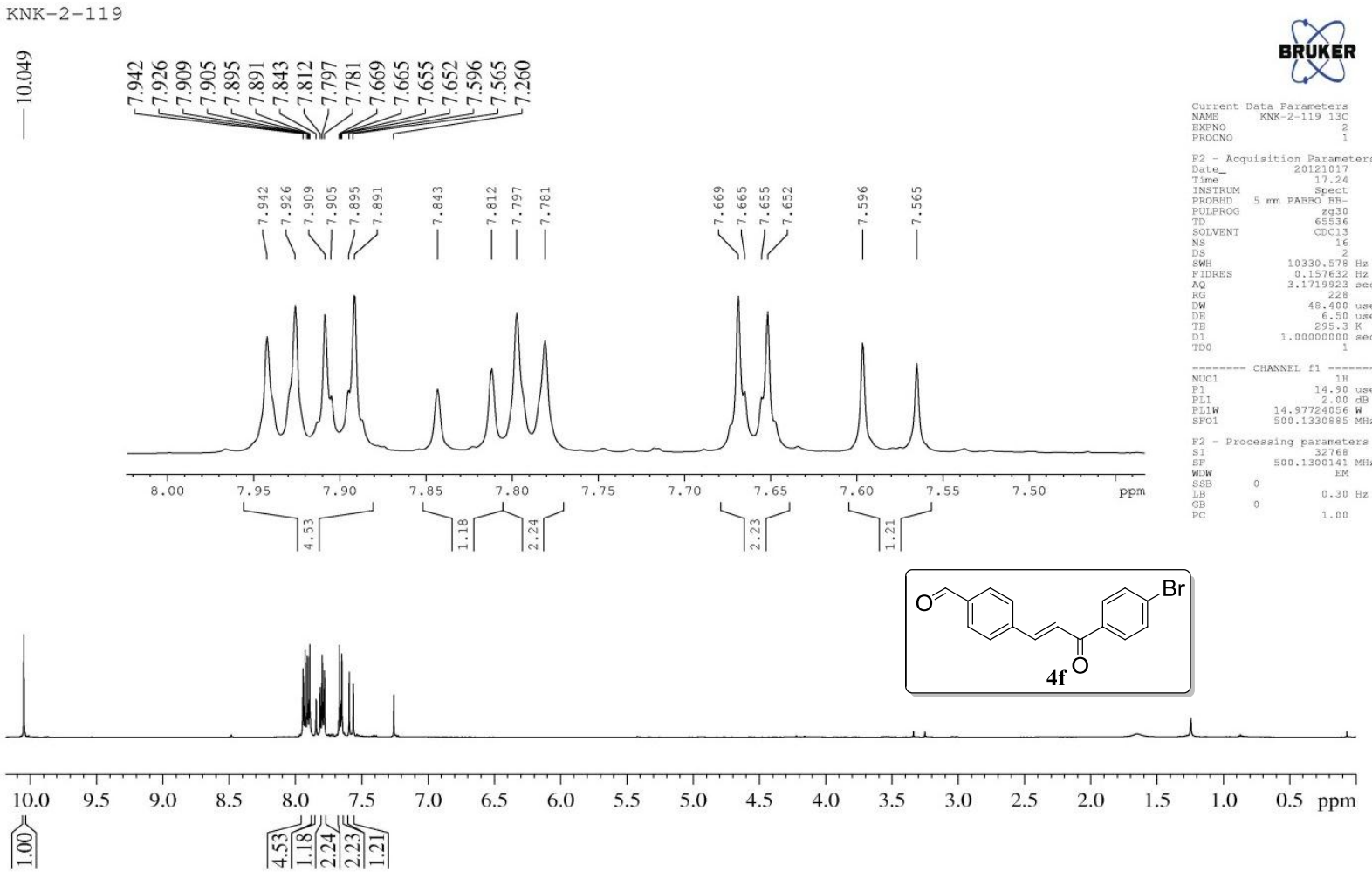


Figure S-21: ^{1}H NMR spectrum of compound 4f

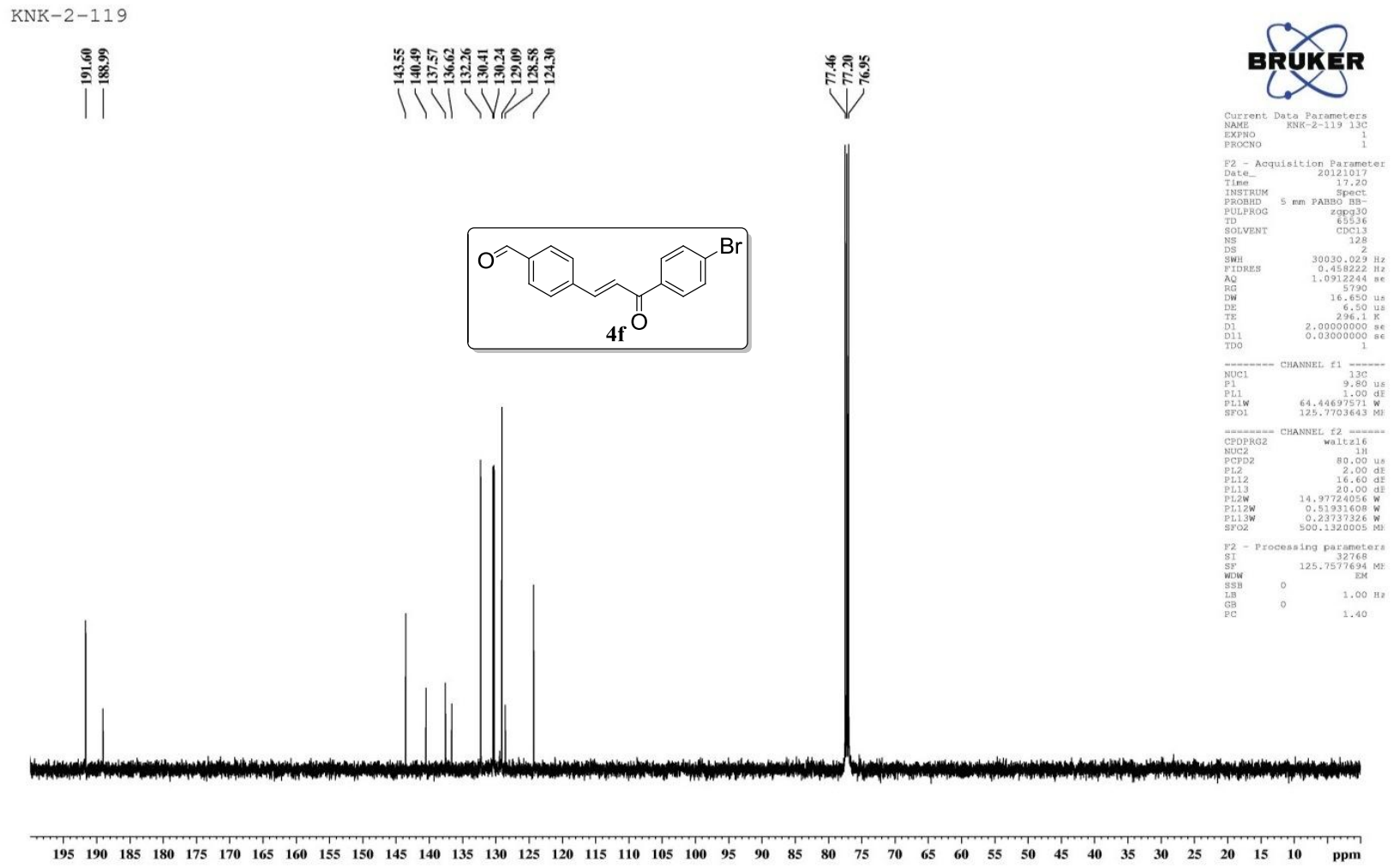


Figure S-22: ^{13}C NMR spectrum of compound 4f

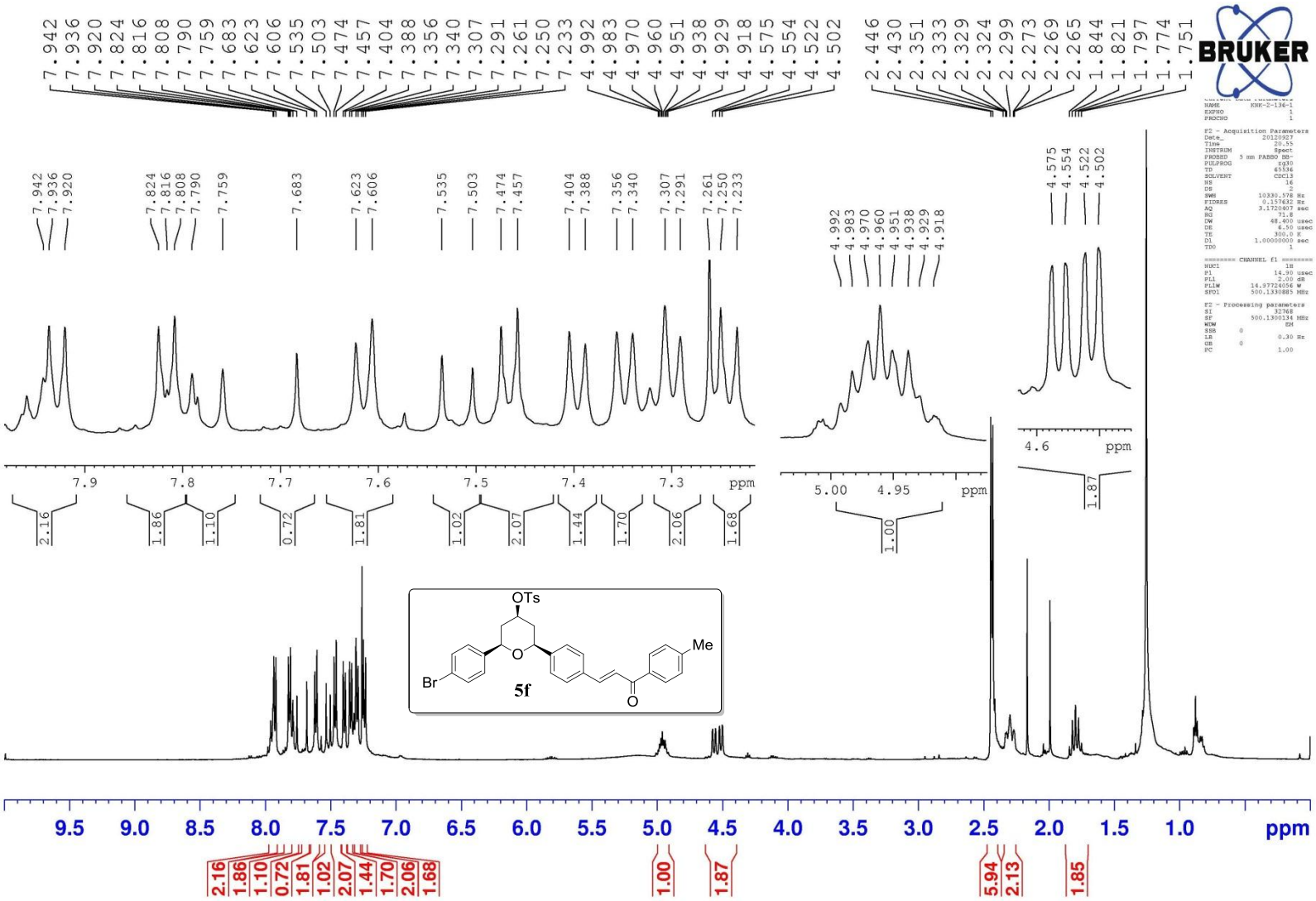


Figure S-23: ^{1}H NMR spectrum of compound 5f

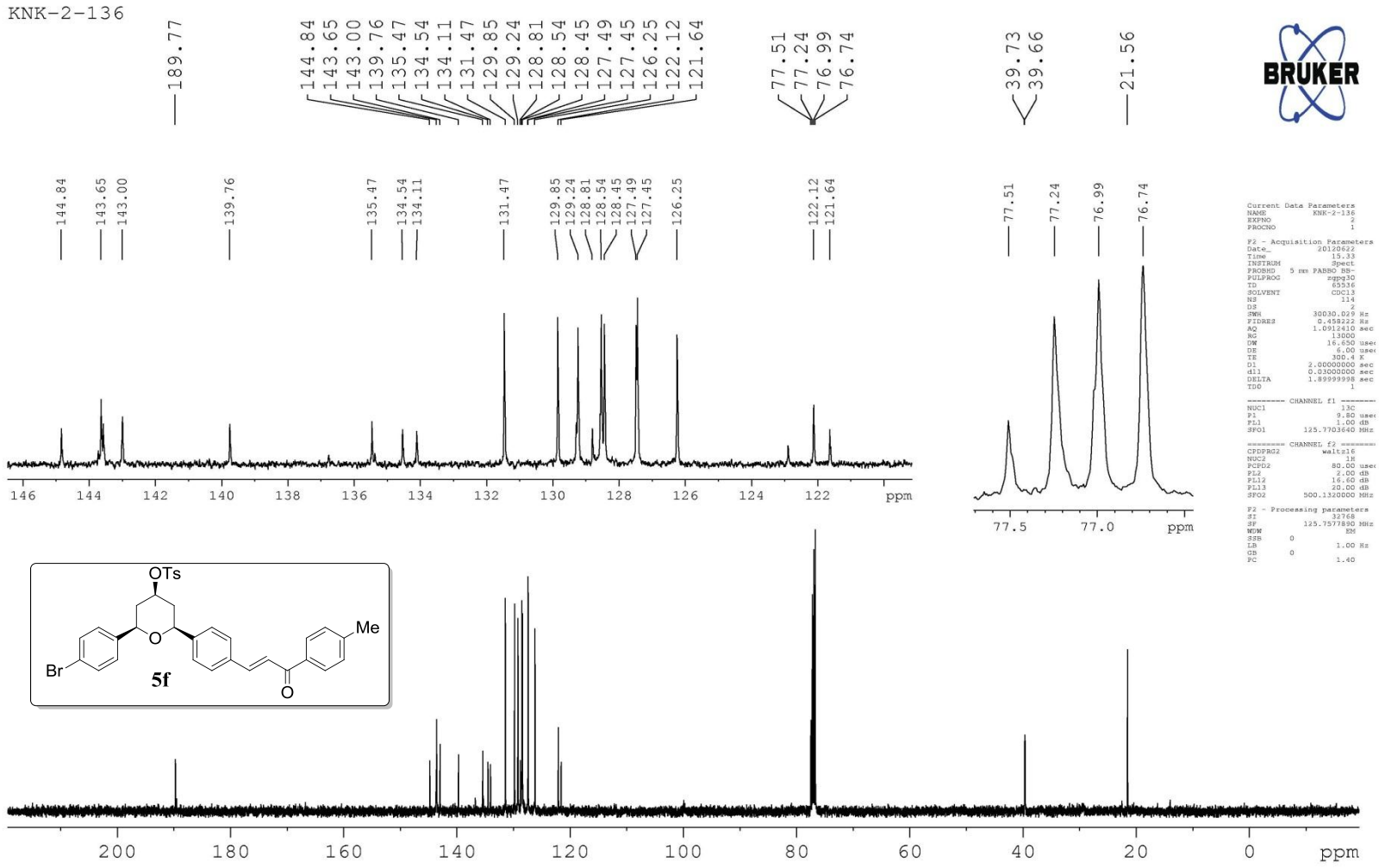


Figure S-24: ^{13}C NMR spectrum of compound 5f

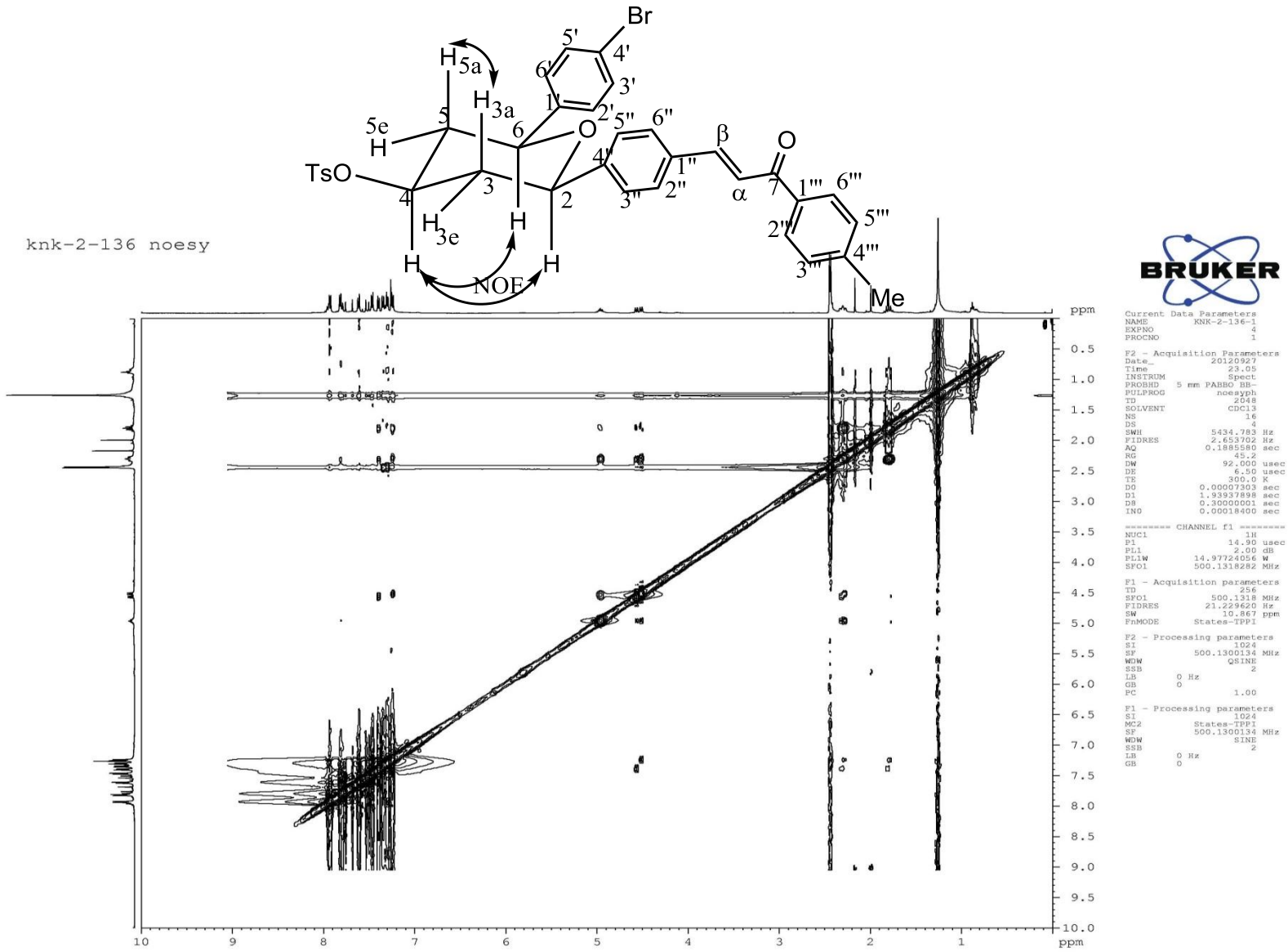


Figure S-25: NOESY spectrum of compound 5f

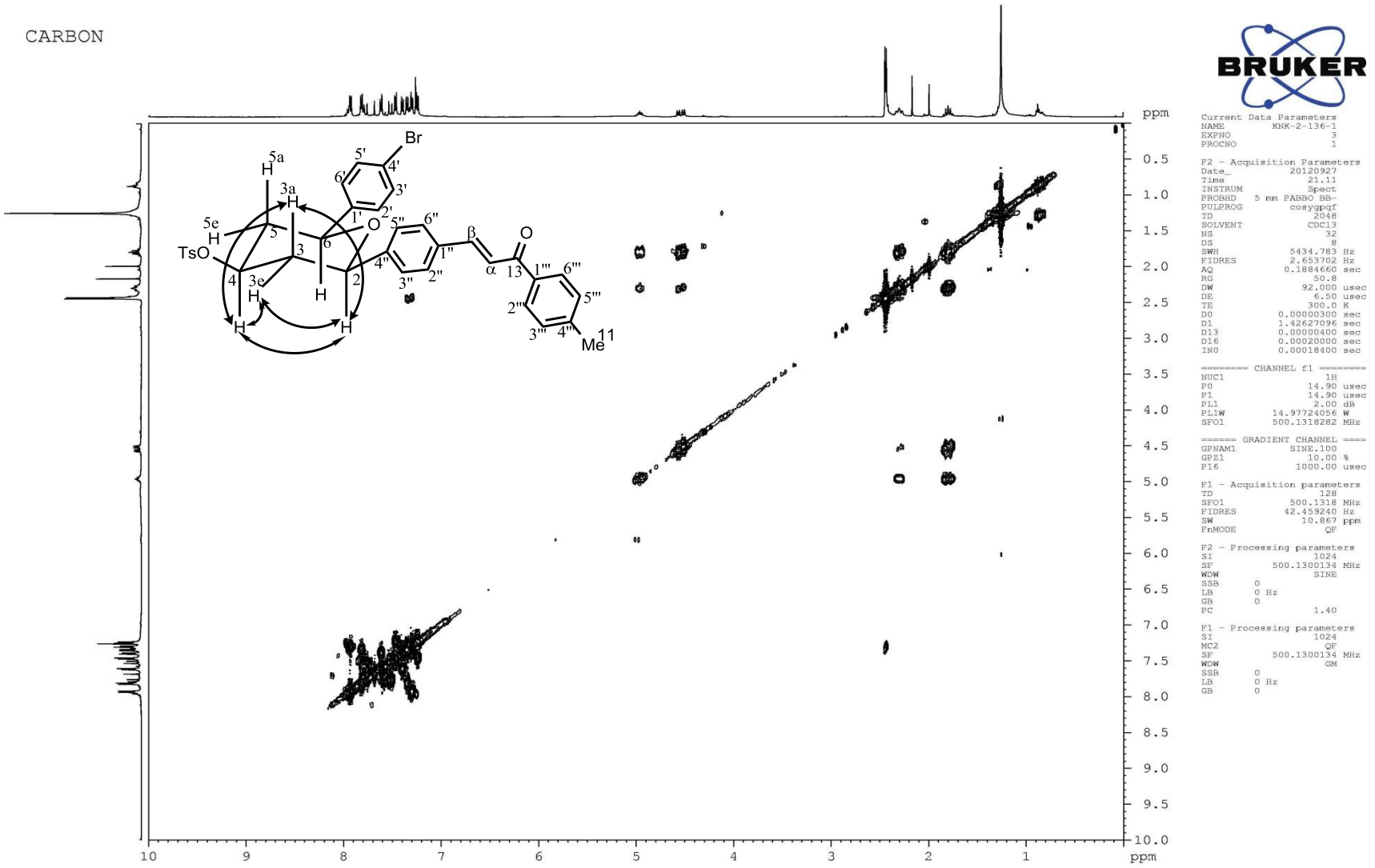


Figure S-26: ^{1}H-^{1}H COSY spectrum of compound 5f

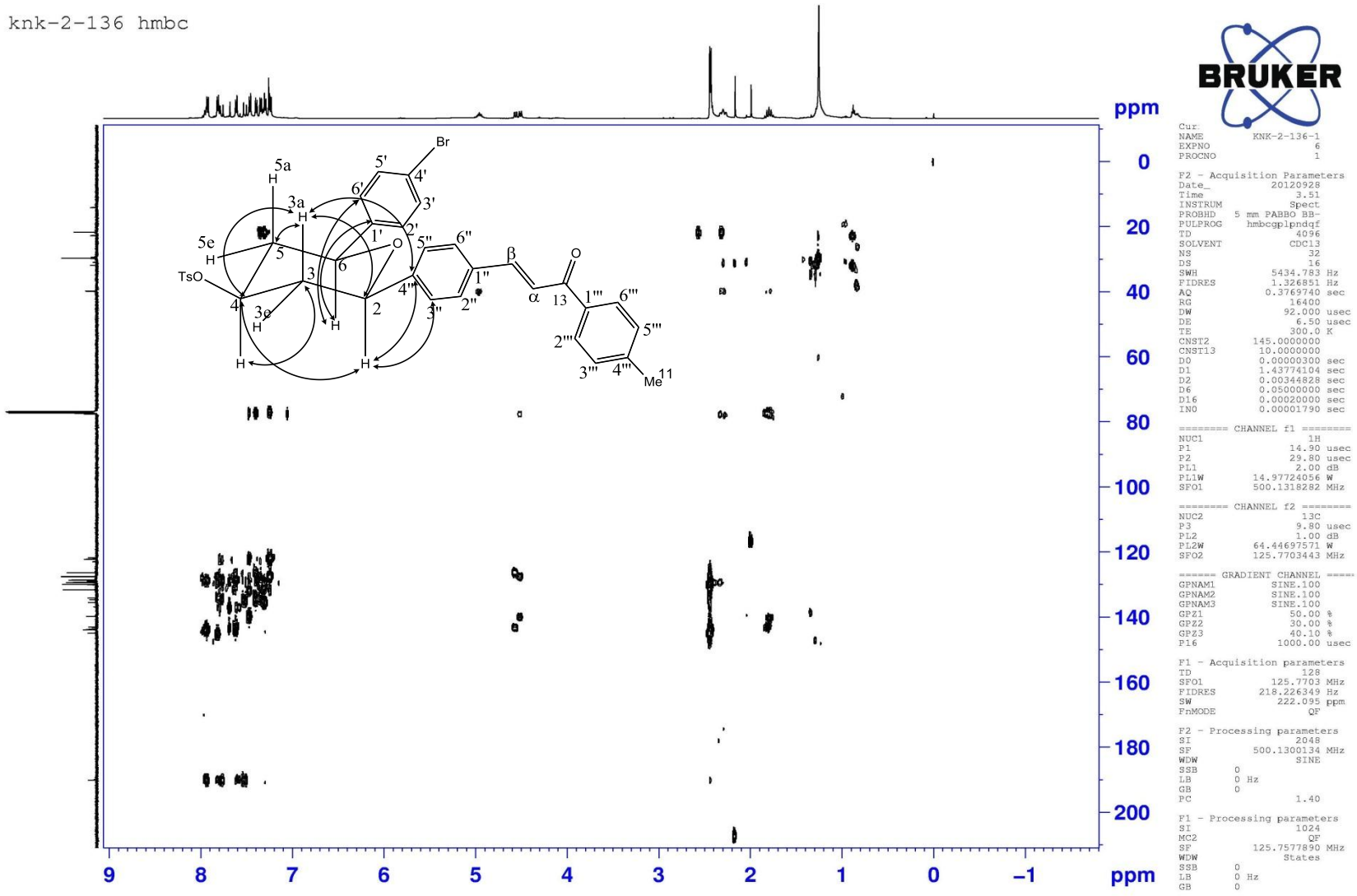


Figure S-27: HMBC spectrum of compound 5f

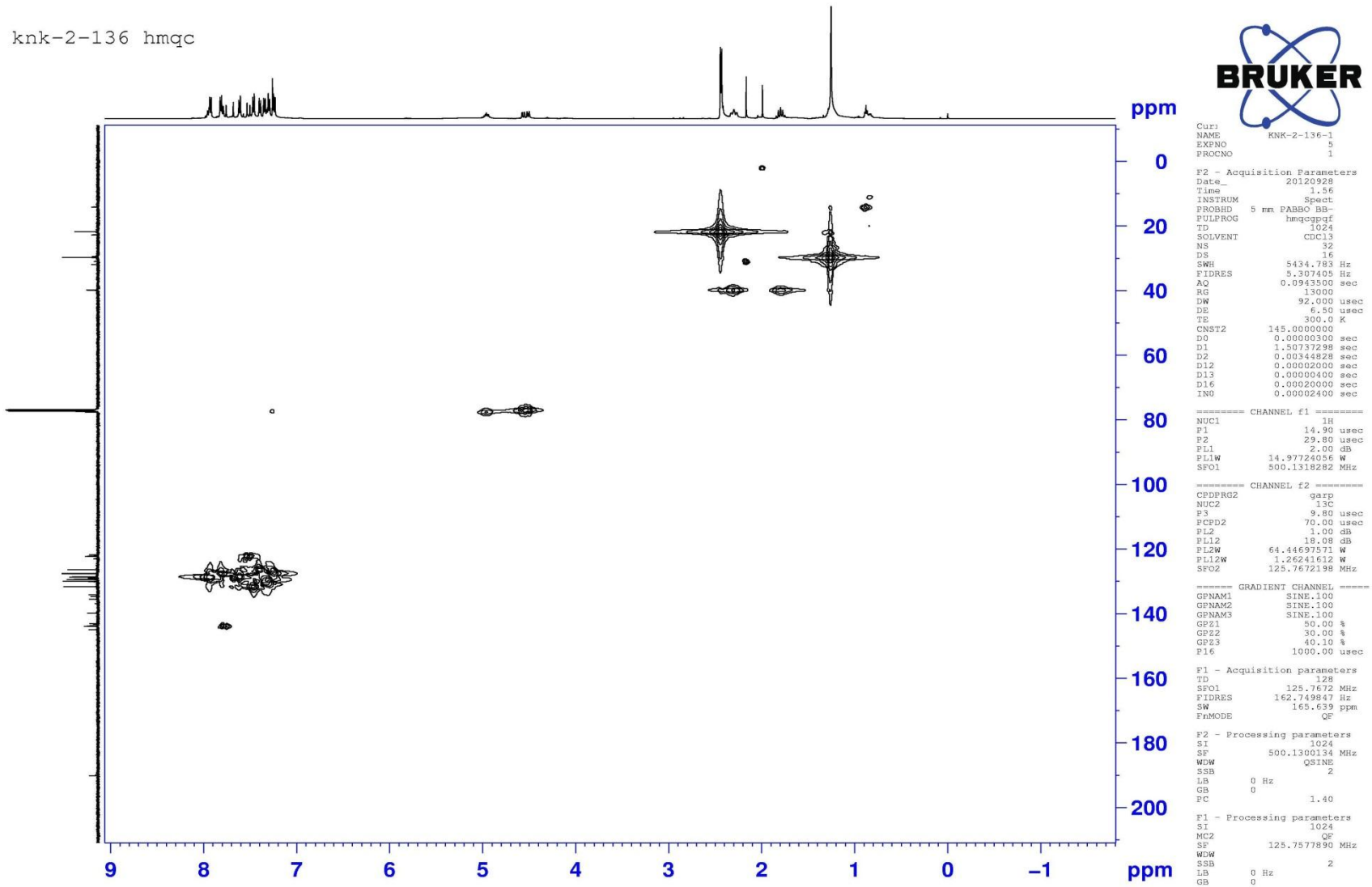


Figure S-28: HMQC spectrum of compound 5f

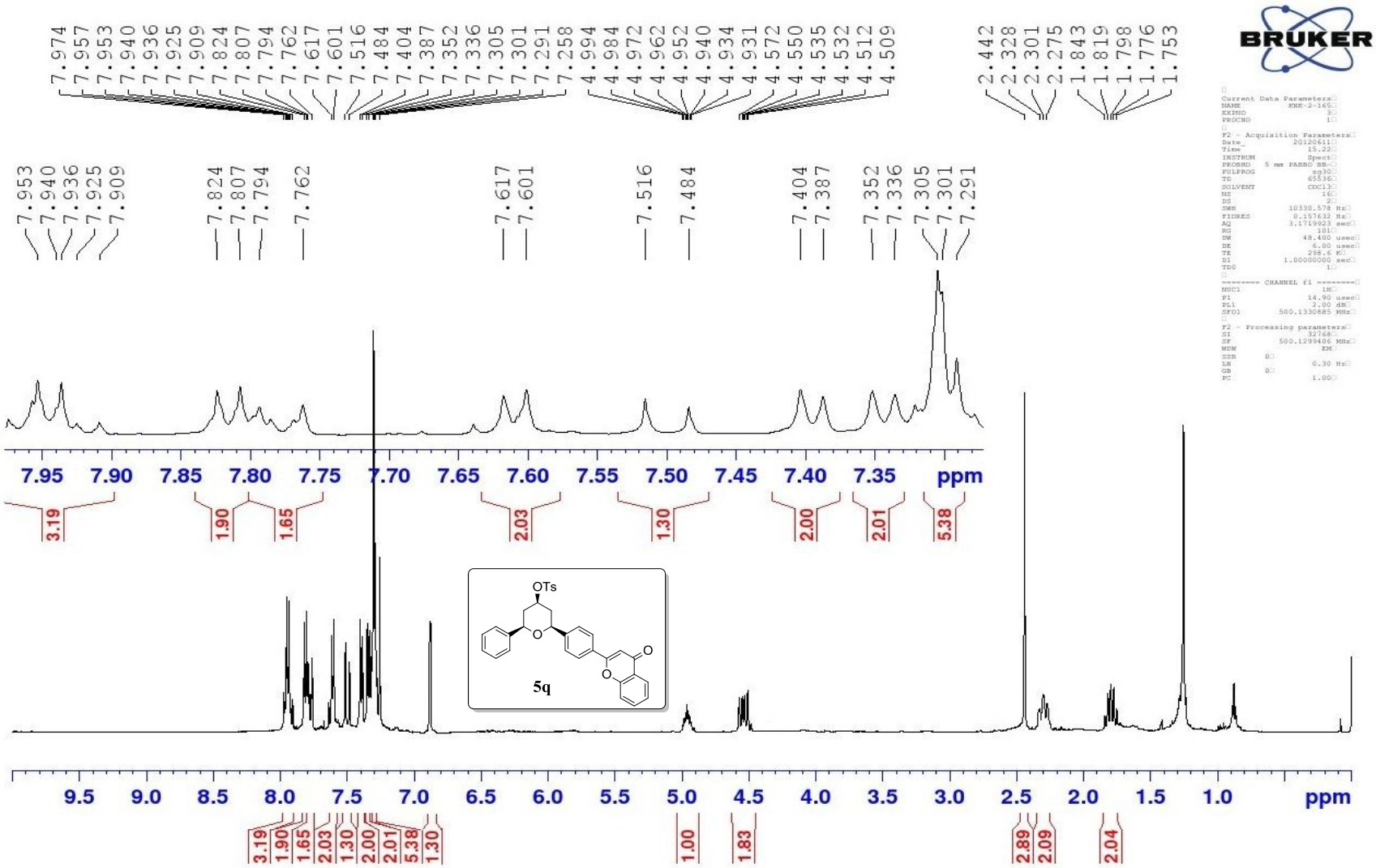


Figure S-29: ^{1}H NMR spectrum of compound 5q

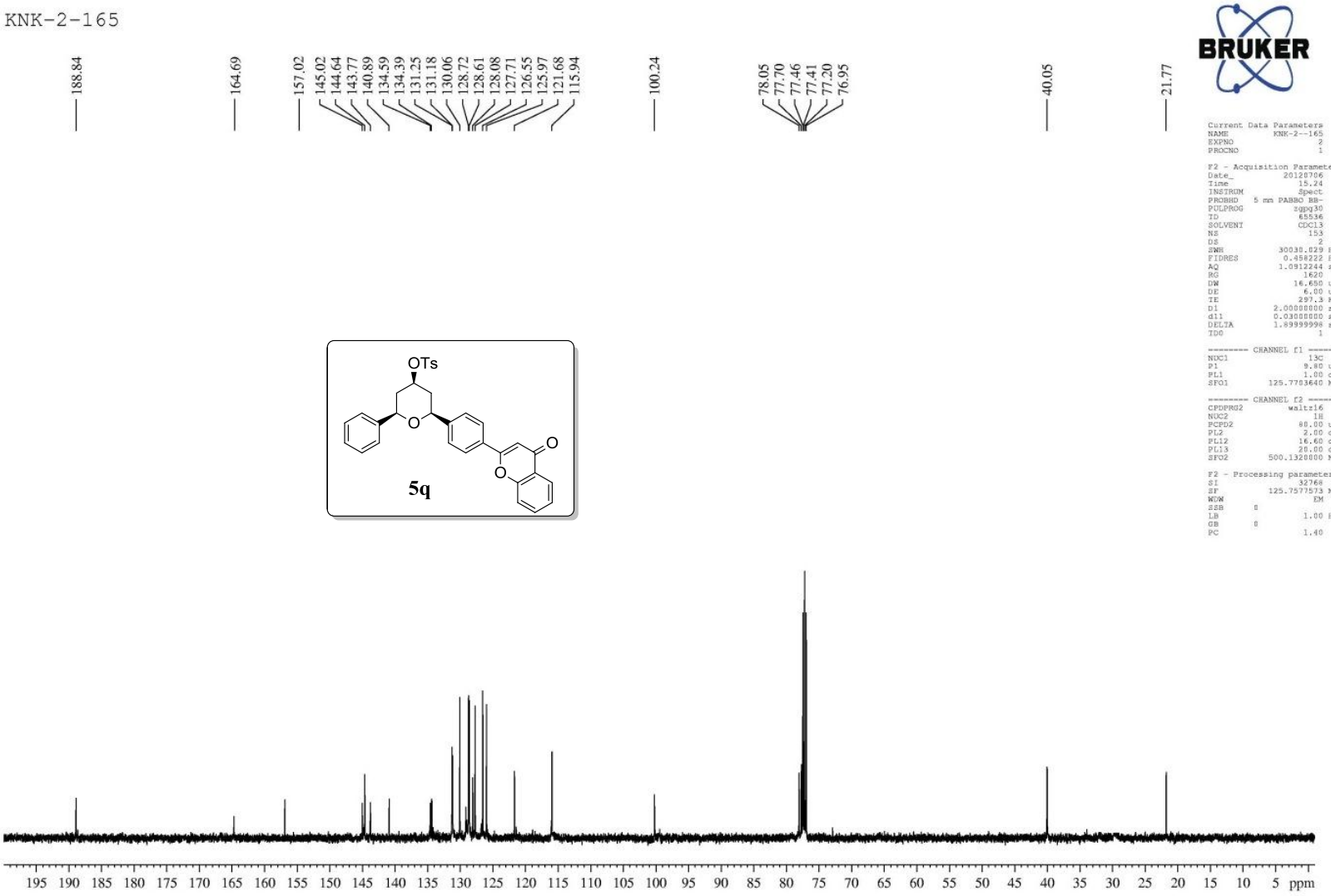


Figure S-30: ^{13}C NMR spectrum of compound 5q

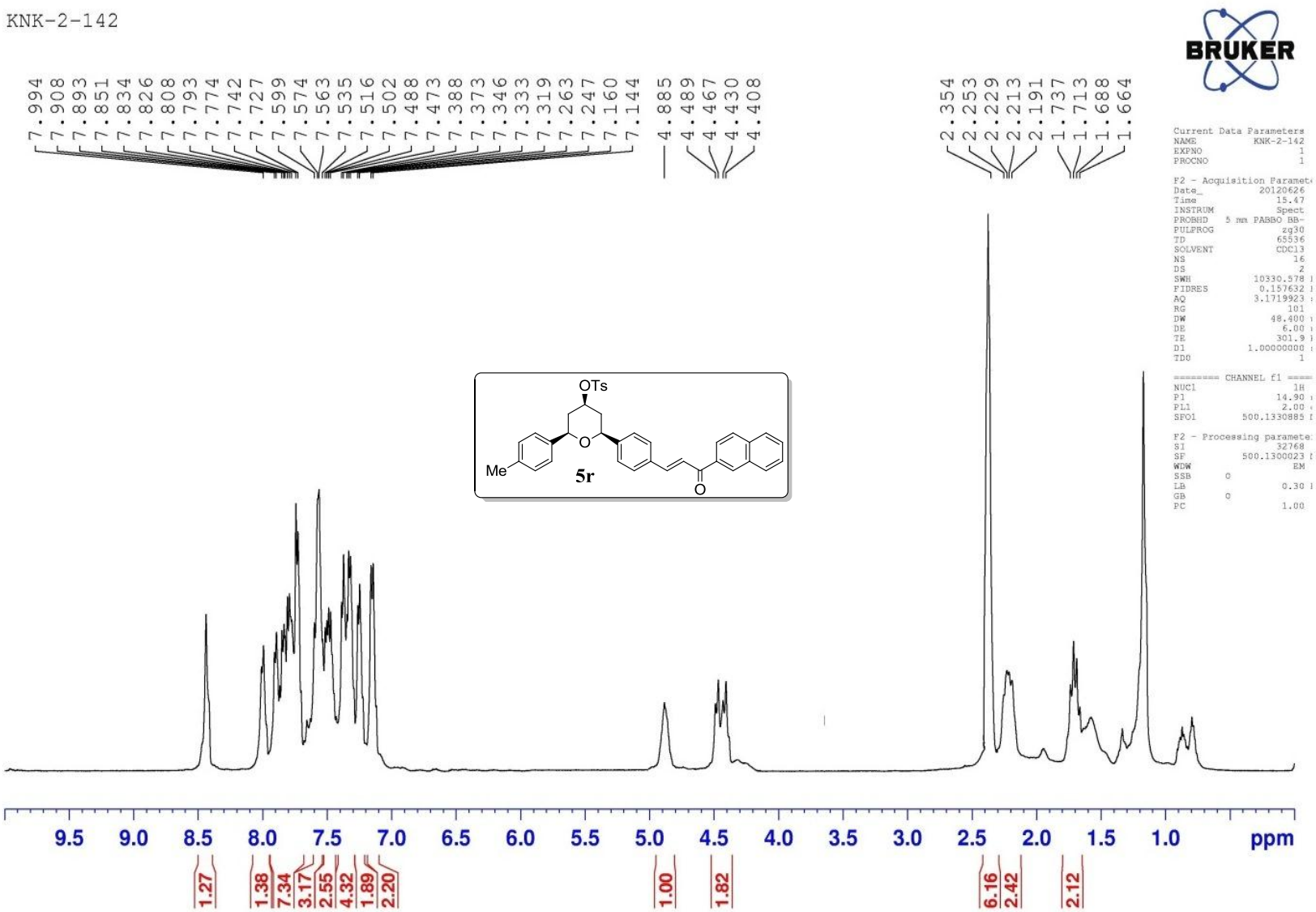
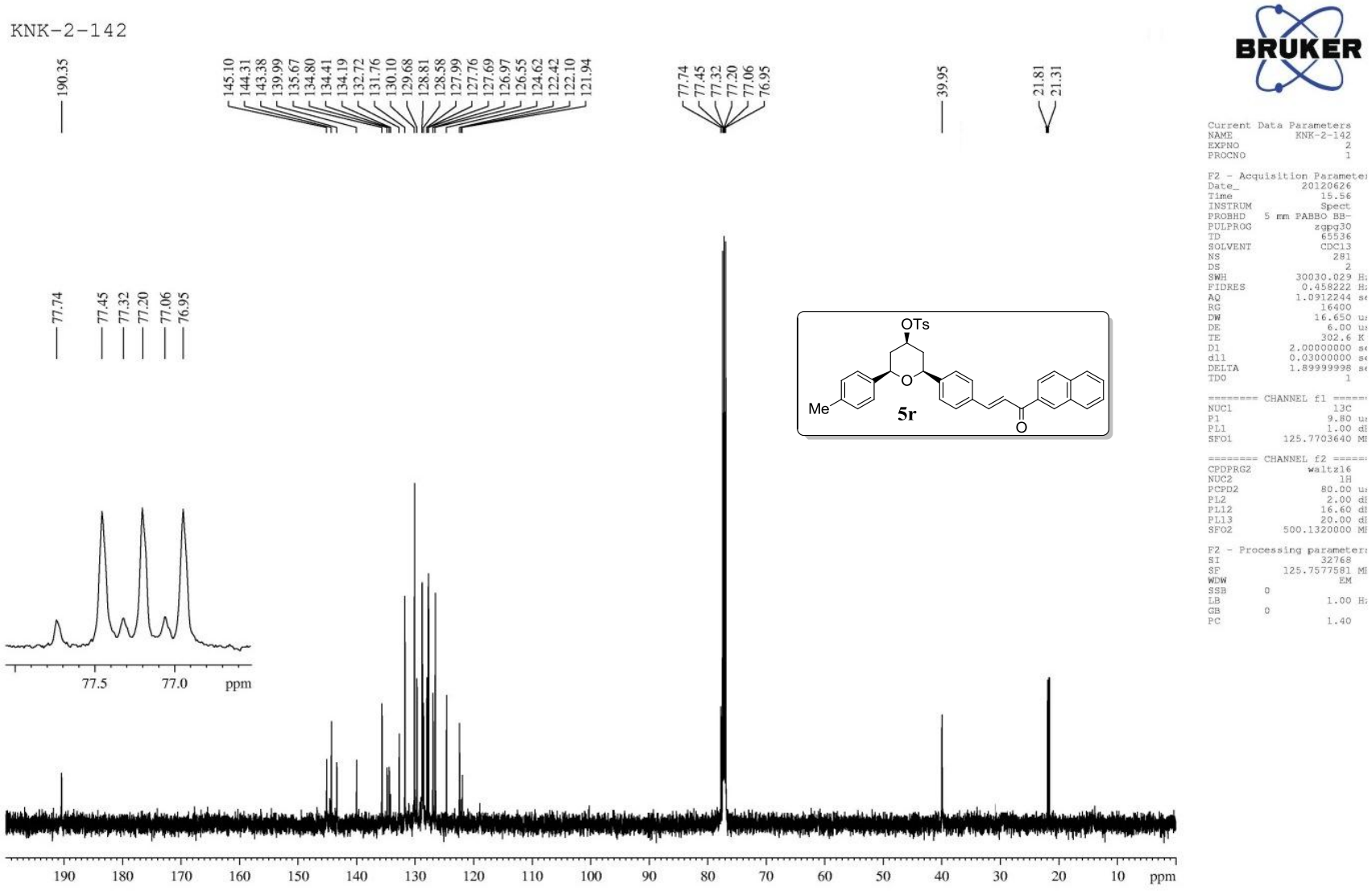


Figure S-31: ^{1}H NMR spectrum of compound 5r



Current Data Parameters
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EXPNO 2
PROCNO 1

F2 - Acquisition Parameter
Date_ 20120626
Time 15.56
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TD 65536
SOLVENT CDCl3
NS 281
DS 2
SWH 30030.029 H
FIDRES 0.458222 H
AQ 1.0912244 s
RG 16400
DW 16.650 u
DE 6.00 u
TE 302.6 K
D1 2.00000000 s
d11 0.03000000 s
DELTA 1.89999998 s
TD0 1

======== CHANNEL f1 ======
NUC1 13C
P1 9.80 u
PL1 1.00 d
SFO1 125.7703640 M

======== CHANNEL f2 ======
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 u
PL2 2.00 d
PL12 16.60 d
PL13 20.00 d
SFO2 500.1320000 M

F2 - Processing parameter
SI 32768
SF 125.7577581 M
WDW EM
SSB 0
LB 1.00 H
GB 0
PC 1.40

Figure S-32: ^{13}C NMR spectrum of compound 5r

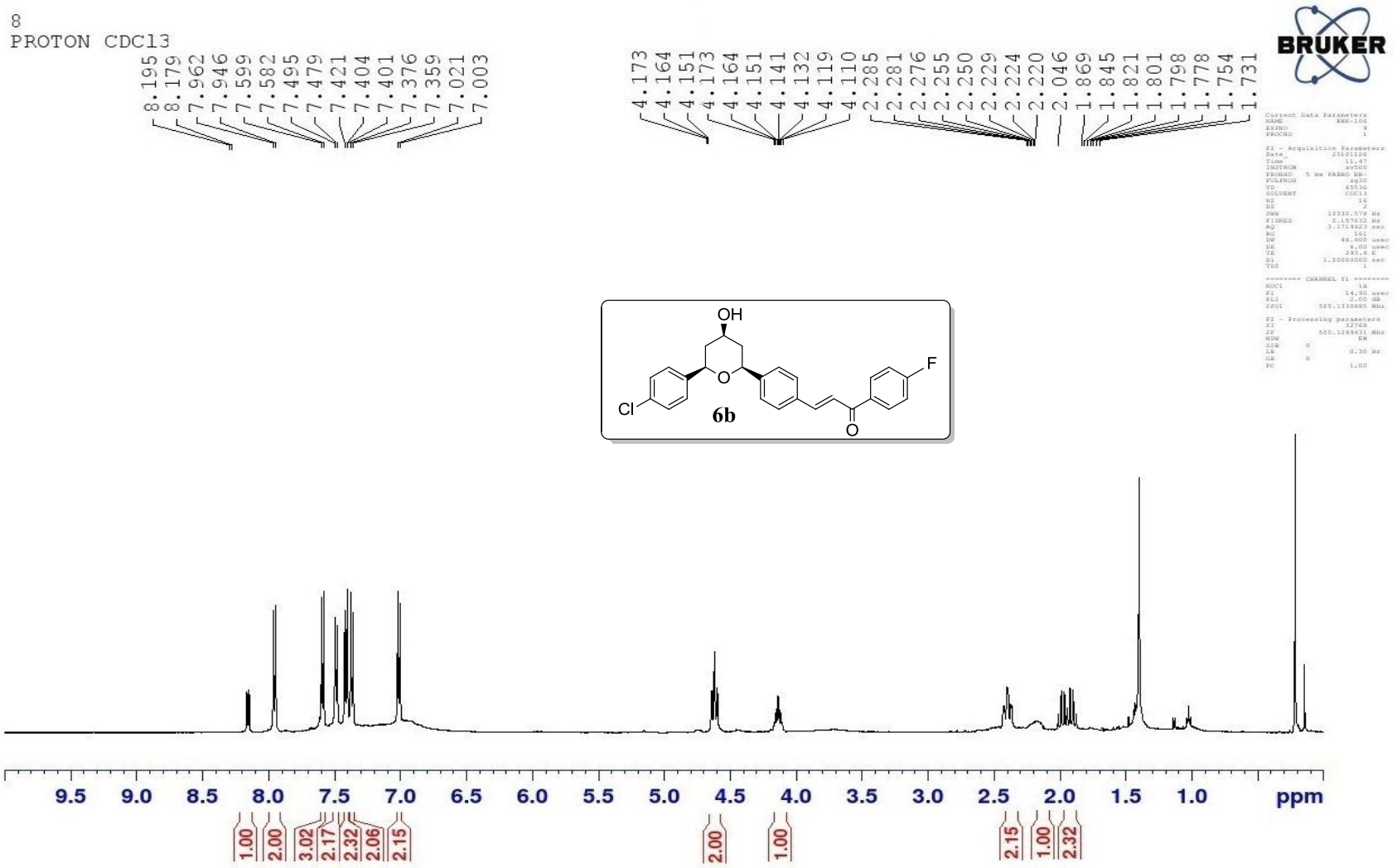
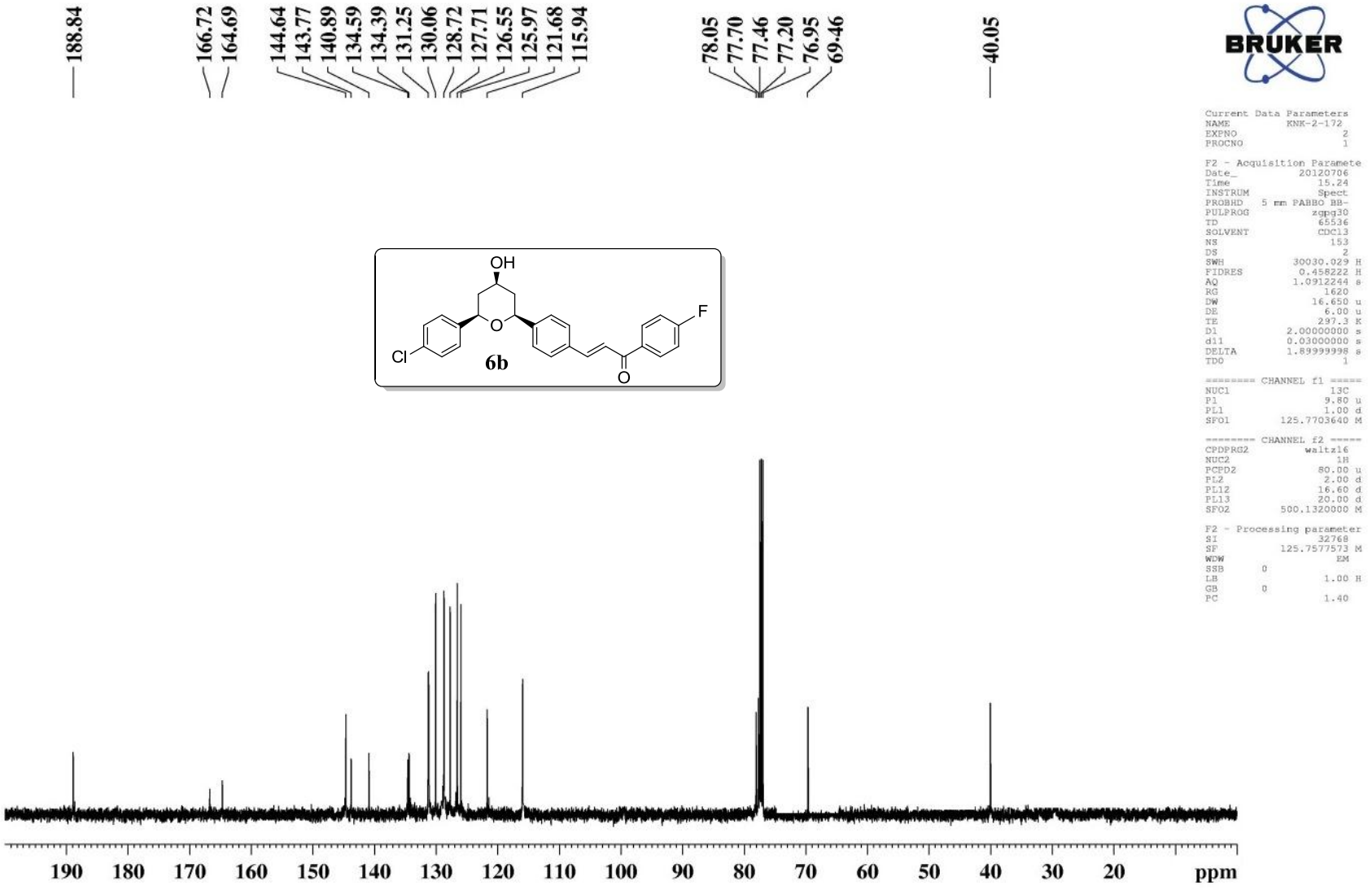


Figure S-33: ^{1}H NMR spectrum of compound 6b



BRUKER

Current Data Parameters
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EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
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Time 15.24
INSTRUM Spect
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TD 65536
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NS 153
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SWH 30030.029 Hz
FIDRES 0.458222 Hz
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RG 1620
DW 16.650 usec
DE 6.00 usec
TE 297.3 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1

======== CHANNEL f1 ======
NUC1 13C
P1 9.80 usec
PL1 1.00 dB
SFO1 125.7703640 MHz

======== CHANNEL f2 ======
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 16.60 dB
PL13 20.00 dB
SFO2 500.1320000 MHz

F2 - Processing parameters
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SF 125.7577573 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Figure S-34: ^{13}C NMR spectrum of compound 6b

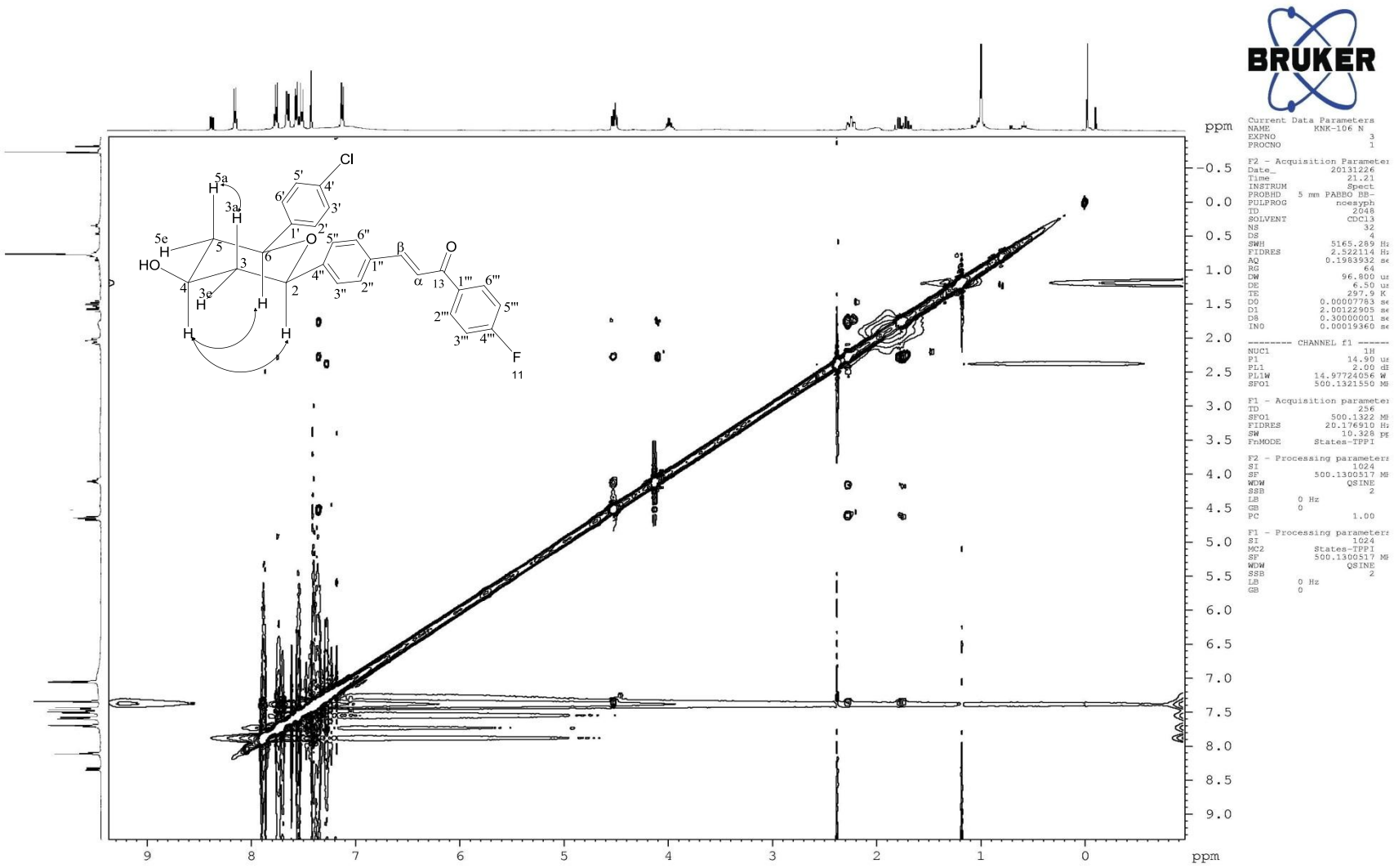


Figure S-35: NOESY spectrum of compound 6b

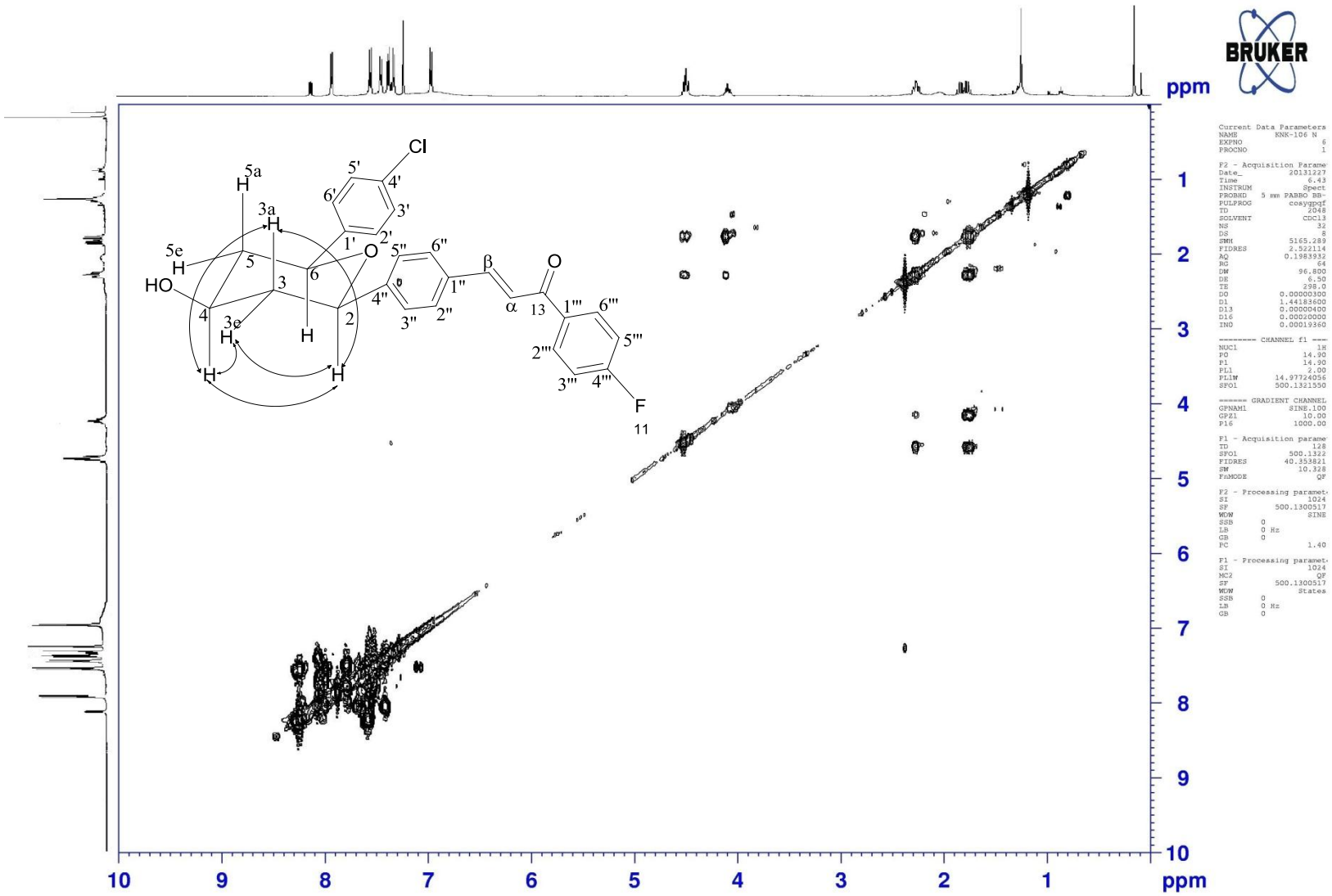


Figure S-36: COSY spectrum of compound 6b

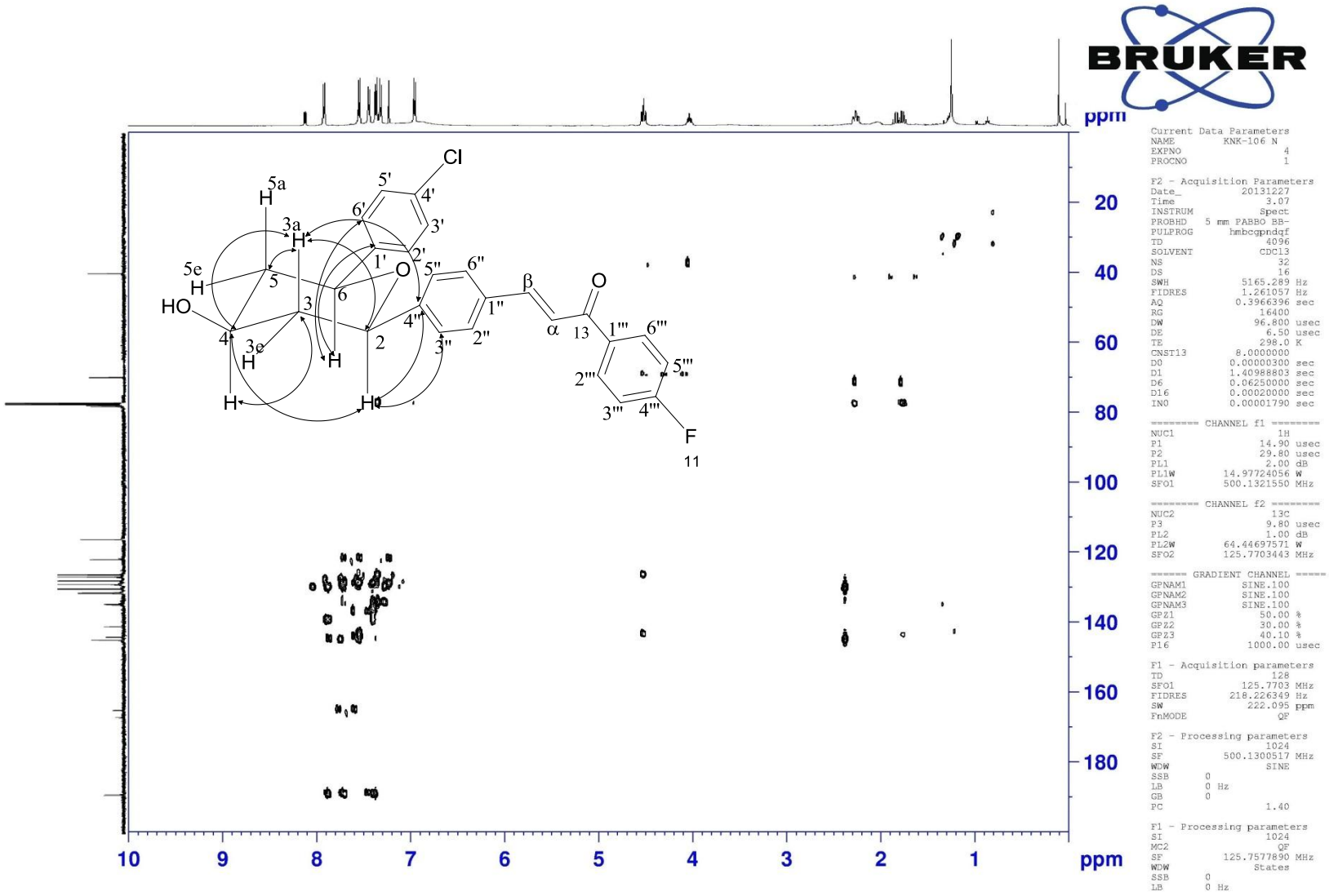


Figure S-37: HMBC spectrum of compound 6b

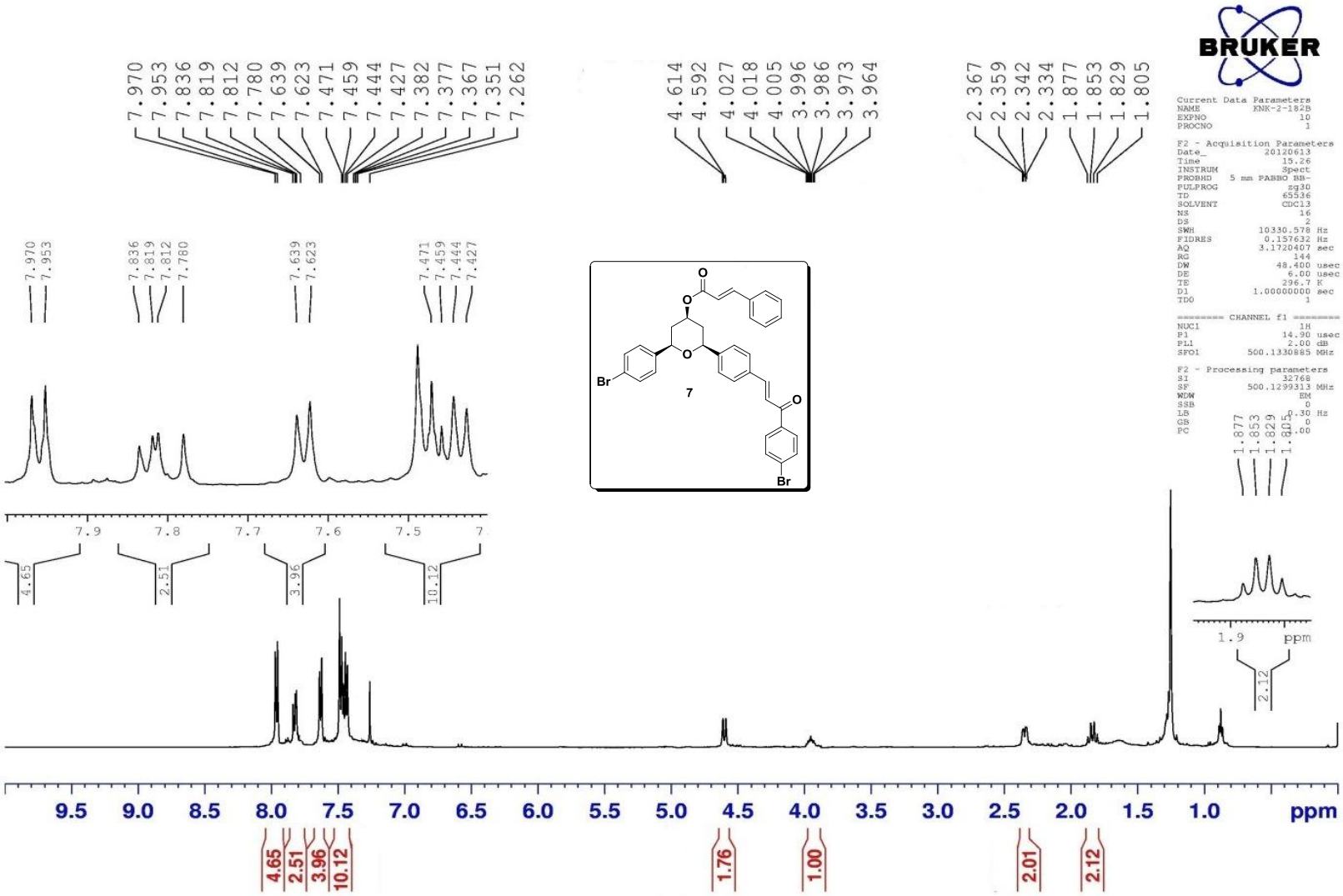


Figure S-38: ^{1}H NMR spectrum of compound 7

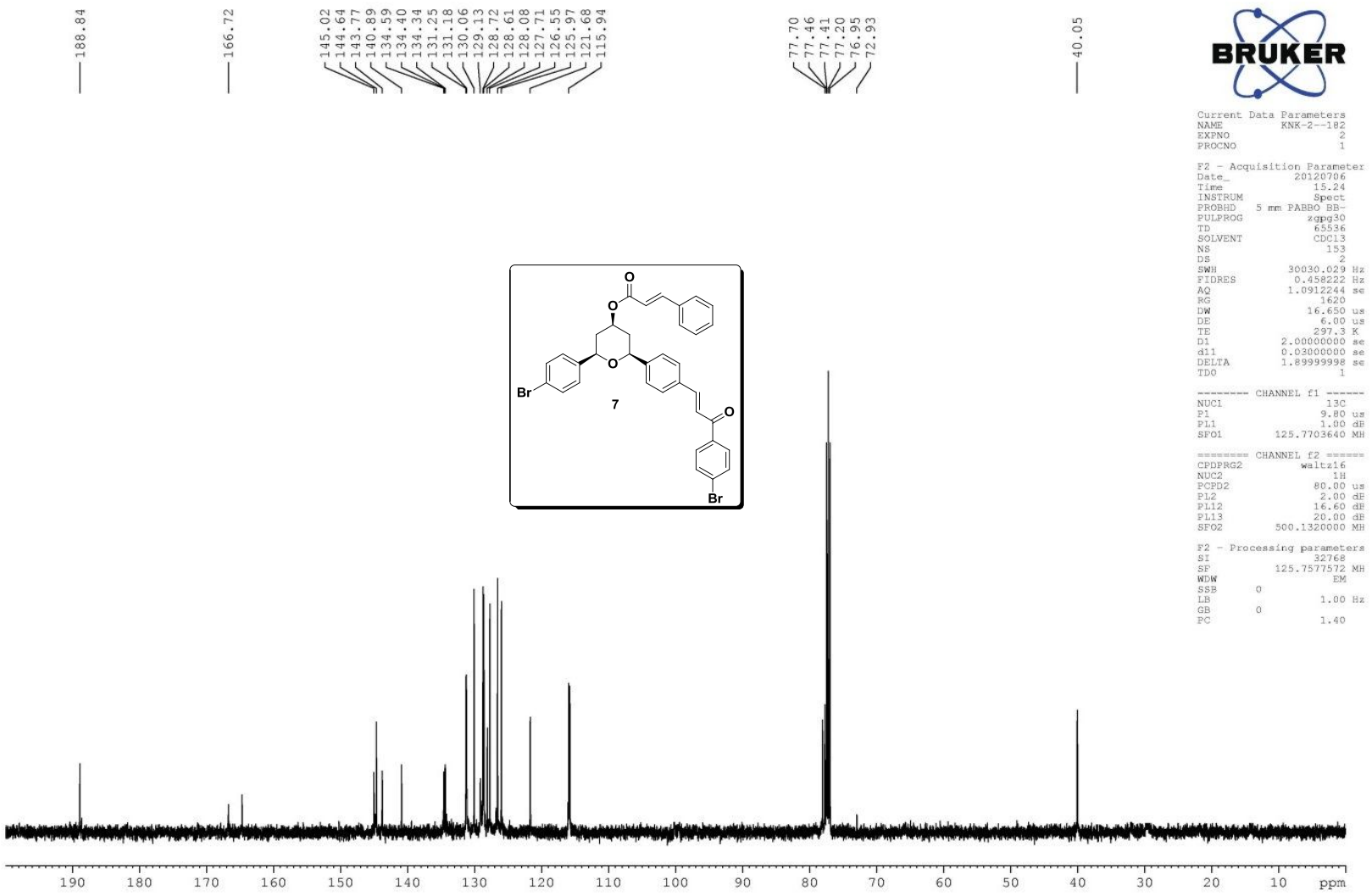


Figure S-39: ^{13}C NMR spectrum of compound 7

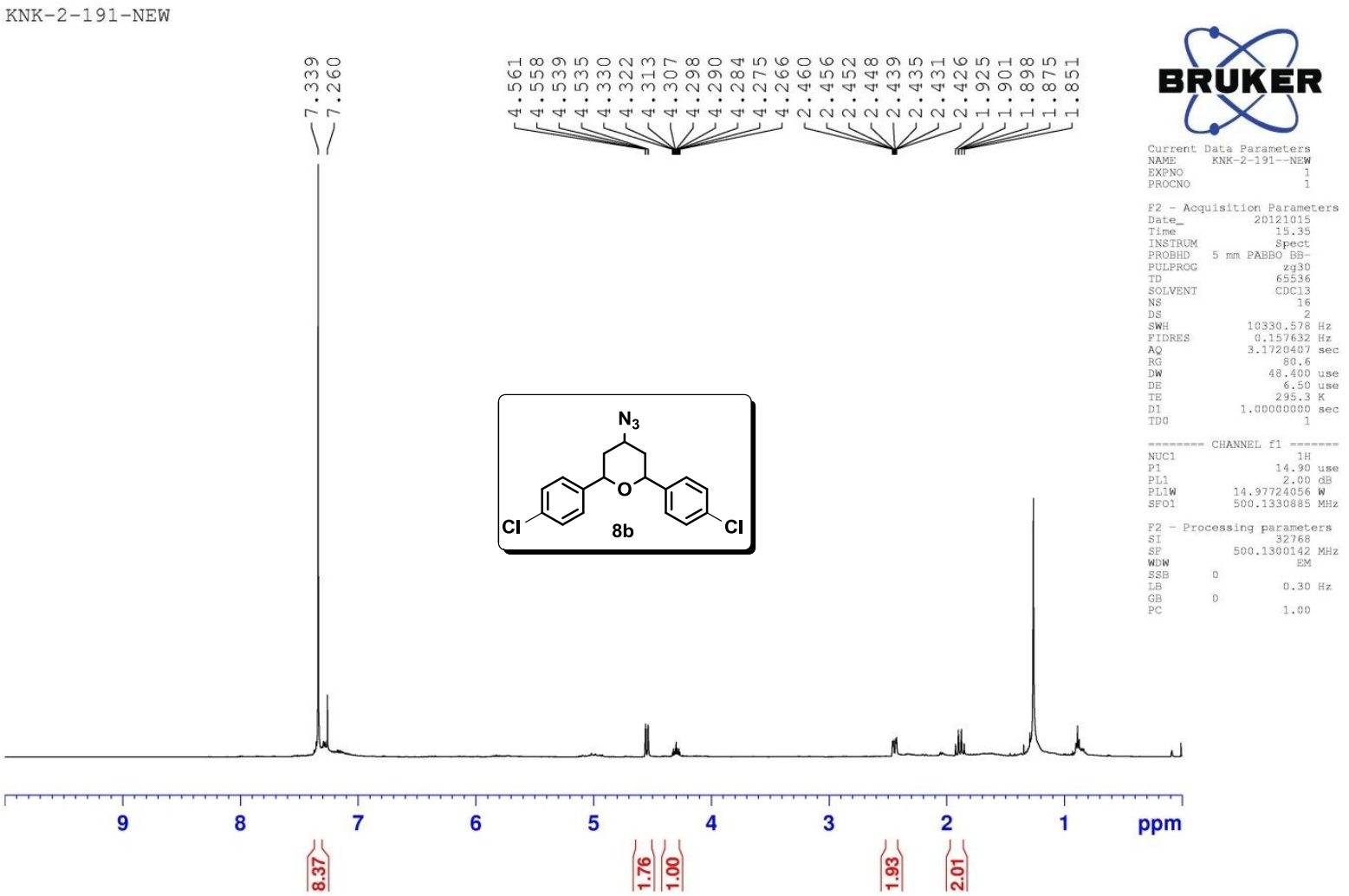


Figure S-40: ^{1}H NMR spectrum of compound 8b

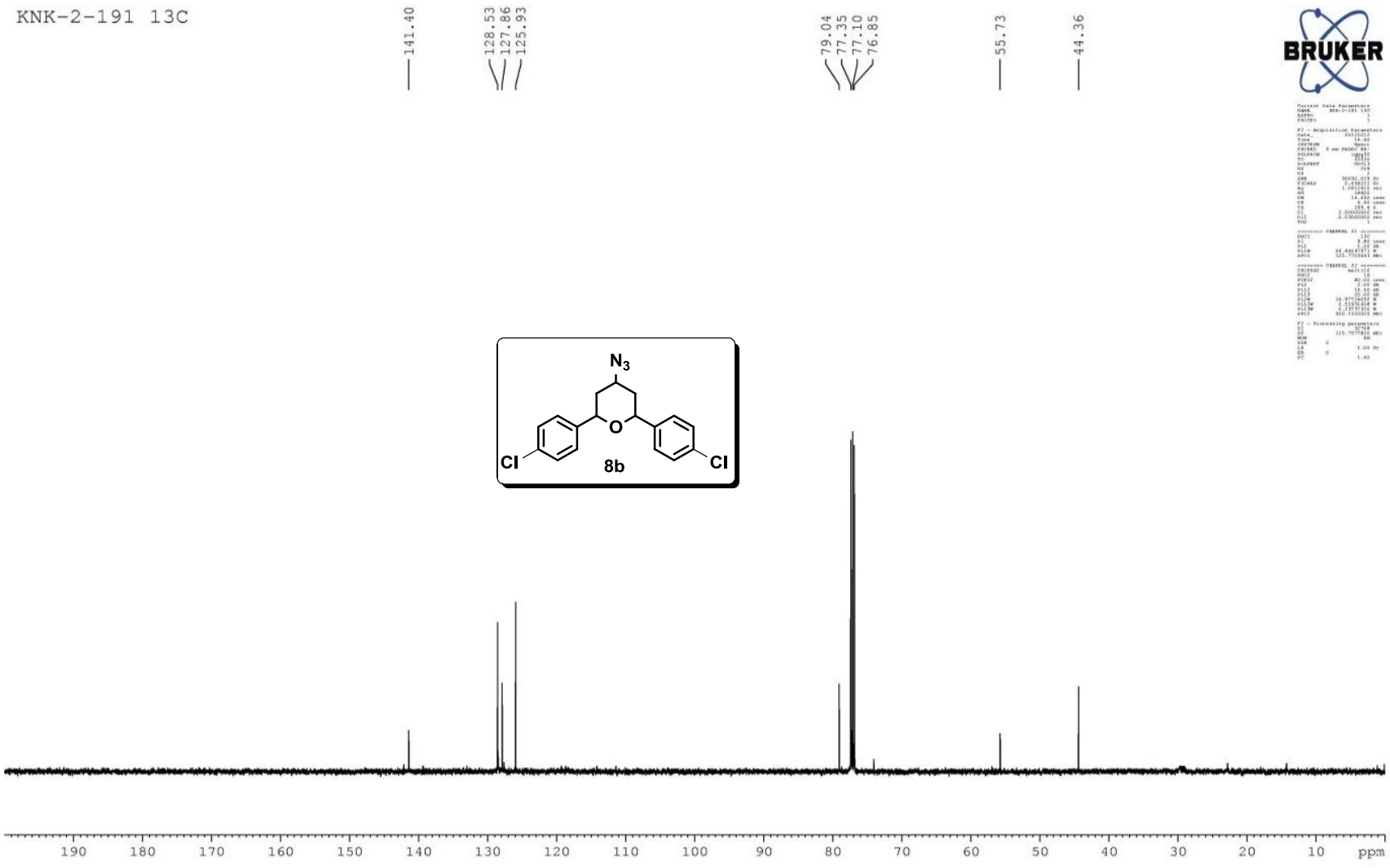


Figure S-41: ^{13}C NMR spectrum of compound 8b

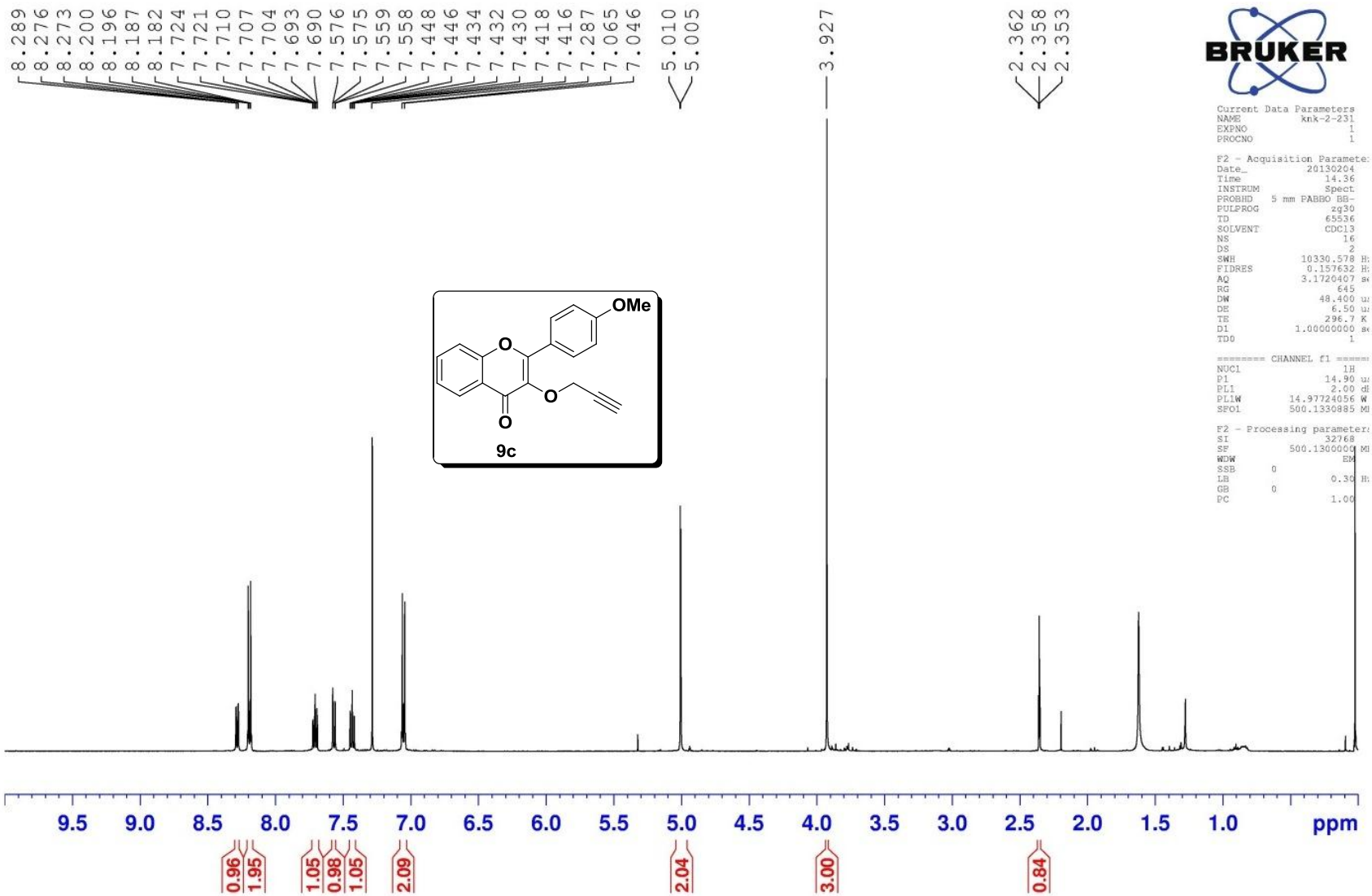


Figure S-42: ^{1}H NMR spectrum of compound 9c

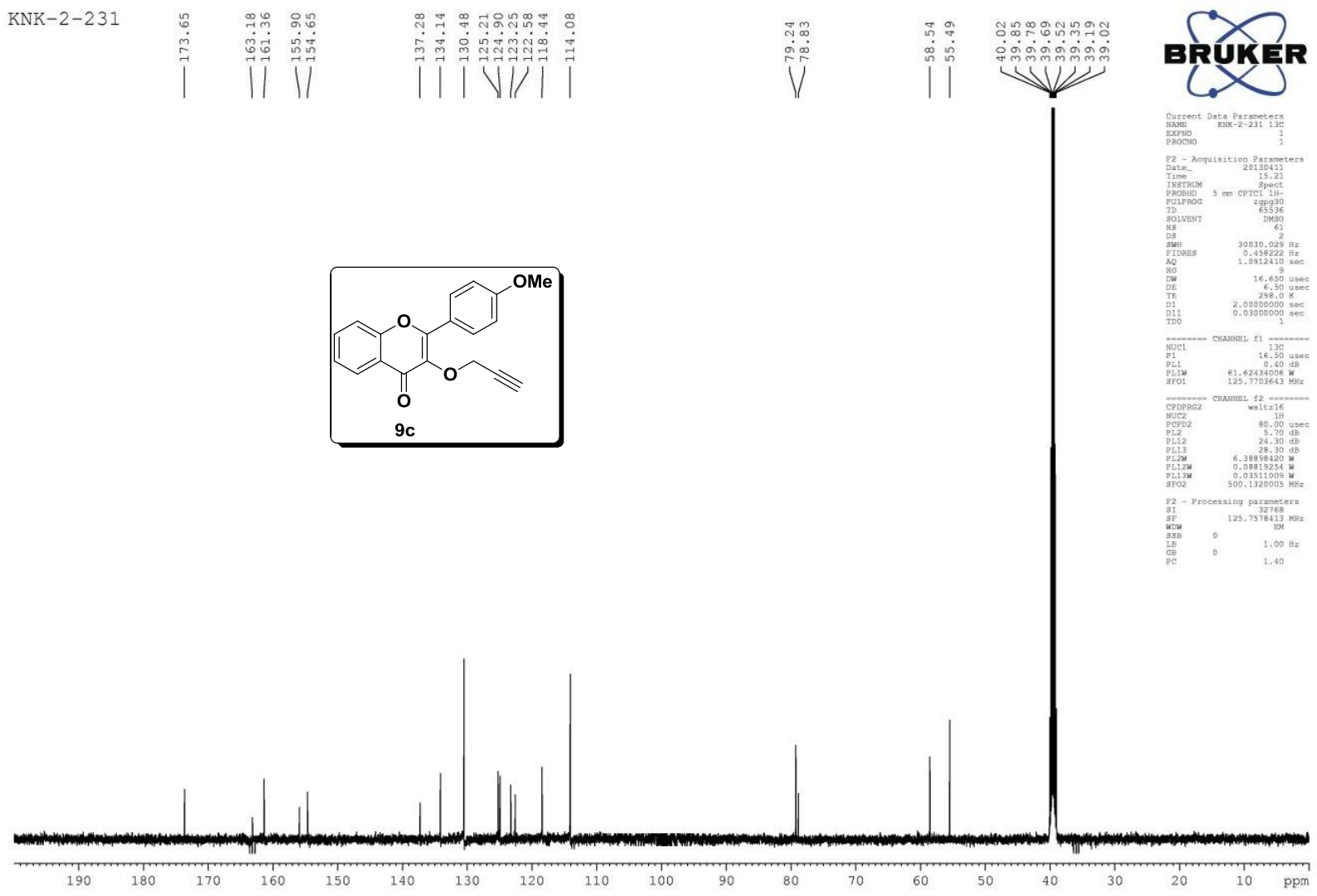


Figure S-43: ^{13}C NMR spectrum of compound 9c

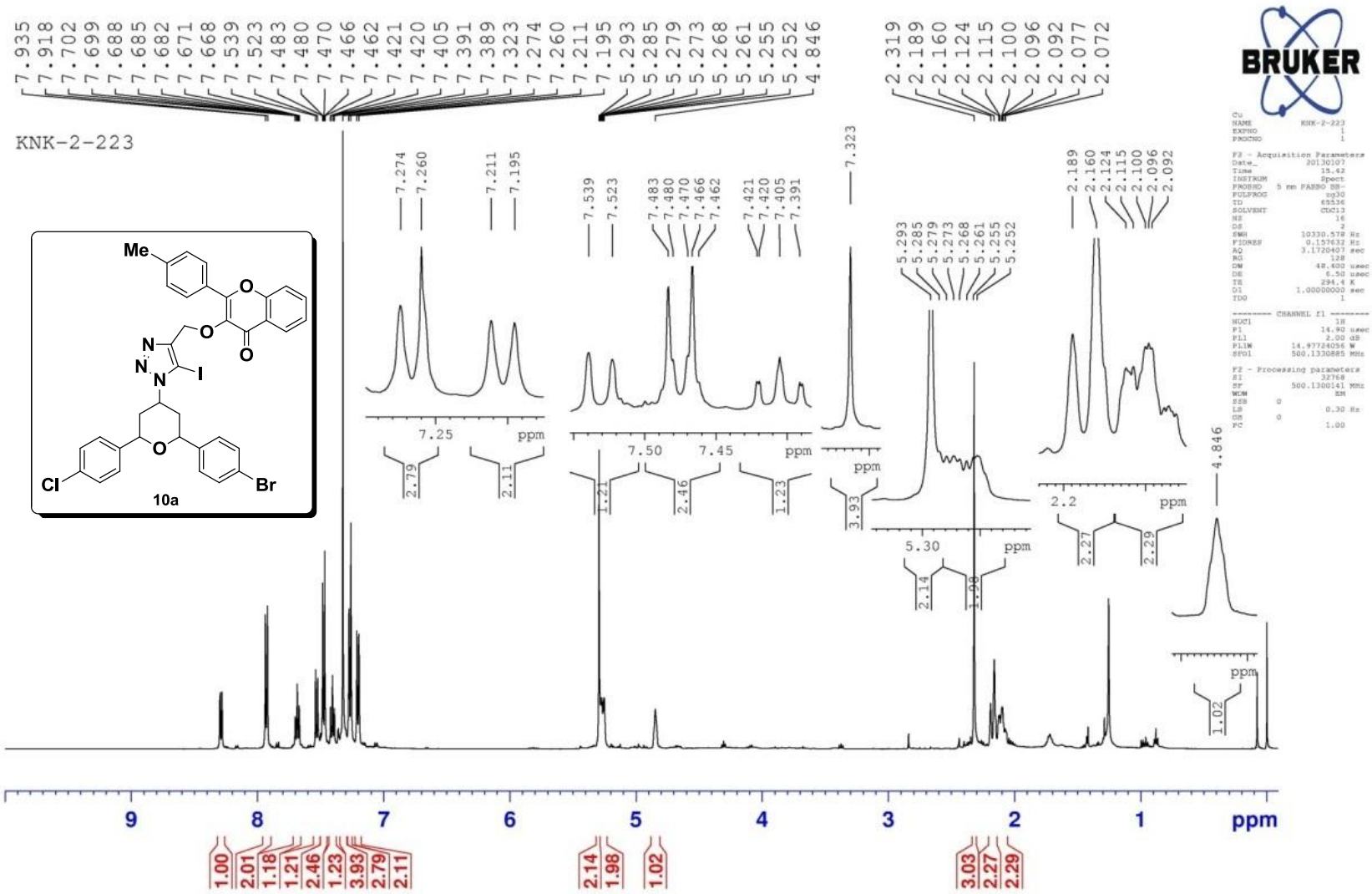


Figure S-44: ^{1}H NMR spectrum of compound 10a

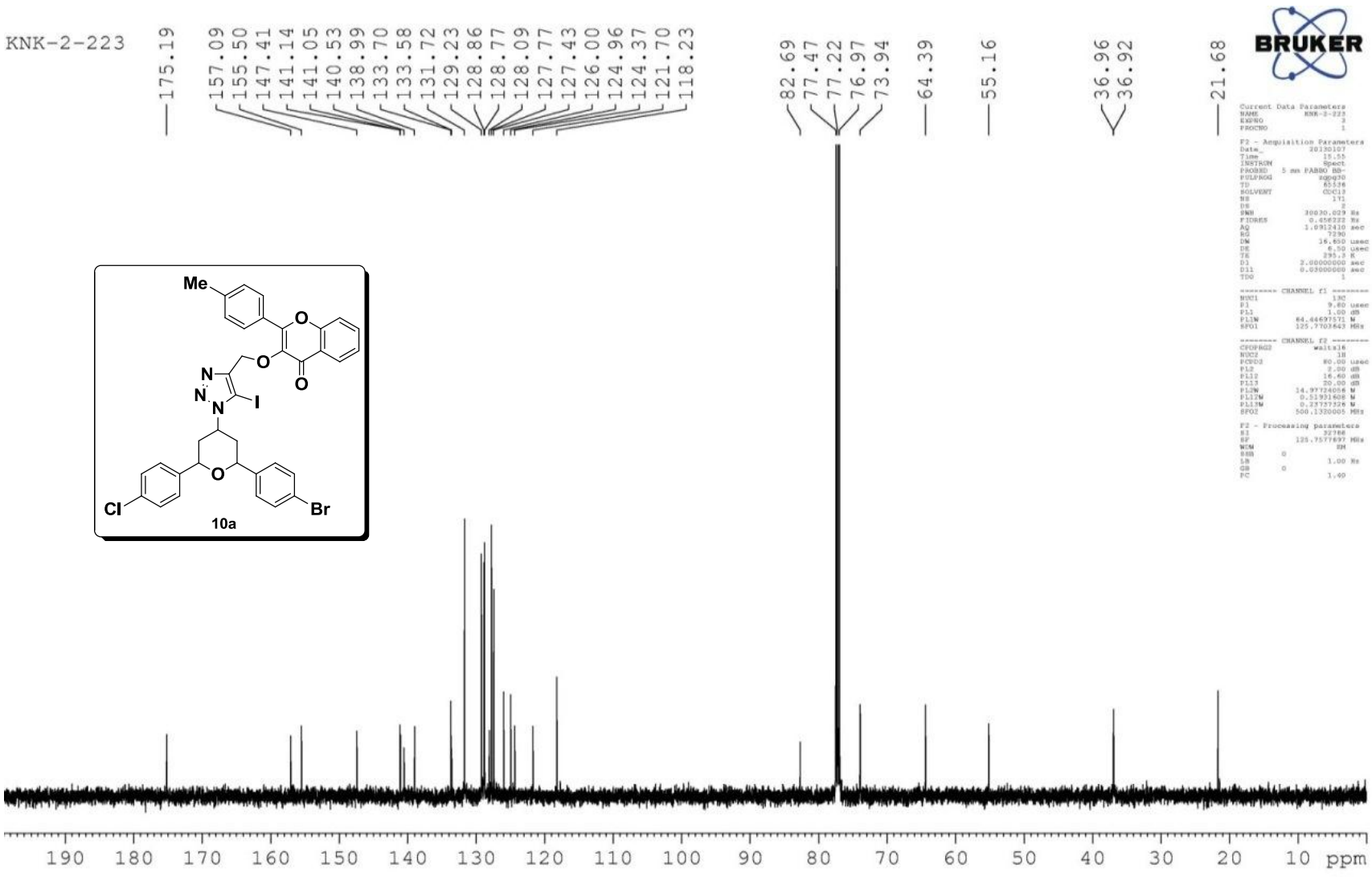


Figure S-45: ^{13}C NMR spectrum of compound 10a

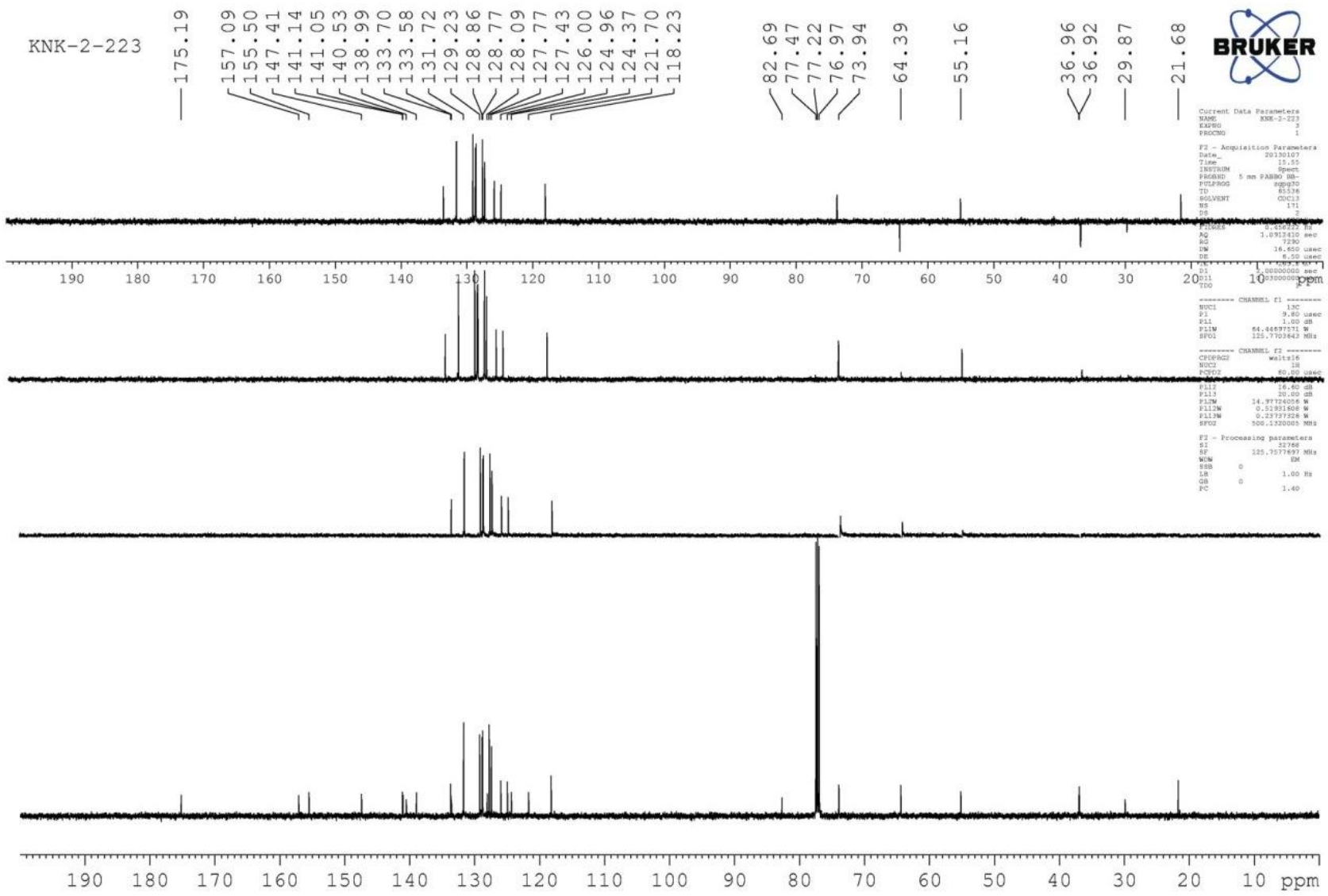


Figure S-46: ^{13}C NMR and DEPT spectrum of compound 10a

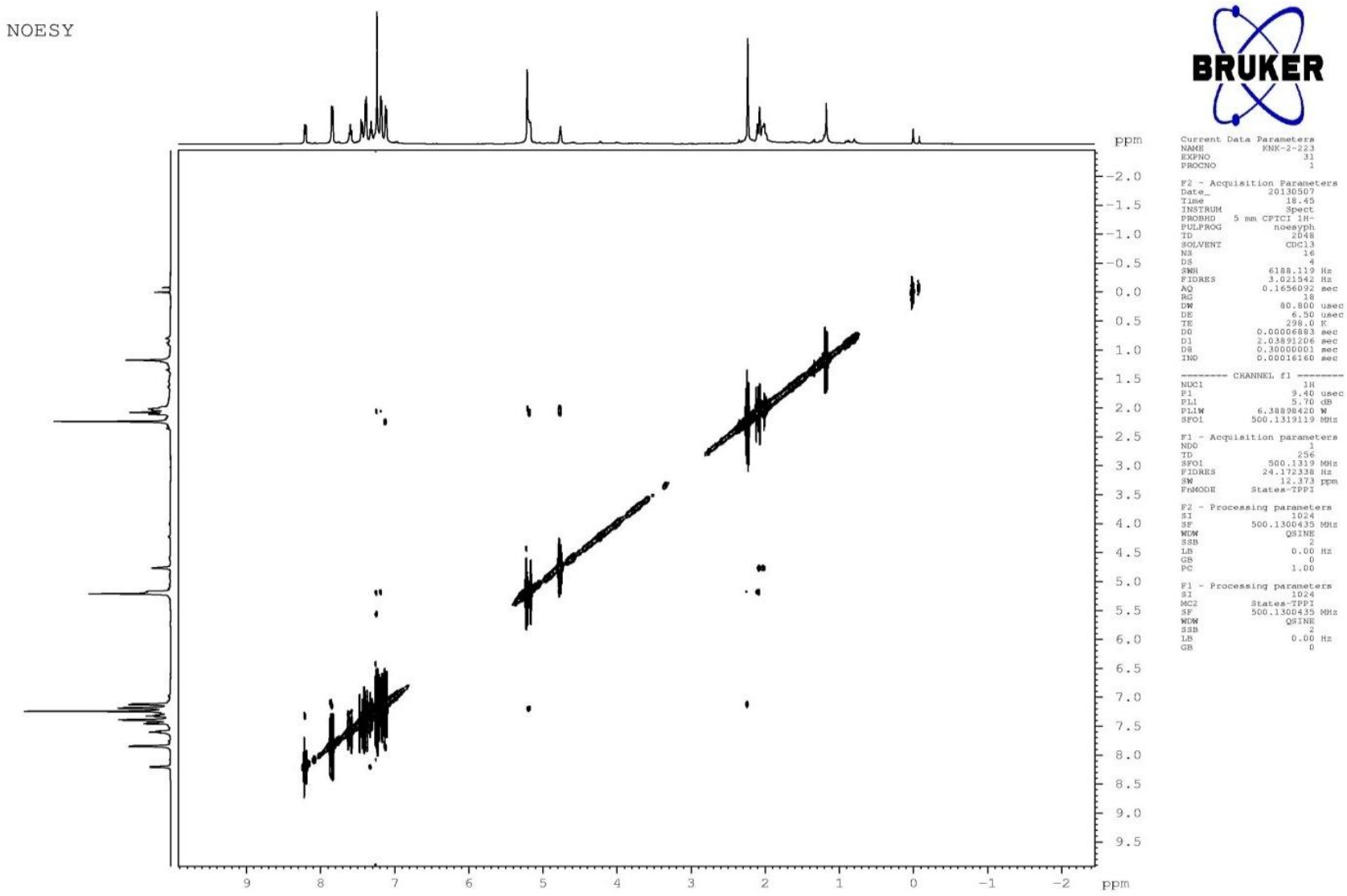


Figure S-47: NOESY spectrum of compound 10a

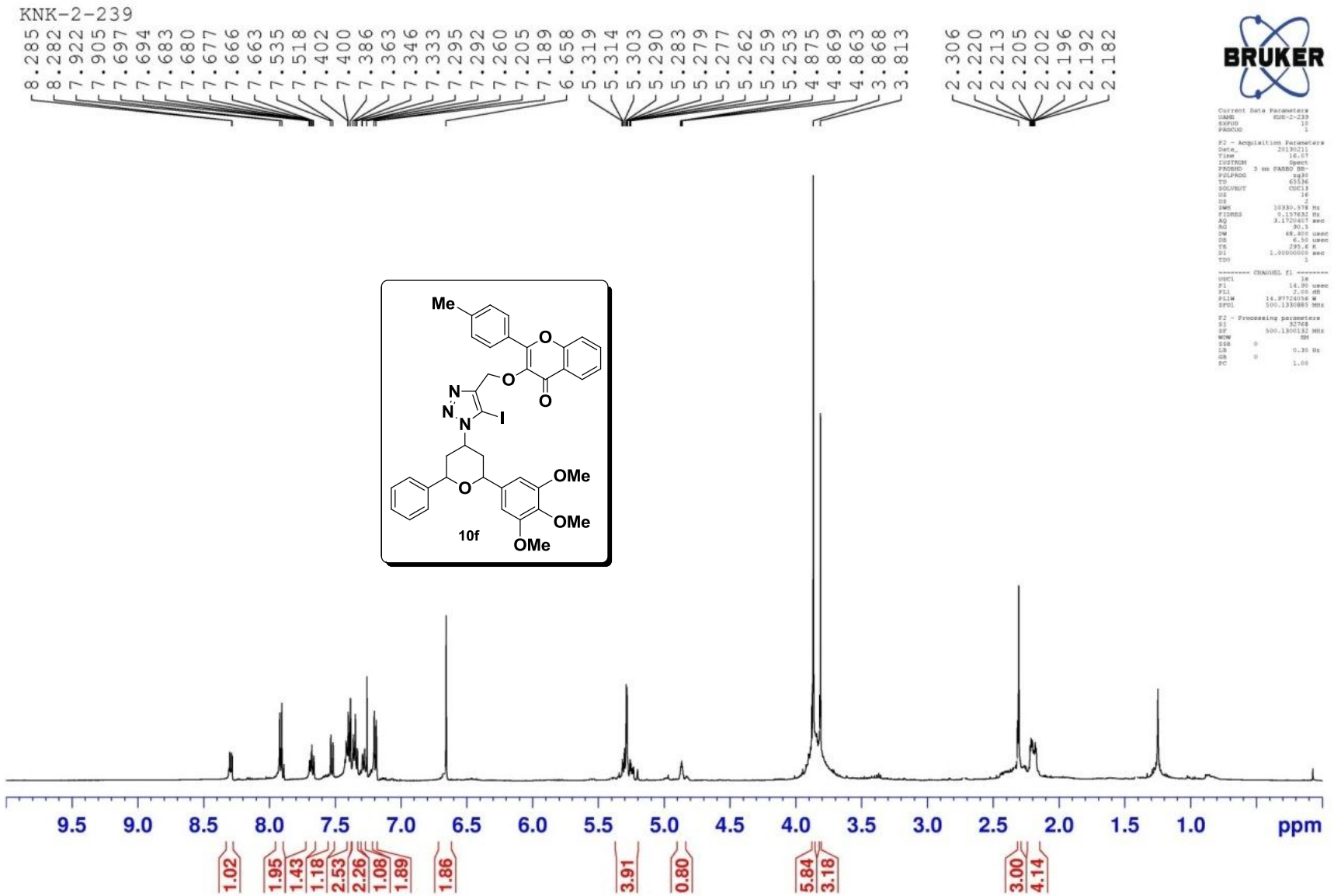


Figure S-48: ^{1}H NMR spectrum of compound 10f

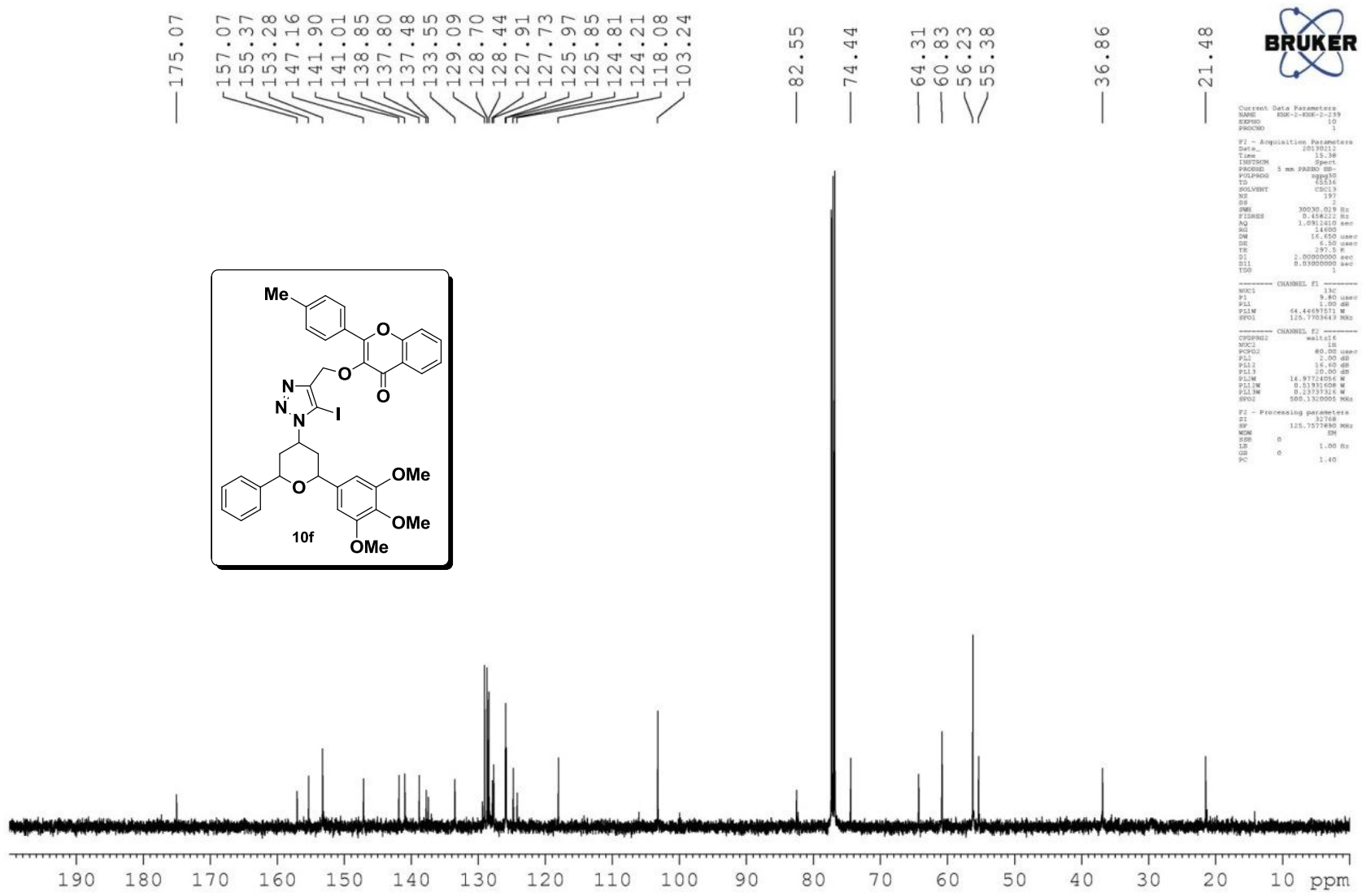


Figure S-49: ^{13}C NMR spectrum of compound 10f

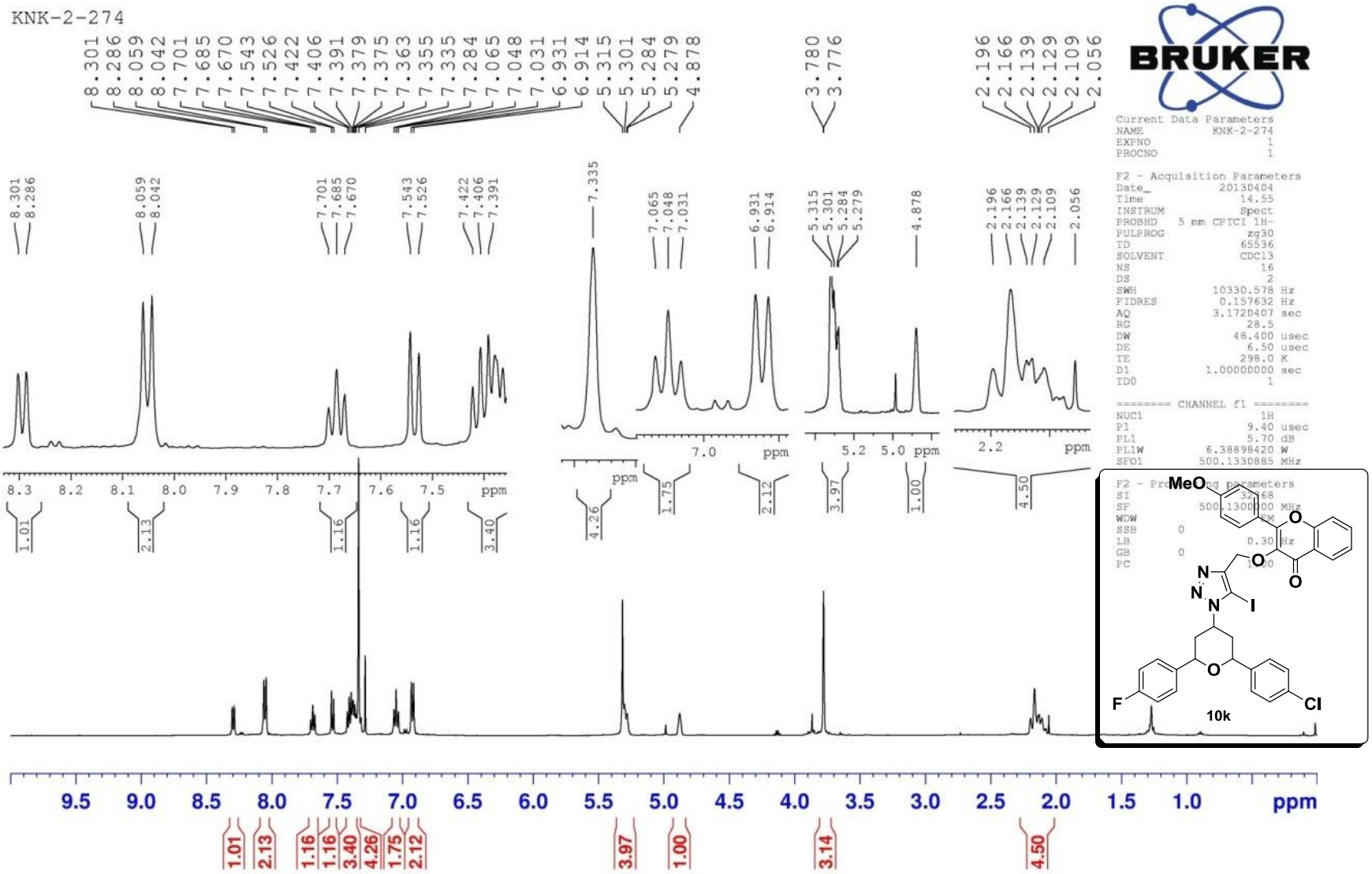


Figure S-50: ^{1}H NMR spectrum of compound 10k

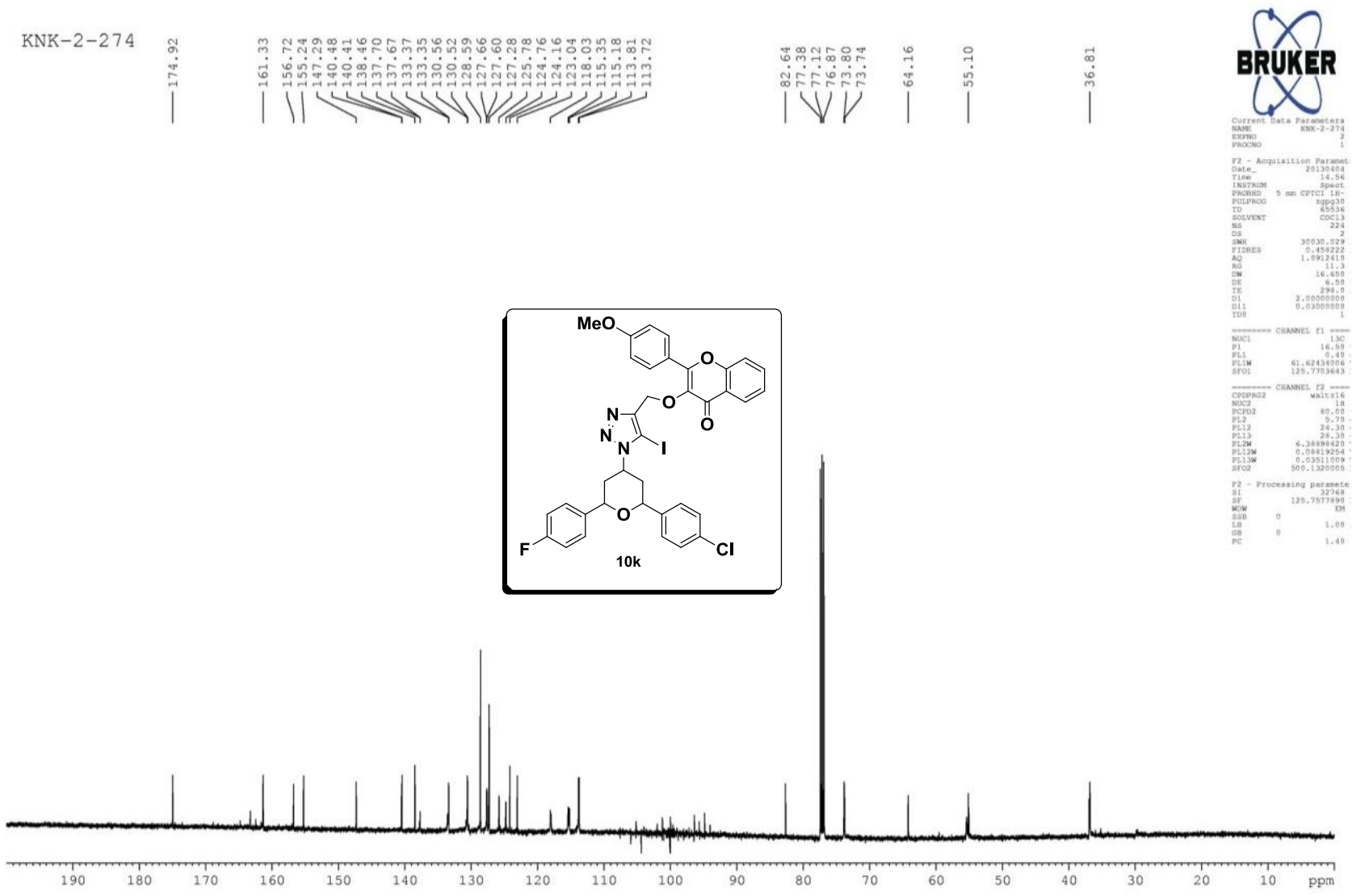


Figure S-51: ^{13}C NMR spectrum of compound 10k

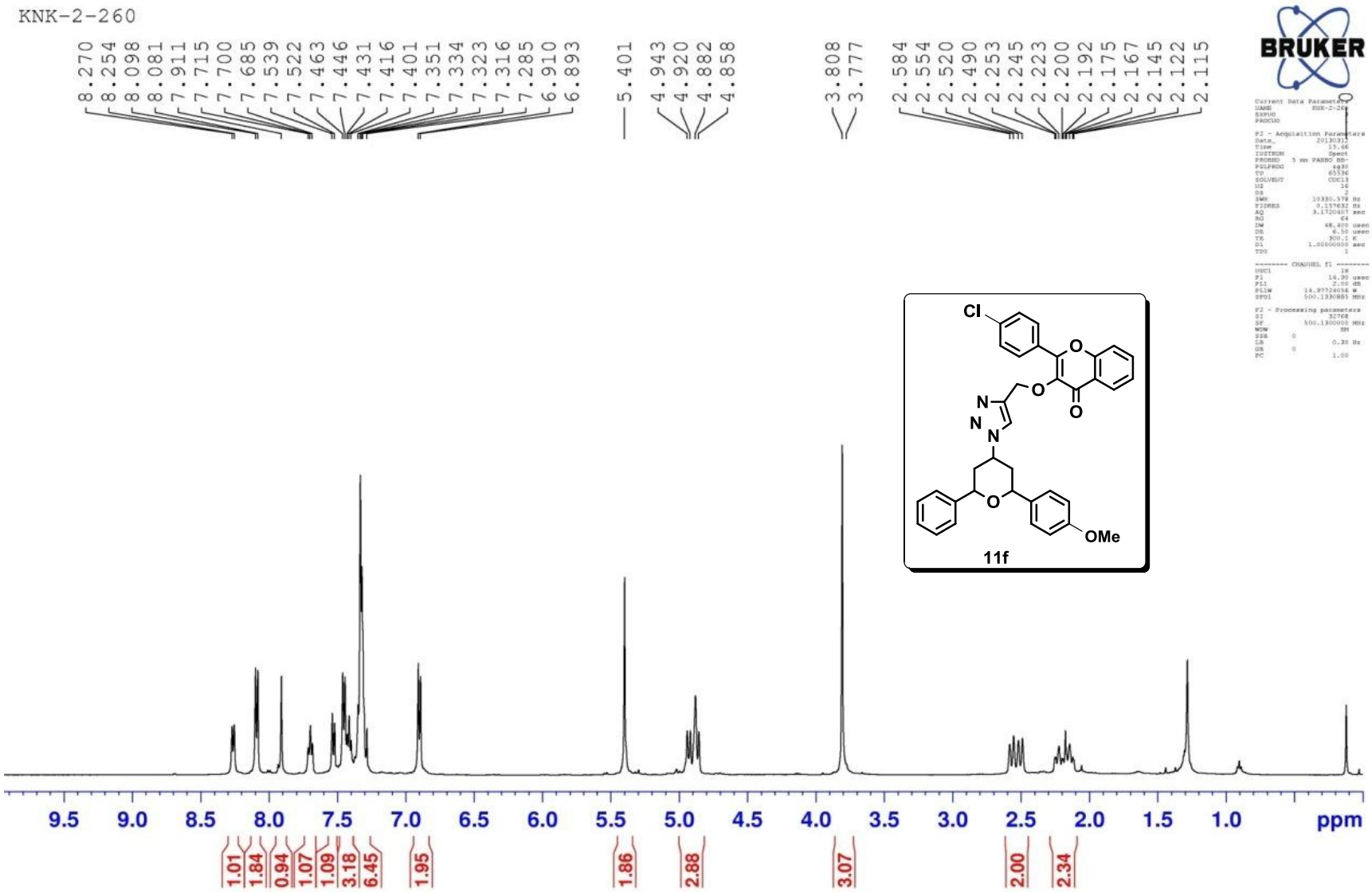


Figure S-52: ^{1}H NMR spectrum of compound 11f

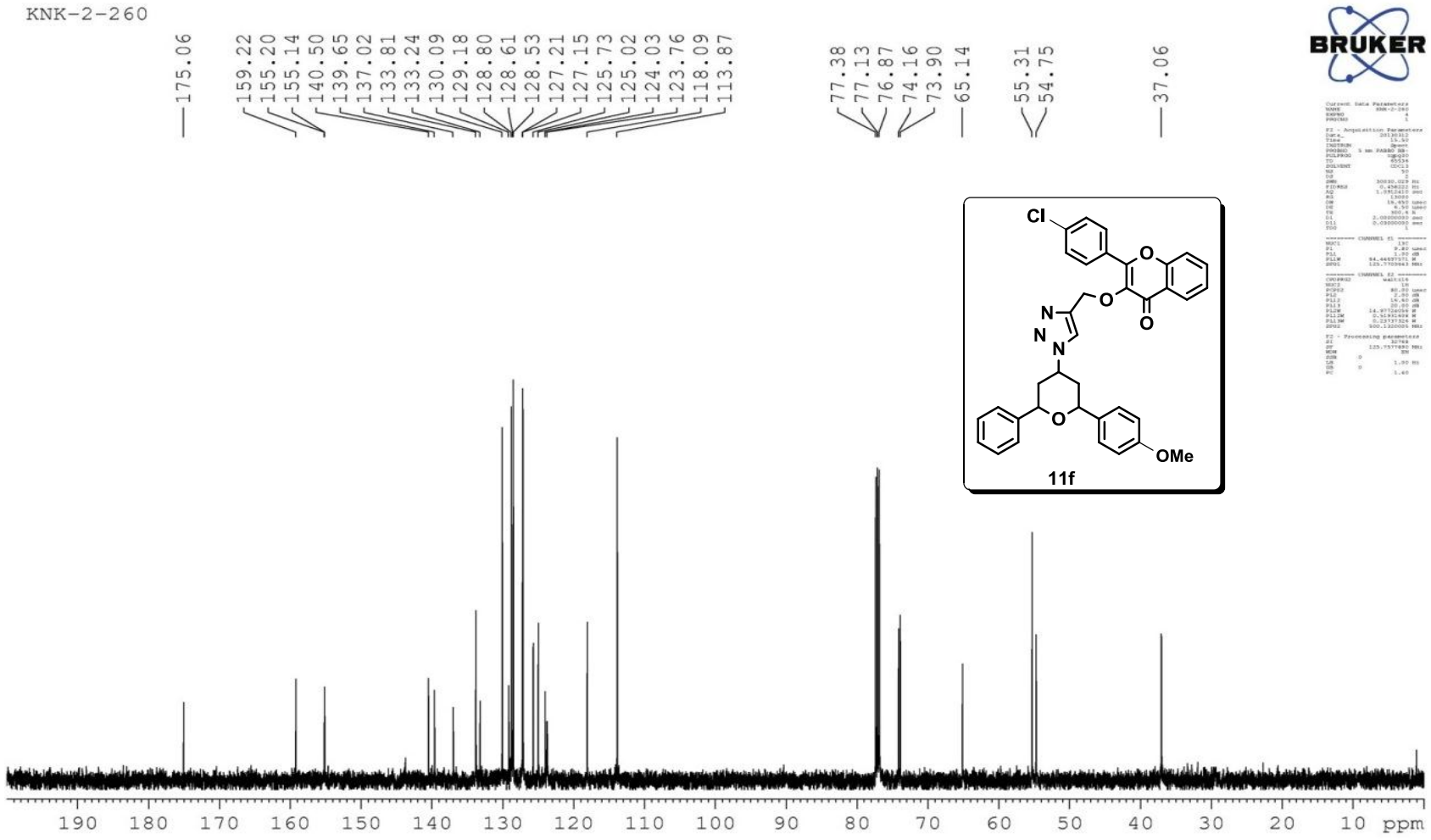


Figure S-53: ^{13}C NMR spectrum of compound 11f

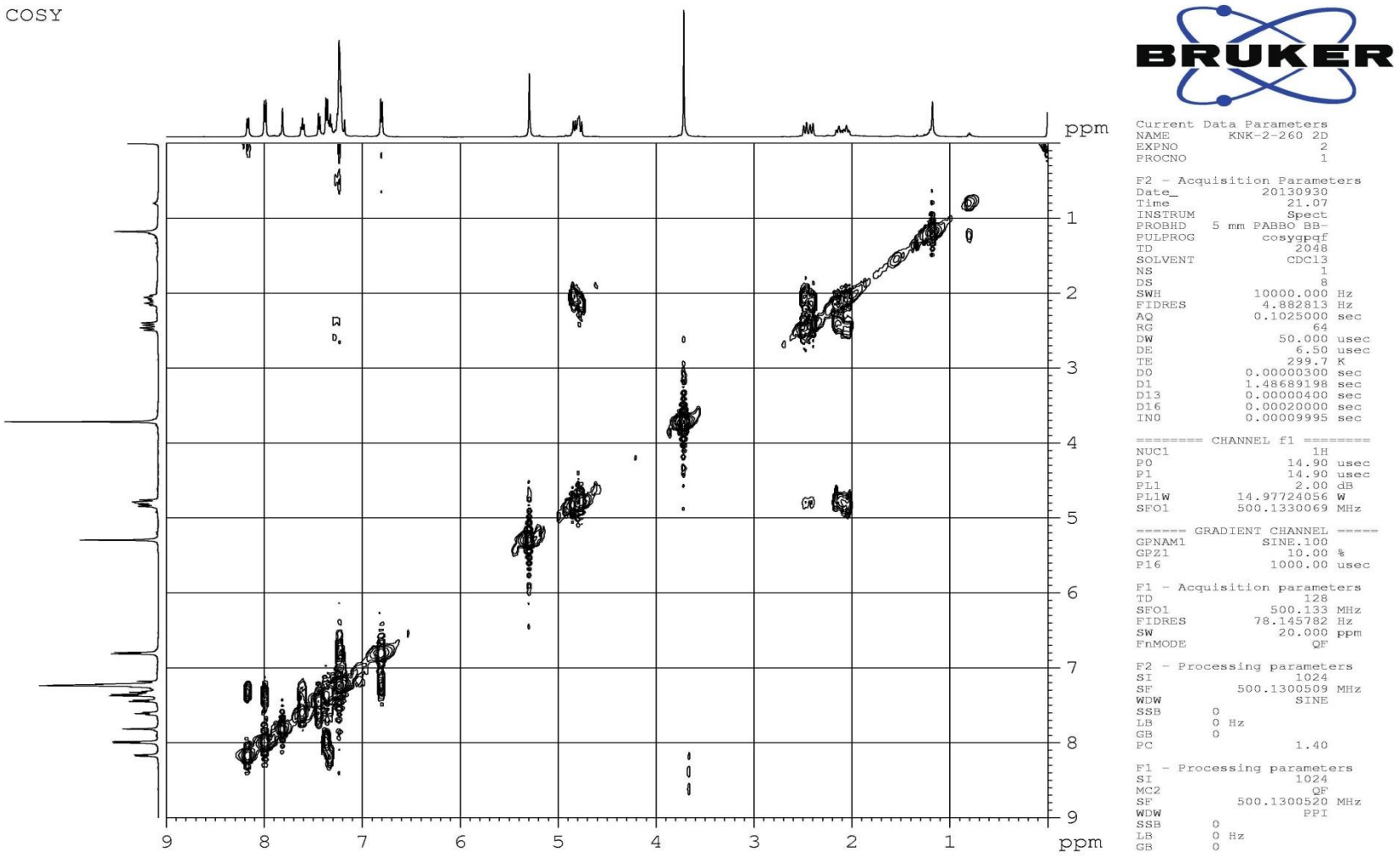


Figure S-54: ^{1}H-^{1}H COSEY NMR spectrum of compound 11f

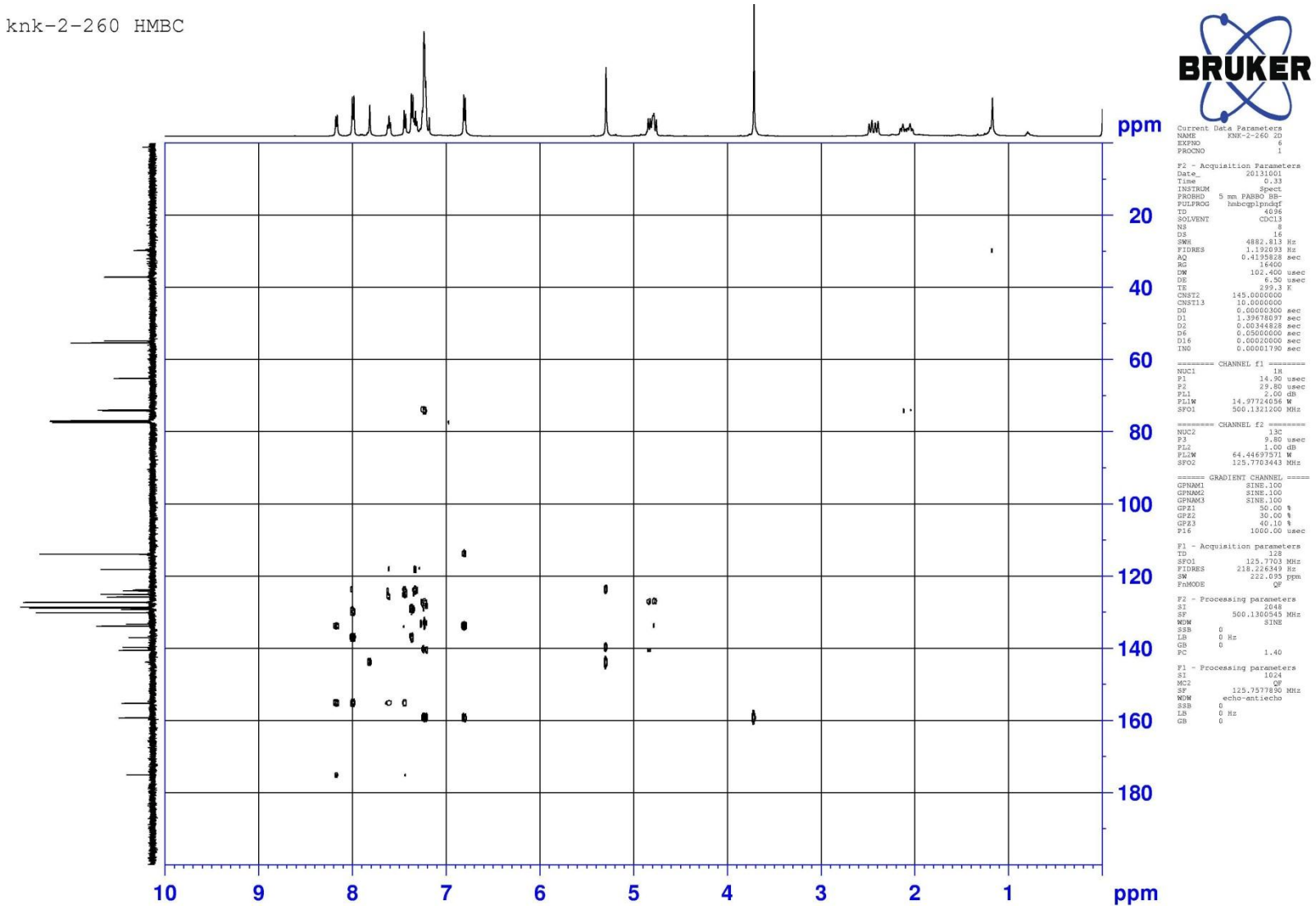


Figure S-55: HMBC NMR spectrum of compound 11f

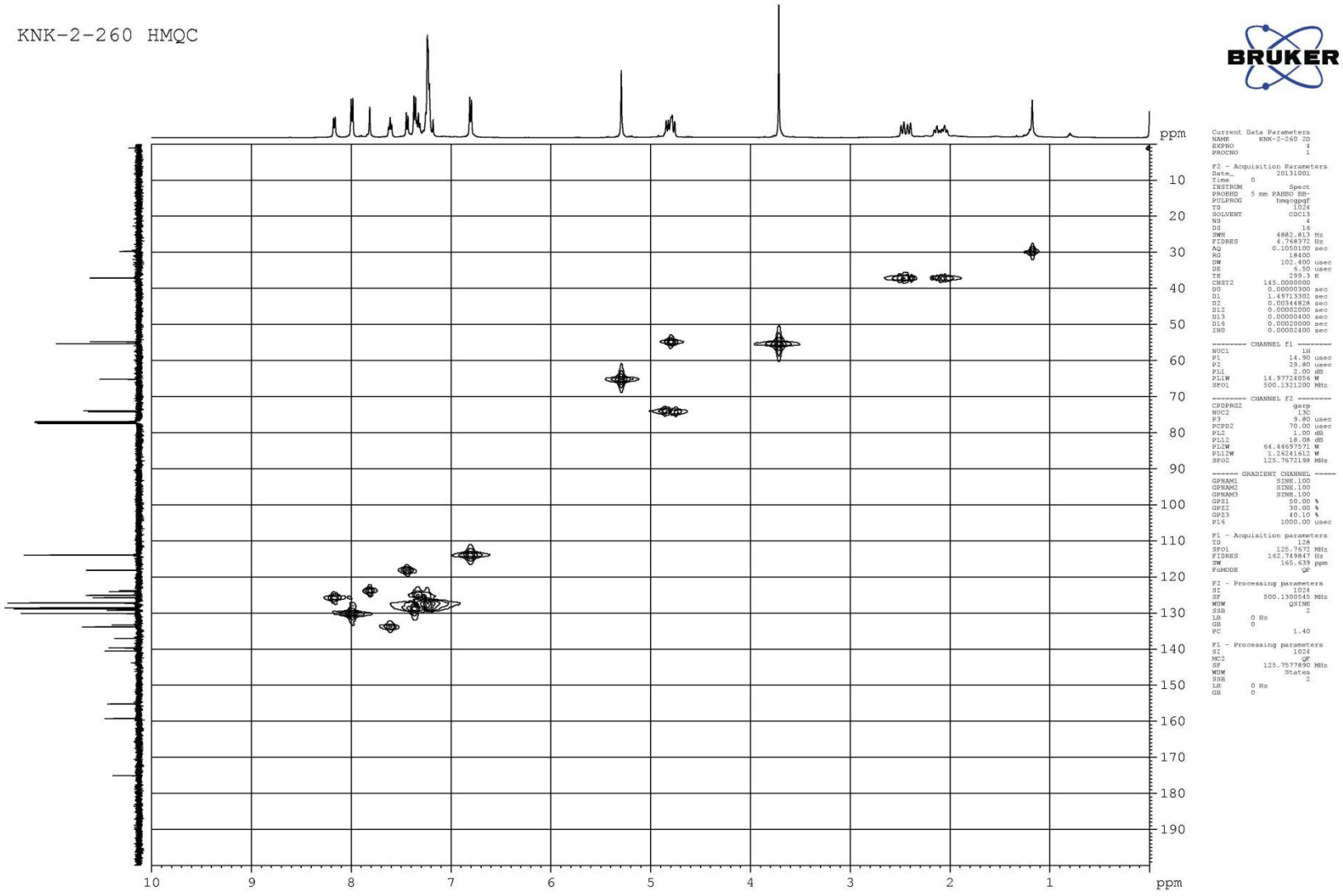


Figure S-56: HMQC NMR spectrum of compound 11f

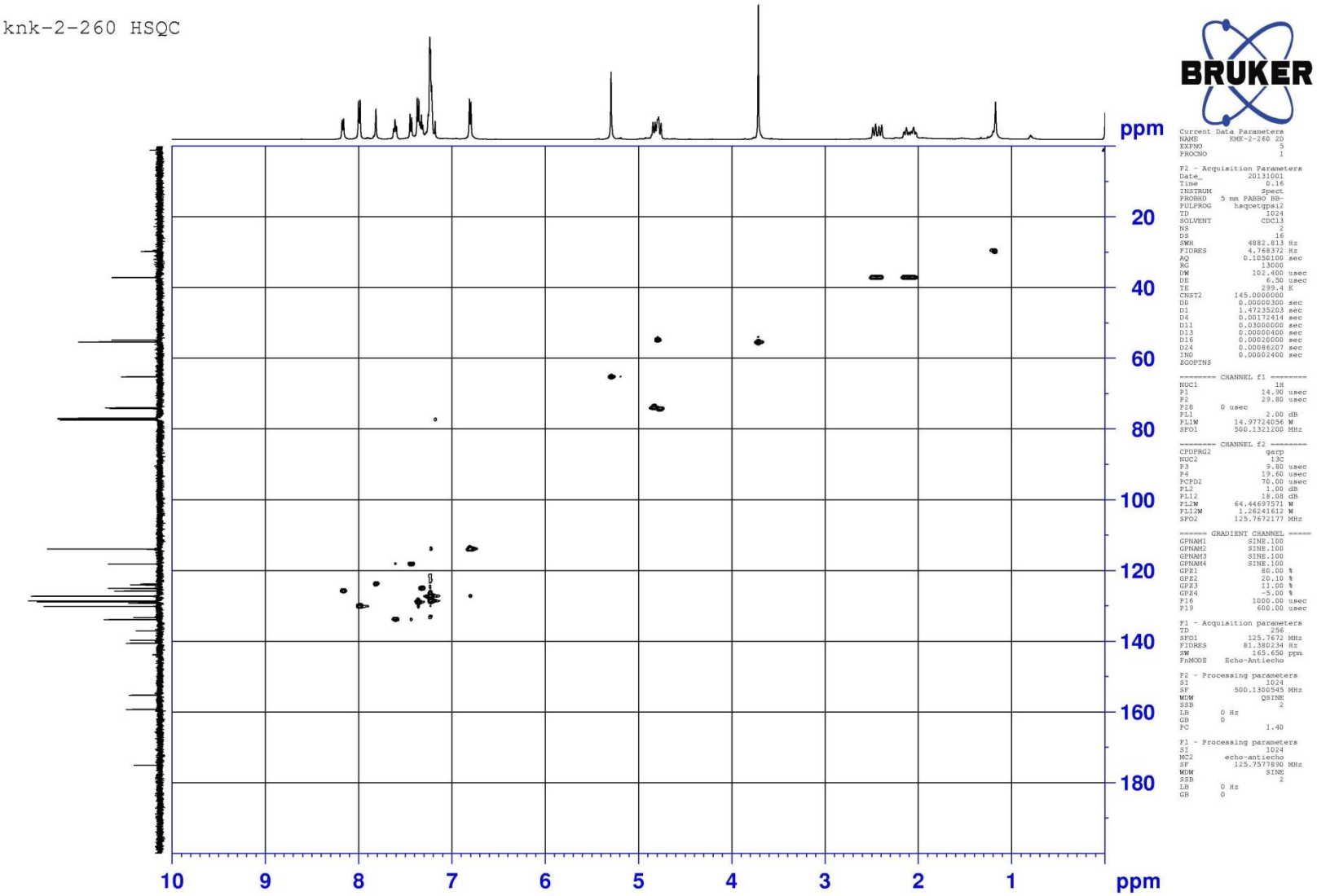


Figure S-57: HSQC NMR spectrum of compound 11f

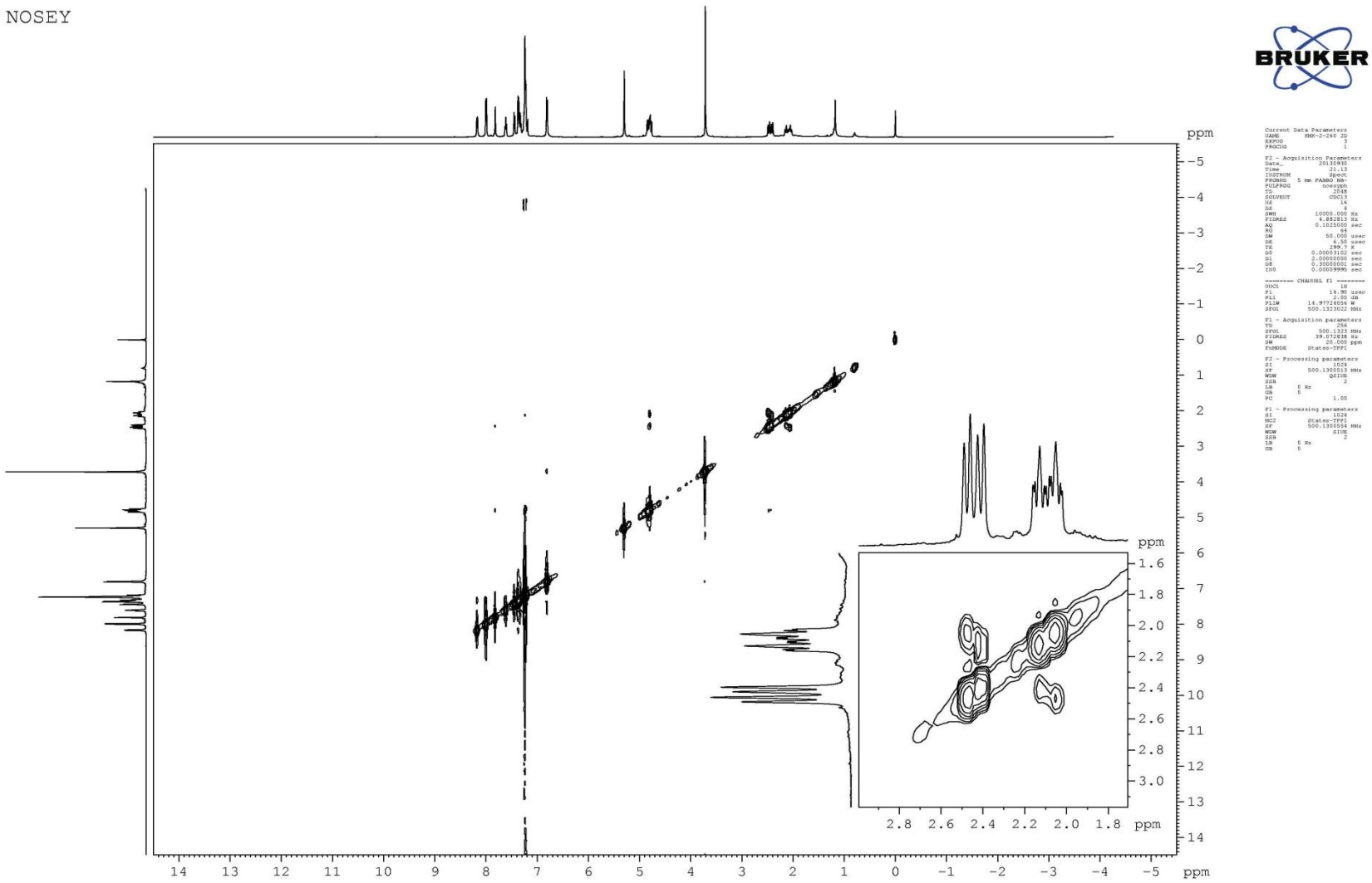


Figure S-58: NOESY NMR spectrum of compound 11f

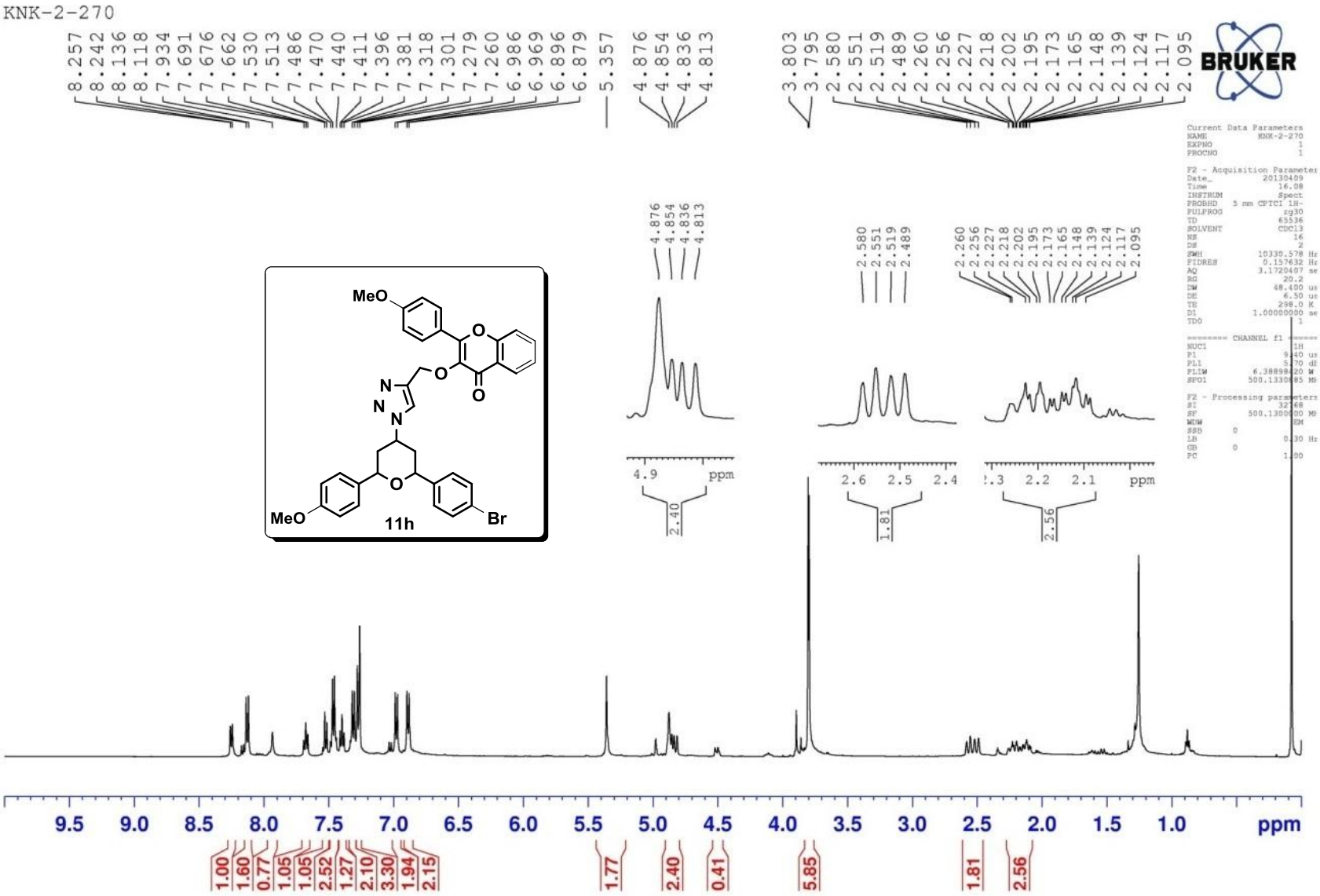


Figure S-59: ^{1}H NMR spectrum of compound 11h

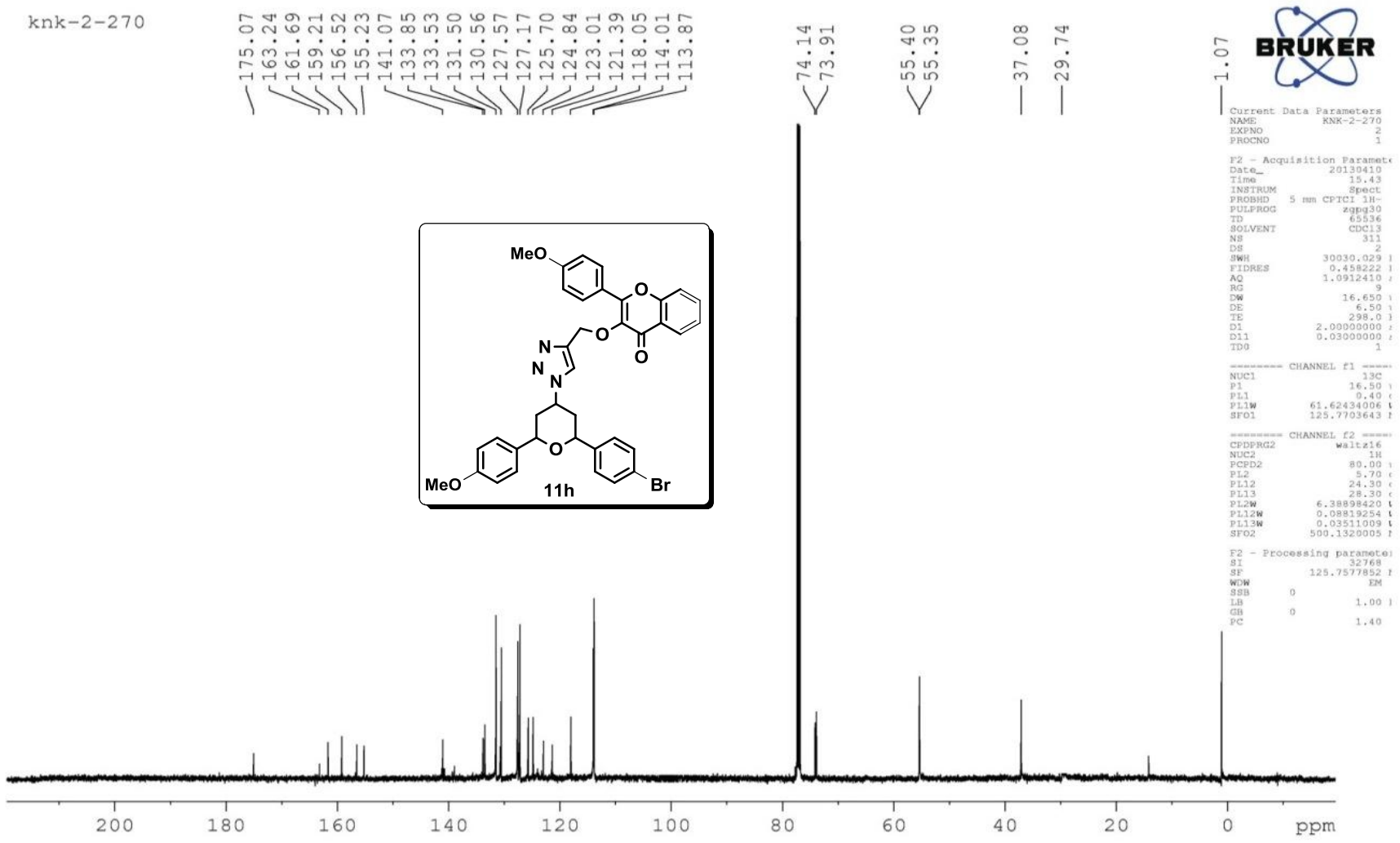


Figure S-60: ^{13}C NMR spectrum of compound 11h

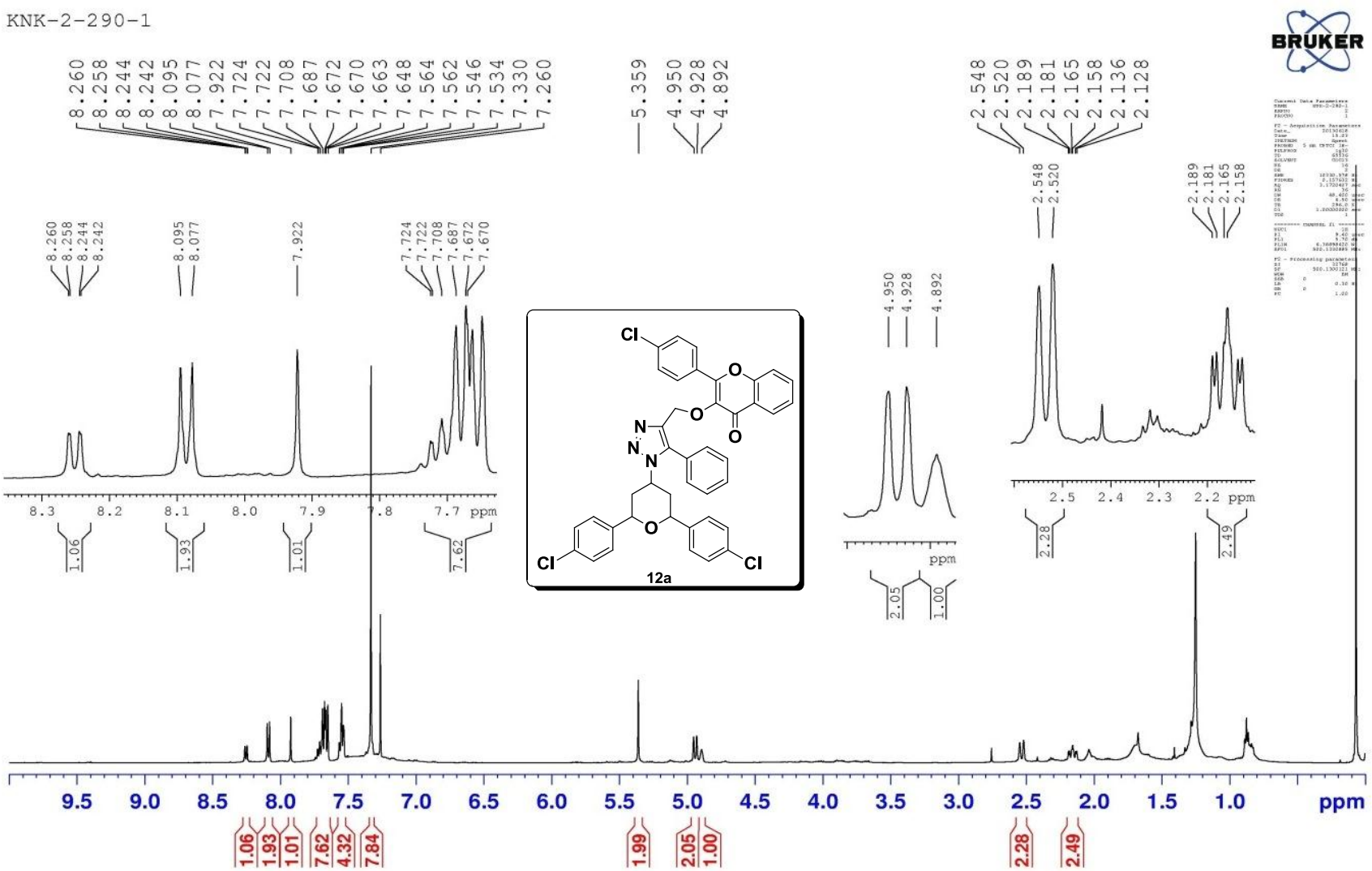


Figure S-61: ^{1}H NMR spectrum of compound 12a

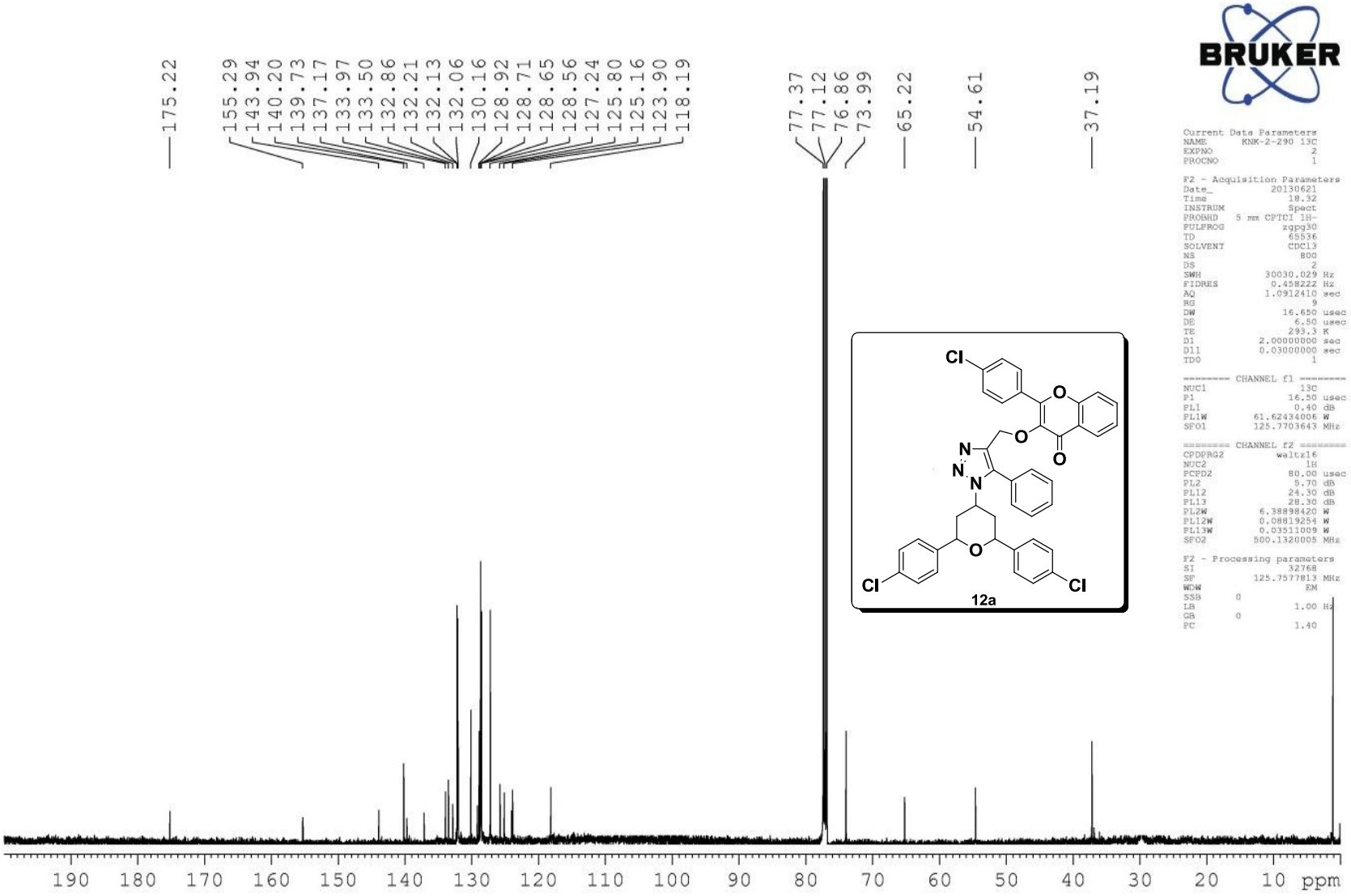


Figure S-62: ^{13}C NMR spectrum of compound 12a

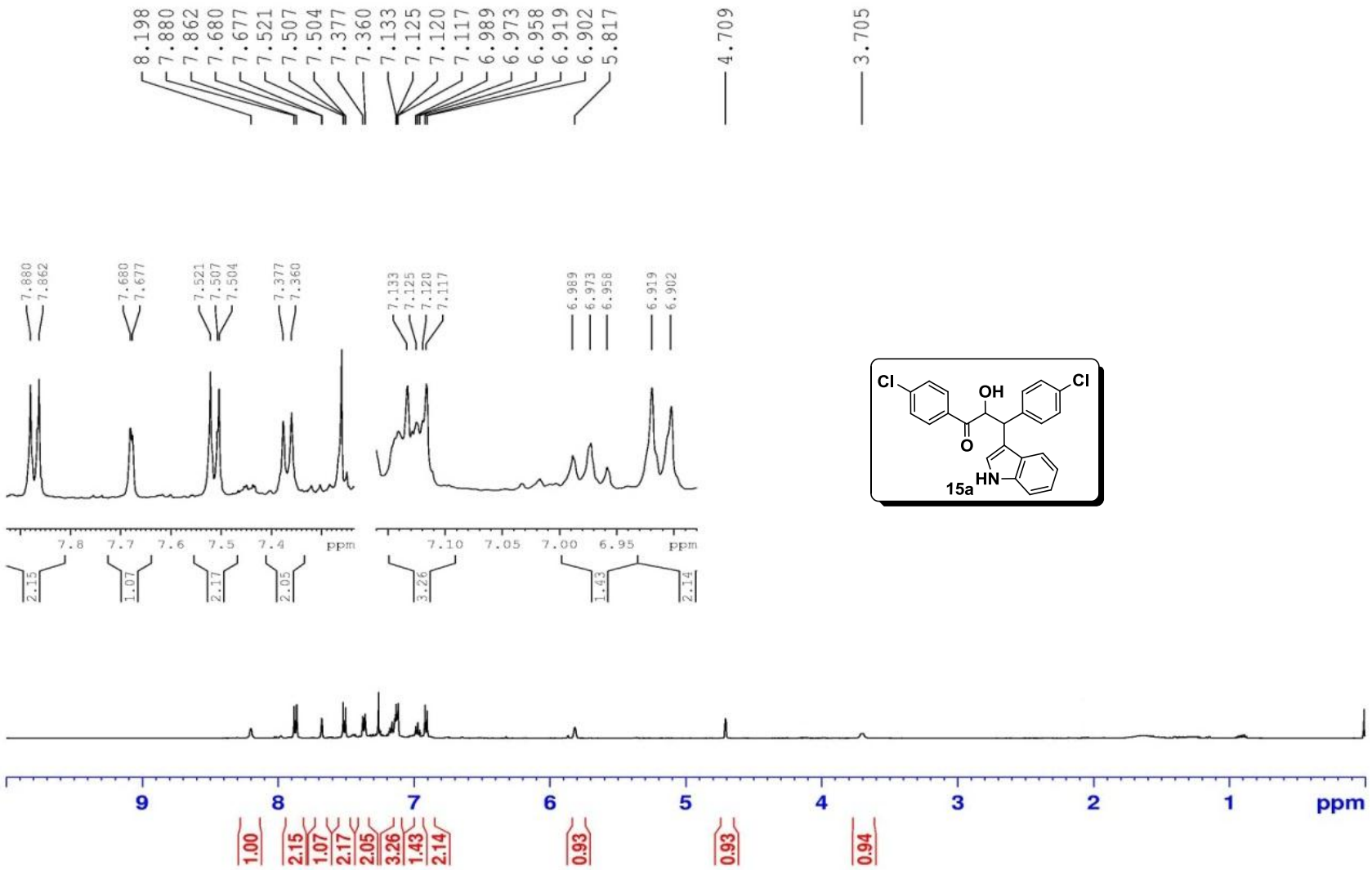


Figure S-63: ^{1}H NMR spectrum of compound 15a

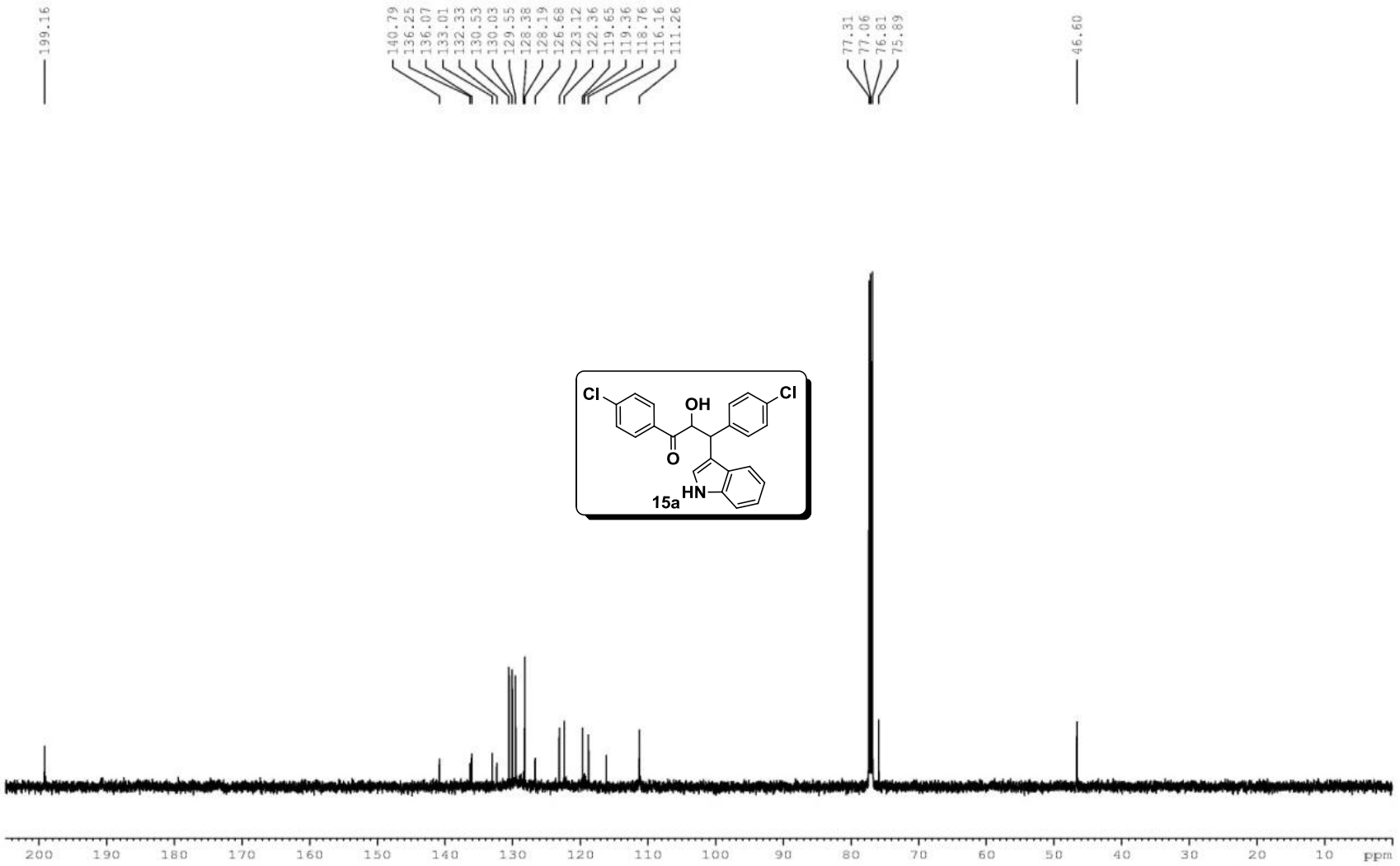


Figure S-64: ^{13}C NMR spectrum of compound 15a

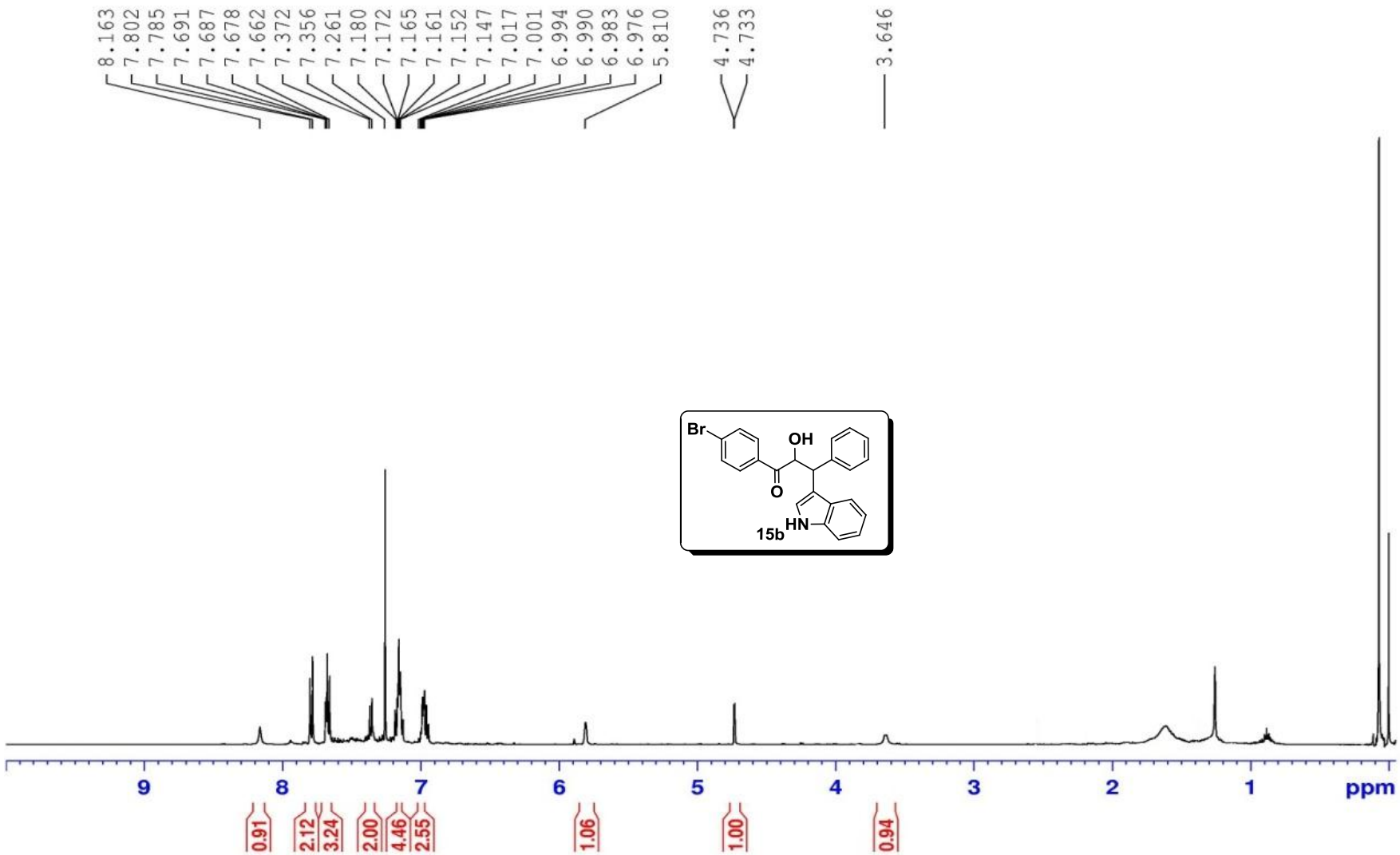


Figure S-65: ^{1}H NMR spectrum of compound 15b

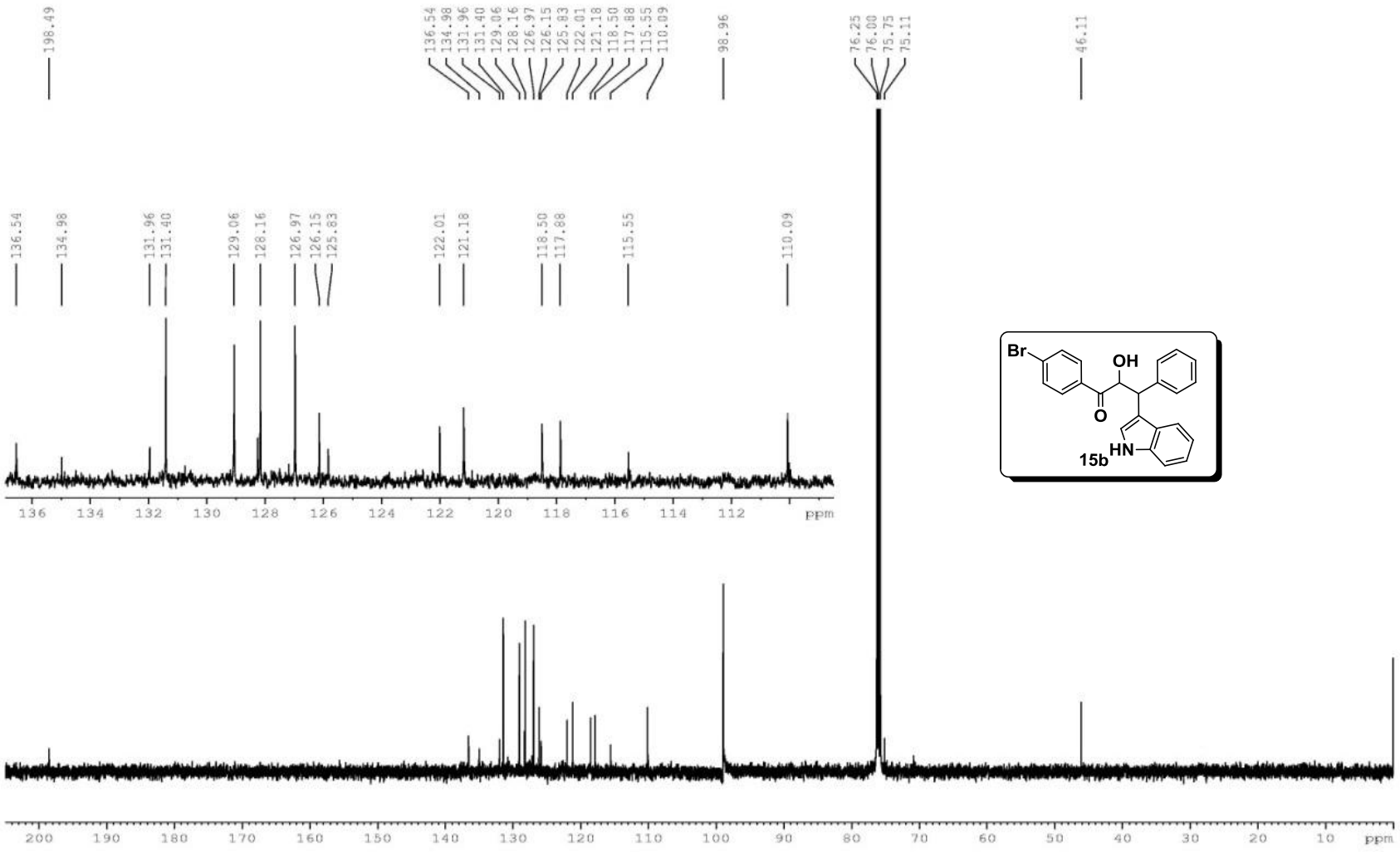


Figure S-66: ^{13}C NMR spectrum of compound 15b

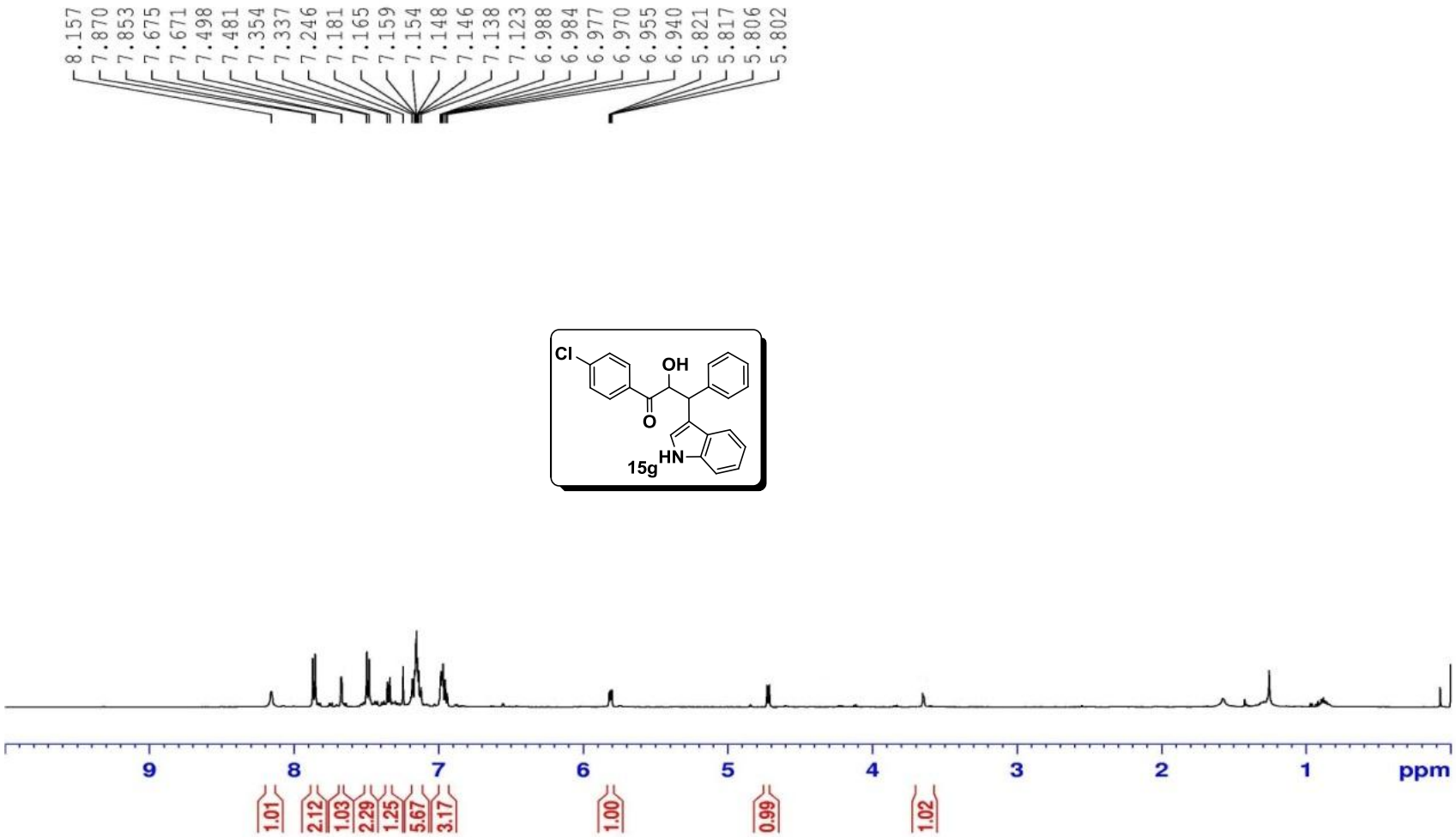


Figure S-67: ^{1}H NMR spectrum of compound 15g

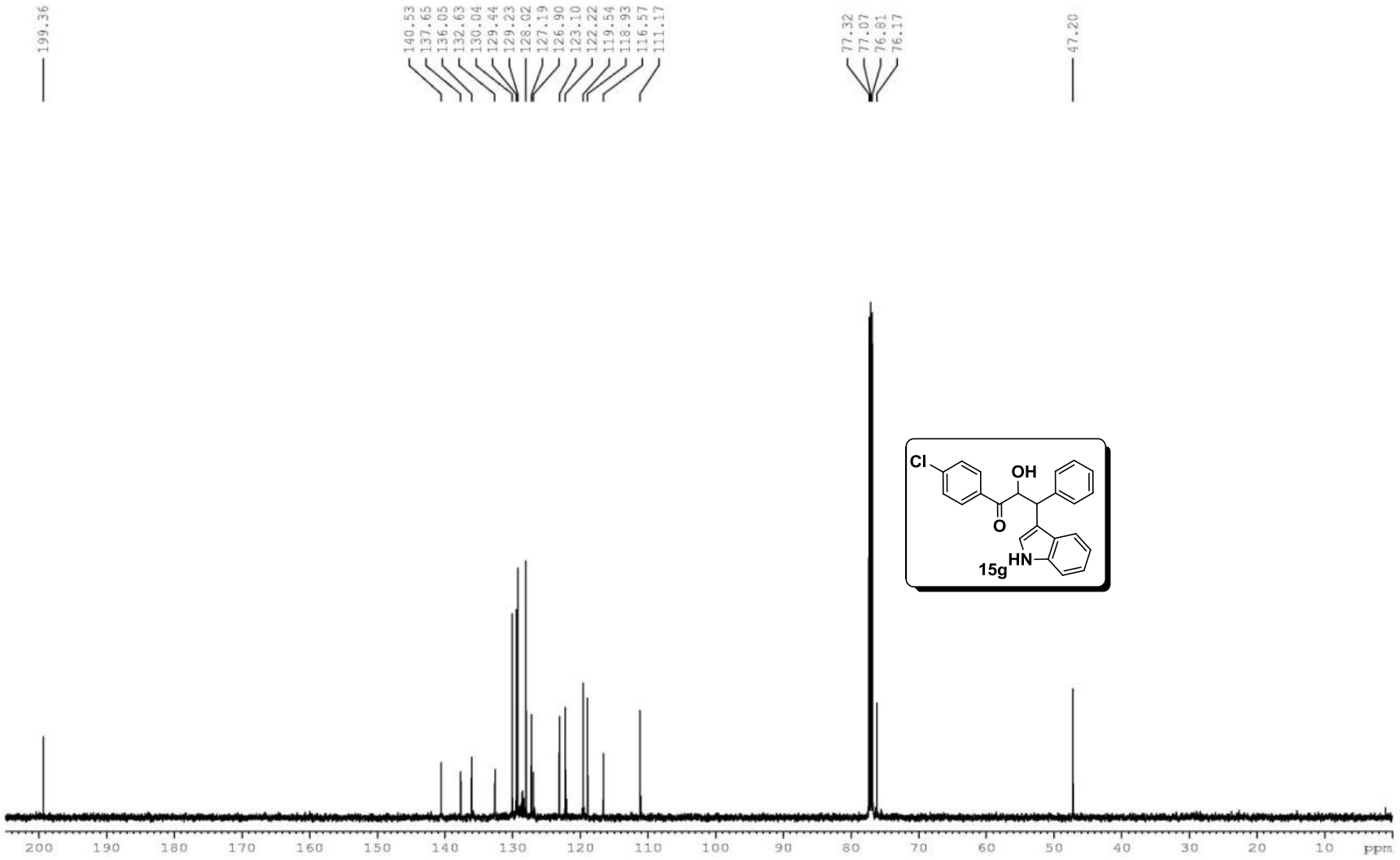


Figure S-68: ^{13}C NMR spectrum of compound 15g

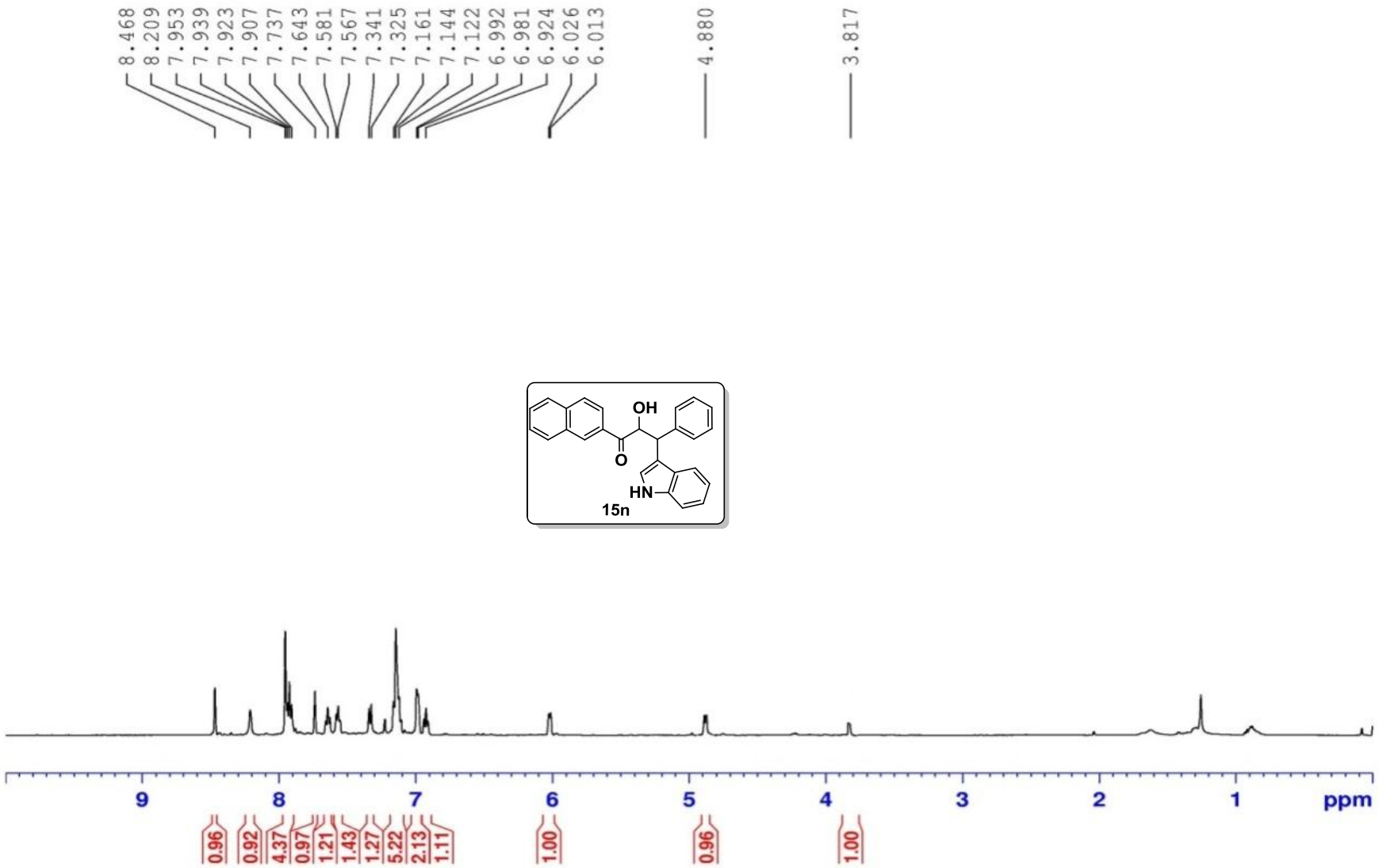


Figure S-69: ^{1}H NMR spectrum of compound 15n

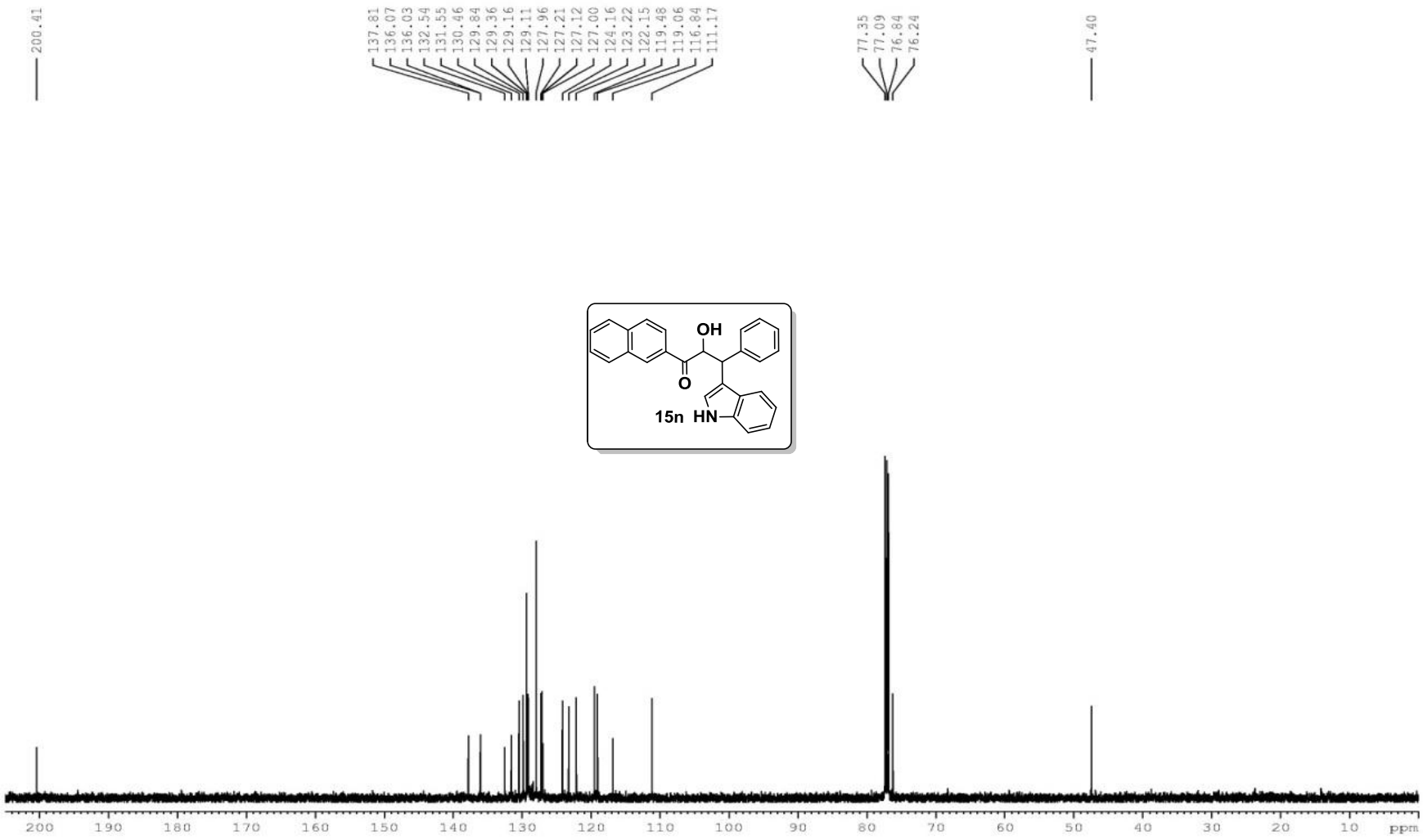


Figure S-70: ^{13}C NMR spectrum of compound 15n

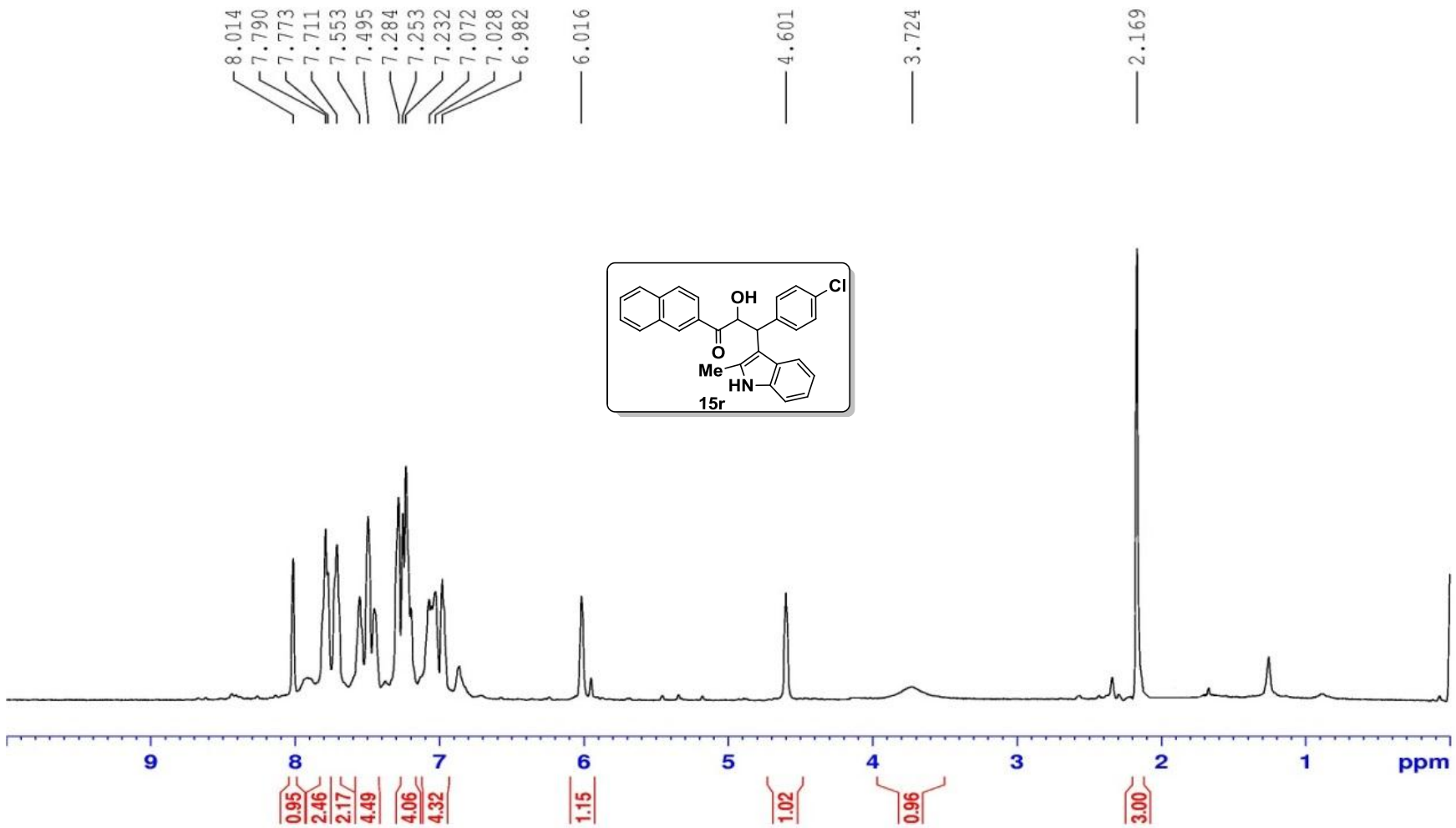


Figure S-71: ^{1}H NMR spectrum of compound 15r

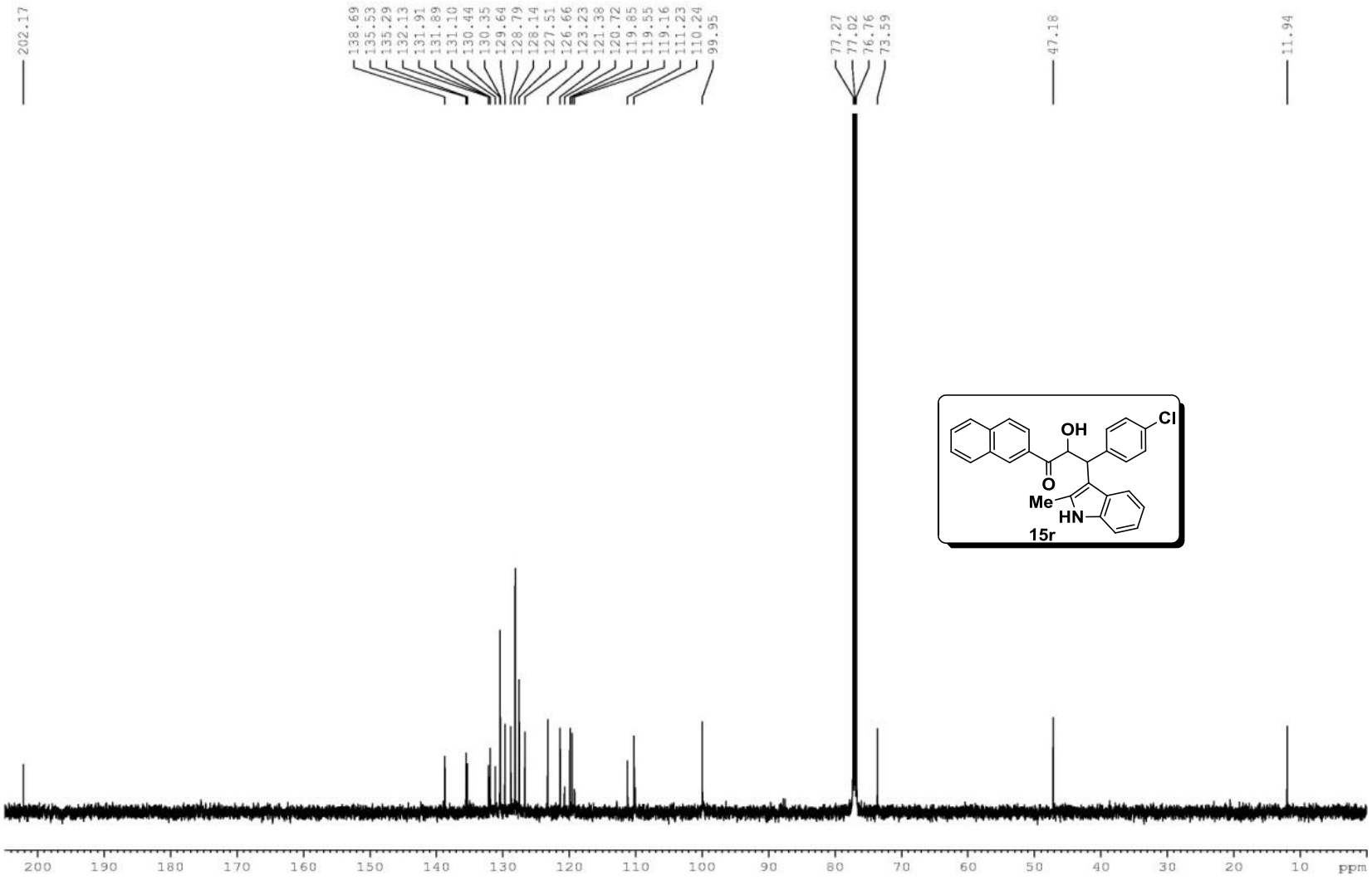


Figure S-72: ^{13}C NMR spectrum of compound 15r

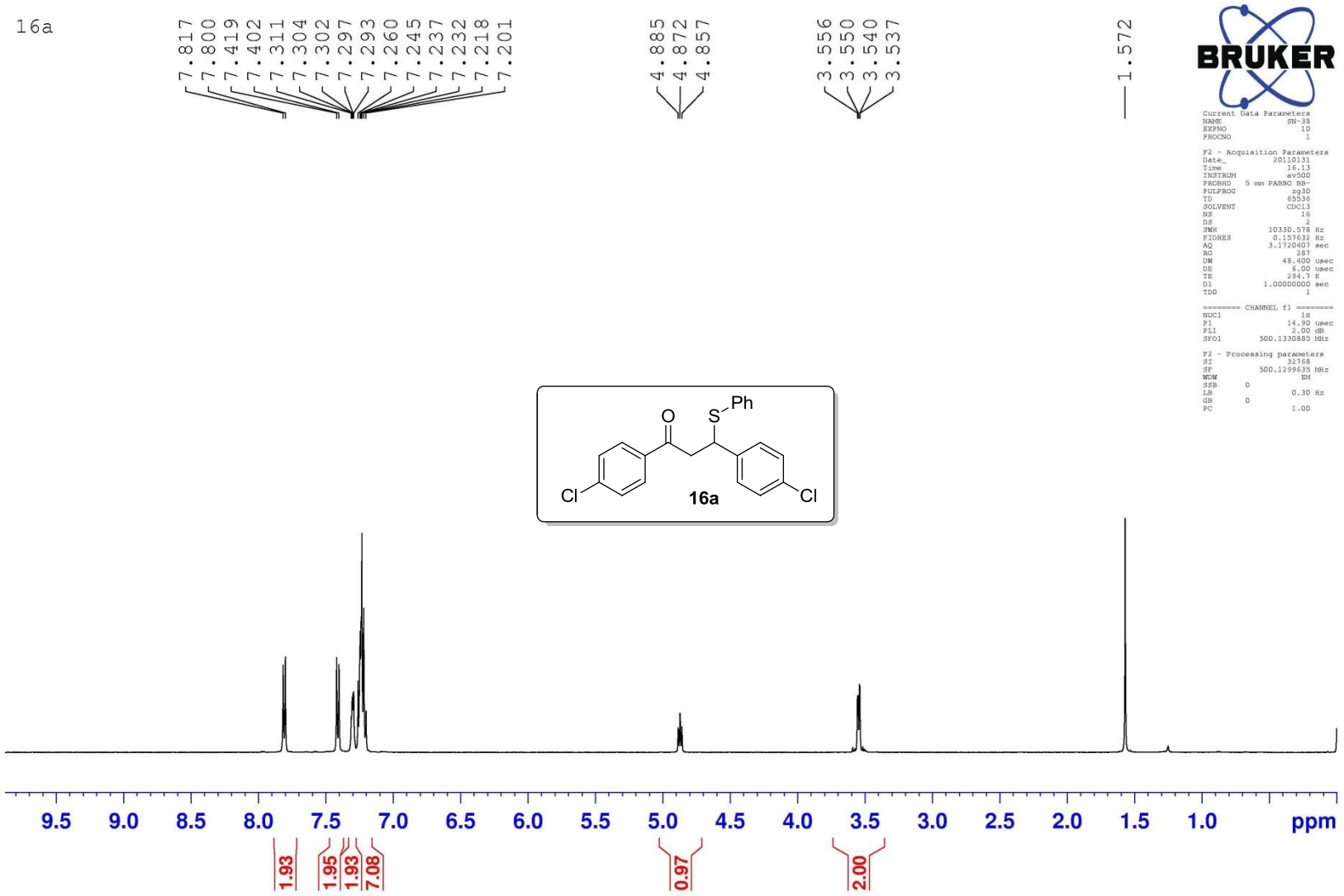


Figure S-73: ^{1}H NMR spectrum of compound 16a

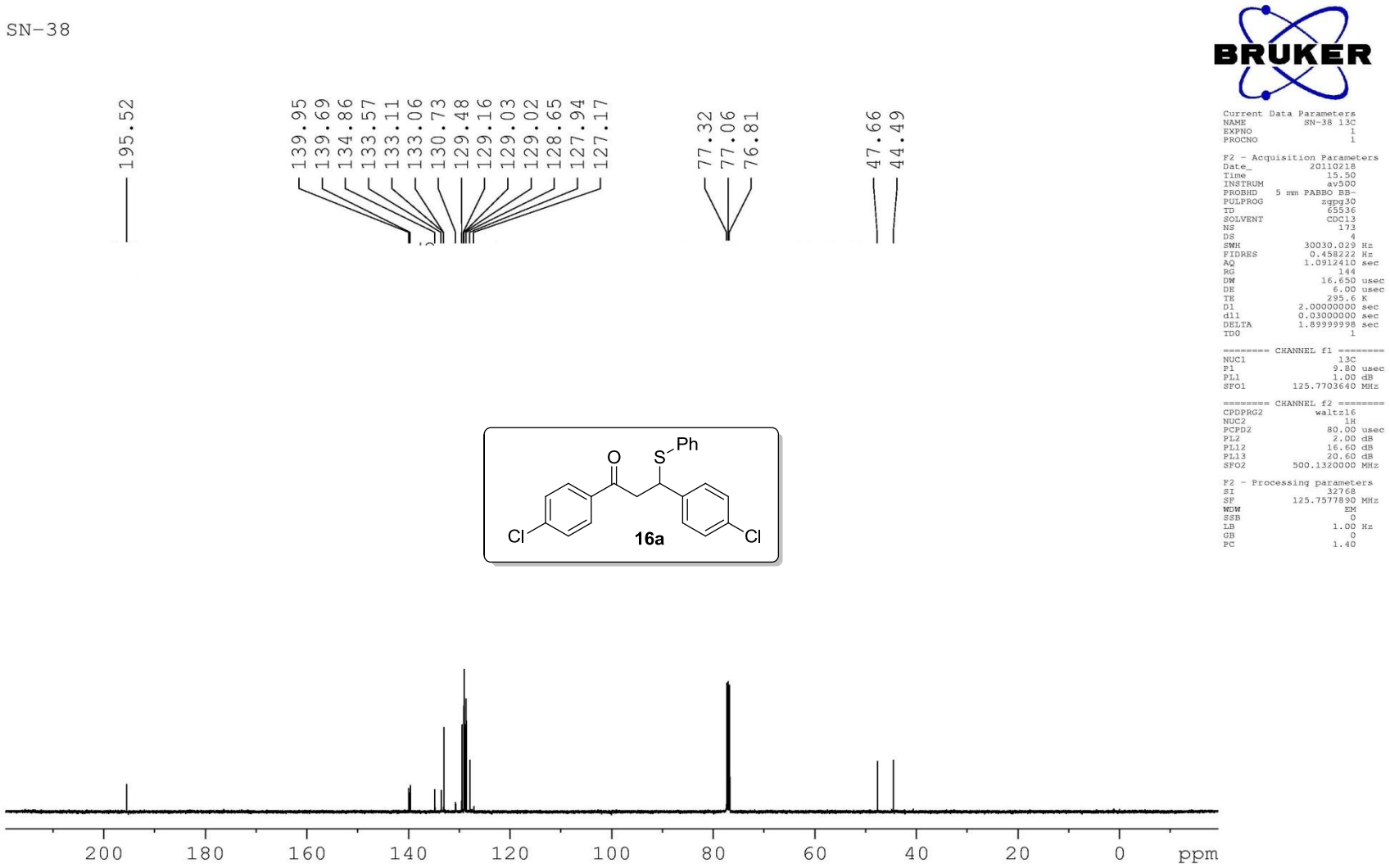


Figure S-74: ^{13}C NMR spectrum of compound 16a

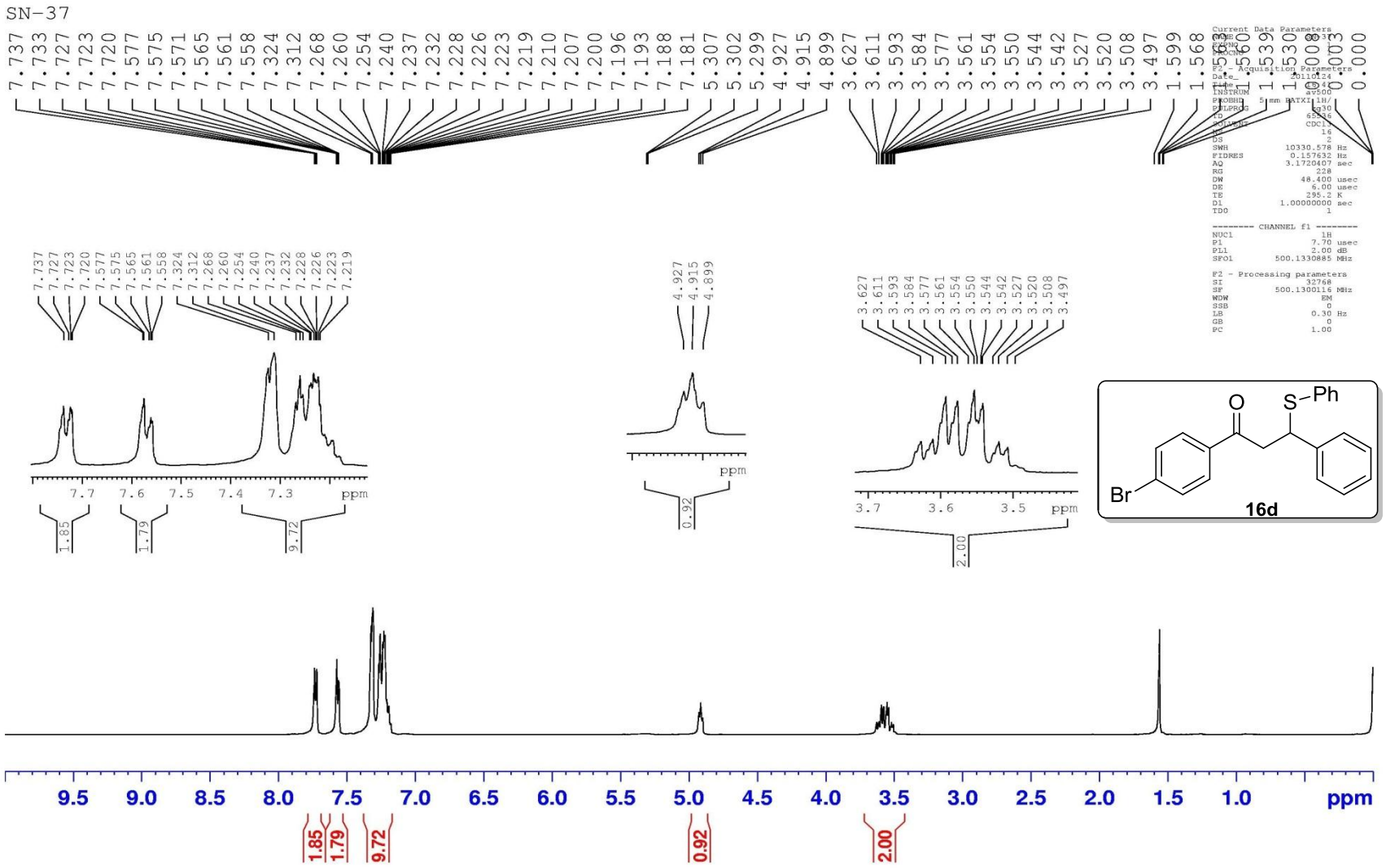


Figure S-75: ^{1}H NMR spectrum of compound 16d

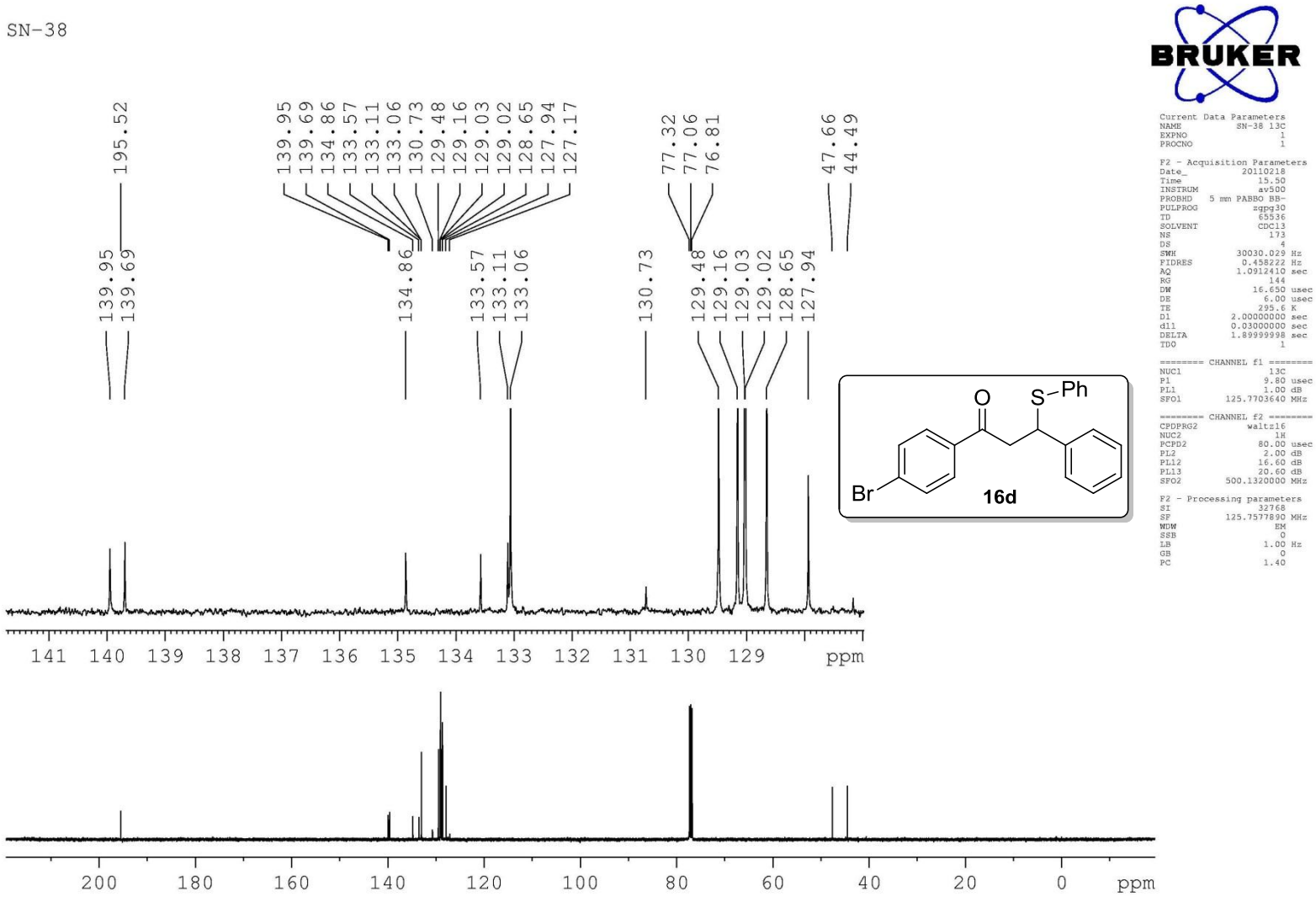


Figure S-76: ^{13}C NMR spectrum of compound 16d

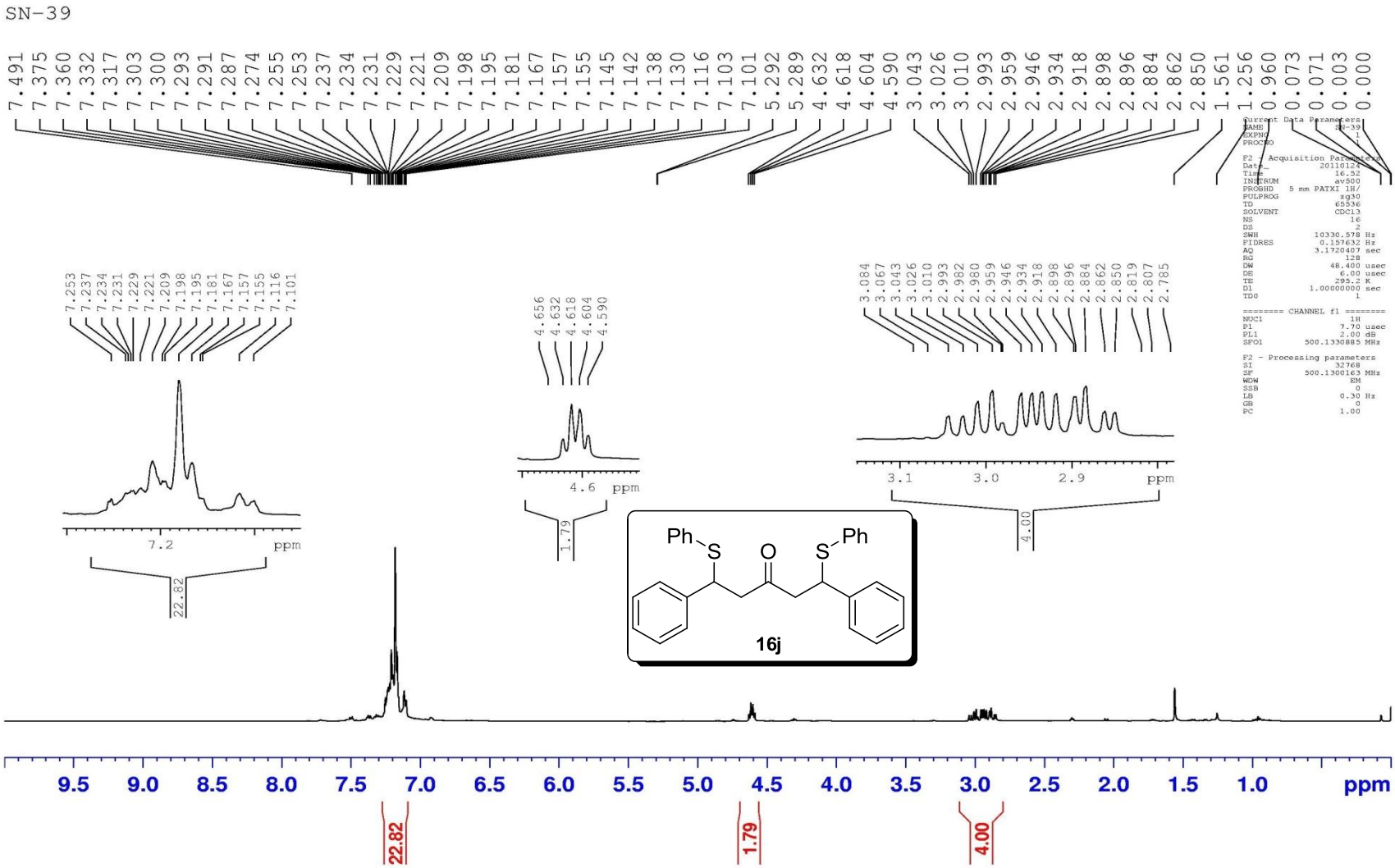
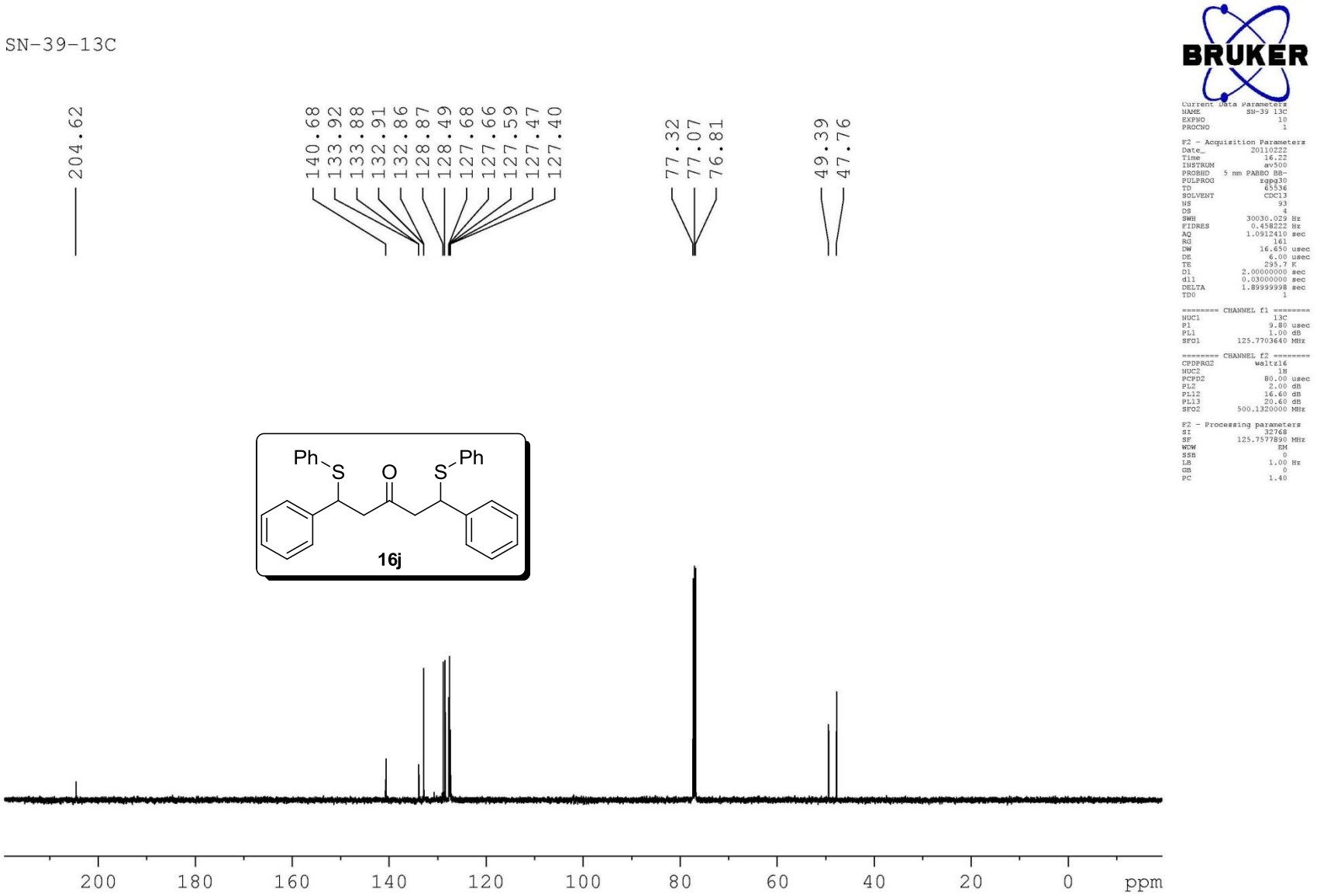


Figure S-77: ^{1}H NMR spectrum of compound 16j



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PROCNO 1

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SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912410 sec
RG 161
DW 16.650 usec
DE 6.00 usec
TE 295.7 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1

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P1 9.80 usec
PL1 1.00 dB
SFO1 125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 16.60 dB
PL13 20.60 dB
SFO2 500.1320000 MHz

F2 - Processing parameters
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WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Figure S-78: ^{13}C NMR spectrum of compound 16j

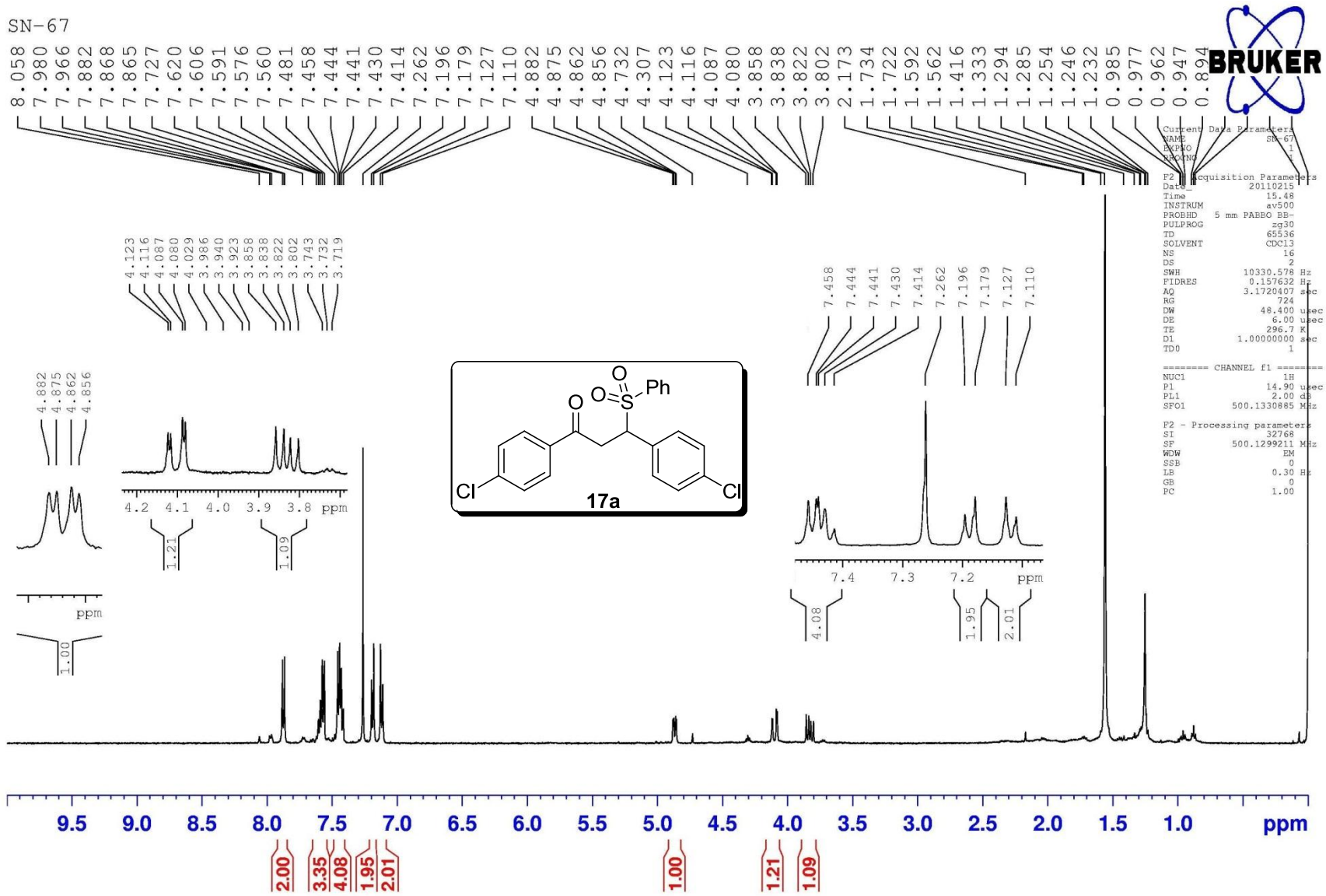


Figure S-79: ^{1}H NMR spectrum of compound 17a

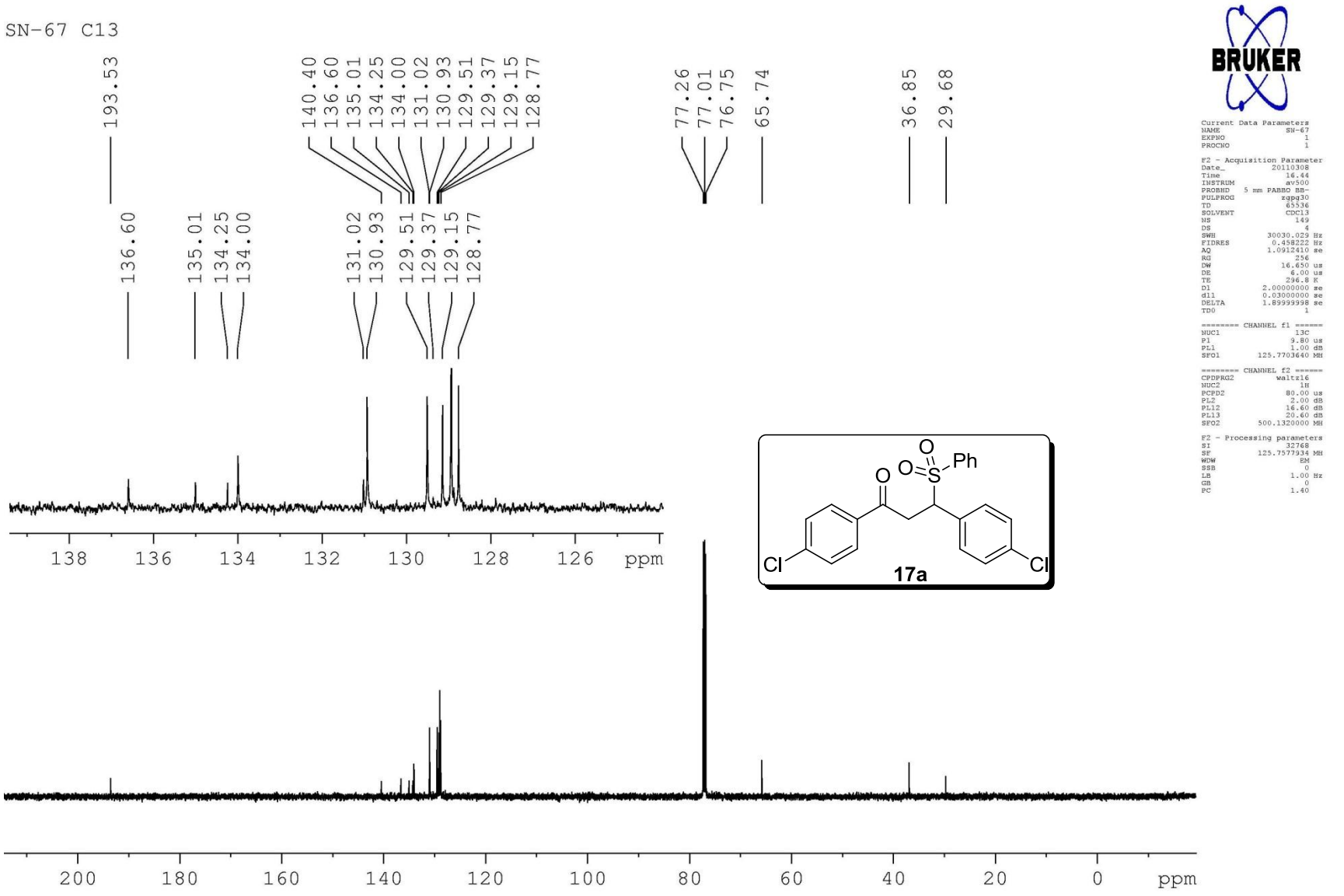


Figure S-80: ^{13}C NMR spectrum of compound 17a

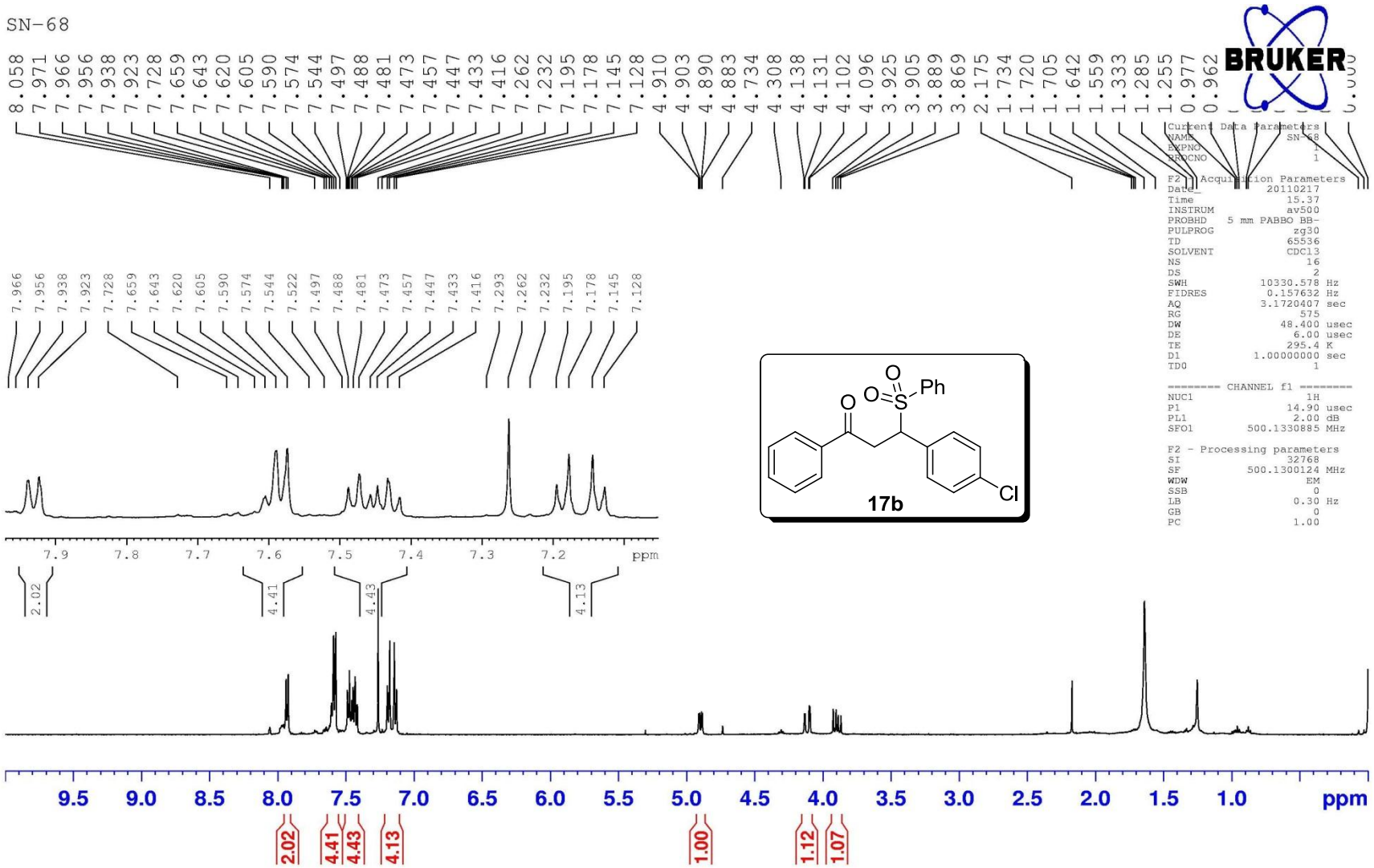


Figure S-81: ^{1}H NMR spectrum of compound 17b

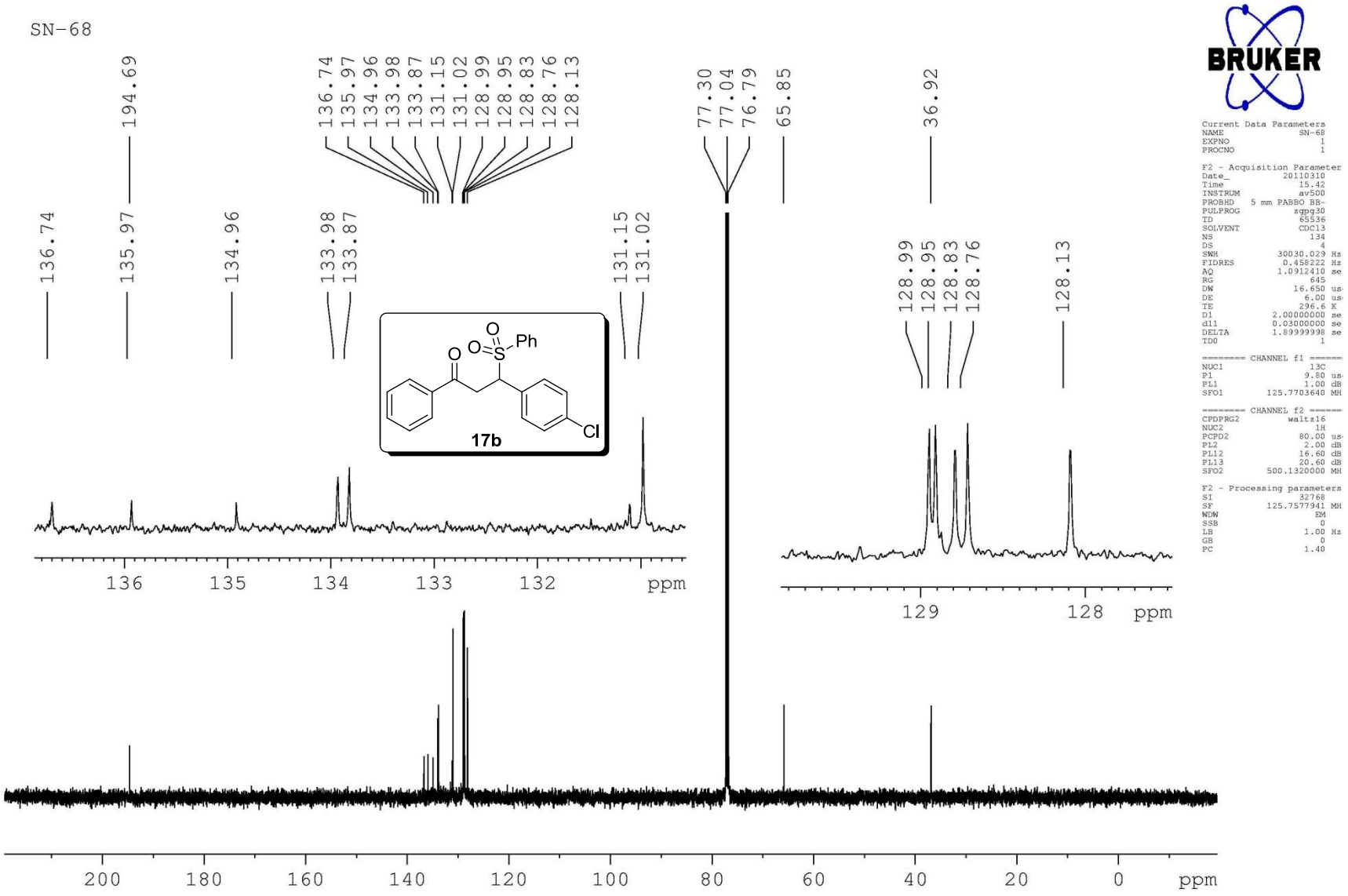


Figure S-82: ^{13}C NMR spectrum of compound 17b

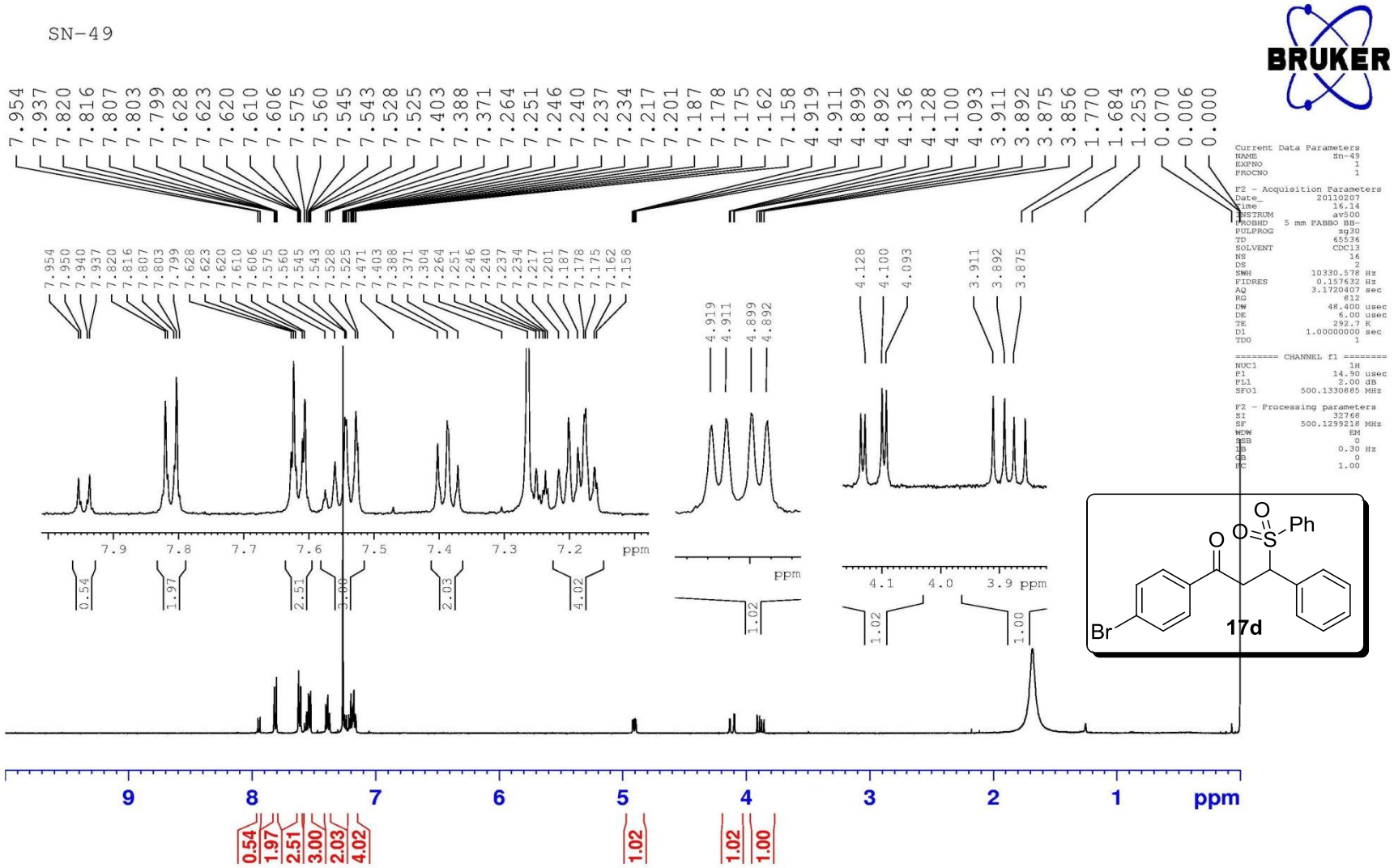


Figure S-83: ^{1}H NMR spectrum of compound 17d

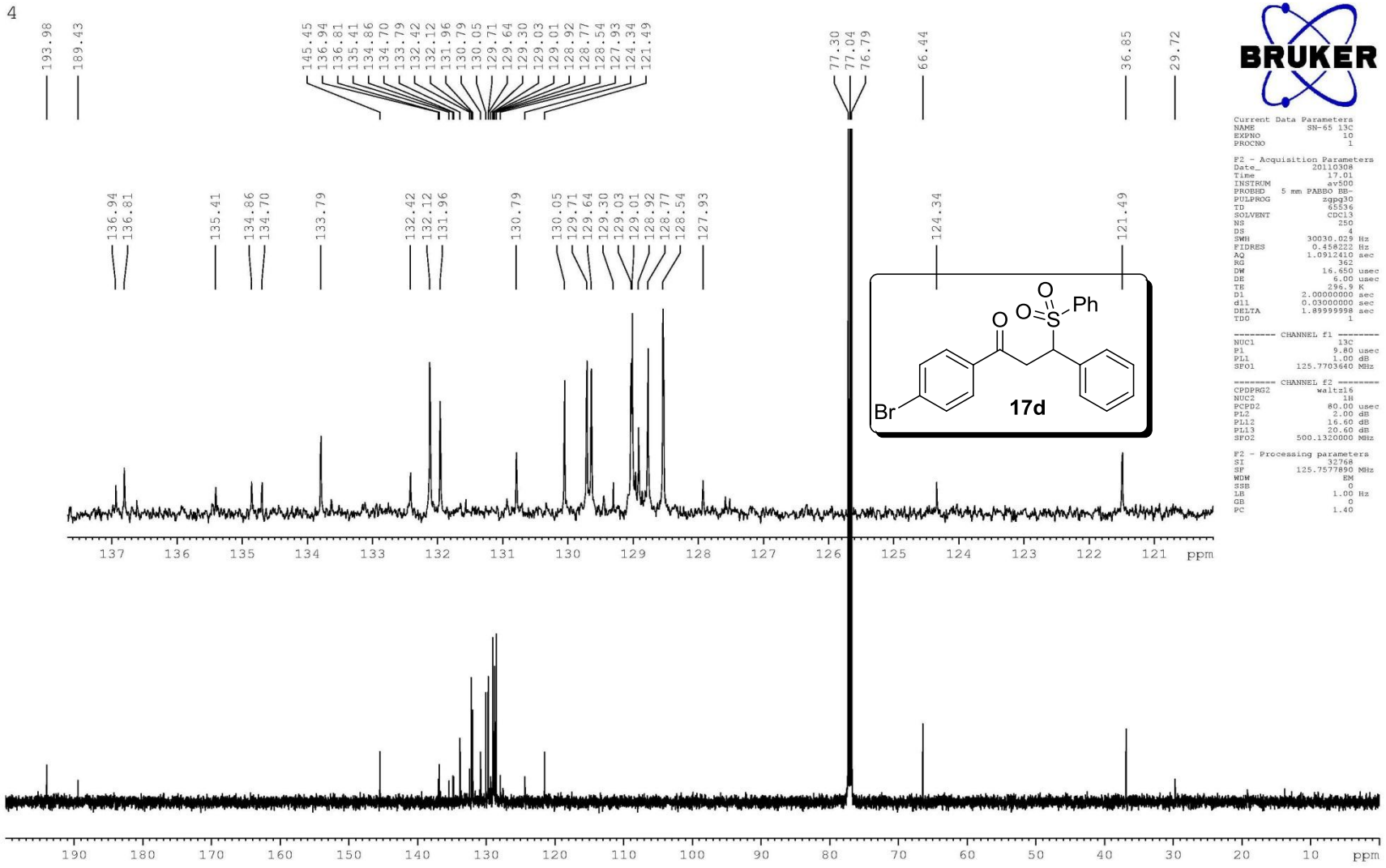


Figure S-84: ^{13}C NMR spectrum of compound 17d

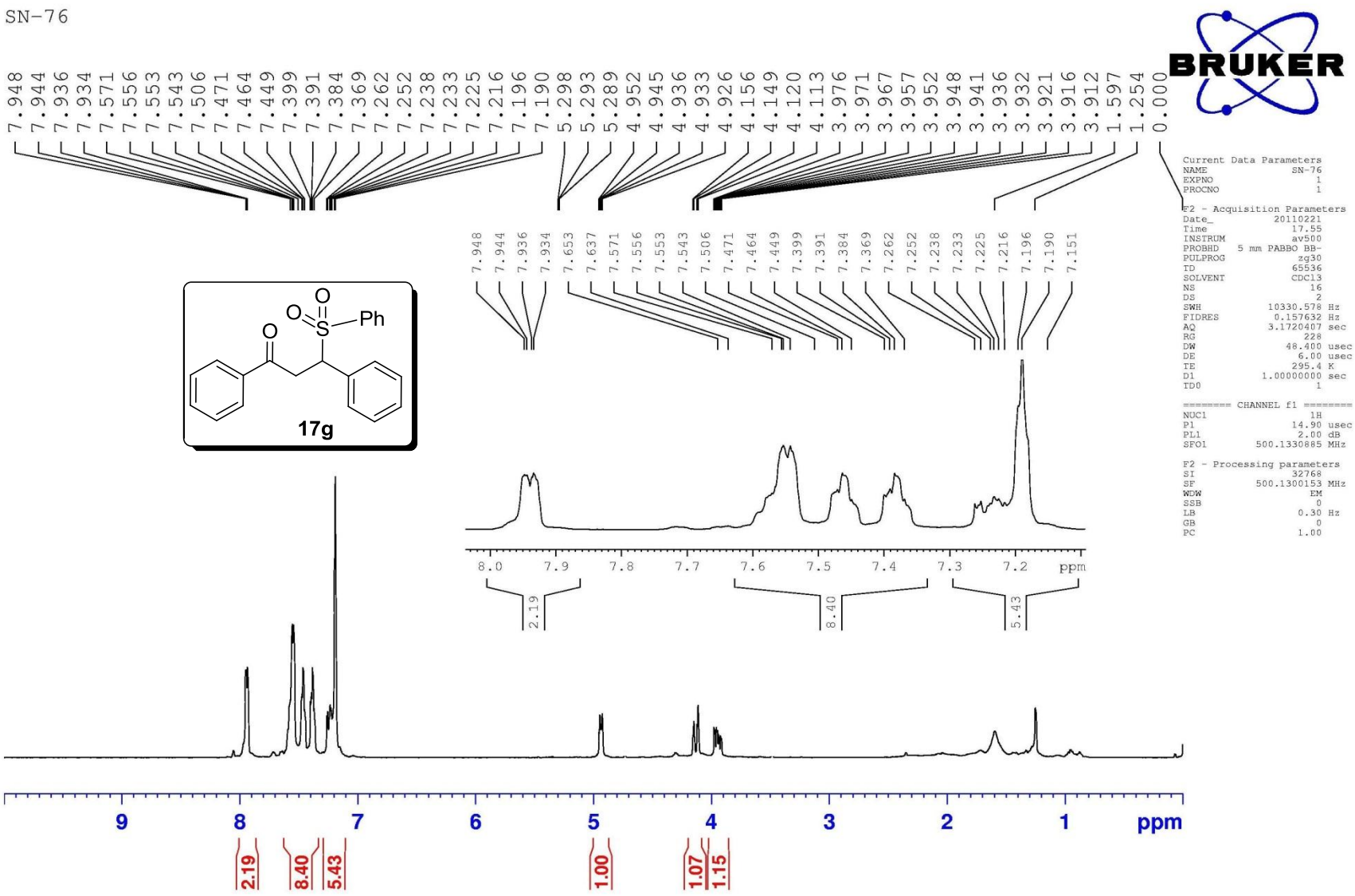


Figure S-85: ^{1}H NMR spectrum of compound 17g

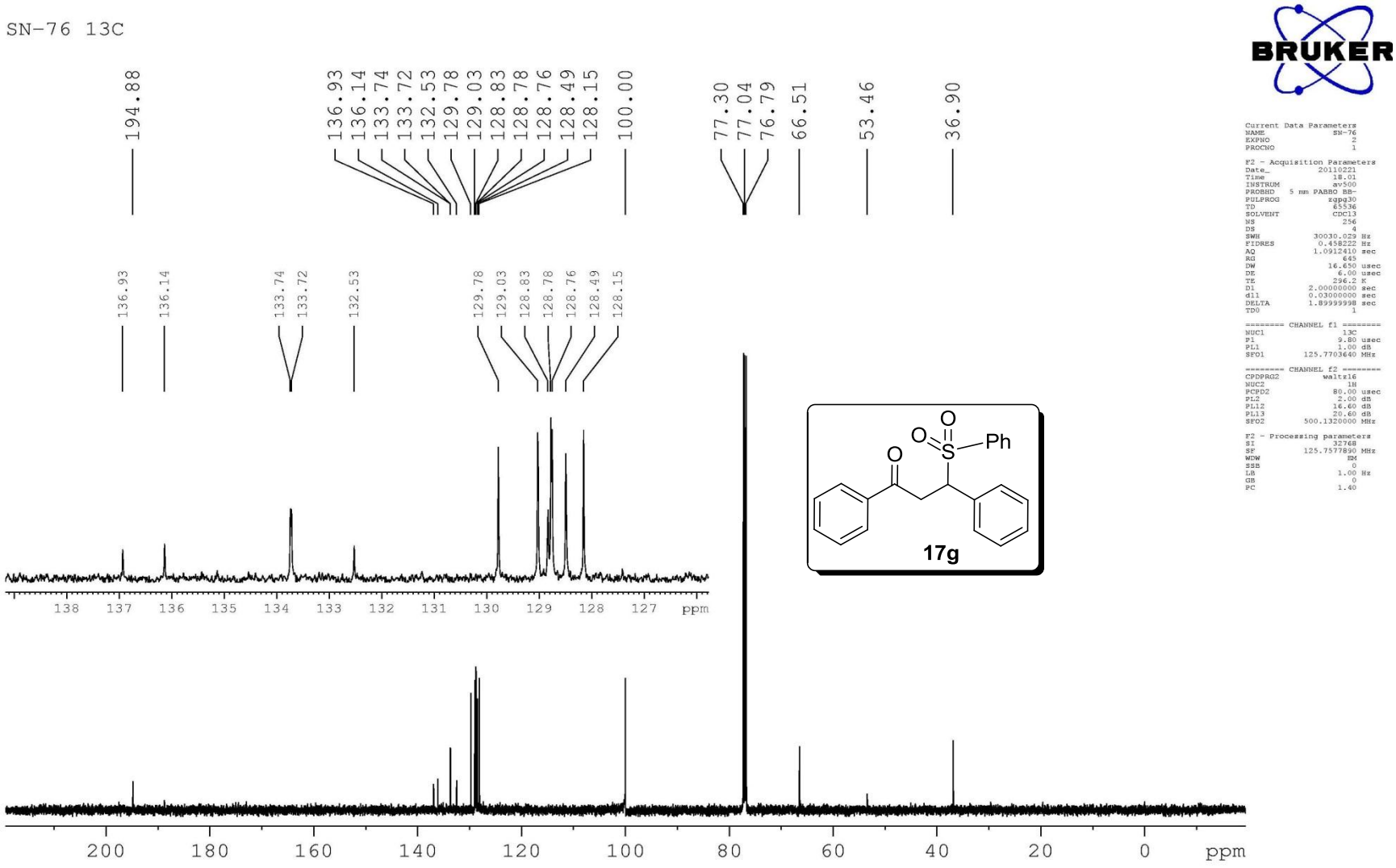


Figure S-86: ^{13}C NMR spectrum of compound 17g

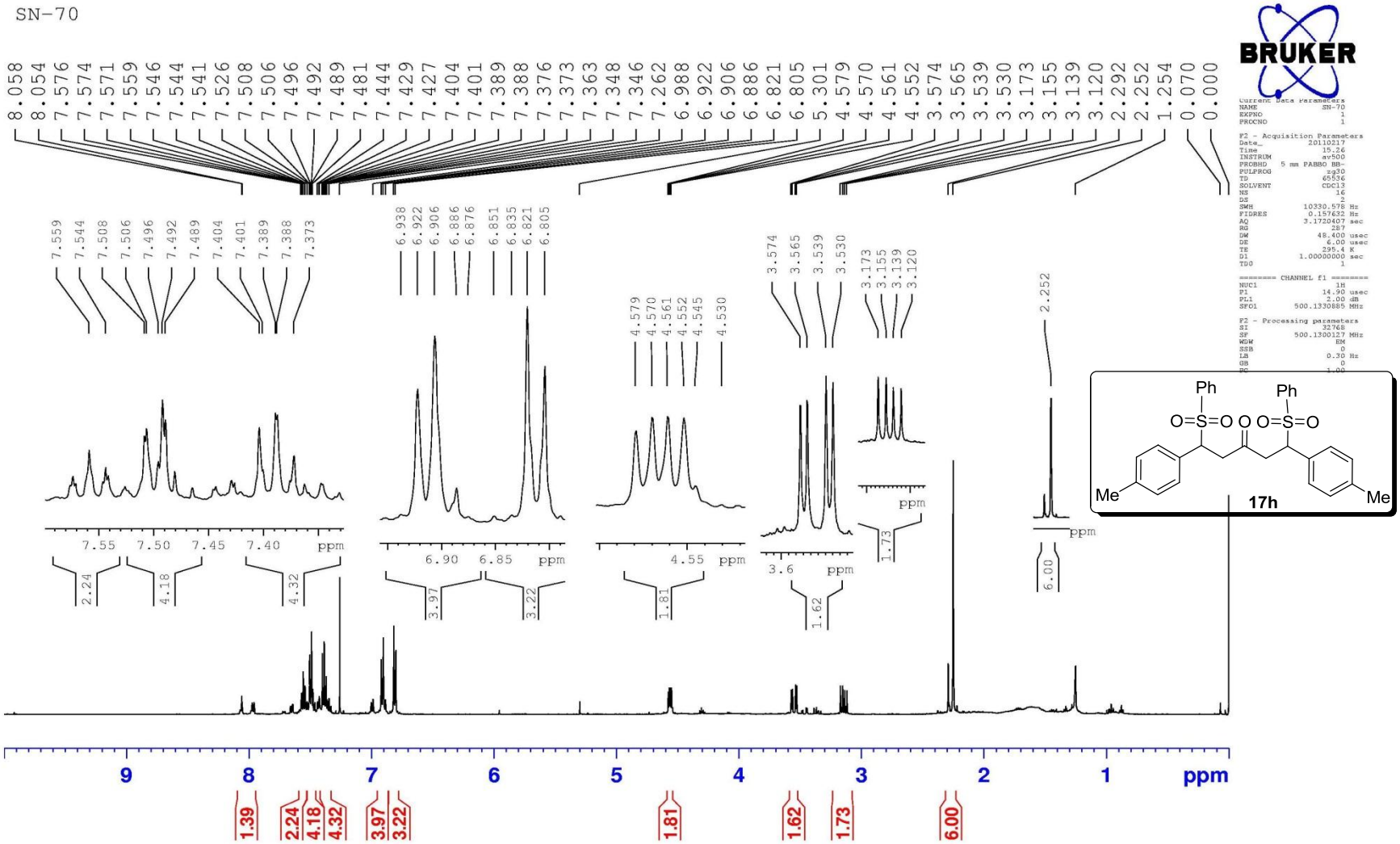


Figure S-87: ^{1}H NMR spectrum of compound 17h

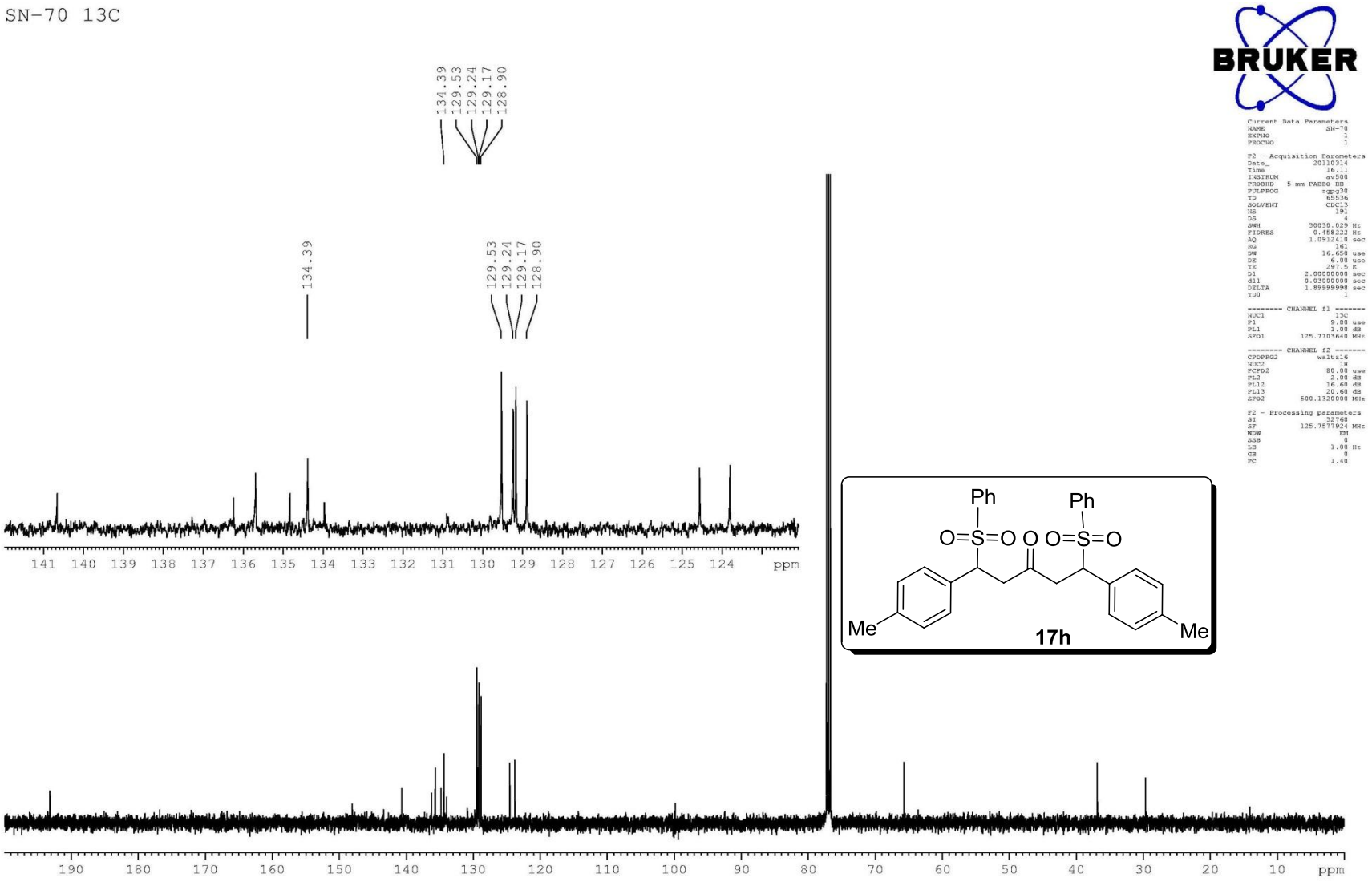


Figure S-88: ^{13}C NMR spectrum of compound 17h

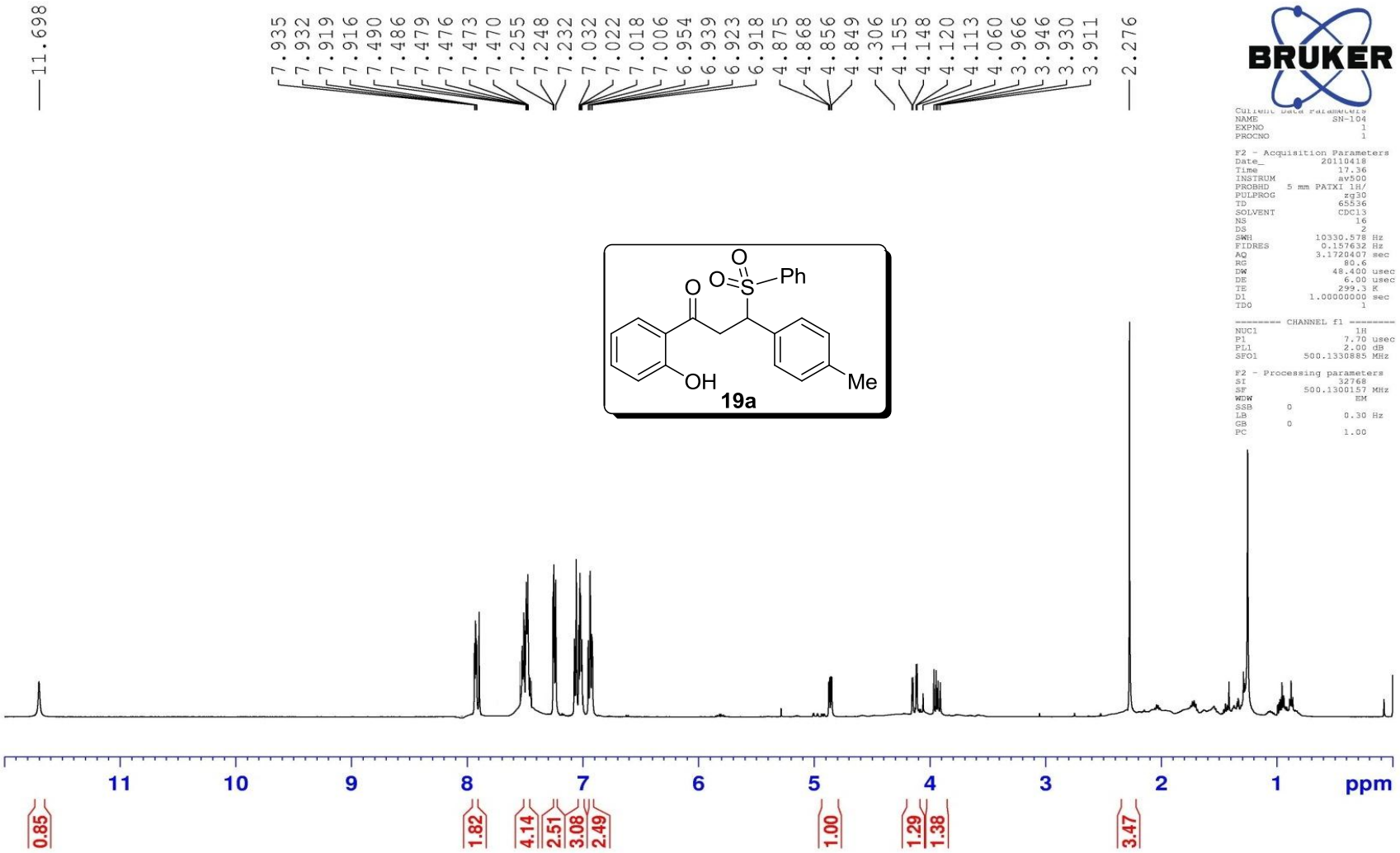


Figure S-89: ^{1}H NMR spectrum of compound 19a

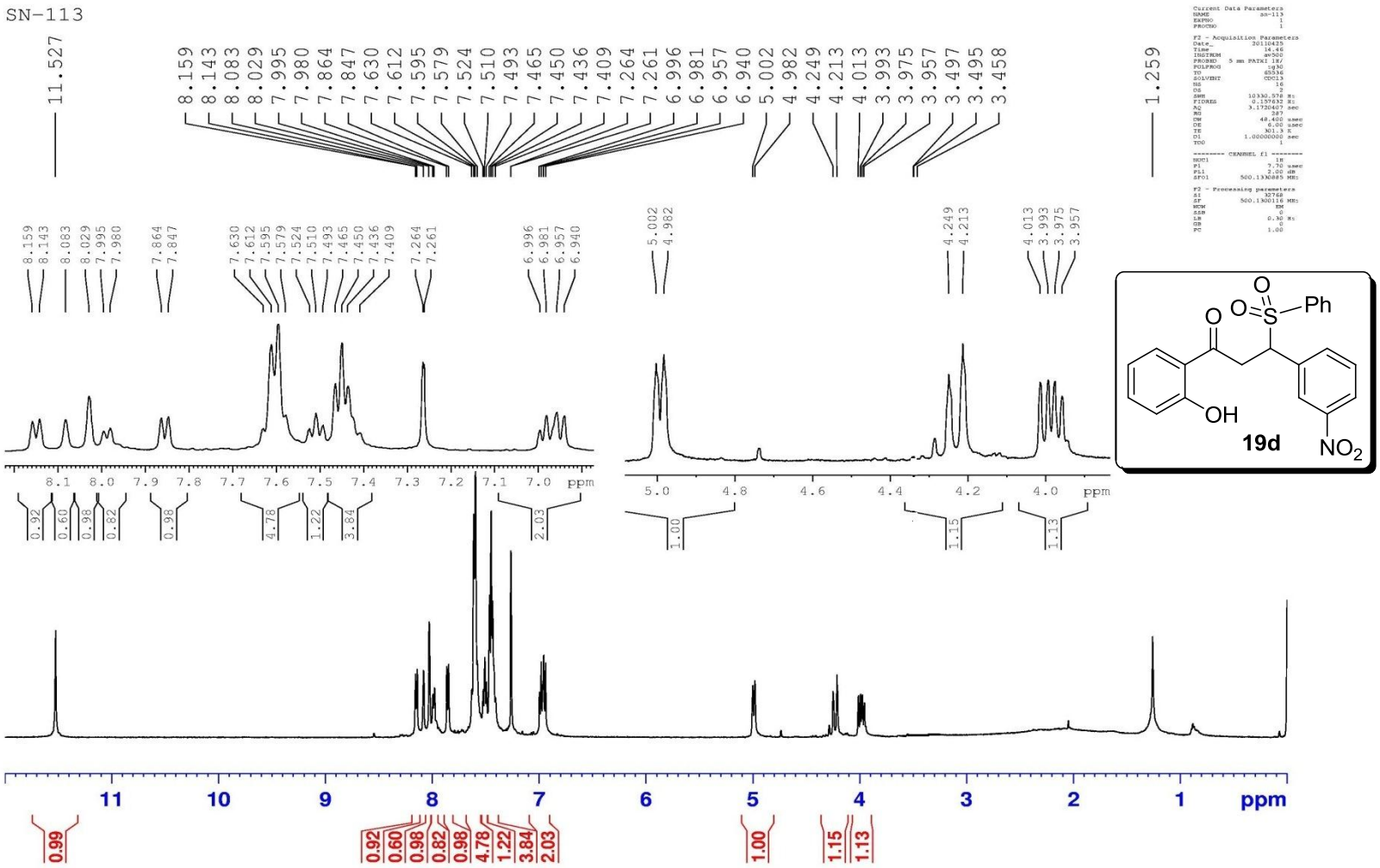


Figure S-90: ^{1}H NMR spectrum of compound 19d

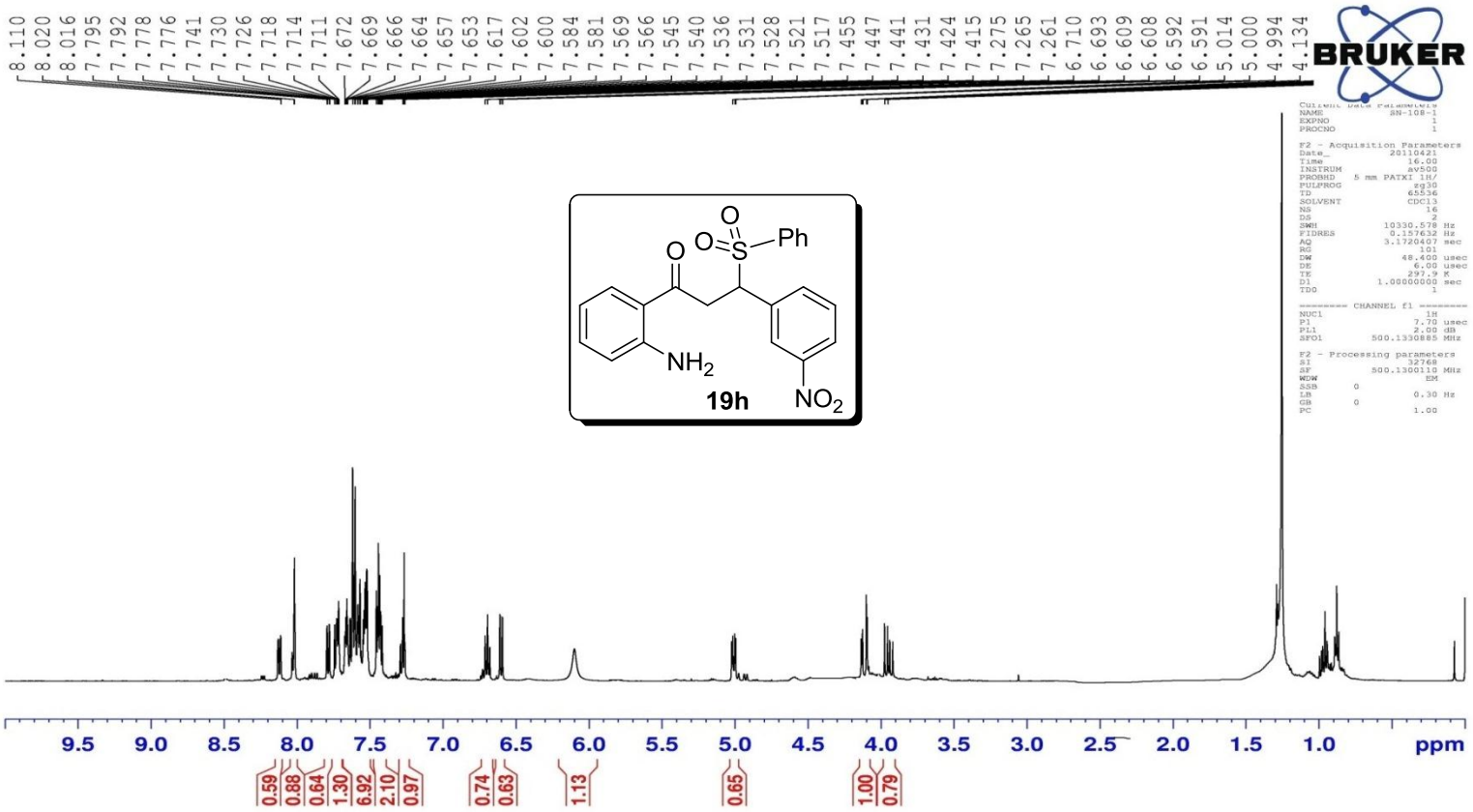


Figure S-91: ^{1}H NMR spectrum of compound 19h

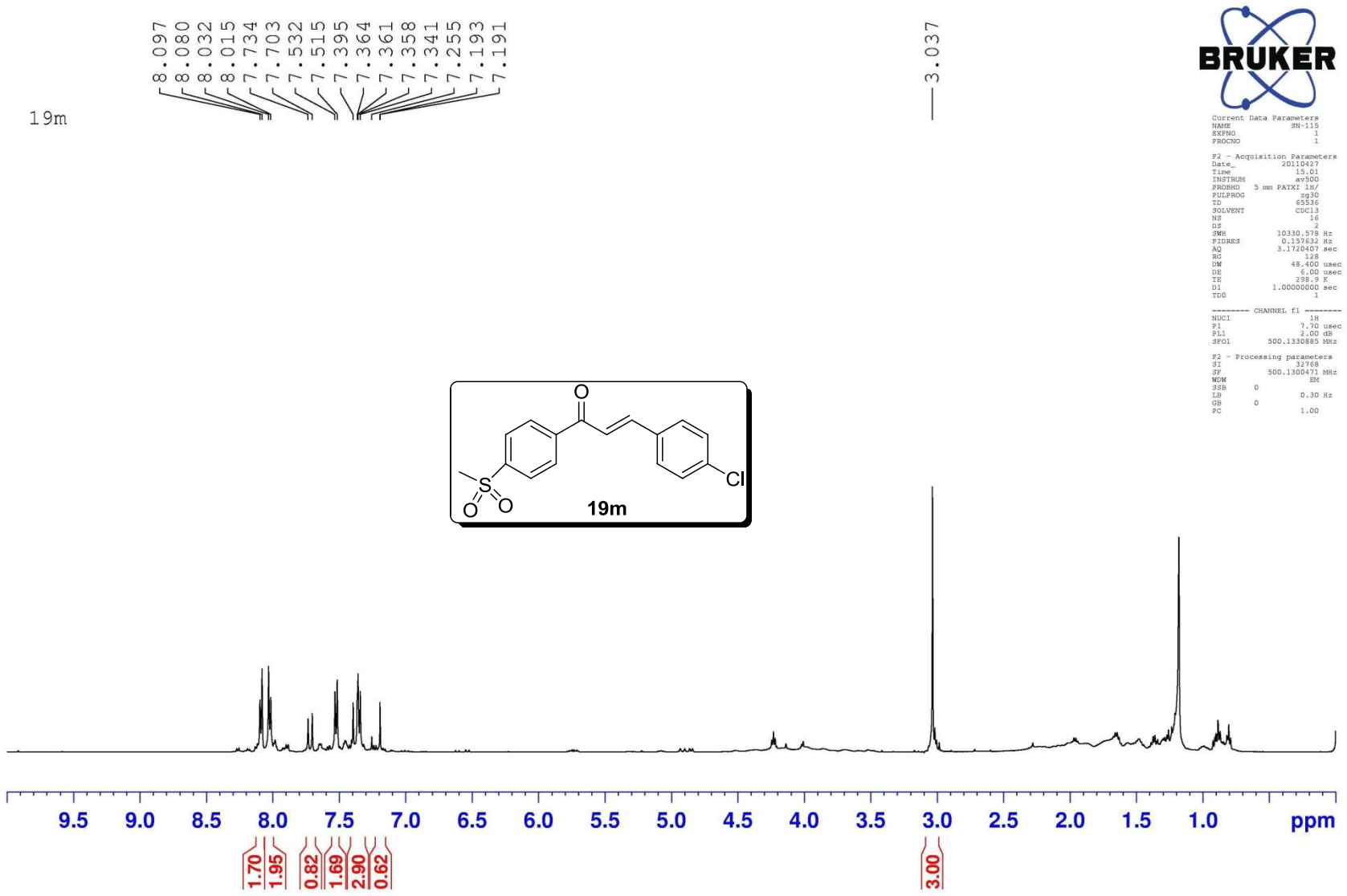


Figure S-92: ^{1}H NMR spectrum of compound 19m

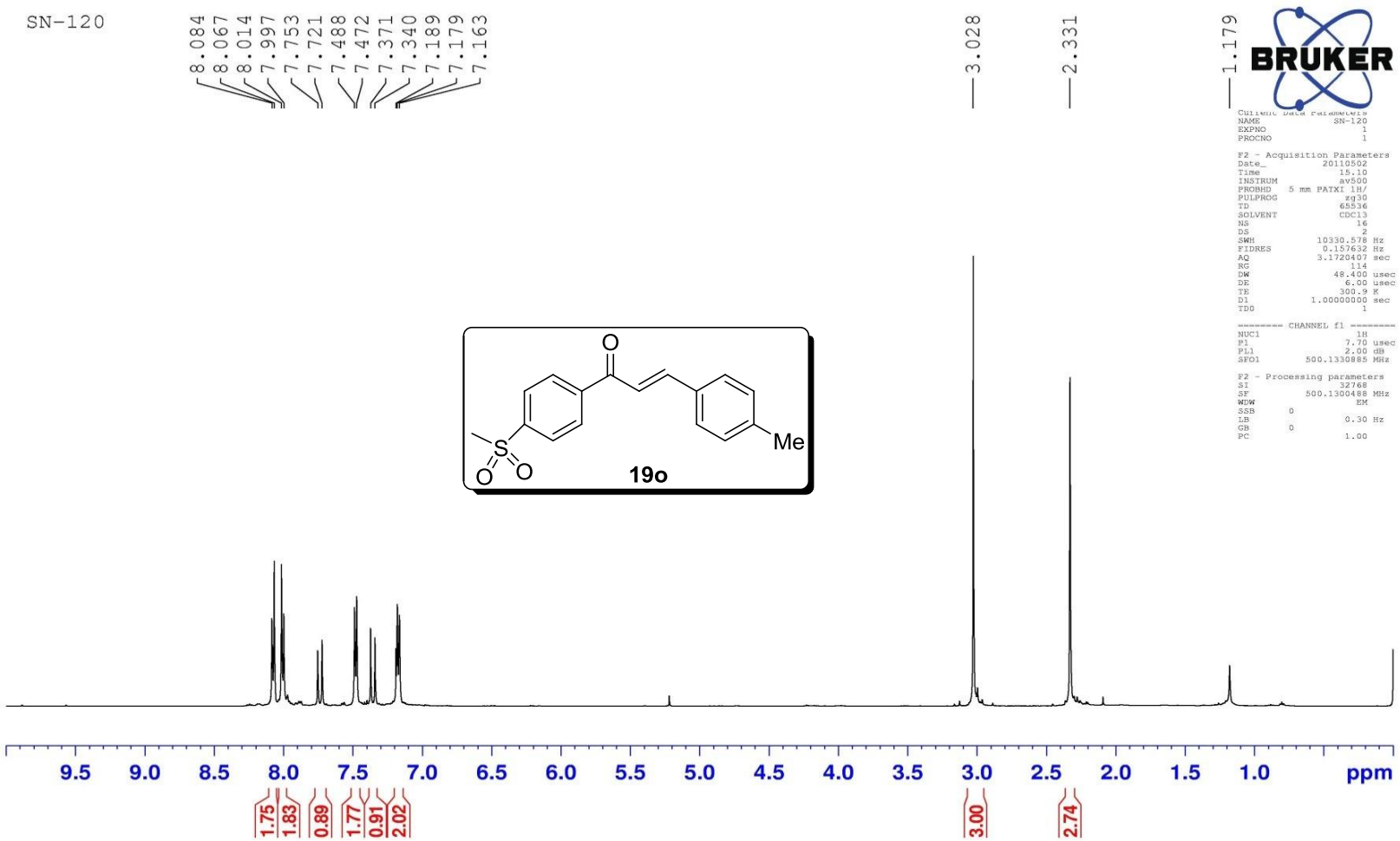
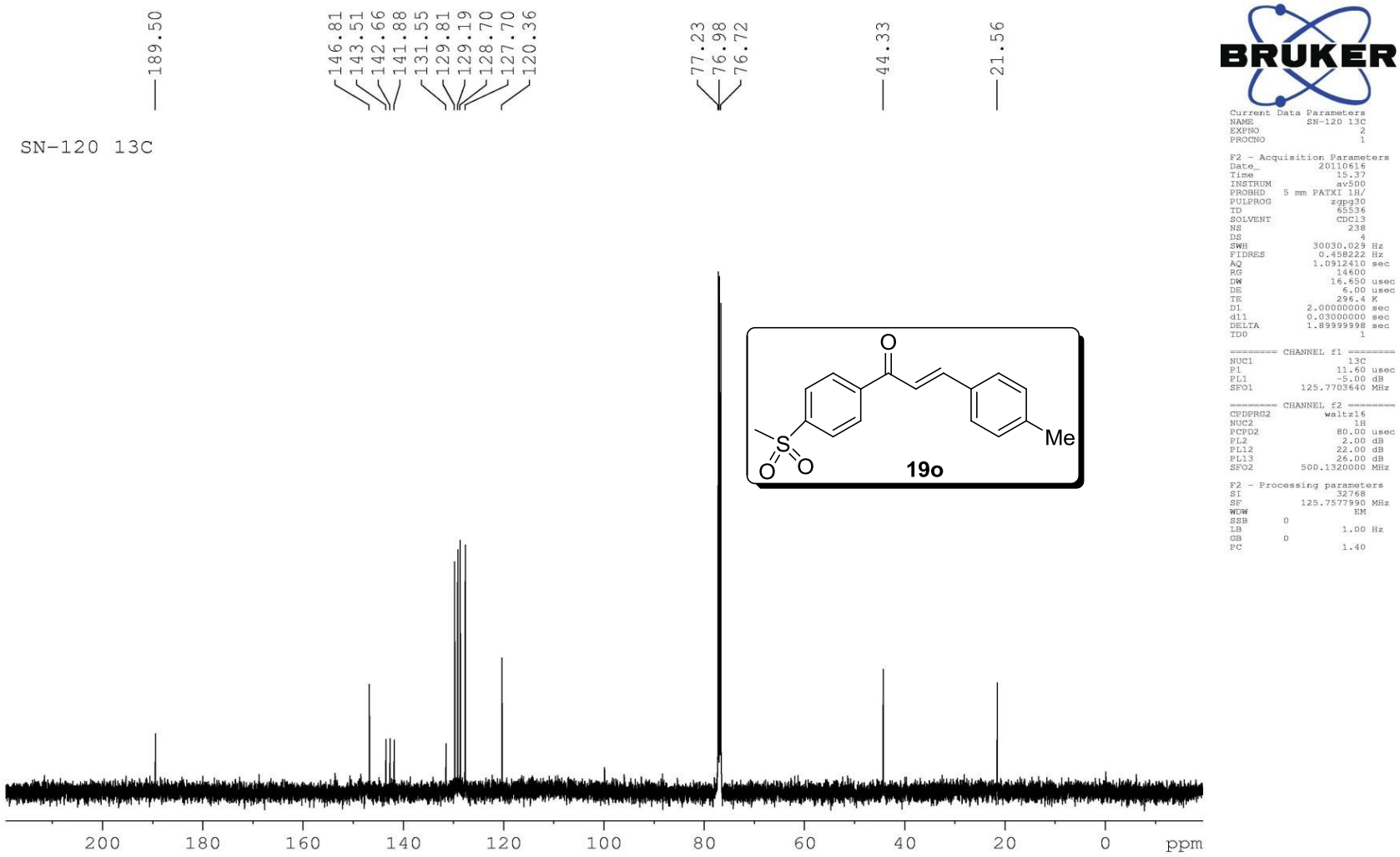


Figure S-93: ^{1}H NMR spectrum of compound 19o



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PROCNO 1

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SWH 30030.029 Hz
FIDRES 0.458222 Hz
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RG 14600
DW 16.650 usec
DE 6.00 usec
TE 296.4 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1

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P1 11.60 usec
PL1 -5.00 dB
SFO1 125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 22.00 dB
PL13 26.00 dB
SFO2 500.1320000 MHz

F2 - Processing parameters
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SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Figure S-94: ^{13}C NMR spectrum of compound 19o

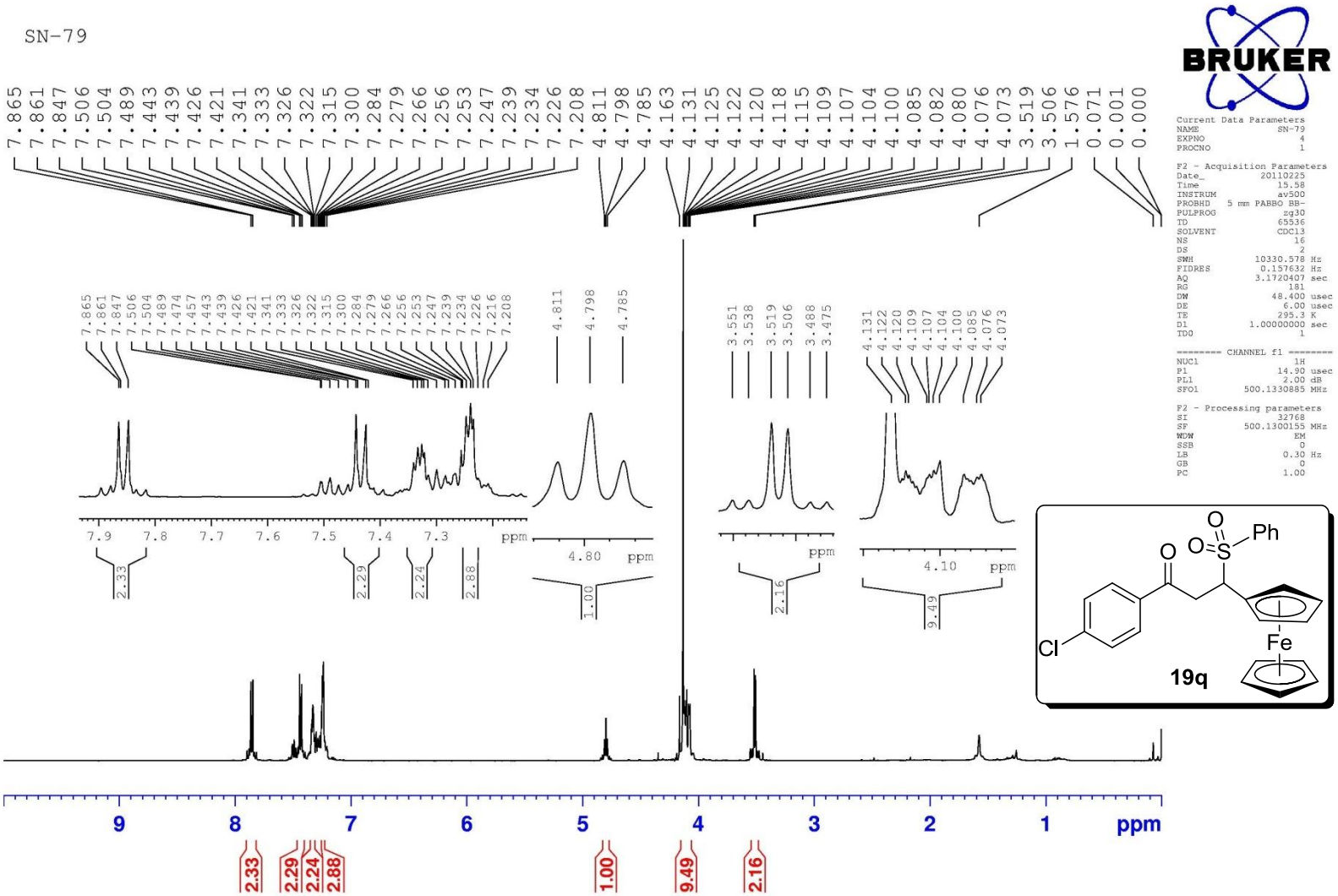


Figure S-95: ^{1}H NMR spectrum of compound 19q

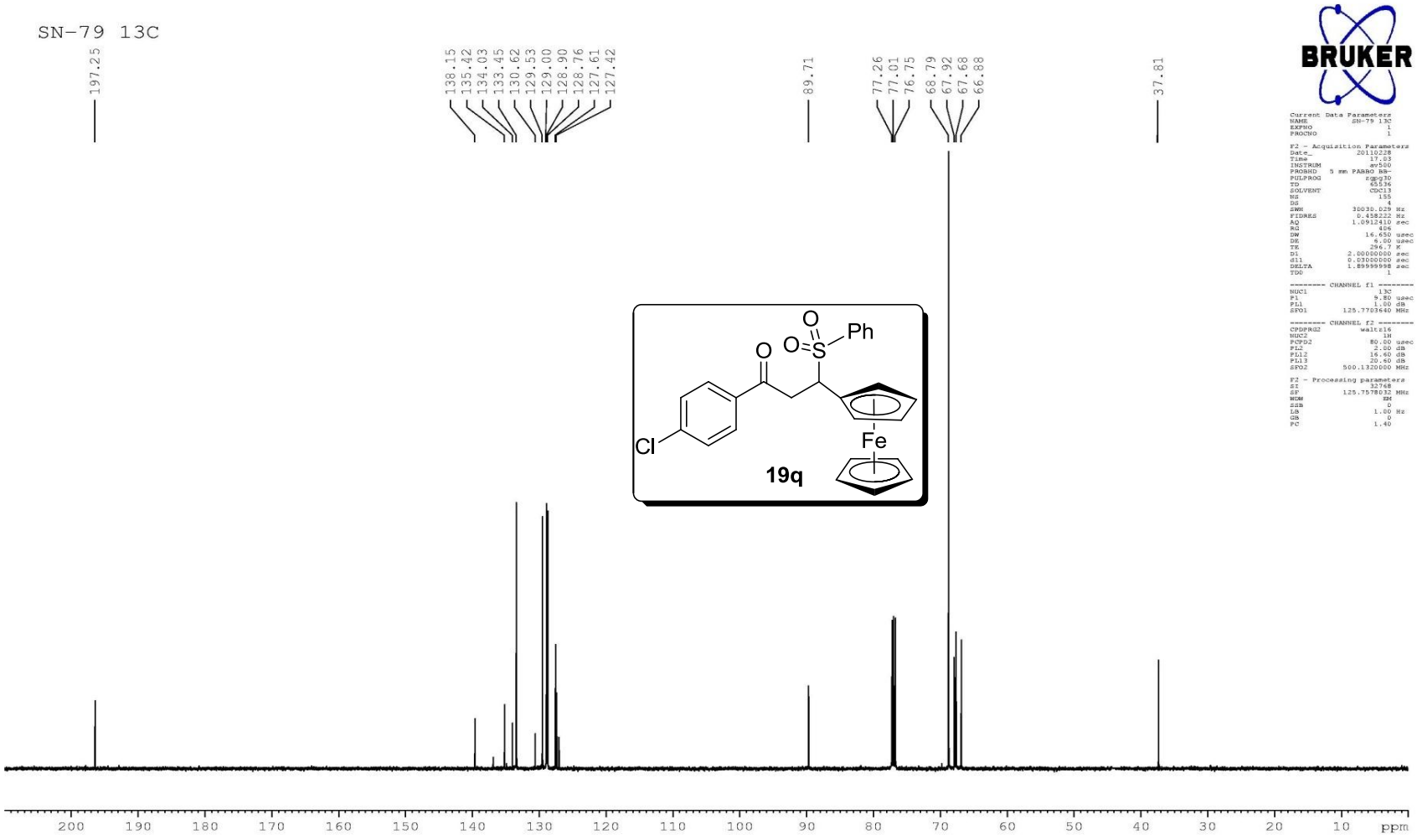


Figure S-96: ^{13}C NMR spectrum of compound 19q

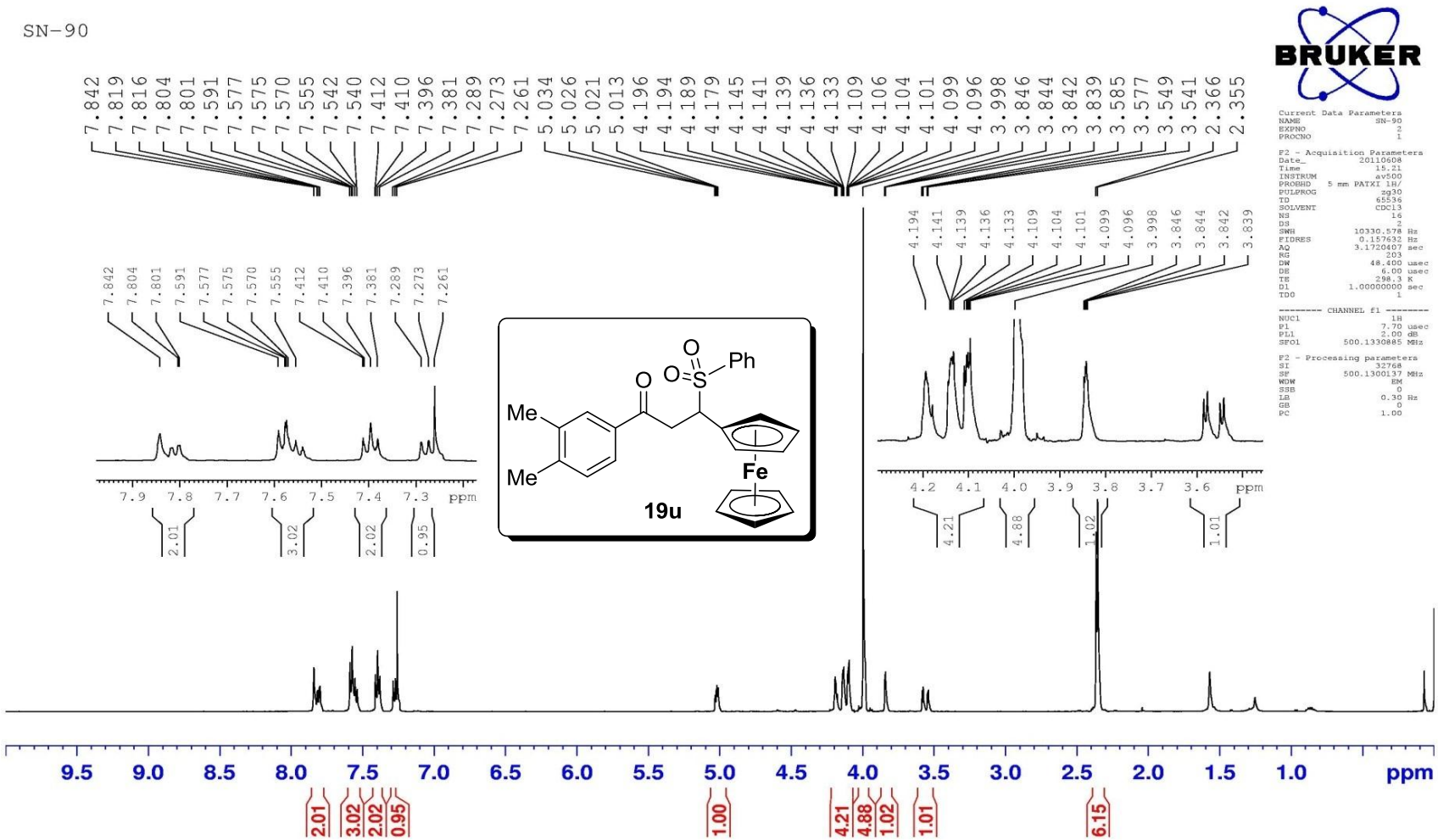
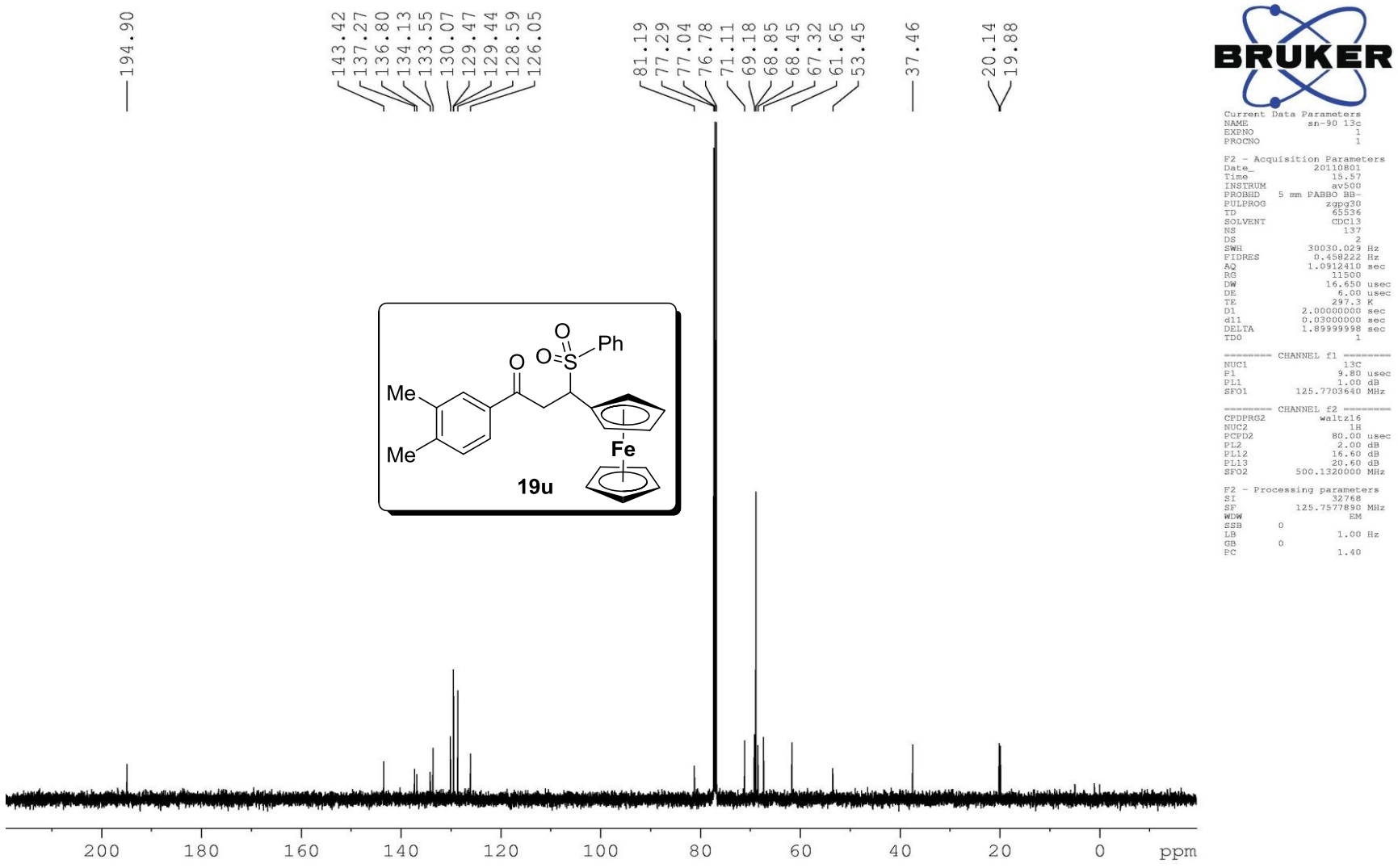


Figure S-97: ^{1}H NMR spectrum of compound 19u



Current Data Parameters
NAME sn-90 13c
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20110801
Time 15.57
INSTRUM av500
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 137
DS 2
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912410 sec
RG 11500
DW 16.650 usec
DE 6.00 usec
TE 297.3 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 9.80 usec
PL1 1.00 dB
SFO1 125.7703640 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 16.60 dB
PL13 20.60 dB
SFO2 500.1320000 MHz

F2 - Processing parameters
SI 32768
SF 125.7577890 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Figure S-98: ^{13}C NMR spectrum of compound 19u

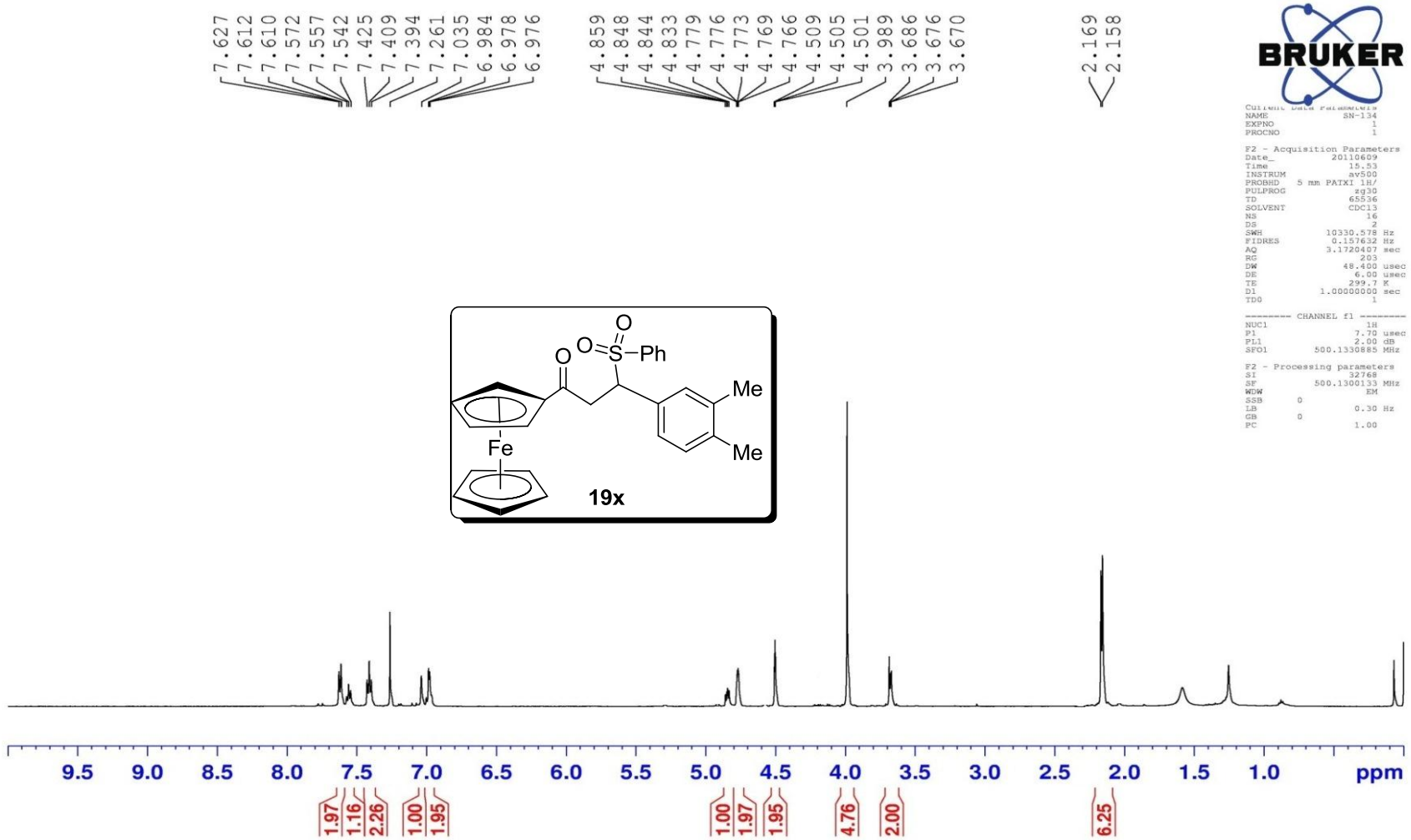


Figure S-99: ^{1}H NMR spectrum of compound 19x

FUTURE SUGGESTIONS

In recent years, the research has focused on studying the antimicrobial and anti-proliferative activity of flavonoids with encouraging results because of their better activity. Nucleobases such as purine and pyrimidine have emerged as important therapeutic agents for the development of antiviral, antimicrobial and anti-tumor drugs. Many compounds bind to DNA by intercalating the base pairs. These compounds also stabilize the double helical structure interrupting the transcription and replication of the DNA in the dividing cell. Similarly, computational biology analysis and indirect biological studies have demonstrated that the higher structures (quadruplexes in DNA) could be present in several genomes, being responsible for many transcription processes.

Flavonoids are polyphenolic compounds which are widely present in the vegetal kingdom. Numerous investigations for the many chemical and biological activities of this family of natural products including antioxidant, chelating, anti-carcinogenic, bacteriostatic, and secretory activities have been reported. Flavonoids gave stable conjugated molecules, they can transfer electron therefore they can act as Π-linkers between donor and acceptor. Here we can couple flavonoids with various donors and acceptors and investigate how they are useful in the field of organic electronics. We may develop new synthetic methods to couple flavonoids with various nucleobases with different substitution which may be useful in chemical biology.

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3. Silica supported-double metal cyanides (DMCs): A green and highly efficient catalytic protocol for isomerisation of 2'-hydroxychalcones to flavanones.
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   Naveen Kumar Konduru and Naseem Ahmed, *Synth. Commun.* **2013**, *43*, 2008-2018.
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7. Design, synthesis a new class of chalcone based sulfone derivatives and biological evaluation of their antimicrobial activities
   Naveen Kumar Konduru, Sarfaraz Ahmad, Mohammad Owais, Naseem Ahmed, *J. Heterocycle Chemistry*, **2014** under review.
8. Design and efficient synthesis of functionalized flavone-triazole-tetrahydropyran conjugates via click chemistry
   Naveen Kumar Konduru, Naseem Ahmed, Manuscript under prepation.

CONFERENCES

1. Poster Presentation on 'Design and Synthesis of Highly Functionalized Flavonoid based THP Derivatives' in "8th J-NOST conference" during December 15-17, 2012 at IIT Guwahati
2. Participated in "BRNS-AEACI Winter School on Analytical Chemistry (SAC-5)" during May 13-20, 2013 at IIT Roorkee.
3. Participated in "Modern Trends in Inorganic Chemistry (MTIC-XV)" during December 13-16, 2013 at IIT Roorkee.