Final Technical Report

On

"Citric acid mediated organic transformations"

MINOR RESEARCH PROJECT

FINANCIALLY ASSISTED BY

UGC-SERO, HYDERABAD

MRP No: F MRP - 6951/16 (SERO/UGC)

(Dec 2017 – Nov 2019)

ज्ञान-विज्ञान विमुक्तये

Submitted by

MADALA SUBRAMANYAM *M. Sc., M. Ed.*

Principal Investigator

Department of Chemistry

S.R & B.G.N.R. GOVT ARTS AND SCIENCE COLLEGE (AUTONOMOUS), KHAMMAM.

TELENGANA – 507 002

Khammam

02-11-2019.

To

The Joint Secretary,

South Eastern Regional office (SERO),

University Grants Commission,

Hyderabad.

// Through Proper Channel //

Sub: Minor Research Project – Madala Subramanyam, Lecturer in Chemistry, SR&BGNR. Govt. Arts & Science College (A), Khammam - Final Technical Report of MRP No: F MRP 6951/16 -Submitted – Req - Regd.

Ref: Your file No: F MRP-6951/16, Link No: 6951, Dated: 02-08-2017.

* * * * * *

Sir/Madam,

With reference to the subject cited above, I'm herewith submitting the final technical report of Minor Research Project No: F MRP-6951/16, entitled **"Citric acid mediated organic transformations"** which was undertaken by me during the period 2017-19, for your consideration and release of second installment of financial assistance.

Thanking you sir.

Yours sincerely,

(MADALA SUBRAMANYAM)

Principal Investigator

(Department of Chemistry)

Enclosures: Final audit report.

02-11-2019,

Khammam.

To

The Principal,

SR & BGNR. Govt. Arts & Science College (Autonomous),

KHAMMAM

Sir,

Sub:- Submission of final technical report-MRP No: F MRP-6951/16 (SERO/UGC) - Request for forwarding-Regd.

I'm herewith submitting the final technical report of Minor Research Project No: F MRP-6951/16, entitled **"Citric acid mediated organic transformations"** which was undertaken by me at our college during the period 2017-19. Hence, I'm requesting you to kindly forward to the UGC-SERO, Hyderabad.

Thanking your sir,

Yours faithfully,

(MADALA SUBRAMANYAM)

Lecturer in Chemistry.

Enclosures: 1). Final technical report-2017-19.

2). Final audit report-2017-19.

DECLARATION

I hereby declare that the Minor Research Project No: F MRP-6951/16 (SERO/UGC) entitled **"Citric acid mediated organic transformations"** is based on the original work carried out by me at the Department of Chemistry, SR&BGNR.Govt. Arts & Science College (A), Khammam. The extent and sources of information derived from the existing literature have been indicated throughout the report at appropriate places. I also affirm that this work is original and has not been submitted in part or full, for any other degree or diploma to any University or Institution.

Place: Khammam,

Date: 02-11-2019

(MADALA SUBRAMANYAM)
Lecturer in Chemistry
SR&BGNR.Govt. Arts &Scicence College(A),
Khammam.

GOVERNMENT OF TELENGANA

EDUCATION DEPARTMENT

CERTIFICATE

I, **Dr. B. Venkateswara Reddy**, Principal (FAC), SR & BGNR Government Arts and Science College (A), Khammam hereby certify that Mr. MADALA SUBRAMANYAM, Lecturer in Chemistry has carried out this minor research project work No: F MRP-6951/16 (SERO/UGC) entitled **"Citric acid mediated organic transformations"** in this institution during Dec 2017- Nov 2019.

Place: KHAMMAM

Date: 02-11-2019

PRINCIPAL

PRINCIPAL
SR&BGNR Govt. Arts & Science College
(Autonomous)
KHAMMAM.

ACKNOWLEDGEMENTS

This minor research project No: F MRP-6951/16 (SERO/UGC) was financially supported by generous grant from the UGC-SERO. I thankfully acknowledge the financial assistance provided be the UGC-SERO, Hyderabad.

I sincerely thank **Prof. M.V. Basaveswara Rao**, Dept. of chemisty, Krishna University, Machilipatnam and special officer, Dr.M.R.A.R. P.G-Centre, Nuzivid-521201, Andhra Pradesh, for his valuable guidance and constant encouragement, which enabled me in bringing this Project Report to the present form.

It gives me an immense pleasure and pride to express my deep sense of gratitude and respect to **Dr. K. Suresh Babu**, Principal Scientist, Centre for Natural Products & Traditional Knowledge, CSIR-Indian Institute of Chemical Technology, Hyderabad and **Dr. Koya Prabhakar Rao**, Assoc. Professor of Chemistry, Vignan's Foundation for Science, Technology and Research (VFSTR), Guntur, for their guidance and co-operation throughout the period of this project work and also for giving the spectral data of the compounds.

It is with high regards and profound respect that I express a deep sense of sincere gratitude to our JVR. Govt. College, Sathupally principal **Dr. G. Narasimha Rao** and my present working college principal **Dr. B. Venkateswara Reddy,** for their stimulating guidance, persistent inspiration and the support as and when needed throughout the project work.

I take this opportunity to thank all my colleagues of our Department of Chemistry, S.R&B.G.N.R. Govt. College (A), Khammam for their unreserved help and suggestions.

Special thanks to teaching and non-teaching staff of S.R&B.G.N.R. Govt. College (A), Khammam for their help, support and encouragement.

I express my heartfelt love and affection to my Parents, my Wife, my son Snehith, niece Lucky and all my family members for their moral support, constant encouragement and benevolence without which this work would remain unfinished.

I pay my devoted thanks to the almighty for giving me strength and the favorable circumstances to make this accomplishment.

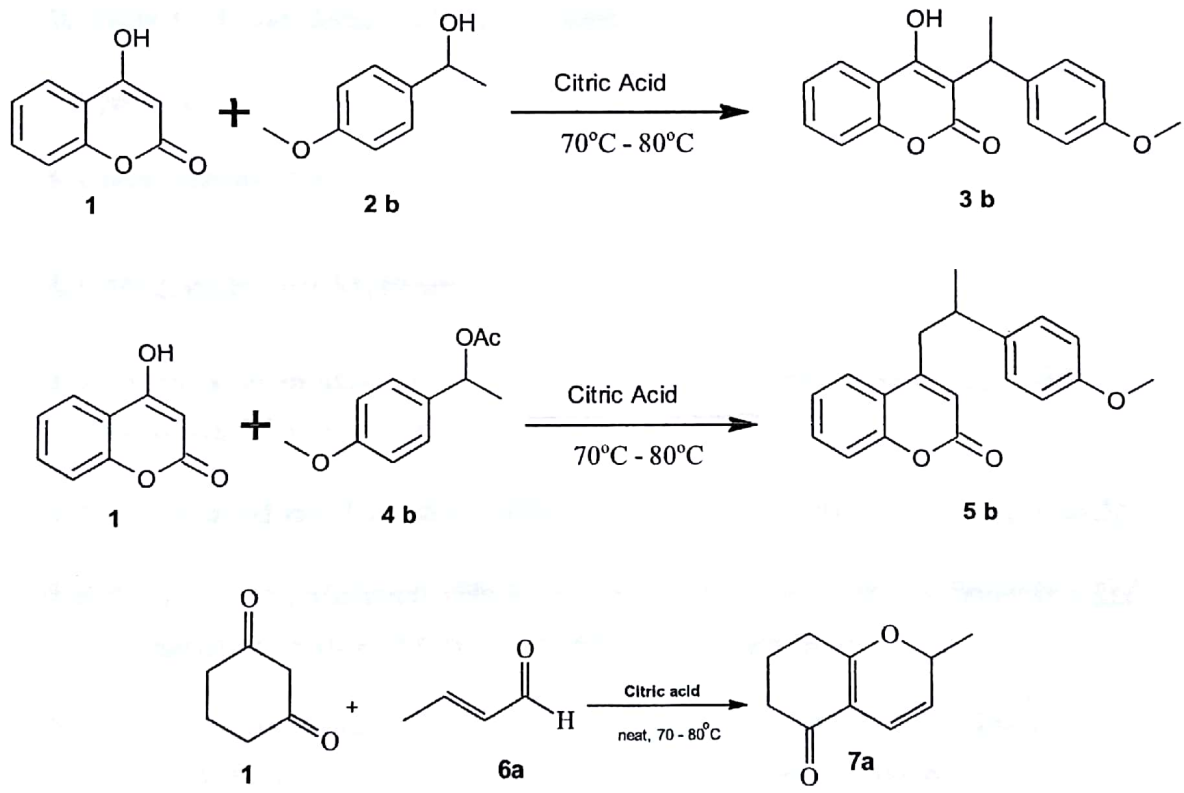
Finally I express my sincere thanks to one and all those who have contributed directly or indirectly for bringing out my investigation successfully.

(MADALA SUBRAMANYAM)

Principal Investigator

ABSTRACT

4-Hydroxycoumarins (2H-1-benzopyran-2-ones) have evoked a great deal of interest due to their biological properties and characteristic conjugated molecular architecture. Citric acid is a tricarboxylic weak organo acid which serves as organo catalyst several organic syntheses such as efficient synthesis of Quinolines and Biginelli compounds under solvent free conditions. Citric acid is used as the efficient catalyst for the C3-Alkylation of 4-Hydroxycoumarin with secondary benzyl alcohols and O-Alkylation with O-Acetyl compounds and also one-pot synthesis of 7,8-Dihydro-2H-Chrome-5-ones by formal [3+3] cycloaddition and 1,8-Dioxo-octahydroxanthanes via a Knoevenagal condensation.



CONTENTS

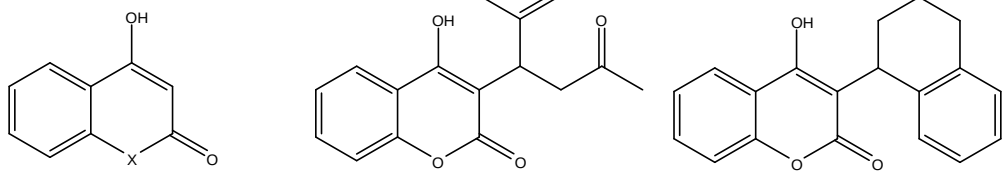
Chapter 1

Introduction

1. Introduction

4-Hydroxycoumarins (2H-1-benzopyran-2-ones, Figure 1) have evoked a great deal of interest due to their biological properties and characteristic conjugated molecular architecture. Many of them display important pharmacological effects, including analgesic,[1] anti-arthritis,[2] anti-inflammatory,[3] anti-pyretic,[4] anti-bacterial,[5] anti-viral,[6] and anti-cancer[7] properties. 4-Hydroxycoumarin and its derivatives have been effectively used as anticoagulants for the treatment of disorders in which there is excessive or undesirable clotting, such as thrombo phlebitis,[8] pulmonary embolism,[9] and certain cardiac conditions[10]. A number of comparative pharmacological investigations of the 4-hydroxycoumarin derivatives have shown good anticoagulant activity combined with low side effects and little toxicity.[11]

Figure 1: Structures of the 4-hydroxycoumarin (1), 4-hydroxythiocoumarin (2), and derivatives 3-4.



1 X=O, 4-Hydroxycoumarin
2 X=S, 4-Hydroxythiocoumarin

3 Warfarin

4 Coumatetralyl

The C_3 or O-alkylation of 4-hydroxycoumarin (formation of new C-C and C-O bond) is undoubtedly one of the most important and challenging reactions in synthetic chemistry due to its pharmaceutical utility as mentioned above and also can be diversified to synthesize 3,4-sub-stitued compounds.[12-15] Although there are several reports about the C_3-alkylation of 4-hydroxycoumarins, most of them need organic halides or boronic acid as substrates by Pd-catalyzed C-C bond formation or base mediated alkylation reactions.[16-20]

From the synthetic point of view, alcohols are an attractive source compared to the corresponding halides or boronic acid because of easy availability of starting materials and the generation of water as the only side product. Alternatively, the alkylation can also be performed under acidic conditions with alcohols as alkylating agents, which is not well

explored. A few methods that have been reported for the C_3-alkylation of 4-hydroxycoumarin so far with alcohols including strong acids, such as HCl, H_2SO_4, etc.[21-23], $Yb(OTf)_3$[24], $FeCl_3 \cdot 6H_2O$[25], Amberlite IR-120[26], molecular iodine[27], $Bi(OTf)_3$[28], $Fe(ClO_4)_3 \cdot xH_2O$[29], TMSOTf [30], $Bi(NO_3)_3 \cdot 5H_2O$/ Ionic liquid system[31], Ir-Sn bimetallic system[32]. However, processes involving conventional acids, are inherently associated with problems such as high toxicity, corrosion, catalyst waste and difficulty in separation and recovery. Some of these catalytic systems have several limitations such as longer reaction times, lack of reusability, poor yields, as well. Therefore, the development of a new efficient, catalytic method for the direct C_3-alkylation of hydroxy coumarin using alcohols is of greater importance and highly desirable.

In recent years, non-polluting and efficient catalytic technologies are much required, considering that environmental restrictions on emissions are covered in several legislations throughout the world. The substitution of homogeneous liquid acids by heterogeneous solid superacids as catalysts is expected to ease their separation from reaction mixture, less corrosion, allowing continuous operation as well as regeneration and neutralization of the catalyst and lowering the cost of process installation and maintenance.[33,34]

Synthesis of xanthenediones is a continuing hot topic because these moieties are privileged pharmacophores as well as valuable reactive intermediates for both synthetic and medicinal chemists.[35] Furthermore, these compounds can be used as dyes,[36] in laser technologies,[37] and as P^H sensitive fluorescent materials for visualization of biomolecules.[38] In addition, substituted xanthenes are structural key-units in several natural products.[39]

Many procedures exist for the synthesis of 1,8-dioxo-xanthenes involving $InCl_3/P_2O_5$,[40] [Hbim]BF_4/ultrasound,[41] silica-bonded S-sulfonic acid,[42] $PMA.SiO_2$,[43] p-dodecylbenzene sulfonic acid,[44] amberlyst-15,[45] $SmCl_3$,[46] Fe_3O_4 nanoparticles,[47] PEG-6000,[48] molecular iodine,[49] cat. H_2SO_4,[50] $ZrOCl_2 \cdot 8H_2O$,[51] p-TSA,[52] [bmim]HSO_4,[53] $Fe(HSO_4)_3$,[54] diammonium hydrogen phosphate,[55] etc. However, many of these methods include strong acidic reaction conditions, low yields, long reaction times, high temperatures or they are dedicated only to the application of aromatic aldehydes, use of toxic and costly reagents/catalysts, complex workup procedures, etc. Moreover, the recovery of the catalyst is also a problem.

Chapter 2

Origin of the Research Problem

2. Origin of the Research Problem

Promising synthetic approach to environmentally friendly chemistry is to minimize or eliminate the use of harmful organic solvents. Organic reactions under solvent-free conditions, cleaner product formation, and toxic or often volatile solvents are avoided.[56] In recent years, a lot of attention has been paid to organo catalysts owing to their eco-friendly and can proceed under aerobic atmosphere, other notable advantages are: usually less expensive and commercially available.[57] Citric acid is a tricarboxylic weak organo acid which serves as organo catalyst several organic syntheses such as efficient synthesis of Quinolines and Biginelli compounds under solvent free conditions.[58]

Now, in my present proposal of work Citric acid is will be tested and used as catalyst for the C_3-Alkylation of 4-Hydroxycoumarin with secondary benzyl alcohols and O-Alkylation with O-Acetyl compounds and also one-pot synthesis of 7,8-Dihydro-2H-Chrome-5-ones by formal [3+3] cyclo addition and 1,8-Dioxo-octahydroxanthanes via a Knoevenagal condensation.

Chapter 3

Review and Development on the Topic

3. Review and Development on the topic

The synthetic work related to the present proposed work is extensively studied and published in national and many international journals. The proposed work which is simpler, uses less expensive and less toxic catalyst citric acid. Hence, I am expecting the publication of the proposed work in international or national journal.

The C_3 or *O*-alkylation of 4-hydroxycoumarin (formation of new C-C and C-O bond) is undoubtedly one of the most important and challenging reactions in synthetic chemistry due to its pharmaceutical utility as mentioned above and also can be diversified to synthesize 3,4-substitued compounds.

Although there are several reports about the C_3-alkylation of 4-hydroxy- coumarins, most of them need organic halides or boronic acid as substrates by Pd-catalyzed C–C bond formation or base mediated alkylation reactions. From the synthetic point of view, alcohols are an attractive source compared to the corresponding halides or boronic acid because of easy availability of starting materials and the generation of water as the only side product.

Alternatively, the alkylation can also be performed under acidic conditions with alcohols as alkylating agents, which is not well explored. However, processes involving conventional acids, are inherently associated with problems such as high toxicity, corrosion, catalyst waste and difficulty in separation and recovery. Some of these catalytic systems have several limitations such as longer reaction times, lack of reusability, poor yields, as well. Therefore, the development of a new efficient, catalytic method for the direct C_3-alkylation of 4-hydroxycoumarin using alcohols is of greater importance and highly desirable.

Chapter 4

Objectives

4. Objectives

The main attention of this study is testing and use of citric acid as the efficient catalyst for the C3-Alkylation of 4-Hydroxycoumarin with secondary benzyl alcohols and O-Alkylation with O-Acetyl compounds and also one-pot synthesis of 7,8-Dihydro-2H-Chrome-5-ones by formal [3+3] cycloaddition and 1,8-Dioxo-octahydroxanthanes via a Knoevenagal condensation.

1). C3-Alkylation of 4-Hydroxycoumarin with secondary benzyl alcohols and O-Alkylation with O-Acetyl compounds mediated by citric acid.

2). Citric acid catalyzed efficient one-pot synthesis of 7,8-Dihydro-2H-Chrome-5-ones by formal [3+3] cycloaddition and 1,8-Dioxo-octahydroxanthanes via a Knoevenagal condensation.


Chapter 5

Experimental Work

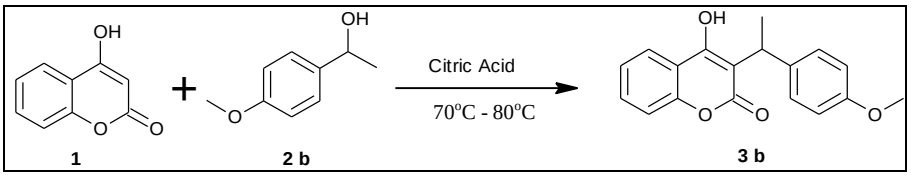
5. Experimental Work

5.1. Materials and methods

All melting points were determined on an Electrothermal Gallenkamp apparatus. 1H and 13C NMR spectra were recorded on a Varian Gemini Spectrometer 300 and 400 MHz respectively. IR spectra were recorded on Nicolet Fourier Transform spectrometer. Mass spectra were obtained on a 7070H or VG Autospec Mass spectrometer using LSIMS technique. Thin-layer chromatography (TLC) was performed on GF-25U (Anal. Tech) plates and silica gel glass-backed plates. Routine column chromatography was conducted using silica gel 100-200 mesh.

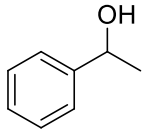
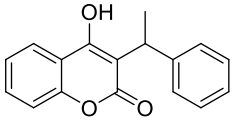
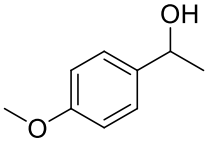
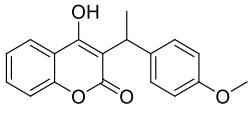
5.2. Citric acid mediated C_3-Alkylation of 4-Hydroxycoumarin with Secondary Benzyl Alcohols:

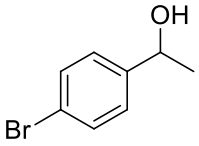
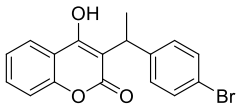
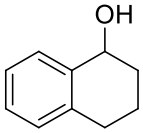
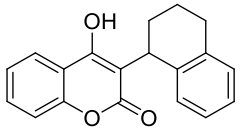
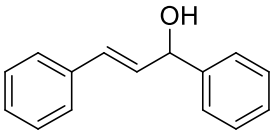
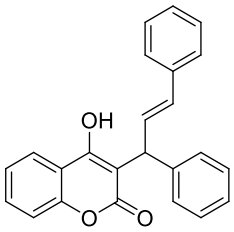
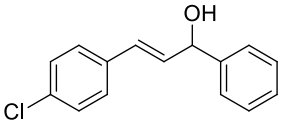
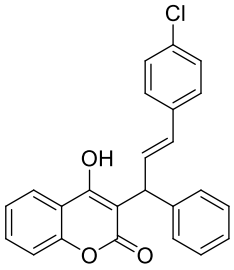
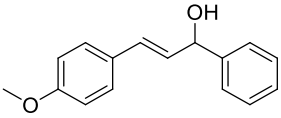
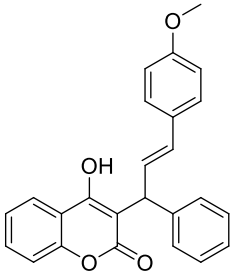
Citric acid, an eco-friendly catalyst for the direct C_3-alkylation of 4-hydroxycoumarins under neat conditions then gave high yields of alkylated derivatives with high purity. The schematic representation as shown in Scheme 1.

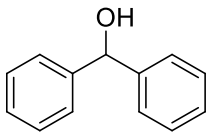
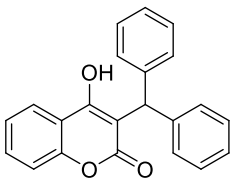


Scheme 1: C_3-Alkylation of 4-Hydroxycoumarin with Secondary Benzyl Alcohols.

Table 1: C_3-alkylation of 4-hydroxycomarin with various alcohols

Entry	Alcohol	Product	Time (h)	Yield(%)[a]
1			4	81
	2a	3a		
2			4	82

	2b	3b		
3	 2c	 3c	4	75
4	 2d	 3d	4.8	79
5	 2e	 3e	5	75
6	 2f	 3f	**5**	84
7	 2g	 3g	5	78

8	 2h	 3h	20	90

[a]Isolated yield after column chromatography

As is evident from Table 1, the alkylation proceeded well to afford the corresponding products in 75-81% yields, after 4h (entries 1-3, **Table 1**). As expected benzylic alcohols bearing electron donating groups such as methoxy (entry 2, **Table 1**) gave better yields compared to benzylic alcohol containing electron withdrawing group. Intrigued by these results, we adapted this protocol to synthesize an anti-coagulant compound, Coumatetralyl (C, **Scheme 4**; **3d**, **Table 1**) in 79% yield using 4-hydroxycoumarin with 1, 2, 3,4-tetrahydro-1-napthanol **(2d**).

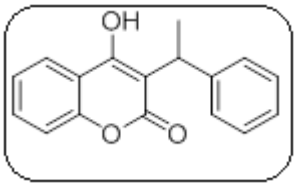
Moreover, we performed this reaction with substituted allylic alcohols (entries 5-6 and 7, Table 1) and excellent yields were obtained. When primary benzyl alcohols were used, they failed to give the expected product. These results clearly demonstrate that the direct C_3-alkylation of 4-hydroxycoumarin was successful only with secondary benzylic alcohols. Reaction of benzhydrol (**3h**) with 4-hydroxycoumarin did not proceed even after refluxing for 20 h (entry 8, **Table 1**).

5.2.1. General experimental procedure for the C_3-alkylation of 4-hydroxy coumarins

To a mixture of 4-hydroxycoumarin (1, 1.0 mmol) and secondary benzyl alcohol (2 a-h, 1.1 mmol) in citric acid (2.0 mmol) and the reaction mixture was heated for given time (**Table 1**) at 70-80^{o}C. After completion of the reaction (monitored by TLC), the reaction mixture was added into water. Adjusted to pH neutral with sodium carbonate and extracted in ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by silica gel column with petroleum ether/ethyl acetate (1:3) as eluent to afford the corresponding C_3-alkylated 4-hydroxycoumarin (3**a-g**).

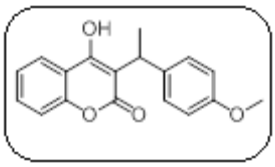
5.2.2. Spectral data:

4-Hydroxy-3-(1-phenylethyl)-2H-chromen-2-one (3a):



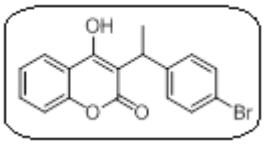
Off whitesolid; mp: 202–204 °C. IR (KBr): 3243, 1670, 1623, 1494, 1213,1160, 752 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): d 7.74 (d, J 8.4 Hz, 1H),7.61–7.53 (m, 3H), 7.45 (m, 2H), 7.36–7.23 (m, 3H), 6.42 (br s, 1H),4.70 (q, 6.4 Hz, 1H), 1.67 (d, J 6.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): d 163.6, 159.8, 152.4, 141.6, 131.8, 129.6, 127.7,127.3, 123.8, 122.9, 116.3, 116.0, 110.0, 34.5, 16.5 ppm. MS (ESI): m/z (rel. abund.%) 267 ($[M+1]^+$, 100).

4-Hydroxy-3-(1-(4-methoxyphenyl)ethyl)-2H-chromen-2-one (3b).



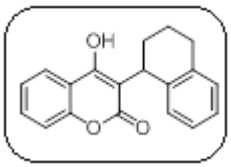
Off white solid; mp: 169–171°C. IR (KBr): 3384, 2970, 1670, 1520, 1241, 753 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d ,J 8.0 Hz, 1H), 7.52–7.48 (m, 1H), 7.40 (d, J 8.4 Hz, 2H), 7.30–7.21(m, 2H), 7.40 (d, J 8.4 Hz, 2H), 6.47 (br s, 1H), 4.66 (q, J 7.6 Hz, 1H),3.81 (s, 3H), 1.64 (d, J 7.6 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$):d 163.5, 159.8, 159.0, 152.4, 133.0, 131.7, 128.4, 123.8, 122.8, 116.3,116.1, 114.9, 110.0, 55.3, 33.7, 16.7 ppm. MS (ESI): m/z (rel. abund.%) ($[M+1]^+$, 100).

3-(1-(4-bromophenyl)ethyl)-4-hydroxy-2H-chromen-2-one (3c)



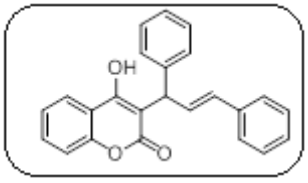
White solid, IR (KBr): 3430 (br),1721, 1664, 1610, 1210, 752 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02–7.70 (d, 1 H), 7.63–7.58 (m, 1 H), 7.45–7.25 (m, 6 H), 4.57 (d, *J* = 7.3 Hz, 1 H), 1.62 (d, *J* = 7.3 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0,160.1, 153.0, 140.9, 133.2, 132.5, 128.9, 124.3, 122.6,116.8, 115.7, 110.1, 34.3, 16.8. MS (ESI): m/z (rel. abund.%) =345.0(100) $[M]^+$, 347.0(98) $[M]^+$, 348.0(22) $[M]^+$, 343.0(17) $[M]^+$.

4-hydroxy-3-(1,2,3,4-tetrahydronaphthalen-1-yl)-2H-chromen-2-one (3d)



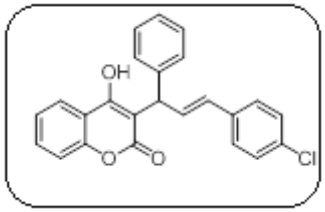
White solid, mp: ν 165-170 °C.IR (KBr): 2930, 1672, 1631, 1221, 1139, 753 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (dd, *J* =14.2 Hz, 1H), 7.50 (t, 1H), 7.30-7.29 (m, 3H),7.23-7.22(m, 3H), 4.62 (t, *J* =9.8 Hz, 1H), 3.0 (t, *J* =9.0 Hz, 2H), 2.27-2.21 (m, 1H), 2.0-1.9 (m, 3H) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0, 160.3, 152.6, 138.1, 134.7, 132.0, 130.7, 129.4, 128.3, 127.8, 124.1, 123.3, 116.4, 116.1, 109.4, 36.5, 30.3, 29.8, 22.1 ppm. MS (ESI): m/z (rel. abund.%) 293.0 ($[M+1]^+$,100).

3-[(E)-1,3-diphenyl-2-propenyl]-4-hydroxy-2H-2-chromenone (3e).



White solid.mp: 155-157 °C. IR (KBr): 3330, 1671, 1624, 1610, 1494, 1392, 1201, 754 cm^{-1}. 1H NMR ($CDCl_3$, 400 MHz): δ 7.78 (dd, J=6.8, 8.0 Hz, 1H),7.57-7.54 (m, 2H),), 7.44-7.22 (m, 10H), 6.81(dd, J=6.0, 16.0 Hz, 2H), 6.50 (d, J=16.0 Hz, 1H), 5.49 (d, J=6.5 Hz, 1H).^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.5, 161.2, 152.7, 140.0, 136.4, 133.8, 132.2, 129.2, 128.7, 128.4, 128.1, 128.1, 127.6, 126.6, 124.1, 123.3, 116.6, 116.0, 106.7, 44.1. MS (ESI): m/z (rel. abund.%) 353 ($[M-1]^-$, 100)

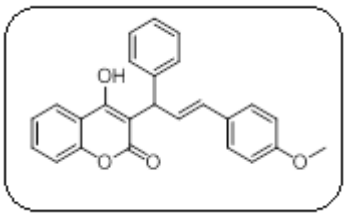
3-((*E*)-3-(4-chlorophenyl)-1-phenylallyl)-4-hydroxy-2*H*-chromen-2-one (3f):



Pale yellow solid, mp: 168-171°C. IR (KBr): 3327, 1673, 1630, 1619, 1474, 1401, 1212, 752 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84-7.75 (m, 1H), 7.56-7.1 (m, 1H), 7.42-7.26 (m, 10H),7.26 (br S 1H) 6.78-6.67 (m, 2H), 6.50 (d, *J*=16.4 Hz, 1H), 5.48 (d, *J*=6 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9, 160.9, 152.5, 140.1, 136.2, 133.7, 132.2, 1130.0, 128.7, 128.2, 127.9, 127.6, 126.6, 124.1, 123.2, 116.5, 115.8, 106.5, 44.0 ppm. MS (ESI): m/z (rel. abund.%) 389 (M^+, 100), 391 (M^+, 38), 390 (M^+, 25) ($[M+1]^+$).

(E)-3-(1,3-Diphenylallyl)-6-ethoxy-4-hydroxy-2H-chromen-2-one (3g).



White solid; mp: 154–155 °C. IR (KBr): 3339, 1721, 1570, 1490, 1216, 1199, 743, 721 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.24 (m,11H), 7.19 (d, 2.8 Hz,1H), 7.12 (dd, J 6.0, 9.2 Hz,1H), 6.99 (s,1H), 6.75 (dd, J 6.0,16.0 Hz,1H), 6.52 (d, J 16.0 Hz,1H), 5.48(d, J 6.0 Hz,1H), 4.03 (q, J 6.8 Hz, 2H),1.14 (t, J 6.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): d δ 163.4, 160.8,155.2, 147.1,139.6,136.1, 133.8, 129.2, 128.6, 128.2, 128.0, 128.0, 127.6, 126.5, 120.9, 117.6, 116.1, 106.5, 105.4, 64.1, 44.0, 14.7 ppm. MS (ESI): m/z (rel. abund.%) ($[M+1]^+$, 100).

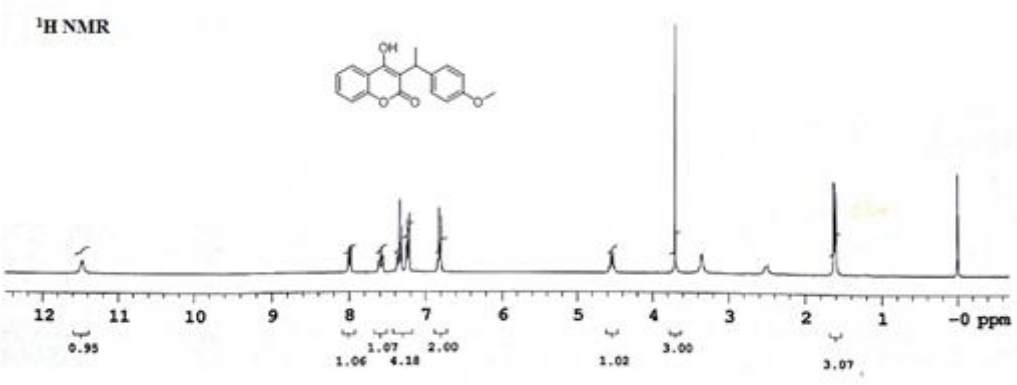


Figure 1. ^{1}H NMR of 4-Hydroxy-3-(1-(4-methoxyphenyl)ethyl)-2H-chromen-2-one (3b)

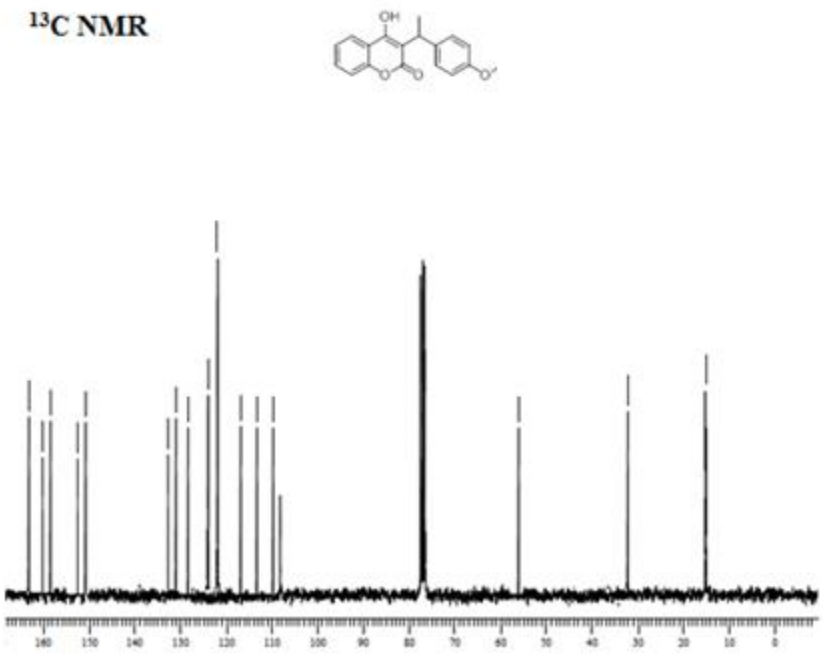


Figure 2. ^{13}C NMR of 4-Hydroxy-3-(1-(4-methoxyphenyl)ethyl)-2H-chromen-2-one (3b)

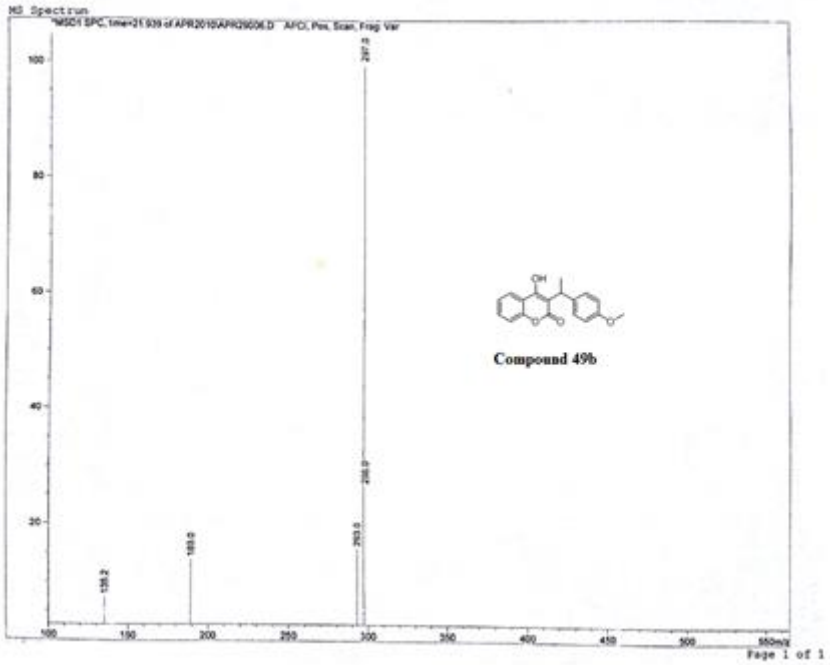


Figure 3: Ms-Spectra of 4-Hydroxy-3-(1-(4-methoxyphenyl) ethyl)-2H-chromen-2-one (3b)

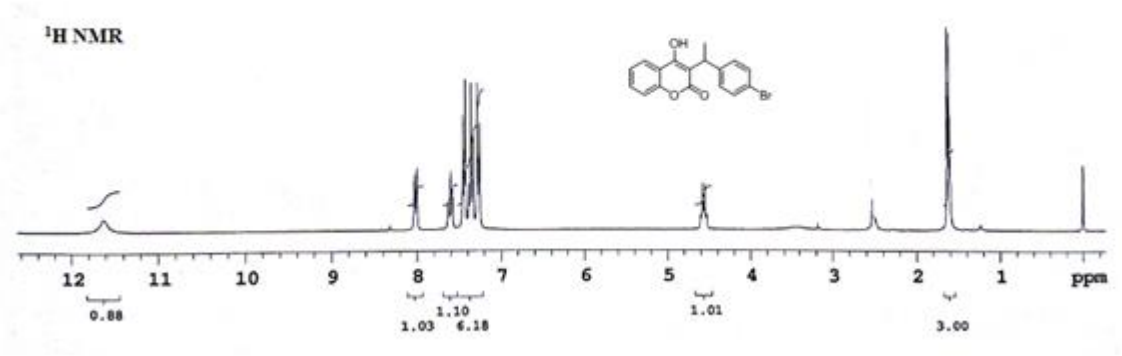


Figure 4. ^{1}H NMR 3-(1-(4-bromophenyl)ethyl)-4-hydroxy-2H-chromen-2-one (3c)

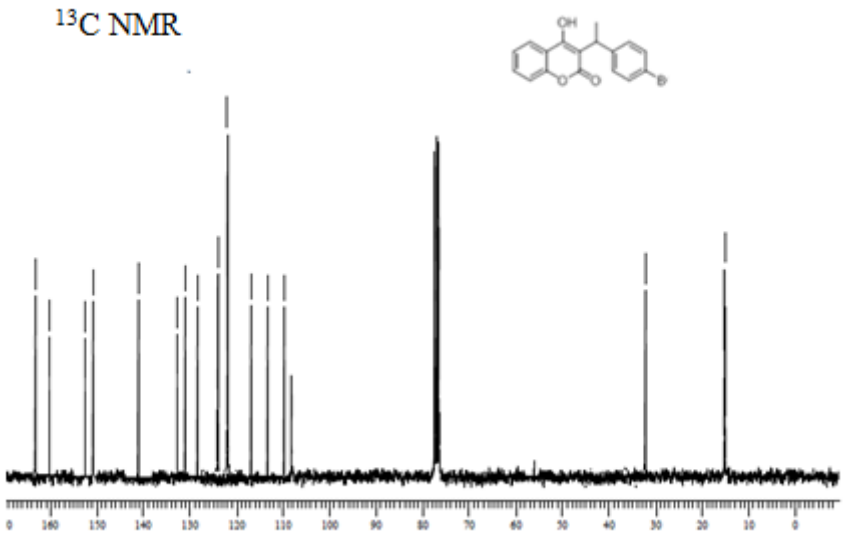


Figure 5 . ^{13}C NMR 3-(1-(4-bromophenyl)ethyl)-4-hydroxy-2H-chromen-2-one (3c)

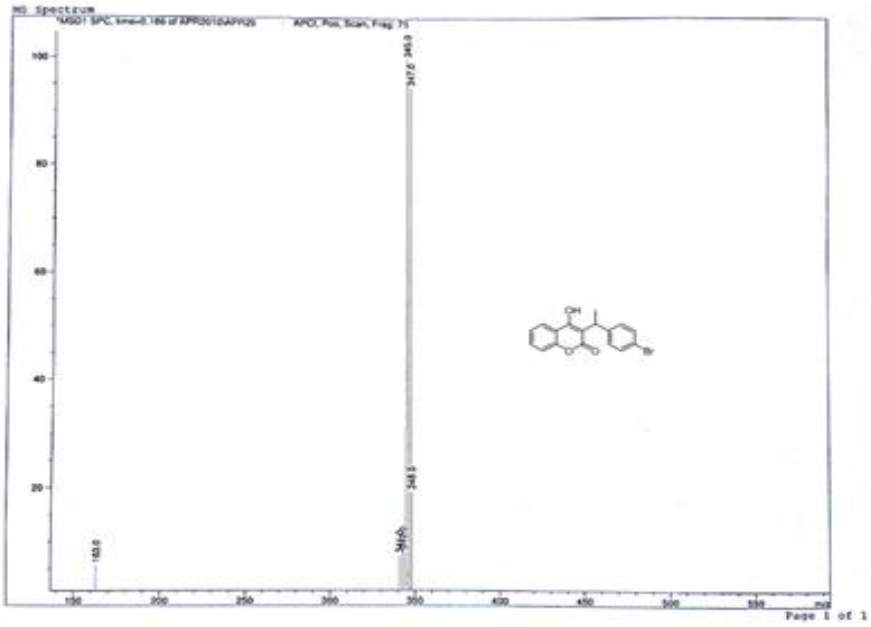


Figure 6. Ms-Spectra of 3-(1-(4-bromophenyl)ethyl)-4-hydroxy-2H-chromen-2-one (3c)

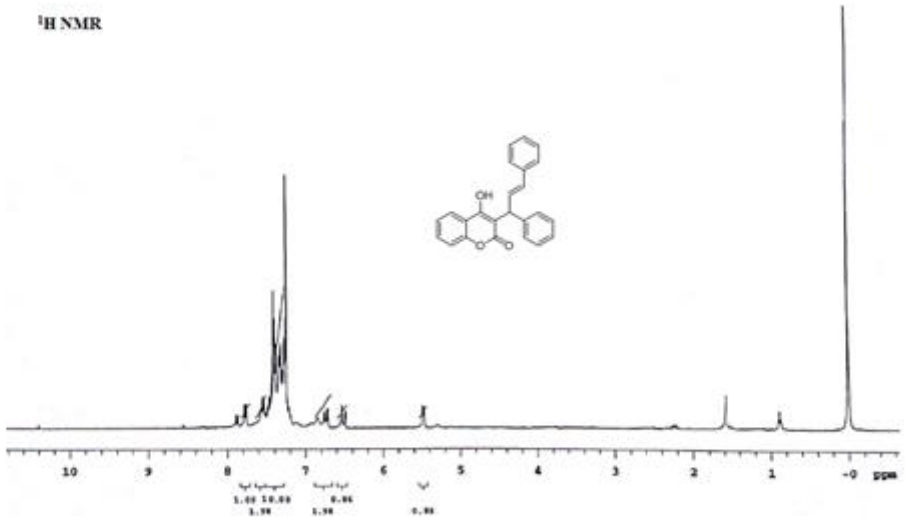


Figure 7. ^{1}H NMR of 3-[(E)-1,3-diphenyl-2-propenyl]-4-hydroxy-2H-2-chromenone (3e).

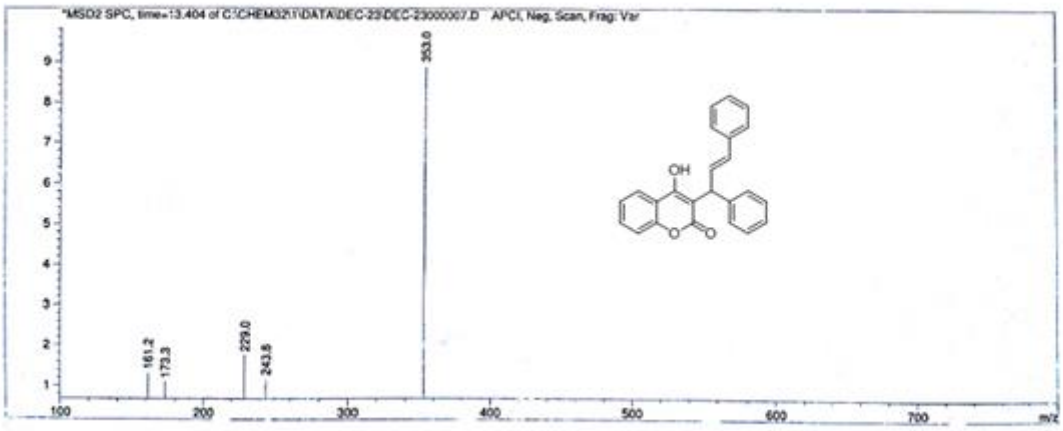


Figure 8. ^{13}C NMR of 3-[(E)-1,3-diphenyl-2-propenyl]-4-hydroxy-2H-2-chromenone (3e)

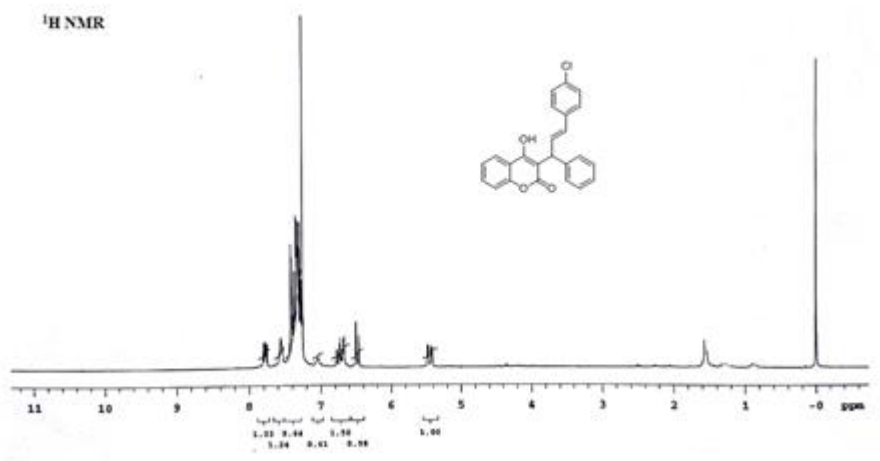


Figure 9. ^{1}H NMR of 3-((*E*)-3-(4-chlorophenyl)-1-phenylallyl)-4-hydroxy-2*H*-chromen-2-one (3f)

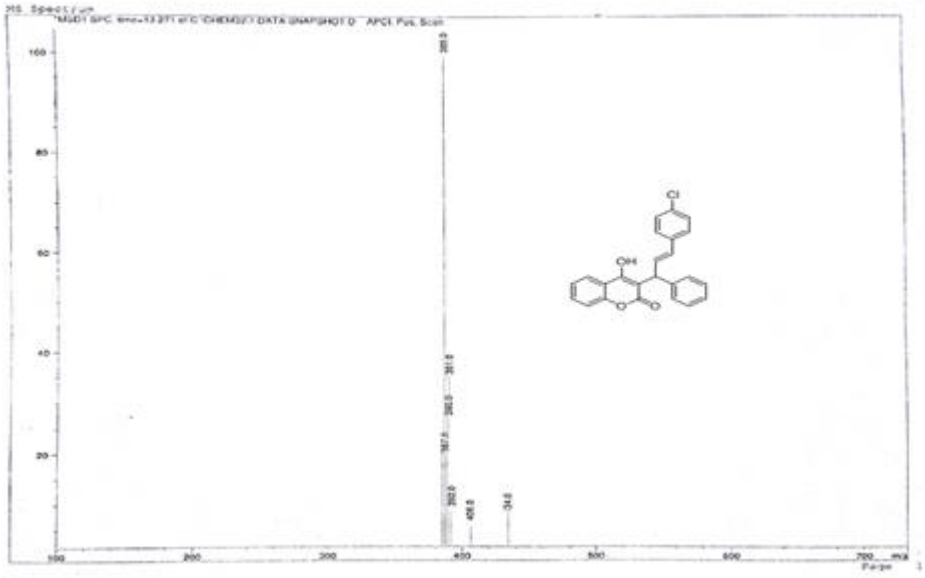


Figure 10. Ms-Spectra of 3-((*E*)-3-(4-chlorophenyl)-1-phenylallyl)-4-hydroxy-2*H*-chromen-2-one(3f)

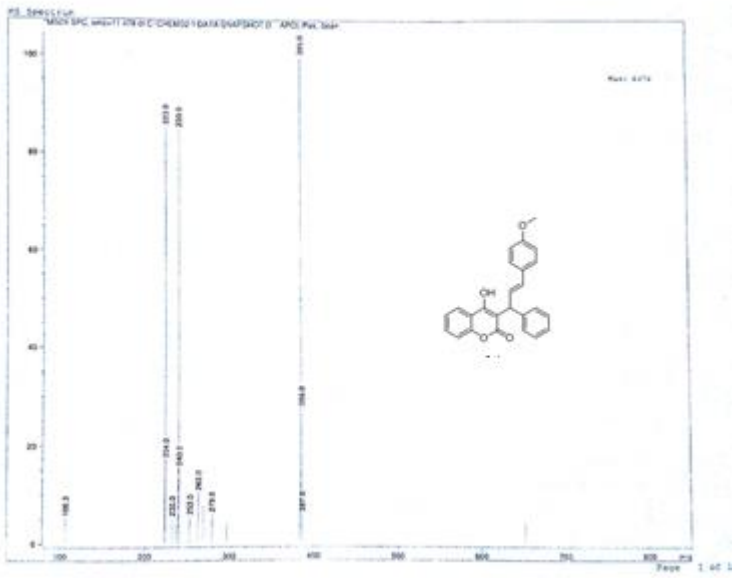
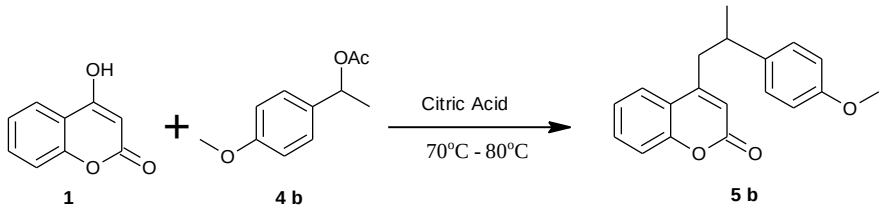


Figure 11. Ms-Spectra of (E)-3-(1,3-Diphenylallyl)-6-ethoxy-4-hydroxy-2H-chromen-2-one (3g)

5.3. Citric acid mediated *O*-Alkylation with *O*-Acetyl Compounds:

After successful C_3-alkylation of 4-hydroxycoumarin with secondary benzyl alcohols (new C-C bond formation), we turned our attention to test the feasibility of secondary benzyl acetates (prepared instantly for the purpose) reacting with 4-hydroxycoumarins.

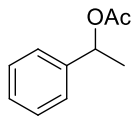
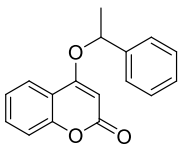
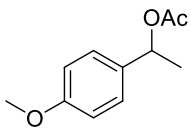
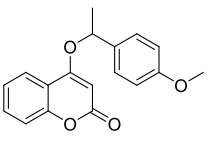
We reported the *O*-Alkylation of 4-hydroxycoumarins with *O*-Acetyl Compounds with eco-friendly catalyst, citric acid under neat reaction conditions at 70°C to 80°C was shown in scheme 2.

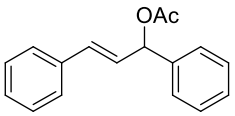
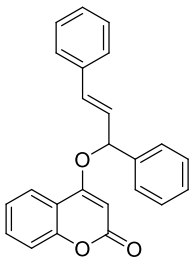
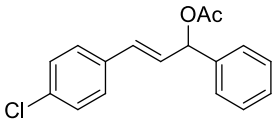
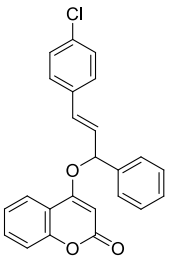
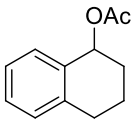
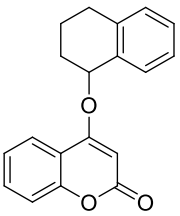
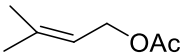
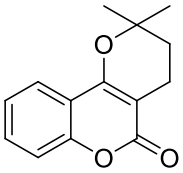


Scheme 2: *O*-Alkylation of 4-Hydroxycoumarin with *O*-Acetyl Compounds

The alkylation proceeded extremely well to afford O- alkylated coumarins (**5a-e**) in moderate to good yields (69-87%) in the specified time (**Table 2**). Unexpectedly, when prenyl acetate (**4f**) was reacted with 4-hydroxycoumarin, we isolated pyranocoumarin in good yield (entry **6**, **Table 2**) instead of expected *O*-alkylated product. This method provides a mild and straight forward route to multi-substituted pyranocoumarins.

Table 2: Citric acid mediated *O*-Alkylation to *O*-Acetylated derivatives

Entry	Alcohol	Product	Time (h)	Yield(%)a
1	 4a	 5a	4	76
2	 4b	 5b	4	83

3	 4c	 5c	5	79
4	 4d	 5d	5	74
5	 4e	 5e	6	87
6	 4f	 5f	5	69

[a]Isolated yield after column chromatography

5.3.1. General experimental procedure for the O-alkylation of 4-hydroxy coumarins

To a mixture of 4-hydroxycoumarin (1, 1.0 mmol) and secondary benzyl acetate (4 a-f, 1.1 mmol) in citric acid (2.0 mmol) and the reaction mixture was heated for given time (**Table 2**) at 70-80^{o}C. After completion of the reaction (monitored by TLC), the reaction mixture was added into water. Adjusted to pH neutral with sodium carbonate and extracted in ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by silica gel column with petroleum ether/ethyl acetate (1:3) as eluent to afford the corresponding C_3-alkylated 4-hydroxycoumarin (5**a-f**).

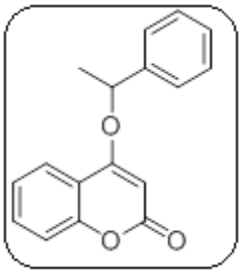
5.3.2. Characterization of compound:

The ^{1}H and ^{13}C NMR spectrum of **(5a)** was compared with 1-phenyl ethyl acetate **(4a)**, the absence of acetyl three protons with appearance of five aromatic protons and one olefinic proton it indicates the O-alkylation on 4-hydroxy coumarin. Aliphatic signal corresponding to three and one protons indicate presence of saturated phenyl ethoxy proton at 1.68 (d, *J*= 9.6 Hz, 3H), and 4.74 (q, *J*=9.6 Hz, 1H). Brod singlet at 5.99 (br s, 1H), 7.64 (d, *J* =12.4 Hz, 1H), corresponds to coumarin olifenic proton and signel at 7.64 (d, *J* =12.4 Hz, 1H), 7.64-7.43 (m, 5H), 7.64-7.42 attributed to CH aromatic protons.

This is further supported by ^{13}C with two aliphatic carbons at δ 16.8, 34.8 and 110.3 as expected for methyl and ethylene carbons along with expected two number of attached oxygen and carbonyl signels in the region 163.8,152.6 and 160.0 expected aromatic signals 152.6, 141.8, 132.1, 129.8, 127.7, 127.5, 123.9, 123.0, 116.3 and 116.2. In the mass spectrum M^{+} appears at 267.3 as per interpretation confirm the structure of (**5a)**.

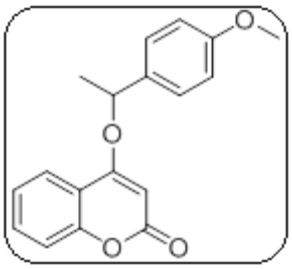
5.3.3. Selected Spectral data:

4-(1-Phenylethoxy)-2H-chromen-2-one (5a).



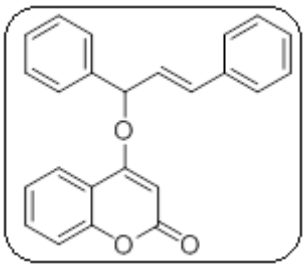
Off white solid; mp: 214-218 °C. IR (KBr): 1669, 1621, 1492, 1401, 1218, 1168, 741 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* =12.4 Hz, 1H), 7.64-7.43 (m, 5H), 7.64-7.42 (m, 2H), 7.23 (dd, *J* =10.8 Hz, 1H), 5.99 (br s, 1H), 4.74 (q, *J*=9.6 Hz, 1H), 1.68 (d, *J*= 9.6 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 160.0, 152.6, 141.8, 132.1, 129.8, 127.7, 127.5, 123.9, 123.0, 116.3, 116.2, 110.3, 34.8, 16.8 ppm. MS (ESI): m/z (rel. abund.%) 267.3 ($[M+1]^{+}$, 100).

4-(1-(4-methoxyphenyl) ethoxy)-2H-chromen-2-one (5b):



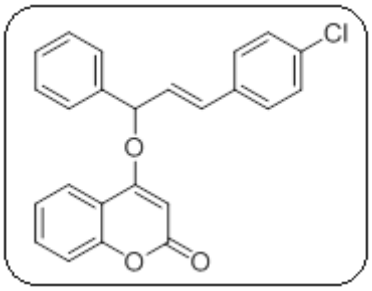
Off white solid. mp: 180-184 °C. IR (KBr): 1673, 1628, 1514, 1249 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (dd, *J* = 8.8Hz, 1H), 7.48-7.52 (m, 2H), 7.41 (d, *J* =11.2 Hz, 1H), 7.26-7.22 (m, 2H), 6.99 (d, *J* =4 Hz, 2H), 6.04 (s, 1H), 4.65 (q, *J* =10 Hz, 1H), 3.79 (s, 3H), 1.60 (d, *J* = 9.6 Hz, 3H). ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 159.8, 159.1, 152.3, 133.1, 131.7, 128.5, 123.8, 122.6, 116.2, 116.1, 114.9, 110.0, 55.3, 33.6, 16.8 ppm. MS (ESI): m/z (rel. abund.%) 297.2 ($[M+1]^+$, 100).

4-((E)-1,3-diphenylallyloxy)-2H-chromen-2-one (5c):



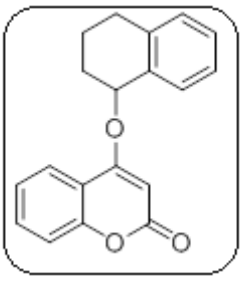
Pale yellow solid, mp: 132-136 °C. IR (KBr): 1678, 1626, 1613, 1501, 1394, 1203, 757 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* =7.2 Hz, 1H), 7.55 (t, *J* =8 Hz, 1H), 7.24-7.64 (m, 12H), 6.94 (br, s 1H), 6.67 (dd, *J* =6.4, 9.6 Hz, 1H), 6.52 (d, *J* =16.4 Hz, 1H), 5.47 (d, *J* = 5.6 Hz, 1H) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 161.5, 152.4, 139.7, 136.3, 133.9, 132.4, 129.2, 128.7, 128.2, 128.7, 127.7, 126.4, 124.4, 123.1, 116.5, 115.7, 106.4, 43.5 ppm. MS (ESI): m/z (rel. abund.%) 355.0 ($[M+1]^+$,100).

4-((E)-3-(4-chlorophenyl)-1-phenylallyloxy)-2H-chromen-2-one (5d):



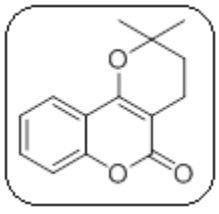
Pale yellow solid, mp: 154-158 °C. IR (KBr): 1676, 1629, 1616, 1502, 1398, 1210, 758 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (dd, *J* =8, 14.8 Hz, 1H), 7.41-7.14 (m, 12H), 6.78-6.67 (m, 1H), 6.48 (d, *J* =16.4 Hz, 1H), 6.41-6.35 (m, 1H), 5.44 (dd, *J*=5.9 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4, 161.1, 152.8, 139.7, 136.2, 133.7, 132.4, 129.6, 128.4, 128.1, 128.0, 127.8, 126.5, 124.1, 123.3, 116.7, 115.6, 106.5, 43.9 ppm. MS (ESI): m/z (rel. abund.%) 387 (M^-,100), 389 (M^-, 30) ($[M-1]^-$).

4-(1,2,3,4-tetrahydronaphthalen-4-yloxy)-2H-chromen-2-one (5e):



Off white solid, mp: 178-180 °C. IR (KBr): 2938, 1674, 1628, 1389, 1214, 1148, 751 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ7.65 (dd, *J* =12.8 Hz, 1H), 7.52 (t, 1H), 7.34-7.21 (m, 6H), 5.78 (s, 1H), 4.60 (t, *J* =10 Hz, 1H), 2.93 (t, *J* =8.8 Hz, 2H), 2.25-2.20 (m, 1H), 1.94-1.80 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0, 160.3, 152.6, 138.1, 134.7, 132.0, 130.7, 129.4, 128.3, 127.8, 124.1, 123.3, 116.4, 116.1, 109.4, 36.5, 30.3, 29.8, 22.1 ppm. MS (ESI): m/z (rel. abund.%) 293 ($[M+1]^+$,100).

3,4-dihydro-2,2-dimethylpyrano [3,2-c]chromen-5(2H)-one (5f):



Semi solid. IR (KBr): 1721, 1636, 1614, 1497, 1451, 1383, 1276, 1203, 1171, 1118, 1016, 764, 698 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (dd, *J* =10 Hz, 1H), 7.61-7.57 (m, 1H), 7.39-7.30 (m, 2H), 2.66 (t, *J* = 6.8 Hz, 2H), 1.87 (t, *J* = 6.4 Hz, 2H) 1.47 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.03, 60.1, 150.3, 128.4, 125.5, 121.6, 117.4, 100, 78.2, 35.5, 27.7, 15.8 ppm. MS (ESI): m/z (rel. abund.%) 231.3 ($[M+1]^+$,100).

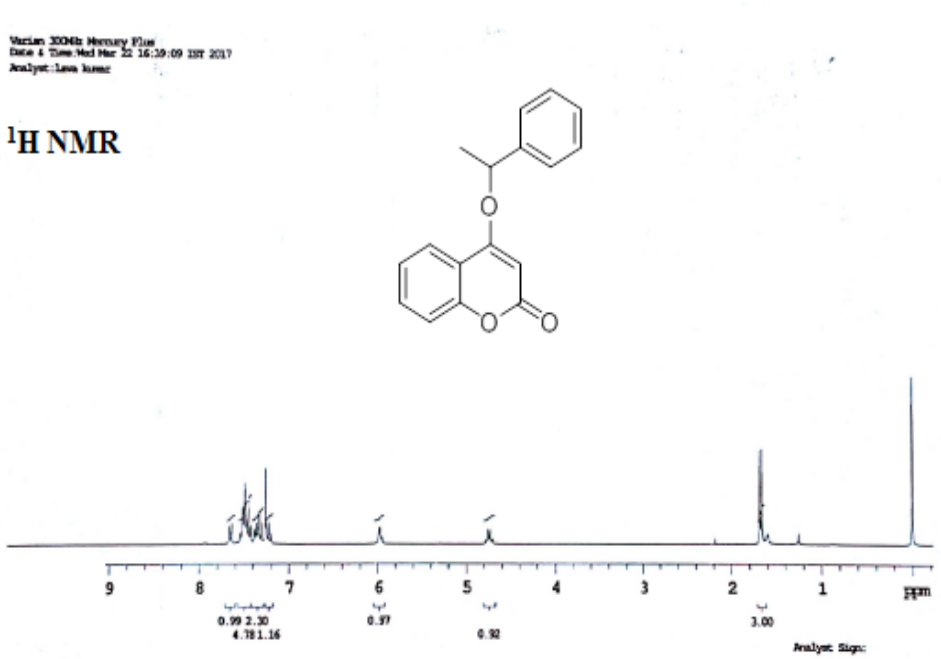


Figure:12 ^{1}H NMR of 4-(1-Phenylethoxy)-2H-chromen-2-one (5a).

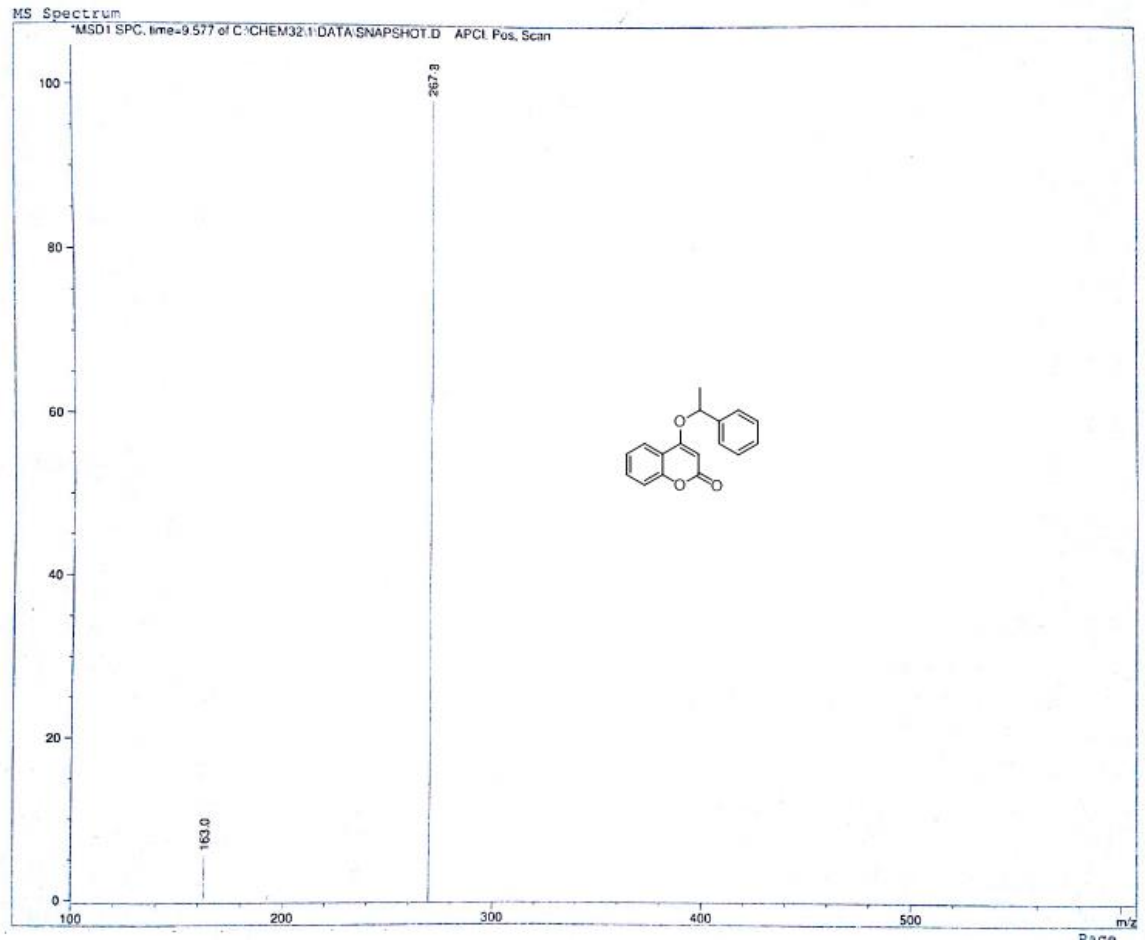


Figure:13 Ms-Spectra of 4-(1-Phenylethoxy)-2H-chromen-2-one (5a)

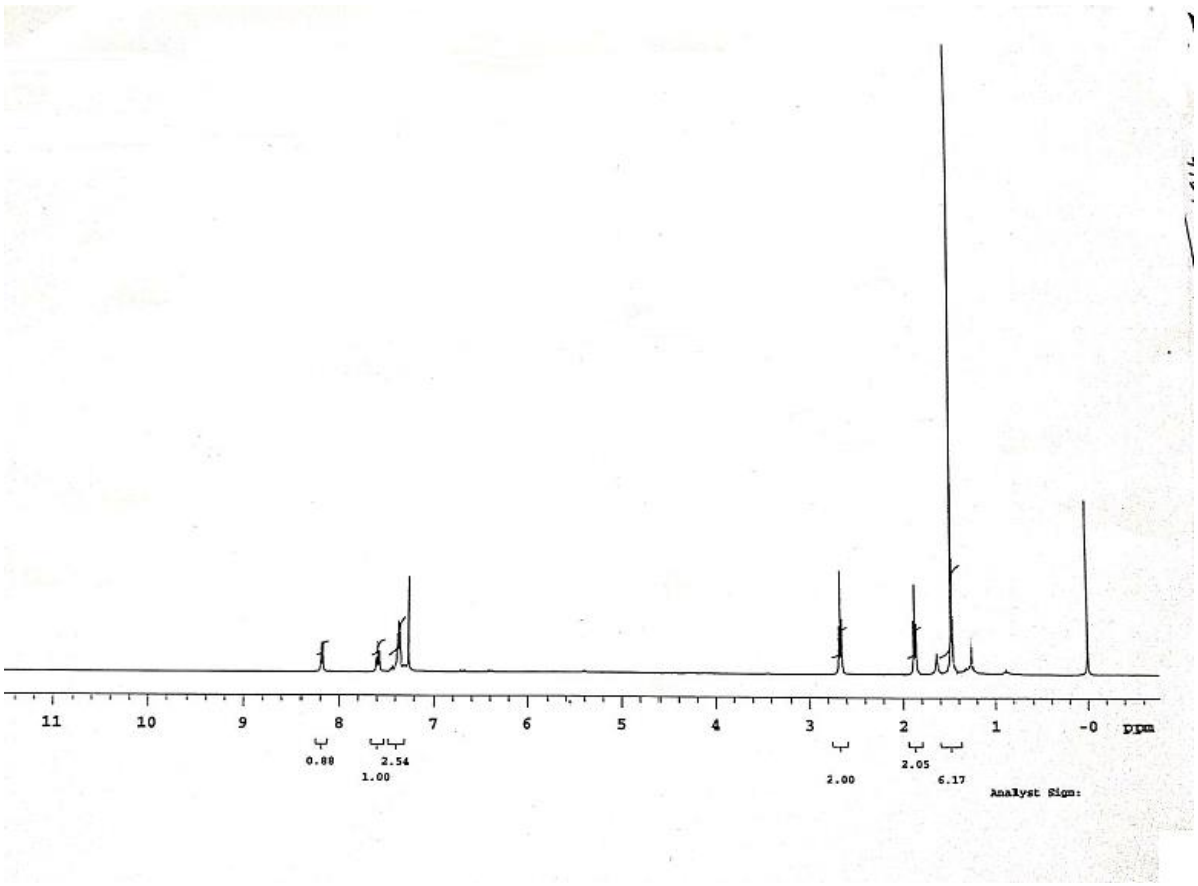


Figure:14 ^{1}H NMR of 3,4-dihydro-2,2-dimethylpyrano [3,2-c]chromen-5(2H)-one (5f)

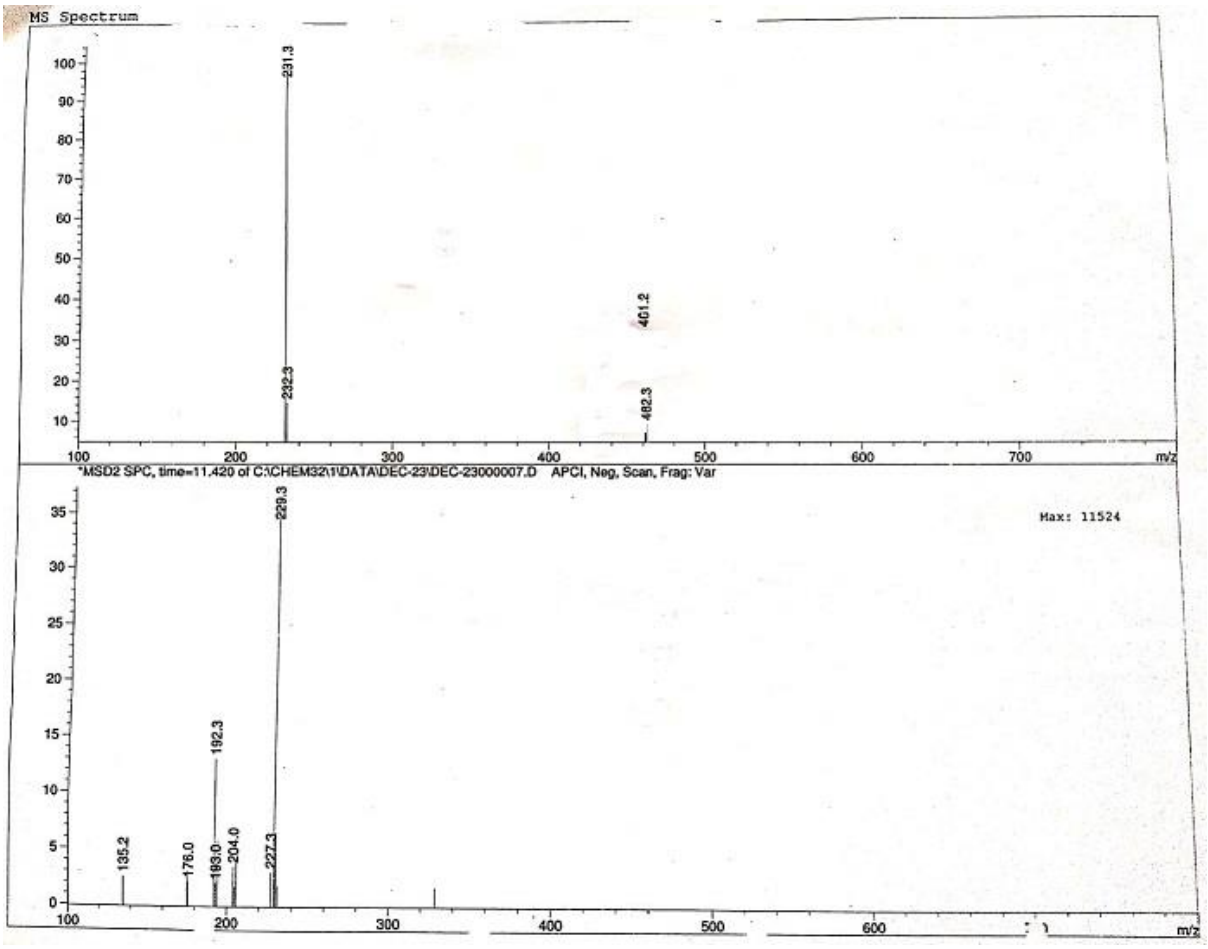
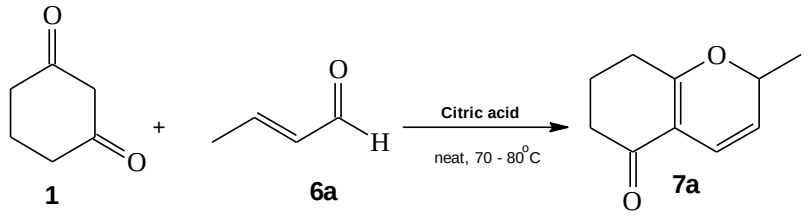


Figure:15 Mass spectra of 3,4-dihydro-2,2-dimethylpyrano [3,2-c]chromen-5(2H)-one (5f)

5.4. Citric acid catalyzed efficient one-pot synthesis of 7,8-Dihydro-2*H*-Chromen-5-ones by formal [3+3] cycloaddition.

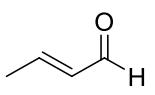
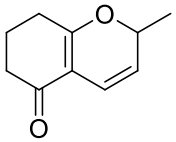
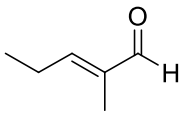
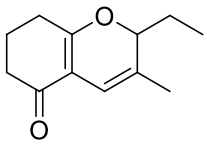
In continuation of our interest in developing novel synthetic methodologies, particularly carbon-carbon, carbon-heteroatom bond formations to synthesize pharmaceutically relevant heterocycles, here in we report our contribution to the synthesis of several 7,8-dihydro-2H-chromen-5(6H)-one derivatives from β-diketones and conjugated enals in the presence of a catalytic amount of cetric acid under neat conditions and shown in **Scheme 3**.

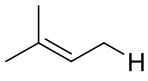
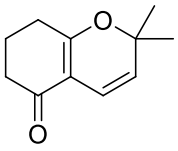
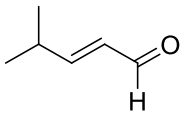
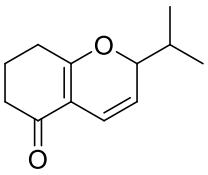
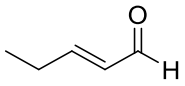
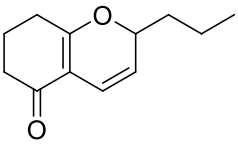


Scheme 3: One-pot synthesis of 7,8-Dihydro-2*H*-Chromen-5-ones by formal [3+3] cycloaddition with Citric acid

We extended this methodology to various reactive aliphatic α,β-unsaturated aldehydes such as 2-methylbutenal, 3-methylbutenal, 4-methyl 2-butenal, *trans*-2-hexenal with 1,3-cyclohexanedione (**4**) and dimedone (**1**), respectively to give corresponding chromenone derivatives within 45-60 min.(Table 3, entries 1-5).

Table 3: Synthesis of 7,8-Dihydro-2H-Chromen-5(6H)-ones

Entry	Alcohol	Product	Time (h)	Yield(%)[a]
1	 6a	 7a	50 min	90
2			50 min	78

	6b	7b		
3	 6c	 7c	40 min	85
4	 6d	 7d	50 min	83
5	 6e	 7e	1 h	70

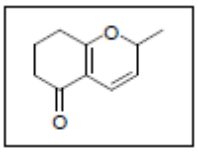
[a]Isolated yield after column chromatography

5.4.1. General experimental procedure for the 7,8 dihydro 2*H* chromen-5(6*H*)-ones

To a mixture 1,3-cyclohexanedione or dimedone (1.0 mmol) and aliphatic α,β-unsaturated aldehyde (1.1 mmol), Citric acid (2 mmol) was added and the reaction mixture was heated at 70 ^{o}C to 80 ^{o}C under neat conditions **(Table 3)**. After completion of the reaction (monitored by TLC), the mixture was neutralized with aq. $NaHCO_3$ and diluted with methylene dichloride. Removal of solvent under reduced pressure followed by purification by silica gel column with petroleum ether/ethyl acetate (1:3) as eluent afforded the corresponding 7,8- Dihydro-2*H*-Chromen-5(6*H*)-ones.

5.4.2. Spectral Data:

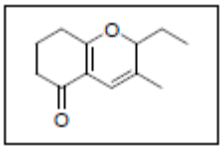
2-Methyl-2,6,7,8-tetrahydro-chromen-5-one (7a):



Pale yellow liquid IR (neat): 2960, 1651, 1633, 1422, 1408, 1370, 1224, 1140, 1054, 947 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (d, 3H, J = 6.5 Hz), 1.90-2.02 (m, 2H), 2.34-2.42 (m, 4H), 4.99 (m, 1H), 5.26 (dd, 1H, J = 10.0, 3.0 Hz), 6.43 (d, 1H, J = 10.0 Hz) ppm; ^{13}C NMR

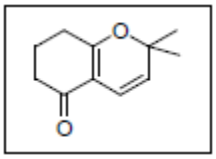
(75 MHz, $CDCl_3$): d 20.5, 21.5, 28.3, 28.5, 36.2, 111.1, 117.2, 118.8, 171.7, 194.9 ppm; MS (ESI): m/z (rel.abund. %) 165.1 ($[M^{+1}]$+,100)

2-Ethyl-7,8-dihydro-3-methyl-2H-chromen-5(6H)-one (7b)



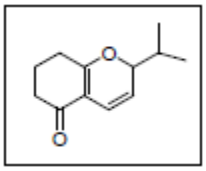
Pale yellow liquid IR (Polyethylene glycol): 2976, 2940, 1641, 1589, 1457, 1411, 1362, 1347, 1193, 1016, 850 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.98 (t, J =10 Hz, 3H), 1.66-1.75 (m, 5H), 1.93-2.01 (m, 2H), 2.34-2.42 (m, 4H), 4.69-4.73 (q, J = 5.6 Hz, 1H), 6.22 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.66, 19.06, 26.19, 27.93, 36.28, 82.07, 111.35, 112.60, 125.87, 170.13, 194.97 ppm; MS (ESI): m/z (rel.abund. %) 193.09 ($[M^{+1}]$+,100).

7,8-dihydro-2,2-dimethyl-2H-chromen-5(6H)-one (7c)



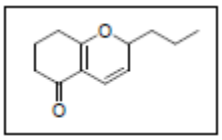
Solid (mp. 40-42 °C)IR (neat): 2926, 1645, 1611, 1455, 1399, 1375, 1266, 1188, 1130, 1010, 905cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (s, 6H), 1.93-2.01 (m, 2H), 2.36-2.42 (m, 4H), 5.23 (d, J = 10.0 Hz, 1H), 6.41 (d, J =10.0 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.54, 28.32, 28.54, 36.26, 79.69, 110.38, 115.64, 115.96, 122.34, 122.82, 171.77, 194.93 ppm; MS (ESI): m/z (rel.abund. %) 179.09 ($[M^{+1}]$+,100).

7,8-dihydro-2-isopropyl-2H-chromen-5(6H)-one (7d)



Pale yellow liquid IR (Polyethylene glycol): 2958, 2926, 1654, 1594, 1462, 1419, 1350, 1225, 1165, 1135, 1038, 950, 865, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.95 (d, J =6.3 Hz, 6H), 1.93-2.01 (m, 2H), 2.05-2.07 (m, 1H), 2.21-2.30 (m, 4H) 4.70- 4.72 (m, 1H), 5.27 (dd, J=12.4 Hz, 1H), 6.50 (d, J=12 Hz, 1H) ppm; MS (ESI): m/z (rel. abund. %) 193.1 ($[M^{+1}]$+,100).

7,8-dihydro-2-propyl-4H-chromen-5(6H)-one (7e)



Pale yellow liquid IR (Polyethylene glycol): 2965, 2937, 1649, 1605, 1456, 1400, 1195, 1168, 1133, 1071, 908, 738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.96 (t, J=9.8 Hz, 3H) 1.34-1.50 (m, 4H), 1.98-2.08 (m, 2H), 2.12-2.24 (m, 2H), 2.25-2.49 (m, 2H), 4.90 (m, 1H), 5.27 (d, J=10 Hz, 1H), 6.45 (d, J=10 Hz, 1H) ppm; MS (ESI): m/z (rel.abund. %) 193.09 ($[M^{+1}]$+,100).

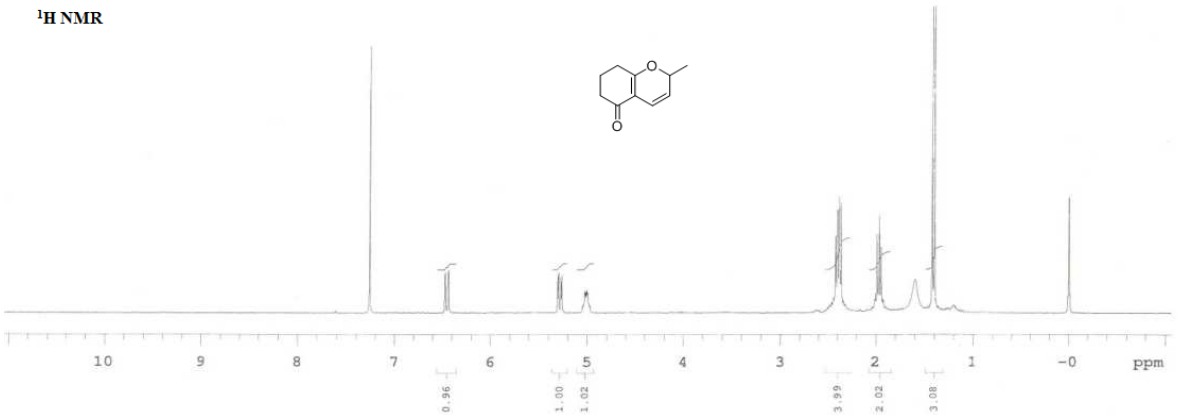


Figure:16 ^{1}H NMR of 2-Methyl-2,6,7,8-tetrahydro-chromen-5-one (7a)

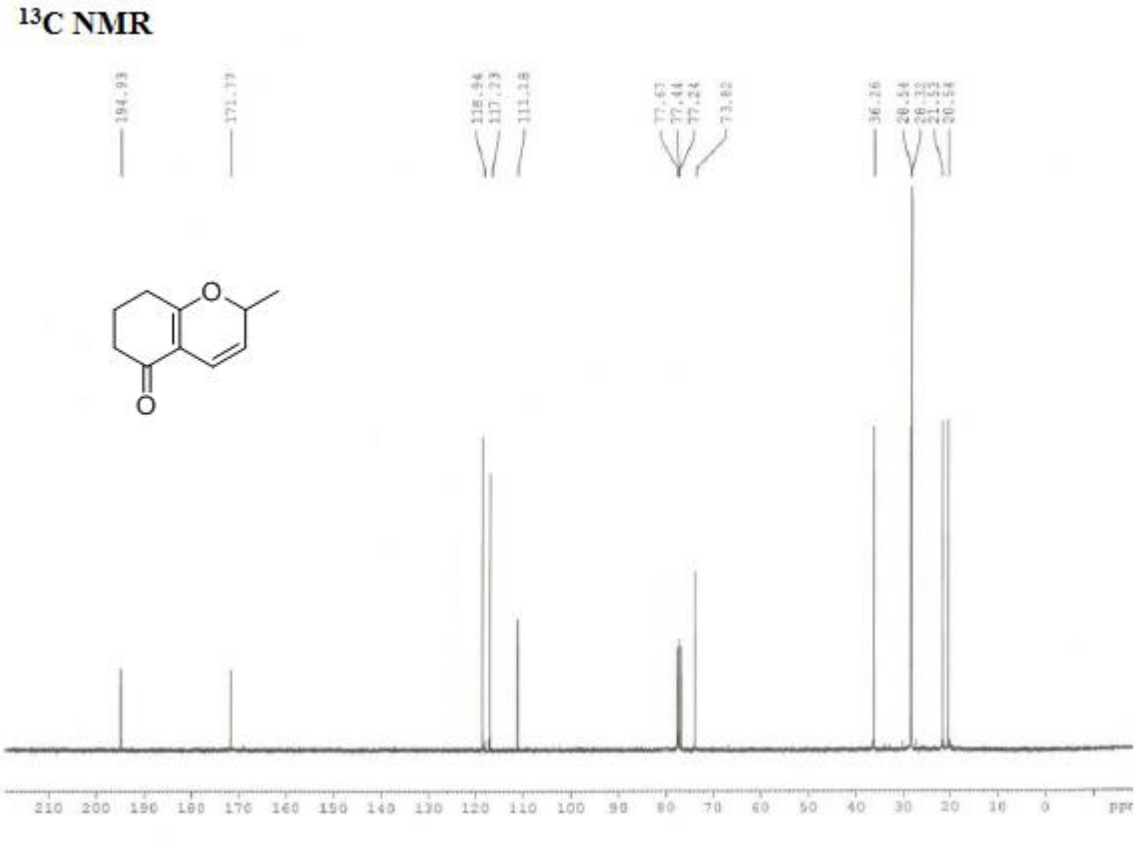


Figure:17 ^{13}C NMR of 2-Methyl-2,6,7,8-tetrahydro-chromen-5-one (7a)

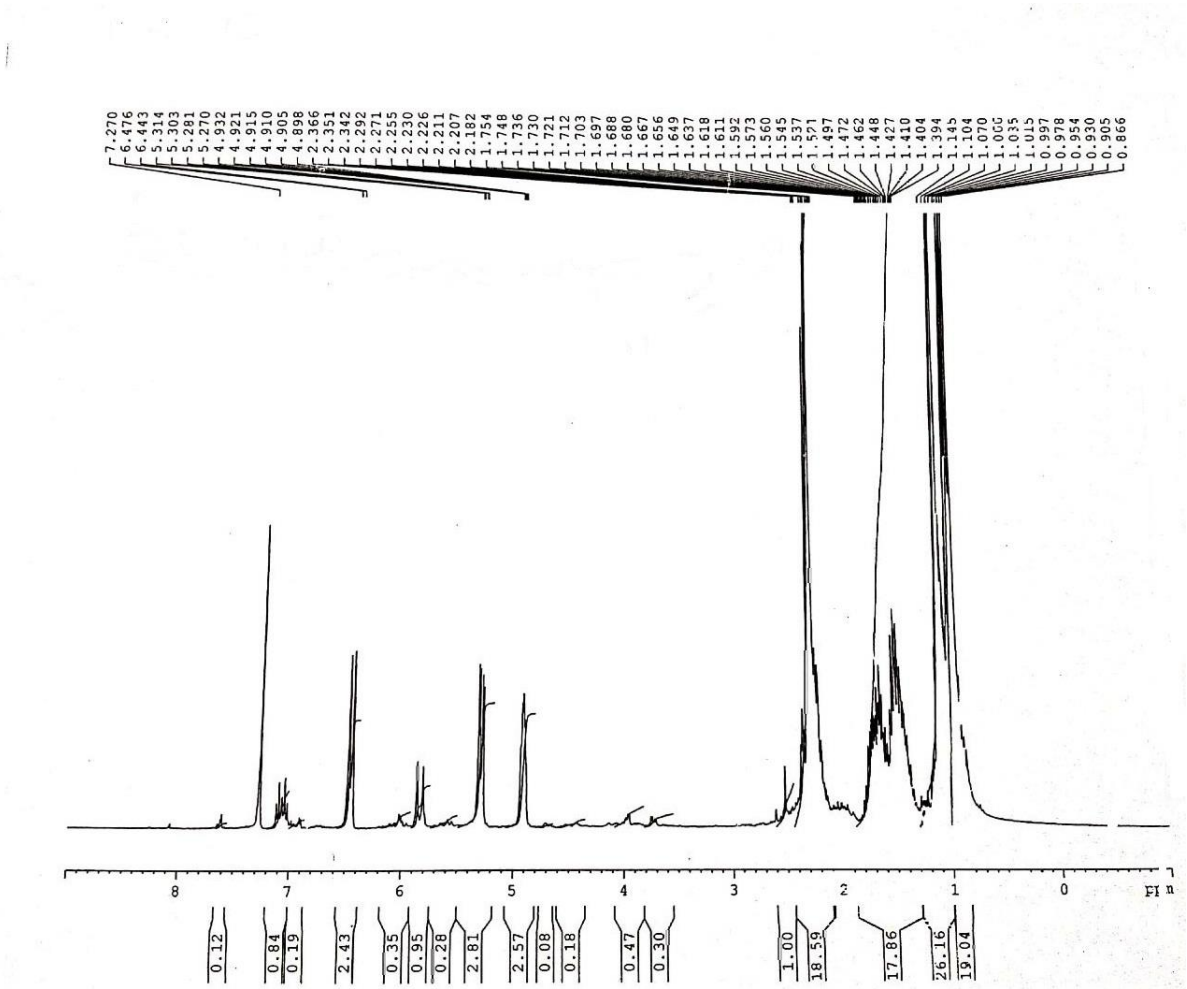
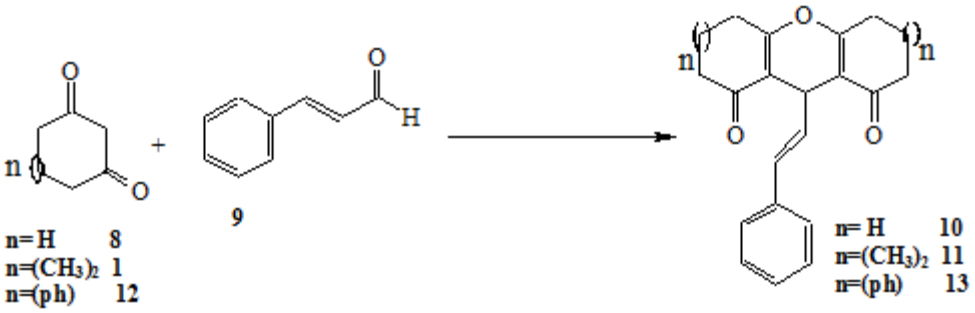


Figure:18 7,8-dihydro-2-propyl-4H-chromen-5(6H)-one (7e)

5.5. Citric acid catalyzed efficient one-pot synthesis of 1,8-Dioxo-octahydroxanthenes *via* a Knoevenagel condensation:

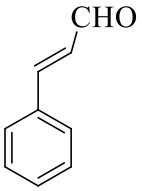
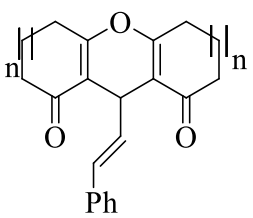
The present work describes scope of citric acid catalyzed annulation for the synthesis of 1,8-dioxo-octahydroxanthenes using 2:1 molar ratio of diketones and aldehydes. Initially, the synthesis of (**10)** from cinnamaldehyde (**9)** and1,3-cyclohexane-dione (**8**) using citric acid was studied as model reaction under solvent-free conditions at different temperatures (RT, 70 and 100^{o}C). It was found that desired compound, **10a,** was obtained in moderate yield (52%) at 100 ^{o}C with no solvent **(Scheme 4**).

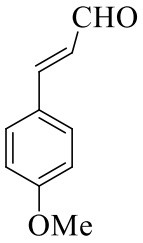
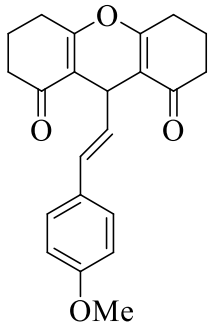
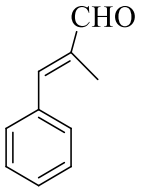
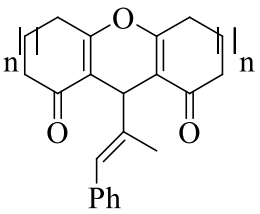
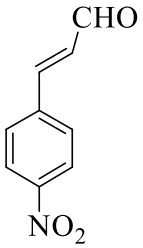
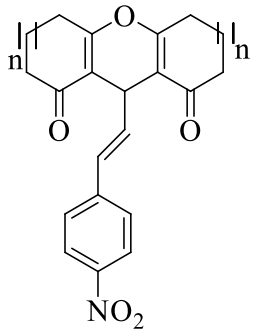
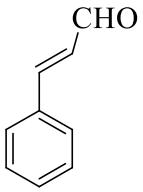
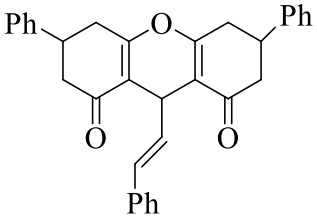


Scheme 4: Synthesis of Xanthene mediated with citric acid

Once again neat conditions proved to be effective for good transformation to desired product. Having established the ideal reaction conditions, the methodology was studied with a variety of substituted cinnamaldehydes and the results are presented in **Table 4.** This protocol tolerates well with electronically divergent cinnamaldehydes containing both electron donating and electron-withdrawing substituents such as –OMe and –NO_2 using 1,3-cyclohexanedione (**8**) and 5,5-dimethyl 1,3-cyclohexanedione (**1**), respectively (**Table 4,** entries **1-8**).

Table 4: Synthesis of 1,8-dioxo-octahydroxanthenes

Entry	Aldehyde	Product		Time	Yield (%)
1			n=H (**10a**)	4	86/82/85/84/84
	9a		n=CH_3 (**11a**)		
2				4.5	84

3		9b		10b	5	78
4		9c		n=H (**10c**) n=CH_3 **(11b)**	4	76
5					4.5	75
6		9d		n=H (**10d**) n=CH_3 (**11c**)	4	83
7					5	88
8		9a		13a	5.5	75

5-Phenyl-1,3- cyclohexanedione (**13**) also reacted well with cinnamaldehyde to give the corresponding xanthene in good yield (**Table 4**, entry 8). The conversion was complete within 4-5.5 h. In no case, we were able to detect Knoevenagel intermediate products. The

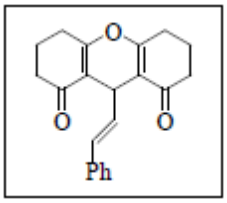
structure of the products was established from their spectral data (IR, ^{1}H, ^{13}C NMR and mass). The carbonyl group in ^{13}C appear in the expected region around 195.3-197.5 ppm. The proton at the bridge between the two dimedone rings appears as doublet in the region of 4.40-4.45 ppm and the bridge carbon appears around 40.83 ppm. The four methyl groups of the dimedone give rise to two close singlets each with six hydrogens at around 1.12 and 1.16 ppm, respectively forming two sets of axial and equatorial methyl groups. Recycling of catalyst was examined using the condensation reaction of cinnamaldehyde (**9)** and1,3-cyclohexane-dione (**8**) in acetic acid under the optimized conditions. After the reaction was complete, the mixture was filtered and the residue was washed with DCM. (**Table 4, entry**

5.5.1. General experimental procedure for 1,8-dioxooctahydroxanthenes

A mixture of 1,3-cyclohexanedione, dimedone or 5-phenyl-1,3-cyclohexanedione (2 mmol) and aromatic α,β-unsaturated aldehyde (1 mmol) and Citric acid (2 mmol) was heated at 90^{o}C to 100^{o}C neat reaction conditions (see **Table 4**). After completion of the reaction (monitored by TLC), the filtrate was cooled to 50 °C, distilled off completely under vacuum, cooled to room temperature. Water (5 mL) was added, neutralized using Na_2CO_3 and extracted with ethyl acetate (2x5 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give the desired product, which was recrystallized from ethanol to afford the pure product or purified by column chromatography using silica 100-200 mesh.

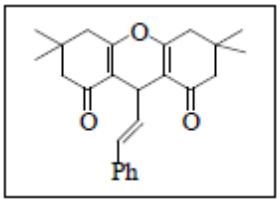
5.5.2. Selected Spectral Data:

3,4,6,7-tetrahydro-9-styryl-2*H*-xanthene-1,8-(5*H*,9*H*)-dione (10a)



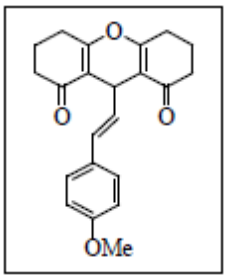
Off white solid, mp. 176-177^{o}C (lit. 182-184 ^{o}C); IR (KBr): 3044, 2930, 2963, 1647, 1431, 1366, 1172, 975, 875, 701, 755 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 2.03-2.11 (m, 4H), 2.32-2.68 (m, 8H), 4.45 (d, 1H, *J*=3 Hz), 6.19-6.31 (m, 2H), 7.13-7.32 (m, 5H); ^{13}C NMR ($CDCl_3$,75MHz): δ 20.4, 27.2, 28.0, 37.0, 115.4, 126.4, 127.1, 128.3, 130.0, 131.2, 137.2, 164.8, 196.7 ppm; MS (ESI): *m/z* (rel. abund. %) 321.18 ($[M+1]^{+}$,100)

3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-9-styryl-2*H*-xanthene-1,8-(5*H*,9*H*)-dione (**11a**)



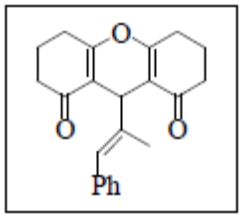
White solid, mp. 174–176 ^{o}C (lit. 175-177 ^{o}C); IR (KBr): 3019, 2963, 2930, 1710, 1668, 1598, 1499, 1431, 1372, 1310, 1264, 1208, 1040, 970, 869, 747 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.12 (s, 6H), 1.16 (s, 6H), 2.38 (s, 4H), 2.46 (s, 4H), 4.43 (d, 1H, *J*=6 Hz), 6.26-6.40 (m, 1H), 7.17-7.20 (m, 1H), 7.28-7.25 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.6, 29.2, 31.2, 32.3, 41.4, 50.9, 112.1, 117.0, 123.7, 124.9, 126.2, 127.0, 127.1, 128.2, 128.3, 128.7, 130.6, 130.8, 131.2, 137.0, 147.8, 165.0, 197.2; MS (ESI): *m/z* (rel.abund. %) 377.3 ([M+1]$^{+}$,100)

9-[(*E*)-2-(4-methoxyphenyl)-1-ethenyl]-2,3,4,5,6,7,8,9-octahydro-1*H*-1,8-xanthenedione (**10b**)



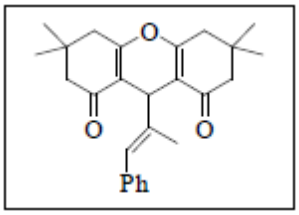
Off white solid, mp 143-144 ^{o}C (lit. 157-159 ^{o}C); IR (KBr): 3088, 2953, 1668, 1622, 1469, 1424, 1363, 1204, 1137, 746 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.05- 2.11 (m, 4H), 2.32-2.66 (m, 8H), 3.78 (s, 3H), 4.42 (d, *J*=5.7 Hz, 1H), 6.05-6.21 (m, 2H), 6.79 (d, *J*= 8.7 Hz, 2H), 7.24 (d, *J*= 8.4 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.39, 27.20, 27.91, 36.99, 55.25, 113.71, 115.54, 127.47, 129.01, 129.27, 130.02, 158.86, 164.64, 196.72 ppm; MS (ESI): *m/z* (rel.abund. %) 351 ([M+1]$^{+}$,100).

9-[(*E*)-1-methyl-2-phenyl-1-ethenyl]-2,3,4,5,6,7,8,9-octahydro-1*H*-1,8xanthenedione (10c)



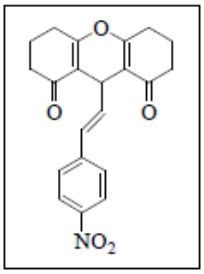
Off white solid, mp 154-156 ºC (lit. 154-155 ºC); IR (KBr): 3032, 2958, 2855, 1726, 1654, 1641, 1462, 1410, 1135, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.94 (s, 3H), 2.25-2.41 (m, 4H), 2.48-2.54 (4H), 4.33 (s, 1H), 6.37 (s, 1H), 7.13-7.27 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.1, 20.4, 27.2, 34.8, 37.1, 116.2, 126.0, 127.8, 128.1, 128.9, 138.2, 141.1, 164.3, 196.9 ppm; MS (ESI): *m/z* (rel. abund.%) 335 ($[M+1]^+$, 100).

3,3,6,6-tetramethyl-9-[(*E*)-1-methyl-2-phenyl-1-ethenyl]-2,3,4,5,6,7,8,9-octahydro-1*H*-1,8-xanthenedione (11b)



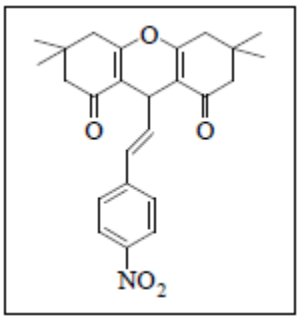
Off white solid, mp. 187-189 ºC (lit. 188-189 ºC); IR (KBr): 3042, 2989, 2964, 2856, 1651, 1640, 1462, 1411, 1130, 749 cm-1; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.08 (s, 6H), 1.11 (s, 6H), 2.05 (s, 3H), 2.27 (s, 4H), 2.45 (s, 4H), 4.18 (s, 1H), 6.31 (s, 1H), 7.09-7.16 (m, 2H), 7.23-7.28 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.4, 27.1, 29.4, 32.1, 34.6, 40.8, 50.9, 115.5, 125.9, 127.8, 128.1, 128.8, 138.2, 143.2, 162.4, 196.8 ppm; MS (ESI): m/z (rel.abund. %) 391 ($[M+1]^+$,100).

9-(4-nitrostyryl)-3,4,6,7-tetrahydro-2*H*-xanthene-1,8-(5*H*,9*H*)-dione (10d)



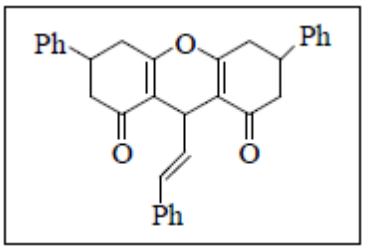
Pale yellow solid, mp. 209-211 ºC (lit. 209-214 ºC); IR (KBr): 3085, 2991, 2960, 1651, 1549, 1489, 1430, 1368, 1172, 970, 869, 749 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.12-2.17 (m, 4H), 2.43-2.75 (m, 8H), 4.47 (d, 1H, *J*=6 Hz, CH), 6.38-6.49 (m, 2H), 7.38 (d, 2H), 8.10 (d, 2H) ppm; MS (ESI): *m/z* (rel.abund. %) 366 ($[M+1]^+$,100).

9-(4-nitrostyryl)-3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-2*H*-xanthene-1,8 (5*H*, 9*H*)-dione (**11c**)



Pale yellow solid, mp. 217-219 ºC (lit. 217-220 ºC); IR (KBr):): u 3089, 2988, 2930, 2963, 1647, 1547, 1490, 1431, 1366, 1172, 975, 875, 701, 755 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.12 (s, 6H), 1.14 (s, 6H), 2.32 (s, 4H), 2.47 (s, 4H), 4.44 (d, 1H, *J*=6 Hz, CH), 6.36-6.50 (m, 2H), 7.40 (d, *J*= 8.7 Hz, 2H), 8.10 (d, *J*= 8.7 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.6, 28.5, 29.2, 32.2, 40.9, 50.8, 113.7, 123.8, 126.8, 136.3, 143.9, 146.6, 163.5, 196.6 ppm; MS (ESI): *m/z* (rel.abund. %) 422.1 ($[M+1]^+$,100).

3,4,6,7-tetrahydro-3,6-diphenyl-9-styryl-2*H*-xanthene-1,8-(5*H*,9*H*)-dione (**13a**)



Off white solid, mp. 183-184 ºC (lit. >280 ºC); IR (KBr): 3060, 3027, 2953, 1663, 1623, 1602, 1496, 1375, 1355, 1182, 1133, 992, 763, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.58-2.99 (m, 8H, CH_2), 3.40-3.51 (m, 2H, CH_2), 4.53 (d, 1H, *J*=6.4 Hz, CH), 6.15-6.42 (m, 2H, CH), 7.16-7.41 (m, 15 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.27, 34.60, 38.55 44.05, 115.5, 126.67, 128.39, 130.47, 137.07, 142.1, 163.28, 164.12, 195.7 ppm; MS (ESI): *m/z* (rel.abund. %) 473.2 ($[M+1]^+$,100).

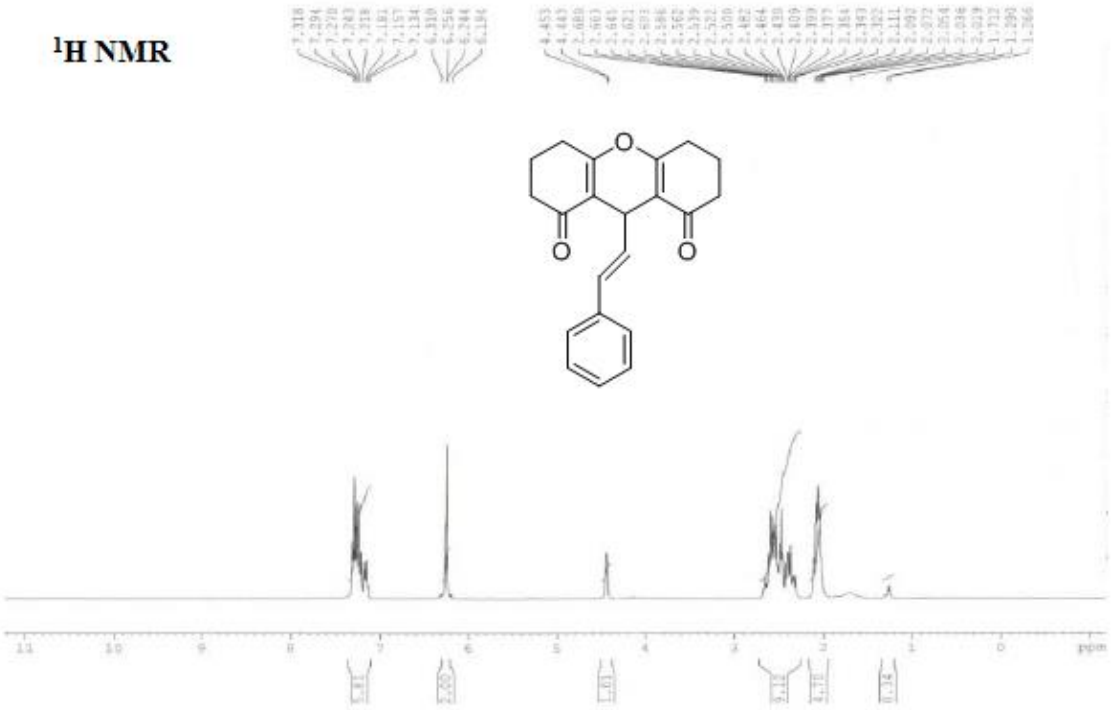


Figure:19 ^{1}H NMR of 3,4,6,7-tetrahydro-9-styryl-2*H*-xanthene-1,8-(5*H*,9*H*)-dione (10a)

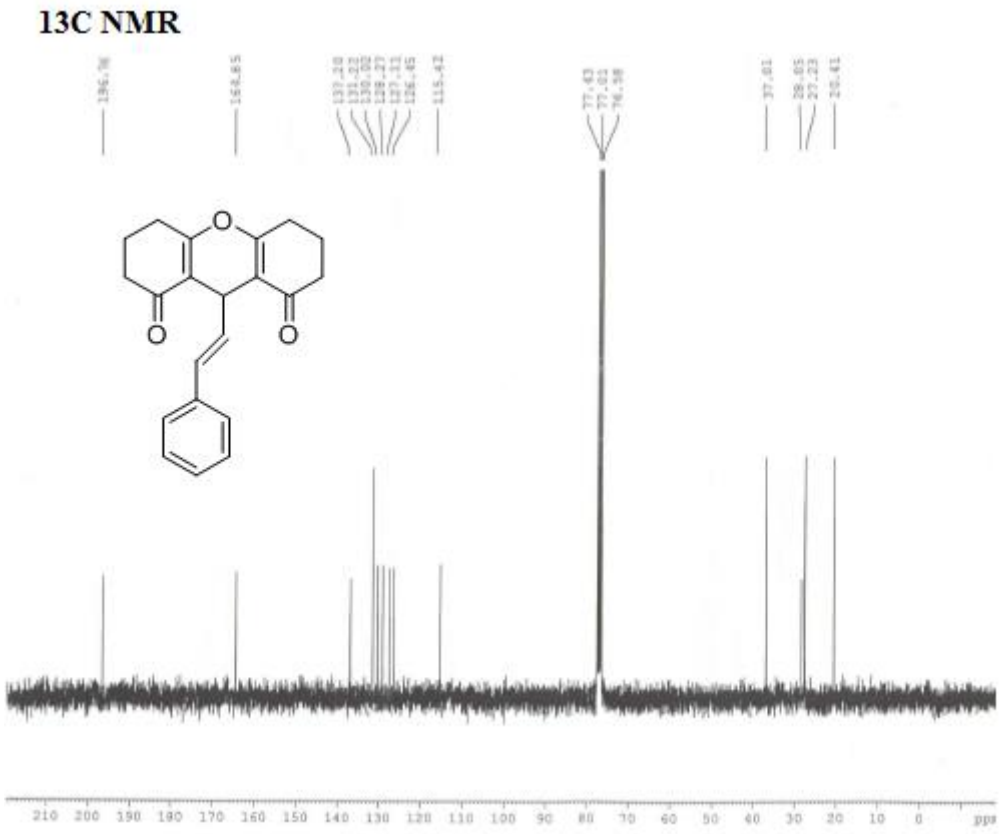


Figure:20 ^{13}C NMR of 3,4,6,7-tetrahydro-9-styryl-2*H*-xanthene-1,8-(5*H*,9*H*)-dione (10a)

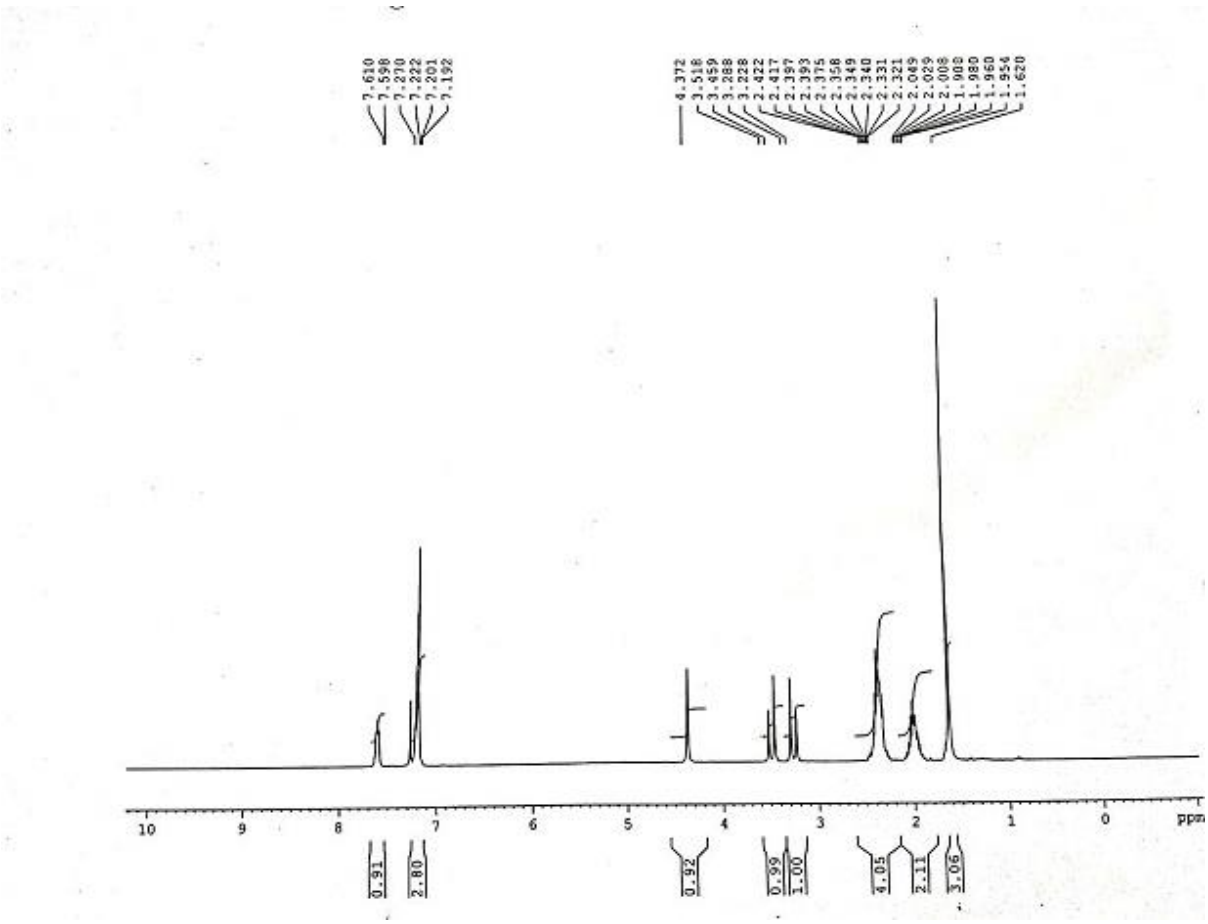


Figure:21 1H NMR of 9-[(*E*)-1-methyl-2-phenyl-1-ethenyl]-2,3,4,5,6,7,8,9-octahydro-1*H*-1,8xanthenedione (10c)

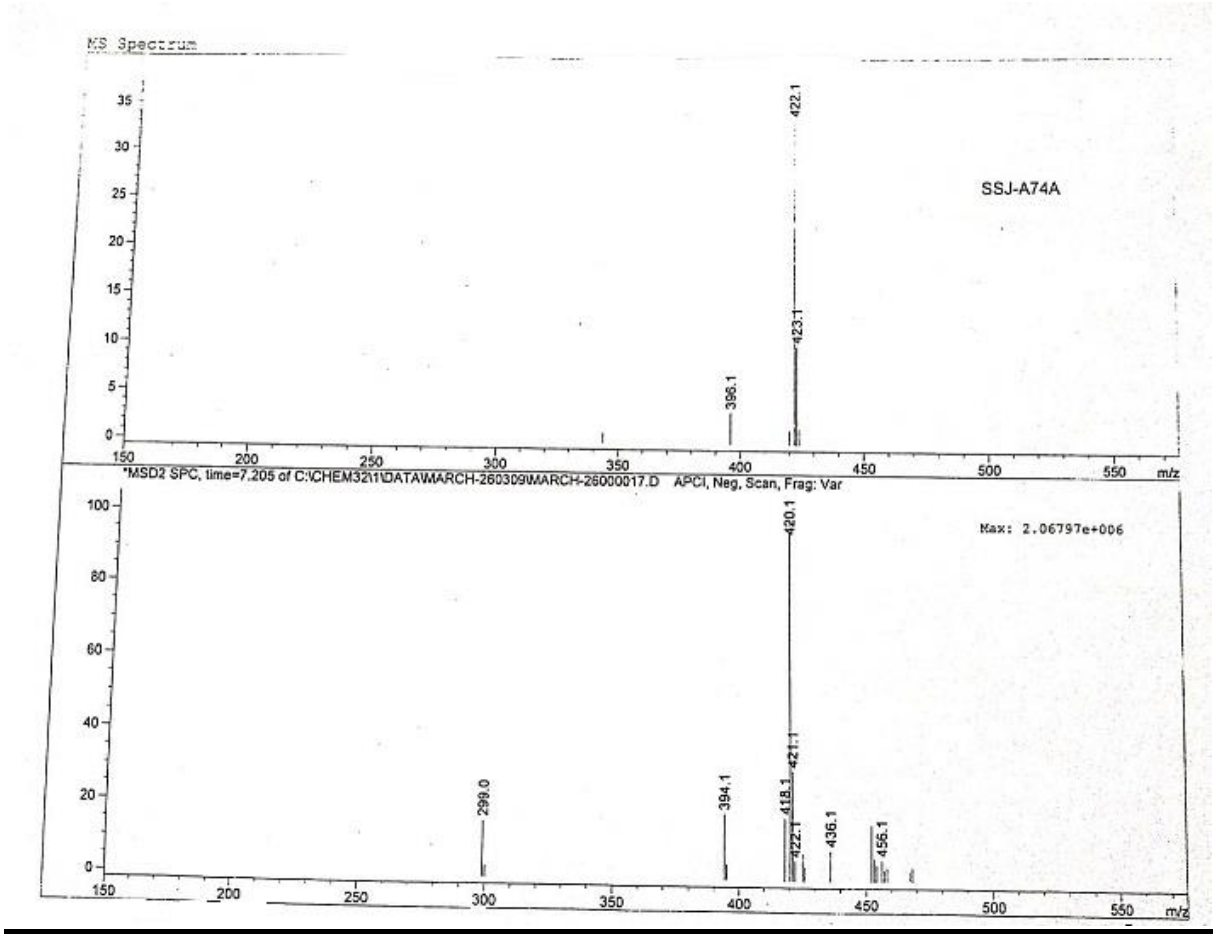


Figure:22 Ms-spectra of 9-(4-nitrostyryl)-3,4,6,7-tetrahydro-2*H*-xanthene-1,8-(5*H*,9*H*)-dione (10d)

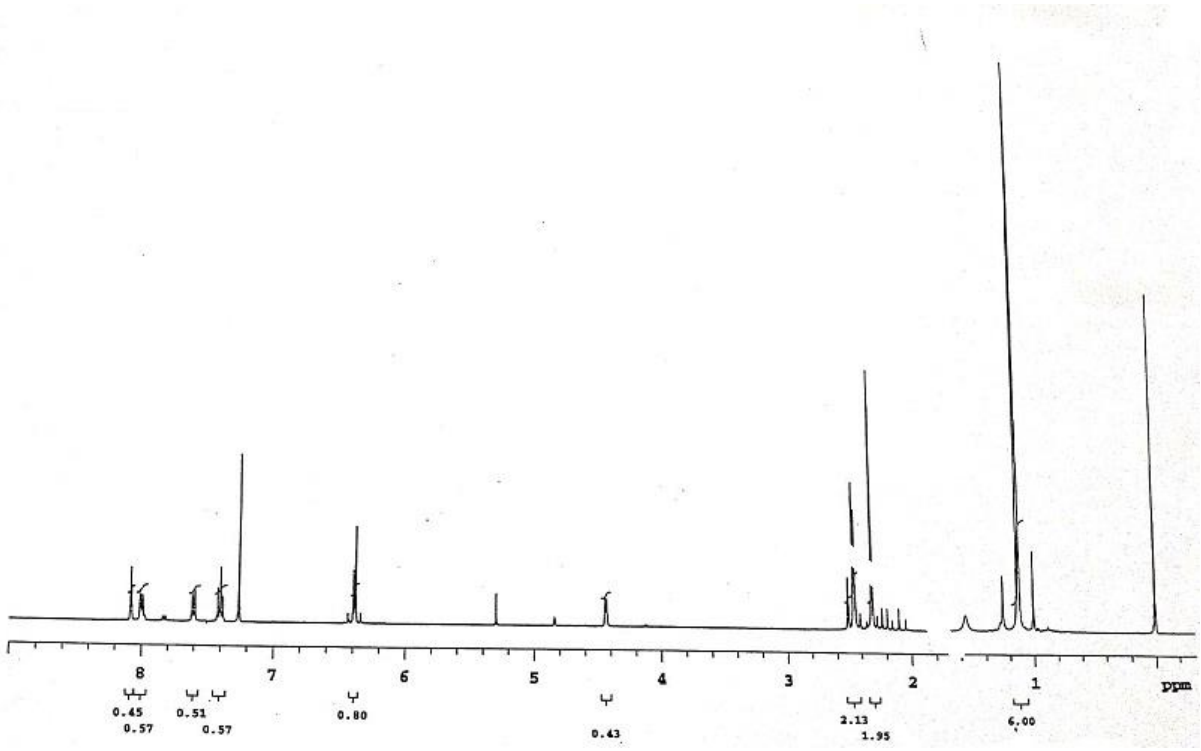


Figure:23 1H NMR of 9-(4-nitrostyryl)-3,4,6,7-tetrahydro-2*H*-xanthene-1,8-(5*H*,9*H*)-dione (10d)

Chapter 6

Summary and Achievements of the Project

6. Summary and achievements of the project

1. C3-Alkylation of 4-Hydroxycoumarin with secondary benzyl alcohols in the presence of citric acid under neat conditions achieved with good yields.
2. O-Alkylation of 4-Hydroxycoumarin with O-Acetyl compounds mediated by citric acid under neat conditions achieved with good yields.
3. Citric acid catalysed efficient one-pot synthesis of 7,8-Dihydro-2H-Chrome-5-ones by formal [3+3] cycloaddition achieved under neat conditions with good yields.
4. An efficient synthesis of 1,8-Dioxo-octahydroxanthanes via a Knoevenagal condensation in the presence of citric acid under neat conditions achieved with good yields.

Chapter 7

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7. References

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