A Thesis Entitled

SYNTHETIC STUDIES IN OXYGEN HETEROCYCLES

Submitted to Goa University for the Award of the Degree of

DOCTOR OF PHILOSOPHY

In

CHEMISTRY

By

Ms. MAYURI MADHUKER NAIK

M. Sc.

Under the Guidance of

PROF. VIJAYENDRA P. KAMAT

Department of Chemistry

and

PROF. SANTOSH G. TILVE

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Taleigao Plateau, Goa 403 206

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DEPARTMENT OF CHEMISTRY

CERTIFICATE

This is to certify that the thesis entitled, "**Synthetic Studies in Oxygen Heterocycles**" submitted by Ms. **MAYURI MADHUKER NAIK**, is a record of research work carried out by the candidate during the period of study under our supervision and that it has not previously formed the basis for the award of any degree or diploma or other similar titles.

Goa University
April 2018

Prof. Vijayendra P. Kamat
Research Guide
Department of Chemistry
Goa University

Prof. Santosh G. Tilve
Research Guide
Department of Chemistry
Goa University

DECLARATION

I hereby declare that the work embodied in the thesis entitled "**Synthetic Studies in Oxygen Heterocycles**" is the result of investigations carried out by me under the guidance of **PROF. VIJAYENDRA P. KAMAT** and **PROF. SANTOSH G. TILVE** at Department of Chemistry, Goa University and that it has not previously formed the basis for the award of any degree or diploma or other similar titles.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

Goa University
April 2018

Ms. Mayuri M. Naik
Ph. D. Student
Department of Chemistry
Goa University

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I am also thankful to **Dr. Gopakumar** (Librarian, Goa University) for his assistance in the plagiarism check of thesis. I also acknowledge the **staff members of Library** and **administrative members** Goa University for being kind and helpful. I also thank all the **non-teaching staff,** Department of Chemistry, Goa University for helping at numerous times.

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Last but not the least, I thank Almighty for giving me good health, strength and support to overcome all the barriers in my life and become a good human being by continuously showering his kind blessings.

Ms. Mayuri M. Naik

Dedicated

To My

Beloved Parents

TABLE OF CONTENT

GENERAL REMARKS

1) The compound numbers, figure numbers, scheme numbers and reference numbers given in each chapter refer to that particular chapter only.

2) All melting points and boiling points were recorded using Thiele's tube and are uncorrected.

3) Commercial reagents were used without further purification.

4) All solvents were distilled prior to use and then dried using standard procedure.

5) All reagents were prepared using literature methods.

6) Chromatographic purification was conducted by column chromatography using silica gel (60 – 120 mesh size) or by flash chromatography using silica gel (200-400 mesh size).

7) Thin layer chromatography (TLC) was carried out on silica gel 60 F254 aluminium plates purchased from Merck.

8) The IR spectra were recorded on Shimadzu FT-IR spectrophotometer.

9) ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Brucker AVANCE 400 instrument and the multiplicities of carbon signals were obtained from DEPT experiment. Chemical shifts are expressed in δ relative to tetramethylsilane (TMS) which is expressed in ppm.

10) The high resolution mass spectra (HRMS) were recorded on MicroMass ES-QTOF mass spectrometer.

11) The absorbance values were obtained from UV-Vis spectrophotometer (Shimadzu-1800) at 517 nm.

DEFINITION OF ABBREVIATIONS

General Abbreviations

g	Gram/s	*ee*	Enantiomeric excess
mg	Milligram/s	*dr*	Diastereomeric ratio
µg	Microgram/s	conc.	Concentrated
mol	Mole/s	aq.	Aqueous
mmol	Millimole/s	*o*	Ortho
mL	Milliliter/s	*m*	Meta
mm	Millimeter/s	*p*	Para
nm	Nanometre/s	*MS*	Molecular sieves
m.p.	Melting point	*psi*	Pounds per square inch
b.p.	Boiling point	*cat.*	Catalytic
ev	Electron volt	*atm.*	Atmospheric
lit.	Literature	*et al.*	Et alia (and others)
d	Day/s	TLC	Thin layer chromatography
h	Hour/s	sat.	Saturated
min	Minute/s	MW	Microwave
sec	Second/s	anhyd.	Anhydrous
µM	Micromolar	°C	Degree Celcius
nM	Nanomolar	rt	Room temperature
ppm	Parts per million	*Z*	Zussamen (together)
hv	Irradiation	*E*	Eentegegen (opposite)
%	Percentage	equiv	Equivalent
R	Rectus	wt./wt.	Weight per unit weight
S	Sinister	Å	Ångström

Compound Abbreviations

Ac	Acetyl	dppp	1,3-Bis(diphenylphosphino)propane
acac	Acetylacetone	DTDB	Di-*tert*-butyl peroxide
AcOH	Acetic acid	EtOAc	Ethyl acetate
Ac_2O	Acetic anhydride	EtOH	Ethanol
AgOTf	Silver trifluoromethanesulfonate	Et_2O	Diethyl ether
AIBN	2,2′-Azobisisobutyronitrile	Et_3N	Triethylamine
$BF_3.OEt_2$	Boron trifluoride diethyl etherate	$Fe(OTf)_3$	Iron(III) trifluoromethanesulfonate
binap	(2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl)	$Ga(OTf)_3$	Gadolinium(III) trifluoromethanesulfonate
$Bi(OTf)_3$	Bismuth(III)	IBX	2-Iodoxybenzoic acid

	trifluoromethanesulfonate		
bipy	2,2′-Bipyridine	$In(OTf)_3$	Indium(III) trifluoromethanesulfonate
BMIM	1-Butyl-3-methyimidazolium	KO*t*-Bu	Potassium *t*-butoxide
Bn	Benzyl	LDA	Lithium diisopropylamide
BnBr	Benzyl bromide	LTA	Lead tetraacaetate
Boc	*t*-Butyloxycarbonyl	$MeNO_2$	Nitromethane
n-Bu/Bu	normal (primary) Butyl	MOM	Methoxymethyl ether
n-BuLi	*n*-Butyl lithium	NBS	*N*-Bromosuccinimide
t-Bu	*t*-Butyl	NCS	*N*-Chlorosuccinimide
t-BuLi	*t*-Butyl lithium	NIS	*N*-Iodosuccinimide
t-BuOH	*t*-Butyl alcohol	NMP	*N*-Methyl-2-pyrrolidone
t-BuOK / KTBT	Potassium tertiary butoxide	PCC	Pyridinium chlorochromate
CH_3SO_3H	Methane sulfonic acid	Pd/C	Palladium on activated charcoal
COD	Cycloocta-1,5-diene	Phen/1,10-phen	1,10-Phenanthroline
m-CPBA	*m*-Chloroperbenzoic acid	Ph_2O	Diphenyl ether
$Cu(OAc)_2$	Copper(II) acetate	S-Phos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
$Cu(OTf)_2$	Copper(II) trifluoromethanesulfonate	PIFA	Phenyliodine(III)bis(trifluoroacetate)
CuTc	Copper(I) thiophene-2-carboxylate	PPA	Polyphosphoric acid
Cy	Cyclohexyl	PPh_3	Triphenylphosphine
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene	Py	Pyridine
o-DCB	*o*-Dichlorobenzene	$Sc(OTf)_3$	Scandium(III) trifluoromethanesulfonate
DCC	Dicyclohexylcabodiimide	TBACl	Tetrabutylammonium chloride
DCE	1,2-Dichloroethane	TBAF	Tetra-*n*-butylammonium fluoride
DCM	Dichloromethane	TBHP	*tert*-Butyl hydroperoxide
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone	TEBAC	Benzyltriethylammonium chloride
DEAD	Diethyl azodicarboxylate	TEMPO	2,2,6,6-Tetramethylpiperidin-1-yl
DIAD	Diisopropyl azodicarboxylate	TFA	Trifluoroacetic acid
DIH	1,3-Diiodo-5,5-dimethylhydantoin	TFAT	Trifluoroacetyltriflate
DMA	Dimethylacetamide	TFE	2,2,2-Trifluoroethanol
DMAP	4-Dimethylaminopyridine	TfOH	Triflic acid
DME	Dimethoxyethane	THF	Tetrahydrofuran
DMF	*N*,*N*-Dimethylformamide	TMOF	Trimethyl orthoformate
DMSO	Dimethyl sulfoxide	TMS	Tetramethylsilane

dppb	1, 4-Bis(diphenylphosphino)butane	Tol-BINAP	(*S*)-(-)-2,2'-Bis(di-*p*-tolylphosphino)-1,1'-binaphthyl
dppf	1,1'-Bis(diphenylphosphino)ferrocene	*p*-TsOH/*p*-TSA	*p*-Toluene sulfonic acid
DPPH	2,2-Diphenyl-1-picrylhydrazyl	$Zn(OTf)_2$	Zinc trifluoromethanesulfonate

Spectroscopic Abbreviations

IR	Infrared	XRD	X-ray diffraction
υ_{max}	Frequency maximum	ppm	Parts per million
cm^{-1}	Frequency in wavenumber	ppb	Parts per billion
UV	Ultra violet	δ	Delta (Chemical shift in ppm)
NMR	Nuclear magnetic resonance	MHz	Megahertz
$CDCl_3$	Deuterated chloroform	Hz	Hertz
DMSO-d_6	Deuterated dimethyl sulfoxide	s	Singlet
acetone-d6	Deuterated acetone	d	Doublet
m	Multiplet	t	Triplet
dd	Doublet of doublet	q	Quartet
td	Triplet of a doublet	*J*	Coupling constant
dt	Doublet of a triplet	DEPT	Distortionless Enhancement by Polarization Transfer
br s	Broad singlet	HRMS	High Resolution Mass Spectrometry
M^+	Molecular ion	HPLC	High performance liquid chromatography
m/z	Mass to charge ratio	ICP-MS	Inductively coupled plasma mass spectrometry

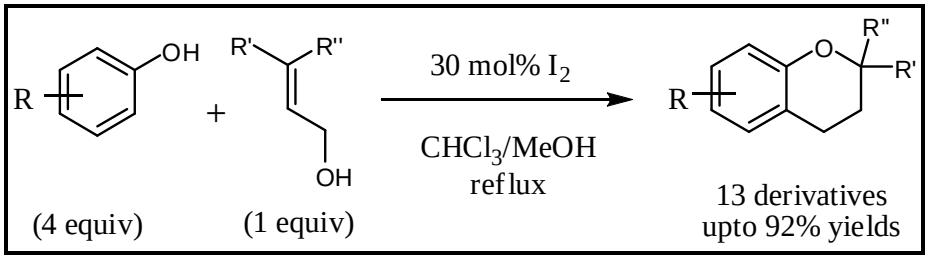
ABSTRACT OF THESIS

TITLE: **SYNTHETIC STUDIES IN OXYGEN HETEROCYCLES**

Oxygen heterocyclic compounds occupy a prominent place in organic chemistry. Multifarious naturally occurring oxygen heterocycles exhibit various biological activities. The objective of this thesis was to develop short and efficient methodologies for the synthesis of selected oxygen heterocycles such as chromans, flavones and coumestans and evaluating some synthesized analogues for anti-diabetic activity. The thesis is divided into 4 chapters.

The first chapter provides a short review on the molecular iodine mediated recent developments in the synthesis of diverse heterocycles. The role of molecular iodine either as a sole catalyst or reagent and/or in presence of oxidant has been presented. The importance and versatility of iodine in organic synthesis can be understood from the documented one pot or two step one pot synthesis of several nitrogen, oxygen and sulphur heterocycles having simple to complex structures with diverse functional groups.

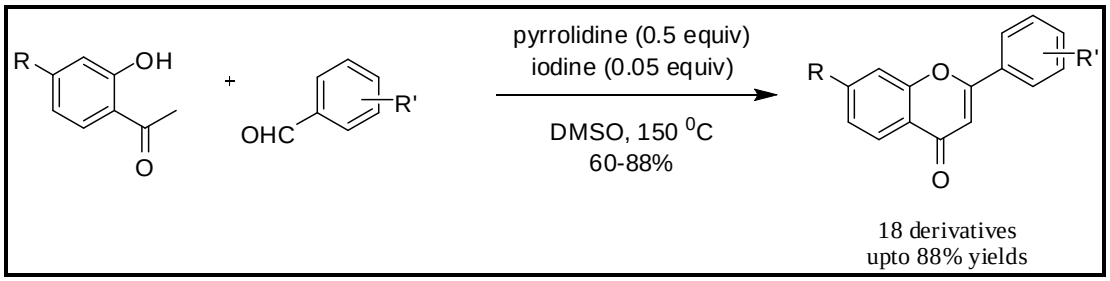
The second chapter describes a one pot method for the synthesis of chromans *via* [3+3] cyclocoupling of phenols with allylic alcohols using molecular iodine as a catalyst in refluxing chloroform or methanol solvent (Scheme I). The usefulness of this method is presented by synthesizing 13 chroman derivatives including naturally occurring dihydrolapachenole. Also, the synthesis of naturally occurring chromenes *viz.* precocene II and lapachenole has been demonstrated by conventional dehydrogenation of corresponding chromans.



Scheme I

The third chapter discusses a one pot method for the synthesis of flavones from 2'-hydroxyacetophenones and aromatic aldehydes using pyrrolidine as a base and iodine as an oxidant in DMSO solvent at 150 °C (Scheme II). The wide substrate scope was demonstrated by synthesizing 18 derivatives of flavones in good yields. The flavone formation involves domino aldol-Michael-dehydrogenation sequence. Inexpensive catalysts, use of simple

substrates which eliminates the preparation and isolation of chalcone or flavanone intermediate, good substrate generality, absence of metal catalysts and high yields of products without any side reactions make this method more advantageous.



Scheme II

Also, this chapter includes the anti-diabetic activity studies of flavones. Among several synthesized flavones, derivative **A** (Figure 1) showed highest inhibition of *α*–glucosidase enzyme. Dose dependent inhibition of *α*-glucosidase by **A** ranged from 8.4± 0.37% at 1 µg/mL to 99.3± 0.26% at 7.6 µg/mL. Thus, it is active in very low concentration as compared to the standard anti-diabetic drug acarbose which shows maximum inhibition at 400 µg/mL. Kinetic study of **A** showed non-competitive type of inhibition whereas molecular docking study showed that the **A** occupy the allosteric site and is involved in the hydrogen bonding with amino acid Lys373 of *α*–glucosidase enzyme.

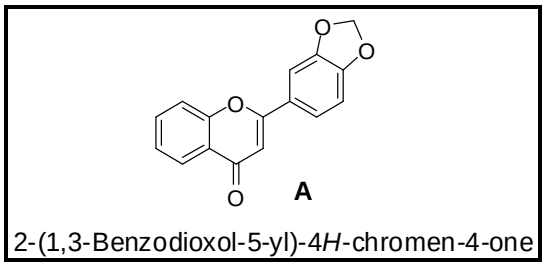
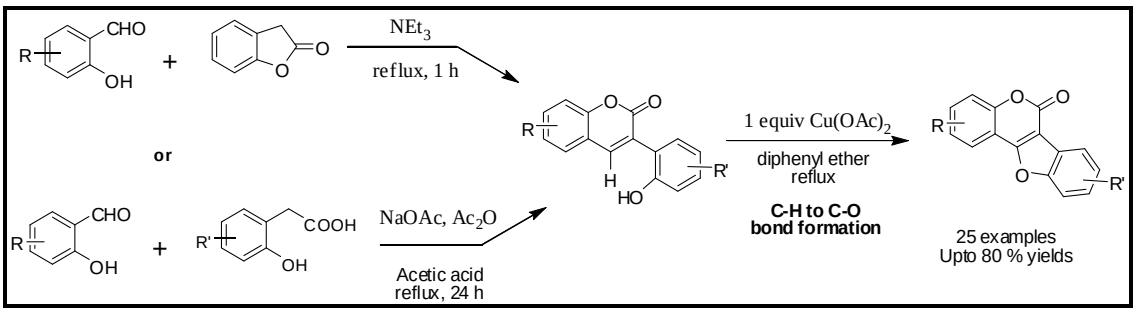


Figure 1

The fourth chapter deals with a two step synthesis of coumestan from 3-(2-hydroxyphenyl)coumarin which in turn was prepared by the condensation of salicylaldehydes and 2-coumaranone or 2-hydroxyphenylacetic acids (Scheme III). The oxidative cyclization of 3-(2-hydroxyphenyl)coumarin to produce coumestans was achieved using 1 equiv of anhydrous $Cu(OAc)_2$ in diphenyl ether under refluxing condition.



Scheme III

The broad scope of this method was demonstrated by synthesizing 23 coumestans with electron donating as well as electron releasing functionalities. These derivatives include dimethyl ether of naturally occurring coumestrol and sativol and trimethyl ether of lucernol obtained in 53-80 % yields. This efficient methodology was also successfully applied for the direct synthesis of hydroxyl substituted natural coumestans *viz*. coumestrol and 4'-*O*-methylcoumestrol (Figure 2) without any protection making this method superior.

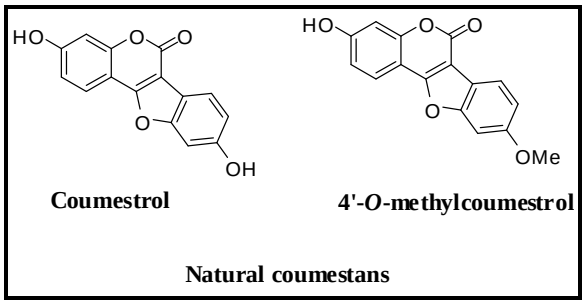


Figure 2

Use of economical $Cu(OAc)_2$, absence of any additional reagent/additive, simple reaction procedure, large substrate scope, effortless product isolation & good yields are several advantages of this method. Additional advantages includes stepwise one pot synthesis, large scale preparation, and possible use of catalytic amount of $Cu(OAc)_2$. The probable mechanism is discussed by performing additional control experiments.

LIST OF PUBLICATIONS

1. Molecular iodine catalyst promoted synthesis of chromans and 4-aryl-3,4-dihydrobenzopyran-2-ones via [3+3] cyclocoupling, **Naik, M. M.;** Kamat, D. P.; Tilve, S. G.; Kamat, V. P. *Tetrahedron* **2014**, *70*, 5221-5233.
https://doi.org/10.1016/j.tet.2014.05.093

2. Pyrrolidine and iodine catalyzed domino aldol-Michael-dehydrogenative synthesis of flavones, **Naik, M. M.;** Tilve, S. G.; Kamat, V. P. *Tetrahedron Lett.* **2014**, *55*, 3340-3343.
https://doi.org/10.1016/j.tetlet.2014.04.051

3. Graphite as an effective catalyst for Michael addition of indoles to nitroolefins in aqueous alcoholic solution, Parsekar, S. B.; Naik, S.; **Naik, M. M.;** Tilve, S. G. *Monatsch. chem.* **2015**, *146*, 691-696.
https://doi.org/10.1007/s00706-014-1347-x

4. Molecular iodine, **Naik, M. M.** *Iran. J. Catal. SPOTLIGHT* **2015**, *5*, 383-385.

5. Copper-mediated synthesis of coumestans *via* C(sp2)-H functionalization: Protective group free route to coumestrol and 4'-*O*-methylcoumestrol, **Naik, M. M.;** Kamat, V. P.; Tilve, S. G. *Tetrahedron* **2017**, *73*, 5528-5536.
https://doi.org/10.1016/j.tet.2017.07.057

6. A comprehensive review on coumestan synthesis, **Naik, M. M.;** Kamat, V. P.; Tilve, S. G. *(Manuscript under preparation).*

7. *α*-Glucosidase inhibition activity & *in silico* study of synthetic flavone derivative as a potential anti-diabetic drug nominee
Meena, S. N.; Kumar, U.; **Naik, M. M.;** Ghadi, S. S.; Kamat, V. P.; Tilve, S. G.
(Manuscript under preparation).

Posters presented at National/ International conferences:

1. Presented poster entitled **"Molecular iodine catalyst promoted cyclocoupling of phenols and allylic alcohols to Chromans"** at **Second UK-India MedChem Congress 2013 symposium** in CSIR Indian Institute of Chemical Technology, Hyderabad (22^{nd} – 23^{rd} March **2013**).
2. Presented poster entitled **"Pyrrolidine and iodine catalyzed one pot synthesis of flavones from 2'-hydroxyacetophenone and aromatic aldehydes"** at **16^{th} CRSI National Symposium in Chemistry (NSC-16)** in Department of Chemistry, IIT Bombay (7^{th} – 9^{th} February **2014**).
3. Presented poster entitled **"Synthesis of coumestans *via* C-H functionalization of 3-(2-hydroxyphenyl)-2*H*-chromen-2-one using $Cu(OAc)_2$"** at **National Conference on New Frontiers in Chemistry-From Fundamentals to Applications (NFCFA)** in Department of Chemistry**,** Birla Institute of Technology and Science Pilani, K. K. Birla Goa (18^{th} – 19^{th} December **2015**).

Conferences attended:

1. Participated in **Junior-National Organic Symposium Trust (J-NOST)** Conference for Research Scholars held in Indian Institute of Science Education and Research Bhopal (IISER) Bhopal, Madhya Pradesh (4^{th} – 6^{th} December **2013**).
2. Participated in Conference on **Chemical Industrial Disaster Management (CIDM): Emergency Planning and Disaster Management in Chemical, Petroleum, Petrochemical and Pharmaceutical Industry** at Cidade De Goa, Goa (29^{th} September – 1^{st} October **2014**).
3. Participated in **National Symposium on Transcending Frontiers in Organic Chemistry (TFOC)** at CSIR-National Institute for Interdisciplinary Science and Technology (NIIST), Trivandrum, Kerala (9^{th} – 11^{th} October **2014**).
4. Participated in **International Conference on Green Chemistry: Catalysis, Energy and Environment (ICGC)** at Chemistry Seminar Hall, Faculty Block E, Goa University, Goa (22^{nd} – 24^{th} January **2015**).

CHAPTER 1

A short review on the recent advancements in the synthesis of heterocycles using molecular iodine as a catalyst or reagent

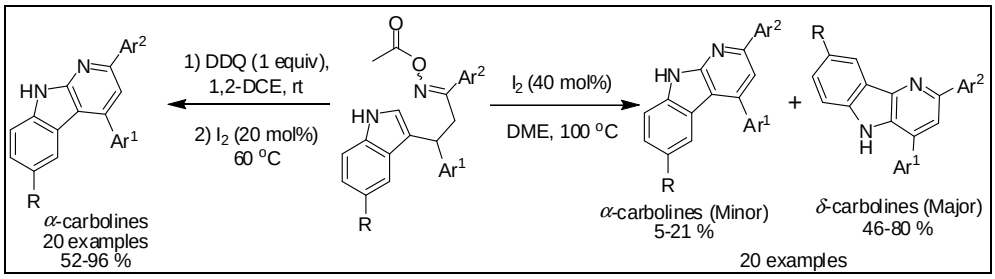
1.1: Introduction

Molecular iodine in the recent years has emerged as an attractive tool in the field of synthetic organic chemistry. Being an environmentally benign chemical, it has been extensively employed in organic synthesis either as a catalyst or as a reagent. A number of reviews on its wide applications have been well documented in the literature.[1] Some of the recent reviews focus on C-N bond formation through redox reaction,[1a] synthesis of heterocycles *via* electrophilic cylization of alkynes,[1b] oxidative coupling reactions utilizing C-H and X-H as nucleophiles,[1c] iodine catalysis as a green alternative to transition metals in organic chemistry and technology,[1d] recent advances in organic reactions,[1e] its use in monomer and polymer designing,[1f] multicomponent reactions,[1g] five and six membered heterocycles synthesis,[1h] iodination and protection-deprotection of functional groups[1i] and synthesis of chromone type compounds.[1j] Also the synthetic applications of hypervalent iodine compounds have been recently reviewed.[2] Our group has also explored its applications in the synthesis of diverse heterocycles.[3]

Various advantages associated with molecular iodine include low cost, less-toxicity, ready availability and easy removal after reaction by simply washing with reducing agent such as sodium thiosulphate solution. In addition, its stability to air and moisture makes it easy to handle. The amount of iodine used varies from catalytic to stoichiometric or even excess for some reactions. Reactions employing iodine provides mild operating conditions usually allowing large substrate scope, high yields, regio/stereoselectivities, short reaction time and simple work up procedure. Solvent-less reactions and solid-supported iodine adds to the advantages of iodine. The mild Lewis acidity of iodine has enhanced its use in the organic synthesis. In many reactions it acts as a substitute to costly and hazardous acid/metal catalysts and/or reagents thus enabling the elimination of hazardous metals and providing a “metal free” approach. This makes iodine an eco-friendly alternative to acid/metal based reagents/catalysts which pose serious health and safety problems. As a result, it has gained considerable attention in the past decades and several green methodologies are being continuously developed using iodine. The present mini review highlights the recent applications of environmentally benign molecular iodine either as a sole catalyst or reagent in the synthesis of heterocycles.

1.2.1: Iodine as a sole catalyst

Yang *et al.*[4] devised a metal free regio-divergent approach for the synthesis of α and δ-carbolines from a common indolyldihydrochalcone oxime ester substrate. Several derivatives of δ-carbolines were synthesized using catalytic iodine in DME at 100 °C. However, α-carbolines were obtained when the reaction was carried out in presence of DDQ (Scheme 1).

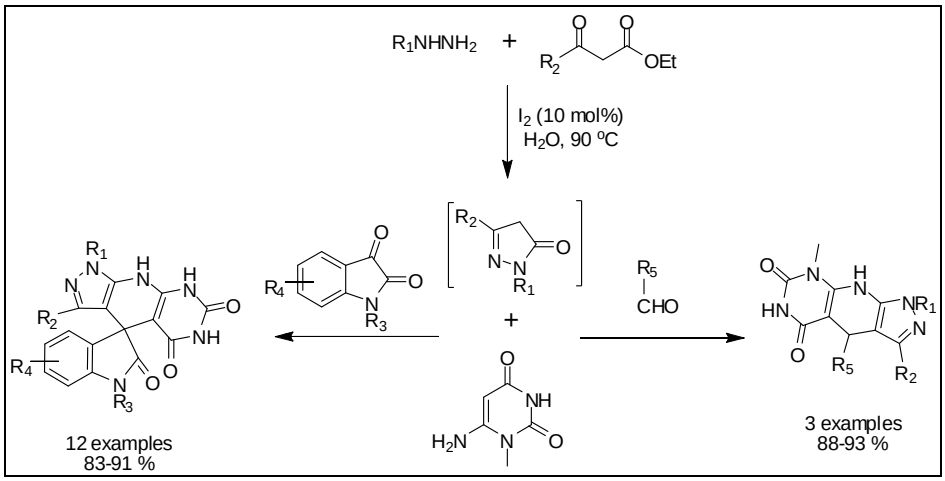


Scheme 1

A wide range of 2-aryl substituted benzimidazoles have been synthesized by Ravi *et al.*[5] from aryl alkyl ketones and 2-amino anilines using molecular iodine. This one step strategy involves consecutive C-N bond formation and C(sp^2)−C bond cleavage giving products in moderate to good yields (Scheme 2).

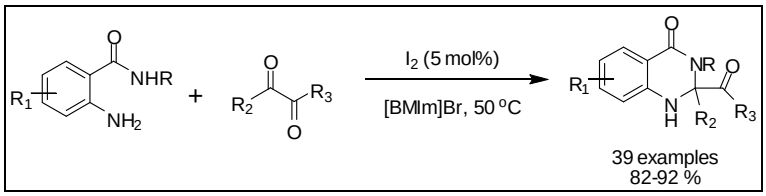
Scheme 2

Sagir *et al.*[6] developed an iodine catalyzed green methodology for the synthesis of multisubstituted pyrazolo-pyrido-pyrimidines and its spiro analogues in high yields. It involves a one pot four-component reaction of hydrazine, ethyl acetoacetate, 6-amino-1-methyl uracil and isatin or aldehyde in water as solvent. The method is operationally simple allowing products to obtain by filtration without any chromatography or recrystallization (Scheme 3).



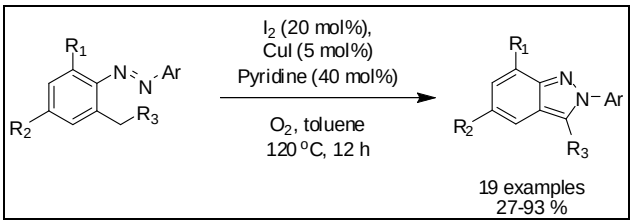
Scheme 3

Wang *et al.*[7] synthesized iodine catalyzed quinazolin-4-(1*H*)-one scaffolds by reacting different types of 1,2-dicarbonyl compounds with 2-aminobenzamides in 1-butyl-3-methylimidazolium bromide [BMIm]Br ionic liquid. Its wide scope is demonstrated by synthesizing library of 39 compounds and the recyclability of [BMIm]Br makes it environmentally benign (Scheme 4).



Scheme 4

Yi and Xi[8] presented the synthesis of 2*H*-indazoles *via* aerobic-oxidative C-H functionalization of *o*-alkylazoarenes with iodine as catalyst, CuI as additive, pyridine as base and oxygen as terminal oxidant. Both electron rich and electron deficient azozrens were successfully converted to corresponding 2*H*-indazoles and the reaction can also be scaled up to gram level (Scheme 5).

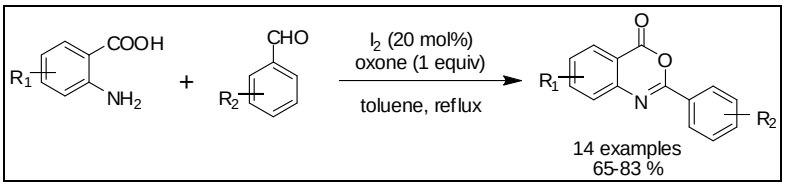


Scheme 5

Sun *et al*.[9] presented a convenient iodine catalyzed synthesis of C-4 sulfenylated pyrazoles. It is a domino multicomponent reaction involving 1,3-diketones, hydrazines and thiols which undergoes cyclocondensation and direct C-H bond sulphenylation reaction. Two new C-N bonds and one C-S bond are generated simultaneously in this protocol leading to target molecule (Scheme 6).

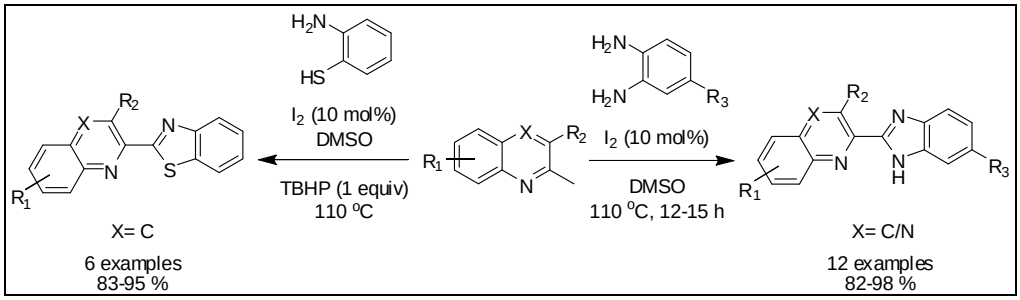
Scheme 6

Iyer and co-workers[10] prepared aryl 4*H*-3,1-benzoxazin-4-ones using 2-aminobenzoic acid and aryl aldehydes. It is catalyzed by iodine in presence of oxone as an oxidant. This straight forward metal free approach employs readily available starting materials using environmentally benign oxidant (Scheme 7).



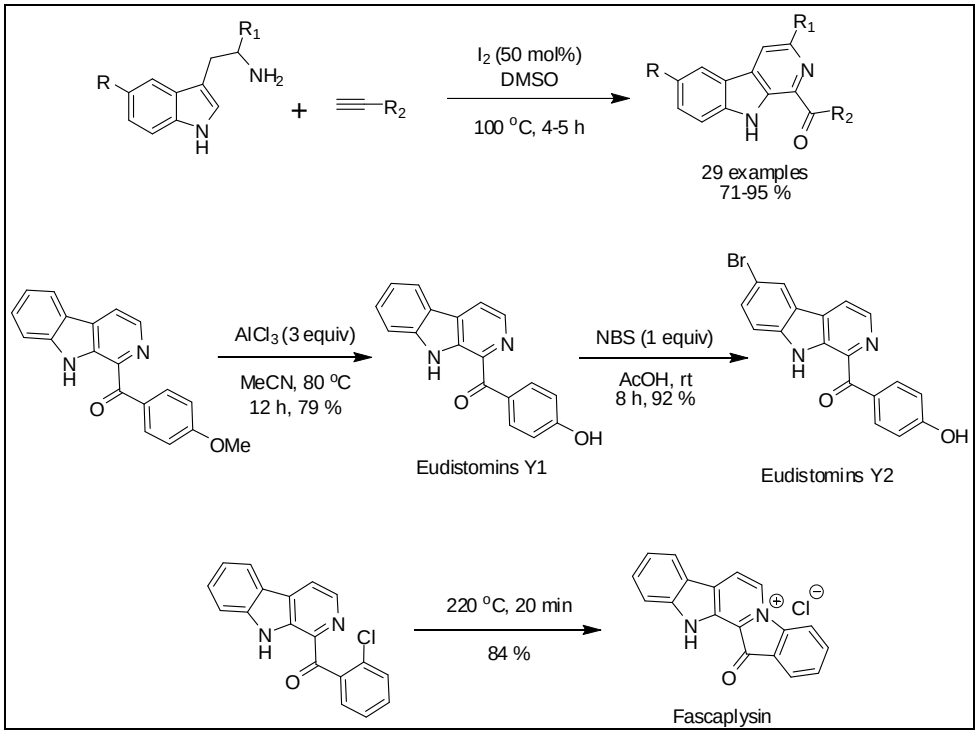
Scheme 7

An iodine catalyzed synthesis of 2-azaarenyl benzimidazoles and 2-azaarenyl benzothiazoles has been achieved by Yaragorla and Babu[11] from 2-methylazaarenes and *o*-phenylenediamine/2-aminothiophenol in DMSO. The umpolung behaviour of the methyl group of 2-methylazaarenes serving as an electrophile is executed. This oxidative C(sp^3)−H functionalization of 2-methylazaarenes provides a broad substrate scope and high yields under open air conditions (Scheme 8).



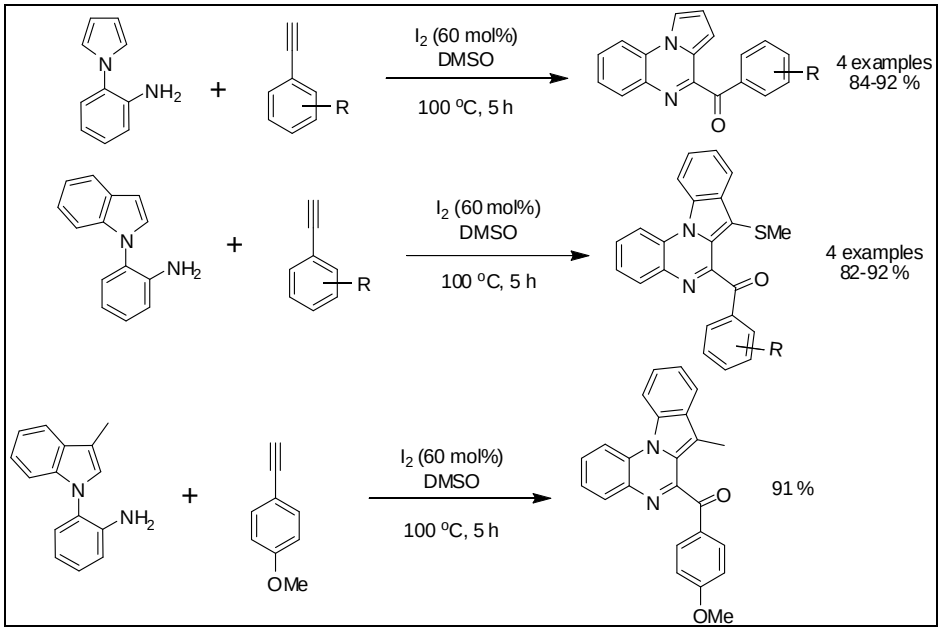
Scheme 8

Dighe *et al.*[12] presented the synthesis of 1-aroyl-*β*-carbolines by oxidative Pictet-Spengler reaction and terminal alkynes serving as the 2-oxoaldehyde surrogate mediated by iodine in DMSO. The broad substrate scope is well explored by synthesizing variety of derivatives, some of which were utilized for the total synthesis of naturally occurring Fascaplysin, Eudistomins Y1 and Y2 (Scheme 9).



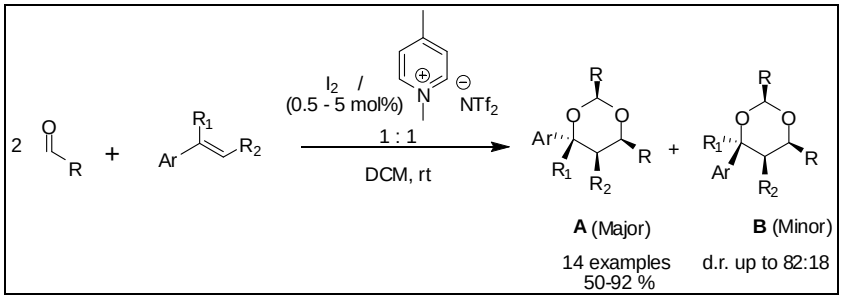
Scheme 9

Further applications includes the synthesis of pyrrolo[1,2-*a*]-quinoxaline and indolo[1,2-*a*]quinoxaline derivatives from respective pyrrole- and indole-based substrates. Interestingly, *N*-substituted indoles with no substituent at C-3 reacted with aromatic alkynes to form 3-thiomethylated indolo[1,2-*a*]quinoxalines. However on blocking C-3 position of indole with methyl group, desired product was formed. Also further utility of 1-aroyl-*β*-carbolines was shown by synthesizing thiomethylated and 4-aryl substituted canthin-6-ones derivatives (Scheme 10).



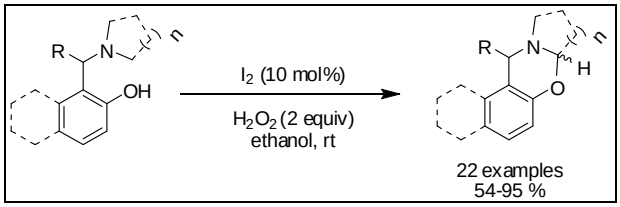
Scheme 10

Harnying *et al.*[13] employed catalytic iodine as low as 0.5-5 mol% in Prins reaction giving *rac*-1,3-dioxanes from substituted styrenes and aliphatic aldehydes. Prior to this report, Yadav *et al.*[14] had explored the application of molecular iodine (1 equiv) in Prins reaction. However the amount of iodine was greatly reduced from stoichiometric to catalytic in the present work in presence of pyridinium bis(trifluoromethanesulfonyl)imide (TFSI) salt in 1:1 ratio to iodine. Diasteroselectivity of **A**:**B** up to 82:18 was observed by the isomerization of 1,3-dioxane products to the thermodynamically favoured one **A** (Scheme 11).



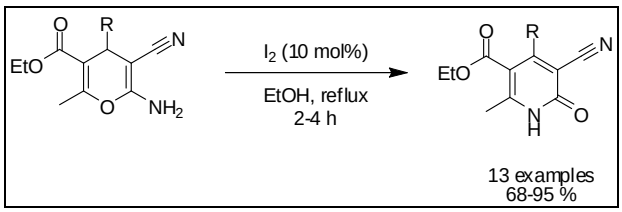
Scheme 11

Deb *et al.*[15] presented an I_2/H_2O_2 promoted synthesis of 1,3-oxazines in moderate to good yields from 1-(aminoalkyl)-2-naphthols or 2-(aminoalkyl)phenols. This reaction involving an oxidative intramolecular C–O bond formation by catalytic iodine and H_2O_2 oxidant smoothly occurs at room temperature (Scheme 12).



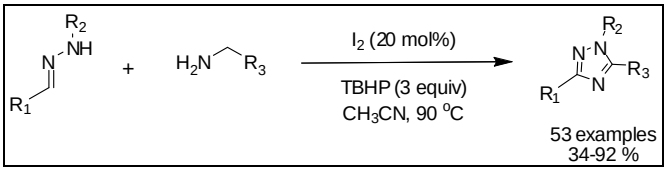
Scheme 12

Buduma *et al.*[16] developed a simple and efficient synthesis of 2-pyridones using iodine catalyst in refluxing ethanol from 4*H*-pyrans. Both aromatic as well as hetero aromatic ring containing 4*H*-pyrans were successfully converted to the respective 2-pyridones. The analogues synthesized were tested for in vitro antiproliferative activity (Scheme 13).



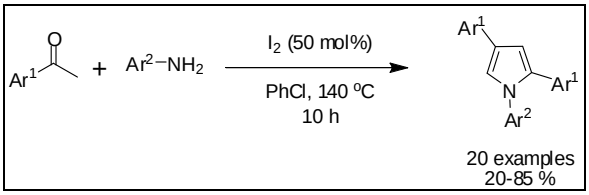
Scheme 13

An I_2/TBHP mediated efficient route to the synthesis of 1,3,5-trisubstituted 1,2,4-triazoles was described by Chen *et al.*[17] from hydrazones and aliphatic amines. The substrate scope is well demonstrated by synthesizing a library of analogues in moderate to excellent yields. It also allows the synthesis of products in gram scale (Scheme 14).



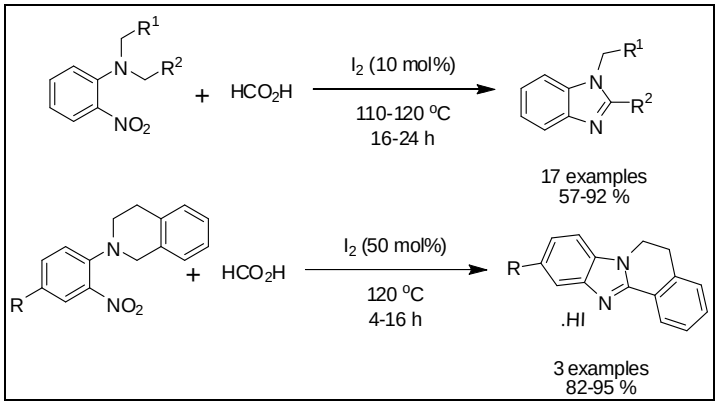
Scheme 14

Zhang and co-workers[18] synthesized 1,2,4-triarylpyrroles using a novel iodine mediated approach in moderate to good yields. It involved a cascade condensation-cyclization of simple substrates such as aryl methyl ketones and anilines avoiding any intermediate preparation (Scheme 15).



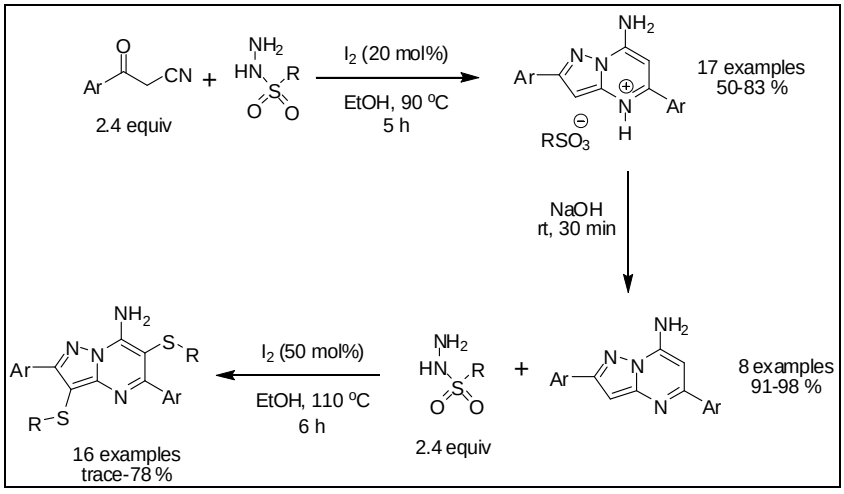
Scheme 15

Iodine catalyzed reductive redox cyclization of *o*-nitro-*t*-anilines with formic acid into fused tricyclic or 1,2-disubstituted benzimidazoles was successfully established by Nguyen *et al.*[19] Broad substrate scope has been demonstrated. Also 1,2-disubstituted benzimidazole hydriodide derivatives were prepared by using 0.5 equiv of iodine thus playing dual role as catalyst as well as iodide source (Scheme 16).



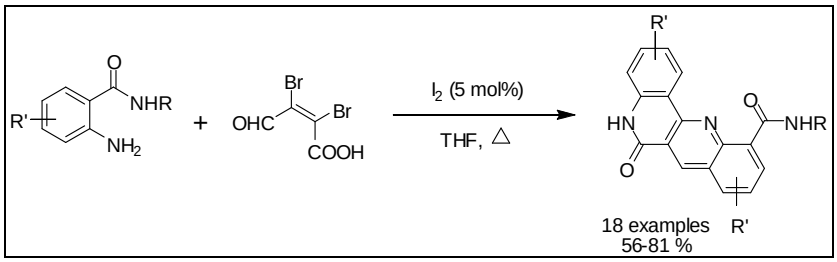
Scheme 16

Sun *et al.*[20] reported iodine catalyzed route to new pyrazolo-[1,5-*a*]pyrimidin-4-ium sulfonates *via* regioselective bicyclization reaction of *β*-ketonitriles with sulfonyl hydrazides which under alkaline medium delivered densely functionalized pyrazolo[1,5-*a*]pyrimidines. Unprecedented direct C(sp^2)−H bond bifunctionalization of these compounds on treatment with sulfonyl hydrazides provided fully substituted pyrazolo-[1,5-*a*]pyrimidines (Scheme 17).



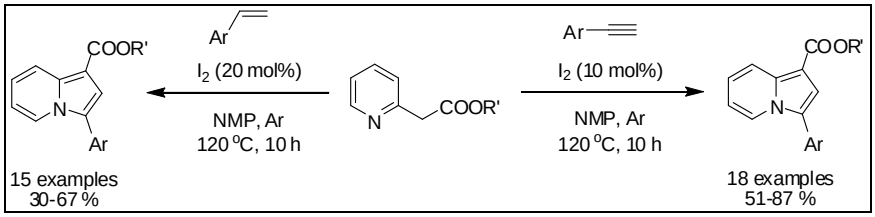
Scheme 17

Feng *et al.*[21] developed a convenient iodine catalyzed route to 6-oxo-5,6-dihydrodibenzo[*b*,*h*][1,6]naphthyridine-11-carboxamide derivatives. 2-Aminobenzamides and mucobromic acid on refluxing in THF undergoes a domino-type mechanism involving double elimination of hydrogen bromide (Scheme 18).



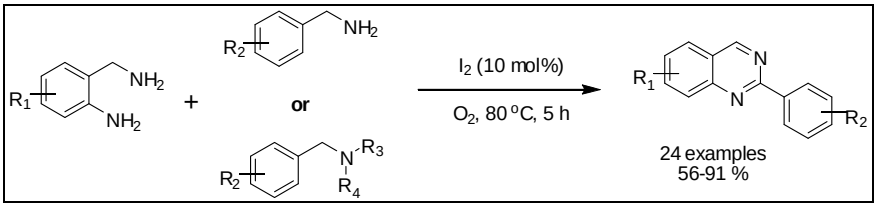
Scheme 18

Reddy *et al.*[22] described an efficient iodine catalyzed route to indolizine-1-carboxylates from 2-pyridyl acetates and alkynes/alkenes. It comprises of oxidative C-C and C-N bond formations in absence of any metal, oxidant or base. The exact reaction mechanism is not proposed, however control experiments suggests a radical pathway (Scheme 19).



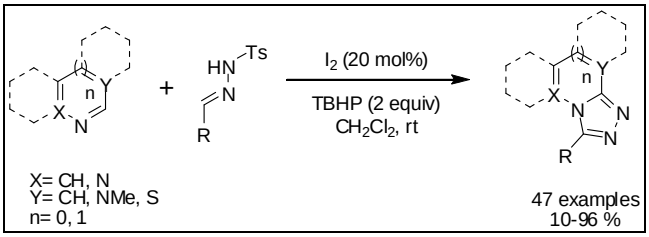
Scheme 19

A methodology for quinazolines preparation was developed by Tiwari and Bhanage[23] starting from 2-aminobenzylamines and with or without *N*-substituted benzylamines. The method employs iodine catalyst in presence of oxygen as an oxidant under solvent-free and additive-free conditions (Scheme 20).



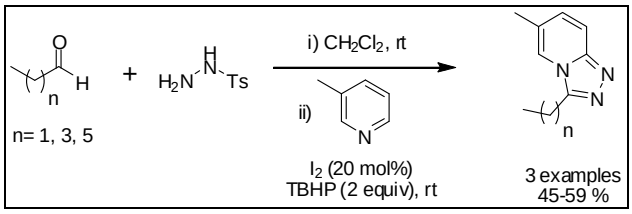
Scheme 20

Inturi *et al.*[24] presented an I_2-TBHP catalyzed 4,3-fused 1,2,4-triazoles synthesis from *N*-tosylhydrazones and aromatic *N*-heterocycles. It occurs through generation of azomethine imine which undergoes regioselective 1,3-dipolar cycloaddition with variety of aromatic *N*-heterocycles. Large substrate scope has also been accomplished by synthesising variety of derivatives (Scheme 21).



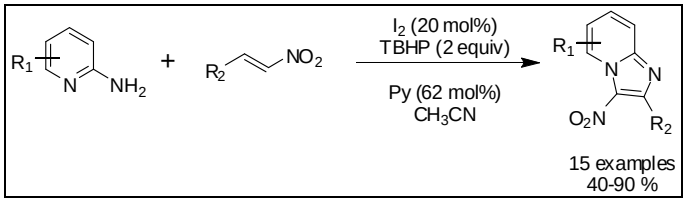
Scheme 21

Also, the same group designed a two step one pot procedure to introduce R as linear alkyl groups in the product. Accordingly, the aldehyde substrates were treated with 4-methylbenzenesulfonohydrazide in CH_2Cl_2 at room temperature followed by treatment with 3-methylpyridine in presence of catalytic iodine and TBHP. This allowed the synthesis of triazole derivatives with aliphatic linkage (Scheme 22).



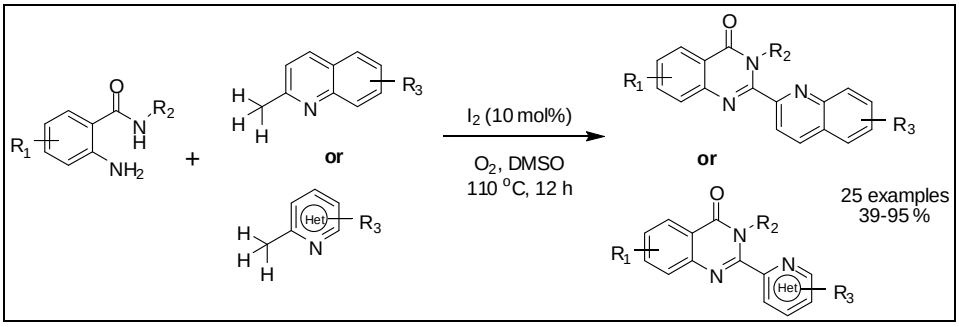
Scheme 22

An *et al.*[25] prepared 3-nitro-2-arylimidazo[1,2-*a*]pyridine derivatives by an iodine/TBHP/Py mediated approach. It occurs *via* a Michael addition and oxidative coupling tandem reaction (Scheme 23).



Scheme 23

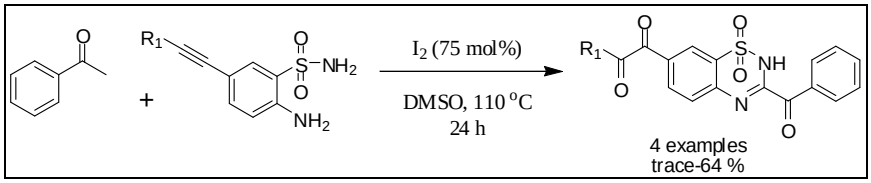
Yang *et al.*[26] developed an iodine catalyzed synthetic methodology for 2-heteroaryl quinazolinones from azaarenes through oxidative benzylic C-H bond amination. Several derivatives synthesized up to 95% yield exhibits wide substrate scope of this method (Scheme 24).



Scheme 24

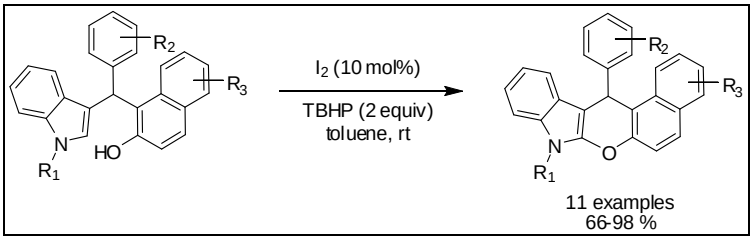
Xi *et al.*[27] synthesized 3-acylbenzothiadiazine 1,1-dioxides from different acetophenones and various 2-aminobenzenesulfonamides using molecular iodine (Scheme 25). However when 2-aminobenzenesulfonamides with an alkynyl group were treated under similar reaction condition, the triple bond was oxidized to *o*-diketone group along with the formation of 3-acylbenzothiadiazine 1,1-dioxide ring (Scheme 26).

Scheme 25



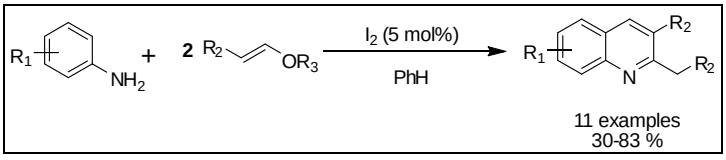
Scheme 26

Synthesis of chromeno[2,3-*b*]indoles was achieved by Deb *et al.*[28] from 3-(*α*,*α*-diarylmethyl)indoles through intramolecular dehydrogenative coupling reaction to form C-O bond. I_2/TBHP has been found to be an efficient medium for this conversion (Scheme 27).



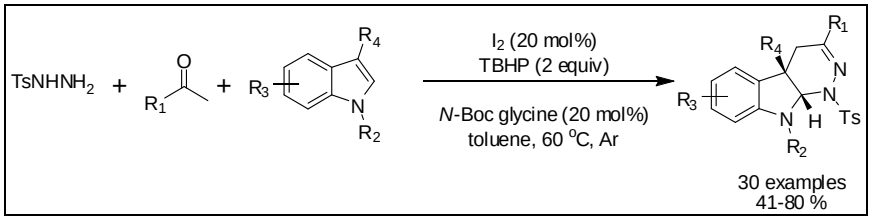
Scheme 27

Le *et al.*[29] developed a method to synthesize 2-methylquinolines by the condensation reaction of substituted anilines and vinyl ethers using iodine catalyst. The dual role of iodine species is explored wherein molecular iodine acts as an oxidant and hydrogen iodide acts as an activating agent by activating vinyl ether. Thus, this redox reaction allows molecular iodine to be employed in catalytic amount (Scheme 28).



Scheme 28

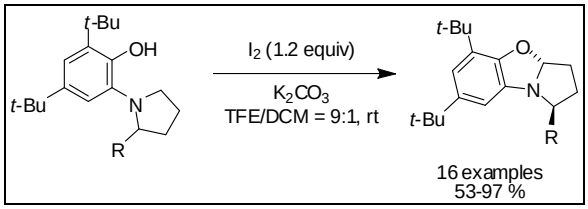
Wei *et al.*[30] designed a methodology for the synthesis of [2,3]-fused indoline tetrahydropyridazines *via* direct functionalization of the C(sp^3)-H bond. It employs iodine catalyst in presence of TBHP oxidant and *N*-Boc glycine as an acidic additive. It is a three component reaction of substituted indoles, hydrazines and acetophenones which undergoes dearomative oxidative coupling to furnish desired products in moderate to good yields (Scheme 29).



Scheme 29

1.2.2: Iodine as a sole reagent

Qu and co-workers[31] described an iodine mediated synthesis of cyclic *N,O*-acetals through regio- and diastereoselective oxidation of the secondary *α*–C-H bonds of 2-functionalized pyrrolidines (Scheme 30). The methodology was also applied for the total synthesis of naturally occurring (±)-preussin and its C(3) epimer (Figure 1) from (±)-Boc pyrrolidin-3-ol in nine steps (22% overall yield).



Scheme 30

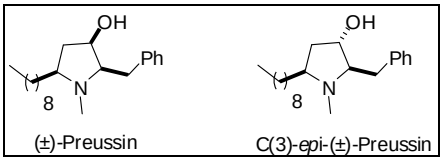
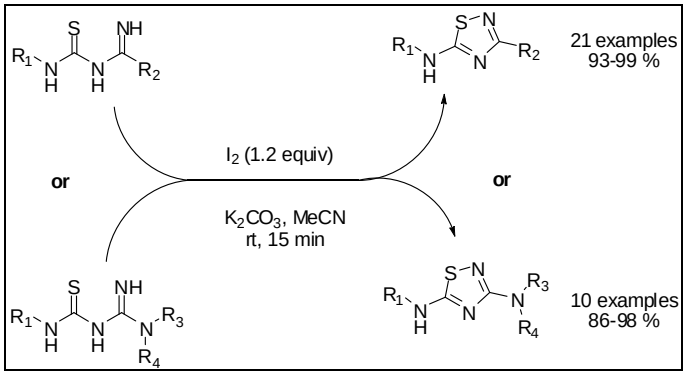


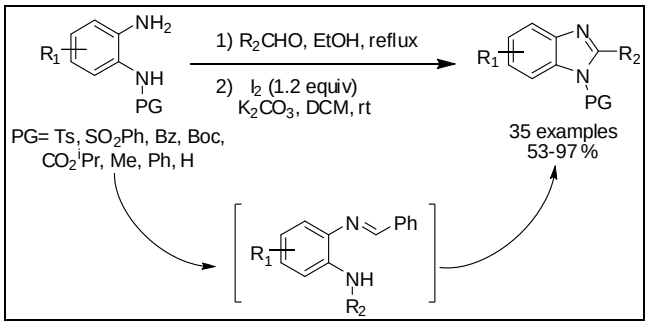
Figure 1: Structures of (±)-preussin and C(3)-*epi*-(±)-preussin

An efficient and scalable synthesis of 5-amino and 3,5-diamino substituted 1,2,4-thiadiazoles has been developed by Wang *et al.*[32] Molecular iodine as an exclusive oxidant is responsible for the newly formed N-S bond. Its broad substrate scope is well demonstrated by synthesizing numerous derivatives from various imidoyl and guanyl substrates (Scheme 31).



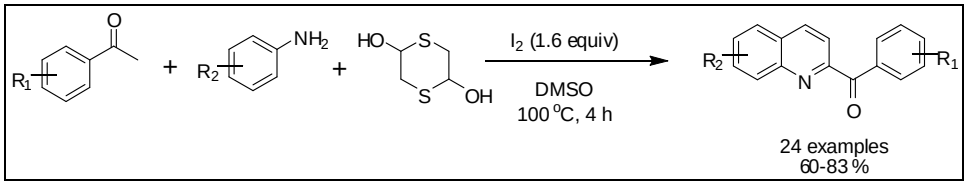
Scheme 31

Hu *et al*.[33] developed a methodology for the synthesis of *N*-protected benzimidazoles by a sequential one pot two step process. The simple *o*-phenylenediamines and aromatic/aliphatic/cinnamic aldehydes condense to form imine intermediates which without any purification on iodine treatment under basic condition led to 1,2-disubstituted benzimidazoles. Authors exhibited broad scope of this intramolecular C−H amidation methodology by synthesizing large number of derivatives including *N*-unsubstituted benzimidazoles. Also the method works well on gram scale (Scheme 32).



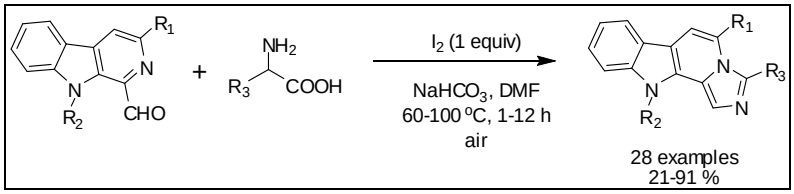
Scheme 32

Wu *et al*.[34] have prepared 2-acylquinolines from methyl ketones, arylamines and 1,4-dithiane-2,5-diol as an ethylene surrogate *via* an iodine promoted formal [4+2] cycloaddition. Arylamine substrate also promoted 1,4-dithiane-2,5-diol participation in Povarov reaction. The mechanistic studies showed the mechanism operates *via* an iodination-Kornblum-oxidation-Povarov-aromatization process. This interesting reaction exhibits the use of 1,4-dithiane-2,5-diol in the synthesis of *N*-hetrocycles rather than *S*-heterocycles through desulfurization (Scheme 33).



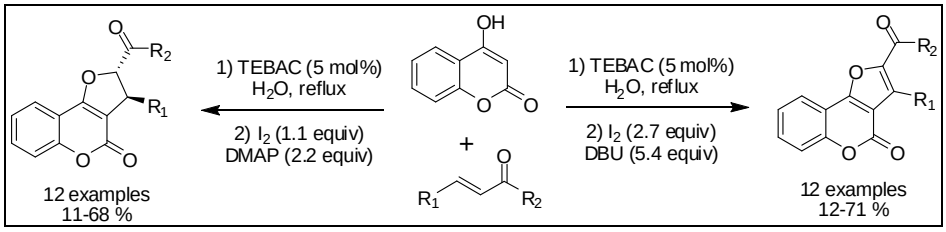
Scheme 33

Singh and co-workers[35] designed an efficient regioselective methodology for the synthesis of *β*-carboline *N*-fused imidazoles from natural *α*-amino acids/benzyl amines and 1-formyl pyrido[3,4-*b*]indoles *via* molecular iodine promoted decarboxylative amination. Several derivatives were synthesized using aliphatic, aromatic and heteroaromatic *α*-amino acids up to 91% yield. The plausible mechanism is also well explained (Scheme 34).

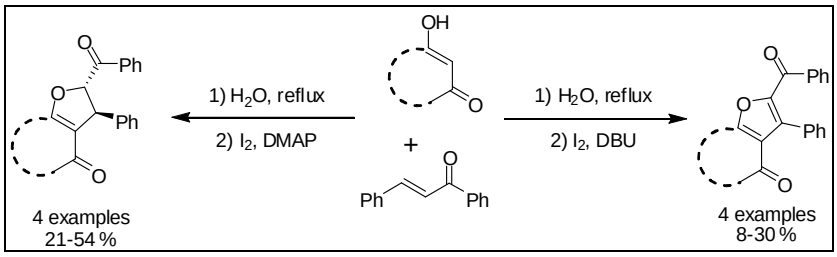


Scheme 34

Miao *et al.*[36] presented an iodine mediated one pot two step process to synthesize dihydrofurans and furans *via* formal [3 + 2] cycloaddition of 1,3-dicarbonyl compounds with enones. Firstly, the substrates undergo Michael addition on refluxing 4-hydroxycoumarin with benzyl triethyl ammonium chloride in water followed by iodine mediated cyclization. The reaction product depends on the type of base employed in the second step wherein I_2/DMAP furnishes dihydrofurans with high trans diastereoselectivity whereas I_2/DBU leads to furans (Scheme 35). Similarly, other 1,3-dicarbonyl compounds reacted to furnish respective products but in low yields (Scheme 36).

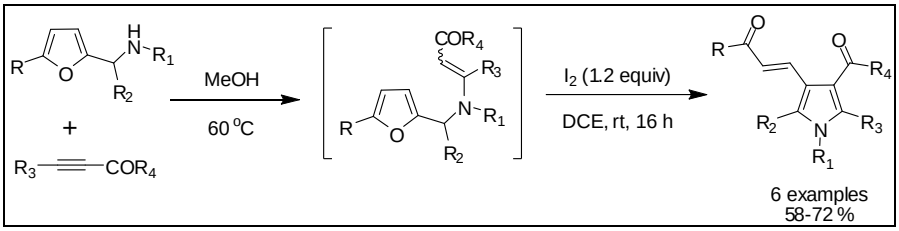


Scheme 35



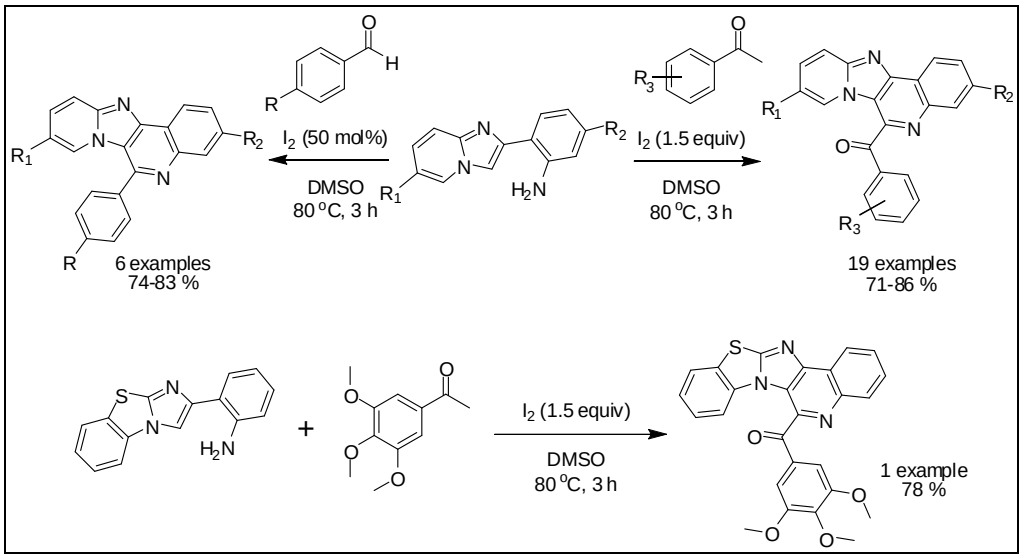
Scheme 36

Zou *et al.*[37] synthesized polyfunctionalized pyrroles from furfurylamines and ynones involving a two step one pot approach. The reaction between furfurylamines and ynones in methanol generated *N*-furfuryl-*β*-enaminones *in situ* which led to polyfunctionalized pyrroles through iodine mediated oxidative annulation reaction (Scheme 37).



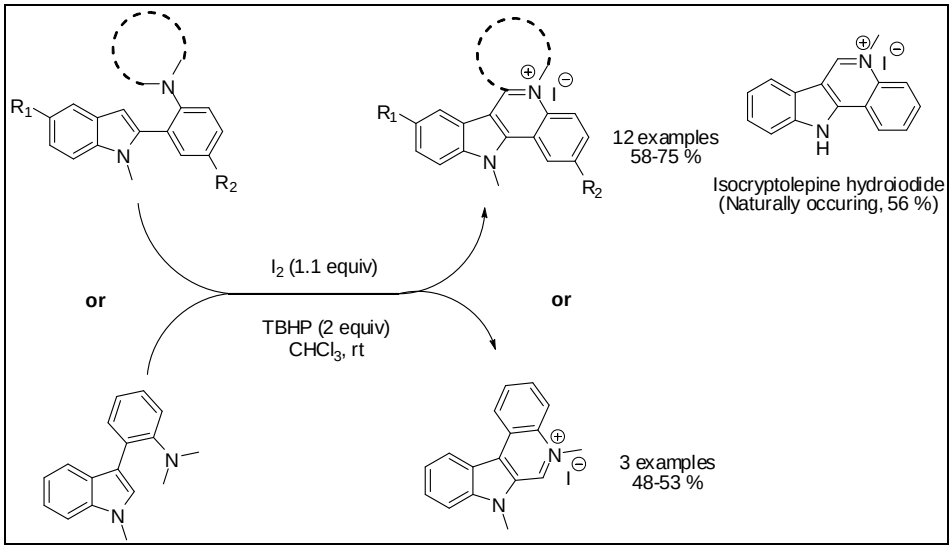
Scheme 37

Kale *et al*.[38] developed a one pot methodology involving iodine-dimethyl sulfoxide for the synthesis of pyrido-fused imidazo[4,5-*c*]quinolines. The substrates pyridoimidazole arylamines and carbonyl compounds undergoes oxidative cross coupling followed by intramolecular cyclization to deliver products in high yields. A series of compounds were synthesized using different substrates and iodine concentration (Scheme 38).



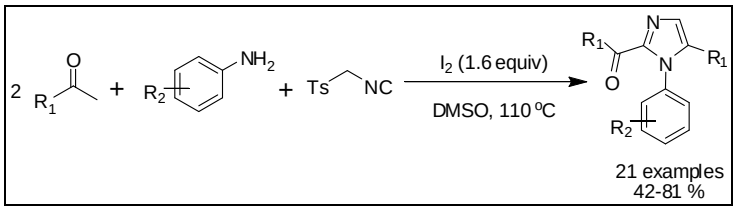
Scheme 38

Volvoikar and Tilve[3g] (our group) developed an iodine/TBHP procedure for the synthesis of 5,11-dialkylindolo[3,2-*c*]quinoline salts and 5,7-dimethylindolo[2,3-*c*]quinoline salts *via* intramolecular dehydrogenative coupling. Control experiments were performed to support the hypoiodite mediated mechanism for the annulation followed by aromatization sequence. The application of the methodology was demonstrated by synthesizing naturally occurring isocryptolepine hydroiodide, an indoloquinoline alkaloid (Scheme 39).



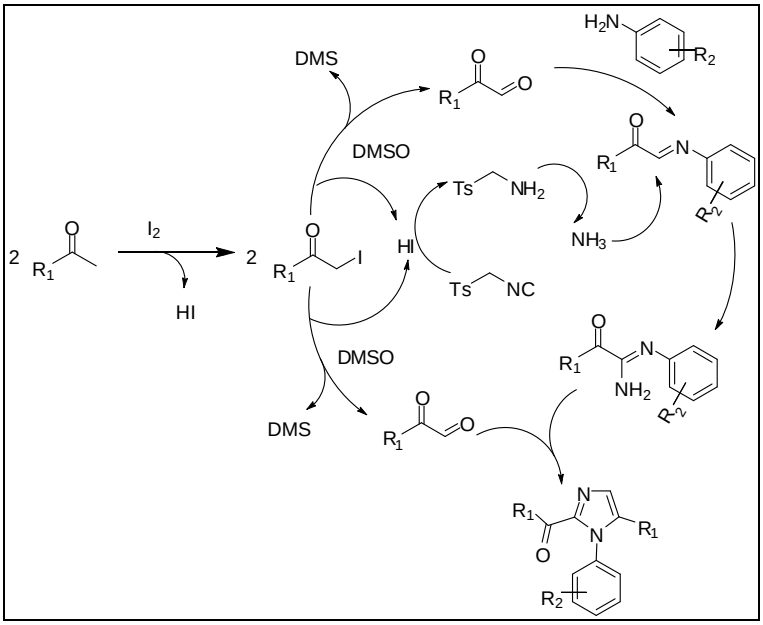
Scheme 39

Synthesis of 1,2,5-trisubstituted imidazoles *via* Radziszewski-type reaction between methyl ketones, anilines and tosylmethyl isocyanide was reported by Zhang *et al*.[39] employing molecular iodine. It occurs *via* Radziszewski-type reaction mechanism wherein methyl ketones play a dual role as *α*–dicarbonyl compounds and aldehyde (Scheme 40).



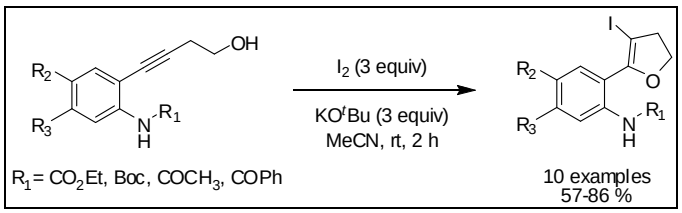
Scheme 40

The mechanistic pathway involves the reaction of methyl ketone with iodine to form *α*-iodoketone which then with the liberation of HI forms phenylglyoxal *via* Kornblum oxidation in DMSO. The aniline substrate reacts with the aldehyde group of phenylglyoxal to form C-acylimine which on reaction with *in situ* formed amine from tosylmethyl isocyanide and HI results in the formation of intermediate *via* an *in situ* cross-trapping process. Lastly, the cyclocondensation of intermediate formed with another phenylglyoxal molecule provides the target molecule (Scheme 41).



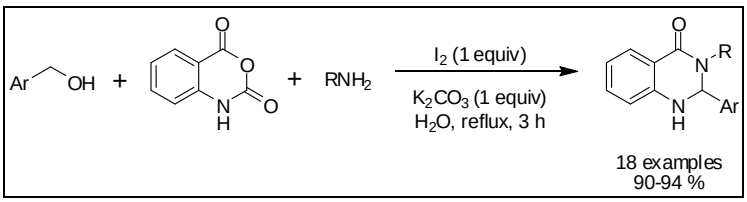
Scheme 41

Likhar and co-workers[40] achieved iodo-substituted dihydrofurans regioselectively from amine substituted alkynols *via* iodocyclization in presence of excess of iodine, base and solvent (Scheme 42). As a part of further application, the products obtained with iodo substituent were functionalized by performing different C-C and C-N coupling reactions.



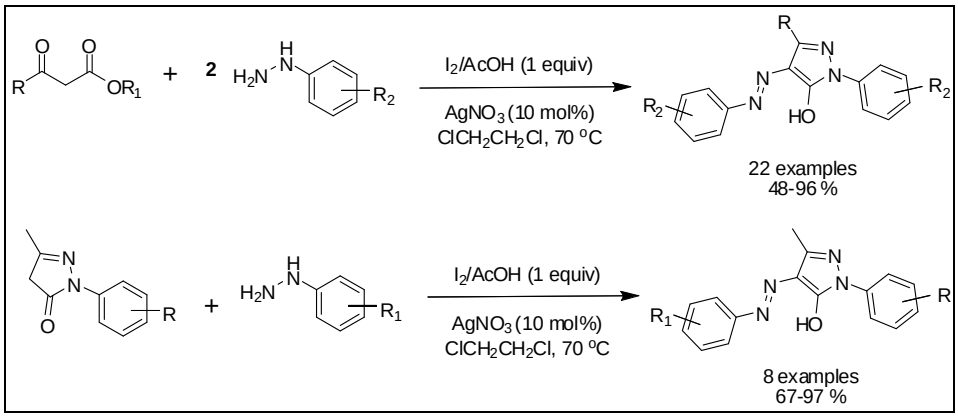
Scheme 42

Azimi and Azizian[41] described a mild, one pot three component, high yielding synthetic protocol for 2,3-dihydroquinazolin-4(1*H*)-ones preparation by employing benzyl alcohols, isatoic anhydride and primary amines as substrates using iodine under basic condition (Scheme 43). *In situ* oxidation of benzyl alcohols to benzaldehydes allows avoiding the use of unstable aldehydes. Author claims this work as the first report using benzyl alcohols instead of benzaldehydes in dihydroquinazolins synthesis.



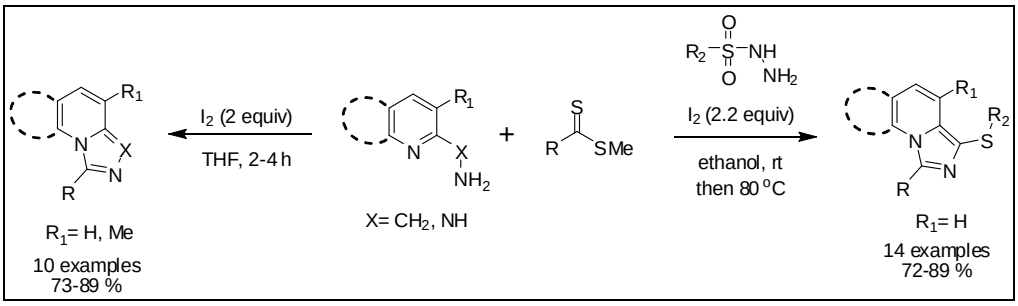
Scheme 43

An iodine-mediated synthesis of highly functionalized arylazopyrazoles was achieved by Pandit *et al*.[42] from *β*-ketoesters and arylhydrazines (2 equiv) in presence of catalytic $AgNO_3$. The product formation occurs *via* *α*-iodination of *β*-ketoesters, formation of pyrazol-3-one followed by substitution with a nitrogen nucleophile and finally oxidation followed by enolization. Also 2-arylpyrazol-3-ones were reacted with arylhydrazines (1 equiv) to prepare arylazopyrazoles with two different arylhydrazine entities (Scheme 44).



Scheme 44

Ramesha *et al*.[43] reported an iodine-mediated approach for the synthesis of 3-sulfenylimidazo[1,5-*a*]pyridines through C–H functionalization in good yields. It makes use of dithioesters, 2-methylaminopyridines and sulfonyl hydrazides as substrates. Also a series of imidazopyridines have been synthesized in good yields from dithioesters, 2-methylaminopyridines (Scheme 45).



Scheme 45

1.3: Conclusion

The present mini review has included the recent developments in diverse heterocycles synthesis using molecular iodine either as a sole catalyst or reagent and/or in presence of oxidant. Numerous nitrogen heterocycles and a few of oxygen and sulphur heterocycles synthesis with a wide range of functional group diversity comprising of simple to complex structural skeleton in one pot or two step one pot method suggests the importance and versatility of iodine in organic synthesis. Thus from future point of view, an efficient, green, economic and very useful molecular iodine will be explored further as catalyst/reagent to accomplish the synthesis of many more diversified complex heterocycles.

1.4: References

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CHAPTER 2

Synthetic studies of chromans using molecular iodine catalyst

2.1: Introduction

Dihydrobenzopyran (chroman) ring system, more appropriately described as 3,4-dihydro-2*H*-1-benzopyran **1**, (Figure 1) is an oxygen heterocyclic compound having a benzene ring and a 3,4-dihydropyran ring fused together sharing a common C=C bond. It is a saturated analogue of benzopyran (chromene) constituting the basic unit in numerous naturally occurring scaffolds isolated from different sources.[1]

2,2-Disubstituted chromans **2** (Figure 2) are of utmost importance as diversified analogues with a wide range of activities have been reported bearing such substitution pattern. Diverse range of compounds bearing chroman skeleton shows a broad range of biological activities. Hence it has attracted the attention of a large group of chemists. Chroman skeleton prevalently appears in important naturally occurring bioactive compounds such as vitamin E and its derivatives,[2] flavonoids,[3] etc. In addition to biologically active natural products, several dihydrobenzopyrans are pervasive motifs in pharmaceutical drug targets exhibiting diverse activities.

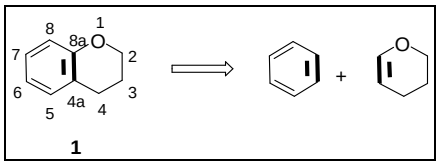


Figure 1: Structure of chroman **1** with general numbering.

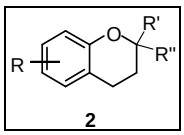


Figure 2: General structure of 2,2-disubstituted chromans **2**.

2.2: Occurrence

Several naturally occurring biologically active dihydrobenzopyrans having substituent/s at 2-position have been isolated from diverse plant sources. Some of these chroman members along with their sources are represented below (Figures 3-6, Table 1-2).

Vitamin E **3** has been predominantly found in various sources such as corn, soybean, olive oil, palm, rice bran, and barley oils and also been isolated from *Vitis labrusca*, *Allium sativum* and *Garcinia kola*.[4] It bears a chroman ring system with a hydrocarbon chain at 2-position. It constitutes a group of 8 naturally occurring compounds which are subdivided into four

tocopherols **3a** and four tocotrienols **3b** differing in the degree of saturation of the hydrocarbon chain. The tocopherols have fully saturated chain whereas tocotrienols have chain with 3 double bonds. Tocopherols and tocotrienols are collectively called as tocols. The 8 tocols include *α*-, *β*-, *γ*- and *δ*-tocopherols and *α*-, *β*-, *γ*- and *δ*-tocotrienols. It is well known for its role as antioxidant.[4a] Also tocotrienols have been found to achieve potent anti-cancer effects.[5] Tocotrienols possesses potent neuroprotective properties[6] *γ*-Tocotrienol was found to be a blocker of signal transducer and activator of transcription 3 (STAT3) activation pathway and may have a potential in the treatment of cancers.[7]

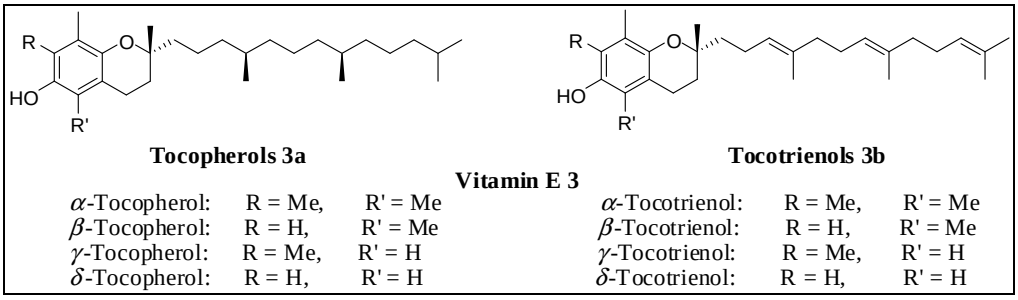


Figure 3: Structures of Vitamin E **3**: Tocopherols **3a** and Tocotrienols **3b**.

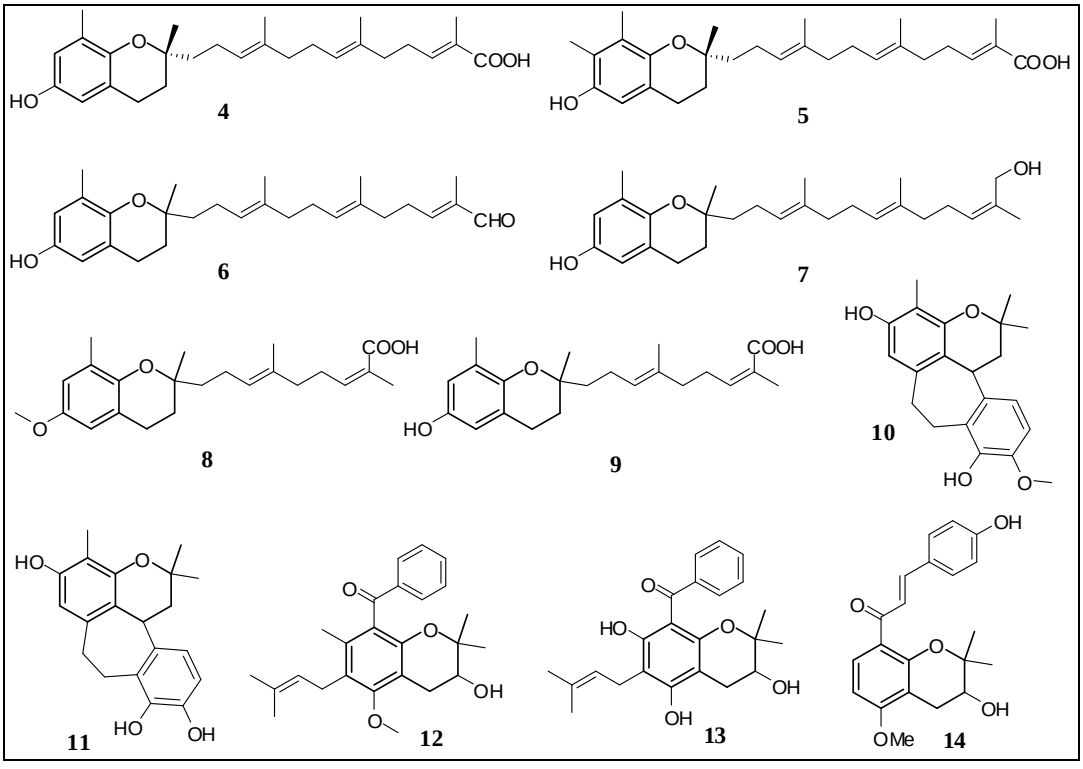


Figure 4: Structures of natural chromans **4-14**.

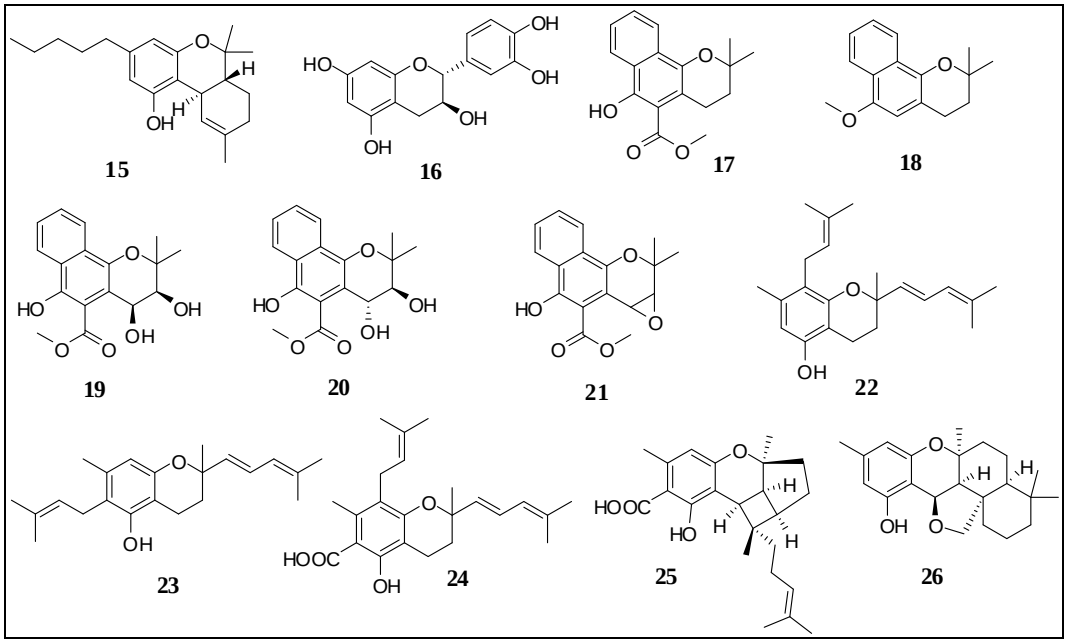


Figure 5: Structures of natural chromans **15-26**.

Table 1: Source of isolation of naturally occurring chromans **4-26**.

No.	Name ***Source of isolation***
4	δ-Garcinoic acid (δ-tocotrienolic acid)[4c,8] *Garcinia kola, Clusia grandiflora, Tovomitopsis psychotriifolia, Clusia obdeltifolia*
5	γ-Garcinoic acid (γ-tocotrienolic acid)[9] *Garcinia amplexicaulis*
6	Garcinal[4c] *Garcinia kola*
7	δ-Tocotrienilic alcohol[8c] *Clusia obdeltifolia*
8	Polycerasoidin[10] *Polyalthia cerasoides*
9	Polycerasoidol[10] *Polyalthia cerasoides*
10	Racemosol[11] *Bauhinia racemosa*
11	de-*O*-Methylracemosol[11b] *Bauhinia racemosa*

12	Pseudoguttiaphenone-A[12] *Garcinia pseudoguttifera*
13	Vismiaguianone A[13] *Vismia guianensis*
14	4'-Methoxy-bavachromanol[14] Propolis
15	Δ^9-Tetrahydrocannabinol[15] *Cannabis sativa*
16	(+)-Catechin[16] *Streblus asper, Byrsonima crassa, Harpephyllum caffrum, Cassia fistula, Acacia catechu, Terminalia fagifolia*
17	3,4-Dihydromollugin[17] *Rubia cordifolia*
18	Dihydrolapachenole[18] *Tabebuia chrysantha*
19	*cis*-3,4-Dihydroxy-3,4-dihydromollugin[19] *Pentas longiflora, Rubia cordifolia*
20	*trans*-3,4-Dihydroxy-3,4-dihydromollugin[19] *Pentas longiflora, Rubia cordifolia*
21	Epoxymollugin[20] *Rubia cordifolia*
22	Peperobtusin A[21] *Peperomia clusiifolia, Peperomia obtusifolia*
23	Clusifoliol/Isopeperobtusin A[21c-d] *Peperomia obtusifolia*
24	3,4-Dihydro-5-hydroxy-2,7-dimethyl-8-(2''-methyl-2''-butenyl)-2-(4'-methyl-1',3'-pentadienyl)-2*H*-1-benzopyran-6-carboxylic acid[21b,d] *Peperomia amplexicaulis, Peperomia obtusifolia*
25	Rhododaurichromanic acid A[22] *Rhododendron dauricum*
26	(-)-Siccanin A[23] *Helminthosposium siccans*

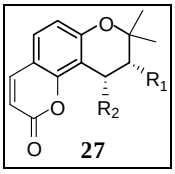
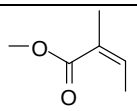
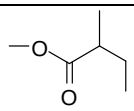
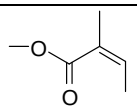
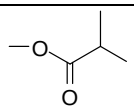
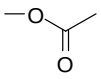
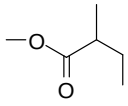
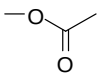
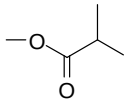
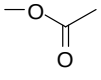
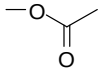
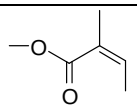
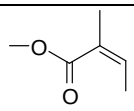
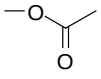
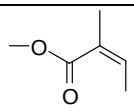
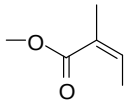
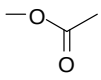
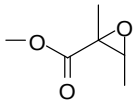
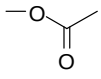
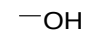
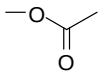
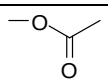
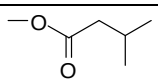
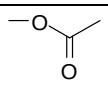
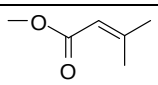
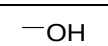
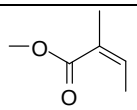
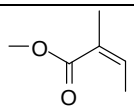


Figure 6: Naturally occurring pyranocoumarins **27**.

Table 2: Source of isolation of naturally occurring chromans **27a-r**.

No.	Name ***Source of isolation***	R_1	R_2
27a	Hyuganin A[24] *Angelica furcijuga*		
27b	Hyuganin B[24] *Angelica furcijuga*		
27c	Hyuganin C[24] *Angelica furcijuga*		
27d	Hyuganin D[24] *Angelica furcijuga*		
27e	(+)-*cis*-Khellactone[24] *Angelica furcijuga*	−OH	−OH
27f	(-)-*cis*-3',4'-Diacetylkhellactone[24] *Angelica furcijuga*		
27g	Anomalin[24] *Angelica furcijuga*		
27h	Pteryxin[24,25] *Angelica furcijuga, Pteryxia terebinthina*		
27i	Isopteryxin[24] *Angelica furcijuga*		
27j	Isoepoxypteryxin[24] *Angelica furcijuga*		
27k	Praeroside II[24] *Angelica furcijuga*	−O−Glc	−OH
27l	Praeroside IV[24] *Angelica furcijuga*	−O−Glc	−H

27m	(+)-Lomatin[24] *Angelica furcijuga*		
27n	(+)-Acetyllomatin[24] *Angelica furcijuga*		
27o	Suksdorfin[24-26] *Angelica furcijuga, Lomatium suksdorfii, Arracacia nelsonii*		
27p	(-)-Isosamidin[26b] *Arracacia nelsonii*		
27q	Laserpitin[14,27] Propilis, *Angelica keiskei, Musineon divaricatum*		
27r	Isolaserpitin[14,27] Propilis, *Angelica keiskei, Musineon divaricatum*		

δ-Garcinoic acid **4** shows an antibacterial activity.[8b] Also **4** and *γ*-garcinoic acid **5** are potent mPGES-1 inhibitors.[9] *δ*-Garcinoic acid **4** and garcinal **6** are known for antioxidant activity.[4c] Racemosol **10** and de-*O*-methylracemosol **11** exhibited antioxidant activities by using the scavenging of 2-2-diphenyl-1-picrylhydrazyl radical (DPPH) and FRAP total reduction capability methods wherein **11** was found to be active at all concentrations. These compounds also displayed partial cleavage of DNA.[28]

Vismiaguianone A **13** displayed cytotoxic activity.[13] 4'-Methoxy-bavachromanol **14** showed a strong soybean lipoxygenase inhibitory activity.[14] Δ^9-Tetrahydrocannabinol **15** showed antidepressant-like actions[29a] and also found to induce mouse-killing behaviour (muricide).[29b] (+)-Catechin **16** is a strong antioxidant[16c,f] as well as possesses a potential agonist characteristic that can activate insulin receptor and peroxisome proliferator-activated receptor gamma, thus exhibiting the hypoglycemic effect of catechin.[16d] 3,4-Dihydromollugin **17** exhibits high antioxidant activity in DPPH inhibition[30a] and also possesses antiviral activity with an IC_{50} value of 2.0 μg/mL in human hepatoma Hep3B cells.[30b]

Epoxymollugin **21** isolated from *Rubia cordifolia* showed inhibition of DNA topoisomerases I and II and cytotoxic activity against MCF-7 cell line.[20] Peperobtusin A **22**, clusifoliol **23** and 3,4-dihydro-5-hydroxy-2,7-dimethyl-8-(2-methyl-2-butenyl)-2-(4-methyl-1,3-pentadienyl)-2*H*-1-benzopyran-6-carboxylic acid **24** were obtained from *Peperomia obtusifolia* and exhibited potent trypanocidal activity.[21d] Rhododaurichromanic acid A **25** is a potent anti-HIV

agent[22] whereas (-)-Siccanin **26** is a potent antifungal agent.[23] Suksdorfin **27o** was found to exhibit anti-HIV activity.[26a] Also many chroman derivatives are used as antioxidants for fats and oils[31] and some exhibit weak estrogenic activity.[32]

Besides a large number of naturally occurring dihydrobenzopyrans, several synthetic analogues of chromans **28-41** have been well characterized and studied for their biological activities. Selected examples are given below (Figure 7, Table 3).

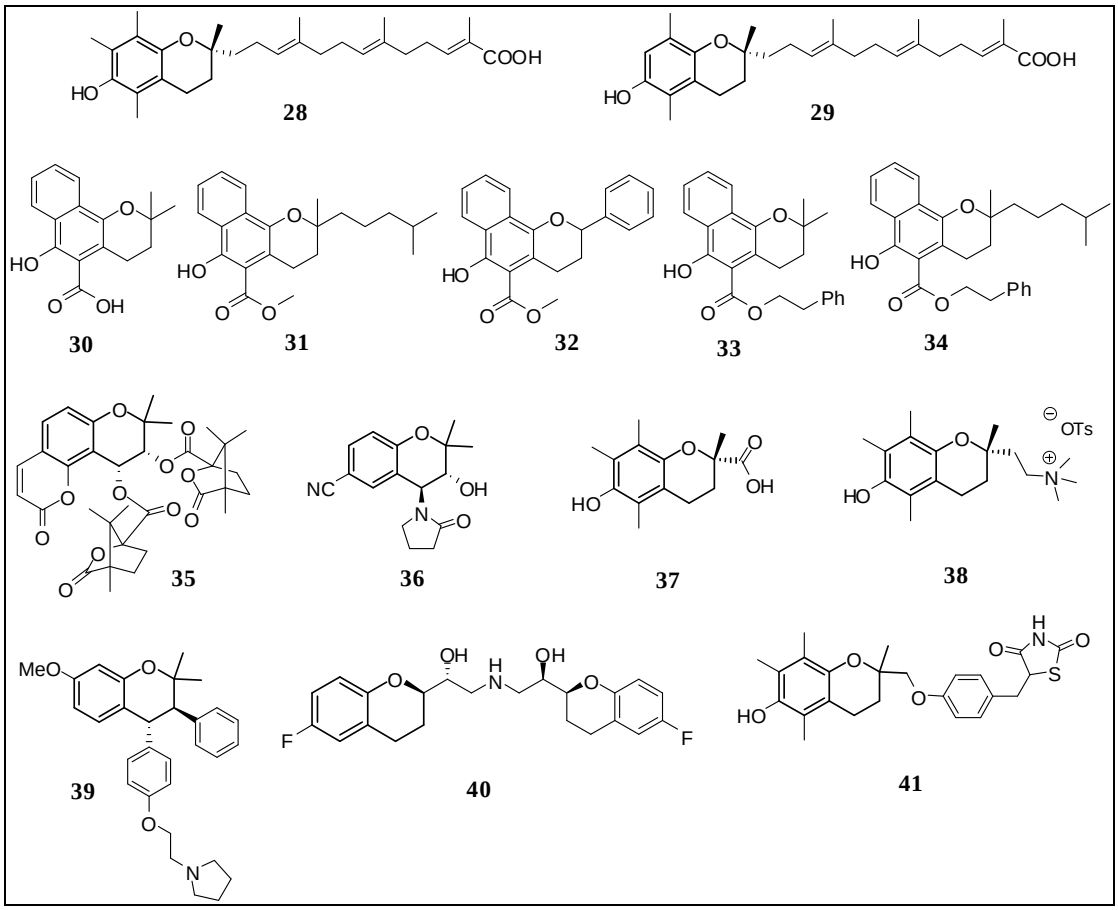


Figure 7: Structures of bioactive synthetic chromans **28-41**.

Table 3: Bioactive synthetic chromans **28-41**.

No.	Name
28	α-Garcinoic acid (α-tocotrienolic acid)[9]
29	β-Garcinoic acid (β-tocotrienolic acid)[9]
30	6-Hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*h*]chromene-5-carboxylic acid[30a]
31	Methyl 6-hydroxy-2-methyl-2-(4-methylpentyl)-3,4-dihydro-2*H*-benzo[*h*]chromene-5-carboxylate[30a]

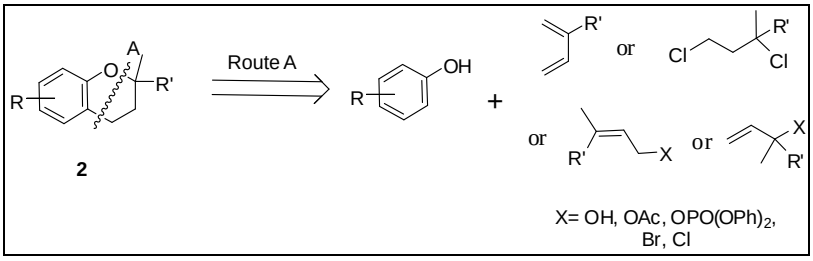
32	Methyl 6-hydroxy-2-phenyl-3,4-dihydro-2*H*-benzo[*h*]chromene-5-carboxylate[30a]
33	Phenethyl 6-hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*h*]chromene-5-carboxylate[30a]
34	Phenethyl 6-hydroxy-2-methyl-2-(4-methylpentyl)-3,4-dihydro-2*H*-benzo[*h*]chromene-5-carboxylate[30a]
35	3',4'-Di-*O*-(-)-Camphanoyl-(+)-*cis*-Khellactone[33]
36	Cromakalim[34]
37	Trolox[35]
38	MDL-73404[36]
39	Centchroman[37]
40	Nebivolol[38]
41	Troglitazone[39]

α- and *β*-Garcinoic acids **28**-**29** are potent mPGES-1 inhibitors.[9] Generally chromenes are more potent than their corresponding saturated analogues (chromans). Interestingly, Idhayadhulla *et al.*[30a] synthesized different dihydromollugin analogues **30**-**34** which were found to exhibit little better antioxidant activity than their corresponding dehydro (chromene) compounds. Also, all these synthetic derivatives showed antibacterial activities. 3',4'-Di-*O*-(-)-camphanoyl-(+)-*cis*-khellactone **35** demonstrated anti-HIV activity.[33] Cromakalim **36** acts as an antihypertensive agent[34a] and vasodilators.[34b-c] It inhibits transmitter acetylcholine release by the activation of ATP-sensitive potassium channels from atrial parasympathetic nerves and cholinergic nerves in rat trachea on cells in the epithelial layer.[34d-f] Trolox **37** is a synthetic water soluble analogue of vitamin E is widely known for its antioxidant activity.[35] MDL-73404 **38** is an antioxidant and also reduces myocardial infarct size.[36] Centchroman **39** is an antifertility agent and used as oral contraceptive pills.[37] Nebivolol **40** is an anti-hypertensive agent.[38] Troglitazone **41** inhibits serum-induced proliferation of human umbilical vascular endothelial cell (HUVEC) by suppressing casein kinase 2 activity.[39a] It also inhibits insulin hypersecretion.[39b-c]

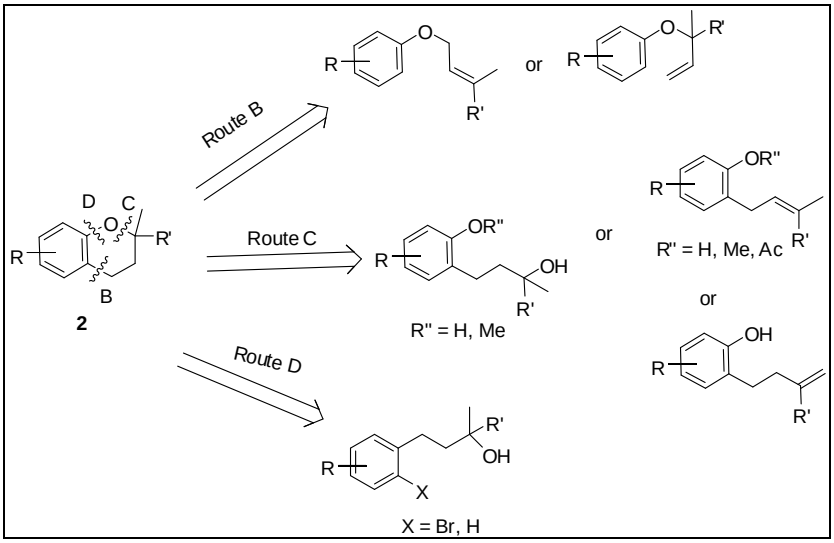
2.3: Literature synthetic methods

Owing to the various biological benefits of chromans, they have attracted the attention of several chemists in recent years and numerous synthetic routes have been devised and reviewed.[40] The retrosynthetic analysis of these synthetic methods can be broadly divided into 5 categories as depicted below. These 5 approaches have been classified on the basis of i)

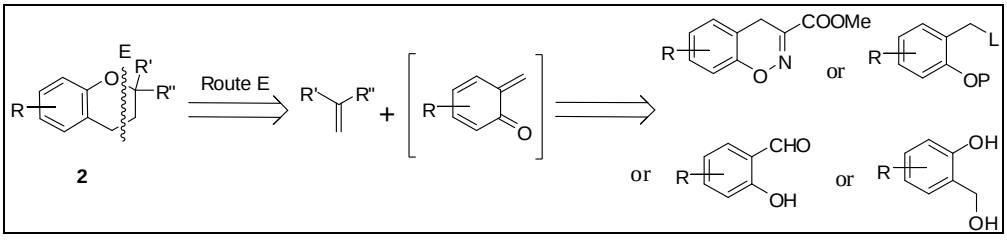
reaction of phenols with various electrophiles (Scheme 1, Route A), ii) intramolecular cyclization involving C-O or C-C bond forming reactions (Scheme 2, Routes B-D), iii) Diels Alder reaction between *ortho*-quinone methides intermediate and olefins (Scheme 3, Route E), iv) interconversion of functional group (Scheme 4, Route F), and v) miscellaneous routes (Scheme 5, Route G).



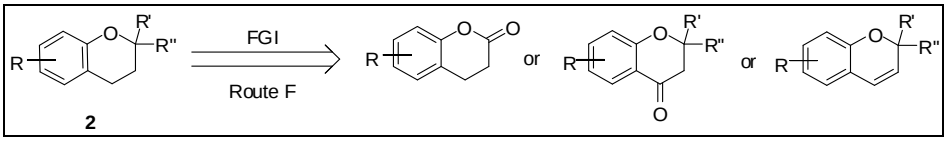
Scheme 1: Reaction of phenols with various electrophiles (Route A).



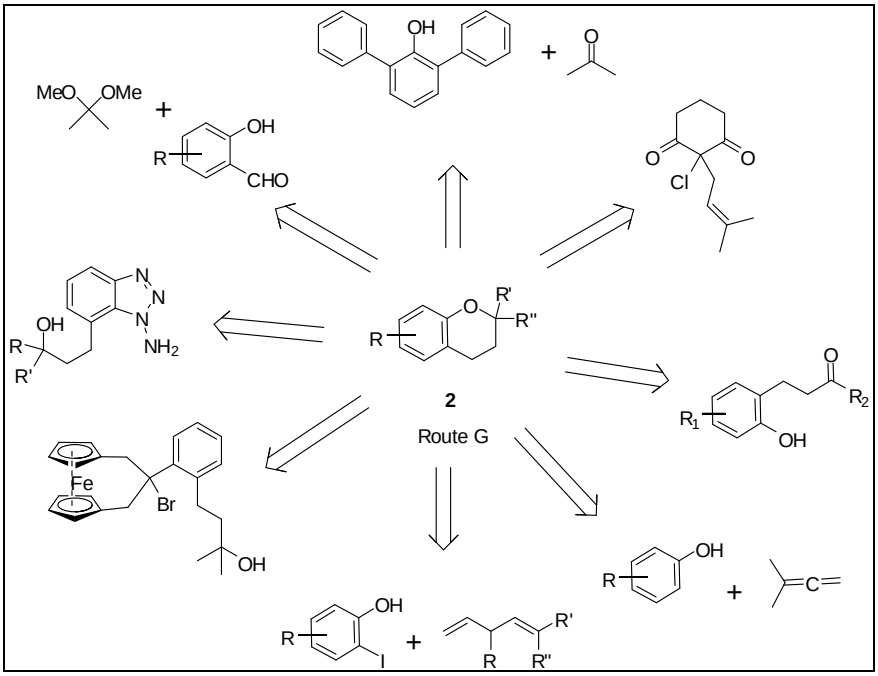
Scheme 2: Intramolecular cyclization involving C-O or C-C bond forming reactions (Routes B-D).



Scheme 3: Diels Alder reaction between *ortho*-quinone methides intermediate and olefins (Route E).



Scheme 4: Interconversion of functional group (Route F).



Scheme 5: Miscellaneous routes (Route G).

Diverse methodologies have been devised for chroman synthesis some of which involves the construction of the parent chroman. Asymmetric syntheses of several chroman molecules have been developed and reviewed.[41] The various chroman syntheses known are discussed below.

2.3.1: Reaction of phenols with various electrophiles (Route A)

2.3.1.1: From phenols and 1,3-dienes

Most of the methodologies involves coupling of phenols and 1,3-dienes by using several homogenous or heterogenous acids as reagents/catalysts which is an atom economical way of constructing these heterocycles. These are included in the following table 4.[42-57]

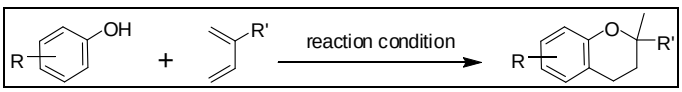


Table 4: Synthesis of chromans from phenols and 1,3-dienes using various reagents or catalysts.

Sr. No.	Reagent/catalyst	Reaction condition	Ref.
1)	Potassium phenoxide, $AlCl_3$	benzene, rt	42
2)	PPA	xylene, 30-35 °C	43
3)	cat. $ZnCl_2$/HCl	acetic acid, 0 °C	44
4)	cat. Phosphoric acid	20 °C, 16 h or xylene, 30-35 °C or light petroleum, 30-35 °C	45
5)	cat. Aluminum phenoxide	110 °C	46
6)	cat. (+)-10-Camphorsulfonic acid	octane, reflux	47
7)	cat. $AlCl_3$-$[Bu_4N]I$ /$AlCl_3$-$[(C_8H_{17})_4N]Br$	octane/dibutyl ether, reflux	48
8)	cat. Amberlyst 15	THF, 65-70 °C	49
9)	cat. Zeolite HSZ-360	chlorobenzene, 120 °C	50
10)	cat. $[RhCl(COD)]_2$	i) cat. dppb, K_2CO_3, toluene, 110 °C ii) $MeAlCl_2$ or *p*-TSA, hexane, 100°C	51
11)	cat. AgOTf	$ClCH_2CH_2Cl$, 40 °C	52
12)	cat. AgOTf, *t*-BuCl	$ClCH_2CH_2Cl$, rt	53
13)	cat. $Sc(OTf)_3$–[bmim][PF_6]	toluene, 60 / 100 °C	54
14)	cat. $Cu(OTf)_2$	(bipy)/PPh_3, DCE, 50 °C	55
15)	cat. $Bi(OTf)_3$	toluene, 40 °C	56
16)	cat. $FeCl_3$/$AgBF_4$	DCE, 60 °C	57

Bolzoni *et al.*[42] synthesized chroman in good yields by employing potassium phenoxide and $AlCl_3$ reagents in benzene at room temperature. Recently, Raju *et al.*[43] employed polyphosphoric acid in xylene to carry out this cyclization.

Several catalytic systems have also been reported for the annulation of phenols with 1,3-dienes forming chromans. Smith *et al.*[44] synthesized chromans by dissolving phenol and isoprene in acetic acid in presence of dry HCl or $ZnCl_2$. Bader and Bean[45a] explored phosphoric acid catalyst for the reaction of isoprene and phenol. However along with

chroman product, other products like *o*- and *p*-3-methylcrotylphenols and *γ*-hydroxyisoamylphenols were also isolated. Later, polyhydroxyacetophenones were condensed with isoprene in phosphoric acid by Ahluwalia *et al.*[45b-c] to form acetylchromans.

Dewhirst and Rust[46] isolated the mixture of alkenylphenols and chromans on carrying out a reaction between phenol and dienes in presence of catalytic amount of aluminium phenoxide. The catalytic activity of (+)-10-camphorsulfonic acid was investigated by Matsui and Yamamoto[47] to obtain chromans including *α*-tocopherol in 2 steps. However spiro compound was formed as the side product in small amounts.

Matsui and Yamamoto[48] explored the catalytic effect of $AlCl_3$ in presence of phase transfer catalyst such as tetraalkylammonium salts. These salts were found to accelerate Lewis acid catalyzed Friedel-Crafts alkylation reaction of phenol with 1,3-diene. Among the several tetraalkylammonium salts studied, tetrabutylammonium iodide-aluminium chloride and tetraoctylammonium bromide-aluminium chloride complexes effectively catalyzed the reaction between trimethylhydroquinone with myrecene followed by cyclization to form *α*-tocopherol. Kalena *et al*.[49] obtained chromans after slow addition of isoprene to the mixture of phenols and cation exchange resin amberlyst 15 in THF at 65-70 °C. However, the use of polyhydroxyphenols substrates resulted in a mixture of isomeric chroman products.

Zeolite HSZ-360 have been successfully utilized as catalyst to synthesize chromans by Bigi *et al.*[50] The one pot method selectively delivered chromans in chlorobenzene at 120 °C with traces of *o*-isopentenylphenols. However, the solid acid catalysis is also useful to obtain *o*-isopentenylphenols as major product by maintaining the temperature at 80 °C. Bienaymé *et al.*[51] investigated the regioselective arylation of *β*-springene with trimethylhydroquinone using $[RhCl(COD)]_2$ catalyst followed by cyclization in presence of $MeAlCl_2$ or *p*-TSA resulting in chroman skeleton.

Recently, several environmentally sound catalytic systems have been reported. AgOTf was investigated to form C-C/C-O bond sequentially between phenols and dienes by Youn and Eom.[52] The method is mild, efficient, and economical but dihydrobenzofuran ring compounds were also isolated in some cases along with the desired dihydrobenzopyrans. The hidden Brønsted acid catalyst HOTf generated from AgOTf in presence of co-catalyst *tert*-butyl chloride have been utilized for chroman synthesis by Dang *et al*.[53]

Youn[54] developed reusable catalytic system $Sc(OTf)_3$–$[bmim][PF_6]$ to afford dihydrobenzopyrans along with dihydrobenzofuran ring systems. The ionic liquid $[bmim][PF_6]$ plays dual role as an additive and an immobilizing agent for facilitating recycling of catalyst. Adrio and Hii[55] explained chroman formation from phenols to 1,3-dienes with recyclable $Cu(OTf)_2$ catalyst along with 2,2'-bipyridine (bipy) or PPh_3 ligands in

moderate to good yields. Both ligands were equally effective, however the cheap availability and higher resistivity of bipy to oxidation than PPh_3 makes it a preferred ligand. The method involves tandem hydroalkoxylation–rearrangement–hydroalkylation sequence. However few derivatives resulted in a mixture of dihydrobenzopyran and dihydrobenzofuran ring compounds.

Judd and Caggiano[56] explained the utility of $Bi(OTf)_3$ catalyst in the formation of chromans from substituted phenols and excess of isoprene. However, the products in the few examples demonstrated are obtained in low to moderate yields due to the unreacted phenol. Villani-Gale and Eichman[57] discussed the formation of regioselective prenylation of phenols followed by cyclization to chromans by employing catalytic mount of $FeCl_3$ and $AgBF_4$. The method allows employing isoprene directly and also avoids the use of stoichiometric Lewis/Bronsted acids.

2.3.1.2: From phenols and allylic alcohols/acetates

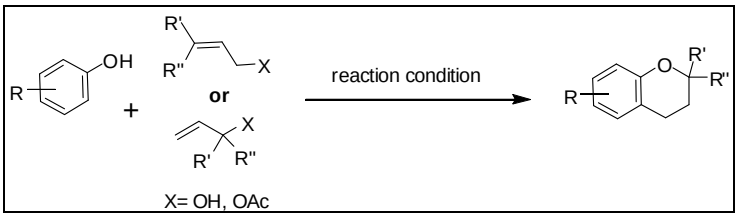


Table 5: Synthesis of chromans from phenols and allylic alcohols/acetates using various reagents or catalysts.

Sr. No.	Reagent/Catalyst	Reaction condition	Ref.
1)	Formic acid	benzene reflux/100 °C	58
2)	$BF_3/AlCl_3$	CH_2Cl_2, CH_3NO_2	59
3)	TFA/H_2O	Ar, rt, 15-30 min	60
4)	$ZnCl_2$	CH_2Cl_2, reflux	61
5)	cat. $(acac)_2Mo(SbF_6)_2$	CH_2Cl_2, rt	62
6)	cat. $[Mo(CO)_4Br_2]_2$	CH_2Cl_2, rt	63
7)	cat. $CpMoCl(CO)_3$/*o*-chloranil	MW, 150 °C	64
8)	cat. *p*-TsOH	DCE, reflux	65
9)	cat. $In(OTf)_3$	$CH_2Cl_2/CH_3CN/CH_3NO_2$	66
10)	cat. CuAl-SBA-15	cyclohexane, reflux	67
11)	cat. CuAl-KIT-5-10	1,2-dichloroethane, 60-85 °C	68
12)	cat. Polyphosphoric acid	CH_2Cl_2, rt	69

13)	cat. $BF_3.Et_2O$	CH_2Cl_2, rt	70
14)	cat. PPh_3AuNTf_2	toluene	71

Another route to chromans involves condensation of phenols with allylic alcohols/acetates in presence of Bronsted or Lewis acids and various catalysts (Table 5). Mamalis *et al.*[58a] synthesized tocol from quinol monobenzyl ether or from quinol by adding phytol in refluxing benzene in presence of formic acid. Recently Harel *et al.*[58b] achieved the total synthesis of encecalol angelate wherein the first step was the synthesis of chroman from resorcinol and 2-methylbut-3-en-2-ol in formic acid at 100 °C. Wehrli *et al.*[59] investigated the reaction of trimethylhydroquinone with isophytol in presence of BF_3 or $AlCl_3$ reagents. The reaction involved the formation of trimethylhydroquinone-boron trifluoride or trimethylhydroquinone-aluminium trichloride complex which on alkylation with isophytol followed by cyclization delivered chroman.

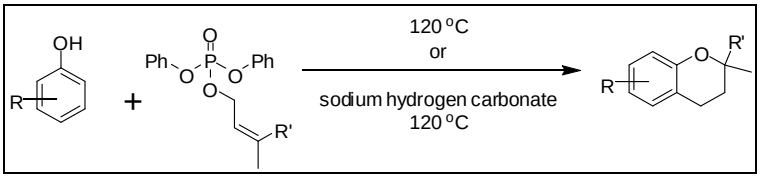
Ismail *et al.*[60] showed the utility of trifluoroacetic acid/H_2O combination for benzopyran synthesis. The presence of water in trifluoroacetic acid was found to accelerate the reaction. Jun and co-workers[61] studied the condensation reaction of resorcinol with 2-methyl-3-buten-2-ol using several acid catalysts or acid solvents among which zinc chloride furnished chroman product in 70 % yield.

A large number of catalytic systems (Table 5) have also been devised for chroman synthesis from phenols and allylic alcohols/acetates. Various molybdenum complexes such as $(acac)_2Mo(SbF_6)_2$, $[Mo(CO)_4Br_2]_2$, and $CpMoCl(CO)_3$/*o*-chloranil have been explored. Chroman formation on treatment of prenyl alcohol or its isomer 2-methylbut-3-en-2-ol with *p*-cresol using $(acac)_2Mo(SbF_6)_2$ was studied by Malkov *et al.*[62] However the product yields were poor. The same group also studied the catalytic activity of $[Mo(CO)_4Br_2]_2$ for the reaction between aliphatic allylic acetate or its isomer and phenol furnishing chroman.[63] The cyclocoupling of phenol with allylic alcohols was well explored by Yamamoto and Itonaga[64] using $CpMoCl(CO)_3$/*o*-chloranil catalytic system under microwave conditions. The chromans were obtained rapidly in moderate to good yields. The methodology was also applied for the synthesis of naturally occurring *α*-tocopherol derivatives and 3,4-dihydromollugin.

Several chroman derivatives were obtained by Ishino *et al.*[65] from phenols and unsaturated alcohols by employing catalytic amount of *p*-toluenesulfonic acid in 1,2-dichloroethane solvent. The cyclocoupling of phenols and allylic acetates was also achieved by Vece *et al.*[66] with indium triflate catalyst. The efficiency of catalyst can be easily identified as the reaction smoothly proceeded with just 1 mol% of the catalyst. It involves tandem allylation–

intramolecular hydroalkoxylation sequence. However noncyclised *o*- and *p*-allylated products and dihydrobenzofuran in some cases were also recovered along with the desired chroman. Varghese *et al.*[67] utilized mesoporous and hexagonally ordered CuAl-SBA-15 catalyst for chroman synthesis in good yields from phenols and allylic alcohols. The recyclable catalyst allows tandem C-C and C-O bond formation leading to several chroman derivatives including vitamin E. The same group[68] also showed the scope of CuAl-KIT-5-10 catalyst to obtain chromans from phenols and 2-methylbut-3-en-2-ol at 85 °C. However, a mixture of *o*-prenylated phenol and chromans were obtained on decreasing the temperature to 60 °C.

Polyphosphoric acid was employed for the construction of benzopyran skeleton by Murthy *et al.*[69] It was further functionalized to obtain several novel compounds which were evaluated for antimicrobial activities. Madabhushi *et al.*[70] extended the scope of methodology employing $BF_3.Et_2O$ catalyst for chroman synthesis wherein 2-methylbut-3-en-2-ol was treated with *p*-cresol to yield chroman in 80 %. However on changing the unsaturated alcohol to 1,1-diphenylprop-2-en-1-ol no product was isolated. Coutant *et al.*[71] demonstrated cyclocoupling of phenols and allylic alcohols using catalytic amount of PPh_3AuNTf_2. The method involves a one-pot regioselective Friedel–Crafts allylation reaction followed by intramolecular hydroalkoxylation. A large range of derivatives have been synthesized.



Scheme 6

Miller and Wood[72] synthesized 2,2-dimethylchroman derivatives by the treatment of 3,3-dimethylallyl diphenyl phosphates with an excess of phenols at 120 °C in absence or presence of solid sodium hydrogen carbonate (Scheme 6).

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2.3.1.3: From phenols and allylic halides

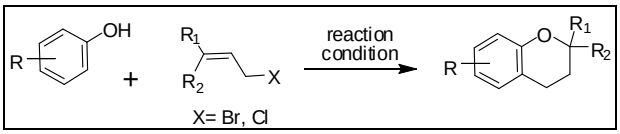


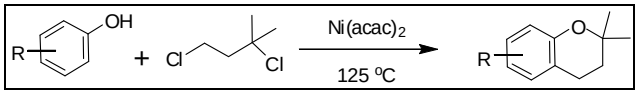
Table 6: Synthesis of chromans from phenols and allylic halides using various reagents or catalysts.

Sr. No.	Reagent/ Catalyst	Reaction condition	Ref.
1)	BuLi	benzene, reflux	73

2)	Montmorillonite K-10	CCl_4	74
3)	cat. $Ni(acac)_2$	90 °C	75
4)	cat. *p*-TSA	toluene, reflux	76

Chromans have also been obtained by the cyclization of phenols with allylic bromides/chlorides using some reagents/catalysts (Table 6). Cardillo *et al.*[73] obtained chromans by treating lithium salts of phenol obtained from phenol and butyllithium with prenyl bromide in refluxing benzene. The products were dehydrogenated further with DDQ to form chromenes. Similarly, Dintzner *et al.*[74] demonstrated cyclocondensation of substituted phenols with prenyl bromide to afford 2,2-dimethylbenzopyrans using montmorillonite K-10. However mixture of regioisomers was obtained in few cases. Camps *et al.*[75] carried out the cycloaddition of 4-methoxyphenol and prenyl chloride to produce 2,2-dimethyl-6-methoxychroman using $Ni(acac)_2$ catalyst at 90 °C. Jetter *et al.*[76] observed the reaction of 7-hydroxycoumarins with allyl halides, homoallyl halides or alcohols in presence of catalytic amount of *p*-toluenesulphonic acid. It delivered chromans/reduced derivatives of naturally occurring xanthyletin and seselin *via* a one step alkylation followed by cyclization.

2.3.1.4: From phenols and 1,3-dichloro-3-methylbutane



Scheme 7

Camps *et al.*[75] also explored the effectiveness of $Ni(acac)_2$ catalyst to obtain chroman product from phenol and 1,3-dichloro-3-methylbutane. Different derivatives were obtained, some of which were accompanied by overalkylation (Scheme 7).

2.3.2: Intramolecular cyclization involving C-O or C-C bond forming reactions (Routes B, C and D)

2.3.2.1: From aryl prenyl ethers (Route B)

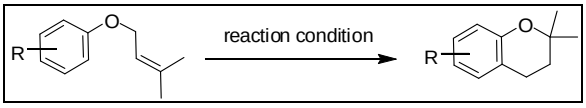


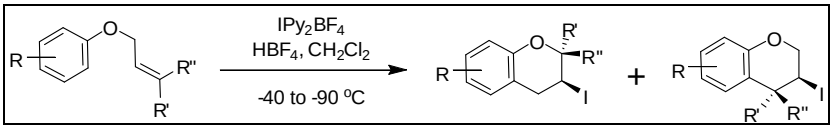
Table 7: Synthesis of chromans from aryl prenyl ethers using various reagents or catalysts.

Sr. No.	Reagent/Catalyst	Reaction condition	Ref.
1)	Montmorillonite clay	benzene, 50 °C, N_2	77

2)	Calcined SiO_2	neat, 60-70 °C or benzene, reflux	78
3)	cat. $Mo(CO)_6$	toluene, 115 °C, Ar	79
4)	cat. $Bi(OTf)_3 \cdot 4H_2O$	toluene, 0-22 °C	80

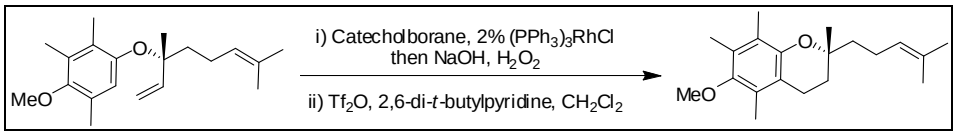
Rearrangement of aryl prenyl ethers is an alternative route to obtain chromans (Table 7). Dauben *et al.*[77] carried out rearrangement of aryl prenyl ethers using montmorillonite clay *via* [1,3] shift of ethers followed by cyclization to synthesize chromans. However, some substrates delivered *o*-allyl phenols and coumarans. Similarly aryl prenyl ether was rearranged with calcined SiO_2 (300 °C, 5 h) by Pogrebnoi *et al.*[78] either under neat heating or refluxing benzene conditions.

Bernard *et al.*[79] showed the usefulness of $Mo(CO)_6$ catalyst in carrying out Claisen rearrangement of aryl prenyl ethers followed by cyclization leading to chromans. In some cases, the products were accompanied with small amounts of corresponding starting phenols. Later, Ollevier and Mwene-Mbeja[80] employed bismuth triflate catalyst for [1,3] rearrangement of aryl prenyl ethers to synthesize chromans. However, *p*-prenylphenols are isolated as side products.



Scheme 8

Barluenga *et al.*[81] found the selective rearrangement of allylphenyl ethers followed by cyclization to 2-substituted 3-iodochromans using IPy_2BF_4 which promotes C-C bond formation and also serves as a source of iodonium ion. Also isomeric 4-substituted 3-iodochromans were obtained *via* an intramolecular cyclization reaction (Scheme 8).

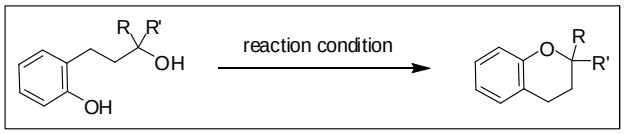


Scheme 9

The tertiary ether was chemoselectively hydroborated with catecholborane in the presence of 2 % Wilkinson's catalyst by Trost and Toste[82] which underwent electrophilic cycloalkylation to chroman upon activation of the primary alcohol as its triflate (Scheme 9).

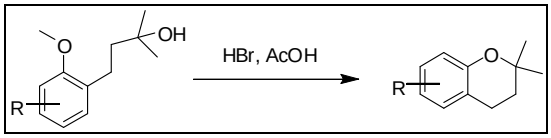
2.3.2.2.1: From 2-(3-hydroxyalkyl)phenols/anisoles (Route C)

Table 8: Synthesis of chromans from 2-(3-hydroxyalkyl)phenols using various reagents or catalyst.



Sr. No.	Reagent/Catalyst	Reaction condition	Ref.
1)	DEAD, triphenylphosphine	dioxane, rt	83
2)	H_3PO_4	toluene, reflux	84
3)	H_2SO_4	toluene	85
4)	cat. *p*-TsOH	benzene, reflux	86

Dehydration of substituted 2-(3-hydroxyalkyl)phenols also delivers chromans (Table 8). Aristoff *et al.*[83] carried out an intramolecular dehydration of substituted 2-(3-hydroxyalkyl)phenols to the corresponding extremely potent benzopyran prostacyclin mimics through an intramolecular Mitsunobu reaction as the key step. In addition, few structurally simple substrates on treatment with DEAD and triphenylphosphine in dioxane delivered chromans and dihydrobenzofurans in moderate to excellent yields. Only few examples reported suggest the limited scope of the method. Yus *et al.* [84] carried out acidic intramolecular dehydration of 2-(3-hydroxy-3-substituted)phenols to chromans using 85 % phosphoric acid in refluxing toluene. However substrate scope is limited. Erhardt and co-workers[85] used 15 % H_2SO_4 in toluene for dehydration of diol. Chroman obtained was further functionalized over several steps to accomplish synthesis of complex molecule. Tanaka *et al.*[86] obtained 3,4-dihydro-2,2,6-trimethyl-2*H*-1-benzopyran from the corresponding 2-(3-hydroxy-3-methylbutyl)-4-methylphenol using *p*-toluenesulfonic acid as catalyst.

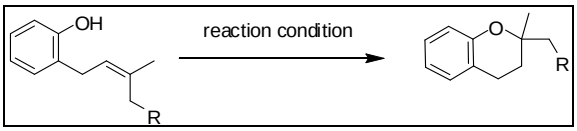


Scheme 10

Demethylative cyclisation of substituted *o*-methoxy tertiary alcohols was carried out by Nilsson *et al.*[87] with HBr in acetic acid condition to furnish chromans (Scheme 10).

2.3.2.2.2: From 2-(3',3'-dialkylallyl)phenols/anisoles/phenyl acetates (Route C)

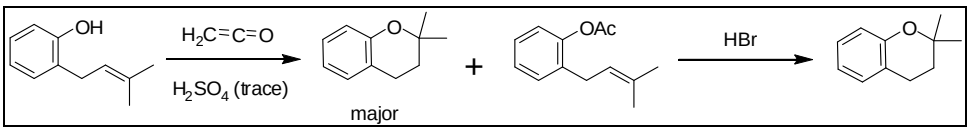
Table 9: Synthesis of chromans from 2-(3',3'-dialkylallyl)phenols using various reagents or catalysts.



Sr. No.	Reagent/Catalyst	Reaction condition	Ref.
1)	Phenol (excess) diphenyl hydrogen phosphate sodium hydrogen carbonate	100 °C	72
2)	HCl/AlC1$_3$	cyclohexane, rt	88
3)	cat. FeCl$_3$	25 °C	89
4)	cat. Al(O*i*Pr)$_3$	PhCl, 250 °C, MW	90
5)	cat. Fe-montmorillonite/ Bi-montmorillonite	dimethyl carbonate, 80 °C	91

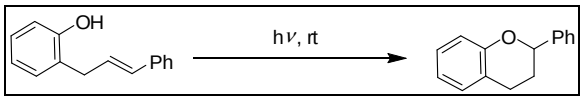
2-(3',3'-Dialkylallyl)phenols have also been converted to the respective chromans (Table 9). 2-(3',3'-Dimethylallyl)phenol, phenol, diphenyl hydrogen phosphate, and sodium hydrogen carbonate were heated at 100 °C by Miller and Wood[72] to form chroman products. Later, Wang *et al.*[88] obtained chromans by the intramolecular cyclization of 2-(3-methyl-2-buteny1)phenols along with 1,1-dimethyl-4-indanols. Also the substrate scope is limited. The cyclization of *2*-(3',3'-dimethylallyl)phenol derivatives to the corresponding chromans using catalytic FeCl$_3$ was carried out by Macone *et al.*[89] The products were evaluated for cytotoxicity and pro-apoptotic activity.

Later, Schlüter *et al.*[90] converted 2-allylphenols to cyclic ethers *via* intramolecular hydroxylation using cat. aluminium isopropoxide under microwave irradiation. The scope of the catalyst was extended by synthesising chroman skeleton from 2-(3',3'-dimethylallyl)phenol. Recently, Francesco *et al.*[91] employed recyclable heterogeneous catalyst Fe/Bi-Montmorillonite in dimethyl carbonate solvent to achieve chromans. In addition, a wide range of cyclic ethers were produced.



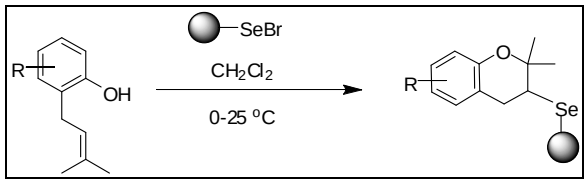
Scheme 11

Hurd and Hoffman[92] prepared chroman from 2-(3',3'-dimethylallyl)phenol upon treatment with ketene and trace amount of sulfuric acid along with minor acetylation product *viz*. *o*-(*γ*, *γ*-dimethylallyl)phenyl acetate. However when the acetate product separately treated with hydrogen bromide, 2,2-dimethylchroman was produced (Scheme 11).



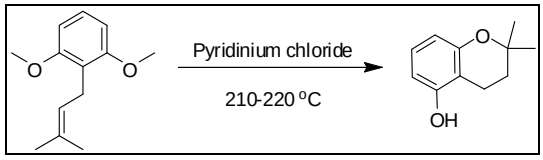
Scheme 12

Jiménez *et al.*[93] carried out irradiation of trans-2-cinnamylphenol using various conditions to deliver 2-phenylchroman along with cis-2-cinnamylphenol and 2-benzyl-2,3-dihydrobenzofuran (Scheme 12).



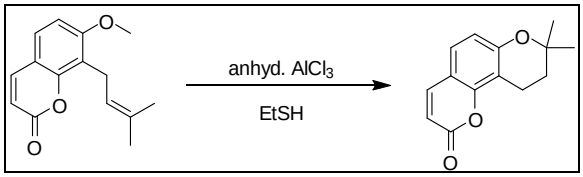
Scheme 13

Nicolaou *et al.*[94] employed a selenium-based methodology for the solid phase construction of resin bound 2,2-dimethylbenzopyrans wherein the loading step is a key ring-forming reaction. A library of derivatives has been synthesized (Scheme 13).



Scheme 14

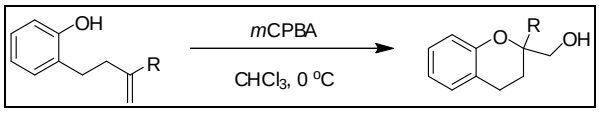
Boltze and Dell[95] on heating 2-(3-methyl-2-butenyl)resorcinol dimethyl ether with pyridinium chloride at 210-220 °C for 5 h delivered the desired chroman skeleton (Scheme 14).



Scheme 15

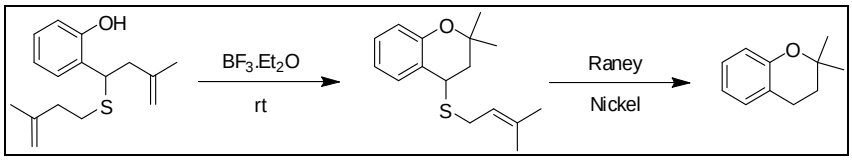
Gopalakrishnan *et al.*[96] employed $AlCl_3$/EtSH reagent to carry out a tandem demethylation-cyclisation reaction to form pyran rings (Scheme 15).

2.3.2.2.3: From substituted 2-(3-butenyl)phenols (Route C)



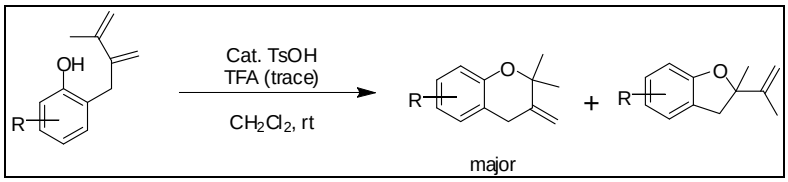
Scheme 16

Bravo and Ticozzi[97] converted the olefin starting to the epoxide using *m*-chloroperbenzoic acid which was converted to chroman by the attack of the phenolic oxygen on the quaternary epoxide carbon in epoxide intermediate during work up (Scheme 16).



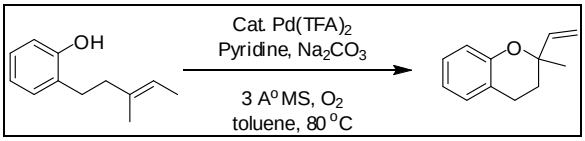
Scheme 17

Chroman derivative was synthesized by Sato *et al.*[98] by treating the *o*-alkylphenol starting with boron trifluoride etherate followed by desulphurization with Raney nickel (Scheme 17).



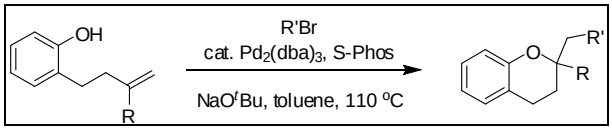
Scheme 18

Exo-methylene chromans were obtained by Grigg *et al.*[99] along with dihydrobenzofurans through cyclization of dienylmethyl phenols with *p*-toluenesulphonic acid and trace amount of TFA (Scheme 18).



Scheme 19

According to Stoltz and co-workers[100] 5 mol% of $Pd(TFA)_2$ catalyst in presence of pyridine and Na_2CO_3 using molecular oxygen as oxidant was effective in constructing chroman skeleton *via* aerobic oxidative cyclization of oxygen nucleophile onto olefin (Scheme 19).



Scheme 20

Pd-catalyzed carboetherification reactions between 2-(but-3-en-1-yl)phenols and aryl/alkenyl halides was described by Ward *et al.*[101] Several 2-substituted and 2,2-disubstituted derivatives have been prepared (Scheme 20).

2.3.2.3: From 3-(2-bromoaryl)-1-propanols/3-aryl-1-propanols (Route D)

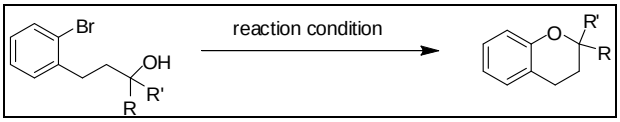


Table 10: Synthesis of chromans from 3-(2-bromoaryl)-1-propanols using various reagents or catalysts.

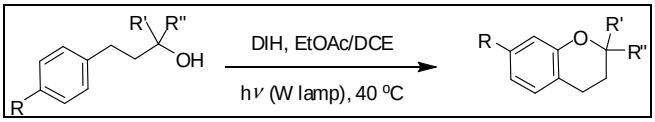
Sr. No.	Reagent/Catalyst	Reaction condition	Ref.
1)	*t*-BuOK	DMSO, MW, 140 W	102
2)	cat. $Pd(OAc)_2$, Tol-BINAP/DPPF	K_2CO_3/NaO*t*-Bu, toluene, 80-100 °C	103
3)	cat. $Pd(OAc)_2$, 2-(di-*tert*-butylphosphino)-1,1'-binaphthyl/ 2-di-*tert*-butylphosphinobiphenyl	Cs_2CO_3, toluene, 50-80 °C	104
4)	cat. $Pd(dba)_2$, $Ph_5FcP(t\text{-}Bu)_2$	toluene, rt	105
5)	cat. CuI, 8-hydroxyquinoline	Cs_2CO_3, toluene, Ar atm, 110 °C	106
6)	cat. CuI, 2,2-bipyridyl	KO*t*-Bu, DMF, 120 °C	107

Intramolecular coupling of aryl bromides with alcohol is another way to obtain chromans (Table 10). Xu *et al.*[102] investigated an efficient aromatic C–O bond forming reaction using potassium *tert*-butoxide under microwave irradiation. Diverse products were synthesized including chromans avoiding the use of transition-metal catalyst. The method is also useful for the synthesis of bioactive natural flavans.

Palladium catalysis in presence of various ligands is also well known for such cyclization reactions. Palucki *et al.*[103] studied the role of $Pd(OAc)_2$ catalyst in presence of (*S*)-(-)-2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthyl (Tol-BINAP) and 1,1'-bis(diphenylphosphino)-ferrocene (DPPF) in the synthesis of chromans. Cyclization of intramolecular substrates was carried out in toluene in presence of NaO*t*-Bu or K_2CO_3 base. However, the reactions were accompanied by side products including dehalogenation of the aryl halides and oxidation of the alcohol to the ketone in case of substrates containing a secondary alcohol.

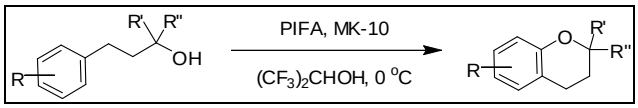
Later, to overcome the above problems, Torraca *et al.*[104] explored 2-(di-*tert*-butylphosphino)-1,1'-binaphthyl and 2-di-*tert*-butylphosphinobiphenyl as ligands, the former being more general, in presence of $Pd(OAc)_2$ catalyst. The products were obtained in good yields. Shelby *et al.*[105] successfully explored a combination of cat. $Pd(dba)_2$ with $Ph_5FcP(t\text{-}Bu)_2$ ligand which is effective at room temperature for aromatic C-O bond formation reactions. Two chromans were synthesized in good yields along with several acyclic ethers.

Copper catalysis is also effective to render chromans. Niu *et al.*[106] developed a methodology using copper (I) iodide catalyst, 8-hydroxyquinoline ligand and K_3PO_4 base. The method involves C-O coupling between aliphatic alcohols and aryl bromides to form acyclic ethers. Further intramolecular coupling resulted in chromans and benzofurans in presence of Cs_2CO_3 base. Suchand *et al.*[107] also reported copper catalyzed intramolecular C-O bond formation reactions of secondary and tertiary alcohol substrates in presence of 2,2-bipyridyl ligand. Several 2-substituted and 2,2-disubstituted chroman derivatives were synthesized in good yields.



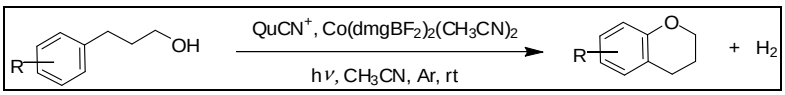
Scheme 21

Furuyama and Togo[108] irradiated various 3-aryl-1-propanols with excess of 1,3-diiodo-5,5-dimethylhydantoin (DIH) with tungsten lamp in presence of ethyl acetate or 1,2-dichloroethane to produce chroman derivatives. Products were obtained in moderate to good yields (Scheme 21).



Scheme 22

Hamamoto *et al.*[109] utilized phenyliodine(III)bis(trifluoroacetate) (PIFA), a hypervalent iodine (III) reagent for the direct aromatic carbon–oxygen bond forming reaction of 3-aryl-1-propanols leading to chromans. It involves an aromatic cation radical pathway (Scheme 22).



Scheme 23

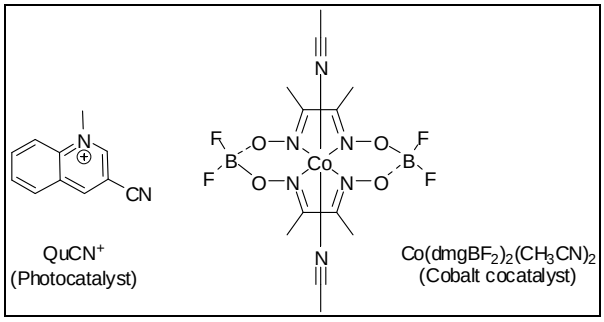
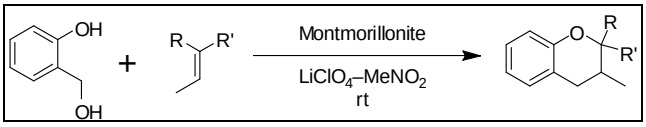


Figure 8: Structures of $QuCN^+$ and $Co(dmgBF_2)_2(CH_3CN)_2$.

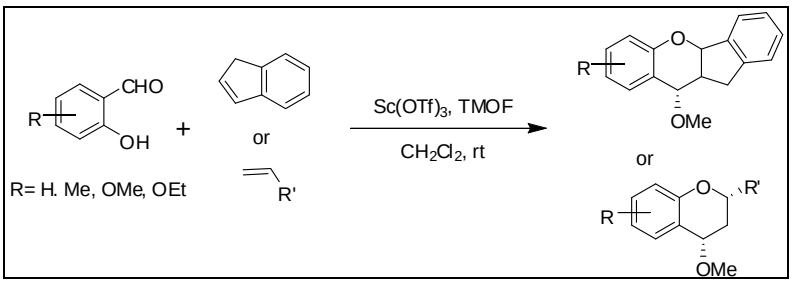
Recently, Zheng *et al.*[110] demonstrated the scope of a dual catalytic system consisting of 3-cyano-1-methylquinolinum as a photocatalyst and $Co(dmgBF_2)_2(CH_3CN)_2$ as a cocatalyst for the chroman synthesis. It allows the direct intramolecular alkoxylation of 3-aryl-1-propanols with the evolution of hydrogen gas as the only byproduct (Scheme 23, Figure 8).

2.3.3: Diels Alder reaction between *ortho*-quinone methides intermediate and olefins (Route E)



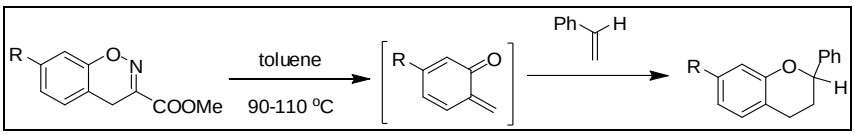
Scheme 24

Chiba *et al.*[111] carried out hetero-Diels–Alder reaction of *o*-quinomethanes and unactivated alkenes using montmorillonite catalyst in a $LiClO_4$–$MeNO_2$ solution (Scheme 24).



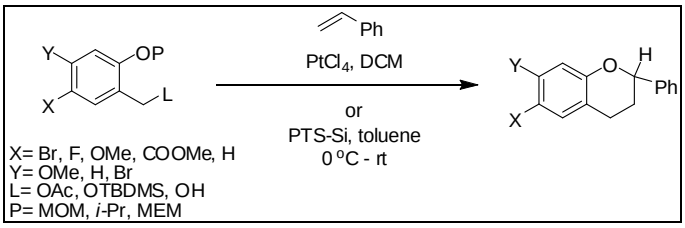
Scheme 25

Yadav *et al.*[112] reported an efficient scandium triflate catalyst for the cyclocondensation of *o*-hydroxybenzaldehydes with olefins in the presence of trimethyl orthoformate to form chromanes with high diastereoselectivity (Scheme 25). It involves *o*-quinone methides intermediate generated from salicylaldehyde and trimethyl orthoformate.



Scheme 26

Nakamura *et al.*[113] synthesized chroman by heating 4*H*-1,2-benzoxazine with styrene in toluene. It involves Diels-Alder reaction between *in situ* formed *o*-benzoquinone methide intermediate with styrene (Scheme 26).



Scheme 27

Radomkit *et al.*[114] developed a method for the preparation of chromans through generation of *ortho*-quinone methides intermediate which underwent $PtCl_4$ catalysed cycloaddition reaction with olefins. Also the conversion takes place in presence of *p*-TsOH immobilized on silica (PTS-Si) however in low yields (Scheme 27).

2.3.4: Interconversion of functional group (Route F)

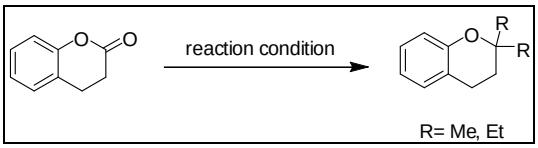
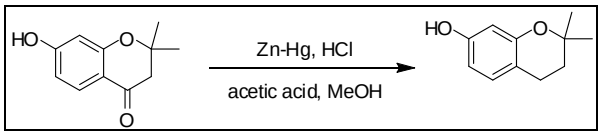


Table 11: Synthesis of chromans from coumarin using various reagents or catalysts.

Sr. No.	Reagent/Catalyst	Reaction condition	Ref.
1)	i) EtMgBr (excess)	i) ether, reflux ii) recrystallization	115
2)	i) MeMgI (excess) ii) H_2SO_4/H_2O	i) ether, rt ii) reflux	116
3)	i) MeMgCl (excess) ii) H_2SO_4/H_2O	i) THF, 0 °C - rt ii) benzene, 105 °C	117
4)	i) MeLi (excess) ii) cat. TsOH	i) THF, 0 °C - rt ii) toluene, reflux	118

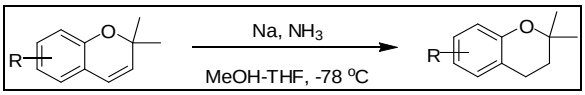
Dihydrocoumarin has been converted to chromans (Table 11). Smith *et al.*[115] treated dihydrocoumarin with Grignard reagent to form carbinol followed by recrystallization which resulted in the cyclization leading to chromans. Later, Fatope and Abraham[116] and Teng *et al.*[117] also exposed dihydrocoumarin to Grignard reagent forming tertiary alcohol which underwent cyclization in presence of aqueous H_2SO_4. Further, Bernier and Brückner[118]

converted dihydrocoumarin to chroman using MeLi followed by cyclodehydration with TsOH.



Scheme 28

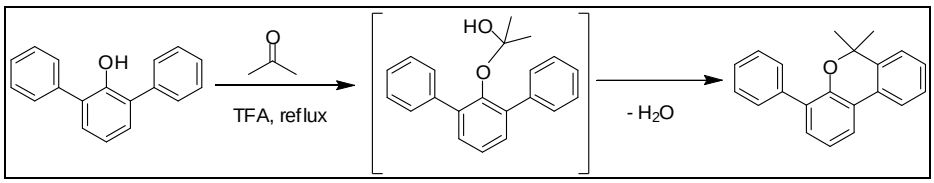
Chroman has also been synthesized from chromanone by Clemmensen reduction[119] (Scheme 28).



Scheme 29

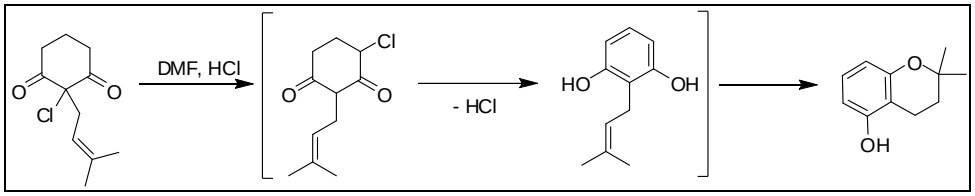
Anioł *et al.*[120] converted chromene to chroman by reducing with sodium, however in low yields as several other products were also obtained (Scheme 29).

2.3.5: Miscellaneous routes (Route G)



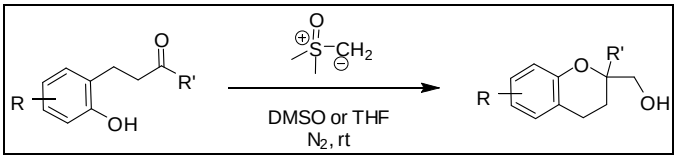
Scheme 30

Webb and Hall[121] showed the formation of chroman in TFA from 2,6-diphenyl phenol and acetone. It involves the reversible formation of the phenol hemiacetal of acetone followed by its protonation and loss of water forming carbonium ion which then attacks either of the phenyl groups to form chroman (Scheme 30).



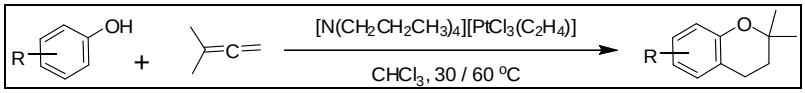
Scheme 31

Verhé *et al.*[122] heated 2-chloro-2-(3-methyl-2-butenyl)-1,3-cyclohexanedione in DMF in presence of HCl at 140 °C which rearranged to the 4-chloro isomer. It then underwent HCl elimination to form 2-(3-methyl-2-butenyl)resorcinol which cyclized to produce 2,2-dimethyl-5-hydroxychroman (Scheme 31).



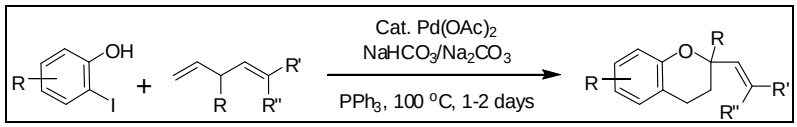
Scheme 32

Bravo *et al.*[123] obtained chromans, however in low yields by reacting the phenolic substrate with dimethyloxosulphoxonium methylide in DMSO/THF. However, the reaction favoured the formation of 7-membered 3-hydroxy-2,3,4,5-tetrahydro-1-benzo-oxepin as major product (Scheme 32).



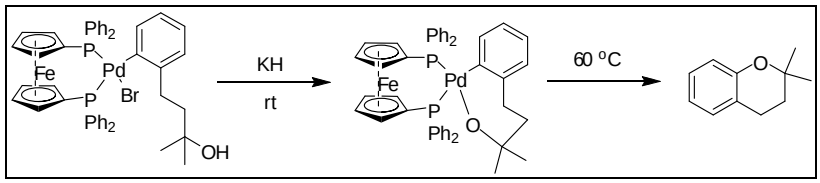
Scheme 33

De Renzi *et al.*[124] treated phenol with 1,1-dimethylallene in presence of platinum catalyst to afford a mixture of 2,2-dimethylchroman and *o*-isopentenylphenol. The amount of the products varied depending upon the temperature, reaction time and phenolic substrate. Chromans are formed *via* a regiospecific C-alkenylation followed by cyclization (Scheme 33).



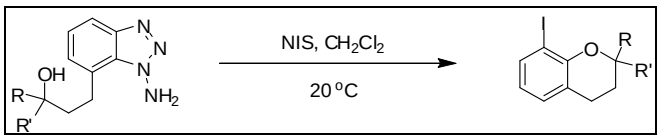
Scheme 34

Larock *et al.*[125] carried out palladium catalyzed annulations of *o*-iodophenols with 1,4-dienes to produce chromans in good yields. It involves heating the starting materials with catalytic palladium acetate and base in presence or absence of PPh_3 for prolonged time (Scheme 34).



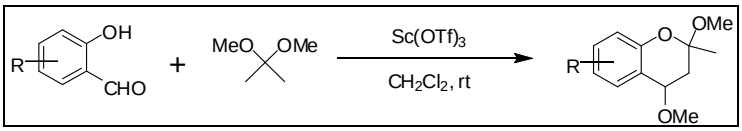
Scheme 35

Buchwald and co-workers[126] treated aryl bromide complex (dppf)Pd[*o*-$C_6H_4(CH_2)_2C(Me)_2OH$]Br with KH in THF at room temperature forming oxapalladacycle (dppf)$\overline{Pd[o\text{-}C_6H_4(CH_2)_2C(Me)_2O]}$ which produced chroman on thermolysis (Scheme 35).



Scheme 36

Knight and Little[127] treated the starting alcohol with *N*-iodosuccinimide to generate 8-iodochroman *via* benzyne intermediate. Only few derivatives have been reported (Scheme 36).

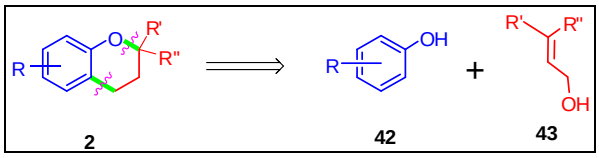


Scheme 37

2,4-Dimethoxy-2-methylbenzopyrans were synthesized by Yadav *et al.*[128] by the cyclocondensation of *o*-hydroxybenzaldehydes with 2,2-dimethoxypropane at room temperature using scandium triflate catalyst. Several advantages associated with the methodology includes high yields, high diastereoselectivity, short reaction times, easy availability of starting materials, reusable catalyst and simple experimental/isolation procedures which makes it an useful method (Scheme 37).

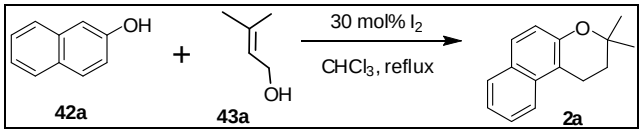
2.4: Results and Discussion

Several syntheses of chromans have been reported as discussed above. However these methods make use of either hazardous or costly catalysts, associated with side products resulting in poor yields, requires additional preparation of substrates and lack of substrate scope which led us to develop a new synthetic methodology for chromans synthesis using an environmentally benign inexpensive catalyst. We envisioned that the Lewis acidity of iodine can be employed for its synthesis. Accordingly the retrosynthetic analysis of this one pot approach suggested simple substrates such as phenols **42** and unsaturated alcohols **43** (Scheme 38).



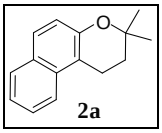
Scheme 38: Retrosynthetic analysis of chroman **2**.

We began chroman synthesis from *β*-naphthol **42a** and prenyl alcohol **43a** and examined the effect of iodine catalyst (0.3 equiv) on its cyclization in chloroform at room temperature. After prolonged stirring it was pleasing to see a new spot which was further isolated as colorless solid and characterized as the desired chroman **2a**. On refluxing, the reaction time was reduced and product formation was observed within short period (1 h) (Scheme 39). The reaction was also accompanied by another very light spot (TLC) and was later characterized as **2a'**. The structures of **2a** and **2a'** were confirmed by the following spectral data.



Scheme 39: Reaction of *β*-naphthol with prenyl alcohol.

Spectral data of 3,3-dimethyl-2,3-dihydro-1*H*-benzo[f]chromene (2a)



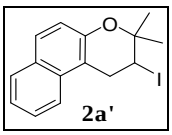
colorless solid; m.p. 68-70 °C; lit.[64] 68-69 °C.

IR (KBr): $\tilde{\nu}$ = 2974, 1620, 1597, 1236 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.38 (s, 6 H), 1.95 (t, *J* = 6.8 Hz, 2 H), 3.03 (t, *J* = 6.8 Hz, 2 H), 7.02 (d, *J* = 8.8 Hz, 1 H), 7.32 (ddd, *J* = 8.0, 7.6, 0.8 Hz, 1 H), 7.47 (ddd, *J* = 8.4, 6.8, 1.2 Hz, 1 H), 7.61 (d, *J* = 8.8 Hz, 1 H), 7.75 (d, *J* = 8.0 Hz, 1 H), 7.82 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.3 (CH_2), 26.6 (2 X CH_3), 32.7 (CH_2), 74.0 (Cq), 112.4 (Cq), 119.8 (CH), 121.9 (CH), 122.9 (CH), 126.2 (CH), 127.7 (CH), 128.4 (CH), 128.7 (Cq), 133.1 (Cq), 151.3 (Cq).

Spectral data of 2-iodo-3,3-dimethyl-2,3-dihydro-1*H*-benzo[*f*]chromene (2a')



colorless solid; m.p. 108-110 °C.

Rf: 0.56 (5 % ethyl acetate/petroleum ether).

IR (KBr): $\tilde{\nu}$ = 2974, 1622, 1597, 1236 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.45 (s, 3 H), 1.57 (s, 3 H), 3.55-3.75 (m, 2 H), 4.51 (dd, *J* = 9.6, 6.0 Hz, 1 H), 6.96 (d, *J* = 9.2 Hz, 1 H), 7.29 (t, *J* = 7.2 Hz, 1 H), 7.43 (t, *J* = 7.2 Hz, 1 H), 7.60 (d, *J* = 9.2 Hz, 1 H), 7.67 (d, *J* = 8.8 Hz, 1 H), 7.71 (d, *J* = 8.0 Hz, 1 H).

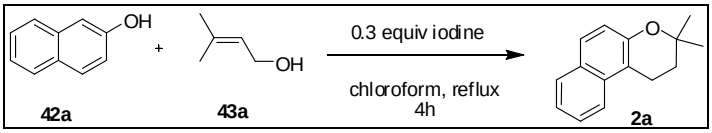
^{13}C NMR (DMSO, 100 MHz): δ 24.3 (CH_3), 26.6 (CH_3), 33.1 (CH_2), 34.3 (CH), 76.1 (Cq), 111.5 (Cq), 119.0 (CH), 121.9 (CH), 123.4 (CH), 126.6 (CH), 128.2 (2 X CH), 128.5 (Cq), 131.9 (Cq), 149.6 (Cq).

Anal. Calcd. For $C_{15}H_{15}IO$: C, 53.3; H, 4.4 %; Found: C, 53.4; H, 4.5 %.

Next, we went on to examine the stoichiometry of the substrates (Table 12). First, the stoichiometry of substrate **42a** was varied from 1-5 equivalents. It was observed that the yield goes on increasing with increasing *β*–naphthol concentration up to 4 equivalents (entries 1-4),

however, further increasing concentration to 5 equivalents resulted in decreased product yield (entry 5). Hence 4 equivalents of *β*–naphthol was found to be the optimum concentration to give maximum yield of 92 % after 4 h (entry 4). On the other side, increasing the concentration of prenyl alcohol did not show any increase in product yield, moreover it led to a complex mixture. Hence, further optimization was carried out with 4 equivalents of *β*–naphthol.

Table 12: Optimization of stoichiometry of starting materials **42a** and **43a**.



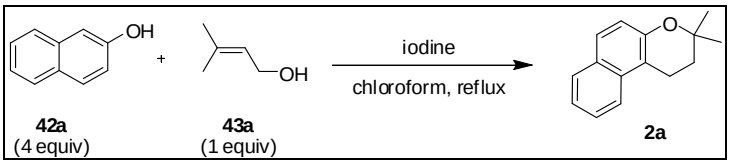
Sr. No.	42a (equiv)	43a (equiv)	Time (h)	Yield (%)[a,b]
1)	1	1	4	78
2)	2	1	4	80
3)	3	1	4	88
4)	**4**	**1**	**4**	**92**
5)	5	1	4	85

[a] Isolated yields of **2a** based on substrate **43a**.

[b] Trace amount of **2a'** was formed.

Further optimization of iodine concentration was studied by varying the amount of iodine (Table 13). No product was formed in the absence of iodine (entry 1). When 10 mol% iodine was used, **2a** was formed in 85 % yield (entry 2) and the product yield was found to increase with increase in catalyst loading and with reduction in time (entries 3-4). 30 Mol% of iodine in refluxing chloroform was found to be the optimum concentration (entry 4). Further increase in iodine concentration resulted in decreased product yield (entry 5). When the reaction was carried out with stoichiometric amount of iodine at room temperature with 1:1 ratio of **42a**:**43a**, the formation of mixture of 3,3-dimethyl-2,3-dihydro-1*H*-benzo[*f*]chromene **2a** and 2-iodo-3,3-dimethyl-2,3-dihydro-1*H*-benzo[*f*]chromene **2a'** was observed. As **2a'** was formed in appreciable amount, it was purified further to obtain as colorless solid and characterized at this stage.

Table 13: Optimization of iodine concentration in refluxing chloroform.



Sr. No.	Iodine (mol%)	Time (h)	Yield (%)[a]
1)	0	24	0
2)	10	24	85
3)	20	24	89
4)	**30**	**4**	**92**
5)	40	2	79
6)[b]	100	1.3	58, 31[c]

[a] Isolated yields of **2a** based on substrate **43a**.

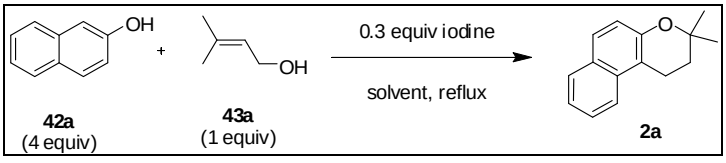
[b] Reaction carried out at room temperature.

[c] % yield of **2a'**.

Thus the yield of the reaction product can be modulated by changing the concentration of iodine. Catalytic iodine furnished chroman **2a** as the major product with trace amount of **2a'** under chloroform reflux whereas stoichiometric amount of iodine resulted in increased quantity of **2a'** in chloroform solvent at room temperature along with **2a**.

Next, the effect of solvents was studied by carrying out the reaction in different solvents (Table 14). The product formation was seen in all the studied solvents (entries 1-9). The time required for product formation was more when refluxed in protic solvents like methanol and ethanol (entries 1-2). Chlorinated solvents such as chloroform and dichloromethane gave better results with less duration of time (entries 3-4), of which chloroform gave maximum product yield (entry 3). Other solvents like toluene, tetrahydrofuran, 1,4-dioxane, 1,2-dichloroethane and acetonitrile also showed product formation but in moderate yields (entries 5-9). Among all these solvents, chloroform gave highest product yield and hence was selected for further studies.

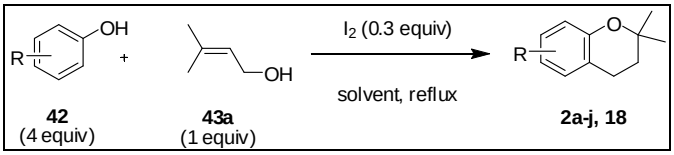
Table 14: Solvent screening.

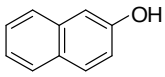
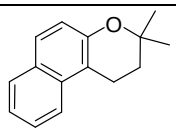
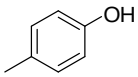
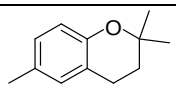
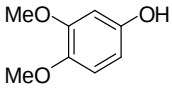
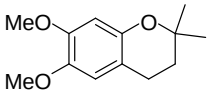
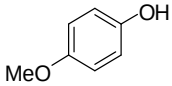
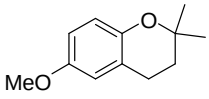
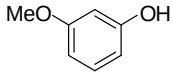
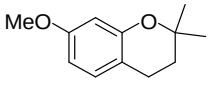


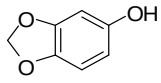
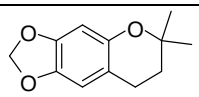
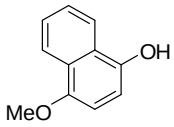
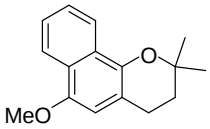
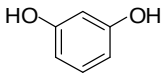
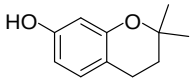
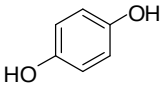
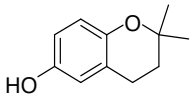
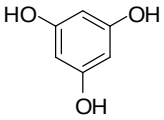
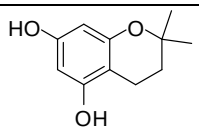
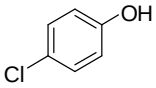
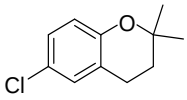
Sr. No.	Solvent	Time (h)	Yield (%)[a]
1)	Methanol	24	50
2)	Ethanol	24	45
3)	**Chloroform**	**4**	**92**
4)	Dichloromethane	4	90
5)	Toluene	24	30
6)	Tetrahydrofuran	7	65
7)	1,4-Dioxane	7	60
8)	1,2-Dichloroethane	5	68
9)	Acetonitrile	24	25

[a] Isolated yields based on substrate **43a**.

Table 15: Synthesis of various chroman derivatives **2a-j, 18** using phenol derivatives **42** and prenyl alcohol **43a** under optimized reaction condition.



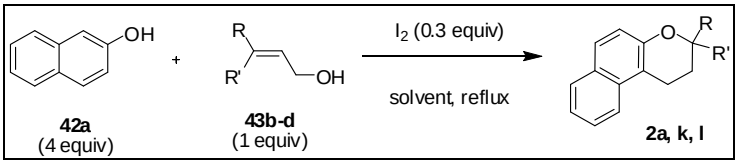
Sr. No.	Substituted Phenol	Chroman	Solvent (reflux)	Time (h)	Yield[a] (%)
1)	 **42a**	 **2a**	$CHCl_3$	4	92
2)	 **42b**	 **2b**	$CHCl_3$	4	48
3)	 **42c**	 **2c**	$CHCl_3$	2	77
4)	 **42d**	 **2d**	$CHCl_3$	4	58
					

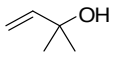
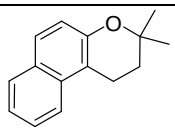
5)	**42e**	**2e**	$CHCl_3$	4	45
6)	 **42f**	 **2f**	$CHCl_3$	4	58
7)	 **42g**	 **18**	$CHCl_3$	2	60
8)	 **42h**	 **2g**	MeOH	4	46
9)	 **42i**	 **2h**	MeOH	4	33
10)	 **42j**	 **2i**	MeOH	4	56
11)	 **42k**	 **2j**	$CHCl_3$	24	20

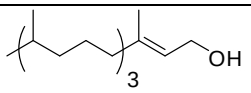
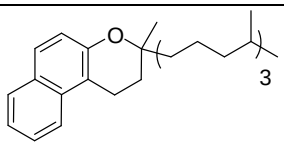
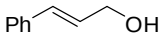
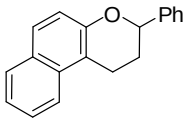
[a] Isolated % yield of chroman product based on substrate **43a**.

Unreacted and excess phenol substrates were recovered.

Table 16: Synthesis of chroman derivatives **2a, k, l** using *β*-naphthol **42a** and unsaturated alcohols **43b-d** under optimized reaction conditions.



Sr. No.	Unsaturated alcohol	Chroman	Solvent (reflux)	Time (h)	Yield[a] (%)
1)	 **43b**	 **2a**	$CHCl_3$	4	87

2)	 **43c**	 **2k**	$CHCl_3$	4	76
3)	 **43d**	 **2l**	$CHCl_3$	4	60

[a] Isolated % yield of chroman product based on unsaturated alcohol substrate **43b**-**d**.

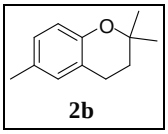
Unreacted and excess *β*-naphthol substrate was recovered.

Once the optimum condition was established, the generality of this reaction was explored by subjecting various phenols to the optimum reaction condition (Table 15-16). The reaction of *ß*-naphthol **42a** with prenyl alcohol **43a** gave chroman **2a** in 92 % yield. Electron rich phenols with methyl and methoxy substituents were converted to respective chromans **2b**-**e** in good to moderate yields. Similarly 3,4-methylenedioxyphenol underwent cyclization readily to afford chroman **2f**. Naturally occurring dihydrolapachenole **18**[18] was synthesized from 4-methoxynaphthol in good yield. Dihydroxy compounds like resorcinol and quinol when refluxed in methanol due to lack of solubility in chloroform solvent, afforded respective chromans **2g** and **2h** in moderate yields. Interestingly, the resorcinol substrate which may result in mixture of isomeric chromans delivered exclusively one regioisomer **2g**. Further the trihydroxy compound phloroglucinol in refluxing methanol afforded chroman **2i** in 56 % yield. *p*-Chlorophenol was converted to corresponding chroman **5k** in low yield. The slow reaction and low yield is attributed to the electron withdrawing effect of chloro group.

Also, we examined the reaction of *ß*-naphthol **42a** with different unsaturated alcohols such as 2-methylbut-3-en-2-ol **43b**, phytol **43c** and cinnamyl alcohol **43d** to afford desired chromans **2a**, **2k** and **2l** in 87, 76 and 60 % yields respectively.

Spectral data of chromans

6-Methyl-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran (2b)



2b

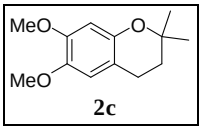
yield (0.099 g, 48 %); colorless oil.[64]

IR (neat): $\tilde{\nu}$ = 2976, 1498, 1261, 1105 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.23 (s, 6 H), 1.69 (t, *J* = 6.8 Hz, 2 H), 2.16 (s, 3 H), 2.64 (t, *J* = 6.8 Hz, 2 H), 6.60 (d, *J* = 8.0 Hz, 1 H), 6.78 (s, 1 H), 6.80 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.4 (CH_3), 21.4 (CH_2), 25.8 (2 X CH_3), 31.8 (CH_2), 72.8 (Cq), 115.9 (CH), 119.5 (Cq), 126.9 (CH), 127.6 (Cq), 128.7 (CH), 150.6 (Cq).

6,7-Dimethoxy-2,2-dimethyl-3,4-dihydro-2*H*-chromene (2c)



2c

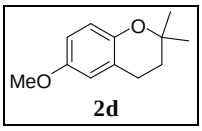
yield (0.199 g, 77 %); colorless oil.[129]

IR (neat): $\tilde{\nu}$ = 2974, 2933, 1620, 1514, 1122 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.24 (s, 6 H), 1.70 (t, *J* = 6.8 Hz, 2 H), 2.61 (t, *J* = 6.8 Hz, 2 H), 3.74 (s, 6 H), 6.30 (s, 1 H), 6.48 (s, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.1 (CH_2), 26.7 (2 X CH_3), 32.9 (CH_2), 55.8 (CH_3), 56.4 (CH_3), 73.9 (Cq), 101.2 (CH), 111.2 (Cq), 112.2 (CH), 142.6 (Cq), 147.6 (Cq), 148.3 (Cq).

6-Methoxy-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran (2d)



2d

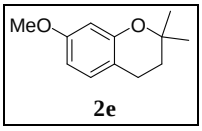
yield (0.130 g, 58 %); colorless oil.[52]

IR (neat): $\tilde{\nu}$ = 2972, 1492, 1247 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.23 (s, 6 H), 1.69 (t, *J* = 6.8 Hz, 2 H), 2.66 (t, *J* = 6.8 Hz, 2 H), 3.65 (s, 3 H), 6.52 (d, *J* = 2.4 Hz, 1 H), 6.60-6.64 (m, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.8 (CH_2), 26.8 (2 X CH_3), 32.8 (CH_2), 55.7 (CH_3), 73.8 (Cq), 113.4 (CH), 113.9 (CH), 117.8 (CH), 121.5 (Cq), 148.0 (Cq), 152.9 (Cq).

7-Methoxy-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran (2e)



2e

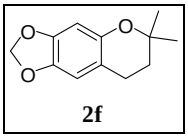
yield (0.101 g, 45 %); colorless oil.[124]

IR (neat): $\tilde{\nu}$ = 2974, 1620, 1504, 1151 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25 (s, 6 H), 1.71 (t, *J* = 6.8 Hz, 2 H), 2.63 (t, *J* = 6.8 Hz, 2 H), 3.67 (s, 3 H), 6.28 (d, *J* = 2.4 Hz, 1 H), 6.36 (dd, *J* = 8.4, 2.4 Hz, 1 H), 6.87 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.8 (CH_2), 26.9 (2 X CH_3), 32.9 (CH_2), 55.2 (CH_3), 74.3 (Cq), 101.7 (CH), 106.9 (CH), 112.9 (Cq), 129.9 (CH), 154.7 (Cq), 159.1 (Cq).

6,6-Dimethyl-7,8-dihydro-6*H*-[1,3]dioxolo[4,5-*g*]chromene (2f)



2f

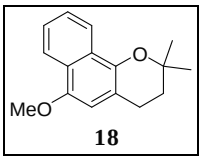
yield (0.139 g, 58 %); colorless oil.[52]

IR (neat): $\tilde{\nu}$ = 2974, 1504, 1479, 1151 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.22 (s, 6 H), 1.67 (t, *J* = 6.8 Hz, 2 H), 2.59 (t, *J* = 6.8 Hz, 2 H), 5.77 (s, 2 H), 6.26 (s, 1 H), 6.42 (s, 1 H).

^{13}C NMR (CDCl3, 100 MHz): δ 22.6 (CH_2), 26.6 (2 X CH_3), 32.8 (CH_2), 73.9 (Cq), 98.9 (CH), 100.7 (CH_2), 108.1 (CH), 112.2 (Cq), 140.9 (Cq), 146.4 (Cq), 148.4 (Cq).

6-Methoxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*h*]chromene (18)



18

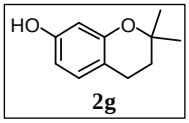
yield (0.169 g, 60 %); colorless solid; m.p. 74-75 °C; lit.[64] 77-78 °C.

IR (KBr): $\tilde{\nu}$ = 2974, 1633, 1597, 1273 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.30 (s, 6 H), 1.79 (t, *J* = 6.8 Hz, 2 H), 2.73 (t, *J* = 6.8 Hz, 2 H), 3.82 (s, 3 H), 6.38 (s, 1 H), 7.33 (dt, *J* = 7.6, 1.6 Hz, 1 H); 7.37 (dt, *J* = 7.2, 1.6 Hz, 1 H); 8.05 (dd, *J* = 8.4, 1.6 Hz, 1 H); 8.08 (dd, *J* = 8.8, 1.6 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.4 (CH_2), 26.9 (2 X CH_3), 33.1 (CH_2), 55.8 (CH_3), 73.9 (Cq), 105.4 (CH), 113.4 (Cq), 121.4 (CH), 121.7 (CH), 125.0 (CH), 125.3 (Cq), 125.7 (CH), 126.5 (Cq), 142.5 (Cq), 148.5 (Cq).

7-Hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran (2g)



2g

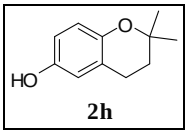
yield (0.096 g, 46 %); colorless solid; m.p. 68-70 °C; lit.[45c] 72-73 °C.

IR (KBr): $\tilde{\nu}$ = 3383, 2974, 1593, 1149 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.24 (s, 6 H), 1.69 (t, *J* = 6.8 Hz, 2 H), 2.60 (t, *J* = 6.8 Hz, 2 H), 6.22 (s, 1 H), 6.28 (dd, *J* = 8.4, 2.0 Hz, 1 H), 6.81 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.7 (CH_2), 25.8 (2 X CH_3), 31.9 (CH_2), 73.5 (Cq), 102.7 (CH), 106.5 (CH), 112.2 (Cq), 129.1 (CH), 153.5 (Cq), 153.8 (Cq).

6-Hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran (2h)



2h

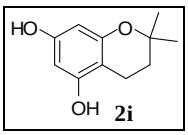
yield (0.069 g, 33 %); colorless solid; m.p. 77-78 °C; lit.[50] 77-78 °C.

IR (KBr): $\tilde{\nu}$ = 3379, 2974, 1502, 1195 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.23 (s, 6 H), 1.69 (t, *J* = 6.8 Hz, 2 H), 2.63 (t, *J* = 6.8 Hz, 2 H), 6.48 (d, *J* = 2.8 Hz, 1 H), 6.52 (dd, *J* = 8.8, 2.8 Hz, 1 H), 6.57 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.6 (CH_2), 25.7 (2 X CH_3), 31.7 (CH_2), 72.9 (Cq), 113.4 (CH), 114.4 (CH), 116.8 (CH), 120.8 (Cq), 146.8 (Cq), 147.5 (Cq).

2,2-Dimethyl-3,4-dihydro-2*H*-chromene-5,7-diol (2i)



2i

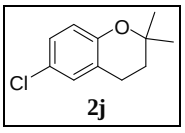
yield (0.127 g, 56 %); colorless solid; m.p. 158-160 °C; lit.[45c,130] 163-164 °C.

IR (KBr): $\tilde{\nu}$ = 3375, 1600, 1144, 1053 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.13 (s, 6 H), 1.56 (t, *J* = 6.4 Hz, 2 H), 2.39 (t, *J* = 6.4 Hz, 2 H), 5.21 (s, 2H), 5.81 (s, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.4 (CH_2), 26.6 (2 X CH_3), 32.2 (CH_2), 74.4 (Cq), 94.7 (CH), 96.6 (CH), 100.9 (Cq), 154.6 (Cq), 155.0 (Cq), 155.5 (Cq).

6-Chloro-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran (2j)



2j

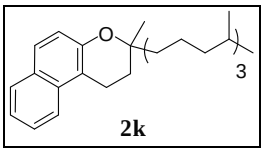
yield (0.046 g, 20 %); colorless oil.[64]

IR (neat): $\tilde{\nu}$ = 2976, 1479, 1261, 1122 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.31 (s, 6 H), 1.77 (t, *J* = 6.8 Hz, 2 H), 2.73 (t, *J* = 6.8 Hz, 2 H), 6.70 (d, *J* = 9.2 Hz, 1 H), 7.02 (d, *J* = 9.6 Hz, 1 H), 7.03 (s, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.4 (CH_2), 26.8 (2 X CH_3), 32.4 (CH_2), 74.5 (Cq), 118.6 (CH), 122.5 (Cq), 124.2 (Cq), 127.2 (CH), 128.9 (CH), 152.6 (Cq).

3-Methyl-3-(4,8,12-trimethyltridecyl)-2,3-dihydro-1*H*-benzo[*f*]chromene (2k)



2k

yield (0.109 g, 76 %); pale yellow oil.

Rf: 0.50 (5 % ethyl acetate/petroleum ether).

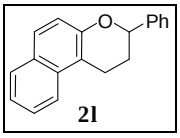
IR (neat): $\tilde{\nu}$ = 2951, 1625, 1598, 1234 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.80-0.87 (m, 12 H), 1.10-1.15 (m, 7 H), 1.24-1.67 (m, 14 H), 1.32 (s, 3 H), 1.89-1.99 (m, 2 H), 2.99 (t, *J* = 6.8 Hz, 2 H) 7.03 (d, *J* = 8.8 Hz, 1 H), 7.31 (t, *J* = 7.6 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.60 (d, *J* = 8.8 Hz, 1 H), 7.74 (d, *J* = 8.0 Hz, 1 H), 7.81 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.1 (CH_2), 19.7-19.8 (3 peak tops, CH_3), 21.2 (CH_2), 22.7-22.8 (2 peak tops, CH_3), 23.9 (CH_3), 24.5 (CH_2), 24.8-24.9 (2 peak tops, CH_2), 28.0 (CH), 30.8-30.9 (2 peak tops, CH_2), 32.7-32.8 (4 peak tops, CH), 37.3-37.6 (6 peak tops, CH_2), 39.4-39.6 (3 peak tops, CH_2), 76.1 (Cq), 112.6 (Cq), 119.9 (CH), 121.9 (CH), 122.9 (CH), 126.2 (CH), 127.7 (CH), 128.4 (CH), 128.7 (Cq), 133.1 (Cq), 151.4 (Cq).

Anal. Calcd. For $C_{30}H_{46}O$: C, 85.3; H, 10.9 %; Found: C, 85.6; H, 11.1 %; GCMS: *m/z* calcd for $C_{30}H_{46}O$ $[M]^+$: 422.68; found: 422.22.

3-Phenyl-2,3-dihydro-1*H*-benzo[*f*]chromene (2l)



2l

yield (0.117 g, 60 %); colorless solid; m.p. 84-86 °C; lit.[131] 86 °C.

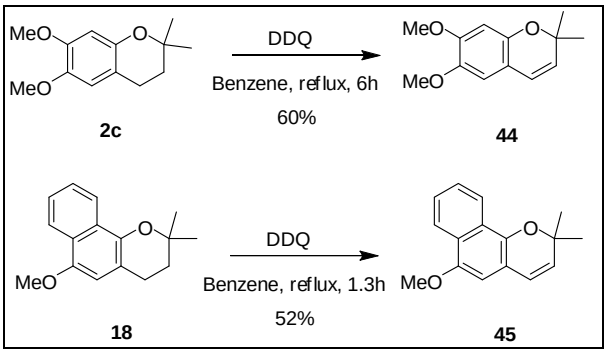
IR (KBr): $\tilde{\nu}$ = 3062, 2924, 1597, 1236 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.11-2.19 (m, 1 H), 2.28-2.33 (m, 1 H), 3.06-3.10 (m, 2 H), 5.04 (dd, *J* = 10.0, 2.0 Hz, 1 H), 7.07 (d, *J* = 8.8 Hz, 1 H), 7.23-7.43 (m, 7 H), 7.56 (d, *J* = 8.8 Hz, 1 H), 7.69 (d, *J* = 8.0 Hz, 1 H), 7.73 (d, *J* = 8.8 Hz, 1 H).

^{13}C NMR (CDCl3, 100 MHz): δ 21.8 (CH_2), 29.7 (CH_2), 77.5 (CH), 113.6 (Cq), 119.2 (CH), 121.9 (CH), 123.3 (CH), 126.1 (2 X CH), 126.4 (CH), 127.8 (CH), 127.9 (CH), 128.5 (CH), 128.6 (2 X CH), 129.0 (Cq), 133.0 (Cq), 141.6 (Cq), 152.7 (Cq).

As a further application to our work, synthesis of naturally occurring precocene II **44** and lapachenole **45** was performed (Scheme 40). Compound **44** is an insect growth regulator, genotoxic and produces hepatic centrolobular necrosis in rats.[132] Compound **45** has been used

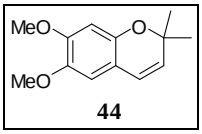
as a fluorescent photoaffinity label[133] and also shows cancer chemopreventive activity.[134] Chroman **2c** was refluxed in benzene with DDQ for 6 h to give **44** in 60 % yield.[135] Similarly chroman **18** on refluxing for 1.3 h in benzene delivered **45** in 52 % yield.



Scheme 40: Synthesis of precocene II **44** and lapachenole **45**.

Spectral data of chromenes

6,7-Dimethoxy-2,2-dimethyl-2*H*-chromene/Precocene II (44)



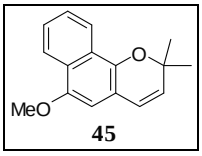
yield (0.059 g, 60 %); colorless solid; m.p. 46-48 °C; lit.[136] 45-46 °C.

IR (KBr): $\tilde{\nu}$ = 2974, 1500, 1458, 1278, 1195 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.34 (s, 6 H), 3.75 (s, 3 H), 3.76 (s, 3 H), 5.41 (d, *J* = 10.0 Hz, 1 H), 6.17 (d, *J* = 10.0 Hz, 1 H), 6.34 (s, 1 H), 6.46 (s, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.6 (2 X CH_3), 54.9 (OCH_3), 55.5 (OCH_3), 74.9 (Cq), 99.9 (CH), 108.7 (CH), 112.0 (Cq), 120.9 (CH), 127.2 (CH), 142.0 (Cq), 146.2 (Cq), 148.6 (Cq).

6-Methoxy-2,2-dimethyl-2*H*-benzo[*h*]chromene/Lapachenole (45)

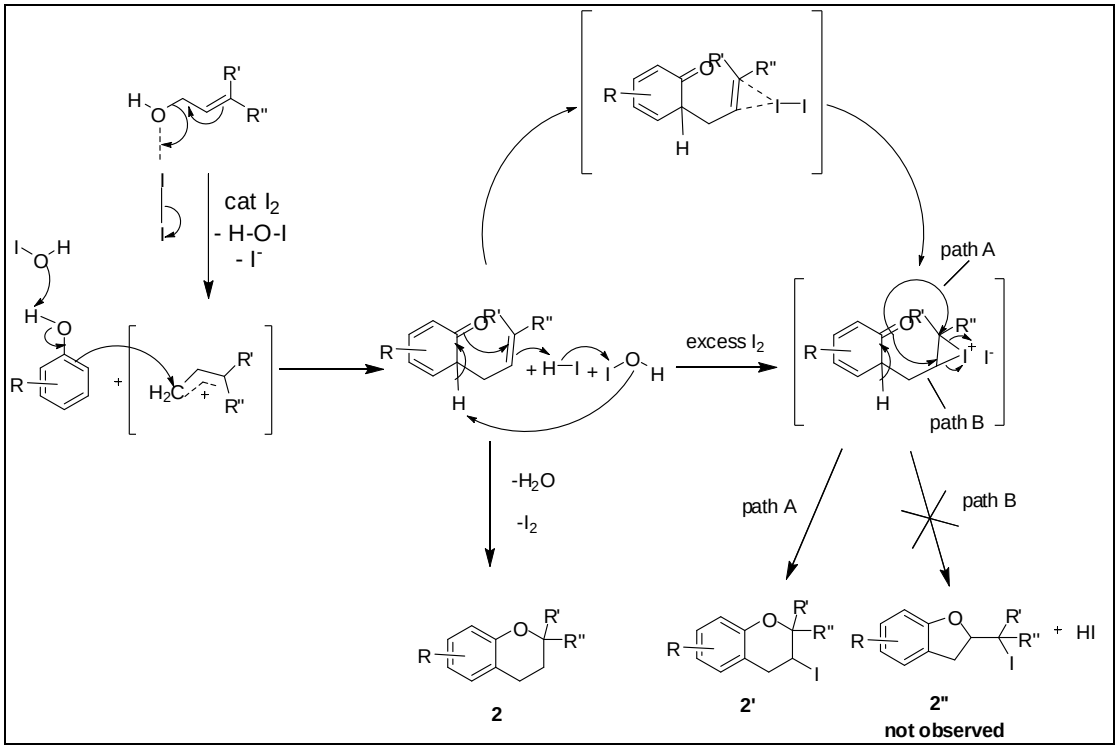


yield (0.051 g, 52 %); colorless solid; m.p. 63-64 °C; lit.[137] 63-64 °C.

IR (KBr): $\tilde{\nu}$ = 2974, 2933, 1641, 1597, 1276 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.42 (s, 6 H), 3.89 (s, 3 H), 5.58 (d, *J* = 9.6 Hz, 1 H), 6.33 (d, *J* = 9.6 Hz, 1 H), 6.44 (s, 1 H), 7.34-7.42 (m, 2 H), 8.08 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.6 (2 X CH_3), 55.8 (OCH_3), 76.2 (Cq), 102.5 (CH), 114.8 (Cq), 121.7 (CH), 121.8 (CH), 123.0 (CH), 125.5 (CH), 125.9 (CH), 126.0 (Cq), 128.3 (Cq), 129.9 (CH), 141.9 (Cq), 149.3 (Cq).



Scheme 41: Proposed mechanism for the formation of chromans.

The proposed mechanistic pathway for the formation of chroman is shown in scheme 41. Loss of alcoholic OH group takes place by coordination of iodine making it a better leaving group facilitated by allylic double bond. Intermolecular electrophillic attack by the phenolic arene ring on less hindered carbon atom of thus formed carbocation followed by intramolecular oxygen attack on more substituted carbon atom of double bond and subsequent aromatization delivered chroman. On the other hand if the double bond coordinates with iodine to form iodinium ion prior to the intramolecular oxygen attack, oxygen attack can take place either by path A or path B to give **2'** or **2''** respectively. But the obtained product **2a'** indicates the attack at more substituted carbon atom which is favoured when excess of iodine is used.

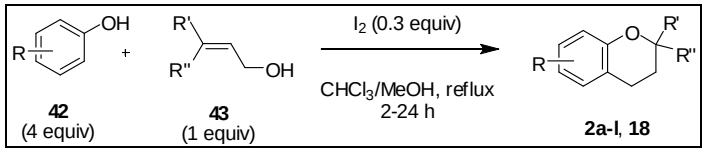
2.5: Conclusion

We have demonstrated the utility of molecular iodine as a mild Lewis acid for the synthesis of oxygen heterocycle chromans *via* [3+3] cyclocoupling of phenols and allylic alcohols. 30 Mol % of iodine was effective in chloroform or methanol solvent under refluxing condition.

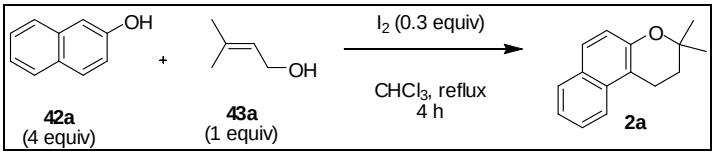
The usefulness of the method is demonstrated by synthesis of naturally occurring chroman dihydrolapachenole **18**.

Further these chromans can be used for the synthesis of natural chromenes by conventional dehydrogenation which is demonstrated by synthesizing precocene II **44** and lapachenole **45**.

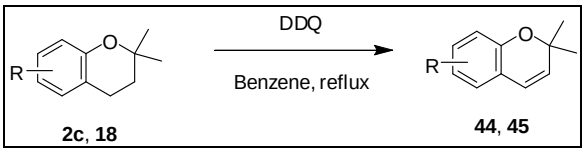
2.6: Experimental



2.6.1: A general procedure for the synthesis of chromans 2a-l, 18: In a 50 mL round bottom flask, unsaturated alcohol **43** (1.16 mmol) was mixed with chloroform/methanol (10 mL). To it, substituted phenol **42** (4.65 mmol) and iodine (0.35 mmol) were added at room temperature. This reaction mixture was then subjected to reflux with stirring for the mentioned 2-24 h. It was then cooled to room temperature. Chloroform was directly washed with saturated solution of sodium thiosulphate whereas methanol was removed under reduced pressure followed by addition of chloroform solvent. Chloroform was then washed with dilute sodium hydroxide solution and then with water, dried over sodium sulphate and concentrated to furnish the crude product. This was then purified using 60-120 mesh silica gel column chromatography with petroleum ether-ethyl acetate as an eluent to give chromans **2a-l, 18** in 20-92 % yield.

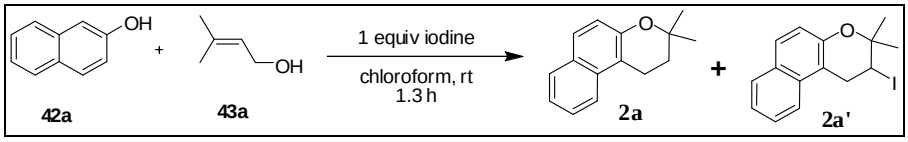


2.6.2: A procedure for the synthesis of chroman 2a: In a 50 mL round bottom flask, prenyl alcohol **43a** (0.1 g, 1.16 mmol) was mixed with chloroform (10 mL). To it, *β*-naphthol **42a** (0.67 g, 4.65 mmol) and iodine (0.044 g, 0.35 mmol) were added at room temperature. This reaction mixture was then subjected to reflux with stirring for 4 h. It was then cooled to room temperature. Chloroform was directly washed with saturated sodium thiosulphate solution followed by washings with dilute sodium hydroxide solution and water, dried over sodium sulphate and concentrated to furnish the crude product. This was then purified using 60-120 mesh silica gel column chromatography to give chroman **2a** (0.227 g, 92 %) with petroleum ether-ethyl acetate (9.8:0.2) as an eluent.



2.6.3: A procedure for the synthesis of chromenes 44, 45: To 3,4-dimethoxychroman **2c** (0.1 g, 0.45 mmol) /dihydrolapachenole **18** (0.1 g, 0.41 mmol) in a 50 mL round bottom flask, was added DDQ (1 equiv) and was subjected to reflux in benzene (10 mL). After completion of reaction, benzene was removed by distillation and crude reaction mixture thus obtained was purified by column chromatography to furnish chromenes **44** (0.059 g, 60 %) and **45**

(0.051 g, 52 %) with petroleum ether-ethyl acetate (9:1) and (9.5:0.5) respectively as an eluent.



2.6.4: A procedure for the synthesis of 2-iodo-3,3-dimethyl-2,3-dihydro-1*H*-benzo[*f*]chromene 2a': A mixture of prenyl alcohol **43a** (0.1 g, 1.16 mmol), *β*-naphthol **42a** (1.16 mmol) and iodine (1.16 mmol) in chloroform (10 mL) was stirred for 1.3 h at room temperature. Chloroform was then directly washed with saturated solution of sodium thiosulphate followed by dilute sodium hydroxide solution. Finally chloroform layer was washed with water, dried over sodium sulphate and concentrated to furnish the crude mixture of **2a** and **2a'**. This was then purified using 60-120 mesh silica gel column chromatography to give pure **2a** (0.143 g, 58 %) and **2a'** (0.122 g, 31 %) with petroleum ether-ethyl acetate (9.8:0.2) and (9.95:0.05) respectively as an eluent.

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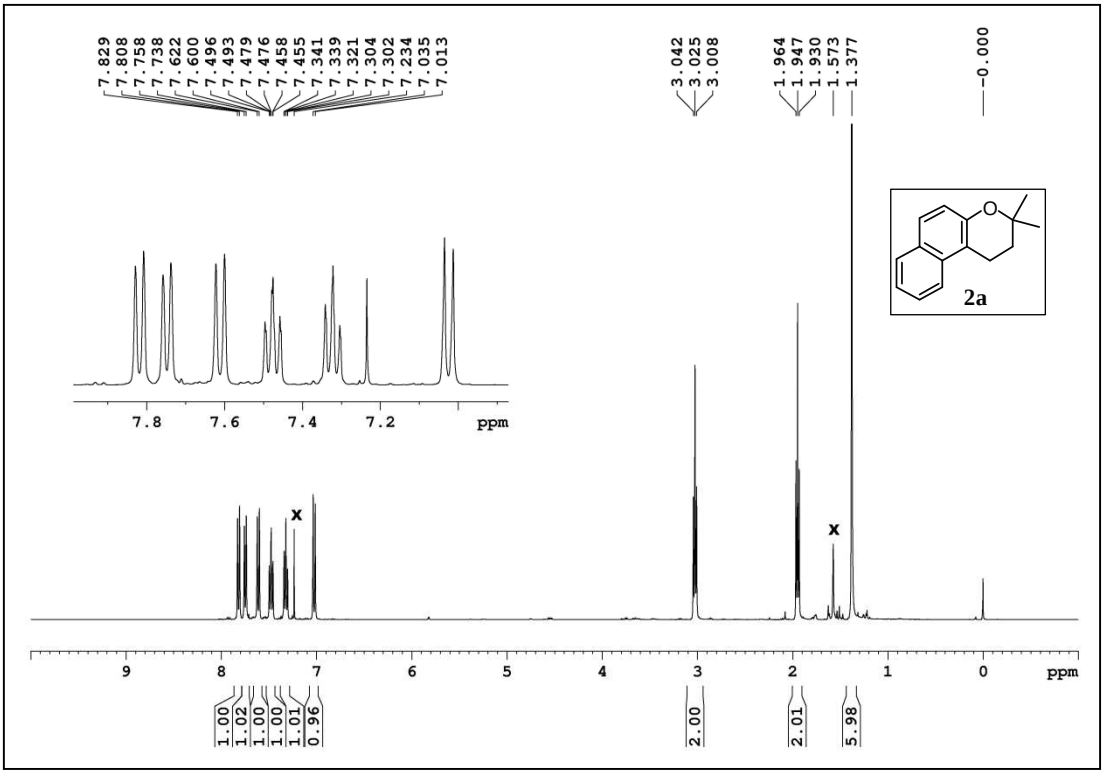
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7.339
7.321
7.304
7.302
7.234
7.035
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3.042
3.025
3.008
1.964
1.947
1.930
1.573
1.377
0.000
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x
x
ppm
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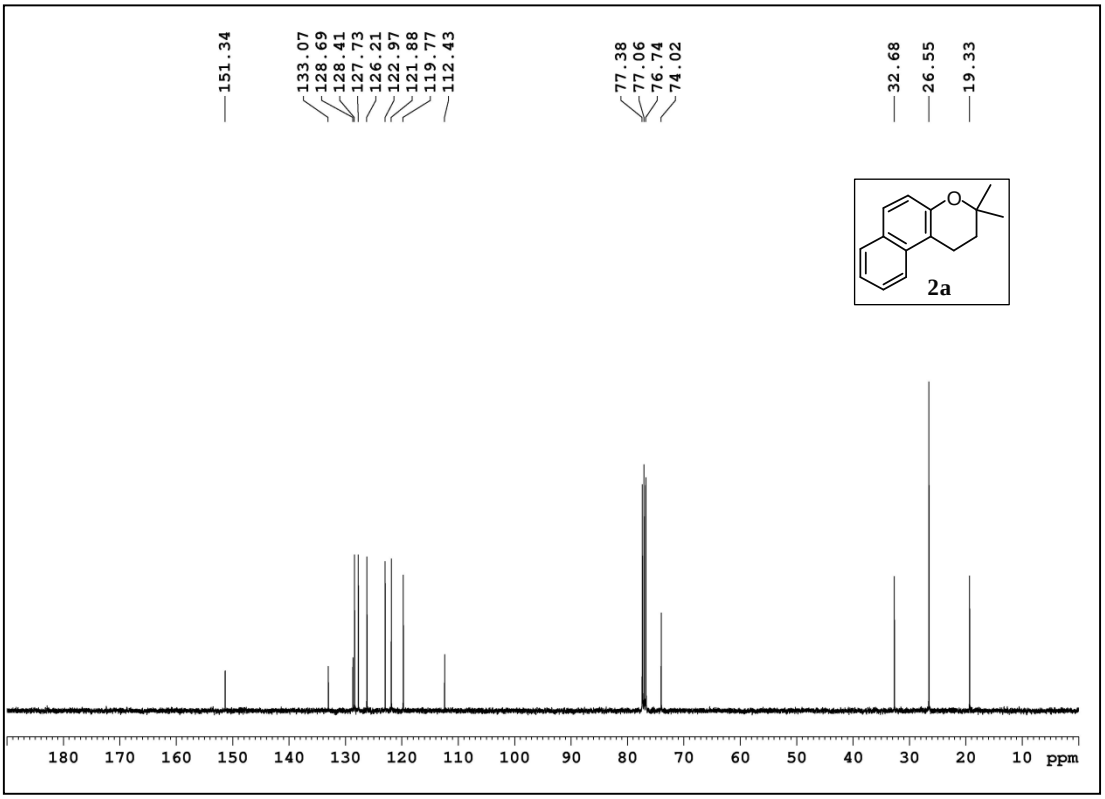
2.01
5.98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126.21
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112.43
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74.02
32.68
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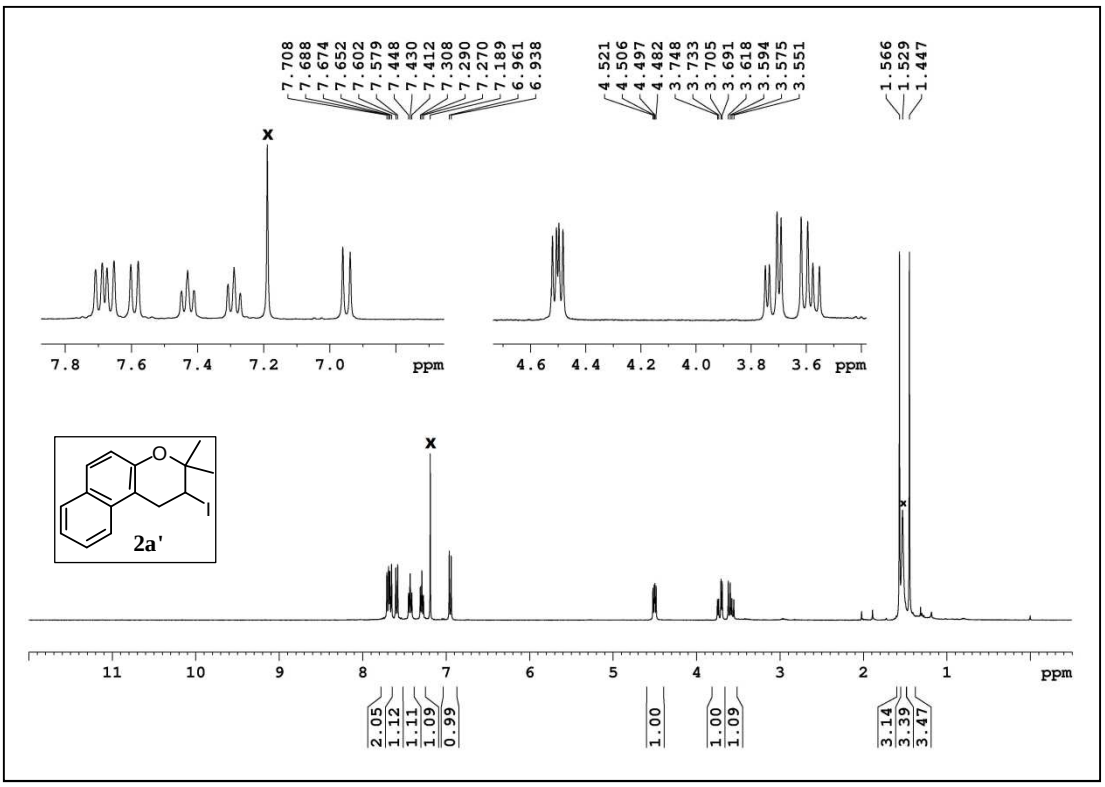
19.33
2a
ppm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7.602
7.579
7.448
7.430
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7.308
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7.189
6.961
6.938
4.521
4.506
4.497
4.482
3.748
3.733
3.705
3.691
3.618
3.594
3.575
3.551
1.566
1.529
1.447
x
7.8 7.6 7.4 7.2 7.0 ppm
4.6 4.4 4.2 4.0 3.8 3.6 ppm
O
I
2a'
11 10 9 8 7 6 5 4 3 2 1 ppm
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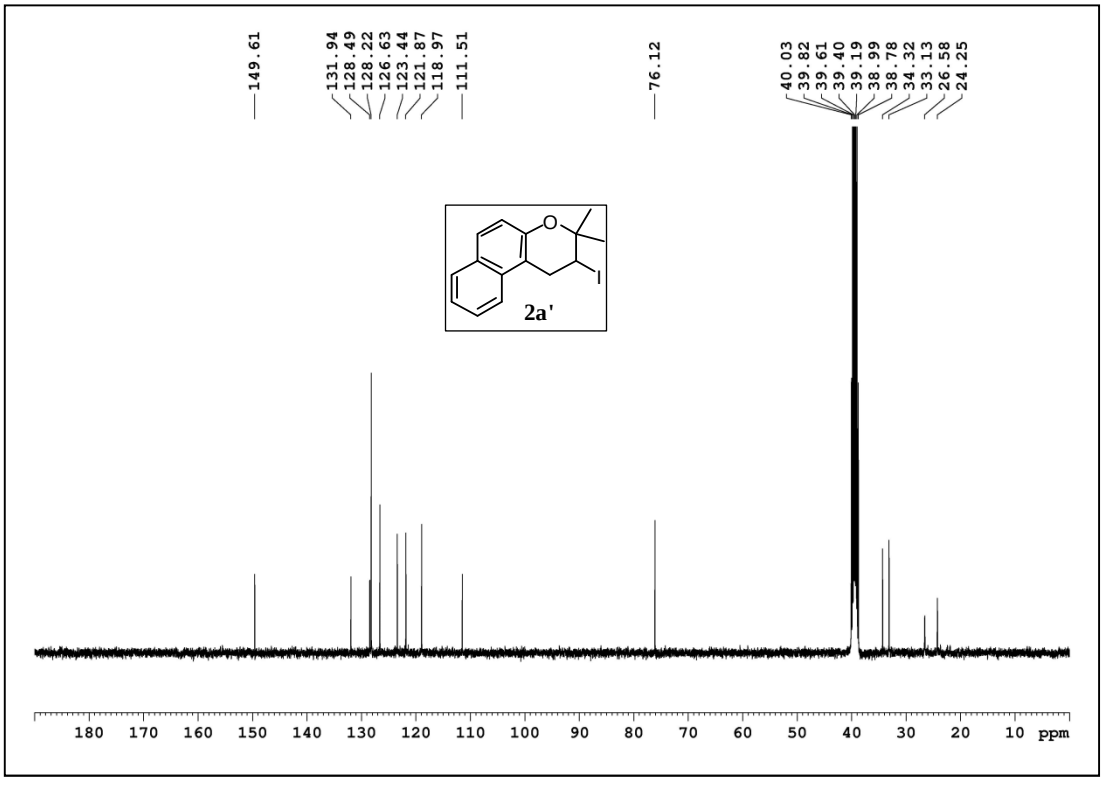
1.12
1.11
1.09
0.99
1.00
1.00
1.09
3.14
3.39
3.47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123.44
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118.97
111.51
76.12
40.03
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39.61
39.40
39.19
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O
I
2a'
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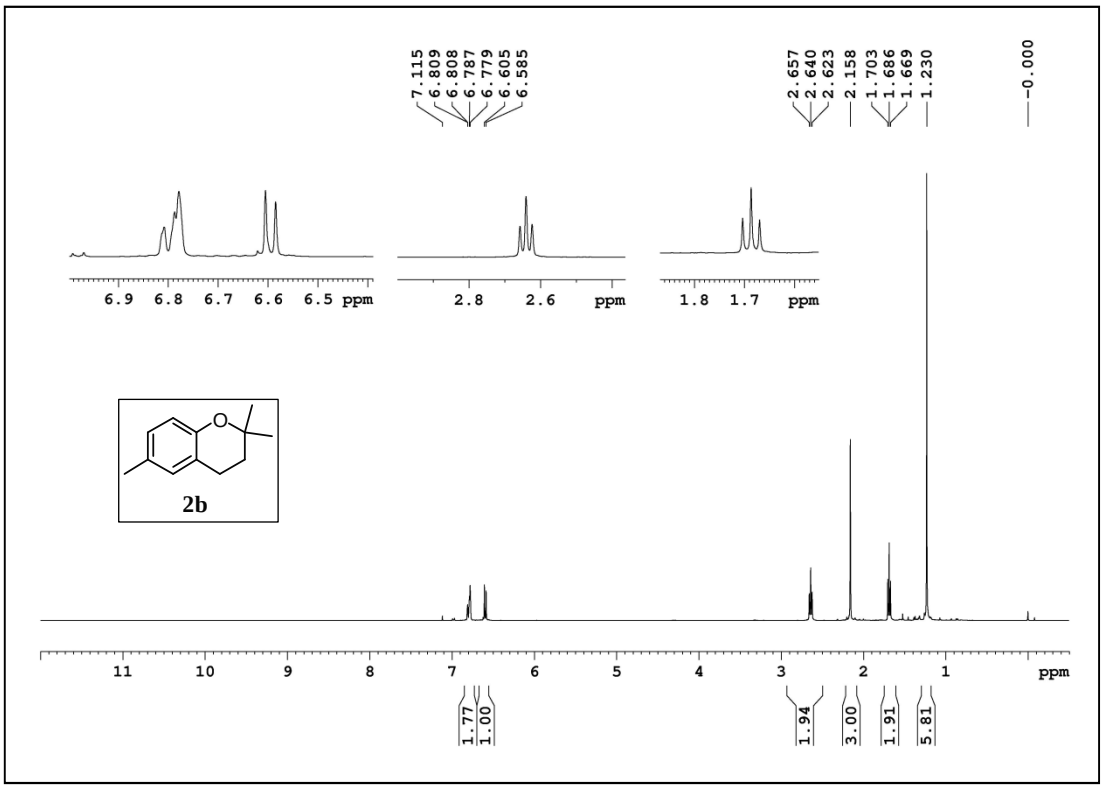
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2.657
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1.686
1.669
1.230
0.000
6.9 6.8 6.7 6.6 6.5 ppm
2.8 2.6 ppm
1.8 1.7 ppm
2b
11 10 9 8 7 6 5 4 3 2 1 ppm
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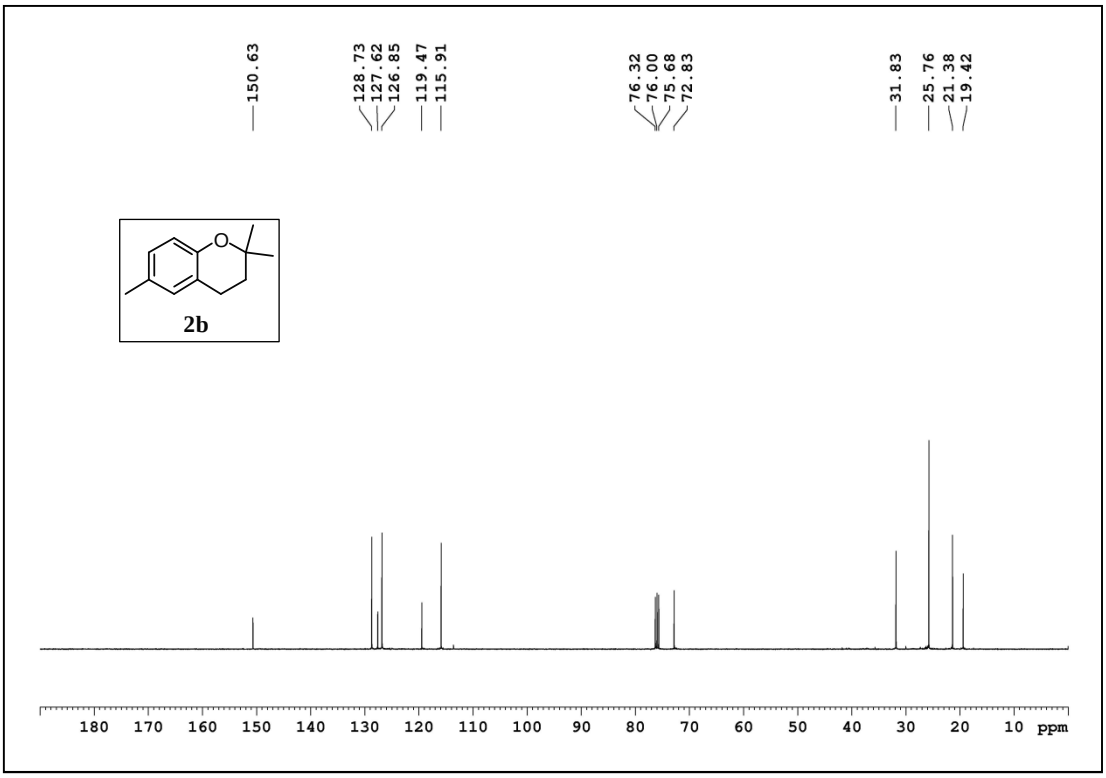
1.00
1.94
3.00
1.91
5.81


150.63
128.73
127.62
126.85
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115.91
76.32
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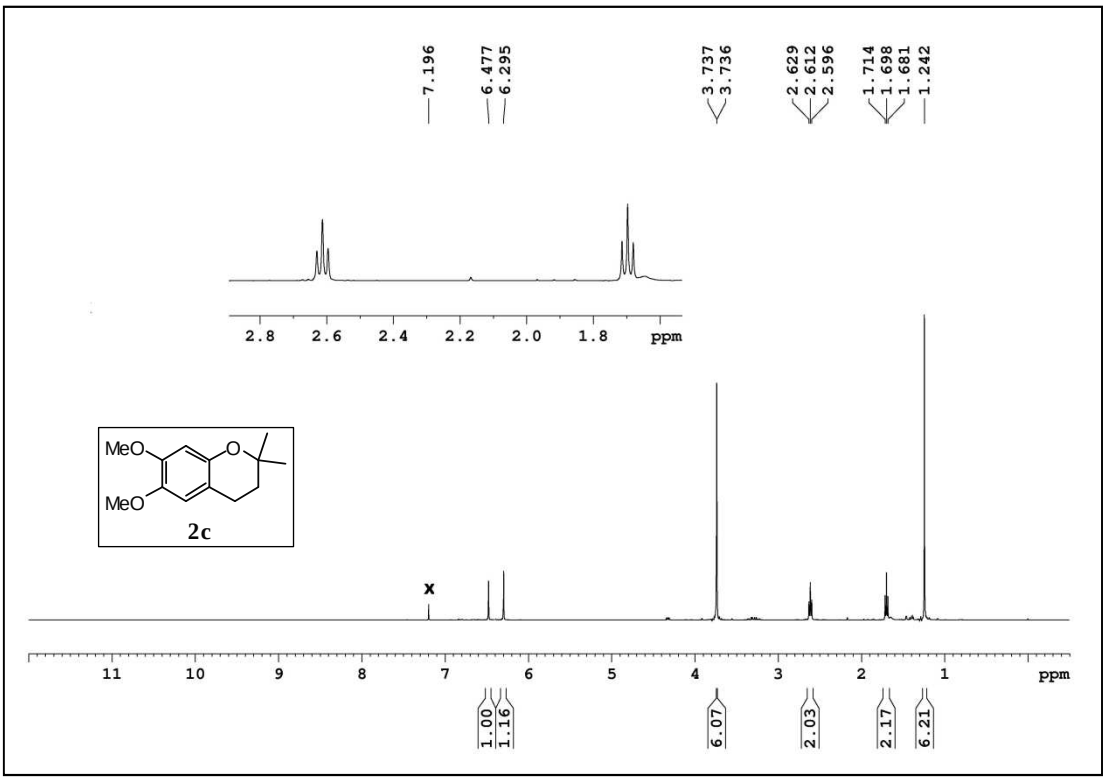
19.42
2b
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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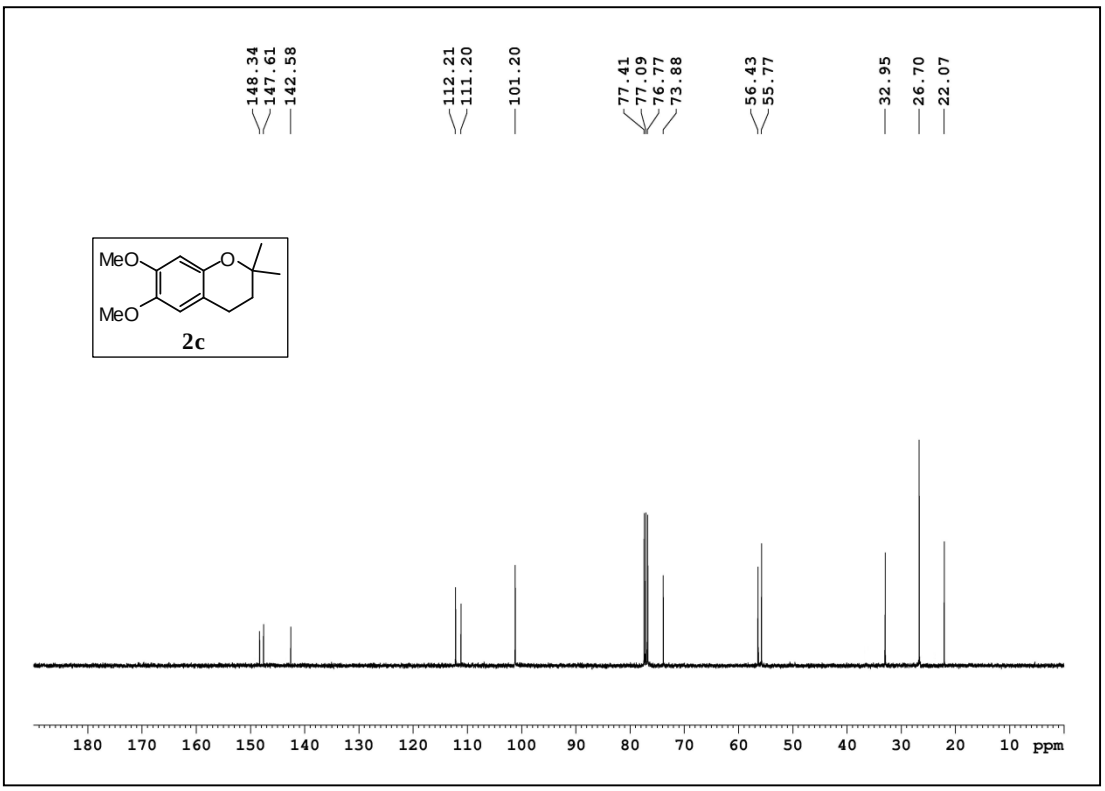
2.8
2.6
2.4
2.2
2.0
1.8
ppm
MeO
MeO
O
2c
x
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.16
6.07
2.03
2.17
6.21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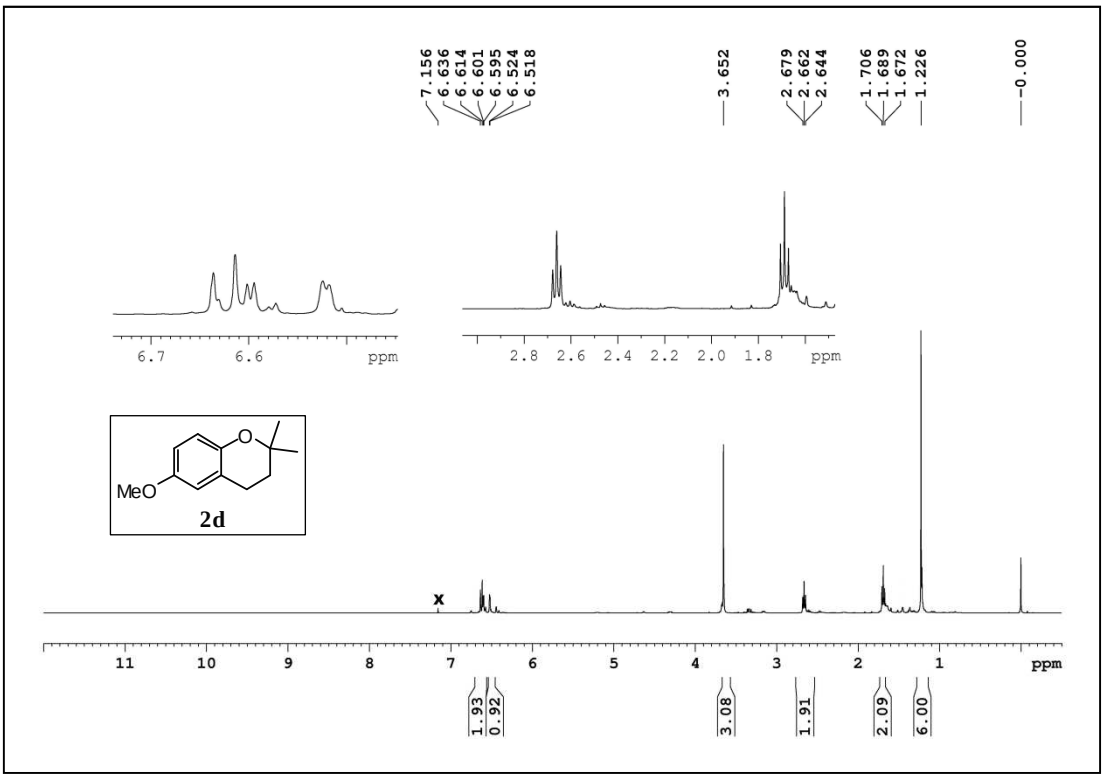
112.21
111.20
101.20
77.41
77.09
76.77
73.88
56.43
55.77
32.95
26.70
22.07
MeO
MeO
O
2c
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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6.518
3.652
2.679
2.662
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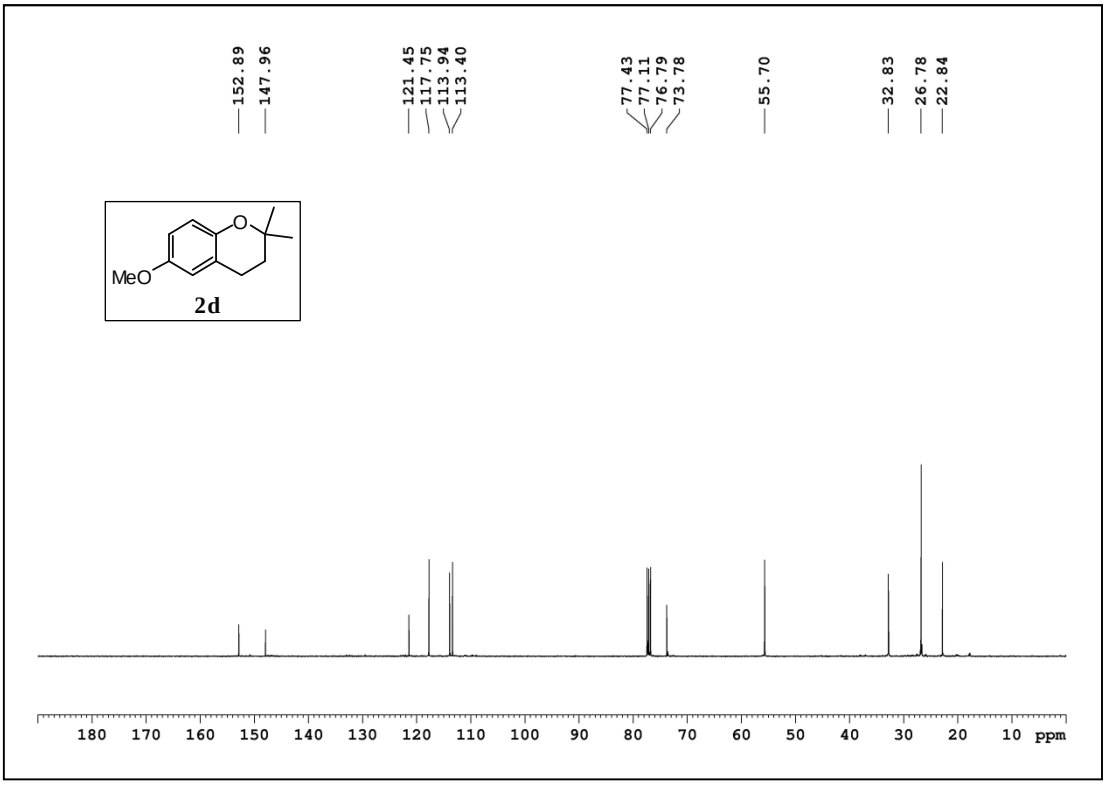
1.689
1.672
1.226
-0.000
6.7
6.6
ppm
2.8 2.6 2.4 2.2 2.0 1.8
ppm
MeO
2d
x
11 10 9 8 7 6 5 4 3 2 1
ppm
1.93
0.92
3.08
1.91
2.09
6.00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77.11
76.79
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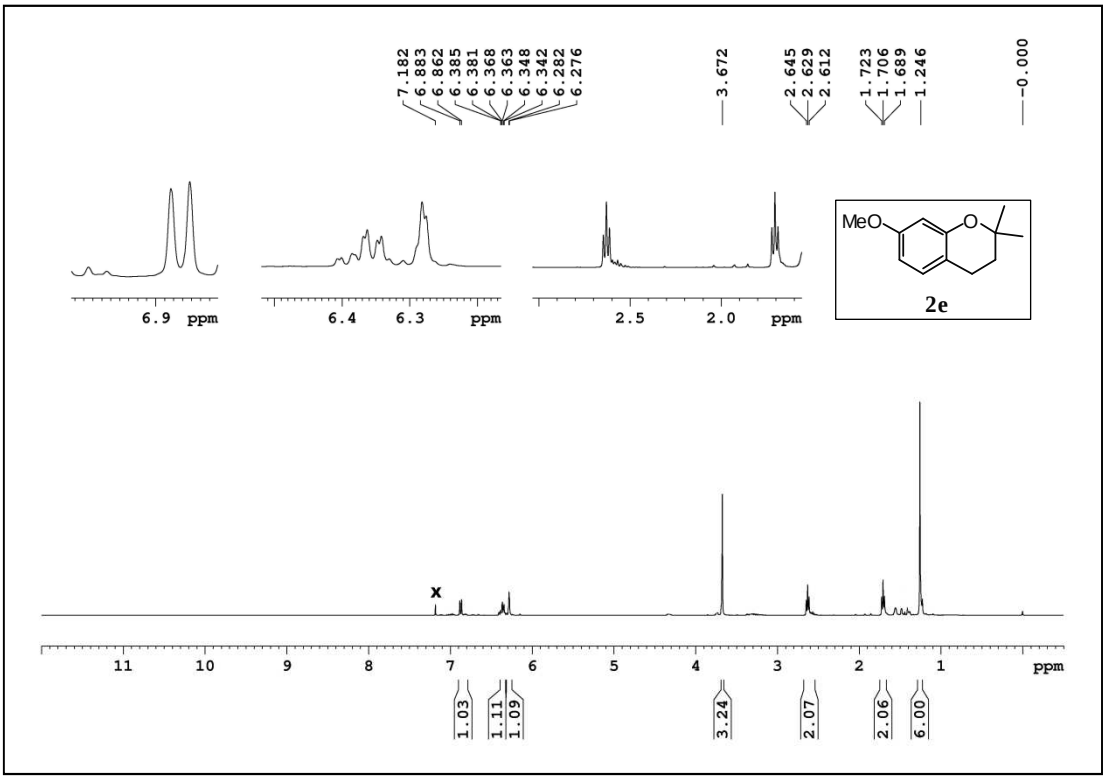
32.83
26.78
22.84
MeO
2d
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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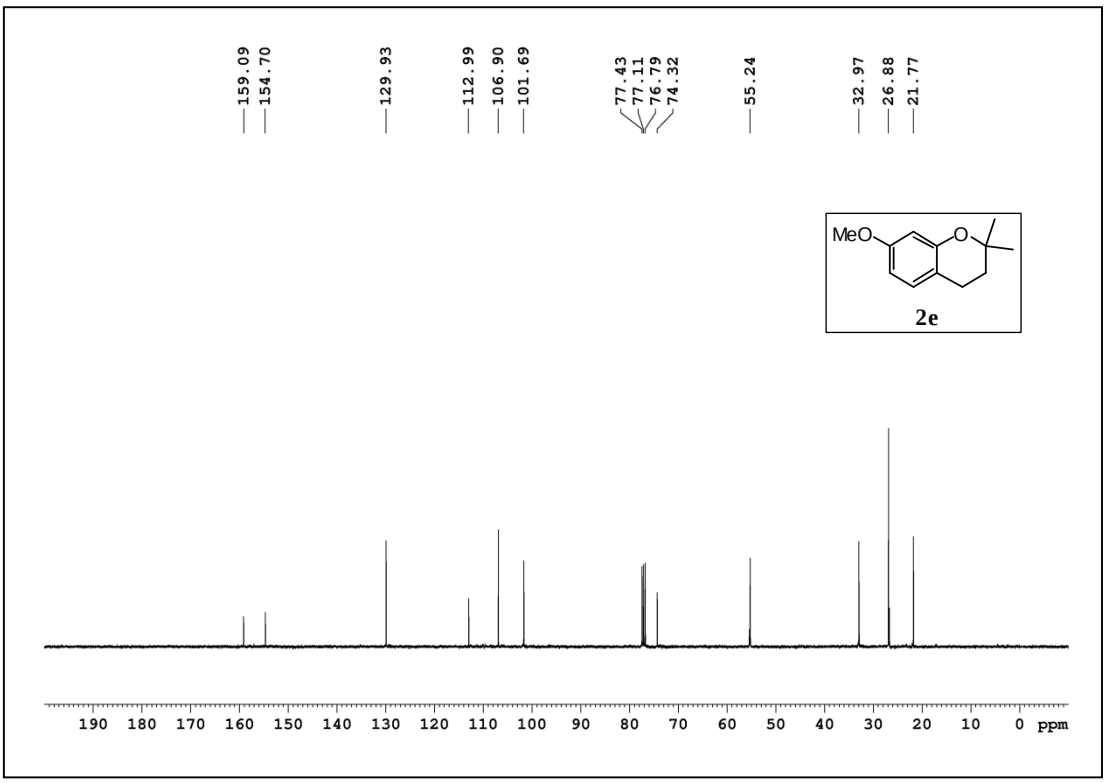
6.862
6.385
6.381
6.368
6.363
6.348
6.342
6.282
6.276
3.672
2.645
2.629
2.612
1.723
1.706
1.689
1.246
-0.000
MeO
O
2e
6.9 ppm
6.4 6.3 ppm
2.5 2.0 ppm
x
11 10 9 8 7 6 5 4 3 2 1 ppm
1.03
1.11
1.09
3.24
2.07
2.06
6.00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129.93
112.99
106.90
101.69
77.43
77.11
76.79
74.32
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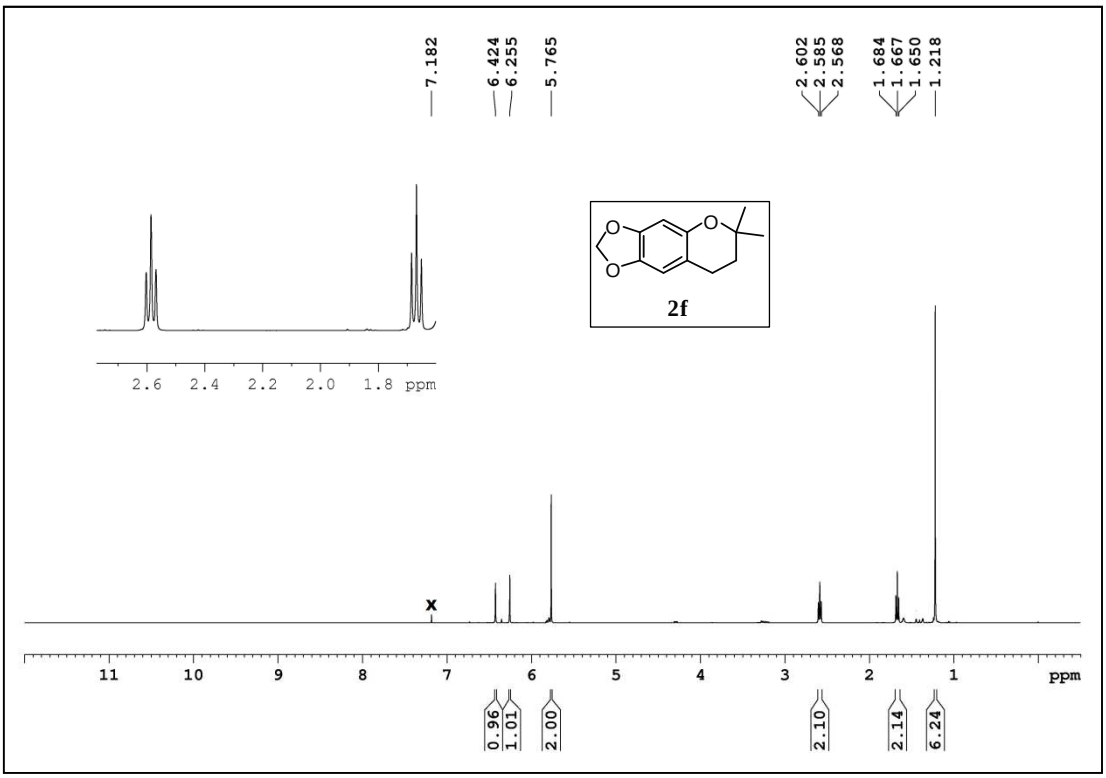
26.88
21.77
MeO
O
2e
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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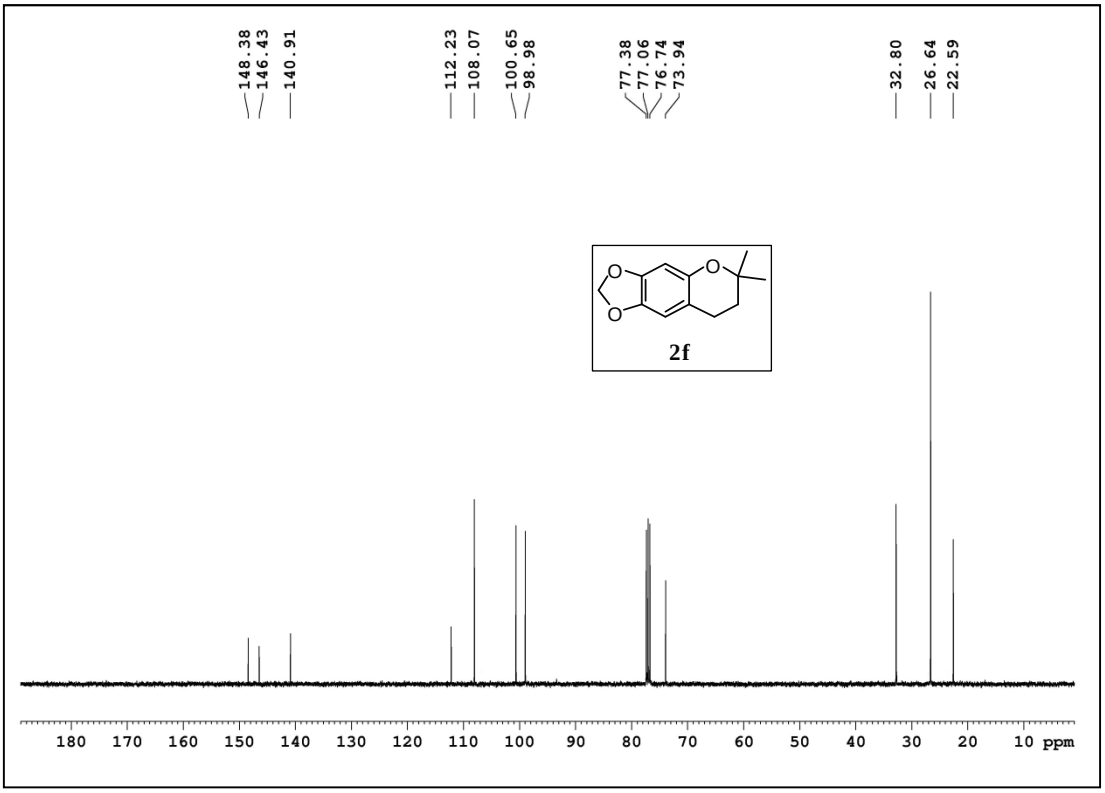
6.255
5.765
2.602
2.585
2.568
1.684
1.667
1.650
1.218
2.6 2.4 2.2 2.0 1.8 ppm
2f
x
11 10 9 8 7 6 5 4 3 2 1 ppm
0.96
1.01
2.00
2.10
2.14
6.24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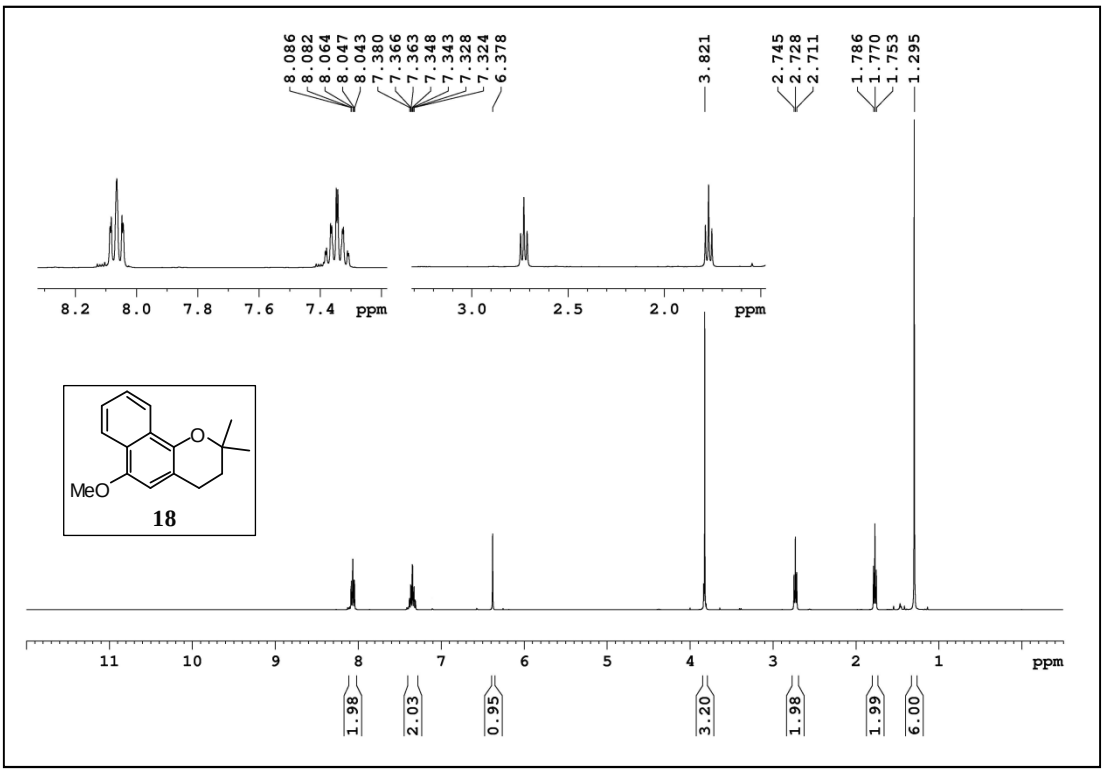
22.59
2f
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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8.043
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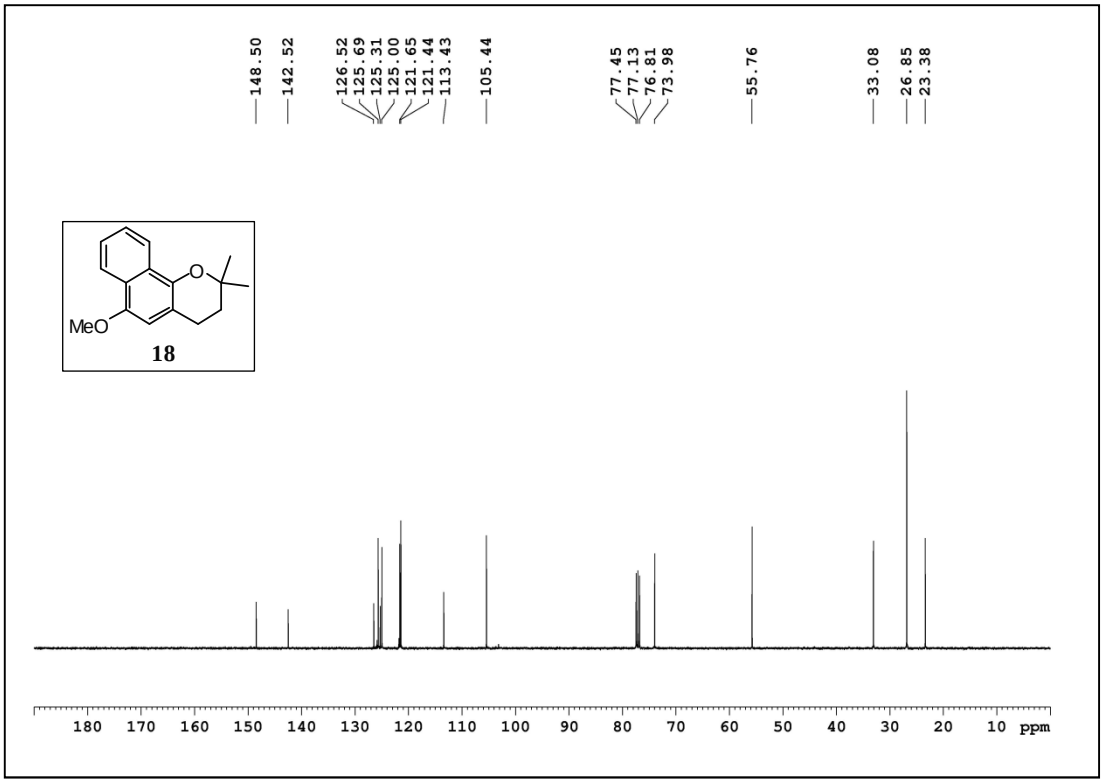
7.363
7.348
7.343
7.328
7.324
6.378
3.821
2.745
2.728
2.711
1.786
1.770
1.753
1.295
8.2
8.0
7.8
7.6
7.4
ppm
3.0
2.5
2.0
ppm
MeO
18
11
10
9
8
7
6
5
4
3
2
1
ppm
1.98
2.03
0.95
3.20
1.98
1.99
6.00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126.52
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125.31
125.00
121.65
121.44
113.43
105.44
77.45
77.13
76.81
73.98
55.76
33.08
26.85
23.38
MeO
18
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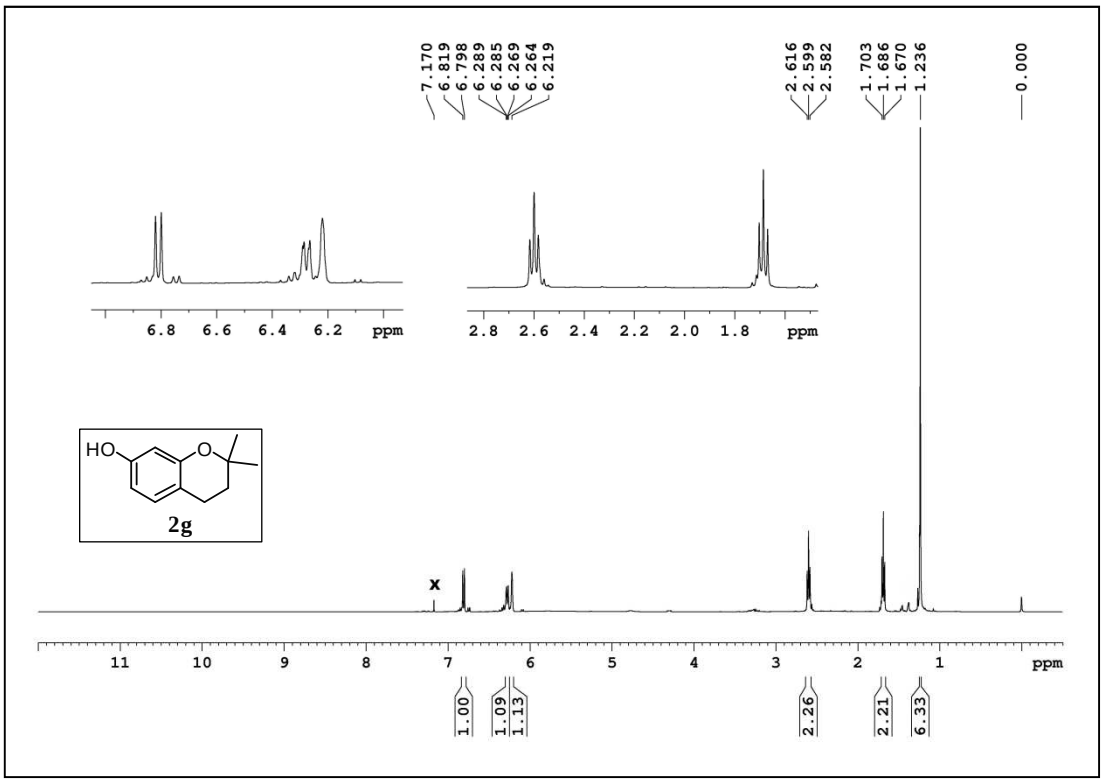
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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6.798
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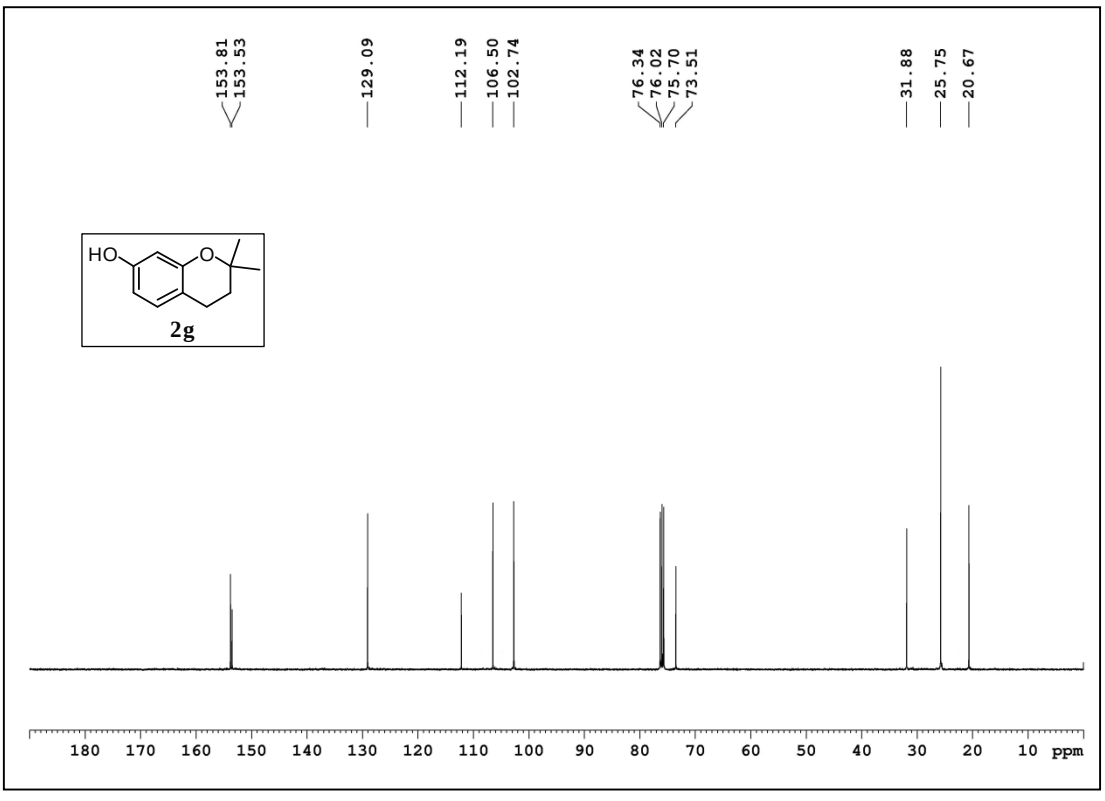
6.285
6.269
6.264
6.219
2.616
2.599
2.582
1.703
1.686
1.670
1.236
0.000
6.8 6.6 6.4 6.2 ppm
2.8 2.6 2.4 2.2 2.0 1.8 ppm
HO
O
2g
x
11 10 9 8 7 6 5 4 3 2 1 ppm
1.00
1.09
1.13
2.26
2.21
6.33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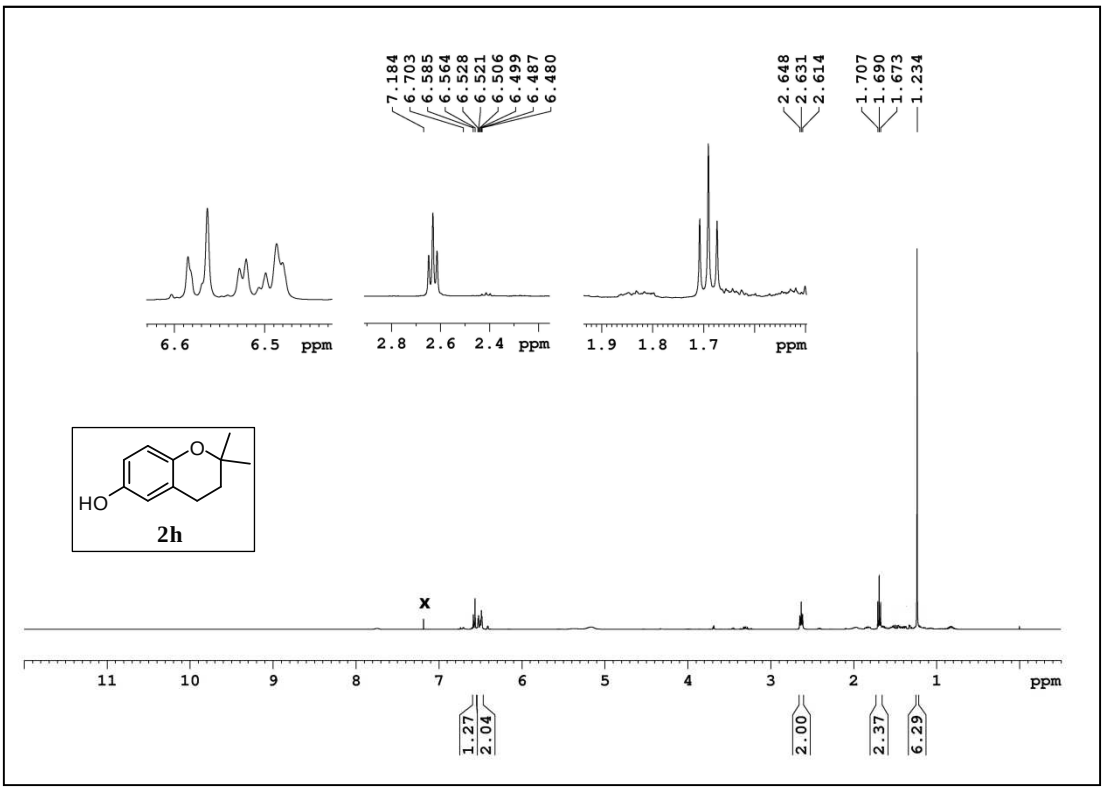
129.09
112.19
106.50
102.74
76.34
76.02
75.70
73.51
31.88
25.75
20.67
HO
O
2g
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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6.564
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6.499
6.487
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2.631
2.614
1.707
1.690
1.673
1.234
6.6
6.5
ppm
2.8
2.6
2.4
ppm
1.9
1.8
1.7
ppm
HO
O
2h
x
11
10
9
8
7
6
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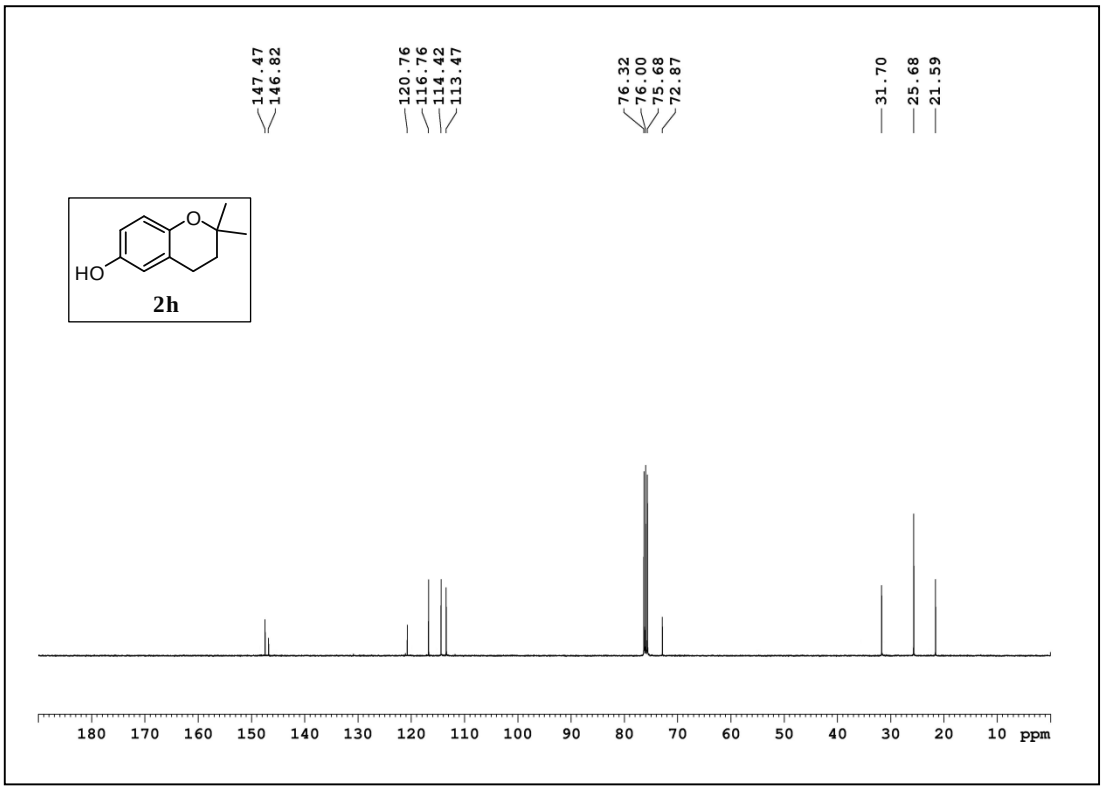
ppm
1.27
2.04
2.00
2.37
6.29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76.00
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72.87
31.70
25.68
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HO
O
2h
180
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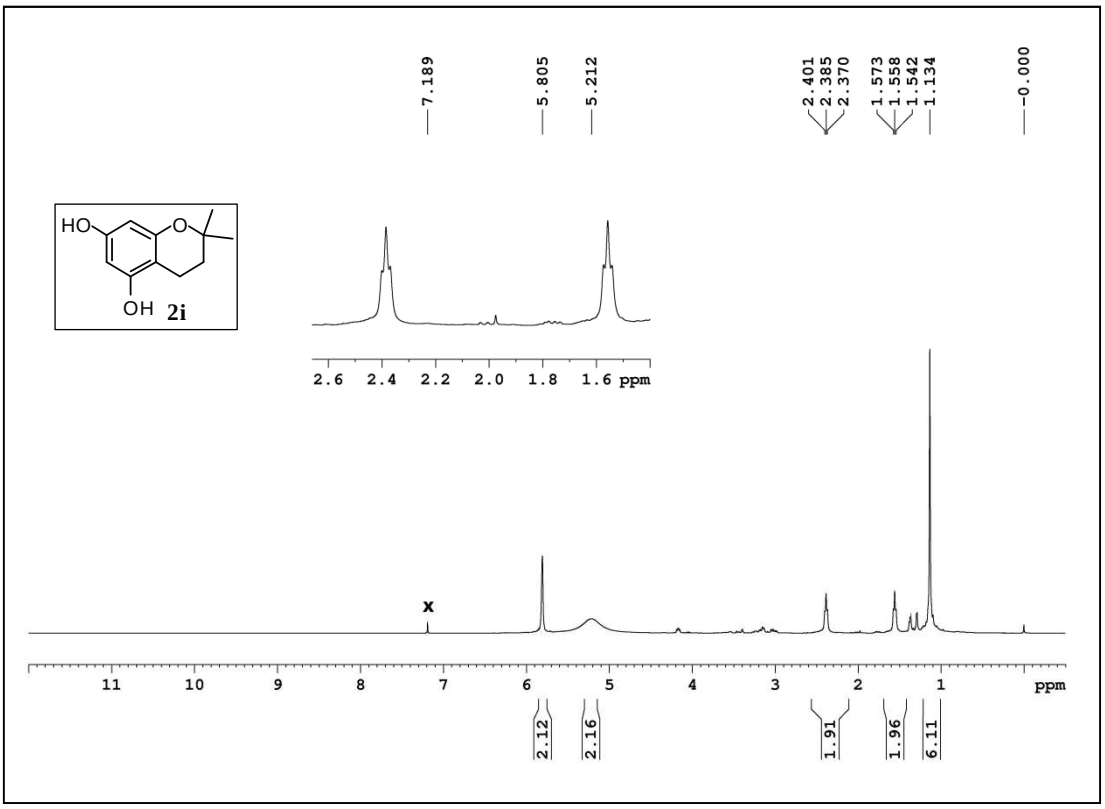
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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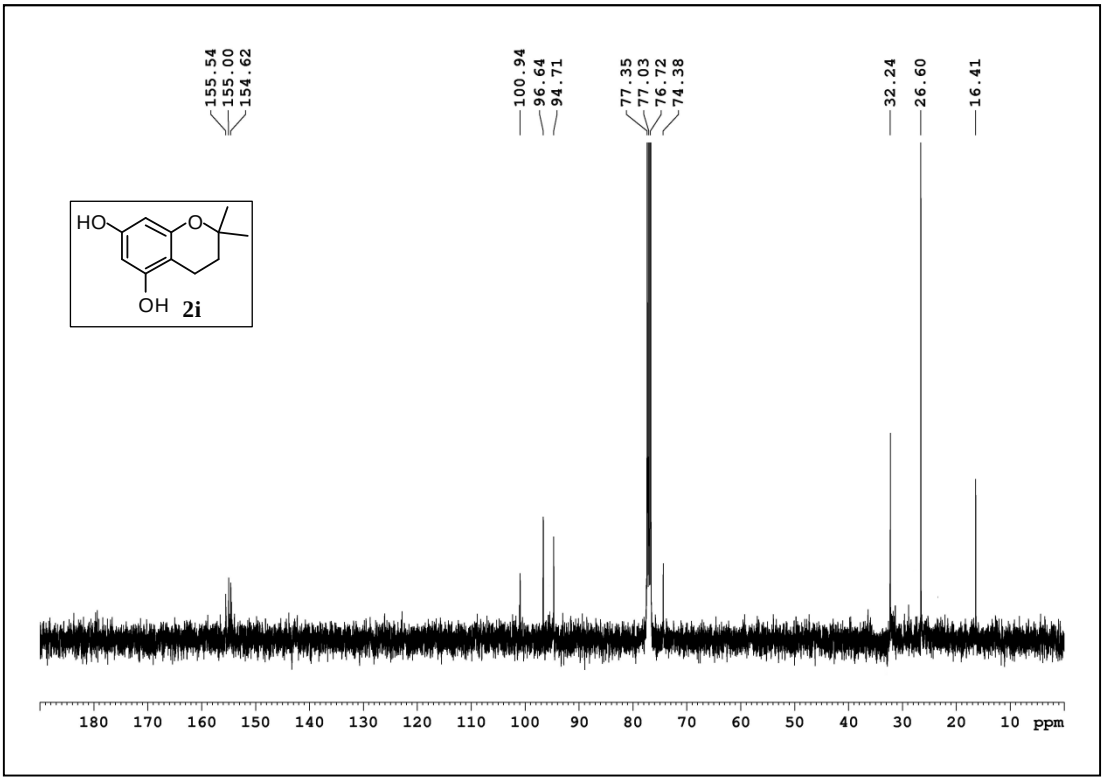
5.212
2.401
2.385
2.370
1.573
1.558
1.542
1.134
0.000
HO
O
OH
2i
2.6 2.4 2.2 2.0 1.8 1.6 ppm
x
11 10 9 8 7 6 5 4 3 2 1 ppm
2.12
2.16
1.91
1.96
6.11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77.35
77.03
76.72
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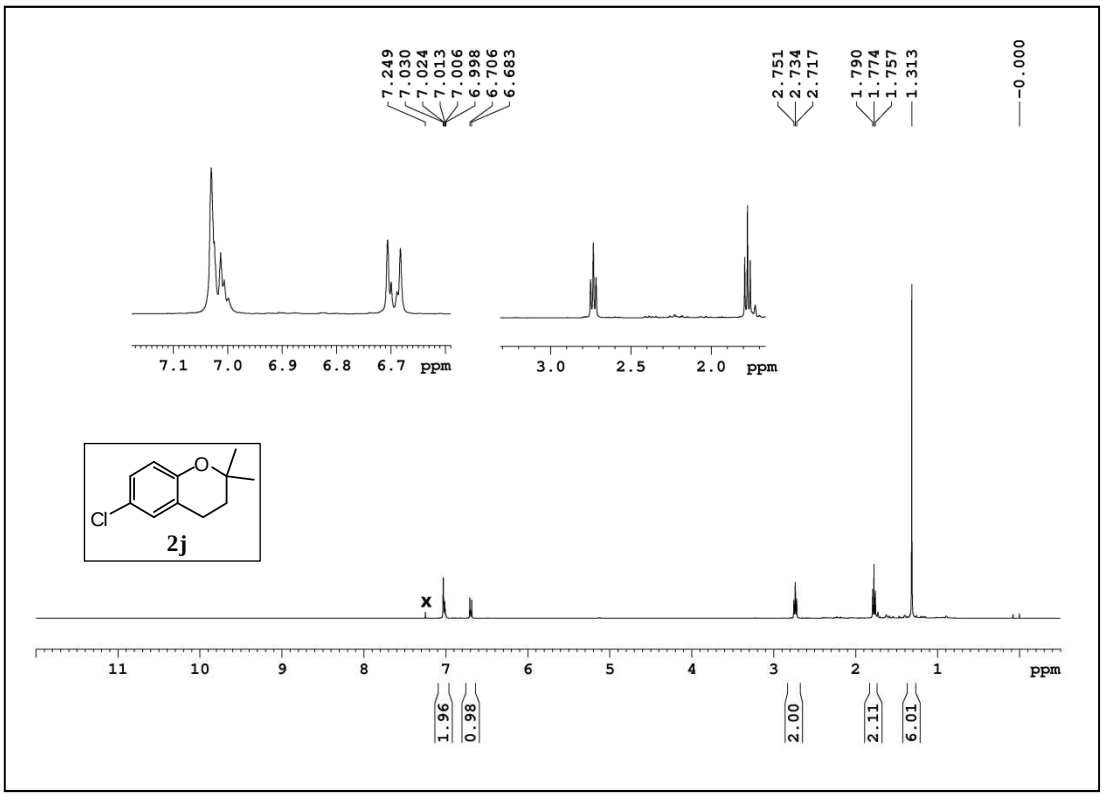
32.24
26.60
16.41
HO
O
OH
2i
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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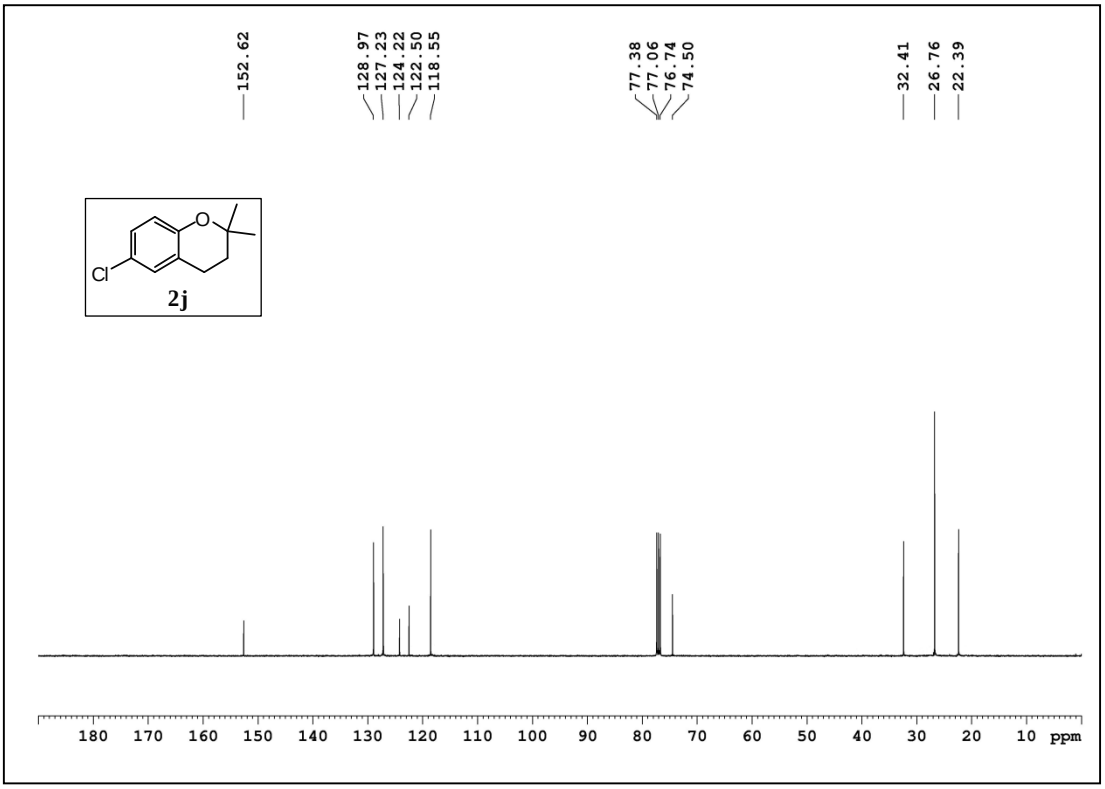
7.030
7.024
7.013
7.006
6.998
6.706
6.683
2.751
2.734
2.717
1.790
1.774
1.757
1.313
0.000
7.1 7.0 6.9 6.8 6.7 ppm
3.0 2.5 2.0 ppm
Cl
O
2j
x
11 10 9 8 7 6 5 4 3 2 1 ppm
1.96
0.98
2.00
2.11
6.01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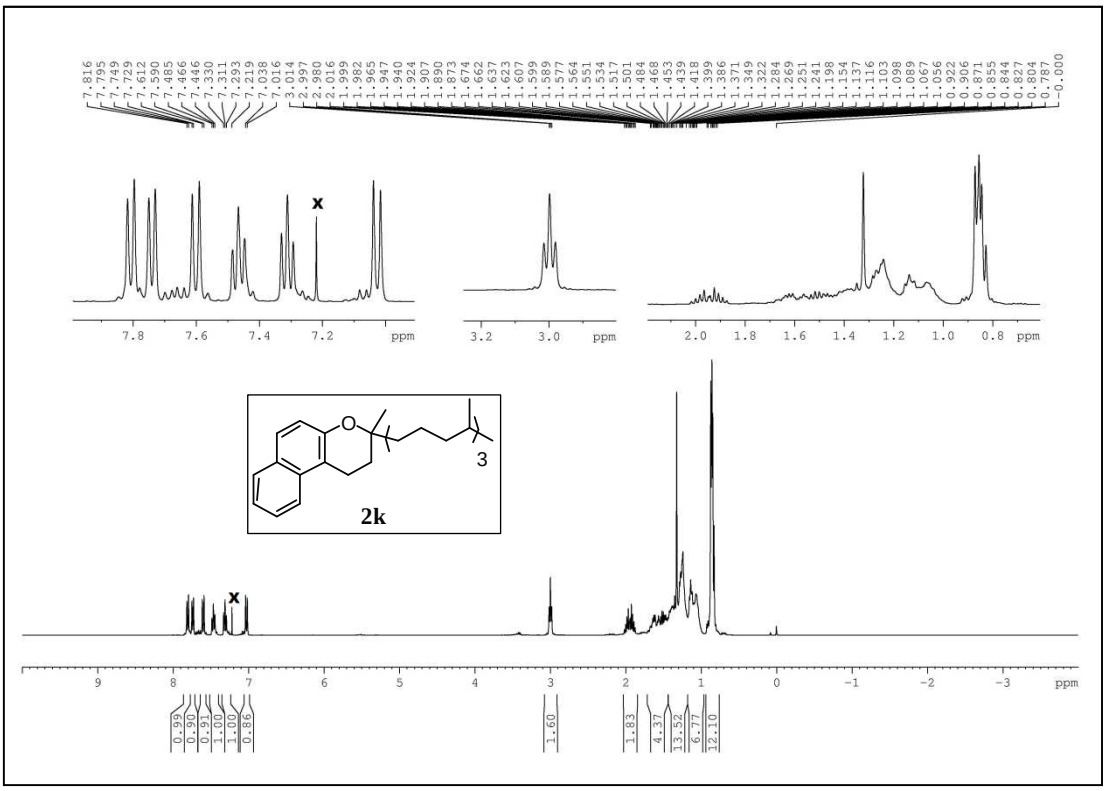
127.23
124.22
122.50
118.55
77.38
77.06
76.74
74.50
32.41
26.76
22.39
Cl
O
2j
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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7.480
7.466
7.446
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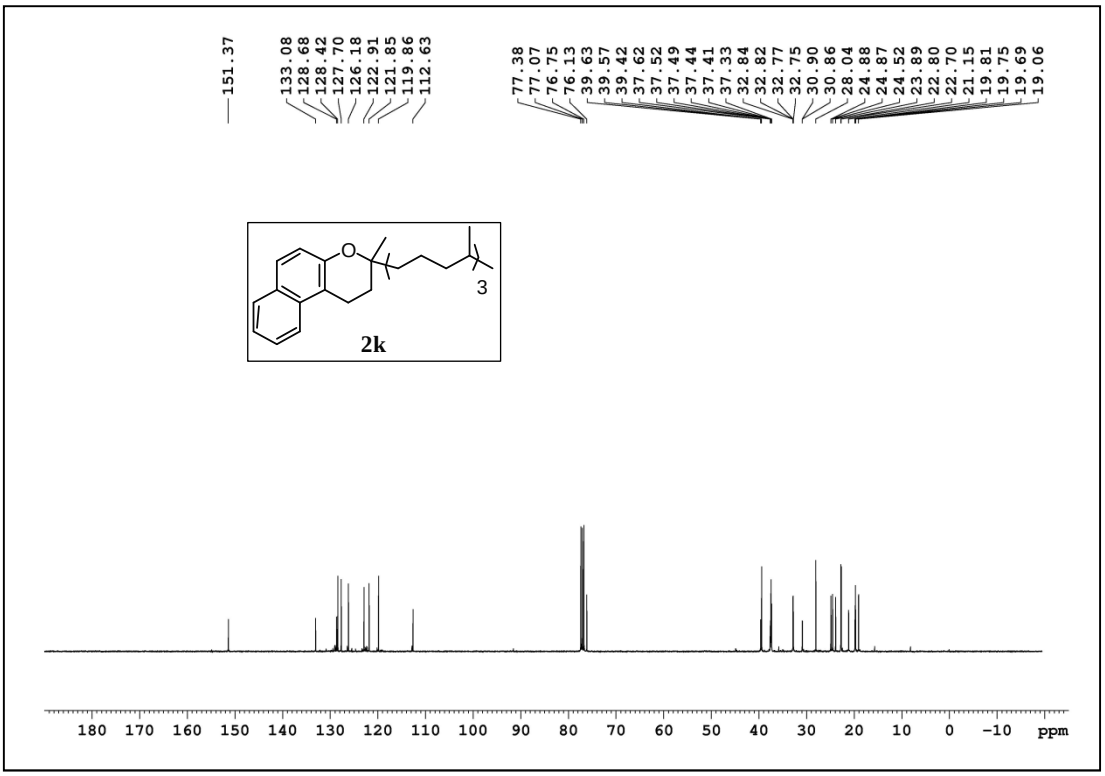
7.293
7.219
7.038
7.016
3.014
2.997
2.980
2.016
1.999
1.982
1.965
1.947
1.940
1.924
1.907
1.890
1.873
1.674
1.662
1.637
1.623
1.607
1.589
1.577
1.564
1.551
1.534
1.517
1.501
1.484
1.468
1.453
1.439
1.418
1.399
1.386
1.371
1.349
1.322
1.284
1.269
1.251
1.241
1.198
1.154
1.137
1.116
1.103
1.089
1.067
1.056
0.922
0.906
0.871
0.855
0.844
0.827
0.804
0.787
-0.000
x
7.8
7.6
7.4
7.2
ppm
3.2
3.0
ppm
2.0
1.8
1.6
1.4
1.2
1.0
0.8
ppm
O
3
2k
x
9
8
7
6
5
4
3
2
1
0
−1
−2
−3
ppm
0.99
0.90
0.91
1.00
1.00
0.86
1.60
1.83
4.37
13.52
6.77
12.10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121.85
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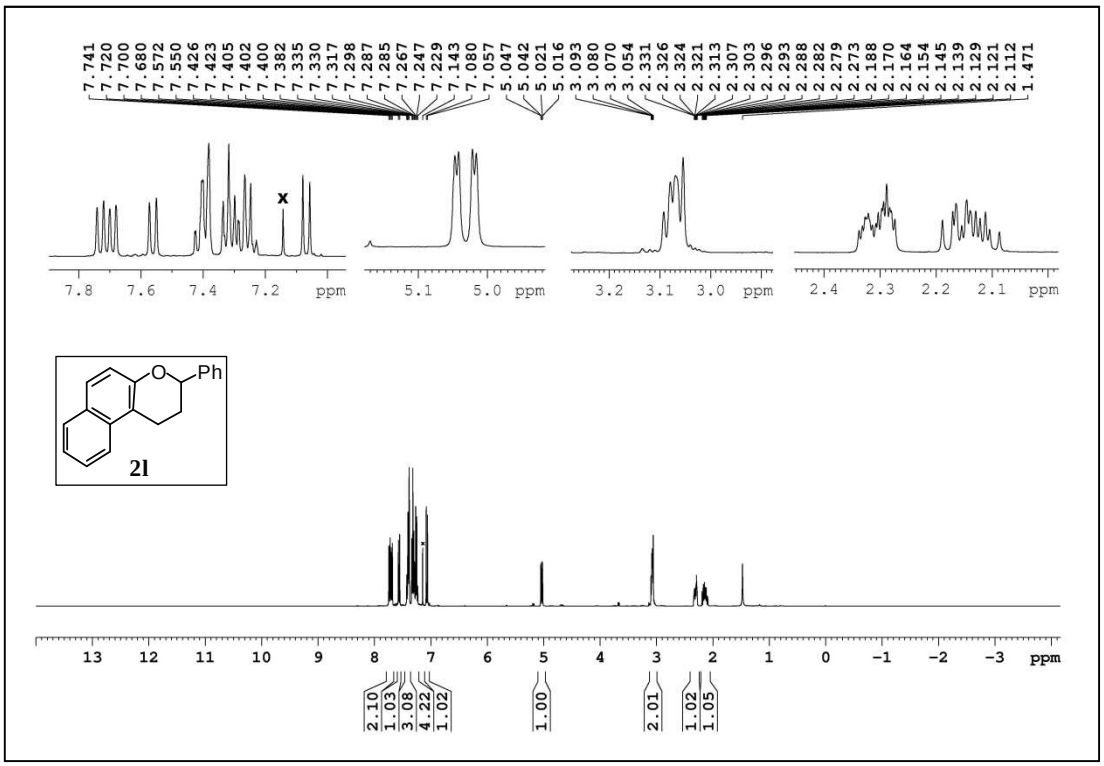
77.07
76.75
76.13
39.63
39.57
39.42
37.62
37.52
37.49
37.44
37.41
37.33
32.84
32.82
32.77
32.75
30.90
30.86
28.04
24.88
24.87
24.52
23.89
22.80
22.70
21.15
19.81
19.75
19.69
19.06
O
3
2k
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
ppm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7.700
7.680
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7.550
7.426
7.423
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7.402
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7.335
7.330
7.317
7.298
7.287
7.285
7.267
7.247
7.229
7.143
7.080
7.057
5.047
5.042
5.021
5.016
3.093
3.080
3.070
3.054
2.331
2.326
2.324
2.321
2.313
2.307
2.303
2.296
2.293
2.288
2.282
2.279
2.273
2.188
2.170
2.164
2.154
2.145
2.139
2.129
2.121
2.112
1.471
x
7.8 7.6 7.4 7.2 ppm
5.1 5.0 ppm
3.2 3.1 3.0 ppm
2.4 2.3 2.2 2.1 ppm
O
Ph
2l
13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 −3 ppm
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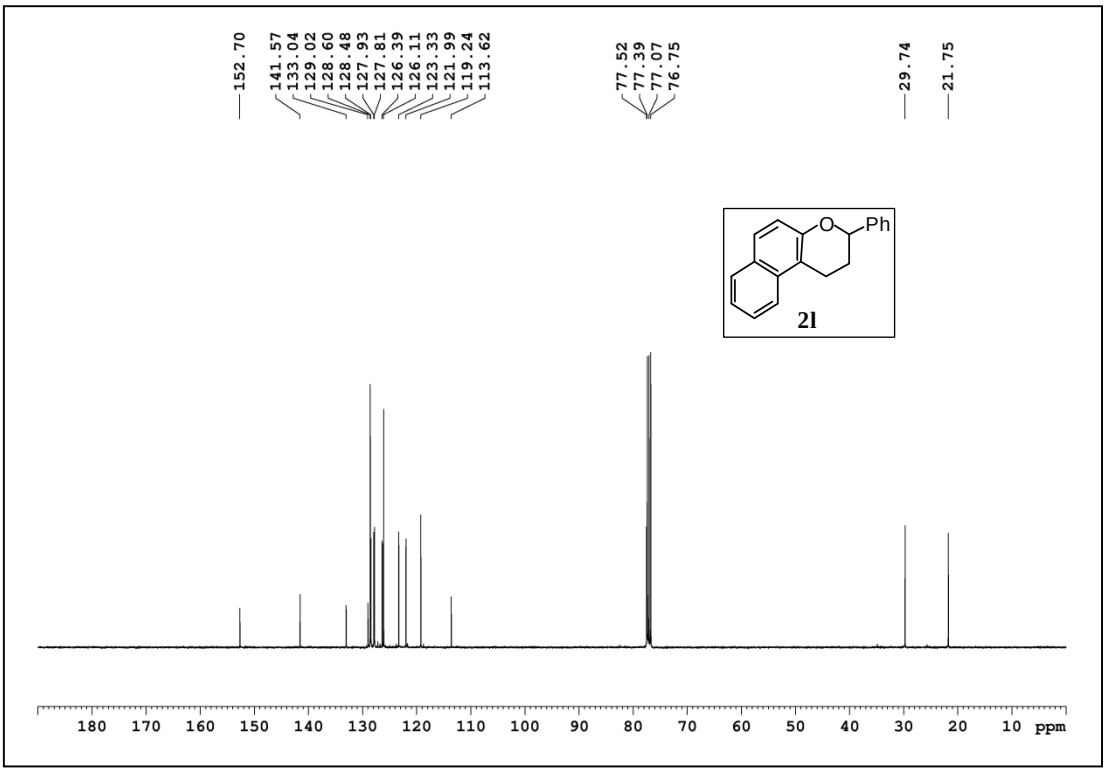
3.08
4.22
1.02
1.00
2.01
1.02
1.05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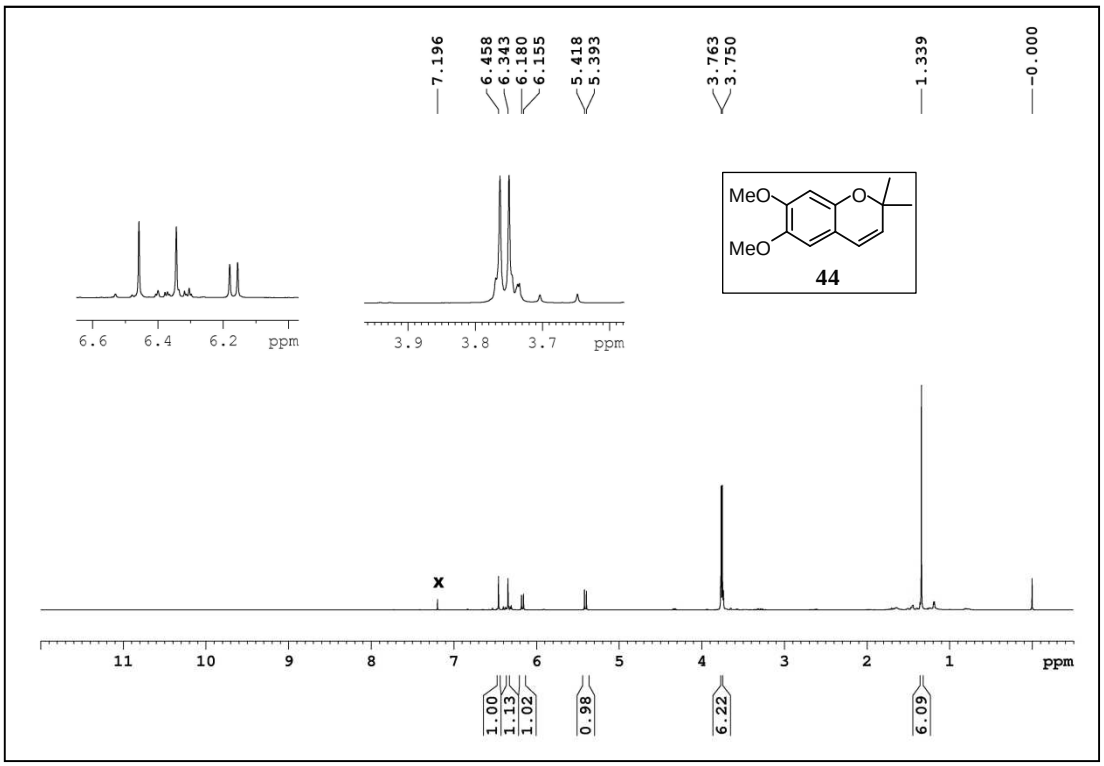
127.81
126.39
126.11
123.33
121.99
119.24
113.62
77.52
77.39
77.07
76.75
29.74
21.75
O
Ph
2l
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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5.418
5.393
3.763
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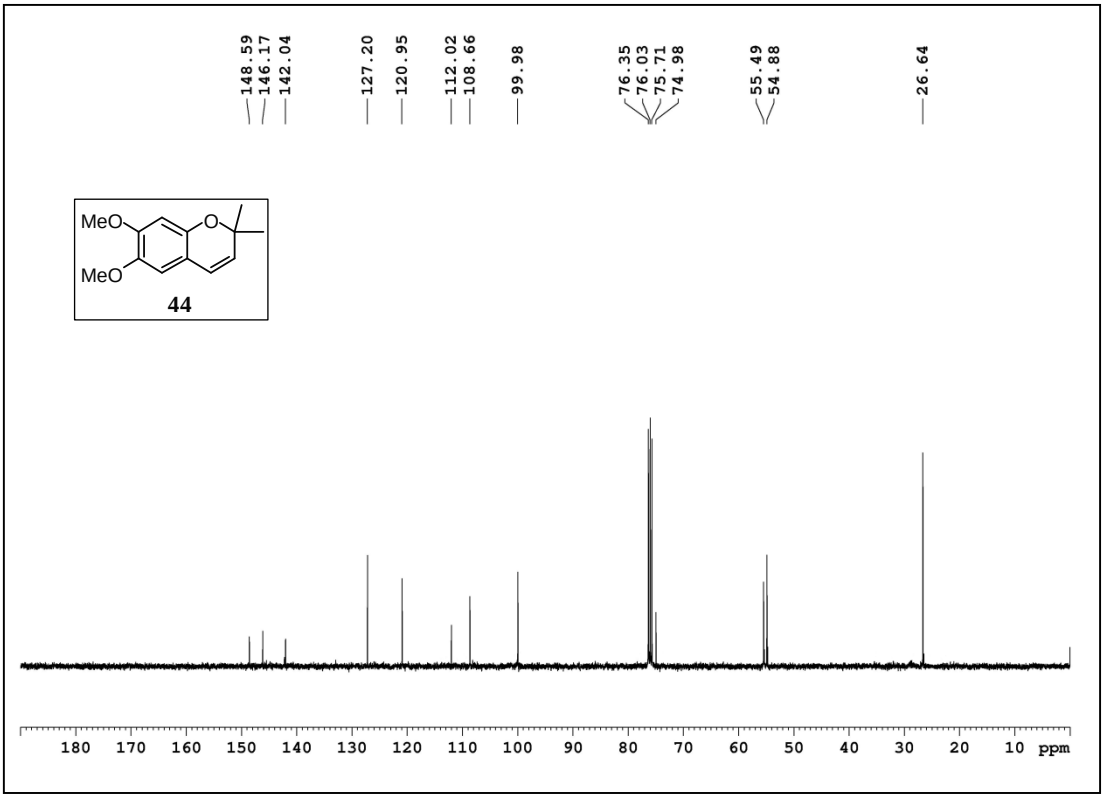
1.339
0.000
MeO
MeO
O
44
6.6
6.4
6.2
ppm
3.9
3.8
3.7
ppm
x
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.13
1.02
0.98
6.22
6.09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76.03
75.71
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55.49
54.88
26.64
MeO
MeO
O
44
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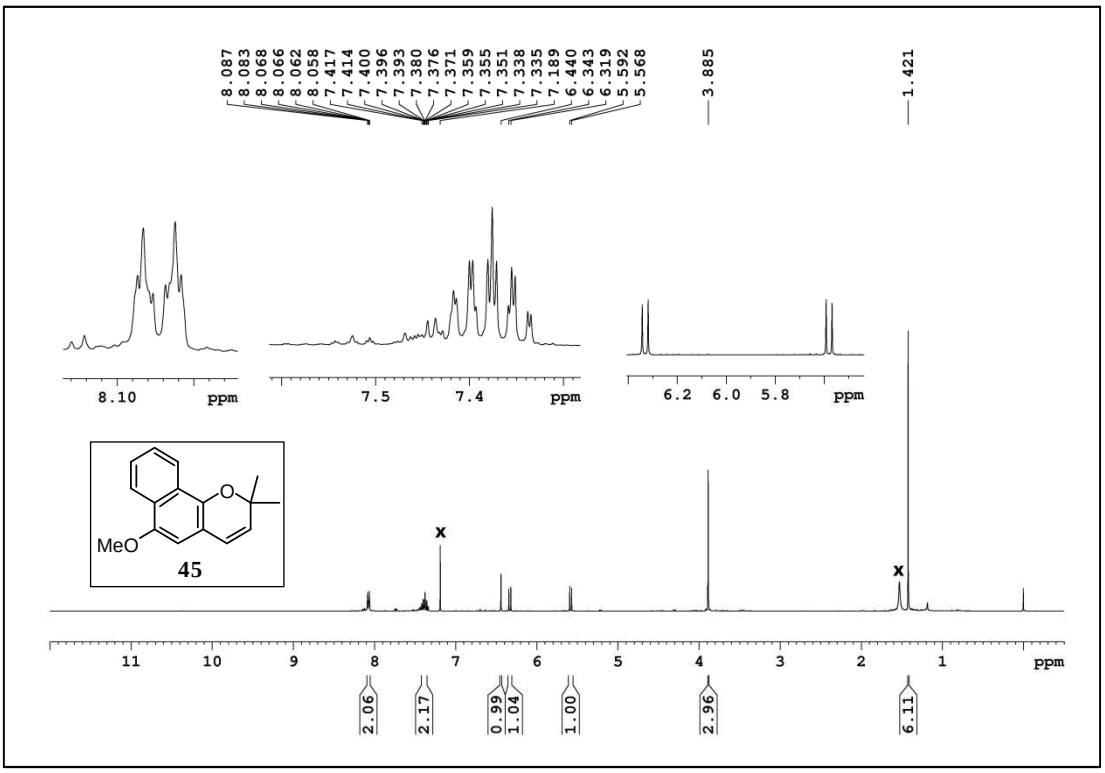
80
70
60
50
40
30
20
10
ppm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7.393
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7.371
7.359
7.355
7.351
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7.335
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6.440
6.343
6.319
5.592
5.568
3.885
1.421
8.10
ppm
7.5
7.4
ppm
6.2
6.0
5.8
ppm
MeO
45
x
x
11
10
9
8
7
6
5
4
3
2
1
ppm
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1.04
1.00
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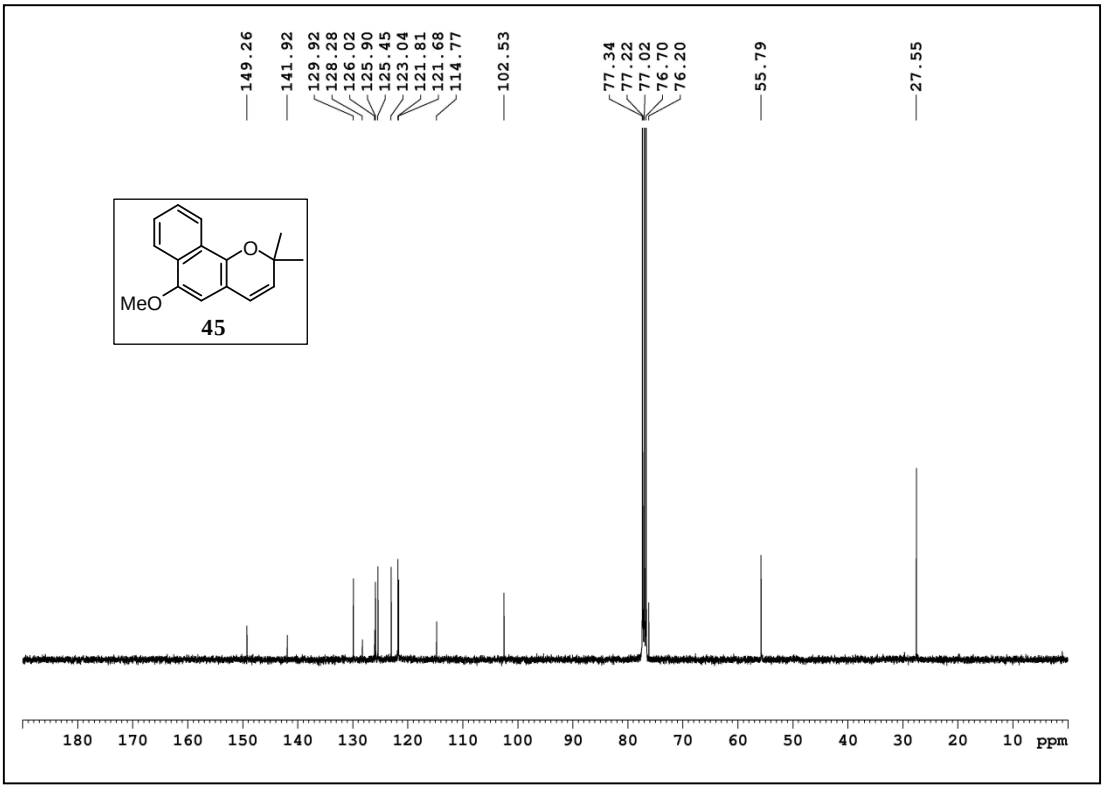
6.11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123.04
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121.68
114.77
102.53
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77.22
77.02
76.70
76.20
55.79
27.55
MeO
45
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

CHAPTER 3

Synthetic studies of flavones using pyrrolidine and molecular iodine catalysts and their anti-diabetic activity

3.1: Introduction

Flavones **1** (flavus = yellow) also known as 2-phenyl-4*H*-chromen-4-one or 2-phenylchromones (Figure 1) are naturally occurring oxygen heterocyclic compounds belonging to a class of compounds called as flavonoids. These are the secondary metabolites secreted by plants for protection from microbial attack, ultra violet rays and attract insects for pollination. In addition to flavones, flavonoids family comprises of several other members such as flavonols, flavanones, flavans, isoflavones, anthocyanidins, etc. These compounds occur in various parts of plants including bark, grains, stems, fruits, flowers, vegetables, roots, tea and wine.[1]

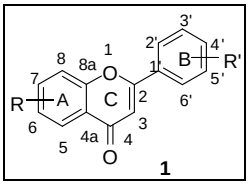


Figure 1: General structure of Flavone **1**.

3.2: Occurrence

Owing to their broad range of biological activities continuous investigation has led to the isolation of over 4000 chemically unique flavonoids from plants.[2] These multifarious naturally occurring compounds occur in free state known as aglycones as well as *O*- and/or *C*-glycosides exhibiting simple to complex structure diversity. Some of the common members attributing important and diverse biological activities are listed below (Figure 2, Table 1).

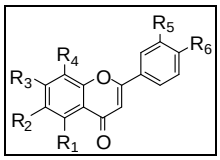


Figure 2: Naturally occurring biologically potent flavones **2**.

Table 1: Source of isolation of naturally occurring flavones **2**.

2	Name	R_1	R_2	R_3	R_4	R_5	R_6
a	Chrysin[3] *Passiflora coerulea L., Passiflora incarnata, Pleurotus ostreatus*	OH	H	OH	H	H	H
b	Apigenin[4]	OH	H	OH	H	H	OH

	Perilla frutescens, Matricaria chamomilla						
c	Luteolin[4,5] *Perilla frutescens, Matricaria chamomilla, Scutellaria lateriflora L., Aiphanes aculeata*	OH	H	OH	H	OH	OH
d	Nobiletin[6] *Citrus sinensis, Citrus aurantium*	OMe	OMe	OMe	OMe	OMe	OMe
e	Tangeritin[6] *Citrus sinensis, Citrus aurantium*	OMe	OMe	OMe	OMe	H	OMe
f	Scutellarein[7] *Asplenium belangeri, Scutellaria baicalensis*	OH	OH	OH	H	H	OH
g	Jaceosidin[8] *Artemisia princeps, Artemisia argyi*	OH	OMe	OH	H	OMe	OH
h	Eupatilin[8a,9] *Artemisia princeps, Artemisia asiatica*	OH	OMe	OH	H	OMe	OMe
i	Baicalein[10] *Scutellaria baicalensis, Scutellaria lateriflora, Oroxylum indicum*	OH	OH	OH	H	H	H
j	Wogonin[11] *Scutellaria baicalensis*	OH	H	OH	OMe	H	H

Structures of some of the selected naturally occurring flavone glycosides **3-14** are listed below along with their source of isolation (Figure 3, Table 2).

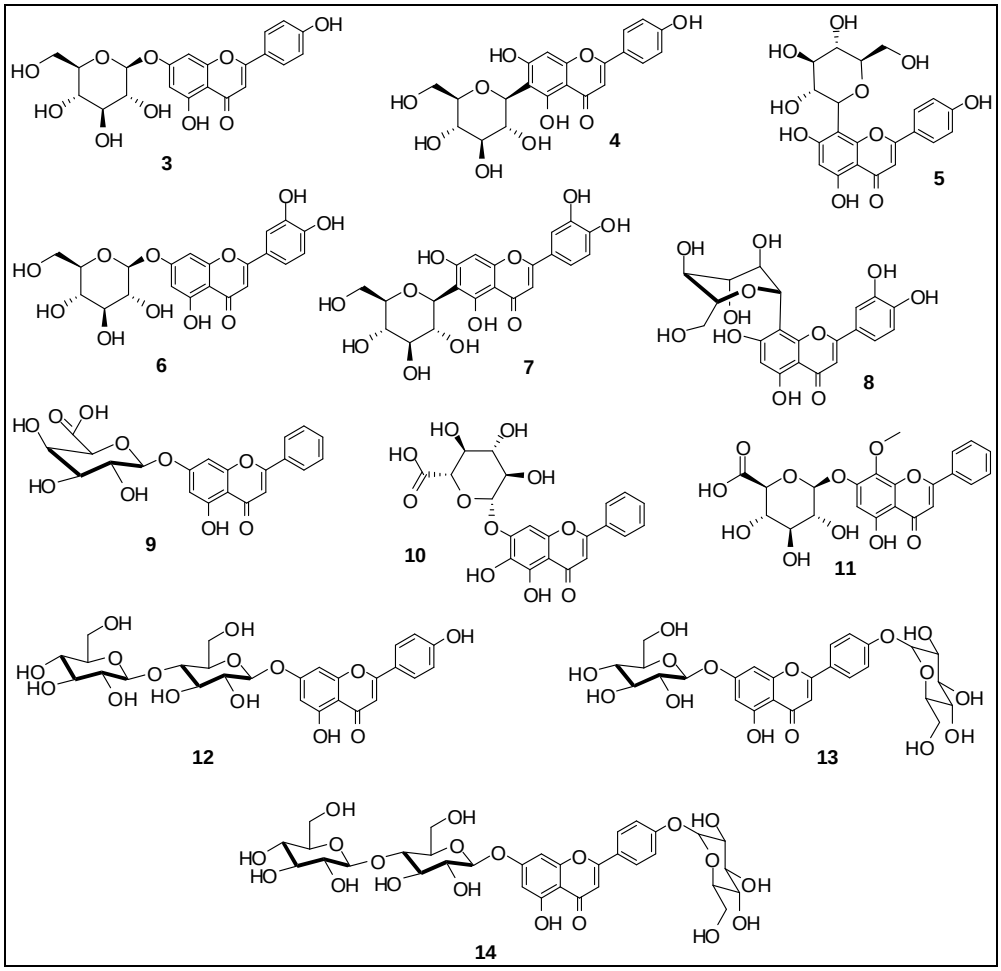


Figure 3: Structures of naturally occurring flavone glycosides **3-14**.

Table 2: Source of isolation of naturally occurring flavone glycosides **3-14**.

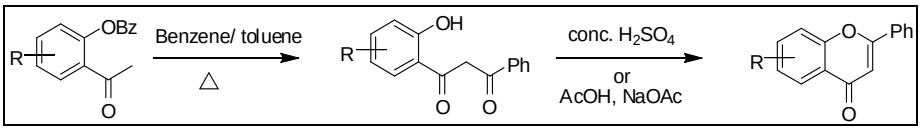
No.	Name ***Source of isolation***
3	Apigenin 7-*O*-glucoside (Apigetrin)[12] *Teucrium gnaphalodes*
4	Apigenin 6-*C*-glucoside (Isovitexin)[13] *Serjania erecta*
5	Apigenin 8-*C*-glucoside (Vitexin)[13] *Serjania erecta*
6	Luteolin 7-*O*-glucoside (Luteoloside)[12] *Teucrium gnaphalodes*
7	Luteolin 6-*C*-glucoside (Isoorientin)[14] *Gentiana olivieri ,Pueraria tuberosa*
8	Luteolin 8-*C*-glucoside (Orientin)[15]

	Cannabis sativa
9	Chrysin 7-*O*-*β*-galactopyranuronoside[16] *Centaurea pseudoscabiosa*, *Scutellaria schachristanica*
10	Baicalein 7-*O*-glucuronide (Baicalin)[10c,17] *Scutellaria baicalensis, Oroxylum indicum*
11	Wogonin 7-*O*-*β*-D-glucuronide (Oroxindin)[18] *Oroxylum indicum, Bacopa monnieri, Holmskioldia sanguinea*
12	Apigenin 7-*O*-cellobioside[19] *Salvia uliginosa*
13	Apigenin 7,4'-*O*,*O*-diglucoside[19] *Salvia uliginosa*
14	Apigenin 7-*O*-cellobioside-4'-*O*-glucoside[19] *Salvia uliginosa*

Thousands of flavone compounds isolated have been found to exhibit immense biological activities.[20] A broad range of activities exhibited by several members of flavone includes anti-inflammatory,[21] anti-viral,[22] estrogenic/anti-estrogenic,[23] anticancer,[24] antioxidants,[25] leishmanicidal,[26] anticonvulsants,[3a,27] antihistamines,[28] ovipositor stimulant phytoalexins,[29] anti-HIV,[30] vasodilators,[31] antispasmodics,[32] antidiabetics,[33] antimutagenic,[34] antiallergic,[35] DNA cleavage,[36] antiaging,[37] antidepressant,[38] etc. Some flavonoids are known to show monoamine oxidase (MAO) inhibitory activity[39] whereas some have a repelling property against insects acting as antifeedant.[40]

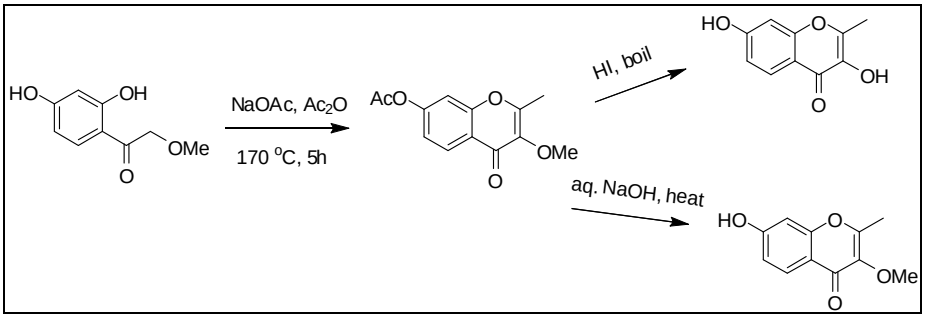
3.3: Literature synthetic methods

The numerous biological activities exhibited by several members of flavones have attracted scientists to constantly study flavones and develop variety of new strategies to synthesize them in large quantities. Among these Baker-Venkataraman rearrangement[41] and Allan-Robinson reaction[42] are well established methods. Several reviews incorporating diverse routes to flavones have appeared recently.[43]



Scheme 1: Baker-Venkataraman rearrangement.

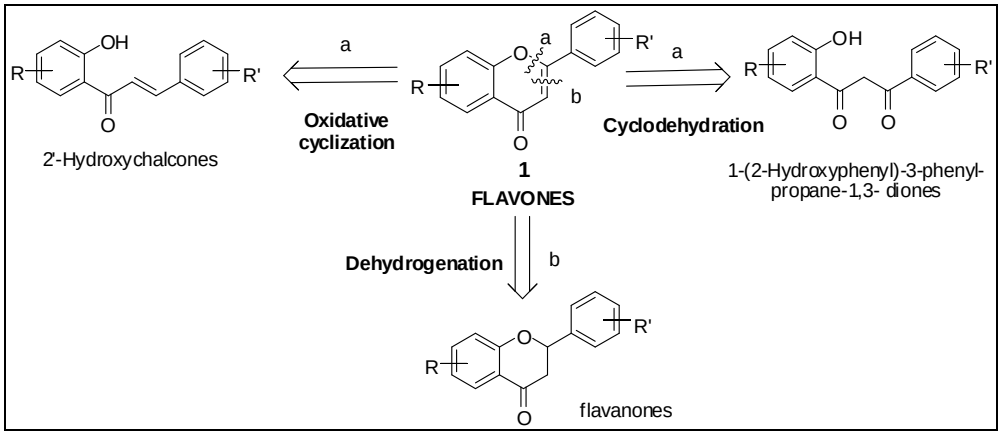
Baker-Venkataraman rearrangement[41] involves 2-*O*-benzoylacetophenone as substrate which undergoes intramolecular rearrangement to 2-hydroxydibenzoylmethane on heating. It further on treatment with conc. H_2SO_4 or in boiling AcOH and AcONa gives flavones (Scheme 1).



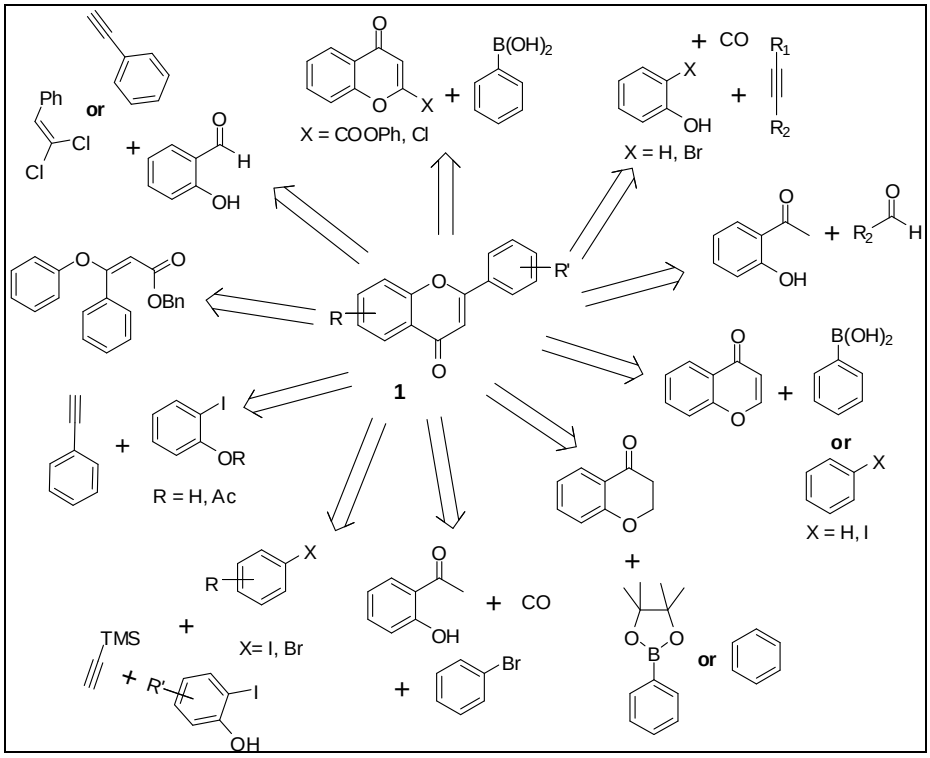
Scheme 2: Allan-Robinson synthesis.

Allan-Robinson synthesis[42] involves the reaction of *o*-hydroxyaryl ketones with anhydrides in presence of base to form flavones (Scheme 2).

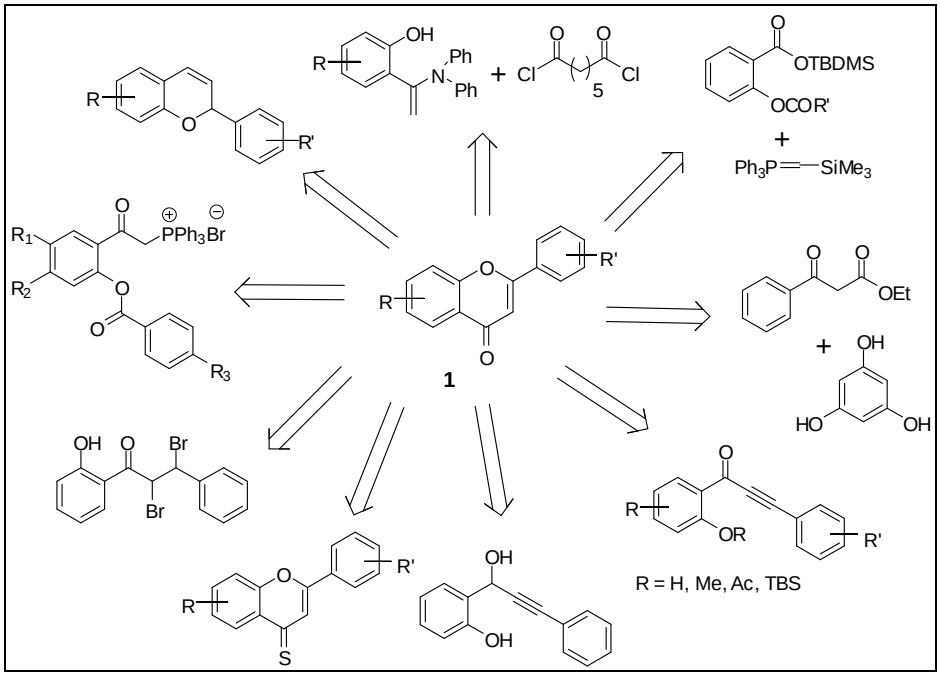
Other routes to obtain flavones have been broadly divided into 5 categories and retrosynthetically depicted as shown in the following schemes. These 5 classes have been categorized on the basis of i) oxidative cyclization of 2'-hydroxychalcones (Scheme 3A), ii) cyclodehydration of 1-(2-hydroxyphenyl)-3-phenyl- propane-1,3- diones (Scheme 3B), iii) dehydrogenation of flavanones (Scheme 3C), iv) metal catalyzed reactions from various substrates (Scheme 4) and v) miscellaneous routes (Scheme 5).



Scheme 3: A) Oxidative cyclization of 2'-hydroxychalcones; **B)** Cyclodehydration of 1-(2-hydroxyphenyl)-3-phenyl-propane-1,3-diones; **C)** Dehydrogenation of flavanones.



Scheme 4: Metal catalyzed reactions from various substrates.



Scheme 5: Miscellaneous routes.

3.3.1: Oxidative cyclization of 2'-hydroxychalcones

Most of the methodologies have been developed by using 2'-hydroxychalcones, 1-(2-hydroxyphenyl)-3-phenyl-propane-1,3-diones and flavanones as substrates. Oxidative

cyclization of 2'-hydroxychalcones using various reagents/catalysts as oxidants have been carried out to form large number of flavone derivatives (Table 3-4).[44-74]

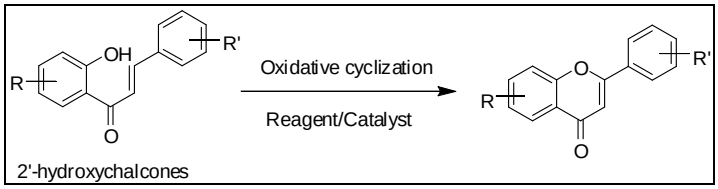


Table 3: Synthesis of flavones by oxidative cyclization of 2'-hydroxychalcones using various reagents.

Sr. No.	Reagent	Reaction condition	Ref.
1)	$Ce(SO_4)_2.4H_2O$	DMSO, 110 °C	44
2)	Silica gel supported $Ce(SO_4)_2 \cdot 4H_2O$	solvent-free, 100 °C	45
3)	ICl-DMSO, ultrasound	50 °C, 30 min	46
4)	Na_2SeO_3-DMSO	heat/MW	47
5)	Na_2TeO_3-DMSO	130-140 °C	48
6)	a) Selenium bromide resin, cat. $ZnCl_2$ b) 30 % H_2O_2	CH_2Cl_2, rt, 12 h THF, 0 °C-rt	49
7)	SeO_2	isoamyl alcohol/DMSO, heat	50
8)	SeO_2, SiO_2	DMSO, MW	51
9)	Sodium perborate tetrahydrate	AcOH, 50-60 °C	52
10)	Ph-S-S-Ph	260-290 °C	53
11)	$FeCl_3.6H_2O$	MeOH, reflux	54
12)	a) NH_4Br-$(NH_4)_2S_2O_8$ b) $Ba(OH)_2$	H_2O, grinding, rt EtOH, grinding, rt	55
13)	Nickel peroxide	benzene	56
14)	PIDA	MeOH, KOH	57
15)	$[EtNH_3]NO_3$	MW, 250 °C	58
16)	Li_2PdCl_4	NaOMe, EtOH/MeCN, rt	59

The diverse reagents used for the oxidative cyclization of 2'-hydroxychalcones are listed in Table 3. Recently, Liu *et al.*[44] reported $Ce(SO_4)_2 \cdot 4H_2O$ mediated synthesis of flavones from 2'-hydroxychalcones in DMSO solvent at 100 °C. Later, the same group[45] developed an environmentally friendly approach using silica gel supported $Ce(SO_4)_2 \cdot 4H_2O$ as an efficient

reagent under solvent-free at 100 °C for the synthesis of flavones. Iodine monochloride in DMSO solvent under ultrasound irradiation was reported by Lahyani and Trabelsi.[46] The cyclization reaction was enhanced by ultrasound irradiation with reduced reaction time and temperature with high yields of flavones. Lamba and Makrandi[47] explored sodium selenite-dimethylsulfoxide reagent for this oxidative cyclization under thermal as well as microwave condition. Similarly, Kumar and Sharma[48] synthesized flavones using sodium tellurite on heating. Huang *et al.*[49] reported $ZnCl_2$ catalysed solid phase oxidative cyclization of 2'-hydroxychalcones using polystyrene supported selenium bromide resin. The oxidative cleavage of selenium resins led to flavones. Selenium dioxide has also been used for synthesis of flavones.[50] Gupta *et al.*[51] later modified the reaction condition by employing selenium dioxide over silica in DMSO solvent under microwave irradiation. Ganguly *et al.*[52] utilized excess of sodium perborate tetrahydrate in acetic acid to convert 2'-hydroxychalcones to flavones. Diphenyl disulphide is another reagent reported by Hoshino *et al.*[53] for this conversion. Kumar and Perumal[54] employed $FeCl_3.6H_2O$ in methanol under reflux condition. Jakhar and Makrandi[55] prepared *α,β*-dibromo-2'-hydroxychalcones using ammonium bromide and ammonium persulphate by grinding at room temperature which were converted to flavones by cyclodebromination using barium hydroxide. Nickel peroxide[56] is also known to give flavones from 2'-hydroxychalcones along with aurones. Flavone product was isolated on treatment of substituted 2'-hydroxychalcone with phenyliodine(III) diacetate (PIDA).[57] Parveen[58] carried out flavone synthesis in ethyl ammonium nitrate ($[EtNH_3]NO_3$) under microwave irradiation. Also, on treatment of lithium chloropalladite (Li_2PdCl_4) with sodium salt of 2'-hydroxychalcones in polar solvent such as ethanol or acetonitrile delivered flavones.[59] However expensive metal used as reagent and flavones accompanied with small amounts of flavanone makes it less efficient.

Table 4: Synthesis of flavones by oxidative cyclization of 2'-hydroxychalcones using various catalysts.

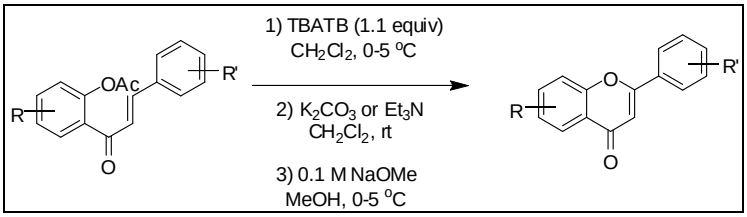
Sr. No.	Catalyst	Reaction condition	Ref.
1)	CuI	[Bmim][NTf_2], O_2 (1 atm), 50 °C	60
2)	CuI	DMA, 130 °C	61
3)	NH_4I	solvent-free, 120 °C	62
4)	Oxalic acid	EtOH, reflux	63
5)	Silica gel supported $InBr_3$ and $InCl_3$	solvent-free, 130-140 °C	64

6)	I_2-SiO_2	80 °C	65
7)	$Na_2PdCl_4.3H_2O$ (10 mol%)	NaOAc, AcOH, *t*-BuOH:H_2O (1:1), *t*-BuOOH, 70 °C	66
8)	I_2	DMSO, reflux	67
9)	I_2	triethylene glycol, 150 °C	68
10)	I_2	solvent-free, 110-130 °C	69
11)	I_2-Al_2O_3	solvent-free, MW, 400 W	70
12)	I_2 (20 mol%)	DMSO, MW	71

Besides these reagents several catalysts have also been reported for the synthesis of flavones from chalcones (Table 4). CuI catalyzed ionic liquid [Bmim][NTf_2] (1-butyl-3-methylimidazolium *bis*(trifluoromethanesulfonyl)imide) mediated *oxa*-Michael-oxidation was disclosed by Wang and co-workers[60] to deliver flavones in good yields. Recently, Chen and Liu[61] also employed CuI in *N*,*N*-dimethylacetamide solvent to synthesize flavones. Varala and co-workers[62] demonstrated the catalytic activity of NH_4I as an alternative source for iodine in this oxidative cyclization under solvent-free condition. Zambare *et al.*[63] carried out the cyclization using oxalic acid catalyst giving flavones in good yields.

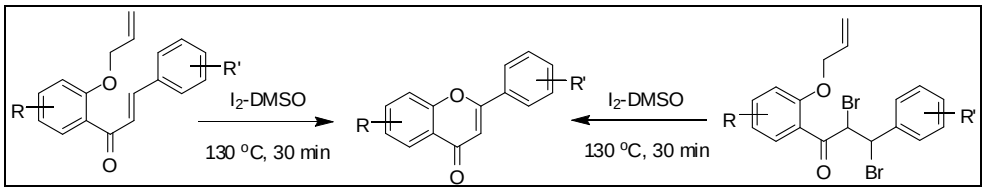
Ahmed *et al.*[64] employed silica gel supported $InBr_3$ and $InCl_3$ catalyst for the conversion of 2'-hydroxychalcones to flavones under solvent-free condition. Madhavarao and co-workers[65] carried out flavones synthesis using silica gel supported iodine (I_2-SiO_2) as an heterogeneous catalyst at 80 °C. Lorenz *et al.*[66] developed a catalytic oxidation procedure employing $Na_2PdCl_4.3H_2O$ catalyst and excess of *t*-BuOOH. Iodine is one of the widely used reagent for flavones synthesis. Catalytic amount of iodine in DMSO solvent,[67] triethylene glycol at 150 °C[68] and solvent-free condition at 110-130 °C[69] are some of the conditions used to deliver flavones.

Also microwave irradiation was reported by several groups to yield flavones in short duration of time. Sarda *et al.*[70] used I_2-Al_2O_3 as an heterogeneous catalyst under solvent-free microwave condition. Our group[71a] also carried out microwave assisted synthesis of flavones using iodine catalyst in DMSO solvent. Later, Borse *et al.*[71b] and Belsare and Kazi[71c] focused on the comparative study of flavones synthesis using iodine catalyst by conventional and microwave methods.



Scheme 6

Bose *et al.*[72] reported an environmentally benign synthesis of natural flavones in 3 steps from 2'-acetoxychalcones through bromination using *n*-tetrabutylammonium tribromide (TBATB) followed by dehydrobromination and finally cyclization (Scheme 6).



Scheme 7

Lokhande *et al.*[73] carried out one pot deprotection of 2'-allyloxychalcones followed by oxidative cyclization on treatment with catalytic iodine in DMSO solvent to deliver flavones. Recently they have also reported flavones synthesis from 2'-allyloxy-*α*-*β*-dibromochalcones *via* deallylation and cyclization leading to the formation of 3-bromoflavanones followed by dehydrobromination using same oxidative reaction condition[74] (Scheme 7).

3.3.2: Cyclodehydration of 1-(2-hydroxyphenyl)-3-phenyl-propane-1,3-diones

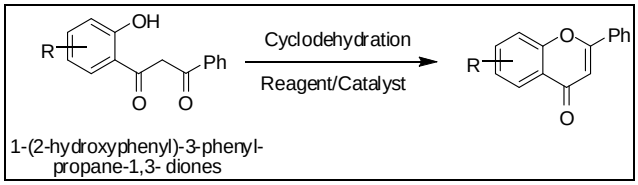


Table 5: Synthesis of flavones by cyclodehydration of 1-(2-hydroxyphenyl)-3-phenyl-propane-1,3-diones by using various reagent.

Sr. No.	Reagent	Reaction condition	Ref.
1)	$[EtNH_3]NO_3$	MW, 22-50 sec	75
2)	$[bmim]BF_4$	100 °C, 45-75 min	76
3)	$AcOH/H_2SO_4$	rt/100 °C	77
4)	Conc. H_2SO_4	CH_3CN, rt	78
5)	AcOH/HCl	100 °C	79
6)	AcOH/HI	100 °C, 2 h	80
7)	I_2	DMSO, heat	81

8)	P_2O_5	grinding, rt, 10-15 min	82
9)	*p*-TSA	grinding, rt	83
10)	Br_2/I_2	h*v*, $CHCl_3$/MeOH	84
11)	Montmorillonite K-10	MW, 1-1.5 min	85
12)	NH_4OAc	solvent-free, heat/MW	86
13)	Silica-H_2SO_4	grinding, rt, 8-9 h	87
14)	Malic acid	solvent-free, heat/MW	88
15)	$CuBr_2$	DMF, 130 °C	89

Another extensively used starting material for flavones synthesis has been 1-(2-hydroxyphenyl)-3-phenyl-propane-1,3-diones which can be converted in presence of various reagents/catalysts *via* cyclodehydration (Table 5-6). Pawar and co-workers[75] carried out flavones synthesis from this substrate in ionic liquid ethyl ammonium nitrate $[EtNH_3]NO_3$ under microwave irradiation. Similarly, ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate [bmim]BF_4 at 100 °C delivered flavones.[76] Acetic acid in presence of conc. H_2SO_4[77] was employed to carry out cyclodehydration. Later, conc. H_2SO_4[78] in acetonitrile solvent has also been used. Acetic acid containing hydrochloric acid[79] or hydriodic acid[80] is also known to give flavones. Heating in presence of iodine in DMSO[81] is another way to obtain flavones. Grinding technique was used by Sharma and Makrandi employing phosphorous pentoxide[82] and by Jakhar and Makrandi using *p*-toluenesulphonic acid[83] to synthesize flavone derivatives. Photochemical transformation using $Br_2/CHCl_3$ or I_2/MeOH[84] is also known. Solid state cyclodehydration was reported by Varma *et al.*[85] using montmorillonite K-10 under microwave irradiation. Recently, ammonium acetate promoted solvent-free synthesis of flavones under thermal and microwave condition.[86] Also, silica-sulphuric acid was utilized as a heterogeneous acidic reusable medium by solvent-free grinding method at room temperature.[87] Natural organic acid like malic acid[88] promoted the solvent-free synthesis of flavones under conventional thermal and microwave heating condition. 3-Bromoflavones were synthesized by employing $CuBr_2$ in DMF.[89]

Table 6: Synthesis of flavones by cyclodehydration of 1-(2-hydroxyphenyl)-3-phenyl-propane-1,3-diones by using various catalysts.

Sr. No.	Catalyst	Reaction condition	Ref.
1)	Tungstophosphoric/molybdoph	AcOH, 90 °C	90

	osphoric acids (bulk/silica supported)		
2)	Trifluoromethanesulfonic acid (supported on titanium, calcined at 100 °C)	toluene, reflux	91
3)	Trifluoromethanesulfonic acid (supported on carbon)	toluene, reflux	92
4)	$H_6P_2W_{18}O_{62}.24H_2O$ (bulk/silica supported)	bulk- solvent-free & silica supported- toluene, 110 °C	93
5)	$H_6P_2W_{18}O_{62}.24H_2O$ (silica supported)	MW, solvent-free	94
6)	Preyssler, Keggin heteropolyacids & Preyssler (silica supported)	solvent-free, 110 °C or $CHCl_3$, reflux	95
7)	Keggin heteropolyacids	$CHCl_3$, reflux or acetonitrile reflux or solvent-free, 110 °C	96
8)	P and Si Keggin heteropolyacids	MeCN	97
9)	Amberlyst 15	isopropyl alcohol, reflux	98
10)	$NaHSO_4$-silica	toluene, reflux, 1-4 h	99
11)	$KHSO_4$, silica	high speed ball milling, 5-15 min	100
12)	$KHSO_4$	solvent-free, 120 °C	101
13)	$FeCl_3$	CH_2Cl_2, rt	102
14)	Silica-PCl_5	solvent-free	103
15)	$TiO_2/H_3PW_{12}O_{40}$	toluene or solvent-free, 110 °C	104
16)	$Ga(OTf)_3$	$MeNO_2$/DCE, 80 °C	105
17)	$InCl_3$	toluene, reflux	106
18)	L-Ascorbic acid	solvent-free heat/MW	107
19)	*bis*-(Trichloromethyl)carbonate/ DMF	CH_2Cl_2, 0 °C to rt, 1.5-3.5 h	108
20)	$CuCl_2$	EtOH, MW, 80 °C, 5 min	109
21)	Proline phenylsulphonylhydrazide or	MeOH, H_2O, 55 °C	110

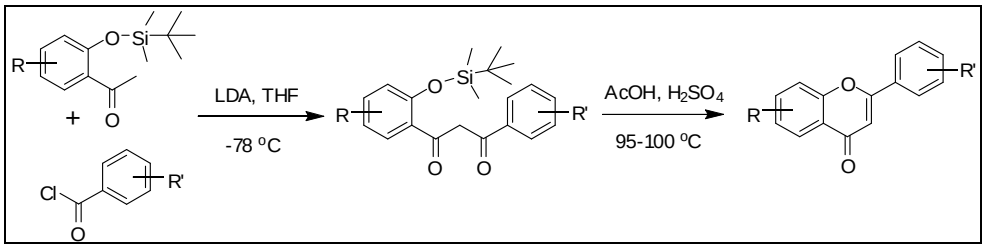
	pyrrolidine		
22)	Co(salpr)(OH)	MeOH, 60 °C	111
23)	*N*-Triflyl phosphoramide	MeOH, 40 °C, 16 h	112

Tungstophosphoric acid ($H_3PW_{12}O_{40}.nH_2O$) or molybdophosphoric acid ($H_3PMo_{12}O_{40}.nH_2O$) both bulk or supported on silica were explored as catalysts for flavones synthesis.[90] Trifluoromethanesulfonic acid supported on titanium after calcined at 100 °C catalyzed cyclodehydration reaction to yield flavones.[91] Trifluoromethanesulfonic acid supported on carbon was also found to catalyze this reaction.[92] Wells-Dawson heteropolyacid $H_6P_2W_{18}O_{62}.24H_2O$ either as bulk under solvent-free or silica supported in toluene at 110 °C was also employed as catalyst.[93] Solvent-free synthesis using silica supported $H_6P_2W_{18}O_{62}.24H_2O$ was also employed under microwave irradiation.[94]

Preyssler structured heteropolyacid catalysts such as $H_{14}[NaP_5W_{30}O_{110}]$, ($H_{14}P_5$), $H_{14}[NaP_5W_{29}MoO_{110}]$, ($H_{14}$-$P_5Mo$) and Keggin structured heteropolyacid catalyst $H_3[PW_{12}O_{40}]$ successfully delivered flavones under solvent-free conditions. Also silica supported Preyssler catalysts $H_{14}[NaP_5W_{30}O_{110}]$, ($H_{14}P_5/SiO_2$ 50 %, $H_{14}P_5/SiO_2$ 40 %, $H_{14}P_5/SiO_2$ 30 %) in refluxing chloroform are effective. [95] Keggin heteropolyacids such as tungstophosphoric acid ($H_3PW_{12}O_{40}.nH_2O$), tungstosilicic acid ($H_4SiW_{12}O_{40}.nH_2O$), molybdophosphoric acid ($H_3PMo_{12}O_{40}.nH_2O$) and molybdosilicic acid ($H_4SiMo_{12}O_{40}.nH_2O$) without or with dehydration at 100 and 200 °C for 6 h were utilized to synthesize flavone in homogeneous condition in refluxing acetonitrile as well as in heterogeneous condition in refluxing toluene. Also molybdophosphoric acid calcined at 100 °C successfully delivered substituted flavones in refluxing acetonitrile and under solvent-free conditions.[96] P and Si Keggin heteropolyacids have also been utilized to obtain flavones.[97] Amberlyst 15, a nonaqueous cation exchange resin is also known to deliver flavones.[98] Kucukislamoglu *et al.*[99] developed flavones synthesis using silica gel supported sodium bisulphate ($NaHSO_4$) catalyst in toluene. Later, Su and co-workers[100] explored the catalytic activity of potassium bisulphate ($KHSO_4$) in presence of silica to synthesize flavones using high speed ball milling technique. Recently, Romanelli and co-workers[101] investigated the catalytic activity and recyclability of $KHSO_4$ to synthesize flavones under solvent-free conditions.

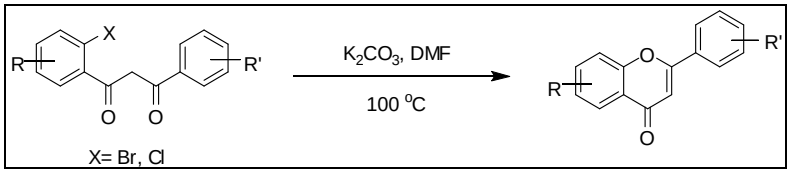
Catalytic $FeCl_3$ was also effective in the dehydrative cyclization reaction.[102] Also an efficient and reusable silica-PCl_5 as solid acid catalyst was utilized to afford flavones under solvent-free conditions.[103] Mesoporous titania/tungstophosphoric acid ($TiO_2/H_3PW_{12}O_{40}$, 10 w/w) composite was prepared and investigated by Pérez *et al.*[104] to synthesize flavones in toluene or solvent-free conditions at 110 °C. Catalytic gallium(III) triflate[105] on heating at 80 °C in

nitromethane or dichloroethane converted 1-(2-hydroxyphenyl)-3-phenyl-propane-1,3-diones to flavones. Similarly, indium(III) chloride[106] in toluene at reflux can be used to carry out intramolecular cyclization. Recently, L-ascorbic acid[107] promoted synthesis of flavones under conventional and microwave heating. Flavones can also be synthesized under Vilsmeier-Haack conditions using *bis*-(trichloromethyl)carbonate and dimethylformamide.[108] Microwave irradiation in presence of 10 mol% $CuCl_2$[109] is another way to acquire flavones. A facile organocatalytic approach employing proline phenylsulphonylhydrazide or pyrrolidine has been developed recently by Yang and co-workers.[110] Co(salpr)(OH)[111] complex is also known to promote cyclization leading to flavones. Recently, an organocatalytic method for the dehydrative cyclization utilizing *N*-triflyl phosphoramide has been developed.[112]



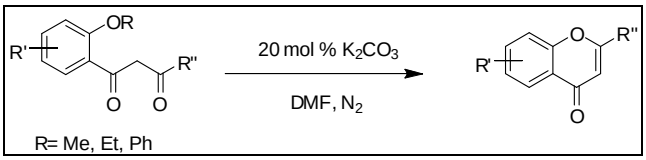
Scheme 8

Ismail and Aziem[113] acylated 2-(*t*-butyldimethylsilyloxy)-4-methoxyacetophenone with acyl chloride using lithium diisopropylamide to form 1-[2'-(*t*-butyldimethylsilyloxy)-3-substituted propane-1,3-diones. These on treatment with glacial acetic acid containing H_2SO_4 on heating delivered flavones through the cleavage of the silyl protecting group followed by cyclization (Scheme 8).



Scheme 9

Fu and co-workers[114] developed an intramolecular Ullmann-type *O*-arylation method which converted substituted 1-(2-haloaryl)-propane-1,3-diones to flavones using K_2CO_3 base in DMF solvent (Scheme 9).



Scheme 10

Also, Fu and co-workers[115] developed a methodology employing K_2CO_3 as a catalyst for flavones synthesis in moderate to good yields. This transition metal free base catalyzed

intramolecular nucleophilic substitution reaction involves selective cleavage of the aromatic C-O bond of 1-(2-alkoxyphenyl)-3-alkylpropane-1,3-diones (Scheme 10).

3.3.3: Dehydrogenation of flavanones

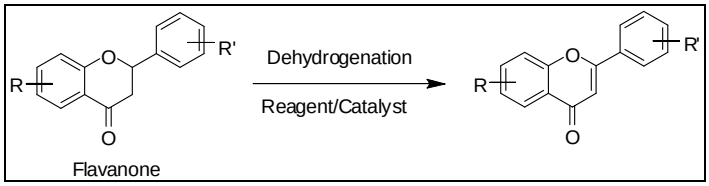


Table 7: Synthesis of flavones from dehydrogenation of flavanone by using various reagents.

Sr. No.	Reagent	Reaction condition	Ref.
1)	SeO_2	xylene, 140-150 °C, 5 h	50a
2)	LTA	90 °C, 2.5 h	116
3)	DDQ	dioxane/ AcOH	117
4)	Ph-S-S-Ph	260-290 °C	53
5)	Nickel peroxide	benzene	56
6)	2,4,6-Triphenylpyrylium tetrafluoroborate	CH_2Cl_2, hν	118
7)	$Tl(NO_3)_3$	MeOH, rt	119
8)	$Tl(OAc)_3$	AcOH or MeOH or MeCN	120
9)	$Mn(OAc)_3$,	$HClO_4$, AcOH, 100 °C, 1 h	121
10)	NBS, cat. AIBN	MW, 10 min	122
11)	Na_2SeO_3-DMSO	heat/MW	47
12)	Nano Fe_3O_4, NiO_2	toluene, 90 °C, 24 h flow reactor	123
13)	PPh_3.HBr	DMSO, 50 °C	124
14)	$PhI(OAc)_2$	MeOH	125
15)	$PhI(OAc)_2$	0.1 N KOH in MeOH, MW, 4-5 min	126
16)	[Hydroxy(tosyloxy)iodo]benzene	MeOH	127
17)	[Hydroxy(tosyloxy)iodo]benzene	($[bbim]^+Br^-$), 60-70 °C, 2-4 h	128
18)	IBX	DMSO, 90 °C, 24 h	129
19)	$CuCl_2.2H_2O$	DMSO, 110 °C	130

Flavanone is another widely used substrate to synthesize flavones *via* dehydrogenation. Several reagents/catalysts have been explored for this conversion (Table 7-8). Selenium dioxide was developed many decades ago to carry out oxidation of flavanones.[50a] Similarly,

lead tetraacetate can also be used.[116] DDQ in dioxane or acetic acid was an effective reagent for dehydrogenation reaction.[117] Diphenyl disulphide[53] is also used for this conversion. Also, the use of nickel peroxide was demonstrated.[56] Photosensitized dehydrogenation of flavanones to flavones was carried out using 2,4,6-triphenylpyrylium tetrafluoroborate.[118] Thallium(III) nitrate[119] and thallium(III) acetate[120] have also been explored for this conversion. Singh *et al.*[121] heated manganese(III) acetate in presence of perchloric acid in acetic acid to synthesize flavones. A highly selective transformation of flavanones to 3-bromoflavones or flavones using *N*-bromosuccinimide (NBS) in presence of catalytic amount of 2,2′-azobis(isobutyronitrile) under microwave irradiation was reported by Yang and co-workers.[122]

Sodium selenite-dimethylsulfoxide[47] combination is also effective for this oxidation process under thermal as well as microwave condition. Flavanone oxidation was carried out by inductive heating of Fe_3O_4 nanoparticles and nickel peroxide as solid oxidant in fixed bed reactors.[123] Recently, the applicability of PPh_3.HBr-DMSO reagent system was unveiled by Das and co-workers[124] in the flavone synthesis.

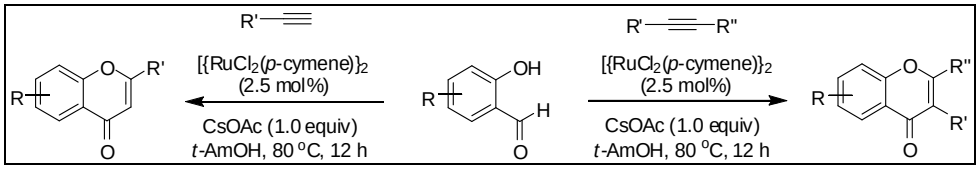
Hypervalent iodine reagent such as (diacetoxyiodo)benzene has also been utilized in flavanone oxidation.[125] Later, it was also studied under microwave irradiation.[126] Similarly, [hydroxy(tosyloxy)iodo]benzene[127] in methanol was explored for this reaction and it was also effective in presence 1,3-di-*n*-butylimadazolium bromide ($[bbim]^+Br^-$) ionic liquid.[128] The ability of 2-iodoxybenzoic acid (IBX) has also been examined for flavanone conversion to flavones.[129] Lokhande *et al.*[130] employed copper (II) chloride for oxidative aromatization of flavanones to obtain flavones in high yields.

Table 8: Synthesis of flavones from dehydrogenation of flavanone by using various catalysts.

Sr. No.	Catalyst	Reaction condition	Ref.
1)	I_2	DMSO	67a
2)	I_2	conc. H_2SO_4, DMSO, 100 °C	131
3)	Silica gel supported $InBr_3$ and $InCl_3$	solvent-free, 130-140 °C, 120 min	64
4)	CuI	[Bmim][NTf_2], O_2 (1 atm), 50 °C, 18 h	60
5)	$Pd(DMSO)_2(TFA)_2$	O_2 (1 atm), AcOH, 100 °C	132
6)	$Pd(TFA)_2$/4,5-diazaflurenone	O_2 (1 atm), DMSO, 100 °C	133

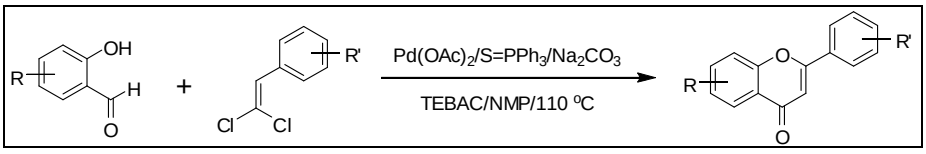
Several catalysts have also been reported for dehydrogenation of flavanones (Table 8). Catalytic iodine[67a, 131] in DMSO solvent alone or in presence of a drop of conc. H_2SO_4 has been used. Silica gel supported $InBr_3$ and $InCl_3$ has also been employed at 130-140 °C to oxidize flavones under solvent-free conditions.[64] Wang and co-workers[60] demonstrated the conversion of parent flavanone to flavone using 10 mol% of CuI in [Bmim][NTf_2] ionic liquid. Diao and Stahl[132] revealed the application of $Pd(DMSO)_2(TFA)_2$ as catalyst using oxygen as an oxidant. Later, another catalytic system containing $Pd(TFA)_2$ and 4,5-diazaflurenone was also developed to carry out flavanone oxidation.[133]

3.3.4: Metal catalyzed reactions from various substrates



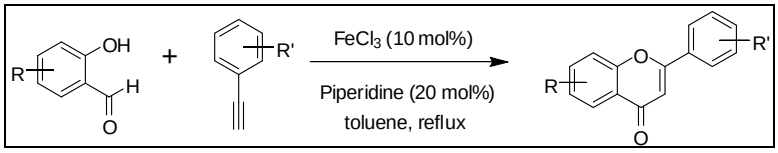
Scheme 11

Gogoi and co-workers[134] carried out Ru(II)-catalyzed C-H activation and annulation reaction between salicylaldehydes and terminal/internal alkynes to afford variety of flavones. Broad substrate scope, lower catalyst loading and high regioselectivity are some of the advantages of this methodology (Scheme 11).



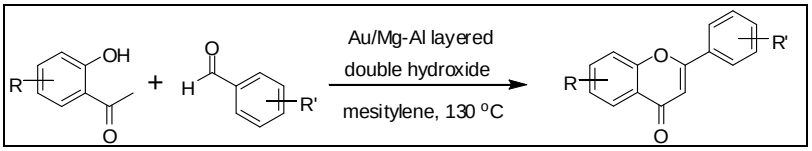
Scheme 12

Liu *et al.*[135] synthesized flavones by a Pd-catalyzed regioselective intramoleular nucleophilic substitution of *gem*-dichloroalkene derivatives with salicylaldehydes. It works well to deliver various flavones in presence of triphenylphosphine sulphide ligand, sodium carbonate base and benzyltrietylammonium chloride as additive (Scheme 12).



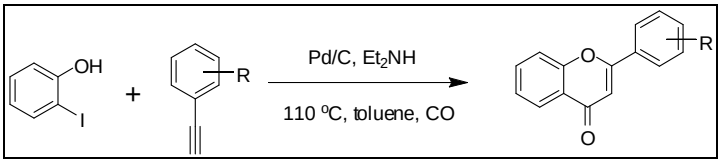
Scheme 13

Maiti *et al.*[136] demonstrated dual catalytic role of $FeCl_3$–Lewis acid and piperidine-an organocatalyst for one pot synthesis of flavones. It involves *o*-hydroxy aromatic aldehydes and phenyl acetylenes as substrates (Scheme 13).



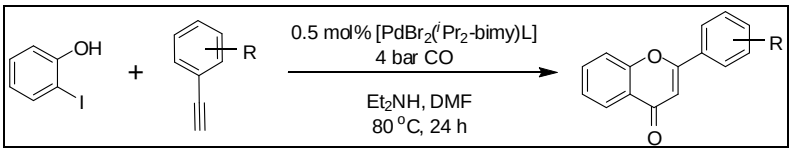
Scheme 14

Mizuno and co-workers[137] developed a one pot flavone synthesis from 2'-hydroxyacetophenones and benzaldehydes using gold nanoparticles supported on a Mg-Al layered double hydroxide (Au/LDH) catalyst in moderate to good yields (Scheme 14).



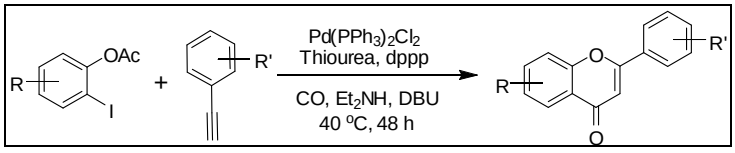
Scheme 15

Zhu *et al.*[138] developed a highly efficient and selective flavone synthesis by Pd/C catalyzed ligand-free cyclocarbonylation reaction between 2-iodophenols and terminal acetylenes in CO atmosphere. Various derivatives were synthesized in excellent yields. Also catalyst was reusable (Scheme 15).



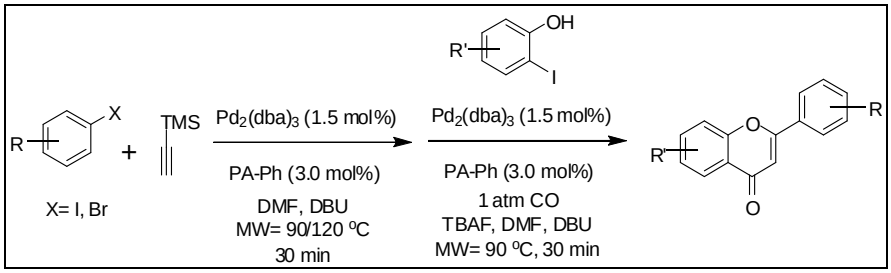
Scheme 16

Carbene complex palladium(II) benzimidazolin-2-ylidene [$PdBr_2$($^{i}Pr_2$-bimy)L] with co-ligand L= *N*-phenylimidazole has been used as a catalyst for flavones synthesis by Li and co-workers[139] from 2-iodophenols and phenyl acetylenes (Scheme 16).

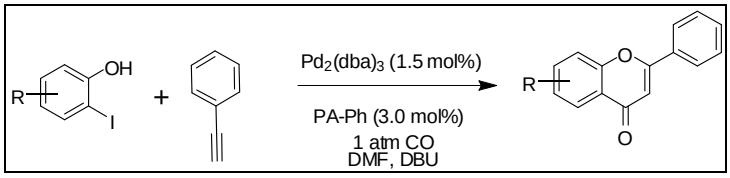


Scheme 17

Miao and Yang[140] reported a regiospecific carbonylative annulation of *o*-iodophenol acetates and acetylenes using catalytic medium containing palladium-thiourea-dppp complex, base and CO at 40 °C (Scheme 17).

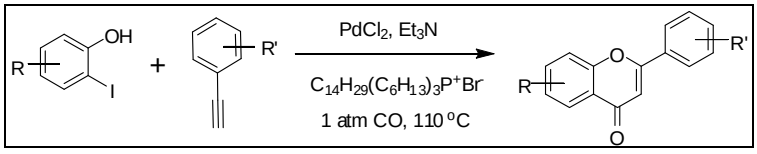


Scheme 18



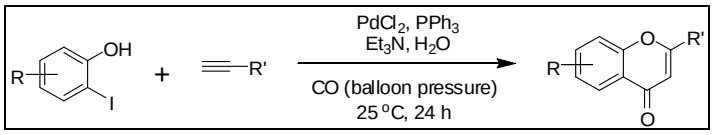
Scheme 19

Awuah and Capretta[141] synthesized flavones through palladium catalyzed microwave-assisted sequential Sonogashira and carbonylative annulation reactions from aryl halide, TMS acetylene and iodophenols in presence of 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane (PA-Ph) ligand (Scheme 18). Also they separately synthesized flavones from carbonylative cyclization of 2-iodophenol and terminal alkynes under this reaction condition (Scheme 19).



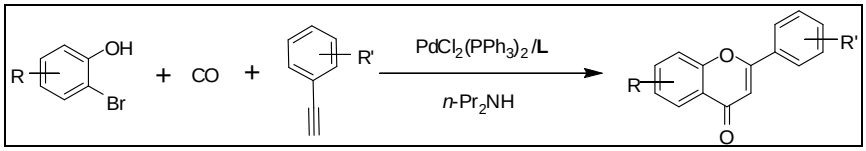
Scheme 20

Yang and Alper[142] synthesized flavones through ligand-free palladium catalyzed cyclocarbonylation of *o*-iodophenols with terminal acetylenes in presence of CO and phosphonium salt ionic liquid $C_{14}H_{29}(C_6H_{13})_3P^+Br^-$. Different derivatives of flavones were obtained in good to excellent yields (Scheme 20).



Scheme 21

Liang *et al.*[143] carried out palladium catalyzed sequential carbonylative coupling of *o*-iodophenols with terminal acetylenes to obtain *α,β*-unsaturated ketones which underwent an intramolecular cyclization to deliver flavones (Scheme 21). The competing side reaction leading to aurones was not observed.



Scheme 22

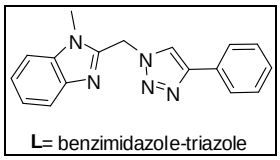
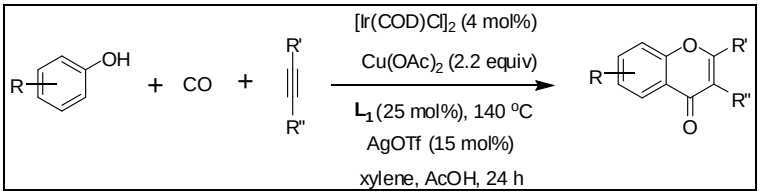


Figure 4

A simple and efficient Pd-catalyzed cascade carbonylative cyclization of 2-bromophenols and phenylacetylenes for the synthesis of flavones was reported by Liu *et al.*[144] The ligand employed in the reaction medium is benzimidazole-triazole (Figure 4) and dipropylamine as solvent (Scheme 22).



Scheme 23

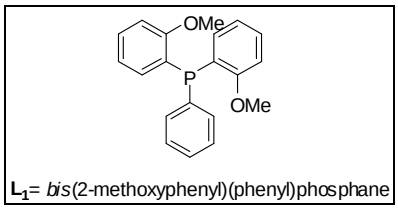
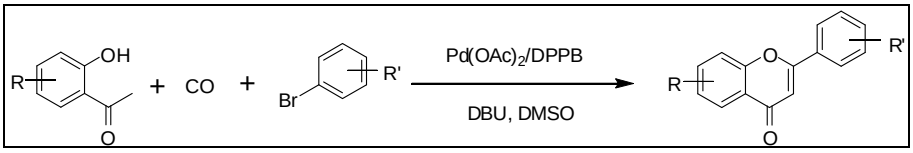


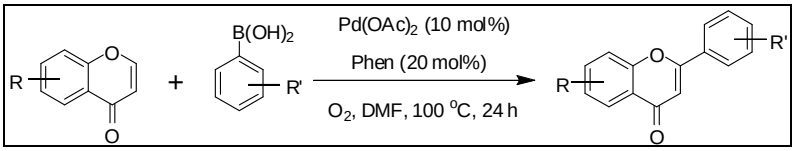
Figure 5

Wu and co-workers[145] developed a carbonylative synthesis of flavones from phenols and internal alkynes using Ir catalyst in presence of $Cu(OAc)_2$ as oxidant and *bis*(2-methoxyphenyl)(phenyl)phosphane **L_1** (Figure 5) as ligand (Scheme 23).



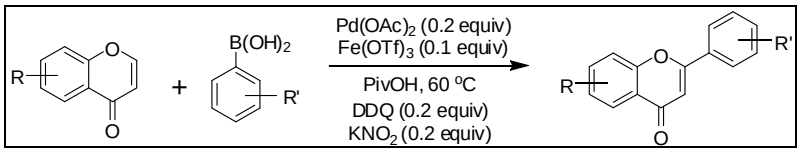
Scheme 24

Wu and co-workers[146] developed a palladium catalyzed carbonylative synthesis of flavones in moderate to good yields from easily available 2'-hydroxyacetophenones and (hetero)aryl bromides in presence of 1,4-*bis*(diphenylphosphino)butane (DPPB) ligand, DBU base and DMSO solvent. This approach is better than other carbonylative reactions as they involve expensive substrates such as 2-iodophenols and terminal/internal alkynes (Scheme 24).



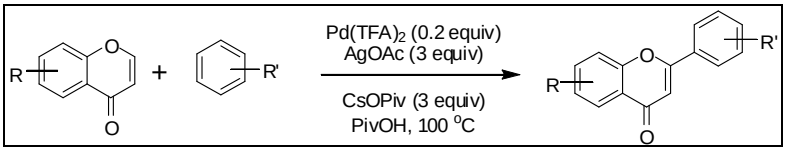
Scheme 25

An oxidative Heck reaction was reported by Jafarpour and Khoobi *et al.*[147] It is an atom economical base-free palladium catalyzed reaction allowing regioselective direct arylation of chromenones to give flavones (Scheme 25).



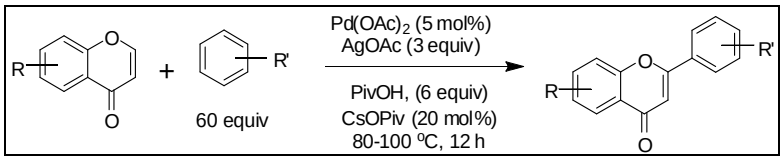
Scheme 26

A palladium catalyzed 1,4-addition of arylboronic acids to chromones has been developed by Hong and co-workers[148] In addition to Pd catalyst, $Fe(OTf)_3$, DDQ and KNO_2 in catalytic amounts were required to obtain flavones in good yields (Scheme 26).



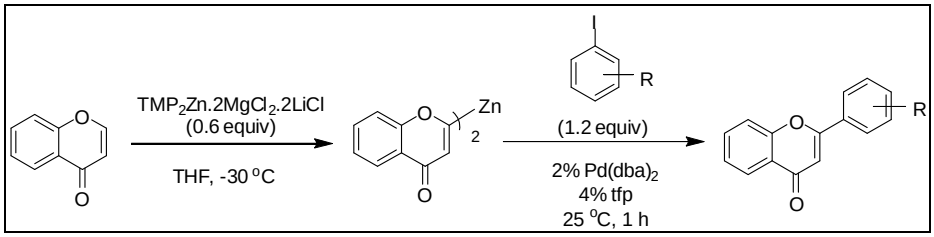
Scheme 27

Pd(II) trifluoroacetate catalyst was employed in the flavones synthesis by Hong and co-workers.[149] It involves oxidative cross coupling of chromones and non-activated arenes *via* twofold C-H functionalization in conjunction of AgOAc/CsOPiv in pivalic acid (PivOH) (Scheme 27).



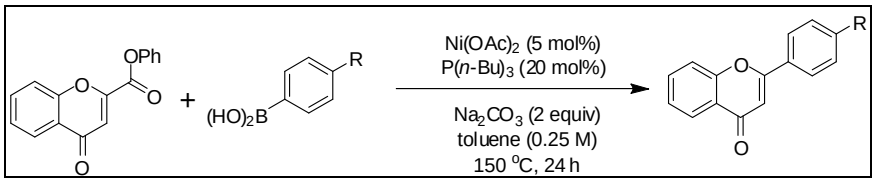
Scheme 28

Kim *et al.*[150] developed a palladium catalyzed oxidative arylation of chromones to give flavones in moderate to good yields. It involves a regioselective 2-arylation of chromone *via* a double C-H activation process (Scheme 28).



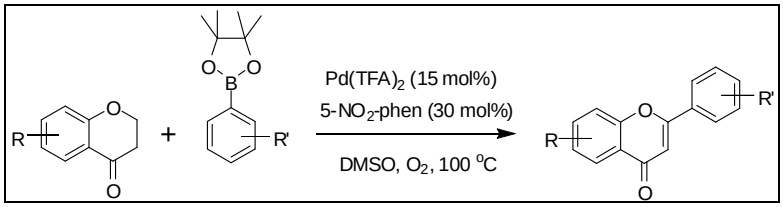
Scheme 29

Regioselective zincation at C-2 using $TMP_2Zn.2MgCl_2.2LiCl$ (TMP = 2,2,6,6-tetramethylpiperidide) was applied for the synthesis of naturally occuring flavones by Klier *et al.*[151] The *bis*-heterocyclic zinc intermediate formed was converted to desired flavone products in presence of Pd catalyst, aryl iodide and *tris*-(2-furyl)phosphine (tfp) (Scheme 29).



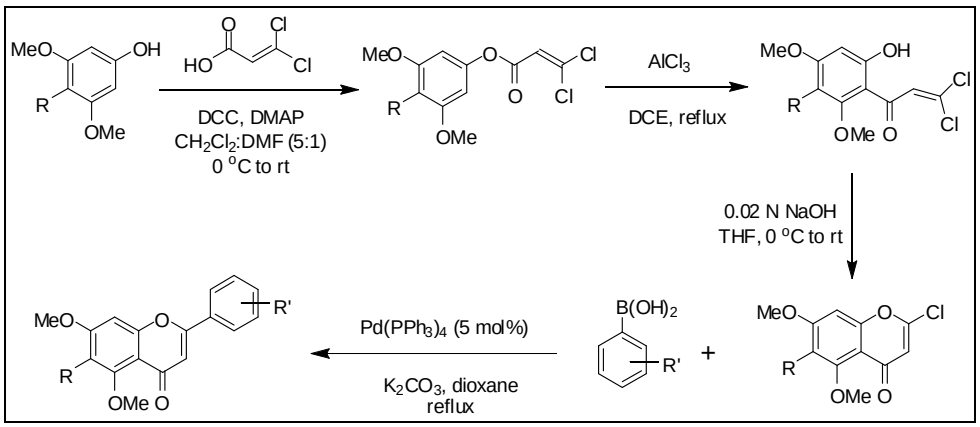
Scheme 30

Two flavone derivatives were synthesized along with several other compounds by Muto *et al.*[152] *via* decarbonylative organoboron cross coupling of corresponding phenyl ester with phenyl boronic acids using nickel catalyst (Scheme 30).



Scheme 31

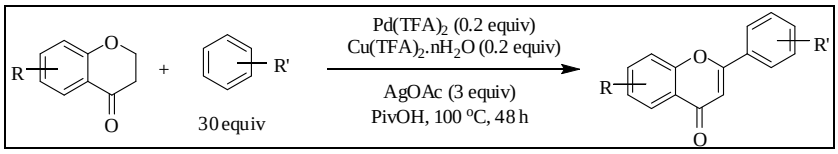
Lee *et al.*[153] reported a one pot synthesis of flavones from chromanones and arylboronic acid pinacol esters by palladium catalyzed dehydrogenation and oxidative boron-Heck coupling. In addition, the methodology is also useful for synthesis of naturally occurring apigenin and luteolin (Scheme 31).



Scheme 32

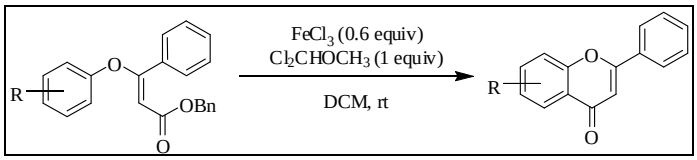
Kraus and Gupta[154] devised a synthetic route to flavones from phenol and 3,3-dichloroacrylic acid using DCC and DMAP. It was converted into ketone by Fries rearrangement using $AlCl_3$

which was further on treatment with dilute base afforded chromones. Finally Suzuki reaction delivered flavones in good yields (Scheme 32).



Scheme 33

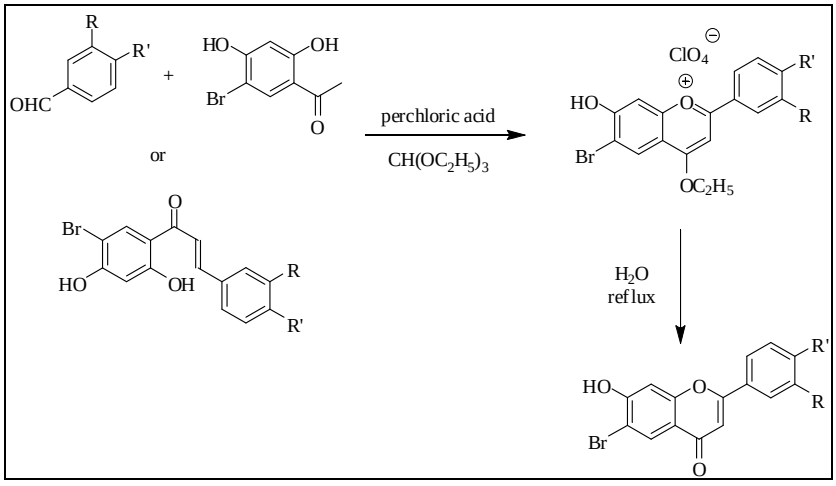
Palladium catalyzed sequential dehydrogenation/arylation of chromanones was carried out successfully by Hong and co-workers[155] in presence of Cu and Ag oxidants. The intermediate chromones formed undergoes oxidative cross-coupling with arenes *via* a twofold C-H functionalization leading to flavones (Scheme 33).



Scheme 34

Jiang *et al.*[156] reported a direct intramolecular acylation of esters using catalytic $FeCl_3$ with 1,1-dichloromethyl methyl ether (Cl_2CHOCH_3) to yield flavones (Scheme 34).

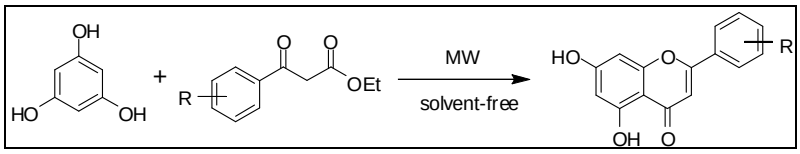
3.3.5: Miscellaneous routes



Scheme 35

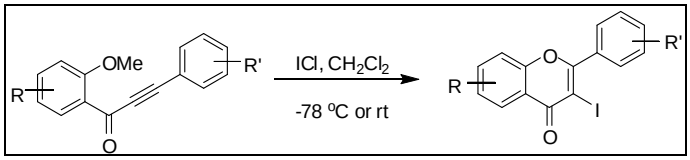
A convenient one pot synthesis of 6-bromo-7-hydroxyflavones was developed by Yakovenko *et al.*[157] from hydrolysis of the substituted 4-ethoxy-6-bromo-7-hydroxyflavylium salts. These salts were obtained either from the corresponding chalcones or by condensation of 5-bromoresacetophenone with the corresponding aryl aldehydes using ethyl orthoformate in the

presence of perchloric acid (Scheme 35). This method has also been utilised for the preparation of a library of synthetic 4'-hydroxyflavones exhibiting casein kinase 2 (CK2) inhibition activity.[158]



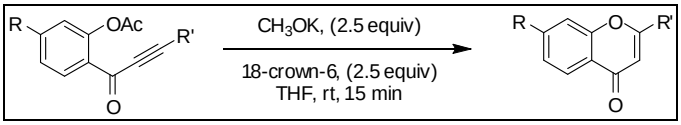
Scheme 36

Seijas *et al.*[159] carried out microwave irradiation of phloroglucinol and *β*–ketoesters under solvent-free condition to deliver flavones. It proceeds *via* a cycloaddition of *α*–oxo ketene intermediate which then undergoes thermal Fries rearrangement in absence of any catalyst (Scheme 36).



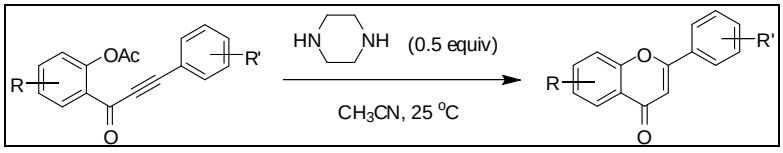
Scheme 37

Larock and co-workers[160] developed ICl induced cyclization of alkynones to 3-iodoflavones in CH_2Cl_2 solvent at low temperature (Scheme 37).



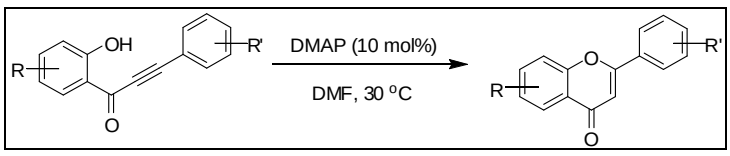
Scheme 38

An efficient method for flavones synthesis was developed by Chuang *et al.*[161] from 6-endo cyclization of *o*-alkynoylphenyl acetates using 18-crown-6 ether in moderate to good yields (Scheme 38).



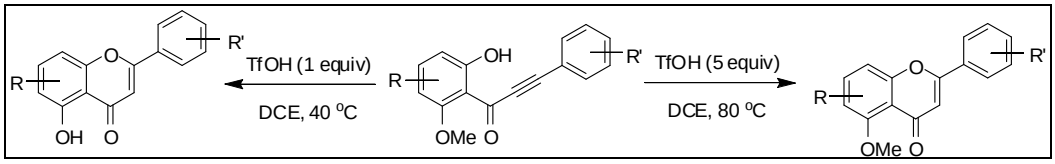
Scheme 39

Similarly, flavones were synthesized in excellent yields *via* 6-endo cyclization of acylated *o*-alkynoylphenols by Yang *et al.*[162] using piperazine catalyst (Scheme 39).



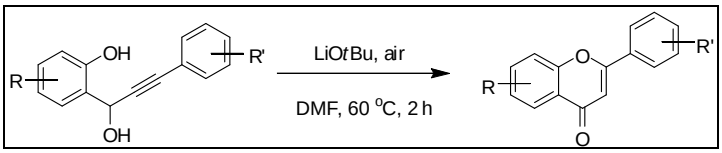
Scheme 40

Doi and co-workers[163] demonstrated DMAP catalyzed 6-endo cyclization of 1-(2-hydroxyphenyl)-2-propyn-1-ones in good yields (Scheme 40).



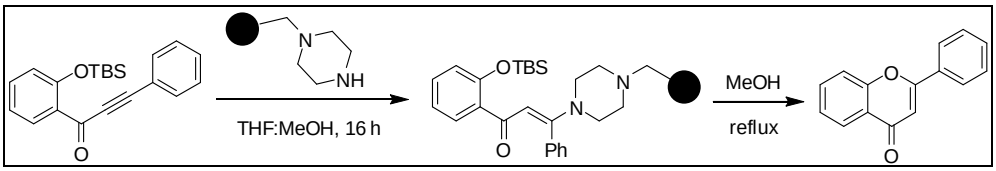
Scheme 41

6-Endo cyclization of *o*-alkynoylphenol compounds was demonstrated by Doi and co-workers[164a] to desired flavone products under acidic condition using trifluoromethanesulfonic acid (TfOH). Also demethylation was observed in 3-methoxy substrates to provide 5-hydroxy flavones derivatives. However, later Taylor and Bolshan[164b] carried out similar cyclization of 3-methoxy-*2*-alkynoylphenol substrates in excess of trifluoromethanesulfonic acid to provide 5-methoxy flavone derivatives without demethylation (Scheme 41).



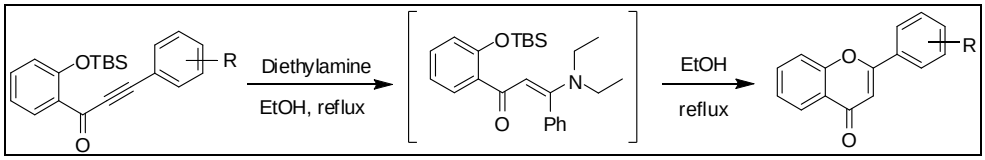
Scheme 42

Also Zhang *et al*.[165] developed LiO*t*Bu mediated synthesis of flavones from substituted 2-(1-hydroxy-3-phenylprop-2yn-1-yl)phenol *via* 6-*endo-dig* cyclization (Scheme 42).



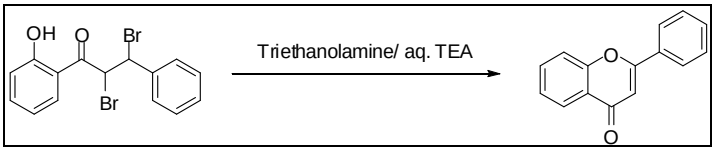
Scheme 43

Resin capture method employing piperazinyl Merrifield resin was developed by Brueggemeier and co-workers[166] for the flavones synthesis. It involves reaction of alkynyl ketone with piperazine thethered to a solid support to form support bound enaminones which undergoes cyclization to deliver final product (Scheme 43).



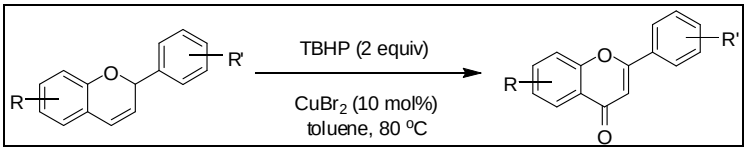
Scheme 44

Brueggemeier and co-workers[167] carried out the cyclization of alkynones on refluxing with 10 equiv of diethylamine to yield flavones *via* enaminoketone intermediate. Dimethylamine and *N*-benzylethylamine also gave similar results (Scheme 44).



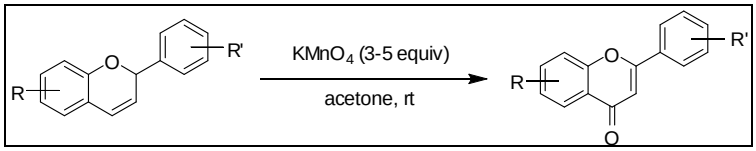
Scheme 45

Agarwal and Soni[168] converted 2'-hydroxy chalcone dibromide to flavones by heating in triethanolamine or aqueous triethylamine for 10-15 min (Scheme 45).



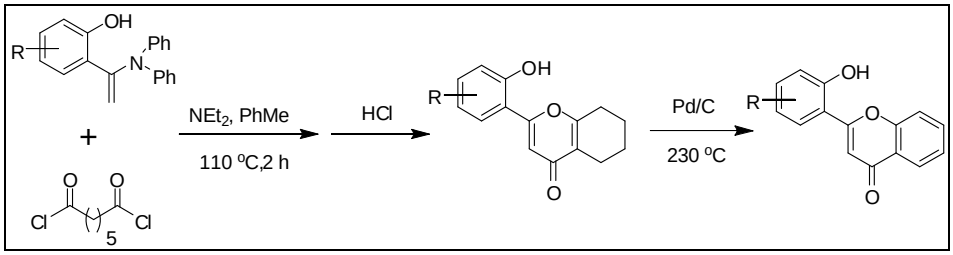
Scheme 46

Oxidative conversion of chromenes to flavones in excellent yields was demonstrated by Banerjee *et al.*[169] using *tert*-butylhydroperoxide and catalytic copper bromide (Scheme 46).



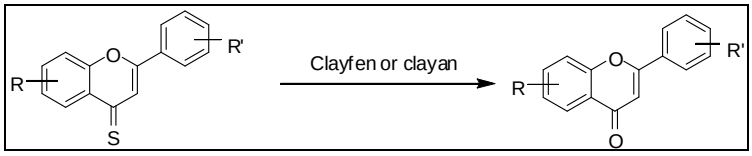
Scheme 47

Nagata and co-workers[170] reported $KMnO_4$ oxidation of chromenes to flavones in acetone solvent at room temperature (Scheme 47).



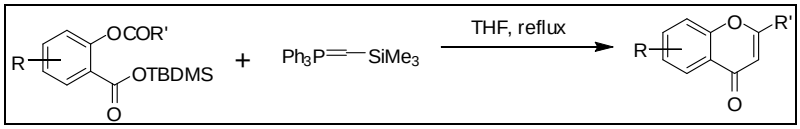
Scheme 48

Ghodile[171] synthesized flavones from substituted 1-(2-hydroxy-5-chlorophenyl)ethyldiphenylamines with heptanedioylchloride to form intermediate which was later dehydrogenated using Pd/C (Scheme 48).



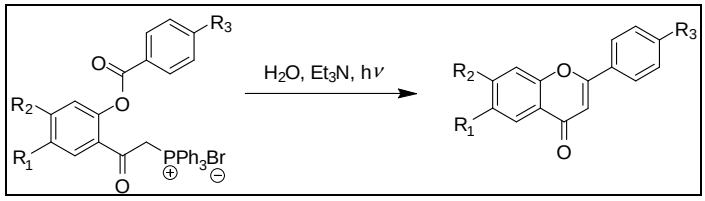
Scheme 49

Varma and Kumar[172] used clay supported nitrite salts “clayfen or clayan” for microwave thermolysis of thioketones under solvent-free condition to form flavones (Scheme 49).



Scheme 50

A method developed by Kumar and Bodas[173] utilised acylphosphoranes prepared by treating silyl ester of *O*-acyl(aroyl)salicylic acids with (trimethylsilyl)-methylenetriphenylphosphorane to furnish flavones in good to excellent yields *via* intramolecular Wittig reaction (Scheme 50).

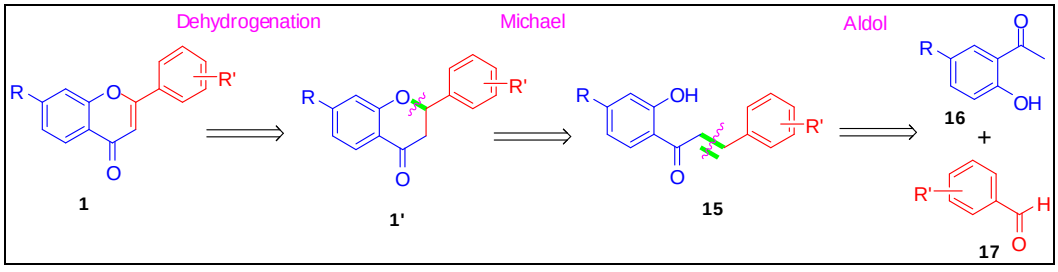


Scheme 51

Similarly, intramolecular photochemical Wittig reaction in water was developed by Das and Ghosh[174] to synthesize flavones from suitable starting materials (Scheme 51).

3.4: Results and Discussion

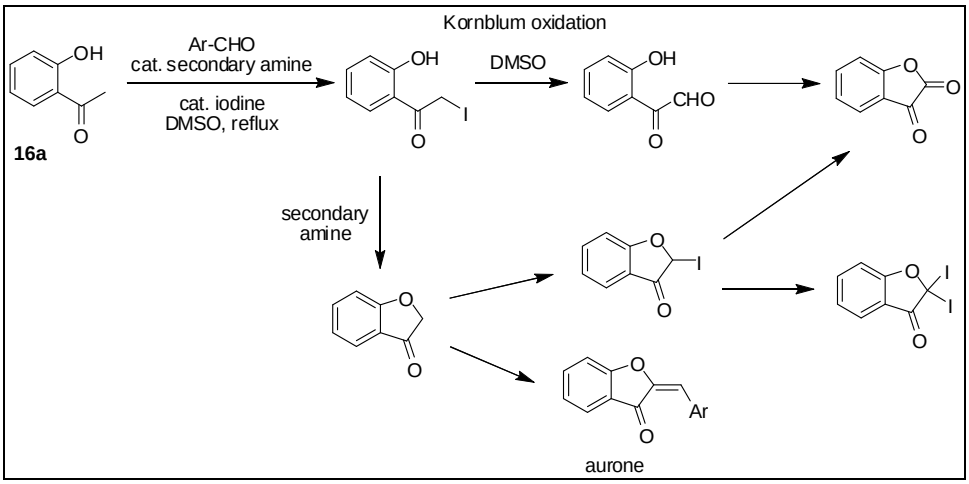
Literature studies showed various routes for the synthesis of flavones. Recently flavanone synthesis is reported using aniline and catalytic amount of iodine from 2'-hydroxyacetophenone and aryl aldehydes.[175] Also it is well known that 2'-hydroxychalcone/flavanone get cyclised to flavone using catalytic iodine in DMSO solvent.[67,71,131] In view of this we speculated that it should be possible to devise a new synthetic route to flavones directly from aryl aldehyde and 2'-hydroxyacetophenone in one pot (Scheme 52). However the use of iodine catalyst from simple substrates in one pot was so far not reported.



Scheme 52: Retrosynthetic analysis of flavones **1**.

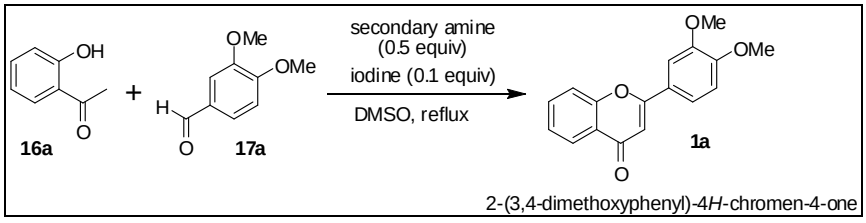
We envisioned that a combination of secondary amine and iodine as oxidant would be a perfect combination for obtaining flavone **1** in one pot. The secondary amine would catalyze the aldol reaction of 2'-hydroxyacetophenone **16** and aromatic aldehydes **17** and also further the intramolecular Michael reaction of the resulting 2'-hydroxychalcone **15** and finally iodine

would bring about the oxidation of *in situ* formed flavanone **1'**. However sequential catalysis has its own limitation. For example, in the present case, firstly iodine and secondary amine should no way interfere with their roles of catalyst in aldol reaction and oxidation i.e. iodine should not poison secondary amine or vice versa. Secondly, regeneration of secondary amine and iodine *via* oxidation of HI by DMSO should also be not affected. Thirdly, α-iodination followed by Kornblum oxidation should not take place. Lastly, the formation of frequently encountered side product aurone, the flavone isomer was to be prevented (Scheme 53).



Scheme 53: Various possible products in the synthesis of flavone **1**.

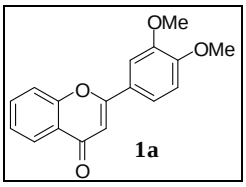
We commenced our work by carrying out a reaction between 2'-hydroxyacetophenone **16a** and 3,4-dimethoxybenzaldehyde **17a** as model substrates in presence of secondary amine and catalytic amount of iodine in DMSO solvent under reflux condition (Scheme 54).



Scheme 54: Synthesis of flavone **1**.

At the outset, various secondary amines such as pyrrolidine, L-proline, piperidine, *N*-methylaniline and morpholine were screened individually (Table 9). To our delight, a new spot was observed when the reaction was carried out using pyrrolidine in DMSO solvent. Its isolation and characterization showed the formation of the desired flavone **1a** in 75 % yield (entry 1). The structure of **1a** was confirmed by the following spectral data.

2-(3,4-Dimethoxyphenyl)-4*H*-chromen-4-one (1a)



1a

colorless solid; m.p. 155-157 °C; lit.[164a] 156-157 °C.

IR (KBr): $\tilde{\nu}$ = 3061, 2841, 1643 (C=O), 1514, 1465, 1145 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.99 (s, 3H), 4.01 (s, 3H), 6.85 (s, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 7.42 (s, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.73 (t, *J* = 8.0 Hz, 1H), 8.25 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 56.2 (2 X OCH_3), 106.0 (CH), 108.9 (CH), 111.2 (CH), 118.1 (CH), 120.4 (CH), 123.4 (Cq), 123.9 (Cq), 125.5 (CH), 125.7 (CH), 134.0 (CH), 149.4 (Cq), 152.4 (Cq), 156.2 (Cq), 164.2 (Cq), 178.4 (Cq).

Other amines such as L-proline and piperidine were also effective to deliver the desired product but with diminished yields (entries 2-3). However, *N*-methylaniline showed two minor spots (not characterized) along with the unreacted substrates whereas morpholine was unreactive under given reaction condition and failed to give the desired product (entries 4-5).

Table 9: Screening of secondary amines in the flavone formation.

Sr. No.	Secondary amine (0.5 equiv)	Time (h)	Yield (%)[a]
1)	Pyrrolidine	2	75
2)	L-proline	3	36
3)	Piperidine	3	22
4)	*N*-methylaniline	2	00[b]
5)	Morpholine	2	00[c]

[a] Isolated yields of **1a**.

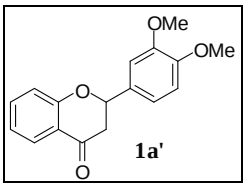
[b] Two minor spots were formed.

[c] No reaction.

With the successful product formation, standardization of various parameters such as pyrrolidine concentration, temperature (neat/DMSO), solvents and iodine concentration were examined in succession. Firstly, the standardization of pyrrolidine was investigated by performing the reaction in absence of iodine. The reaction furnished a new spot which was

characterized as 2-(3,4-dimethoxyphenyl)chroman-4-one **1a'** (Scheme 55) using the following spectral data.

2-(3,4-Dimethoxyphenyl)chroman-4-one (1a')



colorless solid; m.p. 120-122 °C; lit.[176] 123-124 °C.

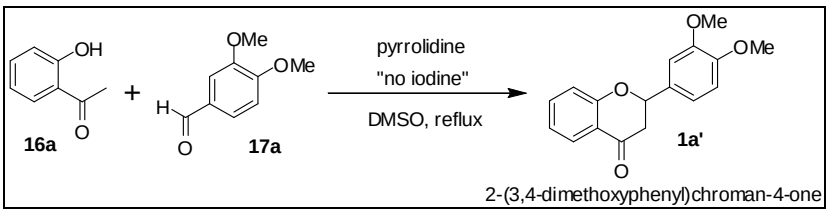
IR (KBr): $\tilde{\nu}$ = 3010, 2837, 1687 (C=O), 1598, 1026 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.88 (dd, *J* = 16.8, 2.4 Hz, 1H), 3.13 (dd, *J* = 16.8, 13.6 Hz, 1H), 3.91 (s, 3H), 3.93 (s, 3H), 5.43 (dd, *J* = 13.2, 2.0 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 7.01-7.08 (m, 4H), 7.51 (t, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 44.6 (CH_2), 55.9 (OCH_3), 56.0 (OCH_3), 79.6 (CH), 109.4 (CH), 111.1 (CH), 118.2 (CH), 118.8 (CH), 120.9 (Cq), 121.6 (CH), 127.1 (CH), 131.2 (Cq), 136.2 (CH), 149.3 (Cq), 149.4 (Cq), 161.6 (Cq), 192.2 (Cq).

The exclusive formation of flavanone **1a'** without flavone formation suggested the mandatory role of iodine as oxidant and discounting the possibilities of oxidation taking place due to dissolved oxygen or DMSO. Also, when flavanone **1a'** (prepared separately) was subjected to heating in DMSO in absence of iodine no flavone formation was observed on TLC even after prolonged heating, thus indicating the role of iodine as an exclusive oxidant.

The amount of pyrrolidine was varied from 0.1-1.5 equiv (Table 10). 0.1 and 0.2 equiv of pyrrolidine were not very effective and resulted in incomplete conversion even after refluxing for prolonged reaction time (entries 1-2). On increasing the concentration to 0.3 equiv the reaction completed in 45 min (entry 3). Similarly, the reaction completed in 15 min when 0.5 and 1 equiv of pyrrolidine were screened (entries 4-5). Further increase to 1.5 equiv reduced the time considerably to 5 min (entry 6). Based on these observations 0.5 equiv of pyrolidine was found to be the optimum concentration and was selected for further studies.

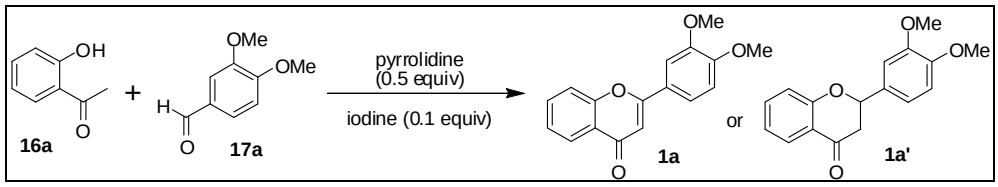


Scheme 55: Synthesis of flavanone **1a'**.

Table 10: Standardization of pyrrolidine in absence of iodine.

Sr. No.	Pyrrolidine (equiv)	Time (min)	Result
1)	0.1	120	Incomplete reaction
2)	0.2	120	Incomplete reaction
3)	0.3	45	Reaction completed
4)	**0.5**	**15**	**Reaction completed**
5)	1.0	15	Reaction completed
6)	1.5	5	Reaction completed

Table 11: Temperature study under neat and in DMSO solvent.



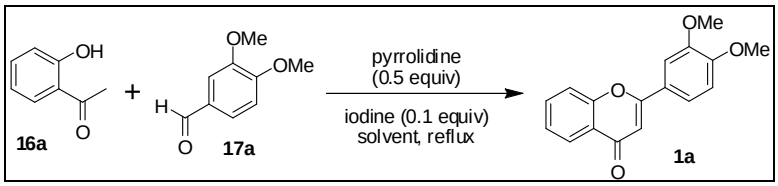
Sr. No.	Solvent	Temperature (°C)	Time (min)	Result
1)	Neat	60	24	Formation of **1a'** No formation of **1a**
2)	Neat	100	24	Formation of **1a'** No formation of **1a**
3)	Neat	150	24	No reaction
4)	DMSO	room temperature	48	No reaction
5)	DMSO	60	24	Formation of **1a'** No formation of **1a**
6)	DMSO	100	24	Formation of **1a'** and little **1a**
7)	DMSO	150	6	Formation of **1a** (80 %)
8)	DMSO	reflux	2	Formation of **1a** (60 %)

Temperature study was carried out under neat condition as well as in DMSO solvent (Table 11). Neat or solvent-less reaction was carried out at different temperatures such as 60, 100 and 150 °C. At 60 °C, the formation of flavanone **1a'** was observed but the desired product **1a** was not seen even after heating for 24 h (entry 1). This may be attributed to the high temperature required for the conversion of flavanone **1a'** to flavone **1a**. Similar results were obtained at 100 °C (entry 2). Further increasing the temperature to 150 °C did not show any

formation of **1a'** or **1a** which may be because of the loss of pyrrolidine from the reaction mixture prior to commencement of reaction owing to high temperature (entry 3).

Next, the temperature studies were performed in DMSO solvent. At room temperature, there was no reaction even after stirring for 48 h (entry 4). On heating at 60 °C, formation of flavanone **1a'** was seen but no flavone **1a** was formed even after heating for 24 h (entry 5). Similarly, at 100 °C, showed formation of flavanone along with the detection of trace amount of flavone **1a** (not isolated) (entry 6). This may be attributed to the high temperature needed for the formation of flavone **1a** from flavanone **1a'**. Further heating the reaction mixture to 150 °C exclusively offered flavone **1a** in 80 % yield in 6 h (entry 7) whereas on refluxing the reaction, the yield got reduced to 60 % (entry 8). Hence, 150 °C was found to be the optimum temperature.

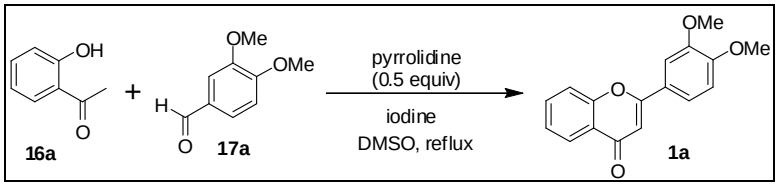
Table 12: Solvent screening.



Sr. No.	Solvent (reflux)	Time (h)	Yield (%)
1)	Ethanol	24	00
2)	Methanol	24	00
3)	Toluene	24	00
4)	Xylene	24	00
5)	Tetrahydrofuran	24	00
6)	**DMSO**	**2**	**75**

Solvent study was performed by carrying out the reaction in various solvents (Table 12). Ethanol, methanol, toluene, xylene and tetrahydrofuran were screened but none of these solvents showed any product formation even after refluxing for 24 h (entries 1-5). The reaction was effective only in DMSO solvent (entry 6).

Table 13: Optimization of iodine concentration at 150 °C.



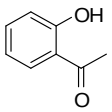
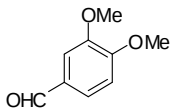
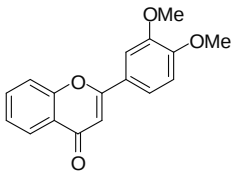
Sr. No.	Iodine (equiv)	Time (h)	Yield (%)
1)	0.01	24	30
2)	**0.05**	**10**	**88**
3)	0.1	6	80
4)	0.15	7	76
5)	0.2	6	38
6)	1.0	24	ND

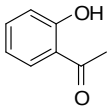
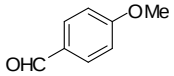
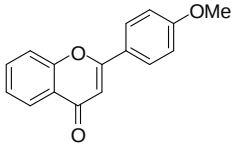
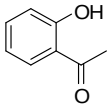
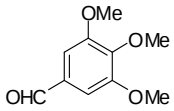
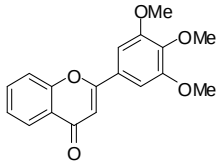
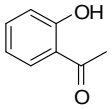
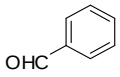
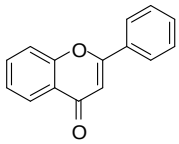
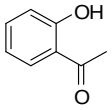
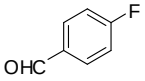
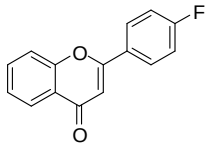
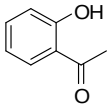
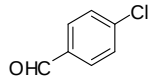
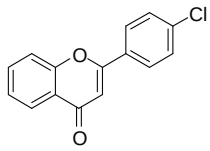
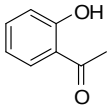
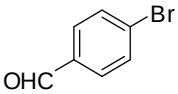
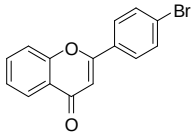
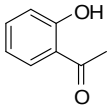
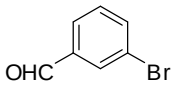
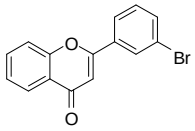
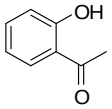
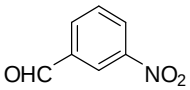
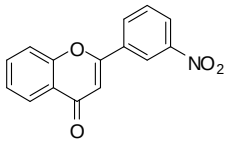
ND: Not Determined.

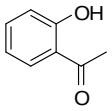
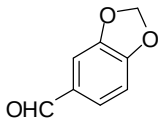
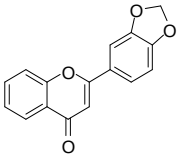
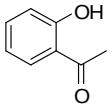
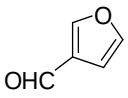
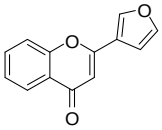
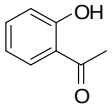
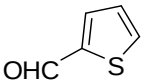
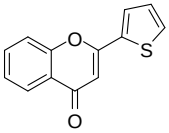
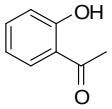
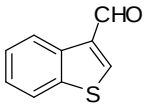
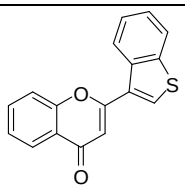
With these observations in hand we persuaded to detect the ideal iodine concentration. It was optimized by varying its concentration from 0.01-1 equiv (Table 13). When 0.01 equiv was employed 30 % of product **1a** was obtained after 24 h (entry 1). A slight increase to 0.05 equiv delivered maximum yield of 88 % (entry 2). Similarly on increasing the iodine concentration to 0.1, 0.15 and 0.2 equiv resulted in 80, 76 and 38 % yields respectively (entries 3-5). 1 equiv of iodine showed trace amount of product on TLC even after 24 h, hence yield of the product was not determined (entry 6). Thus, 5 mo% of iodine was considered as standard iodine concentration.

Scheme 56: Optimum reaction condition used for flavones synthesis.

Table 14: Screening of aromatic aldehydes.

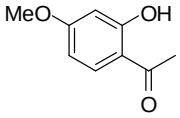
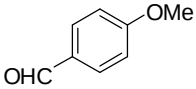
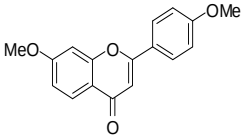
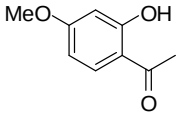
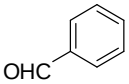
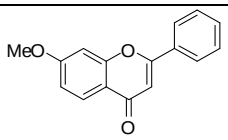
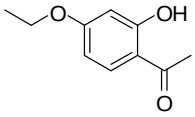
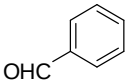
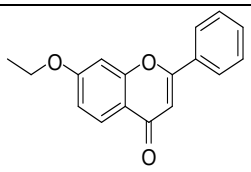
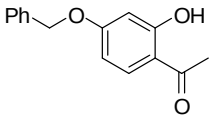
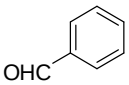
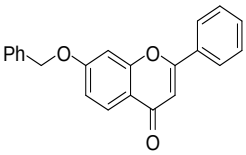
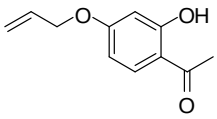
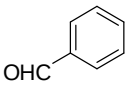
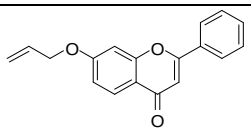
Sr. No.	2'-Hydroxy-acetophenone (16a)	Substituted aromatic aldehydes (17)	Time (h)	Product (1)	Yield (%)
1)	 **16a**	 **17a**	10	 **1a**	88

2)	 **16a**	 **17b**	24	 **1b**	82
3)	 **16a**	 **17c**	7	 **1c**	78
4)	 **16a**	 **17d**	9	 **1d**	85
5)	 **16a**	 **17e**	9	 **1e**	82
6)	 **16a**	 **17f**	12	 **1f**	84
7)	 **16a**	 **17g**	13	 **1g**	80
8)	 **16a**	 **17h**	6	 **1h**	70
9)	 **16a**	 **17i**	12	 **1i**	62

10)	 **16a**	 **17j**	24	 **1j**	74
11)	 **16a**	 **17k**	9	 **1k**	80
12)	 **16a**	 **17l**	6	 **1l**	75
13)	 **16a**	 **17m**	8	 **1m**	72

On obtaining the ideal reaction condition (Scheme 56) in hand, we subjected 2'-hydroxyacetophenone **16a** with various aromatic aldehydes **17a-m** to check the feasibility of our one pot method (Table 14). Electron rich aromatic aldehydes **17a-c** furnished desired flavones **1a-c** in good yields (entries 1-3). Benzaldehyde **17d** also smoothly reacted to form required product **1d** in good yield (entry 4). Aromatic aldehydes with *p*-halogen atoms (fluoro, chloro, bromo) were well tolerated to provide flavones **1e-1g** in good yields which are good scaffolds for further functionalization (entries 5-7). *m*-Bromobenzaldehyde **17h** as well as *m*-nitrobenzaldehyde **17i** with electron withdrawing groups at *m*-position delivered flavones **1h** and **1i** but with slightly diminished yields (entries 8-9). Thus our methodology could be applied to both electron rich as well as electron deficient aromatic aldehydes which are well tolerated under the reaction condition as the yields were unchanged on changing the substituent. Furthermore, 3,4-methylenedioxy benzaldehyde **17j** smoothly furnished the desired flavone **1j** in satisfactory yield (entry 10). Reports have shown that the biological activity of flavones is enhanced when 5 or 6 membered heterocyclic group is attached at its C-2 position.[160,177] Motivated from this we subjected different heterocyclic aromatic aldehydes to the reaction condition to achieve the desired products **1k-1m** in good yields (entries 11-13).

Table 15: Screening of 2'-hydroxyacetophenones.

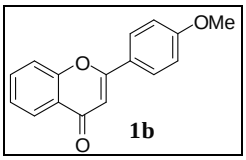
Sr. No.	Substituted 2'-hydroxy-acetophenone (16b-e)	Substituted aromatic aldehydes (17)	Time (h)	Product (1)	Yield (%)
1)	 **16b**	 **17b**	8	 **1n**	81
2)	 **16b**	 **17d**	10	 **1o**	88
3)	 **16c**	 **17d**	12	 **1p**	78
4)	 **16d**	 **17d**	12	 **1q**	60
5)	 **16e**	 **17d**	8	 **1r**	70

After scanning aromatic aldehydes, substituted 2'-hydroxyacetophenones **16b-e** were put forth for determining the substrate scope (Table 15). 4-Methoxy-2'-hydroxyacetophenone **16b** was reacted with benzaldehydes **17b** and **17d** to provide flavones **1n**-**o** in good yields (entries 14-15). Similarly, 4-ethoxy-2'-hydroxyacetophenone **16c** and 4-benzyloxy-2'-hydroxyacetophenone **17d** reacted under standardized condition to furnish respective flavones **1p** and **1q** in reasonable yields (entries 16-17). One of the reports had shown deprotection of 2'-allyloxychalcone leading to flavone in I_2-DMSO.[73] Interestingly, we got the desired flavone **1r** from 4-allyloxy-2'-hydroxyacetophenone **16e** without the cleavage of the allyloxy group (entry 18). It could be due to the difference in the position of the allyloxy group as 2'-

position is comparatively more reactive one. The reaction protocol was also successfully scaled up to 5 g of starting aryl aldehyde **17a** to get consistent yield of desired flavone **1a**. Although the literature survey shows a one pot method[157] with perchloric acid and ethyl chloroformate (Scheme 35) but our approach is an alternative route avoiding the use of explosive perchloric acid.

Spectral data of flavones

2-(4-Methoxyphenyl)-4*H*-chromen-4-one (1b)



1b

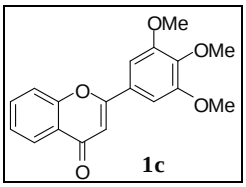
yield (0.152 g, 82 %); colorless solid; m.p. 154-156 °C; lit.[65] 154-156 °C.

IR (KBr): $\tilde{\nu}$ = 3051, 1641 (C=O), 1465, 1377, 1026 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.88 (s, 3H), 6.77 (s, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.68 (t, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 2H), 8.22 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.5 (OCH_3), 106.1 (CH), 114.5 (2 X CH), 117.9 (CH), 123.9 (Cq), 123.9 (Cq), 125.1 (CH), 125.7 (CH), 128.0 (2 X CH), 133.6 (CH), 156.2 (Cq), 162.4 (Cq), 163.5 (Cq), 178.5 (Cq).

2-(3,4,5-Trimethoxyphenyl)-4*H*-chromen-4-one (1c)



1c

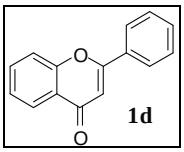
yield (0.179 g, 78 %); colorless solid; m.p. 175-177 °C; lit.[164a] 176-178 °C.

IR (KBr): $\tilde{\nu}$ = 3076, 1641 (C=O), 1467, 1367, 1128 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.94 (s, 3H), 3.97 (s, 6H), 6.79 (s, 1H), 7.14 (s, 2H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.71 (t, *J* = 8.0 Hz, 1H), 8.23 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 56.3 (2 X OCH_3), 61.1 (OCH_3), 103.7 (2 X CH), 107.4 (CH), 118.1 (CH), 123.9 (Cq), 125.3 (CH), 125.7 (CH), 126.9 (Cq), 133.8 (CH), 141.2 (Cq), 153.6 (2 X Cq), 156.2 (Cq), 163.3 (Cq), 178.4 (Cq).

2-Phenyl-4*H*-chromen-4-one (1d)



1d

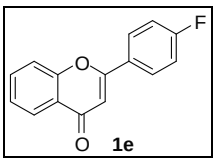
yield (0.139 g, 85 %); colorless solid; m.p. 94-96 °C; lit.[164a] 95-97 °C.

IR (KBr): $\tilde{\nu}$ = 3070, 1643 (C=O), 1465, 1375, 1130 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.88 (s, 1 H), 7.45 (t, *J* = 7.6 Hz, 1 H), 7.53-7.61 (m, 4 H), 7.73 (t, *J* = 8.8 Hz, 1 H), 7.94-7.96 (m, 2 H), 8.25 (dd, *J* = 8.0, 1.2 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 107.6 (CH), 118.1 (CH), 123.9 (Cq), 125.3 (CH), 125.7 (CH), 126.4 (2 X CH), 129.1 (2 X CH), 131.7 (CH), 131.7 (Cq), 133.9 (CH), 156.3 (Cq), 163.5 (Cq), 178.6 (Cq).

2-(4-Fluorophenyl)-4*H*-chromen-4-one (1e)



1e

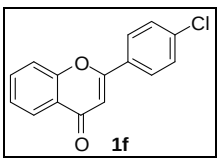
yield (0.145 g, 82 %); colorless solid; m.p. 144-146 °C; lit.[178] 145-148 °C.

IR (KBr): $\tilde{\nu}$ = 3076, 1662 (C=O), 1508, 1234, 835 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.78 (s, 1H), 7.22 (t, *J* = 8.4 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.71 (t, *J* = 7.6 Hz, 1H), 7.93 (t, *J* = 7.6 Hz, 2H), 8.23 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 107.3 (CH), 116.2 (CH), 116.4 (CH), 118.0 (CH), 123.8 (Cq), 125.3 (CH), 125.7 (CH), 127.8 (Cq), 127.9 (Cq), 128.4 (CH), 128.5 (CH), 133.9 (CH), 156.1 (Cq), 162.3 (Cq), 163.5 (Cq), 165.9 (Cq), 178.3 (Cq).

2-(4-Chlorophenyl)-4*H*-chromen-4-one (1f)



1f

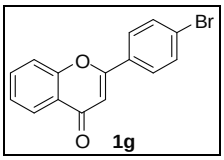
yield (0.159 g, 84 %); colorless solid; m.p. 186-188 °C; lit.[179] 187-188 °C.

IR (KBr): $\tilde{\nu}$ = 3072, 1639 (C=O), 1467, 1375, 1093, 754 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.79 (s, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.69 (t, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 8.20 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 107.5 (CH), 118.0 (CH), 123.8 (Cq), 125.4 (CH), 125.7 (CH), 127.5 (2 X CH), 129.4 (2 X CH), 130.1 (Cq), 133.9 (CH), 137.9 (Cq), 156.1 (Cq), 162.2 (Cq), 178.4 (Cq).

2-(4-Bromophenyl)-4*H*-chromen-4-one (1g)



1g

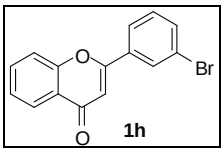
yield (0.176 g, 80 %); colorless solid; m.p. 174-177 °C; lit.[180] 177 °C.

IR (KBr): $\tilde{\nu}$ = 3086, 1666 (C=O), 1465, 1259, 1130 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.79 (s, 1H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.65 (dt, *J* = 8.8, 1.6 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 8.16 (dd, *J* = 8.0, 1.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 107.7 (CH), 118.1 (CH), 123.9 (Cq), 125.4 (CH), 125.9 (CH), 126.4 (Cq), 127.8 (2 X CH), 130.7 (Cq), 132.4 (2 X CH), 133.9 (CH), 156.2 (Cq), 162.4 (Cq), 178.3 (Cq).

2-(3-Bromophenyl)-4*H*-chromen-4-one (1h)



1h

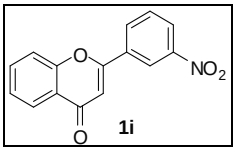
yield (0.154 g, 70 %); colorless solid; m.p. 113-115 °C; lit.[180] 115 °C.

IR (KBr): $\tilde{\nu}$ = 3064, 1641 (C=O), 1467, 1261, 1128 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.77 (s, 1H), 7.30-7.38 (m, 2H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.65 (dt, *J* = 8.4, 1.6 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 8.00 (s, 1H), 8.15 (dd, *J* = 8.0, 1.2 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 108.1 (CH), 118.2 (CH), 123.3 (Cq), 123.8 (Cq), 124.9 (CH), 125.6 (CH), 125.8 (CH), 129.3 (CH), 130.6 (CH), 133.7 (Cq), 134.2 (CH), 134.6 (CH), 156.2 (Cq), 161.9 (Cq), 178.4 (Cq).

2-(3-Nitrophenyl)-4*H*-chromen-4-one (1i)



1i

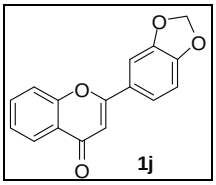
yield (0.122 g, 62 %); colorless solid; m.p. 194-197 °C; lit.[148] 195-198 °C.

IR (KBr): $\tilde{\nu}$ = 3086, 1643 (C=O), 1527, 1350, 1138 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.87 (s, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.67-7.72 (m, 2H), 8.17 (dd, *J* = 7.6, 1.6 Hz, 2H), 8.33 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.75 (t, *J* = 1.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 108.8 (CH), 118.2 (CH), 121.3 (CH), 123.8 (Cq), 125.8 (CH), 125.9 (CH), 126.0 (CH), 130.4 (CH), 131.8 (CH), 133.6 (Cq), 134.4 (CH), 148.8 (Cq), 156.2 (Cq), 160.6 (Cq), 178.2 (Cq).

2-(1,3-Benzodioxol-5-yl)-4*H*-chromen-4-one (1j)



1j

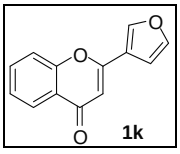
yield (0.145 g, 74 %); colorless solid; m.p. 196-198 °C; lit.[49a] 198-200 °C.

IR (KBr): $\tilde{\nu}$ = 3078, 1643 (C=O), 1446, 1346, 1026 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.09 (s, 2H), 6.72 (s, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 7.38 (s, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.50-7.56 (m, 2H), 7.69 (t, *J* = 8.4 Hz, 1H), 8.22 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 101.9 (CH_2), 106.3 (CH), 106.6 (CH), 108.8 (CH), 117.9 (CH), 121.5 (CH), 123.9 (Cq), 125.2 (CH), 125.7 (CH, Cq), 133.7 (CH), 148.5 (Cq), 150.7 (Cq), 156.1 (Cq), 163.1 (Cq), 178.4 (Cq).

2-(Furan-3-yl)-4*H*-chromen-4-one (1k)



1k

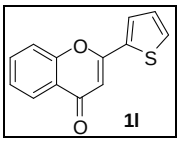
yield (0.125 g, 80 %); colorless solid; m.p. 118-119 °C; lit.[181] 119 °C.

IR (KBr): $\tilde{\nu}$ = 3118, 1631 (C=O), 1463, 1357, 756 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.54 (s, 1H), 6.76 (s, 1H), 7.42 (d, *J* = 5.6 Hz, 1H), 7.50 (s, 1H), 7.56 (s, 1H), 7.69 (d, *J* = 5.6 Hz, 1H), 8.09 (s, 1H), 8.22 (s, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 107.2 (CH), 107.6 (CH), 117.9 (CH), 120.3 (Cq), 123.9 (Cq), 125.2 (CH), 125.7 (CH), 133.8 (CH), 143.1 (CH), 144.7 (CH), 156.0 (Cq), 158.8 (Cq), 178.2 (Cq).

2-(Thiophen-2-yl)-4*H*-chromen-4-one (1l)



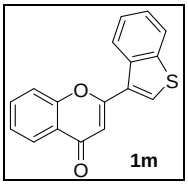
yield (0.126 g, 75 %); colorless solid; m.p. 90-92 °C; lit.[182] 91-94 °C.

IR (KBr): $\tilde{\nu}$ = 3072, 1631 (C=O), 1460, 1261, 1126 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.71 (s, 1H), 7.11 (t, *J* = 4.0 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.52 (d, *J* = 5.2 Hz, 1H), 7.62 (dt, *J* = 8.4, 2.0 Hz, 1H), 7.67 (d, *J* = 3.6 Hz, 1H), 8.13 (dd, *J* = 8.0, 1.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 104.9 (CH), 116.9 (CH), 122.7 (Cq), 124.4 (CH), 124.7 (CH), 127.6 (CH), 127.8 (CH), 129.6 (CH), 132.9 (CH), 133.9 (Cq), 154.9 (Cq), 158.4 (Cq), 176.9 (Cq).

2-(Benzo[*b*]thiophen-3-yl)-4*H*-chromen-4-one (1m)



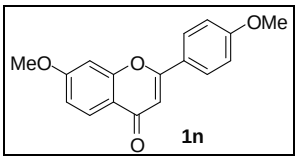
yield (0.147 g, 72 %); colorless solid; m.p. 142-144 °C.[146]

IR (KBr): $\tilde{\nu}$ = 3082, 1629 (C=O), 1465, 1220, 1118 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.77 (s, 1H), 7.35-7.47 (m, 3H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.63-7.67 (m, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 8.04 (s, 1H), 8.18-8.22 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 109.4 (CH), 118.0 (CH), 123.2 (CH), 123.4 (CH), 124.0 (Cq), 125.4 (CH), 125.5 (CH), 125.8 (CH), 128.9 (Cq), 130.5 (CH), 133.9 (CH), 135.5 (Cq), 140.7 (Cq), 156.3 (Cq), 160.4 (Cq), 178.4 (Cq).

7-Methoxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (1n)



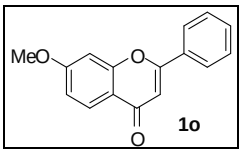
yield (0.168 g, 81 %); colorless solid; m.p. 140-142 °C; lit.[180] 143 °C.

IR (KBr): $\tilde{\nu}$ = 2983, 1653 (C=O), 1438, 1265, 1184 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.81 (s, 3H), 3.86 (s, 3H), 6.76 (s, 1H), 6.89-6.95 (m, 4H), 7.80 (d, *J* = 8.8 Hz, 2H), 8.05 (d, *J* = 8.4 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.5 (OCH_3), 55.9 (OCH_3), 100.4 (CH), 105.5 (CH), 114.5 (2 X CH), 114.6 (CH), 117.2 (Cq), 123.8 (Cq), 126.9 (CH), 128.1 (2 X CH), 158.0 (Cq), 162.5 (Cq), 163.7 (Cq), 164.4 (Cq), 177.8 (Cq).

7-Methoxy-2-phenyl-4*H*-chromen-4-one (1o)



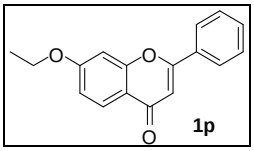
yield (0.163 g, 88 %); colorless solid; m.p. 104-106 °C; lit.[164a] 105-106 °C.

IR (KBr): $\tilde{\nu}$ = 3059, 1654 (C=O), 1438, 1274, 1165 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.96 (s, 3H), 6.81 (s, 1H), 7.00-7.04 (m, 2H), 7.54-7.56 (m, 3H), 7.93-7.96 (m, 2H), 8.15-8.18 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.8 (OCH_3), 100.3 (CH), 107.3 (CH), 114.5 (CH), 117.6 (Cq), 126.1 (2 X CH), 126.9 (CH), 128.9 (2 X CH), 131.5 (CH), 131.6 (Cq), 157.9 (Cq), 163.0 (Cq), 164.2 (Cq), 177.9 (Cq).

7-Ethoxy-2-phenyl-4*H*-chromen-4-one (1p)



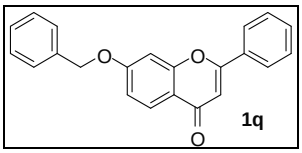
yield (0.153 g, 78 %); colorless solid; m.p. 136-138 °C; lit.[183] 138-139 °C.

IR (KBr): $\tilde{\nu}$ = 2983, 1631 (C=O), 1494, 1246, 1180 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.42 (t, *J* = 6.8 Hz, 3H), 4.09 (q, *J* = 6.8 Hz, 2H), 6.70 (s, 1H), 6.88-6.92 (m, 2H), 7.43-7.47 (m, 3H), 7.82-7.85 (m, 2H), 8.06 (d, *J* = 8.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.6 (CH_3), 64.3 (CH_2), 100.8 (CH), 107.5 (CH), 114.8 (CH), 117.7 (Cq), 126.2 (2 X CH), 126.9 (CH), 129.0 (2 X CH), 131.4 (CH), 131.9 (Cq), 158.0 (Cq), 162.9 (Cq), 163.6 (Cq), 177.9 (Cq).

7-(Benzyloxy)-2-phenyl-4*H*-chromen-4-one (1q)



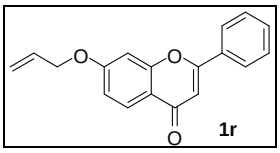
yield (0.144 g, 60 %); colorless solid; m.p. 173-175 °C; lit.[184] 174-175 °C.

IR (KBr): $\tilde{\nu}$ = 3066, 1635 (C=O), 1450, 1253, 1180 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.11 (s, 2H), 6.81 (d, *J* = 6.8 Hz, 1H), 6.99 (s, 1H), 7.01 (s, 1H), 7.29-7.45 (m, 8H), 7.83 (d, *J* = 7.2 Hz, 2H), 8.07 (d, *J* = 8.4 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 70.6 (CH_2), 101.5 (CH), 107.3 (CH), 115.2 (CH), 117.7 (Cq), 126.3 (2 X CH), 127.2 (CH), 127.6 (2 X CH), 128.5 (CH), 128.8 (2 X CH), 129.1 (2 X CH), 131.7 (CH), 135.7 (Cq), 158.0 (Cq), 163.5 (Cq), 177.9 (Cq).

7-Allyloxy-2-phenyl-4*H*-chromen-4-one (1r)



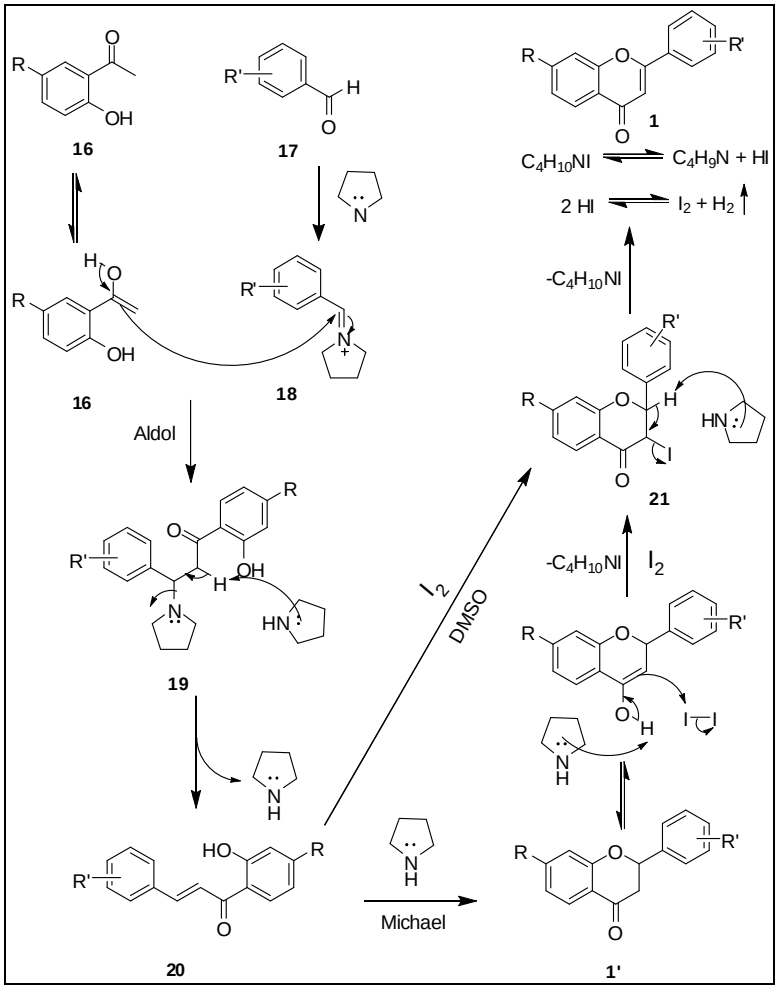
yield (0.143 g, 70 %); colorless solid; m.p. 94-96 °C; lit.[185] 95-96 °C.

IR (KBr): $\tilde{\nu}$ = 3061, 1629 (C=O), 1450, 1261, 1166 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.59-4.61 (m, 2H), 5.28-5.32 (m, 1H), 5.38-5.44 (m, 1H), 5.97-6.07 (m, 1H), 6.72 (s, 1H), 6.91-6.96 (m, 2H), 7.45-7.48 (m, 3H), 7.83-7.86 (m, 2H), 8.07 (d, *J* = 8.8 Hz, 1H).

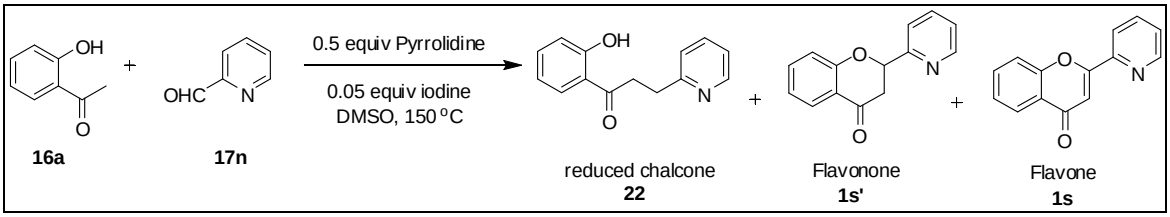
^{13}C NMR ($CDCl_3$, 100 MHz): δ 68.3 (CH_2), 100.3 (CH), 106.4 (CH), 113.9 (CH), 116.8 (Cq), 117.5 (CH_2), 125.2 (2 X CH), 126.1 (CH), 127.9 (2 X CH), 130.4 (CH), 130.7 (Cq), 131.0 (CH), 156.9 (Cq), 162.1 (2 X Cq), 176.9 (Cq).

The probable mechanism was proposed for the synthesis of flavones (Scheme 57). Aromatic aldehyde **17** forms iminium ion **18** by reacting with secondary amine. The substrate **16** can enolise due to which its enolic form can act as a nucleophile attacking **18** to form intermediate **19**. Regeneration of pyrrolidine results in chalcone **20** which undergoes Michael addition to form flavanone **1'** in presence of pyrrolidine. Further reaction with iodine leads to the formation of iodo intermediate **21**. Alternatively **21** could also be obtained directly from **20** in presence of iodine. The loss of HI results in the completely oxidized required flavone **1**. The steps involved in the regeneration of pyrrolidine and iodine catalysts plays an important role for the successful formation of flavones.



Scheme 57: Probable mechanism for the formation of flavone **1** *via* chalcone **20** and flavanone **1'**.

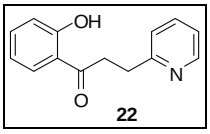
Regarding the proposed mechanism, hydrogen release by dissociation of HI is a well known reaction. This is supported by our observation of formation of 1-(2-hydroxyphenyl)-3-(pyridin-2-yl)propan-1-one **22** along with the corresponding flavanone **1s'** and flavone **1s** when 2'-hydroxyacetophenone **16a** and 2-pyridinecarboxaldehyde **17n** were subjected to this protocol (Scheme 58). 1-(2-Hydroxyphenyl)-3-(pyridin-2-yl)propan-1-one **22** was obtained due to the reduction of the intermediate chalcone by the liberated hydrogen gas. However, we do admit that so far in literature to our knowledge whenever people have used iodine as an oxidant there is no clear cut mention of decomposition of HI to I_2 and H_2 though it is a well established reaction and formation of HI is invoked to explain iodine catalyzed reactions. May be it is considered as an obvious pathway whenever iodine is used as an oxidant for aromatization reaction.



Scheme 58: Reaction of 2'-hydroxyacetophenone and 2-pyridinecarboxaldehyde led to formation of the reduced product 1-(2-hydroxyphenyl)-3-(pyridin-2-yl)propan-1-one **22** along with the corresponding flavanone **1s'** and flavones **1s**.

Spectral data of 22, 1s' and 1s

1-(2-Hydroxyphenyl)-3-(pyridin-2-yl)propan-1-one (22)



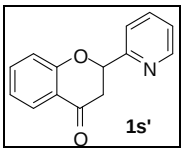
yield (0.033 g, 10 %); pale yellow liquid.[186]

IR (neat): $\tilde{\nu}$ = 3053, 2927, 1643 (C=O), 1487, 752 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.17 (t, *J* = 7.2 Hz, 2H), 3.48 (t, *J* = 7.2 Hz, 2H), 6.79-6.83 (m, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 7.06 (dd, *J* = 7.2, 5.6 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.36-7.40 (m, 1H), 7.52-7.56 (m, 1H), 7.77 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.45 (d, *J* = 4.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 30.7 (CH_2), 36.3 (CH_2), 117.4 (CH), 117.9 (CH), 118.4 (Cq), 120.4 (CH), 122.4 (CH), 129.0 (CH), 135.4 (CH), 135.6 (CH), 148.1 (CH), 159.1 (Cq), 161.2 (Cq), 204.4 (Cq).

2-(Pyridin-2-yl)chroman-4-one (1s')



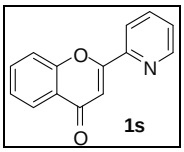
yield (0.031 g, 9 %); colorless solid; m.p. 64-68 °C; lit.[187] 68 °C.

IR (KBr): $\tilde{\nu}$ = 3064, 2926, 1693 (C=O), 1606, 1462, 1305, 763 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.06-3.16 (m, 2H), 5.60 (dd, *J* = 10.8, 5.2 Hz, 1H), 6.98-7.03 (m, 2H), 7.26-7.29 (m, 1H), 7.44-7.48 (m, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.75-7.79 (m, 1H), 7.87 (dd, *J* = 8.0, 2.0 Hz, 1H), 8.58 (d, *J* = 4.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 42.8 (CH_2), 79.1 (CH), 118.1 (CH), 121.2 (Cq), 121.4 (CH), 121.9 (CH), 123.8 (CH), 127.1 (CH),136.2 (CH), 138.3 (CH), 148.4 (CH), 157.1 (Cq), 160.8 (Cq), 191.2 (Cq).

2-(Pyridin-2-yl)-4*H*-chromen-4-one (1s)



1s

yield (0.01 g, 3 %); colorless solid; m.p. 120-122 °C.[139]

IR (KBr): $\tilde{\nu}$ = 3007, 2927, 1643 (C=O), 1465, 1381, 756 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37 (s, 1H), 7.38-7.41 (m, 1H), 7.54 (dd, *J* = 7.2, 5.2 Hz, 1H), 7.67-7.69 (m, 2H), 8.00 (t, *J* = 7.6, 1H), 8.12 (d, *J* = 7.6 Hz, 1H), 8.18 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.81 (d, *J* = 4.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 108.3 (CH), 117.3 (CH), 120.4 (CH), 123.3 (Cq), 124.5 (CH), 124.8 (CH), 124.9 (CH), 133.1 (CH), 137.2 (CH), 147.7 (Cq), 148.3 (CH), 155.1 (Cq), 159.4 (Cq), 177.4 (Cq).

3.5: Anti-diabetic activity

Diabetes mellitus (DM) is a metabolic and heterogeneous disorder caused by inherited and/or acquired insulin secretion deficiency and/or by lowered responsiveness of the organs to the secreted insulin, affecting approximately 5 % of total global population.[188] Among the two major types of diabetes, Type I diabetes mellitus also known as insulin dependent diabetes mellitus (IDDM) commonly occurs in children and accounts to only 5-10 % of total diabetic patients. However, Type II diabetes mellitus also known as non-insulin dependent diabetes mellitus (NIDDM) is highly related to diet or lifestyle and is prevalent in adults, called as adult-onset diabetes. The high blood-glucose level arises due to high consumption of carbohydrate enriched diet leading to hyperglycemia in affected individuals. In a study done by Shaw *et al.*[189] 6.4 % of adults of world (aged 20–79 years) were found to be affected in 2010 and it is estimated to increase to 7.7 % by 2030. Recently, Guariguata *et al.*[190] conducted a literature search depicting diabetes prevalence globally for 2013 and estimated the greatest increase by 55 % up to 2035.

Herbal drugs have been a major source of medicines over the centuries for the prevention and cure of various diseases including diabetes mellitus. There are more than 200 species of plants that exhibit hypoglycaemic properties and its use along with drugs including insulin helps to lower the drug dosage and/or decrease the frequency of drug administration with reduced side effects.[191] But the detection of anti-diabetic compound and purification from plant crude extracts is a tedious work allowing the isolation of anti-diabetic compounds only in trace amounts from herbs due to which the number of drugs is limited. Number of

natural compounds belonging to major classes of chemical compounds like alkaloid, carbohydrate, terpenoids, flavonoids and phenolic compounds extracted from various plant medicated sources are reported to be potential inhibitors for the two enzymes *viz*. *α*-glucosidase and *α*-amylase responsible for Type 2 DM. In the process of screening, anti-diabetic compounds are all natural compounds such as pycnogenol, galegine (isolated from plants) and acarbose, miglitol, and voglibose (isolated from microbes) which were found to demonstrate inhibitory activity of these enzymes.[192] Zhao *et al*.[193] investigated the anti-diabetic activity of flavone, the main pharmacological ingredient isolated from *Ipomoea batatas* leaf. It was found effective against non-insulin dependent diabetes mellitus (NIDDM) in rats.

Natural compound can be modified into more potential derivatives on the basis of structure activity relationship (SAR) studies. Various dose dependent inhibition assays have been shown that synthetic derivatives show more potent *α*-glucosidase inhibitory activity than their parent compound/s.[194] For example, salacinol derivatives inhibited rat small intestinal *α*-glucosidase more strongly than the naturally occurring salacinol.[195] Few natural as well as synthetic flavones have been studied for anti-diabetic activity.[33] This encouraged us to evaluate the flavones **1a**-**r** synthesized in our laboratory for their anti-diabetic activity.

The synthesized 18 flavones **1a**-**r** were submitted for *in vitro* inhibition of *α*-glucosidase activity in the Marine Biotechnology Department of Goa University. These derivatives were firstly dissolved in methanol solvent (1 mg/mL). It was observed that only 5 derivatives **1c**, **1d**, **1i**, **1j** and **1r** were completely soluble whereas the remaining derivatives were partially soluble forming aggregates in the solution. Hence these partially soluble derivatives were excluded from further studies. The selected compounds **1c**, **1d**, **1i**, **1j** and **1r** were then evaluated for their *in vitro* inhibition of *α*-glucosidase activity.

The selected samples **1c**, **1d**, **1i** and **1r** showed *α*-glucosidase inhibition of 74, 53, 98 and 93 % respectively at 300 μg/mL, however, 2-(1,3-benzodioxol-5-yl)-4*H*-chromen-4-one **1j** showed highest inhibitory activity of 99 % at 300 μg/mL. Further, the dose dependent studies of these 5 samples showed proper graph pattern only for **1j**, hence it was selected for further studies.

α-Glucosidase inhibition assay:

In vitro studies using **1j** demonstrated remarkable inhibition of *α*-glucosidase suggesting the presence of potential enzyme inhibiting activity of a synthetic compound. Significant *α*-glucosidase inhibitions were depicted at all the doses of **1j** in comparison to their respective

controls (t-test) (Figure 6). Dose dependent inhibition of *α*-glucosidase by **1j** ranged from 8.4 ± 0.37 % at 1 µg/mL to 99.3 ± 0.26 % at 7.6 µg/mL. Further ANOVA of the percentage inhibition of *α*-glucosidase observed in the control and different doses of **1j** showed significant difference at $P < 0.0001$.

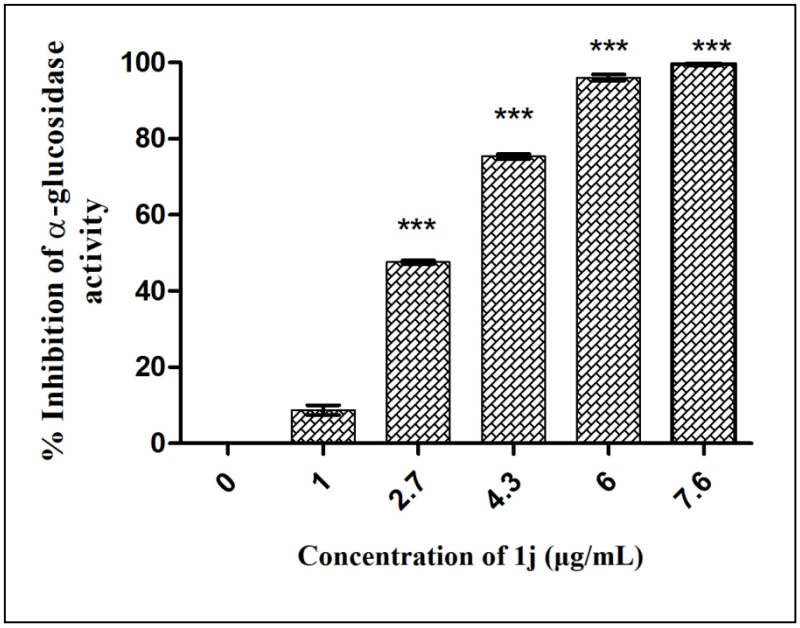


Figure 6: Percentage of inhibition of *α*-glucosidase in presence of various doses of **1j**. Data are mean ± SD (*P < 0.05, **P < 0.01, ***P < 0.001 denotes statistically significant difference from the test control as determined by student's t-test significance).

Enzyme Kinetic studies

Enzyme kinetic study results were analyzed using Michaelis–Menten plot & Lineweaver–Burk plot analysis. The type of *α*-glucosidase inhibition shown by **1j** was non-competitive (Figure 7). In non-competitive type of reactions, Michaelli's-Menten constant (Km) remains same whereas maximum velocity (Vmax) of the enzymatic reaction decreases. In this type of reaction, inhibitor reduces the activity of the enzyme irrespective of substrate binding. The Km and Vmax of *α*-glucosidase with **1j** inhibitor were depicted as 71.42 μM^{-1} and 0.02 µM/min and without inhibitor (control) as 71.42 μM^{-1} and 0.04 µM/min respectively. Whereas the acarbose, a standard anti-diabetic drug is reported to show a competitive type inhibition of *α*-glucosidase.[196] However, for the management of type-2 diabetes, use of drugs which shows non-competitive type inhibition of *α*-glucosidase enzyme should be given preference over the drugs that depict competitive type inhibition (e.g. acarbose). Competitive type inhibition depends on the substrate concentration and *α*-glucosidase inhibition potential of these drugs can be overcome by increasing the concentration of substrate. So, if a type-2 diabetes patient is given acarbose tablets and is having excess food with more carbohydrates,

then the acarbose effect on enzyme would be overcome by higher concentration of carbohydrates whereas if a patient is taking a drug which shows non-competitive type of inhibition and simultaneously having higher carbohydrate containing diet, the carbohydrates would have no effect on the enzyme inhibition potential of the drug.

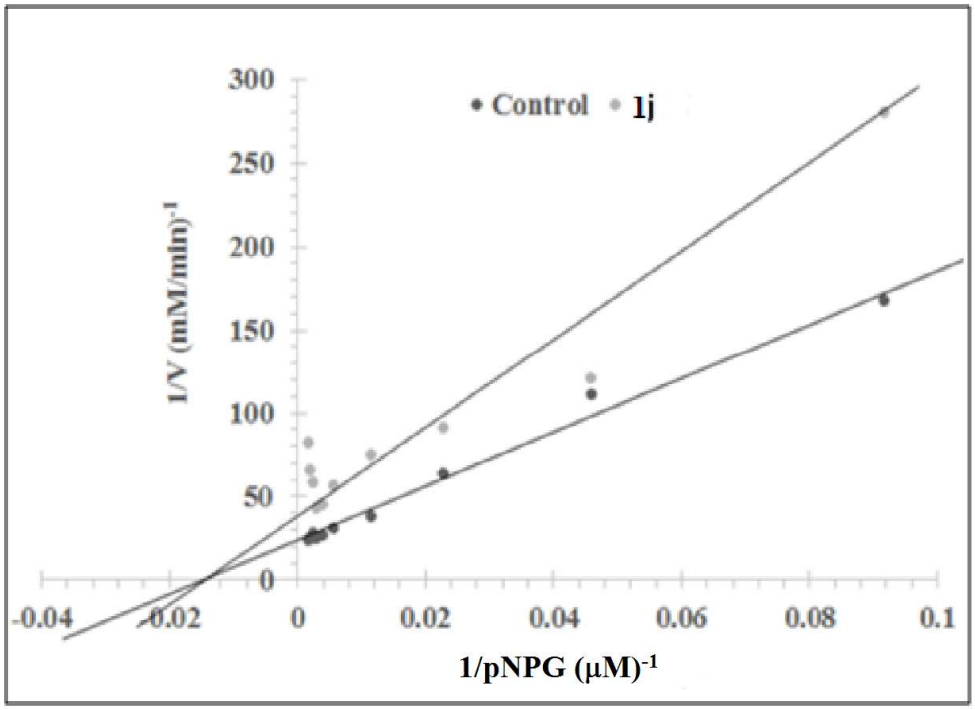


Figure 7: Lineweaver–Burk plots of *α*-glucosidase inhibition at different concentrations of substrate and 2-(benzo[*d*][1,3]dioxol-5-yl)-4*H*-chromen-4-one **1j**.

Statistical analysis

Statistical analysis for α-glucosidase assay was carried out using graph pad prism-5 software. All samples were evaluated in triplicates and standard deviation was calculated. Sample data were analyzed with student's t-test and one-way ANOVA with tukey's test that was performed using graph pad prism version 5.00 for windows, graph pad software, San Diego California USA (www.graphpad.com).

α- glucosidase inhibition assay

The *α*-glucosidase inhibition was determined spectrophotometrically using *p*-nitrophenyl-*α*-D-glucopyranoside (*p*NPG) as substrate.[197] *α*-Glucosidase, 7.5 µL (0.5 U/mL) was mixed with various concentrations of **1j**. After incubation of this mixture at 37 °C for 30 min, 100 µL of *p*NPG (3 mM) was added. Reaction mixture was then again incubated for 10 min at 37 °C. To stop the reaction, 750 µL of Na_2CO_3 (0.1 M) was added and absorbance was determined at 405 nm in triplicates. Standard anti-diabetic drug acarbose (PHR1253, Fluka)

was used as a positive control for *α*-glucosidase inhibition assay. The percentage inhibition of the enzyme activity was calculated by using the following formula.

Inhibition (%) = Absorbance of test control - Absorbance of sample/ Absorbance of control ×100.

Kinetic analysis of *α*-glucosidase inhibition

For kinetic studies, *α*-glucosidase enzyme 7.5 µL (0.5 U/mL) mixed with **1j** (12.5 µg/mL) and incubated for 15 min. Further, *p*NPG was added at different concentrations (0.0109-0.612 mM) to individual reactions and the absorbance was recorded at 405 nm with the time interval of 3 sec up to 180 sec. The Km and Vmax values were determined from the Michaelis-Menten equation and mode of inhibition by **1j** are represented graphically using Lineweaver–Burk plot.

Molecular docking studies of 1j

Allosteric and competitive binding mode can be possible with more than one pocket present in protein. Acarbose competes with substrate for active sites of *α*-glucosidase enzyme. Acarbose binding to active site of *α*-glucosidase was determined using Autodock 4.2 tool. Total 10 best docking models were obtained, out of them the best fit docked model was chosen to reveal the molecular interaction between acarbose and *α*-glucosidase with the minimum binding energy of (ΔG) of -6.04 and minimum inhibition constant (Ki) of 37.38 µM. The structural model of the complex between acarbose and α-glucosidase and its 3D representation is depicted in figures 8A and 8B respectively. The 2D representation of the interaction between acarbose and *α*-glucosidase enzyme was analyzed by LIG-PLOT (Figure 8C). Acarbose depicted hydrogen bonding with His 98, His 207 amino acids of active sites of *α*-glucosidase. Other amino acids shows the hydrophobic and Pi-Pi interaction with the acarbose (Figure 8C).

In contrary to the acarbose, flavone **1j** depicted allosteric interaction with *α*-glucosidase (Figure 9A). Binding pocket on *α*-glucosidase for **1j** was different from that of the acarbose binding site (Figure 9B), so these results support the results obtained in enzyme kinetic study that enzyme inhibition behaviour of **1j** is non-competitive. Out of total 10 docked model obtained, the best fit model depicted the allosteric interaction of **1j** with *α*-glucosidase with minimum binding energy of -0.6.39 and minimum inhibition constant (Ki) of 20.76 µM. It was observed that amino acid Lys373 was involved in hydrogen bonding with **1j** inhibitor (Figure 9C). The other surrounding amino acids depicted hydrophobic and Pi-Pi interaction with **1j** inhibitor.

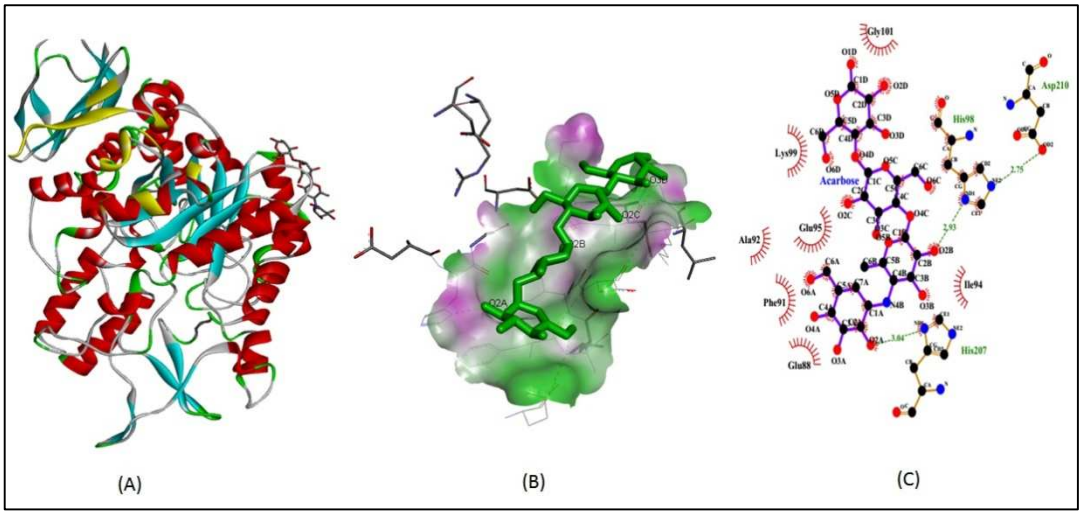


Figure 8: (A) Structural model of the complex between acarbose and α-glucosidase; (B) 3D Representation of the interaction between acarbose and α-glucosidase in the predicted binding site; (C) 2D Representation of the interactions between α-glucosidase and acarbose.

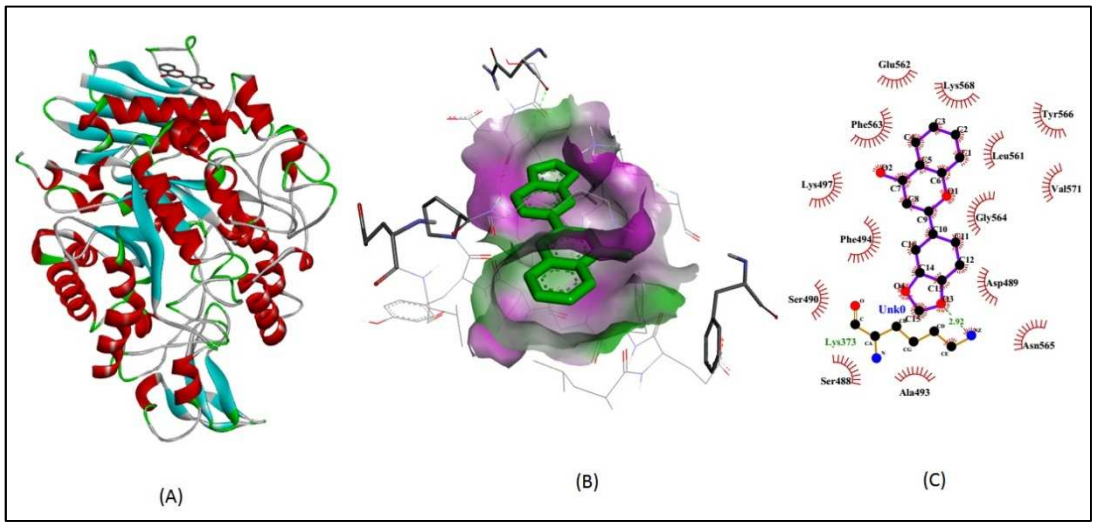


Figure 9: (A) Structural model of the complex between **1j** and α-glucosidase; (B) 3D Representation of the interaction between **1j** and α-glucosidase in the predicted binding site; (C) 2D Representation of the interactions between α-glucosidase and **1j**.

The mode of α-glucosidase inhibition shown by **1j** is a non-competitive type and is different from acarbose which shows competitive type of inhibition. Since, non-competitive inhibition of α-glucosidase exhibited by any drug is independent on substrate (carbohydrate) concentration, during the clinical trials, drugs having non-competitive type of α-glucosidase inhibition are more preferable over competitive type inhibiting drugs. Hence, at this stage, **1j** has shown a significant anti-diabetic potential which is more advantageous than acarbose, so

in future, along with the other lead compounds, **1j** can also be a potent future lead compound for the management of type-2 diabetes.

Molecular docking

General remarks: PDB structure of α-glucosidase was downloaded from Pubchem (PDB ID: 3A4A). Acarbose a standard molecule for docking studies was downloaded from https://pubchem.ncbi.nlm.nih.gov/. The 3D structure of the **1j** was drawn and validated using Marvin sketch (https://www.chemaxon.com /products/marvin/marvinsketch). Windows based automated docking tool Autodock 4.2 was used for docking study. Discovery studio (http://accelrys.com/products/collaborative-science/biovia-discovery-studio/) and LIGPLOT v.5.4.3 (http://www.ebi.ac.uk/thornton-srv/software/LIGPLOT/) were used to analyze the molecular interactions between docked molecules.

Using the Autodock 4.2 tools, all water molecules of α-glucosidase were removed and essential hydrogen atoms and Gasteiger charges were assigned. Grid parameter file (GPF) was prepared with the grid spacing of 1 and ligand dimension 88×87×126 for acarbose and 0.819 and ligand dimension 98×88×104 for **1j**. Docking parameter file (DPF) was prepared using Lamarckian Genetic Algorithm (LGA) with parameters set to 10 runs, whereas energy evaluation was set to 2,500,000 and 27,000 generation. Autogrid4 and autodock4 were run to calculate the lowest energy conformation between ligand and target. Different energy terms including intermolecular energy (vdm + hbond + desolv energy + electrostatic energy), internal energy, torsional energy and binding energy can be obtained from the output DLG (Docking Log file) format which was further analysed using as PyMOL and LIG-PLOT.

3.6: Conclusion

Synthesis of flavones is established from 2'-hydroxyacetophenones and aromatic aldehydes in one pot using pyrrolidine and iodine catalysts in DMSO solvent at 150 °C in 60-88 %. The methodology involves domino aldol-Michael-oxidation reaction sequence catalyzed by pyrrolidine and iodine as base and oxidant respectively.

Also, this method avoids the step of isolation of chalcone or flavanone intermediates and then subjecting them to further oxidation as in case of most of the reported methods for flavones. Thus providing a straightforward route to flavones.

Several advantages of this methodology including inexpensive catalysts, broad substrate scope, lack of metal catalysts and products in high yields with no side reactions makes it a better synthetic approach to flavones.

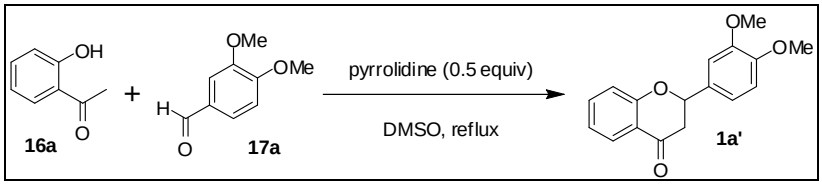
The reaction protocol was also successfully scaled up to 5 g of starting aryl aldehyde **17a** to get consistent yield of the desired flavone **1a**.

The selected synthesized flavones were screened for their *in vitro* anti-diabetic activity with acarbose as standard, among which flavone **1j** exhibited highest activity.

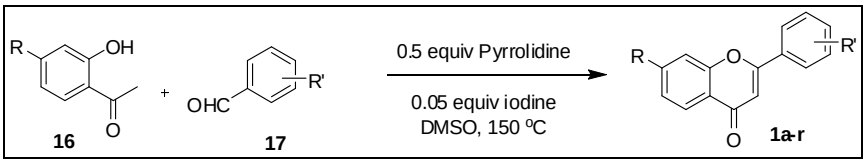
Significant α-glucosidase inhibitions were performed at different doses of **1j** showing very high % inhibition of 99.3 ± 0.26 % at very low concentration of 7.6 µg/mL.

The inhibition kinetics analyzed by Lineweaver-Burk and Michaelis–Menten plot analysis indicated non-competitive type of inhibition of α-glucosidase enzyme by **1j** which is different from the standard acarbose which shows competitive type of inhibition.

3.7: Experimental

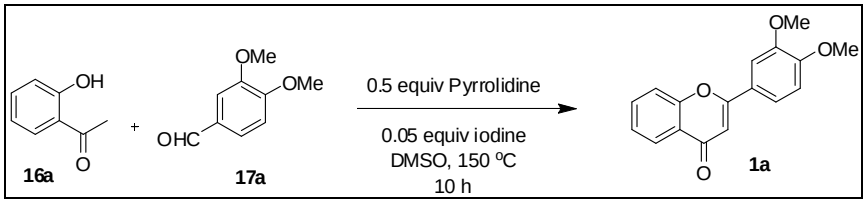


3.7.1: A procedure for the synthesis of 2-(3,4-dimethoxyphenyl)chroman-4-one 1a': 2'-Hydroxyacetophenone **16a** (0.1 g, 0.7 mmol) and 3,4-dimethoxybenzaldehyde **17a** (0.12 g, 0.7 mmol) were mixed together along with pyrrolidine (0.026 g, 0.35 mmol) in DMSO solvent (10 mL). The resulting mixture was then refluxed for 15 minutes. After completion of reaction (monitored by TLC) the reaction mass was allowed to cool and diluted with ethyl acetate (20 mL). The resulting solution was then washed with water (5-6 times, 10 mL each). Combined water layers were extracted with ethyl acetate (3-4 times, 10 mL each) and the two ethyl acetate extracts were combined which was washed with dilute HCl solution. It was followed by water washing, drying over anhydrous sodium sulphate and concentrating under reduced pressure to furnish the crude product. The residue obtained was purified by column chromatography using benzene as an eluent to afford flavanone **1a'**.

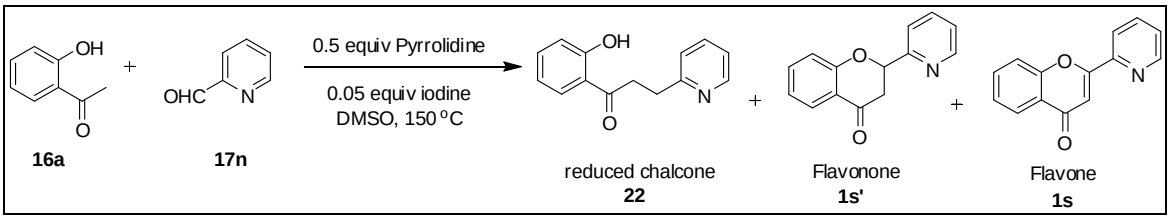


3.7.2: A general procedure for the synthesis of flavones 1a-r: Substituted 2'-hydroxyacetophenone **16** (0.7 mmol) and substituted aromatic/heteroaromatic aldehyde **17** (0.7 mmol) were mixed together along with pyrrolidine (0.35 mmol) and iodine (0.035 mmol) in DMSO solvent (10 mL). The resulting mixture was then heated at 150 °C for the given time. After completion of reaction (monitored by TLC) the reaction mass was allowed to cool and diluted with ethyl acetate (20 mL). The resulting solution was then washed with water (5-

6 times, 10 mL each). Combined water layers were extracted with ethyl acetate (3-4 times, 10 mL each) and the two ethyl acetate extracts were combined which was washed with saturated sodium thiosulphate solution. It was followed by drying over anhydrous sodium sulphate and concentrating under reduced pressure to furnish the crude product. The residue obtained was purified by column chromatography using petroleum ether-ethyl acetate as an eluent to afford flavones **1a-r**.



3.7.3: A procedure for the synthesis of flavone 1a: 2'-Hydroxyacetophenone **16a** (0.1 g, 0.7 mmol) and 3,4-dimethoxybenzaldehyde **17a** (0.12 g, 0.7 mmol) were mixed together along with pyrrolidine (0.025 g, 0.35 mmol) and iodine (0.0045 g, 0.035 mmol) in DMSO solvent (10 mL). The resulting mixture was then heated at 150 °C for 10 h. After completion of reaction (monitored by TLC) the reaction mass was allowed to cool and diluted with ethyl acetate (20 mL). The resulting solution was then washed with water (5-6 times, 10 mL each). Combined water layers were extracted with ethyl acetate (3-4 times, 10 mL each) and the two ethyl acetate extracts were combined which was washed with saturated sodium thiosulphate solution. It was followed by drying over anhydrous sodium sulphate and concentrating under reduced pressure to furnish the crude product. The residue obtained was purified by column chromatography using petroleum ether-ethyl acetate (6:4) as an eluent to afford flavone **1a** (0.182 g, 88 %).



3.7.4: A procedure for the synthesis of 1-(2-hydroxyphenyl)-3-(pyridin-2-yl)propan-1-one 22, 2-(pyridin-2-yl)chroman-4-one 1s' and 2-(pyridin-2-yl)-4*H*-chromen-4-one 1s: 2'-Hydroxyacetophenone **16a** (0.2 g, 1.5 mmol) and 2-pyridinecarboxaldehyde **17n** (0.16 g, 1.5 mmol) were mixed together along with pyrrolidine (0.052 g, 0.35 mmol) and iodine (0.019 g, 0.035 mmol) in DMSO solvent (10 mL). The resulting mixture was then heated at 150 °C for 2 h. After completion of reaction (monitored by TLC) the reaction mass was

allowed to cool and diluted with ethyl acetate (20 mL). The resulting solution was then washed with water (5-6 times, 10 mL each). Combined water layers were extracted with ethyl acetate (3-4 times, 10 mL each) and the two ethyl acetate extracts were combined which was washed with saturated sodium thiosulphate solution. It was then washed with 2N NaOH solution (2 times, 10 mL each) and then with water. The ethyl acetate layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to furnish the crude product. The residue obtained was purified by column chromatography to afford 2-(pyridin-2-yl)chroman-4-one **1s'** and 2-(pyridin-2-yl)-4*H*-chromen-4-one **1s** using petroleum ether-ethyl acetate (8:2) and (7.5:2.5) as an eluent respectively.

The NaOH layer was neutralized by adding conc. HCl solution and then extracted with ethyl acetate (3-4 times, 10 mL each). It was then dried over anhydrous sodium sulphate and concentrated under reduced pressure to furnish the crude product. The residue obtained was purified by column chromatography using petroleum ether-ethyl acetate (1:1) as an eluent to afford 1-(2-hydroxyphenyl)-3-(pyridin-2-yl)propan-1-one **22**.

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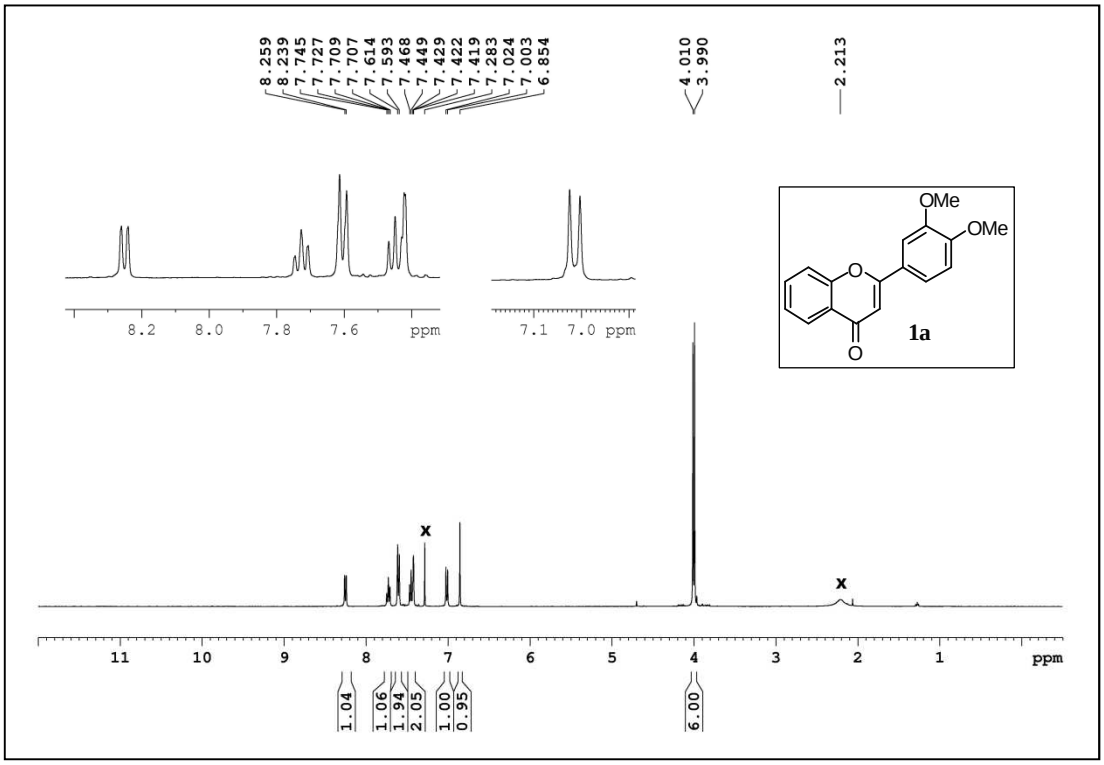
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7.283
7.024
7.003
6.854
4.010
3.990
2.213
OMe
OMe
O
O
1a
8.2
8.0
7.8
7.6
ppm
7.1
7.0 ppm
x
x
11
10
9
8
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2
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ppm
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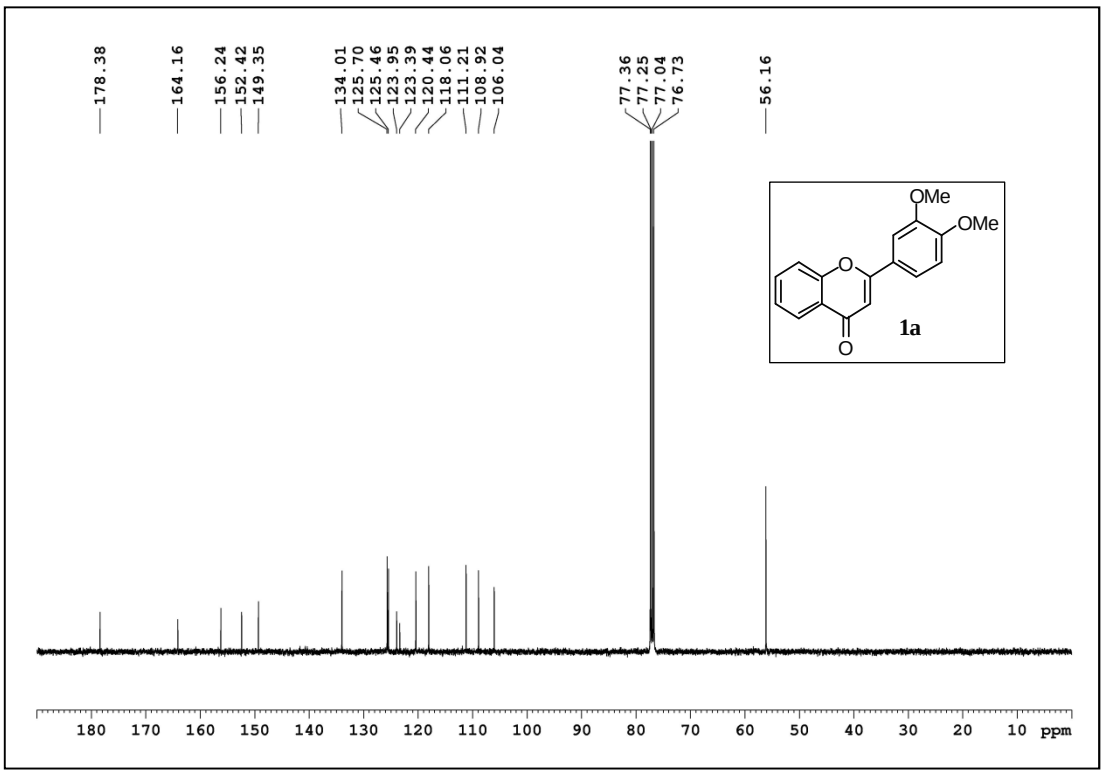
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111.21
108.92
106.04
77.36
77.25
77.04
76.73
56.16
OMe
OMe
O
O
1a
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150
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110
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70
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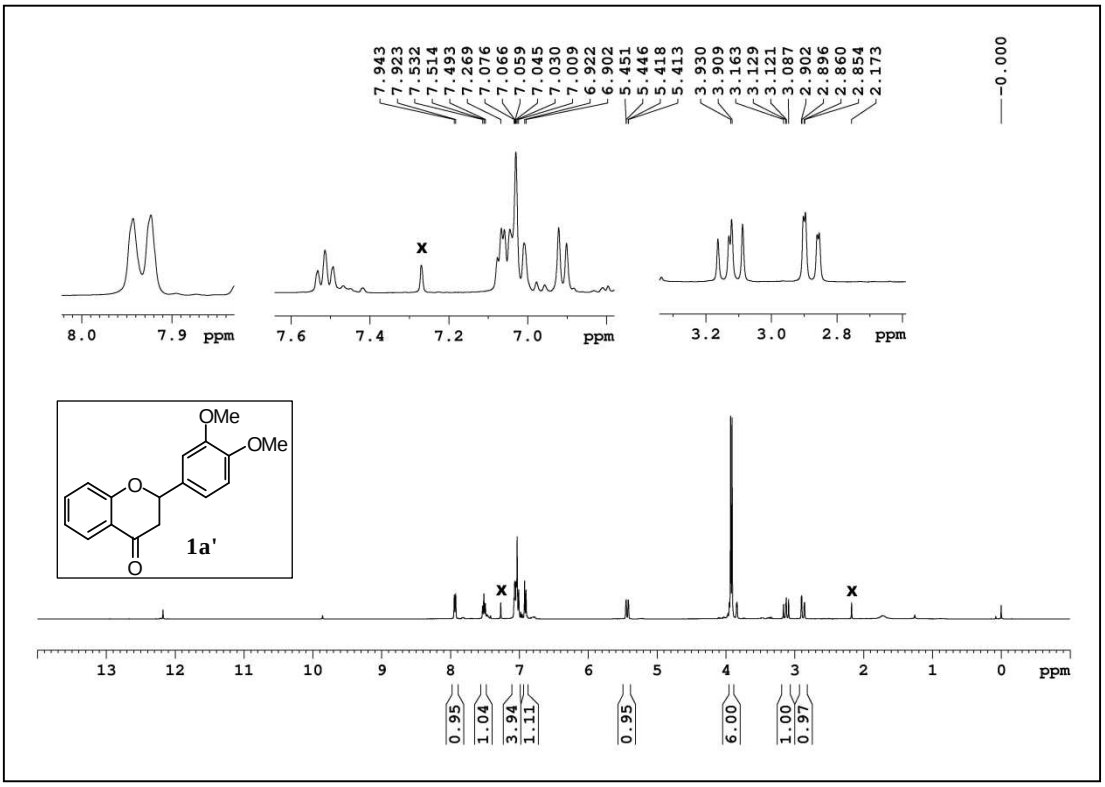
30
20
10
ppm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5.413
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3.121
3.087
2.902
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2.854
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-0.000
x
8.0
7.9
ppm
7.6
7.4
7.2
7.0
ppm
3.2
3.0
2.8
ppm
OMe
OMe
O
O
1a'
x
x
13
12
11
10
9
8
7
6
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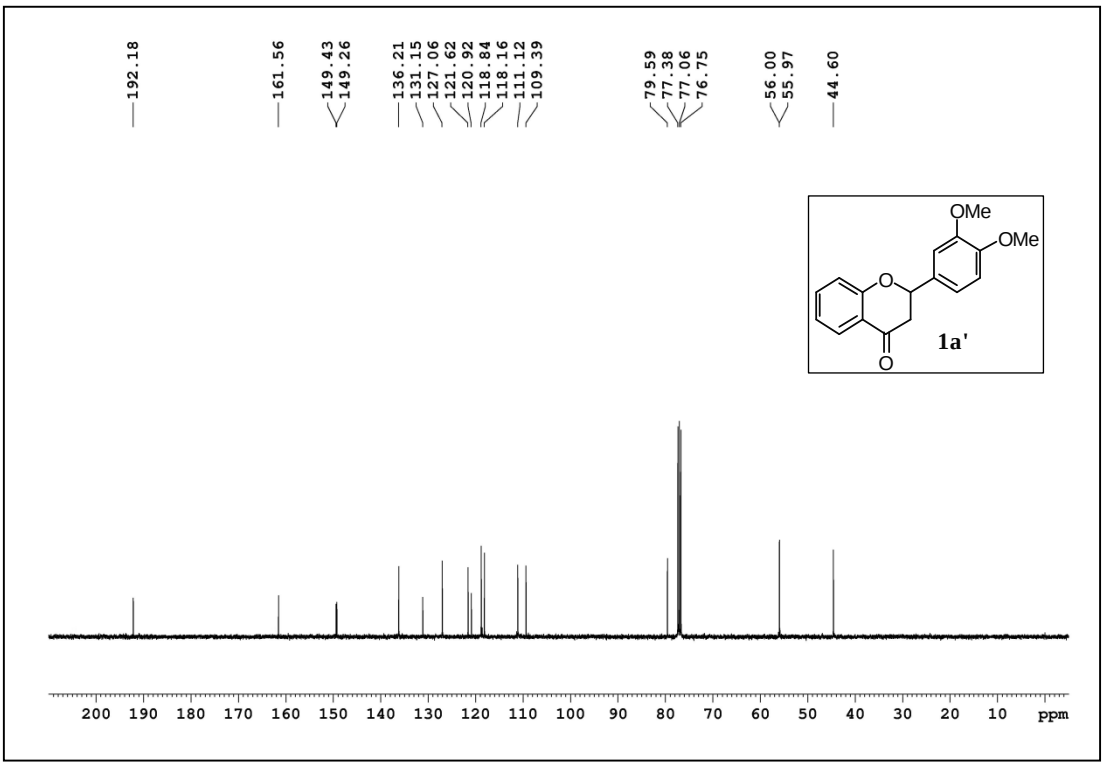
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77.38
77.06
76.75
56.00
55.97
44.60
OMe
OMe
O
O
1a'
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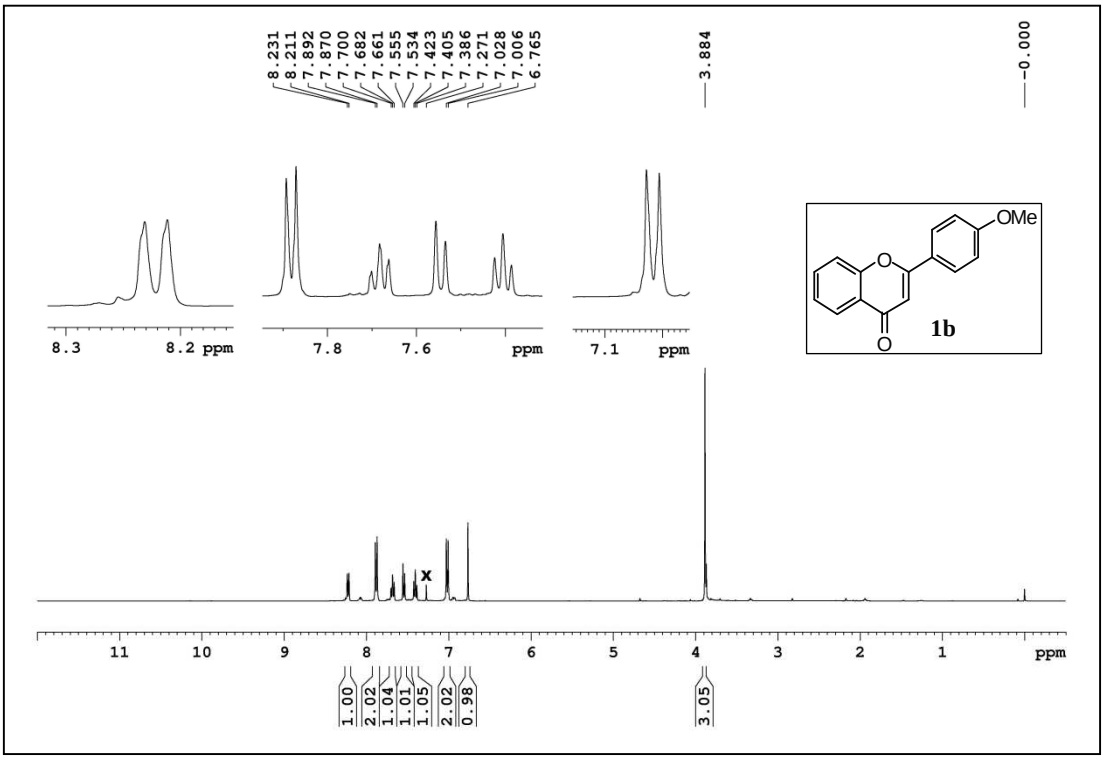
ppm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7.028
7.006
6.765
3.884
0.000
OMe
O
O
1b
8.3
8.2 ppm
7.8
7.6
ppm
7.1
ppm
x
11
10
9
8
7
6
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ppm
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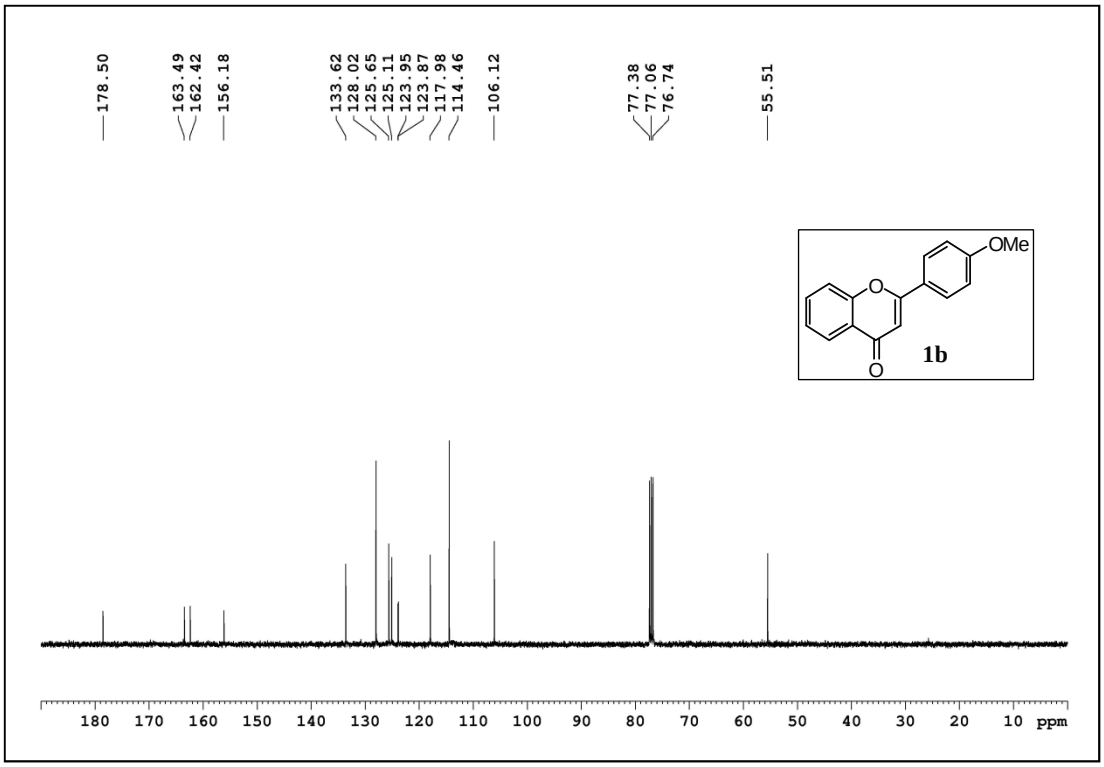
3.05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125.11
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106.12
77.38
77.06
76.74
55.51
OMe
O
O
1b
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150
140
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120
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90
80
70
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40
30
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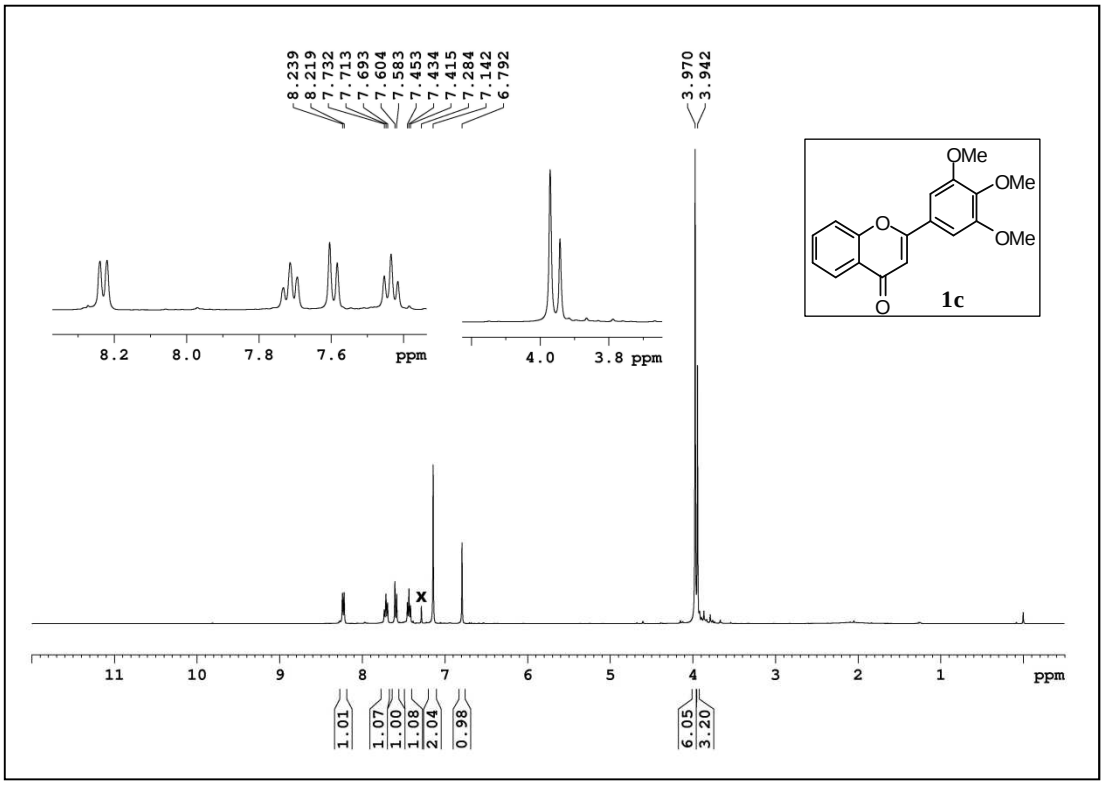
10
ppm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7.453
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6.792
3.970
3.942
OMe
OMe
OMe
O
O
1c
8.2
8.0
7.8
7.6
ppm
4.0
3.8 ppm
x
11
10
9
8
7
6
5
4
3
2
1
ppm
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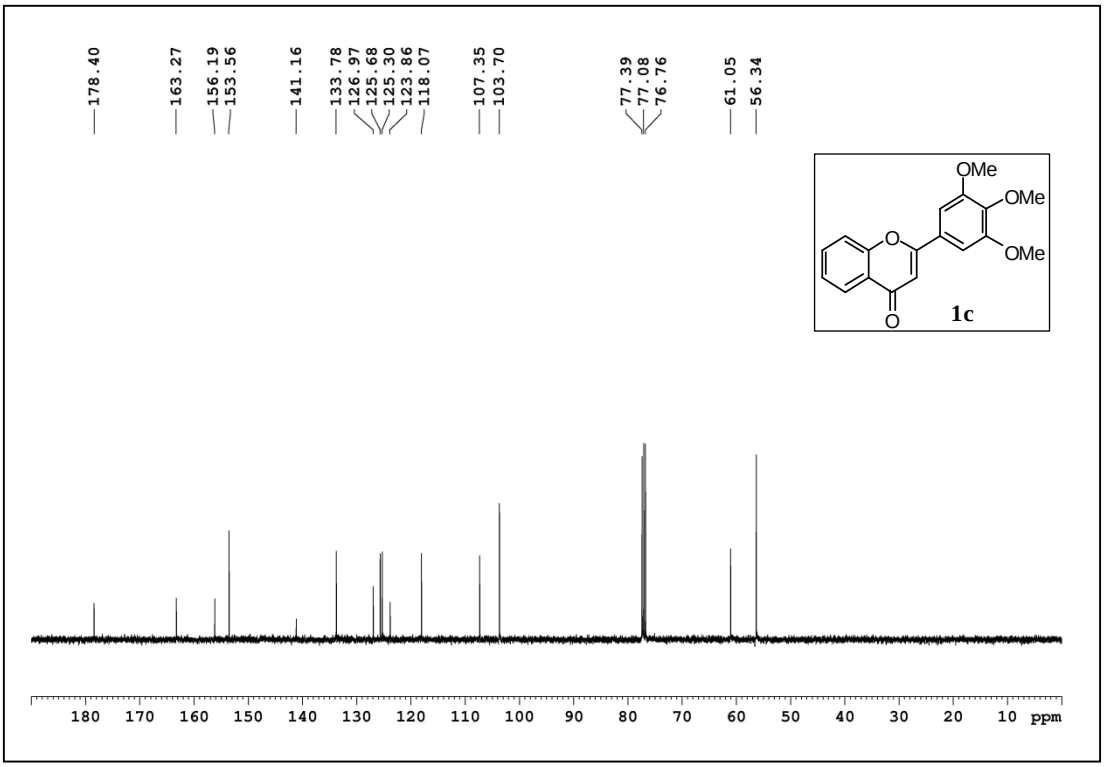
1.07
1.00
1.08
2.04
0.98
6.05
3.20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103.70
77.39
77.08
76.76
61.05
56.34
OMe
OMe
OMe
O
O
1c
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150
140
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70
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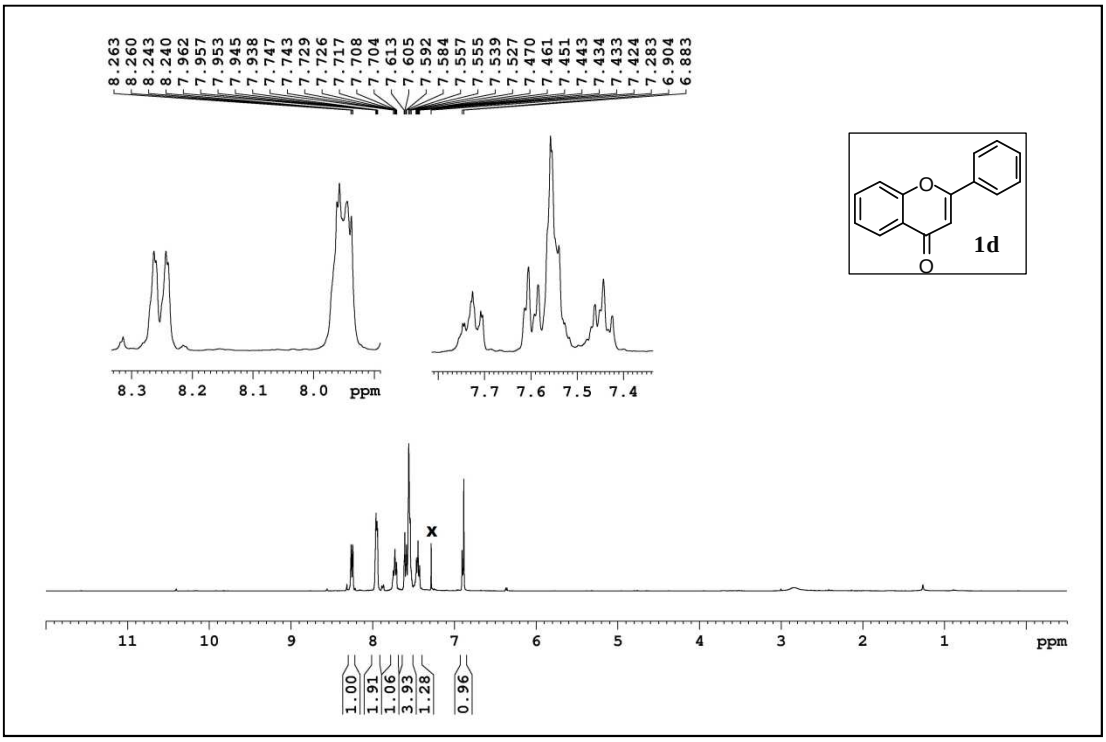
10
ppm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7.283
6.904
6.883
8.3 8.2 8.1 8.0 ppm
7.7 7.6 7.5 7.4
1d
x
11 10 9 8 7 6 5 4 3 2 1 ppm
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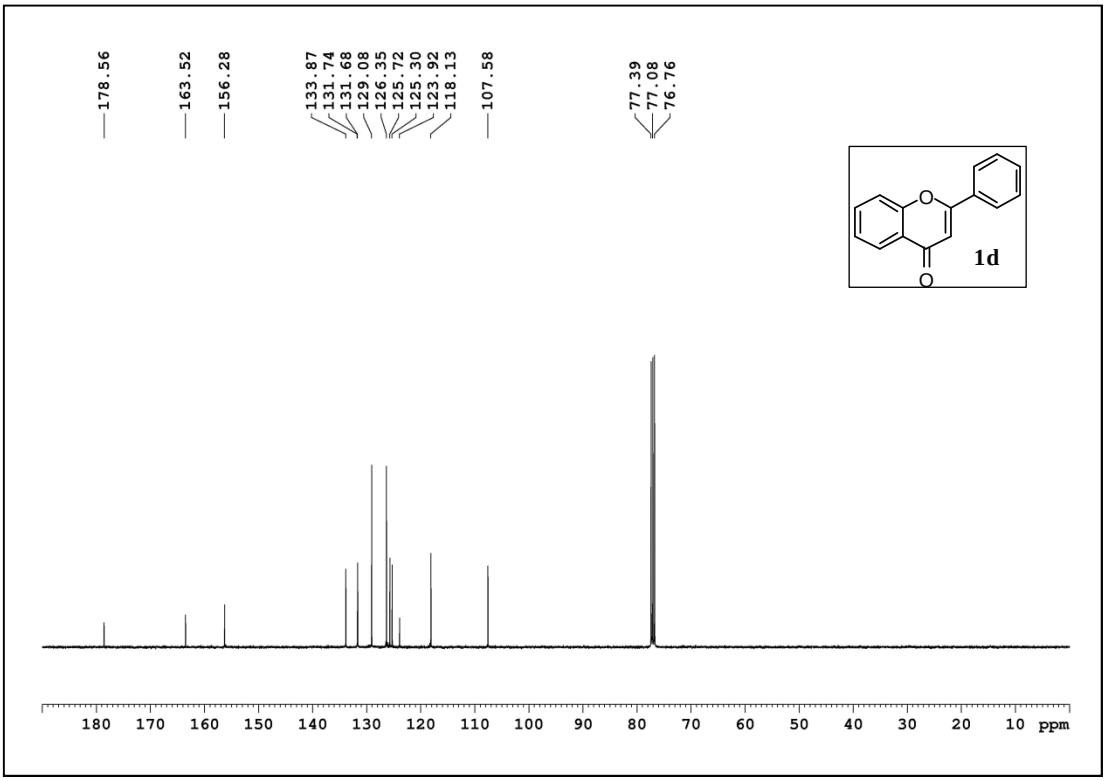
3.93
1.28
0.96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126.35
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107.58
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76.76
1d
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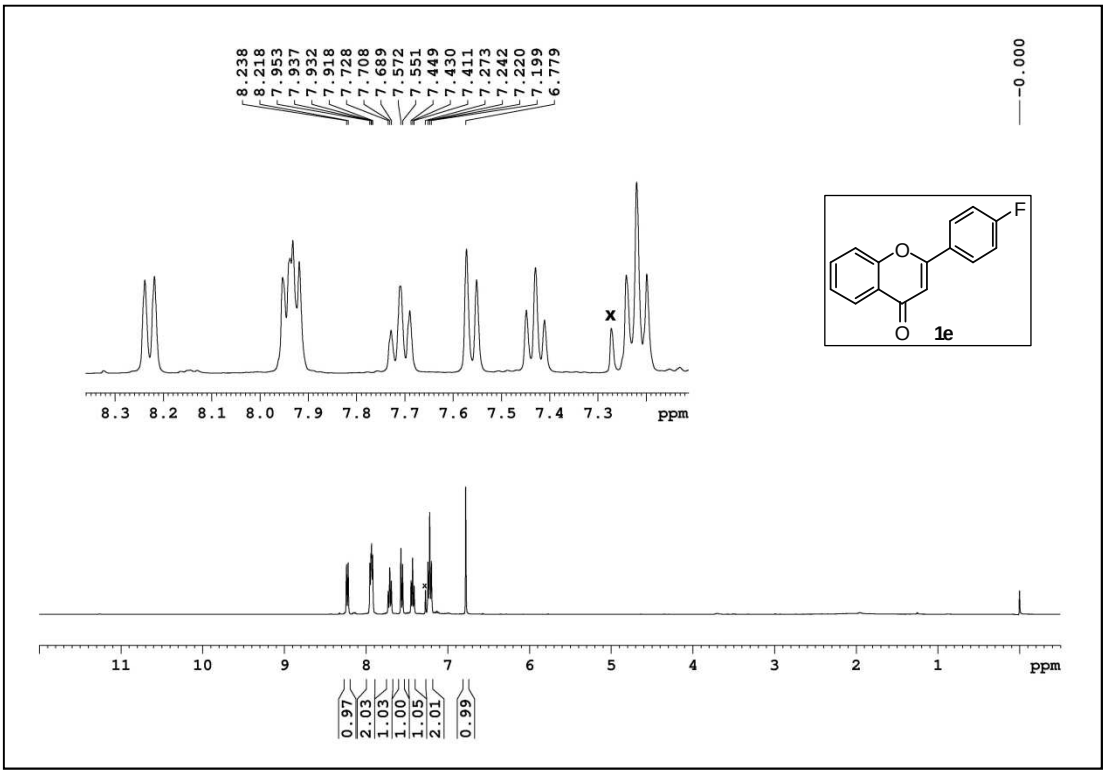
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7.449
7.430
7.411
7.273
7.242
7.220
7.199
6.779
0.000
x
8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 ppm
F
O
O
1e
11 10 9 8 7 6 5 4 3 2 1 ppm
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2.03
1.03
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1.05
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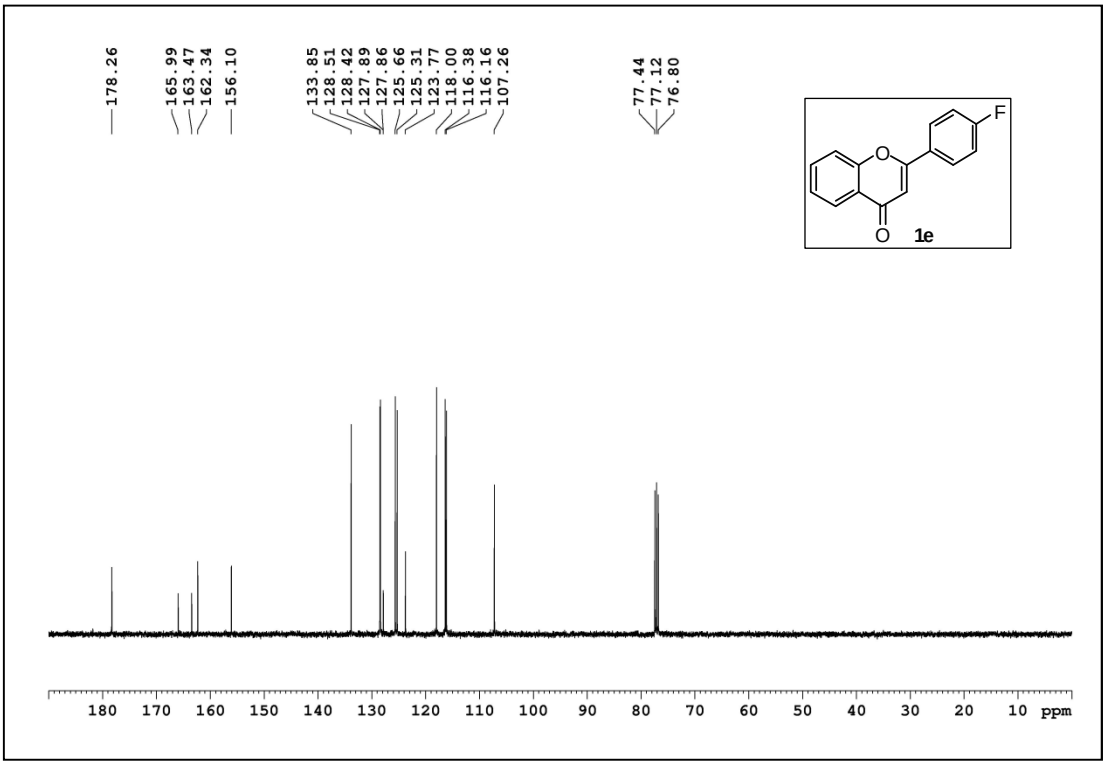
0.99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125.31
123.77
118.00
116.38
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77.44
77.12
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F
O
O
1e
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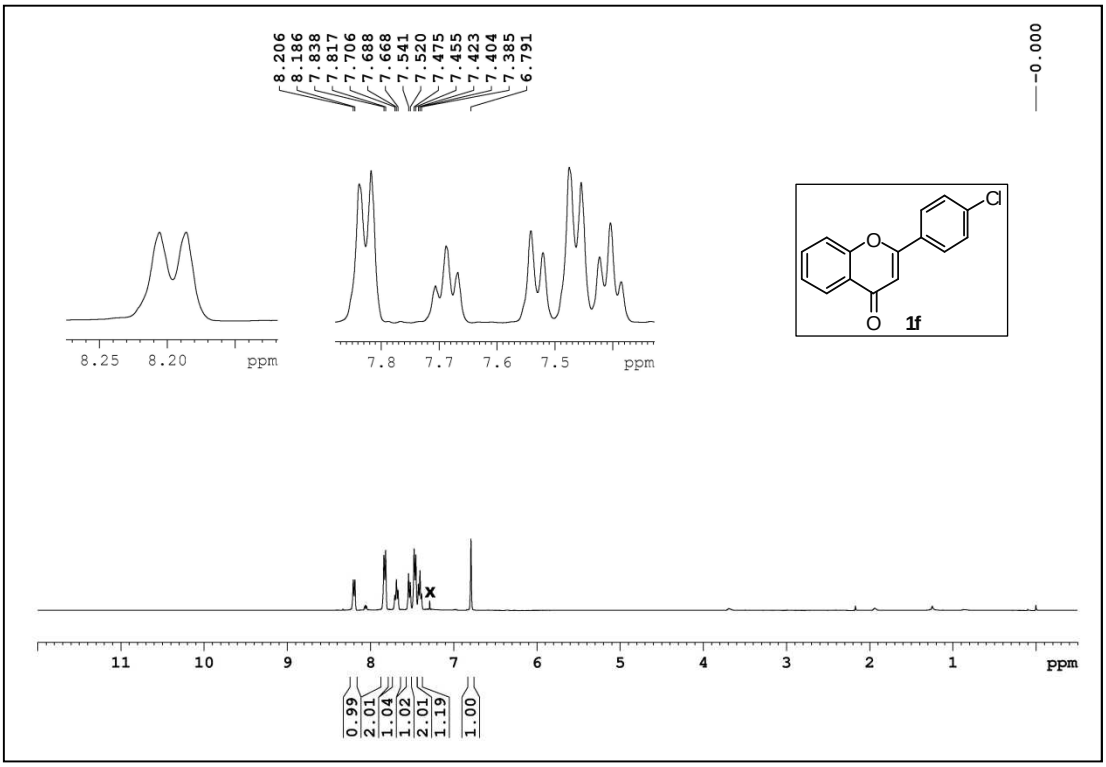
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7.475
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7.404
7.385
6.791
-0.000
8.25
8.20
ppm
7.8
7.7
7.6
7.5
ppm
Cl
O
O
1f
x
11
10
9
8
7
6
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4
3
2
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ppm
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1.04
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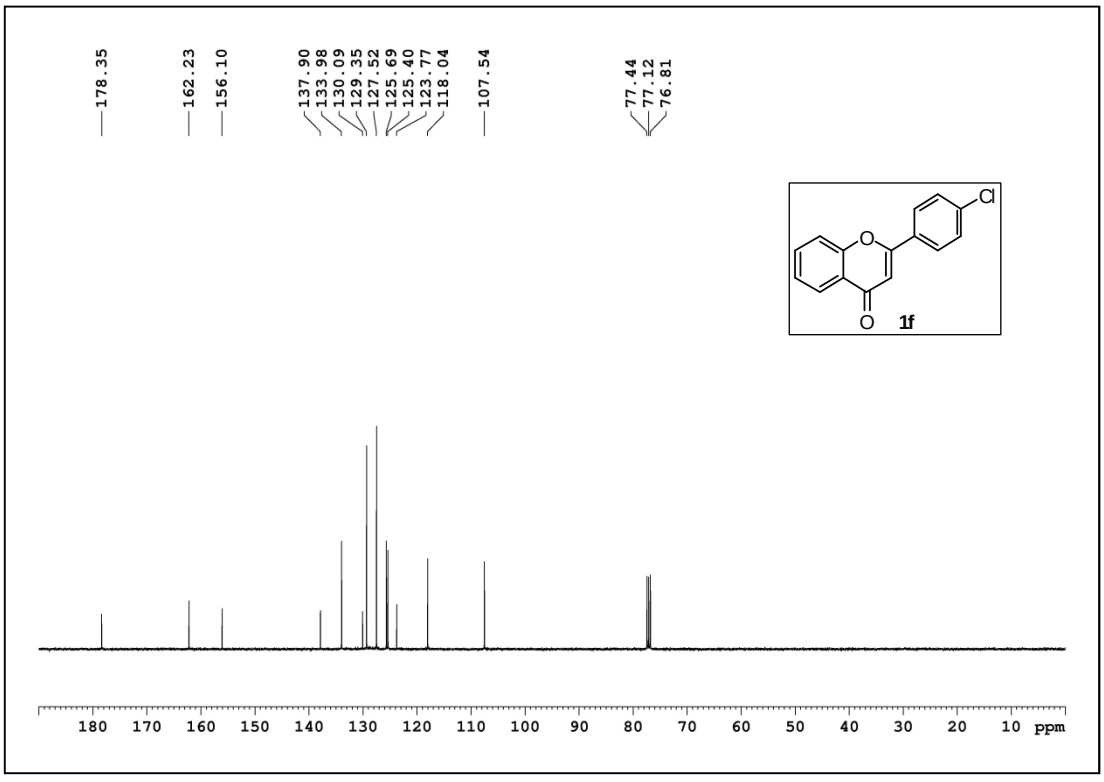
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127.52
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125.40
123.77
118.04
107.54
77.44
77.12
76.81
Cl
O
O
1f
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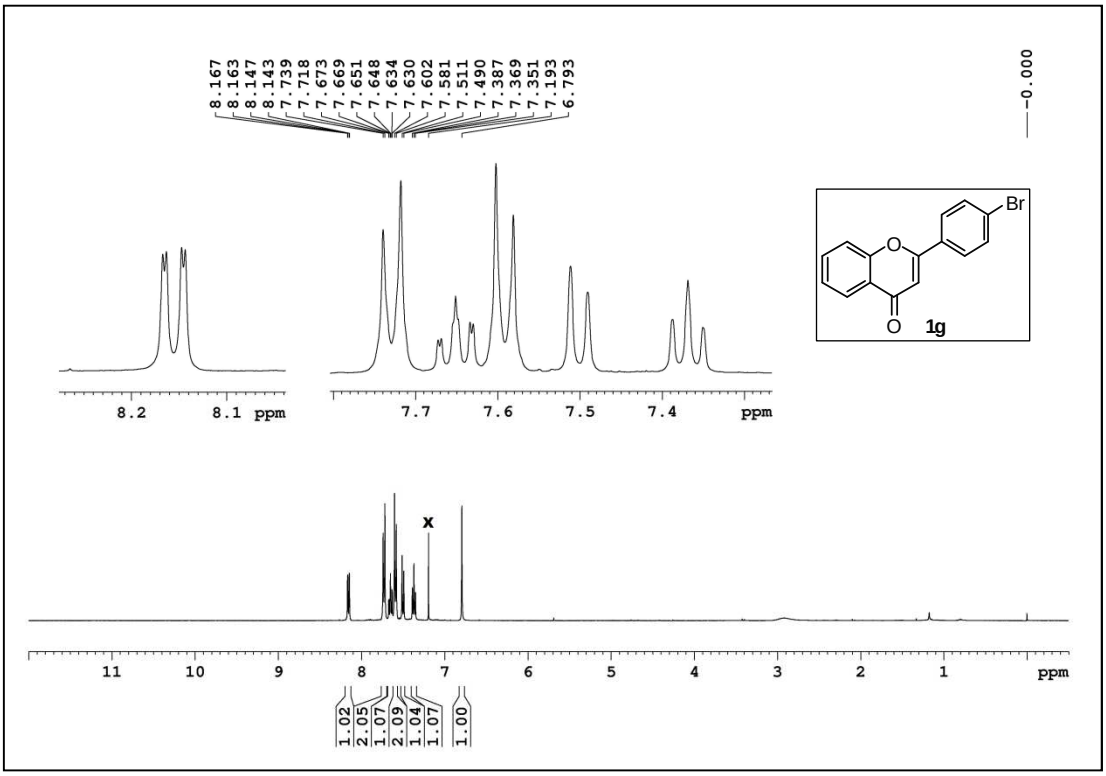
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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7.669
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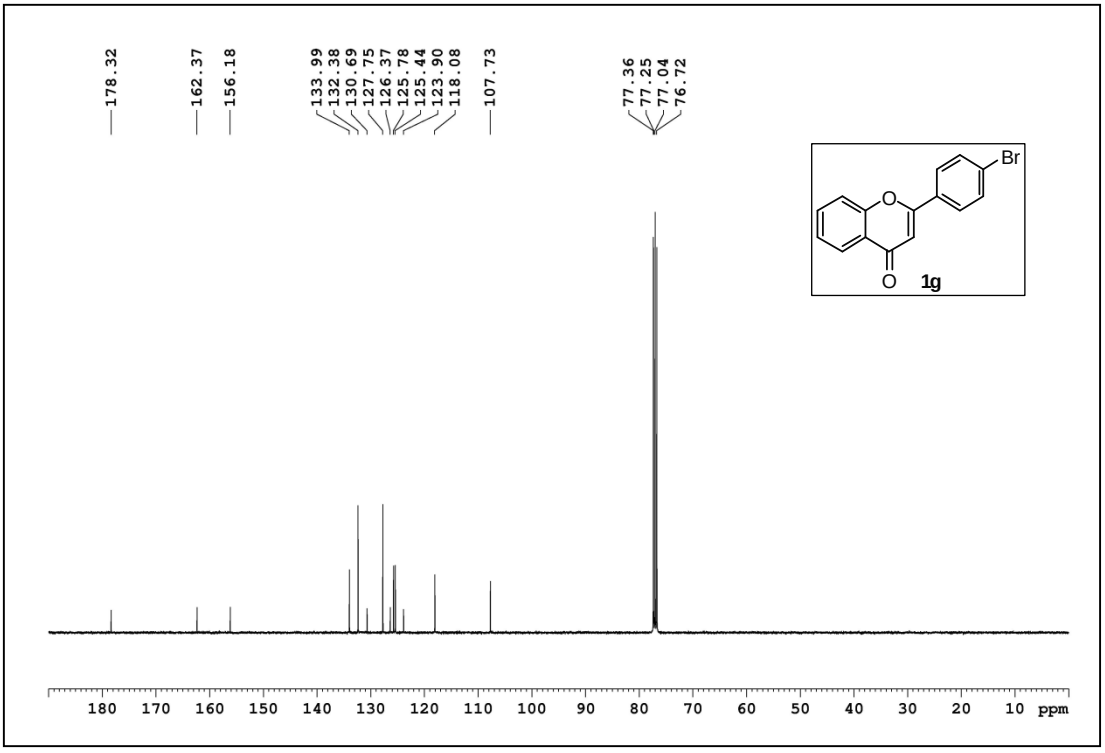
7.648
7.634
7.630
7.602
7.581
7.511
7.490
7.387
7.369
7.351
7.193
6.793
0.000
Br
O
O
1g
8.2
8.1 ppm
7.7
7.6
7.5
7.4 ppm
x
11
10
9
8
7
6
5
4
3
2
1 ppm
1.02
2.05
1.07
2.09
1.04
1.07
1.00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126.37
125.78
125.44
123.90
118.08
107.73
77.36
77.25
77.04
76.72
Br
O
O
1g
180
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160
150
140
130
120
110
100
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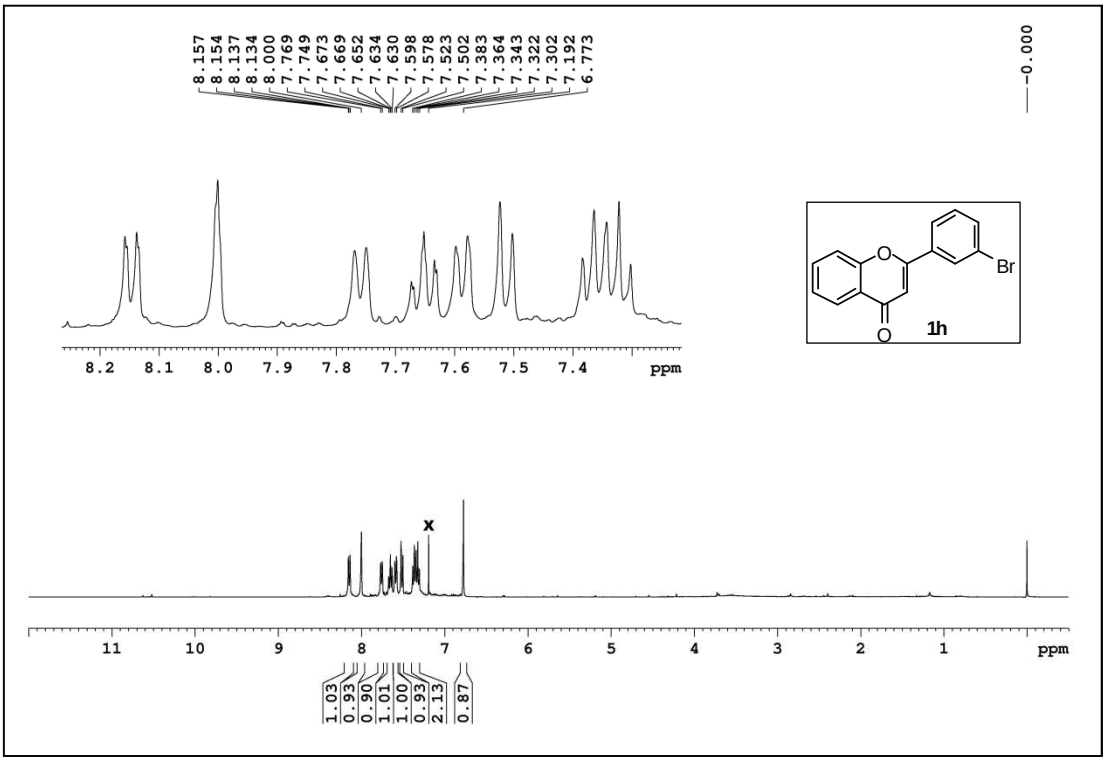
80
70
60
50
40
30
20
10 ppm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8.137
8.134
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7.769
7.749
7.673
7.669
7.652
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7.630
7.598
7.578
7.523
7.502
7.383
7.364
7.343
7.322
7.302
7.192
6.773
0.000
Br
O
O
1h
8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 ppm
x
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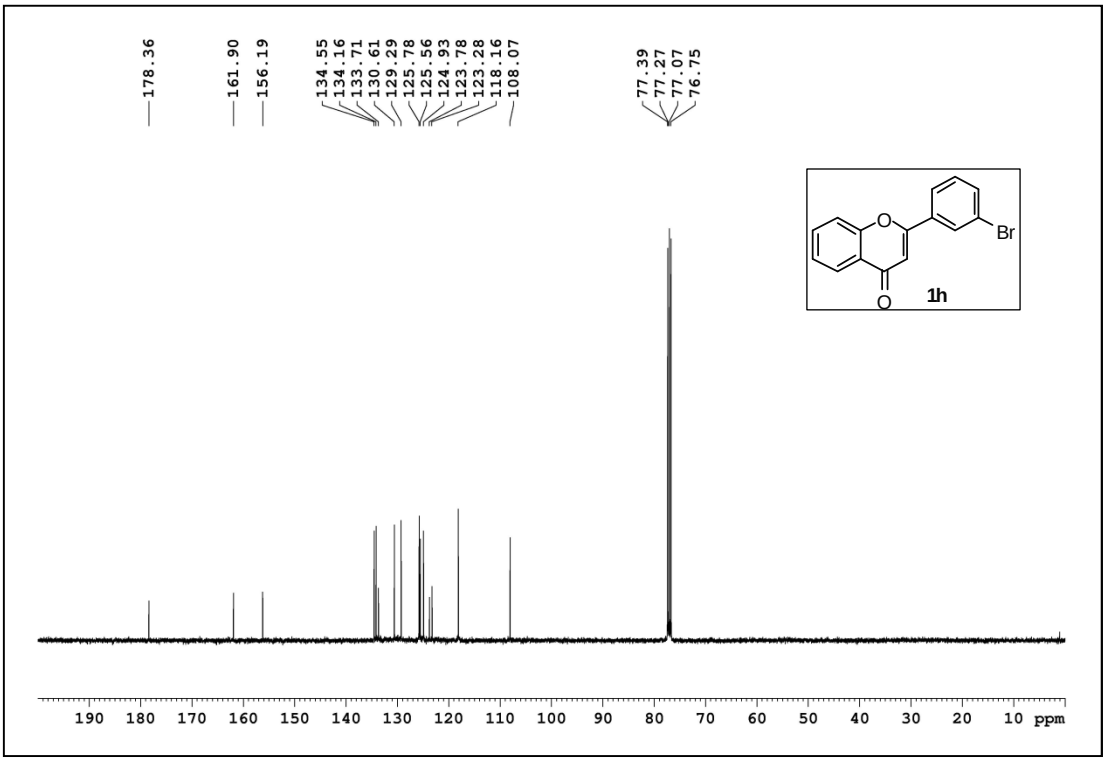
1.03
0.93
0.90
1.01
1.00
0.93
2.13
0.87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125.56
124.93
123.78
123.28
118.16
108.07
77.39
77.27
77.07
76.75
Br
O
O
1h
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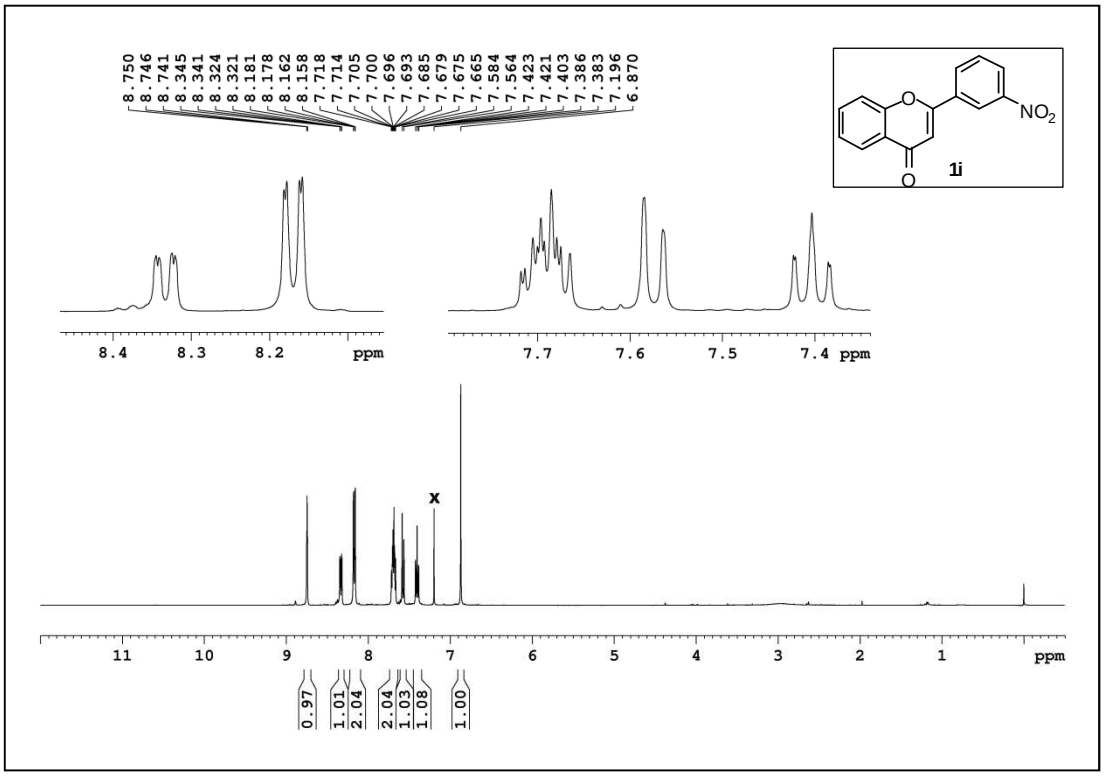
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8.162
8.158
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7.714
7.705
7.700
7.696
7.693
7.685
7.679
7.675
7.665
7.584
7.564
7.423
7.421
7.403
7.386
7.383
7.196
6.870
O
NO2
O
1i
8.4
8.3
8.2
ppm
7.7
7.6
7.5
7.4 ppm
x
11
10
9
8
7
6
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4
3
2
1
ppm
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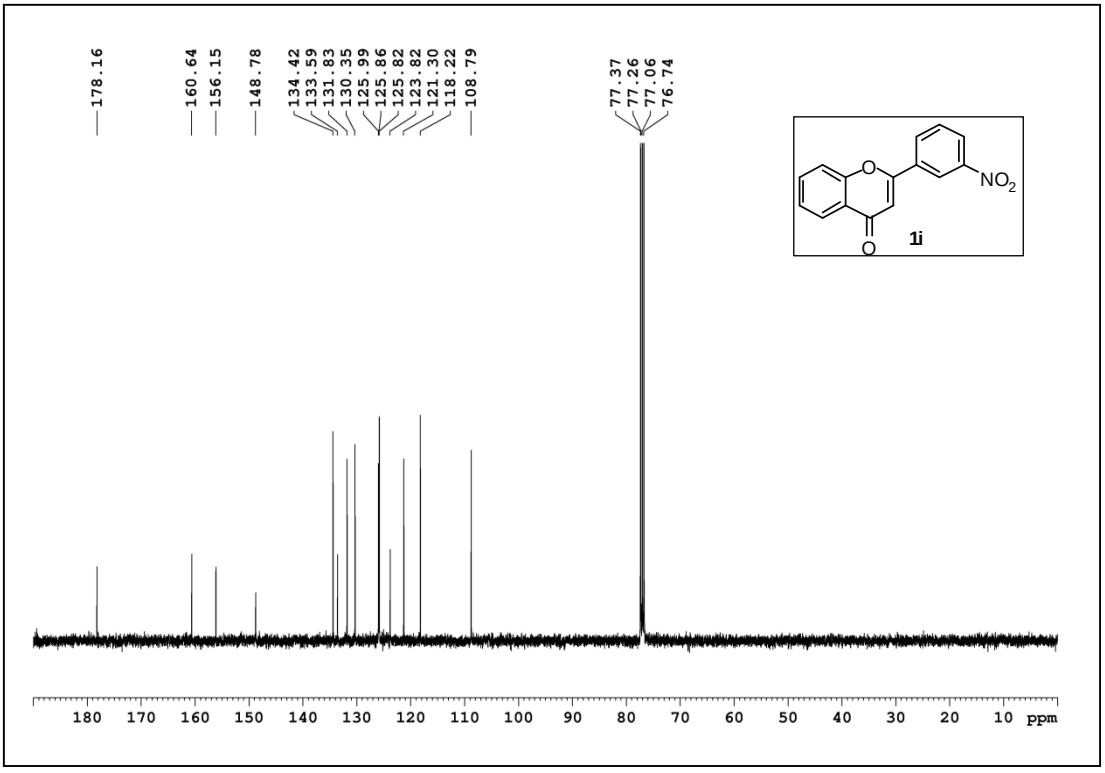
2.04
2.04
1.03
1.08
1.00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130.35
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125.86
125.82
123.82
121.30
118.22
108.79
77.37
77.26
77.06
76.74
O
NO2
O
1i
180
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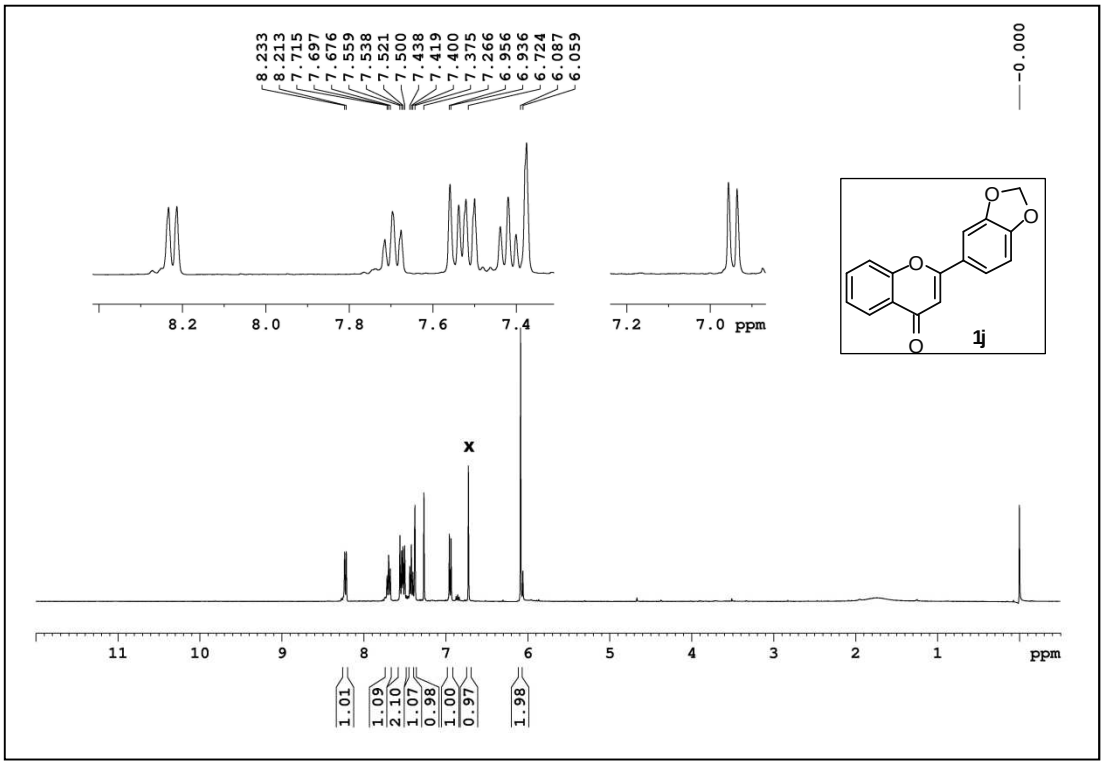
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10 ppm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7.697
7.676
7.559
7.538
7.521
7.500
7.438
7.419
7.400
7.375
7.266
6.956
6.936
6.724
6.087
6.059
-0.000
8.2
8.0
7.8
7.6
7.4
7.2
7.0 ppm
1j
x
11
10
9
8
7
6
5
4
3
2
1
ppm
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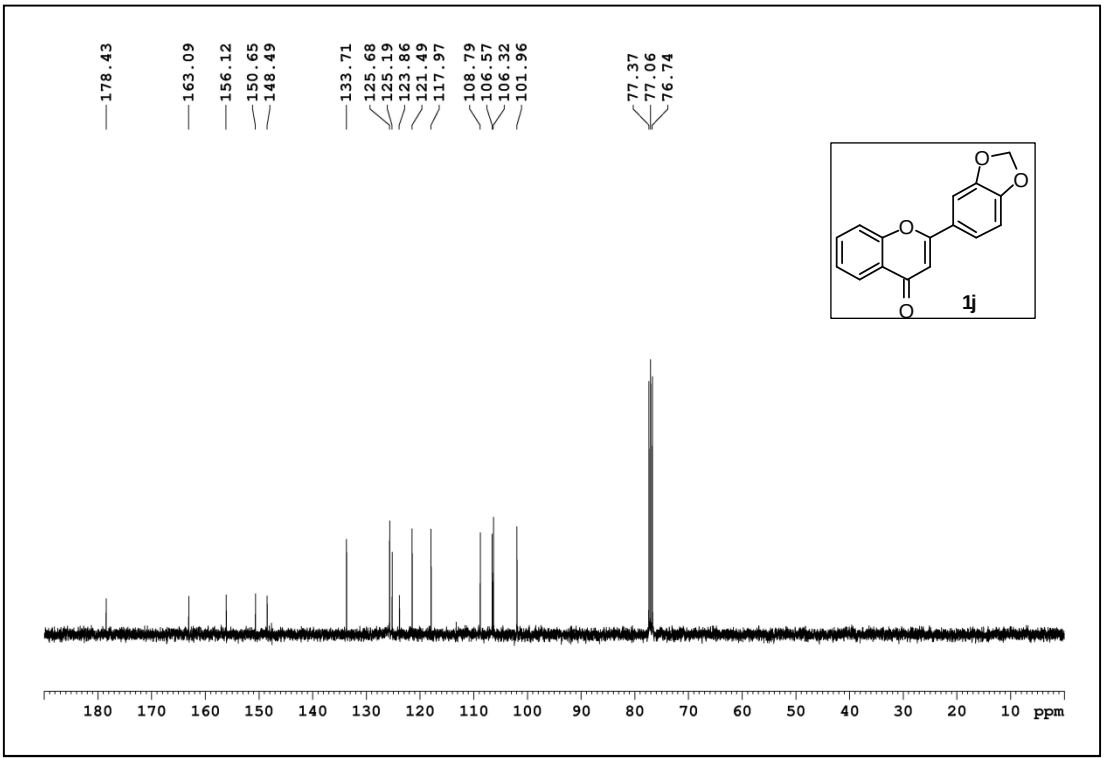
1.09
2.10
1.07
0.98
1.00
0.97
1.98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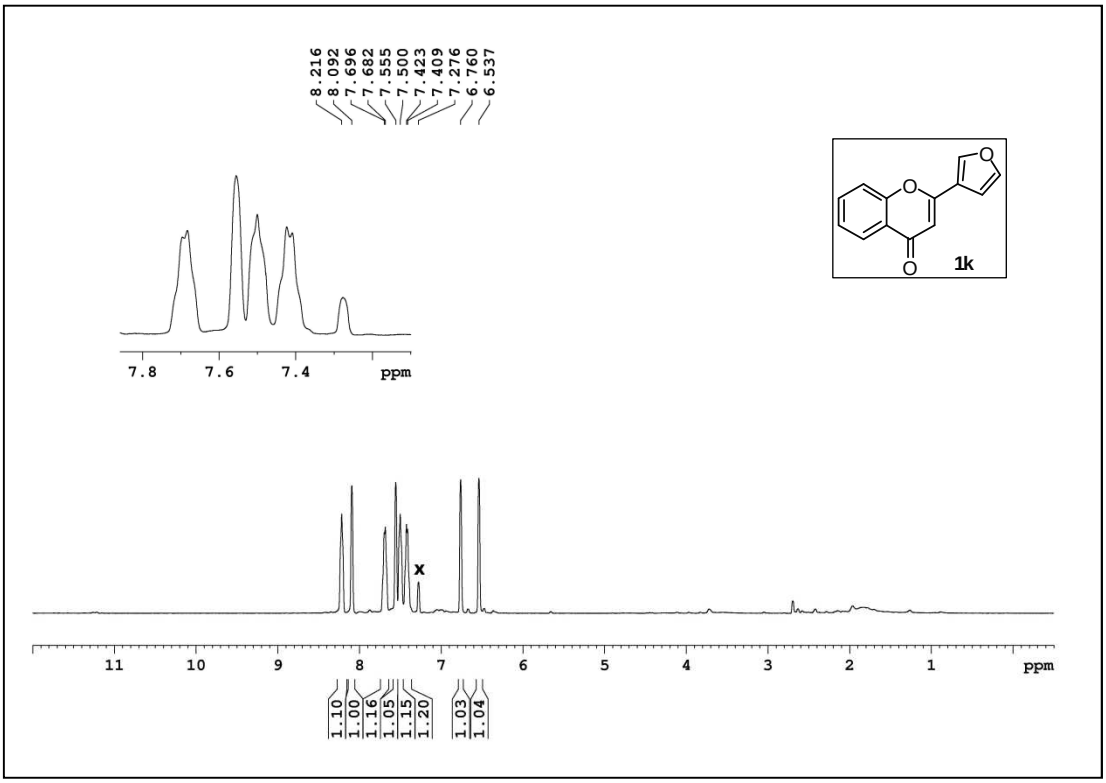
106.32
101.96
77.37
77.06
76.74
1j
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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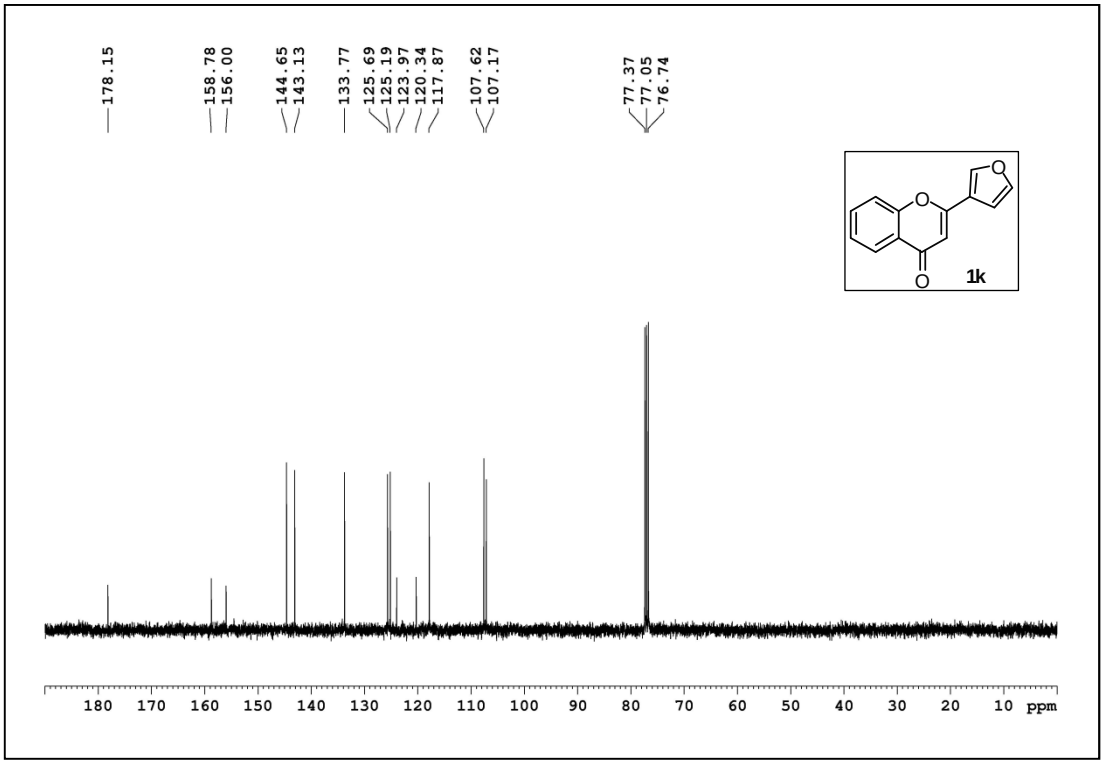
7.500
7.423
7.409
7.276
6.760
6.537
7.8
7.6
7.4
ppm
1k
x
11
10
9
8
7
6
5
4
3
2
1
ppm
1.10
1.00
1.16
1.05
1.15
1.20
1.03
1.04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156.00
144.65
143.13
133.77
125.69
125.19
123.97
120.34
117.87
107.62
107.17
77.37
77.05
76.74
1k
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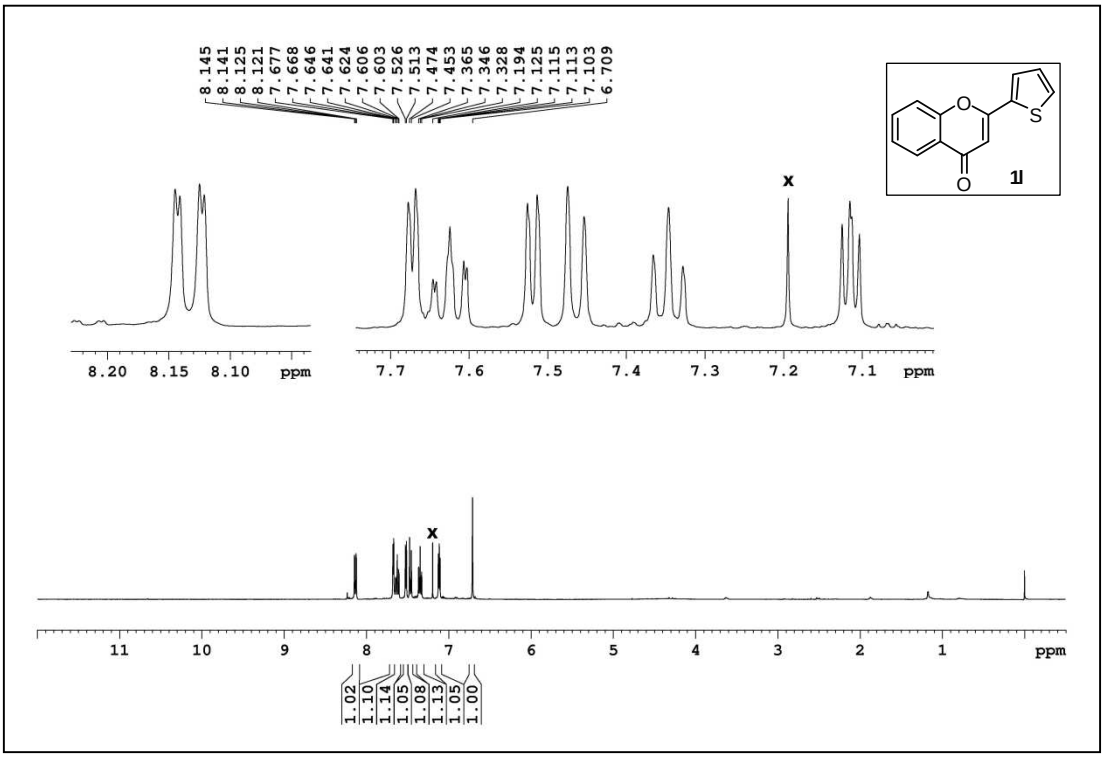
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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7.641
7.624
7.606
7.603
7.526
7.513
7.474
7.453
7.365
7.346
7.328
7.194
7.125
7.115
7.113
7.103
6.709
x
1l
8.20 8.15 8.10 ppm
7.7 7.6 7.5 7.4 7.3 7.2 7.1 ppm
x
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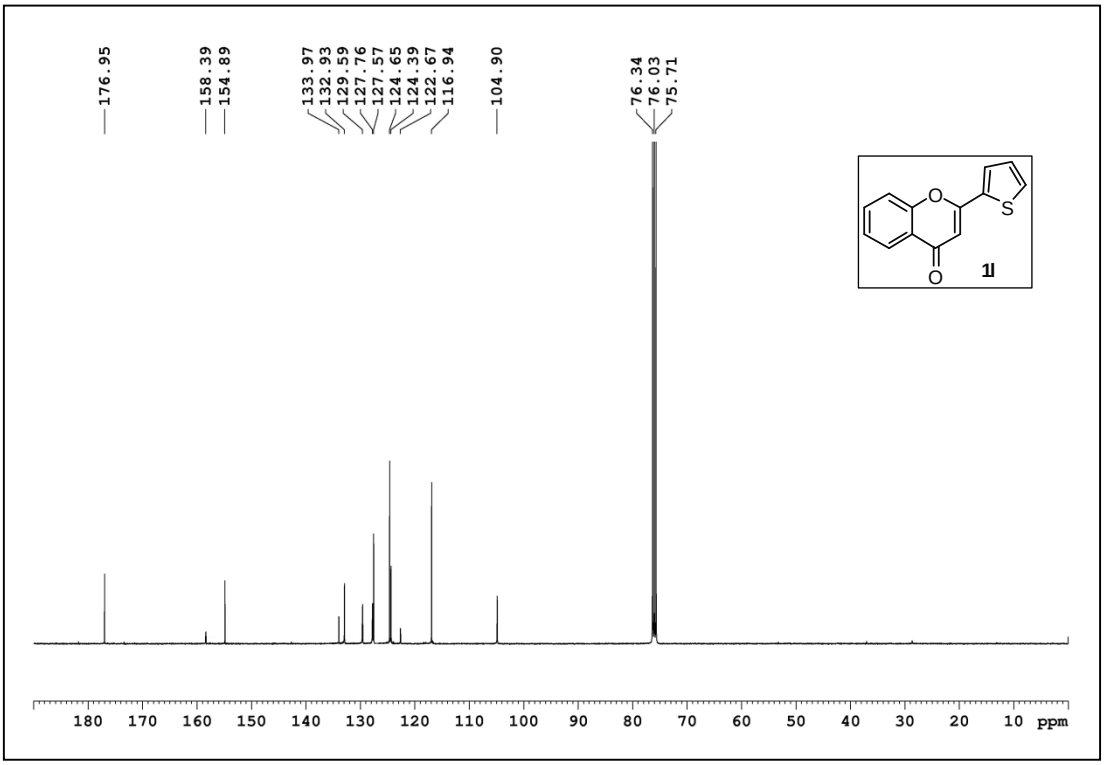
1.10
1.14
1.05
1.08
1.13
1.05
1.00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127.57
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104.90
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76.03
75.71
1l
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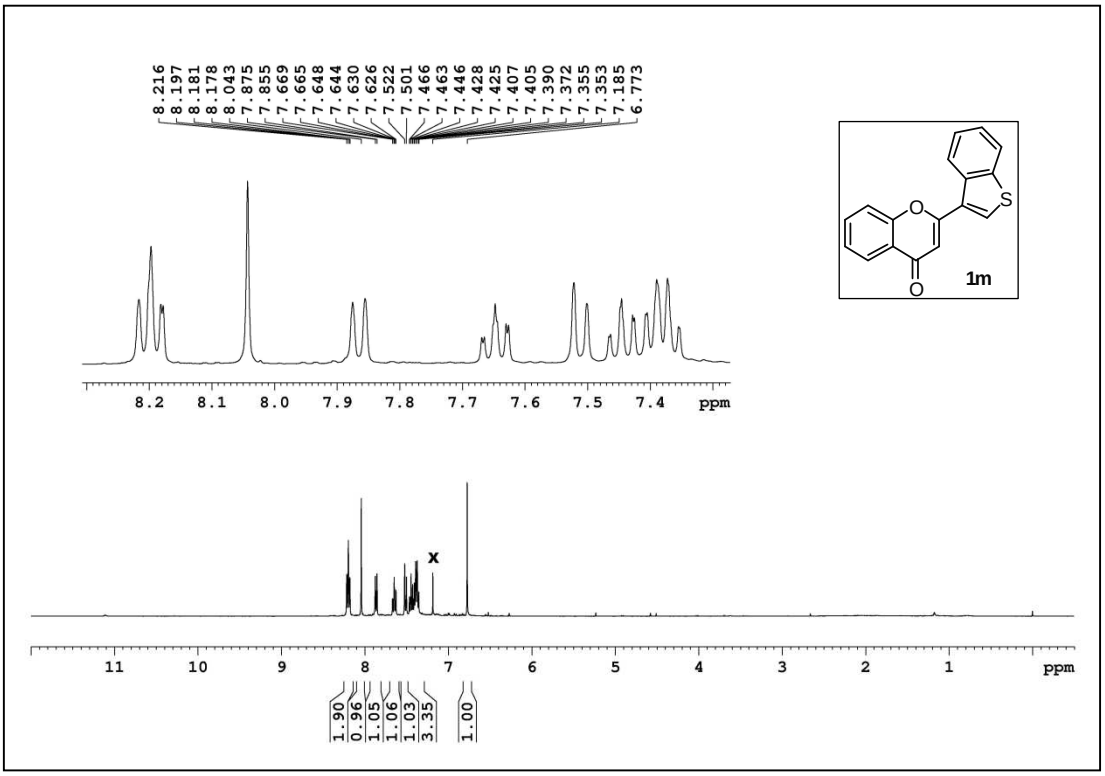
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8.043
7.875
7.855
7.669
7.665
7.648
7.644
7.630
7.626
7.522
7.501
7.466
7.463
7.446
7.428
7.425
7.407
7.405
7.390
7.372
7.355
7.353
7.185
6.773
8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 ppm
O
S
O
1m
x
11 10 9 8 7 6 5 4 3 2 1 ppm
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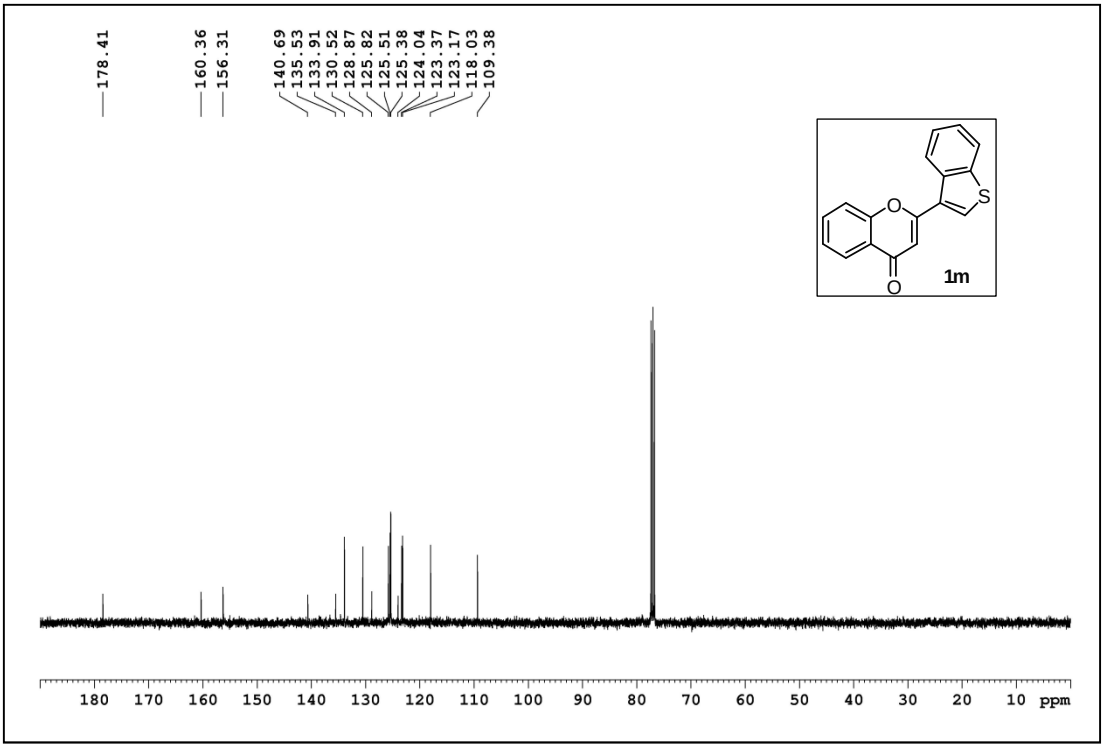
1.06
1.03
3.35
1.00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128.87
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125.51
125.38
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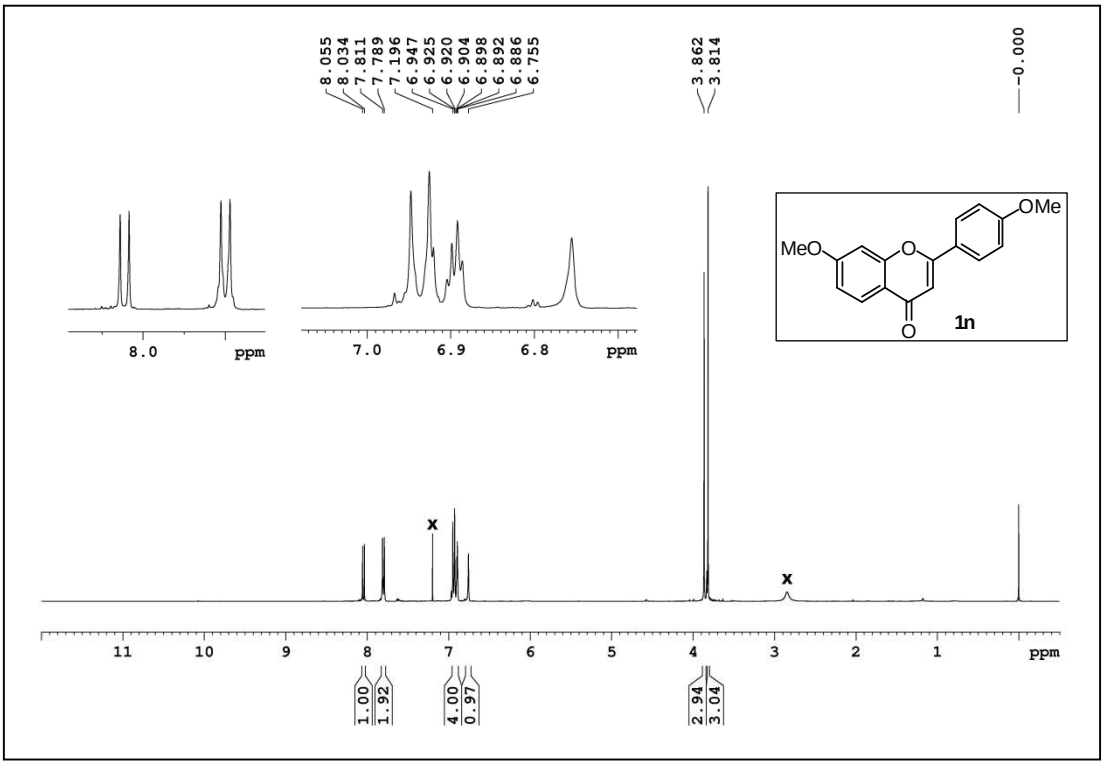
123.17
118.03
109.38
O
S
O
1m
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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6.947
6.925
6.920
6.904
6.898
6.892
6.886
6.755
3.862
3.814
-0.000
8.0
ppm
7.0
6.9
6.8
ppm
MeO
OMe
O
O
1n
x
x
11
10
9
8
7
6
5
4
3
2
1
ppm
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1.92
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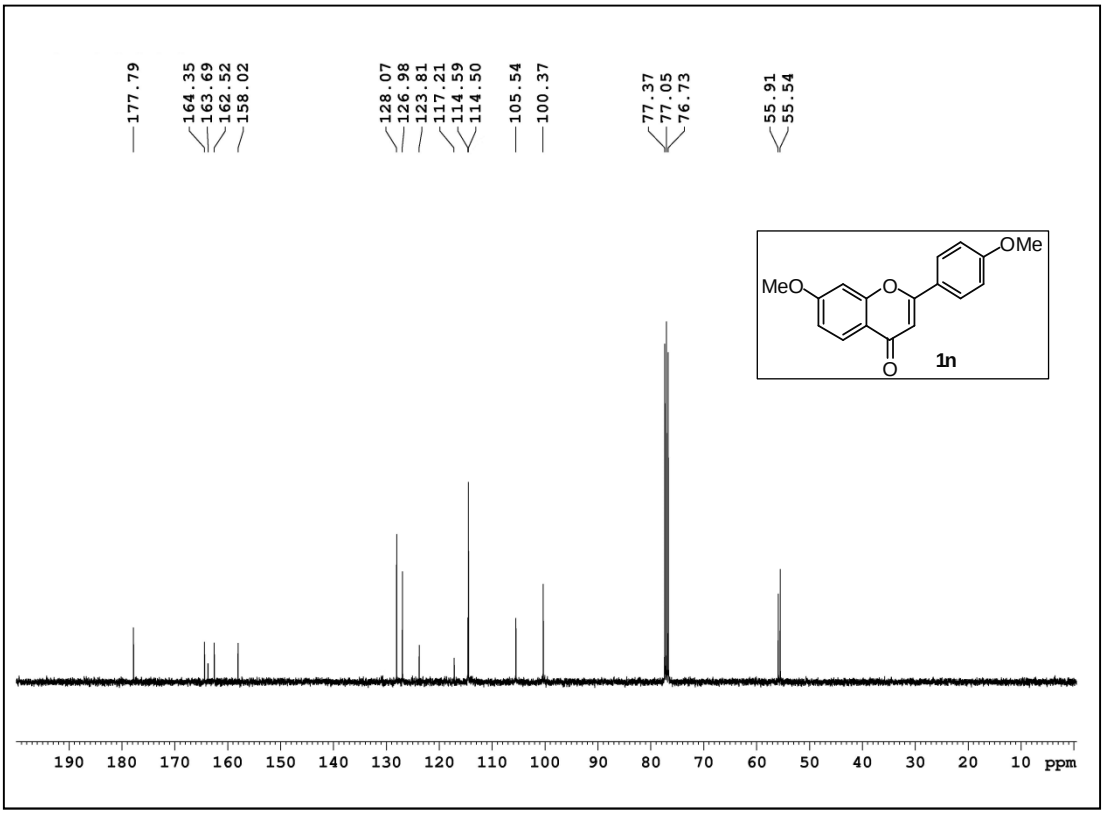
3.04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123.81
117.21
114.59
114.50
105.54
100.37
77.37
77.05
76.73
55.91
55.54
MeO
OMe
O
O
1n
190
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170
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150
140
130
120
110
100
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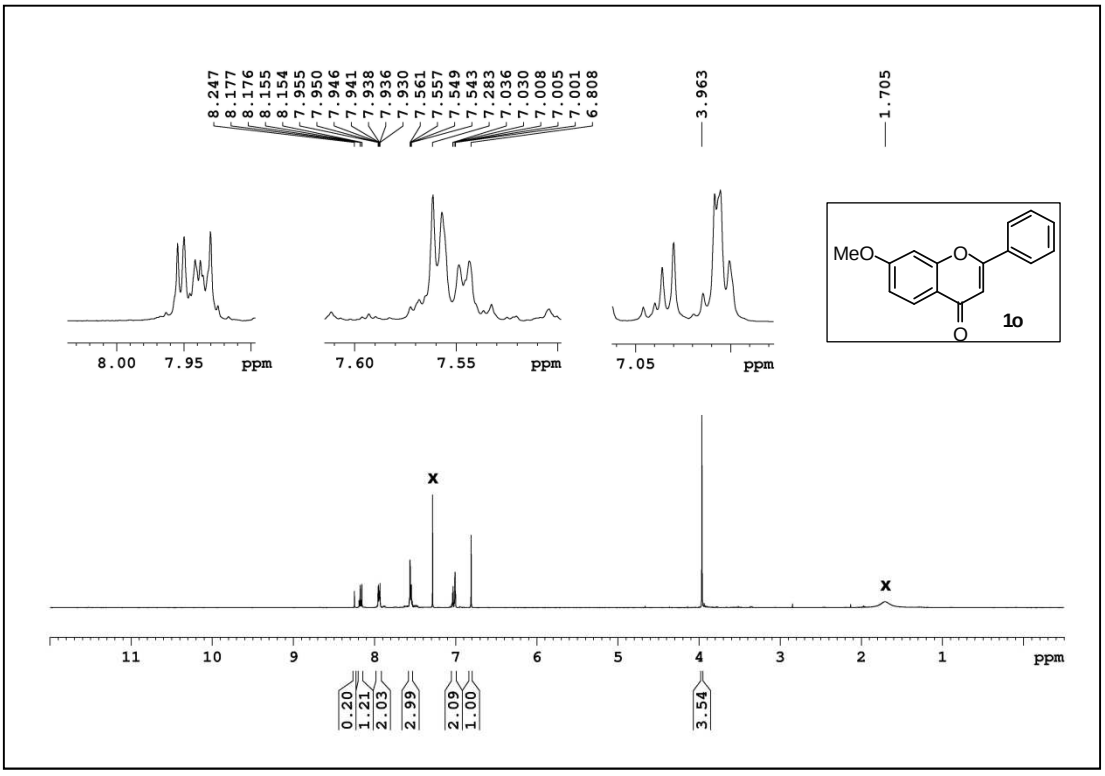
80
70
60
50
40
30
20
10
ppm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7.946
7.941
7.938
7.936
7.930
7.561
7.557
7.549
7.543
7.283
7.036
7.030
7.008
7.005
7.001
6.808
3.963
1.705
MeO
O
O
1o
8.00
7.95
ppm
7.60
7.55
ppm
7.05
ppm
x
x
11
10
9
8
7
6
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3
2
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ppm
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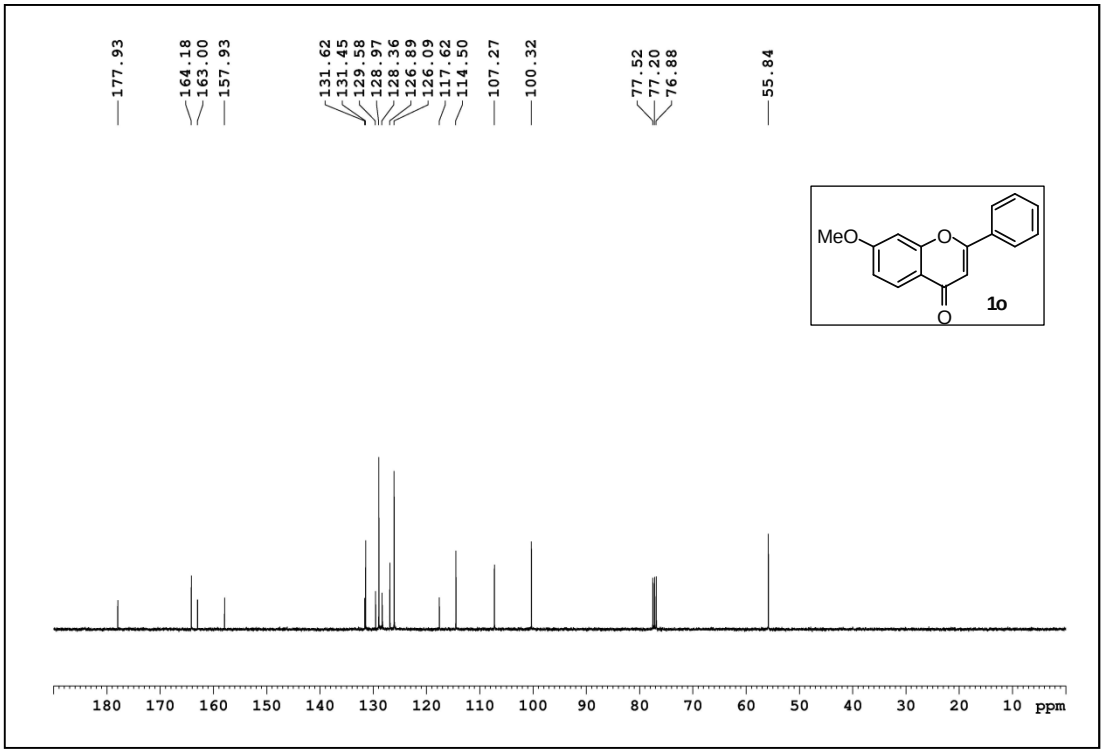
2.03
2.99
2.09
1.00
3.54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107.27
100.32
77.52
77.20
76.88
55.84
MeO
O
O
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150
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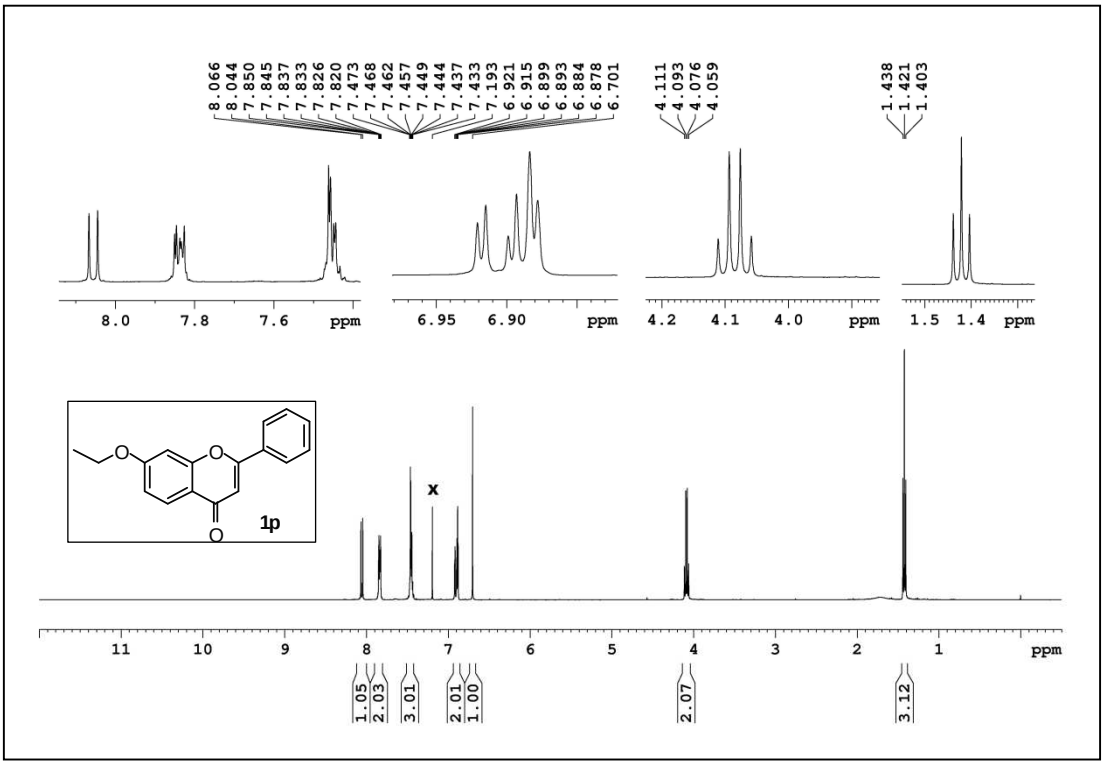
30
20
10
ppm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7.473
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7.462
7.457
7.449
7.444
7.437
7.433
7.193
6.921
6.915
6.899
6.893
6.884
6.878
6.701
4.111
4.093
4.076
4.059
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ppm
1p
x
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3.01
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1.00
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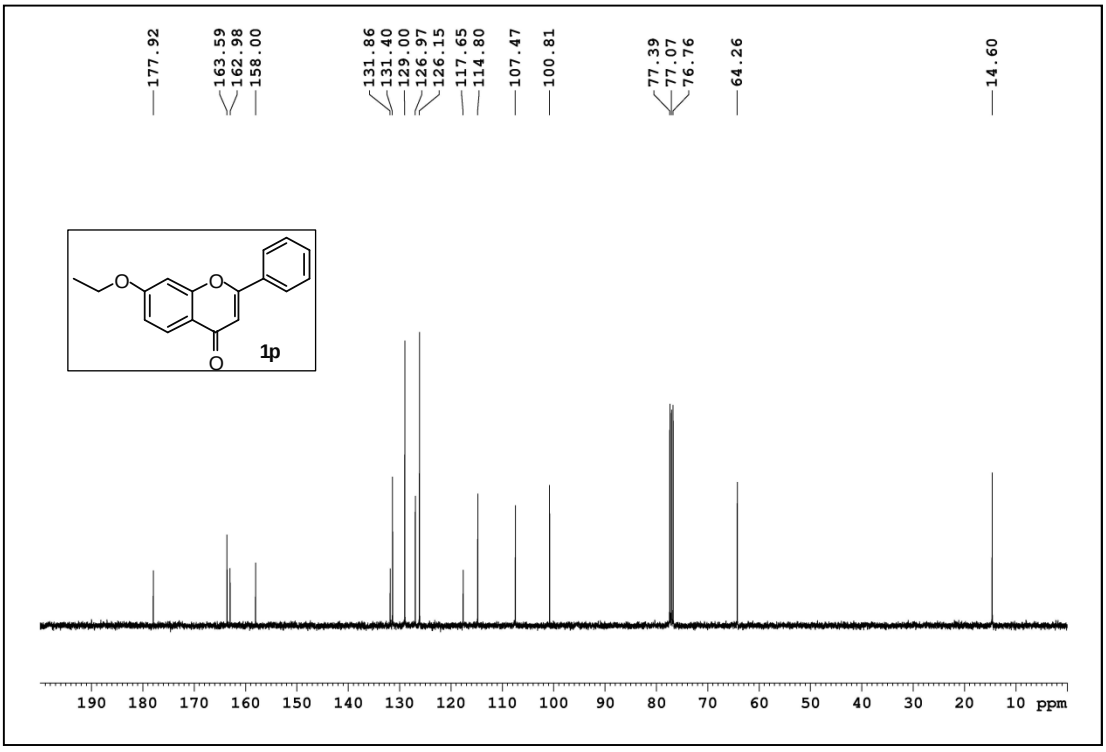
3.12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77.07
76.76
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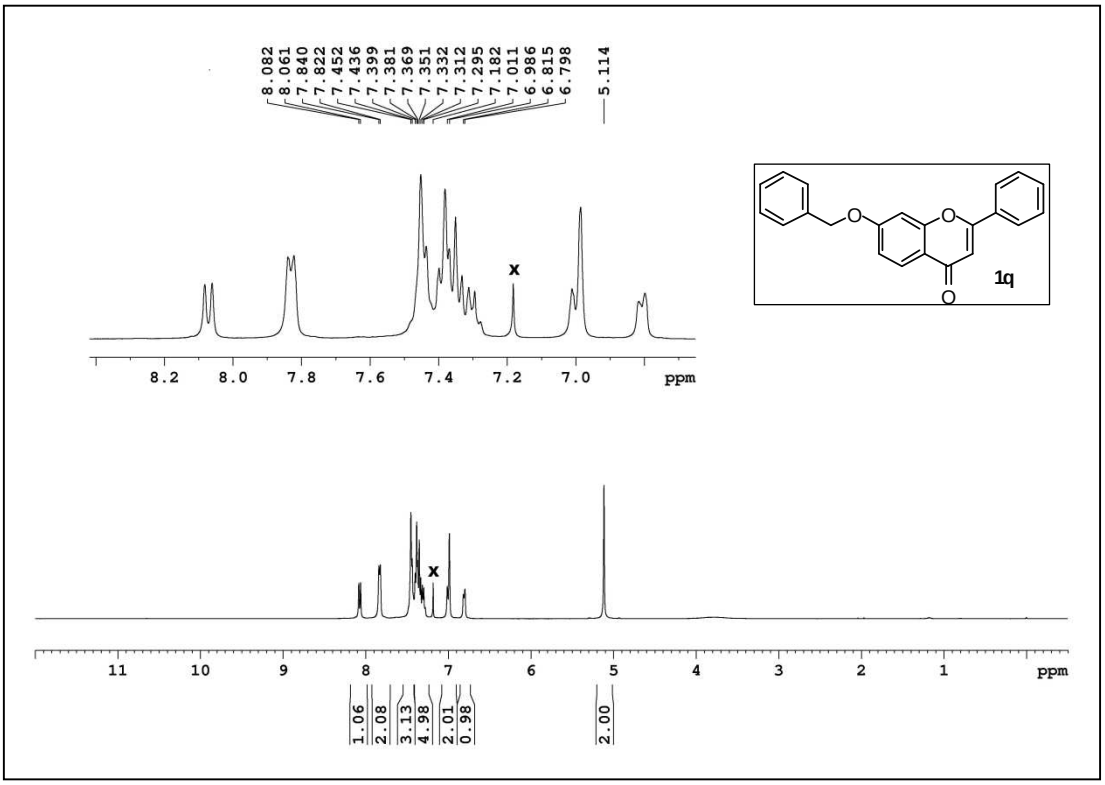
14.60
1p
ppm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7.295
7.182
7.011
6.986
6.815
6.798
5.114
x
8.2
8.0
7.8
7.6
7.4
7.2
7.0
ppm
1q
x
11
10
9
8
7
6
5
4
3
2
1
ppm
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2.08
3.13
4.98
2.01
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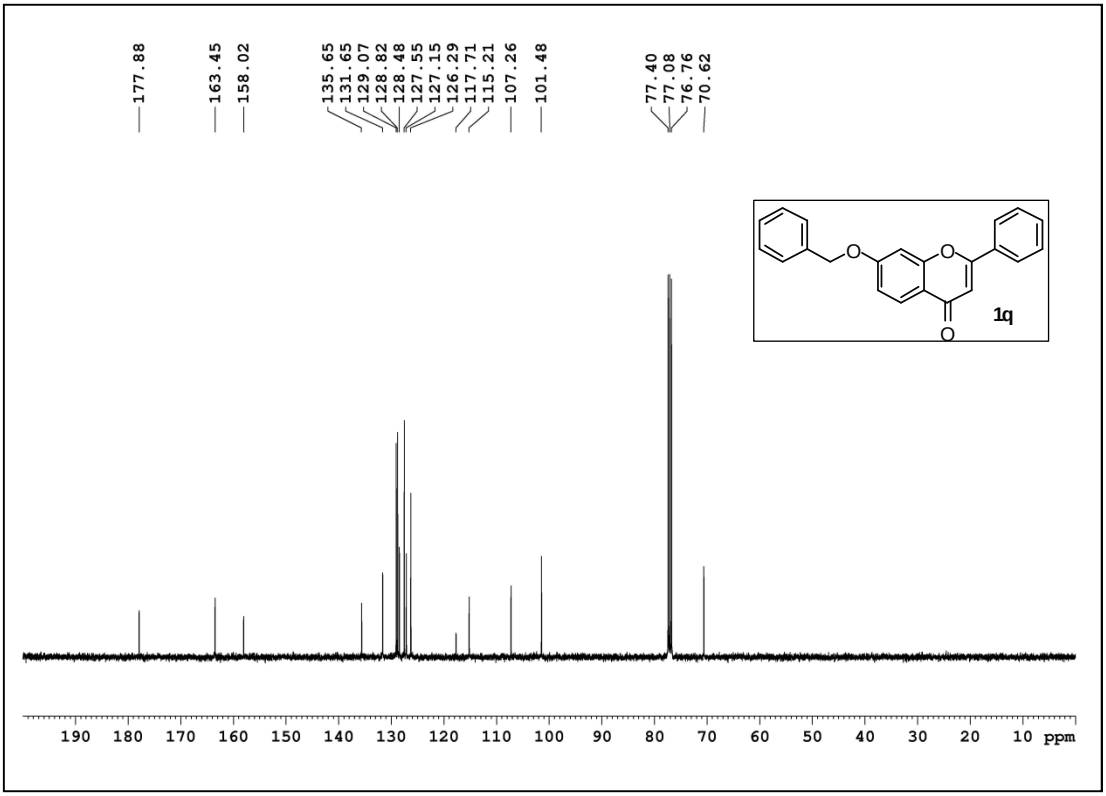
2.00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115.21
107.26
101.48
77.40
77.08
76.76
70.62
1q
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150
140
130
120
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90
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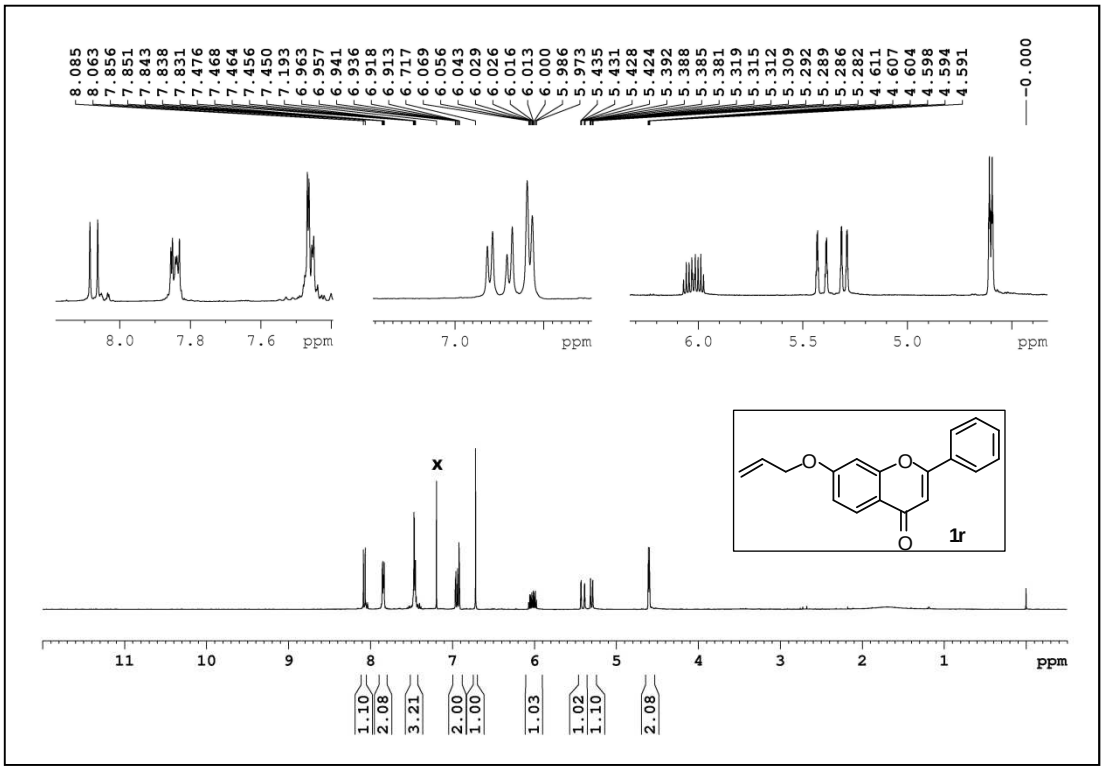
70
60
50
40
30
20
10
ppm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7.838
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7.476
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7.464
7.456
7.450
7.193
6.963
6.957
6.941
6.936
6.918
6.913
6.717
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6.043
6.029
6.026
6.016
6.013
6.000
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5.282
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4.607
4.604
4.598
4.594
4.591
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7.8
7.6
ppm
7.0
ppm
6.0
5.5
5.0
ppm
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1r
11
10
9
8
7
6
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4
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ppm
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1.00
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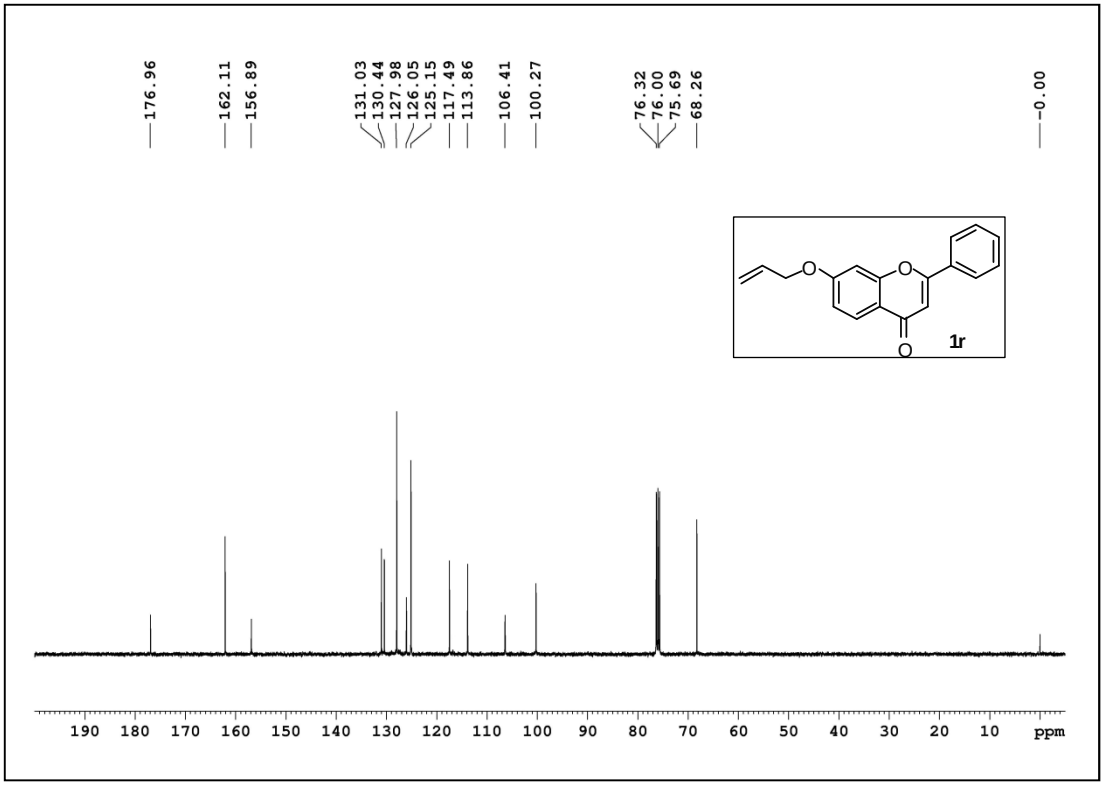
1.02
1.10
2.08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117.49
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76.00
75.69
68.26
0.00
1r
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150
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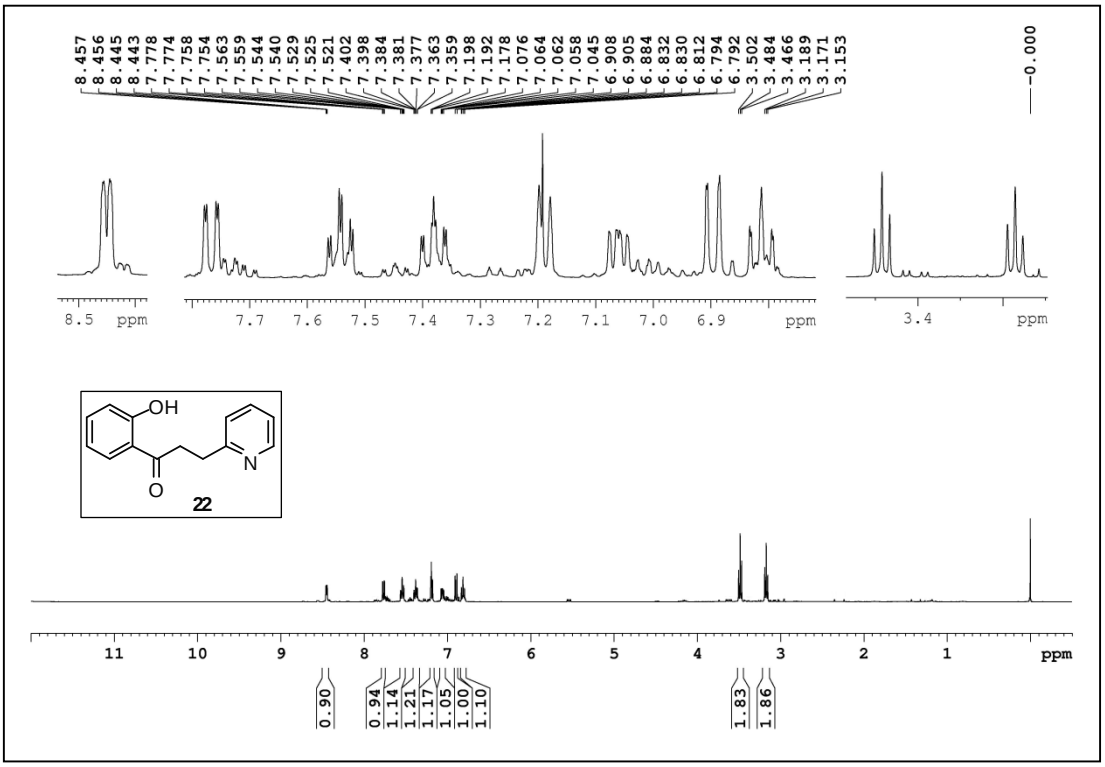
90
80
70
60
50
40
30
20
10
ppm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7.529
7.525
7.521
7.402
7.398
7.384
7.381
7.377
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7.359
7.198
7.192
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7.064
7.062
7.058
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6.884
6.832
6.830
6.812
6.794
6.792
3.502
3.484
3.466
3.189
3.171
3.153
-0.000
8.5 ppm
7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 ppm
3.4 ppm
OH
N
O
22
11 10 9 8 7 6 5 4 3 2 1 ppm
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0.94
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1.21
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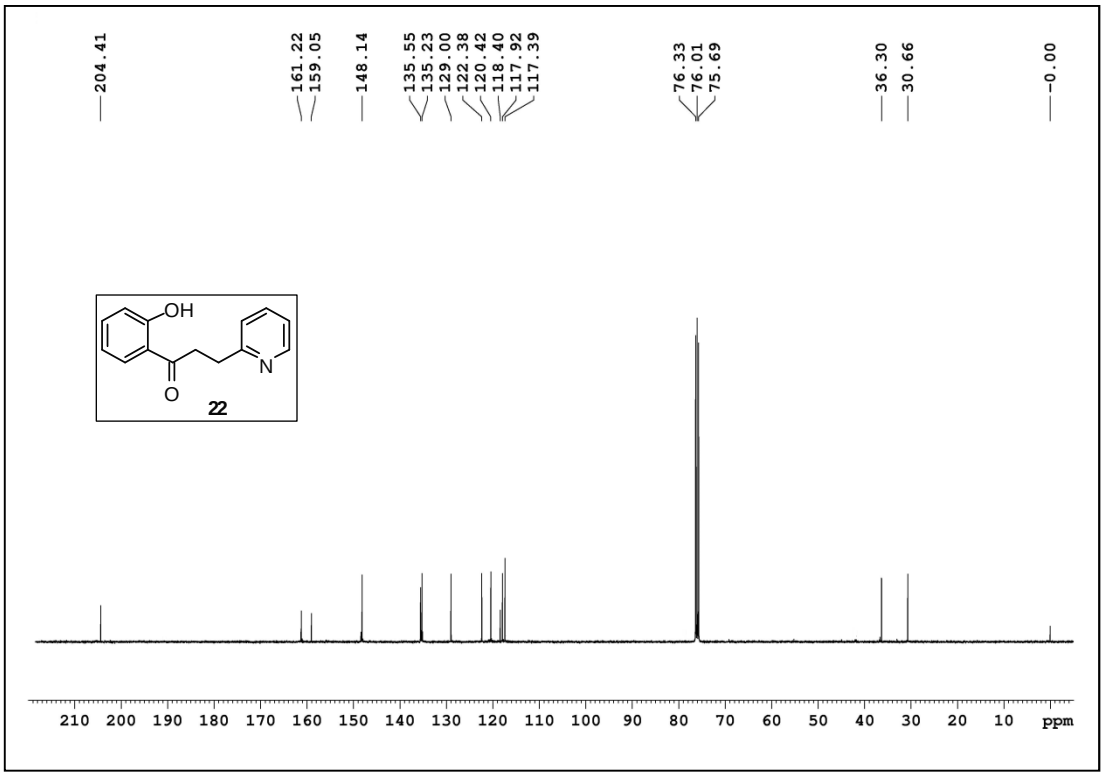
1.05
1.00
1.10
1.83
1.86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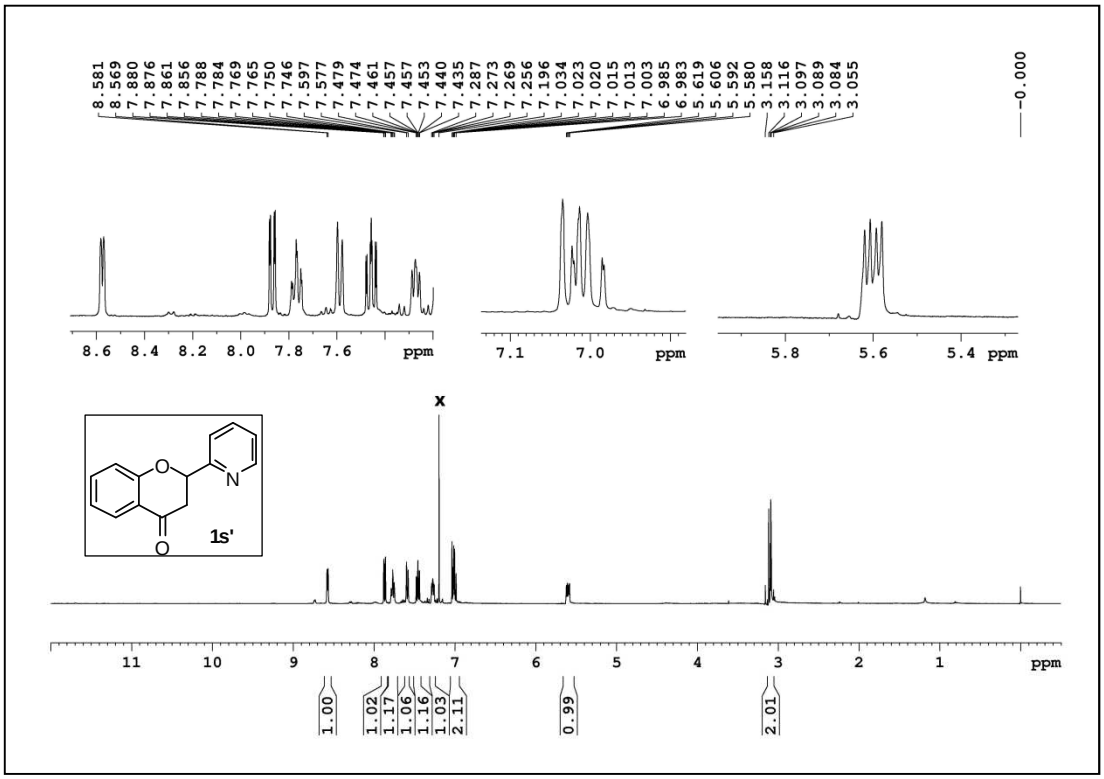
122.38
120.42
118.40
117.92
117.39
76.33
76.01
75.69
36.30
30.66
-0.00
OH
N
O
22
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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7.597
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7.453
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7.273
7.269
7.256
7.196
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7.023
7.020
7.015
7.013
7.003
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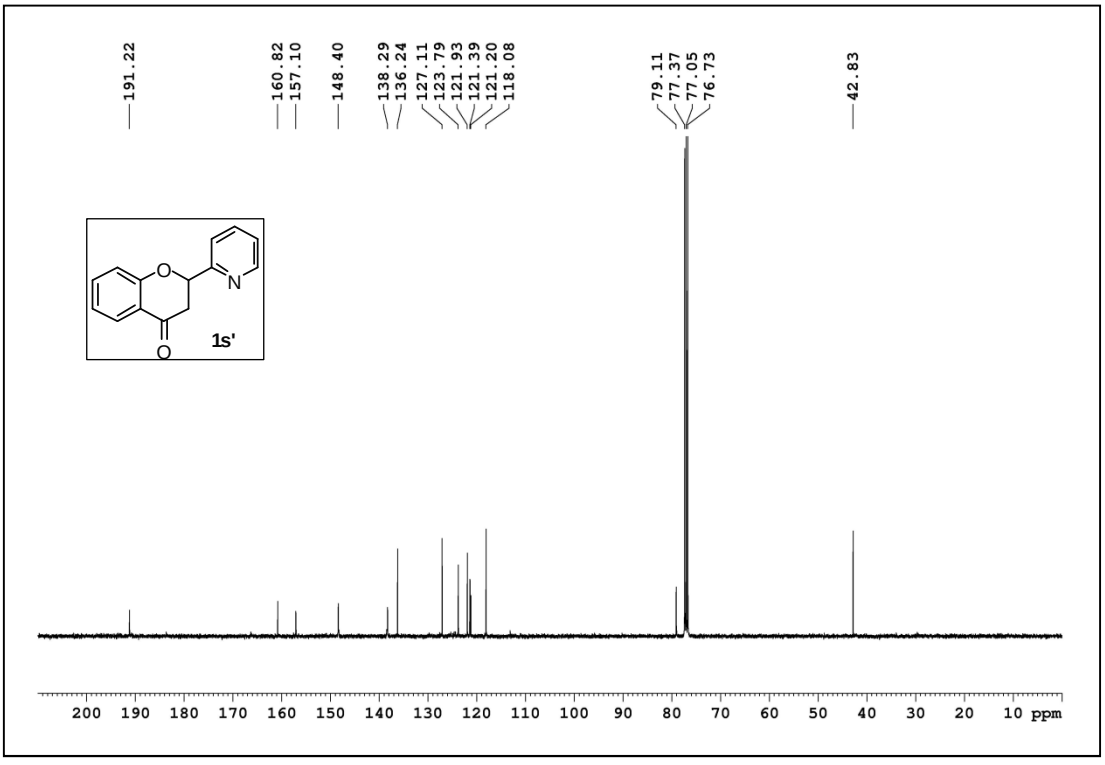
6.983
5.619
5.606
5.592
5.580
3.158
3.116
3.097
3.089
3.084
3.055
-0.000
8.6 8.4 8.2 8.0 7.8 7.6 ppm
7.1 7.0 ppm
5.8 5.6 5.4 ppm
x
1s'
11 10 9 8 7 6 5 4 3 2 1 ppm
1.00
1.02
1.17
1.06
1.16
1.03
2.11
0.99
2.01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138.29
136.24
127.11
123.79
121.93
121.39
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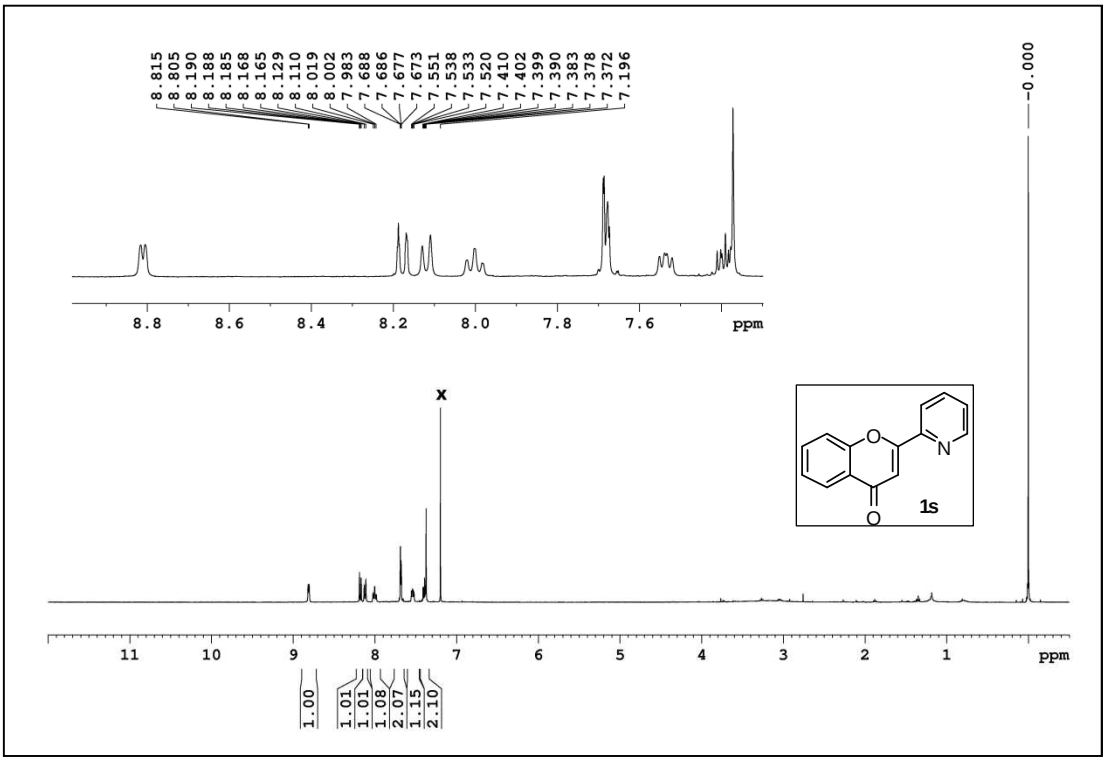
77.37
77.05
76.73
42.83
1s'
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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8.185
8.168
8.165
8.129
8.110
8.019
8.002
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7.551
7.538
7.533
7.520
7.410
7.402
7.399
7.390
7.383
7.378
7.372
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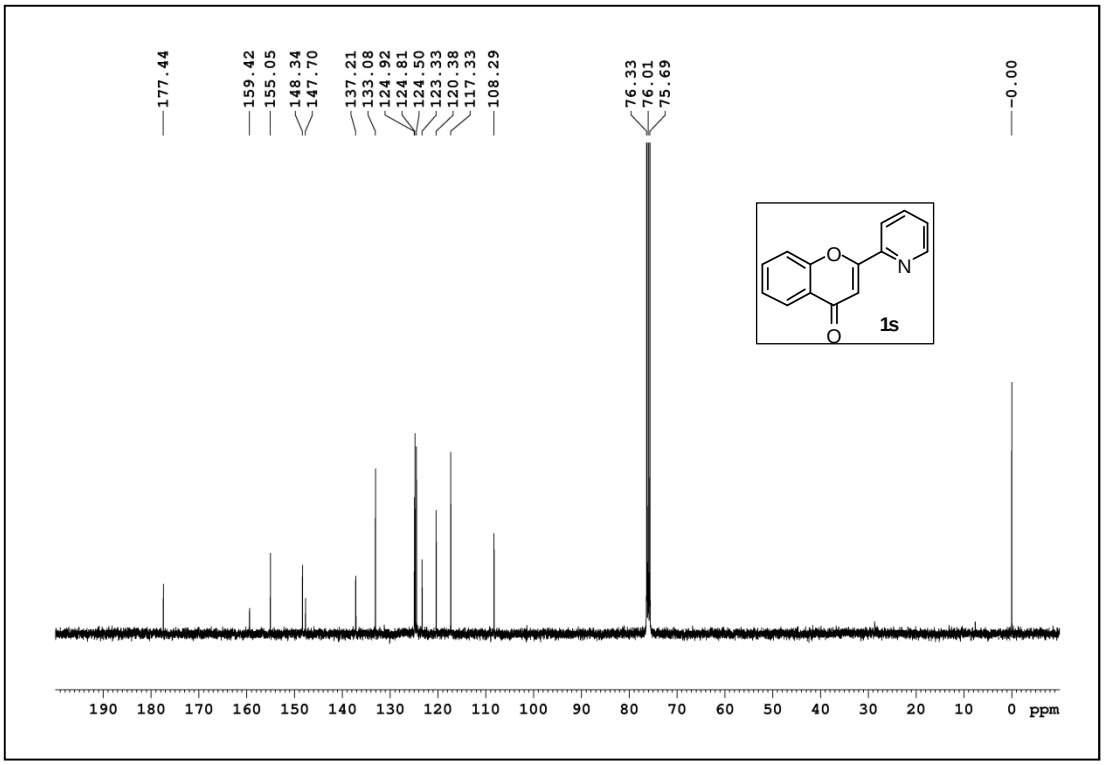
x
1s
1.00
1.01
1.01
1.08
2.07
1.15
2.10
ppm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148.34
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137.21
133.08
124.92
124.81
124.50
123.33
120.38
117.33
108.29
76.33
76.01
75.69
0.00
1s
ppm

CHAPTER 4

Synthetic studies of coumestans using $Cu(OAc)_2$

4.1: Introduction

6*H*-Benzofuro[3,2-*c*][1]-benzopyran-6-ones **1**, commonly known as coumestans, are polycyclic ring systems having a coumarin ring and a benzofuran ring fused together sharing a common C=C bond. A number of oxygenated compounds with this ring system are isolated from several natural sources, however parent coumestan **1a** is not known to occur in nature.

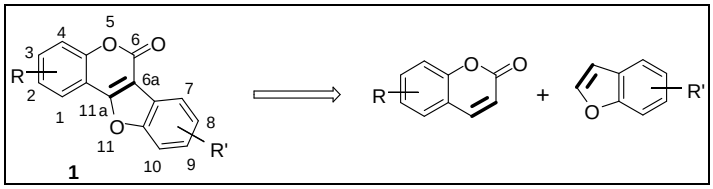


Figure 1: Structure of coumestan **1** with general numbering.

The general numbering of **1** is shown in figure 1. However it has been numbered in other 3 ways in the literature as shown below (Figure 2). Various names such as coumarino[3':4'-3:2]coumarone, benzofurano[3',2':3,4]coumarin, coumarino-benzofuran, 6-*oxo*-pterocarp-6a-ene, pterocarpone, 6*H*-[1]benzofuro[3,2-*c*]chromen-6-ones, benzofuro-*α*-benzopyrone, and coumestones are given to this class of compounds from which the coumestones was proposed by Ollis in 1966.[1] The name pterocarpone signifies that it is one of the member of pterocarponoids group analogous to flavonoids.

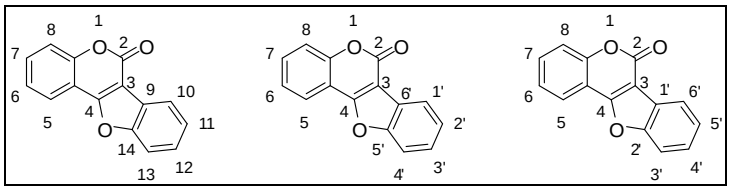


Figure 2: Different numberings of **1a**.

4.2: Occurrence

Coumestans[2] are found in diverse parts of plants such as leaves, roots and seeds.[3] The different plant sources belongs to *Papilionaceae*, *Leguminosae*, and *Compositae* families, most of them being isolated from *Leguminosae* plants. Coumestans are the final oxidation products of pterocarpans and pterocarpenes. It consists of several natural members among which wedelolactone **2a** was the first natural compound isolated by Govindachari *et al*. in 1956[4] from the leaves of *Wedelia calendulacea* (*Compositae*). Later it was also isolated from *Eclipta species*.[5] It is interesting to know that most of the natural coumestans isolated from diverse plant sources consists of a resorcinol unit in both the benzene rings i.e. presence of oxygen functionality at C_3 and C_9 positions **2** (Figure 3, Table 1). Also few of the natural members **3** do have oxygen functionality at C_4 and/or C_8 positions (Figure 4, Table 2) whereas other compounds **4** are shown in figure 5 (Table 3).

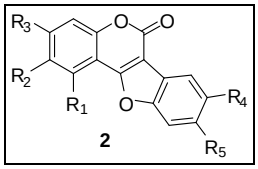


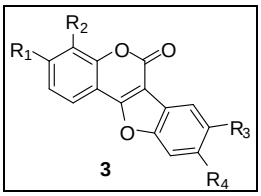
Figure 3: Naturally occurring coumestans **2**.

Table 1: Source of isolation of naturally occurring coumestans **2**.

No.	Name ***Source of isolation***	R_1	R_2	R_3	R_4	R_5
2a	Wedelolactone[4,5] *Wedelia calendulacea, Eclipta alba, Eclipta prostrata, Wedelia chinensis*	OH	H	OMe	OH	OH
2b	Norwedelolactone[5b-c,5e] *Eclipta alba, Eclipta prostrate, Wedelia chinensis*	OH	H	OH	OH	OH
2c	Coumestrol[6,8a-c,14a,23a,26a-b,31a,33a-c,34,49] *Medicago sativa, Trifolium repens, Trifolium fragiferum,* leguminous plants, *Trifolium pratense, Trifolium subterraneum,* annual medics, Chinese milk vetch, Soyabean, legume shoots & sprouts, processed food, *Derris species, Melilotus messanensis, Phaseolus aureus, Soja hispida,* soyabean roots, *Solanum iyratum, Pueraria mirifica, Pueraria lobata, Dolichos biflorus, Phaseolus lunatus, Melilotus indica*	H	H	OH	H	OH
2d	8-Methoxycoumestrol[7,8c] *Medicago sativa, Arachis hypogaea, Tephrosia purpurea*	H	H	OH	OMe	OH
2e	9-Methoxycoumestrol[8] *Dalbergia odorifera, Cicer species, Melilotus messanensis, Medicago sativa, Dalbergia oliveri, Dalbergia stevensonii, Trifolium pratense, Centrolobium species, Spatholobi*	H	H	OH	H	OMe

	caulis					
2f	Coumestrol dimethyl ether[9] *Dalbergia decipularis*	H	H	OMe	H	OMe
2g	Medicagol[8c-i,10] *Cicer species, Medicago sativa, Sophora chrysophylla, Cyclopia intermedia, Maackia amurensis, Galega officinalis, Flemingia macrophylla, Sophora japonica, Dalbergia oliveri, Dalbergia stevensonii, Sophora tomentosa, Euchresta japonica, Trifolium pratense*	H	H	OH	-O-CH_2-O-	
2h	Lucernol[8c,11] *Medicago sativa*	H	OH	OH	H	OH
2i	Flemichapparin C[10b-c,12] *Flemingia chappar, Tephrosia hamiltonii, Eysenhardtia polystachya, Cyclopia intermedia, Galega officinalis, Derris scandens*	H	H	OMe	-O-CH_2-O-	
2j	2-Hydroxyflemichapparin C[13] *Swartzia leiocalycina*	H	OH	OMe	-O-CH_2-O-	
2k	Aureol[10d,14] *Phaseolus aureus, Hedysarum multijugum, Flemingia macrophylla*	OH	H	OH	H	OH
2l	6-hydroxy-5,7-dimethoxy-11,12-methylenedioxycoumestone[13a] *Swartzia leiocalycina*	OMe	OH	OMe	-O-CH_2-O-	
2m	7-hydroxy,11,12-dimethoxycoumestan[8b,15] *Alfalfa, Melilotus messanensis*	H	H	OH	OMe	OMe
2n	Flemicoumestan A[16] *Flemingia philippinensis*	OH	H	OH	OMe	OH
2o	Hedysarimcoumestan A[14b-c] *Hedysarum multijugum*	OH	H	OMe	H	OMe

2p	Hedysarimcoumestan B[14b-c] *Hedysarum multijugum*	OH	H	OH	H	OMe
2q	Hedysarimcoumestan E[14b-c] *Hedysarum multijugum*	OH	H	OH	OMe	OMe
2r	1,3,9-Trimethoxycoumestan[14b] *Hedysarum multijugum*	OMe	H	OMe	H	OMe
2s	2-methoxy-3,9-dihydroxy coumestan[12a] *Tephrosia hamiltonii*	H	OMe	OH	H	OH
2t	Isotrifoliol[17] *Glycyrrhiza uralensis*	OMe	H	OH	H	OH



3

Figure 4: Naturally occurring coumestans **3**.

Table 2: Source of isolation of naturally occurring coumestans **3**.

No.	**Name** ***Source of isolation***	**R_1**	**R_2**	**R_3**	**R_4**
3a	Sophoracoumestan B[10b,18] *Sophora franchetiana, Cyclopia intermedia*	OH	OMe	-O-CH_2-O-	
3b	Sativol[8c,11] *Medicago sativa*	OMe	OH	H	OH
3c	Pongacoumestan[7a,19] *Pongamia pinnata*, *Arachis hypogaea*	OH	OMe	H	OH
3d	4-Hydroxycoumestrol[20] *Erythrina sigmoidea*	OH	OH	H	OH
3e	3-Hydroxy-4,9-dimethoxycoumestan[21] *Ononis vaginalis*	OH	OMe	H	OMe
3f	3,9-dihydroxy-4, 8-dimethoxycoumestan[7a] *Arachis hypogaea*	OH	OMe	OMe	OH
3g	3-Hydroxy-8-methoxycoumestan[8j] *Medicago species*	OH	H	OMe	H

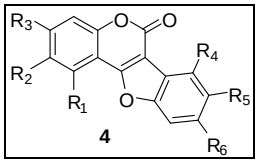


Figure 5: Naturally occurring coumestans **4**.

Table 3: Source of isolation of naturally occurring coumestans **4**.

No.	Name ***Source of isolation***	R_1	R_2	R_3	R_4	R_5	R_6
4a	Hedysarimcoumestan F[14b-c] *Hedysarum multijugum*	OH	H	OMe	OH	H	OMe
4b	Wairol[22] *Medicago sativa*	H	H	OH	OMe	H	OMe
4c	Tephrosol[23] *Tephrosia villosa*	H	OMe	OH	H	-O-CH_2-O-	
4d	Repensol[8a] *Trifolium repens*	H	H	OH	OH	H	OH
4e	Trifoliol[8a,c,24] *Trifolium repens, Medicago sativa*	H	H	OH	OH	H	OMe
4f	Melimessanol A[8b] *Melilotus messanensis*	H	OH	OMe	H	H	H
4g	Mutisifurocoumarin[25] *Mutisia orbignyana, Mutisia acuminata*	CH_3	H	H	H	OH	OH

Some of the prenylated coumestans **5** and **6** are shown in figures 6 and 7 respectively have been isolated from various sources (Table 4-5).

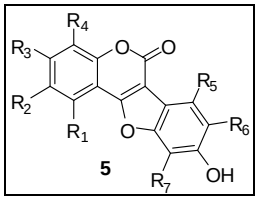
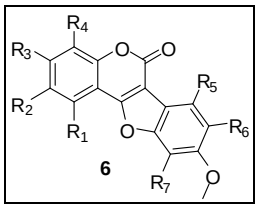


Figure 6: Naturally occurring prenylated coumestans **5**.

Table 4: Source of isolation of naturally occurring coumestans **5**.

No.	Name ***Source of isolation***	R_1	R_2	R_3	R_4	R_5	R_6	R_7
5a	Psoralidin[26] *Psoralea corylifolia*, *Dolichos biflorus*, *Phaseolus lunatus*	H	Prenyl	OH	H	H	H	H
5b	Glycyrol[17b] *Glycyrrhiza uralensis*	OMe	Prenyl	OH	H	H	H	H
5c	3-*O*-Methylglycyrol[27b-c] *Glycyrrhiza species*	OMe	Prenyl	OMe	H	H	H	H
5d	Phaseol[14a] *Phaseolus aureus*	H	H	OH	Prenyl	H	H	H
5e	Isosojagol[28] *Phaseolus coccineus*, *Erythrina abyssinica*	H	H	OH	H	H	H	Prenyl
5f	Sigmoidin K[28b,29] *Erythrina sigmoidea*, *Erythrina abyssinica*	H	Prenyl	OH	H	H	H	Prenyl
5g	Puerarostan[30] *Pueraria tuberosa*	H	H	OH	OMe	H	Prenyl	H
5h	Mirificoumestan[31] *Pueraria mirifica*, *Pueraria hirsuta*	H	H	OH	H	Prenyl	OMe	H



6

Figure 7: Naturally occurring prenylated coumestans **6**.

Table 5: Source of isolation of naturally occurring coumestans **6**.

No.	Name ***Source of isolation***	R_1	R_2	R_3	R_4	R_5	R_6	R_7
6a	Erythribyssin N[28b] *Erythrina abyssinica*	H	H	OH	H	H	H	Prenyl
6b	Hedysarimcoumestan D[14b-c] *Hedysarum multijugum*	OH	H	OH	H	H	H	Prenyl
6c	Hedysarimcoumestan G[14b-c] *Hedysarum multijugum*	OH	H	OH	H	OH	H	Prenyl
6d	Hedysarimcoumestan H[14b-c] *Hedysarum multijugum*	OH	H	OH	H	OH	Prenyl	H
6e	Methylhedysarimcoumestan H[14c] *Hedysarum multijugum*	OH	H	OMe	H	OH	Prenyl	H

Other natural compounds **7-32** (Figure 8, Table 6) bearing pyran ring, hydroxyalkyl substituent, epoxide, furan ring, chromene ring, isoprenyl, geranyl and sulphate substituents are also known. Also some complex coumestans **33-43** (Figure 9, Table 7) with glucoside rings have also been isolated.

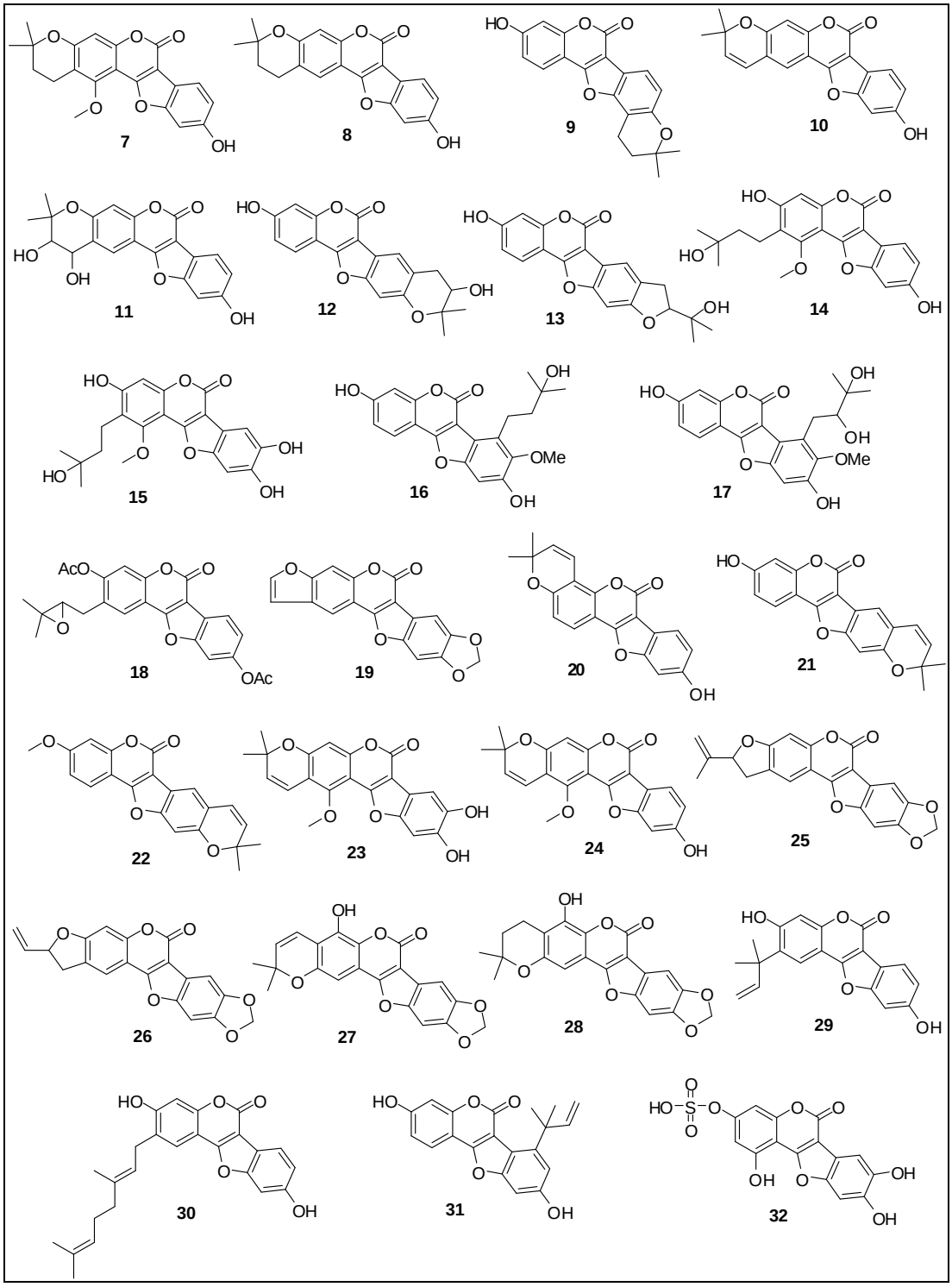


Figure 8: Structurally diverse naturally occurring coumestans **7**-**32**.

Table 6: Source of isolation of naturally occurring coumestans **7**-**32**.

No.	Name ***Source of isolation***
7	Iso-glycyrol[27a-e] *Glycyrrhiza species*

8	Isopsoralidin[32] *Psoralea corylifolia*
9	Sojagol[6z,33] *Soja hispida*, Soyabean, leaves (Glycine max) *Phaseolus aureus*, *Cylicodiscus gabunensis*
10	9-Hydroxy-2',2'-dimethylpyrano[5',6':2,3]-coumestan[34] *Solanum iyratum*
11	Corylidin[35] *Psoralea corylifolia*
12	Bavacoumestan A[36] *Psoralea corylifolia*
13	Bavacoumestan B[36] *Psoralea corylifolia*
14	Glycyrurol[17b] *Glycyrrhiza uralensis*
15	Lespedezacoumestan[37] *Lespedeza virgata*
16	Mirificoumestan hydrate[31a] *Pueraria mirifica*
17	Mirificoumestan glycol[31a] *Pueraria mirifica*
18	Psoralidin 2',3'-oxide diacetate[38] *Psoralea corylifolia*
19	Erosnin[39] *Pachyrrhizus erosus*
20	Plicadin[40] *Psoralea plicata*
21	Sophoracoumestan A [10a,36,41] *Sophora franchetiana, Psoralea corylifolia, Sophora chrysophylla*
22	Tuberostan[42] *Pueraria tuberose*
23	Hirtellanines B[43] *Ficus hirta, Campylotropis hirtella*
24	Gancaonin F[27d]

	Glycyrrhiza species
25	Tephcalostan[44] *Tephrosia calophylla*
26	Tephcalostan B[45] *Tephrosia calophylla*
27	Tephcalostan C[45] *Tephrosia calophylla*
28	Tephcalostan D[45] *Tephrosia calophylla*
29	2-(*α*,*α*-Dimethylallyl)coumestrol[46] *Pueraria lobata*
30	Puerarol[47] *Pueraria radix*
31	Solalyratin A[34] *Solanum iyratum*
32	Demethylwedelolactone 3-sulfate[5e,48] *Eclipta prostrate*

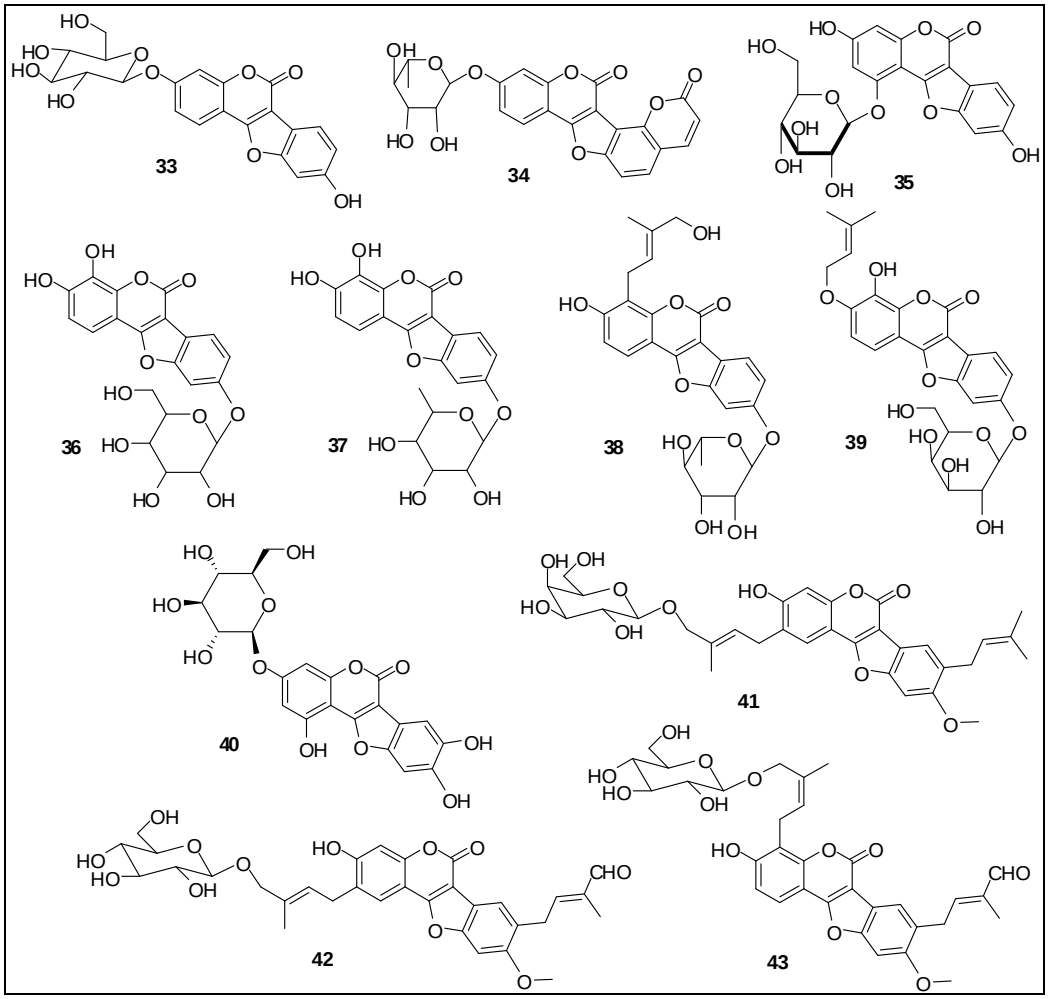


Figure 9: Naturally occurring coumestans with glucoside rings **33-43**.

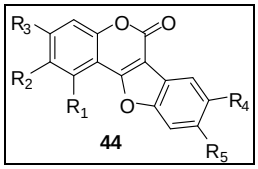
Table 7: Source of isolation of naturally occurring coumestans **33-43**.

No.	Name ***Source of isolation***
33	Coumestrin[49] soybean roots
34	Eriocephaloside[50] *Lasiosiphon eriocephalus*
35	Hedysarimcoumestan C[14b] *Hedysarum multijugum*
36	Coumestoside A[33d] *Cylicodiscus gabunensis*
37	Coumestoside B[33d] *Cylicodiscus gabunensis*

38	Coumestoside C[51] *Cylicodiscus gabunensis*
39	Coumestoside D[51] *Cylicodiscus gabunensis*
40	Demethylwedelolactone glucoside[5b,52] *Eclipta alba*
41	3-Hydroxy-9-methoxy-2-[2'(*E*)-3'-methyl-4'-*O*-*β*-D-galactopyranosylbutenyl]-8-isoprenylcoumestan[53] *Picralima nitida*
42	3-Hydroxy-9-methoxy-2-[2'(*E*)-3'-methyl-4'-*O*-*β*-D-glucopyranosylbutenyl]-8-[2''(*E*)-3''-methyl-4''-oxobutenyl]coumestan[53] *Picralima nitida*
43	3-Hydroxy-9-methoxy-4-[2'(*E*)-3'-methyl-4'-*O*-*β*-D-glucopyranosylbutenyl]-8-[2''(*E*)-3''-methyl-4''-oxobutenyl]coumestan[53] *Picralima nitida*

Most of these naturally occurring coumestans are known for exhibiting diverse pharmacological activities.[54] Many herbs/plants rich in coumestans have been used as traditional medicines mostly in China and India to treat varied diseases.[5c,14c,55] Wedelolactone, the first natural member of coumestan inhibits many enzymes such as IKK kinase,[56] 5-lipoxygenase,[57] Na^+, K^+ -ATPase,[58] hepatitis virus C RNA-polymerase[59] and trypsin.[60] Also its other activities includes antibacterial,[61] antimicrobial,[62] antihepatotoxic,[63] antimyotoxic,[64] antitumour,[65] hepatoprotective,[66] anticancer,[67] and electrochemical[68] activities. It also enhances interferon Y signalling[69] and is a potent glucosidase inhibitor and anti-glycemic agent.[70] Recently its metabolism in rats has been studied.[71] Coumestrol is another immensely studied member showing diverse biological activities. It has higher binding affinity for ER*β* than other phytoestrogens.[72] It is also known to inhibit bone resorption and to stimulate bone mineralization[73] including some other activities.[74] Some coumestans inhibit protein-tyrosine phosphatase 1B[75] and some are used in the treatment of liver diseases.[76] Other activities shown by coumestans includes anticancer,[77] antitumour,[78] and anti-inflammatory[79] activities. Also studies have shown their widespread use as phytoalexins,[80] estrogenic,[81] antibacterial[82] and antidepressant.[83] These tremendous biological activities prompted us to develop an efficient method for coumestan synthesis.

Several synthetic coumestan analogues have also been prepared and studied for biological activities. Some of them such as **44-49** exhibit peculiar biological activities and their structures are depicted below (Figures 10-11, Table 8-9).



44

Figure 10: Synthetic coumestans **44**.

Table 8: Synthetic coumestans **44**.

No.	Name	R_1	R_1	R_2	R_3	R_4
44a	3-Methoxy-2,8,9-trihydroxy coumestan[84]	H	OH	OMe	OH	OH
44b	2-Methoxy-3,8,9-trihydroxy coumestan[59,85]	H	OMe	OH	OH	OH
44c	6*H*-Benzofuro[3,2-*c*]chromen-6-one[86]	H	H	H	H	H
44d	9-Methoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one[86]	H	H	H	H	OMe
44e	8,9-Dimethoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one[86]	H	H	H	OMe	OMe
44f	9-Chloro-6*H*-benzofuro[3,2-*c*]chromen-6-one[86]	H	H	H	H	Cl
44g	9-Bromo-6*H*-benzofuro[3,2-*c*]chromen-6-one[86]	H	H	H	H	Br
44h	9-Hydroxy-6*H*-benzofuro[3,2-*c*]chromen-6-one[86]	H	H	H	H	OH
44i	8,9-Dihydroxy-6*H*-benzofuro[3,2-*c*]chromen-6-one[86,87]	H	H	H	OH	OH
44j	3-Ethoxy-1,8,9-trihydroxy-6*H*-benzofuro[3,2-*c*]chromen-6-one[88]	OH	H	OEt	OH	OH
44k	3-Decyloxy-1,8,9-trihydroxy-6*H*-benzofuro[3,2-*c*]chromen-6-one[88]	OH	$(CH_2)_9CH_3$	OEt	OH	OH

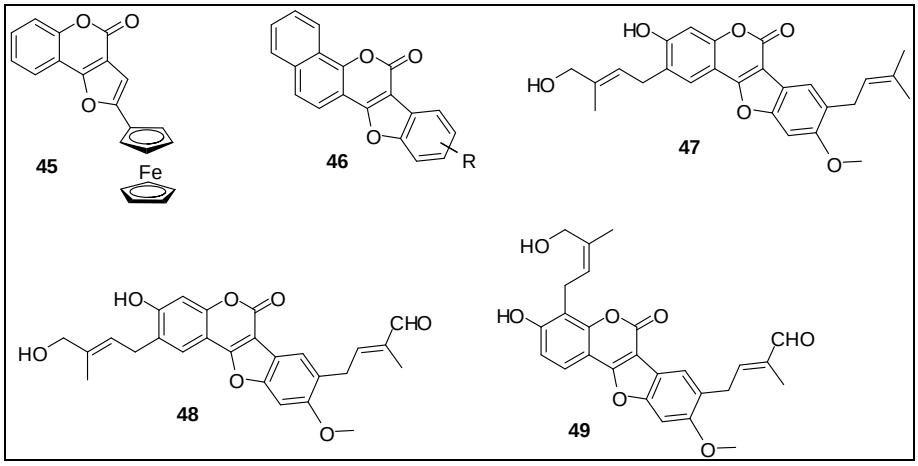


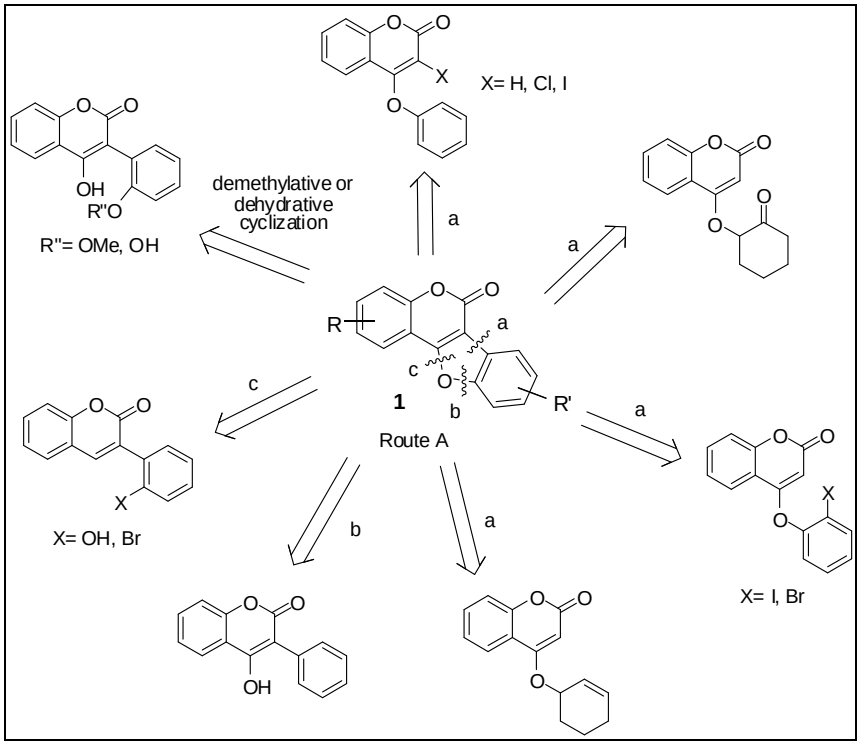
Figure 11: Complex synthetic coumestans **45**-**49**.

Table 9: Complex synthetic coumestans **45**-**49**.

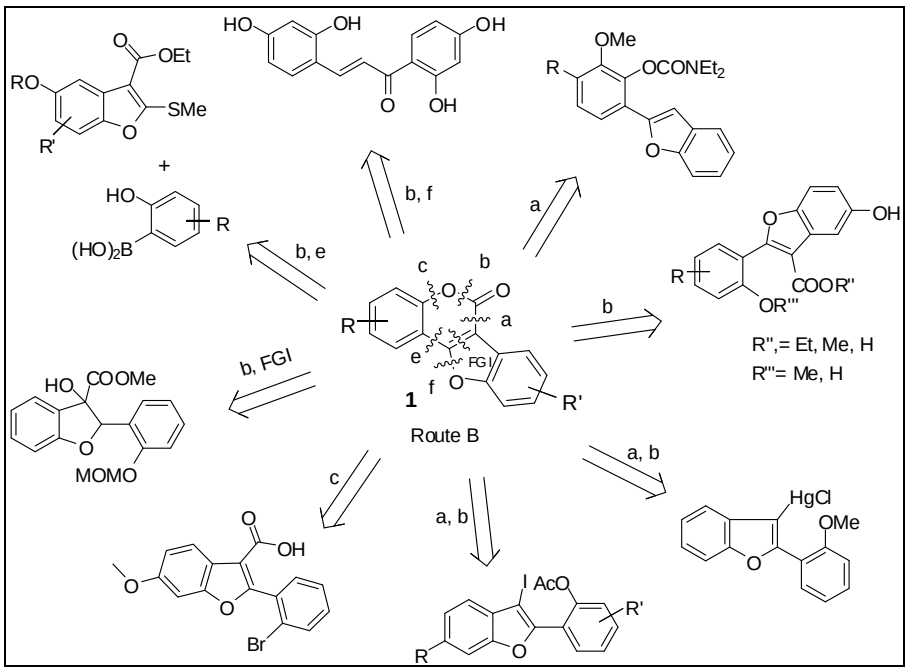
No.	Name
45	2-ferrocenyl-furo[3,2-c]chromen-4-one[89]
46	Naphtho coumestans[90]
47	3-Hydroxy-9-methoxy-2-[2'(*E*)-4'-hydroxy-3'-methylbutenyl]-8-isoprenylcoumestan[53]
48	3-Hydroxy-9-methoxy-2-[2'(*E*)-4'-hydroxy-3'-methylbutenyl]-8-[2''(*E*)-3''-methyl-4''-oxobutenyl]coumestan[53]
49	3-Hydroxy-9-methoxy-4-[2'(*E*)-4'-hydroxy-3'-methylbutenyl]-8-[2''(*E*)-3''-methyl-4''-oxobutenyl]coumestan[53]

4.3: Literature synthetic methods

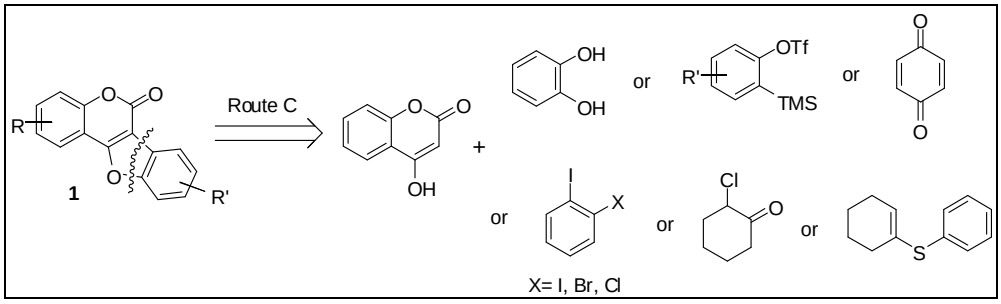
Owing to immense biological importance of coumestan compounds, several methods for the synthesis of this tetracyclic ring system have been reported.[91] Based on retrosynthetic analysis, the synthetic methods can be broadly divided into 4 categories as depicted below. These 4 approaches have been classified on the basis of i) formation of furan ring on preformed coumarin ring (Scheme 1, Route A), ii) formation of coumarin ring on preformed furan ring (Scheme 2, Route B), iii) simultaneous formation of C-C and C-O bonds to form furan ring (Scheme 3, Route C), iv) from flavonoids (Scheme 4, Route D) and v) miscellaneous routes (Scheme 5, Route E).



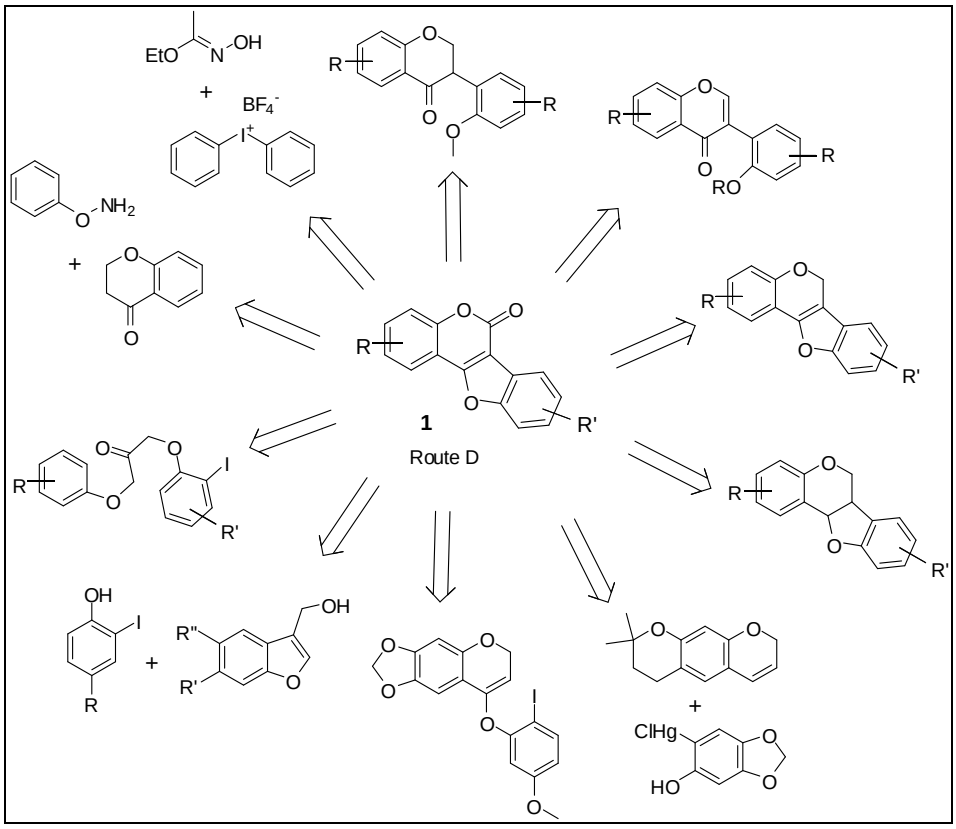
Scheme 1: Formation of furan ring on preformed coumarin ring (Route A).



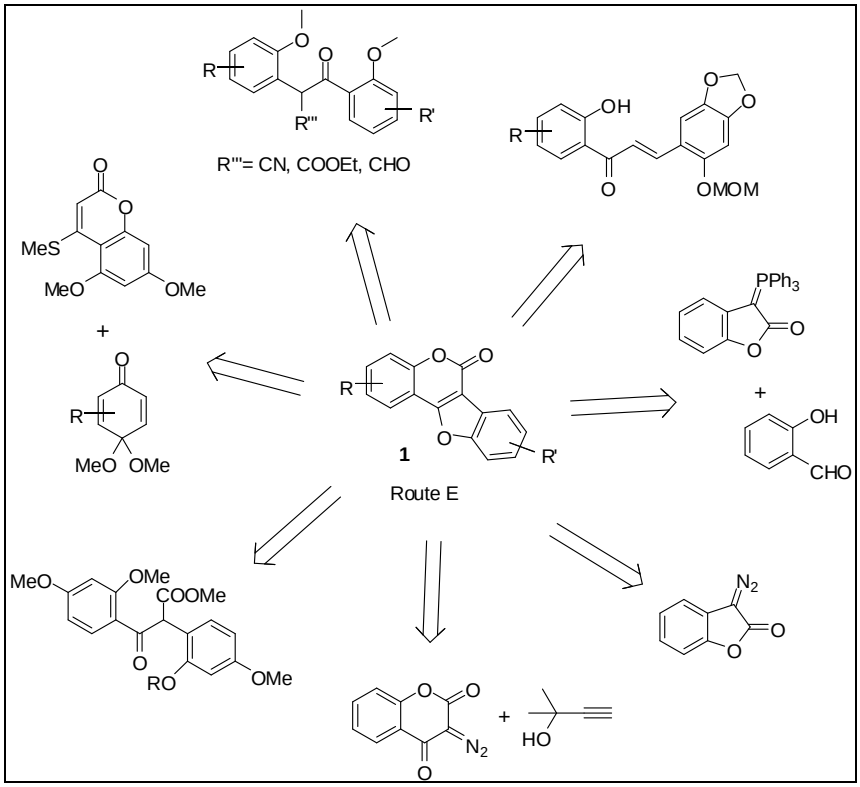
Scheme 2: Formation of coumarin ring on preformed furan ring (Route B).



Scheme 3: Simultaneous formation of C-C and C-O bonds to form furan ring (Route C).



Scheme 4: From flavanoids (Route D).



Scheme 5: Miscellaneous routes (Route E).

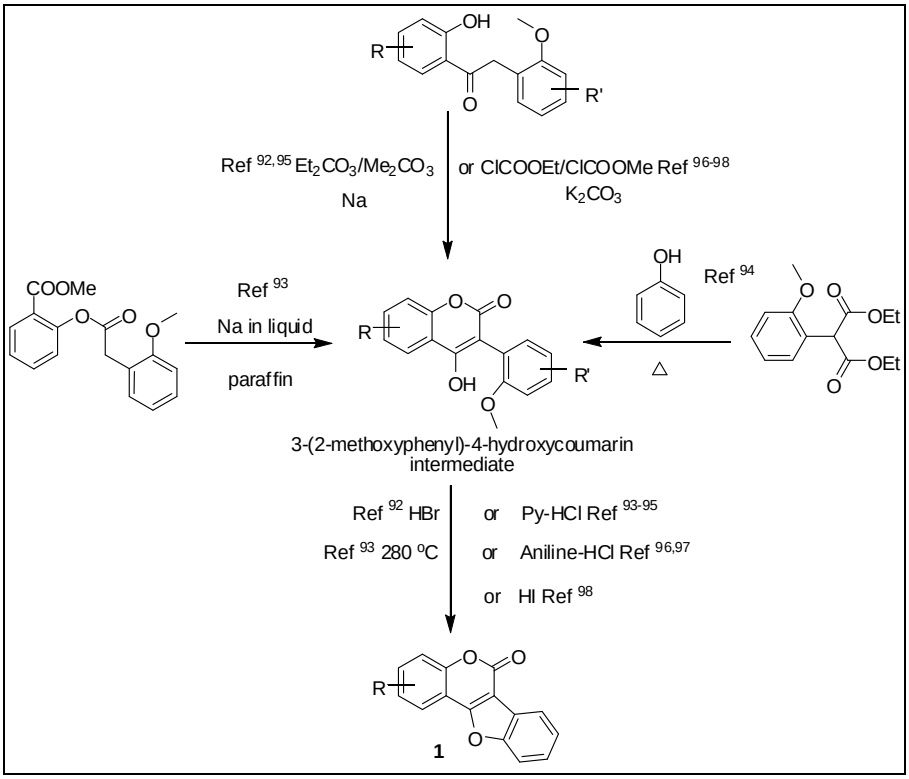
All these approaches involving diverse substrates have been discussed ahead. Some of the methods have also been applied for the synthesis of natural coumestans.

4.3.1: Formation of furan ring on preformed coumarin ring (Route A)

4.3.1.1: From demethylative or dehydrative cyclization

Syntheses of coumestans were reported many decades ago from 3-(2-methoxyphenyl)-4-hydroxycoumarin intermediate (Scheme 6). This was prepared by various groups using different methods. Bowyer *et al.*[92] synthesized it *via* cyclization of corresponding deoxybenzoin with ethyl carbonate and sodium dust in 1957. This intermediate was then converted to coumestan using 48 % HBr in boiling acetic acid.

Synthesis of parent ring system **1** present in wedelolactone **2a** and of tri-*O*-methylwedelolactone was reported by Govindachari *et al.*[93] in the same year. The coumarin intermediate was prepared from intramolecular Claisen condensation of methyl-*O*,*O*'-methoxyphenylacetoxybenzoate in presence of sodium. It was further demethylated on prolonged treatment of pyridine hydrochloride or by heating at 280 °C.



Scheme 6

Deschampo-Vallet and Mentzer[94] reported coumestan synthesis from the coumarin intermediate by treatment with pyridine hydrochloride. The intermediate was obtained on thermal condensation of phenol with *o*-methoxyphenyl diethyl malonate.

Govindachari *et al.*[95] synthesized the coumarin intermediate by condensation of corresponding deoxybenzoin with diethyl carbonate and pulverized sodium. Demethylative cyclization of the intermediate with pyridine hydrochloride resulted in coumestan.

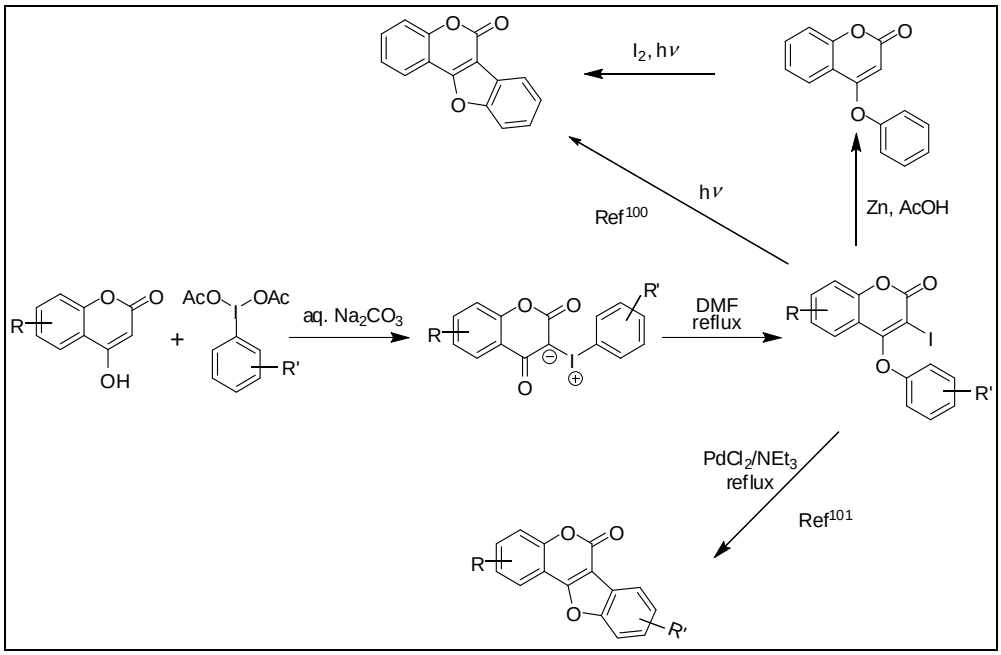
Similarly Emerson and Bickoff[96] synthesized the coumarin intermediate by condensation of deoxybenzoin with methyl chloroformate in presence of potassium carbonate. Subjecting it to aniline hydrochloride delivered coumestan. Aniline hydrochloride was also utilized by Nasipuri and Pyne[97] for coumestan synthesis. The intermediate coumarin was obtained by treating deoxybenzoin with ethyl chloroformate method. Finally demethylative ring closure with HI at 170 °C yielded coumestan.[98]

Uma Rani and Darbarwar[99] synthesized various oxygenated coumestans and their acetates by dehydrative cyclization of 4-hydroxy-3-arylcoumarins using methanolic hydrogen chloride (Scheme 7).

Scheme 7

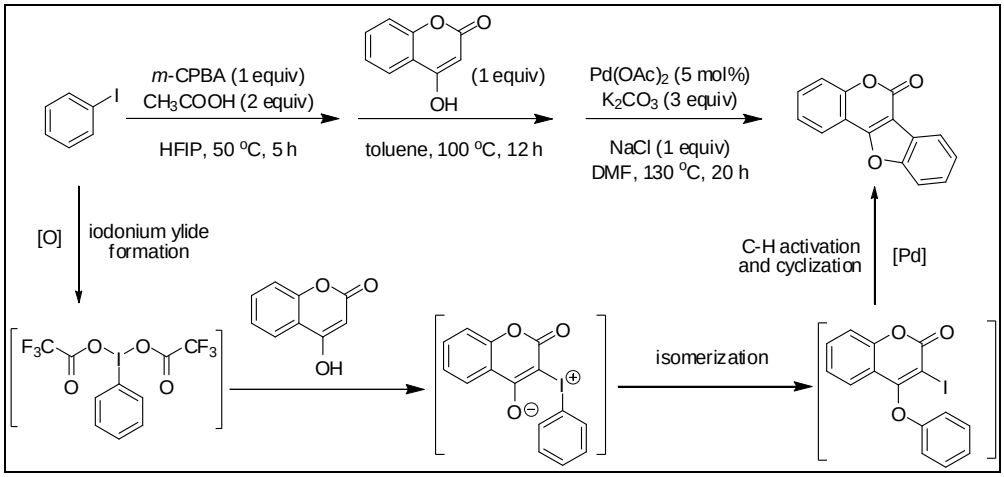
4.3.1.2: From disconnection a

Kappe *et al.*[100] demonstrated the preparation of coumestan in 1978. 4-Hydroxycoumarin was reacted with (diacetoxy)iodoarene to from iodonium ylide which rearranged to 4-aryloxy-3-iodocoumarin on heating. Reductive deiodination occurred when it was heated with Zn-HOAc to give 4-aryloxycoumarin which was converted to coumestan on photocyclization in presence of iodine. Also 4-aryloxy-3-iodocoumarin provided coumestan on photocyclization. However, low substrate scope and poor yield limited the use of this approach. Later this method was modified wherein 4-aryloxy-3-iodocoumarin was cyclised using Heck condition[101] (Scheme 8).



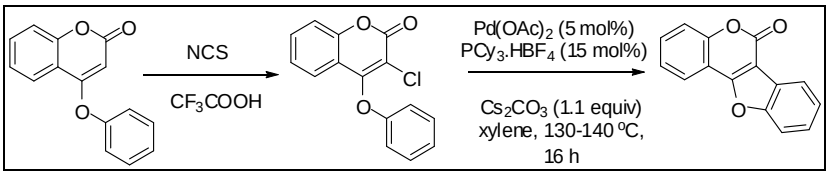
Scheme 8

Also Hong *et al.*[102] developed an efficient one pot cyclization process by reacting iodoarenes and various arylols *via* oxidative palladium catalysis (Scheme 9). The methodology was extended towards the synthesis of parent coumestan *via* sequential oxidation of iodophenol to hypervalent iodine (III) species, 3-iodination of 4-hydroxycoumarin to form 3-iodo-4-phenoxycoumarin through iodonium ylide intermediate and Pd catalyzed C-H functionalization and cyclization.



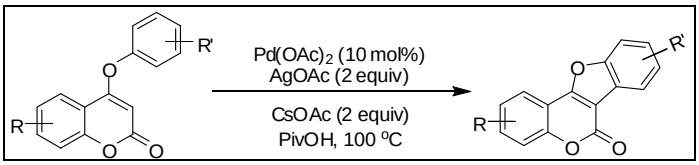
Scheme 9

Recently, McGlacken and co-workers[103] synthesized coumestan by an intramolecular coupling using palladium catalyst. Accordingly 4-phenoxycoumarin was chlorinated at 3 position using NCS in trifluoroacetic acid which on intramolecular coupling between C-Cl and phenoxy C-H bond yielded coumestan. This strategy was successfully applied to the synthesis of natural coumestan flemichapparin C (Scheme 10).



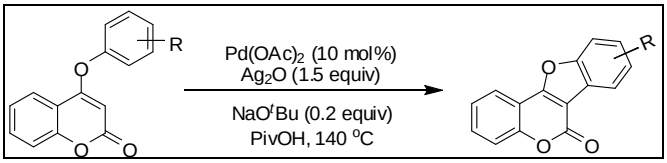
Scheme 10

A palladium catalyzed intramolecular cross dehydrogenative coupling (CDC) was designed by Cheng *et al.*[104] for the synthesis of coumestans. The methodology was also applied for the synthesis of Coumestrol and Flemichapparin C (Scheme 11).



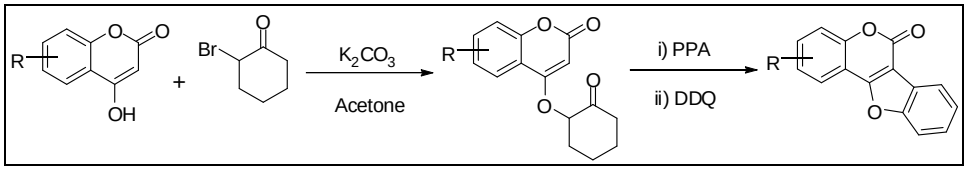
Scheme 11

McGlacken and co-workers[105] reported a palladium catalyzed double C-H activation of coumarin moieties to form coumestans. Flemichapparin C was synthesized using this methodology (Scheme 12).



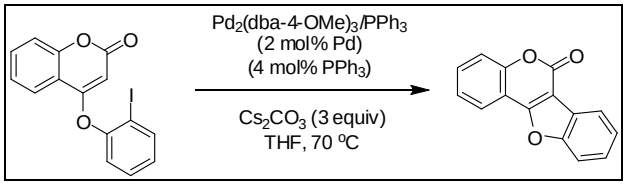
Scheme 12

Singh and Singh[106] prepared alkylated product from 4-hydroxycoumarin and 2-bromocyclohexanone which was cyclised and dehydrogenated by polyphosphoric acid and DDQ respectively (Scheme 13).



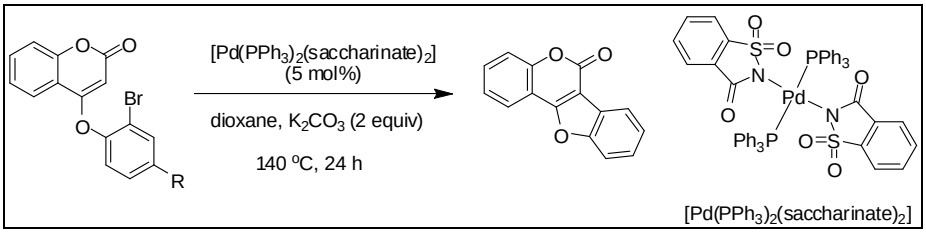
Scheme 13

Burns *et al.*[107] developed a palladium catalyzed methodology for the C-H functionalization of 2-pyrones which was extended for the synthesis of parent coumestan (Scheme 14).



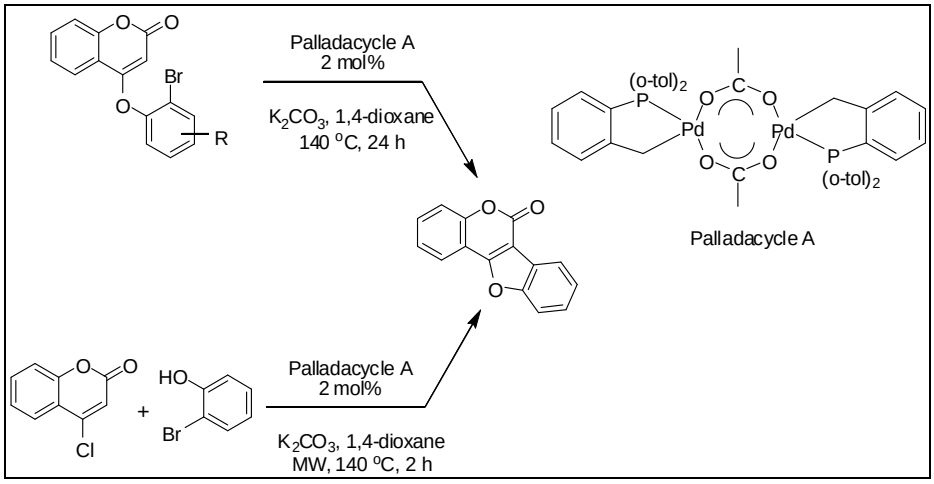
Scheme 14

Kapdi and co-workers[108] achieved an intramolecular C-H bond functionalization of 4-(2-bromophenoxy)coumarins with $[Pd(PPh_3)_2(saccharinate)_2]$ as the palladium catalyst source (Scheme 15). The substrates with electron releasing/withdrawing substituent gave good yield of the products.



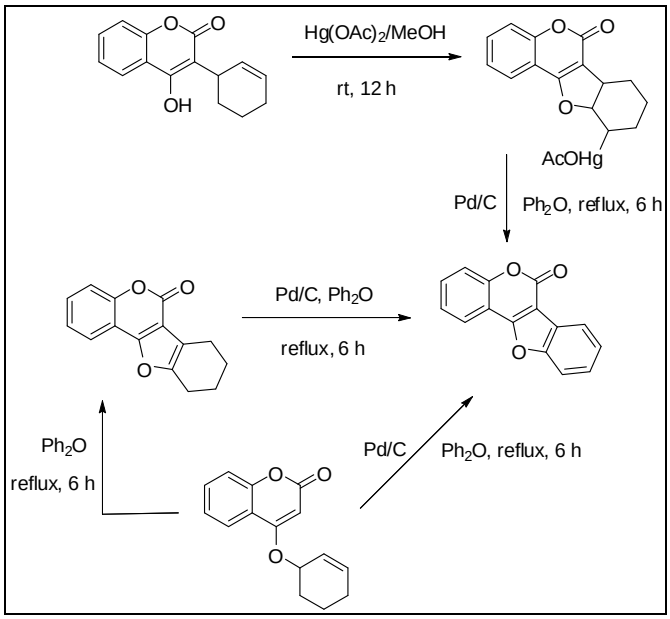
Scheme 15

A variety of coumesatns were synthesized by Kapdi *et al.*[109] by using phospha-palladacycle *via* intramolecular C-H bond functionalization of 4-(2-bromophenoxy)coumarins. The direct one pot conversion of 4-chlorocoumarin to coumestan was also achieved under microwave irradiation (Scheme 16).



Scheme 16

Coumestan has been synthesized from 3-[2-cyclohexenyl]-4-hydroxy-1-benzopyran-2(*H*)-one by Majumdar *et al.*[110] *via* oxymercuration. It was treated with mercuric acetate in methanol followed by dehydrogenative demercuration with Pd/C in refluxing diphenyl ether. Alternatively it was prepared in 2 steps from 4-(2-cyclohexenyloxy)-1-benzopyran-2(*H*)-one by refluxing in diphenyl ether first followed by addition of Pd/C. Also direct synthesis of coumestan was obtained when 4-(2-cyclohexenyloxy)-1-benzopyran-2(*H*)-one was refluxed in presence of Pd/C in diphenyl ether (Scheme 17).

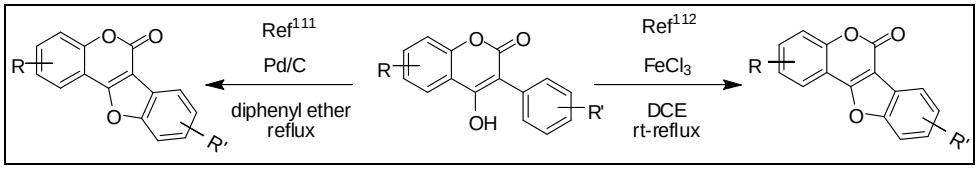


Scheme 17

4.3.1.3: From disconnection b

Synthesis of coumestans was carried out by the oxidative cyclization of 4-hydroxy-3-phenyl-2*H*-chromen-2-one as a starting material[111-112] (Scheme 18). Kappe and Schmidt had employed Pd/C in refluxing diphenyl ether at 258 °C.[111a] Later coumestrol was synthesized

using this method.[111b] Recently, Tang *et al.*[112] accomplished $FeCl_3$ mediated synthesis from 4-hydroxy-3-phenyl-2*H*-chromen-2-one.

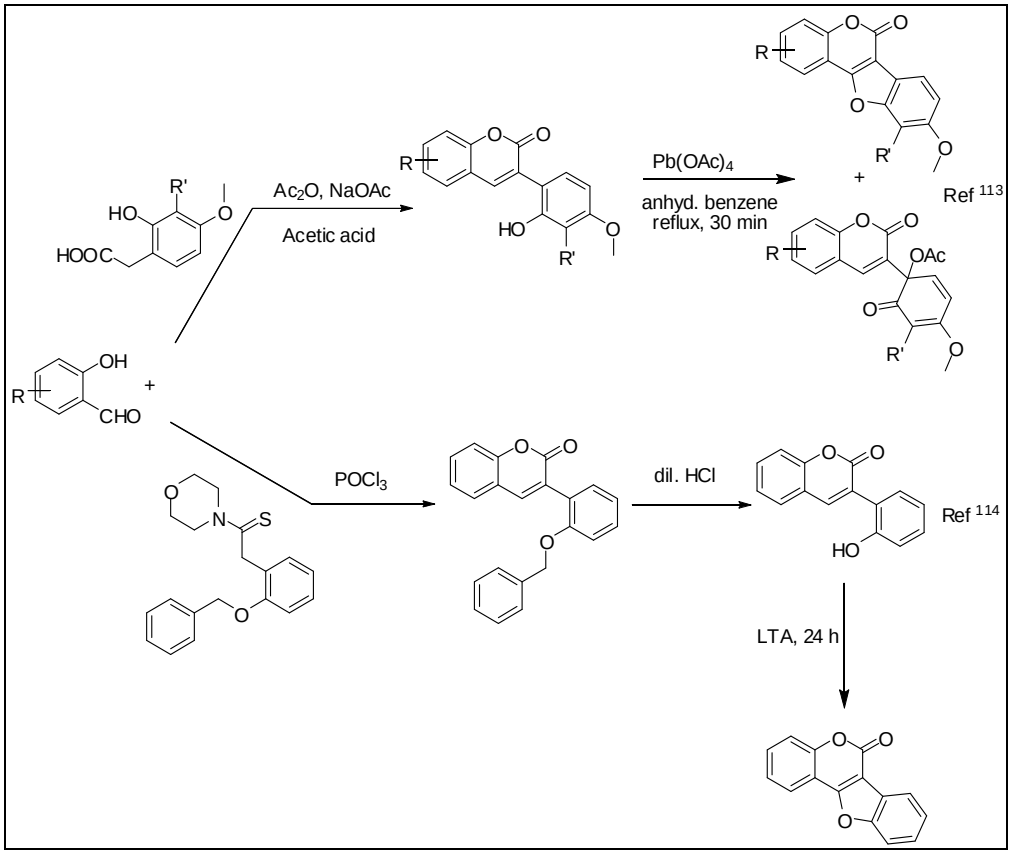


Scheme 18

4.3.1.4: From disconnection c

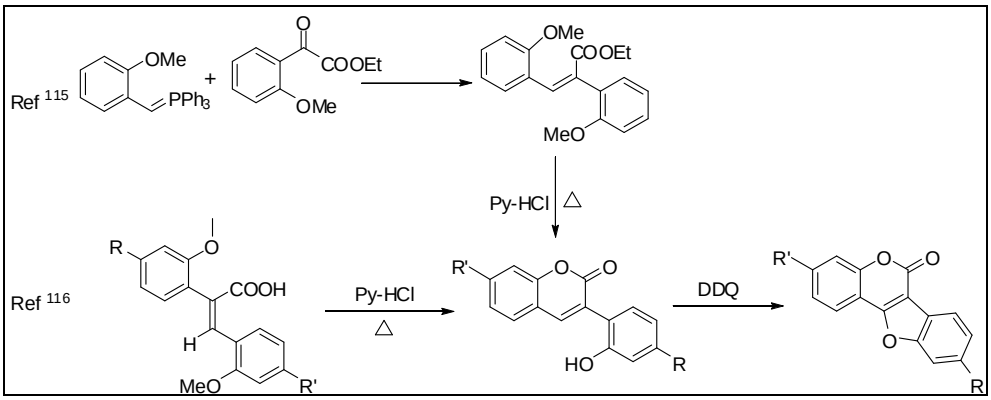
Kurosawa and Nogami[113] synthesized coumestans by the oxidative cyclization of 3-(2-hydroxyphenyl)coumarins using lead tetraacetate (LTA). These 3-(2-hydroxyphenyl)coumarins intermediate were obtained by the Perkin reaction of salicylaldehydes and 2'-hydroxyphenylacetic acids. Along with coumestans, 3-(1-acetoxy-4-methoxy-2-oxo-3,5-cyclohexadienyl)coumarins were also formed (Scheme 19).

Wadia and co-workers[114] also reported the synthesis of coumestan by using LTA. The method involves the use of salicylaldehyde and 2-phenylthioacetamide as starting materials in presence of $POCl_3$ to give 3-(2-benzyloxyphenyl)coumarin which underwent debenzylation in acidic medium forming 3-(2-hydroxyphenyl)coumarin. Oxidative cyclization using LTA converted this coumarin to corresponding parent coumestan (Scheme 19).



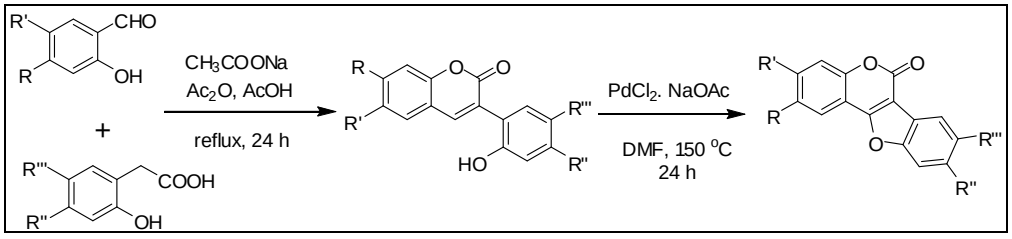
Scheme 19

Mali and Tilve[115] carried out Wittig reaction between phosphorane and ethyl-2-(2-methoxyphenyl)-2-oxoacetate to form ester which was converted to 3-(2-hydroxyphenyl)coumarin by heating with pyridine hydrochloride. DDQ was then employed for the oxidative cyclization to afford coumestan (Scheme 20). Similar strategy was used by Pandit and Gadre[116] however 3-(2-hydroxyphenyl)coumarin was developed by an alternative route involving demethylation followed by cyclization of cinnamic acid with pyridine hydrochloride (Scheme 20).



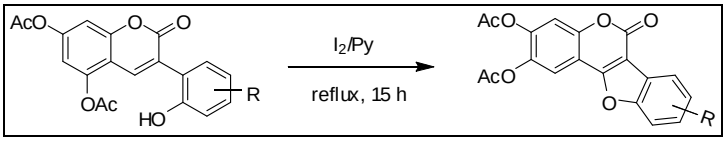
Scheme 20

Gong *et al.*[117] prepared 3-(2-hydroxyphenyl)coumarin intermediate by using Perkin reaction from salicylaldehydes and *o*-hydroxyphenylacetic acids in the presence of sodium acetate, acetic anhydride and acetic acid. The oxidative cyclization of this intermediate was easily achieved by using stoichiometric $PdCl_2$ in DMF at 150 °C (Scheme 21).



Scheme 21

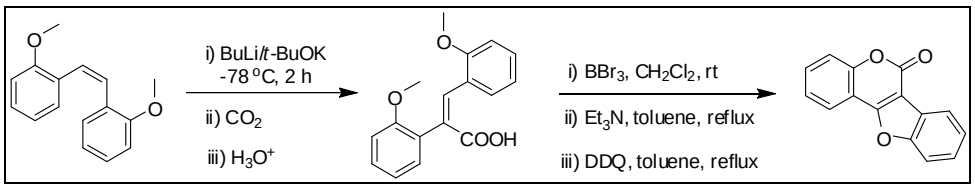
Chang *et al.*[118] described the total synthesis of hedysarimcoumestan B, demethylwedelolactone and wedelolactone by using I_2 in anhyd. pyridine for oxidative cyclization as one of the key steps (Scheme 22).



Scheme 22

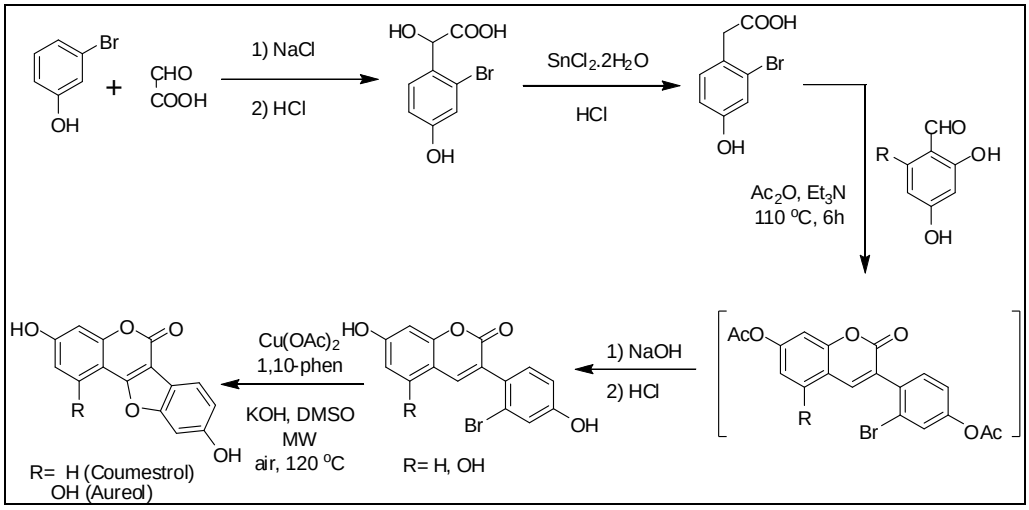
Vinyl C-H lithiation of bis-*ortho*-methoxy *cis*-stilbene was carried out by O'Shea and co-workers[119] followed by CO_2 quench to provide access to the targeted cinnamic acid. This acid

underwent demethylation with BBr_3 followed by treatment with base and oxidative cyclization with DDQ to form coumestan (Scheme 23).



Scheme 23

Recently Sheng *et al.*[120] reported the total synthesis of naturally occurring coumestrol and aureol. Nucleophilic addition of *m*-bromophenol to glyoxylic acid resulted in the formation of 2-bromo-4-hydroxymandelic acid which further on reduction with $SnCl_2$/HCl afforded 2-bromo-4-hydroxyphenylacetic acid. This on Perkin condensation with *o*-hydroxybenzaldehydes gave acylated 2'bromo-3-arylcoumarins which was deacetylated in hot NaOH followed by acidification. Finally a consecutive Cu-catalyzed hydroxylation and aerobic oxidative cyclization carried out with $Cu(OAc)_2$/1,10-phen, KOH in DMSO, MW at 120 °C afforded coumestrol and aureol (Scheme 24).

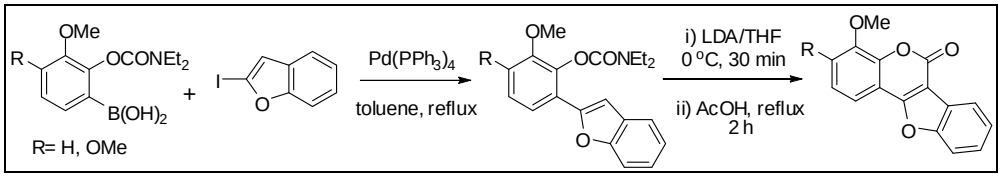


Scheme 24

4.3.2: Formation of coumarin ring on preformed furan ring (Route B)

4.3.2.1: From disconnection a

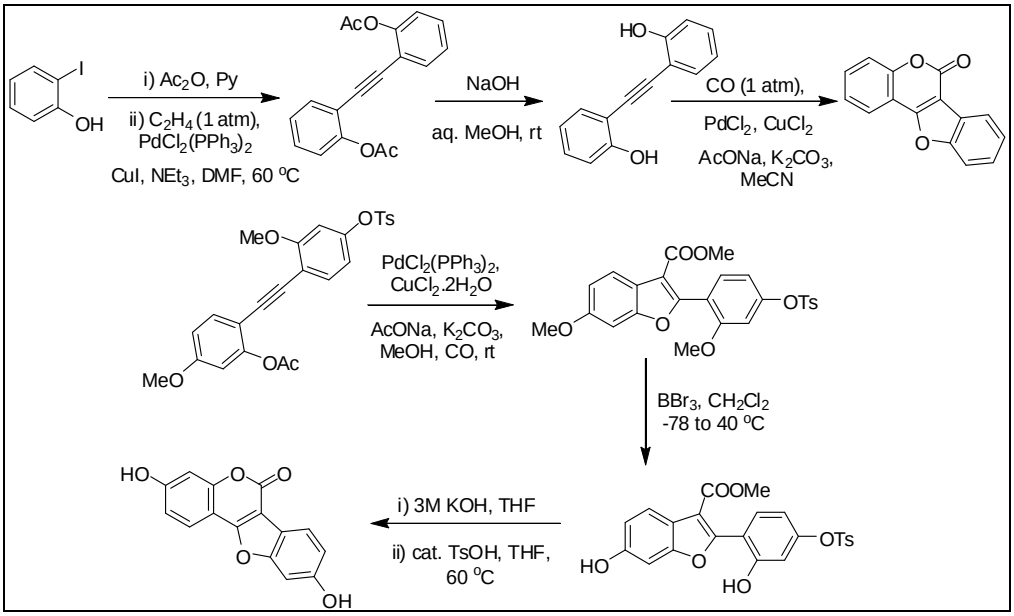
James *et al.*[121] carried out Suzuki Miyaura cross coupling reaction of aryl-*O*-carbamoyl *ortho*-boronic acids with benzofuran iodide delivered to form coupled product. This was converted to coumestans on treatment with LDA *via* directed ortho lithiation followed by acetic acid reflux (Scheme 25).



Scheme 25

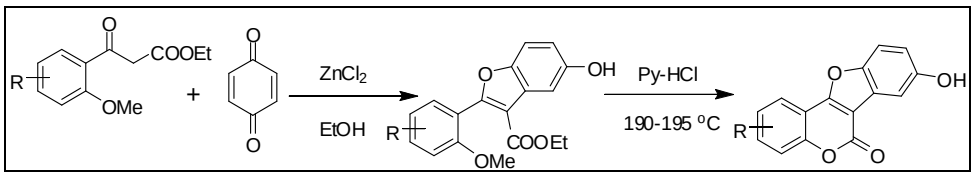
4.3.2.2: From disconnection b

Hiroya *et al.*[122] reported the synthesis of parent coumestan and coumestrol. 2-Iodophenol was converted to diaryl acetylene under an acetylene atmosphere by using palladium catalyzed cross coupling reaction. Next deacetylation was carried out followed by the intramolecular carbonylative cyclization reaction under carbon monoxide atmosphere leading to parent coumestan. For the synthesis of coumestrol appropriately protected compound was converted to corresponding benzofuran tosyl ester. When this compound was treated with BBr_3 double demethylation occurred to obtain corresponding dihydroxy compound. This on alkaline hydrolysis followed by lactonization in presence of acid catalyst rendered coumestrol (Scheme 26).



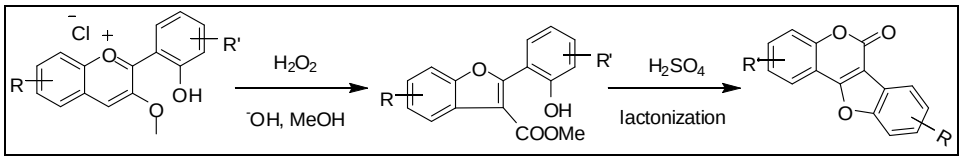
Scheme 26

Ethyl 2-methoxybenzoylacetates on Michael addition with 1,4-benzoquinone produced benzofuran-carboxylates in presence of $ZnCl_2$, was reported by McPherson and Ponder.[123] Further treatment with anhyd. pyridine-HCl at 190-195 °C delivered coumestans (Scheme 27).



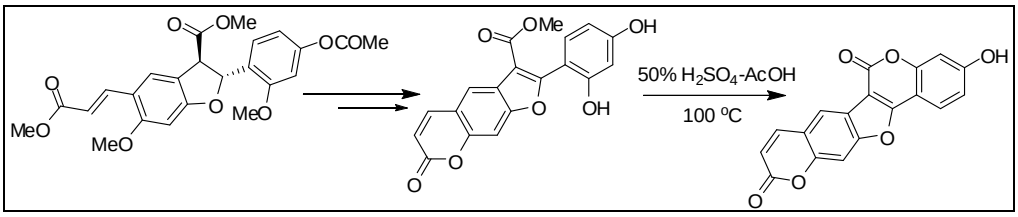
Scheme 27

Jurd[124] developed a method starting from appropriate flavylium chloride salt which was oxidized using hydrogen peroxide in aqueous methanol (Scheme 28). This resulted in the formation of carbomethoxybenzofuran intermediate which rapidly lactonised on acidification to deliver coumestrol.[124a-c] Later Jurd[125] synthesized 7-methoxycoumestrol and 12-methoxycoumestrol using this strategy. Spencer *et al.* [126] synthesized three position isomers of coumestrol from appropriately substituted flavylium salts, their dimethyl ethers and diacetates and many monomethyl ethers and their acetates.



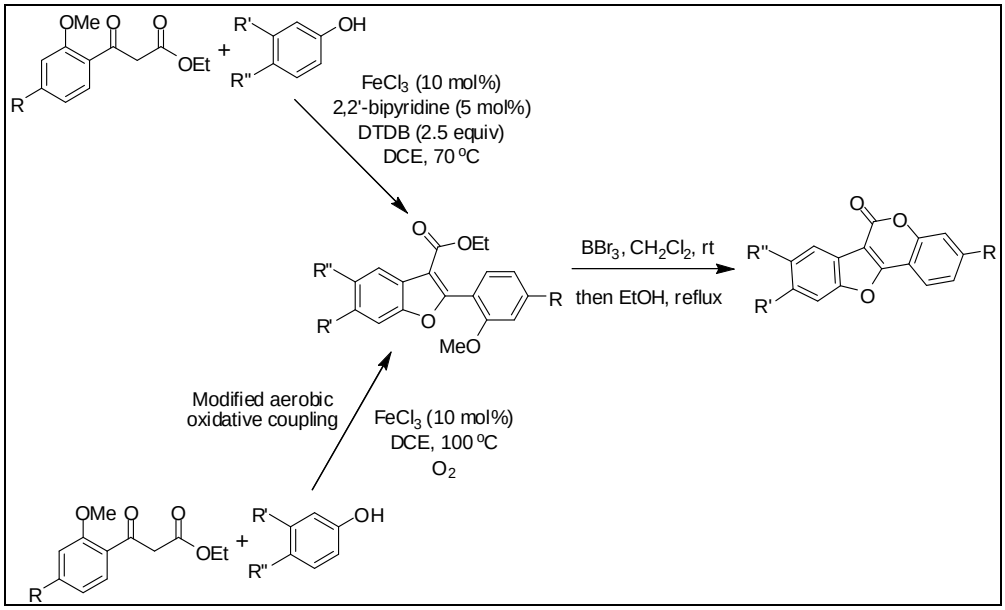
Scheme 28

Maeda *et al.*[127] carried out studies towards the preparation of lignans by oxidative coupling reaction. In addition to this, a coumestan derivative was synthesized from the ester starting in 3 steps involving hydrolysis and lactonization forming coumarin ring in the last step (Scheme 29).



Scheme 29

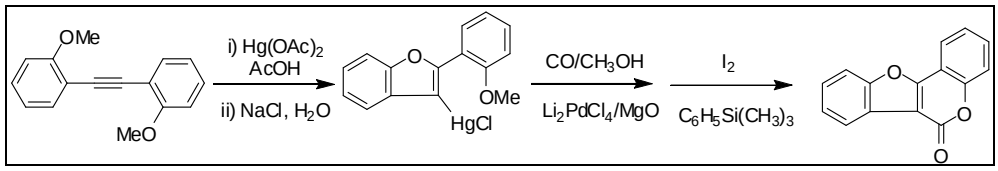
Coumestrol and its analogues formation from iron based cross dehydrogenative coupling (CDC) approach was disclosed by Pappo and co-workers[128] This two step method employed $FeCl_3$, 2,2'-bipyridine and di-*tert*-butyl peroxide (DTDB) as the oxidant for cross coupling of *β*-ketoesters and phenols to form benzofuran derivatives. Authors later modified the conditions wherein catalytic $FeCl_3$ in aerobic medium was preferred over the former condition. Benzofuran derivatives were then converted to coumestrol analogues by performing deprotection and lactonization steps in one pot (Scheme 30).



Scheme 30

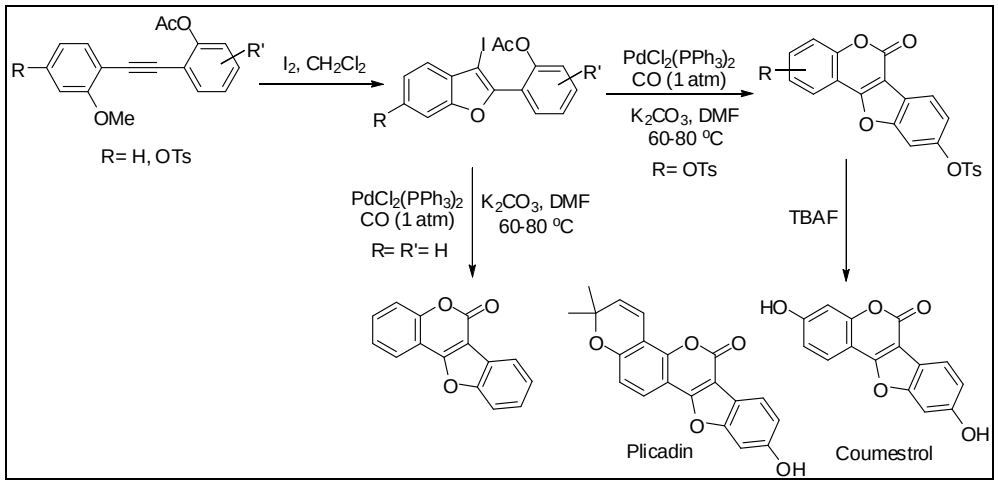
4.3.2.3: From disconnection a, b

Larock and Harrison[129] has developed a method using organomercurial compound prepared by acetoxymercuration of 1,2-*bis*-(*o*-methoxyphenyl)acetylene. It involves carbonylation, subsequent demethylation and cyclization of organomercurial to provide coumestan ring system in 90 % yield (Scheme 31).



Scheme 31

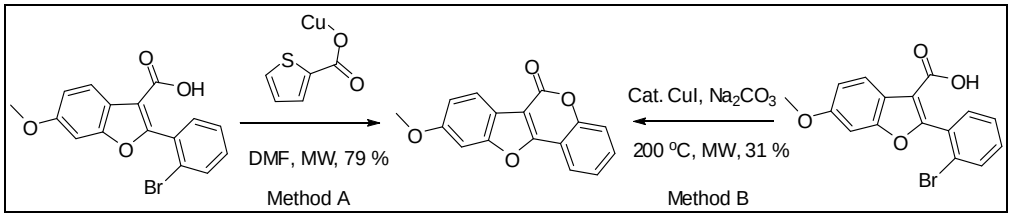
Larock and co-workers[130] synthesized parent coumestan, coumestrol and plicadin from corresponding starting materials by iodocyclization, Pd-catalyzed intramolecular lactonization and deprotection (Scheme 32).



Scheme 32

4.3.2.4: From disconnection c

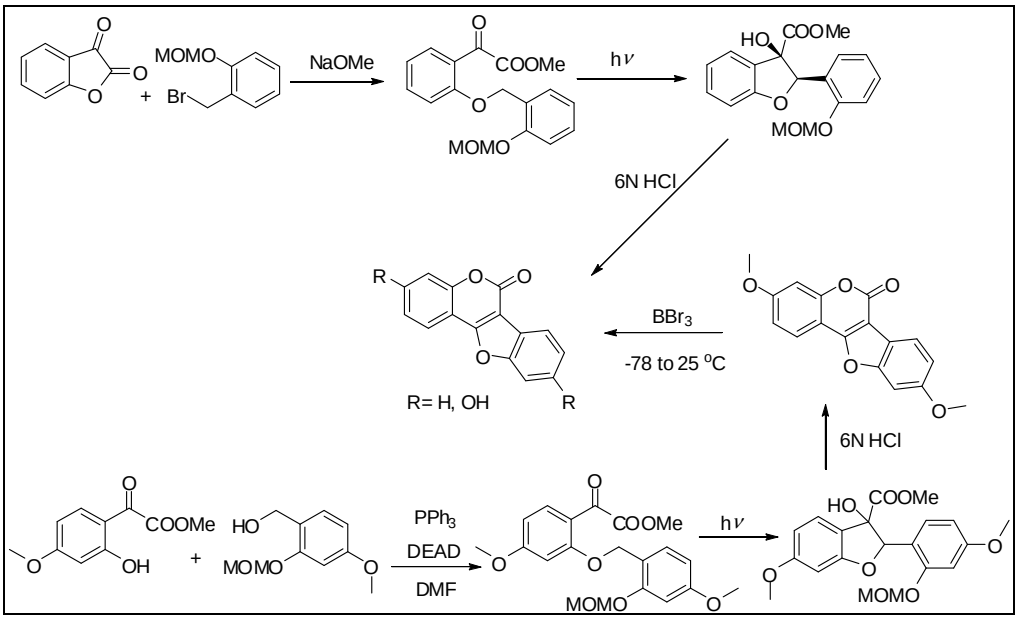
Thasana *et al.*[131] synthesized coumestan from C-O coupling reaction of 2-(2-bromophenyl)-6-methoxybenzofuran-3-carboxylic acid catalyzed by copper (I) salts using microwave irradiation. Authors developed two methods of which Cu(I) thiophene-2-carboxylate (CuTc) mediated lactonization (method A) gave better results than CuI catalyzed lactonization (method B) (Scheme 33).



Scheme 33

4.3.2.5: From disconnection b, FGI

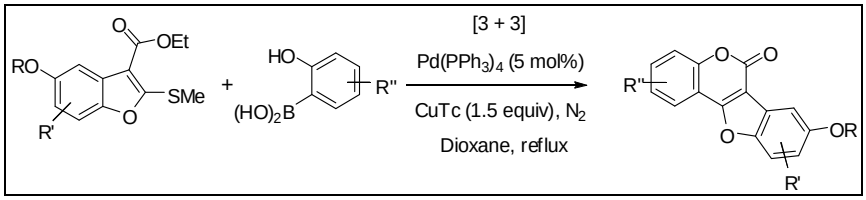
Kraus and Zhang[132] synthesized parent coumestan and coumestrol involving photochemical reaction as the key step. Benzofuran dione reacted with MOM protected benzyl bromide in presence of sodium methoxide leading to methyl-2-(2-methoxymethoxybenzyloxy)phenyl glyoxylate which on photochemical irradiation cyclises to give methyl-(2-hydroxy-4-methoxyphenyl) glyoxylate. Treatment with HCl generated required coumestan *via* deprotection, dehydration and lactonization. Similarly for coumestrol synthesis, an appropriate starting keto ester was coupled with the benzyl alcohol substrate forming keto ester intermediate which on irradiation followed by acid treatment resulted in coumestrol dimethyl ether. Finally it was converted to coumestrol using BBr_3 (Scheme 34).



Scheme 34

4.3.2.6: From disconnection b, e

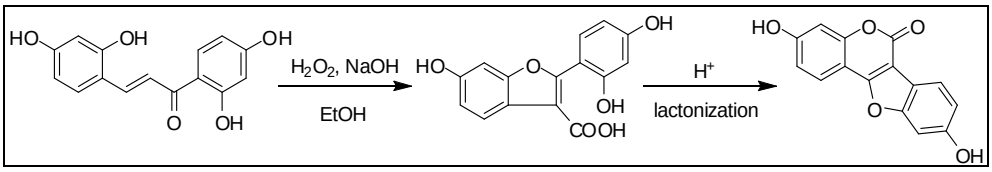
Liu *et al.*[133] reported an efficient synthesis of coumestans by a novel [3 + 3] annulation strategy (Scheme 35). Authors carried out the palladium catalyzed and copper(I) thiophene-2-carboxylate (CuTc) mediated C-S activated cross coupling of 2-(methylthio)benzofuran-3-carboxylates with 2-hydroxyphenylboronic acids and sequential intramolecular transesterification process under Liebeskind-Srogl conditions.



Scheme 35

4.3.2.7: From disconnection b, f

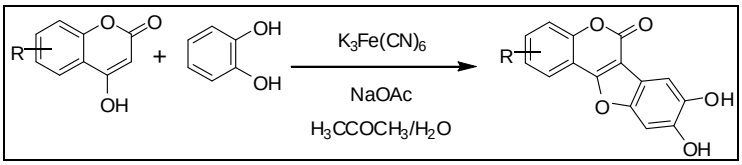
Donnelly *et al.*[134] carried out the oxidation of 2,4,2',4'-tetrahydroxychalcone using alkaline hydrogen peroxide to form 2',4',6-trihydroxy-2-phenylbenzofuran-3-carboxylic acid which lactonized to coumestrol (Scheme 36).



Scheme 36

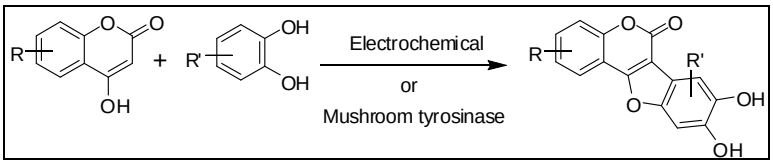
4.3.3: Simultaneous formation of C-C and C-O bonds to form furan ring (Route C)

Wanzlick *et al.*[135] synthesized coumestan by dehydrogenative coupling of catechol with 4-hydroxycoumarins in presence of potassium ferricyanide, sodium acetate and aqueous acetone (Scheme 37). Potassium iodate has also been used in place of potassium ferricyanide for coumestan preparation. This method is suitable for the preparation of 8,9-oxygenated coumestans in high yields, however other coumestans without 8,9-oxygenation pattern cannot be synthesized. This procedure has been adopted in the synthesis of many natural and non-natural coumestan analogs.[10h,136]



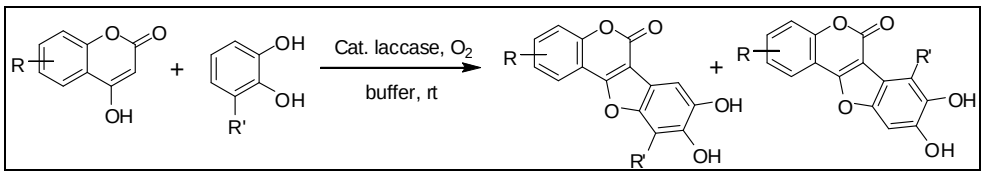
Scheme 37

Many syntheses have employed 4-hydroxycoumarin along with catechol as the starting materials (Scheme 38).[137] These are mostly electrochemical synthesis wherein catechol and its derivatives produces *o*-quinones which act as a Michael acceptor and a variety of coumarin derivatives act as nucleophile. Also a report showed mushroom tyrosinase catalysed the synthesis of coumestans from same substrates.[138]



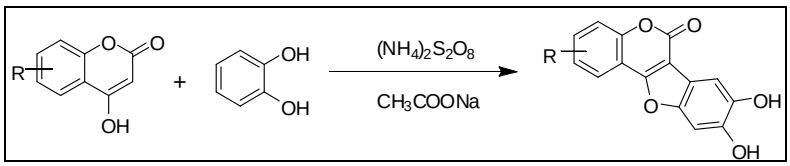
Scheme 38

Leutbecher *et al.*[139] developed a Laccase-catalyzed domino method by which coumestans were synthesized from 4-hydroxycoumarins and catechols using molecular oxygen as an oxidant. Similarly, recently Wellington and co-workers[140] synthesized several coumestan derivatives *via* one pot laccase-catalyzed methodology and were evaluated for anticancer activity (Scheme 39).



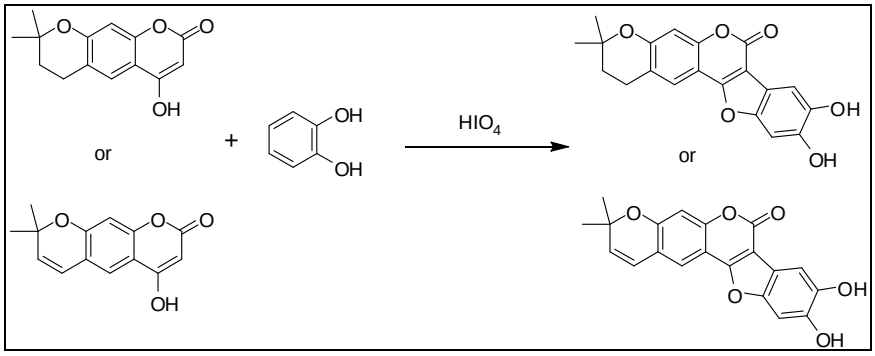
Scheme 39

Gong *et al.*[141] later synthesized wedelolactone derivatives by developing a methodology involving an intermolecular cycloaddition reaction from catechol and 4-hydroxycoumarins using ammonium persulphate as oxidant (Scheme 40).



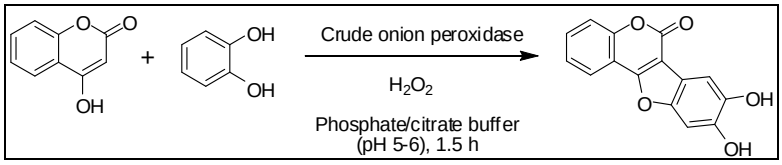
Scheme 40

Shah and Trivedi[142] obtained 3,4-dihydropyranocoumestans and 3,4-didehydropyranocoumestans by oxidative coupling of pyranobenzopyrans with catechol in the presence of HIO_4 (Scheme 41).



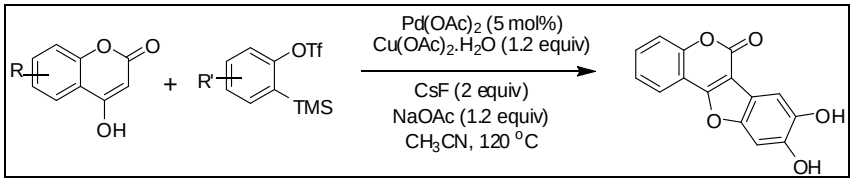
Scheme 41

Crude onion peroxidase extract catalyzed the reaction of catechol and different heterocyclic 1,3-dicarbonyl compounds as studied by Angeleska *et al.*[143] When 4-hydroxycoumarin was employed, domino reaction occur leading to the formation of coumestan product which exhibited potent antioxidant activity (Scheme 42).



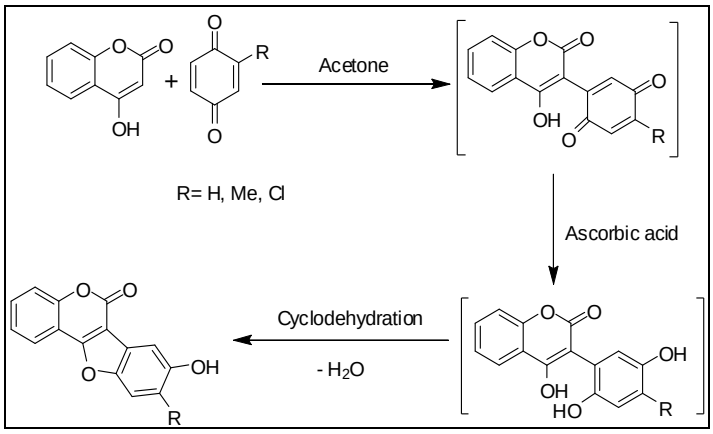
Scheme 42

Neog *et al.*[144] developed a palladium catalyzed cascade reaction of 4-hydroxycoumarins and *in situ* generated arynes. It involves C-H bond activation and C-O and C-C bond formation. The methodology was applied for the synthesis of flemichapparin C (Scheme 43).



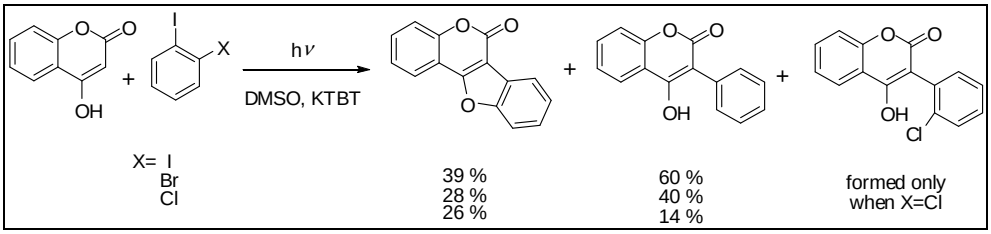
Scheme 43

4-Hydroxycoumarin was coupled readily with *p*-benzoquinone and its derivatives to afford the corresponding 3-(*p*-benzoquinonyl)-4-hydroxycoumarins by Wagh and Usgaonkar[145] They were successfully reduced with ascorbic acid to the corresponding 3-(2,5-dihydroxyphenyl)-4-hydroxycoumarins which were cyclodehydrated to give 8-hydroxycoumestans (Scheme 44).



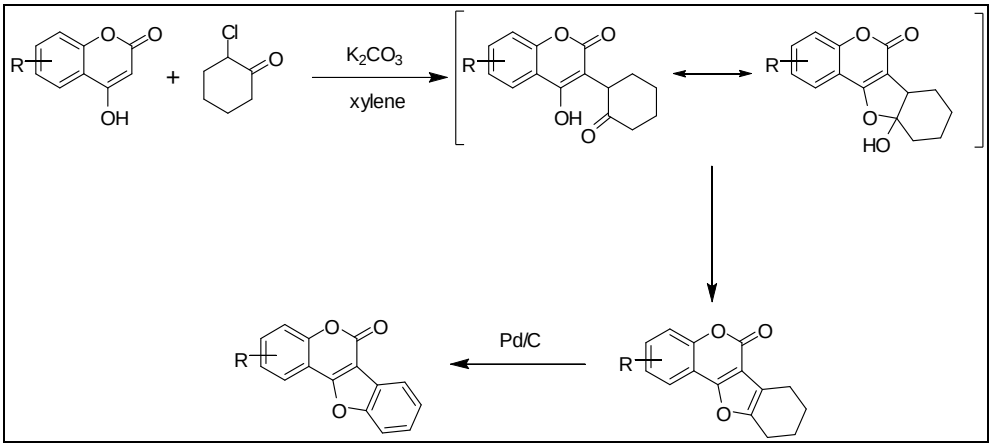
Scheme 44

Another photochemical study was carried out by Rodríguez and Baumgartner[146] wherein 4-hydroxycoumarin on treatment with *o*-dihalobenzenes resulted in biaryl coupling followed by intramolecular heterocyclization affording coumestan and reduced product 4-hydroxy-3-phenylcoumarin. In addition, 4-hydroxy-3-(2-chlorophenyl)coumarin was also obtained when 2-chloroiodobenzene was used as starting (Scheme 45).



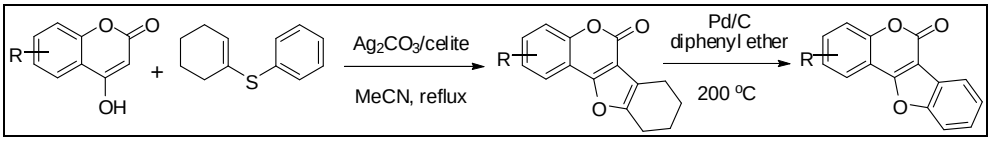
Scheme 45

Darbarwar *et al.*[147] carried out a condensation reaction of 4-hydroxycoumarin and 2-chlorocyclohexanone in the presence of anhyd. potassium carbonate and xylene to form an intermediate which on intramolecular cyclization resulted in a hemiketal. This was then easily dehydrated giving rise to tetrahydrocoumestan. Finally its dehydrogenation using Pd/C resulted in coumestan formation (Scheme 46). The disadvantage includes the inability to prepare halo substituted coumestans due to dehalogenation occurring during dehydrogenation.



Scheme 46

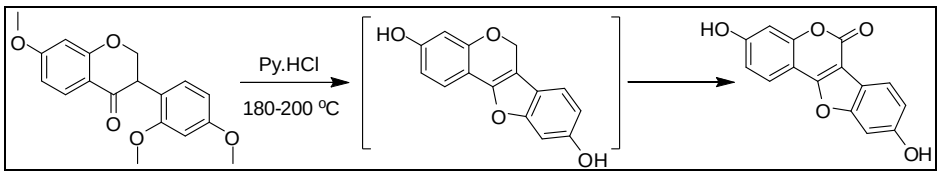
Various 4-hydroxycoumarin derivatives were treated with vinyl sulfide in the presence of silver carbonate on celite giving rise to furocoumarins by Lee *et al*.[148] These compounds were then dehydrogenated using Pd/C in diphenyl ether to provide coumetstans (Scheme 47).



Scheme 47

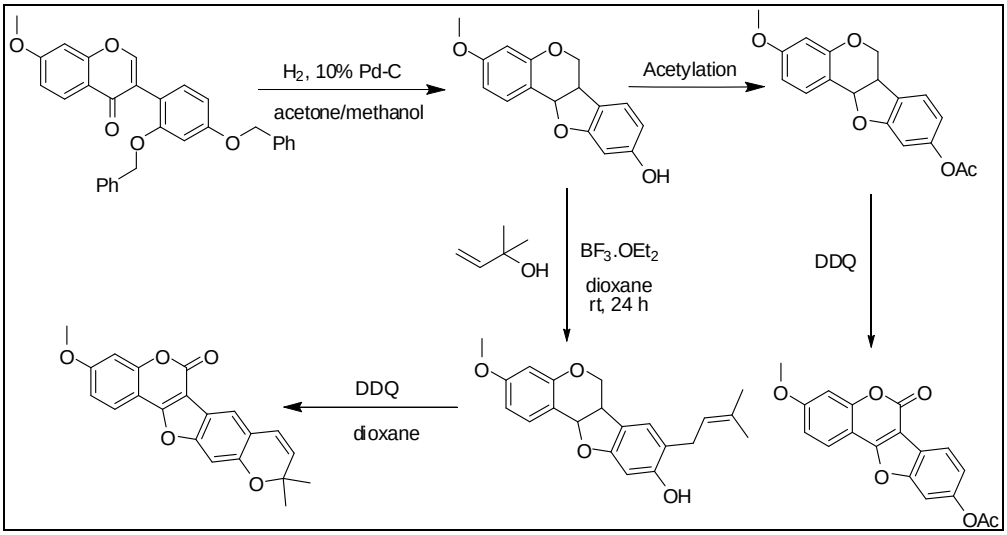
4.3.4: From Flavonoids (Route D)

Conversion of 2',4',7-trimethoxyisoflavanone into coumestrol using pyridine hydrochloride at 180-200 °C was reported by Dewick *et al.*[149] (Scheme 48).



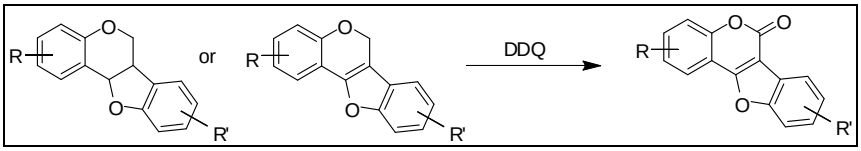
Scheme 48

Krishna Prasad *et al.*[150] reported an efficient three step synthesis of tuberostan from benzyloxyisoflavone. This isoflavone was converted to pterocarpan *via* hydrogenative cyclization involving debenzylation, reduction of double bond and carbonyl function and cyclization steps. Condensation of it with 2-methylbut-3-en-2-ol in presence of boron-trifluoride-diethyl ether gave prenylated compound which on treatment with DDQ afforded tuberostan. Also, acetylation of pterocarpan followed by DDQ oxidation resulted in the formation of 9-acetoxy-3-methoxy coumestan (Scheme 49).



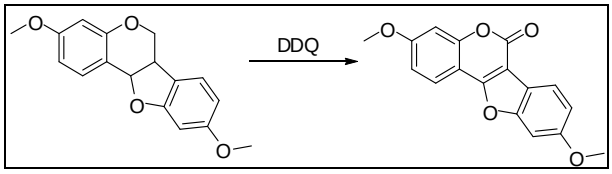
Scheme 49

Oxidation of the pterocarpan and pterocarpene systems to coumestanes has been carried out by Ferreira *et al.*[151] using DDQ (Scheme 50).



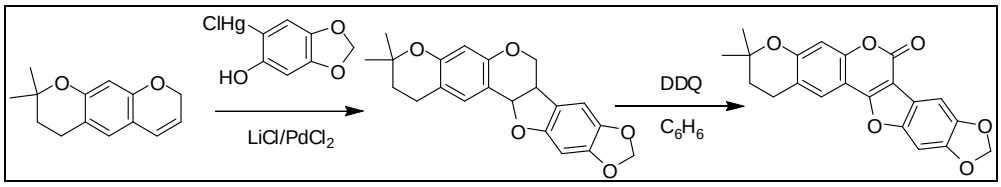
Scheme 50

Gunning *et al.*[152] synthesized coumestrol dimethyl ether from the corresponding pterocarpan by employing DDQ (Scheme 51).



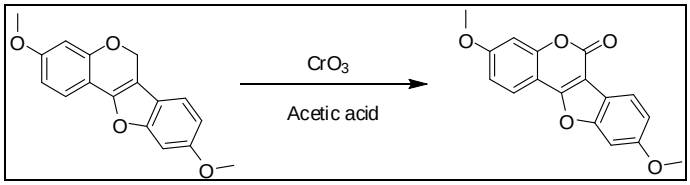
Scheme 51

Rukmani Iyer and co-workers[153] condensed chromene with 2-chloromercurio-4,5-methylenedioxyphenol in presence of lithium chloropalladite to form neorautane which was oxidized using DDQ to render coumestan derivative (Scheme 52). Later using this method many reports have been published wherein various coumestan derivatives have been synthesized.[84a,154]



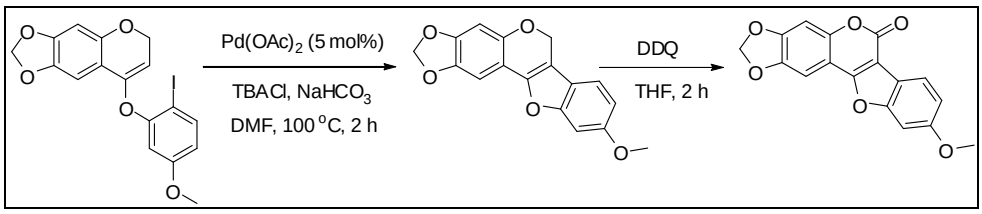
Scheme 52

Bowyer *et al.*[155] prepared coumestrol dimethyl ether from corresponding pterocarpene using chromic oxide (CrO_3) (Scheme 53).



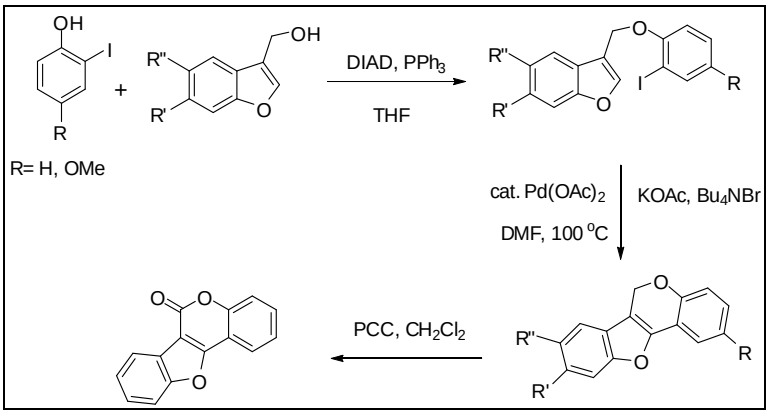
Scheme 53

Sant'Ana *et al.*[156] also used DDQ for the synthesis of coumestan from the appropriate pterocarpene which was obtained from the corresponding iodo compound by an intramolecular Heck reaction (Scheme 54).



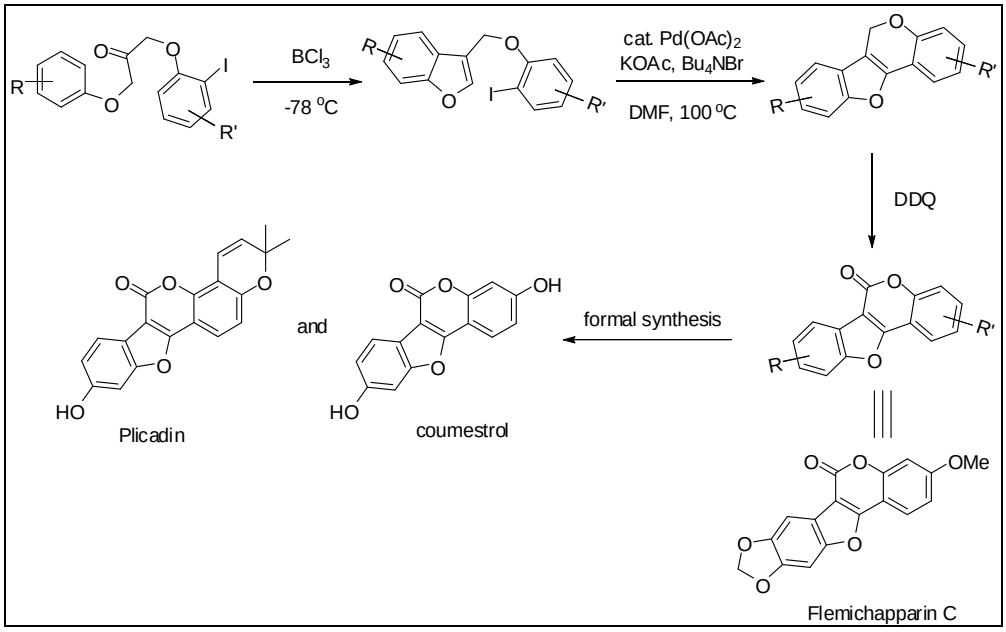
Scheme 54

A Mitsunobu coupling of 3-hydroxymethylbenzofurans with *o*-iodophenols carried out by Fowler *et al.*[157] resulted in 3-(2-iodophenoxy)methylbenzofurans which on 6-endo Heck cyclization under Jeffery conditions provided access to pterocarpenes. The parent coumestan was obtained when the unsubstituted pterocarpene was oxidized using PCC (Scheme 55).



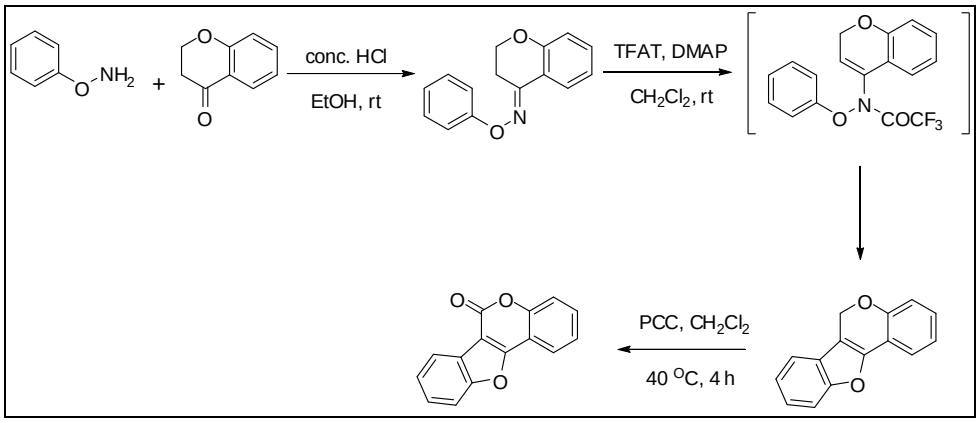
Scheme 55

Recently Kim and co-workers[158] demonstrated the formal synthesis of coumestrol and plicadin as well as the total synthesis of flemichapparin C using similar strategy wherein the respective starting iodo carbonyl compounds on treatment with BCl_3 delievered the corresponding benzofurans by regioselective ring closure. Further, palladium catalyzed intramolecular direct arylation of these benzofurans resulted in the pterocarpenes which on oxidation with DDQ afforded naturally occurring coumestans (Scheme 56).



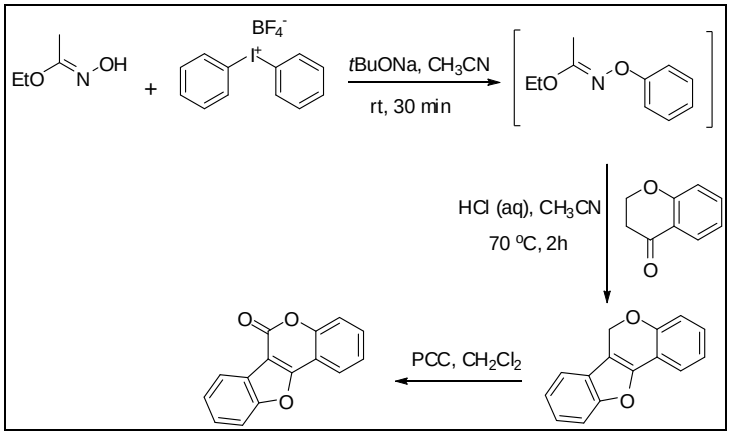
Scheme 56

Takeda *et al.*[159] synthesized coumestan by constructing its benzofuran ring first. *O*-Phenylhydroxylamine and 4-chromanone were condensed to give oxime ether which underwent sequential acylation and rearrangement on treatment with trifluoroacetyltriflate (TFAT) furnishing tetracyclic derivative. It was finally converted to the desired coumestan product by PCC as oxidizing reagent (Scheme 57).



Scheme 57

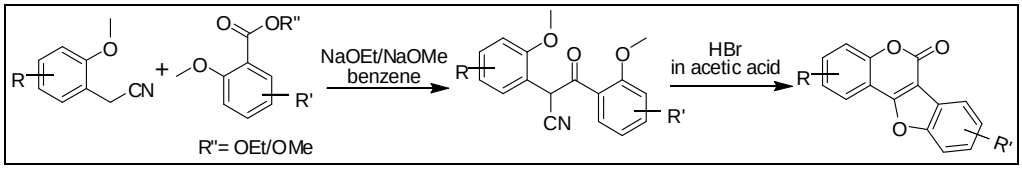
Ghosh *et al.*[160] developed a one pot method which involves the arylation of ethyl acetohydroxamate with diphenyliodonium tetrafluoroborate in absence of any transition metal. The *O*-arylated product thus formed was reacted *in situ* with ketone under acidic medium to form benzofuran through oxime formation, [3,3]-rearrangement and cyclization. The coumestan has been formally synthesized from this benzofuran using PCC oxidation (Scheme 58).



Scheme 58

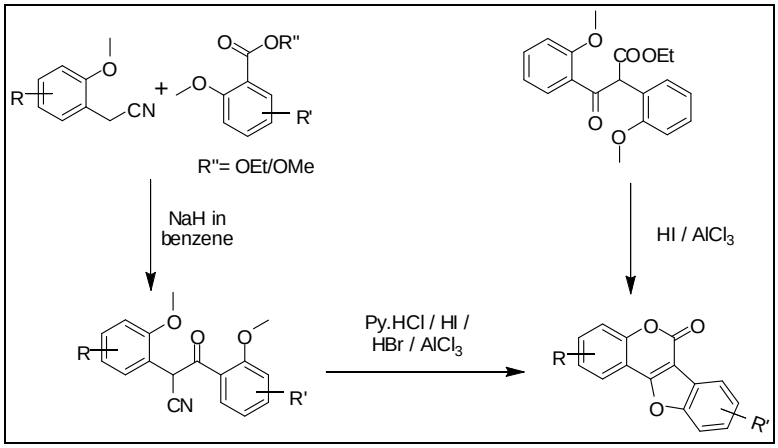
4.3.5: Miscellaneous routes (Route E)

Chatterjea and Roy[161] obtained ketonitrile intermediate on condensing *o*-methoxyphenylacetonitrile with ethyl-*o*-methoxybenzoate in the presence of sodium ethoxide in benzene. Ketonitrile was then converted to coumestan by treating with HBr in acetic acid (Scheme 59). Chatterjea later synthesised coumestrol from corresponding ketonitrile using this method.[162]



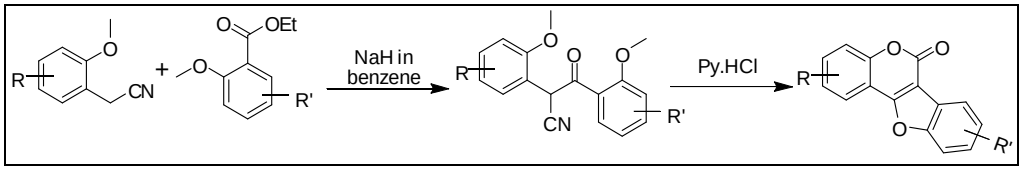
Scheme 59

Kawase[163] synthesized coumestrol from ketonitrile intermediate 2,4-dimethoxybenzoyl-2,4-dimethoxyphenylacetonitrile by the action of pyridine hydrochloride or hydriodic acid. The ketonitrile intermediate was obtained from the corresponding phenylacetonitrile and ester in the presence of sodium hydride. Kawase later described the action of HBr, HI, Py.HCl and $AlCl_3$ on ketonitrile and ketoester intermediate giving coumestan derivatives (Scheme 60).[164]



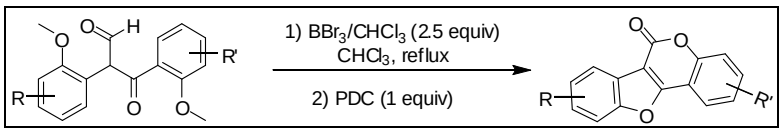
Scheme 60

Chatterjea and Prasad[165] synthesized tri-*O*-methylwedelolactone and dihydroerosnin from the corresponding ketonitrile intermediate by employing pyridine hydrochloride (Scheme 61). The ketonitrile intermediate was prepared by reacting the corresponding phenylacetonitrile with ester using sodium hydride.



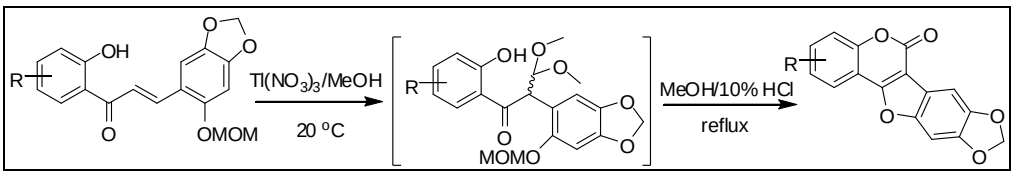
Scheme 61

Zhang *et al.*[166] synthesized coumestans *via* a two-step one-pot tandem demethylation-annulation-oxidation reaction from 2,3-*bis*(2-methoxyphenyl)-3-oxopropanals (Scheme 62). The products were obtained in good to excellent yields and halo-substituted products were further functionalized by using transition metal catalyzed cross-coupling reactions.



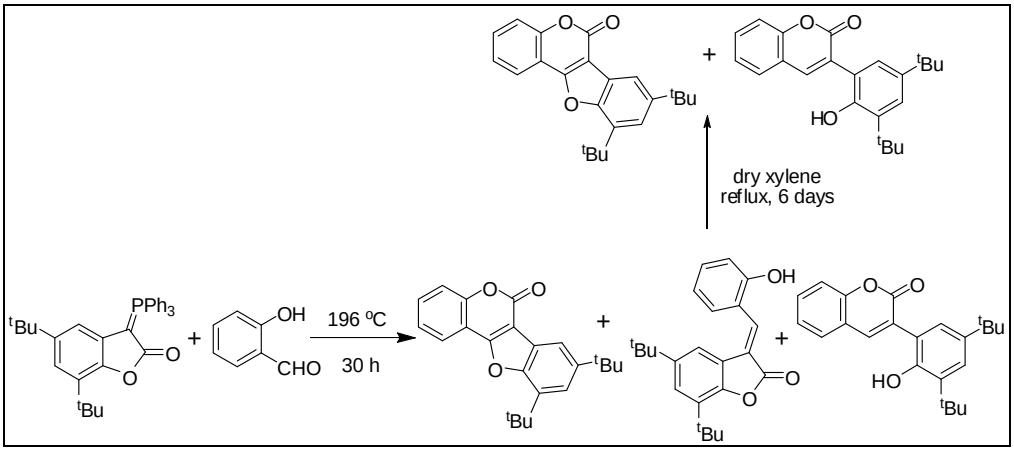
Scheme 62

Kamara *et al.*[167] used chalcones for direct transformation into coumestans in presence of thallium(III)nitrate *via* oxidative rearrangement (Scheme 63). Three natural coumestans namely flemichapparin C, medicagol and sophoracoumestan B have been synthesized. However chalcone was previously converted to coumestan using thallium(III)nitrate with a longer route.[168] Also flemichapparin-B and flemichapparin-C have been synthesized using this approach.[169]



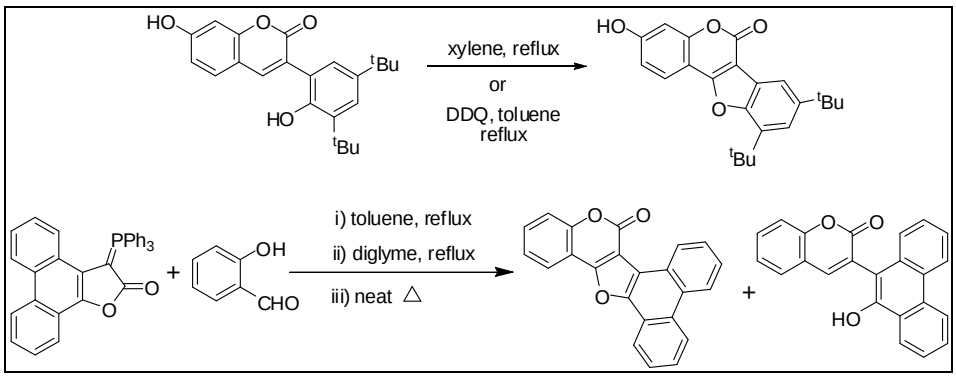
Scheme 63

Litinas and Stampelos[170] studied the reaction between phosphorous ylide and salicylaldehydes under various reaction conditions. When heated at the reflux temperature of salicylaldehyde the reaction resulted in the formation of coumestan, benzofuranone and coumarin derived compounds. When benzofuranone derivative was refluxed in xylene, coumestan along with coumarin derivative were produced (Scheme 64).



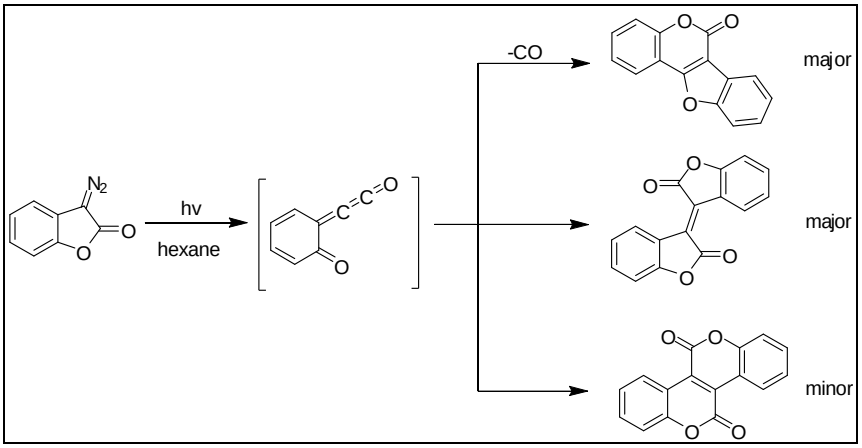
Scheme 64

Authors also prepared coumestan by refluxing coumarin derivative in xylene or with DDQ in toluene. Also, a reaction between another ylide and salicylaldehyde was studied which on refluxing in toluene or diglyme or under neat heating at the boiling point of salicylaldehyde provided coumestan and coumarin derivatives (Scheme 65).



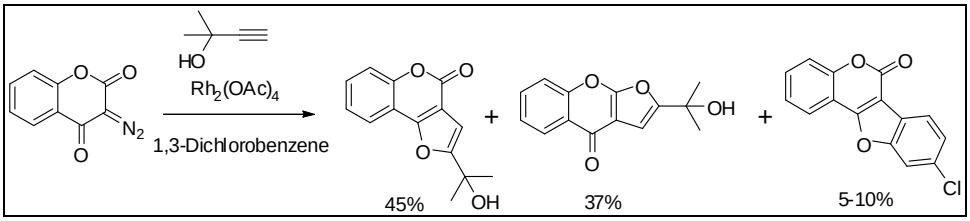
Scheme 65

Chiang *et al.*[171] converted 3-diazo-2-oxo-2,3-dihydrobenzofuran photochemically into quinonoid cumulenone which formed coumestan along with other two dimerized products by a remarkably facile addition-cyclization-(elimination) reaction (Scheme 66).



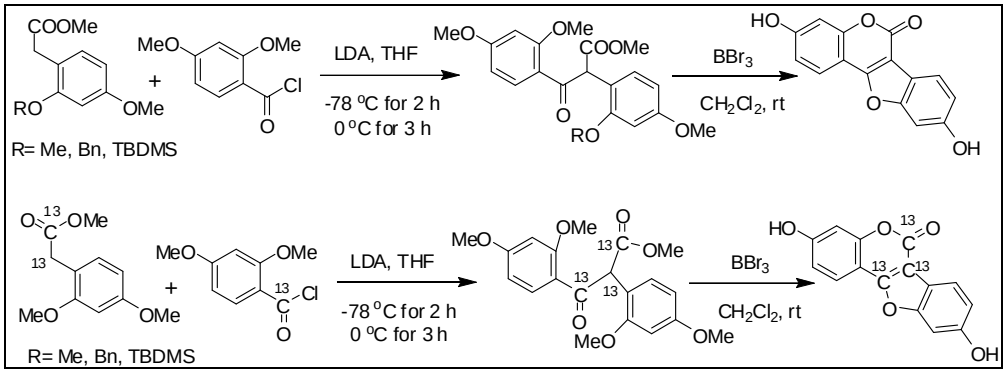
Scheme 66

Tollari *et al.*[172] disclosed a rare example of coumestan synthesis from the rhodium (II) acetate catalyzed decomposition of 3-diazobenzopyran-2,4(3*H*)-dione. Coumestan was obtained as minor product (5-10 %) along with isomeric 2-substituted furo[3,2-*c*]coumarin in 45 % and furo[2,3-*b*]coumarin in 37 % by a formal [3 + 2] cycloaddition (Scheme 67). Coumestan is formed by insertion of Rh-stabilized carbenoid into the solvent followed by intramolecular etherification.



Scheme 67

A short coumestrol synthesis was achieved by Al-Maharik and Botting[173] It involved reaction of methyl 2-hydroxy-4-methoxy-phenylacetate with protected hydroxyl group and 2,4-dimethoxybenzoyl chloride to afford methyl ester of 3-oxo propanoates. Among these, the methoxy protected intermediate on treating with excess of BBr_3 directly led to the formation of coumestrol via tandem demethylation and intramolecular cyclization. Also the authors have synthesized multiple ^{13}C labelled coumestrols *viz*. [6,6a,11a-$^{13}C_3$]coumestrol by adapting this method from suitable starting materials (Scheme 68).

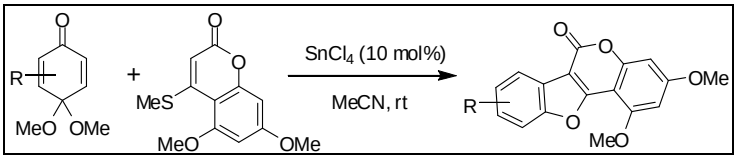


Scheme 68

Recently, Pahari *et al.*[174] reported synthesis of various psoralidin derivatives using similar strategy *via* BBr_3 mediated one pot demethylation and cyclization sequence. Authors have also reported the first synthesis of lespeflorin I_1.

Liu *et al.*[175] investigated a tin tetrachloride catalyzed synthesis of substituted benzofurans by highly regioselective allylic substitution of quinone monoketals with *α*-oxoketene dithioacetals *via* a formal [3 + 2] cycloaddition process. Accordingly coumestan derivatives

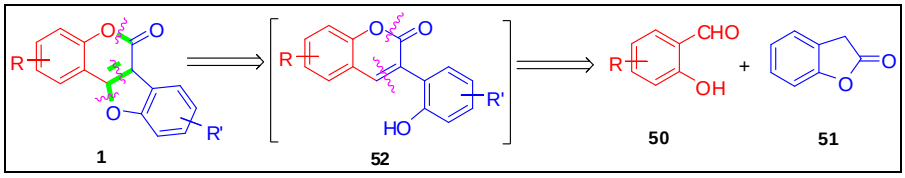
were obtained from quinone monoketals and vinylogous thioester by employing $SnCl_4$ as catalyst (Scheme 69).



Scheme 69

4.4: Results and Discussion

Literature studies show various routes for the synthesis of coumestans. However many of these methods have their own limitations like multistep syntheses, expensive reagents/catalysts usage, hazardous metal catalysts, difficulty in handling of reagents and/or its excessive requirement, troublesome reaction work up and product isolation. Hence continuous search for new method/reagent/catalyst for coumestan synthesis is pursued. In order to overcome the aforementioned limitations we devised a retrosynthetic route for coumestan formation which would require simple substrates and reagents.



Scheme 70: Retrosynthetic analysis of coumestan **1**.

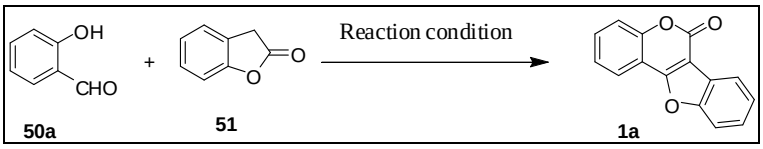
Initially a one pot retrosynthetic pathway was thought from simple substrates such as 2'-hydroxybenzaldehydes **50** and 2-coumaranone **51** (Scheme 70). We thought that any suitable reagent could directly provide us the target molecule **1** *via* intermediate 3-(2-hydroxyphenyl)coumarins **52** through condensation followed by oxidative cyclization.

4.4.1: One pot approach

Thus a one pot synthesis of coumestan **1a** from 2-coumaranone **51** and 2'-hydroxybenzaldehyde **50a** as the starting materials was visualized. Various reaction conditions were tried for its synthesis (Table 10). $FeCl_3$ is already known for C-O bond formation (Scheme 18),[112] so we envisioned its use in coumestan synthesis. Firstly, the reaction was carried out using $FeCl_3$ (2.5 equiv) in presence of triethylamine in 1,2-dichloroethane solvent under reflux condition for 24 h (entry 1). However no coumestan formation was seen. Similarly several other reaction conditions including NEt_3 and I_2 in

absence or presence of pyridine under reflux condition (entries 2-3), *N*,*N*-dimethylaniline in presence of I_2 at 150 and 170 °C (entries 4-5) and *N*,*N*-dimethylaniline in presence of 0.3 equiv of $PdCl_2$ (entry 6) failed to give product formation. Further stepwise one pot approach was tried wherein the reaction was first refluxed in NEt_3 solvent for 1 h followed by its removal and then the addition of catalyst such as $Pd(PPh_3)_4$ (0.1 equiv) (entry 7) and reagent $FeCl_3$ (2.5 equiv) in 1,2-dichloroethane under reflux for 24 h was carried out (entry 8). However both these attempts were unsuccessful. Similarly, the stepwise one pot reaction was carried out using $FeCl_3$ (2.5 equiv) in presence of 230-400 silica gel (1:1 wt./wt. $FeCl_3$), but no desired product was formed (entry 9). Since 2.5 equiv of $FeCl_3$ was used in previous reactions, we thought to further increase the amount of $FeCl_3$ to look for any product formation. Hence directly 10 equiv of $FeCl_3$ and 1,2-dichloroethane solvent were added and refluxed for 24 h after 1 h refluxing in NEt_3. It was delightful to see coumestan formation (characterized later) albeit in trace amount (entry 10). The product formation was encouraging but in unacceptable yield so further standardisation was required. Also some more one pot reaction conditions were tried including 10 wt % Pd/C, 20 wt % Pd/C and 20 wt % Pd/C along with 10 mol% L-proline in diphenyl ether solvent which failed to give the desired product (entries 11-13).

Table 10: Various reaction conditions attempted for direct synthesis of **1a** from **50a** & **51**.



50a **51** **1a**

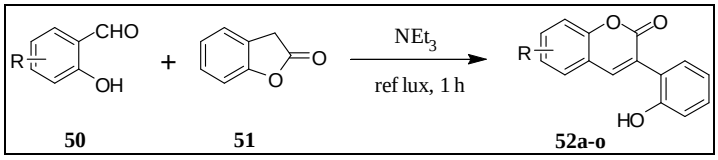
Sr. No.	Reaction condition	Time (h)	Temperature	Yield (%)
1)	NEt_3, $FeCl_3$ (2.5 equiv), 1,2-dichloroethane	24	reflux	0
2)	NEt_3, I_2 (1 equiv)	4	reflux	0
3)	NEt_3, I_2 (1 equiv), py	24	reflux	0
4)	*N*,*N*-Dimethylaniline, I_2 (1 equiv)	4	150 °C	0
5)	*N*,*N*-Dimethylaniline, I_2 (1 equiv)	4	170 °C	0
6)	*N*,*N*-Dimethylaniline, $PdCl_2$ (0.3 equiv)	24	150 °C	0
7)	NEt_3, $Pd(PPh_3)_4$ (0.1 equiv)	7	reflux	0
8)	NEt_3, later $FeCl_3$ (2.5 equiv), 1,2-dichloroethane	24	reflux	0

9)	NEt_3, later $FeCl_3$ (2.5 equiv), 230-400 silica gel (1:1 wt./wt. $FeCl_3$), 1,2-dichloroethane	24	reflux	0
10)	**NEt_3, later $FeCl_3$ (10 equiv), 1,2-dichloroethane**	**24**	**reflux**	**trace**
11)	Pd/C (10 wt %), diphenyl ether	2	reflux	0
12)	Pd/C (20 wt %), diphenyl ether	3	reflux	0
13)	Pd/C (20 wt %), L-proline (10 mol%), diphenyl ether	3	reflux	0

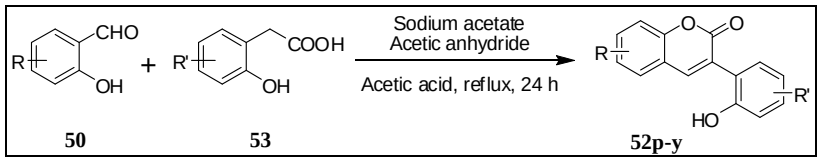
Since one pot approach employing **50a** and **51** as starting materials either failed or resulted in trace amount of the desired coumestan product, a two step protocol was undertaken wherein the intermediate 3-(2-hydroxyphenyl)coumarin **52a** was to be isolated and then oxidatively cyclized.

4.4.2: Two step approach

The required substrates 3-(2-hydroxyphenyl)-coumarin **52a-y** in case of two step approach were prepared from salicylaldehydes **50** and 2-coumaranone **51** (Schemes 71)[176] and salicylaldehydes **50** and 2'-hydroxyphenylacetic acids **53** (Schemes 72)[177] as shown below.

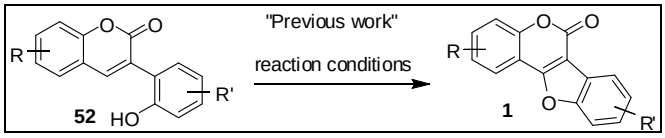


Scheme 71: Synthesis of substrates **52a-o**.



Scheme 72: Synthesis of substrates **52p-y**.

From the literature survey it was clear that only four reagents are available for the oxidative cyclization of **52** (Scheme 73).[113,115,117-118] First $Pb(OAc)_4$ in refluxing anhyd. benzene,[113] later DDQ in refluxing anhyd. benzene,[115] then $PdCl_2$ in presence of sodium acetate in DMF at 150 °C[117] and recently iodine in refluxing pyridine.[118] These oxidative cyclization methods have some limitations including low product yields, utilization of expensive reagent and limited substrate scope. Hence we thought of exploring some potential reagents for this oxidative cyclization.



1) $Pb(OAc)_4$ (1.5 mmol), anhyd. benzene (30 mL), reflux, 30 min.

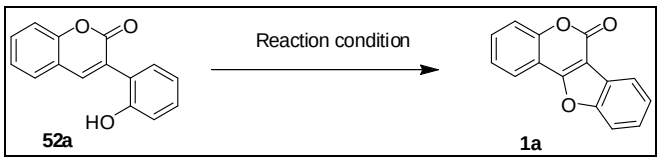
2) DDQ (1 mmol), benzene, reflux, 72 h.

3) $PdCl_2$ (1 mmol), NaOAc (13.6 mmol), DMF (10 mL), 150 °C, 24 h.

4) I_2 (1 mmol), anhyd. Py (10 mL), reflux, 15 h.

Scheme 73: Reported syntheses of coumestans **1** *via* oxidative cyclization from **52**.

Table 11: Various reaction conditions from **52a**.

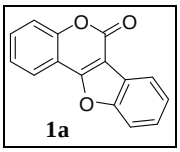


Sr. No.	Reaction condition	Time (h)	Temperature (°C)	Yield (%)
1)	Fe_3O_4 (2 equiv), 1,2-dichloroethane	24	rt	0
2)	Fe_3O_4 (2 equiv) 1,2-dichloroethane	24	reflux	0
3)	I_2 (1 equiv), py	24	110	0
4)	I_2 (0.3 equiv), DMSO	24	150	0
5)	$CuBr_2$ (2.2 equiv), 1,2-dichloroethane	24	rt	0
6)	$FeCl_3.6H_2O$ (2.5 equiv)	24	150	0
7)	$FeCl_3$ (2.5 equiv), TFA	24	reflux	0
8)	**$FeCl_3$ (10 equiv), 1,2-dichloroethane**	**24**	**reflux**	**20**

For our studies, 3-(2-hydroxyphenyl)-2*H*-chromen-2-one **52a** was selected as a model substrate. It was subjected to various reaction conditions as shown in below table 11. In the beginning **52a** was subjected to excess of Fe_3O_4 in DCE solvent. However the reaction failed to provide any product at rt as well as under reflux condition (entries 1-2). Then we changed the reagent to iodine in presence of pyridine (entry 3) but no product formation was seen. Also, a reaction using catalytic amount of iodine in DMSO solvent was attempted (entry 4). $CuBr_2$ also did not provide any product (entry 5). As discussed before, a trace amount of product formation was seen when $FeCl_3$ was employed, we further screened $FeCl_3$ reagent using substrate **52a**. $FeCl_3.6H_2O$ and $FeCl_3$ in TFA failed to show any product formation (entries 6-7) but when the reaction was carried out using large excess of $FeCl_3$ in DCE, 20 %

of the desired coumestan **1a** was isolated (entry 8). The product **1a** showed band in its IR spectrum at 1732 cm^{-1} accounting for C=O group and its structure was confirmed by the spectral data given below.

Spectral data of 6*H*-benzofuro[3,2-*c*]chromen-6-one (1a)



1a

colorless solid; m.p. 186-188 °C; lit.[106] 187-188 °C.

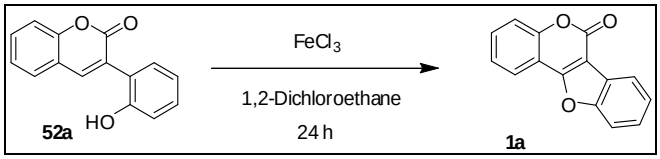
IR (KBr): $\tilde{\nu}$ = 3078, 3045, 1732 (C=O), 1498, 1082, 752 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33-7.45 (m, 4H), 7.52-7.56 (m, 1H), 7.59-7.61 (m, 1H), 7.96 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.06-8.08 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 105.9 (Cq), 111.8 (CH), 112.6 (Cq), 117.5 (CH), 121.8 (CH), 121.9 (CH), 123.4 (Cq), 124.7 (CH), 125.2 (CH), 126.8 (CH), 131.9 (CH), 153.6 (Cq), 155.5 (Cq), 158.1 (Cq), 159.9 (Cq).

Inspired with the product formation, however in low yield, we next went on to standardize the amount of $FeCl_3$ to improve the yield.

Table 12: Standardization of $FeCl_3$.

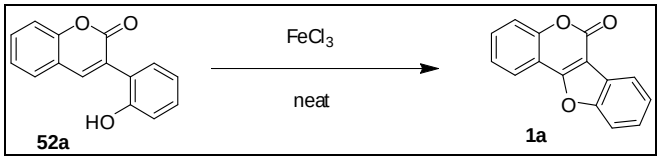


Sr. No.	$FeCl_3$ (equiv)	230-400 silica gel	Temperature (°C)	Yield (%)
1)	0.3	-----	reflux	0
2)	0.3	1:1 wt./wt. $FeCl_3$	reflux	0
3)	2.5	-----	reflux	0
4)	2.5	1:1 wt./wt. $FeCl_3$	reflux	0
5)	5	-----	reflux	0
6)	8	-----	reflux	0
7)	10	-----	rt	0
8)	**10**	**-----**	**reflux**	**20**
9)[a]	3	-----	120	11

[a] Neat reaction

Since the product formation was observed with 3 equiv of $FeCl_3$ under neat condition, the reaction was further examined using various conditions (Table 12). We started with catalytic amount of $FeCl_3$ but no product formation was observed (entry 1). Recently a report had claimed that $FeCl_3$ in presence of 230-400 mesh sized silica gel gave better results than $FeCl_3$ used alone for coumestan synthesis from 4-hydroxy-3-phenylcoumarins.[112] With this fact we tried next reaction with catalytic amount of $FeCl_3$ along with 230-400 silica gel (1:1 wt./wt. $FeCl_3$) but again no product formation was observed (entry 2). Similar results were obtained when the amount of $FeCl_3$ was increased to 2.5 equiv (entries 3-4). Further increase in amount of $FeCl_3$ up to 5 and 8 equiv did not help to get any product (entries 5-6). However when 10 equiv of $FeCl_3$ was employed product formation was not visible when the reaction was carried out at room temperature but at reflux temperature gave 20 % yield of product (entries 7-8). This suggested the requirement of large amount of $FeCl_3$ for the reaction to occur. Also a neat reaction using 3 equiv of $FeCl_3$ at 120 °C was tried wherein product was isolated in 11 % yield (entry 9). Since 10 equiv of $FeCl_3$ is a large amount, we thought of experimenting further to get the product in good yields by employing low amount of $FeCl_3$.

Table 13: Optimization of $FeCl_3$ with 230-400 silica gel under neat condition.



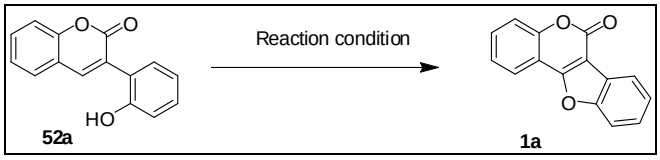
Sr. No.	$FeCl_3$ (equiv)	230-400 silica gel	Time (h)	Temperature (°C)	Yield (%)
1)	2	-----	24	120	0
2)	2.5	-----	24	150	12
3)	3	-----	15	120	11
4)	2.5	1:1 wt./wt. $FeCl_3$	24	150	19
5)	2.5, then water	1:1 wt./wt. $FeCl_3$	24, 24	150, H_2O reflux	24
6)	2.5, then sonicated	-----	24	150	33
7)	3, then sonicated	1:1 wt./wt. $FeCl_3$	24	150	36
8)	4, then sonicated	-----	24	180	25

9)	**4, then sonicated**	**1:1 wt./wt. $FeCl_3$**	**24**	**150**	**42**
10)	5, then sonicated	1:1 wt./wt. $FeCl_3$	24	150	39

In search of an ideal condition, we went for neat conditions (Table 13). At the outset 2, 2.5 and 3 equiv of $FeCl_3$ was tried at different temperatures but the product was isolated in low yields in only the latter 2 cases (entries 1-3). Further 2.5 equiv in presence of 230-400 silica gel gave slightly increased product yield of 19 % (entry 4). Next, the reaction was carried out with 2.5 equiv of $FeCl_3$ for 24 h followed by the addition of water and refluxing for 24 more hours, however only 24 % of product could be isolated (entry 5). Since the product was not getting isolated in appreciable yield, next we thought to sonicate the reaction mixture after neat heating. Accordingly, a neat reaction was carried out in 2.5 equiv of $FeCl_3$ in absence of silica gel for 24 and later sonicated after addition of ethyl acetate. This resulted in slight increased product yield of 33 % (entry 6). Similarly, 3 equiv of $FeCl_3$ in presence of silica gel following similar procedure delivered 36 % yield of coumestan (entry 7). Further increasing $FeCl_3$ amount to 4 equiv in absence of silica gel at 180 °C delivered 25 % yield (entry 8) whereas when the reaction was carried out in presence of silica gel at lower temperature (150 °C) gave maximum yield of 42 % (entry 9). On using higher amount of $FeCl_3$ (5 equiv) in presence of silica gel at same temperature resulted in lowered product yield (entry 10).

In spite of carrying out various reactions, improvement in the yield of the desired coumestan was unsuccessful. So, next we tried screening some other common reagents as shown below.

Table 14: Various reaction conditions from **52a**.



Sr. No.	Reaction condition	Time (h)	Temperature (°C)	Yield (%)
1)	10 wt % Pd/C, 1,4-dioxane	12	reflux	0
2)	10 wt % Pd/C, 0.1 equiv tetrabutylammonium iodide, 1,4-dioxane	16	reflux	0

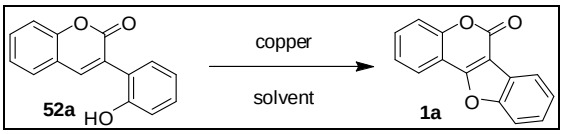
3)	10 wt % Pd/C, 1 equiv tetrabutylammonium iodide, 1,4-dioxane	5	reflux	0
4)	10 wt % Pd/C, 1 equiv tetrabutylammonium iodide, 1 equiv K_2CO_3, 1,4-dioxane	5	reflux	0
5)	0.3 equiv $Cu(OTf)_2$, dichloromethane	24	rt	0
6)	0.3 equiv $Cu(OTf)_2$, dichloromethane	24	reflux	0
7)	0.3 equiv $Cu(OTf)_2$, dichloroethane	24	reflux	0

Table 14 shows various reaction conditions examined for coumestan formation from **52a**. In the beginning 10 wt % Pd/C was tested in 1,4-dioxane under reflux condition, however no product formation was observed (entry 1). So Pd/C was used in addition with tetrabutylammonium iodide in catalytic as well as stoichiometric amount in 1,4-dioxane under reflux condition but could not give any product (entries 2-3). Above reaction was then attempted in presence of mild base K_2CO_3 but again no product was formed (entry 4). Next we moved on to use copper triflate. Catalytic amount of $Cu(OTf)_2$ in dichloromethane as well as dichloroethane proved to be ineffective (entries 5-7).

Copper salts have been widely used in organic reactions owing to its cheap availibility and low toxicity. Several reviews have appeared on its role either as reagent and/or catalyst.[178] In particular $Cu(OAc)_2$ is a mild reagent/catalyst known for the synthesis of several heterocycles.[179] It has gained considerable attention for its role in the intamolecular C-O cyclization *via* C-H functionalization[179c-d] for the construction of heterocyclic compounds, however the area is not fully explored.

From the above literature discussion the effective role of $Cu(OAc)_2$ in the C-O cyclization of some compounds is clearly seen. However its use in the oxidative cyclization is limited and needs to be explored further. Also it is clear that $Cu(OAc)_2$ has not been employed for coumestan synthesis. With regard to this we envisioned the role of $Cu(OAc)_2$ in the C-O cyclization of 3-(2-hydroxyphenyl)coumarin **52** which may lead to important biologically active coumestan **1** compounds.

Table 15: Screening of $Cu(OAc)_2$ in the coumestan formation.



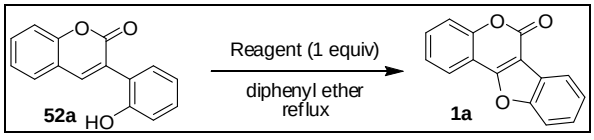
Sr. No.	$Cu(OAc)_2.H_2O$ (equiv)	Solvent	Time (h)	Temperature (°C)	Yield (%)
1)	0.5	dichloromethane	24	rt	0
2)	0.5	dichloromethane	24	reflux	0
3)	0.5	dichloroethane	24	reflux	0
4)	0.2	acetic acid	24	reflux	0
5)	1	acetic acid	24	reflux	0
6)	1	diphenyl ether	5	reflux	55
7)[a]	1	diphenyl ether	6	reflux	mixture of products
8)[b]	**1**	**diphenyl ether**	**6**	**reflux**	**76**

[a] 2 equiv K_2CO_3 was used.

[b] Anhyd. $Cu(OAc)_2$ was used.

In order to check the feasibility of this reaction 3-(2-hydroxyphenyl)-2*H*-chromen-2-one **52a** was treated with 0.5 equiv of $Cu(OAc)_2.H_2O$. The reactions carried out in dichloromethane at rt as well as reflux condition failed to provide any product (Table 15, entries 1-2). Similarly changing the solvent to dichloroethane did not prove to be effective (entry 3). Attempts to carry out the reaction in acetic acid in presence of catalytic as well as equivalent amounts of $Cu(OAc)_2.H_2O$ failed to provide any product (entries 4-5). The solvent was then changed to diphenyl ether. When the reaction was carried out in this high boiling solvent we were delighted to see the coumestan **1a** formation which occurred within 5 h in 55 % yield (entry 6). To see the effect of base on this reaction, a reaction was attempted in presence of K_2CO_3 but it ended in mixture of products (entry 7). Finally, anhyd. $Cu(OAc)_2$ proved to be efficient reagent for this oxidative cyclization (entry 8).

Table 16: Screening of various reagents in the coumestan formation.



Sr. No.	Reagent	Time (h)	Yield (%)
1)	$Cu(OAc)_2.H_2O$	5	55
2)	**$Cu(OAc)_2$**	**6**	**76**
3)[a]	$Cu(OAc)_2$:$Zn(OTf)_2$	24	7
4)	$CuCl_2$	24	69
5)	$CuBr_2$	24	48
6)	CuI	24	19
7)	Cu_2O	24	75
8)	CuO	16	60
9)[b]	$Cu(OTf)_2$	24	40
10)	$Cu(OTf)_2$	16	63
11)	Cu (nanopowder)	24	74
12)	Cu (metal powder)	24	72
13)	Ag.OAc	2	complex mixture
14)[c]	Ag.OAc	24	57
15)	$Mn(OAc)_3.2H_2O$	14	18
16)	$Zn(OAc)_2.2H_2O$	24	30
17)	$ZnCl_2$	24	15
18)	ZnO	24	30
19)	$MgCl_2$	24	41
20)	TiO_2	24	32
21)	Fe_3O_4 (nanopowder)	15	68
22)	**$Pd(OAc)_2$**	**18**	**86**
23)[d]	$Pd(OAc)_2$	24	RI
24)[d]	$PdCl_2$	24	RI
25)[e]	10 % Pd/C	12	RI
26)[f]	10 % Pd/C	12	RI
27)[g]	10 % Pd/C	12	RI
28)[h]	**10 % Pd/C**	**12**	**78**
29)	-----	6	00

[a] Toluene:DMSO (20:1) was used as solvent. [b] *p*-xylene solvent was used. [c] 0.5 equiv of reagent was used. [d] 0.1 equiv of reagent was used. [e ,f ,g ,h] 10, 20, 30, 50 wt % of reagent was used respectively. RI: Reaction Incomplete.

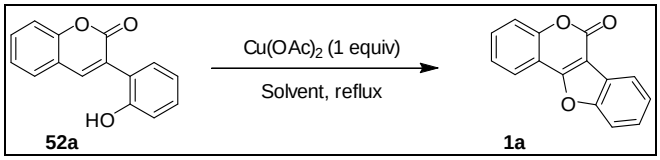
Encouraged with the coumestan formation using easily available inexpensive Cu reagents (Table 16, entries 1-2) we went ahead with the screening of other copper and various metal reagents (entries 3-28).

Recently, Hong and co-workers[179c] have demonstrated the synthesis of 6*H*-benzofuro[2,3-*c*]chromen-6-one using a combination of 1.2 equiv $Cu(OAc)_2$ and 0.2 equiv of $Zn(OTf)_2$ in toluene:DMSO (20:1) *via* C-H functionalization/C-O cyclization. Interestingly, it was not explored for the synthesis of isomeric 6*H*-benzofuro[3,2-*c*]chromen-6-one (coumestans) *via* insertion of oxygen into aromatic rings. Hence we tried to see coumestan formation using $Cu(OAc)_2$ and $Zn(OTf)_2$ combination. However, we could isolate only 7 % coumestan product using this reaction condition (entry 3).

Employing $CuCl_2$ and $CuBr_2$ diminished the product yield (entries 4-5). Other Cu reagents such as CuI, Cu_2O and CuO also showed the formation of product among which Cu_2O gave highest yield of 75 % (entries 6-8). However $Cu(OTf)_2$ was reactive enough to give 40 % yield in refluxing *p*-xylene (entry 9) but in diphenyl ether the yield was increased to 63 % (entry 10). Employing Cu nanopowder and metal powder also proved effective for this cyclization (entries 11-12).

Ag.OAc was found to give a complex mixture when used as a reagent (entry 13). However, reducing its amount by half resulted in 57 % of coumestan formation (entry 14). $Mn(OAc)_3.2H_2O$ was ineffective under above reaction condition and provided coumestan in only 18 % due to poor conversion (entry 15). Zinc metal compounds such as $Zn(OAc)_2.2H_2O$, $ZnCl_2$ and ZnO were less effective for the cyclization reaction providing low yields of product (entries 16-18). Similarly $MgCl_2$, TiO_2 and Fe_3O_4 (nanopowder) were also less effective (entries 19-21). Application of $Pd(OAc)_2$ under the present reaction condition afforded maximum yield of 86 % (entry 22). On using catalytic amount of $Pd(OAc)_2$ and $PdCl_2$ reaction was found to be incomplete even after refluxing for 24 h (entries 23-24). Similarly we tried 10, 20 & 30 wt % of 10 % Pd/C which also resulted in incomplete reaction (entries 25-27). Further, when the amount was increased to 50 wt %, 78 % of coumestan was isolated (entry 28). However due to stoichiometric requirement we did not continued with expensive Pd reagents further. Among all the above reagents, anhyd. $Cu(OAc)_2$ was concluded to be more efficient and best source for the present oxidative cyclization with respect to cost, availability and reaction time giving yield of 76 % (entry 2). It must be noted that the absence of any reagent did not show any product formation (entry 29).

Table 17: Solvent screening.

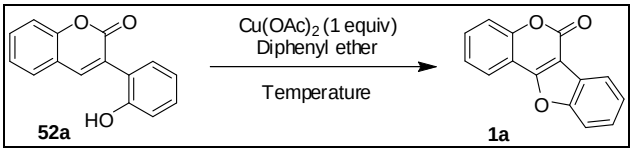


Sr. No.	Solvent	Temperature (°C)	Time (h)	Yield (%)
1)	Toluene	110	24	7
2)	AcOH	118	24	0
3)	*p*-Xylene	138	24	20
4)	DMF	153	24	15
5)	DMA	165	24	6
6)	*o*-DCB	180	24	30
7)	DMSO	189	24	ND
8)	**Diphenyl ether**	**258**	**6**	**76**

ND: Not Determined

To check the feasibility of this reaction in other solvents, solvent screening was done (Table 17). At the outset a reaction with anhyd. $Cu(OAc)_2$ (1 equiv) in toluene under refluxing condition for 24 h delivered product albeit in poor yield of 7 % (entry 1). Acetic acid did not show any product formation even after 24 h (entry 2). Examining different solvents with varying boiling points such as, *p*-xylene, DMF, DMA and *o*-DCB proved to be inefficient to provide desired product in good yields (entries 3-6). Reaction in DMSO resulted in charring and no coumestan product was isolated (entry 7). Among these solvents, diphenyl ether proved to be the optimum solvent as substantial product yield of 76 % was isolated (entry 8).

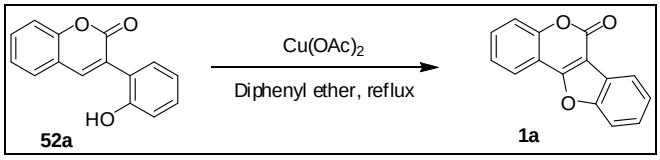
Table 18: Standardization of reaction temperature.



Sr. No.	Temperature (°C)	Time (h)	Yield (%)
1)	100	24	25
2)	150	24	50
3)	170-180	12	62
4)	200	10	64
5)	**258**	**6**	**76**

Temperature studies were done by carrying out the reactions at different temperatures starting from 100 °C to reflux temperature in diphenyl ether solvent (Table 18). It was observed that at 100 °C only 25 % yield was isolated (entry 1). Increasing the reaction temperature to 150 °C allowed increase in product yield to 50 % (entry 2). Further increase up to 62 % was observed when the reaction temperature was maintained between 170-180 °C (entry 3). At 200 °C no much increase in product yield was observed (entry 4). However maximum yield of 76 % was observed at 258 °C (entry 5). Hence refluxing temperature was found to be the optimum temperature as lowering in temperature showed decreased product yield.

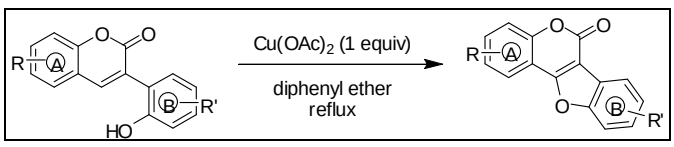
Table 19: Standardization of $Cu(OAc)_2$ concentration.

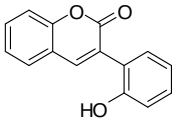
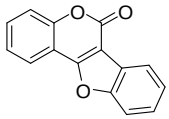
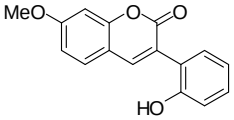
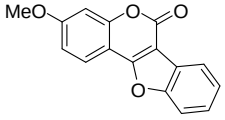
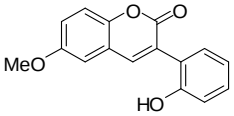
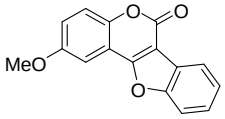
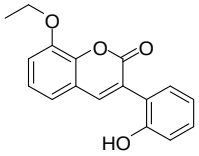
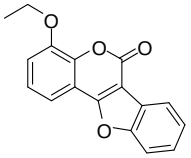
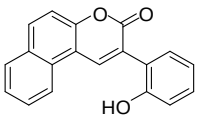
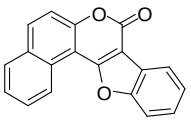
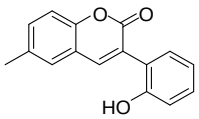
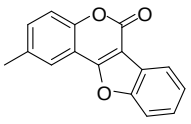
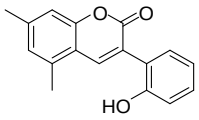
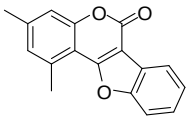
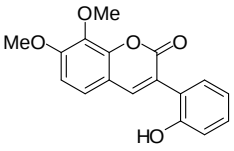
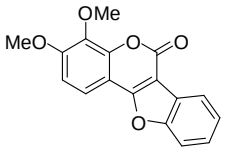


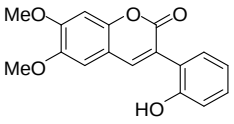
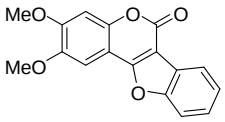
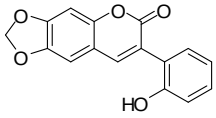
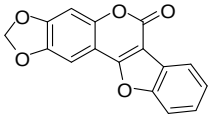
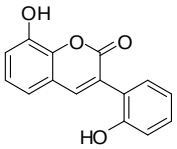
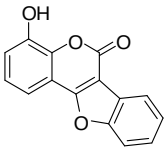
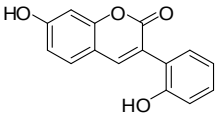
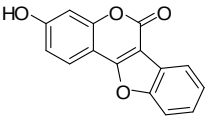
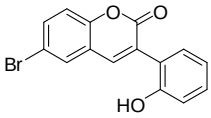
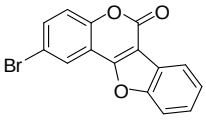
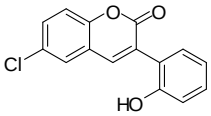
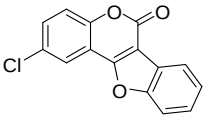
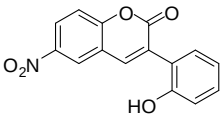
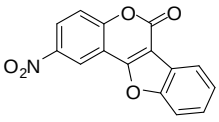
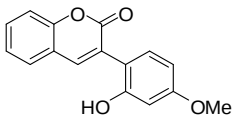
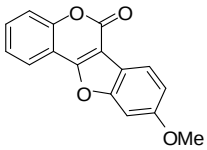
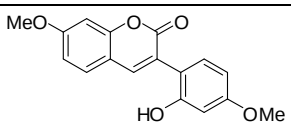
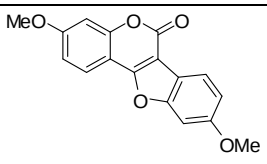
Sr. No.	$Cu(OAc)_2$ (equiv)	Time (h)	Yield (%)
1)	0.2	24	66
2)	0.5	12	70
3)	**1**	**6**	**76**
4)	1.2	11	70
5)	2	14	56

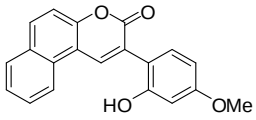
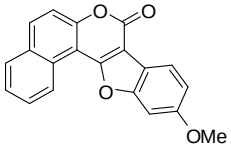
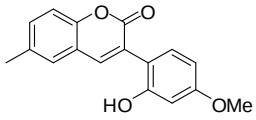
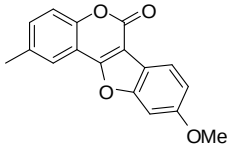
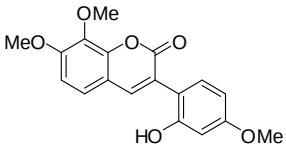
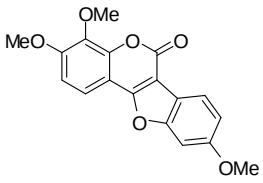
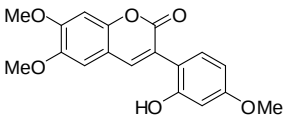
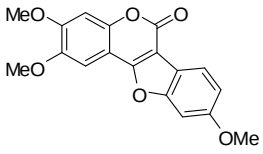
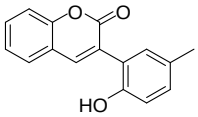
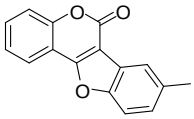
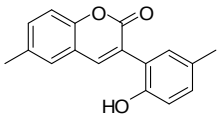
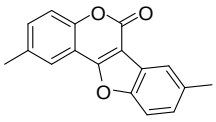
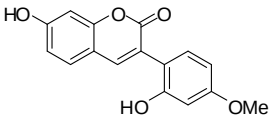
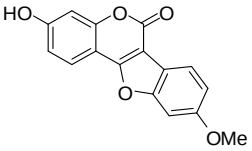
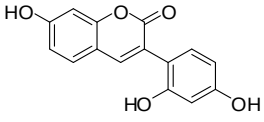
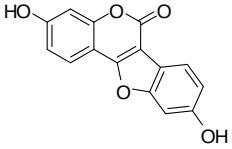
Standardization of $Cu(OAc)_2$ concentration was done by carrying out different reactions with varying amount of $Cu(OAc)_2$ from catalytic (0.2 equiv) to excess (2 equiv) (Table 19). It was endearing to see that even catalytic amount of $Cu(OAc)_2$ was effective enough to provide product yield of 66 % (entry 1). Similarly 0.5 equiv of $Cu(OAc)_2$ worked well to deliver increased yield of 70 % (entry 2). Best quantity was found to be 1 equiv of $Cu(OAc)_2$ giving highest yield of 76 % in just 6 h (entry 3). Slight increase in reagent quantity resulted in yield drop (entry 4). Excess of the reagent caused further drop to 56 % (entry 5).

Table 20: Synthesis of coumestans using optimized reaction condition.



Sr. No.	Substituted 3-(2-hydroxyphenyl)-2*H*-chromen-2-one	Coumestan	Time (h)	Yield (%)
1)	 **52a**	 **1a**	6	76
2)	 **52b**	 **1b**	13	66
3)	 **52c**	 **1c**	6	72
4)	 **52d**	 **1d**	13	70
5)	 **52e**	 **1e**	8	80
6)	 **52f**	 **1f**	10	65
7)	 **52g**	 **1g**	17	67
8)	 **52h**	 **1h**	6	80

9)	 **52i**	 **1i**	8	77
10)	 **52j**	 **1j**	14	61
11)	 **52k**	 **1k**	16	62
12)	 **52l**	 **1l**	14	68
13)	 **52m**	 **1m**	24 18[a]	30 53[a]
14)	 **52n**	 **1n**	24	67
15)	 **52o**	 **1o**	13	54
16)	 **52p**	 **1p**	5	70
17)	 **52q**	 **2f**	5	65

18)	 **52r**	 **1q**	5	55
19)	 **52s**	 **1r**	6	66
20)	 **52t**	 **1s**	4	60
21)	 **52u**	 **1t**	7	54
22)	 **52v**	 **1u**	10	65
23)	 **52w**	 **1v**	7	60
24)	 **52x**	 **2e**	12	59
25)	 **52y**	 **2c**	18	55

[a] Reaction was carried out in 1.5 equiv of $Cu(OAc)_2$.

After obtaining the optimum reaction conditions further studies to check the substrate scope were undertaken (Table 20). Substituents on both the phenyl rings A and B were evaluated. Parent coumestan was obtained in 76 % yield. Study on ring A revealed that the electron releasing methoxy and ethoxy substituents reacted smoothly to give the desired products **1b**-**1d** in good yields. Naphthol group was very reactive to provide the expected coumestan **1e** in 80 % yield. Monomethyl and dimethyl substituents were also successfully converted into the desired products **1f** and **1g**. Coumestans **1h**-**1j** were formed when dimethoxy and methylenedioxy substitutions were examined on ring A. Hydroxy substituents also reacted to produce the required coumestans **1k** and **1l** without any protection thus exhibiting good efficiency and practicability of this method. Coumestan bearing electron withdrawing bromo group **1m** was isolated in low yield when 1 equiv of $Cu(OAc)_2$ was employed. However when the amount of $Cu(OAc)_2$ was increased to 1.5 equiv the product yield also increased to 53 %. Similarly electron deficient coumestan with chloro substituent **1n** was synthesised in 67 % yield. Strong electron withdrawing nitro group was quite reactive enough to offer the desired product **1o**.

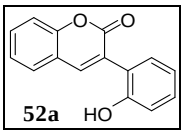
On successfully synthesising above derivatives, we went on to explore the substitution pattern on ring B. When methoxy substituent was employed on ring B without any substituent on ring A, reaction went on smoothly to afford coumestan **1p** in 70 % yield. Similarly various substituents on ring A provided diverse coumestans **2f**, **1q**-**1t** in moderate to good yields in presence of methoxy substituent on ring B. Among these the dimethyl ether of natural compounds coumestrol **2f**[9] and sativol **1s** were isolated. Moreover trimethyl ether of lucernol **1t** was also successfully formed. Various reports exhibiting the conversion of compound **2f** to naturally occurring coumestrol **2c** have been demonstrated.[111b,132] With the introduction of methyl group on ring B also successfully delivered coumestans **1u** and **1v** in 65 and 60 % yields respectively without affecting the side chain.

Encouraged by the formation of hydroxyl coumestans **1k** and **1l** we thought to apply this methodology towards the protective group free synthesis of naturally occurring 4'-*O*-methylcoumestrol/9-methoxycoumestrol **2e**[8] and coumestrol **2c**.[6,8a-c,14a,23a,26a-b,31a,33a-c,34,49] Several syntheses of these coumestans have been reported but an efficient method without any protection-deprotection strategy is still in high demand. On subjecting the necessary starting materials to the above reaction condition it was endearing to see the formation of both coumestans **2e** and **2c** in 59 and 55 % yields respectively thus eliminating the need of protection-deprotection steps as reported in literature methods. As most of the naturally

occurring coumestans contain hydroxyl and/or methoxy group/s, our methodology provides a broad scope for synthesis of more natural members of coumestan family.

Spectral data of all compounds

3-(2-Hydroxyphenyl)-2*H*-chromen-2-one (52a)



52a

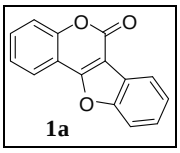
yield (0.869 g, 98 %); colorless solid; m.p. 212-214 °C; lit.[176] 212-213 °C.

IR (KBr): $\tilde{\nu}$ = 3340 (OH), 3062, 1697 (C=O), 1604, 1350, 750 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.84-6.90 (m, 2H), 7.21-7.26 (m, 2H), 7.35 (td, *J* = 7.6, 0.8 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.61 (td, *J* = 8.4, 1.6 Hz, 1H), 7.73 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.98 (s, 1H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 115.6 (CH), 115.8 (CH), 118.8 (CH), 119.2 (Cq), 122.1 (Cq), 124.6 (CH), 125.9 (Cq), 128.3 (CH), 129.8 (CH), 130.7 (CH), 131.6 (CH), 141.9 (CH), 152.9 (Cq), 154.9 (Cq), 159.5 (Cq).

6*H*-Benzofuro[3,2-*c*]chromen-6-one (1a)



1a

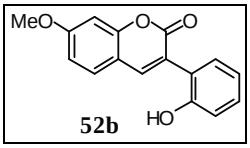
yield (0.075 g, 76 %); colorless solid; m.p. 186-188 °C; lit.[106] 187-188 °C.

IR (KBr): $\tilde{\nu}$ = 3078, 3045, 1732 (C=O), 1498, 1082, 752 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33-7.45 (m, 4H), 7.52-7.56 (m, 1H), 7.59-7.61 (m, 1H), 7.96 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.06-8.08 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 105.9 (Cq), 111.8 (CH), 112.6 (Cq), 117.5 (CH), 121.8 (CH), 121.9 (CH), 123.4 (Cq), 124.7 (CH), 125.2 (CH), 126.8 (CH), 131.9 (CH), 153.6 (Cq), 155.5 (Cq), 158.1 (Cq), 159.9 (Cq).

3-(2-Hydroxyphenyl)-7-methoxy-2*H*-chromen-2-one (52b)



52b

yield (0.950 g, 95 %); colorless solid; m.p. 160-162 °C.

Rf: 0.56 (40 % ethyl acetate/petroleum ether).

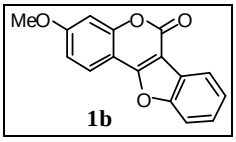
IR (KBr): $\tilde{\nu}$ = 3346 (OH), 1685 (C=O), 1622, 1508, 1280, 738 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.87 (s, 3H), 6.86 (td, *J* = 7.6, 1.2 Hz, 1H), 6.92 (dd, *J* = 8.0, 0.8 Hz, 1H), 6.97 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.03 (d, *J* = 2.4 Hz, 1H), 7.22 (ddd, *J* = 8.0, 7.6, 1.6 Hz, 1H), 7.26 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.96 (s, 1H), 9.57 (s, 1H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 55.9 (OCH_3), 100.3 (CH), 112.3 (CH), 112.8 (Cq), 115.6 (CH), 118.7 (CH), 122.2 (Cq), 122.4 (Cq), 129.3 (CH), 129.4 (CH), 130.8 (CH), 142.1 (CH), 154.8 (Cq), 155.0 (Cq), 159.6 (Cq), 162.1 (Cq).

HRMS (ESI): for $C_{16}H_{12}O_4Na$: m/z $[M + Na]^+$, calcd: 291.0633, found: 291.0632.

3-Methoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one (1b)



1b

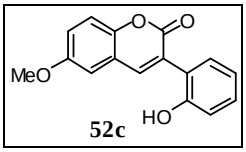
yield (0.065 g, 66 %); colorless solid; m.p. 196-198 °C; lit.[180] 195-197 °C.

IR (KBr): $\tilde{\nu}$ = 2985, 1735 (C=O), 1627, 1274, 754 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.85 (s, 3H), 6.91-6.93 (m, 2H), 7.35-7.39 (m, 2H), 7.55-7.59 (m, 1H), 7.86 (d, *J* = 9.2 Hz, 1H), 8.01-8.05 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.8 (OCH_3), 101.4 (CH), 103.2 (Cq), 105.7 (Cq), 111.5 (CH), 112.9 (CH), 121.4 (CH), 122.8 (CH), 123.6 (Cq), 125.0 (CH), 126.1 (CH), 155.2 (Cq), 155.5 (Cq), 158.2 (Cq), 160.5 (Cq), 162.9 (Cq).

3-(2-Hydroxyphenyl)-6-methoxy-2*H*-chromen-2-one (52c)



52c

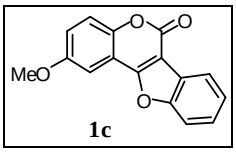
yield (0.960 g, 96 %); colorless solid; m.p. 144-146 °C; lit.[117] 144-145 °C.

IR (KBr): $\tilde{\nu}$ = 3327 (OH), 1689 (C=O), 1577, 1487, 1031, 750 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.82 (s, 3H), 6.86 (t, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 7.19-7.28 (m, 3H), 7.31 (d, *J* = 2.8 Hz, 1H) 7.38 (d, *J* = 8.8 Hz, 1H), 7.98 (s, 1H), 9.62 (br s, 1H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 55.7 (OCH_3), 110.5 (CH), 115.7 (CH), 116.9 (CH), 118.7 (CH), 118.9 (CH), 119.7 (Cq), 122.2 (Cq), 126.2 (Cq), 129.7 (CH), 130.8 (CH), 141.7 (CH), 147.4 (Cq), 155.0 (Cq), 155.6 (Cq), 159.5 (Cq).

2-Methoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one (1c)



1c

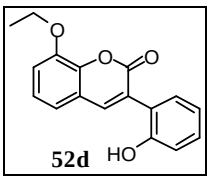
yield (0.071 g, 72 %); colorless solid; m.p. 156-158 °C; lit.[111a] 155-157 °C.

IR (KBr): $\tilde{\nu}$ = 3089, 2941, 1735 (C=O), 1566, 1074, 777 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.83 (s, 3H), 7.03 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.25-7.29 (m, 2H), 7.32-7.39 (m, 2H), 7.54 (dd, *J* = 6.8, 2.0 Hz, 1H), 8.00-8.02 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.9 (OCH_3), 103.2 (CH), 105.9 (Cq), 111.6 (CH), 112.7 (Cq), 118.6 (CH), 120.2 (CH), 121.8 (CH), 123.4 (Cq), 125.2 (CH), 126.7 (CH), 148.1 (Cq), 155.4 (Cq), 156.3 (Cq), 158.2 (Cq), 159.8 (Cq).

8-Ethoxy-3-(2-hydroxyphenyl)-2*H*-chromen-2-one (52d)



52d

yield (0.988 g, 94 %); colorless solid; m.p. 170-172 °C.

Rf: 0.48 (40 % ethyl acetate/petroleum ether).

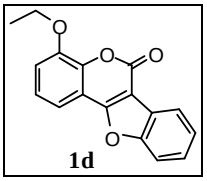
IR (KBr): $\tilde{\nu}$ = 3300 (OH), 1695 (C=O), 1469, 1278, 1111, 779 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.42 (t, *J* = 7.2 Hz, 3H), 4.19 (q, *J* = 14.0, 7.2 Hz, 2H), 6.87 (td, *J* = 7.6, 1.2 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 7.21-7.28 (m, 5H), 8.01 (s, 1H) 9.60 (s, 1H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 14.6 (CH_3), 64.3 (OCH_2), 114.6 (CH), 115.6 (CH), 118.7 (CH), 119.5 (CH), 119.9 (Cq), 122.1 (Cq), 124.4 (CH), 126.0 (Cq), 129.7 (CH), 130.7 (CH), 142.1 (CH), 142.4 (Cq), 145.5 (Cq), 155.0 (Cq), 159.1 (Cq).

HRMS (ESI): for $C_{17}H_{14}O_4Na$: m/z $[M + Na]^+$, calcd: 305.0790, found: 305.0790.

4-Ethoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one (1d)



1d

yield (0.069 g, 70 %); colorless solid; m.p. 172-174 °C.

Rf: 0.52 (30 % ethyl acetate/petroleum ether).

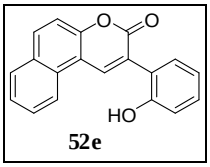
IR (KBr): $\tilde{\nu}$ = 3084, 2972, 1722 (C=O), 1566, 1284, 1058, 746 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.48 (t, *J* = 7.2 Hz, 3H), 4.17 (q, *J* = 14.0, 6.8 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.36-7.43 (m, 2H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.59 (dd, *J* = 6.8, 2.4 Hz, 1H), 8.08-8.10 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.8 (CH_3), 65.1 (CH_2), 105.9 (Cq), 111.7 (CH), 113.1 (CH), 113.4 (Cq), 114.9 (CH), 121.9 (CH), 123.5 (Cq), 124.7 (CH), 125.2 (CH), 126.7 (CH), 143.6 (Cq), 147.1 (Cq), 155.5 (Cq), 157.7 (Cq), 160.2 (Cq).

HRMS (ESI): for $C_{17}H_{12}O_4H$: m/z $[M + H]^+$, calcd: 281.0814, found: 281.0814.

2-(2-Hydroxyphenyl)-3*H*-benzo[*f*]chromen-3-one (52e)



52e

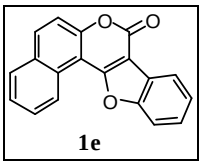
yield (0.990 g, 92 %); colorless solid; m.p. 216-218 °C; lit.[181] 216-217 °C.

IR (KBr): $\tilde{\nu}$ = 3282 (OH), 1707 (C=O), 1454, 1355, 808, 734 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.91 (td, *J* = 7.6, 1.2 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 7.25-7.29 (m, 1H), 7.38 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.61-7.64 (m, 2H), 7.71 (t, *J* = 7.2 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 8.20 (d, *J* = 8.8 Hz, 1H), 8.61 (d, *J* = 8.8 Hz, 1H), 8.86 (s, 1H), 9.65 (br s, 1H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 113.2 (Cq), 115.7 (CH), 116.5 (CH), 118.7 (CH), 122.5 (CH), 122.6 (Cq), 125.5 (Cq), 125.9 (CH), 128.2 (CH), 128.8 (CH), 128.8 (Cq), 129.7 (CH), 129.9 (Cq), 131.1 (CH), 132.6 (CH), 138.0 (CH), 152.6 (Cq), 155.2 (Cq), 159.3 (Cq).

8*H*-Benzo[*f*]benzofuro[3,2-*c*]chromen-8-one (1e)



1e

yield (0.079 g, 80 %); colorless solid; m.p. 210-212 °C.

Rf: 0.5 (20 % ethyl acetate/petroleum ether).

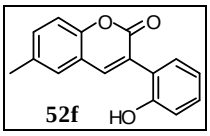
IR (KBr): $\tilde{\nu}$ = 3066, 1741 (C=O), 1560, 1008, 746 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43-7.50 (m, 2H), 7.56-7.60 (m, 2H), 7.73-7.78 (m, 2H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 8.8 Hz, 1H), 8.15-8.18 (m, 1H), 9.21 (d, *J* = 7.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 105.9 (Cq), 106.8 (Cq), 111.6 (CH), 117.2 (CH), 121.7 (CH), 122.7 (Cq), 125.3 (2 X CH), 126.3 (CH), 126.7 (CH), 127.2 (Cq), 128.7 (2 X CH), 130.2 (Cq), 132.9 (CH), 153.7 (Cq), 155.3 (Cq), 157.9 (Cq), 161.1 (Cq).

HRMS (ESI): for $C_{19}H_{10}O_3H$: m/z $[M + H]^+$, calcd: 287.0708, found: 287.0708.

3-(2-Hydroxyphenyl)-6-methyl-2*H*-chromen-2-one (52f)



52f

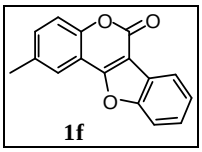
yield (0.845 g, 90 %); colorless solid; m.p. 166-168 °C; lit.[182] 167-168 °C.

IR (KBr): $\tilde{\nu}$ = 3398 (OH), 3068, 1710 (C=O), 1452, 1228, 742 cm^{-1}.

^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ 2.38 (s, 3H), 6.86 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 7.21-7.28 (m, 2H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.53 (s, 1H), 7.96 (s, 1H), 9.61 (s, 1H).

^{13}C NMR (DMSO-*d*$_6$, 100 MHz): δ 20.2 (CH_3), 115.6 (2 X CH), 118.7 (CH), 119.0 (Cq), 122.3 (Cq), 125.8 (Cq), 127.9 (CH), 129.6 (CH), 130.8 (CH), 132.3 (CH), 133.6 (Cq), 141.8 (CH), 151.2 (Cq), 155.0 (Cq), 159.5 (Cq).

2-Methyl-6*H*-benzofuro[3,2-*c*]chromen-6-one (1f)



1f

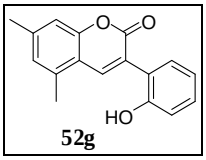
yield (0.064 g, 65 %); colorless solid; m.p. 156-158 °C; lit.[111a] 157-158 °C.

IR (KBr): $\tilde{\nu}$ = 2924, 1730 (C=O), 1570, 1444, 748 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.52 (s, 3H), 7.44 (s, 2H), 7.47-7.53 (m, 2H), 7.69 (dd, *J* = 6.8, 3.2 Hz, 1H), 7.86 (s, 1H), 8.16-8.18 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.9 (CH_3), 105.7 (Cq), 111.7 (CH), 112.2 (Cq), 117.2 (CH), 121.5 (CH), 121.8 (CH), 123.5 (Cq), 125.1 (CH), 126.6 (CH), 133.0 (CH), 134.6 (Cq), 151.8 (Cq), 155.4 (Cq), 158.3 (Cq), 159.9 (Cq).

3-(2-Hydroxyphenyl)-5,7-dimethyl-2*H*-chromen-2-one (52g)



52g

yield (0.850 g, 86 %); colorless solid; m.p. 166-168 °C.

Rf: 0.63 (40 % ethyl acetate/petroleum ether).

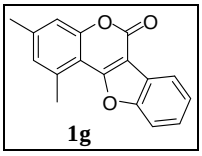
IR (KBr): $\tilde{\nu}$ = 3348 (OH), 3016, 1728 (C=O), 1448, 1232, 846 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.36 (s, 3H), 2.45 (s, 3H), 6.84-6.89 (m, 2H), 7.02 (s, 1H), 7.06 (s, 1H), 7.22 (td, *J* = 7.6, 1.6 Hz, 1H), 7.27 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.99 (s, 1H), 9.70 (br s, 1H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 17.8 (CH_3), 21.1 (CH_3), 113.9 (CH), 115.4 (Cq), 115.5 (CH), 118.8 (CH), 122.6 (Cq), 124.1 (Cq), 126.8 (CH), 129.6 (CH), 130.9 (CH), 136.1 (Cq), 138.9 (CH), 141.9 (Cq), 153.6 (Cq), 154.9 (Cq), 159.5 (Cq).

HRMS (ESI): for $C_{17}H_{14}O_3Na$: m/z $[M + Na]^+$, calcd: 289.0841, found: 289.0841.

1,3-Dimethyl-6*H*-benzofuro[3,2-*c*]chromen-6-one (1g)



1g

yield (0.066 g, 67 %); colorless solid; m.p. 252-254 °C.

Rf: 0.59 (20 % ethyl acetate/petroleum ether).

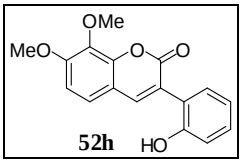
IR (KBr): $\tilde{\nu}$ = 2924, 1737 (C=O), 1606, 1446, 1083, 783 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.42 (s, 3H), 2.86 (s, 3H), 6.98 (s, 1H), 7.12 (s, 1H), 7.42-7.47 (m, 2H), 7.62-7.66 (m, 1H), 8.11-8.15 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.2 (CH_3), 21.7 (CH_3), 105.0 (Cq), 109.5 (Cq), 111.6 (CH), 115.4 (CH), 121.7 (CH), 123.1 (Cq), 125.1 (CH), 126.2 (CH), 128.0 (CH), 134.9 (Cq), 142.5 (Cq), 154.6 (Cq), 155.3 (Cq), 158.4 (Cq), 161.4 (Cq).

HRMS (ESI): for $C_{17}H_{12}O_3H$ $[M + H]^+$, calcd: 265.0865, found: 265.0865.

3-(2-Hydroxyphenyl)-7,8-dimethoxy-2*H*-chromen-2-one (52h)



52h

yield (0.890 g, 80 %); colorless solid; m.p. 162-164 °C.

Rf: 0.42 (50 % ethyl acetate/petroleum ether).

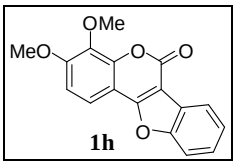
IR (KBr): $\tilde{\nu}$ = 3286 (OH), 1689 (C=O), 1604, 1284, 1107, 781 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.87 (s, 3H), 3.93 (s, 3H), 6.85 (td, *J* = 7.6, 1.2 Hz, 1H), 6.91 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 1H), 7.19-7.27 (m, 2H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.95 (s, 1H), 9.56 (s, 1H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 56.3 (OCH_3), 60.8 (OCH_3), 109.2 (CH), 113.9 (Cq), 115.6 (CH), 118.7 (CH), 122.3 (Cq), 122.6 (Cq), 123.5 (CH), 129.5 (CH), 130.8 (CH), 134.9 (Cq), 142.3 (CH), 146.8 (Cq), 154.8 (Cq), 155.1 (Cq), 159.2 (Cq).

HRMS (ESI): for $C_{17}H_{14}O_5Na$: m/z $[M + Na]^+$, calcd: 321.0739, found: 321.0739.

3,4-Dimethoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one (1h)



1h

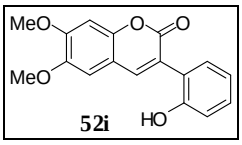
yield (0.079 g, 80 %); colorless solid; m.p. 188-190 °C; lit.[106] 189-190 °C.

IR (KBr): $\tilde{\nu}$ = 2947, 1743 (C=O), 1292, 1087, 1031, 748 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.94 (s, 3H), 3.99 (s, 3H), 6.96 (d, *J* = 9.2 Hz, 1H), 7.37-7.39 (m, 2H), 7.56-7.58 (m, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 8.05-8.07 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 56.5 (OCH_3), 61.6 (OCH_3), 103.6 (Cq), 107.2 (Cq), 109.0 (CH), 111.5 (CH), 116.8 (CH), 121.6 (CH), 123.6 (Cq), 125.1 (CH), 126.3 (CH), 136.9 (Cq), 147.8 (Cq), 155.3 (Cq), 155.9 (Cq), 157.8 (Cq), 160.5 (Cq).

3-(2-Hydroxyphenyl)-6,7-dimethoxy-2*H*-chromen-2-one (52i)



52i

yield (0.910 g, 82 %); colorless solid; m.p. 164-166 °C.

Rf: 0.5 (50 % ethyl acetate/petroleum ether).

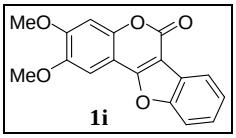
IR (KBr): $\tilde{\nu}$ = 3523 (OH), 3078, 1703 (C=O), 1571, 1292, 758 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.78 (s, 3H), 3.85 (s, 3H), 6.82-6.89 (m, 2H), 7.05 (s, 1H), 7.18-7.23 (m, 2H), 7.24 (s, 1H), 7.87 (s, 1H), 9.75 (br s, 1H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 55.8 (OCH_3), 56.1 (OCH_3), 99.5 (CH), 108.7 (CH), 111.6 (Cq), 115.5 (CH), 118.8 (CH), 122.3 (Cq), 122.4 (Cq), 129.4 (CH), 130.8 (CH), 142.2 (CH), 145.8 (Cq), 148.8 (Cq), 152.1 (Cq), 154.9 (Cq), 160.1 (Cq).

HRMS (ESI): for $C_{17}H_{14}O_5Na$: m/z $[M + Na]^+$, calcd: 321.0739, found: 321.0739.

2,3-Dimethoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one (1i)



1i

yield (0.059 g, 60 %); colorless solid; m.p. 256-258 °C.

Rf: 0.55 (40 % ethyl acetate/petroleum ether).

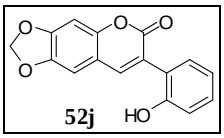
IR (KBr): $\tilde{\nu}$ = 2941, 1730 (C=O), 1517, 1273, 775 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.93 (s, 3H), 3.97 (s, 3H), 6.96 (s, 1H), 7.32 (s, 1H), 7.37-7.41 (m, 2H), 7.56-7.59 (m, 1H), 8.04-8.06 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 56.5 (2 X OCH_3), 100.7 (CH), 101.9 (CH), 103.7 (Cq), 104.7 (Cq), 111.5 (CH), 121.6 (CH), 123.7 (Cq), 125.1 (CH), 126.2 (CH), 146.9 (Cq), 149.8 (Cq), 153.1 (Cq), 155.3 (Cq), 158.5 (Cq), 160.7 (Cq).

HRMS (ESI): for $C_{17}H_{12}O_5H$: m/z $[M + H]^+$, calcd: 297.0763, found: 297.0763.

7-(2-Hydroxyphenyl)-6*H*-[1,3]dioxolo[4,5-*g*]chromen-6-one (52j)



52j

yield (0.735 g, 70 %); colorless solid; m.p. 242-244 °C.

Rf: 0.48 (40 % ethyl acetate/petroleum ether).

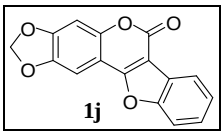
IR (KBr): $\tilde{\nu}$ = 3388 (OH), 1683 (C=O), 1492, 1278, 734 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.18 (s, 2H), 6.84 (td, *J* = 7.6, 1.2 Hz, 1H), 6.89 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.16 (s, 1H), 7.19-7.26 (m, 3H), 7.91 (s, 1H), 9.56 (s, 1H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 97.6 (CH), 102.4 (CH_2), 105.3 (CH), 112.9 (Cq), 115.6 (CH), 118.6 (CH), 122.3 (Cq), 122.4 (Cq), 129.4 (CH), 130.8 (CH), 142.3 (CH), 144.4 (Cq), 150.0 (Cq), 150.5 (Cq), 154.9 (Cq), 159.6 (Cq).

HRMS (ESI): for $C_{16}H_{10}O_5Na$: m/z $[M + Na]^+$, calcd: 305.0426, found: 305.0425.

6*H*-Benzofuro[3,2-*c*][1,3]dioxolo[4,5-*g*]chromen-6-one (1j)



1j

yield (0.069 g, 70 %); colorless solid; m.p. 272-274 °C.

Rf: 0.42 (20 % ethyl acetate/petroleum ether).

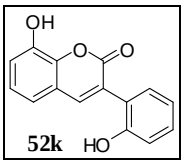
IR (KBr): $\tilde{\nu}$ = 2924, 1751 (C=O), 1458, 1261, 773 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.06 (s, 2H), 6.92 (s, 1H), 7.29 (s, 1H), 7.37-7.39 (m, 2H), 7.55-7.57 (m, 1H), 8.02-8.04 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 98.1 (CH), 98.4 (CH), 101.5 (CH_2), 102.5 (Cq), 104.9 (Cq), 110.5 (CH), 120.6 (CH), 122.5 (Cq), 124.1 (CH), 125.3 (CH), 144.3 (Cq), 149.9 (Cq), 150.6 (Cq), 154.2 (Cq), 157.3 (Cq), 159.7 (Cq).

HRMS (ESI): for $C_{16}H_8O_5H$: m/z $[M + H]^+$, calcd: 281.0450, found: 281.0450.

8-Hydroxy-3-(2-hydroxyphenyl)-2*H*-chromen-2-one (52k)



yield (0.715 g, 75 %); colorless solid; m.p. 210-212 °C.

Rf: 0.48 (50 % ethyl acetate/petroleum ether).

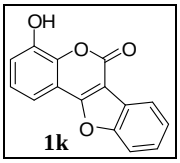
IR (KBr): $\tilde{\nu}$ = 3452 (OH), 3305 (OH), 3047, 1674 (C=O), 1604, 1483, 1184, 758 cm^{-1}.

^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ 6.87 (td, *J* = 7.6, 1.2 Hz, 1H), 6.92 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.08-7.12 (m, 1H), 7.14-7.19 (m, 2H), 7.24 (ddd, *J* = 8.0, 7.6, 1.6 Hz, 1H), 7.28 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.97 (s, 1H), 9.62 (br s, 1H), 10.23 (br s, 1H).

^{13}C NMR (DMSO-*d*$_6$, 100 MHz): δ 115.6 (CH), 117.7 (CH), 118.3 (CH), 118.7 (CH), 120.2 (Cq), 122.3 (Cq), 124.4 (CH), 125.8 (Cq), 129.6 (CH), 130.8 (CH), 141.7 (Cq), 142.3 (CH), 144.3 (Cq), 155.0 (Cq), 159.3 (Cq).

HRMS (ESI): for $C_{15}H_{10}O_4Na$: m/z $[M + Na]^+$, calcd: 277.0477, found: 277.0477.

4-Hydroxy-6*H*-benzofuro[3,2-*c*]chromen-6-one (1k)



yield (0.061 g, 62 %); colorless solid; m.p. 246-248 °C.

Rf: 0.55 (40 % ethyl acetate/petroleum ether).

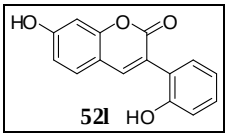
IR (KBr): $\tilde{\nu}$ = 3230 (OH), 2924, 1703 (C=O), 1566, 1184, 740 cm^{-1}.

^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ 7.22 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.51-7.60 (m, 3H), 7.91 (d, *J* = 8.0 Hz, 1H), 8.01 (dd, *J* = 7.2, 1.6 Hz, 1H), 10.53 (s, 1H).

^{13}C NMR (DMSO-*d*$_6$, 100 MHz): δ 104.9 (Cq), 111.6 (CH), 112.2 (CH), 112.9 (Cq), 118.7 (CH), 120.8 (CH), 122.9 (Cq), 125.2 (CH), 125.4 (CH), 126.9 (CH), 141.9 (Cq), 145.4 (Cq), 154.9 (Cq), 157.0 (Cq), 160.0 (Cq).

HRMS (ESI): for $C_{15}H_8O_4H$: m/z $[M + H]^+$, calcd: 253.0501, found: 253.0501.

7-Hydroxy-3-(2-hydroxyphenyl)-2*H*-chromen-2-one (52l)



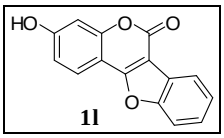
yield (0.736 g, 78 %); colorless solid; m.p. 200-202 °C; lit.[117] 201-202 °C.

IR (KBr): $\tilde{\nu}$ = 3232 (OH), 2746, 1676 (C=O), 1585, 1228, 756 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.76-6.91 (m, 4H), 7.20 (ddd, *J* = 8.0, 7.2, 1.6 Hz, 1H), 7.24 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.90 (s, 1H), 9.52 (br s, 1H), 10.56 (br s, 1H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 101.8 (CH), 111.7 (Cq), 113.1 (CH), 115.6 (CH), 118.6 (CH), 121.2 (Cq), 122.6 (Cq), 129.3 (CH), 129.6 (CH), 130.9 (CH), 142.4 (CH), 154.9 (Cq), 155.0 (Cq), 159.7 (Cq), 160.9 (Cq).

3-Hydroxy-6*H*-benzofuro[3,2-*c*]chromen-6-one (1l)



1l

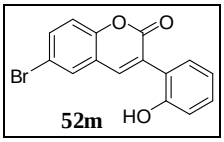
yield (0.067 g, 68 %); colorless solid; m.p. 270-272 °C; lit.[125] 270-272 °C.

IR (KBr): $\tilde{\nu}$ = 3317 (OH), 2924, 1724 (C=O), 1438, 1093, 748 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.65 (d, *J* = 1.6 Hz, 1H), 6.75 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.26-7.33 (m, 2H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.63 (d, *J* = 6.8 Hz, 1H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 101.7 (Cq), 103.0 (CH), 103.8 (Cq), 111.9 (CH), 113.9 (CH), 120.3 (CH), 123.1 (Cq), 123.3 (CH), 125.2 (CH), 126.2 (CH), 154.5 (Cq), 155.2 (Cq), 157.4 (Cq), 160.6 (Cq), 161.9 (Cq).

6-Bromo-3-(2-hydroxyphenyl)-2*H*-chromen-2-one (52m)



52m

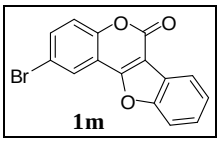
yield (1.090 g, 92 %); pale yellow solid; m.p. 234-236 °C; lit.[176] 235-236 °C.

IR (KBr): $\tilde{\nu}$ = 3350 (OH), 3049, 1691 (C=O), 1483, 1197, 754 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.88 (td, *J* = 7.6, 1.2 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 7.23-7.28 (m, 2H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.77 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.99 (s, 1H), 8.01 (d, *J* = 2.4 Hz, 1H), 9.76 (br s, 1H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 115.6 (CH), 116.0 (Cq), 118.2 (CH), 118.8 (CH), 121.1 (Cq), 121.8 (Cq), 127.1 (Cq), 129.9 (CH), 130.3 (CH), 130.7 (CH), 133.8 (CH), 140.6 (CH), 152.0 (Cq), 154.9 (Cq), 158.9 (Cq).

2-Bromo-6*H*-benzofuro[3,2-*c*]chromen-6-one (1m)



1m

yield (0.030 g, 30 %; 0.052 g, 53 %); colorless solid; m.p. 242-244 °C.

Rf: 0.64 (20 % ethyl acetate/petroleum ether).

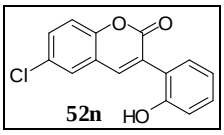
IR (KBr): $\tilde{\nu}$ = 3074, 1749 (C=O), 1550, 1446, 1103, 979, 750 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32 (d, *J* = 8.8 Hz, 1H), 7.39-7.47 (m, 2H), 7.59-7.63 (m, 2H), 8.06-8.08 (m, 1H), 8.09 (d, *J* = 2.4 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 106.6 (Cq), 111.9 (CH), 114.2 (Cq), 117.5 (Cq), 119.2 (CH), 122.0 (CH), 123.2 (Cq), 124.4 (CH), 125.5 (CH), 127.3 (CH), 134.7 (CH), 152.4 (Cq), 155.7 (Cq), 157.4 (Cq), 158.5 (Cq).

HRMS (ESI): for $C_{15}H_7BrO_3Na$: m/z $[M + Na]^+$, calcd: 336.9476, found: 336.9477.

6-Chloro-3-(2-hydroxyphenyl)-2*H*-chromen-2-one (52n)



52n

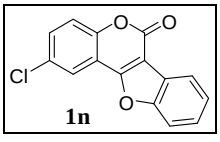
yield (0.880 g, 86 %); pale brown solid; m.p. 230-232 °C; lit.[176] 230-231 °C.

IR (KBr): $\tilde{\nu}$ = 3344 (OH), 3061, 1689 (C=O), 1483, 1199, 754 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.87 (td, *J* = 7.6, 1.2 Hz, 1H), 6.92 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.22-7.28 (m, 2H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.66 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.89 (d, *J* = 2.4 Hz, 1H), 8.01 (s, 1H), 9.67 (s, 1H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 115.7 (CH), 117.9 (CH), 118.7 (CH), 120.7 (Cq), 121.8 (Cq), 127.1 (Cq), 127.3 (CH), 128.2 (Cq), 129.9 (CH), 130.7 (CH), 130.9 (CH), 140.6 (CH), 151.7 (Cq), 155.0 (Cq), 158.9 (Cq).

2-Chloro-6*H*-benzofuro[3,2-*c*]chromen-6-one (1n)



1n

yield (0.066 g, 67 %); colorless solid; m.p. 236-238 °C.

Rf: 0.5 (10 % ethyl acetate/petroleum ether).

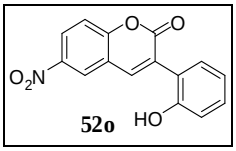
IR (KBr): $\tilde{\nu}$ = 3089, 1755 (C=O), 1556, 1111, 983, 821 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 (d, *J* = 8.8 Hz, 1H), 7.43 (td, *J* = 8.0, 2.0 Hz, 2H), 7.48 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.61 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.94 (d, *J* = 2.4 Hz, 1H), 8.06-8.08 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 106.6 (Cq), 111.9 (CH), 113.7 (Cq), 118.9 (CH), 121.4 (CH), 122.0 (CH), 123.2 (Cq), 125.5 (CH), 127.3 (CH), 130.3 (Cq), 131.9 (CH), 151.9 (Cq), 155.7 (Cq), 157.5 (Cq), 158.7 (Cq).

HRMS (ESI): for $C_{15}H_7ClO_3H$: m/z $[M + H]^+$, calcd: 271.0162, found: 271.0193.

3-(2-Hydroxyphenyl)-6-nitro-2*H*-chromen-2-one (52o)



52o

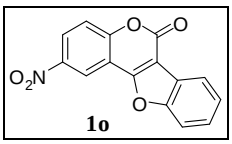
yield (0.999 g, 95 %); colorless solid; m.p. 236-238 °C; lit.[176] 236-237 °C.

IR (KBr): $\tilde{\nu}$ = 3417 (OH), 3078, 1724 (C=O), 1537, 1348, 761 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.87-6.92 (m, 2H), 7.24-7.29 (m, 2H), 7.64 (d, *J* = 9.2 Hz, 1H), 8.17 (s, 1H), 8.41 (dd, *J* = 9.2, 2.8 Hz, 1H), 8.72 (d, *J* = 2.8 Hz, 1H), 9.87 (s, 1H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 115.6 (CH), 117.4 (CH), 118.9 (CH), 119.5 (Cq), 121.4 (Cq), 124.1 (CH), 126.1 (CH), 127.8 (Cq), 130.2 (CH), 130.7 (CH), 140.8 (CH), 143.6 (Cq), 154.9 (Cq), 156.6 (Cq), 158.4 (Cq).

2-Nitro-6*H*-benzofuro[3,2-*c*]chromen-6-one (1o)



1o

yield (0.053 g, 54 %); colorless solid; m.p. 264-266 °C.

Rf: 0.5 (35 % ethyl acetate/petroleum ether).

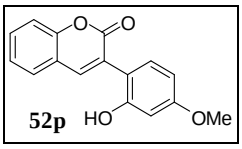
IR (KBr): $\tilde{\nu}$ = 3091, 1757 (C=O), 1533, 1348, 974, 750 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43-7.53 (m, 2H), 7.58 (d, *J* = 9.2 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 8.08 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.40 (dd, *J* = 9.2, 2.8 Hz, 1H), 8.88 (d, *J* = 2.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 107.3 (Cq), 112.1 (CH), 113.1 (Cq), 118.2 (CH), 118.7 (CH), 122.1 (CH), 122.8 (Cq), 125.8 (CH), 126.4 (CH), 127.9 (CH), 144.2 (Cq), 155.9 (Cq), 156.5 (Cq), 156.6 (Cq), 158.2 (Cq).

HRMS (ESI): for $C_{15}H_7NO_5H$: m/z $[M + H]^+$, calcd: 282.0397, found: 282.0397.

3-(2-Hydroxy-4-methoxyphenyl)-2*H*-chromen-2-one (52p)



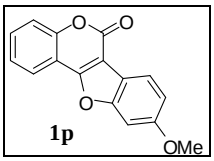
yield (0.215 g, 80 %); colorless solid; m.p. 170-172 °C; lit.[113] 171-172 °C.

IR (KBr): $\tilde{\nu}$ = 3192 (OH), 2960, 1724 (C=O), 1602, 1203, 761 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.72 (s, 3H), 6.44-6.46 (m, 2H), 7.19 (d, *J* = 8.8 Hz, 1H), 7.33 (td, *J* = 8.4, 1.2 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.58 (td, *J* = 8.4, 1.6 Hz, 1H), 7.69 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.93 (s, 1H), 9.87 (br s, 1H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 55.0 (OCH_3), 101.3 (CH), 104.5 (CH), 114.8 (Cq), 115.8 (CH), 119.3 (Cq), 124.5 (CH), 125.5 (Cq), 128.2 (CH), 131.3 (CH), 131.5 (CH), 141.4 (CH), 152.8 (Cq), 156.1 (Cq), 159.7 (Cq), 160.5 (Cq).

9-Methoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one (1p)



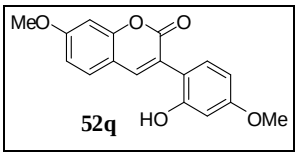
yield (0.069 g, 70 %); colorless solid; m.p. 216-218 °C; lit.[112] 216 °C.

IR (KBr): $\tilde{\nu}$ = 2993, 1743 (C=O), 1504, 1282, 750 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.94 (s, 3H), 7.09 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.21 (d, *J* = 2.0 Hz, 1H), 7.42 (td, *J* = 8.4, 1.2 Hz, 1H), 7.52 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.58-7.62 (m, 1H), 7.99-8.02 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.9 (OCH_3), 96.8 (CH), 106.1 (Cq), 112.9 (Cq), 113.6 (CH), 116.5 (Cq), 117.4 (CH), 121.5 (CH), 122.0 (CH), 124.6 (CH), 131.3 (CH), 153.2 (Cq), 156.8 (Cq), 158.3 (Cq), 159.3 (Cq), 159.7 (Cq).

3-(2-Hydroxy-4-methoxyphenyl)-7-methoxy-2*H*-chromen-2-one (52q)



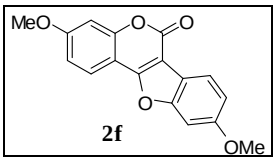
yield (0.167 g, 56 %); colorless solid; m.p. 160-162 °C; lit.[113] 160-161 °C.

IR (KBr): $\tilde{\nu}$ = 3304 (OH), 2956, 1691 (C=O), 1604, 1510, 1278, 835 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.72 (s, 3H), 3.84 (s, 3H), 6.43-6.45 (m, 2H), 6.93 (d, *J* = 8.8 Hz, 1H), 6.97 (s, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.87 (s, 1H), 9.76 (br s, 1H).

^{13}C NMR (DMSO-*d*$_6$, 100 MHz): δ 54.9 (OCH_3), 55.8 (OCH_3), 100.2 (CH), 101.3 (CH), 104.4 (CH), 112.3 (CH), 112.8 (Cq), 115.0 (Cq), 121.9 (Cq), 129.2 (CH), 131.5 (CH), 141.7 (CH), 154.6 (Cq), 156.0 (Cq), 159.9 (Cq), 160.2 (Cq), 161.9 (Cq).

3,9-Dimethoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one (2f)



2f

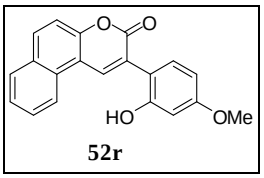
yield (0.064 g, 65 %); colorless solid; m.p. 198-200 °C; lit.[112] 199-200 °C.

IR (KBr): $\tilde{\nu}$ = 2951, 1739 (C=O), 1498, 1257, 1099, 840 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.83 (s, 3H), 3.84 (s, 3H), 6.88-6.91 (m, 2H), 6.96 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.08 (d, *J* = 2.4 Hz, 1H), 7.79 (d, *J* = 9.2 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.8 (OCH_3), 55.9 (OCH_3), 96.8 (CH), 101.4 (CH), 103.5 (Cq), 106.1 (Cq), 113.0 (CH), 113.2 (CH), 116.6 (Cq), 121.6 (CH), 122.5 (CH), 155.1 (Cq), 156.5 (Cq), 158.5 (Cq), 159.2 (Cq), 160.1 (Cq), 162.6 (Cq).

3-(2-Hydroxy-4-methoxyphenyl)-3*H*-benzo[*f*]chromen-3-one (52r)



52r

yield (0.250 g, 79 %); colorless solid; m.p. 208-210 °C.

Rf: 0.58 (50 % ethyl acetate/petroleum ether).

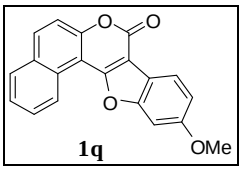
IR (KBr): $\tilde{\nu}$ = 3315 (OH), 2993, 1689 (C=O), 1257, 1105, 808 cm^{-1}.

^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ 3.74 (s, 3H), 6.49-6.52 (m, 2H), 7.29 (d, *J* = 9.2 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.61 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.68-7.72 (m, 1H), 8.03 (d, *J* = 7.2 Hz, 1H), 8.14 (d, *J* = 9.2 Hz, 1H), 8.49 (d, *J* = 8.4 Hz, 1H), 8.74 (s, 1H), 9.88 (br s, 1H).

^{13}C NMR (DMSO-*d*$_6$, 100 MHz): δ 55.1 (OCH_3), 101.3 (CH), 104.6 (CH), 113.2 (Cq), 115.2 (Cq), 116.4 (CH), 122.2 (CH), 124.9 (Cq), 125.9 (CH), 128.2 (CH), 128.6 (Cq), 128.8 (CH), 129.8 (Cq), 131.8 (CH), 132.4 (CH), 137.5 (CH), 152.3 (Cq), 156.2 (Cq), 159.7 (Cq), 160.6 (Cq).

HRMS (ESI): for $C_{20}H_{14}O_4Na$: m/z $[M + Na]^+$, calcd: 341.0790, found: 341.0790.

11-Methoxy-8*H*-benzo[*f*]benzofuro[3,2-*c*]chromen-8-one (1q)



1q

yield (0.054 g, 55 %); colorless solid; m.p. 238-240 °C.

Rf: 0.65 (35 % ethyl acetate/petroleum ether).

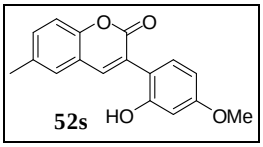
IR (KBr): $\tilde{\nu}$ = 2972, 1730 (C=O), 1504, 1273, 812 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.87 (s, 3H), 7.01-7.03 (m, 1H), 7.22 (br s, 1H), 7.49-7.55 (m, 2H), 7.69 (t, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 8.8 Hz, 1H), 7.97 (dd, *J* = 8.8, 1.2 Hz, 1H), 9.09 (d, *J* = 7.2 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.9 (OCH_3), 96.6 (CH), 106.3 (Cq), 107.4 (Cq), 113.9 (CH), 115.8 (Cq), 117.4 (CH), 122.0 (CH), 125.5 (CH), 126.3 (CH), 127.4 (Cq), 128.6 (CH), 128.8 (CH), 130.4 (Cq), 132.5 (CH), 153.2 (Cq), 156.7 (Cq), 158.2 (Cq), 159.7 (Cq), 160.7 (Cq).

HRMS (ESI): for $C_{20}H_{12}O_4Na$: m/z $[M + Na]^+$, calcd: 339.0633, found: 339.0633.

3-(2-Hydroxy-4-methoxyphenyl)-6-methyl-2*H*-chromen-2-one (52s)



52s

yield (0.220 g, 78 %); colorless solid; m.p. 180-182 °C.

Rf: 0.5 (50 % ethyl acetate/petroleum ether).

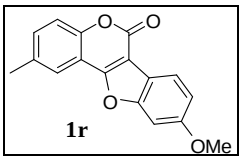
IR (KBr): $\tilde{\nu}$ = 3342 (OH), 2912, 1678 (C=O), 1502, 1153, 796 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.35 (s, 3H), 3.72 (s, 3H), 6.44-6.47 (m, 2H), 7.18 (d, *J* = 8.8 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 7.39 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.49 (d, *J* = 1.2 Hz, 1H), 7.87 (s, 1H), 9.82 (br s, 1H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 20.2 (CH_3), 55.0 (OCH_3), 101.3 (CH), 104.5 (CH), 114.9 (Cq), 115.5 (CH), 119.0 (Cq), 125.4 (Cq), 127.8 (CH), 131.5 (CH), 132.1 (CH), 133.7 (Cq), 141.4 (CH), 150.9 (Cq), 156.1 (Cq), 159.9 (Cq), 160.4 (Cq).

HRMS (ESI): for $C_{17}H_{14}O_4Na$: m/z $[M + Na]^+$, calcd: 305.0790, found: 305.0791.

9-Methoxy-2-methyl-6*H*-benzofuro[3,2-*c*]chromen-6-one (1r)



yield (0.065 g, 66 %); colorless solid; m.p. 198-200 °C.

Rf: 0.64 (40 % ethyl acetate/petroleum ether).

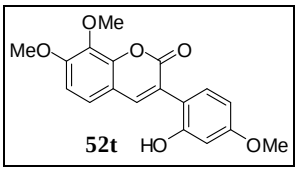
IR (KBr): $\tilde{\nu}$ = 3008, 1743 (C=O), 1508, 1273, 812 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.42 (s, 3H), 3.85 (s, 3H), 6.99 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.11 (d, *J* = 2.4 Hz, 1H), 7.31 (s, 2H), 7.70 (s, 1H), 7.92 (d, *J* = 8.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.9 (CH_3), 55.9 (OCH_3), 96.8 (CH), 105.9 (Cq), 112.5 (Cq), 113.5 (CH), 116.6 (Cq), 117.1 (CH), 121.1 (CH), 121.9 (CH), 132.4 (CH), 134.5 (Cq), 151.5 (Cq), 156.7 (Cq), 158.4 (Cq), 159.4 (Cq), 159.6 (Cq).

HRMS (ESI): for $C_{17}H_{12}O_4Na$: m/z $[M + Na]^+$, calcd: 303.0633, found: 303.0633.

3-(2-Hydroxy-4-methoxyphenyl)-7,8-dimethoxy-2*H*-chromen-2-one (52t)



yield (0.198 g, 60 %); colorless solid; m.p. 194-196 °C.

Rf: 0.45 (50 % ethyl acetate/petroleum ether).

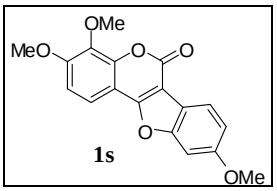
IR (KBr): $\tilde{\nu}$ = 3377 (OH), 2943, 1703 (C=O), 1606, 1284, 802 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.71 (s, 3H), 3.83 (s, 3H), 3.89 (s, 3H), 6.43-6.46 (m, 2H), 7.09 (d, *J* = 8.8 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 1H), 7.86 (s, 1H), 9.81 (br s, 1H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 55.0 (OCH_3), 56.3 (OCH_3), 60.8 (OCH_3), 101.2 (CH), 104.5 (CH), 109.2 (CH), 113.9 (Cq), 114.9 (Cq), 122.2 (Cq), 123.4 (CH), 131.5 (CH), 134.8 (Cq), 141.9 (CH), 146.6 (Cq), 154.6 (Cq), 156.0 (Cq), 159.6 (Cq), 160.3 (Cq).

HRMS (ESI): for $C_{18}H_{16}O_6Na$: m/z $[M + Na]^+$, calcd: 351.0845, found: 351.0845.

3,4,9-Trimethoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one (1s)



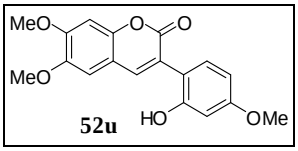
yield (0.059 g, 60 %); colorless solid; m.p. 208-210 °C; lit.[98] 209-210 °C.

IR (KBr): $\tilde{\nu}$ = 2953, 1743 (C=O), 1502, 1290, 1097, 798 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.84 (s, 3H), 3.93 (s, 3H), 3.98 (s, 3H), 6.93 (d, *J* = 8.8 Hz, 1H), 6.97 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.9 (OCH_3), 56.5 (OCH_3), 61.7 (OCH_3), 96.8 (CH), 103.8 (Cq), 107.4 (Cq), 108.9 (CH), 113.2 (CH), 116.4 (CH), 116.6 (Cq), 121.7 (CH), 136.9 (Cq), 147.4 (Cq), 155.4 (Cq), 156.5 (Cq), 157.9 (Cq), 159.3 (Cq), 159.8 (Cq).

3-(2-Hydroxy-4-methoxyphenyl)-6,7-dimethoxy-2*H*-chromen-2-one (52u)



52u

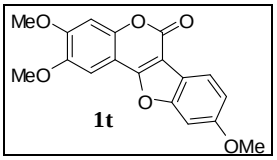
yield (0.209 g, 64 %); colorless solid; m.p. 200-202 °C; lit.[113] 200-201 °C.

IR (KBr): $\tilde{\nu}$ = 3313 (OH), 2989, 1666 (C=O), 1514, 1244, 1008, 821, cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.69 (s, 3H), 3.76 (s, 3H), 3.82 (s, 3H), 6.43-6.45 (m, 2H), 6.99 (s, 1H), 7.13 (d, *J* = 8.8 Hz, 1H), 7.18 (s, 1H), 7.80 (s, 1H), 9.88 (br s, 1H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 54.9 (OCH_3), 55.8 (OCH_3), 56.1 (OCH_3), 99.5 (CH), 101.2 (CH), 104.5 (CH), 108.6 (CH), 111.7 (Cq), 115.1 (Cq), 122.0 (Cq), 131.5 (CH), 141.9 (CH), 145.8 (Cq), 148.6 (Cq), 151.9 (Cq), 155.9 (Cq), 160.2 (Cq), 160.4 (Cq).

2,3,9-Trimethoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one (1t)



1t

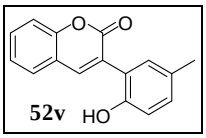
yield (0.059 g, 60 %); colorless solid; m.p. 252-254 °C; lit.[113] 253-254 °C.

IR (KBr): $\tilde{\nu}$ = 2951, 1726 (C=O), 1517, 1271, 1002, 825 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.83 (s, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 6.91 (s, 1H), 6.96 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.07 (d, *J* = 2.0 Hz, 1H), 7.23 (s, 1H), 7.87 (d, *J* = 8.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.9 (OCH_3), 56.4 (2 X OCH_3), 96.8 (CH), 100.6 (CH), 101.6 (CH), 103.8 (Cq), 104.9 (Cq), 113.1 (CH), 116.7 (Cq), 121.7 (CH), 146.8 (Cq), 149.2 (Cq), 152.6 (Cq), 156.4 (Cq), 158.6 (Cq), 159.2 (Cq), 159.9 (Cq).

3-(2-Hydroxy-5-methylphenyl)-2*H*-chromen-2-one (52v)



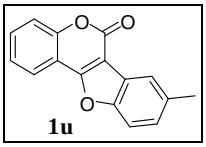
yield (0.182 g, 72 %); colorless solid; m.p. 138-140 °C; lit.[176] 138-140 °C.

IR (KBr): $\tilde{\nu}$ = 3398 (OH), 2918, 1710 (C=O), 1610, 1510, 744 cm^{-1}.

^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ 2.21 (s, 3H), 6.78 (d, *J* = 8.0 Hz, 1H), 7.01-7.05 (m, 2H), 7.35 (td, *J* = 7.6, 1.2 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.58-7.62 (m, 1H), 7.72 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.96 (s, 1H), 9.50 (br s, 1H).

^{13}C NMR (DMSO-*d*$_6$, 100 MHz): δ 19.9 (CH_3), 115.5 (CH), 115.8 (CH), 119.2 (Cq), 121.9 (Cq), 124.5 (CH), 126.1 (Cq), 127.3 (Cq), 128.3 (CH), 130.2 (CH), 130.9 (CH), 131.5 (CH), 141.8 (CH), 152.6 (Cq), 152.9 (Cq), 159.5 (Cq).

8-Methyl-6*H*-benzofuro[3,2-*c*]chromen-6-one (1u)



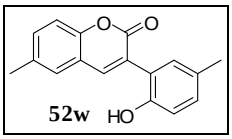
yield (0.064 g, 65 %); colorless solid; m.p. 190-192 °C; lit.[176] 189-191 °C.

IR (KBr): $\tilde{\nu}$ = 2924, 1737 (C=O), 1631, 1082, 756 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.39 (s, 3H), 7.14 (d, *J* = 8.4 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 9.2 Hz, 2H), 7.48 (t, *J* = 8.4 Hz, 1H), 7.78 (s, 1H), 7.87 (d, *J* = 7.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.3 (CH_3), 105.6 (Cq), 111.2 (CH), 112.7 (Cq), 117.4 (CH), 121.6 (CH), 121.8 (CH), 123.3 (Cq), 124.6 (CH), 127.9 (CH), 131.7 (CH), 135.1 (Cq), 153.5 (Cq), 153.9 (Cq), 158.2 (Cq), 159.9 (Cq).

3-(2-Hydroxy-5-methylphenyl)-6-methyl-2*H*-chromen-2-one (52w)



yield (0.180 g, 68 %); colorless solid; m.p. 190-192 °C.

Rf: 0.58 (40 % ethyl acetate/petroleum ether).

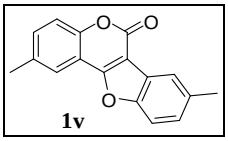
IR (KBr): $\tilde{\nu}$ = 3367 (OH), 2922, 1720 (C=O), 1581, 808 cm^{-1}.

^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ 2.23 (s, 3H), 2.38 (s, 3H), 6.79 (d, *J* = 8.0 Hz, 1H), 7.03-7.07 (m, 2H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.43 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.53 (d, *J* = 1.6 Hz, 1H), 7.93 (s, 1H), 9.44 (s, 1H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 19.9 (CH_3), 20.2 (CH_3), 115.5 (CH), 115.6 (CH), 118.9 (Cq), 121.9 (Cq), 125.9 (Cq), 127.2 (Cq), 127.9 (CH), 130.1 (CH), 130.9 (CH), 132.3 (CH), 133.7 (Cq), 141.7 (CH), 151.1 (Cq), 152.7 (Cq), 159.6 (Cq).

HRMS (ESI): for $C_{17}H_{14}O_3Na$: m/z $[M + Na]^+$, calcd: 289.0841, found: 289.0841.

2,8-Dimethyl-6*H*-benzofuro[3,2-*c*]chromen-6-one (1v)



1v

yield (0.059 g, 60 %); colorless solid; m.p. 202-204 °C.

Rf: 0.48 (10 % ethyl acetate/petroleum ether).

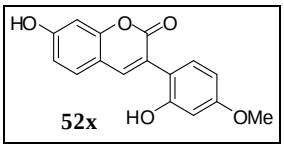
IR (KBr): $\tilde{\nu}$ = 2920, 1753 (C=O), 1571, 1074, 794 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.49 (s, 3H), 2.52 (s, 3H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.39 (s, 2H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.79 (s, 1H), 7.93 (s, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.9 (CH_3), 21.3 (CH_3), 105.6 (Cq), 111.1 (CH), 112.4 (Cq), 117.2 (CH), 121.5 (CH), 121.6 (CH), 123.5 (Cq), 127.8 (CH), 132.9 (CH), 134.5 (Cq), 135.1 (Cq), 151.8 (Cq), 153.9 (Cq), 158.5 (Cq), 160.1 (Cq).

HRMS (ESI): for $C_{17}H_{12}O_3H$: m/z $[M + H]^+$, calcd: 265.0865, found: 265.0865.

7-Hydroxy-3-(2-hydroxy-4-methoxyphenyl)-2*H*-chromen-2-one (52x)



52x

yield (0.149 g, 53 %); pale yellow solid; m.p. 248-250 °C.

Rf: 0.43 (50 % ethyl acetate/petroleum ether).

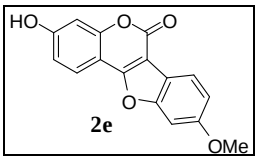
IR (KBr): $\tilde{\nu}$ = 3414 (OH), 3257 (OH), 2997, 1676 (C=O), 1610, 1153, 812 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.73 (s, 3H), 6.44-6.46 (m, 2H), 6.75 (d, *J* = 2.4 Hz, 1H), 6.79 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.85 (s, 1H), 9.67 (s, 1H), 10.65 (br s, 1H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 54.9 (OCH_3), 101.2 (CH), 101.6 (CH), 104.3 (CH), 111.8 (Cq), 112.9 (CH), 115.1 (Cq), 120.8 (Cq), 129.4 (CH), 131.5 (CH), 141.9 (CH), 154.7 (Cq), 155.9 (Cq), 160.0 (Cq), 160.1 (Cq), 160.6 (Cq).

HRMS (ESI): for $C_{16}H_{12}O_5Na$: m/z $[M + Na]^+$, calcd: 307.0582, found: 307.0582.

3-Hydroxy-9-methoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one (2e)



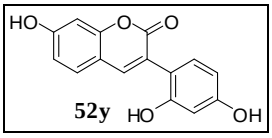
yield (0.058 g, 59 %); pale yellow solid; m.p. >300 °C; lit.[112] >300 °C.

IR (KBr): $\tilde{\nu}$ = 3267 (OH), 2920, 1708 (C=O), 1500, 1267, 1101, 840 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.86 (s, 3H), 6.92 (d, *J* = 1.6 Hz, 1H), 6.96 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.09 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.47 (d, *J* = 1.6 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 10.89 (br s, 1H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 55.8 (OCH_3), 97.2 (CH), 101.8 (Cq), 103.0 (CH), 104.0 (Cq), 113.4 (CH), 113.9 (CH), 115.8 (Cq), 120.5 (CH), 122.8 (CH), 154.7 (Cq), 155.8 (Cq), 157.6 (Cq), 158.8 (Cq), 159.9 (Cq), 161.3 (Cq).

3-(2,4-Dihydroxyphenyl)-7-hydroxy-2*H*-chromen-2-one (52y)



yield (0.132 g, 49 %); pale yellow solid; m.p. >280 °C (decomp).

Rf: 0.48 (70 % ethyl acetate/petroleum ether).

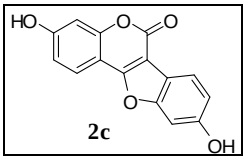
IR (KBr): $\tilde{\nu}$ = 3410 (OH), 3315 (OH), 3147 (OH), 2746, 1693 (C=O), 1598, 1463, 1224, 995 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.27 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.35 (d, *J* = 2.4 Hz, 1H), 6.74 (d, *J* = 2.4 Hz, 1H), 6.79 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.81 (s, 1H), 9.46 (s, 1H), 9.51 (s, 1H), 10.62 (br s, 1H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 101.6 (CH), 102.5 (CH), 106.2 (CH), 111.9 (Cq), 112.9 (CH), 113.6 (Cq), 121.2 (Cq), 129.4 (CH), 131.4 (CH), 141.7 (CH), 154.6 (Cq), 155.9 (Cq), 158.3 (Cq), 160.2 (Cq), 160.5 (Cq).

HRMS (ESI): for $C_{15}H_{10}O_5H$: m/z $[M + H]^+$, calcd: 271.0601, found: 271.0601.

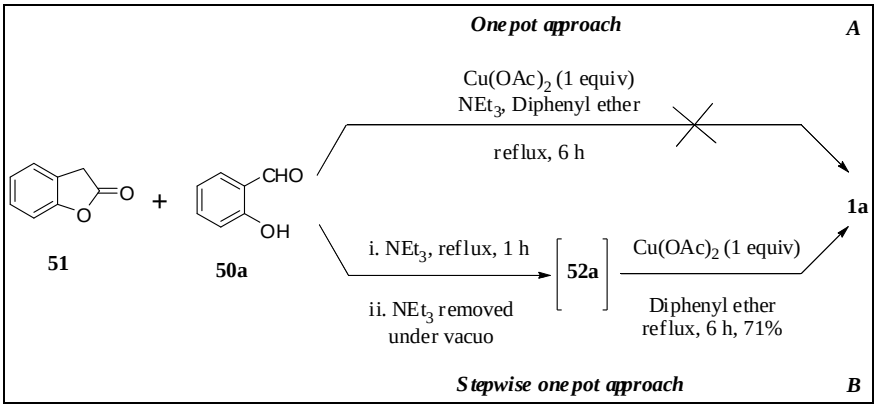
3,9-Dihydroxy-6*H*-benzofuro[3,2-*c*]chromen-6-one (2c)



yield (0.054 g, 55 %); pale yellow solid; m.p. >300 °C; lit.[183] >300 °C.

IR (KBr): $\tilde{\nu}$ = 3398 (OH), 3082, 2372, 1701 (C=O), 1629, 1300, 1091, 810 cm^{-1}.

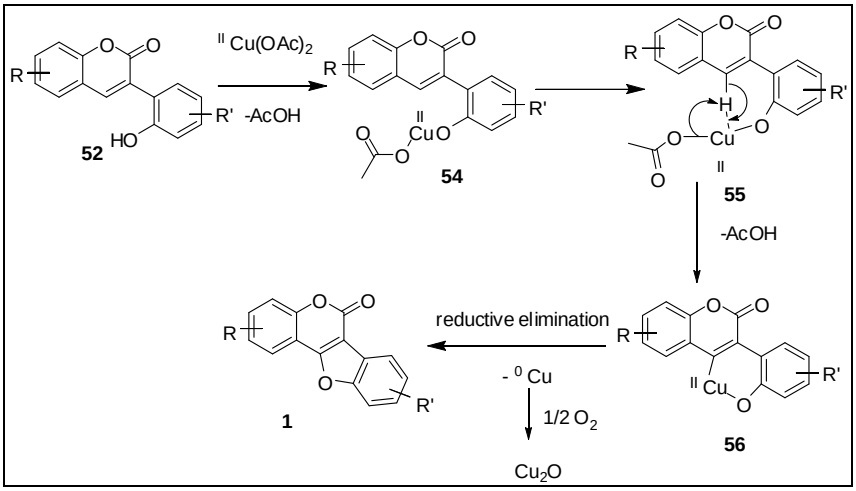
^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.92-6.98 (m, 3H), 7.19 (d, *J* = 2.0 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 10.20 (br s, 1H), 10.88 (br s, 1H).
^{13}C NMR (DMSO-d_6, 100 MHz): δ 98.7 (CH), 101.9 (Cq), 102.9 (CH), 104.1 (Cq), 113.8 (CH), 114.0 (CH), 114.5 (Cq), 120.6 (CH), 122.8 (CH), 154.6 (Cq), 155.9 (Cq), 156.9 (Cq), 157.7 (Cq), 159.5 (Cq), 161.1 (Cq).



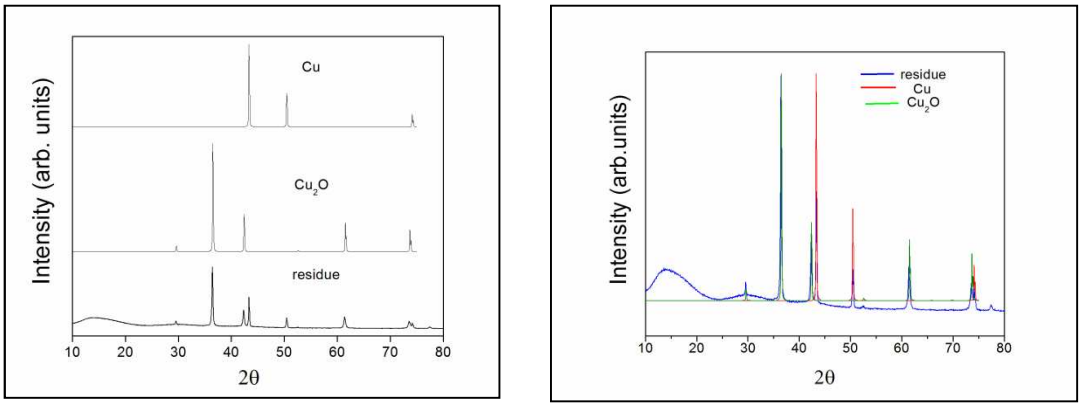
Scheme 74: Stepwise one pot synthesis of coumestan **1a**.

The protocol was then successfully tested for the preparation of **1a** from **52a** on a larger scale (2 mmol) thus demonstrating its utility. Further, a one pot procedure was attempted by mixing 2-coumaranone **51**, salicylaldehyde **50a**, $Cu(OAc)_2$ and NEt_3 in diphenyl ether as the solvent system. However, no formation of **1a** was observed (Scheme 74-*A*). Hence a stepwise one pot approach was developed wherein NEt_3 was removed under reduced pressure before addition of $Cu(OAc)_2$ giving product **1a** in good yield (Scheme 74-*B*).

Mechanistic studies were performed to check whether the mechanism is following a radical pathway. Hence the reaction was performed in presence of a radical scavenger TEMPO. It was found to show no effect on the yield of product **1a** suggesting an alternative mechanism. Based on this observation a speculative mechanism is proposed for this intramolecular C-O cyclization (Scheme 75). Cu(II) from $Cu(OAc)_2$ binds to electronegative hydroxyl oxygen atom of substrate **52** with the liberation of one molecule of acetic acid to form intermediate **54**. Intramolecular oxidative addition of copper to the C-H bond renders **56** *via* the elimination of another molecule of acetic acid from **55**. Finally the reductive elimination of **56** furnished coumestan **1** and metallic copper which was supported from recorded XRD (Figure 12) of the residue left after reaction and also from the copper mirror deposits on the walls of the reaction flask. The Cu_2O visible from XRD could be due to the aerobic oxidation of Cu at high reaction temperature.



Scheme 75: Proposed mechanism for the formation of coumestans using $Cu(OAc)_2$.

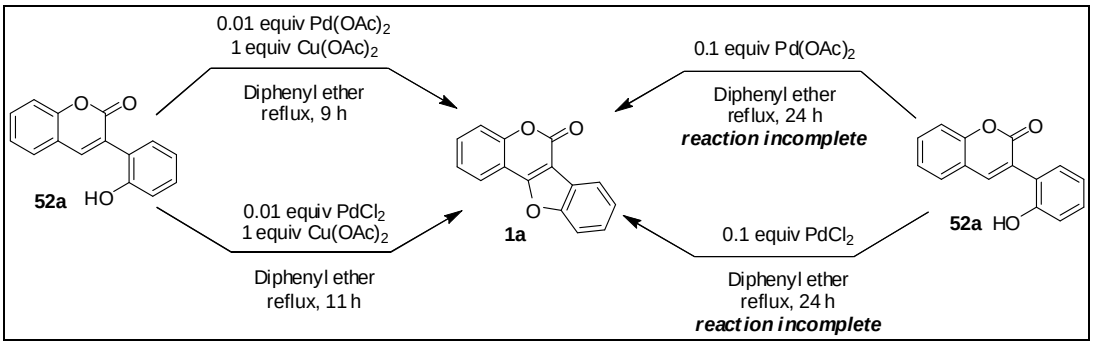


(A) (B)

Figure 12: (A) XRD of Cu, Cu_2O and the residue left after reaction (B) Overlay.

It is known that the presence of other metal impurity or "homeopathic" metal can also be responsible for such results.[184] But, it was essential to confirm that presence of Pd impurity was not responsible for this $Cu(OAc)_2$ mediated cylization. Hence $Cu(OAc)_2$ sample was tested for the presence of Pd by ICP-MS analysis which showed the presence of 1817.97 ppb of Pd. So accordingly to gain some clarity in whether Pd has any role in this oxidative cyclization we conducted two experiments in presence of 1 equiv of $Cu(OAc)_2$ along with 0.01 equiv of $Pd(OAc)_2$ or $PdCl_2$ (Scheme 76). It was observed that on addition of external Pd source there was no much difference visible in terms of reaction time or product yield. Also the incomplete conversion of starting resulted in partial product formation when 0.1 equiv of $Pd(OAc)_2$ or $PdCl_2$ was exclusively employed. As discussed previously, Gong *et al.*[117] had employed 1 equiv of $PdCl_2$ for coumestan synthesis over longer duration of time (24 h) which support our observation. Also, a reaction using catalytic $PdCl_2$ under Wacker condition in presence of $CuCl_2$ in DMF:DMA (1:1) solvent system at 150 °C was attempted giving trace amount of product. All these results suggests that Cu is playing the major role in the present

oxidative cyclization reaction and not the Pd impurity present in copper. However the probable role of Pd present in ppb level in contact with copper and their synergestic effect cannot be ruled out completely.



Scheme 76: Reactions in Pd source in presence/absence of $Cu(OAc)_2$.

4.5: Conclusion

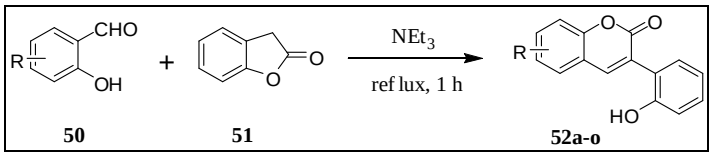
We developed an efficient methodology for the synthesis of coumestans by implementing economical $Cu(OAc)_2$ as the sole reagent in absence of any additional reagent/additive in diphenyl ether solvent *via* C-H activation.

Several advantages are associated such as simple reaction procedure, large substrate scope, effortless product isolation & good yields which makes this method superior over reported methods.

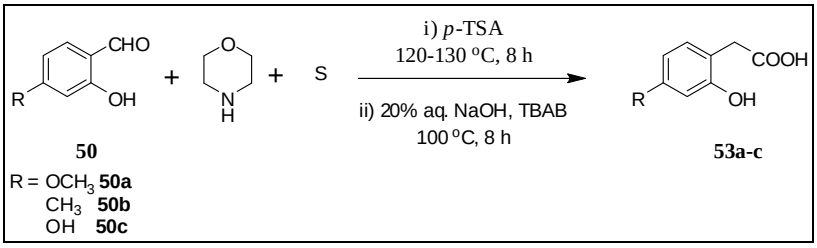
Method was applied successfully for the synthesis of hydroxy substituted naturally occurring coumestans *viz.* coumestrol and 4'-*O*-methylcoumestrol without protection/deprotection strategies making this method attractive.

Also one pot synthesis and possible use of catalytic amount of $Cu(OAc)_2$ is demonstrated.

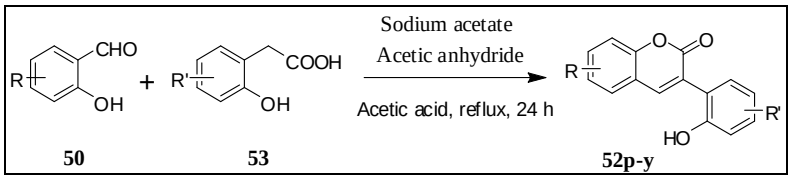
4.6: Experimental



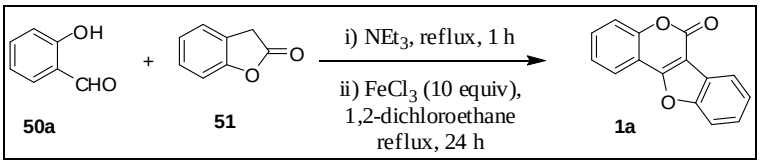
4.6.1: A general procedure for the synthesis of substrates 52a-o:[176] Substituted salicylaldehyde derivative **50** (3.7 mmol) and 2-coumaranone **51** (0.5 g, 3.7 mmol) were mixed together in a round bottom flask. To it triethylamine (15 mL) was added and refluxed for 1 h. After 1 h the solvent was removed under vacuum and the crude solid was recrystallized from ethanol to afford pure product 3-(2-hydroxyphenyl)-2*H*-chromen-2-one **52a-o**.



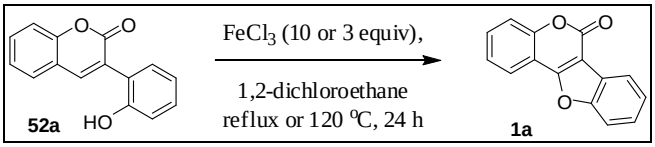
4.6.2: A general procedure for the synthesis of substituted 2-hydroxyphenylacetic acid 53a-c:[185] Substituted salicylaldehyde derivative **50** (29 mmol) along with morpholine (87 mmol), sulphur (58 mmol) and *p*-toluenesulphonic acid (1 mmol) were refluxed with stirring at 120-130 °C for 8 h. After reaction completion the mixture was cooled to room temperature. Hydrolysis was carried out by heating in presence of 20 % aq. NaOH (41 mL) and tetrabutylammonium bromide (0.46 mmol) at 100 °C for 8 h. The reaction mixture was cooled and filtered. The filtrate was acidified with HCl to pH 2. It was then extracted with ethyl acetate (3 times) and combined organic layer was washed with water and dried over sodium sulphate. The crude product obtained was purified by column chromatography using petroleum ether-ethyl acetate as eluents.



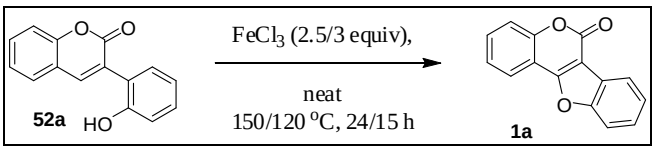
4.6.3: A general procedure for the synthesis of substrates 52p-y:[177] Substituted salicylaldehyde derivative **50** (1 mmol), substituted 2-hydroxyphenylacetic acid **53** (1 mmol), sodium acetate (5.0 mmol) and acetic anhydride (2.4 mmol) were mixed together in a round bottom flask. To it acetic acid (4 mL) was added and refluxed for 24 h. After 24 h the solvent was removed under vacuum and water was added to it. The crude solid obtained was filtered and then loaded on column (eluent: petroleum ether-ethyl acetate) to afford pure product 3-(2-hydroxyphenyl)-2*H*-chromen-2-one **52p-y**.



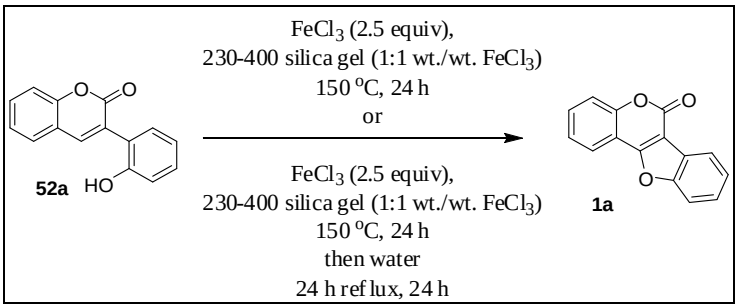
4.6.4: A procedure for the attempted one pot synthesis of coumestan 1a: 2-coumaranone **51** (0.1 g, 0.75 mmol) and 2'-hydroxybenzaldehyde **50a** (0.091 g, 0.75 mmol) were mixed together and refluxed in 10 mL of triethylamine in a 50 mL round bottom flask. After 1 h refluxing, the solvent was removed under reduced pressure and to the same vessel, anhyd. $FeCl_3$ (1.209 g, 7.5 mmol) was added along with 5 mL of 1,2-dichloroethane solvent. The reaction mixture was then refluxed for 24 h and showed trace amount of product **1a** on TLC.



4.6.5: A procedure for the synthesis of coumestan 1a using $FeCl_3$ in 1,2-dichloroethane solvent: Anhyd. $FeCl_3$ (0.68 g, 4.2 mmol) or (0.21 g, 1.26 mmol) was added to 3-(2-hydroxyphenyl)-2*H*-chromen-2-one **52a** (0.1 g, 0.42 mmol) in a 25 mL round bottom flask. To it 10 mL of 1,2-dichloroethane solvent was added. The resulting mixtures were then heated to reflux/120 °C respectively. After 24 h, the solvent was removed under reduced pressure and was loaded on column to afford product 6*H*-benzofuro[3,2-*c*]chromen-6-one **1a** as colorless solid (0.020 g, 20 %) or (0.011 g, 11 %) respectively with petroleum ether-ethyl acetate (8.5:1.5) as an eluent.

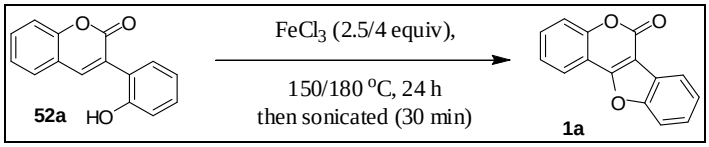


4.6.6: A procedure for the synthesis of coumestan 1a using $FeCl_3$ under neat condition in absence of 230-400 mesh silica gel: Anhyd. $FeCl_3$ (0.17 g, 1.05 mmol) or (0.21 g, 1.26 mmol) was added to 3-(2-hydroxyphenyl)-2*H*-chromen-2-one **52a** (0.1 g, 0.42 mmol) in a 25 mL round bottom flask. The resulting mixtures were then heated in absence of solvent (neat) at 150/120 °C for 24/15 h respectively. After the specified time, the reaction mixture was loaded on column to afford product **1a** (0.012 g, 12 %) or (0.011 g, 11 %) respectively with petroleum ether-ethyl acetate (8.5:1.5) as an eluent.

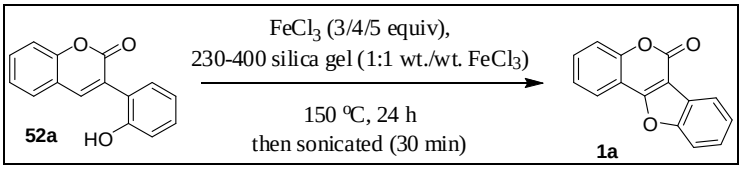


4.6.7: A procedure for the synthesis of coumestan 1a using $FeCl_3$ under neat condition in presence of 230-400 mesh silica gel: Anhyd. $FeCl_3$ (0.17 g, 1.05 mmol) was added to 3-(2-hydroxyphenyl)-2*H*-chromen-2-one **52a** (0.1 g, 0.42 mmol) and 230-400 silica gel (0.17 g) in a 25 mL round bottom flask. The resulting mixture was then heated in absence of solvent (neat) at 150 °C for 24 h. Then the reaction mixture was loaded on column to afford product 6*H*-benzofuro[3,2-*c*]chromen-6-one **1a** as colorless solid (0.019 g, 19 %) with petroleum ether-ethyl acetate (8.5:1.5) as an eluent. In other case, similar reaction was carried out to which after 24 h water was added and refluxed for 24 h. The water was then removed under

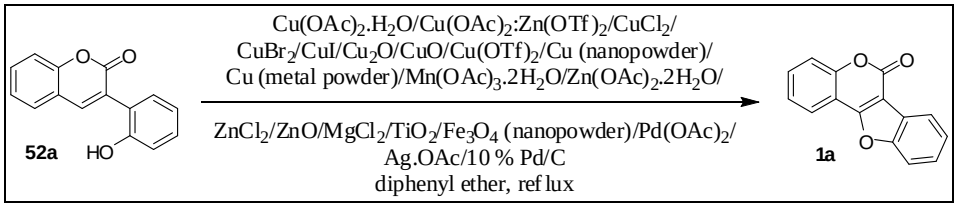
reduced pressure and the reaction mixture was loaded on column to afford product **1a** (0.024 g, 24 %) with petroleum ether-ethyl acetate (8.5:1.5) as an eluent.



4.6.8: A procedure for the synthesis of coumestan 1a using $FeCl_3$ under neat condition: Anhyd. $FeCl_3$ (0.17 g, 1.05 mmol) or (0.27 g, 1.68 mmol) was added to 3-(2-hydroxyphenyl)-2*H*-chromen-2-one **52a** (0.1 g, 0.42 mmol) in a 25 mL round bottom flask. The resulting mixtures were then heated in absence of solvent (neat) at 150/180 °C for 24 h respectively. Then the reaction mixture was sonicated for 30 minutes with a gap after every 5 minutes and then loaded on column to afford product **1a** (0.033 g, 33 %)/(0.025 g, 25 %) respectively with petroleum ether-ethyl acetate (8.5:1.5) as an eluent.

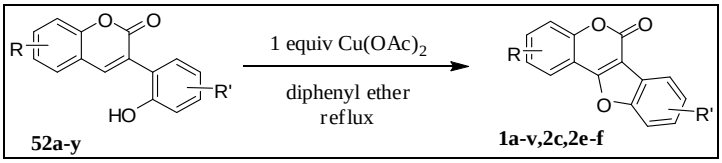


4.6.9: A procedure for the synthesis of coumestan 1a using $FeCl_3$ under neat condition in presence of 230-400 mesh silica gel: Anhyd. $FeCl_3$ (0.20 g, 1.26 mmol) or (0.27 g, 1.68 mmol) or (0.34 g, 2.1 mmol) was added to 3-(2-hydroxyphenyl)-2*H*-chromen-2-one **52a** (0.1 g, 0.42 mmol) and 230-400 silica gel (0.20/0.27/0.34 g) respectively in a 25 mL round bottom flask. The resulting mixtures were then heated in absence of solvent (neat) at 150 °C for 24 h. Then the reaction mixtures were sonicated for 30 minutes with a gap after every 5 minutes and loaded on column to afford **1a** (0.036 g, 36 %)/(0.042 g, 42 %)/(0.039 g, 39 %) respectively with petroleum ether-ethyl acetate (8.5:1.5) as an eluent.

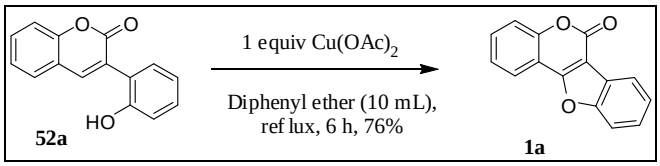


4.6.10: A general procedure for the synthesis of coumestan using various reagents: Above mentioned reagent from $Cu(OAc)_2.H_2O$ to $Pd(OAc)_2$ (0.4 mmol) or Ag.OAc (0.2 mmol) or 50 wt % of 10 % Pd/C was added to substituted 3-(2-hydroxyphenyl)-2*H*-chromen-2-one **52a** (0.4 mmol) in a 25 mL round bottom flask. To it 10 mL of diphenyl ether was added. The resulting mixture was then heated to reflux for 5-24 h. After completion of the reaction (monitored by TLC) the reaction mass was cooled to room temperature. Without any

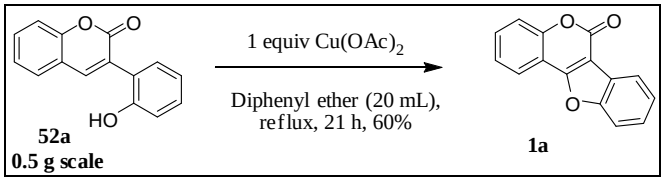
further work up it was directly loaded on column to afford pure product **1a** in 7-86 % yield with petroleum ether-ethyl acetate (8.5:1.5) as an eluent.



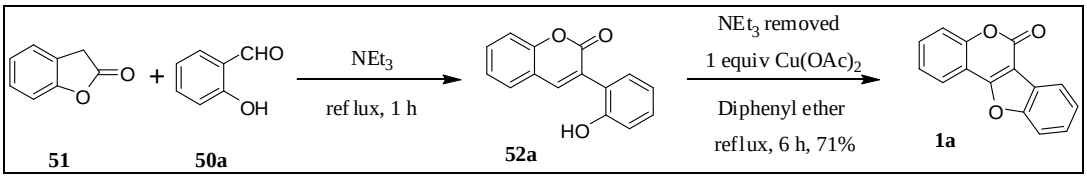
4.6.11: A general procedure for the synthesis of coumestans 1a-v,2c,2e-f using $Cu(OAc)_2$: $Cu(OAc)_2$ (0.4 mmol) was added to substituted 3-(2-hydroxyphenyl)-2*H*-chromen-2-one **52a-y** (0.4 mmol) in a 25 mL round bottom flask. To it 10 mL of diphenyl ether was added. The resulting mixture was then heated to reflux for 4-24 h. After completion of the reaction (monitored by TLC) the reaction mass was cooled to room temperature. Without any further work up it was directly loaded on column to afford pure product 6*H*-benzofuro[3,2-*c*]chromen-6-one **1a-v,2c,2e-f** in 30-80 % yield with petroleum ether-ethyl acetate as an eluent.



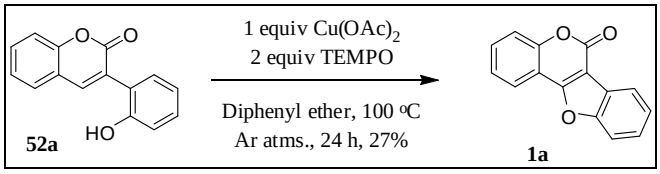
4.6.12: Procedure for the synthesis of coumestan 1a: $Cu(OAc)_2$ (0.076 g, 0.42 mmol) was added to 3-(2-hydroxyphenyl)-2*H*-chromen-2-one **52a** (0.1 g, 0.42 mmol) in a 50 mL round bottom flask. To it 10 mL of diphenyl ether was added. The resulting mixture was then heated to reflux for 6 h. After completion of the reaction (monitored by TLC) the reaction mass was cooled to room temperature. Without any further work up it was directly loaded on column to afford product **1a** (0.075 g, 76 %) with petroleum ether-ethyl acetate (8.5:1.5) as an eluent.



4.6.13: Procedure for the synthesis of coumestan 1a on 0.5 g scale: $Cu(OAc)_2$ (0.382 g, 2.1 mmol) was added to 3-(2-hydroxyphenyl)-2*H*-chromen-2-one **52a** (0.5 g, 2.1 mmol) in a 50 mL round bottom flask. To it 20 mL of diphenyl ether was added. The resulting mixture was then heated to reflux for 21 h. After completion of the reaction (monitored by TLC) the reaction mass was cooled to room temperature. Without any further work up it was directly loaded on column to afford product **1a** (0.296 g, 60 %) with petroleum ether-ethyl acetate (8.5:1.5) as an eluent.



4.6.14: Procedure for stepwise one pot synthesis of coumestan 1a: 2-coumaranone **51** (0.057 g, 0.4 mmol) and salicylaldehyde **50a** (0.052 g, 0.4 mmol) were mixed together in a 25 mL round bottom flask. To it triethylamine (5 mL) was added and refluxed for 1 h. After reaction solvent was removed under vacuum and to the product formed 3-(2-hydroxyphenyl)-2*H*-chromen-2-one **52a**, $Cu(OAc)_2$ (0.077 g, 0.4 mmol) and 10 mL of diphenyl ether were added. The resulting mixture was then heated to reflux for 6 h. After completion of the reaction (monitored by TLC) the reaction mass was cooled to room temperature. Without any further work up it was directly loaded on column to afford product **1a** (0.070 g, 71 %) with petroleum ether-ethyl acetate (8.5:1.5) as an eluent.



4.6.15: Procedure for synthesis of coumestan 1a in presence of radical scavenger TEMPO: TEMPO (0.131 g, 0.8 mmol) was added to 3-(2-hydroxyphenyl)-2*H*-chromen-2-one **52a** (0.1 g, 0.4 mmol) and $Cu(OAc)_2$ (0.077 g, 0.4 mmol) in a 25 mL round bottom flask. To it 10 mL of diphenyl ether was added. The resulting mixture was flushed with argon gas few times and then heated with stirring at 100 °C for 24 h in argon atmosphere. After 24 h the reaction mass was cooled to room temperature. Without any further work up it was directly loaded on column to afford product **1a** (0.027 g, 27 %) with petroleum ether-ethyl acetate (8.5:1.5) as an eluent.

4.7: References

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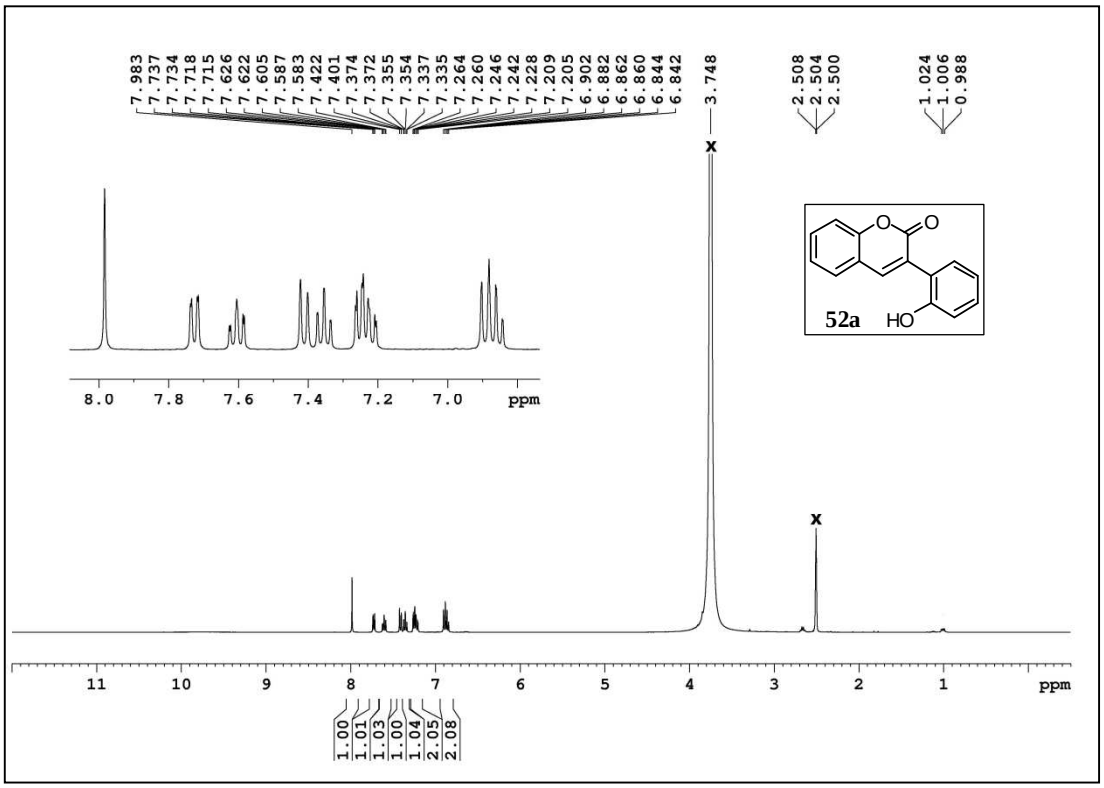
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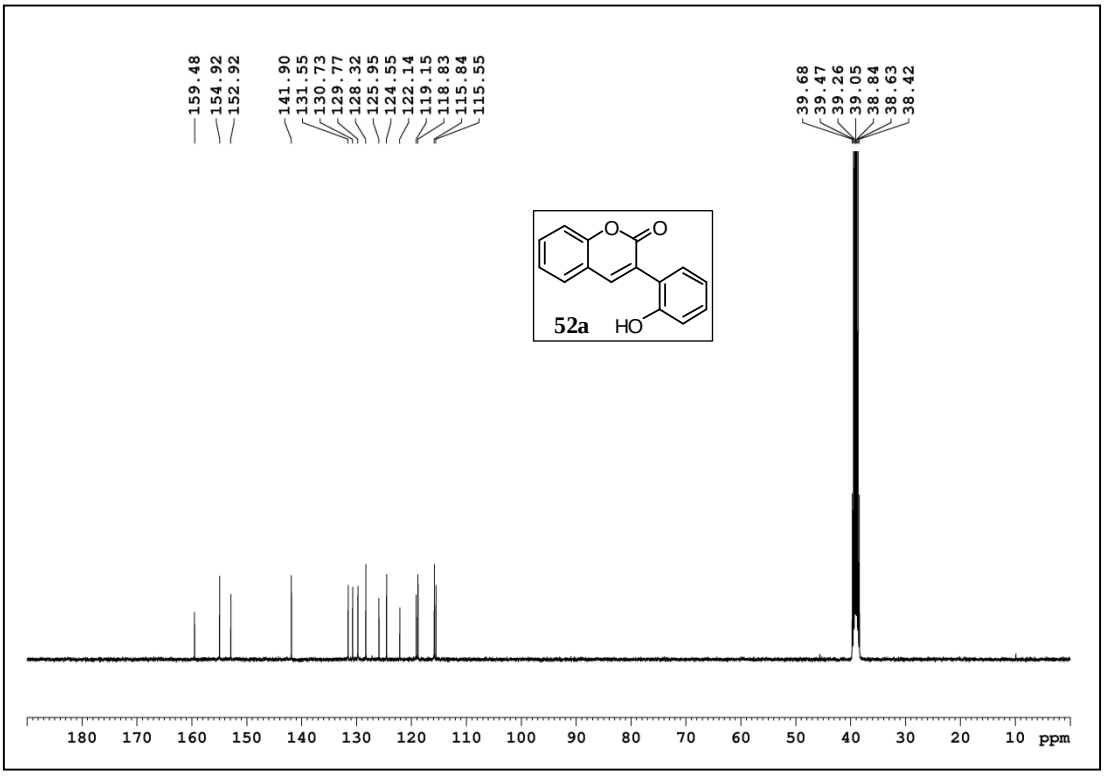
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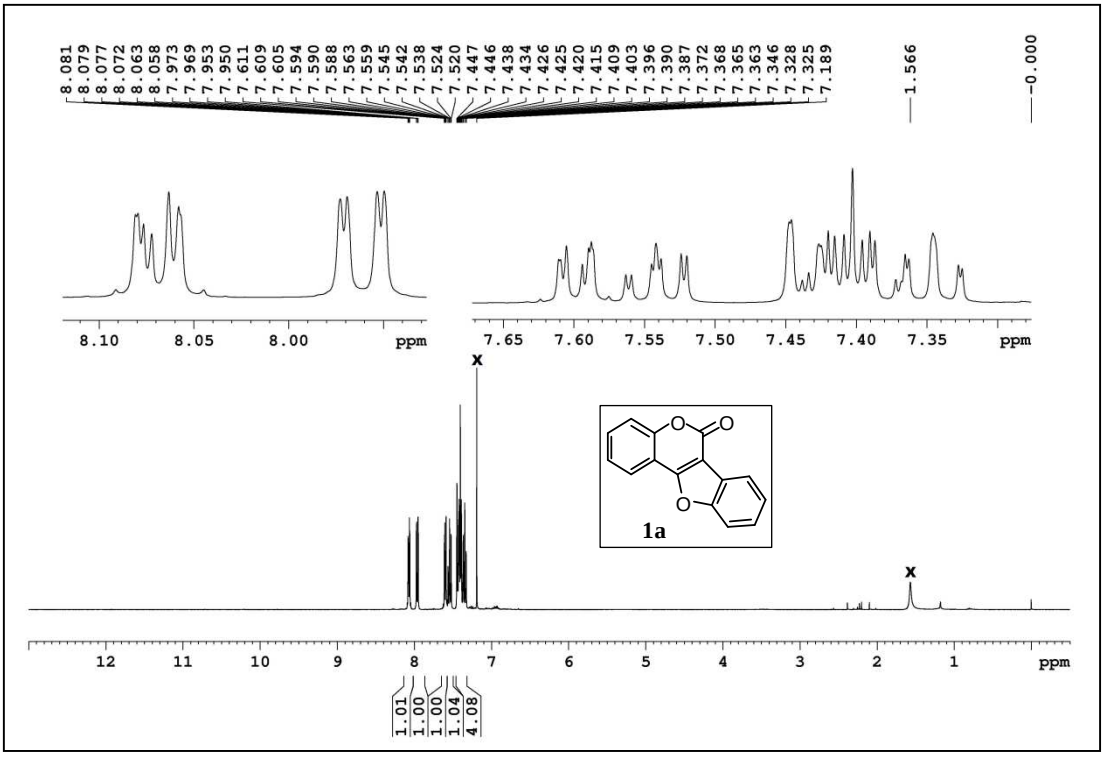
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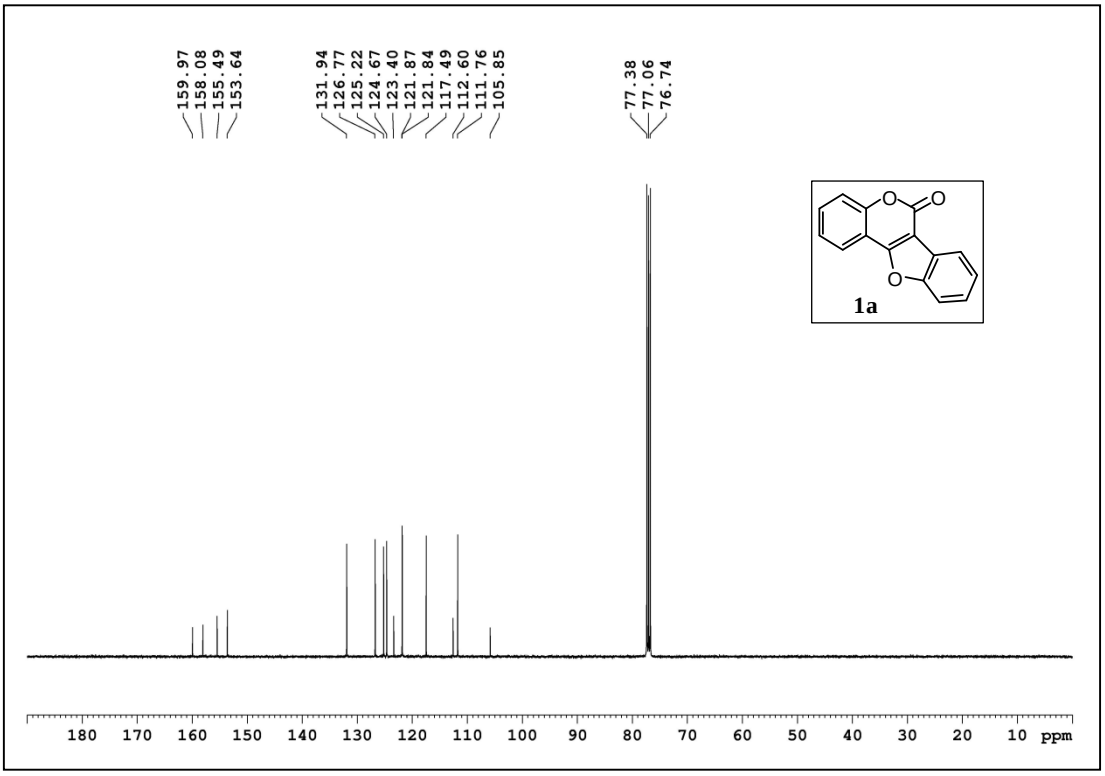
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112.60
111.76
105.85
77.38
77.06
76.74
1a
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150
140
130
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110
100
90
80
70
60
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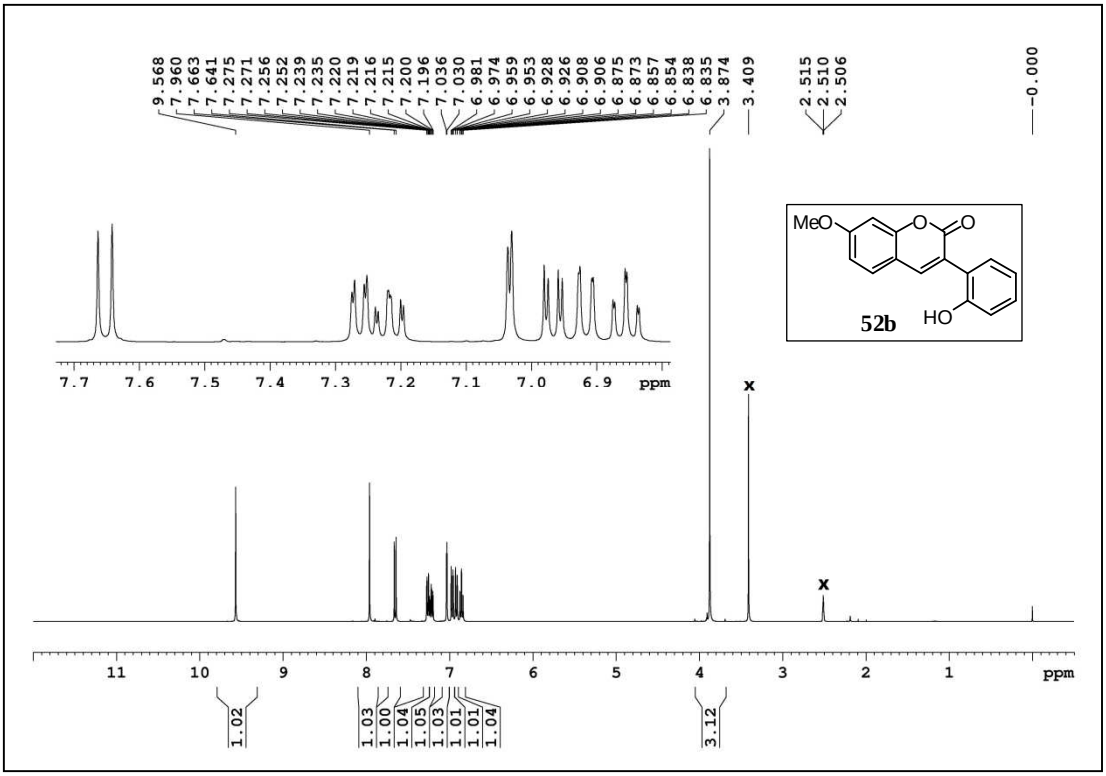
30
20
10
ppm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7.252
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7.235
7.220
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7.216
7.215
7.200
7.196
7.036
7.030
6.981
6.974
6.959
6.953
6.928
6.926
6.908
6.906
6.875
6.873
6.857
6.854
6.838
6.835
3.874
3.409
2.515
2.510
2.506
0.000
MeO
O
O
HO
52b
x
x
ppm
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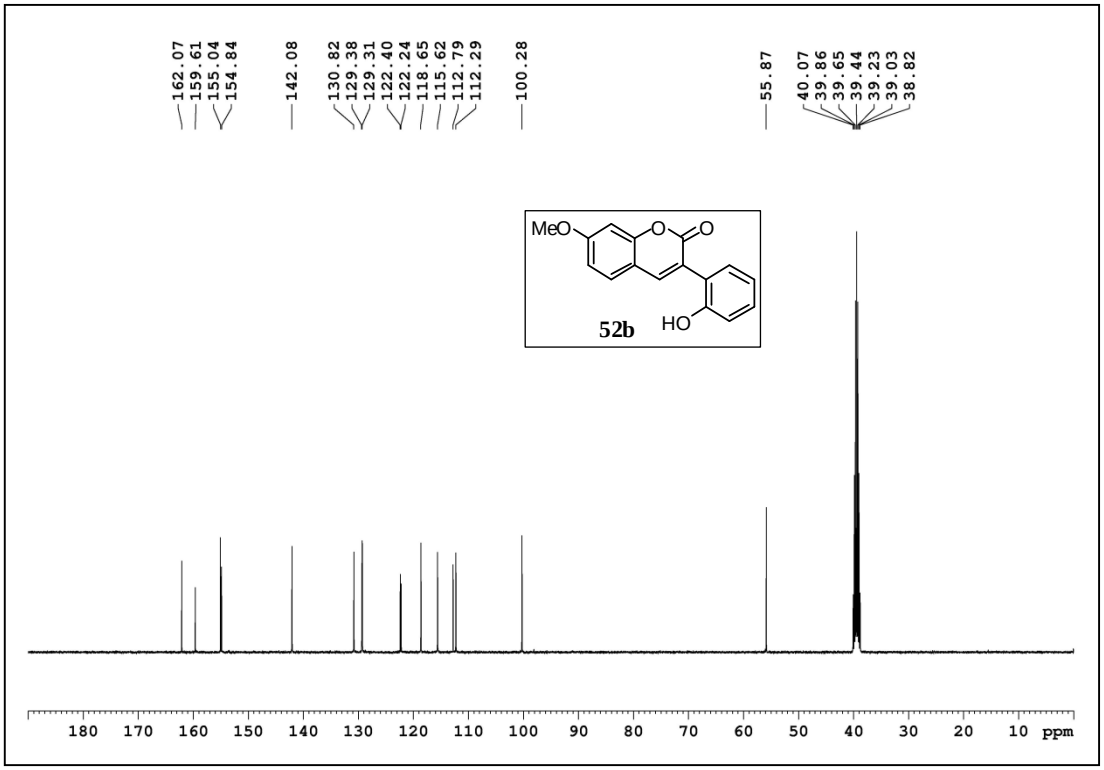
1.03
1.00
1.04
1.05
1.03
1.01
1.01
1.04
3.12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112.29
100.28
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39.65
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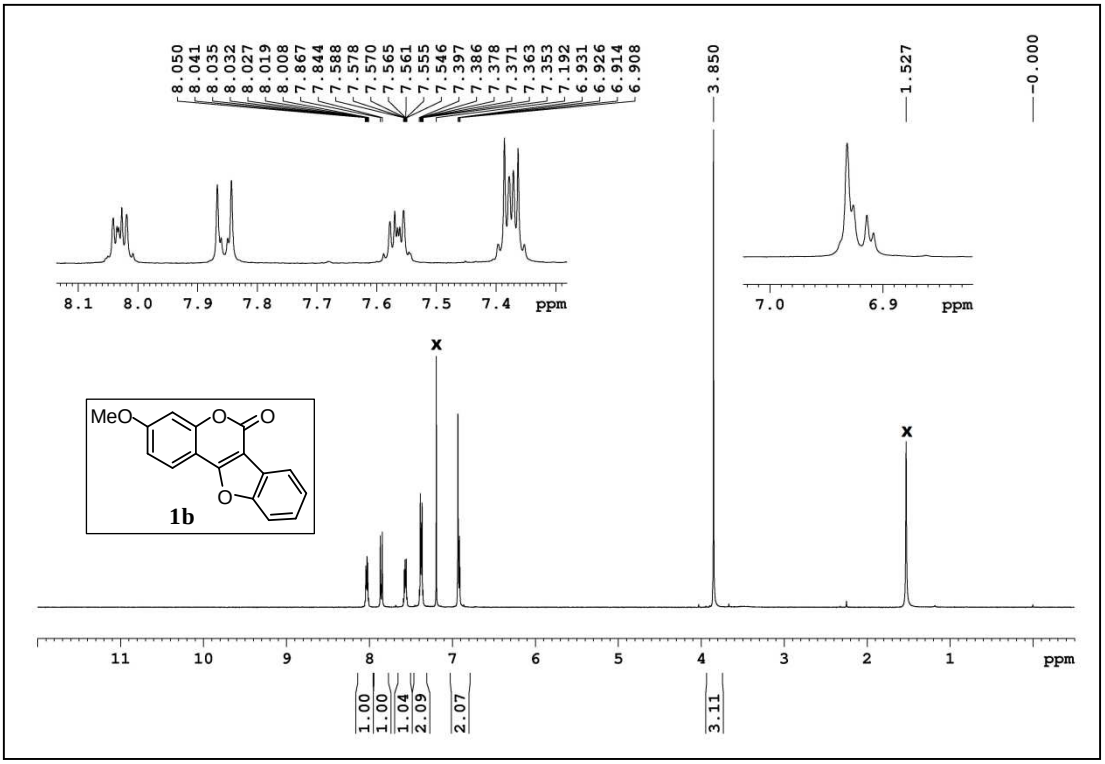
39.23
39.03
38.82
MeO
O
O
HO
52b
ppm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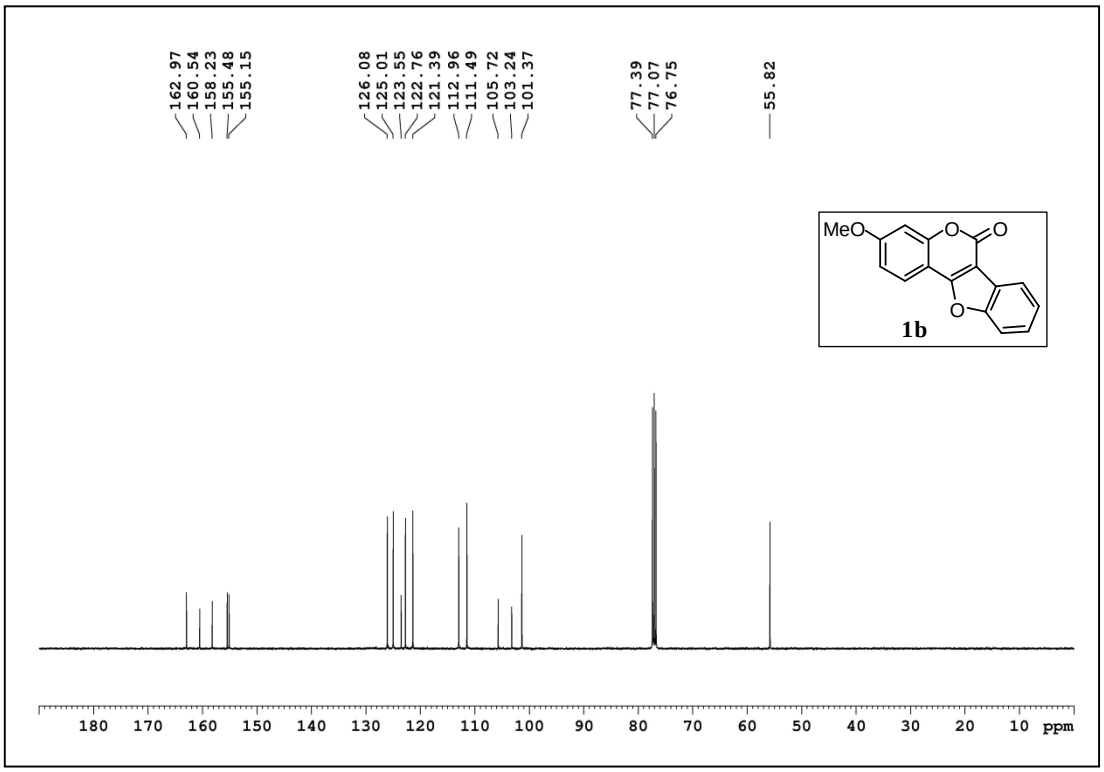
7.578
7.570
7.565
7.561
7.555
7.546
7.397
7.386
7.378
7.371
7.363
7.353
7.192
6.931
6.926
6.914
6.908
3.850
1.527
-0.000
8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 ppm
7.0 6.9 ppm
x
x
MeO
O
O
O
1b
11 10 9 8 7 6 5 4 3 2 1 ppm
1.00
1.00
1.04
2.09
2.07
3.11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111.49
105.72
103.24
101.37
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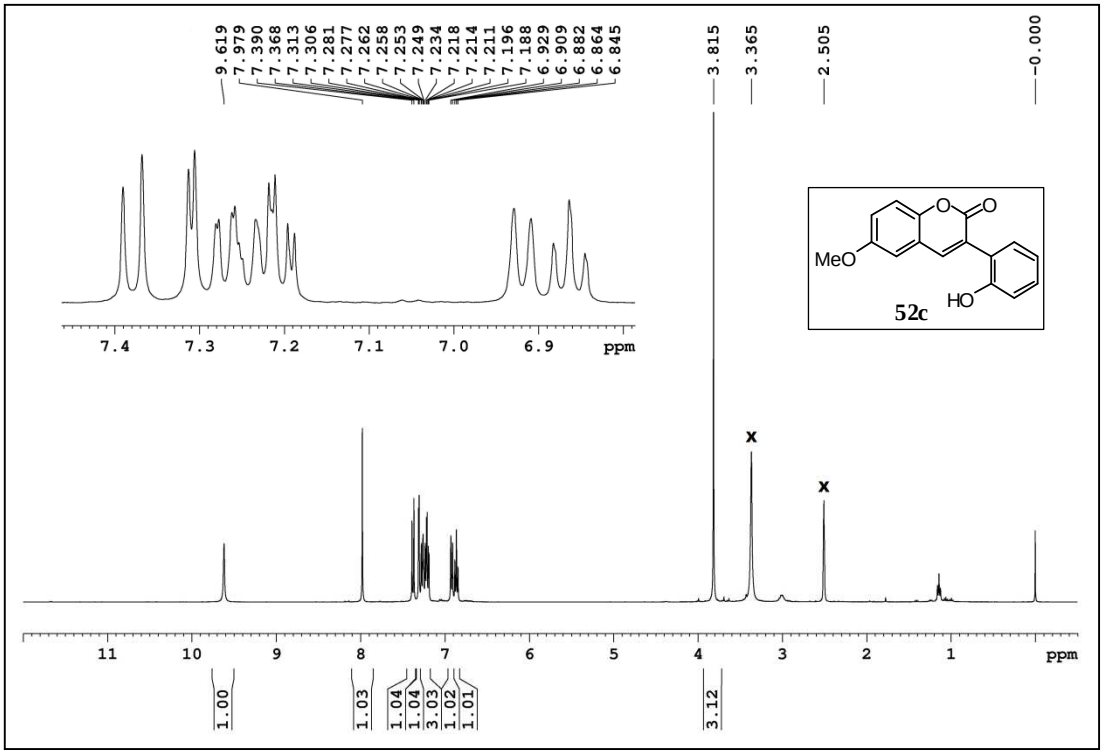
76.75
55.82
MeO
O
O
O
1b
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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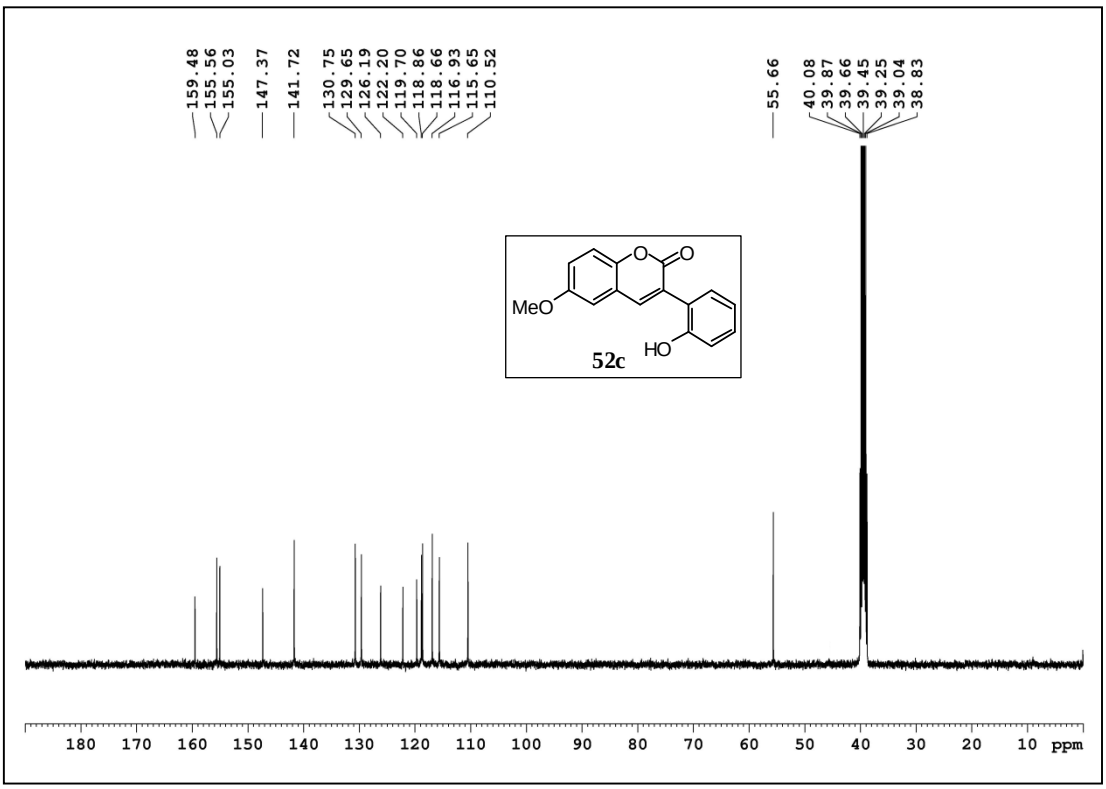
7.234
7.218
7.214
7.211
7.196
7.188
6.929
6.909
6.882
6.864
6.845
3.815
3.365
2.505
-0.000
MeO
HO
52c
x
x
ppm
1.00
1.03
1.04
1.04
3.03
1.02
1.01
3.12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116.93
115.65
110.52
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40.08
39.87
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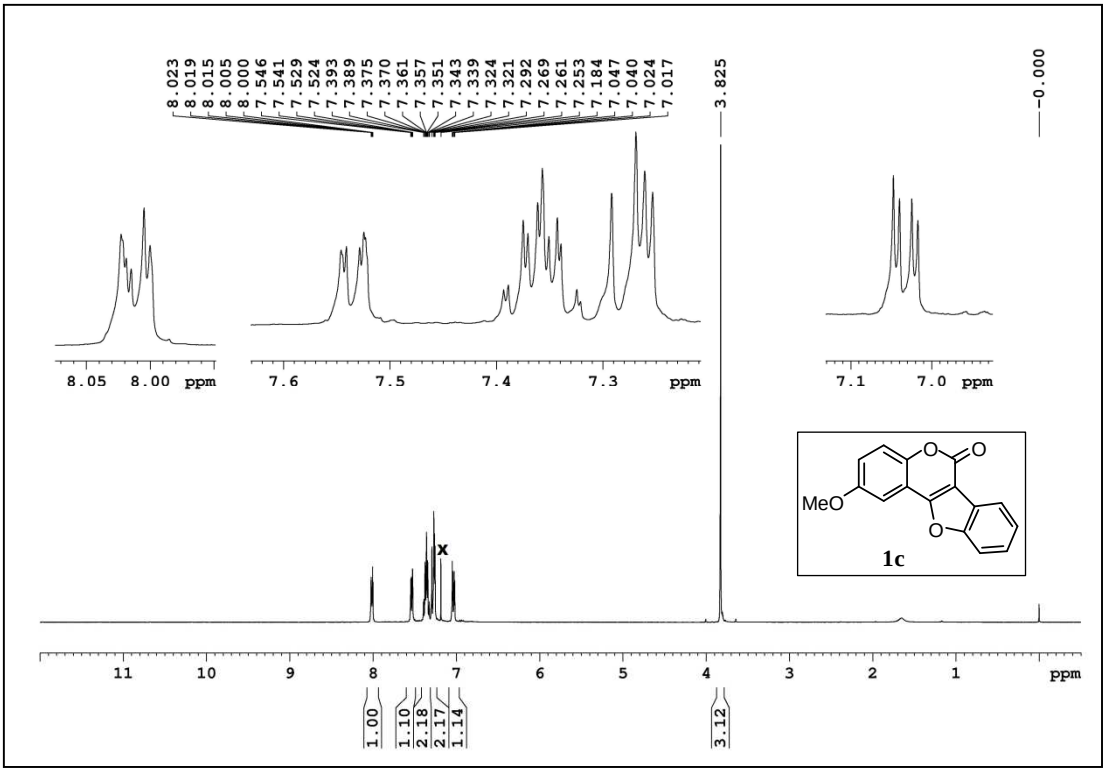
39.25
39.04
38.83
MeO
HO
52c
ppm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8.015
8.005
8.000
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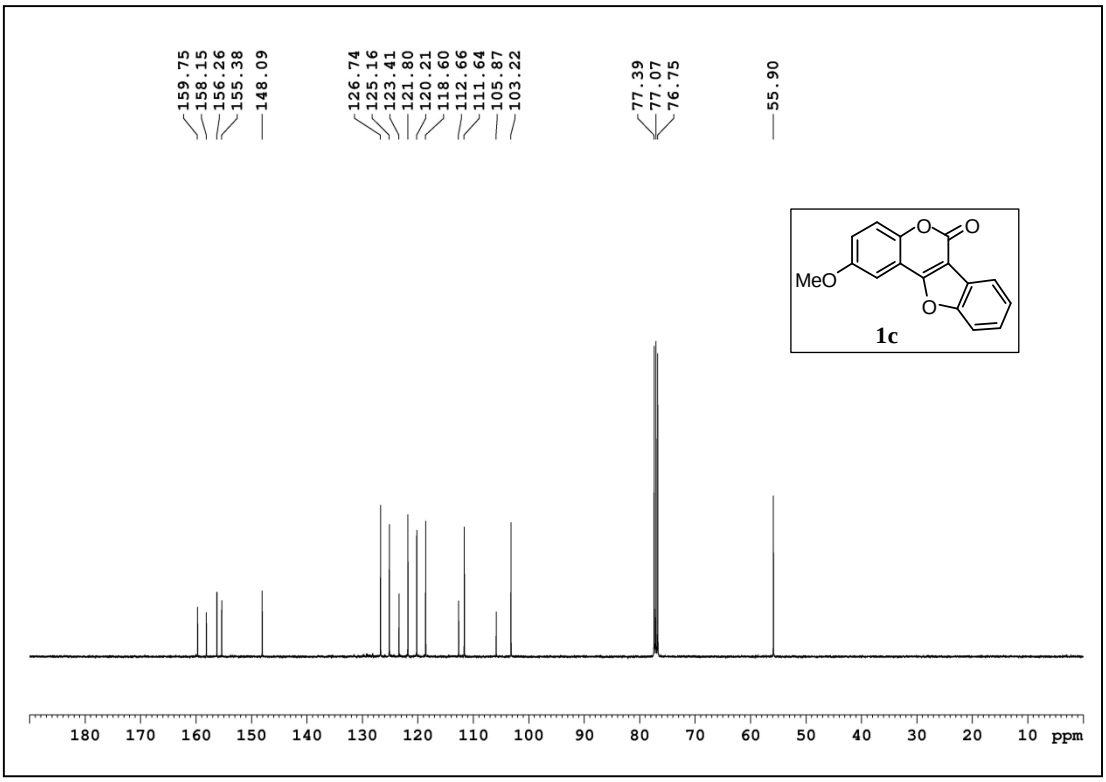
7.541
7.529
7.524
7.393
7.389
7.375
7.370
7.361
7.357
7.351
7.343
7.339
7.324
7.321
7.292
7.269
7.261
7.253
7.184
7.047
7.040
7.024
7.017
3.825
0.000
8.05 8.00 ppm
7.6 7.5 7.4 7.3 ppm
7.1 7.0 ppm
MeO
O
O
O
1c
x
11 10 9 8 7 6 5 4 3 2 1 ppm
1.00
1.10
2.18
2.17
1.14
3.12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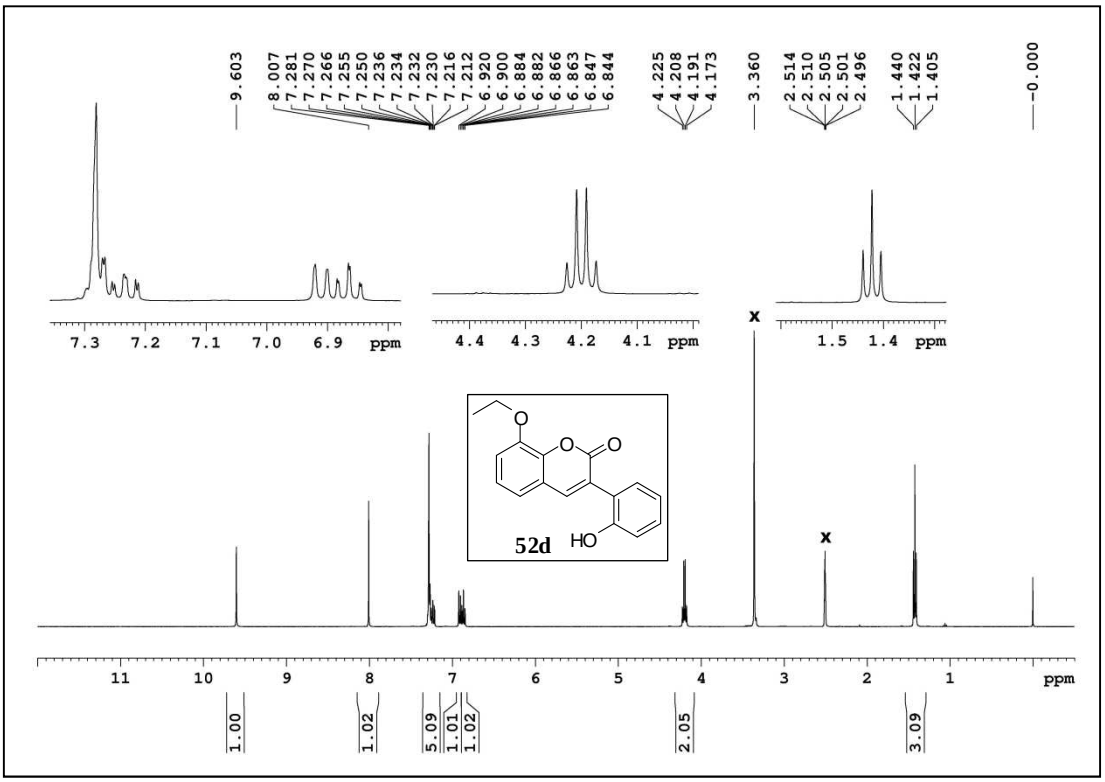
123.41
121.80
120.21
118.60
112.66
111.64
105.87
103.22
77.39
77.07
76.75
55.90
MeO
O
O
O
1c
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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7.230
7.216
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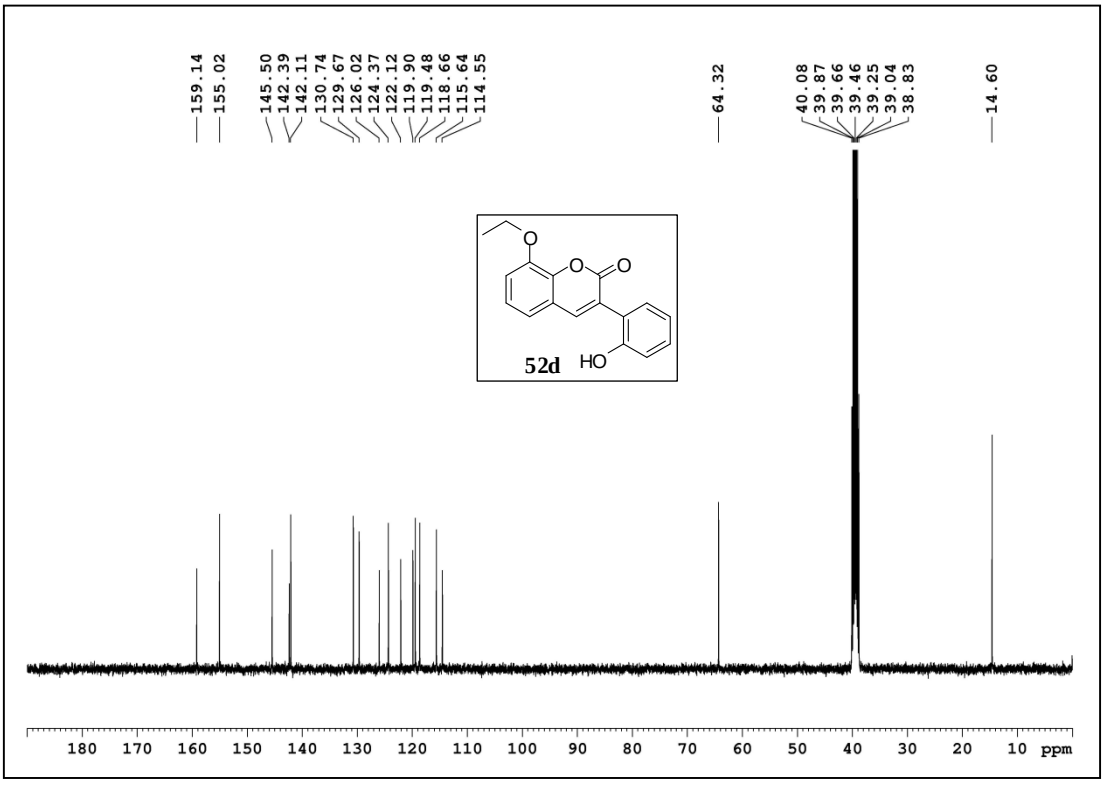
6.920
6.900
6.884
6.882
6.866
6.863
6.847
6.844
4.225
4.208
4.191
4.173
3.360
2.514
2.510
2.505
2.501
2.496
1.440
1.422
1.405
0.000
52d
HO
x
x
ppm
1.00
1.02
5.09
1.01
1.02
2.05
3.09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142.11
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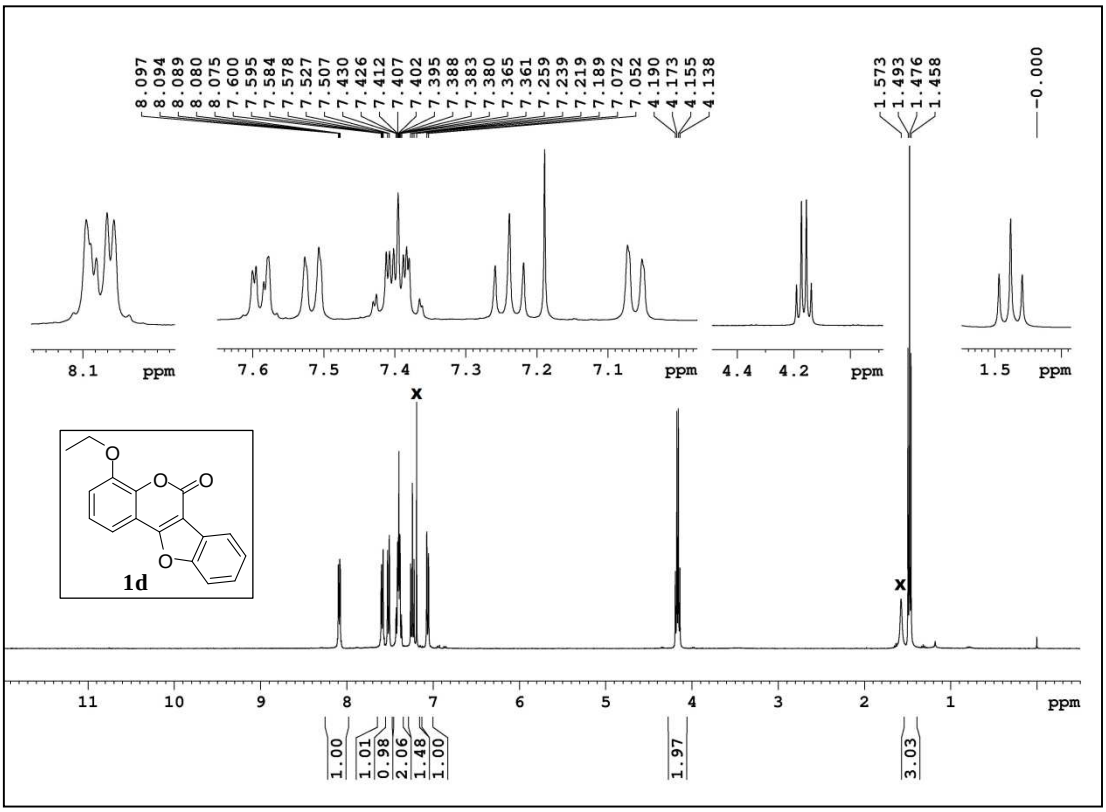
126.02
124.37
122.12
119.90
119.48
118.66
115.64
114.55
64.32
40.08
39.87
39.66
39.46
39.25
39.04
38.83
14.60
52d
HO
ppm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8.094
8.089
8.080
8.075
7.600
7.595
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7.578
7.527
7.507
7.430
7.426
7.412
7.407
7.402
7.395
7.388
7.383
7.380
7.365
7.361
7.259
7.239
7.219
7.189
7.072
7.052
4.190
4.173
4.155
4.138
1.573
1.493
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1.458
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1d
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1.01
0.98
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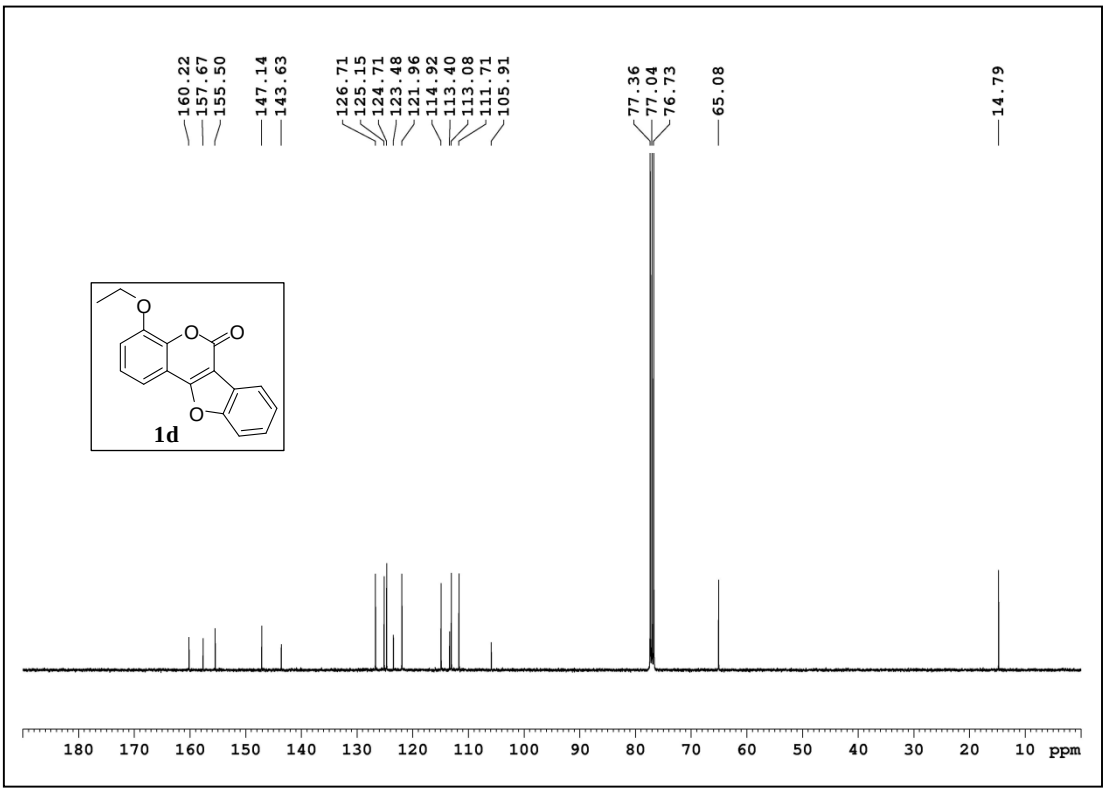
1.48
1.00
1.97
3.03
ppm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143.63
126.71
125.15
124.71
123.48
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114.92
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113.08
111.71
105.91
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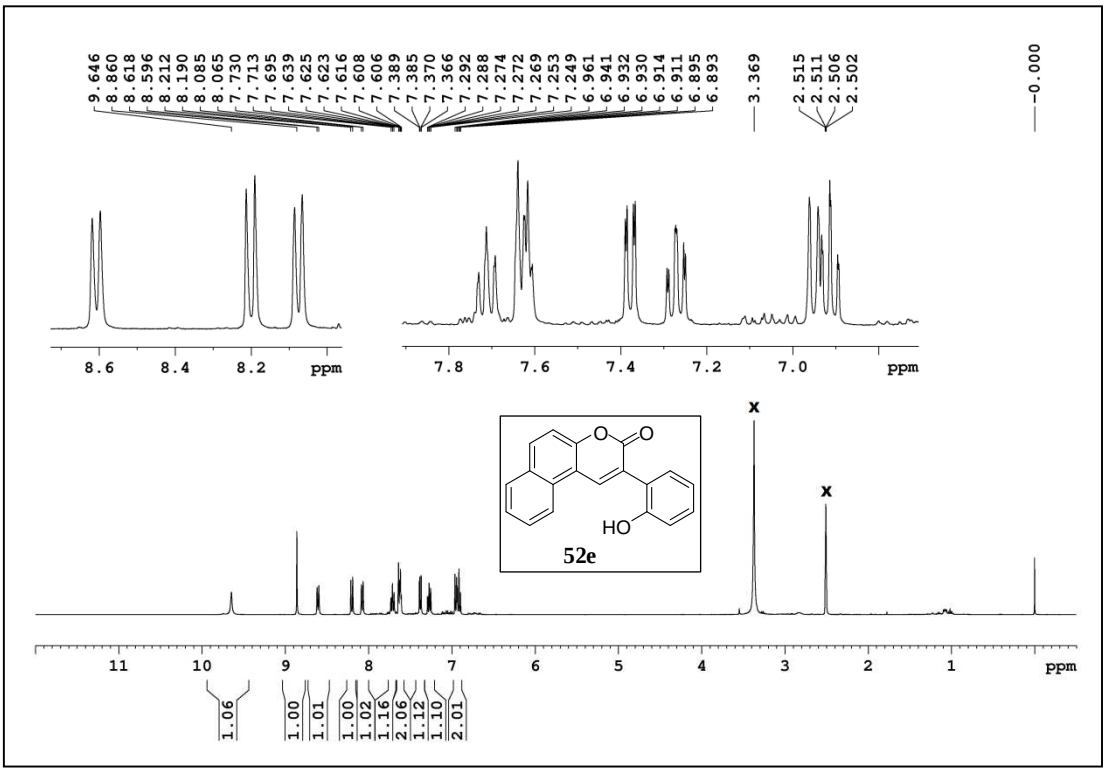
77.04
76.73
65.08
14.79
1d
ppm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8.212
8.190
8.085
8.065
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7.713
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7.625
7.623
7.616
7.608
7.606
7.389
7.385
7.370
7.366
7.292
7.288
7.274
7.272
7.269
7.253
7.249
6.961
6.941
6.932
6.930
6.914
6.911
6.895
6.893
3.369
2.515
2.511
2.506
2.502
0.000
8.6
8.4
8.2
ppm
7.8
7.6
7.4
7.2
7.0
ppm
O
O
HO
52e
x
x
11
10
9
8
7
6
5
4
3
2
1
ppm
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1.00
1.01
1.00
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1.16
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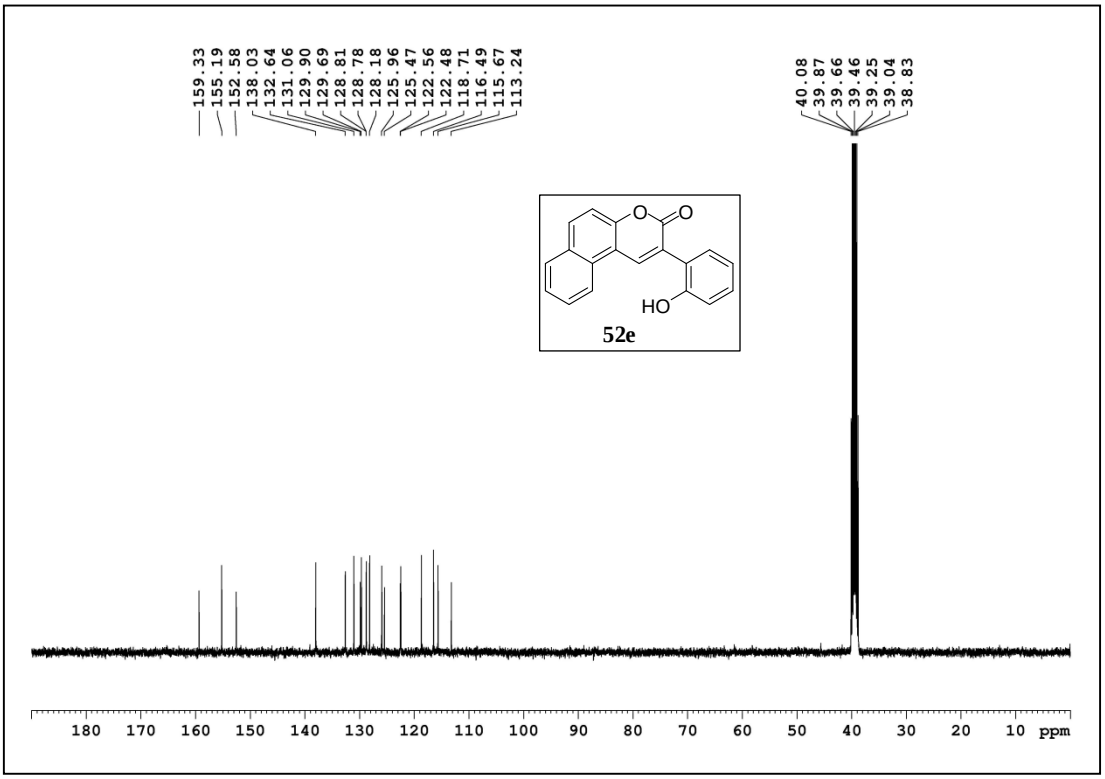
1.12
1.10
2.01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125.47
122.56
122.48
118.71
116.49
115.67
113.24
40.08
39.87
39.66
39.46
39.25
39.04
38.83
O
O
HO
52e
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150
140
130
120
110
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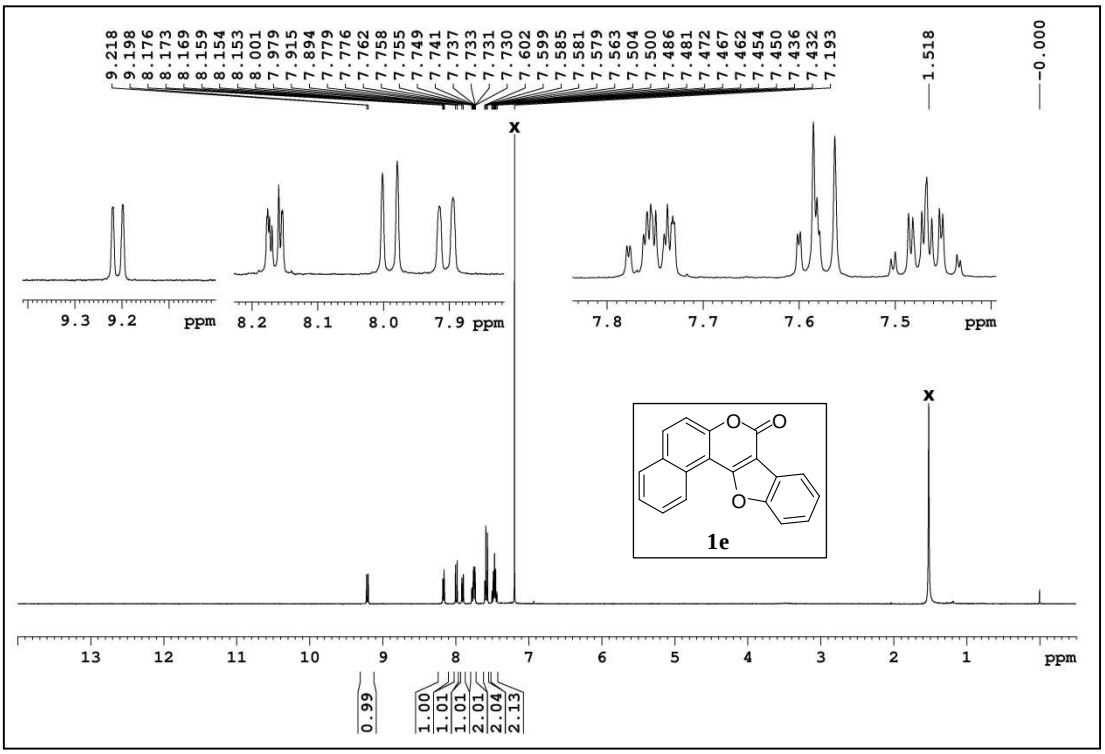
70
60
50
40
30
20
10
ppm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8.153
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7.779
7.776
7.762
7.758
7.755
7.749
7.741
7.737
7.733
7.731
7.730
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7.599
7.585
7.581
7.579
7.563
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7.500
7.486
7.481
7.472
7.467
7.462
7.454
7.450
7.436
7.432
7.193
1.518
0.000
x
9.3 9.2 ppm
8.2 8.1 8.0 7.9 ppm
7.8 7.7 7.6 7.5 ppm
1e
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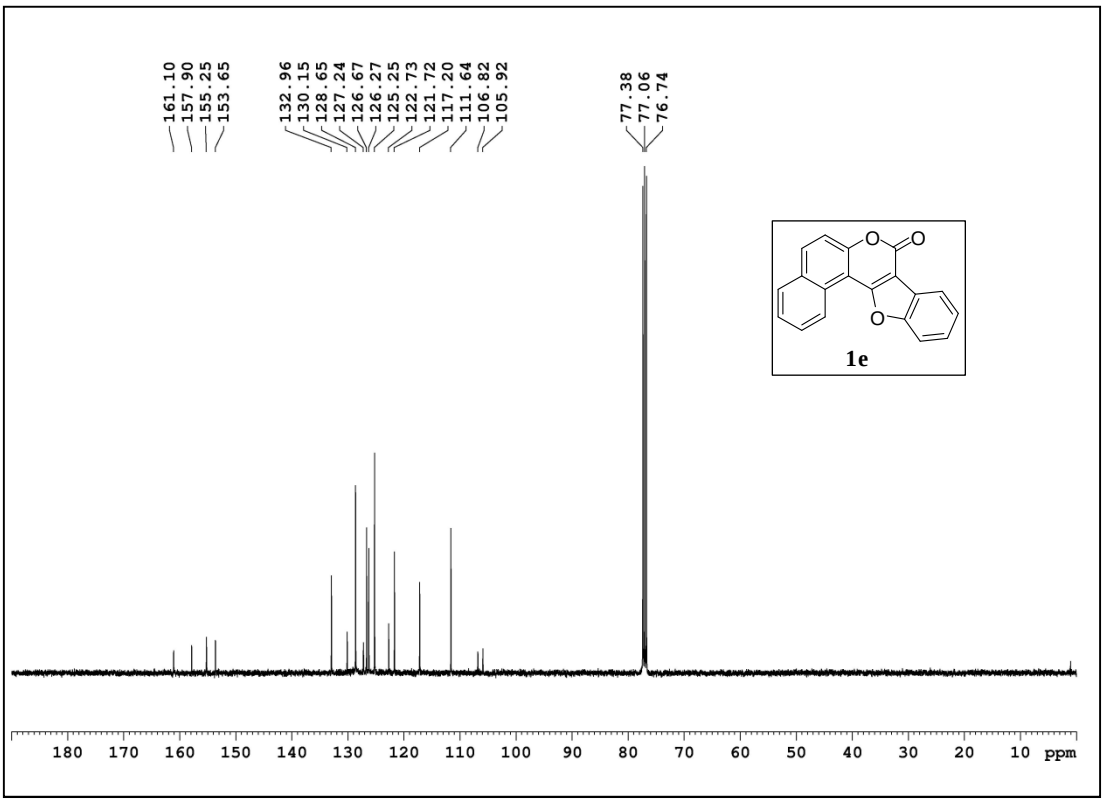
1.00
1.01
1.01
2.01
2.04
2.13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122.73
121.72
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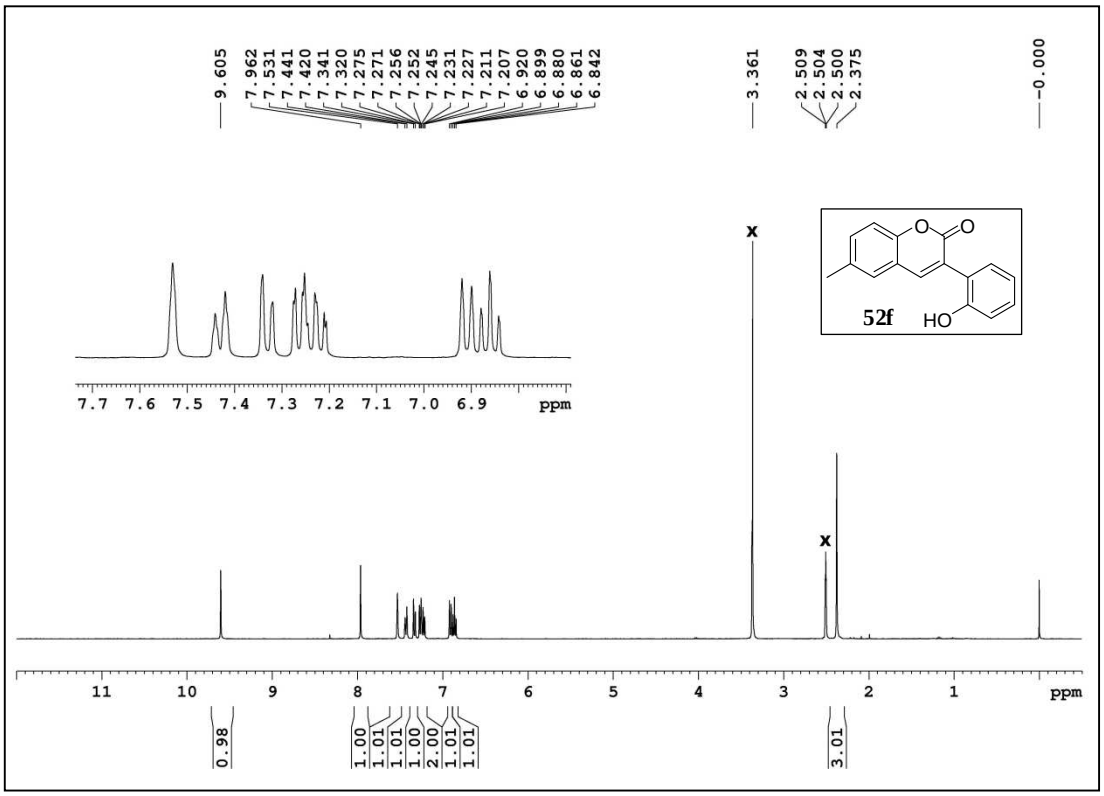
111.64
106.82
105.92
77.38
77.06
76.74
1e
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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7.256
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7.245
7.231
7.227
7.211
7.207
6.920
6.899
6.880
6.861
6.842
3.361
2.509
2.504
2.500
2.375
0.000
x
x
52f
HO
7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 ppm
11 10 9 8 7 6 5 4 3 2 1 ppm
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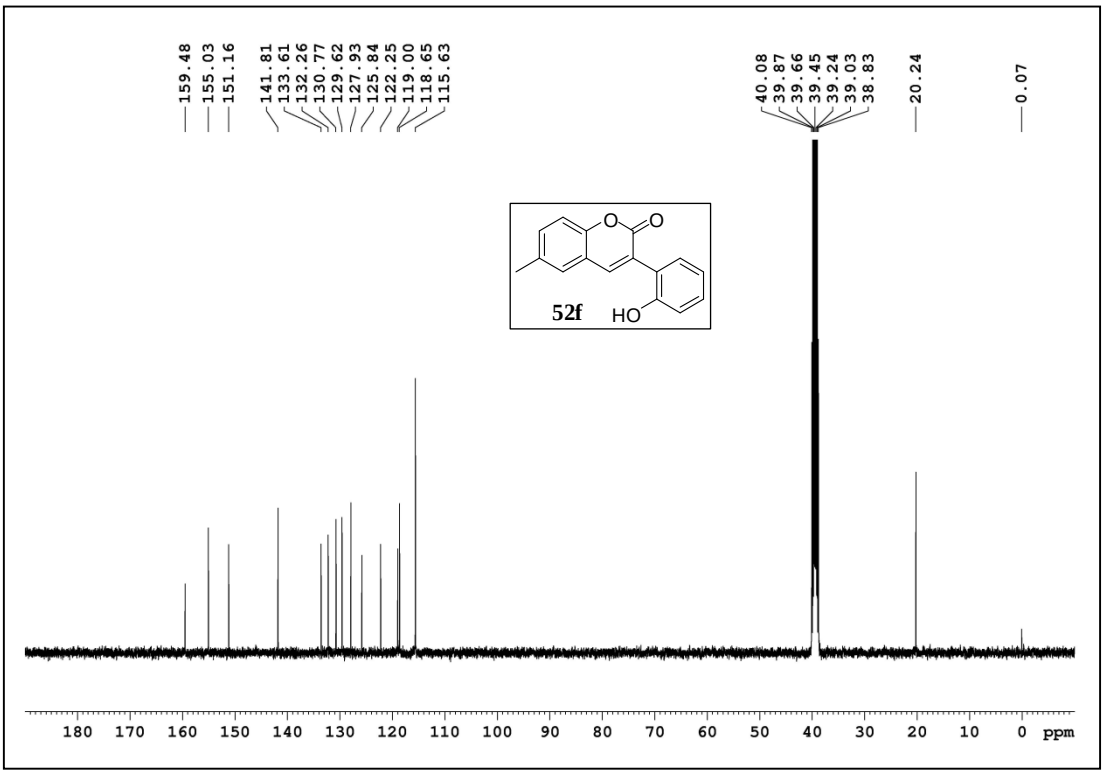
1.01
1.00
2.00
1.01
1.01
3.01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118.65
115.63
40.08
39.87
39.66
39.45
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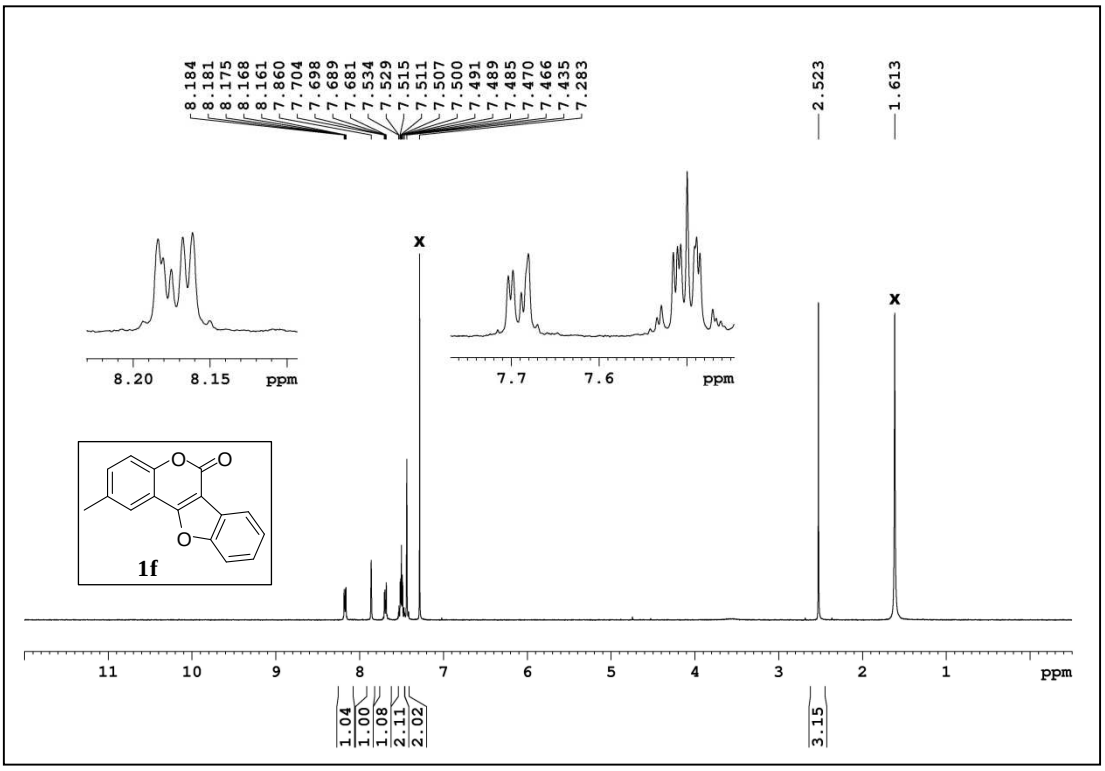
39.03
38.83
20.24
0.07
52f
HO
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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7.515
7.511
7.507
7.500
7.491
7.489
7.485
7.470
7.466
7.435
7.283
2.523
1.613
x
x
8.20
8.15
ppm
7.7
7.6
ppm
1f
11
10
9
8
7
6
5
4
3
2
1
ppm
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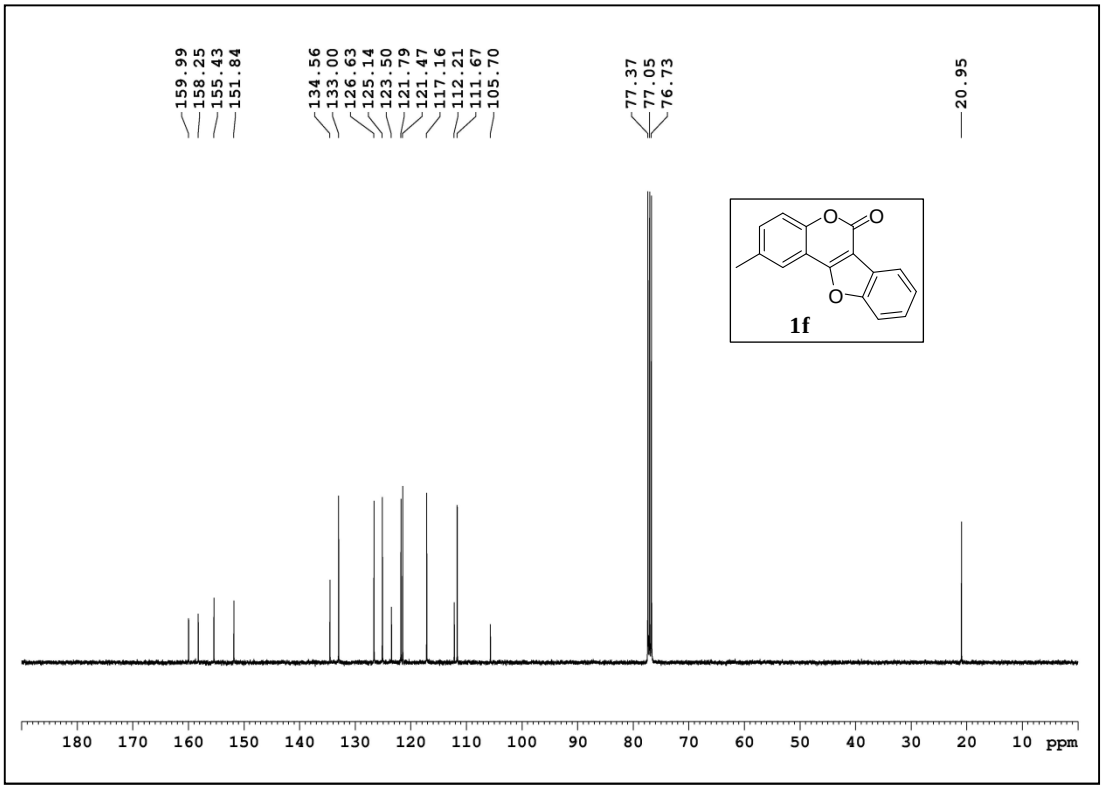
1.00
1.08
2.11
2.02
3.15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77.37
77.05
76.73
20.95
1f
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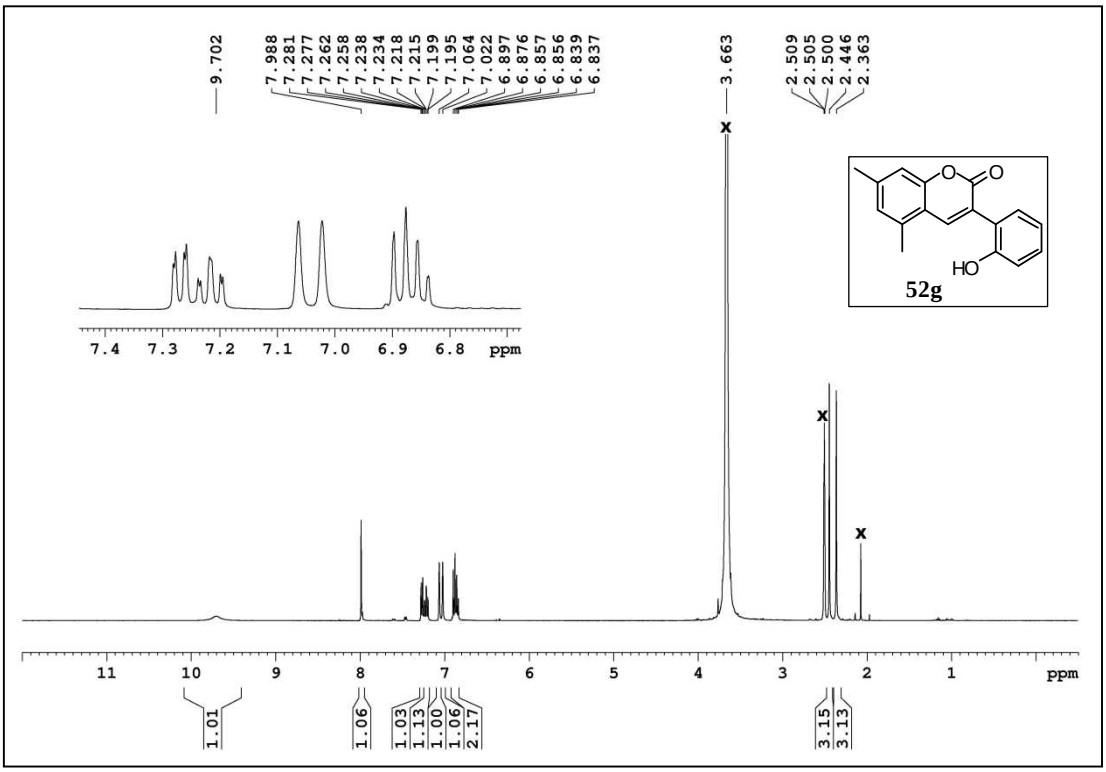
40
30
20
10
ppm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7.064
7.022
6.897
6.876
6.857
6.856
6.839
6.837
3.663
2.509
2.505
2.500
2.446
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52g
ppm
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1.03
1.13
1.00
1.06
2.17
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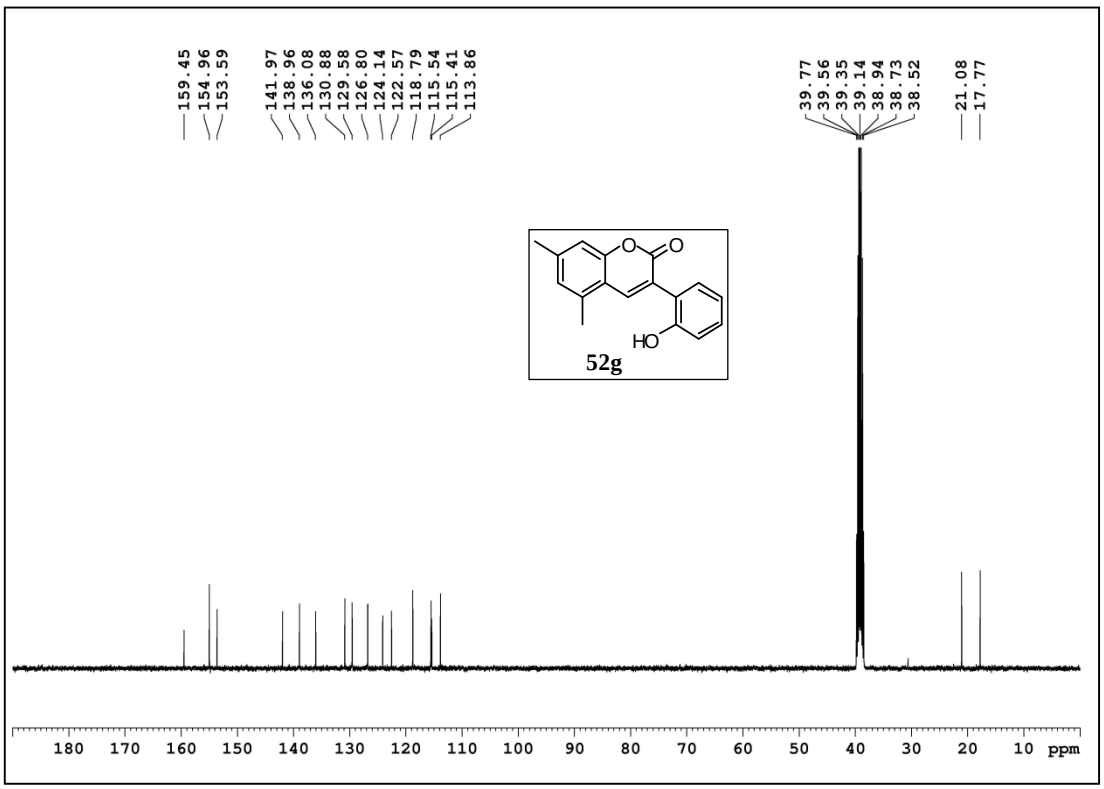
3.13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122.57
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115.54
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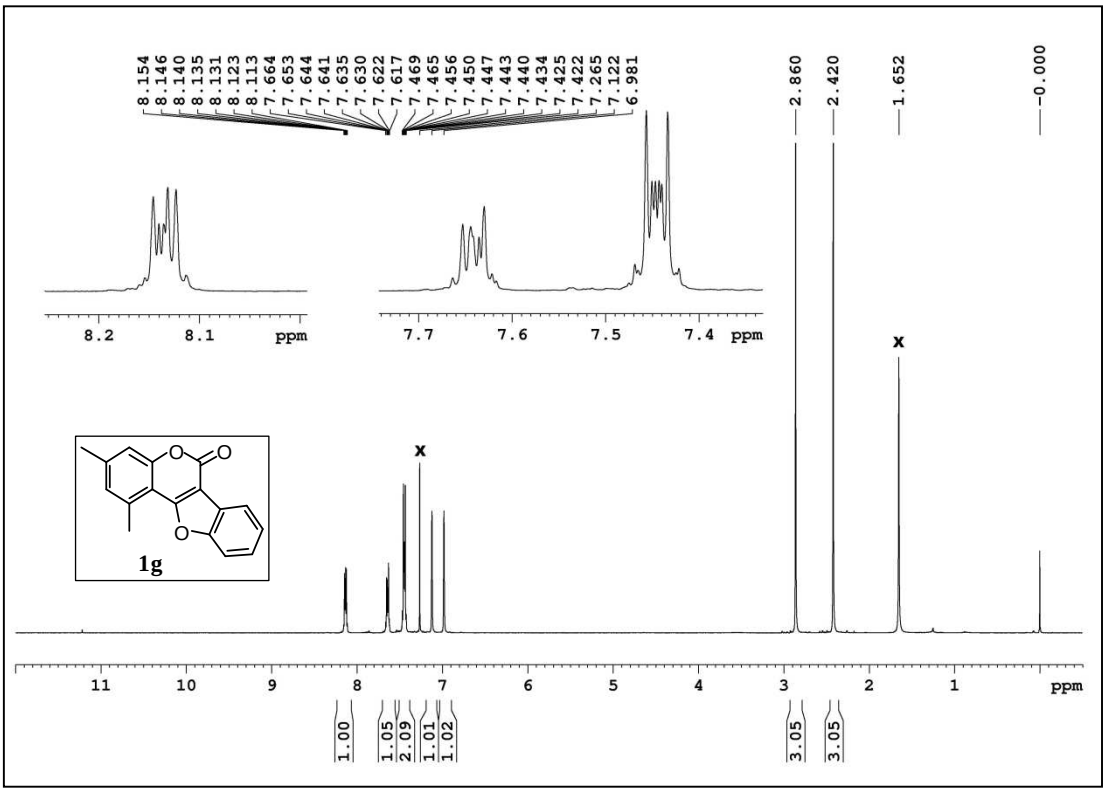
38.52
21.08
17.77
52g
ppm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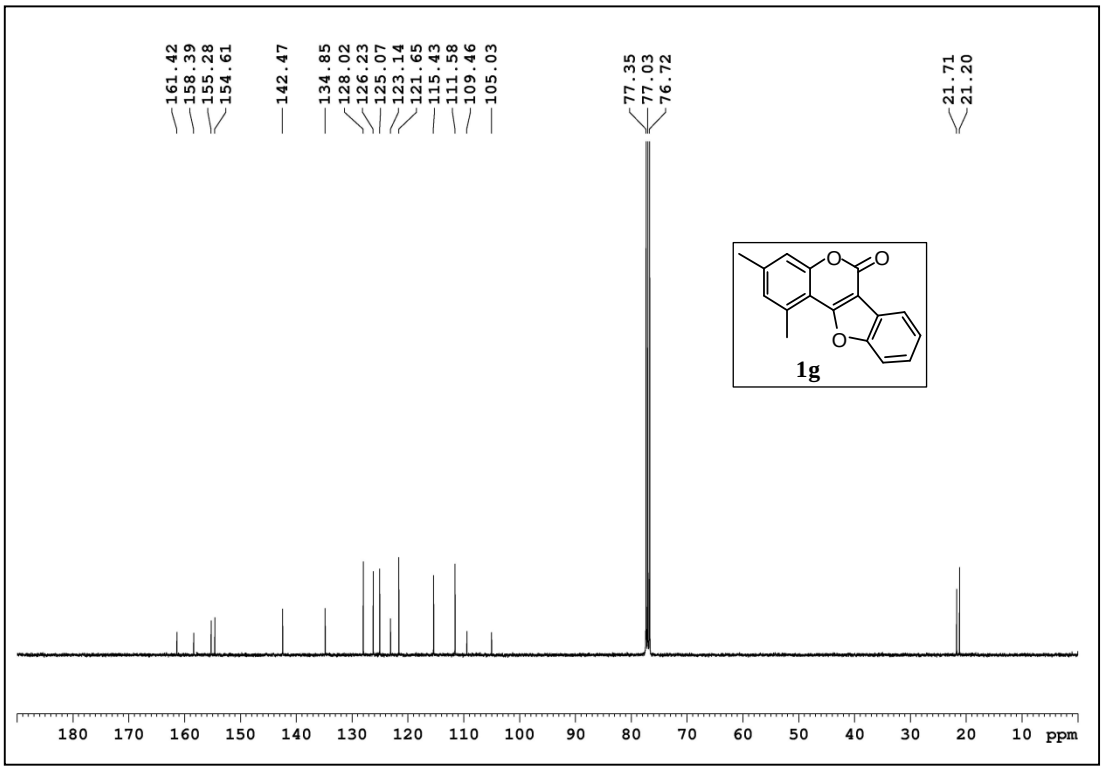
8.146
8.140
8.135
8.131
8.123
8.113
7.664
7.653
7.644
7.641
7.635
7.630
7.622
7.617
7.469
7.465
7.456
7.450
7.447
7.443
7.440
7.434
7.425
7.422
7.265
7.122
6.981
2.860
2.420
1.652
0.000
8.2
8.1
ppm
7.7
7.6
7.5
7.4
ppm
x
x
1g
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.05
2.09
1.01
1.02
3.05
3.05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128.02
126.23
125.07
123.14
121.65
115.43
111.58
109.46
105.03
77.35
77.03
76.72
21.71
21.20
1g
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170
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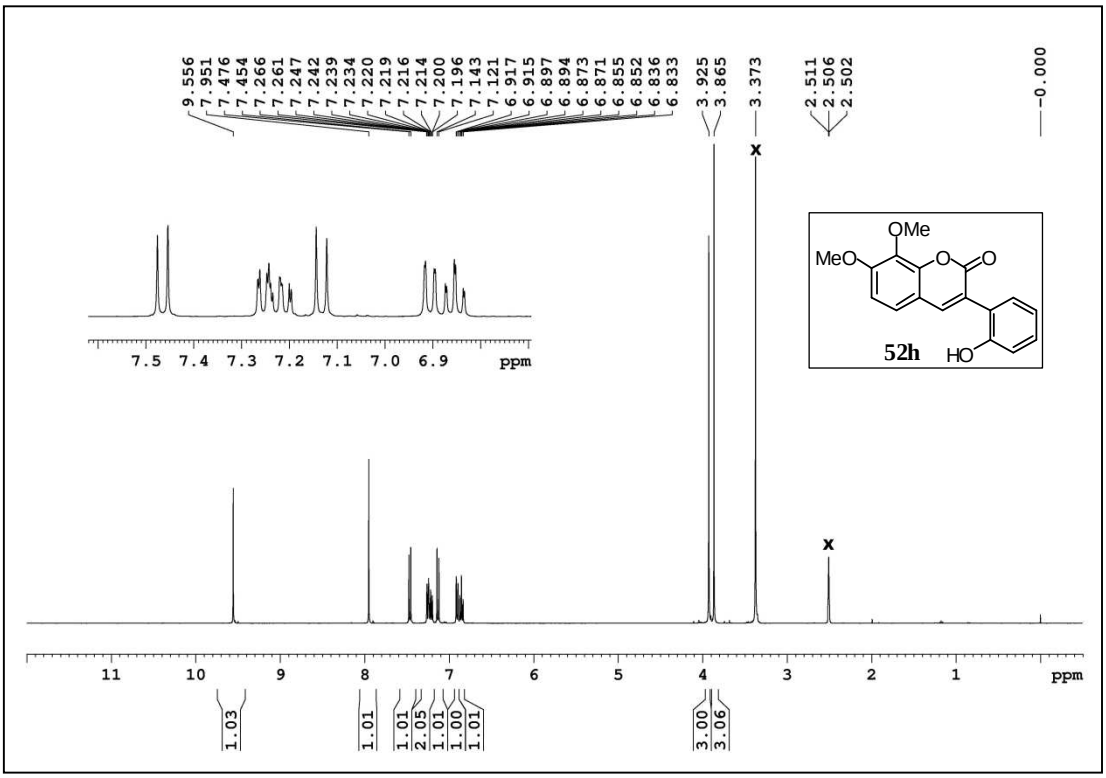
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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7.951
7.476
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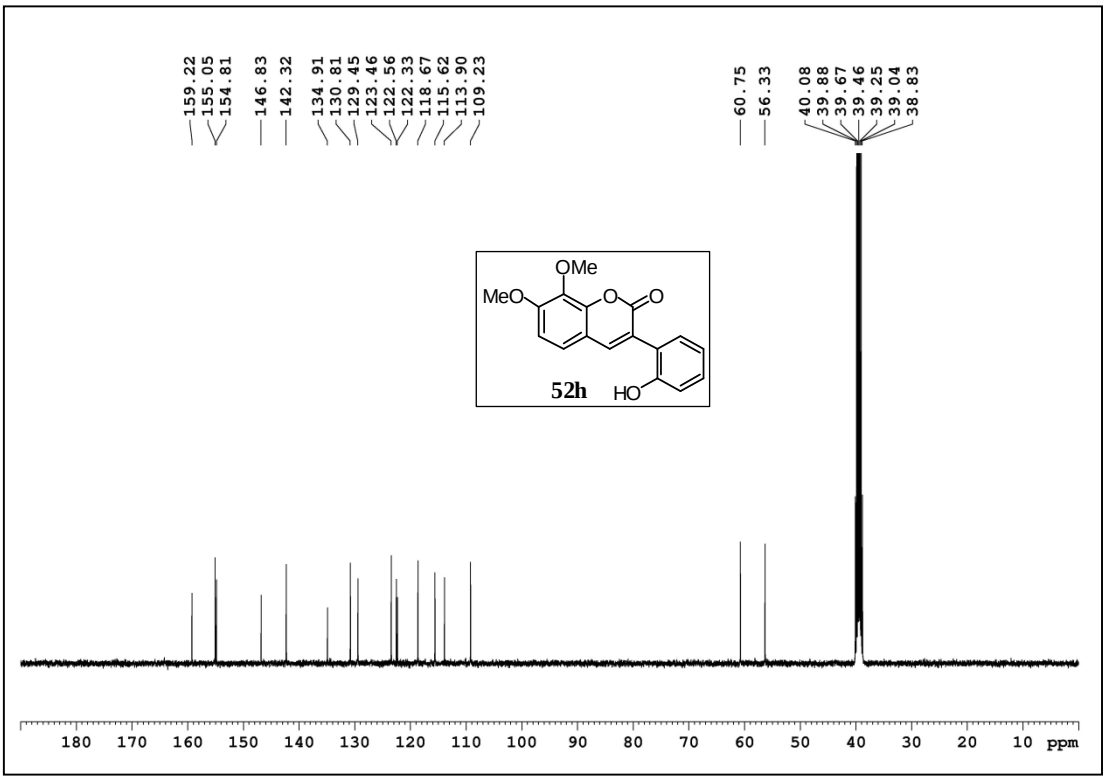
7.247
7.242
7.239
7.234
7.220
7.219
7.216
7.214
7.200
7.196
7.143
7.121
6.917
6.915
6.897
6.894
6.873
6.871
6.855
6.852
6.836
6.833
3.925
3.865
3.373
2.511
2.506
2.502
0.000
x
x
OMe
MeO
O
O
52h
HO
7.5 7.4 7.3 7.2 7.1 7.0 6.9 ppm
11 10 9 8 7 6 5 4 3 2 1 ppm
1.03
1.01
1.01
2.05
1.01
1.00
1.01
3.00
3.06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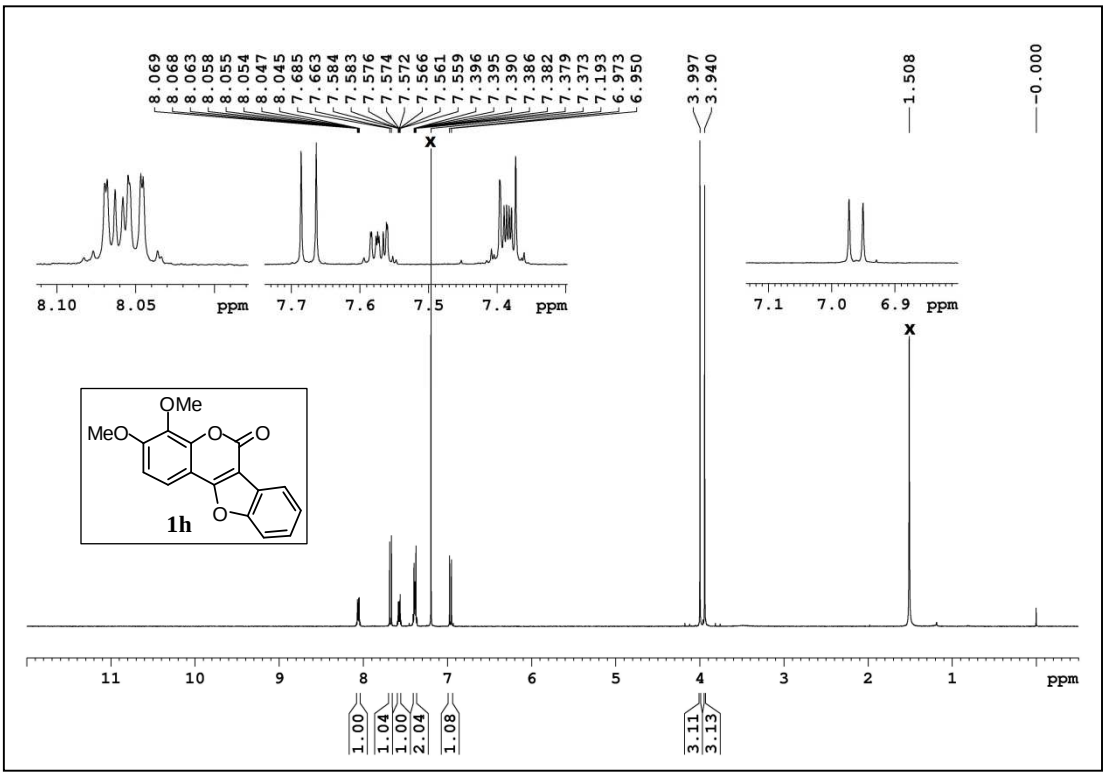
130.81
129.45
123.46
122.56
122.33
118.67
115.62
113.90
109.23
60.75
56.33
40.08
39.88
39.67
39.46
39.25
39.04
38.83
OMe
MeO
O
O
52h
HO
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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8.068
8.063
8.058
8.055
8.054
8.047
8.045
7.685
7.663
7.584
7.583
7.576
7.574
7.572
7.566
7.561
7.559
7.396
7.395
7.390
7.386
7.382
7.379
7.373
7.193
6.973
6.950
3.997
3.940
1.508
-0.000
8.10
8.05
ppm
7.7
7.6
7.5
7.4
ppm
7.1
7.0
6.9
ppm
OMe
MeO
O
O
O
1h
11
10
9
8
7
6
5
4
3
2
1
ppm
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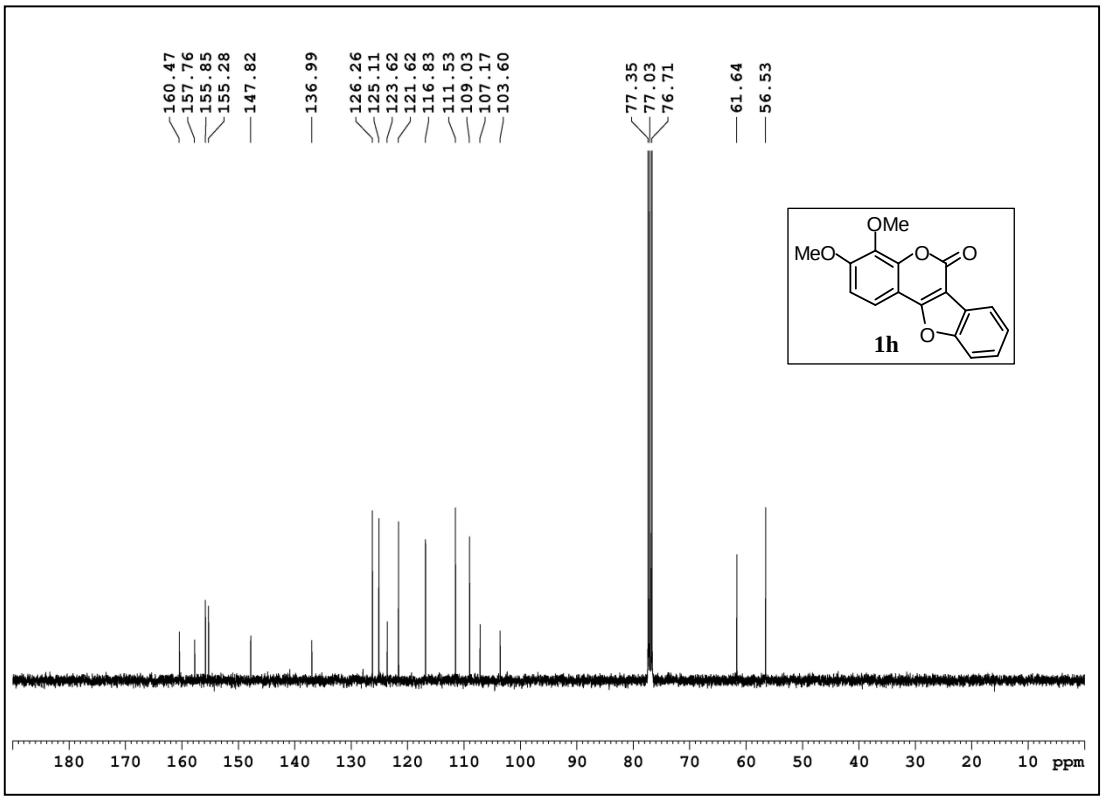
1.04
1.00
2.04
1.08
3.11
3.13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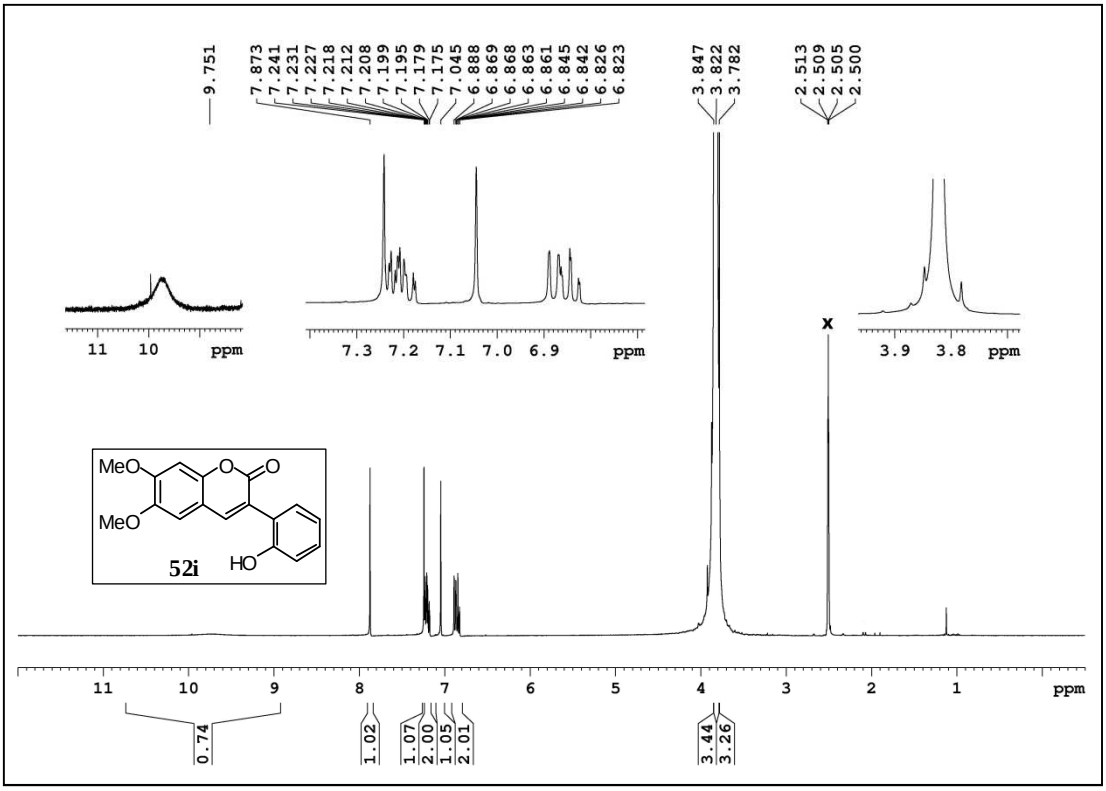
157.76
155.85
155.28
147.82
136.99
126.26
125.11
123.62
121.62
116.83
111.53
109.03
107.17
103.60
77.35
77.03
76.71
61.64
56.53
OMe
MeO
O
O
O
1h
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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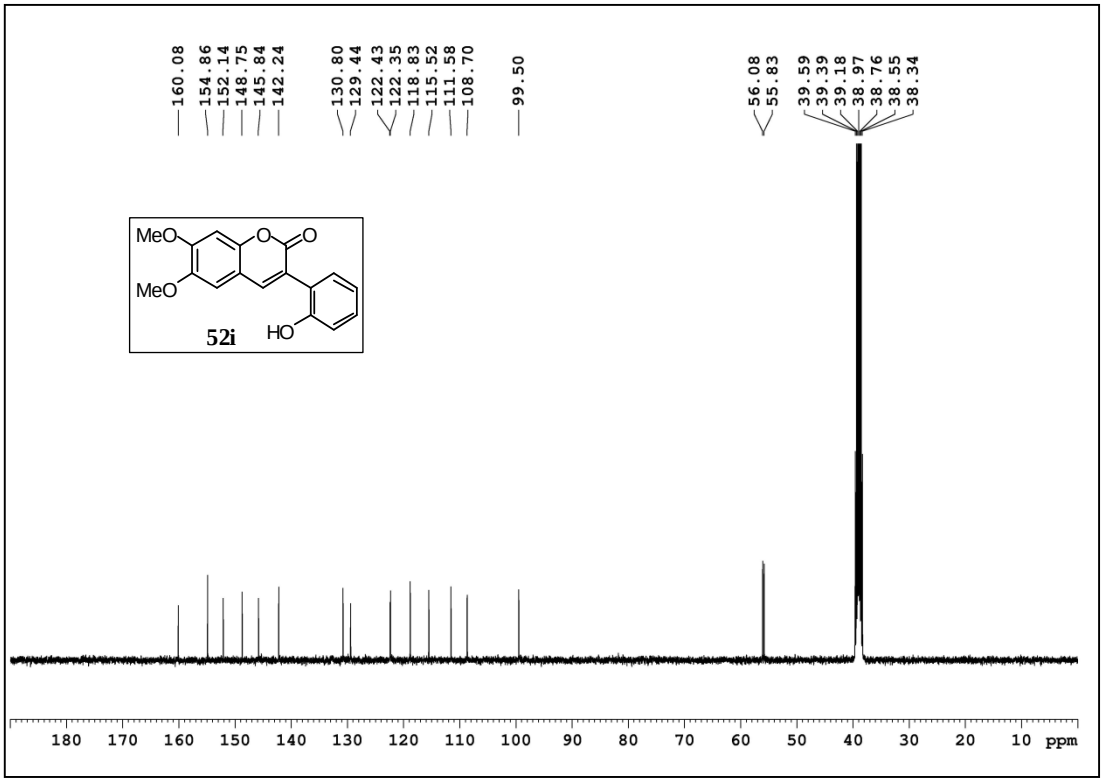
7.873
7.241
7.231
7.227
7.218
7.212
7.208
7.199
7.195
7.179
7.175
7.045
6.888
6.869
6.868
6.863
6.861
6.845
6.842
6.826
6.823
3.847
3.822
3.782
2.513
2.509
2.505
2.500
11 10 ppm
7.3 7.2 7.1 7.0 6.9 ppm
3.9 3.8 ppm
x
MeO
MeO
O
O
HO
52i
11 10 9 8 7 6 5 4 3 2 1 ppm
0.74
1.02
1.07
2.00
1.05
2.01
3.44
3.26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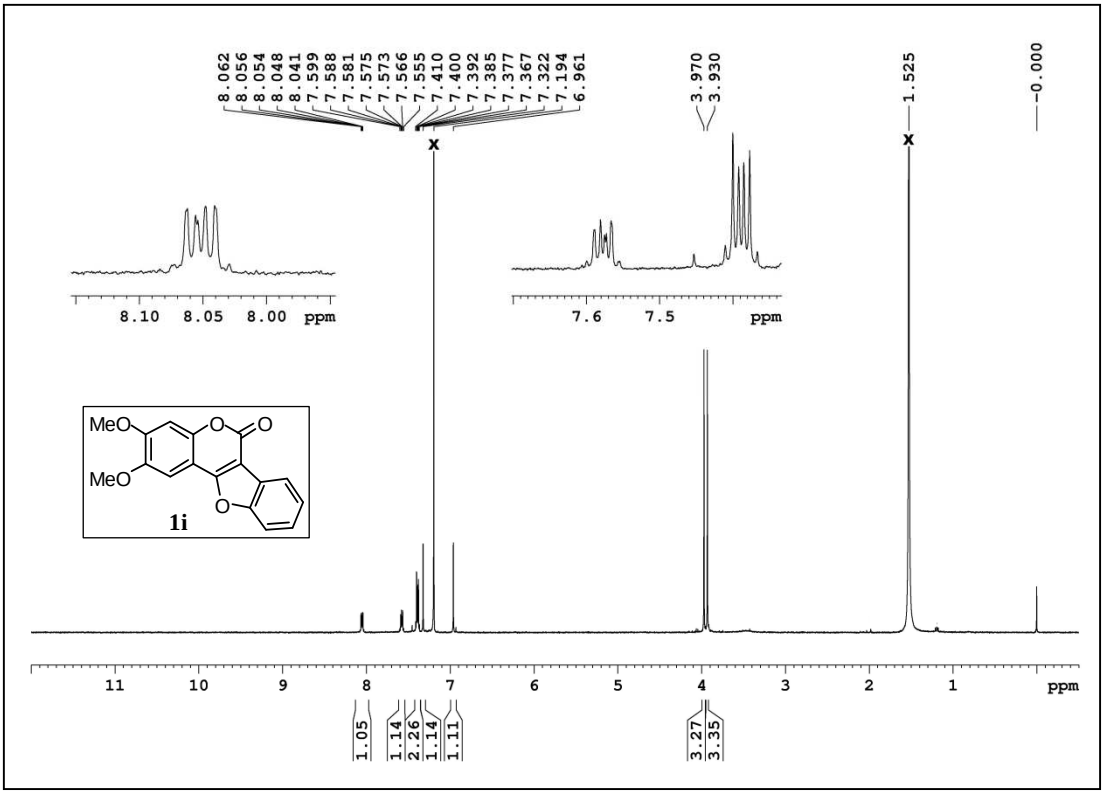
154.86
152.14
148.75
145.84
142.24
130.80
129.44
122.43
122.35
118.83
115.52
111.58
108.70
99.50
56.08
55.83
39.59
39.39
39.18
38.97
38.76
38.55
38.34
MeO
MeO
O
O
HO
52i
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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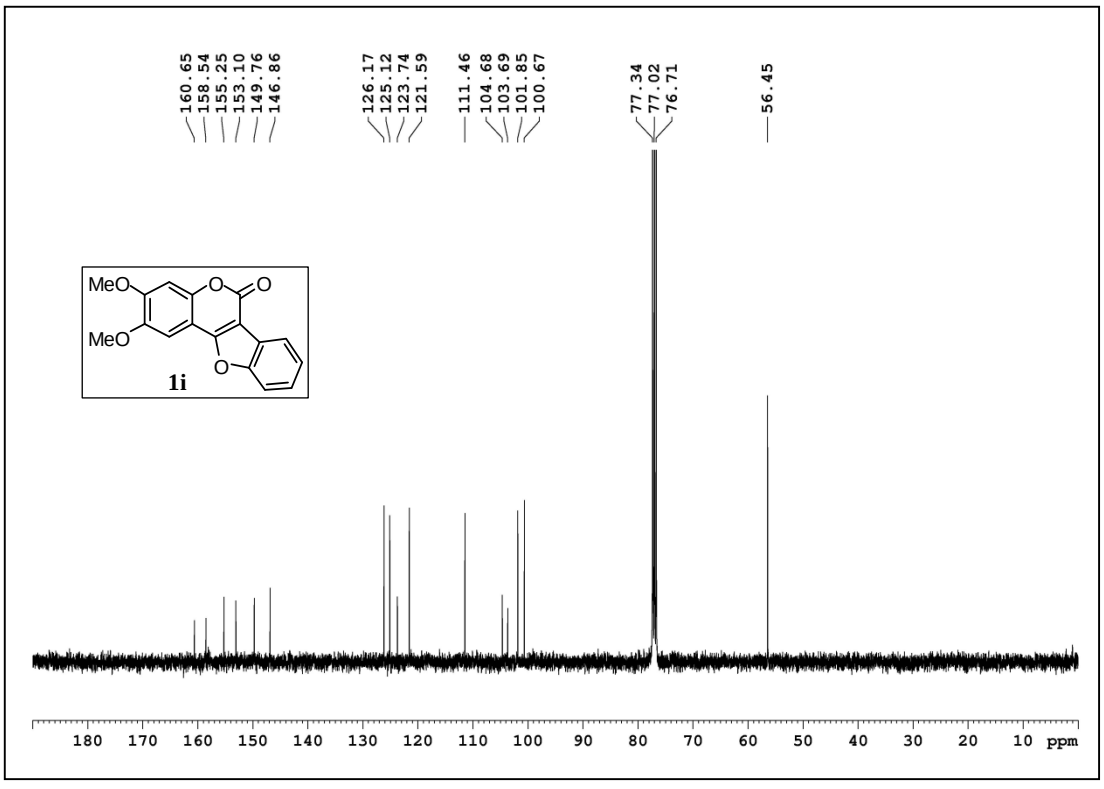
8.056
8.054
8.048
8.041
7.599
7.588
7.581
7.575
7.573
7.566
7.555
7.410
7.400
7.392
7.385
7.377
7.367
7.322
7.194
6.961
3.970
3.930
1.525
0.000
8.10 8.05 8.00 ppm
7.6 7.5 ppm
MeO
MeO
O
O
O
1i
11 10 9 8 7 6 5 4 3 2 1 ppm
1.05
1.14
2.26
1.14
1.11
3.27
3.35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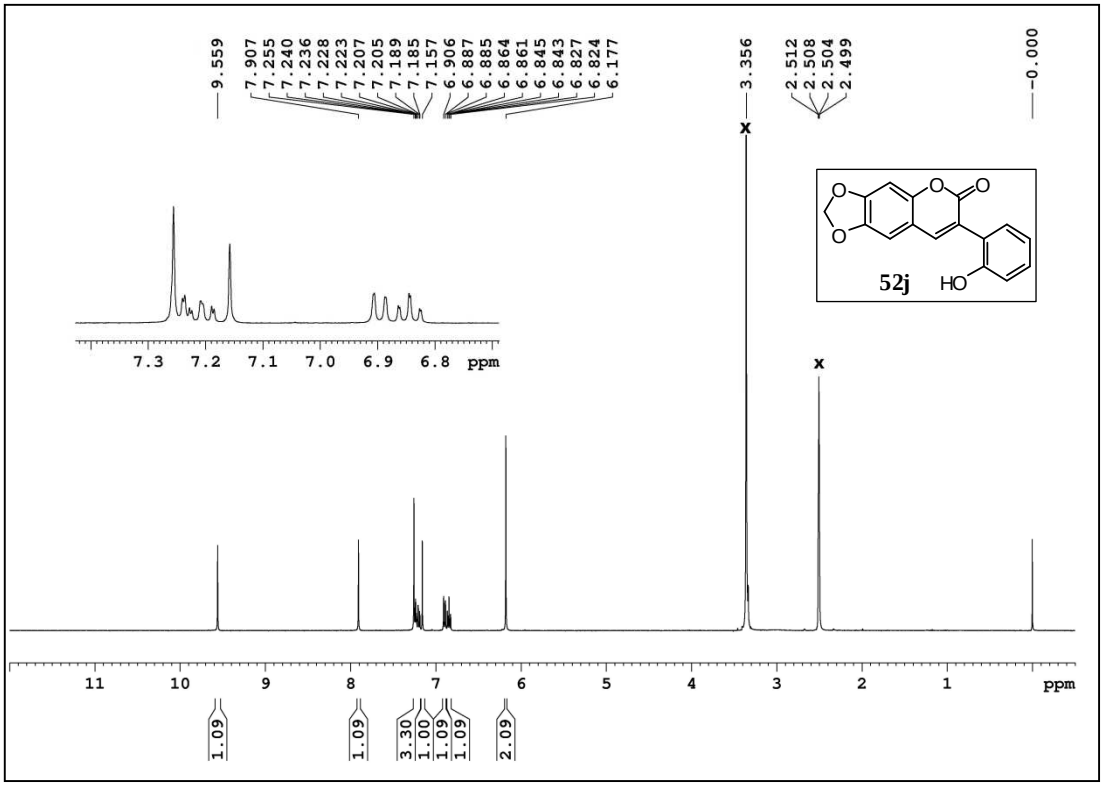
158.54
155.25
153.10
149.76
146.86
126.17
125.12
123.74
121.59
111.46
104.68
103.69
101.85
100.67
77.34
77.02
76.71
56.45
MeO
MeO
O
O
O
1i
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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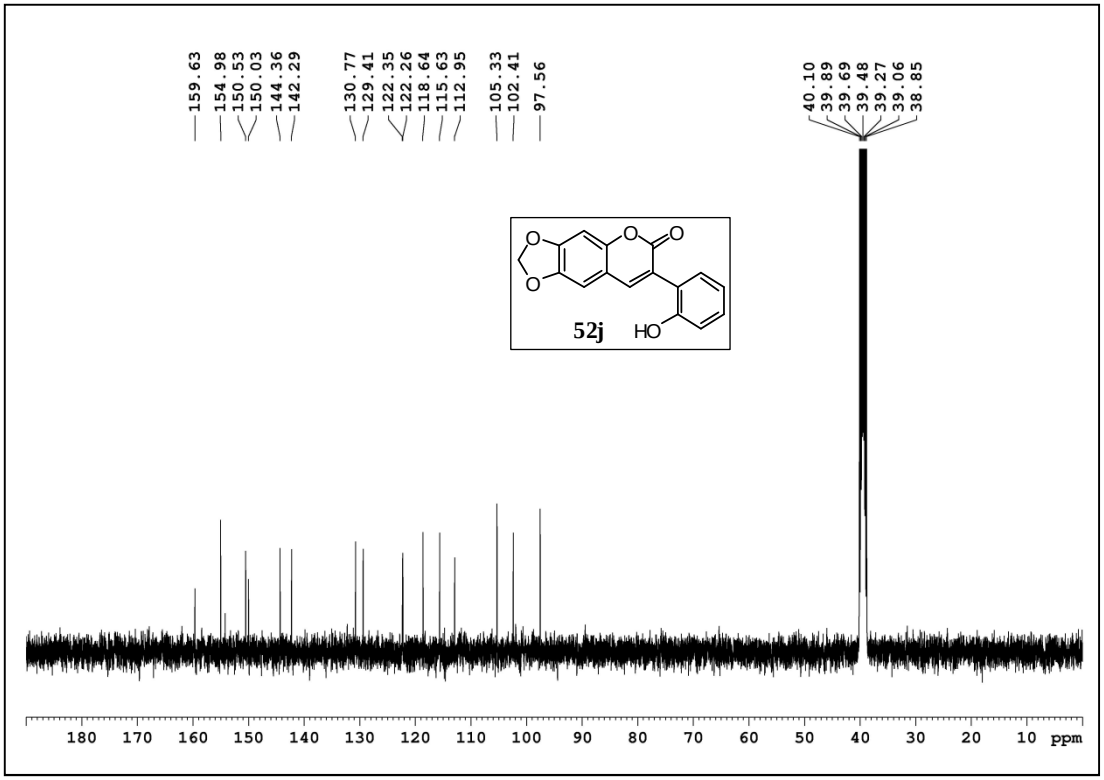
7.907
7.255
7.240
7.236
7.228
7.223
7.207
7.205
7.189
7.185
7.157
6.906
6.887
6.885
6.864
6.861
6.845
6.843
6.827
6.824
6.177
3.356
2.512
2.508
2.504
2.499
-0.000
52j
HO
ppm
1.09
1.09
3.30
1.00
1.09
1.09
2.09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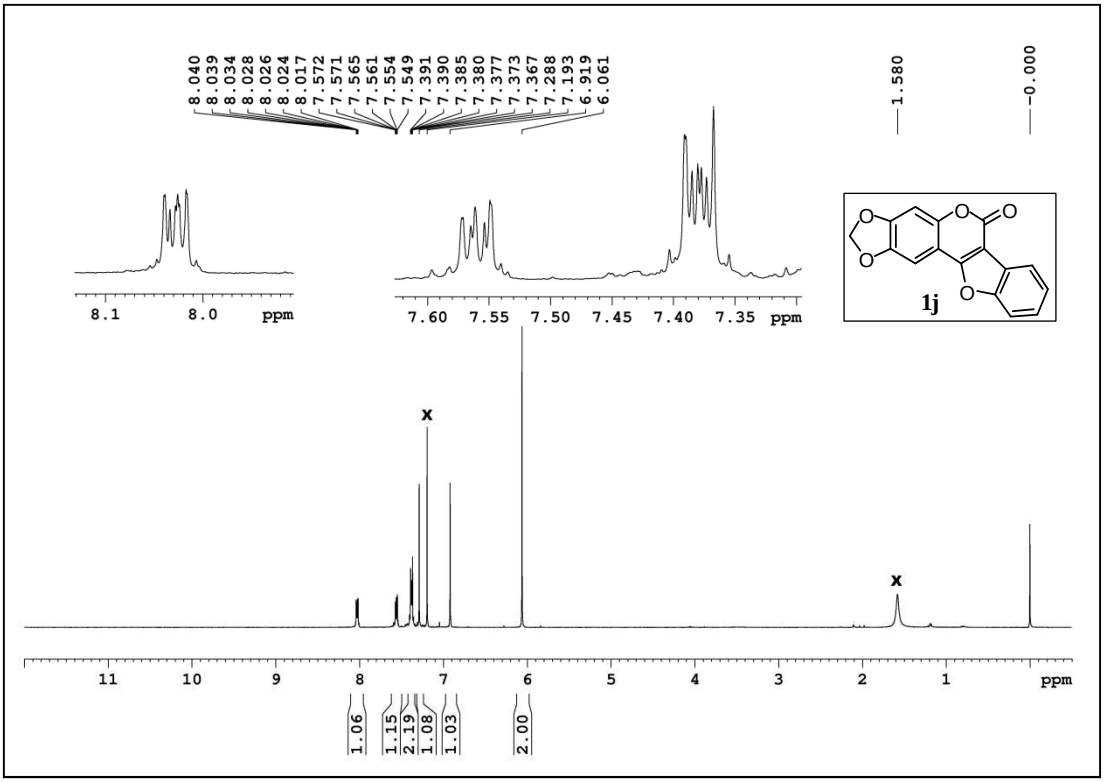
154.98
150.53
150.03
144.36
142.29
130.77
129.41
122.35
122.26
118.64
115.63
112.95
105.33
102.41
97.56
40.10
39.89
39.69
39.48
39.27
39.06
38.85
52j
HO
ppm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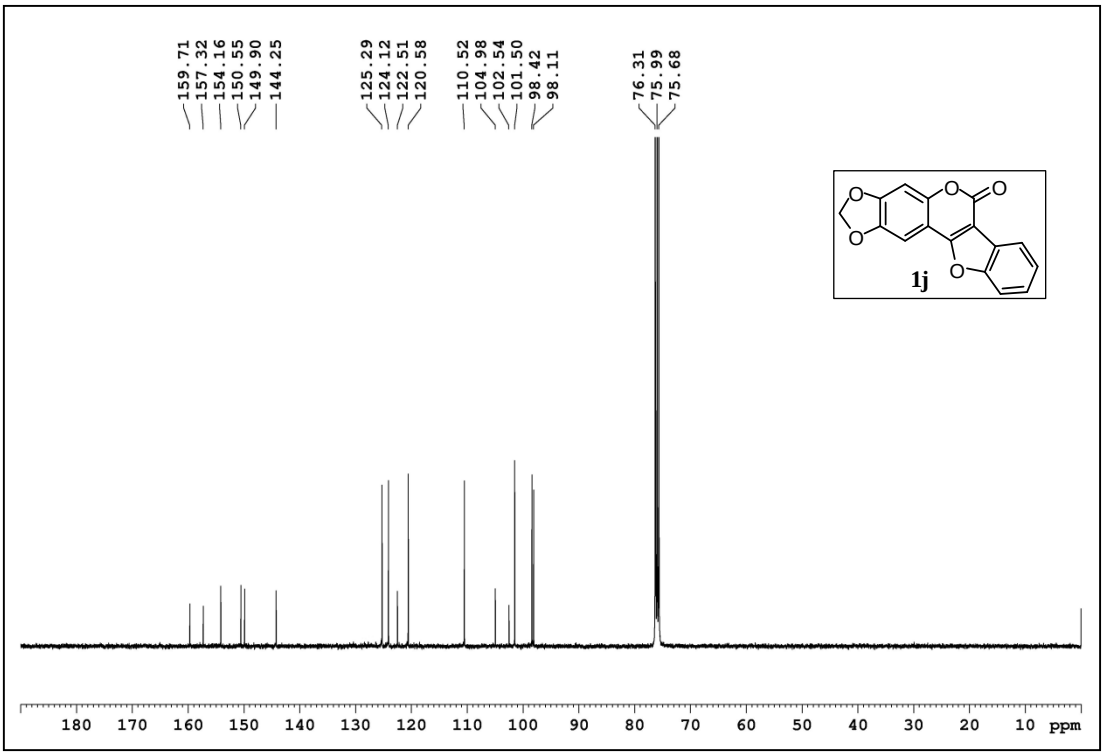
8.039
8.034
8.028
8.026
8.024
8.017
7.572
7.571
7.565
7.561
7.554
7.549
7.391
7.390
7.385
7.380
7.377
7.373
7.367
7.288
7.193
6.919
6.061
1.580
0.000
8.1
8.0
ppm
7.60
7.55
7.50
7.45
7.40
7.35
ppm
1j
x
x
11
10
9
8
7
6
5
4
3
2
1
ppm
1.06
1.15
2.19
1.08
1.03
2.00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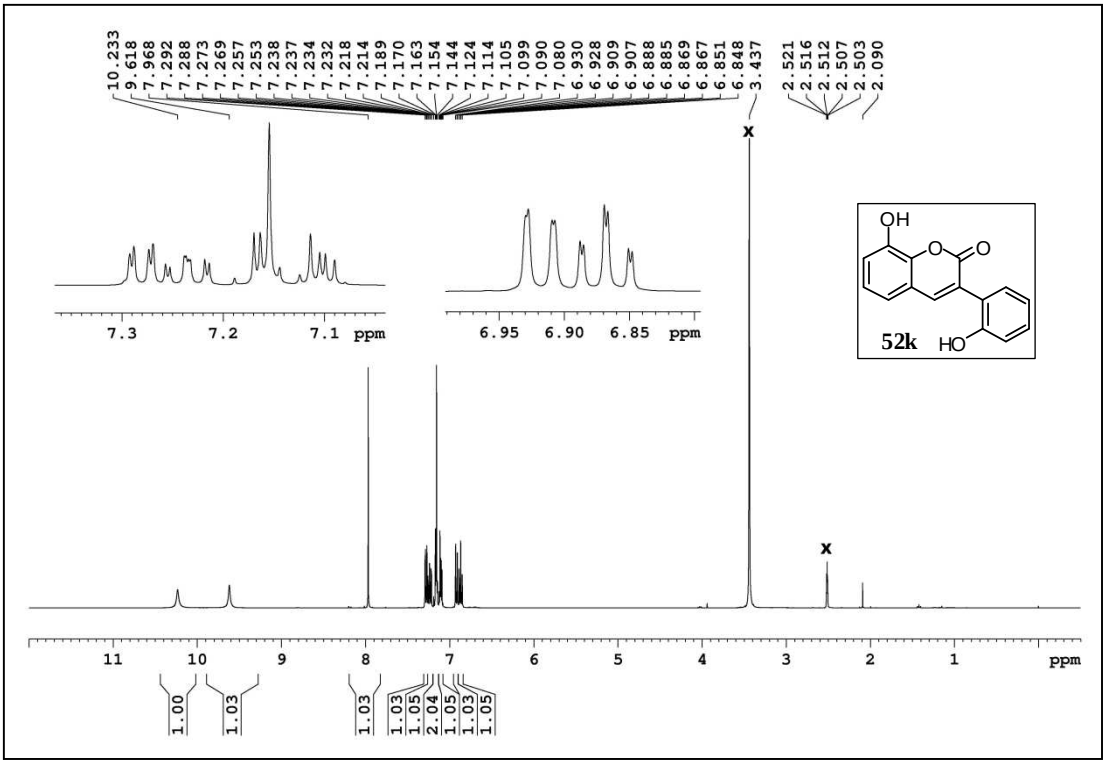
154.16
150.55
149.90
144.25
125.29
124.12
122.51
120.58
110.52
104.98
102.54
101.50
98.42
98.11
76.31
75.99
75.68
1j
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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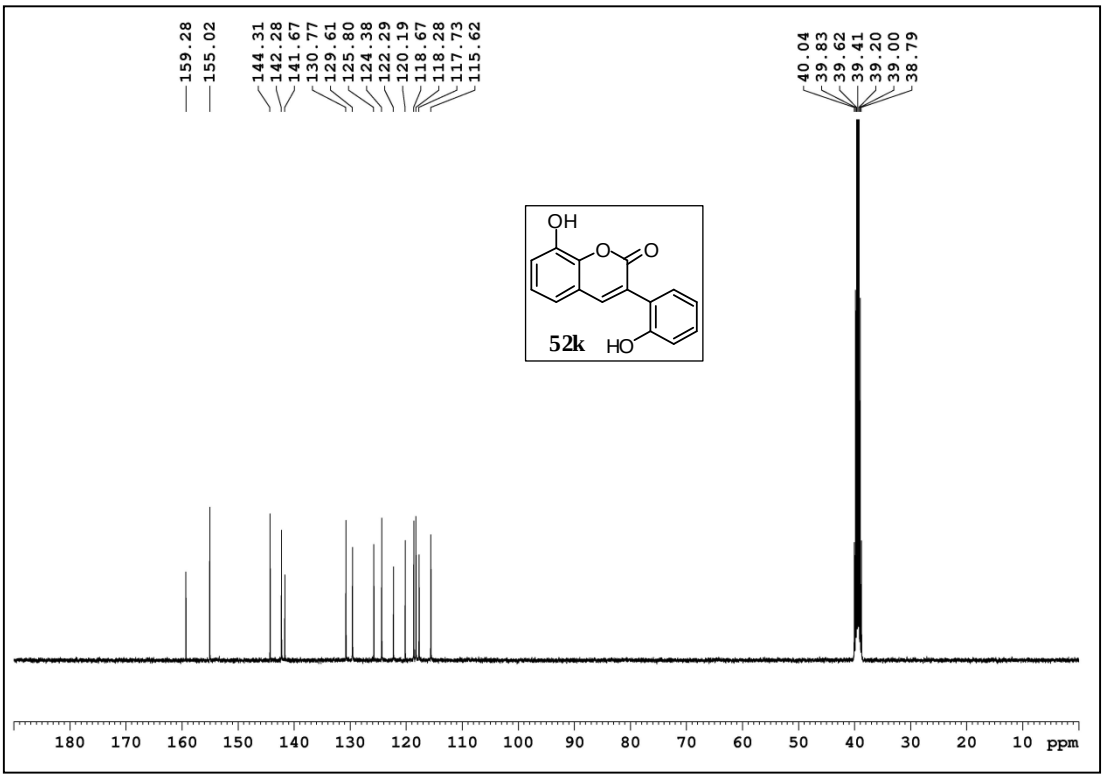
7.288
7.273
7.269
7.257
7.253
7.238
7.237
7.234
7.232
7.218
7.214
7.189
7.170
7.163
7.154
7.144
7.124
7.114
7.105
7.099
7.090
7.080
6.930
6.928
6.909
6.907
6.888
6.885
6.869
6.867
6.851
6.848
3.437
2.521
2.516
2.512
2.507
2.503
2.090
7.3
7.2
7.1 ppm
6.95
6.90
6.85 ppm
OH
O
O
52k
HO
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.03
1.03
1.03
1.05
2.04
1.05
1.03
1.05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144.31
142.28
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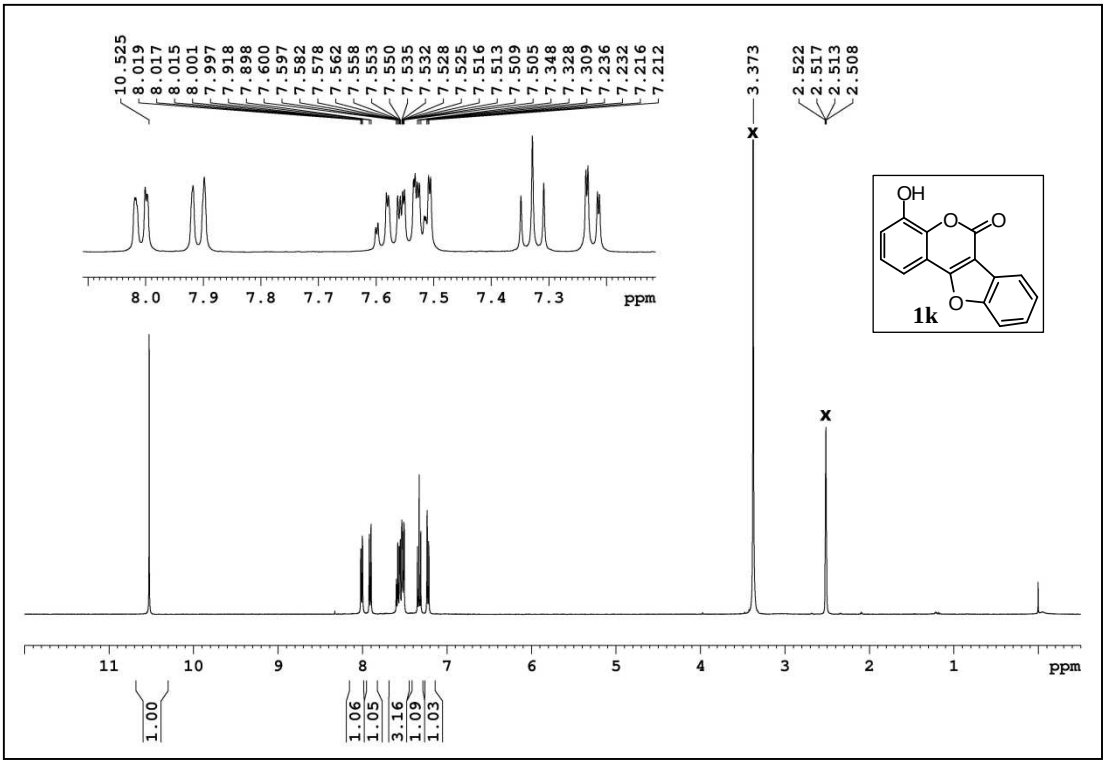
130.77
129.61
125.80
124.38
122.29
120.19
118.67
118.28
117.73
115.62
40.04
39.83
39.62
39.41
39.20
39.00
38.79
OH
O
O
52k
HO
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10 ppm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8.017
8.015
8.001
7.997
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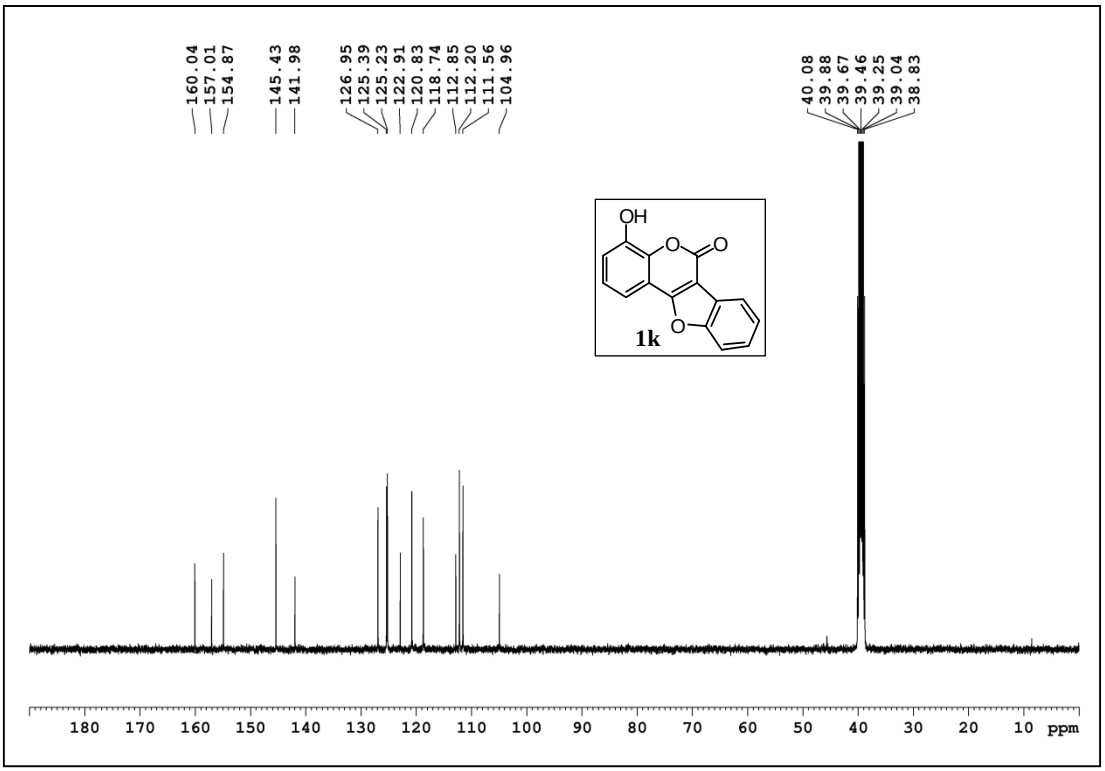
7.898
7.600
7.597
7.582
7.578
7.562
7.558
7.553
7.550
7.535
7.532
7.528
7.525
7.516
7.513
7.509
7.505
7.348
7.328
7.309
7.236
7.232
7.216
7.212
3.373
2.522
2.517
2.513
2.508
x
x
OH
O
O
O
1k
8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 ppm
11 10 9 8 7 6 5 4 3 2 1 ppm
1.00
1.06
1.05
3.16
1.09
1.03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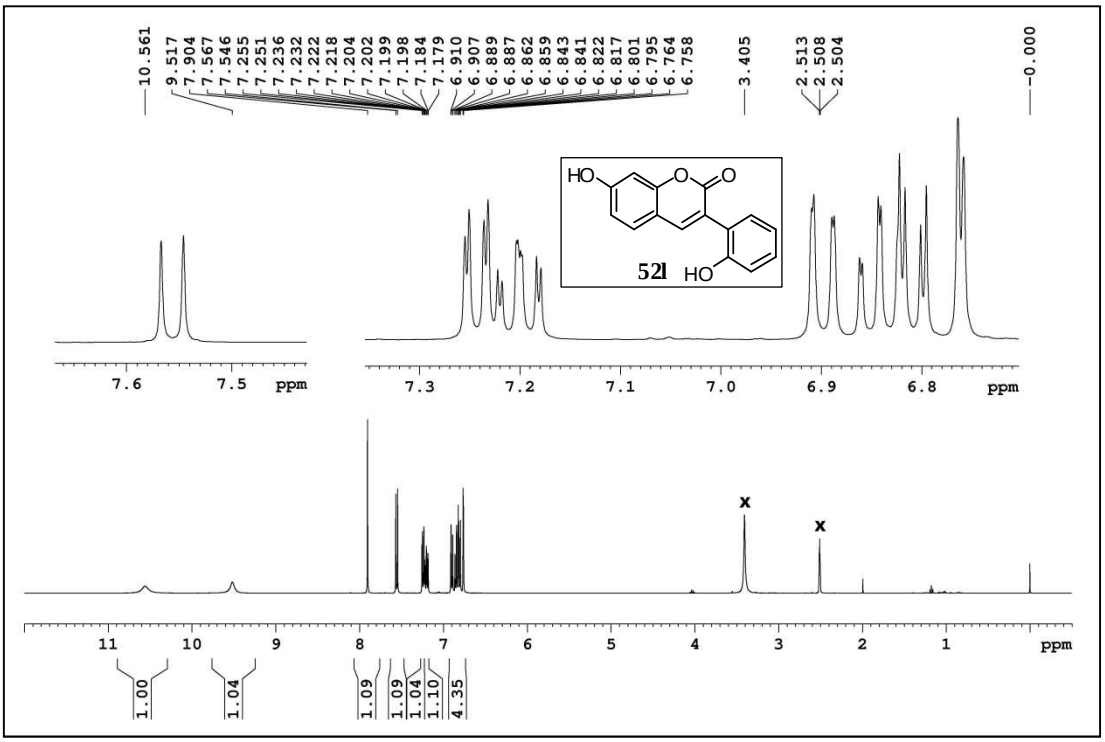
145.43
141.98
126.95
125.39
125.23
122.91
120.83
118.74
112.85
112.20
111.56
104.96
40.08
39.88
39.67
39.46
39.25
39.04
38.83
OH
O
O
O
1k
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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7.567
7.546
7.255
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7.236
7.232
7.222
7.218
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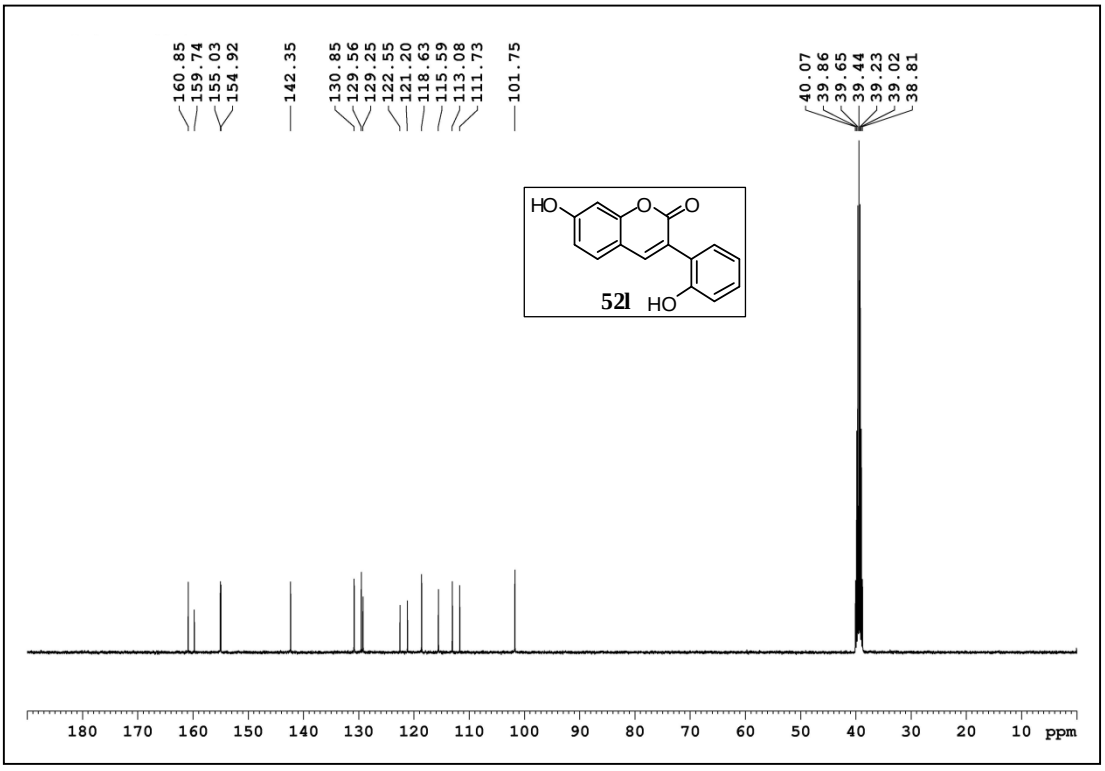
7.202
7.199
7.198
7.184
7.179
6.910
6.907
6.889
6.887
6.862
6.859
6.843
6.841
6.822
6.817
6.801
6.795
6.764
6.758
3.405
2.513
2.508
2.504
0.000
HO
O
O
HO
52l
7.6
7.5
ppm
7.3
7.2
7.1
7.0
6.9
6.8
ppm
x
x
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.04
1.09
1.09
1.04
1.10
4.35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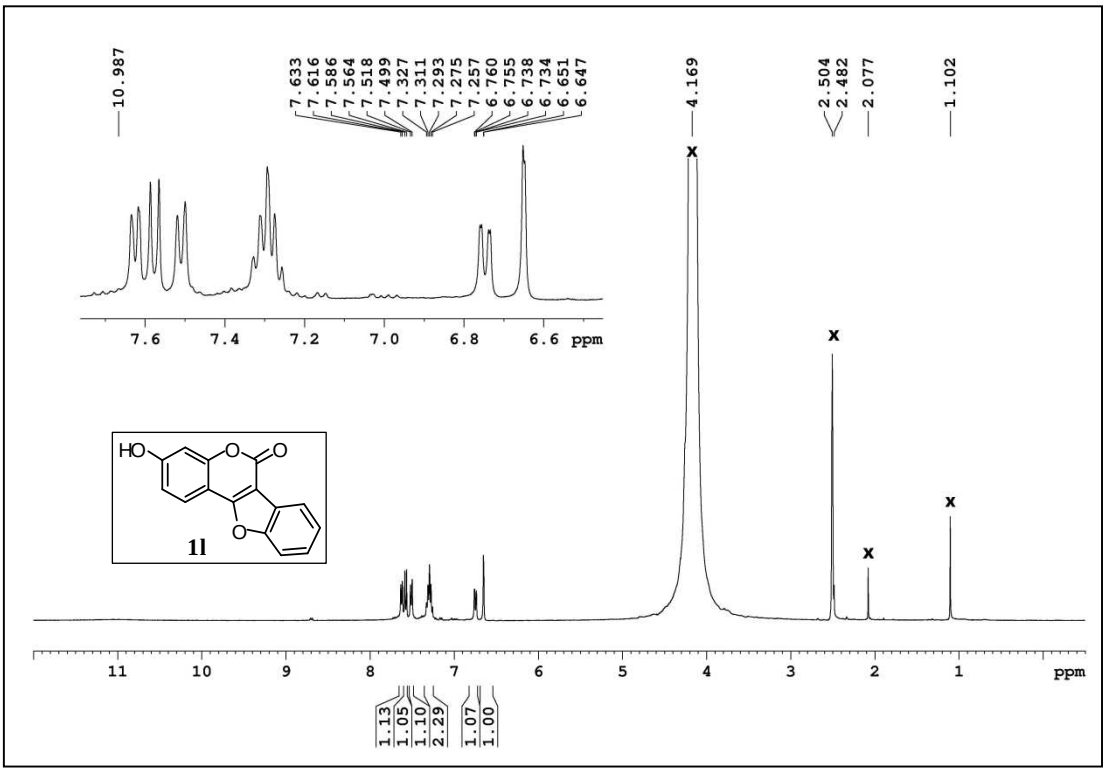
154.92
142.35
130.85
129.56
129.25
122.55
121.20
118.63
115.59
113.08
111.73
101.75
40.07
39.86
39.65
39.44
39.23
39.02
38.81
HO
O
O
HO
52l
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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7.518
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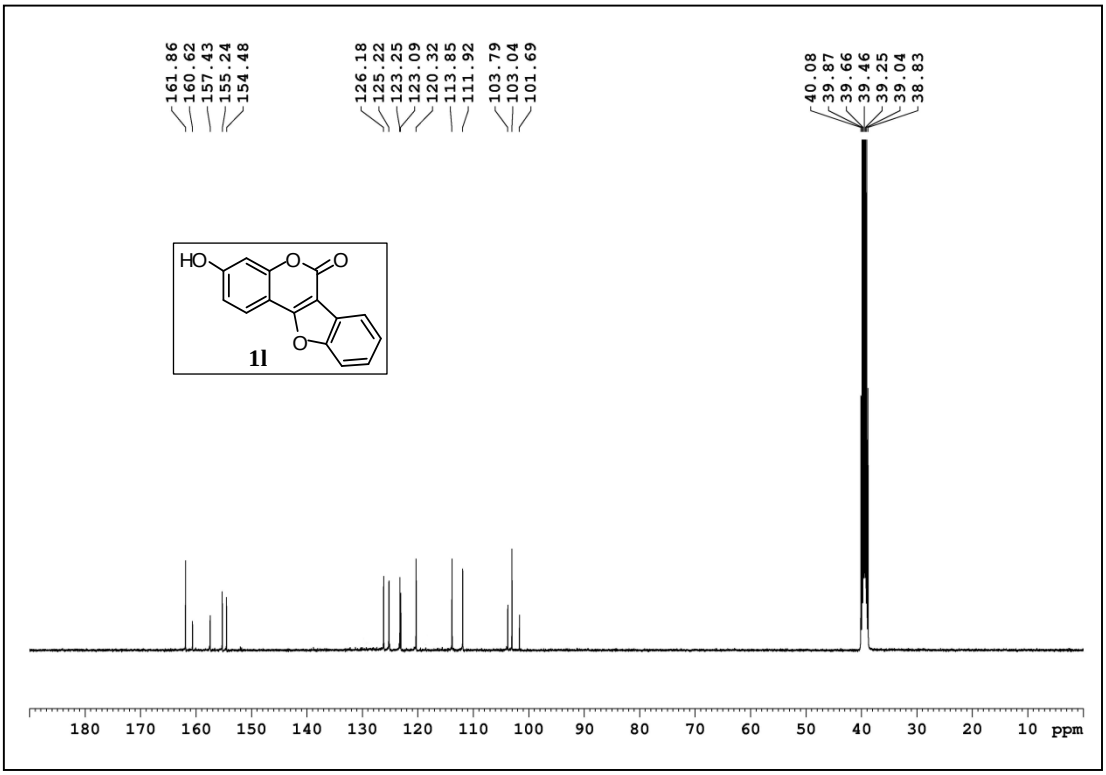
7.327
7.311
7.293
7.275
7.257
6.760
6.755
6.738
6.734
6.651
6.647
4.169
2.504
2.482
2.077
1.102
7.6
7.4
7.2
7.0
6.8
6.6 ppm
HO
O
O
O
1l
11
10
9
8
7
6
5
4
3
2
1
ppm
1.13
1.05
1.10
2.29
1.07
1.00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160.62
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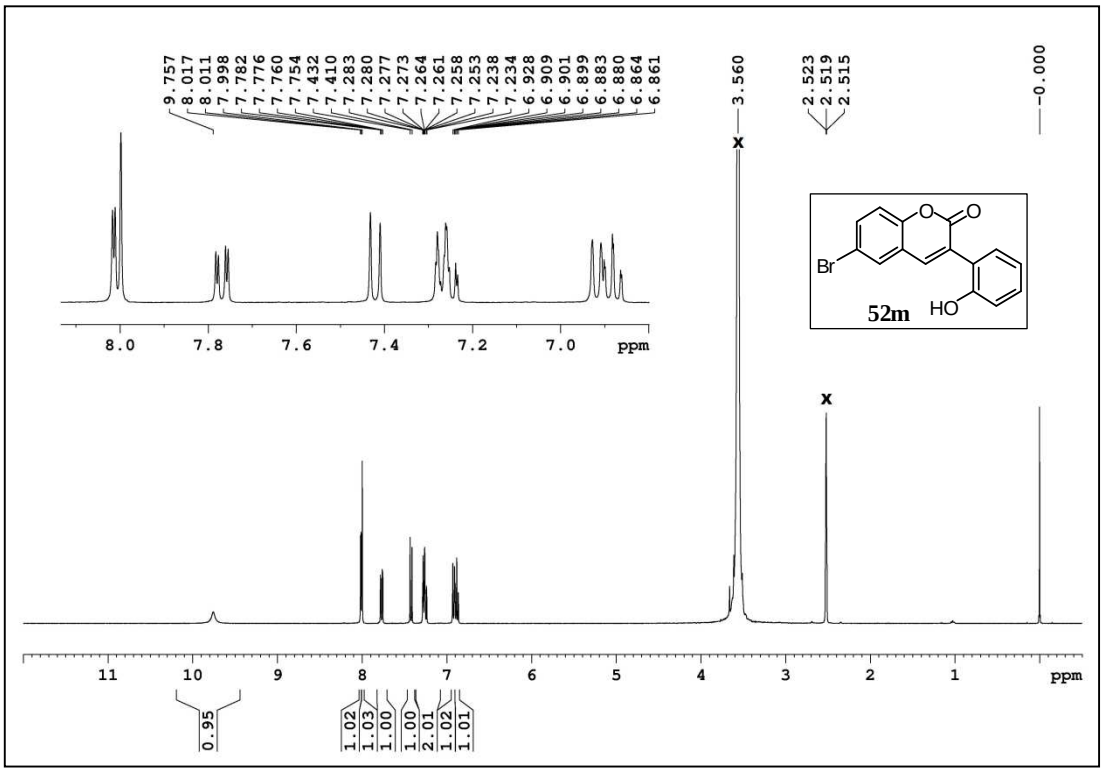
154.48
126.18
125.22
123.25
123.09
120.32
113.85
111.92
103.79
103.04
101.69
40.08
39.87
39.66
39.46
39.25
39.04
38.83
HO
O
O
O
1l
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10 ppm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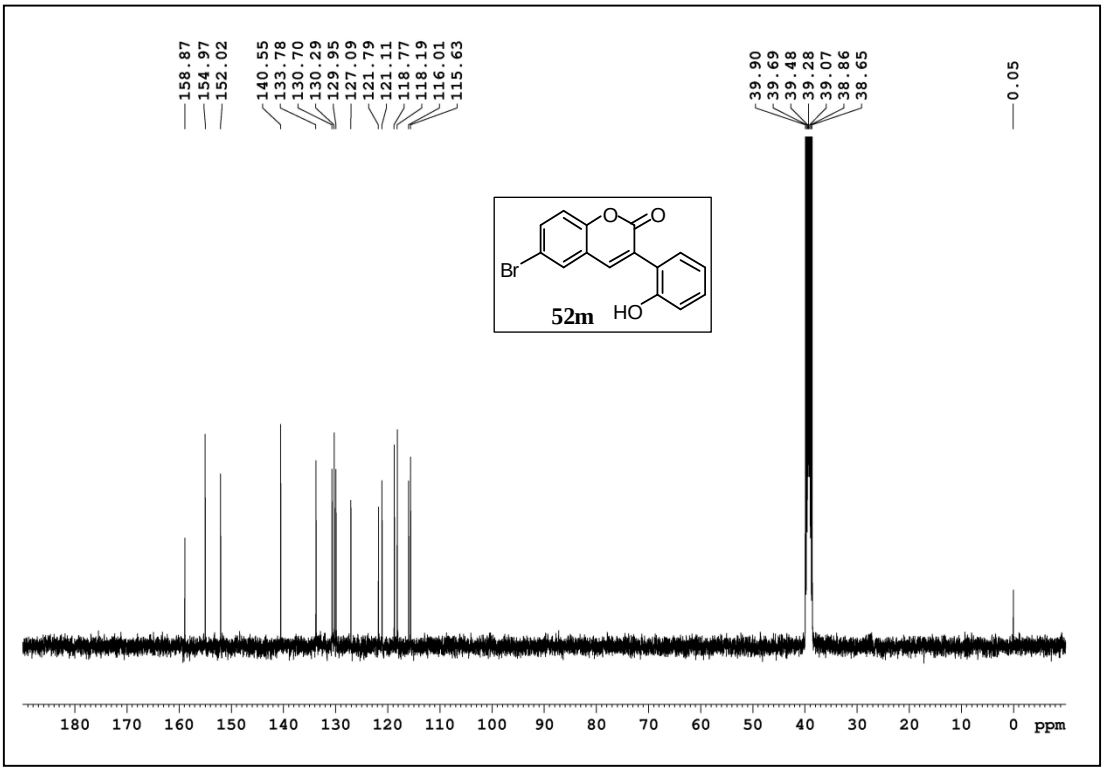
8.017
8.011
7.998
7.782
7.776
7.760
7.754
7.432
7.410
7.283
7.280
7.277
7.273
7.264
7.261
7.258
7.253
7.238
7.234
6.928
6.909
6.901
6.899
6.883
6.880
6.864
6.861
3.560
2.523
2.519
2.515
0.000
x
x
Br
O
O
HO
52m
8.0
7.8
7.6
7.4
7.2
7.0
ppm
11
10
9
8
7
6
5
4
3
2
1
ppm
0.95
1.02
1.03
1.00
1.00
2.01
1.02
1.01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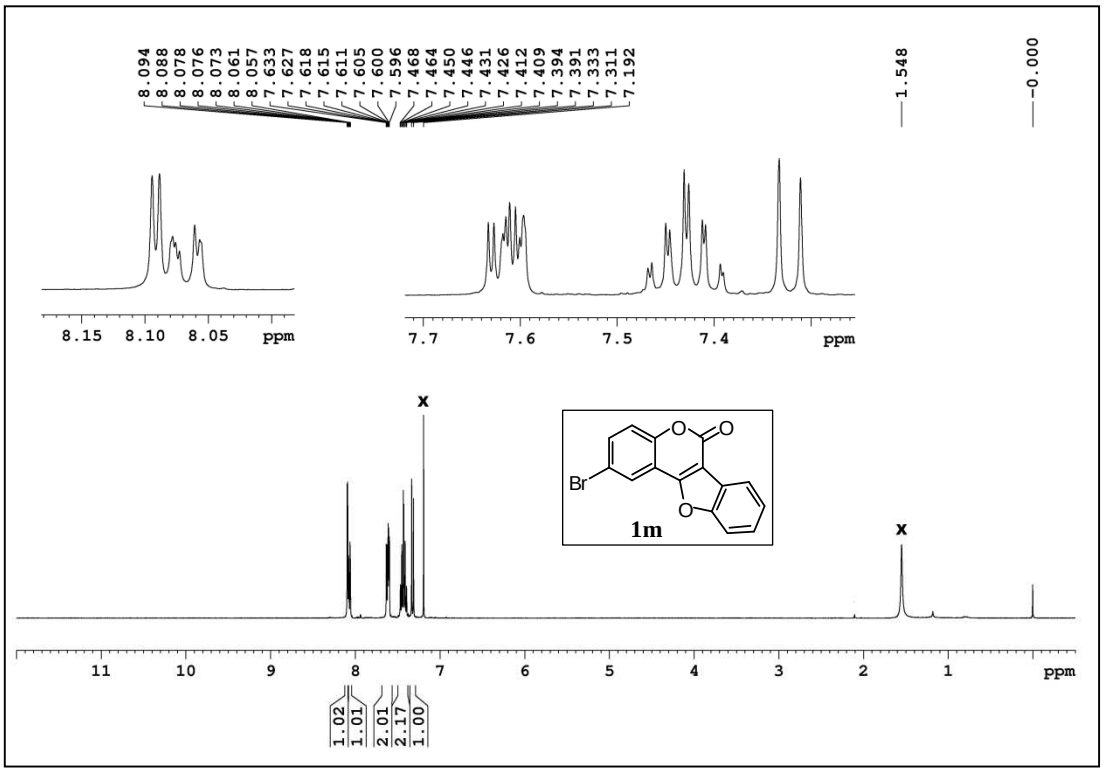
154.97
152.02
140.55
133.78
130.70
130.29
129.95
127.09
121.79
121.11
118.77
118.19
116.01
115.63
39.90
39.69
39.48
39.28
39.07
38.86
38.65
0.05
Br
O
O
HO
52m
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm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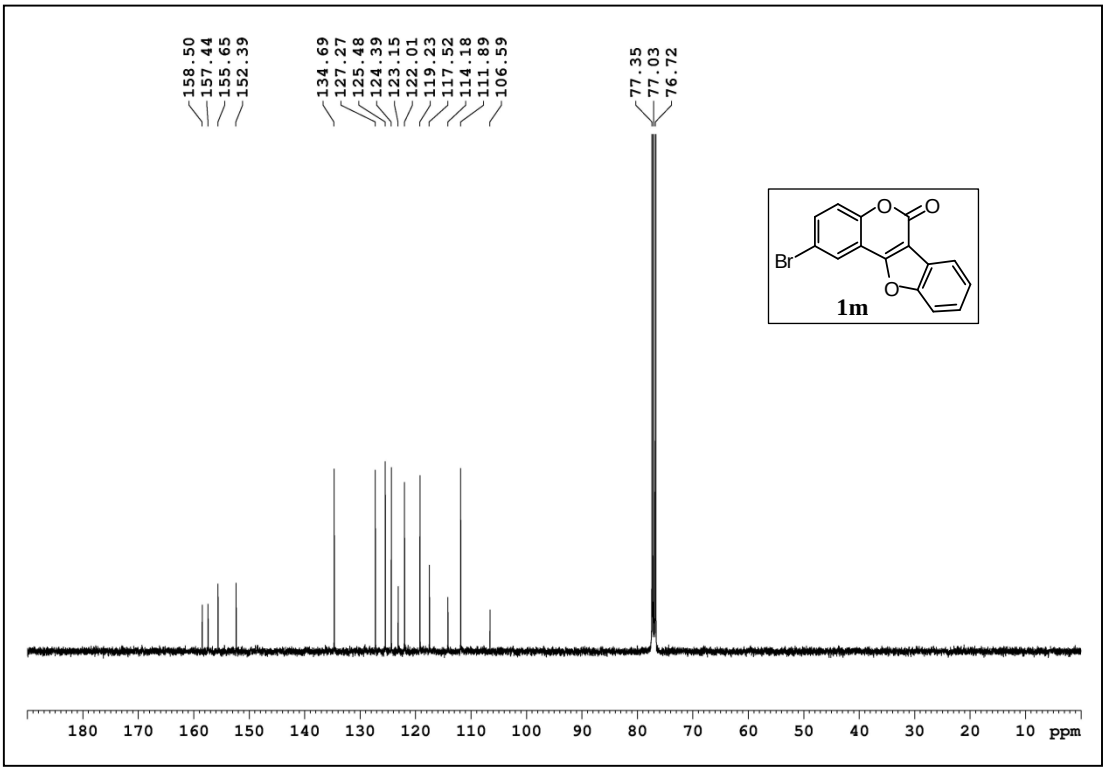
8.088
8.078
8.076
8.073
8.061
8.057
7.633
7.627
7.618
7.615
7.611
7.605
7.600
7.596
7.468
7.464
7.450
7.446
7.431
7.426
7.412
7.409
7.394
7.391
7.333
7.311
7.192
1.548
0.000
8.15 8.10 8.05 ppm
7.7 7.6 7.5 7.4 ppm
x
x
Br
O
O
O
1m
11 10 9 8 7 6 5 4 3 2 1 ppm
1.02
1.01
2.01
2.17
1.00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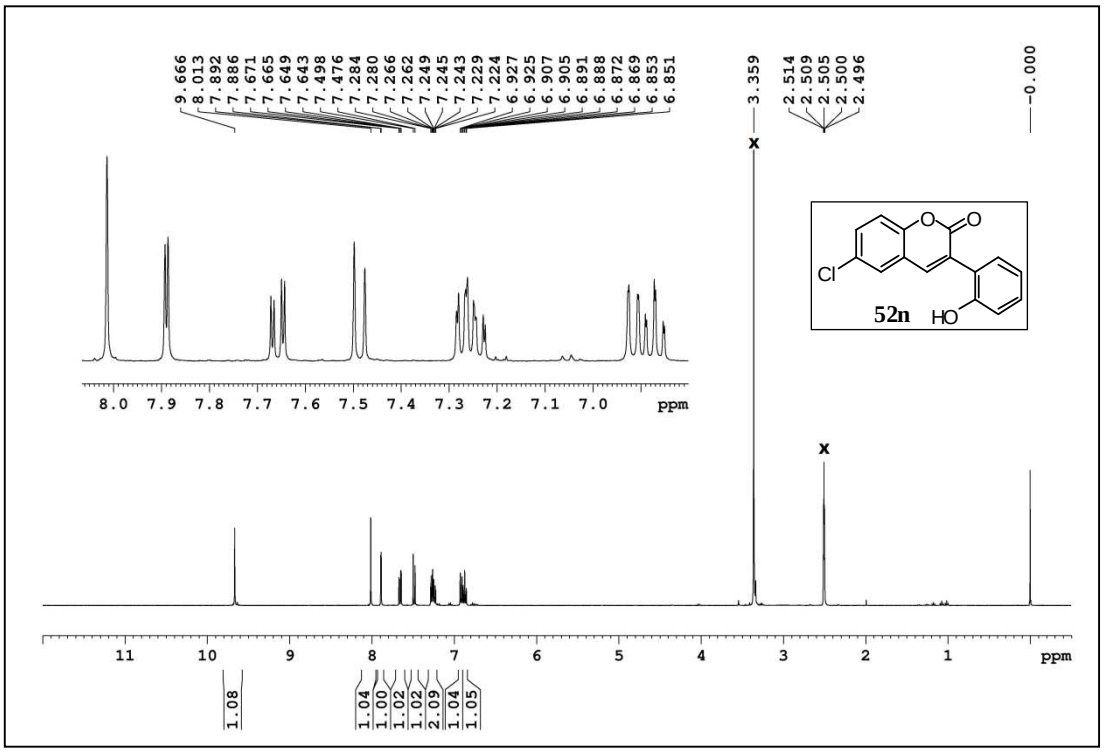
157.44
155.65
152.39
134.69
127.27
125.48
124.39
123.15
122.01
119.23
117.52
114.18
111.89
106.59
77.35
77.03
76.72
Br
O
O
O
1m
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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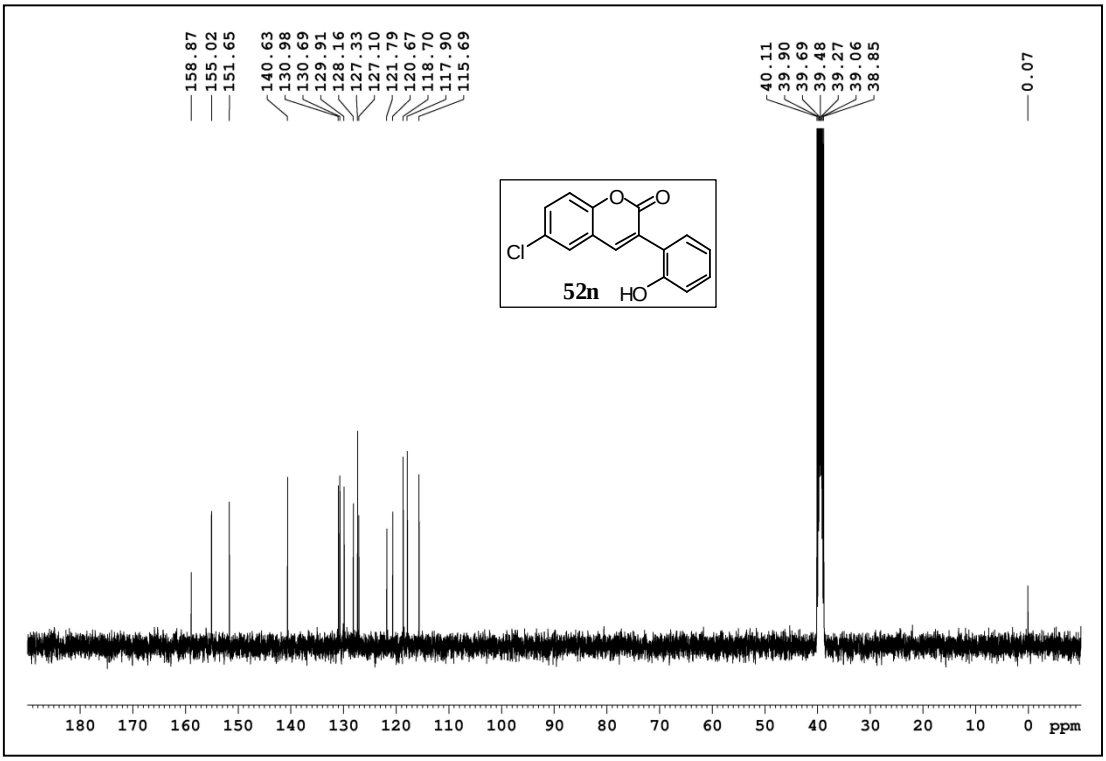
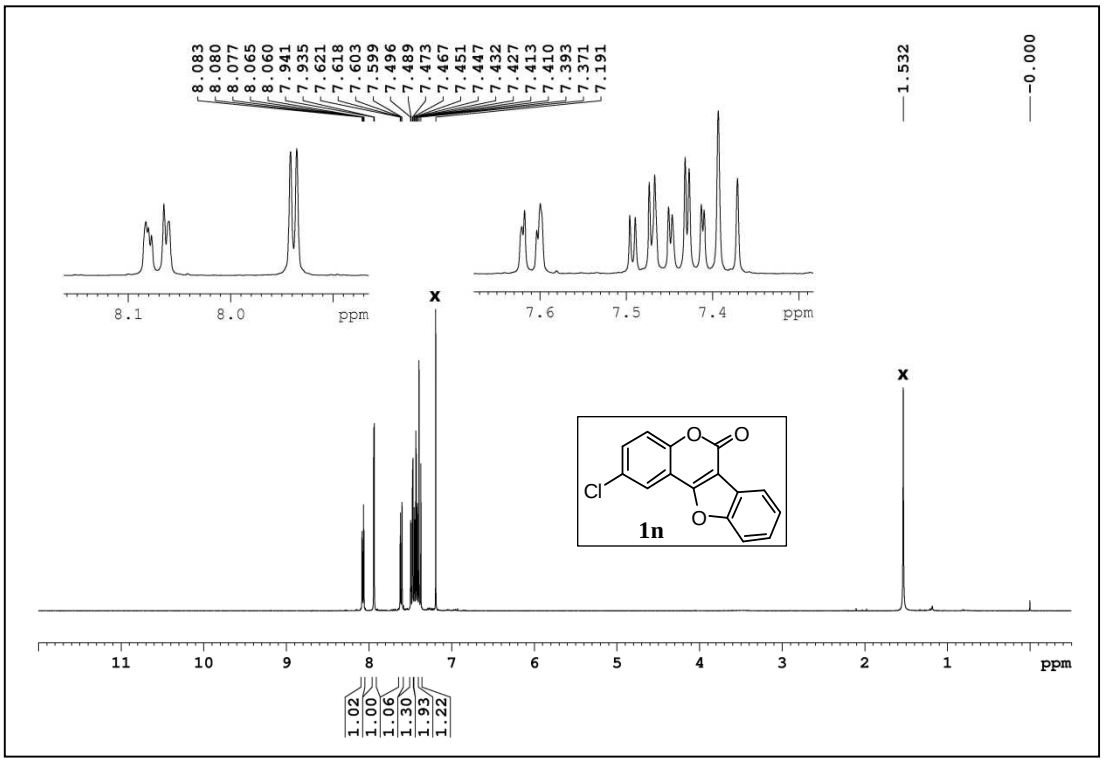
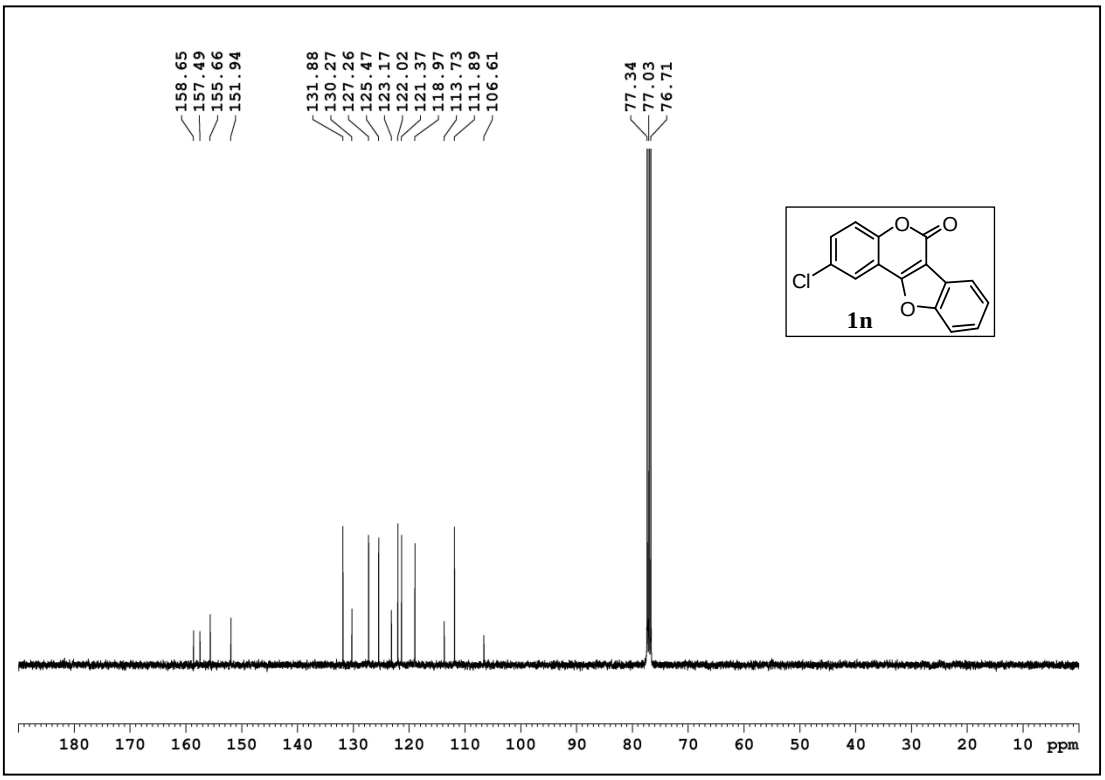
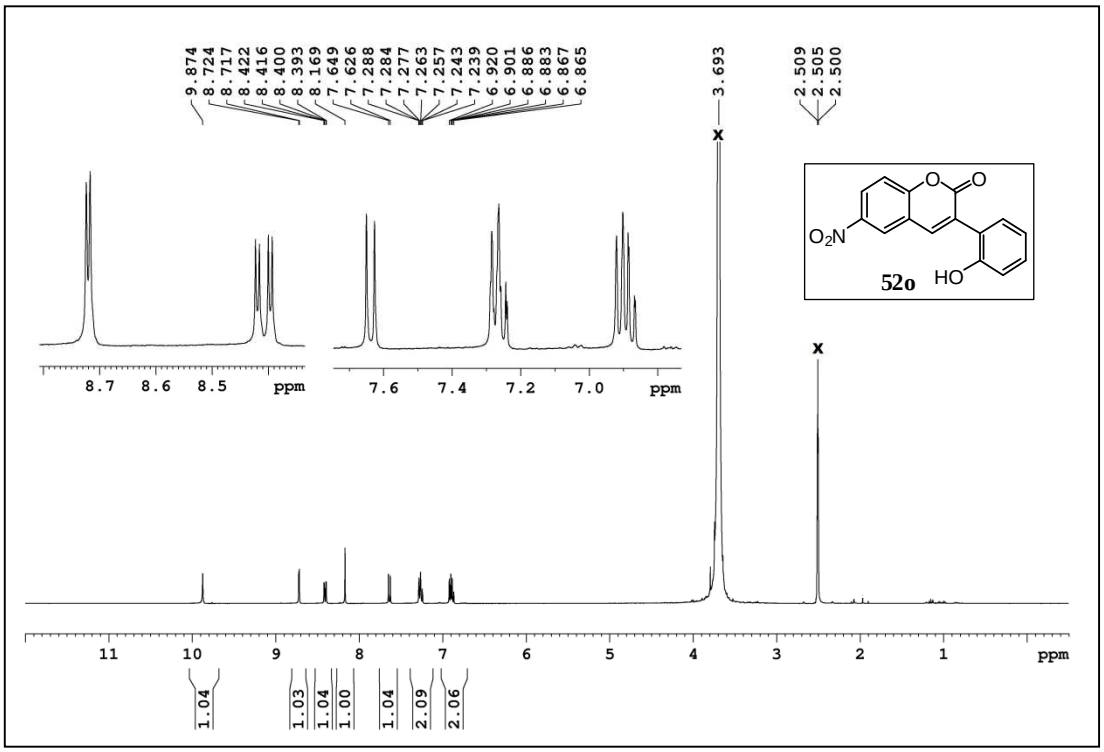
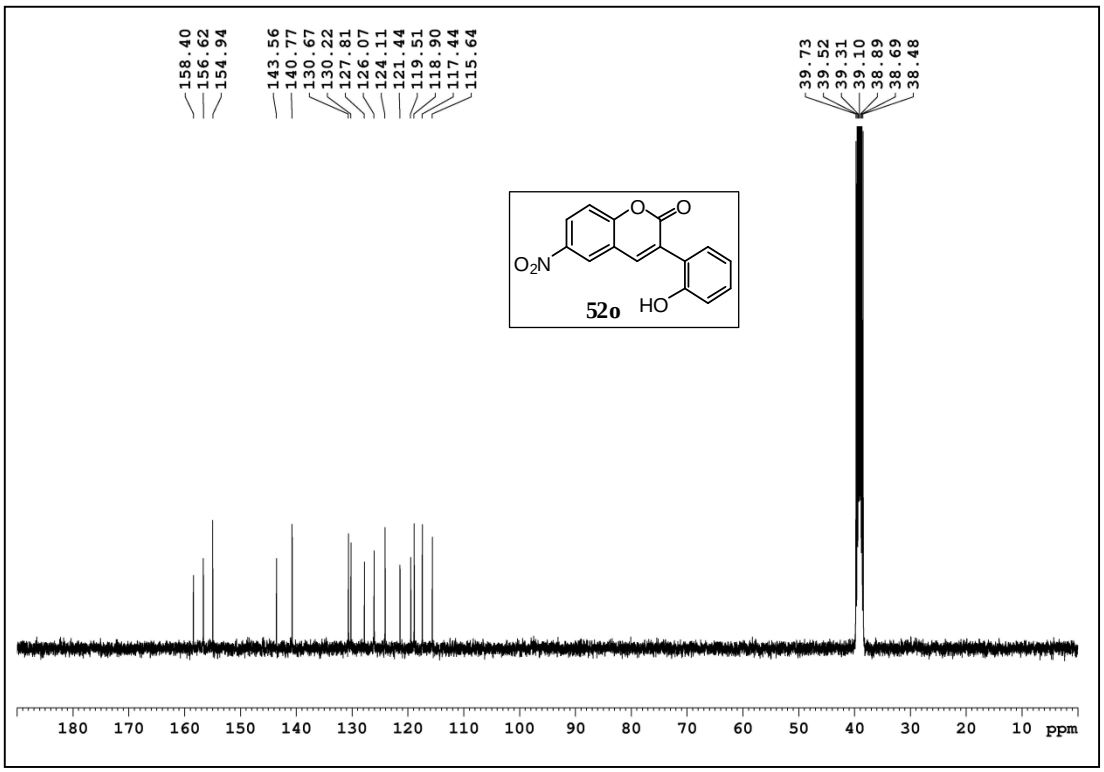
8.013
7.892
7.886
7.671
7.665
7.649
7.643
7.498
7.476
7.284
7.280
7.266
7.262
7.249
7.245
7.243
7.229
7.224
6.927
6.925
6.907
6.905
6.891
6.888
6.872
6.869
6.853
6.851
3.359
2.514
2.509
2.505
2.500
2.496
-0.000
x
x
Cl
O
O
HO
52n
8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 ppm
11 10 9 8 7 6 5 4 3 2 1 ppm
1.08
1.04
1.00
1.02
1.02
2.09
1.04
1.05


158.87
155.02
151.65
140.63
130.98
130.69
129.91
128.16
127.33
127.10
121.79
120.67
118.70
117.90
115.69
40.11
39.90
39.69
39.48
39.27
39.06
38.85
0.07
Cl
O
O
HO
52n
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


8.083
8.080
8.077
8.065
8.060
7.941
7.935
7.621
7.618
7.603
7.599
7.496
7.489
7.473
7.467
7.451
7.447
7.432
7.427
7.413
7.410
7.393
7.371
7.191
1.532
0.000
8.1
8.0
ppm
7.6
7.5
7.4
ppm
x
x
Cl
O
O
O
1n
11
10
9
8
7
6
5
4
3
2
1
ppm
1.02
1.00
1.06
1.30
1.93
1.22


158.65
157.49
155.66
151.94
131.88
130.27
127.26
125.47
123.17
122.02
121.37
118.97
113.73
111.89
106.61
77.34
77.03
76.71
Cl
O
O
O
1n
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


9.874
8.724
8.717
8.422
8.416
8.400
8.393
8.169
7.649
7.626
7.288
7.284
7.277
7.263
7.257
7.243
7.239
6.920
6.901
6.886
6.883
6.867
6.865
3.693
2.509
2.505
2.500
O2N
HO
52o
ppm
1.04
1.03
1.04
1.00
1.04
2.09
2.06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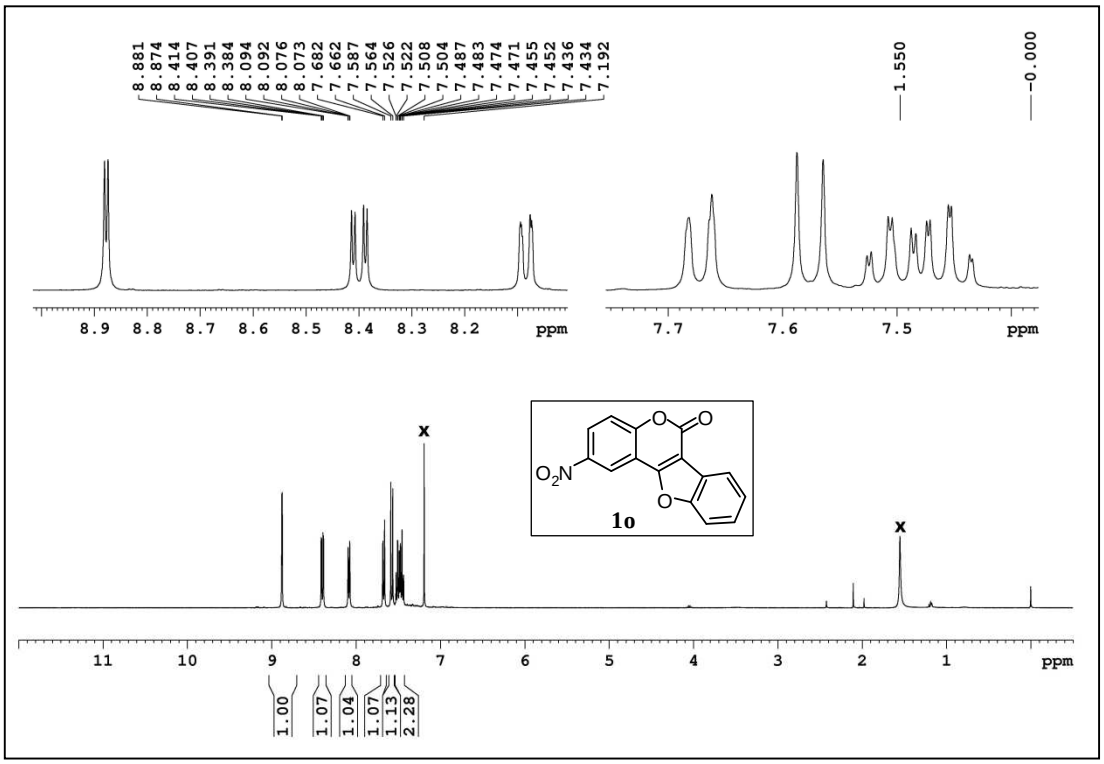
156.62
154.94
143.56
140.77
130.67
130.22
127.81
126.07
124.11
121.44
119.51
118.90
117.44
115.64
39.73
39.52
39.31
39.10
38.89
38.69
38.48
O2N
HO
52o
ppm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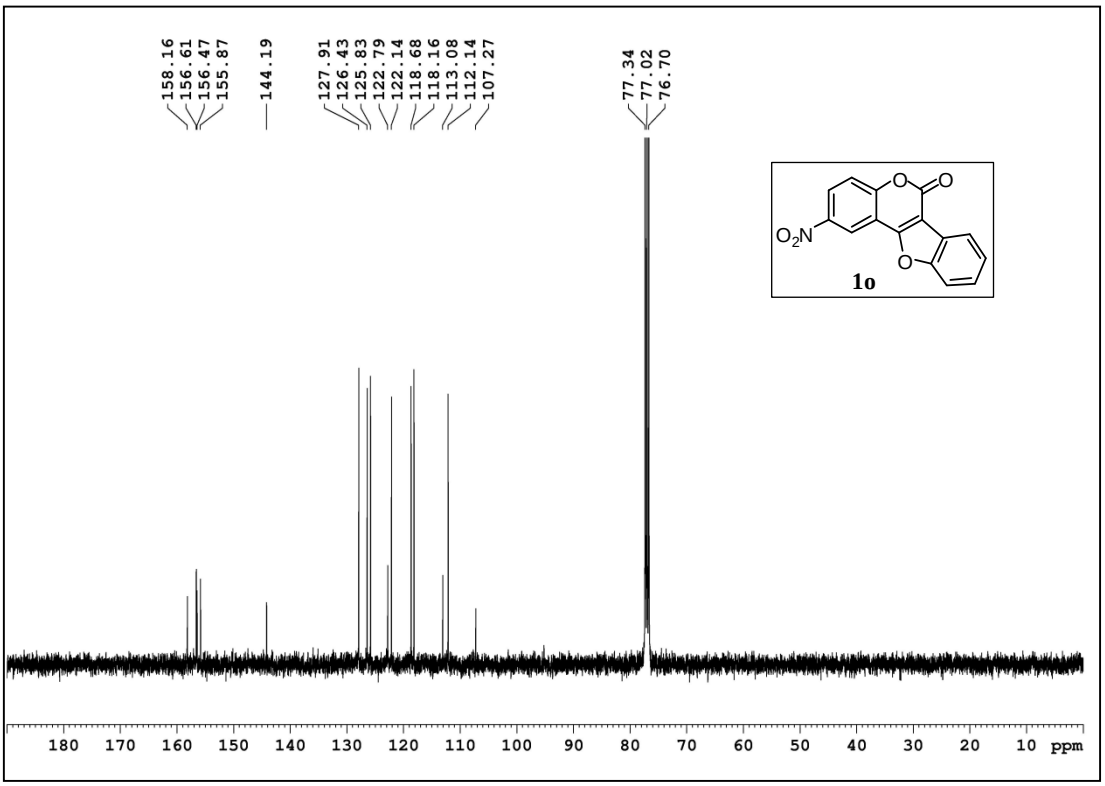
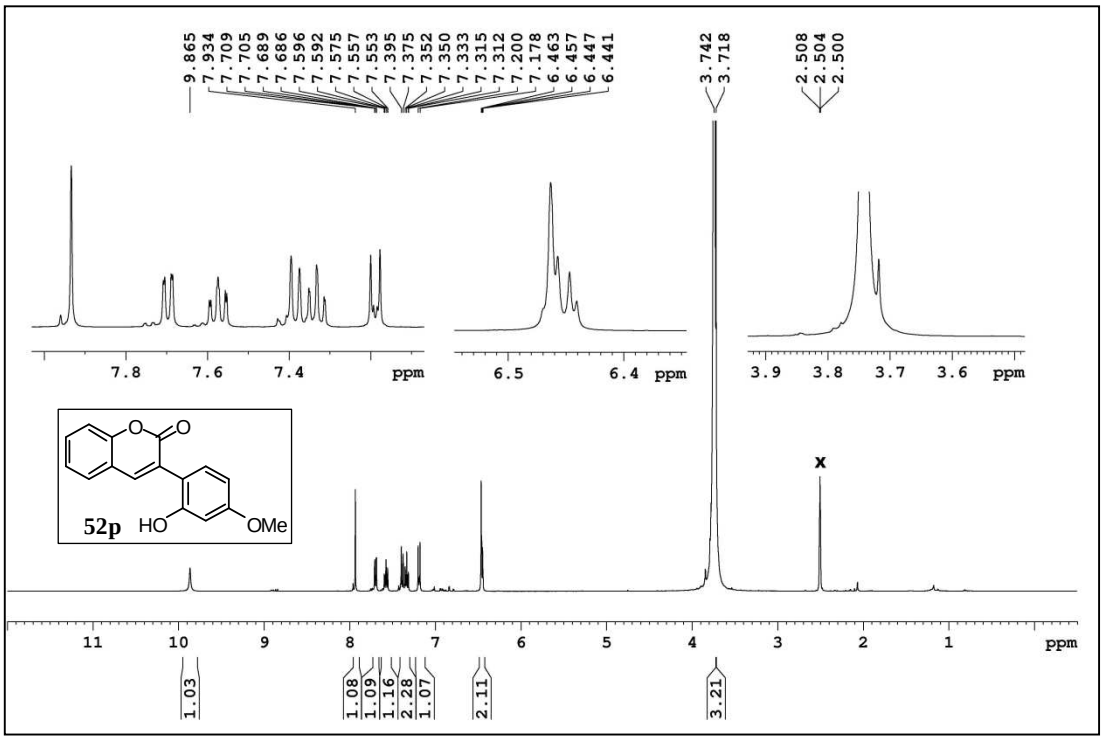
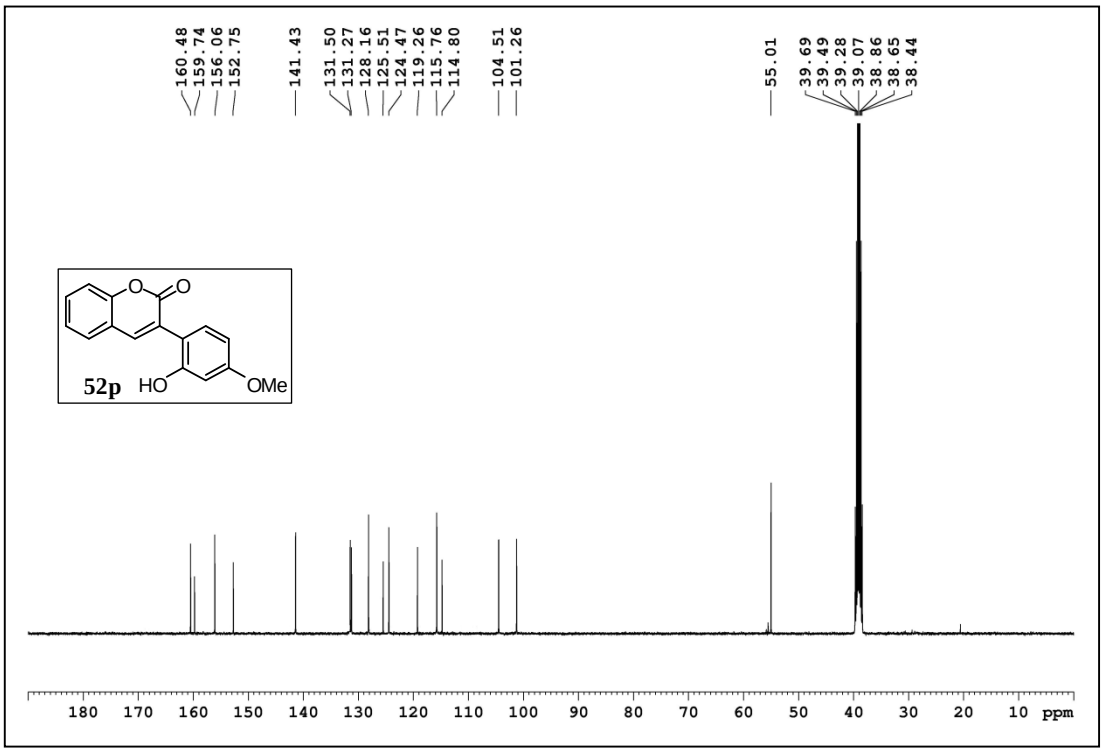
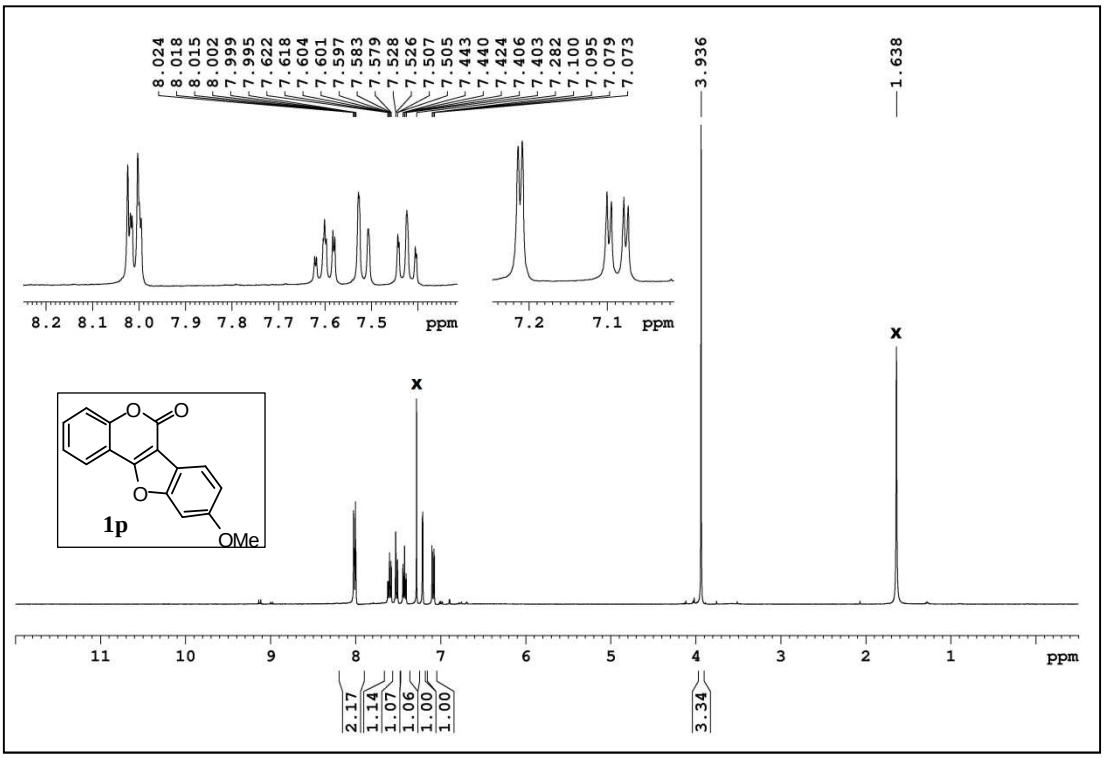
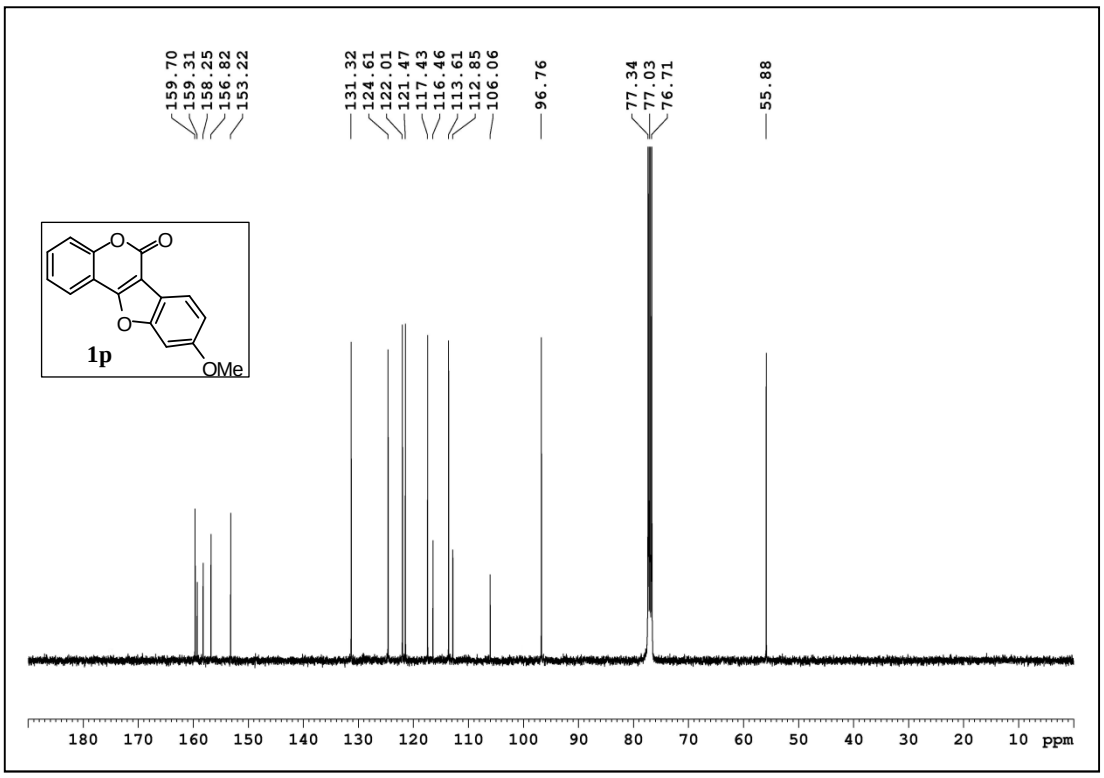
8.874
8.414
8.407
8.391
8.384
8.094
8.092
8.076
8.073
7.682
7.662
7.587
7.564
7.526
7.522
7.508
7.504
7.487
7.483
7.474
7.471
7.455
7.452
7.436
7.434
7.192
1.550
0.000
8.9 8.8 8.7 8.6 8.5 8.4 8.3 8.2 ppm
7.7 7.6 7.5 ppm
x
x
O2N
O
O
O
1o
11 10 9 8 7 6 5 4 3 2 1 ppm
1.00
1.07
1.04
1.07
1.13
2.28


158.16
156.61
156.47
155.87
144.19
127.91
126.43
125.83
122.79
122.14
118.68
118.16
113.08
112.14
107.27
77.34
77.02
76.70
O2N
O
O
O
1o
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


9.865
7.934
7.709
7.705
7.689
7.686
7.596
7.592
7.575
7.557
7.553
7.395
7.375
7.352
7.350
7.333
7.315
7.312
7.200
7.178
6.463
6.457
6.447
6.441
3.742
3.718
2.508
2.504
2.500
7.8
7.6
7.4
ppm
6.5
6.4 ppm
3.9
3.8
3.7
3.6 ppm
O
O
HO
OMe
52p
x
11
10
9
8
7
6
5
4
3
2
1
ppm
1.03
1.08
1.09
1.16
2.28
1.07
2.11
3.21


160.48
159.74
156.06
152.75
141.43
131.50
131.27
128.16
125.51
124.47
119.26
115.76
114.80
104.51
101.26
55.01
39.69
39.49
39.28
39.07
38.86
38.65
38.44
O
O
HO
OMe
52p
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


8.024
8.018
8.015
8.002
7.999
7.995
7.622
7.618
7.604
7.601
7.597
7.583
7.579
7.528
7.526
7.507
7.505
7.443
7.440
7.424
7.406
7.403
7.282
7.100
7.095
7.079
7.073
3.936
1.638
x
x
1p
OMe
ppm
2.17
1.14
1.07
1.06
1.00
1.00
3.34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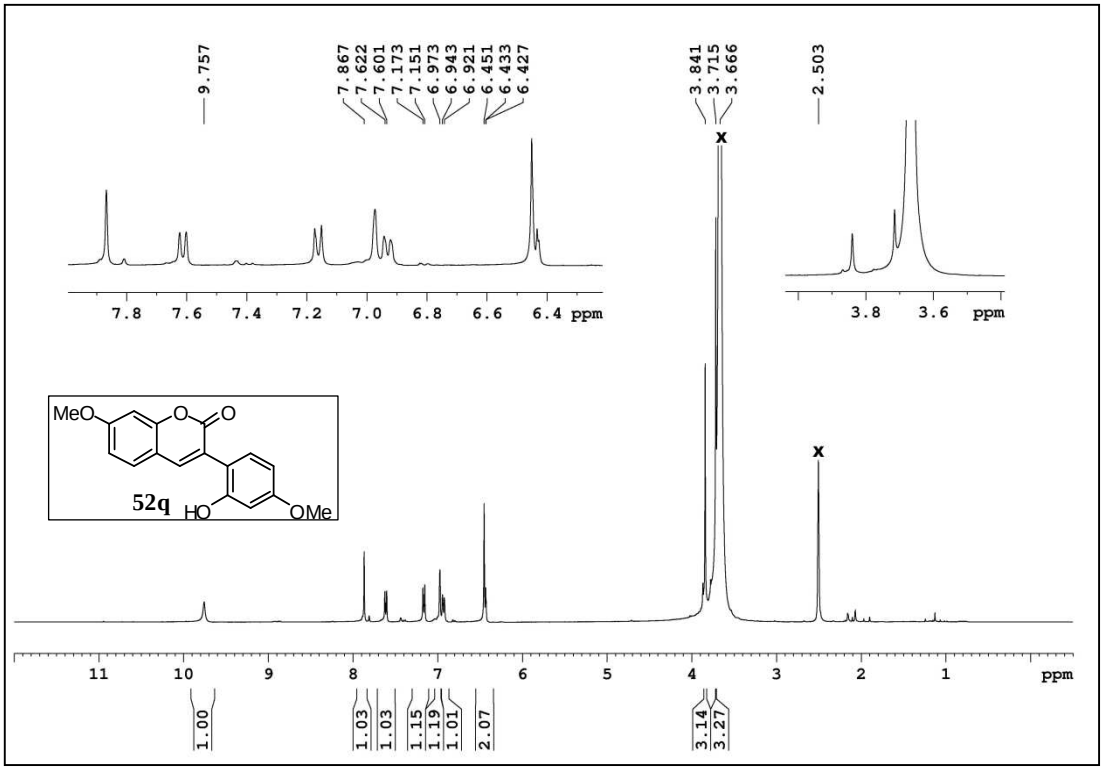
159.31
158.25
156.82
153.22
131.32
124.61
122.01
121.47
117.43
116.46
113.61
112.85
106.06
96.76
77.34
77.03
76.71
55.88
1p
OMe
ppm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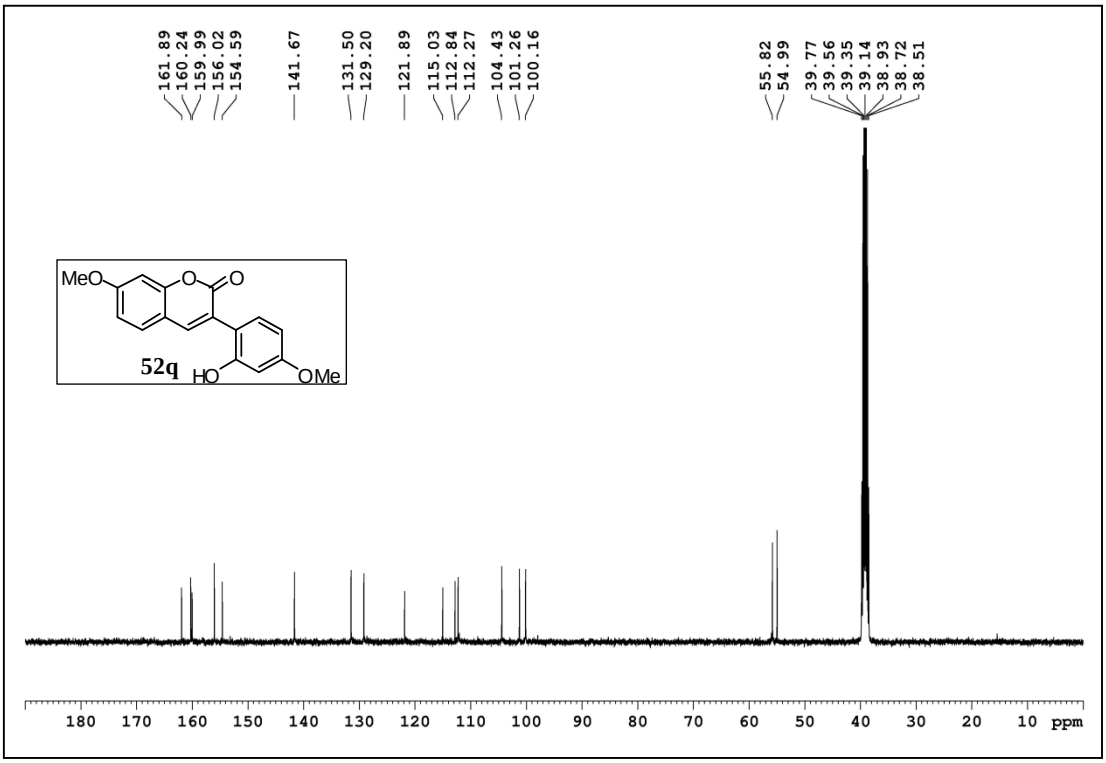
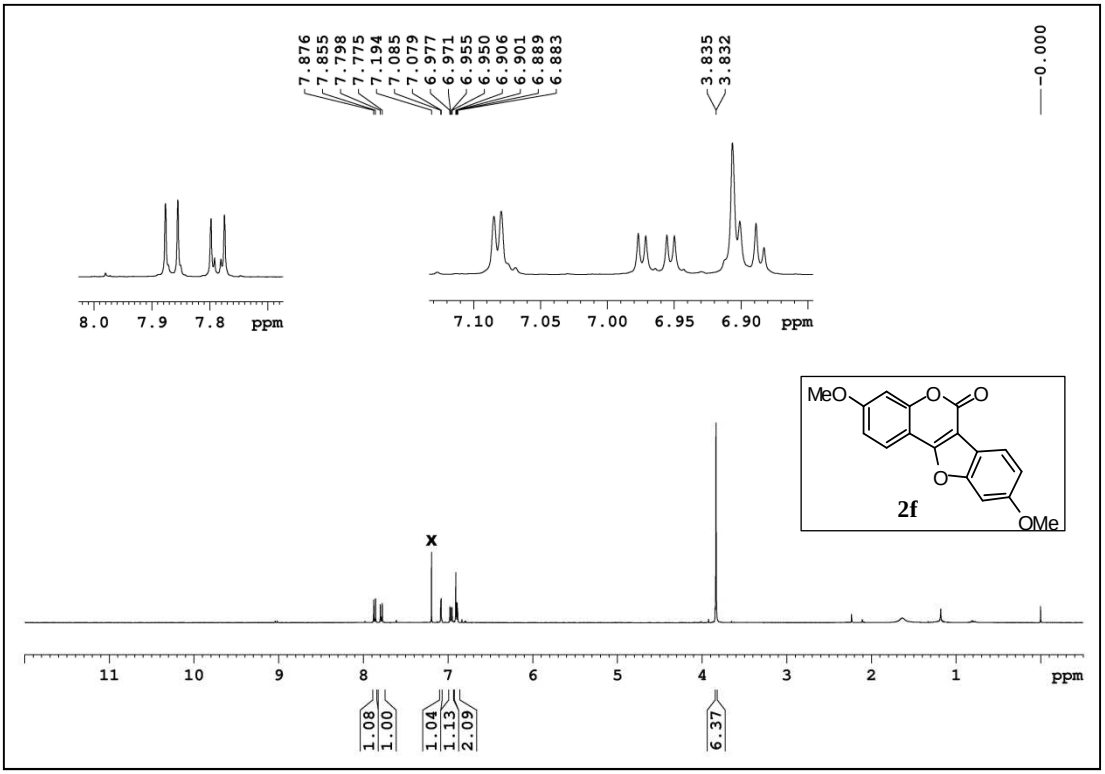
7.867
7.622
7.601
7.173
7.151
6.973
6.943
6.921
6.451
6.433
6.427
3.841
3.715
3.666
2.503
MeO
O
O
HO
OMe
52q
x
x
ppm
1.00
1.03
1.03
1.15
1.19
1.01
2.07
3.14
3.27


161.89
160.24
159.99
156.02
154.59
141.67
131.50
129.20
121.89
115.03
112.84
112.27
104.43
101.26
100.16
55.82
54.99
39.77
39.56
39.35
39.14
38.93
38.72
38.51
MeO
O
O
HO
OMe
52q
ppm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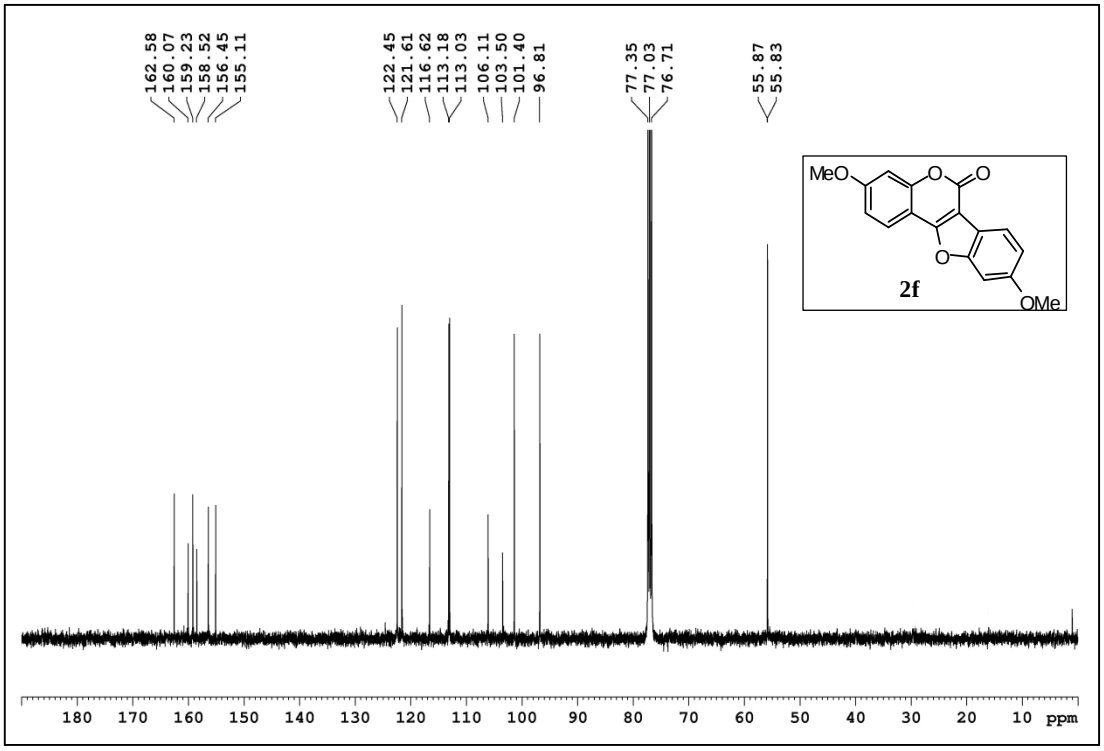
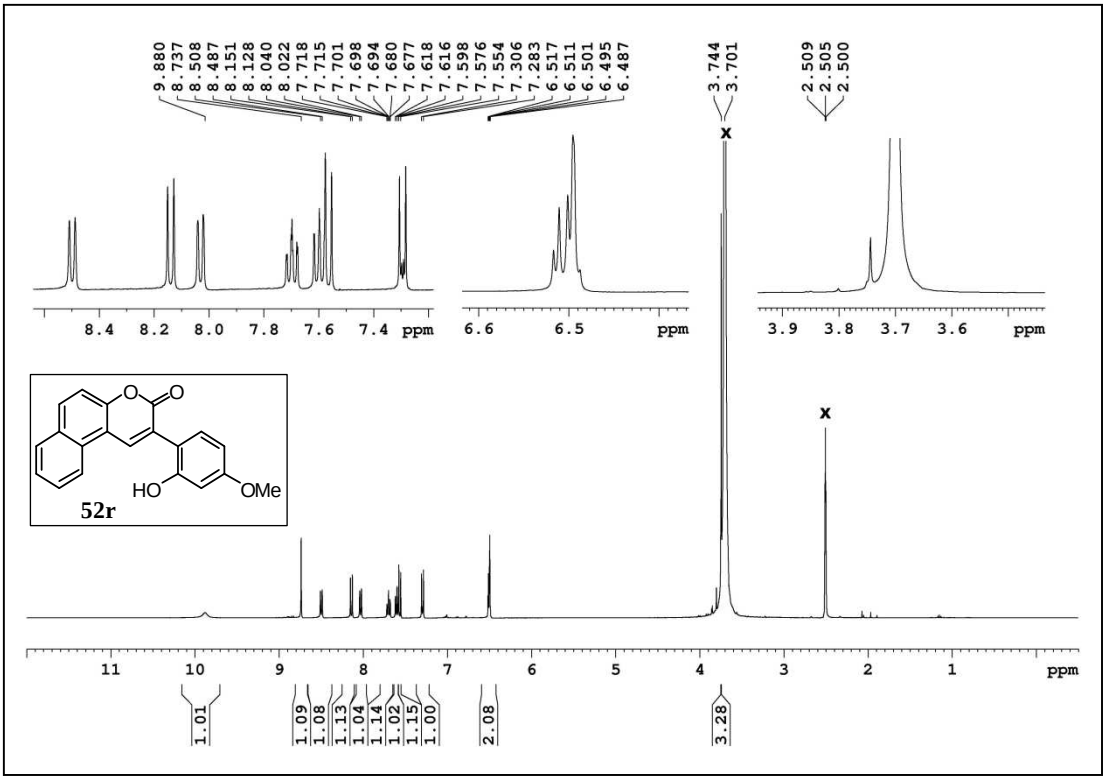
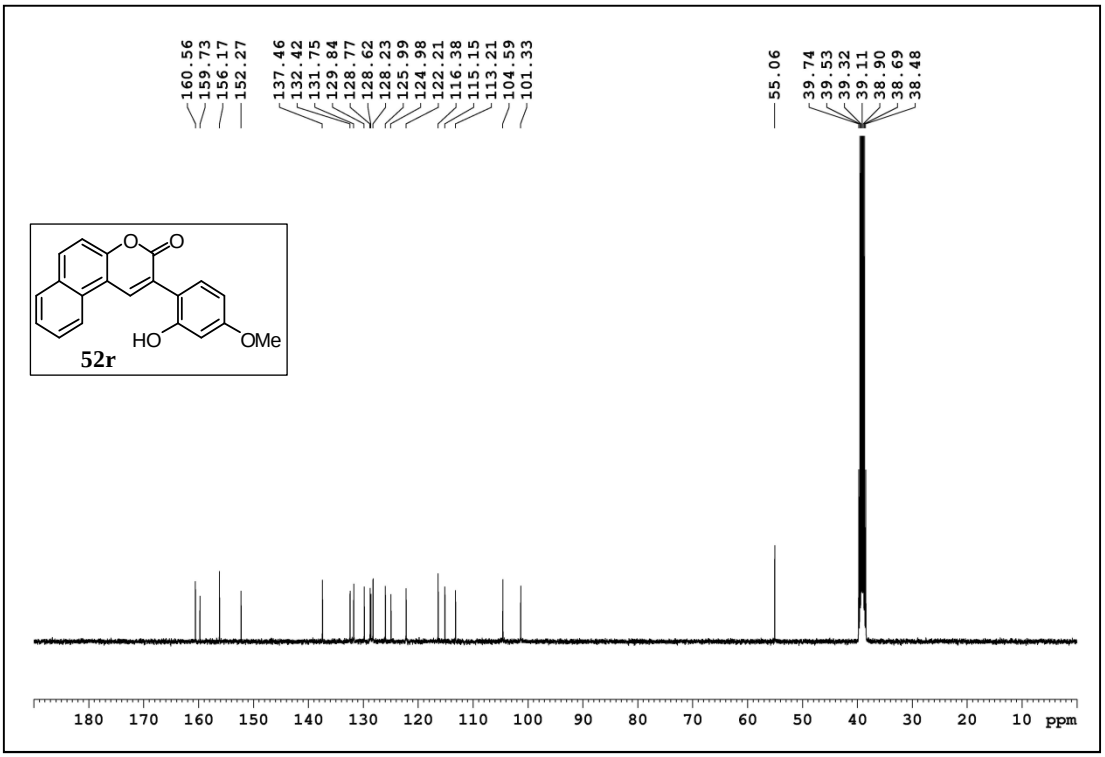
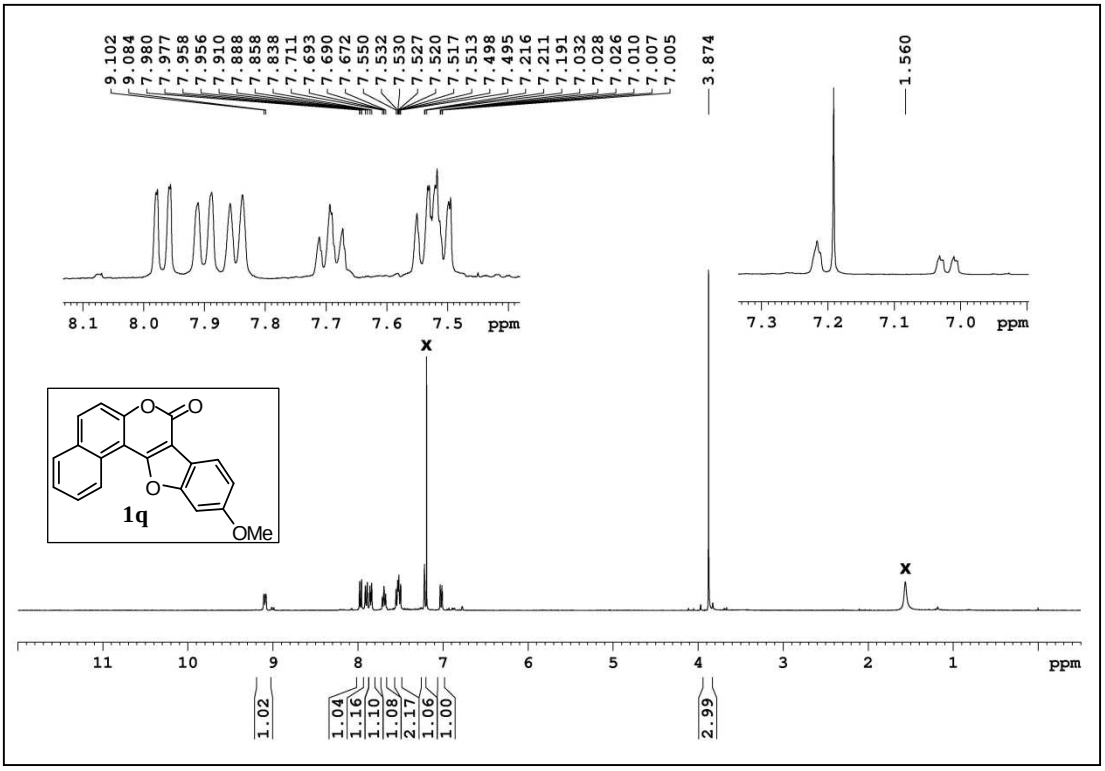
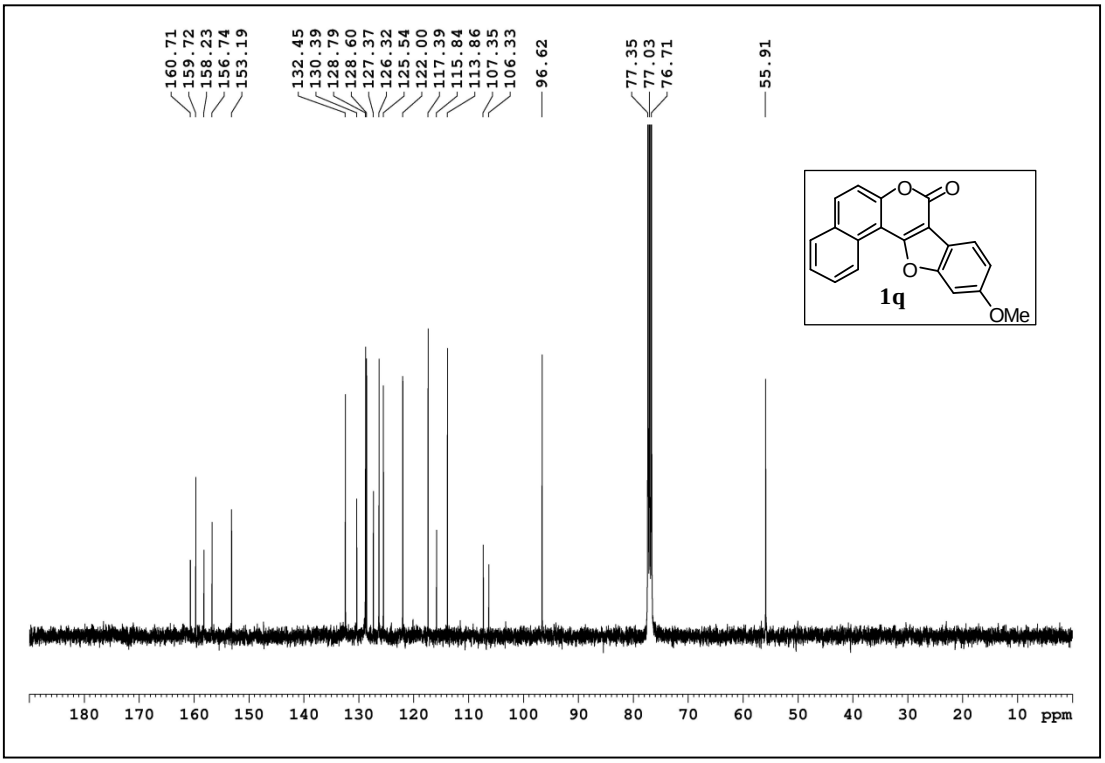
7.855
7.798
7.775
7.194
7.085
7.079
6.977
6.971
6.955
6.950
6.906
6.901
6.889
6.883
3.835
3.832
-0.000
8.0 7.9 7.8 ppm
7.10 7.05 7.00 6.95 6.90 ppm
MeO
O
O
O
OMe
2f
x
11 10 9 8 7 6 5 4 3 2 1 ppm
1.08
1.00
1.04
1.13
2.09
6.37


162.58
160.07
159.23
158.52
156.45
155.11
122.45
121.61
116.62
113.18
113.03
106.11
103.50
101.40
96.81
77.35
77.03
76.71
55.87
55.83
MeO
O
O
O
OMe
2f
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


9.880
8.737
8.508
8.487
8.151
8.128
8.040
8.022
7.718
7.715
7.701
7.698
7.694
7.680
7.677
7.618
7.616
7.598
7.576
7.554
7.306
7.283
6.517
6.511
6.501
6.495
6.487
3.744
3.701
2.509
2.505
2.500
X
X
8.4 8.2 8.0 7.8 7.6 7.4 ppm
6.6 6.5 ppm
3.9 3.8 3.7 3.6 ppm
HO
OMe
52r
11 10 9 8 7 6 5 4 3 2 1 ppm
1.01
1.09
1.08
1.13
1.04
1.14
1.02
1.15
1.00
2.08
3.28


160.56
159.73
156.17
152.27
137.46
132.42
131.75
129.84
128.77
128.62
128.23
125.99
124.98
122.21
116.38
115.15
113.21
104.59
101.33
55.06
39.74
39.53
39.32
39.11
38.90
38.69
38.48
HO
OMe
52r
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


9.102
9.084
7.980
7.977
7.958
7.956
7.910
7.888
7.858
7.838
7.711
7.693
7.690
7.672
7.550
7.532
7.530
7.527
7.520
7.517
7.513
7.498
7.495
7.216
7.211
7.191
7.032
7.028
7.026
7.010
7.007
7.005
3.874
1.560
8.1 8.0 7.9 7.8 7.7 7.6 7.5 ppm
7.3 7.2 7.1 7.0 ppm
x
1q
OMe
x
11 10 9 8 7 6 5 4 3 2 1 ppm
1.02
1.04
1.16
1.10
1.08
2.17
1.06
1.00
2.99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159.72
158.23
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153.19
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130.39
128.79
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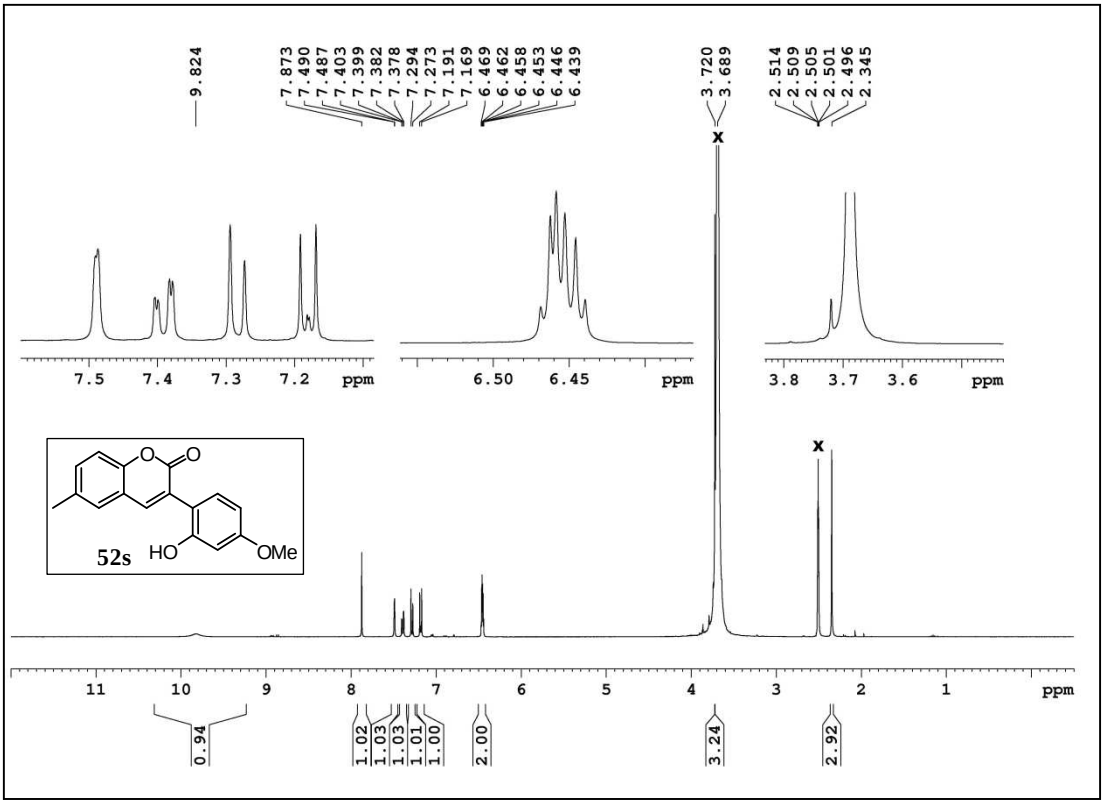
127.37
126.32
125.54
122.00
117.39
115.84
113.86
107.35
106.33
96.62
77.35
77.03
76.71
55.91
1q
OMe
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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7.490
7.487
7.403
7.399
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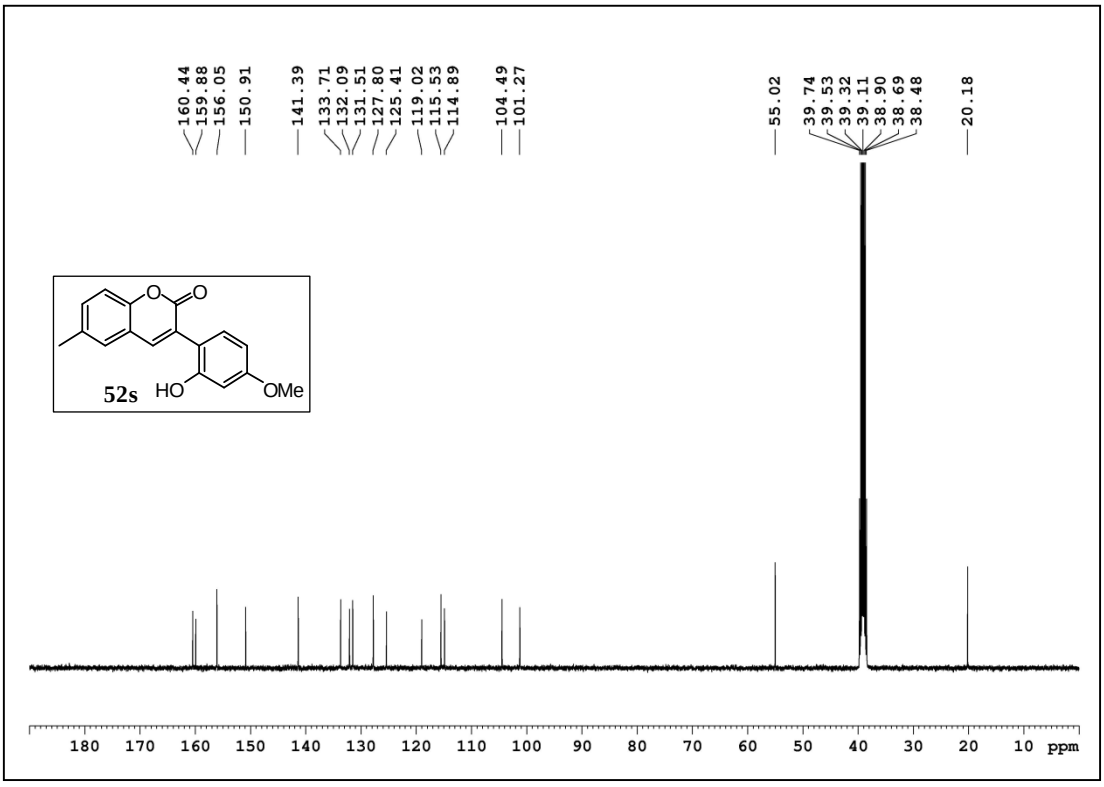
7.378
7.294
7.273
7.191
7.169
6.469
6.462
6.458
6.453
6.446
6.439
3.720
3.689
2.514
2.509
2.505
2.501
2.496
2.345
7.5 7.4 7.3 7.2 ppm
6.50 6.45 ppm
3.8 3.7 3.6 ppm
52s
HO
OMe
11 10 9 8 7 6 5 4 3 2 1 ppm
0.94
1.02
1.03
1.03
1.01
1.00
2.00
3.24
2.92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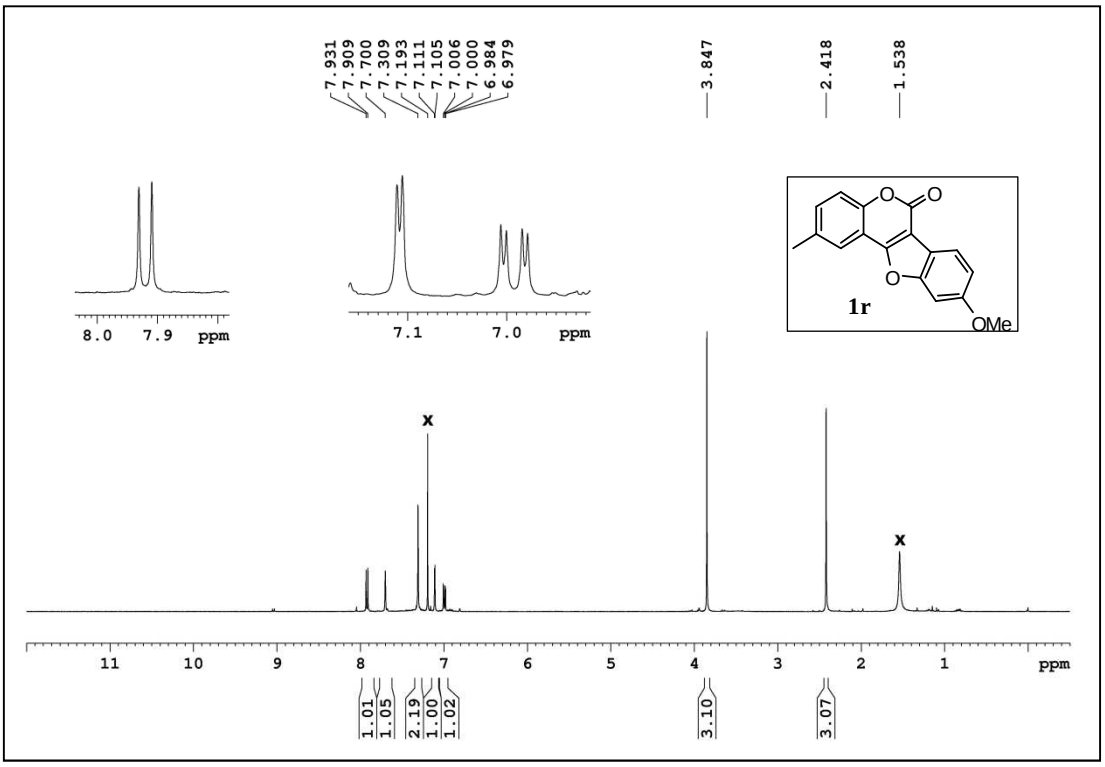
150.91
141.39
133.71
132.09
131.51
127.80
125.41
119.02
115.53
114.89
104.49
101.27
55.02
39.74
39.53
39.32
39.11
38.90
38.69
38.48
20.18
52s
HO
OMe
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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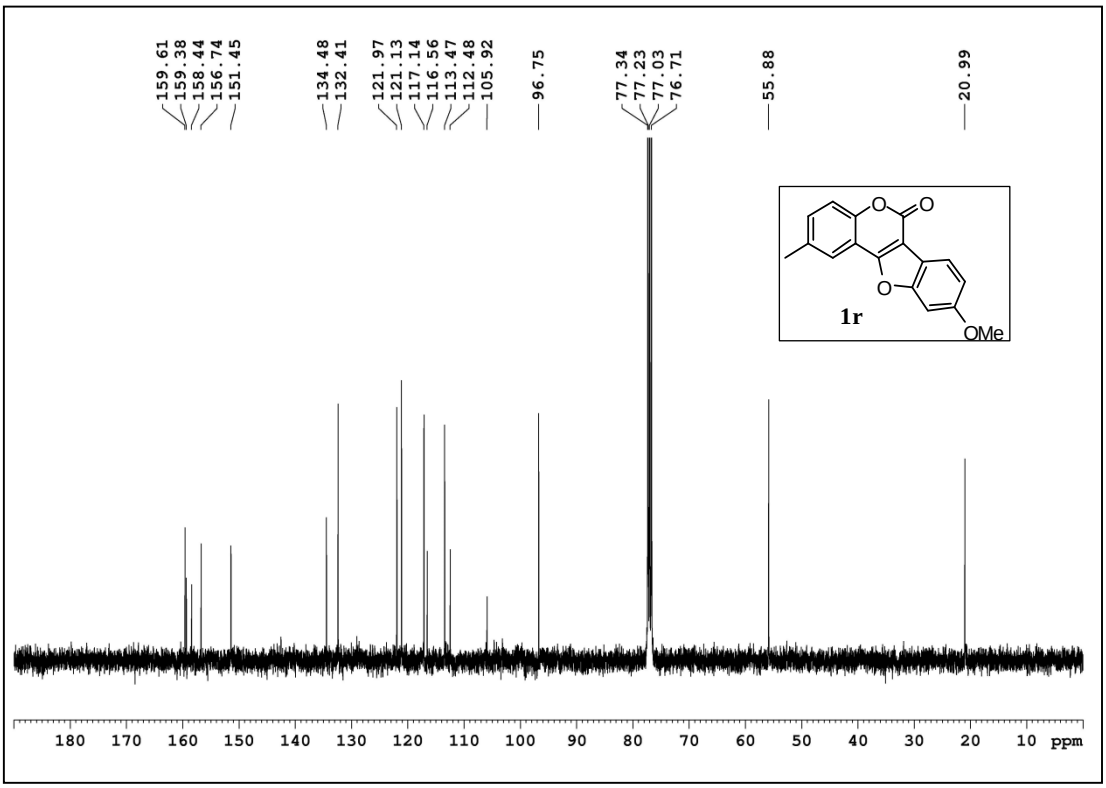
7.700
7.309
7.193
7.111
7.105
7.006
7.000
6.984
6.979
3.847
2.418
1.538
8.0
7.9
ppm
7.1
7.0
ppm
1r
OMe
x
x
11
10
9
8
7
6
5
4
3
2
1
ppm
1.01
1.05
2.19
1.00
1.02
3.10
3.07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159.38
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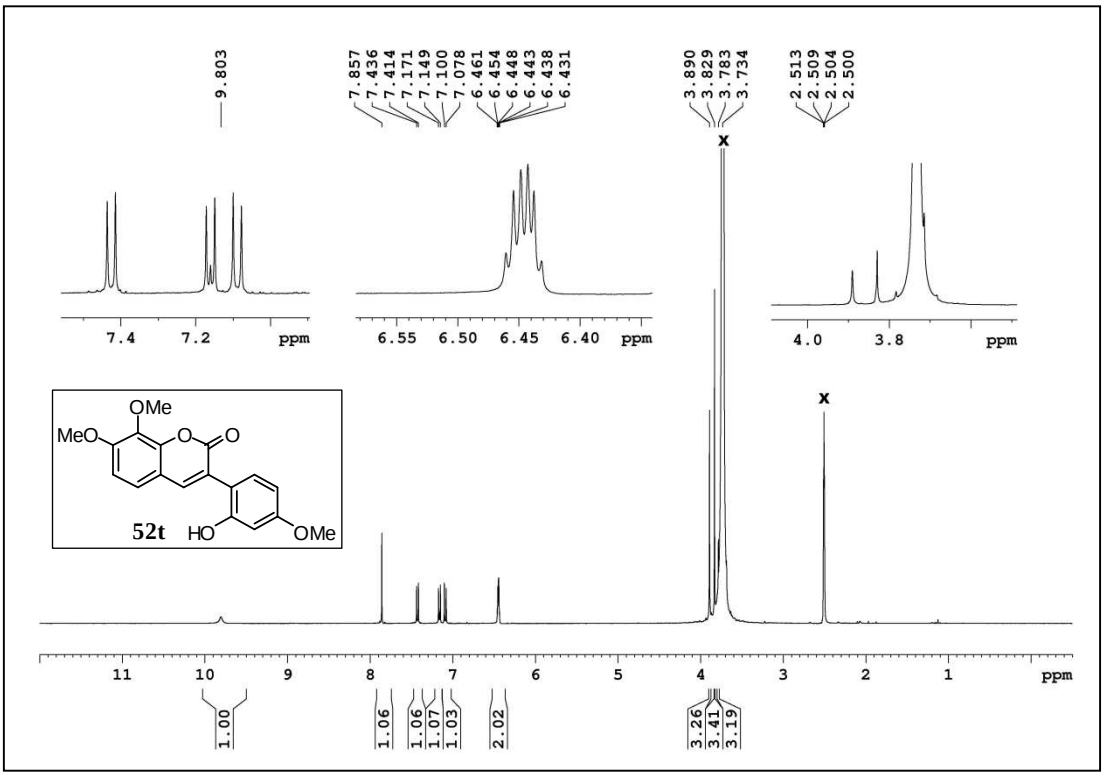
151.45
134.48
132.41
121.97
121.13
117.14
116.56
113.47
112.48
105.92
96.75
77.34
77.23
77.03
76.71
55.88
20.99
1r
OMe
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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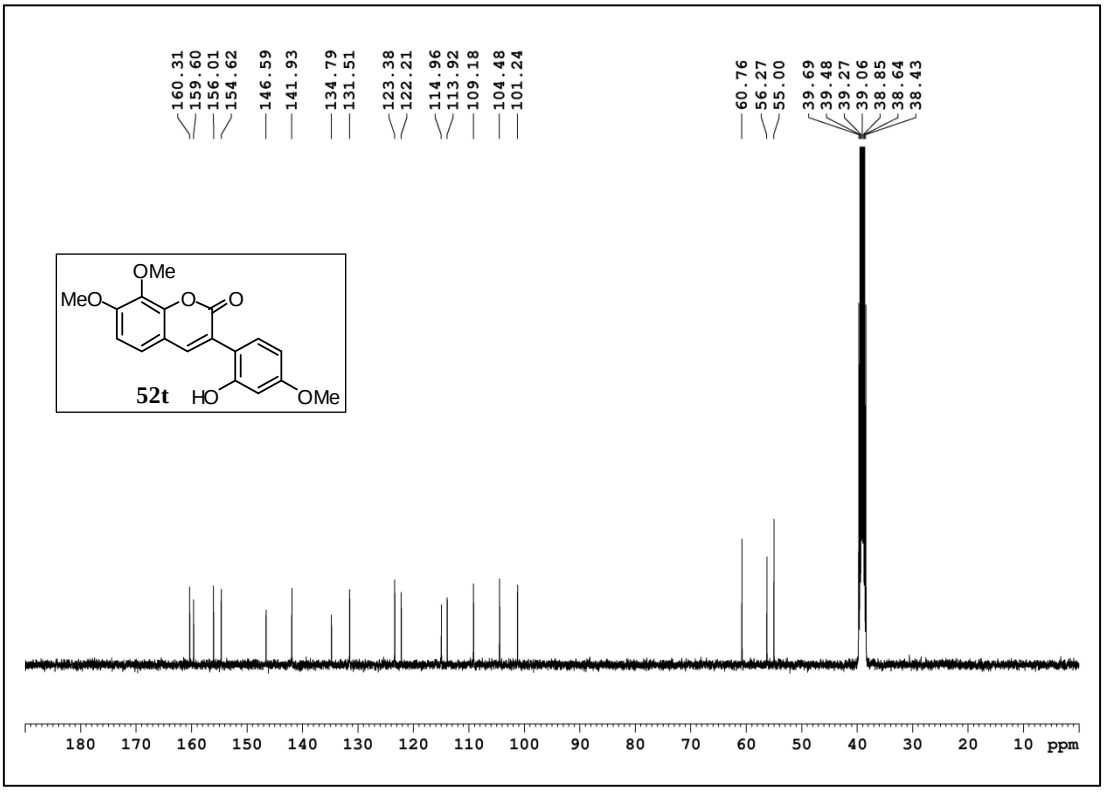
7.857
7.436
7.414
7.171
7.149
7.100
7.078
6.461
6.454
6.448
6.443
6.438
6.431
3.890
3.829
3.783
3.734
2.513
2.509
2.504
2.500
x
x
OMe
MeO
O
O
52t
HO
OMe
7.4
7.2
ppm
6.55
6.50
6.45
6.40
ppm
4.0
3.8
ppm
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.06
1.06
1.07
1.03
2.02
3.26
3.41
3.19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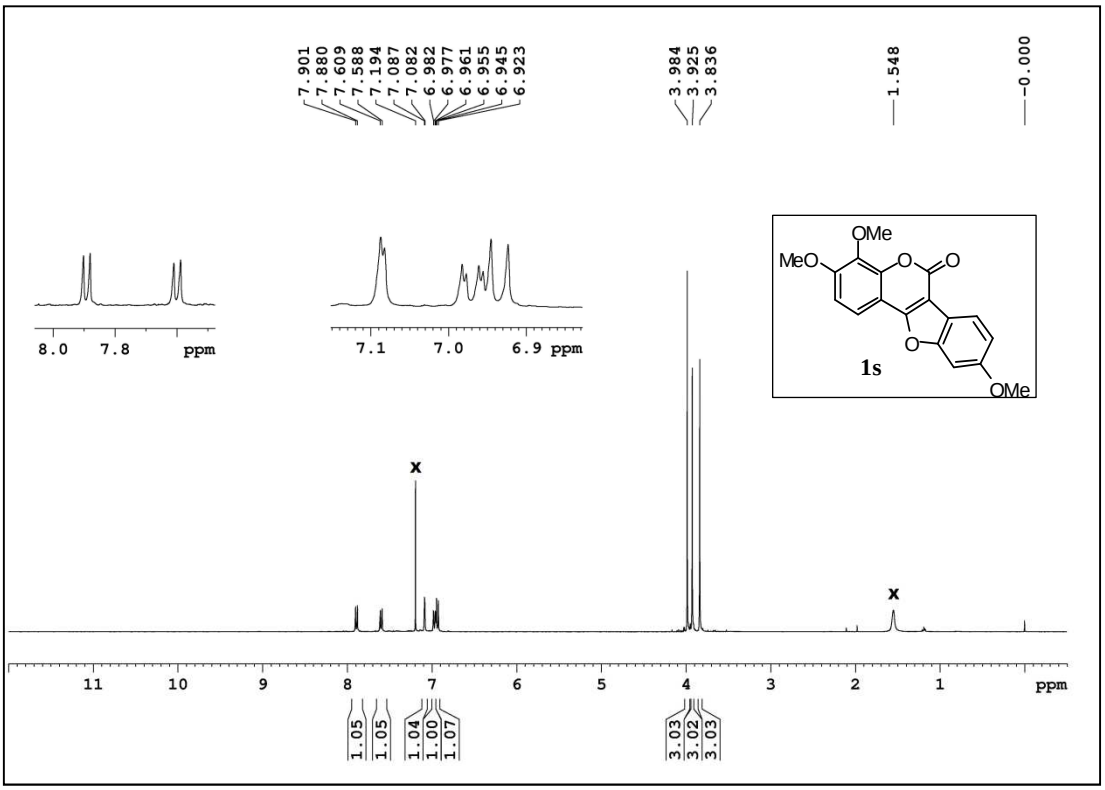
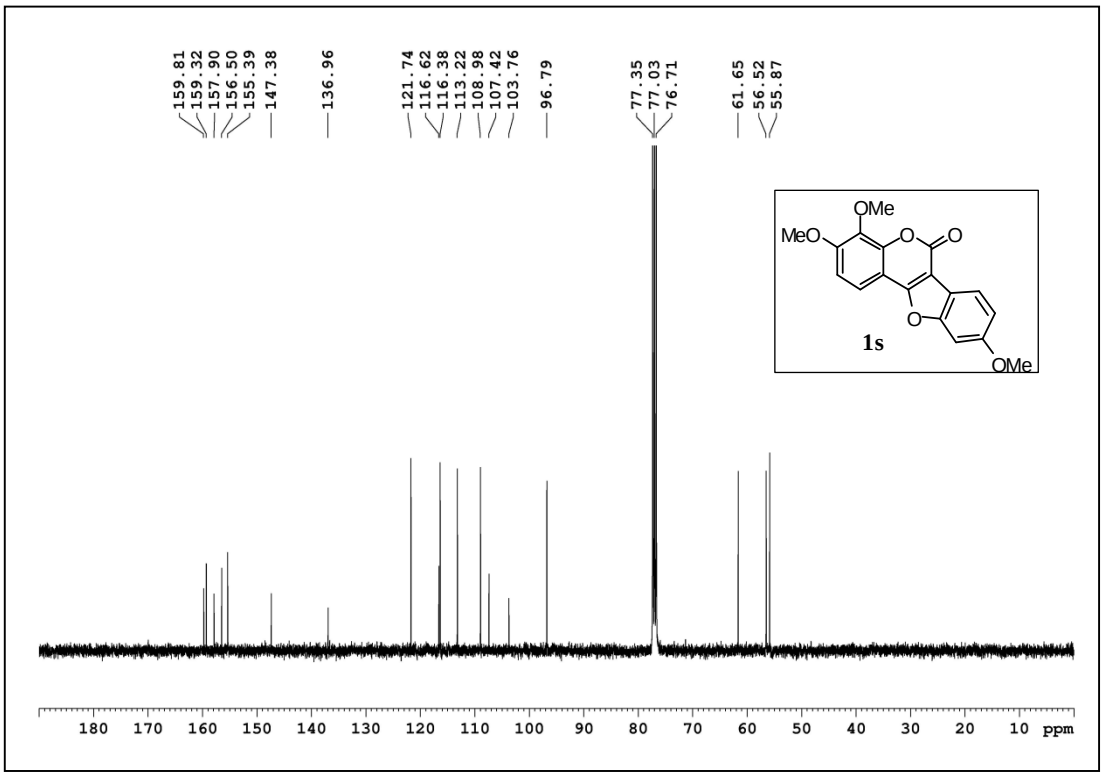
159.60
156.01
154.62
146.59
141.93
134.79
131.51
123.38
122.21
114.96
113.92
109.18
104.48
101.24
60.76
56.27
55.00
39.69
39.48
39.27
39.06
38.85
38.64
38.43
OMe
MeO
O
O
52t
HO
OMe
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


7.901
7.880
7.609
7.588
7.194
7.087
7.082
6.982
6.977
6.961
6.955
6.945
6.923
3.984
3.925
3.836
1.548
0.000
8.0
7.8
ppm
7.1
7.0
6.9 ppm
OMe
MeO
O
O
O
OMe
1s
x
x
11
10
9
8
7
6
5
4
3
2
1
ppm
1.05
1.05
1.04
1.00
1.07
3.03
3.02
3.03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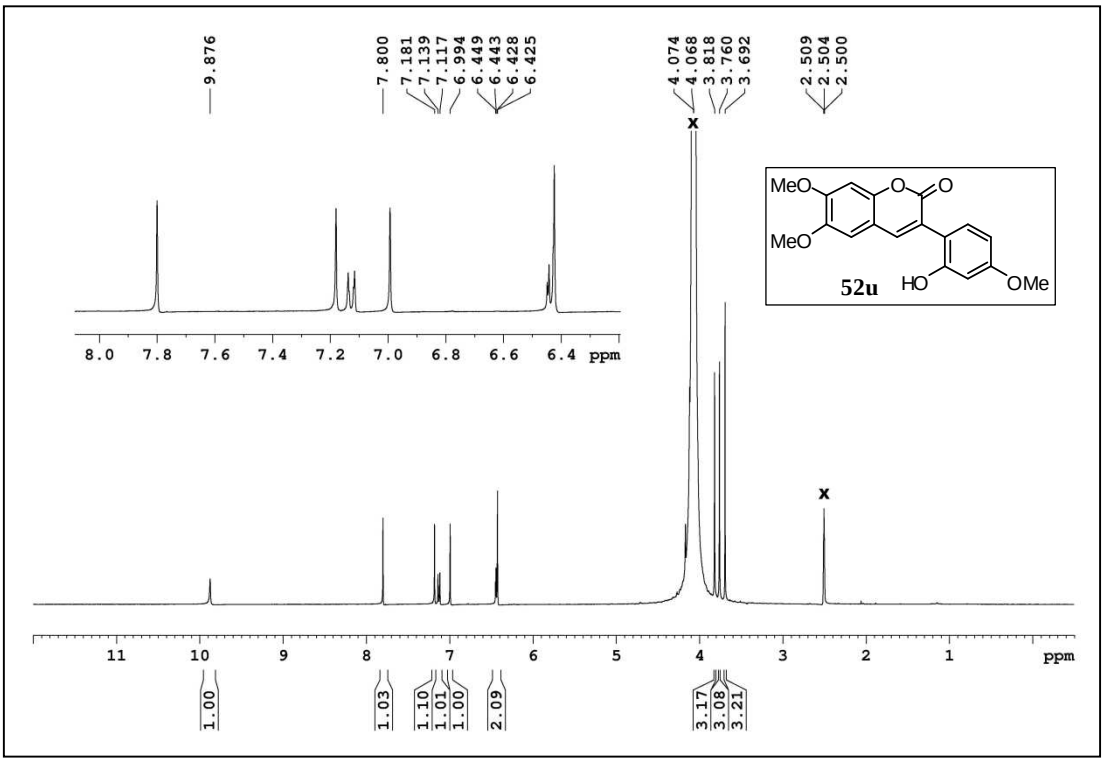
159.32
157.90
156.50
155.39
147.38
136.96
121.74
116.62
116.38
113.22
108.98
107.42
103.76
96.79
77.35
77.03
76.71
61.65
56.52
55.87
OMe
MeO
O
O
O
OMe
1s
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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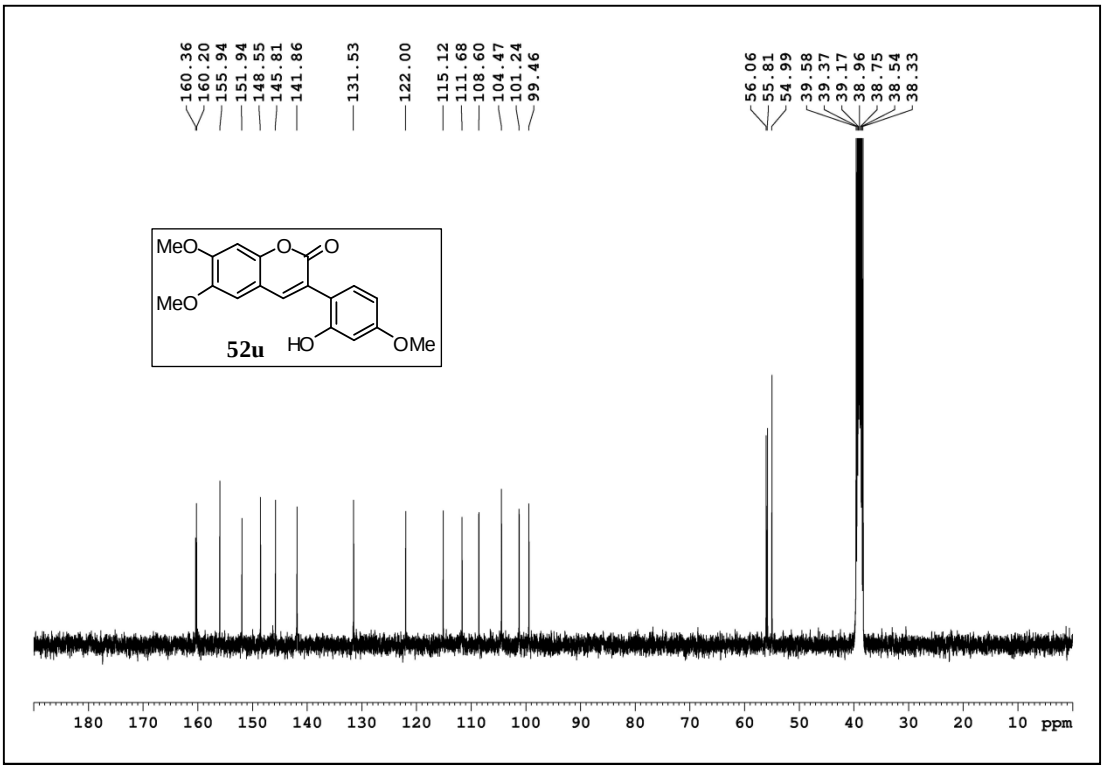
7.800
7.181
7.139
7.117
6.994
6.449
6.443
6.428
6.425
4.074
4.068
3.818
3.760
3.692
2.509
2.504
2.500
x
x
MeO
MeO
O
O
HO
OMe
52u
8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 ppm
11 10 9 8 7 6 5 4 3 2 1 ppm
1.00
1.03
1.10
1.01
1.00
2.09
3.17
3.08
3.21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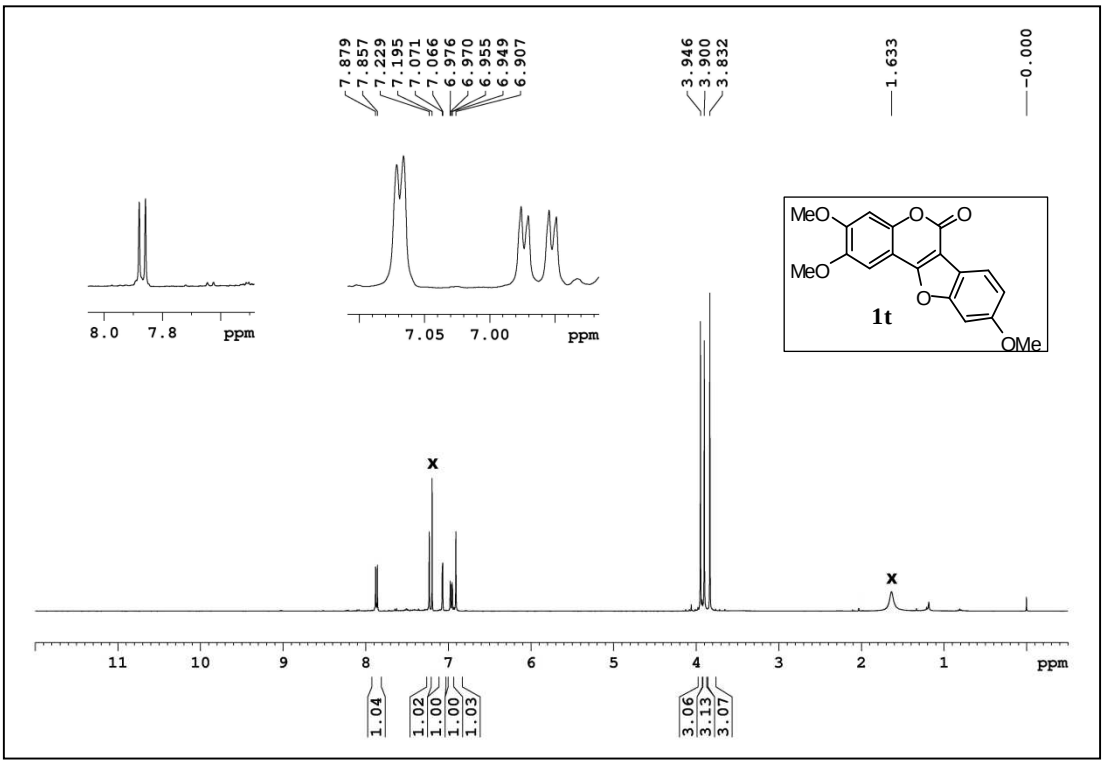
160.20
155.94
151.94
148.55
145.81
141.86
131.53
122.00
115.12
111.68
108.60
104.47
101.24
99.46
56.06
55.81
54.99
39.58
39.37
39.17
38.96
38.75
38.54
38.33
MeO
MeO
O
O
HO
OMe
52u
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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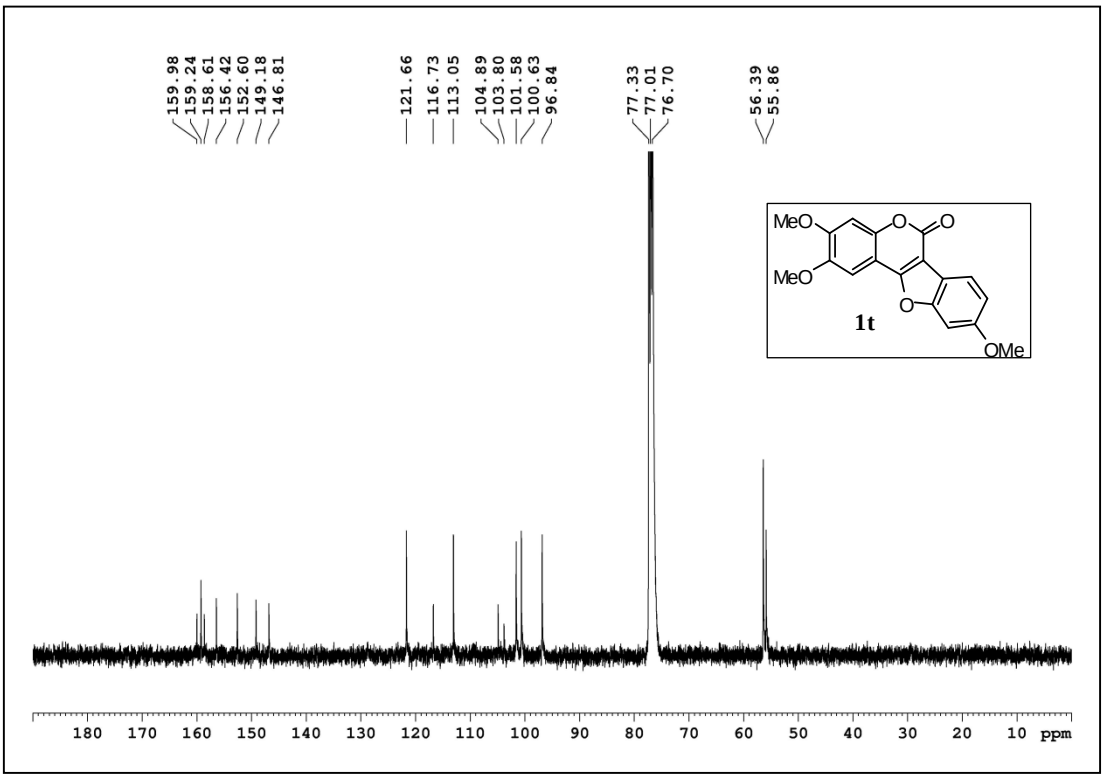
7.857
7.229
7.195
7.071
7.066
6.976
6.970
6.955
6.949
6.907
3.946
3.900
3.832
1.633
0.000
MeO
MeO
O
O
O
1t
OMe
8.0
7.8
ppm
7.05
7.00
ppm
x
x
11
10
9
8
7
6
5
4
3
2
1
ppm
1.04
1.02
1.00
1.00
1.03
3.06
3.13
3.07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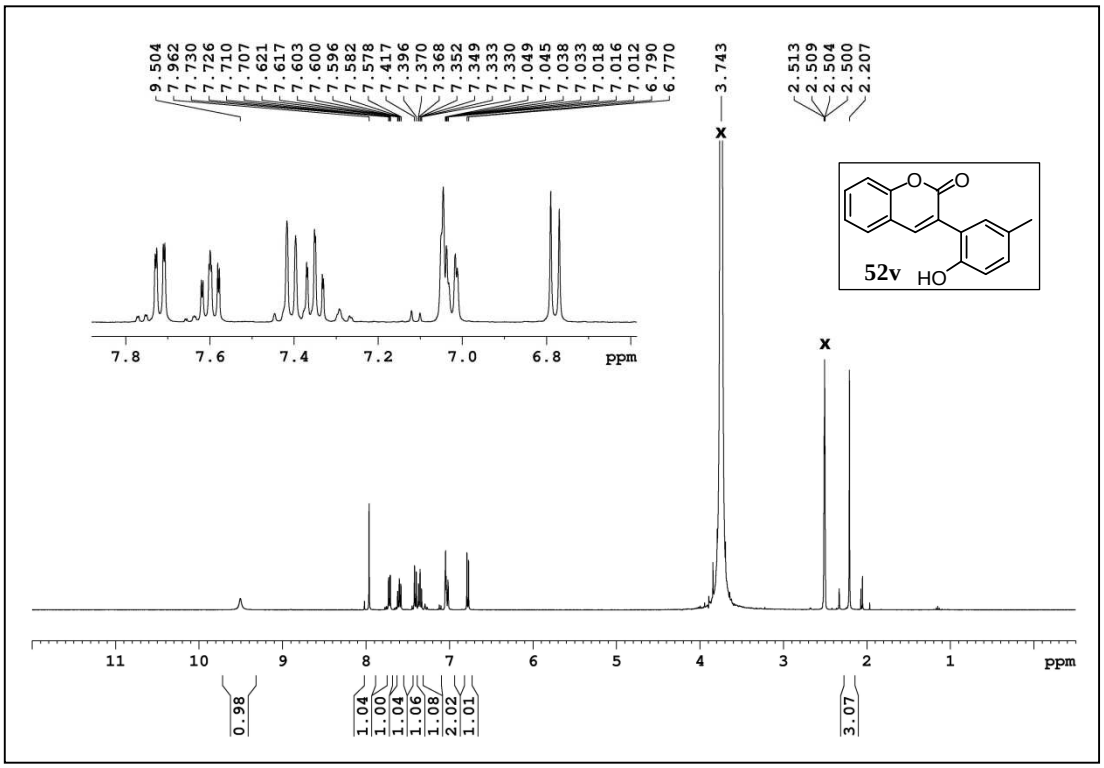
159.24
158.61
156.42
152.60
149.18
146.81
121.66
116.73
113.05
104.89
103.80
101.58
100.63
96.84
77.33
77.01
76.70
56.39
55.86
MeO
MeO
O
O
O
1t
OMe
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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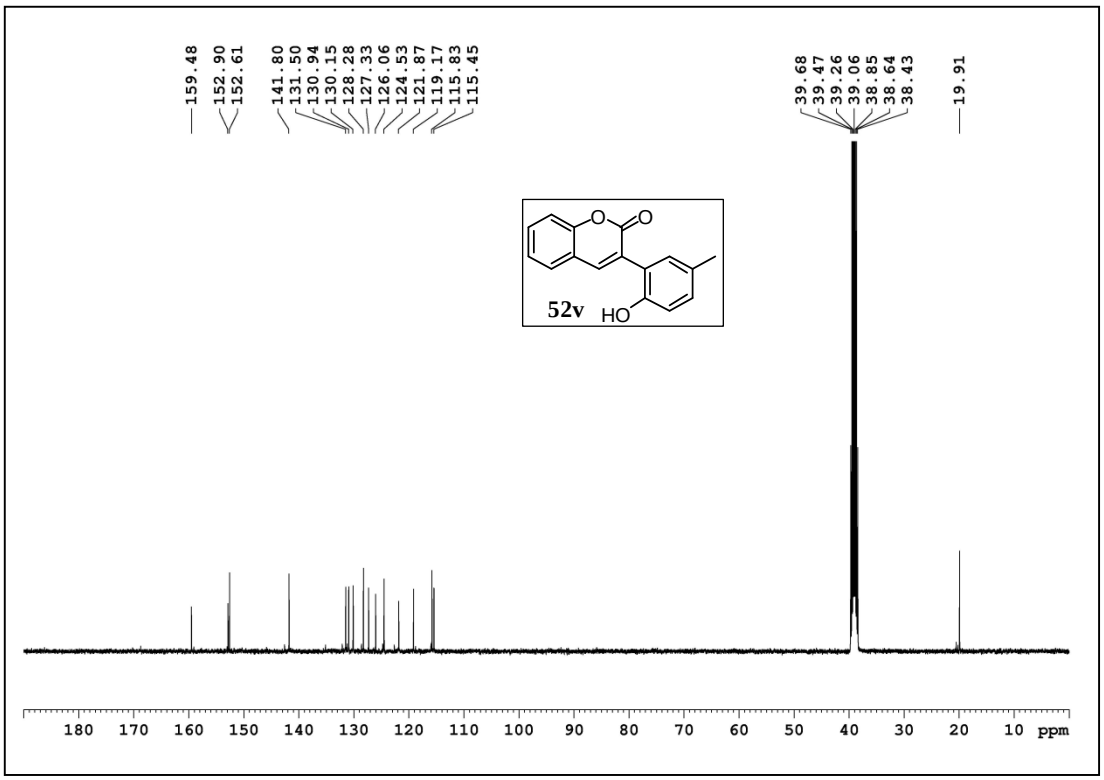
7.962
7.730
7.726
7.710
7.707
7.621
7.617
7.603
7.600
7.596
7.582
7.578
7.417
7.396
7.370
7.368
7.352
7.349
7.333
7.330
7.049
7.045
7.038
7.033
7.018
7.016
7.012
6.790
6.770
3.743
2.513
2.509
2.504
2.500
2.207
52v
HO
ppm
0.98
1.04
1.00
1.04
1.06
1.08
2.02
1.01
3.07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152.90
152.61
141.80
131.50
130.94
130.15
128.28
127.33
126.06
124.53
121.87
119.17
115.83
115.45
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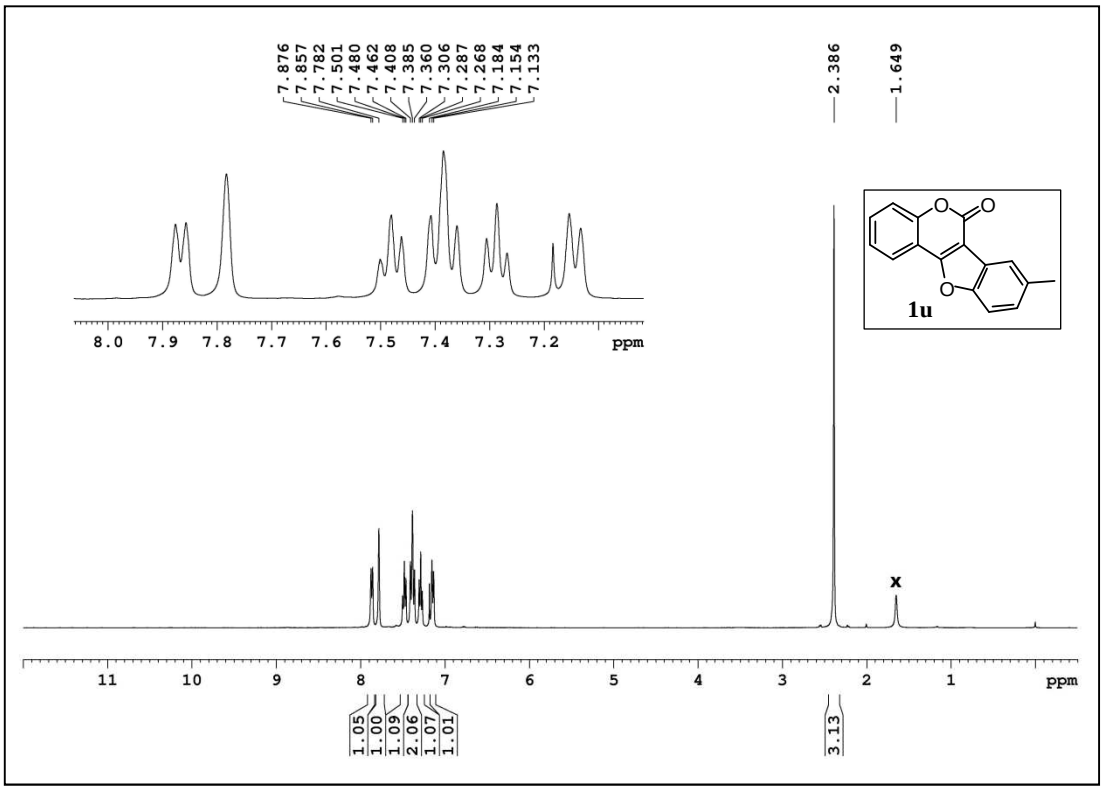
39.47
39.26
39.06
38.85
38.64
38.43
19.91
52v
HO
ppm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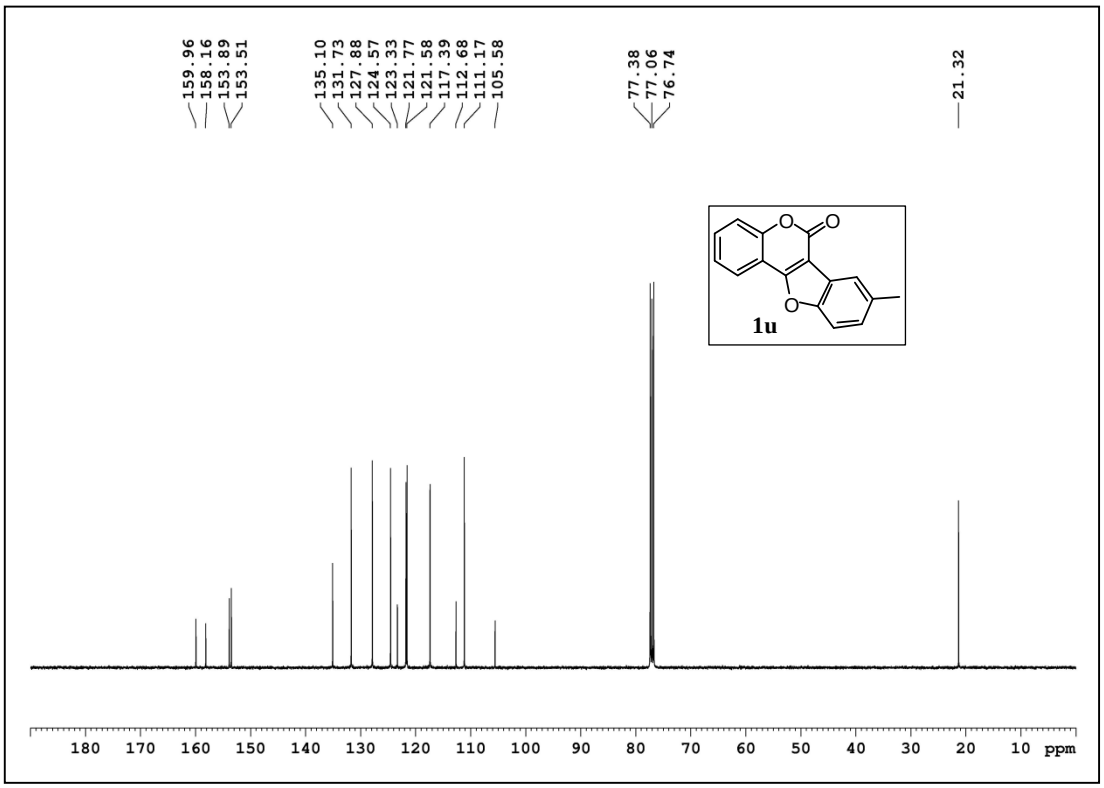
7.782
7.501
7.480
7.462
7.408
7.385
7.360
7.306
7.287
7.268
7.184
7.154
7.133
2.386
1.649
1u
x
ppm
1.05
1.00
1.09
2.06
1.07
1.01
3.13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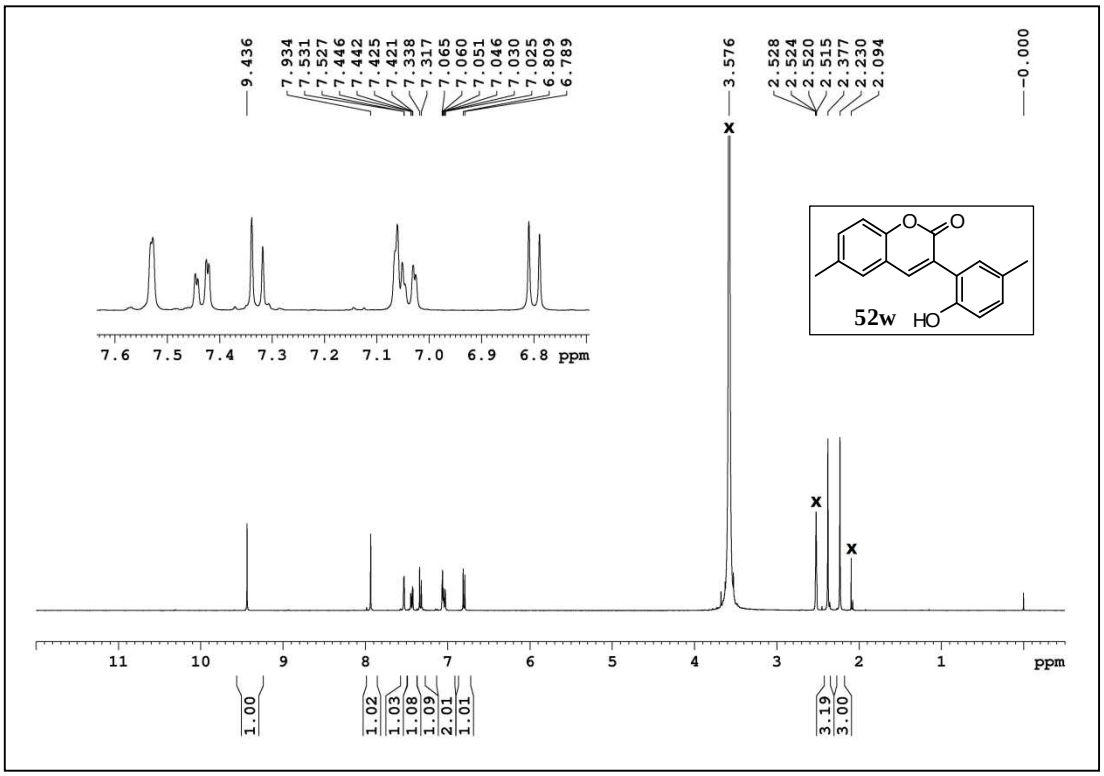
158.16
153.89
153.51
135.10
131.73
127.88
124.57
123.33
121.77
121.58
117.39
112.68
111.17
105.58
77.38
77.06
76.74
21.32
1u
ppm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7.934
7.531
7.527
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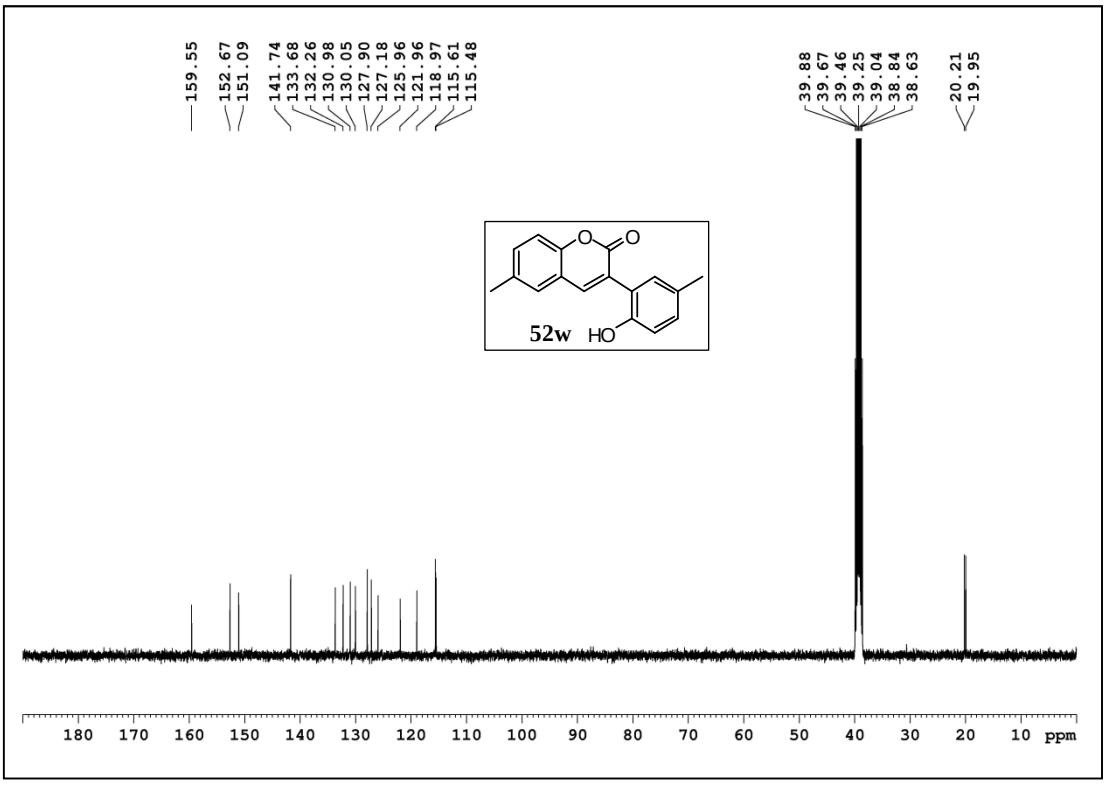
7.442
7.425
7.421
7.338
7.317
7.065
7.060
7.051
7.046
7.030
7.025
6.809
6.789
3.576
2.528
2.524
2.520
2.515
2.377
2.230
2.094
0.000
52w HO
7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 ppm
11 10 9 8 7 6 5 4 3 2 1 ppm
1.00
1.02
1.03
1.08
1.09
2.01
1.01
3.19
3.00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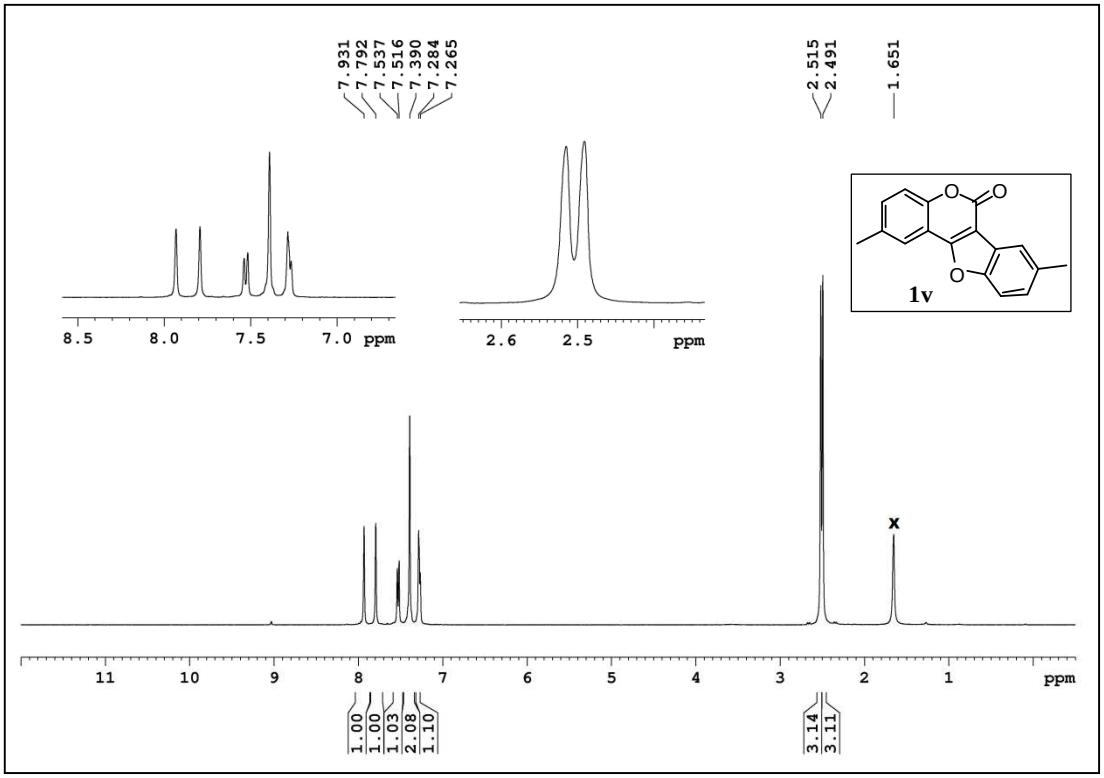
141.74
133.68
132.26
130.98
130.05
127.90
127.18
125.96
121.96
118.97
115.61
115.48
39.88
39.67
39.46
39.25
39.04
38.84
38.63
20.21
19.95
52w HO
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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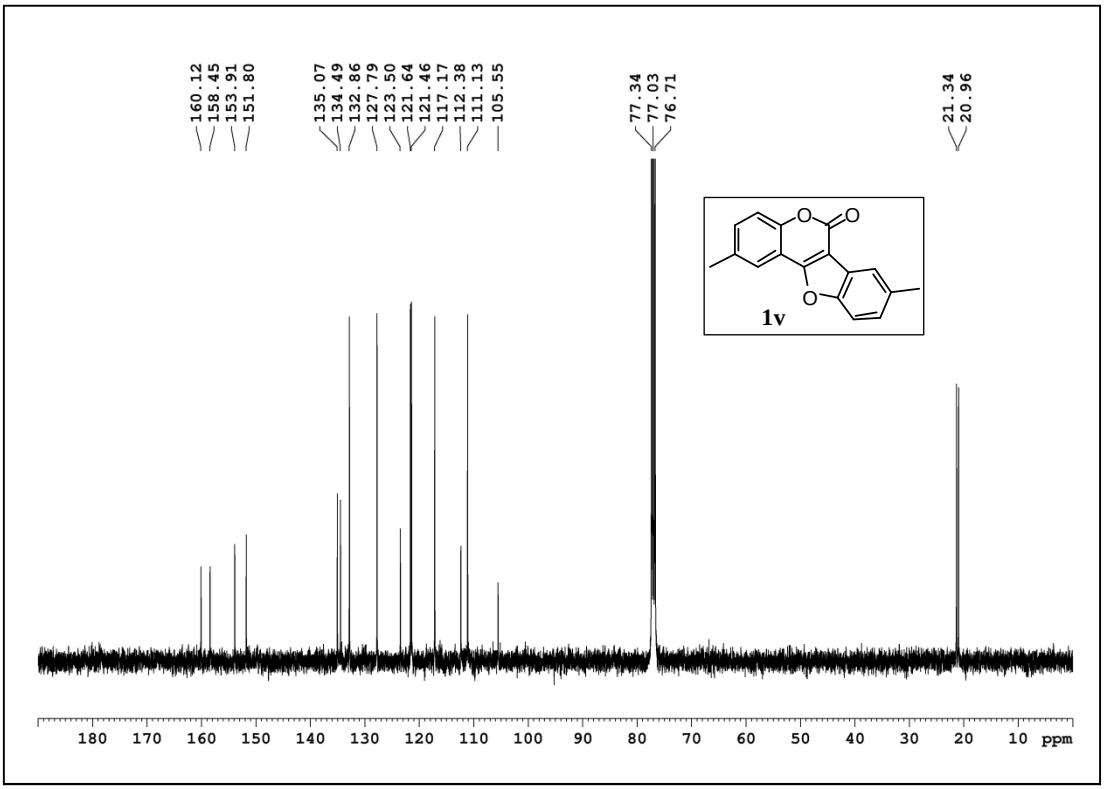
7.792
7.537
7.516
7.390
7.284
7.265
2.515
2.491
1.651
1v
x
ppm
1.00
1.00
1.03
2.08
1.10
3.14
3.11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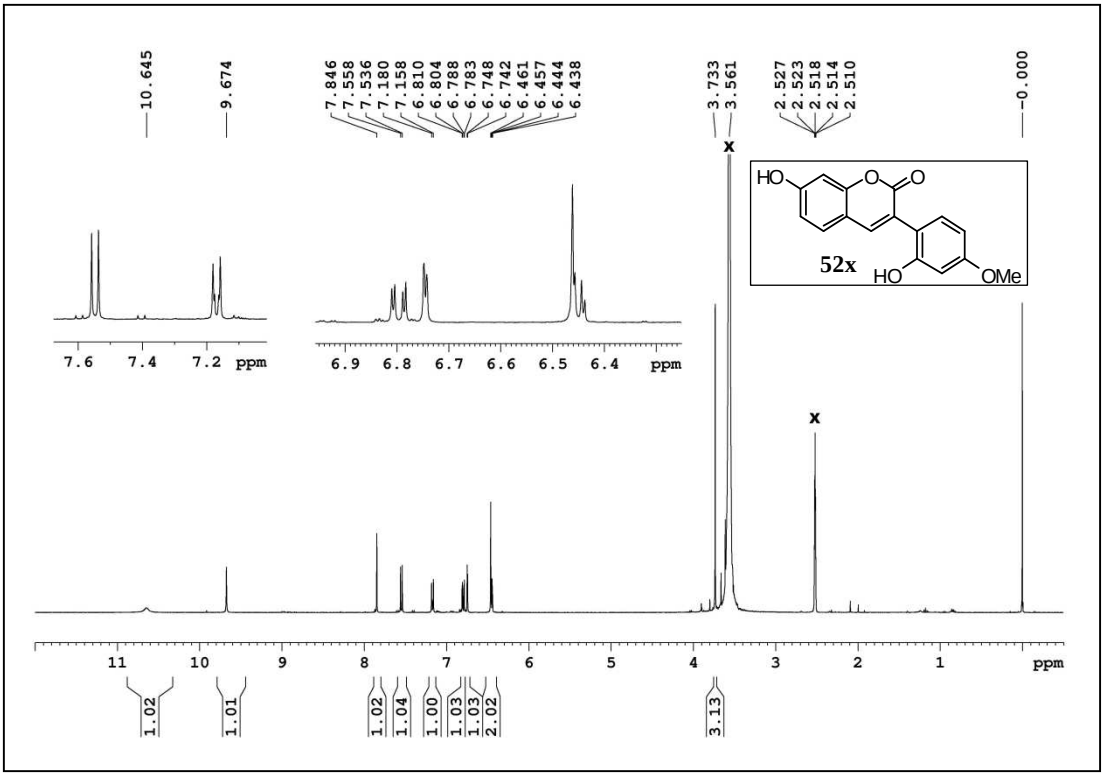
158.45
153.91
151.80
135.07
134.49
132.86
127.79
123.50
121.64
121.46
117.17
112.38
111.13
105.55
77.34
77.03
76.71
21.34
20.96
1v
ppm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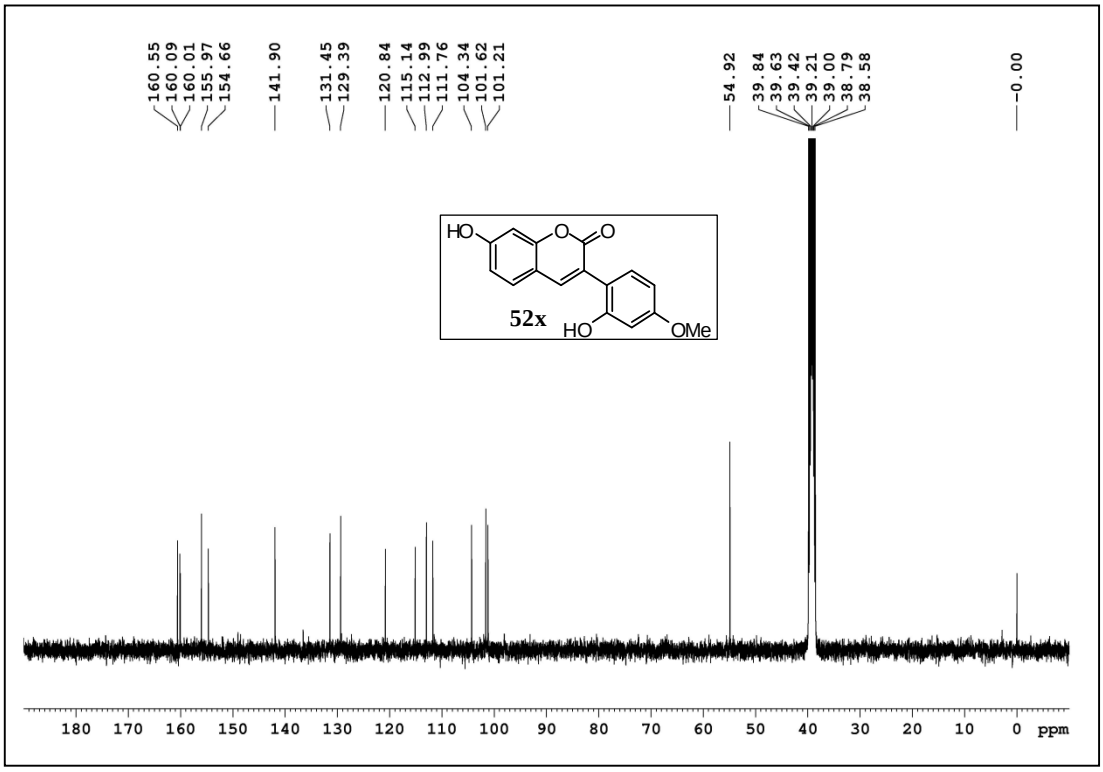
9.674
7.846
7.558
7.536
7.180
7.158
6.810
6.804
6.788
6.783
6.748
6.742
6.461
6.457
6.444
6.438
3.733
3.561
2.527
2.523
2.518
2.514
2.510
-0.000
x
x
HO
O
O
52x
HO
OMe
7.6
7.4
7.2 ppm
6.9
6.8
6.7
6.6
6.5
6.4 ppm
11
10
9
8
7
6
5
4
3
2
1 ppm
1.02
1.01
1.02
1.04
1.00
1.03
1.03
2.02
3.13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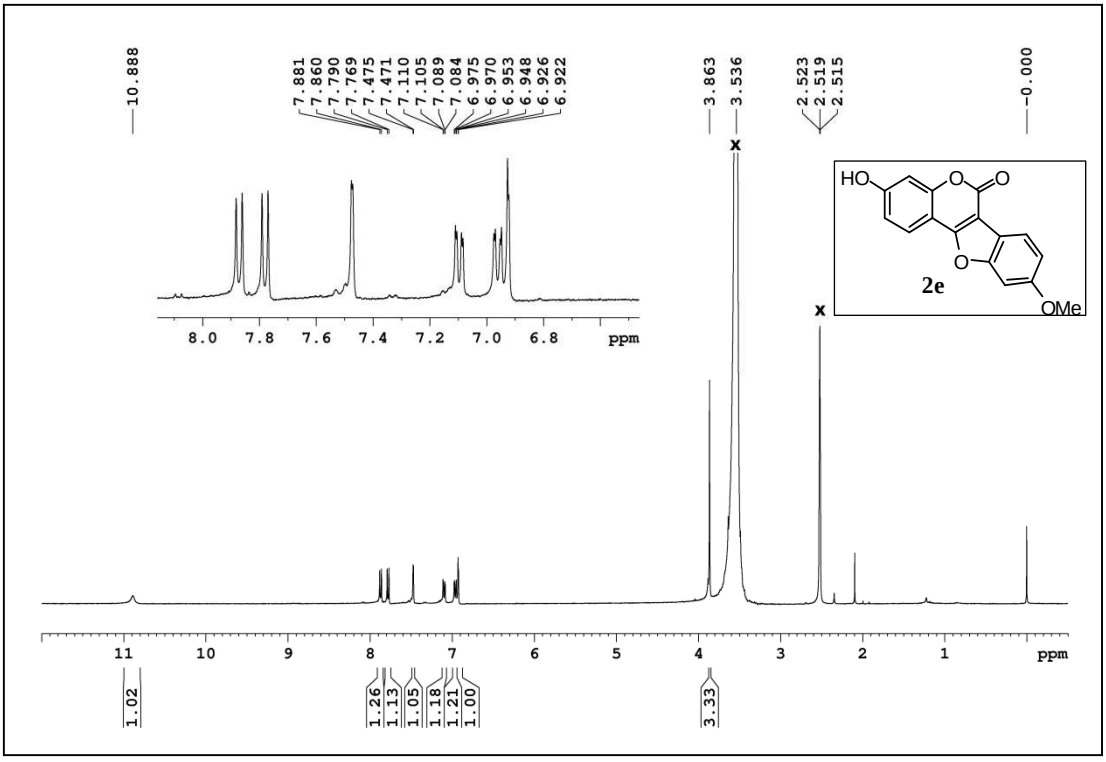
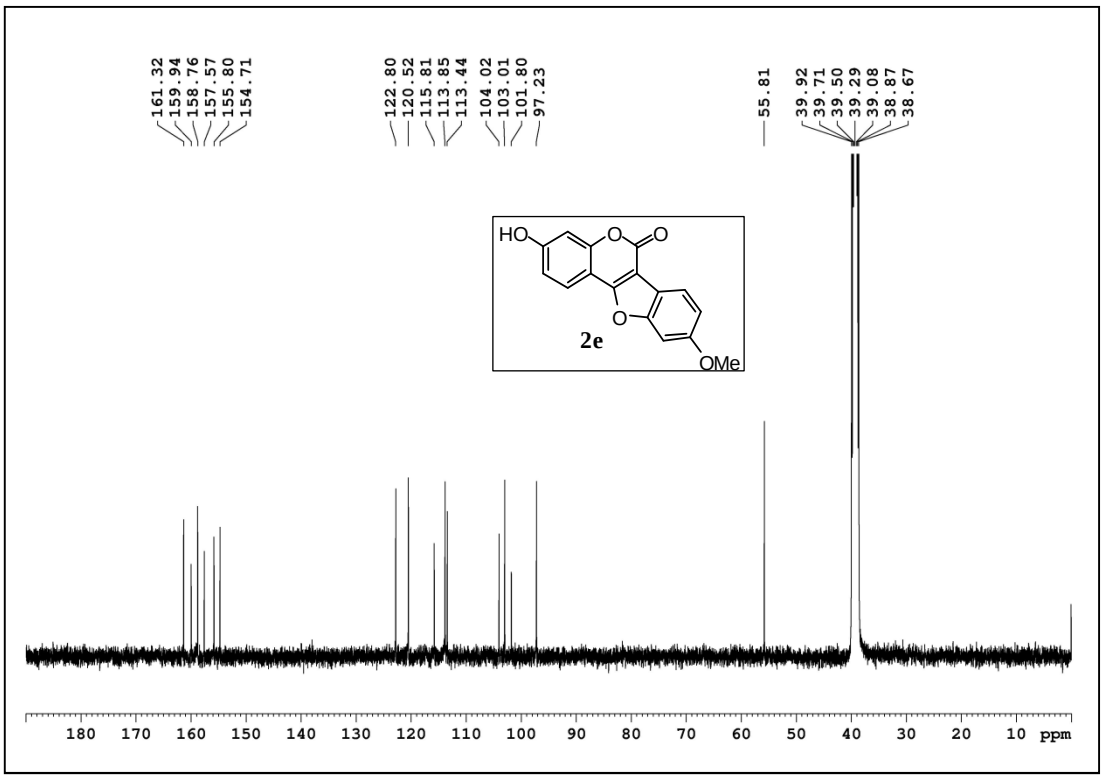
160.09
160.01
155.97
154.66
141.90
131.45
129.39
120.84
115.14
112.99
111.76
104.34
101.62
101.21
54.92
39.84
39.63
39.42
39.21
39.00
38.79
38.58
-0.00
HO
O
O
52x
HO
OMe
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm


10.888
7.881
7.860
7.790
7.769
7.475
7.471
7.110
7.105
7.089
7.084
6.975
6.970
6.953
6.948
6.926
6.922
3.863
3.536
2.523
2.519
2.515
0.000
HO
O
O
O
2e
OMe
ppm
1.02
1.26
1.13
1.05
1.18
1.21
1.00
3.33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158.76
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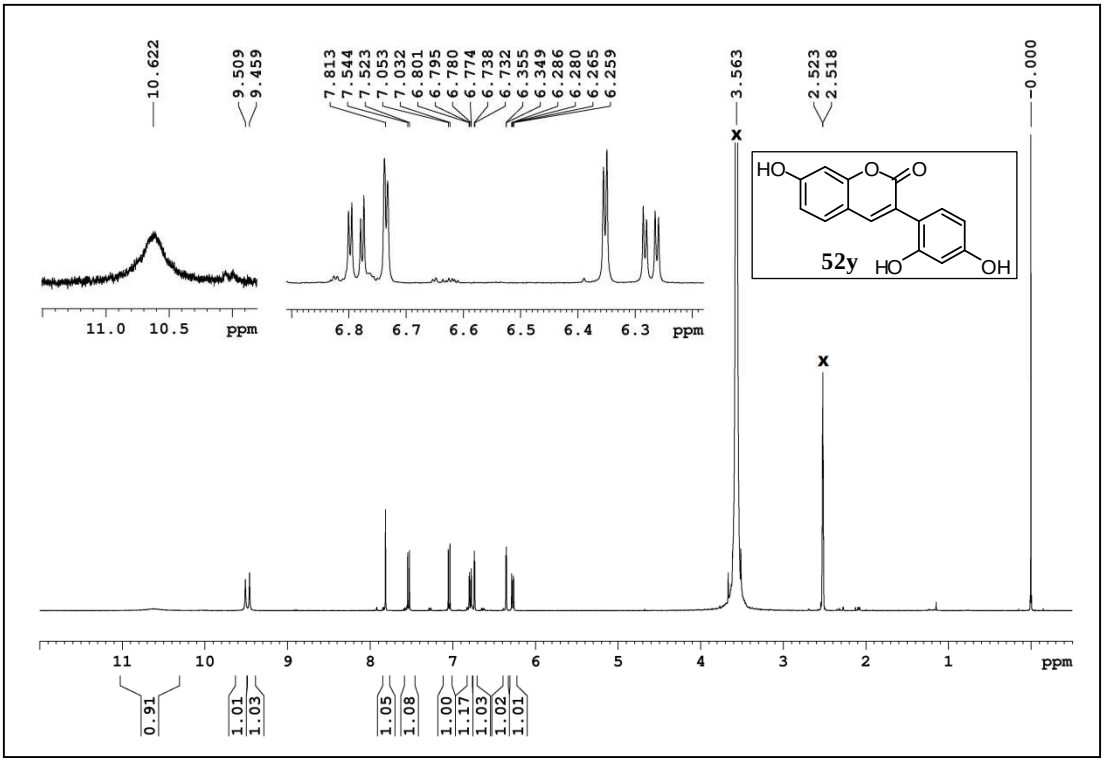
155.80
154.71
122.80
120.52
115.81
113.85
113.44
104.02
103.01
101.80
97.23
55.81
39.92
39.71
39.50
39.29
39.08
38.87
38.67
HO
O
O
O
2e
OMe
ppm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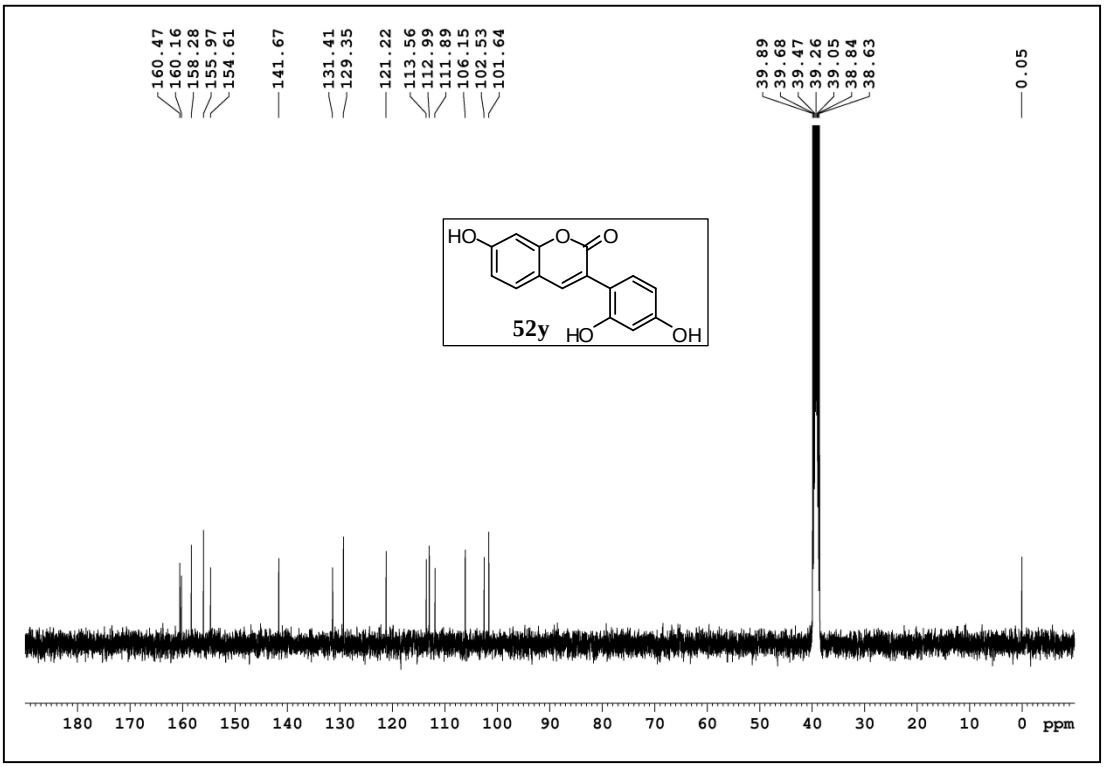
9.509
9.459
7.813
7.544
7.523
7.053
7.032
6.801
6.795
6.780
6.774
6.738
6.732
6.355
6.349
6.286
6.280
6.265
6.259
3.563
2.523
2.518
0.000
x
x
HO
O
O
52y
HO
OH
11.0
10.5
ppm
6.8
6.7
6.6
6.5
6.4
6.3
ppm
11
10
9
8
7
6
5
4
3
2
1
ppm
0.91
1.01
1.03
1.05
1.08
1.00
1.17
1.03
1.02
1.01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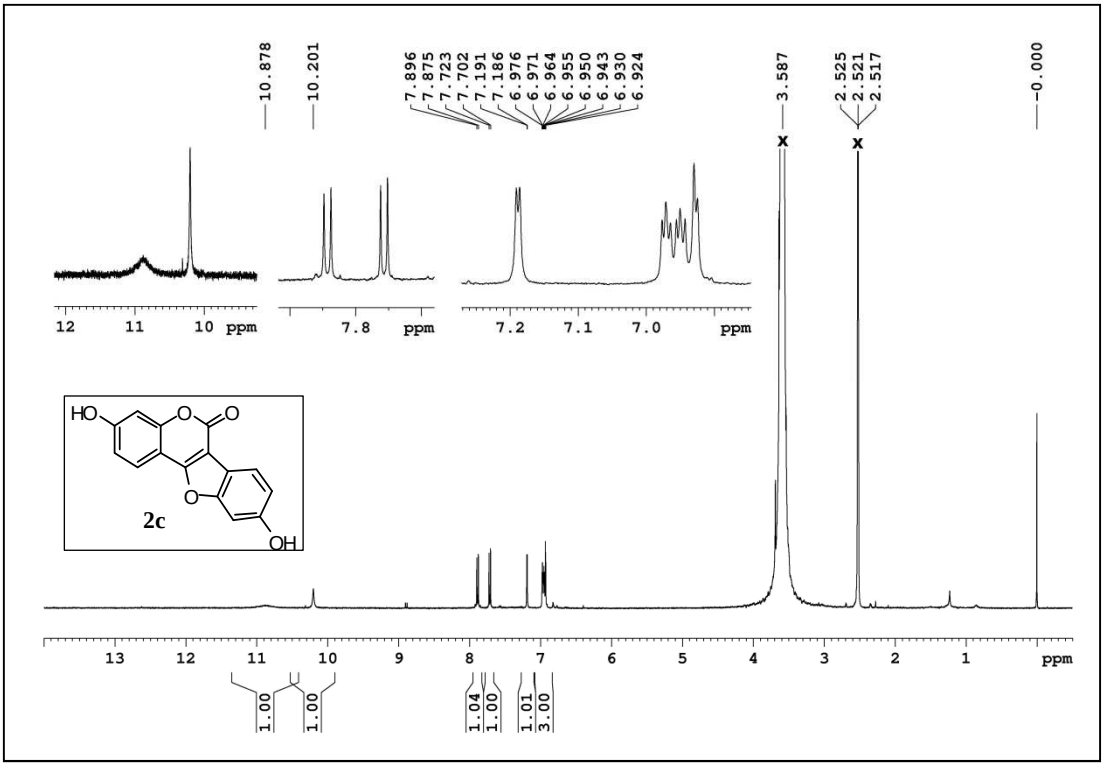
158.28
155.97
154.61
141.67
131.41
129.35
121.22
113.56
112.99
111.89
106.15
102.53
101.64
39.89
39.68
39.47
39.26
39.05
38.84
38.63
0.05
HO
O
O
52y
HO
OH
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm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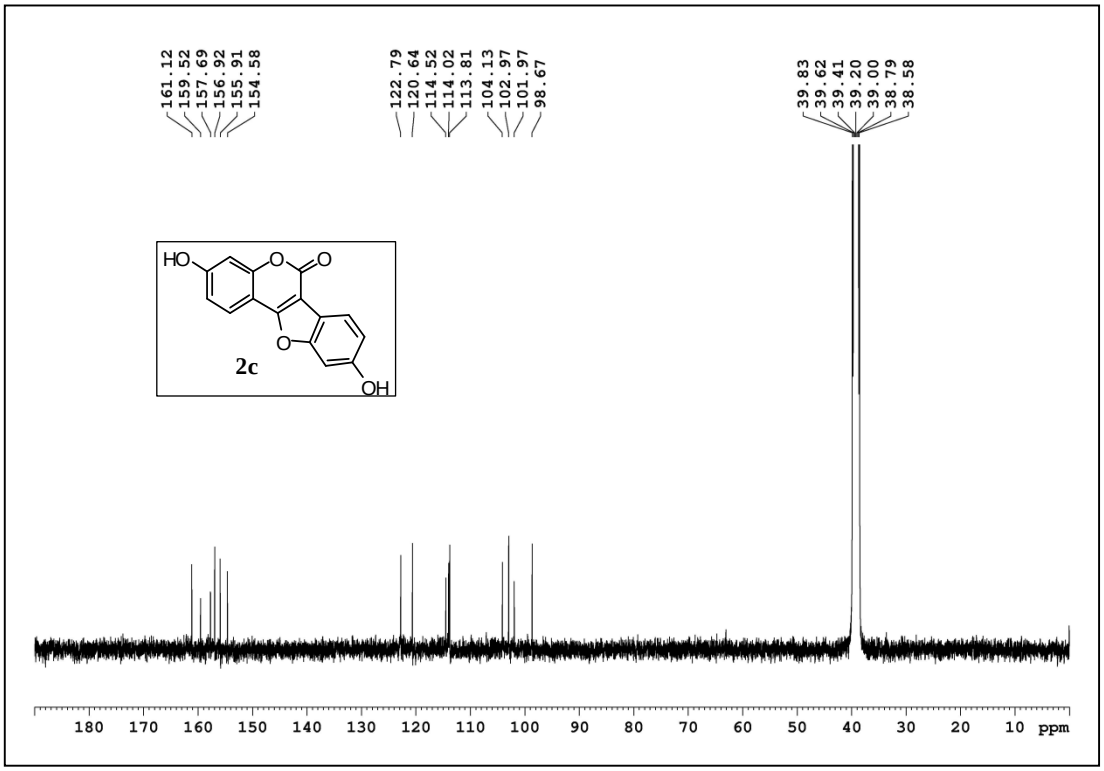
10.201
7.896
7.875
7.723
7.702
7.191
7.186
6.976
6.971
6.964
6.955
6.950
6.943
6.930
6.924
3.587
2.525
2.521
2.517
0.000
HO
O
O
O
OH
2c
ppm
1.00
1.00
1.04
1.00
1.01
3.00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154.58
122.79
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114.52
114.02
113.81
104.13
102.97
101.97
98.67
39.83
39.62
39.41
39.20
39.00
38.79
38.58
HO
O
O
O
OH
2c
ppm