Natural Isocoumarin Analogues, Functionalized Pyrazoles, *N*-Substituted Dihydropyridinones, Iminothiazolidinones, Iminothiazolines and Related Heterocycles: Synthesis and Characterization

Islamabad

By

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2012

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A dissertation submitted to the Department of Chemistry, Quaid-i-Azam University, Islamabad, in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

in

Organic Chemistry

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2012

IN THE NAME OF ALLAH

THE COMPASSIONATE

THE MERCIFUL

DECLARATION

This is to certify that this dissertation entitled "*Natural Isocoumarin Analogues, Functionalized Pyrazoles, N-Substituted Dihydropyridinones, Iminothiazolidinones, Iminothiazolines and Related Heterocycles: Synthesis and Characterization*" submitted by ***Hummera Rafique*** is accepted in its present form by the Department of Chemistry, Quaid-i-Azam University, Islamabad, Pakistan, as satisfying the partial requirement for the degree of ***Doctor of Philosophy*** in ***Organic Chemistry***.

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This dissertation entitled "*Natural Isocoumarin Analogues, Functionalized Pyrazoles, N-Substituted Dihydropyridinones, Iminothiazolidinones, Iminothiazolines and Related Heterocycles: Synthesis and Characterization*" submitted by ***Hummera Rafique*** *D/o* ***Muhammad Rafique*** to the Department of Chemistry, Quaid-i-Azam University, Islamabad, for the degree of ***Doctor of Philosophy*** in ***Organic Chemistry*** has been evaluated by the panel of following Foreign Referees.

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DEDICATED TO

OUR BELOVED HOLY PROPHET

HAZRAT MUHAMMAD (S.A.W.W)

FOR WHOM

THE UNIVERSE WAS CREATED

"ALLAH will exalt those who believe among you and those

have Knowledge to high Ranks".

(*Al-Quran*)

Sayings of Holy Prophet (S.A.W.W)

"If anybody goes on his way in search of Knowledge, ALLAH Almighty will make easy for him the way to Paradise".

(*Sahih Muslim*)

ACKNOWLEDGEMENTS

All praises to **Almighty ALLAH**, the Creator of all the creatures of the universe and who created us as a Muslim and blessed us with knowledge to differentiate between right and wrong. Many, many thanks to ALLAH who blessed us with our beloved **Holy Prophet Hazrat Muhammad (S.A.W.W)**, who exhorted His followers to seek for knowledge from cradle to grave.

I feel great pleasure and privilege in expressing my sincere and humble gratitude to my inspirational and encouraging supervisor **Prof. Dr. Aamer Saeed Bhatti**, Associate Professor, Department of Chemistry, Quaid-i-Azam University, Islamabad, whose personal interest, inspiring guidance, valuable suggestions and discussions enabled me to complete this research project.

I am thankful to Chairman, **Prof. Dr. Amin Badshah**, Department of Chemistry, Quaid-i-Azam University, Islamabad and Head of Organic Section, **Prof. Dr. Shahid Hameed** for providing necessary research facilities. Special thanks are due to all the faculty members of Department of Chemistry, especially **Prof. Dr. Javaid H. Zaidi** for his guidance, encouraging and kind behaviour.

I am thankful to my co-supervisor **Prof. Dr. Peter Langer**, Institute of Chemistry, University of Rostock, Germany, for his guidance, encouraging behavior and valuable discussions and suggestions during my research project in his lab.

I am grateful to **Prof. Dr. David Aitken**, Organic Synthesis Lab, University of Paris Sud-11, Paris (Orsay), France for his guidance, support, valuable suggestions and providing me space in his lab during my research work.

I am thankful to **Dr. Hameed** of Department of Biological Sciences (MicroLab), Quaid-i-Azam University, Islamabad and **Dr. M. Zaman Ashraf** of Department of Chemistry, Allama Iqbal Open University Islamabad, Pakistan (AIOU) for biological evaluation of our synthesized compounds.

I would like to thank all my fellows especially **Dr. Maj. Baseer Khan, Dr. Umer Rashid, Dr. Khushi Muhammad, Touheed Akhtar, Tariq Mehmood Babar, Sajid Ali, Tahir Mehmood, Sher Wali Khan, Ameer Badshah, Farukh Jabeen, Saima Kulsoom** and **Auj-e-Sana** for their support and kind co-operation.

My special thanks are due to my lab-fellows: **Dr. M. Zaman Ashraf, Dr. Amara Mumtaz, Naeem Abbas, Shams-ul-Mehmood, Syeda Aliya Shehzadi, Madiha Irfan, Aaliya Ibrar, Saba Ashraf, Mubeen Arif, Saira Shabbir, Asma Khurshid, Uzma Ilyas, Sidra**

Jamal, Ifzan Arshad, M. Qasim, Mudassar Shehzad, Pervez Mahesar and **Jamal-ud-Din** for their help and co-operation during my research work.

I would like to express my sincere thanks to my lab-fellows at university of Rostock, Germany: **Muhammad Zeeshan (Shani)** **[May his soul rest in peace]**, **Aneela Malik**, **Jovana Tatar, Muhammad Sharif, M. Obaid-ur-Rehman, Rasheed Ahmed Khera, Muhammad Nawaz, Ihsan-Ullah Marwat, Iftikhar Ali, Faiz M. Khan, Imran Malik, Zeeshan Ahmed** and **Dr. Kamran.**

My special thanks are due to my very dear Iraqi brothers **Zafar Zinad, Ghazwan Salman, Umer Akherawi, Ahmed Mahal** and **Nadi** for their nice company, encouragement and support during my stay at Rostock.

I would like to express my sincere thanks to **Abdul Rehman** at university of Paris Sud-11, for his help, support, and co-operation during my stay at Paris.

*S*pecial thanks are due to my dear friends **Fouzia Perveen, Fakhar-un-Nisa Bajwa**, **Iram Batool**, **Madiha Kazmi** & and all my well wishers who remembered me in their prayers.

I am thankful to Pakistan Science Foundation (PSF) for two years funding during my research project.

I am thankful to Higher Education Commission (HEC) of Pakistan for six month International Research Support Initiative Program (IRSIP) scholarship for University of Rostock, Germany.

My special thanks are due to French Embassy in Islamabad, Pakistan for providing me "Sandwich Ph.D Fellowship" for University of Paris Sud-11, Paris (Orsay), France.

I have no words to acknowledge the sacrifices, lot of prayers, efforts, guidance, support, encouragement and appreciation of my **loving parents**, my brothers **M. Shahbaz**, **M. Shahzad**, **Hamid Rafique** and my loving sisters **Samia, Saira, Bhabhi** and my very cute nephew **M. Awais**. Their endless prayers contributed to the successful completion of this research project.

At the end I am thankful to all those hands who pray for my betterment and success.

(Hummera Rafique)

ABSTRACT

The work presented in this thesis consists of synthesis and characterization of natural isocoumarin analogues and novel heterocyclic compounds. For convenience, the work has been divided into two parts, part one deals with the synthesis of various structural analogues of well known bioactive natural 3,4-dihydroisocoumarins *viz. Annulatomarin, Montroumarin, Scorzocreticin, Typharin,* and *Hiburipyranone,* along with the total synthesis of natural products 8-hydroxy-7-hydoxymethyl-6-methoxy-3,4-dihydroisochromen-1-one (*Stellatin*) and (±) 7-butyl-6,8-dihydroxy-3-pentyl-1H-3,4-dihydroisochromen-1-one have been carried out, starting from 3,5-dimethoxy-4-methyl homophthalic acid precursor.

The synthesis of 3,5-dimethoxy-4-methylhomophthalic acid was carried out starting from commercially available *p*-toluic acid. It was then condensed with various aryl/alkyl acid chlorides to afford the corresponding 6,8-dimethoxy-7-methyl-3-aryl/alkylisochromen-1-ones **(5a-j)**. These isochromen-1-ones were hydrolysed to keto-acids **(6a-j)** and then reduced to corresponding hydroxyacids, followed by cyclodehydration with acetic anhydride into corresponding 6,8-dimethoxy-7-methyl-3-aryl/alkyl-3,4-dihydroisochromen-1-ones **(7a-j)**. Finally, demethylation of 3,4-dihydroisochromen-1-ones was carried out to afford 6,8-dihydroxy-7-methyl-3-aryl/alkyl-3,4-dihydroisochromen-1-ones **(8a-j)**.

Biological screening of all the synthesized compounds were carried out against ten bacterial strains, six were gram negative *viz. Pseudomonas aeroginosa, Escherichia coli, Salmonella typhi, Shigella specie, Salmonella para typhi, Proteus mirabilis* and four were gram positive *viz Bacillus subtilus, Micrococcus aureus, Staphylococcus aureus* and *Streptococcus specie,* bacterial strains, it was concluded that isochromen-1-ones **(5a-j)** and 3,4-dihydroisochromen-1-ones **(7a-j)** are more active against gram positive bacteria then gram negative. However, the 6,8-dihydroxy-3,4-dihydroisochromen-1-one derivatives **(8a-j)** are more active against gram negative then gram positive bacteria.

Part two describes the synthesis of novel heterocyclic systems: functionalized pyrazoles, *N*-substituted dihydropyridinones, iminothiazolidinones and iminothiazolines.

N-Methyl-3,4,5-tribromopyrazole was prepared by treating commercially available 3,4,5-tribromopyrazole with triethyl amine and methyl iodide in

dibromoethane. A variety of *N*-protected 3,4,5-triaryl-pyrazoles, 3,5-diaryl-4-bromopyrazoles, and 5-aryl-3,4-dibromopyrazoles were efficiently prepared by Suzuki Miyaura reactions. All the reactions were proceed with excellent site-selectivity with good yields.

N-Substituted aza-bicyclo[3.1.0]hexan-1-ols were prepared *via* Kulinkovich reaction by treating titanium isopropoxide with variously substituted amino ester derivatives in anhy. Et_2O/THF (1:1), followed by the addition of Grignard's reagent (isopropylmagnesium bromide in ether). These bicyclo compounds were then stirred with the suspension of anhy. $FeCl_3$ in diethyl ether to afford dihydropyridinones in good yields. *N*-Substituted dihydropyridinones were subjected to [2+2] photochemically induced cycloaddition reactions, in order to explore the mechanism of unexpected rearranged product of *N*-benzyl dihydropyridinone while going through [2+2] photo cycloaddition reaction.

1-[Benzo[d]thiazol-2-yl)-3-(substituted] thioureas and ethyl 4-(3-benzoylthioureido) benzoates are exceptionally versatile building blocks towards the synthesis of wide variety of heterocyclic compounds. These thioureas were converted into novel five membered heterocycles like methyl 2-[2-benzamido-3-(2-benzothiazolyl)-4-oxothiazolidin-5-ylidene] acetates and ethyl 4-[2-benzamido-5-(2-methoxy-2-oxoethylidene)-4-oxothiazolidin-3-yl] benzoates in good yields, by the direct cyclization of these thioureas with dimethyl but-2-ynedioate (DMAD) in methanol.

Ethyl 4-(3-benzoylthioureido) benzoates and 1-(benzo[d]thiazol-2-yl)-3-(substituted) thioureas serves as precursors for the synthesis of variety of biologically significant heterocyclic compounds like *N*-[3-(2-benzothiazolyl)-4-methylthiazol-2(3H)-ylidene] benzamides and *N*-[3-(benzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene] benzamides. These heterocycles were efficiently synthesized by the base-catalyzed cyclization of corresponding thioureas with 2-bromoacetone and triethylamine in moderate to good yields.

Benzo[d]thiazol-2-amines, 1-(benzo[d]thiazol-2-yl)-3-(substituted) thioureas and ethyl 4-(3-benzoylthioureido) benzoates were examined *in vitro* for antibacterial activity against gram positive and gram negative bacteria and were found to exhibit good to potent activity as compared to the standard drugs. Benzo[d]thiazol-2-amines and 1-(benzo[d]thiazol-2-yl)-3-(substituted) thioureas were tested *in vitro* for their antifungal

activity against various fungal strains and were found to exhibit moderate activity as compared to the standard drug.

The structures of all the synthesized compounds were confirmed by physical data, FTIR, ^{1}H NMR, ^{13}C NMR, mass spectrometry and elemental analysis.

CONTENTS

Chapter–1

INTRODUCTION

1.1 Natural Isocoumarin Analogues

Isocoumarins and 3,4-dihydroisocoumarins are naturally occurring lactone widely spread in nature as secondary metabolites of a wide variety of fungi, lichens, bacteria, molds, higher plants, marine organisms and also among insect venoms and pheromones.[1] Majority of the isocoumarins derivatives have been obtained from various species of fungal genera, *Penicillum, Streptomyces, Ceratocystis, Fusarium, Artemisia, Aspergillus* etc. These metabolites were isolated to lesser extent from few families of higher plants e.g *Leguminoseae, Compositae, Bignoniaceae, Saxifragaceae,* and *Myricaceae*.

Many Literature reviews were published on synthesis and biological applications of isocoumarins that includes the chemical reviews by Dighe, N. S[2] *et al*. (2010), Musa, M. A[3] *et al*. (2008), Bin[4] *et al*. (2000), E. Napolitano[5] (1997), R. A. Hill[6] (1986), V. Yamato[7] (1983), W. B. Turner and Aldridge[8] (1983) and R. D. Barry[9] (1964).

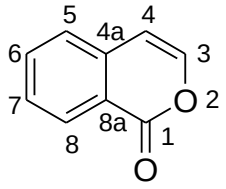
1.1.2 Nomenclature

i) Derived Names

The word 'isocoumarin' for naming of these compounds was derived from the fact that isocoumarins **(1)** are isomeric to coumarin **(2)**. Coumarin[10] was isolated in 1820 from beens of tonka tree known as *Coumarouna odorata*.

ii) IUPAC Names

Isocoumarin skeleton is made up of a lactonic pyran ring fused with benzene. The IUPAC name for isocoumarin and their 3,4-dihydroisocoumarins analogues are 1*H*-2-benzopyran-1-one (**1**) and 3,4-dihydro-1*H*-2-benzopyran-1-ones (**2**), respectively.



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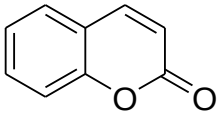
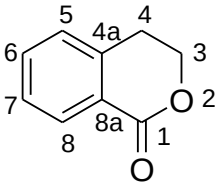




(2)

iii) Trivial Names

No systematic nomenclature exists for isocoumarins like other classes of the natural products flavonoids, alkaloids, etc. Commonly trivial names[11] are assigned to majority of naturally occurring isocoumarins and 3,4-dihydroisocoumarins metabolites derived from their generic or specific names of plants and other natural sources. Names derived from those of parent genera are fusamarin (*Fusarium spp*.), agrimonolide (*Agrimonia pilosa*), alternariol (*Alternaria spp.*), peniolactol (*Peniophora sanguinea*), artemidin (*Artemisia glauca),* homalicine (*Homalium zeylancum*), oosponol (*Oospora astringes*), cladosporin (*Cladosporium spp.*) etc. The names derived from species fron which they were isolated e.g mellein (*Aspergillus melleus*), duclauxin (*P. duclauxi*), ustic acid (*A. ustus*), capillarin (*Artemisia capillaris*),ochratoxin A, B and C (*A. ochraceus*), moncerin (*H. monoceros*), viridotoxin (*A. virinutans*) etc.

Trivial names of a large number of isocoumarins end in the suffix "-in" for example artemidin, bactobolin A, B and C, bergenin, actinobolin, coriandrin, baciphelacin, canescin, asperentin, fusamarin, stellatin, mellein, etc.

However, isocoumarin names ending in other suffixes like “-ol, -one, -ide. -oic acid, anhydride” are also very common, which indicates their chemical classes e.g are hydrangenol, altenuisol, oosponol, oospoglycol, reticulol, oospolactone, peniolactol, agrimonolide, monocerolide, feralolide, ustic acid, ardisic acid B, chebulic acid, *β*-callatolic acid, *β*-alectoronic acid and lamellicolic anhydride, naphthalic anhydride etc.

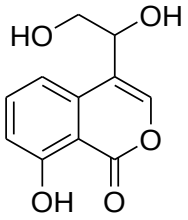
Isocoumarin nucleus **(1)** itself has never been found but its many simple derivatives exsists in nature. Isocoumarin analogues have substituents e.g alkyl, aryl, alkoxy, nitro, halo etc on both rings and either on aromatic or on the lactonic rings.

1.1.3 Biological Applications

Isocoumarins and their 3,4-dihydro analogues constitutes a class of natural products, a huge number of them have been isolated from fungi, lichens, bacteria, insects, to lesser extent from higher plants and marine organisms are also rich source of these metabolites[12-17]. These secondary metabolites have been found to possess wide spectrum of remarkable pharmacological applications including anti-allergic, antifungal, necrotic, anti-inflammatory, immunomodulatory, antibacterial, anti-diabetic, antitumor, cytotoxic antitubercular and antiangiogenic[18-23] etc.

i) As Antibiotics

Five naturally occurring 4-substituted isocoumarins e.g oospoglycol **(1)**,[24] oosponol **(2)**,[25] 4-acetyl-6,8-dihydroxy-5-methylisocoumarin **(3)**,[26] and (-)-sescandelin **(4)**[27] and AGI-7 **(5)** has been reported to exhibit interesting antibiotic activities against plant cells, bacteria, and plant-pathogenic fungi,[28] they also possess root-promoting activity.[29]



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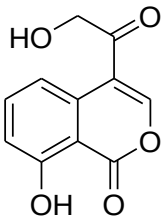

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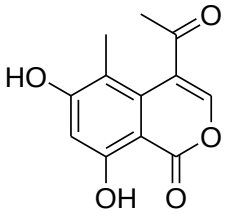

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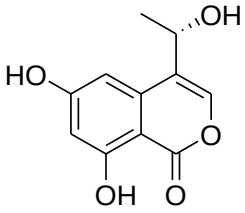

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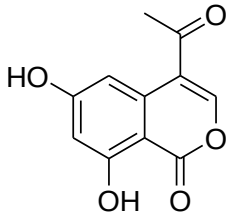
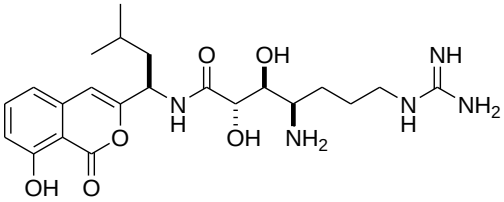


(5)

Gram negative gamma *proteo*-bacterium *Xenorhabdus spp.* forms an entomopathogenic symbioses relationship with various soil nematodes. The bacteria produce important antibiotics Xenocoumacins 1 (**6)** and Xenocoumacins 2 (**7)**, and numerous other products including intracellular protein crystals etc.[30]



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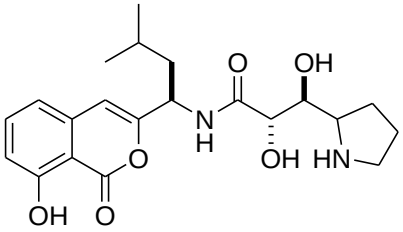

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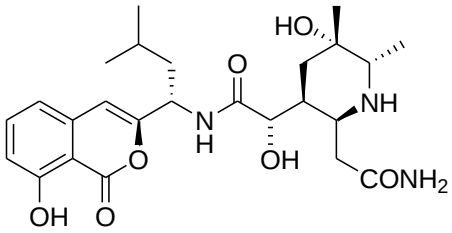
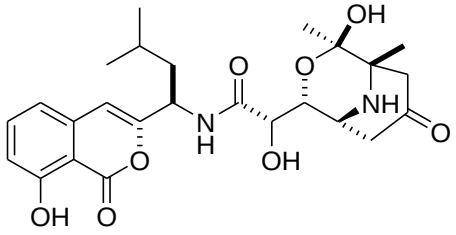
ii) Growth Inhibitors

Bacilosarcin B **(8)** is a secondary metabolite of a marine-derived bacterium i.e *Bacillus subtilis.* It possess significant growth inhibition against barnyard millet.



(8)

Dihydroisocoumarins bacilosarcin A **(9)** and B **(10)** were isolated from the TP-B0611 strain of *Bacillus subtilis* and they are inhibitors of plant growth. Bacilosarcins are structurally very important because they contains morpholine ring, which is rarely found in natural products. Bacilosarcin A showed 82 % inhibition of barnyard millet sprouts at 50 PM, while bacilosarcin B showed very weak 7 % inhibition.[31]



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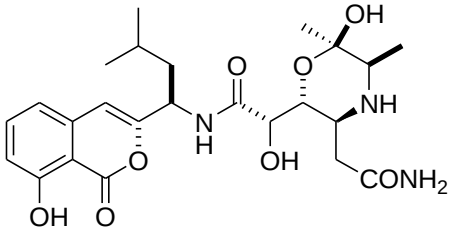

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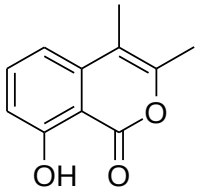
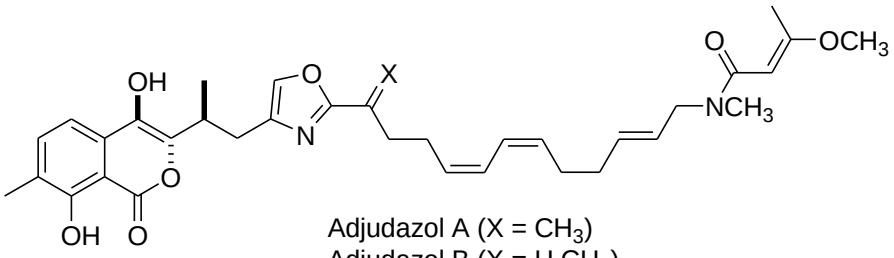
iii) Antifungal Activities

Antifungal agent an oospolactone (**11**) is a secondary metabolite of *Gleophyllum sepiarium.* This compound showed remarkable activity against different strains of asexual ascomycetes '*Alternaria'*.[32]



(11)

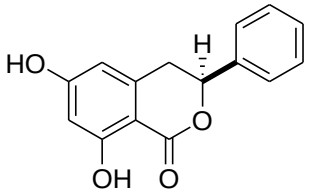
The ajudazol A **(12)** and B **(13)** were isolated in 2004 and have antifungal activity against several important food spoilers. Ajudazols A and B share the isocoumarin core, although the literature names this structure an isochromanone,[33] both compounds have complex functionality in their respective linear chains.



(12,13)

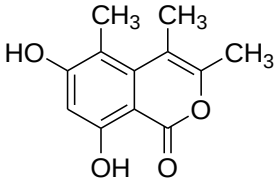
Some naturally occurring 3-butylisocoumarins were isolated from *Asteraceae-Anthemideae* and antifungal activities of all the derivatives were determined against rice blast fungus *Pyricularia grisea.* The side-chain containing 3-butyl moiety is observed to impart high activity.[34]

(*3S*)-6,8-Dihydroxy-3-phenyl-3,4-dihydroisocoumarin is commonly known as 'montroumarin' **(14)**, was isolated from *Montrouziera sphaeroidea.* This metabolite was reported to exhibit *in vitro* antifungal activities.[35]



(14)

Novel metabolites cercophorins A-C along with two new isocoumarins i.e decarboxycitrinone (**15**) and 4-acetyl-8-hydroxy-6-methoxy-5-methylisocoumarin (**16**), along with three other compounds (**17-19)** were isolated from the coprophilous fungus *Cercophora areolata.* These metabolites were known to possess antifungal and cytotoxic activities.[36]



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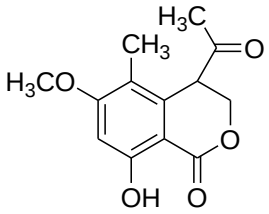

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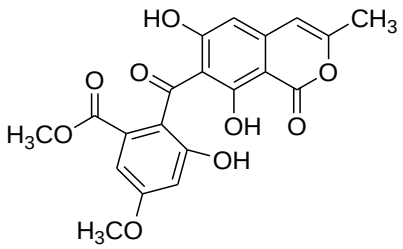
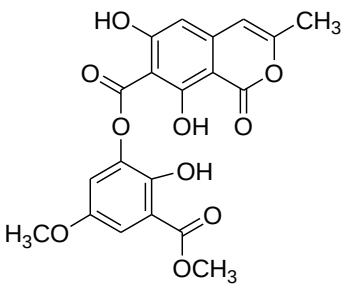


(17)



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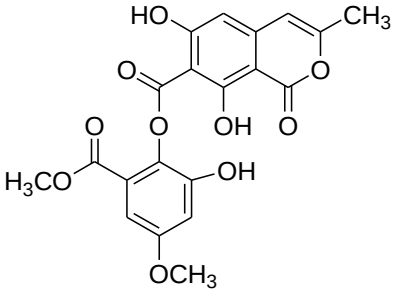
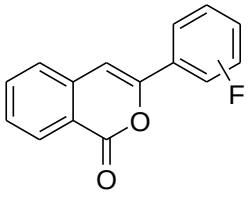


(19)

iv) Anti-inflammatory Activity

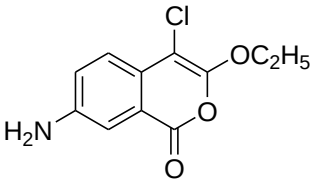
Isocoumarin nucleus in many natural products has been reported to have a wide spectrum of biological applications. Few fluorinated isocoumarins and 3,4-dihydro-isocoumarin **(20)** derivatives were known to exhibit good anti-inflammatory activities.[37]



(20)

v) Pancreatic Cholesterol Esterase Inhibitors

3-Alkoxychloroisocoumarins represents a class of halogenated lactones that are potent to inhibit serine proteases and serine hydrolases. 7-Amino-4-chloro-3-ethoxy-isocoumarin **(21)** is one of the derivative that are potent inhibitors of CEase.[38,39]

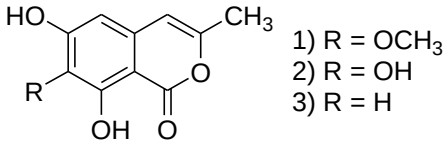


(21)

vi) Inhibitors of Calmodulin-sensitive cyclic Guanosine-3',5'-monophosphate phosphodiesterase (Ca-PDE)

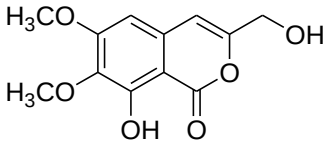
Three natural isocoumarins **(22-24)** were isolated from *StreptoverticilIium sp.* strain and all these isocoumarins are inhibitor of the calmodulin-sensitive cyclic guanosine 3',5'-monophosphate phosphodiesterase. 6,8-Dihydroxy-3-methyl isocoumarin **(22)**, a fermentation product was also found from a fungal species *Ceratocystis minor*

associated with the blue stain disease of pines. Other two derivatives, 6,7,8-trihydroxy-3-methyl isocoumarin **(23)** and 6,8-dihydroxy-7-methoxy-3-methylisocoumarin **(24)** have been previously isolated from *Streptomyces.*[40]



(22-24)

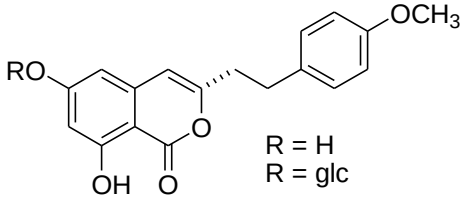
A secondy metabolite of *Streptomyces mobaraensis* and structural analogue of cytogenin and reticulol i.e 8-hydroxy-6,7-dimethoxy-3-hydroxymethyl isocoumarin **(25)** was reported as a potent cyclic nucleotide phosphodiesterase inhibitor.[41]



(25)

vii) Hepatoprotective Activity

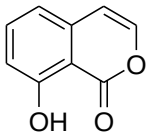
Two isocoumarins agrimonolide **(26)** and agrimonolide 6-*O*-*β*-D-glucoside **(27)** were obtained from the aqueous extract of the roots of *Agrimonia pilosa* Ledeb.(*Rosaceae*), were known to possess *in vitro* hepatoprotective activity in Hep G2 and primary hepatocytes *Agrimonolide* exhibit hepatoprotective effects in human liver-derived Hep G2 cells tacrine-induced cytotoxicity and cytotoxicity in rat primary hepatocytes induced by *tert*-butyl hydroperoxide.[42]



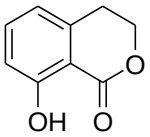
(26,27)

viii) In Defensive Secretions of Beetles

Defensive secretions of many insects contains a wide variety of organic compounds. 8-Hydroxyisocoumarin **(28)** and it 3,4-dihydroisocoumarin **(29)** analogue along with 1,4-benzoquinones were found in the defensive secretions of tenebrionid beetle '*Apsena pubescens'*.[43]



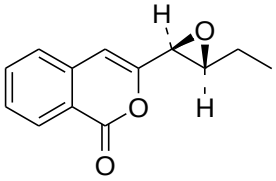
(28)



(29)

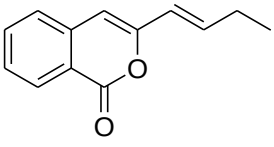
ix) Antimalarial Activities

Some isocoumarin derivatives **(30), (31)** and **(32)** were isolated from a shrub *Artemisia campestris* growing in highlands of Algeria. There this is commonly known as ‘‘Taguq’’ and is used in decoction as a diuretic. Several species of genus Artemisia (*Asteraceae*) were growing in europe and africa. The interest was increased to explore this genus (Alberto Marco *et al.,* 1997), after the discovery of a potent antimalarial drug artemisinin isolated from *Artemisia annua* and it is in successful clinical trials.[44]



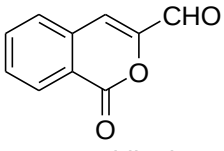
(+) epoxyartemidin

(30)



artemidin

(31)

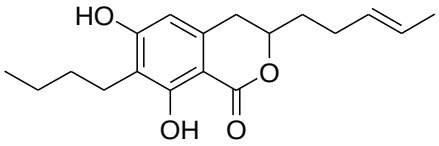


artemidinal

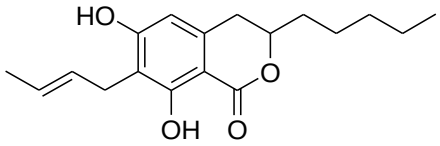
(32)

x) Antitubercular Activity

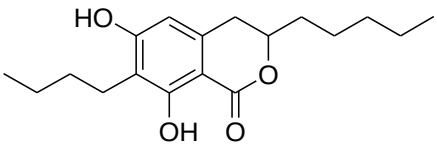
Three novel alkylated dihydroisocoumarin derivatives **(33-35)** were isolated from an endophytic fungi *Geotrichum sp.*, which was collected from *Crassocephalum crepidioides*. These metabolites exhibit potent antitubercular, antimalarial, and antifungal activities.[45]



(33)



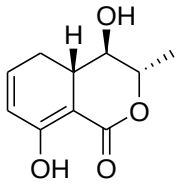
(34)



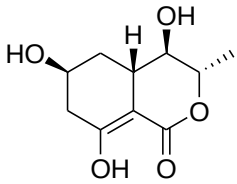
(35)

xi) Insecticidal Activities

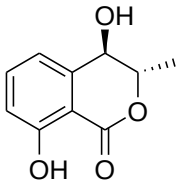
Findlay *et al.*[46] isolated an insecticidal hydroxy substituted tetrahydroisocoumarin derivatives i.e (3R,4S,4aR)-4,8-dihydroxy-3-methyl-3,4,4a,5-tetrahydro-1H-2-benzopyr-an-1-one **(36)**, **(37)** and **(38)** from the culture of filtrates of *Canoplea elegantula,* a conifer endophytic fungi.[47-49]



(36)



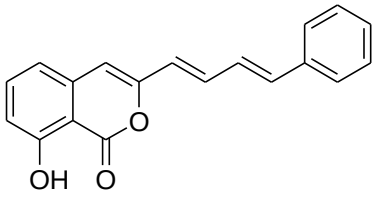
(37)



(38)

xii) Blue-white Autofluorescence in Fluoribacter

A new isocoumarin iegioliulin **(39)**, is responsible for blue-white autofluorescence under long-wavelength UV light in *Legionella dumoffii* (Fluoribacter). *Legionella dumoffii* is one of the highly causative agent of *Legionnaires* disease. 10 species of genus *Legionella* including *L. dumoffii* are known to possess blue-white autofluorescence.[50]

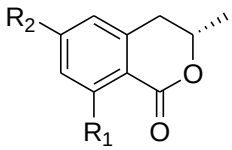


(39)

xiii) Phytotoxicity and Phytoalexin Activities

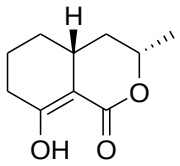
Mellein **(40)**[51-52] 8-hydroxy-3-methyl-3,4-dihydroisocoumarin and its derivatives **(41-43)** or a non-aromatic derivative ramulosin **(44)** were isolated from insects and several fungal species, known to possess a variety of biological applications.[53]

Mellein derivatives *o*-methylmellein **(41)**, 8 6-hydroxymellein **(42)**,[54-57] and 6-methoxymellein **(43)**[58-62] have been isolated from many plant and phytopathogen, fungi. They possess remarkable phytotoxicity, cytotoxicity and phytoalexin applications, while ramulosin **(44)**,[63,46] exhibits antimicrobial and antigerminating activities.



Mellein (40) R_1 = OH, R_2 = H
O-Methylmellein (41) R_1 = OCH_3, R_2 = H
6-Hydroxymellein (42) R_1, R_2 = OH
6-Methoxymellein (43) R_1 = OH, R_2 = OCH_3

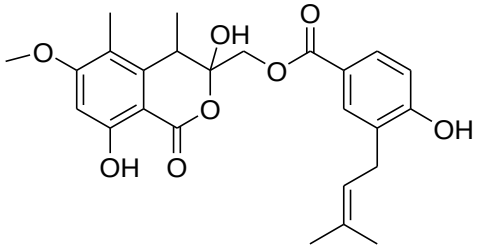
(40-43)



(44)

xiv) Insect GABA Receptors

The insecticides which selectively act on the GABA receptors of insects have toxic effects on them but not for mammals[64]. A new dihydroisocoumarin derivative **(45)**, a novel GABA receptor ligand was isolated from a *Neosartorya quadricincta* fungal culture extract. It was considered as the lead compound for the development of new insecticides, which specifically acts at the insect GABA receptors.[65]

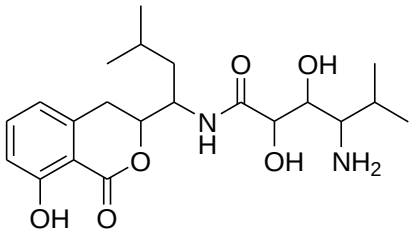


(45)

Some naturally occurring terpenoids such as anisatin and picrodendrins binds with the antagonist site of the GABA receptors of insects and exhibit insecticidal activities[66-69]. Picrodendrin *O*-lactones showed its affinity selectively for insect GABA receptors rather than mammals.

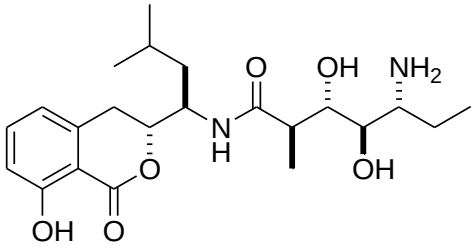
xv) Anti-leukemic Activities

An antibiotic isocoumarin PM-94128 **(46)** was isolated from the culture broth of *Bacillus sp*. The compound **(46)** is highly active against different strains of gram-negative and gram-positive bacteria and possess remarkable cytotoxic activities against the lymphoid leukemia cell lines P388 and L1210. It also showed significant *in vivo* antitumor activity against P388 cell lines of mice.[70]



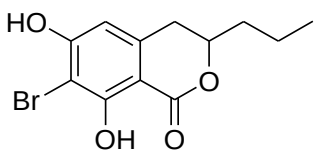
PM-94128 **(46)**

Bachiphelacin **(47)** possesses antibiotic activity against *S.aureus* strain of gram positive bacteria and cytotoxic properties against P-388 lymphatic leukaemia cells, respectively. Carrasco *et al.* found that bachiphelacin exhibit a potent toxic effect against HeLa cells[71], it was concluded while studying its mode of action that this antibiotic inhibits the synthesis of protein in eukaryotic cells. This antibiotic also inhibited the protozoan *Trypanosoma brucei* but it had no effect on protein synthesis of *Escherichia coli* or *Saccharomyces cerevisiae*[72], It is highly active against a strain of *Bacillus subtilis* and a multi-resistant *Staphylococcus aureus* strain of bacteria. It also demonstrates an antiviral activity against disease called as '*Newcastle*' (a contagious disease that highly affects the domestic poultry, wild birds, cage and aviary birds).[73]



(47)

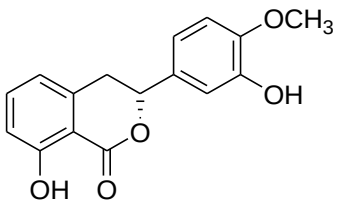
Hiburipyranone **(48)** was isolated from a marine sponge *Mycale adhaerens* by Fusetani *et al.* in 1991. This compound containing dihydroisocoumarin nucleus was reported to possess strong cytotoxic activities against P388 murine leukemia cells (IC 50 = 0.19 ug/ml).[74]



(48)

xvi) Antimicrobial and Sweetening Properties

Naturally occurring 3-aryl-3,4-dihydroisocoumarin i.e phyllodulcin (**49**) is a secondary metabolite of *Hydrangea* genus (*Saxifragaceae*) was famous to exhibits antimicrobial properties. It was explore as the sweet component of the plant in Japan named as "amacha" (*Hydrangea macrophylla* Seringe var. *thumbergii*), whose leaves were traditionally fermented and dried for the manufacture of beverage due to its refreshing taste and very strong sweetening power i.e thousand times that of sucrose. Phyllodulcin (**49**) was consider as a lead compound to developed a new class of sweeteners with low-calories designated as isovanillins.[75]



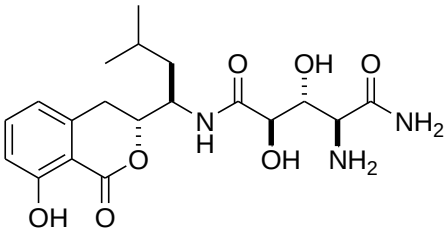
(49)

xvii) Antiulcer Properties

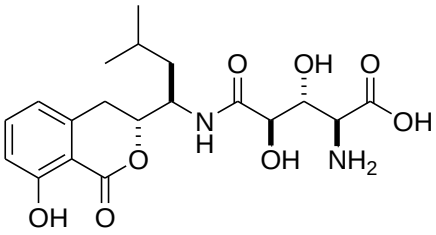
Amicoumacin A **(50)**, B **(51)** and C **(52)** (amicoumacin B is also known as AI-77-B) are dihydroisocoumarin derivatives, they have been reported to exhibit antiulcer activities[76,77], and they also possess antibacterial and anti-inflammatory properties[78]. As they display potent antiulcerogenic, gastoprotective and other significant biological activities, they have been highlighted as potential therapeutic leads.[79]

The antiulcer property of amicoumacin-A was investigated by using stress induced gastric ulceration method[80,81]. When these ulcers were treated with amicoumacin A, it showed substantial inhibition ratio of 72 % at 25 mg/kg, while amicoumacin-B and C had greater protective effects 100 % and 83 %, respectively.

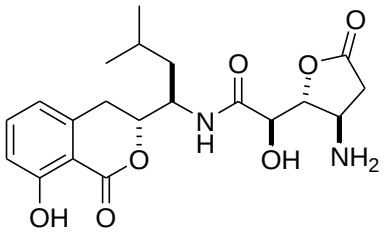
Gastroprotective microbial agent AI-77-B has been isolated from culture broth of *Bacillus pumilus.* AI-77-B **(51)** has a dihydroxy *β*-amino acid side chain linked to 3,4-dihydroisocoumarin unit, was known to possess potent antiulcer properties.[82]



(50)



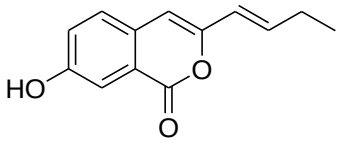
(51)



(52)

xviii) Headache and Blood Dilution

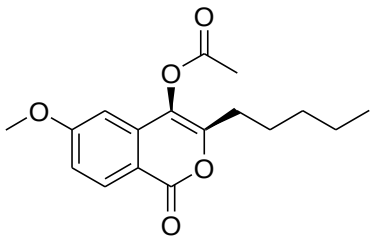
A metabolite 7-hydroxyartemidin **(53)** was isolated from the aq. ethanol extract of *Artemisia drucunculus* L. leaves. Long ago, this table vegetable was used in folk medicine for the treatment of headache and dizziness and also as a natural food cure for diluting and cleaning of blood.[83]



(53)

xix) Aromatase Inhibitors

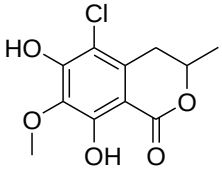
Dihydroisocoumarin analogue **(54)** was isolated from aerial parts of a small shrub *Xyris pterygoblephara*[84]. For the chemoprevention of breast cancer aromatase enzyme is a well-established target, this compound showed potent aromatase inhibitory activity.[85]



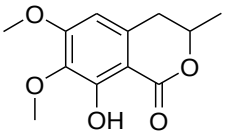
(54)

xx) As Drugs and Biocontrol Agents

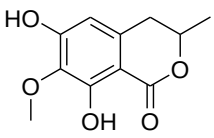
Novel secondary metabolites were potentially produced and isolated from endophytic fungi and they can be used as drugs and possible biocontrol agents[86]. Two new 3,4-dihydroisocoumarins avicennin A **(55)** and B **(56)**, with other two derivatives **(57)** and **(58)** were isolated from the endophytic fungus mangrove.



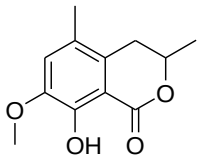
(55)



(56)



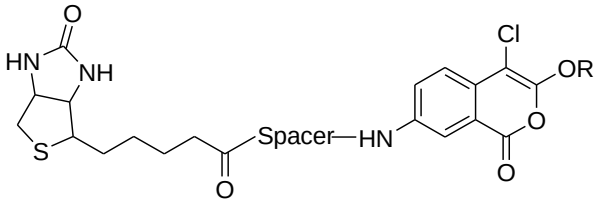
(57)



(58)

xxi) Serine Proteases Inhibitors

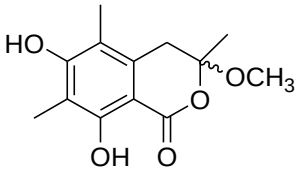
Biotinylated isocoumarins (BICs) with 3-alkoxy substituents on ring **(59)** and various spacer groups were reported as inhibitors of various serine proteases including porcine pancreatic elastase (PPE), human leukocyte elastase (HLE), trypsin, chymotrypsin, cathepsin and.human recombinant granzyme A.[87]



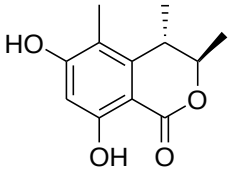
(59)

xxii) Cytotoxic Activities

Stoloniferol A **(60)** and B **(61)** these two new dihydroisocoumarins were isolated from a halophilic fungus *penicillium notatum* and the ethyl acetate extract of *penicillium stoloniferum*, sea squirt fungus. These metabolites possess cytotoxic activity against the BEL-7402, P388, HL-60 and A-549 cell lines.[88]

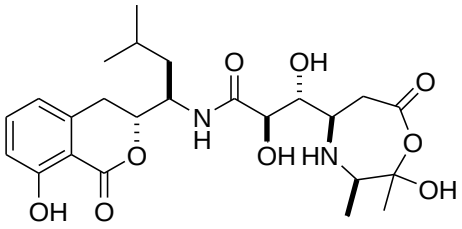


(60)



(61)

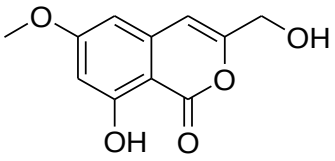
Novel dihydroxyisocoumarin derivative Sg17-1-4 **(62)** was isolated from marine fungal strains of *Alternaria tenuis.* This compound exhibit cytotoxicity against human cervicial cancer Hela cells and human malignant A375-S2[89]. It is structural analogue of xenocoumacins and amicoumacins, was known to displayed potent antiulcer, antitumor and antibacterial activities.[90-92]



(62)

xxiii) Antitumor Activity

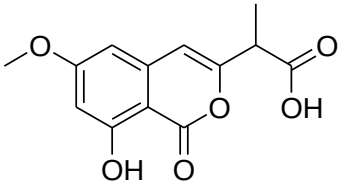
A well known natural antibiotic cytogenin (**63**) was isolated from a cultural broth of *Streptoverticillium eurocidium*. It was reported to exhibit potent antitumor activity against Ehrlich carcinoma. It showed significant *in vivo* and *in vitro* cytotoxicities[93] and it also exerts antitumor effects by modulation or activation of macrophages and T-cells.[94] Cytogenin was also considered as highly effective immunological regulatory agent.[95]



(63)

xxiv) Angiogenesis Inhibitor NM-3

The angiogenesis process is the growth and development of new vasculature, it involved in a variety of normal biological functions of body and also in disease states that includes cancer, arthritis and psoriasis.[96,97]



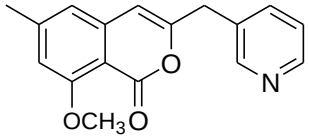
(64)

2-(8-Hydroxy-6-methoxy-1-oxo-1*H*-2-benzopyran-3-yl) propionic acid (NM-3) **(64)**, is a novel synthetic analogue of natural isocoumarin cytogenin, isolated from culture broth of *Streptoverticillium eurocidium.*[98,99]. NM-3 ia a potent inhibitor of endothelial cell proliferation, sprouting, migration, *in vivo* tumor growth and *in vitro* tube formation[100]. NM-3 was reported to be highly orally active as anti-angiogenic agent and it display low toxicity in humans. Currently, NM-3 is going through phase I clinical trails[101] and it also possess significant anti-arthritic activity.[102]

NM-3 induces lethality by both apoptotic and nonapoptotic mechanism to human carcinoma cells and it also potentiates the effects of cytotoxic chemotherapeutic agents. NM-3 potently effects the killing of both dexamethasone-resistant RPMI8226 and U266 multiple myeloma and dexamethasone-sensitive multiple myeloma (MM1.S) cells[103] induced by dexamethasone.

The mechanisms involved in progression of diabetic nephropathy, the common cause of end stage renal failure is associated with angiogenic phenomenon i.e vascular endothelial growth factor VEGF-A and the angiopoietin Ang-2, which antagonist Ang-1. Increase of VEGF induced by high glucose in cultured podocytes and the increase of VEGF and TGF-β induced by high glucose in cultured mesangial cells was significantly suppressed by NM-3. It serves as a novel therapeutic agent in type-2 diabetes for renal alterations.[104]

Pyridyl-isocoumarin derivative 185322 **(65)** has been reported in literature as a novel inhibitor of microtubule assembly that induces a mitotic phase arrest and also apoptosis of human multiple myeloma cells.[105]

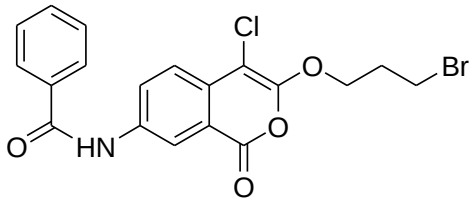


185322 **(65)**

xxv) Inhibitor of Urokinase-type Plasminogen Activator (uPA[64])

Urokinase-type plasminogen activator (uPA) is an attractive target for the development of new compounds as inhibitors because uPA play a lead role in extracellular proteolytic events, which are associated with tumor cell growth and

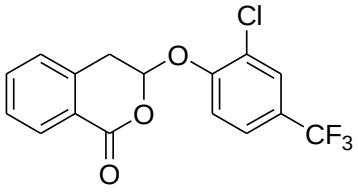
angiogenesis. The hydrolysis of extracellular plasminogen to plasmin was catalyzed by uPA. Over production of plasmin leads to extracellular matrix degradation, which assists the directional migration of cancerous cells[106,107]. Complex of uPA with its receptor uPAR affects many biological processes like signaling pathways and it also has an influence on cell proliferation[108]. Potent inhibitors of uPA with uncharged substituents were designed based upon isocoumarin scaffold. *N*-[3-(3-Bromopropoxy)-4-chloro-1-oxo-1*H*-isochromen-7-yl]benzamide **(66)** was reported as a lead uncharged inhibitor of uPA[109]. In which Br and an aromatic ring play an important role for binding.



(66)

xxvi) Herbicidal Activity

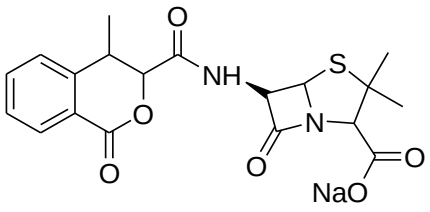
6-[2-Chloro-4-(trifluoromethyl)phenoxy]-3,4-dihydroisocoumarin **(67)** has shown herbicidal activity and its application of 1kg/ha almost totally controlled *Schinochloa Sinapis alba, crus-galli* and other weeds.[110]



(67)

xxvii) Antibacterial Activity

Penicillin dihydroisocoumarin derivatives **(68)** were quite effective bacteriocidal agents at 3.15-100 mg/mL.[111]



(68)

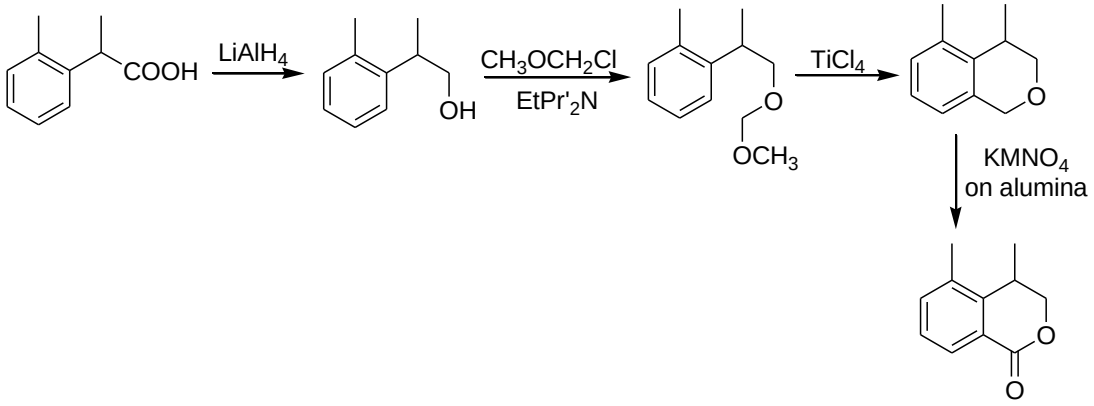
1.1.4 Synthetic Methods of Isocoumarins and 3,4-Dihydroisocoumarins

Many new methods are being developed and a number of synthetic approaches have been reported every year[112-114], for the synthesis of isocoumarins and their 3,4-dihydroisocoumarin derivatives[116]. Following are some reactions in which high yielded synthetic strategies were adopted for the preparation of isocoumarins and 3,4-dihydroisocoumarins:[117-119]

1) By Oxidation Methods:

i) Oxidation of Isochromans

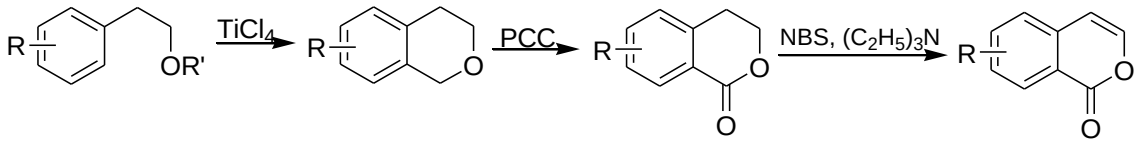
To build the carbon framework of isocoumarins, a traditional method of electrophilic oxyalkylation or formylation reaction was used to introduce C-1 into a β-arylethanol moeity. the free -OH of the alkyl chain intercepted the electrophile carbon of formaldehyde or its derivatives, by directing its selective attack at the *ortho* position of the ring. The isochroman obtained from this reaction can be oxidized selectively to a 3,4-dihydroisocoumarin **(69)** by a variety of oxidizing agents. Many natural products and a number of isocoumarins derivatives have been synthesized efficiently by adopting this route (Scheme 1.1).[120-122]



(69)

(Scheme 1.1)

Isochromans prepared by 2-arylated ethanol[123] were oxidized in the presence of boiling dichloromethane[124] and pyridiniumchlorochromate yields 3,4-dihydroisocoumarins, which were then treated with triethylamine and n-bromosuccinimide to afford isocoumarins **(70)** (R = H, 7-CH_3, 5-CF_3, 5,6-C_4H_4) (Scheme 1.2).

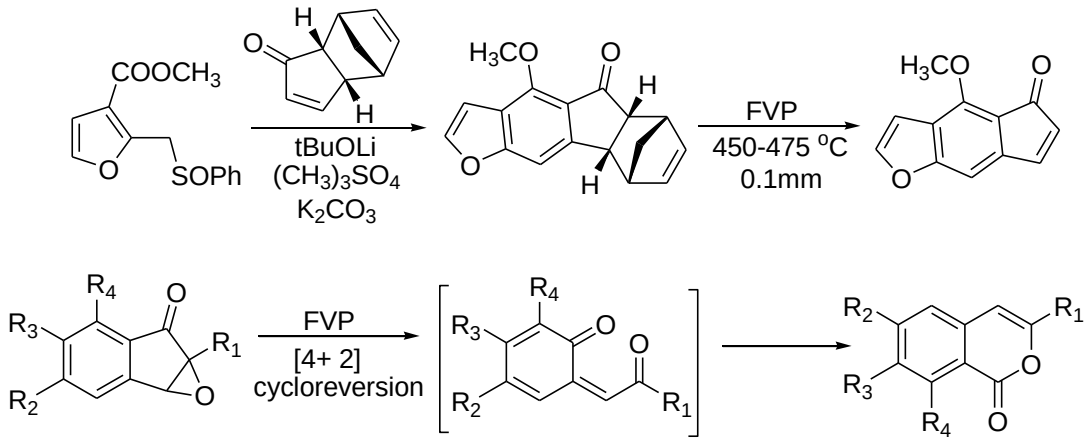


(70)

(Scheme 1.2)

ii) Oxidation of Indenones and Indanones

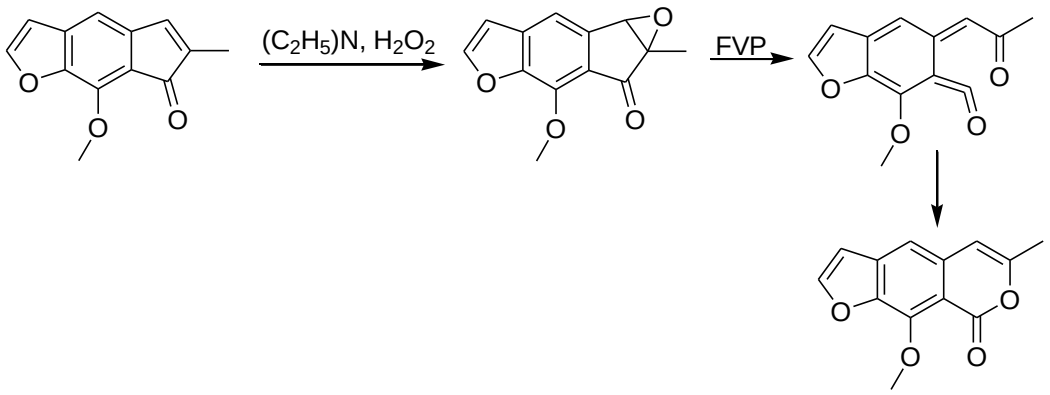
Oxa-indacenone can readily be prepared in high yield from furoate in three steps. Indenone epoxide can be prepared by epoxidation of indenone with $H_2O_2/NaCO_3$ in dry acetone. The ketene-aldehyde intermediate is formed by the thermally allowed [π4a+ π2a] cycloconversion[125-127]. The crude pyrolysate after chromatographic purification afforded the isocoumarin derivative **(71)** in 95 % yield (Scheme 1.3).



(71)

(Scheme 1.3)

Epoxidation of indanone with $H_2O_2/(C_2H_5)_3N$ was carried out in dry acetone to afford indanone epoxide. Then resulting epoxide derivative was subjected to flash vacuum pyrolysis[128] (FVP) (450 °C/0.1 mm), during FVP they undergoes through a rearrangement step yielded isocoumarin **(72)**[124] (Scheme1.4).

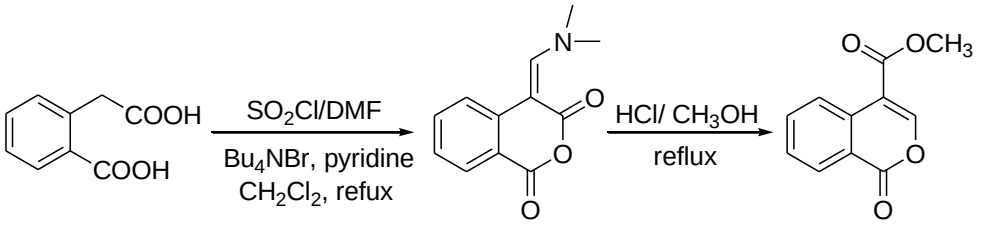


(72)

(Scheme 1.4)

2) From Homophthalic Acids, Esters and Anhydride Precursors

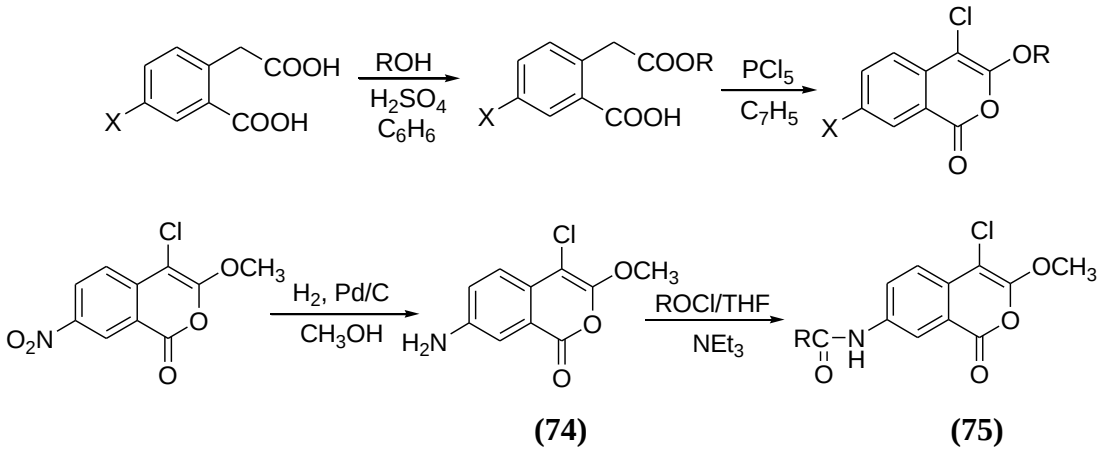
i) Homophthalic acid was reacted with thionyl chloride, DMF and sodium azide in the presence of tetrabutylammonium bromide as catalyst using CH_2Cl_2 as the solvent. Intermediate was further converted to isocoumarin derivative (**73)** in 76 % yield by reaction with methanol saturated with hydrogen chloride[129,130] (Scheme 1.5).



(73)

(Scheme 1.5)

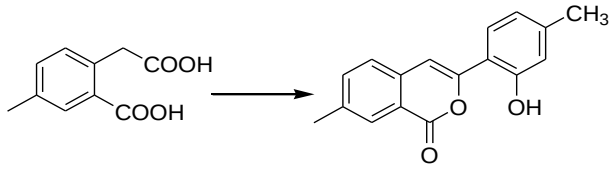
ii) Homophthalic acid or 5-nitrohomophthalic acid was esterified to afford monoesters by using two equivalents of dry alcohols. Cyclization of these monoesters with phosphorus pentachloride in toluene yield 3-alkoxy-4-chloroisocoumarins. 7-Amino-4-chloro-3-methoxyisocoumarin **(74)** was prepared by catalytic hydrogenation of the nitro group. Amino isocoumarins were treated with cyclohexanecrbonyl chloride and benzoyl chloride respectively, in the presence of triethylamine amide derivatives[131] **(75)** (Scheme 1.6).



(74) **(75)**

(Scheme 1.6)

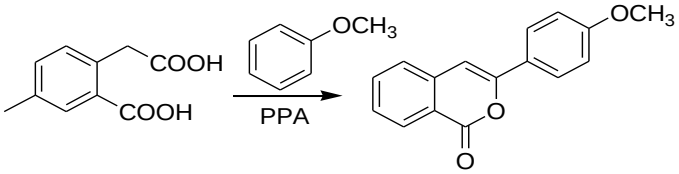
iii) A. large number of 3-(hydroxyphenyl)isocoumarins were synthesized by Rose[132] and H. Yoshikawa[133] by condensation of homophthalic acids e.g 7-methylhomophthalic acid with substituted phenols in the presence of anhydrous stannic chloride and polyphosphouric acid affored 7-methyl-3-(2′-hydroxy-4′-methylphenyl)isocoumarin **(76)** (Scheme 1.7) in good yield.



(76)

(Scheme 1.7)

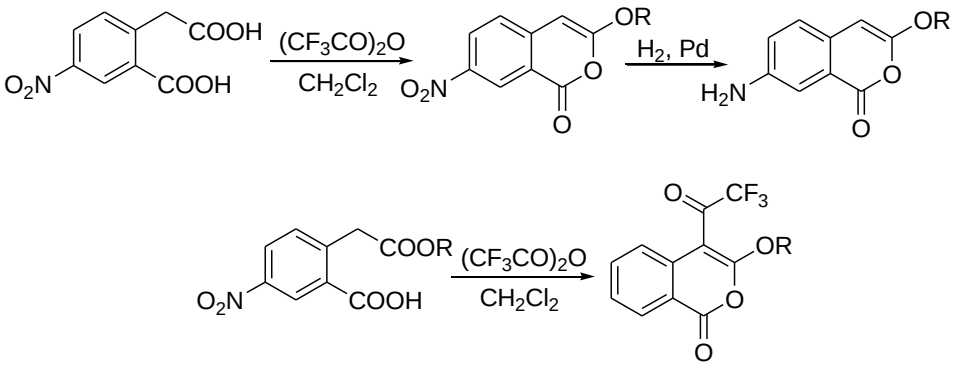
iv) 3-(2’,4’-Dimethoxyphenyl) isocoumarins and 3-(2’-methyl-4’-hydroxyphenyl) isocoumarins and related analogues were prepared[134] by direct condensation of homophthalic anhydride with variously substituted phenols. 3-(4'-Methoxyphenyl) isocoumarin **(77)** was synthesized by condensation of anisole moiety with homophthalic acid precursor in the presence of PPA. (Scheme 1.8).



(77)

(Scheme 1.8)

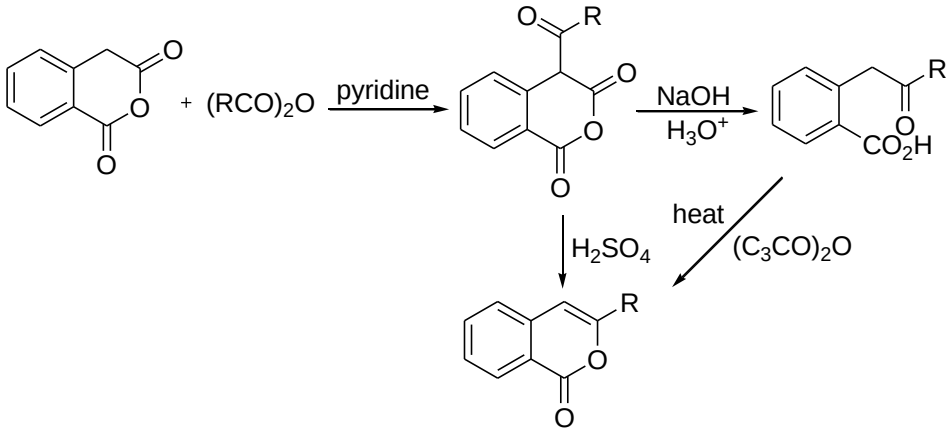
v) Many isocoumarin derivatives were prepared by the cyclization of corresponding monoesters with triflouroacetic anhydride. The reduction of the nitro-group was carried out by catalytic hydrogenation provided amino substituted derivatives. The esters without nitro groups on the ring gave products with trifluoroacetyl groups at the 4-position **(78)**[38,109] (Scheme 1.9).



(78)

(Scheme 1.9)

vi) The acylation of homophthalic anhydrides with anhydrides using an pyridine as catalyst gave acylation product, which can be converted to the isocoumarin derivatives either by heating it with conc. sulfuric acid or through hydrolysis and then decarboxylation to the keto acid, which undergo intramolecular dehydration to give isocoumarin products **(79)**[135] (Scheme 1.10).



(79)

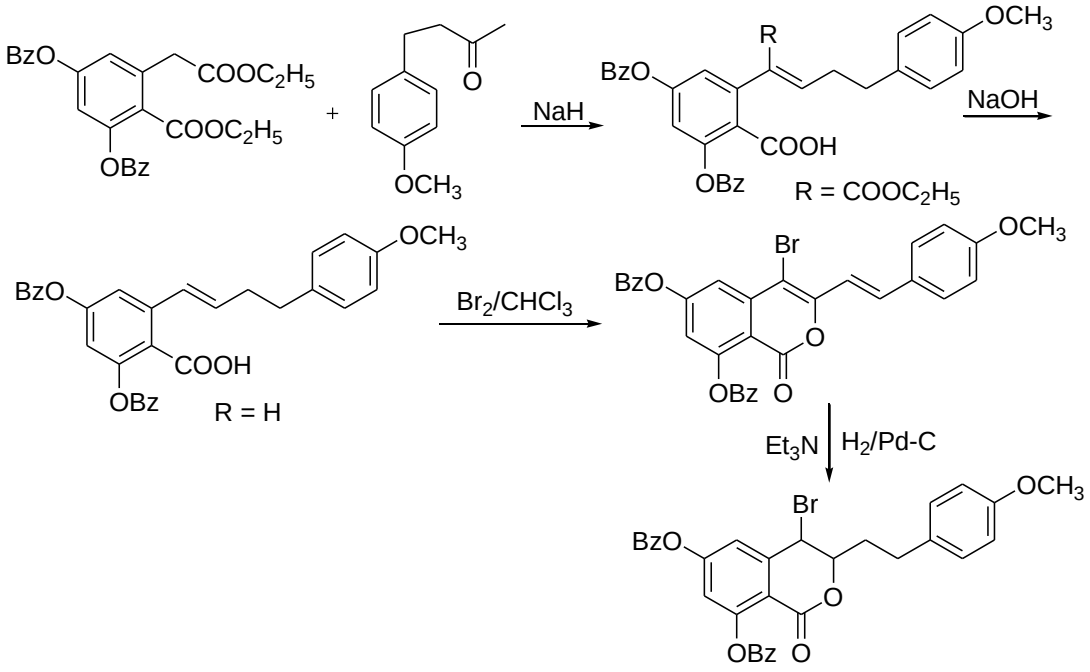
(Scheme 1.10).

3) By Aldol-type Condensation Reactions

Condensation reactions are most commonly used for the synthesis of isocoumarins and 3,4-dihydroisocoumarin derivatives. Following are some important aldol type condensation methods.

i) Stobbe Condensation Reaction

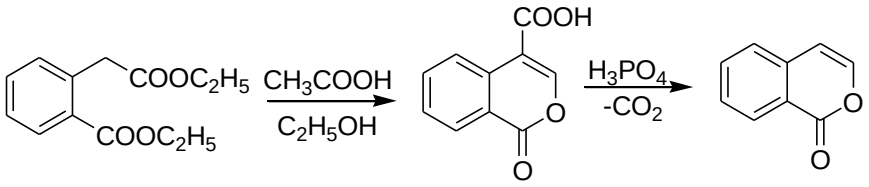
Stobbe condensation have been widely employed for the preparation of number of isocoumarins and 3,4-dihydroisocoumarins[136-139]. Synthesis of (±)-agrimonolide is good example of application of Stobbe's condensation reaction. Diethyl 3,4-dibenzyloxyhomophthalate was condense with 4-methoxybenzaldehyde in the presence of sodium hydride yields 2,4-dibenzyloxy-6-[1-ethoxycarbonyl-4-(4'-methoxyphenyl) buten-1-yl]benzoic acid. Followed by hydrolysis and then decarboxylation gave 2,4-dibenzyloxy-6-[4-(4'-methoxyphenyl) buten-1-yl]benzoic acid, which on cyclization with bromine afforded the 4-bromo-3,4-dihydroisocoumarin. Reductive debromination and debenzylation was carried out by adding triethyl amine and then catalytic reduction furnished (±)-agrimonolide **(80)** (Scheme 1.11).[140,141]



(Scheme 1.11)

ii) Claisen Condensation of Homophthalates with Formates

Isocoumarin-4-carboxylic acid was prepared by the condensation of diethyl homophthalate with methyl formate in the presence of sodium ethoxide, followed by decarboxylation with phosphoric acid yields isocoumarin **(81)** (Scheme 1.12).



(81)

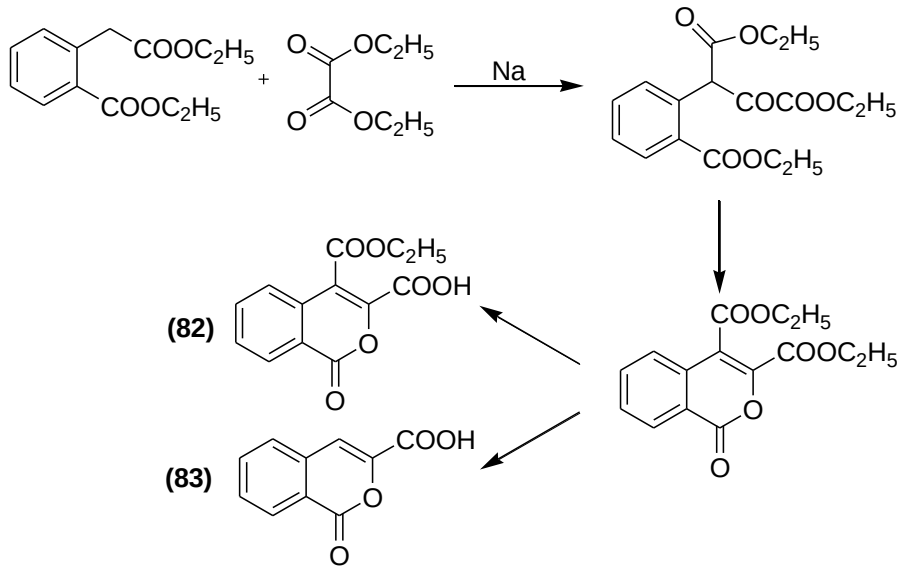
(Scheme 1.12)

Ethyl 5,6,7-trimethoxyisocoumarin-4-carboxylate was prepared by the condensation of corresponding homophthalate with ethyl formate in the presence of potassium ethoxide in high yield.[142]

iii) Claisen Condensation of Homophthalates with Oxalates

Metallic sodium in ether or without any solvent effects ready condensation between diethyl homophthalate and diethyl oxalate gave a triester product with 67 % yield. The triester product when heated loses ethanol molecule yield diethyl isocoumarin-3,4-dicarboxylate. Different products are formed under different hydrolysis conditions. By heating diethyl isocoumarin-3,4-dicarboxylate at 68-72 °C for 3 hr afford ethyl isocoumarin-3-(carboxylic acid)-4-carboxylate **(82)** and prolonged heating yields isocoumarin-3-carboxylic acid **(83)**.

Boiling hydrochloric acid or heating in a sealed tube at 180-190 °C converts diethyl isocoumarin-3,4-dicarboxylate to isocoumarin-3-carboxylic acid in 84 % yield[143]. Thus, these results indicates that the hydrolysis of ester at position 3 in diethyl isocoumarin-3,4-dicarboxylate undergo first, but the decarboxylation of acid at position 4 is more easy (Scheme 1.13).

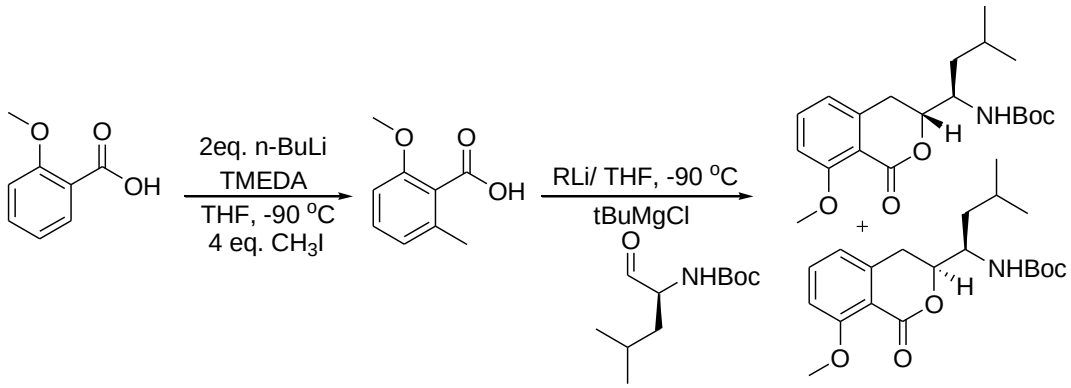


(Scheme 1.13)

4) By Metal Catalysed Reactions:

i) Ortho-Lithiation Reaction

3,4-Dihydroisocoumarin derivatives **(84)** and **(85)** can be obtained by a regioselective ortho-lithiation reactions of commercially available 2-methoxybenzoic acid. The benzylic carbanion was generated and then followed by the addition of *N*-Boc-protected leucinal during a mild acid hydrolysis reaction conditions, it readily undergoes a spontaneous lactone formation[144-146] (Scheme 1.14).



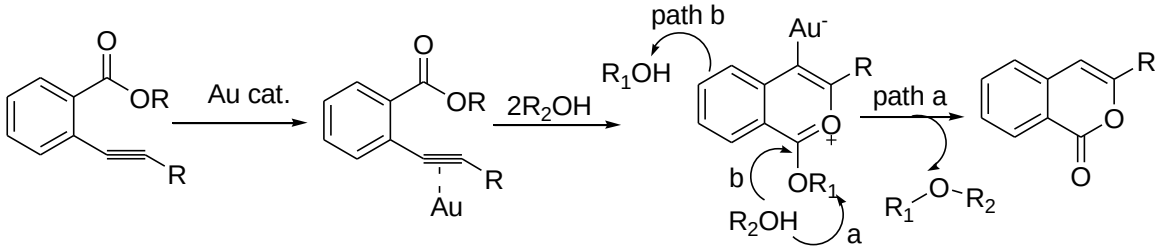
(84,85)

(Scheme 1:14)

ii) Au-Catalyzed

The electrophilicity of the alkyne part was enhanced by Au catalyst followed by the intramolecular nucleophilic attack of the carbonyl oxygen to the alkyne moiety leads to the formation of a zwitter-ion intermediate. The nucleophilic attack of alcohol to R_1 part was facile due to strong electrophilicity of an intermediate yields isocoumarins **(86)** *via* path a.[147]

Dibenzyl ethers were obtained in low yields as a byproduct in the reactions of benzyl esters. If an alcohol attack to the intermediate benzyl alcohol was liberated *via* path b.[148-151] (Scheme 1.15).

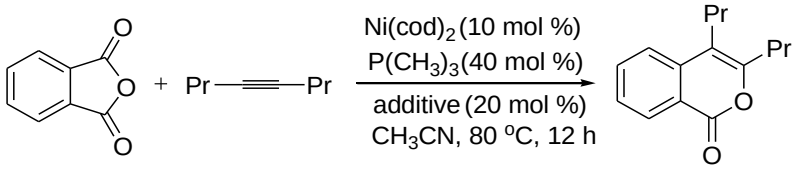


(86)

(Scheme 1.15)

iii) Ni-Catalyzed

Phthalic anhydride was addition to alkyne derivative with 40 mol % of $P(CH_3)_3$ and 10 mol % of $Ni(cod)_2$. By refluxing the reaction mixture in methylnitrile at 80 ^oC for 12 hr resulted in the formation of substituted isocoumarin **(89)**[152,153] (Scheme 1.16).

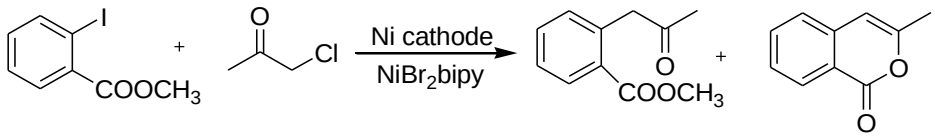


(89)

(Scheme 1.16)

The photochemical cross-coupling of alkali metal enolates with *o*-iodobenzoic acids was quite known and direct method not only for the synthesis of isocoumarins and 3,4-dihydroisocoumarins but also employed for the preparation of an important intermediates i-e benzophenantridine alkaloids etc.[154]

Electrochemical Ni-catalyzed cross-coupling reaction between activated alkyl halides and aryl halides furnished isocoumarin **(90)**. Aromatic halides act as a donor in this process rather than acceptor[155] (Scheme 1.17).

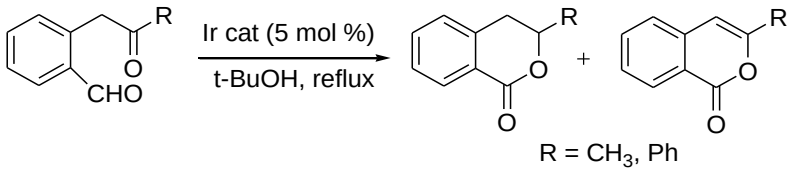


(90)

(Scheme 1.17)

iv) Iridium Catalyzed

The formyl ester derivative was reacted with 5 mol % of Ir catalyst generated *in situ* and by refluxing it in *t*-BuOH leads to the formation of 3-substituted dihydroisocoumarin **(91)** in high yield 70 % and interestingly substituted isocoumarin derivative **(92)** was also obtained but in low yield 28 % under the same reaction conditions.[156,157] (Scheme 1.18).



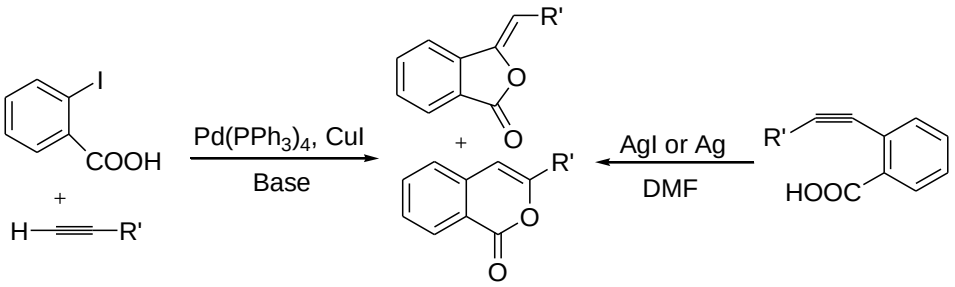
(91) **(92)**

(Scheme 1.18)

v) Cu & Ag Catalyzed

Recently, so much attention has been given particularly to synthesized selectively 3-substituted isocoumarins and 3-ylidenephthalides by heteroannulation reactions[158,119] catalyzed by transition metals.

3-Substituted isocoumarin **(93)** and (*Z*)-3-(1-alkylidene)-phthalides can be synthesized either by the reaction of 1-alkynes with 2-iodobenzoic acid in the presence of catalytic amounts of $Pd(PPh_3)_4$ and CuI[159] and a base or by direct cyclization of 2-(1-alkynyl)benzoic acids in the presence of catalytic quantities of AgI or Ag[160] in dry DMF (Scheme 1.19).

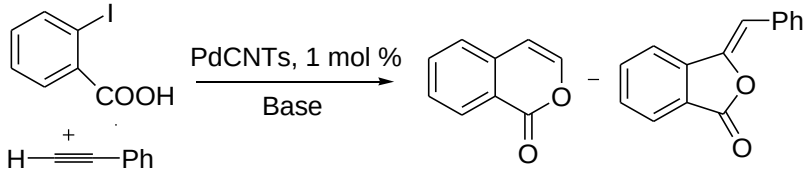


(93)

(Scheme 1.19)

vi) Pd-Catalyzed

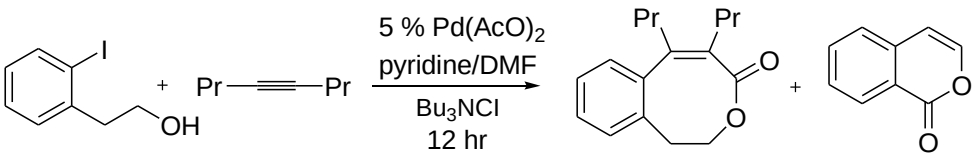
1-Iodobenzoic acid and phenyl acetylene in the presence of a base were treated with catalytic amount of Pd/CNTs (1 mol %). Reaction conditions were optimized initially by using four different kind of bases including NaOAc, NEt_3, DABCO and K_2CO_3. DABCO was observed to be the most effective base for affording the isocoumarin derivative **(94)** (Scheme 1.20).[161,162]



(94)

(Scheme 1.20)

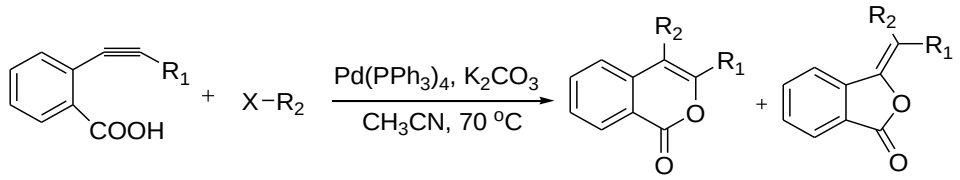
Isocoumarin **(95)** and eight-membered lactone rings were obtained by the Pd catalysed reaction of *o*-iodophenethyl alcohol by the insersion of alkyne in pyridine and DMF afforded mixture of products in moderate yields[163] (Scheme 1.21).



(95)

(Scheme 1.21)

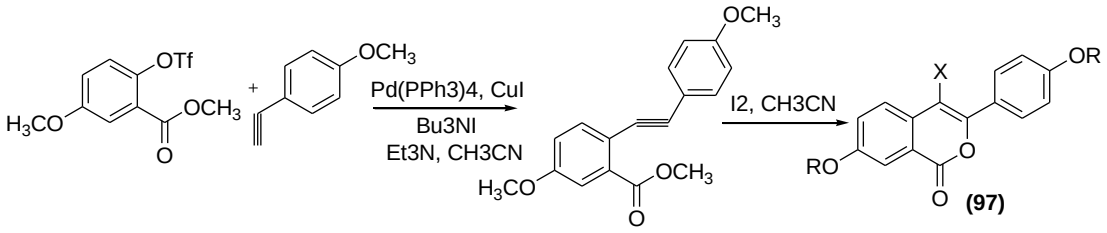
2-(1-Alkynyl)-benzoic acids were treated with 1.2 eq. of heteroarylhalides, 5 mol % $Pd(PPH_3)_4$ and K_2CO_3 in dry methylnitirle under an inert atmosphere at 70 ^oC gives mixtures of products i.e 3-[(1,1-disubstituted)methylidene]isobenzofuran-1(3H)-ones and 3-substituted 4-arylisocoumarin **(96)** in excellent yields[164,165] (Scheme 1.22).



(96)

(Scheme 1.22)

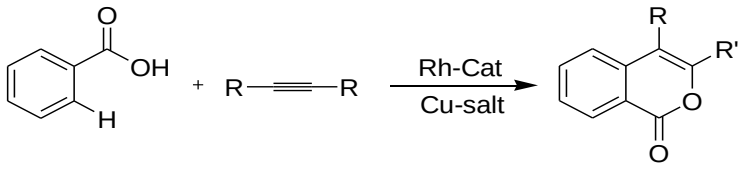
Palladium-catalyzed sonogashira cross coupling reactions between 4-ethynylanisole and aromatic derivatives were also employed for the synthesis of wide variety of substituted isocoumarin **(97)** (Scheme 1.23).[166,167]



(Scheme 1.23)

vii) Rhodium-Catalyzed Oxidative Coupling

The oxidative coupling of internal alkynes with benzoic acids proceeds effectively in the presence of a catalyst[168] $[Cp^*RhCl_2]_2$ and an oxidant $Cu(OAc)_2.\ H_2O$ respectively to yield corresponding isocoumarin **(98)**. The catalytic quantity of copper salt can be obtained under air. (Scheme 1.24).

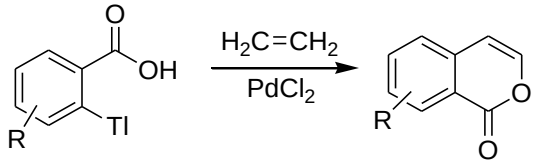


(98)

(Scheme 1.24)

viii) Thallation-Olefination of Arenes

One pot cyclization reaction[169] of electrophilic thallium salt with benzoic acids in the presence of dry organic solvents gives corresponding *O*-thalliated benzoic acids followed by its reaction with an alkene in the presence of a catalyst $PdCl_2$ afforded isocoumarin **(99)** and 3,4-dihydroisocoumarins in good yields. (Scheme 1.25).

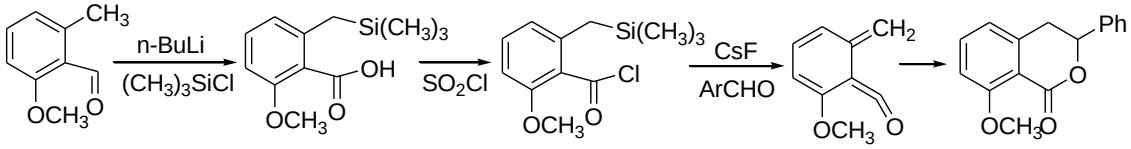


(99)

(Scheme 1.25)

ix) Silylation Reaction

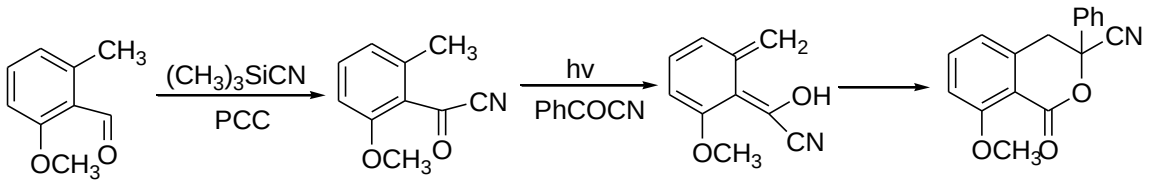
a) 2-(Trimethylsilylmethyl)-benzamides undergo desilylation to generate carbanions, which serves as a suitable substrates for the addition of aldehydes[170]. The desilylation of 2-(trimethylsilylmethyl)benzoyl chloride not occurs through a carbanions intermediates rather then it involves an ortho-quinodimethanes intermediates formed by concerted mechanism followed by aldehyde addition to furnished 3,4-dihydroisocoumarins **(100)** (Scheme 1.26).[171]



(100)

(Scheme 1.26)

b) UV irradiation products of *o*-tolulyl cyanides when treated with aromatic and aliphatic acyl cyanides yields 3-cyano-3-phenyl-8-methoxy-3,4-dihydroisocoumarin **(101)**. These 3,4-dihydro derivatives were converted into their isocoumarin analogues by reacting them with strong bases. (Scheme 1.27).[172]

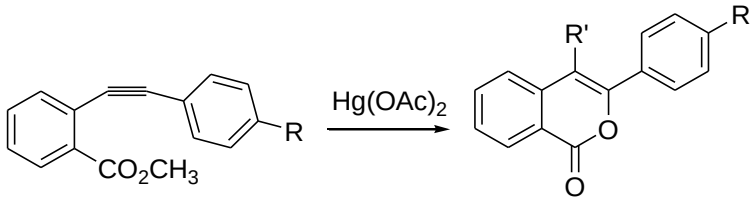


(101)

(Scheme 1.27)

x) Organo-Hg Catalyzed

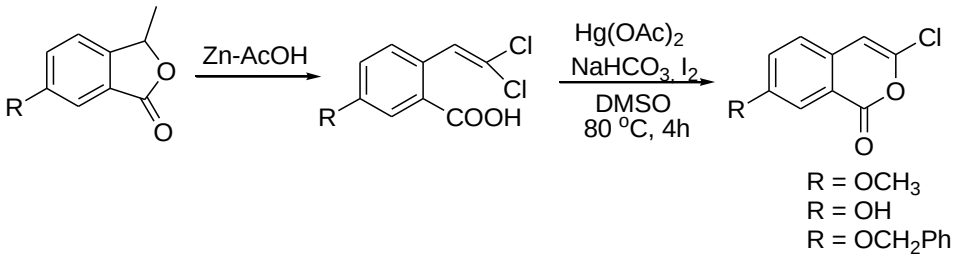
A facile and efficient method for the preparation of 3-substituted isocoumarins involves the reaction of alkyne esters (R=H, Br, Cl, I, Ac)[173] with mercuric acetate to afford mercurial isocoumarin intermediates, which readily undergoes through a substitution reaction to furnish the substituted isocoumarins **(102)** (R^1=H, CH_3, Cl, Br; R=H, Br, Cl, I, Ac) (Scheme 1.28).



(102)

(Scheme 1.28)

Trichlorophthalides were prepared by chloral hydrate sulphuric acid-catalyzed condensation with substituted benzoic acids, which were reduced with Zn+AcOH to afford various dichloro derivatives. These derivatives were treated with alkaline $Hg(OAc)_2$+I_2 to yield variously substituted isocoumarin derivatives **(103-105)** (Scheme 1.29)[174].

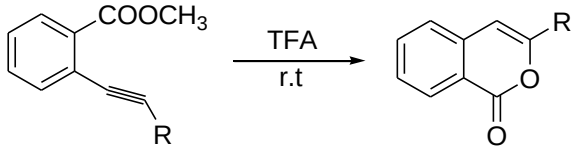


(103-105)

(Scheme 1.29)

5) By Cyclization Reactions

Methyl 2-(2-arylethynyl) benzoate was cyclized to the corresponding isocoumarins **(106)** in high yields under acidic conditions at room temperature. The electronic bias of the triple bond on both the carbons favours (6-endo-dig) Michael-type cyclization[175,176], in which trifluoroacetic acid (TFA) act as a bronsted acid (Scheme 1.30).



(106)

(Scheme 1.30)

1.1.5 Interconverision of Isocoumarins and 3,4-Dihydroisocumarins

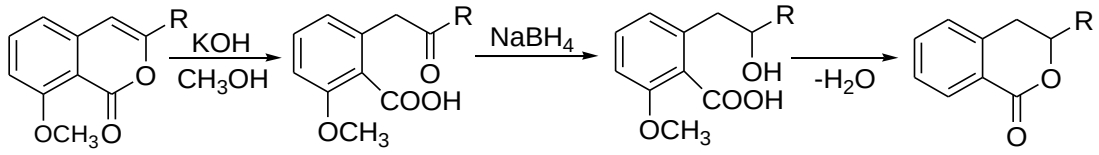
Some methods directly provides the isocoumarins while others produce dihydroisocoumarins, their interconversion can be employed depending upon wheather the preparation of isocoumarin is easier or that of its 3,4-dihydro analogues.

I) Conversion of Isocoumarins to 3,4-Dihydroisocoumarins

Different methods of reduction are mainly used for conversion of isocoumarins to 3,4-dihydroisocoumarins:

a) Alkaline Hydrolysis Followed by Reduction and Recyclization

Alkaline hydrolysis of isocoumarins with dilute aqueous alkali affords the keto-acids, which upon reduction with sodium borohydride are converted into corresponding hydroxy-acids. Cyclodehydration of the hydroxy-acids affords dihydroisocoumarin (Scheme 1.31).



(Scheme 1.31)

b) Catalytic Reduction

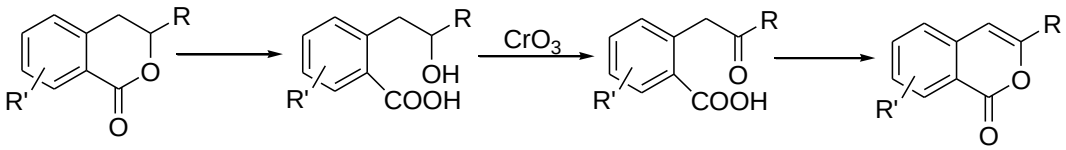
Hydrogenationin the presence of palladium charcoal or some other catalyst has been used to reduce the 3,4-double bond of isocoumarins to convert them directly into 3,4-dihydroisocoumarins.[177,178]

II) Conversion of 3,4-Dihydroisocoumarins to Isocoumarins

Two routes are mainly used for the conversion of 3,4-dihydroisocoumarins to isocoumarins:

a) Alkaline Hydrolysis Followed by Oxidation and Recyclization

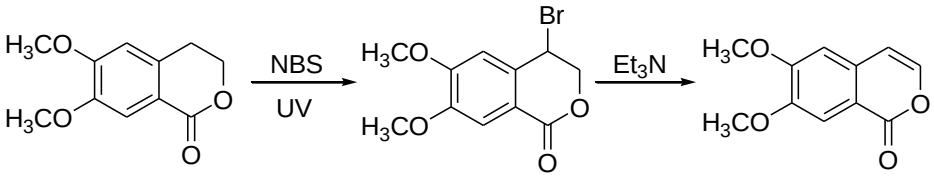
Alkaline hydrolysis of 3,4-dihydroisocoumarins yields the hydroxy acids which could be oxidized to corresponding keto-acids. Since the hydroxy acids on standing recyclize to parent dihydroisocoumarins, the oxidation should be carried out immediately. The keto-acids are readily cyclized e.g by heating with acetic anhydride to corresponding isocoumarins (Scheme 1.32).[179]



(Scheme 1.32)

b) Benzylic Bromination Followed by Dehydrobromination

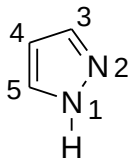
Isocoumarins can be prepared from 3,4-dihydroisocoumarin *via.* benzylic bromination with *N*-bromosuccinimide (NBS), followed by dehydrohalogenation with triethylamine (Scheme 1.33).[180]



(Scheme 1.33)

1.2 Functionalized Pyrazoles

Pyrazoles represents an important class of five membered heterocyclic compounds belongs to alkaloids, containing two nitrogen atoms present at adjacent positions in the ring.[181]



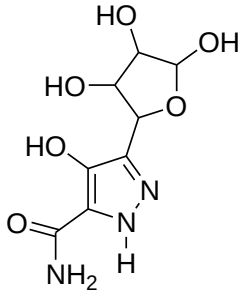
Pyrazole nucleus present in various heterocyclic systems or found in numerous natural products,[182] imparts significant biological activities associated with these compounds including pharmaceuticals properties,[183,184] along with a wide spectrum of other biological applications.[185]

1.2.1 Biological Significance of Pyrazoles

Heterocyclic compounds particularly nitrogen-containing heterocycles[186] are of great chemical and biological significance,[187] are also present as structural constituents of many bioactive natural products, medicinally important compounds and other organic materials.[188]

i) As Antibiotics

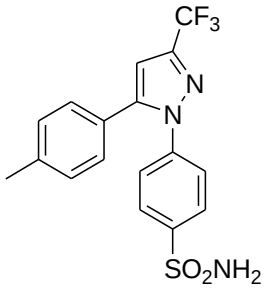
Many naturally occurring compounds containing pyrazole ring such as pyrazofurin **(1)** isolated from *Streptomyces candidus*, have been found as an antibiotic[189] which possess potent anticancer and a wide-spectrum of antiviral activity especially against many RNA and DNA viruses and also exhibit significant antimicrobial properties.[190,191]



(1)

ii) Antitumor and Anti-angiogenic Properties

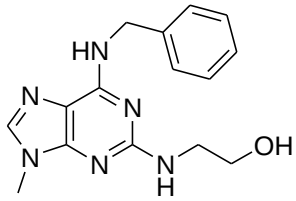
N-arylated pyrazole derivatives[192-195] have been extensively investigated for the last few years after the discovery of celecoxib **(2)**, which exhibits significant antitumor and anti-angiogenic properties[196,197]. Celecoxib is highly effective for the treatment of wide range of human cancers and currently, it is in clinical trials.[198]



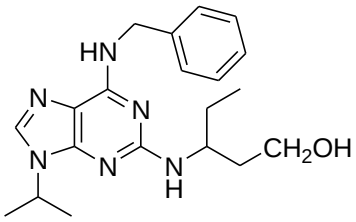
Celecoxib **(2)**

iii) Antimicrobial Activity

Purine derivatives of pyrazoles such as olomoucine **(3)** and roscovitine **(4)** were found to exhibit moderate inhibitory activity but good selectivity for a panel of cyclin-dependent kinases (CDK),[199] which play a key role during cell division and a pyrazolo[3,4-d]pyrimidin-4-one subunit is a significant antimicrobial activity enhancing group which inhibits DNA polymerase III.[200,201]



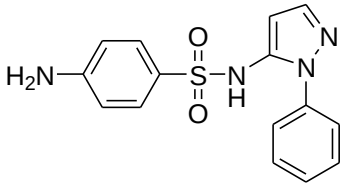
Olomoucine **(3)**



Roscovitine **(4)**

iv) Potent Antibacterial Activities

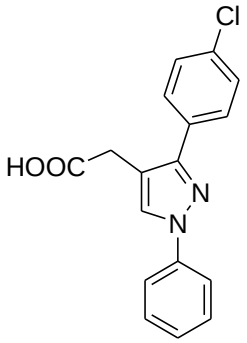
Various pyrazole derivatives represents selective inhibitors of bacterial DNA. Sulfaphenazole **(5)** containing pyrazole nucleus in its core structure, is a potent antibacterial drug.[202]



Sulfaphenazole **(5)**

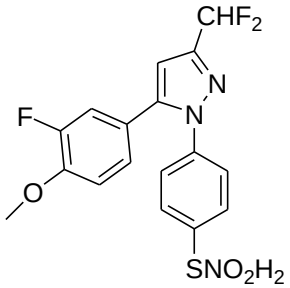
v) Anti-Inflammatory Activities

1,3-Diphenyl-(1H-pyrazol-4-yl)acetic acid derivatives i.e lonazolac **(6)** is an anti-inflammatory nonsteroidal drug.[203]



Lonazolac **(6)**

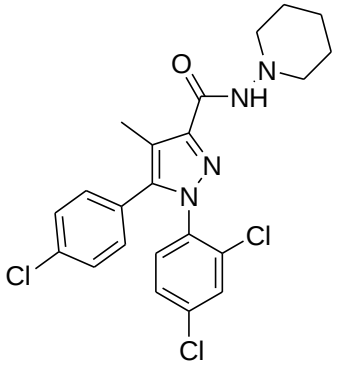
Deracoxib **(7)** (DeramaxxTM)[204] is one of the marketed agents for the treatment of inflammation and pain for dogs, have demonstrated moderate COX-2 selectivity.



Deracoxib **(7)**

vi) Obesity and Addictions

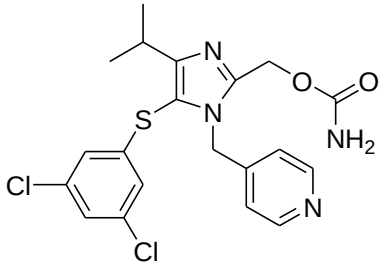
The diarylated pyrazole derivatives are another type of cannabinoid analogues which were developed by Sanofi, one of them is SR141716A, which is currently in clinical phase for the treatment of obesity and addictions[205]. Rimonabant **(8)** is another antiobestic drug, which was extensively used in Europe for obesty.[206]



SR141716A **(8)**

vii) Potential Anti-HIV Agents

Capravirine **(9)** is a pyrazole derived Anti-HIV drug, it is very effective against different drug resistant strains of HIV including K103N.[207]



Capravirine **(9)**

viii) Insecticidal and Molluscicidal Activities

Heterocyclic compounds containing pyrazole nucleus in their structure possess significant insecticidal and molluscicidal properties.[208-210]

ix) Cholesterol Lowering Properties

Many natural products and synthetic compounds containing pyrazole moieties were reported to possess varied biological activities i.e cholesterol lowering.[211]

x) Anti-depressant and Anti-psychotic Agents

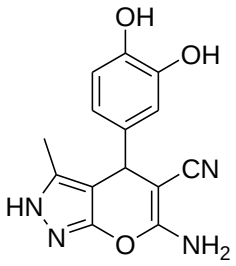
Nitrogen-containing heterocyclic systems like substituted pyrazoles were intensively investigated for their pharmaceutical activities[212]. Many pyrazole derivatives possess anti-depressant and anti-psychotic activities.[213]

xi) Acetyl Cholinesterase Inhibitors

N-1 or *N*-2 substituted analogues of pyrazoles have been known for their biological applications as an acetyl cholinesterase inhibitors.[214]

xii) Inhibitors of Human Chk-1 Kinase

Dihydropyrano[2,3-c]pyrazole derivatives like 6-amino-5-cyanodihydropyrano [2,3-c]-pyrazole **(10)** were reported as potential inhibitors of human Chk-1 kinase enzyme.[215]



(10)

The marine alkaloidic metabolites i.e granulatimide, isogranulatimide and their structural analogues having pyrazole rings were potent as Chk1 kinase inhibitors.[216]

xiii) Antimalarial and Antiallergic Properties

N-hydroxy-substituted quinoline and isoquinoline derivatives of pyrazoles[217] like pyrazolo[3,4-*c*]quinoline, pyrazolo[3,4-*c*]isoquinoline and their analogues were known to possess good antimalarial and antiallergic activities.[218]

xiv) Antiviral Agents

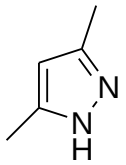
1β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide and different analogues of pyrazole containing five-membered nucleoside rings were reported to be effective as an antiviral agents.[219-222]

xv) Anticancer Agents

Many heterocyclic systems containing pyrazole moieties were known as potent for their anticancer properties.[223-227]

xvi) Anti-diabetic Agents

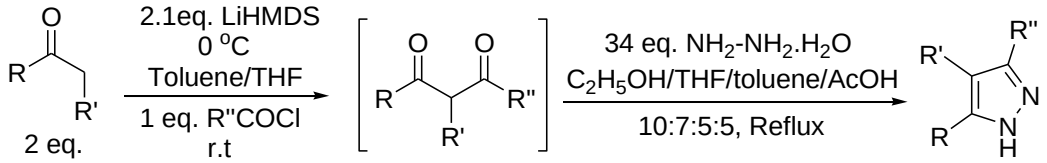
Methyl substituted pyrazole analogues e.g 3,5-dimethylpyrazole **(11)** were potent to possess remarkable anti-diabetic activities.[228]



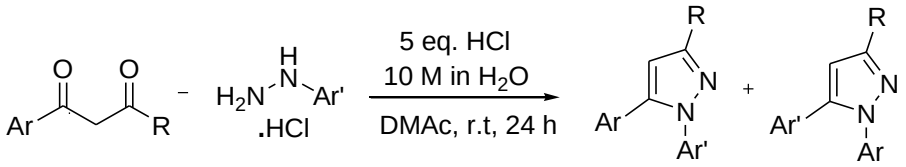
(11)

1.2.2 Synthetic Methods of Pyrazoles

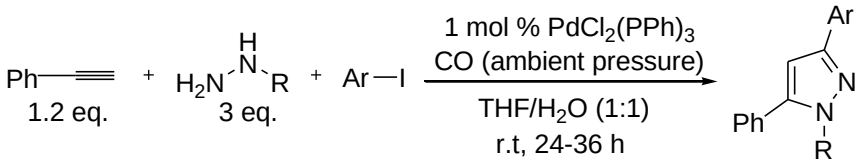
(i) 1,3-Diketones, which were synthesized *in situ* from ketones and acid chlorides, were converted into pyrazoles by the addition of hydrazine. This method allows a fast and general synthesis of previously inaccessible pyrazoles and synthetically demanding pyrazole containing fused rings.[229]



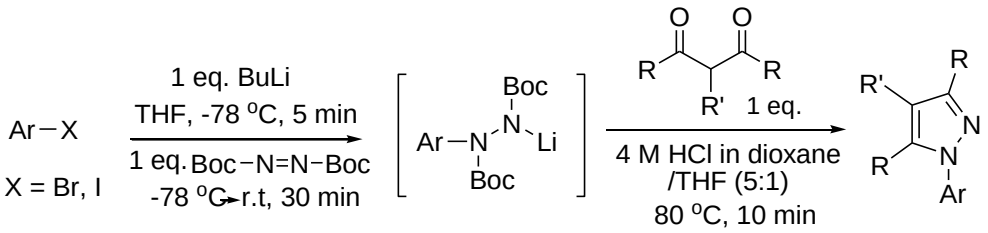
(ii) A highly regioselective synthesis of 1-aryl-3,4,5-substituted pyrazoles based on the condensation of 1,3-diketones with arylhydrazines proceeds at room temperature in *N*,*N*-dimethylacetamide furnishes pyrazoles in good yields.[230]



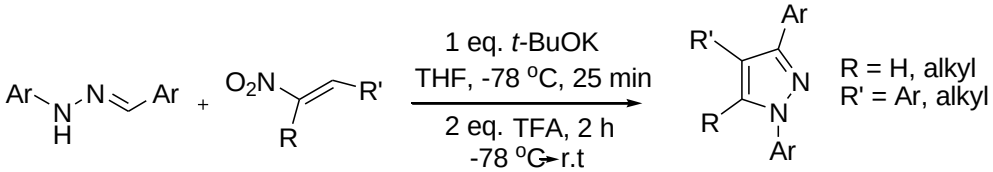
(iii) Pyrazole or isoxazole derivatives are prepared by a palladium-catalyzed four-component coupling of a terminal alkyne, hydrazine (hydroxylamine), carbon monoxide under ambient pressure, and an aryl iodide.[231]



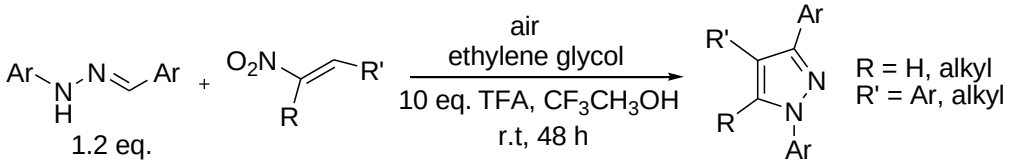
(iv) A simple one-pot method allows the synthesis of diversely functionalized *N*-arylpyrazoles from aryl nucleophiles, di-*tert*-butylazodicarboxlate, and 1,3-dicarbonyl or equivalent compounds.[232]



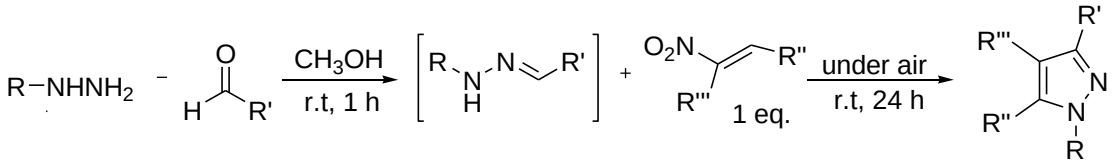
(v) A regioselective synthesis of tri- or tetrasubstituted pyrazoles by the reaction of hydrazones with nitro-olefins mediated with strong bases such as *t*-BuOK exhibits a reversed, exclusive 1,3,4-regioselectivity. Subsequent quenching with strong acids such as TFA is essential to achieve good yields.[233]



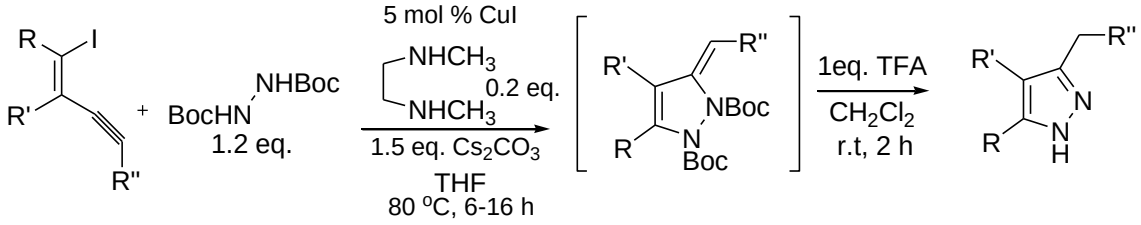
(vi) Two general protocols for the reaction of electron-deficient *N*-arylhydrazones with nitro-olefins allow a regioselective synthesis of 1,3,5-tri- and 1,3,4,5-tetrasubstituted pyrazoles. Studies on the stereochemistry of the key pyrazolidine intermediate suggest a stepwise cycloaddition mechanism.[234]



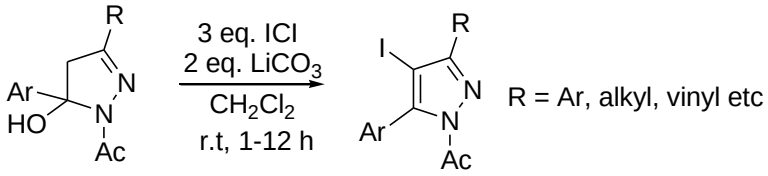
(vii) A regioselective one-pot synthesis of substituted pyrazoles from *N*-monosubstituted hydrazones and nitro-olefins gives products in good yields. A key nitropyrazolidine intermediate is characterized and a plausible mechanism is proposed.[235]



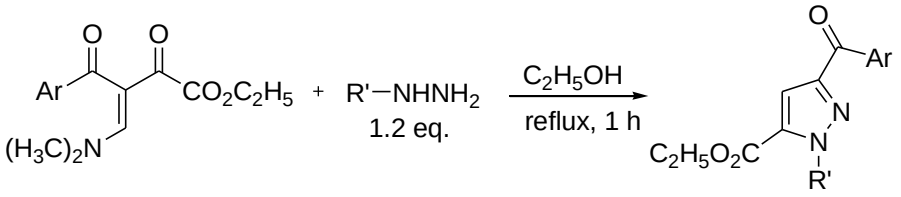
(viii) A general, highly flexible Cu-catalyzed domino C-N coupling/hydroamination reaction constitutes a straightforward alternative to existing methodology for the preparation of pyrroles and pyrazoles.[236]



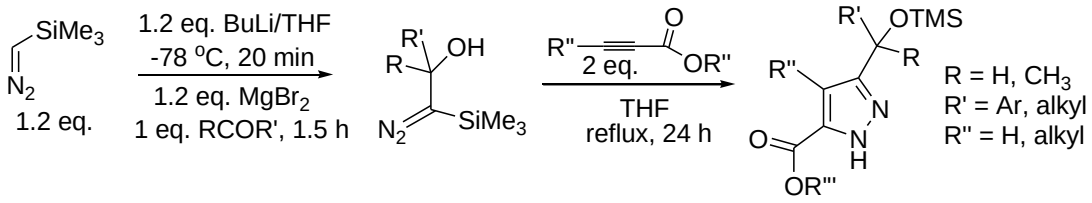
(ix) Various 1-acyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles have been prepared in good yields from the corresponding 2-alkyn-1-ones. The resulting dihydropyrazoles undergo dehydration and iodination in the presence of ICl and Li_2CO_3 at room temperature to provide 1-acyl-4-iodo-1*H*-pyrazoles.[237]



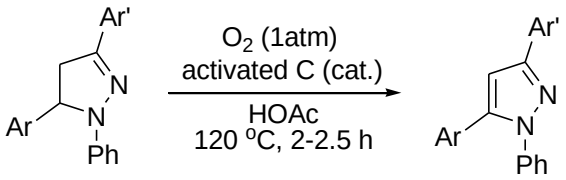
(x) A series of 4-substituted 1*H*-pyrazole-5-carboxylates were prepared from the cyclocondensation reaction of unsymmetrical enaminodiketones with *tert*-butylhydrazine hydrochloride or carboxymethylhydrazine. The products were obtained regiospecifically and in very good yields.[238]



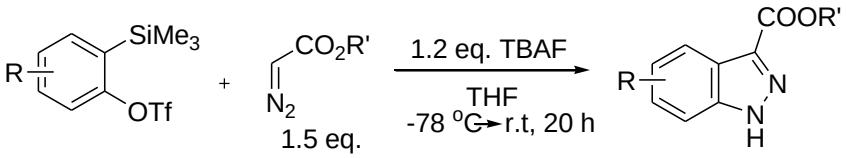
(xi) The reaction of diazo(trimethylsilyl)methylmagnesium bromide with aldehydes or ketones gave 2-diazo-2-(trimethylsilyl)ethanols, which were applied to the synthesis of di- and trisubstituted pyrazoles via [3+2] cycloaddition reaction with ethyl propiolate or dimethyl acetylenedicarboxylate.[239]



(xii) In the presence of activated carbon, Hantzsch 1,4-dihydropyridines and 1,3,5-trisubstituted pyrazolines were aromatized with molecular oxygen to the corresponding pyridines and pyrazoles in excellent yields.[240]

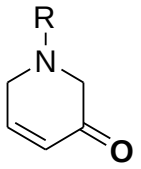


(xiii) The [3+2] cycloaddition of a variety of diazo compounds with *o*-(trimethylsilyl) aryl triflates in the presence of CsF or TBAF at room temperature provides a very direct, efficient approach to a wide range of potentially biologically active and pharmaceutically interesting substituted indazoles in good to excellent yields under mild reaction conditions.[241]



1.3 *N*-Substituted Dihydropyridinones

1,6-Dihydropyridin-3(2H)-one are a class of nitrogen-containing heterocyclic organic compounds having a six-membered ring with a keto-group.



The dihydropyridinones were found as core in substructure of many biologically active natural and synthetic analogues that possess broad range of medicinal activities. These compounds have been used for the treatment of acute coronary syndrome, chronic obstructive pulmonary diseases, heart failure and acute myocardial infection.[242]

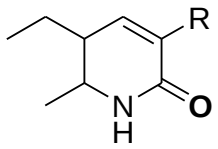
Heterocyclic rings condensed with dihydropyridinones were rarely studied, few synthetic methods and biological activities of pyrazolopyridinones were reported in literature.[243-245]

1.3.1 Biological Significance of Dihydropyridinones

Dihydropyridinones are commonly found in many pharmacologically active heterocyclic compounds of natural or synthetic origin that possess a wide spectrum of biological properties.[246,247]

i) Antiviral Activity

Some alkyl derivatives of dihydropyridinones **(12)** were reported to exhibit potent antiviral activities.[248]



(12)

ii) Hypotensive and Cardiotropic Activity

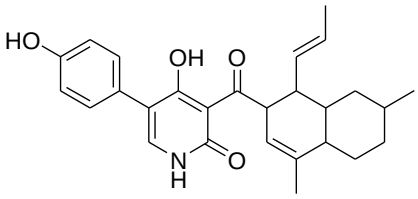
Many synthetic analogues of dihydropyridinones have been known to possess high hypotensive and cardiotropic activities.[249]

iii) Hepatoprotective Agents

Few dihydropyridinone derivatives have been reported to be very effective as hepatoprotective agents.[250]

iv) As Antibiotics

Ilicicolin H **(13)** an antibiotic, is a novel fungal metabolite, isolated from the imperfect fungus *Cylindrocladium iliicola.*[251-253]



Ilicicolin H **(13)**

v) Antibacterial Properties

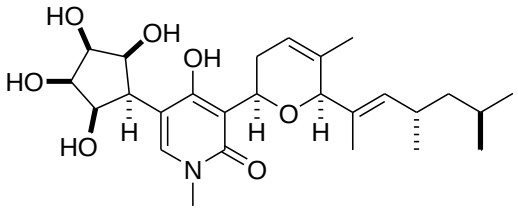
Many heterocyclic systems with pyridinone moieties exhibit remarkable antibacterial activities.[254-256]

vi) Herbicidal Activities

Synthesis of poly-substituted 5,6-dihydropyridones attracts considerable interest due to their strong herbicidal properties.[257-259]

vii) Antitumor Activity

Funiculosin **(14)** is a unique fungal metabolite that has a central 4-hydroxy-2-pyridinone heterocyclic ring[260-263]. This unique secondary metabolite exhibit antitumor and antiviral properties as well as it is potent antifungal agent.[264-267]



Funiculosin **(14)**

viii) Human Leukocyte Elastase Inhibitors

N-Substituted dihydropyridinones were employed as an active ingredient in drugs for therapy of fibrotic disease[268] and they have been tested as human leukocyte elastase inhibitors.[269]

ix) As Free Radical Scavengers

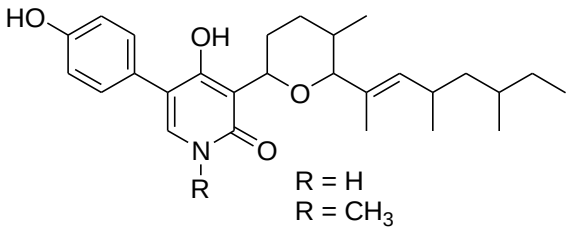
Dihydropyridinone analogues were also reported to act as a free radical scavengers[270] and they play an effective role in different diseases including inflammatory disorder, connective tissue damage, cardiovascular and central nervous injury.[271]

x) Potent Acetyl Cholinesterase Inhibitors

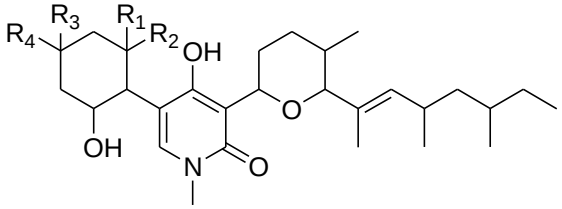
Many nitrogen containing heterocycles like pyridinones are potent inhibitors of acetyl cholinesterase. Huperzine A, a potent inhibitor of acetyl cholinesterase was isolated from the Chinese drug *Huperziaserrata.* For senile dementia diseases including an *Alzheimer* problem, huperzine A is a promising drug candidate. It is very effective for the treatment of memory impairment, multi-infarct dementia and myasthenia gravis with no side effects.[272]

xi) Antifungal and Insecticidal Activities

(-)-Sambutoxin (**15**), *N*-demethylsambutoxin (**16**), and a novel 3,5-disubstituted *N*-methyl-4-hydroxy-2-pyridone (-) oxysporidinone (**17**), along with two new *N*-methyl-4-hydroxy-2-pyridinone analogues 6-*epi*-oxysporidinone (**18**), and oxysporidinone (**19**), were isolated from the fermentations of *Fusarium oxysporu.*[273-275]. All these fungal metabolites possess significant antifungal and insecticidal activities.[276,277]



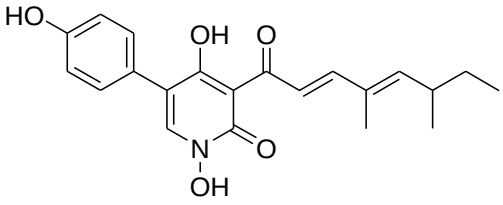
(15,16)



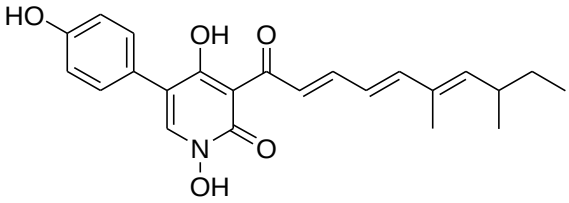
R_1 = OH, R_2 = H, R_3,R_4= =O
R_1 = H, R_2 = OH, R_3,R_4 = =O
R_1 = OH, R_2 = H, R_3,R_4 = OCH_3

(17-19)

Tenellin **(20)** and bassianin **(21)**. have been isolated from mycelium extracts of two insect pathogenic fungi *Beauveria basiana* and *Beauveria tenella* that often develop a yellow pigmentation in their cultures.[278-280]



Tenellin **(20)**

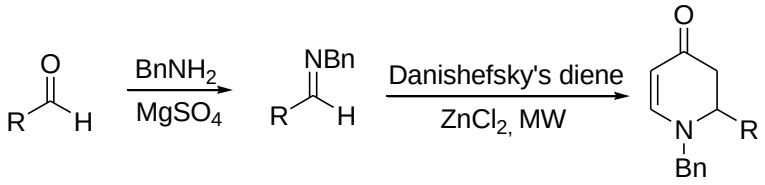


Bassianin **(21)**

1.3.2 Synthetic Methods of Dihydropyridinones

Many synthetic methods and a number of new approaches have being developed for the synthesis of dihydropyridinones. Following are some synthetic strategies described below.

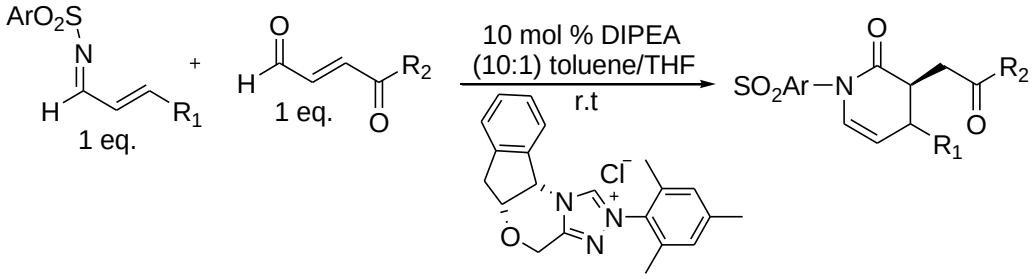
1) Imines were prepared by treating substituted aldehydes under anhydrous conditions with benzylamine. Then these imines were reacted *in situ* with danishefsky's diene with $ZnCl_2$ by microwave irradiation afforded corresponding dihydropyridinone derivatives.[281]



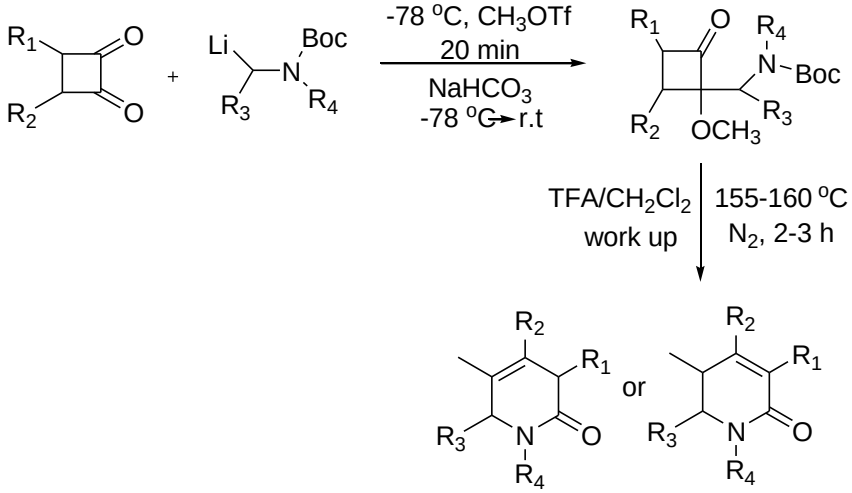
2) By Catalytic Enantioselective Diels-Alder Reactions

i) Enantiomerically pure dihydropyridinones were synthesized by mixing an equimolar quantity of α, β-unsaturated aldehydes and unsaturated imines in the presence of 10 mol % of DIPEA and 10 mol % of catalyst at room temperature for 24-48 hr. The

solvent was removed and were purification by chromatography technique gives products with enantiomeric excess > 99 %.[282]



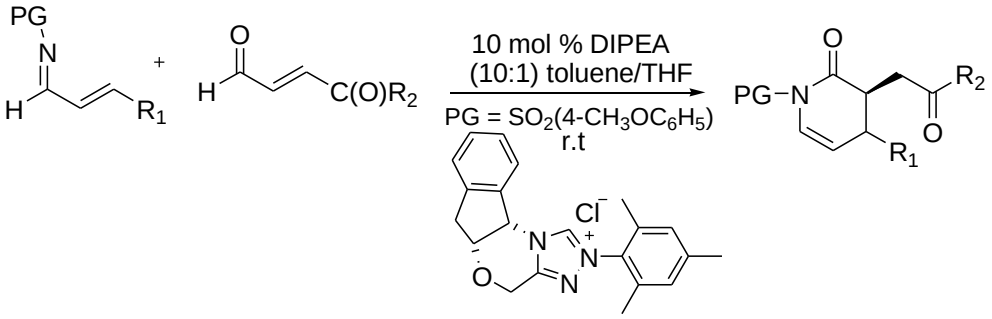
ii) The reaction of cyclobutenediones and *N*-Boc-protected R-amino carbanions with (2.5 eq.) of $MeOT_f$ for 20 min at -78 °C, then the reaction mixture was quenched with aqueous $NaHCO_3$ afforded the alkoxides followed by methylation yielded the 4-(1-*N*-Boc-aminoalkyl)-4-methoxy-3-cyclobutenones. Deprotection of Boc group and then by thermal ring expansion dihydropyridones were synthesized in moderate to high yields.[283]



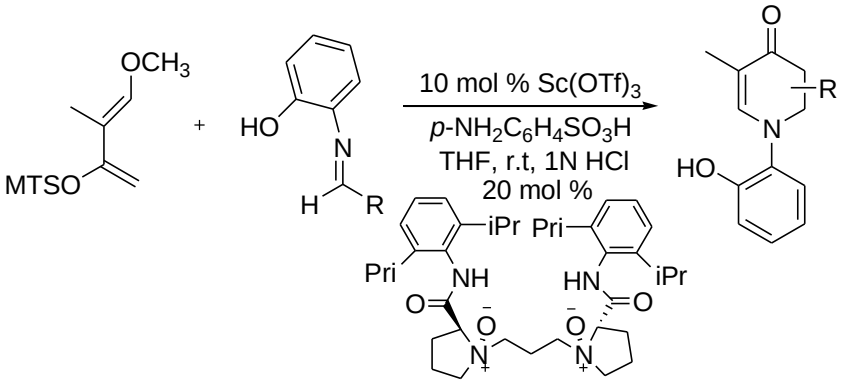
3) By Aza-Diels-Alder Reactions

i) Bode and his co-workers in 2006 extended the use of homoenolates generated by *N*-heterocyclic carbenes NHCs to the Diels-Alder reaction. They proposed that a proton transfer occurs in homoenolate to generate a triazolium enolate, which serves as dienophile with α,β-unsaturated imines in an azadiene Diels-Alder reaction. Both the reactants are similar to each other so, the imidazoliums induced homoenolates were reluctant to protonate but the triazolium salts were more efficient that their tendency to react with enimine primarily then that of the enal. Enal is more activated as it bears an

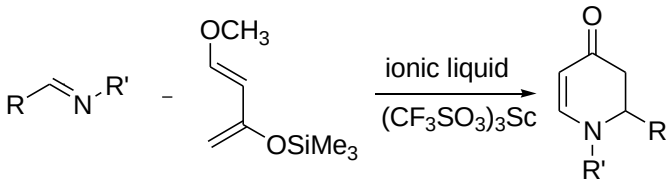
ester moeity trans to the aldehydic group, is in conjugation with a bulky triazolium afforded dihydropyridinones in high yields.[284,282]



ii) Enantioselective aza-Diels-Alder reaction of 1,3-butadiene with aldimines was catalyzed by a complex prepared from L-proline derived *N*,*N*-dioxides and scandium (III) triflate, at optimal temperature yields the corresponding substituted dihydropyridinones with good enantioselectivities up to 90 % (ee) in good yields.[285]

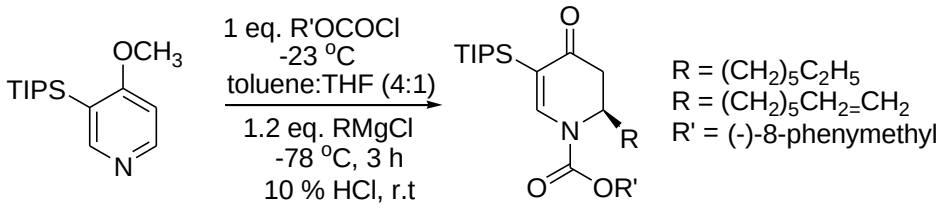


iii) One-pot aza-Diels-Alder reaction in ionic liquids catalyzed by Lewis acids BF_3, $TiCl_4$ and $ZnCl_2$ afforded dihydropyridone derivatives. The reaction of 1-methoxy-3-(trimethylsilyl)oxybuta-1,3-diene with *N*-diphenyl imine catalysed by microencapsulated scandium trifluoromethanesulfonate in ionic liquids e.g ILs, 1-ethyl-3-methyl-1*H*-imidazolium trifluoromethanesulfonate and 8-ethyl-1,8-diazabicyclo[5.4.0]-7-undecenium trifluoromethanesulfonate etc produces *N*-phenyl-5,6 dihydro-4-pyridone in good yields.[286-288]



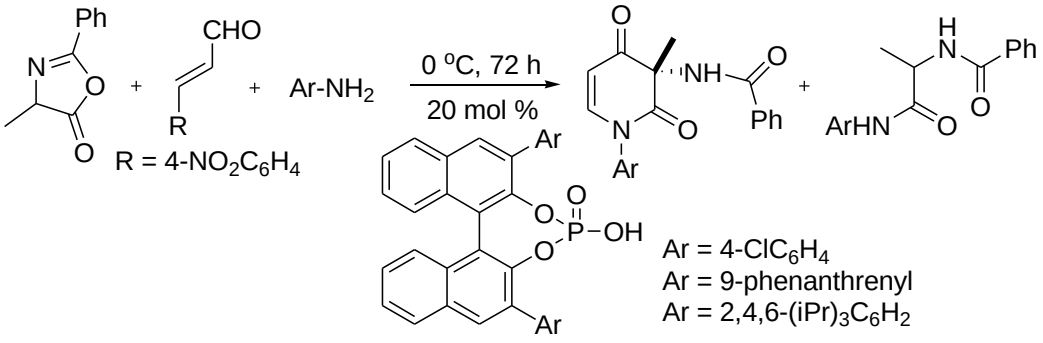
4) By Grignard reagent

Dihydropyridinones were stereoselectively synthesized by nucleophilic addition of (1.2 eq.) of Grignard reagents in ether bearing aliphatic side chain of barrenazines to (1.0 eq.) of chiral acylpyridinium salt i.e 4-methoxy-3-(triisopropylsilyl)pyridine and (1.0 eq.) of the chiral auxiliary (-)-8-phenylmenthyl carbamate or chloroformate in (4:1) toluene/THF solution, followed by acidic work up with 10 % HCl afforded dihydropyridinones in good yields.[289]



5) By Three-Component Reaction

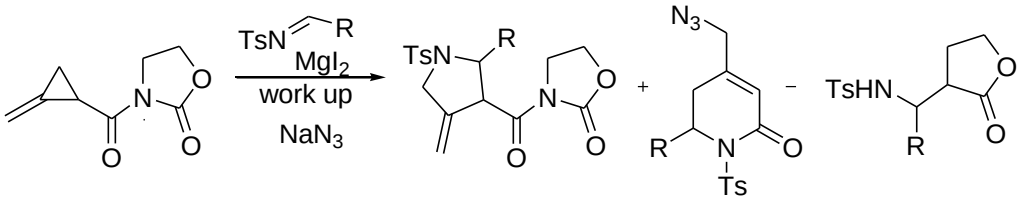
Reaction of 4-methyl-2-phenyloxazolone with *p*-anisidine and *p*-nitrocinnam-aldehyde progressed smoothly without any promoter yielded 38 % dihydropyridinone, along with 33 % amidation product. However, if the same reaction was proceed in the presence of a catalyst, it accelerated towards more amidation reaction afforded 79 % yield, with a small quantity of dihydropyridinone product.[290]



6) By Ring Expansion Reaction

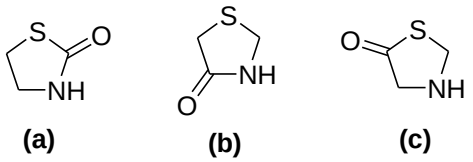
A novel method for the preparation of five and six-membered nitrogen-heterocyclics *via* ring expansion of activated methylenecyclopropanes (MCPs) with aldehydes and aldimines in the presence of MgI_2. Strongly activated MCP imide having 2-oxazolidone moeity could undergo the facile ring opening reaction with aldimines very quickly even at 0 °C.

In contrast, the reaction with diphenyl amide produces exclusively six-membered heterocycles having an allyl iodide group and lacking the oxazolidone moiety. The completion of this reaction required a stoichiometric amount of MgI_2. The the iodo-substituted products were obtained by functional group transformation as they were not very stable to silica gel flash chromatography, so dihydropyridinone products were isolated in good yields.[291]



1.4 Thiazolidinones

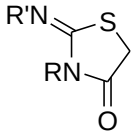
Thiazolidinones are five membered structure based 1,3-thiazolidine heterocycles having carbonyl group at their 2, 4 or 5 positions.[292]



4-Thiazolidinone derivatives represent an important class of heterocyclic compounds, as they possess wide range of potential biological applications.[293-297]

1.4.1 2-Imino-1,3-thiazolidin-4-ones

2-Imino-1,3-thiazolidin-4-ones are the analogues of thiazolidinones with an exocyclic double bond (C=N) at 2-position.



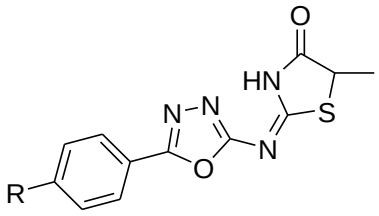
While R and R' can be hydrogen, alkyl, alkanoyl, aryl, or aroyl groups etc.

1.4.2 Biological Significance of Thiazolidinones

2-Iminothiazolidinones, thiohydantoins and their derivatives exhibit a wide variety of chemotherapeutic activities like antiviral,[298] anticancer,[299] anticonvulsant,[300] antitubercular,[301] and anti-inflammatory.[302]

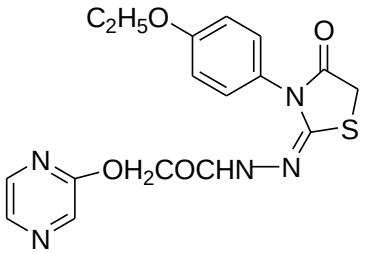
i) Antibacterial Activity

Oxadiazole substituted iminothiazolidinone derivative **(22)** showed potent antibacterial activity.[303]



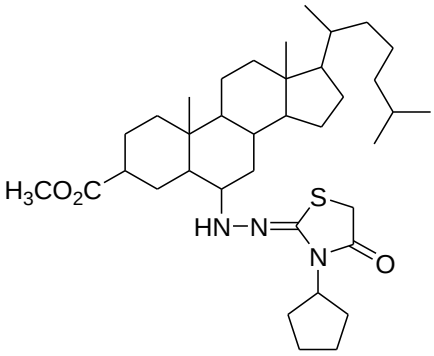
(22)

Various derivatives with thiazolidinone ring like (pyrazin-2-yloxy)-acetic acid[3-(4-ethoxy-phenyl)-4-oxothiazolidin-2-ylidene]-hydrazide **(23)** showed significant antibacterial activity against the *S. aureus* and *B. subtilis* strains of gram positive and *E. coli* and *S. typhi* strains of gram negative bacteria.[304]

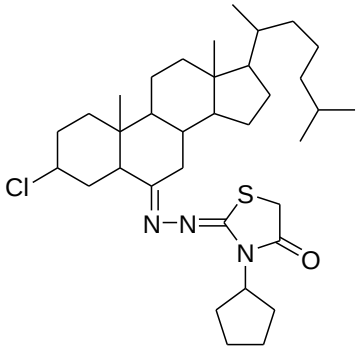


(23)

Cholesterol derivatives containing 2-iminothiazolidinone moieties e.g 3b-acetoxycholest-5-ene **(24)** and 3b-chlorocholest-5-ene **(25)** compounds possess significant antibacterial activites.[305]



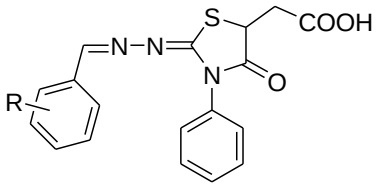
(24)



(25)

ii) Anti-Toxoplasma Gondii Activity

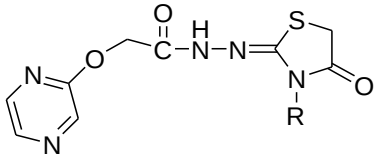
Thiosemicarbazones and 2-iminothiazolidinones with phenyl and carboxylic acid groups **(26)** showed a remarkable anti-toxoplasma gondii activities.[306,307]



(26)

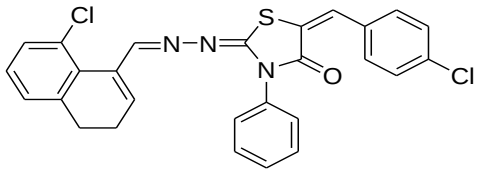
iii) Antimicrobial Agents

N-{(2Z)-2-[(4-alkyl/arylsubstituted)imino]-4-oxo-1,3-thiazolidin-3-yl}-2-(pyrazin -2-yloxy)acetamide **(27)** is a good antimicrobial agent, it also exhibit antimycobacterial activities.[304]



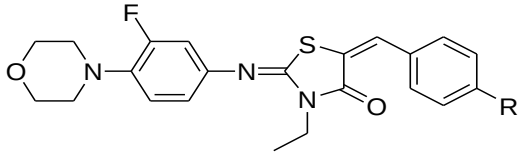
(27)

Chloro substituted heterocycles like 2-(2-(4-chloro-1,2-dihydronaphthalen-3-yl)methylene)hydrazono)-5-(4-chlorobenzylidene)-3-phenylthiazolidin-4-one **(28)** also possess significant antimicrobial activity.



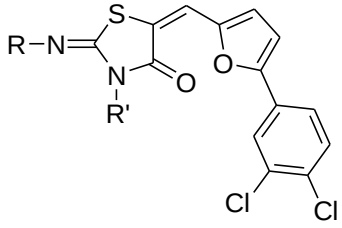
(28)

Morpholine substituted thiazolidinone derivatives 5-benzylidene-3-ethyl-2-(3-fluoro-4-morpholin-4-yl-phenylimino)-thiazolin-4-one **(29)** were reported to possess excellent antimicrobial activities.[308]



(29)

2-(*p*-Tolylimino)-3-(4-tolyl)-5-[5-(3,4-dichlorophenyl)-2'-furylidene]-4-thiazolidinone **(30)** and their structural analogues were reported as powerful antimicrobial agents. They possess significant *in vitro* antimicrobial activity against various bacterial strains *S. aureus, B. mega, P. vulgaris, E. coli* and also against fungal strain *Aspergillus niger*.[309]

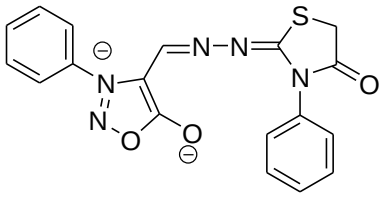


R, R' = phenyl, 2-methoxyphenyl, o-tolyl, m-tolyl, 4-nitrophenyl etc

(30)

iv) Antioxidant Activity

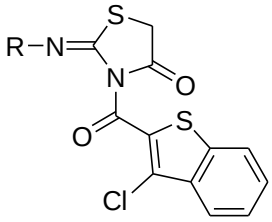
Sydnonyl substituted iminothiazolidinone derivatives like 2-[(3-aryl-sydnon-4-ylmethylene)hydrazono]-3-phenyl-thiazolidin-4-one **(31)** exhibit good antioxidant properties.[310]



(31)

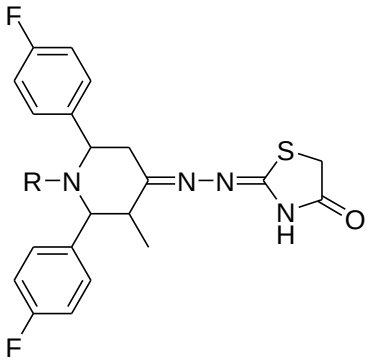
v) Antitubercular Activity

2-Arylimino-3-(3-chloro-2-benzo[*b*]thenoyl)-4-thiazolidinones derivatives **(32)** bearing iminothiazolidinone nucleus possess remarkable antitubercular activities.[311]



(32)

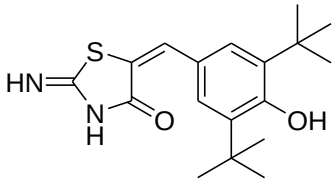
Piperidine derivatives of thiazolidinones like 2-[3-methyl-2,6-bis(4-fluorophenyl) piperidin-4-hydrazono]-1,3-thiazolidin-4-one **(33)** exhibit significant antitubercular activities.[312]



(33)

vi) Potent Anti-inflammatory Activity

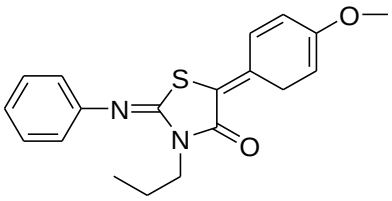
Bioactive heterocyclic compounds having iminothiazolidinone ring e.g darbufelone **(34)** is a potent anti-inflammatory drug.[313,314]



(134)

vii) COX-Inhibitors

One of the most interesting compound 5-(4-methoxyphenylidene)-2-phenylimino-3-propyl-4-thiazolidinone **(35)**, showed good anti-inflammatory activity with promising selectivity for its interaction with COX-2.[315]

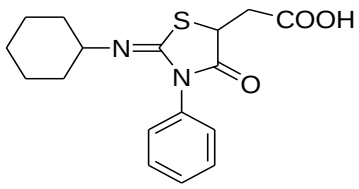


(35)

viii) Hypotensive Activity

A series of 2-cyclopentyl/(cyclohexylimino)-3-aryl-4-thiazolidinone-5-ylacetic acid derivatives **(36)** showed cardiovascular effects on adult cats[316]. All thiazolidinone

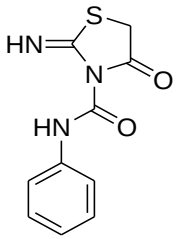
derivatives exhibit hypotension activity, of varying degree but not last more than 15 minutes.[317]



(36)

ix) Anthelmintic Activity

2-Imino-3-(2-acetamidophenyl)-4-thiazolidinone derivatives **(37)** have been effective as anthelmintic agent, it showed good *in vitro* activities against horse *Strongyloids* even at low concentration.[318]

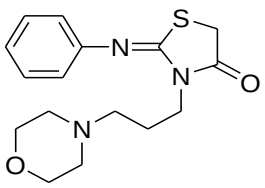


(37)

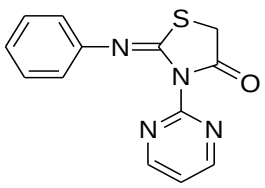
Various 2-thiono-3-methyl-5-[(2,4-dinitrophenyl)azo]-4-thiazolidinone and 2-thiono-3-substituted-5-[(2-methyl-4-nitrophenyl)azo]-4-thiazolidinone are potent anthelmintic agents, which were highly effective not alone but also possess strong activity with other parasiticides as wel.[319]

x) Hypnotic Activity

Several 2-iminothiazolidinone derivatives i.e 3-[3-(*N*-morpholin-4-yl-propyl)-2-(arylimino)]-4-thiazolidinones **(38)** and 2-(arylimino)-3-(pyrimidin-2-yl)-4-thiazolidinones **(39)** were evaluated for their ability to potentiate pentobarbital-induced hypnosis. All the thiazolidinone derivatives were found to exhibit hypnotic activity during sleeping time.[320]



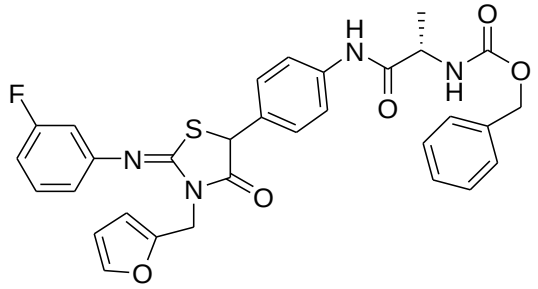
(38)



(39)

xi) Anti-HCV Activity

BMS-858 compound **(40)** containing iminothiazolidinone ring, displayed potent activity against (HCV) Hepatitis C virus.[321]



BMS-858 **(40)**

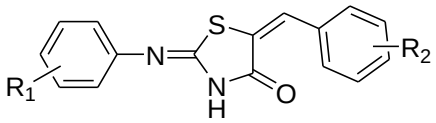
Recently another compound was discovered (BMS-790052), reported as HCV NS5A inhibitor and demonstrates a potent antiviral effect in HCV genotype 1-infections.[322]

xii) Anti-HIV Activities

Various heterocyclic systems containing 2-iminothiazolidinone moieties were known to exhibit potent anti-HIV activities.[323]

xiii) Anticancer and Anti-proliferative Activities

Many iminothiazolidinone analogues **(41)** were reported to possess remarkable anticancer and anti-proliferative activities, as they selectively killed not only the non-small cell lung cancer cell line H460 but also its paclitaxel-resistant variant H460taxRatan. It showed much lesser toxicity towards normal human fibroblasts at low concentrations.[324]

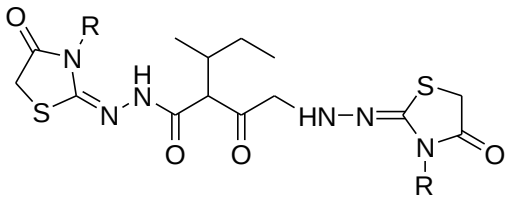


(41)

Various 4-thiazolidinone derivatives were reported to possess *in vitro* anti-proliferative activity against different human cell lines e.g colon cancers.[325-329]

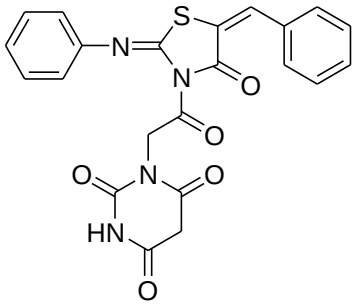
xiv) Anticonvulsant Activity

N,N'-substituted *bis*(4-thiazolidinone) derivatives **(42)** exhibit upto 90 % protection in the pentylenetetrazole seizure.[330]

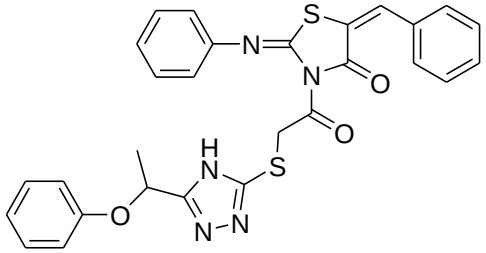


(42)

It is reported that thiazolidinone-barbituric acid with different phenylthiazolidinonyl amino moieties at position-5 **(43)** and thiazolidinone-triazole derivatives **(44)** have shown significant anticonvulsant activities.[331,332]



(43)

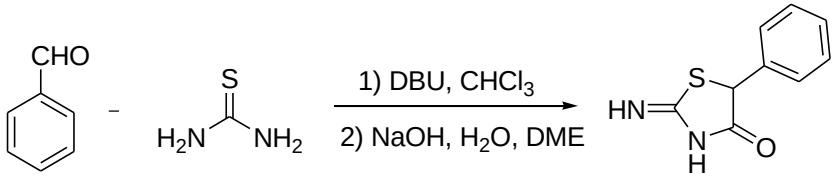


(44)

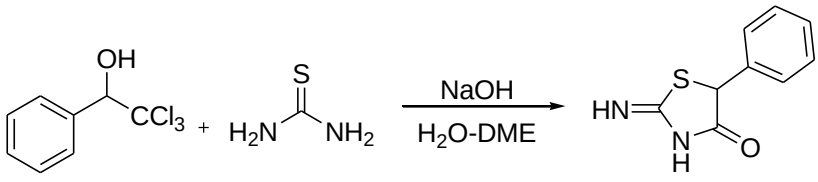
1.4.3 Synthetic Methods of 2-Imino-1,3-thiazolidinones

Several methods have been reported in the literature for the preparation of 2-iminothiazolidin-4-one derivatives[333-336]. Recently, different protocols have been developed for the efficient synthesis of iminothiazolidin-4-one skeletons.[337,338]

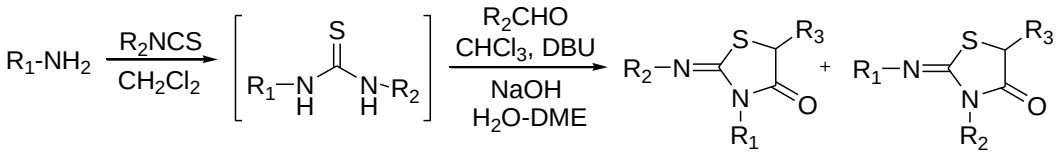
i) 2-Imino-4-thiazolidinone derivatives were efficiently prepared by one pot three component synthesis containing aldehyde, thiourea and chloroform in DME.[339]



ii) An efficient and convenient method for the synthesis of 2-imino-4-thiazolidinones was reported, starting from thioureas and alkyl/aryl trichloromethylcarbinols in the presence of a base in aq. DME.[340]

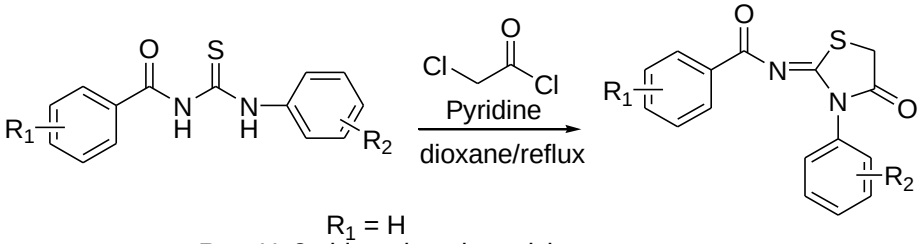


iii) A convenient one-pot protocol was developed for the synthesis of 2-imino-1,3-thiazolidin-4-ones by the reaction of amines, isocyanates, aldehydes, and chloroform in the presence of sodium hydroxide under ultrasonic conditions in high yields and shorter reaction times (12-15 min).[341]



R1 = H, C_2H_5, benzyl, vinyl, cyclohexyl etc
R_2 = H, C_2H_5, phenyl, vinyl, *p*-tolyl etc
R_3 = H, phenyl, *p*-tolyl etc

iv) Another efficient and regioselective synthetic method for the preparation of some 2-aroylimino-3-aryl-thiazolidin-4-ones involves base-catalyzed cyclization of 1-aroyl-3-aryl thioureas with chloroacetyl chloride in dioxane.[342]

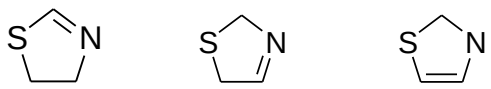


R_1 = H
R_2 = H, 3-chlorophenyl, *o*-tolyl etc

1.5 Thiazolines

Thiazolines are five membered sulfur and nitrogen containing heterocycles, with an endo cyclic double bond. Although these thiazoline heterocyclic rings itself are rarely encountered but their derivatives are distributed widely in nature.

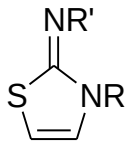
Thiazolines exist in three isomeric forms depending upon the position of the double bond in the rings, namely 2-thiazoline **(i)**, 3-thiazoline **(ii)**, 4-thiazoline **(iii)**.



(i) **(ii)** **(iii)**

1.5.1 2-Imino-1,3-thiazolines

2-Imino-1,3-thiazolines are the derivatives of thiazolines with an exocyclic double bond formed by imino moiety with the ring at 2-position.

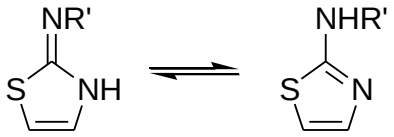


(iv)

Where R and R' group varies e.g hydrogen, alkyl, aryl, alkanoyl, or aroyl moeities.

1.5.2 Tautomeric forms of Thiazolines

Iminothiazolines shows two tautomeric forms i.e 2-imino-1,3-thiazoline and 2-aminothiazole, which co-exists in equilibrium with each other.

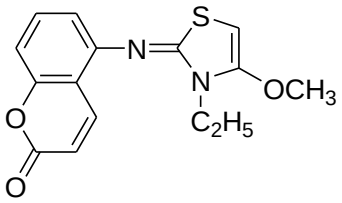


1.5.3 Biological Significance of 2-Imino-1,3-thiazolines

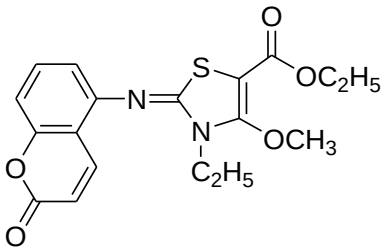
2-Iminothiazoline ring is present as a core in many bioactive heterocycles, they exhibit a wide variety of important pharmaceutical and other biological applications.

vi) Anticonvulsant Activity

Coumarin derivatives of iminothioazolines **(45)** and **(46)** were reported to possess significant anticonvulsant activities against PTZ induced seizures.[343,344]



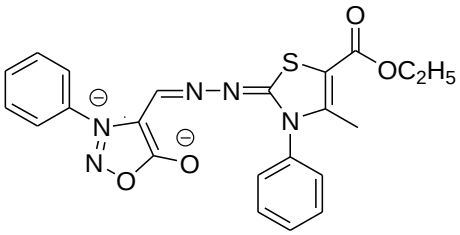
(45)



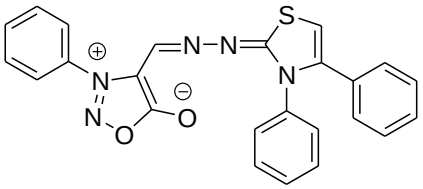
(46)

vii) Antioxidant Activity

Sydnonyl-thiazoline derivatives like 2-[(3-arylsydnon-4-ylmethylene)hydrazono]-4-methyl-3-phenyl-2,3-dihydro-thiazole-5-carboxylic acid ethyl esters **(47)** and 3,4-diphenyl-2-[(3-arylsydnon-4-ylmethylene)hydrazono]-2,3-dihydrothiazoles **(48)** possess strong antioxidant activity.[345]



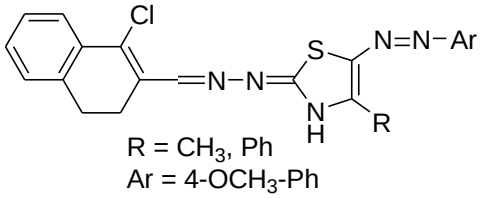
(47)



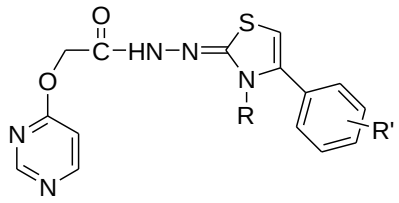
(48)

iii) Antimicrobial Agents

Chloro-thiazoline derivative **(49)** is potent, selective and less toxic antimicrobial agent. *N*'-[3,4-disubstituted-1,3-thiazol-2(3H)-ylidene]-2-(pyrazin-2-yloxy)acetohydrazide **(50)** derivatives exhibit good antibacterial activity against different strains of gram positive and gram negative bacteria, while they also shows remarkable antimycobacterial activity against (H37 Rv) strain of *M. tuberculosis*.[346]



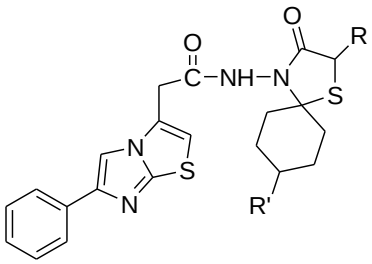
(49)



(50)

iv) Anti-tubercular Agent

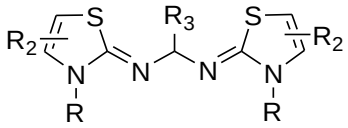
Thiazoline derivatives **(51)** were known to exhibit good antimycobacterial activity against different strains of *Mycobacterium tuberculosis*.[347,348]



(51)

v) Psychomimetic Agents

Iminothiazoline ring containing compounds e.g **(52)** inhibit indoleamine-*N*-methyl transferase enzyme, which catalyses the biosynthetic steps of some psychomimetic agents,[349] which are useful for the treatment of certain mental aberrations such as *Schizophrenia* in human beings.

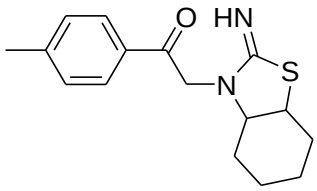


(52)

Where R is C_{1-3} alkyl, C_{3-5} alkenyl or C_{3-5} alkynyl; R_2 is hydrogen, C_{1-3} alkyl, or trifuoromethyl and R_3 is hydrogen or C_{1-5} alkyl.

vi) Genotoxic Agents

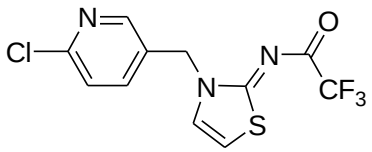
Pifithrin-α (PFT-α) **(53)** is a reversible inhibitor of p53-mediated apoptosis and p53-dependent gene transcription and potent to improve therapeutic selectivity and higher doses of cytotoxic treatments on humans and also helps in the protection against many genotoxic agents.[350,351]



Pifithrin-α (PFT-α) **(53)**

viii) Insecticidal Activity

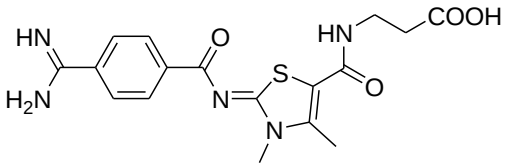
Highly potent and selective nicotinic insecticides were obtained by the pharmacophore modification of neonicotinoids with extended and hydrophobic substituents fitting in the nicotinic acetylcholine receptor, which is an important target of insecticides for crop protection, public health and of therapeutic agents for neurological dysfunction. Compound **(54)** has an excellent target site selectivity, high insecticidal activity, and low toxicity to mammals.[352]



(54)

ix) Potent Platelet Aggregation Inhibitors

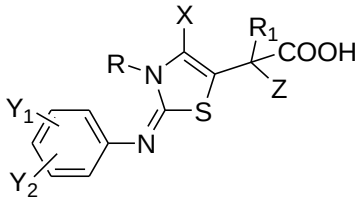
PS-028 **(55)** thiazoline derivative is orally active lead compound, potent for platelet aggregation inhibition as it antagonist receptors GP IIb/IIIa.[353]



PS-028 **(55)**

x) Anti-pyretic, Analgesic and Anti-reumatic Activities

Some iminothiazoline heterocycles like **(56)**, have been found to exhibit a wide range of biological applications as analgesic, anti-pyretic and they also shows anti-reumatic properties.[354]

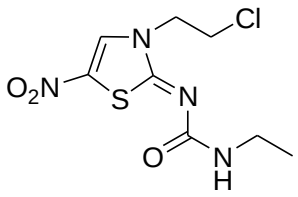


(56)

Where R represents C_{1-3} alkyl or C_{3-5} alkenyl, R_1 represents hydrogen, methyl or ethyl, X represents hydrogen or methyl, $Y_1$and Y_2 each represent hydrogen, halogen, C_{1-3} alkyl or C_{3-5} alkenyl while Z represents hydrogen, carboxy or carboxy ester group.

xi) Anti-*Schistosomiasis* Agents

A wide variety of iminothiazoline analogues **(57)** were found to be highly active against *Schistosoma mansoni*, a root cause of a disease *Schistosomiasis.* This disease not only adversely affects the skin but it also damage the internal organs of the body.[355]



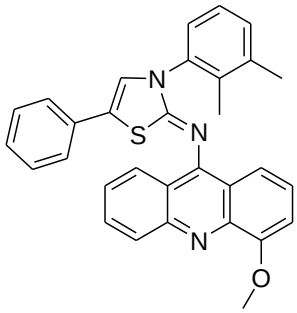
(57)

xii) Anti-HIV and Anti-cancer Activities

Some thiazoline derivatives possess an interesting anti-HIV or potent anticancer activities and they also known to inhibit cell division process.[356-358]

xiii) Kinase CDK1 Inhibitors

Acridinyl-thiazoline derivatives have been found to exhibit moderate CDK1 inhibitory activities against kinase CDK1[359]. Thiazoline derivative **(58)** possesses significant kinase CDK1 inhibitory properties.



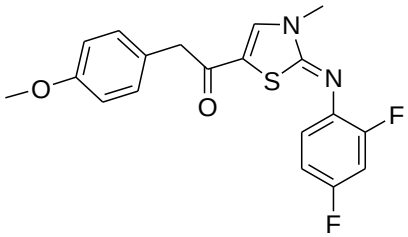
(58)

xiv) Antifungal Activity

Iminothiazoline derivative i.e 2-phenylimino-1,3-thiazoline-4-acetanilide showed remarkable potent activity against *Pyricularia oryzae,* a rice blast fungus.[360]

xv) Skin Whitening Agent

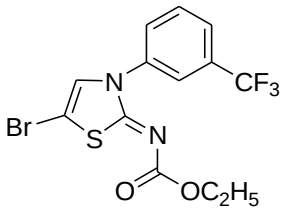
A novel 2-imino-1,3-thiazoline derivative KHG22394 **(59)** is a skin whitening agent as it inhibits melanin production.[361]



KHG22394 **(59)**

xvi) Herbicidal Activity

2-Acylimino-1,3-thiazolines **(60)** exhibit a bleaching herbicidal activity against various up-land weeds and selectivity against different crops.[362]



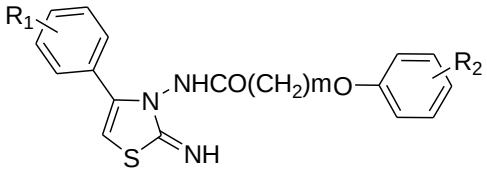
(60)

xvii) Antihistaminic Activity

Many heterocycles having thiazoline ring in their core structure, were known to exhibit potent antihistaminic activity.[363]

xviii) Plant Growth Regulators

2-Iminothiazoline derivatives like **(61)** are potent plant growth regulators as they cause 100 % inhibition of suckering of bean *Phaseolus vulgaris.*[364]



R_1 = H,alkyl, halo, alkoxy, NO_2
R_2 = H,alkyl, halo, OH, NO_2
m = 1, 2, 3

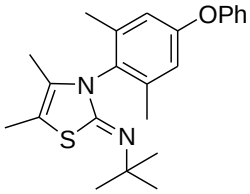
(61)

xix) Anti-hypertensive Agents

A wide variety of iminothiazoline containing heterocycles were reported as anti-hypertensive agents.[365]

xx) As Acaricides

Thiazoline derivative **(62)** was reported that it have shown 100 % control of imagoes of *Tetranycus urticae*.[366]



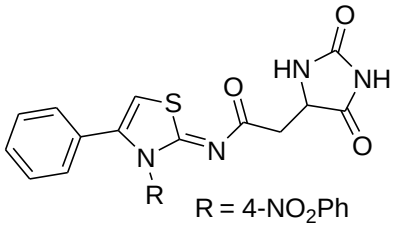
(62)

xxi) Hypnotic Activity

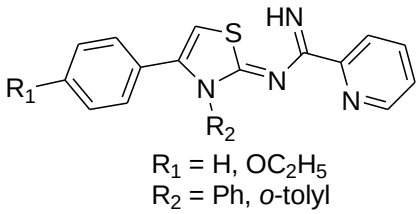
Few heterocyclic compounds having thiazoline rings were potent as they showed good hypnotic activity.[367]

xxii) Anti-inflammatory and Analgesic Agent

Various iminothiazoline derivatives exhibits significant anti-inflammatory **(63)** and analgesic properties **(64)**.[368]



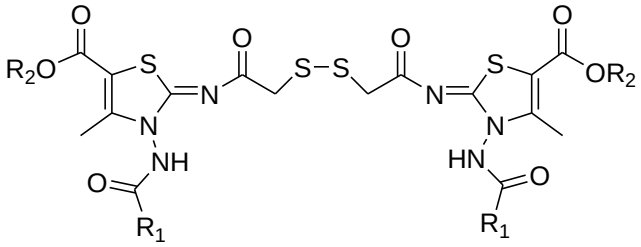
(63)



(64)

xxiii) Antitumor Activity

Cancer is a leading cause of death in the world every year. Bis-thiazoline derivatives like **(65)** have shown remarkable antitumor activity against various human cell lines.[369,370]



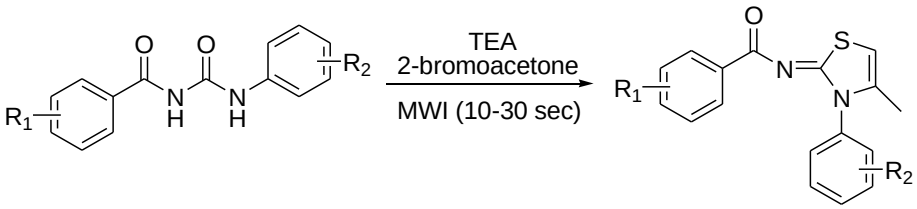
(65)

1.5.4 Synthetic Methods of 2-Imino-1,3-thiazolines

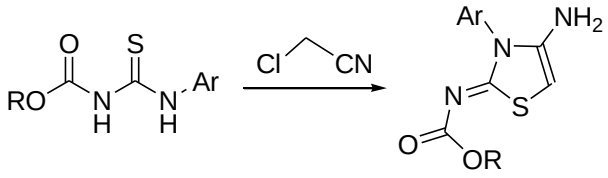
The synthesis of 2-iminothiazolines is intensively studied in the past due to their great pharmacological importance. The synthetic strategies for 2-imino-1,3-thiazolines are as follows.

1) From Thioureas

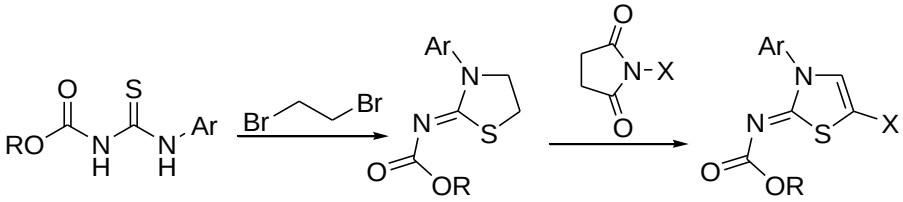
i) *N*-(4-Methyl-3-tolylthiazol-2(3H)-ylidene) benzamides were synthesized by the base-catalyzed direct cyclization of corresponding 1-tolyl-3-aryl thioureas with 2-bromoacetone in solvent-free medium through a microwave irradiation method.[371]



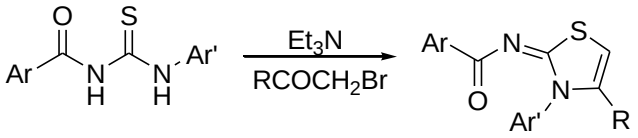
ii) Reaction of 1-aroyl-3-aryl thiourea derivatives with α-chloroacetonitrile to afford 4-amino derivatives of 2-iminothiazolines.



The reaction of thioureas with 1,2-dibromoethane in the presence of excess of potassium carbonate yields 2-(*N*-acylimino)-3-aryl-1,3-thiazolidene, which when reacted with *N*-halogenated succinimide gives corresponding 5-halogenated 2-(*N*-acylimino)-1,3-thiazoline.[372]



iii) A straight forward method for an efficient synthesis of 2-imino-1,3-thiazolines is the direct cyclization of 1-aroyl-3-arylthiourea with α-bromoketone in the presence of a base triethyl amine.[373]

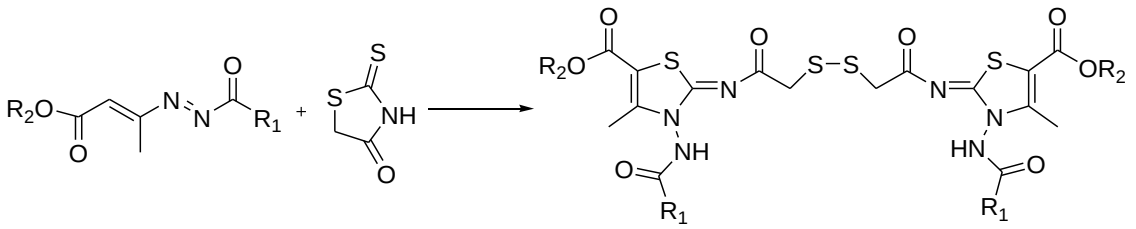


iv) 2-Iminothiazolines can be obtained by the condensation of thioureas with α-haloketones.[374,375]

2) By Conjugate Addition Method

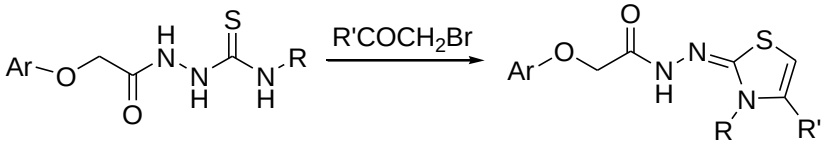
The reaction of rhodanine and 1,2-diaza-1,3-butadienes and a similar compound

having thioamide functionality can afford 2-iminothiazoline derivatives by a sequential conjugate addition.[376,377]



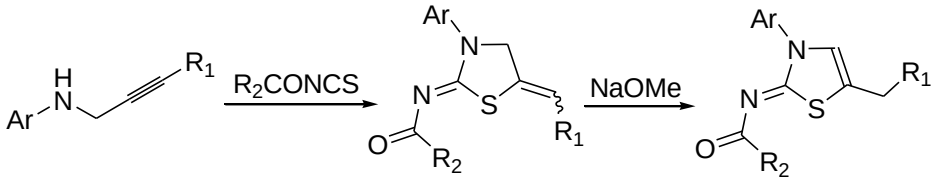
3) From Thiosemicarbazides

Iminothiazolines can also be prepared by the reaction of α-haloketones with thiosemicarbazides in acidic medium.[378,379]



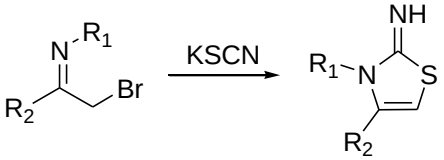
4) Reaction of Acyl isothiocyanates with *N*-Propargylic Anilines

The first step is the reaction of acyl isocyanate with *N*-propargylic aniline to afford 2-(*N*-acylimino)-1,3-thiazolidene. In the second step sodium methoxide was treated with 2-(*N*-acylimino)-1,3-thiazolidene yields *N*-acyl-5-alkyl-2-imino-1,3-thiazoline.[372]



5) From α-Bromomethyl Ketimine

α-Bromomethyl ketimines also act as a key precursor for 2-imino-1,3-thiazolines derivatives, when it is reacted with potassium thiocyanate.[380,381]



1.6 Plan of Work

A survey of literature shows that isocoumarin and 3,4-dihydroisocoumarin display a wide range of synthetic applications and their biologically significance as pharmaceuticals. For the last few decades, number of new isocoumarins has been found in nature still increasing and their analogues exhibits a wide structural diversity in their natural sources and biosynthetic pathways. These compounds were selected, by keeping in mind the biological importance of these natural isocoumarins. We have successfully synthesized various structural analogues of well known bioactive natural 3,4-dihydroisocoumarins *viz. Annulatomarin, Montroumarin, Scorzocreticin, Typharin,* and *Hiburipyranone*, along with the total synthesis of natural products (±) 7-butyl-6,8-dihydroxy-3-pentyl-1H-3,4-dihydroisochromen-1-one and (*Stellatin*) 8-hydroxy-7-hydoxymethyl-6-methoxy-3,4-dihydroisochromen-1-one.

In view of wide spectrum of biological applications of heterocyclic systems, it was planned to synthesize some novel heterocyclic compounds. In this regard we have tried to established routes for the synthesis of various heterocycles *viz.* pyrazoles, dihydropyridinones, iminothiazolidinones and iminothiazolines. The work is divided in two parts.

Part-I: Synthesis of Natural Isocoumarin Analogues

Part-II: Synthesis of Novel Heterocyclic Compounds

The routes for the synthesis of homophthalic acids precursors were established by adopting multistep synthetic strategy. Later on, these precursors were converted into various 3,4-dihydroisocoumarin derivatives by following standard procedures.[37,120, 382]

Part-I: Synthesis of Natural Isocoumarin Analogues

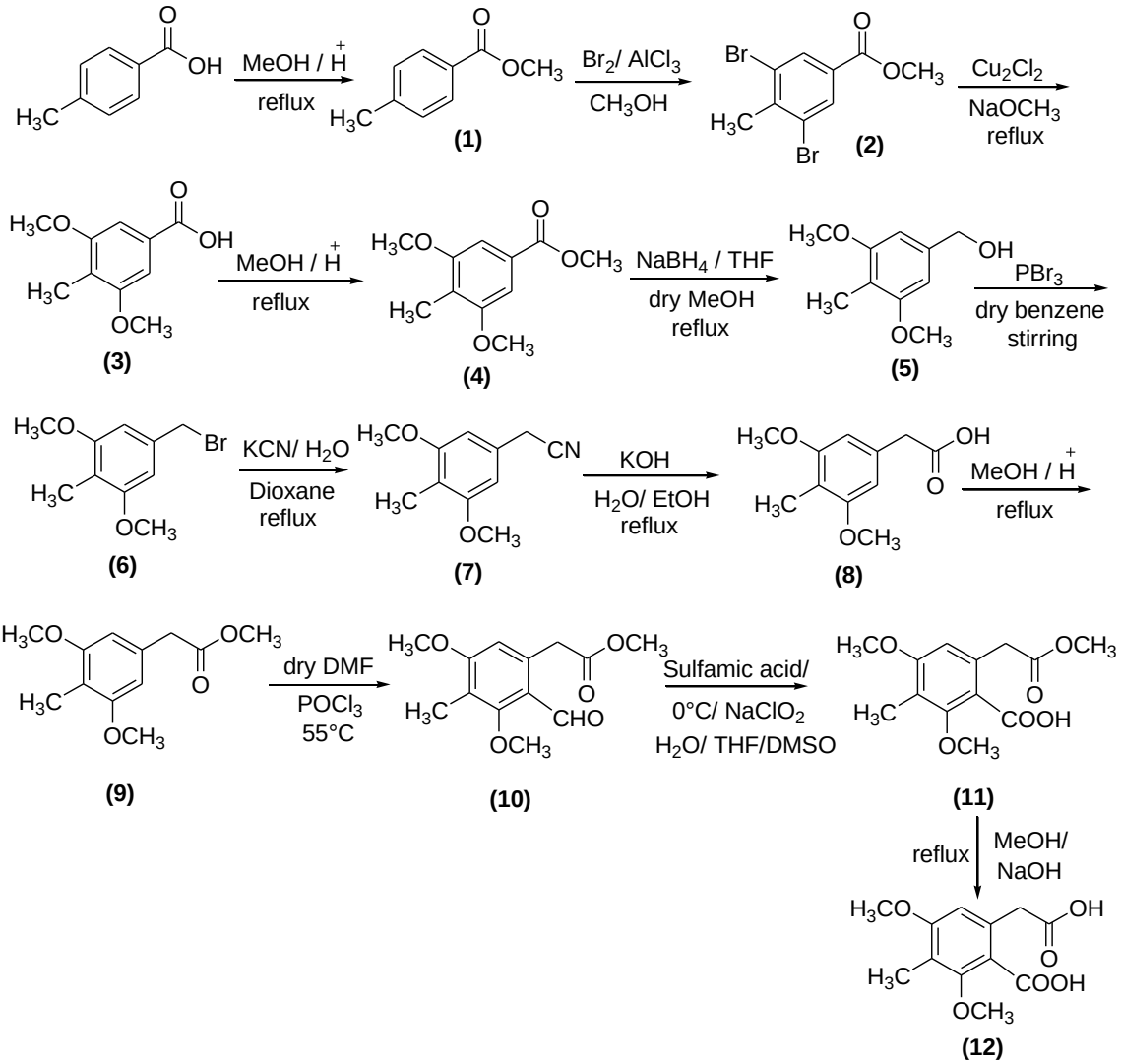
Synthesis of all these compounds was based on the following known principles, which are illustrated below:

i.) Direct condensation of homophthalic acid with corresponding aryl chlorides to obtain 3-substituted isocoumarins.

ii.) Alkaline hydrolysis of the isocoumarins to obtain corresponding keto-acids.

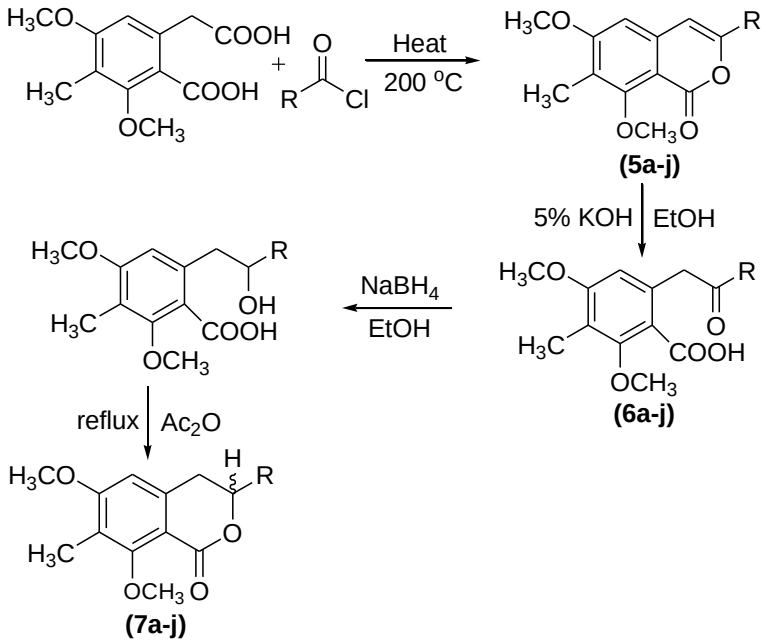
iii.) Preparation of (±)-3,4-dihydroisocoumarins by reduction of keto-acids using sodium borohydride to afford corresponding hydroxy-acids followed by cyclodehydration with acetic anhydride yield corresponding (±)-dihydroxy-3,4-dihydroisocoumarins.

General Scheme-1



Scheme 1: Synthesis of 3,5-Dimethmethoxy-4-methylhomophthalic acid (12)

General Scheme-2

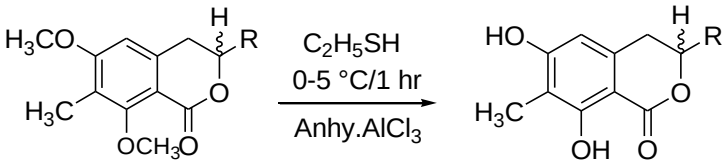


R = Cinnamoyl, Phenyl, *p*-tolyl, 4-Chlorophenyl, 4-Methoxyphenyl, 4-Nitrophenyl,

$-C_4H_9$, $-C_5H_{11}$, $-C_8H_{17}$, $-C_{11}H_{23}$.

Scheme 2: Synthesis of 6,8-Dimethoxy-7-methyl-3-aryl/alkyl-3,4-dihydroisochromen-1-ones (7a-j)

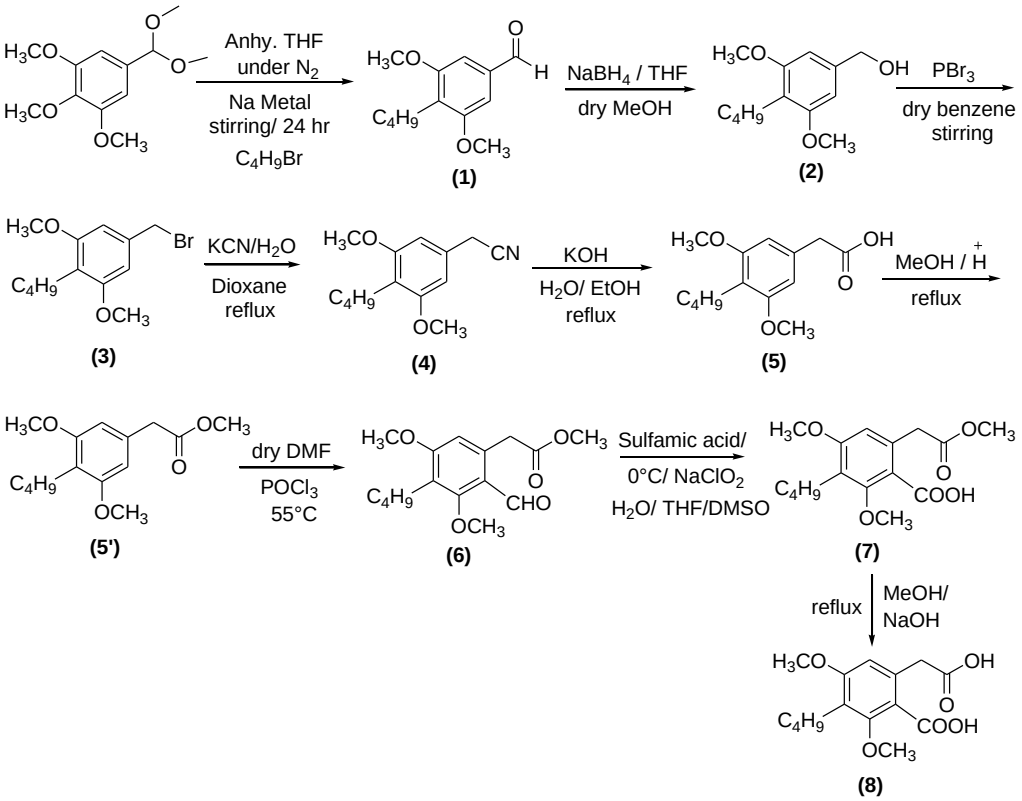
General Scheme-3



R = Cinnamoyl, Phenyl, *p*-tolyl, 4-Chlorophenyl, 4-Methoxyphenyl, 4-Nitrophenyl, $-C_4H_9$, $-C_5H_{11}$, $-C_8H_{17}$, $-C_{11}H_{23}$.

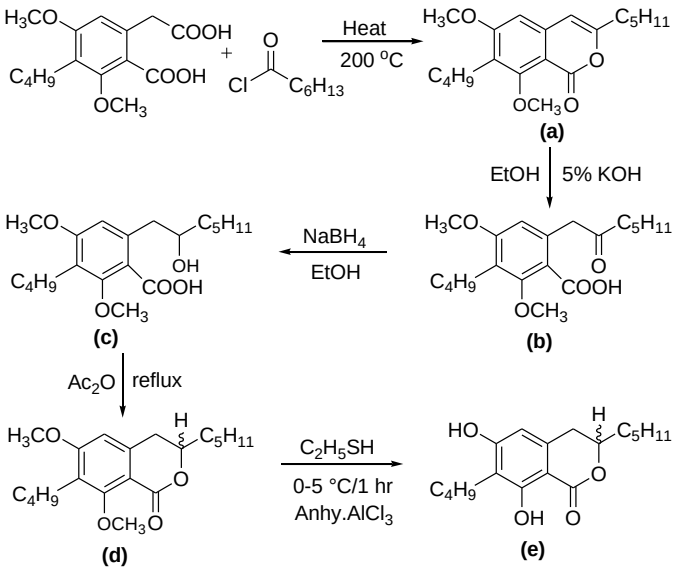
Scheme 3: Synthesis of 6,8-Dihydroxy-7-methyl-3-aryl/alkyl-3,4-dihydroisochromen-1-ones (8a-j)

General Scheme-4



Scheme 4: Synthesis of 4-Butyl-3,5-dimethoxyhomophthalic acid (8)

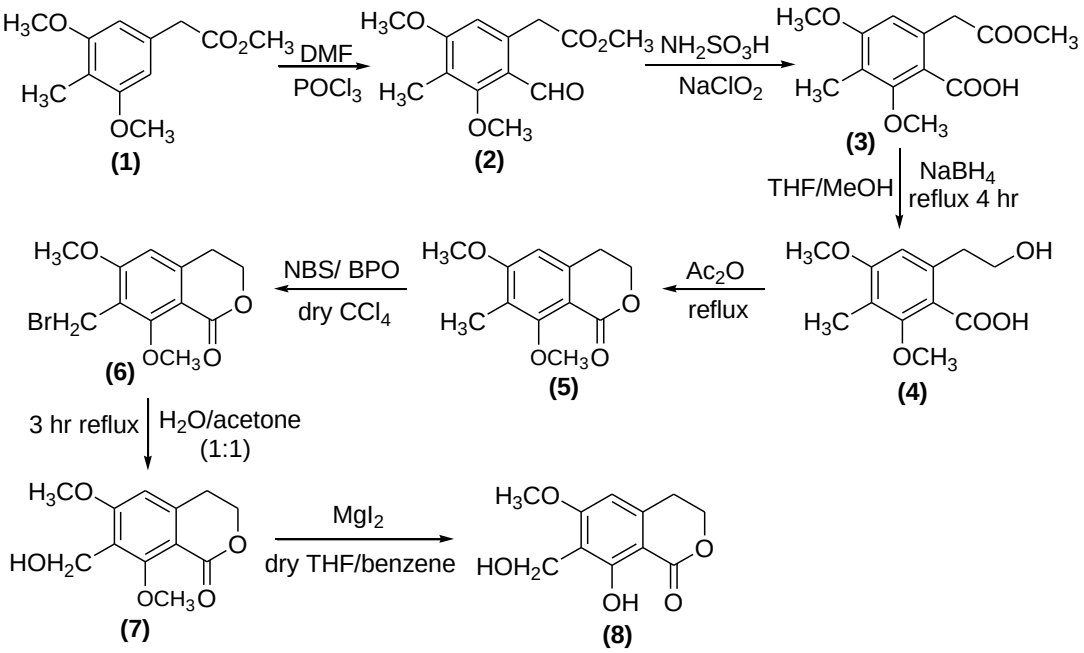
General Scheme-5



Scheme 5: Synthesis of (±) 7-Butyl-6,8-hydroxy-3-pentyl-3,4-dihydro-isochromen-1-one (10a-e)

Total synthesis of a natural product *Stellatin*

General Scheme-6



Scheme 6: Total synthesis of 8-hydroxy-7-hydoxymethyl-6-methoxy-3,4-dihydroisochromen-1-one (*Stellatin*) (1-8)

Part-II: Synthesis of Novel Heterocyclic Compounds

i) Functionalized Pyrazoles

ii) *N*-Substituted Dihydropyridinones

iii) Iminothiazolidinones

iv) Iminothiazolines

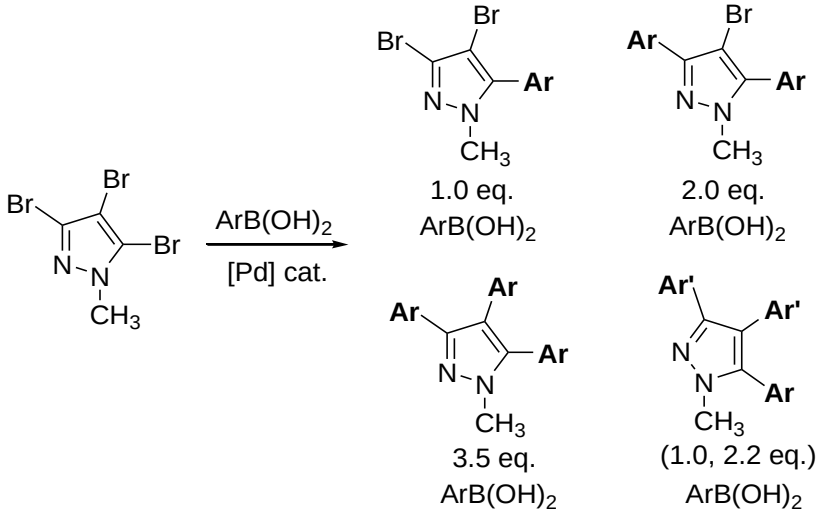
The synthesis of thiourea precursors were carried out by adopting standard procedures[383]. Later on, these precursors were converted into various novel heterocyclic systems by following simple and well established synthetic route.[373,384,385]

The synthetic schemes for novel heterocyclic compounds described as follows.

i) Functionalized Pyrazoles

Mono, di and tri-arylated pyrazoles were synthesized by following well known Suzuki-Miyaura Pd(0) catalyzed cross-coupling reactions

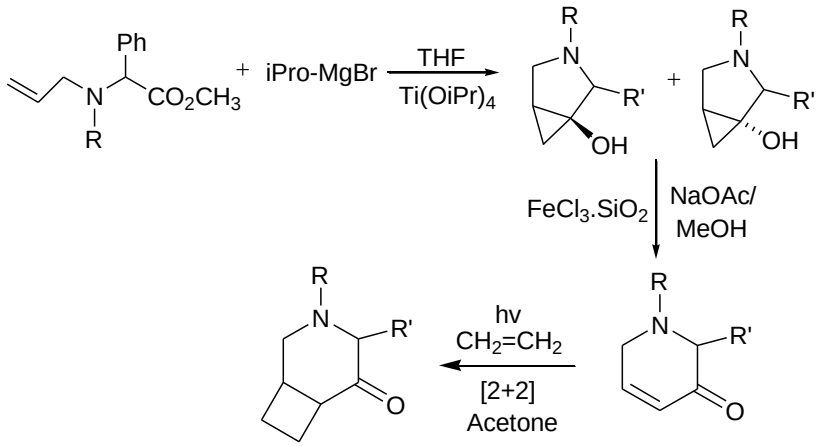
General Scheme-7



Scheme 7: Synthesis of Mono, Di and 3,4,5-tri-arylated Pyrazoles

ii) *N*-Substituted Dihydropyridinones

General Scheme-8



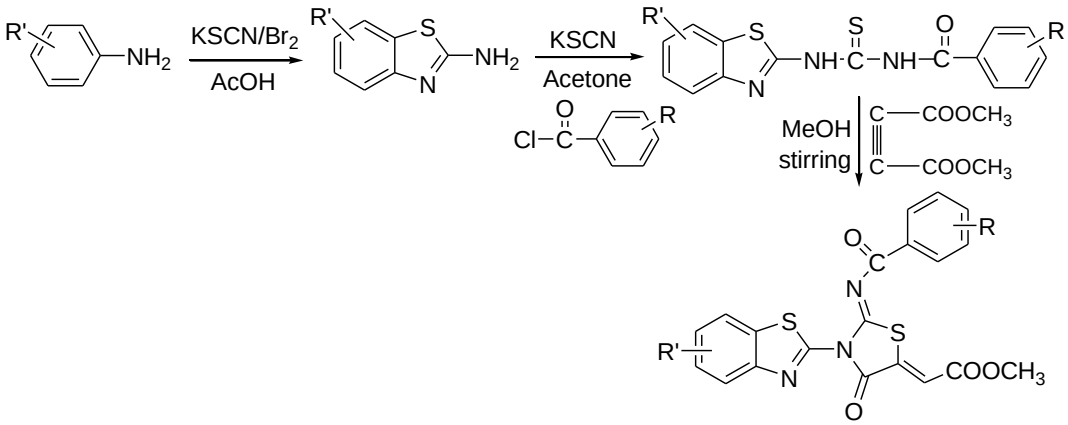
R = Allyl, Boc, Benzyl, Tosyl

R' = H, Ph

Scheme 8: Synthesis of *N*-Substituted Dihydropyridinones (4a-e)

iii) Iminothiazolidinones

General Scheme-9

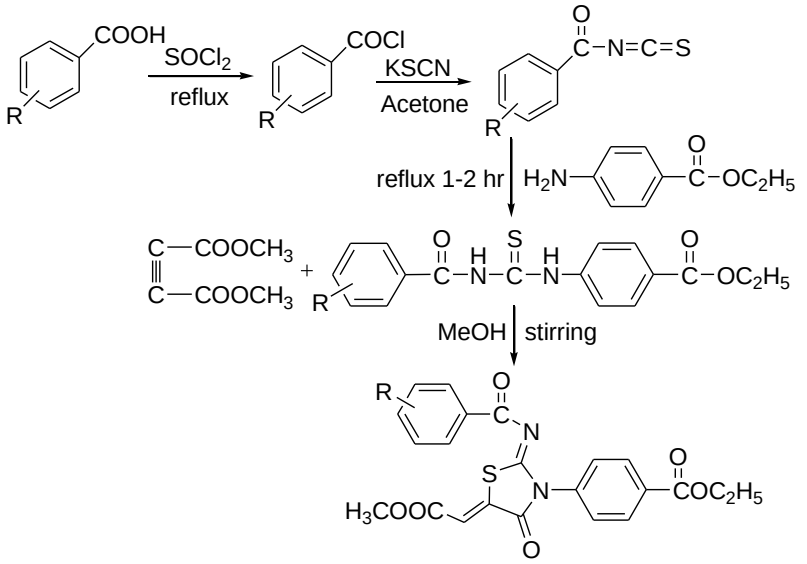


R = H, -Br, -CH_3, -OCH_3, 2,4-Dichloro.

R' = H, 2-OCH_3, 4-CH_3, 3-Cl, 2-F, 2-Br, 2,4-Dichloro.

Scheme 9: Synthesis of Methyl 2-[2-benzamido-3-(benzo[d]thiazol-2-yl)-4-oxo-thiazolidin-5-ylidene] acetates (3a-k)

General Scheme-10

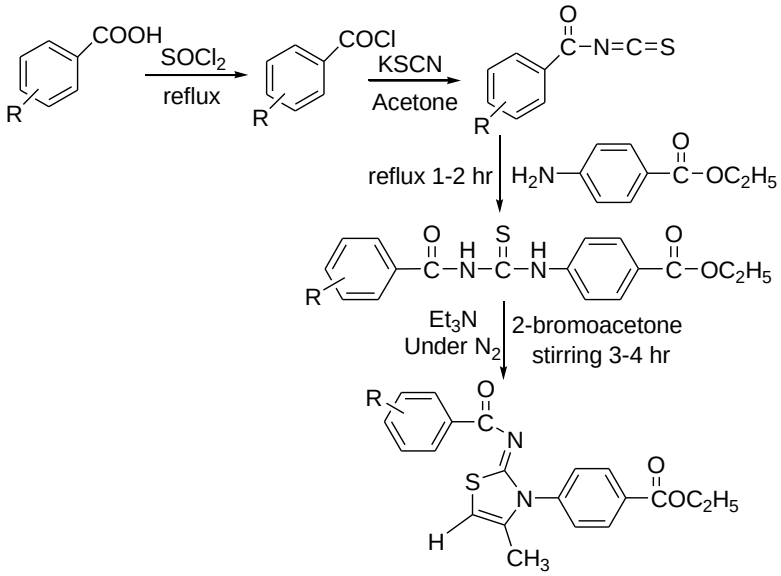


R = H, 3-Cl, 2,4-Dichloro, 4-CH_3, 3-CH_3, 4-OCH_3, 3,4-Dimethoxy, 3-OCH_3, 2-Br, 2-F.

Scheme 10: Synthesis of Ethyl 4-[2-benzamido-5-(2-methoxy-2-oxoethylidene)-4-oxothiazolidin-3-yl] benzoates (4a-j)

iv) Iminothiazolines

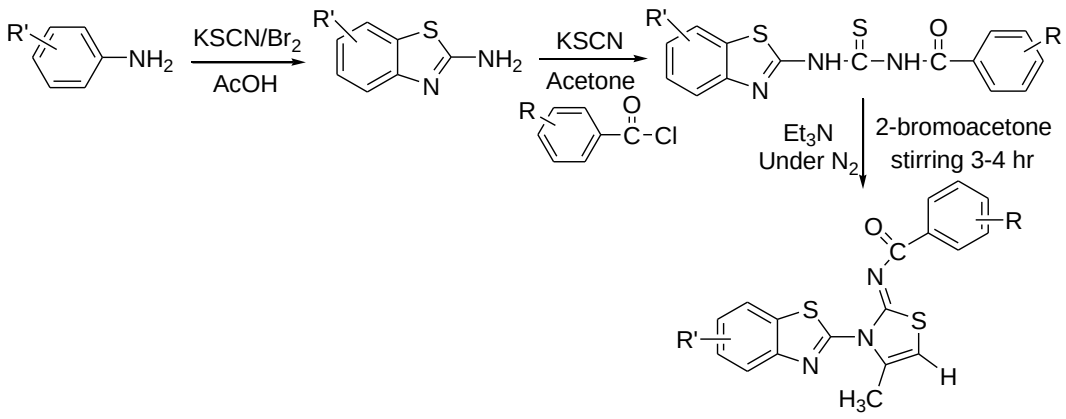
General Scheme-11



R = H, 3-Cl, 2,4-Dichloro, 4-CH_3, 3-CH_3, 4-OCH_3, 3,4-Dimethoxy, 3-OCH_3, 2-Br, 2-F.

Scheme 11: Synthesis of Ethyl 4-[2-benzamido-4-methylthiazol-3(2H)-yl] benzoates (2a-j)

General Scheme-12



R = H, -Br, -CH_3, -OCH_3, 2,4-Dichloro.

R' = H, 2-OCH_3, 4-CH_3, 3-Cl, 2-F, 2-Br, 2,4-Dichloro.

Scheme 12: Synthesis of *N*-[3-(Benzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene] benzamides (3a-k)

Chapter–2

RESULTS AND DISCUSSION

2.1 Natural Isocoumarin Analogues

Naturally occuring 3,4-dihydroisocoumarins (±) 7-butyl-6,8-dihydroxy-3-pentyl-3,4-dihydro-1H-isochromen-1-one and (*Stellatin*) 8-hydroxy-7-hydoxymethyl-6-methoxy-3,4-dihydro-1H-isochromen-1-one were synthesized along with the total synthesis of various structural analogues of well known bioactive natural 3,4-dihydroisocoumarins *viz. Annulatomarin, Montroumarin, Scorzocreticin, Typharin,* and *Hiburipyranone* have been carried out.

3,5-Dimethoxy-4-methylhomophthalic acid **(12)** was synthesized starting from commercially available 4-methylbenzoic acid. It was then condensed with various aroyl/acyl acid chlorides to afford the corresponding 6,8-dimethoxy-7-methyl-3-aryl/alkylisochromen-1-ones **(5a-j)**. These isocoumarins were hydrolysed to keto-acids **(6a-j)** and then reduced to corresponding hydroxyacids, which were then cyclized to corresponding 6,8-dimethoxy-7-methyl-3-aryl/alkyl-3,4-dihydroisochromen-1-ones **(7a-j)**. Finally, demethylation of 3,4-dihydroisochromen-1-ones was carried out to give 6,8-dihydroxy-7-methyl-3-aryl/alkyl-3,4-dihydroisochromen-1-ones **(8a-j)**.

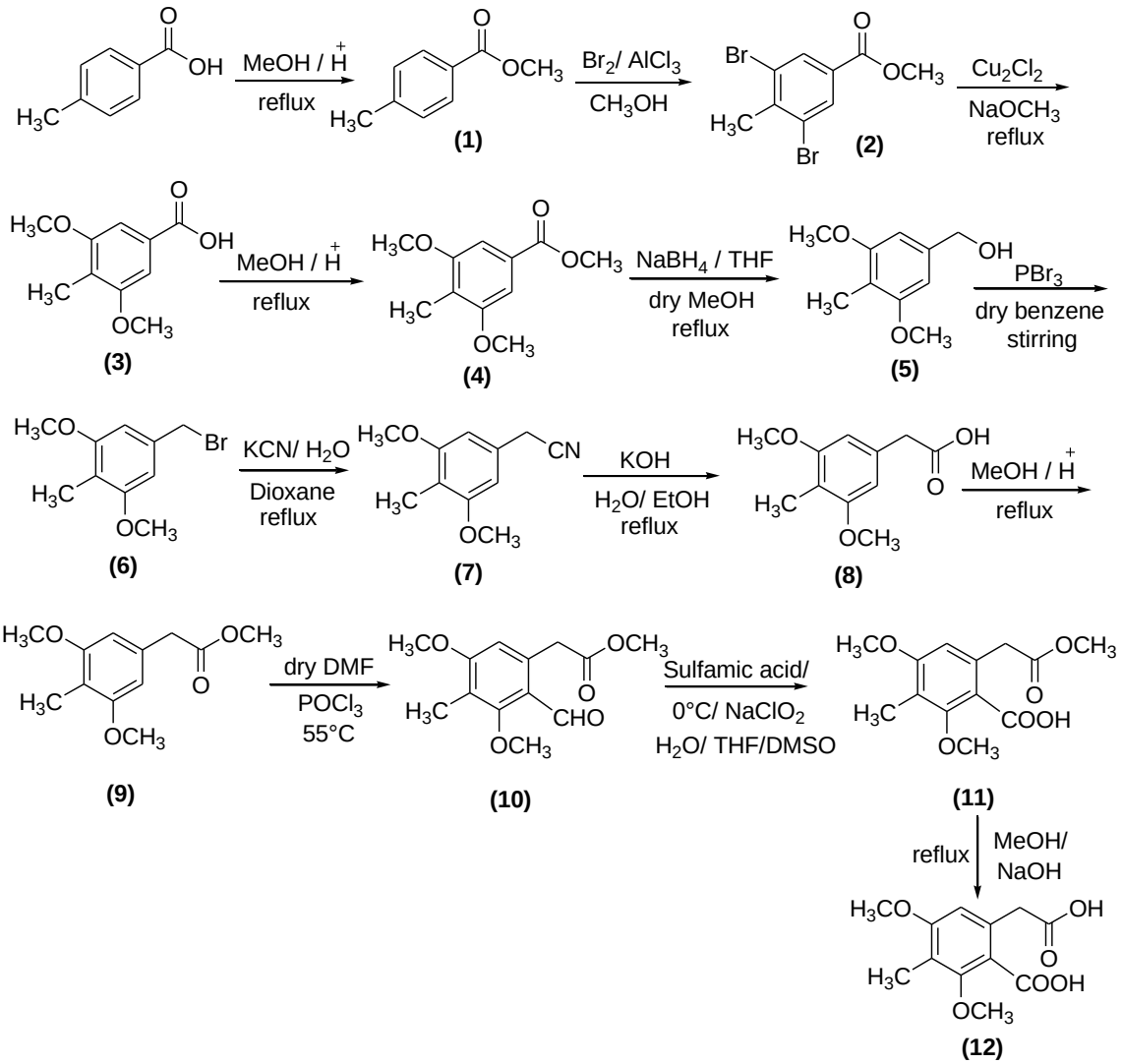
2.1.1 Synthesis of 3,5-dimethoxy-4-methylhomophthalic acid (12)

Methyl 4-methylbenzoate **(1)** was prepared by esterification of 4-methylbenzoic acid in dry methanol using few drops of conc. sulfuric acid as catalyst. It showed characteristic (C=O) stretching absorption in FTIR spectrum at 1732 cm^{-1}. In ^{13}C NMR carbonyl carbon signal observed at 166.7 ppm.

'*Swamping catalyst method'* was employed to carry out nuclear halogenation of ester derivative **(1)** to afford methyl 3,5-dibromobenzoate **(2)**. It involves an excess use of anhydrous $AlCl_3$ without any solvent and it also acts as a catalyst by forming a complex with the carbonyl group of the ester derivative, so that the side chain halogenation was suppressed. $AlCl_3$ not only complexes with the carbonyl group but it also produce ion pair Br^+ $AlCl_3$ Br^- or highly electrophilic free Br^+ ion, which thus increases the activity of attacking reagent. The incoming bromide were directed to 3 and 5 positions by ideally situated 4-methyl group in **(1)** and thus dibromination of methyl 4-methylbenzoate yields methyl 3,5-dibromo-4-methylbenzoate.

Methyl 3,5-dibromobenzoate **(2)** was converted into methyl 3,5-dimethoxy-4-methylbenzoate by nucleophilic substitution in pyridine solution with sodium methoxide

and freshly prepared copper (I) chloride as a catalyst. 3,5-dimethoxy-4-methylbenzoic acid **(3)** was directly obtained upon concurrent hydrolysis during this reaction. It was confirmed by broad stretching absorption for (O-H) at 3216 cm^{-1} in FTIR spectrum. In ^{1}H NMR a singlet (s) for six methoxy protons appeared at δ 3.86 ppm and characteristic carboxyl singlet (s) at δ 9.31 ppm. In ^{13}C NMR, a signal for carboxyl carbon appeared at δ 168.3 ppm and for the methoxy carbons at δ 56.5 ppm.



Scheme 1.1: Synthesis of 3,5-Dimethoxy-4-methyl homophthalic acid (12)

The acid derivative **(3)** was converted into methyl ester. The IR spectrum showed the disappearance of a broad band for (O-H) of acidic group at 3216 cm-^{1}. The methyl ester **(4)** was then reduced by sodium borohydride-in dry methanol system refluxed in THF to afford 3,5-dimethoxy-4-methylbenzyl alcohol **(5)**. The IR spectrum confirms the presence of -OH by a broad band at 3362 cm^{-1}, along with the disappearance of carbonyl carbon absorption. The sodium borohydride reduction of esters and related functional

groups is relatively difficult to achieve. However, the sodium borohydride reactivity was enhanced by proceeding reduction in the presence of $NaBH_4$/MeOH.

The benzyl alcohol **(5)** was treated phosphorous tribromide (PBr_3) in dry benzene in order to transform it to 3,5-dimethoxy-4-methylbenzyl bromide **(6)**. In IR spectrum showed the absence of broad band signal due to -OH group. The benzylbromide **(6)** was converted to benzyl cyanide by nucleophilic substitution with potassium cyanide and ethanol to afford 3,5-dimethoxy-4-methylbenzyl cyanide **(7)**, which is confirmed by the presence of characteristic nitrile absorption at 2267 cm^{-1} in IR spectrum.

3,5-Dimethoxy-4-methylphenyl acetic acid **(8)** was synthesized by the alkaline hydrolysis of the nitrile **(7)** using aqueous methanolic KOH in dioxane solvent. The IR spectrum showed a strong absorption for carbonyl carbon at 1706 cm^{-1} and a broad band for -OH at 3242 cm^{-1}. The phenylacetic acid derivative **(8)** was then converted into its methyl ester **(9)**. The IR spectrum showed a carbonyl absorption peak at 1731 cm^{-1} and a disappearance of a broad band for -OH group was also observed. In the ^1H NMR a singlet (s) appeared at δ 3.87 ppm for methyl ester protons.

Methyl (2-formyl-3,5-dimethoxy-4-methyl phenyl) acetate **(10)** was prepared by the introduction of formyl moiety to methyl ester **(9)** by Vilsmeier Haack formylation method using phosphorus oxychloride in DMF. The IR spectrum showed a new very strong carbonyl carbon absorption for aldehydic group at 1685 cm^{-1} and ester carbonyl peak at 1725 cm^{-1}. In the ^1H NMR spectrum a singlet (s) for formyl proton appeared at δ 9.84 ppm. In ^{13}C NMR the aldehydic carbonyl carbon showed a peak at δ 178.5 ppm for and for ester at δ 163.2 ppm. The structure was also confirmed by mass spectrometry as molecular ion peak was observed at *m/z* 252 and the base peak at *m/z* 165.

The formyl moiety **(10)** was oxidized to acidic group to afford 2,4-dimethoxy-6-(2-methoxy-2-oxoethyl)-3-methylbenzoic acid **(11)** by sulfamic acid and sodium chlorite at 0 °C. The carbonyl carbon absorption in IR spectrum shifted from 1685 cm^{-1} to 1717 cm^{-1} as aldehydic function oxidizied to acidic group. The broad band absorption for (O-H) observed at 3273 cm^{-1}. In ^1H NMR spectrum a singlet (s) for acidic proton was appeared at δ 10.13 ppm and a downfield shift for carboxylic carbon was also observed in ^{13}C NMR spectrum from δ 178.6 to δ 197.5 ppm.

In the final step, 3,5-dimethoxy-4-methylhomophthalic acid **(12)** was afforded by the alkaline hydrolysis of the ester acid derivative **(11)** using 10 % KOH and ethanol.

The physical data of the compounds **(1-12)** is presented in Table 1.1.

Table 1.1: Physical data of all the compounds (1-12)

Compounds	M.P. (^{o}C)	Rf[a] Values	Yield (%)	Solvent of Recrystallization
1	34-35	0.7	84	Methanol
2	83-84	0.6	63	"
3	211-212	0.4	87	"
4	77-78	0.6	85	Ethanol
5	45-56	0.5	81	Pet. ether
6	68-70	0.6	86	"
6'	oil	0.7	77	-
7	48-50	0.5	83	"
8	129-131	0.4	73	Ethanol
9	38-39	0.65	82	"
10	51-52	0.55	85	"
11	164-165	0.4	78	Pet. ether
12	152-153	0.35	85	Ethyl acetate

[Pet. ether : ethyl acetate (8:2)]

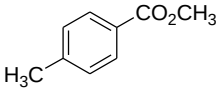
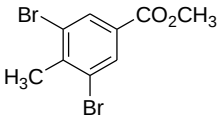
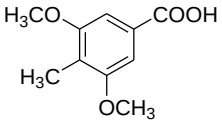
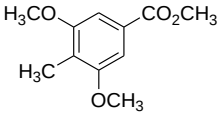
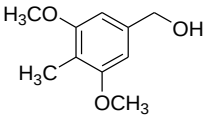
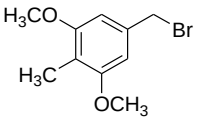
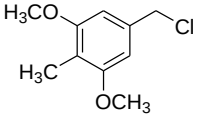
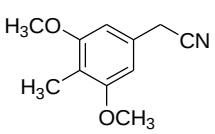
The FTIR spectral data of the compounds **(1-12)** is presented in Table 1.2.

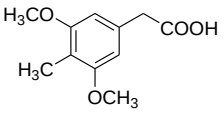
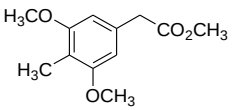
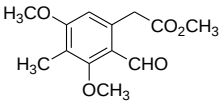
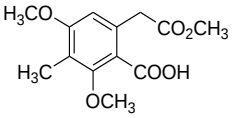
Table 1.2: FTIR spectral data of all the compounds (1-12)

Compounds.	(C=C-H) cm^{-1}	(C=O) cm^{-1}	(C=C) cm^{-1}	(O-H) cm^{-1}
1	3014	1732	1588	-
2	3025	1719	1583	-
3	3027	1711	1586	3216
4	3021	1728	1578	-
5	3024	-	1574	3362
6	3018	-	1575	-
6'	3044	-	1586	-
7	3015	-	1577	-
8	3010	1706	1573	3234
9	3022	1731	1582	-
10	3032	1685, 1725	1568	-
11	3042	1733, 1717	1581	3273
12	3027	1718, 1727	1587	3213

The ^{1}H and ^{13}C NMR spectral data of the compounds **(1-11)** is presented in Table 1.3.

Table 1.3: ^{1}H and ^{13}C NMR spectral data of all the compounds (1-11)

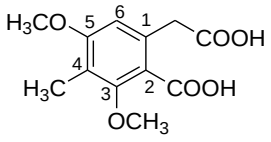
Sr No.	Structures	^{1}H NMR(δ) (ppm)	^{13}C NMR(δ) (ppm)
1		7.83 (2H, d, *J* = 7.2 Hz, H-2, H-6), 7.41 (2H, d, *J* = 7.2 Hz, H-3, H-5), 3.76 (3H, s, -OCH_3), 2.43 (3H, s, Ar-CH_3)	166.7 (ester C=O), 136.4 (C-1), 134.2 (C-2,C-6), 130.8 (C-3,C-5), 127.6 (C-4), 28.7 (-CH_3), 54.6 (-OCH_3)
2		7.86 (2H, s, H-2, H-6), 3.78 (3H, s, -OCH_3), 2.46 (3H, s, -CH_3)	167.3 (ester C=O), 138.2 (C-1), 136.8 (C-3,C-5), 132.7 (C-2-C-6), 128.6 (C-4), 29.2 (-CH_3), 56.7 (-OCH_3);
3		9.31 (1H, s, -COOH), 7.82 (2H, s, H-2,H-6), 3.86 (6H, s, -OCH_3), 2.54 (3H, s, -CH_3)	168.3 (carboxylic C=O), 138.4 (C-1), 137.6 (C-2,C-5), 128.5 (C-2,C-6), 116.7 (C-4), 56.5 (-OCH_3), 28.7 (-CH_3)
4		7.72 (2H, s, H-2, H-6), 2.24 (3H, s, -CH_3), 3.62 (6H, s, -OCH_3), 3.78 (3H, s, ester -OCH_3)	167.4 (ester C=O), 137.4 (C-3,C-5), 134.3 (C-1), 127.6 (C-2,C-6), 117.5 (C-4), 58.3 (ester OCH_3), 62.6 (Ar-OCH_3), 29.1 (-CH_3)
5		7.56 (2H, s, H-2,H-6), 4.47 (1H, bs, -OH), 3.74 (6H, s, -OCH_3), 2.57 (1H, s, Ar-CH_2), 2.34 (3H, s, -CH_3)	138.7 (C-3,C-5), 137.3 (C-2,C-6), 128.6 (C-4), 118.5 (C-1), 63.3 (-OCH_3), 42.7 (-CH_2), 29.3 (-CH_3)
6		7.35 (2H, s, H-2, H-6), 3.81 (6H, s, -OCH_3), 2.87 (2H, s, Ar-CH_2), 2.54 (3H, s, Ar-CH_3)	138.5 (C-3,C-5), 136.4 (C-2, C-6), 128.3 (C-4), 118.3 (C-1), 62.4 (-OCH_3), 42.4 (-CH_2), 28.6 (Ar-CH_3)
6'		7.51 (2H, s, H-2, H-6), 3.78 (6H, s, -OCH_3), 2.83 (2H, s, Ar-CH_2), 2.52 (3H, s, Ar-CH_3)	137.7 (C-3,C-5), 134.6 (C-2,C-6), 127.5 (C-4), 117.4 (C-1), 62.5 (-OCH_3), 41.7 (-CH_2), 28.4 (Ar-CH_3)
7		7.43 (2H, s, H-2, H-6), 3.78 (6H, s, -OCH_3), 2.86 (2H, s, Ar-CH_2), 2.56 (3H, s, -CH_3)	138.4 (C-3,C-5), 134.6 (C-2,C-6), 128.5 (-CN), 126.3 (C-4), 116.8 (C-1), 63.5 (-OCH_3), 41.3 (-CH_2), 29.4 (Ar-CH_3)

8		10.41 (1H, s, COOH); 7.64 (2H, s, H-2, H-6), 3.77 (6H, s, -OCH_3), 3.58 (2H, s, Ar-CH_2), 2.52 (3H, s, -CH_3)	167.6 (carboxylic C=O), 136.4 (C-3,C-5), 134.3 (C-2,C-6), 126.4 (C-4), 116.2 (C-1), 63.6 (ester -OCH_3), 56.7 (Ar-OCH_3), 43.2 (-CH_2), 30.4 (Ar-CH_3)
9		7.34 (2H, s, H-2,H-6), 3.87 (6H, s, -OCH_3), 3.56 (3H, s, -$COOCH_3$), 2.71 (2H, s, Ar-CH_2), 2.42 (3H, s, Ar-CH_3)	168.5 (ester C=O), 131.5 (C-3,C-5), 127.7 (C-2,C-6), 118.4 (C-4), 113.2 (C-1), 67.6 (ester -OCH_3), 56.4 (Ar-OCH_3), 42.6 (-CH_2), 29.4 (Ar-CH_3)
10		9.84 (1H, s, -CHO), 7.97 (1H, s, H-6), 3.62 (3H, s, -OCH_3), 3.54 (3H, s, -OCH_3), 3.24 (3H, s, ester OCH_3), 2.84 (2H, s, Ar-CH_2), 2.63 (3H, s, Ar-CH_3)	178.6 (aldehyde C=O), 163.2 (ester C=O), 137.5 (C-3), 136.7 (C-5), 132.6 (C-2), 127.4 (C-6), 121.3 (C-4), 118.2 (C-1), 62.7 (ester -OCH_3), 58.4 (Ar-OCH_3), 41.2 (Ar-CH_2), 31.5 (Ar-CH_3)
11		10.13 (1H, s, -COOH), 7.74 (1H, s, H-6), 3.83 (3H, s, -OCH_3), 3.77 (3H, s, -OCH_3), 3.65 (3H, s, ester OCH_3), 2.62 (2H, s, Ar-CH_2), 2.34 (3H, s, Ar-CH_3)	197.5 (carboxylic C=O), 167.6 (ester C=O), 138.2 (C-3), 137.6 (C-5), 134.7 (C-2), 127.2 (C-6), 121.6 (C-4), 115.7 (C-1), 64.4 (ester -OCH_3), 56.5 (Ar-OCH_3), 41.3 (Ar-CH_2), 29.4 (Ar-CH_3)

The formation of 3,5-dimethoxy-4-methylhomophthalic acid **(12)** was confirmed by the presence of two characteristic singlets in ^{1}H NMR spectrum at δ 10.94 and 10.76 ppm for two acidic protons. In ^{13}C NMR spectrum two characteristic peaks for C=O groups of carboxylic acid appeared at δ 204.6 and 171.4 ppm.

The ^{1}H and ^{13}C NMR spectral data of the compound **(12)** is presented in Table 1.4.

Table 1.4: ^{1}H and ^{13}C NMR spectral data of 3,5-Dimethoxy-4-methylhomophthalic acid (12)



Carbons	δ (ppm) and multiplicity	
	^{1}H NMR	^{13}C NMR
C-1	-	123.6
C-2	-	134.7
C-3	-	136.3
C-4	-	126.2
C-5	-	135.5
C-6	7.64, (s)	133.4
3-OCH_3	3.87, (s)	56.4
5-OCH_3	3.68, (s)	55.6
4-CH_3	2.37, (s)	28.6
Ar-CH_2	2.56, (s)	42.5
COOH	10.76, (s)	171.4
Ar-COOH	10.94, (s)	204.6

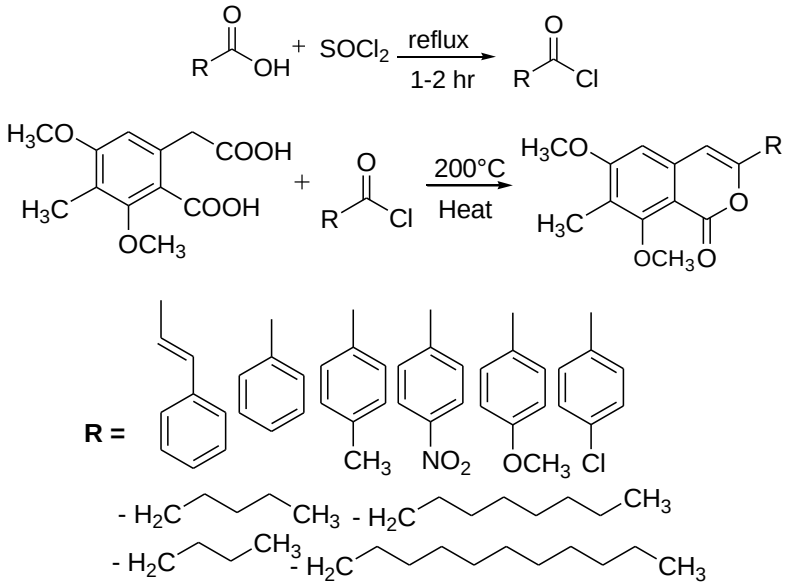
Elemental analysis also confirmed the formation of 3,5-dimethoxy-4-methyl-homophthalic acid **(12)**. The elemental analysis data of the compounds **(1-12)** is presented in Table 1.5.

Table 1.5: Elemental analysis data of all the compounds (1-12)

Compounds	Formulae	Elemental Analysis					
		% Calculated			% Found		
		C	H	N	C	H	N
1	$C_9H_{10}O_2$	72.12	6.75	-	71.94	6.56	-
2	$C_9H_{10}BrO_2$	35.12	2.65	-	35.04	2.57	-
3	$C_{10}H_{12}O_4$	61.21	6.12	-	60.17	6.03	-
4	$C_{10}H_{12}O_4$	62.83	6.72	-	62.75	6.67	-
5	$C_{10}H_{14}O_3$	65.93	7.72	-	65.86	7.64	-
6	$C_{10}H_{13}BrO_2$	49.01	5.34	-	48.96	5.28	-
6a	$C_{10}H_{13}ClO_2$	59.85	6.53.	-	59.77	6.46	-
7	$C_{11}H_{13}NO_2$	69.10	6.84	7.32	68.87	7.01	7.26
8	$C_{11}H_{14}O_4$	62.86	6.64	-	62.78	6.57	-
9	$C_{12}H_{16}O_4$	64.26	7.17	-	64.21	7.11	-
10	$C_{13}H_{16}O_5$	61.91	6.37	-	61.84	6.28	-
11	$C_{13}H_{16}O_6$	58.21	5.97	-	58.18	5.86	-
12	$C_{12}H_{14}O_6$	56.68	5.51	-	56.61	5.47	-

2.1.2 Synthesis of 6,8-Dimethoxy-7-methyl-3-aryl/alkyl-1H-isochromen-1-ones (5a-j)

Aliphatic acid chlorides were commercially used and aromatic acid chlorides were prepared. The aromatic carboxylic acids were converted into their respective acid chlorides by treating them with thionyl chloride **(a-j)** in the presence of catalytic amount of DMF. These acid chlorides were then condensed with 3,5-dimethoxy-4-methyl-homophthalic acid **(12)** to afford 6,8-dimethoxy-7-methyl-3-aryl/alkylisochromen-1-ones **(5a-j)**. These isohromen-1-ones were purified by preparative thin layer chromatography.



Scheme 1.2: Synthesis of 6,8-Dimethoxy-7-methyl-3-aryl/alkylisochromen-1-ones (5a-j)

The physical data of 6,8-dimethoxy-7-methyl-3-aryl/alkylisochromen-1-ones **(5a-j)** is presented in Table 1.6

Table 1.6: Physical data of all the compounds (5a-j)

Sr. No.	Compounds (R)	M.P. (^{o}C)	Rf[a] Values	Yield (%)
5a	3-Cinnamoyl	123-124	0.65	71
5b	3-Phenyl	108-110	0.6	86
5c	4-*p*-tolyl	oil	0.55	80
5d	4-Nitrophenyl	224-226	0.5	78
5e	4-Methoxyphenyl	153-155	0.55	82
5f	4-Chlorophenyl	oil	0.7	78
5g	3-Butyl	oil	0.6	70
5h	3-Pentyl	oil	0.55	73
5i	3-Octyl	88-90	0.5	76
5j	3-Undecyl	137-139	0.5	72

[Pet. ether: ethyl acetate (4:1)]

The FTIR spectral data of 6,8-dimethoxy-7-methyl-3-aryl/alkylisochromen-1-ones **(5a-j)** is presented in Table 1.7.

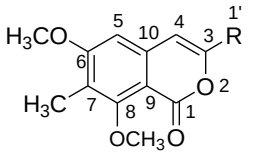
Table 1.7: FTIR spectral data of all the compounds (5a-j)

Sr. No.	Compounds (R)	(C=C-H) cm^{-1}	(O-H) cm^{-1}	(C=O) cm^{-1}	(C=C) cm^{-1}
5a	3-Cinnamoyl	3023	2914	1723	1567
5b	3-Phenyl	3033	2936	1715	1571
5c	4-*p*-tolyl	3032	2943	1717	1573
5d	4-Nitrophenyl	3035	2946	1726	1583
5e	4-Methoxyphenyl	3037	2937	1724	1574
5f	4-Chlorophenyl	3029	2934	1721	1576
5g	3-Butyl	3038	2973	1718	1587
5h	3-Pentyl	3051	2964	1712	1557
5i	3-Octyl	3036	2972	1716	1565
5j	3-Undecyl	3022	2923	1713	1543

The ^{1}H NMR spectra of 6,8-dimethoxy-7-methyl-3-aryl/alkylisohromen-1-ones **(5a-j)** showed the characteristic singlet (s) at δ 6.43-7.82 ppm for (H-4) proton of isochromen-1-one. In ^{13}C NMR spectra, the characteristic lactonic carbonyl carbon peak appeared in the range δ 163.4-170.5 ppm.

The ^{1}H and ^{13}C NMR spectral data of 6,8-dimethoxy-7-methyl-3-aryl/alkyliso-chromen-1-ones **(5a-j)** is presented in Table 1.8.

Table 1.8: ^{1}H and ^{13}C NMR spectral data of all the compounds (5a-j)



Sr. No.	Compounds (R)	^{1}H NMR(δ) (ppm)	^{13}C NMR(δ) (ppm)
5a	3-Cinnamoyl	7.21-7.76 (5H, m, Ar), 6.82 (1H, d, *J* = 7.2 Hz, Ha), 6.63 (1H, d, *J* = 7.2 Hz, Hb), 6.57 (1H, s, H-5), 6.43 (1H, s, H-4), 3.86 (3H, s, $-OCH_3$), 3.83 (3H, s, $-OCH_3$), 2.63 (1H, s, $-CH_3$)	168.4 (C=O), 150.5 (C-3), 142.7 (C-6), 141.5 (C-8), 138.6 (C-10), 137.7 (C-1'), 135.4 (C-1a), 134.8 (C-1b), 127.8 (C-9), 127.4 (C-2',C-6'), 126.7 (C-3',C-5'), 123.3 (C-4'), 118.5 (C-7), 109.3 (C-4), 104.6 (C-5), 56.4 ($-OCH_3$), 56.2 ($-OCH_3$), 28.6 (Ar-CH_3)
5b	3-Phenyl	7.91-8.13 (5H, m, Ph), 7.86 (1H, s, H-5), 6.52	171.5 (C=O), 142.6 (C-3), 140.6 (C-6), 140.2 (C-8), 134.3

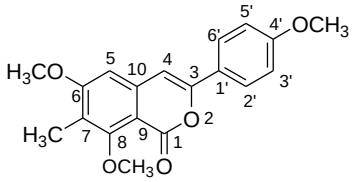
		(1H, s, H-4), 3.76 (3H, s, -OCH_3), 3.73 (3H, s, -OCH_3), 2.61 (3H, s, Ar-CH_3)	(C-10), 132.4 (C-9), 130.2 (C-1'), 127.8 (C-3',C-5'), 126.5 (C-4'), 124.7 (C-2',C-6'), 118.6 (C-7), 113.3 (C-4), 108.5 (C-5), 62.6 (-OCH_3), 62.4 (-OCH_3), 28.6 (Ar-CH_3)
5c	4-*p*-tolyl	7.64 (2H, d, *J* = 7.2 Hz, H-2',6'), 7.58 (2H, d, *J* = 7.2 Hz, H-3',H-5'), 7.41 (1H, s, H-5), 6.64 (1H, s, H-4), 3.71 (3H, s, -OCH_3), 3.68 (3H, s, -OCH_3), 2.48 (3H, s, Ar-CH_3)	164.7 (C=O), 143.4 (C-6), 142.6 (C-8), 140.3 (C-3), 134.7 (C-10), 134.1 (C-9), 133.4 (C-4'), 128.5 (C-3',C-5'), 127.3 (C-1'), 126.2 (C-2',C-6'), 114.8 (C-7), 110.4 (C-4), 104.3 (C-5), 62.7 (-OCH_3), 62.4 (-OCH_3), 27.6 (Ar-CH_3)
5d	4-Nitrophenyl	7.83 (2H, d, *J* = 6.7 Hz, H-2',H-6'), 7.78 (2H, d, *J* = 6.7 Hz, H-3',H-5'), 7.67 (1H, s, H-5), 6.73 (1H, s, H-4), 3.81 (3H, s, -OCH_3), 3.78 (3H, s, -OCH_3), 2.71 (3H, s, Ar-CH_3)	162.4 (C=O), 146.3 (C-4'), 143.6 (C-3), 141.4 (C-6), 141.1 (C-8), 136.8 (C-1'), 134.7 (C-10), 133.6 (C-9), 128.7 (C-3',C-5'), 126.5 (C-2',C-6'), 118.4 (C-7), 114.6 (C-4), 107.8 (C-5), 64.7 (-OCH_3), 64.4 (-OCH_3), 28.7 (Ar-CH_3)
5f	4-Chlorophenyl	7.76 (2H, d, *J* = 7.1 Hz, H-2',6'), 7.71 (2H, d, *J* = 7.1 Hz, H-3',H-5'), 7.68 (1H, s, H-5), 6.72 (1H, s, H-4), 3.74 (6H, s, -OCH_3), 2.57 (3H, s, Ar-CH_3)	163.8 (C=O), 141.3 (C-3), 137.5 (C-6), 137.2 (C-8), 135.3 (C-10), 134.4 (C-9), 133.6 (C-4'), 129.7 (C-3',C-5'), 128.6 (C-1'), 127.5 (C-2',C-6'), 117.6 (C-7), 112.2 (C-4), 106.3 (C-5), 64.5 (-OCH_3), 28.7 (Ar-CH_3)
5g	3-Butyl	7.73 (1H, s, H-5), 6.81 (1H, s, H-4), 3.75 (3H, s, -OCH_3), 3.71 (3H, s, -OCH_3), 2.67 (3H, s, Ar-CH_3), 2.48 (2H, t, *J* = 3.8 Hz, H-1'), 1.33-1.38 (2H, m, H-2',H-3'), 0.94 (2H, t, *J* = 7.4 Hz, H-4')	164.3 (C=O), 150.6 (C-3), 146.1 (C-6), 145.4 (C-8), 134.6 (C-10), 127.3 (C-9), 117.8 (C-7), 109.4 (C-4), 103.7 (C-5), 54.6 (-OCH_3), 54.2 (-OCH_3), 34.3 (C-1'), 28.7 (Ar-CH_3), 25.5 (C-2'), 23.2 (C-3'), 14.6 (C-4')
5i	3-Octyl	7.61 (1H, s, H-5), 6.78 (1H, s, H-4), 3.74 (3H, s, -OCH_3), 3.71 (3H, s, -OCH_3), 2.47 (3H, s, Ar-CH_3), 1.53 (2H, t, *J* = 6.8 Hz, H-1'), 1.26-1.73 (12H, m, H-2',H-3',H-4',H-5',H-6',H-7'), 0.92	164.2 (C=O), 153.6 (C-3), 144.5 (C-6), 143.7 (C-8), 133.4 (C-10), 131.7 (C-9), 123.2 (C-7), 115.8 (C-4), 105.4 (C-5), 56.5 (-OCH_3), 56.2 (-OCH_3), 36.7 (C-1'), 29.3 (Ar-CH_3), 27.6 (C-2'), 23.7 (C-3'), 21.5 (C-4'), 16.7 (C-5'), 14.6 (C-6'),

		(3H, t, *J* = 6.9 Hz, H-8')	13.2 (C-7'), 11.8 (C-8')
5j	3-Undecyl	7.55 (1H, s, H-5), 6.82 (1H, s, H-4), 3.76 (3H, s, -OCH_3), 3.73 (3H, s, -OCH_3), 2.57 (3H, s, Ar-CH_3), 1.54 (2H, t, *J* = 6.8 Hz, H-1'), 1.24-1.38 (10H, m, H-2',H-3',H-4',H-5',H-6',H-7',H-8',H-9',H-10'), 0.93 (3H, t, *J* = 6.7 Hz, H-11')	163.7 (C=O), 152.9 (C-3), 143.8 (C-6), 142.6 (C-8), 133.2 (C-9), 132.7 (C-10), 122.8 (C-7), 114.7 (C-4), 104.7 (C-5), 56.6 (-OCH_3), 56.2 (-OCH_3), 38.7 (C-1'), 29.1 (Ar-CH_3), 27.8 (C-2'), 21.7 (C-3'), 16.8 (C-4'), 11.7 (C-5'), 10.8 (C-6'), 9.7 (C-7')

The formation of the 6,8-dimethoxy-7-methyl-3-(4-methoxyphenyl)isochromen-1-one **(5e)** was confirmed by the presence of a characteristic singlet in ^{1}H NMR spectrum for H-4 proton at δ 6.85 ppm. In ^{13}C NMR spectrum a characteristic lactonic carbonyl carbon peak appeared at δ 164.5 ppm.

The ^{1}H and ^{13}C NMR spectral data of the compound **(5e)** is presented in Table 1.9.

Table 1.9: ^{1}H and ^{13}C NMR spectral data of 6,8-Dimethoxy-7-methyl-3-(4-methoxy phenyl)isochromen-1-one (5e)



Carbons	δ (ppm) and multiplicity	
	^{1}H NMR	**^{13}C NMR**
C-1 (C=O)	-	164.2
C-3	-	142.5
C-4	6.85, (s)	119.2
C-5	7.76, (s)	112.3
C-6	-	138.7
C-7	-	122.5
C-8	-	137.3
C-9	-	133.4
C-10		135.6
C-1'	-	130.6
C-2'	7.36, (d), *J* = 7.8 Hz	124.6
C-3'	7.97, (d), *J* = 7.6 Hz	127.4
C-4'	-	136.5
C-5'	7.97, d, *J* = 7.6 Hz	127.4
C-6'	7.36, d, *J* = 7.8 Hz	124.6

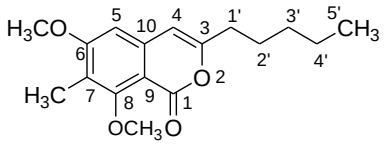
4'-OCH_3	3.67, (s)	53.7
6-OCH_3	3.87, (s)	56.6
8-OCH_3	3.82, (s)	55.3
Ar-CH_3	2.73, (s)	28.2

In the mass spectrum the molecular ion peak was observed at *m/z* 326 with 51 % abundance, which confirmed the formation of isochromen-1-one **(5e)**. By the removal of 4-methoxypentyl radical from molecular ion, a peak appeared at *m/z* 219 with 43 % abundance and a base peak appeared at *m/z* 191.

The formation of the 6,8-dimethoxy-7-methyl-3-pentylisocoumarin **(5h)** was confirmed by the presence of a characteristic singlet (s) in ^{1}H NMR spectrum for H-4 proton at δ 7.36 ppm. In ^{13}C NMR spectrum a characteristic lactonic carbonyl carbon peak appeared at δ 165.6 ppm.

The ^{1}H and ^{13}C NMR spectral data of the compound **(5h)** is presented in Table 1.10.

Table 1.10: ^{1}H and ^{13}C NMR spectral data of 6,8-Dimethoxy-7-methyl-3-pentyl isocoumarin (5h)



Carbons	**δ (ppm) and multiplicity**	
	^{1}H NMR	**^{13}C NMR**
C-1 (C=O)	-	165.6
C-3	-	150.2
C-4	7.36, (s)	109.5
C-10	-	133.5
C-5	7.82, (s)	105.3
C-6	-	142.4
C-7	-	118.5
C-8	-	141.6
C-9	-	128.6
C-1'	2.53, t, *J* = 3.7 Hz	38.7
C-2'	1.64, (m)	24.5
C-3'	1.32, (m)	19.3
C-4'	1.25, (m)	14.5
C-5'	0.93, t, *J* = 7.2 Hz	13.4
6-OCH_3	3.85, (s)	54.6
8-OCH_3	3.76, (s)	53.4
7-CH_3	2.74, (s)	29.2

In the mass spectrum the molecular ion peak observed at *m/z* 290 with 41 % abundance, which confirmed the formation of isochromen-1-one **(5h)**. By the removal of pentyl radical from molecular ion, a peak appeared at *m/z* 219 with 27 % abundance and a base peak at *m/z* 191.

The elemental analysis data of 6,8-dimethoxy-7-methyl-3-aryl/alkylisochromen-1-ones **(5a-j)** is presented in Table 1.11.

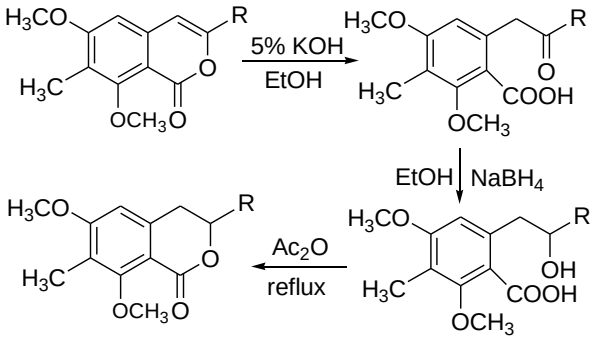
Table 1.11: Elemental analysis data of all the compounds (5a-j)

Compounds	Formulae	Elemental Analysis					
		% Calculated			% Found		
		C	H	N	C	H	N
5a	$C_{20}H_{18}O_4$	74.53	5.59	-	73.14	5.26	-
5b	$C_{18}H_{16}O_4$	72.97	5.41	-	72.73	5.25	-
5c	$C_{19}H_{18}O_4$	73.54	5.81	-	73.17	5.31	-
5d	$C_{18}H_{15}O_6N$	63.34	4.39	4.11	63.20	4.25	3.96
5e	$C_{19}H_{18}O_5$	69.94	5.52	-	69.67	5.33	-
5f	$C_{18}H_{15}O_4Cl$	64.96	4.51	-	65.07	4.23	-
5g	$C_{16}H_{20}O_4$	69.57	7.25	-	69.24	7.16	-
5h	$C_{17}H_{22}O_4$	70.32	7.63	-	70.16	7.26	-
5i	$C_{20}H_{28}O_4$	72.28	8.43		72.10	8.19	
5j	$C_{23}H_{34}O_4$	72.26	8.49		72.13	8.26	
5k	$C_{20}H_{18}O_4$	74.53	5.59		73.14	5.26	

The structures of all the isochromen-1-ones (5a-j) were confirmed by the presence H-4 singlet (s) in ^{1}H NMR, along with other signals in expected regions. The signals for lactonic carbonyl carbon in ^{13}C NMR also helpful for the confirmation of structures of all the compounds.

2.1.3 Synthesis of 2,4-Dimethoxy-3-methyl-6-(2-oxoaryl/alkyl) benzoic acid (6a-j)

Alkaline hydrolysis of 6,8-dimethoxy-7-methyl-3-aryl/alkylisochromen-1-ones **(5a-j)** yields their corresponding 2,4-dimethoxy-3-methyl-6-(2-oxoaryl/alkyl) benzoic acids **(6a-j)** as illustrated in Scheme 1.3.



Scheme 1.3: Synthesis of 2,4-Dimethoxy-3-methyl-6-(2-oxoaryl/alkyl) benzoic acids (6a-j)

The physical data of 2,4-dimethoxy-3-methyl-6-(2-oxoaryl/alkyl) benzoic acids **(6a-j)** is presented in Table 1.12.

Table 1.12: Physical data of all the compounds (6a-j)

Sr. No.	Compounds (R)	M.P. (^{o}C)	Rf[a] Values	Yield (%)
6a	3-Cinnamoyl	158-159	0.3	70
6b	3-Phenyl	168-170	0.4	87
6c	4-*p*-tolyl	178-180	0.35	84
6d	4-Nitrophenyl	145-146	0.3	81
6e	4-Methoxyphenyl	161-162	0.32	86
6f	4-Chlorophenyl	157-158	0.45	82
6g	3-Butyl	136-137	0.37	76
6h	3-Pentyl	139-140	0.33	75
6i	3-Octyl	144-145	0.35	80
6j	3-Undecyl	150-151	0.36	78

[Pet. Ether: ethyl acetate (8:2)]

In IR spectra, the characteristics peaks for ketonic carbonyl carbon absorptions of keto-acid derivatives observed at 1734-1741 cm^{-1} and for carboxylic carbonyl carbon signals ranges from 1707-1721 cm^{-1} respectively.

The FTIR data of 2,4-dimethoxy-3-methyl-6-(2-oxoaryl/alkyl) benzoic acids **(6a-j)** is presented in Table 1.13.

Table 1.13: FTIR spectral data of the compounds (6a-j)

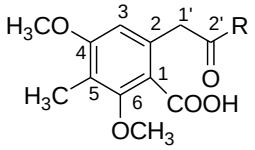
Compounds	C=C-H (cm^{-1})	C=O (keto) (cm^{-1})	C=O (carboxylic) (cm^{-1})	C=C (cm^{-1})	O-H (cm^{-1})
6a	3023	1736	1712	1597	3444
6b	3034	1738	1714	1587	3324
6c	3041	1736	1712	1567	3326
6d	3043	1741	1721	1583	3352
6e	3032	1737	1711	1568	3326

6f	3035	1738	1715	1574	3341
6g	3037	1734	1711	1577	3321
6h	3036	1735	1708	1564	3325
6i	3033	1737	1707	1573	3327
6j	3035	1736	1709	1576	3324

The ^{1}H NMR spectra of keto acids **(6a-j)** shows the characteristic singlets (s) for (H-4, Ar-CH_2) protons in the range of δ 4.24-4.36 ppm. Two characteristics carbonyl carbon signals for ketonic and acidic groups in ^{13}C NMR spectra appeared in the range of δ 195.2-198.5 and δ 164.4-167.5 ppm respectively, in addition to C-4 signals observed at δ 43.5-46.7 ppm.

The ^{1}H and ^{13}C NMR spectral data of 2,4-dimethoxy-3-methyl-6-(2-oxoaryl/alkyl) benzoic acids **(6a-j)** is presented in Table 1.14

Table 1.14: ^{1}H and ^{13}C NMR spectral data of all the compounds (6a-j)



Sr. No.	Compounds (R)	^{1}H NMR(δ) (ppm)	^{13}C NMR(δ) (ppm)
6a	**3-Cinnamoyl**	10.21 (1H, s, -COOH), 7.86-8.11 (5H, m, Ar), 7.74 (2H, d, *J* = 7.6 Hz, H-a), 7.41 (1H, d, *J* = 7.6 Hz, Hb), 7.23 (1H, s, H-5), 4.31 (2H, s, -CH_2), 3.93 (3H, s, -OCH_3), 3.87 (3H, s, -OCH_3), 2.35 (3H, s, Ar-CH_3)	196.8 (ketonic C=O), 167.6 (carboxylic C=O), 146.2 (C-2), 141.5 (C-4), 138.8 (C-1), 138.1 (C-1a), 137.5 (C-1b), 136.7 (C-1'), 131.3 (C-5), 129.4 (C-6), 128.7 (C-2',C-6'), 127.6 (C-3',C-5'), 124.6 (C-4'), 120.4 (C-3), 64.3 (-OCH_3), 63.8 (-OCH_3), 46.7 (-CH_2), 29.6 (Ar-CH_3)
6c	**4-*p*-tolyl**	10.7 (1H, s, -COOH), 8.07 (1H, s, H-5), 7.91 (2H, d, *J* = 7.4 Hz, H-2',H-6'), 7.6 (2H, d, *J* = 7.2 Hz, H-3',H-5'), 4.27 (2H, s, -CH_2), 3.78 (3H, s, -OCH_3), 3.74 (3H, s, -OCH_3), 2.72 (3H, s, Ar-CH_3), 2.32 (3H, s, Ar-CH_3)	195.2 (ketonic C=O), 166.4 (carboxylic C=O), 141.6 (C-1), 138.5 (C-2), 136.2 (C-4), 135.2 (C-1'), 132.4 (C-2',C-6'), 128.6 (C-3',C-5'), 126.5 (C-4'), 122.3 (C-3), 116.7 (C-5), 62.3 (-OCH_3), 61.8 (-OCH_3), 44.5 (C-1''), 28.6 (Ar-CH_3), 27.4 (Ar-CH_3)

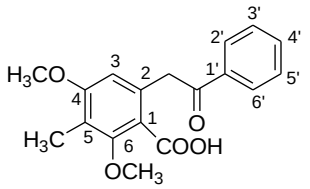
6d	**4-Nitrophenyl**	11.9 (1H, s, -COOH), 8.24 (2H, d, *J* = 7.1 Hz, H-3',H-5'), 8.13 (2H, d, *J* = 7.2 Hz, H-2',H-6'), 7.91 (1H, s, H-5), 4.26 (2H, s, -CH_2), 3.93 (3H, s, -OCH_3), 3.88 (3H, s, -OCH_3), 2.74 (3H, s, Ar-CH_3)	198.5 (ketonic C=O), 167.2 (carboxylic C=O), 142.5 (C-1), 140.7 (C-1'), 138.2 (C-2), 137.4 (C-4'), 136.7 (C-2',C-6'), 135.5 (C-3',C-5'), 134.6 (C-4), 124.3 (C-3), 122.5 (C-3), 117.3 (C-5), 63.2 (-OCH_3), 62.7 (-OCH_3), 45.2 (C-1''), 29.4 (Ar-CH_3)
6e	**4-Methoxyphenyl**	11.9 (1H, s, -COOH), 7.92 (1H, s, Ar-H-5), 7.86 (2H, d, *J* = 7.2 Hz, H-2',H-6'), 7.75 (2H, d, *J* = 7.1 Hz, H-3' H-5'), 4.33 (2H, s, -CH_2), 3.86 (3H, s, -OCH_3), 3.82 (3H, s, -OCH_3), 3.67 (3H, s, 4'-OCH_3), 2.82 (3H, s, Ar-CH_3)	196.4 (ketonic C=O), 167.5 (carboxylic C=O), 141.5 (C-1), 138.2 (C-2), 137.8 (C-4), 136.6 (C-1'), 132.3 (C-2',C-6'), 128.6 (C-2',C-5'), 126.4 (C-4'), 122.5 (C-3), 116.4 (C-5), 62.5 (-OCH_3), 62.2 (-OCH_3), 57.6 (4'-OCH_3), 43.5 (C-1''), 27.6 (Ar-CH_3)
6f	**4-Chlorophenyl**	11.3 (1H, s, -COOH), 8.11 (2H, d, *J* = 7.4 Hz, H-2',H-6'), 7.97 (2H, d, *J* = 7.2 Hz, H-3',H-5'), 7.74 (1H, s, H-5), 4.26 (2H, s, -CH_2), 3.91 (3H, s, -OCH_3), 3.86 (3H, s, -OCH_3), 2.68 (3H, s, Ar-CH_3)	197.6 (ketonic C=O), 167.4 (carboxylic C=O), 143.5 (C-1), 138.2 (C-2), 137.3 (C1'), 136.2 (C-4), 134.5 (C-2',C-6'), 134.3 (C-4'), 132.8 (C-3',(C-5'), 127.5 (C-3), 116.4 (C-5), 62.6 (-OCH_3), 62.2 (-OCH_3), 44.7 (C-1''), 30.3 (Ar-CH_3)
6h	**3-Butyl**	10.2 (1H, s, -COOH), 7.46 (1H, s, H-5), 4.24 (2H, s, -CH_2), 3.88 (3H, s, -OCH_3), 3.83 (3H, s, -OCH_3), 3.67 (2H, t, *J* = 3.7 Hz, H-3'), 2.26 (3H, s, Ar-CH_3), 123-1.65 (6H, m, H-4'-6'), 0.95 (3H, t, *J* = 5.7 Hz, H-7')	197.4 (ketonic C=O), 167.5 (carboxylic C=O), 144.3 (C-2), 137.8 (C-4), 136.5 (C-1), 127.6 (C-6), 121.3 (C-3), 107.4 (C-5), 63.1 (-OCH_3), 62.7 (-OCH_3), 46.7 (C-1''), 43.6 (C-3'), 27.4 (Ar-CH_3), 21.7 (C-4'), 18.5 (C-5'), 15.8 (C-6'), 13.7 (C-7')
6i	**3-Octyl**	10.6 (1H, s, -COOH), 7.76 (1H, s, H-5), 4.25 (2H, s, -CH_2), 3.85 (3H, s, -OCH_3), 3.76 (3H, s, -OCH_3), 3.55 (2H, t, *J* = 3.6 Hz, H-3'), 2.34 (3H, s, Ar-CH_3), 1.56-1.63 (12H, m, H-4'-H-9'), 0.96 (3H, t, *J* = 7.2 Hz, H-10')	195.8 (ketonic C=O), 166.5 (carboxylic C=O), 142.3 (C-2), 138.5 (C-4), 135.7 (C-1), 126.4 (C-6), 118.6 (C-3), 111.4 (C-5), 62.3 (-OCH_3), 61.8 (-OCH_3), 44.7 (C-1''), 41.5 (C-3'), 27.4 (Ar-CH_3), 19.6 (C-4'), 16.2 (C-5'), 15.5 (C-6'), 14.7 (C-7'), 13.8 (C-

			8’), 12.4 (C-9’), 11.5 (C-10’)
6j	**3-undecyl**	10.4 (1H, s, -COOH), 7.83 (1H, s, H-5), 4.26 (2H, s, -CH_2), 3.82 (3H, s, -OCH_3), 3.78 (3H, s, -OCH_3), 3.62 (2H, t, *J* = 3.5 Hz, H-3’), 2.36 (3H, s, Ar-CH_3), 1.52-1.68 (16H, m, H-4’-12’), 0.95 (3H, t, *J* = 7.1 Hz, H-13’)	195.3 (ketonic C=O), 165.4 (carboxylic C=O), 141.5 (C-2), 137.4 (C-4), 135.8 (C-1), 132.4 (C-6), 121.5 (C-3), 112.4 (C-5), 61.4 (-OCH_3), 58.5 (-OCH_3), 44.8 (C-1’’), 41.3 (C-3’), 27.6 (Ar-CH_3), 19.7 (C-4’), 18.3 (C-5’), 17.5 (C-6’), 16.4 (C-7’), 15.8 (C-8’), 14.7 (C-9’), 13.6 (C-10’), 12.5 (C-11’), 11.7 (C-12’) 10.6 (C-13’)

The formation of the keto acid **(6b)** was confirmed by the presence of a singlet (s) for acidic proton at δ 11.4 ppm and another singlet (s) for Ar-CH_2 protons in ^{1}H NMR at δ 4.33 ppm. In ^{13}C NMR spectrum a characteristic carbonyl carbon of keto group appeared at δ 194.4 ppm and a peak for carboxylic acid observed at δ 166.8 ppm.

The ^{1}H and ^{13}C NMR spectral data of the compound **(6b)** is presented in Table 1.15.

Table 1.15: ^{1}H and ^{13}C NMR spectral data of 2,4-Dimethoxy-3-methyl-6-(2-oxophenyl) benzoic acid (6b)



Carbons	δ (ppm) and multiplicity	
	^{1}H NMR	**^{13}C NMR**
keto C=O	-	194.4
-COOH	11.4, (s)	166.8
C-1	-	142.5
C-2	-	132.5
C-3	-	121.7
C-4	-	137.5
C-5	7.87, (s)	115.4
C-6	-	136.8
C-1’	-	137.5
C-2’	8.02, (d), *J* = 7.4 Hz	126.4
C-3’	7.62, (dd), *J* = 7.3, 7.1 Hz	124.6
C-4’	7.76, (dd), *J* = 7.2, 7.1 Hz	122.4
C-5’	7.62, (dd), *J* = 7.3, 7.1 Hz	124.6
C-6’	8.02, (d), *J* = 7.4 Hz	126.4

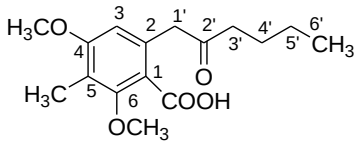
-CH_2	4.23, (s)	44.3
2-OCH_3	3.92, (s)	62.6
4-OCH_3	3.87, (s)	58.3
3-CH_3	2.61, (s)	28.5

The structure of the compound **(6b)** was further confirmed by mass spectrometry. The molecular ion peak appeared at *m/z* 314 with 42 % abundance which confirmed the formation of keto-acid **(6b)**. By the removal of a CO_2 molecule from molecular ion a peak at *m/z* 270 with abundance of 43 %. Base peak appeared at *m/z* 219.

The formation of the keto acid **(6f)** was confirmed by the presence of a singlet (s) for acidic proton at δ 10.7 ppm and another singlet (s) for Ar-CH_2 protons in ^{1}H NMR at δ 4.23 ppm. In ^{13}C NMR spectrum a characteristic carbonyl carbon of keto group appeared at δ 195.2 ppm and a peak for carboxylic acid observed at δ 167.8 ppm.

The ^{1}H and ^{13}C NMR spectral data of the compound **(6f)** is presented in Table 1.16.

Table 1.16: ^{1}H and ^{13}C NMR spectral data of 2,4-Dimethoxy-3-methyl-6-(2-oxohexyl) benzoic acid (6f)



Carbons	**δ (ppm) and multiplicity**	
	^{1}H NMR	**^{13}C NMR**
keto C=O	-	197.6
-COOH	11.3, (s)	167.4
C-1	-	143.5
C-2	-	138.2
C-3	-	127.5
C-4	-	136.2
C-5	7.74 (s)	116.4
C-6	-	126.2
-CH_2	4.26, (s)	137.3
C-2'	8.11, (d), *J* = 7.4 Hz	134.5
C-3'	7.97, (d), *J* = 7.2 Hz	132.8
C-4'	1.63, (m)	134.3
C-5'	7.97, (d), *J* = 7.2 Hz	132.8
C-6'	8.11 (d), *J* = 7.4 Hz	134.5
2-OCH_3	3.91, (s)	62.6
4-OCH_3	3.86, (s)	62.2
3-CH_3	2.68, (s)	30.3

The structure of the compound **(6g)** was further confirmed by mass spectrometry. The molecular ion peak appeared at *m/z* 294 with 23 % abundance, which confirmed the formation of keto-acid **(6g)**. By the removal of a CO_2 molecule from molecular ion a peak observed at *m/z* 248 of 36 % abundance and a base peak appeared at *m/z* 219.

The elemental analysis data of 2,4-dimethoxy-3-methyl-6-(2-oxoaryl/alkyl) benzoic acids **(6a-j)** is presented in Table 1.17.

Table 1.17: Elemental analysis data of all the compounds (6a-j)

Compounds	Formulae	Elemental Analysis					
		% Calculated			% Found		
		C	H	N	C	H	N
6a	$C_{20}H_{20}O_5$	70.58	5.88	-	70.31	5.42	-
6b	$C_{18}H_{18}O_5$	68.78	5.74	-	68.56	5.57	-
6c	$C_{19}H_{20}O_5$	69.49	6.14	-	69.33	5.97	-
6d	$C_{18}H_{17}O_6N$	60.16	4.76	3.91	60.09	4.67	3.76
6e	$C_{19}H_{20}O_6$	66.26	5.81	-	66.14	5.66	-
6f	$C_{18}H_{17}O_5Cl$	61.97	4.86	-	61.86	4.68	-
6g	$C_{16}H_{22}O_5$	65.28	7.54	-	65.15	7.42	-
6h	$C_{17}H_{24}O_5$	67.10	7.79	-	67.02	7.65	-
6i	$C_{20}H_{30}O_5$	68.54	8.63	-	68.36	8.45	-
6j	$C_{23}H_{36}O_5$	70.38	9.23	-	70.27	9.16	-
6k	$C_{20}H_{20}O_5$	70.58	5.88	-	70.31	5.42	-

The structures of 2,4-dimethoxy-3-methyl-6-(2-oxoaryl/alkyl) benzoic acids **(6b-j)** were confirmed by the presence of a singlet in ^{1}H NMR for acidic protons and all other protonic signals within acceptable regions. In ^{13}C NMR the characteristics signals for carboxylic and keto carbonyl carbon also confirms the structures of all these compounds **(6b-j)**.

Sodium borohydride reduction of the keto acids **(6a-j)** afforded the corresponding racemic hydroxy acids, which undergo cyclodehydration on refluxing with Ac_2O afforded (±)-6,8-dimethoxy-7-methyl-3-aryl/alkyl-3,4-dihydroisochromen-1-ones **(7a-j)**.

2.1.4 Synthesis of 6,8-Dimethoxy-7-methyl-3-aryl/alkyl-3,4-dihydroisochromen-1-ones (7a-j)

The physical data of 6,8-dimethoxy-7-methyl-3-aryl/alkyl-3,4-dihydroisochromen-1-ones **(7a-j)** is presented in Table 1.18.

Table 1.18: Physical data of all the compounds (7a-j)

Sr. No.	Compounds (R)	M.P. (^{o}C)	Rf[a] Values	Yield (%)
7a	3-Cinnamoyl	134-135	0.5	68
7b	3-Phenyl	93-94	0.5	86
7c	4-*p*-tolyl	109-110	0.55	84
7d	4-Nitrophenyl	214-215	0.45	74
7e	4-Methoxyphenyl	142-143	0.4	83
7f	4-Chlorophenyl	115-117	0.65	85
7g	3-Butyl	oil	0.5	73
7h	3-Pentyl	oil	0.45	77
7i	3-Octyl	76-77	0.5	83
7j	3-Undecyl	oil	0.5	782

[Pet. ether: ethyl acetate (8:2)]

In IR spectra, the characteristics peaks for ketonic carbonyl carbon absorptions 6,8-dimethoxy-7-methyl-3-aryl/alkyl-3,4-dihydroisochromen-1-ones observed in the range of 1713-1726 cm^{-1}.

The FTIR spectral data of 6,8-dimethoxy-7-methyl-3-aryl/alkyl-3,4-dihydroisochromen-1-ones **(7a-j)** is presented in Table 1.19.

Table 1.19: FTIR spectral data of all the compounds (7a-j)

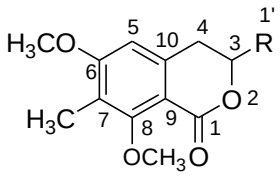
Sr. No.	Compounds. (R)	C=C-H (cm^{-1})	C-H (cm^{-1})	C=O (cm^{-1})	C=C (cm^{-1})
1	3-Cinnamoyl	3023	2914	1723	1567
2	3-Phenyl	3033	2936	1715	1571
3	4-*p*-tolyl	3032	2943	1717	1573
4	4-Nitrophenyl	3035	2946	1726	1583
5	4-Methoxyphenyl	3037	2937	1724	1574
6	4-Chlorophenyl	3029	2934	1721	1576
7	3-Butyl	3038	2973	1718	1587
8	3-Pentyl	3051	2964	1712	1557
9	3-Octyl	3036	2972	1716	1565
10	3-Undecyl	3022	2923	1713	1543

The ^{1}H NMR spectra of 6,8-dimethoxy-7-methyl-3-aryl/alkyl-3,4-dihydroisochromen-1-ones **(7a-j)** shows two characteristics double doublets (dd) for (H-4,4') protons in the range of δ 3.11-3.38 ppm and another double doublet (dd) for H-3 proton

of aryl derivatives from δ 5.34-5.46 ppm and multiplets (m) of H-3 protons for alkyl derivatives of 3,4-dihydroisochromen-1-ones. In ^{13}C NMR spectra characteristics lactonic carbonyl carbon signals were appeared in the range of δ 195.2-198.5 ppm and C-4 signals from δ 42.3-44.6 ppm.

The ^{1}H and ^{13}C NMR spectral data of 6,8-dimethoxy-7-methyl-3-aryl/alkyl-3,4-dihydroisochromen-1-ones **(7a-j)** is presented in Table 1.20.

Table 1.20: ^{1}H and ^{13}C NMR spectral data of all the compounds (7a-j)



Sr. No.	Compounds (R)	^{1}H NMR(δ) (ppm)	^{13}C NMR(δ) (ppm)
7a	3-Cinnamoyl	7.28-7.83 (5H, m, Ar), 6.81 (1H, d, *J* = 7.4 Hz, Ha), 6.63 (1H, d, *J* = 7.4 Hz, Hb), 6.21 (1H, s, H-5), 5.34 (1H, dd, J_{trans} = 12.2 Hz, J_{cis} = 3.1 Hz, H-3), 3.81 (3H, s, -OCH_3), 3.78 (3H, s, -OCH_3), 3.38 (1H, dd, J_{gem} = 15.8 Hz, J_{trans} = 12.2 Hz, H-4), 3.13 (1H, dd, J_{gem} = 12.1 Hz, J_{cis} = 3.5 Hz, H-4'), 2.47 (1H, s, -CH_3	168.4 (C=O), 144.5 (C-6), 143.6 (C-8), 141.7 (C-10), 138.6 (C-1'), 137.2 (C-1a), 136.4 (C-1b), 134.3 (C-9), 131.8 (C-7), 130.5 (C-5), 128.5 (C-2',C-6'), 127.3 (C-3',C-5'), 123.6 (C-4'), 84.5 (C-3), 56.6 (-OCH_3), 56.3 (-OCH_3), 43.5 (C-4); 28.7 (Ar-CH_3)
7b	3-Phenyl	7.87 (2H, d, *J* = 7.2 Hz, H-2',H-6'), 7.74 (2H, dd, *J* = 7.1,6.8 Hz, H-3',H-5'), 7.65 (1H, m, H-4'), 6.86 (1H, s, Ar-H-5), 5.43 (1H, dd, J_{trans} = 12.2 Hz, J_{cis} = 3.4 Hz, H-3), 3.85 (3H, s, -OCH_3), 3.78 (3H, s, -OCH_3), 3.32 (1H, dd, J_{gem} = 16.1 Hz, J_{trans} = 12.2 Hz, H-4), 3.17 (1H, dd, J_{gem} = 12.4 Hz, J_{cis} = 3.6 Hz, H-4'), 2.84 (3H, s, Ar-CH_3)	167.3 (C=O), 142.3 (C-6), 141.6 (C-8), 139.5 (C-10), 138.1 (C-1'), 137.2 (C-9), 132.8 (C-7), 131.7 (C-5), 130.6 (C-2',C-6'), 124.5 (C-3',C-5'), 118.4 (C-4'), 82.6 (C-3), 57.2 (6-OCH_3, 56.6 (8-OCH_3), 43.2 (C-4)
7c	4-*p*-tolyl	7.81 (2H, d, *J* = 6.8 Hz, H-3',H-5'), 7.73 (2H, d, *J* = 7.2 Hz, H-2',H-6'), 6.68 (1H, s, H-5), 5.34 (1H, dd, J_{trans} = 12.4 Hz, J_{cis}= 3.7 Hz, H-3), 3.83 (3H, s, 6-OCH_3), 3.76 (3H, s, 8-OCH_3), 3.34 (1H, dd, J_{gem} = 16.2 Hz, J_{trans} = 12.4 Hz, H-4), 3.15 (1H, dd, J_{gem} =	166.3 (C=O), 141.5 (C-6), 140.7 (C-8), 139.2 (C-10), 138.4 (C-1'), 136.3 (C-9), 133.6 (C-4'), 132.7 (C-2',C-6'), 131.2 (C-5), 130.5 (C-3',C-5'), 127.4 (C-7), 81.5 (C-3), 56.7 (-OCH_3), 56.2 (-OCH_3), 42.6

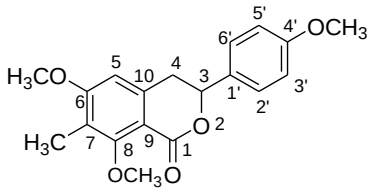
		12.4 Hz, J_{cis} = 3.7 Hz, H-4), 2.81 (3H, s, Ar-CH_3)	(C-4), 27.3 (Ar-CH_3), 23.7 (4'-CH_3)
7d	4-Nitrophenyl	7.94 (2H, d, *J* = 6.8 Hz, H-3',H-5'), 7.82 (2H, d, *J* = 7.1 Hz, H-2',H-6'), 6.87 (1H, s, H-5), 5.46 (1H, dd, J_{trans} = 12.2 Hz, J_{cis} = 3.6 Hz, H-3), 3.93 (3H, s, -OCH_3), 3.86 (3H, s, -OCH_3), 3.35 (1H, dd, J_{gem}= 15.8 Hz, J_{trans} = 12.1 Hz, H-4), 3.18 (1H, dd, J_{gem} = 12.2 Hz, J_{cis} = 3.6 Hz, H-4), 2.87 (3H, s, Ar-CH_3)	167.6 (C=O), 143.2 (C-6), 142.5 (C-8), 140.4 (C-10), 139.6 (C-1'), 138.5 (C-9), 136.3 (C-4'), 134.2 (C-2',C-6'), 133.4 (C-5), 131.5 (C-3',C-5'), 128.7 (C-7), 83.6 (C-3), 58.4 (-OCH_3), 57.8 (-OCH_3), 44.6 (C-4), 29.4 (Ar-CH_3)
7f	4-Chlorophenyl	7.91 (1H, d, *J* = 7.2 Hz, H-3',H-5'), 7.83 (1H, d, *J* = 6.8 Hz, H-2',H-6'), 6.85 (1H, s, H-5), 5.39 (1H, dd, J_{trans} = 12.4 Hz, J_{cis} = 3.6 Hz, H-3), 3.92 (3H, s, -OCH_3), 3.87 (3H, s, -OCH_3), 3.37 (1H, dd, J_{gem} = 16.2 Hz, J_{trans} = 12.2 Hz, H-4), 3.16 (1H, dd, J_{gem} = 12.4 Hz, J_{cis} = 3.6 Hz, H-4), 2.65 (3H, s, Ar-CH_3)	164.6 (C=O), 143.4 (C-6), 142.7 (C-8), 141.2 (C-10), 139.4 (C-1'), 137.8 (C-9), 136.7 (C-4'), 133.5 (C-2',C-6'), 132.3 (C-5), 131.4 (C-3',C-5'), 128.6 (C-7), 88.3 (C-3), 56.3 (-OCH_3), 55.8 (-OCH_3), 44.3 (C-4), 28.8 (Ar-CH_3)
7h	3-Butyl	6.87 (1H, s, H-5), 4.57-4.64 (1H, m, H-3), 3.83 (3H, s, -OCH_3), 3.78 (3H, s, -OCH_3), 3.34 (1H, dd, J_{gem} = 16.4 Hz, J_{trans} = 12.8 Hz, H-4), 3.11 (1H, dd, J_{gem} = 16.2 Hz, J_{cis} = 3.6 Hz, H-4), 2.67 (3H, s, Ar-CH_3), 2.36-2.41 (2H, m, H-1'), 1.27-1.56 (6H, m, H-2'-4'), 0.92 (3H, t, *J* = 5.8, H-5')	168.5 (C=O), 139.8 (C-10), 138.7 (C-8), 137.8 (C-6), 136.3 (C-9), 126.4 (C-5), 122.5 (C-7), 80.2 (C-3), 55.8 (-OCH_3), 55.4 (-OCH_3), 42.6 (C-4), 38.5 (C-1'), 27.6 (Ar-CH_3), 19.4 (C-2'), 14.5 (C-3'), 12.6 (C-4'), 11.5 (C-5')
7i	3-Octyl	6.83 (1H, s, Ar-H-5), 4.43-4.52 (1H, m, H-3), 3.82 (3H, s, -OCH_3), 3.77 (3H, s, -OCH_3), 3.44 (1H, dd, J_{gem} = 16.2 Hz, J_{trans} = 12.4 Hz, H-4), 3.16 (1H, dd, J_{gem} = 16.2 Hz, J_{cis} = 3.6 Hz, H-4), 2.66 (3H, s, Ar-CH_3), 2.42 (2H, *J* = 6.1 Hz, H-1'), 1.31-1.62 (12H, m, H-2'-7'), 0.91 (3H, t, *J* = 5.8, H-8')	165.6 (C=O), 140.1 (C-10), 138.4 (C-6), 137.6 (C-8), 136.7 (C-9), 126.5 (C-5), 123.6 (C-7), 81.5 (C-3), 56.7 (-OCH_3), 56.3 (-OCH_3), 42.7 (C-4), 38.6 (C-1'), 28.5 (Ar-CH_3), 19.2 (C-2'), 14.7 (C-3'), 13.2 (C-4'), 12.5 (C-5'), 11.8 (C-6'), 11.2 (C-7'), 10.4 (C-8')

7j	3-Undecyl	6.78 (1H, s, Ar-H-5), 4-38-4.47 (1H, m, H-3), 3.85 (3H, s, -OCH_3), 3.74 (3H, s, -OCH_3), 3.36 (1H, dd, J_{gem} = 16.1 Hz, J_{trans} = 12.2 Hz, H-4), 3.13 (1H, dd, J_{gem} = 16.1 Hz, J_{cis} = 3.6 Hz, H-4), 2.72 (3H, s, Ar-CH_3), 2.34 (2H, *J* = 6.1 Hz, H-1'), 1.32-1.56 (12H, m, H-2'-10'), 0.93 (3H, t, *J* = 5.8 Hz, H-11')	166.2 (C=O), 140.3 (C-10), 138.6 (C-6), 137.4 (C-8), 136.8 (C-9), 126.3 (C-5), 122.7 (C-7), 80.8 (C-3), 57.6 (-OCH_3), 57.1 (-OCH_3), 42.3 (C-4), 38.6 (C-1'), 28.5 (Ar-CH_3), 19.5 (C-2'), 15.6 (C-3'), 14.2 (C-4'), 13.5 (C-5'), 12.8 (C-6'), 12.4 (C-7'), 11.7 (C-8'), 11.2 (C-9'), 10.8 (C-10'), 10.3 (C-11')

The ^{1}H NMR spectrum confirmed the formation of 6,8-dimethoxy-7-methyl-3-(4-methoxyphenyl)-3,4-dihydroisochromen-1-one **(7e)** by the presence of two double doublets for H-4 protons at δ 3.15 ppm and δ 3.37 ppm and a double doublet for H-3 proton at δ 5.41 ppm, along with the disappearance of a singlet of carboxylic acid proton. In ^{13}C NMR spectrum by the lactonic carbonyl carbon signal observed at δ 166.4 ppm.

The ^{1}H and ^{13}C NMR spectral data of the compound **(7e)** is presented in Table 1.21.

Table 1.21 ^{1}H and ^{13}C NMR spectral data of 6,8-Dimethoxy-3-(4-methoxyphenyl)-7-methyl-3,4-dihydroisochromen-1-one (7e)



Carbons	δ (ppm) and multiplicity	
	^{1}H NMR	**^{13}C NMR**
C-1	-	166.4
C-3	5.41, (dd), *J* = 12.2, 3.6 Hz	82.8
C-4	3.15, (dd), *J* = 12.4, 3.6 Hz, 3.37, (dd), *J* = 16.2, 12.4 Hz	42.5
C-10	-	140.5
C-5	6.76, (s)	131.3
C-6	-	143.1
C-7	-	128.5
C-8	-	142.4
C-9	-	137.5
C-1'	-	138.6
C-2'	7.72, (d), *J* = 7.1 Hz	132.4

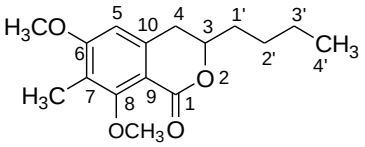
C-3'	7.83, (d), *J* = 6.8 Hz	126.6
C-4'-OCH_3	53.4, (s)	134.2
C-5'	7.83, (d), *J* = 6.8 Hz	126.6
C-6'	7.72, (d), *J* = 7.1 Hz	132.4
6-OCH_3	3.87, (s)	57.4
8-OCH_3	3.74, (s)	56.3
7-CH_3	2.83, (s)	28.6

The formation of 6,8-dimethoxy-3-(4-methoxyphenyl)-7-methyl-3,4-dihydroisochromen-1-one **(7e)** also confirmed by mass spectrometry. The molecular ion peak appeared at *m/z* 328 with 47 % abundance. By the removal of 4-methoxyphenyl radical from molecular ion, a peak of 28 %. abundance appeared at *m/z* 221 and a base peak observed at *m/z* 192.

The ^{1}H NMR spectrum confirmed the formation of of 6,8-dimethoxy-3-(4-butyl)-7-methyl-3,4-dihydroisochromen-1-one **(7g)** by the presence of two double doublets (dd) for H-4 protons at δ 3.14 and δ 3.38 ppm and a multiplet (m) for H-3 proton at δ 4.52 ppm. In ^{13}C NMR spectrum by the lactonic carbonyl carbon signal observed at δ 166.2 ppm.

The ^{1}H and ^{13}C NMR spectral data of compound **(7g)** is presented in Table 1.22.

Table 1.22: ^{1}H and ^{13}C NMR spectral data of 6,8-Dimethoxy-3-(4-butyl)-7-methyl-3,4-dihydroisochromen-1-one (7g)



Carbons	**δ (ppm) and multiplicity**	
	^{1}H NMR	**^{13}C NMR**
C-1	-	166.2
C-3	4.52, (m)	81.3
C-4	3.14, (dd), *J* = 16.2, 3.6 Hz, 3.38, (dd), *J* = 16.2, 12.6 Hz	42.6
C-10	-	140.4
C-5	6.78, (s)	126.4
C-6	-	139.7
C-7	-	118.2
C-8	-	138.6
C-9	-	136.4
C-1'	2.47, (m)	37.5
C-2'	1.46, (m)	19.2
C-3'	1.23, (m)	14.5
C-4'	0.93, (t), *J* = 6.7 Hz	12.4

6-OCH_3	3.84, (s)	56.5
8-OCH_3	3.75, (s)	55.7
7-CH_3	2.81, (s)	28.4

The formation of 6,8-dimethoxy-3-(4-butyl)-7-methyl-3,4-dihydroisochromen-1-one **(7g)** was also confirmed by mass spectrometry. The molecular ion peak appeared at *m/z* 278 with 54 % abundance. By the removal of butyl radical from molecular ion, a peak with 17 % abundance was appeared at *m/z* 221 and a base peak observed at *m/z* 192.

The elemental analysis data of 6,8-dimethoxy-7-methyl-3-aryl/alkyl-3,4-dihydro-isochromen-1-ones **(7a-j)** is presented in Table 1.23.

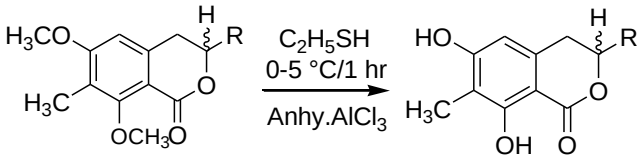
Table 1.23: Elemental analysis data of all the compounds (7a-j)

Compounds	**Formulae**	**Elemental Analysis**					
		% Calculated			**% Found**		
		C	**H**	**N**	**C**	**H**	**N**
7a	$C_{20}H_{20}O_4$	74.07	6.17	-	73.96	6.04	-
7b	$C_{18}H_{18}O_4$	72.47	6.05	-	72.35	5.87	-
7c	$C_{19}H_{20}O_4$	73.04	6.44	-	72.93	6.26	-
7d	$C_{18}H_{17}O_6N$	62.96	4.98	4.07	69.74	4.82	3.96
7e	$C_{19}H_{20}O_5$	69.52	6.08	-	69.35	5.93	-
7f	$C_{18}H_{17}O_4Cl$	64.94	5.13	-	64.82	5.07	-
7g	$C_{16}H_{22}O_4$	69.05	7.96	-	68.94	7.85	-
7h	$C_{17}H_{24}O_4$	69.84	8.26	-	69.72	8.11	-
7i	$C_{20}H_{30}O_4$	71.83	9.05	-	71.65	8.87	-
7j	$C_{23}H_{36}O_4$	73.36	9.65	-	71.23	9.54	-
7k	$C_{20}H_{20}O_4$	74.07	6.17	-	73.96	6.04	-

The structures of 6,8-dimethoxy-7-methyl-3-aryl/alkyl-3,4-dihydroisochromen-1-ones **(7b-j)** were confirmed by the presence of a characteristic double doublets (dd) in ^1H NMR for H-4,4' protons and all other protonic signals appeared within acceptable regions. In ^{13}C NMR the characteristics signals for lactonic carbonyl carbon also confirms the structures of all these compounds **(7b-j)**.

2.1.5 Synthesis of 6,8-Dihydroxy-7-methyl-3-aryl/alkyl-3,4-dihydroisochromen-1-ones (8a-j)

Demethylation of the 6,8-dihydroxy-7-methyl-3-aryl/alkylisochromen-1-ones **(7a-j)** was achieved by using ethanethiol (C_2H_5SH) and an excess of anhydrous $AlCl_3$ to furnish the corresponding 6,8-dihydroxy-7-methyl-3-aryl/alkyl-3,4-dihydroisochromen-1-ones **(8a-j)**.



Scheme 1.4: Synthesis of 6,8-Dihydroxy-7-methyl-3-aryl/alkyl-3,4-dihydro-isochromen-1-ones (8a-j)

The physical data of 6,8-dihydroxy-7-methyl-3-aryl/alkyl-3,4-dihydroisochromen -1-ones **(8a-j)** is presented in Table 1.24

Table 1.24: Physical data of all the compounds (8a-j)

Sr. No.	Compounds (R)	M.P. (^oC)	Rf[a] Values	Yield (%)
8a	3-Cinnamoyl	168-169	0.3	73
8b	3-Phenyl	124-125	0.4	84
8c	4-*p*-tolyl	113-114	0.3	83
8d	4-Nitrophenyl	137-138	0.25	81
8e	4-Methoxyphenyl	161-162	0.25	80
8f	4-Chlorophenyl	126-127	0.35	87
8g	3-Butyl	84-85	0.45	73
8h	3-Pentyl	91-92	0.3	75
8i	3-Octyl	110-111	0.3	77
8j	3-Undecyl	117-118	0.31	78

[Pet. ether: ethyl acetate (8:2)]

In IR spectra, the characteristics carbonyl carbon absorptions peaks of 6,8-dihydroxy-7-methyl-3-aryl/alkyl-3,4-dihydroisochromen-1-ones **(8a-j)** observed in the range of 1717-1726 $cm^{-1}$and a broad (O-H) absorption bands appeared at 3446-3484 cm^{-1}.

The FTIR spectral data of 6,8-dihydroxy-7-methyl-3-alkyl/aryl-3,4-dihydro-isochromen-1-ones **(8a-j)** is presented in Table 1.25.

Table 1.25: FTIR spectral data of all the compounds (8a-j)

Sr. No.	Compounds (R)	(C=C-H) cm^{-1}	(C=O) cm^{-1}	(C=C) cm^{-1}	(O-H) cm^{-1}
8a	3-Cinnamoyl	3035	1712	1567	3446
8b	3-Phenyl	3031	1723	1581	3482
8c	4-*p*-tolyl	3035	1724	1575	3464
8d	4-Nitrophenyl	3037	1723	1578	3484

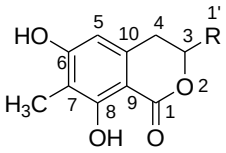
8e	4-Methoxyphenyl	3042	1726	1582	3461
8f	4-Chlorophenyl	3036	1721	1575	3472
8g	3-Butyl	3027	1719	1574	3466
8h	3-Pentyl	3025	1717	1576	3458
8i	3-Octyl	3026	1722	1565	3467
8j	3-Undecyl	3028	1720	1583	3456

The 6,8-dihydroxy-7-methyl-3-aryl/alkyl-3,4-dihydroisochromen-1-ones **(8a-j)** were characterized by the absence of both methoxy singlets and presence of singlets (s) for hydroxyl protons in ^{1}H NMR spectra. In ^{13}C NMR spectra, the signals for methoxy carbons are also absent.

The ^{1}H NMR spectra of 3,4-dihydroisochromen-1-ones **(7a-j)** shows two characteristic double doublets (dd) for (H-4,4') protons in the range of δ 3.22-3.53 ppm and another double doublet (dd) for H-3 proton of aryl derivatives from δ 5.32-5.48 ppm and multiplets (m) of H-3 protons for alkyl derivatives of 3,4-dihydroisochromen-1-ones. In ^{13}C NMR spectra characteristics lactonic carbonyl carbon signals appeared in the range of δ 165.6-168.5 ppm and C-4 signals observed at δ 43.3-44.8 ppm.

The ^{1}H and ^{13}C NMR spectral data of 6,8-dihydroxy-7-methyl-3-aryl/alkyl-3,4-dihydroisochromen-1-ones **(8a-j)** is presented in Tables 1.26.

Table 1.26: ^{1}H and ^{13}C NMR spectral data of all the compounds (8a-j)



Sr. No.	Compounds (R)	^{1}H NMR(δ) (ppm)	^{13}C NMR(δ) (ppm)
8a	**Cinnamoyl**	8.13-7.43 (5H, m, Ar), 7.21 (1H, s, H-5), 6.78 (1H, d, *J* = 6.9 Hz, Ha), 6.43 (1H, d, *J* = 6.9 Hz, Hb), 5.43 (1H, dd, J_{trans} = 12 Hz , J_{cis} = 3.2 Hz, H-3), 3.53 (1H, dd, J_{gem} = 15.4 Hz, J_{trans} = 12.1 Hz , H-4), 3.31 (1H, dd, J_{gem} = 12.2 Hz , J_{cis} = 3.4 Hz , H-4'), 4.81 (2H, s, -OH), 2.51 (3H, s, -CH_3)	168.5 (=O), 146.3 (C-6) , 145.6 (C-8), 141.6 (C-10), 139.5 (C-1'), 138.6 (C-1a), 137.4 (C-1b), 135.2 (C-9), 132.3 (C-7), 131.5 (C-5), 129.4 (C-2',C-6'), 126.4 (C-3',C-5'), 125.3 (C-4'), 85.4 (C-3), 44.5 (C-4); 29.4 (Ar-CH_3)
8c	**4-*p*-tolyl**	7.88 (2H, d, *J* = 7.2 Hz, H-3',H-5'), 7.71 (2H, d, *J* = 7.1 Hz, H-2',H-6'), 6.87 (1H, s, H-5), 5.34 (1H, dd, J_{trans} = 12.2	167.6 (C=O), 148.5 (C-6), 147.3 (C-8), 142.6 (C-10), 140.5 (C-1'), 136.3 (C-9), 134.2 (C-

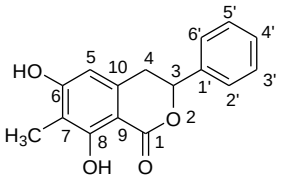
		Hz, J_{cis} = 3.7 Hz, H-3), 4.84 (2H, s, -OH), 3.43 (1H, dd, J_{gem} = 16.3 Hz, J_{trans} = 12.2 Hz, H-4), 3.22 (1H, dd, J_{gem} = 12.2 Hz, J_{cis} = 3.8 Hz, H-4'), 2.86 (3H, s, Ar-CH_3)	4'), 132.5 (C-2',C-6'), 130.6 (C-5), 130.8 (C-3',C-5'), 128.7 (C-7), 83.6 (C-3), 44.3 (C-4), 29.4 (Ar-CH_3), 23.6 (4'-CH_3)
8d	**4-Nitrophenyl**	8.03 (1H, d, J = 7.1 Hz, H-3',H-5'), 7.95 (1H, d, J = 6.7 Hz, H-2',H-6'), 6.96 (1H, s, H-5), 5.48 (1H, dd, J_{trans} = 12.1 Hz, J_{cis} = 3.5 Hz, H-3), 4.87 (2H, s, -OH), 3.51 (1H, dd, J_{gem} = 16.2 Hz, J_{trans} = 12.1 Hz, H-4), 3.32 (1H, dd, J_{gem} = 12.1 Hz, J_{cis} = 3.6 Hz, H-4'), 2.87 (3H, s, Ar-CH_3)	167.6 (C=O), 148.7 (C-6), 147.6 (C-8), 143.8 (C-10), 142.4 (C-1'), 139.2 (C-9), 138.5 (C-4'), 134.6 (C-2',C-6'), 133.4 (C-5), 132.7 (C-3',C-5'), 129.3 (C-7), 83.8 (C-3), 44.8 (C-4), 29.8 (Ar-CH_3)
8e	**4-Methoxyphenyl**	7.85 (2H, d, J = 7.3 Hz, H-3',H-5'), 7.68 (2H, d, J = 7.1 Hz, H-2',H-6'), 6.92 (1H, s, H-5), 5.32 (1H, dd, J_{trans} = 12.4 Hz, J_{cis} = 3.7 Hz, H-3), 4.82 (2H, s, -OH), 3.42 (1H, dd, J_{gem} = 16.2 Hz, J_{trans} = 12.1 Hz, H-4), 3.25 (1H, dd, J_{gem} = 12.1 Hz, J_{cis} = 3.8 Hz, H-4'), 2.84 (3H, s, Ar-CH_3)	166.3 (C=O), 148.2 (C-6), 147.5 (C-8), 142.4 (C-10), 140.3 (C-1'), 136.7 (C-9), 133.4 (C-4'), 131.6 (C-2',C-6'), 131.7 (C-5), 130.3 (C-3',C-5'), 128.5 (C-7), 83.4 (C-3), 56.5 (4'-OCH_3), 44.2 (C-4), 29.5 (Ar-CH_3)
8f	**4-Chlorophenyl**	7.93 (1H, d, J = 7.1 Hz, H-3',H-5'), 7.88 (1H, d, J = 6.8 Hz, H-2',H-6'), 6.93 (1H, s, H-5), 5.41 (1H, dd, J_{trans} = 12.1 Hz, J_{cis} = 3.6 Hz, H-3), 4.85 (2H, s, -OH), 3.46 (1H, dd, J_{gem} = 16.1 Hz, J_{trans}= 12.2 Hz, H-4), 3.28 (1H, dd, J_{gem} = 12.2 Hz, J_{cis}= 3.7 Hz, H-4'), 2.85 (3H, s, Ar-CH_3)	165.2 (C=O), 148.5 (C-6), 147.4 (C-8), 143.5 (C-10), 141.5 (C-1'), 138.3 (C-9), 137.7 (C-4'), 133.5 (C-2',C-6'), 132.1 (C-5), 131.3 (C-3',C-5'), 128.7 (C-7), 83.5 (C-3), 44.6 (C-4), 29.6 (Ar-CH_3)
8g	**3-Butyl**	7.09 (1H, s, H-5), 5.22-5.27 (1H, m, H-3), 4.64 (2H, s, -OH), 3.42 (1H, dd, J_{gem} = 16.2 Hz, J_{trans} = 12.6 Hz, H-4), 3.21 (1H, dd, J_{gem} = 16.2 Hz, J_{cis} = 3.8 Hz, H-4), 2.76 (3H, s, Ar-CH_3), 2.24 (2H, t, J = 6.1 Hz, H-1'), 1.22-1.83 (4H, m, H-2',H-3'), 0.93 (3H, t, J = 5.8 Hz, H-4')	165.7 (C=O), 148.5 (C-6), 147.4 (C-8), 142.3 (C-10), 140.5 (C-9), 128.6 (C-5), 118.5 (C-7), 81.7 (C-3), 43.6 (C-4), 38.5 (C-1'), 29.5 (Ar-CH_3), 19.3 (C-2'), 14.2 (C-3'), 12.5 (C-4')

8i	**3-octyl**	7.16 (1H, s, H-5), 5.28-5.33 (1H, m, H-3), 4.64 (2H, s, -OH), 3.47 (1H, dd, J_{gem} = 16.2 Hz, J_{trans} = 12.4 Hz, H-4), 3.26 (1H, dd, J_{gem} = 16.2 Hz, J_{cis} = 3.8 Hz, H-4'), 2.64 (3H, s, Ar-CH_3), 2.23 (2H, t, J = 6.1 Hz, H-1'), 1.34-1.86 (12H, m, H-2',H-3',H-4',H-5',H-6',H-7'), 0.94 (3H, t, J = 5.8 Hz, H-8')	165.8 (C=O), 148.5 (C-6), 147.4 (C-8), 142.6 (C-10), 138.3 (C-9), 124.2 (C-7), 118.5 (C-5), 81.4 (C-3), 43.3 (C-4), 38.5 (C-1'), 29.3 (Ar-CH_3), 19.7 (C-2'), 14.5 (C-3'), 13.8 (C-4'), 13.2 (C-5'), 12.6 (C-6'), 11.7 (C-7'), 11.2 (C-8')
8j	**3-undecyl**	7.17 (1H, s, H-5), 5.31-5.36 (1H, m, H-3), 4.72 (2H, s, -OH), 3.44 (1H, dd, J_{gem} = 16.2 Hz, J_{trans}= 12.2 Hz, H-4), 3.25 (1H, dd, J_{gem} = 16.2 Hz, J_{cis} = 3.6 Hz, H-4), 2.71 (3H, s, Ar-CH_3), 2.26 (2H, t, J = 6.1 Hz, H-1'), 1.32-1.87 (18H, m, H-2',H-3',H-4',H-5',H-6', H-7', H-8', H-9',H-10'), 0.92 (3H, t, J = 5.8 Hz, H-11')	165.6 (C=O), 148.3 (C-6), 147.5 (C-8), 142.4 (C-10), 138.7 (C-9), 124.5 (C-7), 119.2 (C-5), 81.6 (C-3), 43.5 (C-4), 38.7 (C-1'), 29.4 (Ar-CH_3), 19.6 (C-2'), 18.5 (C-3'), 14.8 (C-4'), 14.2 (C-5'), 13.6 (C-6'), 12.7 (C-7'), 12.1 (C-8'), 11.8 (C-9'), 11.3 (C-10'), 10.4 (C-11')

The ^{1}H NMR spectrum confirmed the formation of 6,8-dihydroxy-7-methyl-3-phenyl-3,4-dihydroisochromen-1-ones **(8b)** by the disappearance of methoxy signals and presence of singlet (s) for hydroxy protons at δ 4.67 ppm. In ^{13}C NMR spectrum the lactonic carbonyl carbon peak appeared at δ 166.8 ppm.

The ^{1}H and ^{13}C NMR spectral data of the compound **(8b)** is presented in Table 1.27.

Table 1.27: ^{1}H and ^{13}C NMR spectral data of 6,8-Dihydroxy-7-methyl-3-phenyl-3,4-dihydroisochromen-1-one (8b)



Carbons	δ (ppm) and multiplicity	
	^{1}H NMR	**^{13}C NMR**
C-1	-	166.8
C-3	5.35, (dd), J = 12.2, 3.8 Hz	82.4
C-4	3.38, (dd), J = 16.4, 12.2 Hz, 3.16, (dd), J = 12.2, 3.7 Hz	44.4

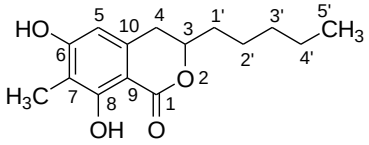
C-5	6.87, (s)	122.7
C-6	-	148.5
C-7	-	132.3
C-8	-	147.2
C-5	6.87, (s)	122.7
C-1'	-	138.4
C-2'	7.95, (d), *J* = 6.8 Hz	128.5
C-3'	7.73, (dd), *J* = 6.7, 5.8 Hz	126.2
C-4'	7.64, (dd), *J* = 6.4, 5.6 Hz	118.6
C-5'	7.73, (dd), *J* = 6.7, 5.8 Hz	126.2
C-6'	7.95, (d), *J* = 6.8 Hz	128.5
6-OH	4.67, (s)	-
7-CH_3	2.64, (s)	29.3
8-OH	4.67, (s)	-
C-9	-	137.5
C-10	-	142.5

The molecular ion peak appeared at *m/z* 270 with 39 % abundance, confirmed the formation of compound **(8b)** and a base peak observed at *m/z* 164.

The ^{1}H NMR spectrum confirmed the formation of 6,8-dihydroxy-7-methyl-3-pentyl-3,4-dihydroisochromen-1-one **(8h)** by the disappearance of methoxy signals and presence of characteristic singlet (s) for hydroxy protons at δ 4.71 ppm. In ^{13}C NMR spectrum the lactonic carbonyl carbon peak appeared at δ 165.4 ppm.

The ^{1}H and ^{13}C NMR spectral data of the 6,8-dihydroxy-7-methyl-3-pentyl-3,4-dihydroisochromen-1-one **(8h)** is presented in Table 1.28.

Table 1.28: ^{1}H and ^{13}C NMR spectral data of 6,8-Dihydroxy-7-methyl-3-pentyl-3,4-dihydroisochromen-1-one (8h)



Carbons	**δ (ppm) and multiplicity**	
	^{1}H NMR	**^{13}C NMR**
C-1	-	165.4
C-3	5.32-5.36, (m)	81.5
C-4,4	3.23, (dd), *J* = 16.2, 3.8 Hz, 3.46, (dd), *J* = 16.2, 12.4 Hz	43.4
C-10	-	142.3
C-5	7.13, (m)	128.6
C-6	-	148.2
C-7	-	118.4
C-8	-	147.6
C-9	-	140.5

C-1'	2.25, (m)	38.7
C-2'	1.63, (m)	19.2
C-3'	1.54, (m)	17.6
C-4'	1.26, (m)	14.8
C-5'	0.92, (t), *J* = 6.8 Hz	12.4
6-OH	4.71, (s)	-
8-OH	4.71, (s)	-
7-CH_3	2.73, (s)	29.6

The molecular ion peak appeared at *m/z* 264 with 61 % abundance, confirmed the formation of compound **(8h)** and a base peak observed at *m/z* 164.

The elemental analysis data of the 6,8-dihydroxy-7-methyl-3-aryl/alkyl-3,4-dihydroisochromen-1-ones **(8a-j)** is presented in Table 1.29.

Table 1.29: Elemental analysis data of all the compounds (8a-j)

Compounds	**Formulae**	**Elemental Analysis**					
		% Calculated			**% Found**		
		C	**H**	**N**	**C**	**H**	**N**
8a	$C_{18}H_{16}O_4$	72.97	5.41	-	72.82	5.24	-
8b	$C_{16}H_{14}O_4$	71.12	5.17	-	71.02	5.09	-
8c	$C_{17}H_{16}O_4$	71.82	5.66	-	71.68	5.42	-
8d	$C_{16}H_{11}O_6N$	61.34	3.52	4.47	61.27	3.41	4.36
8e	$C_{17}H_{16}O_5$	68.02	5.34	-	67.88	5.22	-
8f	$C_{16}H_{13}O_4Cl$	63.04	4.26	-	62.95	4.14	-
8g	$C_{14}H_{18}O_4$	67.16	7.24	-	67.07	7.16	-
8h	$C_{15}H_{20}O_4$	68.17	7.58	-	68.08	7.44	-
8i	$C_{18}H_{26}O_4$	70.56	8.54	-	70.38	8.43	-
8j	$C_{21}H_{32}O_4$	72.36	9.25	-	72.28	9.16	-
8k	$C_{18}H_{16}O_4$	72.97	5.41	-	72.82	5.24	-

2.1.6 Synthesis of 4-Butyl-3,5-dimethoxyhomophathalic acid (8)

4-Butyl-3,5-dimethoxyhomophthalic acid **(8)** was synthesized starting from commercially available 3,4,5-trimethoxybenzaldehyde dimethyl acetal.

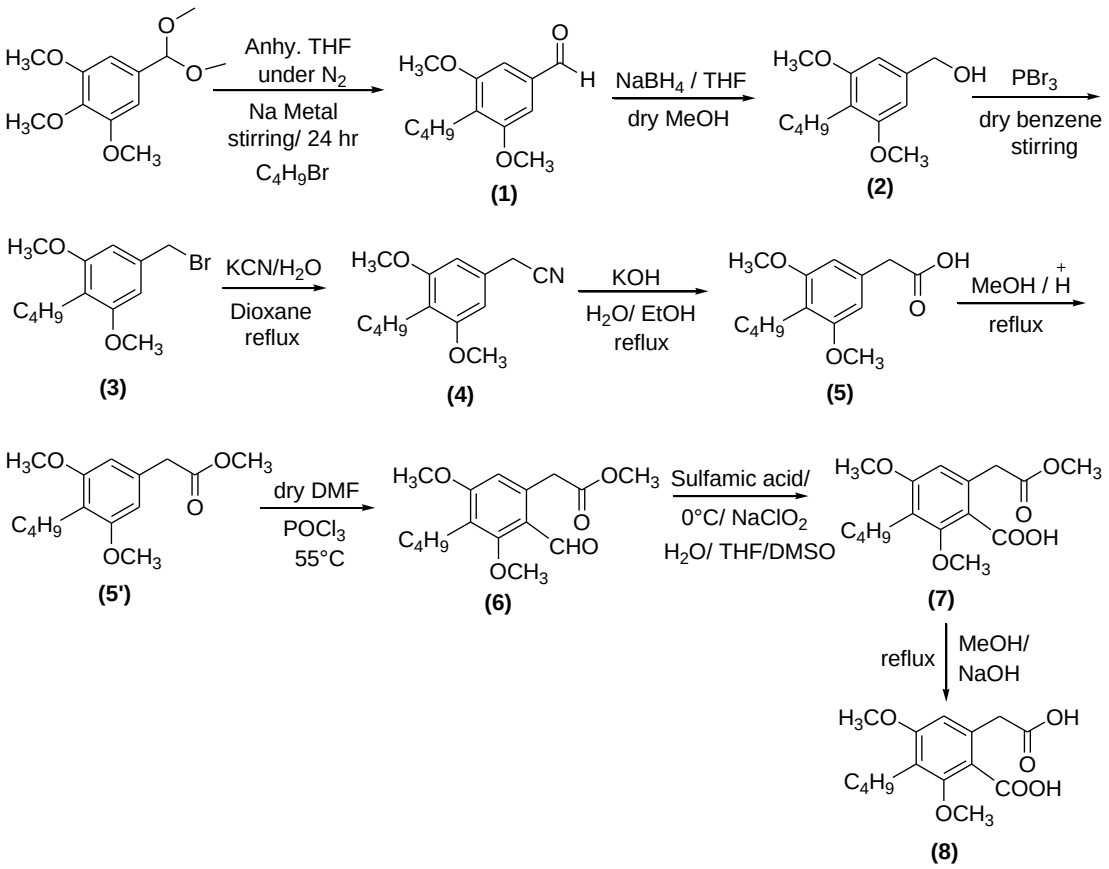
4-Butyl-3,5-dimethoxybenzylaldehyde **(1)** was prepared by the reductive metalation of 3,4,5-trimethoxybenzaldehyde dimethyl acetal with freshly cut Na metal in dry THF, followed by reaction with suitable electrophile like butylbromide yields **(1)**. It

showed characteristic (C=O) stretching absorption FTIR spectrum at 1732 cm^{-1}. In ^{13}C NMR carbonyl signal observed at δ 166.7 ppm.

4-Butyl-3,5-dimethoxybenzyl alcohol **(2)** was prepared by the reduction of aldehyde derivative **(1)** by refluxing it with sodium borohydride-and dry drop wise addition of dry methanol in THF. The IR spectrum showed the disappearance of carbonyl absorption and a broad band for hydroxyl group observed at 3342 cm^{-1}. In ^{1}H NMR a characteristic broad singlet (s) appeared at δ 5.07 ppm for -OH proton.

The alcohol derivative **(2)** was converted into 4-butyl-3,5-dimethoxybenzyl bromide **(3)** by treating it with PBr_3 in dry benzene. In IR spectrum, the broad signal due to hydroxyl group was diappeared.

Then nucleophilic substitution of the benzylbromide derivative **(3)** by cyanide was done by refluxing it with potassium cyanide in aqueous ethanol yields the 2-(4-butyl-3,5-dimethoxyphenyl) acetonitrile **(4)**. In IR spectrum, it is confirmed by the nitrile absorption at 2268 cm^{-1}.



Scheme 1.5: Synthesis of 4-Butyl-3,5-dimethoxyhomophthalic acid (8)

In IR spectrum a strong absorption for C=O was appeared at 1711 cm^{-1} and a broad peak for hydroxyl group observed at 3284 cm^{-1}. Then esterification of phenylacetic acid **(5)** was done in dry methanol with few drops of acid to get methyl ester derivative **(5')**. In IR spectrum a broad signal for hydroxyl group was disappear and (C=O) absorption for ester observed at 1732 cm^{-1} and a singlet (s) for methoxy protons of ester appeared at δ 3.63 ppm in ^{1}H NMR. In ^{13}C NMR a characteristic signal for ester carbonyl observed at 164.5 ppm.

The formylation of methyl ester derivative **(5')** was carried out by *Vilsmeier Haack formylation* method by using phosphorus oxychloride in dry DMF to afford methyl 4-butyl-2-formyl-3,5-dimethoxyphenyl acetate **(6)**. In IR spectrum, a new carbonyl absorption observed for formyl at 1686 cm^{-1} along with another peak at 1724 cm^{-1} for ester carbonyl moeity. The ^{1}H NMR showed an aldehydic proton singlet (s) at δ 9.83 ppm. In ^{13}C NMR a peak for aldehydic carboyl carbon appeared at δ 179.5 ppm and for ester at δ 163.4 ppm.

The oxidation of formyl derivative **(7)** to 2,4-dimethoxy-6-(2-methoxy-2-oxoethyl)-3-methylbenzoic acid **(8)** was done by using sulfamic acid and sodium chlorite at 0 °C. The IR spectrum showed a shifted in carbonyl absorption from 1690 cm^{-1} to 1716 cm^{-1} due to oxidation of aldehydic moiety into acidic group and the (O-H) absorption appeared at 3276 cm^{-1}. In ^{1}H NMR, a singlet (s) for acidic proton appeared at δ 8.76 ppm. In ^{13}C NMR spectrum, a downfield in chemical shifts was also observed for carboxylic carbon from δ 179.5 to δ 198.4.

Finally, 4-butyl-3,5-dimethoxyhomophthalic acid **(8)** was prepared by the alkaline hydrolysis of the methyl ester acid derivative **(7)** by treating it with 10 % potassium hydroxide in aqueous methanol. (Scheme 1.5)

The physical data of the compounds **(1-8)** is presented in Table 1.30.

Table 1.30: Physical data of all the compounds (1-8)

Compounds	M.P. (^{o}C)	Rf[a] Values	Yield (%)
1	47-48	0.7	82
2	180-182	0.2	74
3	oil	0.6	70
4	64-66	0.25	68
5	123-125	0.7	73
5'	oil	0.8	81
6	-	0.3	72

7	oil	0.35	67
8	-	0.3	76

[Pet. ether: ethyl acetate (8:2)]

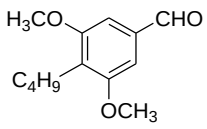
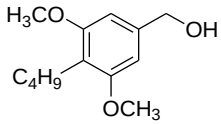
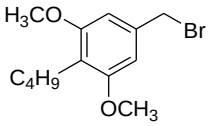
The FTIR spectral data of the compounds **(1-8)** is presented in Table 1.31.

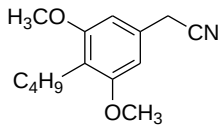
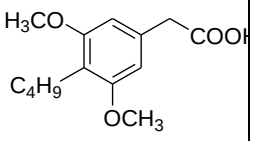
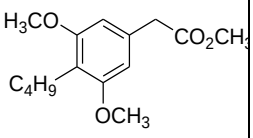
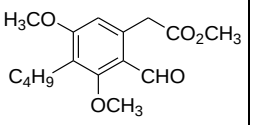
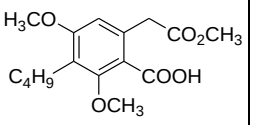
Table 1.31: FTIR spectral data of all the compounds (1-8)

Compounds.	**(C=C-H) cm^{-1}**	**(C=O) cm^{-1}**	**(C=C) cm^{-1}**	**(O-H) cm^{-1}**
1	3014	1742	1562	-
2	3025	-	1554	3421
3	3027	-	1571	-
4	3021	-	1561	-
5	3024	1707	1567	3242
5'	3018	1734	1573	-
6	3044	1690, 1722	1545	-
7	3015	1734, 1715	1562	3265
8	3010	1741	1587	3195

The ^{1}H and ^{13}C NMR spectral data of the compounds **(1-8)** is presented in Table 1.32.

Table 1.32: ^{1}H and ^{13}C NMR spectral data of all the compounds (1-8)

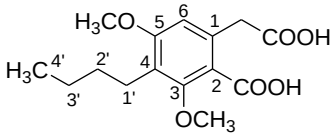
Compds	**Structures**	**^{1}H NMR(δ) (ppm)**	**^{13}C NMR(δ) (ppm)**
1		10.2 (1H, s, -CHO), 7.63 (2H, s, Ar), 3.87 (6H, s, -OCH_3), 2.78 (2H, t, *J* = 6 Hz, H-1'), 1.21-1.34 (4H, m, H-2',H-3'), 0.91 (3H, t, *J* = 6.2 Hz, H-4')	196.8 (aldehydic C=O), 138.7 (C-3, C-5), 136.4 (C-2,C-6), 128.3 (C-4), 117.6 (C-1), 62.8 (-OCH_3), 34.3 (C-1'), 31.2 (C-2'), 28.5 (C-3'), 23.6 (C-4′)
2		7.41 (2H, s, Ar), 5.07 (1H, s, -OH), 3.68 (6H, s, -OCH_3), 2.81 (2H, t, *J* = 6 Hz, H-1'), 2.54 (2H, s, -CH_2), 1.23-1.36 (4H, m, H-2',H-3'), 0.93 (3H, t, *J* = 6.1 Hz, H-4')	138.6 (C-3,C-5), 136.4 (C-2,C-6), 127.3 (C-4), 117.6 (C-1), 63.7 (-OCH_3), 43.3 (-CH_2), 36.4 (C-1'), 34.6 (C-2'), 29.5 (C-3'), 23.7 (C-4′)
3		7.32 (2H, s, Ar), 3.73 (6H, s, -OCH_3), 2.73 (2H, t, *J* = 5.8 Hz, H-1'), 2.57 (2H, s, -CH_2), 1.22-1.31 (4H, m, H-2',H-3'), 0.94 (3H, t, *J* = 6 Hz, H-4')	139.4 (C-3,C-5), 138.5 (C-2,C-6), 127.5 (C-4), 117.3 (C-1), 62.5 (-OCH_3), 43.2 (-CH_2), 36.5 (C-1'), 34.8 (C-2'), 29.7 (C-3'), 24.6 (C-4′)

4		7.29 (2H, s, Ar), 3.67 (6H, s, -OCH_3), 2.75 (2H, t, *J* = 5.8 Hz, H-1’), 2.63 (2H, s, -CH_2), 1.24-1.33 (4H, m, H-2’,H-3’), 0.93 (3H, t, *J* = 6 Hz, H-4’)	138.7 (C-3,C-5), 134.6 (C-2,C-6), 129.5 (-CN), 128.3 (C-4), 117.6 (C-1), 63.4 (-OCH_3), 44.3 (-CH_2), 36.7 (C-1’), 34.5 (C-2’), 29.6 (C-3’), 23.8 (C-4′)
5		11.32 (1H, s, -COOH), 7.36 (2H, s, Ar), 4.26 (2H, s, -CH_2), 3.67 (6H, s, -OCH_3), 2.79 (2H, t, *J* = 5.8 Hz, H-1’), 1.23-1.35 (4H, m, H-2’,H-3’), 0.94 (3H, t, *J* = 6 Hz, H-4’)	168.3 (-COOH), 138.6 (C-3,C-5), 136.4 (C-2,C-6), 127.5 (C-4), 118.6 (C-1), 62.6 (-OCH_3), 47.2 (-CH_2), 36.5 (C-1’), 34.7 (C-2’), 29.8 (C-3’), 24.7 (C-4′)
5’		11.3 (1H, s, -COOH), 7.76 (2H, s, Ar), 4.28 (2H, s, -CH_2), 3.67 (6H, s, -OCH_3), 2.75 (2H, t, *J* = 5.8 Hz, H-1’), 1.21-1.34 (4H, m, H-2’,H-3’), 0.93 (3H, t, *J* = 6 Hz, H-4’)	162.5 (ester C=O), 136.7 (C-3,C-5), 134.5 (C-2,C-6), 126.3 (C-4), 116.6 (C-1), 61.7 (-$COCH_3$), 57.4 (-OCH_3), 44.5 (-CH_2), 36.6 (C-1’), 34.3 (C-2’), 29.4 (C-3’), 24.5 (C-4’)
6		9.83 (1H, s, -CHO), 7.87 (1H, s, Ar), 4.32 (2H, s, -CH_2), 3.83 (3H, s, -OCH_3), 3.54 (3H, s, -OCH_3), 3.26 (3H, s, -(ester OCH_3), 2.78 (2H, t, *J* = 5.8 Hz, H-1’), 1.25-1.36 (4H, m, H-2’,H-3’), 0.93 (3H, t, *J* = 6.0 Hz, H-4’)	179.5 (aldehyde C=O), 163.4 (ester C=O), 136.7 (C-3,C-5), 133.5 (C-2), 127.2 (C-6), 121.6 (C-4), 117.5 (C-1), 63.4 (-$COCH_3$), 57.3 (Ar-OCH_3), 43.2 (Ar-CH_2), 36.3 (C-1’), 34.7 (C-2’), 29.5 (C-3’), 23.9 (C-4′)
7		8.76 (1H, s, -COOH), 7.56 (1H, s, Ar-H-6), 4.34 (2H, s, Ar-CH_2), 3.84 (3H, s, -OCH_3), 3.66 (3H, s, -OCH_3), 3.63 (3H, s, (ester OCH_3), 2.81 (2H, t, *J* = 6 Hz, H-1’), 1.24-1.38 (4H, m, H-2’,H-3’), 0.94 (3H, t, *J* = 6.1 Hz, H-4’)	198.4 (carboxylic C=O), 163.6 (ester C=O), 140.3 (C-3,C-5), 136.7 (C-2), 127.13 (C-6), 121.6 (C-4), 117.4 (C-1), 64.4 (ester OCH_3), 57.5 (Ar-OCH_3), 43.2 (Ar-CH_2), 36.3 (C-1’), 34.7 (C-2’), 29.6 (C-3’), 23.5 (C-4′)

The formation of the 4-butyl-3,5-dimethoxyhomophthalic acid **(8)** was confirmed by the presence of two characteristics singlets (s) for two carboxylic acid protons at δ 11.21 and 10.91 ppm in ^{1}H NMR spectrum. In ^{13}C NMR spectrum, the two peaks for carboxylic groups appeared at δ 204.6 and 171.5 ppm.

The ^{1}H and ^{13}C NMR data of the compound **(8)** is presented in Table 1.33.

Table 1.33: ^{1}H and ^{13}C NMR data of the 4-Butyl-3,5-dimethoxyhomophthalic acid (8).



Carbons	δ (ppm) and multiplicity	
	^{1}H NMR	**^{13}C NMR**
C-1	-	124.3
C-2	-	135.2
C-3	-	137.5
C-4	-	125.4
C-5	-	136.7
C-6	7.64, (s)	133.7
3-OCH_3	3.76, (s)	55.6
5-OCH_3	3.67, (s)	55.3
C-1'	2.84, (t), *J* = 6.1 Hz	34.6
C-2'	1.37, (m)	32.4
C-3'	1.21, (m)	28.5
C-4'	0.92, (t), *J* = 6.2 Hz	24.3
Ar-CH_2	4.37, (s)	43.4
CH_2-COOH	10.91, (s)	171.4
Ar-COOH	11.21, (s)	204.3

The formation of 4-butyl-3,5-dimethoxyhomophthalic acid **(8)**.was also confirmed by mass spectrometry. The molecular ion peak appeared at *m/z* 296 with 57 % abundance and a base peak observed at *m/z* 147.

The elemental analysis data of all the compounds **(1-8)** is presented in Table 1.34.

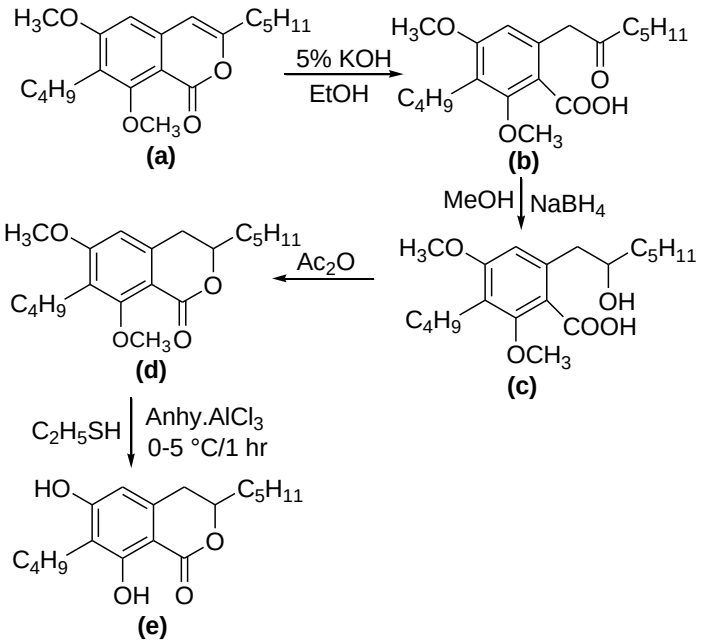
Table 1.34: Elemental analysis data of all the compounds (1-8)

Compounds	Formulae	Elemental Analysis					
		% Calculated			% Found		
		C	**H**	**N**	**C**	**H**	**N**
1	$C_{13}H_{18}O_3$	70.23	8.15	-	70.17	8.04	-
2	$C_{13}H_{20}O_3$	69.60	8.97	-	69.47	8.84	-
3	$C_{13}H_{19}BrO_2$	54.36	6.65	-	54.27	6.56.	-

4	$C_{14}H_{19}NO_2$	72.06	8.20	5.98	71.97	8.13	5.91
5	$C_{14}H_{20}O_4$	66.64	7.97	-	66.56	7.86.	-
5'	$C_{15}H_{22}O_4$	67.64	8.32	-	67.57	8.26.	-
6	$C_{16}H_{22}O_5$	65.28	7.52	-	65.17	7.46.	-
7	$C_{16}H_{22}O_6$	61.91	7.13	-	61.83	7.07	-
8	$C_{15}H_{20}O_6$	60.80	6.78	-	60.63	6.65.	-

2.1.7 Synthesis of (±) 7-Butyl-6,8-hydroxy-3-pentyl-3,4-dihydroisochromen-1-one. (10a-e)

4-Butyl-3,5-dimethoxyhomophthalic acid was condensed with commercially available hexanoyl chloride to afford 7-butyl-6,8-dimethoxy-3-isochromen-1-one. This isochromen-1-one was hydrolysed to keto-acid and then to hydroxy acid derivative by reduction. Followed by cyclodehydration to convert into its corresponding 7-butyl-6,8-dimethoxy-3-pentyl-3,4-dihydroisochromen-1-one. Finally, demethylation was carried out by ethanthiol to give (±) 7-butyl-6,8-hydroxy-3-pentyl-3,4-dihydroisochromen-1-one.



Scheme-1.6: Synthesis of (±) 7-Butyl-6,8-dihydroxy-3-pentyl-3,4-dihydro-isochromen-1-one. (10a-e)

The physical data of the compounds **(10a-e)** is presented in Table 1.35.

Table 1.35: Physical data of all the compounds (10a-e)

Compounds	M.P. (^{o}C)	Rf[a] Values	Yield (%)	Solvent of Recrystallization
10a	195-196	0.7	75	Methanol
10b	-	0.5	72	"
10c	-	0.4	74	Ethanol
10d	oil	0.7	68	"
10e	123-125	0.3	67	"

[Pet. ether: ethyl acetate (8:2)]

The characteristic absorption for lactonic carbonyl was observed at 1714 cm^{-1} in IR spectrum of 7-butyl-6,8-dimethoxy-3-pentyl-1H-isochromen-1-one. The ket-acid derivative was also confirmed by the presence of two carbonyl peaks for acidic and ketonic groups at 1721 and 1712 cm^{-1} and broad peak for O-H at 3342 cm^{-1}. The hydroxy derivative showed O-H broad peak at 3453 cm^{-1} and carbonyl peak at 1726 cm^{-1} for acidic group.

The IR spectra of 3,4-dihydroisochromen-1-one showed a characteristic carbonyl absorption at 1721 cm^{-1}. 7-Butyl-6,8-dihydroxy-3-pentyl-3,4-dihydroisochromen-1-one formation was confirmed by the presence of broad absorption peak for O-H at 3421 cm^{-1}.and carbonyl frequency at 1724 cm^{-1}.

The FTIR spectral data of the compounds **(10a-e)** is presented in Table 1.36.

Table 1.36: FTIR spectral data of all the compounds (10a-e)

Compounds.	(C=C-H) cm^{-1}	(C=O) cm^{-1}	(C=C) cm^{-1}	(O-H) cm^{-1}
10a	3027	1714	1577	-
10b	3023	1721, 1712	1584	3342
10c	3026	1726	1581	3453
10d	3037	1721	1586	-
10e	3046	1724	1587	3421

The formation of the (±) 7-butyl-6,8-dimethoxy-3-pentyl-1H-isochromen-1-one **(a)** was confirmed by the presence of a characteristic singlet at δ 6.54 ppm in ^{1}H NMR and in ^{13}C NMR spectrum a lactonic carbonyl carbon peak appeared at δ 164.3 ppm. The ^{1}H NMR spectrum of keto-acid **(b)** showed a singlet at δ 10.3 ppm for acidic proton and in ^{13}C NMR spectrum two characteristic carbonyl carbon signals appeared at δ 197.3 and δ 168.2 ppm for ketonic and acidic carbonyl carbons.

The ^{1}H NMR spectrum of hydroxy acid **(c)** showed a broad singlet for -OH at δ 4.43 ppm and another singlet for acidic proton at δ 10.7 ppm. In ^{13}C NMR a characteristic carbonyl carbon signal appeared at δ 171.6 ppm for acidic carbonyl carbon. (±) 7-Butyl-6,8-dimethoxy-3-pentyl-3,4-dihydroisochromen-1-one **(a)** was confirmed by the presence of two characteristic double doublets (dd) at δ 3.32 and δ 3.12 ppm in ^{1}H NMR for H-4,4' protons. In ^{13}C NMR spectrum lactonic carbon peak appeared at δ 168.4 ppm.

The ^{1}H and ^{13}C NMR spectral data of the compounds **(10a-d)** is presented in Table 1.37.

Table 1.37: ^{1}H and ^{13}C NMR spectral data of all the compounds (10a-d)

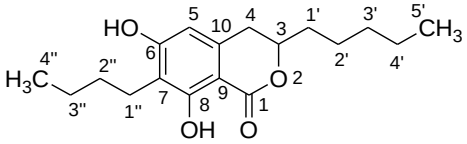
Sr No.	Compounds	^{1}H NMR(δ) (ppm)	^{13}C NMR(δ) (ppm)
1	**10a**	8.04 (1H, s, Ar-H-5), 6.54 (1H, s, H-4), 3.76 (3H, s, -OCH_3), 3.72 (3H, s, -OCH_3), 2.54 (2H, t, *J* = 7.2 Hz, H-1''), 2.38 (2H, t, *J* = 7.4 Hz, H-1'), 1.61-1.43 (10H, m, H-2',H-3',H-4',H-2'',H-3''), 0.92 (3H, t, *J* = 7.2 Hz, H-4''), 0.87 (3H, t, *J* = 6.8 Hz, H-5')	164.3 (C-1), 150.3 (C-3), 146.5 (C-6), 147.5 (C-8), 136.4 (C-10), 127.8 (C-9), 116.5 (C-7), 108.3 (C-4), 104.6 (C-5), 56.7 (6-OCH_3), 56.4 (8-OCH_3), 36.7 (C-1''), 34.5 (C-1''), 24.1 (C-2'), 23.6 (C-2''), 17.8 (C-3'), 15.4 (C-4'), 13.5 (C-3''), 11.7 (C-4''); 11.2 (C-5')
2	**10b**	10.3 (1H, s, -COOH), 7.86 (1H, s, H-5), 4.45 (2H, s, -CH_2), 3.78 (3H, s, 2-OCH_3), 3.74 (3H, s, 4-OCH_3), 3.69 (2H, t, *J* = 3.7 Hz, H-3'), 3.26 (3H, s, Ar-CH_3), 2.56 (2H, t, *J* = 7.2 Hz, H-1''), 2.36 (2H, t, *J* = 7.4 Hz, H-1'), 1.66-1.53 (10H, m, H-2',H-3',H-4',H-2'',H-3''), 0.93 (3H, t, *J* = 7.2 Hz, H-4''), 0.89 (3H, t, *J* = 6.8 Hz, H-5')	197.3 (C=O), 168.2 (-COOH), 144.6 (C-2), 138.5 (C-4), 136.2 (C-1), 128.7 (C-6), 120.3 (C-3), 106.4 (C-5), 61.5 (2-OCH_3), 58.4 (4-OCH_3), 47.7 (C-1'), 44.5 (C-3'), 29.4 (Ar-CH_3), 23.4 (C-1''), 22.7 (C-4'), 21.6 (C-2''), 18.5 (C-5'), 15.8 (C-3''), 13.7 (C-6'), 11.6 (C-4''), 10.2 (C-7')
3	**10c**	10.7 (1H, s, -COOH), 7.88 (1H, s, H-5), 4.55 (2H, m, -CH_2), 4.43 (1H, s, -OH), 3.78 (3H, s, 6-OCH_3), 3.76 (3H, s, 8-OCH_3), 3.71 (2H, t, *J* = 3.7 Hz, H-3'), 3.32 (3H, s, Ar-CH_3), 2.62 (2H, t, *J* = 7.2 Hz, H-1''), 2.43 (2H, t, *J* = 7.4 Hz, H-1'), 1.71-1.57 (10H, m, H-2',H-3',H-4',H-2'',H-3''), 0.95 (3H, t, *J* = 7.1	171.6 (C=O), 146.2 (C-2), 145.8 (C-4), 142.3 (C-6), 112.3 (C-1), 110.6 (C-3), 108.4 (C-5), 86.7 (C-OH), 64.7 (2-OCH_3), 64.3 (4-OCH_3), 48.5 (-CH_2), 38.6 (C-1'), 36.4 (C-1''), 23.8 (C-2'), 23.2 (C-2''), 18.7 (C-3'), 15.6 (C-4'), 13.2 (C-3''), 12.8 (C-

		Hz, H-4’’), 0.91 (3H, t, J = 6.7 Hz, H-5’)	4’’), 12.4 (C-5’)
4	**10d**	7.61 (1H, s, Ar-H-5), 5.57 (1H, m, H-3), 3.87 (3H, s, 6-OCH_3), 3.83 (3H, s, 8-OCH_3), 3.32 (1H, dd, J_{gem} = 16.1 Hz, J_{trans} = 12.8 Hz, H-4), 3.12 (1H, dd, J_{gem} = 16.2, Hz, J_{cis} = 3.6 Hz, H-4’), 2.64 (2H, t, J = 7.1 Hz, H-1’’), 2.53 (2H, t, J = 7.4 Hz, H-1’), 1.66-1.52 (10H, m, H-2’,H-3’,H-4’,H-2’’,H-3’’), 0.94 (3H, t, J = 7.2 Hz, H-4’’), 0.89 (3H, t, J = 6.8 Hz, H-5’)	168.4 (C-1), 148.7 (C-6), 147.8 (C-8), 144.5 (C-10), 140.2 (C-9), 128.6 (C-5), 122.3 (C-7), 87.5 (C-3), 63.4 (6-OCH_3), 62.6 (8-OCH_3), 46.4 (C-4), 38.3 (C-1’), 36.2 (C-1’’), 23.4 (C-2’), 22.7 (C-2’’), 18.4 (C-3’), 15.2 (C-4’), 13.3 (C-3’’), 11.6 (C-4’’), 11.3 (C-5’)

The formation of 7-butyl-6,8-dihydroxy-3-pentyl-3,4-dihydroisochromen-1-one **(e)** was confirmed by the presence of a singlet (s) for -OH protons at δ 4.84 ppm in ^{1}H NMR. In ^{13}C NMR spectrum the lactonic carbonyl carbon signal appeared at δ 169.6 ppm, which also confirms the formation 7-butyl-6,8-dihydroxy-3-pentyl-1H-3,4-dihydro-isochromen-1-one **(e)**.

The ^{1}H and ^{13}C NMR data of the compound **(10e)** is presented in Table 1.38.

Table 1.38: ^{1}H and ^{13}C NMR data of 7-Butyl-6,8-dihydroxy-3-pentyl-3,4-dihydroisochromen-1-one (10e)



Carbons	δ (ppm) and multiplicity	
	^{1}H NMR	**^{13}C NMR**
C-1	-	169.6
C-2	-	135.2
C-3	5.63, (m)	88.4
C-4, 4	3.42 (dd), J_{gem} = 16.1 Hz, J_{trans} = 12.7 Hz, 3.28 (dd), J_{gem} = 16.1, Hz, J_{cis} = 3.8 Hz	47.6
C-5	7.67, (1H, s, H-5)	128.3
C-6	-	160.7
C-7	-	123.5
C-8	-	160.2
C-9	-	140.7
C-10	-	142.5

C-1'	2.53, (t), *J* = 7.3 Hz	34.6
C-2'	1.76, (m)	31.4
C-3'	1.74, (m)	23.5
C-4'	1.71, (m)	22.6
C-5'	0.94, (t), *J* = 6.7 Hz	14.4
C-1''	2.71, (t), *J* = 7.1 Hz	37.2
C-2''	1.68, (m)	30.8
C-3''	1.66, (m)	19.5
C-4''	0.97, (t), *J* = 7.1 Hz	14.7
-OH	4.84, (s)	-

In mass spectrometry the molecular ion peak appeared at *m/z* 306 with 57 % abundance, which confirmed the formation of 7-butyl-6,8-dihydroxy-3-pentyl-1H-3,4-dihydroisochromen-1-one **(e)**. Two peaks appeared at *m/z* 278 and *m/z* 262 with 35 % ans 26 % abundance by the removal of CO and CO_2 from molecular ion. By the removal of pentyl radical from molecular ion, a peak appeared at *m/z* 235 with 67% abundance and a base peak peak appeared at *m/z* 206.

The elemental analysis data of the compounds **(10a-e)** is presented in Table 1.39.

Table 1.39: Elemental analysis data of all the compounds (10a-e)

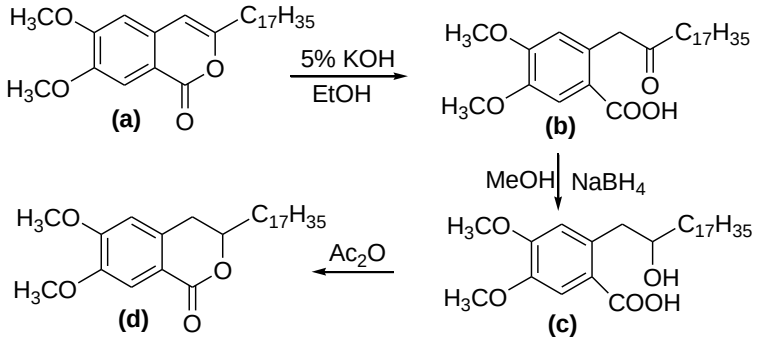
Compounds	**Formulae**	**Elemental Analysis**			
		% Calculated		**% Found**	
		C	**H**	**C**	**H**
10a	$C_{13}H_{18}O_3$	72.28	8.43.	72.14	8.36.
10b	$C_{20}H_{30}O_5$	68.57	8.57	68.47	8.41.
10c	$C_{20}H_{32}O_5$	68.15	9.16	68.10	9.08.
10d	$C_{20}H_{30}O_4$	71.85	9.04	71.73	8.97.
10e	$C_{18}H_{26}O_4$	70.55	8.54	70.43	8.47.

The structures of all the compounds **(10a-e)** were confirmed by physical data, FTIR, ^{1}H NMR and ^{13}C NMR spectral data, Mass spectrometry and elemental analysis. data also confirmed the formation of all these compounds.

2.1.8 Synthesis of (±) 3-Heptadecyl-6,7-dimethoxy-3,4-dihydroisochromen-1-one (11a-d)

(±) 3-Heptadecyl-6,7-dimethoxy-1H-isochromen-1-one **(a)** was converted to keto-acid **(b)** by alkaline hydrolysis and then reduction was done by $NaBH_4$ to hydroxy

acid **(c)**, which was then converted into its corresponding (±) 3-heptadecyl-6,7-dimethoxy-3,4-dihydroisochromen-1-one **(e)** by cyclodehydration with acetic anhydride. (Scheme 1.7)



Scheme 1.7: (±) 3-Heptadecyl-6,7-dimethoxy-3,4-dihydroisochromen-1-one

The physical data of the compounds **(11a-d)** is presented in Table 1.40.

Table 1.40: Physical data of all the compounds (11a-d)

Compounds	M.P. (^{o}C)	Rf[a] Values	Yield (%)	Solvent of Recrystallization
11a	45-48	0.65	75	Methanol
11b	58-59	0.5	73	"
11c	156-158	0.3	77	Ethanol
11d	214-216	0.6	71	"

[Pet. ether: ethyl acetate (8:2)]

In IR spectrum the characteristic absorption for lactonic carbonyl of 3-heptadecyl-6,7-dimethoxy-1H-isochromen-1-one **(a)** observed at 1715 cm^{-1}. The keto-acid **(b)** was also confirmed by the presence of two carbonyl peaks (C=O) for acidic and ketonic groups at 1726 and 1714 cm^{-1} and broad peak for O-H absorption appeared at 3433 cm^{-1}. The hydroxy acid derivative **(c)** showed O-H broad peak at 3446 cm^{-1} and carbonyl peak at 1722 cm^{-1} for acidic group. The IR spectrum of 3-heptadecyl-6,7-dimethoxy-3,4-dihydroisochromen-1-one **(d)** showed a characteristic carbonyl carbon (C=O) absorption at 1718 cm^{-1}.

The FTIR spectral data of the compounds **(11a-d)** is presented in Table 1.41.

Table 1.41: FTIR spectral data of all the compounds (11a-d)

Compounds.	(C=C-H) cm^{-1}	(C=O) cm^{-1}	(C=C) cm^{-1}	(O-H) cm^{-1}
11a	3043	1715	1573	-
11b	3025	1726, 1714	1567	3433
11c	3031	1722	1587	3446
11d	3037	1718	1576	-

The formation of 3-heptadecyl-6,7-dimethoxyisochromen-1-one **(a)** was confirmed by the presence of a characteristic singlet (s) at δ 7.63 ppm in ^{1}H NMR and in ^{13}C NMR spectrum by the presence of lactonic carbonyl carbon peak at δ 166.7 ppm. The ^{1}H NMR spectrum of keto-acid **(b)** showed a singlet (s) at δ 10.2 ppm for acidic proton. In ^{13}C NMR spectrum two characteristic carbonyl carbon signals (s) appeared at δ 197.4 and δ 168.5 ppm for ketonic and acidic carbonyl carbons.

The ^{1}H NMR spectrum, of hydroxy acid **(c)** showed a broad singlet (s) for -OH at δ 4.41 ppm and another singlet (s) for acidic proton at δ 10.85 ppm. In ^{13}C NMR a characteristic carbonyl carbon signal appeared at δ 176.4 ppm for acidic carbonyl carbon.

The ^{1}H and ^{13}C NMR spectral data of the compounds **(11a-c)** is presented in Table 1.42.

Table 1.42: ^{1}H and ^{13}C NMR spectral data of all the compounds (11a-c)

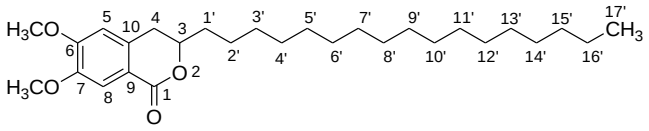
Sr No.	Compounds	^{1}H NMR(δ) (ppm)	^{13}C NMR(δ) (ppm)
1	**11a**	7.78 (1H, s, H-8), 7.63 (1H, s, H-5), 6.23 (1H, s, H-4), 3.78 (3H, s, 3-OCH_3), 3.76 (3H, s, 4-OCH_3), 2.43 (2H, m, H-1'), 1.65-1.22 (30H, m, H-2',H-3',H-4',H-5',H-6',H-7',H-8',H-9',H-10',H-11',H-12',H-13',H-14',H-15',H-16'), 0.94 (3H, t, *J* = 5.8 Hz, H-17')	166.7 (C-1), 150.4 (C-6,C-7), 146.5 (C-3), 137.4 (C-10), 134.8 (C-9), 123.5 (C-8), 121.7 (C-5), 112.6 (C-4), 56.8 (-OCH_3), 36.4 (C-1'), 35.8 (C-2'), 33.6 (C-3'), 33.4 (C-4'), 31.7 (C-5'), 29.5 (C-6'), 29.6 (C-7'), 27.4 (C-8'), 24.1 (C-9'), 22.6 (C-10'), 19.2 (C-11'), 17.3 (C-12'), 14.7 (C-13'), 13.5 (C-14'), 12.6 (C-15'), 11.3 (C-16'), 10.4 (C-17')
2	**11b**	10.26 (1H, s, COOH), 8.11 (1H, s, Ar-H-2), 7.67 (1H, s, Ar-H-5), 4.33 (2H, s, -CH_2), 3.84 (3H, s, 3-OCH_3), 3.78 (3H, s, 4-OCH_3), 2.53 (2H, t, *J* = 3.5 Hz, H-1'), 168-1.23 (30H, m, H-2',H-3',H-4',H-5',H-6',H-7',H-8',H-9',H-10',H-11',H-12',H-13',H-14',H-15',H-16'), 0.93 (3H, t, *J* = 5.7 Hz, H-17')	197.4 (C=O), 168.5 (-COOH), 144.6 (C-3), 137.4 (C-4), 136.6 (C-1), 127.5 (C-3), 121.4 (C-6), 106.7 (C-5), 60.5 (3-OCH_3), 58.6 (4-OCH_3), 43.6 (-CH_2), 36.8 (C-1'), 35.4 (C-2'), 33.6 (C-3'), 32.5 (C-4'), 31.2 (C-5'), 29.4 (C-6'), 28.5 (C-7'), 26.3 (C-8'), 22.8 (C-9'), 21.7 (C-10'), 19.2 (C-11'), 17.4 (C-12'), 14.3 (C-13'), 13.5 (C-14'), 12.7 (C-15'), 11.8 (C-16'), 11.2 (C-17')
		10.85 (1H, s, -COOH), 8.23 (1H, s, Ar), 7.97 (1H, s, Ar), 3.82 (1H, dd, J_{vic} = 3.3,J_{vic} =	176.4 (Carboylic C=O), 77.5 (C-OH), 128.6 (C-1), 137.5 (C-2), 119.3 (C-3), 158.5 (C-

3	**11c**	3.4), 2.94 (1H, dd, J_{vic} = 3.3, J_{gem} = 18.2), 3.26 (1H, dd, J_{vic} = 3.4, J_{gem} = 18.2), 2.58 (2H, t, J = 3.4Hz, H-1'), 176-1.37 (30H, m, H-2',H-3',H-4',H-5',H-6',H-7',H-8',H-9',H-10',H-11',H-12',H-13',H-14',H-15',H-16'), 0.96 (3H, t, J = 5.6 Hz, H-17'), 4.41(1H, s, -OH), 3.87 (3H, s, 3-OCH_3), 3.84 (3H, s, 4-OCH_3)	4), 152.4 (C-5), 123.6 (C-6), 66.2 (-OCH_3), 65.7 (-OCH_3), 42.4 (-CH_2), 37.1 (C-1'), 36.5 (C-2'), 35.6 (C-3'), 34.3 (C-4'), 32.5 (C-5'), 30.7 (C-6'), 29.4 (C-7'), 27.5 (C-8'), 23.6 (C-9'), 22.3 (C-10'), 21.2 (C-11'), 19.4 (C-12'), 16.6 (C-13'), 14.7 (C-14'), 14.2 (C-15'), 13.8 (C-16'), 13.4 (C-17')

The formation of 3-heptadecyl-6,7-dimethoxy-3,4-dihydroisochromen-1-one **(d)** was confirmed by the presence of two characteristic double doublets (dd) at δ 3.46 and δ 3.21 ppm in ^{1}H NMR for H-4,4' protons. In ^{13}C NMR spectrum lactonic carbonyl carbon peak appeared at δ 167.4 ppm.

The ^{1}H and ^{13}C NMR data of 3-heptadecyl-6,7-dimethoxy-3,4-dihydroisochromen-1-one **(d)** is presented in Table 1.43.

Table 1.43: ^{1}H and ^{13}C NMR data of (±) 3-Heptadecyl-6,7-dimethoxy-3,4-dihydroisochromen-1-one (d)



Carbons	δ (ppm) and multiplicity	
	^{1}H NMR	**^{13}C NMR**
C-1	-	167.4
C-2	-	-
C-3	5.34, (m)	82.7
C-4, 4	3.46, (dd), J_{gem} = 15.1 Hz, J_{trans} = 12 Hz, 3.21, (dd), J_{gem} = 16. 2 Hz, J_{cis} = 3.6 Hz	45.2
C-5	7.56, (s)	121.3
C-6		151.6
C-7	-	151.2
C-8	7.74, (s)	123.5
C-9	-	134.4
C-10	-	137.5
6,7-OCH_3	3.76, (s)	56.8
C-1'	2.42, (m)	36.7
C-2'	1.67, (m)	35.3
C-3'	"	33.7

C-4'	"	33.1
C-5'	"	31.4
C-6'	"	29.8
C-7'	"	29.2
C-8'	"	26.5
C-9'	"	23.7
C-10'	"	22.5
C-11'	"	19.3
C-12'	"	17.5
C-13'	"	14.6
C-14'	"	13.2
C-15'	"	12.4
C-16'	1.16, (m)	11.2
C-17'	0.94, (t), *J* = 5.8 Hz	10.6

In mass spectrometry the molecular ion peak appeared at *m/z* 446 with 47 % abundance, which confirmed the formation of 3-heptadecyl-6,7-dimethoxy-3,4-dihydroisochromen-1-one **(d)**. By the removal of heptadecyl radical from molecular ion a peak appeared at *m/z* 207 with 31 % abundance and base peak appeared at *m/z* 178.

The elemental analysis data of all the compounds **(11a-e)** is presented in Table 1.44.

Table 1.44: Elemental analysis data of all the compounds (11a-d)

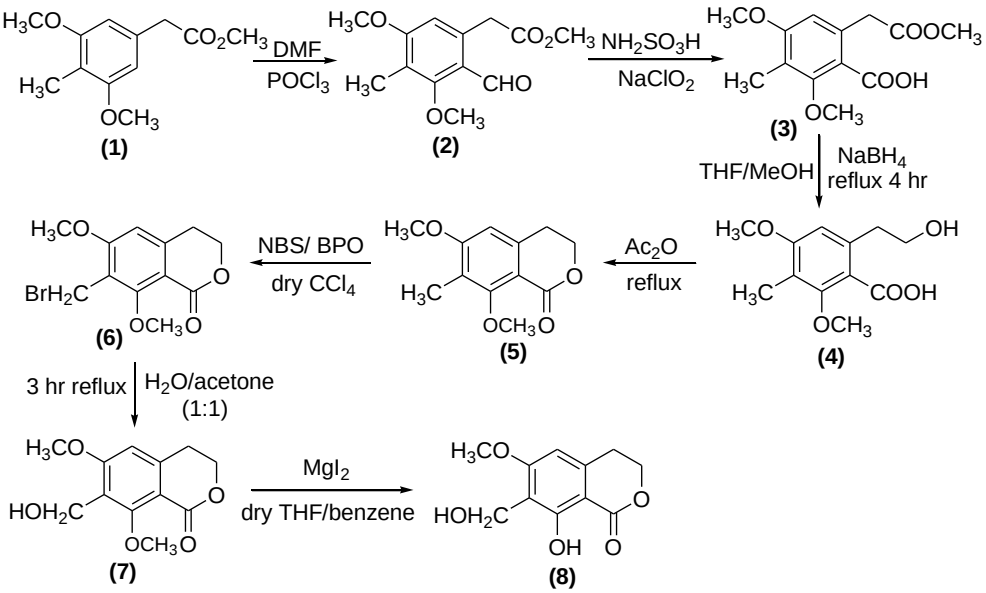
Compounds	**Formulae**	**Elemental Analysis**			
		% Calculated		**% Found**	
		C	**H**	**C**	**H**
11a	$C_{28}H_{44}O_4$	75.67	9.91	75.48	9.85
11b	$C_{28}H_{46}O_5$	72.68	10.02	72.53	9.96
11c	$C_{28}H_{48}O_5$	72.37	10.41	72.28	10.32
11d	$C_{28}H_{46}O_4$	75.34	10.31	75.27	10.25

The structures of all the compounds **(11a-d)** were confirmed by physical data, FTIR, ^{1}H NMR and ^{13}C NMR, MS spectral data and elemental analysis also confirms the formation of all these compounds.

2.1.9 Total synthesis of 8-Hydroxy-7-(hydroxymethyl)-6-methoxy-3,4-dihydro-1H-isochromen-1-one (*Stellatin*).

3,5-Dimethoxy-4-methylphenylacetic acid **(1)** is the key starting material, which is itself prepared from the commercially available 4-methylbenzoic acid. Thus, the

esterification of *p*-toluic acid followed by the nuclear bromination using "*swamping catalyst effect"* involving bromine and an excess of anhydrous $AlCl_3$ yields 3,5-dibromo-4-methylbenzoic acid. The copper (I) chloride catalyzed nucleophilic substitution was done with Na-methoxide in dry methanol furnished 3,5-dimethoxy-4-methylbenzoic acid. Which was then converted by the standard homologation sequence into 3,5-dimethoxy-4-methylphenylacetic acid **(1)**.



Scheme 1.8: Total synthesis of 8-Hydroxy-7-hydoxymethyl-6-methoxy-3,4-dihydro-1H-isochromen-1-one (*Stellatin*) (1-8)

The physical data of all the compounds **(1'-8)** is presented in Table 1.45.

Table 1.45: Physical data of all the compounds (1'-8)

Compounds	M.P. (^oC)	Rf[a] Values	Yield (%)	Solvent of Recrystallization
1'	38-40	0.7	88	Methanol
2	51-53	0.55	84	"
3	164-166	0.4	78	Ethanol
4	72-74	0.3	77	"
5	145-146	0.6	78	"
6	91-93	0.6	81	"
7	136-138	0.4	76	"
8	127-128	0.5	64	"

[Pet. ether: ethyl acetate (8:2)]

Methyl ester derivative **(1)** was subjected to *Vilsmeier-Haack formylation* to give methyl 2-formyl-3,5-dimethoxyphenyl acetate **(2)**. In ^1H NMR, a singlet for aldehydic proton appeared at δ 9.75 ppm and in ^{13}C NMR spectrum the carbonyl carbon (C=O) peak oserved at δ 179.3 ppm. Oxidation of the formyl group was achieved by using

sulfamic acid and sodium chlorite at 0 ºC, then esterification was carried out to afford carboxy ester derivative **(3)**. The carbonyl carbon (C=O) absorption in IR spectrum, shifted from 1690 to 1715 cm-^{1} and a broad absorption band for carboxylic hydroxyl appeared at 3265 cm-^{1}. In ^{1}H NMR spectrum, a singlet (s) observed at δ 8.19 ppm for acidic proton and a downfield shift for carboxylic carbon from δ 179.3 to δ 197.7 ppm was also noticed in ^{13}C NMR spectrum.

Ester moeity **(3)** was chemoselectively reduced, leaving acidic group intact by using $NaBH_4$/THF/MeOH to afford the hydroxy acid derivative **(4)**. The cyclodehydration of **(4)** was done by refluxing it with acetic anhydride to afford 3,4-dihydro-6,8-dimethoxy-7-methylisochromen-1-one **(5)**. The IR spectrum of the 3,4-dihydroisochromen-1-one showed the lactonic carbonyl carbon (C=O) absorption at 1725 cm^{-1}. The C-4 methylene protons showed a triplet (t) at δ 2.56 ppm and that of C-3 methylene protons slightly downfield triplet (t) appeared at δ 4.25 ppm.

The benzylic bromination of 7-methyl group was carried out by using NBS/benzoyl peroxide in dry CCl_4 to yield the benzylic bromide derivative **(6)**. In ^{1}H NMR spectrum, 7-methyl protons singlet (s) showed a downfield shift from δ 2.66 to δ 4.85 ppm. As lactonic ring is base-sensitive, so a mild method is used for nucleophilic substitution of bromo group with hydroxyl group, this was achieved by refluxing bromide derivative **(6)** in aqueous acetone (1:2) for 2 hr to afford 7-(hydroxymethyl)-6,8-dimethoxy-3,4-dihydroisochromen-1-one **(7)**. The IR spectrum a broad band peak for hydroxyl group observed at 3467 cm^{-1}. In the ^{1}H NMR spectrum, a singlet for -OH appeared at δ 2.36 ppm. Regioselective demethylation of 7-(hydroxymethyl)-6,8-dimethoxy-3,4-dihydroisochromen-1-one **(7)** was accomplished by refluxing it with Mg/I_2 in THF/benzene to afford 8-hydroxy-7-(hydroxymethyl)-6-methoxy-3,4-dihydro-1H-isochromen-1-one (*stellatin*) **(8)** (Scheme 1.8).

The FTIR spectral data of the compounds **(1'-8)** is presented in Table 1.46.

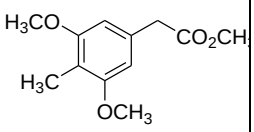
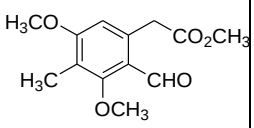
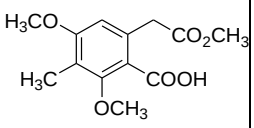
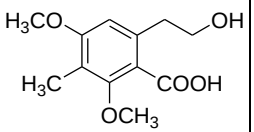
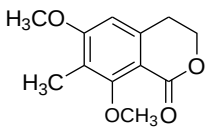
Table 1.46: The FTIR spectral data of all the compounds (1'-8)

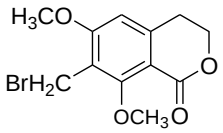
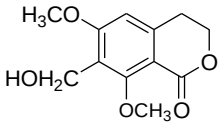
Compounds.	**(C=C-H) cm^{-1}**	**(C=O) cm^{-1}**	**(C=C) cm^{-1}**	**(O-H) cm^{-1}**
1	3026	1732	1572	-
2	3027	1721, 1692	1575	-
3	3036	1733, 1716	1571	3267
4	3028	1711	1573	3486
5	3021	1708	1578	-

6	3023	1718	1583	-
7	3044	1715	1584	3472
8	3051	1705	1591	3456

The ^{1}H and ^{13}C NMR spectral data of all the compounds **(1-8)** is presented in Table 1.47.

Table 1.47: ^{1}H and ^{13}C NMR spectral data of all the compounds (1-8)

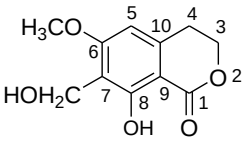
Compds	Structures	^{1}H NMR(δ) (ppm)	^{13}C NMR(δ) (ppm)
1		7.45 (2H, s, H-2,H-6), 3.96 (6H, s, -OCH_3), 3.54 (2H, s, Ar-CH_2), 3.47 (3H, s, $COOCH_3$), 2.55 (3H, s, Ar-CH_3)	168.2 (C=O), 132.5 (C-3,C-5), 128.3 (C-2,C-6), 119.4(C-4), 112.2 (C-1), 68.5 (ester OCH_3), 55.3 (Ar-OCH_3), 36.9 (-CH_2), 28.6 (Ar-CH_3)
2		9.75 (1H, s, CHO), 7.96 (1H, s, H-6), 3.42 (3H, s, 3-OCH_3), 3.25 (3H, s, 5-OCH_3), 3.11 (3H, s, CO_2CH_3), 2.92 (2H, s, Ar-CH_2), 2.80 (3H, s, Ar-CH_3)	179.3 (aldehyde C=O), 162.4 (ester C=O), 136.7 (C-3,C-5), 131.9 (C-2), 126.2 (C-6), 121.3 (C-4), 117.5 (C-1), 61.6 (ester OCH_3), 57.3 (Ar-OCH_3), 39.1 (Ar-CH_2), 32.0 (Ar-CH_3)
3		8.19 (1H, s, COOH), 7.66 (1H, s, H-6), 3.82 (3H, s, 3-OCH_3), 3.67 (3H, s, 5-OCH_3), 3.63 (3H, s, CO_2CH_3), 2.54 (2H, s, Ar-CH_2), 2.25 (3H, s, Ar-CH_3)	197.8 (carboxylic C=O), 168.5 (ester C=O), 139.3 (C-2,C-4), 134.3 (C-6), 127.1 (C-5), 120.6 (C-3), 114.1 (C-1), 66.0 (ester -OCH_3), 55.4 (Ar-OCH_3), 35.0 (Ar-CH_2), 29.8 (Ar-CH_3)
4		8.22 (1H, s, -COOH), 7.48 (1H, s, H-5), 4.21 (2H, t, *J* = 3.8 Hz, H-10), 3.90 (3H, s, 2-OCH_3), 3.75 (3H, s, 4-OCH_3), 2.65 (2H, t, *J* = 3.8 Hz, H-20), 2.51 (3H, s, Ar-CH_3)	190.5 (-COOH), 166.2 (C-2), 162.4 (C-4), 141.3 (C-6), 108.1 (C-3), 105.6 (C-1), 101.2 (C-5), 63.2 (C-20), 56.4 (2-OCH_3, 4-OCH_3), 32.3 (C-10), 28.8 (Ar-CH_3)
5		7.48 (1H, s, H-5), 4.25 (2H, t, *J* = 3.6 Hz, H-3), 3.90 (6H, s, 6- OCH_3, 8-OCH_3), 2.66 (3H, s, Ar-CH_3), 2.56 (2H, t, *J* = 3.6 Hz, H-4)	163.9 (C-1), 152.3 (C-6,C-8), 140.8 (C-10), 134.6 (C-9), 108.9 (C-7), 103.7 (C-5), 65.9 (C-3), 56.4 (6-OCH_3, 8-OCH_3), 27.4 (C-4), 26.2 (Ar-CH_3)

6		7.50 (1H, s, H-5), 4.85 (2H, s, CH_2-Br), 4.24 (2H, t, *J* = 3.6 Hz, H-3), 3.90 (6H, s, 6- OCH_3, 8-OCH_3), 2.58 (2H, t, *J* = 3.6 Hz, H-4)	169.2 (C-1), 155.4 (C-6,C-8), 144.1 (C-10), 110.7 (C-7), 106.2 (C-9), 104.6 (C-5), 67.4 (C-3), 53.7 (6-OCH_3, 8-OCH_3), 39.5 (CH_2-Br), 26.4 (C-4)
7		7.62 (1H, s, H-5), 4.88 (2H, s, CH_2-OH), 4.20 (2H, t, *J* = 3.7 Hz, H-3), 3.90 (6H, s, 6-OCH_3,8-OCH_3), 2.56 (2H, t, *J* = 3.7 Hz, H-4), 2.36 (1H, s, O-H)	168.6 (C-1), 157.3 (C-6,C-8), 142.1 (C-10), 115.2 (C-7), 105.2 (C-9), 102.6 (C-5), 64.5 (C-3), 55.7 (6-OCH_3, 8-OCH_3), 48.6 (CH_2-OH), 27.4 (C-4)

In the ^{1}H NMR spectrum, a singlet (s) for -OH proton appeared at δ 10.8 ppm, while that of 7-hydroxy proton at δ 2.28 ppm. The phenolic hydroxyl presence was confirmed by purple ferric chloride test and its solubility in dilute aqueous NaOH. In IR spectrum, the lactonic carbonyl absorption (C=O) was lowered from 1714 to 1695 cm^{-1} due to chelation with hydroxyl group at position 8, its absorption occure at 3559 cm^{-1}. The ^{1}H NMR data also confirms the formation of a natural product *stellatin* **(8)** as two characteristics triplets (t) observed at δ 4.12 and δ 2.86 ppm for protons present at 4 & 3 position and in ^{13}C NMR carbonyl carbon signal appeared at δ 166.5 ppm.

The ^{1}H and ^{13}C NMR spectral data of the compound **(8)** is presented in Table 1.48.

Table 1.48: ^{1}H and ^{13}C NMR spectral data of 8-Hydroxy-7-(hydroxymethyl)-6-methoxy-3,4-dihydroisochromen-1-one (8)



Carbons	δ (ppm) and multiplicity	
	^{1}H NMR	**^{13}C NMR**
C-1	-	166.5
C-2	-	-
C-3	4.12, (t), *J* = 3.7 Hz	64.6
C-4	2.86, (t), *J* = 3.7 Hz	32.4
C-5	7.06, (s)	102.6
C-6	-	151.4
C-7	-	116.7
C-8	-	158.7

C-9	-	105.2
C-10	-	143.1
-OCH_3	3.91, (s)	56.8
-CH_2	4.54, (s)	47.1
CH_2-OH	2.28, (s)	-
-OH	10.8, (s)	-

In mass spectrometry the molecular ion peak appeared at *m/z* 224 with 59 % abundance, which confirmed the formation of a natural product *stellatin* **(8)**. A peak was appeared at *m/z* 207 by the removal of hydroxyl radical from molecular ion with 42 % abundance and a base peak observed at *m/z* 194.

The elemental analysis data of compounds **(1-8)** is presented in Table 1.49.

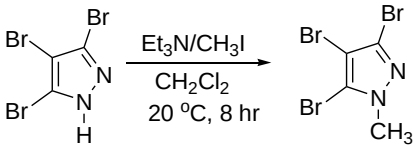
Table 1.49: Elemental analysis data of all the compounds (1-8)

Compounds	**Formulae**	**Elemental Analysis**			
		% Calculated		**% Found**	
		C	**H**	**C**	**H**
1'	$C_{12}H_{16}O_4$	64.28	7.14	64.18	7.06
2	$C_{13}H_{16}O_5$	61.90	6.34	61.77	6.26
3	$C_{13}H_{16}O_6$	58.20	5.97	58.14	5.86
4	$C_{12}H_{16}O_5$	60.02	6.65	59.88	6.57
5	$C_{12}H_{14}O_4$	64.86	6.30	64.75	6.21
6	$C_{12}H_{13}O_4Br$	47.84	4.31	47.72	4.23
7	$C_{12}H_{14}O_5$	60.50	5.88	60.38	5.76
8	$C_{11}H_{10}O_5$	59.45	4.50	59.37	4.38

2.2 Functionalized Pyrazoles

2.2.1 *N*-Methyl-3,4,5-tribromopyrazole (1)

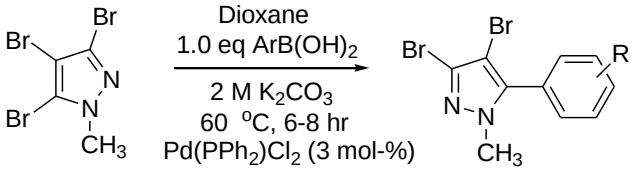
Tribromopyrazole solution in CH_2Cl_2 was treating treated with methyl iodide in the presence of few drops of triethylamine under inert atmosphere afforded *N*-methyl-3,4,5-tribromopyrazole **(1)**.



Scheme 2.1: Synthesis of *N*-Methyl-3,4,5-tribromopyrazole (1)

2.2.2 Synthesis of 3,4-Dibromo-5-(substituted-phenyl)-1-methyl-1H-pyrazoles (2a-g)

Mono-arylated pyrazoles were prepared by reacting *N*-methyl-tribromopyrazole in dioxane solution with (1.0 eq.) of $ArB(OH)_2$, 3 mol % of $Pd(PPh_2)Cl_2$ and few drops of aqueous K_2CO_3 under argon atmosphere at 20 °C. The reaction mixture was heated at 60 °C for 6-8 hr furnished 3,4-dibromo-5-(substituted-phenyl)-1-methyl-1H-pyrazoles **(2a-g)**.



R = *p*-tolyl, 4-methoxyphenyl, 4-ethylphenyl, 3-chlorophenyl, 4-*tert*-butylphenyl, 3-chlorophenyl, 4-fluorophenyl.

Scheme 2.2: 3,4-Dibromo-5-(substituted-phenyl)-1-methyl-1H-pyrazoles (2a-g).

The physical data of 3,4-dibromo-5-(substituted-phenyl)-1-methyl-1H-pyrazoles **(2a-g)** is presented in Table 2.1.

Table 2.1: Physical data of all the compounds (2a-g).

Sr. No	Compound	M.P. (^oC)	R_f Values	Yield (%)	Physical States
2a	4-*p*-tolyl	55-57	0.5	76	white solid
2b	4-methoxyphenyl	72-73	0.4	79	"
2c	4-ethylphenyl	60-61	0.45	81	"

2d	3-chlorophenyl	66-67	0.6	73	“
2e	4-*tert*-butylphenyl	61-62	0.45	82	“
2f	4-chlorophenyl	52-53	0.6	71	“
2g	4-fluorophenyl	55-56	0.65	75	“

[Heptane : ethyl acetate (8:2)]

The characteristic absorptions in IR spectra for ring (C=N) bond were observed in the range of 1611-1626 cm^{-1}. The (C-N) stretching absorptions appeared in the range of 1471-1485 cm^{-1}.

The FTIR spectral data of 3,4-dibromo-5-(substituted-phenyl)-1-methyl-1H-pyrazoles **(2a-g)** is presented in Table 2.2.

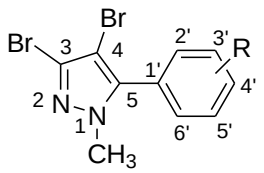
Table 2.2: FTIR data of all the compounds (2a-g).

Sr. No	Compound	Aromatic (C=C-H) cm^{-1}	(C=C) cm^{-1}	(C=N) cm^{-1}	(C–O) cm^{-1}	(C–N) cm^{-1}
2a	4-*p*-tolyl	3048	1564	1621	-	1483
2b	4-methoxyphenyl	3031	1561	1617	1025	1481
2c	4-ethylphenyl	3053	1556	1613	-	1485
2d	3-chlorophenyl	3045	1565	1611	-	1471
2e	4-*tert*-butylphenyl	3055	1563	1623	-	1474
2f	4-chlorophenyl	3052	1567	1626	-	1473
2g	4-fluorophenyl	3051	1558	1616	-	1484

The synthesis of 3,4-dibromo-5-(substituted-phenyl)-1-methyl-1H-pyrazoles **(2b-g)** were confirmed by ^{1}H NMR due to the presence of a characteristic singlet for *N*-CH_3 protons in the range of δ 3.69-3.78 ppm. In ^{13}C NMR spectra the characteristics carbon peaks for *N*-CH_3 appeared at δ 37.8-38.8 ppm.

The ^{1}H and ^{13}C NMR spectral data of 3,4-dibromo-5-(substituted-phenyl)-1-methyl-1H-pyrazoles **(2b-g)** is given in Table 2.3.

Table 2.3: ^{1}H and ^{13}C NMR spectral data of all the compounds (2b-g)



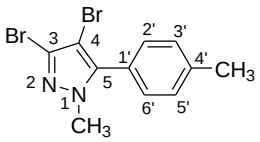
Sr. No	Compounds	^{1}H NMR(δ) (ppm)	^{13}C NMR(δ) (ppm)
2b	4-methoxyphenyl	7.23 (2H, d, *J* = 8.8 Hz, Ar-H), 6.93 (2H, d, *J* = 8.8 Hz, Ar-H), 3.75 (3H, s, *N*-CH_3), 3.67 (3H, s, -OCH_3)	159.5 (C-4'), 142.1 (C-5), 129.8 (C-2',C-6'), 126.1 (C-3), 125.6 (C-1'), 118.2 (C-3',C-5'), 95.2 (C-4), 54.3 (-OCH_3), 37.8 (*N*-CH_3)
2c	4-ethylphenyl	7.25 (2H, d, *J* = 8.4 Hz, Ar-H), 7.20 (2H, d, *J* = 8.4 Hz, Ar-H), 3.69 (3H, s, *N*-CH_3), 2.63 (2H, q, *J* = 7.6 Hz, -CH_2), 1.20 (3H, t, *J* = 7.4 Hz, -CH_3)	143.3 (C-5), 140.6 (C-4'), 129.5 (C-1'), 128.3 (C-3',C-5'), 127.1 (C-3), 126.1 (C-2',C-6'), 96.2 (C-4), 38.5 (*N*-CH_3), 28.7 (Ar-CH_2), 15.2 (-CH_3)
2d	3-chlorophenyl	7.39-7.40 (1H, m, ArH-4'), 7.38 (1H, s, *J* = 2.4 Hz, H-2'), 7.31-7.33 (1H, m, Ar-H-5'), 7.23 (1H, dd, *J* = 7.4,2.4 Hz, ArH-6'), 3.73 (3H, s, *N*-CH_3)	141.8 (C-5), 134.8 (C-3'), 130.2 (C-1'), 129.9 (C-5'), 96.8 (C-4), 129.6 (C-4'), 127.8 (C-2'), 127.4 (C-3), 125.7 (C-6'), 38.7 (*N*-CH_3)
2e	4-*tert*-butylphenyl	7.44 (2H, d, *J* = 6.9 Hz, Ar-H), 7.25 (2H, d, *J* = 7.1 Hz, Ar-H), 3.72 (3H, s, *N*-CH_3), 1.29 (9H, s, 3CH_3)	152.8 (C-4'), 143.3 (C-5), 130.2 (C-1'), 127.2 (C-3), 126.7 (C-2',C-6'), 124.8 (C-3',C-5'), 96.2 (C-4), 38.4 (*N*-CH_3), 34.8 (*tert*-C), 31.2 (-CH_3)
2f	4-chlorophenyl	7.42 (2H, d, *J* = 8.5 Hz, Ar-H), 7.26 (2H, d, *J* = 8.5 Hz, Ar-H), 3.76 (3H, s, *N*-CH_3)	142.1 (C-5). 135.4 (C-4'), 130.6 (C-1'), 129.2 (C-3',C-5'), 128.3 (C-2',C-6'), 127.3 (C-3), 96.6 (C-4), 38.6 (*N*-CH_3)
2g	4-fluorophenyl	7.34 (2H, d, *J* = 7.5 Hz, Ar-H), 7.23 (2H, d, *J* = 7.5 Hz, Ar-H), 3.78 (3H, s, *N*-CH_3); ^{19}F NMR (282.4 MHz, $CDCl_3$, δ ppm): -110.1	163.4 (d, J_{F-C} = 244.7 Hz, C-F), 142.3 (C-5), 131.6 (d, J_{F-C} = 10.8 Hz, C-2',C-6'), 127.2 (C-3), 123.8 (d, J_{F-C} = 3.2 Hz, C-1'), 116.1 (d, J_{F-C} = 21.8 Hz, C-3',C-5'), 96.6 (C-4), 38.8 (*N*-CH_3)

The synthesis of 3,4-dibromo-1-methyl-5-*p*-tolyl-1H-pyrazole **(2a)** was confirmed by ^{1}H NMR due to the presence of a characteristic singlet for *N*-CH_3 and Ar-CH_3 protons

at δ 3.71 and δ 2.35 ppm. In ^{13}C NMR spectra the characteristics carbon peaks for *N*-CH_3 and Ar-CH_3 appeared at δ 38.5 and δ 21.4 ppm.

The ^{1}H and ^{13}C NMR spectral data of compound **(2a)** is presented in Table 2.4.

Table 2.4.: ^{1}H and ^{13}C NMR data of 3,4-Dibromo-1-methyl-5-*p*-tolyl-1H-pyrazole (2a)



Carbons	δ (ppm) and multiplicity	
	^{1}H NMR	**^{13}C NMR**
C-3	-	127.1
C-4	-	96.2
C-5	-	143.3
C-1'	-	129.7
C-4'		139.8
C-2', C-6',	7.24, (d), *J* = 8.5 Hz	125.2
C-3', C-5',	7.19, (d), *J* = 8.5 Hz	129.5
***N*-CH_3**	3.71, (s)	38.5
-CH_3	2.35, (s)	21.4

In the mass spectrum the molecular ion peak was observed at *m/z* 328 with 51 % abundance. The formation of 3,4-dibromo-1-methyl-5-*p*-tolyl-1H-pyrazole **(2a)** was also confirmed by HRMS, calcd for $C_{11}H_{10}N_2Br_2$ (M^+, [^{79}Br, ^{81}Br]): 329.9184. Found. 329.9182.

The elemental analysis data of 3,4-dibromo-5-(substituted-phenyl)-1-methyl-1H-pyrazoles **(2a-g)** is presented in Table 2.5.

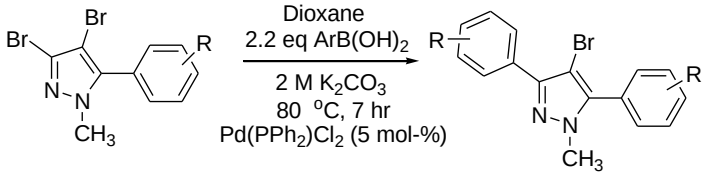
Table 2.5: Elemental analysis data of all the compounds (2a-g).

Compounds	Formulae	HRMS	
		% Calculated	**% Found**
4-*p*-tolyl	$C_{11}H_{10}N_2Br_2$	329.9184	329.9182
4-methoxyphenyl	$C_{11}H_{10}Br_2N_2O$	343.9233	343.9234
4-ethylphenyl	$C_{12}H_{12}Br_2N_2$	341.9443	341.9442
3-chlorophenyl	$C_{10}H_7Br_2ClN_2$	347.8737	347.8745

4-*tert*-butylphenyl	$C_{14}H_{16}Br_2N_2$	369.9753	369.9751
4-chlorophenyl	$C_{10}H_7Br_2ClN_2$	348.8736	348.8734
4-fluorophenyl	$C_{10}H_7Br_2N_2F$	333.9013	333.9016

2.2.3 Synthesis of 4-Bromo-3,5-bis(substituted-phenyl)-1-methyl-1H-pyrazoles (3a-c)

3,5-Diaryled-4-bromopyrazoles were prepared by treating dioxane solution of *N*-methyl-tribromopyrazole with (2.2 eq.) of $ArB(OH)_2$, 5 mol % of $Pd(PPh_2)Cl_2$ and few drops of aqueous K_2CO_3 under argon atmosphere at 20 °C. The reaction mixture was heated at 80 °C for 7 hr afforded 4-bromo-3,5-bis(substituted-phenyl)-1-methyl-1H-pyrazoles **(3a-c)**.



R = *p*-tolyl, 4-methoxyphenyl, 4-fluorophenyl.

Scheme 2.3: Synthesis of 4-Bromo-3,5-bis(substituted-phenyl)-1-methyl-1H-pyrazoles (3a-c).

The physical data of 4-bromo-3,5-bis(substituted-phenyl)-1-methyl-1H-pyrazoles **(3a-c)** is presented in Table 2.6.

Table 2.6: Physical data of all the compounds (3a-c).

Sr. No	Compound	M.P. (^oC)	R_f Values	Yield (%)	Physical States
3a	*Bis*-(4-methoxyphenyl)	91-92	0.35	60	white solid
3b	*Bis*-(4-*p*-tolyl)	83-84	0.45	62	“
3c	*Bis*-(4-flourophenyl)	105-106	0.5	67	“

In the IR spectra, the characteristic absorptions for ring (C=N) bond were observed in the range of 1613-1618 cm^{-1}. The (C-N) stretching absorptions appeared at 1441-1446 cm^{-1}.

The FTIR spectral data of 4-bromo-3,5-bis(substituted-phenyl)-1-methyl-1H-pyrazoles **(3a-c)** is presented in Table 2.7.

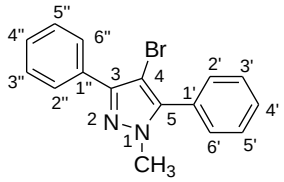
Table 2.7: FTIR data of all the compounds (3a-c).

Sr. No	Compound	Aromatic (C=C-H) cm^{-1}	(C=C) cm^{-1}	(C=N) cm^{-1}	(C–O) cm^{-1}	(C–N) cm^{-1}
3a	*Bis*-(4-methoxyphenyl)	3023	1561	1613	1028	1441
3b	*Bis*-(4-*p*-tolyl)	3026	1563	1618	-	1446
3c	*Bis*-(4-flourophenyl)	3034	1565	1614	-	1443

The synthesis of 4-bromo-3,5-bis(substituted-phenyl)-1-methyl-1H-pyrazoles **(3b-c)** were confirmed by ^{1}H NMR due to the presence of a characteristic singlet for *N*-CH_3 protons at δ 3.75 and δ 3.78 ppm. In ^{13}C NMR spectra the characteristics carbon peaks for *N*-CH_3 appeared at δ 38.6 and δ 38.8 ppm.

The ^{1}H NMR and ^{13}C NMR spectral data of 4-bromo-3,5-bis(substituted-phenyl)-1-methyl-1H-pyrazoles **(3b-c)** is represented in Table 2.8.

Table 2.8: ^{1}H NMR and ^{13}C NMR spectral data of all the compounds (3b-c)

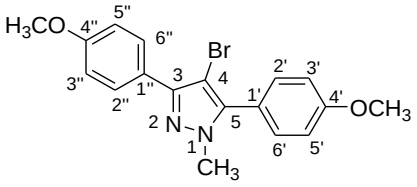


Sr. No	Compounds	^{1}H NMR(δ) (ppm)	^{13}C NMR(δ) (ppm)
3b	*Bis*-(4-*p*-tolyl)	7.78 (2H, d, *J* = 8.2 Hz, H-2',H-6'), 7.32 (2H, d, *J* = 8.4 Hz, H-2'',H-6''), 6.94 (2H, d, *J* = 8.2 Hz, H-3',H-5'), 6.85 (2H, d, *J* = 8.4 Hz, H-3'',H-5''), 3.75 (*N*-CH_3), 2.33 (4'-CH_3), 2.31 (4''-CH_3)	156.8 (C-3), 143.6 (C-5), 138.7 (C-4'), 138.2 (C-4''), 130.7 (C-1'), 130.3 (C-1''), 129.9 (C-3',C-5'), 129.7 (C-3'',C-5''), 127.6 (C-2',C-6'), 127.2 (C-2'',C-6''), 91.6 (C-4), 38.6 (*N*-CH_3), 23.3 (C-4'-CH_3), 23.1 (C-4''-CH_3)
3c	*Bis*-(4-flourophenyl)	7.91 (2H, d, *J* = 7.3 Hz, H-2',H-6'), 7.82 (2H, d, *J* = 7.2 Hz, H-2'',H-6''), 7.23 (2H, d, *J* = 7.3 Hz, H-3',H-5'), 6.97 (2H, d, *J* = 7.2 Hz, H-3'',H-5''), 3.78 (*N*-CH_3); ^{19}F NMR (300 MHz, $CDCl_3$, δ ppm): -113.5, -110.8	164.4 (d, $J_{F,C}$ = 248.5 Hz, 4''-C-F), 163.8 (d, $J_{F,C}$ = 249.2 Hz, 4'-C-F), 156.5 (C-3),. 142.3 (C-5), 131.7 (d, $J_{F,C}$ = 8.4 Hz, C-2',C-6'), 129.5 (d, $J_{F,C}$ = 8.1 Hz, C-2'',C-6''), 128.6 (C-1'),128.4 (C-1''), 115.0 (d, $J_{F,C}$ = 21.8 Hz, C-3',C-5'), 114.3 (d, $J_{F,C}$ = 21.5 Hz, C-3'',C-5''), 92.8 (C-4), 38.8 (*N*-CH_3)

The synthesis of 4-bromo-3,5-bis(4-methoxyphenyl)-1-methyl-1H-pyrazole **(3a)** was confirmed by ^{1}H NMR due to the presence of a characteristic singlet for *N*-CH_3 protons at δ 3.76 and two singlets for Ar-OCH_3 protons appeared at δ 3.83 and δ 3.87 ppm. In ^{13}C NMR spectra the characteristics carbon peaks for *N*-CH_3 appeared at δ 38.7 and two carbon peaks Ar-CH_3 observed at δ 55.2 and δ 55.4 ppm.

The ^{1}H and ^{13}C NMR of compound **(3a)** is presented in Table 2.9.

Table 2.9: ^{1}H and ^{13}C NMR of 4-Bromo-3,5-bis(4-methoxyphenyl)-1-methyl-1H-pyrazole (3a)



Carbons	δ (ppm) and multiplicity	
	^{1}H NMR	**^{13}C NMR**
C-3	-	147.9
C-4	-	93.6
C-5		158.7
C-4'	-	158.2
C-4''	-	158.2
C-1'	-	124.9
C-1''	-	123.3
C-2', C-6'	7.71, (d), *J* = 8.3Hz	130.6
C-2'', C-6''	7.29, (d), *J* = 8.6 Hz	128.6
C-3', C-5'	6.90, (d), *J* = 8.1 Hz	115.6
C-3'', C-5''	6.87, (d), *J* = 8.4 Hz	113.8
4'-OCH_3	3.87, (s)	55.4
4''-OCH_3	3.83, (s)	55.2
***N*-CH_3**	3.76, (s)	38.7

In the mass spectrum, the molecular ion peak observed at *m/z* 372 with 52 % abundance. The formation of 4-bromo-3,5-bis(4-methoxyphenyl)-1-methyl-1H-pyrazole **(3a)** was also confirmed by HRMS, calcd for $C_{18}H_{17}N_2BrO_2$ $[M+1,^{81}Br]^{+}$: 374.1327. found. 372.1346.

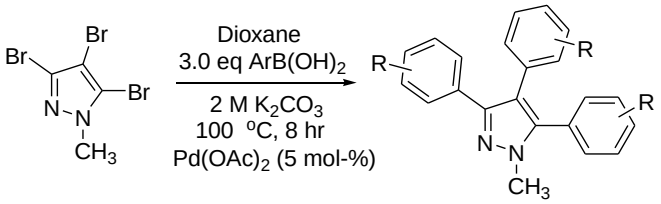
The elemental analysis data of 4-bromo-3,5-bis(substituted-phenyl)-1-methyl-1H-pyrazoles **(3b-c)** is presented in Table 2.10.

Table 2.10: Elemental analysis data of all the compounds (3a-c).

Compounds	Formulae	HRMS	
		% Calculated	% Found
Bis-(4-methoxyphenyl)	$C_{18}H_{16}N_2BrO_2$	371.1346	371.1346
Bis-(4-*p*-tolyl)	$C_{18}H_{16}N_2Br$	339.0613	339.0613
Bis-(4-flourophenyl)	$C_{16}H_{12}N_2BrF_2$	347.0134	347.0134

2.2.4 Synthesis of 1-Methyl-3,4,5-*tri*-(substituted-phenyl)-1H-pyrazoles (4a-g)

3,4,5-Triarylated-pyrazoles were synthesized by the addition of (3.0 eq.) of $ArB(OH)_2$, 5 mol % $Pd(OAc)_2$ and few drops of aqueous K_2CO_3 to a dioxane solution of *N*-methyl-tribromopyrazole under argon atmosphere at 20 °C. By heating the reaction mixture at 100 °C for 8 hr yielded 1-methyl-3,4,5-*tri*-(substituted-phenyl)-1H-pyrazoles **(4a-g)**



R = *p*-tolyl, 4-methoxyphenyl, 4-ethylphenyl, 3-chlorophenyl, 4-*tert*-butylphenyl, 4-fluorophenyl, 3,5-dimethyphenyl, 2,6-dimethyphenyl.

Scheme 2.4: Synthesis of 1-Methyl-3,4,5-*tri*-(substituted-phenyl)-1H-pyrazoles (4a-g)

The physical data of 1-methyl-3,4,5-*tri*-(substituted-phenyl)-1H-pyrazoles **(4a-g)** is presented in Table 2.11.

Table 2.11: Physical data of all the compounds (4a-g).

Sr. No	Compound	M.P. (^oC)	R_f Values	Yield (%)	Physical States
4a	*Tris*-(4-*p*-tolyl)	145-146	0.4	91	white solid
4b	*Tris*-(4-ethylphenyl)	133-134	0.4	89	"
4c	*Tris*-(4-*tert*-butylphenyl)	123-124	0.3	86	"
4d	*Tris*-(4-(3,5-	167-168	0.35	84	"

	dimethylphenyl)				
4e	*Tris*-(4-fluorophenyl)	121-122	0.45	87	“
4f	*Tris*-(4-methoxyphenyl)	160-161	0.3	81	“
4g	*Tris*-(3,5-dimethylphenyl)	150-151	0.4	75	“

In IR spectra, the characteristic absorptions for ring (C=N) bond were observed in the range of 1622-1630 cm^{-1}. The (C-N) stretching absorptions were appeared in the range of 1438-1447 cm^{-1}.

The FTIR spectral data of 1-methyl-3,4,5-*tri*-(substituted-phenyl)-1H-pyrazoles **(4a-g)** is presented in Table 2.12.

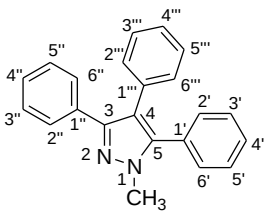
Table 2.12: FTIR data of all the compounds (4a-g).

Sr. No	Compounds	Aromatic (C=C-H) cm^{-1}	(C=C) cm^{-1}	(C=N) cm^{-1}	(C–O) cm^{-1}	(C–N) cm^{-1}
4a	*Tris*-(4-*p*-tolyl)	3028	1578	1622	-	1440
4b	*Tris*-(4-ethylphenyl)	3033	1573	1624	-	1442
4c	*Tris*-(4-*tert*-butylphenyl)	3035	1575	1627	-	1438
4d	*Tris*-(4-(3,5-dimethylphenyl)	3038	1578	1630	-	1445
4e	*Tris*-(4-fluorophenyl)	3042	1572	1626	-	1443
4f	*Tris*-(4-methoxyphenyl)	3036	1574	1628	1037	1447
4g	*Tris*-(3,5-dimethylphenyl)	3034	1577	1625	-	1441

The synthesis of 1-methyl-3,4,5-*tri*-(substituted-phenyl)-1H-pyrazoles **(4b-g)** were confirmed by ^{1}H NMR due to the presence of a characteristic singlet for *N*-CH_3 protons in the range of δ 3.74-3.77 ppm. In ^{13}C NMR spectra the characteristics carbon peaks for *N*-CH_3 appeared at δ 37.2-37.8 ppm.

The ^{1}H and ^{13}C NMR spectral data of 1-methyl-3,4,5-*tri*-(substituted-phenyl)-1H-pyrazoles **(4b-g)** is presented in Table 2.13.

Table 2.13: ^{1}H and ^{13}C NMR spectral data of all the compounds (4b-g)



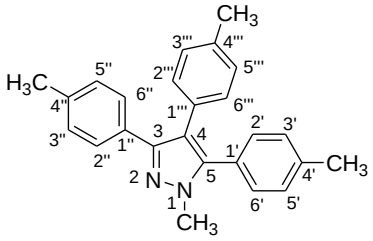
Sr. No	Compounds	^{1}H NMR(δ) (ppm)	^{13}C NMR(δ) (ppm)
4b	*Tris*-(4-ethylphenyl)	7.30 (2H, d, *J* = 8.2 Hz, H-2',H-6'), 7.10 (2H, d, *J* = 8.7 Hz, H-2'',H-6''), 7.06 (2H, d, *J* = 8.3 Hz, H-2''',H-6'''), 7.02 (2H, d, *J* = 8.0 Hz, H-3'',H-5''), 6.92 (2H, d, *J* = 8.4 Hz, H-3''',H-5'''), 6.89 (2H, d, *J* = 8.2 Hz, H-3',H-5'), 3.76 (3H, s, *N*-CH_3), 2,46-2.63 (6H, m, 3CH_2), 1.09-1.20 (9H, m, 3CH_3)	147.4 (C-3), 143.3 (C-5), 142.0 (C-4''), 141.1(C-4'), 140.8 (C-4'''), 130.0 (C-1'''), 129.7 (C-1''), 129.2 (C-1'), 127.1 (C-3',C-5'), 126.9 (C-5''',C-5'''), 126.8 (C-3'',C-5''), 126.6 (C-2',C-6'), 126.5 (C-2''',C-6'''), 126.4 (C-2'',C-6''), 117.6 (C-4), 37.4 (*N*CH_3), 27.6 (-CH_2), 27.5 (-CH_2), 27.3 (-CH_2), 14.3 (4'-CH_3), 14.2 (4''-CH_3), 14.1 (4'''-CH_3)
4c	*Tris*-(4-*tert*-butylphenyl)	7.33 (2H, d, *J* = 8.5 Hz, H-2',H-6'), 7.28 (2H, d, *J* = 8.2 Hz, H-2''',H-6'''), 7.18 (2H, d, *J* = 8.2 Hz, H-2'',H-6''), 7.10 (2H, d, *J* = 8.3 Hz, H-2''',H-6'''), 7.08 (2H, d, *J* = 8.5 Hz, H-3',H-5'), 6.93 (2H, d, *J* = 8.4 Hz, H-2'',H-6''), 3.75 (3H, s, *N*-CH_3), 1.25 (9H, s, 3CH_3), 1.22 (9H, s, 3CH_3), 1.20 (9H, s, 3CH_3)	151.2 (C-4'), 149.9 (C-4''), 148.8 (C-4'''), 142.1 (C-5), 141.3 (C-3), 130.8 (C-1'''), 130.4 (C-1'), 130.1 (C-1''), 127.8 (C-2',C-6'), 127.5 (C-2'',C-6''), 126.2 (C-2''',C-6'''), 125.2, (C-3',C-5'), 125.0 (C-3'',C-5''), 124.8 (C-3''',C-5'''), 118.6 (C-4), 37.3 (*N*-CH_3), 31.4 (3CH_3),, 31.3 (3CH_3), 31.2 (3CH_3)
4d	*Tris*-(4-(3,5-dimethylphenyl)	7.04 (2H, d, *J* = 7.2 Hz, H-6',H-6''), 6.87 (1H, d, *J* = 7.3 Hz, Ar-H-6'''), 6.78 (2H, d, *J* = 7.2 Hz, H-5',H-5''), 6.74 (1H, d, *J* = 7.3 Hz, Ar-H5'''), 6.69 (1H, d, *J* = 2.2 Hz, Ar-H-3'), 6.61 (2H, d, *J* = 2.2 Hz, H-3'',H-3'''), 3.74 (3H, s, *N*-CH_3), 2.20 (6H, s, 2CH_3), 2.14 (6H, s, 2CH_3), 2.06 (6H, s, 2CH_3)	148.3 (C-3), 142.3 (C-5); 138.0 (C-4''), 137.3 (C-4'), 136.9 (C-4'''), 133.4 (C-2''), 133.2 (C-2'), 131.4 (C-1'''), 130.2 (C-2'''), 130.0 (C-3''), 128.8 (C-3'), 128.2 (C-3''), 127.9 (C-6''), 127.8 (C-6'), 127.4 (C-6'''), 126.7 (C-5',C-5''), 126.3 (C-5'''), 125.8 (C-1',C-1''), 123.3 (C-4), 37.5 (*N*-CH_3), 21.3 (6CH_3), 21.2 (6CH_3), 21.1 (6CH_3)
4e	*Tris*-(4-fluorophenyl)	7.33 (2H, d, *J* = 8.7 Hz, H-2''',H-6'''), 7.13 (2H, d, *J* = 8.6 Hz, H-2',H-6'), 7.00 (2H, d, *J* = 8.5 Hz, H-2',H-6'), 6.92 (2H, d, *J* = 8.7 Hz,	164.7 (d, $J_{F,C}$ = 248.4 Hz, 4''-C-F), 163.6 (d, $J_{F,C}$ = 249.1 Hz, 4'''-C-F), 163.3 (d, $J_{F,C}$ = 249.4 Hz, 4'-C-F), 142.8 (C-3), 140.3 (C-5), 131.9 (d, $J_{F,C}$ = 8.1 Hz, C-2'',C-6''), 131.7

		H-3’’’,H-5’’’), 6.87 (2H, d, *J* = 8.4 Hz, H-3’,H-5’), 6.81 (2H, d, *J* = 8.6 Hz, H-3’’,H-5’’), 3.77 (3H, s, *N*-CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, δ ppm): -111.9, -114.5, -115.5	(d, $J_{F,C}$ = 8.0 Hz, C-2’,C-6’), 130.6 (d, $J_{F,C}$ = 8.1 Hz, C-2’’’,C-6’’’), 129.6 (d, $J_{F,C}$ = 3.2 Hz, C-1’’’), 129.2 (d, $J_{F,C}$ = 3.2 Hz, C-1’), 125.7 (d, $J_{F,C}$ = 3.6 Hz, C-1’’), 124.5 (C-4), 115.8 (d, $J_{F,C}$ = 21.6 Hz, C-3’’’,C-5’’’), 115.4 (d, $J_{F,C}$ = 21.4 Hz, C-3’,C-5’), 115.2 (d, $J_{F,C}$ = 21.4 Hz, C-3’’,C-5’’), 37.8 (*N*-CH_3)
4f	*Tris*-(4-methoxyphenyl)	7.31 (2H, d, *J* = 8.5 Hz, H-2’,H-6’), 7.06 (2H, d, *J* = 8.6 Hz, H-2’’,H-6’’), 6.88 (2H, d, *J* = 8.8 Hz, H-2’’’,H-6’’’), 6.79 (2H, d, *J* = 8.5 Hz, H-3’,H-5’), 6.72 (2H, d, *J* = 8.6 Hz, H-3’’,H-5’’), 6.63 (2H, d, *J* = 8.8 Hz, H-3’’’,H-5’’’), 3.75 (3H, s, *N*-CH_3), 3.71 (3H, s, -OCH_3), 3.69 (3H, s, -OCH_3), 3.66 (3H, s, -OCH_3)	159.9 (C-4’), 158.8 (C-4’’), 158.2 (C-4’’’), 143.2 (C-5), 141.7 (C-3), 131.5 (C-2’,C-6’), 131.4 (C-2’’,C-6’’), 129.2 (C-2’’’,C-6’’’), 128.7 (C-1’’’), 126.3 (C-1’), 126.1 (C-1’’), 123.5 (C-4), 113.9 (C-3’,C-5’), 113.7 (C-3’’,C-5’’), 113.6 (C-3’’’,C-5’’’), 55.8 (4’-OCH_3), 55.7 (4’’-OCH_3), 55.4 (4’’’-OCH_3), 37.2 (*N*-CH_3)
4g	*Tris*-(3,5-dimethylphenyl)	7.06 (1H, s, Ar-H-4’), 7.01 (1H, s, Ar-H-4’’), 6.88 (2H, s, H-2’,H-6’), 6.78 (1H, s, Ar-H-4’’’), 6.76 (2H, s, H-2’’,H-6’’), 6.68 (2H, s, H-2’’’,H-6’’’), 3.74 (3H, s, *N*-CH_3), 2.20 (6H, s, $2CH_3$), 2.14 (s, 6H, s, $2CH_3$), 2.06 (s, 6H, s, $2CH_3$)	142.3 (C-3), 140.3 (C-5), 138.2 (C-3’,C-5’), 137.7 (C-3’’,C-5’’), 137.3 (C-3’’’,C-5’’’), 136.8 (C-1’’’), 133.4 (C-1’), 133.2 (C-1’’), 130.0 (C-4’), 129.8 (C-4’’), 129.4 (C-4’’’), 127.8 (C-2’,C-6’), 127.6 (C-2’’,C-6’’), 127.4 (C-2’’’,C-6’’’), 123.6 (C-4), 37.3 (*N*-CH_3), 21.3 ($6CH_3$), 21.2 ($6CH_3$), 21.1 ($6CH_3$)

The synthesis of 1-methyl-3,4,5-tri-(*p*-tolyl)-1H-pyrazole **(4a)** was confirmed by ^{1}H NMR due to the presence of a characteristic singlet for *N*-CH_3 protons at δ 3.76 and three singlets for Ar-CH_3 protons at δ 2.28, 2.24, 2.21 ppm. In ^{13}C NMR spectra the characteristics carbon peak for *N*-CH_3 was observed at δ 37.2 and three carbon signals for Ar-CH_3 were appeared at δ 21.3, 21.2, 21.1 ppm.

The ^{1}H and ^{13}C NMR spectral data of compound **(4a)** is presented in Table 2.14.

Table 2.14: ^{1}H and ^{13}C NMR spectral data of 1-Methyl-3,4,5-tri-(*p*-tolyl)-1H-pyrazole (4a)



Carbons	δ (ppm) and multiplicity	
	^{1}H NMR	^{13}C NMR
C-3	-	142.1
C-5	-	148.4
C-4	-	123.7
C-1''	-	136.3
C-1'	-	130.3
C-1''		130.1
C-1'''		130.7
C-2', C-6'	7.27, (d), *J* = 8.1 Hz	128.7
C-2'', C-6''	7.09, (d), *J* = 7.8 Hz	127.9
C-2''', C-6'''	7.03, (d), *J* = 8.3 Hz	127.3
C-3', C-5'	6.99, (d), *J* = 8.1 Hz	129.3
C-3'', C-5''	6.89, (d), *J* = 8.3 Hz	129.1
C-3''', C-5'''	6.84, (d), *J* = 8.3 Hz	128.9
C-4'	-	138.2
C-4''	-	136.8
C-4'''	-	135.6
***N*-CH$_3$**	3.76, (s)	37.2
4'-CH$_3$	2.28, (s)	21.3
4''-CH$_3$	2.24, (s)	21.2
4'''-CH$_3$	2.21, (s)	21.1

In the mass spectrum, the molecular ion peak was observed at *m/z* 352 as base peak with 100 % abundance. The formation of 1-methyl-3,4,5-tri-(*p*-tolyl)-1H-pyrazole **(4a)** was also confirmed by HRMS, calcd for $C_{25}H_{24}N_2$ $[M+1]^+$: 353.2012. found 353.2012.

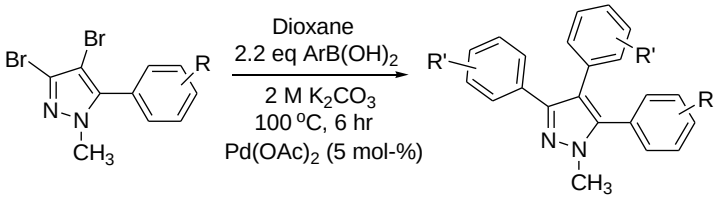
The elemental analysis data of 1-methyl-3,4,5-*tri*-(substituted-phenyl)-1H-pyrazoles **(4a-g)** is presented in Table 2.15.

Table 2.15: Elemental analysis data of all the compounds (4a-g).

Compounds	Formulae	HRMS	
		% Calculated	% Found
Tris-(4-*p*-tolyl)	$C_{25}H_{23}N_2$	352.2012	352.2012
Tris-(4-ethylphenyl)	$C_{28}H_{30}N_2$	394.2482	394.2486
Tris-(4-*tert*-butylphenyl)	$C_{34}H_{41}N_2$	340.9443	340.9442
Tris-(4-(3,5-dimethylphenyl)	$C_{28}H_{30}N_2$	394.2482	394.2483
Tris-(4-fluorophenyl)	$C_{22}H_{15}N_2F_3$	364.1264	364.1263
Tris-(4-methoxyphenyl)	$C_{25}H_{24}N_2O_3$	400.1867	400.1868
Tris-(3,5-dimethylphenyl)	$C_{28}H_{30}N_2$	390.2482	390.2483

2.2.5 Synthesis of 1-Methyl-3,4-diphenyl-5-(substituted-phenyl)-1H-pyrazoles (5a-i)

3,4,5-Triarylated-pyrazoles were prepared by the addition of (2.2 eq.) of $ArB(OH)_2$, 5 mol % $Pd(OAc)_2$ and few drops of aqueous K_2CO_3 to a dioxane solution of 3,4-dibromo-5-arylated pyrazoles under argon atmosphere at 20 °C. By heating the reaction mixture at 100 °C for 6 hr afforded 1-methyl-3,4-diphenyl-5-(substituted-phenyl)-1H-pyrazoles **(5a-i)**.



R = *p*-tolyl, 4-methoxyphenyl, 4-ethylphenyl, 3-chlorophenyl, 4-*tert*-butylphenyl, 3-chlorophenyl, 4-fluorophenyl, 3,4-dimethylphenyl, 2,6-dimethylphenyl.

Scheme 2.5: Synthesis of 1-Methyl-3,4-diphenyl-5-(substituted-phenyl)-1H-pyrazoles (5a-i)

The physical data of 1-methyl-3,4-diphenyl-5-(substituted-phenyl)-1H-pyrazoles **(5a-i)** is presented in Table 2.16.

Table 2.16: Physical data of all the compounds (5a-i).

Sr. No	Compound	M.P. (^oC)	R_f Values	Yield (%)	Physical States
5a	1-Methyl-3,4-diphenyl-5-*p*-tolyl-1H-pyrazole	146-147	0.5	92	white solid
5b	3,4-Bis(4-methoxyphenyl)-1-methyl-5-(4-methylphenyl)-1H-pyrazole	159-160	0.35	84	"
5c	5-(4-Ethylphenyl)-1-methyl-3,4-diphenyl-1H-pyrazole	152-153	0.5	89	"
5d	3,4-Bis(3-chlorophenyl)-5-(4-ethylphenyl)-1-methyl-1H-pyrazole	147-148	0.55	82	"
5e	5-(4-Ethylphenyl)-3,4-bis(4-methoxyphenyl)-1-methyl-1H-pyrazole	168-169	0.3	86	"
5f	5-(4-Chlorophenyl)-1-methyl-3,4-diphenyl-1H-pyrazole	156-157	0.45	79	"
5g	5-(4-Chlorophenyl)-3,4-bis(4-ethylphenyl)-1-methyl-1H-pyrazole	148-149	0.4	81	"
5h	5-(4-Methoxyphenyl)-1-methyl-3,4-di-4-methylphenyl-1H-pyrazole	157-158	0.35	83	"
5i	3,4-Bis(4-chlorophenyl)-5-(4-methoxyphenyl)-1-methyl-1H-pyrazole	170-171	0.35	82	"

In IR spectra, the characteristic absorptions for ring (C=N) bond were observed in the range of 1630-1638 cm^{-1}. The (C-N) stretching absorptions appeared in the range of 1440-1456 cm^{-1}.

The FTIR spectral data of 1-methyl-3,4-diphenyl-5-(substituted-phenyl)-1H-pyrazoles **(5a-i)** is presented in Table 2.17.

Table 2.17: FTIR data of all the compounds (5a-i).

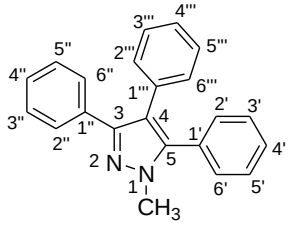
Sr. No	Compound	Aromatic (C=C-H) cm^{-1}	(C=C) cm^{-1}	(C=N) cm^{-1}	(C–O) cm^{-1}	(C–N) cm^{-1}
5a	1-Methyl-3,4-diphenyl-5-*p*-tolyl-1H-pyrazole	3035	1574	1628	-	1441
5b	3,4-Bis(4-methoxyphenyl)-	3041	1578	1632		1447

	1-methyl-5-(4-methylphenyl)-1H-pyrazole				1035	
5c	5-(4-Ethylphenyl)-1-methyl-3,4-diphenyl-1H-pyrazole	3043	1580	1634	-	1452
5d	3,4-Bis(3-chlorophenyl)-5-(4-ethylphenyl)-1-methyl-1H-pyrazole	3046	1586	1637	-	1454
5e	5-(4-Ethylphenyl)-3,4-bis(4-methoxyphenyl)-1-methyl-1H-pyrazole	3052	1584	1638	1043	1456
5f	5-(4-Chlorophenyl)-1-methyl-3,4-diphenyl-1H-pyrazole	3045	1575	1633	-	1446
5g	5-(4-Chlorophenyl)-3,4-bis(4-ethylphenyl)-1-methyl-1H-pyrazole	3041	1582	1631	-	1443
5h	5-(4-Methoxyphenyl)-1-methyl-3,4-di-4-methylphenyl-1H-pyrazole	3053	1576	1630	1037	1440
5i	3,4-Bis(4-chlorophenyl)-5-(4-methoxyphenyl)-1-methyl-1H-pyrazole	3050	1583	1636	1040	1453

The synthesis of 1-methyl-3,4-diphenyl-5-(substituted-phenyl)-1H-pyrazoles **(5b-i)** were confirmed by ^{1}H NMR due to the presence of a characteristic singlet for *N*-CH_3 protons in the range of δ 3.72-3.85 ppm. In ^{13}C NMR spectra the characteristics carbon peaks for *N*-CH_3 appeared at δ 37.2-37.6 ppm.

The ^{1}H and ^{13}C NMR spectral data of 1-methyl-3,4-diphenyl-5-(substituted-phenyl)-1H-pyrazoles **(5b-i)** is presented in Table 2.18.

Table 2.18: ^{1}H and ^{13}C NMR spectral data of all the compounds (5b-i)



Sr. No	Compounds	^{1}H NMR(δ) (ppm)	^{13}C NMR(δ) (ppm)
5b	3,4-Bis(4-methoxyphenyl)-1-	7.30-7.33 (2H, d, *J* = 7.2 Hz, Ar-H-2'',H-6''), 7.12-7.21 (2H,	157.9 (C-4'''), 158.8 (C-4''), 142.3 (C-3), 140.5 (C-

	methyl-5-(4-methylphenyl)-1H-pyrazole	d, *J* = 7.3 Hz, Ar-H-2',H-6'), 6.97-7.04 (2H, d, *J* = 7.2 Hz, Ar-H-2''',H-6'''), 6.81-6.85 (2H, d, *J* = 7.3 Hz, Ar-H-3',H-5'), 6.73-6.78 (4H, d, *J* = 7.2 Hz, H-3'',5'',H-3''',5'''), 3.76 (3H, s, *N*-CH_3), 3.71 (3H, s, -OCH_3), 3.68 (3H, s, -OCH_3), 2.28 (3H, s, Ar-CH_3)	5), 138.1 (C-4'), 131.4 (C-1'), 130.1 (C-3',C-5'), 129.3 (C-3'',C-5''), 129.1 (C-3''',C-5'''), 128.4 (C-1'''), 127.3 (C-2',C-6'), 126.7 (C-2'',C-6''), 126.2 (C-2''',C-6'''), 125.3 (C-1''), 123.6 (C-4), 118.1, 55.3 (4'''-OCH_3), 55.1 (4''-OCH_3), 37.2 (*N*-CH_3), 21.3 (-CH_3)
5c	5-(4-Ethylphenyl)-1-methyl-3,4-diphenyl-1H-pyrazole	7.37-7.40 (2H, d, *J* = 7.2 Hz, Ar-H-2',H-6'), 7.17-7.21 (5H, m, Ar-H), 7.05-7.10 (5H, m, Ar-H), 6.96-6.99 (2H, d, *J* = 7.2 Hz, Ar-H-3',H-5'), 3.79 (3H, s, *N*-CH_3), 2.58 (2H, q, *J* = 7.6 Hz, -CH_2), 1.18 (3H, t, *J* = 7.5 Hz, -CH_3)	142.3 (C-3), 141.4 (C-5), 140.5 (C-4'), 133.5 (C-1'''), 130.4 (C-1''), 130.1 (C-1'), 129.8 (C-3'',C-5''), 129.5 (C-3''',C-5'''), 128.7 (C-4'''), 128.5 (C-4''), 128.2 (C-3',C-5'), 127.8 (C-2'',C-6''), 127.4 (C-2''',C-6'''), 127.1 (C-2',C-6'), 123.5 (C-4), 37.3 (*N*-CH_3), 28.5 (-CH_2), 15.3 (-CH_3)
5d	3,4-Bis(3-chlorophenyl)-5-(4-ethylphenyl)-1-methyl-1H-pyrazole	7.37-7.40 (2H, d, *J* = 7.1 Hz, Ar-H-2',H-6'), 7.17-7.21 (2H, d, *J* = 2.1 Hz, Ar-H-2',H-2'''), 7.10-7.16 (4H, m, H-4'',5'',H-4'''.5'''), 7.03-7.08 (2H, d, *J* = 7.2 Hz, Ar-H-6',H-6'''), 6.95-6.98 (2H, d, *J* = 7.1 Hz, Ar-H-3',H-5'), 3.79 (3H, s, *N*-CH_3), 2.57 (2H, q, *J* = 7.6 Hz, -CH_2), 1.18 (3H, t, *J* = 7.5 Hz, -CH_3)	142.7 (C-3), 141.3 (C-5), 141.3 (C-5), 140.6 (C-4'), 138.3 (C-1'''), 135.1 (C-3'''), 134.8 (C-3'''), 133.8 (C-1''), 130.6 (C-5''), 130.3 (C-5'''), 130.1 (C-1'), 129.8 (C-4''), 129.4 (C-4'''), 128.7 (C-3',C-5'), 128.5 (C-2''), 128.2 (C-2'''), 127.5 (C-2',C-6'), 126.7 (C-6''), 126.5 (C-6'''), 123.7 (C-4), 37.6 (*N*-CH_3), 28.5 (-CH_2), 15.4 (-CH_3)
5e	5-(4-Ethylphenyl)-3,4-bis(4-methoxyphenyl)-1-methyl-1H-pyrazole	7.42 (2H, d, *J* = 7.4 Hz, Ar-H-2',H-6'), 7.37 (2H, d, *J* = 7.8 Hz, Ar-H-2'',H-6''), 7.31 (2H, d, *J* = 7.8 Hz, Ar-H-2''',H-6'''), 7.18 (2H, d, *J* = 7.4 Hz, Ar-H-3',H-5'), 6.88 (2H, d, *J* = 7.8 Hz, Ar-H-3''',H-5'''), 6.74	158.8 (C-4''), 158.3 (C-4'''), 142.1 (C-3), 140.3 (C-5), 139.4 (C-4'), 130.0 (C-1'), 129.2 (C-1'''), 128.9 (C-2'',C-6''), 128.5 (C-2''',C-6'''), 128.3 (C-2',C-6'), 127.3 (C-3',C-5'),

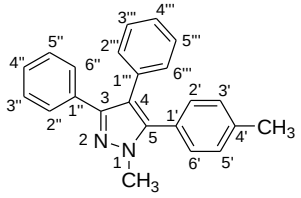
		(2H, d, *J* = 7.8 Hz, Ar-H-3’’,H-5’’), 3.76 (3H, s, *N*-CH_3), 3.71 (3H, s, OCH_3), 3.68 (3H, s, -OCH_3), 2.58 (2H, q, *J* = 7.6 Hz, -CH_2), 1.17 (3H, t, *J* = 7.5 Hz, -CH_3)	125.7 (C-1’’), 123.6 (C-4), 113.6 (C-3’’’,C-5’’’), 113.4 (C-3’’,C-5’’), 55.3 (4’’-OCH_3), 55.1 (4’’’-OCH_3), 37.2 (*N*-CH_3), 28.5 (-CH_2), 15.2 (-CH_3)
5f	5-(4-Chlorophenyl)-1-methyl-3,4-diphenyl-1H-pyrazole	7.50-7.54 (2H, d, *J* = 7.1 Hz, Ar-H-2’,H-6’), 7.38-7.42 (2H, d, *J* = 7.2 Hz, Ar-H-2’’,H-6’’), 7.28-7.34 (2H, d, *J* = 7.2 Hz, Ar-H-2’’’,H-6’’’), 7.20-7.26 (4H, m, H-3’’,5’’,H-3’’’,5’’’), 7.09-7.14 (2H, m, H-4’’,H-4’’’), 6.97-7.02 (2H, d, *J* = 7.2 Hz, Ar-H-3’,H-5’), 3.85 (3H, s, *N*-CH_3)	142.1 (C-3), 140.2 (C-5), 136.4 (C-1’’’), 133.7 (C-4’), 133.4 (C-1’’), 131.4 (C-1’), 130.5 (C-3’,C-5’), 129.8 (C-3’’,C-5’’), 129.4 (C-3’’’,C-5’’’), 128.8 (C-2’,C-6’), 128.3 (C-4’’), 128.1 (C-4’’’), 127.4 (C-2’’,C-6’’), 127.1 (C-2’’’,C-6’’’), 123.7 (C-4), 37.5 (*N*-CH_3)
5g	5-(4-Chlorophenyl)-3,4-bis(4-ethylphenyl)-1-methyl-1H-pyrazole	7.30 (2H, d, *J* = 7.2 Hz, Ar-H-2’,H-6’), 7.26 (2H, d, *J* = 7.3 Hz, Ar-H-2’’,H-6’’), 7.09 (2H, d, *J* = 7.3 Hz, Ar-H-2’’’,H-6’’’), 7.02 (2H, d, *J* = 7.2 Hz, Ar-H-3’,H-5’), 6.93 (2H, d, *J* = 7.3 Hz, Ar-H-3’’’,H-5’’’), 6.86 (2H, d, *J* = 7.3 Hz, Ar-H-3’’,H-5’’), 3.75 (3H, s, *N*-CH_3), 2.54 (2H, q, *J* = 7.5 Hz, -CH_2), 2.48 (2H, q, *J* = 7.5 Hz, -CH_2), 1.17 (3H, t, *J* = 7.4 Hz, -CH_3), 1.12 (3H, t, *J* = 7.4 Hz, -CH_3)	143.5 (C-3), 142.3 (C-5), 141.2 (C-4’’), 139.8 (C-4’’’), 134.5 (C-4’), 133.5 (C-1’’’), 131.4 (C-1’), 130.2 (C-1’’), 129.5 (C-3’,C-5’), 128.8 (C-2’,C-6’), 128.3 (C-3’’,C-5’’), 127.9 (C-3’’’,C-5’’’), 127.6 (C-2’’,C-6’’), 127.4 (C-2’’’,C-6’’’), 123.7 (C-4), 37.3 (*N*-CH_3), 28.5 (-CH_2), 28.4 (-CH_2), 14.3 (-CH_3), 14.1 (-CH_3)
5h	5-(4-Methoxyphenyl)-1-methyl-3,4-di-4-methylphenyl-1H-pyrazole	7.38 (2H, d, *J* = 7.8 Hz, Ar-H-2’,H-6’), 7.36 (2H, d, *J* = 7.4 Hz, Ar-H-2’’,H-6’’), 7.32 (2H, d, *J* = 7.4 Hz, Ar-H-2’’’,H-6’’’), 7.14 (2H, d, *J* = 7.4 Hz, Ar-H-3’’,H-5’’), 7.08 (2H, d, *J* = 7.4 Hz, Ar-H-3’’’,H-5’’’), 6.86 (2H, d, *J* = 7.8 Hz, Ar-H-3’,H-5’), 3.75 (3H, - s, *N*-CH_3), 3.72 (3H, s, -OCH_3), 2.24 (3H, s, -CH_3), 2.21 (3H, s, -CH_3)	159.5 (C-4’), 143.4 (C-3), 141.8 (C-5), 136.8 (C-4’’), 136.5 (C-4’’’), 131.4 (C-1’’’), 130.8 (C-1’’), 130.6 (C-3’’,C-5’’), 130.2 (C-3’’’,C-5’’’), 128.8 (C-2’,C-6’), 127.8 (C-2’’,C-6’’), 127.4 (C-2’’’,C-6’’’), 125.4 (C-1’), 122.5 (C-4), 113.8 (C-3’,C-5’), 55.2 (4’-OCH_3), 37.2 (*N*-CH_3), 21.2 (4’’’-CH_3), 21.1 (4’’-CH_3)
5i	3,4-Bis(4-	7.43-7.48 (2H, d, *J* = 7.2 Hz,	158.8 (C-4’), 142.5 (C-3),

	chlorophenyl)-5-(4-methoxyphenyl)-1-methyl-1H-pyrazole	Ar-H-2'',H-6''), 7.36-7.41 (2H, d, *J* = 7.2 Hz, Ar-H-2''',H-6'''), 7.28-7.34 (2H, d, *J* = 7.3 Hz, Ar-H-2',H-6'), 7.26-7.31 (2H, d, *J* = 7.2 Hz, Ar-H-3'',H-5''), 7.18-7.23 (2H, d, *J* = 7.2 Hz, Ar-H-3''',H-5'''), 6.87-6.94 (2H, d, *J* = 7.3 Hz, Ar-H-3',H-5'), 3.76 (3H, s, *N*-CH_3), 3.74 (3H, s, -OCH_3)	140.6 (C-5), 135.4 (C-1'''), 134.6 (C-4''), 134.3 (C-4'''), 131.4 (C-1''), 130.1 (C-3'',C-5''), 129.6 (C-3''',C-5'''), 128.7 (C-2''',C-6'''), 128.5 (C-2'',C-6''), 128.3 (C-2',C-6'), 126.2 (C-1'), 123.4 (C-4), 116.7 (C-3',C-5'), 55.2 (4'-OCH_3), 37.5 (*N*-CH_3)

The synthesis of 1-methyl-3,4-diphenyl-5-*p*-tolyl-1H-pyrazole **(5a)** was confirmed by ^{1}H NMR due to the presence of a characteristic singlet for *N*-CH_3 protons at δ 3.78 and a singlet for Ar-CH_3 proton at δ 2.28 ppm. In ^{13}C NMR spectra the characteristics carbon peak for *N*-CH_3 was observed at δ 37.4 and three carbon signals for Ar-CH_3 were appeared at δ 21.3 ppm.

The ^{1}H and ^{13}C NMR spectral data of compound **(5a)** is presented in Table 2.19.

Table 2.19: ^{1}H and ^{13}C NMR spectral data of 1-Methyl-3,4-diphenyl-5-*p*-tolyl-1H-pyrazole (5a)



Carbons	δ (ppm) and multiplicity	
	^{1}H NMR	**^{13}C NMR**
C-3	-	142.3
C-4	-	122.5
C-5	-	141.4
C-1'	-	130.2
C-1''	-	133.4
C-1'''	-	136.6
C-4'	-	138.3
C-4''	7.03-7.05, (m)	128.8
C-4'''	7.03-7.05, (m)	128.6
C-2', C-6'	7.21, (d), *J* = 7.2 Hz	127.8
C-2'', C-6''	7.37-7.40, (m)	127.6
C-2''', C-6'''	7.06-7.09, (m)	127.4
C-3', C-5'	6.95, (d), *J* = 7.2 Hz	129.8
C-3'', C-5''	7.07-7.10, (m)	129.6

C-3''', C-5'''	7.07-7.10, (m)	129.3
***N*-CH_3**	3.78, (s)	37.4
4'-CH_3	2.28, (s)	21.3

In the mass spectrum, the molecular ion peak observed at *m/z* 324 as base peak with 100 % abundance. The formation of 1-methyl-3,4-diphenyl-5-*p*-tolyl-1H-pyrazole **(5a)** was also confirmed by HRMS, calcd for $C_{23}H_{21}N_2$ $[M+1]^+$: 325.1699. found 325.1703.

The elemental analysis data of 1-methyl-3,4-diphenyl-5-(substituted-phenyl)-1H-pyrazoles **(5a-i)** is presented in Table 2.20.

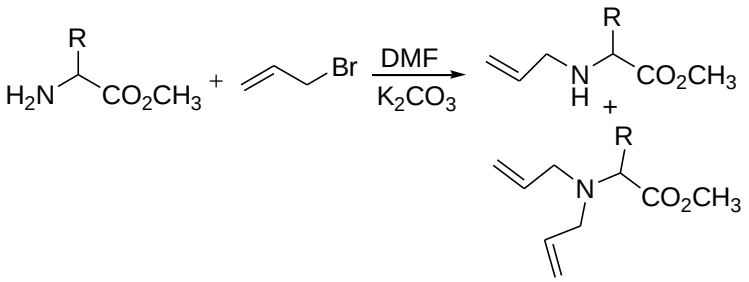
Table 2.20: Elemental analysis data of all the compounds (5a-i).

Compounds	**Formulae**	**HRMS**	
		% Calculated	**% Found**
1-Methyl-3,4-diphenyl-5-*p*-tolyl-1H-pyrazole	$C_{23}H_{20}N_2$	324.1699	324.1703
3,4-Bis(4-methoxyphenyl)-1-methyl-5-(4-methylphenyl)-1H-pyrazole	$C_{25}H_{24}N_2O_2$	384.1911	384.1914
5-(4-Ethylphenyl)-1-methyl-3,4-diphenyl-1H-pyrazole	$C_{24}H_{22}N_2$	338.1856	338.1861
3,4-Bis(3-chlorophenyl)-5-(4-ethylphenyl)-1-methyl-1H-pyrazole	$C_{24}H_{22}Cl_2N_2$	406.1076	406.1074
5-(4-Ethylphenyl)-3,4-bis(4-methoxyphenyl)-1-methyl-1H-pyrazole	$C_{26}H_{26}N_2O_2$	398.2067	398.2071
5-(4-Chlorophenyl)-1-methyl-3,4-diphenyl-1H-pyrazole	$C_{22}H_{17}N_2Cl$	344.9132	344.9133
5-(4-Chlorophenyl)-3,4-bis(4-ethylphenyl)-1-methyl-1H-pyrazole	$C_{26}H_{25}ClN_2$	400.1779	400.1781
5-(4-Methoxyphenyl)-1-methyl-3,4-di-4-methylphenyl-1H-pyrazole	$C_{25}H_{24}N_2O$	368.1961	368.1962
3,4-Bis(4-chlorophenyl)-5-(4-methoxyphenyl)-1-methyl-1H-pyrazole	$C_{23}H_{18}Cl_2N_2O$	408.0869	408.0867

2.3 *N*-Substituted Dihydropyridinones

2.3.1 Synthesis of Mono and Diallylation Products (1a-d)

Mono and diallylation was done by the successive addition of Potassium carbonate and allyl bromide to the stirred solution of amino ester hydrochloride derivatives in dry DMF under inert atmosphere. The reaction mixture was stirred over night, diluted with water (20 mL) and extracted with diethyl ether yields both mono and diallyl products **(1a-d)**.



R = H, Ph.

Scheme 3.1: Synthesis of Mono and Diallylation Products (1a-d)

The physical data of mono and diallylated compounds **(1a-d)** is presented in Table 3.1.

Table 3.1: Physical data of all the compounds (1a-d).

Sr. No	Compound	R_f Values	Yield (%)	Physical States
1a	*N*-Allyl, R-H	0.45	82	colorless liquid
1b	*N*-Diallyl, R-H	0.7	71	colorless liquid
1c	*N*-Allyl, R-Ph	0.4	86	colorless liquid
1d	*N*-Diallyl, R-Ph	0.67	75	colorless liquid

[Diethyl ether : ethyl acetate (5:5)]

In the IR spectra, the characteristic absorptions for carbonyl carbons of ester moiety were observed in the range of 1734-1738 cm^{-1}. The N-H peaks for mono allylated products in IR spectra were appeared at 3432 and 3436 cm^{-1}.

The FTIR spectral data of all the compounds **(1a-d)** is presented in Table 3.2.

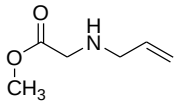
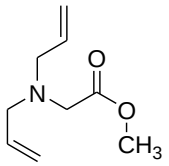
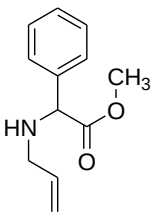
Table 3.2: FTIR data of all the compounds (1a-d).

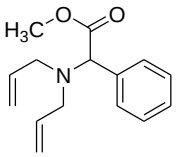
Sr. No	Compound	(C=C) cm^{-1}	(ester C=O) cm^{-1}	(N-H) cm^{-1}	(C–O) cm^{-1}	(C–N) cm^{-1}
1a	*N*-Allyl, R-H	1576	1738	3432	1021	1465
1b	*N*-Diallyl, R-H	1572	1735	-	1024	1467
1c	*N*-Allyl, R-Ph	1581	1734	3436	1032	1455
1d	*N*-Diallyl, R-Ph	1585	1737	-	1037	1458

The synthesis of mono and diallyled amino ester derivatives were **(1a-d)** confirmed by ^{1}H NMR due to the presence of a characteristic singlet for -NH protons at δ 1.54 ppm and δ 2.18 ppm for mono allylated products. In ^{13}C NMR spectra the characteristics carbonyl carbon peaks were appeared, ranges from δ 172.4 to 173.7 ppm.

The ^{1}H and ^{13}C NMR spectral data of mono and diallylated compounds **(1a-d)** is presented in Table 3.3.

Table 3.3: ^{1}H and ^{13}C NMR spectral data of all the compounds (1a-d)

Compounds	Structures	^{1}H NMR(δ) (ppm)	^{13}C NMR(δ) (ppm)
N-Allyl, R-H		5.76-5.87 (1H, m, H-6), 5.27 (1H, dd, *J* = 16.8,1.4 Hz, H-7), 5.21 (1H, dd, *J* = 9.8,1.4 Hz, H-7'), 3.96 (2H, d, *J* = 5.8 Hz, H-5), 3.81 (3H, s, -OCH_3), 3.51 (2H, s, H-3,H-3'), 1.54 (1H, s, -NH)	173.1 (C=O) , 135.8 (C-6), 117.2 (C-7), 58.2 (C-5), 52.3 (C-1), 49.8 (C-3)
N-Diallyl, R-H		5.71-5.83 (2H, m, H-6,H-6'), 5.21 (2H, dd, *J* = 16.8,1.2 Hz, H-7), 5.07 (1H, dd, *J* = 9.8,1.2 Hz, H-7'), 3.59 (3H, s, -OCH_3), 3.23 (2H, s, H-3,H-3'), 3.15 (4H, d, *J* = 6.4 Hz, H-5,H-5')	172.4 (C=O) , 136.1 (C-6,C-6'), 118.7 (C-7,C-7'), 58.2 (C-5,C-5'), 54.1 (C-3), 52.3 (C-1)
N-Allyl, R-Ph		7.28-7.41 (5H, m, Ph), 5.78-5.87 (1H, m, H-6), 5.23 (1H, dd, *J* = 16.8,1.4 Hz, H-7), 5.16 (1H, dd, *J* = 9.8,1.4 Hz, H-7'), 4.51 (1H, s, H-3), 3.82 (3H, s, -OCH_3), 3.24 (2H, d, *J* = 5.8 Hz, H-5,H-5'), 2.18 (1H, s, -NH)	173.7 (C=O), 140.1 (C-1'), 137.3 (C-6), 128.9 (C-2',C-6'), 127.8 (C-3',C-5'), 126.6 (C-4'), 117.2 (C-7), 64.5 (C-3), 52.4 (C-5), 50.2 (C-1)

N-Diallyl, R-Ph		7.31-7.42 (5H, m, Ph), 5.77-5.88 (2H, m, H-6,H-6'), 5.21 (2H, dd, *J* = 16.8,1.5 Hz, H-7), 5.12 (1H, dd, *J* = 10.4,1.5 Hz, H-7'), 4.56 (2H, s, H-3,H3'), 3.72 (3H, s, -OCH_3), 3.22 (4H, d, *J* = 6.1 Hz, H-5,5',H-5,5'')	173.1 (C=O), 137.3 (C-1'), 136.2 (C-6,C-6'), 129.4 (C-2',C-6'), 128.6 (C-3',C-5'), 127.8 (C-4'), 118.5 (C-7,C-7'), 68.3 (C-3), 53.2 (C-5,C-5'), 51.6 (C-1)

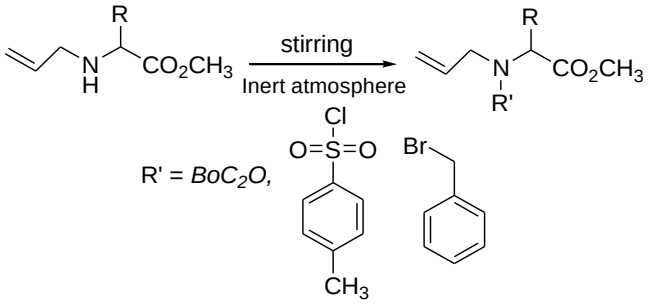
The elemental analysis data of mono and diallylated compounds **(1a-d)** is presented in Table 3.4.

Table 3.4: Elemental analysis data of all the compounds (1a-d).

Compounds	Formulae	Elemental Analysis					
		% Calculated			% Found		
		C	H	N	C	H	N
1a	$C_6H_{11}NO_2$	55.81	8.52	10.84	55.68	8.41	10.63
1b	$C_9H_{15}NO_2$	63.91	8.87	8.28	63.83	8.72	8.15
1c	$C_{12}H_{15}NO_2$	70.24	7.32	6.83	70.18	7.27	6.75
1d	$C_{15}H_{19}NO_2$	73.47	7.76	5.71	73.38	7.63	5.62

2.3.2 Synthesis of *N*-Allyl-*N*-Substituted amino ester derivatives (2a-e)

Mono allylated amino ester derivatives were converted to *N*-tosyl, *N*-benzyl and *N*-Boc protected products **(2a-e)** by adopting the literature procedures.



R = H, Ph.

R'= *N*-Tosyl, *N*-Benzyl and *N*-Boc protections.

Scheme 3.2: *N*-protection of *N*-allyl substituted amino ester derivatives (2a-e)

The physical data of *N*-Allyl-*N*-substituted amino ester derivatives **(2a-e)** is presented in Table 3.5.

Table 3.5: Physical data of all the compounds (2a-e).

Sr. No	Compounds	R_f Values	Yield (%)	Physical States
2a	*N*-Tosyl	0.4	88	yellow amorphous solid
2b	*N*-Allyl, *N*-Tosyl	0.65	87	colorless liquid
2c	*N*-Benzyl	0.5	70	yellow oil
2d	*N*-Allyl, *N*-Benzyl	0.75	77	yellow oil
2e	*N*-Allyl, *N*-Boc	0.45	74	colorless liquid

[Diethyl ether : ethyl acetate (5:5)]

In the IR spectra, the characteristic absorptions for carbonyl carbons of ester moiety were observed in the range of 1726-1731 cm^{-1}, along with the characteristics absorption peaks (S=O) of tosyl group for **(2a)** at 1723 cm^{-1} and for **(2b)** 1725 cm^{-1}. In case of **(2e)** carbonyl carbon absorption was appeared for Boc moiety at 1673 cm^{-1}. The N-H peaks for mono substituted products **(2a** & **2c)** in IR spectra were appeared at 3423 and 3431 cm^{-1}.

The FTIR spectral data of all the compounds **(2a-e)** is presented in Table 3.6.

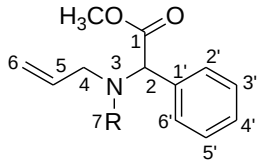
Table 3.6: FTIR data of all the compounds (2a-e).

Sr. No	Compounds	(C=C) cm^{-1}	(ester C=O) cm^{-1}	(Boc C=O) (S=O) cm^{-1}	(N-H) cm^{-1}	(C-O) cm^{-1}	(C-N) cm^{-1}
2a	*N*-Tosyl	1575	1728	1723	3423	1036	1456
2b	*N*-Allyl, *N*-Tosyl	1578	1731	1725	-	1034	1452
2c	*N*-Benzyl	1573	1727	-	3431	1028	1462
2d	*N*-Allyl, *N*-Benzyl	1587	1732	-	-	1035	1455
2e	*N*-Allyl, *N*-Boc	1577	1726	1673	-	1042	1465

N-Allyl-*N*-substituted amino ester derivatives were **(2a-e)** confirmed by ^{1}H NMR due to the presence of a characteristics singlet for -NH protons at δ 2.25 ppm and δ 2.23 ppm for **(2a** & **2c)**. In ^{13}C NMR spectra the characteristics carbonyl carbon peaks ester moiety were appeared, ranges from δ 169.1 to 172.6 ppm.

The ^{1}H and ^{13}C NMR spectral data of *N*-Allyl-*N*-substituted amino ester derivatives **(2a-e)** is presented in Table 3.7.

Table 3.7: ^{1}H and ^{13}C NMR spectral data of all the compounds (2a-e)



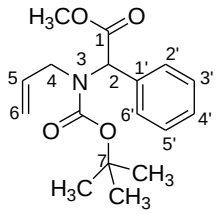
Sr. No	Compounds	^{1}H NMR(δ) (ppm)	^{13}C NMR(δ) (ppm)
2a	*N*-Tosyl	7.80 (1H, d, *J* = 7.6 Hz, H-2'',H-6''), 7.72 (1H, d, *J* = 7.6 Hz, H-3'',H-5''), 7.29-7.69 (5H, m, Ph), 5.21 (1H, s, H-3), 3.66 (3H, s, -OCH_3), 2.47 (1H, s, -CH_3), 2.25 (1H, s, -NH)	169.1 (C=O), 141.8 (C-1'), 140.3 (C-1''), 132.2 (C-4''), 130.3 (C-2',C-6'), 129.9 (C-3'',C-5''), 129.4 (C-3',C-5'), 128.6 (C-2'',C-6''), 128.3 (C-4'), 57.1 (C-3), 53.6 (-OCH_3), 21.7 (-CH_3)
2b	*N*-Allyl, *N*-Tosyl	7.83 (1H, d, *J* = 7.6 Hz, H-2'',H-6''), 7.77 (1H, d, *J* = 7.6 Hz, H-3'',H-5''), 7.19-7.72 (5H, m, Ph), 5.78 (1H, s, H-3), 5.42-5.51 (1H, m, H-5), 4.78-4.67 (2H, m, H-6,H-6'), 3.73-3.88 (2H, m, H-4,H-4'), 3.71 (3H, s, -OCH_3), 2.37 (3H, s, -CH_3)	170.6 (C=O), 143.8 (C-4''), 138.5 (C-1''), 137.2 (C-1'), 135.1 (C-5), 129.8 (C-3'',C-5''), 129.3 (C-2'',C-6''), 128.9 (C-2',C-6'), 128.6 (C-3,C-5'), 127.7 (C-4'), 116.8 (C-6), 63.1 (C-3), 52.3 (-OCH_3), 48.5 (C-4), 21.5 (-CH_3)
2c	*N*-Benzyl	7.15-7.52 (10H, m, Ph), 4.67 (1H, s, H-3), 3.86 (2H, s, H-4), 3.67 (3H, s, -OCH_3), 2.25 (1H, s, -NH)	172.3 (C-2) , 136.7 (C-1'), 135.8 (C-1''), 130.3 (C-2'',C-6''), 129.4 (C-3'',C-5''), 128.8 (C-3',C-5'), 128.2 (C-2',C-6'), 127.9 (C-4''), 127.3 (C-4'), 65.2 (C-3), 52.4 (-OCH_3), 51.6 (-CH_2)
2d	*N*-Allyl, *N*-Benzyl	7.32-7.67 (10H, m, Ph), 5.76-5.89 (1H, m, H-5), 5.22 (1H, dd, *J* = 16.8,2.1 Hz, H-6), 5.16 (1H, dd, *J* = 10.4,2.1 Hz, H-6'), 4.72 (1H, s, H-3), 3.81 (2H, *J* = 14.8 Hz, H-7,H-7'), 3.76 (3H, s, -OCH_3), 3.23 (2H, d, *J* = 5.8 Hz, H-4,H-4')	172.6 (C=O) , 140.1 (C-1''), 137.3 (C-1'), 136.2 (C-5), 129.1 (C-9,9'), 128.9 (C-2'',6''), 128.7 (C-3'',5''), 128.3 (C-3',5'), 128.1 (C-4''), 127.8 (C-4'), 118.2 (C-6), 67.3 (C-3), 54.4 (-CH_2), 53.5 (C-4), 51.7 (-OCH_3)

In the IR spectrum of methyl 2-[allyl(*tert*-butoxycarbonyl)amino]-2-phenylacetate **(2e)** two characteristics absorption peaks for carbonyl carbon (C=O) of Boc and ester groups observed at 1673 and 1726 cm^{-1}.

^{1}H NMR spectrum of **(2e)** also confirmed the structure due to the presence of a characteristics singlet for CH_3 proton at δ 2.14 ppm and another singlet for H-2 proton observed at δ 5.41 ppm. In ^{13}C NMR spectrum, two characteristics signals for carbonyl carbon (C=O) of Boc and ester groups appeared at 163.2 and 171.8 cm^{-1}.

The ^{1}H and ^{13}C NMR spectral data of the compound **(2e)** is presented in Table 3.8.

Table 3.8: ^{1}H and ^{13}C NMR data of Methyl 2(S)-[allyl(*tert*-butoxycarbonyl) amino]-2-phenylacetate (2e)



Carbons	δ (ppm) and multiplicity	
	^{1}H NMR	**^{13}C NMR**
ester (C=O)	-	171.8
amidic (C=O)	-	163.2
C-2	5.41, (s)	63.9
C-4	3.64-3.73, (m)	47.4
C-5	5.76-5.85, (m)	134.7
C-6	5.12-5.19, (m)	116.7
C-7	-	79.5
C-1'	7.13, (m)	136.6
C-2',	"	129.8
C-3'	"	129.1
C-4'	"	127.4
C-5'	"	129.1
C-6'	7.22, (m)	129.8
3×CH_3	2.14, (s)	28.3
-OCH_3	3.56, (s)	52.3

The structure of methyl 2-[allyl(*tert*-butoxycarbonyl)amino]-2-phenylacetate **(2e)** was also confirmed by mass spectrometry. Base peak observed at *m/z* 156 and the molecular ion peak appeared at *m/z* 305 with 30 % abundance.

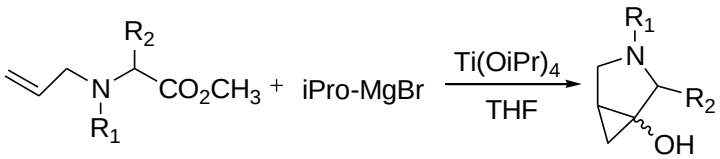
The elemental analysis data of *N*-Allyl-*N*-substituted amino ester derivatives **(2a-e)** is presented in Table 3.9.

Table 3.9: Elemental analysis data of all the compounds (2a-e).

Compounds	Formulae	Elemental Analysis							
		% Calculated				% Found			
		C	H	N	S	C	H	N	S
2a	$C_{16}H_{17}NO_4S$	60.18	5.33	4.38	10.03	60.07	5.26	4.27	9.94
2b	$C_{19}H_{21}NO_4S$	65.51	5.85	3.91	8.92	65.43	5.68	3.84	8.81
2c	$C_{16}H_{17}NO_3$	75.31	6.67	5.51	-	75.27	6.52	5.42	-
2d	$C_{19}H_{21}NO_2$	77.28	7.12	4.75	-	77.14	7.03	4.63	-
2e	$C_{17}H_{23}NO_4$	66.87	4.26	4.58	-	66.76	4.16	4.47	-

2.3.3 Synthesis of *N*-Substituted-3-aza-bicyclo[3.1.0]hexan-1-ols (3a-e')

N-Substituted-3-aza-bicyclo[3.1.0]hexan-1-ols were prepared by the addition of titanium isopropoxide to the stirred solution of variously substituted amino ester derivatives in anhydrous Et_2O/THF (1:1), under inert atmosphere. Grignard's reagent (isopropylmagnesium bromide in ether) was added drop wise with the help of syringe over the period of 3 hr. The reaction mixture was stirred for 1 additional hr. Precipitates were appeared, precipitates were filter off and the aqueous phase was extracted with ethyl acetate furnished 3-aza-bicyclo[3.1.0]hexan-1-ols **(3a-e')**.



R_1 = H, Allyl, Boc, Benzyl, Tosyl

R_2 = H, Ph

Scheme 3.3: Synthesis of *N*-Substituted-3-aza-bicyclo[3.1.0]hexan-1-ols (3a-e')

The physical data of *N*-substituted-3-aza-bicyclo[3.1.0]hexan-1-ols **(3a-e')** is presented in Table 3.10.

Table 3.10: Physical data of all the compounds (3a-e')

Sr. No	Compounds	R_f Values	Yield (%)	Physical States
3a	*N*-Allyl, R-H	0.6	70	colorless liquid
3b	*N*-Allyl, R-Ph	0.55	74	yellow oil
3b'	*N*-Allyl, R-Ph	0.6	77	yellow oil
3c	*N*-Tosyl, R-Ph	0.7	86	yellow semi-solid
3c'	*N*-Tosyl, R-Ph	0.57	83	yellow semi-solid
3d	*N*-Benzyl, R-Ph	0.5	75	yellow oil
3d'	*N*-Benzyl, R-Ph	0.4	71	off white solid
3e	*N*-BoC, R-Ph	0.65	68	colorless liquid
3e'	*N*-BoC, R-Ph	0.4	63	colorless liquid

[Diethyl ether : ethyl acetate (5:5)]

In the IR spectra, the characteristics O-H broad band peaks were appeared in the range of 3372 to 3475 cm^{-1}. The peaks for (S=O) of tosyl group for **(3c)** at 1725 cm^{-1} and for **(3c')** 1723 cm^{-1}. In case of **(3e** & **3e')** characteristics absorption peaks for carbonyl carbon were appeared for Boc moiety at 1732 and 1730 cm^{-1}.

The FTIR data of *N*-substituted-3-aza-bicyclo[3.1.0]hexan-1-ols **(3a-e')** is presented in Table 3.11.

Table 3.11: FTIR data of all the compounds (3a-e').

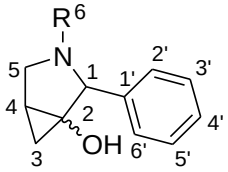
Sr. No	Compounds	(C=C) cm^{-1}	(O-H) cm^{-1}	(S=O) (C=O) cm^{-1}	(C-O) cm^{-1}	(C-N) cm^{-1}
3a	*N*-Allyl, R-H	1581	3387	-	1032	1456
3b	*N*-Allyl, R-Ph	1583	3392	-	1037	1452
3b'	*N*-Allyl, R-Ph	1578	3377	-	1027	1454
3c	*N*-Tosyl, R-Ph	1587	3454	1725	1034	1462
3c'	*N*-Tosyl, R-Ph	1585	3463	1723	1031	1467
3d	*N*-Benzyl, R-Ph	1574	3376	-	1032	1464
3d'	*N*-Benzyl, R-Ph	1583	3372	-	1030	1453
3e	*N*-Boc, R-Ph	1584	3475	1732	1035	1451
3e'	*N*-Boc, R-Ph	1582	3471	1730	1036	1463

The *N*-Allyl-Substituted Kulinkovich Products were **(3a-e')** confirmed by ^1H NMR spectra due to the presence of a characteristics broad singlet for -OH protons

ranges from δ 2.11 to δ 2.58 ppm and another singlet for H-1 proton ranges from δ 3.83-4.98 ppm. Two characteristics double doublets for H-3,3' appeared in the range of δ 0.51-1.42 ppm and dd for H-5,5' observed at δ 2.56-4.11 ppm. In ^{13}C NMR spectra the characteristics peaks for carbon of C-OH moiety were appeared at δ 65.3-70.2 ppm.

The ^{1}H and ^{13}C NMR spectral data of *N*-substituted-3-aza-bicyclo[3.1.0]hexan-1-ols **(3a-e')** is presented in Table 3.12.

Table 3.12: ^{1}H NMR and ^{13}C NMR spectral data of all the compounds (3a-e')



Sr. No	Compounds	^{1}H NMR(δ) (ppm)	^{13}C NMR(δ) (ppm)
3a	*N*-Allyl, R-H	5.79-5.87 (1H, m, H-7), 5.20 (1H, dd, *J* = 9.6,2.2 Hz, H-8), 5.12 (1H, dd, *J* = 9.6,2.2 Hz, H-8'), 4.27 (1H, s, H-1), 3.27 (1H, dd, *J* = 7.6,6.1 Hz, H-5), 3.12 (1H, dd, *J* = 7.6,6.1 Hz, H-5'), 2.48 (1H, dd, *J* = 12.6,4.1Hz, H-6), 2.39 (1H, dd, *J* = 12.6,4.1 Hz, H-6'), 2.58 (1H, s, -OH), 1.86-1.90 (1H, m, H-4), 1.24 (1H, dd, *J* = 7.4,3.6 Hz, H-3), 1.03 (1H, dd, *J* = 7.4,3.6 Hz, H-3')	134.7 (C-7), 116.5 (C-8), 67.6 (C-1), 65.7 (C-2), 60.2 (C-5), 58.1 (C-6), 25.8 (C-4), 16.5 (C-3)
3b	*N*-Allyl, R-Ph	7.31-7.54 (5H, m, Ph), 5.33-5.68 (1H, m, H-7), 5.12 (1H, dd, *J* = 16.8,1.4 Hz, H-8), 5.01 (1H, dd, *J* = 16.8,1.4 Hz, H-8'), 4.21 (1H, s, H-1), 3.09 (1H, dd, *J* = 8.8,3.8 Hz, H-5), 2.87 (1H, dd, *J* = 13.8,6.1 Hz, H-6), 2.77 (1H, dd, *J* = 8.8,3.8 Hz, H-5'), 2.67 (1H, dd, *J* = 13.8,6.1 Hz, H-6'), 2.04 (1H, s, -OH), 1.71-1.76 (1H, m, H-4), 1.22 (1H, dd, *J* = 8.7,4.2 Hz, H-3), 0.91 (1H, dd, *J* = 8.7,4.2 Hz, H-3')	138.5 (C-9), 136.7 (C-7), 129.6 (C-10,C-10'), 128.8 (C-11,C-11'), 127.9 (C-12), 116.3 (C-8), 70.1 (C-1), 65.3 (C-2), 54.1 (C-6), 53.2 (C-5), 24.1 (C-4), 17.3 (C-3)
3b'	*N*-Allyl, R-Ph	7.31-7.43 (5H, m, Ph), 5.75-5.84 (1H, m, H-7), 5.21 (1H, dd, *J* =	140.3 (C-9), 136.8 (C-7), 130.2 (C-10,C-10'),

		16.8,1.2 Hz, H-8), 5.13 (1H, dd, *J* = 16.8,1.2 Hz, H-8'), 4.11 (1H, s, H-1), 3.21 (1H, dd, *J* = 8.8,3.8 Hz, H-5), 2.78 (1H, dd, *J* = 13.8,6.1 Hz, H-6), 2.75 (1H, dd, *J* = 8.8,3.8 Hz, H-5'), 2.64 (1H, dd, *J* = 13.8,6.1 Hz, H-6'), 2.11 (1H, s, -OH), 1.60-1.64 (1H, m, H-4), 1.18 (1H, dd, *J* = 8.7,4.1 Hz, H-3), 0.85 (1H, dd, *J* = 8.7,4.1 Hz, H-3')	129.9 (C-11,C-11'), 128.6 (C-12), 117.4 (C-8), 72.2 (C-1), 65.5 (C-2), 56.4 (C-6), 53.7 (C-5), 22.6 (C-4), 14.1 (C-3)
3c	*N*-Tosyl, R-Ph	7.64 (1H, d, *J* = 7.1 Hz, H-2,H-6), 7.33-7.57 (5H, m, Ph), 7.24 (1H, d, *J* = 7.1 Hz, H-3,H-5), 4.87 (1H, s, H-1), 3.68 (1H, dd, *J* = 10.1,3.6 Hz, H-5), 3.49 (1H, d, *J* = 10.1 Hz, H-5'), 2.46 (1H,s, -OH), 2.17 (3H, s, -CH_3), 1.69-1.74 (1H, m, H-4), 1.19 (1H, dd, *J* = 9.1,4.2 Hz, H-3), 0.51 (1H, t, *J* = 4.2,4.2 Hz, H-3')	143.4 (C-4'), 138.3 (C-1''), 132.2 (C-1'), 130.3 (C-2',C-6'), 129.5 (C-3'',C-5''), 128.8 (C-2'',C-6''), 127.8 (C-3',C-5'), 126.7 (C-4''), 66.3 (C-1), 68.6 (C-2), 50.2 (C-5), 23.4 (Ar-CH_3), 22.1 (C-4), 16.2 (C-3)
3c'	*N*-Tosyl, R-Ph	7.67 (1H, d, *J* = 7.1 Hz, H-2,H-6), 7.32-7.64 (5H, m, Ph), 7.26 (1H, d, *J* = 7.1 Hz, H-2,H-6), 4.98 (1H, s, H-1), 3.63 (1H, d, *J* = 9.8 Hz, H-5'), 3.42 (1H, dd, *J* = 9.8,4.2 Hz, H-5), 2.47 (1H, s, -OH), 2.18 (3H, s, -CH_3), 1.88-1.94 (1H, m, H-4), 1.42 (1H, t, *J* = 4.5,4.5 Hz, H-3), 1.12 (1H, dd, *J* = 9.2,4.5 Hz, H-3')	144.7 (C-4'), 138.4 (C-1''), 132.5 (C-1'), 130.3 (C-2',C-6'), 129.5 (C-3'',C-5''), 128.9 (C-2'',C-6''), 128.3 (C-3',C-5'), 126.2 (C-4''), 68.7 (C-2), 67.8 (C-1), 52.6 (C-5), 22.3 (Ar-CH_3), 21.7 (C-4), 15.8 (C-3)
3d	*N*-Benzyl, R-Ph	7.13-7.41 (10H, m, Ph), 4.18 (1H, s, H-1), 3.37 (2H, *J* = 13.8 Hz, H-6,H-6'), 3.14 (1H, dd, *J* = 9.1,4.5 Hz, H-5), 2.76 (1H, d, *J* = 9.1 Hz, H-5'), 2.18 (1H, s, -OH), 1.67-1.85 (1H, m, H-4), 1.28 (1H, t, *J* = 4.6,4.6 Hz, H-3), 1.21 (1H, dd, *J* = 9.2,4.6 Hz, H-3')	140.2 (C-1'), 138.5 (C-1''), 128.8 (C-2'',C-6''), 128.6 (C-3'',C-5''), 128.4 (C-2',C-6'), 128.1 (C-3',C-5'), 127.8 (C-4''), 127.1 (C-4'), 69.5 (C-1), 68.4 (C-2), 54.6 (C-6), 53.2 (C-5), 24.3 (C-4), 17.4 (C-3)
3d'	*N*-Benzyl, R-Ph	7.31-7.65 (10H, m, Ph), 3.83 (1H, s, H-1), 3.77 (2H, *J* = 12.8 Hz, H-6,H-6'), 2.87 (1H, d, *J* = 9.2 Hz, H-5), 2.56 (1H, dd, *J* = 9.1,3.8 Hz, H-5'), 2.14 (1H, s, -OH), 1.48-1.61 (1H, m, H-4), 1.26 (1H, t, *J* =	140.1 (C-1'), 138.7 (C-1''), 129.6 (C-2'',C-6''), 128.7 (C-3'',C-5''), 128.5 (C-2',C-6'), 128.2 (C-3',C-5'), 127.9 (C-4''), 126.8 (C-4'), 71.8

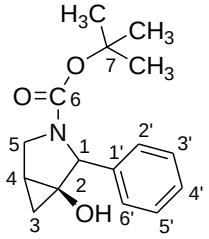
		4.2,4.2 Hz, H-3), 0.71 (1H, dd, *J* = 9.1,4.2 Hz, H-3')	(C-1), 70.2 (C-2), 57.1 (C-6), 53.4 (C-5), 22.3 (C-4), 14.2 (C-3)
3e'	*N*-Boc, R-Ph	7.52-7.73 (5H, m, Ph), 4.68 (1H, s, H-1), 3.43 (1H, dd, *J* = 9.5,3.4 Hz, H-5'), 3.26 (1H, dd, *J* = 9.5,3.4 Hz, H-5), 2.38 (1H, s, -OH), 1.58-1.67 (1H, m, H-4), 1.37 (9H, s, 3×CH_3), 1.32 (1H, dd, *J* = 9.4,3.6 Hz, H-3), 1.12 (1H, dd, *J* = 9.4,3.6 Hz,H-3')	158.3 (C=O), 141.2 (C-1'), 130.4 (C-3',C-5'), 129.5 (C-2',C-6'), 126.4 (C-4'), 78.1 (C-7), 72.3 (C-1), 67.6 (C-2), 52.2 (C-5), 27.8 (-CH_3), 21.6 (C-4), 13.7 (C-3)

In the IR spectrum of *tert*-butyl 1-hydroxy-2-phenyl-3-aza-bicyclo[3.1.0]hexane-3-carboxylate **(3a)** the characteristics O-H broad band peak appeared at 3475 $cm^{-1}$and a characteristics absorption peak for carbonyl carbon bserved for Boc moiety at 1732 cm^{-1}.

^{1}H NMR spectrum of **(3a)** also confirmed the structure due to the presence of a characteristics broad singlet for -OH proton at δ 2.38 ppm and another singlet for H-1 proton observed at δ 4.68 ppm. Two characteristics double doublets for H-3,3' appeared at δ 1.32 and 1.12 ppm, another double doublets for H-5,5' protons observed at δ 3.43 and 3.26 ppm. In ^{13}C NMR spectra the characteristics peaks for carbonyl carbon and C-OH appeared at δ 157.8 and 68.2 ppm.

The ^{1}H and ^{13}C NMR spectral data of the compounds **(3e)** is presented in Table 3.13.

Table 3.13: ^{1}H and ^{13}C NMR data of (1R,2S,5R)-*Tert*-Butyl 1-hydroxy-2-phenyl-3-aza-bicyclo[3.1.0]hexane-3-carboxylate (3e)



Carbons	δ (ppm) and multiplicity	
	^{1}H NMR	^{13}C NMR
amidic C=O	-	157.8
C-1	4.68, (s)	71.8
C-OH	(OH) 2.38, (s)	68.2
C-3,3'	1.32, (dd), *J* = 9.4,3.6 Hz 1.12, (dd), *J* = 9.4,3.6 Hz	14.4
C-4	1.58-1.67, (m)	22.8
C-5,5'	3.43, (dd), *J* = 9.5,3.4 Hz 3.26, (dd), *J* = 9.5,3.4 Hz	51.6
C-7	-	78.7
C-1'	7.52 (m)	140.3
C-2'	"	129.1
C-3'	"	129.8
C-4'	"	126.4
C-5'	"	129.8
C-6'	7.73, (m)	129.1
3×CH_3	1.37, (s)	28.5

The structure of *tert*-Butyl 1-hydroxy-2-phenyl-3-aza-bicyclo[3.1.0]hexane-3-carboxylate **(3e)** was also confirmed by mass spectrometry. Base peak observed at *m/z* 202 and the molecular ion peak appeared at *m/z* 275 with 45 % abundance.

The elemental analysis data of all the compounds **(3a-e')** is presented in Table 3.14.

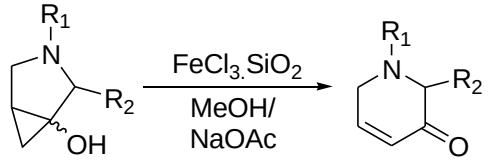
Table 3.14: Elemental analysis data of compounds (3a-e').

Compounds	Formulae	Elemental Analysis							
		% Calculated				% Found			
		C	H	N	S	C	H	N	S
3a	$C_8H_{13}NO$	69.06	9.35	10.07	-	68.96	9.27	9.94	-
3b	$C_{14}H_{17}NO$	78.14	7.91	6.51	-	78.04	7.83	6.43.	-
3b'	$C_{14}H_{17}NO$	78.13	7.90	6.52	-	78.06	7.78	6.47	-
3c	$C_{18}H_{19}NO_3S$	65.65	5.78	4.26	9.72	65.54	5.64	4.21	9.63
3c'	$C_{18}H_{19}NO_3S$	65.65	5.77	4.25	9.73	65.43	5.64	4.17	9.61
3d	$C_{18}H_{19}NO$	81.50	7.16	5.28	-	81.42	7.08	5.15	-

3d'	$C_{18}H_{19}NO$	81.51	7.17	5.28	-	81.41	7.05	4.18	-
3e	$C_{16}H_{21}NO_3$	69.82	7.64	5.10	-	69.74	7.52	4.98	-
3e'	$C_{16}H_{21}NO_3$	69.81	7.63	5.09	-	69.72	7.55	4.97	-

2.3.4 Synthesis of *N*-Substituted-1,6-dihydro-3(2H)-pyridinones (4a-e)

N-Substituted dihydropyridinones were synthesized by the dropwise addition of anhydrous $FeCl_3$ suspension in diethyl ether to the stirred solution of variously substituted aza-bicyclo[3.1.0]hexan-1-ols in diethyl ether at 0 °C under inert atmosphere. The reaction mixture was diluted with freshly distilled methanol after 3 hr and then anhyd. sodium acetate was added porsionwise. The mixture was stirred over night at room temperature yields crude dihydropyridinones **(4a-e)**.



R_1= H, Allyl, Boc, Benzyl, Tosyl

R_2= H, Ph

Scheme 3.4: Synthesis of *N*-Substituted-1,6-dihydro-3(2H)-pyridinones (4a-e)

The Physical data of *N*-Substituted-1,6-dihydro-3(2H)-pyridinones **(4a-e)** is presented in Table 3.15.

Table 3.15: The Physical data of all the compounds (4a-e).

Sr. No	Compound	R_f Values	Yield (%)	Physical States
4a	*N*-Allyl, R-H	0.6	71	reddish brown oil
4b	*N*-Allyl, R-Ph	0.65	75	reddish brown oil
4c	*N*-Tosyl, R-Ph	0.6	78	light yellow oil
4d	*N*-Benzyl, R-Ph	0.7	84	off-white solid
4e	*N*-Boc, R-Ph	0.5	67	yellow oil

[Diethyl ether: ethyl acetate (5:5)]

In the IR spectra, the characteristics carbonyl carbon absorption peaks appeared in the range of 1773 to 1787 cm^{-1}. The absorption peak for (S=O) of tosyl group for **(4c)** observed at 1716 cm^{-1} and in case of **(4e)** characteristics absorption peaks for carbonyl carbon appeared for Boc moiety at 1721 cm^{-1}.

The FTIR data of *N*-Substituted-1,6-dihydro-3(2H)-pyridinones **(4a-e)** is presented in Table 3.16.

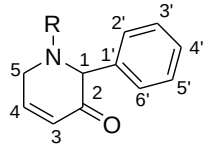
Table 3.16: FTIR data of all the compounds (4a-e).

Sr. No	Compound	(C=C) cm^{-1}	(ring C=O) cm^{-1}	(S=O) (C=O) cm^{-1}	(C-N) cm^{-1}
4a	*N*-Allyl, R-H	1583	1673	-	1452
4b	*N*-Allyl, R-Ph	1586	1676	-	1445
4c	*N*-Tosyl, R-Ph	1591	1678	1716	1446
4d	*N*-Benzyl, R-Ph	1585	1684	-	1453
4e	*N*-Boc, R-Ph	1587	1687	1721	1455

The *N*-Allyl-substituted-dihydropyridinones were **(4a-d)** confirmed by ^{1}H NMR spectra due to the disappearance of a characteristics broad singlet for -OH protons ranges from δ 2.11 to δ 2.58 ppm. Two characteristics double of triplets for H-4 protons appeared in the range of δ 6.69-7.11 ppm and for H-3 protons dt observed at δ 5.87-6.58 ppm. In ^{13}C NMR spectra the characteristics peaks for carbonyl carbon (C=O) appeared in the range of δ 191.8-196.7 ppm.

The ^{1}H and ^{13}C NMR spectral data of *N*-Substituted-1,6-dihydro-3(2H)-pyridinones **(4a-d)** is presented in Table 3.17.

Table 3.17: ^{1}H and ^{13}C NMR spectral data of all the compounds (4a-d)



Sr. No	Compounds	^{1}H NMR(δ) (ppm)	^{13}C NMR(δ) (ppm)
4a	*N*-Allyl, R-H	7.02 (1H, dt, *J* = 10.2 Hz, *J* = 2.4 Hz, H-4), 6.58 (1H, d, *J* = 10.2 Hz, H-3), 5.74-5.84 (1H, m, H-7), 5.19 (1H, dd, *J* = 1.2,16.4 Hz, H-8), 5.23 (1H, dd, *J* = 1.2,8.2 Hz, H-8'), 3.98 (1H, dd, *J* = 8.4,2.2 Hz, H-5), 3.94 (1H, dd, *J* = 8.4,2.2 Hz, H-5'), 3.74 (2H, s, H-1), 3.37-3.48 (2H, m, H-6,H-6')	196.7 (C=O), 134.6 (C-7), 128.8 (C-3), 124.6 (C-4), 117.1 (C-8), 68.4 (C-1), 58.4 (C-6), 52.5 (C-5)

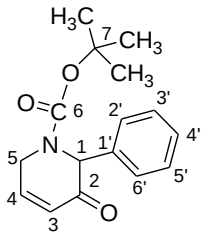
4b	*N*-Allyl, R-Ph	7.33-7.43 (5H, m, Ph), 7.11 (1H, dt, *J* = 10.2,3.4 Hz, H-4), 6.28 (1H, dt, *J* = 10.2,3.2 Hz, H-3), 5.79-5.84 (1H, m, H-7), 5.21 (1H, dd, *J* = 2.1,16.8 Hz, H-8), 5.16 (1H, dd, *J* = 2.1,10.2 Hz, H-8'), 4.26 (1H, s, H-1), 3.54 (1H, ddd, *J* = 19.8, 3.4, 1.5 Hz, H-5), 3.38 (1H, ddd, *J* = 19.8, 3.4, 1.5 Hz, H-5'), 3.08-3.15 (2H, m, H-6,H-6')	195.7 (C=O), 147.4 (C-3), 138.3 (C-1'), 135.2 (C-7), 130.2 (C-2',C-6'), 129.1 (C-3',C-5'), 128.7 (C-4'), 127.2 (C-4), 119.3 (C-8), 73.5 (C-1), 58.4 (C-6), 47.6 (C-5)
4c	*N*-Tosyl, R-Ph	7.69 (1H, d, *J* = 7.4 Hz, H-2,H-6), 7.27-7.56 (5H, m, Ph), 7.19 (1H, d, *J* = 7.4 Hz, H-3,H-5), 6.69 (1H, dt, *J* = 10.2,4.5 Hz, H-4), 5.87 (1H, d, *J* = 10.6 Hz, H-3), 4.51 (1H, ddd, *J* = 19.6, 4.6, 2.4 Hz, H-5), 4.31 (1H, s, H-1), 3.79 (1H, ddd, *J* = 19.6, 4.5, 2.4 Hz, H-5'), 2.38 (3H, s, $-CH_3$)	191.8 (C=O), 145.1 (C-3), 136.7 (C-1''), 133.8 (C-4'), 132.6 (C-1'), 130.3 (C-3',C-5'), 129.4 (C-3'',C-5''), 128.7 (C-2'',C-6''), 127.8 (C-2',C-6'), 127.2 (C-4''), 126.8 (C-4), 64.3 (C-1), 42.1 (C-5), 22.3 (Ar-CH_3)
4d	*N*-Benzyl, R-Ph	7.21-7.93 (10H, m, Ph), 6.94 (1H, dt, *J* = 10.4,3.6 Hz, H-4), 6.25 (1H, dt, *J* = 10.4,3.2 Hz, H-3), 4.28 (1H, s, H-1), 3.76 (2H, s, $-CH_2$), 3.57 (1H, ddd, *J* = 18.2,3.4,2.1 Hz, H-5), 3.24 (1H, ddd, *J* = 18.6,3.4,2.1 Hz, H-5')	195.8 (C=O), 148.2 (C-3), 138.3 (C-1'), 136.8 (C-1''), 129.2 (C-2'',C-6''), 128.8 (C-3'',C-5''), 128.6 (C-2',C-6'), 128.4 (C-3',C-5'), 128.2 (C-4''), 128.1 (C-4'), 127.6 (C-4), 72.8 (C-1), 58.7 (C-6), 48.6 (C-5)

In the IR spectrum of 1-*tert*-Butyl-5-oxo-6-phenyl-5,6-dihydropyridine-1-(2H)-carboxylate **(4e)**, two characteristics carbonyl carbon (C=O) absorption peaks for Boc and keto group appeared at 1687 and 1692 cm^{-1}.

^{1}H NMR spectrum of **(4e)** also confirmed the structure due to the presence of a characteristics singlet for CH_3 proton at δ 3.31 ppm and another singlet for H-1 proton observed at δ 4.53 ppm. In ^{13}C NMR spectrum, the characteristics peaks for carbonyl carbon (C=O) absorption peaks for Boc and keto group appeared at 160.7 and 196.5 cm^{-1}.

The ^{1}H and ^{13}C NMR spectral data of the compounds **(4e)** is presented in Table 3.18.

Table 3.18: ^{1}H and ^{13}C NMR data of (2S)-1-*tert*-Butyl-5-oxo-6-phenyl-5,6-dihydropyridine-1(2H)-carboxylate (4e)



Carbons	δ (ppm) and multiplicity	
	^{1}H NMR	^{13}C NMR
N-C=O	-	160.7
C-2 (C=O)	-	196.5
C-1	4.53, (s)	72.1
C-3	6.17, (dt), *J* = 10.2,2.6 Hz	129.2
C-4	6.67, (dt), *J* = 10.2,3.6 Hz	123.2
C-5,5'	3.61, (ddd), *J* = 19.6, 3.4, 2.2 Hz 3.68, (ddd), *J* = 19.6, 3.4, 2.2 Hz	43.5
C-6	-	156.7
C-7	-	78.4
C-1'	7.15, (m)	134.7
C-2',	"	128.8
C-3'	"	128.3
C-4'	"	127.1
C-5'	"	128.3
C-6'	7.05, (m)	128.8
3×CH_3	3.31, (s)	27.6
O-C	-	52.3

Tert-Butyl-5-oxo-6-phenyl-5,6-dihydropyridine-1(2H)-carboxylate **(4e)** was also confirmed by mass spectrometry. Base peak observed at *m/z* 200 and the molecular ion peak appeared at *m/z* 273 with 45 % abundance.

The elemental analysis data of all the compounds **(4a-e)** is presented in Table 3.19.

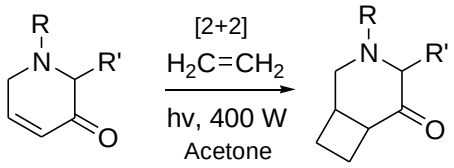
Table 3.19: Elemental analysis data of compounds (4a-e).

Compounds	Formulae	Elemental Analysis							
		% Calculated				% Found			
		C	H	N	S	C	H	N	S
4a	$C_8H_{11}NO$	70.07	8.03	10.2	-	69.94	7.92	9.91	-
4b	$C_{14}H_{15}NO$	78.87	7.04	6.57	-	78.66	6.96	6.45	-
4c	$C_{18}H_{17}NO_3S$	66.05	5.21	4.28	9.78	65.93	5.16	4.21	9.62
4d	$C_{18}H_{17}NO$	82.13	6.46	5.32	-	82.04	6.32	5.37	-
4e	$C_{16}H_{19}NO_3$	70.33	6.95	5.13	-	70.24	6.83	5.01	-

2.3.5 [2+2] Photocycloaddition Reactions of Dihydropyridinones (5a-d)

Objective of the Project:

Various *N*-substituted dihydropyridinones were synthesized step wise *via* Kulinkovich reaction followed by oxidative ring opening reactions of bicyclo compounds. Dihydropyridinones were treated photochemically with ethylene in the presence of acetone, to explore the mechanism of photochemically induced unexpected transformation of 1-benzyl-2-phenyl-1,6-dihydro-3(2H)-pyridinone into β-lactam ring instead of going through a regular [2+2] cycloaddition reaction.



R = H, Allyl, Boc, Tosyl

R' = H, Ph

Scheme 3.5: [2+2] Photocycloaddition Reactions of *N*-Substituted Dihydropyridinones (5a-d)

The Physical data of 3-substituted-3-aza-bicyclo[4.2.0]octan-5-ones **(5a-d)** is presented in Table 3.20.

Table 3.20: The Physical data of all the compounds (5a-d).

Sr. No	Compound	R_f Values	Yield (%)
5a	*N*-Allyl, R = H	0.4	54
5b	*N*-Allyl, R = Ph	0.35	57
5c	*N*-Tosyl, R = Ph	0.3	55
5d	*N*-Boc, R = Ph	0.7	45

[Diethyl ether: ethyl acetate (5:5)]

In the IR spectra, the characteristics ring carbonyl carbon absorption peak appeared in the range of 1674 to 1684 cm^{-1}. The absorption peak for (S=O) of tosyl group for **(5c)** was observed at 1714 cm^{-1} and in case of **(5d)** characteristics absorption peak for carbonyl carbon for Boc moiety appeared at 1722 cm^{-1}.

The FTIR data of 3-substituted-3-aza-bicyclo[4.2.0]octan-5-ones **(5a-d)** is presented in Table 3.21.

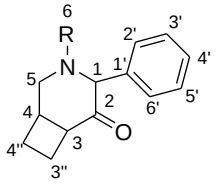
Table 3.21: FTIR data of all the compounds (5a-d).

Sr. No	Compounds	(C=C) cm^{-1}	(ring C=O) cm^{-1}	(C=O) (C=S) cm^{-1}
5a	*N*-Allyl, R = H	1587	1675	-
5b	*N*-Allyl, R = Ph	1581	1674	-
5c	*N*-Tosyl, R = Ph	1582	1673	1716
5d	*N*-Boc, R = Ph	1585	1684	1722

The 3-substituted-3-aza-bicyclo[4.2.0]octan-5-ones **(5a-d)** were also confirmed by ^{1}H NMR spectra, a characteristics singlet for H-1 protons observed in the range of δ 4.54-5.74 ppm and a characteristics multiplets for -CH_2 protons of cyclobutane ring observed between δ 1.72-2.37 ppm. In ^{13}C NMR spectra, the characteristics peaks for ring carbonyl carbons (C=O) appeared in the range of δ 207.6-208.7 ppm. The carbonyl carbon for Boc appeared at δ 164.2 ppm.

The ^{1}H and ^{13}C NMR spectral data of 3-substituted-3-aza-bicyclo[4.2.0]octan-5-ones **(5a-d)** is presented in Table 3.22.

Table 3.22: ^{1}H and ^{13}C NMR spectral data of all the compounds (5a-d)



Sr. No	Compounds	^{1}H NMR(δ) (ppm)	^{13}C NMR(δ) (ppm)
5a	*N*-Allyl, R = H	5.82 (1H, m, H-7), 5.16 (1H, dd, *J* = 1.2,16.4 Hz, H-8), 5.15 (1H, dd, *J* = 1.2,8.2 Hz, H-8'), 4.54 (2H, s, H-1), 3.34 (1H, dd, *J* = 7.6,6.1 Hz, H-5), 3.17-3.28 (2H, m, H-6,H-6'), 3.15 (1H, dd, *J* = 7.6,6.1 Hz, H-5'), 2.78 (1H, m, H-3), 2.41 (1H, m, H-4), 1.72-2.31 (4H, m, cyclobutane ring)	207.5 (C=O), 134.1 (C-7), 115.7 (C-8), 64.3 (C-1), 63.5 (C-5), 58.4 (C-6), 38.2 (C-3), 32.6 (C-4), 23.1 (cyclobutane C-3'), 22.3 (cyclobutane C-4')
5b	*N*-Allyl, R = Ph	7.04-7.24 (5H, m, Ph), 5.85 (1H, m, H-7), 5.21 (1H, dd, *J* = 1.2,16.4 Hz, H-8), 5.17 (1H, dd, *J* = 1.2,8.2 Hz, H-8'), 4.71 (1H, s, H-1), 3.36 (1H, dd, *J* = 7.6,6.1 Hz, H-5), 3.18-3.31 (2H, m, H-6,H-6'), 3.16 (1H, dd, *J* = 7.6,6.1 Hz, H-5'), 2.81 (1H, m, H-3), 2.42 (1H, m, H-4), 1.74-2.33 (4H, m, cyclobutane ring)	207.8 (C=O), 136.5 (C-1'), 134.7 (C-7), 130.4 (C-2',C-6'), 128.6 (C-2',C-5'), 127.3 (C-4'), 117.2 (C-8), 74.3 (C-1), 60.1 (C-5), 56.3 (C-6), 38.8 (C-3), 33.1 (C-4), 23.3 (cyclobutane C-3''), 22.6 (cyclobutane C-4'')
5c	*N*-Tosyl, R = Ph	7.86 (1H, d, *J* = 7.4 Hz, H-7,H-7'), 7.42 (1H, d, *J* = 7.4 Hz, H-8,H-8'), 7.11-7.31 (5H, m, Ph), 4.76 (1H, s, H-1), 3.41 (1H, dd, *J* = 7.5,6.1 Hz, H-5), 3.21 (1H, dd, *J* = 7.5,6.1 Hz, H-5'), 2.82 (1H, m, H-3), 2.43 (1H, m, H-4), 1.78-2.37 (4H, m, cyclobutane ring), 2.28 (3H, s, -CH_3)	208.7 (C=O), 144.5 (C-9), 136.7 (C-1'), 132.6 (C-6), 130.3 (C-8,C-8'), 129.4 (C-3',C-5'), 128.7 (C-2',C-6'), 127.8 (C-7,C-7'), 127.2 (C-4'), 66.3 (C-1), 48.5 (C-5), 38.4 (C-3), 32.8 (C-4), 24.3 (-CH_3), 23.4 (cyclobutane C-3''), 22.5 (cyclobutane C-4'')
5d	*N*-Boc, R = Ph	7.08-7.27 (5H, m, Ph), 5.74 (1H, s, H-1), 3.38 (1H, dd, *J* = 7.6,6.1 Hz, H-5), 3.19 (1H, dd, *J* = 7.6,6.1 Hz, H-5'), 2.81 (1H, m, H-3), 2.80 (1H, m, H-4), 1.76-2.35 (4H, m, cyclobutane ring), 1.46 (9H, s, -CH_3)	208.4 (C=O), 164.2 (N-C=O), 136.4 (C-1'), 134.6 (C-7), 130.7 (C-2',C-6'), 128.3 (C-2',C-5'), 127.5 (C-4'), 117.2 (C-8), 80.3 (C), 54.5 (C-5), 56.3 (C-6), 38.7 (C-3), 33.4 (C-4), 27.4 (3×CH_3), 23.6 (cyclobutane C-3''), 22.7 (cyclobutane C-4'')

The elemental analysis data of 3-substituted-3-aza-bicyclo[4.2.0]octan-5-ones **(5a-d)** is presented in Table 3.23.

Table 3.23: Elemental analysis data of all the compounds (5a-d).

Compounds (R)	Formulae	Elemental Analysis							
		% Calculated				% Found			
		C	H	N	S	C	H	N	S
N-Allyl, R = H	$C_{10}H_{15}NO$	72.68	9.15	8.48	-	72.57	9.07	8.37	-
N-Allyl, R = Ph	$C_{16}H_{19}NO$	79.62	7.93	5.81	-	79.52	7.81	5.73	-
N-Tosyl, R = Ph	$C_{20}H_{21}NO_3S$	67.58	5.95	3.93	9.01	67.44	4.86	3.81	8.91
N-Boc, R = Ph	$C_{18}H_{23}NO_3$	71.72	7.69	4.65	-	71.54	7.53	4.57	-

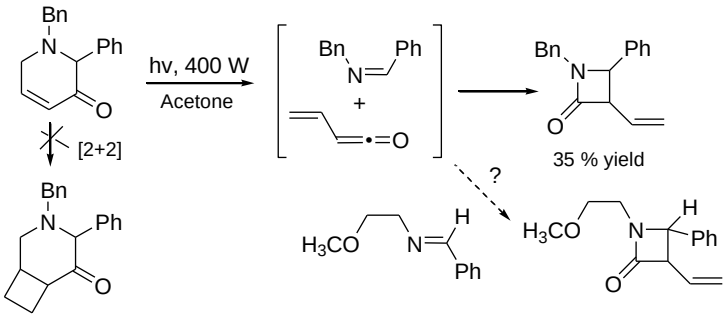
2.3.6 [2+2] Photocycloaddition Reactions of *N*-Benzyl Dihydropyridinone (6a-b)

Proposed Mechanism

The hypothetical mechanism was proposed that this transformation occurs in two steps by the formation of vinyl ketene and imine *via* [4+2] reaction, which recombine again quickly to form β-Lactam.

Inorder to confirm this hypothetical mechanism that actually *N*-benzyl dihydropyridinone molecule breaks into vinyl ketene and imine, then these intermediates recombine to give β-Lactam ring.

However, if the mechanism is correct, then other imine present in the reaction mixture could compete in the second step and thus provide access to a substituted β-Lactam. *N*-Benzylidene-2-methoxyethanamine was synthesized and then reactions carried out in the presence of this imine as well as ethylene.



Scheme 3.6: Synthesis of *N*-Substituted-4-phenyl-3-vinylazetidin-2-one (6a-b)

The Physical data of *N*-substituted-4-phenyl-3-vinylazetidin-2-one **(6a-b)** is presented in Table 3.24.

Table 3.24: The Physical data of all the compounds (6a-b)

Sr. No	Compound	R_f Values	Yield (%)
6a	*N*-Ph	0.35	35
6b	*N*-2-Methoxyethane	0.3	33

[Diethyl ether: ethyl acetate (5:5)]

In the IR spectra, the characteristics ring carbonyl carbon (C=O) absorption peak appeared at 1663 and 1671 cm^{-1}.

The FTIR data of *N*-substituted-4-phenyl-3-vinylazetidin-2-one **(6a-b)** is presented in Table 3.25.

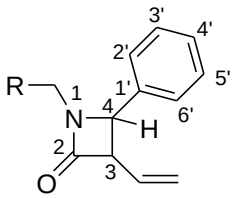
Table 3.25: FTIR data of all the compounds (6a-b)

Sr. No	Compounds	(C=C) cm^{-1}	(ring C=O) cm^{-1}	(C-O) cm^{-1}
6a	*N*-Ph	1568	1663	-
6b	*N*-2-Methoxyethane	1561	1671	1022

The *N*-substituted-4-phenyl-3-vinylazetidin-2-ones **(6a-b)** were also confirmed by ^1H NMR spectra, a characteristics singlet for $-CH_2$ protons of **(6a)** observed at δ 4.37 ppm and a characteristics singlet for $-OCH_3$ protons of **(6b)** observed at δ 2.41 ppm. In ^{13}C NMR spectra, the characteristics peaks for ring carbonyl carbons (C=O) of **(6a)** and **(6b)** appeared at δ 186.2 and 185.7 ppm.

The ^1H and ^{13}C NMR spectral data of *N*-substituted-4-phenyl-3-vinylazetidin-2-one **(6a-b)** is presented in Table 3.26.

Table 3.26: ^1H and ^{13}C NMR spectral data of all the compounds (6a-b)



Sr. No	Compounds	^{1}H NMR(δ) (ppm)	^{13}C NMR(δ) (ppm)
6a	*N*-Ph	7.24-7.73 (10H, m, Ph), 5.93 (1H, m, H-a), 5.22 (1H, dd, *J* = 1.3,16.2 Hz, H-b), 5.18 (1H, dd, *J* = 1.3,8.2 Hz, H-c), 4.46 (2H, s, -CH_2), 4.37 (1H, s, C-4), 3.92 (1H, s, C-3)	186.2 (C=O), 138.4 (C-1'), 137.5 (C-a), 136.5 (C-1''), 129.7 (C-3',C-5'), 129.1 (C-3'',C-5''), 128.8 (C-2',C-6'), 128.2 (C-2'',C-6''), 127.3 (C-4'), 127.1 (C-4''), 116.8 (C-b), 57.8 (C-4), 49.7 (-CH_2), 48.7 (C-3)
6b	*N*-2-Methoxyethane	8.12 (N=C-H), 7.54-7.68 (5H, m, Ph), 3.72 (2H, s, C-2), 3.71 (2H, s, C-1), 2.41 (3H, s, -OCH_3)	185.7 (C=O), 141.8 (C-1'), 132.4 (C-4'), 130.6 (C-2',C-6'), 129.3 (C-3',C-5'), 74.5 (C-2), 68.2 (C-1), 56.7 (-OCH_3)

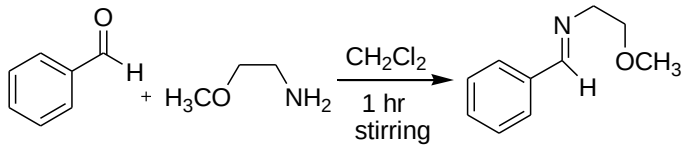
The elemental analysis data of *N*-substituted-4-phenyl-3-vinylazetidin-2-one **(6a-b)** is presented in Table 3.27.

Table 3.27: Elemental analysis data of all the compounds (6a-b)

Compounds (R)	Formulae	Elemental Analysis					
		% Calculated			% Found		
		C	H	N	C	H	N
N-Ph	$C_{17}H_{15}NO$	81.89	6.05	5.61	81.74	5.96	5.53
N-2-Methoxyethane	$C_{14}H_{17}NO_2$	79.62	7.93	5.81	79.52	7.81	5.73

2.3.7 Synthesis of *N*-Benzylidene-2-methoxyethanamine (7a)

N-benzylidene-2-methoxyethanamine was synthesized by stirring aldehyde with 2-methoxyethanamine at room temperature in CH_2Cl_2 in the presence of molecular sieves (4 Aº, 2 gm).



Scheme 3.7: Synthesis of *N*-Benzylidene-2-methoxyethanamine

Conclusion

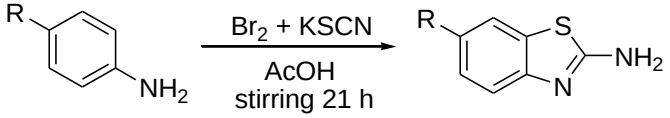
All the synthesized *N*-substituted dihydropyridinones were subjected to photochemical transformations, they all give typical [2+2] photocycloaddition reactions except *N*-benzyl dihydropyridinone. Instead of giving bicyclic adduct as a result of [2+2] cycloaddition reaction, it gives an unexpected rearranged product.

The proposed mechanism was correct and confirmed by NMR studies. We got β-Lactam ring substituted with *N*-benzylidene-2-methoxyethanamine and the yield of the reaction was not very high.

2.4 Iminothiazolidinones

2.4.1 Substituted Benzo[d]thiazol-2-amines (1a-e)

The substituted anilines were converted into respective bicyclic amines, containing a thiazole ring condensed with benzene ring by their reaction with thiocyanogen which was generated *in situ* from bromine and potassium thiocyanate in acetic acid medium to afford substituted benzo[d]thiazol-2-amines. The synthetic pathway is illustrated in Scheme 4.1.



R = H, -Br, -CH_3, -OCH_3, 2,4-Dichloro.

Scheme 4.1: Synthesis of Substituted Benzo[d]thiazol-2-amines (1a-e)

The Physical data of substituted benzo[d]thiazol-2-amines **(1a-e)** is represented in Table 4.1.

Table 4.1: Physical data of all the compounds (1a-e)

Sr. No	Compounds (R)	M.P. (^oC)	Rf[a] Values	Yield (%)	Solvent of Recrystallization
1a	R = H	128-130	0.35	91	Methanol
1b	R = 6-Br	161-163	0.2	79	Ethanol
1c	R = 6-CH_3	135-137	0.2	76	Ethyl acetate
1d	R = 6-OCH_3	145-147	0.3	83	Ethanol
1e	R = 4,6-Dicholro	153-154	0.4	85	Methanol

[Pet. ether : ethyl acetate (7:3)]

In the IR spectra, the characteristic absorptions for the N-H protons of benzo[d]thiazol-2-amines appeared at 3388-3458 cm^{-1}. The (C=N) absorptions peaks observed in the range of 1631-1647 cm^{-1}.

The FTIR spectral data of benzo[d]thiazol-2-amines **(1a-e)** is presented in Table 4.2.

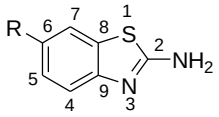
Table 4.2: FTIR data of all the compounds (1a-e)

Sr. No	Compounds (R)	(C=C) cm^{-1}	(C=N) cm^{-1}	(N-H) cm^{-1}	(C-N) cm^{-1}
1a	R = H	1583	1637	3458	1428
1b	R = 6-Br	1587	1631	3450	1427
1c	R = 6-CH_3	1582	1635	3396	1434
1d	R = 6-OCH_3	1585	1644	3388	1442
1e	R = 4,6-Dicholro	1586	1647	3456	1432

The synthesis of benzo[d]thiazol-2-amines were **(1a-e)** confirmed by ^{1}H NMR due to the presence of a characteristic broad band singlet for -NH_2 protons at δ 5.41-5.44 ppm. In ^{13}C NMR spectra the characteristics (C=N) carbon peaks appeared in the range of δ 166.2-166.7 ppm.

The ^{1}H and ^{13}C NMR spectral data of benzo[d]thiazol-2-amines **(1a-e)** is presented in Table 4.3.

Table 4.3: ^{1}H and ^{13}C NMR spectral data of all the compounds (1a-e)



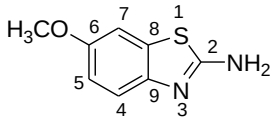
Sr. No.	Compounds	^{1}H NMR(δ) (ppm)	^{13}C NMR(δ) (ppm)
1a	R = H	7.47 (1H, d, *J* = 8.7 Hz, H-1), 7.16 (1H, d, *J* = 8.6 Hz, H-4), 7.52-7.58 (2H, m, H-2,H-3), 5.41 (1H, bs, -NH)	166.2 (S-C=N), 146.8 (C-9), 127.4 (C-6), 126.8 (C-5), 125.7 (C-8), 123.5 (C-7), 122.6 (C-4)
1b	R = 6-Br	7.45 (1H, d, *J* = 8.7 Hz, H-3), 7.16 (1H, d, *J* = 8.7 Hz, H-1), 6.87 (1H, dd, *J* = 8.7,2.4 Hz, H-2), 5.42 (1H, bs, -NH)	166.4 (S-C=N), 146.3 (C-9), 129.4 (C-5), 127.8 (C-8), 125.4 (C-4), 124.5 (C-7), 118.6 (C-6)
1c	R = 6-CH_3	7.46 (1H,d, *J* = 8.7 Hz, H-1),	166.3 (S-C=N), 145.7 (C-

		7.10 (1H, d, *J* = 2.4 Hz, H-3), 6.91 (1H, dd, *J* = 8.7,2.4 Hz, H-2), 5.43 (1H, bs, -NH), 2.51 (3H, s, Ar-CH_3)	9), 132.4 (C-6), 127.5 (C-5), 125.6 (C-8), 123.4 (C-4), 122.5 (C-7), 23.6 (-CH_3)
1e	R = 4,6-Dichloro	7.47 (1H, d, *J* = 2.4 Hz, H-3), 7.14 (1H, d, *J* = 2.4 Hz, H-2), 5.44 (1H, bs, -NH)	166.7 (S-C=N), 147.5 (C-9), 133.4 (C-6), 128.6 (C-8), 126.8 (C-4), 124.6 (C-5), 121.7 (C-7)

The ^{1}H NMR spectrum confirmed the formation of 6-methoxy-benzo[d]thiazol-2-amine **(1d)** by the presence of a characteristics singlet for -NH protons at δ 5.41 ppm and another singlet for methoxy protons at δ 3.84 ppm. In ^{13}C NMR spectrum the methoxy carbon signal observed at δ 56.8 ppm.

The ^{1}H and ^{13}C NMR spectral data of 6-methoxybenzo[d]thiazol-2-amine **(1d)** is presented in Table 4.4.

Table 4.4: ^{1}H and ^{13}C NMR spectral of 6-Methoxybenzo[d]thiazol-2-amine (1d)



Carbons	**δ (ppm) and multiplicity**	
	^{1}H NMR	**^{13}C NMR**
(S-C=N)	-	166.2
C-4	7.47, (d), *J* = 8.7 Hz	124.6
C-5	6.93, (dd), *J* = 8.7,2.4 Hz	121.4
C-6	-	138.6
C-7	7.14, (d), *J* = 2.4 Hz	116.5
C-8	-	126.5
C-9	-	145.1
-OCH_3	3.84, (s)	56.8
-NH_2	5.41, (bs)	-

The structure of 6-methoxy-benzo[d]thiazol-2-amine **(1d)** was also confirmed by mass spectrometry. The molecular ion peak appeared at *m/z* 180 with 51 % abundance.

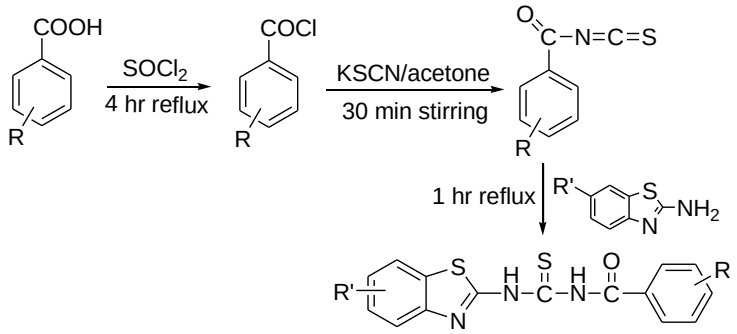
The elemental analysis data of benzo[d]thiazol-2-amines **(1a-e)** is presented in Table 4.5.

Table 4.5: Elemental analysis data of all the compounds (1a-e)

Compounds (R)	Formulae	Elemental Analysis							
		% Calculated				% Found			
		C	H	N	S	C	H	N	S
R = H	$C_7H_6N_2S$	55.47	4.54	18.46	20.96	55.34	4.36	18.37	20.82
R = 6-Br	$C_7H_5N_2SBr$	37.68	2.18	12.22	18.97	37.46	2.11	12.14	18.74
R = 6-CH_3	$C_8H_8N_2S$	54.54	4.88	17.07	19.51	54.46	4.69	16.95	19.33
R = 6-OCH_3	$C_8H_8N_2OS$	52.33	4.44	15.55	17.77	52.26	4.35	15.37	17.61
R = 4,6-Dicholro	$C_7H_4Cl_2N_2S$	38.91	1.21	13.24	14.83	38.76	1.13	13.18	14.74

2.4.2 1-(Benzo[d]thiazol-2-yl)-3-(substituted)thioureas (2a-k)

The substituted benzoic acids were converted into respective acid chlorides by their reaction with thionyl chloride. The acid chlorides were then treated with potassium thiocyanate solution in acetone followed by its treatment with benzo[d]thiazol-2-amines to afford 1-(benzo[d]thiazol-2-yl)-3-(substituted) thioureas **(2a-k)**. The synthetic pathway is illustrated in Scheme 4.2.



R = H, -Br, -CH_3, -OCH_3, 2,4-Dichloro.

R' = H, 2-OCH_3, 4-CH_3, 3-Cl, 2-F, 2-Br, 2,4-Dichloro.

Scheme 4.2: Synthesis of 1-(Benzo[d]thiazol-2-yl)-3-(substituted)thioureas (2a-k)

The Physical data of 1-(benzo[d]thiazol-2-yl)-3-(substituted)thioureas **(2a-k)** is presented in Table 4.6.

Table 4.6: Physical data of all the compounds (2a-k)

Sr. No	Compounds (R)	M.P. (^oC)	Rf[a] Values	Yield (%)	Solvent of Recrystallization
2a	R′ = H, R = H	114-116	0.7	87	Methanol
2b	R′ = H, R = 2-OCH_3	105-106	0.6	75	"
2c	R′ = H, R = 4-CH_3	112-113	0.7	86	"
2d	R′ = Br, R = 3-Cl	130-132	0.65	76	Ethanol
2e	R′ = Br, R = 2-F	110-112	0.75	72	"
2f	R′ = CH_3, R = 3-Cl	164-166	0.8	75	"
2g	R′ = CH_3, R = 2-Br	158-159	0.7	70	Methanol
2h	R′ = OCH_3, R = H	85-86	0.6	73	"
2i	R′ = OCH_3, R = 2,4-Dichloro	168-169	0.75	76	Ethanol
2j.	R′ = 4,6-Dichloro, R = 2,4-Dichloro	138-139	0.8	88	"
2k.	R′ = 4,6-Dichloro, R = H	158-160	0.8	78	"

[Pet.ether : ethylacetate (8:2)]

In the IR spectra, the characteristic absorptions for the N-H protons of 1-(benzo[d]thiazol-2-yl)-3-(substituted)thioureas appeared at 3257-3282 cm^{-1}. The carbonyl carbon (C=O) absorptions peaks observed in the range of 1670-1684 cm^{-1}. The (C=S) absorptions peaks observed at 1238-1263 cm^{-1}

The FTIR spectral data of 1-(benzo[d]thiazol-2-yl)-3-(substituted)thioureas **(2a-k)** are presented in Table 4.7.

Table 4.7: FTIR data of all the compounds (2a-k).

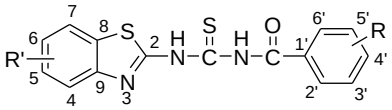
Sr. No	Compounds	(C=C) cm^{-1}	C=O) cm^{-1}	(N-H) cm^{-1}	(C=S) cm^{-1}	(C=N) cm^{-1}
2a	R′ = H, R = H	1576	1674	3273	1254	1632
2b	R′ = H, R = 2-OCH_3	1575	1676	3254	1248	1636
2c	R′ = H, R = 4- CH_3	1578	1670	3282	1255	1631
2d	R′ = Br, R = 3-Cl	1573	1683	3257	1244	1633
2e	R′ = Br, R = 2-F	1587	1675	3265	1247	1632
2f	R′ = CH_3, R = 3-Cl	1583	1672	3270	1245	1634
2g	R′ = CH_3, R = 2-Br	1577	1683	3263	1238	1641
2h	R′ = OCH_3, R = H	1576	1673	3266	1245	1633
2i	R′ = OCH_3, R = 2,4-	1581	1676	3272	1247	1643

	Dichloro					
2j.	R′ = 4,6-Dichloro, R = 2,4-Dichloro	1584	1682	3267	1254	1642
2k.	R′ = 4,6-Dichloro, R = H	1588	1684	3278	1263	1633

The synthesis of 1-(benzo[d]thiazol-2-yl)-3-(substituted)thioureas were **(2a-k)** confirmed by ^{1}H NMR due to the presence of a two characteristic broad band singlet for -NH protons at δ 9.34-11.34 ppm and other -NH peaks at δ 9.15-10.06 ppm. In ^{13}C NMR spectra the characteristics (C=S) carbon peaks appeared in the range of δ 180.4-182.4 ppm. The characteristics carbonyl carbon (C=O) peaks observed at δ 168.2-169.3 ppm.

The ^{1}H and ^{13}C NMR spectral data of 1-(benzo[d]thiazol-2-yl)-3-(substituted) thioureas **(2a-k)** is presented in Table 4.8.

Table 4.8: ^{1}H and ^{13}C NMR spectral data of the compounds (2a-k)



Sr. No.	Compounds	^{1}H NMR(δ) (ppm)	^{13}C NMR(δ) (ppm)
2a	R′ = H, R = H	11.34 (1H, s, -NH), 10.06 (1H, s, -NH), 7.66-8.26 (5H, m, Ar), 7.56 (1H, dd, *J* = 6.9,7.4 Hz, H-3), 7.42 (1H, dd, *J* = 7.2,6.8 Hz, H-4), 7.17 (1H, d, *J* = 8.4 Hz, H-1), 7.15 (1H, d, *J* = 8.2 Hz, H-2)	180.4 (C=S), 172.2 (S-C=N), 168.3 (amide C=O), 147.3 (C-9), 135.7 (C-1'), 133.6 (C-4'), 130.4 (C-3',C-5'), 128.5 (C-2',C-6'), 127.2 (C-6), 126.4 (C-5), 125.5 (C-8), 123.3 (C-4), 122.7 (C-7)
2c	R′ = H, R = 4-CH_3	10.68 (1H, s, -NH), 9.18 (1H, s, -NH), 8.25 (1H, d, *J* = 7.4 Hz, H-1), 7.91 (1H, d, *J* = 7.4 Hz, H-4), 7.82 (1H, dd, *J* = 7.1,7.8 Hz, H-2), 7.56 (1H, dd, *J* = 7.1,7.8 Hz, H-3), 7.51 (1H, d, *J* = 7.8 Hz, H-2'-,H-6'), 7.37 (1H, d, *J* = 7.8 Hz, H-3',H-5'), 2.47 (3H, s, Ar-CH_3)	180.6 (C=S), 172.5 (S-C=N), 168.2 (amide C=O), 147.3 (C-9), 136.2 (C-4'), 132.6 (C-1'), 130.3 (C-3',C-5'), 128.2 (C-2',C-6'), 126.7 (C-6), 126.2 (C-6), 125.5 (C-8), 123.2 (C-4), 122.7 (C-7), 23.6 (-CH_3)
2d	R′ = 6-Br, R = 3-Cl	10.81 (1H, s, -NH), 9.37 (1H, s, -NH), 8.11 (1H, d, *J* = 7.4 Hz, H-1), 7.96 (1H, d, *J* = 2.4 Hz, H-3), 7.94 (1H, d, *J* = 7.4 Hz, H-2), 7.84 (1H, d, *J* = 7.2	181.7 (C=S), 172.5 (S-C=N), 168.7 (amide C=O), 147.8 (C-9), 136.5 (C-1'), 135.4 (C-3'), 133.6 (C-4'), 130.8 (C-5'), 129.5 (C-5), 128.6 (C-2'),

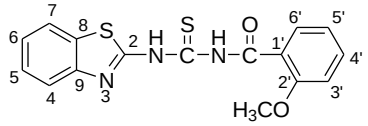
		Hz, H-6'), 7.71 (1H, d, *J* = 2.3 Hz, H-2'), 7.69 (1H, dd, *J* = 7.1,2.3 Hz, H-4'), 7.31 (1H, d, *J* = 7.2 Hz, H-5')	127.4 (C-8), 126.5 (C-6'), 124.8 (C-4), 124.3 (C-7), 118.6 (C-6)
2e	R′ = 6-Br, R = 2-F	9.61 (1H, s, -NH), 9.31 (1H, s, -NH), 7.80 (1H, d, *J* = 7.6 Hz, H-1), 7.73 (1H, d, *J* = 2.4 Hz, H-2), 7.49 (1H, d, *J* = 7.6 Hz, H-3), 7.35 (1H, d, *J* = 7.1 Hz, H-6'), 7.29 (1H, dd, *J* = 7.1,7.3 Hz, H-5'), 7.09 (1H, dd, *J* = 7.3,7.1 Hz, H-4'), 6.89 (1H, d, *J* = 7.3 Hz, H-3')	182.4 (C=S), 172.7 (S-C=N), 168.9 (amide C=O), 148.1 (C-9), 140.5 (C-2'), 134.7 (C-4'), 131.6 (C-1'), 130.4 (C-6'), 129.6 (C-5), 127.5 (C-8), 125.5 (C-5'), 124.7 (C-4), 124.2 (C-7), 118.4 (C-6), 116.7 (C-3')
2f	R′ = 6-CH_3, R = 3-Cl	10.78 (1H, s, -NH), 9.35 (1H, s, -NH), 8.11 (1H, d, *J* = 7.6 Hz, H-1), 7.96 (1H, d, *J* = 2.4 Hz, H-2), 7.92 (1H, d, *J* = 7.8 Hz, H-3'), 7.81 (1H, d, *J* = 2.3 Hz, H-2'), 7.74 (1H, d, *J* = 7.1 Hz, H-6'), 7.62 (1H, dd, *J* = 7.2,2.3 Hz, H-4'), 7.35 (1H, dd, *J* = 7.1,7.2 Hz, H-5'), 2.47 (3H, s, -CH_3)	181.5 (C=S), 172.6 (S-C=N), 168.7 (amide C=O), 146.4 (C-9), 136.7 (C-1'), 135.6 (C-3'), 134.5 (C-6), 133.5 (C-4'), 131.4 (C-5'), 128.7 (C-2'), 128.3 (C-2'), 127.6 (C-5), 126.5 (C-6'), 125.4 (C-8), 123.4 (C-4), 122.6 (C-7), 23.4 (-CH_3)
2g	R′ = 6-CH_3, R = 2-Br	9.58 (1H, s, -NH), 9.25 (1H, s, -NH), 7.78 (1H, d, *J* = 7.6 Hz, H-1), 7.71 (1H, dd, *J* = 2.4 Hz, H-3), 7.49 (1H, d, *J* = 7.6 Hz, H-2), 7.38 (1H, d, *J* = 7.1 Hz, H-6'), 7.27 (1H, dd, *J* = 7.1,7.3 Hz, H-5'), 7.01 (1H, dd, *J* = 7.4,7.1 Hz, H-4'), 6.88 (1H, d, *J* = 7.4 Hz, H-3'), 2.47 (3H, s, -CH_3)	180.5 (C=S), 172.4 (S-C=N), 168.5 (amide C=O), 146.2 (C-9), 138.3 (C-1'), 136.2 (C-4'), 135.7 (C-6), 132.6 (C-3'), 130.7 (C-6'), 129.2 (C-5'), 127.4 (C-5), 125.5 (C-8), 123.2 (C-4), 122.4 (C-7), 121.6 (C-2'), 23.5 (-CH_3)
2h	R′ = 6-OCH_3, R = H	9.38 (1H, s, -NH), 9.15 (1H, s, -NH), 8.09 (1H, d, *J* = 2.4 Hz, H-3), 7.86 (1H, d, *J* = 7.8 Hz, H-1), 7.36-7.64 (5H, m, Ar), 7.21 (1H, dd, *J* = 2.4,7.7 Hz, H-2), 4.22 (3H, s, -OCH_3)	180.8 (C=S), 172.4 (S-C=N), 168.2 (amide C=O), 142.5 (C-9), 137.6 (C-6), 135.8 (C-1'), 133.7 (C-4'), 130.2 (C-3',C-5'), 128.7 (C-2',C-6'), 126.4 (C-8), 124.3 (C-4), 116.7 (C-5), 112.5 (C-7), 56.5 (-OCH_3)
2i	R′ = 6-	9.41 (1H, s, -NH), 9.18 (1H, s, -NH), 8.14 (1H, d, *J* = 8.6 Hz,	181.5 (C=S), 172.4 (S-C=N), 168.2 (amide C=O), 142.5 (C-

	OCH_3, R = 2,4-Dichloro	H-1), 8.09 (1H, d, *J* = 2.4 Hz, H-3), 7.38-7.64 (3H, m, Ar), 7.21 (1H, dd, *J* = 2.4,8.4 Hz, H-2), 4.21 (3H, s, -OCH_3)	9), 138.5 (C-6), 137.8 (C-4'), 134.7 (C-2'), 132.2 (C-1'), 131.5 (C-3'), 130.7 (C-6'), 127.6 (C-6'), 126.5 (C-8), 124.2 (C-4), 117.5 (C-5), 113.4 (C-7), 56.7 (-OCH_3)
2j	R′ = 4,6-Dichloro, R = 2,4-Dichloro	10.38 (1H, s, -NH), 9.25 (1H, s, -NH), 8.07 (1H, d, *J* = 2.3 Hz, H-1), 7.97 (1H, d, *J* = 2.3 Hz, H-2), 7.69 (1H, d, *J* = 8.2 Hz, H-6'), 7.11 (1H, d, *J* = 2.4 Hz, H-3'), 6.78 (1H, dd, *J* = 7.8,2.4 Hz, H-4')	181.6 (C=S), 173.5 (S-C=N), 169.3 (amide C=O), 147.8 (C-9), 138.4 (C-4'), 135.6 (C-2'), 133.5 (C-6), 132.4 (C-4), 131.6 (C-1'), 130.8 (C-3'), 130.2 (C-6'), 128.6 (C-5'), 125.3 (C-8), 123.4 (C-5), 122.8 (C-7)
2k	R′ = 4,6-Dichloro, R = H	10.32 (1H, s, -NH), 9.21 (1H, s, -NH), 8.02 (1H, d, *J* = 2.3 Hz, H-1), 7.64 (2H, d, *J* = 8.2 Hz, H-2',H-6'), 7.43 (1H, d, *J* = 2.3 Hz, H-2), 7.13-7.23 (1H, m, Ar-H-4'), 6.73 (2H, dd, *J* = 8.2,7.8 Hz, H-3',H-5')	181.4 (C=S), 172.5 (S-C=N), 168.6 (amide C=O), 147.4 (C-9), 135.3 (C-1'), 133.2 (C-4'), 132.5 (C-6), 131.4 (C-4), 130.2 (C-3',C-5'), 128.7 (C-2',C-6'), 124.5 (C-8), 123.6 (C-5), 122.8 (C-7)

The ^{1}H NMR spectrum confirmed the formation of 1-(benzo[d]thiazol-2-yl)-3-(2-methoxybenzoyl) thiourea **(2b)** by the presence of two singlets for -NH protons at δ 11.38 and δ 10.09 ppm and a singlet for methoxy proton at δ 4.15 ppm. In ^{13}C NMR spectrum the carbonyl carbon signal observed at δ 168.5 ppm and methoxy carbon signal appeared at δ 56.4 ppm.

The ^{1}H and ^{13}C NMR spectral data of 1-(benzo[d]thiazol-2-yl)-3-(2-methoxybenzoyl) thiourea **(2b)** is presented in Table 4.9.

Table 4.9: ^{1}H and ^{13}C NMR spectral data of 1-(Benzo[d]thiazol-2-yl)-3-(2-methoxybenzoyl) thiourea (2b)



Carbons	δ (ppm) and multiplicity	
	^{1}H NMR	^{13}C NMR
(S=C)	-	181.3
(amidic C=O)	-	168.5
C-2 (S-C=N)	-	172.4
C-4	8.28, (d), *J* = 7.4 Hz	123.7
C-5	7.24, (m)	126.5
C-6	7.63, (m)	127.4
C-7	7.81, (d), *J* = 7.4 Hz	123.2
C-8	-	125.3
C-9	-	147.5
C-1'	-	118.7
C-2'	-	138.7
C-3'	7.08, (d), *J* = 8.4 Hz	116.4
C-4'	7.18, (dd), *J* = 7.8,8.3 Hz	133.5
C-5'	7.47, (dd), *J* = 8.4,7.8 Hz	121.5
C-6'	7.74, (d), *J* = 7.1 Hz	129.3
-OCH_3	4.15, (s)	56.4
-NH	11.38, (s)	-
-NH	10.09, (s)	-

The structure of 1-(benzo[d]thiazol-2-yl)-3-(2-methoxyben-zoyl) thiourea **(2b)** was also confirmed by mass spectrometry. The molecular ion peak appeared at *m/z* 343 with 53 % abundance.

The elemental analysis of 1-(benzo[d]thiazol-2-yl)-3-(substituted)thioureas **(2a-k)** is presented in Table 4.10.

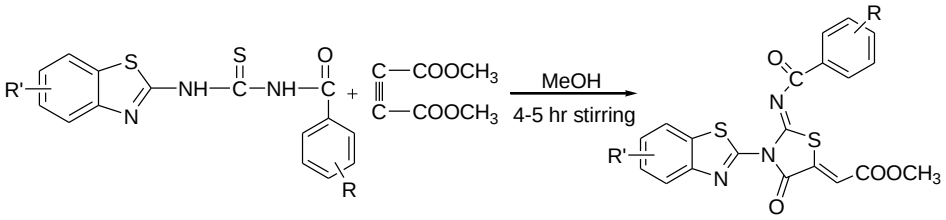
Table 4.10: Elemental analysis of all the compounds (2a-k)

Compounds (R)	Formulae	Elemental Analysis							
		% Calculated				% Found			
		C	H	N	S	C	H	N	S
R′ = H, R = H	$C_{15}H_{11}N_3S_2O$	57.50	3.51	13.41	20.44	57.36	3.38	13.27	20.23
R′ = H, R = 2-OCH_3	$C_{16}H_{13}N_3O_2S_2$	50.97	3.79	12.24	18.65	55.52	3.65	12.17	18.46
R′ = H, R = 4-Me	$C_{16}H_{13}N_3OS_2$	58.71	3.97	13.84	19.57	58.49	3.61	13.58	19.34

R′ = Br, R = 3-Cl	$C_{15}H_9BrClN_3OS_2$	42.15	2.11	9.83	14.98	42.06	2.04	9.70	14.85
R′ = Br, R = 2-F	$C_{15}H_9BrFN_3OS_2$	43.79	2.19	10.22	15.57	43.61	2.13	10.13	15.44
R′ = CH_3, R = 3-Cl	$C_{16}H_{12}ClN_3OS_2$	53.18	3.32	11.63	17.73	53.07	3.27	11.57	17.52
R′ = CH_3, R = 2-Br	$C_{16}H_{12}BrN_3OS_2$	47.17	2.95	10.32	15.72	47.08	2.82	10.24	15.53
R′ = OCH_3, R = H	$C_{16}H_{13}N_3O_2S_2$	55.97	3.97	12.24	18.67	55.74	3.87	12.19	18.53
R′ = OCH_3, R = 2,4-Dichloro	$C_{16}H_{11}C_{l2}N_3O_2S_2$	46.71	2.68	10.22	15.57	46.62	2.53	10.14	15.46
R′ = 4,6-Dichloro, R = 2,4-Dichloro	$C_{15}H_7Cl_4N_3OS_2$	39.91	1.55	9.31	14.19	39.84	1.37	9.18	14.13
R′ = 4,6-Dichloro, R = H	$C_{15}H_9Cl_2N_3OS_2$	47.24	2.36	11.02	16.79	47.12	2.32	10.96	16.63

2.4.3 Methyl 2-[2-benzamido-3-(benzo[d]thiazol-2-yl)-4-oxothiazolidin-5-ylidene] acetates (3a-k)

Benzothiazolyl thioureas were converted into five membered heterocycles with imino moiety like methyl 2-[2-benzamido-3-(2-benzothiazolyl)-4-oxothiazolidin-5-ylidene] acetates by direct cyclization of these thioureas with dimethyl but-2-ynedioate (DMAD) in dry methanol at room temperature.



R = H, -Br, -CH_3, -OCH_3, 2,4-Dichloro.

R’ = H, 2-OCH_3, 4-CH_3, 3-Cl, 2-F, 2-Br, 2,4-Dichloro.

Scheme 4.3: Synthesis of Methyl 2-[2-benzamido-3-(benzo[d]thiazol-2-yl)-4-oxothiazolidin-5-ylidene] acetates (3a-k)

The Physical data of methyl 2-[2-benzamido-3-(benzo[d]thiazol-2-yl)-4-oxothiazolidin-5-ylidene] acetates **(3a-k)** is presented in Table 4.11.

Table 4.11: Physical data of all the compounds (3a-k).

Sr. No	Compounds (R)	M.P. (^{o}C)	Rf[a] Values	Yield (%)	Solvent of Recrystallization
3a	R′ = H, R = H	195-196	0.4	72	Methanol
3b	R′ = H, R = 2-OCH_3	233-234	0.35	73	"
3c	R′ = H, R = 4- CH_3	287-288	0.4	71	"
3d	R′ = Br, R = 3-Cl	266-267	0.45	76	"
3e	R′ = Br, R = 2-F	151-153	0.5	72	"
3f	R′ = CH_3, R = 3-Cl	223-224	0.45	74	"
3g	R′ = CH_3, R = 2-Br	134-136	0.45	76	"
3h	R′ = OCH_3, R = H	183-184	0.35	75	"
3i	R′ = OCH_3, R = 2,4-Dichloro	146-147	0.4	74	"
3j.	R′ = 4,6-Dichloro, R = 2,4-Dichloro	116-117	0.5	78	"
3k.	R′ = 4,6-Dichloro, R = H	169-170	0.4	77	"

[Pet.ether : ethylacetate (8:2)]

In the IR spectra, the absorptions for the N-H protons of 1-Aroyl-3-(substituted-2-benzothiazolyl) thioureas were disappeared and the characteristics carbonyl carbon (C=O) absorptions peaks for ester moiety were observed in the range of 1719-1684 cm^{-1}. The characteristics carbonyl carbon (C=O) absorptions peaks for amidic moiety were observed from 1652-1668 cm^{-1}, another carbonyl absorption of thiazolidinone rings appeared at 1685-1693 cm^{-1}.

The FTIR spectral data of methyl 2-[2-benzamido-3-(benzo[d]thiazol-2-yl)-4-oxothiazolidin-5-ylidene] acetates **(3a-k)** is presented in Table 4.12.

Table 4:12: FTIR data of all the compounds (3a-k).

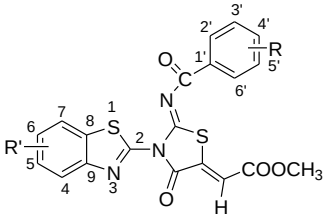
Sr. No	Compounds	(C=C) cm^{-1}	(ring C=O) cm^{-1}	ester (C=O) cm^{-1}	amide (C=O) cm^{-1}	(C=N) cm^{-1}
3a	R′ = H, R = H	1554	1688	1721	1653	1568
3b	R′ = H, R = 2-OCH_3	1552	1691	1719	1655	1573

3c	R′ = H, R = 4- CH_3	1558	1693	1722	1658	1576
3d	R′ = Br, R = 3-Cl	1553	1689	1723	1652	1571
3e	R′ = Br, R = 2-F	1556	1690	1724	1656	1573
3f	R′ = CH_3, R = 3-Cl	1555	1685	1721	1667	1574
3g	R′ = CH_3, R = 2-Br	1557	1687	1725	1664	1576
3h	R′ = OCH_3, R = H	1552	1686	1723	1662	1577
3i	R′ = OCH_3, R = 2,4-Dichloro	1556	1685	1726	1668	1578
3j.	R′ = 4,6-Dichloro, R = 2,4-Dichloro	1558	1691	1724	1667	1578
3k.	R′ = 4,6-Dichloro, R = H	1554	1693	1725	1656	1576

The synthesis of methyl 2-[2-benzamido-3-(benzo[d]thiazol-2-yl)-4-oxothiazolid-in-5-ylidene] acetates **(3a-k)** was confirmed by ^{1}H NMR due to the presence of a two characteristic broad band singlet for -NH protons at δ 9.34-11.34 ppm and other -NH peaks at δ 9.15-10.06 ppm. In ^{13}C NMR spectra the characteristics (C=S) carbon peaks appeared in the range of δ 180.4-182.4 ppm. The characteristics carbonyl carbon (C=O) peaks observed in the range of δ 168.2-169.3 ppm.

The ^{1}H and ^{13}C NMR spectral data of methyl 2-[2-benzamido-3-(benzo[d]thiazol-2-yl)-4-oxothiazolidin-5-ylidene] acetates **(3a-k)** is presented in Table 4.13.

Table 4.13: ^{1}H and ^{13}C NMR spectral data of the compounds (3a-k)



Sr. No.	Compounds	^{1}H NMR(δ) (ppm)	^{13}C NMR(δ) (ppm)
2a	R′ = H, R = H	8.17 (1H, d, *J* = 7.6 Hz, H-1), 8.12 (1H, d, *J* = 7.4 Hz, H-4), 7.66-8.03 (5H, m, Ar), 7.57 (1H, dd, *J* = 7.2,7.4 Hz, H-3), 7.36 (1H, dd, *J* = 7.2,7.3 Hz, H-2), 7.11 (1H, s, C=C-*H*), 3.74 (-OCH_3)	168.3 (amide C=O), 166.2 (ring C=O), 165.5 (ester C=O), 162.4 (C=N), 156.5 (S-C=N), 146.3 (C-9), 140.6 (=CH), 136.7 (C-1'), 134.5 (C-2',C-6'), 133.4 (C-3',C-5'), 131.5 (S-C=), 128.2 (C-4'), 127.4 (C-6), 125.6 (C-5), 124.3 (C-8), 123.7 (C-4), 122.5

			(C-7), 54.2 (-OCH_3)
2b	R′ = H, R = 2-OCH_3	8.28 (1H, d, *J* = 7.4 Hz, H-1), 8.16 (1H, d, *J* = 7.4 Hz, H-4), 7.81 (1H, d, *J* = 7.2 Hz, H-6'), 7.76 (1H, dd, *J* = 7.8,7.6 Hz, H-2), 7.63 (1H, dd, *J* = 7.6,7.8 Hz, H-3), 7.52 (1H, dd, *J* = 7.1,7.2 Hz, H-5'), 7.45 (1H, dd, *J* = 7.3,7.2 Hz, H-4'), 7.32 (1H, d, *J* = 7.3 Hz, H-4'), 7.13 (1H, s, C=C-*H*), 3.84 (3H, s, Ar-OCH_3), 3.76 (3H, s, -OCH_3)	168.4 (amide C=O), 166.4 (ring C=O), 165.2 (ester C=O), 162.2 (C=N), 156.4 (S-C=N), 146.4 (C-9), 140.5 (=CH), 137.8 (C-1'), 136.6 (C-2'), 135.5 (C-6'), 134.4 (C-3'), 133.5 (C-5'), 131.4 (S-C=), 127.8 (C-4'), 126.6 (C-6), 125.3 (C-5), 124.7 (C-8), 123.5 (C-4), 122.6 (C-7), 54.4 (-OCH_3)
2d	R′ = 6-Br, R = 3-Cl	8.16 (1H, d, *J* = 7.4 Hz, H-1), 8.10 (1H, d, *J* = 2.4 Hz, H-3), 7.95 (1H, d, *J* = 7.4 Hz, H-2), 7.83 (1H, d, *J* = 7.2 Hz, H-2',H-6'), 7.76 (1H, d, *J* = 2.3 Hz, H-3',H-5'), 7.14 (1H, s, C=C-*H*), 3.77 (3H, s, -OCH_3)	168.7 (amide C=O), 166.5 (ring C=O), 165.6 (ester C=O), 162.6 (C=N), 156.7 (S-C=N), 146.6 (C-9), 140.6 (=CH), 138.6 (C-1'), 137.5 (C-3',C-5'), 136.3 (C-2',C-6'), 135.7 (C-4'), 134.5 (C-6), 132.6 (C-5), 131.7 (S-C=), 127.5 (C-8), 125.6 (C-4), 124.3 (C-7), 123.4 (C-6), 54.5 (-OCH_3)
2e	R′ = 6-Br, R = 2-F	8.19 (1H, d, *J* = 7.4 Hz, H-1), 8.13 (1H, d, *J* = 2.3 Hz, H-3), 7.87 (1H, d, *J* = 7.4 Hz, H-2), 7.76 (1H, d, *J* = 7.2 Hz, H-6'), 7.68 (1H, dd, *J* = 7.2,7.3 Hz, H-5'), 7.54 (1H, dd, *J* = 7.4,7.2 Hz, H-4'), 7.34 (1H, d, *J* = 7.4 Hz, H-3'), 7.15 (1H, s, C=C-*H*), 3.76 (3H, s, -OCH_3)	168.6 (amide C=O), 166.8 (ring C=O), 165.7 (ester C=O), 162.7 (C=N), 156.8 (S-C=N), 146.5 (C-9), 140.8 (=CH), 140.5 (C-2'), 137.6 (C-1'), 136.5 (C-6'), 134.6 (C-4'), 131.4 (C-5), 131.9 (S-C=), 128.6 (C-5'), 127.8 (C-3'), 126.5 (C-8), 125.7 (C-4), 124.8 (C-7), 122.4 (C-6), 54.7 (-OCH_3)
2f	R′ = 6-CH_3, R = 3-Cl	8.13 (1H, d, *J* = 7.5 Hz, H-1), 8.08 (1H, d, *J* = 2.4 Hz, H-3), 7.91 (1H, d, *J* = 7.5 Hz, H-2), 7.83 (1H, d, *J* = 7.2 Hz, H-6'), 7.74 (1H, d, *J* = 2.3 Hz, H-2'), 7.62 (1H, dd, *J* = 7.1,2.3 Hz, H-4'), 7.36 (1H, dd, *J* = 7.2,7.1 Hz, H-5'), 7.14 (1H, s, C=C-*H*), 3.75 (3H, s, -OCH_3), 2.57	168.5 (amide C=O), 166.4 (ring C=O), 165.5 (ester C=O), 162.7 (C=N), 156.6 (S-C=N), 146.5 (C-9), 140.7 (=CH), 138.6 (C-1'), 137.5 (C-3'), 136.4 (C-6'), 135.7 (C-4'), 134.5 (C-6), 133.4 (C-5'), 131.7 (S-C=), 128.5 (C-2'), 126.6 (C-5), 124.7 (C-8), 123.3 (C-4), 122.5 (C-7), 54.6 (-OCH_3), 23.4 (Ar-CH_3)

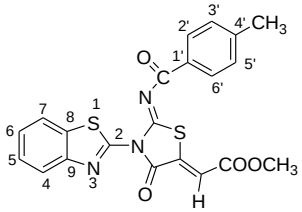
		(3H, s, Ar-CH_3)	
2g	R′ = 6-CH_3, R = 2-Br	8.13 (1H, d, *J* = 7.6 Hz, H-1), 8.06 (1H, d, *J* = 2.4 Hz, H-3), 7.82 (1H, d, *J* = 7.4 Hz, H-2), 7.73 (1H, d, *J* = 7.2 Hz, H-6'), 7.42 (1H, dd, *J* = 7.3,7.2 Hz, H-5'), 7.31 (1H, dd, *J* = 7.2,7.1 Hz, H-4'), 7.18 (1H, d, *J* = 7.1 Hz, H-3'), 7.15 (1H, s, C=C-*H*), 3.76 (3H, s, -OCH_3), 2.56 (3H, s, Ar-CH_3)	168.2 (amide C=O), 166.1 (ring C=O), 165.3 (ester C=O), 162.5 (C=N), 156.3 (S-C=N), 146.4 (C-9), 140.4 (=CH), 138.4 (C-1'), 137.5 (C-6'), 136.6 (C-4'), 135.7 (C-3'), 134.5 (C-5'), 133.6 (C-6), 131.5 (S-C=), 127.8 (C-2'), 126.7 (C-5), 125.6 (C-8), 124.5 (C-4), 122.6 (C-7), 54.3 (-OCH_3), 23.2 (Ar-CH_3)
2h	R′ = 6-OCH_3, R = H	8.11 (1H, d, *J* = 7.6 Hz, H-1), 8.04 (1H, d, *J* = 2.3 Hz, H-3), 7.81 (1H, d, *J* = 7.4 Hz, H-2), 7.37-7.74 (5H, m, Ar), 7.13 (1H, s, C=C-*H*), 3.86 (3H, s, Ar-OCH_3), 3.74 (3H, s, -OCH_3)	168.4 (amide C=O), 166.4 (ring C=O), 165.4 (ester C=O), 162.3 (C=N), 156.4 (S-C=N), 146.2 (C-9), 140.5 (=CH), 137.6 (C-6), 135.7 (C-1'), 134.5 (C-2',C-6'), 132.6 (C-3',C-5'), 131.6 (S-C=), 128.7 (C-4'), 127.5 (C-8), 126.4 (C-4), 124.5 (C-5), 122.3 (C-7), 56.2 (Ar-OCH_3), 54.4 (-OCH_3)
2i	R′ = 6-OCH_3, R = 2,4-Dichloro	8.19 (1H, d, *J* = 7.6 Hz, H-1), 8.08 (1H, d, *J* = 2.4 Hz, H-2), 7.81 (1H, d, *J* = 7.6 Hz, H-3), 7.73 (1H, d, *J* = 7.4 Hz, H-6'), 7.66 (1H, d, *J* = 2.4 Hz, H-3'), 7.37 (1H, d, *J* = 7.4 Hz, H-5'), 7.16 (1H, s, C=C-*H*), 3.87 (3H, s, Ar-OCH_3), 3.75 (3H, s, -OCH_3)	168.8 (amide C=O), 166.5 (ring C=O), 165.7 (ester C=O), 162.6 (C=N), 156.8 (S-C=N), 146.3 (C-9), 141.5 (=C-S), 138.5 (C-1'), 137.3 (C-2'), 136.7 (C-4'), 135.6 (C-'6), 134.5 (C-3'), 133.4 (C-5'), 132.1 (S-C=), 127.5 (C-8), 126.6 (C-4), 124.5 (C-5), 122.7 (C-7), 56.5 (Ar-OCH_3), 54.6 (-OCH_3)
2j	R′ = 2,4-dichloro, R = 2,4-Dichloro	8.26 (1H, d, *J* = 2.3 Hz, H-1), 8.18 (1H, d, *J* = 2.3 Hz, H-2), 7.88 (1H, d, *J* = 7.2 Hz, H-6'), 7.75 (1H, d, *J* = 2.3 Hz, H-3'), 7.67 (1H, d, *J* = 7.2 Hz, H-5'), 7.19 (1H, s, C=C-*H*), 3.78 (3H, s, -OCH_3)	169.3 (amide C=O), 166.8 (ring C=O), 165.8 (ester C=O), 162.8 (C=N), 156.9 (S-C=N), 146.5 (C-9), 141.8 (=CH), 138.6 (C-1'), 137.5 (C-2'), 136.6 (C-4'), 135.8 (C-6'), 134.4 (C-6), 133.5 (C-4), 132.6 (C-3'), 132.4 (=C-S), 128.5 (C-5'), 126.4 (C-8), 124.6 (C-5), 123.7 (C-7), 54.8 (-OCH_3)

2k	R′ = H, R = 2,4-Dichloro	8.22 (1H, d, *J* = 2.3 Hz, H-1), 8.14 (1H, d, *J* = 2.3 Hz, H-2), 7.66-7.93 (5H, m, Ar), 7.17 (1H, s, C=C-*H*), 3.77 (3H, s, -OCH_3)	168.9 (amide C=O), 166.7 (ring C=O), 165.6 (ester C=O), 162.7 (C=N), 156.7 (S-C=N), 146.3 (C-9), 141.6 (=CH), 136.7 (C-1'), 135.6 (C-6), 134.5 (C-4), 133.6 (C-2',C-6'), 132.4 (C-3',C-5'), 132.2 (S-C=), 127.4 (C-4'), 125.5 (C-8), 124.6 (C-5), 122.8 (C-7), 54.6 (-OCH_3)

The ^{1}H NMR spectrum confirmed the formation of methyl 2-[3-(benzo[d]thiazol-2-yl)-2-(4-methylbenzamido)-4-oxo-thiazolidin-5-ylidene]acetate **(3c)** by the presence of a characteristic singlet for the ring proton at δ 7.12 ppm and a singlet for methyl proton at δ 2.55 ppm and a singlet for methyl ester protons appeared at δ 3.75 ppm. In ^{13}C NMR spectrum the amidic and ester carbonyl carbon signals observed at δ 168.5 and δ 165.4 ppm and a carbonyl signal appeared at δ 166.3 ppm. The methyl carbon signal appeared at δ 22.4 ppm.

The ^{1}H and ^{13}C NMR data of methyl 2-[3-(benzo[d]thiazol-2-yl)-2-(4-methyl-benzamido)-4-oxothiazolidin-5-ylidene]acetate **(3c)** is presented in Table 4.14.

Table 4.14: ^{1}H and ^{13}C NMR data of Methyl 2-[3-(benzo[d]thiazol-2-yl)-2-(4-methylbenzamido)-4-oxothiazolidin-5-ylidene]acetate (3c)



Carbons	δ (ppm) and multiplicity	
	^{1}H NMR	**^{13}C NMR**
amide C=O	-	168.5
ring C=O	-	166.3
ester C=O	-	165.4
(C=N)	-	162.3
C-2 (S-C=N)	-	156.4
(=CH)	7.12, (s)	140.4
(S-C=)	-	131.6

C-4	8.25, (d), *J* = 7.4 Hz	124.6
C-5	7.61, (dd), *J* = 7.2,7.6 Hz	126.5
C-6	7.34, (dd), *J* = 7.2,7.6 Hz	127.3
C-7	8.14, d, *J* = 7.4 Hz	123.4
C-8	-	125.7
C-9	-	146.6
C-1'	-	135.4
C-2'	7.91 (d), *J* = 7.2 Hz	134.6
C-3'	7.82 (d), *J* = 7.2 Hz	132.7
C-4'	-	128.4
C-5'	7.82 (d), *J* = 7.2 Hz	132.7
C-6'	7.91, (d), *J* = 7.2 Hz	134.6
-OCH_3	3.75, (s)	54.2
4-CH_3	2.55, (s)	22.4

The structure of methyl 2-[3-(benzo[d]thiazol-2-yl)-2-(4-methylbenzamido)-4-oxothiazolidin-5-ylidene]acetate **(3c)** was also confirmed by mass spectrometry. The molecular ion peak appeared at *m/z* 437 with 67 % abundance. and a base peak observed at *m/z* 184.

The elemental analysis of methyl 2-[2-benzamido-3-(benzo[d]thiazol-2-yl)-4-oxothiazolidin-5-ylidene] acetates **(3a-k)** is presented in Table 4.15.

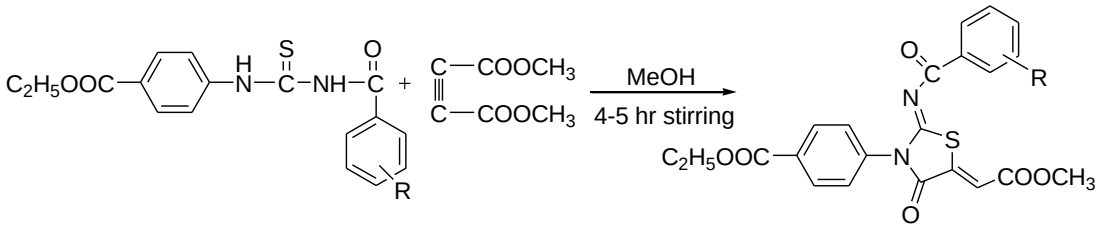
Table 4.15: Elemental analysis of all the compounds (3a-k)

Compounds (R)	**Formulae**	**Elemental Analysis**							
		% Calculated				**% Found**			
		C	**H**	**N**	**S**	**C**	**H**	**N**	**S**
R′ = H, R = H	$C_{20}H_{13}N_3O_4S_2$	56.73	3.07	9.93	15.13	56.62	2.96	9.87	15.09
R′ = H, R = 2-OCH_3	$C_{21}H_{15}N_3O_5S_2$	55.63	3.31	9.27	14.13	55.54	3.22	9.16	14.09
R′ = H, R = 4-Me	$C_{21}H_{15}N_3O_4S_2$	57.66	3.43	9.61	14.65	57.41	3.34	9.48	14.52
R′ = Br, R = 3-Cl	$C_{20}H_{11}N_3O_4S_2ClBr$	44.73	2.05	7.83	11.93	44.56	1.97	7.74	11.86
R′ = Br, R = 2-F	$C_{20}H_{11}N_3O_4S_2ClF$	46.15	2.12	8.07	12.31	46.08	2.04	7.95	12.21
R′ = CH_3, R = 3-Cl	$C_{21}H_{14}N_3O_4S_2Cl$	53.45	2.97	8.91	13.57	53.33	2.88	8.75	13.37

R′ = CH_3, R = 2-Br	$C_{21}H_{14}N_3O_4S_2Br$	48.84	2.71	8.14	12.40	48.73	2.54	8.07	12.28
R′ = OCH_3, R = H	$C_{21}H_{15}N_3O_5S_2$	55.63	3.31	9.27	14.13	55.51	3.26	9.16	14.02
R′ = OCH_3, R = 2,4-Dichloro	$C_{21}H_{13}N_3O_5S_2Cl_2$	48.37	2.49	8.06	12.28	48.21	2.37	7.94	12.16
R′ = 4,6-Dichloro, R = 2,4-Dichloro	$C_{20}H_9N_3O_4S_2Cl_4$	42.93	1.61	7.51	11.45	42.84	1.54	7.36	11.38
R′ = 4,6-Dichloro, R = H	$C_{20}H_{11}N_3O_4S_2Cl_2$	48.88	2.24	8.55	13.03	48.78	2.17	8.41	12.94

2.4.4 Synthesis of Ethyl 4-[2-benzamido-5-(2-methoxy-2-oxoethylidene)-4-oxothiazolidin-3-yl] benzoates (4a-j)

Ethyl 4-(3-benzoylthioureido) benzoates were converted into five membered heterocycles with imino group like methyl ethyl 4-[2-benzamido-5-(2-methoxy-2-oxoethylidene)-4-oxothiazolidin-3-yl] benzoates by direct cyclization of these ester substituted thioureas with dimethyl but-2-ynedioate (DMAD) in dry methanol at room temperature.



R = H, 3-Cl, 2,4-Dichloro, 4-CH_3, 3-CH_3, 4-OCH_3, 3,4-Dimethoxy,2-Br, 3-OCH_3, 2-F.

Scheme 4.4: Synthesis of Ethyl 4-[2-benzamido-5-(2-methoxy-2-oxoethylidene)-4-oxothiazolidin-3-yl] benzoates (4a-j)

The Physical data of ethyl 4-[2-benzamido-5-(2-methoxy-2-oxoethylidene)-4-oxothiazolidin-3-yl] benzoates **(4a-j)** is presented in Table 4.16.

Table 4.16: Physical data of all the compounds (4a-j).

Sr. No	Compounds (R)	M.P. (^oC)	Rf[a] Values	Yield (%)	Solvent of Recrystallization
4a	H	121-122	0.65	65	Methanol
4b	3-Cl	137-138	0.7	69	"
4c	2,4-Dichloro	130-131	0.65	67	"
4d	4-CH_3	119-120	0.6	72	"
4e	3-CH_3	122-123	0.6	68	"
4f	4-OCH_3	126-127	0.55	71	"
4g	3,4-Dimethoxy	147-148	0.55	74	"
4h	1-Br	127-128	0.7	72	"
4i	3-OCH_3	134-135	0.6	66	"
4j	2-F	142-143	0.71	65	"

[Pet. Ether : ethyl acetate (7:3)]

In the IR spectra, the absorptions for the N-H protons of thioureas were disappeared and the characteristics carbonyl carbon (C=O) absorptions peaks for ester moiety observed in the range of 1718-1726 cm^{-1} and for other ester group from 1720-1727 cm^{-1}. The characteristics carbonyl carbon (C=O) absorptions peaks for amidic moiety observed at 1653-1668 cm^{-1}, another carbonyl absorption of thiazolidinone rings appeared in the range of 1672-1779 cm^{-1}.

The FTIR spectral data of ethyl 4-[2-benzamido-5-(2-methoxy-2-oxoethylidene)-4-oxothiazolidin-3-yl] benzoates **(4a-j)** is presented in Table 4.17.

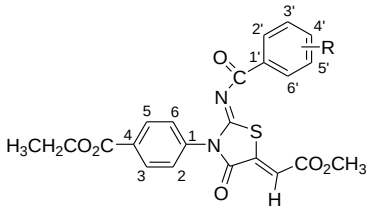
Table 4.17: FTIR data of all the compounds (4a-j).

Sr. No	Compounds R	(C=C) cm^{-1}	(ring C=O) cm^{-1}	(ester C=O) cm^{-1}	(amide C=O) cm^{-1}
4a	H	1546	1676	1724, 1721	1653
4b	3-Cl	1544	1677	1732, 1722	1656
4c	2,4-Dichloro	1562	1672	1725, 1721	1663
4d	4-CH_3	1553	1674	1727, 1723	1665
4e	3-CH_3	1564	1677	1722, 1718	1664
4f	4-OCH_3	1558	1681	1724, 1720	1661
4g	3,4-Dimethoxy	1552	1676	1726, 1723	1662
4h	1-Br	1554	1678	1731, 1726	1664
4i	3-OCH_3	1561	1682	1733, 1728	1667
4j	2-F	1556	1679	1730, 1722	1668

In the ^{1}H NMR spectra of ethyl 4-[2-benzamido-5-(2-methoxy-2-oxoethylidene)-4-oxothiazolidin-3-yl] benzoates **(4a-j)**, characteristics singlets for thiazolidinone rings appeared in the range of δ 7.11-7.21 ppm. In ^{13}C NMR the characteristics carbonyl carbon (C=O) absorptions peaks for ester moiety appeared in the range of δ 164.4-166.8 ppm and for other ester group from δ 164.3-165.8 ppm. The characteristics carbonyl carbon (C=O) absorptions peaks for amidic moiety observed from δ 175.2-176.4 ppm, another carbonyl absorption of thiazolidinone rings appeared in the range of δ 165.6-167.7 ppm.

The ^{1}H and ^{13}C NMR spectral data of ethyl 4-[2-benzamido-5-(2-methoxy-2-oxoethylidene)-4-oxothia-zolidin-3-yl] benzoates **(4a-j)** is presented in Table 4.18.

Table 4.18: ^{1}H and ^{13}C NMR spectral data of the compounds (4a-j)



Sr. No.	Compounds	^{1}H NMR(δ) (ppm)	^{13}C NMR(δ) (ppm)
4a	H	7.91 (1H, d, *J* = 7.6 Hz, H-2,H-6), 7.64-7.83 (5H, m, Ar), 7.57 (1H, d, *J* = 7.6 Hz, H-3,H-5), 7.13 (1H, s, C=C-*H*), 4.26 (2H, q, *J* = 7.1 Hz, -CH_2), 3.76 (3H, s, -OCH_3), 2.23 (3H, t, *J* = 5.6 Hz, -CH_3)	168.4 (amide C=O), 167.1 (ring C=O), 166.2 (-CH_3 ester C=O), 165.4 (-C_2H_5 ester C=O), 162.6 (C=N), 140.2 (=CH), 137.4 (C-4), 136.3 (C-1'), 134.7 (C-2',C-6'), 132.4 (C-3',C-5'), 131.3 (S-C=), 130.4 (C-2,C-6), 128.2 (C-4'), 126.7 (C-1), 122.4 (C-3,C-5), 59.4 (-OCH_2), 53.4 (-OCH_3), 15.2 (-CH_3)
4b	3-Cl	7.94 (1H, d, *J* = 7.6 Hz, H-2,H-6), 7.85 (1H, d, *J* = 2.3 Hz, H-2'), 7.78 (1H, d, *J* = 7.2 Hz, H-6'), 7.67 (1H, d, *J* = 7.6 Hz, H-3,H-5), 7.58 (1H, dd, *J* = 7.2,7.3 Hz, H-5'), 7.56 (1H, dd, *J* = 7.3,2.3 Hz, H-4'), 7.17 (1H, s, C=C-*H*), 4.28 (2H, q, *J* = 7.1 Hz, -CH_2), 3.82 (3H, s, -OCH_3), 2.26 (3H, t, *J* = 5.6 Hz, -CH_3)	168.6 (amide C=O), 167.3 (ring C=O), 166.4 (-CH_3 ester C=O), 165.5 (-C_2H_5 ester C=O), 162.7 (C=N), 140.4 (=CH), 137.5 (C-4), 136.5 (C-1'), 135.2 (C-3'), 134.8 (C-4'), 133.2 (C-5'), 132.5 (C-2'), 131.6 (S-C=), 130.5 (C-2,C-6), 128.6 (C-6'), 126.6 (C-1), 122.7 (C-3,C-5), 59.8 (-OCH_2), 53.5 (-OCH_3), 15.6 (-CH_3)

4c	2,4-Dichloro	7.96 (1H, d, *J* = 7.6 Hz, H-2,H-6), 7.87 (1H, d, *J* = 2.3 Hz, H-3', 7.74 (1H, d, *J* = 7.2 Hz, H-6'), 7.65 (1H, dd, *J* = 7.2,2.3 Hz, H-5'), 7.56 (1H, d, *J* = 7.6 Hz, H-3,H-5), 7.21 (1H, s, C=C-*H*), 4.31 (2H, q, *J* = 7.1 Hz, -CH_2), 3.86 (3H, s, -OCH_3), 2.29 (3H, t, *J* = 5.6 Hz, -CH_3)	168.8 (amide C=O), 167.6 (ring C=O), 166.7 (-CH_3 ester C=O), 165.8 (-C_2H_5 ester C=O), 162.9 (C=N), 140.5 (=CH), 138.8 (C-4'), 137.6 (C-4), 136.4 (C-2'), 135.5 (C-1'), 133.6 (C-6'), 131.8 (S-C=), 131.2 (C-3'), 130.5 (C-2,C-6), 127.6 (C-5'), 126.6 (C-1), 122.7 (C-3,C-5), 60.1 (-OCH_2), 53.7 (-OCH_3), 15.8 (-CH_3)
4e	3-CH_3	7.87 (1H, d, *J* = 7.6 Hz, H-2,H-6), 7.79 (1H, d, *J* = 7.1 Hz, H-6'), 7.72 (1H, d, *J* = 2.4 Hz, H-2'), 7.68 (1H, d, *J* = 7.6 Hz, H-3,H-5), 7.61 (1H, dd, *J* = 7.1,7.2 Hz, H-5'), 7.55 (1H, dd, *J* = 7.2,2.4 Hz, H-4'), 7.15 (1H, s, C=C-*H*), 4.24 (2H, q, *J* = 7.1 Hz, -CH_2), 3.83 (3H, s, -OCH_3), 2.66 (3H, s, Ar-CH_3), 2.25 (3H, t, *J* = 5.6 Hz, -CH_3)	168.2 (amide C=O), 167.1 (ring C=O), 166.3 (-CH_3 ester C=O), 165.4 (-C_2H_5 ester C=O), 162.5 (C=N), 140.3 (=CH), 137.5 (C-4), 135.7 (C-1'), 134.6 (C-3'), 133.5 (C-6'), 132.7 (C-4'), 131.6 (S-C=), 130.3 (C-2,C-6), 129.5 (C-5'), 126.7 (C-1), 122.5 (C-3,C-5), 59.6 (2H, s, -OCH_2), 53.5 (3H, s, -OCH_3), 23.8 (3H, s, Ar-CH_3), 15.4 (3H, s, -CH_3)
4f	4-OCH_3	7.88 (1H, d, *J* = 7.6 Hz, H-2,H-6), 7.78 (1H, d, *J* = 7.4 Hz, H-2',H-6'), 7.67 (1H, d, *J* = 7.4 Hz, H-3',H-5'), 7.56 (1H, d, *J* = 7.6 Hz, H-3,H-5), 7.14 (1H, s, C=C-*H*), 4.24 (2H, q, *J* = 7.1 Hz,-CH_2), 3.86 (3H, s, Ar-OCH_3), 3.78 (3H, s, -OCH_3), 2.23 (3H, t, *J* = 5.6 Hz, -CH_3)	168.5 (amide C=O), 167.7 (ring C=O), 166.3 (-CH_3 ester C=O), 165.5 (-C_2H_5 ester C=O), 162.4 (C=N), 140.3 (=CH), 138.6 (C-4'), 137.4 (C-4), 131.5 (S-C=), 130.8 (C-2',C-6'), 130.3 (C-2,C-6), 128.4 (C-1'), 126.5 (C-1), 122.4 (C-3,C-5), 117.6 (C-3',C-5'), 59.3 (2H, s, -OCH_2), 56.4 (3H, s, Ar-OCH_3), 53.2 (3H, s, -OCH_3), 15.3 (3H, s, -CH_3)
4g	3,4-Dimethoxy	7.92 (1H, d, *J* = 7.6 Hz, H-2,H-6), 7.85 (1H, d, *J* = 7.2 Hz, H-6'), 7.74 (1H, s, Ar-2'), 7.65 (1H, d, *J* = 7.2 Hz, H-5'), 7.57 (1H, d, *J* = 7.6 Hz, H-3,H-5), 7.12 (1H, s, C=C-*H*), 4.25 (2H, q, *J* = 7.1 Hz, -CH_2), 3.85 (6H, s, Ar-OCH_3), 3.77 (3H, s, -OCH_3), 2.26 (3H, t, *J* = 5.6 Hz, -CH_3)	168.7 (amide C=O), 167.6 (ring C=O), 166.2 (-CH_3 ester C=O), 165.3 (-C_2H_5 ester C=O), 162.5 (C=N), 140.2 (=CH), 138.5 (C-4'), 137.4 (C-4), 136.7 (C-3'), 131.3 (S-C=), 130.5 (C-2,C-6), 129.4 (C-1'), 126.6 (C-1), 124.3 (C-6'), 122.2 (C-3,C-5), 118.3 (C-5'), 117.6 (C-2'), 59.2 (2H, s, -OCH_2), 56.5 (6H, s, Ar-OCH_3),

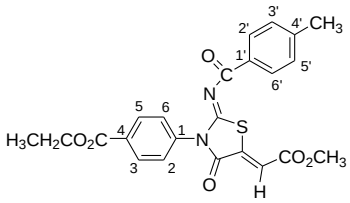
			53.1 (3H, s, -OCH_3), 15.2 (3H, s, -CH_3)
4h	1-Br	7.89 (1H, d, *J* = 7.6 Hz, H-2,H-6), 7.58-7.84 (4H, m, Ar), 7.53 (1H, d, *J* = 7.6 Hz, H-3,H-5), 7.11 (1H, s, C=C-*H*), 4.24 (2H, q, *J* = 7.1 Hz,-CH_2), 3.76 (3H, s, -OCH_3), 2.25 (3H, t, *J* = 5.6 Hz**,** -CH_3)	168.3 (amide C=O), 165.6 (ring C=O), 165.4 (-CH_3 ester C=O), 164.3 (-C_2H_5 ester C=O), 162.6 (C=N), 140.5 (=CH), 138.2 (C-1'), 137.6 (C-4), 136.7 (C-4'), 134.6 (C-6'), 133.5 (C-3'), 131.6 (S-C=), 130.4 (C-2,C-6), 128.5 (C-5'), 126.6 (C-1), 123.5 (C-2'), 122.4 (C-3,C-5), 59.5 (2H, s, -OCH_2), 53.3 (3H, s, -OCH_3), 15.6 (3H, s, -CH_3)
4i	3-OCH_3	7.88 (1H, d, *J* = 7.6 Hz, H-2,H-6), 7.56-7.82 (4H, m, Ar), 7.52 (1H, d, *J* = 7.6 Hz, H-3,H-5), 7.13 (1H, s, C=C-*H*), 4.26 (2H, q, *J* = 7.1 Hz,-CH_2), 3.84 (3H, s, Ar-OCH_3), 3.75 (3H, s, -OCH_3), 2.24 (3H, t, *J* = 5.6 Hz, -CH_3)	168.5 (amide C=O), 167.7 (ring C=O), 166.3 (-CH_3 ester C=O), 165.6 (-C_2H_5 ester C=O), 162.5 (C=N), 140.4 (=CH), 138.7 (C-3'), 137.4 (C-4), 136.3 (C-4'), 133.6 (C-6'), 131.4 (S-C=), 130.5 (C-2,C-6), 126.3 (C-1), 124.8 (C-1'), 123.5 (C-5'), 122.6 (C-3,C-5), 118.3 (C-2'), 59.2 (2H, s, -OCH_2), 56.1 (3H, s, Ar-OCH_3), 53.5 (3H, s, -OCH_3), 15.4 (3H, s, -CH_3)
4j	2-F	7.97 (1H, d, *J* = 7.6 Hz, H-2,H-6), 7.92-7.65 (4H, m, Ar), 7.61 (1H, d, *J* = 7.6 Hz, H-3,H-5), 7.18 (1H, s, C=C-*H*), 4.28 (2H, q, *J* = 7.1 Hz,-CH_2), 3.79 (3H, s, -OCH_3), 2.31 (3H, t, *J* = 5.5 Hz, -CH_3)	169.4 (amide C=O), 167.5 (ring C=O), 166.8 (-CH_3 ester C=O), 165.7 (-C_2H_5 ester C=O), 163.2 (C=N), 141.4 (=CH), 139.3 (C-2'), 137.8 (C-4), 136.5 (C-4'), 134.3 (C-6'), 131.7 (S-C=), 130.4 (C-2,C-6), 128.7 (C-5'), 126.8 (C-1), 125.5 (C-1'), 122.7 (C-3,C-5), 118.5 (C-3'), 60.4 (2H, s, -OCH_2), 53.6 (3H, s, -OCH_3), 15.7 (3H, s, -CH_3)

The ^{1}H NMR spectrum confirmed the formation of ethyl 4-[5-(2-methoxy-2-oxoethyl-idene)-2-(4-methylbenzamido)-4-oxothiazolidin-3-yl]benzoate **(4e)** by the presence of a characteristic singlet for the thiazolidinone ring proton at δ 7.16 ppm and a

singlet for methyl proton at δ 2.68 ppm and another singlet for methyl ester protons appeared at δ 3.86 ppm. Two characteristic signals triplet and a quartet observed for ethyl ester protons at δ 2.26 and δ 4.26 ppm. In ^{13}C NMR spectrum the amidic and two ester carbonyl carbon signals observed at δ 168.3 ppm and δ 166.6 and δ 165.5 ppm and a ring carbonyl signal appeared at δ 167.2 ppm. The methyl carbon signal appeared at δ 23.6 ppm.

The ^{1}H and ^{13}C NMR spectral data of the compound **(4e)** is presented in Table 4.19.

Table 4.19: ^{1}H and ^{13}C NMR data of Ethyl 4-[5-(2-methoxy-2-oxoethylidene)-2-(4-methylbenzamido)-4-oxothiazolidin-3-yl]benzoate (4e)



Carbons	δ (ppm) and multiplicity	
	^{1}H NMR	^{13}C NMR
(amide C=O)	-	168.3
(ring C=O)	-	167.2
(-CH_3 ester C=O)	-	166.6
(-C_2H_5 ester C=O)	-	165.5
ring (C=N)	-	162.5
ring (=CH)	7.16, (s)	140.4
(S-C=)	-	131.5
C-1	-	126.7
C-2	7.92, (d), *J* = 7.6 Hz	130.5
C-3	7.63, (d), *J* = 7.6 Hz	122.6
C-4	-	137.5
C-5	7.63, (d), *J* = 7.6 Hz	122.6
C-6	7.92, (d), *J* = 7.6 Hz	130.5
C-1'	-	134.3
C-2'	7.84, (d), *J* = 7.4 Hz	129.7
C-3'	7.75, (d), *J* = 7.4 Hz	129.3
C-4'	-	132.6
C-5'	7.75, (d), *J* = 7.4 Hz	129.3
C-6'	7.84, (d), *J* = 7.4 Hz	129.7
ester-OCH_2	4.26, (q), *J* = 7.1 Hz	59.6
ester-OCH_3	3.86, (s)	53.5
4'-CH_3	2.68, (s)	23.6
ester-CH_3	2.26, (t), *J* = 5.6 Hz	15.3

The structure of ethyl 4-[5-(2-methoxy-2-oxoethyl-idene)-2-(4-methylbenzamido) -4-oxothiazolidin-3-yl]benzoate **(4e)** was also confirmed by mass spectrometry. The molecular ion peak appeared at *m/z* 452 with 57 % abundance. and a base peak observed at *m/z* 149.

The elemental analysis of ethyl 4-[2-benzamido-5-(2-methoxy-2-oxoethylidene)-4 -oxothiazolidin-3-yl] benzoates **(4a-j)** is presented in Table 4.20.

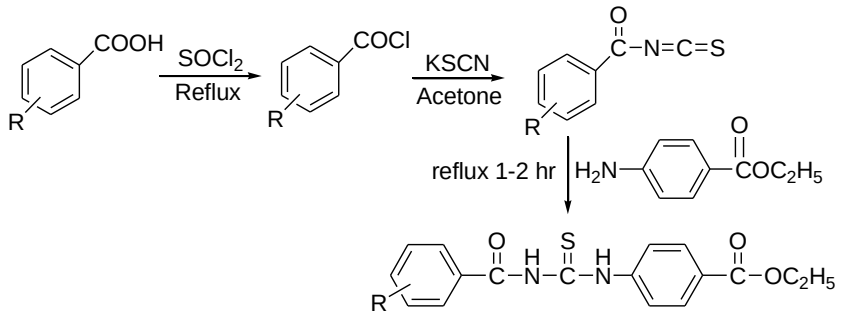
Table 4.20: Elemental analysis of all the compounds (4a-j)

Compounds (R)	Formulae	Elemental Analysis							
		% Calculated				% Found			
		C	H	N	S	C	H	N	S
H	$C_{22}H_{18}N_2O_6S$	60.27	4.11	6.39	7.31	60.19	4.03	6.28	7.24
3-Cl	$C_{22}H_{17}N_2O_6ClS$	55.93	3.60	5.93	6.78	55.81	3.46	5.78	6.56
2,4-Dichloro	$C_{22}H_{16}N_2O_6SCl_2$	52.17	3.16	5.53	6.32	52.13	3.09	5.43	6.26
4-CH_3	$C_{23}H_{20}N_2O_6S$	61.06	4.42	6.19	7.08	60.94	4.31	6.13	7.01
3-CH_3	$C_{23}H_{20}N_2O_6S$	61.07	4.43	6.18	7.07	60.96	4.34	6.11	6.98
4-OCH_3	$C_{23}H_{20}N_2O_7S$	58.97	4.27	5.98	6.84	58.83	4.16	5.91	6.73
3,4-Dimethoxy	$C_{24}H_{22}N_2O_8S$	57.83	4.42	5.62	6.42	57.72	4.33	5.48	6.34
1-Br	$C_{22}H_{17}N_2O_6SBr$	51.16	3.29	5.43	6.20	51.11	3.16	5.36	6.14
3-OCH_3	$C_{23}H_{20}N_2O_7S$	58.97	4.26	5.97	6.83	58.84	4.16	5.86	6.71.
2-F	$C_{22}H_{17}N_2O_6SF$	57.89	3.73	6.14	7.02	57.49	3.61	6.05	6.95

2.5 Iminothiazolines

2.5.1 Ethyl 4-(3-benzoylthioureido) benzoates (1a-j)

The substituted benzoic acids were converted into corresponding acid chlorides by their reaction with thionyl chloride. These acid chlorides were then treated with potassium thiocyanate in acetone and then reaction mixture was refluxed with 4-5 hr afforded aminoethylbenzoate to afford 1-aroyl-3-(*p*-ethylbenzoato)thioureas, which were further purified by recrystallization from ethanol. The synthetic pathway is illustrated in Scheme 5.1



R = H, 3-Cl, 2,4-Dichloro, 4-CH_3, 3-CH_3, 4-OCH_3, 3,4-Dimethoxy, 3-OCH_3, 2-Br, 2-F.

Scheme 5.1: Ethyl 4-(3-benzoylthioureido) benzoates (1a-j)

The physical data of ethyl 4-(3-benzoylthioureido) benzoates **(1a-j)** is presented in Table 5.1.

Table 5.1: Physical data of all the compounds (1a-j).

Sr. No	Compound (R)	M.P. (^oC)	Rf[a] Values	Yield (%)	Solvent for Recrystallization
1a	R = H	140-142	0.8	74	Ethanol
1b	R = 3-Cl	156-158	0.7	78	"
1c	R = 2,4-Dichloro	117-118	0.75	80	"
1d	R = 4-CH_3	223-224	0.7	71	"
1e	R = 3-CH_3	196-198	0.7	78	Methanol
1f	R = 4-OCH_3	207-208	0.65	76	"
1g	R = 3,4-Dimethoxy	232-234	0.6	72	Ethanol
1h	R = 2-Br	213-215	0.67	74	"
1i	R = 3-OCH_3	173-174	0.6	73	Methanol
1j	R = 2-F	123-124	0.7	68	"

[Pet. ether : ethyl acetate (7:3)]

In the IR spectra, the characteristic absorptions for the N-H protons of ethyl 4-(3-benzoylthioureido) benzoates **(1a-j)** appeared in the range of 3298-3332 cm^{-1}. The ester carbonyl carbon absorptions peaks observed at 1722-1729 $cm^{-1}$and the amidic carbonyl absorptions appeared at 1671-1688 cm^{-1}.

The FTIR spectral data of ethyl 4-(3-benzoylthioureido) benzoates **(1a-j)** is presented in Table 5.2.

Table 5.2: FTIR data of all the compounds (1a-j).

Sr. No	Compound	(C=C) cm^{-1}	ester (C=O) cm^{-1}	amide (C=O) cm^{-1}	(C=S) cm^{-1}	(N-H) cm^{-1}
1a	R = H	1583	1724	1675	1272	3298
1b	R = 3-Cl	1578	1727	1673	1280	3302
1c	R = 2,4-Dichloro	1586	1723	1678	1283	3309
1d	R = 4-CH_3	1584	1726	1681	1286	3329
1e	R = 3-CH_3	1588	1722	1671	1284	3322
1f	R = 4-OCH_3	1587	1726	1676	1282	3315
1g	R = 3,4-Dimethoxy	1585	1724	1678	1267	3321
1h	R = 2-Br	1576	1728	1683	1262	3317
1i	R = 3-OCH_3	1581	1725	1685	1264	3325
1j	R = 2-F	1591	1729	1688	1271	3332

The synthesis of ethyl 4-(3-benzoylthioureido) benzoates **(1a-j)** was also confirmed by ^{1}H NMR due to the presence of a two characteristic broad band singlet for -NH protons at δ 11.31-11.42 ppm and another -NH peak observed at δ 10.23-10.38 ppm. In ^{13}C NMR spectra the characteristics carbonyl carbon peaks of ester moeity observed in the range of δ 165.4-166.2 ppm and amide carbonyl carbon appeared at δ 167.2-168.2 ppm. The (C=S) carbon signal appeared in the range of δ 180.4-181.2 ppm.

The ^{1}H and ^{13}C NMR spectral data of ethyl 4-(3-benzoylthioureido) benzoates **(1a-j)** is presented in Table 5.3.

Table 5.3: ^{1}H and ^{13}C NMR spectral data of all the compounds (1a-j)

Sr. No.	Compounds	^{1}H NMR(δ) (ppm)	^{13}C NMR(δ) (ppm)
1a	R = H	11.31 (1H, s, -NH), 10.24 (1H, s, -NH), 7.92 (1H, d, *J* = 7.8 Hz, H-2,H-6), 7.56-7.87 (5H, m, Ar), 7.47 (1H, d, *J* = 7.8 Hz, H-3,H-5), 4.21 (2H, q, *J* = 7.2 Hz, -CH_2), 2.21 (3H, t, *J* = 5.6 Hz, -CH_3)	180.4 (C=S), 167.3 (amide C=O), 165.4 (ester C=O), 138.6 (C-4), 135.4 (C-1'), 132.6 (C-4'), 130.5 (C-2,C-6), 129.4 (C-3',C-5'), 128.7 (C-2',C-6'), 127.6 (C-3,C-5), 126.7 (C-1), 60.2 (-OCH_2), 14.3 (-CH_3)

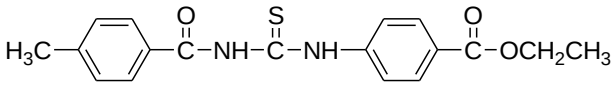
1b	R = 3-Cl	11.37 (1H, s, -NH), 10.32 (1H, s, -NH), 7.95 (1H, d, *J* = 7.8 Hz, H-2,H-6), 7.84 (1H, d, *J* = 2.4 Hz, H-2'), 7.76 (1H, d, *J* = 7.4 Hz, H-6'), 7.66 (1H, d, *J* = 7.8 Hz, H-3,H-5), 7.58 (1H, dd, *J* = 7.2,2.4 Hz, H-4'), 7.49 (1H, dd, *J* = 7.2,7.4 Hz, H-5'), 4.26 (2H, q, *J* = 7.2 Hz, -CH_2), 2.26 (3H, t, *J* = 5.6 Hz, -CH_3)	180.8 (C=S), 167.5 (amide C=O), 165.6 (ester C=O), 138.7 (C-4), 136.4 (C-1'), 135.5 (C-3'), 133.7 (C-4'), 130.7 (C-2,C-6), 129.4 (C-5'), 128.5 (C-2'), 127.4 (C-3,C-5), 126.5 (C-1), 125.8 (C-6'), 60.3 (-OCH_2), 14.2 (-CH_3)
1c	R = 2,4-Dichloro	11.42 (1H, s, -NH), 10.38 (1H, s, -NH), 7.97 (1H, d, *J* = 7.8 Hz, H-2,H-6), 7.86 (1H, d, *J* = 2.3 Hz, H-3'), 7.78 (1H, d, *J* = 7.2 Hz, H-6'), 7.67 (1H, dd, *J* = 7.2,2.3 Hz, H-5'), 7.54 (1H, d, *J* = 7.8 Hz, H-3,H-5), 4.27 (2H, q, *J* = 7.2 Hz, -CH_2), 2.28 (3H, t, *J* = 5.6 Hz, -CH_3)	181.2 (C=S), 167.8 (amide C=O), 166.2 (ester C=O), 139.5 (C-4), 138.4 (C-4'), 135.2 (C-2'), 132.3 (C-3'), 131.7 (C-1'), 130.8 (C-6'), 130.3 (C-2,C-6), 128.1 (C-5'), 127.2 (C-3,C-5), 126.8 (C-1), 60.8 (-OCH_2), 14.5 (-CH_3)
1e	R = 3-CH_3	11.35 (1H, s, -NH), 10.31 (1H, s, -NH), 7.86 (1H, d, *J* = 7.8 Hz H-2,H-6), 7.75 (1H, d, *J* = 7.2 Hz, H-6'), 7.66 (1H, d, *J* = 2.4 Hz, H-2'), 7.58 (1H, dd, *J* = 7.4,7.2 Hz, H-5'), 7.53 (1H, dd, *J* = 7.4,2.4 Hz, H-4'), 7.46 (1H, d, *J* = 7.8 Hz, H-3,H-5), 4.23 (2H, q, *J* = 7.2 Hz, -CH_2), 2.61 (3H, s, Ar-CH_3), 2.24 (3H, t, *J* = 5.6 Hz, -CH_3)	180.5 (C=S), 167.6 (amide C=O), 165.7 (ester C=O), 138.9 (C-4), 137.8 (C-3'), 134.5 (C-1'), 133.2 (C-4'), 130.5 (C-2,C-6), 129.3 (C-5'), 128.2 (C-2'), 127.1 (C-3,C-5), 126.4 (C-1), 125.4 (C-6'), 60.5 (-OCH_2), 24.1 (Ar-CH_3), 14.3 (-CH_3)
1f	R = 4-OCH_3	11.38 (1H, s, -NH), 10.29 (1H, s, -NH), 7.86 (1H, d, *J* = 7.8 Hz, H-2,H-6), 7.73 (1H, d, *J* = 7.5 Hz, H-2',H-6'), 7.64 (1H, d, *J* = 7.5 Hz, H-3',H-5'), 7.54 (1H, d, *J* = 7.8 Hz, H-3,H-5), 4.27 (2H, q, *J* = 7.2 Hz, -CH_2), 3.72 (3H, s, -OCH_3), 2.25 (3H, t, *J* = 5.6 Hz, -CH_3)	180.6 (C=S), 167.4 (amide C=O), 165.5 (ester C=O), 139.6 (C-4'), 138.5 (C-4), 134.5 (C-1'), 130.7 (C-2,C-6), 129.5 (C-2',C-6'), 127.2 (C-3,C-5), 126.7 (C-1), 117.4 (C-3',C-5'), 60.6 (-OCH_2), 56.5 (Ar-OCH_3), 14.2 (-CH_3)
1g	R = 3,4-Dimethoxy	11.40 (1H, s, -NH), 10.32 (1H, s, -NH), 7.90 (1H, d, *J* = 7.8 Hz, H-2,H-6), 7.84 (1H, d, *J* =	180.7 (C=S), 167.7 (amide C=O), 165.8 (ester C=O), 139.8 (C-4'), 138.7 (C-3'), 137.6 (C-

		7.4 Hz, H-6'), 7.73 (1H, d, *J* = 7.8 Hz, H-3,H-5), 7.65 (1H, s, Ar-H-2'), 7.56 (1H, d, *J* = 7.5 Hz, H-5'), 4.27 (2H, q, *J* = 7.2 Hz, -CH_2), 3.78 (3H, s, 3-OCH_3), 3.75 (3H, s, 4-OCH_3), 2.25 (3H, t, *J* = 5.6 Hz, -CH_3)	4), 130.8 (C-2,C-6), 128.3 (C-1'), 127.1 (C-3,C-5), 126.5 (C-1), 121.6 (C-6'), 117.4 (C-5'), 115.5 (C-2'), 60.6 (-OCH_2), 56.5 (Ar-OCH_3), 14.2 (-CH_3)
1h	R = 2-Br	11.34 (1H, s, -NH), 10.23 (1H, s, -NH), 7.85 (1H, d, *J* = 7.8 Hz, H-2,H-6), 7.63-7.81 (4H, m, Ar), 7.56 (1H, d, *J* = 7.8 Hz, H-3,H-5), 4.23 (2H, q, *J* = 7.2 Hz, -CH_2), 2.26 (3H, t, *J* = 5.6 Hz, -CH_3)	180.4 (C=S), 167.2 (amide C=O), 165.6 (ester C=O), 138.6 (C-4), 137.5 (C-1'), 135.4 (C-4'), 132.7 (C-3'), 131.2 (C-2,C-6), 130.5 (C-6'), 128.4 (C-5'), 127.3 (C-3,C-5), 126.8 (C-1), 121.4 (C-2'), 60.4 (-OCH_2), 14.3 (-CH_3)
1i	R = 3-OCH_3	11.36 (1H, s, -NH), 10.27 (1H, s, -NH), 7.87 (1H, d, *J* = 7.8 Hz, H-2,H-6), 7.57-7.77 (4H, m, Ar), 7.53 (1H, d, *J* = 7.8 Hz, H-3,H-5), 4.25 (2H, q, *J* = 7.2 Hz, -CH_2), 3.73 (3H, s, -OCH_3), 2.26 (3H, t, *J* = 5.6 Hz, -CH_3)	180.5 (C=S), 167.6 (amide C=O), 165.7 (ester C=O), 138.7 (C-3'), 137.6 (C-4), 134.2 (C-4'), 131.3 (C-2,C-6), 129.1 (C-6'), 127.4 (C-3,C-5), 126.6 (C-1), 122.5 (C-5'), 118.4 (C-1'), 116.5 (C-2'), 60.7 (-OCH_2), 56.4 (Ar-OCH_3), 14.5 (-CH_3)
1j	R = 2-F	11.42 (1H, s, -NH), 10.34 (1H, s, -NH), 7.93 (1H, d, *J* = 7.8 Hz, H-2,H-6), 7.64-7.89 (4H, m, Ar), 7.58 (1H, d, *J* = 7.8, Hz H-3,H-5), 4.26 (2H, q, *J* = 7.2 Hz, -CH_2), 2.28 (3H, t, *J* = 5.6 Hz, -CH_3)	181.4 (C=S), 168.2 (amide C=O), 166.5 (ester C=O), 140.6 (C-2'), 138.7 (C-4), 134.7 (C-4'), 131.2 (C-2,C-6), 129.3 (C-6'), 127.3 (C-3,C-5), 126.7 (C-1), 126.3 (C-1'), 125.6 (C-5'), 117.6 (C-3'), 61.2 (-OCH_2), 14.8 (-CH_3)

The ^{1}H NMR also confirmed the formation of ethyl 4-[3-(4-methylbenzoyl) thioureido] benzoate **(1d)** due to the presence of a two characteristic broad band singlet for -NH protons at δ 11.34 and δ 10.27 ppm. In ^{13}C NMR spectra the characteristics carbonyl carbon peaks of ester moeity observed at δ 165.4 ppm and amide carbonyl carbon appeared at δ 167.5 ppm. The (C=S) carbon signal appeared at δ 180.6 ppm.

The ^{1}H and ^{13}C NMR spectral data of ethyl 4-[3-(4-methylbenzoyl)thioureido] benzoate **(1d)** is presented in Table 5.4.

Table 5.4: ^{1}H NMR data of Ethyl 4-[3-(4-methylbenzoyl)thioureido] benzoate (1d)



Carbons	δ (ppm) and multiplicity	
	^{1}H NMR	^{13}C NMR
(C=S)	-	180.6
(amide-C=O)	7.11, (s)	167.5
(ester C=O)	-	165.4
C-1	-	126.7
C-2	7.88, (d), *J* = 7.8 Hz	131.4
C-3	7.68, (d), *J* = 7.8 Hz	127.6
C-4	-	138.7
C-5	7.68, (d), *J* = 7.8 Hz	127.6
C-6	7.88, (d), *J* = 7.8 Hz	131.4
C-1'	-	132.6
C-2'	7.57, d, *J* = 7.4 Hz	128.2
C-3'	7.77,(d), *J* = 7.4 Hz	130.3
C-4'	-	137.8
C-5'	7.77, (d), *J* = 7.4 Hz	130.3
C-6'	7.57, (d), *J* = 7.4 Hz	128.2
-OCH_2	4.24, (q), *J* = 7.1 Hz	60.4
Ar-CH_3	2.62,(s)	24.3
-CH_3	2.25, (t), *J* = 5.6 Hz	14.4
-NH	11.34, (s)	-
-NH	10.27, (s)	-

The structure of ethyl 4-[3-(4-methylbenzoyl)thioureido] benzoate **(1d)** was also confirmed by mass spectrometry. The molecular ion peak appeared at *m/z* 342 with 61 % abundance.

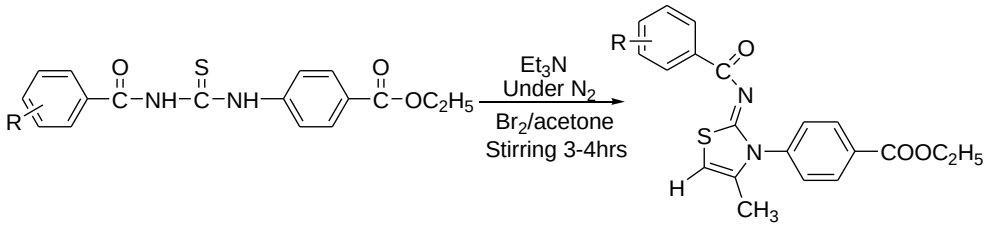
The elemental analysis data of ethyl 4-(3-benzoylthioureido) benzoates **(1a-j)** is presented in Table 5.5.

Table 5.5: Elemental analysis data of all the compounds (1a-j)

Compounds (R)	Formulae	Elemental Analysis							
		% Calculated				% Found			
		C	H	N	S	C	H	N	S
R = H	$C_{17}H_{16}N_2O_3S$	62.19	4.88	8.54	9.76	62.11	4.64	8.33	9.54
R = 3-Cl	$C_{17}H_{15}N_2O_3ClS$	56.27	4.14	7.72	8.83	56.14	4.06	7.53	8.64
R = 2,4-Dichloro	$C_{17}H_{14}N_2O_3SCl_2$	51.38	3.53	7.05	8.06	51.27	3.35	6.93	7.93
R = 4-CH_3	$C_{18}H_{18}N_2O_3S$	63.16	5.26	7.02	9.36	63.07	5.14	6.95	9.21
R = 2-CH_3	$C_{18}H_{18}N_2O_3S$	63.15	5.25	7.01	9.35	63.08	5.17	6.94	9.24
R = 4-OCH_3	$C_{18}H_{18}N_2O_4S$	60.33	5.03	6.70	8.94	60.27	4.92	6.58	8.86
R = 3,4-Dimethoxy	$C_{19}H_{20}N_2O_5S$	58.76	5.15	6.18	8.25	58.57	5.09	6.11	8.17
R = 2-Br	$C_{17}H_{15}N_2O_3SBr$	50.25	3.69	6.90	7.88	50.17	3.56	6.76	7.74
R = 3-OCH_3	$C_{18}H_{18}N_2O_4S$	60.34	3.02	6.70	8.93	60.23	4.93	6.53	8.81
R = 2-F	$C_{17}H_{15}N_2O_3SF$	58.96	4.34	6.94	9.25	58.87	4.21	6.73	9.12

2.5.2 Ethyl 4-[2-benzamido-4-methylthiazol-3(2H)-yl]benzoates (2a-j)

Ethyl 4-(3-benzoylthioureido) benzoates **(1a-j)** were cyclized by treating them with triethyl-amine and bromine in acetone and after 1 hour stirring under nitrogen yields ethyl 4-[2-benzamido-4-methylthiazol-3(2H)-yl]benzoates **(2a-j)**. The synthetic pathway is illustrated in Scheme 5.2.



R = H, 3-Cl, 2,4-Dichloro, 4-CH_3, 3-CH_3, 4-OCH_3, 3,4-Dimethoxy, 3-OCH_3, 2-Br, 2-F.

Scheme 5.2: Synthesis of Ethyl 4-[2-benzamido-4-methylthiazol-3(2H)-yl]benzoates (2a-j)

The physical data of ethyl 4-[2-benzamido-4-methylthiazol-3(2H)-yl] benzoates **(2a-j)**.is presented in Table 5.6.

Table 5.6: Physical data of all the compounds (2a-j).

Sr. No	Compound (R)	M.P. (^{o}C)	Rf[a] Values	Yield (%)	Solvent for Recrystallization
2a	R = H	108-110	0.4	70	Ethanol
2b	R = 3-Cl	87-88	0.5	68	"
2c	R = 2,4-Dichloro	96-97	0.5	76	"
2d	R = 4-CH_3	118-119	0.45	74	"
2e	R = 2-CH_3	112-113	0.45	72	"
2f	R = 4-OCH_3	125-126	0.4	71	"
2g	R = 3,4-Dimethoxy	132-133	0.35	78	"
2h	R = 2-Br	128-129	0.5	73	"
2i	R = 3-OCH_3	101-103	0.4	75	"
2j	R = 2-F	82-83	0.55	65	"

[Pet. ether : ethyl acetate (7:3)]

The FTIR spectral data of ethyl 4-[2-benzamido-4-methylthiazol-3(2H)-yl] benzoates **(2a-j)** shows that disappearance of the (N-H) peaks and appearance of some new absorption peaks of (C=N) at 1643-1657 cm^{-1}. Two characteristics carbonyl carbon peaks for ester and amidic moieties appeared in the range of 1721-1728 cm^{-1} and 1673-1692 cm^{-1}.

The FTIR spectral data of ethyl 4-[2-benzamido-4-methylthiazol-3(2H)-yl] benzoates **(2a-j)** is presented in Table 5.7.

Table 5.7: FTIR data of all the compounds (2a-j).

Sr. No	Compounds	(C=C) cm^{-1}	ester (C=O) cm^{-1}	amide (C=O) cm^{-1}	(C-S) cm^{-1}	(C=N) cm^{-1}
2a	R = H	1578	1724	1676	1147	1643
2b	R = 3-Cl	1582	1726	1685	1150	1648
2c	R = 2,4-Dichloro	1584	1734	1692	1160	1657
2d	R = 4-CH_3	1574	1725	1683	1147	1646
2e	R = 3-CH_3	1583	1726	1685	1153	1651
2f	R = 4-OCH_3	1587	1723	1677	1155	1645
2g	R = 3,4-Dimethoxy	1576	1721	1684	1152	1644
2h	R = 2-Br	1582	1722	1675	1160	1643
2i	R = 3-OCH_3	1580	1724	1673	1163	1646
2j	R = 2-F	1586	1728	1688	1176	1654

In the ^{1}H NMR spectra of ethyl 4-[2-benzamido-4-methylthiazol-3(2H)-yl] benzoates **(2a-j)** characteristics singlets for thiazoline rings appeared in the range of δ 6.34-6.48 ppm and singlets for ring methyl protons observed at δ 2.62-2.71 ppm. In ^{13}C NMR spectra the characteristics carbonyl carbon absorptions peaks for ester moiety appeared in the range of δ 166.2-166.8 ppm and the carbonyl carbon absorptions peaks for amidic moiety observed at δ 168.2-168.8 ppm.

The ^{1}H and ^{13}C NMR spectral data of ethyl 4-[2-benzamido-4-methylthiazol-3(2H)-yl] benzoates **(2a-j)** is presented in Table 5.8.

Table 5.8: ^{1}H and ^{13}C NMR spectral data of all the compounds (2a-j)

Sr. No.	Compounds	^{1}H NMR(δ) (ppm)	^{13}C NMR(δ) (ppm)
2a	R = H	7.86 (2H, d, *J* = 7.4 Hz, H-2',H-6'), 7.79 (2H, d, *J* = 7.8 Hz, H-3,H-5), 7.62 (1H, d, *J* = 7.1 Hz, H-4'), 7.55 (1H, dd, *J* = 7.4,7.1 Hz, H-3',H-5'), 6.63 (2H, d, *J* = 7.8 Hz, H-2,H-6), 6.42 (1H, s, C=C-*H*), 4.31 (2H, q, *J* = 7.1 Hz, -CH_2), 2.23 (3H, t, *J* = 5.6 Hz, -CH_3), 2.64 (-CH_3)	168.4 (amide C=O), 166.2 (ester C=O), 162.5 (N=C), 150.3 (N-C=), 145.5 (C-1), 136.6 (C-1'), 134.5 (C-4'), 132.2 (C-3,C-5), 131.2 (C-2',C-6'), 130.4 (C-3',C-5'), 122.5 (C-4), 117.3 (C-2,C-6), 101.2 (=CH), 61.4 (-CH_2), 21.3 (-CH_3), 15.2 (ester-CH_3)
2b	R = 3-Cl	7.93 (1H, d, *J* = 2.3 Hz, H-2'), 7.84 (2H, d, *J* = 7.8 Hz, H-3,H-5), 7.75 (1H, d, *J* = 7.2 Hz, H-6'), 7.66 (1H, dd, *J* = 7.1,2.2 Hz, H-4'), 7.47 (1H, dd, *J* = 7.2,7.1 Hz, H-5'), 6.72 (2H, d, *J* = 7.8 Hz, H-2,H-6), 6.46 (1H, s, C=C-*H*), 4.37 (2H, q, *J* = 7.1 Hz, -CH_2), 2.27 (3H, t, *J* = 5.6 Hz, -CH_3), 2.66 (-CH_3)	168.6 (amide C=O), 166.5 (ester C=O), 163.2 (N=C), 150.6 (N-C=), 145.5 (C-1), 137.6 (C-1'), 135.5 (C-3'), 134.4 (C-4'), 132.6 (C-3,C-5), 131.4 (C-5'), 130.2 (C-2'), 128.3 (C-6'), 122.7 (C-4), 118.2 (C-2,C-6), 101.6 (=CH), 61.7 (-CH_2), 21.5 (-CH_3), 15.6 (ester-CH_3)
2c	R = 2,4-Dichloro	7.88 (2H, d, *J* = 7.8 Hz, H-3,H-5), 7.73 (1H, d, *J* = 7.1 Hz, H-6'), 7.57 (1H, s, H-3'), 7.48 (1H, d, *J* = 7.1 Hz, H-5'), 6.68 (2H, d, *J* = 7.8 Hz, H-2,H-6), 6.48 (1H, s, C=C-*H*), 4.39 (2H, q, *J* = 7.1 Hz, -CH_2), 2.31 (3H, t, *J* = 5.6 Hz, -CH_3), 2.68 (-CH_3)	168.7 (N-C=O), 166.7 (ester C=O), 163.4 (N=C), 150.7 (N-C=), 145.7 (C-1), 140.6 (C-4'), 137.4 (C-2'), 136.5 (C-1'), 133.4 (C-6'), 132.7 (C-3,C-5), 131.4 (C-3'), 128.5 (C-5'), 122.6 (C-4), 118.4 (C-2,C-6), 101.8 (=CH), 61.7 (-CH_2), 21.8 (-CH_3), 15.7 (ester-CH_3)

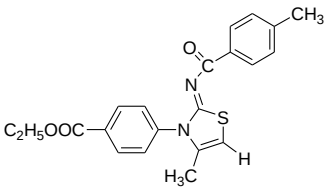
2e	R = 3-CH_3	7.86 (2H, d, *J* = 7.8 Hz, H-3,H-5), 7.78 (1H, d, *J* = 2.4 Hz, H-2'), 7.73 (1H, d, *J* = 7.2 Hz, H-6'), 7.65 (1H, dd, *J* = 7.1,2.4 Hz, H-4'), 7.58 (1H, dd, *J* = 7.2, 7.1 Hz, H-5'), 6.71 (2H, d, *J* = 7.8 Hz, H-2,H-6), 6.44 (1H, s, C=C-*H*), 4.36 (2H, q, *J* = 7.1 Hz, -CH_2), 2.25 (3H, t, *J* = 5.6 Hz, -CH_3), 2.73 (Ar-CH_3), 2.64 (-CH_3)	168.6 (amide C=O), 166.5 (ester C=O), 162.6 (N=C), 150.6 (N-C=), 145.5 (C-1), 137.6 (C-3'), 136.3 (C-1'), 135.4 (C-4'), 132.2 (C-3,C-5), 131.3 (C-2'), 130.7 (C-6'), 129.4 (C-5'), 122.5 (C-4), 117.4 (C-2,C-6), 101.6 (=CH), 61.3 (-CH_2), 24.6 (Ar-CH_3), 21.5 (-CH_3), 15.4 (ester-CH_3)
2f	R = 4-OCH_3	7.81 (2H, d, *J* = 7.8 Hz, H-3,H-5), 7.74 (2H, d, *J* = 7.4 Hz, H-2',H-6'), 7.26 (2H, d, *J* = 7.4 Hz, H-3', H-5'), 6.73 (2H, d, *J* = 7.8 Hz, H-2,H-6), 6.42 (1H, s, C=C-*H*), 4.32 (2H, q, *J* = 7.1 Hz, -CH_2), 3.74 (Ar-OCH_3), 2.24 (3H, t, *J* = 5.6 Hz, -CH_3), 2.63 (-CH_3)	168.4 (amide C=O), 166.3 (ester C=O), 162.6 (N=C), 150.5 (N-C=), 145.7 (C-1), 142.3 (C-4'), 132.5 (C-3,C-5), 131.8 (C-2',C-6'), 128.4 (C-1'), 121.7 (C-4), 120.3 (C-2,C-6), 118.5 (C-3',C-5'), 101.5 (=CH), 61.2 (-CH_2), 56.3 (Ar-OCH_3), 21.6 (-CH_3), 15.5 (ester-CH_3)
2g	R = 3,4-Dimethoxy	7.87 (2H, d, *J* = 7.8 Hz, H-3,H-5), 7.44 (1H, d, *J* = 7.2 Hz, H-6'), 7.35 (1H, s, Ar-H-2'), 6.96 (1H, d, *J* = 7.2 Hz, H-5'), 6.68 (2H, d, *J* = 7.8 Hz, H-2,H-6), 6.41 (1H, s, C=C-*H*), 4.31 (2H, q, *J* = 7.1 Hz, -CH_2), 3.76 (3'-OCH_3), 3.73 (4'-OCH_3), 2.21 (3H, t, *J* = 5.6 Hz, -CH_3), 2.62 (-CH_3)	168.2 (amide C=O), 166.2 (ester C=O), 162.6 (N=C), 154.2 (C-4'), 150.4 (C-3'), 149.5 (N-C=), 145.7 (C-1), 142.3 (C-4'), 132.3 (C-3,C-5), 128.6 (C-1'), 124.8 (C-6'), 121.7 (C-4), 120.3 (C-2,C-6), 118.2 (C-5'), 117.5 (C-2'), 101.5 (=CH), 61.2 (-CH_2), 56.4 (3'-OCH_3), 56.2 (4'-OCH_3), 21.3 (-CH_3), 15.2 (ester-CH_3)
2h	R = 2-Br	7.89 (2H, d, *J* = 7.8 Hz, H-3,H-5), 7.81 (1H, d, *J* = 7.4 Hz, H-6'), 7.77 (1H, dd, *J* = 7.2,2.4 Hz, H-3'), 7.54 (1H, dd, *J* = 7.2,7.1 Hz, H-4'), 7.46 (1H, dd, *J* = 7.3,7.1 Hz, H-5'), 6.71 (2H, d, *J* = 7.8 Hz, H-2,H-6), 6.43 (1H, s, C=C-*H*), 4.31 (2H, q, *J* = 7.1 Hz, -CH_2), 2.23 (3H, t, *J* = 5.6 Hz, -CH_3), 2.67 (-CH_3)	168.3 (amide C=O), 166.4 (ester C=O), 162.7 (N=C), 150.2 (N-C=), 145.6 (C-1), 140.3 (C-1'), 137.6 (C-4'), 133.5 (C-3'), 132.4 (C-6'), 131.8 (C-3,C-5), 129.6 (C-5'), 124.2 (C-2'), 122.5 (C-4), 118.2 (C-2,C-6), 101.8 (=CH), 61.6 (-CH_2), 24.7 (Ar-CH_3), 21.4 (-CH_3), 15.1 (ester-CH_3)

2i	R = 3-OCH_3	7.85 (2H, d, *J* = 7.8 Hz, H-3,H-5), 7.41 (1H, d, *J* = 7.2 Hz, H-6'), 7.33 (1H, s, Ar-H-2'), 6.94 (1H, d, *J* = 7.2 Hz, H-5'), 6.67 (2H, d, *J* = 7.8 Hz, H-2,H-6), 6.34 (1H, s, C=C-*H*), 4.27 (2H, q, *J* = 7.1 Hz, -CH_2), 3.74 (3'-OCH_3), 2.24 (3H, t, *J* = 5.6 Hz, -CH_3), 2.63 (-CH_3)	168.5 (amide C=O), 166.3 (ester C=O), 162.7 (N=C), 160.5 (C-3'), 150.2 (N-C=), 145.3 (C-1), 137.5 (C-1'), 132.6 (C-3,C-5), 131.4 (C-5'), 124.6 (C-6'), 122.5 (C-4'), 121.6 (C-4), 118.7 (C-2,C-6), 116.5 (C-2'), 101.5 (=CH), 61.2 (-CH_2), 55.8 (4'-OCH_3), 21.5 (-CH_3), 15.3 (ester-CH_3)
2j	R = 2-F	7.94 (1H, d, *J* = 7.3 Hz, H-6'), 7.86 (2H, d, *J* = 7.8 Hz, H-3,H-5), 7.68 (1H, dd, *J* = 7.2,6.9 Hz, H-4'), 7.37 (1H, dd, *J* = 7.2,7.1 Hz, H-5'), 7.26 (1H, dd, *J* = 7.1,6.8 Hz, H-5'), 6.64 (2H, d, *J* = 7.8 Hz, H-2,H-6), 6.48 (1H, s, C=C-*H*), 4.43 (2H, q, *J* = 7.1 Hz, -CH_2), 2.36 (3H, t, *J* = 5.6 Hz, -CH_3), 2.71 (-CH_3)	168.8 (amide C=O), 166.8 (ester C=O), 163.6 (N=C), 160.5 (C-2'), 150.6 (N-C=), 145.7 (C-1), 137.8 (C-4'), 132.6 (C-6'), 131.8 (C-3,C-5), 126.5 (C-5'), 124.6 (C-1'), 122.7 (C-4), 118.6 (C-2,C-6), 117.5 (C-3'), 101.9 (=CH), 62.1 (-CH_2), 24.8 (Ar-CH_3), 21.7 (-CH_3), 15.8 (ester-CH_3)

The ^{1}H NMR spectrum confirmed the formation of ethyl 4-[4-methyl-2-(4-methylbenzamido)thiazol-3(2H)-yl] benzoate **(2d)** by the presence of a characteristic singlet for thiazoline ring proton at δ 6.43 ppm and a singlet for ring methyl protons at δ 2.65 ppm and another singlet for methyl protons appeared at δ 2.75 ppm. Two characteristic signals triplet and a quartet observed for ethyl ester protons at δ 2.26 and δ 4.34 ppm. In ^{13}C NMR spectrum the amidic and ester carbonyl carbon signals observed at δ 168.5 ppm. The methyl carbon signal of ring appeared at δ 21.3 ppm and eater methyl carbon signal observed at δ 15.4 ppm.

The ^{1}H and ^{13}C NMR spectral data of the compound **(2d)** is presented in Table 5.9.

Table 5.9: ^{1}H and ^{13}C NMR data of Ethyl 4-[4-methyl-2-(4-methylbenzamido) thiazol-3(2H)-yl] benzoate (2d)



Carbons	δ (ppm) and multiplicity	
	^{1}H NMR	^{13}C NMR
(amidic C=O)	-	168.5
(ester C=O)	-	166.4
(C=N)	-	162.4
(S-C=N)	-	160.7
(N-C=)	-	150.3
(=C-H)	6.43, (s)	101.4
C-1	-	145.3
C-2	6.65, (d), *J* = 7.8 Hz	117.2
C-3	7.88, (d), *J* = 7.8 Hz	132.2
C-4	-	122.4
C-5	7.88, (d), *J* = 7.8 Hz	132.2
C-6	6.65, (d), *J* = 7.8 Hz	117.2
C-1'	-	133.5
C-2'	7.76, (d), *J* = 7.3 Hz	131.5
C-3'	7.36, (d), *J* = 7.3 Hz	130.6
C-4'	7.47, (dd), *J* = 7.3, 7.2 Hz	134.7
C-5'	7.36, (d), *J* = 7.3 Hz	130.6
C-6'	7.76, (d), *J* = 7.3 Hz	131.5
-CH_2	4.34, (q), *J* = 7.1 Hz	61.3
Ar-CH_3	2.75, (s)	24.7
ester -CH_3	2.26, (t), *J* = 5.6 Hz	15.4
ring-CH_3	2.65, (s)	21.3

The structure of ethyl 4-[4-methyl-2-(4-methylbenzamido)thiazol-3(2H)-yl] benzoate **(2d)** was also confirmed by mass spectrometry. The molecular ion peak appeared at *m/z* 380 with 61 % abundance. and a base peak observed at *m/z* 261.

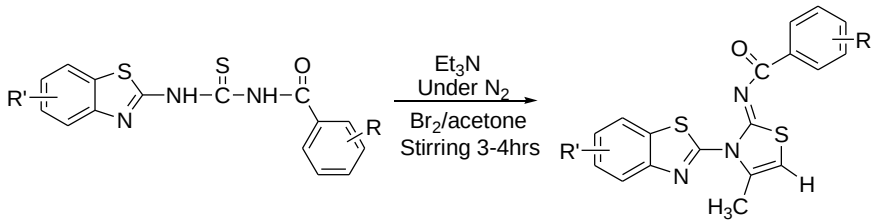
The elemental analysis of ethyl 4-[2-benzamido-4-methylthiazol-3(2H)-yl] benzoates **(2a-j)** is presented in Table 5.10.

Table 5.10: Elemental analysis of all the compounds (2a-j)

Compounds (R)	Formulae	Elemental Analysis							
		% Calculated				% Found			
		C	H	N	S	C	H	N	S
R = H	$C_{20}H_{18}N_2O_3S$	65.55	4.94	7.63	8.75	65.46	4.83	7.48	8.62
R = 3-Cl	$C_{20}H_{17}N_2O_3SCl$	59.91	4.26	6.98	7.98	59.83	4.16	6.87	7.86
R = 2,4-Dichloro	$C_{20}H_{16}N_2O_3SCl_2$	55.17	3.69	6.43	6.37	55.11	3.53	6.34	6.28
R = 4-CH_3	$C_{21}H_{20}N_2O_3S$	66.28	5.30	7.36	8.42	66.14	5.21	7.23	8.33
R = 3-CH_3	$C_{21}H_{20}N_2O_3S$	66.28	5.30	7.36	8.42	66.12	5.23	7.25	8.34
R = 4-OCH_3	$C_{21}H_{20}N_2O_4S$	63.61	5.07	7.07	8.09	63.53	4.96	7.95	8.01
R = 3,4-Dimethoxy	$C_{22}H_{22}N_2O_5S$	61.95	5.19	6.56	7.52	61.88	5.12	6.63	7.44
R = 2-Br	$C_{21}H_{17}N_2O_3SBr$	53.93	3.84	6.28	7.19	53.84	3.76	6.16	7.11
R = 3-OCH_3	$C_{21}H_{20}N_2O_4S$	63.62	5.06	7.06	8.07	63.53	4.95	7.96	8.01
R = 2-F	$C_{20}H_{17}N_2O_3SF$	62.48	4.45	7.28	8.33	62.34	4.36	7.17	8.25

2.5.3 *N*-[3-(Benzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene]benzamides (3a-k)

1-(Benzo[d]thiazol-2-yl)-3-(substituted) thioureas **(2a-k)** (Section 4.2) were cyclized by treating them with triethyl-amine and bromine in acetone and after 1 hour stirring under nitrogen afforded *N*-[3-(benzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene]benzamides **(3a-k)**. The synthetic pathway is illustrated in Scheme 5.3.



R = H, -Br, -CH_3, -OCH_3, 2,4-Dichloro.

R' = H, 2-OCH_3, 4-CH_3, 3-Cl, 2-F, 2-Br, 2,4-Dichloro.

Scheme 5.3: Synthesis of *N*-[3-(Benzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene]benzamides (3a-k).

The physcial data of *N*-[3-(benzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene] benzamides **(3a-k)** is presented in Table 5.11.

Table 5.11: Physical data of all the compounds (3a-k).

Sr. No	Compound (R)	M.P. (^{o}C)	Rf[a] Values	Yield (%)	Solvent of Recrystallization
3a	R′ = H, R = H	97-98	0.4	70	Methanol
3b	R′ = H, R = 2-OCH_3	76-77	0.45	74	“
3c	R′ = H, R = 4-CH_3	84-85	0.5	71	“
3d	R′ = 6-Br, R = 3-Cl	89-90	0.5	73	“
3e	R′ = 6-Br, R = 2-F	66-67	0.55	68	“
3f	R′ = 6-CH_3, R = 3-Cl	86-87	0.45	72	“
3g	R′ = 6-CH_3, R = 2-Br	90-91	0.4	77	“
3h	R′ = 6-OCH_3, R = H	82-83	0.35	71	“
3i	R′ = 6-OCH_3, R = 2,4-dichloro	79-80	0.4	76	“
3j	R′ = 4,6-dichloro, R = 2,4-dichloro	74-76	0.6	75	“
3k	R′ = 4,6-dichloro, R = H	70-71	0.4	78	

[Pet. ether : ethyl acetate (7:3)]

In the IR spectra, the absorptions for the N-H protons of 1-(benzo[d]thiazol-2-yl)-3-(substituted) thioureas **(2a-k)** were disappeared and the characteristics carbonyl carbon (C=O) absorptions peaks for for amidic moiety were observed in the range of 1674-1691 cm^{-1} and (C=N) absorptions peaks appeared at 1570-1588 cm^{-1}.

The FTIR spectral data of *N*-[3-(benzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene] benzamides **(3a-k)** is presented in Table 5.12.

Table 5.12: FTIR data of all the compounds (3a-k).

Sr. No	Compounds	(C=C) cm^{-1}	amide (C=O) cm^{-1}	(C-N) cm^{-1}	(C-S) cm^{-1}	(C=N) cm^{-1}
3a	R′ = H, R = H	1558	1678	1461	1168	1582
3b	R′ = H, R = 2-OCH_3	1553	1674	1466	1171	1586
3c	R′ = H, R = 4-CH_3	1555	1676	1464	1173	1588
3d	R′ = 6-Br, R = 3-Cl	1563	1685	1462	1172	1576
3e	R′ = 6-Br, R = 2-F	1568	1684	1485	1187	1585
3f	R′ = 6-CH_3, R = 3-Cl	1561	1683	1463	1165	1576
3g	R′ = 6-CH_3, R = 2-Br	1554	1677	1454	1157	1570
3h	R′ = 6-OCH_3, R = H	1556	1675	1453	1162	1572

3i	R′ = 6-OCH_3, R = 2,4-dichloro	1564	1687	1471	1181	1584
3j	R′ = 4,6-dichloro, R = 2,4-dichloro	1568	1691	1477	1186	1587
3k	R′ = 4,6-dichloro, R = H	1565	1686	1474	1183	1583

The synthesis of *N*-[3-(benzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene] benzamides **(3a-k)** was confirmed by ^{1}H NMR due to the presence of a characteristic singlet for the ring protons in the range of δ 6.43-6.48 ppm and a singlet for methyl protons of thiazoline ring appeared at δ 2.22-2.31 ppm. In ^{13}C NMR spectrum the amidic carbonyl carbon signal observed at δ 165.3-166.2 ppm and (C=N) carbon signal appeared at δ 162.2-163.1 ppm.

The ^{1}H and ^{13}C NMR spectral data of *N*-[3-(benzo[d]thiazol-2-yl)-4-methylthiazol -2(3H)-ylidene] benzamides **(3a-k)** is presented in Table 5.12.

Table 5.12: ^{1}H and ^{13}C NMR spectral data of all the compounds (3a-k)

Sr. No.	Compounds	^{1}H NMR(δ) (ppm)	^{13}C NMR(δ) (ppm)
3a	R′ = H, R = H	8.12 (1H, d, *J* = 7.6 Hz, H-1), 8.06 (1H, d, *J* = 7.6 Hz, H-4), 7.61-7.94 (5H, m, Ar), 7.57 (1H, dd, *J* = 7.2,7.4 Hz, H-2), 7.34 (1H, dd, *J* = 7.1,7.4 Hz, H-3), 6.44 (1H, s, C=C-*H*), 2.23 (-CH_3)	165.3 (amide C=O), 162.4 (C=N), 160.5 (S-C=N), 151.3 (N-C=), 146.3 (C-9), 136.7 (C-1'), 134.5 (C-2',C-6'), 133.4 (C-3',C-5'), 128.2 (C-4'), 127.4 (C-6), 125.6 (C-5), 124.3 (C-8), 123.7 (C-4), 122.5 (C-7), 101.6 (=CH), 17.4 (-CH_3)
3c	R′ = H, R = 4-CH_3	8.11 (1H, d, *J* = 7.6 Hz, H-1), 8.05 (1H, d, *J* = 7.6 Hz, H-4), 7.84 (1H, d, *J* = 7.2 Hz, H-2',H-6'). 7.73 (1H, d, *J* = 7.2 Hz, H-3',H-5'), 7.66 (1H, dd, *J* = 7.2,7.4 Hz, H-2), 7.57 (1H, dd, *J* = 7.2,7.4 Hz, H-3), 6.43 (1H, s, C=C-*H*), 2.56 (3H, s, Ar-CH_3), 2.22 (3H, s, -CH_3)	165.4 (amide C=O), 162.6 (C=N), 156.6 (S-C=N), 151.3 (N-C=), 146.8 (C-9), 134.4 (C-1'), 132.7 (C-2',C-6'), 131.5 (C-3',C-5'), 127.4 (C-4'), 126.3 (C-6), 125.5 (C-5), 124.7 (C-8), 123.6 (C-4), 122.4 (C-7), 101.6 (=CH), 21.3 (Ar-CH_3), 17.8 (-CH_3)
3d	R′ = 6-Br, R = 3-Cl	8.26 (1H, d, *J* = 7.4 Hz, H-3), 8.14 (1H, d, *J* = 2.3 Hz, H-1), 7.83 (1H, d, *J* = 2.4 Hz, H-2'), 7.75 (1H, d, *J* = 7.4 Hz, H-2), 7.71 (1H, d, *J* = 7.2 Hz, H-6'),	166.2 (amide C=O), 162.5 (C=N), 156.4 (S-C=N), 152.3 (N-C=), 146.5 (C-9), 136.7 (C-1'), 135.6 (C-3'), 134.5 (C-4'), 130.6 (C-5'), 130.3 (C-2'),

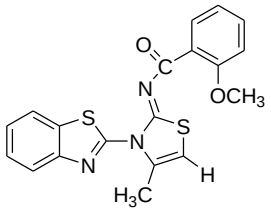
		7.54 (1H, dd, *J* = 7.2,2.2 Hz, H-4'), 7.42 (1H, d, *J* = 7.2,7.1 Hz, H-5'), 6.44 (1H, s, C=C-*H*), 2.26 (3H, s, -CH_3)	128.3 (C-6'), 128.5 (C-5), 126.7 (C-8), 124.5 (C-7), 124.2 (C-4), 117.4 (C-6), 101.6 (=CH), 18.4 (-CH_3)
3e	R′ = 6-Br, R = 2-F	8.17 (1H, d, *J* = 7.6 Hz, H-1), 8.11 (1H, d, *J* = 2.3 Hz, H-3), 7.81 (1H, d, *J* = 7.4 Hz, H-2), 7.73 (1H, d, *J* = 7.1 Hz, H-3'), 7.64 (1H, dd, *J* = 7.1,7.3 Hz, H-5'), 7.52 (1H, dd, *J* = 7.4,7.1 Hz, H-4'), 7.32 (1H, d, *J* = 7.4 Hz, H-6'), 6.46 (1H, s, C=C-*H*), 2.27 (3H, s, -CH_3)	165.8 (amide C=O), 162.7 (C=N), 156.7 (S-C=N), 151.6 (N-C=), 146.8 (C-9), 141.6 (C-2'), 137.3 (C-1'), 136.4 (C-6'), 134.6 (C-4'), 132.5 (C-5), 128.7 (C-5'), 127.5 (C-3'), 126.4 (C-8), 125.6 (C-4), 124.7 (C-7), 121.6 (C-6), 101.7 (=CH), 18.6 (-CH_3)
3f	R′ = 6-CH_3, R = 3-Cl	8.12 (1H, d, *J* = 7.4 Hz, H-1), 8.07 (1H, d, *J* = 2.3 Hz, H-3), 7.76 (1H, d, *J* = 7.4 Hz, H-2), 7.65 (1H, d, *J* = 7.2 Hz, H-6'), 7.56 (1H, d, *J* = 2.2 Hz, H-2'), 7.34 (1H, dd, *J* = 7.2,2.2 Hz, H-5'), 7.28 (1H, d, *J* = 7.2,7.1 Hz, H-4'), 6.45 (1H, s, C=C-*H*), 2.55 (3H, s, Ar-CH_3), 2.26 (3H, s, -CH_3)	165.7 (amide C=O), 162.6 (C=N), 156.5 (S-C=N), 151.7 (N-C=), 146.8 (C-9), 138.7 (C-1'), 137.6 (C-3'), 136.5 (C-6'), 135.4 (C-4'), 134.2 (C-6), 133.6 (C-5'), 128.3 (C-2'), 126.5 (C-5), 124.4 (C-8), 122.5 (C-4), 121.6 (C-7), 101.8 (=CH), 22.7 (Ar-CH_3), 18.5 (-CH_3)
3g	R′ = 6-CH_3, R = 2-Br	8.13 (1H, d, *J* = 7.6 Hz, H-1), 8.09 (1H, d, *J* = 2.4 Hz, H-3), 7.74 (1H, d, *J* = 7.6 Hz, H-2), 7.65 (1H, d, *J* = 7.1 Hz, H-6'), 7.52 (1H, dd, *J* = 7.1,7.2 Hz, H-5'), 7.43 (1H, dd, *J* = 7.4,7.1 Hz, H-4'), 7.23 (1H, d, *J* = 7.4 Hz, H-3'), 6.42 (1H, s, C=C-*H*), 2.57 (3H, s, Ar-CH_3), 2.25 (3H, s, -CH_3)	165.4 (amide C=O), 162.5 (C=N), 156.3 (S-C=N), 151.5 (N-C=), 146.4 (C-9), 138.3 (C-1'), 137.4 (C-6'), 136.5 (C-4'), 135.4 (C-3'), 134.6 (C-5'), 133.5 (C-6), 128.7 (C-2'), 127.5 (C-5), 125.4 (C-8), 123.6 (C-4), 122.7 (C-7), 101.6 (=CH), 22.4 (Ar-CH_3), 18.2 (-CH_3)
3h	R′ = 6-OCH_3, R = H	8.11 (1H, d, *J* = 7.6 Hz, H-1), 8.06 (1H, d, *J* = 2.4 Hz, H-3), 7.82 (1H, d, *J* = 7.6 Hz, H-2), 7.38-7.78 (5H, m, Ar), 6.43 (1H, s, C=C-*H*), 3.78 (3H, s, -OCH_3), 2.24 (3H, s, -CH_3)	165.3 (amide C=O), 162.4 (C=N), 156.5 (S-C=N), 151.3 (N-C=), 146.3 (C-9), 127.4 (C-6), 135.6 (C-1'), 134.3 (C-2',C-6'), 132.8 (C-3',C-5'), 128.5 (C-4'), 127.6 (C-8), 126.3 (C-4), 124.2 (C-5), 122.4 (C-7), 101.7 (=CH), 54.7 (-OCH_3), 17.6 (-CH_3)

3i	R′ = 6-OCH_3, R = 2,4-dichloro	8.16 (1H, d, *J* = 7.6 Hz, H-1), 8.08 (1H, d, *J* = 2.4 Hz, H-3), 7.84 (1H, d, *J* = 7.6 Hz, H-2), 7.73 (1H, d, *J* = 7.4 Hz, H-6'), 7.64 (1H, d, *J* = 2.4 Hz, H-3'), 7.48 (1H, d, *J* = 7.4 Hz, H-5'), 6.46 (1H, s, C=C-*H*), 3.83 (3H, s, -OCH_3), 2.27 (3H, s, -CH_3)	166.2 (amide C=O), 162.8 (C=N), 157.2 (S-C=N), 152.3 (N-C=), 147.5 (C-9), 138.6 (C-6), 137.5 (C-1'), 136.3 (C-2'), 134.7 (C-4'), 133.6 (C-'6), 132.5 (C-3'), 131.8 (C-5'), 128.4 (C-8), 126.4 (C-4), 124.6 (C-5), 121.8 (C-7), 102.6 (=CH), 54.6 (-OCH_3), 18.4 (-CH_3)
3j	R′ = 4,6-dichloro, R = 2,4-dichloro	8.24 (1H, d, *J* = 2.2 Hz, H-1), 8.17 (1H, d, *J* = 2.2 Hz, H-2), 7.96 (1H, d, *J* = 7.6 Hz, H-6'), 7.87 (1H, d, *J* = 2.3 Hz, H-3'), 7.78 (1H, d, *J* = 7.6 Hz, H-5'), 6.48 (1H, s, C=C-*H*), 2.31 (3H, s, -CH_3)	166.5 (amide C=O), 163.1 (C=N), 157.6 (S-C=N), 152.5 (N-C=), 147.7 (C-9), 138.4 (C-1'), 137.6 (C-2'), 136.5 (C-4'), 134.8 (C-6'), 133.4 (C-6), 132.3 (C-4), 131.8 (C-3'), 128.2 (C-5'), 125.1 (C-8), 124.6 (C-5), 123.7 (C-7), 102.8 (=CH), 18.7 (-CH_3)
3k	R′ = 4,6-dichloro, R = H	8.21 (1H, d, *J* = 2.3 Hz, H-1), 8.16 (1H, d, *J* = 2.3 Hz, H-2), 7.63-7.91 (5H, m, Ar), 6.47 (1H, s, C=C-*H*), 2.28 (3H, s, -CH_3)	166.1 (amide C=O), 162.6 (C=N), 157.4 (S-C=N), 152.3 (N-C=), 147.3 (C-9), 136.5 (C-1'), 134.7 (C-6), 133.8 (C-4), 132.6 (C-2',C-6'), 131.5 (C-3',C-5'), 127.4 (C-4'), 124.6 (C-8), 123.8 (C-5), 122.7 (C-7), 102.3 (=CH), 18.3 (-CH_3)

The ^{1}H NMR spectrum confirmed the formation of *N*-[3-(benzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene]-2-methoxybenzamide **(3b)** by the presence of a characteristic singlet for the ring proton at δ 6.45 ppm and a singlet for methyl protons of thiazoline ring appeared at δ 2.24 ppm. Methoxy protons give singlet at δ 3.76 ppm. In ^{13}C NMR spectrum the amidic carbonyl carbon signal observed at δ 165.5 and (C=N) carbon signal appeared at δ 162.7 ppm. The methyl and methoxy carbon signals appeared at δ 17.8 and δ 54.3 ppm, respectively.

The ^{1}H and ^{13}C NMR data of *N*-[3-(Benzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene]-2-methoxybenzamide **(3b)** is presented in Table 5.14.

Table 5.14: ^{1}H and ^{13}C NMR data of *N*-[3-(Benzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene]-2-methoxybenzamide (3b)



Carbons	δ (ppm) and multiplicity	
	^{1}H NMR	^{13}C NMR
(amidic C=O)	-	165.5
(C=N)	-	162.7
(S-C=N)	-	160.7
(N-C=)	-	151.6
(C=C-H)	6.45, (s)	101.5
C-4	8.14, (d), *J* = 7.6 Hz	124.6
C-5	7.84, (dd), *J* = 7.4,7.6 Hz	126.3
C-6	7.76, (dd), *J* = 7.6,7.4 Hz	127.4
C-7	8.08, (d), *J* = 7.6 Hz	123.4
C-8	-	125.7
C-9	-	146.4
C-1'	-	137.5
C-2'	-	136.4
C-3'	7.38, (d), *J* = 7.3 Hz	134.6
C-4'	7.47, (dd), *J* = 7.3, 7.2 Hz	128.6
C-5'	7.61, (dd), *J* = 7.1, 7.2 Hz	133.2
C-6'	7.91, (d), *J* = 7.1 Hz	135.7
-OCH_3	3.76, (s)	54.3
-CH_3	2.24, (s)	17.8

The structure of *N*-[3-(benzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene]-2-methoxybenzamide **(3b)** was also confirmed by mass spectrometry. The molecular ion peak appeared at *m/z* 381 with 67 % abundance and a base peak observed at *m/z* 140.

The elemental analysis of *N*-[3-(benzo[d]thiazol-2-yl)-4-methylthiazol-2(3H) ylidene]benzamides **(3a-k)** is presented in Table 5.15.

Table 5.15: Elemental analysis of all the compounds (3a-k).

Compounds (R, R')	Formulae	Elemental Analysis							
		% Calculated				% Found			
		C	H	N	S	C	H	N	S
R′ = H, R = H	$C_{18}H_{13}N_3OS_2$	61.53	3.70	11.96	18.23	61.47	3.51	11.83	18.14
R′ = H, R = 2-OCH_3	$C_{19}H_{15}N_3O_2S_2$	59.84	3.94	11.02	16.78	59.77	3.82	10.93	16.67
R′ = H, R = 4-CH_3	$C_{19}H_{15}N_3OS_2$	62.47	4.11	11.51	17.53	62.34	3.97	11.38	17.43
R′ = 6-Br, R = 3-Cl	$C_{18}H_{11}N_3OS_2BrCl$	46.50	2.37	9.04	13.78	46.34	2.21	8.87	13.64
R′ = 6-Br, R = 2-F	$C_{18}H_{11}N_3OS_2BrF$	48.21	2.46	9.37	14.28	48.13	2.35	9.23	14.17
R′ = 6-CH_3, R = 3-Cl	$C_{19}H_{14}N_3OS_2Cl$	57.07	3.50	10.51	16.02	56.96	3.31	10.43	15.84
R′ = 6-CH_3, R = 2-Br	$C_{19}H_{14}N_3OS_2Br$	51.35	3.15	9.46	14.41	51.24	3.09	9.23	14.27
R′ = 6-OCH_3, R = H	$C_{19}H_{15}N_3O_2S_2$	59.84	3.94	11.02	16.78	59.75	3.81	10.93	16.64
R′ = 6-OCH_3, R = 2,4-dichloro	$C_{19}H_{13}N_3O_2S_2Cl_2$	50.67	2.88	9.33	14.22	50.44	2.73	9.18	14.13
R′ = 4,6-dichloro, R = 2,4-dichloro	$C_{18}H_9N_3OS_2Cl_4$	44.17	1.84	8.58	13.08	44.09	1.61	8.43	13.01
R′ = 4,6-dichloro, R = H	$C_{18}H_{11}N_3OS_2Cl_2$	51.42	2.62	10.01	15.24	51.37	2.43	9.92	15.14

Chapter–3

EXPERIMENTAL

3.1.1 Purification of Solvents

All the necessary purification and drying of solvents were carried out according to standard procedures. The dried solvents were stored over molecular sieves (4Å).

3.1.2 Instrumentation

Melting points were determined on a digital Gallenkamp (SANYO) melting point apparatus model (MP-D) BM 3.5 and are uncorrected. FTIR spectra were recorded on a Bio-Rad-Excalibur Series Model No.FTS 3000 MX spectrophotometer.

^{1}H NMR and ^{13}C NMR spectra were recorded using $CDCl_3$ solutions at 300 MHz on a Bruker AM-300 spectrophotometer. Mass spectra were recorded using an EI source of (70 eV) on a GC-MS instrument Agilent technologies 6890N and elemental analyses were determined by a LECO-183 (CHNS) analyzer Agilent Technologies.

3.1.3 Chromatographic Techniques

i) Thin Layer Chromatography (TLC)

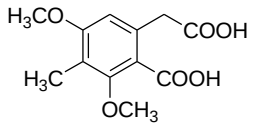
The progress of reactions was monitored through thin layer chromatography by using pre-coated silica gel aluminium plates (layer thickness 0.2 mm, HF_{254}, Reidal-de-Haen from Merck).

ii) Preparative Thin Layer Chromatography (PTLC)

Glass plates (20 x 20 cm) were coated with silica gel (HF-254, Fluka) of 0.5 mm layer thickness and precoated silica gel glass plates (0.25 mm, Aldrich) were also used for the purification of targeted compounds.

Synthesis of Compounds

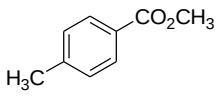
3.1.4 Synthesis of 3,5-Dimethoxy-4-methylhomophthalic acid (12)



Methyl 4-methyl benzoate (1)

To the stirred solution of *p*-toluic acid (25.1 g, 184 mmol) in dry methanol (100 mL), conc. H_2SO_4 (4-5 mL) was added drop wise. The reaction mixture was refluxed for 7-8 hr. After the completion of reaction, mixture was concentrated to 55 mL and

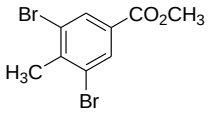
extracted with ethyl acetate (3x50 mL). The extract was washed with saturated brine, dried and concentrated followed by vacuum distillation and crystallized from methanol to afford methyl 4-methylbenzoate **(1)**.



Yield = 84 %; Rf = 0.7; M.P. = 34-35 ^{o}C; IR (KBr) ν_{max}: 3014 (C=C-H), 1732 (ester C=O), 1588 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.83 (2H, d, *J* = 7.2 Hz, H-2, H-6), 7.41 (2H, d, *J* = 7.2 Hz, H-3, H-5), 3.76 (3H, s, -OCH_3), 2.43 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 166.7 (ester C=O), 136.4 (C-1), 134.2 (C-2,C-6), 130.8 (C-3,C-5), 127.6 (C-4), 28.7 (-CH_3), 54.6 (-OCH_3); Anal. Calcd for $C_9H_{10}O_2$: C, 72.12; H, 6.75. Found: C, 71.94; H, 6.56.

Methyl-3,5-dibromo-4-methyl benzoate (2)

Anhydrous $AlCl_3$ (36.6 g, 273 mmol) was added portion wise to the stirred solution of methyl 4-methyl benzoate **(1)** (18.3 g, 102 mmol), which was cooled to 0 °C. Bromine (17.5 mL) was added drop wise over 45 min interval at such a rate to keep the temperature constant or below 20 °C. Stirring was continued at room temperature for 30 min and then for additional 1 hr at 80-85 °C. The mixture was cooled to 30 °C, treated with methanol (75 mL) during 30 min and then stirred overnight. The crude product was collected by filtration, washed with cooled (10 °C) methanol and recrystallized from methanol to afford methyl 3,5-dibromo-4-methyl benzoate **(2)** as colorless crystals.

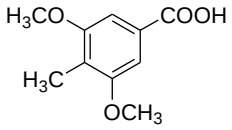


Yield = 63 %; Rf = 0.6; M.P. = 83-84 ^{o}C; IR (KBr) ν_{max}: 3025 (C=C-H), 1719 (ester C=O), 1583 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.86 (2H, s, H-2, H-6), 3.78 (3H, s, -OCH_3), 2.46 (3H, s, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 167.3 (ester C=O), 138.2 (C-1), 136.8 (C-3,C-5), 132.7 (C-2-C-6), 128.6 (C-4), 29.2 (-CH_3), 56.7 (-OCH_3); Anal. Calcd for $C_9H_{10}BrO_2$: C, 35.12; H, 2.64. Found: C, 35.04; H, 2.57.

3,5-Dimethoxy-4-methylbenzoic acid (3)

A pyridine solution of methyl 3,5-dibromo-4-methylbenzoate **(2)** (4.63 g, 16 mmol) was added to a solution of sodium methoxide (2.11 g, 100 mmol) in dry methanol and freshly prepared anhydrous copper (I) chloride (0.211 g, 1.2 mmol). The reaction mixture was refluxed under N_2 for 15 hr, then cooled to room temperature and filtered. The filtered cake was washed with warm methanol. The solution was refluxed for 1 additional hr, cooled to room temperature and diluted it with saturated brine (35 mL). The mixture was extracted with ethyl acetate (35 mL), the extract discarded and the

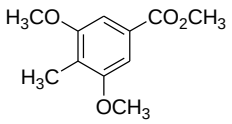
aqueous phase was acidified with cold conc. HCl (10 mL) and then again it was extracted with ethyl acetate (2x30 mL). The extract was washed with saturated brine, dried and evaporated. Rerystallization of residue from aqueous methanol (1:2) yielded methyl 3,5-dimethoxy-4-methyl benzoic acid **(3)**.



Yield = 87 %; Rf = 0.4; M.P. = 211-212 ^{o}C; IR (KBr) ν_{max}: 3216 (O-H), 3027 (C=C-H), 1711 (C=O), 1586 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 9.31 (1H, s, -COOH), 7.82 (2H, s, H-2,H-6), 3.86 (6H, s, -OCH_3), 2.54 (3H, s, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.3 (carboxylic C=O), 138.4 (C-1), 137.6 (C-2,C-5), 128.5 (C-2,C-6), 116.7 (C-4), 56.5 (-OCH_3), 28.7 (-CH_3); Anal.Calcd for $C_{10}H_{12}O_4$: C, 61.21; H, 6.12. Found: C, 61.17; H, 6.03.

Methyl-3,5-dimethoxy-4-methyl benzoate (4)

3,5-Dimethoxy-4-methyl benzoic acid **(3)** (5 g, 25 mmol) was dissolved in dry methanol (25 mL) and then few drops of conc. sulphuric acid (2-3 mL) were added. The mixture was refluxed for 12-13 hr. After completion, the mixture reaction was concentrated and then extracted with ethyl acetate (3x15 mL). The extract was washed with saturated brine, dried and evaporated. Recrystallization of crude product from ethanol afford methyl 3,5-dimethoxy-4-methyl benzoate **(4)** as colorless crystals.

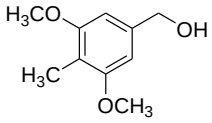


Yield = 85 %; Rf = 0.6; M.P. = 77-78 ^{o}C; IR (KBr) ν_{max}: 3021 (C=C-H), 1728 (ester C=O), 1578 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.72 (2H, s, H-2, H-6), 2.24 (3H, s, -CH_3), 3.62 (6H, s, -OCH_3), 3.78 (3H, s, ester -OCH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 167.4 (ester C=O), 137.4 (C-3,C-5), 134.3 (C-1), 127.6 (C-2,C-6), 117.5 (C-4), 58.3 (ester OCH_3), 62.6 (Ar-OCH_3), 29.1 (-CH_3); Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.83; H, 6.72. Found: C, 62.75; H, 6.67.

3,5-Dimethoxy-4-methylbenzyl alcohol (5)

Methyl 3,5-dimethoxy-4-methyl benzoate **(4)** (4.1 g, 20 mmol) and sodium borohydride (4.4 g, 120 mmol) were suspended in freshly distilled THF (145 mL). The reaction mixture was stirred for 15 min at 65 °C and then methanol (145 mL) was added drop wise during 30 min. The mixture was refluxed for 4 hr, then cooled to room temperature and treated with saturated ammonium chloride solution (140 mL). Stirring was continued for 1 hr, acidified with dilute hydrochloric acid and extracted with ethyl acetate (3x25 mL). The extract was dried, evaporated and product was recryatallized

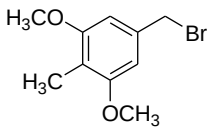
with petroleum ether to afford prism like crystals of 3,5-dimethoxy-4-methylbenzyl alcohol **(5)**.



Yield = 81 %; Rf = 0.5; M.P. = 45-46 ^{o}C; IR (KBr) ν_{max}: 3362 (O-H), 3024 (C=C-H), 1574 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.56 (2H, s, H-2,H-6), 4.47 (1H, bs, -OH), 3.74 (6H, s, -OCH_3), 2.57 (1H, s, Ar-CH_2), 2.34 (3H, s, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 138.7 (C-3,C-5), 137.3 (C-2,C-6), 128.6 (C-4), 118.5 (C-1), 63.3 (-OCH_3), 42.7 (-CH_2), 29.3 (-CH_3); Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.93; H, 7.72. Found: C, 65.86; H, 7.64.

3,5-Dimethoxy-4-methylbenzyl bromide (6)

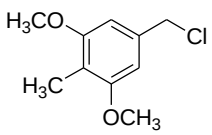
3,5-Dimethoxy-4-methylbenzyl alcohol **(5)** (10 g, 54 mmol) was dissolved in dry benzene (45-50 mL), the solution was treated with PBr_3 (14.88 g, 5.1 mL, 54 mmol) and the reaction mixture was stirred for 4 hr. The reaction mixture was then poured into ice cold water, the organic layer was separated and evaporated to afford crude 3,5-dimethoxy-4-methylbenzyl bromide **(6)**. Prisms like crystals were obtained after recrystallization with petroleum ether.



Yield = 86 %; Rf = 0.6; M.P. = 68-70 ^{o}C; IR (KBr) ν_{max}: 3018 (C=C-H), 1575 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.35 (2H, s, H-2, H-6), 3.81 (6H, s, -OCH_3), 2.87 (2H, s, Ar-CH_2), 2.54 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 138.5 (C-3,C-5), 136.4 (C-2, C-6), 128.3 (C-4), 118.3 (C-1), 62.4 (-OCH_3), 42.4 (-CH_2), 28.6 (Ar-CH_3); Anal. Calcd for $C_{10}H_{13}BrO_2$: C, 49.01; H, 5.34. Found: C, 48.96; H, 5.28.

3,5-Dimethoxy-4-methylbenzyl chloride (6a)

3,5-Dimethoxy-4-methylbenzyl alcohol **(5)** (1.5 g, 8.2 mmol) was dissolved in dry methanol (30-40 mL), the solution was treated with thionyl chloride (1.47 g, 1.1 mL, 12 mmol) and the reaction mixture was refluxed for 3 hr. The reaction mixture was poured into ice cold water, separated the organic layer and evaporated to afford crude 3,5-dimethoxy-4-methylbenzyl chloride **(6a)**, which was recrystallized in petroleum ether.

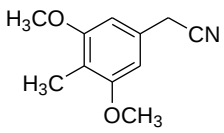


Yield = 77 %; Rf = 0.7; oil; IR (KBr) ν_{max}: 3044 (C=C-H), 1621 (C-Cl), 1586 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.51 (2H, s, H-2, H-6), 3.78 (6H, s, -OCH_3), 2.83 (2H, s, Ar-CH_2), 2.52 (3H, s, Ar-CH_3);

^{13}C NMR ($CDCl_3$, δ ppm): 137.7 (C-3,C-5), 134.6 (C-2,C-6), 127.5 (C-4), 117.4 (C-1), 62.5 (-OCH_3), 41.7 (-CH_2), 28.4 (Ar-CH_3); Anal. Calcd for $C_{10}H_{13}ClO_2$: C, 59.85; H, 6.53. Found: C, 59.77; H, 6.46.

3,5-Dimethoxy-4-methylbenzyl cyanide (7)

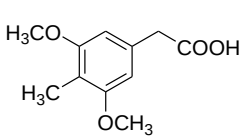
3,5-Dimethoxy-4-methylbenzyl bromide **(6)** (7.4 g, 33 mmol) was dissolved in a mixture of ethanol (150 mL) and water (150 mL). Potassium cyanide (2.8 g, 50 mmol) was then added to the reaction flask and resulting mixture was reflux for 2 hr. Reaction mixture was poured into ice cold water and extracted with ethyl acetate (3x25 mL). The extract was dried over anhydrous Na_2SO_4, evaporated to afford the 3,5-dimethoxy-4-methylbenzyl cyanide **(7)** and it was recryatallized with petroleum ether to get prism like crystals.



Yield = 83 %; Rf = 0.5; M.P. = 48-50 ^{o}C; IR (KBr) ν_{max}: 3015 (C=C-H), 2267 (C≡N), 1577 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.43 (2H, s, H-2, H-6), 3.78 (6H, s, -OCH_3), 2.86 (2H, s, Ar-CH_2), 2.56 (3H, s, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 138.4 (C-3,C-5), 134.6 (C-2,C-6), 128.5 (-CN), 126.3 (C-4), 116.8 (C-1), 63.5 (-OCH_3), 41.3 (-CH_2), 29.4 (Ar-CH_3); Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.10; H, 6.84; N, 7.32. Found: C, 68.87; H, 7.01, N, 7.26.

3,5-Dimethoxy-4-methylphenyl acetic acid (8)

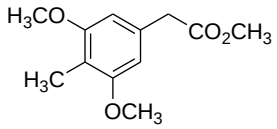
3,5-Dimethoxy-4-methylbenzyl cyanide **(7)** (2.5 g, 10.4 mmol) was dissolved in a mixture of water (7.5 mL), dioxane (10 mL) and methanol (10 mL). KOH (6.8 g in 5 mL H_2O) was added and the mixture was refluxed for 48 hr. After the completion of reaction, the mixture was poured into ice cold water and then extracted with ethyl acetate (10 mL). The extract was discarded and aqueous layer was acidified with dilute HCl. Precipitates were filtered out and recrystallized in ethanol to afford 3,5-dimethoxy-4-methyl phenyl acetic acid **(8)**.



Yield = 73 %; Rf = 0.4; M.P. = 129-131 ^{o}C; IR (KBr) ν_{max}: 3234 (O-H), 3010 (C=C-H), 1706 (carboxylic C=O), 1573 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 10.41 (1H, s, COOH); 7.64 (2H, s, H-2, H-6), 3.77 (6H, s, -OCH_3), 3.58 (2H, s, Ar-CH_2), 2.52 (3H, s, -CH_3); ^{13}C NMR ($CDCl_3$ δ ppm): 167.6 (carboxylic C=O), 136.4 (C-3,C-5), 134.3 (C-2,C-6), 126.4 (C-4), 116.2 (C-1), 63.6 (ester -OCH_3), 56.7 (Ar-OCH_3), 43.2 (-CH_2), 30.4 (Ar-CH_3); Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.86; H, 6.64. Found: C, 62.78; H, 6.57.

Methyl 3,5-dimethoxy-4-methylphenyl acetate (9)

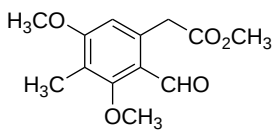
3,5-Dimethoxy-4-methylphenyl acetic acid **(8)** (2.3 g, 11 mmol) in dry methanol (25 mL) was treated with conc. H_2SO_4 (1 mL) drop wise and the mixture was refluxed for 7-8 hr. After completion, the reaction mixture was concentrated to 55 mL and extracted with ethyl acetate (2x50 mL). The extract was washed with saturated brine, dried and concentrated. The crude oil was vacuum distilled to afford methyl 3,5-dimethoxy-4-methylphenyl acetate **(9)**.



Yield = 82 %; Rf = 0.68; M.P. = 38-39 °C; IR (KBr) ν_{max}: 3022 (C=C-H), 1731 (ester C=O), 1582 (C=C), 1133 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.34 (2H, s, H-2,H-6), 3.87 (6H, s, -OCH_3), 3.56 (3H, s, -$COOCH_3$), 2.71 (2H, s, Ar-CH_2), 2.42 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$ δ ppm): 168.5 (ester C=O), 131.5 (C-3,C-5), 127.7 (C-2,C-6), 118.4 (C-4), 113.2 (C-1), 67.6 (ester -OCH_3), 56.4 (Ar-OCH_3), 42.6 (-CH_2), 29.4 (Ar-CH_3); MS (70eV): *m/z* (%); 224 $[M]^{+\cdot}$ (42), 193 (37), 165 (100%), 59 (21); Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.26; H, 7.17. Found: C, 64.21; H, 7.11.

Methyl 2-(2-formyl-3,5-dimethoxy-4-methylphenyl) acetate (10)

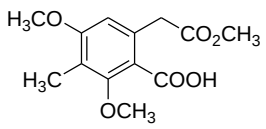
Phosphorous oxychloride (1.62 g, 10.5 mmol) was added dropwise to a stirred solution of methyl 3,5-dimethoxy-4-methylphenyl acetate **(9)** (2.0 g, 9 mmol) in dry DMF (15 mL) at 55 °C. Reaction mixture was heated at about 100 °C for 2 hr and stirred it overnight at room temperature. Then the reaction mixture was poured into aqueous solution of sodium acetate (10 %, 10 mL) and shake vigorously. Methyl 2-(2-formyl-3,5-dimethoxy-4-methylphenyl) acetate **(10)** was precipitated out as yellowish precipitates, which was then recrystallized with ethanol.



Yield = 85 %; Rf = 0.56; M.P. = 51-52 ^oC; IR (KBr) ν_{max}: 3032 (C=C-H), 1725 (ester C=O), 1685 (aldehyde C=O), 1568 (C=C), 1033 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 9.84 (1H, s, -CHO), 7.97 (1H, s, H-6), 3.62 (3H, s, -OCH_3), 3.54 (3H, s, -OCH_3), 3.24 (3H, s, ester OCH_3), 2.84 (2H, s, Ar-CH_2), 2.63 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 178.6 (aldehyde C=O), 163.2 (ester C=O), 137.5 (C-3), 136.7 (C-5), 132.6 (C-2), 127.4 (C-6), 121.3 (C-4), 118.2 (C-1), 62.7 (ester -OCH_3), 58.4 (Ar-OCH_3), 41.2 (Ar-CH_2), 31.5 (Ar-CH_3); MS (70 eV): *m/z* (%); 252 $[M]^{+\cdot}$ (27), 251 (61), 224 (43), 223 (31), 165 (100 %), 29 (25); Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.91; H, 6.37. Found: C, 61.84; H, 6.28.

Methyl 2-(2-carboxy-3,5-dimethoxy-4-methylphenyl) acetate (11)

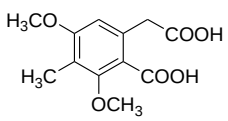
Methyl 2-(2-formyl-3,5-dimethoxy-4-methylphenyl) acetate **(10)** (1.6 g, 6 mmol) and sulfamic acid (1.6 g, 0.21 mmol) in 20 mL H_2O:THF:DMSO (20:10:1) were treated at 0 °C with $NaClO_2$ (1.4 g, 0.16 mmol) in 20 mL H_2O. The reaction mixture was stirred for 20 min at 0 °C and then diluted with ethyl acetate (100 mL), washed with saturated aqueous ammonium chloride (2x130 mL) saturated aqueous sodium chloride (130 mL). Organic layer was dried over anhydrous sodium sulfate, evaporated and recrystallized in petroleum ether to afford methyl 2-(2-carboxy-3,5-dimethoxy-4-methylphenyl) acetate **(11)**.



Yield = 78 %; Rf = 0.3; M.P. = 164-165 ^oC; IR (KBr) ν_{max}: 3273 (O-H), 3042 (C=C-H), 1733 (ester C=O), 1717 (carboxylic C=O), 1581 (C=C), 1043 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 10.13 (1H, s, -COOH), 7.74 (1H, s, H-6), 3.83 (3H, s, $-OCH_3$), 3.77 (3H, s, $-OCH_3$), 3.65 (3H, s, ester OCH_3), 2.62 (2H, s, Ar-CH_2), 2.34 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 197.5 (carboxylic C=O), 167.6 (ester C=O), 138.2 (C-3), 137.6 (C-5), 134.7 (C-2), 127.2 (C-6), 121.6 (C-4), 115.7 (C-1), 64.4 (ester $-OCH_3$), 56.5 (Ar-OCH_3), 41.3 (Ar-CH_2), 29.4 (Ar-CH_3); MS (70 eV): *m/z* (%); 268 $[M]^{+\cdot}$ (28), 251 (48), 224 (57), 165 (100 %), 45 (21); Anal. Calcd for $C_{13}H_{16}O_6$: C, 58.21; H, 5.97. Found: C, 58.18; H, 5.86.

3,5-Dimethoxy-4-methylhomophthalic acid (12)

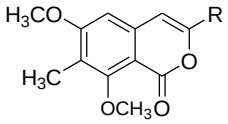
Methyl 2-(2-carboxy-3,5-dimethoxy-4-methylphenyl) acetate **(11)** (1.4 g, 5.23 mmol) was dissolved in ethanol (12 mL) and treated with KOH (5 %, 21 mL). The reaction mixture was refluxed for 1 hr and then ethanol was evaporated. The aqueous layer was acidified with dilute hydrochloric acid to afford crude 6-(carboxymethyl)-2,4-dimethoxy-3-methylbenzoic acid **(12)**, it was then recrystallized with ethyl acetate.



Yield = 85 %; Rf = 0.25; M.P. = 152-153 ^oC, (lit. M.P. = 151-153); IR (KBr) ν_{max}: 3213 (O-H), 3027 (C=C-H), 1727 (carboxylic C=O), 1718 (carboxylic CH_2-C=O), 1587 (C=C), 1045 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 10.94 (1H, s, -COOH), 10.76 (1H, s, -CH_2-COOH), 7.64 (1H, s, H-6), 3.73 (3H, s, $-OCH_3$), 3.67 (3H, s, $-OCH_3$), 2.56 (2H, s, -CH_2), 2.37 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 204.6 (carboxylic C=O), 171.4 (carboxylic CH_2-C=O), 136.3 (C-3), 135.5 (C-5), 134.7 (C-2), 133.4 (C-6), 126.2 (C-4), 123.6 (C-1), 56.5 ($-OCH_3$), 56.1 ($-OCH_3$), 42.5 (Ar-CH_2), 28.6 (Ar-CH_3); MS (70 eV): *m/z* (%); 254 $[M]^{+\cdot}$ (43), 237

(54), 210 (31), 165 (100 %); Anal. Calcd for $C_{12}H_{14}O_6$: C, 56.68; H, 5.51. Found: C, 56.61; H, 5.47.

3.1.5 Synthesis of 6,8-Dimethoxy-7-methyl-3-aryl/alkyl-1H-isochromen-1-ones (5a-j)

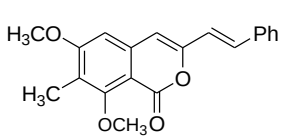


General Procedure

A mixture of aromatic/aliphatic carboxylic acids (1 mmol) and thionyl chloride (1.2 mmol) was refluxed for 1-2 hr in the presence of a drop of DMF. Excess of the thionyl chloride was rotary evaporated to afford corresponding acid chlorides **(a-j)**.

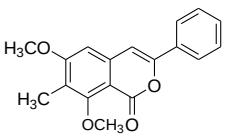
3,5-Dimethoxy-4-methylhomophthalic acid **(12)** (2.0 mmol) and aryl/alkyl acid chlorides (3.1 mmol) were heated under reflux at an internal temperature of 200 °C for 3-4 hr. After completion, the reaction mixture was allowed to cool, was concentrated and then extracted with ethyl acetate. The two phases were separated, and the organic layer was washed with saturated sodium chloride solution and then dried over anhydrous (Na_2SO_4). Isochromen-1-ones **(5a-j)** were then purified by preparative thin layer chromatography using (petroleum ether and ethyl acetate, (7:3) as eluent.

6,8-Dimethoxy-7-methyl-3-styryl-1H-isochromen-1-one (5a)



Yield = 71 %; Rf = 0.65; M.P. = 123-124^o C; IR (KBr) ν_{max}: 3026 (C=C-H), 2914 (C-H), 1723 (C=O), 1567 (C=C) cm^1; ^{1}H NMR ($CDCl_3$, δ ppm): 7.21-7.76 (5H, m, Ar), 6.82 (1H, d, *J* = 7.2 Hz, Ha), 6.63 (1H, d, *J* = 7.2 Hz, Hb), 6.57 (1H, s, H-5), 6.43 (1H, s, H-4), 3.86 (3H, s, -OCH_3), 3.83 (3H, s, -OCH_3), 2.63 (1H, s, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.4 (C=O), 150.5 (C-3), 142.7 (C-6), 141.5 (C-8), 138.6 (C-10), 137.7 (C-1'), 135.4 (C-1a), 134.8 (C-1b), 127.8 (C-9), 127.4 (C-2',C-6'), 126.7 (C-3',C-5'), 123.3 (C-4'), 118.5 (C-7), 109.3 (C-4), 104.6 (C-5), 56.4 (-OCH_3), 56.2 (-OCH_3), 28.6 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 322 (24), 245 (32), 192 (100 %), 132 (53), 103 (41), 77 (13); Anal. Calcd. for $C_{20}H_{18}O_4$: C, 74.53; H, 5.59. Found: C, 74.41; H, 5.26.

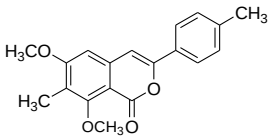
6,8-Dimethoxy-7-methyl-3-phenyl-1H-isochromen-1-one (5b)



Yield = 86 %; Rf = 0.6; M.P. = 108-110 ^{o}C; IR (KBr) ν_{max}: 3033 (C=C-H), 2936 (C-H), 1716 (C=O), 1571 (C=C) cm^{-1}; ^{1}H NMR

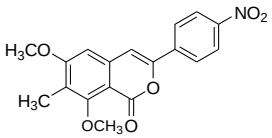
($CDCl_3$, δ ppm): 7.91-8.13 (5H, m, Ph), 7.86 (1H, s, H-5), 6.52 (1H, s, H-4), 3.76 (3H, s, -OCH_3), 3.73 (3H, s, -OCH_3), 2.61 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 171.5 (C=O), 142.6 (C-3), 140.6 (C-6), 140.2 (C-8), 134.3 (C-10), 132.4 (C-9), 130.2 (C-1'), 127.8 (C-3',C-5'), 126.5 (C-4'), 124.7 (C-2',C-6'), 118.6 (C-7), 113.3 (C-4), 108.5 (C-5), 62.6 (-OCH_3), 62.4 (-OCH_3), 28.6 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 296 (54), 191 (100 %), 105 (61), 77 (45); Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.97; H, 5.41. Found: C, 72.73; H, 5.25.

6,8-Dimethoxy-7-methyl-3-(4-methylphenyl)-1H-isochromen-1-one (5c)



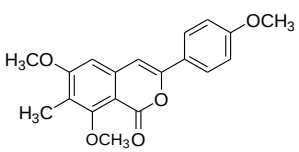
Yield = 80 %; Rf = 0.55; oil; IR (KBr) ν_{max}: 3032 (C=C-H), 2943 (C-H), 1717 (C=O), 1571 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.64 (2H, d, *J* = 7.2 Hz, H-2',6'), 7.58 (2H, d, *J* = 7.2 Hz, H-3',H-5'), 7.41 (1H, s, H-5), 6.64 (1H, s, H-4), 3.71 (3H, s, -OCH_3), 3.68 (3H, s, -OCH_3), 2.48 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 164.7 (C=O), 143.4 (C-6), 142.6 (C-8), 140.3 (C-3), 134.7 (C-10), 134.1 (C-9), 133.4 (C-4'), 128.5 (C-3',C-5'), 127.3 (C-1'), 126.2 (C-2',C-6'), 114.8 (C-7), 110.4 (C-4), 104.3 (C-5), 62.7 (-OCH_3), 62.4 (-OCH_3), 27.6 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 310 (48), 219 (16), 191 (100 %), 179 (37), 105 (52), 77 (17); Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.54; H, 5.81. Found: C, 73.47; H, 5.53.

6,8-Dimethoxy-7-methyl-3-(4-nitrophenyl)-1H-isochromen-1-one (5d)



Yield = 78 %; Rf = 0.5; M.P.= 224-226 ^{o}C; IR (KBr) ν_{max}: 3035 (C=C-H), 2946 (C-H), 1726 (C=O), 1583 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.83 (2H, d, *J* = 6.7 Hz, H-2',H-6'), 7.78 (2H, d, *J* = 6.7 Hz, H-3',H-5'), 7.67 (1H, s, H-5), 6.73 (1H, s, H-4), 3.81 (3H, s, -OCH_3), 3.78 (3H, s, -OCH_3), 2.71 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 162.4 (C=O), 146.3 (C-4'), 143.6 (C-3), 141.4 (C-6), 141.1 (C-8), 136.8 (C-1'), 134.7 (C-10), 133.6 (C-9), 128.7 (C-3',C-5'), 126.5 (C-2',C-6'), 118.4 (C-7), 114.6 (C-4), 107.8 (C-5), 64.7 (-OCH_3), 64.4 (-OCH_3), 28.7 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 341 (64), 313 (23), 297 (30) 191 (100 %), 165 (58), 137 (44); Anal. Calcd for $C_{18}H_{15}NO_6$: C, 63.34; H, 4.42; N, 4.11. Found: C, 63.20; H, 4.25; N, 3.96.

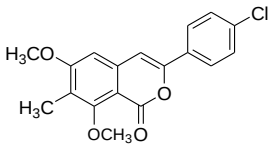
3-(4-Methoxyphenyl)-6,8-dimethoxy-7-methyl-1H-isochromen-1-one (5e)



Yield = 82 %; Rf = 0.55; M.P.= 153-155 ^{o}C; IR (KBr) ν_{max}: 3037 (C=C-H), 1724 (C=O), 1574 (C=C) cm^{-1};^{1}H NMR ($CDCl_3$, δ ppm): 7.97 (1H, d, *J* = 7.6, Hz, H-3',H-5'), 7.76 (1H, s, H-5), 7.36 (1H, d, *J* = 7.8 Hz, H-2',H-6'), 6.85 (1H, s, H-4), 3.87 (3H, s, -OCH_3), 3.82 (3H, s, -

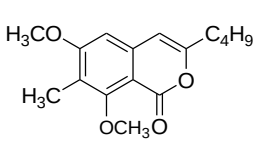
OCH_3), 3.67 (3H, s, 4'-OCH_3), 2.73 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 164.2 (C=O), 142.5 (C-3), 138.7 (C-6), 137.3 (C-8), 136.5 (C-4'), 135.6 (C-10), 133.4 (C-9), 130.6 (C-1'), 127.4 (C-3',C-5'), 124.6 (C-2',C-6'), 122.5 (C-7), 119.2 (C-4), 112.3 (C-5), 56.6 (-OCH_3), 55.3 (-OCH_3), 53.7 (4'-OCH_3), 28.2 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 326 (51), 219 (43), 191 (100 %), 135 (58), 107 (36), 77 (21) ; Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.94; H, 5.52. Found: C, 69.67; H, 5.33.

3-(4-Chlorophenyl)-6,8-dimethoxy-7-methyl-1H-isochromen-1-one (5f)



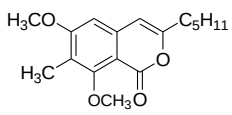
Yield = 78 %; Rf = 0.7; oil; IR (KBr) ν_{max}: 3029 (C=C-H), 2934 (C-H), 1721 (C=O), 1575 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.76 (2H, d, *J* = 7.1 Hz, H-2',6'), 7.71 (2H, d, *J* = 7.1 Hz, H-3',H-5'), 7.68 (1H, s, H-5), 6.72 (1H, s, H-4), 3.74 (6H, s, -OCH_3), 2.57 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 163.8 (C=O), 141.3 (C-3), 137.5 (C-6), 137.2 (C-8), 135.3 (C-10), 134.4 (C-9), 133.6 (C-4'), 129.7 (C-3',C-5'), 128.6 (C-1'), 127.5 (C-2',C-6'), 117.6 (C-7), 112.2 (C-4), 106.3 (C-5), 64.5 (-OCH_3), 28.7 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 330.5 (48), 332.5 [$(M+2)^{+\cdot}$] (31), 191 (100 %), 139.5 (68), 111.5 (37), 77 (17); Anal. Calcd for $C_{18}H_{15}ClO_4$: C, 64.96; H, 4.51. Found: C, 65.07; H, 4.23.

6,8-Dimethoxy-7-methyl-3-butyl-1H-isochromen-1-one (5g)



Yield = 70 %; Rf = 0.6; oil; IR (KBr) ν_{max}: 3038 (C=C-H), 2973 (C-H), 1718 (C=O), 1587 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.73 (1H, s, H-5), 6.81 (1H, s, H-4), 3.75 (3H, s, -OCH_3), 3.71 (3H, s, -OCH_3), 2.67 (3H, s, Ar-CH_3), 2.48 (2H, t, *J* = 3.8 Hz, H-1'), 1.33-1.38 (2H, m, H-2',H-3'), 0.94 (2H, t, *J* = 7.4 Hz, H-4'); ^{13}C NMR ($CDCl_3$, δ ppm): 164.3 (C=O), 150.6 (C-3), 146.1 (C-6), 145.4 (C-8), 134.6 (C-10), 127.3 (C-9), 117.8 (C-7), 109.4 (C-4), 103.7 (C-5), 54.6 (-OCH_3), 54.2 (-OCH_3), 34.3 (C-1'), 28.7 (Ar-CH_3), 25.5 (C-2'), 23.2 (C-3'), 14.6 (C-4'); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 276 (24), 219 (18), 179 (36), 191 (100 %), 103 (41), 83 (33), 57 (48); Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.57; H, 7.25. Found: C, 69.24; H, 7.16.

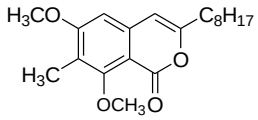
6,8-Dimethoxy-7-methyl-3-pentyl-1H-isochromen-1-one (5h)



Yield = 73 %; Rf = 0.55; oil; IR (KBr) ν_{max}: 3051 (C=C-H), 2964 (C-H), 1712 (C=O), 1574 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.82 (1H, s, H-5), 7.36 (1H, s, H-4), 3.84 (3H, s, -OCH_3), 3.80 (3H, s, -OCH_3), 2.74 (3H, s, Ar-CH_3), 2.53 (2H, t, *J* = 3.7 Hz, H-1'), 1.25-1.64 (6H, m, H-2',3',4'), 0.93 (3H, t, *J* = 7.2 Hz, H-5'); ^{13}C NMR ($CDCl_3$, δ ppm): 165.6 (C=O), 150.2

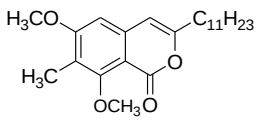
(C-3), 142.4 (C-6), 141.6 (C-8), 133.5 (C-10), 128.6 (C-9), 118.5 (C-7), 109.5 (C-4), 105.3 (C-5), 54.6 (-OCH_3), 54.3 (-OCH_3), 38.7 (C-1'), 29.2 (Ar-CH_3), 24.5 (C-2'), 19.3 (C-3'), 14.5 (C-4'), 13.4 (C-5'); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 290 (41), 219 (27), 191 (100 %), 99 (39), 71 (52); Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.63. Found: C, 70.16; H, 7.26.

6,8-Dimethoxy-7-methyl-3-octyl-1H-isochromen-1-one (5i)



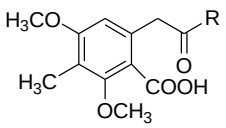
Yield = 76 %; Rf = 0.5; M.P.= 88-90 ºC; IR (KBr) ν_{max}: 3036 (C=C-H), 2972 (C-H), 1716 (C=O), 1565 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.61 (1H, s, H-5), 6.78 (1H, s, H-4), 3.74 (3H, s, -OCH_3), 3.71 (3H, s, -OCH_3), 2.47 (3H, s, Ar-CH_3), 1.53 (2H, t, *J* = 6.8 Hz, H-1'), 1.26-1.73 (12H, m, H-2',H-3',H-4',H-5',H-6',H-7'), 0.92 (3H, t, *J* = 6.9 Hz, H-8'); ^{13}C NMR ($CDCl_3$, δ ppm): 164.2 (C=O), 153.6 (C-3), 144.5 (C-6), 143.7 (C-8), 133.4 (C-10), 131.7 (C-9), 123.2 (C-7), 115.8 (C-4), 105.4 (C-5), 56.5 (-OCH_3), 56.2 (-OCH_3), 36.7 (C-1'), 29.3 (Ar-CH_3), 27.6 (C-2'), 23.7 (C-3'), 21.5 (C-4'), 16.7 (C-5'), 14.6 (C-6'), 13.2 (C-7'), 11.8 (C-8'); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 332 (38), 191 (100 %), 127 (57), 99 (32); Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.28; H, 8.43. Found: C, 72.10; H, 8.19.

6,8-Dimethoxy-7-methyl-3-undecyl-1H-isochromen-1-one (5j)



Yield = 72 %; Rf = 0.5; M.P.= 137-139 ºC; IR (KBr) ν_{max}: 3012 (C=C-H), 2923 (C-H), 1713 (C=O), 1576 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.55 (1H, s, H-5), 6.82 (1H, s, H-4), 3.76 (3H, s, -OCH_3), 3.73 (3H, s, -OCH_3), 2.57 (3H, s, Ar-CH_3), 1.54 (2H, t, *J* = 6.8 Hz, H-1'), 1.24-1.38 (10H, m, H-2',H-3',H-4',H-5',H-6',H-7',H-8',H-9',H-10'), 0.93 (3H, t, *J* = 6.7 Hz, H-11'); ^{13}C NMR ($CDCl_3$, δ ppm): 163.7 (C=O), 152.9 (C-3), 143.8 (C-6), 142.6 (C-8), 133.2 (C-9), 132.7 (C-10), 122.8 (C-7), 114.7 (C-4), 104.7 (C-5), 56.6 (-OCH_3), 56.2 (-OCH_3), 38.7 (C-1'), 29.1 (Ar-CH_3), 27.8 (C-2'), 21.7 (C-3'), 16.8 (C-4'), 11.7 (C-5'), 10.8 (C-6'), 9.7 (C-7'); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 374 (46), 191 (100 %), 179 (52), 99 (23); Anal. Calcd for $C_{23}H_{34}O_4$: C, 72.26; H, 8.49. Found: C, 72.13; H, 8.26.

3.1.6 Synthesis of 2,4-Dimethoxy-3-methyl-6-(2-oxoaryl/alkyl) benzoic acid (6a-j)

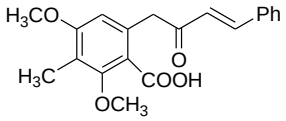


Procedure

6,8-Dimethoxy-7-methyl-3-aryl/alkyl-1H-isochromen-1-ones **(5a-j)** (1.42 mmol)

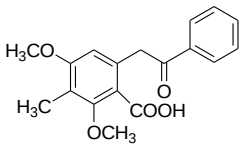
in ethanol (20 mL) were treated with 5 % KOH (40 mL) and the mixture was refluxed for 4 hr. After cooling the reaction mixture, the ethanol was evaporated under reduced pressure. Cold water (20 mL) was added and the mixture acidified with dilute hydrochloric acid when solid was precipitated. Filtration followed by drying under vacuum afforded 2,4-dimethoxy-3-methyl-6-(2-oxoaryl/alkyl) benzoic acids **(6a-j)**.

2,4-Dimethoxy-3-methyl-6-(2-oxo-4-phenylbut-3-enyl)benzoic acid (6a)



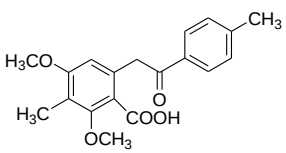
Yield = 70 %; Rf = 0.3; M.P. = 158-159 ^{o}C; IR (KBr) ν_{max}: 3444 (O-H), 3023 (C-H), 1736 (carboxylic C=O), 1712 (ketonic C=O), 1597 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 10.21 (1H, s, -COOH), 7.86-8.11 (5H, m, Ar), 7.74 (2H, d, *J* = 7.6 Hz, H-a), 7.41 (1H, d, *J* = 7.6 Hz, Hb), 7.23 (1H, s, H-5), 4.31 (2H, s, -CH_2), 3.93 (3H, s, -OCH_3), 3.87 (3H, s, -OCH_3), 2.35 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 196.8 (ketonic C=O), 167.6 (carboxylic C=O), 146.2 (C-2), 141.5 (C-4), 138.8 (C-1), 138.1 (C-1a), 137.5 (C-1b), 136.7 (C-1'), 131.3 (C-5), 129.4 (C-6), 128.7 (C-2',C-6'), 127.6 (C-3',C-5'), 124.6 (C-4'), 120.4 (C-3), 64.3 (-OCH_3), 63.8 (-OCH_3), 46.7 (-CH_2), 29.6 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 340 (31), 237 (16), 219 (100 %), 192 (62), 131 (43), 77 (22); Anal. Calcd. for $C_{20}H_{20}O_5$: C, 70.58; H, 5.88. Found: C, 70.31; H, 5.42.

2,4-Dimethoxy-3-methyl-6-(2-oxo-2-phenylethyl)benzoic acid (6b)



Yield = 87 %; Rf = 0.4; M.P.= 168-170 ^{o}C; IR (KBr) ν_{max}: 3324 (O-H), 3034 (C=C-H), 1738 (carboxylic C=O), 1714 (ketonic C=O), 1587 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 11.4 (1H, s, -COOH), 8.02 (2H, d, *J* = 7.4 Hz, H-2',H-6'), 7.87 (1H, s, H-5), 7.76 (1H, dd, *J* = 7.2,7.1 Hz, H-4'), 7.62 (2H, dd, *J* = 7.3,7.1 Hz, H-3',H-5'), 4.33 (2H, s,-CH_2), 3.92 (3H, s, -OCH_3), 3.88 (3H, s, -OCH_3), 2.61 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 194.4 (ketonic C=O), 166.8 (carboxylic C=O), 142.5 (C-1), 138.6 (C-2), 137.5 (C-1'), 136.8 (C-6), 132.5 (C-4), 126.4 (C-2',C-6'), 124.6 (C-3',C-5'), 122.4 (C-4'), 121.7 (C-3), 115.4 (C-5), 62.6 (-OCH_3), 58.3 (-OCH_3), 44.3 (C-1''), 28.5 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 314 (42), 296 (55), 270 (68), 237 (31), 219 (100 %), 192 (24), 161 (16), 105 (27); Anal. calcd for $C_{18}H_{18}O_5$: C, 68.78 H, 5.74; Found: C, 68.56 H, 5.57.

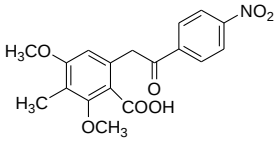
2,4-Dimethoxy-6-[2-(4-methylphenyl)-2-oxoethyl]-3-methylbenzoic acid (6c)



Yield = 84 %; Rf = 0.35; M.P.= 168-169 ^{o}C; IR (KBr) ν_{max}: 3326 (O-H), 3041 (C=C-H), 1736 (carboxylic C=O), 1712 (ketonic C=O), 1567 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 10.7

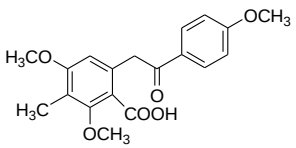
(1H, s, -COOH), 8.07 (1H, s, H-5), 7.91 (2H, d, *J* = 7.4 Hz, H-2',H-6'), 7.6 (2H, d, *J* = 7.2 Hz, H-3',H-5'), 4.27 (2H, s, $-CH_2$), 3.78 (3H, s, $-OCH_3$), 3.74 (3H, s, $-OCH_3$), 2.72 (3H, s, Ar-CH_3), 2.32 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 195.2 (ketonic C=O), 166.4 (carboxylic C=O), 141.6 (C-1), 138.5 (C-2), 136.2 (C-4), 135.2 (C-1'), 132.4 (C-2',C-6'), 128.6 (C-3',C-5'), 126.5 (C-4'), 122.3 (C-3), 116.7 (C-5), 62.3 ($-OCH_3$), 61.8 ($-OCH_3$), 44.5 (C-1''), 28.6 (Ar-CH_3), 27.4 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 328 (53), 284 (60), 237 (26), 219 (100 %), 192 (27), 119 (32), 91 (23); Anal. calcd for $C_{19}H_{20}O_5$: C, 69.49 H, 6.14; Found: C, 69.33 H, 5.97.

2,4-Dimethoxy-6-[2-(4-nitrophenyl)-2-oxoethyl]-3-methylbenzoic acid (6d)



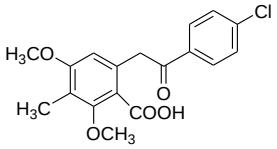
Yield = 81 %; Rf = 0.3; M.P.= 145-146 ^{o}C; IR (KBr) ν_{max}: 3352 (O-H), 3043 (C=C-H), 1741 (carboxylic C=O), 1721 (ketonic C=O), 1583 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 11.9 (1H, s, -COOH), 8.24 (2H, d, *J* = 7.1 Hz, H-3',H-5'), 8.13 (2H, d, *J* = 7.2 Hz, H-2',H-6'), 7.91 (1H, s, H-5), 4.26 (2H, s, $-CH_2$), 3.93 (3H, s, $-OCH_3$), 3.88 (3H, s, $-OCH_3$), 2.74 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 198.5 (ketonic C=O), 167.2 (carboxylic C=O), 142.5 (C-1), 140.7 (C-1'), 138.2 (C-2), 137.4 (C-4'), 136.7 (C-2',C-6'), 135.5 (C-3',C-5'), 134.6 (C-4), 124.3 (C-3), 122.5 (C-3), 117.3 (C-5), 63.2 ($-OCH_3$), 62.7 ($-OCH_3$), 45.2 (C-1''), 29.4 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 359 (33), 326 (57), 315 (64), 237 (19), 219 (100 %), 192 (36), 162 (14); Anal. calcd for $C_{18}H_{17}NO_7$: C, 60.16 H, 4.76 N, 3.91; Found: C, 60.09 H, 4.67 N, 3.76.

2,4-Dimethoxy-6-[2-(4-methoxyphenyl)-2-oxoethyl]-3-methylbenzoic acid (6e)



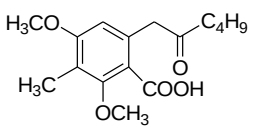
Yield = 86 %; Rf = 0.32; M.P.= 161-162 ^{o}C; IR (KBr) ν_{max}: 3326 (O-H), 3032 (C=C-H), 1737 (carboxylic C=O), 1711 (ketonic C=O), 1568 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 11.9 (1H, s, -COOH), 7.92 (1H, s, Ar-H-5), 7.86 (2H, d, *J* = 7.2 Hz, H-2',H-6'), 7.75 (2H, d, *J* = 7.1 Hz, H-3' H-5'), 4.33 (2H, s, $-CH_2$), 3.86 (3H, s, $-OCH_3$), 3.82 (3H, s, $-OCH_3$), 3.67 (3H, s, 4'-OCH_3), 2.82 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 196.4 (ketonic C=O), 167.5 (carboxylic C=O), 141.5 (C-1), 138.2 (C-2), 137.8 (C-4), 136.6 (C-1'), 132.3 (C-2',C-6'), 128.6 (C-2',C-5'), 126.4 (C-4'), 122.5 (C-3), 116.4 (C-5), 62.5 ($-OCH_3$), 62.2 ($-OCH_3$), 57.6 (4'-OCH_3), 43.5 (C-1''), 27.6 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 344 (46), 341 (63), 237 (29), 219 (100 %), 192 (21), 135 (16), 107 (17); Anal. calcd for $C_{19}H_{20}O_6$: C, 66.26 H, 5.81; Found: C, 66.14 H, 5.66.

6-[2-(4-Chlorophenyl)-2-oxoethyl]-2,4-dimethoxy-3-methylbenzoic acid (6f)



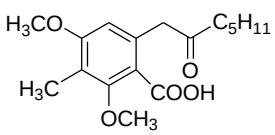
Yield = 82 %; Rf = 0.45; M.P.= 157-158 ^{o}C; IR (KBr) ν_{max}: 3341 (O-H), 3035 (C=C-H), 1738 (carboxylic C=O), 1715 (ketonic C=O), 1574 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 11.3 (1H, s, -COOH), 8.11 (2H, d, *J* = 7.4 Hz, H-2',H-6'), 7.97 (2H, d, *J* = 7.2 Hz, H-3',H-5'), 7.74 (1H, s, H-5), 4.26 (2H, s, -CH_2), 3.91 (3H, s, -OCH_3), 3.86 (3H, s, -OCH_3), 2.68 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 197.6 (ketonic C=O), 167.4 (carboxylic C=O), 143.5 (C-1), 138.2 (C-2), 137.3 (C1'), 136.2 (C-4), 134.5 (C-2',C-6'), 134.3 (C-4'), 132.8 (C-3',(C-5'), 127.5 (C-3), 116.4 (C-5), 62.6 (-OCH_3), 62.2 (-OCH_3), 44.7 (C-1''), 30.3 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 348.5 (40), 350.5 [$(M+2)^{+\cdot}$] (32), 330.5 (65), 304.5 (37), 237 (23), 219 (100 %), 192 (22), 138.5 (17), 111.5 (20); Anal. calcd for $C_{18}H_{17}O_5Cl$: C, 61.97 H, 4.86; Found: C, 61.86 H, 4.68.

2,4-Dimethoxy-3-methyl-6-(2-oxohexyl)benzoic acid (6g)



Yield = 76 %; Rf = 0.37; M.P.= 136-137 ^{o}C; IR (KBr) ν_{max}: 3321 (O-H), 3037 (C=C-H), 1734 (carboxylic C=O), 1711 (ketonic C=O), 1577 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 10.7 (1H, s, -COOH), 7.73 (1H, s, H-5), 4.23 (2H, s, H-1'), 3.86 (3H, s, -OCH_3), 3.82 (3H, s, -OCH_3), 3.56 (2H, t, *J* = 3.6 Hz, H-3'), 3.12 (3H, s, Ar-CH_3), 1.21-1.63 (4H, m, H-4',H-5'), 0.94 (3H, t, *J* = 7.1 Hz, H-6'); ^{13}C NMR ($CDCl_3$, δ ppm): 196.5 (ketonic C=O), 167.8 (carboxylic C=O), 144.7 (C-2), 138.7 (C-4), 132.4 (C-1), 126.2 (C-6), 122.5 (C-3), 107.6 (C-5), 61.7 (-OCH_3), 61.2 (-OCH_3), 46.7 (C-1''), 43.5 (C-3'), 31.2 (3H, s, Ar-CH_3), 19.6 (C-4'), 14.5 (C-5'), 13.7 (C-6'); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 294 (23), 248 (36), 236 (52), 219 (100 %), 192 (13), 165 (35); Anal. calcd for $C_{16}H_{22}O_5$: C, 65.28 H, 7.54; Found: C, 65.15 H, 7.42.

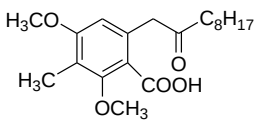
2,4-Dimethoxy-3-methyl-6-(2-oxoheptyl)benzoic acid (6h)



Yield = 75 %; Rf = 0.33; M.P.= 139-140 ^{o}C; IR (KBr) ν_{max}: 3325 (O-H), 3036 (C=C-H), 1735 (carboxylic C=O), 1708 (ketonic C=O), 1564 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 10.2 (1H, s, -COOH), 7.46 (1H, s, H-5), 4.24 (2H, s, -CH_2), 3.88 (3H, s, -OCH_3), 3.83 (3H, s, -OCH_3), 3.67 (2H, t, *J* = 3.7 Hz, H-3'), 2.26 (3H, s, Ar-CH_3), 123-1.65 (6H, m, H-4'-6'), 0.95 (3H, t, *J* = 5.7 Hz, H-7'); ^{13}C NMR ($CDCl_3$, δ ppm): 197.4 (ketonic C=O), 167.5 (carboxylic C=O), 144.3 (C-2), 137.8 (C-4), 136.5 (C-1), 127.6 (C-6), 121.3 (C-3), 107.4 (C-5), 63.1 (-OCH_3), 62.7 (-OCH_3), 46.7 (C-1''), 43.6 (C-3'), 27.4 (Ar-CH_3), 21.7 (C-4'), 18.5 (C-

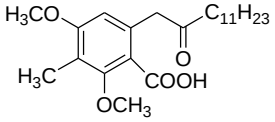
5'), 15.8 (C-6'), 13.7 (C-7'); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 308 (25), 290 (51), 263 (64) 219 (100 %), 192 (32), 165 (28); Anal. calcd for $C_{17}H_{24}O_5$: C, 67.10 H, 7.79; Found: C, 67.02 H, 7.65.

2,4-Dimethoxy-3-methyl-6-(2-oxodecyl)benzoic acid (6i)



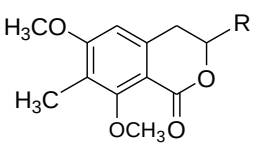
Yield = 80 %; Rf = 0.35; M.P.= 144-145 ^{o}C; IR (KBr) ν_{max}: 3323 (O-H), 3033 (C=C-H), 1737 (carboxylic C=O), 1707 (ketonic C=O), 1573 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 10.6 (1H, s, -COOH), 7.76 (1H, s, H-5), 4.25 (2H, s, $-CH_2$), 3.85 (3H, s, $-OCH_3$), 3.76 (3H, s, $-OCH_3$), 3.55 (2H, t, *J* = 3.6 Hz, H-3'), 2.34 (3H, s, Ar-CH_3), 1.56-1.63 (12H, m, H-4'-H-9'), 0.96 (3H, t, *J* = 7.2 Hz, H-10'); ^{13}C NMR ($CDCl_3$, δ ppm): 195.8 (ketonic C=O), 166.5 (carboxylic C=O), 142.3 (C-2), 138.5 (C-4), 135.7 (C-1), 126.4 (C-6), 118.6 (C-3), 111.4 (C-5), 62.3 ($-OCH_3$), 61.8 ($-OCH_3$), 44.7 (C-1''), 41.5 (C-3'), 27.4 (Ar-CH_3), 19.6 (C-4'), 16.2 (C-5'), 15.5 (C-6'), 14.7 (C-7'), 13.8 (C-8'), 12.4 (C-9'), 11.5 (C-10'); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 350 (25), 304 (31), 236 (45), 219 (100 %), 192 (16), 165 (23); Anal. calcd for $C_{20}H_{30}O_5$: C, 68.54 H, 8.63; Found: C, 68.36 H, 8.45.

2,4-Dimethoxy-3-methyl-6-(2-oxotridecyl)benzoic acid (6j)



Yield = 78 %; Rf = 0.36; M.P.= 150-151 ^{o}C; IR (KBr) ν_{max}: 3327 (O-H), 3035 (C=C-H), 1736 (carboxylic C=O), 1709 (ketonic C=O), 1576 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 10.4 (1H, s, -COOH), 7.83 (1H, s, H-5), 4.26 (2H, s, $-CH_2$), 3.82 (3H, s, $-OCH_3$), 3.78 (3H, s, $-OCH_3$), 3.62 (2H, t, *J* = 3.5 Hz, H-3'), 2.36 (3H, s, Ar-CH_3), 1.52-1.68 (16H, m, H-4'-12'), 0.95 (3H, t, *J* = 7.1 Hz, H-13'); ^{13}C NMR ($CDCl_3$, δ ppm): 195.3 (ketonic C=O), 165.4 (carboxylic C=O), 141.5 (C-2), 137.4 (C-4), 135.8 (C-1), 132.4 (C-6), 121.5 (C-3), 112.4 (C-5), 61.4 ($-OCH_3$), 58.5 ($-OCH_3$), 44.8 (C-1''), 41.3 (C-3'), 27.6 (Ar-CH_3), 19.7 (C-4'), 18.3 (C-5'), 17.5 (C-6'), 16.4 (C-7'), 15.8 (C-8'), 14.7 (C-9'), 13.6 (C-10'), 12.5 (C-11'), 11.7 (C-12') 10.6 (C-13'); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 392 (32), 346 (27), 237 (48) 219 (100 %), 192 (11), 155 (16); Anal. calcd for $C_{23}H_{36}O_5$: C, 70.38 H, 9.23; Found: C, 70.16 H, 9.16.

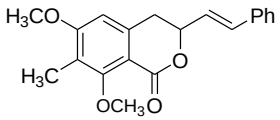
3.1.7 6,8-Dimethoxy-7-methyl-3-alkyl/aryl-3,4-dihydroisochromen-1-ones (7a-j)



Procedure

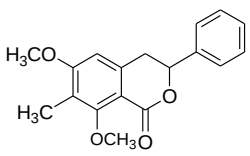
Sodium borohydride (18 mmol) was added portion wise to a stirred solution of keto acids **(6a-j)** (0.66 mmol) in ethanol (25 mL) and water (75 mL). The reaction mixture was stirred for 2 hr at room temperature, diluted with water (150 mL), acidified with conc. HCl and stirred for 2 additional hrs. The mixture was then saturated with ammonium sulfate and extracted with ethyl acetate (3x100 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated to get 6,8-dimethoxy-7-methyl-3-aryl/alkyl-3,4-dihydroisochromen-1-ones **(7a-j)**. It was purified by preparative thin layer chromatography using (petroleum ether and ethyl acetate 7:3) as eluent.

6,8-Dimethoxy-7-methyl-3-styryl-3,4-dihydroisochromen-1-one (7a)



Yield = 68 %; Rf = 0.5; M.P. = 134-135 ^{o}C; IR (KBr) ν_{max}: 3046 (C=C-H), 2941 (C-H), 1724 (C=O), 1581 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.28-7.83 (5H, m, Ar), 6.81 (1H, d, *J* = 7.4 Hz, Ha), 6.63 (1H, d, *J* = 7.4 Hz, Hb), 6.21 (1H, s, H-5), 5.34 (1H, dd, J_{trans} = 12.2 Hz, J_{cis} = 3.1 Hz, H-3), 3.81 (3H, s, -OCH_3), 3.78 (3H, s, -OCH_3), 3.38 (1H, dd, J_{gem} = 15.8 Hz, J_{trans} = 12.2 Hz, H-4), 3.13 (1H, dd, J_{gem} = 12.1 Hz, J_{cis} = 3.5 Hz, H-4'), 2.47 (1H, s, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.4 (C=O), 144.5 (C-6), 143.6 (C-8), 141.7 (C-10), 138.6 (C-1'), 137.2 (C-1a), 136.4 (C-1b), 134.3 (C-9), 131.8 (C-7), 130.5 (C-5), 128.5 (C-2',C-6'), 127.3 (C-3',C-5'), 123.6 (C-4'), 84.5 (C-3), 56.6 (-OCH_3), 56.3 (-OCH_3), 43.5 (C-4); 28.7 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 324 (31), 263 (17), 249 (26), 192 (100 %), 103 (14), 77 (21); Anal. Calcd. for $C_{20}H_{20}O_4$: C, 74.07; H, 6.17. Found: C, 73.96; H, 6.04.

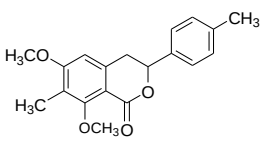
6,8-Dimethoxy-7-methyl-3-phenyl-3,4-dihydroisochromen-1-one (7b)



Yield = 86 %; Rf = 0.5; M.P.= 93-94 ºC; IR (KBr) ν_{max}: 3042 (C=C-H), 2937 (C-H), 1716 (C=O), 1583 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.87 (2H, d, *J* = 7.2 Hz, H-2',H-6'), 7.74 (2H, dd, *J* = 7.1,6.8 Hz, H-3',H-5'), 7.65 (1H, m, H-4'), 6.86 (1H, s, Ar-H-5), 5.43 (1H, dd, J_{trans} = 12.2 Hz, J_{cis} = 3.4 Hz, H-3), 3.85 (3H, s, -OCH_3), 3.78 (3H, s, -OCH_3), 3.32 (1H, dd, J_{gem} = 16.1 Hz, J_{trans} = 12.2 Hz, H-4), 3.17 (1H, dd, J_{gem} = 12.4 Hz, J_{cis} = 3.6 Hz, H-4'), 2.84 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 167.3 (C=O), 142.3 (C-6), 141.6 (C-8), 139.5 (C-10), 138.1 (C-1'), 137.2 (C-9), 132.8 (C-7), 131.7 (C-5), 130.6 (C-2',C-6'), 124.5 (C-3',C-5'), 118.4 (C-4'), 82.6 (C-3), 57.2 (6-OCH_3, 56.6 (8-OCH_3), 43.2 (C-4);

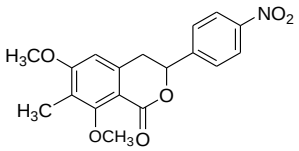
MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 298 (58), 192 (100 %), 164 (41), 137 (22), 105 (62), 77 (54); Anal. calcd for $C_{18}H_{18}O_4$: C, 72.47 H, 6.05; Found: C, 72.35 H, 5.87.

6,8-Dimethoxy-7-methyl-3-(4-methylphenyl)-3,4-dihydroisochromen-1-one (7c)



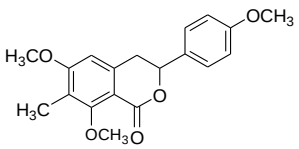
Yield = 84 %; Rf = 0.5; M.P.= 109-110 ºC; IR (KBr) ν_{max}: 3028 (C=C-H), 2934 (C-H), 1724 (C=O), 1575 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.81 (2H, d, *J* = 6.8 Hz, H-3',H-5'), 7.73 (2H, d, *J* = 7.2 Hz, H-2',H-6'), 6.68 (1H, s, H-5), 5.34 (1H, dd, J_{trans} = 12.4 Hz, J_{cis}= 3.7 Hz, H-3), 3.83 (3H, s, 6-OCH_3), 3.76 (3H, s, 8-OCH_3), 3.34 (1H, dd, J_{gem} = 16.2 Hz, J_{trans} = 12.4 Hz, H-4), 3.15 (1H, dd, J_{gem} = 12.4 Hz, J_{cis} = 3.7 Hz, H-4), 2.81 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 166.3 (C=O), 141.5 (C-6), 140.7 (C-8), 139.2 (C-10), 138.4 (C-1'), 136.3 (C-9), 133.6 (C-4'), 132.7 (C-2',C-6'), 131.2 (C-5), 130.5 (C-3',C-5'), 127.4 (C-7), 81.5 (C-3), 56.7 (-OCH_3), 56.2 (-OCH_3), 42.6 (C-4), 27.3 (Ar-CH_3), 23.7 (4'-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 312 (56), 192 (100 %), 164 (44), 137 (63), 107 (28); Anal. calcd for $C_{19}H_{20}O_4$: C, 73.04 H, 6.44; Found: C, 72.93 H, 6.26.

6,8-Dimethoxy-7-methyl-3-(4-nitrophenyl)-3,4-dihydroisochromen-1-one (7d)



Yield = 74 %; Rf = 0.5; M.P.= 214-215 ºC; IR (KBr) ν_{max}: 3056 (C=C-H), 2941 (C-H), 1727 (C=O), 1588 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.94 (2H, d, *J* = 6.8 Hz, H-3',H-5'), 7.82 (2H, d, *J* = 7.1 Hz, H-2',H-6'), 6.87 (1H, s, H-5), 5.46 (1H, dd, J_{trans} = 12.2 Hz, J_{cis} = 3.6 Hz, H-3), 3.93 (3H, s, -OCH_3), 3.86 (3H, s, -OCH_3), 3.35 (1H, dd, J_{gem}= 15.8 Hz, J_{trans} = 12.1 Hz, H-4), 3.18 (1H, dd, J_{gem} = 12.2 Hz, J_{cis} = 3.6 Hz, H-4), 2.87 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 167.6 (C=O), 143.2 (C-6), 142.5 (C-8), 140.4 (C-10), 139.6 (C-1'), 138.5 (C-9), 136.3 (C-4'), 134.2 (C-2',C-6'), 133.4 (C-5), 131.5 (C-3',C-5'), 128.7 (C-7), 83.6 (C-3), 58.4 (-OCH_3), 57.8 (-OCH_3), 44.6 (C-4), 29.4 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 343 (44), 297 (16), 192 (100 %), 164 (37), 137 (57), 107 (37); Anal. calcd for $C_{18}H_{17}NO_6$: C, 62.96 H, 4.98; N, 4.07; Found: C, 62.74 H, 4.82, N, 3.96;

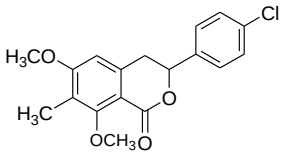
6,8-Dimethoxy-7-methyl-3-(4-methoxyphenyl)-3,4-dihydroisochromen-1-one (7e)



Yield = 84 %; Rf = 0.5; M.P.= 142-143 ºC; IR (KBr) ν_{max}: 3036 (C=C-H), 2941 (C-H), 1725 (C=O), 1577 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.83 (2H, d, *J* = 6.8 Hz, H-3',H-5'), 7.72 (2H, d, *J* = 7.1 Hz, H-2',H-6'), 6.76 (1H, s, H-5), 5.41 (1H, dd, J_{trans} = 12.2 Hz, J_{cis} = 3.6 Hz, H-3), 3.78 (3H, s, -OCH_3), 3.74 (3H, s, -OCH_3), 3.15 (1H, dd, J_{gem} = 16.2 Hz, J_{trans} = 12.4 Hz, H-4), 3.18 (1H, dd, J_{gem} = 12.4 Hz, J_{cis}= 3.6 Hz, H-4'), 2.83 (3H, s, Ar-CH_3);

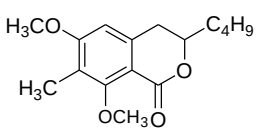
^{13}C NMR ($CDCl_3$, δ ppm): 166.4 (C=O), 143.1 (C-6), 142.4 (C-8), 140.5 (C-10), 138.6 (C-1'), 137.5 (C-9), 134.2 (C-4'), 132.4 (C-2',C-6'), 131.3 (C-5), 128.5 (C-7), 126.6 (C-3',C-5'), 82.8 (C-3), 57.4 (-OCH_3), 56.9 (-OCH_3), 53.4 (4'-OCH_3), 42.5 (C-4), 28.6 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 328 (47), 221 (28), 192 (100 %), 164 (42), 137 (61), 107 (34); Anal. calcd for $C_{19}H_{20}O_5$: C, 69.52 H, 6.08; Found: C, 69.35 H, 5.93.

6,8-Dimethoxy-7-methyl-3-(4-chlorophenyl)-3,4-dihydroisochromen-1-one (7f)



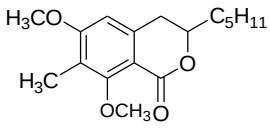
Yield = 85 %; Rf = 0.5; M.P.= 115-117 ºC; IR (KBr) ν_{max}: 3023 (C=C-H), 2937 (C-H), 1723 (C=O), 1576 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.91 (1H, d, *J* = 7.2 Hz, H-3',H-5'), 7.83 (1H, d, *J* = 6.8 Hz, H-2',H-6'), 6.85 (1H, s, H-5), 5.39 (1H, dd, J_{trans} = 12.4 Hz, J_{cis} = 3.6 Hz, H-3), 3.92 (3H, s, -OCH_3), 3.87 (3H, s, -OCH_3), 3.37 (1H, dd, J_{gem} = 16.2 Hz, J_{trans} = 12.2 Hz, H-4), 3.16 (1H, dd, J_{gem} = 12.4 Hz, J_{cis} = 3.6 Hz, H-4), 2.65 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 164.6 (C=O), 143.4 (C-6), 142.7 (C-8), 141.2 (C-10), 139.4 (C-1'), 137.8 (C-9), 136.7 (C-4'), 133.5 (C-2',C-6'), 132.3 (C-5), 131.4 (C-3',C-5'), 128.6 (C-7), 88.3 (C-3), 56.3 (-OCH_3), 55.8 (-OCH_3), 44.3 (C-4), 28.8 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 332.5 (61), 334.5 [M+2] (38), 192 (100 %), 164 (33), 139.5 (65), 111.5 (53); Anal. calcd for $C_{18}H_{17}O_4Cl$: C, 64.94 H, 5.13; Found: C, 64.82 H, 5.07.

6,8-Dimethoxy-7-methyl-3-Butyl-3,4-dihydroisochromen-1-one (7g)



Yield = 73 %; Rf = 0.5; oil; IR (KBr) ν_{max}: 3033 (C=C-H), 2935 (C-H), 1718 (C=O), 1578 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 6.78 (1H, s, H-5), 4.46-4.52 (1H, m, H-3), 3.84 (3H, s, -OCH_3), 3.79 (3H, s, -OCH_3), 3.38 (1H, dd, J_{gem} = 16.2 Hz, J_{trans} = 12.6 Hz, H-4), 3.14 (1H, dd, J_{gem} = 16.2 Hz, J_{cis} = 3.6 Hz, H-4), 2.81 (3H, s, Ar-CH_3), 2.33-2.47 (2H, m, H-1'), 1.23-1.46 (4H, m, H-2', H-3'), 0.93 (3H, t, *J* = 6.7 Hz, H-4'); ^{13}C NMR ($CDCl_3$, δ ppm): 166.2 (C=O), 140.4 (C-10), 139.7 (C-6), 138.6 (C-8), 136.4 (C-9), 126.4 (C-5), 118.2 (C-7), 81.3 (C-3), 56.5 (6-OCH_3), 55.7 (8-OCH_3), 42.5 (C-4), 37.5 (C-1'), 28.4 (Ar-CH_3), 19.2 (C-2'), 14.5 (C-3'), 12.4 (C-4'); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 278 (54), 221 (17), 192 (100 %), 71 (42), 43 (67); Anal. calcd for $C_{16}H_{22}O_4$: C, 69.05 H, 7.96; Found: C, 68.94 H, 7.85.

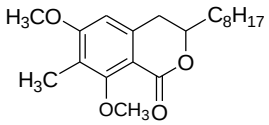
6,8-Dimethoxy-7-methyl-3-pentyl-3,4-dihydroisochromen-1-one (7h)



Yield = 77 %; Rf = 0.5; oil; IR (KBr) ν_{max}: 3034 (C=C-H), 2933 (C-H), 1726 (C=O), 1581 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 6.87 (1H, s, H-5), 4.57-4.64 (1H, m, H-3), 3.83 (3H, s, -OCH_3),

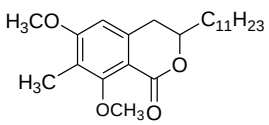
3.78 (3H, s, -OCH_3), 3.34 (1H, dd, J_{gem} = 16.4 Hz, J_{trans} = 12.8 Hz, H-4), 3.11 (1H, dd, J_{gem} = 16.2 Hz, J_{cis} = 3.6 Hz, H-4), 2.67 (3H, s, Ar-CH_3), 2.36-2.41 (2H, m, H-1'), 1.27-1.56 (6H, m, H-2'-4'), 0.92 (3H, t, *J* = 5.8, H-5'); ^{13}C NMR ($CDCl_3$, δ ppm): 168.5 (C=O), 139.8 (C-10), 138.7 (C-8), 137.8 (C-6), 136.3 (C-9), 126.4 (C-5), 122.5 (C-7), 80.2 (C-3), 55.8 (-OCH_3), 55.4 (-OCH_3), 42.6 (C-4), 38.5 (C-1'), 27.6 (Ar-CH_3), 19.4 (C-2'), 14.5 (C-3'), 12.6 (C-4'), 11.5 (C-5'); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 292 (51), 192 (100 %), 99 (57), 71 (32); Anal. calcd for $C_{17}H_{24}O_4$: C, 69.83 H, 8.26; Found: C, 69.72 H, 8.11.

6,8-Dimethoxy-7-methyl-3-octyl-3,4-dihydroisochromen-1-one (7i)



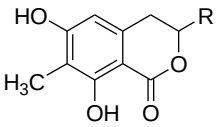
Yield = 83 %; Rf = 0.5; M.P.= 76-77 ºC; IR (KBr) ν_{max}: 3037 (C=C-H), 2932 (C-H), 1716 (C=O), 1572 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 6.83 (1H, s, Ar-H-5), 4.43-4.52 (1H, m, H-3), 3.82 (3H, s, -OCH_3), 3.77 (3H, s, -OCH_3), 3.44 (1H, dd, J_{gem} = 16.2 Hz, J_{trans} = 12.4 Hz, H-4), 3.16 (1H, dd, J_{gem} = 16.2 Hz, J_{cis} = 3.6 Hz, H-4), 2.66 (3H, s, Ar-CH_3), 2.42 (2H, *J* = 6.1 Hz, H-1'), 1.31-1.62 (12H, m, H-2'-7'), 0.91 (3H, t, *J* = 5.8, H-8'); ^{13}C NMR ($CDCl_3$, δ ppm): 165.6 (C=O), 140.1 (C-10), 138.4 (C-6), 137.6 (C-8), 136.7 (C-9), 126.5 (C-5), 123.6 (C-7), 81.5 (C-3), 56.7 (-OCH_3), 56.3 (-OCH_3), 42.7 (C-4), 38.6 (C-1'), 28.5 (Ar-CH_3), 19.2 (C-2'), 14.7 (C-3'), 13.2 (C-4'), 12.5 (C-5'), 11.8 (C-6'), 11.2 (C-7'), 10.4 (C-8'); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 334 (61), 221 (13), 192 (100 %), 151 (42), 99 (22); Anal. calcd for $C_{20}H_{30}O_4$: C, 71.83 H, 9.05; Found: C, 71.65 H, 8.87.

6,8-Dimethoxy-7-methyl-3-undecyl-3,4-dihydroisochromen-1-one (7j)



Yield = 82 %; Rf = 0.5; oil; IR (KBr) ν_{max}: 3038 (C=C-H), 2931 (C-H), 1717 (C=O), 1582 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 6.78 (1H, s, Ar-H-5), 4-38-4.47 (1H, m, H-3), 3.85 (3H, s, -OCH_3), 3.74 (3H, s, -OCH_3), 3.36 (1H, dd, J_{gem} = 16.1 Hz, J_{trans} = 12.2 Hz, H-4), 3.13 (1H, dd, J_{gem} = 16.1 Hz, J_{cis} = 3.6 Hz, H-4), 2.72 (3H, s, Ar-CH_3), 2.34 (2H, *J* = 6.1 Hz, H-1'), 1.32-1.56 (12H, m, H-2'-10'), 0.93 (3H, t, *J* = 5.8 Hz, H-11'); ^{13}C NMR ($CDCl_3$, δ ppm): 166.2 (C=O), 140.3 (C-10), 138.6 (C-6), 137.4 (C-8), 136.8 (C-9), 126.3 (C-5), 122.7 (C-7), 80.8 (C-3), 57.6 (-OCH_3), 57.1 (-OCH_3), 42.3 (C-4), 38.6 (C-1'), 28.5 (Ar-CH_3), 19.5 (C-2'), 15.6 (C-3'), 14.2 (C-4'), 13.5 (C-5'), 12.8 (C-6'), 12.4 (C-7'), 11.7 (C-8'), 11.2 (C-9'), 10.8 (C-10'), 10.3 (C-11'); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 376 (49), 333 (17), 221 (23), 192 (100 %), 151 (22), 127 (53), 99 (24); Anal. calcd for $C_{23}H_{36}O_4$: C, 73.36 H, 9.65; Found: C, 71.23 H, 9.54.

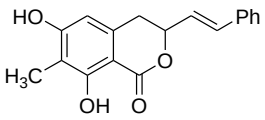
3.1.8 6,8-Dihydroxy-7-methyl-3-aryl/alkyl-3,4-dihydroisochromen-1-ones (8a-j)



Procedure

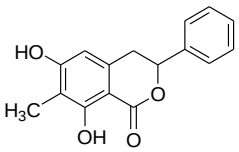
6,8-Dimethoxy-7-methyl-3-aryl/alkyl-3,4-dihydroisochromen-1-ones **(7a-j)** (1.25 mmol) were dissolved in ethanethiol (3.5 mL) and solution was cooled on ice bath. Aluminium chloride (3.8 mmol) was added in 3 portions during an interval of 30 min. After the addition of aluminium chloride, the reaction mixture was stirred on ice bath for 1 hr. The reaction was quenched with 10 % $NaHCO_3$ and extracted with ethyl acetate, sodium chloride was added to enhance the layer separation. The combined organic layers were washed once with brine, dried over sodium sulfate and concentrated to give 6,8-dihydroxy-7-methyl-3-aryl/alkyl-3,4-dihydroisochromen-1-ones **(8a-j)**.

6,8-Dihydroxy-7-methyl-3-styryl-3,4-dihydroisochromen-1-one (8a)



Yield = 73 %; Rf = 0.3; M.P. = 168-169 ^{o}C; IR (KBr) ν_{max}: 3425 (O-H), 3065 (C=C-H), 1712 C=O, 1567 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 8.13-7.43 (5H, m, Ar), 7.21 (1H, s, H-5), 6.78 (1H, d, *J* = 6.9 Hz, Ha), 6.43 (1H, d, *J* = 6.9 Hz, Hb), 5.43 (1H, dd, J_{trans} = 12 Hz , J_{cis} = 3.2 Hz, H-3), 3.53 (1H, dd, J_{gem} = 15.4 Hz, J_{trans} = 12.1 Hz , H-4), 3.31 (1H, dd, J_{gem} = 12.2 Hz , J_{cis} = 3.4 Hz , H-4'), 4.81 (2H, s, -OH), 2.51 (3H, s, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.5 (=O), 146.3 (C-6) , 145.6 (C-8), 141.6 (C-10), 139.5 (C-1'), 138.6 (C-1a), 137.4 (C-1b), 135.2 (C-9), 132.3 (C-7), 131.5 (C-5), 129.4 (C-2',C-6'), 126.4 (C-3',C-5'), 125.3 (C-4'), 85.4 (C-3), 44.5 (C-4); 29.4 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 296 (37), 263 (23), 219 (61), 164 (100 %), 151 (43), 91 (21), 77 (31); Anal. Calcd. for $C_{18}H_{16}O_4$; C, 72.97; H, 5.41. Found: C, 72.82; H, 5.24.

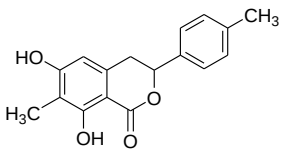
6,8-Dihydroxy-7-methyl-3-phenyl-3,4-dihydroisochromen-1-one (8b)



Yield = 84 %; Rf = 0.4; M.P.= 124-125 ^{o}C; IR (KBr) ν_{max}: 3482 (O-H), 3031 (C=C-H), 1723 (C=O), 1581 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.95 (2H, d, *J* = 6.8 Hz, H-2',H-6'), 7.73, (2H, dd, *J* = 6.7,5.8 Hz, H-3',H-5'), 7.64 (1H, dd, *J* = 6.4,5.6, Hz, H-5'), 6.87 (1H, s, H-5), 5.35 (1H, dd, J_{trans} = 12.2 Hz, J_{cis} = 3.8 Hz, H-3), 4.67 (2H, s, -OH), 3.38 (1H, dd, J_{gem} = 16.4 Hz, J_{trans} = 12.2 Hz, H-4), 3.16 (1H, dd, J_{gem} = 12.2 Hz, J_{cis} = 3.7 Hz, H-4'), 2.64 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 166.8 (C=O), 148.5 (C-6), 147.2 (C-8), 142.5 (C-10),

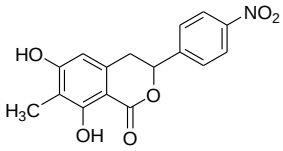
138.4 (C-1'), 137.5 (C-9), 132.3 (C-7), 128.5 (C-2',C-6'), 126.2 (C-3',C-5'), 122.7 (C-5), 118.6 (C-4'), 82.4 (C-3), 44.4 (C-4), 29.3 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 270 (39), 164 (100 %), 136 (48), 105 (56), 77 (31); Anal. calcd for $C_{16}H_{14}O_4$: C, 71.12 H, 5.17; Found: C, 71.02 H, 5.09.

6,8-Dihydroxy-7-methyl-3-(4-methylphenyl)-3,4-dihydroisochromen-1-one (8c)



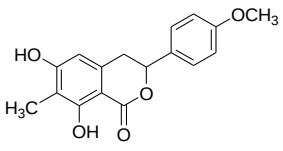
Yield = 83 %; Rf = 0.3; M.P.= 113-114 ºC; IR (KBr) ν_{max}: 3464 (O-H), 3035 (C=C-H), 1724 (C=O), 1575 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.88 (2H, d, *J* = 7.2 Hz, H-3',H-5'), 7.71 (2H, d, *J* = 7.1 Hz, H-2',H-6'), 6.87 (1H, s, H-5), 5.34 (1H, dd, J_{trans} = 12.2 Hz, J_{cis} = 3.7 Hz, H-3), 4.84 (2H, s, -OH), 3.43 (1H, dd, J_{gem} = 16.3 Hz, J_{trans} = 12.2 Hz, H-4), 3.22 (1H, dd, J_{gem} = 12.2 Hz, J_{cis} = 3.8 Hz, H-4'), 2.86 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 167.6 (C=O), 148.5 (C-6), 147.3 (C-8), 142.6 (C-10), 140.5 (C-1'), 136.3 (C-9), 134.2 (C-4'), 132.5 (C-2',C-6'), 130.6 (C-5), 130.8 (C-3',C-5'), 128.7 (C-7), 83.6 (C-3), 44.3 (C-4), 29.4 (Ar-CH_3), 23.6 (4'-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 284 (40), 256 (21), 240 (23), 164 (100 %), 136 (28), 105 (31), 91 (16); Anal. calcd for $C_{17}H_{16}O_4$: C, 71.82 H, 5.66; Found: C, 71.68 H, 5.42.

6,8-Dihydroxy-7-methyl-3-(4-nitrophenyl)-3,4-dihydroisochromen-1-one (8d)



Yield = 81 %; Rf = 0.25; M.P.= 137-138 ºC; IR (KBr) ν_{max}: 3484 (O-H), 3037 (C=C-H), 1723 (C=O), 1778 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 8.03 (1H, d, *J* = 7.1 Hz, H-3',H-5'), 7.95 (1H, d, *J* = 6.7 Hz, H-2',H-6'), 6.96 (1H, s, H-5), 5.48 (1H, dd, J_{trans} = 12.1 Hz, J_{cis} = 3.5 Hz, H-3), 4.87 (2H, s, -OH), 3.51 (1H, dd, J_{gem} = 16.2 Hz, J_{trans} = 12.1 Hz, H-4), 3.32 (1H, dd, J_{gem} = 12.1 Hz, J_{cis} = 3.6 Hz, H-4'), 2.87 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 167.6 (C=O), 148.7 (C-6), 147.6 (C-8), 143.8 (C-10), 142.4 (C-1'), 139.2 (C-9), 138.5 (C-4'), 134.6 (C-2',C-6'), 133.4 (C-5), 132.7 (C-3',C-5'), 129.3 (C-7), 83.8 (C-3), 44.8 (C-4), 29.8 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 315 (38), 287 (35), 269 (27), 164 (100 %), 136 (26), 105 (32), 91 (14); Anal. calcd for $C_{16}H_{13}O_6$ N: C, 60.95; H, 4.15; N, 4.43; Found: C, 60.87 H, 4.11, N, 4.36.

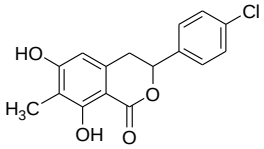
6,8-Dihydroxy-7-methyl-3-(4-methoxyphenyl)-3,4-dihydroisochromen-1-one (8e)



Yield = 81 %; Rf = 0.25; M.P.= 161-162 ºC; IR (KBr) ν_{max}: 3461 (O-H), 3042 (C=C-H), 1726 (C=O), 1582 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.85 (2H, d, *J* = 7.3 Hz, H-3',H-5'), 7.68 (2H, d, *J* = 7.1 Hz, H-2',H-6'), 6.92 (1H, s, H-5), 5.32 (1H, dd, J_{trans} = 12.4 Hz, J_{cis} = 3.7 Hz, H-

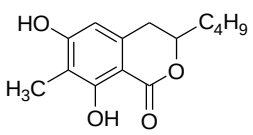
3), 4.82 (2H, s, -OH), 3.42 (1H, dd, J_{gem} = 16.2 Hz, J_{trans} = 12.1 Hz, H-4), 3.25 (1H, dd, J_{gem} = 12.1 Hz, J_{cis} = 3.8 Hz, H-4'), 2.84 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 166.3 (C=O), 148.2 (C-6), 147.5 (C-8), 142.4 (C-10), 140.3 (C-1'), 136.7 (C-9), 133.4 (C-4'), 131.6 (C-2',C-6'), 131.7 (C-5), 130.3 (C-3',C-5'), 128.5 (C-7), 83.4 (C-3), 56.5 (4'-OCH_3), 44.2 (C-4), 29.5 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 300 (40), 164 (100 %), 136 (27), 135 (48), 107 (23); Anal. calcd for $C_{17}H_{16}O_5$: C, 68.02 H, 5.34; Found: C, 67.88 H, 5.22.

6,8-Dihydroxy-7-methyl-3-(4-chlorophenyl)-3,4-dihydroisochromen-1-one (8f)



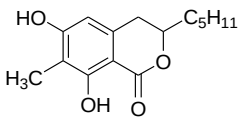
Yield = 87 %; Rf = 0.35; M.P.= 126-127 ºC; IR (KBr) ν_{max}: 3472 (O-H), 3036 (C=C-H), 1721 (C=O), 1775 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.93 (1H, d, J = 7.1 Hz, H-3',H-5'), 7.88 (1H, d, J = 6.8 Hz, H-2',H-6'), 6.93 (1H, s, H-5), 5.41 (1H, dd, J_{trans} = 12.1 Hz, J_{cis} = 3.6 Hz, H-3), 4.85 (2H, s, -OH), 3.46 (1H, dd, J_{gem} = 16.1 Hz, J_{trans}= 12.2 Hz, H-4), 3.28 (1H, dd, J_{gem} = 12.2 Hz, J_{cis}= 3.7 Hz, H-4'), 2.85 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 165.2 (C=O), 148.5 (C-6), 147.4 (C-8), 143.5 (C-10), 141.5 (C-1'), 138.3 (C-9), 137.7 (C-4'), 133.5 (C-2',C-6'), 132.1 (C-5), 131.3 (C-3',C-5'), 128.7 (C-7), 83.5 (C-3), 44.6 (C-4), 29.6 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 304.5 (38), 306.5 [$(M+2)^{+\cdot}$] (23), 164 (100 %), 136.5 (21), 139.5 (53), 111.5 (48); Anal. calcd for $C_{16}H_{13}O_4Cl$: C, 63.04 H, 4.26; Found: C, 62.95 H, 4.14.

6,8-Dihydroxy-7-methyl-3-butyl-3,4-dihydroisochromen-1-one (8g)



Yield = 73 %; Rf = 0.45; M.P.= 84-85 °C; IR (KBr) ν_{max}: 3466 (O-H), 3027 (C=C-H), 1719 (C=O), 1574 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.09 (1H, s, H-5), 5.22-5.27 (1H, m, H-3), 4.64 (2H, s, -OH), 3.42 (1H, dd, J_{gem} = 16.2 Hz, J_{trans} = 12.6 Hz, H-4), 3.21 (1H, dd, J_{gem} = 16.2 Hz, J_{cis} = 3.8 Hz, H-4), 2.76 (3H, s, Ar-CH_3), 2.24 (2H, t, J = 6.1 Hz, H-1'), 1.22-1.83 (4H, m, H-2',H-3'), 0.93 (3H, t, J = 5.8 Hz, H-4'); ^{13}C NMR ($CDCl_3$, δ ppm): 165.7 (C=O), 148.5 (C-6), 147.4 (C-8), 142.3 (C-10), 140.5 (C-9), 128.6 (C-5), 118.5 (C-7), 81.7 (C-3), 43.6 (C-4), 38.5 (C-1'), 29.5 (Ar-CH_3), 19.3 (C-2'), 14.2 (C-3'), 12.5 (C-4'); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 250 (43), 218 (24), 206 (16),193 (34), 164 (100 %), 136 (25), 71 (17); Anal. calcd for $C_{14}H_{18}O_4$: C, 67.16 H, 7.24; Found: C, 67.07 H, 7.16.

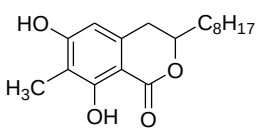
6,8-Dihydroxy-7-methyl-3-pentyl-3,4-dihydroisochromen-1-one (8h)



Yield = 75 %; Rf = 0.3; M.P.= 91-92 °C; IR (KBr) ν_{max}: 3458 (O-H), 3025 (C=C-H), 1717 (C=O), 1571 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ

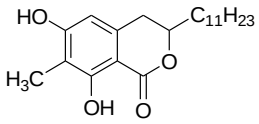
ppm): 7.13 (1H, s, H-5), 5.32-5.36 (1H, m, H-3), 4.71 (2H, s, -OH), 3.46 (1H, dd, J_{gem} = 16.2 Hz, J_{trans} = 12.4 Hz, H-4), 3.23 (1H, dd, J_{gem} = 16.2 Hz, J_{cis} = 3.8 Hz, H-4), 2.73 (3H, s, Ar-CH_3), 2.25 (2H, t, J = 6.1 Hz, H-1'), 1.33-1.86 (6H, m, H-2',H-3',H-4'), 0.92 (3H, t, J = 6.8 Hz, H-5'); ^{13}C NMR ($CDCl_3$, δ ppm): 165.4 (C=O), 148.2 (C-6), 147.6 (C-8), 142.3 (C-10), 140.5 (C-9), 128.6 (C-5), 118.4 (C-7), 81.5 (C-3), 43.4 (C-4), 38.7 (C-1'), 29.6 (Ar-CH_3), 19.2 (C-2'), 17.6 (C-3'), 14.8 (C-4'), 12.4 (C-5'); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 264 (61), 220 (21), 193 (18), 164 (100 %), 136 (24), 99 (66), 71 (18); Anal. calcd for $C_{15}H_{20}O_4$: C, 68.17 H, 7.58; Found: C, 68.08 H, 7.44.

6,8-Dihydroxy-7-methyl-3-octyl-3,4-dihydroisochromen-1-one (8i)



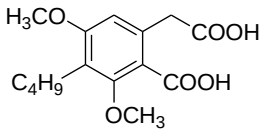
Yield = 77 %; Rf = 0.3; M.P.= 111-112 ºC; IR (KBr) ν_{max}: 3467 (O-H), 3026 (C=C-H), 1722 (C=O), 1576 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.16 (1H, s, H-5), 5.28-5.33 (1H, m, H-3), 4.64 (2H, s, -OH), 3.47 (1H, dd, J_{gem} = 16.2 Hz, J_{trans} = 12.4 Hz, H-4), 3.26 (1H, dd, J_{gem} = 16.2 Hz, J_{cis} = 3.8 Hz, H-4'), 2.64 (3H, s, Ar-CH_3), 2.23 (2H, t, J = 6.1 Hz, H-1'), 1.34-1.86 (12H, m, H-2',H-3',H-4',H-5',H-6',H-7'), 0.94 (3H, t, J = 5.8 Hz, H-8'); ^{13}C NMR ($CDCl_3$, δ ppm): 165.8 (C=O), 148.5 (C-6), 147.4 (C-8), 142.6 (C-10), 138.3 (C-9), 124.2 (C-7), 118.5 (C-5), 81.4 (C-3), 43.3 (C-4), 38.5 (C-1'), 29.3 (Ar-CH_3), 19.7 (C-2'), 14.5 (C-3'), 13.8 (C-4'), 13.2 (C-5'), 12.6 (C-6'), 11.7 (C-7'), 11.2 (C-8'); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 306 (42), 262 (26), 193 (13), 164 (100 %), 136 (15), 99 (35), 77 (16); Anal. calcd for $C_{18}H_{26}O_4$: C, 70.56 H, 8.54; Found: C, 70.38 H, 8.43.

6,8-Dihydroxy-7-methyl-3-undectyl-3,4-dihydroisochromen-1-one (8j)



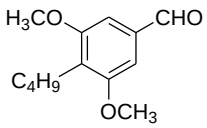
Yield = 78 %; Rf = 0.3; M.P.= 117-118 ºC; IR (KBr) ν_{max}: 3456 (O-H), 3028 (C=C-H), 1720 (C=O), 1583 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.17 (1H, s, H-5), 5.31-5.36 (1H, m, H-3), 4.72 (2H, s, -OH), 3.44 (1H, dd, J_{gem} = 16.2 Hz, J_{trans}= 12.2 Hz, H-4), 3.25 (1H, dd, J_{gem} = 16.2 Hz, J_{cis} = 3.6 Hz, H-4), 2.71 (3H, s, Ar-CH_3), 2.26 (2H, t, J = 6.1 Hz, H-1'), 1.32-1.87 (18H, m, H-2',H-3',H-4',H-5',H-6', H-7', H-8', H-9',H-10'), 0.92 (3H, t, J = 5.8 Hz, H-11'); ^{13}C NMR ($CDCl_3$, δ ppm): 165.6 (C=O), 148.3 (C-6), 147.5 (C-8), 142.4 (C-10), 138.7 (C-9), 124.5 (C-7), 119.2 (C-5), 81.6 (C-3), 43.5 (C-4), 38.7 (C-1'), 29.4 (Ar-CH_3), 19.6 (C-2'), 18.5 (C-3'), 14.8 (C-4'), 14.2 (C-5'), 13.6 (C-6'), 12.7 (C-7'), 12.1 (C-8'), 11.8 (C-9'), 11.3 (C-10'), 10.4 (C-11'); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 348 (55), 304 (31), 164 (100 %), 136 (45), 99 (38), 77 (14); Anal. calcd for $C_{21}H_{32}O_4$: C, 72.36 H, 9.25; Found: C, 72.28 H, 9.16.

3.1.9 Synthesis of 4-Butyl-3,5-dimethoxyhomophathalic acid (8)



4-Butyl-3,5-dimethoxybenzaldehyde (1)

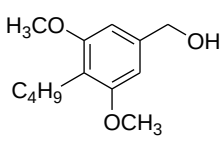
To a suspension of the freshly cut sodium metal (1.43 g, 61.98 mmol) in anhydrous THF (30 mL), a solution of 3,4,5-trimethoxy benzaldehyde dimethyl acetal (5 g, 20.66 mmol) in anhydrous THF (15 mL) was added under inert atmosphere. The reaction mixture was stirred at room temperature for 24 hr, then mixture was allowed to cool to 0 ^{o}C and butyl bromide (3.3 mL, 30.99 mmol) in THF was added slowly. The resulting mixture was stirred overnight. The reaction was quenched with slow dropwise addition of H_2O (20 mL) and then extracted with ether. The organic phase was washed with saturated aqueous $NaHCO_3$, dried and evaporated to get 4-butyl-3,5-dimethoxybenzaldehyde **(1)**. The residue was then purified by preparative thin layer chromatography using (petroleum ether and ethyl acetate, 7:3) as eluent.



Yield = 82 %; Rf = 0.5; M.P. = 47-48 ^{o}C; IR (KBr) ν_{max}: 2936 (C=C-H), 1734 (C=O), 1568 (C=C), 1056 (C-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 10.2 (1H, s, -CHO), 7.63 (2H, s, Ar), 3.87 (6H, s, -OCH_3), 2.78 (2H, t, *J* = 6 Hz, H-1'), 1.21-134 (4H, m, H-2',H-3'), 0.91 (3H, t, *J* = 6.2 Hz, H-4'); ^{13}C NMR ($CDCl_3$, δ ppm): 196.8 (aldehydic C=O), 138.7 (C-3,C-5), 136.4 (C-2,C-6), 128.3 (C-4), 117.6 (C-1), 62.8 (-OCH_3), 34.3 (C-1'), 31.2 (C-2'), 28.5 (C-3'), 23.6 (C-4′); Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.23; H, 8.15. Found: C, 70.17; H, 8.04.

4-Butyl-3,5-dimethoxybenzyl alcohol (2)

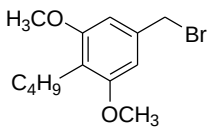
4-Butyl-3,5-dimethoxybenzaldehyde **(1)** (4.3 g, 19.3 mmol) and sodium borohydride (4.18 g, 116 mmol) were suspended in freshly distilled THF (120 mL). The reaction mixture was stirred for 15-20 min at 65 °C and then methanol (120 mL) was added drop wise over 30 min. The mixture was refluxed for 4 hr then cooled to room temperature and treated with saturated ammonium chloride solution (100 mL). Stirring was continued for 1 additional hr then acidified with dilute hydrochloric acid and extracted with ethyl acetate (3x25 mL). The extract was dried, evaporated and 4-butyl-3,5-dimethoxybenzyl alcohol **(2)** product was recryatallized with petroleum ether.



Yield = 74 %; Rf = 0.2; M.P. = 180-182 ^{o}C; IR (KBr) ν_{max}: 3342 (O-H), 2933 (C=C-H), 1575 (C=C), 1034 (C-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.41 (2H, s, Ar), 5.07 (1H, s, -OH), 3.68 (6H, s, -OCH_3), 2.81 (2H, t, *J* = 6 Hz, H-1'), 2.54 (2H, s, -CH_2), 1.23-136 (4H, m, H-2',H-3'), 0.93 (3H, t, *J* = 6.1 Hz, H-4'); ^{13}C NMR ($CDCl_3$, δ ppm): 138.6 (C-3,C-5), 136.4 (C-2,C-6), 127.3 (C-4), 117.6 (C-1), 63.7 (-OCH_3), 43.3 (-CH_2), 36.4 (C-1'), 34.6 (C-2'), 29.5 (C-3'), 23.7 (C-4′); Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.60; H, 8.97. Found: C, 69.47; H, 8.84.

4-Butyl-3,5-dimethoxybenzyl bromide (3)

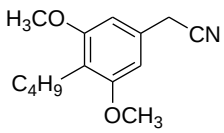
4-Butyl-3,5-dimethoxybenzyl alcohol **(2)** (4.1 g, 18 mmol) was dissolved in dry benzene (30-35 mL), the solution was treated with phosphorous tribromide (6.7 mL, 36 mmol) and the resulting mixture was stirred for 4 hr. Then poured the reaction mixture into ice cold water, separated the organic layer and evaporated to afford crude 4-butyl-3,5-dimethoxybenzyl bromide **(3)**.



Yield = 70 %; Rf = 0.6; oil; IR (KBr) ν_{max}: 2931 (C=C-H), 1581 (C=C), 1026 (C-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.32 (2H, s, Ar), 3.73 (6H, s, -OCH_3), 2.73 (2H, t, *J* = 5.8 Hz, H-1'), 2.57 (2H, s, -CH_2), 1.22-1.32 (4H, m, H-2',H-3'), 0.94 (3H, t, *J* = 6 Hz, H-4'); ^{13}C NMR ($CDCl_3$, δ ppm): 139.4 (C-3,C-5), 138.5 (C-2,C-6), 127.5 (C-4), 117.3 (C-1), 62.5 (-OCH_3), 43.2 (-CH_2), 36.5 (C-1'), 34.8 (C-2'), 29.7 (C-3'), 24.6 (C-4′); Anal. Calcd. for $C_{13}H_{19}BrO_2$: C, 54.36; H, 6.65. Found: C, 54.27; H, 6.56.

2-(4-Butyl-3,5-dimethoxyphenyl) acetonitrile (4)

4-Butyl-3,5-dimethoxybenzyl bromide **(3)** (4.0 g, 1.34 mmol) was dissolved in a mixture of ethyl alcohol (100 mL) and water (100 mL). Potassium cyanide (1.3 g, 1.91 mmol) was then added and the resulting mixture was refluxed for 4 hr. After completion, the reaction mixture was poured onto ice cold water and extracted with ethyl acetate (3x20 mL). The extract was dried over anhydrous Na_2SO_4, evaporated to afford the 2-(4-butyl-3,5-dimethoxyphenyl) acetonitrile **(4)** and recryatallized in petroleum ether.

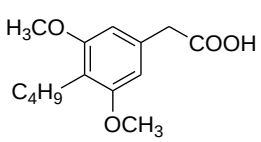


Yield = 68 %; Rf = 0.25; M.P. = 64-66 ^{o}C; IR (KBr) ν_{max}: 2933 (C=C-H), 2268 (-CN), 1576 (C=C), 1028 (C-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.29 (2H, s, Ar), 3.67 (6H, s, -OCH_3), 2.75 (2H, t, *J* = 5.8 Hz, H-1'), 2.63 (2H, s, -CH_2), 1.23-134 (4H, m, H-2',H-3'), 0.93 (3H, t, *J* = 6 Hz,

H-4'); ^{13}C NMR ($CDCl_3$, δ ppm): 138.7 (C-3,C-5), 134.6 (C-2,C-6), 129.5 (-CN), 128.3 (C-4), 117.6 (C-1), 63.4 (-OCH_3), 44.3 (-CH_2), 36.7 (C-1'), 34.5 (C-2'), 29.6 (C-3'), 23.8 (C-4′); Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.06; H, 8.20; N, 5.98. Found: C, 71.97; H, 8.13; N, 5.91.

2-(4-Butyl-3,5-dimethoxyphenyl) acetic acid (5)

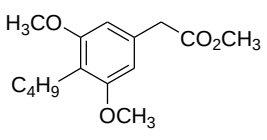
2-(4-Butyl-3,5-dimethoxyphenyl) acetonitrile **(4)** (3.8 g, 19.8 mmol) was dissolved in a mixture of water (15 mL) and dioxane (15 mL). Then potassium hydroxide (12.81 g in 12 mL of H_2O, 228 mmol) was added and the mixture was refluxed for 11-12 hr. After completion, the reaction mixture was poured onto ice cold water and extracted with ethyl acetate (25 mL). The extract was discarded and aqueous layer was acidified with dilute HCl. Precipitates were filtered out to afford 2-(4-butyl-3,5-dimethoxyphenyl) acetic acid **(5)**.



Yield = 73 %; Rf = 0.7; M.P.= 123-125^o C; IR (KBr) ν_{max}: 3284 (-OH), 2924 (C=C-H), 1711 (carboxylic C=O), 1575 (C=C), 1046 (C-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 11.32 (1H, s, -COOH), 7.36 (2H, s, Ar), 4.26 (2H, s, -CH_2), 3.67 (6H, s, -OCH_3), 2.79 (2H, t, *J* = 5.8 Hz, H-1'), 1.23-1.35 (4H, m, H-2',H-3'), 0.94 (3H, t, *J* = 6 Hz, H-4'); ^{13}C NMR ($CDCl_3$, δ ppm): 168.3 (carboxylic C=O), 138.6 (C-3,C-5), 136.4 (C-2,C-6), 127.5 (C-4), 118.6 (C-1), 62.6 (-OCH_3), 47.2 (-CH_2), 36.5 (C-1'), 34.7 (C-2'), 29.8 (C-3'), 24.7 (C-4′); Anal. Calcd. for $C_{14}H_{20}NO_4$: C, 66.64; H, 7.97. Found: C, 66.56; H, 7.86.

Methyl 2-(4-Butyl-3,5-dimethoxyphenyl) acetate (5')

2-(4-Butyl-3,5-dimethoxyphenyl) acetic acid **(5)** (3.5 g, 13.8 mmol) in dry methanol (20 mL), was treated with of conc. H_2SO_4 (3 mL) drop wise. The reaction mixture was refluxed for 7-8 hr. After completion, the reaction mixture was concentrated to 55 mL and then extracted with ethyl acetate (3x30 mL). The extract was washed with saturated brine, dried and concentrated to give crude oil which was distilled to afford methyl 2-(4-butyl-3,5-dimethoxyphenyl) acetate **(5')**.

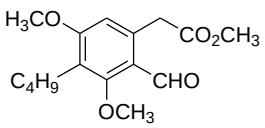


Yield = 81 %; Rf = 0.8; oil ; IR (KBr) ν_{max}: 2926 (C=C-H), 1732 (C=O), 1587 (C=C), 1053 (C-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.76 (2H, s, Ar), 4.28 (2H, s, -CH_2), 3.67 (6H, s, -OCH_3), 2.75 (2H, t, *J* = 5.8 Hz, H-1'), 1.21-1.35 (4H, m, H-2',H-3'), 0.93 (3H, t, *J* = 6 Hz, H-4'), 3.63

(3H, s, -OCH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 164.5 (ester C=O), 136.7 (C-3,C-5), 134.5 (C-2,C-6), 126.3 (C-4), 116.6 (C-1), 61.7 (ester OCH_3), 57.4 (-OCH_3), 44.5 (-CH_2), 36.6 (C-1'), 34.3 (C-2'), 29.4 (C-3'), 24.5 (C-4'); Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.32. Found: C, 67.57; H, 8.26.

Methyl 4-butyl-2-formyl-3,5-dimethoxyphenyl acetate (6)

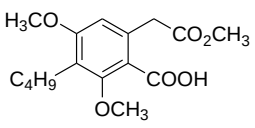
Phosphorous oxychloride (1.24 mL, 11.3 mmol) was added drop wise in to a stirred solution of methyl 2-(4-butyl-3,5-dimethoxyphenyl) acetate **(5')** (3.0 g, 11.3 mmol) in dry DMF (15 mL) at 55 °C. Reaction mixture was heated at about 100 °C for 2 hr and stirred overnight at room temperature. Then poured the reaction mixture into aqueous solution of sodium acetate (10 %, 10 mL) and shake vigorously methyl 4-butyl-2-formyl-3,5-dimethoxyphenyl acetate **(6)** was precipitated out.



Yield = 72 %; Rf = 0.3; M.P. = -; IR (KBr) ν_{max}: 2932 (C=C-H), 1724 (ester C=O), 1686 (aldehyde C=O), 1577 (C=C), 1052 (C-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 9.83 (1H, s, -CHO), 7.87 (1H, s, Ar), 4.32 (2H, s, -CH_2), 3.83 (3H, s, -OCH_3), 3.54 (3H, s, -OCH_3), 3.26 (3H, s, -(ester OCH_3), 2.78 (2H, t, *J* = 5.8 Hz, H-1'), 1.25-1.36 (4H, m, H-2',H-3'), 0.93 (3H, t, *J* = 6.0 Hz, H-4'); ^{13}C NMR ($CDCl_3$, δ ppm): 179.5 (aldehyde C=O), 163.4 (ester C=O), 136.7 (C-3,C-5), 133.5 (C-2), 127.2 (C-6), 121.6 (C-4), 117.5 (C-1), 63.4 (-$COCH_3$), 57.3 (Ar-OCH_3), 43.2 (Ar-CH_2), 36.3 (C-1'), 34.7 (C-2'), 29.5 (C-3'), 23.9 (C-4′); Anal. Calcd. for $C_{16}H_{22}O_5$: C, 65.28; H, 7.52. Found: C, 65.17; H, 7.46.

Methyl 4-butyl 2-carboxy-3,5-dimethoxyphenyl acetate (7)

Methyl 4-butyl-2-formyl-3,5-dimethoxyphenyl acetate **(6)** (2 g, 6.802 mmol) and sulfamic acid (2.24 g, 23.13 mmol) in 30 mL H_2O:THF:DMSO (20:10:1) at 0 °C was treated with $NaClO_2$ (1.99 g, 22.01 mmol) in 5 mL H_2O. The reaction mixture was stirred for 20 min at 0 °C and then diluted with ethyl acetate (100 mL), washed with saturated aqueous ammonium chloride (2x30 mL) and saturated aqueous sodium chloride (30 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to afford methyl 4-butyl 2-carboxy-3,5-dimethoxyphenyl acetate **(7)**.

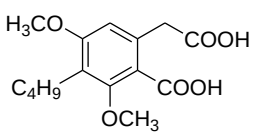


Yield = 67 %; Rf = 0.35; oil; IR (KBr) ν_{max}: 3276 (O-H), 2935 (C=C-H), 1731 (ester C=O), 1716 (carboxylic C=O), 1564 (C=C), 1046 (C-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 8.76 (1H, s, -COOH),

7.56 (1H, s, Ar-H-6), 4.34 (2H, s, Ar-CH_2), 3.84 (3H, s, -OCH_3), 3.66 (3H, s, -OCH_3), 3.63 (3H, s, (ester OCH_3), 2.81 (2H, t, *J* = 6 Hz, H-1'), 1.24-1.38 (4H, m, H-2',H-3'), 0.94 (3H, t, *J* = 6.1 Hz, H-4'); ^{13}C NMR ($CDCl_3$, δ ppm): 198.4 (carboxylic C=O), 163.6 (ester C=O), 140.3 (C-3,C-5), 136.7 (C-2), 127.13 (C-6), 121.6 (C-4), 117.4 (C-1), 64.4 (ester OCH_3), 57.5 (Ar-OCH_3), 43.2 (Ar-CH_2), 36.3 (C-1'), 34.7 (C-2'), 29.6 (C-3'), 23.5 (C-4′); Anal. Calcd. for $C_{16}H_{22}O_6$: C, 61.91; H, 7.13. Found: C, 61.83; H, 7.07.

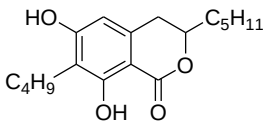
4-Butyl-3,5-dimethoxyhomophthalic acid (8)

Methyl 4-butyl-2-carboxy-3,5-dimethoxyphenyl acetate **(7)** (1.5 g, 4.84 mmol) was dissolved in ethanol (15 mL) and treated with KOH (5 %, 10 mL). The reaction mixture was refluxed for 1-2 hr and the ethanol was rotary evaporated. The aqueous layer was acidified with dilute hydrochloric acid to afford 4-butyl-3,5-dimethoxyhomophthalic acid **(8)**.



Yield = 76 %; Rf = 0.3; (semi-solid), M.P. = 123-125 °C; IR (KBr) ν_{max}: 3226 (O-H), 2937 (C=C-H), 1737 (carboxylic C=O), 1718 (carboxylic CH_2-C=O), 1586 (C=C), 1044 (C-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 11.21 (1H, s, -COOH), 10.91 (1H, s, -CH_2-COOH), 7.64 (1H, s, H-6), 4.37 (2H, s, -CH_2), 3.76 (3H, s, -OCH_3), 3.67 (3H, s, -OCH_3), 2.84 (2H, t, *J* = 6.1 Hz, H-1'), 2.73 (3H, s, -CH_3), 1.21-1.37 (4H, m, H-2',H-3'), 0.92 (3H, t, *J* = 6.2 Hz, H-4'); ^{13}C NMR ($CDCl_3$, δ ppm): 204.6 (carboxylic -C=O), 171.5 (carboxylic -CH_2-C=O), 137.5 (C-3), 136.7 (C-5), 135.2 (C-2), 133.7 (C-6), 125.4 (C-4), 124.3 (C-1), 55.6 (3-OCH_3), 55.3 (5-OCH_3), 43.4 (Ar-CH_2), 34.6 (C-1'), 32.4 (C-2'), 28.5 (C-3'), 24.3 (C-4′); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 296 (57), 219 (64), 251 (54), 207 (32), 177 (16), 147 (100 %), 91 (18), 77 (11); Anal. Calcd. for $C_{15}H_{20}O_6$: C, 60.80; H, 6.78. Found: C, 60.63; H, 6.65.

3.1.10 Total synthesis of (±) 7-Butyl-6,8-hydroxy-3-pentyl-3,4-dihydroisochromen-1-one. (10a-e)

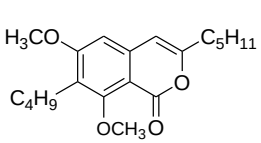


Procedure

4-Butyl-3,5-dimethoxyhomophthalic acid **(8)** (0.5 g, 1.96 mmol) and hexanoyl chloride (1.14 mL, 8.29 mmol) were heated under reflux at an internal temperature of 200 °C for 3 hr. After the completion of reaction, the cooling bath was removed and

allowed it to cool. The reaction mixture was concentrated and then extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution and then dried over anhydrous (Na_2SO_4) to get 7-butyl-6,8-dimethoxy-3-pentylisochromen-1-one **(a)**, was then purified by preparative thin layer chromatography using (petroleum ether and ethyl acetate, 7:3) as eluent.

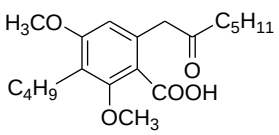
7-Butyl-6,8-dimethoxy-3-pentyl-isochromen-1-one (a)



Yield = 75 %; Rf = 0.7; M.P. = 195-196 ^oC; IR (KBr) ν_{max}: 3027 (C=C-H), 2956 (C-H), 1725 (C=O), 1577 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.04 (1H, s, Ar-H-5), 6.53 (1H, s, H-4), 3.76 (3H, s, $-OCH_3$), 3.72 (3H, s, $-OCH_3$), 2.54 (2H, t, *J* = 7.2 Hz, H-1''), 2.38 (2H, t, *J* = 7.4 Hz, H-1'), 1.43-1.61 (10H, m, H-2',H-3',H-4',H-2'',H-3''), 0.92 (3H, t, *J* = 7.2 Hz, H-4''), 0.87 (3H, t, *J* = 6.8 Hz, H-5'); ^{13}C NMR ($CDCl_3$, δ ppm): 164.3 (C=O), 150.3 (C-3), 146.5 (C-6), 147.5 (C-8), 136.4 (C-10), 127.8 (C-9), 116.5 (C-7), 108.3 (C-4), 104.6 (C-5), 56.7 (Ar-OCH_3), 56.4 (Ar-OCH_3), 36.7 (C-1''), 34.5 (C-1''), 24.1 (C-2'), 23.6 (C-2''), 17.8 (C-3'), 15.4 (C-4'), 13.5 (C-3''), 11.7 (C-4''); 11.2 (C-5'); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 332 (37), 304 (41), 275 (19), 261 (62), 234 (100 %), 218 (33), 206 (26), 157 (18); Anal. Calcd. for $C_{20}H_{28}O_4$: C, 72.28; H, 8.43. Found: C, 72.14; H, 8.36.

3-Butyl-2,4-dimethoxy-6-(2-oxoheptyl)benzoic acid (b)

To the stirred solution of 7-butyl-6,8-dimethoxy-3-pentylisocoumarin **(a)** (0.35 g, 1.05 mmol) in ethanol (7-8 mL) was treated with 5 % KOH (15 mL) and the mixture was refluxed for 4 hr. After cooling the reaction mixture, the ethanol was evaporated under reduced pressure. Cold water (20 mL) was added and then mixture was acidified with dilute hydrochloric acid till solid was precipitated. Filtration followed by drying under vacuum afforded 3-butyl-2,4-dimethoxy-6-(2-oxoheptyl) benzoic acid **(b)**.

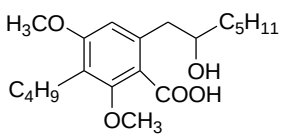


Yield = 72 %; Rf = 0.5; sticky solid ; IR (KBr) ν_{max}: 3342 (O-H), 3023 (C=C-H), 2952 (C-H), 1734 (carboxylic C=O), 1712 (ketonic C=O), 1584 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 10.3 (1H, s, -COOH), 7.86 (1H, s, H-5), 4.45 (2H, s, $-CH_2$), 3.78 (3H, s, $-OCH_3$), 3.74 (3H, s, $-OCH_3$), 3.69 (2H, t, *J* = 3.7 Hz, H-3'), 3.26 (3H, s, Ar-CH_3), 2.56 (2H, t, *J* = 7.2 Hz, H-1''), 2.36 (2H, t, *J* = 7.4 Hz, H-1'), 1.53-1.66 (10H, m, H-2',H-3',H-4',H-2'',H-3''), 0.93 (3H, t, *J* = 7.2 Hz, H-4''), 0.89 (3H, t, *J* = 6.8 Hz, H-5'); ^{13}C NMR ($CDCl_3$, δ ppm): 197.3 (ketonic C=O), 168.2 (carboxylic C=O), 144.6 (C-2), 138.5 (C-4), 136.2 (C-1),

128.7 (C-6), 120.3 (C-3), 106.4 (C-5), 61.5 (Ar-OCH_3), 58.4 (Ar-OCH_3), 47.7 (C-1'), 44.5 (C-3'), 29.4 (Ar-CH_3), 23.4 (C-1''), 22.7 (C-4'), 21.6 (C-2''), 18.5 (C-5'), 15.8 (C-3''), 13.7 (C-6'), 11.6 (C-4''), 10.2 (C-7'); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 350 (31), 306 (37), 279 (42), 251 (56), 235 (17), 191 (100 %), 91 (25); Anal. Calcd. for $C_{20}H_{30}O_5$: C, 68.57; H, 8.57. Found: C, 68.47; H, 8.41.

3-Butyl-6-(2-hydroxyheptyl)-2,4-dimethoxy benzoic acid (c)

Sodium borohydride (0.13 g, 3.43 mmol) was added portion wise to a stirred solution of 3-butyl-2,4-dimethoxy-6-(2-oxoheptyl) benzoic acid **(10b)** (0.2 g, 0.573 mmol) in absolute ethanol (15 mL). The reaction mixture was stirred for 2 hr at room temperature, diluted with water (50 mL), acidified with conc. HCl and stirred for 2 additional hr. It was then saturated with ammonium sulfate, and extracted with ethyl acetate (3x30 mL). The organic layer dried over anhydrous magnesium sulfate and concentrated to afford 3-butyl -6-(2-hydroxyheptyl)-2,4-dimethoxy benzoic acid **(c)**.

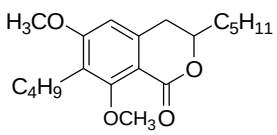


Yield = 74 %; Rf = 0.4; M.P. = (semi-solid); IR (KBr) ν_{max}: 3453 (O-H), 3026 (C=C-H), 2914 (C-H), 1726 (carboxylic C=O), 1581 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 10.7 (1H, s, -COOH), 7.88 (1H, s, H-5), 4.46-4.55 (2H, m, -CH_2), 4.43 (1H, s, -OH), 3.78 (3H, s, -OCH_3), 3.76 (3H, s, -OCH_3), 3.71 (2H, t, *J* = 3.7 Hz, H-3'), 3.32 (3H, s, Ar-CH_3), 2.62 (2H, t, *J* = 7.2 Hz, H-1''), 2.43 (2H, t, *J* = 7.4 Hz, H-1'), 1.57-1.71 (10H, m, H-2',H-3',H-4',H-2'',H-3''), 0.95 (3H, t, *J* = 7.1 Hz, H-4''), 0.91 (3H, t, *J* = 6.7 Hz, H-5'); ^{13}C NMR ($CDCl_3$, δ ppm): 171.6 (carboxylic C=O), 146.2 (C-2), 145.8 (C-4), 142.3 (C-6), 112.3 (C-1), 110.6 (C-3), 108.4 (C-5), 86.7 (C-OH), 64.7 (Ar-OCH_3), 64.3 (Ar-OCH_3), 48.5 (-CH_2), 38.6 (C-1'), 36.4 (C-1''), 23.8 (C-2'), 23.2 (C-2''), 18.7 (C-3'), 15.6 (C-4'), 13.2 (C-3''), 12.8 (C-4''), 12.4 (C-5'); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 352 (25), 335 (44), 307 (32), 291 (100 %), 251 (22), 193 (13), 133 (10); Anal. Calcd. for $C_{20}H_{32}O_5$: C, 68.15; H, 9.16. Found: C, 68.10; H, 9.08.

7-Butyl-6,8-dimethoxy-3-pentyl-3,4-dihydroisochromen-1-one (d)

3-Butyl-6-(2-hydroxyheptyl)-2,4-dimethoxy benzoic acid **(c)** (0.14 g, 0.41 mmol) was dissolved in acetic anhydride (4 mL) and the reaction mixture was refluxed for 3 hr. Then poured it into chilled water and it was extracted with ethyl acetate (2x20 mL). Organic layer was washed with 1 % $NaHCO_3$ and water. The organic layer was dried

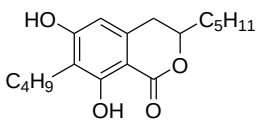
with Na_2SO_4 and concentrate to get 7-butyl-6,8-dimethoxy-3-pentyl-3,4-dihydroiso-coumarin **(d)**.



Yield = 68 %; Rf = 0.7; yellow oil; IR (KBr) ν_{max}: 3037 (C=C-H), 2943 (C-H), 1721 (C=O), 1586 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.61 (1H, s, Ar-H-5), 5.46-5.57 (1H, m, H-3), 3.87 (3H, s, $-OCH_3$), 3.83 (3H, s, $-OCH_3$), 3.32 (1H, dd, J_{gem} = 16.1 Hz, J_{trans} = 12.8 Hz, H-4), 3.12 (1H, dd, J_{gem} = 16.2, Hz, J_{cis} = 3.6 Hz, H-4'), 2.64 (2H, t, J = 7.1 Hz, H-1''), 2.53 (2H, t, J = 7.4 Hz, H-1'), 1.52-1.67 (10H, m, H-2',H-3',H-4',H-2'',H-3''), 0.94 (3H, t, J = 7.2 Hz, H-4''), 0.89 (3H, t, J = 6.8 Hz, H-5'); ^{13}C NMR ($CDCl_3$, δ ppm): 168.4 (C=O), 148.7 (C-6), 147.8 (C-8), 144.5 (C-10), 140.2 (C-9), 128.6 (C-5), 122.3 (C-7), 87.5 (C-3), 63.4 (Ar-OCH_3), 62.6 (Ar-OCH_3), 46.4 (C-4), 38.3 (C-1'), 36.2 (C-1''), 23.4 (C-2'), 22.7 (C-2''), 18.4 (C-3'), 15.2 (C-4'), 13.3 (C-3''), 11.6 (C-4''), 11.3 (C-5'); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 334 (37), 306 (53), 290 (28), 263 (28), 234 (100 %), 218 (27), 206 (36), 194 (46), 165 (21), 109 (18); Anal. Calcd. for $C_{20}H_{30}O_4$: C, 71.85; H, 9.04. Found: C, 71.73; H, 8.97.

7-Butyl-6,8-hydroxy-3-pentyl-3,4-dihydroisochromen-1-one. (e)

7-Butyl-6,8-dimethoxy-3-pentyl-3,4-dihydroisochromen-1-one **(d)** (1.25 mmol) was dissolved in ethanethiol (3.5 mL) and solution was cooled on ice. Aluminium chloride (3.8 mmol) was added in 3 portions during an interval of 30 min. After the addition of aluminium chloride, the reaction mixture was stirred on ice for 1 hr. Then the reaction was quenched with 10 % $NaHCO_3$ and extracted with ethyl acetate, sodium chloride was added to enhance the layer separation. The combined organic layers were washed once with brine, dried over sodium sulfate and concentrated to give 7-butyl-6,8-hydroxy-3-pentyl-3,4-dihydroisochromen-1-one. **(e)**

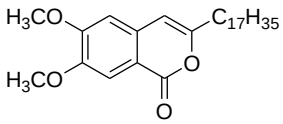


Yield = 57 %; Rf = 0.3; oil; IR (KBr) ν_{max}: 3421 (O-H), 3046 (C=C-H), 2954 (C-H), 1724 (C=O), 1587 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.67 (1H, s, Ar-H-5), 5.63 (1H, m, H-3), 4.84 (2H, s, -OH), 3.42 (1H, dd, J_{gem} = 16.1 Hz, J_{trans} = 12.7 Hz, H-4), 3.28 (1H, dd, J_{gem} = 16.1, Hz, J_{cis} = 3.8 Hz, H-4'), 2.71 (2H, t, J = 7.1 Hz, H-1''), 2.53 (2H, t, J = 7.3 Hz, H-1'), 1.66-1.76 (10H, m, H-2',H-3',H-4',H-2'',H-3''), 0.97 (3H, t, J = 7.1 Hz, H-4''), 0.94 (3H, t, J = 6.7 Hz, H-5'); ^{13}C NMR ($CDCl_3$, δ ppm): 169.6 (C=O), 160.7 (C-6), 160.2 (C-8), 142.5 (C-10), 140.7 (C-9), 128.3 (C-5), 123.5 (C-7), 88.4 (C-3), 47.6 (C-4), 40.3 (C-1'), 37.2 (C-1''), 31.4 (C-2'), 30.8 (C-2''), 23.5 (C-3'), 22.6 (C-4'), 19.5 (C-3''), 14.7

(C-4''), 14.4 (C-5'); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 306 (57), 278 (35), 262 (26), 235 (67), 206 (100 %), 189 (43), 173 (44), 146 (34), 134 (23), 77 (17); Anal. Calcd. for $C_{18}H_{26}O_4$: C, 70.55; H, 8.54. Found: C, 70.43; H, 8.47.

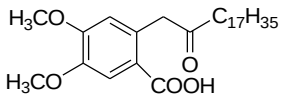
3.1.11 Synthesis of (±) 3-heptadecyl-6,7-dimethoxy-3,4-dihydroisochromen-1-one (11a-d)

3-Heptadecyl-6,7-dimethoxy-1H-isochromen-1-one (a)



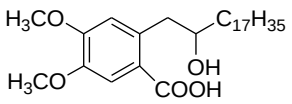
Yield = 75 %; Rf = 0.65; M.P. = 45-48 ^{o}C; IR (KBr) ν_{max}: 3043 (C=C-H), 2924 (C-H), 1715 (C=O), 1573 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.78 (1H, s, H-8), 7.63 (1H, s, H-5), 6.23 (1H, s, H-4), 3.78 (3H, s, -OCH_3), 3.76 (3H, s, -OCH_3), 2.42 (2H, t, *J* = 5.6 Hz, H-1'), 1.22-1.65 (30H, m, H-2',H-3',H-4',H-5',H-6',H-7',H-8',H-9',H-10',H-11',H-12',H-13',H-14',H-15',H-16'), 0.94 (3H, t, *J* = 5.8 Hz, H-17'); ^{13}C NMR ($CDCl_3$, δ ppm): 166.7 (C=O), 150.4 (C-6,C-7), 146.5 (C-3), 137.4 (C-10), 134.8 (C-9), 123.5 (C-8), 121.7 (C-5), 112.6 (C-4), 56.8 (-OCH_3), 36.4 (C-1'), 35.8 (C-2'), 33.6 (C-3'), 33.4 (C-4'), 31.7 (C-5'), 29.5 (C-6'), 29.6 (C-7'), 27.4 (C-8'), 24.1 (C-9'), 22.6 (C-10'), 19.2 (C-11'), 17.3 (C-12'), 14.7 (C-13'), 13.5 (C-14'), 12.6 (C-15'), 11.3 (C-16'), 10.4 (C-17'); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 444 (52), 400 (23), 205(27), 177 (100 %), 161 (45), 149 (26), 101 (31); Anal. Calcd. for $C_{28}H_{44}O_4$: C, 75.67; H, 9.91. Found: C, 75.48; H, 9.85.

4,5-Dimethoxy-2-(2-oxononadecyl)benzoic acid (b)



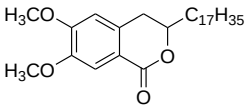
Yield = 73 %; Rf = 0.5; M.P. = 58-59 ^{o}C; IR (KBr) ν_{max}: 3433 (-OH), 3025 (C=C-H), 2947 (C-H), 1726 (carboxylic C=O), 1714 (ketonic C=O), 1567 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 10.26 (1H, s, COOH), 8.11 (1H, s, Ar-H-2), 7.67 (1H, s, Ar-H-5), 4.33 (2H, s, -CH_2), 3.84 (3H, s, -OCH_3), 3.78 (3H, s, -OCH_3), 2.53 (2H, t, *J* = 5.5 Hz, H-1'), 123-1.68 (30H, m, H-2',H-3',H-4',H-5',H-6',H-7',H-8',H-9',H-10',H-11',H-12',H-13',H-14',H-15',H-16'), 0.93 (3H, t, *J* = 5.7 Hz, H-17'); ^{13}C NMR ($CDCl_3$, δ ppm): 197.4 (ketone C=O), 168.5 (carboxylic C=O), 144.6 (C-3), 137.4 (C-4), 136.6 (C-1), 127.5 (C-3), 121.4 (C-6), 106.7 (C-5), 60.5 (Ar-OCH_3), 58.6 (Ar-OCH_3), 43.6 (-CH_2), 36.8 (C-1'), 35.4 (C-2'), 33.6 (C-3'), 32.5 (C-4'), 31.2 (C-5'), 29.4 (C-6'), 28.5 (C-7'), 26.3 (C-8'), 22.8 (C-9'), 21.7 (C-10'), 19.2 (C-11'), 17.4 (C-12'), 14.3 (C-13'), 13.5 (C-14'), 12.7 (C-15'), 11.8 (C-16'), 11.2 (C-17'); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 462 (62), 418 (31), 179 (100 %), 151 (42), 91 (36), 77 (24); Anal. Calcd. for $C_{28}H_{46}O_5$: C, 72.68; H, 10.02. Found: C, 72.53; H, 9.96.

2-(2-Hydroxynonadecyl)-4,5-dimethoxybenzoic acid (c)



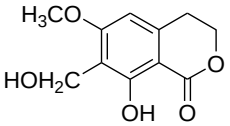
Yield = 77 %; Rf = 0.3; M.P. = 156-158 ^{o}C; IR (KBr) ν_{max}: 3446 (-OH), 3031 (C=C-H), 2954 (C-H), 1722 (carboxylic C=O), 1587 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm):10.85 (1H, s, -COOH), 8.23 (1H, s, Ar-H-2), 7.97 (1H, s, Ar-H-4), 5-26-5.43 (1H, m, H-2'), 3.52 (1H, dd, J_{gem} = 15.1 Hz, J_{trans} = 12 Hz , H-1'), 3.24 (1H, dd, J_{gem} = 16. 2 Hz , J_{cis} = 3.6 Hz, H-1''), 2.28 (3H, t, J = 5.6 Hz, H-3'), 137-1.76 (30H, m, H-4'-18'), 0.96 (3H, t, J = 5.6 Hz, H-19'), 4.41(1H, s, -OH), 3.87 (3H, s, 3-OCH_3), 3.84 (3H, s, 4-OCH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 176.4 (carboxylic C=O), 77.5 (C-OH), 128.6 (C-1), 137.5 (C-2), 119.3 (C-3), 158.5 (C-4), 152.4 (C-5), 123.6 (C-6), 66.2 (-OCH_3), 65.7 (-OCH_3), 42.4 (-CH_2), 37.1 (C-1'), 36.5 (C-2'), 35.6 (C-3'), 34.3 (C-4'), 32.5 (C-5'), 30.7 (C-6'), 29.4 (C-7'), 27.5 (C-8'), 23.6 (C-9'), 22.3 (C-10'), 21.2 (C-11'), 19.4 (C-12'), 16.6 (C-13'), 14.7 (C-14'), 14.2 (C-15'), 13.8 (C-16'), 13.4 (C-17'); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 464 (56), 447 (41), 420 (27), 403 (100 %), 151 (31), 91 (24), 77 (15); Anal. Calcd. for $C_{28}H_{48}O_5$: C, 72.37; H, 10.41. Found: C, 72.28; H, 10.32.

3-Heptadecyl-6,7-dimethoxy-3,4-dihydroisochromen-1-one (d)



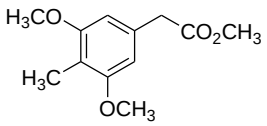
Yield = 71 %; Rf = 0.6; M.P. = 214-216 ^{o}C; IR (KBr) ν_{max}: 3037 (C=C-H), 2925 (C-H), 1718 (C=O), 1576 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.74 (1H, s, H-8), 7.56 (1H, s, H-5), 5-21-5.34 (1H, m, H-3), 3.76 (6H, s, -OCH_3), 3.46 (1H, dd, J_{gem} = 15.1 Hz, J_{trans} = 12 Hz , H-4), 3.21 (1H, dd, J_{gem} = 16. 2 Hz , J_{cis} = 3.6 Hz, H-4'), 2.44 (2H, t, J = 5.6 Hz, H-1'), 1.16-1.67 (30H, m, H-2'-16'), 0.94 (3H, t, J = 5.8 Hz, H-17'); ^{13}C NMR ($CDCl_3$, δ ppm): 167.4 (C=O), 151.6 (C-6), 151.2 (C-7), 137.5 (C-10), 134.4 (C-9), 123.5 (C-8), 121.3 (C-5), 82.7 (C-3), 56.8 (-OCH_3), 45.2 (C-4), 36.7 (C-1'), 35.3 (C-2'), 33.7 (C-3'), 33.1 (C-4'), 31.4 (C-5'), 29.8 (C-6'), 29.2 (C-7'), 26.5 (C-8'), 23.7 (C-9'), 22.5 (C-10'), 19.3 (C-11'), 17.5 (C-12'), 14.6 (C-13'), 13.2 (C-14'), 12.4 (C-15'), 11.2 (C-16'), 10.6 (C-17'); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 446 (47), 402 (28), 207 (31), 178 (100 %), 163 (36), 151 (23), 103 (13); Anal. Calcd. for $C_{28}H_{46}O_4$: C, 75.34; H, 10.31. Found: C, 75.27; H, 10.25.

3.1.12 Total synthesis of 8-Hydroxy-7-(hydroxymethyl)-6-methoxy-3,4-dihydroisochromen-1-one (*Stellatin)* (1-8).



Methyl (3,5-dimethoxy-4-methylphenyl) acetate (1')

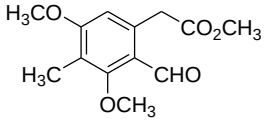
Stirred solution of 3,5-dimethoxy-4-methylphenylacetic acid **(1)** (5.0 g, 23.8 mmol) in dry methanol (30 mL) was treated with conc. H_2SO_4 (5 mL) dropwise. The mixture was refluxed for 8-9 hr. After completion, the reaction mixture was concentrated to 55 mL and extracted with ethyl acetate (3×50 mL). The extract was washed with saturated brine, dried, and concentrated to give crude oil that was distilled to afford methyl ester **(1')**.



Yield = 88 %; Rf = 0.7; M.P.= 38-40 ^oC; IR (KBr): ν_{max}: 3026 (C=C-H), 2935 (C-H), 1732 (C=O), 1572 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.45 (2H, s, H-2,H-6), 3.96 (6H, s, $-OCH_3$), 3.54 (2H, s, Ar-CH_2), 3.47 (3H, s, ester OCH_3), 2.55 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.2 (C=O), 132.5 (C-3,C-5), 128.3 (C-2,C-6), 119.4(C-4), 112.2 (C-1), 68.5 (ester OCH_3), 55.3 (Ar-OCH_3), 36.9 ($-CH_2$), 28.6 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 224 (46), 193 (43), 165 (100 %), 59 (12); Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.28; H, 7.14; Found: C, 64.18; H, 7.06.

Methyl (2-formyl-3,5-dimethoxy-4-methyl phenyl) acetate (2)

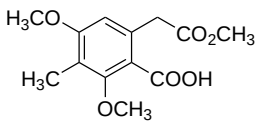
Phosphorous oxychloride (1.61 g, 10 mmol) was added dropwise, to a stirred solution of methyl (3,5-dimethoxy-4-methyl phenyl) acetate (2.0 g, 8.9 mmol) in freshly distilled DMF (10 mL) at 55 °C. Reaction mixture was heated at about, 100 °C for 2 hr and then stirred it overnight at room temperature. The reaction mixture was poured into the aqueous solution of sodium acetate (10 %, 10 mL) and shaked vigorously. Methyl (2-formyl-3,5-dimethoxy-4-methylphenyl) acetate **(2)** was precipitated out as yellowish precipitates.



Yield = 84 %; Rf = 0.55; M.P.= 51-53 ^oC; IR (KBr): ν_{max}: 3027 (C-H), 1721 (C=O), 1692 (-CHO), 1575 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 9.75 (1H, s,-CHO), 7.96 (1H, s, H-6), 3.62 (3H, s, $-OCH_3$), 3.65 (3H, s, $-OCH_3$), 3.11 (3H, s, ester OCH_3), 2.92 (2H, s, Ar-CH_2), 2.80 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 179.3 (aldehyde C=O), 162.4 (ester C=O), 136.7 (C-3,C-5), 131.9 (C-2), 126.2 (C-6), 121.3 (C-4), 117.5 (C-1), 61.6 (ester OCH_3), 57.3 (Ar-OCH_3), 57.1 (Ar-OCH_3), 39.1 (Ar-CH_2), 32.0 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 252 (25), 251 (65), 224 (49), 223 (34), 165 (100 %), 29 (31); Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.90; H, 6.34; Found: C, 61.77; H, 6.26.

2,4-Dimethoxy-6-(2-methoxy-2-oxoethyl)-3-methylbenzoic acid (3)

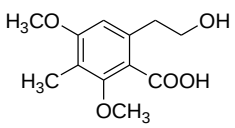
Formyl ester **(2)** (6.3 g, 25 mmol) and sulfamic acid (8.3 g, 86 mmol) in 150 mL H_2O: THF: DMSO (20:10:1) at 0 ^oC were treated with $NaClO_2$ (7.24 g, 80 mmol) in 20 mL H_2O. The reaction mixture was stirred for 20 min at 0 ^oC and then diluted with ethyl acetate (100 mL), washed with saturated aqueous ammonium chloride (2×15 mL), and saturated aqueous sodium chloride (130 mL). Organic layer was dried over anhydrous sodium sulfate and evaporated to afford the keto acid **(3)**.



Yield = 78 %; Rf = 0.4; M.P.= 164-166 ^oC; IR (KBr): ν_{max}: 3267 (O-H), 3036 (C=C-H), 1733 (C=O), 1716 (-COOH), 1571 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 8.19 (1H, s, COOH), 7.66 (1H, s, H-6), 3.82 (3H, s, $-OCH_3$), 3.77 (3H, s, $-OCH_3$), 3.63 (3H, s, ester OCH_3), 2.54 (2H, s, Ar-CH_2), 2.25 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 197.8 (carboxylic C=O), 168.5 (ester C=O), 139.3 (C-2,C-4), 134.3 (C-6), 127.1 (C-5), 120.6 (C-3), 114.1 (C-1), 66.1 (ester -OCH_3), 55.4 (Ar-OCH_3), 55.2 (Ar-OCH_3), 35.0 (Ar-CH_2), 29.8 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 268 (32), 251 (51), 224 (65), 165 (100 %), 45 (25); Anal. Calcd. for $C_{13}H_{16}O_6$: C, 58.20; H,5.97; Found: C, 58.14; H, 5.86.

2,4-Dimethoxy-6-(2-hydroxyethyl)-3-methylbenzoic acid (4)

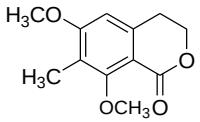
Keto acid derivative **(3)** (0.5 g, 1.86 mmol) and sodium borohydride (0.84 g, 22.32 mmol) were suspended in freshly distilled THF (10 mL). The reaction mixture was stirred for 15 min at 65 ^oC and then methanol (10 mL) was added dropwise for 30 min. The mixture was refluxed for 4 hr, then cooled to room temperature, and treated with saturated ammonium chloride solution (10 mL). Stirring was continued for 1 hr, then acidified with dilute hydrochloric acid, and extracted with ethyl acetate (3×20 mL). The extract was dried, evaporated to afford hydroxyl acid **(4)**.



Yield = 77 %; Rf = 0.3; M.P.= 72-74 ^oC; IR (KBr): ν_{max}: 3486 (O-H), 3028 (C=C-H), 2933 (C-H), 1711 (C=O), 1573 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 8.22 (1H, s, -COOH), 7.48 (1H, s, H-5), 4.21 (2H, t, *J* = 3.8 Hz, $-CH_2OH$), 3.90 (3H, s, $-OCH_3$), 3.75 (3H, s, $-OCH_3$), 2.65 (2H, t, *J* = 3.8 Hz, Ar-CH_2), 2.51 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 190.5 (-C=O), 166.2 (C-2), 162.4 (C-4), 141.3 (C-6), 108.1 (C-3), 105.6 (C-1), 101.2 (C-5), 63.2 (C-20), 56.5 (Ar-OCH_3), 56.3 (Ar-OCH_3), 32.3 (C-10), 28.8 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 240 (32), 223 (24), 196 (43), 165 (100 %), 45 (19), 31 (37); Anal. Calcd. for $C_{12}H_{16}O_5$: C, 60.02; H, 6.65; Found: C, 59.88; H, 6.57.

6,8-Dimethoxy-7-methyl-3,4-dihydroisochromen-1-one (5)

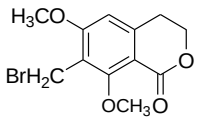
Hydroxy acid derivative **(4)** (1.0 g, 4.16 mmol) was dissolved in acetic anhydride (5 mL) and refluxed for 1 hr. Then, the reaction mixture was poured into ice-cold water and extracted with ethyl acetate (3×20 mL). The combined ethyl acetate extract was washed with 1 % $NaHCO_3$ and then with water. Ethyl acetate was evaporated under reduced pressure to afford 6,8-dimethoxy- 7-methyl-3,4-dihydroisochromen-1-one **(5)**.



Yield = 78 %; Rf = 0.6; M.P.= 145-147 ^{o}C; IR (KBr): ν_{max}: 3021 (C=C-H), 2931 (C-H), 1708 (C=O), 1578 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.48 (1H, s, H-5), 4.25 (2H, t, *J* = 3.6 Hz, H-3,H-3'), 3.91 (3H, s, - OCH_3), 3.88 (3H, s, -OCH_3), 2.66 (3H, s, Ar-CH_3), 2.56 (2H, t, *J* = 3.6 Hz, H-4,H-4'); ^{13}C NMR ($CDCl_3$, δ ppm): 163.9 (C=O), 152.3 (C-6,C-8), 140.8 (C-10), 134.6 (C-9), 108.9 (C-7), 103.7 (C-5), 65.9 (C-3), 56.4 (Ar-OCH_3), 56.1 (Ar-OCH_3), 27.4 (C-4), 26.2 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 222 (52), 194 (45), 192 (100 %), 164 (31), 30 (21); Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.86; H, 6.30; Found: C, 64.75; H, 6.21.

6,8-Dimethoxy-7-(bromomethyl)-3,4-dihydroisochromen-1-one (6)

To a stirred solution of dihydroisocoumarin **(5)** (0.5 g, 2.25 mmol) in dry carbontetrachloride (10 mL), *N*-bromosuccinimide (0.6 g, 3.37 mmol) and benzoyl peroxide (7.5 mg) were added. The reaction mixture was refluxed for 6 hr, then cooled, filtered, and washed with a little carbon tetrachloride. The solvent was rotary evaporated to leave 6,8-dimethoxy-7-(bromomethyl)-3,4-dihydroisochromen-1-one **(6)**.

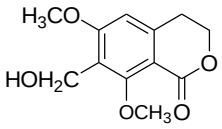


Yield = 81 %; Rf = 0.6; M.P.= 91-93 ^{o}C; IR (KBr): ν_{max}: 3023 (C=C-H), 2924 (C-H), 1718 (C=O), 1583 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.50 (1H, s, H-5), 4.85 (2H, s, CH_2-Br), 4.24 (2H, t, *J* = 3.6 Hz, H-3,H-3'), 3.92 (3H, s,- OCH_3), 3.89 (3H, s, -OCH_3), 2.58 (2H, t, *J* = 3.6 Hz, H-4,H-4'); ^{13}C NMR ($CDCl_3$, δ ppm): 169.2 (C=O), 155.4 (C-6,C-8), 144.1 (C-10), 110.7 (C-7), 106.2 (C-9), 104.6 (C-5), 67.4 (C-3), 53.7 (Ar-OCH_3), 53.4 (Ar-OCH_3), 39.5 (CH_2-Br), 26.4 (C-4); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 300 (24), 302 [M+2] (24), 272 (39), 221 (19), 191 (100 %), 30 (28); Anal. Calcd. for $C_{12}H_{13}O_4Br$: C, 47.84; H, 4.31; Found: C, 47.72; H, 4.23.

7-(Hydroxymethyl)-6,8-dimethoxy-3,4-dihydroisochromen-1-one (7)

6,8-Dimethoxy-7-(bromomethyl)-3,4-dihydroisochromen-1-one (1.0 g, 3.32 mmol) **(6)** was dissolved in a mixture of water and acetone (10 mL, 1:1). The reaction mixture was refluxed for 1 hr, then most of the acetone was rotary evaporated, and the

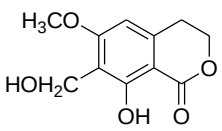
residue was poured into ice-cold water and the solid was filtered, washed with water, and dried to afford 7-(hydroxymethyl)-6,8-dimethoxy-3,4-dihydroisochromen-1-one **(7)**.



Yield = 76 %; Rf = 0.4; M.P.= 136-138 ^{o}C; IR (KBr): ν_{max}: 3472 (O-H), 3044 (C=C-H), 2916 (C-H), 1715 (C=O), 1584 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.62 (1H, s, H-5), 4.88 (2H, s, CH_2-OH), 4.20 (2H, t, *J* = 3.7 Hz, H-3,H-3'), 3.91 (3H, s, -OCH_3), 3. 87 (3H, s, -OCH_3), 2.56 (2H, t, *J* = 3.7 Hz, H-4,H-4'), 2.36 (1H, s, -OH); ^{13}C NMR ($CDCl_3$, δ ppm): 168.6 (C=O), 157.3 (C-6,C-8), 142.1 (C-10), 115.2 (C-7), 105.2 (C-9), 102.6 (C-5), 64.5 (C-3), 55.7 (Ar-OCH_3), 55.4 (Ar-OCH_3), 48.6 (CH_2-OH), 27.4 (C-4); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 238 (49), 221 (31), 210 (55), 208 (100 %), 30 (19); Anal. Calcd. for $C_{12}H_{14}O_5$: C, 60.50; H, 5.88; Found: C, 60.38; H, 5.76.

8-Hydroxy-7-(hydroxymethyl)-6-methoxy-3,4-dihydroisochromen-1-one (8)

7-(Hydroxymethyl)-6,8-dimethoxy-3,4-dihydroisochromen-1-one **(7)** (1.5 g, 6.3 mmol) was dissolved in dry THF (20 mL) and treated with magnesium (0.2 g, 7.58 mmol) and iodine (1.0 g, 8.38 mmol) in dry benzene (30 mL). The resulting mixture was refluxed for 30 min and then poured into water. The organic layer was separated and washed with water. Evaporation of the solvent under reduced pressure afforded *stellatin* **(8)**.

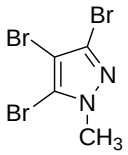


Yield = 54 %; Rf = 0.5; M.P.= 127-128 ^{o}C; IR (KBr): ν_{max}: 3456 (O-H), 3051 (C=C-H), 2922 (C-H), 1705 (C=O), 1591 C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 10.8 (1H, bs, -OH), 7.06 (1H, s, H-5), 4.54 (2H, s, -CH_2OH), 4.12 (2H, t, *J* = 3.7 Hz, H-3,H-3'), 3.91 (3H, s, -OCH_3), 2.86 (2H, t, *J* = 3.7 Hz, H-4,H-4'), 2.28 (1H, s, CH_2OH); ^{13}C NMR ($CDCl_3$, δ ppm): 166.5 (C=O), 158.7 (C-8), 151.4 (C-6), 143.1 (C-10), 116.9 (C-7), 105.2 (C-9), 102.6 (C-5), 64.6 (C-3), 56.8 (Ar-OCH_3), 56.5 (Ar-OCH_3), 47.1 (CH_2-OH), 32.4 (C-4); MS (70 eV): *m/z* (%);[$M^{+\cdot}$] 224 (59), 222 (21), 207 (42), 194 (100 %), 177 (29), 147 (31); Anal. Calcd. for $C_{11}H_{10}O_5$: C, 59.45; H, 4.50; Found C, 59.37; H, 4.38.

[Pet.ether : Ethyl acetate (7:3)]

3.2 Functionalized Pyrazoles

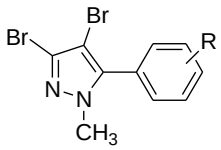
3.2.1 Synthesis of *N*-Methyl-3,4,5-tribromopyrazole



General Procedure

N-Methyl-tribromopyrazole was synthesized by dissolving commercially available tribromopyrazole in 5 mL of CH_2Cl_2 under argon at 20 °C. It was then treated with (1.1 eq.) of NEt_3, followed by the addition of (1.0 eq.) of methyl iodide. The reaction mixture was allowed to stirr for 8 hr to afford *N*-methyl-3,4,5-tribromopyrazole and the product was purified by column chromatography (heptane : ethyl acetate) (8:2).

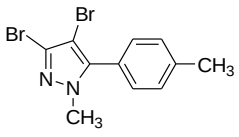
3.2.2 Synthesis of 3,4-Dibromo-5-(substituted-phenyl)-1-methyl-1H-pyrazoles (2a-g)



General Procedure

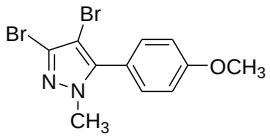
To a 1,4-dioxane solution (4-5 mL) of (1.0 eq.) of *N*-methyl-tribromopyrazole (0.5 mmol) was added $Pd(PPh_2)Cl_2$ (3 mol %) at 20 °C under argon atmosphere. After stirring for 30 min, (1.0 eq.) of $ArB(OH)_2$ (0.55 mmol) and (2 M, 0.5 mL) of aqueous solution of K_2CO_3 were added. The reaction mixture was heated for 6-8 hr at 60 °C. After cooling, the mixture was diluted with H_2O, extracted with CH_2Cl_2 (3x25 mL), dried (Na_2SO_4), and filtered. The solvent of the filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (heptane : ethyl acetate) (8:2).

3,4-Dibromo-5-(4-methylphenyl)-1-methyl-1H-pyrazole (2a)



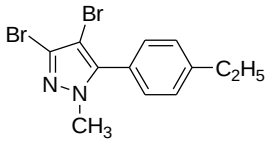
Yield = 76 %; Rf = 0.5; M.P. = 55-57 °C; IR (KBr) ν_{max}: 3048 (C=C-H), 1621 (C=N), 1564 (C=C), 1483 (C-N) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.24 (2H, d, *J* = 8.5 Hz, Ar-H), 7.19 (2H, d, *J* = 8.5 Hz, Ar-H), 3.71 (3H, s, *N*-CH_3), 2.35 (3H, s, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 143.3 (C-5), 139.8 (C-4'), 129.7 (C-1'), 129.5 (C-3',C-5'), 127.1 (C-3), 125.2 (C-2',C-6'), 96.2 (C-4), 38.5 (*N*-CH_3), 21.4 (Ar-CH_3); GC-MS (EI, 70 eV): *m/z* (%) = 330 ($[M]^+$, 100), 329 ($[M]^+$, 100), 328 ($[M, {}^{79}Br_2]^+$, 51), 170 (11), 169 (10); HRMS (EI, 70 eV): Calcd for $C_{11}H_{10}N_2Br_2$ (M^+, [^{79}Br, ^{81}Br]): 329.9184. Found: 329.9187.

3,4-Dibromo-5-(4-methoxyphenyl)-1-methyl-1H-pyrazole (2b)



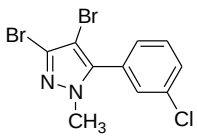
Yield = 79 %; Rf = 0.4; M.P. = 72-73 °C; IR (KBr) ν_{max}: 3031 (C=C-H), 1617 (C=N), 1561 (C=C), 1481 (C-N), 1025 (C-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.23 (2H, d, *J* = 8.8 Hz, Ar-H), 6.93 (2H, d, *J* = 8.8 Hz, Ar-H), 3.75 (3H, s, *N*-CH_3), 3.67 (3H, s, -OCH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 159.5 (C-4'), 142.1 (C-5), 129.8 (C-2',C-6'), 126.1 (C-3), 125.6 (C-1'), 118.2 (C-3',C-5'), 95.2 (C-4), 54.3 (-OCH_3), 37.8 (*N*-CH_3); GC-MS (EI, 70 eV): *m/z* (%) = 346 ([M, $^{81}Br_2]^+$, 100), 345 ([M, $^{79}Br\,^{81}Br]^+$, 8), 344 ([M, $^{79}Br]^+$, 51), 333 (11), 331 (23), 329 (11); HRMS (ESI^+): Calcd for $C_{11}H_{11}Br_2N_2O$ ($[M+1]^+$, $^{79}Br_2$): 344.9233. Found 344.9234; Calcd for ($[M+1]^+$, $^{79}Br^{81}Br$): 346.9213. Found 346.9214; Calcd for ($[M+1]^+$, $^{81}Br_2$): 348.9193. Found 348.9194.

3,4-Dibromo-5-(4-ethylphenyl)-1-methyl-1H-pyrazole (2c)



Yield = 81 %; Rf = 0.45; M.P. = 60-61 °C; IR (KBr) ν_{max}: 3053 (C=C-H), 1613 (C=N), 1556 (C=C), 1485 (C-N) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.25 (2H, d, *J* = 8.4 Hz, Ar-H), 7.20 (2H, d, *J* = 8.4 Hz, Ar-H), 3.69 (3H, s, *N*-CH_3), 2.63 (2H, q, *J* = 7.6 Hz, -CH_2), 1.20 (3H, t, *J* = 7.4 Hz, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 143.3 (C-5), 140.6 (C-4'), 129.5 (C-1'), 128.3 (C-3',C-5'), 127.1 (C-3), 126.1 (C-2',C-6'), 96.2 (C-4), 38.5 (*N*-CH_3), 28.7 (Ar-CH_2), 15.2 (-CH_3); GC-MS (EI, 70 eV): *m/z* (%) = 344 ([M, $^{81}Br_2]^+$, 100), 343 ([M, $^{79}Br^{81}Br]^+$, 100), 342 ([M, $^{79}Br_2]^+$, 51), 331 (37), 329 (75), 327 (38); HRMS (ESI^+): Calcd for $C_{12}H_{13}Br_2N_2$ ($[M+1]^+$, $^{79}Br_2$): 342.9443. Found 342.9442; Calcd for ($[M+1]^+$, $^{79}Br^{81}Br$): 344.9425. Found 344.9424; Calcd for ($[M+1]^+$, $^{81}Br_2$): 346.9401. Found 346.9402.

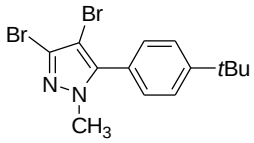
3,4-Dibromo-5-(3-chlorophenyl)-1-methyl-1H-pyrazole (2d)



Yield = 73 %; Rf = 0.6; M.P. = 66-67 °C; IR (KBr) ν_{max}: 3045 (C=C-H), 1611 (C=N), 1565 (C=C), 1471 (C-N) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.39-7.42 (1H, m, Ar-H-4'), 7.38 (1H, s, *J* = 2.4 Hz, H-2'), 7.31-7.35 (1H, m, Ar-H-5'), 7.23 (1H, dd, *J* = 7.4,2.4 Hz, ArH-6'), 3.73 (3H, s, *N*-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 141.8 (C-5), 134.8 (C-3'), 130.2 (C-1'), 129.9 (C-5'), 96.8 (C-4), 129.6 (C-4'), 127.8 (C-2'), 127.4 (C-3), 125.7 (C-6'), 38.7 (*N*-CH_3); GC-MS (EI, 70 eV): *m/z* (%) = 354 ([M, $^{81}Br_2{}^{37}Cl_2]^+$, 14), 353 ([M, $^{81}Br_2{}^{37}Cl^{35}Cl]^+$, 8), 352 ([M, $^{81}Br_2{}^{35}Cl]^+$, 70), 351 ([M, $^{81}Br^{37}Cl]^+$, 100), 350 ([M, $^{81}Br_2]^+$, 100), 349 ([M, $^{79}Br^{81}Br]^+$, 9), 348 ([M, $^{79}Br_2]^+$, 45), 147 (10); HRMS (ESI^+): Calcd for $C_{10}H_8Br_2ClN_2$ ($[M+1]^+$, $^{79}Br_2$): 348.8737.

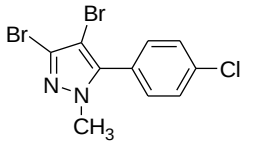
Found 348.8745; Calcd for ($[M+1]^+$, $^{81}Br_2$): 350.8716. Found 350.8726; Calcd for ($[M+1]^+$, $^{81}Br_2{}^{35}Cl_2$): 352.8693. Found 352.8700.

3,4-Dibromo-5-(4-*tert*-butylphenyl)-1-methyl-1H-pyrazole (2e)



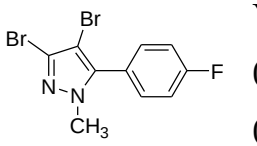
Yield = 82 %; Rf = 0.45; M.P. = 61-62 °C; IR (KBr) ν_{max}: 3055 (C=C-H), 1623 (C=N), 1563 (C=C), 1474 (C-N) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.44 (2H, d, *J* = 6.9 Hz, Ar-H), 7.25 (2H, d, *J* = 7.1 Hz, Ar-H), 3.72 (3H, s, *N*-CH_3), 1.29 (9H, s, $3CH_3$); ^{13}C NMR ($CDCl_3$, δ ppm): 152.8 (C-4'), 143.3 (C-5), 130.2 (C-1'), 127.2 (C-3), 126.7 (C-2',C-6'), 124.8 (C-3',C-5'), 96.2 (C-4), 38.4 (*N*-CH_3), 34.8 (*tert*-C), 31.2 (-CH_3); GC-MS (EI, 70 eV): *m/z* (%) = 374 ([M, $^{81}Br_2]^+$, 23), 373 ([M, $^{79}Br_2{}^{81}Br_2]^+$, 7), 372 ([M, $^{79}Br_2]^+$, 48), 370 (27), 359 (45), 358 (11), 357 (100), 356 (13), 355 (54), 329 (18), 164 (17); HRMS (ESI^+): Calcd for $C_{14}H_{17}Br_2N_2$ ($[M+1]^+$, $^{79}Br_2$): 370.9753. Found 370.9751; Calcd for ($[M+1]^+$, $^{79}Br^{81}Br$): 372.9733. Found 372.9732; Calcd for ($[M+1]^+$, $^{81}Br_2$): 374.9714. Found 374.9709.

3,4-Dibromo-5-(4-chlorophenyl)-1-methyl-1H-pyrazole (2f)



Yield = 71 %; Rf = 0.6; M.P = 52-53 °C; IR (KBr) ν_{max}: 3052 (C=C-H), 1626 (C=N), 1567 (C=C), 1473 (C-N) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.42 (2H, d, *J* = 8.5 Hz, Ar-H), 7.26 (2H, d, *J* = 8.5 Hz, Ar-H), 3.76 (3H, s, *N*-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 142.1 (C-5). 135.4 (C-4'), 130.6 (C-1'), 129.2 (C-3',C-5'), 128.3 (C-2',C-6'), 127.3 (C-3), 96.6 (C-4), 38.6 (*N*-CH_3); GC-MS (EI, 70 eV): *m/z* (%) = 354 ([M, $^{81}Br_2{}^{37}Cl_2]^+$, 13), 353 ([M, $^{81}Br_2{}^{37}Cl^{35}Cl]^+$, 8), 352 ([M, $^{81}Br_2{}^{35}Cl]^+$, 70), 351 ([M, $^{81}Br^{37}Cl]^+$, 12), 350 ([M, $^{81}Br_2]^+$, 100), 349 ([M, $^{79}Br^{81}Br]^+$, 8), 348 ([M, $^{79}Br_2]^+$, 45), 147 (11); HRMS (ESI^+): Calcd for $C_{10}H_8Br_2ClN_2$ ($[M+1]^+$, $^{79}Br_2$): 348.8736. Found 348.8734; Calcd for ($[M+1]^+$, $^{81}Br_2$): 350.8715. Found 352.8725; Calcd for ($[M+1]^+$, $^{81}Br_2{}^{35}Cl_2$): 352.8692. Found 352.8709.

3,4-Dibromo-5-(4-fluorophenyl)-1-methyl-1H-pyrazole (2g)

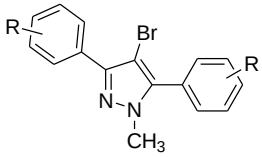


Yield = 75 %; Rf = 0.65; M.P = 55-56 °C; IR (KBr) ν_{max}: 3051 (C=C-H), 1616 (C=N), 1558 (C=C), 1484 (C-N) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.34 (2H, d, *J* = 7.5 Hz, Ar-H), 7.23 (2H, d, *J* = 7.5 Hz, Ar-H), 3.78 (3H, s, *N*-CH_3); ^{19}F NMR (282.4 MHz, $CDCl_3$, δ ppm): -110.1; ^{13}C NMR ($CDCl_3$, δ ppm): 163.4 (d, J_{F-C} = 244.7 Hz, C-F), 142.3 (C-5), 131.6 (d, J_{F-C} = 10.8 Hz, C-2',C-6'), 127.2 (C-3), 123.8 (d, J_{F-C} = 3.2 Hz, C-1'), 116.1 (d, J_{F-C} = 21.8 Hz, C-3',C-5'), 96.6 (C-4), 38.8 (*N*-CH_3); GC-MS (EI, 70 eV): *m/z* (%) = 334 ([M, $^{81}Br_2]^+$, 100), 334

([M, $^{79}Br^{81}Br]^+$, 8), 332 ([M, $^{79}Br_2]^+$, 79), 174, 136 (11), 131 (12); HRMS (ESI^+): Calcd for $C_{10}H_8Br_2N_2F$ ([M+1]$^+$, $^{79}Br^{81}Br$): 334.9013; Found 334.9016.

[heptane : ethyl acetate (8:2)]

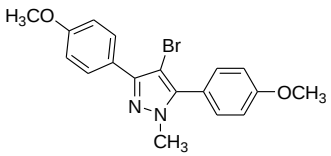
3.2.3 Synthesis of 4-Bromo-3,5-bis(substituted-phenyl)-1-methyl-1H-pyrazoles (3a-c)



General Procedure

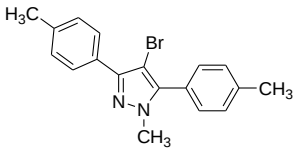
Synthesis of 3,5-diaryled-4-bromopyrazoles was carried out by the addition of $Pd(PPh_2)Cl_2$ (5 mol %), to a 1,4-dioxane solution (4-5 mL) of (1.0 eq.) of *N*-methyl-tribromopyrazole (0.5 mmol) at 20 °C under argon atmosphere. After stirring for 30 min, (2.0 eq.) of $ArB(OH)_2$ and (2 M, 0.5 mL) of aqueous solution of K_2CO_3 were added. The reaction mixture was heated for 6-7 hr at 80 °C. After cooling, the mixture was diluted with H_2O, extracted with CH_2Cl_2 (3x20 mL), dried (Na_2SO_4), and filtered. The solvent of the filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (heptane : ethyl acetate) (8:2).

4-Bromo-3,5-bis(4-methoxyphenyl)-1-methyl-1H-pyrazole (3a)



Yield = 60 %; Rf = 0.35; M.P = 91-92 °C; IR (KBr) ν_{max}: 3023 (C=C-H), 1613 (C=N), 1563 (C=C), 1441 (C-N), 1028 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.71 (2H, d, *J* = 8.3 Hz, H-2',H-6'), 7.29 (2H, d, *J* = 8.6 Hz, H-2'',H-6''), 6.90 (2H, d, *J* = 8.1 Hz, H-3',H-5'), 6.87 (2H, d, *J* = 8.4 Hz, H-3'',H-5''), 3.87 (4'-OCH_3), 3.83 (4''-OCH_3), 3.76 (*N*-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 158.7 (C-4'), 158.2 (C-4''), 147.9 (C-5), 140.6 (C-3), 128.6 (C-2',C-6'), 128.2 (C-2'',C-6''), 124.9 (C-1'), 123.3 (C-1''), 113.9 (C-3',C-5'), 113.8 (C-3'',C-5''), 93.6 (C-4), 55.4 (C-4'-OCH_3), 55.2 (C-4''-OCH_3), 38.7 (*N*-CH_3); GC-MS (EI, 70 eV): *m/z* (%) = 374 ([M, $^{81}Br]^+$, 100), 372 ([M, $^{79}Br]^+$, 52), 265 (15), 107 (07), 281 (13), 207 (100); HRMS (ESI^+): Calcd for $C_{18}H_{17}N_2BrO_2$ [M+1, $^{81}Br]^+$: 374.1327. Found 374.1327; Calcd for [M+1, $^{79}Br]^+$: 372.1346. Found 372.1346.

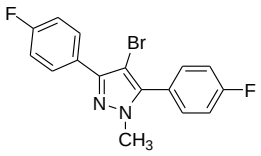
4-Bromo-3,5-bis(4-methylphenyl)-1-methyl-1H-pyrazole (3b)



Yield = 62 %; Rf = 0.45; M.P = 83-84 °C; IR (KBr) ν_{max}: 3026 (C=C-H), 1618 (C=N), 1563 (C=C), 1446 (C-N) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.78 (2H, d, *J* = 8.2 Hz, H-2',H-6'), 7.32 (2H,

d, *J* = 8.4 Hz, H-2'',H-6''), 6.94 (2H, d, *J* = 8.2 Hz, H-3',H-5'), 6.85 (2H, d, *J* = 8.4 Hz, H-3'',H-5''), 3.75 (*N*-CH_3), 2.33 (4'-CH_3), 2.31 (4''-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 156.8 (C-3), 143.6 (C-5), 138.7 (C-4'), 138.2 (C-4''), 130.7 (C-1'), 130.3 (C-1''), 129.9 (C-3',C-5'), 129.7 (C-3'',C-5''), 127.6 (C-2',C-6'), 127.2 (C-2'',C-6''), 91.6 (C-4), 38.6 (*N*-CH_3), 23.3 (C-4'-CH_3), 23.1 (C-4''-CH_3); GC-MS (EI, 70 eV): *m/z* (%) = 342 ([M, ^{81}Br]$^+$, 100), 340 ([M, ^{79}Br]$^+$, 51), 249 (25), 159 (17), 145 (21), 91 (100); HRMS (ESI$^+$): Calcd for $C_{18}H_{17}N_2Br$ [M+1, ^{81}Br]$^+$: 342.0613. Found 342.0613; Calcd for [M+1, ^{79}Br]$^+$: 340.0613. Found 340.0613.

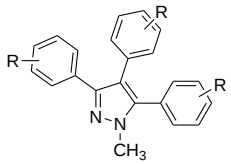
4-Bromo-3,5-bis(4-fluorophenyl)-1-methyl-1H-pyrazole (3c)



Yield = 67 %; Rf = 0.5; M.P = 105-106 °C; IR (KBr) ν_{max}: 3034 (C=C-H), 1614 (C=N), 1565 (C=C), 1443 (C-N) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.91 (2H, d, *J* = 7.3 Hz, H-2',H-6'), 7.82 (2H, d, *J* = 7.2 Hz, H-2'',H-6''), 7.23 (2H, d, *J* = 7.3 Hz, H-3',H-5'), 6.97 (2H, d, *J* = 7.2 Hz, H-3'',H-5''), 3.78 (*N*-CH_3); ^{19}F NMR (300 MHz, $CDCl_3$, δ ppm): -113.5, -110.8; ^{13}C NMR ($CDCl_3$, δ ppm): 164.4 (d, $J_{F,C}$ = 248.5 Hz, 4''-C-F), 163.8 (d, $J_{F,C}$ = 249.2 Hz, 4'-C-F), 156.5 (C-3),. 142.3 (C-5), 131.7 (d, $J_{F,C}$ = 8.4 Hz, C-2',C-6'), 129.5 (d, $J_{F,C}$ = 8.1 Hz, C-2'',C-6''), 128.6 (C-1'),128.4 (C-1''), 115.0 (d, $J_{F,C}$ = 21.8 Hz, C-3',C-5'), 114.3 (d, $J_{F,C}$ = 21.5 Hz, C-3'',C-5''), 92.8 (C-4), 38.8 (*N*-CH_3); GC-MS (EI, 70 eV): *m/z* (%) = 350 ([M, ^{81}Br]$^+$, 100), 348 ([M, ^{79}Br]$^+$, 51), 253 (15), 159 (07), I45 (13), 207 (100); HRMS (ESI$^+$): Calcd for $C_{16}H_{12}N_2BrF_2$ [M+1, ^{81}Br]$^+$: 350.0134. Found 350.0134; Calcd for [M+1, ^{79}Br]$^+$: 348.0134. Found 348.0134.

[heptane : ethyl acetate (8:2)]

3.2.4 Synthesis of 1-Methyl-3,4,5-tri-(substituted-phenyl)-1H-pyrazoles (4a-g)

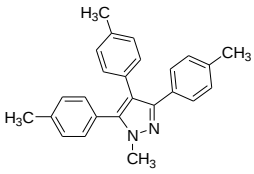


Procedure

3,4,5-Triarylated-pyrazoles synthesis was carried out by the addition of $Pd(OAc)_2$ (5 mol %), to a 1,4-dioxane solution (4-5 mL) of (1.0 eq.) of *N*-methyl-tribromopyrazole (0.5 mmol) at 20 °C under argon atmosphere. After stirring for 30 min, (3.0 eq.) of $ArB(OH)_2$ (1.65 mmol) and (2 M, 1.0 mL) of aqueous solution of K_2CO_3 were added. The reaction mixture was heated for 8 hr at 100 °C. After cooling, the mixture was diluted with H_2O, extracted with CH_2Cl_2 (3 x 30 mL), dried (Na_2SO_4), and filtered. The

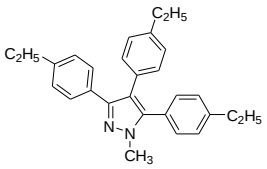
solvent of the filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (heptane : ethyl acetate) (7:3).

1-Methyl-3,4,5-tri-(4-methylphenyl)-1H-pyrazole (4a)



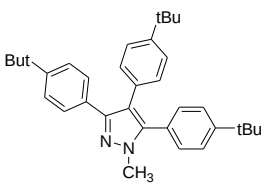
Yield = 91 %; Rf = 0.4; M.P. = 145-146 °C; IR (KBr) ν_{max}: 3028 (C=C-H), 1622 (C=N), 1578 (C=C), 1440 (C-N) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.27 (2H, d, *J* = 8.1 Hz, H-2',H-6'), 7.09 (2H, d, *J* = 7.8 Hz, H-2'',H-6''), 7.03 (2H, d, *J* = 8.3 Hz, H-2''',H-6'''), 6.99 (2H, d, *J* = 8.1 Hz, H-3',H-5'), 6.89 (2H, d, *J* = 8.3 Hz, H-3'',H-5''), 6.84 (2H, d, *J* = 8.3 Hz, H-3''',H-5'''), 3.76 (3H, s, *N*-CH_3), 2.28 (3H, s, 4'-CH_3), 2.24 (3H, s, 4''-CH_3), 2.21 (3H, s, 4'''-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 148.4 (C-5), 142.1 (C-3), 138.2 (C-4'), 136.8 (C-4''), 135.6 (C-4'''), 130.7 (C-1'''), 130.3 (C-1'), 130.1 (C-1''), 129.3 (C-3',C-5'), 129.1 (C-3'',C-5''), 128.9 (C-3''',C-5'''), 128.7 (C-2',C-6'), 127.9 (C-2'',C-6''), 127.3 (C-2''',C-6'''), 123.7 (C-4), 37.2 (*N*-CH_3), 21.3 (4'-CH_3), 21.2 (4''-CH_3), 21.1 (4'''-CH_3); GC-MS (EI, 70 eV): *m/z* (%) = 352 ($[M]^+$, 100), 351 (36); HRMS (ESI^+): Calcd for $C_{25}H_{24}N_2$ $[M+1]^+$: 353.2012; Found 353.2012.

3,4,5-Tris(4-ethylphenyl)-1-methyl-1H-pyrazole (4b)



Yield = 89 %; Rf = 0.4; M.P. = 133-134 °C; IR (KBr) ν_{max}: 3033 (C=C-H), 1624 (C=N), 1573 (C=C), 1442 (C-N) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.30 (2H, d, *J* = 8.2 Hz, H-2',H-6'), 7.10 (2H, d, *J* = 8.7 Hz, H-2'',H-6''), 7.06 (2H, d, *J* = 8.3 Hz, H-2''',H-6'''), 7.02 (2H, d, *J* = 8.0 Hz, H-3'',H-5''), 6.92 (2H, d, *J* = 8.4 Hz, H-3''',H-5'''), 6.89 (2H, d, *J* = 8.2 Hz, H-3',H-5'), 3.76 (3H, s, *N*-CH_3), 2,46-2.63 (6H, m, $3CH_2$), 1.09-1.20 (9H, m, $3CH_3$); ^{13}C NMR ($CDCl_3$, δ ppm): 147.4 (C-3), 143.3 (C-5), 142.0 (C-4''), 141.1(C-4'), 140.8 (C-4'''), 130.0 (C-1'''), 129.7 (C-1''), 129.2 (C-1'), 127.1 (C-3',C-5'), 126.9 (C-5''',C-5'''), 126.8 (C-3'',C-5''), 126.6 (C-2',C-6'), 126.5 (C-2''',C-6'''), 126.4 (C-2'',C-6''), 117.6 (C-4), 37.4 (*N*CH_3), 27.6 (-CH_2), 27.5 (-CH_2), 27.3 (-CH_2), 14.3 (4'-CH_3), 14.2 (4''-CH_3), 14.1 (4'''-CH_3); GC-MS (EI, 70 eV): *m/z* (%) = 394 ($[M]^+$, 100), 379 (29). HRMS (ESI^+): Calcd for $C_{28}H_{31}N_2$ $[M+1]^+$: 395.2482; Found 395.2486.

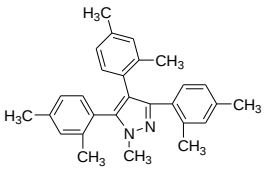
3,4,5-Tris(4-*tert*-butylphenyl)-1-methyl-1H-pyrazole (4c)



Yield = 86 %; Rf = 0.3; M.P. = 123-124 °C; IR (KBr) ν_{max}: 3035 (C=C-H), 1627 (C=N), 1575 (C=C), 1438 (C-N) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.33 (2H, d, *J* = 8.5 Hz, H-2',H-6'), 7.28 (2H, d, *J* = 8.2 Hz, H-2''',H-6'''), 7.18 (2H, d, *J* = 8.2 Hz, H-2'',H-6''),

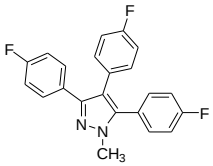
7.10 (2H, d, *J* = 8.3 Hz, H-2’’’,H-6’’’), 7.08 (2H, d, *J* = 8.5 Hz, H-3’,H-5’), 6.93 (2H, d, *J* = 8.4 Hz, H-2’’,H-6’’), 3.75 (3H, s, *N*-CH_3), 1.25 (9H, s, $3CH_3$), 1.22 (9H, s, $3CH_3$), 1.20 (9H, s, $3CH_3$); ^{13}C NMR ($CDCl_3$, δ ppm): 151.2 (C-4’), 149.9 (C-4’’), 148.8 (C-4’’’), 142.1 (C-5), 141.3 (C-3), 130.8 (C-1’’’), 130.4 (C-1’), 130.1 (C-1’’), 127.8 (C-2’,C-6’), 127.5 (C-2’’,C-6’’), 126.2 (C-2’’’,C-6’’’), 125.2, (C-3’,C-5’), 125.0 (C-3’’,C-5’’), 124.8 (C-3’’’,C-5’’’), 118.6 (C-4), 37.3 (*N*-CH_3), 31.4 ($3CH_3$),, 31.3 ($3CH_3$), 31.2 ($3CH_3$); GC-MS (EI, 70 eV): *m/z* (%) = 478 ($[M]^+$, 96), 464 (37), 463 (100), 224 (14); HRMS (ESI, 70 eV): Calcd for $C_{34}H_{42}N_2$ $[M+1]^+$: 478.3342; Found 478.3342.

3,4,5-Tris(3,5-dimethylphenyl)-1-methyl-1H-pyrazole (4d)



Yield = 84 %; Rf = 0.35; M.P. = 167-168 °C; IR (KBr) ν_{max}: 3038 (C=C-H), 1630 (C=N), 1578 (C=C), 1445 (C-N) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.04 (2H, d, *J* = 7.2 Hz, H-6’,H-6’’), 6.87 (1H, d, *J* = 7.3 Hz, Ar-H-6’’’), 6.78 (2H, d, *J* = 7.2 Hz, H-5’,H-5’’), 6.74 (1H, d, *J* = 7.3 Hz, Ar-H5’’’), 6.69 (1H, d, *J* = 2.2 Hz, Ar-H-3’), 6.61 (2H, d, *J* = 2.2 Hz, H-3’’,H-3’’’), 3.74 (3H, s, *N*-CH_3), 2.20 (6H, s, $2CH_3$), 2.14 (6H, s, $2CH_3$), 2.06 (6H, s, $2CH_3$); ^{13}C NMR ($CDCl_3$, δ ppm): 148.3 (C-3), 142.3 (C-5); 138.0 (C-4’’), 137.3 (C-4’), 136.9 (C-4’’’), 133.4 (C-2’’), 133.2 (C-2’), 131.4 (C-1’’’), 130.2 (C-2’’’), 130.0 (C-3’’), 128.8 (C-3’), 128.2 (C-3’’), 127.9 (C-6’’), 127.8 (C-6’), 127.4 (C-6’’’), 126.7 (C-5’,C-5’’), 126.3 (C-5’’’), 125.8 (C-1’,C-1’’), 123.3 (C-4), 37.5 (*N*-CH_3), 21.3 ($6CH_3$), 21.2 ($6CH_3$), 21.1 ($6CH_3$); GC-MS (EI, 70 eV): *m/z* (%) = 394 ($[M]^+$, 100), 393 (26); HRMS (ESI^+): Calcd for $C_{28}H_{31}N_2$ $[M+1]^+$: 395.2482; Found 395.2483.

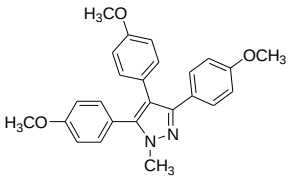
3,4,5-Tris(4-fluorophenyl)-1-methyl-1H-pyrazole (4e)



Yield = 87 %; Rf = 0.45; M.P. = 121-122 °C; IR (KBr) ν_{max}: 3042 (C=C-H), 1626 (C=N), 1572 (C=C), 1443 (C-N) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.33 (2H, d, *J* = 8.7 Hz, H-2’’’,H-6’’’), 7.13 (2H, d, *J* = 8.6 Hz, H-2’,H-6’), 7.00 (2H, d, *J* = 8.5 Hz, H-2’,H-6’), 6.92 (2H, d, *J* = 8.7 Hz, H-3’’’,H-5’’’), 6.87 (2H, d, *J* = 8.4 Hz, H-3’,H-5’), 6.81 (2H, d, *J* = 8.6 Hz, H-3’’,H-5’’), 3.77 (3H, s, *N*-CH_3); ^{19}F NMR (282 MHz, $CDCl_3$, δ ppm): -111.9, -114.5, -115.5; ^{13}C NMR ($CDCl_3$, δ ppm): 164.7 (d, $J_{F,C}$ = 248.4 Hz, 4‘’-C-F), 163.6 (d, $J_{F,C}$ = 249.1 Hz, 4‘‘‘-C-F), 163.3 (d, $J_{F,C}$ = 249.4 Hz, 4‘-C-F), 142.8 (C-3), 140.3 (C-5), 131.9 (d, $J_{F,C}$ = 8.1 Hz, C-2’’,C-6’’), 131.7 (d, $J_{F,C}$ = 8.0 Hz, C-2’,C-6’), 130.6 (d, $J_{F,C}$ = 8.1 Hz, C-2’’’,C-6’’’), 129.6 (d, $J_{F,C}$ = 3.2 Hz, C-1’’’), 129.2 (d, $J_{F,C}$ = 3.2 Hz, C-1’), 125.7 (d, $J_{F,C}$ = 3.6 Hz, C-1’’), 124.5 (C-4), 115.8 (d, $J_{F,C}$ = 21.6 Hz, C-3’’’,C-5’’’), 115.4 (d, $J_{F,C}$ = 21.4 Hz, C-

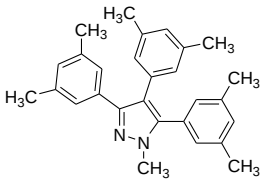
3',C-5'), 115.2 (d, $J_{F,C}$ = 21.4 Hz, C-3'',C-5''), 37.8 (*N*-CH_3); GC-MS (EI, 70 eV): *m/z* (%) = 364([M]$^+$, 100), 393 (26); HRMS (ESI$^+$): Calcd for $C_{22}H_{16}N_2F_3$ [M+1]$^+$: 365.1264; Found 365.1263.

3,4,5-Tris(4-methoxyphenyl)-1-methyl-1H-pyrazole (4f)



Yield = 81 %; Rf = 0.3; M.P. = 160-161 °C; IR (KBr) ν_{max}: 3036 (C=C-H), 1628 (C=N), 1574 (C=C), 1447 (C-N), 1037 (C-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.31 (2H, d, *J* = 8.5 Hz, H-2',H-6'), 7.06 (2H, d, *J* = 8.6 Hz, H-2'',H-6''), 6.88 (2H, d, *J* = 8.8 Hz, H-2''',H-6'''), 6.79 (2H, d, *J* = 8.5 Hz, H-3',H-5'), 6.72 (2H, d, *J* = 8.6 Hz, H-3'',H-5''), 6.63 (2H, d, *J* = 8.8 Hz, H-3''',H-5'''), 3.75 (3H, s, *N*-CH_3), 3.71 (3H, s, -OCH_3), 3.69 (3H, s, -OCH_3), 3.66 (3H, s, -OCH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 159.9 (C-4'), 158.8 (C-4''), 158.2 (C-4'''), 143.2 (C-5), 141.7 (C-3), 131.5 (C-2',C-6'), 131.4 (C-2'',C-6''), 129.2 (C-2''',C-6'''), 128.7 (C-1'''), 126.3 (C-1'), 126.1 (C-1''), 123.5 (C-4), 113.9 (C-3',C-5'), 113.7 (C-3'',C-5''), 113.6 (C-3''',C-5'''), 55.8 (4'-OCH_3), 55.7 (4''-OCH_3), 55.4 (4'''-OCH_3), 37.2 (*N*-CH_3); GC-MS (EI, 70 eV): *m/z* (%) = 400 ([M]$^+$, 100), 399 (13), 385 (20); HRMS (ESI, 70 eV): Calcd for $C_{25}H_{25}N_2O_3$ [M+1]$^+$: 401.1867; Found 401.1868.

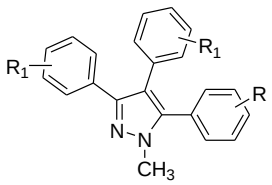
3,4,5-Tris(3,5-dimethylphenyl)-1-methyl-1H-pyrazole (4g)



Yield = 75 %; Rf = 0.5; M.P. = 150-151 °C; IR (KBr) ν_{max}: 3034 (C=C-H), 1625 (C=N), 1577 (C=C), 1441 (C-N) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.06 (1H, s, Ar-H-4'), 7.01 (1H, s, Ar-H-4''), 6.88 (2H, s, H-2',H-6'), 6.78 (1H, s, Ar-H-4'''), 6.76 (2H, s, H-2'',H-6''), 6.68 (2H, s, H-2''',H-6'''), 3.74 (3H, s, *N*-CH_3), 2.20 (6H, s, 2CH_3), 2.14 (s, 6H, s, 2CH_3), 2.06 (s, 6H, s, 2CH_3), ^{13}C NMR ($CDCl_3$, δ ppm): 142.3 (C-3), 140.3 (C-5), 138.2 (C-3',C-5'), 137.7 (C-3'',C-5''), 137.3 (C-3''',C-5'''), 136.8 (C-1'''), 133.4 (C-1'), 133.2 (C-1''), 130.0 (C-4'), 129.8 (C-4''), 129.4 (C-4'''), 127.8 (C-2',C-6'), 127.6 (C-2'',C-6''), 127.4 (C-2''',C-6'''), 123.6 (C-4), 37.3 (*N*-CH_3), 21.3 (6CH_3), 21.2 (6CH_3), 21.1 (6CH_3); GC-MS (EI, 70 eV): *m/z* (%) = 394([M]$^+$, 100), 393 (26); HRMS (ESI, 70 eV): Calcd for $C_{28}H_{31}N_2$ [M+1]$^+$: 395.2482; Found 395.2483.

[heptane : ethyl acetate (7:3)]

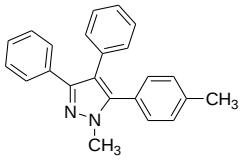
3.2.5 Synthesis of 1-Methyl-3,4-diphenyl-5-(substituted-phenyl)-1H-pyrazoles (5a-i)



Procedure

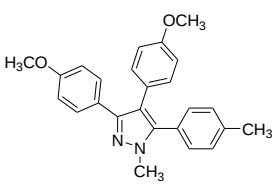
Synthesis of 3,4,5-triarylated-pyrazoles was carried out by the addition of $Pd(OAc)_2$ (5 mol %), to a 1,4-dioxane solution (4-5 mL) of (1.0 eq.) of *N*-methyl-5-arylated-3,4-dibromopyrazole (0.5 mmol) at 20 °C under argon atmosphere. After stirring for 30 min, (2.0 eq.) of $ArB(OH)_2$ and (2 M, 1.0 mL) of aqueous solution of K_2CO_3 were added. The reaction mixture was heated for 6 hr at 100 °C. After cooling, the mixture was diluted with H_2O, extracted with CH_2Cl_2 (3x30 mL), dried (Na_2SO_4), and filtered. The solvent of the filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (heptane : ethyl acetate) (5:5).

1-Methyl-3,4-diphenyl-5-(4-methylphenyl)-1H-pyrazole (5a)



Yield = 92 %; Rf = 0.5; M.P. = 146-147 °C; IR (KBr) ν_{max}: 3035 (C=C-H), 1628 (C=N), 1574 (C=C), 1441 (C-N) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.37-7.40 (2H, m, H-2'',6''), 7.21 (2H, d, *J* = 7.2 Hz, Ar-H-2',H-6'), 7.06-7.09 (2H, m, H-2''',6'''), 7.07-7.10 (4H, m, H-3'',5'', H-3''',5'''), 7.03-7.05 (2H, m, H-4'', H-4'''), 6.95 (2H, d, *J* = 7.2 Hz, Ar-H-3',H-5'), 3.78 (3H, s, *N*-CH_3), 2.28 (3H, s, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 142.3 (C-3), 141.4 (C-5), 138.3 (C-4'), 136.6 (C-1'''), 133.4 (C-1''), 130.2 (C-1'), 129.8 (C-3',C-5'), 129.6 (C-3'',C-5''), 129.3 (C-3''',C-5'''), 128.8 (C-4''), 128.6 (C-4'''), 127.8 (C-2',C-6'), 127.6 (C-2'',C-6''), 127.4 (C-2''',C-6'''), 123.7 (C-4), 37.4 (*N*-CH_3), 21.3 (-CH_3); GC-MS (EI, 70 eV): *m/z* (%) = 324 ($[M]^+$, 100), 323 (53); HRMS (ESI^+): Calcd for $C_{23}H_{21}N_2$ $[M+1]^+$: 325.1699; Found 325.1703.

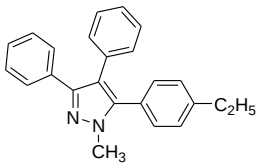
3,4-Bis(4-methoxyphenyl)-1-methyl-5-(4-methylphenyl)-1H-pyrazole (5b)



Yield = 84 %; Rf = 0.35; M.P. = 159-160 °C; IR (KBr) ν_{max}: 3041 (C=C-H), 1632 (C=N), 1578 (C=C), 1447 (C-N), 1035 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.30-7.33 (2H, d, *J* = 7.2 Hz, Ar-H-2'',H-6''), 7.12-7.21 (2H, d, *J* = 7.3 Hz, Ar-H-2',H-6'), 6.97-7.04 (2H, d, *J* = 7.2 Hz, Ar-H-2''',H-6'''), 6.81-6.85 (2H, d, *J* = 7.3 Hz, Ar-H-3',H-5'),

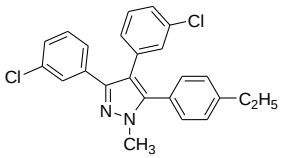
6.73-6.78 (4H, d, *J* = 7.2 Hz, H-3'',5'',H-3''',5'''), 3.76 (3H, s, *N*-CH_3), 3.71 (3H, s, -OCH_3), 3.68 (3H, s, -OCH_3), 2.28 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 157.9 (C-4'''), 158.8 (C-4''), 142.3 (C-3), 140.5 (C-5), 138.1 (C-4'), 131.4 (C-1'), 130.1 (C-3',C-5'), 129.3 (C-3'',C-5''), 129.1 (C-3''',C-5'''), 128.4 (C-1'''), 127.3 (C-2',C-6'), 126.7 (C-2'',C-6''), 126.2 (C-2''',C-6'''), 125.3 (C-1''), 123.6 (C-4), 118.1, 55.3 (4'''-OCH_3), 55.1 (4''-OCH_3), 37.2 (*N*-CH_3), 21.3 (-CH_3); GC-MS (EI, 70 eV): *m/z* (%) = 384 ($[M]^+$, 100), 341 (13), 327 (22), 277 (39), 246 (22), 198 (23); HRMS (ESI^+): Calcd for $C_{25}H_{25}N_2O_2$ $[M+1]^+$: 385.1911; Found 385.1914.

5-(4-Ethylphenyl)-1-methyl-3,4-diphenyl-1H-pyrazole (5c)



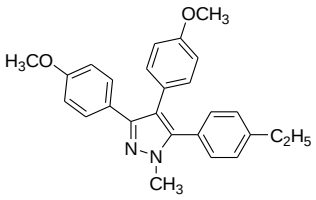
Yield = 89 %; Rf = 0.5; M.P. = 152-153 °C; IR (KBr) ν_{max}: 3043 (C=C-H), 1634 (C=N), 1580 (C=C), 1452 (C-N) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.37-7.40 (2H, d, *J* = 7.2 Hz, Ar-H-2',H-6'), 7.17-7.21 (5H, m, Ar-H), 7.05-7.10 (5H, m, Ar-H), 6.96-6.99 (2H, d, *J* = 7.2 Hz, Ar-H-3',H-5'), 3.79 (3H, s, *N*-CH_3), 2.58 (2H, q, *J* = 7.6 Hz, -CH_2), 1.18 (3H, t, *J* = 7.5 Hz, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 142.3 (C-3), 141.4 (C-5), 140.5 (C-4'), 133.5 (C-1'''), 130.4 (C-1''), 130.1 (C-1'), 129.8 (C-3'',C-5''), 129.5 (C-3''',C-5'''), 128.7 (C-4'''), 128.5 (C-4''), 128.2 (C-3',C-5'), 127.8 (C-2'',C-6''), 127.4 (C-2''',C-6'''), 127.1 (C-2',C-6'), 123.5 (C-4), 37.3 (*N*-CH_3), 28.5 (-CH_2), 15.3 (-CH_3); GC-MS (EI, 70 eV): *m/z* (%) = 338 ($[M]^+$, 100), 337 (45); HRMS (EI, 70 eV): Calcd for $C_{24}H_{23}N_2$ $[M+1]^+$: 339.1856; Found 339.1861.

3,4-Bis(3-chlorophenyl)-5-(4-ethylphenyl)-1-methyl-1H-pyrazole (5d)



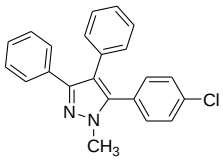
Yield = 82 %; Rf = 0.55; M.P. = 147-148 °C; IR (KBr) ν_{max}: 3046 (C=C-H), 1637 (C=N), 1586 (C=C), 1454 (C-N) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.37-7.40 (2H, d, *J* = 7.1 Hz, Ar-H-2',H-6'), 7.17-7.21 (2H, d, *J* = 2.1 Hz, Ar-H-2',H-2'''), 7.10-7.16 (4H, m, H-4'',5'',H-4'''.5'''), 7.03-7.08 (2H, d, *J* = 7.2 Hz, Ar-H-6',H-6'''), 6.95-6.98 (2H, d, *J* = 7.1 Hz, Ar-H-3',H-5'), 3.79 (3H, s, *N*-CH_3), 2.57 (2H, q, *J* = 7.6 Hz, -CH_2), 1.18 (3H, t, *J* = 7.5 Hz, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 142.7 (C-3), 141.3 (C-5), 141.3 (C-5), 140.6 (C-4'), 138.3 (C-1'''), 135.1 (C-3'''), 134.8 (C-3'''), 133.8 (C-1''), 130.6 (C-5''), 130.3 (C-5'''), 130.1 (C-1'), 129.8 (C-4''), 129.4 (C-4'''), 128.7 (C-3',C-5'), 128.5 (C-2''), 128.2 (C-2'''), 127.5 (C-2',C-6'), 126.7 (C-6''), 126.5 (C-6'''), 123.7 (C-4), 37.6 (*N*-CH_3), 28.5 (-CH_2), 15.4 (-CH_3); GC-MS (EI, 70 eV): *m/z* (%) = 406 ($[M]^+$, 100), 405 (26), 391 (10); HRMS (EI, 70 eV): Calcd for $C_{24}H_{21}Cl_2N_2$ $[M+1]^+$: 407.1076; Found 407.1074.

5-(4-Ethylphenyl)-3,4-bis(4-methoxyphenyl)-1-methyl-1H-pyrazole (5e)



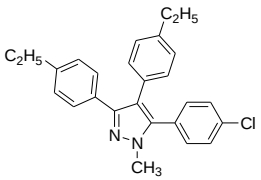
Yield = 86 %; Rf = 0.3; M.P. = 168-169 °C; IR (KBr) ν_{max}: 3052 (C=C-H), 1638 (C=N), 1584 (C=C), 1456 (C-N), 1043 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.42 (2H, d, *J* = 7.4 Hz, Ar-H-2',H-6'), 7.37 (2H, d, *J* = 7.8 Hz, Ar-H-2'',H-6''), 7.31 (2H, d, *J* = 7.8 Hz, Ar-H-2''',H-6'''), 7.18 (2H, d, *J* = 7.4 Hz, Ar-H-3',H-5'), 6.88 (2H, d, *J* = 7.8 Hz, Ar-H-3''',H-5'''), 6.74 (2H, d, *J* = 7.8 Hz, Ar-H-3'',H-5''), 3.76 (3H, s, *N*-CH_3), 3.71 (3H, s, OCH_3), 3.68 (3H, s, -OCH_3), 2.58 (2H, q, *J* = 7.6 Hz, -CH_2), 1.17 (3H, t, *J* = 7.5 Hz, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 158.8 (C-4''), 158.3 (C-4'''), 142.1 (C-3), 140.3 (C-5), 139.4 (C-4'), 130.0 (C-1'), 129.2 (C-1'''), 128.9 (C-2'',C-6''), 128.5 (C-2''',C-6'''), 128.3 (C-2',C-6'), 127.3 (C-3',C-5'), 125.7 (C-1''), 123.6 (C-4), 113.6 (C-3''',C-5'''), 113.4 (C-3'',C-5''), 55.3 (4''-OCH_3), 55.1 (4'''-OCH_3), 37.2 (*N*-CH_3), 28.5 (-CH_2), 15.2 (-CH_3); GC-MS (EI, 70 eV): *m/z* (%) = 398 ($[M]^+$, 100), 397 (12), 383 (18); HRMS (ESI^+): Calcd for $C_{26}H_{27}N_2O_2$ $[M+1]^+$: 399.2067; Found 399.2071.

5-(4-Chlorophenyl)-1-methyl-3,4-diphenyl-1H-pyrazole (5f)



Yield = 79 %; Rf = 0.45; M.P. = 156-157 °C; IR (KBr) ν_{max}: 3045 (C=C-H), 1633 (C=N), 1575 (C=C), 1446 (C-N) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.50-7.54 (2H, d, *J* = 7.1 Hz, Ar-H-2',H-6'), 7.38-7.42 (2H, d, *J* = 7.2 Hz, Ar-H-2'',H-6''), 7.28-7.34 (2H, d, *J* = 7.2 Hz, Ar-H-2''',H-6'''), 7.20-7.26 (4H, m, H-3'',5'',H-3''',5'''), 7.09-7.14 (2H, m, H-4'',H-4'''), 6.97-7.02 (2H, d, *J* = 7.2 Hz, Ar-H-3',H-5'), 3.85 (3H, s, *N*-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): ^{13}C NMR ($CDCl_3$, δ ppm): 142.1 (C-3), 140.2 (C-5), 136.4 (C-1'''), 133.7 (C-4'), 133.4 (C-1''), 131.4 (C-1'), 130.5 (C-3',C-5'), 129.8 (C-3'',C-5''), 129.4 (C-3''',C-5'''), 128.8 (C-2',C-6'), 128.3 (C-4''), 128.1 (C-4'''), 127.4 (C-2'',C-6''), 127.1 (C-2''',C-6'''), 123.7 (C-4), 37.5 (*N*-CH_3); GC-MS (EI, 70eV): *m/z* (%) = 346 ($[M, {}^{37}Cl_2]^+$, 100), 345 ($[M, {}^{35}Cl\ {}^{37}Cl]^+$, 34), 344 ($[M, {}^{35}Cl_2]^+$, 99); HRMS (EI, 70 eV): Calcd for $C_{22}H_{17}N_2Cl$ (M^+, [^{37}Cl]): 346.9143. Found 346.9143; Calcd for (M^+, [^{35}Cl]): 344.9132. Found 344.9133.

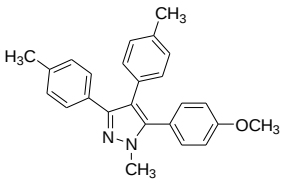
5-(4-Chlorophenyl)-3,4-bis(4-ethylphenyl)-1-methyl-1H-pyrazole (5g)



Yield = 81 %; Rf = 0.4; M.P. = 148-149 °C; IR (KBr) ν_{max}: 3041 (C=C-H), 1632 (C=N), 1578 (C=C), 1443 (C-N) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.30 (2H, d, *J* = 7.2 Hz, Ar-H-2',H-6'), 7.26 (2H, d, *J* = 7.3 Hz, Ar-H-2'',H-6''), 7.09 (2H, d, *J* = 7.3 Hz, Ar-H-2''',H-6'''), 7.02 (2H, d, *J* = 7.2 Hz, Ar-H-3',H-5'), 6.93 (2H, d, *J* = 7.3 Hz, Ar-H-

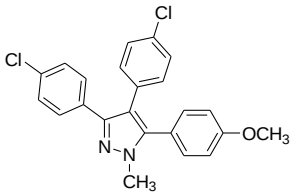
3’’’,H-5’’’), 6.86 (2H, d, *J* = 7.3 Hz, Ar-H-3’’,H-5’’), 3.75 (3H, s, *N*-CH_3), 2.54 (2H, q, *J* = 7.5 Hz, -CH_2), 2.48 (2H, q, *J* = 7.5 Hz, -CH_2), 1.17 (3H, t, *J* = 7.4 Hz, -CH_3), 1.12 (3H, t, *J* = 7.4 Hz, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 143.5 (C-3), 142.3 (C-5), 141.2 (C-4’’), 139.8 (C-4’’’), 134.5 (C-4’), 133.5 (C-1’’’), 131.4 (C-1’), 130.2 (C-1’’), 129.5 (C-3’,C-5’), 128.8 (C-2’,C-6’), 128.3 (C-3’’,C-5’’), 127.9 (C-3’’’,C-5’’’), 127.6 (C-2’’,C-6’’), 127.4 (C-2’’’,C-6’’’), 123.7 (C-4), 37.3 (*N*-CH_3), 28.5 (-CH_2), 28.4 (-CH_2), 14.3 (-CH_3), 14.1 (-CH_3); GC-MS (EI, 70 eV): *m/z* (%) = 400 ([M]$^+$, 100), 399 (13), 387 (12), 386 (10), 385 (35); HRMS (ESI$^+$): Calcd for $C_{26}H_{26}ClN_2$ [M+1]$^+$: 401.1779; Found 401.1781.

5-(4-Methoxyphenyl)-1-methyl-3,4-di-4-methylphenyl-1H-pyrazole (5h)



Yield = 83 %; Rf = 0.35; M.P. = 157-158 °C; IR (KBr) ν_{max}: 3053 (C=C-H), 1630 (C=N), 1576 (C=C), 1440 (C-N), 1037 (C-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.38 (2H, d, *J* = 7.8 Hz, Ar-H-2’,H-6’), 7.36 (2H, d, *J* = 7.4 Hz, Ar-H-2’’,H-6’’), 7.32 (2H, d, *J* = 7.4 Hz, Ar-H-2’’’,H-6’’’), 7.14 (2H, d, *J* = 7.4 Hz, Ar-H-3’’,H-5’’), 7.08 (2H, d, *J* = 7.4 Hz, Ar-H-3’’’,H-5’’’), 6.86 (2H, d, *J* = 7.8 Hz, Ar-H-3’,H-5’), 3.75 (3H, - s, *N*-CH_3), 3.72 (3H, s, -OCH_3), 2.24 (3H, s, -CH_3), 2.21 (3H, s, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 159.5 (C-4’), 143.4 (C-3), 141.8 (C-5), 136.8 (C-4’’), 136.5 (C-4’’’), 131.4 (C-1’’’), 130.8 (C-1’’), 130.6 (C-3’’,C-5’’), 130.2 (C-3’’’,C-5’’’), 128.8 (C-2’,C-6’), 127.8 (C-2’’,C-6’’), 127.4 (C-2’’’,C-6’’’), 125.4 (C-1’), 122.5 (C-4), 113.8 (C-3’,C-5’), 55.2 (4’-OCH_3), 37.2 (*N*-CH_3), 21.2 (4’’’-CH_3), 21.1 (4’’-CH_3); GC-MS (EI, 70 eV): *m/z* (%) = 368 ([M]$^+$, 100), 367 (31); HRMS (ESI$^+$): Calcd for $C_{25}H_{25}N_2O$ [M+1]$^+$: 369.1961; Found 369.1962.

3,4-Bis(4-chlorophenyl)-5-(4-methoxyphenyl)-1-methyl-1H-pyrazole (5i)



Yield = 82 %; Rf = 0.35; M.P. = 170-171 °C; IR (KBr) ν_{max}: 3053 (C=C-H), 1630 (C=N), 1636 (C=C), 1453 (C-N), 1040 (C-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.43-7.48 (2H, d, *J* = 7.2 Hz, Ar-H-2’’,H-6’’), 7.36-7.41 (2H, d, *J* = 7.2 Hz, Ar-H-2’’’,H-6’’’), 7.28-7.34 (2H, d, *J* = 7.3 Hz, Ar-H-2’,H-6’), 7.26-7.31 (2H, d, *J* = 7.2 Hz, Ar-H-3’’,H-5’’), 7.18-7.23 (2H, d, *J* = 7.2 Hz, Ar-H-3’’’,H-5’’’), 6.87-6.94 (2H, d, *J* = 7.3 Hz, Ar-H-3’,H-5’), 3.76 (3H, s, *N*-CH_3), 3.74 (3H, s, -OCH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 158.8 (C-4’), 142.5 (C-3), 140.6 (C-5), 135.4 (C-1’’’), 134.6 (C-4’’), 134.3 (C-4’’’), 131.4 (C-1’’), 130.1 (C-3’’,C-5’’), 129.6 (C-3’’’,C-5’’’), 128.7 (C-2’’’,C-6’’’), 128.5 (C-2’’,C-6’’), 128.3 (C-2’,C-6’), 126.2 (C-1’), 123.4 (C-4), 116.7 (C-3’,C-5’), 55.2 (4’-OCH_3), 37.5

(*N*-CH_3); GC-MS (EI, 70 eV): *m/z* (%) = 410 ([M, $^{37}Cl_2]^+$, 100), 409 ([M, $^{35}Cl^{37}Cl]^+$, 40), 408 ([M, $^{35}Cl_2]^+$, 100), 407 ([M^+, 25]); HRMS (ESI^+): Calcd for $C_{23}H_{19}Cl_2N_2O$ $[M+1]^+$: (M^+, $^{35}Cl^{37}Cl$]): 409.0869. Found 409.0867; Calcd for $[M+1]^+$: (M^+, [$^{37}Cl_2$]): 411.0844. Found 411.0855.

[heptane : ethyl acetate (5:5)]

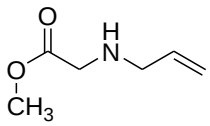
3.3 *N*-Substituted Dihydropyridinones

3.3.1 Synthesis of mono and diallylated amino esters (1a-d)

Procedure

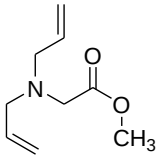
Amino ester hydrochloride derivatives (24.2 mmol) in dry DMF (35 mL) were stirred at room temperature under inert atmosphere. Potassium carbonate (7.37 g, 53.4 mmol, 2.2 eq) and allyl bromide (3.51 g, 29.15 mmol, 1.2 eq) were added successively, and the reaction mixture was stirred over night. After that it was diluted with water (20 mL) and extracted with diethyl ether (3x30 mL). The organic layer was washed with brine, dried and then filterate was concentrated. Both mono and diallyl products were formed. These products were separated and further purified by flash chromatography and (diethyl ether : CH_2Cl_2) 90:10 was used as an eluent.

Methyl 2-(allylamino)acetate (1a)



Yield = 82 %; Rf = 0.45; colorless liquid.; IR (KBr) ν_{max}: 3432 (N-H), 3037 (C=C-H), 1738 (ester C=O), 1576 (C=C), 1465 (C-N), 1021 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 5.76-5.87 (1H, m, H-6), 5.27 (1H, dd, *J* = 16.8,1.4 Hz, H-7), 5.21 (1H, dd, *J* = 9.8,1.4 Hz, H-7'), 3.96 (2H, d, *J* = 5.8 Hz, H-5), 3.81 (3H, s, -OCH_3), 3.51 (2H, s, H-3,H-3'), 1.54 (1H, s, -NH); ^{13}C NMR ($CDCl_3$, δ ppm): 173.1 (C=O) , 135.8 (C-6), 117.2 (C-7), 58.2 (C-5), 52.3 (C-1), 49.8 (C-3); EIMS *m/z* (%); [$M^{+\cdot}$] 129 (45), 110 (100 %), 81 (21), 79 (11), 68 (19), 41(33); Anal. Calcd. for $C_6H_{11}NO_2$: C, 55.81; H, 8.52; N, 10.84. Found: C, 55.68; H, 8.41; N, 10.63.

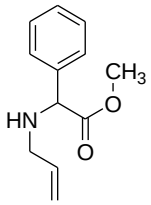
Methyl 2-(diallylamino)acetate (1b)



Yield = 71 %; Rf = 0.7; colorless liquid; IR (KBr) ν_{max}: 3051 (C=C-H), 1735 (ester C=O), 1572 (C=C), 1467 (C-N), 1024 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 5.71-5.83 (2H, m, H-6,H-6'), 5.21 (2H, dd, *J* = 16.8,1.2 Hz, H-7), 5.07 (1H, dd, *J* = 9.8,1.2 Hz, H-7'), 3.59 (3H, s, -OCH_3), 3.23 (2H, s, H-3,H-3'), 3.15 (4H, d, *J* = 6.4 Hz, H-5,H-5'); ^{13}C NMR ($CDCl_3$, δ ppm): 172.4 (C=O) , 136.1

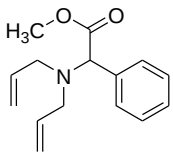
(C-6,C-6'), 118.7 (C-7,C-7'), 58.2 (C-5,C-5'), 54.1 (C-3), 52.3 (C-1); EIMS *m/z* (%); [$M^{+\cdot}$] 169 (17), 128 (27), 110 (100 %), 81 (13), 68 (22), 41 (62); Anal. Calcd. for $C_9H_{15}NO_2$: C, 63.91; H, 8.87, N, 8.28. Found: C, 63.83; H, 8.72; N, 8.15.

Methyl 2(S)-(allylamino)-2-phenylacetate (1c)



Yield = 86 %; Rf = 0.4; colorless liquid; IR (KBr) ν_{max}: 3436 (N-H), 3054 (C=C-H), 1734 (ester C=O), 1581 (C=C), 1455 (C-N), 1032 (C-O); ^{1}H NMR ($CDCl_3$, δ ppm): 7.28-7.41 (5H, m, Ph), 5.78-5.87 (1H, m, H-6), 5.23 (1H, dd, *J* = 16.8,1.4 Hz, H-7), 5.16 (1H, dd, *J* = 9.8,1.4 Hz, H-7'), 4.51 (1H, s, H-3), 3.82 (3H, s, -OCH_3), 3.24 (2H, d, *J* = 5.8 Hz, H-5,H-5'), 2.18 (1H, s, -NH); ^{13}C NMR ($CDCl_3$, δ ppm): 173.7 (C=O), 140.1 (C-1'), 137.3 (C-6), 128.9 (C-2',C-6'), 127.8 (C-3',C-5'), 126.6 (C-4'), 117.2 (C-7), 64.5 (C-3), 52.4 (C-5), 50.2 (C-1); EIMS *m/z* (%); [$M^{+\cdot}$] 205 (40), 186 (100 %), 103 (20), 91 (27), 41 (38); Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.24; H, 7.32, N, 6.83. Found: C, 70.18; H, 7.27; N, 6.75; [α] D^{20} = - 112.3 (c 1; CH_2Cl_2).

Methyl 2(S)-(diallylamino)-2-phenylacetate (1d)



Yield = 75 %; Rf = 0.67; colorless liquid; IR (KBr) ν_{max}: 3045 (C=C-H), 1737 (ester C=O), 1585 (C=C), 1458 (C-N), 1037 (C-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.31-7.42 (5H, m, Ph), 5.77-5.88 (2H, m, H-6,H-6'), 5.21 (2H, dd, *J* = 16.8,1.5 Hz, H-7), 5.12 (1H, dd, *J* = 10.4,1.5 Hz, H-7'), 4.56 (2H, s, H-3,H3'), 3.72 (3H, s, -OCH_3), 3.22 (4H, d, *J* = 6.1 Hz, H-5,5',H-5,5''); ^{13}C NMR ($CDCl_3$, δ ppm): 173.1 (C=O), 137.3 (C-1'), 136.2 (C-6,C-6'), 129.4 (C-2',C-6'), 128.6 (C-3',C-5'), 127.8 (C-4'), 118.5 (C-7,C-7'), 68.3 (C-3), 53.2 (C-5,C-5'), 51.6 (C-1); EIMS *m/z* (%); [$M^{+\cdot}$] 245 (26), 204 (34), 188 (17), 146 (100 %), 104 (19), 91 (23), 77 (14); Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.47; H, 7.76, N, 5.71. Found: C, 73.38; H, 7.63; N, 5.62; [α] D^{20} = - 68.3 (c 1; CH_2Cl_2).

3.3.2 *N*-Allyl-*N*-Protection Reactions (2a-e)

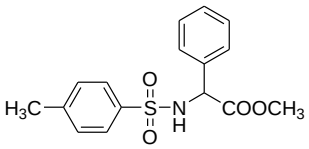
i) Tosylation

Procedure

N-allyl amino ester derivatives (2 mL, 26.1 mmol) were added to the stirred solution of *p*-toluenesulfonyl chloride (1.1 g, 5.12 mmol) in dichloromethane (35 mL) at 0 °C under inert atmosphere. The reaction mixture was stirred for 2-3 hr. After that the

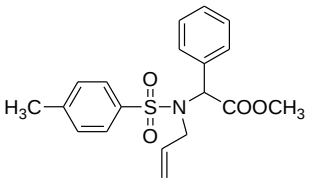
reaction mixture was concentrated and then extracted with ethyl acetate (3x20 mL). The organic layer was washed with brine, dried it over anhydrous sodium sulphate and evaporated to get product. The product was further purified by flash chromatography and (diethyl ether : CH_2Cl_2) 85:15 was used as an eluent.

Methyl 2(S)-[(4-methylphenyl)sulfonyl]amino-2-phenylacetate (2a)



Yield = 88 %; Rf = 0.4; yellow amorphous solid; IR (KBr) ν_{max}: 3423 (N-H), 3037 (C=C-H), 1728 (ester C=O), 1723 (S=O), 1575 (C=C), 1456 (C-N), 1036 (C-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.80 (1H, d, *J* = 7.6 Hz, H-2'',H-6''), 7.72 (1H, d, *J* = 7.6 Hz, H-3'',H-5''), 7.29-7.69 (5H, m, Ph), 5.21 (1H, s, H-3), 3.66 (3H, s, -OCH_3), 2.47 (1H, s, -CH_3), 2.25 (1H, s, -NH); ^{13}C NMR ($CDCl_3$, δ ppm): 169.1 (C=O), 141.8 (C-1'), 140.3 (C-1''), 132.2 (C-4''), 130.3 (C-2',C-6'), 129.9 (C-3'',C-5''), 129.4 (C-3',C-5'), 128.6 (C-2'',C-6''), 128.3 (C-4'), 57.1 (C-3), 53.6 (-OCH_3), 21.7 (-CH_3); EIMS *m/z* (%); [$M^{+\cdot}$] 319 (51), 196 (100 %), 106 (64), 91 (76); Anal. Calcd. for $C_{16}H_{17}NO_4S$: C, 60.18; H, 5.33, N, 4.38, S, 10.03. Found: C, 60.07; H, 5.26; N, 4.27, S, 9.94; [α] D^{20} = - 81.5 (c 0.1; CH_2Cl_2).

Methyl 2(S)-[*N*-allyl-(4-methylphenyl)sulfonyl]amino-2-phenylacetate (2b)



Yield = 87 %; Rf = 0.65; colorless liquid; IR (KBr) ν_{max}: 3043 (C=C-H), 1731 (ester C=O), 1725 (S=O), 1578 (C=C), 1452 (C-N), 1034 (C-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.83 (1H, d, *J* = 7.6 Hz, H-2'',H-6''), 7.77 (1H, d, *J* = 7.6 Hz, H-3'',H-5''), 7.19-7.72 (5H, m, Ph), 5.78 (1H, s, H-3), 5.42-5.51 (1H, m, H-5), 4.78-4.67 (2H, m, H-6,H-6'), 3.73-3.88 (2H, m, H-4,H-4'), 3.71 (3H, s, -OCH_3), 2.37 (3H, s, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 170.6 (C=O), 143.8 (C-4''), 138.5 (C-1''), 137.2 (C-1'), 135.1 (C-5), 129.8 (C-3'',C-5''), 129.3 (C-2'',C-6''), 128.9 (C-2',C-6'), 128.6 (C-3,C-5'), 127.7 (C-4'), 116.8 (C-6), 63.1 (C-3), 52.3 (-OCH_3), 48.5 (C-4), 21.5 (-CH_3); EIMS *m/z* (%); [$M^{+\cdot}$] 359 (13), 207 (14), 186 (100 %), 158 (29), 118 (41), 104 (25), 91 (54), 77 (12); Anal. Calcd. for $C_{19}H_{21}NO_4S$: C, 65.51; H, 5.85, N, 3.91, S, 8.92. Found: C, 65.43; H, 5.68, N, 3.84, S, 8.81; [α] D^{20} = - 203 (c 0.6; CH_2Cl_2).

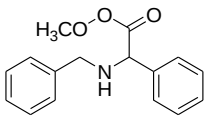
ii) Benzylation

Procedure

N-allyl amino ester derivatives (7 mmol) in dry DMF (20 mL) were stirred at 25 °C under inert atmosphere. Potassium carbonate (2.13 g, 15.4 mmol) and then benzyl

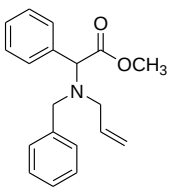
bromide (3.63 g, 30 mmol) were added successively and the reaction mixture was stirred for 24-25 hr. After that the mixture was quench with cold H_2O (10 mL) and extracted with diethyl ether (2x30 mL). The organic layer was washed with brine and dried it over anhydrous sodium sulphate and then concentrated. The product was further purified by flash chromatography and (diethyl ether : CH_2Cl_2) 90:10 was used as an eluent.

Methyl 2(S)-(benzylamino)-2-phenylacetate (2c)



Yield = 70 %; Rf = 0.5; yellow oil; IR (KBr) ν_{max}: 3431 (N-H), 3026 (C=C-H), 1727 (ester C=O), 1573 (C=C), 1462 (C-N), 1028 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.15-7.52 (10H, m, Ph), 4.67 (1H, s, H-3), 3.86 (2H, s, H-4), 3.67 (3H, s, -OCH_3), 2.25 (1H, s, -NH); ^{13}C NMR ($CDCl_3$, δ ppm): 172.3 (C-2) , 136.7 (C-1'), 135.8 (C-1''), 130.3 (C-2'',C-6''), 129.4 (C-3'',C-5''), 128.8 (C-3',C-5'), 128.2 (C-2',C-6'), 127.9 (C-4''), 127.3 (C-4'), 65.2 (C-3), 52.4 (-OCH_3), 51.6 (-CH_2); EIMS *m/z* (%); [$M^{+\cdot}$] 271 (35), 224 (34), 196 (100 %), 180 (52), 165 (37), 149 (41), 106 (25), 91 (31), 77 (24); Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 75.31; H, 6.67, N, 5.51; Found: C, 75.27; H, 6.52, N, 5.42; [α] D^{20} = - 31.4 (c 0.3; CH_2Cl_2).

Methyl 2(S)-[allyl(benzyl)amino]-2-phenylacetate (2d)



Yield = 77 %; Rf = 0.75; yellow oil; IR (KBr) ν_{max}: 3046 (C=C-H), 1732 (ester C=O), 1587 (C=C), 1455 (C-N), 1035 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.32-7.67 (10H, m, Ph), 5.76-5.89 (1H, m, H-5), 5.22 (1H, dd, *J* = 16.8,2.1 Hz, H-6), 5.16 (1H, dd, *J* = 10.4,2.1 Hz, H-6'), 4.72 (1H, s, H-3), 3.81 (2H, *J* = 14.8 Hz, H-7,H-7'), 3.76 (3H, s, -OCH_3), 3.23 (2H, d, *J* = 5.8 Hz, H-4,H-4'); ^{13}C NMR ($CDCl_3$, δ ppm): 172.6 (C=O) , 140.1 (C-1''), 137.3 (C-1'), 136.2 (C-5), 129.1 (C-9,9'), 128.9 (C-2'',6''), 128.7 (C-3'',5''), 128.3 (C-3',5'), 128.1 (C-4''), 127.8 (C-4'), 118.2 (C-6), 67.3 (C-3), 54.4 (-CH_2), 53.5 (C-4), 51.7 (-OCH_3); EIMS *m/z* (%); [$M^{+\cdot}$] 295 (37), 236 (43), 131 (10), 91 (100 %), 76 (16), 41 (12); Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.28; H, 7.12; N, 4.75. Found: C, 77.14; H, 7.03; N, 4.63; [α] D^{20} = - 47.5 (c 0.1; CH_2Cl_2).

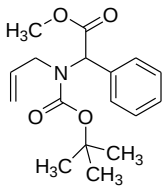
iii) Boc Formation

Procedure

Boc_2O (2.4 g, 11 mmol) was added to the stirred solution of *N*-allyl amino ester derivatives (10 mmol) in dioxane (35 mL) under inert atmosphere. The reaction mixture was stirred for 14-15 hr at room temperature. After that the mixture was concentrated,

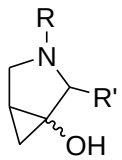
diluted with diethyl ether (5 mL) and then it was extracted with ethyl acetate (3x20 mL). The organic layer was washed with brine, dried and then filtrate was concentrated. The product was further purified by flash chromatography and (diethyl ether : CH_2Cl_2) 80:20 was used as an eluent.

Methyl 2(S)-[allyl(*tert*-butoxycarbonyl)amino]-2-phenylacetate (2e)



Yield = 74 %; Rf = 0.45; colorless liquid; IR (KBr) ν_{max}: 3052 (C=C-H), 1726 (ester C=O), 1673 (Boc C=O), 1577 (C=C), 1465 (C-N), 1042 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.13-7.22 (5H, m, Ph), 5.41 (1H, s, H-1), 5.76-5.85 (1H, m, H-5), 5.12-5.19 (2H, m, H-6), 3.64-3.73 (2H, m, H-4), 3.56 (3H, s, $-OCH_3$), 2.14 (9H, s, $3\times CH_3$); ^{13}C NMR ($CDCl_3$, δ ppm): 171.8 (ester C=O), 163.2 (Boc C=O), 136.6 (C-1'), 134.7 (C-5), 129.8 (C-2',C-6'), 129.1 (C-3',C-5'), 127.4 (C-4'), 116.7 (C-6), 79.5 (C-8), 63.9 (C-3), 52.3 ($-OCH_3$), 47.4 (C-4), 28.3 ($3\times CH_3$); EIMS *m/z* (%); [$M^{+\cdot}$] 305 (30), 264 (46), 246 (42), 232 (31), 204 (37), 174 (28), 156 (100 %), 149 (54), 119 (35), 101 (26), 83 (24), 77 (21); Anal. Calcd. for $C_{17}H_{23}NO_4$: C, 66.87 ; H, 4.26; N, 4.58. Found: C, 66.76; H, 4.16; N, 4.47; [α] D^{20} = - 123.2 (c 0.3; CH_2Cl_2).

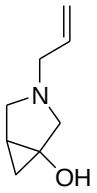
3.3.3 Synthesis of 3-Substituted-3-aza-bicyclo[3.1.0]hexan-1-ols (3a-e')



Procedure

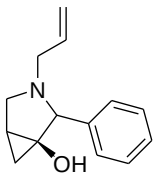
Titanium isopropoxide (0.13 mL, 0.43 mmol) was added to the stirred solution of variously substituted amino ester hydrochloride derivatives (0.5 mmol) in anhydrous Et_2O/THF (1:1, 25 mL) at 20 °C under inert atmosphere. Grignard's reagent (isopropylmagnesium bromide in ether) was added drop wise through a syringe during the period of 3 hr. The reaction mixture was allowed to stirr for 1 additional hr. Precipitates were appeared in reaction flask, filter off these precipitates. The aqueous phase was extracted with ethyl acetate (2x25 mL), organic layer was washed with brine, dried it over anhydrous sodium sulphate and then concentrated. The products were further purified by flash chromatography and (diethyl ether : ethyl acetate) 75:25 was used as an eluent.

3-Allyl-3-aza-bicyclo[3.1.0]hexan-1-ol (3a)



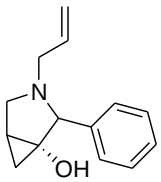
Yield = 70 %; Rf = 0.6; colorless oil; IR (KBr) ν_{max}: 3387 (O-H), 3051 (C=C-H), 1581 (C=C), 1456 (C-N), 1032 (C-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 5.79-5.87 (1H, m, H-7), 5.20 (1H, dd, *J* = 9.6,2.2 Hz, H-8), 5.12 (1H, dd, *J* = 9.6,2.2 Hz, H-8'), 4.27 (1H, s, H-1), 3.27 (1H, dd, *J* = 7.6,6.1 Hz, H-5), 3.12 (1H, dd, *J* = 7.6,6.1 Hz, H-5'), 2.48 (1H, dd, *J* = 12.6,4.1Hz, H-6), 2.39 (1H, dd, *J* = 12.6,4.1 Hz, H-6'), 2.58 (1H, s, -OH), 1.86-1.90 (1H, m, H-4), 1.24 (1H, dd, *J* = 7.4,3.6 Hz, H-3), 1.03 (1H, dd, *J* = 7.4,3.6 Hz, H-3'); ^{13}C NMR ($CDCl_3$, δ ppm): 134.7 (C-7), 116.5 (C-8), 67.6 (C-1), 65.7 (C-2), 60.2 (C-5), 58.1 (C-6), 25.8 (C-4), 16.5 (C-3); EIMS *m/z* (%); [$M^{+\cdot}$] 139 (33), 122 (100 %), 112 (16), 98 (43), 85 (12), 55 (36), 41 (35); Anal. Calcd. for $C_8H_{13}NO$: C, 69.06; H, 9.35, N, 10.07. Found: C, 68.96; H, 9.27, N, 9.98.

(1R,2S,5R)-3-Allyl-2-phenyl-3-aza-bicyclo[3.1.0]hexan-1-ol (3b)



Yield = 74 %; Rf = 0.55; yellow oil; IR (KBr) ν_{max}: 3392 (O-H), 3047 (C=C-H), 1583 (C=C), 1452 (C-N), 1037 (C-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.31-7.54 (5H, m, Ph), 5.33-5.68 (1H, m, H-7), 5.12 (1H, dd, *J* = 16.8,1.4 Hz, H-8), 5.01 (1H, dd, *J* = 16.8,1.4 Hz, H-8'), 4.21 (1H, s, H-1), 3.09 (1H, dd, *J* = 8.8,3.8 Hz, H-5), 2.87 (1H, dd, *J* = 13.8,6.1 Hz, H-6), 2.77 (1H, dd, *J* = 8.8,3.8 Hz, H-5'), 2.67 (1H, dd, *J* = 13.8,6.1 Hz, H-6'), 2.04 (1H, s, -OH), 1.71-1.76 (1H, m, H-4), 1.22 (1H, dd, *J* = 8.7,4.2 Hz, H-3), 0.91 (1H, dd, *J* = 8.7,4.2 Hz, H-3'); ^{13}C NMR ($CDCl_3$, δ ppm): 138.5 (C-9), 136.7 (C-7), 129.6 (C-10,C-10'), 128.8 (C-11,C-11'), 127.9 (C-12), 116.3 (C-8), 70.1 (C-1), 65.3 (C-2), 54.1 (C-6), 53.2 (C-5), 24.1 (C-4), 17.3 (C-3); EIMS *m/z* (%); [$M^{+\cdot}$] 215 (19), 187 (44), 144 (100 %), 118 (39), 104 (57), 91 (75), 77 (32); Anal. Calcd. for $C_{14}H_{17}NO$: C, 78.14; H, 7.91; N, 6.51. Found: C, 78.04; H, 7.83; N, 6.43. [α] D^{20} = -50.3 (c 1; CH_2Cl_2).

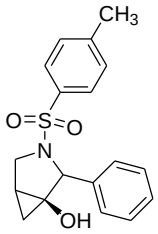
(1R,2S,5S)-3-Allyl-2-phenyl-3-aza-bicyclo[3.1.0]hexan-1-ol (3b')



Yield = 77 %; Rf = 0.6; yellow oil; IR (KBr) ν_{max}: 3377 (O-H), 3052 (C=C-H), 1578 (C=C), 1454 (C-N), 1027 (C-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.31-7.43 (5H, m, Ph), 5.75-5.84 (1H, m, H-7), 5.21 (1H, dd, *J* = 16.8,1.2 Hz, H-8), 5.13 (1H, dd, *J* = 16.8,1.2 Hz, H-8'), 4.11 (1H, s, H-1), 3.21 (1H, dd, *J* = 8.8,3.8 Hz, H-5), 2.78 (1H, dd, *J* = 13.8,6.1 Hz, H-6), 2.75 (1H, dd, *J* = 8.8,3.8 Hz, H-5'), 2.64 (1H, dd, *J* = 13.8,6.1 Hz, H-6'), 2.11 (1H, s, -OH), 1.60-1.64 (1H, m, H-4), 1.18 (1H, dd, *J* = 8.7,4.1 Hz, H-3), 0.85 (1H, dd, *J* = 8.7,4.1 Hz, H-3'); ^{13}C

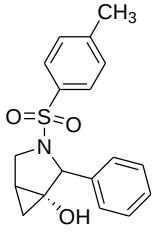
NMR ($CDCl_3$, δ ppm): 140.3 (C-9), 136.8 (C-7), 130.2 (C-10,C-10'), 129.9 (C-11,C-11'), 128.6 (C-12), 117.4 (C-8), 72.2 (C-1), 65.5 (C-2), 56.4 (C-6), 53.7 (C-5), 22.6 (C-4), 14.1 (C-3); EIMS *m/z* (%); [$M^{+\cdot}$] 215 (22), 186 (67), 144 (100 %), 118 (38), 104 (54), 91 (12), 77 (19); Anal. Calcd. for $C_{14}H_{17}NO$: C, 78.13; H, 7.90; N, 6.52. Found: C, 78.06; H, 7.78; N, 6.47; [α] D^{20} = -213.5 (c 1; CH_2Cl_2).

(1S,2S)-2-Phenyl-3-(4-methylphenylsulfonyl)-3-aza-bicyclo[3.1.0]hexan-1-ol (3c)



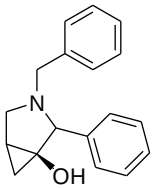
Yield = 66 %; Rf = 0.7; yellow semi-solid; IR (KBr) ν_{max}: 3454 (O-H), 3055 (C=C-H), 1725 (S=O), 1587 (C=C), 1462 (C-N), 1034 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.64 (1H, d, *J* = 7.1 Hz, H-2,H-6), 7.33-7.57 (5H, m, Ph), 7.24 (1H, d, *J* = 7.1 Hz, H-3,H-5), 4.87 (1H, s, H-1), 3.68 (1H, dd, *J* = 10.1,3.6 Hz, H-5), 3.49 (1H, d, *J* = 10.1 Hz, H-5'), 2.46 (1H,s, -OH), 2.17 (3H, s, $-CH_3$), 1.69-1.74 (1H, m, H-4), 1.19 (1H, dd, *J* = 9.1,4.2 Hz, H-3), 0.51 (1H, t, *J* = 4.2,4.2 Hz, H-3'); ^{13}C NMR ($CDCl_3$, δ ppm): 143.4 (C-4'), 138.3 (C-1''), 132.2 (C-1'), 130.3 (C-2',C-6'), 129.5 (C-3'',C-5''), 128.8 (C-2'',C-6''), 127.8 (C-3',C-5'), 126.7 (C-4''), 66.3 (C-1), 68.6 (C-2), 50.2 (C-5), 23.4 (Ar-CH_3), 22.1 (C-4), 16.2 (C-3); EIMS *m/z* (%); [$M^{+\cdot}$] 329 (36), 301 (51), 224 (33), 174 (57), 146 (100 %), 118 (36), 104 (22), 91 (81), 77 (16); Anal. Calcd. for $C_{18}H_{19}NO_3S$: C, 65.65; H, 5.78; N, 4.26, S, 9.72. Found: C, 65.54; H, 5.64; N, 4.21, S, 9.63; [α] D^{20} = -305 (c 0.7; CH_2Cl_2).

(1R,2S)-3-[(4-Methylphenyl)sulfonyl]-2-phenyl-3-azabicyclo[3.1.0]hexan-1-ol (3c')



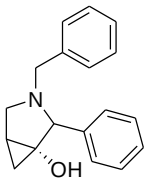
Yield = 53 %; Rf = 0.57; yellow semi-solid; IR (KBr) ν_{max}: 3463 (O-H), 3051 (C=C-H), 1723 (S=O), 1585 (C=C), 1467 (C-N), 1031 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.67 (1H, d, *J* = 7.1 Hz, H-2,H-6), 7.32-7.64 (5H, m, Ph), 7.26 (1H, d, *J* = 7.1 Hz, H-2,H-6), 4.98 (1H, s, H-1), 3.63 (1H, d, *J* = 9.8 Hz, H-5'), 3.42 (1H, dd, *J* = 9.8,4.2 Hz, H-5), 2.47 (1H, s, -OH), 2.18 (3H, s, $-CH_3$), 1.88-1.94 (1H, m, H-4), 1.42 (1H, t, *J* = 4.5,4.5 Hz, H-3), 1.12 (1H, dd, *J* = 9.2,4.5 Hz, H-3'); ^{13}C NMR ($CDCl_3$, δ ppm): 144.7 (C-4'), 138.4 (C-1''), 132.5 (C-1'), 130.3 (C-2',C-6'), 129.5 (C-3'',C-5''), 128.9 (C-2'',C-6''), 128.3 (C-3',C-5'), 126.2 (C-4''), 68.7 (C-2), 67.8 (C-1), 52.6 (C-5), 22.3 (Ar-CH_3), 21.7 (C-4), 15.8 (C-3); EIMS *m/z* (%); [$M^{+\cdot}$] 329 (25), 301 (47), 224 (30), 207 (44), 174 (67), 146 (100 %), 118 (53), 104 (15), 91 (78), 77 (13); Anal. Calcd. for $C_{18}H_{19}NO_3S$: C, 65.65; H, 5.77; N, 4.25, S, 9.73. Found: C, 65.43; H, 5.64; N, 4.17, S, 9.61; [α] D^{20} = -194 (c 0.5; CH_2Cl_2).

(1R,2S,5R)-Benzyl-2-phenyl-3-aza-bicyclo[3.1.0]hexan-1-ol (3d)



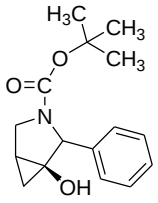
Yield = 75 %; Rf = 0.5; yellow oil; IR (KBr) ν_{max}: 3376 (O-H), 3045 (C=C-H), 1574 (C=C), 1464 (C-N), 1032 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.13-7.54 (10H, m, Ph), 4.18 (1H, s, H-1), 3.37 (2H, *J* = 13.8 Hz, H-6,H-6'), 3.14 (1H, dd, *J* = 9.1,4.5 Hz, H-5), 2.76 (1H, d, *J* = 9.1 Hz, H-5'), 2.18 (1H, s, -OH), 1.67-1.85 (1H, m, H-4), 1.28 (1H, t, *J* = 4.6,4.6 Hz, H-3), 1.21 (1H, dd, *J* = 9.2,4.6 Hz, H-3'); ^{13}C NMR ($CDCl_3$, δ ppm): 140.2 (C-1'), 138.5 (C-1''), 128.8 (C-2'',C-6''), 128.6 (C-3'',C-5''), 128.4 (C-2',C-6'), 128.1 (C-3',C-5'), 127.8 (C-4''), 127.1 (C-4'), 69.5 (C-1), 68.4 (C-2), 54.6 (C-6), 53.2 (C-5), 24.3 (C-4), 17.4 (C-3); EIMS *m/z* (%); [$M^{+\cdot}$] 265 (29), 248 (18), 237 (21), 194 (14), 188 (13), 174 (100 %), 160 (23), 91 (19), 77 (31); Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.50; H, 7.16; N, 5.28. Found: C, 81.42; H, 7.08; N, 5.15; [α] D^{20} = -9.2 (c 0.5; CH_2Cl_2).

(1R,2S,5S)-3-Benzyl-2-phenyl-3-aza-bicyclo[3.1.0]hexan-1-ol (3d')



Yield = 71 %; Rf = 0.4; off-white solid; IR (KBr) ν_{max}: 3372 (O-H), 3047 (C=C-H), 1583 (C=C), 1453 (C-N), 1030 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.31-7.65 (10H, m, Ph), 3.83 (1H, s, H-1), 3.77 (2H, *J* = 12.8 Hz, H-6,H-6'), 2.87 (1H, d, *J* = 9.2 Hz, H-5), 2.56 (1H, dd, *J* = 9.1,3.8 Hz, H-5'), 2.14 (1H, s, -OH), 1.48-1.61 (1H, m, H-4), 1.26 (1H, t, *J* = 4.2,4.2 Hz, H-3), 0.71 (1H, dd, *J* = 9.1,4.2 Hz, H-3'); ^{13}C NMR ($CDCl_3$, δ ppm): 140.1 (C-1'), 138.7 (C-1''), 129.6 (C-2'',C-6''), 128.7 (C-3'',C-5''), 128.5 (C-2',C-6'), 128.2 (C-3',C-5'), 127.9 (C-4''), 126.8 (C-4'), 71.8 (C-1), 70.2 (C-2), 57.1 (C-6), 53.4 (C-5), 22.3 (C-4), 14.2 (C-3); EIMS *m/z* (%); [$M^{+\cdot}$] 265 (33), 248 (16), 237 (26), 194 (25), 188 (11), 174 (100 %), 160 (40), 91 (21), 77 (26); Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.51; H, 7.17, N, 5.28. Found: C, 81.41; H, 7.05; N, 4.18; [α] D^{20} = -50.2 (c 0.5; CH_2Cl_2).

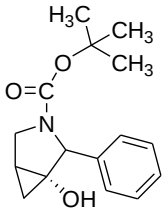
(1R,2S,5R)-*Tert*-Butyl 1-hydroxy-2-phenyl-3-aza-bicyclo[3.1.0]hexane-3-carboxylate (3e)



Yield = 68 %; Rf = 0.65; colorless liquid; IR (KBr) ν_{max}: 3475 (O-H), 3058 (C=C-H), 1732 (C=O), 1584 (C=C), 1451 (C-N), 1035 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.52-7.73 (5H, m, Ph), 4.68 (1H, s, H-1), 3.43 (1H, dd, *J* = 9.5,3.4 Hz, H-5'), 3.26 (1H, dd, *J* = 9.5,3.4 Hz, H-5), 2.38 (1H, s, -OH), 1.37 (9H, s, 3×CH_3), 1.58-1.67 (1H, m, H-4), 1.32 (1H, dd, *J* = 9.4,3.6 Hz, H-3), 1.12 (1H, dd, *J* = 9.4,3.6 Hz,H-3'); ^{13}C NMR ($CDCl_3$, δ ppm): 157.8 (C=O), 140.3 (C-1'),

129.8 (C-3',C-5'), 129.1 (C-2',C-6'), 126.4 (C-4'), 78.7 (C-7), 71.8 (C-1), 68.2 (C-2), 51.6 (C-5), 28.5 (-CH_3), 22.8 (C-4), 14.4 (C-3); EIMS *m/z* (%); [$M^{+\cdot}$] 275 (45), 258 (17), 218 (28), 202 (100 %), 174 (39), 157 (13), 101 (53), 97 (34), 77 (11); Anal. Calcd. for $C_{16}H_{21}NO_3$: C, 69.82; H, 7.64; N, 5.10. Found: C, 69.74; H, 7.52; N, 4.98; [α] D^{20} = -47.3 (c 0.5; CH_2Cl_2).

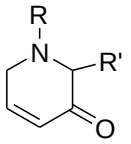
(1R,2S,5S)-*Tert*-Butyl 1-hydroxy-2-phenyl-3-aza-bicyclo[3.1.0]hexane-3-carboxylate (3e')



Yield = 63 %; Rf = 0.4; colorless liquid; IR (KBr) ν_{max}: 3471 (O-H), 3056 (C=C-H), 1730 (C=O), 1582 (C=C), 1463 (C-N), 1036 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.49-7.67 (5H, m, Ph), 4.72 (1H, s, H-1), 3.47 (1H, dd, *J* = 9.4,3.2 Hz, H-5'), 3.29 (1H, dd, *J* = 9.4,3.2 Hz, H-5), 2.41 (1H, s, -OH), 1.28 (9H, s, 3×CH_3), 1.55-1.63 (1H, m, H-4), 1.35 (1H, dd, *J* = 9.4,3.5 Hz, H-3), 1.16 (1H, dd, *J* = 9.4,3.5 Hz, H-3'); ^{13}C NMR ($CDCl_3$, δ ppm): 158.3 (C=O), 141.2 (C-1'), 130.4 (C-3',C-5'), 129.5 (C-2',C-6'), 126.4 (C-4'), 78.1 (C-7), 72.3 (C-1), 67.6 (C-2), 52.2 (C-5), 27.8 (-CH_3), 21.6 (C-4), 13.7 (C-3); EIMS *m/z* (%); [$M^{+\cdot}$] 275 (19), 258 (14), 218 (22), 202 (100 %), 174 (42), 157 (16), 101 (57), 97 (30), 77 (13); Anal. Calcd. for $C_{16}H_{21}NO_3$: C, 69.81; H, 7.63; N, 5.09. Found: C, 69.72; H, 7.55; N, 4.97; [α] D^{20} = -54.6 (c 0.5; CH_2Cl_2).

[Pet.ether : Ether (7:3)]

3.3.4 Synthesis of *N*-Substituted-1,6-dihydro-3(2H)-pyridinones (4a-e)

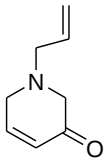


Procedure

Anhydrous $FeCl_3$ (0.18 g, 1.1 mmol) suspension in diethyl ether (2 mL) was added dropwise to the stirred solution of variously substituted aza-bicyclo[3.1.0]hexan-1-ols (0.5 mmol) in diethyl ether (3 mL) at 0 °C under inert atmosphere. The reaction mixture was stirred for 3 hr at 0 °C. The mixture was then diluted with (2 mL) of freshly distilled methanol and anhydrous sodium acetate (205 mg, 5 mmol) was added porsion wise. The temperature of the reaction mixture was rised to 20 °C and stirred it over night. The mixture was concentrated and then extracted with ethyl acetate to get crude

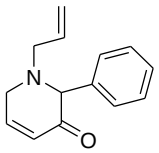
dihydropyridinones. The products were further purified by flash chromatography and (diethyl ether : CH_2Cl_2) 85:15 was used as an eluent.

1-Allyl-1,6-dihydro-3(2H)-pyridinone (4a)



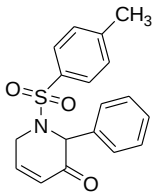
Yield = 71 %; Rf = 0.6; reddish brown oil; IR (KBr) ν_{max}: 3068 (C=C-H), 1673 (ring C=O), 1583 (C=C), 1452 (C-N) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.02 (1H, dt, *J* = 10.2 Hz, *J* = 2.4 Hz, H-4), 6.58 (1H, d, *J* = 10.2 Hz, H-3), 5.74-5.84 (1H, m, H-7), 5.19 (1H, dd, *J* = 1.2,16.4 Hz, H-8), 5.23 (1H, dd, *J* = 1.2,8.2 Hz, H-8'), 3.98 (1H, dd, *J* = 8.4,2.2 Hz, H-5), 3.94 (1H, dd, *J* = 8.4,2.2 Hz, H-5'), 3.74 (2H, s, H-1), 3.37-3.48 (2H, m, H-6,H-6'); ^{13}C NMR ($CDCl_3$, δ ppm): 196.7 (C=O), 134.6 (C-7), 128.8 (C-3), 124.6 (C-4), 117.1 (C-8), 68.4 (C-1), 58.4 (C-6), 52.5 (C-5); EIMS *m/z* (%); [$M^{+\cdot}$] 137 (23), 110 (42), 96 (100 %), 55 (51), 41 (36); Anal. Calcd. for $C_8H_{11}NO$: C, 70.07; H, 8.03; N, 10.2. Found: C, 69.94; H, 7.92, N, 9.91.

(2S)-1-Allyl-2-phenyl-1,6-dihydro-3(2H)-pyridinone (4b)



Yield = 75 %; Rf = 0.65; reddish brown oil; IR (KBr) ν_{max}: 3063 (C=C-H), 1676 (ring C=O), 1586 (C=C), 1445 (C-N) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.33-7.43 (5H, m, Ph), 7.11 (1H, dt, *J* = 10.2,3.4 Hz, H-4), 6.28 (1H, dt, *J* = 10.2,3.2 Hz, H-3), 5.79-5.84 (1H, m, H-7), 5.21 (1H, dd, *J* = 2.1,16.8 Hz, H-8), 5.16 (1H, dd, *J* = 2.1,10.2 Hz, H-8'), 4.26 (1H, s, H-1), 3.54 (1H, ddd, *J* = 19.8, 3.4, 1.5 Hz, H-5), 3.38 (1H, ddd, *J* = 19.8, 3.4, 1.5 Hz, H-5'), 3.15-3.08 (2H, m, H-6,H-6'); ^{13}C NMR ($CDCl_3$, δ ppm): 195.7 (C=O), 147.4 (C-3), 138.3 (C-1'), 135.2 (C-7), 130.2 (C-2',C-6'), 129.1 (C-3',C-5'), 128.7 (C-4'), 127.2 (C-4), 119.3 (C-8), 73.5 (C-1), 58.4 (C-6), 47.6 (C-5); EIMS *m/z* (%); [$M^{+\cdot}$] 213 (43), 172 (100 %), 144 (54), 117 (25), 104 (31), 91 (46), 77 (12), 67 (36); Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.87; H, 7.04; N, 6.57. Found: C, 78.66; H, 6.96, N, 6.45; [α] D^{20} = -103.4 (c 0.8; CH_2Cl_2).

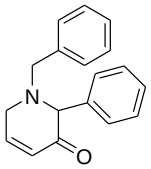
(2S)-2-Phenyl-1-[4-(methylphenylsulfonyl)-1,6-dihydro-3(2H)-pyridinone (4c)



Yield = 58 %; Rf = 0.6; light yellow oil; IR (KBr) ν_{max}: 2956 (C=C-H), 1716 (S=O), 1678 (ring C=O), 1591 (C=C), 1446 (C-N) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.69 (1H, d, *J* = 7.4 Hz, H-2,H-6), 7.27-7.56 (5H, m, Ph), 7.19 (1H, d, *J* = 7.4 Hz, H-3,H-5), 6.69 (1H, dt, *J* = 10.2,4.5 Hz, H-4), 5.87 (1H, d, *J* = 10.6 Hz, H-3), 4.51 (1H, ddd, *J* = 19.6, 4.6, 2.4 Hz, H-5), 4.31 (1H, s, H-1), 3.79 (1H, ddd, *J* = 19.6, 4.5, 2.4 Hz, H-5'), 2.38 (3H, s, $-CH_3$); ^{13}C NMR ($CDCl_3$, δ ppm): 191.8 (C=O), 145.1 (C-3), 136.7 (C-1''), 133.8 (C-4'), 132.6 (C-1'), 130.3 (C-3',C-5'),

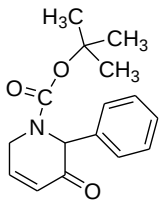
129.4 (C-3'',C-5''), 128.7 (C-2'',C-6''), 127.8 (C-2',C-6'), 127.2 (C-4''), 126.8 (C-4), 64.3 (C-1), 42.1 (C-5), 22.3 (Ar-CH_3); EIMS *m/z* (%); [$M^{+\cdot}$] 327 (34), 207 (19), 196 (74), 172 (100 %), 146 (84), 118 (44), 91 (71), 77 (13); Anal. Calcd. for $C_{18}H_{17}NO_3S$: C, 66.05; H, 5.21; N, 4.28, S, 9.78. Found: C, 65.93; H, 5.16; N, 4.21, S, 9.62; [α] D^{20} = -145 (c 0.3; CH_2Cl_2).

(2S)-1-Benzyl-2-phenyl-1,6-dihydro-3(2H)-pyridinone (4d)



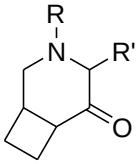
Yield = 84 %; Rf = 0.7; off-white solid; IR (KBr) ν_{max}: 3058 (C=C-H), 1684 (ring C=O), 1585 (C=C), 1453 (C-N) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.21-7.93 (10H, m, Ph), 6.94 (1H, dt, *J* = 10.4,3.6 Hz, H-4), 6.25 (1H, dt, *J* = 10.4,3.2 Hz, H-3), 4.28 (1H, s, H-1), 3.76 (2H, s, -CH_2), 3.57 (1H, ddd, *J* = 18.2,3.4,2.1 Hz, H-5), 3.24 (1H, ddd, *J* = 18.6,3.4,2.1 Hz, H-5'); ^{13}C NMR ($CDCl_3$, δ ppm): 195.8 (C=O), 148.2 (C-3), 138.3 (C-1'), 136.8 (C-1''), 129.2 (C-2'',C-6''), 128.8 (C-3'',C-5''), 128.6 (C-2',C-6'), 128.4 (C-3',C-5'), 128.2 (C-4''), 128.1 (C-4'), 127.6 (C-4), 72.8 (C-1), 58.7 (C-6), 48.6 (C-5); EIMS *m/z* (%); [$M^{+\cdot}$] 263 (31), 196 (74), 194 (38), 172 (100 %), 91 (86), 77 (21); Anal. Calcd. for $C_{18}H_{17}NO$: C, 82.13; H, 6.46, N, 5.32. Found: C, 82.04; H, 6.32; N, 5.37; [α] D^{20} = -74.3 (c 0.8; CH_2Cl_2).

(2S)-1-*tert*-Butyl-5-oxo-6-phenyl-5,6-dihydropyridine-1(2H)-carboxylate (4e)



Yield = 67 %; Rf = 0.5; yellow oil; IR (KBr) ν_{max}: 3057 (C=C-H), 1692 (N-C=O), 1677 (ring C=O), 1587 (C=C), 1455 (C-N), 1036 (C-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.05-7.15 (5H, m, Ph), 6.67 (1H, dt, *J* = 10.2,3.6 Hz, H-4), 6.17 (1H, dt, *J* = 10.2,2.6 Hz, H-3), 4.53 (1H, s, H-1), 3.61 (1H, ddd, *J* = 19.6, 3.4, 2.2 Hz, H-5), 3.68 (1H, ddd, *J* = 19.6, 3.4, 2.2 Hz, H-5'), 3.31 (9H, s, -OCH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 196.7 (C=O), 156.7 (C-6), 134.7 (C-1'), 129.2 (C-3), 128.8 (C-2',C-6'), 128.3 (C-3',C-5'), 127.1 (C-4'), 123.2 (C-4), 78.4 (C-7), 72.1 (C-1), 43.5 (C-5), 27.6 (3-CH_3); EIMS *m/z* (%); [$M^{+\cdot}$] 273 (27), 200 (100 %), 196 (57), 172 (45), 124 101 (33), 96 (31), 77 (24); Anal. Calcd. for $C_{16}H_{19}NO_3$: C, 70.33; H, 6.95; N, 5.13. Found: C, 70.24; H, 6.83; N, 5.01; [α] D^{20} = - 46.7 (c 0.5; CH_2Cl_2).

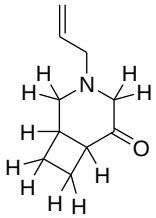
3.3.5 [2+2] Photocycloaddition Reactions of *N*-Substituted Dihydropyridinones (5a-d)



Procedure

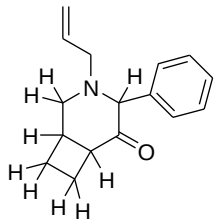
Various *N*-substituted dihydropyridinones were treated photochemically with (N25 grade) ethylene in the presence of acetone, a medium pressure Hg lamp (400 W) in a water-cooled annular reactor (250 mL useful volume) fitted with a Pyrex filter. All the dihydropyridinones were converted into bicyclo adducts, while going through a regular [2+2] photo cycloaddition reaction. *N*-Benzyl dihydropyridinone was photochemically transformed unexpected into a β-lactam ring. After the completion, the reaction mixture was concentrated and then extracted with ethyl acetate to get crude dihydropyridinones. The products were further purified by flash chromatography and (diethyl ether : CH_2Cl_2) 85:15 was used as an eluent.

(2S)-3-Allyl-3-aza-bicyclo[4.2.0]octan-5-one (5a)



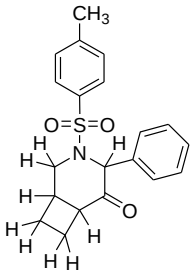
Yield = 54 %; Rf = 0.4; IR (KBr) ν_{max}: 1675 (ring C=O), 1587 (C=C), 1142 (C-N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 5.82 (1H, m, H-7), 5.16 (1H, dd, *J* = 1.2,16.4 Hz, H-8), 5.15 (1H, dd, *J* = 1.2,8.2 Hz, H-8'), 4.54 (2H, s, H-1), 3.34 (1H, dd, *J* = 7.6,6.1 Hz, H-5), 3.17-3.28 (2H, m, H-6,H-6'), 3.15 (1H, dd, *J* = 7.6,6.1 Hz, H-5'), 2.78 (1H, m, H-3), 2.41 (1H, m, H-4), 1.72-2.31 (4H, m, cyclobutane ring); ^{13}C NMR (75 MHz, $CDCl_3$): 207.5 (C=O), 134.1 (C-7), 115.7 (C-8), 64.3 (C-1), 63.5 (C-5), 58.4 (C-6), 38.2 (C-3), 32.6 (C-4), 23.1 (cyclobutane C-3'), 22.3 (cyclobutane C-4'); GC-MS (EI, 70 eV): *m/z* (%): 165 ($[M]^{+\cdot}$, 100); Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.68; H, 9.15; N, 8.48. Found: C, 72.57; H, 9.07; N, 8.37.

(2S)-3-Allyl-4-phenyl-3-aza-bicyclo[4.2.0]octan-5-one (5b)



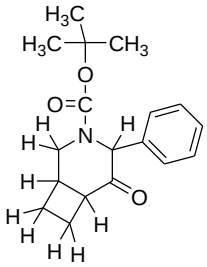
Yield = 57 %; Rf = 0.35; IR (KBr) ν_{max}: 3051 (C=C-H), 1674 (ring C=O), 1581 (C=C), 1136 (C-N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 7.04-7.24 (5H, m, Ph), 5.85 (1H, m, H-7), 5.21 (1H, dd, *J* = 1.2,16.4 Hz, H-8), 5.17 (1H, dd, *J* = 1.2,8.2 Hz, H-8'), 4.71 (1H, s, H-1), 3.36 (1H, dd, *J* = 7.6,6.1 Hz, H-5), 3.18-3.31 (2H, m, H-6,H-6'), 3.16 (1H, dd, *J* = 7.6,6.1 Hz, H-5'), 2.81 (1H, m, H-3), 2.42 (1H, m, H-4), 1.74-2.33 (4H, m, cyclobutane ring); ^{13}C NMR (75 MHz, $CDCl_3$): 207.8 (C=O), 136.5 (C-1'), 134.7 (C-7), 130.4 (C-2',C-6'), 128.6 (C-2',C-5'), 127.3 (C-4'), 117.2 (C-8), 74.3 (C-1), 60.1 (C-5), 56.3 (C-6), 38.8 (C-3), 33.1 (C-4), 23.3 (cyclobutane C-3''), 22.6 (cyclobutane C-4''); GC-MS (EI, 70 eV): *m/z* (%): 241 ($[M]^{+\cdot}$, 100); Anal. Calcd. for $C_{16}H_{19}NO$: C, 79.62; H, 7.93; N, 5.81. Found: C, 79.52; H, 7.81; N, 5.73.

(2S)-4-Phenyl-3-tosyl-3-aza-bicyclo[4.2.0]octan-5-one (5c)



Yield = 55 %; Rf = 0.3; IR (KBr) ν_{max}: 3046 (C=C-H), 1714 (S=O), 1673 (ring C=O), 1582 (C=C), 1143 (C-N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 7.86 (1H, d, *J* = 7.4 Hz, H-7,H-7'), 7.42 (1H, d, *J* = 7.4 Hz, H-8,H-8'), 7.11-7.31 (5H, m, Ph), 4.76 (1H, s, H-1), 3.41 (1H, dd, *J* = 7.5,6.1 Hz, H-5), 3.21 (1H, dd, *J* = 7.5,6.1 Hz, H-5'), 2.82 (1H, m, H-3), 2.43 (1H, m, H-4), 1.78-2.37 (4H, m, cyclobutane ring), 2.28 (3H, s, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): 208.7 (C=O), 144.5 (C-9), 136.7 (C-1'), 132.6 (C-6), 130.3 (C-8,C-8'), 129.4 (C-3',C-5'), 128.7 (C-2',C-6'), 127.8 (C-7,C-7'), 127.2 (C-4'), 66.3 (C-1), 48.5 (C-5), 38.4 (C-3), 32.8 (C-4), 24.3 ($-CH_3$), 23.4 (cyclobutane C-3''), 22.5 (cyclobutane C-4''); GC-MS (EI, 70 eV): *m/z* (%): 355 ($[M]^{+\cdot}$, 100); Anal. Calcd. for $C_{20}H_{21}NO_3S$: C, 67.58; H, 5.95; N, 3.93; S, 9.01. Found: C, 67.44; H, 3.86; N, 3.81; S, 8.91.

(2S)-*tert*-Butyl 5-oxo-4-phenyl-3-aza-bicyclo[4.2.0]octane-3-carboxylate (5d)



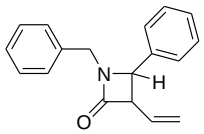
Yield = 45 %; Rf = 0.3; IR (KBr) ν_{max}: 3043 (C=C-H), 1694 (Boc C=O), 1675 (ring C=O), 1579 (C=C), 1146 (C-N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 7.08-7.27 (5H, m, Ph), 5.74 (1H, s, H-1), 3.38 (1H, dd, *J* = 7.6,6.1 Hz, H-5), 3.19 (1H, dd, *J* = 7.6,6.1 Hz, H-5'), 2.81 (1H, m, H-3), 2.80 (1H, m, H-4), 1.76-2.35 (4H, m, cyclobutane ring), 1.46 (9H, s, $-CH_3$); NMR (75 MHz, $CDCl_3$): 208.4 (C=O), 164.2 (N-C=O), 136.4 (C-1'), 134.6 (C-7), 130.7 (C-2',C-6'), 128.3 (C-2',C-5'), 127.5 (C-4'), 117.2 (C-8), 80.3 (C), 54.5 (C-5), 56.3 (C-6), 38.7 (C-3), 33.4 (C-4), 27.4 ($3\times CH_3$), 23.6 (cyclobutane C-3''), 22.7 (cyclobutane C-4''); GC-MS (EI, 70 eV): *m/z* (%): 301 ($[M]^{+\cdot}$, 100); Anal. Calcd. for $C_{18}H_{23}NO_3$: C, 71.72; H, 7.69; N, 4.65. Found: C, 71.54; H, 7.53; N, 4.57.

2.3.6 Synthesis of *N*-Substituted-4-phenyl-3-vinylazetidin-2-ones by [2+2] Photo-cycloaddition Reactions (6a-b)

Various *N*-substituted dihydropyridinones were treated photochemically with ethylene in the presence of acetone, to explore the mechanism of photochemically induced unexpected transformation of 1-benzyl-2-phenyl-1,6-dihydro-3(2H)-pyridinone into β-lactam ring instead of going through a regular [2+2] cycloaddition reaction. This transformation occurs in two steps by the formation of vinyl ketene and imine *via* [4+2] reaction, which recombine again quickly to form β-lactam.

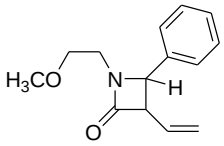
N-Benzylidene-2-methoxyethanamine was synthesized and then the reaction was carried out in the presence of this imine as well as ethylene. This imine competes in the second step and thus provides access to β-lactam ring substituted with *N*-benzylidene-2-methoxyethanamine and the yield of the reaction was not very high. The proposed mechanism was correct and confirmed by NMR.

1-Benzyl-4-phenyl-3-vinylazetidin-2-one (6a)



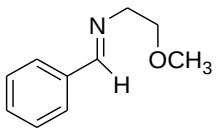
Yield = 35 %; Rf = 0.35; IR (KBr) ν_{max}: 3038 (C=C-H), 1663 (C=O), 1568 (C=C) cm-^{1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.24-7.73 (10H, m, Ph), 5.93 (1H, m, H-a), 5.22 (1H, dd, *J* = 1.3,16.2 Hz, H-b), 5.18 (1H, dd, *J* = 1.3,8.2 Hz, H-c), 4.46 (2H, s, -CH_2), 4.37 (1H, s, C-4), 3.92 (1H, s, C-3); ^{13}C NMR ($CDCl_3$, δ ppm): 186.2 (C=O), 138.4 (C-1'), 137.5 (C-a), 136.5 (C-1''), 129.7 (C-3',C-5'), 129.1 (C-3'',C-5''), 128.8 (C-2',C-6'), 128.2 (C-2'',C-6''), 127.3 (C-4'), 127.1 (C-4''), 116.8 (C-b), 57.8 (C-4), 49.7 (-CH_2), 48.7 (C-3); EIMS (70 eV): *m/z* (%); [$M^{+\cdot}$] 249 (32 %); Anal. Calcd. for $C_{17}H_{15}NO$; C, 81.89; H, 6.05; N, 5.61. Found: C, 81.74; H, 5.96; N, 5.53.

1-(2-Methoxyethyl)-4-phenyl-3-vinylazetidin-2-one (6b)



Yield = 33 %; Rf = 0.3; IR (KBr) ν_{max}: 1661 (C=O), 1571 (C=C), 1022 (C-O) cm-^{1}; ^{1}H NMR ($CDCl_3$, δ ppm): 8.12 (N=C-H), 7.54-7.68 (5H, m, Ph), 3.72 (2H, s, C-2), 3.71 (2H, s, C-1), 2.41 (3H, s, -OCH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 185.7 (C=O), 141.8 (C-1'), 132.4 (C-4'), 130.6 (C-2',C-6'), 129.3 (C-3',C-5'), 74.5 (C-2), 68.2 (C-1), 56.7 (-OCH_3); EIMS (70 eV): *m/z* (%); [$M^{+\cdot}$] 231 (26 %); Anal. Calcd. for $C_{14}H_{17}NO_2$; C, 72.70; H, 7.42; N, 6.05. Found: C, 72.54; H, 7.36; N, 5.97.

2.3.7 Synthesis of *N*-Benzylidene-2-methoxyethanamine (7a)



Procedure

The aldehyde (50 mmol) was added to a stirred solution of 2-methoxyethanamine (50 mmol) in CH_2Cl_2 in the presence of molecular sieves (4 A^{o}, 2 gm). The reaction mixture was stirred at room temperature for 1 hr. The molecular sieves were filtered off and filtrate was dried over anhyd. sodium carbonate and solvent was removed on vacuo to get crude *N*-benzylidene-2-methoxyethanamine.

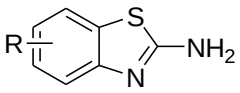
***N*-Benzylidene-2-methoxyethanamine (7a)**

Yield = 63 %; Rf = 0.3; IR (KBr) ν_{max}: 1633 (C=N), 1588 (C=C), 1422 (C-N) cm-^{1}; ^{1}H NMR ($CDCl_3$, δ ppm): 8.12 (N=C-H), 7.54-7.68 (5H, m, Ph), 3.72 (2H, s, C-2), 3.71 (2H, s, C-1), 2.41 (3H, s, -OCH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 161.2 (C=N), 141.8 (C-1'), 132.4 (C-4'), 130.6 (C-2',C-6'), 129.3 (C-3',C-5'), 74.5 (C-2), 68.2 (C-1), 56.7 (OCH_3); EIMS (70 eV): *m/z* (%); [$M^{+\cdot}$] 163 (21 %); Anal. Calcd. for $C_{10}H_{13}NO$; C, 73.57; H, 8.02; N, 8.56. Found: C, 55.34; H, 4.36; N, 18.37; S, 20.82.

[Pet.ether : Ether (7:3)]

3.4 Iminothiazolidinones

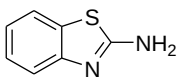
3.4.1 Synthesis of Substituted Benzo[d]thiazol-2-amines (1a-e)



Procedure

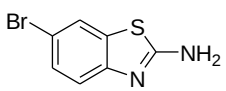
Acetic acid (45 mL), 4-bromoaniline (3 g, 30 mmol) and potassium thiocyanate (11.6 g, 120 mmol) were stirred at 20 ^{o}C for 10 minutes on an ice-bath. Bromine (1.5 mL, 30 mmol) in AcOH (20 mL) was added dropwise over 20 min, during the addition the temperature was increased to 35 ^{o}C. Then the reaction mixture was stirred for 21 hr at room temperature. The mixture was poured into cold NH_4OH (~90 mL) and extracted with ethyl acetate. The organic phase was washed with water (150 mL), dried and then evaporated. The crude product obtained was recrystallized by methanol/ethanol.

Benzo[d]thiazol-2-amine (1a)



Yield = 91 %; Rf = 0.35; M.P. = 128-130 °C; IR (KBr) ν_{max}: 3458 (N-H), 2723 (C-S), 1637 (C=N), 1583 (C=C), 1428 (C-N) cm-^{1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.47 (1H, d, *J* = 8.7 Hz, H-1), 7.16 (1H, d, *J* = 8.6 Hz, H-4), 7.52-7.58 (2H, m, H-2,H-3), 5.41 (1H, bs, -NH); ^{13}C NMR ($CDCl_3$, δ ppm): 166.2 (S-C=N), 146.8 (C-9), 127.4 (C-6), 126.8 (C-5), 125.7 (C-8), 123.5 (C-7), 122.6 (C-4); EIMS (70 eV): *m/z* (%); [$M^{+\cdot}$] 150 (41 %); Anal. Calcd. for $C_7H_6N_2S$; C, 55.47; H, 4.54; N, 18.46; S, 20.96. Found: C, 55.34; H, 4.36; N, 18.37; S, 20.82.

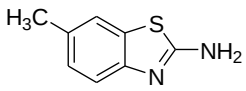
6-Bromo-benzo[d]thiazol-2-amine (1b)



Yield = 79 %; Rf = 0.2; M.P. = 161-163 ^{o}C; IR (KBr) ν_{max}: 3450 (N-H), 2728 (C-S), 1631 (C=N), 1587 (C=C), 1427 (C-N) cm-^{1}; ^{1}H

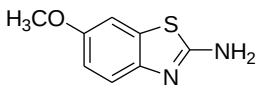
NMR ($CDCl_3$, δ ppm): 7.45 (1H, d, *J* = 8.7 Hz, H-3), 7.16 (1H, d, *J* = 8.7 Hz, H-1), 6.87 (1H, dd, *J* = 8.7,2.4 Hz, H-2), 5.42 (1H, bs, -NH); ^{13}C NMR ($CDCl_3$, δ ppm): 166.4 (S-C=N), 146.3 (C-9), 129.4 (C-5), 127.8 (C-8), 125.4 (C-4), 124.5 (C-7), 118.6 (C-6); EIMS (70 eV): *m/z* (%); [$M^{+\cdot}$] 227.9 (53 %); Anal. Calcd. for $C_7H_5N_2SBr$; C, 37.68; H, 2.18; N, 12.22; S, 18.97. Found: C, 37.46; H, 2.11; N, 12.14; S, 18.74.

6-Methyl-benzo[d]thiazol-2-amine (1c)



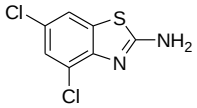
Yield = 76 %; Rf = 0.2; M.P. = 135-137 °C; (lit. M.P. = 137); IR (KBr) ν_{max}: 3396 (N-H), 2725 (C-S), 1635 (C=N) 1582 (C=C), 1434 (C-N) cm-^{1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.46 (1H,d, *J* = 8.7 Hz, H-1), 7.10 (1H, d, *J* = 2.4 Hz, H-3), 6.91 (1H, dd, *J* = 8.7,2.4 Hz, H-2), 5.43 (1H, bs, -NH), 2.51 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 166.3 (S-C=N), 145.7 (C-9), 132.4 (C-6), 127.5 (C-5), 125.6 (C-8), 123.4 (C-4), 122.5 (C-7), 23.6 (-CH_3); EIMS (70 eV): *m/z* (%); [$M^{+\cdot}$] 164 (37 %); Anal. Calcd. for $C_8H_8N_2S$; C, 54.54; H, 4.88; N, 17.07; S, 19.51. Found: C, 54.46; H, 4.69; N, 16.95; S, 19.33.

6-Methoxy-benzo[d]thiazol-2-amine (1d)



Yield = 83 %; Rf = 0.3; M.P. = 145-147 °C, (lit. M.P. = 147); IR (KBr) ν_{max}: 3389 (N-H), 2733 (C-S), 1644 (C=N), 1585 (C=C), 1442 (C-N) cm-^{1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.47 (1H, d, *J* = 8.7 Hz, H-1), 7.14 (1H, d, *J* = 2.4 Hz, H-2), 6.93 (1H, dd, *J* = 8.7,2.4 Hz, H-3), 5.41 (1H, bs, -NH), 3.81 (3H, s, -OCH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 166.2 (S-C=N), 145.1 (C-9), 138.6 (C-6), 126.5 (C-8), 124.6 (C-4), 121.4 (C-5), 116.5 (C-7), 56.8 (-OCH_3); EIMS (70 eV): *m/z* (%); [$M^{+\cdot}$] 180 (51 %); Anal. Calcd. for $C_8H_8N_2OS$; C, 52.33; H, 4.44; N, 15.55; S, 17.77. Found: C, 52.26; H, 4.35; N, 15.37; S, 17.61.

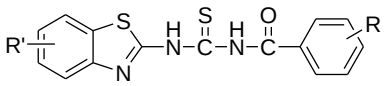
4,6-Dichloro-benzo[d]thiazol-2-amine (1e)



Yield = 85 %; Rf = 0.4; M.P. = 153-154 °C; IR (KBr) ν_{max}: 3356 (N-H), 2734 (C-S), 1647 (C=N), 1586 (C=C), 1432 (C-N) cm-^{1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.47 (1H, d, *J* = 2.4 Hz, H-3), 7.14 (1H, d, *J* = 2.4 Hz, H-2), 5.44 (1H, bs, -NH); ^{13}C NMR ($CDCl_3$, δ ppm): 166.7 (S-C=N), 147.5 (C-9), 133.4 (C-6), 128.6 (C-8), 126.8 (C-4), 124.6 (C-5), 121.7 (C-7); EIMS (70 eV): *m/z* (%); [$M^{+\cdot}$] 218 (46 %); Anal. Calcd. for $C_7H_4Cl_2N_2S$; C, 38.91; H, 1.21; N, 13.24; S, 14.83. Found: C, 38.76; H, 1.13; N, 13.18; S, 14.74.

[Pet. ether : ethyl acetate (7:3)]

3.4.2 Synthesis of 1-(Benzo[d]thiazol-2-yl)-3-(substituted) thioureas (2a-k)

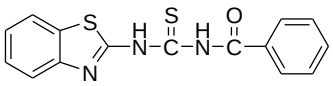


Procedure

Benzoic acid (2.3 g, 20 mmol) was treated with 2 mL (1.3 eq) of thionylchloride, added dropwise through dropping funnel. The reaction mixture was heated under reflux for 2-3 hr to afford corresponding acid chloride.

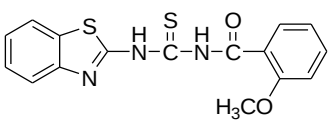
To the stirred solution of potassium thiocyanate (1.2 g, 20 mmol) in 10 mL of dry acetone, freshly prepared (1.5 mL, 20 mmol) of acid chloride was added dropwise. After the initial reaction had subsided, 2-benzothiazolamine (3 g, 20 mmol) in acetone (20 mL) solution was added slowly with constant stirring followed by reflux for 1-2 hr. The mixture was poured into crushed ice, thioureas were precipitated as solid. The solid product was filtered, then dried and recrystallized from methanol/ethanol.

1-(Benzo[d]thiazol-2-yl)-3-benzoylthiourea (2a)



Yield = 87 %; Rf = 0.7; M.P. = 114-116 °C; IR (KBr) ν_{max}: 3237 (N-H), 1674 (amide C=O), 1632 (C=N), 1576 (C=C), 1254 (C=S), 1151 (C-N) cm-^{1}; ^{1}H NMR ($CDCl_3$, δ ppm): 11.34 (1H, s, -NH), 10.06 (1H, s, -NH), 7.66-8.26 (5H, m, Ar), 7.56 (1H, dd, *J* = 6.9,7.4 Hz, H-3), 7.42 (1H, dd, *J* = 7.2,6.8 Hz, H-4), 7.17 (1H, d, *J* = 8.4 Hz, H-1), 7.15 (1H, d, *J* = 8.2 Hz, H-2); ^{13}C NMR ($CDCl_3$, δ ppm): 180.4 (C=S), 172.2 (S-C=N), 168.3 (amide C=O), 147.3 (C-9), 135.7 (C-1'), 133.6 (C-4'), 130.4 (C-3',C-5'), 128.5 (C-2',C-6'), 127.2 (C-6), 126.4 (C-5), 125.5 (C-8), 123.3 (C-4), 122.7 (C-7); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 313 (58 %); Anal. Calcd. for $C_{15}H_{11}N_3S_2O$; C, 57.50; H, 3.51; N, 13.41; S, 20.44 Found: C, 57.36; H, 3.38; N, 13.27; S, 20.23.

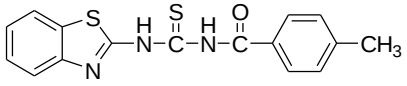
1-(Benzo[d]thiazol-2-yl)-3-(2-methoxybenzoyl) thiourea (2b)



Yield = 75 %; Rf = 0.6; M.P. = 105-106 °C; IR (KBr) ν_{max}: 3254 (N-H), 1676 (amide C=O), 1631 (C=N), 1575 (C=C), 1248 (C=S), 1153 (C-N) cm-^{1}; ^{1}H NMR ($CDCl_3$, δ ppm): 11.38 (1H, s, -NH), 10.09 (1H, s, -NH), 8.28 (1H, d, *J* = 7.4 Hz, H-1), 7.81 (1H, d, *J* = 7.4 Hz, H-4), 7.74 (1H, d, *J* = 7.1 Hz, H-2'), 7.24-7.63 (2H, m, Ar), 7.47 (1H, dd, *J* = 8.4,7.8 Hz, H-4'), 7.18 (1H, dd, *J* = 7.8,8.3 Hz, H-5'), 7.08 (1H, d, *J* = 8.4 Hz, H-3'), 4.15 (3H, s, -OCH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 181.3 (C=S), 172.4 (S-C=N), 168.5

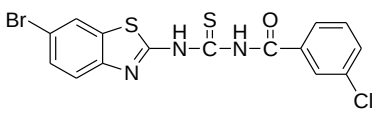
(amide C=O), 147.5 (C-9), 138.7 (C-2'), 133.5 (C-4'), 129.3 (C-6'), 127.4 (C-6), 126.5 (C-5), 125.3 (C-8), 123.7 (C-4), 123.2 (C-7), 121.5 (C-5'), 118.7 (C-1'), 116.4 (C-3'), 56.4 (-OCH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 343 (53 %); Anal. Calcd. for $C_{16}H_{13}N_3O_2S_2$; C, 50.97; H, 3.79; N, 12.24; S, 18.65. Found: C, 55.52; H, 3.65; N, 12.17; S, 18.46.

1-(Benzo[d]thiazol-2-yl)-3-(4-methylbenzoyl)thiourea (2c)



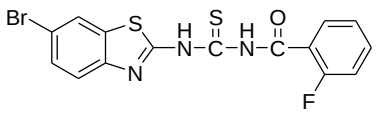
Yield = 86 %; Rf = 0.7; M.P. = 112-114 °C; IR (KBr) ν_{max}: 3282 (N-H), 1670 (amide C=O), 1636 (C=N), 1578 (C=C), 1255 (C=S), 1147 (C-N) cm-^{1}; ^{1}H NMR ($CDCl_3$, δ ppm): 10.68 (1H, s, -NH), 9.18 (1H, s, -NH), 8.25 (1H, d, *J* = 7.4 Hz, H-1), 7.91 (1H, d, *J* = 7.4 Hz, H-4), 7.82 (1H, dd, *J* = 7.1,7.8 Hz, H-2), 7.56 (1H, dd, *J* = 7.1,7.8 Hz, H-3), 7.51 (1H, d, *J* = 7.8 Hz, H-2'-,H-6'), 7.37 (1H, d, *J* = 7.8 Hz, H-3',H-5'), 2.47 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 180.6 (C=S), 172.5 (S-C=N), 168.2 (amide C=O), 147.3 (C-9), 136.2 (C-4'), 132.6 (C-1'), 130.3 (C-3',C-5'), 128.2 (C-2',C-6'), 126.7 (C-6), 126.2 (C-6), 125.5 (C-8), 123.2 (C-4), 122.7 (C-7), 23.6 (-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 327 (60 %); Anal. Calcd. for $C_{16}H_{13}N_3OS_2$; C, 58.71; H, 3.97; N, 13.84; S, 19.57. Found: C, 58.49; H, 3.61; N, 13.58; S, 19.34.

1-(6-Bromobenzo[d]thiazol-2-yl)-3-(3-chlorobenzoyl)thiourea (2d)



Yield = 76 %; Rf = 0.65; M.P. = 180-182 °C; IR (KBr) ν_{max}: 3257 (N-H), 1683 (amide C=O), 1633 (C=N), 1573 (C=C), 1244 (C=S), 1150 (C-N) cm-^{1}; ^{1}H NMR ($CDCl_3$, δ ppm): 10.81 (1H, s, -NH), 9.37 (1H, s, -NH), 8.11 (1H, d, *J* = 7.4 Hz, H-1), 7.96 (1H, d, *J* = 2.4 Hz, H-3), 7.94 (1H, d, *J* = 7.4 Hz, H-2), 7.84 (1H, d, *J* = 7.2 Hz, H-6'), 7.71 (1H, d, *J* = 2.3 Hz, H-2'), 7.69 (1H, dd, *J* = 7.1,2.3 Hz, H-4'), 7.31 (1H, d, *J* = 7.2 Hz, H-5'); ^{13}C NMR ($CDCl_3$, δ ppm): 181.7 (C=S), 172.5 (S-C=N), 168.7 (amide C=O), 147.8 (C-9), 136.5 (C-1'), 135.4 (C-3'), 133.6 (C-4'), 130.8 (C-5'), 129.5 (C-5), 128.6 (C-2'), 127.4 (C-8), 126.5 (C-6'), 124.8 (C-4), 124.3 (C-7), 118.6 (C-6); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 426.9 (100 %); Anal. Calcd. for $C_{15}H_9BrClN_3OS_2$; C, 42.15; H, 2.11; N, 9.83; S, 14.98. Found: C, 42.06; H, 2.04; N, 9.70; S, 14.85.

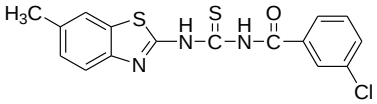
1-(6-Bromobenzo[d]thiazol-2-yl)-3-(2-fluorobenzoyl)thiourea (2e)



Yield = 72 %; Rf = 0.75; M.P. = 110-112 °C; IR (KBr) ν_{max}: 3265 (N-H), 1675 (amide C=O), 1632 (C=N), 1587 (C=C), 1247 (C=S), 1142 (C-N) cm-^{1}; ^{1}H NMR ($CDCl_3$, δ ppm): 9.61 (1H, s, -NH), 9.31 (1H, s, -NH), 7.80 (1H, d, *J* = 7.6 Hz, H-1), 7.73 (1H, d, *J* = 2.4 Hz, H-2), 7.49 (1H, d, *J*

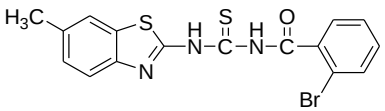
= 7.6 Hz, H-3), 7.35 (1H, d, *J* = 7.1 Hz, H-6'), 7.29 (1H, dd, *J* = 7.1,7.3 Hz, H-5'), 7.09 (1H, dd, *J* = 7.3,7.1 Hz, H-4'), 6.89 (1H, d, *J* = 7.3 Hz, H-3'); ^{13}C NMR ($CDCl_3$, δ ppm): 182.4 (C=S), 172.7 (S-C=N), 168.9 (amide C=O), 148.1 (C-9), 140.5 (C-2'), 134.7 (C-4'), 131.6 (C-1'), 130.4 (C-6'), 129.6 (C-5), 127.5 (C-8), 125.5 (C-5'), 124.7 (C-4), 124.2 (C-7), 118.4 (C-6), 116.7 (C-3'); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 410.9 (64 %); Anal. Calcd. for $C_{15}H_9BrFN_3OS_2$; C, 43.79; H, 2.19; N, 10.22; S, 15.57. Found: C, 43.61; H, 2.13; N, 10.13; S, 15.44.

1-(3-Chlorobenzoyl)-3-(6-methylbenzo[d]thiazol-2-yl)thiourea (2f)



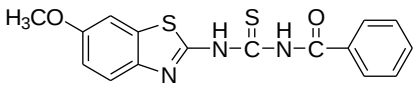
Yield = 75 %; Rf = 0.8; M.P. = 164-166 °C; IR (KBr) ν_{max}: 3270 (N-H), 1672 (amide C=O), 1634 (C=N), 1583 (C=C), 1245 (C=S), 1165 (C-N) cm-^{1}; ^{1}H NMR ($CDCl_3$, δ ppm): 10.78 (1H, s, -NH), 9.35 (1H, s, -NH), 8.11 (1H, d, *J* = 7.6 Hz, H-1), 7.96 (1H, d, *J* = 2.4 Hz, H-2), 7.92 (1H, d, *J* = 7.8 Hz, H-3'), 7.81 (1H, d, *J* = 2.3 Hz, H-2'), 7.74 (1H, d, *J* = 7.1 Hz, H-6'), 7.62 (1H, dd, *J* = 7.2,2.3 Hz, H-4'), 7.35 (1H, dd, *J* = 7.1,7.2 Hz, H-5'), 2.47 (3H, s, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 181.5 (C=S), 172.6 (S-C=N), 168.7 (amide C=O), 146.4 (C-9), 136.7 (C-1'), 135.6 (C-3'), 134.5 (C-6), 133.5 (C-4'), 131.4 (C-5'), 128.7 (C-2'), 128.3 (C-2'), 127.6 (C-5), 126.5 (C-6'), 125.4 (C-8), 123.4 (C-4), 122.6 (C-7), 23.4 (-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 361 (56 %); Anal. Calcd. for $C_{16}H_{12}ClN_3OS_2$; C, 53.18; H, 3.32; N, 11.63; S, 17.73. Found: C, 53.07; H, 3.27; N, 11.57; S, 17.52.

1-(2-Bromobenzoyl)-3-(6-methylbenzo[d]thiazol-2-yl)thiourea (2g)



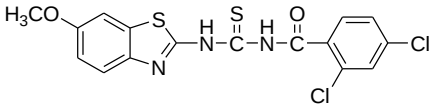
Yield = 70 %; Rf = 0.7; M.P. = 158-159 °C; IR (KBr) ν_{max}: 3263 (N-H), 1682 (amide C=O), 1641 (C=N), 1577 (C=C), 1238 (C=S), 1161 (C-N) cm-^{1}; ^{1}H NMR ($CDCl_3$, δ ppm): 9.58 (1H, s, -NH), 9.25 (1H, s, -NH), 7.78 (1H, d, *J* = 7.6 Hz, H-1), 7.71 (1H, dd, *J* = 2.4 Hz, H-3), 7.49 (1H, d, *J* = 7.6 Hz, H-2), 7.38 (1H, d, *J* = 7.1 Hz, H-6'), 7.27 (1H, dd, *J* = 7.1,7.3 Hz, H-5'), 7.01 (1H, dd, *J* = 7.4,7.1 Hz, H-4'), 6.88 (1H, d, *J* = 7.4 Hz, H-3'), 2.47 (3H, s, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 180.5 (C=S), 172.4 (S-C=N), 168.5 (amide C=O), 146.2 (C-9), 138.3 (C-1'), 136.2 (C-4'), 135.7 (C-6), 132.6 (C-3'), 130.7 (C-6'), 129.2 (C-5'), 127.4 (C-5), 125.5 (C-8), 123.2 (C-4), 122.4 (C-7), 121.6 (C-2'), 23.5 (-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 406.9 (72 %); Anal. Calcd. for $C_{16}H_{12}BrN_3OS_2$; C, 47.17; H, 2.95; N, 10.32; S, 15.72. Found: C, 47.08; H, 2.82; N, 10.24; S, 15.53.

1-Benzoyl-3-(6-methoxybenzo[d]thiazol-2-yl)thiourea (2h)



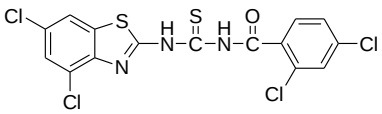
Yield = 73 %; Rf = 0.6; M.P. = 85-86 °C; IR (KBr) ν_{max}: 3266 (N-H), 1673 (amide (C=O), 1637 (C=N), 1576 (C=C), 1245 (C=S), 1152 (C-N) cm-^{1}; ^{1}H NMR ($CDCl_3$, δ ppm): 9.38 (1H, s, -NH), 9.15 (1H, s, -NH), 8.09 (1H, d, *J* = 2.4 Hz, H-3), 7.86 (1H, d, *J* = 7.8 Hz, H-1), 7.36-7.64 (5H, m, Ar), 7.21 (1H, dd, *J* = 2.4,7.7 Hz, H-2), 4.22 (3H, s, -OCH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 180.8 (C=S), 172.4 (S-C=N), 168.2 (amide C=O), 142.5 (C-9), 137.6 (C-6), 135.8 (C-1'), 133.7 (C-4'), 130.2 (C-3',C-5'), 128.7 (C-2',C-6'), 126.4 (C-8), 124.3 (C-4), 116.7 (C-5), 112.5 (C-7), 56.5 (-OCH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 343 (49 %); Anal. Calcd. for $C_{16}H_{13}N_3O_2S_2$; C, 55.97; H, 3.97; N, 12.24; S, 18.67. Found: C, 55.74; H, 3.87; N, 12.19; S, 18.53.

1-(2,4-Dichlorobenzoyl)-3-(6-methoxybenzo[d]thiazol-2-yl)thiourea (2i)



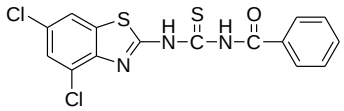
Yield = 76 %; Rf = 0.75; M.P. = 168-169 °C; IR (KBr) ν_{max}: 3272 (N-H), 1676 (amide C=O), 1643 (C=N), 1581 (C=C), 1247 (C=S), 1153 (C-N) cm-^{1}; ^{1}H NMR ($CDCl_3$, δ ppm): 9.41 (1H, s, -NH), 9.18 (1H, s, -NH), 8.14 (1H, d, *J* = 8.6 Hz, H-1), 8.09 (1H, d, *J* = 2.4 Hz, H-3), 7.38-7.64 (3H, m, Ar), 7.21 (1H, dd, *J* = 2.4,8.4 Hz, H-2), 4.21 (3H, s, -OCH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 181.5 (C=S), 172.4 (S-C=N), 168.2 (amide C=O), 142.5 (C-9), 138.5 (C-6), 137.8 (C-4'), 134.7 (C-2'), 132.2 (C-1'), 131.5 (C-3'), 130.7 (C-6'), 127.6 (C-6'), 126.5 (C-8), 124.2 (C-4), 117.5 (C-5), 113.4 (C-7), 56.7 (-OCH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 410.9 (52 %); Anal. Calcd. for $C_{16}H_{11}C_{l2}N_3O_2S_2$; C, 46.71; H, 2.68; N, 10.22; S, 15.57. Found: C, 46.62; H, 2.53; N, 10.14; S, 15.46.

1-(4,6-Dichlorobenzo[d]thiazol-2-yl)-3-(2,4-dichlorobenzoyl)thiourea (2j)



Yield = 88 %; Rf = 0.8; M.P. = 138-139 °C; IR (KBr) ν_{max}: 3267 (N-H), 1682 (amide C=O), 1642 (C=N), 1584 (C=C), 1254 (C=S), 1165 (C-N) cm-^{1}; ^{1}H NMR ($CDCl_3$, δ ppm): 10.38 (1H, s, -NH), 9.25 (1H, s, -NH), 8.07 (1H, d, *J* = 2.3 Hz, H-1), 7.97 (1H, d, *J* = 2.3 Hz, H-2), 7.69 (1H, d, *J* = 8.2 Hz, H-6'), 7.11 (1H, d, *J* = 2.4 Hz, H-3'), 6.78 (1H, dd, *J* = 7.8,2.4 Hz, H-4'); ^{13}C NMR ($CDCl_3$, δ ppm): 181.6 (C=S), 173.5 (S-C=N), 169.3 (amide C=O), 147.8 (C-9), 138.4 (C-4'), 135.6 (C-2'), 133.5 (C-6), 132.4 (C-4), 131.6 (C-1'), 130.8 (C-3'), 130.2 (C-6'), 128.6 (C-5'), 125.3 (C-8), 123.4 (C-5), 122.8 (C-7); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 451 (48 %); Anal. Calcd. for $C_{15}H_7Cl_4N_3OS_2$; C, 39.91; H, 1.55; N, 9.31; S, 14.19. Found: C, 39.84; H, 1.37; N, 9.18; S, 14.13.

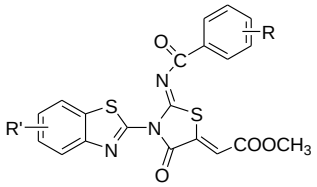
1-Benzoyl-3-(4,6-dichlorobenzo[d]thiazol-2-yl)thiourea (2k)



Yield = 78 %; Rf = 0.8; M.P. = 158-160 °C; IR (KBr) ν_{max}: 3278 (N-H), 1684 (amide C=O), 1633 (C=N), 1588 (C=C), 1263 (C=S), 1173 (C-N) cm-^{1}; ^{1}H NMR ($CDCl_3$, δ ppm): 10.32 (1H, s, -NH), 9.21 (1H, s, -NH), 8.02 (1H, d, *J* = 2.3 Hz, H-1), 7.64 (2H, d, *J* = 8.2 Hz, H-2',H-6'), 7.43 (1H, d, *J* = 2.3 Hz, H-2), 7.13-7.23 (1H, m, Ar-H-4'), 6.73 (2H, dd, *J* = 8.2,7.8 Hz, H-3',H-5'); ^{13}C NMR ($CDCl_3$, δ ppm): 181.4 (C=S), 172.5 (S-C=N), 168.6 (amide C=O), 147.4 (C-9), 135.3 (C-1'), 133.2 (C-4'), 132.5 (C-6), 131.4 (C-4), 130.2 (C-3',C-5'), 128.7 (C-2',C-6'), 124.5 (C-8), 123.6 (C-5), 122.8 (C-7); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 380.9 (100 %); Anal. Calcd. for $C_{15}H_9Cl_2N_3OS_2$; C, 47.24; H, 2.36; N, 11.02; S, 16.79. Found: C, 47.12; H, 2.32; N, 10.96; S, 16.63.

[n-hexane : ethyl acetate (7:3)]

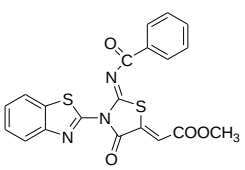
3.4.3 Synthesis of Methyl 2-[2-benzamido-3-(benzo[d]thiazol-2-yl)-4-oxothiazolidin-5-ylidene] acetates (3a-k)



Procedure

1-Benzoyl-3-(benzo[d]thiazol-2-yl)-thioureas (0.5 g, 1.5 mmol) were stirred in 20 mL of dry methanol, dimethyl acetylenedicarboxylate (DMAD) (0.4 mL, 3 mmol) was added dropwise and then the reaction mixture was allowed to stirr for 2-3 hr at room temperature, till the product separated as precipitates. The reaction mixture was filtered to get crude solid of methyl 2-[2-benzamido-3-(benzo[d]thiazol-2-yl)-4-oxothiazolidin-5-ylidene] acetates, which were recrystallized from ethanol.

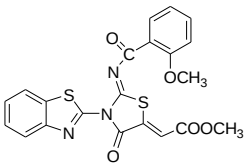
Methyl [2-(2-benzamido)-3-(benzo[d]thiazol-2-yl)-4-oxothiazolidin-5-ylidene]acetate (3a)



Yield = 72 %; Rf = 0.4; M.P. = 195-196 ^{o}C; IR (KBr) ν_{max}: 2921 (C=C-H), 1721 (ester C=O), 1692 (ring C=O), 1653 (amide C=O), 1568 (C=N), 1534 (C=C), 1457 (C-N), 1161 (C-S) cm-^{1}; ^{1}H-NMR (300 MHz, $CDCl_3$): 8.17 (1H, d, *J* = 7.6 Hz, H-1), 8.12 (1H, d, *J* = 7.4 Hz, H-4), 7.66-8.03 (5H, m, Ar), 7.57 (1H, dd, *J* = 7.2,7.4 Hz, H-3), 7.36 (1H, dd, *J* = 7.2,7.3 Hz, H-2),

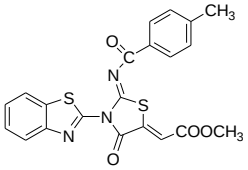
7.11 (1H, s, C=C-*H*), 3.74 (-OCH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.3 (amide C=O), 166.2 (ring C=O), 165.5 (ester C=O), 162.4 (C=N), 156.5 (S-C=N), 146.3 (C-9), 140.6 (=CH), 136.7 (C-1'), 134.5 (C-2',C-6'), 133.4 (C-3',C-5'), 131.5 (S-C=), 128.2 (C-4'), 127.4 (C-6), 125.6 (C-5), 124.3 (C-8), 123.7 (C-4), 122.5 (C-7), 54.2 (-OCH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 423 (64), 318 (37), 184 (100 %), 134 (27), 125 (35), 105 (48), 77 (18); Anal. Calcd. for $C_{20}H_{13}N_3O_4S_2$; C, 56.73; H, 3.07; N, 9.93; S, 15.13. found: C, 56.62; H, 2.96; N, 9.87; S, 15.09.

Methyl [2-(3-(benzo[d]thiazol-2-yl)-2-(2-methoxybenzamido)-4-oxothiazoli-din5-yl-idene] acetate (3b)



Yield = 73 %; Rf = 0.35; M.P. = 233-234 ^{o}C; IR (KBr) ν_{max}: 2925 (C=C-H), 1719 (ester C=O), 1691 (ring C=O), 1651 (amide C=O), 1573 (C=N), 1542 (C=C), 1461 (C-N), 1158 (C-S) cm-^{1}; ^{1}H NMR, ($CDCl_3$, δ ppm): 8.28 (1H, d, *J* = 7.4 Hz, H-1), 8.16 (1H, d, *J* = 7.4 Hz, H-4), 7.81 (1H, d, *J* = 7.2 Hz, H-6'), 7.76 (1H, dd, *J* = 7.8,7.6 Hz, H-2), 7.63 (1H, dd, *J* = 7.6,7.8 Hz, H-3), 7.52 (1H, dd, *J* = 7.1,7.2 Hz, H-5'), 7.45 (1H, dd, *J* = 7.3,7.2 Hz, H-4'), 7.32 (1H, d, *J* = 7.3 Hz, H-4'), 7.13 (1H, s, C=C-*H*), 3.84 (3H, s, Ar-OCH_3), 3.76 (3H, s, -OCH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.4 (amide C=O), 166.4 (ring C=O), 165.2 (ester C=O), 162.2 (C=N), 156.4 (S-C=N), 146.4 (C-9), 140.5 (=CH), 137.8 (C-1'), 136.6 (C-2'), 135.5 (C-6'), 134.4 (C-3'), 133.5 (C-5'), 131.4 (S-C=), 127.8 (C-4'), 126.6 (C-6), 125.3 (C-5), 124.7 (C-8), 123.5 (C-4), 122.6 (C-7), 54.4 (-OCH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 453 (73), 318 (24), 184 (100 %), 135 (37), 134 (17), 125 (25), 107 (53), 77 (21); Anal. Calcd. for $C_{21}H_{15}N_3O_5S_2$; C, 55.63; H, 3.31; N, 9.27; S, 14.13. found: C, 55.54; H, 3.22; N, 9.16; S, 14.09.

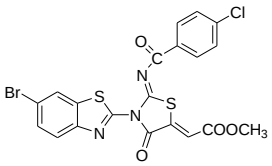
Methyl [2-(3-(benzo[d]thiazol-2-yl)-2-(4-methylbenzamido)-4-oxothiazolidin-5-ylid-ene]acetate (3c)



Yield = 71 %; Rf = 0.4; M.P. = 287-288 ^{o}C; IR (KBr) ν_{max}: 2928 (C=C-H), 1722 (ester C=O), 1693 (ring C=O), 1653 (amide C=O), 1576 (C=N), 1538 (C=C), 1457 (C-N), 1162 (C-S) cm-^{1}; ^{1}H NMR, ($CDCl_3$, δ ppm): 8.25 (1H, d, *J* = 7.4 Hz, H-1), 8.14 (1H, d, *J* = 7.4 Hz, H-4), 7.91 (1H, d, *J* = 7.2 Hz, H-2',H-6'). 7.82 (1H, d, *J* = 7.2 Hz, H-3',H-5'), 7.61 (1H, dd, *J* = 7.2,7.6 Hz, H-2), 7.34 (1H, dd, *J* = 7.2,7.6 Hz, H-3), 7.12 (1H, s, C=C-*H*), 3.75 (3H, s, -OCH_3), 2.55 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.5 (amide C=O), 166.3 (ring C=O),

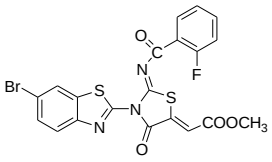
165.4 (ester C=O), 162.3 (C=N), 156.4 (S-C=N), 146.6 (C-9), 140.4 (=CH), 135.4 (C-1'), 134.6 (C-2',C-6'), 132.7 (C-3',C-5'), 131.6 (S-C=), 128.4 (C-4'), 127.3 (C-6), 126.5 (C-5), 125.7 (C-8), 124.6 (C-4), 123.4 (C-7), 54.3 (-OCH_3), 22.4 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 437 (67), 318 (43), 184 (100 %), 134 (28), 125 (30), 119 (56), 91 (41), 77 (29); Anal. Calcd. for $C_{21}H_{15}N_3O_4S_2$; C, 57.66; H, 3.43; N, 9.61; S, 14.65. found: C, 57.41; H, 3.34; N, 9.48; S, 14.52.

Methyl 2-[3-(6-bromobenzo[d]thiazol-2-yl)-2-(3-chlorobenzamido)-4-oxothiazolidin-5-ylidene]acetate (3d)



Yield = 76 %; Rf = 0.45; M.P. = 266-267 ^oC; IR (KBr) ν_{max}: 2934 (C=C-H), 1724 (ester C=O), 1689 (ring C=O), 1652 (amide C=O), 1571 (C=N), 1533 (C=C), 1452 (C-N), 1165 (C-S) cm-^{1}; ^{1}H NMR, ($CDCl_3$, δ ppm): 8.16 (1H, d, *J* = 7.4 Hz, H-1), 8.10 (1H, d, *J* = 2.4 Hz, H-3), 7.95 (1H, d, *J* = 7.4 Hz, H-2), 7.83 (1H, d, *J* = 7.2 Hz, H-2',H-6'), 7.76 (1H, d, *J* = 2.3 Hz, H-3',H-5'), 7.14 (1H, s, C=C-*H*), 3.77 (3H, s, -OCH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.7 (amide C=O), 166.5 (ring C=O), 165.6 (ester C=O), 162.6 (C=N), 156.7 (S-C=N), 146.6 (C-9), 140.6 (=CH), 138.6 (C-1'), 137.5 (C-3',C-5'), 136.3 (C-2',C-6'), 135.7 (C-4'), 134.5 (C-6), 132.6 (C-5), 131.7 (S-C=), 127.5 (C-8), 125.6 (C-4), 124.3 (C-7), 123.4 (C-6), 54.5 (-OCH_3); MS (70 eV): *m/z* (%); [(^{79}Br)$M^{+\cdot}$] 535.5 (57), [(^{81}Br)$M^{+\cdot}$] 537.5 (43), 396 (26), 212 (18), 184 (100 %), 139.5 (33), 134 (28), 125 (23), 111.5 (43), 77 (16); Anal. Calcd. for $C_{20}H_{11}N_3O_4S_2ClBr$; C, 44.73; H, 2.05; N, 7.83; S, 11.93. found: C, 44.56; H, 1.97; N, 7.74; S, 11.86.

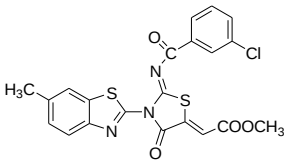
Methyl 2-[3-(6-bromobenzo[d]thiazol-2-yl)-2-(2-fluorobenzamido)-4-oxothiazolidin-5-ylidene]acetate (3e)



Yield = 72 %; Rf = 0.5; M.P. = 151-153 ^oC; IR (KBr) ν_{max}: 2936 (C=C-H), 1725 (ester C=O), 1690 (ring C=O), 1661 (amide C=O), 1573 (C=N), 1536 (C=C), 1457 (C-N), 1163 (C-S) cm-^{1}; ^{1}H NMR, ($CDCl_3$, δ ppm): 8.19 (1H, d, *J* = 7.4 Hz, H-1), 8.13 (1H, d, *J* = 2.3 Hz, H-3), 7.87 (1H, d, *J* = 7.4 Hz, H-2), 7.76 (1H, d, *J* = 7.2 Hz, H-6'), 7.68 (1H, dd, *J* = 7.2,7.3 Hz, H-5'), 7.54 (1H, dd, *J* = 7.4,7.2 Hz, H-4'), 7.34 (1H, d, *J* = 7.4 Hz, H-3'), 7.15 (1H, s, C=C-*H*), 3.76 (3H, s, -OCH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.6 (amide C=O), 166.8 (ring C=O), 165.7 (ester C=O), 162.7 (C=N), 156.8 (S-C=N), 146.5 (C-9), 140.8 (=CH), 140.5 (C-2'), 137.6 (C-1'), 136.5 (C-6'), 134.6 (C-4'), 131.4 (C-5), 131.9 (S-C=), 128.6 (C-5'), 127.8

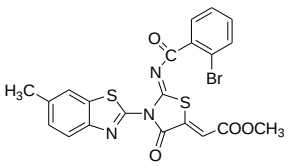
(C-3'), 126.5 (C-8), 125.7 (C-4), 124.8 (C-7), 122.4 (C-6), 54.7 (-OCH_3); MS (70 eV): *m/z* (%); [(^{79}Br)$M^{+\cdot}$] 519 (60), [(^{81}Br)$M^{+\cdot}$] 521 (46), 396 (32), 212 (28), 184 (100 %), 134 (18), 123 (37), 95 (40), 77 (21); Anal. Calcd. for $C_{20}H_{11}N_3O_4S_2ClF$; C, 46.15; H, 2.12; N, 8.07; S, 12.31. found: C, 46.08; H, 2.04; N, 7.95; S, 12.21.

Methyl 2-[2-(3-chlorobenzamido)-3-(6-methylbenzo[d]thiazol-2-yl)-4-oxothiazolidin -5-ylidene]acetate (3f)



Yield = 74 %; Rf = 0.45; M.P. = 223-224 ^{o}C; IR (KBr) ν_{max}: 2947 (C=C-H), 1723 (ester C=O), 1688 (ring C=O), 1653 (amide C=O), 1574 (C=N), 1536 (C=C), 1456 (C-N), 1162 (C-S) cm-^{1}; ^{1}H NMR, ($CDCl_3$, δ ppm): 8.13 (1H, d, *J* = 7.5 Hz, H-1), 8.08 (1H, d, *J* = 2.4 Hz, H-3), 7.91 (1H, d, *J* = 7.5 Hz, H-2), 7.83 (1H, d, *J* = 7.2 Hz, H-6'), 7.74 (1H, d, *J* = 2.3 Hz, H-2'), 7.62 (1H, dd, *J* = 7.1,2.3 Hz, H-4'), 7.36 (1H, dd, *J* = 7.2,7.1 Hz, H-5'), 7.14 (1H, s, C=C-*H*), 3.75 (3H, s, -OCH_3), 2.57 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.5 (amide C=O), 166.4 (ring C=O), 165.5 (ester C=O), 162.7 (C=N), 156.6 (S-C=N), 146.5 (C-9), 140.7 (=CH), 138.6 (C-1'), 137.5 (C-3'), 136.4 (C-6'), 135.7 (C-4'), 134.5 (C-6), 133.4 (C-5'), 131.7 (S-C=), 128.5 (C-2'), 126.6 (C-5), 124.7 (C-8), 123.3 (C-4), 122.5 (C-7), 54.6 (-OCH_3), 23.4 (Ar-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 471.5 (68), 332 (43), 184 (100 %), 148 (38), 139 (32), 134 (21), 111.5 (29), 77 (15); Anal. Calcd. for $C_{21}H_{14}N_3O_4S_2Cl$; C, 53.45; H, 2.97; N, 8.91; S, 13.57. found: C, 53.33; H, 2.88; N, 8.75; S, 13.37.

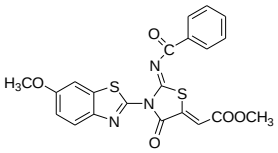
Methyl 2-[-2-(2-bromobenzamido)-3-(6-methylbenzo[d]thiazol-2-yl)-4-oxothiazolidi-n-5-ylidene]acetate (3g)



Yield = 76 %; Rf = 0.45; M.P. = 134-136 ^{o}C; IR (KBr) ν_{max}: 2945 (C=C-H), 1722 (ester C=O), 1687 (ring C=O), 1653 (amide C=O), 1572 (C=N), 1537 (C=C), 1453 (C-N), 1164 (C-S) cm-^{1}; ^{1}H NMR, ($CDCl_3$, δ ppm): 8.13 (1H, d, *J* = 7.6 Hz, H-1), 8.06 (1H, d, *J* = 2.4 Hz, H-3), 7.82 (1H, d, *J* = 7.4 Hz, H-2), 7.73 (1H, d, *J* = 7.2 Hz, H-6'), 7.42 (1H, dd, *J* = 7.3,7.2 Hz, H-5'), 7.31 (1H, dd, *J* = 7.2,7.1 Hz, H-4'), 7.18 (1H, d, *J* = 7.1 Hz, H-3'), 7.15 (1H, s, C=C-*H*), 3.76 (3H, s, -OCH_3), 2.56 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.2 (amide C=O), 166.1 (ring C=O), 165.3 (ester C=O), 162.5 (C=N), 156.3 (S-C=N), 146.4 (C-9), 140.4 (=CH), 138.4 (C-1'), 137.5 (C-6'), 136.6 (C-4'), 135.7 (C-3'), 134.5 (C-5'), 133.6 (C-6), 131.5 (S-C=), 127.8 (C-2'), 126.7 (C-5), 125.6 (C-8), 124.5

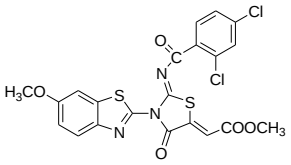
(C-4), 122.6 (C-7), 54.3 (-OCH_3), 23.2 (Ar-CH_3); MS (70 eV): *m/z* (%); [(^{79}Br)$M^{+\cdot}$] 515 (71), [(^{81}Br)$M^{+\cdot}$] 517 (55), 332 (38), 184 (100 %), 155 (45), 148 (30), 134 (22), 125 (15), 77 (28); Anal. Calcd. for $C_{21}H_{14}N_3O_4S_2Br$; C, 48.84; H, 2.71; N, 8.14; S, 12.40. found: C, 48.73; H, 2.54; N, 8.07; S, 12.28.

Methyl 2-[2-benzamido-3-(6-methoxybenzo[d]thiazol-2-yl)-4-oxothiazolidin-5-ylide-ne]acetate (3h)



Yield = 75 %; Rf = 0.35; M.P. = 183-184 ^{o}C; IR (KBr) ν_{max}: 2943 (C=C-H), 1721 (ester C=O), 1688 (ring C=O), 1654 (amide C=O), 1576 (C=N), 1542 (C=C), 1457 (C-N), 1166 (C-S) cm-^{1}; ^{1}H NMR, ($CDCl_3$, δ ppm): 8.11 (1H, d, *J* = 7.6 Hz, H-1), 8.04 (1H, d, *J* = 2.3 Hz, H-3), 7.81 (1H, d, *J* = 7.4 Hz, H-2), 7.37-7.74 (5H, m, Ar), 7.13 (1H, s, C=C-*H*), 3.86 (3H, s, Ar-OCH_3), 3.74 (3H, s, -OCH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.4 (amide C=O), 166.4 (ring C=O), 165.4 (ester C=O), 162.3 (C=N), 156.4 (S-C=N), 146.2 (C-9), 140.5 (=CH), 137.6 (C-6), 135.7 (C-1'), 134.5 (C-2',C-6'), 132.6 (C-3',C-5'), 131.6 (S-C=), 128.7 (C-4'), 127.5 (C-8), 126.4 (C-4), 124.5 (C-5), 122.3 (C-7), 56.2 (Ar-OCH_3), 54.4 (-OCH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 453 (74), 348 (40), 184 (100 %), 164 (48), 134 (20), 125 (17), 105 (35), 77 (24); Anal. Calcd. for $C_{21}H_{15}N_3O_5S_2$; C, 55.63; H, 3.31; N, 9.27; S, 14.13. found: C, 55.51; H, 3.26; N, 9.16; S, 14.02.

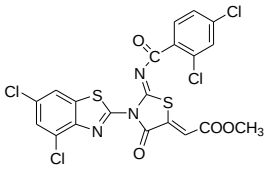
Methyl 2-[2-(2,4-dichlorobenzamido)-3-(6-methoxybenzo[d]thiazol-2-yl)-4-oxothiaz-olidin-5-ylidene]acetate (3i)



Yield = 74 %; Rf = 0.4; M.P. = 146-147 ^{o}C; IR (KBr) ν_{max}: 2953 (C=C-H), 1726 (ester C=O), 1694 (ring C=O), 1657 (amide C=O), 1578 (C=N), 1547 (C=C), 1459 (C-N), 1168 (C-S) cm-^{1}; ^{1}H NMR, ($CDCl_3$, δ ppm): 8.19 (1H, d, *J* = 7.6 Hz, H-1), 8.08 (1H, d, *J* = 2.4 Hz, H-2), 7.81 (1H, d, *J* = 7.6 Hz, H-3), 7.73 (1H, d, *J* = 7.4 Hz, H-6'), 7.66 (1H, d, *J* = 2.4 Hz, H-3'), 7.37 (1H, d, *J* = 7.4 Hz, H-5'), 7.16 (1H, s, C=C-*H*), 3.87 (3H, s, Ar-OCH_3), 3.75 (3H, s, -OCH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.8 (amide C=O), 166.5 (ring C=O), 165.7 (ester C=O), 162.6 (C=N), 156.8 (S-C=N), 146.3 (C-9), 141.5 (=C-S), 138.5 (C-1'), 137.3 (C-2'), 136.7 (C-4'), 135.6 (C-'6), 134.5 (C-3'), 133.4 (C-5'), 132.1 (S-C=), 127.5 (C-8), 126.6 (C-4), 124.5 (C-5), 122.7 (C-7), 56.5 (Ar-OCH_3), 54.6 (-OCH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 521 (56), 348 (30), 184 (100 %), 173 (38), 164 (41), 145 (32), 134

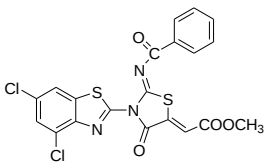
(24), 125 (14), 111.5 (44), 77 (20); Anal. Calcd. for $C_{21}H_{13}N_3O_5S_2Cl_2$; C, 48.37; H, 2.49; N, 8.06; S, 12.28. found: C, 48.21; H, 2.37; N, 7.94; S, 12.16.

Methyl 2-[2-(2,4-dichlorobenzamido)-3-(4,6-dichlorobenzo[d]thiazol-2-yl)-4-oxothiazolidin-5-ylidene]acetate (3j)



Yield = 78 %; Rf = 0.5; M.P. = 116-117 ^oC; IR (KBr) ν_{max}: 2963 (C=C-H), 1727 (ester C=O), 1696 (ring C=O), 1658 (amide C=O), 1578 (C=N), 1547 (C=C), 1460 (C-N), 1167 (C-S) cm-^{1}; ^{1}H NMR, ($CDCl_3$, δ ppm): 8.26 (1H, d, *J* = 2.3 Hz, H-1), 8.18 (1H, d, *J* = 2.3 Hz, H-2), 7.88 (1H, d, *J* = 7.2 Hz, H-6'), 7.75 (1H, d, *J* = 2.3 Hz, H-3'), 7.67 (1H, d, *J* = 7.2 Hz, H-5'), 7.19 (1H, s, C=C-*H*), 3.78 (3H, s, -OCH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 169.3 (amide C=O), 166.3 (ring C=O), 165.8 (ester C=O), 162.8 (C=N), 156.9 (S-C=N), 146.5 (C-9), 141.8 (=CH), 138.6 (C-1'), 137.5 (C-2'), 136.6 (C-4'), 135.8 (C-6'), 134.4 (C-6), 133.5 (C-4), 132.6 (C-3'), 132.4 (=C-S), 128.5 (C-5'), 126.4 (C-8), 124.6 (C-5), 123.7 (C-7), 54.8 (-OCH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 559 (52), 386 (47), 202 (34), 184 (100 %), 173 (41), 168.5 (54), 145 (32), 134 (19), 125 (12), 111.5 (40), 77 (25); Anal. Calcd. for $C_{20}H_9N_3O_4S_2Cl_4$; C, 42.93; H, 1.61; N, 7.51; S, 11.45. found: C, 42.84; H, 1.54; N, 7.36; S, 11.38.

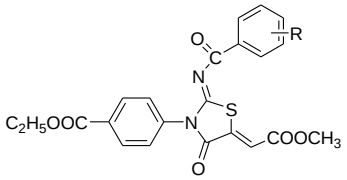
Methyl 2-[2-benzamido-3-(4,6-dichlorobenzo[d]thiazol-2-yl)-4-oxothiazolidin-5-ylidene]acetate (3k)



Yield = 77 %; Rf = 0.4; M.P. = 169-170 ^oC; IR (KBr) ν_{max}: 2961 (C=C-H), 1725 (ester C=O), 1693 (ring C=O), 1656 (amide C=O), 1576 (C=N), 1545 (C=C), 1458 (C-N), 1163 (C-S) cm-^{1}; ^{1}H NMR, ($CDCl_3$, δ ppm): 8.22 (1H, d, *J* = 2.3 Hz, H-1), 8.14 (1H, d, *J* = 2.3 Hz, H-2), 7.66-7.93 (5H, m, Ar), 7.17 (1H, s, C=C-*H*), 3.77 (3H, s, -OCH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.9 (amide C=O), 166.7 (ring C=O), 165.6 (ester C=O), 162.7 (C=N), 156.7 (S-C=N), 146.3 (C-9), 141.6 (=CH), 136.7 (C-1'), 135.6 (C-6), 134.5 (C-4), 133.6 (C-2',C-6'), 132.4 (C-3',C-5'), 132.2 (S-C=), 127.4 (C-4'), 125.5 (C-8), 124.6 (C-5), 122.8 (C-7), 54.6 (-OCH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 491 (66), 386 (51), 202 (41), 184 (100 %), 168.5 (47), 134 (29), 125 (23), 105 (46), 77 (26); Anal. Calcd. for $C_{20}H_{11}N_3O_4S_2Cl_2$; C, 48.88; H, 2.24; N, 8.55; S, 13.03. found: C, 48.78; H, 2.17; N, 8.41; S, 12.94.

[Pet. ether : ethyl acetate (8:2)]

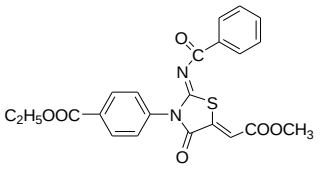
3.4.4 Synthesis of Ethyl 4-[2-benzamido-5-(2-methoxy-2-oxoethylidene)-4-oxothiazolidin-3-yl] benzoates (4a-j)



Procedure

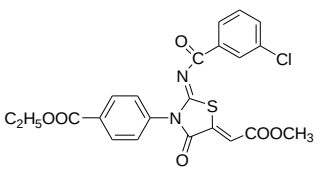
Ethyl 4-[2-benzamido-5-(2-methoxy-2-oxoethylidene)-4-oxothiazolidin-3-yl] benzoates were synthesized according to the same procedure as described in Section 2.4.3 (Scheme-3.4). The crude products were recrystallized with methanol.

Ethyl 4-[2-benzamido-5-(2-methoxy-2-oxoethylidene)-4-oxothiazolidin-3-yl]benzoate (4a)



Yield = 65 %; Rf = 0.65; M.P. = 121-122 ^{o}C; IR (KBr) ν_{max}: 2946 (C=C-H), 1724 (-C_2H_5 ester C=O), 1721 (-CH_3 ester C=O), 1676 (ring C=O), 1653 (amide C=O), 1563 (C=N), 1546 (C=C), 1437 (C-N), 1253 (C-S) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.91 (1H, d, *J* = 7.6 Hz, H-2,H-6), 7.64-7.83 (5H, m, Ar), 7.57 (1H, d, *J* = 7.6 Hz, H-3,H-5), 7.13 (1H, s, C=C-*H*), 4.26 (2H, q, *J* = 7.1 Hz, -CH_2), 3.76 (3H, s, -OCH_3), 2.23 (3H, t, *J* = 5.6 Hz, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.4 (amide C=O), 167.1 (ring C=O), 166.2 (-CH_3 ester C=O), 165.4 (-C_2H_5 ester C=O), 162.6 (C=N), 140.2 (=CH), 137.4 (C-4), 136.3 (C-1'), 134.7 (C-2',C-6'), 132.4 (C-3',C-5'), 131.3 (S-C=), 130.4 (C-2,C-6), 128.2 (C-4'), 126.7 (C-1), 122.4 (C-3,C-5), 59.4 (-OCH_2), 53.4 (-OCH_3), 15.2 (-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 438 (49), 333 (19), 183 (34), 149 (100 %), 124 (26), 105 (43), 77 (26); Anal. Calcd. for $C_{22}H_{18}N_2O_6S$; C, 60.27; H, 4.11; N, 6.39; S, 7.31. Found: C, 60.19; H, 4.03; N, 6.28; S, 7.24.

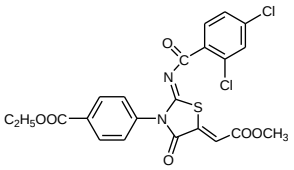
Ethyl 4-[2-(3-chlorobenzamido)-5-(2-methoxy-2-oxoethylidene)-4-oxothiazolidin-3-yl] benzoate (4b)



Yield = 69 %; Rf = 0.7; M.P. = 137-138 ^{o}C; IR (KBr) ν_{max}: 2951 (C=C-H), 1725 (-C_2H_5 ester C=O), 1722 (-CH_3 ester C=O), 1677 (ring C=O), 1656 (amide C=O), 1561 (C=N), 1544 (C=C), 1435 (C-N), 1250 (C-S) cm^{-1}; ^{1}H NMR, ($CDCl_3$, δ ppm): 7.94 (1H, d, *J* = 7.6 Hz, H-2,H-6), 7.85 (1H, d, *J* = 2.3 Hz, H-2'), 7.78 (1H, d, *J* = 7.2 Hz, H-6'), 7.67

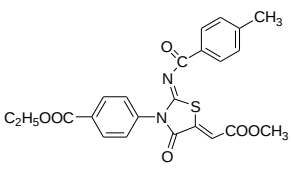
(1H, d, *J* = 7.6 Hz, H-3,H-5), 7.58 (1H, dd, *J* = 7.2,7.3 Hz, H-5'), 7.56 (1H, dd, *J* = 7.3,2.3 Hz, H-4'), 7.17 (1H, s, C=C-*H*), 4.28 (2H, q, *J* = 7.1 Hz, -CH_2), 3.82 (3H, s, -OCH_3), 2.26 (3H, t, *J* = 5.6 Hz, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.6 (amide C=O), 167.3 (ring C=O), 166.4 (-CH_3 ester C=O), 165.5 (-C_2H_5 ester C=O), 162.7 (C=N), 140.4 (=CH), 137.5 (C-4), 136.5 (C-1'), 135.2 (C-3'), 134.8 (C-4'), 133.2 (C-5'), 132.5 (C-2'), 131.6 (S-C=), 130.5 (C-2,C-6), 128.6 (C-6'), 126.6 (C-1), 122.7 (C-3,C-5), 59.8 (-OCH_2), 53.5 (-OCH_3), 15.6 (-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 472.5 (54), [$(M+2)^{+\cdot}$] 474.5 (41), 333 (35), 183 (29), 149 (100 %), 139.5 (38), 124 (17), 111.5 (23); Anal. Calcd. for $C_{22}H_{17}N_2O_6ClS$; C, 55.93; H, 3.60; N, 5.93; S, 6.78. Found: C, 55.81; H, 3.46; N, 5.78; S, 6.56.

Ethyl 4-[2-(2,4-dichlorobenzamido)-5-(2-methoxy-2-oxoethylidene)-4-oxothiazol-idin-3-yl]benzoate (4c)



Yield = 67 %; Rf = 0.65; M.P. = 130-131 ^{o}C; IR (KBr) ν_{max}: 2958 (C=C-H), 1731 (-C_2H_5 ester C=O), 1726 (-CH_3 ester C=O), 1678 (ring C=O), 1664 (Ar C=O), 1567 (C=N), 1554 (C=C), 1451 (C−N), 1260 (C−S) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.96 (1H, d, *J* = 7.6 Hz, H-2,H-6), 7.87 (1H, d, *J* = 2.3 Hz, H-3', 7.74 (1H, d, *J* = 7.2 Hz, H-6'), 7.65 (1H, dd, *J* = 7.2,2.3 Hz, H-5'), 7.56 (1H, d, *J* = 7.6 Hz, H-3,H-5), 7.21 (1H, s, C=C-*H*), 4.31 (2H, q, *J* = 7.1 Hz, -CH_2), 3.86 (3H, s, -OCH_3), 2.29 (3H, t, *J* = 5.6 Hz, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.8 (amide C=O), 167.6 (ring C=O), 166.7 (-CH_3 ester C=O), 165.8 (-C_2H_5 ester C=O), 162.9 (C=N), 140.5 (=CH), 138.8 (C-4'), 137.6 (C-4), 136.4 (C-2'), 135.5 (C-1'), 133.6 (C-6'), 131.8 (S-C=), 131.2 (C-3'), 130.5 (C-2,C-6), 127.6 (C-5'), 126.6 (C-1), 122.7 (C-3,C-5), 60.1 (-OCH_2), 53.7 (-OCH_3), 15.8 (-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 506 (36), 333 (47), 183 (25), 173 (19), 149 (100 %), 145 (56), 138.5 (33), 124 (18), 111.5 (20); Anal. Calcd. for $C_{22}H_{16}N_2O_6SCl_2$; C, 52.17; H, 3.16; N, 5.53; S, 6.32. Found: C, 52.13; H, 3.09; N, 5.43; S, 6.26.

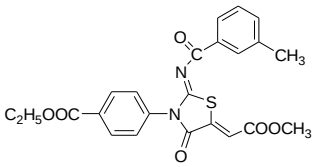
Ethyl 4-[5-(2-methoxy-2-oxoethylidene)-2-(4-methylbenzamido)-4-oxothiazolidin-3-yl]benzoate (4d)



Yield = 72 %; Rf = 0.6; M.P. = 119-120 ^{o}C; IR (KBr) ν_{max}: 2952 (C=C−H), 1725 (-C_2H_5 ester C=O), 1721 (-CH_3 ester C=O), 1672 (ring C=O), 1663 (Ar C=O), 1556 (C=N), 1564 (C=C), 1456 (C−N), 1247 (C−S) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.92 (1H, d, *J* = 7.6 Hz, H-

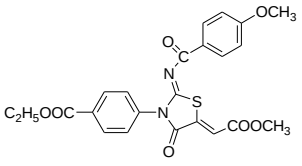
2,H-6), 7.84 (1H, d, *J* = 7.4 Hz, H-2',H-6'), 7.75 (1H, d, *J* = 7.4 Hz, H-3',H-5'), 7.63 (1H, d, *J* = 7.6 Hz, H-3,H-5), 7.16 (1H, s, C=C-*H*), 4.26 (2H, q, *J* = 7.1 Hz, -CH_2), 3.86 (3H, s, -OCH_3), 2.68 (3H, s, Ar-CH_3), 2.26 (3H, t, *J* = 5.6 Hz, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.3 (amide C=O), 167.2 (ring C=O), 166.6 (-CH_3 ester C=O), 165.5 (-C_2H_5 ester C=O), 162.5 (C=N), 140.4 (=CH), 137.5 (C-4), 134.3 (C-1'), 132.6 (C-4'), 131.5 (S-C=), 130.5 (C-2,C-6), 129.7 (C-2',C-6'), 129.3 (C-3',C-5'), 126.7 (C-1), 122.6 (C-3,C-5), 59.6 (2H, s, -OCH_2), 53.5 (3H, s, -OCH_3), 23.6 (3H, s, Ar-CH_3), 15.3 (3H, s, -CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 452 (51), 361 (16), 333 (22), 183 (39), 149 (100 %), 119 (37), 124 (41), 91 (27); Anal. Calcd. for $C_{23}H_{20}N_2O_6S$; C, 61.06; H, 4.42; N, 6.19; S, 7.08. Found: C, 60.94; H, 4.31; N, 6.13; S, 7.01.

Ethyl 4-[5-(2-methoxy-2-oxoethylidene)-2-(3-methylbenzamido)-4-oxothiazolidin-3-yl] benzoate (4e)



Yield = 68 %; Rf = 0.6; M.P. = 122-123 ^{o}C; IR (KBr) ν_{max}: 2954 (C=C−H), 1727 (-C_2H_5 ester C=O), 1723 (-CH_3 ester C=O), 1674 (ring C=O), 1665 (Ar C=O), 1561 (C=N), 1553 (C=C), 1452 (C−N), 1263 (C−S) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.87 (1H, d, *J* = 7.6 Hz, H-2,H-6), 7.79 (1H, d, *J* = 7.1 Hz, H-6'), 7.72 (1H, d, *J* = 2.4 Hz, H-2'), 7.68 (1H, d, *J* = 7.6 Hz, H-3,H-5), 7.61 (1H, dd, *J* = 7.1,7.2 Hz, H-5'), 7.55 (1H, dd, *J* = 7.2,2.4 Hz, H-4'), 7.15 (1H, s, C=C-*H*), 4.24 (2H, q, *J* = 7.1 Hz, -CH_2), 3.83 (3H, s, -OCH_3), 2.66 (3H, s, Ar-CH_3), 2.25 (3H, t, *J* = 5.6 Hz, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.2 (amide C=O), 167.1 (ring C=O), 166.3 (-CH_3 ester C=O), 165.4 (-C_2H_5 ester C=O), 162.5 (C=N), 140.3 (=CH), 137.5 (C-4), 135.7 (C-1'), 134.6 (C-3'), 133.5 (C-6'), 132.7 (C-4'), 131.6 (S-C=), 130.3 (C-2,C-6), 129.5 (C-5'), 126.7 (C-1), 122.5 (C-3,C-5), 59.6 (2H, s, -OCH_2), 53.5 (3H, s, -OCH_3), 23.8 (3H, s, Ar-CH_3), 15.4 (3H, s, -CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 452 (57), 361 (19), 333 (24), 183 (44), 149 (100 %), 119 (33), 124 (44), 91 (25); Anal. Calcd. for $C_{23}H_{20}N_2O_6S$; C, 61.07; H, 4.43; N, 6.18; S, 7.07. Found: C, 60.96; H, 4.34; N, 6.11; S, 6.98.

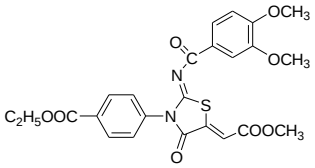
Ethyl 4-[5-(2-methoxy-2-oxoethylidene)-2-(4-methoxybenzamido)-4-oxothiazolidin-3-yl]benzoate (4f)



Yield = 71 %; Rf = 0.55; M.P. = 126-127 ^{o}C; IR (KBr) ν_{max}: 2945 (C=C−H), 1724 (-C_2H_5 ester C=O), 1720 (-CH_3 ester C=O), 1681 (ring C=O), 1661 (Ar C=O), 1558 (C=N), 1557

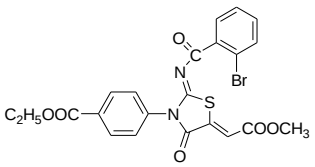
(C=C), 1447 (C−N), 1253 (C−S) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.88 (1H, d, *J* = 7.6 Hz, H-2,H-6), 7.78 (1H, d, *J* = 7.4 Hz, H-2',H-6'), 7.67 (1H, d, *J* = 7.4 Hz, H-3',H-5'), 7.56 (1H, d, *J* = 7.6 Hz, H-3,H-5), 7.14 (1H, s, C=C-*H*), 4.24 (2H, q, *J* = 7.1 Hz,-CH_2), 3.86 (3H, s, Ar-OCH_3), 3.78 (3H, s, -OCH_3), 2.23 (3H, t, *J* = 5.6 Hz, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.5 (amide C=O), 167.7 (ring C=O), 166.3 (-CH_3 ester C=O), 165.5 (-C_2H_5 ester C=O), 162.4 (C=N), 140.3 (=CH), 138.6 (C-4'), 137.4 (C-4), 131.5 (S-C=), 130.8 (C-2',C-6'), 130.3 (C-2,C-6), 128.4 (C-1'), 126.5 (C-1), 122.4 (C-3,C-5), 117.6 (C-3',C-5'), 59.3 (2H, s, -OCH_2), 56.4 (3H, s, Ar-OCH_3), 53.2 (3H, s, -OCH_3), 15.3 (3H, s, -CH_3); MS (70eV): *m/z* (%); [$M^{+\cdot}$] 468 (44), 333 (27), 319 (25), 183 (47), 149 (37), 135 (100 %), 124 (32); Anal. Calcd. for $C_{23}H_{20}N_2O_7S$; C, 58.97; H, 4.27; N, 5.98; S, 6.84. Found: C, 58.83; H, 4.16; N, 5.91; S, 6.73.

Ethyl 4-(5-(2-methoxy-2-oxoethylidene)-2-(3,4-dimethoxybenzamido)-4-oxothiazolidin-3-yl)benzoate (4g)



Yield = 74 %; Rf = 0.55; M.P. = 147-148 ^oC; IR (KBr) ν_{max}: 2937 (C=C−H), 1722 (-C_2H_5 ester C=O), 1718 (-CH_3 ester C=O), 1674 (ring C=O), 1664 (Ar C=O), 1546 (C=N), 1564 (C=C), 1436 (C−N), 1264 (C−S) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.92 (1H, d, *J* = 7.6 Hz, H-2,H-6), 7.85 (1H, d, *J* = 7.2 Hz, H-6'), 7.74 (1H, s, Ar-2'), 7.65 (1H, d, *J* = 7.2 Hz, H-5'), 7.57 (1H, d, *J* = 7.6 Hz, H-3,H-5), 7.12 (1H, s, C=C-*H*), 4.25 (2H, q, *J* = 7.1 Hz, -CH_2), 3.85 (6H, s, Ar-OCH_3), 3.77 (3H, s, -OCH_3), 2.26 (3H, t, *J* = 5.6 Hz, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.7 (amide C=O), 167.6 (ring C=O), 166.2 (-CH_3 ester C=O), 165.3 (-C_2H_5 ester C=O), 162.5 (C=N), 140.2 (=CH), 138.5 (C-4'), 137.4 (C-4), 136.7 (C-3'), 131.3 (S-C=), 130.5 (C-2,C-6), 129.4 (C-1'), 126.6 (C-1), 124.3 (C-6'), 122.2 (C-3,C-5), 118.3 (C-5'), 117.6 (C-2'), 59.2 (2H, s, -OCH_2), 56.5 (6H, s, Ar-OCH_3), 53.1 (3H, s, -OCH_3), 15.2 (3H, s, -CH_3); MS (70eV): *m/z* (%); [$M^{+\cdot}$] 498 (62), 333 (25), 183 (29), 165 (100 %), 149 (72), 135 (42), 105 (36); Anal. Calcd. for $C_{24}H_{22}N_2O_8S$; C, 57.83; H, 4.42; N, 5.62; S, 6.42. Found: C, 57.72; H, 4.33; N, 5.48; S, 6.34.

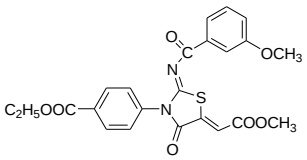
Ethyl 4-[-2-(2-bromobenzamido)-5-(2-methoxy-2-oxoethylidene)-4-oxothiazolidin-3-yl]benzoate (4h)



Yield = 72 %; Rf = 0.7; M.P .= 127-128 ^oC; IR (KBr) ν_{max}: 2945 (C=C−H), 1726 (-C_2H_5 ester C=O), 1723 (-CH_3 ester C=O), 1676 (ring C=O), 1662 (Ar C=O), 1556 (C=N), 1554

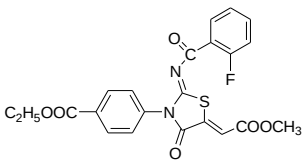
(C=C), 1452 (C−N), 1261 (C−S) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.89 (1H, d, *J* = 7.6 Hz, H-2,H-6), 7.58-7.84 (4H, m, Ar), 7.53 (1H, d, *J* = 7.6 Hz, H-3,H-5), 7.11 (1H, s, C=C-*H*), 4.24 (2H, q, *J* = 7.1 Hz,-CH_2), 3.76 (3H, s, -OCH_3), 2.25 (3H, t, *J* = 5.6 Hz**,** -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.3 (amide C=O), 165.6 (ring C=O), 165.4 (-CH_3 ester C=O), 164.3 (-C_2H_5 ester C=O), 162.6 (C=N), 140.5 (=CH), 138.2 (C-1'), 137.6 (C-4), 136.7 (C-4'), 134.6 (C-6'), 133.5 (C-3'), 131.6 (S-C=), 130.4 (C-2,C-6), 128.5 (C-5'), 126.6 (C-1), 123.5 (C-2'), 122.4 (C-3,C-5), 59.5 (2H, s, -OCH_2), 53.3 (3H, s, -OCH_3), 15.6 (3H, s, -CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 516 (47), [M+2]$^{+\cdot}$ 518 (22), 333 (16), 183 (36), 154 (26), 149 (100 %), 124 (17); Anal. Calcd. for $C_{22}H_{17}N_2O_6SBr$; C, 51.16; H, 3.29; N, 5.43; S, 6.20. Found: C, 51.11; H, 3.16; N, 5.36; S, 6.14.

Ethyl .4-[-2-(3-methoxybenzamido)-5-(2-methoxy-2-oxoethylidene)-4oxothiazolidin-3-yl]benzoate (4i)



Yield = 66 %; Rf = 0.6; M.P. = 134-135 ^oC; IR (KBr) ν_{max}: 2957 (C=C−H), 1724 (-C_2H_5 ester C=O), 1722 (-CH_3 ester C=O), 1679 (ring C=O), 1668 (Ar C=O), 1565 (C=N), 1543 (C=C), 1452 (C−N), 1263 (C−S) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.88 (1H, d, *J* = 7.6 Hz, H-2,H-6), 7.56-7.82 (4H, m, Ar), 7.52 (1H, d, *J* = 7.6 Hz, H-3,H-5), 7.13 (1H, s, C=C-*H*), 4.26 (2H, q, *J* = 7.1 Hz,-CH_2), 3.84 (3H, s, Ar-OCH_3), 3.75 (3H, s, -OCH_3), 2.24 (3H, t, *J* = 5.6 Hz, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.5 (amide C=O), 167.7 (ring C=O), 166.3 (-CH_3 ester C=O), 165.6 (-C_2H_5 ester C=O), 162.5 (C=N), 140.4 (=CH), 138.7 (C-3'), 137.4 (C-4), 136.3 (C-4'), 133.6 (C-6'), 131.4 (S-C=), 130.5 (C-2,C-6), 126.3 (C-1), 124.8 (C-1'), 123.5 (C-5'), 122.6 (C-3,C-5), 118.3 (C-2'), 59.2 (2H, s, -OCH_2), 56.1 (3H, s, Ar-OCH_3), 53.5 (3H, s, -OCH_3), 15.4 (3H, s, -CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 468 (52), 333 (34), 319 (21), 183 (54), 149 (37), 135 (100 %), 124 (44); Anal. Calcd. for $C_{23}H_{20}N_2O_7S$; C, 58.97; H, 4.26; N, 5.97; S, 6.83. Found: C, 58.84; H, 4.16; N, 5.86; S, 6.71.

Ethyl 4-[-2-(2-fluorobenzamido)-5-(2-methoxy-2-oxoethylidene)-4-oxothiazolidin-3-yl] benzoate (4j)



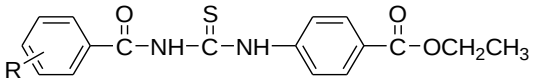
Yield = 65 %; Rf = 0.71; M.P. = 142-143 ^oC; IR (KBr) ν_{max}: 2963 (C=C−H), 1731 (-C_2H_5 ester C=O), 1728 (-CH_3 ester C=O), 1682 (ring C=O), 1667 (Ar C=O), 1571 (C=N), 1564 (C=C), 1454 (C−N), 1276 (C−S) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.97 (1H, d, *J* = 7.6

Hz, H-2,H-6), 7.92-7.65 (4H, m, Ar), 7.61 (1H, d, *J* = 7.6 Hz, H-3,H-5), 7.18 (1H, s, C=C-*H*), 4.28 (2H, q, *J* = 7.1 Hz,-CH_2), 3.79 (3H, s, -OCH_3), 2.31 (3H, t, *J* = 5.5 Hz, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 169.4 (amide C=O), 167.5 (ring C=O), 166.8 (-CH_3 ester C=O), 165.7 (-C_2H_5 ester C=O), 163.2 (C=N), 141.4 (=CH), 139.3 (C-2'), 137.8 (C-4), 136.5 (C-4'), 134.3 (C-6'), 131.7 (S-C=), 130.4 (C-2,C-6), 128.7 (C-5'), 126.8 (C-1), 125.5 (C-1'), 122.7 (C-3,C-5), 118.5 (C-3'), 60.4 (2H, s, -OCH_2), 53.6 (3H, s, -OCH_3), 15.7 (3H, s, -CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 456 (26), 397 (31), 333 (20), 183 (44), 152 (35), 149 (100 %), 124 (15), 105 (23), 95 (12); Anal. Calcd. for $C_{22}H_{17}N_2O_6SF$; C, 57.89; H, 3.73; N, 6.14; S, 7.02. Found: C, 57.49; H, 3.61; N, 6.05; S, 6.95.

[Pet.ether : ethylacetate (7:3)]

3.5 Iminothiazolines

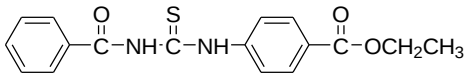
3.5.1 Synthesis of Ethyl 4-(3-substituted-benzoylthioureido) benzoates (1a-j)



Procedure

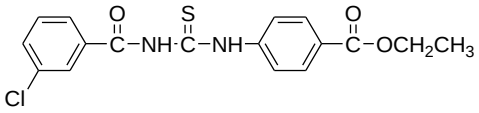
Ethyl 4-(3-substituted-benzoylthioureido) benzoates were synthesized according to the same procedure as described in Section 2.4.2. The crude products were recrystallized with methanol/ethanol.

Ethyl 4-(3-benzoylthioureido)benzoate (1a)



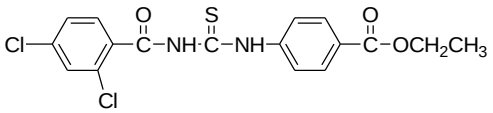
Yield = 74 %; Rf = 0.8; M.P. = 140-142 ^{o}C; IR (KBr) ν_{max}: 3298 (N-H), 1724 (ester C=O), 1675 (amide C=O), 1583 (C=C), 1272 (C=S), 1152 (C-N) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 11.31 (1H, s, -NH), 10.24 (1H, s, -NH), 7.92 (1H, d, *J* = 7.8 Hz, H-2,H-6), 7.56-7.87 (5H, m, Ar), 7.47 (1H, d, *J* = 7.8 Hz, H-3,H-5), 4.21 (2H, q, *J* = 7.2 Hz, -CH_2), 2.21 (3H, t, *J* = 5.6 Hz, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 180.4 (C=S), 167.3 (amide C=O), 165.4 (ester C=O), 138.6 (C-4), 135.4 (C-1'), 132.6 (C-4'), 130.5 (C-2,C-6), 129.4 (C-3',C-5'), 128.7 (C-2',C-6'), 127.6 (C-3,C-5), 126.7 (C-1), 60.2 (-OCH_2), 14.3 (-CH_3); EIMS (70 eV): *m/z* (%); [$M^{+\cdot}$] 328 (42 %); Anal. Calcd. for $C_{17}H_{16}N_2O_3S$; C, 62.19; H, 4.88; N, 8.54; S, 9.76. Found: C, 62.11; H, 4.64; N, 8.33; S, 9.54.

Ethyl 4-[3-(3-chlorobenzoyl)thioureido]benzoate (1b)



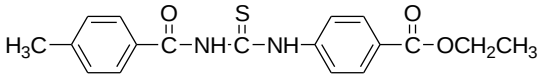
Yield = 78 %; Rf = 0.7; M.P. = 156-158 ^{o}C; IR (KBr) ν_{max}: 3302 (N-H), 1727 (ester C=O), 1673 (amide C=O), 1578 (C=C), 1280 (C=S), 1153 (C-N) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 11.37 (1H, s, -NH), 10.32 (1H, s, -NH), 7.95 (1H, d, *J* = 7.8 Hz, H-2,H-6), 7.84 (1H, d, *J* = 2.4 Hz, H-2'), 7.76 (1H, d, *J* = 7.4 Hz, H-6'), 7.66 (1H, d, *J* = 7.8 Hz, H-3,H-5), 7.58 (1H, dd, *J* = 7.2,2.4 Hz, H-4'), 7.49 (1H, dd, *J* = 7.2,7.4 Hz, H-5'), 4.26 (2H, q, *J* = 7.2 Hz, -CH_2), 2.26 (3H, t, *J* = 5.6 Hz, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 180.8 (C=S), 167.5 (amide C=O), 165.6 (ester C=O), 138.7 (C-4), 136.4 (C-1'), 135.5 (C-3'), 133.7 (C-4'), 130.7 (C-2,C-6), 129.4 (C-5'), 128.5 (C-2'), 127.4 (C-3,C-5), 126.5 (C-1), 125.8 (C-6'), 60.3 (-OCH_2), 14.2 (-CH_3); EIMS (70 eV): *m/z* (%); [$M^{+\cdot}$] 362.5 (53 %); Anal. Calcd. for $C_{17}H_{15}N_2O_3SCl$; C, 56.27; H, 4.14; N, 7.72; S, 8.83. Found: C, 56.14; H, 4.06; N, 7.53; S, 8.64.

Ethyl 4-[3-(2,4-dichlorobenzoyl)thioureido]benzoate (1c)



Yield = 80 %; Rf = 0.75; M.P. = 117-118 ^{o}C; IR (KBr) ν_{max}: 3309 (N-H), 1723 (ester C=O), 1678 (amide C=O), 1586 (C=C), 1283 (C=S), 1157 (C-N) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 11.42 (1H, s, -NH), 10.38 (1H, s, -NH), 7.97 (1H, d, *J* = 7.8 Hz, H-2,H-6), 7.86 (1H, d, *J* = 2.3 Hz, H-3'), 7.78 (1H, d, *J* = 7.2 Hz, H-6'), 7.67 (1H, dd, *J* = 7.2,2.3 Hz, H-5'), 7.54 (1H, d, *J* = 7.8 Hz, H-3,H-5), 4.27 (2H, q, *J* = 7.2 Hz, -CH_2), 2.28 (3H, t, *J* = 5.6 Hz, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 181.2 (C=S), 167.8 (amide C=O), 166.2 (ester C=O), 139.5 (C-4), 138.4 (C-4'), 135.2 (C-2'), 132.3 (C-3'), 131.7 (C-1'), 130.8 (C-6'), 130.3 (C-2,C-6), 128.1 (C-5'), 127.2 (C-3,C-5), 126.8 (C-1), 60.8 (-OCH_2), 14.5 (-CH_3); EIMS (70 eV): *m/z* (%); [$M^{+\cdot}$] 397 (37 %); Anal. Calcd. for $C_{17}H_{14}N_2O_3SCl_2$; C, 51.38; H, 3.53; N, 7.05; S, 8.06. Found: C, 51.27; H, 3.35; N, 6.93; S, 7.93.

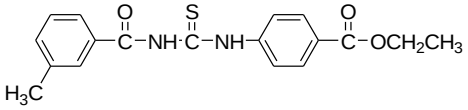
Ethyl 4-[3-(4-methylbenzoyl)thioureido]benzoate (1d)



Yield = 71 %; Rf = 0.7; M.P. = 223-224 ^{o}C; IR (KBr) ν_{max}: 3329 (N-H), 1726 (ester C=O), 1681 (amide C=O), 1584 (C=C), 1286 (C=S), 1154 (C-N) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 11.34 (1H, s, -NH), 10.27 (1H, s, -NH), 7.88 (1H, d, *J* = 7.8 Hz, H-2,H-6), 7.77 (1H, d, *J* = 7.4 Hz, H-2',H-6'), 7.68 (1H, d, *J* = 7.8 Hz, H-3,H-5), 7.57 (1H, d, *J* = 7.4 Hz, H-3',H-5'), 4.24 (2H, q, *J* = 7.2 Hz, -CH_2), 2.62 (3H, s, Ar-CH_3), 2.25 (3H, t, *J* = 5.6

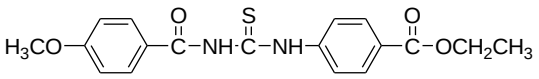
Hz, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 180.6 (C=S), 167.5 (amide C=O), 165.4 (ester C=O), 138.7 (C-4), 137.8 (C-4'), 132.6 (C-1'), 131.4 (C-2,C-6), 130.3 (C-3',C-5'), 128.2 (C-2',C-6'), 127.6 (C-3,C-5), 126.7 (C-1), 60.4 (2H, s, -OCH_2), 24.3 (Ar-CH_3), 14.4 (-CH_3); EIMS (70 eV): *m/z* (%); [$M^{+\cdot}$] 342 (61 %); Anal. Calcd. for $C_{18}H_{18}N_2O_3S$; C, 63.16; H, 5.26; N, 7.02; S, 9.36. Found: C, 63.07; H, 5.14; N, 6.95; S, 9.21.

Ethyl 4-[3-(3-methylbenzoyl)thioureido]benzoate (1e)



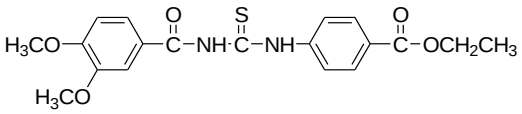
Yield = 78 %; Rf = 0.7; M.P. = 196-198 ^{o}C; IR (KBr) ν_{max}: 3322 (N-H), 1722 (ester C=O), 1671 (amide C=O), 1588 (C=C), 1284 (C=S), 1156 (C-N) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 11.35 (1H, s, -NH), 10.31 (1H, s, -NH), 7.86 (1H, d, *J* = 7.8 Hz H-2,H-6), 7.75 (1H, d, *J* = 7.2 Hz, H-6'), 7.66 (1H, d, *J* = 2.4 Hz, H-2'), 7.58 (1H, dd, *J* = 7.4,7.2 Hz, H-5'), 7.53 (1H, dd, *J* = 7.4,2.4 Hz, H-4'), 7.46 (1H, d, *J* = 7.8 Hz, H-3,H-5), 4.23 (2H, q, *J* = 7.2 Hz, -CH_2), 2.61 (3H, s, Ar-CH_3), 2.24 (3H, t, *J* = 5.6 Hz, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 180.5 (C=S), 167.6 (amide C=O), 165.7 (ester C=O), 138.9 (C-4), 137.8 (C-3'), 134.5 (C-1'), 133.2 (C-4'), 130.5 (C-2,C-6), 129.3 (C-5'), 128.2 (C-2'), 127.1 (C-3,C-5), 126.4 (C-1), 125.4 (C-6'), 60.5 (-OCH_2), 24.1 (Ar-CH_3), 14.3 (-CH_3); EIMS (70 eV): *m/z* (%); [$M^{+\cdot}$] 342 (53 %); Anal. Calcd. for $C_{18}H_{18}N_2O_3S$; C, 63.15; H, 5.25; N, 7.01; S, 9.35. Found: C, 63.08; H, 5.17; N, 6.94; S, 9.24.

Ethyl 4-[3-(4-methoxybenzoyl)thioureido]benzoate (1f)



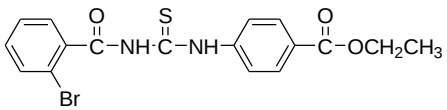
Yield = 76 %; Rf = 0.65; M.P. = 207-208 ^{o}C; IR (KBr) ν_{max}: 3315 (N-H), 1726 (ester C=O), 1674 (amide C=O), 1587 (C=C), 1282 (C=S), 1165 (C-N) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 11.38 (1H, s, -NH), 10.29 (1H, s, -NH), 7.86 (1H, d, *J* = 7.8 Hz, H-2,H-6), 7.73 (1H, d, *J* = 7.5 Hz, H-2',H-6'), 7.64 (1H, d, *J* = 7.5 Hz, H-3',H-5'), 7.54 (1H, d, *J* = 7.8 Hz, H-3,H-5), 4.27 (2H, q, *J* = 7.2 Hz, -CH_2), 3.72 (3H, s, -OCH_3), 2.25 (3H, t, *J* = 5.6 Hz, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 180.6 (C=S), 167.4 (amide C=O), 165.5 (ester C=O), 139.6 (C-4'), 138.5 (C-4), 134.5 (C-1'), 130.7 (C-2,C-6), 129.5 (C-2',C-6'), 127.2 (C-3,C-5), 126.7 (C-1), 117.4 (C-3',C-5'), 60.6 (-OCH_2), 56.5 (Ar-OCH_3), 14.2 (-CH_3); EIMS (70 eV): *m/z* (%); [$M^{+\cdot}$] 358 (46 %); Anal. Calcd. for $C_{18}H_{18}N_2O_4S$; C, 60.33; H, 5.03; N, 6.70; S, 8.94. Found: C, 60.27; H, 4.92; N, 6.58; S, 8.86.

Ethyl 4-[3-(3,4-dimethoxybenzoyl)thioureido]benzoate (1g)



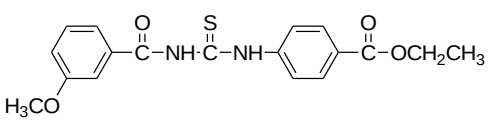
Yield = 72 %; Rf = 0.6; M.P. = 232-234 ^{o}C; IR (KBr) ν_{max}: 3321 (N-H), 1724 (ester C=O), 1678 (amide C=O), 1585 (C=C), 1267 (C=S), 1147 (C-N) cm^{-1}; ^{1}H NMR, ($CDCl_3$, δ ppm): 11.40 (1H, s, -NH), 10.32 (1H, s, -NH), 7.90 (1H, d, *J* = 7.8 Hz, H-2,H-6), 7.84 (1H, d, *J* = 7.4 Hz, H-6'), 7.73 (1H, d, *J* = 7.8 Hz, H-3,H-5), 7.65 (1H, s, Ar-H-2'), 7.56 (1H, d, *J* = 7.5 Hz, H-5'), 4.27 (2H, q, *J* = 7.2 Hz, -CH_2), 3.78 (3H, s, 3-OCH_3), 3.75 (3H, s, 4-OCH_3), 2.25 (3H, t, *J* = 5.6 Hz, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 180.7 (C=S), 167.7 (amide C=O), 165.8 (ester C=O), 139.8 (C-4'), 138.7 (C-3'), 137.6 (C-4), 130.8 (C-2,C-6), 128.3 (C-1'), 127.1 (C-3,C-5), 126.5 (C-1), 121.6 (C-6'), 117.4 (C-5'), 115.5 (C-2'), 60.6 (-OCH_2), 56.5 (Ar-OCH_3), 14.2 (-CH_3); EIMS (70 eV): *m/z* (%); [$M^{+\cdot}$] 388 (33 %); Anal. Calcd. for $C_{19}H_{20}N_2O_5S$; C, 58.76; H, 5.15; N, 6.18; S, 8.25. Found: C, 58.57; H, 5.09; N, 6.11; S, 8.17.

Ethyl 4-[3-(2-bromobenzoyl)thioureido]benzoate (1h)



Yield = 74 %; Rf = 0.67; M.P. = 213-215 ^{o}C; IR (KBr) ν_{max}: 1728 (ester C=O), 3317 (N-H), 1683 (amide C=O), 1576 (C=C), 1262 (C=S), 1165 (C-N) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 11.34 (1H, s, -NH), 10.23 (1H, s, -NH), 7.85 (1H, d, *J* = 7.8 Hz, H-2,H-6), 7.63-7.81 (4H, m, Ar), 7.56 (1H, d, *J* = 7.8 Hz, H-3,H-5), 4.23 (2H, q, *J* = 7.2 Hz, -CH_2), 2.26 (3H, t, *J* = 5.6 Hz, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 180.4 (C=S), 167.2 (amide C=O), 165.6 (ester C=O), 138.6 (C-4), 137.5 (C-1'), 135.4 (C-4'), 132.7 (C-3'), 131.2 (C-2,C-6), 130.5 (C-6'), 128.4 (C-5'), 127.3 (C-3,C-5), 126.8 (C-1), 121.4 (C-2'), 60.4 (-OCH_2), 14.3 (-CH_3); EIMS (70 eV): *m/z* (%); [$M^{+\cdot}$] 406 (46 %); Anal. Calcd. for $C_{17}H_{15}N_2O_3SBr$; C, 50.25; H, 3.69; N, 6.90; S, 7.88. Found: C, 50.17; H, 3.56; N, 6.76; S, 7.74.

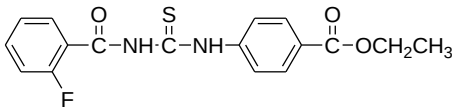
Ethyl 4-[3-(3-methoxybenzoyl)thioureido]benzoate (1i)



Yield = 73 %; Rf = 0.6; M.P. = 173-174 ^{o}C; IR (KBr) ν_{max}: 1725 (ester C=O), 3325 (N-H), 1685 (amide C=O), 1581 (C=C), 1264 (C=S), 1148 (C-N) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 11.36 (1H, s, -NH), 10.27 (1H, s, -NH), 7.87 (1H, d, *J* = 7.8 Hz, H-2,H-6), 7.57-7.77 (4H, m, Ar), 7.53 (1H, d, *J* = 7.8 Hz, H-3,H-5), 4.25 (2H, q, *J* = 7.2 Hz, -CH_2), 3.73 (3H, s, -OCH_3), 2.26 (3H, t, *J* = 5.6 Hz, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 180.5 (C=S), 167.6 (amide C=O), 165.7 (ester C=O), 138.7 (C-3'), 137.6 (C-4), 134.2 (C-4'), 131.3 (C-2,C-

6), 129.1 (C-6'), 127.4 (C-3,C-5), 126.6 (C-1), 122.5 (C-5'), 118.4 (C-1'), 116.5 (C-2'), 60.7 (-OCH_2), 56.4 (Ar-OCH_3), 14.5 (-CH_3); EIMS (70 eV): *m/z* (%); [$M^{+\cdot}$] 358 (54 %); Anal. Calcd. for $C_{18}H_{18}N_2O_4S$; C, 60.34; H, 3.02; N, 6.70; S, 8.93. Found: C, 60.23; H, 4.93; N, 6.53; S, 8.81.

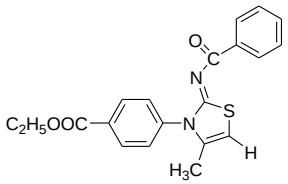
Ethyl 4-[3-(2-fluorobenzoyl)thioureido]benzoate (1j)



Yield = 68 %; Rf = 0.7; M.P. = 123-124 ^oC; IR (KBr) ν_{max}: 1729 (ester C=O), 3332 (N-H), 1688 (amide C=O), 1591 (C=C), 1271 (C=S), 1156 (C-N) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 11.42 (1H, s, -NH), 10.34 (1H, s, -NH), 7.93 (1H, d, *J* = 7.8 Hz, H-2,H-6), 7.64-7.89 (4H, m, Ar), 7.58 (1H, d, *J* = 7.8, Hz H-3,H-5), 4.26 (2H, q, *J* = 7.2 Hz, -CH_2), 2.28 (3H, t, *J* = 5.6 Hz, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 181.4 (C=S), 168.2 (amide C=O), 166.5 (ester C=O), 140.6 (C-2'), 138.7 (C-4), 134.7 (C-4'), 131.2 (C-2,C-6), 129.3 (C-6'), 127.3 (C-3,C-5), 126.7 (C-1), 126.3 (C-1'), 125.6 (C-5'), 117.6 (C-3'), 61.2 (-OCH_2), 14.8 (-CH_3); EIMS (70 eV): *m/z* (%); [$M^{+\cdot}$] 346 (24 %); Anal. Calcd. for $C_{17}H_{15}N_2O_3SF$; C, 58.96; H, 4.34; N, 6.94; S, 9.25. Found: C, 58.87; H, 4.21; N, 6.73; S, 9.12.

[Pet. ether : ethyl acetate (8:2)]

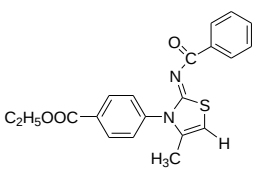
3.5.2 Synthesis of Ethyl 4-[2-benzamido-4-methylthiazol-3(2H)-yl)]benzoates (2a-j)



Procedure

Ethyl 4-[2-benzamido-5-(2-methoxy-2-oxoethylidene)-4-oxothiazolidin-3-yl] benzoates were synthesized according to the same procedure as described in Section 2.5.3. The crude products were recrystallized with ethanol.

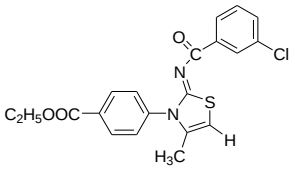
Ethyl 4-[2-benzamido-4-methylthiazol-3(2H)-yl)]benzoates (2a)



Yield = 68 %; Rf = 0.4; M.P. = 108-110 ^oC; IR (KBr) ν_{max}: 3046 (C=C-H), 1724 (ester C=O), 1676 (amide C=O), 1643 (C=N), 1578 (C=C), 1147 (C-S) cm^{-1}; ^1H NMR ($CDCl_3$, δ ppm): 7.86 (2H, d, *J* = 7.4 Hz, H-2',H-6'), 7.79 (2H, d, *J* = 7.8 Hz, H-3,H-5), 7.62 (1H, d, *J* = 7.1 Hz, H-4'), 7.55 (1H, dd, *J* = 7.4,7.1 Hz, H-3',H-5'), 6.63 (2H, d, *J* = 7.8 Hz, H-2,H-6), 6.42 (1H, s,

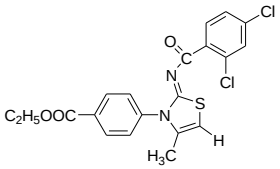
C=C-*H*), 4.31 (2H, q, *J* = 7.1 Hz, -CH_2), 2.23 (3H, t, *J* = 5.6 Hz, -CH_3), 2.64 (-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.4 (amide C=O), 166.2 (ester C=O), 162.5 (N=C), 150.3 (N-C=), 145.5 (C-1), 136.6 (C-1'), 134.5 (C-4'), 132.2 (C-3,C-5), 131.2 (C-2',C-6'), 130.4 (C-3',C-5'), 122.5 (C-4), 117.3 (C-2,C-6), 101.2 (=CH), 61.4 (-CH_2), 21.3 (-CH_3), 15.2 (ester-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 366 (49), 261 (100 %), 217 (26), 188 (53), 112 (18), 105 (21), 96 (31), 77 (20); Anal. Calcd. for $C_{20}H_{18}N_2O_3S$; C, 65.55; H, 4.94; N, 7.63; S, 8.75. Found: C, 65.46; H, 4.83; N, 7.48; S, 8.62.

Ethyl 4-[2-(3-chlorobenzamido)-4-methylthiazol-3(2H)-yl)]benzoate (2b)



Yield = 70 %; Rf = 0.5; M.P. = 87-88 ^{o}C; IR (KBr) ν_{max}: 3051 (C=C-H), 1726 (ester C=O), 1685 (amide C=O), 1648 (C=N), 1582 (C=C), 1150 (C-S) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.93 (1H, d, *J* = 2.3 Hz, H-2'), 7.84 (2H, d, *J* = 7.8 Hz, H-3,H-5), 7.75 (1H, d, *J* = 7.2 Hz, H-6'), 7.66 (1H, dd, *J* = 7.1,2.2 Hz, H-4'), 7.47 (1H, dd, *J* = 7.2,7.1 Hz, H-5'), 6.72 (2H, d, *J* = 7.8 Hz, H-2,H-6), 6.46 (1H, s, C=C-*H*), 4.37 (2H, q, *J* = 7.1 Hz, -CH_2), 2.27 (3H, t, *J* = 5.6 Hz, -CH_3), 2.66 (-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.6 (amide C=O), 166.5 (ester C=O), 163.2 (N=C), 150.6 (N-C=), 145.5 (C-1), 137.6 (C-1'), 135.5 (C-3'), 134.4 (C-4'), 132.6 (C-3,C-5), 131.4 (C-5'), 130.2 (C-2'), 128.3 (C-6'), 122.7 (C-4), 118.2 (C-2,C-6), 101.6 (=CH), 61.7 (-CH_2), 21.5 (-CH_3), 15.6 (ester-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 400.5 (74), [$(M+2)^{+\cdot}$] 402.5 (61), 261 (100 %), 188 (30), 139.5 (36), 112 (23), 111.5 (27), 96 (18), 77 (34); Anal. Calcd. for $C_{20}H_{17}N_2O_3SCl$; C, 59.91; H, 4.26; N, 6.98; S, 7.98. Found: C, 59.83; H, 4.16; N, 6.87; S, 7.86.

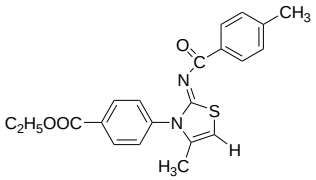
Ethyl 4-[2-(2,4-dichlorobenzamido)-4-methylthiazol-3(2H)-yl)]benzoate (2c)



Yield = 76 %; Rf = 0.5; M.P. = 97-98 ^{o}C; IR (KBr) ν_{max}: 3058 (C=C-H), 1734 (ester C=O), 1692 (amide C=O), 1657 (C=N), 1584 (C=C), 1160 (C-S) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.88 (2H, d, *J* = 7.8 Hz, H-3,H-5), 7.73 (1H, d, *J* = 7.1 Hz, H-6'), 7.57 (1H, s, H-3'), 7.48 (1H, d, *J* = 7.1 Hz, H-5'), 6.68 (2H, d, *J* = 7.8 Hz, H-2,H-6), 6.48 (1H, s, C=C-*H*), 4.39 (2H, q, *J* = 7.1 Hz, -CH_2), 2.31 (3H, t, *J* = 5.6 Hz, -CH_3), 2.68 (-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.7 (N-C=O), 166.7 (ester C=O), 163.4 (N=C), 150.7 (N-C=), 145.7 (C-1), 140.6 (C-4'), 137.4 (C-2'), 136.5 (C-1'), 133.4 (C-6'), 132.7 (C-3,C-5), 131.4 (C-3'), 128.5 (C-5'), 122.6 (C-4), 118.4 (C-2,C-6), 101.8 (=CH), 61.7 (-CH_2), 21.8 (-CH_3), 15.7 (ester-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 434 (56), 261 (100 %), 188 (37), 173 (27), 145

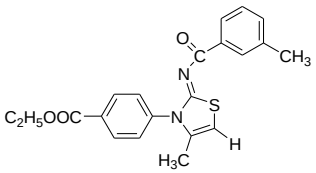
(46), 112 (43), 111.5 (33), 77 (24); Anal. Calcd. for $C_{20}H_{16}N_2O_3SCl_2$; C, 55.17; H, 3.69; N, 6.43; S, 6.37. Found: C, 55.11; H, 3.53; N, 6.34; S, 6.28.

Ethyl 4-[4-methyl-2-(4-methylbenzamido)thiazol-3(2H)-yl)]benzoate (2d)



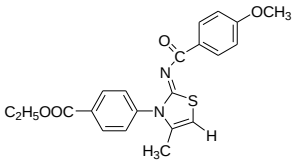
Yield = 74 %; Rf = 0.45; M.P. = 118-119 ^{o}C; IR (KBr) ν_{max}: 3052 (C=C-H), 1725 (ester C=O), 1683 (amide C=O), 1646 (C=N), 1574 (C=C), 1147 (C-S) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.88 (2H, d, *J* = 7.8 Hz, H-3,H-5), 7.76 (2H, d, *J* = 7.3 Hz, H-2',H-6'), 7.36 (2H, d, *J* = 7.3 Hz, H-3',H-5'), 6.65 (2H, d, *J* = 7.8 Hz, H-2,H-6), 6.43 (1H, s, C=C-*H*), 4.34 (2H, q, *J* = 7.1 Hz, -CH_2), 2.26 (3H, t, *J* = 5.6 Hz, -CH_3), 2.75 (Ar-CH_3), 2.65 (-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.5 (amide C=O), 166.4 (ester C=O), 162.4 (N=C), 150.3 (N-C=), 145.3 (C-1), 134.7 (C-4'), 133.5 (C-1'), 132.2 (C-3,C-5), 131.5 (C-2',C-6'), 130.6 (C-3',C-5'), 122.4 (C-4), 117.2 (C-2,C-6), 101.4 (=CH), 61.3 (-CH_2), 24.7 (Ar-CH_3), 21.3 (-CH_3), 15.4 (ester-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 380 (61), 261 (100 %), 188 (36), 119 (47), 112 (22), 91 (37), 77 (28); Anal. Calcd. for $C_{21}H_{20}N_2O_3S$; C, 66.28; H, 5.30; N, 7.36; S, 8.42. Found: C, 66.14; H, 5.21; N, 7.23; S, 8.33.

Ethyl 4-[4-methyl-2-(3-methylbenzamido)thiazol-3(2H)-yl)]benzoate (2e)



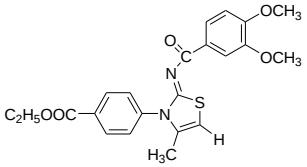
Yield = 72 %; Rf = 0.45; M.P. = 112-113 ^{o}C; IR (KBr) ν_{max}: 3054 (C=C-H), 1726 (ester C=O), 1685 (amide C=O), 1451 (C=N), 1583 (C=C), 1153 (C-S) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.86 (2H, d, *J* = 7.8 Hz, H-3,H-5), 7.78 (1H, d, *J* = 2.4 Hz, H-2'), 7.73 (1H, d, *J* = 7.2 Hz, H-6'), 7.65 (1H, dd, *J* = 7.1,2.4 Hz, H-4'), 7.58 (1H, dd, *J* = 7.2, 7.1 Hz, H-5'), 6.71 (2H, d, *J* = 7.8 Hz, H-2,H-6), 6.44 (1H, s, C=C-*H*), 4.36 (2H, q, *J* = 7.1 Hz, -CH_2), 2.25 (3H, t, *J* = 5.6 Hz, -CH_3), 2.73 (Ar-CH_3), 2.64 (-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.6 (amide C=O), 166.5 (ester C=O), 162.6 (N=C), 150.6 (N-C=), 145.5 (C-1), 137.6 (C-3'), 136.3 (C-1'), 135.4 (C-4'), 132.2 (C-3,C-5), 131.3 (C-2'), 130.7 (C-6'), 129.4 (C-5'), 122.5 (C-4), 117.4 (C-2,C-6), 101.6 (=CH), 61.3 (-CH_2), 24.6 (Ar-CH_3), 21.5 (-CH_3), 15.4 (ester-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 380 (67), 261 (100 %), 188 (56), 119 (34), 112 (16), 91 (41), 77 (23); Anal. Calcd. for $C_{21}H_{20}N_2O_3S$; C, 66.28; H, 5.30; N, 7.36; S, 8.42. Found: C, 66.12; H, 5.23; N, 7.25; S, 8.34.

Ethyl 4-[4-methyl-2-(4-methoxybenzamido)thiazol-3(2H)-yl)]benzoate (2f)



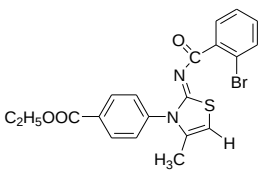
Yield = 71 %; Rf = 0.4; M.P. = 126-127 ^{o}C; IR (KBr) ν_{max}: 3045 (C=C-H), 1723 (ester C=O), 1677 (amide C=O), 1645 (C=N), 1587 (C=C), 1155 (C-S) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.81 (2H, d, *J* = 7.8 Hz, H-3,H-5), 7.74 (2H, d, *J* = 7.4 Hz, H-2',H-6'), 7.26 (2H, d, *J* = 7.4 Hz, H-3', H-5'), 6.73 (2H, d, *J* = 7.8 Hz, H-2,H-6), 6.42 (1H, s, C=C-*H*), 4.32 (2H, q, *J* = 7.1 Hz, -CH_2), 3.74 (Ar-OCH_3), 2.24 (3H, t, *J* = 5.6 Hz, -CH_3), 2.63 (-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.4 (amide C=O), 166.3 (ester C=O), 162.6 (N=C), 150.5 (N-C=), 145.7 (C-1), 142.3 (C-4'), 132.5 (C-3,C-5), 131.8 (C-2',C-6'), 128.4 (C-1'), 121.7 (C-4), 120.3 (C-2,C-6), 118.5 (C-3',C-5'), 101.5 (=CH), 61.2 (-CH_2), 56.3 (Ar-OCH_3), 21.6 (-CH_3), 15.5 (ester-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 396 (46), 261 (100 %), 188 (34), 135 (53), 112 (29), 107 (38), 77 (20); Anal. Calcd. for $C_{21}H_{20}N_2O_4S$; C, 63.61; H, 5.07; N, 7.07; S, 8.09. Found: C, 63.53; H, 4.96; N, 7.95; S, 8.01.

Ethyl 4-[4-methyl-2-(3,4-dimethoxybenzamido)thiazol-3(2H)-yl)]benzoate (2g)



Yield = 78 %; Rf = 0.35; M.P. = 132-133 ^{o}C; IR (KBr) ν_{max}: 3037 (C=C-H), 1721 (ester C=O), 1684 (amide C=O), 1644 (C=N), 1576 (C=C), 1152 (C-S) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.87 (2H, d, *J* = 7.8 Hz, H-3,H-5), 7.44 (1H, d, *J* = 7.2 Hz, H-6'), 7.35 (1H, s, Ar-H-2'), 6.96 (1H, d, *J* = 7.2 Hz, H-5'), 6.68 (2H, d, *J* = 7.8 Hz, H-2,H-6), 6.41 (1H, s, C=C-*H*), 4.31 (2H, q, *J* = 7.1 Hz, -CH_2), 3.76 (3'-OCH_3), 3.73 (4'-OCH_3), 2.21 (3H, t, *J* = 5.6 Hz, -CH_3), 2.62 (-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.2 (amide C=O), 166.2 (ester C=O), 162.6 (N=C), 154.2 (C-4'), 150.4 (C-3'), 149.5 (N-C=), 145.7 (C-1), 142.3 (C-4'), 132.3 (C-3,C-5), 128.6 (C-1'), 124.8 (C-6'), 121.7 (C-4), 120.3 (C-2,C-6), 118.2 (C-5'), 117.5 (C-2'), 101.5 (=CH), 61.2 (-CH_2), 56.4 (3'-OCH_3), 56.2 (4'-OCH_3), 21.3 (-CH_3), 15.2 (ester-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 426 (55), 261 (100 %), 188 (39), 165 (52), 137 (41), 107 (38), 77 (19); Anal. Calcd. for $C_{22}H_{22}N_2O_5S$; C, 61.95; H, 5.19; N, 6.56; S, 7.52. Found: C, 61.88; H, 5.12; N, 6.43; S, 7.44.

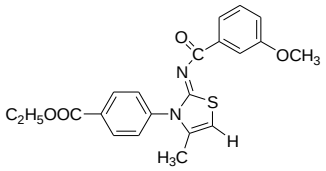
Ethyl 4-[4-methyl-2-(2-bromobenzamido)thiazol-3(2H)-yl)]benzoate (2h)



Yield = 73 %; Rf = 0.5; M.P .= 128-129 ^{o}C; IR (KBr) ν_{max}: 3045 (C=C-H), 1722 (ester C=O), 1675 (amide C=O), 1543 (C=N), 1582 (C=C), 1160 (C-S) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.89 (2H, d, *J* = 7.8 Hz, H-3,H-5), 7.81 (1H, d, *J* = 7.4 Hz, H-6'), 7.77 (1H, dd, *J* = 7.2,2.4

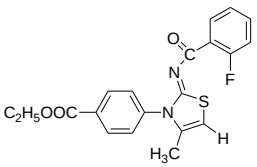
Hz, H-3'), 7.54 (1H, dd, *J* = 7.2,7.1 Hz, H-4'), 7.46 (1H, dd, *J* = 7.3,7.1 Hz, H-5'), 6.71 (2H, d, *J* = 7.8 Hz, H-2,H-6), 6.43 (1H, s, C=C-*H*), 4.31 (2H, q, *J* = 7.1 Hz, -CH_2), 2.23 (3H, t, *J* = 5.6 Hz, -CH_3), 2.67 (-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.3 (amide C=O), 166.4 (ester C=O), 162.7 (N=C), 150.2 (N-C=), 145.6 (C-1), 140.3 (C-1'), 137.6 (C-4'), 133.5 (C-3'), 132.4 (C-6'), 131.8 (C-3,C-5), 129.6 (C-5'), 124.2 (C-2'), 122.5 (C-4), 118.2 (C-2,C-6), 101.8 (=CH), 61.6 (-CH_2), 24.7 (Ar-CH_3), 21.4 (-CH_3), 15.1 (ester-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 444 (67), [(M+2) $^{+\cdot}$] 446 (42), 261 (100 %), 188 (52), 183 (43), 155 (36), 112 (16), 77 (24); Anal. Calcd. for $C_{21}H_{17}N_2O_3SBr$; C, 53.93; H, 3.84; N, 6.28; S, 7.19. Found: C, 53.84; H, 3.76; N, 6.16; S, 7.11.

Ethyl 4-[4-methyl-2-(3-methoxybenzamido)thiazol-3(2H)-yl)]benzoate (2i)



Yield = 75 %; Rf = 0.4; M.P. = 101-103 ^{o}C; IR (KBr) ν_{max}: 3057 (C=C-H), 1724 (ester C=O), 1673 (amide C=O), 1646 (C=N), 1580 (C=C), 1163 (C-S) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.85 (2H, d, *J* = 7.8 Hz, H-3,H-5), 7.41 (1H, d, *J* = 7.2 Hz, H-6'), 7.33 (1H, s, Ar-H-2'), 6.94 (1H, d, *J* = 7.2 Hz, H-5'), 6.67 (2H, d, *J* = 7.8 Hz, H-2,H-6), 6.34 (1H, s, C=C-*H*), 4.27 (2H, q, *J* = 7.1 Hz, -CH_2), 3.74 (3'-OCH_3), 2.24 (3H, t, *J* = 5.6 Hz, -CH_3), 2.63 (-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.5 (amide C=O), 166.3 (ester C=O), 162.7 (N=C), 160.5 (C-3'), 150.2 (N-C=), 145.3 (C-1), 137.5 (C-1'), 132.6 (C-3,C-5), 131.4 (C-5'), 124.6 (C-6'), 122.5 (C-4'), 121.6 (C-4), 118.7 (C-2,C-6), 116.5 (C-2'), 101.5 (=CH), 61.2 (-CH_2), 55.8 (4'-OCH_3), 21.5 (-CH_3), 15.3 (ester-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 396 (63), 261 (100 %), 188 (44), 135 (35), 112 (39), 107 (47), 77 (25); Anal. Calcd. for $C_{21}H_{20}N_2O_4S$; C, 63.62; H, 5.06; N, 7.06; S, 8.07. Found: C, 63.53; H, 4.95; N, 7.96; S, 8.01.

Ethyl 4-[4-methyl-2-(2-fluorobenzamido)thiazol-3(2H)-yl)]benzoate (2j)

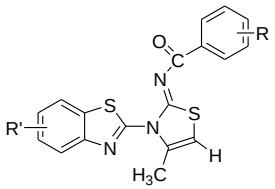


Yield = 65 %; Rf = 0.55; M.P. = 82-83 ^{o}C; IR (KBr) ν_{max}: 3063 (C=C-H), 1728 (ester C=O), 1688 (amide C=O), 1654 (C=N), 1586 (C=C), 1176 (C-S) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ ppm): 7.94 (1H, d, *J* = 7.3 Hz, H-6'), 7.86 (2H, d, *J* = 7.8 Hz, H-3,H-5), 7.68 (1H, dd, *J* = 7.2,6.9 Hz, H-4'), 7.37 (1H, dd, *J* = 7.2,7.1 Hz, H-5'), 7.26 (1H, dd, *J* = 7.1,6.8 Hz, H-5'), 6.64 (2H, d, *J* = 7.8 Hz, H-2,H-6), 6.48 (1H, s, C=C-*H*), 4.43 (2H, q, *J* = 7.1 Hz, -CH_2), 2.36 (3H, t, *J* = 5.6 Hz, -CH_3), 2.71 (-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 168.8 (amide C=O), 166.8 (ester C=O), 163.6 (N=C), 160.5 (C-2'), 150.6 (N-C=), 145.7 (C-1), 137.8 (C-4'), 132.6 (C-6'),

131.8 (C-3,C-5), 126.5 (C-5'), 124.6 (C-1'), 122.7 (C-4), 118.6 (C-2,C-6), 117.5 (C-3'), 101.9 (=CH), 62.1 (-CH_2), 24.8 (Ar-CH_3), 21.7 (-CH_3), 15.8 (ester-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 384 (72), 261 (100 %), 188 (45), 123 (53), 112 (21), 95 (32) 77 (26); Anal. Calcd. for $C_{20}H_{17}N_2O_3SF$; C, 62.48; H, 4.45; N, 7.28; S, 8.33. Found: C, 62.34; H, 4.36; N, 7.17; S, 8.25.

[Pet.ether : ethylacetate (7:3)]

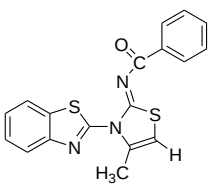
3.5.3 Synthesis of *N*-[3-(Benzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene]benzamides (3a-k)



Procedure

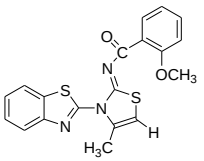
To the stirred solution of 1-benzoyl-3-(benzo[d]thiazol-2-yl) thiourea (1.0 g, 3 mmol) in 20 mL of dry acetone under inert atmosphere, triethylamine (0.4 mL, 3 mmol) was added drop wise through the rubber septum with the syringe (3 mL). Then a solution of 2-bromoactone, (bromine 0.3 mL, 0.003 mol in 10 mL dry acetone) was added slowly and the reaction mixture was stirred for 3-4 hr. After that the reaction mixture was filtered and concentrated to get crude *N*-(3-(benzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene) benzamides which were then recrystallized with methanol.

***N*-[3-(Benzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene]benzamide (3a)**



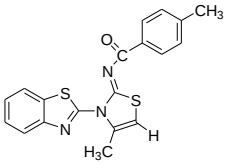
Yield = 70 %; Rf = 0.4; M.P. = 97-98 ^oC; IR (KBr) ν_{max}: 2926 (C=C-H), 2832 (-CH_3), 1678 (amide C=O), 1582 (C=N), 1558 (C=C), 1461 (C-N), 1168 (C-S) cm^{-1}; ^1H NMR, ($CDCl_3$, δ ppm): 8.12 (1H, d, *J* = 7.6 Hz, H-1), 8.06 (1H, d, *J* = 7.6 Hz, H-4), 7.61-7.94 (5H, m, Ar), 7.57 (1H, dd, *J* = 7.2,7.4 Hz, H-2), 7.34 (1H, dd, *J* = 7.1,7.4 Hz, H-3), 6.44 (1H, s, C=C-*H*), 2.23 (-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 165.3 (amide C=O), 162.4 (C=N), 160.5 (S-C=N), 151.3 (N-C=), 146.3 (C-9), 136.7 (C-1'), 134.5 (C-2',C-6'), 133.4 (C-3',C-5'), 128.2 (C-4'), 127.4 (C-6), 125.6 (C-5), 124.3 (C-8), 123.7 (C-4), 122.5 (C-7), 101.6 (=CH), 17.4 (-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 351 (54), 274 (30), 140 (100 %), 134 (36), 112 (25), 96 (13), 77 (19); Anal. Calcd. for $C_{18}H_{13}N_3OS_2$; C, 61.53; H, 3.70, N, 11.96, S, 18.23. Found: C, 61.47, H, 3.51, N, 11.83, S, 18.14.

***N*-[3-(Benzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene]-2-methoxybenzamide (3b)**



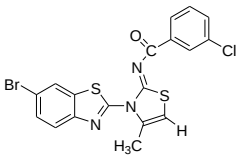
Yield = 74 %; Rf = 0.45; M.P. = 76-77 ^{o}C; IR (KBr) ν_{max}: 2931 (C=C-H), 2834 (-CH_3), 1674 (amide C=O), 1586 (C=N), 1553 (C=C), 1466 (C-N), 1171 (C-S) cm-^{1}; ^{1}H NMR, ($CDCl_3$, δ ppm): 8.14 (1H, d, *J* = 7.6 Hz, H-1), 8.08 (1H, d, *J* = 7.6 Hz, H-4), 7.91 (1H, d, *J* = 7.1 Hz, H-6'), 7.84 (1H, dd, *J* = 7.4,7.6, Hz, H-2), 7.76 (1H, dd, *J* = 7.6,7.4, Hz, H-3), 7.61 (1H, dd, *J* = 7.1, 7.2 Hz, H-5'), 7.47 (1H, dd, *J* = 7.3,7.2, Hz, H-4'), 7.38 (1H, d, *J* = 7.3 Hz, H-3'), 6.45 (1H, s, C=C-*H*), 3.76 (3H, s, -OCH_3), 2.24 (3H, s, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 165.5 (amide C=O), 162.7 (C=N), 160.7 (S-C=N), 151.6 (N-C=), 146.4 (C-9), 137.5 (C-1'), 136.4 (C-2'), 135.7 (C-6'), 134.6 (C-3'), 133.2 (C-5'), 128.6 (C-4'), 127.4 (C-6), 126.3 (C-5), 125.7 (C-8), 124.6 (C-4), 123.4 (C-7), 101.5 (=CH), 54.3 (-OCH_3), 17.8 (-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 381 (67), 274 (36), 140 (100 %), 134 (29), 112 (20), 107 (41), 96 (21), 77 (14); Anal. Calcd. for $C_{19}H_{15}N_3O_2S_2$; C, 59.84, H, 3.94, N, 11.02, S, 16.78. Found: C, 59.77, H, 3.82, N, 10.93, S, 16.67.

***N*-[3-(Benzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene]-4-methylbenzamide (3c)**



Yield = 71 %; Rf = 0.5; M.P. = 84-85^{o} C; IR (KBr) ν_{max}: 2935 (C=C-H), 2826 (-CH_3), 1676 (amide C=O), 1588 (C=N), 1555 (C=C), 1464 (C-N), 1173 (C-S) cm-^{1}; ^{1}H NMR, ($CDCl_3$, δ ppm): 8.11 (1H, d, *J* = 7.6 Hz, H-1), 8.05 (1H, d, *J* = 7.6 Hz, H-4), 7.84 (1H, d, *J* = 7.2 Hz, H-2',H-6'). 7.73 (1H, d, *J* = 7.2 Hz, H-3',H-5'), 7.66 (1H, dd, *J* = 7.2,7.4 Hz, H-2), 7.57 (1H, dd, *J* = 7.2,7.4 Hz, H-3), 6.43 (1H, s, C=C-*H*), 2.56 (3H, s, Ar-CH_3), 2.22 (3H, s, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 165.4 (amide C=O), 162.6 (C=N), 156.6 (S-C=N), 151.3 (N-C=), 146.8 (C-9), 134.4 (C-1'), 132.7 (C-2',C-6'), 131.5 (C-3',C-5'), 127.4 (C-4'), 126.3 (C-6), 125.5 (C-5), 124.7 (C-8), 123.6 (C-4), 122.4 (C-7), 101.6 (=CH), 21.3 (Ar-CH_3), 17.8 (-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 365 (49), 274 (71), 140 (100 %), 134 (50), 112 (30), 107 (38), 96 (24), 91 (45), 77 (20); Anal. Calcd. for $C_{19}H_{15}N_3OS_2$; C, 62.47, H, 4.11, N, 11.51, S, 17.53. Found: C, 62.34, H, 3.97, N, 11.38, S, 17.43.

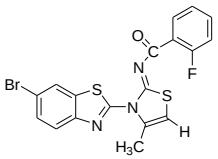
***N*-[3-(6-Bromobenzo[d]thiazol-2-yl)-3-methylthiazol-2(3H)-ylidene]-3-chlorobenzamide (3d)**



Yield = 73 %; Rf = 0.5; M.P. = 89-90 ^{o}C; IR (KBr) ν_{max}: 2955 (C=C-H), 2841 (-CH_3), 1685 (amide C=O), 1576 (C=N), 1563

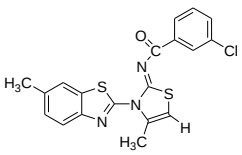
(C=C), 1462 (C-N), 1172 (C-S) cm-^{1}; ^{1}H NMR, ($CDCl_3$, δ ppm): 8.26 (1H, d, *J* = 7.4 Hz, H-3), 8.14 (1H, d, *J* = 2.3 Hz, H-1), 7.83 (1H, d, *J* = 2.4 Hz, H-2'), 7.75 (1H, d, *J* = 7.4 Hz, H-2), 7.71 (1H, d, *J* = 7.2 Hz, H-6'), 7.54 (1H, dd, *J* = 7.2,2.2 Hz, H-4'), 7.42 (1H, d, *J* = 7.2,7.1 Hz, H-5'), 6.44 (1H, s, C=C-*H*), 2.26 (3H, s, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 166.2 (amide C=O), 162.5 (C=N), 156.4 (S-C=N), 152.3 (N-C=), 146.5 (C-9), 136.7 (C-1'), 135.6 (C-3'), 134.5 (C-4'), 130.6 (C-5'), 130.3 (C-2'), 128.3 (C-6'), 128.5 (C-5), 126.7 (C-8), 124.5 (C-7), 124.2 (C-4), 117.4 (C-6), 101.6 (=CH), 18.4 (-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 463.5 (45), 352 (64), 212 (56), 140 (100 %), 134 (24), 112 (10), 111.5 (22), 96 (19) 77 (28); Anal. Calcd. for $C_{18}H_{11}N_3OBrS_2Cl$; C, 46.52, H, 2.38, N, 9.05, S, 13.78. Found: C, 46.36, H, 2.21, N, 8.93, S, 13.64.

_N_-[3-(6-Bromobenzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene]-2-fluorobenzamide (3e)



Yield = 68 %; Rf = 0.55; M.P. = 78-79 ^{o}C; IR (KBr) ν_{max}: 3021 (C=C-H), 2863 (-CH_3), 1684 (amide C=O), 1585 (C=N), 1568 (C=C), 1485 (C-N), 1187 (C-S) cm-^{1}; ^{1}H NMR, ($CDCl_3$, δ ppm): 8.17 (1H, d, *J* = 7.6 Hz, H-1), 8.11 (1H, d, *J* = 2.3 Hz, H-3), 7.81 (1H, d, *J* = 7.4 Hz, H-2), 7.73 (1H, d, *J* = 7.1 Hz, H-3'), 7.64 (1H, dd, *J* = 7.1,7.3 Hz, H-5'), 7.52 (1H, dd, *J* = 7.4,7.1 Hz, H-4'), 7.32 (1H, d, *J* = 7.4 Hz, H-6'), 6.46 (1H, s, C=C-*H*), 2.27 (3H, s, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 165.8 (amide C=O), 162.7 (C=N), 156.7 (S-C=N), 151.6 (N-C=), 146.8 (C-9), 141.6 (C-2'), 137.3 (C-1'), 136.4 (C-6'), 134.6 (C-4'), 132.5 (C-5), 128.7 (C-5'), 127.5 (C-3'), 126.4 (C-8), 125.6 (C-4), 124.7 (C-7), 121.6 (C-6), 101.7 (=CH), 18.6 (-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 448, (37), 351 (61), 211 (48), 140 (100 %), 112 (26), 95 (31), 77 (22); Anal. Calcd. for $C_{18}H_{11}N_3OS_2BrF$; C, 48.21, H, 2.46, N, 9.37, S, 14.28. Found: C, 48.13, H, 2.35, N, 9.23, S, 14.17.

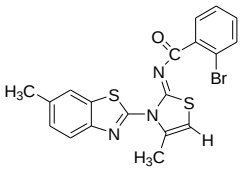
_N_-(3-(6-Methylbenzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene)-3-chlorobenzamide (3f)



Yield = 72 %; Rf = 0.45; M.P. = 86-87 ^{o}C; IR (KBr) ν_{max}: 2965 (C=C-H), 2839 (-CH_3), 1683 (amide C=O), 1576 (C=N), 1561 (C=C), 1463 (C-N), 1165 (C-S) cm-^{1}; ^{1}H NMR, ($CDCl_3$, δ ppm): 8.12 (1H, d, *J* = 7.4 Hz, H-1), 8.07 (1H, d, *J* = 2.3 Hz, H-3), 7.76 (1H, d, *J* = 7.4 Hz, H-2), 7.65 (1H, d, *J* = 7.2 Hz, H-6'), 7.56 (1H, d, *J* = 2.2 Hz, H-2'), 7.34 (1H, dd, *J* = 7.2,2.2 Hz, H-5'), 7.28 (1H, d, *J* = 7.2,7.1 Hz, H-4'), 6.45 (1H, s, C=C-*H*), 2.55 (3H, s,

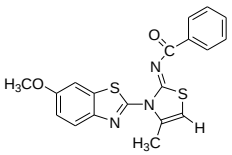
Ar-CH_3), 2.25 (3H, s, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 165.7 (amide C=O), 162.6 (C=N), 156.5 (S-C=N), 151.7 (N-C=), 146.8 (C-9), 138.7 (C-1'), 137.6 (C-3'), 136.5 (C-6'), 135.4 (C-4'), 134.2 (C-6), 133.6 (C-5'), 128.3 (C-2'), 126.5 (C-5), 124.4 (C-8), 122.5 (C-4), 121.6 (C-7), 101.8 (=CH), 22.7 (Ar-CH_3), 18.5 (-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 399.5 (45), 288 (64), 148 (53), 140 (100 %), 134 (26), 112 (30), 111.5 (32), 96 (29) 77 (18); Anal. Calcd. for $C_{19}H_{14}N_3OS_2Cl$; C, 57.07, H, 3.50, N, 10.51, S, 16.02. Found: C, 56.96, H, 3.31, N, 10.43, S, 15.84.

2-Bromo-*N*-[4-methyl-3-(6-methylbenzo[d]thiazol-2-yl)thiazol-2(3H)-ylidene]benzamide (3g)



Yield = 77 %; Rf = 0.35; M.P. = 90-91 ^{o}C; IR (KBr) ν_{max}: 2956 (C=C-H), 2835 (-CH_3), 1677 (amide C=O), 1570 (C=N), 1554 (C=C), 1454 (C-N), 1157 (C-S) cm-^{1}; ^{1}H NMR, ($CDCl_3$, δ ppm): 8.13 (1H, d, *J* = 7.6 Hz, H-1), 8.09 (1H, d, *J* = 2.4 Hz, H-3), 7.74 (1H, d, *J* = 7.6 Hz, H-2), 7.65 (1H, d, *J* = 7.1 Hz, H-6'), 7.52 (1H, dd, *J* = 7.1,7.2 Hz, H-5'), 7.43 (1H, dd, *J* = 7.4,7.1 Hz, H-4'), 7.23 (1H, d, *J* = 7.4 Hz, H-3'), 6.42 (1H, s, C=C-*H*), 2.57 (3H, s, Ar-CH_3), 2.26 (3H, s, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 165.4 (amide C=O), 162.5 (C=N), 156.3 (S-C=N), 151.5 (N-C=), 146.4 (C-9), 138.3 (C-1'), 137.4 (C-6'), 136.5 (C-4'), 135.4 (C-3'), 134.6 (C-5'), 133.5 (C-6), 128.7 (C-2'), 127.5 (C-5), 125.4 (C-8), 123.6 (C-4), 122.7 (C-7), 101.6 (=CH), 22.4 (Ar-CH_3), 18.2 (-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 444 (57), 288 (49), 154 (63), 140 (100 %), 134 (38), 112 (20), 96 (21) 77 (25); Anal. Calcd. for $C_{19}H_{14}N_3OS_2Br$; C, 51.35, H, 3.15, N, 9.46, S, 14.41. Found: C, 51.24, H, 3.09, N, 9.23, S, 14.27.

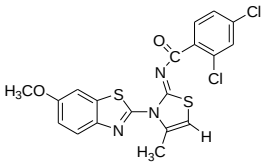
***N*-[3-(6-Methoxybenzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene]benzamide (3h)**



Yield = 71 %; Rf = 0.35; M.P. = 82-83 ^{o}C; IR (KBr) ν_{max}: 2943 (C=C-H), 2843 (-CH_3), 1675 (amide C=O), 1572 (C=N), 1556 (C=C), 1453 (C-N), 1162 (C-S) cm-^{1}; ^{1}H NMR, ($CDCl_3$, δ ppm): 8.11 (1H, d, *J* = 7.6 Hz, H-1), 8.06 (1H, d, *J* = 2.4 Hz, H-3), 7.82 (1H, d, *J* = 7.6 Hz, H-2), 7.38-7.78 (5H, m, Ar), 6.43 (1H, s, C=C-*H*), 3.78 (3H, s, -OCH_3), 2.24 (3H, s, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 165.3 (amide C=O), 162.4 (C=N), 156.5 (S-C=N), 151.3 (N-C=), 146.3 (C-9), 127.4 (C-6), 135.6 (C-1'), 134.3 (C-2',C-6'), 132.8 (C-3',C-5'), 128.5 (C-4'), 127.6 (C-8), 126.3 (C-4), 124.2 (C-5), 122.4 (C-7), 101.7 (=CH), 54.7 (-OCH_3), 17.6 (-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 381 (68), 217 (41), 164 (53), 140 (100 %), 134 (28),

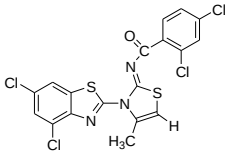
112 (40), 96 (19) 77 (35); Anal. Calcd. for $C_{19}H_{15}N_3O_2S_2$; C, 59.84, H, 3.94, N, 11.02, S, 16.78. Found: C, 59.75, H, 3.81, N, 10.93, S, 16.64.

2,4-Dichloro-*N*-[3-(6-methoxybenzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene] bezamide (3i)



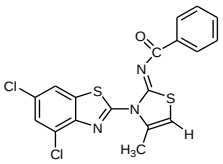
Yield = 76 %; Rf = 0.4; M.P. = 79-80 ^oC; IR (KBr) ν_{max}: 3027 (C=C-H), 2857 (-CH_3), 1687 (amide C=O), 1584 (C=N), 1564 (C=C), 1471 (C-N), 1181 (C-S) cm-^{1}; ^{1}H NMR, ($CDCl_3$, δ ppm): 8.16 (1H, d, *J* = 7.6 Hz, H-1), 8.08 (1H, d, *J* = 2.4 Hz, H-3), 7.84 (1H, d, *J* = 7.6 Hz, H-2), 7.73 (1H, d, *J* = 7.4 Hz, H-6'), 7.64 (1H, d, *J* = 2.4 Hz, H-3'), 7.48 (1H, d, *J* = 7.4 Hz, H-5'), 6.46 (1H, s, C=C-*H*), 3.83 (3H, s, -OCH_3), 2.27 (3H, s, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 166.2 (amide C=O), 162.8 (C=N), 157.2 (S-C=N), 152.3 (N-C=), 147.5 (C-9), 138.6 (C-6), 137.5 (C-1'), 136.3 (C-2'), 134.7 (C-4'), 133.6 (C-'6), 132.5 (C-3'), 131.8 (C-5'), 128.4 (C-8), 126.4 (C-4), 124.6 (C-5), 121.8 (C-7), 102.6 (=CH), 54.6 (-OCH_3), 18.4 (-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 449 (58), 284 (34), 164 (73), 144 (35), 140 (100 %), 112 (20), 96 (23) 77 (13); Anal. Calcd. for $C_{19}H_{13}N_3O_2S_2Cl_2$; C, 50.67, H, 2.88, N, 9.33, S, 14.22. Found: C, 50.44, H, 2.73, N, 9.18, S, 14.13.

2,4-Dichloro-*N*-[3-(4,6-dichlorobenzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene] benzamide (3j)



Yield = 75 %; Rf = 0.6; M.P. = 74-76 ^oC; IR (KBr) ν_{max}: 2963 (C=C-H), 2846 (-CH_3), 1691 (amide C=O), 1587 (C=N), 1568 (C=C), 1477 (C-N), 1186 (C-S); ^{1}H NMR, ($CDCl_3$, δ ppm): 8.24 (1H, d, *J* = 2.2 Hz, H-1), 8.17 (1H, d, *J* = 2.2 Hz, H-2), 7.96 (1H, d, *J* = 7.6 Hz, H-6'), 7.87 (1H, d, *J* = 2.3 Hz, H-3'), 7.78 (1H, d, *J* = 7.6 Hz, H-5'), 6.48 (1H, s, C=C-*H*), 2.31 (3H, s, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 166.5 (amide C=O), 163.1 (C=N), 157.6 (S-C=N), 152.5 (N-C=), 147.7 (C-9), 138.4 (C-1'), 137.6 (C-2'), 136.5 (C-4'), 134.8 (C-6'), 133.4 (C-6), 132.3 (C-4), 131.8 (C-3'), 128.2 (C-5'), 125.1 (C-8), 124.6 (C-5), 123.7 (C-7), 102.8 (=CH), 18.7 (-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 487 (58), 284 (65), 201 (52), 167 (46), 144 (65), 140 (100 %), 134 (42), 112 (31), 111.5 (34), 96 (26), 77 (18); Anal. Calcd. for $C_{18}H_9N_3OS_2Cl_4$; C, 44.17, H, 1.84, N, 8.58, S, 13.08. Found: C, 44.09, H, 1.61, N, 8.43, S, 13.01.

***N*-[3-(4,6-Dichlorobenzo[d]thiazol-2-yl)-4-methylthiazol-2(3H)-ylidene]benzamide (3k)**



Yield = 78 %; Rf = 0.4; M.P. = 70-71 ^{o}C; IR (KBr) ν_{max}: 3031 (C=C-H), 2855 (-CH_3), 1686 (amide C=O), 1583 (C=N), 1565 (C=C), 1474 (C-N), 1183 (C-S) cm-^{1}; ^{1}H NMR, ($CDCl_3$, δ ppm): 8.21 (1H, d, *J* = 2.3 Hz, H-1), 8.16 (1H, d, *J* = 2.3 Hz, H-2), 7.63-7.91 (5H, m, Ar), 6.47 (1H, s, C=C-*H*), 2.28 (3H, s, -CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 166.1 (amide C=O), 162.6 (C=N), 157.4 (S-C=N), 152.3 (N-C=), 147.3 (C-9), 136.5 (C-1'), 134.7 (C-6), 133.8 (C-4), 132.6 (C-2',C-6'), 131.5 (C-3',C-5'), 127.4 (C-4'), 124.6 (C-8), 123.8 (C-5), 122.7 (C-7), 102.3 (=CH), 18.3 (-CH_3); MS (70 eV): *m/z* (%); [$M^{+\cdot}$] 419 (46), 274 (52), 201 (36), 167 (40), 144 (65), 140 (100 %), 134 (33), 112 (23), 96 (16), 77 (24); Anal. Calcd. for $C_{18}H_{11}N_3OS_2Cl_2$; C, 51.42, H, 2.62, N, 10.01, S, 15.24. Found: C, 51.37, H, 2.43, N, 9.92, S, 15.14.

[Pet. ether : ethyl acetate (8:2)]

Chapter–4

BIOASSAY SCREENING

4.1 Introduction

A rapid advance in the development of new techniques for determining the biological activity of synthetic and natural compounds has triggered a renaissance in the drug development. Primary bioassay screening plays a very important role in the drug development program. These screenings act as a tool to conduct activity directed isolation of bioactive compounds for curing humans and animals. Primary screenings provide first indication of bioactivities and thus help in the selection of lead compounds for secondary screening for detailed pharmacological evaluation.

4.1.1 Antibacterial Activity of Isocoumarins, 3,4-Dihydroisocoumarins and their 6,8-Dihydroxy derivatives

Bacteria cause some of the world's deadliest diseases such as tuberculosis, pneumonia, plague, wound sepsis and gas gangrene etc. These infections were responsible in the past for killing of many people around the world than any other disease.

Bacterial infections constitute one of the most serious situations in infectious disease. The detection and identification of these bacteria is one of the most important functions of clinical microbiology. Isolation of an infectious agent from the patient with disease is often not sufficient. For determining proper therapy many bacteria manifest resistance to antimicrobial agents. Since the susceptibility of many bacteria to antimicrobial agents cannot be predicted testing individual pathogens, against appropriate agent (with the most activity against the pathogen, the least toxicity to the most, the least important on normal flora, appropriate pharmacologic characteristics and most economical) can then be chosen allowing a more certain therapeutic outcome.

Isocoumarins, 3,4-dihydroisocoumarins and their 6,8-dihydroxy derivatives were evaluated for their antibacterial activity against ten different strains of Gram positive and Gram negative bacteria. The six were Gram negative *viz. Pseudomonas aeroginosa, Escherichia coli, Salmonella typhi, Shigella specie, Salmonella para typhi* and *Proteus mirabilis* and four were Gram positive *viz. Bacillus subtilus, Micrococcus aureus, Staphylococcus aureus* and *Streptococcus specie*. All tested microorganisms were maintained on nutrient agar at 4 °C and sub-cultured before use. The study of selected

bacterial strains are clinically very important, they can cause several serious infections. It is highly essential to overcome these root cause of fatal infections through some active therapeutic agents.

4.1.2 Antibacterial Technique in Bioassay

Agar Well Diffusion Technique

In vitro evaluation of antibacterial activity of the isocoumarins **(5a-j)**, 3,4-dihydroisocoumarins **(7a-j)** and their 6,8-dihydroxy derivatives **(8a-j)**, were carried out by agar well diffusion assay[386] technique against ten different Gram positive and Gram negative bacterial strains. Antibacterial activity was determined by using the Mueller Hinton Agar (MHA). The fresh inoculums of these bacteria were prepared and diluted by sterilized normal saline. The turbidity of these cultures was adjusted by using 0.5 Mc-Farland. A homogeneous bacterial lawn was developed by sterile cotton swabs. The inoculated plates were bored by 6 mm sized borer to make the wells. The sample dilutions were prepared by dissolving each sample (5.0 mg) in 1.0 mL of DMSO used as negative control in this bioassay. The equimolar concentration of Levofloxacin (5.0 mg/mL), a broad spectrum antibiotic (positive control) was prepared. These plates were incubated at 37 °C for 24 hours. Antibacterial activity of all the synthesized compounds were determined by measuring the diameter of zone of inhibition (mm, ± standard deviation) and presented by subtracting the activity of the negative control. The experiments were repeated thrice to minimize the errors, only the mean values are reported.

4.1.3 Interpretation of Results

i) Antibacterial evaluation of 3-Cinnamoyl-6,8-dimethoxy-7-methylisocoumarin (5a)

In vitro antibacterial evaluation of homophthalic acid precursor **(4)**, and a *Typharin* analogue i.e 3-cinnamoyl-6,8-dimethoxy-7-methyl-isocoumarin **(5a)**, keto acid **(6a)**, 3,4-dihydroisocoumarin **(7a)** and its 6,8-dihydroxy derivative **(8a)** against various strains of Gram positive and Gram negative bacteria, is presented in Table 1.

The homophthalic acid precursor **(HTA)**, showed significant activity against two bacterial strains *Salmonella typhi* and *Micrococcus luteus*.

3-Cinnamoyl-6,8-dimethoxy-7-methyl-isocoumarin **(5a)**, showed significant antibacterial activities against various strains of Gram-negative and Gram-positive

bacteria except *Pseudomonas aeroginosa* and *Shigella specie* strains, as compare to its 3,4-dihydroisocoumarin derivative **(7a)**. Keto acid **(6a)**, is only active against three different bacterial strains, while its 6,8-dihydroxy analogue **(8a)** shows lesser activity than both its isocoumarin and 3,4-dihydroisocoumarin derivatives.

Table 1: Antibacterial Activity of 3-Cinnamoyl-6,8-dihydroxy-7-methyl-3,4-dihydroisocoumarin (5a-8a)

Sample Code	*P aeroginosa*	*E coli*	*S typhi*	*P mirabilis*	*B subtilus*	*M auteus*	*S. aureus*	*S. specie*	*S para typhi*	*S specie*
HTA	-	-	20	16	12	20	14	-	04	09
5a	-	6	11	14	-	21	16	-	24	14
6a	-	-	-	13	9	10	-	-	-	2
7a	-	4	9	14	12	20	09	-	-	-
8a	11	-	15	12	9	12	12	-	-	6
Standard Levofloxacin	**25**	**33**	**24**	**29**	**34**	**38**	**32**	**14**	**21**	**24**

ii) Antibacterial evaluation of Isocoumarins (5b-j)

Antibacterial evaluation showed that most of the isocoumarins **(5b-j)** possess significant activity against Gram positive bacteria as compared to Gram negative bacteria.

Table 2: Antibacterial Bioassay of 3-Aryl/alkyl-substituted isocoumarins (5b-j)

Sample Code	*P aeroginosa*	*E coli*	*S typhi*	*P mirabilis*	*B subtilus*	*M auteus*	*S. aureus*	*S. specie*	*S para typhi*	*S specie*
5b	3	15	6	-	16	2.5	3.5	1.5	12	-
5c	2	3	8	2	5	2.5	2.5	-	1.5	3
5d	10	14	11	1	11	11	12	-	7.5	1
5e	11	4	19	15	16	15	-	1	19	8
5f	-	3	8	2	5	2	0.5	-	1.5	11
5g	2	2	1	1	1	11	10	11	7	5
5h	2	1	10	13	11	12	8	13	0.5	10
5i	3	0.5	19	1	6	9	10	1	5	8
5j	2	1.5	1	0.5	4	10	6.5	2	1	4
Standard Levofloxacin	**25**	**33**	**24**	**29**	**34**	**38**	**32**	**14**	**21**	**24**

Among 3-arylated isocoumarin derivatives, 3-(4-methoxyphenyl)-6,8-dimethoxy-7-methylisocoumarin **(5e)** and 3-(4-chlorophenyl)-6,8-dimethoxy-7-methylisocoumarin **(5f)**, were the most active compounds, as they possess significant activity against various bacterial strains.

The antibacterial evaluation of 3-alkylated isocoumarins showed that the 3-pentylisocoumarin **(5h)** was more active compound among alkyl-substituted isocoumarins.

ii) Antibacterial evaluation of 3,4-Dihydroisocoumarins (7b-j)

Antibacterial evaluation of the 3,4-dihydroisocoumarins **(7b-j)** showed that these were more active against Gram positive bacteria as compared to Gram negative bacteria.

Table 3: Antibacterial Activity of 3-Aryl/alkyl substituted 3,4-dihydroisocoumarins (7b-j)

Sample Code	*P aeroginosa*	*E coli*	*S typhi*	*P mirabilis*	*B subtilus*	*M auteus*	*S. aureus*	*S. specie*	*S para typhi*	*S specie*
7b	2	0.5	0.5	-	16	0.5	2.5	-	12	4
7c	-	15	18	-	2	11.5	12	16	-	1
7d	1	1	11	2	11	2	1	-	14	12
7e	11	4	19	15	16	15	-	-	19	8
7f	-	1	-	-	16	0.5	5	-	12	-
7g	-	-	18	20	-	15	21	16	27	15
7h	9	-	11	14	11	12	12	-	-	10
7i	11	4	19	15	16	15	-	-	19	8
7j	2	0	0	-	16	0.5	2.5	-	12	4
Standard Levofloxacin	**25**	**33**	**24**	**29**	**34**	**38**	**32**	**14**	**21**	**24**

The compound **(7e)** and **(7i)** exhibit higher activity against various Gram negative and Gram positive bacterial strains among all the other compounds, as compared to the rest of the 3,4-dihydroisocoumarins series.

iii) Antibacterial evaluation of 6,8-Dihydroxy-3,4-dihydroisocoumarins (8b-j)

The antibacterial activity results of the 6,8-dihydroxy-3,4-dihydroisocoumarins **(8b-j)** showed that most of these were more effective against Gram negative bacteria as compared to Gram positive. Some 6,8-dihydroxy-3,4-dihydroisocoumarin derivatives also exhibit activity against Gram positive bacterial strains as well.

Among the 6,8-dihydroxy3,4-dihydroisocoumarin derivatives compounds **(8d)** and **(8h)** showed good antibacterial activities against various bacterial strains as compare to the rest of the series.

The antibacterial evaluation results of 6,8-dihydroxy-3,4-dihydroisocoumarins **(8b-j)** are presented in Table 4.

Table 4: Antibacterial activity of 6,8-Dihydroxy-3,4-dihydroisocoumarins (8b-j)

Sample Code	*P aeroginosa*	*E coli*	*S typhi*	*P mirabilis*	*B subtilus*	*M auteus*	*S. aureus*	*S. specie*	*S para typhi*	*S specie*
8b	1	0	0	-	16	0.5	2.5	-	12	4
8c	-	-	18	20	-	15	21	16	27	15
8d	19	0.5	1	11	2	12	16	9	-	13
8e	7	4	19	15	16	15	-	-	19	8
8f	2	0	0	-	16	0.5	2.5	-	12	4
8g	-	15	18	20	-	15	21	16	27	15
8h	9	0.5	11	14	11	12	12	-	-	10
8i	11	14	19	15	16	15	-	-	19	8
8j	2	1	0	-	16	0.5	2.5	-	12	4
Standard Levofloxacin	**25**	**33**	**24**	**29**	**34**	**38**	**32**	**14**	**21**	**24**

4.1.4 Comparison of Antibacterial Evaluations

The comparison of the antibacterial activity among all the series of synthesized compounds indicates that isocoumarins **(5a-j)** and 3,4-dihydroisocoumarins **(7a-j)** were more active against Gram positive bacteria than Gram negative. But the 6,8-dihydroxy-3,4-dihydroisocoumarin **(8a-j)** derivatives were more active against Gram negative than Gram positive.

Antibacterial activity results of 3-aryl-substituted isocoumarins and 3,4-dihydroisocoumarins showed that these compounds were more active than 3-alkylated derivatives.

4.1.5 Antibacterial evaluation of (±)-7-Butyl-6,8-dimethoxy-3-pentyl-3,4-dihydro-isocoumarin (10a-d)

The homophthalic acid precursor **(HTA)**, showed significant activity against two bacterial strains *Salmonella typhi, B.subtilus* and *Micrococcus auteus*.

(±)-7-Butyl-6,8-dimethoxy-3-pentyl-3,4-dihydroisocoumarin **(10a)**, displayed significant antibacterial activities against various strains of Gram-negative and Gram-positive bacteria except *Pseudomonas aeroginosa, B.subtilus* and *Shigella specie* strains and its 3,4-dihydroisocoumarin derivative **(10d)** is only active against *Escherichia coli.*. Keto acid and its dihydroxy acid analogue showed lesser activity than isocoumarin but it was more active than its 3,4-dihydroisocoumarin derivative. Antibacterial evaluation results are presented in Table 5.

Table 5: Antibacterial Activity of 7-Butyl-6,8-dimethoxy-3-pentyl-3,4-dihydroisocoumarin (10a-e)

Sample Code	***P aeroginosa***	***E coli***	***S typhi***	***P mirabilis***	***B subtilus***	***M auteus***	***S. aureus***	***S. specie***	***S para typhi***	***S specie***
HTA	-	9	13	-	16	17	13	-	-	4
10a	-	-	18	20	-	15	21	16	27	15
10b	9	-	11	14	11	12	12	-	-	10
10c	11	4	19	15	16	15	-	-	19	8
10d	-	8	-	-	-	-	-	-	-	-
Standard Levofloxacin	**25**	**33**	**24**	**29**	**34**	**38**	**32**	**14**	**21**	**24**

Key:

– = No activity

Concentration = 5.0 mg/mL.

Antibacterial activity was calculated by measuring the diameter of zone of inhibition in (mm).

4.2 Antibacterial Bioassay Techniques

i) Antibacterial Diffusion Technique

In bacterial diffusion technique antimicrobial agent would diffuse into the medium in a circle and the reservoir (well/disc) inhibiting the growth of the organism whenever the concentration of antimicrobial agent is high.

ii) Agar Well Diffusion Technique (Kirby-Bauer Method)

In the agar well diffusion protocol wells are dug in media with the help of a sterile metal borer with center at least 24 mm apart 2-8 hours old bacteria inoculums ca. 10^4–10^6 colony forming units (CFU)/mL are spread on the surface of nutrient agar with the help of sterile cotton swab. Cotton swab is rotated firmly against the upper inside well of the tube to express excess fluid. Entire agar surface of plate is streaked with the swab twice turning the plate 60^o between each streaking.

Standard drugs used were Imipenem and Sulphamethaxazole, all the samples were taken at the concentration of 2.0 mg/mL in DMSO and then were added to their respective wells in Petri plates for bioassay screening. The plates were incubated immediately at 30 ^{o}C for 14-20 hours or more if necessary.

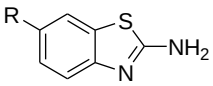
Activity was determined by measuring diameter of zone showing complete inhibition (mm) and growth inhibition was calculated with reference to +ve control. The antibacterial results are presented in Table 4.6 and 4.7.

4.2.1 Interpretation of Results

From the Table 6 it was found that all the compounds (**1a-e**) were active against all bacterial strains and they exhibit high antibacterial activity against all the four strains of bacteria.

Table 7 showed that all the benzothiazolyl thioureas (**2a-k**) were active against all the bacterial strains except (**2d)**, (**2e)** and (**2g)** compounds against *Staphylococcus aureus* and (**2i)** against *E. coli*. It was concluded that the substitution on benzothiazole part or on benzoyl ring enhances its activity especially, when benzoyl ring is substituted with -Cl, -F, -Br. Overall, benzothiazolyl thioureas were less bioactive compounds than benzothiazolamines.

Table 6: Antibacterial bioassay screening of Substituted Benzo[d]thiazol-2-amines (1a-e).



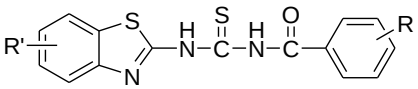
Sample Codes	*Staphylococcus aureus*	*Bacillus subtillus*	*Pseudomonas areuginosa*	*Escherichia coli*
1a	38	30	28	21
1b	26	32	30	21
1c	34	29	24	20
1d	27	16	14	30
1e	35	28	31	24
Imipenem	**30**	**31**	**32**	**30**
Sulphmethaxozole	**31**	**33**	**32**	**30**

Key:

– = No activity

Concentration = 2 mg/mL.

Table 7: Antibacterial bioassay screening of 1-(Benzo[d]thiazol-2-yl)-3-(substituted) thioureas (2a-k).



Sample Codes	*Staphylococcus aureus*	*Bacillus subtillus*	*Pseudomonas areuginosa*	*Escherichia coli*
2a	27	19	23	35
2b	12	17	17	19
2c	28	25	09	10
2d	-	26	23	15
2e	-	22	15	30
2f	27	20	14	10
2g	-	25	23	12
2h	29	30	22	20
2i	30	21	18	-
2j	17	21	13	15
2k	26	29	17	13
Imipenem	**30**	**31**	**32**	**30**
Sulphmethaxozole	**31**	**33**	**32**	**30**

Key:

– = No activity

Concentration = 2.0 mg/mL.

4.2.2 Antibacterial bioassay screening of Ethyl 4-(3-benzoylthioureido) benzoates (2a-j)

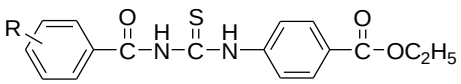
In vitro evaluation of antibacterial activity was carried out by disk diffusion method (Kirby-Bauer method) against four different bacterial strains. The experiments were repeated thrice and the results are reported as means values. Table 4.8 gives the antibacterial activity of ethyl 4-(3-benzoylthioureido) benzoates **(2a-j)**.

4.2.3 Interpretation of Results

All Ethyl 4-(3-benzoylthioureido) benzoates **(2a-j)** exhibited potent inhibitory activity against all the four bacterial strains as compared to standard drugs.

The presence of halo group results in enhancement of inhibitory activity. It was noted that the compounds **(2b)** and **(2c)** having 3-chloro substituents **(2f)** and **(2g)** thioureas also showed potent activity against all four strains. Overall, all thioureas exhibit good antibacterial activity against all bacterial strains, especially against *E. coli, Bacillus subtillus* and *Pseudomonas areuginosa* as compare to standard drugs.

Table 8: Antibacterial bioassay screening of Ethyl 4-(3-benzoylthioureido) benzoates (2a-j).



Sample Codes	*Staphylococcus aureus*	*Bacillus subtillus*	*Pseudomonas areuginosa*	*Escherichia coli*
2a	25	13	21	10
2b	10	17	31	19
2c	32	25	19	31
2d	-	26	23	15
2e	-	22	15	30
2f	21	20	14	12
2g	17	19	23	32
2h	10	17	16	12
2i	28	22	9	10
2j	-	26	23	15
Imipenem	**30**	**31**	**32**	**30**
Sulphmethaxozole	**31**	**33**	**32**	**30**

Key:

– = No activity

Concentration = 2 mg/mL.

4.3 Antifungal Activity

During last two decades, the life threatening infections caused by pathogenic fungi and bacteria become increasingly common, especially in individuals immunocompromised patients with AIDS. Clinically, candidosis, aspergillosis, and cryptococosis are major fungal infections in these patients. Fungi also produced toxin in foods and cause poisoning without being physically present. Another problem caused by fungi is allergy due to their spores.

However, the current antifungal therapy suffers from drug related toxicity; sever drug resistance, non optimal pharmacokinetics and serious drug interaction. Therefore, there is an emergent need to develop novel antifungal drugs with higher efficiency, broad spectrum and low toxicity.

4.3.1 Agar Tube Dilution Method

The agar tube dilution method was adopted for *in vitro* antifungal evaluation of the synthesized benzothiazolamines and benzothiazolyl thioureas, against five different fungal strains.

Fungal strains used:

i) *Rhizopus oryzae*
ii) *Aspergillus terreus*
iii) *Fusarium oxysporum*
iv) *Aspergillus fumigatus*
v) *Aspergillus niger*

All the fungal strains were maintained on sabouraud dextrose agar (SDA) medium at 4 ºC temperature.

4.3.2 Media for Fungal growth

Sabouraud dextrose agar (SDA) was used to grow fungus for inoculums preparations. The (SDA) was composed of:

Glucose = 40 gm/L

Agar =15 gm/L

Peptone complex = 10 gm/L

4.3.3 Preparation of Media (SDA)

Sabouraud dextrose agar was prepared by dissolving 6.5 gm/100mL of (SDA) in distilled water and the PH of it was adjusted at 5.6. All the contents after dissolving were

dispensed and were pour into screw capped tubes of 4 mL volume and then these sealed tubes were autoclaved for 23 minutes at 121 ºC.

4.4.4 Sample Loading

After cooling these tubes to 50 ºC sample loading was done i.e non solidified (SDA) was loaded 66.5 µL of benzo[d]thiazol-2-amines **(BTA-1-5)** and 1-(benzo[d]thiazol-2-yl)-3-(substituted) thioureas **(BU-1-11)** from stocked solution with the help of pipette, this gives the final conc. of 200 µg/mL of the pure compounds in the media. Tubes were then placed in slanting position allowed them to get solidified at room temperature.

4.3.5 Inoculation and Incubation of Fungus

The tubes with solidified media and the tested benzothiazolamine **(BTA-1-5)** and benzothiazolyl thioureas **(BU-1-11)** were inoculated with inoculums of 4mm diameter, which were taken from 1 week old fungal culture, remaining media supplemented with terbinafine and DMSO were used as positive and negative control, respectively. These tubes were incubated for a week at 28 ºC. All the experiments were repeated three times in order to avoid errors.

4.3.6 Measurement of Growth Inhibition

Growth in the (SDA) media was determined by measuring linear growth (cm) and the growth inhibition was calculated with reference to negative control.

Formula:

$$\% \text{ age of Fungal inhibition} = 100 - \frac{\text{(Fungal growth in sample)}}{\text{(Fungal growth in control)}} \times 100$$

4.3.7 Interpretation of results

All benzothiazolamines **(BTA-1-5)** exhibited good activity against five fungal strains. **BTA-1** was most active among all these compounds, it showed remarkable activity against all the fungal strains. **BTA-2** also displayed good activities against *Aspergillus niger* and *Aspergillus fumigatus* strains. All the remaining compounds exhibit moderate activity against these fungal strains.

1-(Benzo[d]thiazol-2-yl)-3-(substituted) thioureas **(BU-1-11)** exhibited moderate to good activity against all the fungal strains. **BU-10** was most active among all these synthesized compounds, it showed remarkable activity against all five fungal strains, comparable with standard. **BU-2** also possesses good activities against four strains out of five. 1-(Benzo[d]thiazol-2-yl)-3-(substituted) thioureas exhibited less antifungal activity

then benzo[d]thiazol-2-amines. The antifungal results are presented in Table 9 and Table 10, respectively.

Table 9: Antifungal bioassay screening of Benzo[d]thiazol-2-amines (BTA-1-5).

Sample Codes	***Rhizopus oryzae***		***Aspergillus tereus***		***Fusarium oxysporum***		***Aspergillus niger***		***Aspergillus fumigatus***	
Turbenafine	Reading in (cm)	% value	Reading in (cm)	% value	Reading in (cm)	% value	Reading in (cm)	% value	Reading in (cm)	% value
Control	**9**	**00**	**9**	**00**	**9**	**00**	**9**	**00**	**9**	**00**
BTA-1	03	66.6	02	77.7	2.5	72.2	01	88.8	01	88.8
BTA-2	8.5	5.5	09	00	8.5	5.5	02	77.7	03	66.6
BTA-3	8.5	5.5	09	00	09	00	04	55.5	08	11.1
BTA-4	08	11.1	4.5	50	06	33.3	8.5	5.5	06	33.3
BTA-5	08	11.1	5.5	38.8	7.5	16.6	04	55.5	06	33.3

Table 10: Antifungal bioassay screening of 1-(Benzo[d]thiazol-2-yl)-3-(substituted) thioureas (BU-1-11).

Sample Codes	***Rhizopus oryzae***		***Aspergillus tereus***		***Fusarium oxysporum***		***Aspergillus niger***		***Aspergillus fumigatus***	
Turbenafine	Reading in (cm)	% value	Reading in (cm)	% value	Reading in (cm)	% value	Reading in (cm)	% value	Reading in (cm)	% value
Control	**9**	**00**	**9**	**00**	**9**	**00**	**9**	**00**	**9**	**00**
BU-1	08	11.1	5.5	38.8	7.5	16.6	04	55.5	06	33.3
BU-2	7.5	16.6	2.5	72.2	4.5	50.0	03	66.6	04	55.5
BU-3	09	00	05	44.4	06	33.3	7.5	16.6	03	66.6
BU-4	09	00	3.5	61.1	04	55.5	04	55.5	07	22.2
BU-5	09	00	09	00	09	00	04	55.5	07	22.2
BU-6	7.5	16.6	3.5	61.1	5.5	38.8	09	00	06	33.3
BU-7	09	00	09	00	09	00	8.5	5.5	06	33.3
BU-8	07	22.2	3.5	61.1	07	22.2	04	55.5	09	00
BU-9	08	11.1	0.4	55.5	05	44.4	08	11.1	03	66.6
BU-10	06	33.3	1.5	83.3	03	66.6	06	33.3	06	33.3
BU-11	08	11.1	04	55.5	06	33.3	05	44.4	02	77.7

CONCLUSIONS

i) Natural Isocoumarin Analogues

- Multistep synthesis of two different types of homophthalic acids were carried out, which serve as precursors for the synthesis of various isocoumarin and 3,4-dihydroisocoumarin analogues.
- Total synthesis of various structural analogues of well known bioactive natural 3,4-dihydroisocoumarins *viz. Typharin*, *Annulatomarin*, *Montroumarin*, *Scorzocreticin*, and *Hiburipyranone* etc have been carried out.
- Total synthesis of naturally occurring 3,4-dihydroisocoumarins (±) 7-butyl-6,8-dihydroxy-3-pentyl-3,4-dihydro-1H-isochromen-1-one have been carried out.
- Total synthesis of natural product *Stellatin* (8-hydroxy-7-hydoxymethyl-6-methoxy-3,4-dihydro-1H-isochromen-1-one) have been carried out.

ii) Functionalized Pyrazoles

- *N*-Protected 3,4,5-tribromopyrazole have been synthesized.
- Four different series of Arylated-pyrazoles were synthesized by site-selective Suzuki-miyuara reactions of *N*-protected tribromopyrazoles.
  - **a)** Mono-arylated Pyrazoles
  - **b)** Di-arylated pyrazoles
  - **c)** Tri-arylated pyrazoles
  - **d)** Mixed tri-arylated pyrazoles

iii) *N*-Substituted Dihydropyridinones

- Syntheses of Mono and Diallyled amino ester products have been carried out.
- Mono allylated amino ester derivatives were converted to *N*-tosyl, *N*-benzyl and *N*-Boc protected products.
- *N*-Substituted-3-aza-bicyclo[3.1.0]hexan-1-ols were prepared by *N*-allyl-*N*-substituted amino esters derivatives through Kulinkovich Reaction.
- *N*-Substituted Dihydropyridinones were synthesized by oxidative ring opening of *N*-Substituted-3-aza-bicyclo[3.1.0]hexan-1-ols.

iv) Iminothiazolidinones

- Benzothiazol-2-amines precursors were prepared.
- 2-Benzothiazol amines precursors were converted into thiourea derivatives.
- Benzothiazolyl thioureas were cyclized into their Iminothiazolidinone derivatives.
- Ester-substituted thioureas were converted into their Iminothiazolidinone derivatives.

v) Iminothiazolines

- Ester-substituted thioureas were synthesized.
- Ester-substituted thioureas were cyclized into their Iminothiazolines derivatives.
- Benzothiazolyl thioureas were converted into their Iminothiazolines derivatives.

Biological Screening

a) Antibacterial Activity

Benzo[d]thiazol-2-amines, 1-(benzo[d]thiazol-2-yl)-3-(substituted) thioureas and ethyl 4-(3-benzoylthioureido) benzoates were examined *in vitro* for antibacterial activity against gram positive and gram negative bacteria and were found to exhibit good to potent activity as compared to the standard drugs.

b) Antifungal Activity

Benzo[d]thiazol-2-amines and 1-(benzo[d]thiazol-2-yl)-3-(substituted) thioureas were tested *in vitro* for their antifungal activity against various fungal strains and were found to exhibit moderate activity as compared to the standard drug.

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