DEAROMATIZATION PROTOCOL FOR THE SYNTHESIS OF *meta*-SUBSTITUTED PHENOLS

Ph.D. THESIS

by

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INDIAN INSTITUTE OF TECHNOLOGY ROORKEE
ROORKEE – 247 667 (INDIA)
JUNE, 2018

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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

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INDAIN INSTITUTE OF TECHNOLOGY ROORKEE
ROORKEE

CANDIDATE'S DECLARATION

I hereby certify that the work which is being presented in the thesis entitled "**DEAROMATIZATION PROTOCOL FOR THE SYNTHESIS OF *meta*-SUBSTITUTED PHENOLS**" in partial fulfilment 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 of January, 2013 to June, 2018 under the supervision of Dr. Rama Krishna Peddinti, Associate Professor, Department of Chemistry, Indian Institute of Technology Roorkee, Roorkee.

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

(**NEHA TANEJA**)

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

Date: June 29, 2018 (R .K. Peddinti)
Supervisor

The Ph.D. Viva-Voce Examination of Mr. **Neha Taneja**, research scholar has been held on 12-09-2018.

Chairman, SRC **Signature of External Examiner**

This is certify that the student has made all the corrections in the thesis.

Signature of Supervisor **Head of the Department**

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Neha Taneja

CONTENTS

LIST OF ABBREVIATIONS

m-CPBA	*meta*-chloroperbenzoic acid
HFIP	hexafluoroisopropanol
TFA	trifluoroacetic acid
DIPEA	N,N-diisopropylethylamine
CNS	central nervous system
DA	Diels-Alder
DCE	1,2-dichloroethane
FAD	flavin adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
DIB	diacetoxyiodobenzene
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TfOH	triflic acid
EDG	electron-donating group
DMA	dimethylacetamide
EWG	electron-withdrawing group
TFAA	trifluoroacetic anhydride
TBAF	tetra-*n*-butylammonium fluoride
HRMS	high resolution mass spectroscopy
IBX	2-iodoxybenzoic acid
TBAB	tetra-*n*-butylammonium bromide
IR	infra red
TFA	trifluoroacetic acid
MOB	masked *o*-benzoquinone
MPB	masked *p*-benzoquinone
DMAP	4-dimethylaminopyridine

NMR	nuclear magnetic resonance
DME	dimethoxyethane
o-QMI	*o*-quinone monoamine
ORTEP	oak ridge thermal ellipsoid plot program
PET	positron emission tomography
PTSA	*p*-Toluenesulfonic acid
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TEBA	triethylammoniumbenzyl chloride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TMSCl	trimethylsilyl chloride
UV	ultra violet
calcd.	calculated

ABSTRACT

The thesis entitled "**Dearomatization protocol for the synthesis of *meta*-substituted phenols**" is divided into three chapters, *viz*. (i) Introduction, (ii) Objectives, Results and Discussion, and (iii) Experimental.

We have developed novel, convenient and rapid protocols for the dearomatization of alkoxy phenols for the *in situ* generation of cyclohexadienones which were further trapped by different dienophiles to synthesis valuable scaffolds *viz.*, bicyclo[2.2.2]octenone derivatives *via* intermolecular Diels-Alder reaction. To further harness the enone functionality of *in situ* generated highly reactive cyclohexa-2,4-dienones, we have carried out the Michael addition of some easily accessible nucleophiles to masked *o*-benzoquinones to furnish diarylsulfones, α-arylated 1,3-diones and 5-arylbarbiturates. The Michael addition reaction resulted in the formation of phenols coupled with different templates at its *meta*-position. Further, we have extended the versatility of our approach for the synthesis of phenol functionalized *N*- and *O*-heterocyclic systems that are counted among the high phramoacological profile frameworks especially for neurological disorders.

Chapter 1: Introduction

Since the 1865, when the concept of aromaticity was introduced to the scientific community, aromatic compounds are widely known for their importance in fundamental and applied chemistry and in result extensive efforts have been made to develop convenient and efficient synthetic strategies for the conversion of planar arenes to high-value added aromatic products. Of particular interest is the dearomatization strategy (disruption of the aromatic system of arenes) as it demonstrates the possibilities for the synthesis of biologically potent sophisticated polycyclic architectures from simple planar aromatic feed stocks. The oxidative dearomatization of phenolic compounds serves as a powerful tool in providing products that are primed for further reaction to synthesize popular structurally complex motifs. So, the advancement of effective and eco-friendly synthetic protocols for the oxidative dearomatization of phenols is highly demanding. It is widely known that the synthesis of *meta*-substituted phenols possesses a significant challenge of bypassing the normal *ortho*/*para* directing effect of

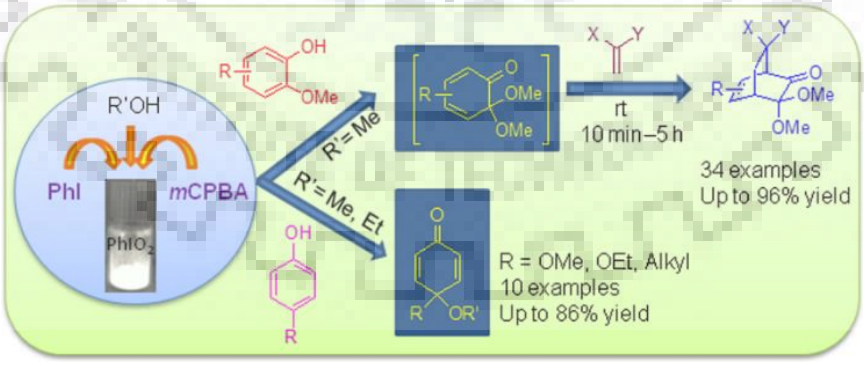
hydroxyl functionality and hence the synthesis of *meta*-substituted phenols is formidable. Till date, *meta*-functionalization has been done either with the involvement of transition metals using harsh conditions or using the directing group strategy that results in lengthy synthetic route and simple-cum-straightforward methods are sporadic in literature.

Chapter 2: Objectives, Results and Discussion

This chapter deals with the objectives, results and discussion which are divided into six sections.

2.1. Dearomatization protocol and synthesis of bicyclo[2.2.2]octenone derivatives

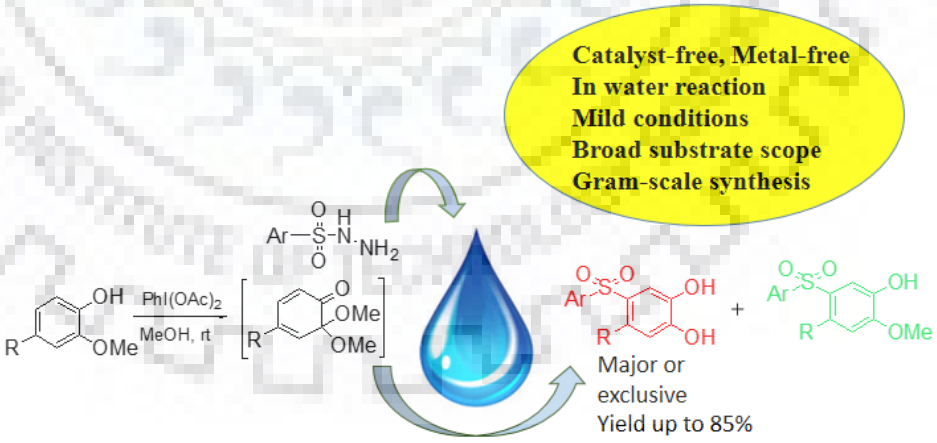
In the first instance, we have thrived a clean and efficient protocol for the oxidative dearomatization of alkoxyphenols with $PhIO_2$ generated *in situ* from using catalytic amount of iodobenzene in the presence of *m*-CPBA as terminal oxidant. This *in situ* generated oxidant $PhIO_2$ readily transforms the 2- and 4-alkoxyphenols into masked *ortho*-benzoquinones (MOBs) and masked *para*-benzoquinones (MPBs), respectively. Further, the highly reactive MOBs underwent Diels–Alder reaction with various dienophiles to give bicyclo[2.2.2]octenone scaffolds. This oxidative ketalization Diels-Alder protocol is high yielding and proceeded under mild and eco-friendly conditions. (Scheme 1).



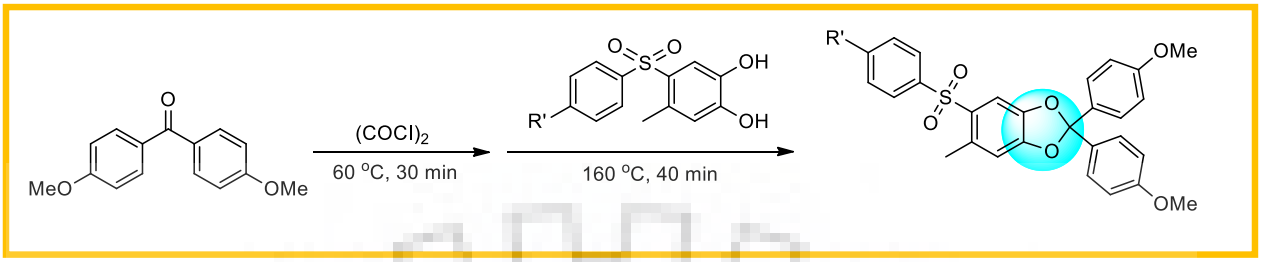
Scheme 1: Oxidative dearomatization strategy for the synthesis of bicyclo[2.2.2]octenones.

2.2. Synthesis of arylsulfonyl catechol derivatives

Organo-sulfone chemistry has undergone a renaissance in the past decades as the sulfonyl-derived functional groups such as sulfones, sulfonamides populate a broad range of pharmaceutical active molecules and agrochemicals. Similarly, catechol structural motifs are stupendously utilized in every zone of chemical industry. However, the dihydroxy substituted arylsulfone is rather more profoundly considered as structural entity of innumerable bioactive molecules of pharmaceutical relevance and is relatively difficult to synthesize. A novel water-assisted, catalyst-free carbon-sulfur bond formation strategy has been described for the direct access of highly valuable arylsulfonyl catechols. This protocol involves a direct Michael attack of aryl sulfinate produced from arylsulfonyl hydrazides as a nucleophile in aqueous media on *in situ* generated MOBs to form carbon-sulfur bond. Mechanistic studies suggested that water molecule play key role in the synthesis of catechols. Thus sulfonylation operates under mild conditions, shows broad substrate scope, gives high conversion and can be applied for gram-scale synthesis (Scheme 2). The arylsulfones further synthetically transformed into molecules that are important precursors for drug discovery especially the analogues of COMT inhibitors the anti-Parkinson's agents and the novel precursors for the treatment of obesity (Scheme 3).



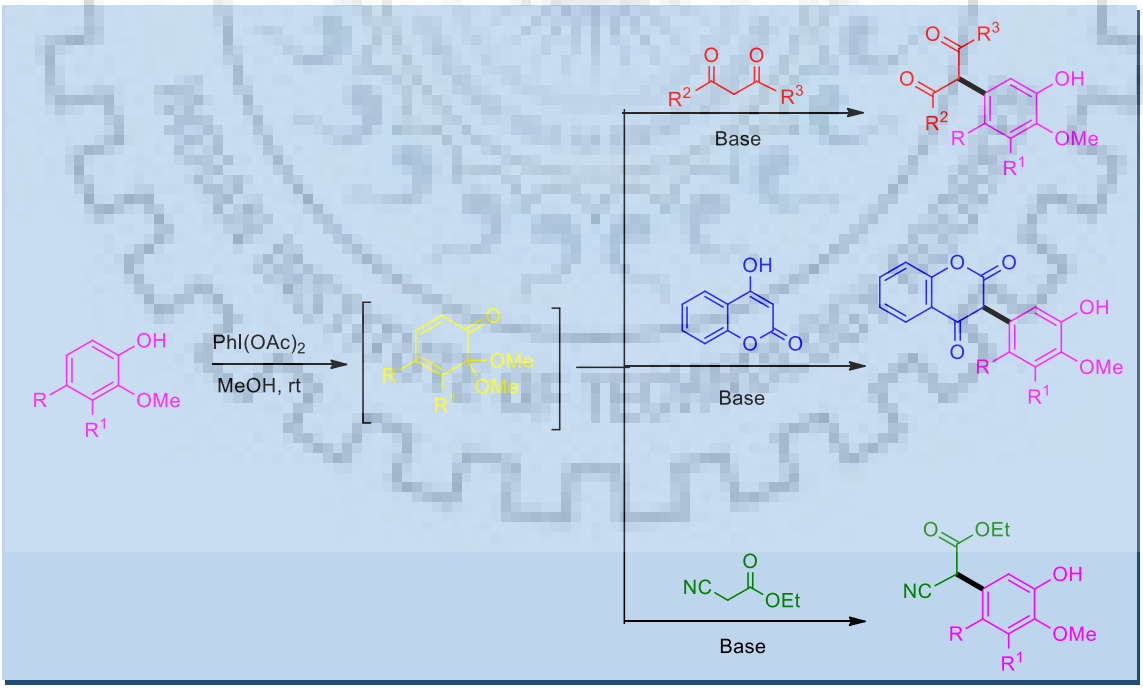
Scheme 2: Synthesis of arylsulfony catechol derivatives in aqueous media.



Scheme 3: Synthetic transformation of arylsulfonyl catechols.

2.3. α-Arylation and Synthesis of *meta* substituted phenols

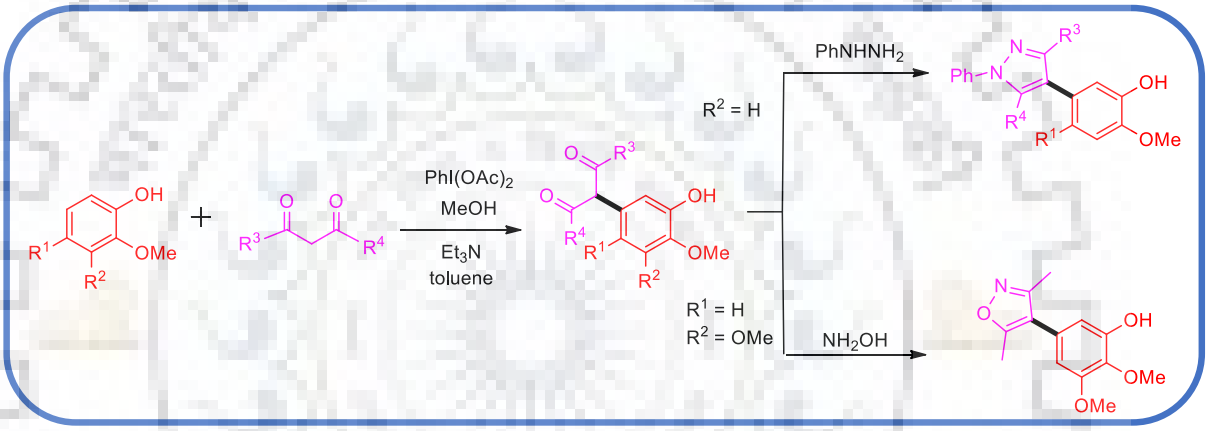
The enolate arylation of 1,3-dicarbonyl compounds and β-cyanoacetates has drawn extensive and revolutionized attention as one of the significant methods for the C–C bond formation, which provides an easy access to complex organic frameworks. Owing to the utilization of α-arylated 1,3-diones and ethyl cyanoacetates as prime substrates for synthetically useful transformations, we exploited the nucleophilicity of various C–H activated acids. Hence, we presented a base-mediated, direct highly convenient strategy for the C-arylation of C–H acti-



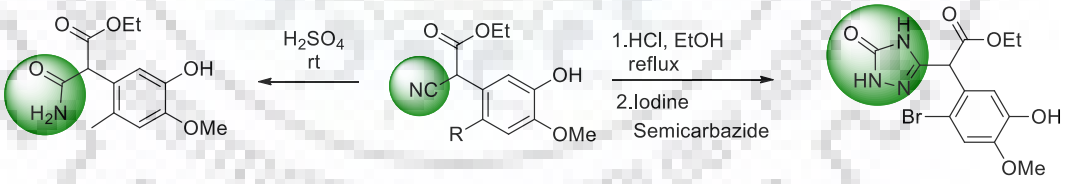
Scheme 4: α-Arylation of C–H activated pronucleophiles.

vated pronucleophiles with various phenol derivatives as aryl partners. The present work excelled in forming C–C bond at the *meta*-position/site of the phenols which is traditionally challenging to achieve (Scheme 4).

Underlining the utility of the obtained products, one-pot, straightforward, clean, high yielding routes for the synthesis of phenol substituted heterocycles such as pyrazoles, isoxazoles, coumarins, triazolones and carboxylic amide were demonstrated, which led the way for the endowment of important biological scaffolds (Schemes 5 and 6).



Scheme 5: Synthesis of phenol substituted pyrazoles and oxazoles.

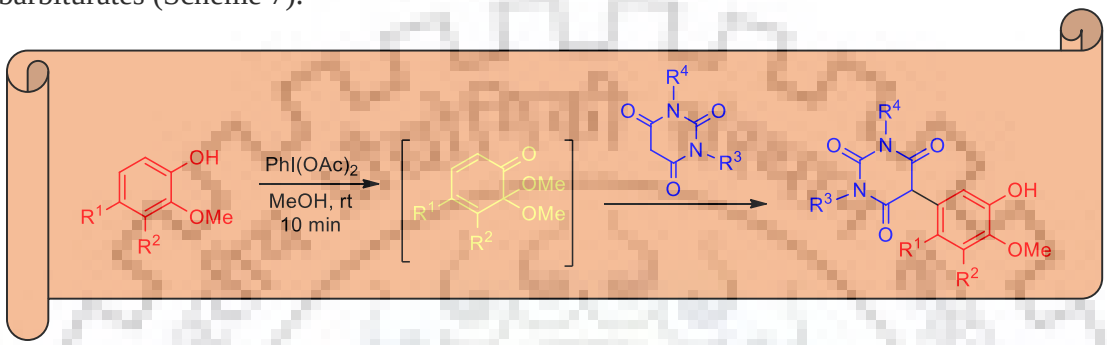


Scheme 6: Transformation of cyano-substituted products.

2.4. Synthesis of substituted-5-aryl barbituric acid

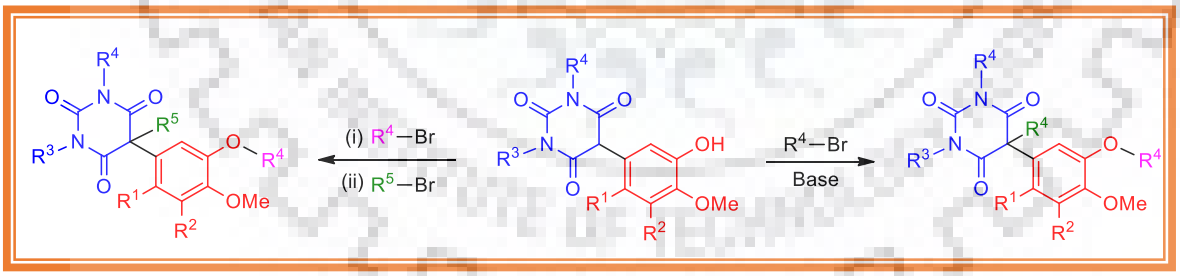
Since 1864, when German chemist Adolf von Baeyer discovered the barbituric acid, barbiturates are privileged with 1,3-diamide scaffolds in medicinal chemistry, because of their sedatives, anti-convulsants, analgesic, hypnotic, antimicrobial, anaesthetic, anticancer and antitumor properties. Although unsubstituted barbituric acid itself does not show any hypnotic or anticonvulsant properties; such features are conferred only when the active methylene

hydrogen atoms at C-5 are substituted. Thus, we have delineated a general, straightforward approach involving the Michael addition of methylene carbon of barbituric acid derivatives to *in situ* generated *ortho*-benzoquinone monoketals for rapidly assembling the phenol functionalized 5-aryl barbiturates (Scheme 7).



Scheme 7: Synthesis of 5-aryl barbiturates.

Further, we have elaborated the utility of 5-aryl barbiturates through the construction of fully substituted barbituric acids consisting in-ring quaternary center. Spurred by the great synthetic medicinal interest of fully substituted barbiturates the 5-aryl barbiturates are subjected to sequential C–H alkylation using various alkyl halides for the synthesis of carbon as well as oxygen alkylated 5-aryl barbiturates (Scheme 8).



Scheme 8: Synthesis of fully substituted barbiturates.

Chapter 3: Experimental

The third chapter provides experimental procedures in detail along with physical constants and spectral data including melting points, IR, ^{1}H NMR, ^{13}C NMR and HRMS data.

1. INTRODUCTION

Since the 1865, when a German chemist Friedrich A. Kekule assigned structure of the benzene and introduced the concept of aromaticity to the scientific community, aromatic compounds are widely known for their importance in fundamental and applied chemistry [1]. Owing to the tremendous demand of aromatic compounds even in our daily life, extensive efforts have been made to develop convenient and efficient synthetic strategy for the conversion of planar arenes to high-value added aromatic products [2–4]. Of particular interest is the dearomatization strategy (disruption of the aromatic system of arenes) as it illustrates the possibilities for the construction of biologically potent sophisticated polycyclic architectures from simple planar aromatic feed stocks [5–7]. Thus, as shown in Figure 1, a myriad of approaches have been utilized by chemists for controlled dearomatization during the course of total synthesis of complex polycyclic scaffolds [8–11].

1.1. Oxidative Dearomatization

The general methods for dearomatization are:

1. Enzymatic dearomatization
2. Photochemical dearomatization
3. Transition-metal mediated dearomatization
4. Oxidative (polyvalent iodine mediated) dearomatization
5. Reductive (Birch reduction/ reductive alkylation) dearomatization

The oxidative dearomatization of phenolic compounds serve as a powerful tool for the generation of popular structural motifs [12–16], providing products that are primed for further reaction and paving an avenue for introducing stereochemical outcomes [17,18]. Our laboratory has exploited the particular class of phenols *i.e.,* amino phenols and alkoxy phenols for synthesis of novel architectures *via* oxidative dearomatization [19,20]. Alkoxy phenols that are widely known as excellent nucleophiles will be transformed to electron-deficient cyclohexadienone derivatives through dearomatization. However, the advancement of effective synthetic methods to this transformation has been challenging due to the aromatic stability of substrates, and the potential to form undesired by-products. The

obtained cyclohexadienones are fascinating starting points to begin total synthesis of a number of natural pharmaceutically relevant molecules.

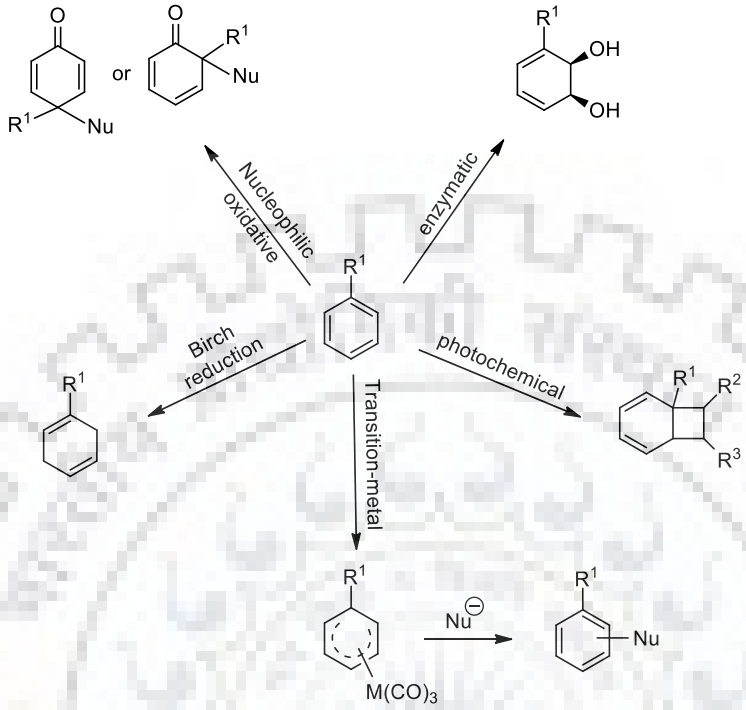


Figure 1: Strategies for dearomatization.

Dearomatization of 2-and 4-substituted phenols with oxygen based nucleophiles (Nu) under the activation of an oxidant leads to respective masked *ortho*-benzoquinone (MOBs) *i.e.,* cyclohexa-2,4-dienones and masked *para*-benzoquinones (MPBs) *i.e.,* cyclohexa-2,5-dienones [21–23] (Figure 2). Over the last fifty years the chemistry of cyclohexa-2,4-dienones is especially interesting and synthetically useful. These reactive species are usually prepared by using various oxidizing system [24, 25] based on heavy metals including Pb(IV), Cu(I), Tl(III), and Br(I). The most accustomed oxidizing reagents are hypervalent iodine species such as I(III), I(V).

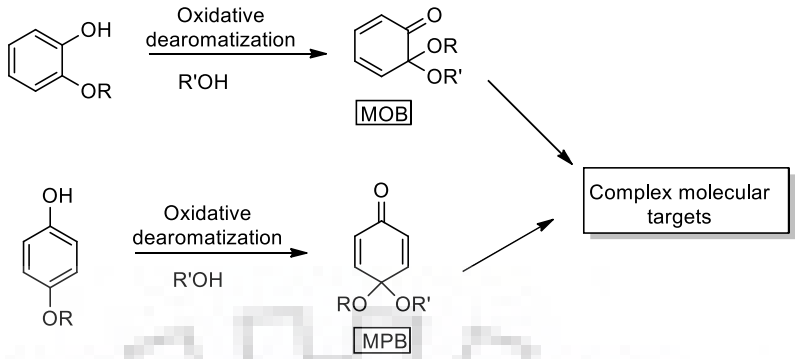
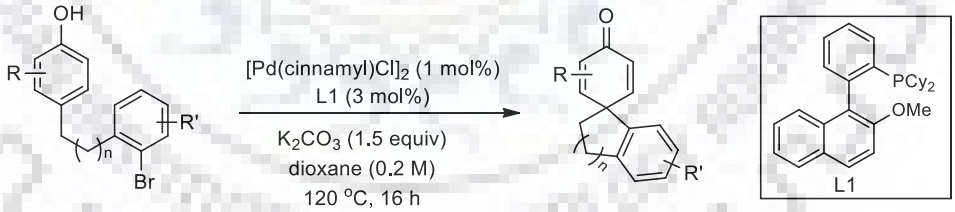


Figure 2: Oxidative dearomatization of alkoxy phenols.

Owing to their remarkable reactivity, the *in situ* generated benzoquinones have been further leveraged by various research groups for the chemical synthesis of a range of bioactive complex molecules and natural products [26, 27].

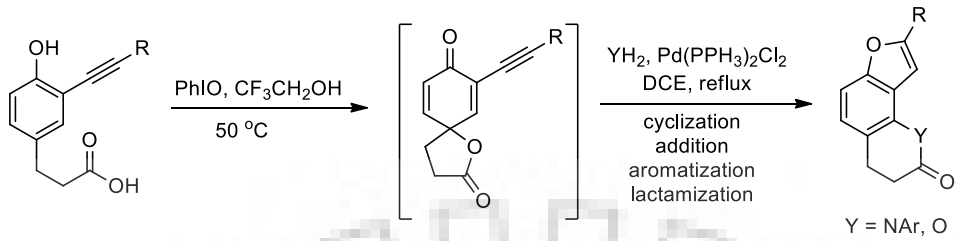
The research group of Buchwald in 2011, demonstrated the use of transition metals for the oxidative dearomatization of phenols. They developed a palladium-catalyzed arylative dearomatization of *para*-substituted phenols to form spirocyclohexadienone products bearing all-carbon quaternary centers in excellent yields. Treatment of *p*-substituted phenols with $[Pd(cinnamyl)Cl]_2$ as a source of palladium with L1 as a ligand in 1,4-dioxane at 120 ^oC gave the optimized results. Substrates bearing electron-neutral and electron-donating groups were well tolerated [28] (Scheme 1).



Scheme 1: Palladium-catalyzed synthesis of spirocyclohexadienones.

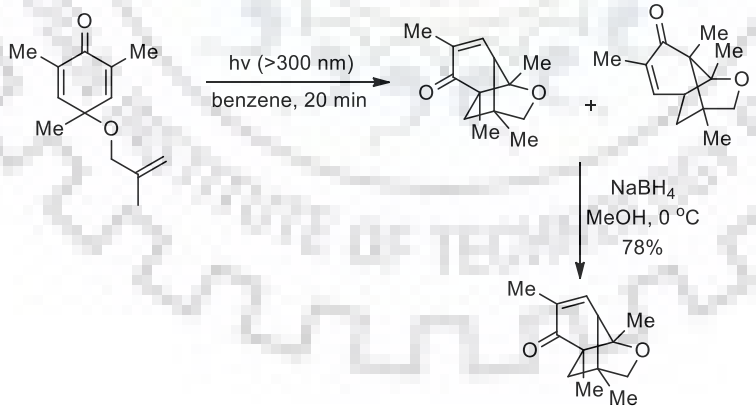
In 2012, Fan *et al.* developed a new methodology for the synthesis of furoquinolinone and angelicin derivatives *via* oxidative dearomatization of 3-(3-alkynyl-4-hydroxyphenyl)-propanoic acids in a convergent manner. Furoquinolinones are the bioisosters of angelicin and are considered as potent photochemotherapeutic agents. They constructed the furoquinolinone scaffolds by the dearomatization of 3-(3-alkynyl-4-hydroxyphenyl)-propanoic acids using PhIO as oxidant in CF_3CH_2OH followed by reaction with aromatic

amines through a sequence of palladium-catalyzed cascade cyclization reaction/ addition/ aromatization reaction and lactamization [29] (Scheme 2).



Scheme 2: Dearomatization strategy for the synthesis of furoquinolinone and angelicin derivatives.

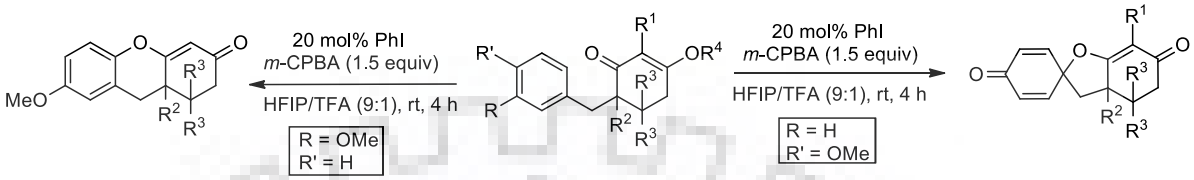
In 2013, the utility of oxidative dearomatization was further explored by Stephenson *et al.* where they reported the synthesis of novel scaffolds for drug development. The dearomatized products obtained from readily available 2,4,6-trimethylphenol and derivatives underwent dienone photorearrangment and subsequent cycloaddition furnished highly functionalized, bridged tri- and tetracyclic frameworks. These substituted cyclohexadienones smoothly underwent [5 + 2] cycloaddition to form 5,1- and 1,5-bonded products in 10:1 ratio upon photoirradiation with wavelength greater than 300 nm in benzene. The major isomer has been confirmed by the structural analysis of alcohol obtained from the reduction with $NaBH_4$ in methanol [30] (Scheme 3).



Scheme 3: Dienone photorearrangement–cycloaddition of alkene-tethered 2,5-cyclohexa-dienones.

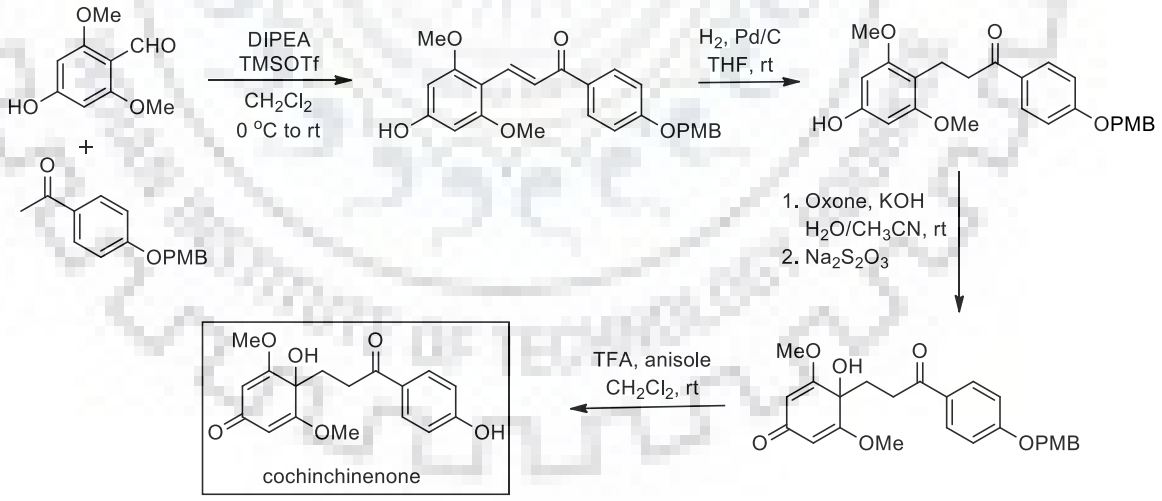
Hutt *et al.* reported the use of catalytic amount of iodobenzene with stoichiometry amount of *m*-CPBA as a terminal oxidant for oxidative cyclization of vinylogous esters to

synthesis spirofurans and benzopyrans [31]. The vinylogous esters that were considered as sufficiently electron-rich aprotic nucleophilic ketone underwent cyclization in 4 h to access quaternary carbon containing spirocyclic furans and benzopyrans in good yields (Scheme 4).



Scheme 4: Iodobenzene-catalyzed synthesis of benzopyrans and spirofurans.

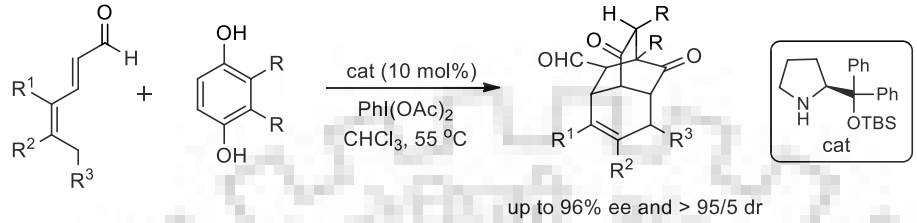
Cochinchinenone, a natural product isolated in 2007 from the stems of *Dracaena cochinchinensis* possesses biological properties such as antitumor, antifungal and anti-inflammatory [32]. It constitutes a chalcone scaffold having a *p*-quinol moiety and shows growth inhibitory effects against *Helicopbacter pylori* (ATCC43504). Carreno *et al.* described the first total synthesis of cochinchinenone *via* oxone-mediated oxidative dearomatization of the chalcone formed from the aldol reaction between a *p*-formyl phenol and OPMB protected hydroxyl acetophenone (Scheme 5).



Scheme 5: Total synthesis of cochinchinenone *via* oxone-mediated oxidative dearomatization.

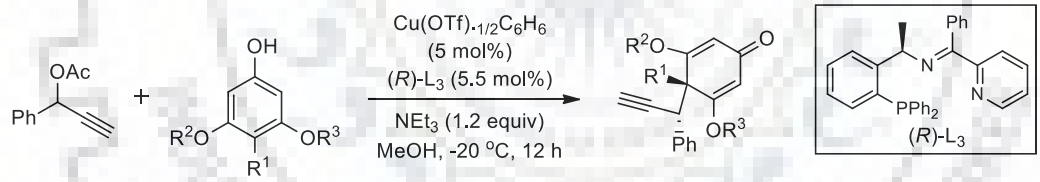
The strategy of oxidative dearomatization combined with trienamine/enamine activation to form complex cyclic optically active structures was described by Greck *et al.*

The route involved an oxidative dearomatization followed by amine-catalyzed Diels–Alder reaction in chloroform to form tricyclic structure containing up to six contiguous stereogenic centers (Scheme 6). The products, obtained with excellent level of enantioselectivity, can undergo various chemoselective transformations [33].



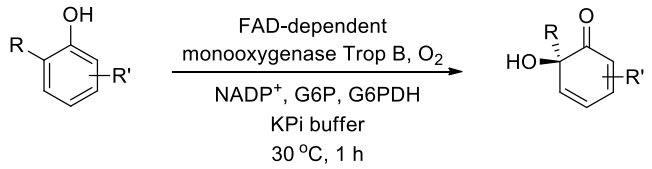
Scheme 6: Enantioselective synthesis of tricyclic architectures.

Hu *et al.* further explored metal-catalyzed dearomatization of phenols. They revealed that the dearomatization reaction proceeded smoothly under the catalysis of Cu(OTf).1/2C_6H_6 garnished with a chiral tridentate ketimine P,N,N-ligand with Et_3N additive in MeOH (Scheme 7). The reaction gave significantly high regio-, chemo- and enantioselectivity when performed at low temperature by avoiding various competitive reactions such as Friedel–Crafts type reaction [34].



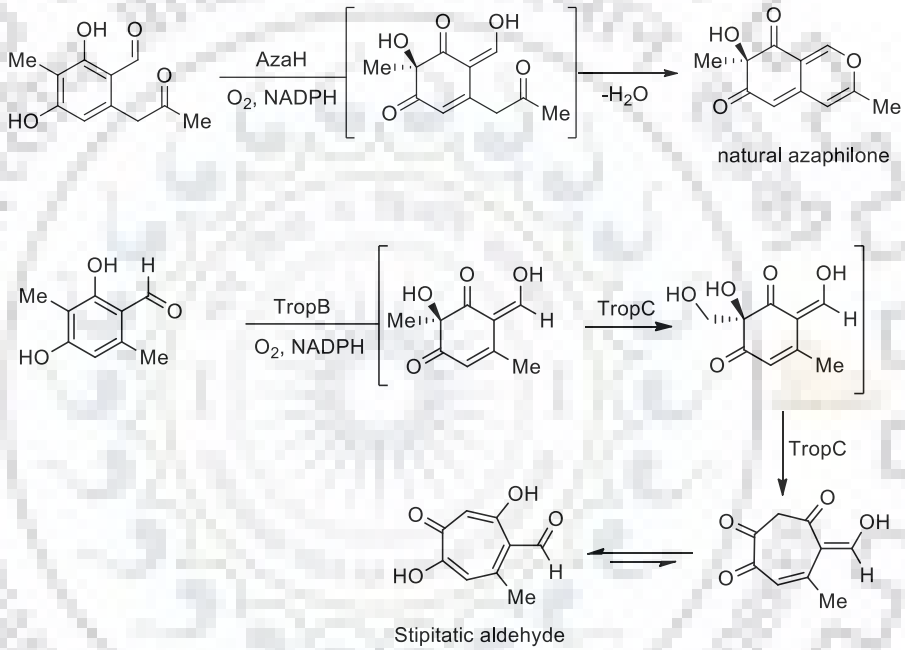
Scheme 7: Copper-catalyzed propargylic dearomatization of phenol derivatives.

Narayan *et al.* demostrated the biocatalytic and enantiocatalytic dearomatization of phenols. They harnessed the biocatalytic activity of the enzyme FAD-dependent monogeneses for site and stereoselective oxidative dearomatization of phenols with wide substrate scope (Scheme 8). They have successfully devised a methodology to form *ortho*-quinol products with controlled site-and stereoselectivity [35].



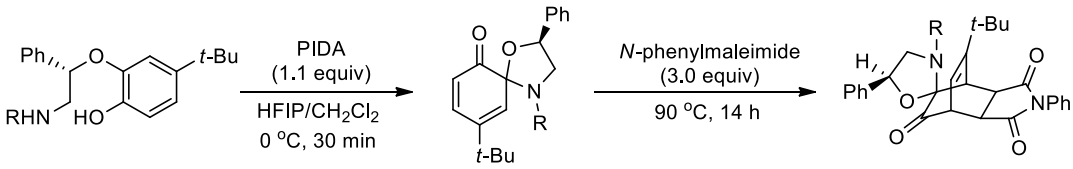
Scheme 8: Synthesis of *ortho*-quinol products from reactions with TropB.

Further, they leveraged the reactivity of these enzymatically generated *ortho*-quinols by carrying *in situ* enzymatic or chemical transformations to rapidly build complex molecular scaffolds (Scheme 9).



Scheme 9: One-pot cascades featuring biocatalytic oxidative dearomatization to access natural products.

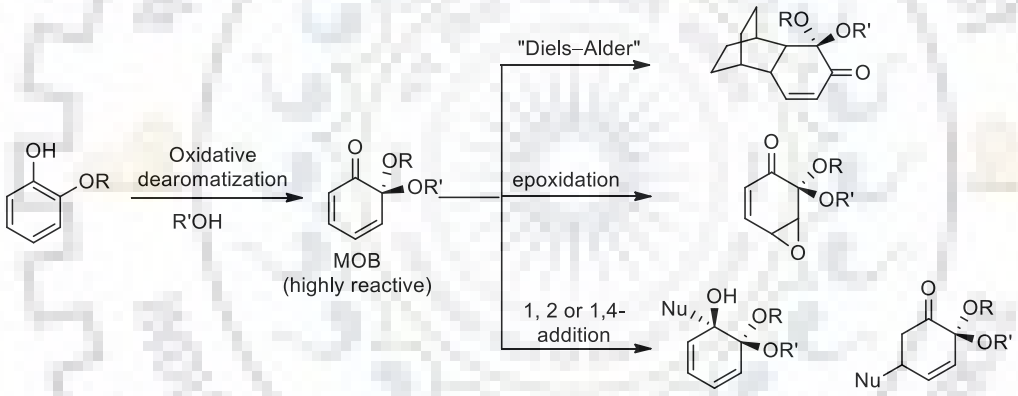
Nakada *et al.* described the oxidative dearomatization of phenols bearing amino moiety that further induced *N*-cyclization to form *ortho*-benzoquinone monohemiaminals. When the phenol was substituted with a chiral amino group, the *N*-cyclization afforded the product stereoselectively [36]. Further, to confirm the promising utility, the chiral *ortho*-benzoquinone monohemiaminals worked as dienes to form Diels–Alder adducts with electron-deficient alkenes (Scheme 10).



Scheme 10: Synthesis and reaction of *ortho*-benzoquinone monohemiaminals.

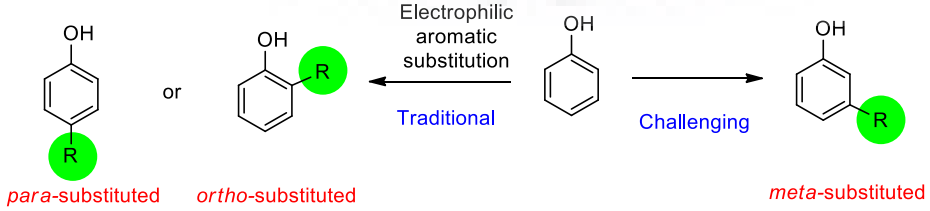
1.2. Synthesis of *meta*-subsituted phenols

Phenols and derivatives are ubiquitous in nature and are important synthons in organic synthesis [37,38]. The cyclohexa-2,4-dienones bearing ketal group at C6 position, well known as masked *ortho*-benzoquinones (MOBs) are important synthons in synthetic chemistry because of their commendable reactivity and ability to undergo various transformation as shown in Scheme 11.



Scheme 11: Synthetically useful transformations of masked *ortho*-benzoquinones.

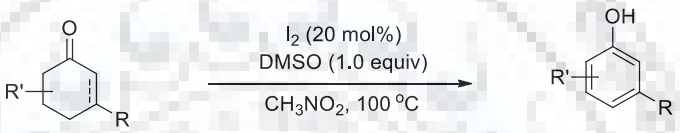
In general, electrophilic aromatic substitution reactions of phenol are well explored to form *ortho*-and *para*-functionalized phenols with ease, although until recently a very few methods are available to functionalize phenol derivatives at other positions, especially *meta*-functionalized phenols [39,40] (Scheme 12).



Scheme 12: Functionalization of phenols.

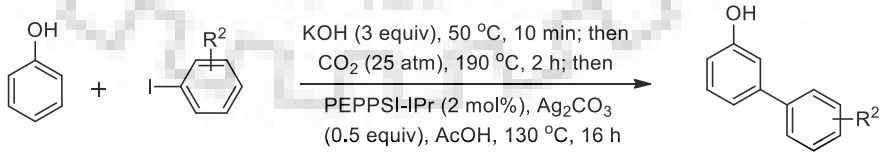
Till date, *meta*-functionalization has been accomplished either with the involvement of transition metals using harsh conditions or using the directing group strategy that results in lengthy synthetic route and there is no any simple and straightforward method available in literature to achieve it.

Jiao *et al.* reported an efficient, metal-free approach to *meta*-substituted phenols from the easily accessible cyclohexenones. The reaction highlighted the use of dimethyl sulfoxide (DMSO) as a mild oxidant and catalytic use of simple and common organic reagent iodine. This catalytic system tolerated various substituted functionalities including some easily reducible or oxidizable groups such as vinyl, allyl, *etc*. [41] (Scheme 13).



Scheme 13: Catalytic oxidative dehydrogenation of cyclohexenones and cyclohexanones to *meta*-substituted phenols.

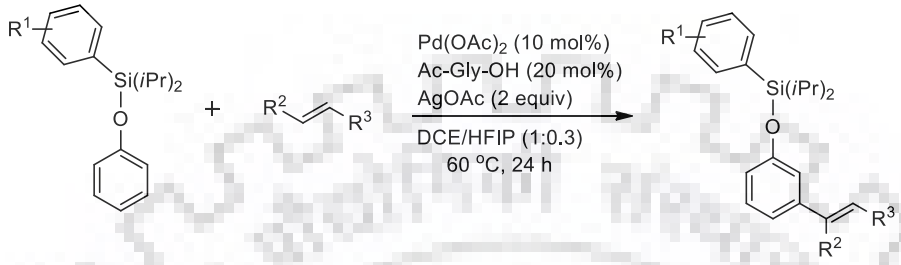
Larrosa and co-workers disclosed a methodology for the one-pot direct, regioselective *meta*-arylation of phenols. The methodology is based on *ortho*-installation of traceless directing group such as CO_2. This group overpowered the directing ability of the hydroxyl group and hence facilitated the incoming group *meta* to hydroxy moiety. The palladium catalyzed (PEPPSI-IPr) transformation showed high compatibility with a number of functional groups in the phenols as well as in iodoarenes. The directing group can easily be cleaved to form the desired *meta*-arylated products without leaving any traces [42] (Scheme 14).



Scheme 14: Traceless directing group mediated *meta*-arylation.

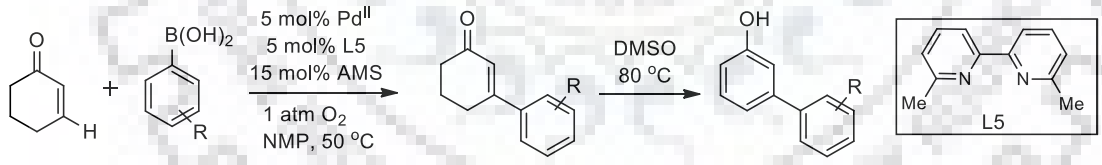
In 2017, Xu research group developed the first example of template-directed *meta*-selective C–H alkenylation of phenols. Organosilicon group has been employed as traceless

template to override the *ortho*/*para*-directing effect of the hydroxyl group. The reaction was catalyzed well by the ligand Ac-Gly-OH in the presence of AgOAc as an oxidant and the used template can easily be removed or recyclable under mild conditions to furnish the *meta*-alkenylated aromatic compounds which are otherwise not easily accessible [43] (Scheme 15).



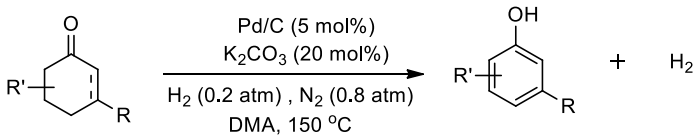
Scheme 15: The template directed *meta*-selective C–H functionalization of phenols.

Stahl *et al.* highlighted an efficient strategy to access *meta*-substituted phenols by an aerobic oxidative Heck reaction followed by dehydrogenation sequence starting from cyclohexenones. They developed a new catalyst/ligand system $[Pd(CH_3CN)_4](BF_4)_2$/L5 that proved to be very effective for oxidative Heck reaction. Use of anthraquinone-2-sulfonic acid sodium salt (AMS) as co-catalyst in *N*-methylpyrrolidone (NMP) as solvent for Heck oxidation and subsequent addition of DMSO for dehydrogenation step enabled good yield of phenols obtained [44] **(**Scheme 16).



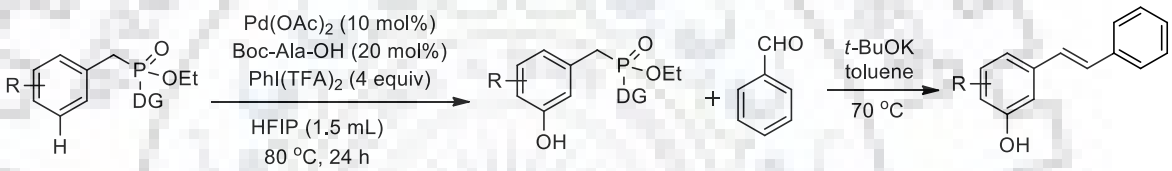
Scheme 16: One-pot oxidative Heck/dehydrogenation reactions for *meta*-substituted phenols.

In 2015, Liu and co-workers reported dehydrogenation of a wide range of substituted 2-cyclohexenones and cyclohexanones to their respective phenols using the combination of commercially available Pd/C and H_2. The reaction proceeded with high isolated yields of *m*-substituted phenols in *N*,*N*-dimethyl-acetamide (DMA) as solvent and avoid the use of oxidants or hydrogen acceptors. Moreover, H_2 is the only by-product of the reaction that could also work as co-catalyst. The protocol showed a good substrate scope, manifest a high atom economy and can show its application in industrial settings [45] (Scheme 17).



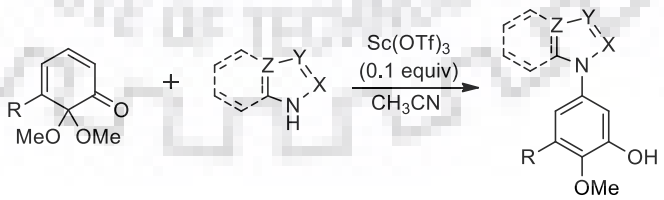
Scheme 17: Palladium-catalyzed dehydrogenation of 2-cyclohexenones to phenols.

Maiti *et al.* developed Pd (II)-catalyzed *meta* C−H functionalization reactions. This was the first template-assisted *meta*-olefination while incorporating a cyanophenol-based directing moiety. They studied a unique catalytic activity of Pd(II)-MPAA *i.e.*, metal−ligand system using $PhI(TFA)_2$ as the hydroxylating agent for the *meta*-hydroxylation, which was then followed by the removal of phosphonates linkers *via* modified Horner−Wadsworth−Emmons reaction in the presence of potassium *tert*-butoxide [46] (Scheme 18).



Scheme 18: Pd(II)-catalyzed template-assisted *meta*-functionalization of arenes.

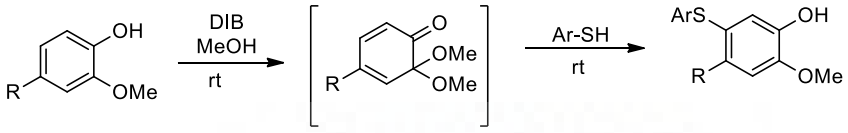
Chittimalla *et al.* delineated the *N*-aryltion of heterocycles by a tandem aza-Michael addition reaction in the presence of scandium(III) triflate. Their approach relied on the aza-Michael attack on cyclohexa-2,4-dien-1-one derivatives by NH-heterocycles followed by aromatization to synthesize *N*-aryl heterocyclic Michael adducts in good yields. The reaction showed wide substrate scope resulting from the easy accessibility of variously substituted cyclohexa-2,4-dienones [47] (Scheme 19).



Scheme 19: Tandem aza-Michael addition/aromatization sequence for the *N*-arylation of NH-heterocycles.

In 2014, our research group reported the metal-free, novel, efficient C–S bond formation with thiols. We have developed a protocol for the formation of unsymmetrical

alkyl aryl/diaryl sulfides in excellent yields *via* Michael addition reaction of *in situ* generated masked *o*-benzoquinones with thiols under catalyst-free and aerobic conditions [48] (Scheme 20).



Scheme 20: Synthesis of diaryl sulfides from MOBs and thiophenols.

1.3. Synthesize diaryl sulfones

Diaryl sulfones served as valuable starting materials for various synthetic applications in biological chemistry (Figure 3) because of its diverse range of behavior and unique features [49–51]. Fuchs *et al*. termed sulfones as "pluripotent" and they have been described as "chemical chameleons" by Trost [52,53]. As a consequence, considerable efforts have been made for the progress towards the development of methodologies to synthesize this building block.

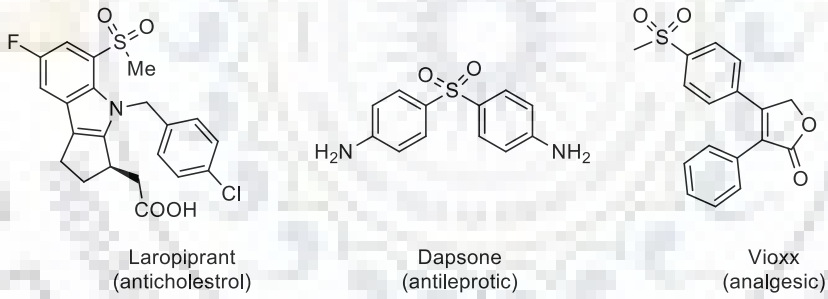
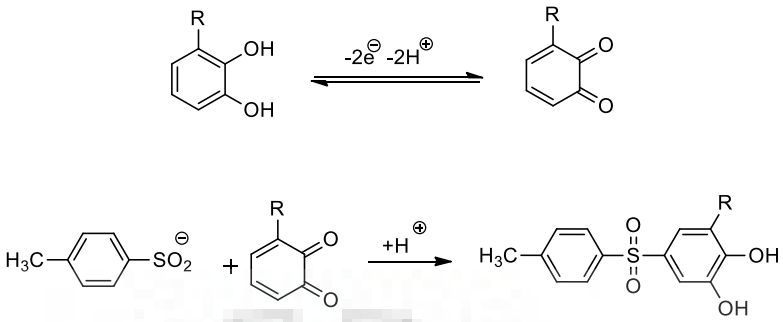


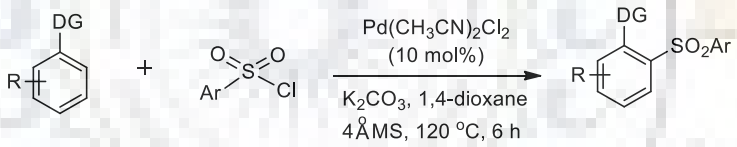
Figure 3: Drugs containing aryl sulfone motif.

The first electrochemical synthesis of arylsulfonylbenzenediol derivatives was described by Nematollahi *et al.* in 2002 by the anodic oxidation of catechols in the presence of arylsulfinic acid in water [54]. The transformation of 1 mM catechol to *o*-benzoquinone within a quasi-reversible two-electron process had traced by cyclic voltammetry. The formed quinones are quite reactive and can easily undergo Michael attack by 4-toluenesulfinic acid to provide the corresponding arylsulfonylbenzenediols in good yields (Scheme 21).



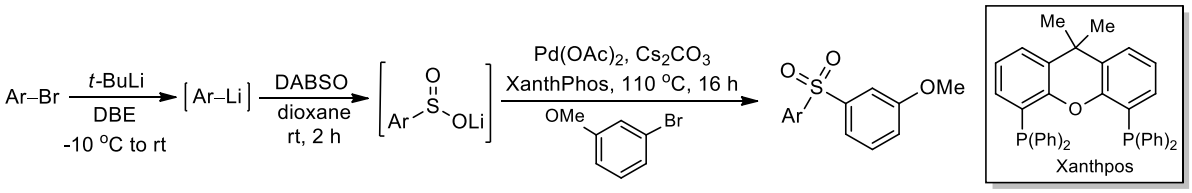
Scheme 21: Electrochemical synthesis of *p*-tolylsulfonylbenzenediols.

Dong *et al.* disclosed the concept of transition metal-mediated C–S bond formation to produce sulfones. The use of arylsulfonyl chlorides as remarkably flexible reagents was highlighted for the Pd catalyzed C–H bond functionalization to access regioselective sulfones. The authors carried out the C–H bond activation using $Pd(CH_3CN)_2Cl_2$ as the catalyst in 1,4-dioxane to form a C–S bond to afford the diaryl sulfones in excellent yields and regioselectivity [55] (Scheme 22).



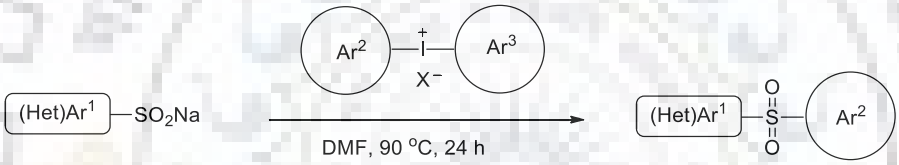
Scheme 22: Pd-catalyzed synthesis of diaryl sulfones.

In 2013, Willis *et al.* introduced a bench-stable sulfonylating agent DABSO, a white solid, formed as a complex between 1,4-diazabicyclo[2.2.2]octane (DABCO) and two sulfur dioxide molecules. They have demonstrated a palladium-catalyzed convergent three-component coupling approach through the combination of two easily available coupling partners *viz*, an aryl lithium species and aryl, heteroaryl, or alkenyl (pseudo)halide. They react with SO_2 delivered from DABSO and by using XantPhos-type ligand to access diverse range of heteroaryl, aryl, and alkenyl sulfones [56] (Scheme 23).



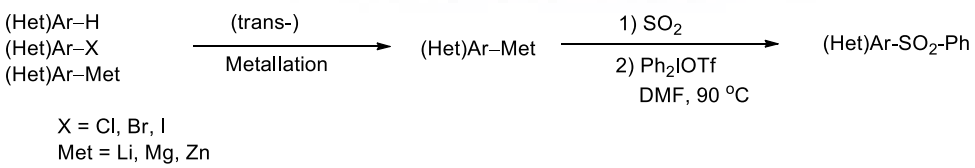
Scheme 23: Palladium-catalyzed preparation of sulfones.

Manolikakes *et al.* reported the utility of arylsulfinic acid salts as readily available substrates for the synthesis of diaryl sulfones. Treatment of sodium salts of arylsulfinic acids with diphenyliodonium triflate in polar aprotic solvents such as *N*,*N*-dimethylformamide (DMF) afforded the desired diaryl sulfones in maximum yields. The reaction tolerated a range of functional groups and displayed high chemoselectivity with unsymmetrical diaryliodonium salts [57] (Scheme 24).



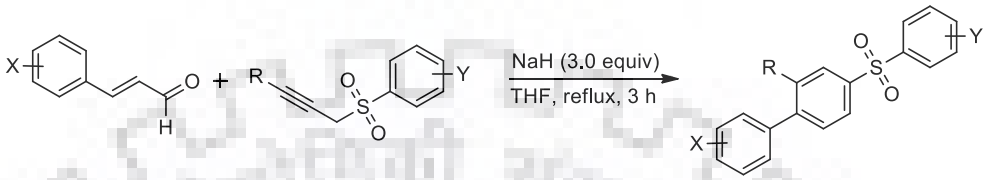
Scheme 24: Metal-free synthesis of diaryl sulfones.

The same research group in 2015, explored the transition metal-free arylation of lithium, magnesium, and zinc salts of sulfinic acids. The salts of sulfinic acids were generated from the reaction of sulfur dioxide and the corresponding organometallic reagents. The three-step, one-pot protocol involved i) the generation of organometallic reagent *via* metal−halogen exchange, and direct metal insertion, ii) reaction of *in situ* generated organometallic reagent with sulfur dioxide, iii) removal of excess sulfur dioxide, and iv) the treatment of crude sulfinate with a diaryliodonium salt to furnish various aryl- and heteroaryl sulfones straightforward in one-pot procedure [58] (Scheme 25).



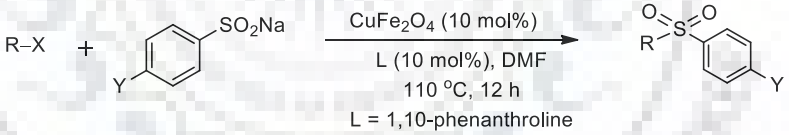
Scheme 25: One-pot route to aryl sulfones from organometallic reagents and iodonium salts.

Lin *et al.* accomplished transition metal-free NaH-mediated synthesis of aryl biaryl sulfones. They presented the synthesis of sulfonyl biphenyls *via* NaH-mediated tandem [C_3 + C_3] annulations of cinnamaldehydes with propargylic sulfones in refluxing THF [59] (Scheme 26).



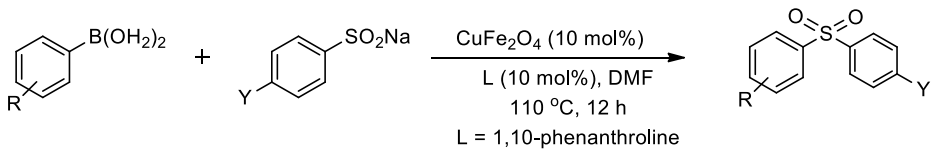
Scheme 26: One-pot synthesis of aryl biaryl sulfones.

An inexpensive, environmentally benign and recyclable heterogeneous catalytic system comprised of magnetic nanoparticles were developed by Sreedhar *et al.* in 2014 for the formation of diaryl and alkyl/aryl sulfones. Magnetically separable copper ferrite ($CuFe_2O_4$) nanoparticle shown excellent catalytic activity when the reactions were performed between various alkyl halides and sodium arylsulfinates to access aryl sulfones in good to excellent yields [60] (Scheme 27).



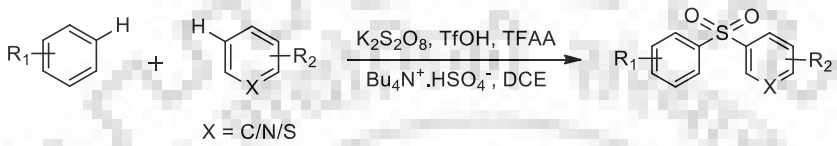
Scheme 27: Recyclable heterogenous catalysis to generate diaryl sulfones.

The similar catalytic condition worked well for the cross-coupling reaction between arylsulfinic acid salts and various alkyl or/aryl boronic acids to generate the corresponding aryl sulfones. The recyclability and the easy magnetic separation of the catalytic system was sustainable attributes of this protocol (Scheme 28).



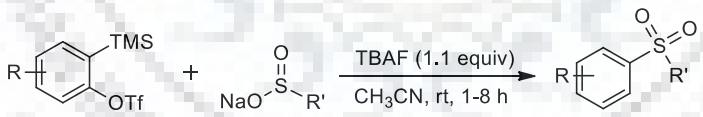
Scheme 28: Copper ferrite nanoparticles-catalyzed synthesis of diaryl sulfones.

Double C–S bond formation method was developed by the research group of Rao in 2014. They explored the use of persulfate salts as sulfonating agents to access both symmetric and unsymmetric diaryl sulfones. Simple arenes underwent sulfonylation in the presence of persulfate salts like potassium persulfate under appropriate acidic conditions. Excellent yields of the products proved potassium persulfate, a highly efficient and atom economical sulfonating reagent [61] (Scheme 29).



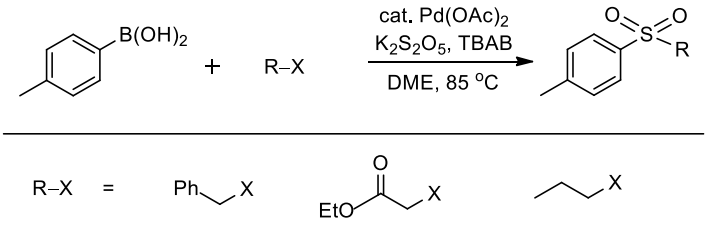
Scheme 29: Preparation of unsymmetrical diarylsulfones.

In 2014, Mhaske research group reported an efficient transition metal-free C−S bond formation strategy to access structurally diverse sulfones in excellent yields. They applied aryne methodology to prepare biologically active and synthetically useful sulfone derivatives by the reaction between *O*-silyl aryl triflates and sodium benzenesulfonates in acetonitrile with TBAF as fluoride source as well as phase transfer catalyst [62]. The protocol was robust, eco-friendly and capable of forming the diversified array of sulfones such as aryl-alkyl sulfones, diaryl sulfones, and aryl-heteroaryl sulfones (Scheme 30).



Scheme 30: Synthesis of aryl sulfones from sodium sulfinates *via* arynes.

Recently, Smith *et al.* also synthesized the (hetero)aryl alkyl sulfones by the reaction of (hetero)aryl boronic acids and inactivated alkyl halides. They established palladium-catalyzed one-step procedure by heating the mixture of 4-tolylboronic acid with an excess of the alkyl electrophile, and potassium metabisulfite in DME in the presence of tetrabutylammonium bromide (TBAB) as phase transfer catalyst. To get the insight of the reaction mechanism, the group performed stoichiometric experimentation and confirmed the structure of *in situ* generated palladium sulfinate by X-ray diffraction analysis [63] (Scheme 31).

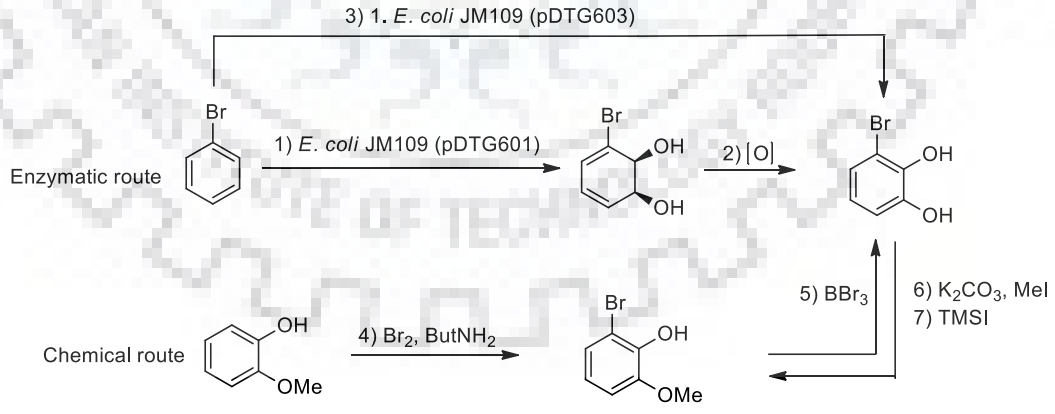


Scheme 31: Synthesis of aryl alkyl sulfone from boronic acids.

1.4 Synthesis of substituted catechols

Catechols are communal structural scaffolds that form the core of many natural products and drugs [64,65], more than 200,000 compounds containing a catechol motif bear useful pharmacological activity. Numerous traditional approaches has been realized for the synthesis of catechols [66,67].

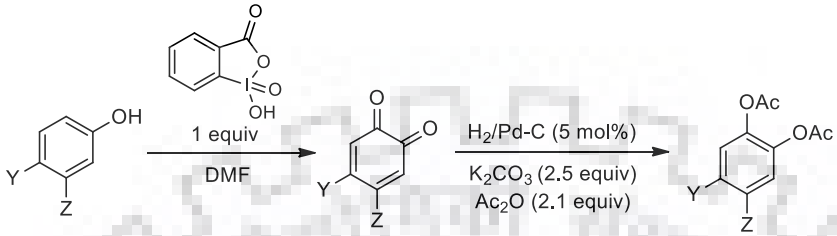
In 2000, Hudlicky *et al.* studied the comparison between enzymatic and traditional chemical methods for the preparation of functionalized catechols. Aromatic precursors transformed to catechols by the treatment of arenes with the recombinant organism *Escherichia coli* JM109 (pDTG602), developed by Gibson and it expressed in both toluene dioxygenase (TDO) and dihydrocatechol dehydrogenase (DHCD) enzyme activity. On comparison, they found the bioenzymatic method superior over the chemical method because of high effective mass yields [68] (Scheme 32).



Scheme 32: Enzymatic and non-enzymatic preparation of 3-bromocatechol.

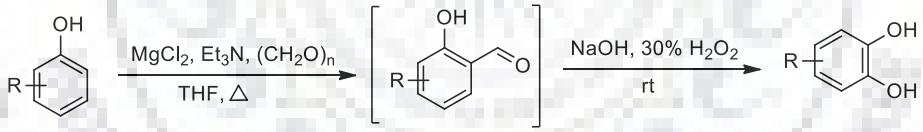
Pettus *et al.* explored the reactivity of *o*-quinones for the formation of variety of catechols. Phenols underwent efficient regioselective oxidation to unsymmetric *o*-quinones

with *o*-iodoxybenzoic acid (IBX) a hypervalent iodine(V) reagents [69]. The *in situ* generated quinones then subjected to reduction in DMF with K_2CO_3, Ac_2O and Pd/C (5 mol%) to synthesize bisacetylated catechol derivatives. This protocol involved the successive oxidation, reduction, and acylation in one-pot to form catechols (Scheme 33).



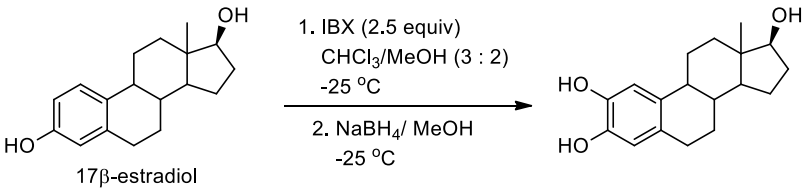
Scheme 33: Regioselective oxidation of phenols to *ortho*-quinones with IBX.

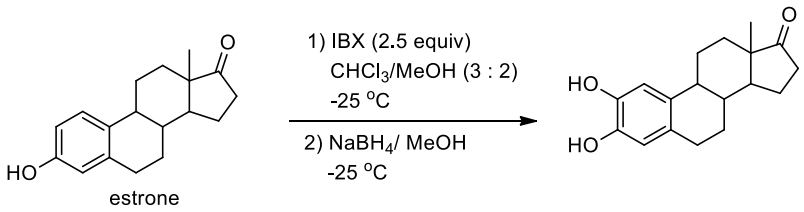
Dakin reaction is among the oldest methods known for the formation of catechols. Skattebøl *et al.* used a simple procedure by refluxing the mixture of the phenol, tri-ethylamine, anhydrous $MgCl_2$, and paraformaldehyde in acetonitrile or THF for the selective *ortho*-formylation of phenols to form salicylaldehydes derivatives in excellent yields [70]. Formylation of substituted phenols followed by the Dakin oxidation using H_2O_2 and aqueous NaOH afforded the corresponding catechols in one-pot (Scheme 34).



Scheme 34: One-pot synthesis of substituted catechols from the corresponding phenols.

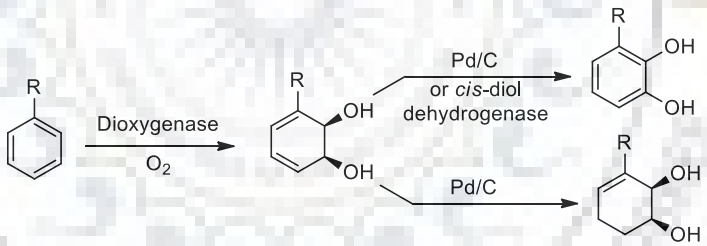
In 2005, Pezzella *et al.* further showed the utility of IBX-mediated oxidation of electron-rich phenols to catechols by applying this procedure to a number of representative substrates such as 17β-estradiol and estrone containg phenols moiety. Phenolic substrates were oxidized to quinones using solid IBX (2.5 equiv) in $CHCl_3$/MeOH 3:2 (v/v) and the formed quinone further reduced to catechol using methanolic $NaBH_4$ [71] (Scheme 35).





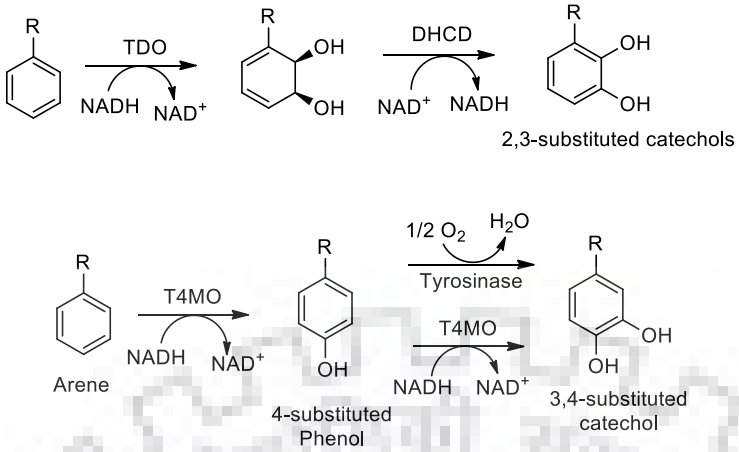
Scheme 35: Synthesis of catechol-estrogens *via* IBX-mediated phenolic oxygenation.

Hardacre *et al.* demonstrated the comparative study of enzymatic and chemo-enzymatic method for the synthesis of 3-substituted catechols. A wide range of substituted benzenes were converted to *cis*-dihydrodiol derivatives through the toluene dioxygenase (TDO) using UV4 mutant strain of *Pseudomonas putida*. These *cis*-dihydrodiols were subjected to dehydrogenation bio-enzymatically by a naphthalene *cis*-diol dehydrogenase {which is originated from *Rhodococcus* species (NDDR), though expressed and utilized in the recombinant strain *Escherichia coli* DH5a (pUC129:nar B)} and chemo-enzymatically by the use of heterogeneous catalyst (Pd/C) to synthesize catechols and *cis*-tetrahydrodiol ,respectively. Both the routes are found to be complementary to each other through the comparative studies [72] (Scheme 36).



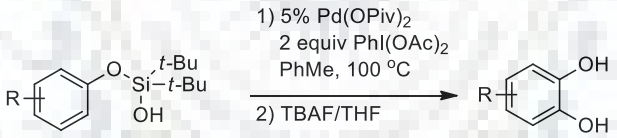
Scheme 36: Synthesis of 3-substituted catechols using an enzymatic and chemo-enzymatic methods.

Connor *et al.* revealed the use of biotechnologically relevant enzymes oxido-reductases, well known for their regio- and stereo-specificity for the synthesis of substituted catechols. Various substituted arenes underwent regiospecific hydroxylation leading to a range of substituted 2,3-catechols under the catalytic influence of toluene dioxygenase (TDO) and dihydrocatechol dehydrogenase (DHCD) [73]. Other oxidoreductases like mushroom tyrosinase, *Pseudomonas putida* F6, bacterial tyrosinase, *Pseudomonas mendocina* KR1 and toluene-4-monooxygenase (T4MO) also worked efficiently for the synthesis of substituted phenols and catechols (Scheme 37).



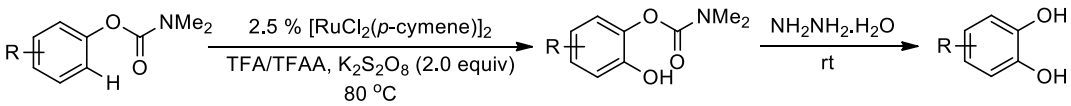
Scheme 37: Preparation of catechols *via* enzymatic activity of microbes.

Gevorgyan research group found another general and highly site-selective method for oxygenation of phenols including the ones bearing electron-deficient groups [74]. They presented Pd-catalyzed and silanol directed acetoxylation followed by a subsequent acid-catalyzed cyclization reaction for the formation of cyclic silicon-protected catechols *i.e.*, silacycle, which upon desilylation with TBAF uncovered the corresponding catechol products (Scheme 38).



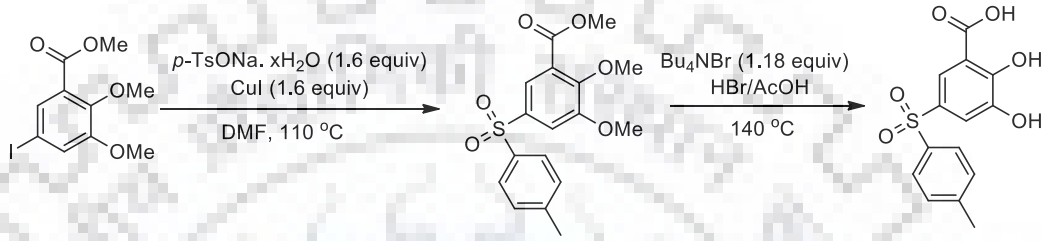
Scheme 38: Synthesis of catechols *via* Pd-catalyzed silanol-directed C –H oxygenation.

In 2014, Rao *et al.* described the use of transition metals for preparing catechol derivatives. They showed the ruthenium(II)- and palladium(II)-catalyzed C–H hydroxylation of aryl carbamates with trifluoroacetic acid/trifluoroacetic anhydride (TFA/TFAA) and oxidant $K_2S_2O_8$ system. The reaction proceeded with high *ortho*-selectivity, high yields and good functional group tolerance [75] (Scheme 39).



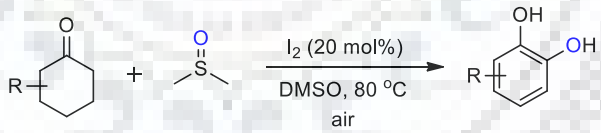
Scheme 39: Synthesis of catechol derivatives using transition metal catalyst.

Diederich *et al.* reported the synthesis of potent inhibitors of COMT (catechol *O*-methyltransferase) an enzyme for the treatment of Parkinson's disease. They demonstrated a convergent approach in which a series of functionalized catechol intermediates coupled to a common sulfone moiety. Firstly, methyl 5-iodo-2,3-dimethoxybenzenecarboxylate was converted to sulfonyl derivative, then methyl ester and ethers were cleaved under harsh acidic conditions to form catechol [76] (Scheme 40).



Scheme 40: Synthesis of catechol building block for COMT inhibitors.

Recently, Jiao *et al.* reported the scope of cyclohexanones, a stable and readily available bulk chemicals for the preparation of substituted catechols. This transformation was catalyzed by mild reagent I_2 in non-toxic solvent DMSO that also worked as an oxidant and hydrogen acceptor. The protocol marked its utility by the easy synthesis of 3,3',4,4'-tetrahydroxybiphenyl, an inhibitor of Alzheimer's amyloid-β peptide [77] (Scheme 41).

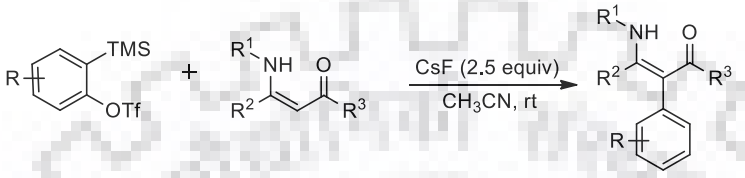


Scheme 41: Aromatization of cyclohexanones to catechols.

1.5 α–arylation of C–H activated pronucleophiles and synthesis of heterocycles

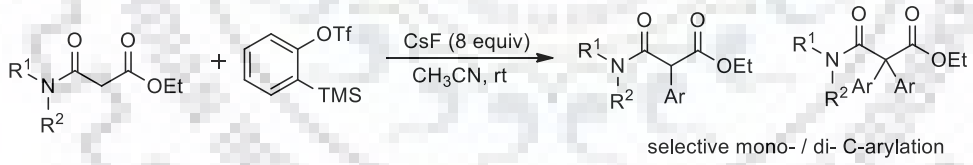
C–arylation has become an immensely well known field in synthetic organic chemistry and give access to a plethora of new functional motifs [78,79]. Of particular importance is the C–H functionalization of 1,3-diones [80]. In recent years, β-dicarbonyl compounds, because of their ability to undergo diverse array of transformations based upon the reactivity of functional groups, have been proved to be attractive synthons for generating high profile pharmaceutical compounds.

Ramtohul and Chartrand reported a convenient, efficient, and general method for the *C*-arylation of α-enamino esters and ketones with arynes. The presented protocol tolerated a wide variety of functionalities to provide an easy and direct access to numerous substituted aromatic α-enamino compounds that could potentially be converted into chiral *α*-amino acids [81] (Scheme 42).



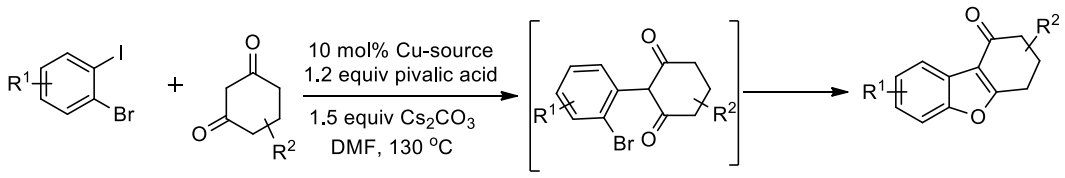
Scheme 42: *C*-arylation of α-enamino esters with benzynes.

The research group of Mhaske explored aryne chemistry by disclosing a facile, transition metal-free, fluoride-induced chemoselective α-arylation of β-dicarbonyl compounds. They also demonstrated the selective mono- or diarylation and generated a quaternary benzylic stereocenter. The distinctive advantage of this methodology was preferential chemoselective *C*-arylation over *N*-arylation. The methodology proposed to be highly useful for the preparation of a library of barbiturate based drugs like phenobarbital popularly known as CNS depressant [82] (Scheme 43).



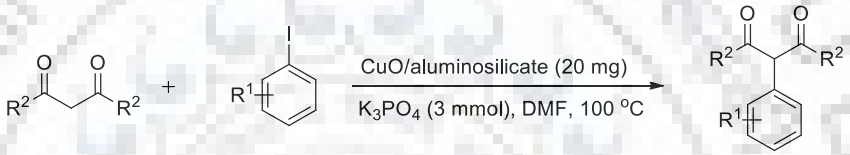
Scheme 43: Transition metal-free *C*-arylation by arynes.

Beifuss *et al.* disclosed Cu(I)-catalyzed reaction of 1,3-cyclohexanediones and bromo-2-iodobenzenes and other 1,2-dihalobenzenes using Cs_2CO_3 in the presence of pivalic acid as an additive in DMF to furnish selectively 3,4-dihydrodibenzo[*b*,*d*]furan-1(2*H*)-ones with moderate to good yields [83]. This highly regioselective CuI-catalyzed domino protocol was based on an intermolecular Ullmann *C*-arylation followed by an intramolecular Ullmann *O*-arylation (Scheme 44).



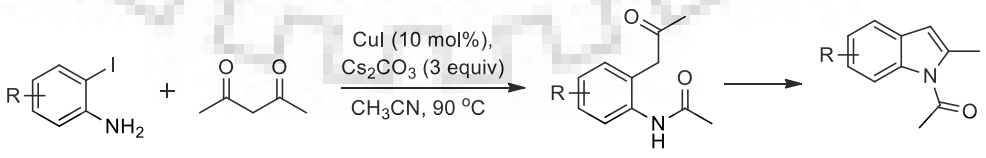
Scheme 44: Cu-catalyzed synthesis of 3,4-dihydrodibenzo[*b*,*d*]furan-1(2*H*)-ones.

Karvembu *et al.* carried out α-arylation of β-diketones over CuO nanoparticles / alumino-silicate catalyst under ligand-free conditions. Aryl halides reacted with acetyl-acetone in the presence of base in DMF to form α-aryl ketones. Reaction showed regioselective nature towards C–Br bond even in the presence of C–Cl bond to afford the corresponding products in good to excellent yields [84] (Scheme 45).



Scheme 45: CuO nanoparticle-catalyzed α-arylation of β-diketones.

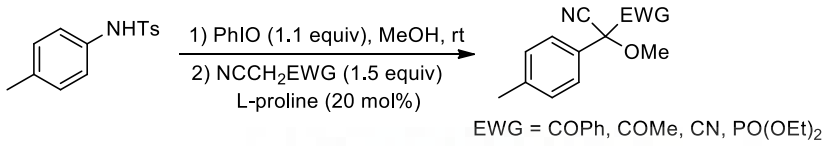
Li and his co-workers developed an efficient copper-catalyzed synthesis of (*N*-acylamino)aryl ketones from 1,3-dicarbonyl compounds and 2-iodoanilines *via* C–C bond cleavage. In this protocol, the internal *ortho* effect between the C–I bond of 4-iodoaniline and amino group played a decisive role on the selectivity of the reaction and also improved the reactivity of the transformation. The distinctive feature of the reaction was that unlike the previous reports, this methodology involves the coupling of both the nucleophilic and electrophilic parts of the 1,3-dicarbonyl compound with 2-iodoaniline by C–C bond cleavage to furnish *o*-(*N*-acylamino)aryl ketones that could be transformed further to multisubstituted indoles [85] (Scheme 46).



Scheme 46: Copper-catalyzed reactions of 1,3-dicarbonyl compounds with 2-iodoanilines.

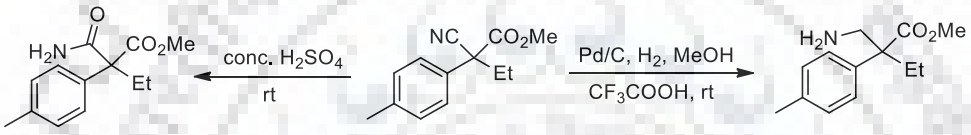
Fan *et al.* reported a simple dearomatization strategy for the synthesis of aromatic compounds. They showed the C–N functionalization of *p*-substituted anilines a potential aryl

source with 2-cyanoacetate to form C–C bond under the catalysis of L-proline and PhIO as an oxidant [86] (Scheme 47).



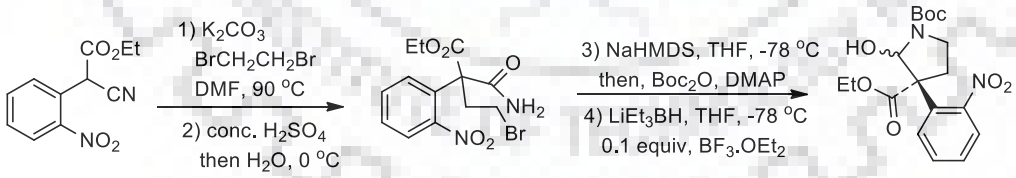
Scheme 47: Construction of cyano-substituted α-aryl quaternary carbon centers.

Cyano group of obtained quaternary products were then manipulated for the construction of diverse array of aromatic molecules such as amides and α-keto esters (Scheme 48).



Scheme 48: Transformation of cyano-substituted quaternary carbon center.

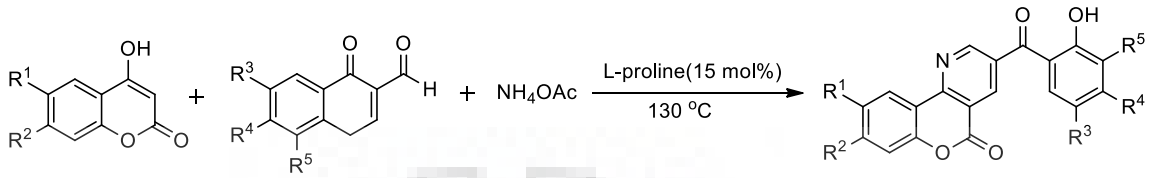
Recently, Gaich research group revealed the utility of α-cyanoacetate in the formal synthesis of strictamine precursor. Strictamine is an akuammiline alkaloid and has good traditional medicinal value. At the outset, α-cyanoacetate was alkylated to generate the quarternary carbon center and the nitrile group was hydrolyzed to form carboxylic amide. The lactum formation followed by its protection as *tert*-butyl carbamate furnished hemiaminal as a starting precursor for strictamine [87] (Scheme 49).



Scheme 49: Establishment of quaternary carbon center.

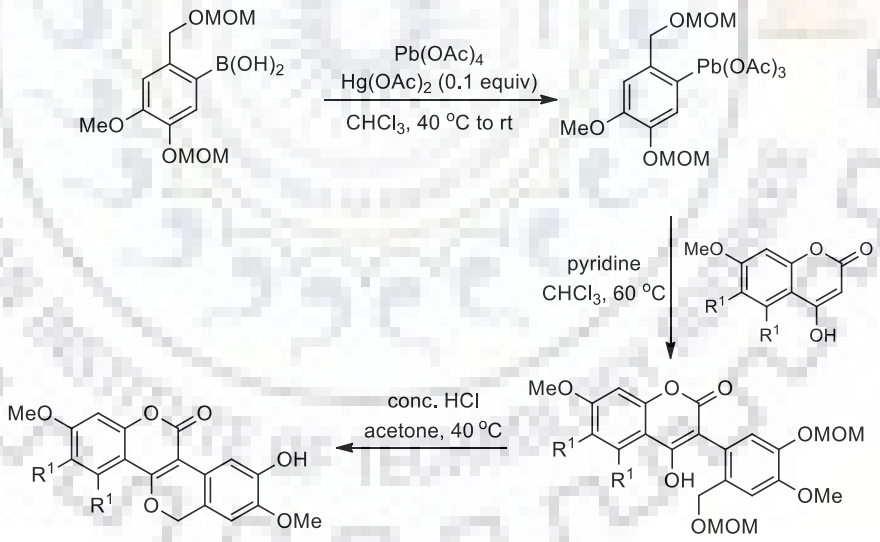
Paul and Lee revealed the utility of 4-hydroxycoumarin moiety for the synthesis of chromenopyridinones. The protocol included one-pot three-component condensation between various 4-hydroxycoumarins with ammonium acetate and 3-formylchromones using *L*-proline as a catalyst under solid-state melt conditions. The scaffolds with electron-donating

groups on chromeno[4,3-*b*]pyridine boost intramolecular charge transfer and exhibit strong fluorescence emission [88] (Scheme 50).



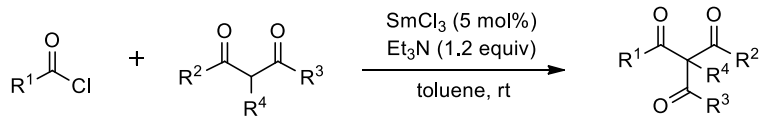
Scheme 50: Construction of chromenopyridinones by the multi-component reaction.

In 2006, Fedorov *et al.* reported the assimiliation of hydroxycoumarin with the phenolic moiety that led to the formation of tetracyclic 6*H*,11*H*-[2]benzopyrano-[4,3-*c*] [1]benzopyran-11-ones in good yields. Initially, the aryl lead triacetates were generated *in situ* by the direct boron-to-lead transmetallation in the presence of a catalytic amount of $Hg(OAc)_2$; thus obtained organoleads were sequentially treated with 4-hydroxycoumarins in the presence of pyridine and dil. HCl to afford benzopyraone derivatives in good yields [89] (Scheme 51).



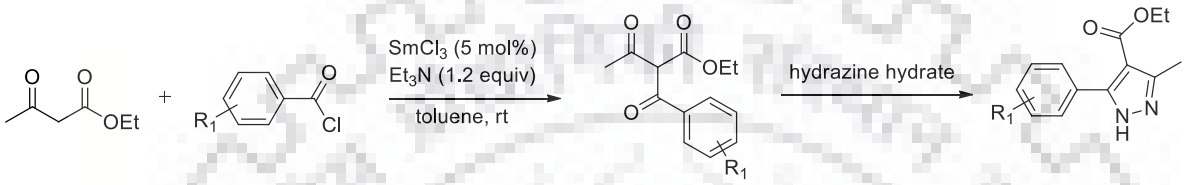
Scheme 51: Synthesis of 3-aryl-4-hydroxycoumarins and their cyclization.

Zhou research group developed a convenient and efficient strategy for the *C*-acylation of malononitrile and 1,3-dicarbonyl compounds with acid chlorides. This was the first $SmCl_3$-catalyzed protocol that obviated the use of strong bases and stoichiometric amounts of Lewis acids and can also tolerate functional groups bearing heteroatoms [90] (Scheme 52).



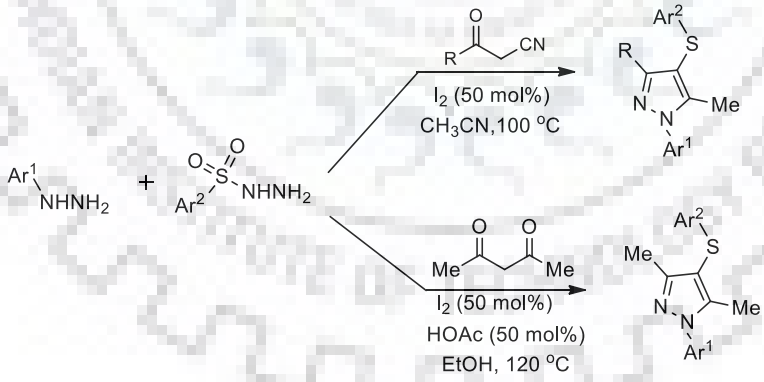
Scheme 52: $SmCl_3$-catalyzed *C*-acylation of 1,3-dicarbonyl compounds.

Straightforward synthesis of pyrazole-4-carboxylate derivatives further proved the synthetic utility of this protocol (Scheme 53).



Scheme 53: One-pot synthesis of pyrazole-4-carboxylates.

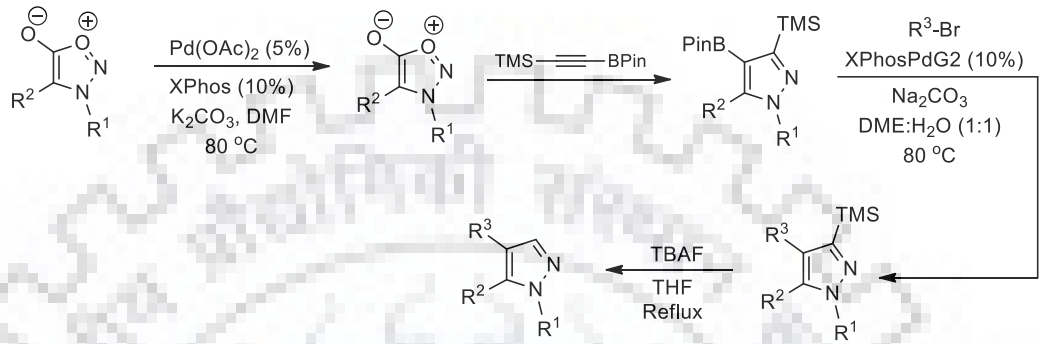
Tu *et al.* established three-component iodine-mediated metal-free access toward fully substituted pyrazoles. The reaction involved [3 + 2] annulation of pentane-2,4-dione/β-ketonitrile, aryl hydrazines and sulfonyl hydrazides and allowed the formation of two C–N and one C–S bonds under mild conditions. The distinctive features of the protocol was operational simplicity, bond-forming efficiency, low-cost and readily accessible substrates [91] (Scheme 54).



Scheme 54: Synthesis of fully substituted pyrazoles and its sulfenylation.

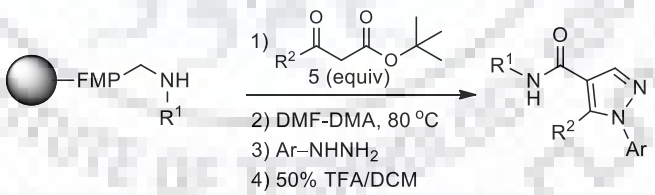
Kanthou *et al.* reported a new route to pyrazole-based analogs of combretastatin A4 which belongs to important class of tubulin-binding agents and are clinically utilized for cancer therapy. This potent pyrazole core was synthesized by using highly regioselective alkyne cycloaddition reactions of sydnones. The synthesis began with arylation of *N*-methyl

and *N*-benzylsydnones to afford C4-arylated sydnones which underwent cycloaddition to form corresponding pyrazoles. These heterocycles were further subjected to the Suzuki−Miyaura reaction followed by silyl deprotection to afford the target analogues [92] (Scheme 55).



Scheme 55: Synthesis of densly substituted pyrazole analogs of combretastatin A4.

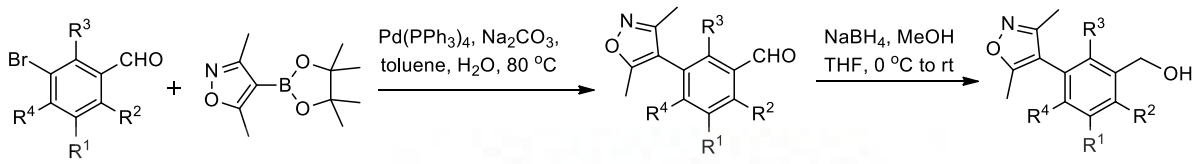
Gerritz and co-workers discovered a novel series of antagonists of the CB-1 receptors from a library of 1,5-diarylpyrazole-4-carboxamides on solid phase using IRORI MicroKan technology. The chemistry started with the acylation of a resin bound secondary amine *via* transamidation with a β-ketoester to form β-ketoamide which was then converted to vinylogous amide on reacting with dimethylformamide-dimethylacetal (DMF-DMA) and the subsequent reaction with hydrazine followed by the cleavage of the resin gave 1,5-substituted pyrazole-4-carboxamides [93] (Scheme 56).



Scheme 56: Solid phase synthesis of 1,5-diarylpyrazole-4-carboxamides.

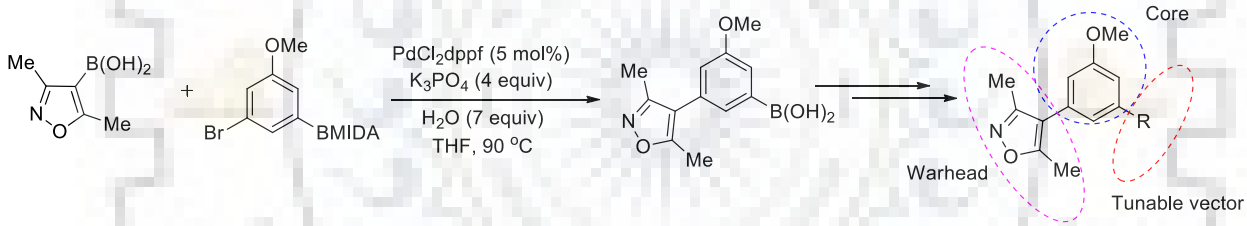
Zhang *et al.* designed and discovered the synthesis and biological evaluation of agonists GPR40 which is an attractive target for insulin secretion with low risk of causing hypoglycemia. The compounds having a core moiety of 3,5-dimethylisoxazole mostly worked well *in vitro* as an excellent GPR40 agonists. Their synthesis started from Suzuki coupling reaction of aldehyde precursors with 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-

dioxaborolan-2-yl)isoxazole followed by the reduction with $NaBH_4$ leading to the formation of 3,5-dimethylisoxazoles [94] (Scheme 57).



Scheme 57: Route to substituted isoxazoles *via* Suzuki coupling.

3,5-Dimethylisoxazole forms a core motif of a series of analogues of a BET bromodomain inhibitor which is a target of particular interest in drug discovery programs. Watson *et al.* demonstrated formal sp^2 homologation reaction between boronic acids and conjunctive bromoaryl/vinyl BMIDA components. This protocol gave an efficient and direct access to functionalized boronic acids. The versatile boronic acids can be used in diverse oriented synthesis within drug discovery [95] (Scheme 58).



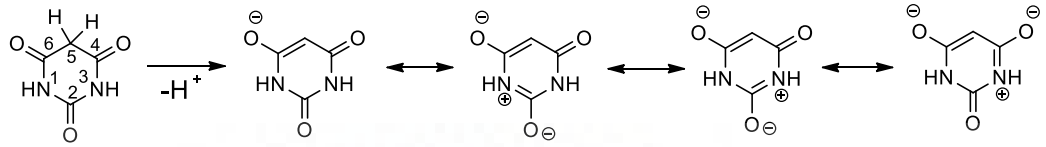
Scheme 58: Formal homologation of boronic acids to form subsitituted isoxazoles.

1.6 Synthesis of barbituric acid derivatives

In the area of medicinal chemistry, since the emergence of hypnotics and sedatives at the turn of the 20th century, barbituric acid (pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione, H_3BA) had a long commendable history. They are found to be the building blocks of not only thousands of privileged biologically active compounds [96] but also in dyes and polymerization catalyst compounds [97].

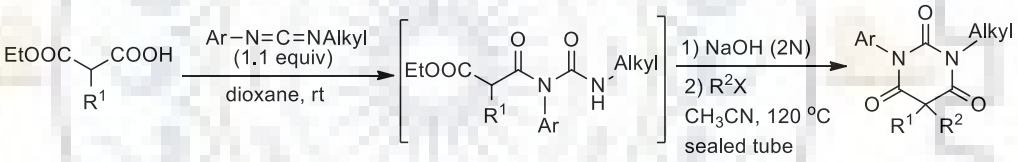
Barbiturates embodying five (three O and two N) potential metal binding (donor–acceptor) sites that makes them versatile polyfunctional ligands in coordination and supramolecular chemistry [98]. Due to the presence of the activated methylene group, the pyrimidine ring is additionally stabilized by resonance delocalization (Scheme 59) [99].

Moreover, the pyrimidine ring of barbiturates can be easily functionalized at position 5 *via* deprotonation of most acidic proton that allows the formation of a planar carboanion. [100].



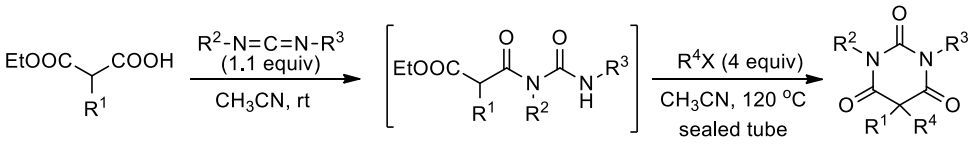
Scheme 59: Molecular structure of barbituric acid (H_3BA) and resonance forms of its deprotonated form.

In 2007, Volonterio and Zanda developed a convenient and efficient protocol for the synthesis of diverse structurally substituted *N*-alkyl, *N*'-aryl barbiturates. They demonstrated a three-component sequential reaction involving condensation between malonic acid monoesters, *N*-alkyl, *N'*-aryl carbodiimides and alkyl halides in one-pot [101]. This process generated *N*-acyl urea derivatives by the condensation of carbodiimides and malonic acid monoesters that could be further cyclized to C-5 substituted barbiturates (Scheme 60).



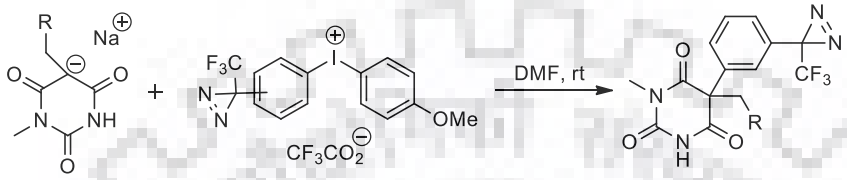
Scheme 60: One-pot sequential synthesis of *N*-aryl, *N'*-alkyl barbiturates.

In 2008, the same group exploited one-pot sequential process starting from carbodiimides and malonic acid monoethylesters for the construction of a diverse array of 1,3,5,5-tetrasubstituted barbiturates [102]. The sequence involved the reaction between carbodiimides and malonic acid monoethylesters to afford *N*-acylurea followed by addition of base for the *in situ* cyclization to form 1,3,5-trisubstituted barbiturates (Scheme 61).



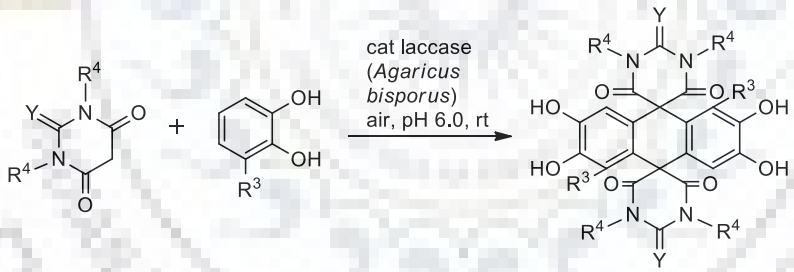
Scheme 61: One-pot sequential synthesis of barbituric acids.

Bruzik research group synthesized trifluoromethyldiazirine containing derivative of general anesthetic mephobarbital *i.e.,* 5-allyl-1-methyl-5-(*m*-trifluoromethyl-diazirynylphenyl)-barbituric acid. They also separated its enantiomer using chiral chromatography and configuration of the dextrorotatory isomer was determined to be *S* through single crystal X-ray crystallography [103] (Scheme 62).



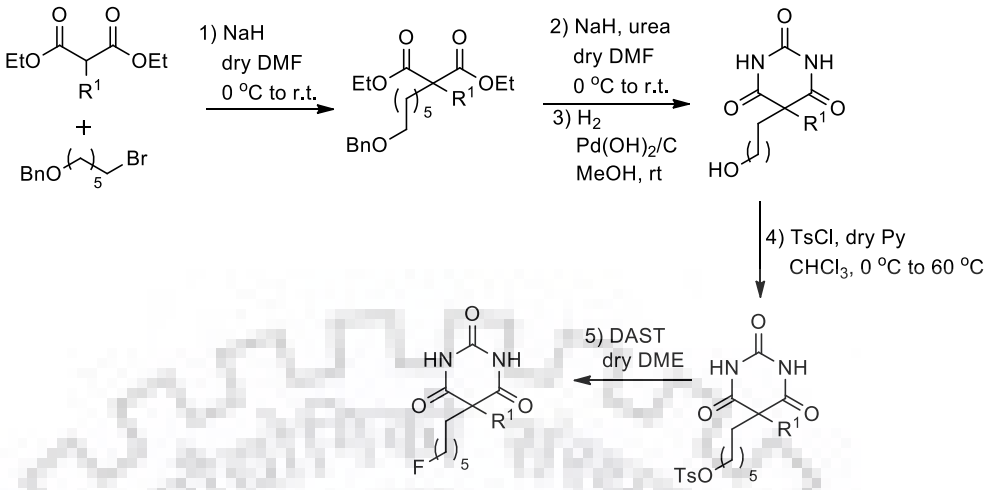
Scheme 62: Synthesis of 5-alkyl-5-aryl-1-methylbarbiturates.

Beifuss *et al.* studied the enzyme-catalyzed reaction of barbituric acid derivatives with catechols. They used the enzyme Laccase (an oxidoreductase enzyme mostly isolated from *Agaricus bisporus* or *Trametes versicolor*) as a catalyst and air as an oxidant for the domino reaction of barbiturates with catechols to form the polycyclic dispiropyrimidinones in excellent yields [104] (Scheme 63).



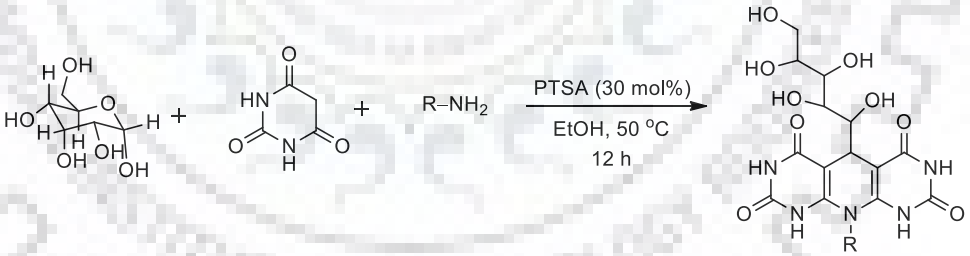
Scheme 63: Laccase-catalyzed reaction between catechols and barbituric acid derivatives.

Zanda *et al.* showcased the synthesis of fluoro-barbiturates and their *in vivo* use in β-amyloid (βA)-expressing transgenic (TG) mice as useful tracers for the PET imaging of CNS disorders. For further proving the role of barbiturates in PET imaging, they synthesized one of the fluoro-barbiturates in radiofluorinated form which was successful in labelling the βA plaques in brain sections of βA mice [105] (Scheme 64).



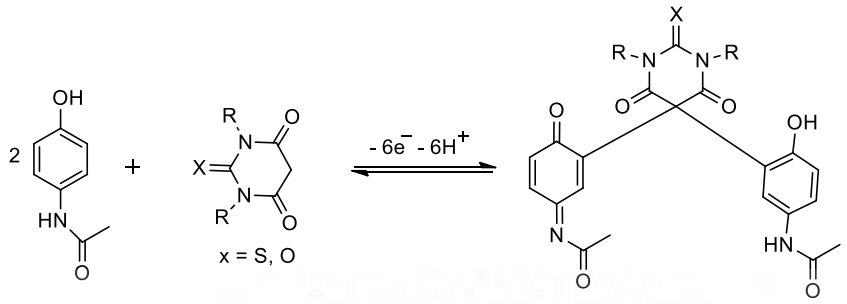
Scheme 64: Synthesis of the F-barbiturates.

Nezhad *et al.* exploited the utility of barbituric acid for the synthesis of pyrimidine-fused heterocycles that formed a novel class of inhibitors for α-glucosidase, which catalyzed the release of α-D-glucopyranose and increased the rate of diabetes mellitus. They prepared poly-hydroxy functionalized pyrimidine-fused heterocycles by stirring the mixture of (+)-D-glucose, barbituric acid, amine and PTSA in EtOH [106]. A series of compounds were synthesized with different amines and their inhibitory activities were examined spectroscopically against yeast and mouse intestinal α-Gls (Scheme 65).



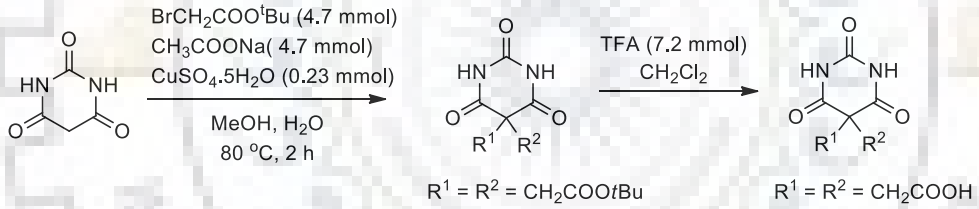
Scheme 65: Synthesis of poly-hydroxy functionalized pyrimidine-fused heterocycles.

In 2014, the barbituric acid derivatives were synthesized by Amani *et al.* through electrochemical oxidation of acetaminophen in the presence of barbituric acid. The results indicated that initially acetaminophen was converted to its *p*-quinone imine by electroxidation in water and then participated in a Michael addition reaction with the enolate anion of barbituric acid to form unique barbiturates in good yields [107] (Scheme 66).



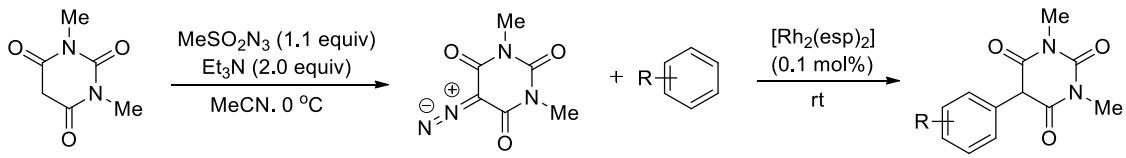
Scheme 66: The electrochemical reaction of acetaminophen with barbituric acids.

In 2014, Aoki and co-workers reported the synthesis and utility of barbital instead of cyanuric acid (CA) for the formation of self-assembly system with Zn_2L^1 and Cu^{2+}.Thus, it induced the complexation of these components in the ratio of 2:2:2 complex to form supramolecular complex which was characterized by UV-Vis spectrophotometric titrations, pH potentiometric, NMR spectroscopic and X-ray crystallographic analysis. Their further studies also confirmed the role of this complex in accelerating the hydrolysis of mono (4-nitrophenyl)phosphate (MNP) [108] (Scheme 67).



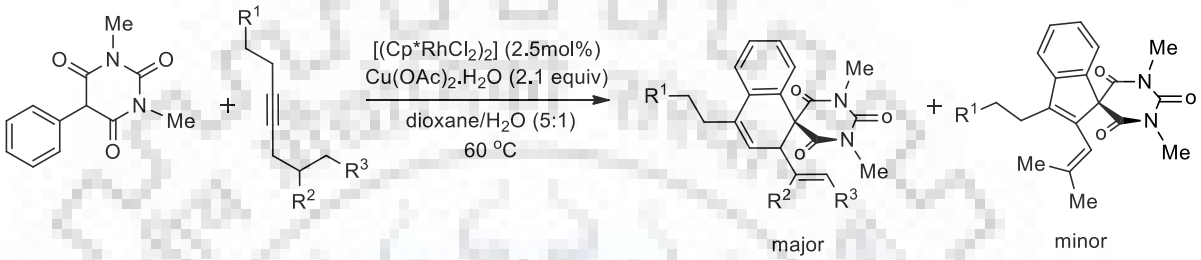
Scheme 67: Synthesis of barbital derivatives for complexation with (Zn_2L^1) and Cu^{2+}.

Barbiturates have a valuable traditional history in medicinal chemistry. With the interest of forming the 5-aryl barbituric acids Lam *et al.* envisioned rhodium(II) complex catalyzed strategy for the coupling of a 5-diazobarbituric acid moiety directly with arenes for giving the direct access to 5-aryl barbituric acids. 1,3-Dicarbonyl compound was first converted to 5-diazobarbituric acid using methanesulfonyl azide and then coupled with arenes under Rh(II) catalysis to provide aryl barbiturates [109] (Scheme 68).



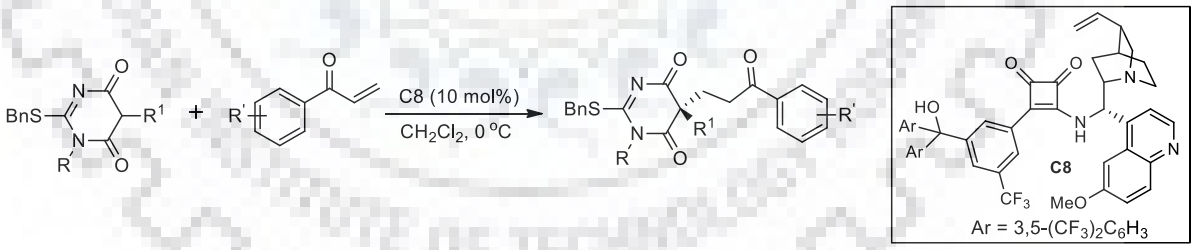
Scheme 68: Synthesis of 5-aryl barbituric acids.

In 2015, the same group showed the utility of 5-aryl barbituric acid as a suitable substrate for C–H functionalization. They have demonstrated the rhodium(III*)* metal-catalyzed all-carbon [3 + 3] oxidative annulations of 1,3-enynes having allylic hydrogens *cis* to the alkyne functionality with 5-aryl barbiturates [110]. This new route of oxidative annulation involved alkenyl-to-allyl 1,4-rhodium(III) migration leading to the formation of polycyclic systems such as spirodialins (Scheme 69).



Scheme 69: Catalytic oxidative annulations of alkynes and 1,3-enynes.

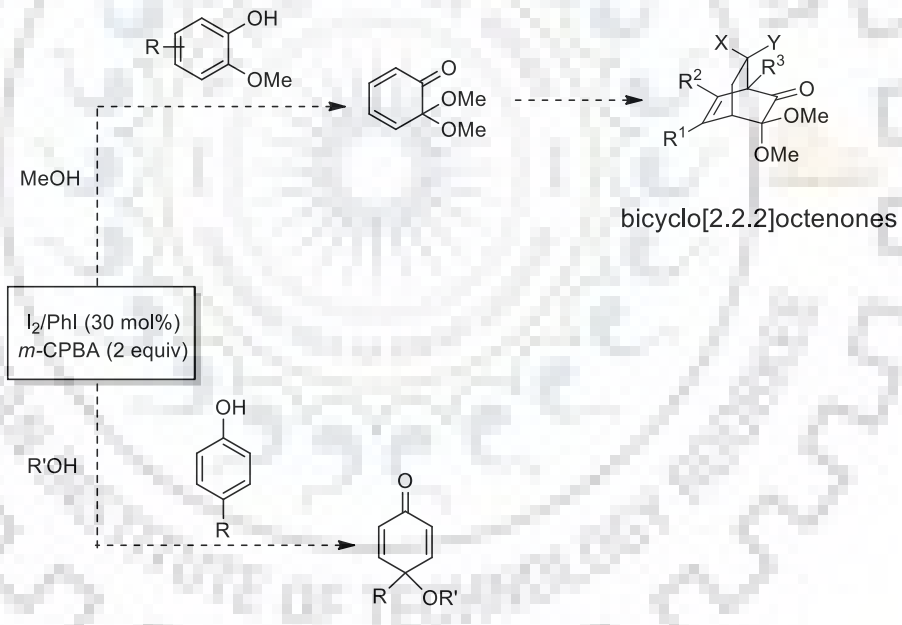
Recently, Palomo *et al.* reported the use of 5-aryl barbituric acid for the catalytic asymmetric synthesis of quaternary barbituric acids. They reported quaternary in-ring stereogenic center by the enantioselective construction of chiral barbiturates. The chemistry involved the highly selective role of bulky squaramide-tertiary amine bifunctional catalysts for the α-functionalization of 2-alkylthio 4,6-dioxopyrimidines with Michael acceptors and subsequent mild hydrolysis to afford the desired products [111] (Scheme 70).



Scheme 70: Asymmetric α-functionalization of 1,3-diamides toward barbituric acid derivatives.

2.1. OBJECTIVES

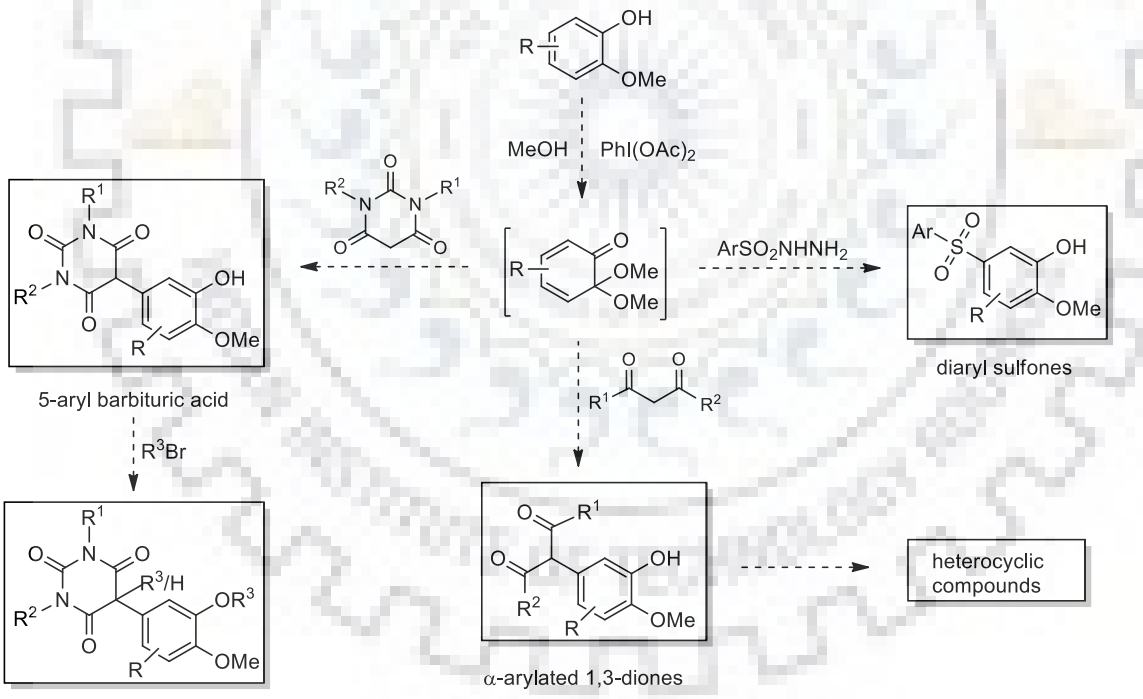
- Inspired by the remarkable reactivity of *ortho*-benzoquinone monoketals that can be utilized in the synthesis of complex natural products, we were interested to develop an ideal route for their generation by dearomatization of 2- and 4-alkoxy phenols, so as to avoid the stoichiometric use of expensive hypervalent iodine(III) reagents and the co-production of stoichiometric amount of iodoarenes. With this aim, we envisaged the catalytic use of easily available elemental iodine or iodobenzene with *m*-CPBA as terminal oxidant for the dearomatization of various substituted alkoxy phenols and the *in situ* generated highly reactive benzoquinones would be trapped by dienophilic partners through Diels–Alder reaction using different dienophiles to form bicyclo[2.2.2]octenones in a one-pot manner.



- Phenols are widely known as a prevalent structural motifs in natural products, medicines, dyes, and materials. They are delineated as an ideal and sustainable class of substrates suitable for diverse modes of bond construction in the chemical synthesis. With the aim of boosting the therapeutic profile of phenols, we envisaged the coupling of phenols with other medicinal important scaffolds to form the novel structural templates. We intended to harness the α,β-unsaturated carbonyl functionality of *ortho*-benzoquinone monoketals generated *in situ* from 2-alkoxy phenols *via* Michael addition with some easily available nucleophiles to access *meta*-substituted phenols.

- Arylsulfonyl hydrazides served as excellent thioarylation reagents in synthetic chemistry. They have been identified either as a source of sulfur nucleophile, electrophile or free radical depending upon reaction conditions. We envisaged the reaction between arylsulfonyl hydrazides and *in situ* generated *ortho*-benzoquinone monoketals in aqueous media that would furnish pharmaceutically active and variously substituted diaryl sulfones.

- Owing to the utilization of α-arylated 1,3-diones and ethyl cyanoacetates as the prime substrates for synthetic useful transformations, we aimed to exploit the nucleophilicity of various C–H activated acids. We were interested for the α-aryaltion of 1,3-diones and ethyl cyanoacetates with 2-methoxy phenols as aryl partners. Further we were interested to extend our investigation for the synthesis of bioactive heterocyclic frameworks such as coumarins, pyrazoles, isooxazoles, carboxylic amides coupled with phenols.



- Intrigued by the various interesting, practically wide applications of C-5 mono/di-substituted barbituric acids, we confronted an operationally simple and efficient protocol for the synthesis of 5-aryl barbituric acids with phenol moiety as an aryl partner under mild conditions. If successful, the subsequent C–H alkylation of phenol coupled barbituric

acids would provide fully substituted barbiturates that could serve as primers for various stereochemical transformations with in-ring quaternary carbon.

2.2. RESULTS AND DISCUSSION

In the previous chapter, various synthetic methodologies for the dearomatization of 2-alkoxy phenols and synthesis of diaryl sulfones, catechols, α-arylated 1,3-diones and substituted barbiturates derivatives are described. This chapter deals with the results and discussion, which is further divided into five sections as shown below:

2.2.1 Iodobenzene and m-chloroperbenzoic acid mediated oxidative dearomatization of phenols

2.2.2. Catalyst-free synthesis of arylsulfonyl catechols in aqueous media

2.2.3. Metal-Free direct C-arylation of C–H activated pronucleophiles: Synthesis of diverse array of meta-functionalized phenols

2.2.4. Synthesis of substituted 5-aryl barbituric acid derivatives

2.2.5. Synthesis of fully substituted barbituric acid derivatives

The starting materials are numbered as shown below for clarity and to facilitate the discussion throughout the thesis:

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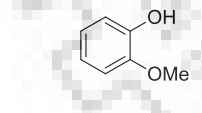

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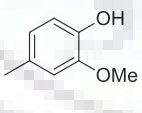

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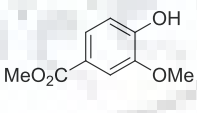

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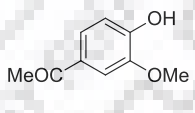

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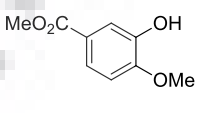

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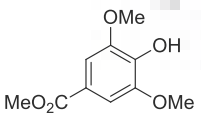

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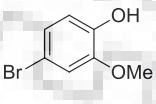

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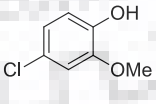

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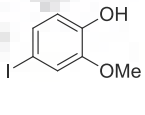

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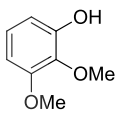

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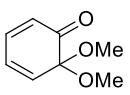
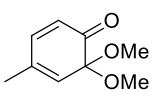
Masked *o*-benzoquinones:





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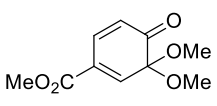

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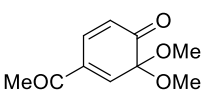

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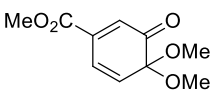

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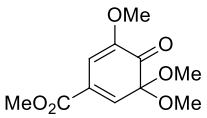

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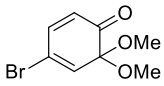

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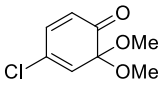

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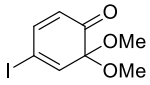

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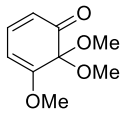

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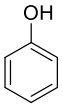
para-Substituted phenols:



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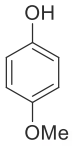

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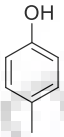

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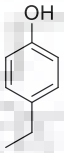

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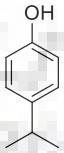

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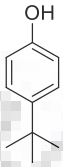

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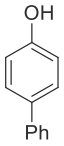

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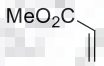

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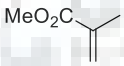
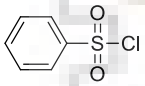


4b

4c

4d

Arylsulfonyl chlorides and hydrazides:



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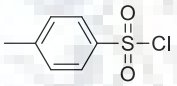

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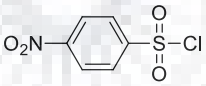

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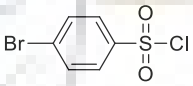

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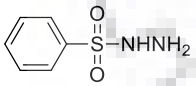

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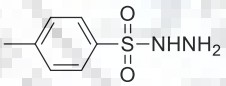
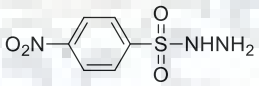
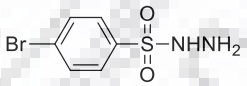


5f

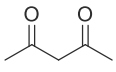


5g

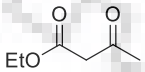


5h

C–H activated pronucleophiles:



6a



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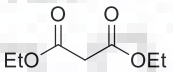

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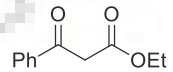

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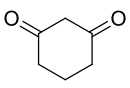

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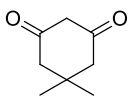

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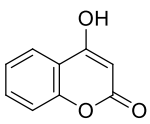

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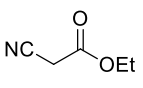
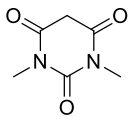


6h

Barbituric acids:



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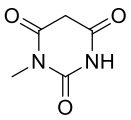

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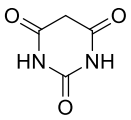

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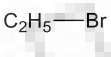
Alkyl halides:

8a



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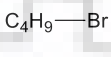

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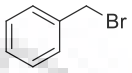

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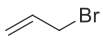


8e

2.2.1. Iodobenzene and *m*-chloroperbenzoic acid mediated oxidative dearomatization of phenols

As a powerful tool, the dearomatization [5,14] of aromatic compounds is an efficient strategy to generate highly reactive intermediates for the facile formation of carbon–carbon, carbon–heteroatom bonds, and to access architecturally complex scaffolds through spontaneous cycloaddition and cascade reactions. The 2- and 4-substituted phenols are by far the most periodically utilized substrates for dearomatization in the presence of nucleophiles to form respective masked *o*-benzoquinones (MOBs) and masked *p*-benzoquinones (MPBs) [22,112,113]. Though the simple *o*- and *p*-benzoquinones have high synthetic potential, they undergo notorious reactions limiting their efficacy in organic synthesis. Consequently, their chemistry is mainly explored by masking one of the carbonyl functionalities in the form of MOBs and MPBs. The benzoquinone monoketals are the molecules of wide synthetic utility because of the presence of alkene, diene, carbonyl, enone, dienone and allyl acetal functionalities. With these intrinsic reactive assemblies, they undergo a variety of desirable annulation reactions such as Diels–Alder reaction [114,115], 1,4-additon [48,116] and [3 + 2] cycloaddition reaction [117,118].

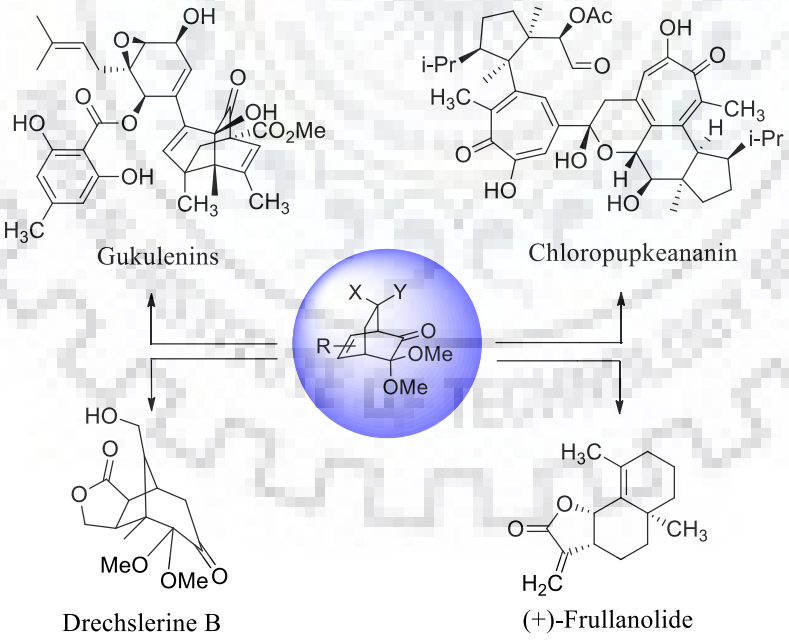


Figure 1: Bicyclo[2.2.2]octenones-derived biologically active compounds.

MOBs undergo Baylis–Hillman (BH) reaction and also show umpolung reactivity to access unsymmetrical oxgyenated biaryls [119,120] in the presence of Lewis acids. However, the Diels–Alder reaction dominates the MOB chemistry due to their proclivity

towards it. MOBs may undergo self-dimerization *via* Diels–Alder cycloaddition because of their high reactivity [121]. However, this event can be successively avoided by trapping these highly reactive MOBs with various external dienophiles to generate highly stereo- and regio-selective bicyclo[2.2.2]octenone scaffolds [122], that have been considered as building blocks for the synthesis of a myriad of complex biological active molecular ensembles (Figure 1) [123–126].

A plethora of strategies [127–130] for the dearomatization of arenols have been emerged to produce these linearly and cross–conjugated cyclohexadienones in the presence of appropriate nucleophiles. The linearly conjugated cyclohexadienones ketals are usually prepared by one of following methods. The very common method is to expose a mono-protected catechol to one equiv of oxidant in the presence of a nucleophilic alcohol. The other one involves the use of two equiv of oxidant for the oxidation of non-*ortho*-substituted phenol in the presence of excess alcohol. Dearomatization can also be done by the ketalization of an *o*-quinone. In addition to this, transketalization of an *ortho*-quinone ketal formed by one of the previous three methods is also well known to synthesize MOBs (Figure 2). The oxidants used in the above cases, contain Pb(IV), I(III), Tl(III), Br(I) and have proven successful for dearomatization. Since decades, dearomatization has also been carried by electrochemical methods.

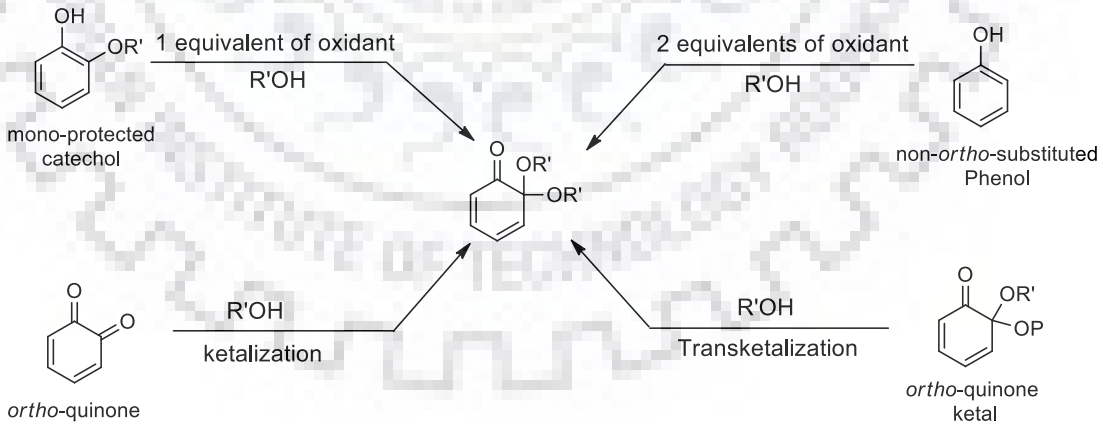


Figure 2: Preparation of *ortho*-benzoquinone ketals.

Similar to linearly conjugated cyclohexadienone ketals, several strategies lead to the cross conjugated cyclohexadienone ketals *i.e.*, MPB (Figure 3). These include oxidation *para*-alkoxy phenols in an alcoholic solvent, double oxidation of non-*para*-substituted phenols in

an alcoholic solvent, monoketalization of *p*-quinone and dearomatization of *p*-hydroquinone to form bis-ketal then followed by partial hydrolysis.

Among the various oxidants used for dearomatization of alkoxyphenols, hypervalent iodine reagents [131], due to their mild reactivity and high stability, have proven to be the most accustomed and valuable oxidants [132]. In spite of being less flourished, λ^5-iodanes [133] such as Dess-Martin periodane (DMP) [134], 2-iodoxybenzoic acid (IBX) [135] and their analogues also documented good synthetic versatility.

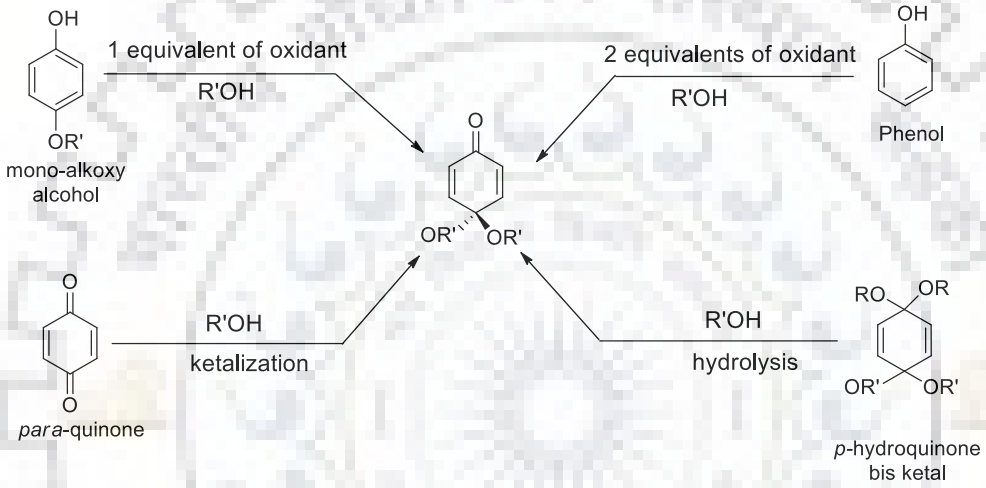


Figure 3: General strategies for the preparation of *para*-benzoquinone ketals.

However, stoichiometric use of these hypervalent iodine reagents results in the co-production of undesired iodoarenes in equimolar amount. This demands an ideal, eco-friendly route for the dearomatization process based on the catalytic utilization of these reagents, similar to the organocatalysts. To circumvent these problems, in 2005, the Ochiai [136] and Kita [137] independently reported iodine(I) arene-mediated catalytic oxidations using *meta*-chloroperbenzoic acid (*m*-CPBA) as co-oxidant. *m*-CPBA is one of the few terminal oxidants that perform the *in situ* conversion of iodine(I) to iodine(III) and make the dearomatization process catalytic (Figure 4). After that, this concept was reported extensively for various useful transformations [138].

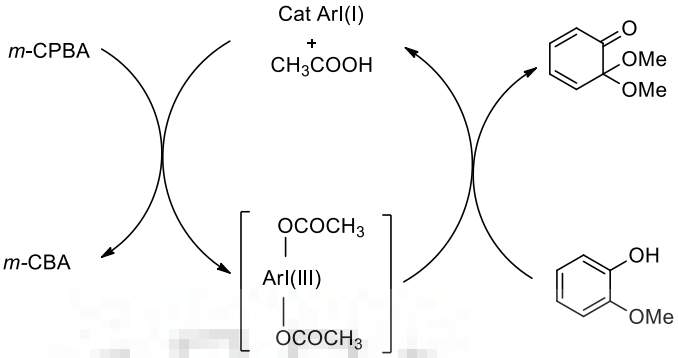
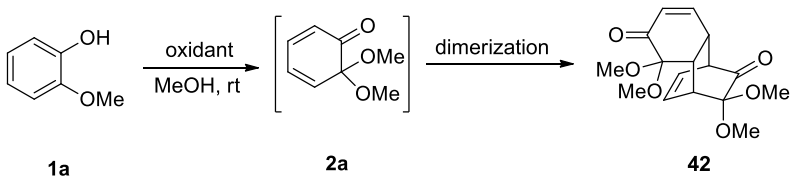


Figure 4: Catalytical cycle for the dearomatization of 2-methoxyphenol.

The main objective of this area is to design an economical, environmentally benign, safer and more practical cleaner process by using iodine(I) arene and low-cost stoichiometric terminal oxidant as a catalytic system. In view of atom economy and green sustainablitity the terminal oxidants could either be molecular oxygen or hydrogen peroxide (H_2O_2). We examined the catalytic activity of iodine(I) arene with *m*-CPBA as terminal oxidant for the dearomatization of alkoxyphenols. These reactions are found to be high yielding and proceed under mild and eco-friendly conditions (*vide infra*).

At the outset, we were with the idea of using elemental iodine in place of hypervalent iodine(III) reagents such as DIB or PIFA to oxidise guaiacol (**1a)** in the presence of methanol for the formation of Diels–Alder dimer **42** of the *in situ* generated MOB **2a**. Initially, methanolic solution of guaiacol was treated with elemental iodine and the contents were allowed to stirr at room temperature. Even in 24 h, formation of dimer was not observed (Table 1, entry 1). To enhance the oxidizing power of iodine, we supplemented various co-oxidants such as $K_2S_2O_8$, $NaIO_4$ and H_2O_2. However, the product formation was not observed in these cases (entries 2–4). Even the combination of $K_2S_2O_8$ and $NaIO_4$ as co-oxidants with iodine proved unsuccessful (entry 5) and the use of oxone also could not deliver the product **42** (entry 6). Gratifyingly, *m*-CPBA successfully worked as a co-oxidant with elemental iodine and resulted in the formation of the expected dimer **42** in 60% yield (entry 7), though *m*-CPBA alone was not capable for oxidation (entry 8). Interestingly, when iodobenzene was used in place of iodine with *m*-CPBA, the Diels–Alder dimer was obtained in remarkably improved yield of 86% (entry 9).

Table 1: Initial optimization of oxidizing agents.[a]



1a **2a** **42**

Entry	Oxidant	Time	Yield (%)[b]
1	I_2	24 h	-
2	$I_2/K_2S_2O_8$	24 h	-
3	$I_2/NaIO_4$	24 h	-
4	I_2/H_2O_2	24 h	-
5	$I_2/NaIO_4/K_2S_2O_8$	24 h	-
6	Oxone	24 h	-
7	I_2/*m*-CPBA	1.5 h	60
8	*m*-CPBA	24 h	-
9	PhI/*m*-CPBA	10 min	86

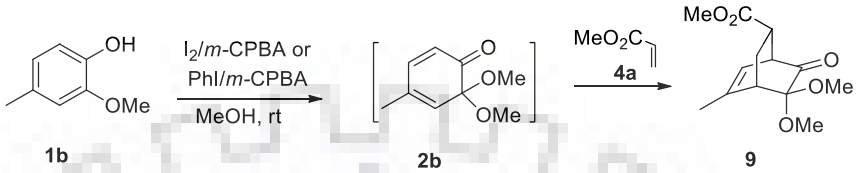
[a] Reactions were carried out by dissolving **1a** (0.5 mmol, 1 equiv) in methanol (3 mL) followed by the addition of oxidant (1 equiv each) at 25 °C.

[b] Isolated yield of **42**.

In order to achieve best reaction conditions, we examined both the oxidizing systems *i.e.* I_2/*m*-CPBA and PhI/*m*-CPBA on our model reaction between creosol (**1b**) and methyl acrylate (**4a**) in methanol leading to the corresponding Diels–Alder adduct **9**. To get the optimized reaction conditions, we performed the reaction under various concentrations of iodine/iodobenzene and *m*-CPBA in methanol as shown in Table 2. Initially, we treated the methanolic solution of creosol with 0.5 equiv of iodine and 1 equiv of *m*-CPBA at room temperature and the desired product **9** was obtained in 50% yield (entry 1). Further increase in the amount of iodine did not improve the yield (entries 2 and 3). However, rise in *m*-CPBA concentration enhanced the yield up to 76% (entries 4–7). Fortunately, the use of 0.5 equiv of iodobenzene instead of iodine furnished **9** in 30 min in 86% yield (entry 8), although 1 equiv of iodobenzene enhanced the reaction rate without any noticable change in the yield of the product (entry 9). Rise in the concentration of co-oxidant did not improve the yield of the adduct significantly (entry 11). Much to our delight, by lowering the concentration of iodobenzene to 30 mol%, the reaction afforded the **9** in 10 min with 93%

yield (entry 12) and further decrease in its quantity resulted in slight drop in the reaction rate (entry 13).

Table 2. Optimization of reaction conditions.[a,b]



1b 2b 9

Entry	I_2 or PhI (equiv)	*m*-CPBA (equiv)	Time (min)	Yield (%)[b]
1	I_2/0.5	1	60	50
2	I_2 /1	1	15	55
3	I_2/2	1	10	54
4	I_2/1	1.5	10	65
5	I_2/1	1.7	10	66
6	I_2/1	2	10	68
7	I_2/1	3	10	76
8	PhI/0.5	1.5	30	86
9	PhI/1	1.5	5	86
10	PhI/0.5	2	5	86
11	PhI/0.5	2.5	5	90
12	PhI/0.3	2	10	93
13	PhI/0.2	2	25	92

[a] Reactions were performed by sequential addition of *m*-CPBA to a solution of iodine or iodobenzene in methanol (3 mL) followed by the addition of methanolic solution (2 mL) of creosol (**1b**, 0.5 mmol, 1 equiv) and methyl acrylate **4a** (10 mmol, 20 equiv) at rt.

[b] Isolated yield of **9**.

With the optimized reaction conditions in hand (Table 2, entry 12), we explored the generality of this novel synthetic protocol on a range of methoxy phenols bearing different substituents with various dienophiles. In order to have better understanding of reaction mechanism, we performed the oxidation and cycloaddition reactions using stoichiometric (Method A) as well as catalytic amount (Method B) of iodobenzene. The Diels-Alder reaction of MOBs having different functionalities with electron-deficient dienophiles such as

methyl acrylate (MA, **4a**), methyl methacrylate (MMA, **4b**), methyl vinyl ketone (MVK, **4c**) as well as with conjugative dienophiles like styrene (**4d)** afforded the bicyclo[2.2.2]octenone derivatives **9**–**20** through *endo* addition in good to excellent yields. The reactions of creosol (**1b**) furnished the cycloadducts **9**–**11** in high yields, except in case of styrene where the bicyclo[2.2.2]octenone **12** was isolated in 45% yield. The MOBs generated from 2-methoxyphenols bearing electron-withdrawing groups *i.e.,* methyl vanillate (**1c**) and acetovanillone (**1d**) afforded the cycloadducts **13**–**16** and **17**–**20**, respectivey, in acceptable to high yields (Scheme 1).

The reaction of methyl isovanillate (**1e**) with MA, MVK and styrene provided the cycloadducts **21**, **23** and **24**, respectively, in good yields, whereas oxidation of **1e** in the presence of MMA furnished substantial amount of dimer **41** along with the Diels–Alder adduct **22**. Methyl syringate (**1f**) under oxidative-acetalization conditions smoothly reacted with MA, MVK and styrene to afford the cycloadducts **25**, **27**, and **28**, respectively, in very good yields (Scheme 2). Due to the less reactivity of MMA appreciable amount of dimer **43** was formed in its reaction with **1f** (Figure 5).

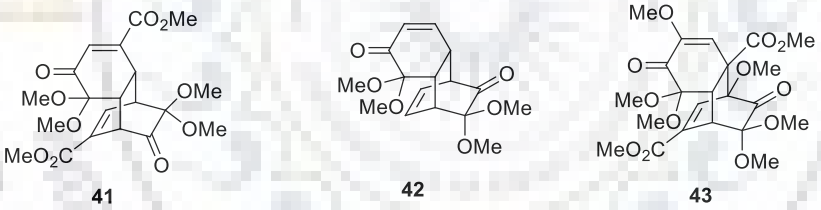
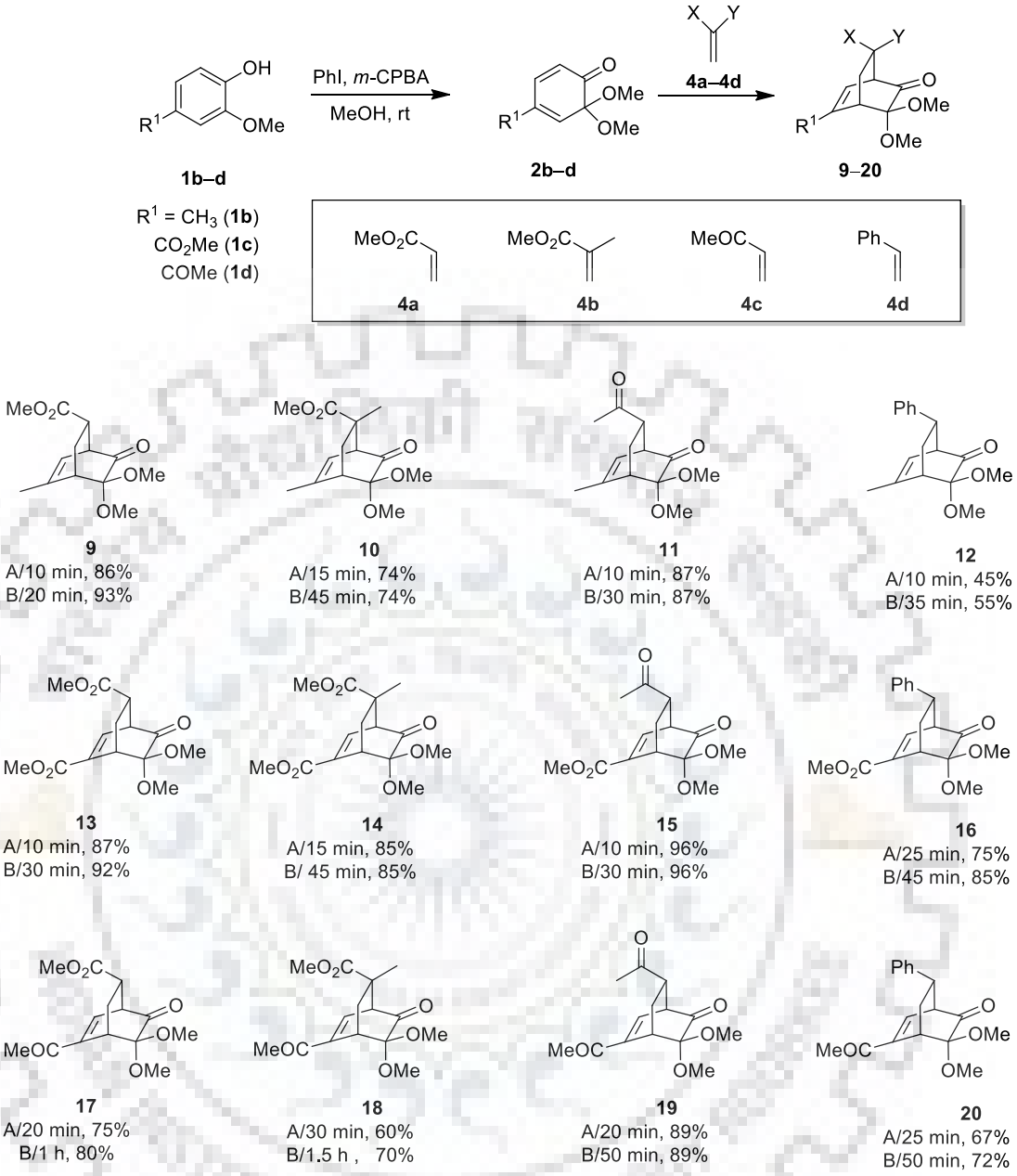


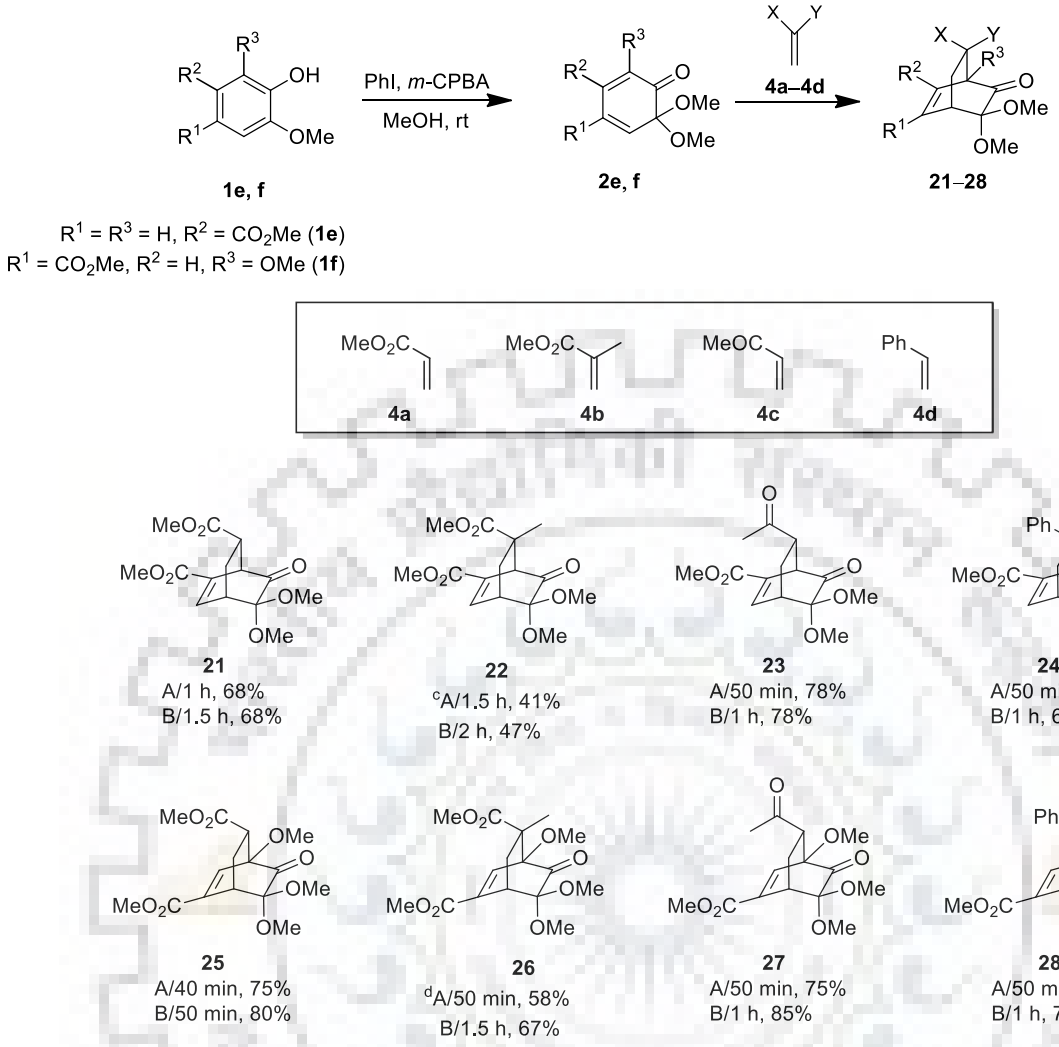
Figure 5: Structures of Diels–Alder dimers.



Scheme 1: Oxidative–acetalization–Diels–Alder strategy of methoxyphenols **1b–d**.[a,b]

[a]Reaction conditions: Method A: a methoxyphenol (**1b**–**d**, 1 mmol), dienophile (**4a–d**, 20 equiv), PhI (1 equiv) and *m*-CPBA (1.5 equiv) in methanol (5 mL) at rt. Method B: a methoxyphenol (**1b**–**d**, 0.5 mmol), dienophile (10 mmol), PhI (0.3mmol), and *m*-CPBA (1 mmol, 2 equiv) in methanol (3 mL) at rt for the given time.

[b]Yield of isolated products.



Scheme 2: Oxidative–acetalization–Diels–Alder strategy of 2-methoxyphenols **1e, f**.[a,b]

[a]Reaction conditions: Method A: a methoxyphenol (**1**, 1 mmol, 1 equiv), dienophile (20 equiv), PhI (1 mmol, 1 equiv) and *m*-CPBA (1.5 mmol) in methanol (5 mL) at rt. Method B: a methoxyphenol (**1**, 0.5 mmol), dienophile (10 mmol), PhI (0.3mmol), and *m*-CPBA (1 mmol, 2 equiv) in methanol (3 mL) at rt for the given time.

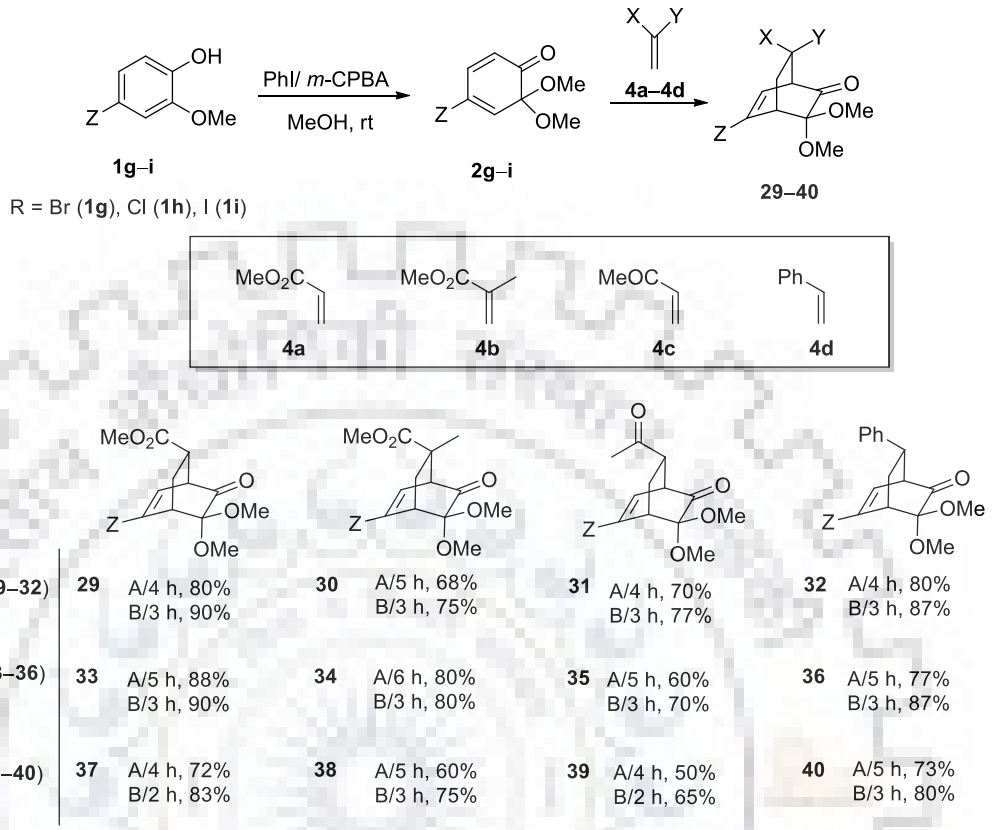
[b]Yield of isolated products.

[c]Dimer **41** was isolated in 57% yield.

[d]Dimer **43** was isolated in 38% yield.

The 4-halogen substituted MOBs **1g**–**1i** are relatively stable enough and resist self-dimerization under the reaction condition and reacted smoothly with dienophiles **4a**–**4d** to furnish the corresponding cycloadducts **29**–**40**. Even the conjugated dienophile styrene conveniently reacted with 4-chloro and 4-bromo-2-mehoxyphenol (**1h, g**) to afford the adducts **29–36** in good yields. Whereas, 4-iodo guaiacols (**1i**) bypassed its steric hindrance

under the reaction conditions to afford the 4-halo adducts **37**–**40** in yields up to 83% (Scheme 3).

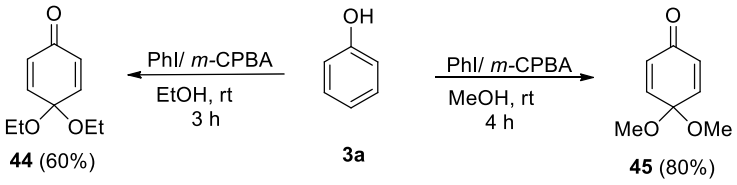


Scheme 3. Reaction of 4-halo guaiacols with olefinic compounds.[a, b]

Reaction conditions: Method A: a 4-halo-2-methoxyphenol **1g**–**i** (1 mmol, 1 equiv), dienophile **4a**–**4d** (20 mmol), PhI (1 mmol, 1 equiv) and *m*-CPBA (1.5 mmol) in methanol (5 mL) at rt. Method B: a 4-halo-2-methoxyphenol **1** (0.5 mmol, 1 equiv), dienophile (10 mmol), PhI (30 mol%), and *m*-CPBA (1 mmol) in methanol (3 mL) at rt for the given time.

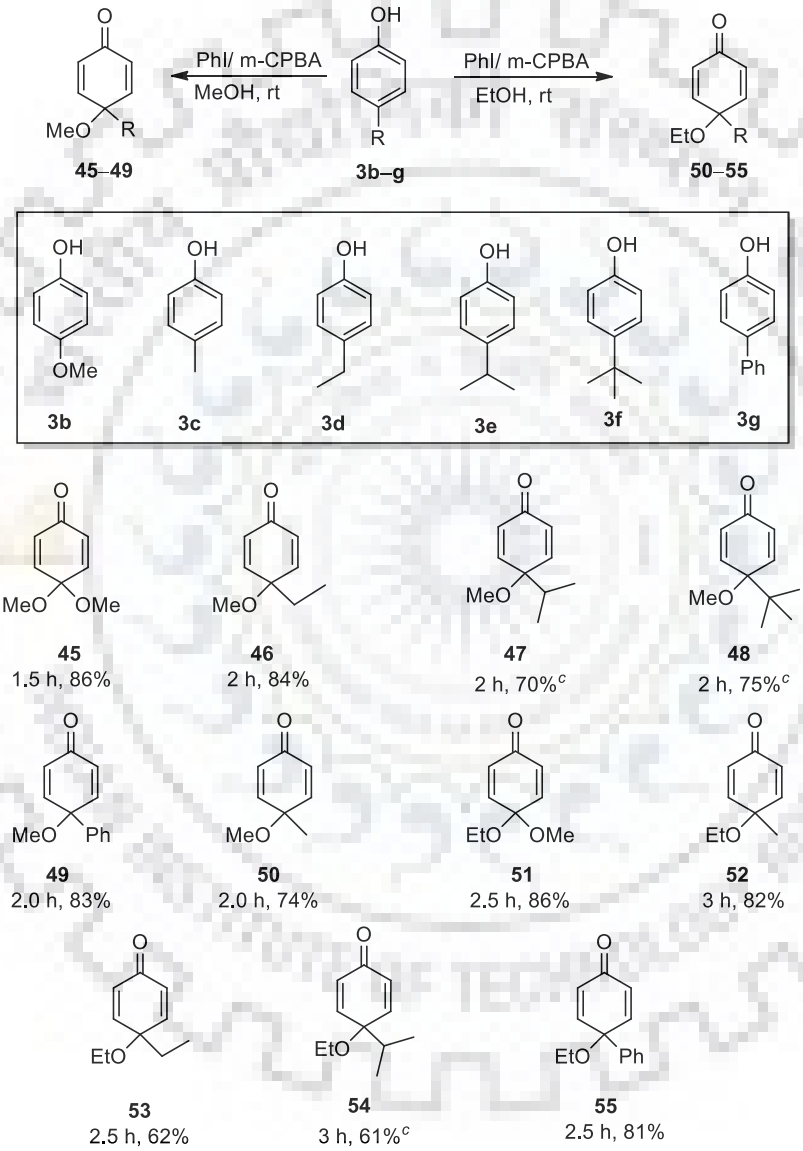
[b]Yield of isolated products.

After the success of oxidative dearomatization of 2-methoxyphenols, next we probed the substrate scope for phenol and *p*-substituted phenols. Keeping the concept of double oxidative dearomatization of phenol to form quinone monoketal in mind, we oxidized phenol (**3a**) using 4 equiv of *m*-CPBA and 30 mol% PhI in the presence of methanol and ethanol and isolated the MPBs **45** and **44** in 2–3 h 80 and 60% yield, respectively (Scheme 4). After further exploration, we found a clean reaction by using only 2 equiv of *m*-CPBA to furnish the products **45** and **44** in similar yields with easy work up (due to the less loading of terminal oxidant) albeit little longer reaction time of 3–4 h.



Scheme 4: Dearomatization of phenol.[a]

[a]Reactions were performed with phenol **3a** (0.5 mmol, 1 equiv), PhI (30 mol%), and *m*-CPBA (1.0 mmol) in solvent (3 mL) at rt.



Scheme 5: Dearomatization reactions of 4-subsituted phenols[a,b]

[a]Reactions were performed with 4-substitued phenols (0.5 mmol), PhI (30 mol%), *m*-CPBA (2 mmol) in solvent (3 mL) at rt.

[b] Yield of isolated products.

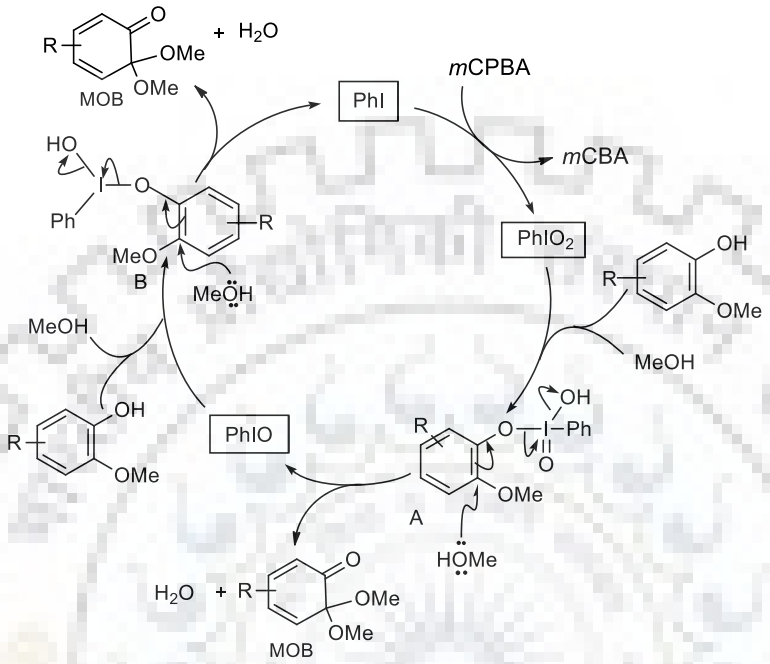
[c] Reactions was done at 50 °C.

Having established an efficient protocol for dearomatization of phenol and 2-methoxyphenols, we extended this strategy by carrying out the oxidation of 4-methoxyphenol with PhI/*m*-CPBA in methanol to afford masked *p*-benzoquinone **45** in 86% yield (Scheme 4). Similarly, 4-alkyl substituted phenols were oxidized to the corresponding cross conjugated cyclohexadienones **46**–**55** in very good yields. Although a relatively low yield was observed in the reactions of phenols bearing bulky isopropyl and *tert*-butyl group wherein the reaction was carried at 50 ºC to improve the yield of the corresponding products **47** and **54** to 70 and 61%, respectively (Scheme 5). The reaction also tolerated phenyl group to furnish cyclohexadienone **49** in 83% yield. To further evaluate the efficacy of the present protocol, we carried out the oxidative dearomatization of 4-substituted phenols using ethanol as an external nucleophile to obtain the corresponding dienones **51**–**55** in good yields. It turned out that the methodology shows unique general reactivity (Scheme 5).

In an effort to understand the course of the reaction, we performed the reaction between iodobenzene and *m*-CPBA in methanol for 10 min, then the reaction mixture was filtered to afford a white solid which was found to be iodoxybenzene ($PhIO_2$) {mp: 234–235 ºC as per the literature [139], IR: ν_{max} 763, 737, 731, 714 cm^{-1}, HRMS (ESI^+): m/z calcd for $PhIO_2Na$ $[M+Na]^+$: 258.9353, found: 258.9226}. To further support the role of $PhIO_2$ as an intermediate, we have prepared $PhIO_2$ and PhIO according to the literature procedure [140] and carried out the oxidation of cresol (**1b**) with these synthesized hypervalent iodine reagents and subsequent DA reaction with MA. It was observed that the reaction of **1b** with $PhIO_2$ in methanol and the cycloaddition was completed in 15 min and afforded DA adduct **9**, whereas the reaction with PhIO did not reach to completion even after 3–4 h.

Proposed mechanism for the reaction is outlined in Scheme 6. Initially, *m*-CPBA oxidizes iodobenzene *in situ* to generate the electrophilic hypervalent iodine(V) species $PhIO_2$. Then the nucleophilic oxygen of phenol attacks on the electrophilic iodine(V) centre of $PhIO_2$ to produce species **A**. After the attack of one molecule of methanol on electrophilic carbon, the species **A** collapses to MOB through dearomatization accompanying the release of water and an iodine(III) species PhIO. The latter participates in the oxidation of arenol into another molecule of MOB *via* species **B**. The influence of the nucleofugality of the phenyliodanyl group helps the two-electron reduction of iodine(III) center with simultaneous regeneration of MOB and PhI which further involves in the catalytic cycle and formed MOB

undergoes [4 + 2] cycloaddition either with dienophile to afford Diels–Alder adduct or participates in the self-dimerization event with another molecule of MOB to provide the corresponding DA dimer.



Scheme 6: Proposed reaction mechanism.

The structures of product bicyclo[2.2.2]octenones were assigned by the collective information obtained from ^{1}H and ^{13}C NMR, and HRMS spectral data. The IR absorptions at 1705–1768 cm^{-1}, displayed a characteristic absorption of carbonyl functionality of cycloadducts *i.e.,* bicyclo[2.2.2]octenones derived from MOBs. The commendable level of stereo- and regioselectivities observed in these adducts was in accordance with the literature reports [232]. Out of the all four possible isomers, only the one possessing *endo* stereochemistry with ERG/EWG is *anti* to octenone carbonyl functional group and *ortho* regiochemistry with EWG/ERG is adjacent to octenone carbonyl functional group has been formed in the present protocol. The regiochemistry of these bicyclo[2.2.2]octenones was elucidated from proton–proton decoupling experiments and compared with reported ones.

2.2.2. Catalyst-free synthesis of arylsulfonyl catechols in aqueous media

Organo-sulfone chemistry [141–144] has undergone a renaissance in the past decades as the sulfonyl-derived functional groups such as sulfones, sulfonamides populate a broad range of pharmaceutical active molecules [145] and agrochemicals [146] (Figure 6). Moreover, sulfones have attracted considerable interest as versatile synthetic intermediates [147,148] for useful organic transformations including enantioselective catalysis [149,150]. They have been found to show attractive biological properties such as antitumour, antibacterial activity or inhibition of HIV-1 reverse transcriptase. This has provided impetus to the research directed at practical, efficient, convenient methods for the synthesis of aryl sulfones *via* carbon-sulfur bond formation (Figure 6).

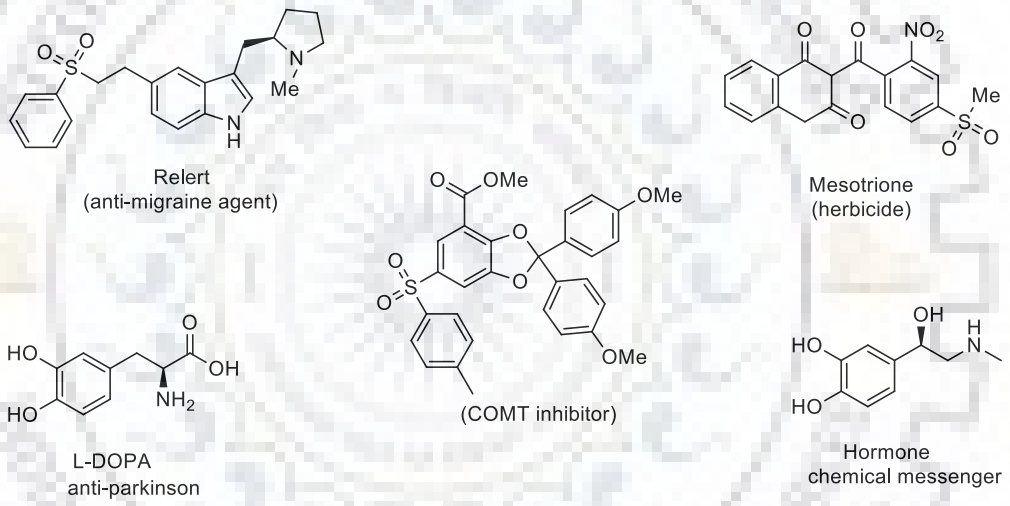


Figure 6: Drugs with diaryl sulfone and catechol skeletons.

Traditionally, synthesis of diaryl sulfones is prevailed by oxidation of sulfides and sulfoxides, reaction of sulfonate esters with organometallic compounds, sulfonylation of arenes, palladium and copper catalyzed oxidative coupling of arylsulfonyl chlorides with aryl boronic acids [151–154]. In addition to this, the research area is authenticated by the overview of latest advances comprising of metal-mediated or metal-free reactions of sodium sulfinates and by direct catalytic introduction of SO_2 for the generation of sulfones [155,156]. Willis [56,157] introduced bench stable reagent DABSO (DABCO+SO_2) as surrogate for SO_2 gas for introducing sulfone functionality. Mhaske group explored aryne methodology [62] and Deng *et al.* utilizes Heck coupling [158] to access sulfone derivatives. Soon after this, a unprecedented method for carbon–sulfur bond formation have been developed by

using $K_2S_2O_8$ and thiosulfonates [159] as highly effective sulfonating agents. However, these protocols are associated with one or the other innate drawbacks such as harsh conditions, limited availability of sodium sulfinates, narrow substrate scope.

Catechol structural motifs are stupendously utilized in every zone of chemical industry [160,161] and are ordinarily accessed by orthoformylation of phenols followed by subsequent Dakin reaction [67]. Another method involves transition metal-catalysed C–H hydroxylation [162–165] and oxidative dehydrogenation of cyclohexanones to phenols [77]. However, multistep procedures with installing and removing functional groups, requirement of strong oxidant and transition metal catalysis limit the applicability of these processes. The high demand of catechols in chemical industries [66] has promoted the development of convenient routes to access catechol derivatives (Figure 6).

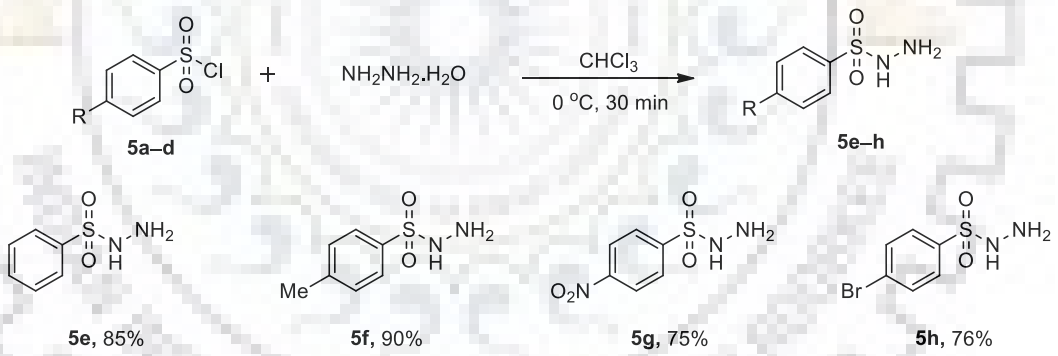
As catechols and sulfones both are of high pharmacological profile, we thought to assemble both of them in one privileged structural template. With this aim, we envisaged the reaction of phenols with arylsulfonyl hydrazides in aqueous media *via* dearomatization startegy. Moreover, dihydroxy substituted arylsulfone [54] is rather more profoundly considered as structural entity for innumerable bioactive molecules of pharmaceutical relevance, particularly they form the integral part of COMT inhibitors [166].

The enzyme catechol *O*-methyltransferase (COMT) is involved in catecholamine catabolism. Thus, its inhibition allows regulation of catechol-based neurotransmitter levels; hence, proved an important pathway for the therapy of central nervous system (CNS) disorders, more specifically Parkinson's disease. So, these dihydroxy substituted arylsulfones are considered as anti-Parkinson's agents and previously being prepared in multisteps under harsh conditions *via* sulfonylation of dimethoxybenzene derivatives followed by conversion of methoxy to hydroxy moiety [76]. In the past two years, sulfonyl hydrazides [167] have been explored as stable solid, non-corrosive, readily accessible, odor-free sulfonylating reagents. The compatibility of sulfonyl hydrazides with water has made them novel green precursors for sulfonylation. Water stimulates these transformations and adds a powerful dimension towards the ecofriendly synthesis of sulfones [168,169].

In concordance of our ecofriendly quest, herein, we unveil one-pot, catalyst-free, water-mediated highly convenient approach for carbon–sulfur bond formation to synthesize

dihydroxy substituted diarylsulfones starting from stable, inexpensive and easily accessible sulfonyl hydrazides and guaiacol derivatives *via* sulfonylation of *in situ* generated masked *o*-benzoquiones, the valuable synthetic intermediates [22,120] obtained from oxidative dearomatization [5,16,170] of phenols. Of particular note, the obtained entities are precursors' analogues for potent COMT inhibitors, important therapeutic agents for the treatment of Parkinson's disease.

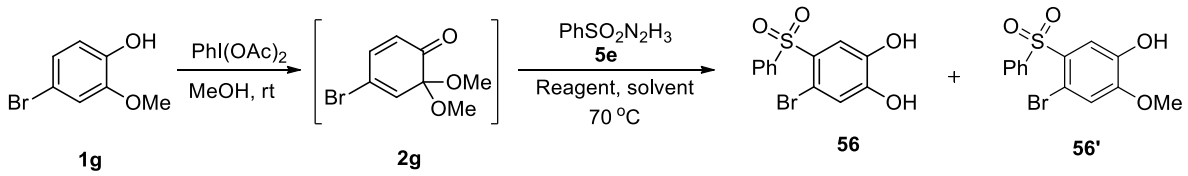
We began our studies by synthesizing the arylsulfonyl hydrazides according to literature procedure [171]. To a solution of arylsulfonyl chloride (**5a-d**, 20 mmol) in chloroform (40 mL) at 0 ^{o}C, hydrazine hydrate (80% in H_2O, 60 mmol, 3 equiv) was added drop-wise over a period of 5 min. Then the reaction mixture was allowed to stir at 0 ^{o}C for 30 min. After completion of reaction, the solvent was evaporated under *vacuo*. To the crude reaction mixture, water was added and extracted with ethyl acetate (2 X 20 mL). The organic layer was separated and dried over anhydrous sodium sulfate to obtain pure arylsulfonyl hydrazide (**5e**–**h**) (Scheme 7).



Scheme 7: Synthesis of arylsulfonyl hydrazides **5e**–**h**.

We have chosen 4-bromoguaiacol (**1g**) and benzenesulfonyl hydrazide (**5e**) as model substrates for sulfonylation reaction. At the outset, 4-bromoguaiacol was dearomatized in the presence of 1.2 equiv $PhI(OAc)_2$ in methanol, after that benzenesulfonyl hydrazide was added and the contents were kept for stirring at 70 ^{o}C. Disappointingly, only yellow spot of MOB was observed on TLC (Table 3, entry 1).

Table 3. Optimization of reaction conditions.[a]



Entry	**5e** /equiv	Reagent	Solvent	Yield(%)[b]	
				56	**56'**
1	1	-	MeOH	Nd	nd
2	1	-	MeOH/H_2O (2:1)	Nd	40
3	1	-	ACN/H_2O (2:1)	30	55
4	1	-	ACN/H_2O (1:1)	58	25
5	1	-	ACN/H_2O (1:2)	65	15
6	1	-	THF/H_2O (1:2)	63	15
7	1	-	DMF/H_2O (1:2)	55	nd
8[c]	1	-	DCM/H_2O (1:2)	Nd	nd
9	1	-	H_2O	65	15
10	1.2	-	ACN/H_2O (1:2)	60	20
11	0.7	-	ACN/H_2O (1:2)	70	15
12	**0.5**	**-**	**ACN/H_2O (1:2)**	**82**	**15**
13	0.5	I_2	ACN/H_2O (1:2)	80	nd
14	0.5	I_2+H_2O_2	ACN/H_2O (1:2)	Nr	nr
15	0.5	I_2+TBHP	ACN/H_2O (1:2)	Nr	nr
16[d]	0.5	-	ACN/H_2O (1:2)	85	10
17[e]	0.5	-	ACN/H_2O (1:2)	60	nd

[a]Reaction conditions: **1g** (0.5 mmol), $PhI(OAc)_2$ (0.6 mmol), **5e** (0.25 mmol), solvent (3 mL) stirred at 70 °C, under air for 2 h.

[b]Pure and isolated yields. nd: Not determined. nr: No reactions.

[c]Reaction was performed in a sealed tube.

[d]Reaction was carried out at room temperature for 24 h.

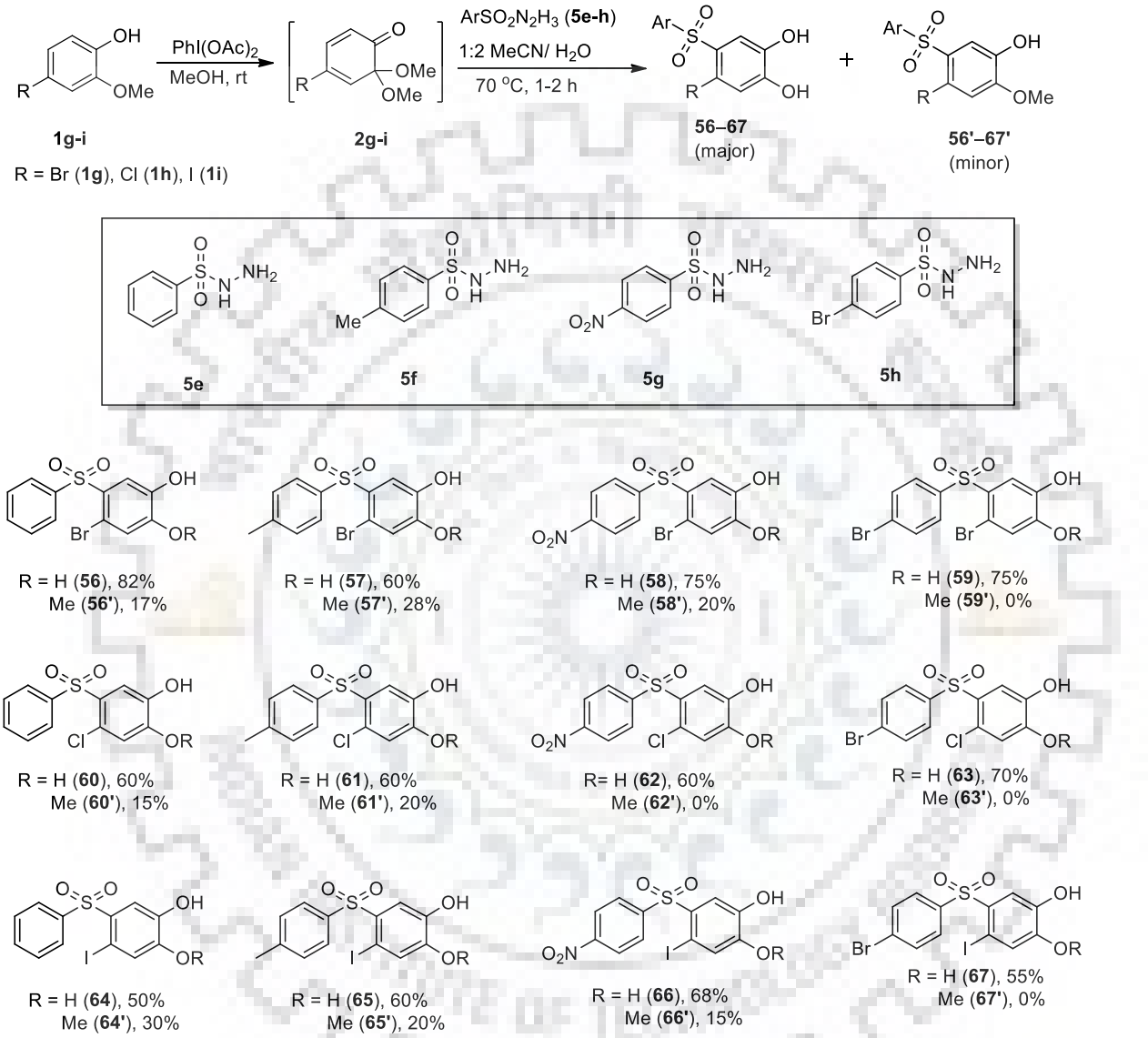
[e]Reaction was done at 100 °C.

With the aim of facilitating the reaction, 1 mL of water was added to the reaction mixture after dearomatization and kept the contents for stirring at 70 °C. To our delight, the expected sulfonated product **56'** was obtained in 40% yield (entry 2). To evaluate the effect of solvents on the reaction, methanol was evaporated from reaction mixture after dearomatization of 4-bromoguaiacol (**1g**) under reduced pressure and the residue was diluted with acetonitrile/water (2:1). Then benzenesulfonyl hydrazide was added to it at 70 °C and the contents were allowed to stirr for 2 h to obtain **56'** in 55% yield along with unexpected product **56** which was isolated in 30% yield (entry 3). To achieve the optimum sulfonylation conditions, the amount of water in solvent system has been increased (entries 4 and 5) to acetonitrile:water (1:2) and the dihydroxy derivative **56** was obtained in 65% yield along with 15% yield of **56'** (entry 5). Significant rise in the yield of **56** by increasing the quantity of water depicts the crucial role of water in this sulfonylation reaction.

Further, the protocol was scrutinized using different solvents, catalysts and by varying the temperature and amount of substrate. Screening of other solvents such as THF, DMF, DCM, H_2O revealed acetonitrile to be the most effective solvent for this transformation (entries 6–9). After this we optimized the reaction with different concentrations of **5e** and it was observed that increasing its amount slightly erode the yield of the **56** (entry 10) although decrease in its quantity from 1 to 0.5 equiv increased the efficiency of the reaction to furnish the corresponding catechol **56** in maximum yield of 82% (entries 11 and 12). Use of catalyst failed to improve the yield (entries 13–15). On the other hand, lowering the temperature from 70 °C caused a substantial drop in the reaction rate. Thus the reaction at rt found to be inefficient (entry 16) and at 100 °C, non-specific decomposition was observed in the reaction (entry 17).

The easily accessible 4-subsituted guaiacols and sulfonyl hydrazides paved the way to study the general scope of this transformation. With the optimized sulfonylation procedure in hand, several arenesulfonyl hydrazides **5e**–**g** with varying electronic groups participated in the reaction with 4-halo-2-methoxyphenols **1g**–**i** and furnished the dihydroxy arylsulfones **56**–**67** in good to high yields ranging from 50–80% along with **56**'–**67**' as minor products in

0–30% yield. The reaction of 4-halo substituted methoxyphenols with 4-bromo-phenylsulfonyl hydrazide (**5h**) resulted in the formation of the corresponding catechols **59**, **63**, **67** in selective manner and sulfonyl attached catechol was not observed (Scheme 8).



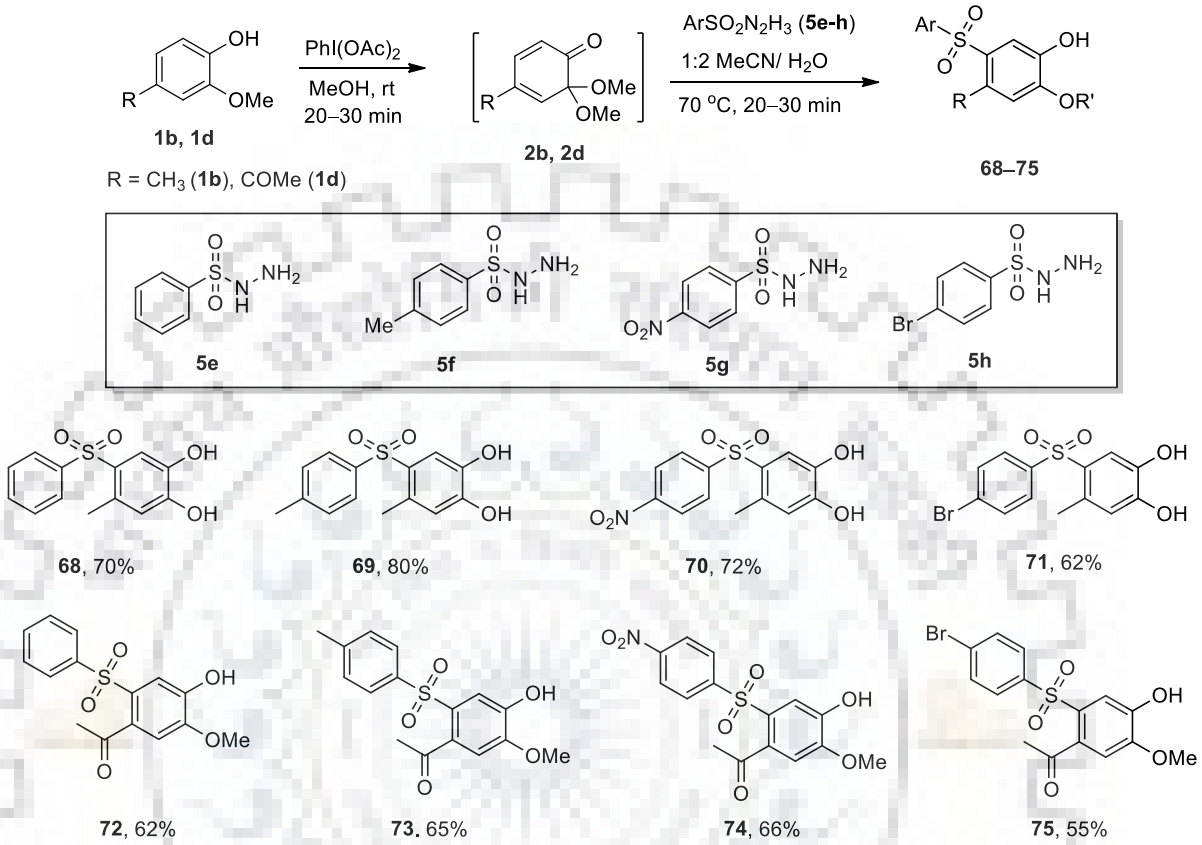
Scheme 8: Sulfonylation of 4-halo-2-methoxyphenols **1g**–**1i**.[a, b]

[a]Reaction conditions: methoxyphenol **1g**–**1i** (0.5 mmol), $PhI(OAc)_2$ (0.6 mmol), in methanol (5 mL), rt, arenesulfonyl hydrazide **5e–h** (0.25 mmol) in acetonitrile:water (1:2) at 70 ° C.

[b]Yield of pure and isolated products.

The substrates **1b** and **1d** bearing electron-donating and electron-withdrawing groups on guaiacol moiety were well tolerated under the optimized conditions and furnished the products in good yields. It is noteworthy that methyl substituted guaiacol **1b** underwent sulfonylation to give catechol substituted phenylsulfones **68**–**71** selectively in 60–80% yield,

although the acetovanillone (**1d**) furnished the corresponding arylsulfonyl guaiacols **72–75** exclusively in 55–66% yield (Scheme 9). This may be attributed to the highly reactive nature of **2d** that resulted in the formation of kinetically stable products **72–75**.

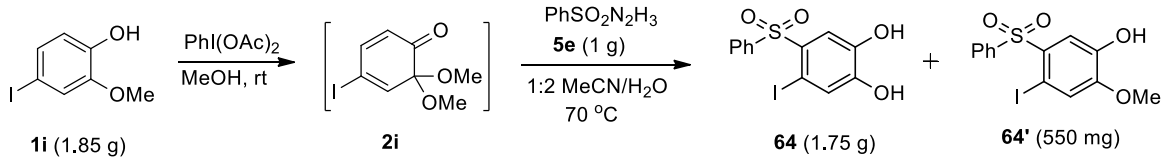


Scheme 9. Sulfonylation of 2-methoxyphenols **1b** and **1d**.[a,b]

[a]Reaction conditions: a methoxyphenol **1b**, **d** (0.5 mmol), $PhI(OAc)_2$ (1.1 equiv), in methanol (5 mL) arenesulfonyl hydrazide **5e**–**5h** (0.25 mmol) in acetonitrile : water (1:2) at 70 °C.

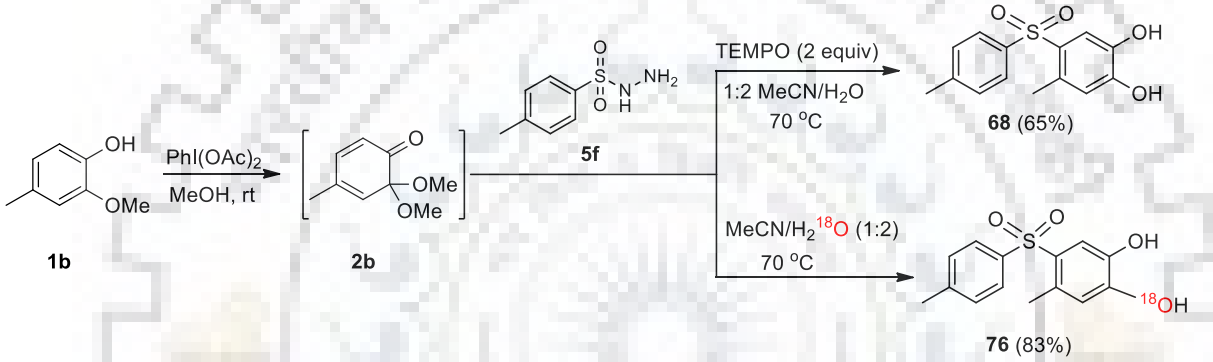
[b]Yield of isolated products.

Encouraged by this green and sustainable protocol for the synthesis of arylsulfonyl catechols, a gram-scale reaction was carried out. The efficacy of the reaction was demonstrated by performing the reaction between 1.85 g (7.4 mmol) of 4-iodoguaiacol (**1i**) and 1 g of phenylsulfonyl hydrazide (**5e**) to furnish the catechol-tethered sulfone **64** in 62% yield along with 24% yield of arylsulfonyl guaiacol **64'** (Scheme 10).



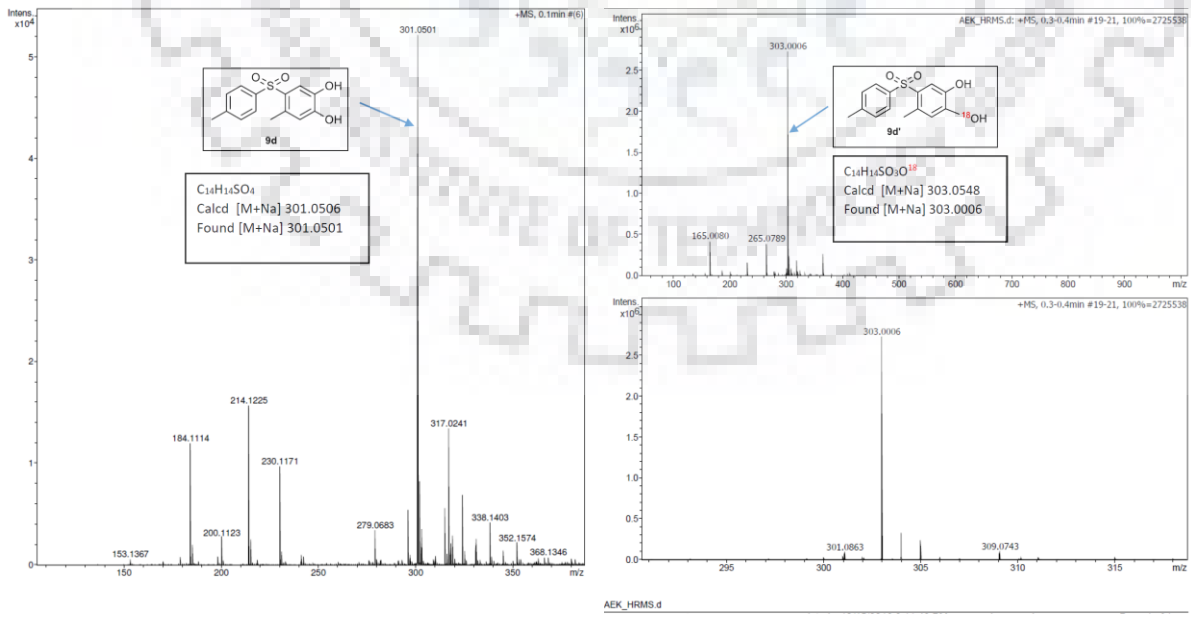
Scheme 10: Gram-scale reaction of 4-iodoguaicol.

We next turned our attention to gain insight into the reaction mechanism. At first, in support of our working hypothesis that relies on the intermediacy of a sulfinyl anion in water [168] When we performed the reaction of **1b** and **5f** using 2 equiv of radical inhibitor TEMPO, the reaction afforded product **68** in 65% yield (Scheme 11), which is consistent with the postulated ionic species as intermediate. Subsequently, to elucidate the source of second hydroxy functionality in the catechol products, an isotope labelling experiment was conducted (Scheme 11). Thus when we performed the above reaction in $H_2{}^{18}O$, the ^{18}O labelled product **76** was obtained and detected from HRMS analysis (Table 4). This isotopic labelling experiment concluded that the oxygen atom of second hydroxy group in the catechol product was originated from water.



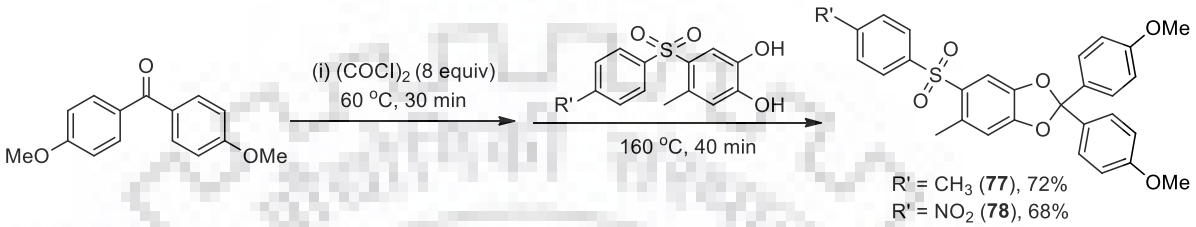
Scheme 11: Mechanistic considerations.

Table 4: Monitoring reaction with HRMS spectra analysis.



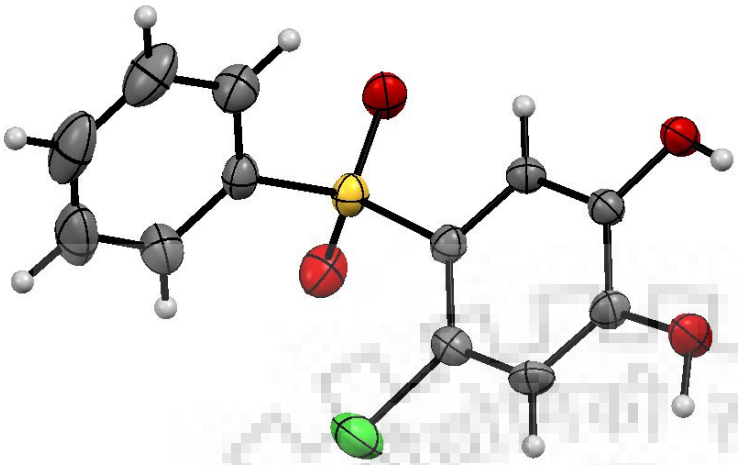
After establishing the scope of the reaction with various hydrazides and 2-methoxyphenols, we further demonstrated the potential of obtained dihydroxy arylsulfone

products (Scheme 12). We envisioned that the two free OH groups could undergo acetalization leading to the formation of corresponding ketals **77** and **78** which are analogues of COMT inhibitor and novel precursors for cannabinoid-1 receptor inverse, an agonist, for the treatment of obesity [172]. So the protocol can be considered as efficient methodology to combat obesity and its associated comorbidities exists.



Scheme 12: Synthetic transformation of arylsulfone catechols.

The structures of the formed disulfones were confirmed by the detailed analysis of spectral data obtained from ^{1}H and ^{13}C NMR and HRMS experiments of pure and isolated products. The regiochemistry of compound **58'** was elucidated by ^{1}H NMR. The methoxy (–OMe) group of guaiacol moiety of **58'**resonates at 3.96 ppm and the aromatic –CH protons of guaiacol template resonate at 7.97 and 7.08 ppm as singlets indicating that there is no *ortho*- or *meta*-coupling between the aromatic protons. Thus it is clear that aromatic –CH protons of guaiacol scaffold are *para* to each other. This supports our observation that the attack of sulfonate anion is occurring at position 3 only. As per the spectral analysis of compound **58**, no signal has been observed near the region of 4.0 to 3.6 ppm which confirms the absence of methoxy group present **58**. Furher, evidence in favor of catechol formation was obtained from the HRMS spectrum of compound **58**, a peak at m/z 395.913 which is well consistent with the calculated value m/z 395.914 for $[M + Na]^{+}$. Furthermore, the formation of catechol was also confirmed by single crystal X-ray analysis of compound **60**, grown through the slow evaporation (at room temperature) of the solvent from dichloromethane-methanol-hexane solution (Figure 7 and Table 5).



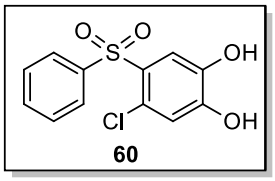


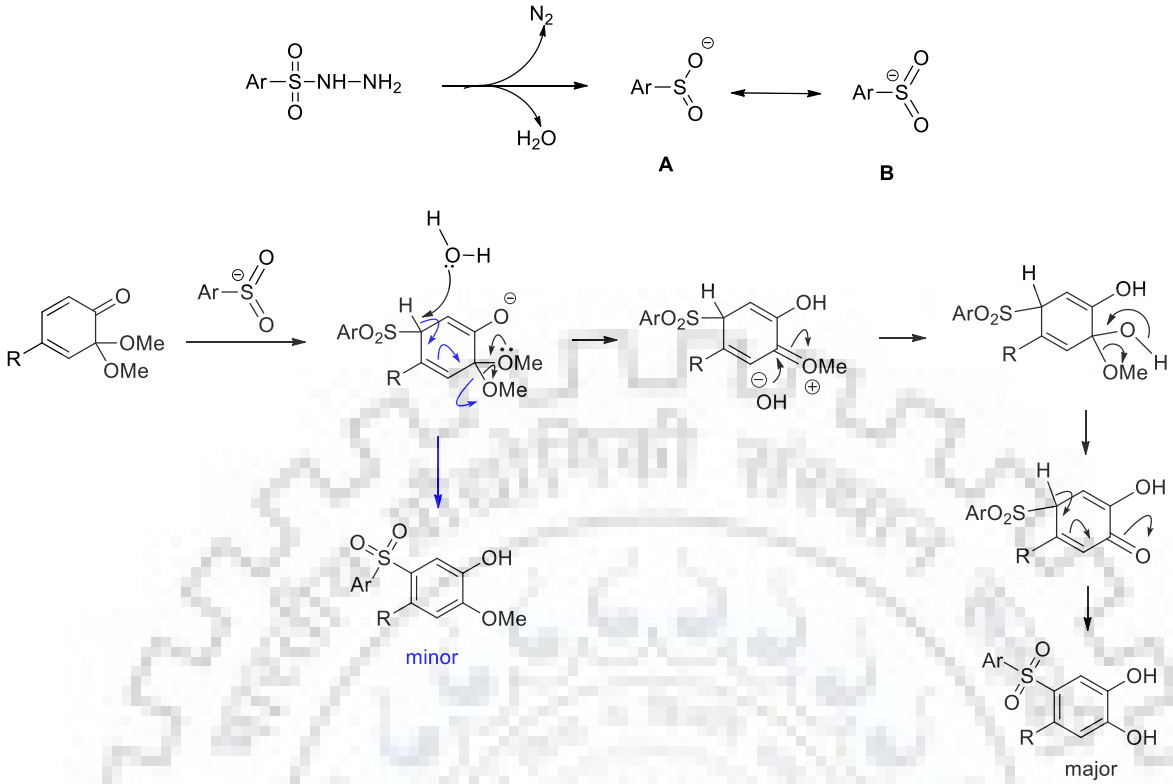
Figure 7. ORTEP plot for compound **60**.

Table 5: Crystallographic data for **60**.

Formula	$C_{12}H_9ClO_4S$
Formula Wt.	302.72
Crystal habit	Blocks
Crystal color	White
Crystal system	Triclinic
Space group	P 21/c
a (Å)	12.906(5)
b (Å)	10.616(5)
c (Å)	9.513(5)
α (deg)	90
β (deg)	103.091(5)
γ (deg)	90
V (Å^3)	1269.5(10)
Z	4
D_{calc} (g cm^{-3})	1.584
T (K)	293
λ (Mo-Kα)	0.71073
μ (mm^{-1})	0.478

2θ range (deg)	50.52
Limiting indices	$-15 \leq h \geq 15$
	$-12 \leq k \geq 12$
	$-11 \leq l \geq 11$
F(000)	624.0
No. of Reflns. Measured	2364
No. of Parameters	188
GOF on F^2	1.252
R1 [I>2σ(I)]	0.0551
wR2	0.1328

Mechanism for sulfonylation is depicted in Scheme 12. Intially, sulfonyl hydrazide get transformed into intermediate **A**, which in the presence of water resonates with species **B**. Further, the sulfur-centered anion attacks on position 3 of MOB to form species **C** and subsequent rearomatization yields the arylsulfonyl guaiacol derivative as minor product. The species **C** develops a positive charge on oxygen atom that facilitates the nucleophilic attack by water on the neighbouring carbon followed by a series of steps towards rearomatization to result in the formation of arylsulfonyl catechol derivative as the major product of the sulfonylation reaction (Scheme 13).



Scheme 13: Proposed reaction mechanism.

2.2.3. Metal-Free direct *C*-arylation of C–H activated pronucleophiles: Synthesis of diverse array of *meta*-functionalized phenols

C-arylation has drawn extensive and revolutionized attention as one of the significant methods for the C–C bond formation, which provides an easy access to complex organic frameworks that manifest a wide range of pharmacological activities [78,173–175]. The chemistry of 1,3-diones is a cornerstone of organic synthesis by virtue of eloquent reactivity of functional groups present. The enolate arylation of 1,3-dicarbonyl compounds and β-cyanoacetates were usually carried out by transition metals [80,176–178] but rarely by organocatalysts [179]. Particularly, Stoltz *et al.* isolated the small amount of C-arylation product during aryne insertion reaction into the C–H σ–bond of 1,3-diones [180]. Wang *et al.* studied the α-arylation of dicarbonyls with CuBr-trichloroacetic acid as a catalyst [181]. Owning to the potential application [182–184] of 2-aryl 1,3-dicarbonyls, a convenient and practical and strategy for the direct α-arylation of 1,3-dicarbonyl compounds and β-cyanoacetates is still challenging.

During our ongoing studies on dearomatization of alkoxy phenols, we found that the *in situ* generated reactive intermediates *i.e.* MOBs [185,186] being rich in functional groups and could potentially participate in various addition reactions. It occurred to us that the addition of 1,3-dicarbonyl compounds and β-cyanoacetates to 2-methoxyphenols-derived *ortho*-benzoquinone monoketals would provide α-arylated products. If this is realised, it would pave a way to highly prudent methodology to furnish *meta*-alkylphenols that widely exist in many pharmaceuticals (Figure 8).

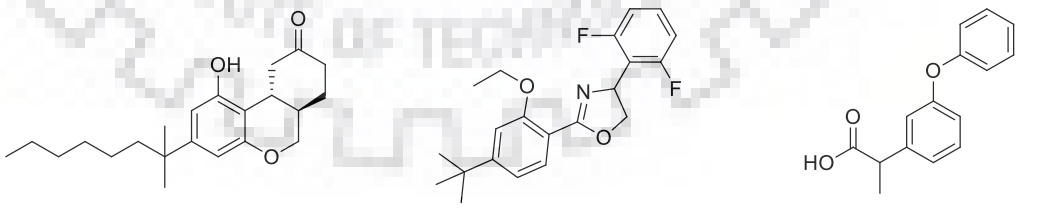


Figure 8: Drugs containing *meta*-alkylphenols scaffolds.

Moreover, synthesis of *meta*-substituted phenols possesses a significant challenge of bypassing the normal *ortho*/*para* directing effect of hydroxyl functionality (Figure 9). Recent reported methods for *meta*-functionalization are mainly based on transition metal- catalysis

and template-based strategies [46,187–190]. Although efficient, these methods often require lengthy synthetic routes, high temperature and prolonged reaction time. Therefore, it is still highly demanding to overcome these shortcomings and discover a metal-free strategy for the transformation of phenols to *meta* substituted phenols.

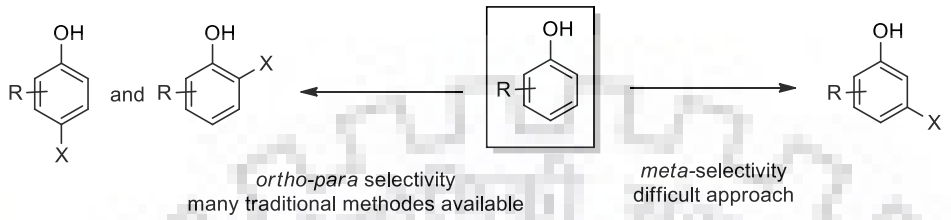


Figure 9: General functionalization of phenol derivatives.

Our results on base-mediated C-arylation of C–H activated pronucleophiles with commercially available, innocuous 2-methoxyphenols as aryl partners are described in this section. These phenols can be easily dearomatized to the corresponding benzoquinone derivatives, also known MOBs. Thus *in situ* generated conjugated cyclohexadienones were then subjected to Michael attack by C–H activated pronucleophiles to access *meta*-selective C–H functionalized products under very mild conditions. Further remarkability of this approach has been proven by extending it for the synthesis of various phenol functionalized *N*- and *O*-heterocyclic scaffolds that utilize β-diketones as essential building blocks *viz.* pyrazole, isoxazole, coumarin, and triazolone derivatives. Some of these heterocyclic compounds that are counted among the most potent biologically active scaffolds [89,191–196] are shown in Figure 10.

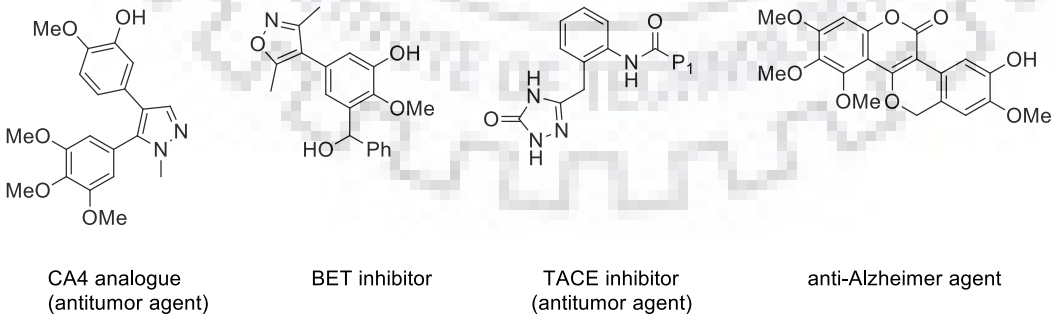
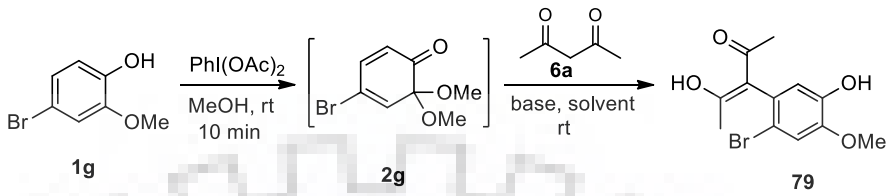


Figure 10: Drugs containing *meta*-heterocyclic phenol skeletons.

The feasibility of the enolate arylation of 1,3-diones is investigated when we attempted the reaction between 4-bromo-2-methoxyphenol (**1g**) and acetylacetone (**6a**). In the initial step, the dearomatization of 4-bromoguaiacol was carried out with

diacetoxyiodobenzene (DIB, 1.2 equiv) in methanol to generate *o*-benzoquinone monoketal **2g**.

Table 6: Screening of reaction conditions.[a]



1g 2g 79

Entry	Acetylacetone (equiv)	Solvent	Base (1 equiv)	Yield[b] (%)
1	1	MeOH	Et_3N	60
2	1	MeOH	-	nr
3	1	MeOH	KO^tBu	61
4	1	MeOH	K_2CO_3	58
5	1	MeOH	Cs_2CO_3	63
6	1	MeOH	NaOH	nd
7	1	MeOH	DABCO	55
8	1	DCM	Et_3N	40
9	1	CAN	Et_3N	55
10	1	THF	Et_3N	50
11	1	Toluene	Et_3N	62
12[c]	1	Toluene	Et_3N	65
13[d]	1	Toluene	Et_3N	68
14[d]	**1.2**	**Toluene**	**Et_3N**	**72**
15[d]	2.0	Toluene	Et_3N	73
16[d, e]	1.2	Toluene	Et_3N	61

Reaction conditions: **1g** (0.30 mmol), DIB (0.36 mmol), acetylacetone (**6a**, 0.45 mmol), base, solvent (3 mL) stirred at rt, in air for 3 h.

[b]Pure and isolated yields. nd: Not determined. nr: No reactions.

[c]Reaction with 1.5 equiv Et_3N at room temperature for 24 h.

[d]Reaction with 2.0 equiv Et_3N at room temperature for 24 h.

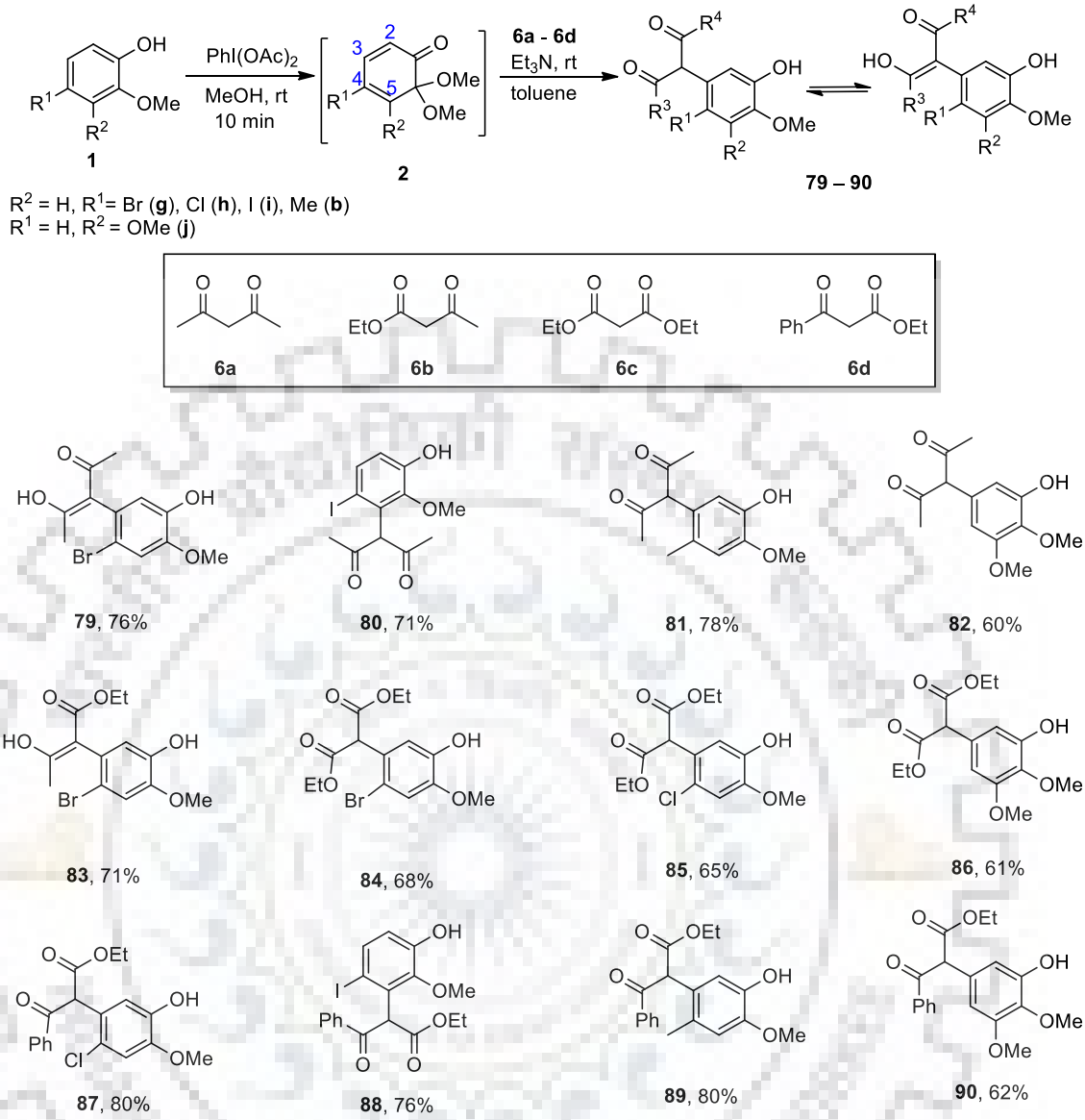
[e]Reaction performed at 80 °C with 1.5 equiv Et_3N.

This transformation then facilitated the Michael addition of C–H activated acid **6a** in the presence of Et_3N (1 equiv) and enabled the synthesis of desired product **79** in 60% yield (Table 5, entry 1). The base additive was found to be crucial to the reaction as no reaction

was observed in its absence (entry 2). Fortified by above results, other reaction conditions were screened, including the choice of base, solvent and temperature. It was observed that with most of the commonly used bases such as Cs_2CO_3, K_2CO_3, NaOH, KO^tBu, DABCO and Et_3N, the reaction went on to completion successfully (entries 3–7). Among these, Et_3N was proved to be efficient base for this enolate arylation. In order to circumvent the nucleophilic attack of MeOH on MOB, after dearomatization, methanol was first removed from the reaction mixture by rotatory evaporator *in vacuo* and the reaction was continued by diluting the residue in another solvent such as THF, ACN, DCM, toluene followed by the addition of base and dicarbonyl compound (entries 8–10). To our delight, when the reaction was carried out in toluene, the arylated product **79** was obtained in enhanced yield of 62% (entry 11). An increment of the product yield was observed by increasing the amount of Et_3N to 2 equiv (entries 12 and 13). However, increasing the stoichiometry amount of acetylacetone also showed a positive effect on the efficiency of the reaction (entries 14 and 15). However, elevating the temperature has no substantial effect on the reaction (entry 16).

Having established the optimum reaction conditions in hand, we were keen to study the generality of this protocol. A number of acyclic dicarbonyls and variously substituted 2-methoxyphenols were subjected to react under these conditions. Thus dicarbonyls **6a–d** and 2-methoxyphenols **1b, 1g–j** successfully furnished the *meta*-functionalized phenols in good to high yields revealing the validity of standard established reaction conditions for α-arylation (Scheme 14). As shown, the alicyclic 1,3-dicarbonyl compounds afforded the products **79–90** in good to high yields. A minor drop in the yield of compounds **84–86** arising from less acidic diethyl malonate (**6c**) may be noted. Furthermore, due to the less reactivity of *ortho* benzoquinone momoketal **2j** derived from 2,3-dimethoxyphenol (**1j**), the Michael addition was performed at 80 ºC

It was envisioned that positions 3 and 5 of *in situ* generated MOB are susceptible for nucleophilic attack. Interestingly, the site for Michael attack in this transformation is directed by the substitution present on cyclohexa-2,4-dienone **2** system. Unlike 4-bromo, 4-chloro, 4-methyl and 5-methoxy guaiacol derivatives, where the Michael attack occurred on C-3 of the corresponding MOBs, the 4-iodoguaiacol exceptionally furnished the products **80** and **88** arising from the addition of nucleophiles on C-5 of 4-iodo masked *ortho* benzoquinone **2i**.



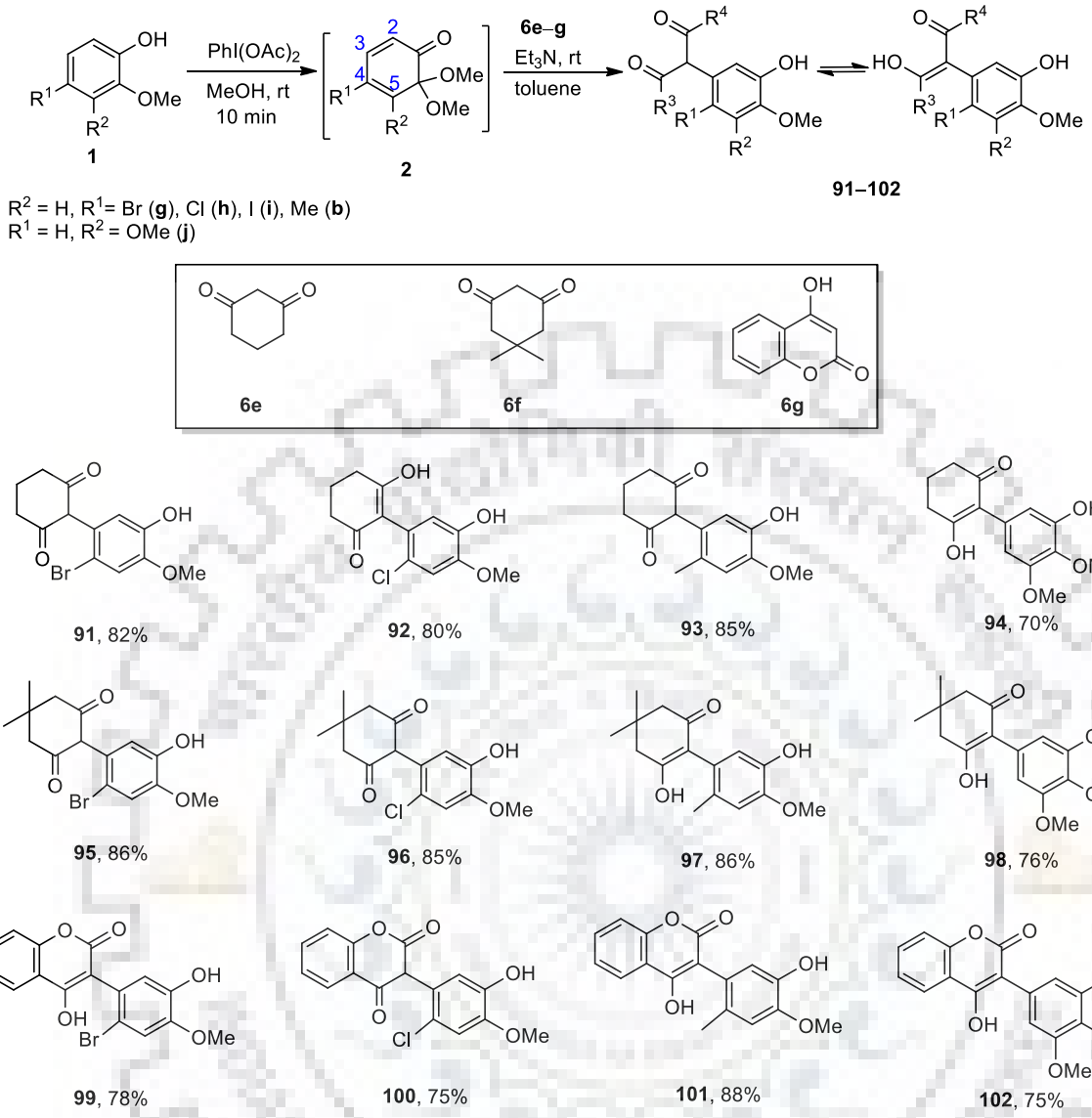
Scheme 14: Reactions of substituted guaiacols with various alicyclic 1,3-dicarbonyl compounds **6a**–**6d.**[a]

[a]Reaction conditions: **1** (0.3 mmol), DIB (0.36 mmol), 1,3-dicarbonyl compound (**6a**–**d**, 0.45 mmol), Et_3N (0.67 mmol), solvent (3 mL) stirred at rt for 3–5 h (see experimental section).

[b]Combined yields of the products.

[c]Reaction was performed at 80 °C.

Enthrallingly, cyclic 1,3-diketones **6e** and **6f** can also be employed in this base mediated transformation to furnish the desired products **91**–**98** in good to very high yields 70–86% (Scheme 15). Although the products formed specifically with one constitutional isomer.



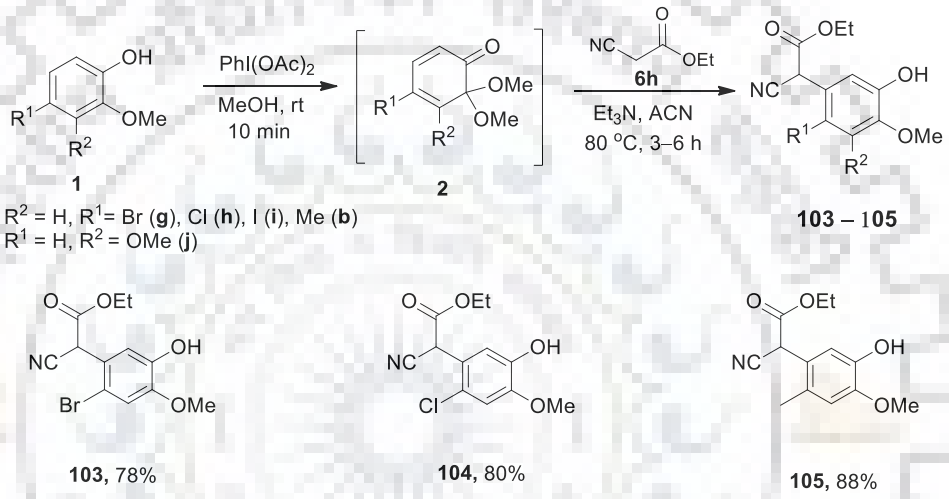
Scheme 15: Reactions of substituted guaiacols with various cyclic 1,3-dicarbonyl compounds **6e–g**. [a,b]

[a]Reaction conditions: **1** (0.3 mmol), DIB (0.36 mmol), 1,3-dicarbonyl compound (**6e–g**, 0.45 mmol), Et_3N (0.67 mmol), toluene (3 mL) stirred at rt for 2–5 h (see experimental section).

[b]Combined yields of the products.

As 1,3-diketones are widely known to show commendable keto-enol tautomerism, it is worth to mention the effect of substituents of phenols and ketones on the tautomerism of the corresponding products. Hence, 4-methyl-2-methoxyphenol (**1b**) in a reaction with **6d** and **6g**, under the optimal conditions, furnished the products that exist in the equilibrium between keto and enol form in 3:1 ratio. It was observed that C–H activated pronucleophiles such as **6c** predominantly exist in keto form and the product from **6b** exist in equilibrium with dominating enol form.

Spurred by the great synthetic medicinal interest of substituted coumarin especially benzopyranocoumarins for the treatment of neurodegenerative diseases such as Alzheimer's disease, the versatility of this approach was extended to the 4-hydroxycoumarin (**6g**). Thus, we carried out the reaction of substituted guaiacols with **6g** under previously established conditions. Delightfully, all the products **99**–**102** obtained in very high yields of 75–88% (Scheme 15). These compounds are quite similar to the precursors of benzopyranocoumarins that worked as potent anti-Alzeimer agents and were formerly prepared through metal catalysis starting from pre-functionalized substrates and in multiple steps [89].



Scheme 16: Reactions of guaiacol derivatives with 2-ethyl cyanoacetate.[a, b]

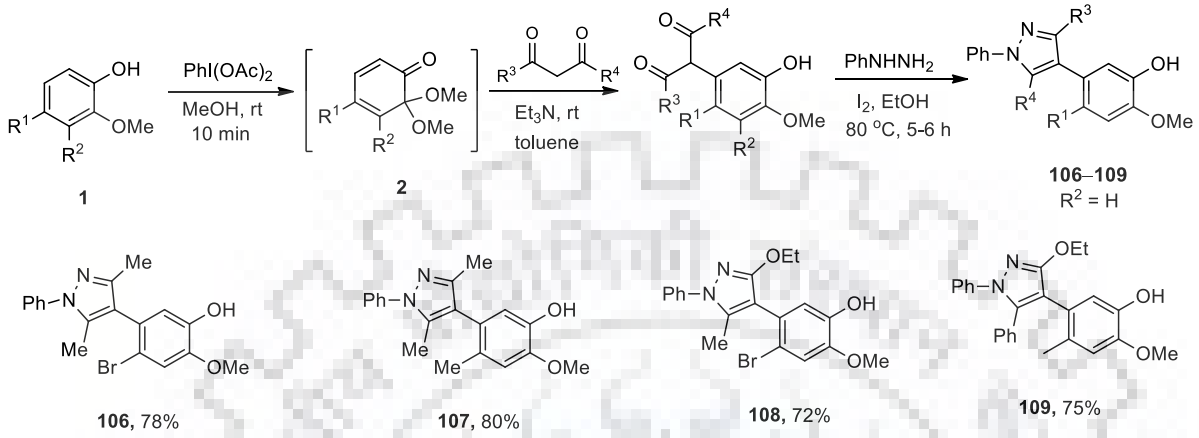
[a]Reaction conditions: **1** (0.3 mmol), DIB (0.36 mmol), 1,3-dicarbonyl compound (**6e**–**g**, 0.45 mmol), Et_3N (0.67 mmol), acetonitrile (3 mL) stirred at rt for 3–5 h (see experimental section).

[b]Isolated yields of the products.

After this, we stepped ahead to explore the reactivity of ethyl 2-cyanoacetate (**6h**). The initial attempts for *meta*-substitution with optimized reaction conditions were unsuccessful due to its low reactivity. However, when we performed the reaction in acetonitrile at 80 °C, the *meta*-substituted product **103** was obtained in 78% isolated yield. All the substituted alkoxy phenols reacted well under these conditions and furnished the substituted cyanoacetate derivatives **103**–**105** in high yields (Scheme 16). It is worth mentioning here that the arylated cyanoacetates worked as excellent starting materials to generate stable quaternary stereocenter *via* C–C bond formation [197, 198].

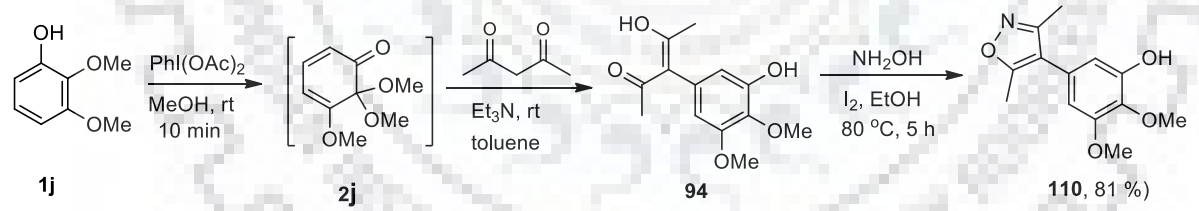
Having successfully developed an efficient protocol for *meta*-substituted phenols, we turned our focus on the utility of these obtained compounds to access phenol functionalized novel heterocyclic scaffolds in one-pot manner. Condensation of α-arylated products with

phenylhydrazine in presence of molecular iodine resulted in the corresponding pyrazoles **106**–**109** (Scheme 17) in high yields. The synergism of phenol with pyrazole introduced an convenient route to pyrazole-based analogues of combretastatin A4 (antitumor agent) [92].



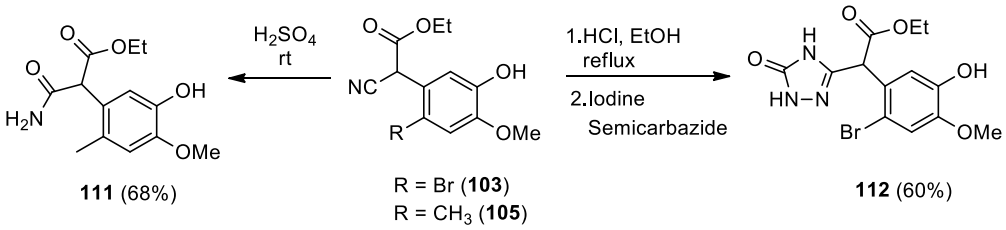
Scheme 17: Synthesis of phenol substituted pyrazoles.

Treatment of *meta*-substituted 2,3-dimethoxyphenol product **94** with hydroxylamine and molecular iodine in presence of ethanol furnished the phenol coupled dimethylisoxazole motif **110**. The key aspect of this molecule is 3,5-dimethylisoxazole scaffold that can act as potent inhibitor of the BET (bromodomain and extra terminal domain) and help in the proper functioning of human body cells (Scheme 18) [94].



Scheme 18: Synthesis of phenol substituted isooxazole.

The reactivity profile of α-arylated cyanoacetate has been further expanded through the manipulation of the cyano group by readily converting it into other functionalities. Thus the treatment of **105** with a few drops of conc. sulfuric acid at rt gave carboxylic amide **111** after stirring of 48 h. The arylated carboxylic amides appear in a variety of drugs, fabrics, plastics, lubricants and fertilizers [200]. The cyano group of **103** can also be transformed to heterocyclic ketone triazolone **112.** Since the last decades, triazolones have been established as potent biological active templates [201] for antitumor and antihamelogic activity (Scheme 19).



Scheme 19: Transformation of cyano-substituted products.

All the obtained structures were unambiguously determined by analyzing the data obtained from ^{1}H and ^{13}C NMR and ESI-MS spectra. The regiochemistry of the products has been established by the proton-NMR studies.

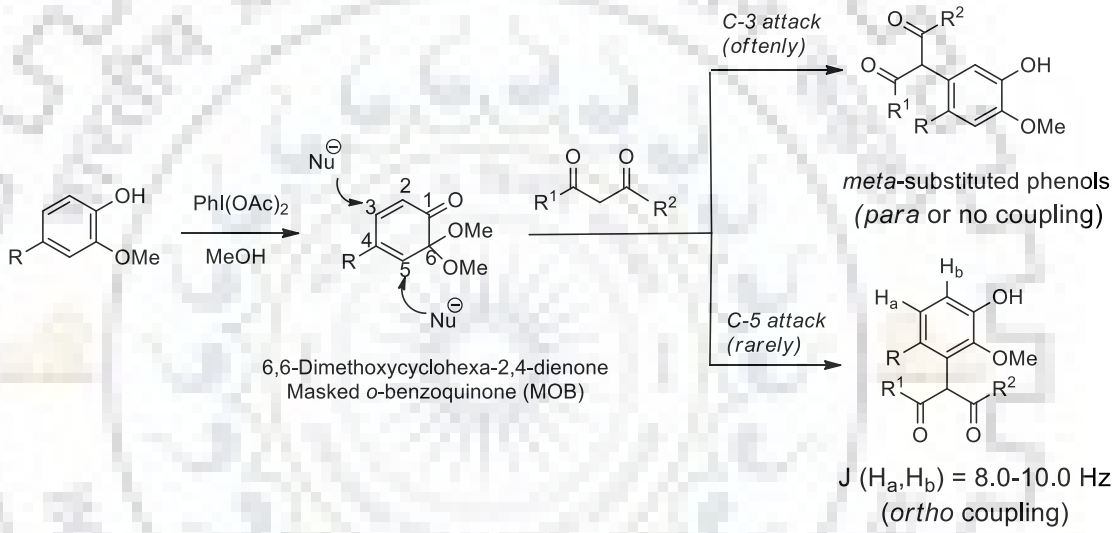


Figure 11: Regiochemistry for the α-arylation.

From the ^{1}H NMR spectrum of all compounds obtained except **80** and **88**, the aromatic –CH protons resonates at the range of 7.56–6.26 ppm as the singlets, that indicates the absence of *ortho* coupling and hence, supporting the nucleophile attack at C-3 position of MOB to form *meta*-substituted phenols in most of the reactions performed. whereas, in the compounds **80** and **88** the aromatic protons H_a and H_b of guaiacol moiety resonate in the range from 7.53 to 6.98 ppm as doublets with coupling constants in the range of 8.0 to 10.0 Hz (*ortho* coupling) indicating that Michael attack in case of 4-iodo guaiacol has been occurred at C-5 position of MOB rather than at C-3. Further, confirmation for the synthesis of *meta*-substituted phenols is given by single crystal X-ray diffraction studies of pyrazole **106**, grown by the slow evaporation of the solvent system of dichloromethane-ethyl acetate-hexane **106** (Figure 12, Table 7). In addition to this, the enolic–OH of compound **83** is

resonating at 13.06 ppm with one proton integration, whereas the α-hydrogen of ethyl acetoacetate is resonating at 5.18 ppm and with 0.3 proton integration relatively and hence giving evidences for the existence of keto-enol tautomers in the ratio of 1:3.

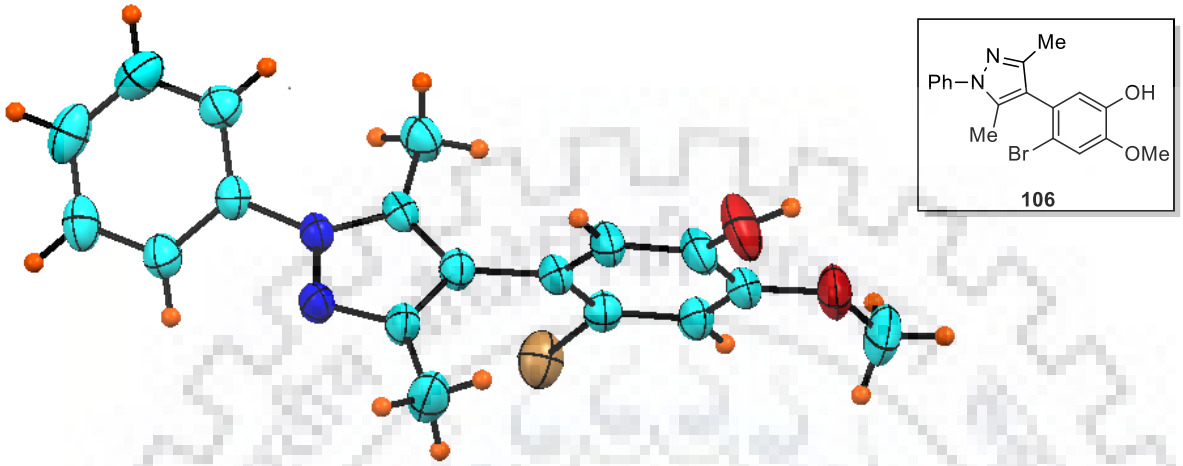


Figure 12: ORTEP plot for compound **106**.

Table 7: Crystallographic data for **106**.

Formula	$C_{18}H_{17}BrN_2O_2$
Formula Wt.	373.24
Crystal color	Brown
Crystal system	Monoclinic
Space group	P 21/c

a (Å)	12.5690(3)
b (Å)	7.6182(2)
c (Å)	17.8411(4)
α (deg)	90
β (deg)	104.1610(1)
γ (deg)	90
V ($Å^3$)	1656.43(7)
Z	4
D_{calc} (g cm^{-3})	1.497
T (K)	296
λ (Mo-Kα)	0.71073
μ (mm^{-1})	2.493
Theta (max)	28.337
Limiting indices	$-16 \leq h \geq 10$ $-9 \leq k \geq 10$ $-23 \leq l \geq 23$
F(000)	760
No. of Reflns. Measured	4119
GOF on F^2	1.085
R(reflections)	0.0400(2824)
wR2	0.1433(4119)

2.2.4. Synthesis of substituted 5-aryl barbituric acid derivatives

Since 1864, when a German chemist Adolf von Baeyer discovered the barbituric acid, they are known to be privileged with 1,3-diamide scaffolds in medicinal chemistry owing to their sedative, anti-convulsant, analgesic, hypnotic, antimicrobial, anaesthetic, anticancer and antitumor properties [96,202–205]. The first barbiturate developed was the barbital and it was widely used as a sedative, hypnotic, as a sleeping aid and anxiolytic. The World Health Organization recommended another barbiturate *i.e.*, phenobarbital as a medication for the treatment of certain types of epilepsy in some countries [206–208]. Moreover, another derivative of barbituric acid is merbarone which exhibited curative activity against L1210 leukemia and some other murine tumors and hence represented a unique class of antineoplastic agents (Figure 13) [209].

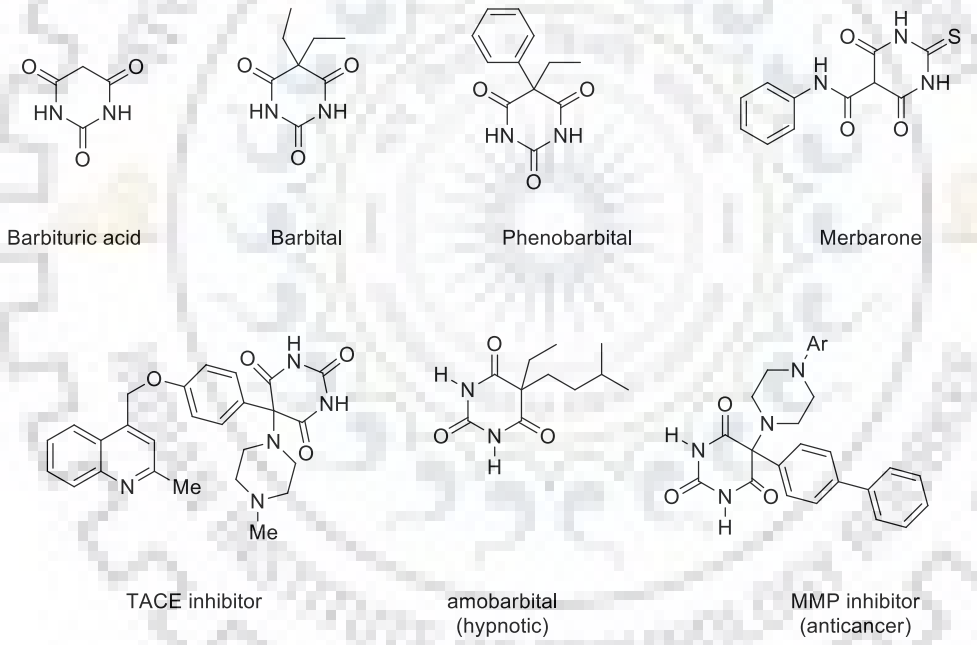


Figure 13: Bioactive derivatives of barbituric acid.

Furthermore, barbituric acid and its derivatives, because of their ability to form multiple hydrogen bonds, have important applications in coordination and supramolecular chemistry and also have been applied as new anchor unit for dye-sensitized solar cells [108,210] (Figure 14).

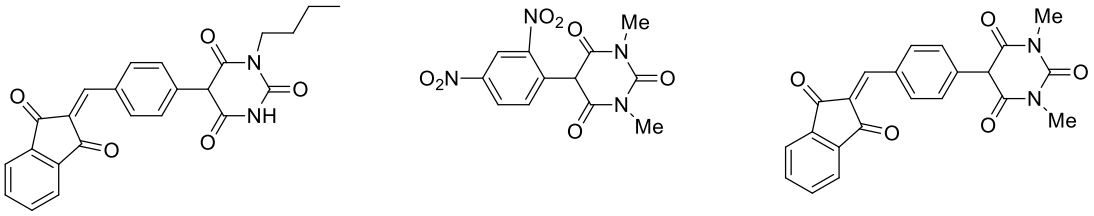
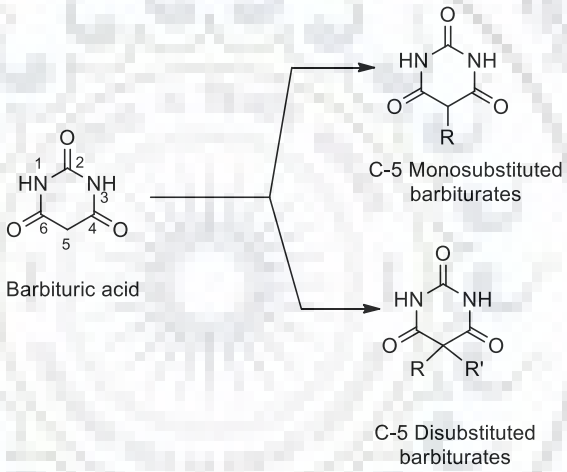


Figure 14: Derivatives of barbituric acid used as dyes.

Although unsubstituted barbituric acid itself does not show any hypnotic, or anticonvulsant properties, such features are conferred only when the active methylene hydrogen atoms at C-5 are functionalized by any organic groups (alkyl or aryl) (Scheme 20). It was proposed that to exhibit a good hypnotic properties, barbituric acids must come under weak acid and should have a lipid/water partition coefficient within certain range [211].



Scheme 20: C-5 substituted barbituric acids.

Of particular note, 5-aryl barbituric acid [103,212,213] endowed with promising bioactivity attributes such as anticancer, antidepressive [214–217] and immune system modulator activities [218,219] and also act as the useful substrates for C–H functionalization [220]. All these properties rekindled the interest of researchers in rapidly accessing these compounds.

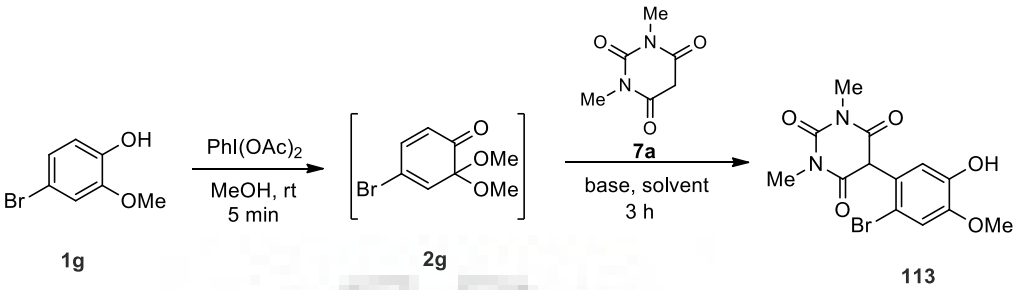
Adolf von Baeyer synthesized the 5,5-diethyl barbituric acid as first clinically used pharmacological agent in 1903, followed by 5-ethyl-5-phenylbarbituric acid in 1912 [221]. Conventionally, aryl barbiturates have been prepared by the condensation of 2-aryl malonic acid or ester with urea [102,222–225] where malonic acid or esters prepared *via* transition metal-catalyzed [226–230] cross coupling reaction that limits their availability. In 2015, lam *et al.* demonstrated the Ru(II)-catalyzed synthesis of 5-aryl barbiturates from diazo

compounds [109]. Although these routes are useful in their own right, the requirement of considerable efforts towards the prefunctionalization of precursors, deployment of transition metal catalysts, prolong reaction time and less accessible reagents, underlines the need for a general, straightforward approach employing easily available precursors to access these commendable pharmacophoric scaffolds.

As mentioned above, 5-monosubstituted, 5,5-disubstituted and 1,5,5-trisubstituted barbituric acid possess acceptable therapeutic activities. This prompted us to choose *ortho*-benzoquinone monoketals to further demonstrate their reactivity with barbituric acid as nucleophiles, Our previous studies on 2-methoxyphenols and its derivatives showed the remarkable reactivity of *in situ* generated MOBs as an intermediates toward the Michael addition reaction [185,231,186]. Thus we envisioned an ideal strategy whereby a facile Michael addition of barbituric acid moiety on MOB would furnish novel scaffolds of barbituric acid directly coupled with phenol at C-5. We developed straightforward, efficient direct C-5 arylation of barbituric acid with phenols as an aryl partner under mild conditions.

As an initial demonstrator of our proposed theme, reaction of maked *ortho*-benzoquinone generated *via* dearomatization of 4-bromo-2-methoxyphenol (**1g)** in presence of diacetoxy-iodobenzene with 1,3-dimethylbarbituric acid (**7a**) in MeOH was investigated. At the outset, 4-bromoguaiacol (**1g**) was stirred in MeOH in the presence of DIB for 10 min to generate *ortho*-benzoquinone monoketal **2g**. The *in situ* generated **2g** was treated with 1,3-dimethylbarbituric acid (1.2 equiv), but no product was obtained (Table 8, entry 1). With a thought of using any deprotonatng agent, we discovered that the addition of 1.5 eqiuv Et_3N smoothly drived the Michael attack of 1,3-dimethylbarbituric acid on *in situ* generated MOB to furnish the desired product **113** in good yield (entry 2), while more productive results were obtained with 2.5 equiv of Et_3N (entry 4). However, increasing the stoichiometry of 1,3-Dimethylbarbituric acid from 1.2 to 2.0 equiv did not contribute towards the reactivity of the reaction (entry 5). Solvent screening studies with ACN, toluene, DCM for the Michael addition step revealed that in addition to dearomatization step, MeOH is suitable for the Michael addition reaction between **2g** and *N,N'*-dimethyl barbituricacid (**7a**) as well (entries 6–8). Increasing the temperature of the reaction mixture did not show any effect on the efficacy of the reaction (entry 9).

Table 8: Optimization studies for the synthesis of 5-aryl barbituric acid.[a]



1g 2g 113

Entry	Solvent	Base	Yield[b] (%)
1	MeOH	---	Nr
2	MeOH	Et_3N (1.5 equiv)	75
3	MeOH	Et_3N (1.0 equiv)	70
4	**MeOH**	**Et_3N (2.5 equiv)**	**88**
5[c]	MeOH	Et_3N (2.5 equiv)	77
6	ACN	Et_3N (2.5 equiv)	80
7	Toluene	Et_3N (2.5 equiv)	75
8	DCM	Et_3N (2.5 equiv)	72
9[d]	MeOH	Et_3N (2.5 equiv)	80

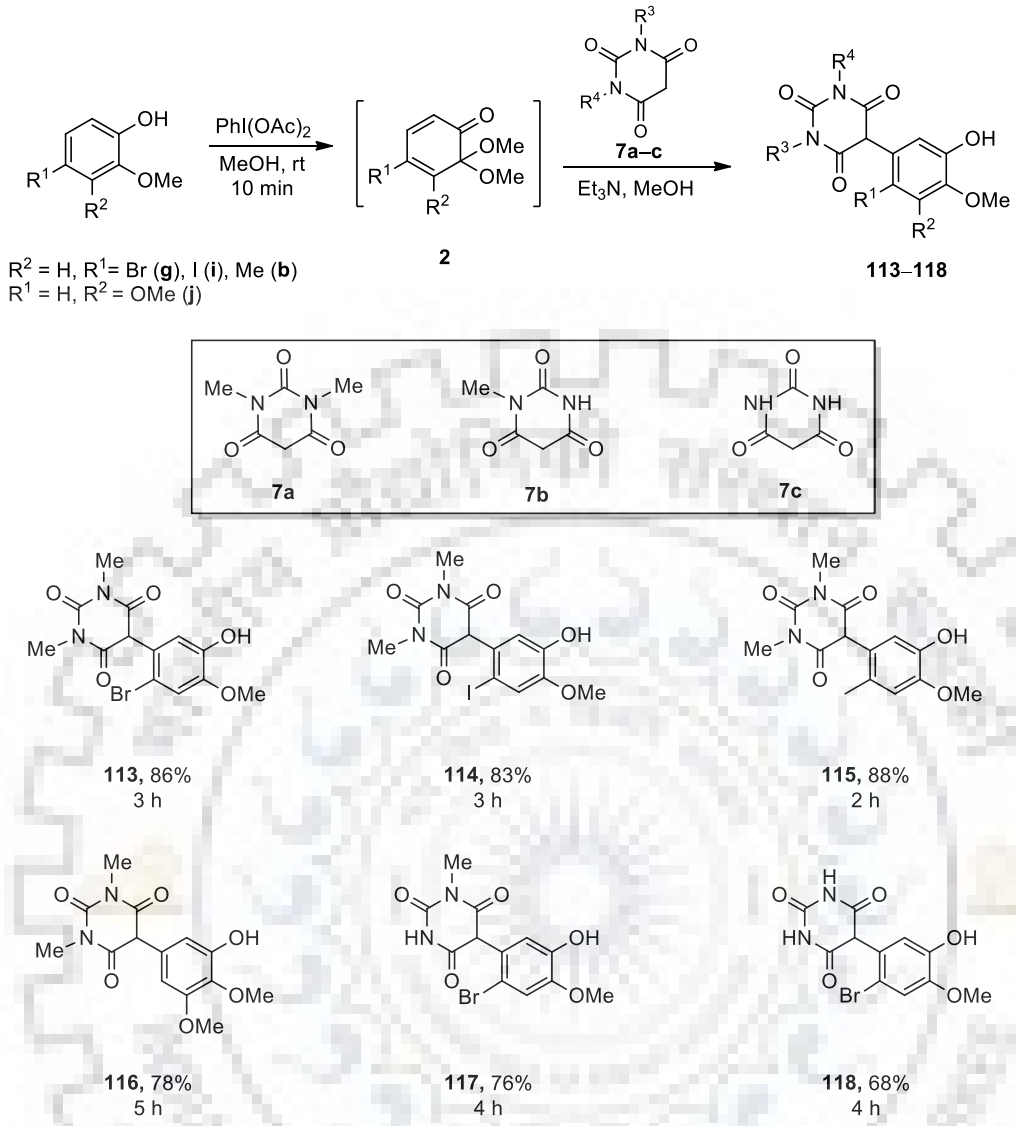
[a]Reaction conditions: **1g** (0.3 mmol), DIB (0.36 mmol), barbituric acid **7a** (1.2 equiv, 0.36 mmol).

[b]Isolated yields of the product.

[c]Reaction performed with 2 equiv, 0.6 mmol of 1,3-dimethylbarbituric acid.

[d]Reaction performed at 80 °C.

After setting the optimized reaction conditions, we next moved ahead to study the reaction between MOBs **2g**–**j** with variegated functional groups and barbituric acids partners **7a**–**c** to demonstrate the degree of generalization (Scheme 21). The 4-halo substituted 2-methoxyphenols **1g** and **1i** reacted well with 1,3-dimethylbarbituric acid and gave the desired products **113** and **114** in 86 and 83% yields, respectively. Further, the reaction with 4-methyl substituted phenol **1i** proceeded cleanly in nearly 2 h owing to its high reactivity, and provided the corresponding arylated product **115** in 88% yield. Even the less reactive MOB **2j** furnished the corresponding aryl barbiturate **116** in good yield to confirm the validity of our protocol. Our focus then turned to the variation of barbituric acid and we found that 1,3-alkylation is not necessary as the 1-methylbarbituric acid (**7b**) reacted well with 4-bromo-2-methoxyphenol (**1g**) to provide arylbarbituric acid **117** in 76% yield.



Scheme 21: Base-mediated arylation of barbituric acids.[a, b]

[a]Reaction conditions: **1** (0.3 mmol), DIB (0.36 mmol), barbituric acid **7** (1.2 equiv, 0.36 mmol) in methanol stirred at rt.

[b]Isolated yields of the products.

Whereas parent barbituric acid **7c**, which bears two free N–H groups, furnished **118** in 68% yield. In all cases, reactions were performed under mild conditions to give the products in high yields with good isomeric purity that can easily be solidified in DCM and hexane and then recrystallized using ethyl acetate/ methanol to give the pure products in good yields. Thus isolation of products was straightforward without column chromatography.

The structures of all the 5-aryl barbiturates were determined on the basis of data obtained from ^{1}H and ^{13}C NMR spectral analysis. The regiochemistry can be easily predicted by the analysis of proton-NMR spectra. The aromatic –CH protons of compounds **113–115, 117, 118** resonate in the range from 7.09 to 6.26 as singlets and as doublet for compound **116** with *meta* coupling (J = 4.0 Hz). This confirms the attack of the barbituric acid only at C-3 carbon of MOB in all the reactions performed. Further, the assignment of structures has been achieved by the single-crystal X-ray diffraction studies on dimethoxy barbiturate derivative **116** (Figure 15, Table 9). All the barbiturates obtained with isomeric purity proved by the singlet of C-5 hydrogen (in keto form) resonating at 4.65 ppm in case of **113** and with no signal resonating in the range of 4 to 5 ppm for rest all the compounds **114**–**118** (enol form).

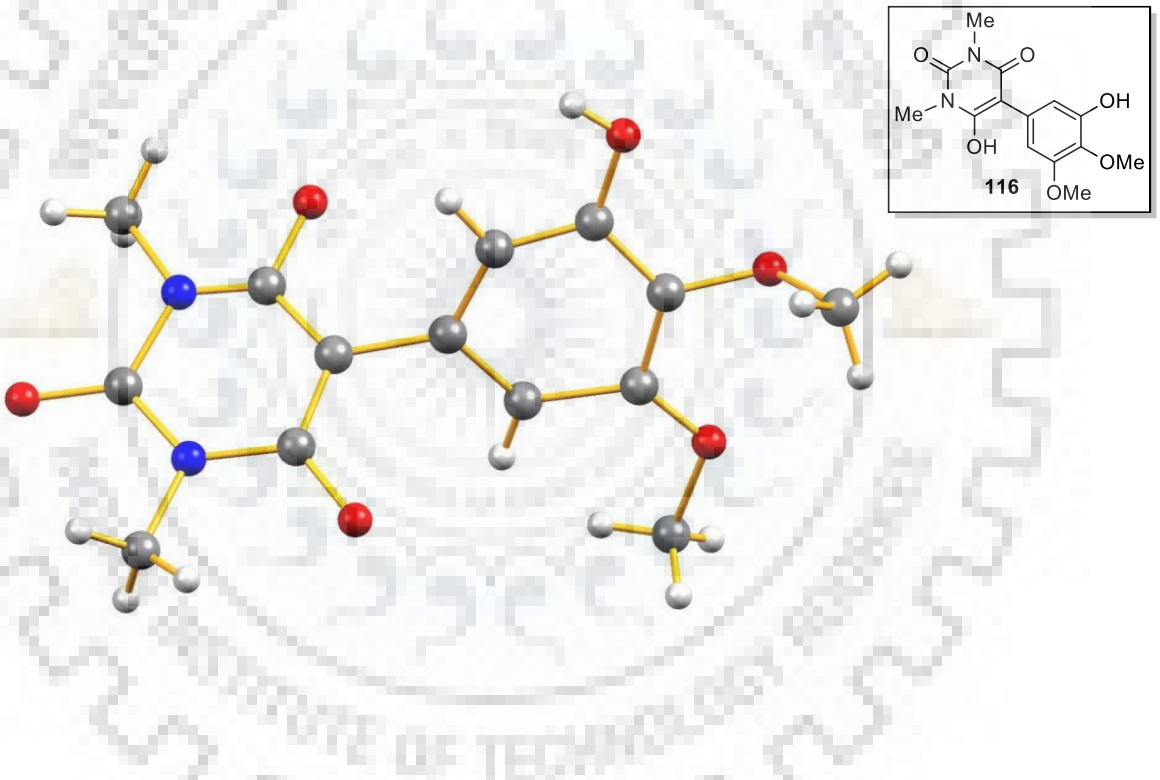


Figure 15: ORTEP plot for compound **116.**

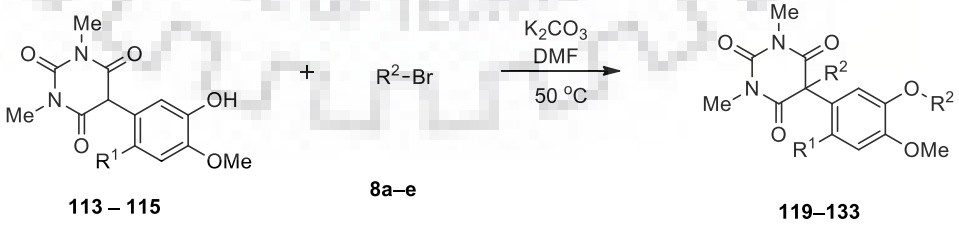
Table 9: Crystallographic data for **116**

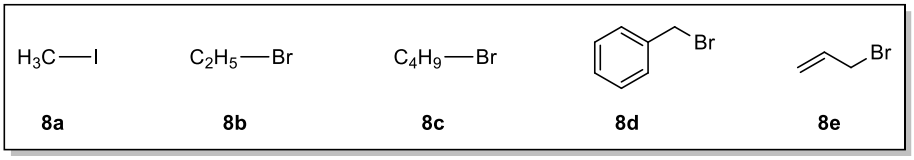
Formula	$C_{14}H_{16}N_2O_6$
Formula Wt.	308.10
Crystal habit	Blocks
Crystal color	Brown
Crystal system	Triclinic
Space group	P 1
a (Å)	7.207(3)
b (Å)	8.376(4)
c (Å)	36.102(17)
α (deg)	89.72(3)
β (deg)	90
γ (deg)	90
V (Å^3)	2179.3(17)
Z	1
D_{calc} (g cm^{-3})	0.936
T (K)	296
λ (Mo-Kα)	0.71073
μ (mm^{-1})	0.074
2θ range (deg)	20.26
Limiting indices	$-9 \leq h \geq 9$
	$-11 \leq k \geq 10$
	$-46 \leq l \geq 44$
F(000)	644
No. of Reflns. Measured	2771
No. of Parameters	816
GOF on F^2	1.769
R1 [I>2σ(I)]	0.0551
wR2	0.5306

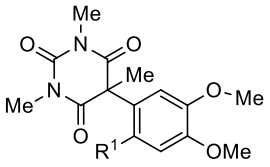
2.2.5. Synthesis of fully substituted barbituric acid derivatives

After having C-5 aryl substituted barbiturates in hand and spurred by the great synthetic and medicinal interest of C-5 disubstituted barbiturates, next we turned our focus towards the another not much explored task of barbituric acid *i.e.* sequential C-5 alkylation of 5-aryl barbiturates for the synthesis of fully substituted barbituric acids having in-ring quarternary center. In the initial studies, we treated the arylated barbiturates with ethyl bromide at room temperature in the presence of K_2CO_3, solvated with DMF, and the obtained products were found to be only *O*-alkylated *C*-5 aryl barbiturates. With the aim of getting *C*-5 arylated as well as alkylated *i.e.* fully substituted barbiturates, we increased the amount of base and alkyl halide and kept the reaction at room temperature. The obtained products were structurally analyzed to have same *C*-as well as *O*-alkyl substituents. Further we studied the reaction of 5-aryl barbiturates with a range of alkyl halides using K_2CO_3 in DMF (Scheme 22).

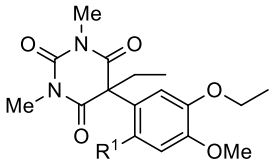
As shown in Scheme 22, several alkyl halides either with saturated carbon chain **8a**–**8c** or resonance stabilized (benzyl and allyl) groups **8d** and **8e** were found to be equally competent alkylating partners. The arylated barbiturates **113–115** reacted well with methyl iodide (**8a**) to impart the products **119**–**121** in 80–85% yields, whereas with ethyl bromide (**8b**) furnished the corresponding fully substituted barbiturates **122**–**124** in good yields. Although the rate of reaction was considerably slower with butyl bromide (**8c**) and reaction went to completion at 80 ^oC to furnish the desired products **125**–**127** in good yields. Owing to the resonating stability of the carbocation formed, allylic and benzyl alkylation gave the adducts **128**–**133** in good to high yields in less time.



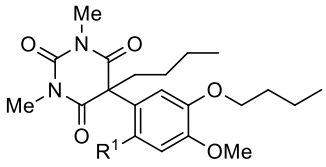




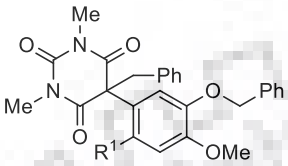
119, 83%, R^1 = Br
120, 80%, R^1 = I
121, 85%, R^1 = Me



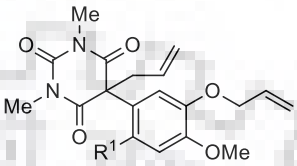
122, 77%, R^1 = Br
123, 72%, R^1 = I
124, 81%, R^1 = Me



[c]**125**, 67%, R^1 = Br
[c]**126**, 67%, R^1 = I
[c]**127**, 71%, R^1 = Me



128, 78%, R^1 = Br
129,77%, R^1 = I
130, 83%, R^1 = Me



131, 80%, R^1 = Br
132, 82%, R^1 = I
133, 88%, R^1 = Me

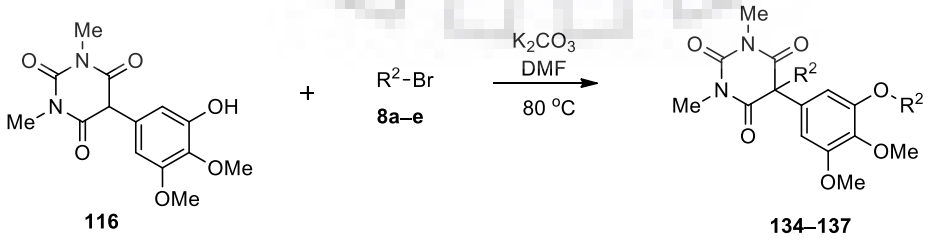
Scheme 22: Reactions of C-5 aryl barbituric acids with alkyl bromides.[a, b]

[a]Reaction conditions: **113–115** (0.3 mmol), K_2CO_3 (0.9 mmol, 3 equiv), alkyl halides **8** (1.26 mmol, 4.2 equiv) in DMF stirred at 50 °C.

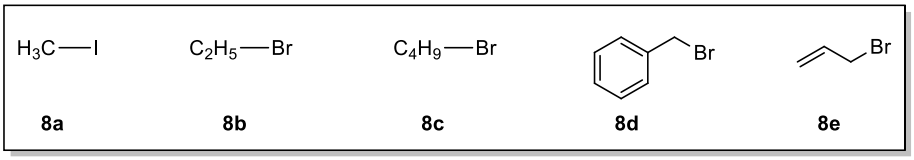
[b]Yield of pure and isolated products.

[c]Reaction was done at 80 °C.

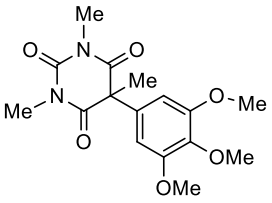
In addition, it was of interest to explore the reactivity of 3-hydroxy-4,5-dimethoxy aryl substituted barbituric acid **116** with alkyl halides **8a**–**e** (Scheme 23). We performed the reaction in sealed tube and the reaction went to completion when stirred at temperature of 80 °C. To our delight all the reactions placidly went to completion to give quaternary barbiturates **134**–**137** in decent yields to validate our protocol. In the process of further illustrating the potential of 5-aryl barbituric acid template and building-up quaternary barbiturates through alkylation at C-5, we were curious to figure out if the similar protocol could be implemented to synthesize frameworks with different alkyl groups on carbon and oxygen atoms of fully substituted barbituric acids.



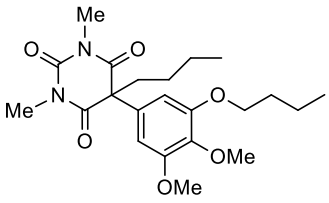
116 **134–137**



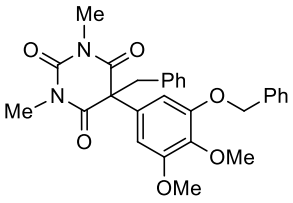
8a **8b** **8c** **8d** **8e**



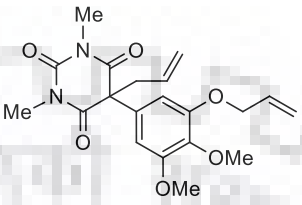
134, 78%



135, 64%



136, 73%



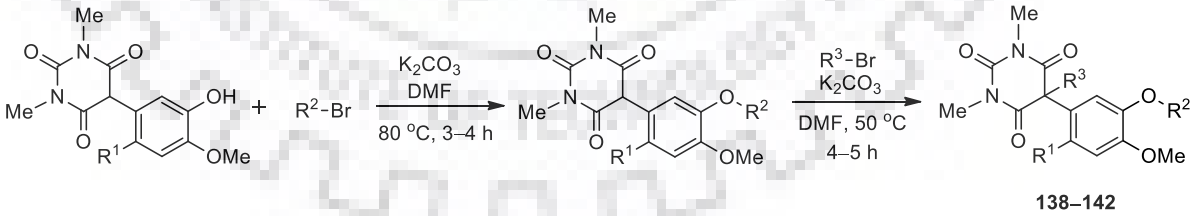
137, 75%

Scheme 23: Reactions of aryl phenyl substituted barbituric acid **116** with alkyl halides.[a,b]

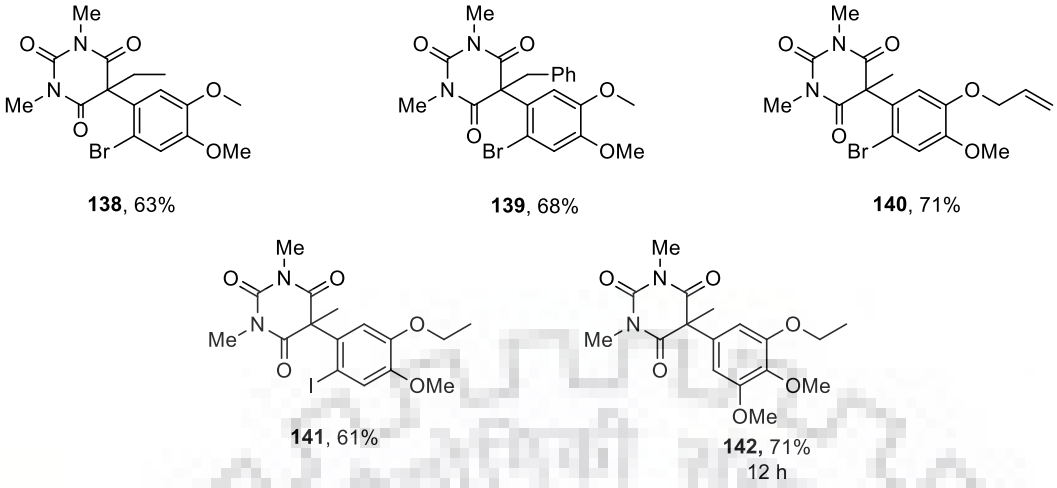
[a]Reaction conditions: **116** (0.3 mmol), K_2CO_3 (0.9 mmol, 3 equiv), alkyl halides **8** (1.26 mmol, 4.2 equiv) in DMF stirred at 80 °C.

[b]Yield of pure and isolated products.

Accordingly, we tried alkylation with different alkyl halides in K_2CO_3 solvated in DMF (Scheme 24). As gleaned from the literature, *O*-alkylation is more feasible in case of highly dissociated cation solvated with dipolar solvent. Thus, the addition of first alkyl halide to the solution of aryl barbiturates in DMF at 80 °C led to the synthesis of only *O*-alkylated products and then sequential addition of congener halide resulted in the *C*-alkylation upon stirring at 50 °C. Similarly, we tested different combinations of alkyl halides and obtained differently *O* and *C*-alkylated quaternary barbiturates **138–142** in good yields.



138–142



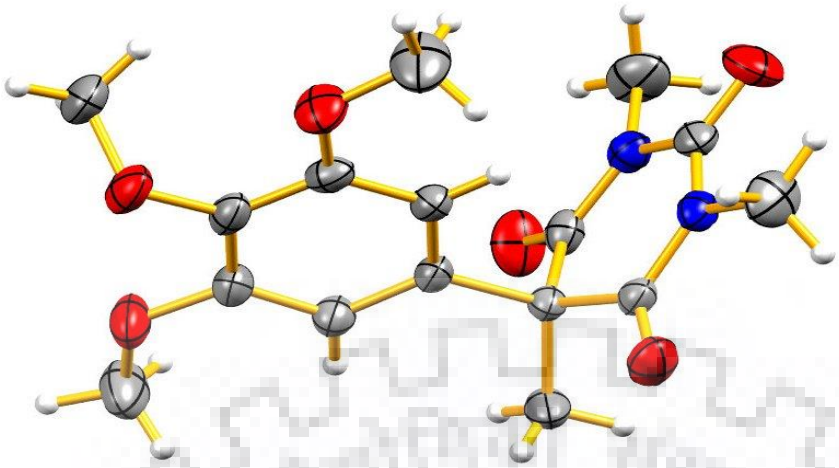
138, 63% **139**, 68% **140**, 71%

141, 61% **142,** 71% 12 h

Scheme 24: Synthesis of quaternary barbiturates.

[a]Reaction conditions: aryl barbiturates (0.3 mmol), K_2CO_3 (0.45 mmol, 1.5 equiv), first alkyl halides (0.42 mmol, 1.5 equiv) in DMF stirred at 80 °C then K_2CO_3 (0.45 mmol, 1.5 equiv), second alkyl halides (0.42 mmol, 1.5 equiv).

The structures of all the fully substituted barbituric acids were confirmed on the basis of data obtained from ^{1}H and ^{13}C NMR spectral analysis. For instances, the carbon-13 spectral analysis of disubstituted barbiturates showed a peak resonating in the range of 50 to 60 ppm (adjacent to the –OMe peak of the guaiacol moiety), indictaing the presence of quarternary carbon. The proton NMR spectrum of compound **119**, displayed two singlets for 3H at 3.92 ppm and 3.81 ppm which indicates the presence of two methoxy groups, thus giving evidence for *O*-alkylation of the hydroxyl group of the guaiacol moiety. Further, a signal for 3H at 1.96 ppm indicated the *C*-alkylation. The structure of the compound **134** was also confirmed by the single crystal X-ray analysis, where the crystals were grown through the slow evaporation of solvent system containing DCM and hexane (Figure 16, Table 10).



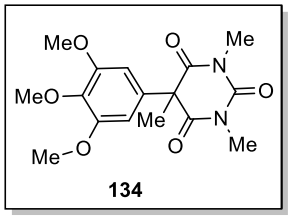


Figure 16: ORTEP plot for compound **134.**

Table 10: Crystallographic data for **134.**

Formula	$C_{16}H_{20}N_2O_6$
Formula Wt.	336.13
Crystal habit	Blocks
Crystal color	Colorless
Crystal system	Orthorhombic
Space group	P c a 21
a (Å)	14.816(4)
b (Å)	14.615(4)
c (Å)	15.299(4)
α (deg)	90
β (deg)	90
γ (deg)	90
V (Å^3)	3312.7(15)
Z	66
D_{calc} (g cm^{-3})	1.424
T (K)	296
λ (Mo-Kα)	0.71073
μ (mm^{-1})	0.128

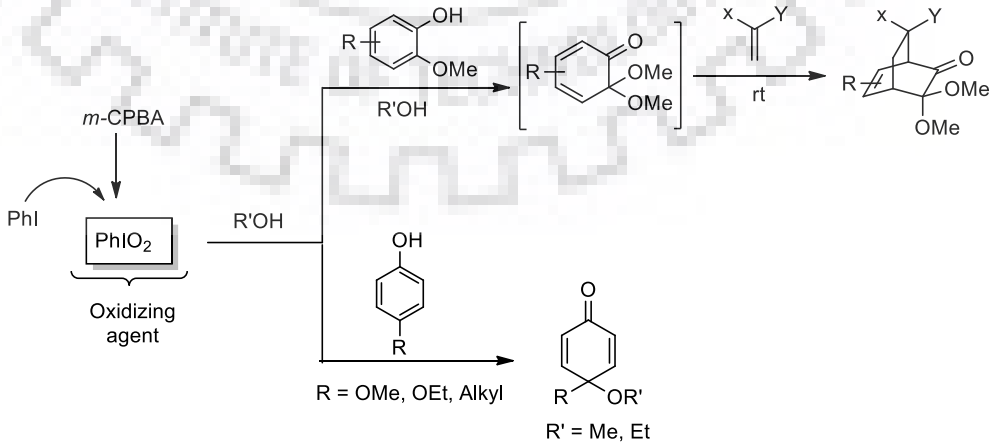
2θ range (deg)	28.766
Limiting indices	$-19 \leq h \geq 19$
	$-19 \leq k \geq 19$
	$-14 \leq l \geq 20$
F(000)	1452
No. of Reflns. Measured	41768
No. of Parameters	445
GOF on F^2	1.048
R1 [$I>2\sigma(I)$]	0.0551
wR2	0.1328

2.3. CONCLUSIONS

We have developed amicable protocol for the dearomatization of alkoxy phenols for the generation of their respective cyclohexadienones and then studied their regio- and stereoselectivity of its Diels–Alder reactions with different dienophiles to obtain bicyclo[2.2.2]octenones. Further, we explored the construction of C–C bonds *via* Michael addition reaction of different nucleophiles with masked *ortho* benzoquinones to synthesize phenols coupled with various heterocyclic scaffolds. We have also leveraged the remarkable reactivity of MOBs to access diaryl sulfones *via* C–S bond formation. We have accomplished the synthesis of *meta*-substituted phenols through the functionalization of acidic CH pronucleophiles, which is not conventionally easy to synthesize.

Iodobenzene catalyzed dearomatization of alkoxy phenols and synthesis of bicyclo[2.2.2]octenone derivatives

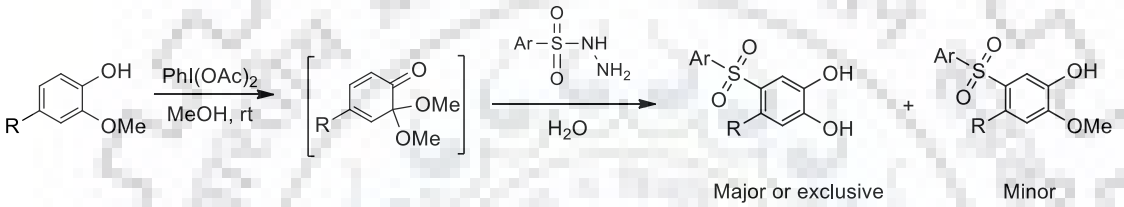
The oxidative dearomatization of 2- and 4-subsituted phenols to their corresponding benzoquinone monoketals by catalytic amount of iodobenzene, and stoichiometric amount of *m*-CPBA as a co-oxidant has been achieved *via in situ* generation of $PhIO_2$, a hypervalent iodine(V) species. The transiently generated *ortho*-benzoquinone monoketals further underwent Diels–Alder reaction with various dienophiles to furnish densly substituted bicyclo[2.2.2]octenones in high selectivities and yields. This methodology featured ready availability of reagents, cost effectiveness, safety, brevity, selectivity, diversity and excellent yields (Scheme 25).



Scheme 25: Oxidative dearomatization strategy for the synthesis of bicyclo[2.2.2]octenones.

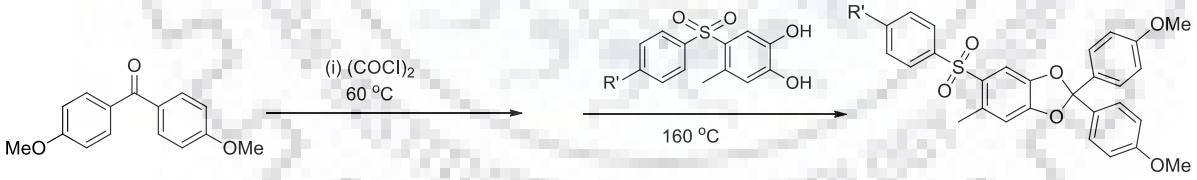
Synthesis of arylsulfonyl catechols in aqueous media

A novel water-assisted carbon–sulfur bond formation strategy has been described for the direct access of highly valuable arylsulfonyl catechols. This transformation was remarkable as tandem dearomatization–sulfonylation and hydroxylation processes enabled the title compounds in one-pot under catalyst-free and metal-free conditions in aqueous media. From the mechanistic studies, water was found to play key role in the synthesis of catechols. The sulfonylation operated under mild conditions, showed broad substrate scope, exhibited gram-scale synthesis and gave high conversion. Thus we developed a green, efficient method for carbon–sulfur bond formation (Scheme 26).



Scheme 26: Synthesis of arylsulfonyl catechol derivatives in aqueous media.

The arylsulfonyl catechols further synthetically subjected to acetalization and transformed to corresponding ketals that are important for drug discovery. Of particular note, these ketals are potent analogues of COMT inhibitors and are novel analogous precursors for the treatment of obesity (Scheme 27).

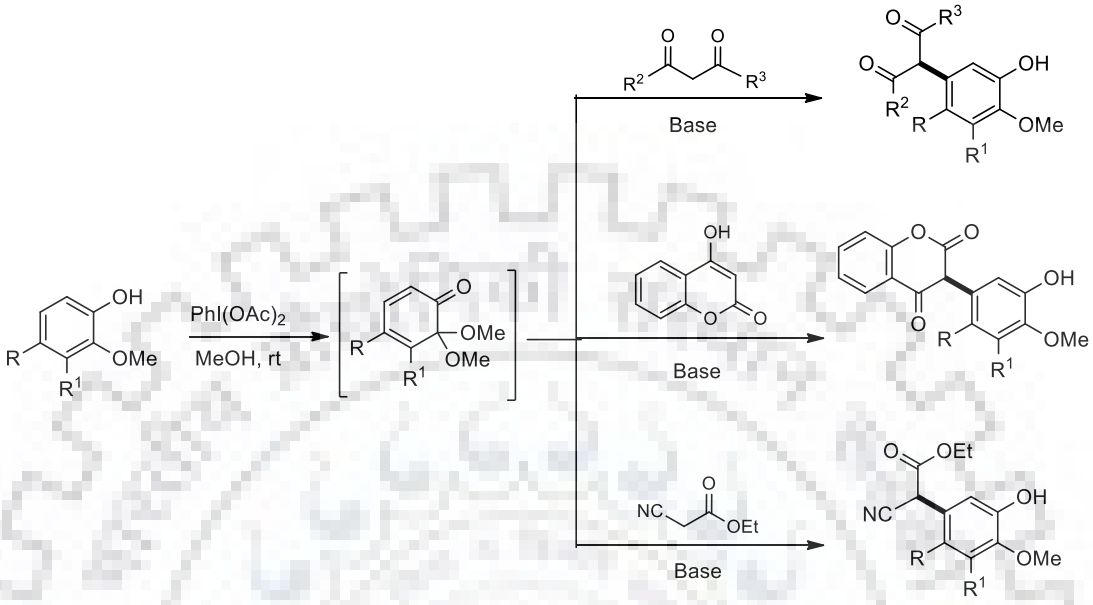


Scheme 27: Synthetic transformation of arylsulfonyl catechols.

α-Arylation of C-H activated pronucleophiles

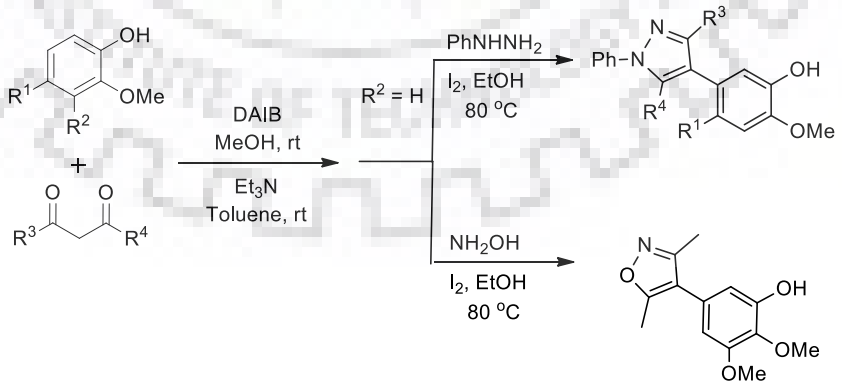
We have explored base-mediated, direct and highly convenient strategy for the *C*-arylation of various C–H activated pronucleophiles with various 2-alkoxy phenol derivatives as aryl partners. The present work excelled in forming C–C bond at the *meta*-position/site of the phenols *via* Michael attack of activated methylene carbanion on the *in situ* generated masked *ortho*-benzoquinones to synthesize the *meta*-substituted phenols which is traditionally challenging to functionalize. Underlining the utility of the obtained products, we

have performed straightforward, one-pot, clean, high yielding route for the synthesis of phenol coupled heterocycles such as pyrazoles, isoxazoles, coumarins, triazolenes and carboxylic amides that led the way for the endowment of important biological scaffolds.



Scheme 28: α-Arylation of C–H activated pronucleophiles.

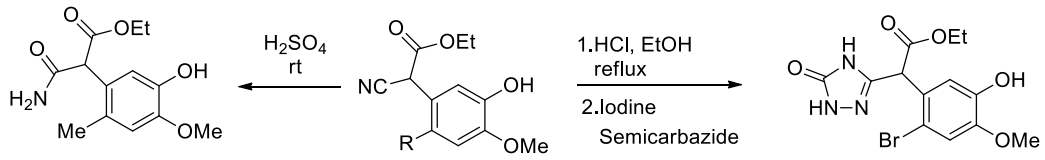
This protocol further led the way to access scalable, straightforward access to phenol assimilated *N*- and *O*-heterocyclic frameworks which have powerful applications both in synthetic chemistry and medicinal research. The phenol coupled with pyrazole and isoxazole moieties resulted in the synthesis of novel analogues of combretastatin A4 (antitumor agent) and dimethylisoxazole scaffold that act as BET inhibitor (epigenetic target), respectively (Scheme 29).



Scheme 29: Synthesis of phenol substituted pyrazoles and oxazoles.

Additionally, we studied the reactivity profile of α-arylated cyanoacetate through the manipulation of the cyano group, by readily converting it into other functionalities. Of

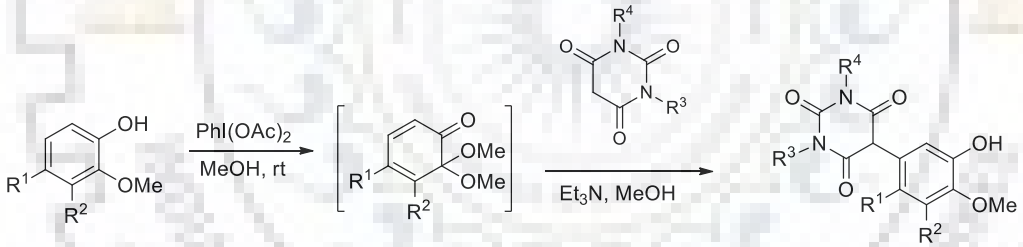
particular interest are carboxylic amide and triazolenes that led the way for the endowment of important biological scaffolds (Scheme 30).



Scheme 30: Transformation of cyano-substituted products.

Synthesis of 5-aryl barbituric acids

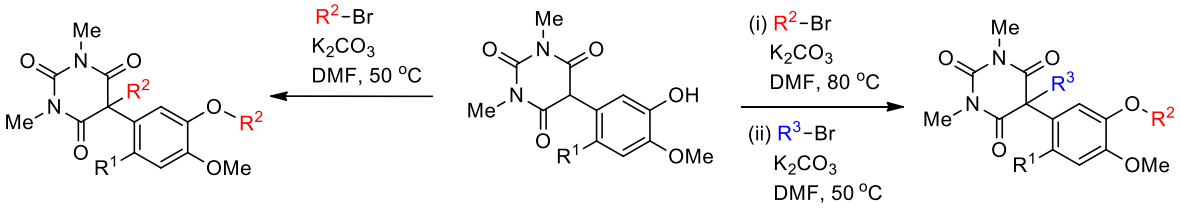
A general, straightforward approach involving the Michael addition reaction of C-5 methylene carbon of barbituric acid derivatives with *in situ* generated *ortho*-benzoquinone monoketals for rapid assembly of phenol functionalized 5-aryl barbiturates has been delineated. The reactions proceeded smoothly to furnish the C-5 arylated barbiturates in methanol under conditions with no involvement of any metal catalyst and straightforward isolation of products without column chromatography. The scaffolds are of high medicinal importance and difficult to synthesize by other means (Scheme 31).



Scheme 31: Synthesis of 5-aryl barbiturates.

Synthesis of fully substituted barbituric acid

We have further elaborated the utility of 5-aryl barbiturates through the construction of fully substituted barbituric acids consisting in-ring quaternary center. Spurred by the great synthetic and medicinal interest of C-5 disubstituted barbiturates, the 5-aryl barbiturates are subjected to sequential C–H alkylation using various alkyl halides in DMF for the synthesis of *O*–as well as *C*– alkylated 5-aryl barbiturates (Scheme 32). A distinctive advantage of this strategy is that it directly assimilates the phenols with barbituric acid to synthesis a novel structural template that may profile the bioactivity of both frameworks.



Scheme 32: Synthesis of fully substituted barbiturates.

3.1. GENERAL REMARKS

The reactions associated with the formation of gases and application of heat were performed in a well ventilated hood for safety reasons. Moisture sensitive reactions were carried out by using guard tube filled with either blue silica gel or calcium chloride. Reagents and solvents were transferred under nitrogen using syringes or cannulae, wherever needed.

3.1.1. Solvents

The solvents for anhydrous reactions were dried and purified according to standard techniques.

CH_3CN	**:**	Distilled over P_2O_5
CH_2Cl_2	**:**	Distilled over P_2O_5
DCE	**:**	Distilled over P_2O_5
EtOH	**:**	Distilled from magnesium cake
MeOH	**:**	Distilled from magnesium cake
THF	**:**	Distilled from Na/benzophenone ketyl radical

The HPLC grade solvens like toluene, DMF, chloroform were used as such without any further purification.

3.1.2. Chemicals

The chemicals were purchased from the companies Sigma-Aldrich, Across, Avra, Hi-Media, S. D. Fine chemicals at the highest purity grade and were used as received unless otherwise stated.

3.1.3. Chromatographic Methods

Thin Layer Chromatography

Support**:** TLC aluminium sheets on 0.25 mm Merck silica gel 60 F_{24} (*Merck*) with a fluorescent indicator.

Detection**:** 1) Exposition to UV-light (λ = 254 nm)

2) Exposed to iodine vapours

Preparative Column Chromatography

Purification by gravity column chromatography were carried out on glass column (10–50 mm diameter) using silica gel with 100–200 mesh and silica gel (100–200 mesh) neutralized with triethylamine.

3.1.4. Determination of physical properties of the synthesized compounds

Melting point

Melting points were measured in open glass capillaries with *Perfit* and optimelt automated melting point apparatus and are uncorrected.

IR Spectroscopy

IR Spectra were measured on a Perkin-Elmer spectrometer as KBr pellets or neat (in case of liquid compounds). Only characteristic absorption bands were reported. Absorptions are given in wavenumbers (cm^{-1}).

^{1}H NMR Spectroscopy

^{1}H NMR Spectra were recorded on Brüker AMX 500 (^{1}H: 500 MHz) and JEOL-delta 400 (^{1}H: 400 MHz). Chemical shifts were given in ppm relative to tetramethylsilane (δ 0.00 ppm). Solvent residual peaks (from $CDCl_3$, δ 7.26 ppm; from DMSO, δ 2.50 ppm) were used as internal standards. Coupling patterns are described by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), dt (doublet of triplet), td (triplet of doublet), br (broad), ddd (doublet of doublet of doublet). Coupling constants are given in Hertz (Hz).

^{13}C NMR Spectroscopy

^{13}C NMR Spectra were recorded on Brüker AMX 500 spectrometer (125 MHz) and JEOL 400 spectrometer (100 MHz). Chemical shifts are reported in ppm units and were determined by comparison with solvent residual peaks (from DMSO, δ 39.5 ppm; from $CDCl_3$, δ 77.0 ppm).

Mass Spectrometry

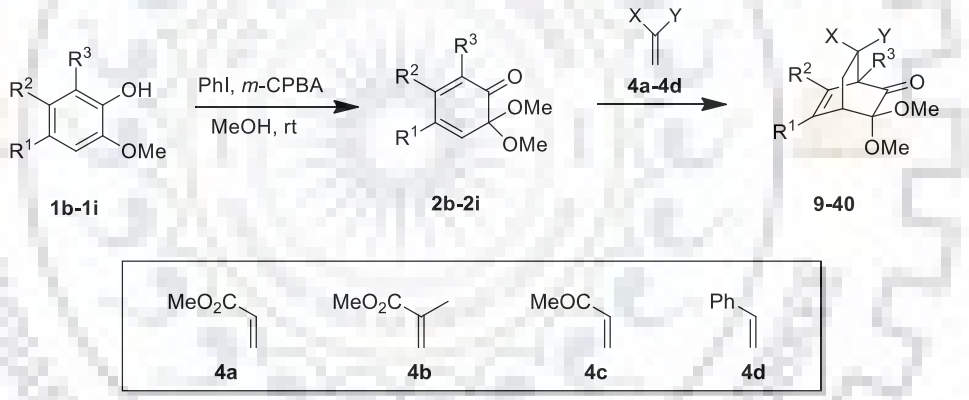
High resolution mass spectra (HRMS) were recorded on Bruker microOTOF-Q II mass spectrometer.

Single crystal X-ray crystallography

Single crystal data of the products were collected on X-ray diffractometer using graphite monochromated MoKa radiation (λ = 0.71070 Å) at 296 K. Suitable size of crystal reported were mounted on nylon Cryoloop. In the correction of the data Lorentz and polarization corrections, empirical absorption corrections were applied.

3.2. SYNTHETIC PROCEDURES

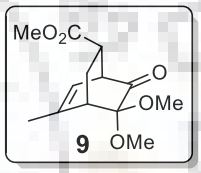
3.2.1. General procedure for the Diels–Alder reaction of MOBs 1b–9b with dienophiles:



Method A: To a stirred solution of iodobenzene (204 mg, 1 mmol, 1 equiv) in dry methanol (3 mL) dry *m*-CPBA (374 mg, 1.5 mmol, 1.5 equiv) was added followed by addition of methanolic solution (2 mL) of guaiacol derivatives (1.0 mmol). To the resulting yellow colour solution, dienophile (20 mmol, 20 equiv) was added and stirred the reaction mixture at room temperature for 10 min to 5 h. After the completion of the reaction, as monitored by TLC, the solvent was evaporated *in vacuo*. The mixture was washed with a saturated aqueous solution of $NaHCO_3$ and extracted twice (2 × 20 mL) with CH_2Cl_2. The combined organic layers were washed with brine, filtered, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using EtOAc (10–20%) in hexanes to afford the pure cycloadducts **9**–**40**.

Method B: To a stirred solution of iodobenzene (30 mol%) in dry methanol (2 mL) dry *m*-CPBA (249 mg, 1 mmol, 2 equiv) was added followed by addition of methanolic solution (1 mL) of guaiacol derivatives (0.5 mmol). To the resulting yellow colour solution dienophile (10 mmol, 20 equiv) was added and stirred the reaction mixture at room temperature for 20 min to 3 h. After the completion of the reaction, as monitored by TLC, the solvent was evaporated *in vacuo*. The mixture was washed with a saturated aqueous solution of $NaHCO_3$ and extracted twice (2 × 20 mL) with CH_2Cl_2. The combined organic layers were washed with brine, filtered, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using EtOAc (10–20%) in hexanes to afford the pure cycloadducts **9**–**40**. The NMR data of the compound from the current study is comparable with that of the compounds reported in literature [232].

3,3-Dimethoxy-7-methoxycarbonyl-5-methylbicyclo[2.2.2]oct-5-en-2-one (9):



Method: B.

Yield: 117 mg (93%) as colourless solid.

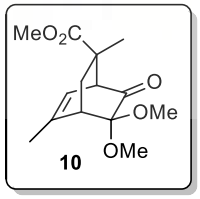
Mp: 59–68 ºC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.67 (d, *J* = 5.5 Hz, 1H), 3.65 (s, 3H), 3.38–3.37 (m, 1H), 3.32 (s, 3H), 3.29 (s, 3H), 2.99–2.96 (m, 1H), 2.91 (d, *J* = 2.0 Hz, 1H), 2.20 (ddd, *J* = 2.5, 10.0, 13.0 Hz, 1H), 1.88 (s, 3H), 1.74 (ddd, *J* = 2.5, 6.0, 13.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 201.1, 173.6, 146.0, 117.5, 94.0, 52.2, 50.5, 49.7, 43.5, 39.1, 24.0, 21.1ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{13}H_{18}O_5Na$ calcd: 277.1154, found: 277.1149.

3,3-Dimethoxy-7-methoxycarbonyl-5,7-dimethylbicyclo[2.2.2]oct-5-en-2-one (10):



Method: B.

Yield: 99 mg (74%) as colourless solid.

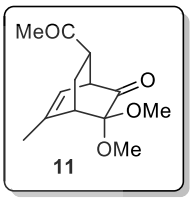
Mp: 66–68 ºC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.74 (td, *J* = 2.0, 6.5 Hz, 1H), 3.69 (s, 3H), 3.37 (s, 3H), 3.35 (s, 3H), 3.28 (d, *J* = 6.0 Hz, 1H), 2.90–2.88 (m, 1H), 2.32 (dd, *J* = 3.5, 14.0 Hz, 1H), 1.89 (s, 3H), 1.80 (dd, *J* = 2.5, 13.5 Hz, 1H), 1.32 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 202.5, 176.5, 145.3, 119.4, 94.2, 56.1, 52.4, 50.5, 49.4, 46.6, 43.7, 31.2, 25.4, 21.2 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{14}H_{20}O_5Na$ calcd: 291.1209, found: 291.1231.

3,3-Dimethoxy-7-ethanoyl-5-methylbicyclo[2.2.2]oct-5-en-2-one (11):



Method: B.

Yield: 103 mg (87%) as colourless solid.

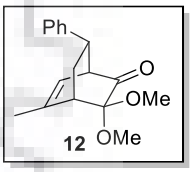
Mp: 69–70°C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.65 (d, *J* = 6.0 Hz, 1H), 3.37–3.36 (m, 1H), 3.35 (s, 3H), 3.33 (s, 3H), 3.04–3.01 (m, 1H), 2.94 (s, 1H), 2.15 (s, 3H), 2.11 (ddd, *J* = 2.5, 9.0, 12.5 Hz, 1H), 1.88 (s, 3H), 1.72 (ddd, *J* = 3.0, 6.5, 13.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 206.1, 201.3, 145.5, 117.1, 94.2, 50.5, 49.8, 49.3, 47.1, 43.6, 28.3, 22.7, 21.0 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{13}H_{18}O_4Na$ calcd: 261.1097, found: 261.1105.

3,3-Dimethoxy-7-phenyl-5-methylbicyclo[2.2.2]oct-5-en-2-one (12):



Method: B.

Yield: 74 mg (55%) as colourless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20–7.17 (m, 2H), 7.13–7.10 (m, 1H), 7.07–7.06 (m, 2H), 5.65 (d, *J* = 6.0 Hz, 1H), 3.31 (s, 1H), 3.30 (s, 3H), 3.29–3.26 (m, 1H), 3.05 (dd, *J* = 1.5, 6.0, 1H), 2.93 (q, *J* = 2.0 Hz, 1H), 2.40 (ddd, *J* = 3.0, 9.5, 12.5 Hz, 1H), 1.93 (s, 3H), 1.47 (ddd, *J* = 2.5, 7.0, 13.5 Hz, 1H) ppm.

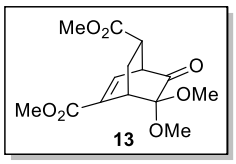
^{13}C NMR (125 MHz, $CDCl_3$): δ 201.9, 145.5, 144.4, 128.4, 127.5, 126.6, 117.7, 94.1, 54.5, 50.5, 49.9, 44.4, 39.7, 29.9, 21.1 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{17}H_{20}O_3Na$ calcd: 272.1412, found: 272.1412.

3,3-Dimethoxy-5,7-bis(methoxycarbonyl)bicyclo[2.2.2]oct-5-en-2-one (13):

Method: B.

Yield: 136 mg (92%) as colourless liquid.



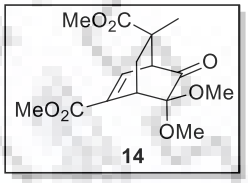
13

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (dd, *J* = 2.0, 6.5 Hz, 1H), 3.81–3.80 (m, 1H), 3.77 (s, 3H), 3.68 (s, 3H), 3.67–3.66 (m, 1H), 3.35 (s, 3H), 3.30 (s, 3H), 3.12 (ddd, *J* = 2.5, 6.0, 10.0 Hz, 1H), 2.40 (ddd, *J* = 3.0, 10.0, 13.0 Hz, 1H), 1.72 (ddd, *J* = 3.0, 6.0, 13.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 199.8, 172.8, 164.1, 138.0, 135.4, 93.2, 52.5, 52.1, 50.8, 50.3, 50.1, 39.2, 38.2, 24.8 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{14}H_{18}O_7Na$ calcd: 321.0944, found: 321.0942.

3,3-Dimethoxy-5,7-bis(methoxycarbonyl)-7-methylbicyclo[2.2.2]oct-5-en-2-one (14):



14

Method: B.

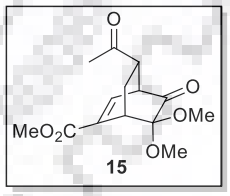
Yield: 133 mg (85%) as colourless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 (dd, *J* = 1.5, 6.5 Hz, 1H), 3.78 (s, 3H), 3.73–3.71 (m, 1H), 3.67 (s, 3H), 3.52 (d, *J* = 6.5 Hz, 1H), 3.37 (s, 3H), 3.30 (s, 3H), 2.23 (dd, *J* = 3.5, 14.0 Hz, 1H), 1.97 (dd, *J* = 2.5, 14.0 Hz, 1H), 1.34 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 201.0, 175.7, 164.3, 137.5, 137.4, 93.4, 57.3, 52.7, 52.1, 50.3, 49.8, 46.8, 38.5, 32.1, 25.5 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{15}H_{20}O_7Na$ calcd: 335.1101, found: 335.1103.

7-Acetyl-3,3-Dimethoxy-5-methoxycarbonylbicyclo[2.2.2]oct-5-en-2-one (15):



15

Method: B.

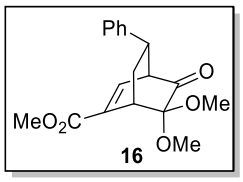
Yield: 135 mg (96%) as colourless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (d, *J* = 6.5 Hz, 1H), 3.81–3.80 (m, 1H), 3.76 (s, 3H), 3.58 (dd, *J* = 2.0, 7.0 Hz, 1H), 3.36 (s, 3H), 3.29 (s, 3H), 3.19–3.16 (m, 1H), 2.40 (ddd, *J* = 3.0, 11.0, 13.0 Hz, 1H), 2.14 (s, 3H), 1.56 (ddd, *J* = 2.5, 6.5, 12.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 205.2, 200.2, 164.1, 137.0, 136.0, 93.3, 52.0, 50.3, 50.2, 50.1, 47.5, 38.2, 28.2, 24.1 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{14}H_{18}O_6Na$ calcd: 305.0995, found: 305.0995.

Methyl 3,3-dimethoxy-2-oxo-7-phenylbicyclo[2.2.2]oct-5-en-5-carboxylate (16):



Method: B.

Yield: 134 mg (85%) as colourless solid.

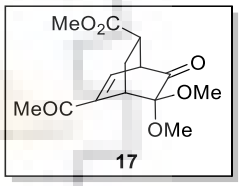
Mp: 112–113 ºC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28–7.24 (m, 2H), 7.21–7.18 (m, 1H), 7.12–7.11 (m, 1H), 7.07 (d, *J* = 7.5 Hz, 2H), 3.87 (q, *J* = 2.5 Hz, 1H), 3.83 (s, 3H), 3.49–3.47 (m, 1H), 3.44 (dd, *J* = 2.5 Hz, 1H), 3.42 (s, 3H), 3.34 (s, 3H), 2.62 (ddd, *J* = 3.0, 10.0, 13.5 Hz, 1H), 1.61 (ddd, *J* = 2.5, 6.5, 13.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 200.1, 164.2, 143.1, 138.2, 135.3, 128.6, 127.2, 126.8, 93.0, 55.8, 51.9, 50.1, 50.0, 40.0, 39.0, 29.9 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{18}H_{20}O_5Na$ calcd: 339.1202, found: 339.1204.

3,3-Dimethoxy-5-ethnoyl-7-methoxycarbonylbicyclo[2.2.2]oct-5-en-2-one (17):



Method: B.

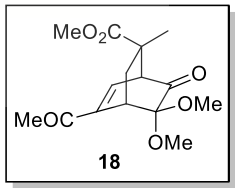
Yield: 113 mg (80%) as yellowish liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.03 (d, *J* = 6.5 Hz, 1H), 3.95–3.94 (m, 1H), 3.68 (s, 3H), 3.66–3.64 (m, 1H), 3.34 (s, 3H), 3.25 (s, 3H), 3.16–3.12 (m, 1H), 2.40 (ddd, *J* = 3.0, 10.5, 13.5 Hz, 1H), 2.34 (s, 3H), 1.57 (ddd, *J* = 2.5, 6.0, 13.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 199.9, 194.2, 173.0, 146.3, 135.6, 93.2, 52.4, 50.8, 50.2, 39.3, 36.1, 24.9, 24.8 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{14}H_{18}O_6Na$ calcd: 305.0995, found: 305.1021.

3,3-Dimethoxy-5-ethnoyl-7-methoxycarbonyl-7-methylbicyclo[2.2.2]oct-5-en-2-one (18):



Method: B.

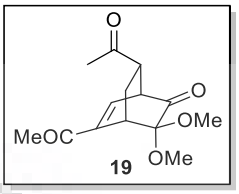
Yield: 68 mg (70%) as yellowish liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (dd, *J* = 2.0, 6.5 Hz, 1H), 3.91–3.89 (m, 1H), 3.70 (s, 3H), 3.55 (d, *J* = 6.0 Hz, 1H), 3.40 (s, 3H), 3.27 (s, 3H), 2.35 (s, 3H), 2.11 (dd, *J* = 3.5, 14.0 Hz, 1H), 2.02 (dd, *J* = 2.5, 14.0 Hz, 1H), 1.38 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 200.9, 175.7, 164.3, 137.3, 93.4, 57.3, 52.6, 52.0, 50.2, 49.7, 46.7, 38.4, 32.0, 25.4 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{15}H_{20}O_6Na$ calcd: 319.1152, found: 319.1152.

3,3-Dimethoxy-5,7-diethnoylbicyclo[2.2.2]oct-5-en-2-one (19):



19

Method: B.

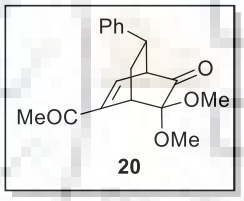
Yield: 125 mg (89%) as yellowish liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.08 (d, *J* = 5.0 Hz, 1H), 3.97–3.96 (m, 1H), 3.59–3.57 (m, 1H), 3.36 (s, 3H), 3.25 (s, 3H), 3.22–3.20 (m, 1H), 2.45 (ddd, *J* = 2.5, 4.5, 15.5 Hz, 1H), 2.32 (s, 3H), 2.12 (s, 3H), 1.39 (ddd, *J* = 3.0, 7.0, 12.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 205.5, 200.5, 194.3, 145.1, 136.5, 93.4, 50.24, 50.21, 47.8, 36.1, 28.2, 24.7, 24.3 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{14}H_{18}O_5Na$ calcd: 289.1046, found: 289.1049.

5-Acetyl-3,3-dimethoxy-7-phenylbicyclo[2.2.2]oct-5-en-2-one (20):



20

Method: B.

Yield: 108 mg (72%) as colourless solid.

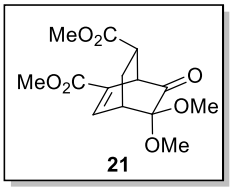
Mp: 119–120 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28–7.25 (m, 2H), 7.22–7.19 (m, 1H), 7.06 (d, *J* = 7.5 Hz, 2H), 7.00 (dd, *J* = 1.5, 6.5 Hz, 1H), 4.02 (q, *J* = 2.5 Hz, 1H), 3.52–3.49 (m, 1H), 3.45 (dd, *J* = 1.5, 6.5 Hz, 1H), 3.41 (s, 3H), 3.28 (s, 3H), 2.59 (ddd, *J* = 3.0, 10.0, 13.0 Hz, 1H), 2.39 (s, 3H), 1.53 (ddd, *J* = 3.0, 6.5, 13.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 200.6, 194.3, 146.8, 143.2, 135.5, 128.7, 127.2, 127.0, 93.2, 56.2, 50.2, 40.4, 37.0, 29.6, 24.9 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{18}H_{20}O_4Na$ calcd: 323.1253, found: 323.1254.

3,3-Dimethoxy-6,7-bis(methoxycarbonyl)bicyclo[2.2.2]oct-5-en-2-one (21):



21

Method: B.

Yield: 102 mg (68%) as colourless liquid.

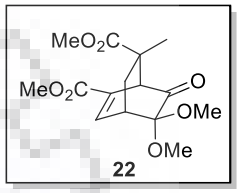
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (dd, *J* = 2.0, 6.5 Hz, 1H), 4.07 (t, *J* = 2.0 Hz, 1H), 3.76 (s, 3H), 3.65 (s, 3H), 3.36–3.35 (m, 1H), 3.34 (s, 3H), 3.30 (s, 3H), 3.10 (ddd, *J* = 2.0, 5.5, 10.0 Hz, 1H), 2.28 (ddd, *J* = 3.0, 10.0, 13.0 Hz, 1H), 1.76 (ddd, *J* = 3.0, 5.5, 13.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 199.6, 172.7, 163.8, 143.5, 129.6, 93.3, 52.3, 52.0, 50.5, 49.7, 49.3, 39.4, 38.7, 23.5 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{14}H_{18}O_7Na$ calcd: 321.0944, found: 321.0957.

3,3-Dimethoxy-6,7-bis(methoxycarbonyl)-7-methylbicyclo[2.2.2]oct-5-en-2-one (22):

Method: B.



22

Yield: 73 mg (47%) as colourless liquid.

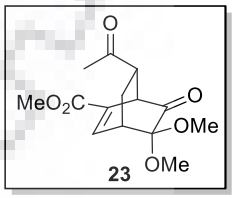
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (dd, *J* = 1.5, 7.0 Hz, 1H), 3.90 (d, *J* = 1.5 Hz, 1H), 3.76 (s, 3H), 3.61 (s, 3H), 3.35 (s, 3H), 3.29 (s, 3H), 3.28–3.27 (m, 1H), 2.27 (dd, *J* = 3.5, 14.0 Hz, 1H), 1.85 (dd, *J* = 2.0, 14.0 Hz, 1H), 1.35 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 200.6, 175.5, 163.8, 143.4, 131.7, 93.6, 55.5, 52.4, 52.0, 50.4, 49.5, 46.2, 39.5, 31.1, 25.0 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{15}H_{20}O_7Na$ calcd: 335.1101, found: 335.1102.

3,3-Dimethoxy-7-ethanoyl-6-methoxycarbonylbicyclo[2.2.2]oct-5-en-2-one (23):

Method: B.



23

Yield: 109 mg (78%) as colourless solid.

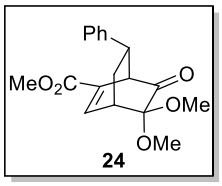
Mp: 100–101 ^oC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (dd, *J* = 2.5, 7.5 Hz, 1H), 4.04 (t, *J* = 2.0 Hz, 1H), 3.71 (s, 3H), 3.34–3.33 (m, 1H), 3.32 (s, 3H), 3.26 (s, 3H), 3.11 (ddd, *J* = 2.0, 5.5, 9.5 Hz, 1H), 2.18 (s, 3H), 2.03 (ddd, *J* = 2.5, 9.5, 12.5 Hz, 1H), 1.83 (ddd, *J* = 3.0, 5.5, 13.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 205.1, 200.0, 163.8, 143.6, 128.7, 93.5, 52.1, 50.6, 49.7, 49.0, 46.6, 39.4, 28.3, 21.2 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{14}H_{18}O_6Na$ calcd: 305.0995, found: 305.1022.

Methyl 3,3-dimethoxy-2-oxo-7-phenylbicyclo[2.2.2]oct-5-en-6-carboxylate (24):



Method: B.

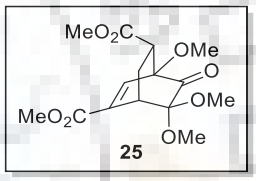
Yield: 103 mg (65%) as colourless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (dd, *J* = 2.0, 7.5 Hz, 1H), 7.26–7.22 (m, 2H), 7.21–7.17 (m, 1H), 7.10–7.08 (m, 2H), 4.38–4.36 (m, 1H), 3.87 (t, *J* = 2.0 Hz, 1H), 3.65 (s, 3H), 3.63–3.59 (m, 1H), 3.41 (s, 3H), 3.34 (s, 3H), 2.57 (ddd, *J* = 2.5, 9.5, 13.0 Hz, 1H), 1.60 (ddd, *J* = 3.0, 6.5, 13.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 200.7, 164.2, 144.2, 142.9, 129.7, 128.6, 127.1, 126.9, 93.3, 53.7, 52.0, 50.5, 49.9, 40.0, 39.3, 28.7 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{18}H_{20}O_5Na$ calcd: 339.1202, found: 339.1202.

1,3,3-Trimethoxy-5,7-bis(methoxycarbonyl)bicyclo[2.2.2]oct-5-en-2-one (25):



Method: B.

Yield: 130 mg (80%) as colourless solid.

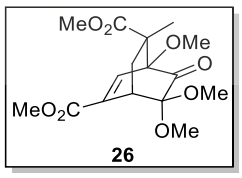
Mp: 120–121 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (s, 1H), 3.78 (s, 3H), 3.75–3.74 (m, 1H), 3.65 (s, 3H), 3.57 (s, 3H), 3.34 (s, 3H), 3.28 (s, 3H), 3.16–3.13 (m, 1H), 2.39 (ddd, *J* = 3.0, 10.5, 13.0 Hz, 1H), 1.62 (ddd, *J* = 4.0, 6.0, 13.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 198.0, 172.5, 163.7, 136.2, 135.2, 93.0, 85.8, 54.6, 52.2, 52.1, 50.2, 50.0, 43.4, 37.6, 27.3 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{15}H_{20}O_8Na$ calcd: 351.1050, found: 351.1032.

1,3,3-Trimethoxy-5,7-bis(methoxycarbonyl)-7-methylbicyclo[2.2.2]oct-5-en-2-one (26):



Method: B.

Yield: 114 mg (67%) as colourless solid.

Mp: 86–87 °C.

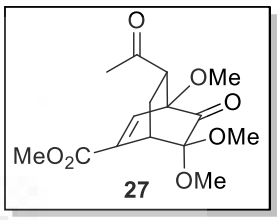
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (s, 1H), 3.77 (s, 3H), 3.68–3.66 (m, 1H), 3.61 (s, 3H), 3.52 (s, 3H), 3.34 (s, 3H), 3.26 (s, 3H), 1.99–1.92 (m, 2H), 1.25 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 199.1, 174.3, 163.8, 137.2, 134.0, 92.8, 89.5, 55.2, 52.3, 52.0, 50.1, 49.9, 49.6, 37.6, 35.9, 20.3 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{16}H_{22}O_8Na$ calcd: 365.1206, found: 365.1202.

1,3,3-Trimethoxy-7-ethanoyl-5-methoxycarbonylbicyclo[2.2.2]oct-5-en-2-one (27):

Method: B.



Yield: 133 mg (85%) as colourless solid.

Mp: 92–93 °C.

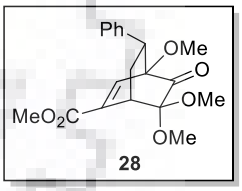
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (s, 1H), 3.80 (s, 3H), 3.78–3.77 (m, 1H), 3.55 (s, 3H), 3.37 (s, 3H), 3.28 (s, 3H), 3.26–3.22 (m, 1H), 2.23 (ddd, *J* = 2.5, 9.5, 12.5 Hz, 1H), 2.18 (s, 3H), 1.62 (ddd, *J* = 2.5, 6.0, 12.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 206.6, 198.5, 163.6, 135.3, 134.6, 92.9, 86.8, 55.0, 52.2, 50.2, 49.9, 49.7, 37.8, 32.0, 25.9 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{15}H_{20}O_7Na$ calcd: 335.1101, found: 335.1105.

Methyl 1,3,3-trimethoxy-2-oxo-7-phenylbicyclo[2.2.2]oct-5-ene-5-carboxylate (28):

Method: B.



Yield: 133 mg (77%) as colourless solid.

Mp: 90–91 °C.

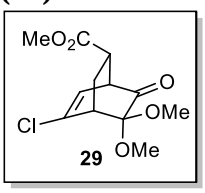
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24–7.17 (m, 4H), 7.07 (d, *J* = 7.0 Hz, 2H), 3.83 (s, 3H), 3.77 (q, *J* = 2.5, 7.0 Hz, 1H), 3.40 (s, 3H), 3.39–3.37 (m, 1H), 3.35 (s, 3H), 3.31 (s, 3H), 2.63 (ddd, *J* = 3.0, 10.0, 13.5 Hz, 1H), 1.61 (ddd, *J* = 3.0, 6.5, 13.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 199.4, 163.8, 141.0, 136.9, 136.2, 128.5, 128.2, 126.9, 93.1, 87.4, 76.9, 54.0, 52.1, 50.2, 50.0, 44.2, 37.9, 32.1 ppm.

HRMS (ESI-TOF) : m/z $[M + Na]^+$ calcd $C_{19}H_{22}O_6Na$: 369.1308, found: 369.1303.

5-Chloro-3,3-dimethoxy-7-methoxycarbonylbicyclo[2.2.2]oct-5-en-2-one (29):

Method: B.



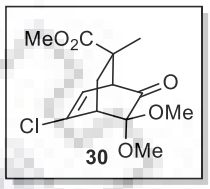
Yield: 123 mg (90%) as colourless viscous liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.04 (dd, *J* = 2.5, 7.0 Hz, 1H), 3.69 (s, 3H), 3.55 (dd, *J* = 1.5, 6.5 Hz, 1H), 3.37 (s, 3H), 3.33 (s, 3H), 3.22 (q, *J* = 2.5 Hz, 1H), 3.02 (ddd, *J* = 1.5, 6.0, 10.0 Hz, 1H), 2.32 (ddd, *J* = 3.0, 10.5, 13.5 Hz, 1H), 2.00 (ddd, 3.0, 5.5, 13.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 199.2, 172.6, 137.1, 120.5, 93.5, 52.4, 50.9, 50.7, 50.1, 47.5, 39.1, 24.8 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{12}H_{15}O_5ClNa$ calcd: 297.0500, found: 297.0507.

5-Cholro-3,3-dimethoxy-7-methoxycarbonyl-7-methylbicyclo[2.2.2]oct-5-en-2-one (30):



30

Method: B.

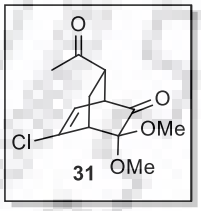
Yield: 108 mg (75%) as viscous liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.02 (d, *J* = 6.5 Hz, 1H), 3.65 (s, 3H), 3.36–3.35 (m, 1H), 3.34 (s, 3H), 3.32 (s, 3H), 3.12 (q, 1.5 Hz, 1H), 2.47 (dd, *J* = 3.0, 14.0 Hz, 1H), 1.86 (d, *J* = 14.0 Hz, 1H), 1.26 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 200.4, 175.6, 137.0, 122.2, 93.7, 57.2, 52.6, 50.6, 49.8, 47.5, 46.6, 31.9, 25.2 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{13}H_{17}O_5ClNa$ calcd: 311.0662, found: 311.0653.

7-Acetyl-5-chloro-3,3-dimethoxybicyclo[2.2.2]oct–5–en-2-one (31):



31

Method: B.

Yield: 199 mg (77%) as colourless solid.

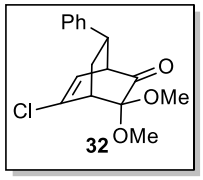
Mp: 59–60 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.01 (dd, *J* = 2.0, 7.0 Hz, 1H), 3.49 (dd, *J* = 1.5, 7.0 Hz, 1H), 3.38 (s, 3H), 3.35 (s, 3H), 3.24 (q, *J* = 3.0 Hz, 1H), 3.07–3.04 (m, 1H), 2.28 (ddd, *J* = 2.5, 10.0, 13.0 Hz, 1H), 2.16 (s, 3H), 1.91 (ddd, *J* = 3.0, 6.5, 13.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 205.0, 199.5, 136.4, 120.4, 93.7, 50.7, 50.4, 50.1, 47.5, 47.1, 28.2, 23.8 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{12}H_{15}O_4ClNa$ calcd: 281.0551, found: 281.0571.

5-Cholro-3,3-dimethoxy-7-phenylbicyclo[2.2.2]oct-5-en-2-one (32):



Method: B.

Yield: 127 mg (87%) as colourless solid.

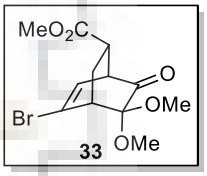
Mp: 68–69 ºC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30–7.27 (m, 2H), 7.25–7.22 (m, 1H), 7.15–7.13 (m, 2H), 6.03 (dd, *J* = 2.5, 7.0 Hz, 1H), 3.42 (s, 3H), 3.41 (s, 3H), 3.39–3.38 (m, 1H), 3.31 (q, *J* = 2.5 Hz, 1H), 3.26 (dd, *J* = 2.0, 7.0 Hz, 1H), 2.57 (ddd, *J* = 3.0, 10.0, 13.5 Hz, 1H), 1.84 (ddd, *J* = 2.5, 6.5, 13.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 200.0, 143.2, 136.8, 128.6, 127.4, 126.9, 120.5, 93.6, 56.0, 50.7, 50.1, 48.4, 40.0, 30.1 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{16}H_{17}O_3ClNa$ calcd: 315.0758, found: 315.0757.

5-Bromo-3,3-dimethoxy-7-methoxycarbonylbicyclo[2.2.2]oct-5-en-2-one (33):



Method: B.

Yield: 143 mg (90%) as brownish solid.

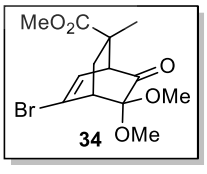
Mp: 75–76 ºC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.27 (dd, *J* = 2.5, 7.0 Hz, 1H), 3.70 (s, 3H), 3.53 (dd, *J* = 2.0, 9.0 Hz, 1H), 3.38 (s, 3H), 3.33 (s, 3H), 3.32–3.31 (m, 1H), 3.02 (ddd, *J* = 2.0, 6.0, 10.0 Hz, 1H), 2.32 (ddd, *J* = 3.0, 10.0, 13.0 Hz, 1H), 1.99 (ddd, *J* = 2.5, 5.5, 13.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 200.3, 173.2, 145.3, 121.9, 100.2, 93.5, 52.1, 50.1, 49.5, 38.8, 38.2, 30.1, 25.7, 22.9, 21.8 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{12}H_{15}O_5BrNa$ calcd: 340.9995, found: 340.9965.

5-Bromo-3,3-dimethoxy-7-methoxycarbonyl-7-methylbicyclo[2.2.2]oct-5-en-2-one (34):



Method: B.

Yield: 133 mg (80%) as brownish solid.

Mp: 63–64 ºC.

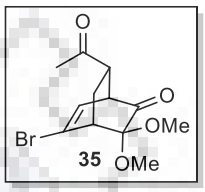
IR (KBr): ν_{max} 2952, 2894, 1743, 1639, 1532, 1269, 1141 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.26 (d, *J* = 7.0 Hz, 1H), 3.66 (s, 3H), 3.34 (s, 3H), 3.34–3.33 (m, 1H), 3.31 (s, 3H), 3.22–3.21 (m, 1H), 2.46 (dd, *J* = 3.0, 14.0 Hz, 1H), 1.85 (d, *J* = 13.5, 1H), 1.26 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 200.1, 175.6, 126.9, 124.9, 93.8, 58.3, 52.6, 50.7, 49.8, 49.2, 46.4, 32.0, 25.2 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{13}H_{17}O_5BrNa$ calcd: 355.0157, found: 355.0152.

7-Acetyl-5-bromo-3,3-dimethoxy-bicyclo[2.2.2]oct-5-en-2-one (35):



35

Method: B.

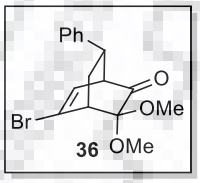
Yield: 106 mg (70%) as brownish liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.22 (dd, *J* = 2.5, 7.0 Hz, 1H), 3.44 (dd, *J* = 1.5, 6.5 Hz, 1H), 3.35 (s, 3H), 3.31 (s, 3H), 3.30–3.29 (m, 1H), 3.04–3.00 (m, 1H), 2.26 (ddd, *J* = 3.0, 10.0, 13.0 Hz, 1H), 2.13 (s, 3H), 1.85 (ddd, *J* = 2.5, 6.5, 13.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 204.9, 199.1, 125.1, 123.9, 93.8, 51.4, 50.7, 50.1, 49.1, 46.8, 28.1, 24.0 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{12}H_{15}O_4BrNa$ calcd: 325.0095, found: 325.0066.

5-Bromo-3,3-dimethoxy-7–phenylbicyclo[2.2.2]oct-5-en-2-one (36):



36

Method: B.

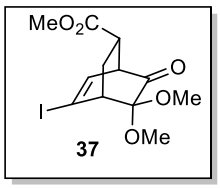
Yield: 147 mg (87%) as colourless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31–7.28 (m, 2H), 7.25–7.23 (m, 1H), 7.16–7.14 (m, 2H), 6.27 (dd, *J* = 2.0, 6.5 Hz, 1H), 3.44 (s, 3H), 3.42 (s, 3H), 3.41–3.37 (m, 2H), 3.25 (dd, *J* = 1.5, 6.5 Hz, 1H), 2.57 (ddd, *J* = 3.5, 10.0, 13.5 Hz, 1H), 1.85 (ddd, *J* = 2.5, 6.5, 13.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ199.6, 143.1, 128.6, 127.4, 126.9, 125.1, 124.7, 93.7, 57.2, 50.7, 50.1, 49.9, 39.8, 30.2 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{16}H_{17}O_3BrNa$ calcd: 359. 0253, found: 359.0254.

3,3-Dimethoxy-5-iodo-7-methoxycarbonylbicyclo[2.2.2]oct-5-en-2-one (37):



Method: B.

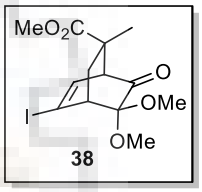
Yield: 149 mg (83%) as yellowish liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.60 (dd, *J* = 1.5, 6.5Hz, 1H), 3.70 (s, 3H), 3.43 (dd, *J* = 2.0, 7.0 Hz, 1H), 3.38 (s, 3H), 3.36 (q, *J* = 2.0 Hz, 1H), 3.33 (s, 3H), 3.01 (ddd, *J* = 1.5, 6.0, 10.0 Hz, 1H), 2.26 (ddd, *J* = 3.0, 10.0, 13.5 Hz, 1H), 1.94 (ddd, *J* = 2.5, 6.0, 13.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 198.8, 172.7, 134.0, 95.8, 94.0, 53.4, 52.5, 52.1, 51.0, 50.1, 38.7, 24.9 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{12}H_{15}O_5INa$ calcd: 388.0012, found: 388.0011.

3,3-Dimethoxy-5-iodo-7-methoxycarbonyl-7-methylbicyclo[2.2.2]oct-5-en-2-one (38):



Method: B.

Yield: 142 mg (75%) as colourless solid.

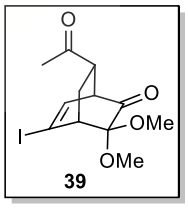
Mp: 87–88 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.63 (dd, *J* = 1.5, 6.5 Hz, 1H), 3.69 (s, 3H), 3.38 (s, 3H), 3.35 (s, 3H), 3.31–3.29 (m, 2H), 2.46 (dd, *J* = 3.0, 14.0 Hz, 1H), 1.82 (dd, *J* = 3.0, 14.0 Hz, 1H), 1.28 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 200.1, 175.7, 135.9, 95.7, 94.2, 59.9, 52.7, 52.2, 51.0, 49.8, 46.4, 32.0, 25.2 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{13}H_{17}O_5INa$ calcd: 403.0012, found: 403.0011.

7-Acetyl-3,3-dimethoxy-5-iodobicyclo[2.2.2]oct-5-en-2-one (39):



Method: B.

Yield: 114 mg (65%) as colourless solid.

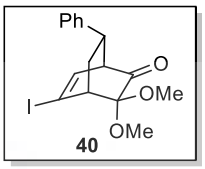
Mp: 75–76 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.55 (dd, *J* = 2.0, 6.5 Hz, 1H), 3.36 (s, 3H), 3.35–3.34 (m, 1H), 3.32 (s, 3H), 3.30–3.28 (m, 1H), 3.04–3.01 (m, 1H), 2.21 (ddd, *J* = 3.0, 10.0, 13.0 Hz, 1H), 2.14 (s, 3H), 1.88 (ddd, *J* = 3.0, 7.0, 13.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 205.0, 199.1, 134.0, 94.7, 94.1, 52.7, 52.0, 51.0, 50.1, 46.7, 28.1, 23.9 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{12}H_{15}O_4INa$ calcd: 372.9907, found: 372.9821.

3,3-Dimethoxy-5-iodo-7-phenylbicyclo[2.2.2]oct-5-en-2-one (40):



40

Method: B.

Yield: 154 mg (80%) as colourless solid.

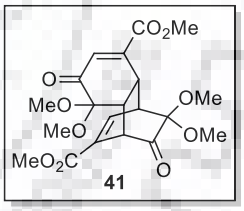
Mp: 68–69 ºC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24–7.21 (m, 2H), 7.18–7.14 (m, 1H), 7.06 (d, *J* = 7.5 Hz, 2H), 6.52 (dd, *J* = 2.0, 7.0 Hz, 1H), 3.39–3.37 (m, 1H), 3.35 (s, 3H), 3.32 (s, 3H), 3.31–3.28 (m, 1H), 3.08 (dd, *J* = 1.5, 6.5 Hz, 1H), 2.41 (ddd, *J* = 3.0, 9.5, 13.0 Hz, 1H),1.73 (ddd, *J* = 2.5, 6.5, 13.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 199.6, 143.2, 134.1, 128.7, 127.4, 127.0, 95.9, 94.0, 58.7, 53.0, 51.0, 50.2, 39.8, 30.0 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{16}H_{17}O_3INa$ calcd: 407.0114, found: 407.0106.

Dimethyl-8,8,9,9-tetramethoxy-7,10-dioxo-1,4,4a,7,8,8a-hexahydro-1,4-ethanonapthalene-2,5-dicarboxylate (41):



41

Method: A.

Yield: 242 mg (57%) as yellowish solid.

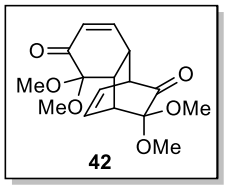
Mp: 102–103 ºC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.08 (dd, *J* = 1.5, 7.0 Hz, 1H), 6.76 (d, *J* = 1.0 Hz, 1H), 4.00–3.99 (m, 1H), 3.87 (s, 3H), 3.85–3.84 (m, 1H), 3.67 (s, 3H), 3.47 (s, 3H), 3.42 (s, 3H), 3.37–3.35 (m, 1H), 3.30 (dd, *J* = 1.5, 7.0 Hz, 1H), 3.22 (s, 3H), 3.06 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 200.4, 194.1, 164.9, 163.4, 144.4, 140.3, 132.8, 132.4, 98.8, 94.4, 52.9, 52.2, 51.6, 50.7, 50.4, 49.9, 49.1, 40.9, 38.3, 38.2 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{20}H_{24}O_{10}Na$ calcd: 447.1261, found: 447.1261.

3,3,10,10-Tetramethoxytricyclo[6.2.2.0]dodeca-5,11-diene-4,9-dione (42):



Method: A.

Yield: 293 mg (95%) as colourless solid.

Mp: 180–181 ºC.

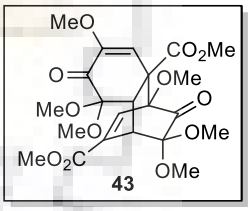
IR (KBr): ν_{max} 2952, 2839, 1740, 1626, 1526, 1444, 1327, 1184 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.44 (dd, *J* = 4.0, 10.5 Hz, 1H), 6.27 (ddd, *J* = 1.0, 6.5, 8.0 Hz, 1H), 6.05 (dd, *J* = 1.5, 10.5 Hz, 1H), 5.93 (ddd, *J* = 1.0, 6.0, 7.5 Hz, 1H), 3.46 (s, 3H), 3.41 (s, 3H), 3.39–3.36 (m, 1H), 3.30 (dd, *J* = 1.5, 8.5 Hz, 1H), 3.25 (s, 3H), 3.24–3.23 (m, 1H), 3.14–3.12 (m, 1H), 3.08 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 202.1, 193.8, 146.4, 132.2, 128.9, 128.5, 98.5, 94.7, 52.5, 50.4, 50.0, 49.6, 48.8, 40.1, 39.2, 38.9 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{16}H_{20}O_6Na$ calcd: 331.1152; found: 331.1158.

Dimethyl 4,6,8,8,10,10-hexamethoxy-7,9-dioxo-1,7,8,8a-tetrahydro-1,4-ethanonapthalene-2,4a(*4H*)-dicarboxylate (43):



Method: A.

Yield: 184 mg (38%) as yellowish solid.

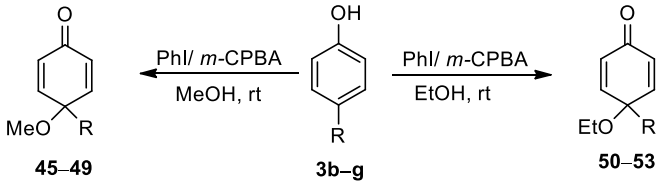
Mp: 152–153 ºC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.96 (d, *J* = 1.5 Hz, 1H), 5.70 (s, 1H), 3.82–3.83 (m, 1H), 3.79 (s, 3H), 3.75 (s, 3H) 3.70–3.69 (m, 1H), 3.63 (s, 3H), 3.56 (s, 3H), 3.55 (s, 3H), 3.36 (s, 3H), 3.23 (s, 3H), 3.03 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 197.9, 187.9, 172.2, 162.8, 151.2, 138.1, 134.3, 109.7, 97.8, 92.9, 92.0, 58.3, 55.9, 55.7, 53.3, 52.6, 51.3, 50.5, 49.1, 48.7, 44.8, 38.9 ppm.

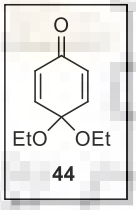
HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{22}H_{28}O_{12}Na$ calcd: 507.1472; found: 507.1502.

3.2.2 General Procedure for the formation of 2,5-cyclohexadienones 44–52:



To a stirred solution of iodobenzene (30 mol%) in dry methanol/ethanol (2 mL) dry *m*-CPBA (249 mg, 1 mmol, 2 equiv) was added followed by addition of phenol or its *p*-substituents. The resulting yellow colour solution was stirred at the given temperature for 2 to 6H. After the completion of the reaction, as monitored by TLC, the solvent was evaporated *in vacuo*. The mixture was washed with a saturated aqueous solution of $NaHCO_3$ and extracted twice (2 x 20 mL) with CH_2Cl_2. The combined organic layers were washed with brine, filtered, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using EtOAc (10–20%) in Hexanes to afford the pure cyclohexadienones 21–24.

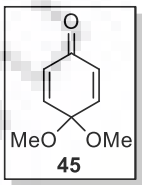
4,4-Diethoxycyclohexa-2,5-dienone (44):



Yield: 55 mg (60%) as brownish liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.83 (d, *J* = 10.4 Hz, 2H), 6.25 (d, *J* = 10.4 Hz, 2H), 3.62 (q, *J* = 7.2 Hz, 4H), 1.23 (t, *J* = 7.2 Hz, 6H) ppm.

4,4-Dimethoxycyclohexa-2,5-dienone (45):

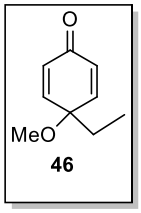


Yield: 66 mg (86%) as yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.81 (d, *J* = 8.4 Hz, 2H), 6.25 (d, *J* = 8.0 Hz, 2H), 3.35 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 185.0, 143.0, 129.8, 92.1, 50.3 ppm.

4-Ethyl-4-methoxycyclohexa-2,5-dienone (46):



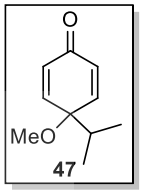
Yield: 63 mg (84%) as yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.71 (d, *J* = 10.4 Hz, 2H), 6.37 (d, *J* = 10.4 Hz, 2H), 3.22 (s, 3H), 1.76 (q, *J* = 7.6 Hz, 2H), 0.82 (t, *J* = 7.6

Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 185.7, 151.0, 131.7, 76.4, 53.0, 31.9, 7.8 ppm.

4-Isopropyl-4-methoxycyclohexa-2,5-dienone (47):

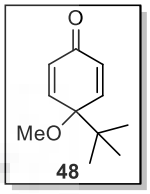


Yield: 58 mg (70%) as yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.70 (d, *J* = 10.0 Hz, 2H), 6.39 (d, *J* = 10.4 Hz, 2H), 3.19 (s, 3H), 2.00–1.93 (m, 1H), 0.92 (d, *J* = 6.8 Hz, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 185.6, 150.3, 132.1, 78.2, 52.9, 36.7, 17.1 ppm.

4-*tert*-Butyl-4-methoxycyclohexa-2,5-dienone (48):

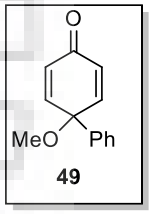


Yield: 67 mg (75%) as yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.88 (d, *J* = 10.4 Hz, 2H), 6.40 (d, *J* = 10.4 Hz, 2H), 3.19 (s, 3H), 0.99 (s, 9H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 185.0, 150.6, 132.4, 79.7, 53.2, 38.9, 25.3 ppm.

4-Methoxy-4-phenycyclohexa-2,5-dienone (49):

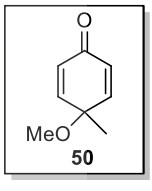


Yield: 83 mg (83%) as yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 7.5 Hz, 2H), 7.37–7.29 (m, 3H), 6.80 (d, *J* = 10.0 Hz, 2H), 6.41 (d, *J* = 10.0 Hz, 2H), 3.43 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 185.9, 150.6, 138.1, 130.0, 128.7, 128.3, 125.7, 76.6, 52.9 ppm.

4-Methoxy-4-methylcyclohexa-2,5-dienone (50):

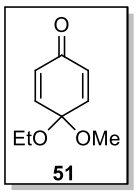


Yield: 51 mg (74%) as yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.80 (d, *J* = 10.0 Hz, 2H), 6.46 (d, *J* = 10.0 Hz, 2H), 3.43 (s, 3H), 1.15 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 185.7, 154.4, 153.6, 133.3, 129.0, 81.5, 53.7, 26.8 ppm

4-Ethoxy-4-methoxycyclohexa-2,5-dienone (51):

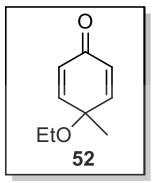


Yield: 72 mg (86%) as yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.83 (d, *J* = 10.0 Hz, 2H), 6.26 (d, *J* = 10.4 Hz, 2H), 3.50 (q, *J* = 7.2 Hz, 2H), 3.36 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 185.0, 143.8, 129.5, 92.3, 58.3, 50.1, 15.3 ppm.

4-Ethoxy-4-methylcyclohexa-2,5-dienone (52):

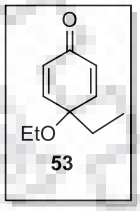


Yield: 62 mg (82%) as yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.77 (d, *J* = 13.2 Hz, 2H), 6.24 (d, *J* = 10.0 Hz, 2H), 3.33 (q, *J* = 7.2 Hz, 2H), 1.40 (s, 3H), 1.14 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 185.2, 152.4, 129.6, 71.8, 60.7, 26.3, 15.4 ppm.

4-Ethoxy-4-ethylcyclohexa-2,5-dienone (53):

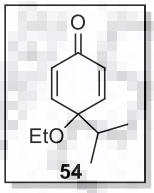


Yield: 52 mg (62%) as colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.86 (d, *J* = 13.2 Hz, 2H), 6.28 (d, *J* = 10.0 Hz, 2H), 3.53 (q, *J* = 7.2 Hz, 2H), 1.40 (q, *J* = 7.2 Hz, 2H), 1.14 (t, *J* = 7.2 Hz, 3H), 0.99 (t, *J* = 6.8 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 185.7, 154.7, 152.4, 129.6, 128.4, 79.8, 65.5, 45.8, 20.1, 14.8 ppm.

4-Ethoxy-4-isopropylcyclohexa-2,5-dienone (54):

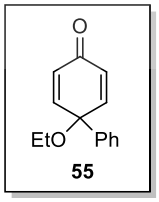


Yield: 55 mg (61%) as yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.74 (d, *J* = 10.0 Hz, 2H), 6.36 (d, *J* = 10.0 Hz, 2H), 3.35 (q, *J* = 7.2 Hz, 2H), 2.01–1.94 (m, 1H), 1.16 (t, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 185.6, 150.6, 131.3, 77.9, 60.4, 36.4, 16.8, 15.7 ppm.

4-Ethoxy-4-phenylcyclohexa-2,5-dienone (55):

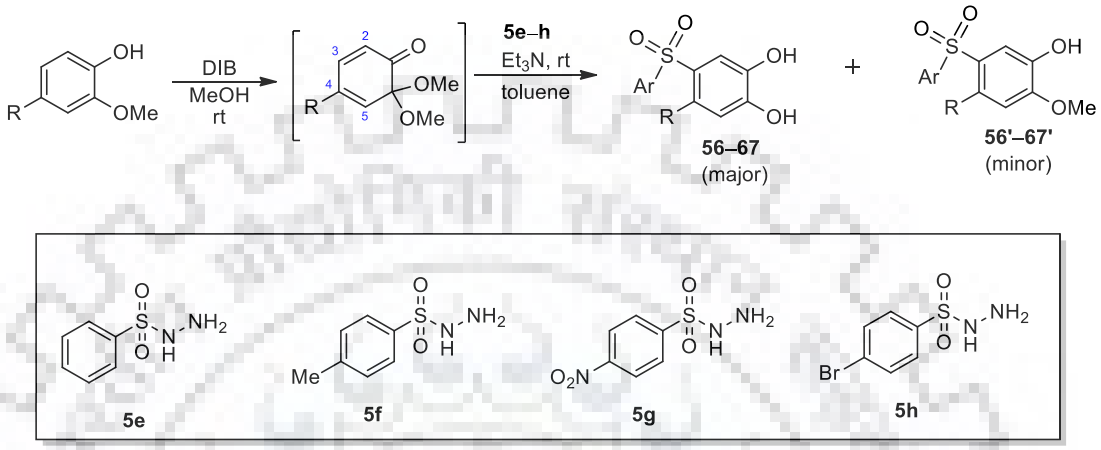


Yield: 87 mg (81%) as yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42–7.39 (m, 2H), 7.31–7.19 (m, 3H), 6.76 (d, *J* = 10.4 Hz, 2H), 6.30 (d, *J* = 10.0 Hz, 2H), 3.35 (q, *J* = 6.8 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H) ppm.

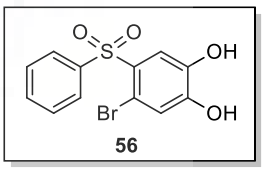
^{13}C NMR (125 MHz, $CDCl_3$): δ 185.6, 151.1, 138.3, 129.4, 128.7, 128.2, 125.5, 76.1, 60.1, 15.6 ppm.

3.2.3. General procedure for the synthesis of diaryl sulfones 56–67:



To a solution of guaiacol derivative (**1**, 0.5 mmol) in dry MeOH (2 mL) was added solid $PhI(OAc)_2$ (0.6 mmol) at room temperature and stirred for 5 min. After complete conversion of guaiacol derivative into its MOB **2**, MeOH was removed under reduced pressure. The residue was dissolved in acetonitrile:water (1:2) (3 mL) and was added sulfonyl hydrazide **5e–h** (0.25 mmol) and reaction mixture kept for stirring at 70 °C. After the completion of the reaction, as checked by the TLC, the mixture was extracted with EtOAc (3 × 5 mL) and then the combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate and filtered. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (hexanes/ethyl acetate = 3:1).

4-Bromo-5-(phenylsulfonyl)benzene-1,2-diol (56):



Reaction time: 1 h.

Yield: 68 mg (82%) as brown solid.

Mp: 110–111 °C.

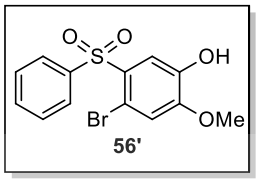
^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 9.25 (br, 1H), 8.95 (br, 1H), 7.76–7.74 (m, 3H), 7.45–7.41 (m, 1H), 7.36–7.32 (m, 2H), 6.95 (s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 150.3, 144.2, 132.8, 128.7, 128.5, 128.2, 128.0, 121.6, 118.1, 110.7 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{12}H_9BrO_4SNa$ calcd: 350.9297, found: 350.9290.

4-Bromo-2-methoxy-5-(phenylsulfonyl)phenol (56'):

Reaction time: 1 h.



56'

Yield: 13 mg (17%) as brown solid.

Mp: 94–95 °C.

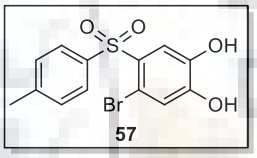
^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 7.95–7.92 (m, 3H), 7.60–7.56 (m, 1H), 7.51–7.47 (m, 2H), 7.05 (s, 1H), 3.92 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 150.5, 144.9, 140.4, 133.1, 132.3, 128.7, 128.4, 117.4, 117.1, 111.4, 56.6 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{13}H_{11}BrO_4SNa$ calcd: 364.9453, found: 364.9456.

4-Bromo-5-tosylbenzene-1,2-diol (57):

Reaction time: 30 min.



57

Yield: 51 mg (60%) as brown solid.

Mp: 210–211 °C.

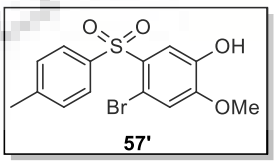
^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 9.18–8.96 (br, 2H), 7.82 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 7.5 Hz, 2H), 7.03 (s, 1H), 2.35 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 150.4, 144.3, 140.5, 132.6, 128.8, 128.4, 127.8, 121.6, 118.0, 110.4, 29.4 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{13}H_{11}BrO_4SNa$ calcd: 364.9453, found: 364.9494.

4-Bromo-2-methoxy-5-tosylphenol (57'):

Reaction time: 30 min.



57'

Yield: 26 mg (28%) as brown solid.

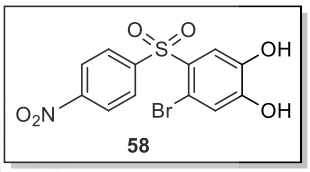
Mp: 200–202 °C.

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 7.93 (s, 1H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.04 (s, 1H), 3.92 (s, 3H), 2.40 (s, 3H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 150.4, 144.8, 144.1, 137.3, 132.5, 129.3, 128.5, 117.3, 117.0, 111.3, 56.6, 21.6 ppm.

HRMS (ESI-TOF) m/z [M + Na]$^+$ $C_{14}H_{13}BrO_4SNa$ calcd: 378.9349, found: 378.9349.

4-Bromo-5-(4-nitrophenylsulphonyl)benzene-1,2-diol (58):



58

Reaction time: 2 h.

Yield: 70 mg (75%) as colourless solid.

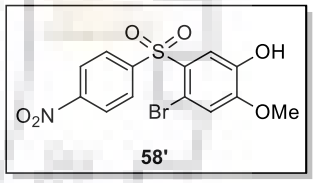
Mp: 94–95 ºC.

^{1}H NMR (400 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 8.89 (br, 1H), 8.70 (br, 1H), 7.82 (s, 1H), 7.71 (d, *J* = 10.4 Hz, 2H), 7.55 (d, *J* = 6.8 Hz, 2H), 7.06 (s, 1H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 151.4, 149.7, 146.4, 144.7, 129.0, 127.5, 123.6, 121.7, 118.2, 110.4 ppm.

HRMS (ESI-TOF) m/z [M + Na]$^+$ $C_{12}H_8BrNO_6SNa$ calcd: 395.9147, found: 395.913.

4-Bromo-2-methoxy-5-(4-nitrophenylsulfonyl)phenol (58'):



58'

Reaction time: 2 h.

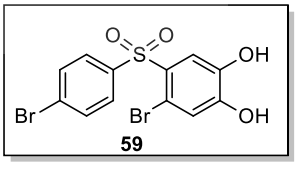
Yield: 34 mg (20%) as yellow solid.

Mp: 87–88 ºC.

^{1}H NMR (400 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 8.33 (d, *J* = 9.2 Hz, 2H), 8.12 (d, *J* = 9.2 Hz, 2H), 7.97 (s, 1H), 7.08 (s, 1H), 3.96 (s, 3H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 151.4, 150.2, 146.0, 145.2, 130.5, 129.6, 127.7, 123.9, 117.5, 111.6, 56.6 ppm

4-(4-Bromophenylsulphonyl)-5-bromobenzene-1,2-diol (59):



59

Reaction time: 2.5 h.

Yield: 76 mg (75%) as brown solid.

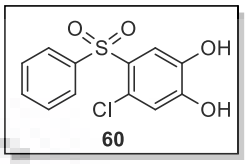
Mp: 112–113 ºC.

^{1}H NMR (400 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 9.09 (br, 1H), 8.84 (br, 1H), 7.79 (s, 1H), 7.71 (d, *J* = 10.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.03 (s, 1H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 150.4, 144.3, 139.8, 131.8, 129.6, 129.4, 128.0, 121.7, 118.1, 110.8 ppm.

HRMS (ESI-TOF) m/z [M + Na]$^+$ $C_{12}H_8Br_2O_4SNa$ calcd: 428.8402, found: 428.8391

4-Chloro-5-(phenylsulfonyl)benzene-1,2-diol (60):



60

Reaction time: 45 min.

Yield: 42 mg (60%) as brown solid.

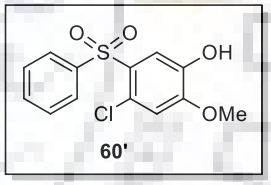
Mp: 173–174 ^{o}C.

^{1}H NMR (400 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 7.88 (d, *J* = 7.6 Hz, 2H), 7.57–7.53 (m, 1H), 7.48–7.44 (m, 3H), 6.88 (s, 1H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 150.4, 143.7, 140.9, 132.8, 128.6, 128.2, 127.9, 123.6, 118.2, 117.4 ppm.

HRMS (ESI-TOF) m/z [M + Na]$^+$ $C_{12}H_9ClO_4SNa$ calcd: 306.9802, found: 306.9806.

4-Chloro-2-methoxy-5-(phenylsulfonyl)phenol (60'):



60'

Reaction time: 45 min.

Yield: 11 mg (15%) as brown solid.

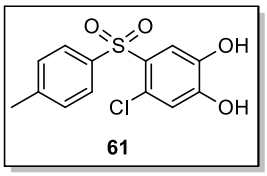
Mp: 144–145 ^{o}C.

^{1}H NMR (400 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 10.59 (br, 1H), 10.12 (br, 1H), 7.84–7.77 (m, 2H), 7.71–7.67 (m, 1H), 7.64 (s, 1H), 7.62–7.58 (m, 2H), 6.87 (s, 1H), 3.38 (s, 3H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 151.6, 144.7, 140.7, 129.3, 129.1, 127.8, 127.5, 127.0, 118.2, 117.1, 59.8 ppm.

HRMS (ESI-TOF) m/z [M + Na]$^+$ $C_{13}H_{11}ClO_4SNa$ calcd: 320.9958, found: 320.9958.

4-Chloro-5-tosylbenzene-1,2-diol (61):



61

Reaction time: 1.5 h.

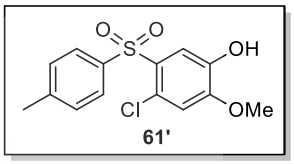
Yield: 45 mg (60%) as brown solid.

^{1}H NMR (400 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 8.99 (br, 1H), 8.79 (br, 1H), 7.72 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 6.79 (s, 1H), 2.32 (s, 3H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 150.5, 143.5, 137.7, 129.1, 128.2, 127.8, 123.2, 118.2, 117.2, 21.5 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{13}H_{11}ClO_4SNa$ calcd: 320.9958, found: 320.9958.

4-Chloro-2-methoxy-5-tosylphenol (61'):



61'

Reaction time: 1.5 h.

Yield: 16 mg (20%) as brown solid.

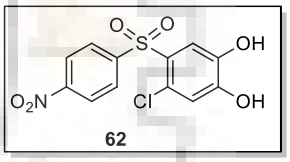
Mp: 99–100 ºC.

^{1}H NMR (400 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 8.94 (br, 1H), 7.68–7.65 (m, 3H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.76 (s, 1H), 3.76 (s, 3H), 2.29 (s, 3H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 150.4, 143.7, 143.5, 137.8, 129.1, 129.0, 127.8, 127.7, 118.1, 117.2, 56.1, 21.2 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{14}H_{13}ClO_4SNa$ calcd: 335.0115, found: 335.0114.

4-Chloro-5-(4-nitrophenylsulphonyl)benzene-1,2-diol (62):



62

Reaction time: 2 h.

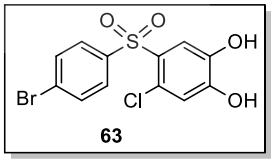
Yield: 50 mg (60%) as yellow viscous liquid.

^{1}H NMR (400 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 9.15 (br, 1H), 8.17 (d, *J* = 11.2 Hz, 2H), 7.93 (d, *J* = 8.8 Hz, 2H), 7.66 (s, 1H), 6.75 (s, 1H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 151.5, 149.9, 146.6, 144.0, 128.9, 126.1, 123.7, 123.5, 118.4, 117.5 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{12}H_8ClNO_6SNa$ calcd: 351.9653, found: 351.9653.

4-(4-Bromophenylsulphonyl)-5-chlorobenzene-1,2-diol (63):



63

Reaction time: 2 h.

Yield: 63 mg (70%) as brown solid.

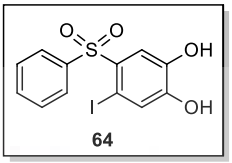
Mp: 131–132 ºC.

^{1}H NMR (400 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 8.17 (br, 1H), 7.95 (s, 1H), 7.77 (d, *J* = 12.0 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.45 (s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 149.8, 144.7, 139.3, 131.9, 130.0, 128.7, 128.1, 128.0, 118.4 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{12}H_8ClBrO_4SNa$ calcd: 384.8907, found: 384.8907.

4-Iodo-5-(phenylsulfonyl)benzene-1,2-diol (64):



64

Reaction time: 1 h.

Yield: 47 mg (50%) as brown solid.

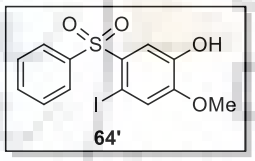
Mp: 109–110 ºC.

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 8.88 (br, 1H), 7.86 (s, 1H), 7.82–7.75 (m, 2H), 7.49–7.45 (m, 1H), 7.41–7.37 (m, 2H) 7.34 (s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 150.4, 144.2, 140.5, 132.7, 129.4, 127.8, 121.7, 117.9, 110.4, 90.9 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{12}H_9IO_4SNa$ calcd: 398.9158, found: 398.9157.

4-Iodo-2-methoxy-5-(phenylsulfonyl)phenol (64'):



64'

Reaction time: 1 h.

Yield: 30 mg (30%) as brown solid.

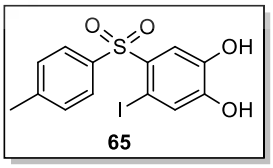
Mp: 105–106 ºC.

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 7.98 (s, 1H), 7.95–7.93 (m, 2H), 7.58–7.55 (m, 1H), 7.50–7.46 (m, 2H), 7.35 (s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 151.4, 146.6, 139.9, 132.9, 128.8, 128.6, 128.3, 126.0, 124.4, 117.9, 80.5, 56.1 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{13}H_{11}IO_4SNa$ calcd: 412.9314, found: 412.9310.

4-Iodo-5-tosylbenzene-1,2-diol (65):



65

Reaction time: 45 min.

Yield: 58 mg (60%) as brown solid.

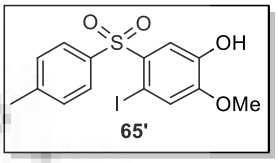
MP: 156–157 ºC.

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 8.64 (br, 1H), 7.89 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.38 (s, 1H), 7.21 (d, *J* = 7.6 Hz, 2H), 2.32 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 149.9, 144.9, 143.5, 137.3, 132.9, 129.1, 128.7, 128.3, 127.0, 118.3, 80.6, 21.5 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{13}H_{11}IO_4SNa$ calcd: 412.9314, found: 412.9314.

4-Iodo-2-methoxy-5-tosylphenol (65'):



65'

Reaction time: 45 min.

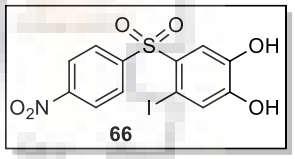
Yield: 20 mg (20%) as brown viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 8.37 (br, 1H), 7.92 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.27 (s, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 3.82 (s, 3H), 2.35 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 151.1, 146.1, 144.0, 136.5, 134.1, 129.2, 128.4, 124.2, 117.6, 80.3, 56.1, 21.4 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{14}H_{13}IO_4SNa$ calcd: 426.9471, found: 426.9450.

4-Iodo-5-(4-nitrophenylsulphonyl)benzene-1,2-diol (66):



66

Reaction time: 1 h.

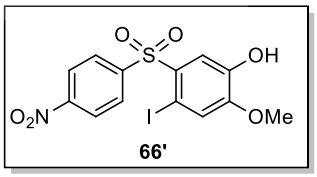
Yield: 71 mg (68%) as colourless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 9.02 (br, 1H), 8.24 (d, *J* = 7.2 Hz, 2H), 8.01 (d, *J* = 5.6 Hz, 2H), 7.82 (s, 1H), 7.04 (s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 150.9, 150.0, 146.5, 144.4, 129.4, 128.3, 123.8, 121.8, 118.3, 111.1 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{12}H_8INO_6SNa$ calcd: 443.9009, found: 443.9008.

4-Iodo-2-methoxy-5-(4-nitrophenylsulfonyl)phenol (66'):



66'

Yield: 17 mg (15%) as colourless solid.

Mp: 85–86 °C.

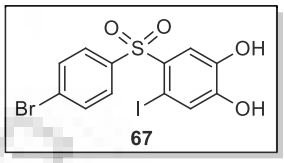
^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 8.32 (d, *J* = 8.4 Hz, 2H), 8.12 (d, *J* = 8.8 Hz, 2H), 8.01 (s, 1H), 7.37 (s, 1H), 3.94 (s, 3H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 150.9, 150.1, 146.1, 145.6, 133.5, 129.8, 124.2, 124.0, 117.8, 81.7, 56.7 ppm.

HRMS (ESI-TOF) m/z: $[M + Na]^+$ $C_{13}H_{10}INO_6SNa$ calcd: 457.9165, found: 457.9165.

4-(4-Bromophenylsulphonyl)-5-iodobenzene-1,2-diol (67):

Reaction time: 1.5 h.



67

Yield: 62 mg (55%) as brown solid.

Mp: 130–131 ºC.

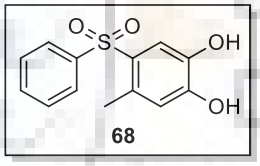
^{1}H NMR (400 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 9.00–8.79 (br, 2H), 7.85 (s, 1H), 7.69 (d, *J* = 6.8 Hz, 2H), 7.53 (d, *J* = 8.8 Hz, 2H), 7.36 (s, 1H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 150.4, 145.2, 139.4, 132.1, 131.7, 129.7, 128.8, 127.7, 118.5, 80.6 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{12}H_8IBrO_4SNa$ calcd: 476.8263, found: 476.8263.

4-Methyl-5-(phenylsulfonyl)benzene-1,2-diol (68):

Reaction time: 20 min.



68

Yield: 42 mg (70%) as colourless solid.

Mp: 118–119 ºC.

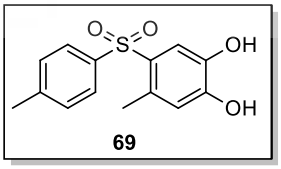
^{1}H NMR (400 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 8.19 (br, 1H), 7.97 (br, 1H), 7.78 (d, *J* = 4.0 Hz, 2H), 7.73 (s, 1H), 7.52–7.48 (m, 1H), 7.45–7.42 (m, 2H), 6.66 (s, 1H), 2.12 (s, 3H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 149.6, 142.5, 142.2, 132.5, 130.8, 128.8, 127.2, 119.0, 116.8, 19.4 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{13}H_{12}O_4SNa$ calcd: 287.0348, found: 287.0348.

4-Methyl-5-tosylbenzene-1,2-diol (69):

Reaction time: 10 min.



69

Yield: 56 mg (80%) as colourless solid.

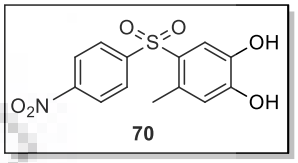
Mp: 137–138 ºC.

^{1}H NMR (400 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 7.92 (s, 1H), 7.71 (d, *J* = 6.4 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 6.72 (s, 1H), 2.40 (s, 3H), 2.28 (s, 3H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 149.3, 143.1, 142.4, 138.9, 130.0, 129.1, 128.6, 126.9, 118.8, 116.5, 21.2, 19.0 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{14}H_{14}O_4SNa$ calcd: 301.0505, found: 301.0506.

4-Methyl-5-(4-nitrophenylsulphonyl)benzene-1,2-diol (70):



70

Reaction time: 35 min.

Yield: 55 mg (72%) as yellow solid.

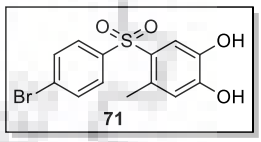
Mp: 111–112 ^oC.

^{1}H NMR (400 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 8.29 (d, *J* = 8.0 Hz, 2H), 7.98 (d, *J* = 9.2 Hz, 2H), 7.74 (s, 1H), 6.71 (s, 1H), 2.25 (s, 3H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 150.6, 149.5, 147.8, 143.0, 128.2, 128.1, 123.92, 123.90, 119.3, 116.9, 19.4 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{13}H_{11}NO_6SNa$ calcd: 332.0199, found: 332.021.

4-(4-Bromophenylsuphonyl)-5-methylbenzene-1,2-diol (71):



71

Reaction time: 30 min.

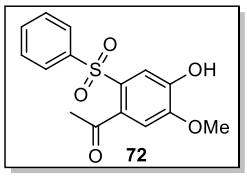
Yield: 53 mg (62%) as colourless solid.

^{1}H NMR (400 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 8.34 (d, *J* = 10.0 Hz, 2H), 7.64 (s, 1H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 6.63 (s, 1H), 2.18 (s, 3H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 149.7, 142.6, 141.1, 131.9, 130.5, 128.6, 127.9, 127.3, 119.1, 116.7, 19.0 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{13}H_{11}BrO_4SNa$ calcd: 364.9453, found: 364.9451.

1-(4-Hydroxy-5-methoxy-2-(phenylsulfonyl)phenyl)ethanone (**72**)**:**



72

Reaction time: 10 min.

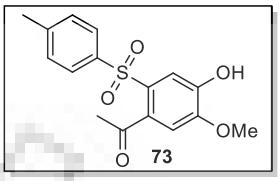
Yield: 48 mg (62%) as viscous colorless liquid.

^{1}H NMR (400 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 7.82–7.80 (m, 2H), 7.46–7.39 (m, 4H), 6.65 (s, 1H), 3.83 (s, 3H), 2.54 (s, 3H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 202.4, 150.9, 147.3, 141.9, 132.7, 128.7, 128.5, 128.1, 127.3, 116.3, 108.7, 56.1, 31.6 ppm.

HRMS (ESI-TOF) m/z [M + Na]$^+$ $C_{15}H_{14}O_5SNa$ calcd: 329.0454, found: 329.0454.

1-(4-Hydroxy-5-methoxy-2-tosylphenyl)ethanone (**73**):



Reaction time: 15 min.

Yield: 52 mg (65%) as colorless solid.

Mp: 106–107 ºC.

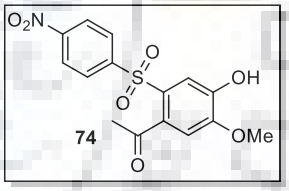
^{1}H NMR (400 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.50 (s, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 6.67 (s, 1H), 3.91 (s, 3H), 2.64 (s, 3H), 2.37 (s, 3H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 201.4, 150.7, 147.1, 143.2, 138.6, 133.8, 129.3, 128.9, 126.9, 115.8, 108.5, 55.5, 31.2, 20.8 ppm.

1-(4-Hydroxy-5-methoxy-2-(4-nitrophenylsulfonyl)phenyl)ethanone (**74**)**:**

Reaction time: 20 min.

Yield: 58 mg (66%) viscous colorless liquid.



^{1}H NMR (400 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 8.32 (d, *J* = 9.2 Hz, 2H), 8.09 (d, *J* = 9.2 Hz, 2H), 7.65 (s, 1H), 6.79 (s, 1H), 3.97 (s, 3H), 2.64 (s, 3H) ppm.

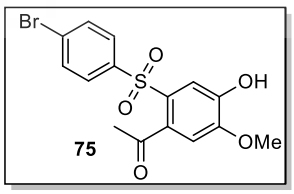
^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 202.0, 150.5, 150.1, 147.7, 146.7, 135.6, 129.2, 129.1, 124.1, 116.4, 108.5, 56.7, 31.6 ppm.

HRMS (ESI-TOF) m/z [M + Na]$^+$ $C_{15}H_{13}NO_7SNa$ calcd: 374.0304, found: 374.0298.

1-(2-(4-Bromophenylsulfonyl)-4-hydroxy-5-methoxyphenyl)ethanone (**75**)**:**

Reaction time: 25 min.

Yield: 53 mg (55%) viscous yellow liquid.

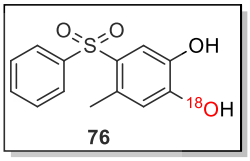


^{1}H NMR (400 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 9.11 (s, 1H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.45 (s, 1H), 6.66 (s, 1H), 3.81 (s, 3H), 2.51 (s, 3H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 206.7, 151.1, 147.5, 140.8, 134.1, 131.7, 129.0, 128.9, 127.6, 116.3, 108.9, 55.7, 30.5 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{15}H_{13}BrO_5SNa$ calcd: 406.9559, found: 406.9614.

4-Methyl-5-(phenylsulfonyl)benzene-1,2-diol (76):



76

Yield: 42 mg (70%) as colourless solid.

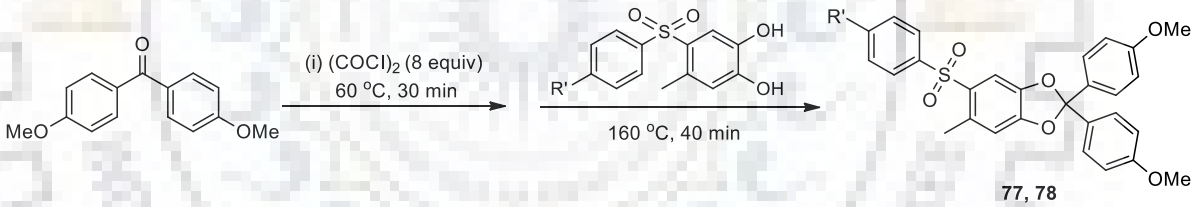
Mp: 118–119 °C.

^{1}H NMR (400 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 8.19 (br, 1H), 7.97 (br, 1H), 7.78 (d, *J* = 4.0 Hz, 2H), 7.73 (s, 1H), 7.52–7.48 (m, 1H), 7.45–7.42 (m, 2H), 6.66 (s, 1H), 2.12 (s, 3H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 149.6, 142.5, 142.2, 132.5, 130.8, 128.8, 127.2, 119.0, 116.8, 19.4 ppm.

HRMS (ESI-TOF) m/z $[M + Na]^+$ $C_{13}H_{12}O_4SNa$ calcd: 303.0548, found: 303.0006.

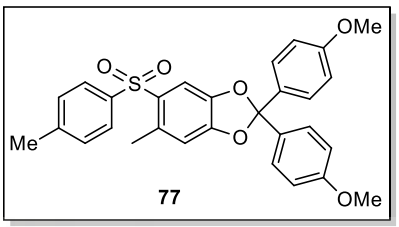
3.2.4. General procedure for protection as bis (4-methoxyphenyl)methylketal



77, 78

4,4'-Dimethoxybenzophenone (1.5 equiv) and oxalyl chloride (8 equiv) were stirred for 30 min at 60 °C and the reaction temperature was raised to 110 °C so as to remove the excess oxalyl chloride from the reaction mixture subsequently followed by the addition of corresponding 2,3-dihydroxysulfone derivative (1 equiv) to the mixture. The dark red solution was stirred for 40 min at 160 °C after cooling, ethyl acetate was added to the viscous mixture, and the solution was washed with saturated aq. NaCl solution dried over Na_2SO_4 and evaporated under *vacuo*. The crude product was purified by flash column chromatography (hexanes/ethyl acetate = 3:1).

2,2-Bis(4-methoxyphenyl)-5-methyl-6-tosylbenzo[1,3]dioxole (77):



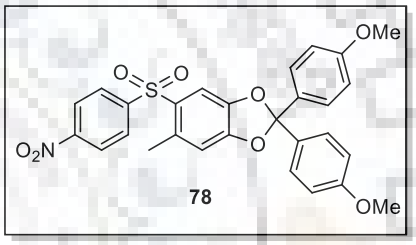
Yield: 180 mg (72%) as colourless liquid.

^{1}H NMR (400 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 7.76–7.73 (m, 3H), 7.47 (d, *J* = 8.8 Hz, 4H), 7.26 (d, *J* = 8.0 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 4H), 6.69 (s, 1H), 3.78 (s, 6H), 2.38 (s, 3H), 2.36 (s, 3H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 160.5, 151.4, 143.8, 138.8, 133.9, 131.9, 131.7, 129.7, 128.0, 127.6, 119.2, 113.7, 112.3, 109.6, 55.4, 21.6, 20.1 ppm.

HRMS (ESI-TOF) m/z [M + Na]$^+$ $C_{29}H_{26}O_6SNa$ calcd: 525.1342, found: 525.1362.

2,2-Bis(4-methoxyphenyl)-5-methyl-6-(4-nitrophenylsulfonyl)benzo[1,3]dioxole (78):



Yield: 181mg (68%) as white solid.

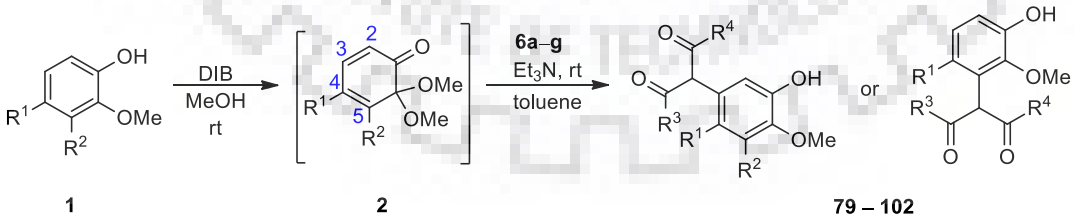
Mp: 206–207 ºC.

^{1}H NMR (400 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 8.31 (d, *J* = 6.8 Hz, 2H), 8.01 (d, *J* = 9.2 Hz, 2H), 7.73 (s, 1H), 7.45 (d, *J* = 6.8 Hz, 4H), 6.89 (d, *J* = 8.8 Hz, 4H), 6.72 (s, 1H), 3.81 (s, 6H), 2.34 (s, 3H) ppm.

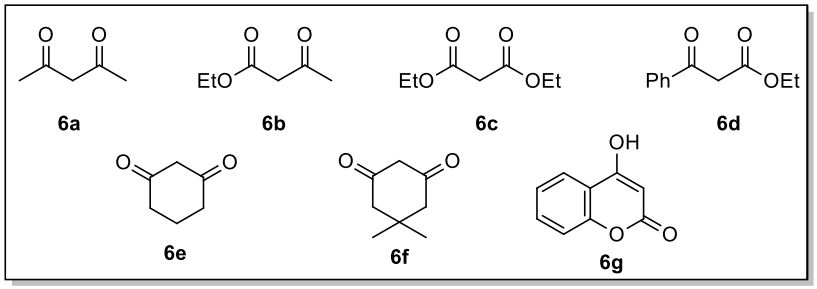
^{13}C NMR (100 MHz, CDCl$_3$ + DMSO-*d*$_6$): δ 160.4, 152.1, 150.0, 147.5, 146.2, 134.4, 131.2, 129.6, 128.6, 127.8, 124.3, 119.6, 113.6, 112.4, 109.7, 55.4, 19.9 ppm.

HRMS (ESI-TOF) m/z [M + Na]$^+$ $C_{28}H_{23}NO_8SNa$ calcd: 556.1036, found: 556.1037.

3.2.5 General procedure for α-arylation of 1,3-dicarbonyls compounds (79–102):

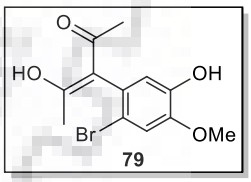


1 **2** **79 – 102**



To a solution of guaiacol derivative (**1**, 0.3 mmol) in dry MeOH (3 mL) was added solid $PhI(OAc)_2$ (0.36 mmol) at room temperature and stirred for 5 min. After complete conversion of guaiacol derivative into its MOB **2**, MeOH was removed under reduced pressure. The residue was dissolved in toluene (3 mL) and was added Et_3N followed by addition of C–H activated pronuclephiles **6a**–**g** (0.45 mmol) and reaction mixture kept for stirring at rt**.** After the completion of the reaction, as checked by the TLC, the mixture was extracted with DCM (3 × 10 mL) and then the combined organic extracts were washed with brine (10 mL) and dried over sodium sulfate, and filtered. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (hexane/ethyl acetate = 3:1) to give corresponding *m*-substituted phenols.

(*Z*)-3-(2-Bromo-5-hydroxy-4-methoxyphenyl)-4-hydroxypent-3-en-2-one (79):



Reaction time: 3 h.

Yield: 64 mg (72%) as colourless solid.

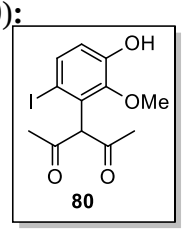
Mp: 120–122 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (s, 1H), 6.80 (s, 1H), 5.70 (br, OH), 3.92 (s, 3H), 1.85 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1, 146.8, 145.1, 129.9, 118.0, 115.9, 114.8, 114.4, 56.2, 23.7 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{12}H_{13}O_4BrNa$ calcd: 322.9889, found: 322.9881.

(*Z*)-4-Hydroxy-3-(3-hydroxy-6-iodo-2-methoxyphenyl)pent-3-en-2-one (80):



Reaction time: 3 h.

Yield: 74 mg (71%) as colourless solid.

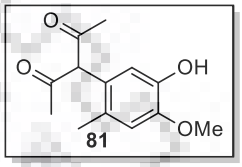
Mp: 129–130 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.4 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 5.73 (s, 1H), 3.95 (s, 3H), 2.77 (s, 3H), 2.61 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.2, 162.8, 144.0, 141.5, 130.8, 121.9, 117.6, 111.4, 108.7, 77.2, 57.1, 31.0, 15.4 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{12}H_{13}O_4INa$ calcd: 370.9750, found: 370.9752.

3-(5-Hydroxy-4-methoxy-2-methylphenyl)pentane-2,4-dione (**81**):



81

Reaction time: 50 min.

Yield: 55 mg (78%) as colourless solid.

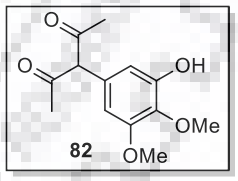
Mp: 109–110 ^{o}C.

^{1}H NMR (400MHz, $CDCl_3$): δ 6.74 (s, 1H), 6.66 (s, 1H), 5.49 (s, 1H), 3.90 (s, 3H), 2.09 (s, 3H), 1.82 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.0, 146.0, 143.6, 129.2, 128.5, 117.1, 113.1, 112.4, 90.6, 55.8, 23.7, 23.6, 19.4 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{13}H_{16}O_4Na$ calcd: 259.0940, found: 259.0946.

3-(3-Hydroxy-4,5-dimethoxyphenyl)pentane-2,4-dione (**82**):



82

Reaction time: 4 h.

Yield: 45 mg (60%) as colourless solid.

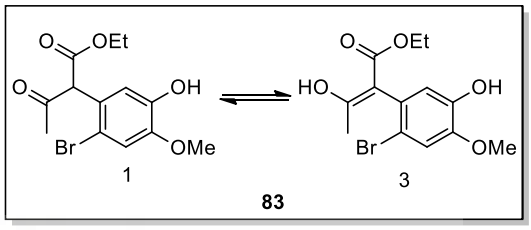
Mp: 144–145 ^{o}C.

^{1}H NMR (400MHz, $CDCl_3$): δ 6.42 (s, 1H), 6.26 (s, 1H), 5.87 (s, 1H), 3.93 (s, 3H), 3.84 (s, 3H), 1.92 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.0, 152.4, 149.3, 134.8, 132.8, 115.0, 110.9, 106.9, 61.0, 55.9, 29.6, 23.9 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{13}H_{16}O_5Na$ calcd: 275.0998, found: 275.0988.

Ethyl 2-(2-bromo-5-hydroxy-4-methoxyphenyl)-3-oxobutanoate (**83**):



Reaction time: 3 h.

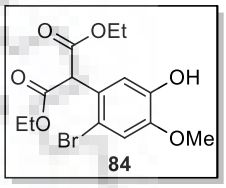
Yield: 70 mg (71%) as colourless liquid.

^{1}H NMR (400MHz, $CDCl_3$): δ 13.06 (br, enol OH), 7.27 (s, 1H), 6.77 (s, 1H), 5.18 (s, 0.3H keto), 4.26–4.21 (m, 2H), 3.91 (s, 3H), 1.79 (s, 3H), 1.19 (t, *J* = 8 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 171.7, 146.4, 144.7, 128.6, 126.8, 118.1, 116.1, 114.5, 60.5, 56.0, 19.3, 14.1 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{13}H_{16}BrO_5Na$ calcd: 352.9995, found: 352.9994**.**

Diethyl 2-(2-bromo-5-hydroxy-4-methoxyphenyl)malonate (**84**):



Reaction time: 5 h.

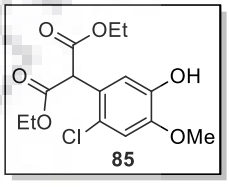
Yield: 74 mg (68%) as colourless liquid.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.06 (s, 1H), 7.02 (s, 1H), 5.59 (br, 1H), 5.08 (s, 1H), 4.27–4.19 (m, 4H), 3.87 (s, 3H), 1.27 (t, *J* = 6.8 Hz, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 147.0, 145.0, 125.4, 115.9, 114.6, 114.1, 61.9, 56.7, 56.1, 14.0 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{14}H_{17}O_6BrNa$ calcd: 383.0100, found: 383.0100.

Diethyl 2-(2-chloro-5-hydroxy-4-methoxyphenyl)malonate (**85**):



Reaction time: 6 h.

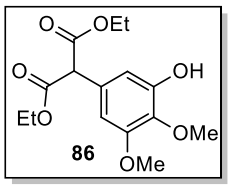
Yield: 61 mg (65%) as colourless liquid.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.04 (s, 1H), 6.87 (s, 1H), 5.55 (br, 1H), 5.08 (s, 1H), 4.28–4.19 (m, 4H), 3.88 (s, 3H), 1.27 (t, *J* = 6.8 Hz, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 147.0, 145.1, 125.6, 115.9, 114.7, 114.2, 61.9, 56.8, 56.2, 14.0 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{14}H_{17}O_6ClNa$ calcd: 339.0605, found: 339.060.

Diethyl 2-(3-hydroxy-4,5-dimethoxyphenyl)malonate (**86**):



86

Reaction time: 7 h.

Yield: 56 mg (61%) as colourless liquid.

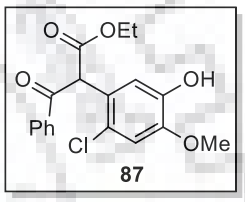
^{1}H NMR (400MHz, $CDCl_3$): δ 6.63 (s, 1H), 6.55 (s, 1H), 5.75 (s, 1H), 4.26–4.17 (m, 4H), 3.89 (s, 3H), 3.86 (s, 3H), 1.27 (t, *J* = 6.8 Hz, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 152.2, 149.2, 135.4, 128.5, 109.4, 105.1, 61.8, 60.8, 57.6, 55.8, 13.9 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{15}H_{20}O_7Na$ calcd: 335.1101, found: 335.1102.

Ethyl 2-(2-chloro-5-hydroxy-4-methoxyphenyl)-3-oxo-3-phenylpropanoate (**87**):

Reaction time: 4 h.



87

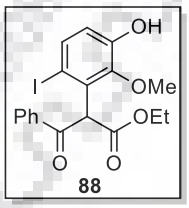
Yield: 83 mg (80%) colourless liquid.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.93–7.92 (m, 2H), 7.55–7.51 (m, 1H), 7.43–7.39 (m, 2H), 6.90 (s, 1H), 6.87 (s, 1H), 6.02 (s, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 3.81 (s, 3H), 1.25 (t, *J* = 6.8 Hz, 3H,) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 187.8, 165.6, 155.5, 148.4, 138.4, 128.4, 128.2, 126.6, 134.5, 133.8, 61.7, 56.4, 53.4, 14.1 ppm.

Ethyl 2-(3-hydroxy-6-iodo-2-methoxyphenyl)-3-oxo-3-phenylpropanoate (**88**):

Reaction time: 5 h.



88

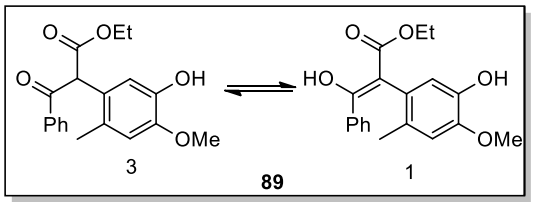
Yield: 100 mg (76%) as colourless liquid.

^{1}H NMR (400MHz, $CDCl_3$): δ 8.04–8.01 (m, 2H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.48–7.45 (m, 3H), 6.98 (d, *J* = 8.4 Hz, 1H), 5.73 (s, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 3.97 (s, 3H), 1.39 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 160.8, 144.5, 141.9, 130.9, 130.1, 129.5, 127.9, 122.9, 112.7, 109.1, 76.7, 60.6, 57.2, 29.7, 14.2 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{18}H_{17}O_5INa$ calcd: 463.0012, found: 463.0012.

Ethyl 2-(5-hydroxy-4-methoxy-2-methylphenyl)-3-oxo-3-phenylpropanoate (**89**):



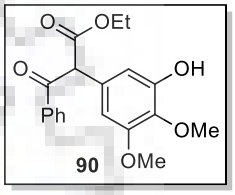
Reaction time: 2 h.

Yield: 78 mg (80%) as colourless liquid.

^{1}H NMR (400MHz, CDCl$_3$): δ 13.6 (br, 0.35OH), 7.86–7.84 (m, 2H), 7.53–7.49 (m, 1H), 7.41–7.37 (m, 2H), 6.79 (s, 1H), 6.70 (s, 1H), 5.61 (s, 1H), 5.38 (s, 1H), 4.28–4.19 (m, 2H), 3.85 (s, 3H), 2.34 (s, 3H), 1.27–1.23 (m, 3H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 194.3, 170.5, 169.1, 146.0, 143.8, 135.7, 133.3, 129.6, 128.7, 128.6, 128.5, 127.6, 115.5, 113.0, 76.7, 61.6, 60.9, 57.3, 19.5, 14.1 ppm.

Ethyl 2-(3-hydroxy-4,5-dimethoxyphenyl)-3-oxo-3-phenylpropanoate (**90**):



Reaction time: 6 h.

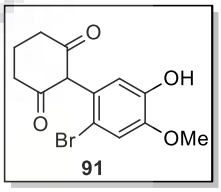
Yield: 64 mg (62%) as colourless liquid.

^{1}H NMR (400MHz, CDCl$_3$): δ 7.97–7.95 (m, 2H), 7.57–7.53 (m, 1H), 7.45–7.42 (m, 2H), 6.63 (s, 1H), 6.52 (s, 1H), 5.75 (br, 1H), 5.47 (s, 1H), 4.25–4.19 (m, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 1.25 (t, 3H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 193.1, 168.8, 152.5, 149.3, 135.7, 135.4, 133.5, 128.9, 128.7, 109.6, 105.4, 61.7, 60.2, 55.9, 29.7, 14.1 ppm .

HRMS (ESI-TOF): m/z $[M]^+$ $C_{19}H_{20}O_6$ calcd: 344.1254, found: 344.1254.

2-(2-Bromo-5-hydroxy-4-methoxyphenyl) cyclohexane-1,3-dione (**91**):



Reaction time: 3 h.

Yield: 76 mg (82%) as colourless solid.

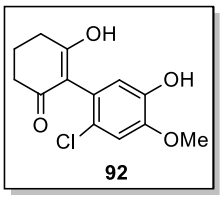
Mp: 178–179 ^{o}C.

^{1}H NMR (400MHz, CDCl$_3$): δ 7.56 (s, 1H), 7.00 (s, 1H), 5.61 (s, 1H), 3.94 (s, 3H), 2.99 (t, *J* = 6.4 Hz, 2H), 2.57 (t, *J* = 7.2 Hz, 2H), 2.28–2.21 (m, 2H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 194.7, 169.7, 148.7, 145.4, 143.8, 116.5, 105.9, 99.9, 94.5, 56.4, 37.8, 23.9, 22.6 ppm.

HRMS (ESI-TOF): m/z $[M + H]^+$ $C_{13}H_{13}O_4Br$ calcd: 313.0069, found: 313.0054.

2-(2-Chloro-5-hydroxy-4-methoxyphenyl)cyclohexane-1,3-dione (**92**):



92

Reaction time: 2 h.

Yield: 64 mg (80%) as colourless solid.

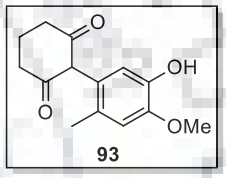
Mp: 186–189 ºC.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.38 (s, 1H), 6.88 (s, 1H), 3.79 (s, 3H), 2.86 (t, *J* = 6.0 Hz, 2H), 2.43 (t, *J* = 6.4 Hz, 2H), 2.15–2.08 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.6, 169.5, 148.1, 145.8, 143.9, 116.2, 115.7, 105.7, 94.6, 55.9, 37.4, 29.2, 23.4, 22.2 ppm.

HRMS (ESI-TOF): m/z $[M + H]^+$ $C_{13}H_{13}O_4Cl$ calcd: 269.0575, found: 269.0575.

2-(5-Hydroxy-4-methoxy-2-methylphenyl)cyclohexane-1,3-dione (**93**):



93

Reaction time: 3 h.

Yield: 63 mg (85%) as colourless solid.

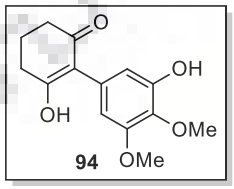
Mp: 272–273 ºC.

^{1}H NMR (400MHz, $CDCl_3$): δ 6.79 (s, 1H), 6.62 (s, 1H), 5.69 (br, 1H), 5.47 (s, 1H), 3.88 (s, 3H), 2.63–2.59 (m, 2H), 2.52–2.48 (m, 2H) 2.13–2.07 (m, 2H), 2.04 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.3, 143.5, 128.9, 123.6, 117.4, 112.8, 77.3, 55.4, 39.6, 20.4, 18.7 ppm.

HRMS (ESI-TOF): m/z $[M + H]^+$ $C_{14}H_{16}O_4$ calcd: 249.1121, found: 249.1103.

2-(3-Hydroxy-4,5-dimethoxyphenyl)cyclohexane-1,3-dione (**94**):



94

Reaction time: 5 h.

Yield: 55 mg (70%) as colourless solid.

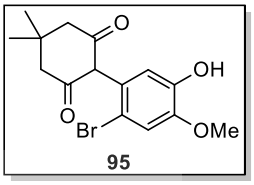
Mp: 117–118 ºC.

^{1}H NMR (400MHz, $CDCl_3$): δ 6.42 (s, 1H), 6.29 (s, 1H), 3.90 (s, 3H), 3.83 (s, 1H), 2.55 (t, *J* = 6.0 Hz, 4H), 2.11–2.04 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2, 150.0, 135.2, 126.5, 117.8, 110.0, 106.6, 60.9, 60.8, 55.9, 55.8, 20.4 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{14}H_{16}O_5Na$ calcd: 287.0867, found: 287.0889.

2-(2-Bromo-5-hydroxy-4-methoxyphenyl)-5,5-dimethylcyclohexane-1,3-dione (95):



95

Reaction time: 4 h.

Yield: 87 mg (86%) as colourless solid.

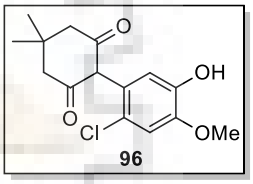
Mp: 144–145 ^oC.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.57 (s, 1H), 6.99 (s, 1H), 5.83 (s, 1H), 3.93 (s, 3H), 2.85 (s, 2H), 2.16 (s, 2H), 1.18 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.3, 169.0, 145.3, 143.8, 116.2, 115.4, 105.7, 94.1, 56.2, 52.2, 37.8, 35.3, 29.7, 28.6 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{15}H_{17}O_4BrNa$ calcd: 363.0202, found: 363.0205.

2-(2-Chloro-5-hydroxy-4-methoxyphenyl)-5,5-dimethylcyclohexane-1,3-dione (96):



96

Reaction time: 3 h.

Yield: 74 mg (85%) as colourless solid.

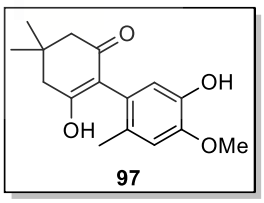
Mp: 145–146 ^oC.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.56 (s, 1H), 7.00 (s, 1H), 5.75 (s, 1H), 3.93 (s, 3H), 2.85 (s, 2H), 2.45 (s, 2H), 1.18 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.3, 168.9, 148.9, 145.3, 143.7, 116.3, 115.4, 105.6, 94.6, 56.3, 52.1, 37.8, 35.3, 28.6 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{15}H_{17}O_4ClNa$ calcd: 319.0707, found: 319.0739.

3-Hydroxy-2-(5-hydroxy-4-methoxy-2-methylphenyl)-5,5-dimethylcyclohex-2- enone (97):



97

Reaction time: 4 h.

Yield: 70 mg (86%) as colourless solid.

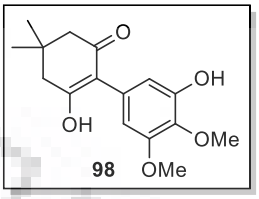
Mp: 235–236 ^oC.

^{1}H NMR (400MHz, $CDCl_3$): δ 6.56 (s, 1H), 6.38 (s, 1H), 3.68 (s, 3H), 2.41–2.40 (m, 2H), 2.21– 2.20 (m, 2H), 1.86 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.4, 146.0, 143.2, 128.5, 123.9, 117.5, 115.1, 112.6, 55.2, 31.3, 28.3, 27.8, 27.5, 18.8 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{16}H_{20}O_4Na$ calcd: 299.1253, found: 299.1256.

3-Hydroxy-2-(3-hydroxy-4,5-dimethoxyphenyl)-5,5-dimethylcyclohex-2-enone (98):



98

Reaction time: 5 h.

Yield: 66 mg (76%) as colourless solid.

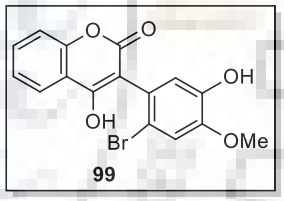
Mp: 225–226 ºC.

^{1}H NMR (400MHz, $CDCl_3$): δ 6.33 (s, 1H), 6.21 (s, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 2.30–2.29 (m, 4H), 1.04 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.6, 152.6, 149.7, 134.9, 127.7, 116.2, 111.0, 106.2, 60.4, 60.3, 55.5, 52.1, 31.4, 28.1 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{16}H_{20}O_5Na$ calcd: 315.1202, found: 315.1202.

3-(2-Bromo-5-hydroxy-4-methoxyphenyl)-4-hydroxy-2H-chromen-2-one (99):



99

Reaction time: 4 h.

Yield: 84 mg (78%) as colourless solid.

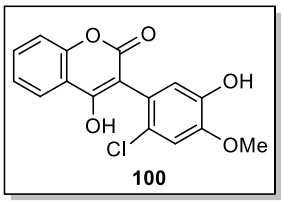
Mp: 208–210 ºC.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.92–7.89 (m, 1H), 7.54–7.48 (m, 2H), 7.43–7.40 (m, 1H), 7.35–7.32 (m, 1H), 7.14 (s, 1H), 3.94 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7, 152.8, 149.7, 147.5, 144.8, 130.8, 124.4, 121.2, 121.1, 117.1, 115.7, 112.7, 105.6, 105.5, 95.0, 56.2 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{16}H_{11}O_5BrNa$ calcd: 384.9682, found: 384.9684.

3-(2-Chloro-5-hydroxy-4-methoxyphenyl)-4-hydroxy-2H-chromen-2-one (100):



100

Reaction time: 4 h.

Yield: 71 mg (75%) as colourless solid.

Mp: 118–220 ºC.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.89–7.87 (m, 1H), 7.48–7.46 (m, 2H), 7.41–7.39 (m, 1H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.19 (s, 1H), 7.12 (s, 1H), 3.93 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 157.5, 152.1, 149.1, 147.6, 144.7, 130.4, 123.9, 120.5, 116.4, 114.8, 112.1, 104.9, 94.8, 55.6 ppm.

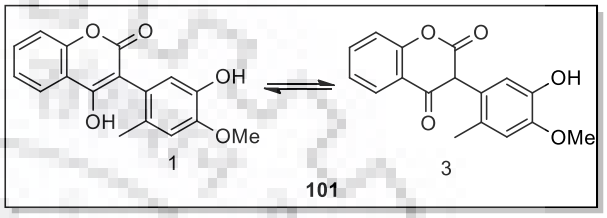
HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{16}H_{11}O_5ClNa$ calcd: 341.0187, found: 341.0188.

4-Hydroxy-3-(5-hydroxy-4-methoxy-2-methylphenyl)-2H-chromen-2-one (101):

Reaction time: 3 h.

Yield: 78 mg (88%) as colourless solid.

Mp: 119–200 ºC.



^{1}H NMR (400MHz, $CDCl_3$): δ 7.84–7.82 (m, 1H), 7.74–7.72 (m, 2H), 7.44–7.38 (m, 3H), 7.21–7.11 (m, 6H) 6.69 (s, 1H), 6.67 (s, 1H), 5.62 (s, 1.5H), 5.19 (s, 0.5H), 3.76 (s, 3H), 2.03 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 163.8, 153.7, 146.7, 143.6, 131.6, 131.1, 123.3, 123.1, 116.7, 116.0, 115.8, 113.0, 90.8, 45.5, 8.2 ppm.

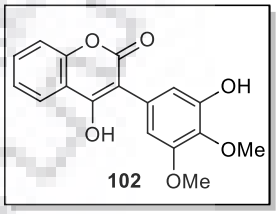
HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{17}H_{14}O_5Na$ calcd: 321.0733, found: 321.0733.

4-Hydroxy-3-(3-hydroxy-4,5-dimethoxyphenyl)-2H-chromen-2-one (102):

Reaction time: 5 h.

Yield: 70 mg (75%) as colourless solid.

Mp: 248–249 ºC.

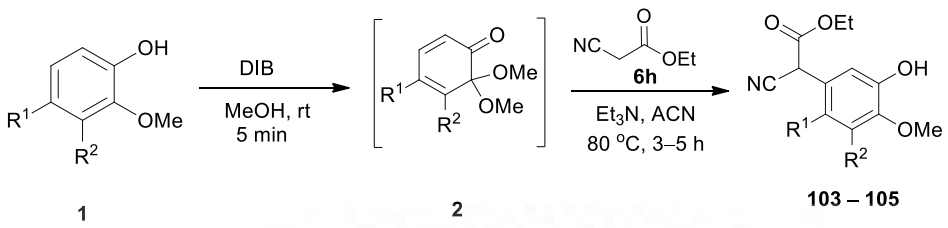


^{1}H NMR (400MHz, $CDCl_3$): δ 7.78–7.77 (d, *J* = 7.6 Hz, 1H), 7.38–7.34 (m, 1H), 7.14–7.08 (m, 2H), 6.48 (s, 1H), 6.34 (s, 1H), 3.71 (s, 3H), 3.67 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4, 160.1, 152.8, 152.3, 131.4, 126.1, 123.5, 123.3, 115.9, 115.8, 111.5, 111.4, 105.84, 105.82, 105.6, 60.1, 55.4 ppm.

HRMS (ESI-TOF): m/z $[M + H]^+$ $C_{17}H_{14}O_6$ calcd: 315.0872, found: 315.0863.

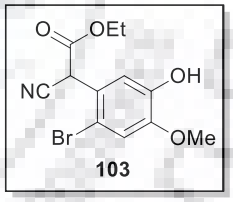
3.2.6 General procedure for α–arylation of ethyl 2-cyanoacetate:



1 **2** **103 – 105**

To a solution of guaiacol derivative (**1**, 0.3 mmol) in dry MeOH (3 mL) was added solid $PhI(OAc)_2$ (0.36 mmol) at room temperature and stirred for 5 min. After complete conversion of guaiacol derivative into its MOB **2**, MeOH was removed under reduced pressure. The residue was dissolved in acetonitrile (3 mL) and was added sequentially Et_3N and 1,3-dieneones **3–6** (0.45 mmol) and reaction mixture kept for stirring at 80 °C. After the completion of the reaction, as checked by the TLC, the mixture was extracted with DCM (3 × 10 mL) and then the combined organic extracts were washed with brine (10 mL), dried over sodium sulfate, and filtered. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (hexane/ethyl acetate = 3:1) to give corresponding *m*-substituted phenols.

Ethyl 2-(2-bromo-5-hydroxy-4-methoxyphenyl)-2-cyanoacetate (103):



103

Reaction time: 4 h.

Yield: 73 mg (78%) as colourless solid.

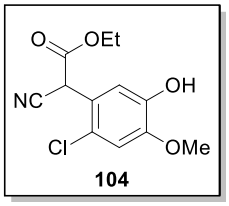
Mp: 122–123 °C.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.13 (s, 1H), 7.05 (s, 1H), 5.10 (s, 1H), 4.31–4.25 (m, 2H), 3.91 (s, 3H), 1.31 (t, *J* = 8.0 Hz, 3H,) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 147.8, 145.7, 122.7, 115.5, 115.2, 115.1, 113.1, 63.4, 56.3, 42.8, 13.9 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{12}H_{12}NO_4BrNa$ calcd: 335.9841, found: 335.9844.

Ethyl 2-(2-chloro-5-hydroxy-4-methoxyphenyl)-2-cyanoacetate (104):



104

Reaction time: 5 h.

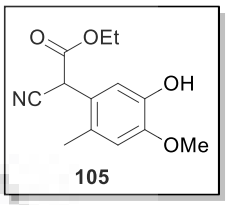
Yield: 64 mg (80%) as colourless liquid.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.09 (s, 1H), 6.89 (s, 1H), 5.07 (s, 1H), 4.31–4.25 (m, 2H), 3.91 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 147.7, 145.1, 124.1, 120.8, 115.4, 115.2, 112.1, 63.3, 55.7, 40.3, 13.9 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{12}H_{12}NO_4ClNa$ calcd: 292.0347, found: 292.0342.

Ethyl 2-cyano-2-(5-hydroxy-4-methoxy-2-methylphenyl)acetate (105):



105

Reaction time: 3 h.

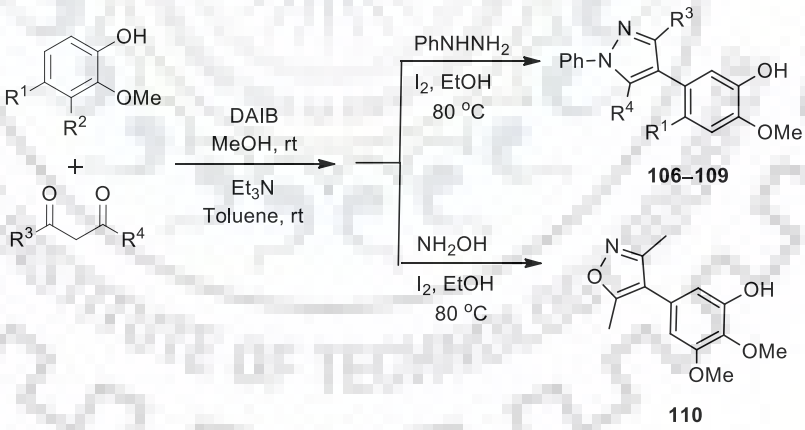
Yield: 65 mg (88%) as colourless solid.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.00 (s, 1H), 6.68 (s, 1H), 5.54 (s, 1H), 4.76 (s, 1H), 4.28–4.20 (m, 2H), 3.88 (s, 3H), 2.32 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 146.9, 144.3, 127.9, 121.2, 115.8, 114.7, 113.2, 63.1, 55.9, 40.6, 19.0, 13.9 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{13}H_{15}NO_4Na$ calcd: 272.0893, found: 272.0860.

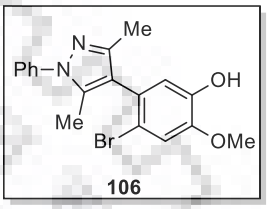
3.2.7 General procedure for the synthesis of pyrazoles 106–109 and isoxazoles 110:



To a solution of guaiacol derivative (**1**, 0.3 mmol) in dry MeOH (3 mL) was added solid $PhI(OAc)_2$ (0.36 mmol) at room temperature and stirred for 5 min. After complete conversion of guaiacol derivative into its MOB **2**, MeOH was removed under reduced pressure. The residue was dissolved in toluene (3 mL) and was added sequentially Et_3N and 1,3-dieneone (0.45 mmol) and the reaction mixture kept for stirring at rt. After the completion of the reaction, checked by the TLC, toluene was evaporated under *vacuo* The residue was diluted with ethanol then hydrazine hydrate 36% (0.75 mmol)/ hydroxylamine

(0.75 mmol for isoxazoles) and molecular iodine (20 mol%) were added sequentially and the mixture were stirred for 5–6 h. The whole mixture was quenched with 1M HCl and extracted with DCM (3 × 10 mL) and then the combined organic extracts were washed with brine (10 mL), dried over sodium sulfate and filtered. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (hexane/ethyl acetate = 3:1) to give the desired pyrazoles **106–109** or isoxazole **110**.

4-Bromo-5-(3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)-2-methoxyphenol (**106**):



106

Yield: 86 mg (78%) as colourless solid.

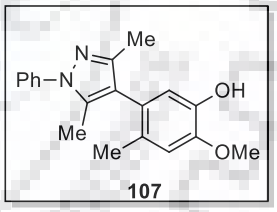
Mp:.157–158 °C.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.50–7.42 (m, 4H), 7.35–7.32 (m, 1H), 7.13 (s, 1H), 6.81 (s, 1H), 3.91 (s, 3H), 2.18 (s, 3H), 2.15 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6, 146.7, 144.8, 139.7, 137.3, 128.9, 127.3, 127.1, 124.7, 120.5, 118.1, 114.9, 114.5, 56.1, 12.3, 11.7 ppm.

HRMS (ESI-TOF): m/z $[M + H]^+$ $C_{18}H_{17}BrN_2O_2$ calcd: 373.0546, found: 373.0546.

5-(3,5-Dimethyl-1-phenyl-1*H*-pyrazol-4-yl)-2-methoxy-4-methylphenol (**107**):



107

Yield: 73 mg (80%) as colourless solid.

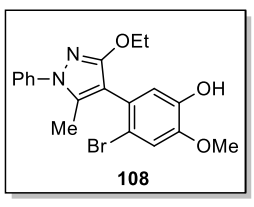
Mp: 160–162 °C.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.51–7.43 (m, 4H), 7.35–7.32 (m, 1H), 6.79 (s, 1H), 6.73 (s, 1H), 3.91 (s, 3H), 2.14 (s, 3H), 2.12 (s, 3H), 2.10 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 145.8, 143.2, 140.0, 136.7, 129.2, 128.9, 125.4, 124.6, 120.3, 117.1, 112.2, 55.8, 19.5, 12.3, 11.5 ppm.

HRMS (ESI-TOF): m/z $[M + H]^+$ $C_{19}H_{20}N_2O_2$ calcd: 309.1597, found: 309.1560.

4-Bromo-5-(3-methoxy-5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2 methoxyphenol (**108**):



108

Yield: 86 mg (72%) as colourless solid.

Mp: 160–161 °C.

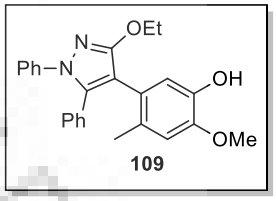
^{1}H NMR (400MHz, $CDCl_3$): δ 7.75–7.73 (m, 2H), 7.44–7.39 (m, 2H),

7.27 (s, 1H), 7.12 (s, 1H), 6.92 (s, 1H), 5.70 (br, 1H), 3.93 (s, 3H), 3.88–3.83 (m, 2H), 2.12 (s, 3H), 1.15 (t, *J* = 6.8 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3, 148.1, 146.7, 144.7, 138.8, 128.7, 126.4, 126.0, 122.2, 121.3, 118.4, 118.2, 115.2, 114.7, 110.2, 69.0, 56.2, 15.2, 13.2 ppm.

HRMS (ESI-TOF): m/z $[M + H]^+$ $C_{19}H_{19}BrN_2O_3$ calcd: 403.0651, found: 403.0641.

5-(3-Ethoxy-1,5-diphenyl-1*H*-pyrazol-4-yl)-2-methoxy-4-methylphenol (**109**):



109

Yield: 86 mg (72%) as colourless solid.

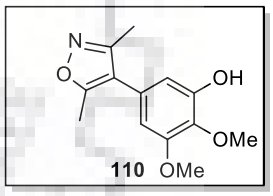
Mp: 217–218 °C.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.50–7.48 (m, 2H), 7.45–7.41 (m, 1H), 7.39–7.33 (m, 3H), 7.26–7.23 (m, 4H), 6.76 (s, 1H), 6.70 (s, 1H), 3.87 (s, 3H), 2.51 (q, *J* = 7.2 Hz, 2H), 2.02 (s, 3H), 0.98 (t, *J* = 7.6 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.8, 145.9, 143.3, 130.4, 129.8, 128.8, 128.7, 128.6, 128.2, 127.9, 126.8, 126.6, 125.2, 119.0, 117.6, 112.7, 55.8, 44.6, 19.6, 8.3 ppm.

HRMS (ESI-TOF): m/z $[M + H]^+$ $C_{25}H_{24}N_2O_3$ calcd: 401.1859, found: 401.1857.

5-(3,5-Dimethylisoxazol-4-yl)-2,3-dimethoxyphenol (**110**):



110

Yield: 60 mg (81%) as colourless solid.

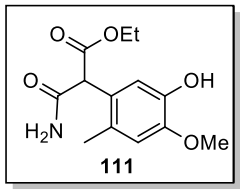
Mp: 152–153 °C.

^{1}H NMR (400MHz, $CDCl_3$): δ 6.48 (s, 1H), 6.32 (s, 1H), 5.95 (s, 1H), 3.94 (s, 3H), 3.87 (s, 3H), 2.40 (s, 3H), 2.27 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 158.6, 152.4, 149.5, 134.9, 126.4, 116.6, 109.0, 105.2, 61.0, 55.9, 11.5, 10.8 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{13}H_{15}NO_4Na$ calcd: 272.0893, found: 272.0897.

(±)-Ethyl 3-amino-2-(2-bromo-5-hydroxy-4-methoxyphenyl)-3-oxopropanoate (**111**):



111

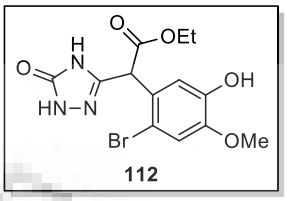
Yield: 54 mg (68%) as colourless solid.

Mp: 154–156 °C.

^{1}H NMR (400MHz, $CDCl_3$): δ 6.97 (s, 1H), 6.69 (s, 1H), 4.65 (s, 1H), 4.25–4.14 (m, 2H), 3.86 (s, 3H), 2.34 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 170.2, 146.1, 144.0, 128.7, 125.0, 113.4, 113.3, 61.8, 55.9, 54.3, 29.7, 14.1 ppm.

Ethyl 2-bromo-5-hydroxy-4-methoxyphenyl)-2-(5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)acetate (112):



112

Yield: 66 mg (60%) as colourless solid.

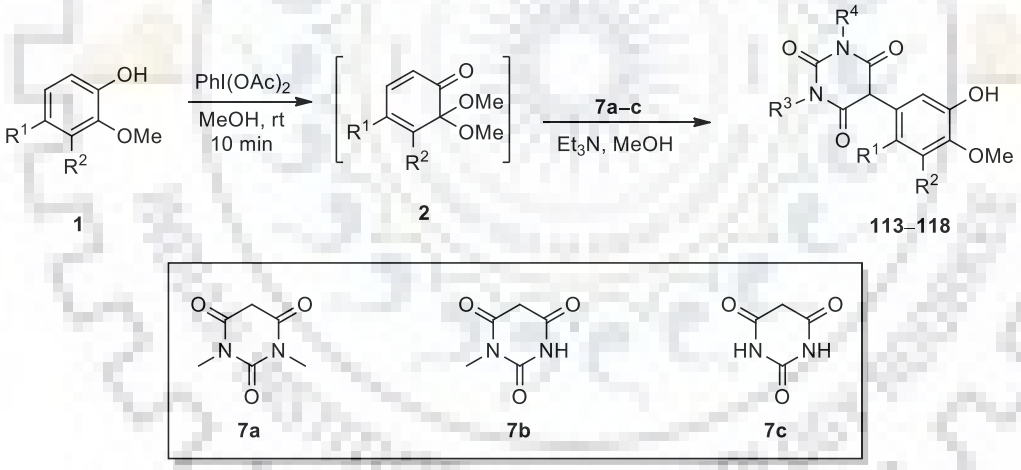
Mp: 66–68 ºC.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.13 (s, 1H), 7.05 (s, 1H), 5.10 (s, 1H), 4.32–4.26 (m, 2H), 3.91 (s, 3H), 3.73 (s, 1H), 1.31 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 158.4, 157.3, 152.6, 146.7, 132.0, 120.9, 118.4, 118.7, 61.3, 56.1, 46.1, 14.1 ppm.

HRMS (ESI-TOF): m/z $[M + H]^+$ $C_{13}H_{14}BrN_3O_4$ calcd: 372.0189, found: 372.0185.

3.2.8 General procedure for the synthesis of 5-aryl barbituric acids 113–118:



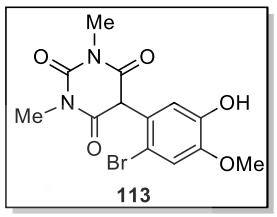
1 2 113–118

7a 7b 7c

To a solution of guaiacol derivative (**1**, 0.3 mmol) in dry MeOH (3 mL) was added solid $PhI(OAc)_2$ (0.36 mmol) at room temperature and stirred for 5 min. After complete conversion of guaiacol derivative into its MOB **2** was added sequentially Et_3N (2.5 equiv) and barbituric acids **7a–7c** (0.32 mmol) and the reaction mixture kept for stirring at room temperature. After the completion of the reaction, as checked by the TLC, solvent was evaporated under *vacuo* and then mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed with brine (10 mL), dried over sodium sulfate, and solidified with

hexane/ diethyl ether then filtered and washed with hexane. Recrystallization was done using ethyl acetate/ methanol to give the pure products.

5-(2-Bromo-5-hydroxy-4-methoxyphenl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (113):



113

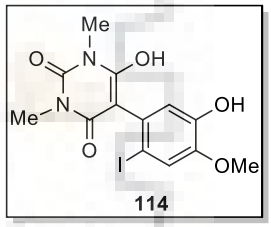
Reaction time: 3 h.

Yield: 91 mg (86%) as brown solid.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.02 (s, 1H), 6.84 (s, 1H), 4.65 (s, 1H), 3.87 (s, 3H), 3.37 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.15, 151.2, 147.4, 145.3, 126.3, 118.5, 115.4, 56.3, 56.2, 28.9 ppm.

6-Hydroxy-5-(5-hydroxy-2-iodo-4-methoxyphenyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (114):



114

Reaction time: 3 h.

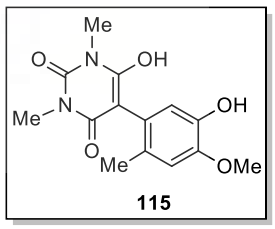
Yield: 100 mg (83%) as brown solid.

Mp: 117–118 ^{o}C.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.09 (s, 1H), 6.54 (s, 1H), 3.67 (s, 3H), 3.01 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 160.8, 153.1, 146.2, 145.9, 136.7, 120.9, 120.7, 92.8, 56.0, 49.1, 27.1 ppm.

6-Hydroxy-5-(5-hydroxy-4-methoxy-2-methylphenyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (115):



115

Reaction time: 2 h.

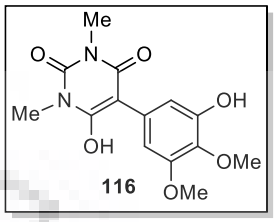
Yield: 76 mg (88%) as colourless solid.

Mp: 110–111 ^{o}C.

^{1}H NMR (400MHz, $CDCl_3$): δ 6.73 (s, 1H), 6.67 (s, 1H), 3.79 (s, 3H), 3.31 (s, 6H), 2.10 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1, 153.2, 144.7, 142.9, 130.9, 128.8, 120.8, 113.3, 55.8, 27.1, 19.7, 14.2 ppm.

5-(3-Hydroxy-4,5-dimethoxyphenyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (116):



116

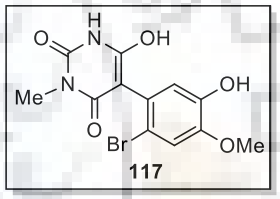
Reaction time: 5 h.

Yield: 71 mg (78%) as colourless solid.

^{1}H NMR (400MHz, $CDCl_3$): δ 11.87 (br, 1H), 6.33 (d, *J* = 4.0 Hz, 1H), 6.26 (d, *J* = 4.0 Hz, 1H), 3.90 (s, 3H), 3.75 (s, 3H), 3.38 (s, 3H), 3.35 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 153.8, 150.7, 137.4, 135.1, 108.6, 107.3, 60.8, 56.1, 50.7, 29.4 ppm.

5-(2-Bromo-5-hydroxy-4-methoxyphenyl)-6-hydroxy-3-methylpyrimidine-2,4(1*H*,3*H*)-ione (117):



117

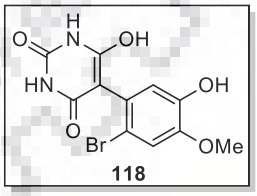
Reaction time: 4 h.

Yield: 77 mg (76%) as brown solid.

Mp: 166–168 ^{o}C.

^{1}H NMR (400MHz, $CDCl_3$): δ 6.85 (s, 1H), 6.72 (s, 1H), 3.70 (s, 3H), 3.14 (s, 3H) ppm.

5-(2-Bromo-5-hydroxy-4-methoxyphenyl)-6-hydroxypyrimidine-2,4(1*H*,3*H*)-dione (118):



118

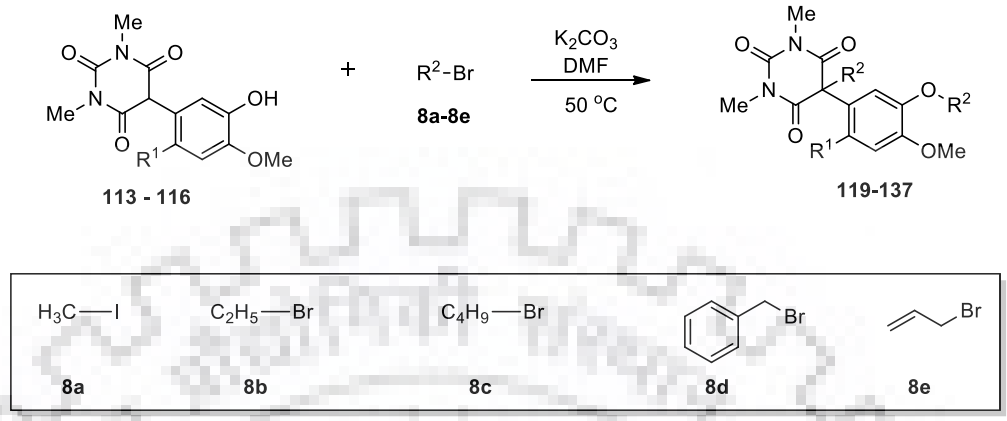
Reaction time: 4 h.

Yield: 66 mg (68%) as brown solid.

Mp: 210–212 ^{o}C.

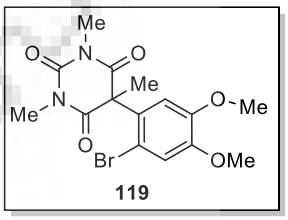
^{1}H NMR (400MHz, $CDCl_3$): δ 6.67 (s, 1H), 6.6 (s, 1H), 3.85 (s, 3H) ppm.

3.2.9 General procedure for the synthesis of C-5 disubstituted barbituric acids 119–137:



C-5 aryl barbituric acid **113**–**116** (0.3 mmol, 1 equiv) was added to the solution of K_2CO_3 (1.14 mmol, 3.8 equiv) under stirring in DMF and the mixture stirred for 10 min followed by the addition of alkyl halide (1.26 mmol, 4.2 equiv) and the resulting mixture was stirred at 50 °C (at 80 °C in case of compound **116**). After the completion of the reaction (typically 5–7 h for less reactive alkyl halides **8a,b,c** and 3–4 h for highly reactive benzyl and allyl halides **8d,e**), as monitored by the TLC, the mixture was quenched with HCl 0.1 M and then extracted with CH_2Cl_2 (3 × 10 mL), dried over sodium sulfate. The solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluentHexane/ethyl acetate 3:1).

5-(2-Bromo-4,5-dimethoxyphenyl)-1,3,5-trimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (119):



Reaction time: 5 h.

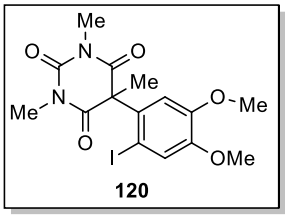
Yield: 95 mg (83%) as colourless solid.

Mp: 216–217 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (s, 2H), 3.92 (s, 3H), 3.84 (s, 3H), 3.36 (s, 6H), 1.96 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 151.2, 149.6, 148.4, 129.7, 116.3, 114.0, 112.8, 56.9, 56.1, 28.9, 25.8 ppm.

5-(2-Iodo-4,5-dimethoxyphenyl)-1,3,5-trimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (120):



120

Reaction time: 5 h.

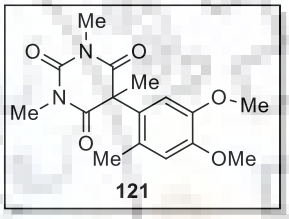
Yield: 103 mg (80%) as colourless solid.

Mp: 122–123 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78 (s, 1H), 6.76 (s, 1H), 3.83 (s, 6H), 3.33 (s, 6H), 1.83 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 151.2, 149.3, 149.2, 131.2, 117.8, 111.3, 108.8, 76.3, 56.1, 55.8, 29.0, 22.3 ppm.

5-(4,5-Dimethoxy-2-methylphenyl)-1,3,5-trimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (121):



121

Reaction time: 4 h.

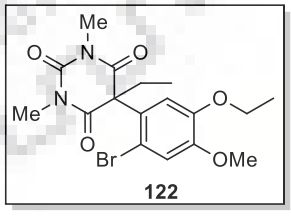
Yield: 82 mg (85%) as colourless solid.

Mp: 162–163 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (s, 1H), 6.65 (s, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 3.37 (s, 6H), 1.97 (s, 3H), 1.91 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 151.1, 148.6, 147.1, 128.2, 127.2, 114.7, 111.7, 56.1, 55.8, 54.8, 29.0, 26.3, 19.5 ppm.

5-(2-Bromo-5-ethoxy-4-methoxyphenyl)-5-ethyl-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (122):



122

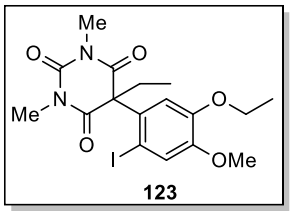
Reaction time: 6 h.

Yield: 94 mg (77%) as colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.103 (s, 1H), 6.78 (s, 1H), 4.09–4.01 (m, 2H), 3.88 (s, 3H), 3.79–3.64 (m, 2H), 3.44 (s, 3H), 3.38 (s, 3H), 1.44 (t, *J* = 7.2 Hz, 3H), 1.19 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 162.8, 157.9, 152.9, 133.9, 122.4, 114.2, 113.2, 71.5, 69.9, 64.5, 56.2, 55.8, 29.6, 15.2 ppm.

5-(5-Ethoxy-2-iodo-4-methoxyphenyl)-5-ethyl-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (123):



123

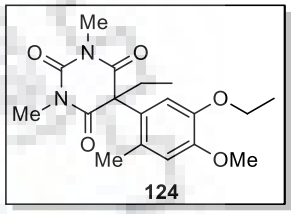
Reaction time: 5 h.

Yield: 99 mg (72%) as colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (s, 1H), 6.77 (s, 1H), 4.09–4.01 (m, 2H), 3.87 (s, 3H), 3.76–3.63 (m, 2H), 3.43 (s, 3H), 3.38 (s, 3H), 1.43 (t, *J* = 4.0 Hz, 3H), 1.18 (t, *J* = 8 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 162.3, 149.2, 148.3, 138.6 ,123.0, 114.5, 93.5, 65.5, 57.4, 56.6, 40.1, 38.2, 25.4, 14.9 ppm.

5-(5-Ethoxy-4-methoxy-2-methylphenyl)-5-ethyl-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (124):



124

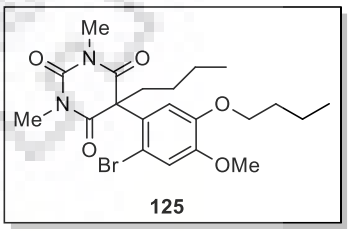
Reaction time: 4 h.

Yield: 84 mg (81%) as colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.76 (s, 1H), 6.70 (s, 1H), 4.11–4.02 (m, 2H), 3.88 (s, 3H), 3.42 (s, 3H), 3.40 (s, 3H), 2.12 (s, 3H), 2.11–2.07 (m, 2H), 1.44 (t, *J* = 4.0 Hz, 3H), 1.12 (t, *J* = 8.0 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 170.3, 153.0, 150.7, 134.1, 124.8, 122.0, 106.4, 103.0, 60.7, 59.7, 56.5, 56.2, 52.2, 29.1, 23.6, 22.3 ppm.

5-(2-Bromo-5-butoxy-4-methoxyphenyl)-5-butyl-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (125):



125

Reaction time: 7 h.

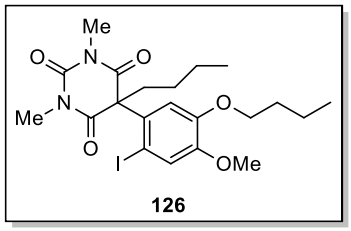
Yield: 93 mg (67%) as colourless solid.

Mp: 168–169 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (s, 1H), 6.77 (s, 1H), 4.00–3.89 (m, 2H), 3.86 (s, 3H), 3.42 (s, 3H), 3.37 (s, 3H), 1.80–1.75 (m, 2H), 1.54–1.43 (m, 5H), 1.28–1.21 (m, 3H), 0.948 (t, *J* = 7.2 Hz, 3H), 0.820 (t, *J* = 7.6 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.6, 158.1, 151.2, 149.9, 147.8, 124.7, 116.9, 115.6, 73.9, 68.9, 56.2, 31.6, 31.1, 29.6, 28.4, 19.1, 18.7, 13.7, 13.4 ppm.

5-(5-Butoxy-2-iodo-4-methoxyphenyl)-5-butyl-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (126):



126

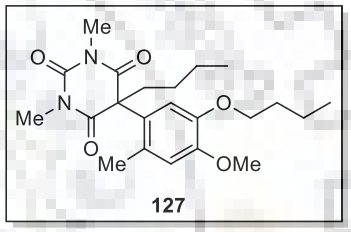
Reaction time: 6 h.

Yield: 103 mg (67%) as colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (s, 1H), 6.76 (s, 1H), 3.97–3.89 (m, 2H), 3.86 (s, 3H), 3.42 (s, 3H), 3.37 (s, 3H), 1.82–1.75 (m, 2H), 1.53–1.41 (m, 5H), 1.28–1.22 (m, 3H), 0.94 (t, *J* = 7.6 Hz, 3H), 1.81 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5, 158.0, 151.1, 149.9, 147.9, 124.7, 117.1, 115.6, 98.0, 73.9, 68.8, 56.1, 31.5, 31.1, 29.6, 28.4, 28.1, 19.1, 18.7, 13.8, 13.4 ppm.

5-(5-Butoxy-4-methoxy-2-methylphenyl)-5-butyl-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (127):



127

Reaction time: 5 h.

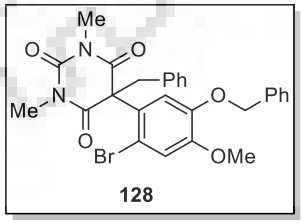
Yield: 86 mg (71%) as colourless solid.

Mp: 185–186 ºC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.74 (s, 1H), 6.67 (s, 1H), 3.97–3.89 (m, 2H), 3.85 (s, 3H), 3.42 (s, 3H), 3.37 (s, 3H), 2.12 (s, 3H), 1.80–1.76 (m, 3H), 1.48–1.44 (m, 4H), 1.24–1.20 (m, 4H), 0.95 (t, *J* = 7.5 Hz, 3H), 0.79 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 163.1, 157.9, 151.3, 149.3, 146.5, 131.1, 122.6, 116.7, 114.8, 113.7, 73.7, 69.0, 55.9, 31.5, 31.3, 29.5, 28.4, 19.5, 19.2, 18.7, 13.8, 13.4 ppm.

5-Benzyl-5-(5-(benzyloxy)-2-bromo-4-methoxyphenyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (128):



128

Reaction time: 3 h.

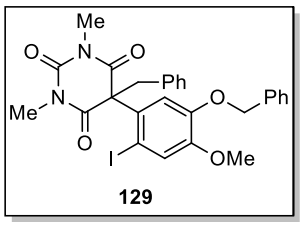
Yield: 124 mg (78%) as colourless solid.

Mp: 193–194 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.46 (m, 2H), 7.41–7.37 (m, 2H), 7.34–7.28 (m, 5H), 7.07 (s, 1H), 6.99–6.97 (m, 2H), 5.21 (s, 2H), 3.86 (s, 3H), 3.54 (s, 2H), 3.08 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 150.3, 147.5, 136.5, 132.8, 130.3, 129.2, 128.7, 128.6, 128.4, 128.2, 127.6, 117.1, 116.3, 114.5, 71.9, 61.6, 56.3, 45.9, 29.7, 28.2 ppm.

5-Benzyl-5-(5-(benzyloxy)-2-iodo-4-methoxyphenyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (129):



129

Reaction time: 3 h.

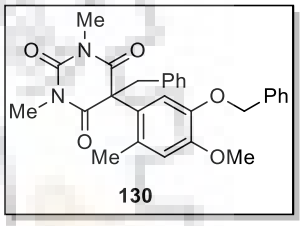
Yield: 134 mg (77%) as yellow solid.

Mp: 294–295 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.41 (m, 2H), 7.38–7.34 (m, 1H), 7.31–7.26 (m, 2H), 7.21–7.15 (m, 5H), 6.87 (s, 2H), 5.16 (s, 2H), 3.88 (s, 3H), 3.66 (s, 2H), 3.13 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ170.9, 151.1, 149.1, 146.0, 133.6, 129.6, 128.4, 127.9, 121.8, 117.9, 115.2, 114.4, 70.5, 58.7, 55.7, 44.3, 28.3, 19.6 ppm.

5-Benzyl-5-(5-(benzyloxy)-4-methoxy-2-methylphenyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (130):



130

Reaction time: 2 h.

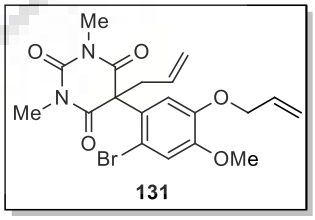
Yield: 117 mg (83%) as colourless solid.

Mp: 178–180 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49–7.48 (m, 2H), 7.39–7.37 (m, 2H), 7.33–7.24 (m, 5H), 6.99 (s, 1H), 6.98 (s, 2H), 5.21 (s, 2H), 3.86 (s, 3H), 3.59 (s, 2H), 3.08 (s, 6H), 1.94 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.5, 151.3, 148.6, 146.3, 137.7 , 136.3, 131.8, 130..5, 128.6, 128.3, 127.1, 127.9, 123.7, 118.5, 110.6, 57.5 ppm.

5-Allyl-5-(5-(allyloxy)-2-bromo-4-methoxyphenyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (131):



131

Reaction time: 4 h.

Yield: 104 mg (80%) as colourless solid.

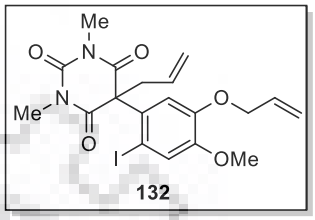
Mp: 194–195 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (s, 1H), 7.02 (s, 1H), 6.13–6.03 (m, 1H), 5.69–5.59 (m, 1H), 5.42 (dd, *J* = 1.6, 17.6 Hz, 1H), 5.32 (dd, *J* = 1.2, 10.4 Hz, 1H), 5.25 (d, *J* = 6.8 Hz,

1H), 5.23 (s, 1H), 4.65 (d, *J* = 5.2 Hz, 2H), 3.84 (s, 3H), 3.33 (s, 6H), 3.07 (d, *J* = 7.2 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 151.3, 150.0, 147.4, 132.9, 129.8, 129.3, 121.9, 118.4, 116.9, 115.5, 114.3, 70.5, 60.4, 56.1, 44.0, 28.5 ppm.

5-Allyl-5-(5-(allyloxy)-2-iodo-4-methoxyphenyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (132):



132

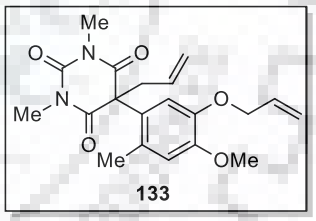
Reaction time: 4 h.

Yield: 118 mg (82%) as colourless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.47 (s, 1H), 6.46 (s, 1H), 6.05–5.97 (m, 1H), 5.68–5.60 (m, 1H), 5.38 (dd, *J* = 17.0, 31.0 Hz, 1H), 5.27 (dd, *J* = 1.0, 10.5 Hz, 1H), 5.22 (d, *J* = 17.0 Hz, 1H), 5.11 (d, *J* = 10.5 Hz, 1H), 4.55 (d, *J* = 5.0 Hz, 1H) 3.82 (s, 3H), 3.33 (s, 3H), 3.10 (d, *J* = 7.0Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): 168.5, 153.6, 152.4, 150.8, 133.1, 132.3, 131.8, 120.7, 117.8 114.8, 105.6, 103.7, 70.2, 61.1, 60.7, 56.3, 41.0, 28.9 ppm.

5-Allyl-5-(5-(allyloxy)-4-methoxy-2-methylphenyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (133):



133

Reaction time: 3 h.

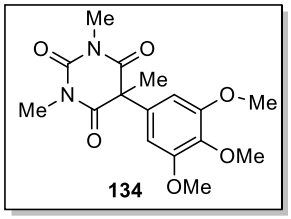
Yield: 98 mg (88%) as colourless solid.

Mp: 109–110 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (s, 1H), 6.65 (s, 1H), 6.15–6.06 (m, 1H), 5.68–5.57 (m, 1H), 5.42 (dd, *J* = 1.2, 17.2 Hz, 1H), 5.29 (dd, *J* = 1.2, 10.4 Hz, 1H), 5.25–5.20 (m, 2H), 4.64 (d, *J* = 5.6 Hz, 2H), 3.83 (s, 3H), 3.34 (s, 6H), 3.13 (d, *J* = 7.2 Hz, 2H), 1.84 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 151.1, 149.2, 146.0, 133.6, 129.6, 128.4, 127.9, 121.8, 117.8, 115.2, 114.4, 70.6, 58.6, 55.8, 44.3, 28.5, 19.6 ppm.

1,3,5-Trimethyl-5-(3,4,5-trimethoxyphenyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (134):



134

Reaction time: 8 h.

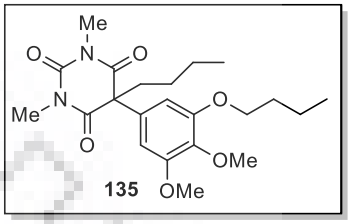
Yield: 78 mg (78%) as colourless solid.

Mp: 1456–146 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.40 (s, 2H), 3.82 (s, 9H), 3.34 (s, 6H), 1.84 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 153.5, 151.1, 138.2, 134.1, 102.9, 60.8, 56.1, 29.1, 22.4 ppm.

5-(3-Butoxy-4,5-dimethoxyphenyl)-5-butyl-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (135):



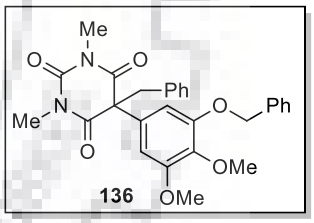
Reaction time: 9 h.

Yield: 81 mg (64%) as colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.42 (s, 2H), 3.94 (t, *J* = 5.2 Hz, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.34 (s, 3H), 2.35–2.32 (m, 2H), 1.78–1.70 (m, 2H), 1.49–1.45 (m, 2H), 1.36–1.32 (m, 2H), 1.19–1.13 (m, 2H), 0.953 (t, *J* = 6.0 Hz, 3H), 0.875 (t, *J* = 6.0 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 153.4, 152.9, 150.9, 138.7, 133.2, 114.9, 104.8, 103.3, 68.9, 61.1, 60.6, 56.2, 37.2, 31.2, 28.9, 28.1, 22.8, 19.2, 13.8, 13.7 ppm.

5-Benzyl-5-(3-(benzyloxy)-4,5-dimethoxyphenyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (136):



Reaction time: 12 h.

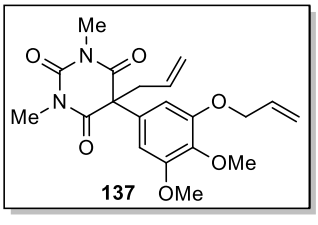
Yield: 106 mg (73%) as colourless solid.

Mp: 150–151 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.35 (m, 4H), 7.32–7.29 (m, 1H), 7.24–7.22 (m, 3H), 7.16–7.14 (m, 2H), 6.61 (s, 1H), 6.49 (s, 1H), 5.13 (s, 2H), 3.87 (s, 6H), 3.68 (s, 2H), 3.14 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 153.6, 152.4, 150.3, 136.8, 135.0, 133.0, 130.0, 128.6, 128.5, 127.9, 127.6, 127.3, 106.8, 104.5, 71.5, 62.1, 60.8, 56.3, 43.0, 28.7 ppm.

5-Allyl-5-(3-(allyloxy)-4,5-dimethoxyphenyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (137):



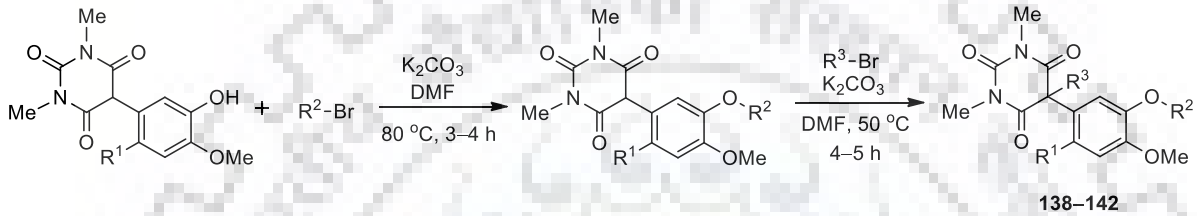
Reaction time: 7 h.

Yield: 87 mg (75%) as colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.45 (s, 1H), 6.44 (s, 1H), 6.03–5.95 (m, 1H), 5.66–5.58 (m, 1H), 5.36 (d, *J* = 13.6 Hz, 1H), 5.26–5.18 (m, 2H), 5.09 (d, *J* = 8.0 Hz, 1H), 4.54 (d, *J* = 3.6 Hz, 2H), 3.81 (s, 6H), 3.31 (s, 6H), 3.08 (d, *J* = 5.6 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 153.5, 152.3, 150.8, 138.9, 133.1, 132.4, 131.7, 120.8, 117.8, 114.9, 105.6, 103.7, 70.1, 60.9, 60.6, 56.2, 40.9, 28.9 ppm.

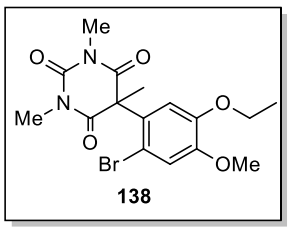
3.2.10 General procedure for the synthesis of C-5 disubstituted barbituric acids 138–142:



138–142

C-5 aryl barbituric acid (0.3 mmol, 1 equiv) was added to the already stirred solution of K_2CO_3 (0.60 mmol, 2.0 equiv) in DMF and the contens were stirred for 10 min. To this, first alkyl halide (0.45 mmol, 1.5 equiv) was added and the resulting mixture was stirred at 80 °C. After the completion of the reaction (typically 3–4 h), as monitored by the TLC, another portion of K_2CO_3 (0.60 mmol, 2.0 equiv) was added to the mixture followed by the addition of second different alkyl halide (0.45 mmol, 1.5 equiv) and the resulting mixture was stirred at 50 °C. After the completion of the reaction (typically 4–5 h), as monitored by the TLC. The mixture was quenched with HCl 0.1 M and then extracted with CH_2Cl_2 (3 × 10 mL), dried over sodium sulfate. The solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluent: hexanes/ethyl acetate 3:1).

5-(2-Bromo-4,5-dimethoxyphenyl)-5-ethyl-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (138):



138

Reaction time: 7 h.

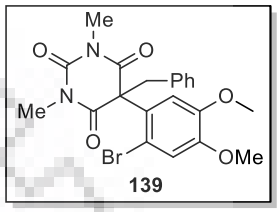
Yield: 75 mg (63%) as colourless solid.

Mp: 171–172 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (s, 1H), 7.02 (s, 1H), 4.14 (q, *J* = 6.8 Hz, 2H), 3.84 (s, 3H), 3.37 (s, 6H), 1.94 (s, 3H), 1.47 (s, *J* = 6.8 Hz, 3H,).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 151.3, 149.9, 147.8, 129.7, 116.4, 114.5, 113.9, 64.8, 56.8, 56.2, 29.0, 28.2, 25.8, 14.8 ppm.

5-Benzyl-5-(2-bromo-4,5-dimethoxyphenyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (139):



139

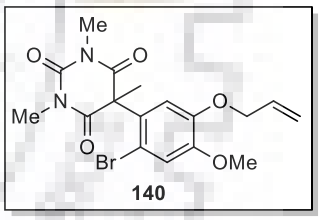
Yield: 94 mg (68%) as colourless solid.

Mp: 179–180 ^{o}C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31–7.23 (m, 5H), 7.05–7.02 (m, 2H), 3.98 (s, 3H), 3.87 (s, 3H), 3.70 (s, 2H), 3.09 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 150.3, 149.5, 148.4, 132.7, 129.2, 128.6, 128.4, 116.6, 113.8, 112.7, 61.7, 56.2, 46.1, 28.2 ppm.

5-(5-(Allyloxy)-2-bromo-4-methoxyphenyl)-1,3,5-trimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (140):



140

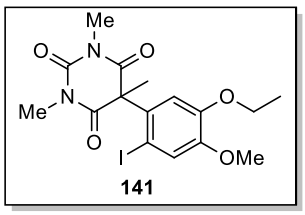
Yield: 87 mg (71%) as colourless solid.

Mp: 152–153 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (s, 1H), 7.03 (s, 1H), 6.15–6.06 (m, 1H), 5.44–5.31 (m, 2H), 4.71–4.62 (m, 2H), 3.85 (s, 3H), 3.37 (s, 6H), 1.92 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 150.1, 147.4, 132.9, 129.7, 118.4, 116.6, 115.4, 114.4, 70.4, 56.8, 56.2, 29.0, 25.8 ppm.

5-(5-(Ethoxy-2-iodo-4-methoxyphenyl)-1,3,5-trimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (141):



141

Yield: 81 mg (61%) as colourless solid.

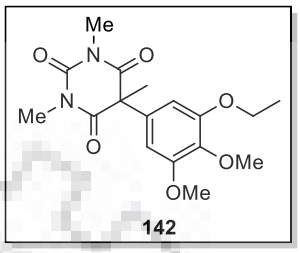
Mp: 162–163 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (s, 1H), 7.00 (s, 1H), 4.13 (q,

J = 7.2 Hz, 2H), 3.84 (s, 3H), 3.38 (s, 6H), 1.95 (s, 3H), 1.47 (t, *J* = 6.8 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 149.7, 148.5, 133.3, 123.1, 114.8, 103.6, 87.5, 64.7, 59.6, 56.2, 29.1, 26.5, 14.7 ppm.

5-(3-ethoxy-4,5-dimethoxyphenyl)-1,3,5-trimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (142):



142

Yield: 74 mg (71%) as colourless liquid.

Mp: 152–153 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.34 (s, 2H), 4.02 (q, *J* = 7.0 Hz, 2H), 3.18 (s, 3H), 3.80 (s, 3H), 3.36 (s, 6H), 1.82 (s, 3H), 1.40 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 153.5, 152.8, 151.1, 138.8, 133.9, 114.9, 104.6, 103.1, 64.7, 60.6, 56.5, 56.3, 29.1, 22.1, 14.8 ppm.

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NMR Spectra for Selected Compounds

Figure S-1: ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of **10**.

Figure S-2: ^{13}C NMR (500 MHz, $CDCl_3$) Spectrum of **10**.

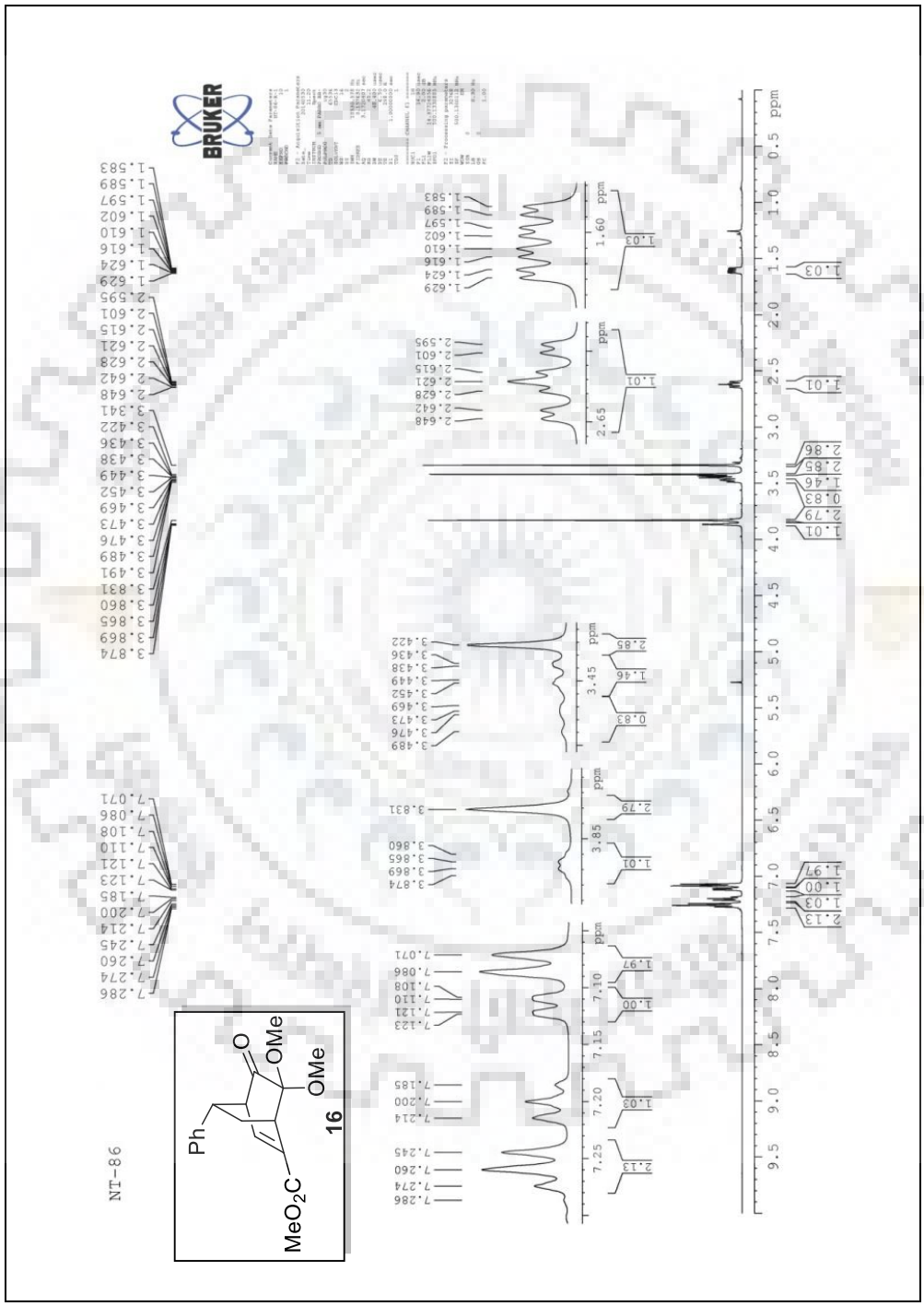


Figure S-3: ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of **16**.

Figure S-4: ^{13}C NMR (500 MHz, $CDCl_3$) Spectrum of **16**.

Figure S-5: ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of **20**.

Figure S-6: ^{13}C NMR (500 MHz, $CDCl_3$) Spectrum of **20**.

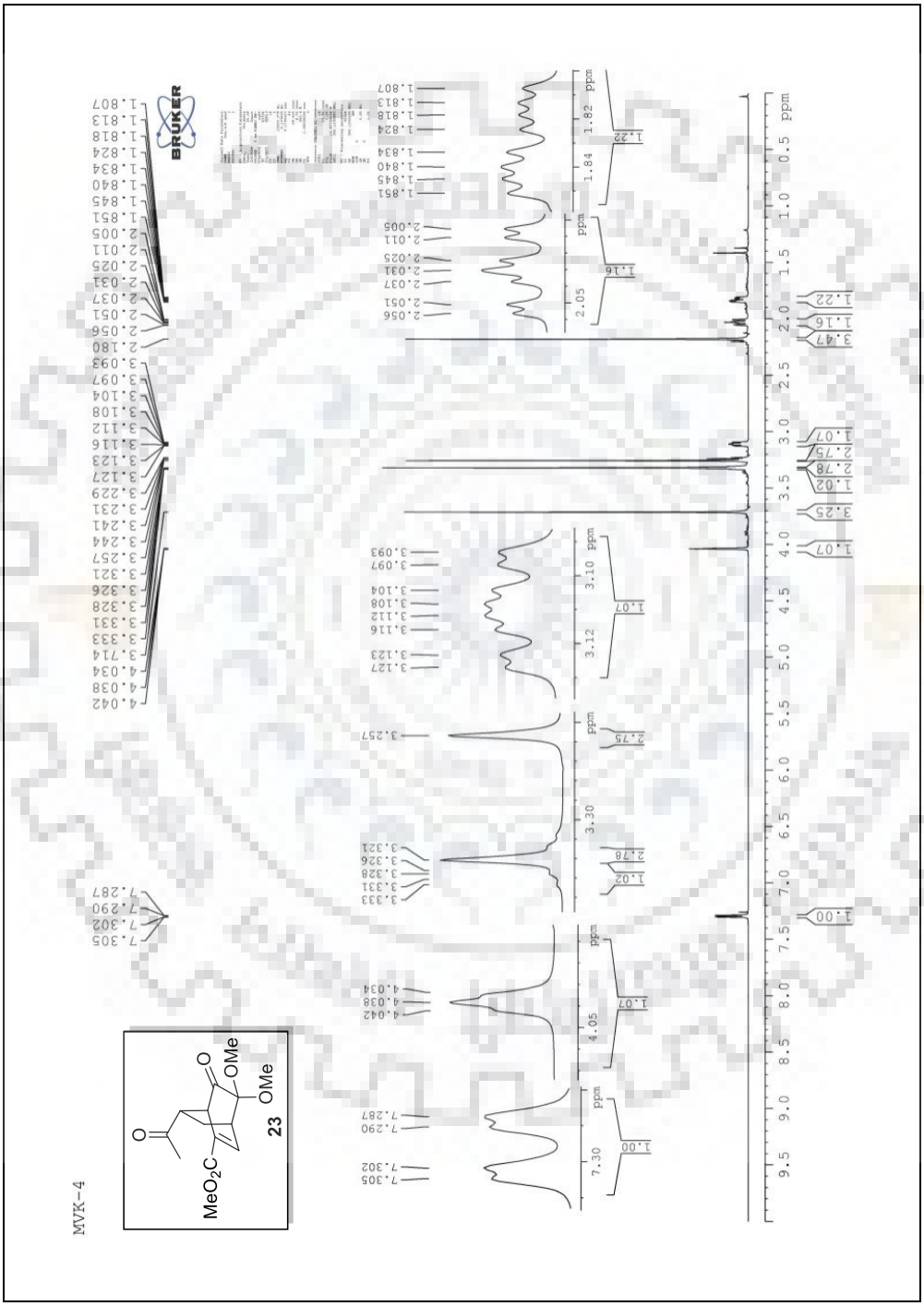


Figure S-7: ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of **23**.

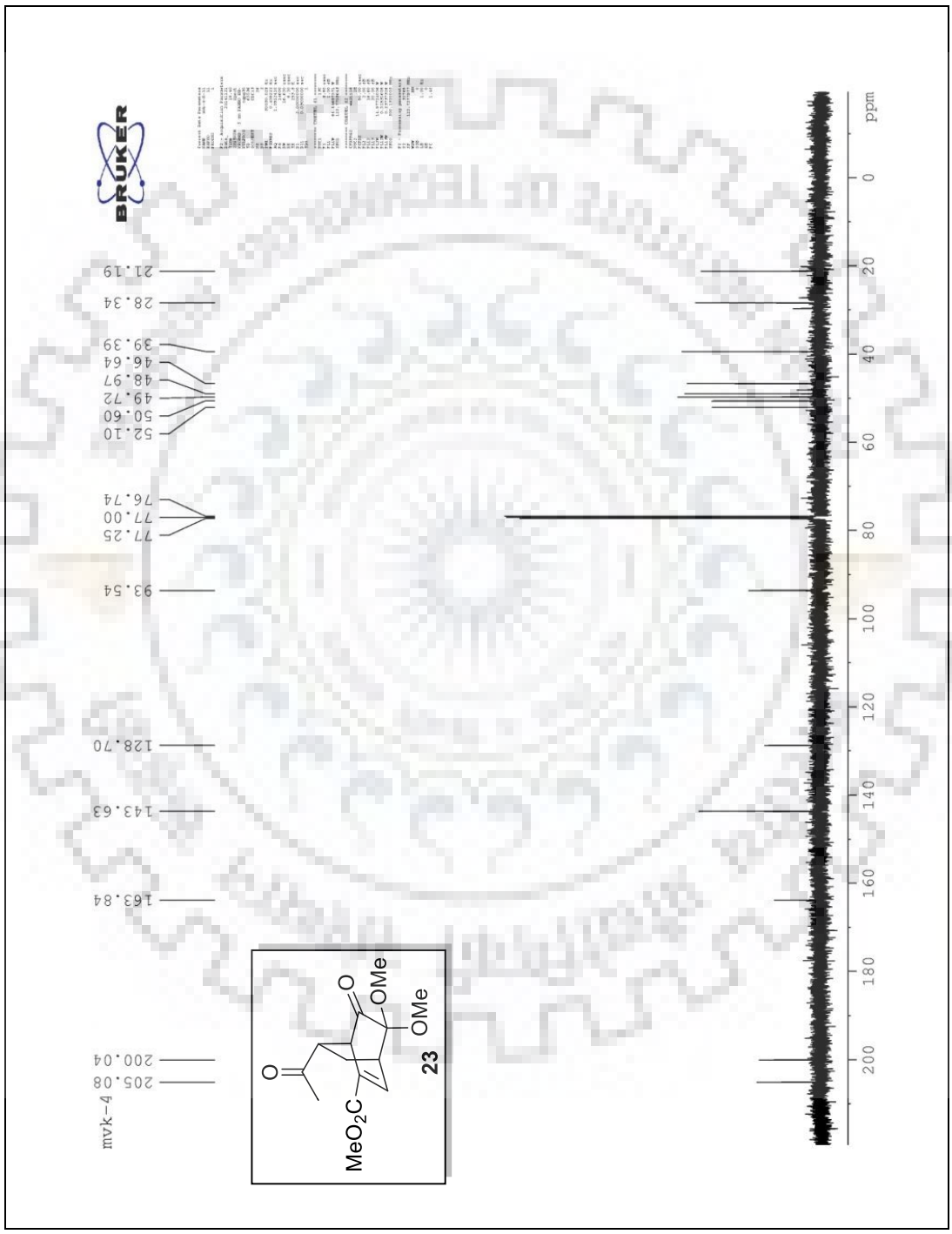


Figure S-8: ^{13}C NMR (500 MHz, $CDCl_3$) Spectrum of **23**.

Figure S-9: ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of **25**.

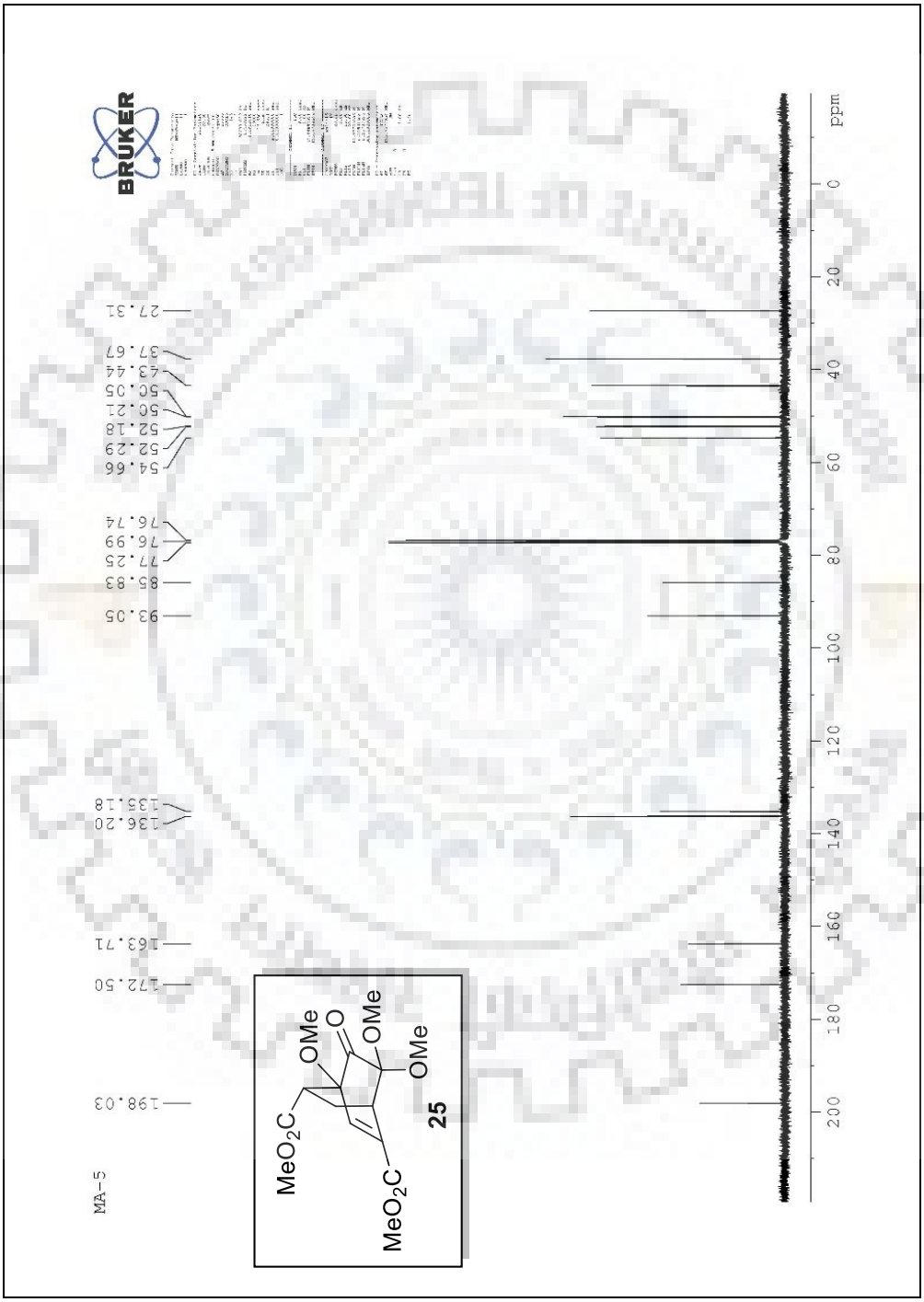


Figure S-10: ^{13}C NMR (500 MHz, $CDCl_3$) Spectrum of **25**.

Figure S-11: ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of **29**.

Figure S-12: ^{13}C NMR (500 MHz, $CDCl_3$) Spectrum of **29**.

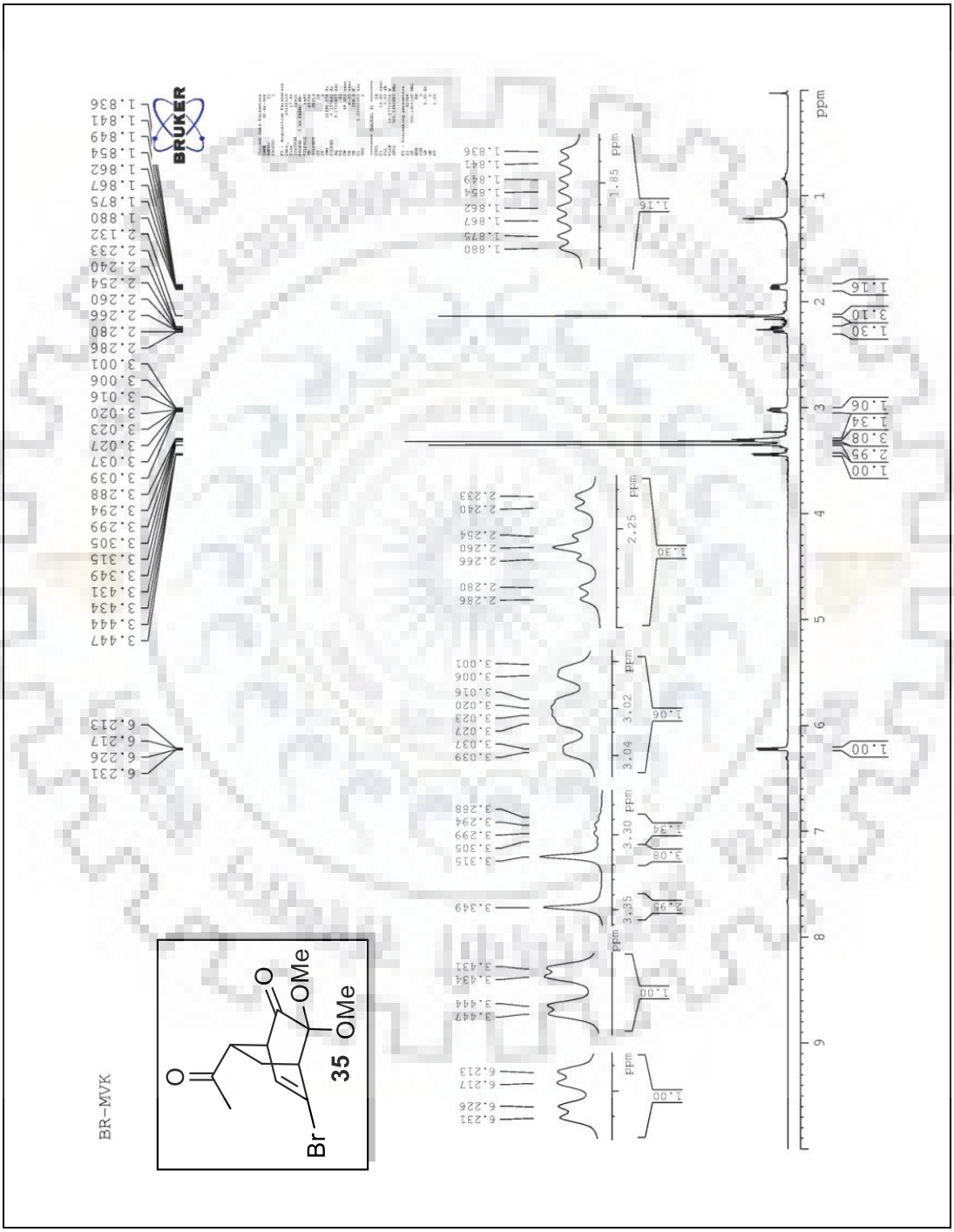


Figure S-13: ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of **35**.

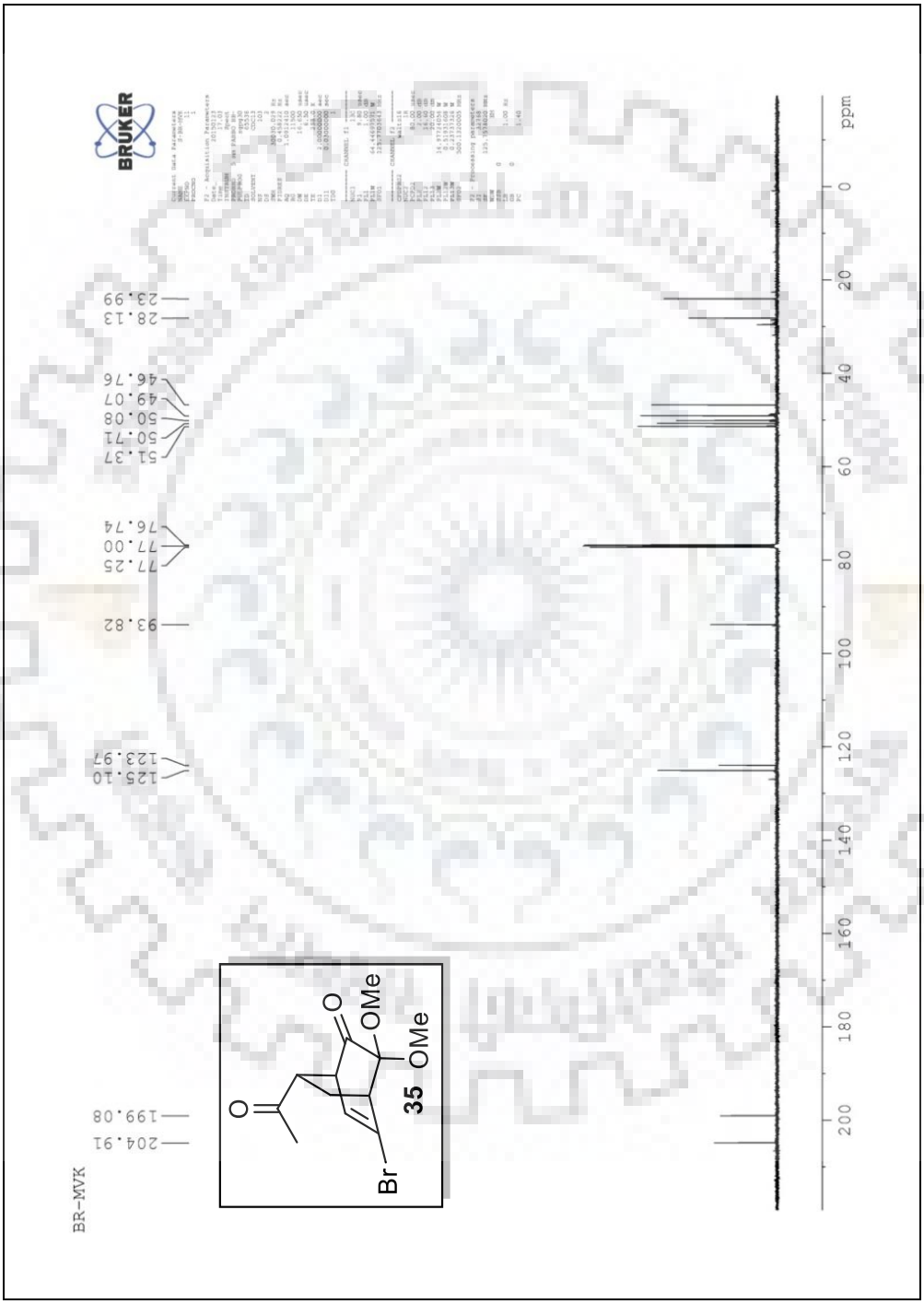


Figure S-14: ^{13}C NMR (500 MHz, $CDCl_3$) Spectrum of **35**.

Figure S-15: ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of **43**.

Figure S-16: ^{13}C NMR (500 MHz, $CDCl_3$) Spectrum of **43**.

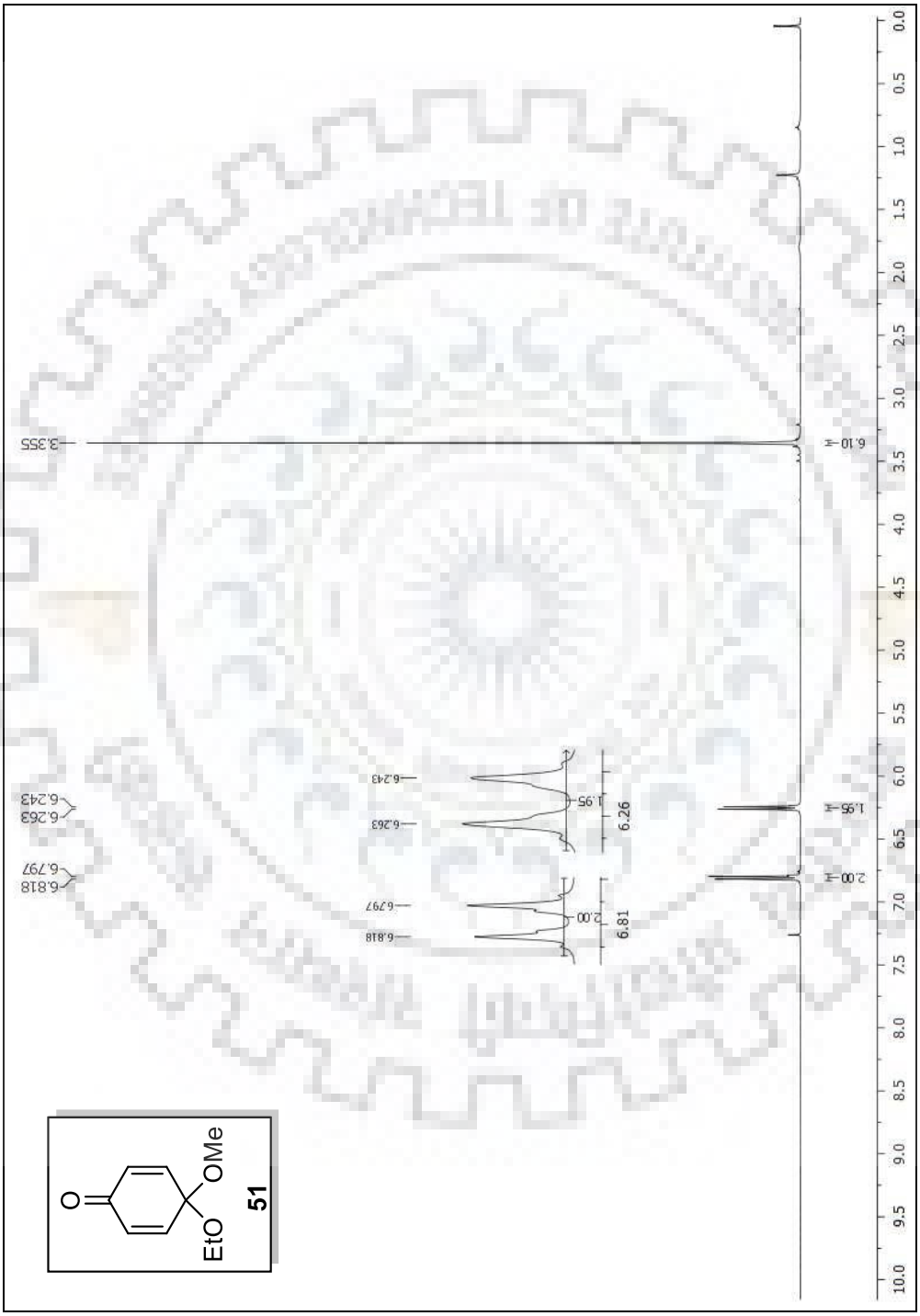


Figure S-17: ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of **51**.

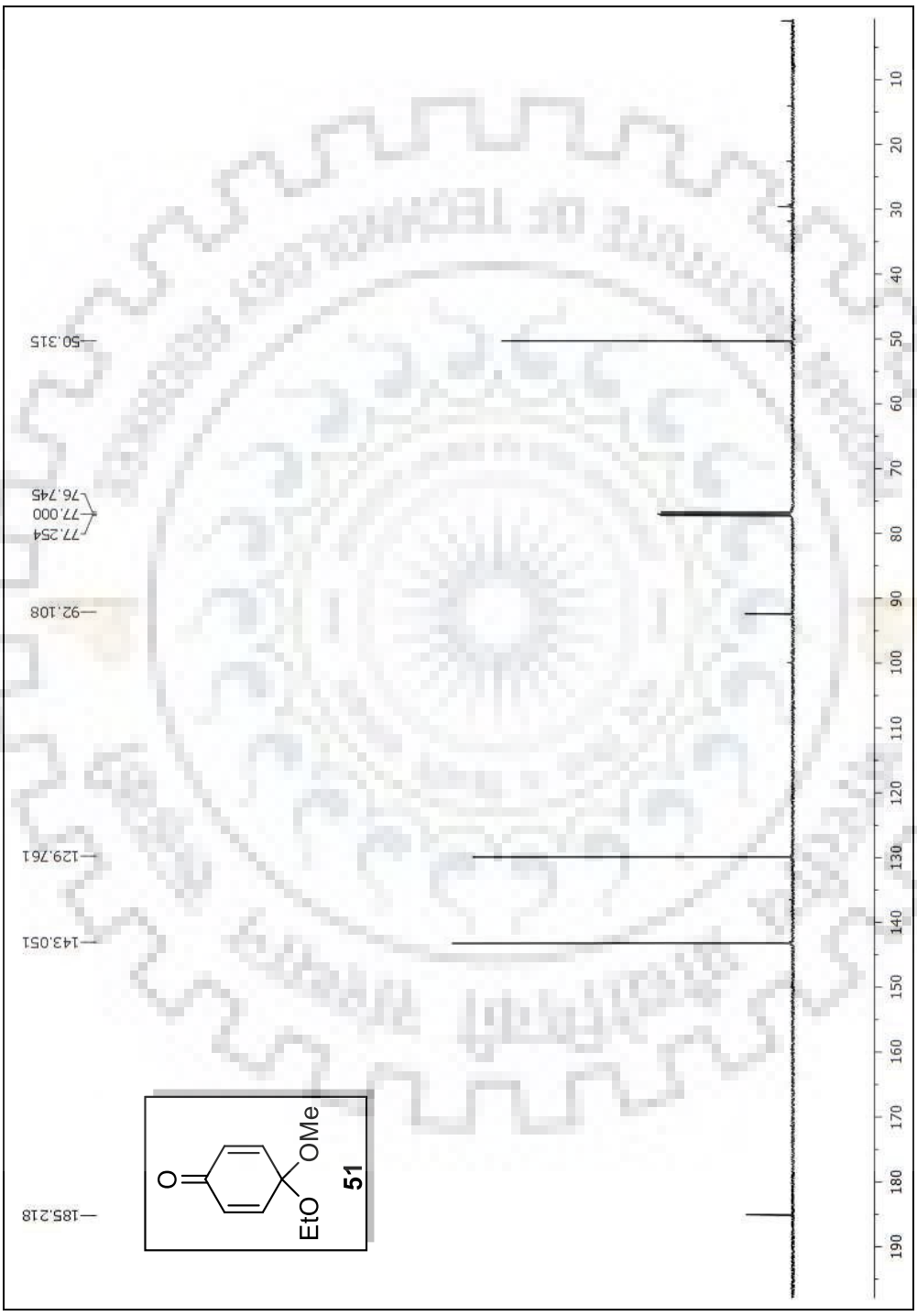


Figure S-18: ^{13}C NMR (500 MHz, $CDCl_3$) Spectrum of **51**.

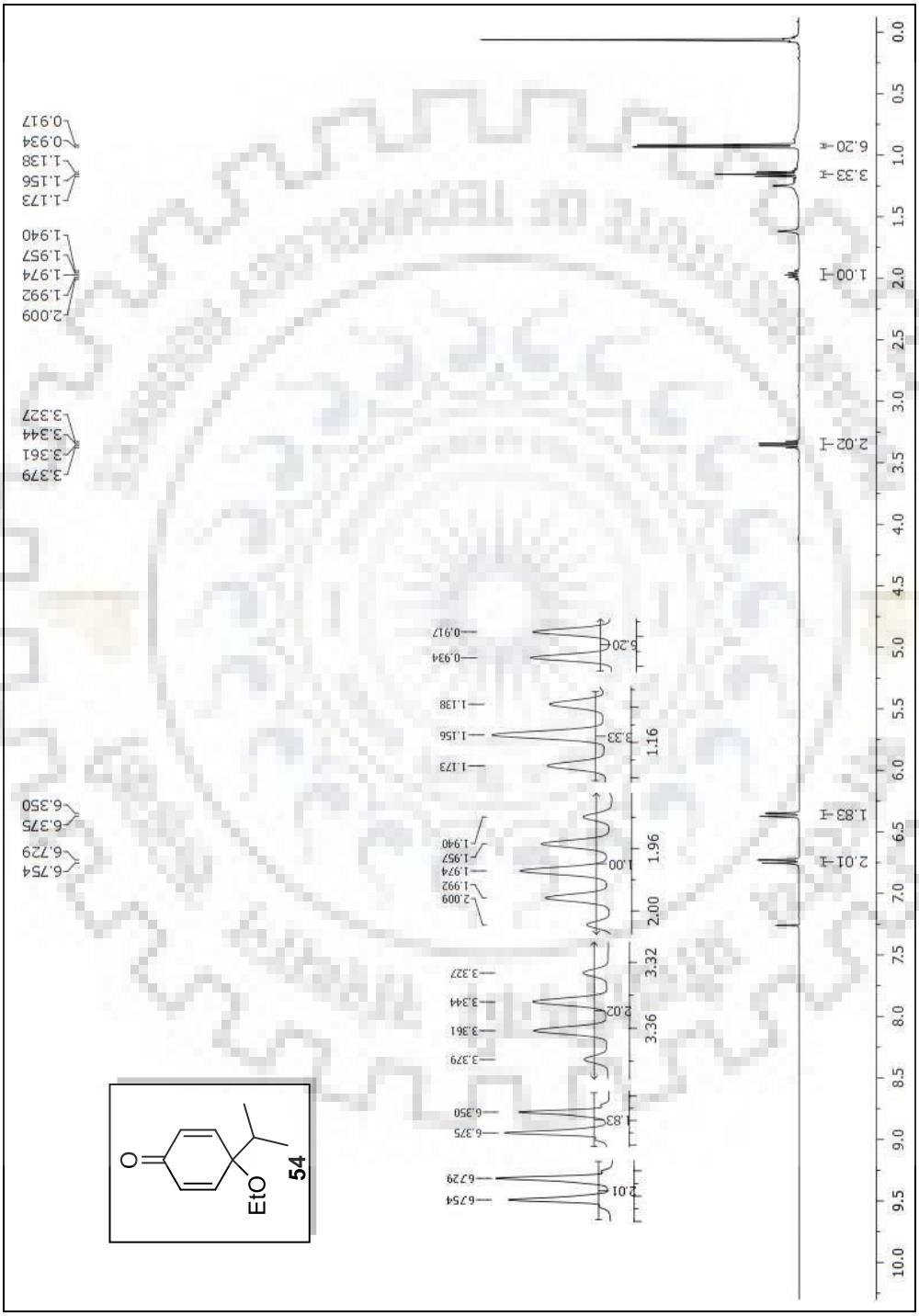


Figure S-19: ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of **54**.

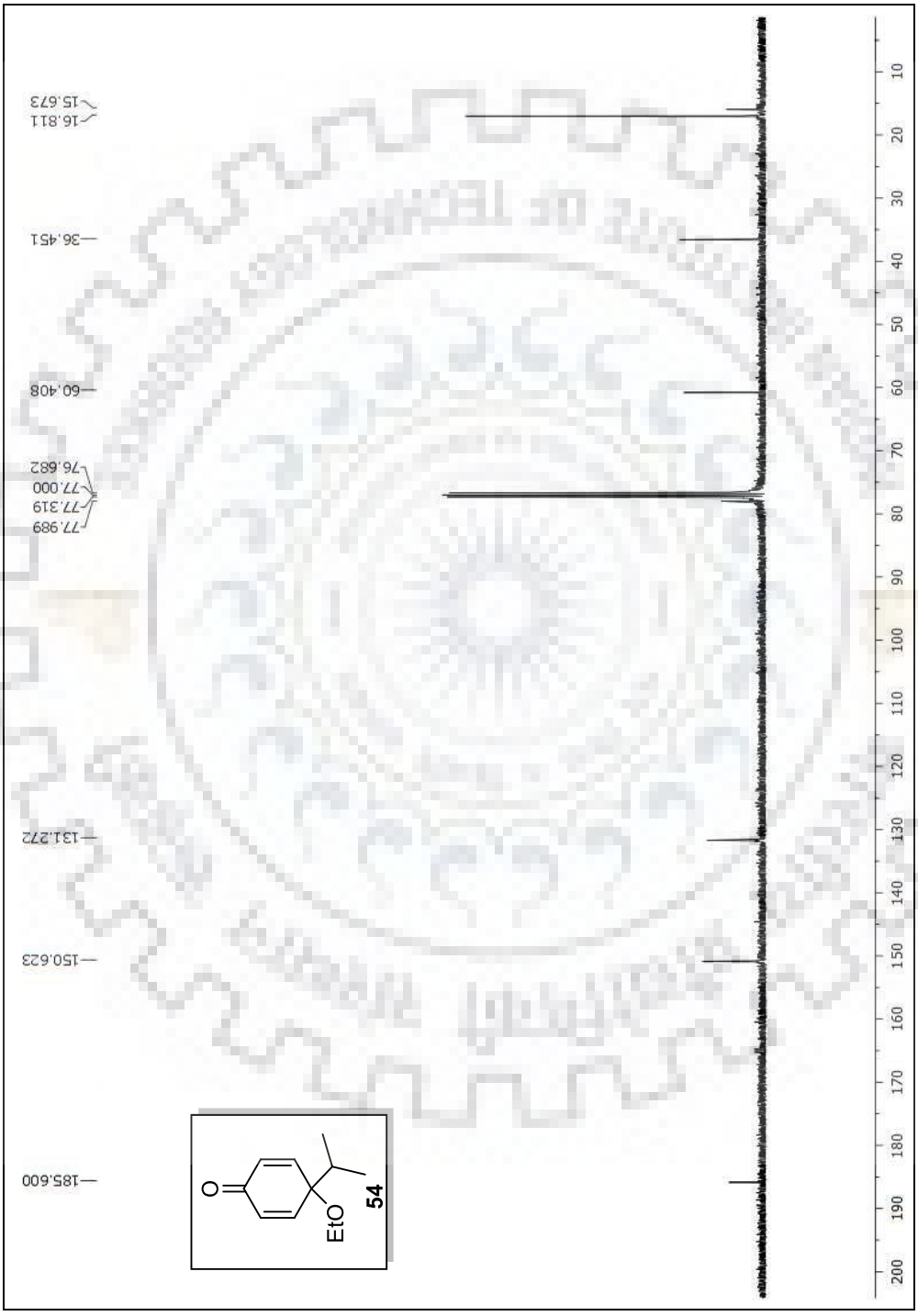


Figure S-20: ^{13}C NMR (500 MHz, $CDCl_3$) Spectrum of **54**.

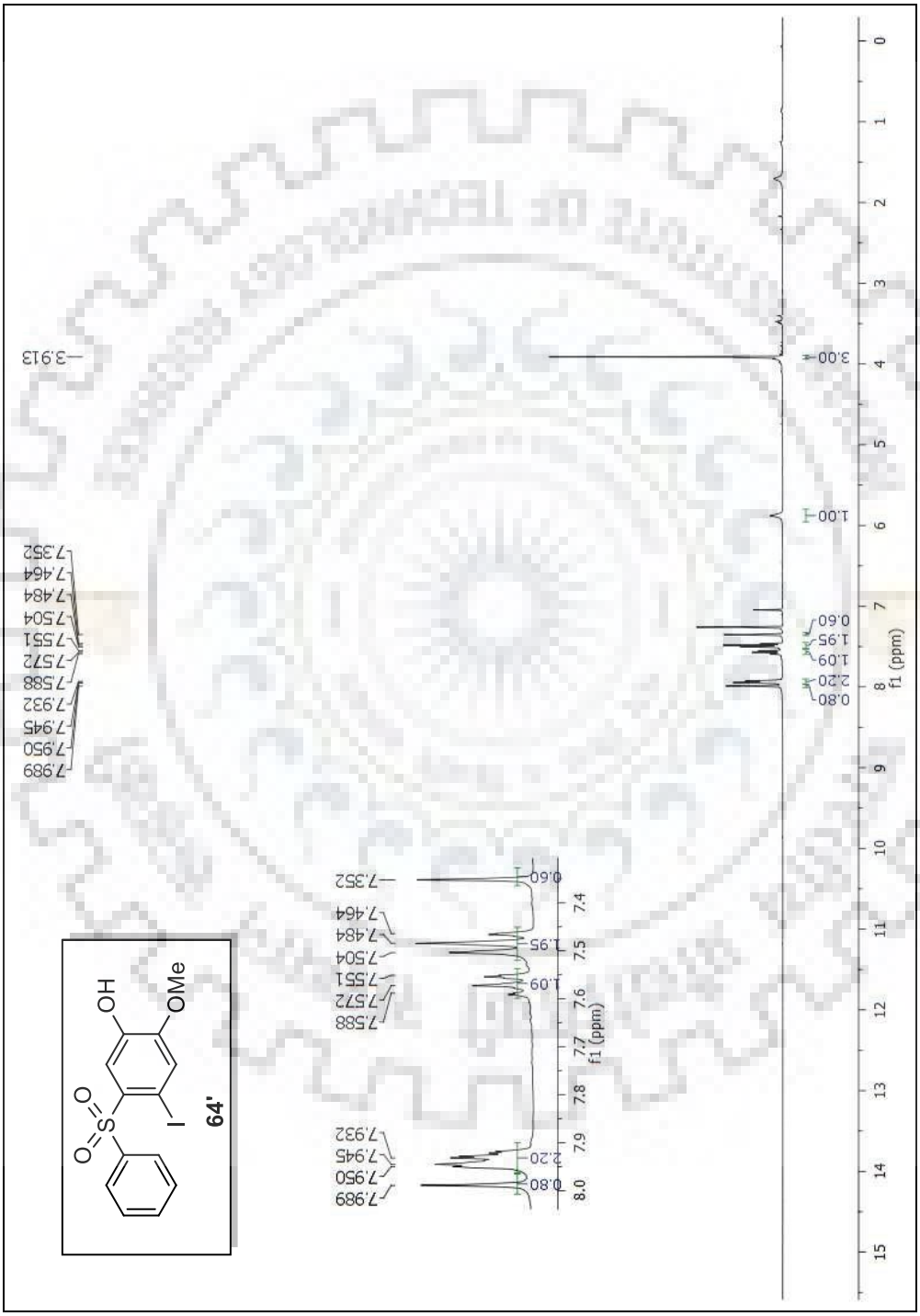


Figure S-21: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **64'**.

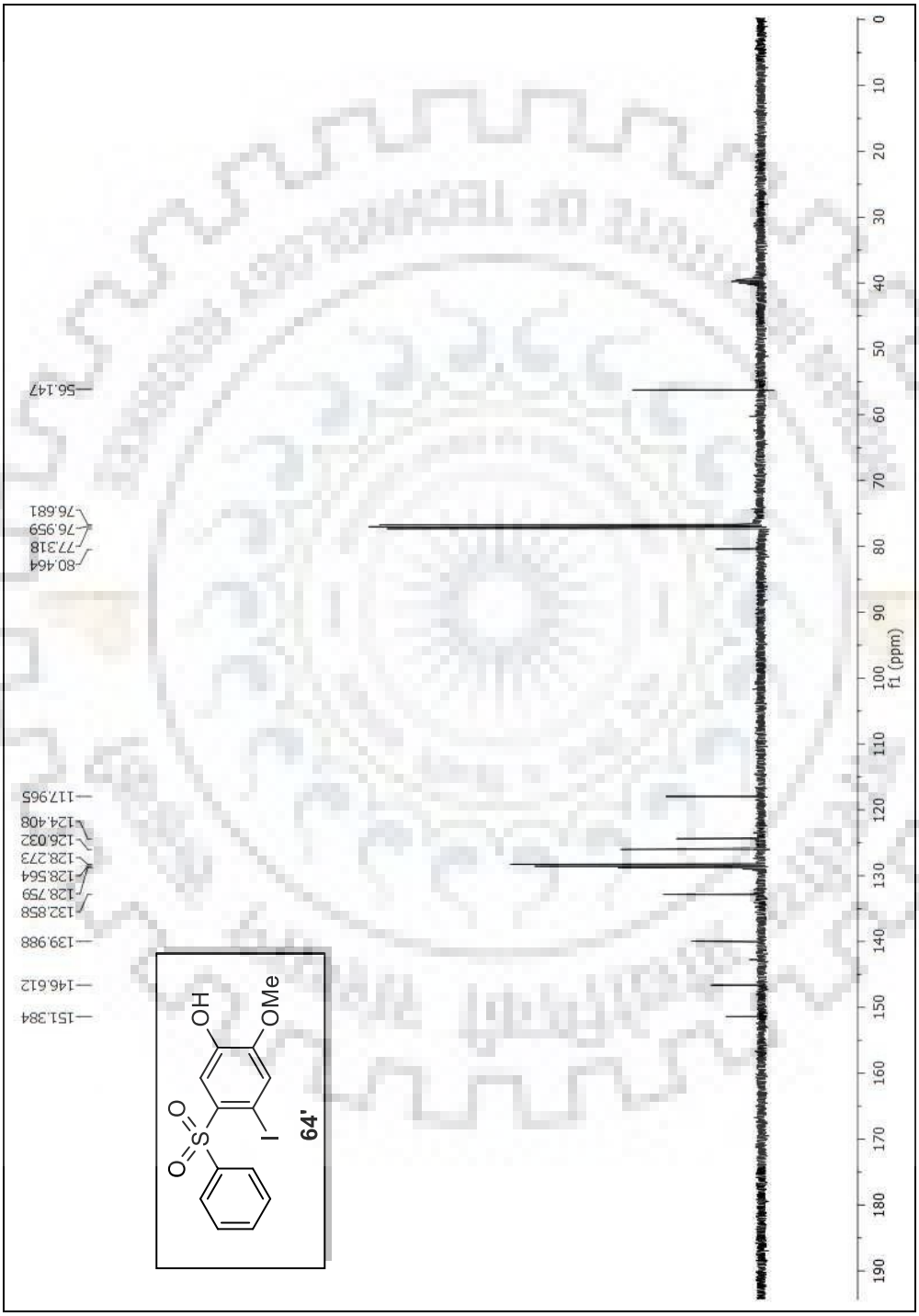


Figure S-22: ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of **64'**.

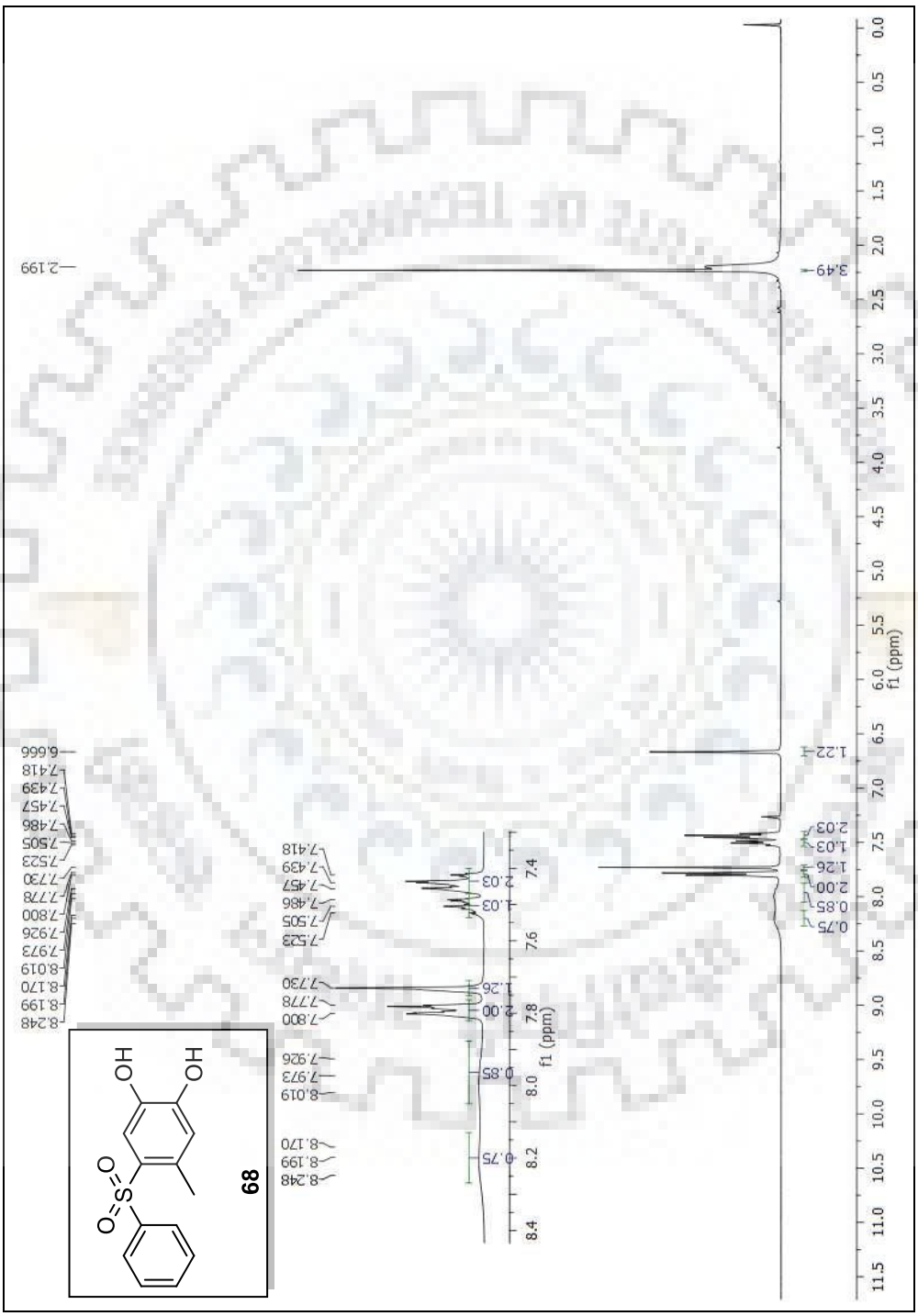


Figure S-23: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **68**.

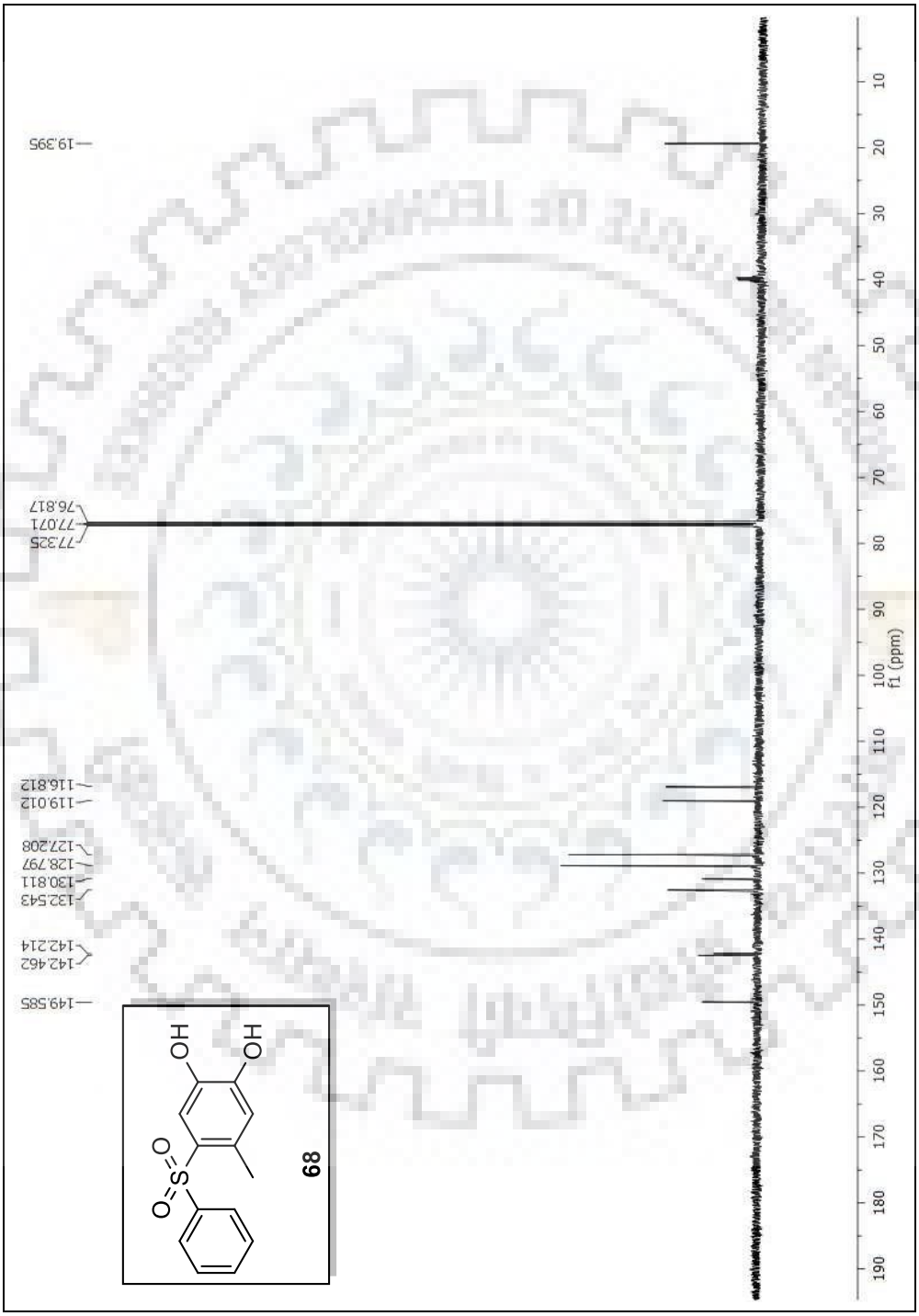


Figure S-24: ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of **68**.

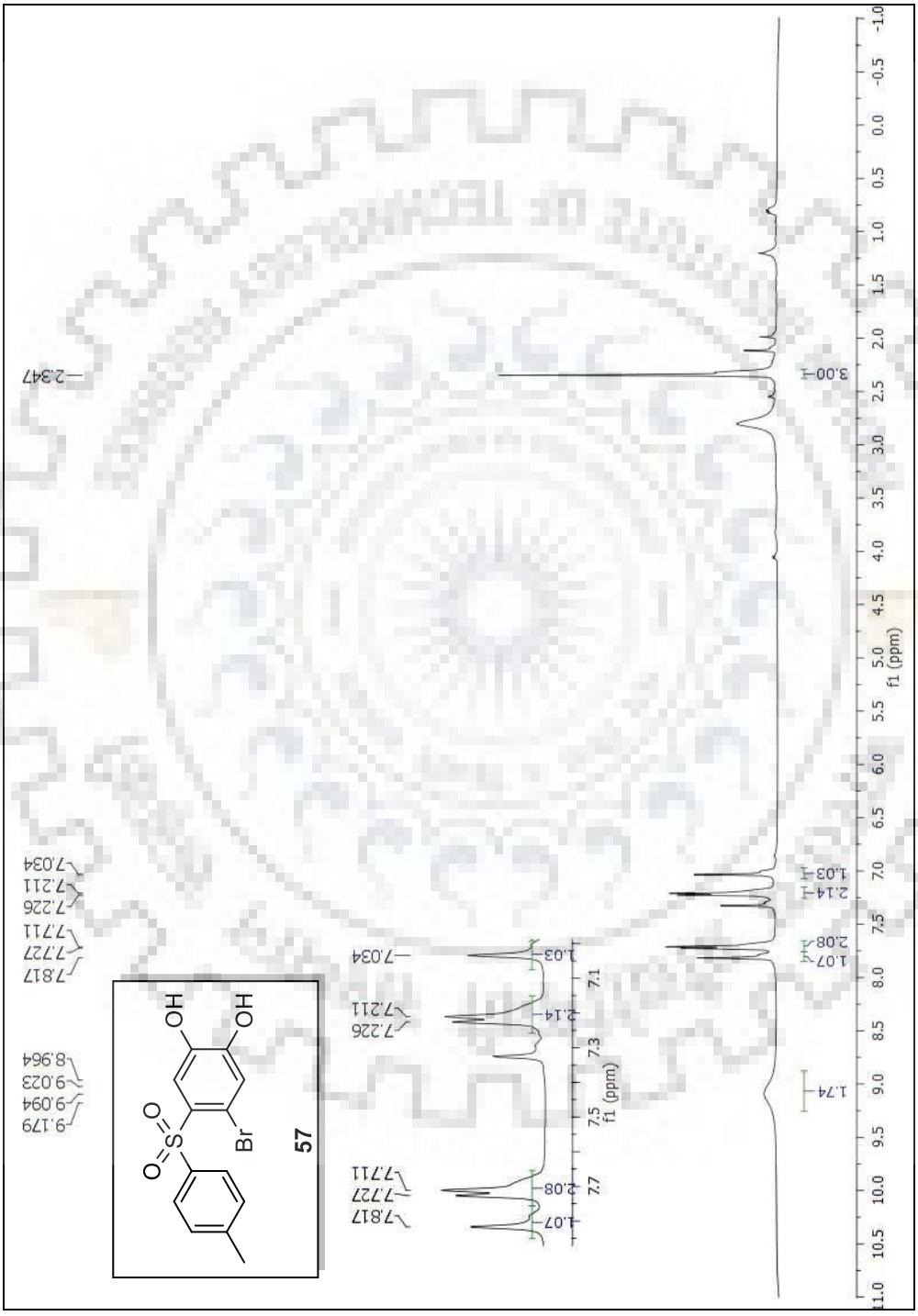


Figure S-25: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **57**.

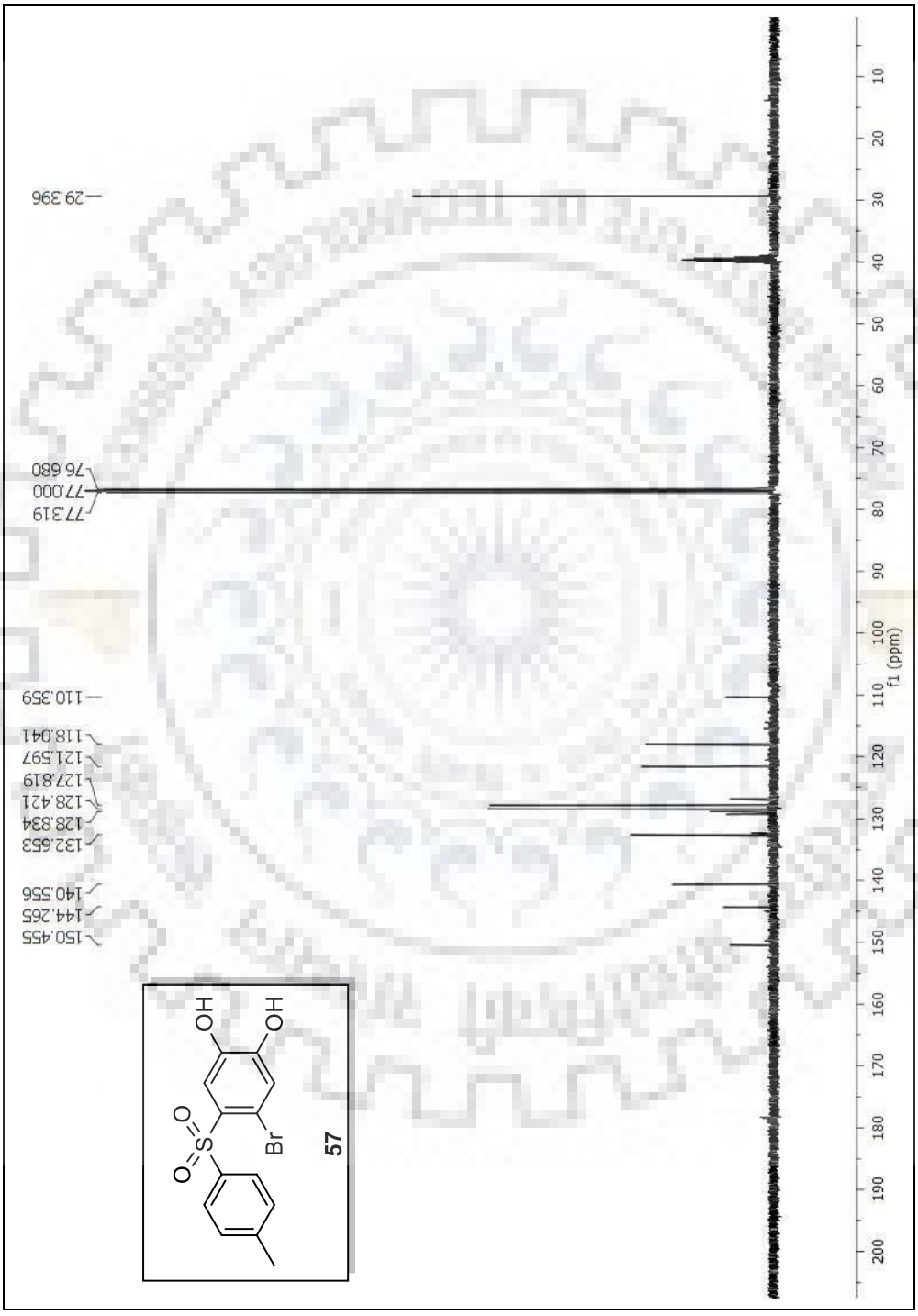


Figure S-26: ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of **57**.

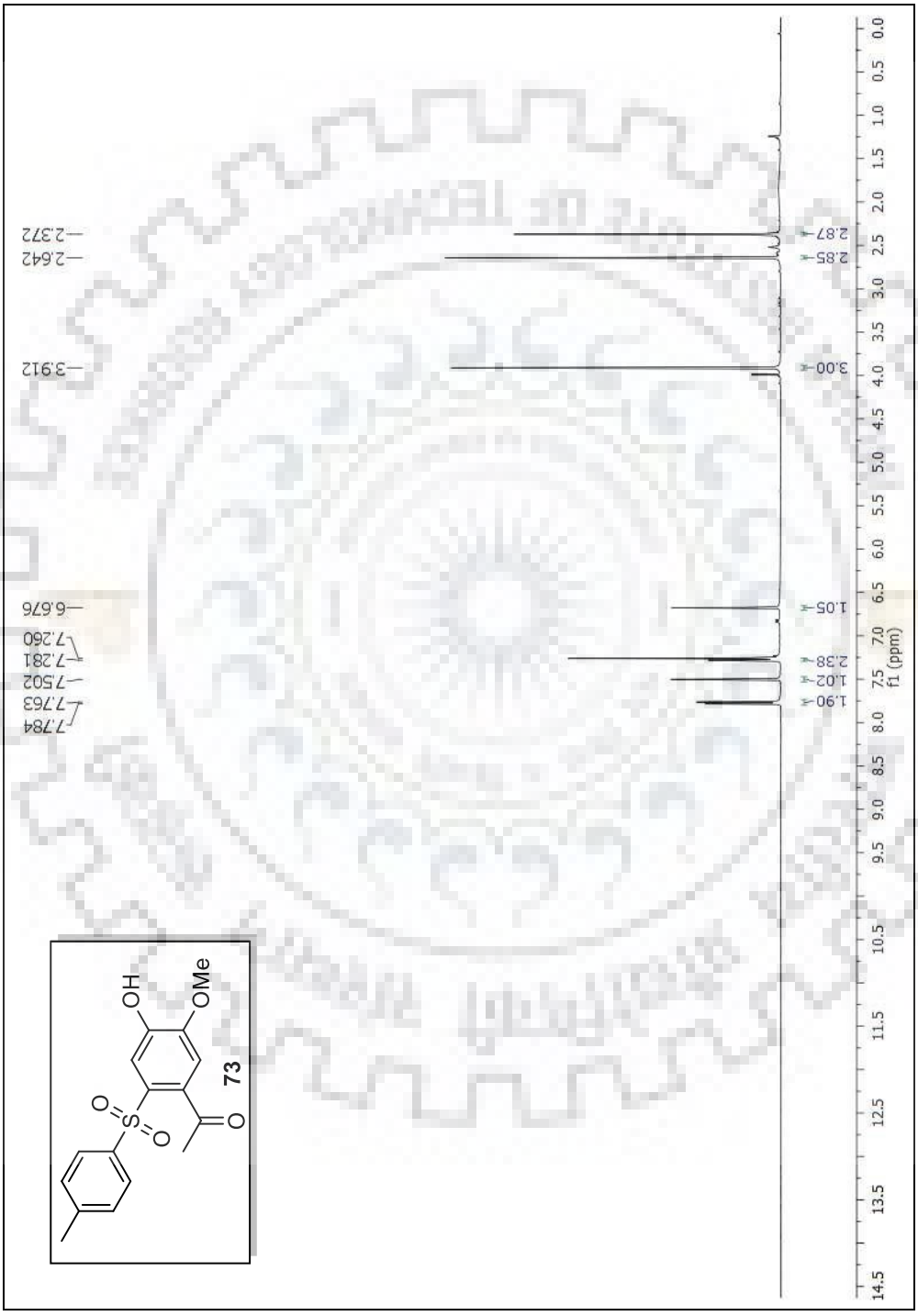


Figure S-27: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **73**.

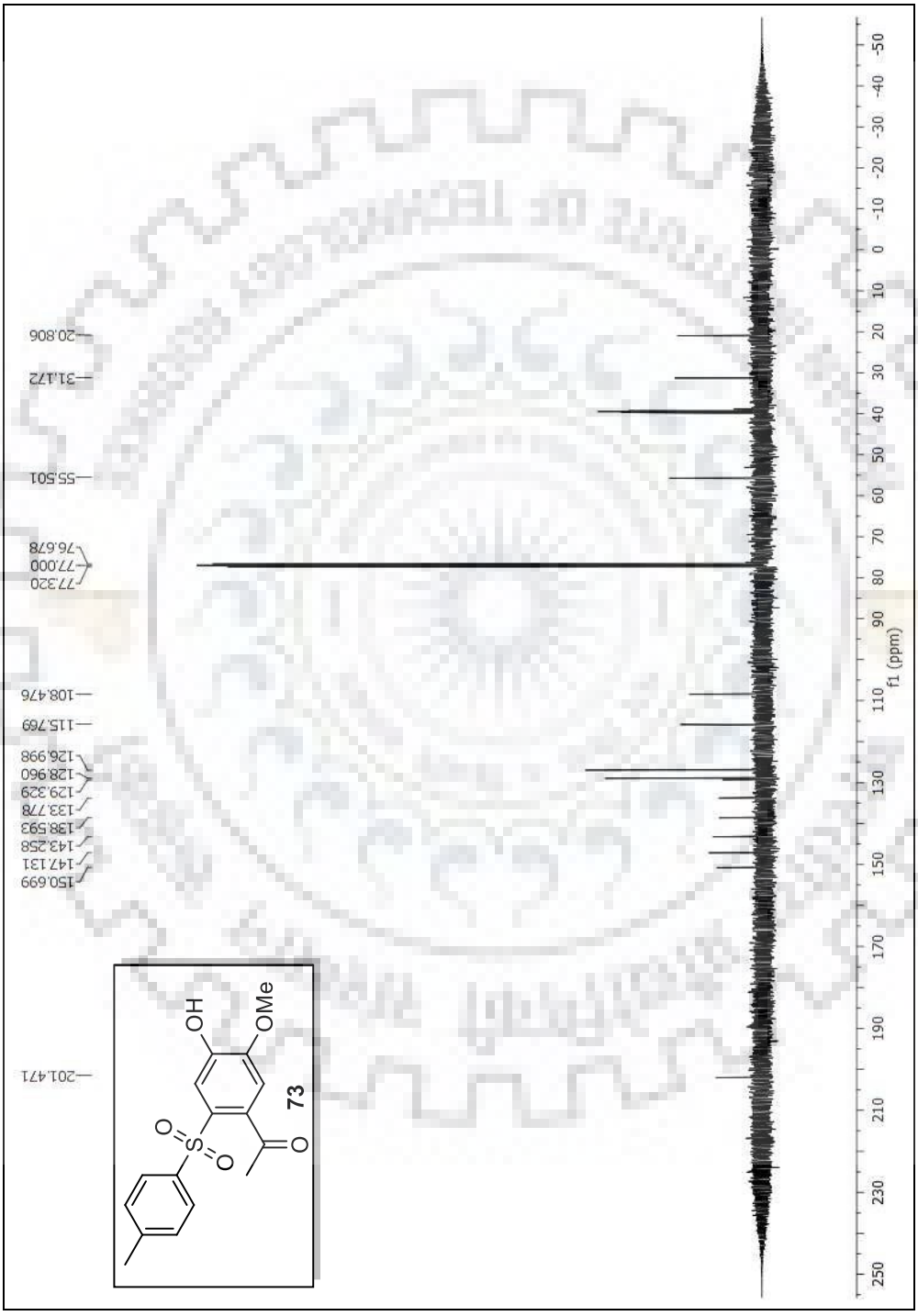


Figure S-28: ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of **73**.

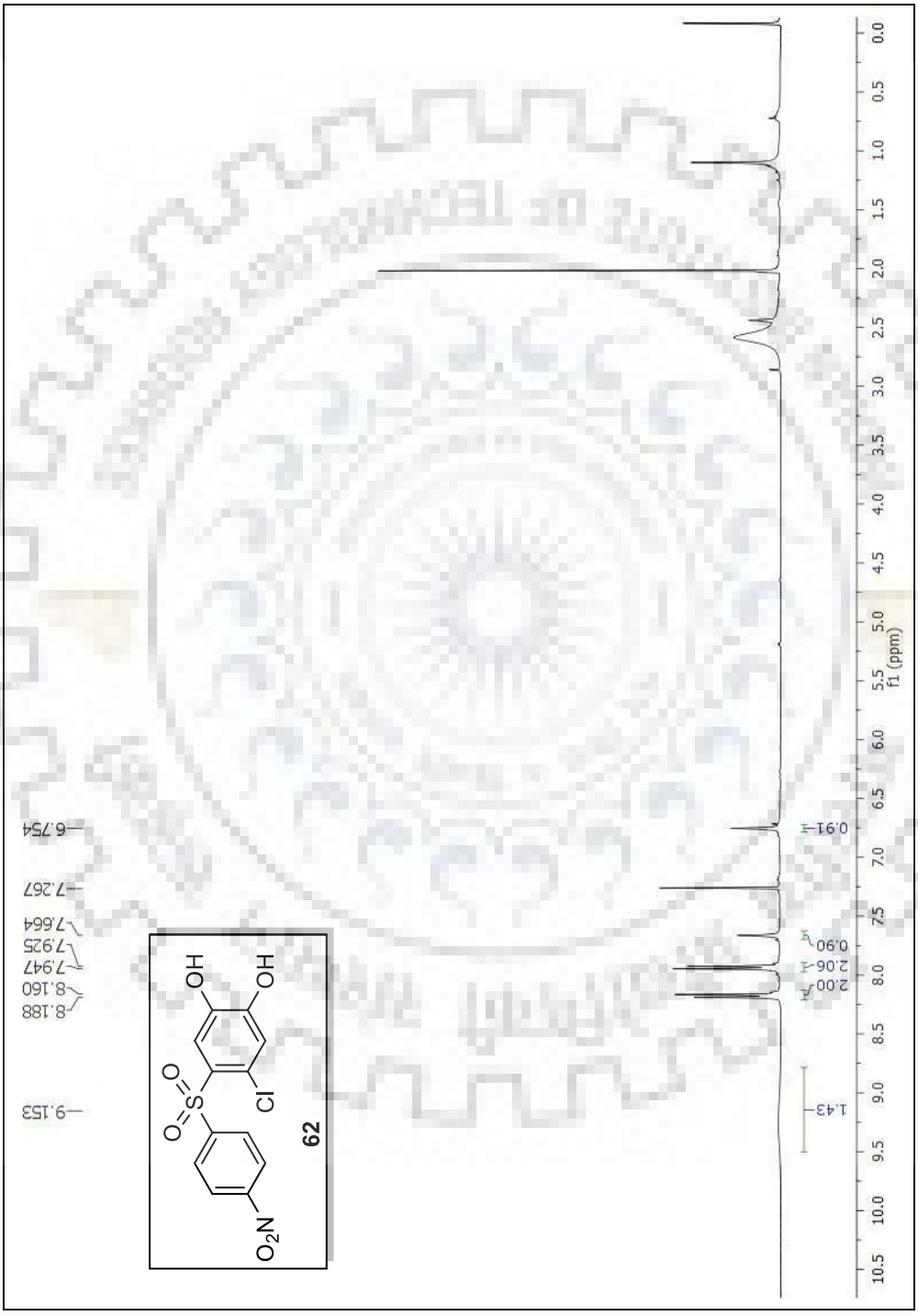


Figure S-29: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **62**.

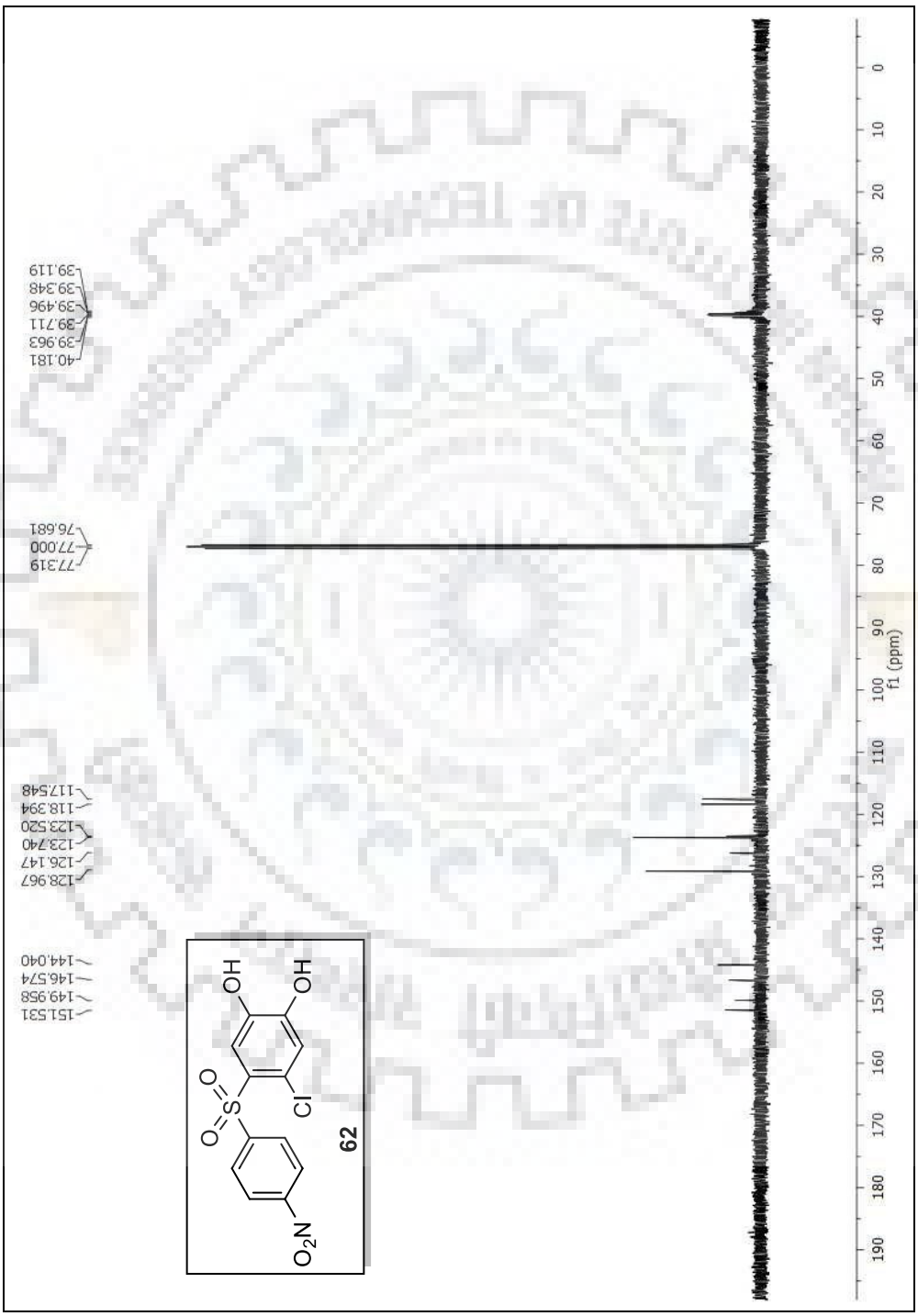


Figure S-30: ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of **62**.

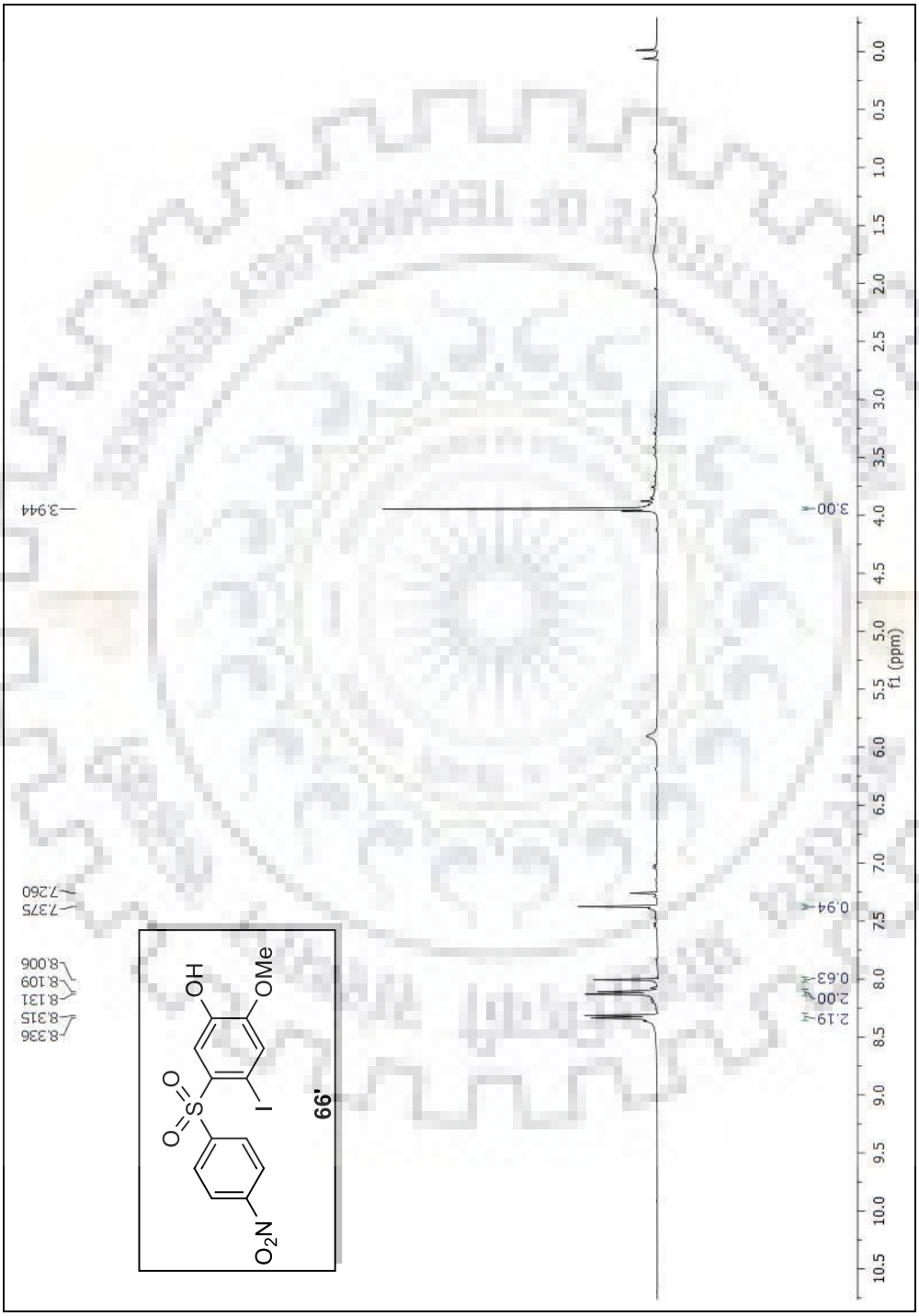


Figure S-31: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **66'**.

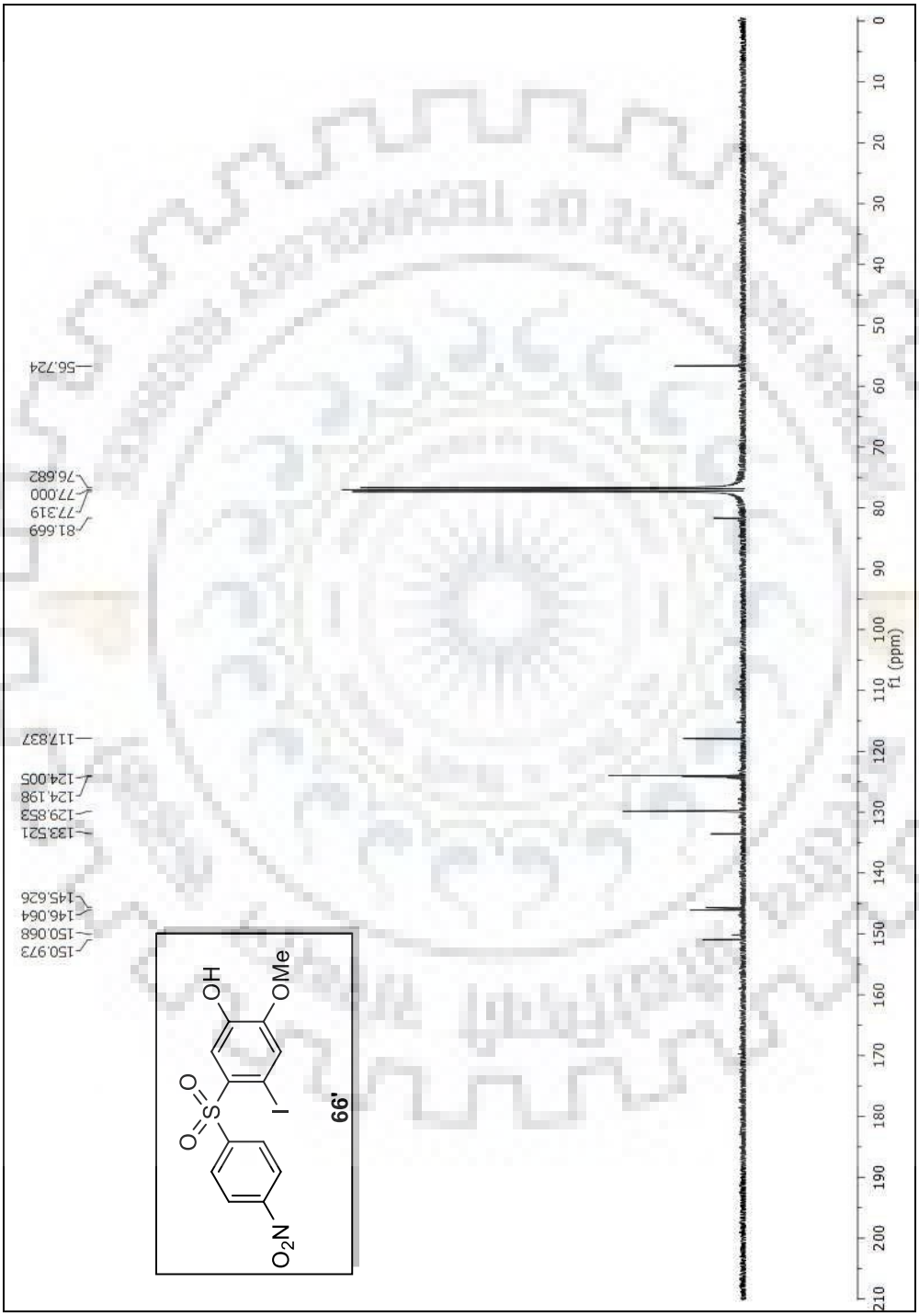


Figure S-32: ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of **66'.**

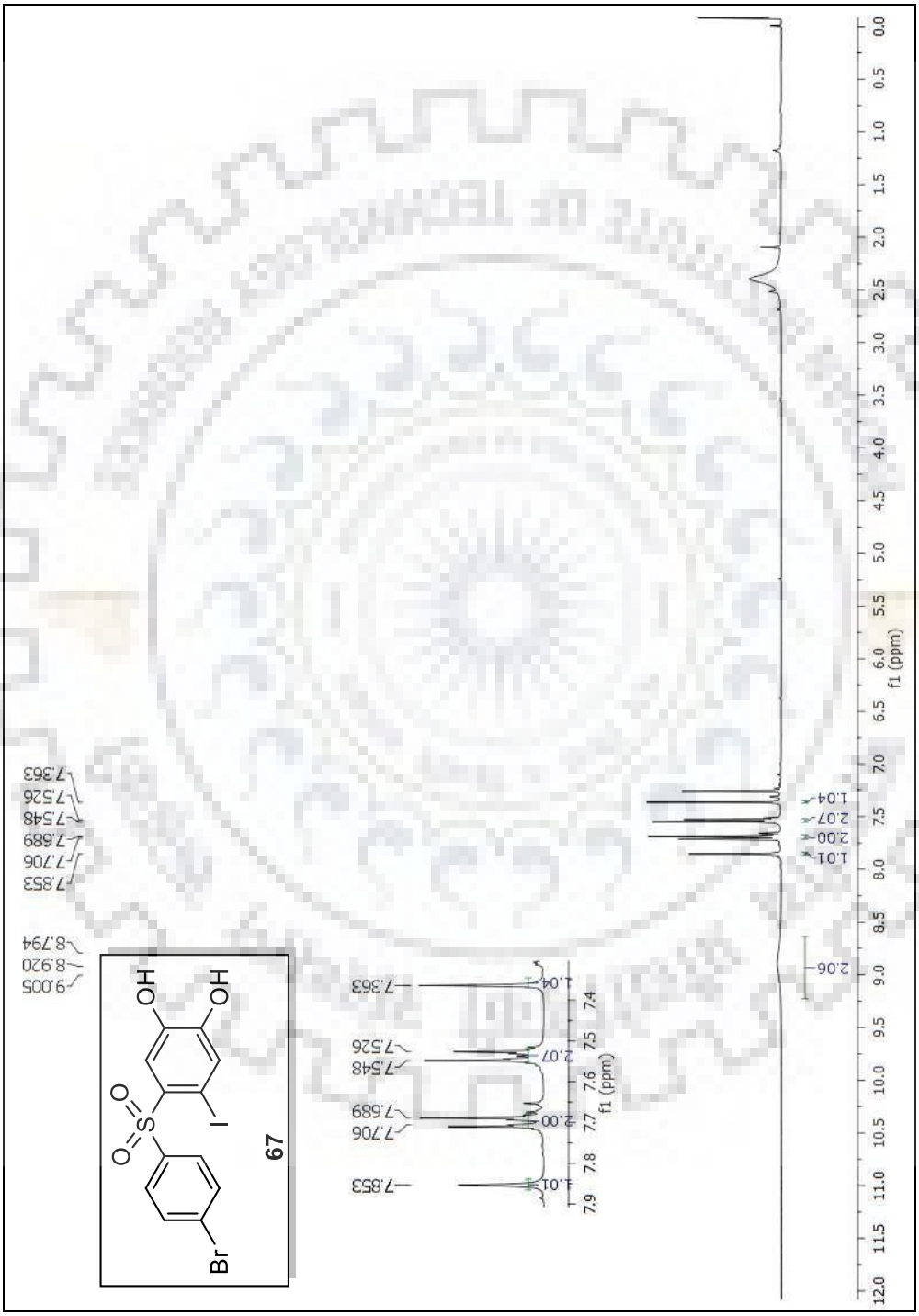


Figure S-33: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **67**.

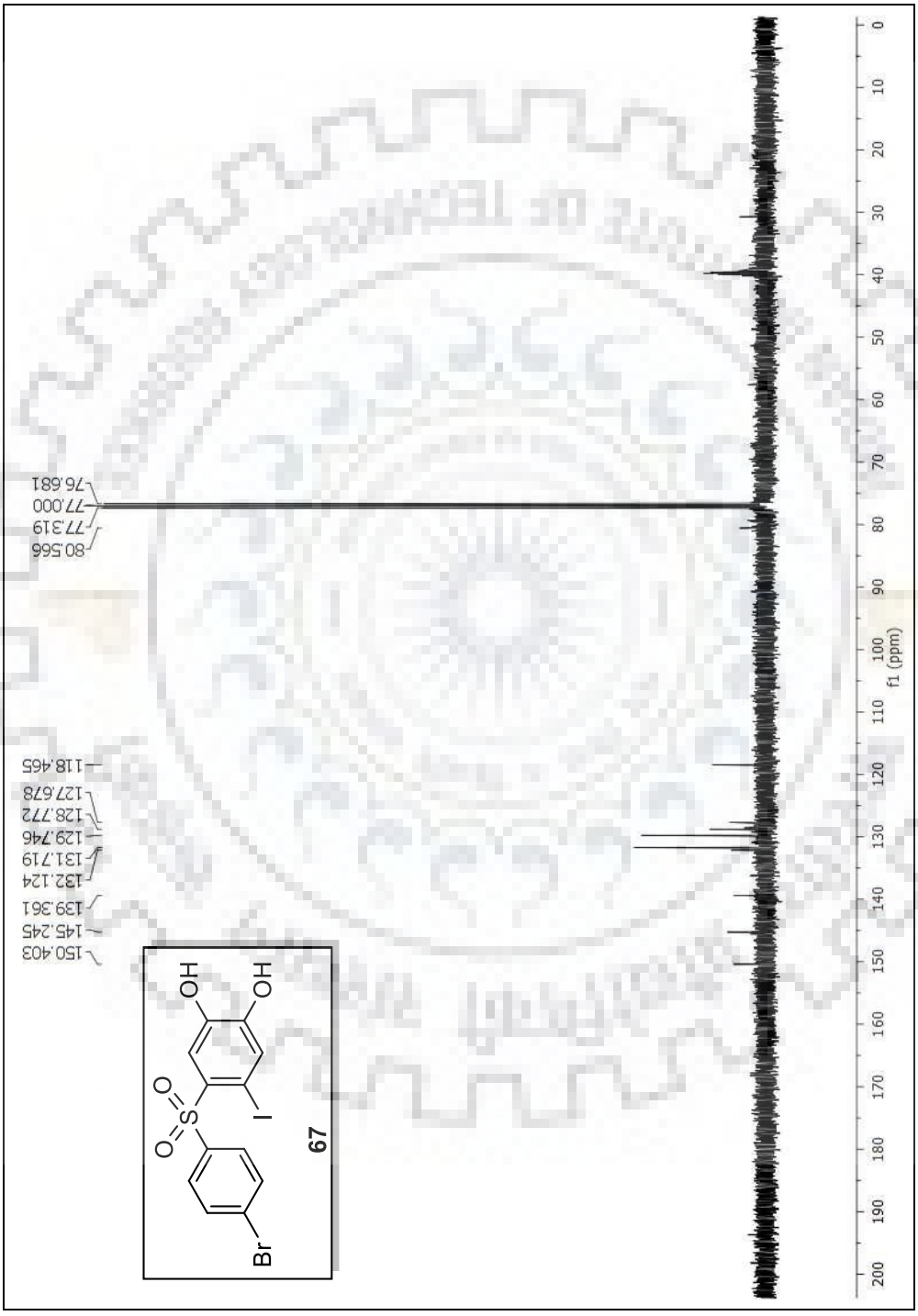


Figure S-34: ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of **67**.

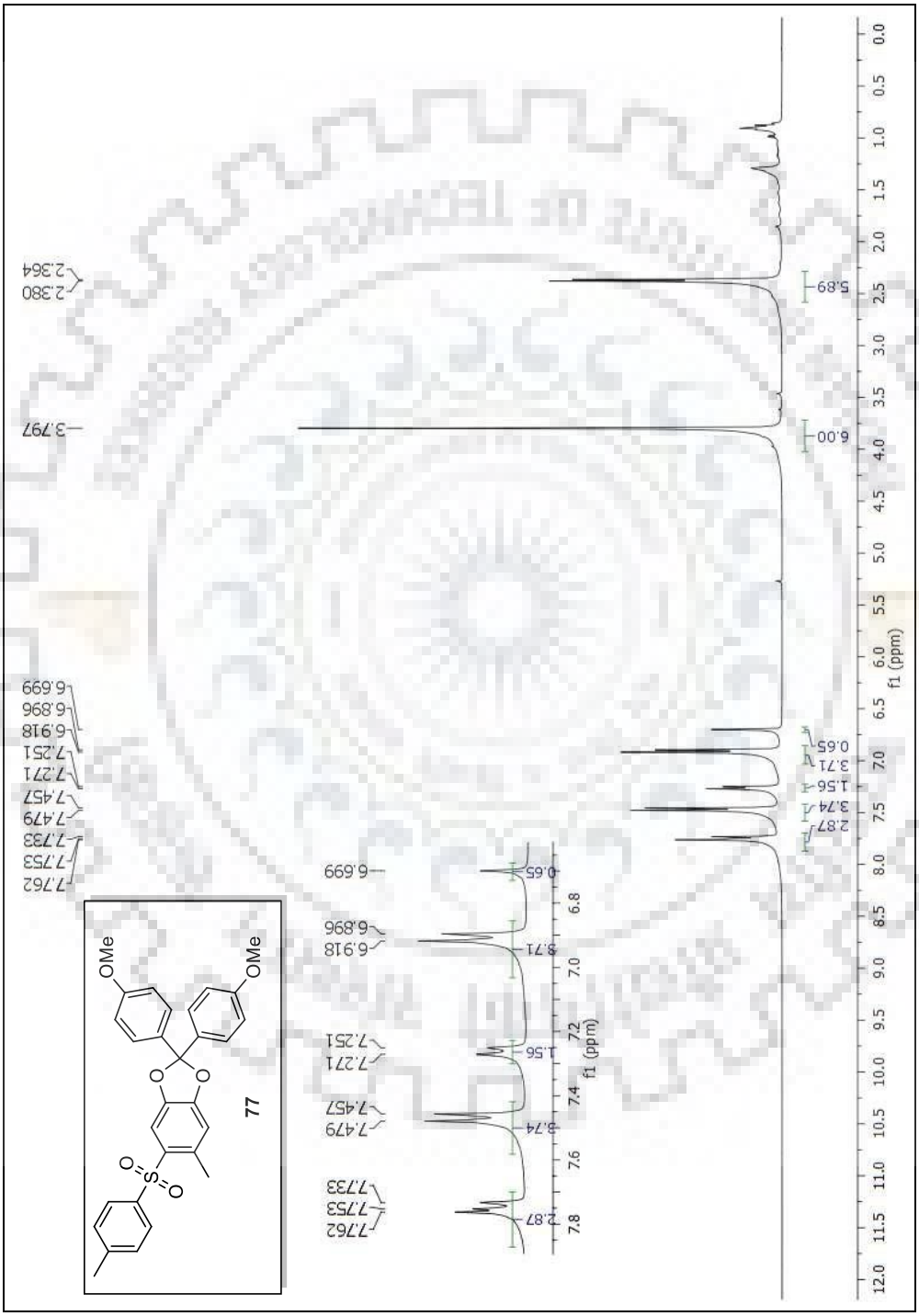


Figure S-35: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **77**.

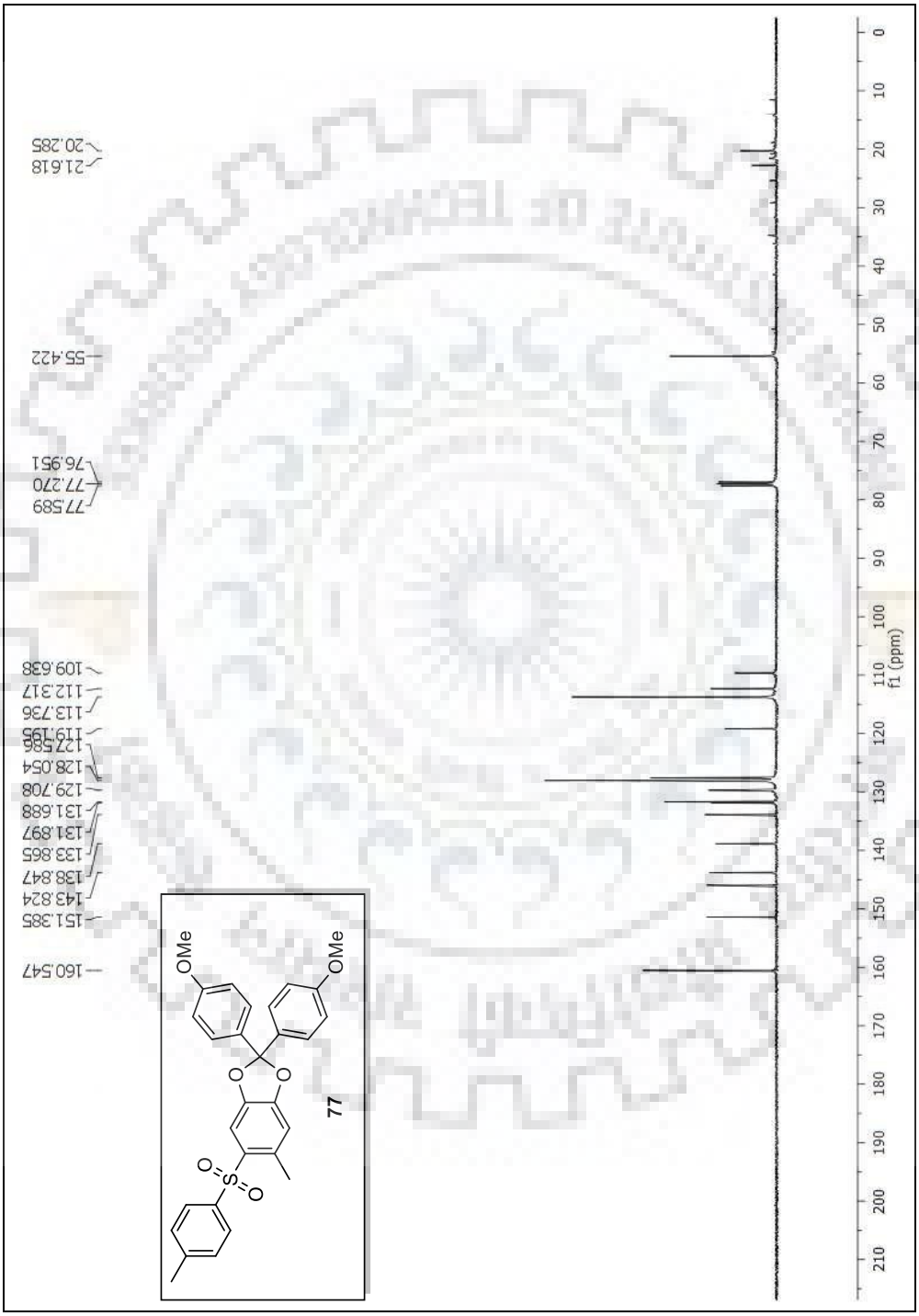


Figure S-36: ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of **77**.

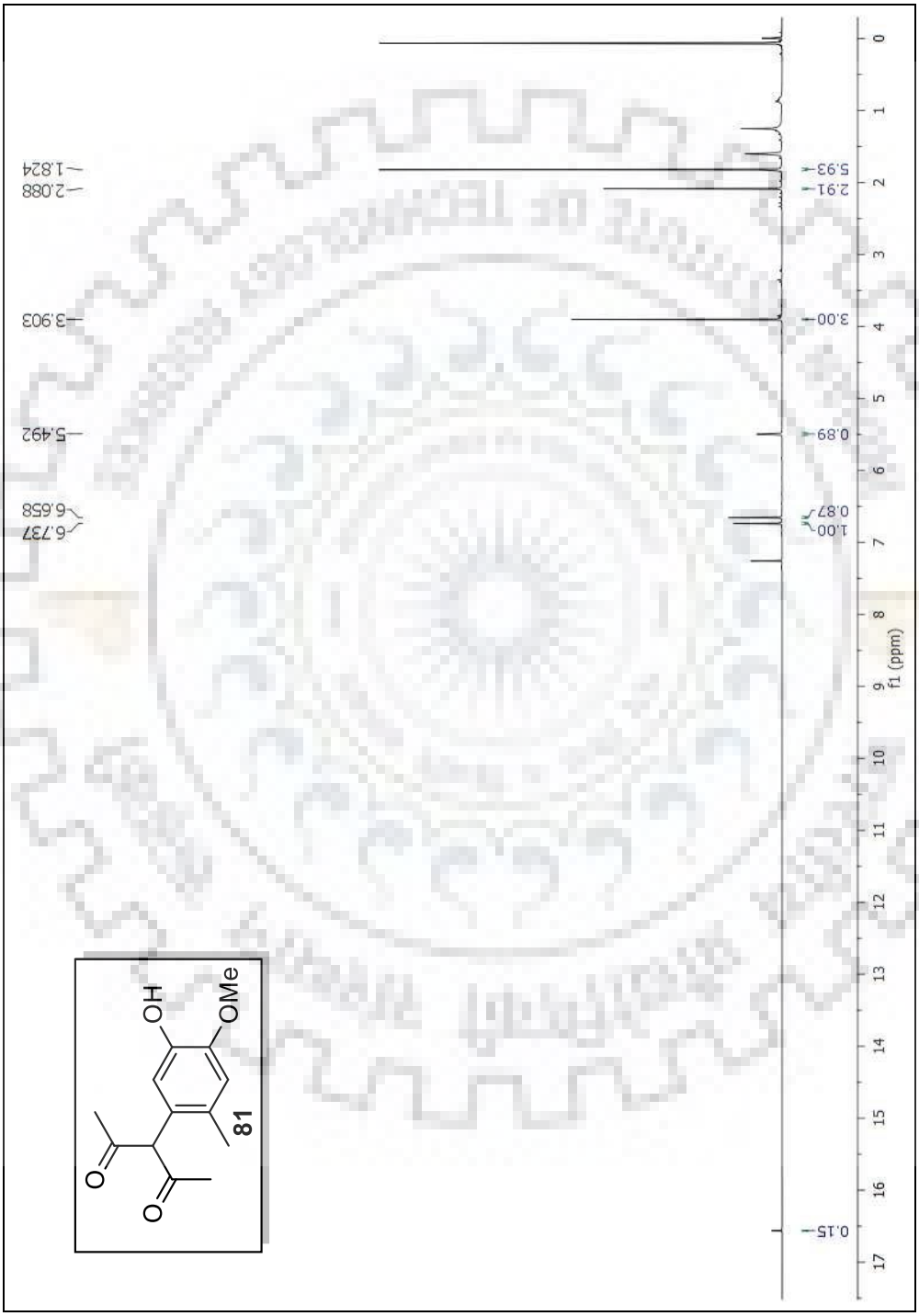


Figure S-37: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **81**.

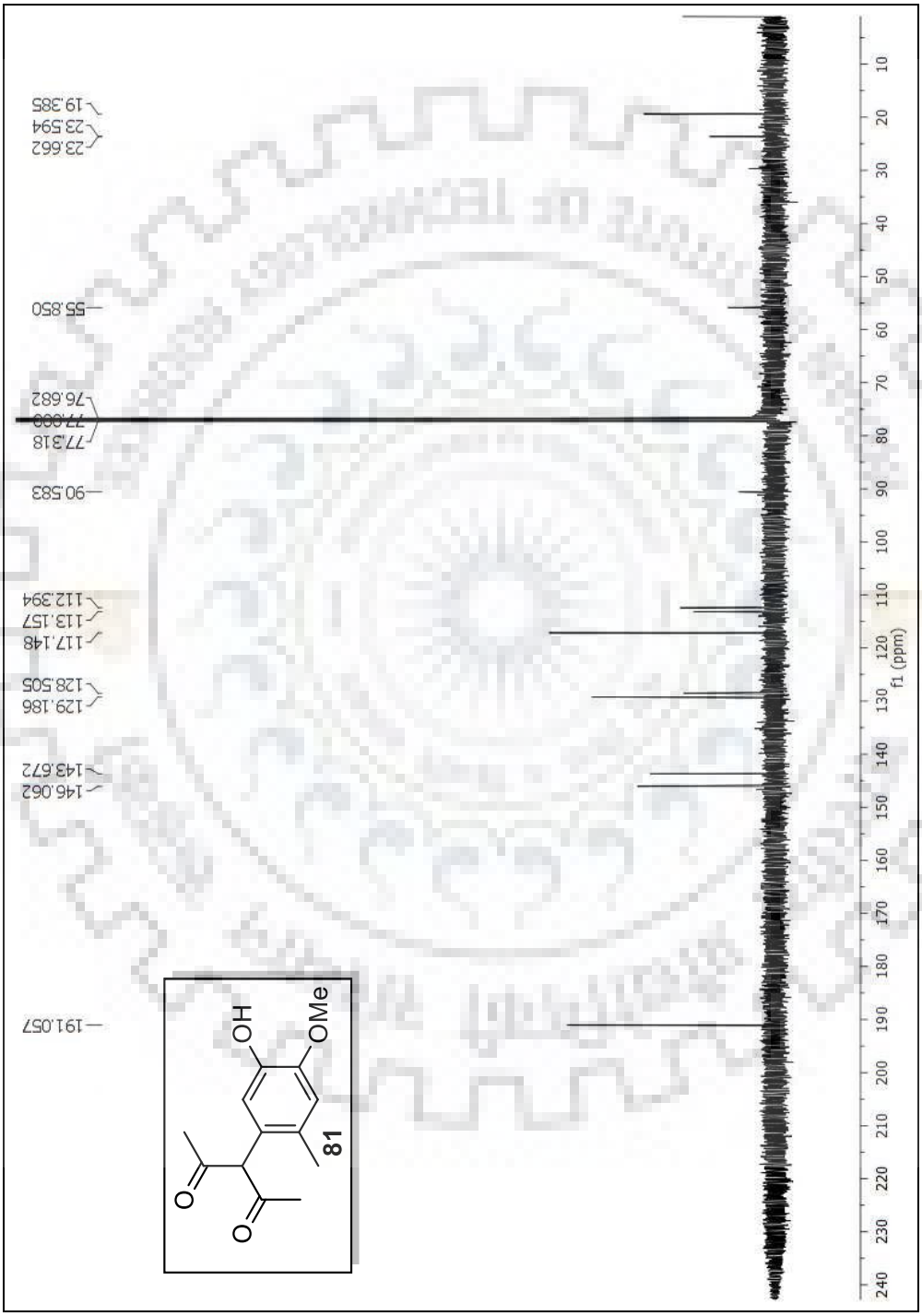


Figure S-38: ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of **81**.

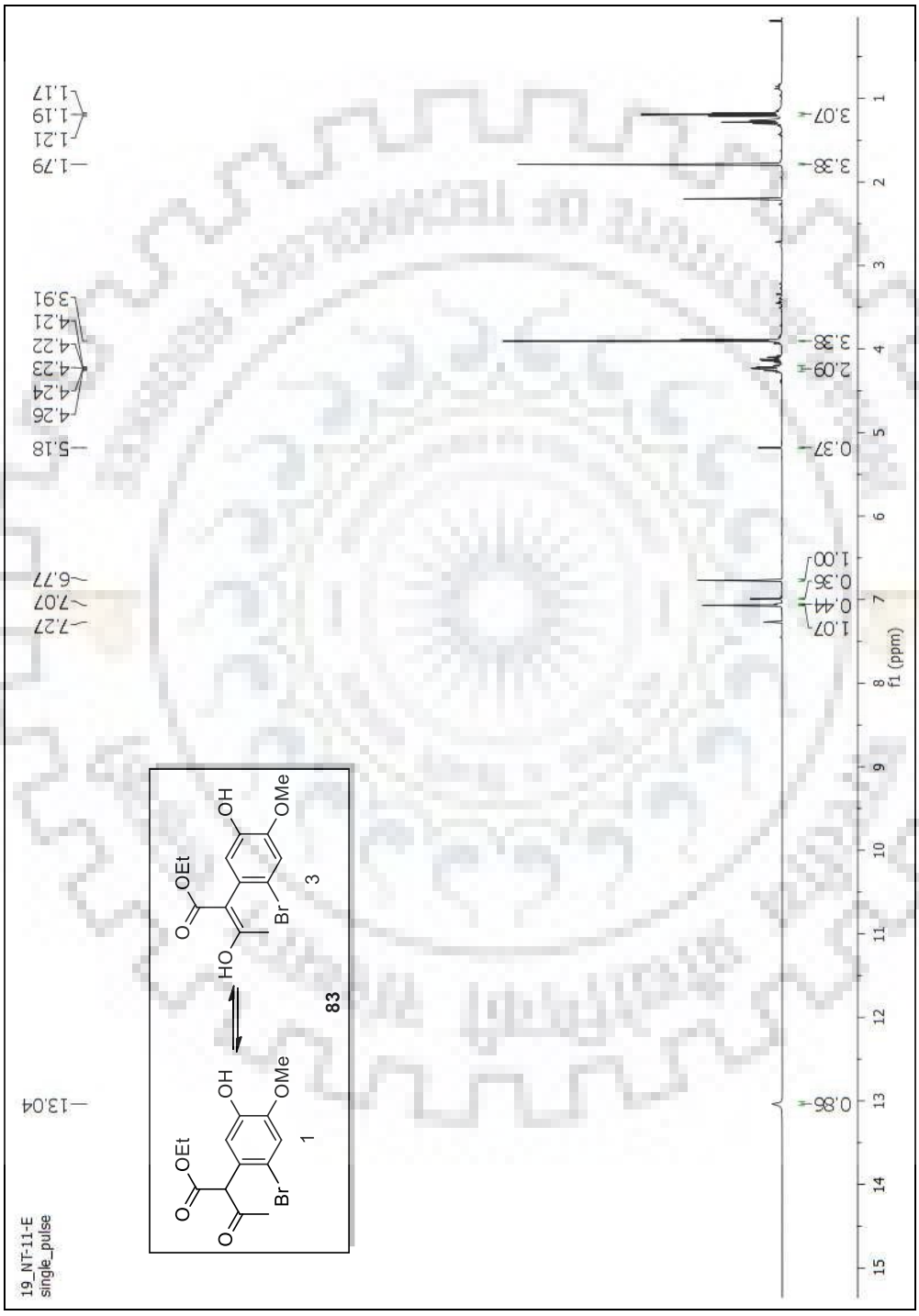


Figure S-39: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **83**.

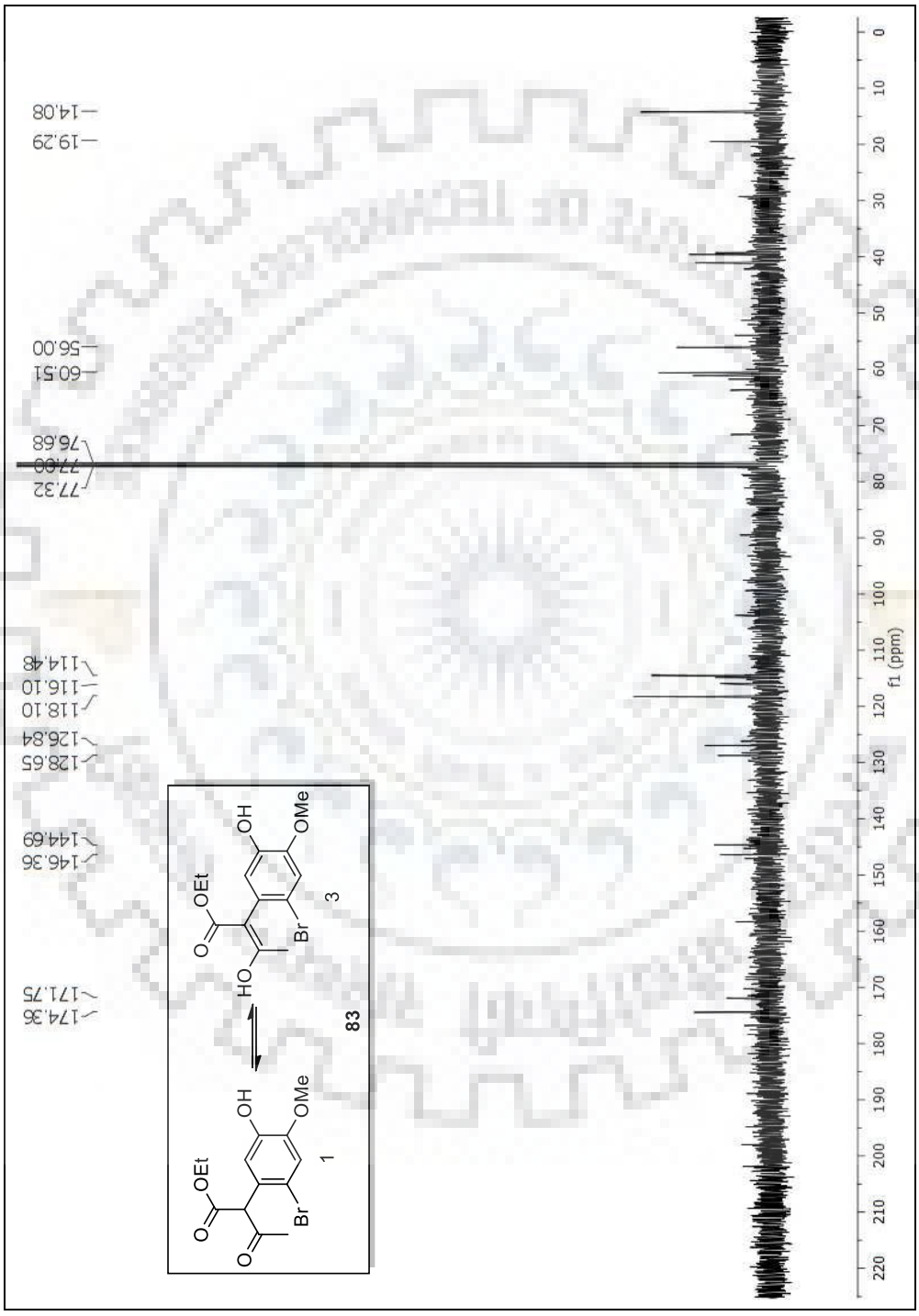


Figure S-40: ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of **83**.

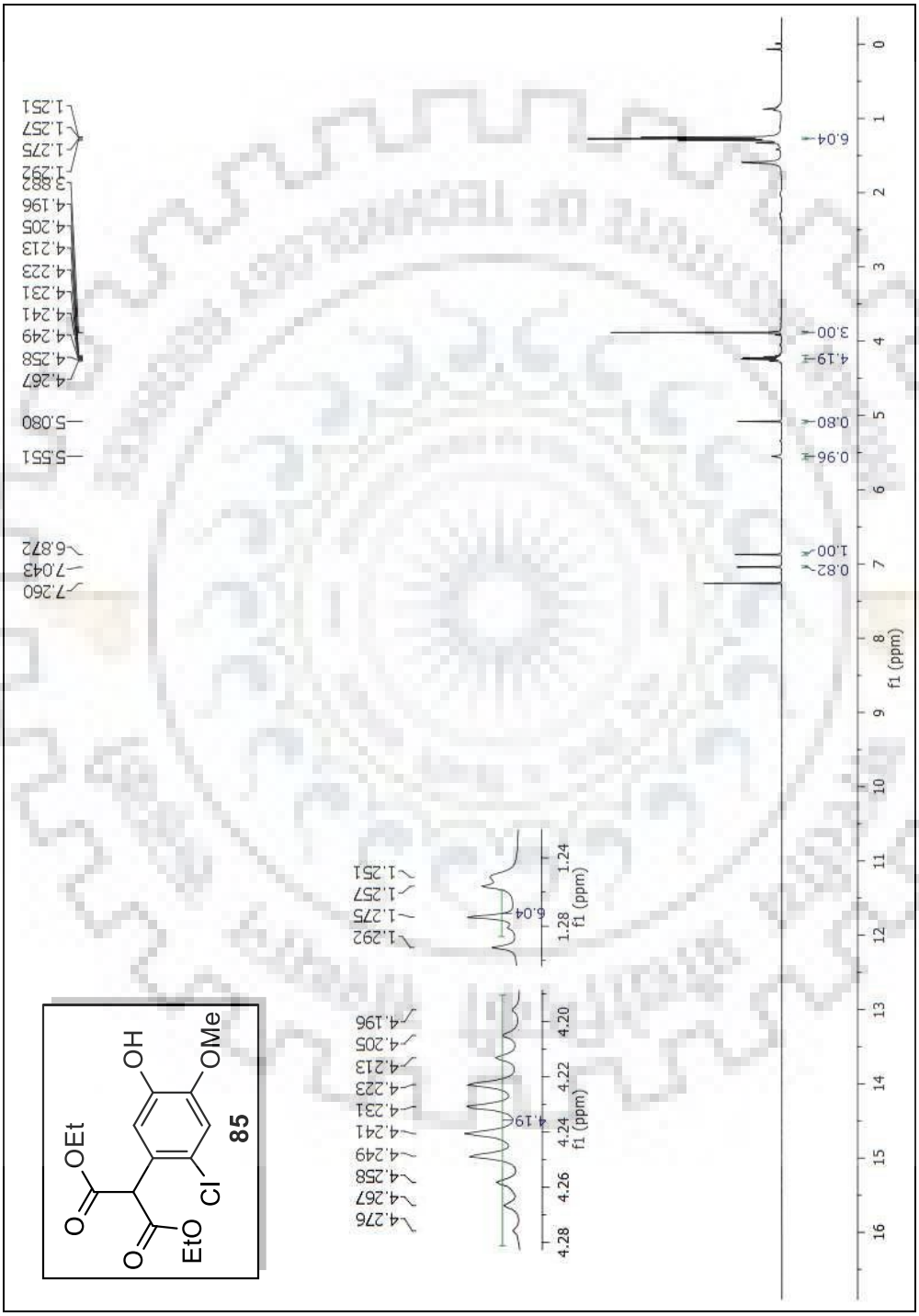


Figure S-41: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **85**.

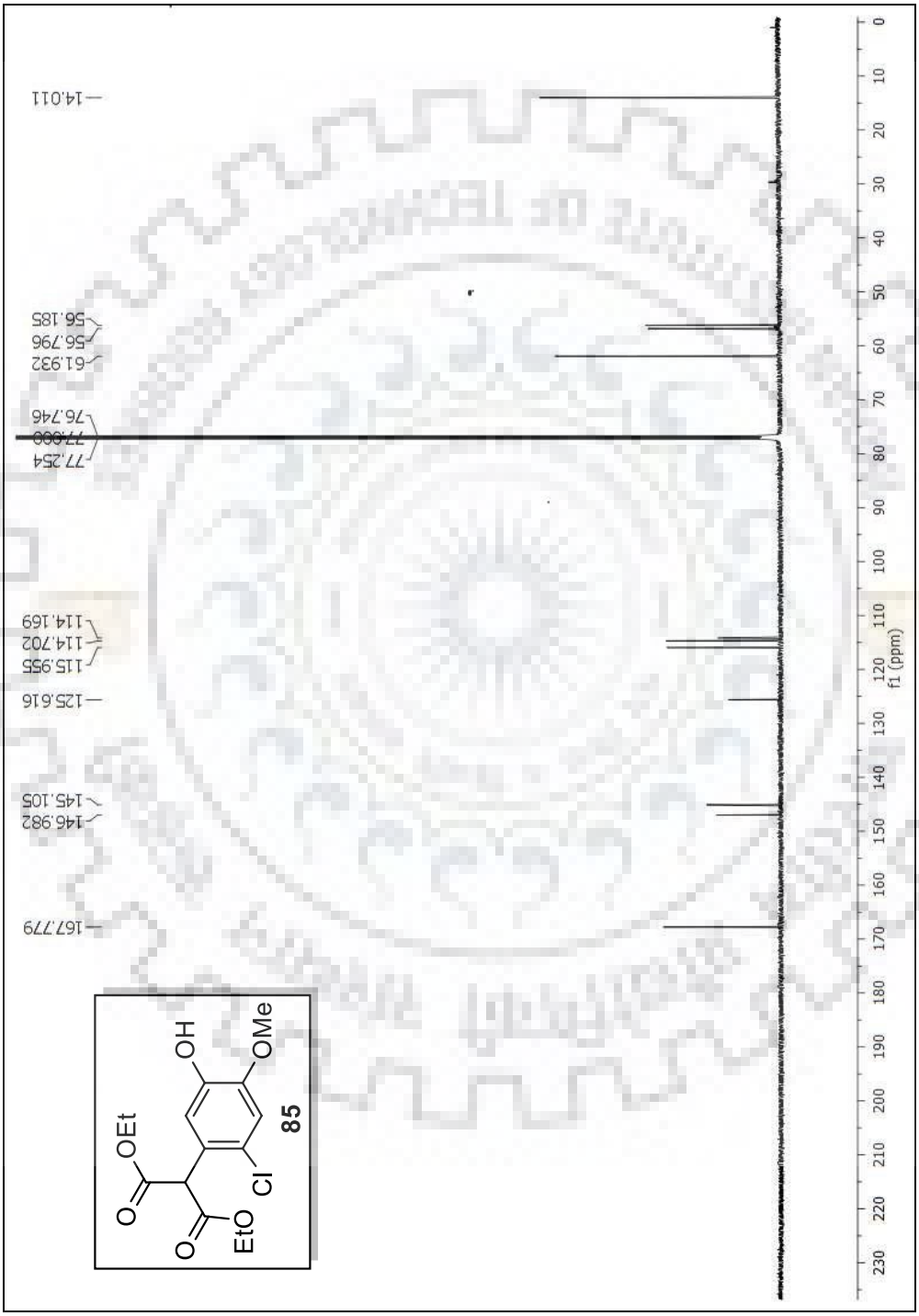


Figure S-42: ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of **85**.

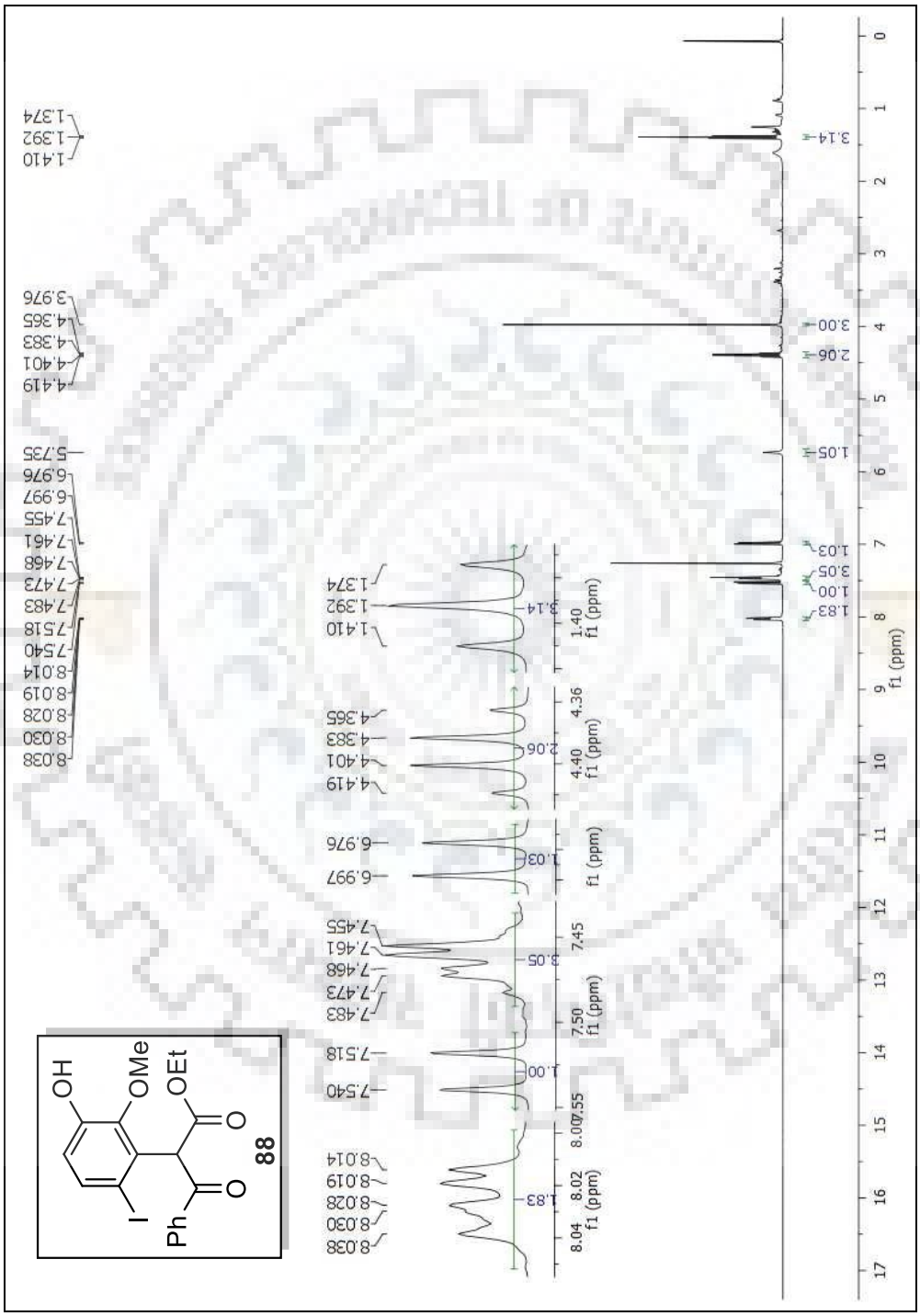


Figure S-43: ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of **88**.

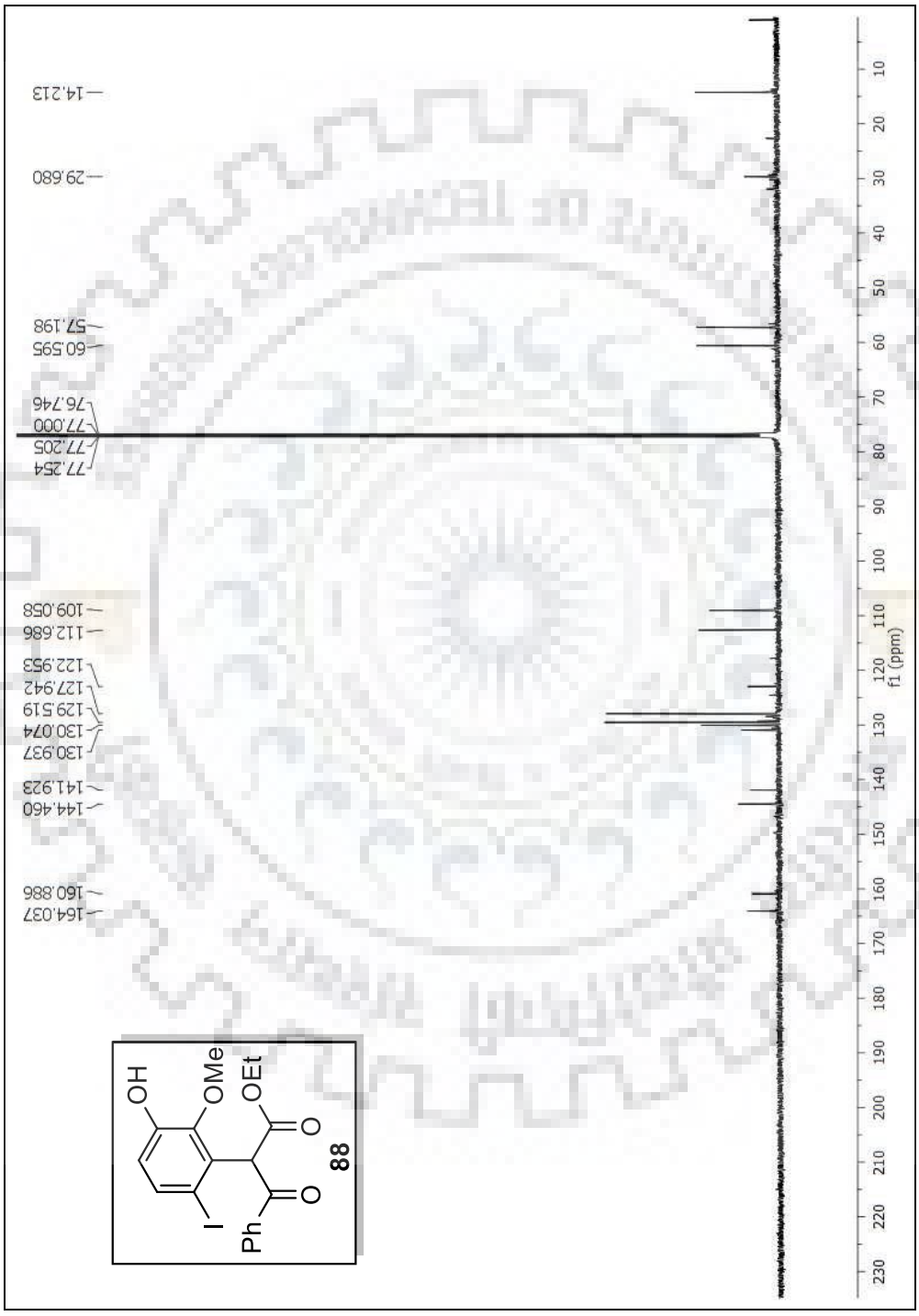


Figure S-44: ^{13}C NMR (500 MHz, $CDCl_3$) Spectrum of **88**.

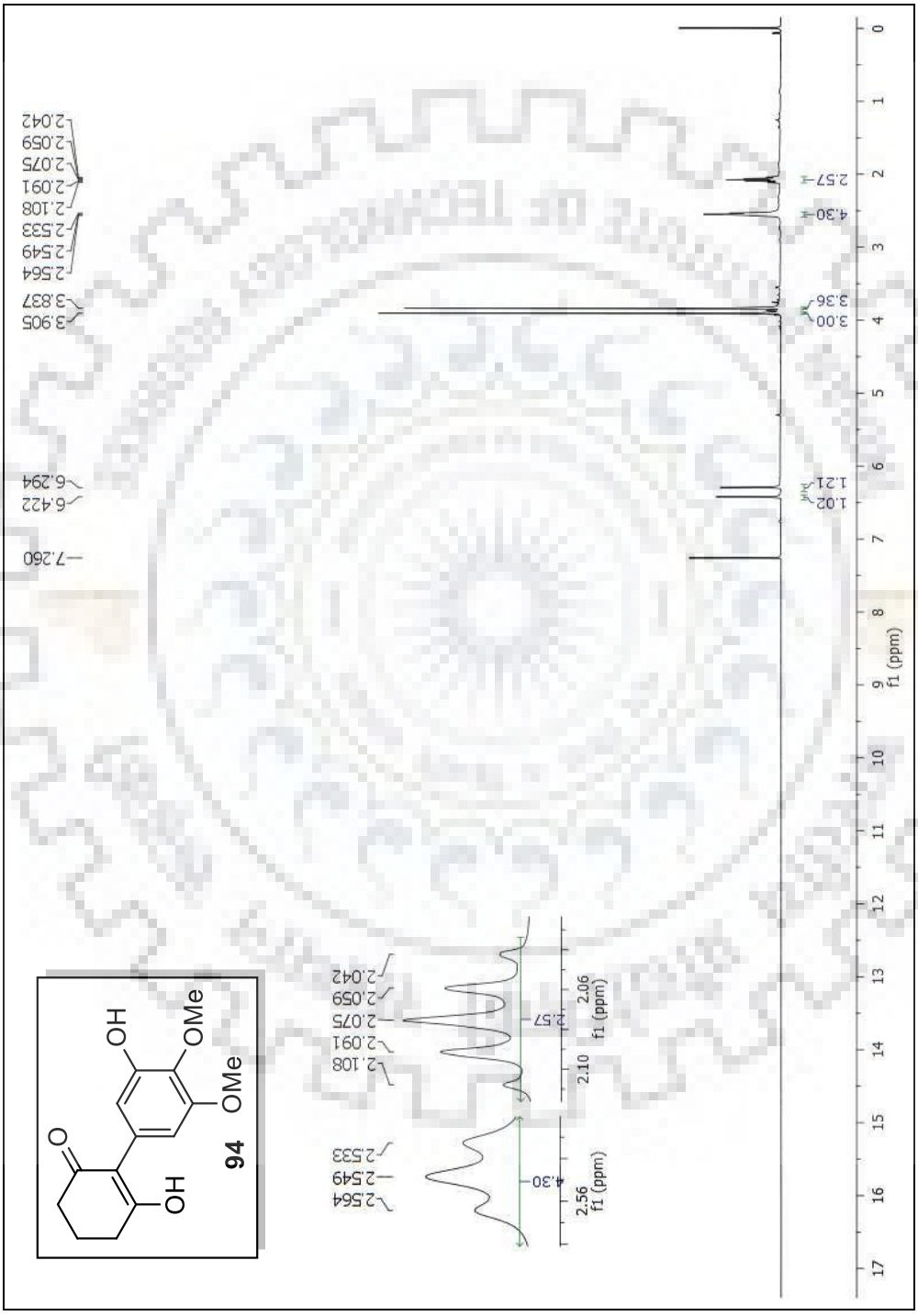


Figure S-45: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **94**.

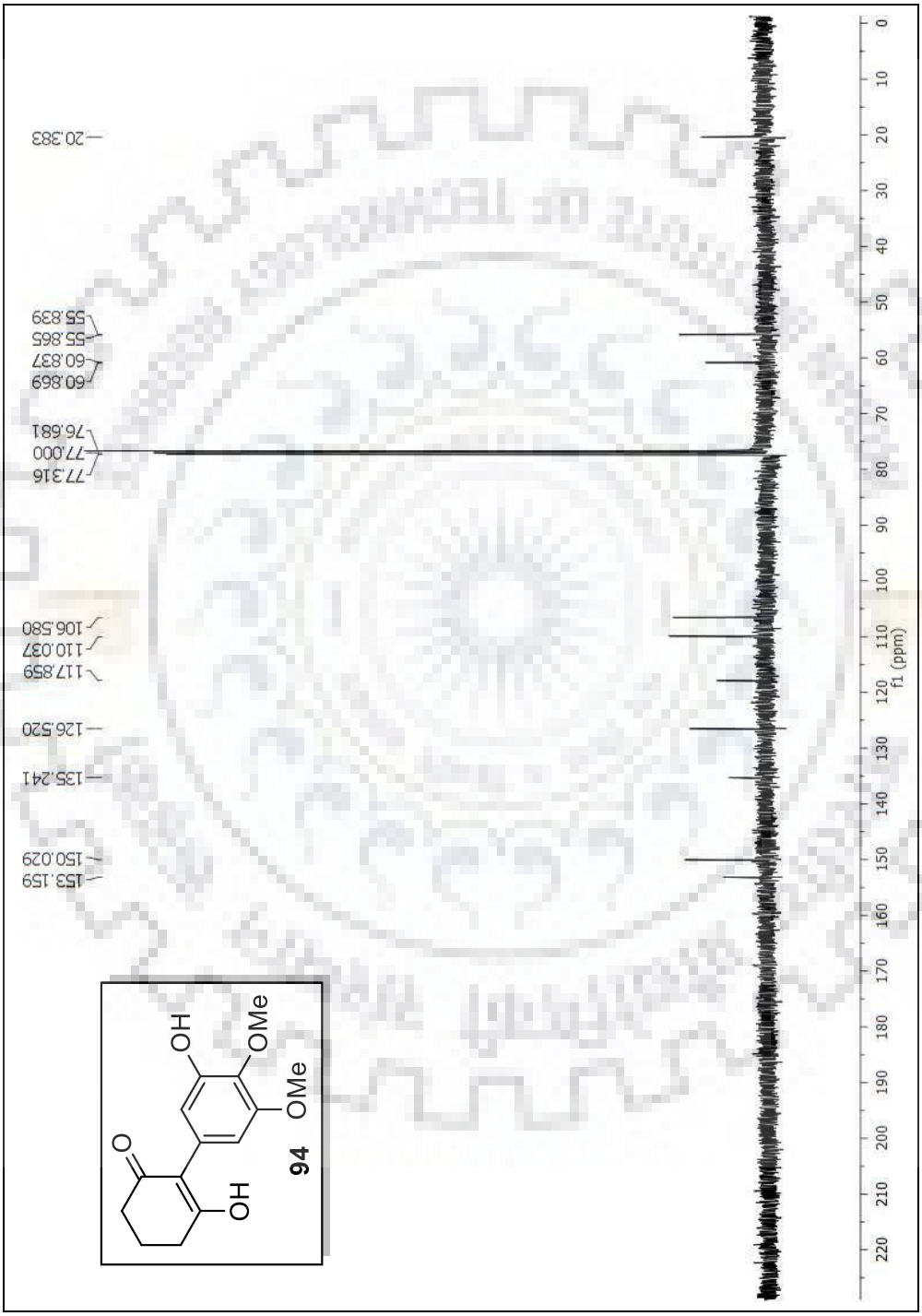


Figure S-46: ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of **94**.

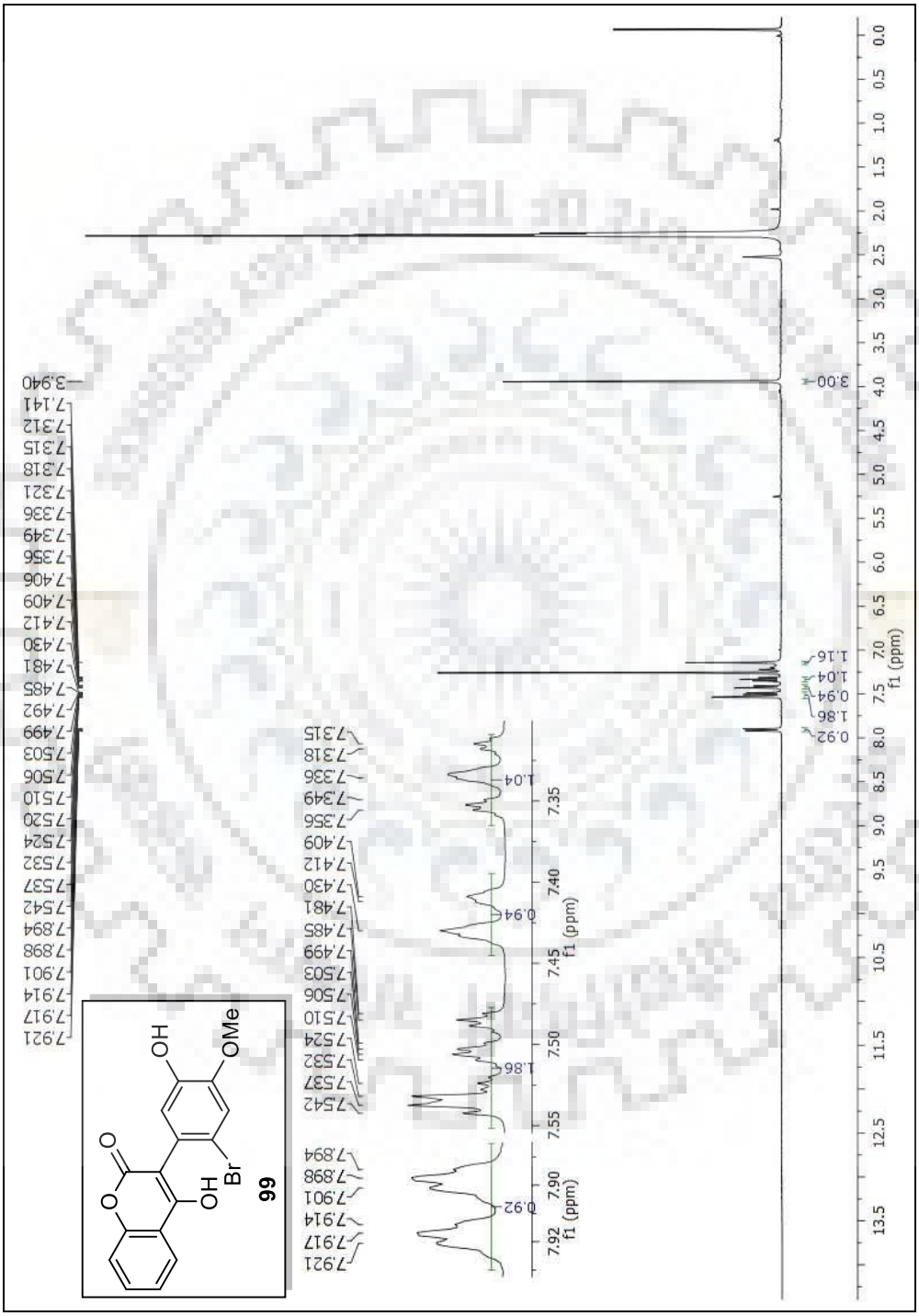


Figure S-47: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **99**.

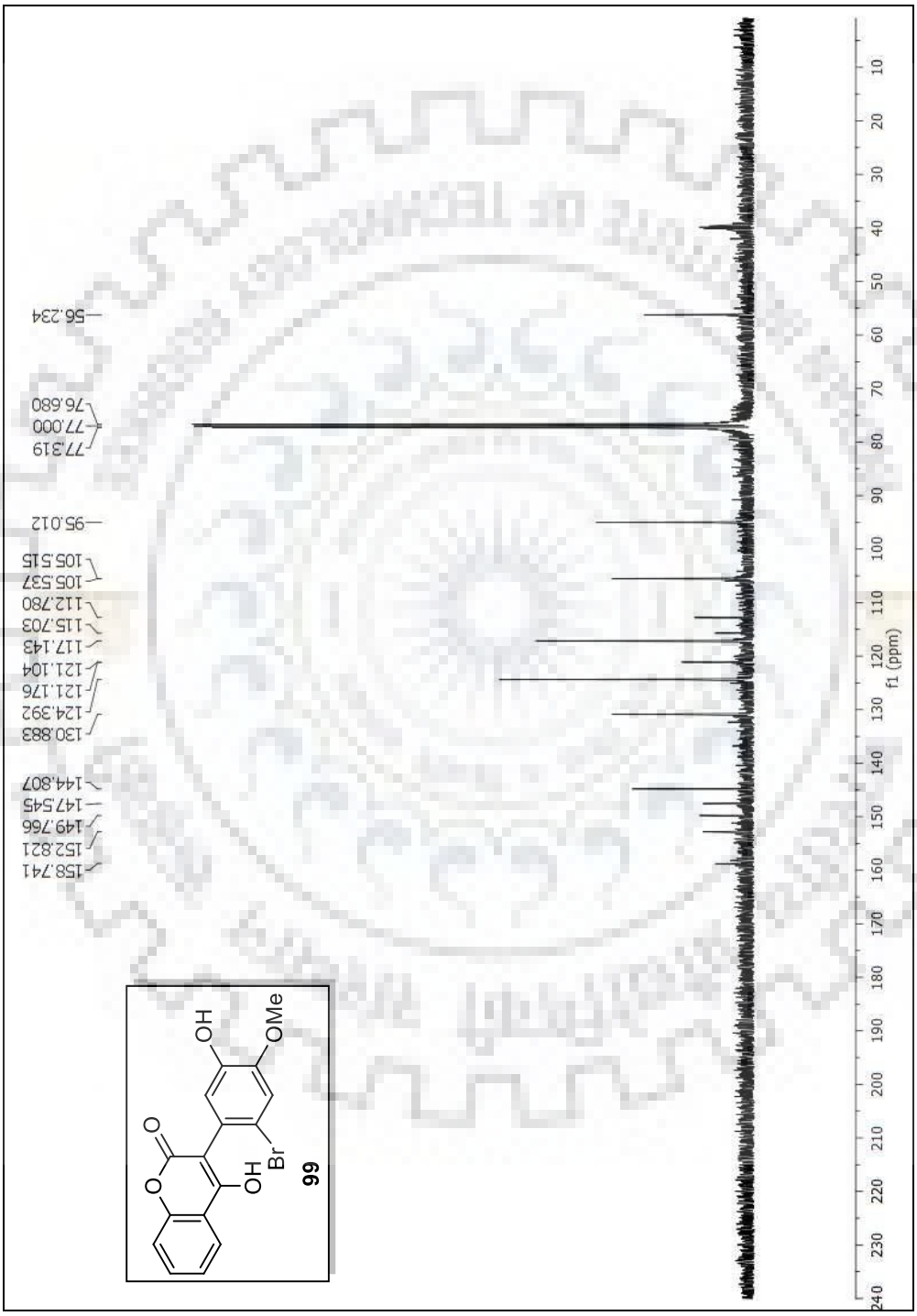


Figure S-48: ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of **99**.

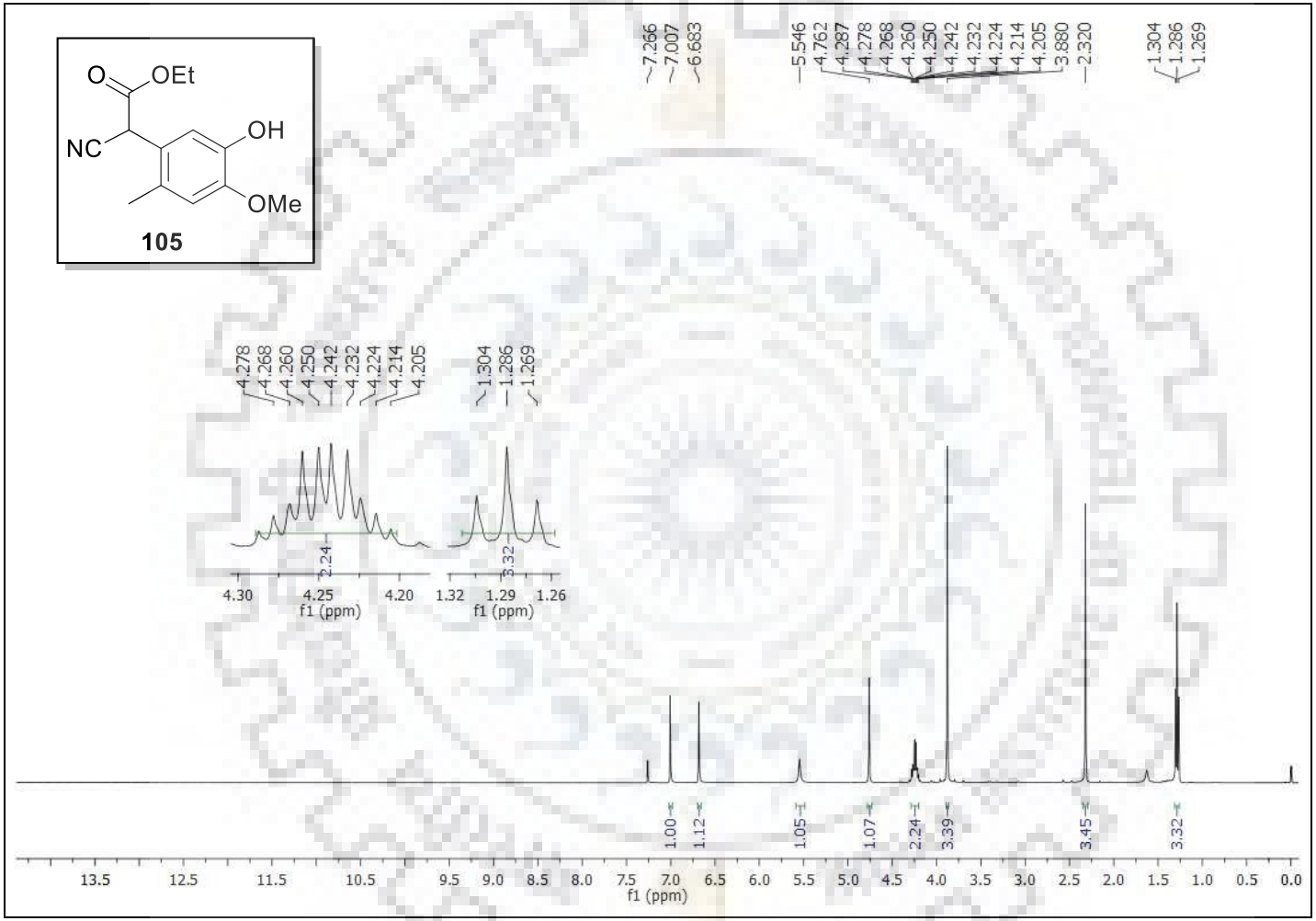


Figure S-49: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **105**.

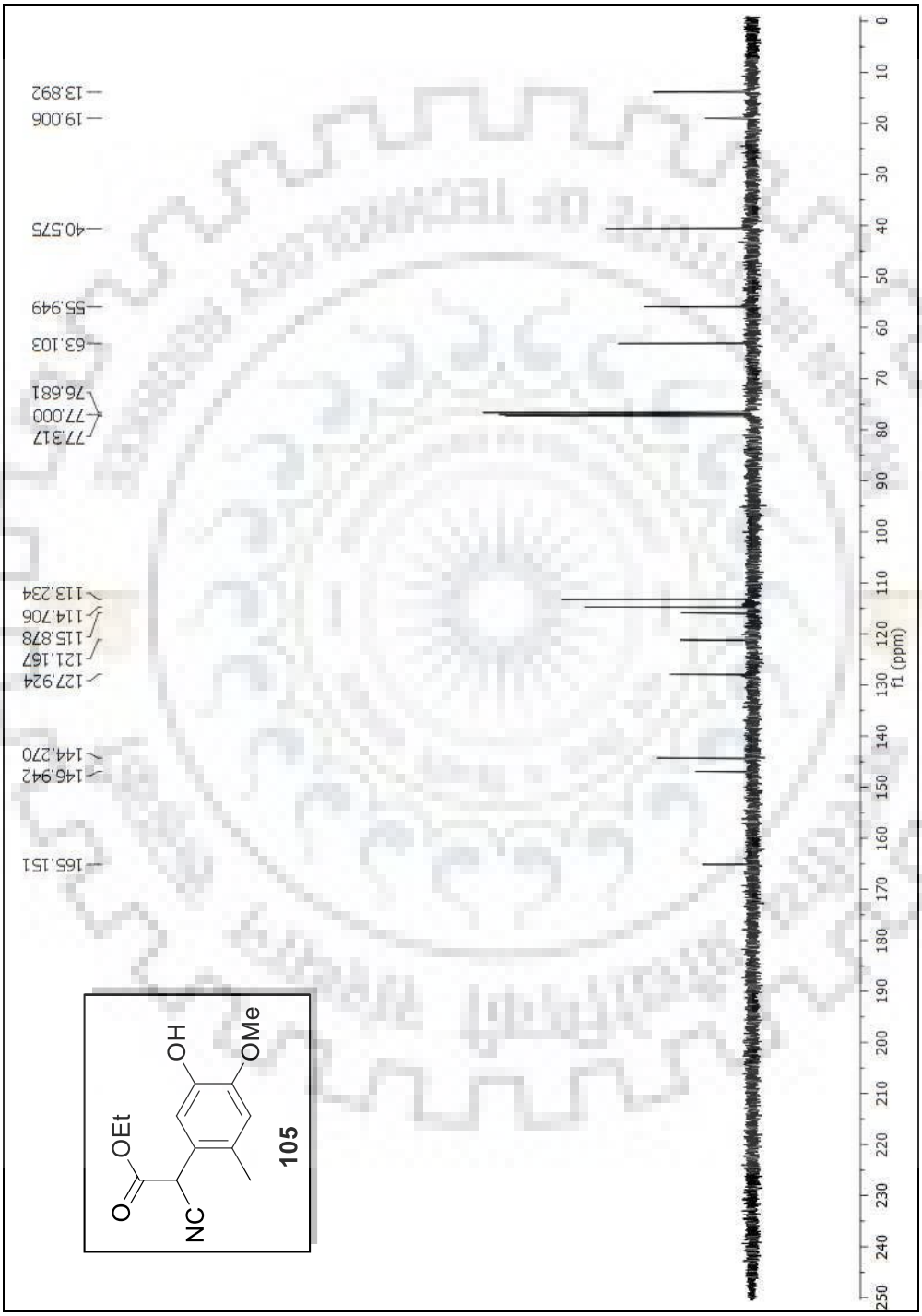


Figure S-50: ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of **105**.

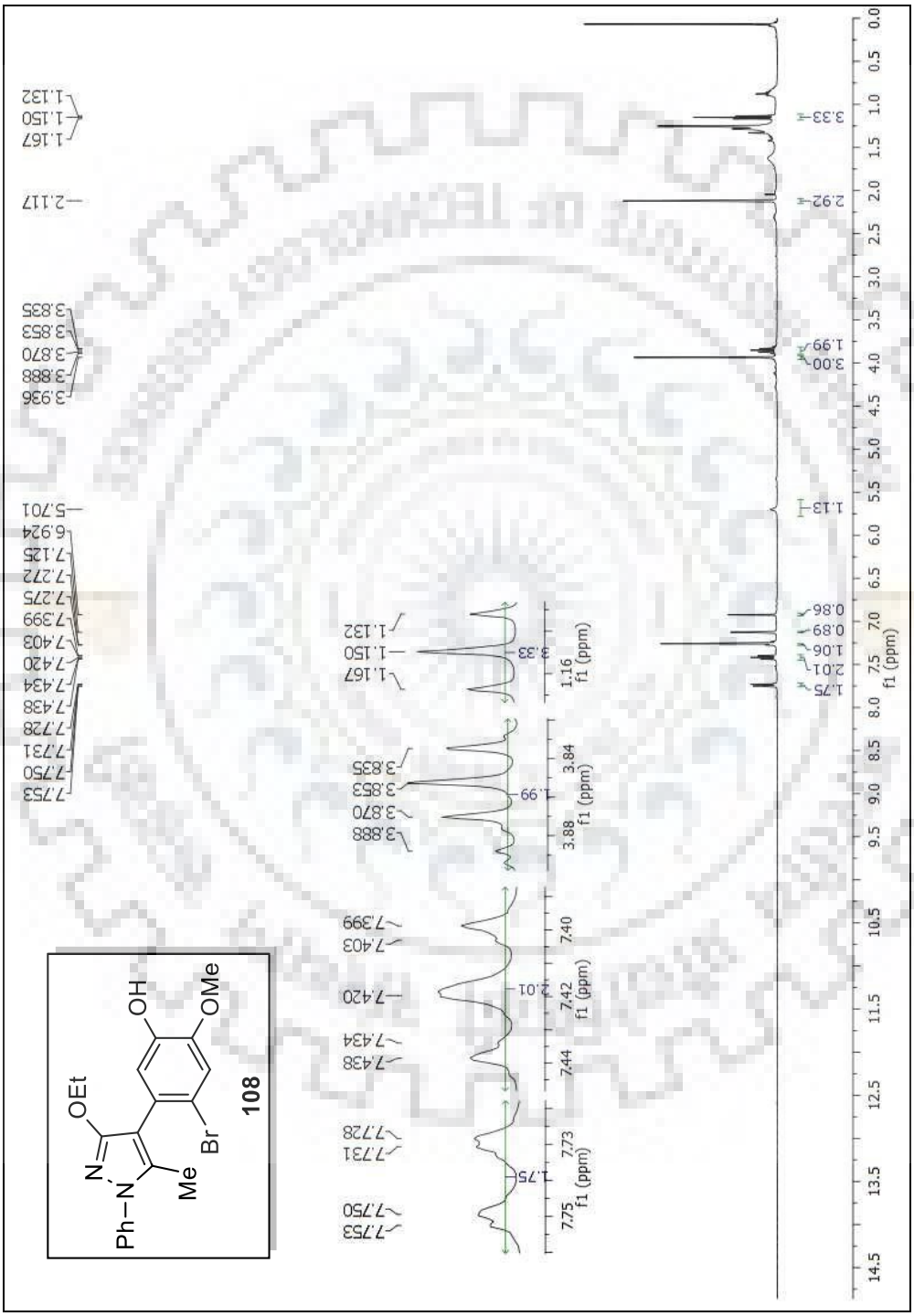


Figure S-51: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **108**.

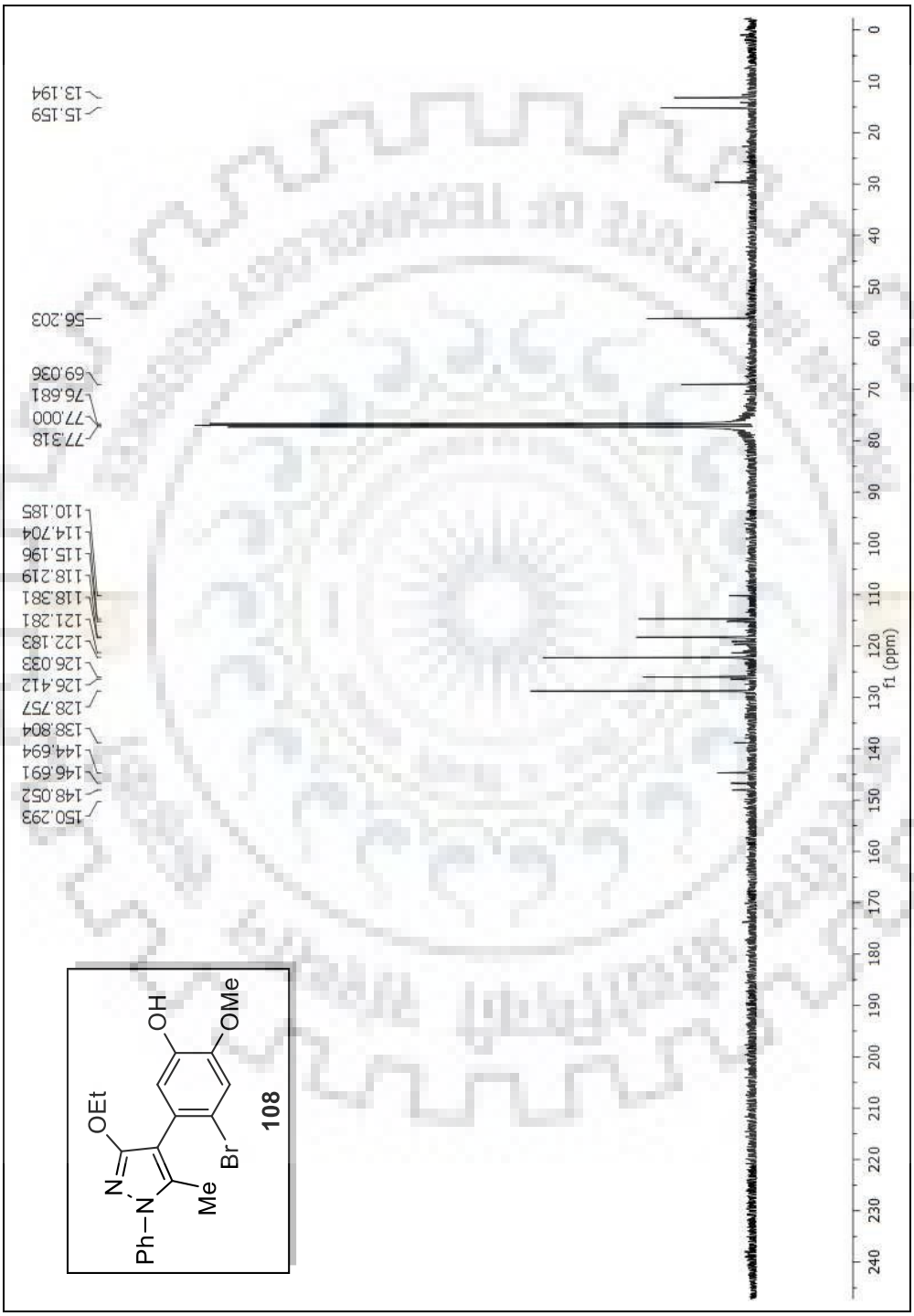


Figure S-52: ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of **108**.

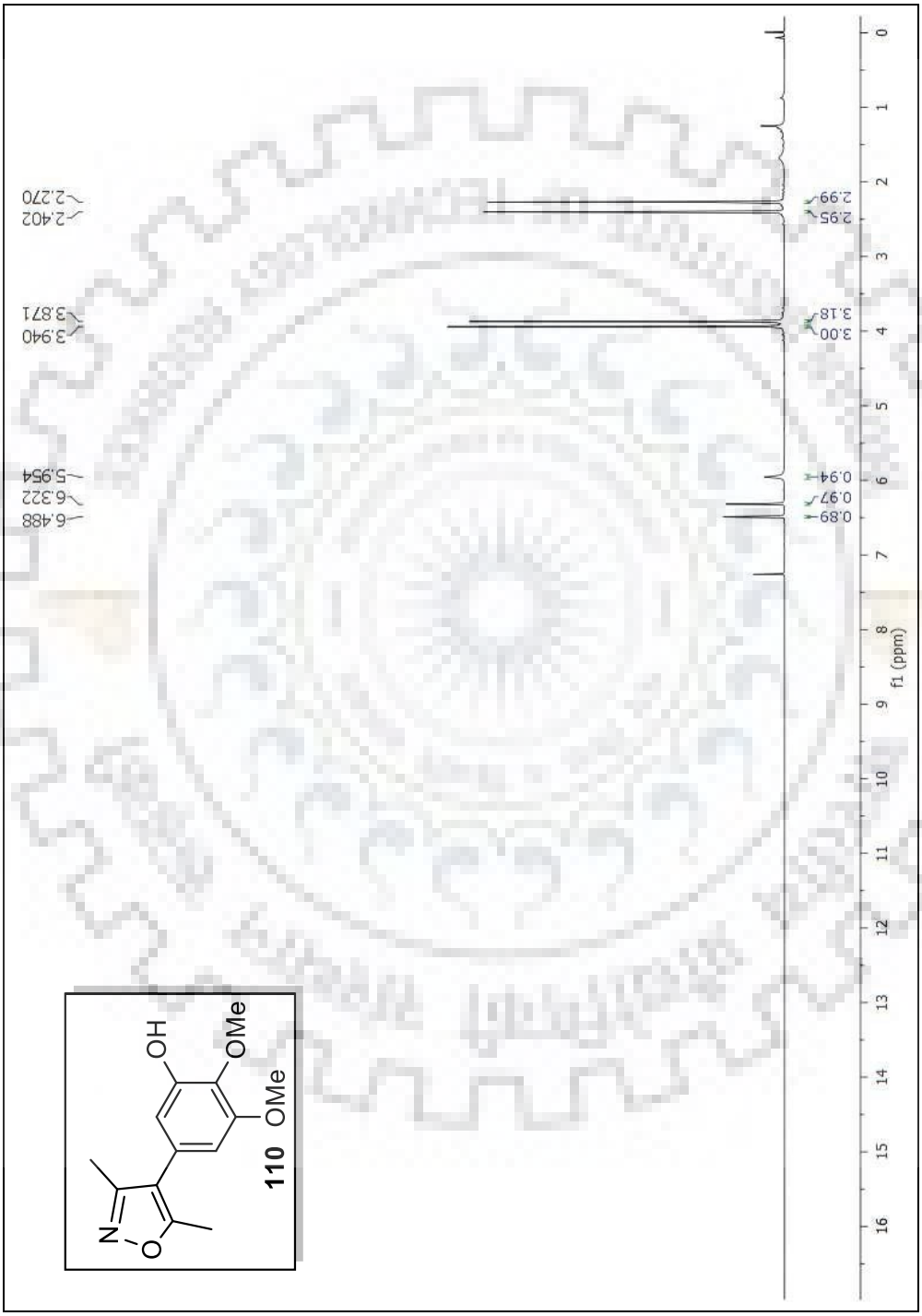


Figure S-53: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **110**.

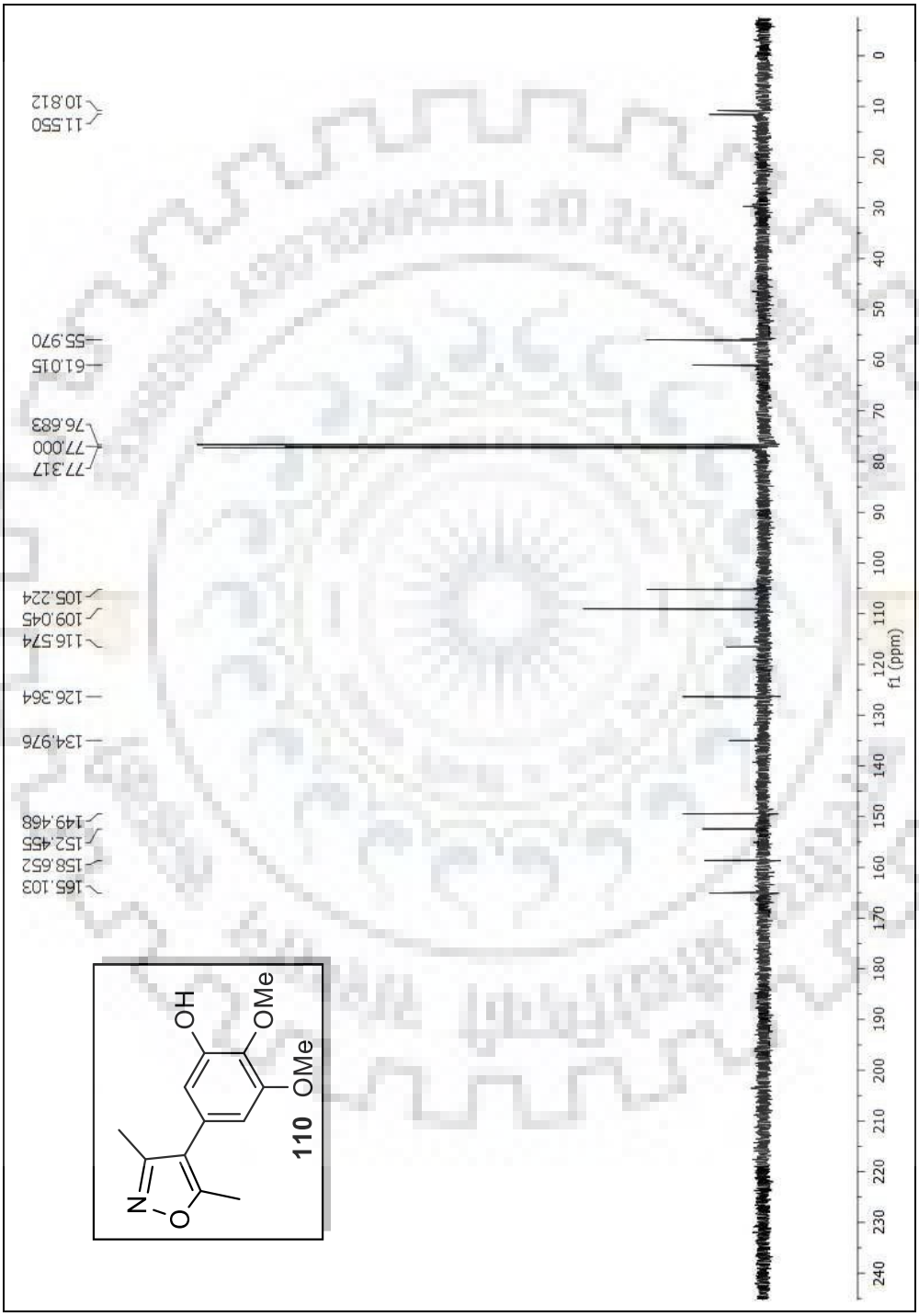


Figure S-54: ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of **110**.

Figure S-55: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **111**.

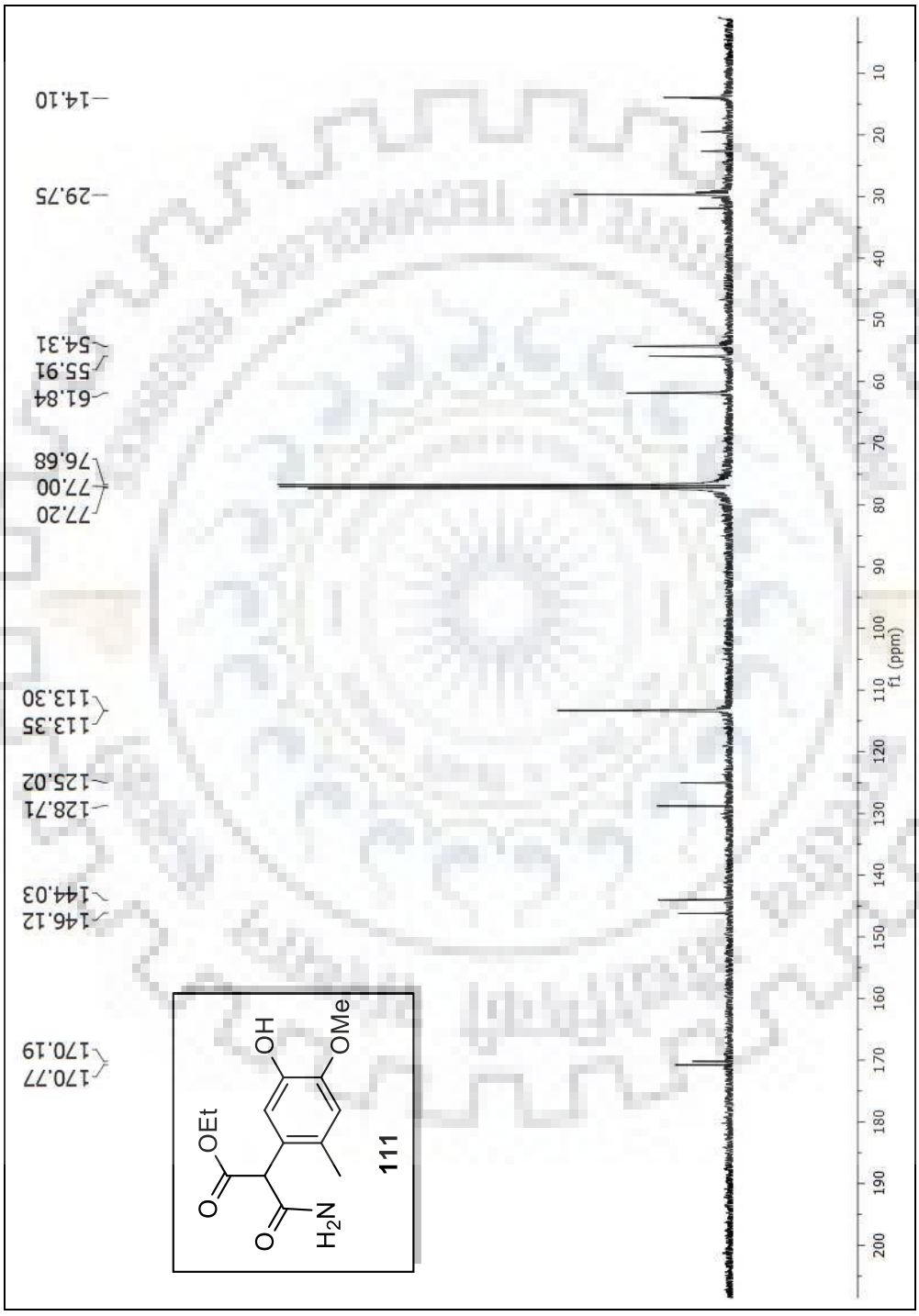


Figure S-56: ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of **111**.

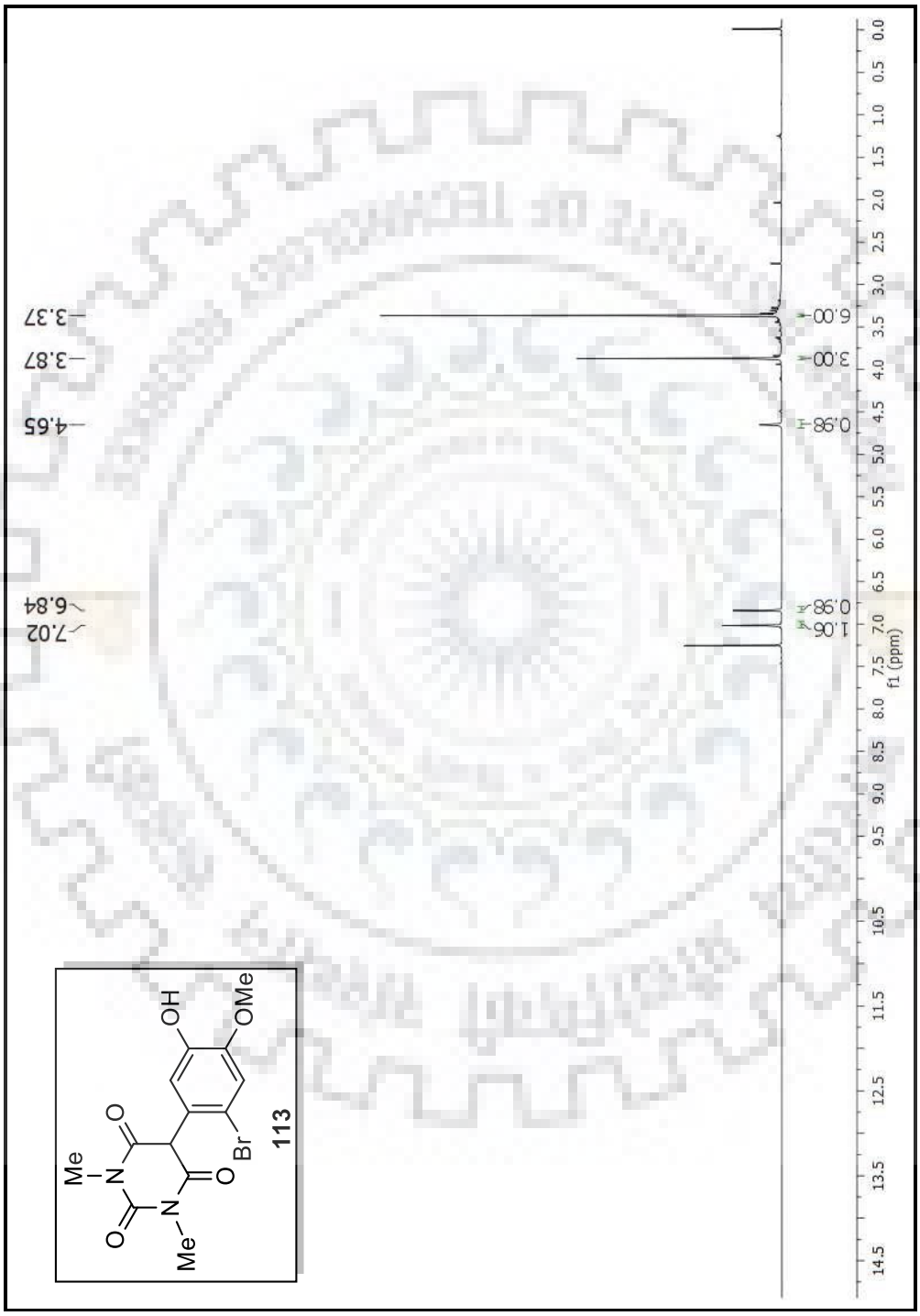


Figure S-57: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **113**.

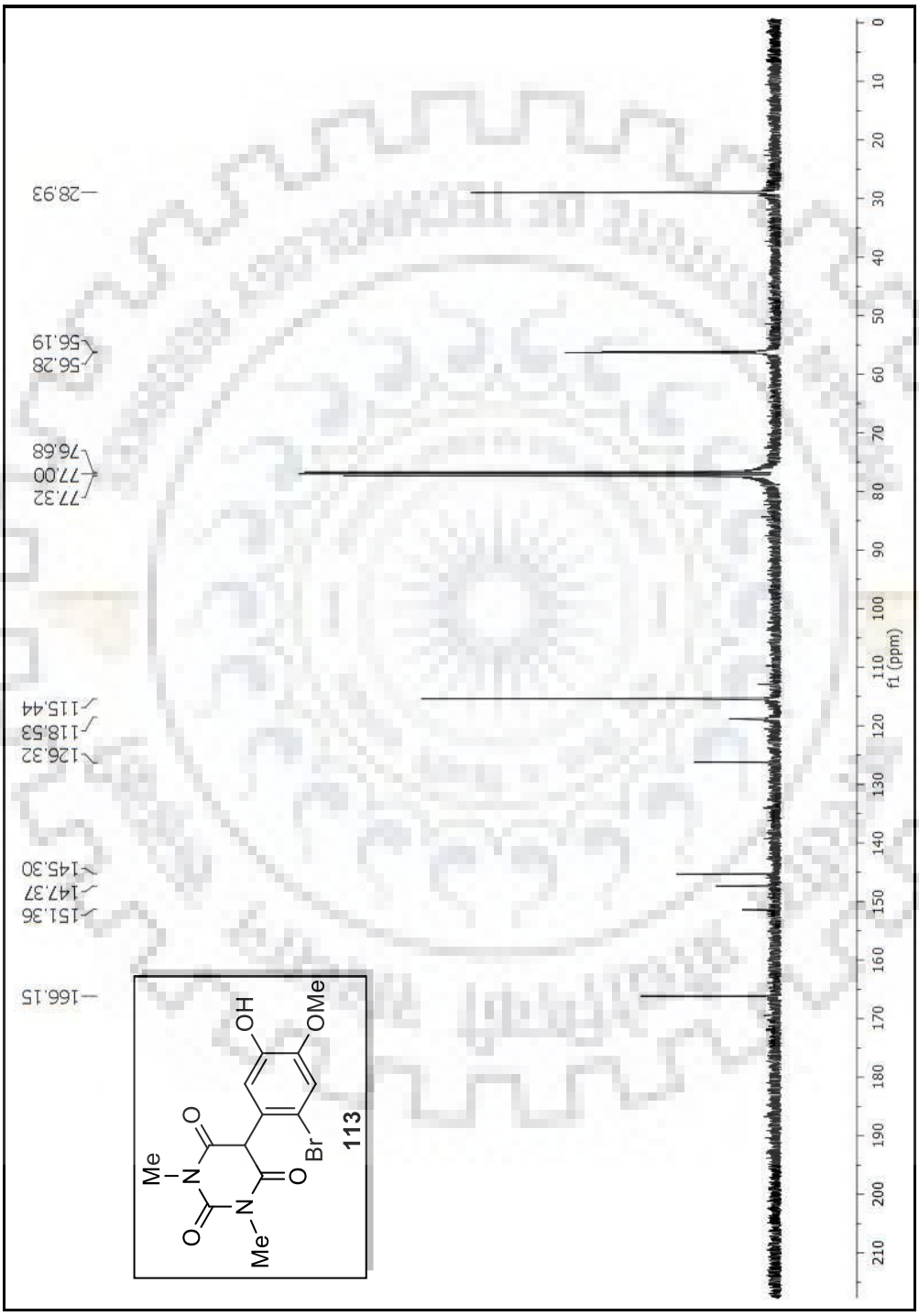


Figure S-58: ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of **113**.

Figure S-59: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **121**.

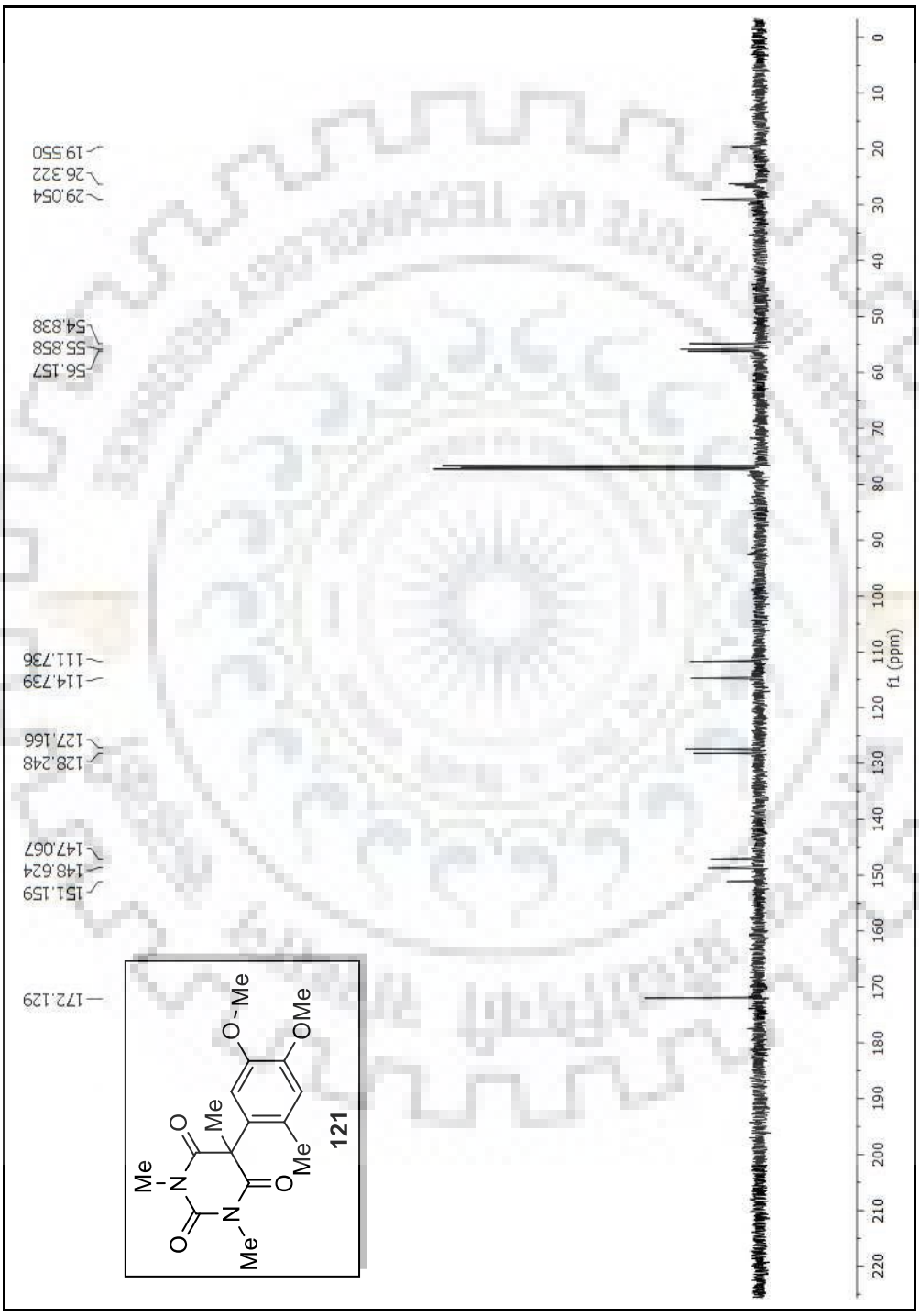


Figure S-60: ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of **121**.

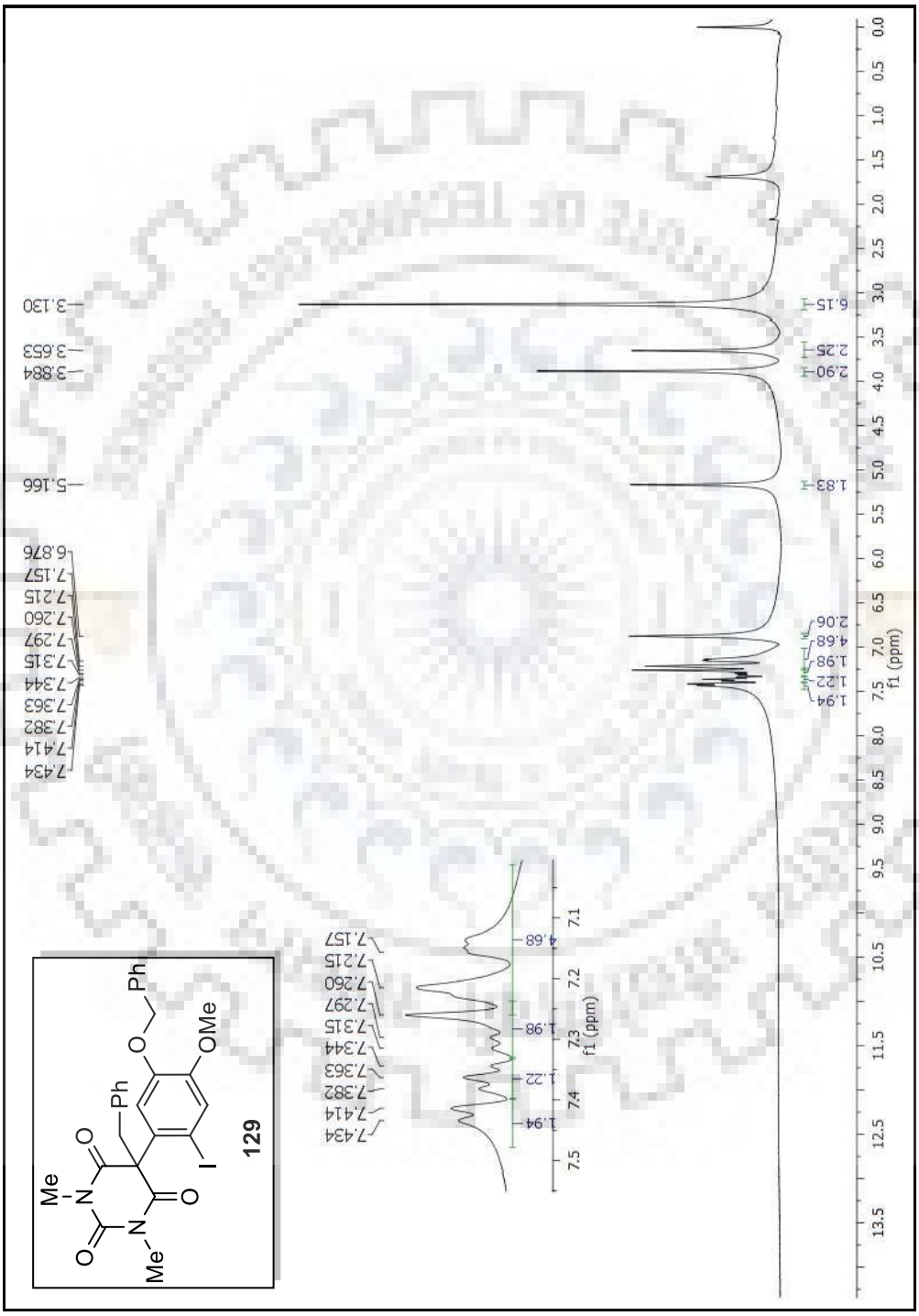


Figure S-61: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **129**.

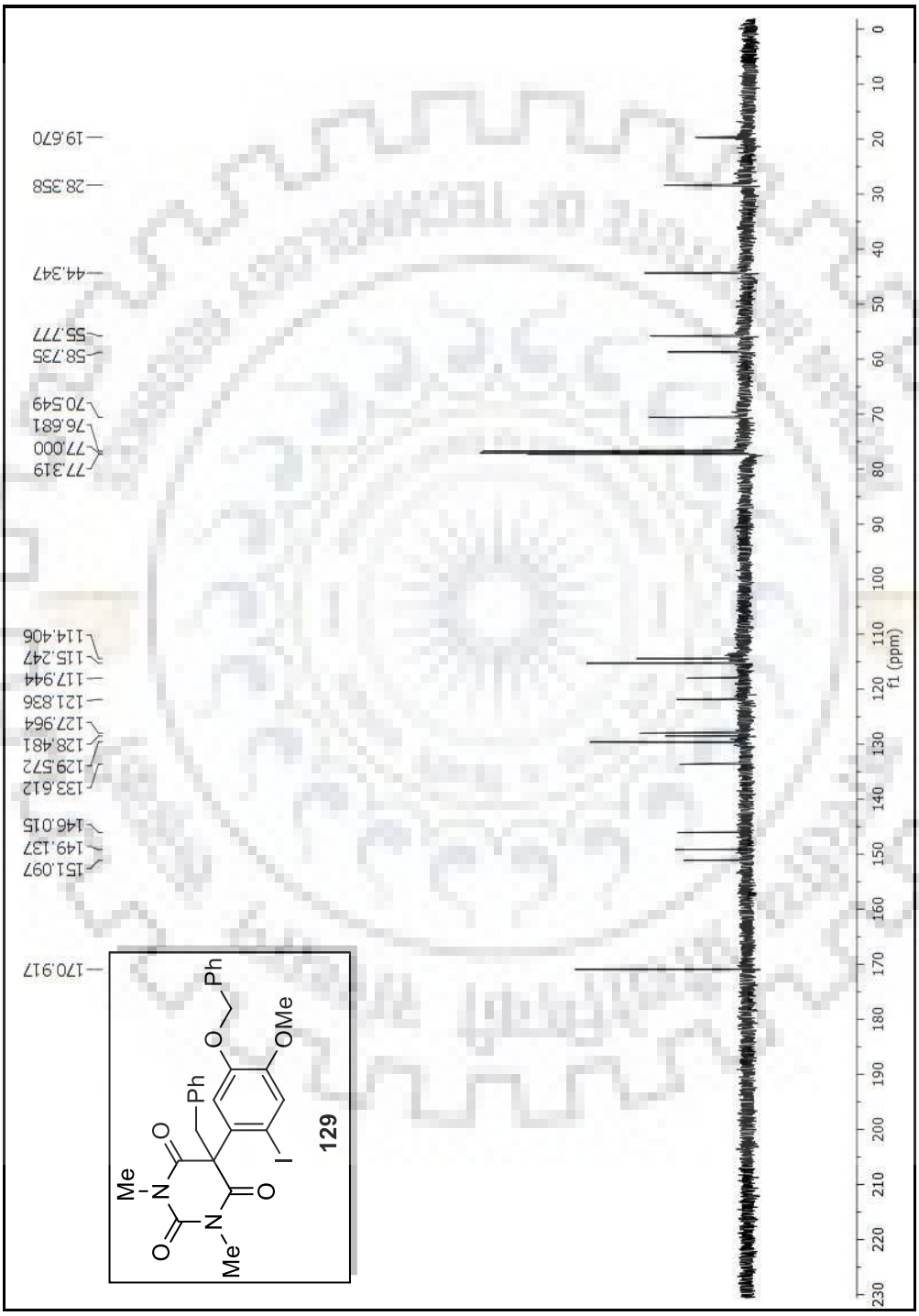


Figure S-62: ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of **129**.

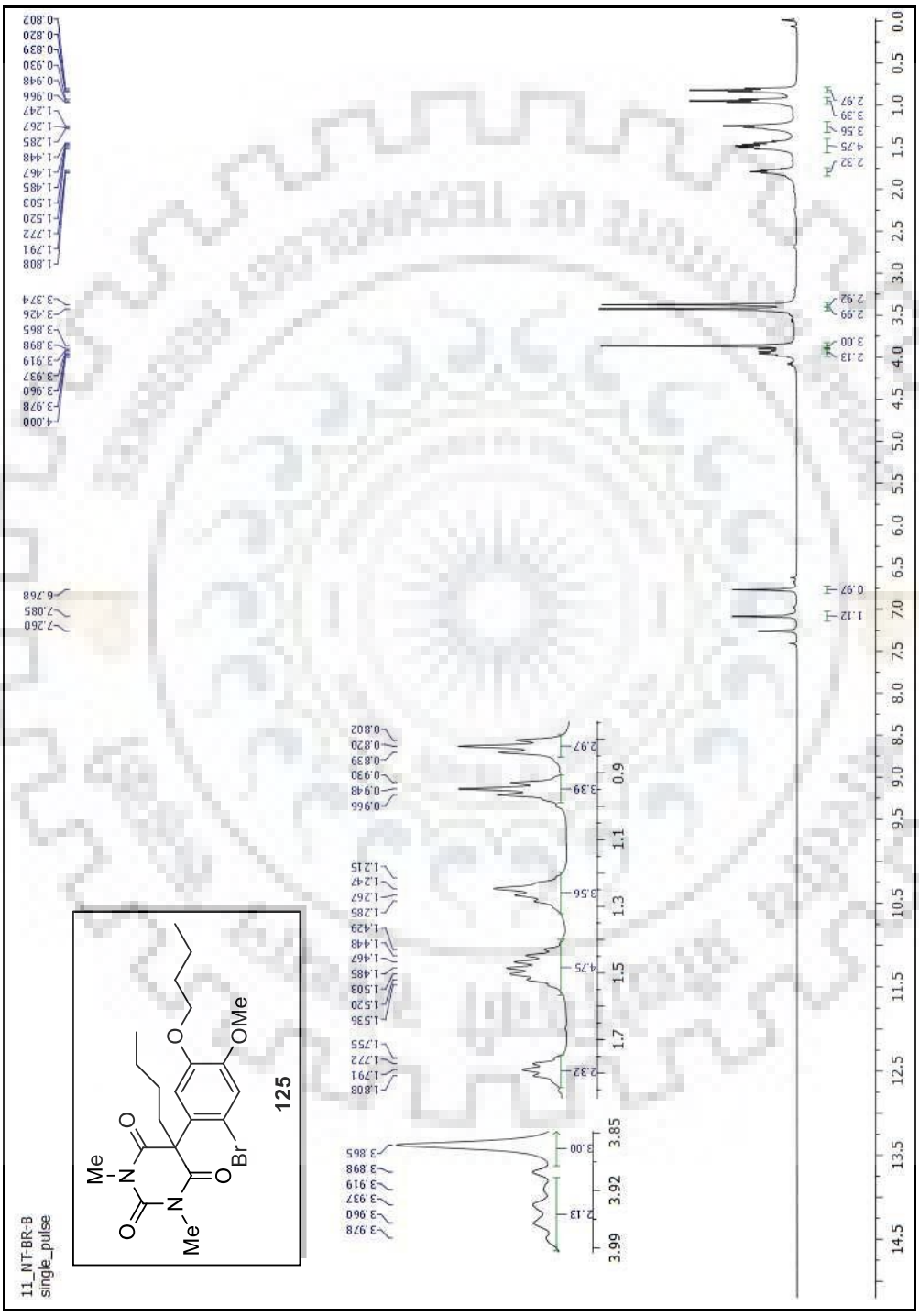


Figure S-63: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **125**.

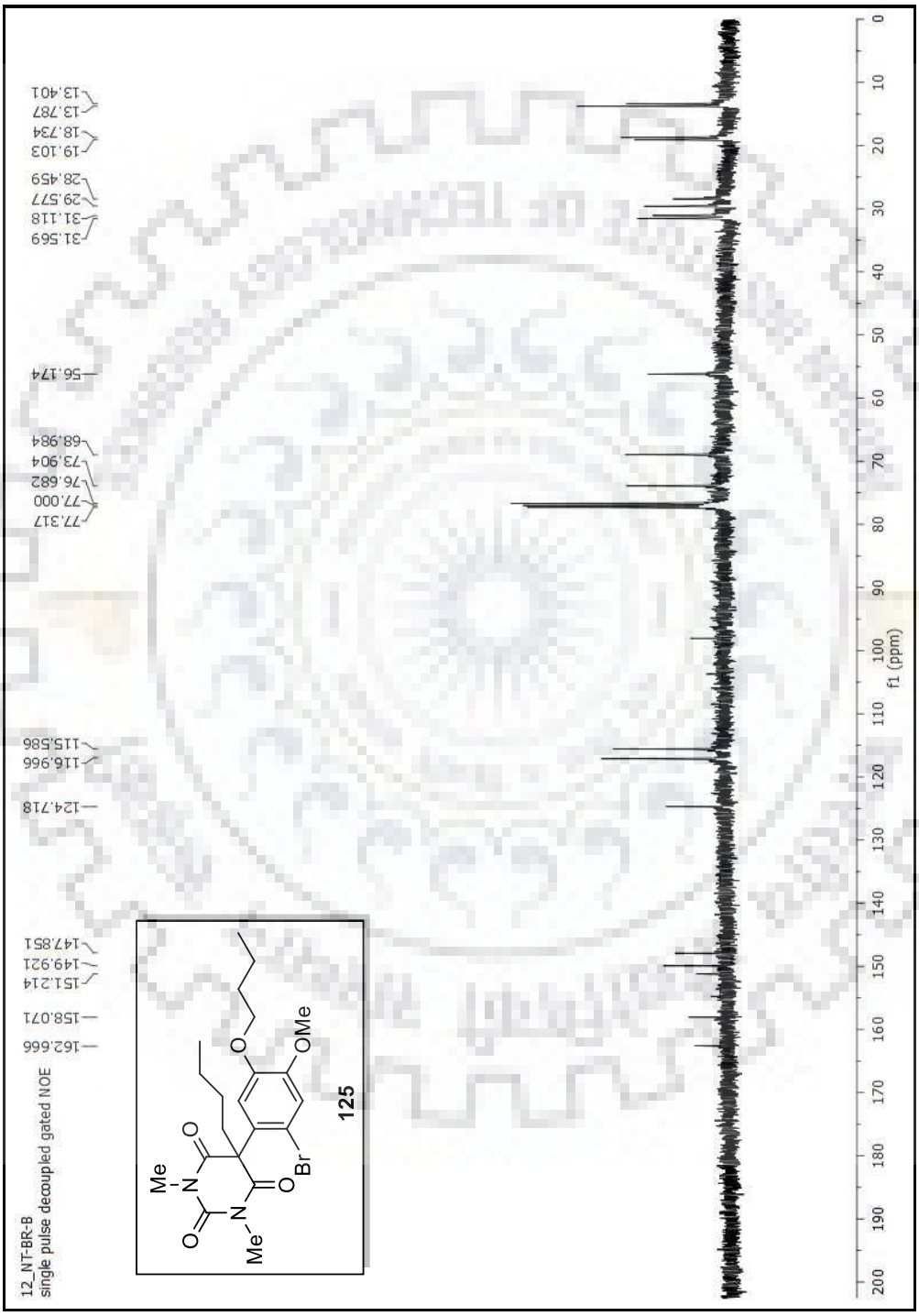


Figure S-64: ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of **125**.

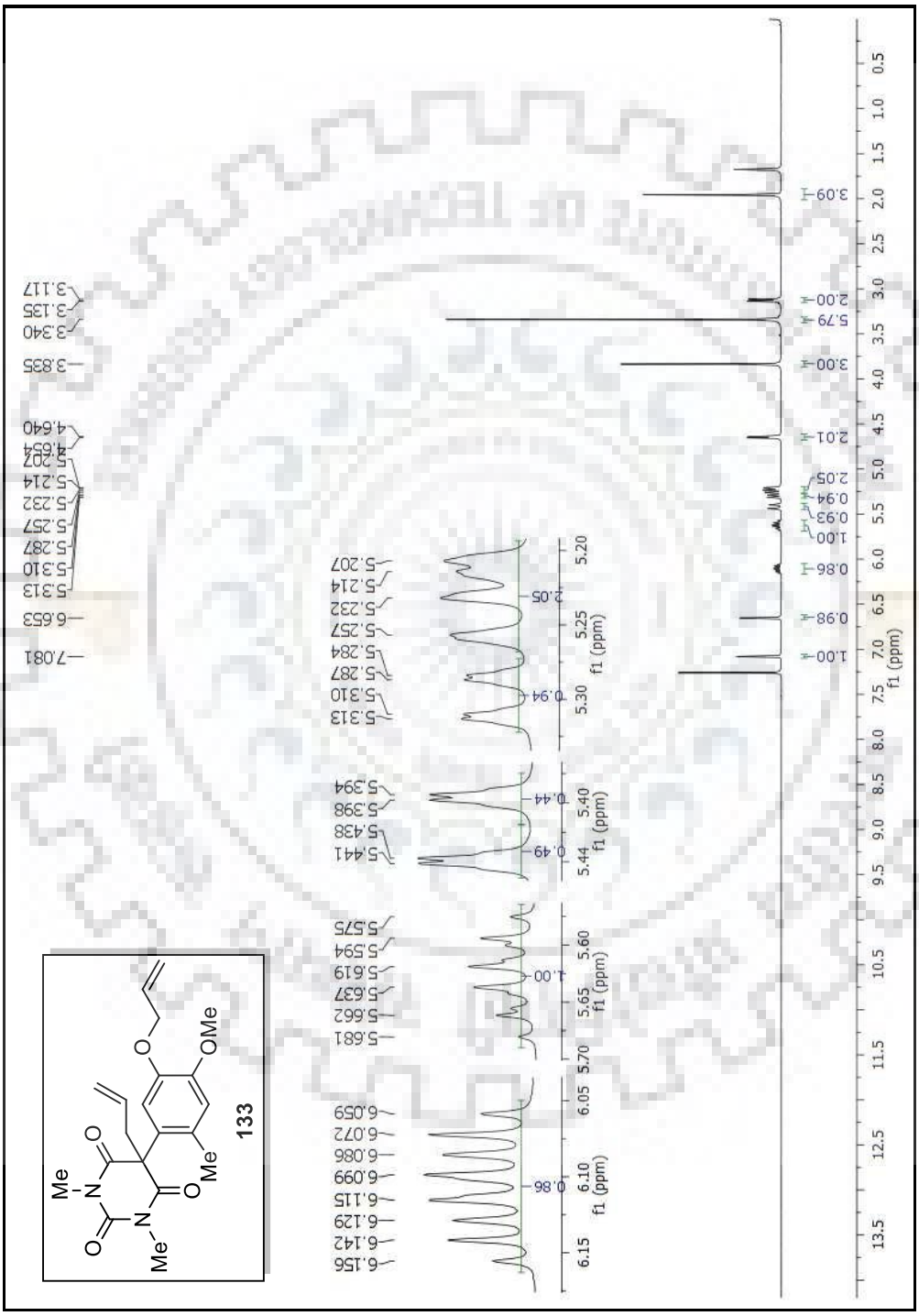


Figure S-65: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **133**.

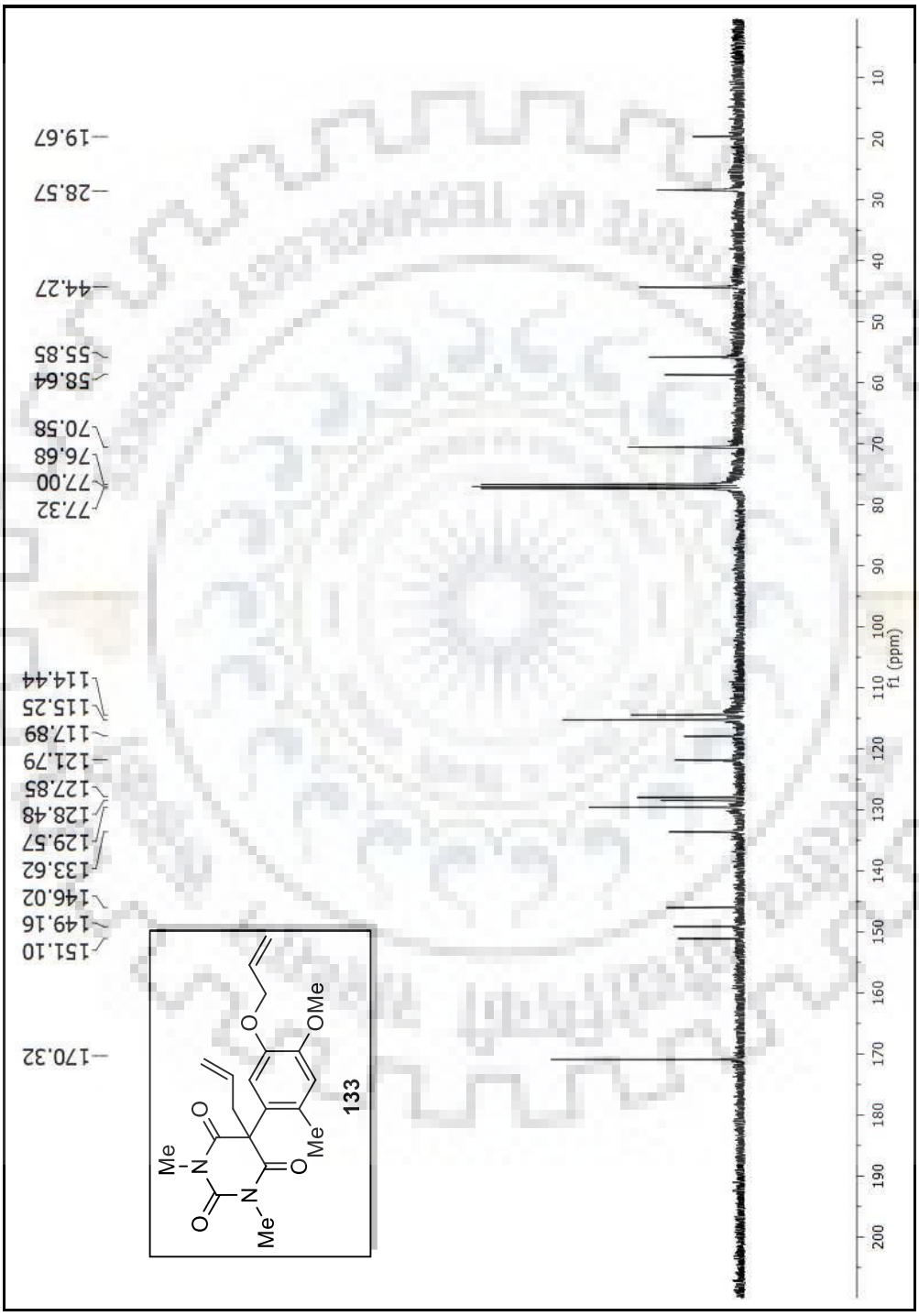


Figure S-66: ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of **133**.

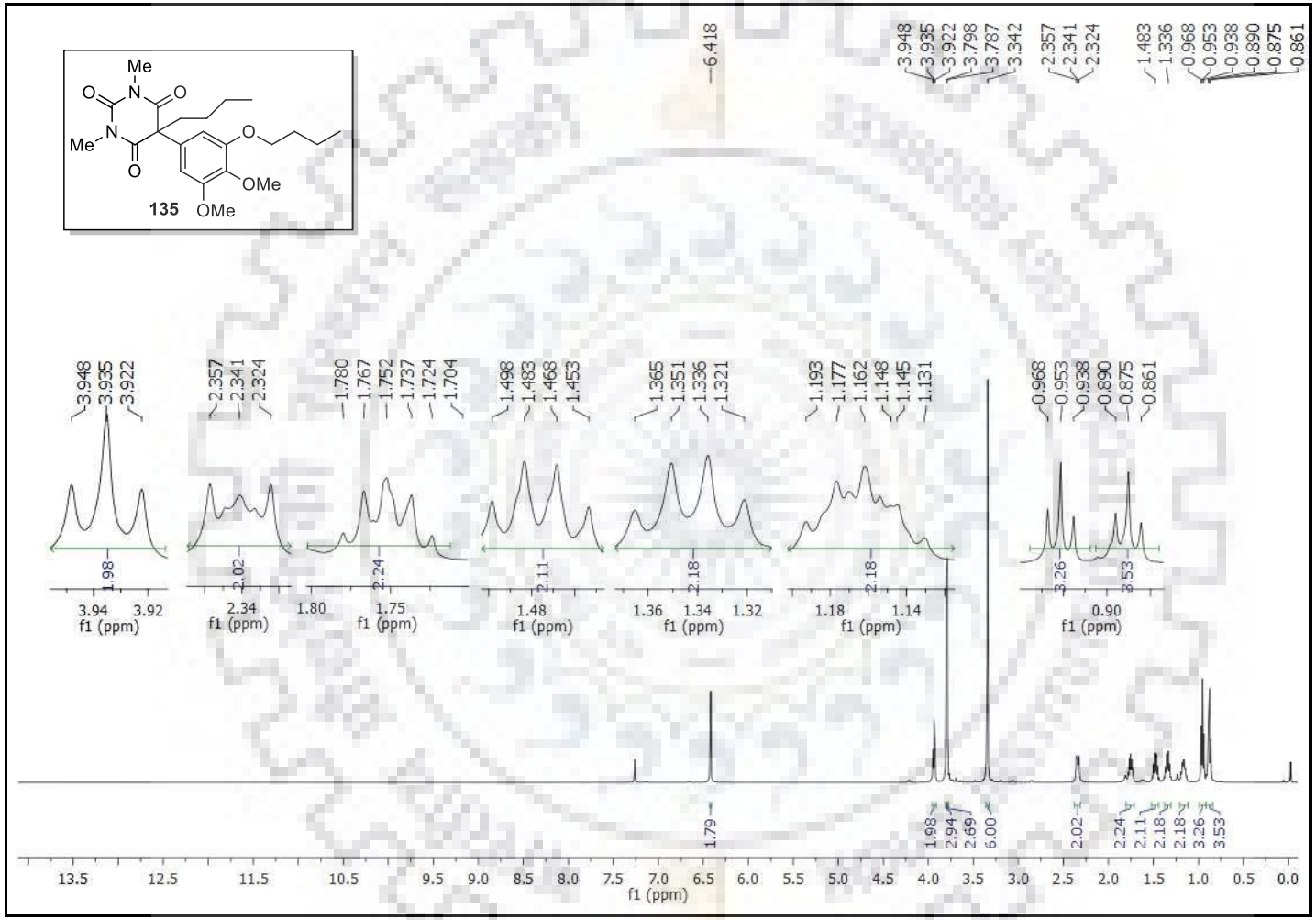


Figure S-67: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **135**.

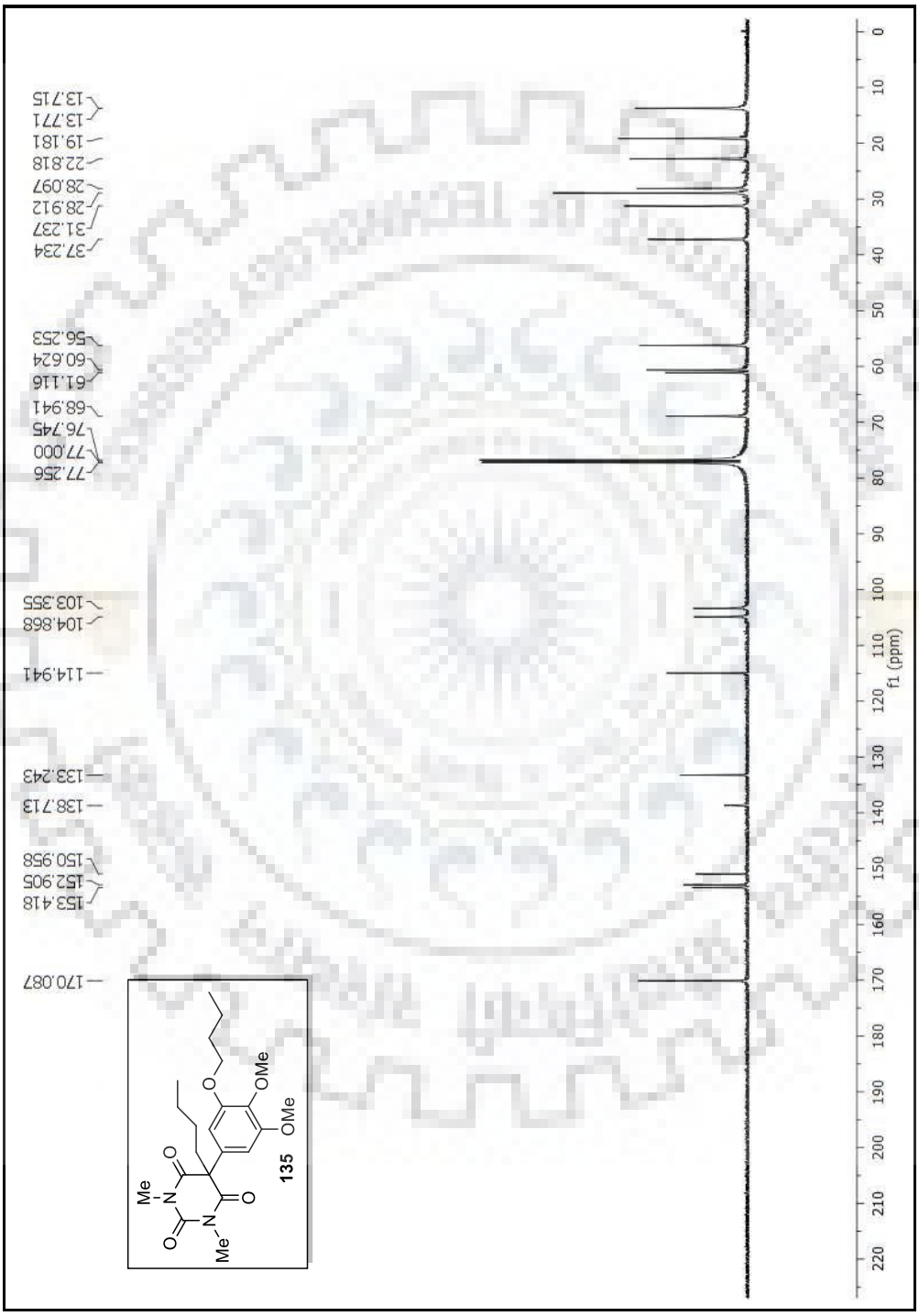


Figure S-68: ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of **135**.

Figure S-69: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **139**.

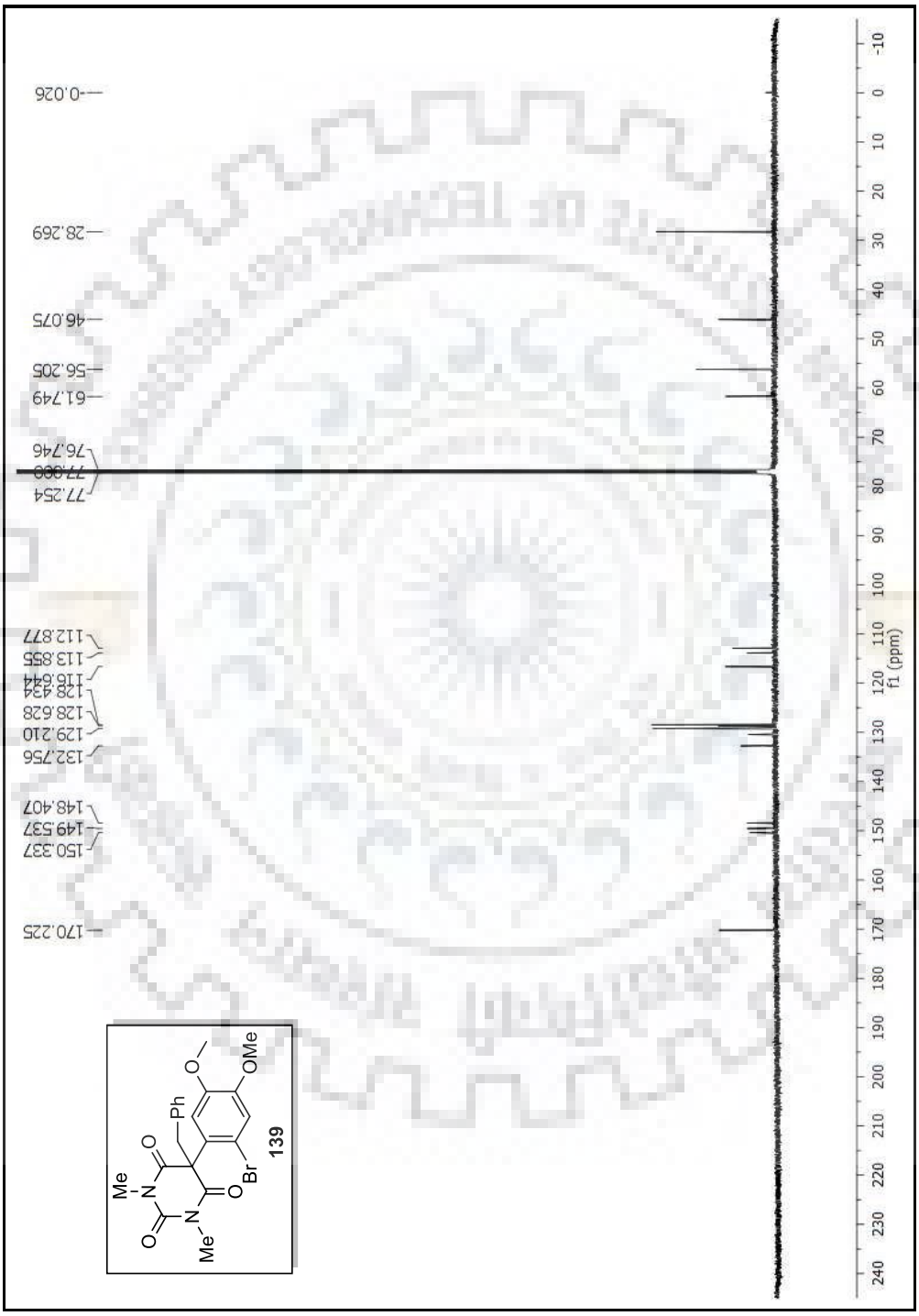
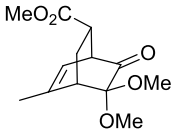


Figure S-70: ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of **139**.

Structures of the Compounds



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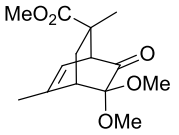

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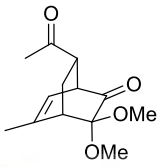

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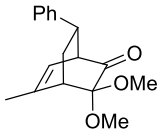

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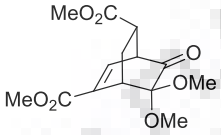

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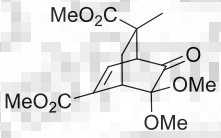

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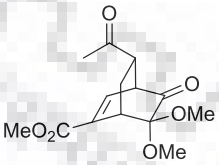

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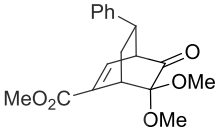

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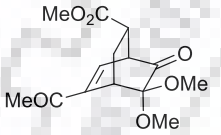

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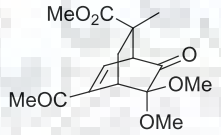

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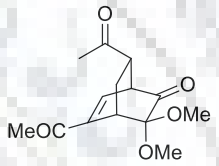

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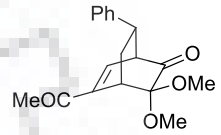

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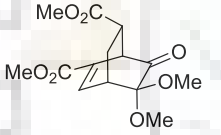

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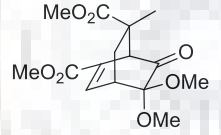

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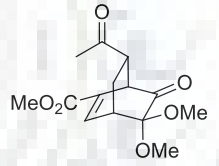

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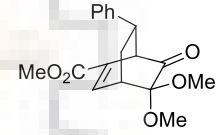

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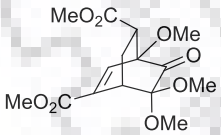

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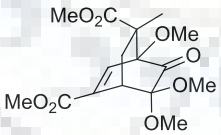

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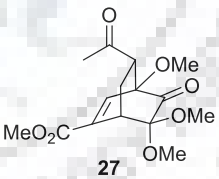

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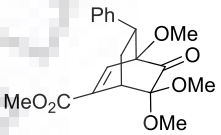

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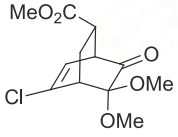

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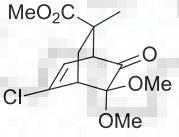

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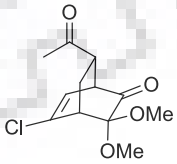

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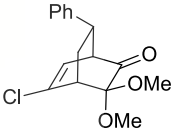

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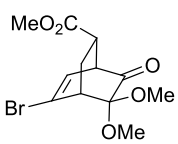

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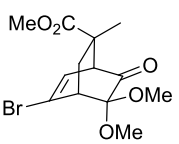

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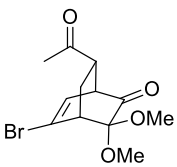

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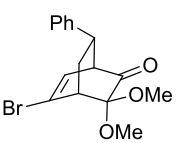

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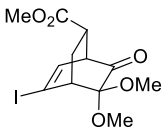

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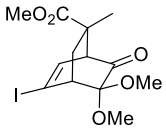

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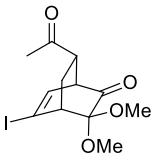

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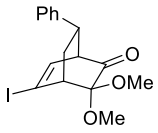

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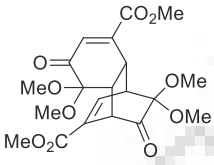

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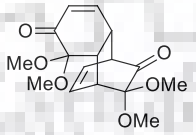

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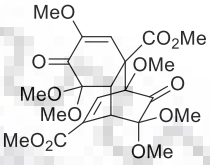

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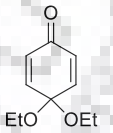

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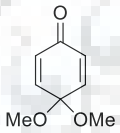

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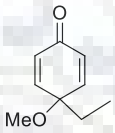

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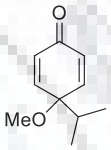

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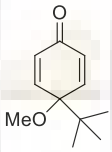

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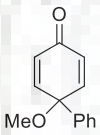

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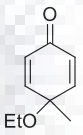

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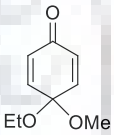

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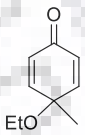

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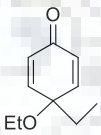

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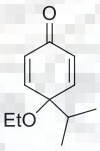

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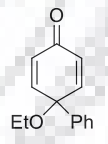

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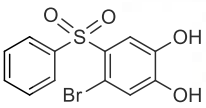

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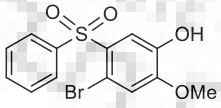

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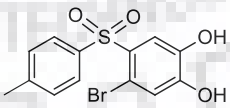

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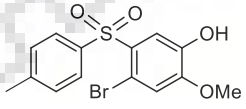

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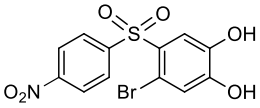

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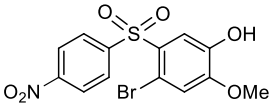

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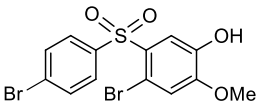

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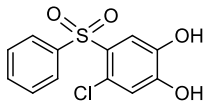

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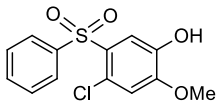

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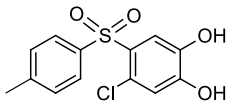

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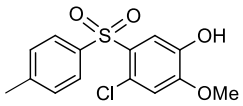

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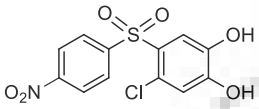

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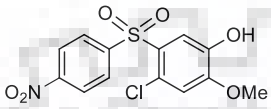

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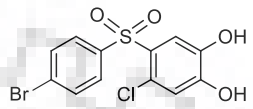

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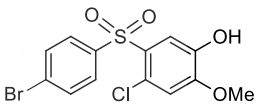

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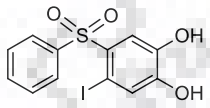

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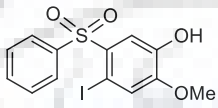

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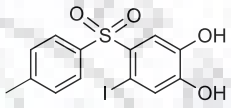

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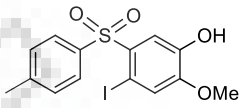

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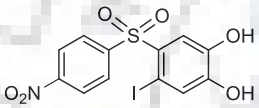

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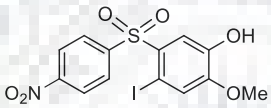

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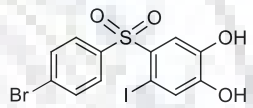

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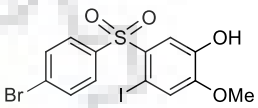

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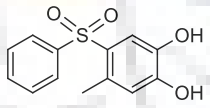

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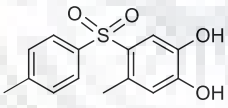

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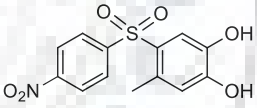

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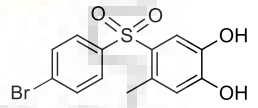

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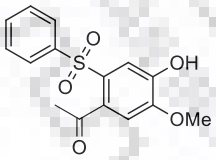

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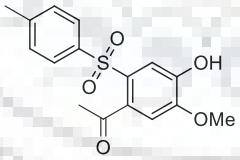

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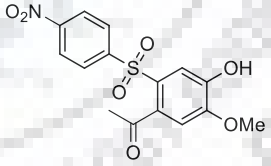

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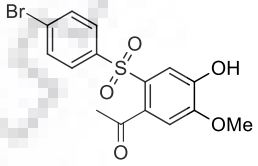

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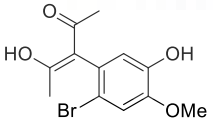

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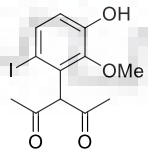

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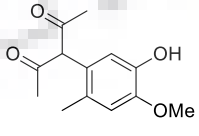

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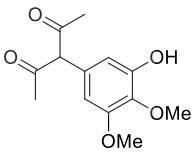

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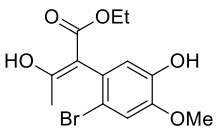

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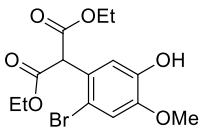

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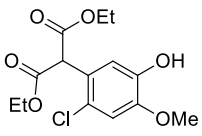

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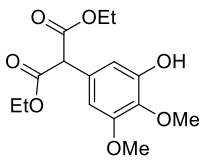

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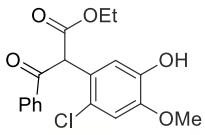

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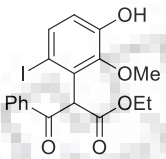

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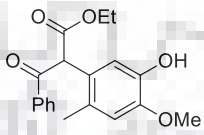

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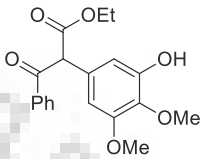

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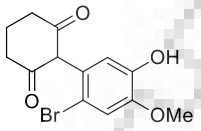

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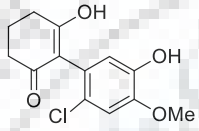

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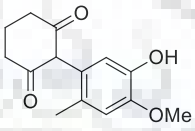

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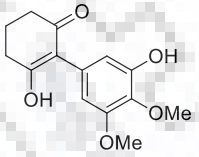

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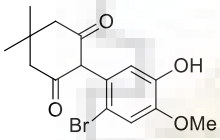

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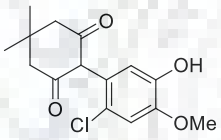

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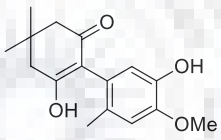

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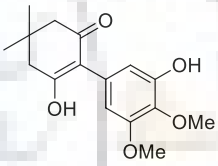

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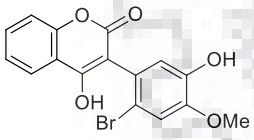

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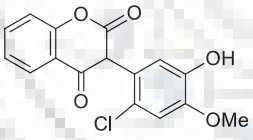

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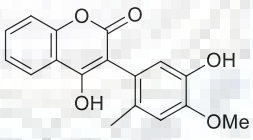

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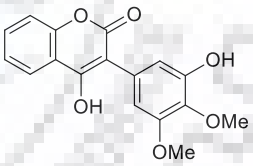

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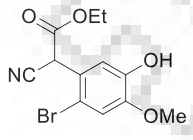

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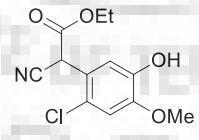

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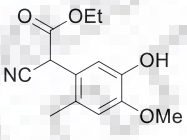

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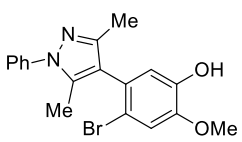

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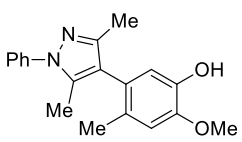

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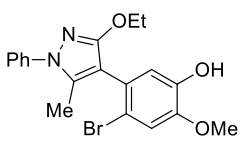

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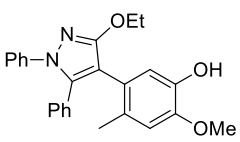

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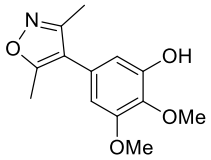

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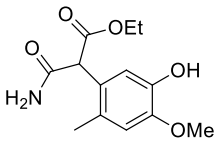

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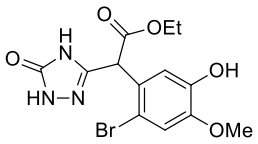

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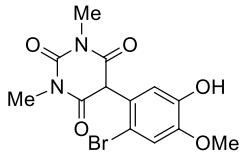

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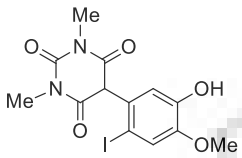

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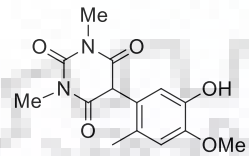

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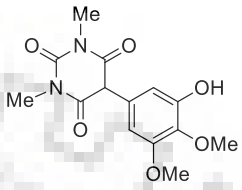

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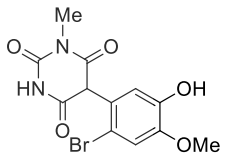

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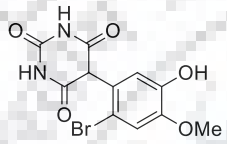

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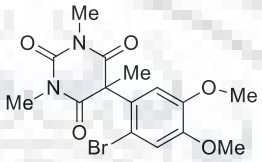

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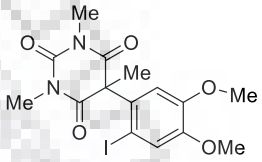

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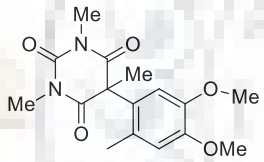

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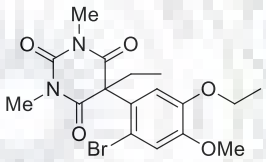

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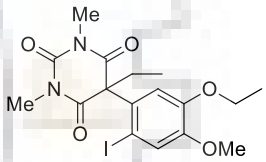

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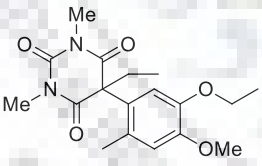

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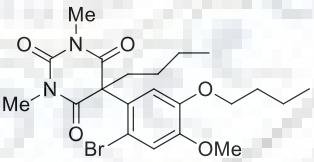

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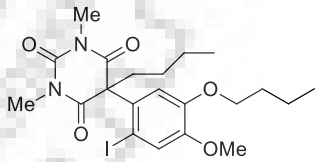

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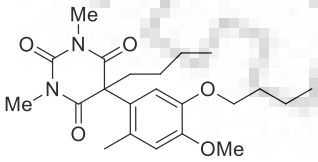

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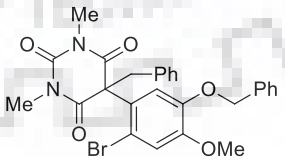

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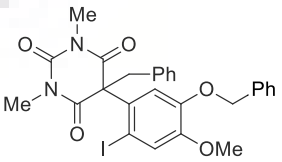

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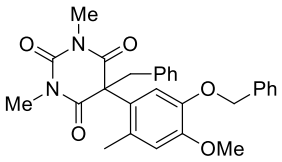

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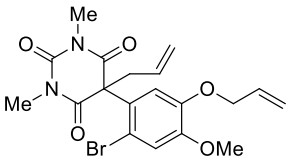

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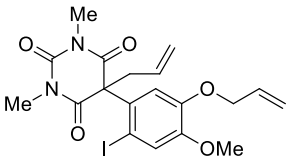

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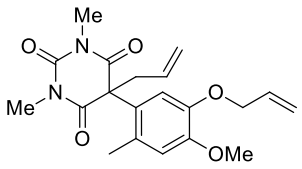

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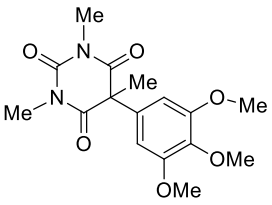

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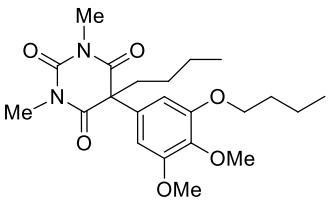

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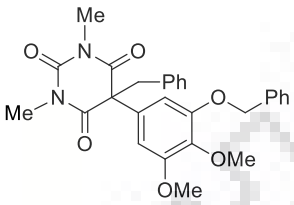

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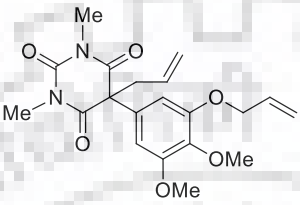

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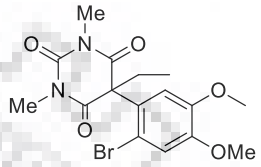

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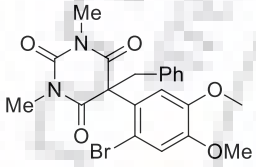

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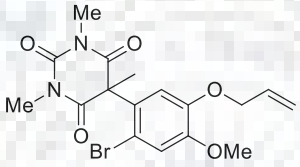

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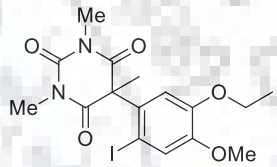

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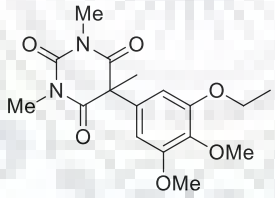

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List of Publications

1. Iodobenzene and *m*-chloroperbenzoic acid mediated oxidative dearomatization of phenols.
   Taneja, **N**.; Peddinti, R. K.
   Tetrahedron Lett. **2016,** *57*, 3958–3963.

2. Catalyst-free sulfonylation of 2-methoxyphenols: Facile one-pot synthesis of (arylsulfonyl)- catechols in aqueous media.
   Taneja, **N**.; Peddinti, R. K.
   Eur. J. Org. Chem. **2017**, 5306–5314.

3. Metal-free direct C-arylation of 1,3-dicarbonyl compounds and β-cyanoacetates: Synthesis of diverse array of *meta*-functionalized phenols.
   Taneja, **N**.; Peddinti, R. K.
   Manuscript under preparation.

4. *meta*-Substitution of phenols: Direct synthesis of C-5 substituted barbituric acids.
   Taneja, **N**.; Peddinti, R. K.
   Manuscript under preparation

List of Conferences attended

1. **Neha Taneja**, R. K. Peddinti
   Iodobenzene and *m*-chloroperbenzoic acid mediated oxidative dearomatization of phenols. Poster presented in XII J-NOST conference held at CSIR-CDRI, Lucknow during during 24-27 Nov, 2016.

2. **Neha Taneja**, R. K. Peddinti
   Iodobenzene and *m*-chloroperbenzoic acid mediated oxidative dearomatization of phenols. Poster presented in ICOS-21st International Conference on Organic Synthesis conference held at IIT Bombay, Powai during December 11-16, 2016.

3. **Neha Taneja**, R. K. Peddinti
   Catalyst-Free Sulfonylation of 2-Methoxyphenols: Facile One-Pot Synthesis of (Arylsulfonyl)catechols in Aqueous Media. Poster presented in 21st CRSI-ACS held at IICT-hyderabad during July 14-16, 2017.

4. **Neha Taneja**, R. K. Peddinti
   Catalyst-Free Sulfonylation of 2-Methoxyphenols: Facile One-Pot Synthesis of (Arylsulfonyl)catechols in Aqueous Media. Poster presented in CFOS held at IIT-Roorkee during December 24-26, 2017.