SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITIES OF SOME NOVEL FIVE AND SIX MEMBERED HETEROCYCLES AND BIHETEROCYCLES

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

by

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2010
DECLARATION

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IN THE NAME OF ALLAH
THE COMPASSIONATE
THE MERCIFUL
Dedicated to

My Dearest Parents
Who Paved This Beautiful Path for Me
DECLARATION

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This thesis describes the synthesis, characterization and bioassay of some novel five and six membered heterocycles and biheterocycles.

Some new 2-(3,5-dimethoxy-4-methylphenyl)-4-aryl-1,3,4-oxadiazoles (1a-h) were synthesized by microwave irradiation of 3,4-dimethoxy-4-methylhydrazide (6’) with substituted benzoic acids in the presence of thionyl chloride. Compound (1b) exhibited significant bacterial inhibition while compounds (1a), (1e) and (1f) showed significant antifungal activities. Except for compounds (1e), (1f) and (1h), the rest were active for their phytotoxic activities.

Some N-aminomethyl substituted aryl-5-aryl-1,3,4-oxadiazole-2-thiones (2a-j) were synthesized. Reaction of substituted hydrazides (1’-8’) with ethanolic solution of carbon disulfide and potassium hydroxide afforded 1,3,4-oxadiazole-2-thiones as key intermediates, which were refluxed with substituted anilines and paraformaldehyde in ethanol to undergo manich condensation to furnish N-aminomethyl substituted aryl-5-aryl-1,3,4-oxadiazole-2-thiones (2a-j). Compounds (2b) and (2g) displayed maximum bacterial inhibition whilst (2b) showed maximum antifungal activity. All compounds were phytotoxic except the compound (2h).

5-Aryl-1,2,4-triazole-3-thiones (3a-f) were synthesized by reaction of substituted hydrazides (1’-8’) with ethanolic solution of carbon disulfide and potassium hydroxide. Compound (3d) and (3e) showed maximum antibacterial activity. In case of antifungal activities compounds (3b) and (3f) were most active. Except compounds (3b) and (3f) all other were active for their phytotoxic activities.

The triazoles (3a-f) were converted into corresponding 3-aryl-6-phenyl-1,2,4-triazolo-[3,4-b][1,3,4]-thiadiazines (8a-f) by the condensation with 2-bromo acetophenone. Compound (8a) and (8e) showed maximum antibacterial and antifungal inhibition respectively. All compounds except (8d) and (8e) showed positive phytotoxic activity.

The substituted hydrazides (1’-8’) were also microwave irradiated with acetyl acetone to afford 3,5-dimethylpyrazoles (4a-h). Compound (4b) was most active antibacterial whilst (4a) and (4d) were most active antifungal agents. All compounds were phytotoxic except (4a), (4f) and (4h).
1-Aroyl-3,5-diarylpyrazolines (5a-h) were synthesized by cyclization of substituted hydrazides (1'-8') with suitably substituted chalcones (a-b). Compounds (5a) and (5c) showed maximum inhibition in case of antibacterial activities and maximum percentage inhibition in case of antifungal activities. All pyrazolines were active for their phytotoxic activities.

Microwave accelerated oxa-Pictet Spengler reaction of 2-chlorophenylethanol with various aryl aldehydes afforded some 1-aryl-5-chloroisochromans (6a-j). Standard homologation sequence of the 2-cholobenzoic acid afforded the 2-chlorophenylacetic acid which was on esterification and reduction with sodium borohydride in tetrahydrofuran and methanol furnished the 2-chlorophenylethanol. The latter was irradiated with substituted benzaldehydes in the presence of p-TsOH acid to afford 1-aryl-5-chloroisochromans (6a-j). Isochroman (6c) showed maximum inhibition against B. subtilis whereas (6e) showed against maximum inhibition E. coli. Isochromans (6a) and (6d) were most active as antifungal agents. All compounds were active for their phytotoxic activities except (6a), (6d) and (6g).

Some N-substituted morpholines (7f-j) were also prepared. Thus α-amino alcohol were protected with para-tolyl methyl sulfinate in the presence of n-butyl lithium to get N-substituted sulafanilamides (7a-e), which were cyclized with bromoethyl diphenyl sulponium triflate in the presence of sodium hydride to get N-substituted morpholines (7f-j). Deprotection of the substituted morpholines was carried out by stirring with 2 N hydrochloric acid to get morpholinium salts (7k-m).

3,4,5-Trimethoxybenzoic acid was converted into corresponding phenylacetic acid. The latter upon esterification followed by reduction with sodium borohydride in tetrahydrofuran and methanol afforded the 3,4,5-trimethoxyphenylethanol. Cyclocondensation of phenylethanol with methyl acetoacetate in the presence of p-TsOH gave methyl isochromanyl esters (a-c) which were treated with hydrazine monohydrate to furnish the corresponding hydrazides. Condensation of the latter with acetyl acetone afforded isochromanyl pyrazoles (9a-c). Compound (9a) was most against both strains of bacteria; compounds (9b) and (9c) were most against in case of antifungal activities. All compounds were active for their phytotoxic activities except (9a), and (9c).

Trimethoxyisochromanyl hydrazide (c) was treated with various substituted phenyl isothiocyanates to obtain the corresponding thiosemicarbazides (10a-e). Acid
catalyzed intramolecular cyclization of thiosemicarbazides afforded the isochromanyl thiadiazoles (11a-e) while base catalyzed intramolecular cyclization furnished the corresponding isochromanyl triazoles (12a-e). In this series compounds (11c) and (12d) showed maximum inhibition against both strains of bacteria while maximum antifungal inhibition was showed by compounds (11b) and (12c). All compounds were phytotoxic.

The structures of all of the synthesized compounds were confirmed by IR, $^1$HNMR, $^{13}$CNMR and Mass analysis.
Chapter - 1

INTRODUCTION & PLAN OF WORK

Heterocyclic chemistry is the branch of chemistry which deals with the synthesis, characterization and applications of heterocycles, the organic compounds that contains at least one atom other than carbon, like sulfur, nitrogen, oxygen, silicon and phosphorus.[1]

This thesis describes the synthesis, characterization and bioactivities of some novel five and six membered heterocycles and biheterocycles.

1.1 1,3,4-Oxadiazoles

1,3,4,-Oxadiazoles are five membered heterocycles having two nitrogen atoms and one oxygen atom. 1,3,4-Oxadiazoles show great utility in synthetic, medicinal and material chemistry.[1a]

\[ \text{1,3,4-Oxadiazole} \]

1.1.1 Significances of 1,3,4-Oxadiazoles

Antihypertensive Drugs

Oxadiazole nucleus is present in antihypertensive drugs such as tiodazosin [2] and nesapidil [3] and antibiotics such as furamizole. [4]

\[ \text{Tiodazosin} \]

HIV-1 Integrase and Angiogenesis Inhibitors

Biologically active molecules containing the oxadiazole motif include the HIV integrase inhibitor [5] and the angiogenesis inhibitor. [6]
Muscle Relaxants and Anti-mitotic Activities

The widespread use of 1,3,4-oxadiazoles as a scaffold in medicinal chemistry is evident from the following examples. 2-Amino-1,3,4-oxadiazoles exhibit muscle relaxants [7] and anti-mitotic activity. [8]

Platelet Aggregation Inhibitor

2,5-Diaryl-1,3,4-oxadiazoles are platelet aggregation inhibitors [9]. 5-Aryl-2-hydroxymethyl-1,3,4-oxadiazole display diuretic, analgesic, anti-inflammatory, anticonvulsive, and antiemetic properties. [10]

Hypnotic and Sedatives Activities

2-Hydroxyphenyl-1,3,4-oxadiazoles act as hypnotics and sedatives agents. [11]
Insecticidal Activities
Symmetrical 2,5-bis(2,4-dichlorophenyl)-1,3,4-oxadiazole and analogues are effective insecticides toward houseflies, faceflies, and hornflies and are shown to inhibit chitin synthesis in *Drosophila* and in *Musca domestica*. 2-[2,2-dimethyl-3-(2,2-dichlorovinyl)-cyclopropyl]-5-substituted-1,3,4-oxadiazoles and 2-substituted-phenoxy-methyl-5-aryl-1,3,4-oxadiazoles, showed good insecticidal activities against larvae of army worm (*Pseudaletia separata* Walker) \[^{[12]}\].

![DCPO](image)

Anticonvulsant Agent
GABA-modulating 1,2,4-oxadiazole derivatives are known for their anticonvulsant activity \[^{[13]}\].

Light Emitting Agents
2,5-Disubstituted 1,3,4-oxadiazoles have also attracted great interest due to their applications in organic light emitting diodes, photoluminescence, polymers and material science \[^{[14-16]}\].

1.1.2 Routes towards the Synthesis of 1,3,4-Oxadiazoles
In view of the great medicinal significances and material applications a number of synthetic routes have been developed for 1,3,4-oxadiazoles. Majority of these are based upon cyclodehydration of diacylhydrazines using different reagents including hexamethyl disilazane \[^{[17]}\], boron trifluoride etherate \[^{[18]}\], triflic anhydride \[^{[19]}\], phosphorus pentoxide \[^{[20]}\], thionyl chloride \[^{[21]}\], phosphorus oxychloride \[^{[22]}\], sulfuric acid \[^{[23]}\] and polyphosphoric acid \[^{[24]}\].

One-pot syntheses of 1,3,4-oxadiazoles include reaction of hydrazine with carboxylic acids \[^{[24]}\].

![Condensation](image)

Condensation of acyl hydrazides and aromatic aldehydes in the presence of ceric
ammonium nitrate\textsuperscript{[25]} are used to get oxadiazoles.

\[
\begin{array}{c}
\text{NH}_2\text{NH}_2 \quad \text{H}_2\text{C} \quad \text{OH} \\
\text{Ph}_3\text{P}, \text{CBr}_4
\end{array}
\]

Cyclodehydration of carboxylic acids and acyl hydrazides with triphenyl phosphine and carbon tetra bromide\textsuperscript{[26]}

and reaction of carboxylic acids with amidoximes using polymer-supported reagents\textsuperscript{[27]}.

1.2 1,3,4-Oxadiazole-2-thiones

1,3,4-Oxadiazole-2-thiones are also called mercaptoxadizoles, it is a class of five
membered ring having oxygen, two nitrogens and a thiol group at the position 2, present
in its tautomeric form. Thione form is in tautomeric with its thiol form\textsuperscript{[28a]} (Fig. 1.1).

These are biologically very important class of heterocycles.

1.2.1 Significances of 1,3,4-Oxadiazoles-2-thiones

Antimicrobial Activities

5-\[2-(2\text{-Methylbenzimidazoles-1-yl})\text{-ethyl}][1,3,4]\text{oxadiazole-2}(3H)\text{-thione} shows
the antimicrobial activity\textsuperscript{[28]}.
**Anti-HIV Activities**

5-(1-Adamantyl)-2-substituted thio-1,3,4-oxadiazoles and 5-(1-adamantyl)-3-substituted aminomethyl-1,3,4-oxadiazoline-2-thiones show antimicrobial, and anti-HIV-1 activity\(^{[29]}\).

![Adamantyl-1,3,4-oxadiazole-2-thione](image)

**Antioxidant Activities**

5-(2-Aroylbenzimidazol-1-yl-methyl)-2-mercapto-1,3,4-oxadiazoles and 5-[1-(4-chlorobenzyl)-2-phenyl-benzimidazole-1-yl-methyl]-2-mercapto-[1,3,4]-oxadiazole show antioxidant activities\(^{[30]}\).

![1,3,4-Oxadiazole-2-thione](image)

**Anticonvulsant Agent**

Some 1,3,4-oxadizoles containing 2-mercapto group are anticonvulsant agents\(^{[31]}\).

![5-(2-Halo-2-benzyloxyphenyl)-2-mercapto-1,3,4-oxadiazole](image)
Anti-microbial Activities

5-(4-Pyrro-1-yl)-1,3,4-oxadiazole-2-thiols are considered as potential antibacterial and anti-tubercular agents.\(^\text{32}\)

\[
\begin{align*}
\text{5-(4-(1H-pyrrol-1-yl)phenyl-1,3,4-oxadiazole} \\
\end{align*}
\]

Some compounds of this class are known for their antifungal activities.\(^\text{33}\)

\[
\begin{align*}
\text{5-(1-(5-Methyl-1,2,4-triazolo-[1,5-a]-pyramidin-2-ylthio)ethyl)-1,3,4-oxadiazole-2-thiol} \\
\end{align*}
\]

1.22: Routes towards the Synthesis of 1,3,4-Oxadiazoles-2-thiones

A synthetic route towards the synthesis of 1,3,4-oxadiazole-2-thiones is to heat the hydrazide with KOH and carbon disulfide in ethanol.\(^\text{29}\)

\[
\begin{align*}
\text{5-(1-(5-Methyl-1,2,4-triazolo-[1,5-a]-pyramidin-2-ylthio)ethyl)-1,3,4-oxadiazole-2-thiol} \\
\end{align*}
\]

1.3 1,2,4-Triazoles

Triazole is a five-membered ring having two carbon atoms and three nitrogen atoms. It has two isomeric forms 1,2,4-triazole and other form is the 1,2,3-triazole.\(^\text{1b}\)

(Fig. 1.2)

1,2,4-Triazole is one of a pair of isomeric chemical compounds.
1.3.1 Significances of 1,2,4-Triazoles

Therapeutically Important Agent

1,2,4-Triazole is an important group in heterocyclic compounds because of wide range of therapeutically importance used in a wide variety of medicines e.g. Ribavirin, (an antiviral drug), Rizatriptan (an antimigraine), Alprazolam (an anxiolytic), Vorozole.

Letrozole and Anastrozole (antitumoral) are some examples of the drugs that contain 1,2,4-triazole ring.\[^{34-38}\]

Antifungal Agents

1,2,4-Triazole is a basic aromatic heterocycle. 1,2,4-Triazole derivatives find use in a wide variety of applications, most notably as antifungal such as fluconazole and itraconazole\[^{39}\].
Anti-inflammatory Activities

A series of 5-aryl-3-alkylthio-1,2,4-triazoles were prepared with the objective of developing better analgesic anti-inflammatory compounds with minimum ulcerogenic risk. These compounds were assayed per os in mice for their anti-inflammatory and analgesic activities as well as the ulcerogenic risk and acute toxicity. Several of these compounds showed significant anti-inflammatory activity. [40]

\[
\begin{align*}
N & \quad N \\
\text{H} & \quad \text{H} \\
\text{N} & \quad \text{SO}_2R
\end{align*}
\]

5-Aryl-3-alkylthio-1,2,4-triazoles

Antibacterial Agents

5-[4-(4-X-phenylsulfonyl)phenyl]-2,4-dihydro-3H-1,2,4-triazole-3-thiones, X = H, Cl, Br show potent antibacterial activities. [41]

\[
\begin{align*}
N & \quad N \\
\text{H} & \quad \text{S} \\
\text{N} & \quad \text{S} \\
\end{align*}
\]

X= H, Cl, Br

5-[4-(4-X-Phenylsulfonyl)phenyl]-2,4-dihydro-3H-1,2,4-triazole-3-thiones

Antituberculosis Agents

2-[4-(1H-[1,2,4]-triazole-1-yl]-1-subsituted-4,6-difluoro-1H-benzole showed antituberculosis activity against Mycobacterium tuberculosis H37Rv strain. [42]

\[
\begin{align*}
\text{F} & \quad \text{N} \\
\text{F} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\end{align*}
\]

2-(4-(1H-1,2,4-Triazol-1-yl)phenyl)-4,6-difluoro-1H-benzo[d]imidazole
**Binding Properties on Endothelium Receptors**

A series of 1,2,4-triazoles derivatives e.g. [3-(arylmethyl)thio-5-aryl-4H-[1,2,4]triazol-4-yl]acetic acids, [5-(arylmethyl)thio-3-aryl-1H-[1,2,4]triazol-1-yl]acetic acids, and [3-(arylmethyl) thio-5-aryl-1H-[1,2,4]triazol-1-yl] acetic acids were tested in binding assays to evaluate their ability as ligands for human ETA and ETB receptors stably expressed in CHO cells; some of the tested compounds showed affinity in the micro molar range. \[^{43}\]

**Luminescence Properties**

Cu and Cd complexes of 1,2-bis(1,2,4-triazol-4-yl)ethane show the excellent luminating properties. \[^{44}\] There are some which used as selective serotonin receptors \[^{45}\], there are some which show resistance to the gamma irradiation. \[^{46}\]

![](image)

1,2-Bis(1,2,4-triazol-4-yl)ethane

**1.3.2 Routes towards the Synthesis of 1,2,4-Triazoles**

Common pathways towards the synthesis of 1,2,4-triazole-3-thiones are the reaction of the acetyldithiocabazates \[^{47, 48}\] or 1,3,4-oxadiazole-2-thiones with hydrazides\[^{49}\]

![](image)

When acetic anhydride reacts with N-acetyl amines triazoles are obtained. \[^{49b}\]

![](image)

3,5-Disubstituted triazole can be obtained by the reaction of ammonia with diacetylhydrazines. \[^{49c}\]
1.4 1,3,4-Thiadiazoles

Thiadiazoles are the five membered heterocycles having one sulphur and two nitrogens at 1, 3 and 4 positions respectively.

1.4.1 Significances of 1,3,4-Thiadiazoles

Anti-Leishmanial Agents

Leishmaniasis is a spectrum disease, some 1-[5-(1-methyl-5-nitro-1H-imidazol-2-yl)-1,3,4-thiadiazol-2-yl]-4-arylpiperazines were tested against Leishmania major and they showed good anti Leishmanial activity. \(^{[50]}\)

\[
\begin{align*}
\text{R} & = \text{Ph, 2-Cl, 3-Cl phenyl, 4-Cl-phenyl} \\
\text{Thiophen-2-yl}
\end{align*}
\]

Antibacterial Activities

A number of gatifloxacin analogues containing a nitroaryl-1,3,4-thiadiazole moiety attached to the piperazine ring at C-7 position show excellent antibacterial activities. \(^{[51]}\)

Gatifloxacin derivative
**Anti-cancerous Activities**

1,3,4-Thiadiazoles possessing γ-substituted butenoid moiety show anti-cancerous activities. \[52\]

![Chemical structure of thiadiazole](image)

R = p-nitrophenyl  
R* = menthyl  

Buteniod substituted 1,3,4-oxadiazole

**Anticonvulsant Activity**

2-(Aminomethyl)-5-(2-biphenylyl)-1,3,4-thiadiazole was when compared with standard drugs like phenytoin, Phenobarbital and carbamazepine posses the anticonvulsant activity in rats and mice. \[53\].

![Chemical structure of aminomethyl-biphenyl-thiadiazole](image)

2-Aminomethyl-5-biphenyl-13,4-thiadiazole

**Antiviral Activity**

Influenza a (H5N1) virus is a cause of large scale deaths in poultry and also of human beings. A large number of compounds are to be synthesised and it was found that adamantly substituted 1,3,4-thiadiazoles show the good antiviral activity against the cowpox virus. \[54\]

![Chemical structure of adamantyl-thiadiazole](image)

Adamantyl substituted 1,3,4-thiadiazole
Alzheimer Disease

Muscarinic acetylcholine subtype 2 (M2) receptor plays an important role in the study of the Alzheimer disease. Alzheimer patients lose M2 receptors in their cortex.

So radiopharmaceuticals are to be synthesised for imaging M2 receptors. In these days C-11 and $^{18}$F labelled derivatives are to be investigated for muscarinic receptors. 3-(4-(3-[$^{18}$F]floropropylthio)-1,2,5-thiadiazol-3-yl)-1-methyl-1,2,5,6-tetra-hydropyridine are the only radiotracer available for imaging M2 receptors in human.$^{[55]}$

![Chemical structure of [F]FP-TZTP](image)

Thyroid Inhibition

Thiadiazole copper is used as a fungicide in China, it’s other importance is that its structure relates with the N,N-methylene-bis(2-amino-1,3,4-thiadiazole)(Bis-A-TDA), which is a teratogen. Studies reveal that thiadiazole fungicides act as endocrine disruptors by disturbing thyroid hormones.$^{[56]}$

![Chemical structure of Bis-A-TDA](image)

Potential Radioprotector

Ionizing radiations are very dangerous for DNA they oxidize the DNA into the hydroxyl radical which is the main species. Some benzothiazoles and thiadiazoles are active molecules which protect DNA against the ionizing radiations.$^{[57]}$

![Chemical structure of potential radioprotector](image)
Determination of Nitrites

Nitrites are used as the preservatives and their excess level causes the oxidation of the haemoglobin which is fatal \[^{58}\]. Also by reacting with amines it forms nitrosoamines which is carcinogenic \[^{59}\]. Electropolymerized films of 5-amino-1,3,4-thiadiazole are used for the determination of the concentration of nitrites in water. \[^{60}\]

Determination of Ascorbic acid, Dopamine and Uric acid

By using electropolymerized film of 5-amino-2-mercapto-1,3,4-thiadiazole(AMT) dopamine(neurotransmitter), uric acid(end product of metabolism) and ascorbic acid can be determine which are otherwise difficult to determine. \[^{61}\]

Water Regulation in Brain Membranes

Acetazoleamide (AZA) and methazolamide (MZA) are the two hormones which contain the thiadiazole ring are responsible for the flow of water in the aquaporin (AQPs) water permeable channel. \[^{62}\]

Fluorescent Sensor

Thiadizole-link naphthalene molecule, 5-(3-(2-(naphthalene-3-yloxy)acetyl)thioureido)-1,3,4-thiadiazole-2-carboxylic acid (NTTA) acts as a florescent sensor for the determination of cystein in aqueous system. \[^{63}\]

Activity Against Sarcocystis neurona

Sarcocystis neurona is an intracellular parasite which causes equine protozoal myeloencephalitis (EPM). 2(OAc)-N-5(X)-thiadiazolyl benzamide is used for the treatment of the above disease. \[^{64}\]
Anticorrosive Agents

Stainless steel is very important from industrial point of view. 4-Phenylthiazole derivatives are used to protect the stainless steel from corrosion\textsuperscript{[65]}. Copper corrosion is successfully inhibited by the 2-methyl-5-mercapto-1,3,4-thiadiazole in NaCl solution and in HCl solution by 5-chloro benztriazole-3,5-diamino-1,2,4-triazole.\textsuperscript{[66]}

1.4.2 Routes towards the Synthesis of 1,3,4-Thiadiazoles

2-Amino-1,3,4-thiadiazoles are obtained by heating the aryl or alkyl carboxylic acid with thiosemicarbazide in the presence of POCl\textsubscript{3}\textsuperscript{[67]}. 1,3,4-thiadiazole ring is obtained by treating the potassium aroyl dithiocarbazate\textsuperscript{[52]}, arylthiosemicarbazide\textsuperscript{[68]} in acidic medium.

Ferric chloride and ferric ammonium sulphate are used for oxidative cyclization of thiosemicarbazides to get substituted 1,3,4-thiadiazoles.\textsuperscript{[68b]}
1.5 Pyrazoles and Pyrazolines

Pyrazoles are the five membered heterocycles with three carbons and two nitrogen atoms. They come under the class of alkaloids, very rare in nature but pharmacologically very important. Pyrazolines are structurally related to the pyrazoles and also very important class of heterocycles. [69]

![Pyrazole and pyrazolines](image)

1.5.1 Significance of Pyrazole

Anticancerous Activities

Platinum complexes of the (pyrazol-1-ylmethyl)pyridine ligand show the cytotoxic activity against the tumour cells. [70]

Neutrophil Chemotaxis Inhibitor

It's a phenomena in which white platelets, which constitute our immune system, migrate (chemotaxis) on the inflammatory site and phagocytose the foreign particles and produce the free radicals. [71, 72]

This process is induced by some chemoattractant if this is not doing properly then acute and chronic autoimmune inflammatory disorders like asthma, arthritis etc can be happen. Many pyrazoles like 5-amino-1-(2-hydroxy-2-phenylethyl)-1H-pyrazole-4-carboxalic acid are used as the potent human neutrophil chemotaxis inhibitors. [73]

![Chemical structure of pyrazoles](image)

R= H, CN, COOC₂H₅
N'R= NHCH(CH₃)₂, Cycloalkylamine etc

Arora Inhibitors

Arora is the family of protein kinasease hormones which are used during the mitosis and help in the cytokinosis. Studies show that if arora protein kinase inhibitors are introduced in the cancerous line cell mitosis can be stopped leading to the death of
the cancerous cells. Amino pyrazol linked to a 2-subsituted quinazole can be used for the inhibition of the Arora protein kinase.\textsuperscript{[74]}

![Compound 1 and Compound 2](image)

(Fig. 1.3) Arora enzyme A

**Antiobestic Drugs**

Obesity, when a person carries too much weight. *Rimonabant* with a pyrazol ring is used as the antiobesity drug in Europe.\textsuperscript{[75]}

![Rimonabant](image)

**Antidiabetic Activity**

1-Substituted-3,5-dimethoxypyrazol is used as hypoglasmic agent.\textsuperscript{[76]}

![3,5-Dimethylpyrazole](image)
Inhibitors of CARM1

Protein Arginine methyl transferase family plays an important role in the cellular processes.\[77\]

Co-activator Associated Arginine Methyl tranferase 1(CARM 1) effect the methyl arginine as a result the function of the protein arginine methyltransferase alter leading to the prostate cancer\[78\].

Pyrazole analogue is used as a potent and selective inhibitor of CARM1.\[79\]

\[
\text{CARM 1}
\]

Antitubercular Activity

Some 2-2-Methoxy-4-[5-(subsituted phenyl)-1-(4-pyridylcarbonyl)-4,5-dihydro-1H-3-pyrazolyl] phenoxyacetic acids are famous for their antitubercular activities.\[80\]

\[
\text{R= phenyl, 4-hydroxyphenyl, 4-nitrophenyl, 4, floro phenyl, 4-methyl, 4-amino phenyl, 2-chlorphenyl, 2-hydroxy phenyl}
\]

2-2-Methoxy-4-[5-(substituted phenyl)-1-(4-pyridylcarbonyl)-4,5-dihydro-1H-3-pyrazolyl]phenoxyacetic acid

Antiamoebiasis Agents

Amoebiasis is a disease cause by Entamoeba histolytica. Some bis-pyrazoline derivatives\[81\], 1-N-subsituted-thiocabamolyl-3-phenyl-2-pyrazolines\[82\] show activity against the E. histolytica.
Fluorescence and Drugs

Pyrazolines are well known fluorescent agents and are very famous in photoconductivity. Small molecule binds with DNA which are very important tool in medicine industry to get the knowledge of drug-DNA interaction. Some 1-phenyl-3-biphenyl-5-(N-ethylcarbazole-3-yl)-2-pyrazolines emits blue light which shows their insertion in the DNA base pair.\(^{[83]}\)

\[
\begin{align*}
\text{1-Phenyl-3-biphenyl-5-(N-ethylcarbazole-3-yl)-2-pyrazolines}
\end{align*}
\]

Antiviral Activity

N-acetyl and N-thiocarbamoyl derivatives of 4,5-dihydropyrazole show the activity against the Vaccinia virus (Lederle strain) in HEL cell culture.\(^{[84]}\)

\[
\begin{align*}
\text{N-Acetyl and N-thiocarbamoyl pyrazoles}
\end{align*}
\]
Antinociceptive Activities

Some derivatives of the pyrazoline e.g. 1-[(benzoxazole/benzimidazole-2-yl)thioacetyl]pyrazole show the antinociceptive activities.\(^8\)

\[
\begin{align*}
\text{X} &= \text{O, N}
\end{align*}
\]

Antimicrobial Activity

2-[1-(5,8-Dihydroquinoxalino[2,3-b]indoloacetyl)-3-(1-benzofuran-2-yl)-4,5-dihydro-1H-pyrazol-5yl]phenyl derivatives show the antibacterial activities.\(^9\)

\[
\begin{align*}
\text{R} &= \text{OH, CH}_3, \text{NO}_2
\end{align*}
\]

Anti-inflammatory Activity

3,5-Diaryl-2-pyrazoline derivatives\(^1\), 5-(substituted)aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazoline,\(^2\) show antiinflammatory activities.

5-(Substituted)aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazolines
1.52: Routes towards the Synthesis of Pyrazoles and Pyrazolines

3,5-Dimethylpyrazoles are to be synthesized by the reaction of hydrazides with the diketones. The pharmacologically active pyrazolines are synthesized by treating the chalcones with the hydrazides or hydrazine in the presence of acidic medium. Kocyiggit et al synthesised 4-substituted-3,5-dimethylpyrazole by reduction of diacyl hydrazones with hydrazine hydrate.

Pyrazolines can be synthesised by reacting chalcone with thiosemicarbazide in NaOH.

Pyrazole and pyrazolines can be synthesised by [3+2] addition of olefin and ethyl diazoacetate.

1.6 Isochromans

Isochromans are 3,4-dihydro-1H-benzopyran derivatives that are generally present in nature as a part of the complex rings (Peng, Lu, and Ralph, 1999), e.g., hydroxy-isochroman like 1-phenyl-6,7-dihydroxy-isochroman, and 1-(3′-methoxy-4′-hydroxy)-phenyl-6,7-dihydroxyisochroman, are present in the extra-virgin oil.
1.6.1 Significance of Isochromans

Secondary Metabolites

Some mycotoxin, 3,7-dimethyl-8-hydroxy-6-methoxyisochroman, and 3,7-dimethyl-1,8-dihydroxy-6-methoxy-isochroman are the well known secondary metabolites. \[^{[91]}\]

\[
\begin{array}{c}
\text{H}_3\text{CO} \\
\text{H}_3\text{C} \\
\text{OH} \\
\text{O} \\
\text{CH}_3 \\
\end{array}
\]
\[R= \text{H, OH}\]

3,7-Dimethyl-8-hydroxy-6-methoxyisochroman, and 3,7-dimethyl-1,8-dihydroxy-6-methoxy-isochroman

Perfumery Industry

*Galaxolide,*(1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopentanta[g]-2-benzopyran; (HHCB) is commercially very important isochroman was discovered by *Heernga* and *Beets* in 1967 and is most important musk used in the perfumery industry. \[^{[92]}\]

\[
\begin{array}{c}
\text{H}_3\text{C} \\
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3 \\
\end{array}
\]

Galaxolide®

Plant Growth Regulator and Herbicidal Activities

Cutler *et al* has separated some 3,7-dimethyl-8-hydroxy-6-methoxyisochroman from *pencillium corylophilium* and their derivatives show plant growth and herbicidal activities. \[^{[9]}\]

\[
\begin{array}{c}
\text{H}_3\text{CO} \\
\text{H}_3\text{C} \\
\text{OH} \\
\text{O} \\
\text{CH}_3 \\
\end{array}
\]

3,7-Dimethyl-8-hydroxy-6-methoxyisochroman
**Anti-Apoptotic Agent**

7-(Isopropoxymethyl)-5-phenyl-7,8-dihydro-5H-[1,3]dioxolo[4,5-g]isochromene (ISO-9) is an antiapoptotic agent and is a useful tool for the study of the molecular mechanism of apoptosis in vascular endothelial cells (VECs). [94]

![ISO-9](image)

**Isochroman as Neurokinin-1 Receptor Antagonist cj-17, 493**

Neurokinin-1 (NK-1) receptor is a member of the seventransmembrane G-protein coupled family of receptor and associated with the sensory neurons in the peripheral and specific area in the central nervous system. It is also associated with the biological disorders like anxiety, depression, emesis, asthma, and anti-inflammatory bowel disease. [95]

(2S,3S)-3-[(1R)-6-methoxy-1-methyl-1-trifloromethylisochroman-7-yl]-methylamino-2-phenylpiperidine shows the selective affinity for human NK_1 receptors and also induces anti-emetic activity. [96]

![Molecule](image)

(2S,3S)-3-[(1R)-6-Methoxy-1-methyl-1-trifloromethylisochroman-7-yl]-methylamino-2-phenylpiperidine

**Anti-tumour Agents**

(±)-Pseudodeflectectusion is an isochroman present in nature and was isolated from the broth of Aspergillus pseudodeflectus is now a days used as a potent anti tumour agent. [97]
Anti-diabetic Agent

Isochroman mono carboxylic acid derivatives are used as the anti-diabetic agents.\[^{98}\]

Hypotensive Agents

1-[1-(3,4-Dihydro-6,7-dimethoxy-1H-2-benzopyran-1-yl)alkyl]-4-arylpiperazine are a series of isochroman used as hypotensive agents to lower the blood pressure.\[^{99}\]

Antiinflammatory Activities

Some 1-alkyl-isochroman-1-yl acetic acid derivatives show anti-inflammatory activity.\[^{100}\]
Physiological Activities

Simple 1-subsituted isochroman have been shown to exhibit a wide variety of physiological activities like antihistimatic, anticholinergic, diuretic, sympathomimetic and antihypertensive ones.\textsuperscript{[101]}

1.62: Routes towards the Synthesis of Isochroman

The oxa-Pictet-Spengler reaction is a variation of the Pictet-Spengler reaction in which a phenylethyl alcohol reacts with a carbonyl compound to give a 1-subsituted isochroman derivative. Typically, aqueous HCl, Zinc chloride HCl gas, p-toulensulfonic acid, titanium tetrachloride or stannic chloride have been used as Friedel Crafts catalysis along with high reaction temperature.\textsuperscript{[102]}

The activated substrates such as 2-(3,4-dihydroxy-phenyl)ethanol undergo the oxa-pictect-spengler reacti on under mild conditions.\textsuperscript{[102, 103, 104]} However, the reaction required to obtain the satisfactory yields varied from 1 day for aldehydes to 2 days to \textit{ca.} 1 week for ketones nevertheless the yield were lower.

1.7 Morpholines

Morpholine is a six membered heterocycle having oxygen and nitrogen at 1 and 4 position and is pharmaceutically important compound. Presence of the nitrogen makes it a useful base in the organic synthesis. Morpholines are both present in the nature as well as can be synthesised in the laboratory.\textsuperscript{[105]}

1.7.1 Significance of Morpholine

Phosphoinositide-3-kinase Inhibitors

4-(1,3-thiaazol-2-yl)morpholine derivatives are used as the Phosphoinositide-3-kinase inhibitors.\textsuperscript{[106]}

(S)-2-((1H-Indol-3-yl)methyl)morpholino)-7,7-dimethyl-5,6,7,8-tetrahydrothiazolo[5,4-c]azepin-4-one
Anti-depressent Drugs

Reboxetine, 2-[α-aryloybenzyl)morpholine (FCE, 20124), contains the morpholine ring is used as the antidepressent drug. [107]

![Reboxetine](image)

Antitumour Agents

Antibiotic C-1027, a novel antitumour chromoprotein was isolated from the broath of *Streptomyces globisporus* contains the morpholine ring. [108]

Antimicrobial Activity

Chelonin (A&C) are alkaloids which were seperated from the marine sponge *Chelonaplysilla* sp. they show antimicrobial activity against *Bacillus Subtillis*. [109]

![Chelonin A](image)

![Chelonin C](image)

Linezolid is a standard drug that contains the morpholine ring, used for the treatment of pneumonia, skin infections and diabetic foot infection, active against the Gram positive strains of bacteria. [109a]

![Linezolid](image)
Fungicidal Activities

N-substituted morpholines like fenpropiomorph is widely used as a leaf fungicide, its major use is to control fungus diseases in cereals. \[110\]

\[\text{Fenpropiomorph}\]

Anti-oxidant Activities

N-substituted morpholines containing 1,2-dithiolane moiety \[111\] and 1,3,4-thiadiazole-2,5-disulfonic acid \[112\] show antioxidant as well as the chelating properties due to the presence of morpholine ring.

\[\text{N-substituted morpholine-1,2-dithiolane moiety}\]

\[\text{1,3,4-Thiadiazole-2,5-disulfonic acid}\]

Bladder-Selective Potassium Channel Opener

Urinary incontinence (UI), is a widely spread and distressing condition with the elderly people. Some morpholine derivatives are used as the Bladder-Selective Potassium channel opener. \[113\]

\[\text{(4aR,10bR)-1-formyl-5,5-dimethyl-1,2,3,4a,5,10b-hexahydrochromeno[3,4-b][1,4]oxazine-9-carbonitrile}\]
Anti-gastic Agents

Some 2-(aminomethyl)-4-benzylmorpholine are used as potent antigastric agents \[114\].

1.72: Routes towards the Synthesis of Morpholines

Morpholines are to be synthesised by the cyclization of amino alcohols with epoxide \[115\], with allylic subsituents \[116\], or with chloroethanol \[117\].

1.8 Plan of Work

1,3,4-Oxadiazoles, 1,3,4-oxadiazole-2-thiones, 3-mercaptotriazoles, 3,5-disubstituted pyrazoles, pyrazolines, 1,2,4-triazoles, 1,3,4-thiadiazoles morpholines and 1-isochromans have great practical importance in the field of medicine, agriculture and industry. Due to the wide range of applications and availability of chemicals we have synthesized some five and six membered heterocycles and biheterocycles from their common precursor hydrazide and observed their biological significances. In this regard the work is divided into three parts.

Part-I: Synthesis of five membered heterocycles

Part-II: Synthesis of six membered heterocycles.

Part-III: Synthesis of biheterocycles

And then tested for their antibacterial, antifungal and phytotoxic activities.

Part-I: Synthesis of Five Membered Heterocycles

Five membered heterocycles includes:

1. Oxadiazoles
2. Mercaptoxadiazoles
3. Mercaptotriazoles
4. Pyrazoles
5. Pyrazolines

Their synthetic routes and final step reaction mechanisms are as follows:
Scheme 1.1: Synthesis of some 2-(3,5-Dimethoxy-4-methylphenyl)-5-aryl-1,3,4-oxadiazoles.

Mechanism
Scheme 1.2: Synthesis of some N-amino methyl oxadiazoles-2-thiones.

Mechanism
Scheme 1.3: Synthesis of some Triazole-2-thiones.

Mechanism
Scheme 1.4: Synthesis of Some 1-Aryl-3,5-dimethyl pyrazoles.

Mechanism
Scheme 1.5: Synthesis of Some 1-Aryl-3,5-Di-substitutedpyrazolines.

Mechanism
Part-II: Synthesis of Six Member Heterocycles

Six membered heterocycles include:

1. Isochromans
2. Morpholines

Scheme 1.6: Synthesis of Some (±)-1-Aryl-5-chloroisochroman.

Mechanism
Scheme 1.7: Synthesis of Some N-substituted morpholines.

Mechanism:
Part-III: Synthesis of Biheterocycles

1. Bis derivatives of triazoles
2. Isochromanyl substituted pyrazoles
3. Isochromanyl substituted triazoles
4. Isochromanyl substituted thiadiazoles

\[
\begin{align*}
\text{Et}_2\text{O} & \quad \text{Br}_2/\text{AlCl}_3 \\
\text{Br} & \quad \text{N} \\
\text{NHN} & \quad \text{S} \\
\text{NH}_2 & \quad \text{EtOH/H} \\
\end{align*}
\]

\[
\begin{align*}
\text{R=} & \quad 2-\text{Br}, 4-\text{F}, 4-\text{CH}_3, 3,4-\text{(OCH}_3)\text{, }3,5-\text{(OCH}_3)\text{, }3-4-\text{CH}_3-3,5\text{(CH}_3)\text{, }3,4,5-\text{(CH}_3)\text{, }\text{Ph-2,4-dienyl}
\end{align*}
\]

Scheme 1.8: Synthesis of Triazole thiadiazines.

**Mechanism**

- \[
\text{R} = 2-\text{Br}, 4-\text{F}, 4-\text{CH}_3, 3,4-\text{(OCH}_3)\text{, }3,5-\text{(OCH}_3)\text{, }3-4-\text{CH}_3-3,5\text{(CH}_3)\text{, }3,4,5-\text{(CH}_3)\text{, }\text{Ph-2,4-dienyl}
\]
Scheme 1.9: Synthesis of 1-(1-Methyl-isochromanyl)-3,5-dimethyl pyrazoles.
Scheme 1.10: Synthesis of N-(phenyl)-5-(6,7,8-trimethoxy-1-methyl-3,4-dihydro-1H-isochromen-1-yl)-1,3,4-thiadiazole-2-amine.

Mechanism
Scheme 1.11: 5-(6,7,8-Trimethoxy-1-methyl-3,4-dihydro-1H-isochromen-1-yl)-4H-1,2,4-triazole-3-thione.

Mechanism
Chapter – 2
RESULTS AND DISCUSSION

2.1 Synthesis of Aryl hydrazides

Substituted benzoic acids were refluxed with methanol in acidic medium to get esters\(^{[118]}\) (1-8) which were then treated with 20 equivalents of hydrazine monohydrate in methanol to get the corresponding hydrazides\(^{[119]}\) (1’-8’) scheme-2.1.

\[
\begin{align*}
\text{R} & \quad \text{OH} \\
& \quad \text{O} \\
& \quad \text{CH}_3 \\
& \quad \text{NH}_2 \quad \text{NH}_2 (20\text{eq})
\end{align*}
\]

Scheme-2.1: Synthesis of aryl hydrazides.

Physical data of the esters and their corresponding hydrazides is given in the Table 2.1.

Table 2.1: Physical data of Aryl esters and hydrazides.

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>Yield (%)</th>
<th>(R_f^*)</th>
<th>M.P. (°C)</th>
<th>Sr. No</th>
<th>Yield (%)</th>
<th>M.P (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-Br</td>
<td>96</td>
<td>0.9</td>
<td>Oil</td>
<td>1’</td>
<td>87</td>
<td>123-124</td>
</tr>
<tr>
<td>2</td>
<td>4-F</td>
<td>92</td>
<td>0.8</td>
<td>Oil</td>
<td>2’</td>
<td>89</td>
<td>133-134</td>
</tr>
<tr>
<td>3</td>
<td>4-CH(_3)</td>
<td>98</td>
<td>0.7</td>
<td>Oil</td>
<td>3’</td>
<td>88</td>
<td>117-118</td>
</tr>
<tr>
<td>4</td>
<td>3,4-(OCH(_3))(_2)</td>
<td>86</td>
<td>0.7</td>
<td>Oil</td>
<td>4’</td>
<td>83</td>
<td>166-167</td>
</tr>
<tr>
<td>5</td>
<td>3,5-(OCH(_3))(_2)</td>
<td>91</td>
<td>0.7</td>
<td>Oil</td>
<td>5’</td>
<td>80</td>
<td>119-120</td>
</tr>
<tr>
<td>6</td>
<td>4-CH(_3),3,5-(OCH(_3))(_2)</td>
<td>89</td>
<td>0.6</td>
<td>Oil</td>
<td>6’</td>
<td>78</td>
<td>161-162</td>
</tr>
<tr>
<td>7</td>
<td>3,4,5-(OCH(_3))(_3)</td>
<td>97</td>
<td>0.6</td>
<td>Oil</td>
<td>7’</td>
<td>82</td>
<td>221-222</td>
</tr>
<tr>
<td>8</td>
<td>1-[Ph-2,4-dienyl]</td>
<td>99</td>
<td>0.8</td>
<td>Oil</td>
<td>8’</td>
<td>81</td>
<td>198-199</td>
</tr>
</tbody>
</table>

* Petroleum ether: Ethyl acetate (9:1)

Disappearance of peak for OCH\(_3\) group at \(\delta\) 3.9 ppm and appearance of new peaks at \(\delta\) 9.91 and at \(\delta\) 5.54 ppm for NH and NH\(_2\) respectively confirmed the structure.
2.2 Synthesis of Some 2-(3,5-Dimethoxy-4-methylphenyl)-5-aryl-1,3,4-oxadiazoles (1a-1h)

3,5-Dimethoxy-4-methylbenzooylhydrazide (6') was microwave irradiated for 2-3 min with one equivalent of substituted benzoic acids in the presence of thionyl chloride to afford 2-(3,5-dimethoxyl-4-methylphenyl)-5-aryl-1,3,4-oxadiazoles \(^{[121]}\) (1a-1h) in 70-85 % yields, a one step reaction to save time and solvent (Scheme-2.2).

![Chemical structure](image)

Scheme 2.2: Synthesis of 1,3,4-Oxadiazole.

The IR spectra revealed disappearance of stretching vibration at 3010 cm\(^{-1}\) and 3345 cm\(^{-1}\) for NH and NH\(_2\) group shows the oxadiazole formation. The physical and IR data is given in Table 2.2.

**Table 2.2: Physical data of 2-(3,5-Dimethoxy-4-methylphenyl)-5-aryl-1,3,4-oxadiazoles (1a-1h).**

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R</th>
<th>Yield (%)</th>
<th>M.P. (°C)</th>
<th>R&lt;sub&gt;f&lt;/sub&gt;</th>
<th>IR (cm(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>2'-CH(_3)</td>
<td>73</td>
<td>95-97</td>
<td>0.9</td>
<td>2930, 1618, 1536, 1491</td>
</tr>
<tr>
<td>1b</td>
<td>4'-CH(_3)</td>
<td>85</td>
<td>97-99</td>
<td>0.9</td>
<td>2925, 1685, 1613, 1285</td>
</tr>
<tr>
<td>1c</td>
<td>2'-Br</td>
<td>74</td>
<td>99-100</td>
<td>0.8</td>
<td>2942, 1641, 1304, 1211</td>
</tr>
<tr>
<td>1d</td>
<td>4'-Cl</td>
<td>71</td>
<td>136-137</td>
<td>0.9</td>
<td>2937, 1730, 1606, 1543</td>
</tr>
<tr>
<td>1e</td>
<td>3'-CH(_3)O-Ph</td>
<td>95</td>
<td>167-168</td>
<td>0.5</td>
<td>2922, 1730, 1606, 1542</td>
</tr>
<tr>
<td>1f</td>
<td>4'-OCH(_3)</td>
<td>72</td>
<td>Oil</td>
<td>0.7</td>
<td>2912, 1730, 1633, 1617</td>
</tr>
<tr>
<td>1g</td>
<td>3',4',5'-(OCH(_3))(_2)</td>
<td>80</td>
<td>138-139</td>
<td>0.3</td>
<td>2941, 1617, 1595, 1516</td>
</tr>
<tr>
<td>1h</td>
<td>3',4',5'-(OCH(_3))(_3)</td>
<td>78</td>
<td>Oil</td>
<td>0.3</td>
<td>2901, 1636, 1616, 1127</td>
</tr>
</tbody>
</table>

* Petroleum ether: Ethyl acetate (7:3)
In case of $^{13}$CNMR a signal at $\delta$ 165.12 for C-2 and that at 141.1 ppm for C-5 carbon of the oxadiazole ring show the ring closure. $^1$HNMR and $^{13}$CNMR data for 1,3,4-oxadiazoles is given in Table 2.3.

Table 2.3: $^1$HNMR and $^{13}$CNMR data of 2-(3,5-Dimethoxy-4-methylphenyl)-5-aryl-1,3,4-oxadiazoles (1a-1h).

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R</th>
<th>$^1$HNMR</th>
<th>$^{13}$CNMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>2'-CH$_3$</td>
<td>8.2 (s, 2H$<em>{arom}$), 7.8-7.3 (m, 4H$</em>{arom}$), 3.96 (s, 6H, 2×OCH$_3$), 2.81 (s, 3H CH$_3$), 2.67 (s, 3H, CH$_3$)</td>
<td>164 (CO), 141.37, 138.71, 138.49, 131.84, 131.54, 131.22, 129.73, 128.96, 126.27, 126.23, 123.99, 123.0, 122.80, 122.56, 107.0 (C-1, C-6), 56.14 (OCH$<em>3$), 29.73 (CH$</em>{arom}$), 23.25(CH$_{arom}$)</td>
</tr>
<tr>
<td>1b</td>
<td>4'-CH$_3$</td>
<td>8.1 (s, 2H$<em>{arom}$), 7.4 (d, $J$=5.7, 2H$</em>{arom}$), 6.95 (d, $J$=5.6, 2H$_{arom}$), 3.9 (s, 6H, 2×OCH$_3$), 2.7 (s, 3H CH$_3$), 2.5 (s, 3H, CH$_3$)</td>
<td>165 (C-1, CO), 141.37 (C-5, CO), 138.36, 138.34, 131.84, , 131.54, 23.25, 131.22, 129.73, 126.27, 123.99, 123.0, 29.17, 122.80, 122.56, 107.0 (C-1, C-6), 56.16 (OCH$_3$)</td>
</tr>
<tr>
<td>1c</td>
<td>2'-Br</td>
<td>8.1 (s, 2H$<em>{arom}$), 7.9-6.8 (m, 4H$</em>{arom}$), 3.8 (s, 6H, 2×OCH$_3$), 2.4 (s, 3H CH$_3$)</td>
<td>161.01 (C-1, CO), 141.37 (C-5, CO), 138.16, 138.49, 131.81, 131.22, 129.72, 128.96, 126.23, 123.99, 123.0, 122.80, 122.56, 107.0 (C-1, C-6), 56.14 (OCH$<em>3$), 29.07(CH$</em>{arom}$);</td>
</tr>
<tr>
<td>1d</td>
<td>4'-Cl</td>
<td>8.28 (s, 2H$<em>{arom}$), 7.7 (dd, $J$= 3.3, 5.4, 2H$</em>{arom}$), 7.55 (dd, $J$=1.8, 7.2, 2H$_{arom}$), 3.96 (s, 6H, 2×OCH$_3$), 2.67 (s, 3H, CH$_3$)</td>
<td>165.12 (C-1, CO), 141.37 (C-5, CO), 138.36, 138.34, 131.84, 131.54, 131.22, 129.27, 126.27, 123.99, 123.0, 122.80, 122.56, 107 (C-1, C-6), 56 (OCH$<em>3$), 29.1 (CH$</em>{arom}$), 23.54(CH$_{arom}$)</td>
</tr>
<tr>
<td>1e</td>
<td>3'-CH$_3$O- Ph</td>
<td>8.21 (s, 2H$<em>{arom}$), 7.71-7.92 (m, 4H$</em>{arom}$), 3.82 (s, 3H, OCH$_3$), 3.80 (s, 6H, 2×OCH$_3$), 3.67 (s, 2H, CH$_2$), 2.65 (s, 3H, CH$_3$)</td>
<td>165.12 (C-1, CO), 141.37 (C-5, CO), 138.36, 138.34, 131.84, 131.54, 131.22, 129.27, 126.27, 123.99, 123.0, 122.80, 122.56, 107 (C-1, C-6), 56, 29 (OCH$_3$), 23.54</td>
</tr>
<tr>
<td>1f</td>
<td>4'-OCH$_3$</td>
<td>8.1 (s, 2H$<em>{arom}$), 7.29 (d, $J$=5.7, 2H$</em>{arom}$), 6.95 (d, $J$=5.7, 2H$_{arom}$), 3.90 (s, 6H, 2×OCH$_3$), 3.89 (s, 3H OCH$_3$), 2.3 (s, 3H, CH$_3$)</td>
<td>151.58 (C-1, CO), 141.37 (C-5, CO), 138.66, 138.39, 131.84, 131.54, 129.73, 128.96, 126.27, 126.23, 123.99, 123.0, 122.76, 122.56, 104.0 (C-1, C-6), 56.71 (OCH$_3$), 56.14 (OCH$_3$), 29.41(CH$_3$)</td>
</tr>
<tr>
<td>1g</td>
<td>3',4'- (OCH$_3$)$_2$</td>
<td>8.2 (s, 2H$<em>{arom}$), 7.29 (s, 1H$</em>{arom}$), 7.02 (d, $J$=8.4, 1H$<em>{arom}$) 6.91, (d, $J$=8.7, 1H$</em>{arom}$), 3.99 (s, 6H, 2×OCH$_3$), 3.89 (s, 3H OCH$_3$), 3.75 (s,3H, OCH$_3$), 3.6 (s, 3H, CH$_3$)</td>
<td>165 (C-1, CO), 141.61 (C-5, CO), 138.76, 138.4, 131.84, 131.54, 131.22, 126.27, 129.73, 126.23, 123.99, 123.0, 122.80, 107.0 (C-1, C-6), 56.73 (OCH$_3$), 56, 0 (OCH$_3$), 29.71 (CH$_3$), 23.25</td>
</tr>
<tr>
<td>1h</td>
<td>3',4',5'-(OCH$_3$)$_3$</td>
<td>7.22 (s, 2H$<em>{arom}$), 7.21 (s, 2H$</em>{arom}$), 3.9 (s, 6H, 2×OCH$_3$), 3.8 (s, 9H, 3×OCH$_3$), 2.4 (s, 3H, CH$_3$)</td>
<td>152.96 (C-1, CO), 153.72 (C-5, CO), 141.37, 138.66, 138.49, 131.54, 131.22, 129.73, 128.96, 126.27, 126.23, 123.99, 123.0, 122.80, 122.56, 107.0 (C-1, C-6), 56.24 (OCH$_3$), 56.56 (OCH$_3$), 26.54 (CH$_3$), 29.71</td>
</tr>
</tbody>
</table>
In mass spectrum of 2-(3,5-dimethoxy-4-methylphenyl)5-(2’-methylphenyl)-1,3,4-oxadiazole (1a) the molecular ion peak was observed at \( m/z \) 310 a.m.u. and most abundant peak at \( m/z \) 91amu for the tropylium ion scheme-2.3.

Scheme 2.3: Mass fragmentation pattern of 2-(3,5-Dimethoxy-4-methylphenyl)5-(2’-methylphenyl)-1,3,4-oxadiazole (1a).

1,3,4-Oxadiazoles were tested for their antibacterial, antifungal and phytotoxic activities. In case of antibacterial activities using agar well diffusion method \([134]\) most significant results were observed for (1b), having CH₃, an electron donating group was substituted at para position of the 2-aryl group of oxadiazole Table 2.4.
Table 2.4: Antibacterial activities of 1,3,4-Oxadiazoles (1a-1h).

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>E. coli</th>
<th>B. subtilis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>1c</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>1d</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>1e</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>1f</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>1g</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>1h</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>-ve control (acetone)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>–</td>
<td>20</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>15</td>
<td>–</td>
</tr>
</tbody>
</table>

Concentration used: 5mg/mL; -: no activity.

Zone of inhibition (radius, mm)

For antifungal activities \[^{134}\] the most significant inhibition was observed in case of compounds (1a), (1e), and (1f) when methyl and methoxy electron donating groups were substituted on aryl group of oxadiazole, while for compound (1b), having methyl group at ortho position of aryl group, (1d), chloro group at para position of aryl group and (1g) methoxy group at para position of aryl group of oxadiazole, showed moderate percentage inhibition Table 2.5.
Table 2.5: Antifungal activities of 1,3,4-Oxadiazoles (1a-1h).

![Structure of 1,3,4-Oxadiazoles (R)](image)

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>(S. \text{cerevisiae} ) (ZI, cm)</th>
<th>(S. \text{cerevisiae} ) (PI, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>0.4</td>
<td>66</td>
</tr>
<tr>
<td>1b</td>
<td>0.7</td>
<td>41.66</td>
</tr>
<tr>
<td>1c</td>
<td>0.8</td>
<td>33.3</td>
</tr>
<tr>
<td>1d</td>
<td>0.5</td>
<td>58.33</td>
</tr>
<tr>
<td>1e</td>
<td>0.3</td>
<td>75</td>
</tr>
<tr>
<td>1f</td>
<td>0.4</td>
<td>66.6</td>
</tr>
<tr>
<td>1g</td>
<td>0.6</td>
<td>50</td>
</tr>
<tr>
<td>1h</td>
<td>0.3</td>
<td>75</td>
</tr>
<tr>
<td>-ve control (acetone)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>12</td>
<td>100</td>
</tr>
</tbody>
</table>

Concentration used: 5mg/mL; -: no activity

ZI: zone of inhibition; PI: percent inhibition = 100-fungal growth in sample (cm) / fungal growth in control (cm) \(\times 100\)

In case of phytotoxic activities all of the compounds were active to remove magnesium ion from chlorophyll molecule in order to stop photosynthesis and as a result pale yellowing and blackening of the leaves was observed except for compounds, (1e), (1f) and (1h) which were inactive Table 2.6.
Table 2.6: Phytotoxic activities of 1,3,4-Oxadiazole (1a-1h).

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Phytotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>1b</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>1c</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>1d</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>1e</td>
<td>–</td>
</tr>
<tr>
<td>1f</td>
<td>–</td>
</tr>
<tr>
<td>1g</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>1h</td>
<td>–</td>
</tr>
</tbody>
</table>

Concentration : 5mg/mL; -: no activity

2.3 Synthesis of some N-aminomethyl substituted aryl-5-aryl-1,3,4-oxadiazole-2-thiones (2a-2j)

Substituted hydrazides (1’-8’) were refluxed with 1.5 equivalents of potassium hydroxide and 1.5 equivalents of carbon disulfide for four hours\(^{[28]}\). Solid precipitates were poured into cold water and treated with dilute hydrochloric acid to get 1,3,4-oxadiazole-2-thiones which underwent Mannich reaction by reacting with one equivalent of substituted anilines in the presence of paraformaldehyde in ethanol after overnight stirring to afford N-aminomethyl aryl-5-aryl-1,3,4-oxadiazole-2-thione\(^{[29]}\) in 83-93 % yields (Scheme 2.4).

![Scheme 2.4: Synthesis of some N-aminomethyl substituted aryl-5-aryl-1,3,4-oxadiazole-2-thiones.](image-url)
IR data shows the stretching at 3111 cm\(^{-1}\) for NH group and that at 2811 cm\(^{-1}\) for CH\(_2\) group respectively. Physical and IR data for 1,3,4-oxadiazole-2-thiones is given in the Table 2.7.

**Table 2.7:** Physical data of some N-aminomethyl substituted aryl-5-aryl-1,3,4-oxadiazole-2-thiones (2a-2j).

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>R'</th>
<th>Yield (%)</th>
<th>M.P.(°C)</th>
<th>R(_f^*)</th>
<th>IR (cm(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>2'-Br</td>
<td>2”-Cl</td>
<td>83</td>
<td>134-135</td>
<td>0.7</td>
<td>3111, 1623, 1453, 1309, 1284</td>
</tr>
<tr>
<td>2b</td>
<td>4’-F</td>
<td>2”-Cl</td>
<td>93</td>
<td>136-137</td>
<td>0.6</td>
<td>3118, 1623, 1443, 1370</td>
</tr>
<tr>
<td>2c</td>
<td>4’-CH(_3)</td>
<td>2”-Cl</td>
<td>93</td>
<td>139-140</td>
<td>0.6</td>
<td>3189, 1627, 1411, 1356</td>
</tr>
<tr>
<td>2d</td>
<td>4’-CH(_3)-3’,5’-(OCH(_3))(_2)</td>
<td>2”-Cl</td>
<td>89</td>
<td>158-159</td>
<td>0.5</td>
<td>3090, 2914, 1613, 1440</td>
</tr>
<tr>
<td>2e</td>
<td>3’,4’,5’-(OCH(_3))(_3)</td>
<td>2”-Cl</td>
<td>93</td>
<td>120-121</td>
<td>0.5</td>
<td>3100, 1619, 1413, 1329</td>
</tr>
<tr>
<td>2f</td>
<td>2'-Br</td>
<td>2”-Cl-4”-NO(_2)</td>
<td>87</td>
<td>157-158</td>
<td>0.7</td>
<td>3143, 1633, 1447, 1379</td>
</tr>
<tr>
<td>2g</td>
<td>4’-F</td>
<td>2”-Cl-4”-NO(_2)</td>
<td>88</td>
<td>109-110</td>
<td>0.7</td>
<td>3118, 1623, 1467, 1345</td>
</tr>
<tr>
<td>2h</td>
<td>4’-CH(_3)</td>
<td>2”-Cl-4”-NO(_2)</td>
<td>91</td>
<td>109-110</td>
<td>0.5</td>
<td>3123, 2825, 1626, 1447</td>
</tr>
<tr>
<td>2i</td>
<td>4’-CH(_3)-3’,5’-(OCH(_3))(_2)</td>
<td>2”-Cl-4”-NO(_2)</td>
<td>90</td>
<td>198-199</td>
<td>0.6</td>
<td>3225, 2953, 1642, 1467</td>
</tr>
<tr>
<td>2j</td>
<td>3’,4’,5’-(OCH(_3))(_3)</td>
<td>2”-Cl-4”-NO(_2)</td>
<td>85</td>
<td>169-170</td>
<td>0.5</td>
<td>3117, 1654, 1455, 1391, 1298</td>
</tr>
</tbody>
</table>

* Petroleum ether: Ethylacetate (7:3)

\(^1\)HNMR shows a singlet at δ 13.1 ppm for NH proton of the 1,3,4-oxadiazole-2-thione, a broad triplet at δ 5.9–6.3 ppm for NH group and a doublet at δ 4.8–5.7 ppm of CH\(_2\) group of the N-substituted aminomethyl aryl-1,3,4-oxadiazole-2-thiones.\(^1\)H and \(^13\)C NMR data is given in the Table 2.8.
Table 2.8: \(^1\)HNMR and \(^{13}\)CNMR data of some N-aminomethyl substituted aryl-5-aryl-1,3,4-oxadiazole-2-thiones (2a-2j).

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>R'</th>
<th>(^1)HNMR</th>
<th>(^{13})CNMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>2'-Br</td>
<td>2''-Cl</td>
<td>7.1(d, 1H\textsubscript{arom}, J = 5.1), 7.0(d, 1H\textsubscript{arom}, J = 11.0), 6.41 (dd, 2H\textsubscript{arom}, J = 8.9), 6.39 (d, 2H\textsubscript{arom}, J = 4.3), 5.93 (bt, 1H, NH, J = 6.3), 4.84 (d, 2H, CH\textsubscript{2}, J = 6.3)</td>
<td>177.1 (C=S), 155.1 (C=N), 144.9 (C-1''), 136.5 (C-1''), 134.3 (C-4''), 132.8 (C-3', C-6''), 129.8 (C-3''), 127.9(C-4''), 127.7 (C-5''), 121.7 (C-2''), 119.9 (C-4''), 115.6 (C-6''), 67.9 (CH\textsubscript{2})</td>
</tr>
<tr>
<td>2b</td>
<td>4'-F</td>
<td>2''-Cl</td>
<td>6.9 (d, 2H\textsubscript{arom}, J = 8.5), 6.41 (dd, 1H\textsubscript{arom}, J = 4.2), 6.39 (d, 2H\textsubscript{arom}, J = 9.0), 6.31 (d, 1H\textsubscript{arom}, J = 7.0), 6.20 (d, 1H\textsubscript{arom}, J = 6.1), 4.8 (bt, 1H, NH, J = 5.7), 4.75 (d, 2H, CH\textsubscript{2}, J = 6.0)</td>
<td>177 (C=S), 156.6 (C=N), 152.1 (C-1''), 149.1 (C-4''), 142.1 (C-4''), 132.6 (C-3', C-5''), 132.1 (C-2', C-6''), 130.1 (C-1''), 126.7 (C-3''), 125.7 (C-5''), 124.9 (C-2''), 119.1 (C-6''), 67.9 (CH\textsubscript{2})</td>
</tr>
<tr>
<td>2c</td>
<td>4'-CH\textsubscript{3}</td>
<td>2''-Cl</td>
<td>7.4(d, 2H\textsubscript{arom}, J = 4.3), 7.1(d, 2H\textsubscript{arom}, J = 4.1), 6.94 (d, 1H\textsubscript{arom}, J = 8.9), 6.39 (d, 2H\textsubscript{arom}, J = 5.93 (bt, 1H, NH, J = 5.6), 4.84 (d, 2H, CH\textsubscript{2}, CH\textsubscript{2}, J = 6.1), 1.56(s,CH\textsubscript{3})</td>
<td>177 (C=S), 156.6 (C=N), 144.2 (C-4''), 142.7 (C-4''), 140.1 (C-3''), 129.2 (C-3', C-5''), 129.1 (C-2', C-6''), 128.7 (C-5''), 127.8 (C-1''), 124.4 (C-2''), 114.6 (C-6''), 67.9 (CH\textsubscript{2}), 25.4 (CH\textsubscript{3})</td>
</tr>
<tr>
<td>2d</td>
<td>4'-CH\textsubscript{3}-3',5'-(OCH\textsubscript{3})\textsubscript{2}</td>
<td>2''-Cl</td>
<td>7.3 (d, 1H\textsubscript{arom}, J = 9.5), 7.22 (d, 2H\textsubscript{arom}, J = 4.4), 6.8 (d, 1H\textsubscript{arom}, J = 8.6), 6.79 (d, 1H\textsubscript{arom}, J = 8.1), 5.7 (bt, 1H, NH, J = 5.9), 5.6 (d, 2H, CH\textsubscript{2}, J = 6.1), 3.89 (d, 6H, OCH\textsubscript{3}), 2.6 (s, 3H, CH\textsubscript{3})</td>
<td>177.1 (C=S), 155.1 (C=N), 144.9 (C-1''), 142.5 (C-4''), 129.3 (C-3''), 128.6 (C-5''), 125.6 (C-1''), 122.4 (C-2''), 120.8 (C-4''), 116.2 (C-6''), 107.1 (C-2', C-6''), 67.9 (CH\textsubscript{2}), 57.6 (2-OCH\textsubscript{3}), 26(CH\textsubscript{3})</td>
</tr>
<tr>
<td>2e</td>
<td>3',4',5'-(OCH\textsubscript{3})\textsubscript{3}</td>
<td>2''-Cl</td>
<td>7.3 (d, 1H\textsubscript{arom}, J = 9.0), 7.1 (s, 2H\textsubscript{arom}, 6.9 (d, 1H\textsubscript{arom}, J = 11.0), 6.8 (d, 1H\textsubscript{arom}, J = 7.5), 5.6 (bt, 1H, NH, J = 6.0), 5.5 (d, 2H, CH\textsubscript{2}, J = 5.6), 3.9 (d, 9H, OCH\textsubscript{3})</td>
<td>177.1 (C=S), 155.1 (C=N), 144.9 (C-1''), 142.5 (C-4''), 129.3 (C-3''), 128.6 (C-5''), 125.6 (C-1''), 122.4 (C-2''), 120.8 (C-4''), 116.2 (C-6''), 107.1 (C-2', C-6''), 67.9 (CH\textsubscript{2}), 57.6 (3-OCH\textsubscript{3})</td>
</tr>
<tr>
<td></td>
<td>2’-Br</td>
<td>2”-Cl-4”-NO₂</td>
<td>8.2 (s, 1H$<em>{arom}$), 7.95 (dd, 1H$</em>{arom}$, J = 1.1), 7.84 (dd, 2H$<em>{arom}$, J = 7.7, 1.1), 7.6 (d, H$</em>{arom}$, J = 7.4), 6.1 (bt, 1H, NH, J = 6.1), 5.6 (d, 2H, CH$_2$, J = 6.0)</td>
<td>177.1 (C=S), 155.1 (C=N), 144.9 (C-1”), 136.5 (C-1’), 134.3 (C-4’), 132.8 (C-3’, C-6’), 129.8 (C-3”), 127.9 (C-4’), 127.7 (C-5”), 121.7 (C-2’), 119.9 (C-4’’), 115.6 (C-6’’), 67.9 (CH$_3$)</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>2g</td>
<td>4’-F</td>
<td>2”-Cl-4”-NO₂</td>
<td>8.3 (s, 1H$<em>{arom}$), 7.8 (d, 1H$</em>{arom}$, J = 6.5), 7.64 (d, 2H$<em>{arom}$, J = 8.1), 7.3 (d, 2H$</em>{arom}$, J = 7.0), 6.9 (d, 1H$_{arom}$, J = 8.0), 6.2 (bt, 1H, NH, J = 5.9), 5.9 (d, 2H, CH$_2$, J = 5.9)</td>
<td>177 (C=S), 166.4 (C-4’), 155.2 (C=N), 152.1 (C-1”), 143.1 (C-4’’), 135.1 (C-2’’), 127.1 (C-1’), 126.9 (C-3”), 124.5 (C-2”), 122.8 (C-5”), 116.6 (C-6”), 115.6 (C-3’, C-5’), 67.9 (CH$_3$), 25.4 (CH$_3$)</td>
</tr>
<tr>
<td>2h</td>
<td>4’-CH$_3$</td>
<td>2”-Cl-4”-NO₂</td>
<td>8.3 (s, 1H$<em>{arom}$), 7.8 (d, 1H$</em>{arom}$, J = 6.5), 7.64 (d, 2H$<em>{arom}$, J = 8.1), 6.4 (d, 2H$</em>{arom}$, J = 7.1), 6.9 (d, 1H$_{arom}$, J = 8.0), 6.0 (bt, 1H, NH, J = 6.1), 5.8 (d, 2H, CH$_2$, J = 6.1), 2.1 (s, 3H, CH$_3$)</td>
<td>177 (C=S), 155.6 (C=N), 152.9 (C-1”), 143.6 (C-4’), 136.16 (C-1’), 133.6 (C-4’’), 131.9 (C-3”), 131.7 (C-6’), 129.1 (C-5’), 125.6 (C-3”), 124.4 (C-2”), 122.1 (C-2’), 118.1 (C-5”), 115.1 (C-6”), 67.9 (CH$_3$), 25.4 (CH$_3$)</td>
</tr>
<tr>
<td>2i</td>
<td>4’-CH$_3$-3’,5’-(OCH$_3$)$_2$</td>
<td>2”-Cl-4”-NO₂</td>
<td>8.1 (s, 1H$<em>{arom}$), 7.7 (d, 1H$</em>{arom}$, J = 7.0), 7.65 (d, 1H$<em>{arom}$, J = 6.5), 6.8 (d, 2H$</em>{arom}$, J = 7.1), 6.0 (bt, 1H, NH, J = 6.1), 5.9 (d, 2H, CH$_2$, J = 5.9), 3.9 (s, 6H, OCH$_3$), 2.1 (s, 3H, CH$_3$)</td>
<td>177 (C=S), 160.1 (C-3’, C-5”), 156.6 (C=N), 152.1 (C-1”), 140.6 (C-4”), 129.8 (C-1’), 125.5 (C-3”), 124.8 (C-2”), 115.8 (C-6”), 114.7 (C-4”), 106.7 (C-2’, C-6’), 67.9 (CH$_3$), 56.6 (2-OCH$_3$) 25.4 (CH$_3$)</td>
</tr>
<tr>
<td>2j</td>
<td>3’,4’,5’-(OCH$_3$)$_3$</td>
<td>2”-Cl-4”-NO₂</td>
<td>8.2 (s, 1H$<em>{arom}$), 7.8 (d, 1H$</em>{arom}$, J = 6.71), 7.6 (d, 1H$<em>{arom}$, J = 5.8), 6.9 (d, 2H$</em>{arom}$, J = 7.1), 6.1 (bt, 1H, NH, J = 6.1), 5.8 (d, 2H, CH$_2$, J = 5.9), 3.9 (s, 9H, OCH$_3$)</td>
<td>177 (C=S), 160.1 (C-3’, C-5”), 156.6 (C=N), 152.1 (C-1”), 140.6 (C-4”), 129.8 (C-1’), 125.5 (C-3”), 124.8 (C-2”), 115.8 (C-6”), 114.7 (C-4”), 106.7 (C-2’, C-6’), 67.9 (CH$_3$), 56.6 (3-OCH$_3$)</td>
</tr>
</tbody>
</table>

In the mass spectrum of 5-[2’-Bromophenyl]-3-[2”-chlorophenyl-5”-nitroamino methyl]-1,3,4-oxadiazole-2-thione (2f) the molecular ion peak appear at m/z 439 which was also the most stable one (scheme-2.5).
Scheme 2.5: Mass fragmentation pattern of 5-[2′-Bromophenyl]-3-[2″-chlorophenyl-5″-nitroamino methyl]-1,3,4-oxadiazole-2-thione (2f).

The antibacterial assay was carried out using agar well diffusion method\[^{[134]}\]. Maximum inhibition was exhibited by compounds (2b) and (2g) when fluoro group was substituted at para position of the aryl group of oxadiazole. Other showed moderate activity. Compound (2a) did not show any activity against \textit{E. coli} while compound (2i) was inactive against both strains of bacteria Table 2.9.
Table 2.9: Antibacterial activities of 1,3,4-Oxadiazole-2-thiones (2a-2j).

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>E. coli</th>
<th>B. subtilis</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>–</td>
<td>12</td>
</tr>
<tr>
<td>2b</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>2c</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>2d</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>2e</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>2f</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>2g</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>2h</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>2i</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2j</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>-ve control (acetone)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>–</td>
<td>20</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>15</td>
<td>–</td>
</tr>
</tbody>
</table>

Concentration used: 5mg/mL; -: no activity.

Zone of inhibition (radius, mm)

In the antifungal activities maximum % age inhibition was observed by compound (2a) having bromo group at ortho position of the aryl group, (2d) having methyl and methoxy electron donating groups, (2h) having methyl group at para position, and (2j) having methoxy electron donating groups at aryl group of oxadiazole-2-thiones, by increasing the electron density at the aryl ring. All other compounds showed moderate percentage inhibition against yeast except compound (2i) which did not show any activity Table 2.10.
Table 2.10: Antifungal activities of 1,3,4-Oxadiazole-2-thiones (2a-2j).

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>\textit{S. cerevisiae} (ZI, cm)</th>
<th>\textit{S. cerevisiae} (PI, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>0.4</td>
<td>66.6</td>
</tr>
<tr>
<td>2b</td>
<td>0.8</td>
<td>33.3</td>
</tr>
<tr>
<td>2c</td>
<td>0.5</td>
<td>58.3</td>
</tr>
<tr>
<td>2d</td>
<td>0.4</td>
<td>66.6</td>
</tr>
<tr>
<td>2e</td>
<td>0.6</td>
<td>50</td>
</tr>
<tr>
<td>2f</td>
<td>0.6</td>
<td>50</td>
</tr>
<tr>
<td>2g</td>
<td>0.7</td>
<td>41.66</td>
</tr>
<tr>
<td>2h</td>
<td>0.3</td>
<td>75</td>
</tr>
<tr>
<td>2i</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2j</td>
<td>0.3</td>
<td>75</td>
</tr>
<tr>
<td>-ve control (acetone)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>1.2</td>
<td>100</td>
</tr>
</tbody>
</table>

Concentration used: 5mg/mL; -: no activity

ZI: zone of inhibition; PI: percent inhibition = 100-fungal growth in sample (cm) / fungal growth in control (cm) \times 100
All compounds were active for their phytotoxic activities as pale yellowing of the Physalis plant leaves was observed except compound (2h) with methyl group at para position Table 2.11.

**Table 2.11: Phytotoxic activity of 1,3,4-Oxadiazole-2-thiones (2a-2j).**

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Phytotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>2b</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>2c</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>2d</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>2e</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>2f</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>2g</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>2h</td>
<td>-</td>
</tr>
<tr>
<td>2i</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>2j</td>
<td>Pale yellow</td>
</tr>
</tbody>
</table>

Concentration used: 5mg/mL
2.4 Synthesis of 5-Aryl-1,2,4-triazole-3-thiones (3a-3f).

Substituted hydrazides were treated with 1.5 equivalents of potassium hydroxide and 1.5 equivalents of carbon disulfide in methanol to afford potassium salt of hydrazide which was then cyclized with 1.3 equivalents of hydrazine in ethanol \[^{[122]}\] to obtain the 1,2,4-triazole-3-thiones in 85-93 % yield (Scheme 2.6).

\[
\begin{align*}
&\text{R-COOH} \xrightarrow{\text{i- MeOH/ H}} \text{R-COOH} \xrightarrow{\text{ii- NH}_2\text{NH}_2} \text{R-NH}_2\text{NH}_2 \\
&\xrightarrow{\text{KOH (1.5 eq)}} \text{R-NH}_2\text{NH}_2 \xrightarrow{\text{CS}_2 (1.5 eq)} \text{R-} \xrightarrow{\text{MeOH/ 4 h reflux}} \text{N}_2\text{H}_4 (1.3 eq) \\
&\xrightarrow{\text{EtOH/ 7h reflux}} \text{N}_2\text{H}_4(NH)_S
\end{align*}
\]

Scheme 2.6: Synthesis of 5-Aryl-1,2,4-triazole-3-thiones.

In the IR spectra stretching were observed at 3214 cm\(^{-1}\) and 3091 cm\(^{-1}\) for NH and NH\(_2\) group of the triazole ring. Physical data and IR values are given in Table 2.12.

Table 2.12: Synthesis of 5-Aryl-1,2,4-triazole-3-thiones (3a-3f).

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>Yield (%)</th>
<th>M.P.(°C)</th>
<th>R(_f)</th>
<th>IR (cm(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>4'-F</td>
<td>93</td>
<td>146-147</td>
<td>0.7</td>
<td>3215, 3091, 1566, 1484, 1278</td>
</tr>
<tr>
<td>3b</td>
<td>4'-CH(_3)</td>
<td>89</td>
<td>158-159</td>
<td>0.6</td>
<td>3150, 3095, 2910, 1584, 1442</td>
</tr>
<tr>
<td>3c</td>
<td>3',4'- (OCH(_3))(_2)</td>
<td>92</td>
<td>218-219</td>
<td>0.4</td>
<td>3078, 3015, 2964, 1599, 1456, 1252</td>
</tr>
<tr>
<td>3d</td>
<td>3',5'- (OCH(_3))(_2)</td>
<td>85</td>
<td>175-176</td>
<td>0.6</td>
<td>3125, 3088, 2924, 1609, 1580, 1458</td>
</tr>
<tr>
<td>3e</td>
<td>4'-CH(_3)-3',5'- (OCH(_3))(_2)</td>
<td>90</td>
<td>245-246</td>
<td>0.5</td>
<td>3069, 3015, 2930, 1609, 1500</td>
</tr>
<tr>
<td>3f</td>
<td>3',4',5'- (OCH(_3))(_3)</td>
<td>92</td>
<td>198-199</td>
<td>0.4</td>
<td>3169, 3115, 1641, 1523, 1336</td>
</tr>
</tbody>
</table>

* Petroleum ether: Ethyl acetate (4:1)
In $^1$HNMR a signal at $\delta$ 11-12.9 for NH group and another signal at $\delta$ 4.7-5.5 ppm for NH$_2$ were observed. In $^{13}$CNMR the signal at $\delta$ 161 for C-5 and another signal at $\delta$ 177 ppm for C=S carbon of the triazole-3-thione were observed. $^1$HNMR and $^{13}$CNMR data of the triazole-3-thiones is given in the Table 2.13.

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>$^1$HNMR</th>
<th>$^{13}$CNMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>4'-F</td>
<td>7.89 (d, 2H$<em>{arom}$, $J = 8.9$), 7.24 (d, 2H$</em>{arom}$, $J = 8.76$), 5.7 (bs, 2H, NH), 2.3 (s, 3H, CH$_3$)</td>
<td>177 (C=S), 166.3 (C-4), 161.5 (C=N), 129.1 (C-2, C-6), 127.5 (C-1), 120.5 (C-3, C-5)</td>
</tr>
<tr>
<td>3b</td>
<td>4'-CH$_3$</td>
<td>7.89 (d, 2H$<em>{arom}$, $J = 9.6$), 7.38 (d, 2H$</em>{arom}$, $J = 8.4$), 5.5 (bs, 2H, NH), 2.3 (s, 3H, CH$_3$)</td>
<td>177 (C=S), 161 (C=N), 143 (C-4), 130.47 (C-3, C-5), 129.52 (C-2, C-6), 126.48 (C-1), 21.6 (CH$_3$)</td>
</tr>
<tr>
<td>3c</td>
<td>3',4'-(OCH$_3$)$_2$</td>
<td>7.60 (d, 1H$<em>{arom}$, $J = 8.5$), 7.3 (d, 1H$</em>{arom}$, $J = 8.4$), 6.5 (d, 1H$_{arom}$, $J = 8.4$), 5.5 (bs, 2H, NH), 3.9 (s, 9H, OCH$_3$)</td>
<td>177.2 (C=S), 161.1 (C=N), 155.7 (C-4), 151.4 (C-3), 126.6 (C-1), 121.7 (C-6), 117.5 (C-5), 112.4 (C-2), 61.9 (2OCH$_3$)</td>
</tr>
<tr>
<td>3d</td>
<td>3',5'-(OCH$_3$)$_2$</td>
<td>7.06 (d, 2H$<em>{arom}$, $J = 2.9$), 6.73 (t, 1H$</em>{arom}$, $J = 2.2$), 5.54 (bs, 2H, NH), 3.9 (s, 6H, 2×OCH$_3$)</td>
<td>177 (C=S), 163.45 (C-3, C-5), 161 (C=N), 133.89 (C-1), 106.6 (C-2, C-6), 103 (C-4), 64.34 (2OCH$_3$)</td>
</tr>
<tr>
<td>3e</td>
<td>4'-CH$_3$-3',5'- (OCH$_3$)$_2$</td>
<td>6.9 (s, 2H$_{arom}$), 5.54 (bs, 2H, NH), 3.9 (s, 6H, 2×OCH$_3$), 2.1 (s, 3H, CH$_3$)</td>
<td>177.0 (C=S), 162.1 (C=N), 161.5 (C-3, C-5), 130.3 (C-1), 119.1 (C-4), 56.6 (2×OCH$_3$), 24.6 (CH$_3$)</td>
</tr>
<tr>
<td>3f</td>
<td>3',4',5'- (OCH$_3$)$_3$</td>
<td>7.16 (s, 2H$_{arom}$), 5.54(bs, 2H, NH), 3.9 (s, 9H,3×OCH$_3$)</td>
<td>177.4 (C=S), 161.5 (C=N), 152.4 (C-3, C-5), 150.2 (C-4), 125.5 (C-1), 106.1 (C-2, C-6), 62.6 (3OCH$_3$)</td>
</tr>
</tbody>
</table>

In mass spectrum of 5-(3',5'-dimethoxyphenyl)-1,2,4-triazole-3-thione (3d) the molecular ion peak appear at $m/z$ 252 a.m.u. and was found to be the most abundant (Scheme-2.7).
Scheme 2.7: Mass fragmentation pattern of 5-(3',5'-Dimethoxyphenyl)-1,2,4-triazole-3-thione(3d).

In antibacterial bioassay [134] the maximum inhibition was observed for compounds (3d) and (3e), when two electron donating methoxy groups were substituted at 3 and 5 positions of aryl group of the triazole, against B. Subtilis. Compound (3e) also showed good inhibition against the growth of E. coli Table 2.14.
Table 2.14: Antibacterial activities of 5-Aryl-1,3,4-triazole-2-thiones (3a-3f).

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>E. coli</th>
<th>B. subtilis</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>3b</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>3c</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>3d</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>3e</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>3f</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>-ve control (Acetone)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>–</td>
<td>20</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>15</td>
<td>–</td>
</tr>
</tbody>
</table>

Concentration used: 5mg/mL; -: no activity.

Zone of inhibition (radius, mm)

In case of antifungal activity\textsuperscript{[134]} maximum % age inhibition was observed for compound (3b) having a methyl an electron donating group at para position and (3f) having three methoxy electron donating groups with increasing electron density at aryl group of the triazole nucleus. While other triazole amines showed moderate activity Table 2.15.
Table 2.15: Antifungal activities of 5-Aryl-1,3,4-triazole-2-thiones (3a-3f).

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>S. cerevisiae (ZI, cm)</th>
<th>S. cerevisiae (PI, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>1.0</td>
<td>16.66</td>
</tr>
<tr>
<td>3b</td>
<td>0.5</td>
<td>58.33</td>
</tr>
<tr>
<td>3c</td>
<td>0.8</td>
<td>33.3</td>
</tr>
<tr>
<td>3d</td>
<td>0.8</td>
<td>33.3</td>
</tr>
<tr>
<td>3e</td>
<td>0.7</td>
<td>41.66</td>
</tr>
<tr>
<td>3f</td>
<td>0.6</td>
<td>50</td>
</tr>
<tr>
<td>-ve control</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Std</td>
<td>1.2</td>
<td>100</td>
</tr>
</tbody>
</table>

Concentration used: 5mg/mL; -: no activity

ZI: zone of inhibition; PI: percent inhibition = 100-fungal growth in sample (cm) / fungal growth in control (cm) × 100

All triazole-2-thione amines were active for pale yellowing of the leaves during the course of their phytotoxic activities except the compounds (3b) and (3f) Table 2.16.

Table 2.16: Phytotoxic activities of 1,2,4-Triazole-3-thione amines (3a-3f).

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>Phytotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>3b</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>3c</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>3d</td>
<td>–</td>
</tr>
<tr>
<td>3e</td>
<td>Blackening</td>
</tr>
<tr>
<td>3f</td>
<td>–</td>
</tr>
</tbody>
</table>

Concentration used: 5mg/mL
2.5 Synthesis of 1-Aroyl-3,5-dimethylpyrazoles (4a-4h)

Substituted pyrazoles can be obtained by cyclization of hydrazides with 1,3-diketones in ethanol but reaction time is very long \(^{[76, 123a]}\) in microwave accelerated reaction substituted hydrazides were irradiated with acetyl acetone in the absence of solvents to afford 3,5-disubstituted pyrazoles in 78-91 % yield to save time \(^{[123]}\) (Scheme- 2.8).

![Scheme 2.8: Synthesis of 1-Aroyl-3,5-dimethylpyrazoles.](image)

In the IR spectra disappearance of stretching for NH and NH\(_2\) groups and appearance of stretching for CH\(_3\) group at 2860-2950 cm\(^{-1}\) was observed. Physical and IR data is given in the Table 2.17.

**Table 2.17: Physical data of 1-Aroyl-3,5-dimethylpyrazoles (4a-4h).**

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>Yield (%)</th>
<th>M.P (°C)</th>
<th>R(_f)*</th>
<th>IR (cm(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>4'-CH(_3)</td>
<td>78</td>
<td>Oil</td>
<td>0.5</td>
<td>3115, 2950, 2910, 1680, 1584, 1432</td>
</tr>
<tr>
<td>4b</td>
<td>4'-F</td>
<td>78</td>
<td>135-136</td>
<td>0.9</td>
<td>3110, 2930, 2910, 1671, 1615, 1582, 1472</td>
</tr>
<tr>
<td>4c</td>
<td>2'-Br</td>
<td>69</td>
<td>Oil</td>
<td>0.5</td>
<td>3103, 2910, 2930, 1880, 1601, 1584</td>
</tr>
<tr>
<td>4d</td>
<td>3',4'-{(OCH(_3))}_2</td>
<td>84</td>
<td>105-106</td>
<td>0.4</td>
<td>3103, 2958, 2929, 1680, 1601, 1584</td>
</tr>
<tr>
<td>4e</td>
<td>3',5'-{(OCH(_3))}_2</td>
<td>74</td>
<td>Oil</td>
<td>0.7</td>
<td>3103, 2958, 2929, 1679, 1615, 1580, 1477</td>
</tr>
<tr>
<td>4f</td>
<td>4'-CH(_3)-3',5'-{(OCH(_3))}_2</td>
<td>87</td>
<td>81-82</td>
<td>0.2</td>
<td>3112, 2970, 2916, 1680, 1605, 1580, 1465</td>
</tr>
<tr>
<td>4g</td>
<td>3',4',5'-{(OCH(_3))}_3</td>
<td>91</td>
<td>185-186</td>
<td>0.2</td>
<td>3015, 2960, 2954, 1677, 1595, 1480</td>
</tr>
<tr>
<td>4h</td>
<td>1'-Ph-2,4-dienyl</td>
<td>83</td>
<td>81-82</td>
<td>0.4</td>
<td>3115, 2950, 2910, 1680, 1620, 1594</td>
</tr>
</tbody>
</table>

* Petroleum ether: Ethyl acetate (7:3)
In $^1$HNMR a characteristic singlet was observed for H-4 proton of the pyrazole ring at $\delta$ 5.9-6.6 ppm. In addition to characteristic peaks, the signals for protons of two methyl groups were observed at $\delta$ 2.7 and $\delta$ 2.2 ppm. In $^{13}$CNMR signal at $\delta$ 104-106.1 ppm for C-4 carbon and for methyl groups were observed at $\delta$ 26 and $\delta$ 17 ppm. $^1$HNMR and $^{13}$CNMR data is given in Table 2.18.

Table 2.18: $^1$HNMR and $^{13}$CNMR data of 1-Aroyl-3,5-dimethylpyrazoles (4a-4h).
In the mass spectrum of 1-(3',5'-dimethoxyphenyl)-3,5-dimethylpyrazole (4e) molecular ion peak was observed at $m/z$ 258 a.m.u. and the base peak was observed at $m/z$ 163 a.m.u. respectively. (Scheme-2.9)

Scheme 2.9: Mass fragmentation pattern of 1-(3',5'-Dimethoxyphenyl)-3,5-dimethylpyrazole(4e)

Compound (4b) having fluoro group at para position of the aroyl ring showed maximum inhibition against both strain of bacteria, while all other showed good to moderate antibacterial activity Table 2.19.
Table 2.19: Antibacterial activities of 1-Aryl-3,5-dimethylpyrazoles (4a-4h).

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>E. coli</th>
<th>B. subtilis</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>4b</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>4c</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4d</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>4e</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>4f</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>4g</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>4h</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>-ve control (acetone)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>–</td>
<td>20</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>15</td>
<td>–</td>
</tr>
</tbody>
</table>

Concentration used: 5mg/mL; -: no activity.
Zone of inhibition (radius, mm)

In case of antifungal activities[^134] the maximum % age inhibition was observed for compound (4a) with methyl group substituted at para position and (4d) having two methoxy groups at 3 and 5 position of aryl ring while other compounds showed moderate activity Table 2.20.
Table 2.20: Antifungal activities of 1-Aryl-3,5-dimethylpyrazoles (4a-4h).

![Chemical Structure]

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>S. cerevisiae (ZI, cm)</th>
<th>S. cerevisiae (PI, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>0.4</td>
<td>66.66</td>
</tr>
<tr>
<td>4b</td>
<td>0.9</td>
<td>25</td>
</tr>
<tr>
<td>4c</td>
<td>0.6</td>
<td>50</td>
</tr>
<tr>
<td>4d</td>
<td>0.4</td>
<td>66.66</td>
</tr>
<tr>
<td>4e</td>
<td>0.9</td>
<td>25</td>
</tr>
<tr>
<td>4f</td>
<td>0.7</td>
<td>41.66</td>
</tr>
<tr>
<td>4g</td>
<td>0.5</td>
<td>58.33</td>
</tr>
<tr>
<td>4h</td>
<td>0.5</td>
<td>58.33</td>
</tr>
<tr>
<td>-ve control (acetone)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>1.2</td>
<td>100</td>
</tr>
</tbody>
</table>

Concentration used: 5mg/mL; -: no activity

ZI: zone of inhibition; PI: percent inhibition = 100-fungal growth in sample (cm) / fungal growth in control (cm) × 100

All compounds were active against the growth of Physalis except (4a), (4f) and (4h) Table 2.21.
Table 2.21: Phytotoxic activity of 3,5-Dimethyl pyrazole (4a-4h).

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Phytotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>–</td>
</tr>
<tr>
<td>4b</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>4c</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>4d</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>4e</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>4f</td>
<td>–</td>
</tr>
<tr>
<td>4g</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>4h</td>
<td>–</td>
</tr>
</tbody>
</table>

Concentration used: 5mg/mL

2.6 Synthesis of 1-Aroyl-3,5-diarylpyrazolines (5a-5h)

For the synthesis of 3,5-diaryl pyrazolines substituted hydrazides were condensed with substituted chalcones [124a] in the presence of piperidine in ethanol [80, 124b] in 78-92% yield (Scheme-2.10).

Scheme 2.10: Synthesis of 1-Aroyl-3,5-diarylpyrazolines.

In IR spectra stretching for NH group at 3021-3310 cm\(^{-1}\) and stretching of the pyrazoline ring at 2800-2934 cm\(^{-1}\) was observed. Physical and IR data is given in Table 2.22.
Table 2.22: Physical data of 1-Aroyl-3,5-diarylpyrazolines (5a-5h).

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>R’</th>
<th>R”</th>
<th>Yield (%)</th>
<th>M.P. (°C)</th>
<th>Rf*</th>
<th>IR(cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>3',5'-(OCH₃)₂</td>
<td>2''-OH-5''-CH₃</td>
<td>4'''-Cl</td>
<td>92</td>
<td>117-118</td>
<td>0.9</td>
<td>3315, 2932, 2812, 1712, 1621, 1596</td>
</tr>
<tr>
<td>5b</td>
<td>3',4',5'-(OCH₃)₃</td>
<td>2''-OH-5''-CH₃</td>
<td>4'''-Cl</td>
<td>85</td>
<td>101-102</td>
<td>0.9</td>
<td>3311, 2965, 2913, 1713, 1622, 1583, 1431</td>
</tr>
<tr>
<td>5c</td>
<td>4'-CH₃-3',5'-(OCH₃)₂</td>
<td>2''-OH-5''-CH₃</td>
<td>4'''-Cl</td>
<td>78</td>
<td>141-142</td>
<td>0.9</td>
<td>3017, 2965, 2911, 1707, 1621, 1597, 1433</td>
</tr>
<tr>
<td>5d</td>
<td>1'-Ph-2,4-dienyl</td>
<td>2''-OH-5''-CH₃</td>
<td>4'''-Cl</td>
<td>85</td>
<td>Oil</td>
<td>0.9</td>
<td>3012, 2966, 2917, 1722, 1665, 1595</td>
</tr>
<tr>
<td>5e</td>
<td>3',4',5'-(OCH₃)₃</td>
<td>2''-OH-5''-Br</td>
<td>4'''-OCH₃</td>
<td>80</td>
<td>170-171</td>
<td>0.8</td>
<td>3121, 2964, 2911, 1706, 1675, 1595</td>
</tr>
<tr>
<td>5f</td>
<td>4'-CH₃-3',5'-(OCH₃)₂</td>
<td>2''-OH-5''-Br</td>
<td>4'''-OCH₃</td>
<td>83</td>
<td>Oil</td>
<td>0.6</td>
<td>3021, 2963, 2943, 1700, 1686, 1595, 1435</td>
</tr>
<tr>
<td>5g</td>
<td>3',4'-(OCH₃)₂</td>
<td>2''-OH-5''-Br</td>
<td>4'''-OCH₃</td>
<td>78</td>
<td>160-161</td>
<td>0.8</td>
<td>3021, 2963, 2919, 1742, 1656, 1595, 1441</td>
</tr>
<tr>
<td>5h</td>
<td>1'-Ph-2,4-dienyl</td>
<td>2''-OH-5''-Br</td>
<td>4'''-OCH₃</td>
<td>82</td>
<td>Oil</td>
<td>0.9</td>
<td>3023, 2961, 2920, 1698, 1656, 1595</td>
</tr>
</tbody>
</table>

* Petroleum ether: Ethyl acetate (3:2)

In ¹H NMR spectra due to the presence of a stereogenic centre at 5 position of the pyrazoline ring, a doublet of a doublet was observed at δ 5.2-5.4 ppm for 5H proton. Two other doublets of doublets were observed at δ 4.1-4.25 and at δ 3.9-4.0 ppm for 4Ha and 4Hb protons of the pyrazoline ring. In ¹³C NMR spectra signal for C-5 carbon at δ 59-62 and that for C-4 carbon at δ 43 ppm were observed. ¹H and ¹³C NMR data of the pyrazolines is given in the Table 2.23.
Table 2.23: $^1$HNMR and $^{13}$CNMR data of 1-Aroyl-3,5-diarylpyrazolines (5a-5h).

![Chemical structure](image_url)

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>R'</th>
<th>R''</th>
<th>$^1$HNMR</th>
<th>$^{13}$CNMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>$3',5'$- (OCH$_3$)$_2$</td>
<td>2&quot;-OH-5&quot;'-CH$_3$</td>
<td>4&quot;'-Cl</td>
<td>6.9-7.7 (m, 10H$_{arom}$), 5.2 (dd, H$_5$, J = 9.0), 4.4 (dd, H$_4a$, J = 5.8, 3.1), 4.2 (dd, H$_4b$, J = 6.1, 3.3), 3.9 (s, 6H), 2.3 (s, 3H)</td>
<td>168 (CO), 162 (C-3), 61 (C-5), 43 (C-4)</td>
</tr>
<tr>
<td>5b</td>
<td>$3',4',5'$- (OCH$_3$)$_3$</td>
<td>2&quot;-OH-5&quot;'-CH$_3$</td>
<td>4&quot;'-Cl</td>
<td>6.9-7.7 (m, 12H$_{arom}$), 5.2 (dd, H$_5$, J = 9.6, 3.9), 4.3 (dd, H$_4a$, J = 5.7, 3.3), 4.2 (dd, H$_4b$, J = 6.1, 3.3), 3.9 (s, 9H), 2.42 (s, 3H)</td>
<td>167 (CO), 163 (C-3), 59 (C-5), 43 (C-4)</td>
</tr>
<tr>
<td>5c</td>
<td>4&quot;'-CH$_3$-3',5'- (OCH$_3$)$_2$</td>
<td>2&quot;-OH-5&quot;'-CH$_3$</td>
<td>4&quot;'-Cl</td>
<td>6.9-7.7 (m, 12H$_{arom}$), 5.4 (dd, H$_5$, J = 9.6, 3.3), 4.2 (dd, H$_4a$, J = 5.7, 3.3), 3.9 (s, 9H), 2.348 (s, 3H)</td>
<td>170 (CO), 161 (C-3), 58 (C-5), 43 (C-4)</td>
</tr>
<tr>
<td>5d</td>
<td>1'-Ph-2,4-dienyl</td>
<td>2&quot;-OH-5&quot;'-CH$_3$</td>
<td>4&quot;'-Cl</td>
<td>6.6-7.30 (m, 12H$_{arom}$), 7.4 (d, 1H, H$_5$, J = 6.3), 7.1 (d, 1H, H$_6$, J = 3.4), 6.9 (d, 1H, H$_7$, J = 4.2), 6.6 (d, 1H, H$_8$, J = 3.6), 5.4 (dd, H$<em>5$, J = 9.6, 3.3), 4.1 (dd, H$<em>4a$, J = 5.7, 3.3), 3.9 (s, 2H$</em>{arom}$), 2.5 (s, 3H$</em>{CH_3}$)</td>
<td>166 (CO), 157 (C-3), 61 (C-5), 43 (C-4)</td>
</tr>
<tr>
<td>5e</td>
<td>$3',4',5'$- (OCH$_3$)$_3$</td>
<td>2&quot;-OH-5&quot;'-Br</td>
<td>4&quot;'-OCH$_3$</td>
<td>6.9-7.7 (m, 9H$_{arom}$), 5.1 (dd, H$_5$, J = 9.0, 3.3), 4.24 (dd, H$_4a$, J = 5.7, 3.6), 4.1 (dd, H$<em>4b$, J = 5.7, 3.6), 3.9 (s, 12H$</em>{OCH_3}$)</td>
<td>167 (CO), 162 (C-3), 60 (C-5), 43 (C-4)</td>
</tr>
<tr>
<td>5f</td>
<td>4&quot;'-CH$_3$-3',5'- (OCH$_3$)$_2$</td>
<td>2&quot;-OH-5&quot;'-Br</td>
<td>4&quot;'-OCH$_3$</td>
<td>6.9-7.7 (m, 10H$<em>{arom}$), 5.1 (dd, H$<em>5$, J = 9.0, 3.3), 4.24 (dd, H$<em>4a$, J = 5.7, 3.6), 3.9 (s, 9H$</em>{OCH_3}$), 2.52 (s, 3H$</em>{CH_3}$), 1.6 (s, 3H$</em>{OCH_3}$)</td>
<td>168 (CO), 161 (C-3), 59 (C-5), 43 (C-4)</td>
</tr>
<tr>
<td>5g</td>
<td>$3',4'$- (OCH$_3$)$_2$</td>
<td>2&quot;-OH-5&quot;'-Br</td>
<td>4&quot;'-OCH$_3$</td>
<td>6.9-7.7 (m, 10H$_{arom}$), 5.1 (dd, H$_5$, J = 9.0, 3.3), 4.2 (dd, H$_4a$, J = 5.1, 3.6), 4.0 (dd, H$<em>4b$, J = 5.1, 3.6), 3.9 (s, 9H$</em>{OCH_3}$)</td>
<td>168 (CO), 162 (C-3), 61 (C-5), 43 (C-4)</td>
</tr>
<tr>
<td>5h</td>
<td>1'-Ph-2,4-dienyl</td>
<td>2&quot;-OH-5&quot;'-Br</td>
<td>4&quot;'-OCH$_3$</td>
<td>6.6-7.30 (m, 12H$_{arom}$), 7.4 (d, 1H, H$_5$, J = 6.3), 7.1 (d, 1H, H$_6$, J = 3.4), 6.9 (d, 1H, H$_7$, J = 4.2), 6.6 (d, 1H, H$_8$, J = 3.6), 5.4 (dd, H$_5$, J = 9.6, 3.3), 4.1 (dd, H$_4a$, J = 5.7, 3.3), 3.9 (dd, H$_4b$, J = 5.7, 3.3)</td>
<td>168 (CO), 162 (C-3), 61 (C-5), 43 (C-4)</td>
</tr>
</tbody>
</table>
In mass fragmentation pattern of pyrazolines, the molecular ion peak, and base peak derived from benzoyl group were observed. In mass fragmentation of 1-4’-methyl-3’,5’-dimethoxybenzoyl-3-(2”-hydroxy-5”-methylaryl)-5-(4”’-chloroaryl)-pyrazoline (5e) molecular ion peak was observed at \( m/z \) 464 a.m.u. and base peak was observed at \( m/z \) 179 a.m.u. (Scheme -2.11).

![Scheme 2.11: Mass fragmentation pattern of 1-4’-Methyl-3’,5’-dimethoxy benzoyl-3-(2”-hydroxy-5”-methyl aryl)-5-(4”’-chloroaryl)pyrazoline (5e).](image)

In the antibacterial bioassay maximum inhibition was observed by compounds (5a) and (5c) due to the presence of two methoxy electron donating groups at 3 and 5 positions of ring ‘A’ and a para chloro group on ring ‘C’ of the pyrazoline Table 2.24.
Table 2.24: Antibacterial activities of 1-Aroyl-3,5-disubstituted aryl pyrazolines (5a-5h).

![Chemical Structure]

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>E. coli</th>
<th>B. subtilis</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>5b</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>5c</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>5d</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>5e</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>5f</td>
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<td>14</td>
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<td>5g</td>
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<td>-</td>
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<tr>
<td>Kanamycin</td>
<td>-</td>
<td>20</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>15</td>
<td>-</td>
</tr>
</tbody>
</table>

Concentration used: 5mg/mL; :- no activity.
Zone of inhibition (radius, mm)

In case of antifungal activities \(^{[134]}\) the maximum % age inhibition was observed for compounds (5a) and (5c) due to the presence of two methoxy electron donating groups at 3 and 5 positions of ring ‘A’ and para chloro group on ring ‘C’ of the pyrazoline while all other pyrazolines showed moderate inhibition against yeast cells.

Table 2.25.
Table 2.25: Antifungal activities of 1-Aroyl-3,5-disubstituted aryl pyrazolines (5a-5h).

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>S. cerevisiae (ZI, cm)</th>
<th>S. cerevisiae (PI, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>0.4</td>
<td>66.66</td>
</tr>
<tr>
<td>5b</td>
<td>0.5</td>
<td>58.33</td>
</tr>
<tr>
<td>5c</td>
<td>0.4</td>
<td>66.6</td>
</tr>
<tr>
<td>5d</td>
<td>0.8</td>
<td>33.3</td>
</tr>
<tr>
<td>5e</td>
<td>0.9</td>
<td>25</td>
</tr>
<tr>
<td>5f</td>
<td>0.5</td>
<td>58.33</td>
</tr>
<tr>
<td>5g</td>
<td>0.5</td>
<td>58.3</td>
</tr>
<tr>
<td>5h</td>
<td>0.4</td>
<td>66.6</td>
</tr>
<tr>
<td>5i</td>
<td>0.7</td>
<td>41.6</td>
</tr>
<tr>
<td>-ve control (acetone)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>1.2</td>
<td>100</td>
</tr>
</tbody>
</table>

Concentration used: 5mg/mL; -: no activity

ZI: zone of inhibition; PI: percent inhibition = 100-fungal growth in sample (cm) / fungal growth in control (cm) × 100

In case of phytotoxic activities all of the pyrazolines were able to extract magnesium ion from the chlorophyll molecule in order to inhibit the growth of plant by ceasing photosynthesis during their phytotoxic assay Table 2.26.
Table 2.26: Phytotoxic activity of 3,5-Diaryl pyrazoline (5a-5h).

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>Phytotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>5b</td>
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<td>5c</td>
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<tr>
<td>5d</td>
<td>Pale yellow</td>
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<td>5e</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>5f</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>5g</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>5h</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>5i</td>
<td>Pale yellow</td>
</tr>
</tbody>
</table>

Concentration used: 5mg/mL

2.7 Synthesis of some 5-Chloro-1-arylisochromans (6a-6j)

Acid catalyzed oxa-Pictet Spengler reaction is used for the synthesis of 1-arylisochroman by refluxing in methanol \cite{126a} but the reaction time varies from 1-day to several and sometimes no reaction takes place \cite{126b, c}. Microwave accelerated synthesis saves time and solvents. The chain lengthening of the 2-chlorobenzoic acid was carried out to get 2-chlorophenylacetic acid \cite{118, 125a-d} which was treated with methanol in acidic media to get methyl ester \cite{118} upon reduction with 6 equivalents of sodium borohydride (NaBH₄) in tetrahydrofuran (THF) and methanol \cite{125a} to get 2-chlorophenyl ethanol used as a precursor for the synthesis of 1-arylisochromans. 2-Chlorophenyl ethanol was irradiated for 12-14 s with substituted aldehydes in the presence of p-TsOH to get 1-isochromans \cite{126} in 76-99 % yield. (Scheme 2.12)
Scheme 2.12: Synthesis of 5-Chloro-1-arylisochroman.

IR spectra show C-O bond stretching at 1050-1116 cm\(^{-1}\). The physical data of 1-arylisochromans with IR data is given in Table 2.27.

Table 2.27: Physical data of 5-Chloro-1-arylisochroman (6a-6j).

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>Yield (%)</th>
<th>M.P. (°C)</th>
<th>R_\text{f}*</th>
<th>IR (cm(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>H</td>
<td>99</td>
<td>95-96</td>
<td>0.3</td>
<td>2924, 2342, 1724, 1116, 713, 456</td>
</tr>
<tr>
<td>6b</td>
<td>4'-F</td>
<td>88</td>
<td>Oil</td>
<td>0.7</td>
<td>2924, 2342, 1723, 713</td>
</tr>
<tr>
<td>6c</td>
<td>2'-Cl</td>
<td>99</td>
<td>123-124</td>
<td>0.8</td>
<td>2926, 1691, 1589, 1476, 1315, 1050</td>
</tr>
<tr>
<td>6d</td>
<td>3'-Cl</td>
<td>87</td>
<td>Oil</td>
<td>0.8</td>
<td>2926, 1691, 1589, 1476, 1315, 1051</td>
</tr>
<tr>
<td>6e</td>
<td>3'-Br</td>
<td>90</td>
<td>Oil</td>
<td>0.7</td>
<td>2926, 1691, 1582, 1478, 1143, 1051</td>
</tr>
<tr>
<td>6f</td>
<td>4'-Br</td>
<td>98</td>
<td>Oil</td>
<td>0.9</td>
<td>2925, 1693, 1589, 1467, 1367, 1100</td>
</tr>
<tr>
<td>6g</td>
<td>4'-OCH(_3)</td>
<td>98</td>
<td>Oil</td>
<td>0.4</td>
<td>2926, 1694, 1581, 1476, 1315, 1112,</td>
</tr>
<tr>
<td>6h</td>
<td>3'-OH-4'-OCH(_3)</td>
<td>89</td>
<td>67-68</td>
<td>0.4</td>
<td>3410, 2921, 1315, 1050</td>
</tr>
<tr>
<td>6i</td>
<td>3',4',5'-(OCH(_3)) (_3)</td>
<td>76</td>
<td>127-128</td>
<td>0.2</td>
<td>1691, 1589, 1476, 1315, 1266, 1051</td>
</tr>
<tr>
<td>6j</td>
<td>1'-furfuryl</td>
<td>69</td>
<td>118-119</td>
<td>0.2</td>
<td>2359, 1634, 1617, 1271, 633</td>
</tr>
</tbody>
</table>

* Petroleum ether: Ethyl acetate (3:2)
In $^1$HNMR a characteristic singlet was observed at $\delta$ 5.47-5.7 ppm for H-1 proton of the isochroman ring. In $^{13}$CNMR the peak for C-1 observed at $\delta$ 78-79 ppm. $^1$HNMR and $^{13}$CNMR data of 1-arylisochromans is given in Table 2.28.

**Table 2.28: $^1$HNMR and $^{13}$CNMR data of 5-Chloro-1-arylisochroman (6a-6j).**

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>$^1$HNMR</th>
<th>$^{13}$CNMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>H</td>
<td>7.41–8.15 (m, 3H, Ar), 7.27 (s, 5H, Ar), 5.50 (s, 1H, C-1), 4.52 (t, 2H, $J = 6.6$, CH$_2$O), 3.24 (t, $J = 7.2$, 2H, CH$_2$CH$_2$)</td>
<td>141, 134, 133.8, 133, 129 (C-3’, C-5’), 128 (C-2’, C-6’), 127 (C-7), 126 (C-6, C-8), 78, 64, 28</td>
</tr>
<tr>
<td>6b</td>
<td>4’-F</td>
<td>7.1–7.43 (m, 3H, Ar), 5.77 (s, 1 H, C-1), 4.57 (t, 2H, $J = 6.9$, CH$_2$O), 3.71 (t, $J = 6.9$, 2H, CH$_2$CH$_2$)</td>
<td>160 (C-4’), 135.9 (C-1), 134.9 (C-9), 133.2 (C-10), 132 (C-5), 129 (C-2’, C-6’), 114 (C-3, C-5), 79 (C-1), 65 (C-3), 26 (C-4)</td>
</tr>
<tr>
<td>6c</td>
<td>2’-Cl</td>
<td>7.25–8.05 (m, 7ArH), 5.52 (s, 1H), 3.93 (t, 2H, $J = 6.9$ CH$_2$O), 3.25 (t, $J = 6.9$, 2H, ArCH$_2$)</td>
<td>140 (C-1’), 135 (C-9), 134 (C-5, C-2’), 133 (C-10), 129 (C-3’, C-6’), 127 (C-5’, C-7), 126 (C-6, C-8), 71 (C-1), 65 (C-3), 24 (C-4)</td>
</tr>
<tr>
<td>6d</td>
<td>3’-Cl</td>
<td>7.15–7.88 (m, 7ArH), 5.51 (s, 1H), 4.59 (t, 2H, $J = 6.9$ CH$_2$O), 3.71 (t, $J = 6.9$, 2H, ArCH$_2$)</td>
<td>142 (C-1’), 134.8 (C-3’), 134.2 (C-9), 133.4 (C-5), 133 (C-10), 130 (C-5’), 129 (C-2’), 127 (C-6), 126 (C-6, C-6’), 71 (C-1), 65 (C-3), 24 (C-4)</td>
</tr>
</tbody>
</table>
In mass fragmentation pattern of 1-arylisochromans molecular ion undergoes Retro-Diels Alder fragmentation to give a characteristic fragment. In mass fragmentation pattern of 1-m-chrophenyl -5-choroisochroman (6c) gives the molecular ion peak at m/z 279, 280, a.m.u. and the most abundant peak was observed at m/z 248 a.m.u. by the removal of a neutral formanyl group from 1-arylisochroman ring (Scheme -2.13).
Scheme 2.13: Mass fragmentation pattern of 1-m-Chrophenyl isochroman (6c).

Maximum inhibition was observed for compound (6c) having chloro group substituted at 2 position of 1-phenyl group of isochroman. Compound (6e) with bromo group at meta position of 1-phenyl of isochroman showed maximum inhibition against the growth of *E. coli* Table 2.29.
Table 2.29: Antibacterial activities of 1-Aryl-5-chloroisochromans (6a-6j).

![Chemical Structure]

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>E. coli</th>
<th>B. subtilis</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>6b</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>6c</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>6d</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>6e</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>6f</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>6g</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>6h</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>6i</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>6j</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>-ve control(acetone)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>-</td>
<td>20</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>15</td>
<td>-</td>
</tr>
</tbody>
</table>

Concentration used: 5mg/mL; -: no activity.
Zone of inhibition (radius, mm)

In case of antifungal activities \[^{134}\] maximum % age inhibition was observed by compounds: (6a) with no substitution, (6d) having chloro group substituted at meta position, and (6g) having methoxy group substituted at para position. While all other compounds showed good to moderate inhibition Table 2.30.
Table 2.30: Antifungal activities of 1-Aryl-5-chloroisochromans (6a-6j).

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th><em>S. cerevisiae</em> (ZI, cm)</th>
<th><em>S. cerevisiae</em> (PI, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>0.6</td>
<td>50</td>
</tr>
<tr>
<td>6b</td>
<td>1.1</td>
<td>8.3</td>
</tr>
<tr>
<td>6c</td>
<td>0.9</td>
<td>25</td>
</tr>
<tr>
<td>6d</td>
<td>0.6</td>
<td>50</td>
</tr>
<tr>
<td>6e</td>
<td>0.9</td>
<td>25</td>
</tr>
<tr>
<td>6f</td>
<td>1.0</td>
<td>16.6</td>
</tr>
<tr>
<td>6g</td>
<td>0.5</td>
<td>58.3</td>
</tr>
<tr>
<td>6h</td>
<td>0.6</td>
<td>50</td>
</tr>
<tr>
<td>6i</td>
<td>1.0</td>
<td>16.6</td>
</tr>
<tr>
<td>6j</td>
<td>0.8</td>
<td>33.3</td>
</tr>
<tr>
<td>-ve control (acetone)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>1.2</td>
<td>100</td>
</tr>
</tbody>
</table>

Concentration used: 5mg/mL; -: no activity

ZI: zone of inhibition; PI: percent inhibition = 100-fungal growth in sample (cm) / fungal growth in control (cm) × 100

In case of phytotoxic studies compounds: (6a), (6c), (6g), (6h) and (6j) did not show any phytotoxic activity, no blackening and pale yellowing was observed Table 2.31.
Table 2.31: Phytotoxic activity of 5-Chloro1-isochroman (6a-6j).

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Phytotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>-</td>
</tr>
<tr>
<td>6b</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>6c</td>
<td>-</td>
</tr>
<tr>
<td>6d</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>6e</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>6f</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>6g</td>
<td>-</td>
</tr>
<tr>
<td>6h</td>
<td>-</td>
</tr>
<tr>
<td>6i</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>6j</td>
<td>-</td>
</tr>
</tbody>
</table>

Concentration used: 5mg/mL; -: no activity
2.8 Synthesis and deprotection of N-substituted morpholines (7a-e)

Aggarwal’s group was working on the chemistry of vinyl sulphonium salt \(^{[127a]}\) which was used for the synthesis of N-substituted morpholines with good yields. Although this reaction was pretty good and was an excellent approach for the synthesis of desire product, the problem in using vinyl sulphonium salt was its oily state so instead of vinyl sulphonium salt its one step crystalline precursor bromo ethyl sulphonium salt was used \(^{[129]}\) a series of substituted morpholines were synthesized by using bromoethyl sulphonium salt the new task was protection of \(\alpha\)-amino alcohols with \(p\)-tolylmethysulfinate. For the synthesis of N-substituted morpholines first step was the protection of \(\alpha\)-amino alcohols with \(p\)-tolylmethysulfinate \(^{[127]}\) in the presence of 2.2 equivalents of \(n\)-butyl lithium in tetrahydrofuran to get N-substituted sulfanilamides \(^{[128]}\) in 37-97 \% yield. \(N\)-p-tolylmethysulfanilamides were cyclized with bromoethyl diphenyl sulfonylumtriflate in the presence of four equivalents of sodium hydride\(^{[129]}\) in dichloromethane on overnight stirring to get N-substituted morpholines which were deprotected by stirring for two hours with 2N hydrochloric acid \(^{[130]}\) (Scheme 2.14).

Scheme 2.14: Synthesis and deprotection of N-substituted morpholines.
Due to the presence of the stereogenic centre diastereomer were observed in 2:1 ratio. Physical data of sulfanilamides is presented in Table 2.32.

Table 2.32: Physical data of N-substituted sulphanilamide (7a-7e).

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>R'</th>
<th>Yield (%)</th>
<th>M.P.</th>
<th>R_f*</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>H</td>
<td>(CH$_3$)$_2$C</td>
<td>97</td>
<td>Oil</td>
<td>0.9</td>
<td>2:1</td>
</tr>
<tr>
<td>7b</td>
<td>Ph</td>
<td>CH$_3$</td>
<td>62</td>
<td>86-87</td>
<td>0.6</td>
<td>2:1</td>
</tr>
<tr>
<td>7c</td>
<td>H</td>
<td>CH$_3$Ph</td>
<td>35</td>
<td>Oil</td>
<td>0.7</td>
<td>2:1</td>
</tr>
<tr>
<td>7d</td>
<td>H</td>
<td>CO$_2$CH$_3$</td>
<td>47</td>
<td>Oil</td>
<td>0.2</td>
<td>2:1</td>
</tr>
<tr>
<td>7e</td>
<td>Ph</td>
<td>Ph</td>
<td>37</td>
<td>oil</td>
<td>0.7</td>
<td>2:1</td>
</tr>
</tbody>
</table>

* Petroleum ether: Dichloromethane (1:1)

In $^1$HNMR spectra of the N-substituted sulfanilamides a signal at $\delta$ 3.7-4.28 ppm for H-1 proton, a signal for H-2 proton at $\delta$ 3.2-3.7 ppm and signal for NH proton at $\delta$ 3.7-5.5 ppm was observed. $^{13}$CNMR shows values for C-1 carbon at $\delta$ 141-142 ppm for C-2 carbon on $\delta$ 52-57 ppm. $^1$HNMR and $^{13}$CNMR data of the sulfanilamide is given in the Table 2.33.
Table 2.33: $^1$HNMR and $^{13}$CNMR data of sulfanilamides (7a-7e).

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>R'</th>
<th>$^1$HNMR</th>
<th>$^{13}$CNMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>H</td>
<td>(CH$_3$)$_2$C</td>
<td>7.62 (d, 2H$<em>{arom}$, $J = 9.0$), 7.29 (d, 2H$</em>{arom}$, $J = 9.0$), 3.72 (d, 2H, $J = 6.0$, CH$_2$OH ), 3.27 (dd, 1H, $J = 12.0$, CH$_2$NH ), 2.41 (s, 3H, CH$_3$), 2.0 (m, 1H, CH(CH$_3$)$_2$), 2.62 (s, 3H, CH$_3$)</td>
<td>141.69, 129.61, 65.99 (OCH$_2$), 52.11, 30.70, 24.5, 24.0</td>
</tr>
<tr>
<td>7b</td>
<td>Ph</td>
<td>CH$_3$</td>
<td>7.62 (d, 2H$<em>{arom}$, $J = 9.0$), 7.29 (d, 2H$</em>{arom}$, $J = 9.0$), 7.20-7.22 (m, 5H$_{arom}$), 4.285 (d, 1H, $J = 6.0$, CHOH ), 3.721 (m, 1H, CH$_2$NH ), 2.35 (s, 3H, CH$_3$), 1.71 (d, 3H, $J = 4.0$, CH$_3$)</td>
<td>141.57, 140.01, 129.70, 129.60, 128.1, 126.2, 125.5, 57.37 (OCH$_3$), 21.32 (CH$_3$), 17.15 (CH$_3$)</td>
</tr>
<tr>
<td>7c</td>
<td>H</td>
<td>CH$_2$Ph</td>
<td>7.40-7.10 (m, 9H$_{arom}$), 4.2 (d, 1H, $J = 6.0$, CHOH ), 3.78 (m, 1H, CH$_2$NH ), 3.81 (d, 2H, Ph(CH$_2$CH$_3$), 2.42 (s, 3H, CH$_3$), 1.71 (d, 3H, $J = 4.0$, CH$_3$)</td>
<td>141.21, 129.43, 128.44, 126.18, 125.6, 65.44 (OCH$_3$), 60.79 (CH$_3$), 30.05 (CH$_3$)</td>
</tr>
<tr>
<td>7d</td>
<td>H</td>
<td>CO$_2$CH$_3$</td>
<td>7.52 (d, 2H$<em>{arom}$, $J = 9.0$), 7.29 (d, 2H$</em>{arom}$, $J = 9.0$), 5.5 (d, 1H, NHSO ), 4.28 (d, 1H, $J = 6.0$, CH$_2$OH ), 4.01 (dd, 1H, CH$_2$OH ), 3.75 (s, 3H, OCH$_3$), 2.38 (s, 3H, CH$_3$)</td>
<td>168 (CO), 142.08, 130.07, 129.89, 126.35, 125.76, 64.04 (OCH$_3$), 58.57 (CH$_3$)</td>
</tr>
<tr>
<td>7e</td>
<td>Ph</td>
<td>Ph</td>
<td>7.57 (d, 2H$<em>{arom}$, $J = 12$), 7.31 (d, 2H$</em>{arom}$, $J = 12$), 3.90 (d, 1H, $J = 5.5$, CNH), 3.18 (td, 2H, $J = 6.0$, OCH$_2$CH$_2$), 2.98 (td, 2H, $J = 4.3$, CH$_2$CH$_2$), 2.82 (m, 1H, CH$_2$(CH$_3$)$_2$), 2.43 (s, 3H, CH$_3$), 0.9 (d, 3H, $J = 5.2$, CH$_3$)</td>
<td>141.2, 129.6, 129.32, 126.3, 68.02 (OCH$_3$), 64.44, 40.52, 26.20, 21.32</td>
</tr>
</tbody>
</table>

In mass spectrum of N-substituted sulfanilamides molecular ion peak and a peak for sulfanilamide group was observed. In mass spectrum of N-p-tolyl-2- methyl -1-phenyl sulfanilamide (7b) the molecular ion peak was observed at $m/z$ 289 a.m.u. and the base peak was observed at $m/z$ 154 a.m.u. (Scheme - 2.15).
Scheme 2.15: Mass fragmentation pattern of N-p-tolyl-2-methyl-1-phenyl sulfinilamide (7b).

N-p-tolylsulfinilamido morpholines were obtained in 49-97% yield. Again diastereomeric ratio was observed in 2:1 ratio, shows that both the diastereomers reacted in same ratio. Physical data of N-p-tolylsulfinilamidomorpholines is given in Table 2.34.
Table 2.34: Physical data of N-\(p\)-tolylsulfanilamidomorpholines (7f-7j).

![Chemical structure](image-url)

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>R'</th>
<th>Yield (%)</th>
<th>M.P. (°C)</th>
<th>R(_f)*</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>7f</td>
<td>H</td>
<td>(CH(_3))(_2)C</td>
<td>73</td>
<td>Oil</td>
<td>0.4</td>
<td>2:1</td>
</tr>
<tr>
<td>7g</td>
<td>Ph</td>
<td>CH(_3)</td>
<td>97</td>
<td>Oil</td>
<td>0.3</td>
<td>2:1</td>
</tr>
<tr>
<td>7h</td>
<td>H</td>
<td>CH(_2)Ph</td>
<td>97</td>
<td>Oil</td>
<td>0.3</td>
<td>2:1</td>
</tr>
<tr>
<td>7i</td>
<td>H</td>
<td>CO(_2)CH(_3)</td>
<td>54</td>
<td>119-120</td>
<td>0.4</td>
<td>2:1</td>
</tr>
<tr>
<td>7j</td>
<td>Ph</td>
<td>Ph</td>
<td>49</td>
<td>oil</td>
<td>0.4</td>
<td>2:1</td>
</tr>
</tbody>
</table>

* Petroleum ether: Dichloromethane (3:2)

In \(^1\)HNMR spectrum a signal for H-1 proton at \(\delta\) 3.9-4.87 ppm, a signal at \(\delta\) 3.3-3.7 ppm for H-2 proton, a signal at \(\delta\) 3.13-3.27 ppm for H-5 proton and a signal at \(\delta\) 3.67-3.9 for H-6 proton of the morpholine ring was observed, multiplicity depends on the substituent attached. \(^1\)HNMR and \(^13\)CNMR data is given in Table 2.35
Table 2.35: \(^1\)HNMR and \(^{13}\)CNMR data of N-\(p\)-tolylsulfanilamidomorpholines (7f-7j).

![Diagram](image)

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>R'</th>
<th>(^1)HNMR</th>
<th>(^{13})CNMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>7f</td>
<td>H</td>
<td>((\text{CH}_3)_2\text{C})</td>
<td>7.57 (d, (2\text{H}<em>{\text{arom}}), (J=12)), 7.31 (d, (2\text{H}</em>{\text{arom}}), (J=12)), 3.90 (d, 1H, (J=3.4), CHNH), 3.18 (td, 2H, (J=4.4), OCH(_2)CH(_2)), 2.98 (td, 2H, (J=5.1), CH(_2)CH(_2)N), 2.82 (m, 1H, CH(CH(_3)(_2))), 2.43 (s, 3H, CH(_3))</td>
<td>141.2, 129.6, 129.32, 126.3, 68.02 (C-2), 64.44 (C-6), 40.52 (C-5), 26.20 (2(\times)CH(_3)), 21.32(CH(_3))</td>
</tr>
<tr>
<td>7g</td>
<td>Ph</td>
<td>(\text{CH}_3)</td>
<td>7.60 (d, (2\text{H}<em>{\text{arom}}), (J=4.2)), 7.37(d, (2\text{H}</em>{\text{arom}}), (J=4.7)), 7.36-7.23 (m, 5H(_{\text{arom}})), 4.85 (d, 1H, CHPh), 4.07 (dd, 1H, dd, (J=4.9), CH(_2)O), 3.91 (q, 1H, (J=7.1), CHCH(_2)), 3.13 (ddd, 1H, (J=4.7), 3.8, CH(_2)N), 2.47 (s, 3H, CH(<em>3)(</em>{\text{arom}})), 1.1 (d, 3H, CH(_3))</td>
<td>141.17, 139, 129.50, 128.66, 126.30, 169.98 (C-2), 68.15 (C-6), 64.1(C-3), 59.20 (C-5), 40.58 (CH(_3)), 36.22 (CH(_3))</td>
</tr>
<tr>
<td>7h</td>
<td>H</td>
<td>CH(_2)Ph</td>
<td>7.37-7.12 (m, 9H(_{\text{arom}})), 3.81 (dd, 2H, (J=6.1), 2.3, OCH(_2)CH(_2)N), 3.70 (m, 1H, PhCH(_3)CH(_2)N), 3.65 (dd, 2H, (J=5.2), 4.0, OCH(_2)CH), 2.99 (dd, 2H, (J=3.3), 2.7, CH(_2)CH(_2)N), 2.47 (s, 3H, CH(<em>3)(</em>{\text{arom}})), 2.38 (s, 3H, CH(<em>3)(</em>{\text{arom}}))</td>
<td>129.50, 121.35, 128.6, 126.31, 69.98 (C-2), 68.15 (C-6), 64.1(C-3), 59.21 (C-5), 40.57, 36.22 (CH(_3))</td>
</tr>
<tr>
<td>7i</td>
<td>H</td>
<td>CO(_2)(_3)H</td>
<td>7.69 (d, (2\text{H}<em>{\text{arom}}), (J=6)), 7.57 (d, (2\text{H}</em>{\text{arom}}), (J=6)), 4.25 (d, 2H, (J=5.3), CHCH(_2)OH), 4.03 (t, 1H, (J=4.9), CHCO(_2)CH(_3)), 3.92 (dd, 2H, (J=3.3), 5.1, CH(_2)OH), 3.73 (s, 3H, OCH(_3)), 3.77 (dd, 2H, (J=4.7), 3.7, OCH(_2)CH), 2.44 (dd, 2H, (J=2.8), 1.3, CH(_2)CH(_2)N), 2.43 (s, 3H, CH(<em>3)(</em>{\text{arom}}))</td>
<td>129.29, 126.70, 126.57, 95.48 (OCH(_3)), 69.09 (C-2), 67.1(C-6), 64.1(C-3), 45.80 (C-5), 34.5(CH(_3))</td>
</tr>
<tr>
<td>7j</td>
<td>Ph</td>
<td>Ph</td>
<td>7.11-7.24 (10 H(<em>{\text{arom}})), 7.59 (d, (2\text{H}</em>{\text{arom}}), (J=6.3)), 7.25 (2H(_{\text{arom}}), d, (J=6)), 5.6 (d, 1H, H-2, (J=4.2)), 4.1 (d, 1H, H-2, (J=4.5)), 3.9 (dt, 2H, H-6, (J=4.2), 6.1), 2.7 (dt, 2H, H-5, (J=4.2), 6.5), 2.3 (3H, s, CH(<em>3)(</em>{\text{arom}}))</td>
<td>133, 129, 127, 124, 87 (C-2), 67 (C-6), 64 (C-5), 60(C-3), 54, 24(CH(_3))</td>
</tr>
</tbody>
</table>
In mass spectrum of (7g) molecular ion peak of the morpholines is the base peak (Scheme- 2.16)

Scheme 2.16: Mass fragmentation pattern of N-p-tolylsulfanilamido-3-methyl-2-phenylmorpholines.
In case of deprotected morpholines morpholinium chloride were obtained in 79-85 % yield. Physical data of morpholinium salt is given in Table 2.36.

**Table 2.36: Physical data of morpholinium salt (7k-7o).**

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>R'</th>
<th>Yields (%)</th>
<th>M.P (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7k</td>
<td>H</td>
<td>(CH₃)₂C</td>
<td>52</td>
<td>177-178</td>
</tr>
<tr>
<td>7l</td>
<td>Ph</td>
<td>CH₃</td>
<td>85</td>
<td>182-183</td>
</tr>
<tr>
<td>7m</td>
<td>H</td>
<td>CH₂Ph</td>
<td>79</td>
<td>156-157</td>
</tr>
<tr>
<td>7n</td>
<td>H</td>
<td>CO₂CH₃</td>
<td>48</td>
<td>201-202</td>
</tr>
<tr>
<td>7o</td>
<td>Ph</td>
<td>Ph</td>
<td>44</td>
<td>166-167</td>
</tr>
</tbody>
</table>

In ¹HNMR a signal was observed at δ 4.04-5.51 ppm for H-2 proton of the ring, a signal at δ 3.77-4.54 ppm was observed for H-6 (OCH₂) proton of the ring for H-5 signal was observed at δ 3.13-4.5 ppm, and for H-3 at δ 3.1-4.14 ppm. In ¹³CNMR for C-2 carbon signal was observed at δ 78-89 ppm, for C-6 at δ 60-67 ppm for C-5 at δ 45-52 ppm in addition to the other peaks Table 2.37.
Table 2.37: $^1$HNMR and $^{13}$CNMR data of morpholinium salt (7k-7o).

![Structure of morpholinium salt]

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>R'</th>
<th>$^1$HNMR</th>
<th>$^{13}$CNMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>7k</td>
<td>H</td>
<td>(CH$_3$)$_2$C</td>
<td>4.12 (1H, d, $J = 4.1$, CH$_2$NH), 3.77 (2H, td, $J = 4.9$, OCH$_2$CH$_3$), 3.21 (2H, td, $J = 3.7$, CH$_2$CH$_2$N), 2.98 (1H, m, CH(CH$_3$)$_2$), 0.9 (6H, d, $J = 4.3$, 2×CH$_3$)</td>
<td>75.1 (C-2), 69.23 (C-6), 64.11 (C-3), 56.1, 27.42, 25.1, 24.22.</td>
</tr>
<tr>
<td>7l</td>
<td>Ph</td>
<td>CH$_3$</td>
<td>7.31-7.12 (m, 5H$_{arom}$), 5.13 (1H, d, CHPh), 4.54 (2H, dd, $J = 4$, CH$_2$O), 3.73 (1H, q, CHCH$_3$), 3.13 (1H, dd, CH$_2$N), 1.2 (3H, d, CH$_3$CH)</td>
<td>139.1, 128.7, 128.5, 128.4, 128.2, 126.4, 90.2 (C-2), 78.6 (C-6), 62.1 (C-3), 45.2 (C-5), 21.22 (CH$_3$)</td>
</tr>
<tr>
<td>7m</td>
<td>H</td>
<td>CH$_2$Ph</td>
<td>7.12-6.89 (m, 5H$_{arom}$), 3.99 (2H, dd, OCH$_2$CH$_2$N), 3.67 (1H, m, PhCH$_2$CHN), 3.60 (2H, dd, OCH$_2$CH), 3.15 (2H, dd, CH$_2$CH$_2$N),</td>
<td>140, 137, 128.3, 128.1, 126.7, 125.1, 89.1 (C-2), 67.2 (C-6), 65.3 (C-3), 40.2 (CH$_2$), 25.1</td>
</tr>
<tr>
<td>7n</td>
<td>H</td>
<td>CO$_2$CH$_3$</td>
<td>4.35 (2H, d, CHCH$_2$OH), 4.23 (1H, t, CHCO$_2$CH$_3$), 4.12 (2H, dd, CH$_2$OH), 3.73 (3H, s, OCH$_3$), 3.37 (2H, dd, OCH$_2$CH), 2.54 (2H, dd, CH$_2$CH$_2$N),</td>
<td>179.9 (CO), 80.2 (C-2), 67.1 (C-6), 56.2 (C-3), 46.7, 56.6 (OCH$_3$), 25.1</td>
</tr>
<tr>
<td>7o</td>
<td>Ph</td>
<td>Ph</td>
<td>7.11-7.24 (10 H$_{arom}$), 5.6 (d, 1H, H-2, $J = 4.2$), 4.1 (d, 1H, H-2, $J = 4.5$), 3.9 (dt, 2H, H-6, $J = 4.2, 6.1$), 2.7 (dt, 2H, H-5, $J = 4.2, 6.5$)</td>
<td>133, 129, 127, 124, 87 (C-2), 67 (C-6), 64</td>
</tr>
</tbody>
</table>
In mass spectrum of 3-methyl-2-phenylmorpholinium chloride (7l) molecular ion peak was found to be base peak. (Scheme-2.17).

Scheme 2.17: Mass fragmentation pattern of 3-methyl-2-phenylmorpholinum chloride (7l).

### 2.9 Synthesis of 3-Aryl-6-phenyl-1,2,4-triazolo-[3,4-b][1,3,4]-thiadiazine (8a-8f).

For the synthesis of triazolo thiadiazine, the triazole 3-thiones were cyclized with one equivalent of α-bromoacetophenone \cite{131} in the presence of anhydrous aluminum chloride in dry ether\cite{132} in 55-88 % yield (Scheme 2.18). Physical and IR data is given in Table 2.38.

Scheme 2-18: Synthesis of 3-Aryl-6-phenyl-1,2,4-triazolo-[3,4-b][1,3,4]-thiadiazine.
Table 2.38: Physical data with IR of 3-Aryl-6-phenyl-1,2,4-triazolo-[3,4-b][1,3,4]-thiadiazine (8a-8f).

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>Yield (%)</th>
<th>M.P.(°C)</th>
<th>Rf*</th>
<th>IR (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>4’-F</td>
<td>88</td>
<td>176-177</td>
<td>0.8</td>
<td>3313, 1634, 1630, 1438, 1359</td>
</tr>
<tr>
<td>8b</td>
<td>4’-CH₃</td>
<td>74</td>
<td>213-214</td>
<td>0.6</td>
<td>3313, 2981, 1631, 1622, 1426,</td>
</tr>
<tr>
<td>8c</td>
<td>3’,4’-(OCH₃)₂</td>
<td>64</td>
<td>200-201</td>
<td>0.5</td>
<td>3312, 2981, 1633, 1598, 1424, 1335</td>
</tr>
<tr>
<td>8d</td>
<td>3’,5’-(OCH₃)₂</td>
<td>64</td>
<td>194-195</td>
<td>0.4</td>
<td>3312, 2981, 1633, 1598, 1424, 1335, 687</td>
</tr>
<tr>
<td>8e</td>
<td>4’-CH₃, 3’,5’-(OCH₃)₂</td>
<td>55</td>
<td>215-216</td>
<td>0.3</td>
<td>3312, 2990, 2981, 1633, 1598, 1424, 1335, 687</td>
</tr>
<tr>
<td>8f</td>
<td>3’,4’,5’-(OCH₃)₃</td>
<td>55</td>
<td>201-202</td>
<td>0.3</td>
<td>3312, 2990, 2981, 1633, 1598, 1424, 1335, 687</td>
</tr>
</tbody>
</table>

* Petroleum ether: Dichloromethane (7:3)

In $^1$HNMR spectra the characteristic singlet at $\delta$ 2.33-2.4 ppm for CH₂ proton of the triazolo thiadiazine ring was observed. In $^{13}$CNMR spectra a signal at $\delta$ 72-73.11 ppm was observed for the same carbon. $^1$HNMR and $^{13}$CNMR of the triazolo thiadiazine is given in Table 2.39.
Table 2.39: $^1$HNMR and $^{13}$CNMR of the triazole thiadiazine (8a-8f).

![Diagram of 1,2,4-triazolo-[3,4-b][1,3,4]-thiadiazine](image)

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>$^1$HNMR</th>
<th>$^{13}$CNMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>4'-F</td>
<td>9.0 (bs, 1H, NH); 7.77 (d, 2H$<em>{arom}$, $J = 8.9$), 7.12 (d, 2H$</em>{arom}$, $J = 8.76$), 7.11-6.88 (m, 5H$_{arom}$), 2.3 (s, 2H, CH$_2$)</td>
<td>161 (ArC=N), 154 (CH$_2$C=N), 143 (CF), 131 (C-4'), 128 (C-3', C-6'), 127 (C-3', C-5'), 124 (C-2, C-6), 122 (C-1), 73 (NCS), 40 (CCS)</td>
</tr>
<tr>
<td>8b</td>
<td>4'-CH$_3$</td>
<td>8.81 (bs, 1H, NH); 7.89 (d, 2H$<em>{arom}$, $J = 9.6$), 7.38 (d, 2H$</em>{arom}$, $J = 8.4$), 7.11-6.8 (m, 5H$<em>{arom}$), 6.5 (d, 1H$</em>{arom}$, $J = 8.4$), 3.9 (s, 9H, 3×OCH$_3$), 2.3 (s, 3H, CH$_3$)</td>
<td>160 (ArC=N), 153 (CH$_2$C=N), 132 (CCH$_3$), 131 (C-4'), 128 (C-2', C-6'), 120 (C-3', C-5'), 118 (C-2, C-6), 112 (C-1), 73 (NCS), 40 (CCS)</td>
</tr>
<tr>
<td>8c</td>
<td>3',4'-(OCH$_3$)$_2$</td>
<td>8.98 (bs, 1H, NH); 7.62 (d, 1H$<em>{arom}$, $J = 8.5$), 7.3 (d, 1H$</em>{arom}$, $J = 8.4$), 7.11-6.8 (m, 5H$<em>{arom}$), 6.5 (d, 1H$</em>{arom}$, $J = 8.4$), 3.9 (s, 9H, 3×OCH$_3$), 2.3 (s, 3H, CH$_3$)</td>
<td>159 (ArC=N), 149 (CH$_2$C=N), 143 (C-4), 140 (C-3), 131 (C-4'), 128 (C-2', C-6'), 120 (C-3', C-5'), 118 (C-2), 112 (C-6), 112 (C-1), 70 (NCS), 41 (CCS)</td>
</tr>
<tr>
<td>8d</td>
<td>3',5'-(OCH$_3$)$_2$</td>
<td>8.91(bs, 1H, NH); 7.06 (d, 2H$<em>{arom}$, $J = 2.9$), 7.11-6.8 (m, 5H$</em>{arom}$), 6.72 (t, 1H$_{arom}$, $J = 2.2$), 5.54 (bs, 2H, NH), 3.9 (s, 6H, 2×OCH$_3$), 2.3 (s, 3H, CH$_3$)</td>
<td>159 (ArC=N), 149 (CH$_2$C=N), 146 (C-3, C-5), 131 (C-4'), 128 (C-2', C-6'), 120 (C-3', C-5'), 118 (C-2), 112 (C-6), 112 (C-1), 109 (C-4), 73 (NCS), 39 (CCS)</td>
</tr>
<tr>
<td>8e</td>
<td>4'-CH$_3$-3',5'-(OCH$_3$)$_2$</td>
<td>9.12 (bs, 1H, NH); 7.11-6.8 (m, 5H$<em>{arom}$), 6.72 (s, 1H$</em>{arom}$), 3.9 (s, 9H, 3×OCH$_3$), 2.3 (s, 3H, CH$_3$)</td>
<td>157 (ArC=N), 156.3 (CH$_2$C=N), 145 (C-3, C-5), 131 (C-4'), 128 (C-2', C-6'), 120 (C-3', C-5'), 118 (C-2), 117 (C-4), 112 (C-6), 112 (C-1), 73 (NCS), 32 (CCS)</td>
</tr>
<tr>
<td>8f</td>
<td>3',4',5'-(OCH$_3$)$_3$</td>
<td>9.12 (bs, 1H, NH); 7.11-6.8 (m, 5H$<em>{arom}$), 6.72 (s, 1H$</em>{arom}$), 3.9 (s, 6H, 3×OCH$_3$), 2.52 (s, 3H, CH$_3$)</td>
<td>157 (ArC=N), 156.3 (CH$_2$C=N), 146 (C-3, C-5), 136 (C-4), 131 (C-4'), 128 (C-2', C-6'), 120 (C-3', C-5'), 118 (C-2), 112 (C-6), 112 (C-1), 73 (NCS), 32 (CCS)</td>
</tr>
</tbody>
</table>

In mass spectrum of 3-(3',5'-dimethoxyphenyl)-6-phenyl-1,2,4-triazolo-[3,4-b][1,3,4]-thiadiazine (8d) molecular ion peak was observed at m/z 354 and was found to be the most stable one.
Scheme 2.19: Mass fragmentation of 3-(3',5'-Dimethoxyphenyl)-6-phenyl-1,2,4-triazolo-[3,4-b][1,3,4-thiadiazole (8d).

Maximum antibacterial inhibition was observed for compound (8a) where fluoro group was substituted at para position, while other compounds showed good to moderate activities Table 2.40.
Table 2.40: Antibacterial activities of Triazole thiadiazine (8a-8f).

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>E. coli</th>
<th>B. subtilis</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>8b</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>8c</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>8d</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>8e</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>8f</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>-ve control (acetone)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>-</td>
<td>20</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>15</td>
<td>-</td>
</tr>
</tbody>
</table>

Concentration used: 5mg/mL; -: no activity.

Zone of inhibition (radius, mm)

In case of antifungal activities [134] maximum % age inhibition was observed by compound (8e) having two methoxy groups substituted at 3 and 5 positions and methyl group at 4 position of aryl group of triazolo thiadiazine. While the remaining compounds showed good to moderate activities against the growth of yeast cells Table 2.41.
Table 2.41: Antifungal activities of Triazole thiadiazine (8a-8f).

![Triazole thiadiazine structure diagram]

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>\textit{S. cerevisiae} (ZI, cm)</th>
<th>\textit{S. cerevisiae} (PI, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>0.9</td>
<td>25</td>
</tr>
<tr>
<td>8b</td>
<td>0.7</td>
<td>41.6</td>
</tr>
<tr>
<td>8c</td>
<td>1.0</td>
<td>16.6</td>
</tr>
<tr>
<td>8d</td>
<td>0.6</td>
<td>50</td>
</tr>
<tr>
<td>8e</td>
<td>0.5</td>
<td>58.3</td>
</tr>
<tr>
<td>8f</td>
<td>0.7</td>
<td>41.6</td>
</tr>
<tr>
<td>-ve control (acetone)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>1.2</td>
<td>100</td>
</tr>
</tbody>
</table>

Concentration used: 5mg/mL; -: no activity

ZI: zone of inhibition; PI: percent inhibition = \(100 - \frac{\text{fungal growth in sample (cm)}}{\text{fungal growth in control (cm)}} \times 100\)

In case of phytotoxic activities all compounds were active except (8d) and (8e) Table 2.42.
Table 2.42: Phytotoxic activities of Triazolo thiadiazine (8a-8f).

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Phytotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>–</td>
</tr>
<tr>
<td>8b</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>8c</td>
<td>–</td>
</tr>
<tr>
<td>8d</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>8e</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>8f</td>
<td>Pale yellow</td>
</tr>
</tbody>
</table>

Concentration used: 5mg/mL; -: no activity.

### 2.10 Synthesis of Methyl 1-methyl Isochromanyl acetic acid and Hydrazides

Isochromanyl group is known for its anti-inflammatory activities \(^{[100]}\). For the synthesis of isochromanyl ester chain lengthening of 3,4,5-trimethoxy and 3,4-dimethoxybenzoic acid was carried out to get 3,4,5-trimethoxy and 3,4-dimethoxyphenyl acetic acid\(^{[118, 125a-d]}\). Thus esterification \(^{[118]}\) followed by reduction with 6 equivalents of sodium borohydride \(^{[125]}\) afford the 3,4,5-trimethoxyphenyl ethanol and 3,4-dimethoxyphenyl ethanol. Substituted phenyl ethanols were reacted with methyl acetoacetate in the presence of \(p\)-TsOH in benzene by using Dean-Stark apparatus to afford methyl 1-isochromanylacetic acid as a result of Friedel-Crafts reaction \(^{[100]}\). This ester was treated with hydrazine monohydrate to get corresponding hydrazides in 79-86% yield (Scheme 2.20).
Scheme 2.20: Synthesis of Methyl 1-methyl 1-isochromanyl acetic acid and hydrazide.

In IR carbonyl stretching at 1730-1734 cm\(^{-1}\) was observed for isochromanyl ester in case of isochromanyl hydrazides stretching for NH and NH\(_2\) group were observed at 3337, 3290-3341 cm\(^{-1}\) respectively. Physical and IR spectral data of isochromanyl ester and hydrazides are given in Tables 2.43 and 2.44.

**Table 2.43: Physical data of Methyl 1-methyl 1-isochromanyl acetic acid.**

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>Yield (%)</th>
<th>M.P(°C)</th>
<th>R(_f)*</th>
<th>IR (cm(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>5-Cl</td>
<td>86</td>
<td>Oil</td>
<td>0.9</td>
<td>2933, 2870, 1724, 1458</td>
</tr>
<tr>
<td>b</td>
<td>6,7-(OCH(_3))(_2)</td>
<td>82</td>
<td>Oil</td>
<td>0.6</td>
<td>2933, 1734, 1467, 1235</td>
</tr>
<tr>
<td>c</td>
<td>6,7,8-(OCH(_3))(_3)</td>
<td>79</td>
<td>Oil</td>
<td>0.4</td>
<td>2930, 1731, 1467, 1235</td>
</tr>
</tbody>
</table>

* Petroleum ether: Ethyl acetate (9:1)
Table 2.44: Physical data of 1-Methyl 1-isochromanyl acetylhydrazide.

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>Yield (%)</th>
<th>M.P(°C)</th>
<th>Rf</th>
<th>IR (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>5-Cl</td>
<td>60</td>
<td>210-211</td>
<td>0.1</td>
<td>3345, 3341, 2952</td>
</tr>
<tr>
<td>b</td>
<td>6,7-(OCH₃)₂</td>
<td>78</td>
<td>Oil</td>
<td>0.1</td>
<td>3372, 3295, 2933, 1655, 1459</td>
</tr>
<tr>
<td>c</td>
<td>6,7,8-(OCH₃)₃</td>
<td>78</td>
<td>164-165</td>
<td>0.1</td>
<td>3372, 3295, 1655, 1459, 1247</td>
</tr>
</tbody>
</table>

* Petroleum ether: Ethyl acetate (1:4)

In ¹HNMR a singlet at δ 1.98-2.3 ppm for CH₃, a singlet at δ 2.2-2.43 ppm for CH₂ group, a multiplet at δ 3.9-4.4 ppm for H-3 proton and a multiplet at δ 2.6-3.8 ppm for H-4 proton was observed of the isochroman ring and singlet at 3.9 ppm for OCH₃ group of the ester. In hydrazides in addition to the characteristics peaks disappearance of singlet for OCH₃ and appearance of signal at 7.8-8.1 ppm for NH and 5.5-6.2 ppm for NH₂ group was observed. Proton and carbon NMR data are given in Tables 2.45 and 2.46 respectively.

Table 2.45: ¹HNMR and ¹³CNMR data of 1-Methyl 1-isochromanyl acetic acid.

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>¹HNMR</th>
<th>¹³CNMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>5-Cl</td>
<td>6.98 (s, 2H arom., H-5, 8), 4.4 (q, 3H, OCH₂CH₃), 4.0 (m, 2H, H-3), 3.9 (s, 6H, OCH₃), 2.91 (s, 2H, H-11), 2.65 (m, 2H, H-4), 2.2 (s, 3H, H-13), 1.37 (t, 3H, OCH₂CH₃)</td>
<td>166 (C=O), 146, 146.3, 136, 127, 112, 111, 75 (C-1), 59 (C-4), 56 (3OCH₃), 44, 32 (C-11), 25</td>
</tr>
<tr>
<td>b</td>
<td>6,7-(OCH₃)₂</td>
<td>6.51 (s, 1H arom., H-5), 4.1 (q, 3H, OCH₂CH₃), 3.95 (m, 2H, H-3), 3.9 (s, 6H, 2×OCH₃), 2.93 (s, 2H, H-11), 2.65 (m, 2H, H-4), 2.2 (s, 3H, H-13), 1.37 (t, 3H, OCH₂CH₃)</td>
<td>169 (C=O), 146148, 146.1, 136, 128, 124, 105, 75 (C-1), 65 (C-4), 59, 56 (3OCH₃), 48, 32 (C-11), 25</td>
</tr>
<tr>
<td>c</td>
<td>6,7,8-(OCH₃)₃</td>
<td>6.51 (s, 1H arom., H-5), 4.1 (q, 3H, OCH₂CH₃), 3.95 (m, 2H, H-3), 3.9 (s, 9H, 3×OCH₃), 2.93 (s, 2H, H-11), 2.65 (m, 2H, H-4), 2.2 (s, 3H, H-13), 1.37 (t, 3H, OCH₂CH₃)</td>
<td>169 (C=O), 146148, 146.1, 136, 128, 124, 105, 75 (C-1), 65, 59, 56 (3OCH₃), 48 (C-11), 32, 25</td>
</tr>
</tbody>
</table>
Table 2.46: $^1$HNMR and $^{13}$CNMR data of 1-Methyl 1-isochromanyl hydrazides.

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>$^1$HNMR</th>
<th>$^{13}$CNMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>5-Cl</td>
<td>8.2 (bs, 1H, NH), 7.78 (d, 1H$<em>{arom}$, $J$ = 4.1), 7.59 (d, 1H$</em>{arom}$, $J$ = 3.2), 7.51 (d, 1H$<em>{arom}$, $J$ = 2.1), 7.24 (d, 1H$</em>{arom}$, $J$ = 3.3), 4.42 (m, 2H, H-3), 3.88 (s, 2H, H-11), 3.01 (m, 2H, H-4), 2.51 (s, 3H, H-13)</td>
<td>165(C=O), 142, 132, 131, 127, 126, 123, 75 (C-1), 59, 56, 44 (C-11)</td>
</tr>
<tr>
<td>b</td>
<td>6,7-(OCH$_3$)$_2$</td>
<td>7.71 (bs, 1H, NH), 6.55 (s, 2H$_{arom}$, H-5,8), 4.0 (m, 2H, H-3), 3.9 (s, 6H, 2×OCH$_3$), 2.91 (s, 2H, H-11), 2.65 (m, 2H, H-4), 2.2 (s,3H,H-13),</td>
<td>166 (C=O), 146, 1.5, 146.3, 136, 127,112, 111, 75, 59, 56 (3OCH$_3$)</td>
</tr>
<tr>
<td>c</td>
<td>6,7,8-(OCH$_3$)$_3$</td>
<td>7.71 (bs, 1H, NH), 6.46 (s, 1H, H-5), 3.99 (m, 2H, H-3), 3.9 (s, 9H, 3×OCH$_3$), 3.07 (s, 2H, H-11), 2.6 (m, 2H, H-4), 1.98 (s, 3H, H-13)</td>
<td>169(CO), 146148, 146.1, 136, 128, 124, 105, 75 (C-1), 65, 59, 56(3OCH$_3$), 48</td>
</tr>
</tbody>
</table>

2.11 Synthesis of 1-Methyl 1-isochromanylacetyl 3’,5’-dimethylpyrazoles (9a-9c).

1-Isochromanyl acetyl hydrazides were irradiated with one equivalent of acetylacetone to get 1-isochromanylacetyl pyrazoles in $^{[123]}$ 67-81% yield (Scheme 2.21).

Scheme 2.21: Synthesis of 1-Isochromanyl pyrazoles.

In the IR spectra disappearance of stretching for NH and NH$_2$ groups at 3345-3372, 3295-3341 cm$^{-1}$ respectively in isochromanyl pyrazoles ring was observed. The physical and IR data is given in Table 2.47.
Table 2.47: Physical data of 1-Methyl 1-isochromanyl 3,5-dimethyl pyrazoles (9a-9c).

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>Yield (%)</th>
<th>M.P(°C)</th>
<th>R$_f$</th>
<th>IR (cm$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9a</td>
<td>5'-Cl</td>
<td>67</td>
<td>Oil</td>
<td>0.8</td>
<td>2991, 2942, 1655, 1467, 1276</td>
</tr>
<tr>
<td>9b</td>
<td>6',7'-(OCH$_3$)$_2$</td>
<td>85</td>
<td>Oil</td>
<td>0.7</td>
<td>2953, 2817, 1675, 1456, 1247</td>
</tr>
<tr>
<td>9c</td>
<td>6',7',8'- (OCH$_3$)$_3$</td>
<td>81</td>
<td>Oil</td>
<td>0.5</td>
<td>2951, 1644, 1459, 1247</td>
</tr>
</tbody>
</table>

* Petroleum ether: Ethyl acetate (3:2)

In addition to the characteristics peaks $^1$HNMR showed a characteristic singlet at 6.5 ppm for H-4 proton of the pyrazole ring of the 1-isochromanyl acetyl pyrazole $^1$HNMR and $^{13}$CNMR data of the 1-isochromanyl acetylpyrazoles is given in Table 2.48.

Table 2.48: $^1$HNMR and $^{13}$C NMR data of 1-Isochromanyl pyrazoles (9a-9c).

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>$^1$HNMR</th>
<th>$^{13}$CNMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>9a</td>
<td>5'-Cl</td>
<td>7.78 (d, 1H, H-7, $J = 3.8$), 7.36 (d, 1H, H-8, $J = 4.1$), 7.24 (d, 1H, H-7, $J = 3.3$), 6.5 (s, 1H, H-4), 4.37 (m, 2H, H-3'), 3.8 (s, 2H, H-11'), 3.28 (m, 2H, H-4'), 2.4 (s, 3H, H-13'), 2.2 (s, 6H, 2×CH$_3$), 1.5 (s, 3H, H-13')</td>
<td>170 (CO), 145, 139, 133, 144.3, 143.1, 127, 126, 122, 105 (C-4), 74.1 (C-1), 59, 29 (CH$_3$), 25, 17, 11</td>
</tr>
<tr>
<td>9b</td>
<td>6',7'-(OCH$_3$)$_2$</td>
<td>6.66 (s, 2H, H-5',8'), 6.4 (s, 1H, H-4), 3.96 (m, 2H, H-3'), 3.9 (s, 6H, 2×CH$_3$), 3.11 (s, 2H, H-11'), 2.47 (m, 2H, H-4'), 2.1 (s, 6H, 2×CH$_3$), 1.5 (s, 3H, H-13')</td>
<td>169 (CO), 147, 146, 144, 143, 136, 112, 111, 105 (C-4), 75 (C-1), 59, 43, 23 (CH$_3$), 17, 11</td>
</tr>
<tr>
<td>9c</td>
<td>6',7',8'-(OCH$_3$)$_3$</td>
<td>6.55 (s, 1H, H-5'), 6.4 (s, 1H, H-4), 3.96 (m, 2H, H-3'), 3.9 (s, 9H, 3×CH$_3$), 3.07 (s, 2H, H-11'), 2.53 (m, 2H, H-4'), 1.81 (s, 6H, 2×CH$_3$), 1.5 (s, 3H, H-13')</td>
<td>169 (CO), 149, 147, 144, 143, 136, 128, 121, 105 (C-4), 75 (C-1), 58, 34(CH$_3$), 17, 11</td>
</tr>
</tbody>
</table>
In the mass spectrum of 1-(6’,7’,8’-trimethoxyisochromanyl)acetyl-3,5,-dimethyl-pyrazole (9c) molecular ion peak was observed at m/z 374 a.m.u. and was found to be most abundant peak. (Scheme- 2.22)


The maximum bacterial inhibition was observed for compound (9a) having chloro group at 5 position of isochromanyl moiety Table 2.49.
Table 2.49: Antibacterial activities of 1-Methyl 1-isochromanyl-3,5-dimethylpyrazoles (9a-9c).

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>E. coli</th>
<th>B. subtilis</th>
</tr>
</thead>
<tbody>
<tr>
<td>9a</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>9b</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>9c</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>-ve control (acetone)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>-</td>
<td>20</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>15</td>
<td>-</td>
</tr>
</tbody>
</table>

Concentration used: 5mg/mL; -: no activity.

Zone of inhibition (radius, mm)

In case of antifungal activities most significant % age inhibitions was observed by compound (9b) and (9c) with electron donating methoxy groups substituted on the isochromanyl moiety of isochromanyl group Table 2.50.

Table 2.50: Antifungal activities of 1-Methyl-1-isochromanyl-3,5-dimethylpyrazoles (9a-9c).

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>S. cerevisiae (ZI, cm)</th>
<th>S. cerevisiae (PI, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9a</td>
<td>1.0</td>
<td>16.6</td>
</tr>
<tr>
<td>9b</td>
<td>0.8</td>
<td>33.3</td>
</tr>
<tr>
<td>9c</td>
<td>0.8</td>
<td>33.3</td>
</tr>
<tr>
<td>-ve control</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>1.2</td>
<td>100</td>
</tr>
</tbody>
</table>

Concentration used: 5mg/mL; -: no activity

ZI: zone of inhibition; PI: percent inhibition = 100-fungal growth in sample (cm) / fungal growth in control (cm) × 100

Compound (9b) with two methoxy electron donating groups substituted at 7 and 8 position was inactive for phytotoxic activities Table 2.51
Table 2.51: Phytotoxic activities of 1-Methyl-1-isochromanyl-3,5-dimethylpyrazoles (9a–9c).

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Phytotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>9a</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>9b</td>
<td>–</td>
</tr>
<tr>
<td>9c</td>
<td>Pale yellow</td>
</tr>
</tbody>
</table>

Concentration used: 5mg/mL; -: no activity.

2.12 Synthesis of 1-Methyl isochromanyl thiosemicarbazides (10a-10e).

Aryl isothiocyanates \[^{133a}\] were refluxed with ethanolic solution of 6’,7’,8’-trimethoxyisochromanylacytelhydrazide to get 6’,7’,8’-trimethoxyisochromanyl acetyl thiosemicarbazides\[^{133}\] in 77-86% yields (Scheme-2.23).

![Scheme 2.23: Synthesis of isochromanyl thiosemicarbazide.](image)

In IR spectra disappearance of NH\(_2\) stretching and appearances of two new stretching for NH-1 and NH-2 protons was observed. Physical and IR data of isochromanyl thiosemicarbazides are given in Table 2.52.

Table 2.52: Physical data of isochromanyl thiosemicarbazides (10a-10e).

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R</th>
<th>Yield (%)</th>
<th>M.P.(°C)</th>
<th>R(_f)*</th>
<th>IR (cm(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>10a</td>
<td>2-OCH(_3)</td>
<td>73</td>
<td>Semisolid</td>
<td>0.5</td>
<td>3272, 3261, 1634, 1451</td>
</tr>
<tr>
<td>10b</td>
<td>4-CH(_3)</td>
<td>82</td>
<td>Semisolid</td>
<td>0.4</td>
<td>3345, 3295, 1636, 1491</td>
</tr>
<tr>
<td>10c</td>
<td>4-OCH(_3)</td>
<td>77</td>
<td>Semisolid</td>
<td>0.3</td>
<td>3314, 3288, 1651, 1467</td>
</tr>
<tr>
<td>10d</td>
<td>4-Cl</td>
<td>80</td>
<td>Semisolid</td>
<td>0.4</td>
<td>3326, 3281, 1634, 1461</td>
</tr>
<tr>
<td>10e</td>
<td>3-OCH(_3)</td>
<td>86</td>
<td>Semisolid</td>
<td>0.6</td>
<td>3372, 3295, 1663, 1462</td>
</tr>
</tbody>
</table>

* Petroleum ether: Ethyl acetate (1:9)
In addition to the characteristic peaks for isochromanyl acetyl group a signal was observed for NH-1 proton at \( \delta \) 8.3-8.9 ppm, for NH-3 proton at \( \delta \) 7.4-7.9 ppm and at 2.3-2.4 ppm for NH-2 proton of the isochromanyl thiosemicarbazides. \(^1\)HNMR and \(^{13}\)CNMR data of thiosemicarbazides is given in Table 2.53.

**Table 2.53: \(^1\)HNMR and \(^{13}\)CNMR data of 1-Isochromanyl thiosemicarbazides (10a-10e).**

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R</th>
<th>(^1)HNMR</th>
<th>(^{13})CNMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>10a</td>
<td>2'-OCH(_3)</td>
<td>8.32 (s, 1H, NH), 7.93 (s, 1H, NH), 7.8 (d, 1H\textsubscript{arom}, ( J = 3.2 )), 7.61 (d, 1H\textsubscript{arom}, ( J = 5.5 )), 7.43 (d, 1H\textsubscript{arom}, ( J = 3.2 )), 7.1 (d, 1H\textsubscript{arom}, ( J = 6.1 )), 6.55 (s, 1H\textsubscript{arom}, H-5'), 6.4 (s, 1H\textsubscript{arom}, H-4), 3.96 (m, 2H, H-3'), 3.9 (s, 9H, 3\times OCH(_3)), 3.07 (s, 2H, H-11), 2.53 (m, 2H, H-4), 1.81 (s, 6H, 2\times CH(_3)), 1.5 (s, 3H, H-13)</td>
<td>181 (CS), 177 (CO), 158 (C-2'), 149 (C-8), 148 (C-6), 136 (C-7), 128 (C-10), 127 (C-6'), 121 (C-9), 114 (C-3'), 75 (C-1), 65 (OCH(_3)), 60 (C-3), 47 (CH(_2)), 27 (CH(_3))</td>
</tr>
<tr>
<td>10b</td>
<td>4'-CH(_3)</td>
<td>8.3 (bs, NH), 7.40 (d, 2H\textsubscript{arom}, H-3',5', ( J = 5.3 )), 7.28 (d, 2H\textsubscript{arom}, H-2',6', ( J = 4.8 )), 7.1 (bs, NH), 6.5 (s, 1H, H-5), 3.9 (s, 9H, 3\times OCH(_3)), 3.81 (m, 2H, H-3), 3.7 (s, 2H, H-11), 2.4 (m, 2H, H-4), 1.69 (s, 3H, CH(_3)), 1.5 (s, 3H, CH(_3))</td>
<td>181 (CS), 177 (CO), 149 (C-8), 148 (C-6), 136 (C-7), 129 (C-3'), 128 (C-10), 126 (C-2', C-6'), 121 (C-9), 75 (C-1), 65 (3\times OCH(_3)), 60 (OCH(_3)), 47 (CH(_2)), 27 (CH(_3))</td>
</tr>
<tr>
<td>10c</td>
<td>4'-OCH(_3)</td>
<td>8.4 (bs, NH), 7.81 (s, NH), 7.3 (d, 2H\textsubscript{arom}, H-3',5', ( J = 5.1 )), 6.9 (d, 2H\textsubscript{arom}, H-2',6', ( J = 5.5 )), 6.5 (s, 1H\textsubscript{arom}, H-5), 4.02 (m, 2H, H-3), 3.84 (s, 12H, 4\times OCH(_3)), 3.7 (s, 2H, H-11), 2.9 (m, 2H, H-4), 2.2 (s, 3H, H-13), 1.5 (s, 3H, CH(_3))</td>
<td>181 (CS), 177 (CO), 149 (C-8), 148 (C-6), 136 (C-7), 129 (C-3'), 128 (C-10), 126 (C-2', C-6'), 121 (C-9), 75 (C-1), 65 (3\times OCH(_3)), 62 (OCH(_3)), 60 (C-3), 47 (CH(_2)), 27 (CH(_3))</td>
</tr>
<tr>
<td>10d</td>
<td>4'-Cl</td>
<td>8.9 (bs, NH), 7.94 (s, NH), 7.5 (d, 2H\textsubscript{arom}, H-3',5', ( J = 5.3 )), 7.3 (d, 2H\textsubscript{arom}, H-2',6', ( J = 4.9 )), 6.3 (s, 1H\textsubscript{arom}, H-5), 3.9 (s, 9H, 3\times OCH(_3)), 3.8 (m, 2H, H-3), 3.71 (s, 2H, H-11), 2.91 (m, 2H, H-4), 2.2 (s, 3H, H-13)</td>
<td>177 (CO), 149 (C-8), 148 (C-6), 136 (C-7), 131 (C-4'), 130 (C-3', C-5'), 129 (C-10), 126 (C-2', C-6'), 121 (C-9), 75 (C-1), 65 (3\times OCH(_3)), 60 (C-3), 47 (CH(_2)), 27 (CH(_3))</td>
</tr>
<tr>
<td>10e</td>
<td>3'-OCH(_3)</td>
<td>8.45 (bs, NH), 7.67 (s, NH), 7.33 (d, 1H\textsubscript{arom}, H-5', 4.3), 7.1 (d, 1H\textsubscript{arom}, H-4', 4.2), 6.5 (d, 1H\textsubscript{arom}, H-5, 3.3), 6.43 (d, 1H\textsubscript{arom}, H-2', 3.9), 6.3 (s, 1H\textsubscript{arom}, H-6'), 3.9 (s, 9H, 3\times OCH(_3)), 3.8 (m, 2H, H-3), 3.71 (s, 2H, H-11), 2.91 (m, 2H, H-4), 2.2 (s, 3H, H-13)</td>
<td>181 (CS), 177 (CO), 162 (C-3'), 149 (C-8), 148 (C-6), 140 (C-1), 136 (C-7), 131 (C-4'), 129 (C-10), 126 (C-2', C-6'), 121 (C-9), 118 (C-5'), 104 (C-5), 75 (C-1), 65 (3\times OCH(_3)), 64 (OCH(_3)), 60 (C-3), 47 (CH(_2)), 27 (CH(_3))</td>
</tr>
</tbody>
</table>
2.13 Synthesis N-phenyl-4-(6’,7’,8’-trimethoxyisochromanyl)-1,3,4-thiadiazoles \[^{[133]}\]

Isochromanyl-1,3,4-thiadiazine were obtained in 77-86% yield by acid catalysed intramolecular cyclization of isochromanylthiosemicarbazides \[^{[133]}\] after three hours stirring (Scheme 2.24).

\[
\text{Scheme 2.24: Isochromanyl thiaiazole.}
\]

IR spectra show disappearance of NH stretching and appearance of C=N and C-S stretching at 1346-1423, and 1231-1271 respectively, which shows ring closure. Physical data with IR stretching is presented in Table 2.54.

**Table 2.54: Physical data of 1-Isochromanyl thiaiazoles (11a-11e).**

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>Yield (%)</th>
<th>M.P.(°C)</th>
<th>R(f^*)</th>
<th>IR (cm(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>11a</td>
<td>2”-OCH(_3)</td>
<td>80</td>
<td>Oil</td>
<td>0.6</td>
<td>3193, 1625, 1423, 1231</td>
</tr>
<tr>
<td>11b</td>
<td>4”-CH(_3)</td>
<td>83</td>
<td>Oil</td>
<td>0.7</td>
<td>3305, 1617, 1367, 1271</td>
</tr>
<tr>
<td>11c</td>
<td>4”-OCH(_3)</td>
<td>77</td>
<td>Oil</td>
<td>0.8</td>
<td>3315, 1622, 1343, 1272</td>
</tr>
<tr>
<td>11d</td>
<td>4”-Cl</td>
<td>81</td>
<td>Oil</td>
<td>0.8</td>
<td>3294, 1632, 1359, 1254,</td>
</tr>
<tr>
<td>11e</td>
<td>3”-OCH(_3)</td>
<td>86</td>
<td>Oil</td>
<td>0.5</td>
<td>3278, 1589, 1346, 1256</td>
</tr>
</tbody>
</table>

\[^{*}\] Petroleum ether: Ethyl acetate (3:2)
In $^1$HNMR spectra disappearance of signals for NH-2 and NH-3 groups of thiosemicarbazides and appearance of one singlet for NH group of the isochromanyl thiadiazole group at $\delta$ 7.7-8.15 ppm was observed. In $^{13}$CNMR signal at $\delta$ 168-171 for C-5 carbon and $\delta$ 150-154 ppm for C-2 carbon of the thiadiazole ring was observed. $^1$HNMR and $^{13}$CNMR data of the isochromanyl thiadiazoles is given in Table 2.55.

**Table 2.55: $^1$HNMR and $^{13}$CNMR data of Isochromanyl thiadiazoles (11a-11e).**

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>$^1$HNMR</th>
<th>$^{13}$CNMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>11a</td>
<td>2'&quot;-OCH$_3$</td>
<td>7.7 (bs, NH), 7.5 (d, 1H$<em>{arom}$, $J$ = 3.2), 7.3 (d, 1H$</em>{arom}$, $J$ = 5.5), 7.1 (d, 1H$<em>{arom}$, $J$ = 3.2), 6.5 (s, 1H$</em>{arom}$), 3.9 (s, 12H, 4×OCH$_3$), 3.82 (m, 2H, H-3), 3.74 (s, 2H, H-11), 2.91 (m, 2H, H-4), 2.2 (s, 3H, H-13)</td>
<td>170 (C=N), 154 (C$_2$N), 148 (C-6', C-8'), 146 (C-2'), 134 (C-7'), 133 (C-1'), 128 (C-10'), 124 (C-9'), 122 (C-4''), 116 (C-5''), 112 (C-4''), 105 (C-5'), 70 (C-3''), 65 (3×OCH$_3$), 63 (OCH$_3$), 35 (C-4''), 26, 23</td>
</tr>
<tr>
<td>11b</td>
<td>4&quot;-CH$_3$</td>
<td>8.0 (bs, NH), 7.3 (d, 2H$<em>{arom}$, $J$ = 5.6), 7.22 (d, 2H$</em>{arom}$, $J$ = 4.3), 6.5 (s, 1H$_{H-5}$), 3.9 (s, 9H, 3×OCH$_3$), 3.84 (m, 2H, H-3), 3.7 (s, 2H, H-11), 2.5 (m, 2H, H-4), 2.3 (s, 3H, CH$_3$)</td>
<td>168 (C=N), 153 (C$_2$N), 148 (C-6', C-8'), 141 (C-1''), 134 (C-7''), 130 (C-3''), C-5''), 129 (C-4''), 128 (C-10'), 124 (C-9''), 113 (C-2''', C-4''), 105 (C-5'), 70 (C-3''), 65 (3×OCH$_3$), 63 (OCH$_3$), 35 (C-4''), 26, 23</td>
</tr>
<tr>
<td>11c</td>
<td>4&quot;-OCH$_3$</td>
<td>8.1 (bs, NH), 7.7 (d, 2H$<em>{arom}$, $J$ = 5.2), 7.4 (d, 2H$</em>{arom}$, $J$ = 5.3), 6.5 (s, 1H, H-5), 3.92 (m, 2H, H-3), 3.84 (s, 12H, 4×OCH$_3$), 3.7 (s, 2H, H-11), 2.9 (m, 2H, H-4), 2.2 (s, 3H, H-13), 1.5 (s, 3H, CH$_3$)</td>
<td>169 (C=N), 155 (C$_2$N), 148 (C-6', C-8'), 141 (C-1''), 134 (C-7''), 130 (C-3''), C-5''), 129 (C-4''), 128 (C-10'), 124 (C-9''), 113 (C-2''', C-4''), 105 (C-5'), 70 (C-3''), 65 (3×OCH$_3$), 63 (OCH$_3$), 35 (C-4''), 26, 23</td>
</tr>
<tr>
<td>11d</td>
<td>4&quot;-Cl</td>
<td>8.1 (bs, NH), 7.8 (d, 2H$<em>{arom}$, $J$= 5.0), 7.5 (d, 2H$</em>{arom}$, $J$ = 5.0), 6.44 (s, 1H, H-5), 3.9 (s, 9H, 3×OCH$_3$), 3.85 (m, 2H, H-3), 3.71 (s, 2H, H-11), 2.93 (m, 2H, H-4), 2.2 (s, 3H, H-13)</td>
<td>171 (C=N), 152 (C$_2$N), 148 (C-6', C-8'), 141 (C-1''), 136 (C-3'', C-5''), 134 (C-7''), 129 (C-4''), 128 (C-10'), 124 (C-9''), 121 (C-2'', C-4''), 105 (C-5'), 70 (C-3''), 65 (3×OCH$_3$), 61 (OCH$_3$), 35 (C-4''), 26, 23</td>
</tr>
<tr>
<td>11e</td>
<td>3&quot;-OCH$_3$</td>
<td>8.15 (bs, NH), 7.7 (s, 1H), 7.66 (d, 1H$<em>{arom}$, $J$ = 4.5), 7.32 (d, 1H$</em>{arom}$, $J$ = 4.5), 6.6 (d, 1H$_{arom}$, $J$ = 3.2), 6.43 (s, 1H, H-5), 3.9 (s, 9H, 3×OCH$_3$), 3.87 (m, 2H, H-3), 3.75 (s, 2H, H-11), 2.91 (m, 2H, H-4), 2.25 (s, 3H, H-13)</td>
<td>169 (C=N), 152 (C$_2$N), 148 (C-6', C-8'), 145 (C-3'''), 141 (C-1''), 134 (C-7''), 130 (C-5''), 128 (C-10'), 124 (C-9''), 121 (C-2'', C-4''), 110 (C-6''), 105 (C-5'), 104 (C-4''), 70 (C-3''), 65 (3×OCH$_3$), 61 (OCH$_3$), 35 (C-4''), 26, 23</td>
</tr>
</tbody>
</table>
In the mass spectrum of N-\(p\)-chlorophenyl-2-(6',7',8'-trimethoxyisochromanyl)-1,3,4-thiadiazole (11d) molecular ion peak was found to the most stable one (Scheme-2.24).

![Scheme 2.24: Mass fragmentation of N-\(p\)-chlorophenyl-2-(6',7',8'-trimethoxyisochromanyl)-1,3,4-thiadiazoles (11d).](image)

Compound (11c) having electron donating methoxy group substituted at para position of the phenyl group attached to the amino group of thiadiazole ring showed maximum bacterial inhibition which was comparable to the standard drugs for both strains of bacteria. While remaining isochromanyl thiadiazoles showed good to moderate inhibition Table 2.56.
Table 2.56: Antibacterial activities of N-(phenyl)-5-(6,7,8-trimethoxy-1-methyl-3,4-dihydro-1H-isochromen-1-yl)-1,3,4-thiadiazole-2-amines (11a-11e).

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>E. coli</th>
<th>B. subtilis</th>
</tr>
</thead>
<tbody>
<tr>
<td>11a</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>11b</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>11c</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>11d</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>11e</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>-ve control (Acetone)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>-</td>
<td>20</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>15</td>
<td>-</td>
</tr>
</tbody>
</table>

Concentration used: 5mg/mL; -: no activity.

Zone of inhibition (radius, mm)

In case of antifungal activities [134] maximum % age inhibition was observed by compound (11b) having methyl group substituted at para to the amino aryl group. While remaining isochromanyl thiazoles showed moderate inhibition against yeast cells.
Table 2.57: Anti-fungal activities of N-(phenyl)-5-(6,7,8-trimethoxy-1-methyl-3,4-dihydro-1H-isochromen-1-yl)-1,3,4-thiadiazole-2-amines (11a-11e).

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>S. cerevisiae (ZI, cm)</th>
<th>S. cerevisiae (PI, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11a</td>
<td>0.9</td>
<td>25</td>
</tr>
<tr>
<td>11b</td>
<td>0.6</td>
<td>50</td>
</tr>
<tr>
<td>11c</td>
<td>1.1</td>
<td>8.3</td>
</tr>
<tr>
<td>11d</td>
<td>1.0</td>
<td>16.6</td>
</tr>
<tr>
<td>11e</td>
<td>1.0</td>
<td>16.6</td>
</tr>
<tr>
<td>-ve control (acetone)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>1.2</td>
<td>100</td>
</tr>
</tbody>
</table>

Concentration used: 5mg/mL; -: no activity

ZI: zone of inhibition; PI: percent inhibition = 100 - fungal growth in sample (cm) / fungal growth in control (cm) \times 100

In case of phytotoxic studies all the thiadiazoles with isochromanyl moiety had ability to inhibit the growth of physalis plant which was observed by blackening and pale yellowing of the Physalis leave Table 2.58.
Table 2.58: Phytotoxic activity of Isochromanyl thiadiazoles (11a-11e).

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Phytotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>12a</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>12b</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>12c</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>12d</td>
<td>Pale yellow</td>
</tr>
<tr>
<td>12e</td>
<td>Pale yellow</td>
</tr>
</tbody>
</table>

Concentration used: 5mg/mL; -: no activity.

2.14 Synthesis of 4-Phenyl-5-(6',7',8'-trimethoxyisochromanyl)acetyl-1,2,4-triazole-3-thiones [133] (12a-12e)

Isochromanyl-1,2,4-triazole-3-thiones were obtained in 64-86% yield by base catalysed intramolecular cyclization of isochromanyl thiosemicarbazides after two hours reflux [133] (Scheme 2.25).

![Scheme-2.25: Synthesis of Isochromanyl triazole.](image-url)
In IR spectra disappearance of NH stretching and appearance of C= N stretching at 1421-1598 which shows that ring closure. Physical and IR data is given in Table 2.59.

**Table 2.59: Physical data of Isochromanyl triazole (12a-12e).**

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>Yield (%)</th>
<th>M.P.(°C)</th>
<th>Rf*</th>
<th>IR (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12a</td>
<td>2”-OCH₃</td>
<td>78</td>
<td>oil</td>
<td>0.6</td>
<td>3012, 1589, 1441, 1218</td>
</tr>
<tr>
<td>12b</td>
<td>4”-CH₃</td>
<td>82</td>
<td>oil</td>
<td>0.5</td>
<td>3122, 1598, 1423, 1247</td>
</tr>
<tr>
<td>12c</td>
<td>4”-OCH₃</td>
<td>64</td>
<td>oil</td>
<td>0.8</td>
<td>3127, 1592, 1423, 1256</td>
</tr>
<tr>
<td>12d</td>
<td>4”-Cl</td>
<td>77</td>
<td>oil</td>
<td>0.7</td>
<td>3011, 1567, 1423, 1247</td>
</tr>
<tr>
<td>12e</td>
<td>3”-OCH₃</td>
<td>86</td>
<td>oil</td>
<td>0.6</td>
<td>3117, 1573, 1421, 1245</td>
</tr>
</tbody>
</table>

* Petroleum ether: Ethyl acetate (4:1)

In ¹HNMR spectra disappearance of signals for NH group and appearance of one singlet for NH group of the isochromanyl triazole group at δ 8.87-11.30 ppm show the ring closure. ¹HNMR and ¹³CNMR data of the isochromanyl triazoles is given in Table 2.60.
Table-2.60: $^1$HNMR and $^{13}$CNMR data of Isochromanyl triazole (12a-12e).

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Compd. No</th>
<th>R</th>
<th>$^1$HNMR</th>
<th>$^{13}$CNMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>12a</td>
<td>2&quot;-OCH$_3$</td>
<td>10.39 (bs, SH), 7.3 (d, 1H$<em>{arom}$, J = 3.2), 7.1 (d, 1H$</em>{arom}$, J = 5.5), 6.9 (d, 1H$<em>{arom}$, J = 3.1), 6.6 (d, 1H$</em>{arom}$, J = 4.1), 6.5 (s, 1H, H-5), 3.9 (s, 12H, 4×OCH$_3$), 3.86 (m, 2H, H-3), 3.74 (s, 2H, H-11), 2.94 (m, 2H, H-4), 2.1 (s, 3H, H-13), 1.6 (s, 3H, CH$_3$)</td>
<td>160 (CS), 158 (C-2''), 150 (CN), 149 (C-8), 148 (C-6), 136 (C-7), 128 (C-10), 127 (C-6''), 121 (C-9, C-5''), 114 (C-3'), 75 (C-1), 65 (OCH$_3$), 60 (C-3), 47 (CH$_2$), 27 (CH$_3$)</td>
</tr>
<tr>
<td>12b</td>
<td>4&quot;-CH$_3$</td>
<td>11.30 (bs, SH), 7.26 (d, 2H$<em>{arom}$, J = 5.1), 7.00 (d, 2H$</em>{arom}$, J = 4.6), 6.53 (s, 1H, H-5), 3.91 (s, 9H, 3×OCH$_3$), 3.85 (m, 2H, H-3), 3.69 (s, 2H, H-11), 2.5 (m, 2H, H-4), 2.3 (s, 3H, CH$_3$)</td>
<td>161 (CS), 152 (CN), 149 (C-8), 148 (C-6), 136 (C-7), 129 (C-3', C-5'), 128 (C-10), 126 (C-2', C-6''), 121 (C-9), 75 (C-1), 65 (3×OCH$_3$), 60 (C-3), 47 (CH$_2$), 27 (CH$_3$)</td>
</tr>
<tr>
<td>12c</td>
<td>4&quot;-OCH$_3$</td>
<td>9.8 (bs, SH), 7.4 (d, 1H$<em>{arom}$, J = 5.2), 7.33 (d, 2H$</em>{arom}$, J = 5.3), 6.58 (s, 1H, H-5), 3.92 (m, 2H, H-3), 3.84 (s, 12H, 4×OCH$_3$), 3.72 (s, 2H, H-11), 2.91 (m, 2H, H-4), 2.24 (s, 3H, CH$_3$)</td>
<td>160 (CS), 149 (C-8), 148 (C-6), 143 (CN), 136 (C-7), 129 (C-3', C-5'), 128 (C-10), 126 (C-2', C-6''), 121 (C-9), 75 (C-1), 65 (3×OCH$_3$), 60 (C-3), 47 (CH$_2$), 27 (CH$_3$)</td>
</tr>
<tr>
<td>12d</td>
<td>4&quot;-Cl</td>
<td>9.1 (bs, SH), 7.65 (d, 2H$<em>{arom}$, J = 4.9), 7.51 (d, 2H$</em>{arom}$, J = 5.1), 6.52 (s, 1H, H-5), 3.9 (s, 9H, 3×OCH$_3$), 3.85 (m, 2H, H-3), 3.71 (s, 2H, H-11), 2.93 (m, 2H, H-4), 1.90 (s, 3H, H-13)</td>
<td>153 (CN), 149 (C-8), 148 (C-6), 136 (C-7), 131 (C-4''), 130 (C-3'', C-5''), 129 (C-10), 126 (C-2'', C-6''), 121 (C-9), 75 (C-1), 65 (3×OCH$_3$), 60 (C-3), 47 (CH$_2$), 27 (CH$_3$)</td>
</tr>
<tr>
<td>12e</td>
<td>3&quot;-OCH$_3$</td>
<td>8.87 (bs, SH), 7.68 (s, 1H), 7.54 (d, 1H, H$<em>{arom}$, J = 4.1), 7.43 (d, 1H$</em>{arom}$, J = 4.6), 6.59 (d, 1H$_{arom}$, J = 5.1), 6.5 (s, 1H, H-5), 3.9 (s, 9H, 3×OCH$_3$), 3.87 (m, 2H, H-3), 3.75 (s, 2H, H-11), 2.92 (m, 2H, H-4), 1.98 (s, 3H, H-11), 1.65 (s, 3H, CH$_3$)</td>
<td>160 (CS), 149.3 (CN), 162 (C-3''), 149 (C-8), 148 (C-6), 140 (C-1), 136 (C-7), 131 (C-4''), 129 (C-10), 126 (C-2'', C-6''), 121 (C-9), 118 (C-5''), 104 (C-5), 75 (C-1), 65 (3×OCH$_3$), 64 (OCH$_3$), 60 (C-3), 47 (CH$_2$), 27 (CH$_3$).</td>
</tr>
</tbody>
</table>
In the mass spectrum molecular ion peak of the isochromanyl triazole is the most stable one. In mass spectrum of 4-(p-chlorophenyl)-5-(6',7',8'-trimethoxyisochromanyl)-1,2,4-triazole-3-thione (12d) molecular ion peak appear at m/z 461 a.m.u and was found to be the most abundant one. (Scheme 2.26)

Scheme 2.26: Mass fragmentation pattern of 4-(p-Chlorophenyl)-5-(6’,7’,8’-trimethoxyisochromanyl) acetyl-1,2,4-triazole-3-thione:

Compound (12d) having chloro group substituted at para position of aryl group of isochromanyl triazole showed maximum inhibition against both strain of bacteria Table 2.61.
Table 2.61: Antibacterial activities of 5-(6,7,8-Trimethoxy-1-methyl-3,4-dihydro-1H-isochromen-1-yl)-4H-1,2,4-triazole-3-thiones (12a-12e).

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>\textit{E. coli}</th>
<th>\textit{B. subtilis}</th>
</tr>
</thead>
<tbody>
<tr>
<td>12a</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>12b</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>12c</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>12d</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>12e</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>-ve control (acetone)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>-</td>
<td>20</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>15</td>
<td>-</td>
</tr>
</tbody>
</table>

Concentration used: 5mg/mL; -: no activity.

Zone of inhibition (radius, mm)

In case of antifungal activities \cite{134} maximum % age inhibition was observed by compound (12c) having electron donating methoxy group substituted at para position of aryl group of isochromanyl triazole. All other isochromanyl triazoles showed moderate percentage inhibition against yeast cells Table 2.62.
Table 2.62: Antifungal activities of 5-(6,7,8-Trimethoxy-1-methyl-3,4-dihydro-1H-isochromen-1-yl)-4H-1,2,4-triazole-3-thiones (12a-12e).

In case of phytotoxic studies, all the isochromanyl triazoles were found active for growth inhibition of Physalis plant Table 2.63.

Table 2.63: Phytotoxic activity of Isochromanyl triazoles (12a-12e).
3.1 Substrates and Reagents

Substituted benzoic acids (o-bromo, p-fluoro, p-methyl, 3,4-dimethoxy, 3,5-dimethoxy, 3,4,5-trimethoxy, cinnamic acid), substituted aldehydes (p-fluoro, o-chloro, m-chloro, m-bromo, p-bromo, p-methoxy, vanillin aldehydes, 3,4,5-trimethoxy, 2-fufuryl aldehydes), substituted anilines (o, m, p-methoxy aniline, p-chloro aniline, o-methyl aniline), alpha amino alcohols, sodium borohydride were purchased from Aldrich. Acetyl acetone, methyl acetoacetate was purchased from fluka. Diethyl ether was purchased from Riedel de Haën. Lead nitrate was purchased from Fisher Scientific and solvents: ethanol, methanol, acetone, dichloromethane, ethyl acetate were obtained from local commercial stores.

3.2 Purification of Solvents \[134a-e\]

Solvent used were purified and dried according to standard procedures and were stored on molecular sieves (4°A).

3.2.1 Methanol \[134a\]

Activated calcium oxide in the oven was added into methanol. Refluxed for 5-6 h and then distilled. Distilled methanol was stored on molecular sieves.

3.2.2 Ethanol \[134a\]

Activated calcium oxide in the oven was added into ethanol. Refluxed for 5-6 h and then distilled. Distilled ethanol was stored on molecular sieves.

3.2.3 Acetone \[134b\]

Activated calcium oxide was added into acetone after 6-7 h reflux acetone was distilled and stored on molecular sieves.

3.2.4 Ethyl acetate \[134c\]

For the purification and drying of ethyl acetate calcium hydride was added stirred for 2 h refluxed for 5-6 h and distilled.
3.2.5 **Diethyl ether** \[^{[134d]}\]

Diethyl ether was refluxed with calcium oxide and then distilled. Distillate was then refluxed with sodium wire and benzophenone till the blue colour persisted, distilled and stored on molecular sieves.

3.2.6 **Benzene** \[^{[134c]}\]

For the drying of benzene first it was refluxed with calcium oxide. Distillate was then refluxed with sodium wire in benzophenone. Distilled and dried benzene was stored on molecular sieve.

3.3 **Instruments used**

Melting points were recorded using a digital Gallenkamp (SANYO) model MPD BM 3.5 apparatus and are uncorrected. \(^1\)H NMR spectra were determined as chloroform-\(d_3\), DMSO-\(d_6\), methanol-\(d_4\) and acetone-\(d_6\) solutions at 300 MHz using a Bruker AM-300 spectrophotometer. FTIR spectra were recorded using an FTS 3000 MX spectrophotometer; Mass Spectra (EI, 70 eV) on a GC-MS instrument Agilent technology USA. The microwave reactions were carried out in an unmodified domestic microwave oven (MW 900 W, frequency 2450 MHz, Power level 1, Dawlance, Pakistan). All compounds were purified by thick layer chromatography using silica gel from Merck (Germany).

3.4 **Synthesis of Some Substituted benzoyl esters** \[^{[118]}\]

To a stirred solution of substituted benzoic acid in methanol, sulfuric acid was added and refluxed for 6-12 hours.

\[
\begin{align*}
\text{R}O & \quad \overset{\text{MeOH, H}}{\text{O}} \quad \overset{\text{6-12h reflux}}{\text{MeOH, H}} \\
\text{OH} & \quad \text{OMe}
\end{align*}
\]

3.4.1 **Methyl 2-bromobenzoate (1)**

Yield: 96%: m.p.: oil, IR (NaCl Cell): 2917, 1730, 1636, 1524, 1426, 1351, 1112, 1141, 712, 688, cm\(^{-1}\); \(^1\)HNMR (CDCl\(_3\)): \(\delta\) 7.66 (dd, 1\(H_{arom}\), CH\(CCO\)), 7.54 (dd, 1\(H_{arom}\), CH\(CCBr\)), 6.93 (dd, 1\(H_{arom}\), CH\(CCBr\)), 6.23 (dd, 1\(H_{arom}\), CH\(CCCO\)), 3.37 (s, 3H, OCH\(_3\)).
3.4.2 Methyl 4-fluorobenzoate (2)

![Methyl 4-fluorobenzoate](image)

Yield: 92%; m.p.: oil; IR (NaCl cell): 2900, 1732, 1613, 1524, 1410, 1353, 1154, 1141, 716, 674, cm⁻¹; ¹HNMR (CDCl₃): δ 7.52 (dd, 2H_arom, CHCCO), 7.34(dd, H_arom, CHCF), 3.37 (s, 3H, OCH₃).

3.4.3 Methyl 4-methylbenzoate (3)

![Methyl 4-methylbenzoate](image)

Yield: 95%; m.p.: oil; IR (NaCl Cell): 2922, 2912, 1735, 1524, 1426, 1343, 1123, 1144, 712, 688, cm⁻¹; ¹HNMR (CDCl₃): δ 7.71 (dd, 2H_arom, CHCCO), 7.34 (dd, 2H_arom, CHCCH₃), 3.37 (s, 3H, OCH₃), 2.56 (s, 3H, CH₃).

3.4.4 Methyl 3,4-dimethoxy benzoate (4)

![Methyl 3,4-dimethoxy benzoate](image)

Yield: 99%; m.p.: oil; IR (NaCl Cell): 2932, 2917, 1735, 1613, 1524, 1426, 1333, 1112, 1141, 722, 653, cm⁻¹; ¹HNMR (CDCl₃): δ 7.54 (d, 1H_arom, CHCCO), 7.54 (s, 1H_arom, CHCCCH₃), 6.97 (d, 1H_arom, CHCHCCO), 3.73 (s, 6H, 2×OCH₃), 3.37 (s, 3H, OCH₃).

3.4.5 Methyl 3,5-dimethoxybenzoate (5)

![Methyl 3,5-dimethoxybenzoate](image)

Yield: 99%; m.p.: oil; IR (NaCl Cell) 2932, 2923, 1734, 1521, 1426, 1287, 1111, 722, 653, cm⁻¹; ¹HNMR (CDCl₃): δ 7.21 (s, 2H_arom, CHCCO), 6.87 (s, 1H_arom, CHCOCH₃), 3.73 (s, 6H, 2×OCH₃), 3.37 (s, 3H, OCH₃).
3.4.6 Methyl 3,4,5-trimethoxy benzoate (6)

Yield: 99%; m.p.: oil; IR (NaCl Cell): 2932, 2917, 1732, 1524, 1426, 1333, 1112, 1141, 722, 653, cm⁻¹;¹HNMR (CDCl₃) δ 6.63 (s, 2H arom, CH₂CO), 3.73 (s, 9H, 3×OCH₃), 3.37 (s, 3H, OCH₃).

3.4.7 Methyl 4-methyl-3,5-dimethoxybenzoate (7)

Methyl 3,5-dibromo-4-methylbenzoate

Aluminium chloride (1.6 mmol) was added portion wise to a stirred solution of (3). Bromine (1.25 mmol) was added to the reaction mixture during 45 min. at such a rate in order to keep the temperature of reaction mixture at or below 20°. The reaction mixture was stirred for further 30 mins and was refluxed at 80-85° for one hour. The reaction was then brought to 30° methanol (20 mL) was added during 30 mins, and stirred for overnight. The solid product was filtered, washed with methanol and subjected to crystallization.

Yield: 81%; m.p (°C): 85-86; Rf: 0.2; IR (KBr): 1695, 1593;¹HNMR (CDCl₃) δ 7.86 (s, 2H arom), 3.78 (s, 3H, OCH₃), 2.31 (s, 3H, CH₃arom).

4-Methyl-3,5-dimethoxymethylbenzoic acid

To a solution of sodium methoxide [made from sodium (0.9 mol) in methanol and copper chloride (0.0125 mol)], a pyridine solution of methyl-3,5-dibromo-4-methylbenzoate was added and refluxed for 15 hour under nitrogen. Solid product was cooled to room temperature and filtered off. Methanol (100 mL) was added to the filter cake and refluxed for 1 h. The reaction mixture was diluted with brine (30 mL) on cooling. Reaction mixture was extracted with ethyl acetate, aqueous layer was acidified with concentrated hydrochloric acid again extracted with ethyl acetate organic layer was collected, dried on anhydrous sodium sulfate filtered and rotary evaporated.

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Yield: 82%; m.p (°C): 2185-219; Rf (Petroleum ether : Ethyl acetate, 9:1): 0.4; IR (KBr): 1723, 1601; $^1$HNMR (CDCl$_3$) δ 10.8 (s, 1H, OH), 6.72 (s, 2H$_{arom}$), 3.89 (s, 6H, 2×OCH$_3$), 2.24 (s, 3H, CH$_3$)$_{arom}$).

Yield: 99%; m.p: oil; IR (NaCl Cell): 2932, 2917, 1732, 1613, 1524, 1426, 1333, 1112, 1141, 722, 653, cm$^{-1}$; $^1$HNMR (CDCl$_3$) δ 6.54 (s, 2H$_{arom}$, CHCCO), 3.73; (s, 9H, 2×OC$_n$H$_3$), 3.37 (s, 3H, OCH$_3$), 2.54(s, 3H, CH$_3$).

**3.4.8 Methyl 5-phenyl-2,4-dienylpentanoate (8)**

Yield: 89%; m.p: oil; IR (NaCl Cell): 2932, 1735, 1621, 1524, 1426, 1333, 1223, 1112, 1012, 722, 653, cm$^{-1}$, $^1$HNMR (CDCl$_3$): δ 7.12-6.33 (m, 5H$_{arom}$), 6.29 (d, 1H$_a$, $J$= 6.3), 6.21 (d, 1H$_b$, $J$= 4.5).6.1 (d, 1H$_b$, $J$ = 5.7), 5.8 (d, 1H$_b$, $J$ = 5.5)3.37 (s, 3H, OCH$_3$).

**3.5 Synthesis of Some Substituted hydrazides $^{[119]}$**

To a stirred solution of hydrazine hydrate (85 %) (0.094 mol) was added the methyl substituted benzoate (1g, 0.0047 mol) portion wise and the mixture was heated under reflux for 15 min. Then methanol (25.0 mL) was then added and the reaction mixture was refluxed for 4 h. The product precipitated out, was filtered, washed with water, dried and recrystallized from methanol to afford corresponding hydrazide as colorless needles.
3.5.1 2-Bromobenzoyl hydrazide (1’)

![2-Bromobenzoyl Hydrazide](image)

Yield: 87%; m.p.(°C): 123-124. **IR** (KBr): 3324, 3134, 3084, 1621, 1543, 1311, 1427, 1110, 1146, 733, 688, 676, 511 cm\(^{-1}\); **\(^1\)HNMR** (DMSO-\(d_6\)): \(\delta 9.11\) (br s, 1H, CONH), 7.62 (dd, 1H\(_{arom}\), CHCO), 7.45(dd, 1H\(_{arom}\), CHCl), 6.67(dd, 1H\(_{arom}\), CHCCl), 6.23(dd, 1H\(_{arom}\), CHCCl), 4.57 (brs, 2H, NH\(_2\)); **EIMS**, m/z (%): 213.97 [M\(^+\)] (63), 182 (46), 154 (25).

3.5.2 4-Fluorobenzoyl hydrazide (2’)

![4-Fluorobenzoyl Hydrazide](image)

Yield: 89%; m.p (°C): 133-134; **IR** (KBr): 3316, 3162, 3110, 1634, 1513, 1311, 1431, 1110, 1146, 733, 688, 676, 511 cm\(^{-1}\); **\(^1\)HNMR** (DMSO-\(d_6\)): \(\delta 9.89\) (bs, 1H, CONH), 7.62 (dd, 2H\(_{arom}\), CHCO), 7.45(dd, 1H\(_{arom}\), CHCl), 4.64 (bs, 2H, NH\(_2\)); **EIMS**, m/z (%): 154 [M\(^+\)] (65), 123 (39), 95 (22).

3.5.3 4-Methylbenzoyl hydrazide (3’)

![4-Methylbenzoyl Hydrazide](image)

Yield: 88%; m.p (°C): 117-118; **IR** (KBr): 3335, 3100, 3034, 2929, 1631, 1522, 1313, 1459, 1117, 1109, 733, 681, 644, 524 cm\(^{-1}\); **\(^1\)HNMR** (DMSO-\(d_6\)): \(\delta 9.91\) (bs, 1H, CONH); 7.87 (dd, 2H\(_{arom}\), CHCO), 7.23(dd, 2H\(_{arom}\), CHCCl), 4.57 (bs, 2H, NH\(_2\)), 2.52(s, 3H, CH\(_3\)); **EIMS** (70 eV) m/z (%): 150 [M\(^+\)] (56), 119 (78), 91 (72).

3.5.4 3,4-Dimethoxybenzoyl hydrazide (4’)

![3,4-Dimethoxybenzoyl Hydrazide](image)

Yield: 83%; m.p (°C): 166-167; **IR** (KBr): 3316, 3129, 3065, 2921, 1636, 1442, 1313, 1459, 1136, 1121, 733, 688, 640, 503 cm\(^{-1}\); **\(^1\)HNMR** (DMSO-\(d_6\)): \(\delta 9.95\) (bs, 1H,
CONH; 7.65 (d, 1H_{arom}, CHCCO), 7.55(s, 1H_{arom}, CHCCOCH_{3}), 7.11 (d, 1H_{arom}, CHCHCCO), 4.77 (bs, 2H, NH_{2}), 3.73,(s, 6H, 2\times OCH_{3}); \textbf{EIMS} (70 eV) m/z (%): 197 [M^+] (56), 165 (51), 137 (38).

3.5.5 3,5-Dimethoxybenzoyl hydrazide (5')

\[
\begin{align*}
\text{MeO} & \quad \text{NH-NH}_2 \\
\text{OMe} & \quad \text{O} \\
\end{align*}
\]

Yield: 80%; m.p. (°C): 119-120; \textbf{IR} (KBr): 3334, 3110, 3023, 1630, 1442, 1313, 1459, 1136, 1121, 733, 688, 640, 503 cm\(^{-1}\); \textbf{\textsuperscript{1}HNMR} (DMSO-d\(_6\)): \(\delta\) 9.95 (bs, 1H, CONH); 7.24 (s, 2H_{arom}, CHCCO), 6.9(s, 1H_{arom}, CHCOCH_{3}), 4.77 (bs, 2H, NH_{2}), 3.73,(s, 6H, 2\times OCH_{3}); \textbf{EIMS} (70 eV): m/z (%): 197 [M^+] (56), 165 (51), 137 (38).

3.5.6 3,4,5-Trimethoxybenzoyl hydrazide (6')

\[
\begin{align*}
\text{MeO} & \quad \text{NH-NH}_2 \\
\text{OMe} & \quad \text{O} \\
\end{align*}
\]

Yield: 78%; m.p. (°C): 161-162; \textbf{IR} (KBr): 3311, 3198, 3172, 2921, 1623, 1516, 1326, 1459, 1113, 1123, 733, 681, 640, 511 cm\(^{-1}\); \textbf{\textsuperscript{1}HNMR} (DMSO-d\(_6\)): \(\delta\) 8.87 (bs, 1H, CONH), 6.67 (s, 2H_{arom}, CHCCO), 4.64 (bs, 2H, NH_{2}), 3.73,(s, 9H, 3\times OCH_{3}); \textbf{EIMS} (70 eV) m/z (%): 226 [M^+] (63), 195 (52), 167 (38).

3.5.7 4-Methyl-3,5-dimethoxybenzoyl hydrazide (7')

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \\
\text{H}_3\text{C} & \quad \text{NHNH}_2 \\
\text{OCH}_3 & \quad \text{O} \\
\end{align*}
\]

Yield: 82%; m.p. (°C): 220-221; \textbf{IR} (KBr): 3311, 3198, 3072, 2921, 1636, 1516, 1326, 1459, 1113, 1151, 733, 688, 640, 503 cm\(^{-1}\); \textbf{\textsuperscript{1}HNMR} (DMSO-d\(_6\)): \(\delta\) 9.95 (bs, 1H, CONH), 8.05 (s, 1H, ArH), 4.57 (bs, 2H, NH_{2}), 3.37 (s, 6H, MeO-x2); 2.53 (s, 3H, ArCH_{3}); \textbf{EIMS} (70 eV), m/z (%): 210 [M^+] (63), 177 (52), 149 (38).
3.5.8 5-Phenylpenta-2,4-dienehydrazide (8’)

![Structural formula of 5-Phenylpenta-2,4-dienehydrazide (8')]()  

Yield: 81%; m.p. (°C): 198-199; IR (KBr): 3323, 3191, 3077, 2922, 1633, 1617, 1545, 1312, 1459, 1113, 1151, 733, 688, 640, 503 cm\(^{-1}\); \(^1\)HNMR (DMSO-\(d_6\)): \(\delta\) 9.95 (bs, 1H, CONH); 8.05 (s, 1H, ArH), 6.29 (d, 1H\(_\alpha\), \(J= 6.3\) ), 6.21 (d, 1H\(_\beta\), \(J= 4.5\) ), 6.1 (d, 1H\(_\delta\), \(J= 5.7\) ), 5.8 (d, 1H\(_\gamma\), \(J= 5.5\) ), 4.57 (br s, 2H, NH\(_2\)); EIMS (70 eV), m/z (%): 188 [M\(^+\)] (56), 98 (51), 90 (88).

3.6 Microwave Assisted Synthesis of Some 2-(3,5-Dimethoxy-4-methylphenyl)-5-aryl-1,3,4-oxadiazoles

**General Procedure for the Preparation of 1,3,4-Oxadiazoles [121]** (1a–h)

A homogenized mixture of hydrazide (1 mmol), carboxylic acid (1 mmol) in thionyl chloride (1-2 drops) was irradiated for 1.3-2.2 min in an alumina bath inside a microwave oven. On completion of the reaction, followed by TLC examination the reaction mixture was diluted with ethyl acetate and subjected directly to thick layer chromatography on silica gel. Recrystallized using ethyl acetate to afford 1,3,4-oxadiazoles (1a–h).

![Scheme 3.1: Solvent-free synthesis of some 2-(3,5-Dimethoxy-4-methylphenyl)-5-aryl-1,3,4-oxadiazoles](image)

**3.6.1 2-(3,5-Dimethoxy-4-methylphenyl)-5-(2’-methyl)aryl-1,3,4-oxadiazole (1a)**

Yield: 73%; m.p (°C): 95-97; R\(_f\) (Petroleum ether : Ethyl acetate, 7:3): 0.9; IR (KBr):
2930, 1618, 1536, 1491, 1452, 1383, 1252, 775, 681, \text{cm}^{-1}; \textsuperscript{1}^\text{HNMR} (\delta) (\text{ppm}) (J=\text{Hz}): 
8.2 (s, 2H\textsubscript{arom}), 7.8-7.3 (m, 4H\textsubscript{arom}), 3.96 (s, 6H, 2\times \text{OCH}_3), 2.81 (s, 3H \text{CH}_3), 2.67 (s, 3H, \text{CH}_3); \textsuperscript{13}^\text{CNMR}: \delta \text{ 164 (CO), 141.37, 138.71, 138.49, 131.84, 131.54, 131.22, 129.73, 128.96, 126.27, 126.23, 123.99, 123.0, 122.80, 122.56, 107.0 (C-1, C-6), 56.14 (\text{OCH}_3), 29.73 (\text{CH}_3\textsubscript{arom}), 23.25; \text{EIMS} (70 \text{eV}), m/z (\%): 310 (M'^{+}), (33), 179 (100).

\textbf{3.6.2 2-(3,5-Dimethoxy-4-methylphenyl)-5-(4'-methyl)aryl-1,3,4-oxadiazole (1b)}

\begin{align*}
\text{H}_3\text{CO} & \quad \text{H}_3\text{C} \\
\text{OCH}_3 & \quad \text{OCH}_3
\end{align*}

Yield: 85%; m.p (°C): 95-97; R\textsubscript{f} (Petroleum ether : Ethyl acetate, 7:3): 0.9; \textbf{IR} (KBr): 
2925, 1684, 1613, 1285, 1180, 734, 471, \text{cm}^{-1}; \textsuperscript{1}^\text{HNMR} (\delta) (\text{ppm}) (J=\text{Hz}): 8.1 (s, 2H\textsubscript{arom}), 7.4 (d, J=5.7, 2H\textsubscript{arom}), 6.95 (d, J =5.6, 2H\textsubscript{arom}), 3.9 (s, 6H, 2\times \text{OCH}_3), 2.7 (s, 3H, \text{CH}_3), 2.5 (s, 3H, \text{CH}_3); \textsuperscript{13}^\text{CNMR}: \delta \text{ 165 (C-1, CO), 141.37 (C-5, CO), 138.36, 138.34, 131.84, 131.54, 23.25, 131.22, 129.73, 126.27, 123.99, 123.0, 29.17, 122.80, 122.56, 107.0 (\text{OCH}_3), 56.16 (\text{CH}_3\textsubscript{arom}), \text{EIMS} m/z (\%): 310 (M'^{+}), (42), 179 (100).

\textbf{3.6.3 2-(3,5-Dimethoxy4-methyl-phenyl)-5-(2'-bromo)aryl-1,3,4-oxadiazole (1c)}

\begin{align*}
\text{H}_3\text{CO} & \quad \text{H}_3\text{C} \\
\text{OCH}_3 & \quad \text{Br}
\end{align*}

Yield: 74 %; m.p (°C): 99-100; R\textsubscript{f}(Petroleum ether : Ethyl acetate, 7:3): 0.8; \textbf{IR} (KBr): 
2942, 1641, 1304, 1027, 730, 617, 473, \text{cm}^{-1}; \textsuperscript{1}^\text{HNMR} (\delta) (\text{ppm}) (J=\text{Hz}): 8.1 (s, 2H\textsubscript{arom}), 7.9-6.8 (m, 4H\textsubscript{arom}), 3.8 (s, 6H, 2\times \text{OCH}_3), 2.4 (s, 3H, \text{CH}_3); \textsuperscript{13}^\text{CNMR}: \delta \text{ 161.01 (C-1, CO), 141.37 (C-5, CO), 138.16, 138.49, 131.81, 131.22, 129.72, 128.96, 126.23, 123.99, 123.0, 122.80, 122.56, 107.0 (C-1, C-6), 56.14 (\text{OCH}_3), 29.07(\text{CH}_3\textsubscript{arom}); \text{EIMS}, m/z (\%): 375, 373 [M'^{+}] (31), 179 (100).
3.6.4 2-(3,5-Dimethoxy4-methyl-phenyl)-5-(4’-chboro)aryl-1,3,4-oxadiazole (1d)

![Chemical structure of 2-(3,5-Dimethoxy4-methyl-phenyl)-5-(4’-chboro)aryl-1,3,4-oxadiazole (1d)](image)

Yield: 71 %; m.p (°C): 136-137; Rf (Petroleum ether : Ethyl acetate, 7:3): 0.9; IR (KBr): 2937, 1730, 1542, 1482, 1271, 1090, 1009, 834, 619, 498, cm⁻¹; ¹H NMR (δ) (ppm) (J = Hz): 8.28 (s, 2H, Ar), 7.7 (dd, J = 3.3, 5.4, 2H arom), 7.55 (dd, J = 1.8, 7.2, 2H arom), 3.96 (s, 6H, 2×OCH₃), 2.67 (s, 3H, CH₃); ¹³C NMR: δ 159.61 (C-1, CO), 141.37 (C-5, CO), 138.36, 138.34, 131.84, 131.54, 131.22, 129.27, 126.27, 123.99, 123.0, 122.80, 122.56, 107 (C-1, C-6), 56 (OCH₃), 29.1 (CH₃ arom), 23.54 (CH₃ arom). EIMS m/z (%): 332, 330 [M⁺], (39), 179 (100).

3.6.5 2-(3,5-Dimethoxy4-methyl-phenyl)-5-(3-methoxybenzoyl)-1,3,4-oxadiazole (1e)

![Chemical structure of 2-(3,5-Dimethoxy4-methyl-phenyl)-5-(3-methoxybenzoyl)-1,3,4-oxadiazole (1e)](image)

Yield: 95%; m.p (°C): 167-168; Rf (Petroleum ether : Ethyl acetate, 7:3): 0.5; IR (KBr): 2922, 1730, 1606, 1542, 1482, 1270, 1090, 1009, 834, 619, 498 cm⁻¹; ¹H NMR (ppm) (J = Hz): δ 8.21 (s, 2H arom), 7.71-7.92 (m, 4H, Ar), 3.82 (s, 3H, OCH₃), 3.80 (s, 6H, 2×OCH₃), 3.67 (s, 2H, CH₂), 2.65 (s, 3H, CH₃); ¹³C NMR: δ 165.12 (C-1, CO), 141.37 (C-5, CO), 138.36, 138.34, 131.84, 131.54, 131.22, 129.27, 126.27, 123.99, 123.0, 122.80, 122.56, 107 (C-1, C-6), 56 (OCH₃), 29.1 (CH₃ arom), 23.54 (CH₃ arom). EIMS m/z (%): 340 [M⁺], (41), 179 (100).

3.6.6 2-(3,5-Dimethoxy4-methyl-phenyl)-5-(4’-methoxy)aryl-1,3,4-oxadiazole (1f)

![Chemical structure of 2-(3,5-Dimethoxy4-methyl-phenyl)-5-(4’-methoxy)aryl-1,3,4-oxadiazole (1f)](image)
Yield: 72%; m.p (°C): oil; R_{f}(Petroleum ether : Ethyl acetate, 7:3): 0.7; IR (KBr): 2912, 1730, 1617, 1237, 766, 614, 473 cm$^{-1}$; $^1$HNMR (ppm) (J=Hz): $\delta$ 8.1 (s, 2H$_{arom}$), 7.29 (d, J = 5.7, 2H$_{arom}$), 6.95 (d, J=5.7, 2H, Ar), 3.90 (s, 6H, 2×OCH$_3$), 3.89 (s, 3H, OCH$_3$), 2.3 (s, 3H, CH$_3$); $^{13}$CNMR: $\delta$, 151.58 (C-1, CO), 141.37 (C-5, CO), 138.66, 138.39, 131.84, 131.54, 129.73, 128.96, 126.27, 126.23, 123.99, 123.0, 122.76, 122.56, 104.0 (C-1, C-6), 56.71 (OCH$_3$), 56.14 (OCH$_3$), 29.41 (CH$_3$); EIMS, m/z (%), 327 [M$^+$], (28), 179 (100).

3.6.7 2-(3,5-Dimethoxy-4-methylphenyl)-5-(3',4'-dimethoxy)aryl-1,3,4-oxadiazole (1g)

Yield : 80%; m.p (°C): 138-139; R$_f$(Petroleum ether : Ethyl acetate, 7:3): 0.3; IR (KBr): 2941, 1617, 1466, 1422, 1350, 1269, 1186, 1024, 762, 467 cm$^{-1}$; $^1$HNMR (ppm) (J=Hz): $\delta$ 8.2 (s, 2H$_{arom}$), 7.29 (s, 1H, Ar), 7.02 (d, J=8.4, 1H$_{arom}$) 6.9, (d, J=8.7, 1H$_{arom}$), 3.99 (s, 6H, 2×OCH$_3$), 3.9 (s, 3H OCH$_3$), 3.86 (s,3H, OCH$_3$), 2.6 (s, 3H, CH$_3$); $^{13}$CNMR: $\delta$ 141.61 (C-5, CO), 138.76, 138.4, 131.84, 131.54, 131.22, 126.27, 129.73, 126.23, 123.99, 123.0, 122.80, 107.0 (C-1, C-6), 56.73 (OCH$_3$), 56.04 (OCH$_3$), 29.71 (CH$_3$), 23.25; EIMS m/z (%): 356 [M$^+$], (35), 179 (100).

3.6.8 2-(3,5-Dimethoxy4-methylphenyl)-5-(3',4',5'-trimethoxy)aryl-1,3,4-oxadiazole (1h)

Yield: 78%; m.p (°C): oil; R$_f$(Petroleum ether : Ethyl acetate, 7:3): 0.2; IR (KBr): 2901, 1636, 1616, 1127, 614, 473, cm$^{-1}$; $^1$HNMR (ppm) (J=Hz): $\delta$ 7.22 (s, 2H$_{arom}$), 7.21(s, 2H$_{arom}$), 3.9(s, 6H, 2×OCH$_3$), 3.8(s, 9H, 3×OCH$_3$) 2.4(s, 3H, CH$_3$); $^{13}$CNMR: $\delta$, 152.96 (C-1, CO), 153.72 (C-5, CO), 141.37, 138.66, 138.49, 131.54, 131.22, 129.73, 128.96, 126.27, 126.23, 123.99, 123.0, 122.80, 122.56, 107.0 (C-1, C-6), 56.24 (OCH$_3$), 56.56 (OCH$_3$), 26.54 (CH$_3$), 29.71; EIMS m/z (%): 386 [M$^+$, 22], 179 (100).
3.7 Synthesis of Some 5-(Aryl)-1,3,4-oxadiazole-2-thiones\textsuperscript{[28]}

An ethanolic solution of substituted hydrazides (1 mmol), KOH (1.5 mmol) and carbon disulfide (1.5 mmol) was refluxed for 12-20 h. Completion of reaction was confirmed by TLC. Upon completion solvent was rotary evaporated, the residue was poured on ice cold water and acidified with dil. hydrochloric acid. The solid product was separated, filtered, dried and subjected to crystallization.

3.7.1 5-[2’-Bromophenyl]-1,3,4-oxadizole-2-thione

Yield: 95%; m.p.(°C): 134-135; R\textsubscript{f} (Petroleum ether : Ethyl acetate, 7:3): 0.8; IR (KBr): 3268, 1603, 1482, 1334, 1277, 1123, 1020, 964, 766 cm\textsuperscript{-1}; \textsuperscript{1}HNMR (MEOD): 7.85 (d, 1H\textsubscript{arom}, J = 10), 7.7 (t, 1H\textsubscript{arom}, J = 5.7), 7.58 (d, 1H\textsubscript{arom}, J = 5.1), 7.56 (d, 1H\textsubscript{arom}, J = 4.8), 4.9 (bs, 1H,NH); \textsuperscript{13}CNMR (MEOD): 160 (C=S), 159 (C=N), 135.3 (C-1), 133.5 (C-4), 132.1 (C-3, C-6), 128.2 (C-5), 122.3 (C-2)); EIMS (m/e): 257.93 [M\textsuperscript{+}] (100%).

3.7.2 5-[4’-Fluoro-4’-methylphenyl]-1,3,4-oxadizole-2-thione

Yield: 87%; m.p. (°C): 108-109; R\textsubscript{f} (Petroleum ether : Ethyl acetate, 7:3): 0.9; IR(KBr): 3110, 1621, 1443, 1309, 1284, 1184, 1076, 956, 784, cm\textsuperscript{-1}; \textsuperscript{1}HNMR (MEOD): δ 7.6 (d, 2H\textsubscript{arom}, J = 11.0), 7.4 (d, 2H\textsubscript{arom}, J = 8.9), 5.24 (bs, 1H, NH), \textsuperscript{13}CNMR (MEOD): δ 166.7 (C-4), 161 (C=S), 159.6 (C=N), 142 (C-), 131.6 (C-2, C-6), 126.5 (C-1), 116.5 (C-3, C,5); EIMS (m/z): 196.01 [M\textsuperscript{+}] (100%), 121 (76), 74(13).
3.7.3 5-[4’-Methylphenyl]-1,3,4-oxadizole-2-thione

![Structural formula of 5-[4’-Methylphenyl]-1,3,4-oxadizole-2-thione]

Yield: 90%; m.p. (°C): 199-200; Rf (Petroleum ether : Ethyl acetate, 7:3): 0.9; IR(KBr): 3088, 2924, 1619, 1566, 1413, 1348, 1278, 1182, 1074, 970, cm⁻¹; ¹HNMR (MEOD): δ 7.4 (d, 2H₂ arom, J =11.5), 6.9 (d, 2H₂ Harm, J =10.2), 4.9 (bs, 1H NH), 1.3 (s, 3H CH₃), ¹³CNMR (MEOD): δ 160 (C=S), 159 (C=N), 142 (C-4), 135.5 (C-1), 130.5 (C-3, C-5), 129.1 (C-2, C-6), 24.6 (CH₃); EIMS(m/z): 192.01 [M⁺] (100%), 117(65), 74(13).

3.7.4 5-[3’,5’-Dimethoxy-4’-methylphenyl]-1,3,4-oxadizole-2-thione

![Structural formula of 5-[3’,5’-Dimethoxy-4’-methylphenyl]-1,3,4-oxadizole-2-thione]

Yield: 97%; m.p. (°C): 165-166; Rf (Petroleum ether : Ethyl acetate, 7:3): (0.6), IR (KBr): 3081, 2966, 1653, 1432, 1311, 1284, 1193, 1092, 964, 784 cm⁻¹; ¹HNMR (MEOD): δ 6.65 (s, 2H₂ arom), 4.21 (bs, 1H NH), 3.9 (s, 9H 3×OCH₃); ¹³CNMR (MEOD): δ 160 (C=S), 159 (C=N), 155.5 (C-3, C-5), 129.6 (C-1), 120.1 (C-4), 108.6 (C-2,C-6), 56.6 (2-OCH₃), 24.6 (CH₃); EIMS (m/z): 252.06 [M⁺] (100%), 177 (46).

3.7.5 5-[3’,4’,5’-Trimethoxyphenyl]-1,3,4-oxadizole-2-thione

![Structural formula of 5-[3’,4’,5’-Trimethoxyphenyl]-1,3,4-oxadizole-2-thione]

Yield: 92%; m.p. (°C): 198-199; Rf (Petroleum ether : Ethyl acetate, 7:3): 0.6; IR(KBr): 3105, 1618, 1472, 1312, 1288, 1121, 1019, 964, 766 cm⁻¹; ¹HNMR (MEOD): 6.5 (s, 2H₂ arom), 4.1 (bs, 1H, NH), 3.9 (s, 9H, 3×OCH₃); ¹³CNMR (MEOD): 160 (C=S), 159 (C=N), 154.5 (C-3, C-5), 142.6 (C-4), 125.1 (C-1), 112.8 (C-2, C-6), 56.6 (3-OCH₃); EIMS (m/z): 268.05 [M⁺] (100%), 195 (43).
3.8 Synthesis of N-amino methyl oxadiazoles-2-thiones [29] (2a-j)

To an ethanolic solution of oxadiazole-2-thione (1mmol), primary aromatic amines (1mmol) and 37.5% formaldehyde solution was added. The reaction mixture was stirred at RT for 2h and allowed to stand for overnight. The solid product was separated filtered, washed with cold ethanol dried and subjected to crystallization.

\[
\text{R'} = 2-\text{Cl} \\
2-\text{Cl}=4-\text{n}=\text{NO}_2
\]

3.8.1 5-[2'-Bromophenyl]-3-[2”-chlorophenylaminomethyl]-1,3,4-oxadizole-2-thione (2a)

Yield: 93%; m.p (°C): 134-135; R<sub>f</sub> (Petroleum ether : Ethyl acetate, 7:3): 0.6; IR (KBr): 3110, 1621, 1443, 1309, 1284, 1184, 1076, 956, 784, cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>), 7.1(d, 1H<sub>arom</sub>, J<sub>arom</sub> = 5.1), 7.0(d, 1H<sub>arom</sub>, J<sub>arom</sub> = 4.9), 6.94 (d, 1H<sub>arom</sub>, J<sub>arom</sub> = 11.0), 6.41 (dd, 2H<sub>arom</sub>, J = 8.9), 6.39 (d, 2H<sub>arom</sub>, J = 4.3), 5.93 (bt, 1H, NH, J = 6.3), 4.84 (d, 2H, CH<sub>2</sub>, J = 6.3), 1.56 (s, CH<sub>3</sub>) ; <sup>13</sup>CNMR 177.1 (C=S), 155.1 (C=N), 144.9 (C-1”), 136.5 (C-1’), 134.3 (C-4”), 132.8 (C-3’, C-6’), 129.8 (C-3”’), 127.9 (C-4’), 127.7 (C-5”’), 121.7 (C-2’), 119.9 (C-4”), 115.6 (C-6”), 67.9 (CH<sub>2</sub>); EIMS (m/z): 396.01, 398.1 [M<sup>+</sup>] (100%), 213 (41), 180.1(32).
3.8.2 5-[4’-Fluorophenyl]-3-[2”-chlorophenylaminomethyl]-1,3,4-oxadizole-2-thione (2b)

Yield: 93%; m.p. (°C): 136-137; \( R_f \) (Petroleum ether : Ethyl acetate, 7:3): 0.6; \( \text{IR} \) (KBr): 3118, 1611, 1443, 1370, 1239, 1184, 1071, 956, 784 cm\(^{-1}\); \( ^1\text{HNMR} \) (CDCl\(_3\)), \( \delta \) 6.9 (d, \( 2H_{arom} \), \( J = 8.5 \)), 6.41 (dd, \( 1H_{arom} \), \( J = 4.2 \)), 6.39 (d, \( 2H_{arom} \), \( J = 9.0 \)), 6.31 (d, \( 1H_{Ar} \), \( J = 7.0 \)), 6.20 (d, \( 1H_{arom} \), \( J = 6.1 \)), 4.8 (bt, \( 1H \), \( NH \), \( J = 5.7 \)), 4.75 (d, \( 2H \), \( CH_2 \), \( J = 6.0 \)); \( ^{13}\text{CNMR} \) \( \delta \) 177 (C=S), 156.6 (C=N), 152.1 (C-1”), 149.1 (C-4’), 142.1 (C-4”), 132.6 (C-3’, C-5’), 132.1 (C-2’, C-6’), 130.1 (C-1’), 126.7 (C-3’), 125.7 (C-5”), 124.9 (C-2”), 119.1 (C-6”), 67.9 (CH\(_2\)), 25.4 (CH\(_3\)), \( \text{EIMS} \) (m/z): 335, 337.1 [M’”] (100%), 213 (54), 121.2(31).

3.8.3 5-[4’-Methylphenyl]-3-[2”-chlorophenylamino methyl]-1,3,4-oxadizole-2-thione (2c)

Yield: 93%; m.p. (°C): 139-140; \( R_f \) (Petroleum ether : Ethyl acetate, 7:3): 0.6; \( \text{IR} \) (KBr): 3189, 1627, 1411, 1356, 1234, 1184, 1013, 956, 784 cm\(^{-1}\); \( ^1\text{HNMR} \) (CDCl\(_3\)), \( \delta \) 7.4 (d, \( 2H_{arom} \), \( J = 4.3 \)), 7.1 (d, \( 2H_{arom} \), \( J = 4.1 \)), 6.94 (d, \( 1H_{arom} \), \( J = 11.0 \)), 6.41 (dd, \( 2H_{arom} \), \( J = 8.9 \)), 6.39 (dd, \( 2H_{arom} \)), 5.93 (bt, \( 1H \), \( NH \), \( J = 5.6 \)), 4.84 (d, \( 2H \), \( CH_2 \), \( J = 6.1 \)), 1.56(s,CH\(_3\)); \( ^{13}\text{CNMR} \): \( \delta \) 177 (C=S), 156.6 (C=N), 144.2 (C-1”), 142.7 (C-4’), 130.1 (C-3”), 129.2 (C-3’, C-5’), 129.1 (C-2’, C-4’), 128.7 (C-5”), 127.8 (C-1’), 124.4 (C-2”), 114.6 (C-6”), 67.9 (CH\(_2\)), 25.4 (CH\(_3\)), \( \text{EIMS} \) (m/z): 394.95 [M’”] (100%), 213 (37), 117 (11).

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3.8.4 5-[3',5'-Dimethoxy-4'-methylphenyl]-3-[2''-chlorophenylamino- methyl]-1,3,4-oxadizole-2-thione (2d)

Yield: 89%; m.p (°C): 159-160; R_f (Petroleum ether : Ethyl acetate, 7:3): 0.5; IR (KBr): 3090, 2914, 1440, 1304, 1288, 1184, 1070, 956, 784 cm^{-1}; {^1}HNMR (CDCl\textsubscript{3}), δ 7.3 (d, 1H\textsubscript{arom}, J = 9.5), 7.28 (d, 2H\textsubscript{arom}, J = 4.4), 6.8 (d, 1H\textsubscript{arom}, J = 8.6), 6.79 (d, 1H\textsubscript{arom}, J = 8.1), 5.7 (bt, 1H, NH, J = 5.9), 5.6 (d, 2H, CH\textsubscript{2}, J = 6.1), 3.89 (d, 6H, OCH\textsubscript{3}), 2.6 (s, 3H, CH\textsubscript{3}); {^{13}CNMR: δ 177.1 (C=S), 155.1 (C=N), 144.9 (C-1''), 142.5 (C-4''), 129.3 (C-3''), 128.6 (C-5''), 125.6 (C-1''), 122.4 (C-2''), 120.8 (C-4''), 116.2 (C-6''), 107.1 (C-2', C-6''), 67.9 (CH\textsubscript{2}), 57.6 (2-OCH\textsubscript{3}), 26 (CH\textsubscript{3}); EIMS (m/z): 390.88 [M\textsuperscript{+}] (100%), 213(13), 177(53)

3.8.5 5-[3',4',5'-Trimethoxyphenyl]-3-[2''-chlorophenylaminomethyl]-1,3,4-oxadizole-2-thione (2e)

Yield: 93%; m.p.(°C): 120-121; R_f (Petroleum ether : Ethyl acetate, 7:3): 0.5; IR (KBr): 3100, 1629, 1413, 1329, 1257, 1169, 1068, 956, 784 cm^{-1}; {^1}HNMR (CDCl\textsubscript{3}): δ 7.3 (d, 1H\textsubscript{arom}, J = 9.0), 7.1 (s, 2H\textsubscript{arom}), 6.9 (d, 1H\textsubscript{arom}, J = 11.0), 6.8 (d, 1H\textsubscript{arom}, J = 7.5), 5.6 (bt, 1H, NH, J = 6.0), 5.5 (d, 2H, CH\textsubscript{2}, J = 5.6 ), 3.9 (d, 9H, OCH\textsubscript{3}); {^{13}CNMR: δ 177.1 (C=S), 155.1 (C=N), 144.9 (C-1''), 142.5 (C-4''), 129.3 (C-3''), 128.6 (C-5''), 125.6 (C-1''), 122.4 (C-2''), 120.8 (C-4''), 116.2 (C-6''), 107.1 (C-2', C-6''), 67.9 (CH\textsubscript{2}), 57.6 (3-OCH\textsubscript{3}); EIMS (m/z): 406.08 [M\textsuperscript{+}] (100%), 213 (13), 193 (43).
3.8.6 5-[2’-Bromophenyl]-3-[2”-chloro-4”-nitrophenylamino methyl]-1,3,4-oxadizole-2-thione (2f)

Yield: 87%; m.p.(°C): 158-159; Rf (Petroleum ether : Ethyl acetate, 7:3): 0.7; IR (KBr): 3143, 1633, 1379, 1264, 1181, 1089, 956, 784 cm⁻¹; ¹HNMR, (C₃D₆O): δ 8.2 (s, 1Hₜₐₐm), 7.95 (dd, 1Hₜₐₐm, J = 1.1), 7.84 (dd, 2Hₜₐₐm, J = 7.7, 1.1), 7.6(d, Hₜₐₐm, J = 8.0), 7.5 (d, 1Hₜₐₐm, J = 7.4), 6.1 (bt, 1H, NH, J = 6.1), 5.6 (d, 2H, CH₂), 6.1 (bt, 1H, NH, J = 6.1), 5.6 (d, 2H, CH₂); ¹³CNMR: δ 177.1 (C=S), 155.1 (C=N), 144.9 (C-1”), 136.5 (C-1’), 134.3 (C-4”), 132.8 (C-3’, C-6”), 129.8 (C-3”’), 127.9 (C-4’), 127.7 (C-5”’), 121.7 (C-2’), 119.9 (C-4”), 115.6 (C-6””), 67.9 (CH₂), EIMS (m/z) (%): 439.95, 441, [M⁺] (100%), 258(47), 180(72).

3.8.7 5-[4’-Fluorophenyl]-3-[2”-chloro-4”-nitrophenylamino methyl]-1,3,4-oxadizole-2-thione (2g)

Yield: 88%; m.p (°C): 109-110; Rf (Petroleum ether : Ethyl acetate, 7:3): 0.7; IR (KBr): 3118, 1625, 1467, 1345, 1244, 1169, 1071, 956, 784 cm⁻¹; ¹HNMR (C₃D₆O): δ 8.3 (s, 1Hₜₐₐm), 7.8 (d, 1Hₜₐₐm, J = 6.5), 7.64 (d, 2Hₜₐₐm, J = 8.1), 7.3 (d, 2Hₜₐₐm, J = 7.0), 6.9 (d, 1Hₜₐₐm, J = 8.0), 6.2 (bt, 1H, NH, J = 5.9), 5.9 (d, 2H, CH₂), 6.1 (bt, 1H, NH, J = 6.1), 5.6 (d, 2H, CH₂); ¹³CNMR: δ 177 (C=S), 166.4 (C-4’), 155.2 (C=N), 152.1 (C-1”), 143.1 (C-4”), 135.1 (C-2’, C-6”), 127.1 (C-1’), 126.9 (C-3”), 124.5 (C-2”), 122.8 (C-5””), 116.6 (C-6””), 115.6 (C-3’, C-5”), 67.9 (CH₂), 25.4 (CH₃); EIMS (m/z) : 380.80 [M⁺] (100%), 258(43), 121 (70).
3.8.8 5-[4’-Methylphenyl]-3-[2’’-chloro-4’’-nitrophenylamino methyl]-1,3,4-oxadizole-2-thione (2h)

Yield: 91%; m.p.(°C): 109-110, Rf (Petroleum ether : Ethyl acetate, 7:3): 0.5; IR (KBr): 3123, 2825, 1626, 1447, 1309, 1284, 1146, 956, 784 cm⁻¹; ^1HNMR(C3D6O), δ 8.3 (s, 1H arom), 7.8 (d, 1H arom, J =6.5), 7.64 (d, 2H arom, J = 8.1), 6.4 (d, 2H arom, J = 7.1), 6.9 (d, 1H arom, J =8.0), 6.0 (bt, 1H, NH, J = 6.1), 5.8 (d, 2H, CH₂, J = 6.1), 2.1 (s, 3H, CH₃);
^13CNMR δ 177 (C=S), 155.6 (C=N), 152.9 (C-1”), 143.6 (C-4”), 136.16 (C-1’), 133.6 (C-4’), 131.9 (C-3’), 131.7 (C-6’), 129.1 (C-5’), 125.6 (C-3’’), 124.4 (C-2’’), 122.1 (C-2’), 118.1 (C-5”’), 115.1 (C-6”), 67.9 (CH₂), 25.4 (CH₃); EIMS (m/z): 376.88 [M⁺] (100%), 258(81), 117(34).

3.8.9 5-[3’,5’-Dimethoxy-4’-methylphenyl]-3-[2’’-chloro-4’’-nitrophenylamino methyl]-1,3,4-oxadizole-2-thione (2i)

Yield: 90%; m.p.(°C): 198-199; Rf (Petroleum ether : Ethyl acetate, 7:3): 0.6; IR (KBr): 3225, 2953, 1642, 1467, 1327, 1271, 1184, 1076, 954, 778 cm⁻¹; ^1HNMR (C3D6O), δ 8.1 (s, 1H arom), 7.7 (d, 1H arom, J =7.0), 7.65 (d, 1H arom, J = 6.5), 6.8 (d, 2H arom, J = 7.1), 6.0 (bt, 1H, NH, J = 6.1), 5.9 (d, 2H, CH₂, J = 5.9), 3.9 (s, 6H, OCH₃ ), 2.1 (s, 3H, CH₃);
^13CNMR δ 177 (C=S), 160.1 (C-3’, C-5’), 156.6 (C=N), 152.1 (C-1”), 140.6 (C-4”), 129.8 (C-1”), 125.5 (C-3”’), 124.8 (C-2”), 115.8 (C-6”), 114.7 (C-4”), 106.7 (C-2’, C-6’), 67.9 (CH₂), 56.6 (2×OCH₃), 25.4 (CH₃); EIMS (m/z): 436.00 [M⁺] (100%), 258(66), 177(62).
3.8.10 5-[3’,4’,5’-Trimethoxyphenyl]-3-[2’’-chloro-4’’-nitrophenyl-amino methyl]-1,3,4-oxadizole-2-thione (2j)

Yield: 89%; m.p.(°C): 165-166; Rf (Petroleum ether : Ethyl acetate, 7:3): 0.5; IR (KBr): 3117, 1654, 1455, 1391, 1298, 1184, 1058, 977, 714 cm⁻¹; ¹HNMR (C₃D₆O): δ 8.2 (s, 1H arom), 7.8 (d, 1H arom, J = 6.71), 7.6 (d, 1H arom, J = 5.8), 6.9 (d, 2H arom, J = 7.1), 6.1 (bt, 1H, NH, J = 6.1), 5.8 (d, 2H, CH₂, J = 5.9), 3.9 (s, 9H, OCH₃); ¹³CNMR: δ 177 (C=S), 160.1 (C-3’, C-5’), 156.6 (C=N), 152.1 (C-1”), 140.6 (C-4”), 129.8 (C-1’), 125.5 (C-3’”), 124.8 (C-2”), 115.8 (C-6”), 114.7 (C-4’), 106.7 (C-2’, C-6’) 67.9 (CH₂), 56.6 (3-OCH₃), EIMS (m/z): 452.06 [M⁺] (100%), 258(19), 193 (23).

3.9 Synthesis of Some 5-Aryl-1,3,4-triazole-2-thiones [¹²²] (3a-f)

An ethanolic solution of KOH (1.5 mmol) was added to a stir mixture of CS₂ (1.5 mmol) and substituted hydrazide (1 mmol) in ethanol. The reaction mixture was stirred for 72 h and then rotary evaporated to dryness. The residual salt was washed with Et₂O afford potassium salt which was used in the next reaction without further purification. To a solution of above salt (1 mmol) in H₂O (10mL) was added 95 % hydrazine (1.3 mmol) and the mixture was heated under reflux for 18 h. Completion of reaction was checked by TLC. Upon completion, solution was acidified with concentrated hydrochloric acid and the precipitate was filtered off. The product was washed with H₂O, dried over sodium sulfate and recrystallized from ethanol.
3.9.1 5-[4’-Fluorophenyl]-1,3,4-triazole-2-thioamine (3a)

\[
\begin{align*}
\text{Yield: } & 93\%; \text{ m.p.: (°C): 146-147; } R_f (\text{Petroleum ether : Ethyl acetate, 4:1}): 0.7; \text{ IR (KBr): } 3215, 3091, 1566, 1484, 1278, 1173, 1016, 914 \text{ cm}^{-1}; \text{ } ^1\text{HNMR (DMSO), } \delta 7.89 (d, 2H_{arom}, J = 8.9), 7.24 (d, 2H_{arom}, J = 8.76), 5.7 (bs, 2H, NH), 2.3 (s, 3H, CH}_{3arom},) \text{, } ^{13}\text{CNMR (MeOH-d}_4): \delta 177 (C=S), 166.3 (C-4), 161.5 (C=N), 129.1 (C-2, C-6), 127.5 (C-1), 120.5 (C-3, C-5); \text{ EIMS (m/z): } 210(100), 212 [M^{+}] (4), 211(36), 89(12).
\end{align*}
\]

3.9.2 5-[4’-Methylphenyl]-1,3,4-triazole-2-thioamine (3b)

\[
\begin{align*}
\text{Yield: } & 89\%; \text{ m.p. (°C): 158-159; } R_f (\text{Petroleum ether : Ethyl acetate, 4:1}): 0.6; \text{ IR (KBr): } 3150, 3095, 2910, 1584, 1442, 1262, 1067, 954; \text{ } ^1\text{HNMR (DMSO): } 7.89 (d, 2H_{arom}, J = 9.6), 7.38 (d, 2H_{arom}, J = 8.4), 5.5 (bs, 2H, NH), 2.3 (s, 3H, CH}_{3arom},) \text{, } ^{13}\text{CNMR (DMSO): } \delta 177 (C=S), 161 (C=N), 143 (C-4), 130.47 (C-3,C-5), 129.52 (C-2, C-6), 126.48 (C-1), 21.6 (CH}_{3); \text{ EIMS (m/z): } 206.27 [M^{+}] (100\%) 117(43), 89(23).
\end{align*}
\]

3.9.3 5-[3’,4’-Dimethoxyphenyl]-1,3,4-triazole-2-thioamine (3c)

\[
\begin{align*}
\text{Yield: } & 92\%; \text{ m.p. (°C): 218-219; } R_f (\text{Petroleum ether : Ethyl acetate, 4:1}): 0.4; \text{ IR (KBr): } 3073, 3015, 2964, 1599, 1456, 1252, 1160, 1067, 953; \text{ } ^1\text{HNMR (MeOH-d}_4): \delta 7.60(d, 1H_{arom}, J = 8.5), 7.3 (d, 1H_{arom}, J = 8.4), 6.5 (d, 1H_{arom}, J = 8.4), 5.5 (bs, 2H, NH), 3.9 (s, 6H, 2\times OCH}_{3}); \text{ } ^{13}\text{CNMR (MeOH-d}_4): \delta 177.2 (C=S), 161.1 (C=N) 155.7 (C-4), 151.4 (C-3), 126.6 (C-1), 121.7 (C-6), 117.5 (C-5), 112.4(C-2), 61.9(2OCH}_{3}) \text{ EIMS (m/z): } 252.09 [M^{+}] (100\%), 252 (37), 89 (16).
\end{align*}
\]
3.9.4 5-[3’,5’-Dimethoxyphenyl]-1,3,4-triazole-2-thioamine (3d)

Yield: 85%; m.p. (°C): 175; R_f(Petroleum ether : Ethyl acetate, 4:1): 0.6; IR (KBr): 3125, 3088, 2924, 1609, 1580, 1458, 1348, 1252, 1157, 1067, 953 cm\(^{-1}\); \(^1\)HNMR (MeOH-\(d_4\)), δ 7.06 (d, 2H\(\text{arom}\), J = 2.9), 6.73 (t, 1H\(\text{arom}\), J = 2.2), 5.54 (bs, 2H, NH), 3.9 (s, 6H, 2×OCH\(_3\)); \(^{13}\)CNMR (MeOH-\(d_4\)): δ 177 (C=S), 163.45 (C-3, C-5), 161 (C=N), 133.89 (C-1), 106.6 (C-2, C-6), 103 (C-4), 64.34 (2×OCH\(_3\)); EIMS (m/z): 252.09 [M\(^+\)] (100%), 252 (37), 89 (16).

3.9.5 5-[3’,5’-Dimethoxy-4’-methylphenyl]-1,3,4-triazole-2-thioamine (3e)

Yield: 90%; m.p.(°C): 245-246; R_f (Petroleum ether : Ethyl acetate, 4:1): 0.5; IR (KBr): 3069, 3015, 2930, 1609, 1500, 1337, 1252, 1179, 968, 737, 715; \(^1\)HNMR (MeOH-\(d_4\)), δ 6.9 (s, 2H\(\text{arom}\)), 5.54 (bs, 2H, NH), 3.9 (s, 6H, 3×OCH\(_3\)), 2.1 (s, 3H, CH\(_3\)); \(^{13}\)CNMR (MeOH-\(d_4\)) : δ 177.0 (C=S), 162.1 (C=N), 161.5 (C-3, C-5), 130.3 (C-1), 119.1 (C-4), 56.6 (2×OCH\(_3\)), 24.6 (CH\(_3\)); EIMS (m/z), 266.32 [M\(^+\)] (100%), 117 (32), 89 (11).

3.9.6 5-[3’,4’,5’-Trimethoxyphenyl]-1,3,4-triazole-2-thioamine (3f)

Yield: 92%; m.p. (°C): 198-199; R_f (Petroleum ether : Ethyl acetate, 4:1): 0.4; IR(KBr, Cm\(^{-1}\)): 3169, 3115, 1641, 1523, 1336, 1252, 1179, 968, 738, 714, \(^1\)HNMR (MeOH-\(d_4\)), 7.16(s, 2H\(\text{arom}\)), 5.54(bs, 2H,NH), 3.9(s, 9H,OCH\(_3\)), \(^{13}\)CNMR (MeOH-\(d_4\)) 177.4(C=S),
161.5(C=N), 152.4 (C-3, C,5), 150.2 (C-4), 125.5 (C-1), 106.1 (C-2, C-6), 62.6 (3×OCH₃); **EIMS (m/z)**, 282.32 [M⁺] (100%), 193 (76), 89 (11).

### 3.10 Microwave–accelerated Synthesis of Some 1-Aryl-3,5-dimethylpyrazole \(^{123}\) (4a-h)

A homogenized mixture of hydrazide and 2,4-pentanedione was irradiated for 30-70 s in an alumina bath inside a microwave oven. On completion of reaction, followed by TLC examination using hexane ethyl acetate (8:2) the reaction mixture was diluted with ethyl acetate and subjected directly to thick layer chromatography on silica gel. Recrystallized using ethyl acetate to afford the respective pyrazoles.

#### 3.10.1 1-(4-Methylaryl)-3,5-dimethylpyrazole (4a):

Yield: 78%; m.p.(oil), Rₜ(Petroleum ether : Ethyl acetate, 7:3): (0.5); **IR** (KBr), 3115, 2950, 2910, 1680, 1584, 1432, 1355, 1256, 1179 cm\(^{-1}\); \(^{1}HNMR\) (CDCl₃), 7.9 (d, 2H), 7.28 (d, 2H), 6.06 (s, 1H), 2.6 (s, 3H), 2.4 (s, 3H), 2.27 (s, 3H), \(^{13}CNMR\) (CDCl₃) 164.5, 144.6, 144.3, 142.9, 129.8 (2C), 127, 126.7(2 C), 105.1, 17.6, 11.0, **EIMS(m/z)**: 214, 119 [M⁺] (100%).

#### 3.10.2 1-(4-Fluoroaryl)-3,5-dimethylpyrazole (4b)

Yield: 78%, m.p.(°C): 135-137; Rₜ(Petroleum ether : Ethyl acetate, 7:3): 0.9); **IR** (KBr): 3110, 2930, 2910, 1671, 1615, 1584, 1472, 1362, 1280, 1190, 1022, 989 cm\(^{-1}\), \(^{1}HNMR\) (CDCl₃), δ 8.18 (dd, 2H), 7.14 (dd, 2H), 5.9 (s, 1H), 2.6 (s, 3H), 2.27 (s, 3H), \(^{13}CNMR\) (CDCl₃) δ 168.2, 165.1, 144.6, 144.3, 142.9, 131.2(2C), 126.3, 114.2(2 C), 105.1, 17.6, 11.0; **EIMS (m/z)**: 218, 107 [M⁺] (100%).
3.10.3 1-(2-Bromoaryl)-3,5-dimethylpyrazole (4c)

\[
\begin{array}{c}
\text{Br} \\
\text{O} \\
\text{N} \\
\text{H}_3\text{C} \\
\text{CH}_3 \\
\end{array}
\]

Yield: 69%; m.p. (oil); R_f (Petroleum ether : Ethyl acetate, 7:3): (0.5); IR (KBr): 3015, 2910, 2905, 1675, 1601, 1570, 1432, 1372, 1270, 1165, 1014, 972 cm\(^{-1}\); \(^{1}\)HNMR(CDC\(_3\)), \(\delta\) 7-7.69 (m, H\(_{\text{arom}}\)), 6.06 (s, 1H), 2.68 (s, 3H), 2.27 (s, 3H); \(^{13}\)CNMR (CDC\(_3\)) \(\delta\) 164.5, 144.3, 143.2, 140, 136.2, 132.2, 132.1, 122.4, 105.1, 17, 11; EIMS (m/z) 278, 183 [M\(^{+}\)] (100%).

3.10.4 Synthesis of Some 1-(3,4-Dimethoxyaryl)-3,5-dimethylpyrazole (4d)

\[
\begin{array}{c}
\text{H}_3\text{CO} \\
\text{O} \\
\text{N} \\
\text{H}_3\text{C} \\
\text{CH}_3 \\
\end{array}
\]

Yield: 84%; m.p: (105-107), Rf (Petroleum ether : Ethyl acetate, 7:3): (0.4), IR (KBr,Cm\(^{1}\)), 3103, 2958, 2930, 1680, 1601, 1584, 1472, \(^{1}\)HNMR (CDC\(_3\)), 7.2 (d, 1H), 6.89 (dd, 1H), 6.7 (dd, 1H), 6.02 (s, 1H), 2.83 (s, 3H), 2.26, \(^{13}\)CNMR (CDC\(_3\)) 164.5, 162.2(2Cs), 144.3, 143.2, 122.4, 106.2 (C-2, C-4), 106.1 (C-4), 140.2, 105.3, 56.6(OCH\(_3\)), 17, 11 (s, 3H), EIMS 260, 165 [M\(^{+}\)] (100%).

3.10.5 1-(3,5-Dimethoxyaryl)-3,5-dimethylpyrazole (4e)

\[
\begin{array}{c}
\text{H}_3\text{CO} \\
\text{O} \\
\text{N} \\
\text{H}_3\text{C} \\
\text{OCH}_3 \\
\end{array}
\]

Yield: 74%; m.p (oil), R_f (Petroleum ether : Ethyl acetate, 7:3): 07; IR (KBr): 3103, 2958, 2929, 1679, 1615, 1580, 1477, 1350, 1284, 1128, 1039, 965 cm\(^{-1}\); \(^{1}\)HNMR (CDC\(_3\)), \(\delta\) 7.14 (d, 2H), 6.67 (t, 1H), 6.07 (s, 1H), 3.84 (s, 6H), 2.83 (s, 3H), 2.26 (s, 3H); \(^{13}\)CNMR (CDC\(_3\)), \(\delta\) 164.5, 155.2 (C-4), 149.1 (C-3), 144.3, 143.2, 129.1, 123.4, 105.2, 105.3, 56.6 (OCH\(_3\)), 17, 11; EIMS (m/z): 260, 165 [M\(^{+}\)] (100%).
3.10.6 1-(3,5-Dimethoxy-4-methylaryl)-3,5-dimethylpyrazole (4f)

![Chemical Structure](image)

Yield: 87%; m.p (°C): 81-83; IR (KBr, Cm⁻¹), 3112, 2970, 2916, 1680, 1605, 1580, 1465, 1275, ¹HNMR (CDCl₃), δ 7.28 (s, 2H), 6.09 (s, 1H), 3.92 (s, 6H), 2.6 (s, 3H), 2.28 (s, 3H), ¹³CNMR (CDCl₃), δ 164.5, 161.2 (C-3, C-5), 144.3, 143.2, 129.1, 120.4, 105.2, 56.6 (2×OCH₃), 25.1, 17, 11, EIMS (m/z): 274, 179 [M⁺] (100%).

3.10.7 1-(3,4,5-Trimethoxyaryl)-3,5-dimethylpyrazole (4g)

![Chemical Structure](image)

Yield: 91%; m.p (°C): 185-187; IR (KBr): 3015, 2960, 2945, 1677, 1595, 1480 cm⁻¹; ¹HNMR (CDCl₃), δ 7.32 (s, 2H), 6.62 (s, 1H), 3.98 (s, 9H), 2.4 (s, 3H), 2.2 (s, 3H), ¹³CNMR (CDCl₃), 164.5, 151.2 (C-3, C-5), 150.3, 143.2, 129.2, 107.1 (C-2, C-6), 105.2, 56.6 (2OCH₃), 25.1, 17, 11, EIMS, (m/z): 290, 195 [M⁺⁺] (100%)

3.10.8 1-(5-Phenyl-2,4-dienyl)-3,5-dimethylpyrazole (4h)

![Chemical Structure](image)

Yield: 83%; m.p (°C): 81-82; IR (KBr): 3115, 2950, 2910, 1680, 1620, 1594, 1432, 1355, 1256, 1179, ¹HNMR (CDCl₃), 7-8 (m, 9H), 6.06 (s, 1H), 2.6 (s, 3H), 2.27 (s, 3H), ¹³CNMR (CDCl₃), 162, 151.3, 144.3, 143, 142, 135, 131, 128, 126, 125, 105, 17, 11.1. EIMS, (m/z) 256 [M⁺⁺] (100%)
3.11 Synthesis of the 3,5-Disubsituted pyrazolines from Chalcones (5a-h)

3.11.1 Synthesis of Some Substituted chalcones [124a]

In a two neck round bottom flask (0.5 mol) of substituted benaldehyde in absolute ethanol was taken. 20 mL of 15% NaOH was added in ice bath. (0.5 mol) of acetophenone was added and mixture was stirred for 3h.

[Diagram]

a) 1-5-Bromo-2-hydroxyphenyl-3-4-methoxyphenylpropen-2-en-1-one

Yield : 78%; M.P.(°C):151-152; Rf : 0.7; IR (KBr): 3351, 2910, 1607, 1581, 1422, 1233, 1047, 917, cm⁻¹; HNMR (CDCl₃), δ 7.87 (s, 1H arom.), 7.44 (d, 1H arom., J = 8.4), 7.21 (d, 2H arom., J = 6.6), 6.81 (d, 1H arom., J = 6.6), 6.61 (d, 2H arom., J = 6.6), 5.7 (d, 1H, CHCH, J = 12), 5.3 (d, 1H, CHCH, J = 12), 3.37 (s, 3H, CH₃arm).

b) 1-2-Hydroxy-5-methylphenyl-3-4-chlorophenylpropen-2-en-1-one

Yield: 82%; m.p.(°C): 132-133; Rf : 0.7; IR (KBr): 3345, 2910, 1601, 1585, 1421, 1212, 1047, 917, cm⁻¹; HNMR (CDCl₃), δ 7.7 (s, 1H arom.), 7.42 (d, 1H arom., J = 8.4), 7.32 (d, 2H arom., J = 6.6), 6.62 (d, 1H arom., J = 6.6), 6.60 (d, 2H arom., J = 6.6), 5.6 (d, 1H, CHCH, J = 12), 5.43 (d, 1H, CHCH, J = 12), 2.52 (s, 3H, CH₃arm).
c) 1-2-Hydroxy-5-methylphenyl-3-4-methylphenylpropen-2-en-1-one

Yield: 88%; m.p.(°C): 166-167; Rf: 0.6; IR (KBr): 3345, 2934, 2918 1612, 1594, 1422, 1213, 1021, 917, cm\(^{-1}\), \(^1\)HNMR (CDCl\(_3\)), \(\delta\) 7.71 (s, 1H\(_{\text{arom}}\)), 7.42 (d, 1H\(_{\text{arom}}\), J = 8.4 ), 7.12 (d, 2H\(_{\text{arom}}\), J = 6.6 ), 6.62 (d, 1H\(_{\text{arom}}\), J = 6.6 ), 6.56 (d, 2H\(_{\text{arom}}\), J = 6.6 ), 5.7 (d, 1H, CHCH, J = 12 ), 5.55 (d, 1H, CHCH, J = 12 ), 2.52 (s, 6H, 2×CH\(_3\)\(_{\text{arom}}\)).

d) 1-Aroyl-3-aryl-5-arylp yrazolines\(^{[80, 124b]}\) (5a-h)

To a reaction mixture of appropriate chalcone and hydrazide in ethanol 2 mL of piperidine was added and reflux for 12-16 h. The resulting mixture was concentrated, cooled and kept overnight. The solid was filtered, washed with ethanol, dried and recrystallized from ethanol.

i) (±)-1-[3′,5′-Dimethoxyaroyl]-5-[-4”'-chlooro]aryl-3-[-2”'-hydroxy-5”'-methyaryl pyrazoline (5a)

Yield: 92 %; Rf(Petroleum ether : Ethyl acetate, 3:2): 0.9;m.p. (°C): 117-118; IR (KBr ): 3315, 2932, 2812, 1712, 1621, 1596, 1437, 1243. \(^1\)HNMR ( CDCl\(_3\)): \(\delta\) 6-9-7.7 (m, 10H\(_{\text{arom}}\) ), 5.2 (dd, 3.9, \(H5\) J = 9.0), 4.4 (dd, H4a, J= 5.8, 3.1), 4.2 (dd, H4b, J=6.1, 3.3), 3.9 (s , 6H), 1.6 ( s, 3H);\(^{13}\)CNMR ( CDCl\(_3\)): 168 (CO), 162 (C-3), 61 (C-5), 43 (C-4). EIMS (70 eV), (m/z)(%): 450 [M]+ (12), 452 (4), 285 (10), 165 (100), 133 (42).
ii) (±)-1-[3',4',5'-Trimethoxyaroyl-5-[-4'”-cloroaryl]-3-[-2”-hydroxy-5”-methylarylpyrazoline (5b)

Yield: 85%; $R_f$ (Petroleum ether : Ethyl acetate, 3:2): 0.9; m.p.(°C): 101-102; IR (KBr): 3311, 2965, 2913, 1713, 1583, 1431, 1257 cm$^{-1}$. $^1$HNMR (CDCl$_3$): δ 6.9-7.7 (m, 12H$_{arom}$), 5.2 (dd, H5, $J = 9.6$, 3.9), 4.3 (dd, H4a, $J = 5.7$, 3.3), 4.2 (dd, H4b, $J = 6.1$, 3.3), 3.9 (s, 9H), 1.6 (s, 3H); $^{13}$CNMR (CDCl$_3$): δ 167 (CO), 163 (C-3), 59 (C-5), 43 (C-4); EIMS (70 eV), (m/z), (%): 460 (21), 462 (5) [M$^+$], 265 (34), 195 (100), 133 (56).

iii) (±)-1-[3’,5’-Dimethoxy-4’-methyaroyl]-5-[4”-cloroaryl]-5-[-2”-hydroxy-5”-methylaryl] pyrazolines (5c)

Yield: 78%; $R_f$ (Petroleum ether : Ethyl acetate, 3:2): 0.9; m.p (°C): 141-142; IR (KBr): 3017, 2965, 2911, 1707, 1621, 1597, 1431, 1257 cm$^{-1}$, $^1$HNMR (CDCl$_3$), δ 6.9-7.7 (m, 12H$_{arom}$), 5.4 (dd, H5, $J = 9.6$, 3.3), 4.2 (dd, H4a, $J = 5.7$, 3.3), 4.1 (dd, H4b, $J = 5.7$, 3.3), 3.9 (s, 6H), 2.348 (s, 3H); $^{13}$CNMR, 170 (CO), 161 (C-3), 58 (C-5), 43 (C-4); EIMS (70 eV), (m/z), (%): 462 (37), 464 (53) [M$^+$], 285 (21), 179 (100), 133 (49).
iv) (±)-1-[α,β-unsaturated]cabonyl-5-[α-4’’-chloro]aryl-5-[β-2”-hydroxy-5”-methyl]aryl pyrazolines (5d)

\[
\begin{align*}
&\text{H}_3\text{C} \\
&\text{O} \\
&\text{N} \\
&\text{OH} \\
&\text{Cl} \\
&\text{H}_3\text{C} \\
&\text{C}=\text{O} \\
&\text{N} \\
&\text{OH} \\
&\text{H}_3\text{C} \\
&\text{O} \\
&\text{N} \\
&\text{OH} \\
&\text{Br}
\end{align*}
\]

Yield: 85%; \( R_f \) (Petroleum ether : Ethyl acetate, 3:2): 0.9; (semisolid); \textbf{IR} (KBr), 3012, 2966, 2917, 1722, 1665, 1571, 1433 cm\(^{-1}\) \textbf{\( ^{1}HNMR \)} (CDCl\(_3\)): \( \delta \) 6.6-7.30(m, 12H\text{arom}), 7.4 (d, 1H, \( H_\beta \), \( J = 6.3 \)), 7.1 (d, 1H, \( H_\alpha \), \( J = 3.4 \)), 6.9 (d, 1H, \( H_\gamma \), \( J = 4.2 \)), 6.6 (d, 1H, \( H_\delta \), \( J = 3.6 \)), 5.4 (dd, H5, \( J = 9.6, 3.3 \)), 4.1 (dd, H4a, \( J = 5.7, 3.3 \)), 3.9 (dd, H4b, \( J = 5.7, 3.3 \)), 2.5 (s, 3H, CH\(_3\)); \textbf{\( ^{13}CNMR \)}: 166 (CO), 157 (C-3), 61 (C-5), 43 (C-4); \textbf{EIMS} (70 eV), (m/z),(%): 442 (21), 444 (11) [M\text{+}], 133 (47), 90(100).


\[
\begin{align*}
&\text{H}_3\text{CO} \\
&\text{O} \\
&\text{N} \\
&\text{OH} \\
&\text{OCH}_3 \\
&\text{H}_3\text{CO} \\
&\text{O} \\
&\text{N} \\
&\text{OH} \\
&\text{Br}
\end{align*}
\]

Yield: 80%; \( R_f \) (Petroleum ether : Ethyl acetate, 3:2): 0.8; m.p.(°C): 170-171); \textbf{IR} (KBr), 3121, 2964, 2911, 1706, 1675, 1595, 1431 \textbf{\( ^{1}HNMR \)} (CDCl\(_3\)), 6.9-7.7 (m, 9H\text{arom}), 5.1 (dd, H5, \( J = 9.0, 3.3 \)), 4.24 (dd , H4a, \( J = 5.7, 3.6 \)), 4.1 (dd , H4b, \( J = 5.7, 3.6 \)), 3.9 (s, 12H, OCH\(_3\)), 1.6 (s, 3H); \textbf{\( ^{13}CNMR \)}: 167 (CO), 162(C-3), 60 (C-5), 43 (C-4); \textbf{EIMS} (70 eV), (m/z),(%): 540 (11), 542 (32) [M\text{+}], 345 (12), 196 (10), 195 (100).
vi) \((\pm)\) 1-[3',5'-Dimethoxy,4'-methyl]aroyl-5-[4'''-methoxy]aryl-3-[2''-hydroxy-4''-methyl]aryl pyrazolines (5f)

\[
\begin{align*}
\text{H}_3\text{CO} & \quad \text{O} \\
\text{H}_3\text{C} & \quad \text{OCH}_3 \\
\end{align*}
\]

Yield: 83%; \(R_f\) (Petroleum ether : Ethyl acetate, 3:2): 0.6; m.p.: (oil ); \(\text{IR}\) (KBr ): 3021, 2963, 1700, 1686, 1595, 1435 cm\(^{-1}\), \(^1\)\text{HNMR} (CDCl\(_3\)): \(\delta\) 6.9-7.7 (m, 9H\text{arom}), 5.1 (dd, H5, \(J = 9.0, 3.3\)), 4.24 (dd , H4a, \(J = 5.7, 3.6\)), 4.1 (dd , H4b, \(J = 5.7, 3.6\)), 3.9 (s, 9H, OCH\(_3\)), 2.52 (s, 3H, CH\(_3\)), 1.6 (s, 3H); \(^{13}\)\text{CNMR}: 168(CO), 161 (C-3), 59 (C-5), 43 (C-4). \(\text{EIMS}\) (70 eV), (m/z),(%): 524 (11), 526 (25) [M\(^+\)], 345 (21), 196 (27), 179 (100).

vii) \((\pm)\) 1-[3',4',-Dimethoxy]aroyl-5-[4'''-methoxy]aryl-3-[2'''-hydroxy-5'''-methyl]aryl pyrazolines (5g)

\[
\begin{align*}
\text{H}_3\text{CO} & \quad \text{O} \\
\text{H}_3\text{C} & \quad \text{OCH}_3 \\
\end{align*}
\]

Yield: 78%; \(R_f\) (Petroleum ether : Ethyl acetate, 3:2): 0.8; m.p.(°C): 160-161; \(\text{IR}\) (KBr ): 3021, 2963, 2919, 1742, 1656, 1595,1441 cm\(^{-1}\); \(^1\)\text{HNMR} (CDCl\(_3\)): 6.9-7.7 (m, 10H\text{arom} ), 5.1 (dd, H5, \(J = 9.0, 3.3\)), 4.2 (dd, H4a, \(J = 5.1, 3.6\)), 4.0 (dd, H4a, \(J = 5.1, 3.6\)), 3.9 (s , 9H, OCH\(_3\)), 1.6 (s, 3H ); \(^{13}\)\text{CNMR}: \(\delta\)168 (CO), 162 (C-3), 61(C-5), 43 (C-4); \(\text{EIMS}\) (70 eV), (m/z),(%): 510, 512 [M\(^+\)] (32), 345 (11), 196 (29), 165 (100).

140
viii) $(\pm)$ 1-[α,β-unsaturated-cabonyl-5-[-4”'-methoxy-aryl-3-[-2”'-hydroxy-5”'-bromo]aryl] pyrazolines (5h)

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{N} & \quad \text{OH}
\end{align*}
\]

Yield: 82%; $R_f$ (Petroleum ether : Ethyl acetate, 3:2): 0.9; m.p. (oil); IR (KBr): 3023, 2961, 2920, 1698, 1595, 1441 cm\(^{-1}\), $^1$HNMR (CDCl\(_3\)): 6.6-7.3 (m, 12H arom), 7.4 (d, 1H, $H_\beta$, $J = 6.3$), 7.1 (d, 1H, $H_\alpha$, $J = 3.4$), 6.9 (d, 1H, $H_\gamma$, $J = 4.2$), 6.6 (d, 1H, $H_\delta$, $J = 3.6$), 5.4 (dd, $H_5$, $J = 9.6, 3.3$), 4.1 (dd, $H_4a$, $J = 5.7, 3.3$), 3.9 (dd, $H_4b$, $J = 5.7, 3.3$); $^{13}$CNMR: $\delta$ 168 (CO), 162 (C-3), 61 (C-5), 43 (C-4), EIMS (70 eV), (m/z),(%): 502, 504 [M$^+$] (19), 198 (23), 90 (100).

### 3.12 Synthesis of Some $(\pm)$-1-Aryl-5-chloroisochromans (6a-j)

#### 3.12.1 Methyl 2-chlorobenzoate \[118\]

\[
\begin{align*}
\text{Cl} & \quad \text{O} \\
\text{OCH}_3
\end{align*}
\]

Yield: 91%; m.p.: oil; IR (NaCl cell): 2910, 1733, 1615, 1541, 1410, 1339, 1155, 1141, 716, 674, cm\(^{-1}\); $^1$HNMR (CHCl\(_3\)-d): $\delta$ 7.1-7.8 (m, 4H arom), 3.9 (s, 3H, OCH\(_3\)).

#### 3.12.2 2-Chlorophenylalchohol \[125a\]

2-Chloromethylbenzoate was stirred for two hours with sodium boron hydride (mmol) in THF methanol. Then 20 mL of dry methanol was added to the complex and was refluxed for two hours. Completion of reaction was checked by TLC. Upon completion cold water was added in the reaction mixture, organic layer was separated, dried on anhydrous sodium sulfate, filtered and concentrated in vacuum.

\[
\begin{align*}
\text{Cl} & \quad \text{OH}
\end{align*}
\]

Yield: 80%; m.p. (°C): (69-71, lit), 68; IR (KBr): 1621, 1590 cm\(^{-1}\); $^1$HNMR (CHCl\(_3\)-d): $\delta$ 6.8-7.7 (m, 4H arom), 4.3 (s, 2H, CH\(_2\)).
3.12.3 2-Chlorolbenzylbromide \[^{[125b]}\]

A solution of appropriate benzoyl alcohol in dry benzene was stirred for four hours with (6mmol) of phosphorous tribromide. The reaction mixture was poured onto ice, the organic layer was separated dried on anhydrous sodium sulfate, filtered and rotary evaporated.  

![Cl\_Br](image)

Yield: 91%; m.p: oil; IR (NaCl cell): 1615, 1541, 1339, 1155, 1141, 716, 674 cm\(^{-1}\); \(^1\)HNMR (CHCl\(_3\)-d): \(\delta\) 6.8-7.7 (m, 4H\(_{arom}\)), 5.1 (s, 2H, CH\(_2\)).

3.12.4 2-Chlorolbenzylcyanide

Appropriate bromide, potassium cyanide (1.5mmol), ethanol (30mL), water (30mL) were refluxed for four hours. The reaction mixture was poured on crushed ice. Organic layer was separated dried and evaporated.  

![Cl\_CN](image)

Yield: 82%; m.p: oil; IR (KBr): 2217, 1603, 1601 cm\(^{-1}\); \(^1\)HNMR (CHCl\(_3\)-d): \(\delta\) 6.8-7.7 (m, 4H\(_{arom}\)), 3.8 (s, 2H, CH\(_2\)).

3.12.5 2-Chlorophenylacetic acid

Appropriate cyanide, methanol (25 mL), dioxane (20 mL), water (25 mL) and potassium hydroxide (1.1 mmol) was refluxed for 72 hours. Upon completion reaction mixture was poured on ice organic layer was separated dried on anhydrous sodium sulfate, filtered and rotary evaporated.  

![Cl\_OH](image)

Yield : 67%; m.p. (°C): (94-97, lit), 96; IR (KBr): 1700, 1620; \(^1\)HNMR (CHCl\(_3\)-d): \(\delta\) 11.1 (s, 1H, OH), 6.6-7.4 (m, 4H\(_{arom}\)), 2.8 (s, 2H, CH\(_2\)).
3.12.6 2-(2-Chlorophenyl)ethanol [125a]

![Chemical Structure]

Yield: 81%; IR (KBr): 3328, 2956, 1587, 1271, 1072, 741 cm\(^{-1}\); \(^1\)HNMR (300 MHz, CDCl\(_3\)): 7.21-7.39 (4H, m, H\(_{\text{arom}}\)), 3.91 (2H, t, \(J = 5.60\)), 2.95-3.11 (2H, t, \(J = 6\)), 2.01 (1H, s, OH).

3.12.7 (±)-1-(4-Methoxyphenyl)-5-chloroisochroman [126] (6a-j)

To a mixture of 2-(2-chlorophenyl)ethanol (0.182 g, 1 mmol) and substituted benzaldehyde (1 mmol), a catalytic amount of \(p\)-toluenesulfonic acid monohydrate was added. The reaction mixture was homogenized and irradiated for 1-2 min. On completion of reaction, as monitored by TLC (every 30 s) using petroleum ether and ethyl acetate (7:2), the reaction mixture was purified by thick layer chromatography. The product obtained was recrystallized from ethyl acetate.

\(i\)  (±)-1-Phenyl-5-chloroisochroman (6a)

![Chemical Structure]

Yield: 99%; m.p. (°C): 95-96, \(R_f\): 0.3, IR (KBr, cm\(^{-1}\)): 2924, 2342, 1724, 1116, 713, 456.\(^1\)HNMR \(\delta\): 7.41–8.15 (m, 3H\(_{\text{arom}}\)), 7.27 (s, 5H\(_{\text{arom}}\)), 5.50 (s, 1H, C-1), 4.52 (t, 2H, \(J = 6.6\), CH\(_2\)O), 3.24 (t, \(J = 7.2\), 2H, CH\(_2\)CH\(_2\)); \(^{13}\)CNMR \(\delta\): 141, 134, 133.8, 133, 129 (C-3’,C-5’); 128 (C-2’, C-6’), 127 (C-7), 126 (C-6, C-8), 78, 64, 28. EIMS: (70 eV),(m/z ,%) 246, 244 [M\(^+\)].
ii) \((\pm)-1-(4\text{-Fluorophenyl})-5\text{-chloroisochroman (6b)}\)

\[
\begin{align*}
\text{Yield: 88 \%; m.p. (oil), } R_f: 0.7; \text{ IR (KBr, cm}^{-1}) & : 2924, 2342, 1724, 1116, 713, 456; \\
1^\text{HNMR} \delta & : 7.1–7.43 (m, 3H_{arom}), 5.77 (s, 1 H, C-1), 4.57 (t, 2H, \text{J}=6.9, \text{CH}_2\text{O}), 3.71 (t, \text{J}=6.9, 2H, \text{CH}_2\text{CH}_2); \\
13^\text{CNMR} \delta & : 160 (C-4'), 135.9 (C-1), 134.9(C-9), 133.2 (C-10), 132 (C-5), 129 (C-2', C-6'), 114 (C-3, C-5), 79 (C-1), 65 (C-3), 26 (C-4). \text{EIMS (70eV): m/z =262, 264 [M}^+])
\end{align*}
\]

iii) \((\pm)-1-(2\text{-Chlorophenyl})-5\text{-chloroisochroman (6c)}\)

\[
\begin{align*}
\text{Yield: 99 \%; m.p.( \degree C): 123-124; } R_f: 0.8; \text{ IR (KBr, cm}^{-1}) & : 2926, 1691, 1589, 1476, 1315, 1367, 1050, 744, 648, 482; \\
1^\text{HNMR} \delta & : 7.25–8.05 (m, 7H_{arom}), 5.52 (s, 1H), 3.93 (t, 2H, \text{J}= 6.9 \text{ CH}_2\text{O}), 3.25 (t, \text{J}=6.9, 2H, \text{ArCH}_2); \\
13^\text{CNMR} \delta & : 140 (C-1'), 135 (C-9), 134 (C-5, C-2'), 133(C-10), 129 (C-3', C-6'), 127 (C-5', C-7), 126 (C-6, C-8), 71 (C-1), 65 (C-3), 24 (C-4). \text{EIMS: m/z=280, 278 [M}^+])
\end{align*}
\]

iv) \((\pm)-1-(3\text{-Chlorophenyl})-5\text{-chloroisochroman (6d)}\)

\[
\begin{align*}
\text{Yield: 87 \%; m.p.: (oil); } R_f: (0.8); \text{ IR (KBr, cm}^{-1}) & : 2926, 1691, 1589, 1476, 1315, 1367, 1051, 744, 648, 482. 1^\text{HNMR} \delta : 7.15-7.88 (m ,7H_{arom}), 5.51 (s, 1H), 4.59 (t, 2H, \text{J}= 6.9}
\end{align*}
\]
CH₂O), 3.71 (t, J=6.9, 2H, ArCH₂), \(^{13}\)CNMR 142 (C-1’), 134.8 (C-3’), 134.2 (C-9), 133.4 (C-5), 133 (C-10), 130 (C-5’), 129 (C-2’), 127 (C-6), 126 (C-6, C-6’), 71 (C-1), 65 (C-3), 24 (C-4). **EIMS:** m/z=280, 278 [M⁺]

v) (±)-1-(3-Bromophenyl)-5-chloroisochroman (6e)

![Chemical structure of 6e]

Yield: 90 %; m.p.(oil), Rₓ: 0.8; **IR** (KBr, cm⁻¹): 2926, 1691, 1589, 1476, 1315, 1367, 1051, 744, 648, 482. **\(^1\)HNMR** δ: 7.15-7.78 (m, 7Hₐrom), 5.5 (s, 1H), 4.58 (t, 2H, J=6.9 CH₂O), 3.92 (t, J=6.6, 2H, ArCH₂); **\(^{13}\)CNMR** 141 (C-1’), 134.9 (C-3’), 134.2 (C-9), 133.4 (C-5), 133 (C-10), 130 (C-5’), 129 (C-2’), 127 (C-6), 126 (C-6, C-6’), 71 (C-1), 65 (C-3), 24 (C-4); **EIMS:** m/z=325, 321, 323 [M⁺]

vi) (±)-1-(4-Bromophenyl)-5-chloroisochroman (6f)

![Chemical structure of 6f]

Yield: 98 %; m.p: (oil); Rₓ (0.9), **IR** (KBr, cm⁻¹): 2926, 1691, 1589, 1476, 1315, 1367, 105, 744, 648, 482. **\(^1\)HNMR** δ: 7.15-7.78 (m, 7Hₐrom), 5.49 (s, 1H), 4.58 (t, 2H, J=6.9 CH₂O), 3.9 (t, J=6.6, 2H, ArCH₂); **\(^{13}\)CNMR**, 141, 134 (C-9), 133 (C-10), 132 (C-5), 132 (C-3’, C-5’), 129 (C-2’, C-6’), 128 (C-7), 127 (C-6, C-8), 81 (C-1’), 65 (C-3), 28 (C-4). **EIMS:** m/z=325, 321, 323 [M⁺]
vii)  (±)-1-(4-Methoxyphenyl)-5-chloroisochroman (6g)

Yield: 98%; m.p.: (oil); Rf: 0.4; IR (KBr, cm⁻¹): 2926, 1691, 1589, 1476, 1315, 1367, 1051, 744, 648, 482. ¹HNMR: δ 8.05 (d, 2H_arom, J = 7.5), 7.02-7.5 (m, 3H_arom), 6.95 (d, 2H_arom, J = 7.5), 3.90 (s, 3H, OCH₃), 3.5 (t, 2H, J = 6.4 CH₂O), 3.31 (t, J=6.4, 2H, ArCH₂); ¹³CNMR: 141, 134 (C-9), 133 (C-10), 132 (C-5), 132 (C-3’, C-5’), 129 (C-2’, C-6’), 128 (C-7), 127 (C-6, C-8), 81 (C-1’), 65 (C-3), 28 (C-4); EIMS: m/z: 274, 272 [M⁺⁺]

viii) (±)-1-(3-Hydroxy-4-methoxyphenyl)-5-chloroisochroman (6h)

Yield: 89%; m.p.: (°C): 67-68; Rf: 0.4; IR(KBr, cm⁻¹): 3410, 2921, 1691, 1589, 1476, 1315, 1367, 1051, 744, 648. ¹HNMR: δ 7.05–7.7 (m, 6H_arom), 5.5(s, 1H), 3.99 (s, 3H, OCH₃), 3.82 (t, 2H, J=6.6 CH₂O), 3.07 (t, J=6.6, 2H, ArCH₂); ¹³CNMR: 156 (C-3’),141, 134 (C-9), 133 (C-10), 132 (C-5), 130 (C-5’), 128 (C-7), 127 (C-6, C-8), 120 (C-6’), 113 (C-2’), 81 (C-1’), 65 (C-3), 28 (C-4).EIMS: m/z : 292, 290 [M⁺⁺].

ix) (±)-1-(3,4,5-Trimethoxyphenyl)-5-chloroisochroman (6i)

Yield: 76%; m.p.: (°C): 127-128; Rf: 0.2; IR (KBr, cm⁻¹): 1691, 1589, 1476, 1315, 1367, 1051, 744, 648; ¹HNMR δ: 7.4–8.15 (m, 3H_arom), 7.28 (s, 2H_arom), 3.91 (s, 9H, 3×OCH₃), 3.82 (t, 2H, J=6.8 CH₂O), 3.30 (t, J=7.2, 2H, ArCH₂). ¹³CNMR: δ 154 (C-
3’,C-5’),141, 134 (C-9), 136 (C-4’), 133 (C-10), 132 (C-5), 128 (C-7), 127 (C-6, C-8),
120 (C-6’), 113 (C-2’), 81 (C-1’), 65 (C-3), 28 (C-4). EIMS: m/z : 306, 304 [M⁺].

x)  (±)-1-Fur-2’-yl-5-chloroisochroman (6j)

\[
\text{Cl} \quad \text{O} \\
\text{Cl} \quad \text{O} \\
\text{O} \quad \text{O} \\
\text{O} \quad \text{O}
\]

Yield: 69 %; m.p.( °C): 118-119, Rf: 0.2, IR (KBr, cm⁻¹), 2359, 1634, 1617, 1271, 633, 475; \[^1^H]\text{NMR} \delta 7.7 (m, 1H_{arom}), 7.68 (d, 1H_{arom}), 7.03 (d, J=6.5, 1H_{arom}), 6.92 (d, J=7.1, 1H_{arom}), 4.23 (t, 2H, J=6.9), 3.9 (t, 2H, J=6.6, ArCH₂); \[^1^C]\text{NMR}: 154 (C-5’),152(C-2’), 134(C-9), 133(C-10), 132 (C-5), 128 (C-7), 127 (C-6, C-8), 120 (C-4’), 112 (C-3’), 81 (C-1’), 65 (C-3), 28 (C-4): EIMS: m/z: 236, 234 [M⁺]

3.13 Synthesis and deprotection of N-substituted morpholines (7a-o)

3.13.1 Methyl sulfinate \[^{127}\]

To a solution of \(p\)-tolyldisulfide (3 g, 0.012 mol ) in MeOH (50 mL), NBS (6.5 g, 0.06mol ) was added at RT. The reaction mixture was stirred for 1 h. Completion of reaction was checked by TLC. Upon completion solution was evaporated under reduced pressure and then diluted with CH₂Cl₂ (30 mL) and later on washed with NaHSO₃ (aqueous solution) and then with NaHCO₃ (aqueous solution). Organic layer was separated and dried on Na₂SO₄, concentrated and subjected to column chromatography (EtOAc-PE) to afford the target compound as an oil. Rf (0.8), yield (97 %), (CDCl₃) δ 7.6 (2Hₘ, d), 7.3 (2Hₘ, d), 3.40 (3H, s, OCH₃), 2.37 (3H, s, CH₃), \[^1^C]\text{NMR} (CDCl₃) δ 130 (2Cₘ), 125 (2Cₘ), 56 (OCH₃), 24(CH₃).
3.13.2 General procedure for the synthesis of N-p-tolylsulfanilamides\cite{128} (7a-e)

To a stirred solution of p-tolylmethanesulfinate (1 g, 5.85 mmol) in THF (16 mL) at RT under argon, a solution of the lithium amide [prepared from of α-amino alcohols in (7.01 mmol) THF (16 mL) and n-BuLi (12.9 mmol) at -78 °C] was added. Completion of the reaction was checked after 2h by TLC. On completion 0.1 M K$_2$HPO$_4$ (5 mL) was added and mixture was extracted by CH$_2$Cl$_2$ (3 × 30 mL) dried over sodium sulfate, filtered and concentrated. Crude was taken to check the dr (diastereomeric ratio) purified by column chromatography (EtOAc-PE, 1:9, 1:1) to the required compound.

\[
\text{R OH} + \text{O S} \xrightarrow{n-\text{BuLi (2.2eq)}} \text{R OH} \quad \text{THF} \quad -78^\circ C
\]

i) N-p-Tolyl-2-amino-3-methylbutasulfinamide (7a)

Yield: 97 %; d.r: (2:1); m.p.(°C): oil, Rf: (0.9); $^1$HNMR, $\delta_H$, (CDCl$_3$): 7.62 (d, 2H$_{arom}$, $J = 9.0$), 7.29 (d, 2H$_{arom}$, $J = 9.0$), 3.72 (d, 2H, $J = 6.0$, CH$_2$OH ), 3.27 (dd, 1H, $J = 12.0$, CHNH ), 2.41 (s, 3H, CH$_3$), 1.84 (m, 1H, CH(CH$_3$)$_2$), 1.02 (d, 3H, 6.0, CH$_3$), 0.95 (d, 3H, 6.0, CH$_3$); $^{13}$CNMR $\delta$ (CDCl$_3$): 141.69, 129.61, 65.99 (OCH$_3$), 52.11, 30.70, 24.5, 24.0EIMS, (70 eV), (m/z, %), 241 [M$^{+}$] (61), 154(100).
ii) N-p-tolyl-2-amino-1-phenylpropasulfanilamide (7b)

Yield: 62 %; d.r.: (2:1); Rf: (0.6); m.p.(°C): 86-88, (EtOAc-PE), \[^1H\text{NMR}\] \(\delta\) (CDCl\(_3\)):

\[
7.40-7.10 \text{ (m, 9H arom)},
4.2 \text{ (d, 1H, } J = 6.0, \text{ CHO/H)},
3.78 \text{ (m, 1H, CHNH)},
3.81 \text{ (d, 2H, PhCH\(_2\)CH)},
2.42 \text{ (s, 3H, CH\(_3\))},
1.71 \text{ (d, 3H, } J=4.0, \text{ CH\(_3\))};
[^{13}\text{C}\text{NMR} \delta_c, (\text{CDCl}_3):}
141.57, 140.01, 129.70, 129.60, 128.2, 126.2, 125.5, 57.37 (OCH\(_2\)), 21.32 (CH\(_3\)arom), 17.15 (CH\(_3\)), \text{EIMS,(70 eV),(m/z, %), 289 [M\text{\textsuperscript{+}}] (22), 154(100).}

iii) N-p-tolyl-2-amino-3-phenylpropasulfanilamide (7c)

Yield: 35 %; d.r.: (2:1); Rf: (0.6); m.p.(°C), oil, \[^1H\text{NMR}\] \(\delta\) (CDCl\(_3\)):

\[
7.40-7.10 \text{ (m, 9H arom)},
4.2 \text{ (d, 1H, } J = 6.0, \text{ CHO/H)},
3.78 \text{ (m, 1H, CHNH)},
3.81 \text{ (d, 2H, PhCH\(_2\)CH)},
2.42 \text{ (s, 3H, CH\(_3\))},
1.71 \text{ (d, 3H, } J=4.0, \text{ CH\(_3\))};
[^{13}\text{C}\text{NMR} \delta_c, (\text{CDCl}_3):}
141.21, 129.43, 128.44, 126.18, 125.6, 65.44 (OCH\(_2\)), 60.79 (CH\(_2\)), 30.05 (CH\(_3\)arom), \text{EIMS,(70 eV),(m/z, %), 289 [M\text{\textsuperscript{+}}] (11), 154(100).}

iv) N-p-tolyl-3-amino-butanolester (7d)

Yield: 26 %; d.r.: (2:1), m.p.(°C): oil, Rf: (0.2); \[^1H\text{NMR}\] \(\delta\) (CDCl\(_3\)):

\[
7.52 \text{ (d, 2H arom, } J = 9.0),
7.29 \text{ (d, 2H arom, d, } J = 9.0),
5.5 \text{ (d, 1H, NHSO)},
4.28 \text{ (d, 1H, } J = 6.0, \text{ CHCHOH}),
2.53 \text{ (t, 2H, } J=7.0, \text{ CH\(_2\)CH}_2\).
4.01 (dd, 1H, CH$_2$OH ), 3.75 (s, 3H, OCH$_3$ ), 2.38 (s, 3H, CH$_3$ ); $^{13}$CNMR $\delta_C$ (CDCl$_3$ ), 168 (CO), 142.08, 130.07, 129.89, 126.35, 125.76, 64.04 (OCH$_2$), 58.57 (OCH$_3$), EIMS, (70 eV), (m/z, %), 289 [M$^+$] (11), 154(100).

v) N-<w> </w>p-tolyl-2-amino-1,2-diphenylethylsulfinamide (7e)

\[
\begin{align*}
\text{Ph}_2^& \text{NH} \\
\text{S}=\text{O} \\
\text{CH}_3
\end{align*}
\]

Yield: 37 %; d.r.: (2:1), m.p.(°C): oil, R$_f$: (0.7); $^1$HNMR $\delta_H$ (CDCl$_3$): 7.57 (d, 2H$_{arom}$, $J$ = 12), 7.31 (d, 2H$_{arom}$, $J$ = 12), 3.90 (d, 1H, $J$=5.5, CH$_3$NH), 3.18 (td, 2H, $J$=6.0, OCH$_2$CH$_2$), 2.98 (td, 2H, $J$ = 4.3, CH$_2$CH$_2$N), 2.82(m, 1H, CH(CH$_3$)$_2$), 2.43 (s, 3H, CH$_3$), 0.9 (d, 3H, $J$ = 5.2, CH$_3$); $^{13}$CNMR $\delta_C$ (CDCl$_3$ ): 141.2, 129.6, 129.32, 126.3, 68.02 (OCH$_2$), 64.44, 40.52, 26.20, 21.32, EIMS (70 eV),(m/z, %): 351 [M$^+$] (10), 154 (100).

General procedure for the synthesis of N-p-tolylsulfanilamido morpholines $^{[129]}$ (7f-j)

To a solution of N-p-tolylsulfanamide (0.414 mmol) in CH$_2$Cl$_2$ (10 ml) at 0 °C under argon NaH (60 %, 1.45 mmol) was added and left for five mins. Then bromoethyl diphenylsulfoxonium salt (0.497 mmol) was added and reaction was stirred for overnight. Upon completion 10 ml of water was added and extracted with CH$_2$Cl$_2$ (3 × 30 mL), dried and concentrated under reduced pressure. Crude was subjected to H$^1$ to check the d.r. for purification column chromatography was to be used to get the title compound as a gummy solid.

vi) N-p-tolylsulfanamido-3-isopropylmorpholine (7f)

\[
\begin{align*}
\text{S}=\text{O} \\
\text{N} \\
\text{CH}_3
\end{align*}
\]

Yield: 73%; d.r.: (2:1); m.p.(°C): oil; R$_f$: (0.4); $^1$HNMR $\delta_H$ (CDCl$_3$), 7.57 (d, 2H$_{arom}$, $J$ =12), 7.31 (d, 2H$_{arom}$, $J$ = 12), 3.90 (d, 1H, $J$ =3.4, CH$_3$NH), 3.18 (td, 2H, $J$ =4.4,
OCH₂CH₂), 2.98 (td, 2H, J=5.1, CH₂CH₂N), 2.82 (m, 1H, CH(CH₃)₂), 2.43 (s, 3H, CH₃), 0.9 (d, 3H, J=5.1, CH₃); ¹³CNMR δc (300 MHz; CDCl₃), 141.2, 129.6, 129.32, 126.3, 68.02 (C-2), 64.44 (C-6), 40.52 (C-5), 26.20 (2×CH₃), 21.32(CH₃), EIMS (70 eV),(m/z, %), 267 [M⁺] (100), 139 (34), 58 (54).

vii) N-p-tolylsulfinamido-2-phenyl-3-methylmorpholine (7g)

Yield: 97%; d.r. (2:1), m.p.(°C): oil, Rf: (0.3); ¹HNMR δH (CDCl₃), 7.60 (d, 2H_arom, J = 4.2), 7.37(d, 2H_arom, J = 4.7), 7.36-7.23 (m, 5H_arom), 4.85 (d, 1H, CHPh), 4.07 (dd, 1H, dd, J=4, 3.9, CH₂O), 3.81 (q, 1H, J = 7.1, CHCH₃), 3.13 (dd, 1H, J = 4.7, 3.8, CH₂N), 2.47 (s, 3H, CH₃arom), 1.1 (d, 3H, CH₃CH); ¹³CNMR δc (400 MHz; CDCl₃), 141.17, 139, 129.50, 128.66, 126.30, 69.98 (C-2), 68.15 (C-6), 64.1(C-3), 59.20 (C-5), 40.58 (2×CH₃), 36.22 (CH₃), EIMS (70 eV),(m/z, %),315 [M⁺] (100), 139 (33), 58 (54).

viii) N-p-tolylsulfinamido-3-benzoylmorpholine (7h)

Yield: 97 %; d.r.: (2:1); m.p.(°C): oil, Rf: (0.3); ¹HNMR δH (CDCl₃): 7.37-7.12 (m, 9H_arom), 3.81 (dd, 2H, J = 6.1, 2.3, OCH₂CH₂N), 3.70 (m, 1H, PhCH₂CH/N), 3.65 (dd, 2H, J = 5.2, 4.0, OCH₂CH), 2.99 (dd, 2H, J = 3.3, 2.7, CH₂CH₂N), 2.47 (s, 3H, CH₃arom), 2.38 (s, 3H, CH₃arom); ¹³CNMR δc (CDCl₃), 129.50, 121.35, 128.6, 126.31, 69.98 (C-2), 68.15 (C-6), 64.1(C-3), 59.21 (C-5), 40.57, 36.22 (CH₃), EIMS (70 eV),(m/z, %),315 [M⁺] (100), 139 (33), 58 (54).
ix) **N-p-tolysulfamido-3-benzoylmorpholine (7i)**

![Structure](attachment:image.png)

Yield: 54 %; d.r.: (2:1); mp(°C): 119-120; Rf (0.4); $^1$H NMR (CDCl$_3$), 7.69 (d, 2H$_{arom}$, J=6.), 7.57 (d, 2H$_{arom}$, J=6.), 4.25 (d, 2H, J = 5.3, CHCH$_2$OH), 4.03 (t, 1H, J = 4.9, CHCO$_2$CH$_3$), 3.92 (dd, 2H, J = 3.3, 5.1, CH$_2$OH), 3.73 (s, 3H, OCH$_3$), 3.37 (dd, J = 2H, J = 4.7, 3.7, OCH$_2$CH), 2.44 (dd, 2H, J = 2.8, 1.3, CH$_2$CH$_2$N), 2.43 (s, 3H, CH$_3$arom); $^{13}$C NMR (CDCl$_3$), 129.29, 126.70, 126.57, 95.48 (OCH$_3$), 69.09 (C-2), 67.1 (C-6), 64.1 (C-3), 45.80 (C-5), 34.5 (CH$_3$); EIMS (70 eV), (m/z, %), 283 [M$^+$] (100), 139 (33), 58 (54).

x) **N-p-tolysulfamido-2,3-diphenylmorpholine (7j)**

![Structure](attachment:image.png)

Yield (49 %), d.r. (2:1), mp(°C), oil, Rf (0.4), $^1$H NMR (CDCl$_3$) 7.11-7.24 (10 H$_{arom}$), 7.11-7.24 (10 H$_{arom}$), 7.59 (d, 2H$_{arom}$, J=6.3), 7.25 (2H$_{arom}$, d, J=6.), 5.6 (d, 1H, H-2, J=4.2), 4.1 (d, 1H, H-2, J=4.5), 3.9 (dt, 2H, H-6, J=4.2, 6.1), 2.7 (dt, 2H, H-5, J=4.2, 6.5), 2.3 (3H, s, CH$_3$arom). $^{13}$C NMR 133, 129, 127, 124, 87 (C-2), 67 (C-6), 64 (C-5), 60 (C-3), 54, 24 (CH$_3$), EIMS (70 eV), (m/z, %), 377 [M$^+$] (100), 139 (33), 58 (54).

**General procedure for the deprotection of N-p-tolysulfamido morpholine** $^{[130]}$

(7k-o)

To a solution of HCl in ether (0.36 mL, 3eq) was added to a solution of N-p-tolysulfamido-morpholine (0.024 g, 0.09 mmol) in dry ether under argon and a white solid precipitated. After 35 min the mixture was filtered via canola into another Schenck flask and washed with diethyl ether.
xi) 3-Isopropylphenylmorpholinium chloride (7k)

Yield: 73%; m.p (°C): 196-197; \(^1\)HNMR δ\(_{H}\) (CDCl\(_3\)): 4.12 (1H, d, J=4.1, CH\(_2\)NH), 3.77 (2H, td, J=4.9, OCH\(_2\)CH\(_2\)), 3.21 (2H, td, J=3.7, CH\(_2\)CH\(_2\)N), 2.98 (1H, m, CH(CH\(_3\))\(_2\)); 0.9(6H, d, J=2.2, 2×CH\(_3\)); \(^{13}\)CNMR δ\(_{C}\) (CDCl\(_3\) ), 75.1 (C-2), 69.23 (C-6), 64.11 (C-3), 56.1, 27.42, 25.1, 24.22. EIMS (70 eV),(m/z, %),129 [M\(^+\)] (100), 86(31), 43(54).

xii) 3-Methyl-2-phenylmorpholinium chloride (7l)

Yield: (89 %), \(^1\)HNMR δ\(_{H}\) (CDCl\(_3\) ), 7.31-7.12(m, 5H\(_{arom}\)), 5.13 (1H, d, CHPh), 4.54 (2H, dd, J=4, CH\(_2\)O), 3.73(1H, q, CH\(_2\)CH\(_3\)), 3.13(1H, dd, CH\(_2\)N), 1.2 (3H, d, CH\(_3\)CH), \(^{13}\)CNMR δ\(_{C}\) (CDCl\(_3\) ), 139.1, 128.7, 128.5, 128.4, 128.2, 126.4, 90.2 (C-2), 78.6 (C-6), 62.1 (C-3), 45.2, 21.22. EIMS (70 eV),(m/z, %),213 [M\(^+\)] (100), 176(10), 75(7).

xiii) 3-Benzolymorpholinium chloride (7m)

Yield: (97 %), \(^1\)HNMR δ\(_{H}\) (CDCl\(_3\) ), 7.12-6.89 (m, 5H\(_{arom}\)), 3.99 (2H, dd, OCH\(_2\)CH\(_2\)N), 3.67(1H, m, PhCH\(_2\)CHN), 3.60 (2H, dd, OCH\(_2\)CH), 3.15 (2H, dd, CH\(_2\)CH\(_2\)N), \(^{13}\)CNMR δ\(_{C}\) (CDCl\(_3\) ), 140, 137, 128.3, 128.1, 126.7, 125.1, 89.1(C-2), 67.2 (C-6), 65.3 (C-3), 40.2 (CH\(_2\)), 25.1. EIMS (70 eV),(m/z, %),177 [M\(^+\)] (100), 91(31), 43(54).

xiv) 3-Methylcarboxalate phenylmorpholinium chloride (7n)
Yield: (47 %), $^1$HNMR $\delta_H$ (CDCl$_3$), 4.35 (2H, d, CHCH$_2$OH), 4.23 (1H, t, CHCO$_2$CH$_3$), 4.12 (2H, dd, CH$_2$OH), 3.73 (3H, s, OCH$_3$), 3.37 (2H, dd, OCH$_2$CH), 2.54 (2H, dd, CH$_2$CH$_2$N), $^{13}$CNMR $\delta^{13}$C (CDCl$_3$), 179.9 (CO), 80.2 (C-2), 67.1 (C-6), 56.2, 46.7(C-5), 56.6, 25.1, EIMS (70 eV),(m/z, %),145 [M$^+$] (100), 43(54).

xv) 2,3-Diphenylmorpholiniumchloride (7o)

Yield: (49 %),$^1$HNMR $\delta_H$ (CDCl$_3$), 7.11-7.24 (10 H$_{arom}$), 5.6 (d, 1H, H-2, $J$=4.2), 4.1 (d, 1H, H-2, $J$=4.5),3.9 (dt, 2H, H-6, $J$=4.2, 6.1),2.7(dt, 2H, H-5, $J$=4.2, 6.5), $^{13}$CNMR 133, 129, 127, 124, 87(C-2), 67 (C-6), 64 (C-3), 54 (C-5), EIMS (70 eV),(m/z, %),239 [M$^+$] (100), 196 (43), 43(54).

3.14 Synthesis of 3-Aryl-6-phenyl-1,2,4-triazolo-[3,4-b][1,3,4]-thiadiazines (8a-f)

3.14.1 Synthesis of Bromoacetophenone $^{[131]}$

In a three neck round bottom flask solution of acetophenone (0.5 mol) in anhydrous ether was cooled at 0°C. Anhydrous aluminium chloride (0.5 mol) and bromine (0.4 mol) was added through dropping funnel and stirred for 15 mins. Ether was removed under reduced pressure, the solid separated was bromo-acetonphenone. Yield(47%), m.p.(obs. 50°, lit 49-51°).
General procedure for the synthesis of 3-Aryl-6-phenyl-1,2,4-triazolo-[3,4-b][1,3,4]-thiadiazines

In a two neck round bottom flask (0.5 mol) of triazoleamine in ethanol bromo-acetophenone (0.5 mol) was added and reflux for 5 h. Completion of the reaction was checked by TLC. Ethanol was removed under reduce pressure. Crude was purified by ethanol.

\[
\begin{align*}
\text{O} & \quad \text{Br} \\
R & \quad \text{N} \quad \text{NHN} \\
\text{NH}_2 & \quad \text{S} \\
& \quad R
\end{align*}
\]

i) 3-(4'-Fluorophenyl)-6-phenyl-1,2,4-triazolo[3,4-b][1,3,4-thiadiazine (8a)

Yield:88%; m.p. (°C): 176-177; R_f: (0.8); IR (KBr): 3313,1634, 1630, 1438, 1359, 688, 624, cm\(^{-1}\); \(^1\)HNMR (CDCl\(_3\)) \(\delta\) 9.0 (brs, 1H, NH); 7.77 (d, 2H_arom, \(J =8.9\)), 7.12 (d, 2H_arom, \(J =8.76\)), 7.11-6.88 (m, 5H_arom), 2.3 (s, 2H, CH\(_2\)); \(^13\)CNMR 161 (ArC=N), 154 (CH\(_2\)C=N), 143 (CF), 131 (C-4’), 128 (C-3’, C-6’), 127 (C-3’,C-5’), 124 (C-2, C-6), 122 (C-1), 73 (NCS), 40 (CCS); EIMS (70 eV): m/z (%): 312 (100), [M\(^{+}\)], 191 (42), 121(78).

ii) 3-(4’-Methylphenyl)-6-phenyl-1,2,4-triazolo[3,4-b][1,3,4-thiadiazine (8b)

Yield:74%; mp (°C): 213-214; R_f: (0.6); IR (KBr): 3313, 2981, 1631, 1622, 1426, 1351, 687, 622, cm\(^{-1}\); \(^1\)HNMR (CDCl\(_3\)) \(\delta\) 8.81 (brs, 1H, NH); 7.89 (d, 2H_arom, \(J =9.6\)), 7.38 (d, 2H_arom, \(J =8.4\)), 7.11-6.8 (m, 5H_arom), 2.3 (s, 2H, CH\(_2\)); \(^13\)CNMR 160 (ArC=N), 153 (CH\(_2\)C=N), 132 (CCH\(_3\)), 131 (C-4’), 128 (C-2’, C-6’), 120 (C-3’,C-5’), 118 (C-2, C-6), 112 (C-1), 73 (NCS), 40 (CCS), EIMS (70 eV) (m/z) (%): 308 [M\(^{+}\)] (100), 191(32), 117(82).
iii) 3-(3’,4’-Dimethoxyphenyl)-6-phenyl-1,2,4-triazolo[3,4-b][1,3,4-thiadiazine (8c)

Yield: 64%; m.p.( °C): 200-201; Rf: (0.5); IR (KBr): 3312, 2981, 1633, 1598, 1424, 1335, 687, 622, cm\(^{-1}\); \(^{1}\)HNMR (CDCl\(_3\)) \(\delta\) 8.98 (brs, 1H, NH); 7.62 (d, 1H\(_{arom}\), \(J = 8.5\)), 7.3 (d, 1H\(_{arom}\), \(J = 8.4\)), 7.11-6.8 (m, 5H\(_{arom}\)), 6.5 (d, 1H\(_{arom}\), \(J = 8.4\)), 3.9 (s, 9H, 3\times\text{OCH}_3), 2.3 (s, 3H, CH\(_2\)); \(^{13}\)CNMR 159 (ArC=N), 149 (CH\(_2\)C=N), 143 (C-4), 140 (C-3), 131 (C-4’), 128 (C-2’, C-6’), 120 (C-3’,C-5’), 118 (C-2), 112 ( C-6), 112 (C-1), 70 (NCS), 41 (CCS); EIMS (70 eV): m/z (%): =354[M\(^{+}\)]\(^{-}\) (100), 191 (37), 163 (76).

iv) 3-(3’,5’-Dimethoxyphenyl)-6-phenyl-1,2,4-triazolo[3,4-b][1,3,4-thiadiazine (8d)

Yield: 64%; mp (°C): 194-195; Rf.(0.4); IR (KBr): 3312, 2981, 1633, 1598, 1424, 1335, 687, 622, cm\(^{-1}\); \(^{1}\)HNMR (CDCl\(_3\)) \(\delta\) 8.91(brs, 1H, NH); 7.06 (d, 2H\(_{arom}\), \(J = 2.9\)), 7.11-6.8 (m, 5H\(_{arom}\)), 6.72 (t, 1H\(_{arom}\), \(J = 2.2\)), 5.54 (bs, 2H, NH\(_2\)), 3.9 (s, 6H, 2\times\text{OCH}_3), 2.3 (s, 3H, CH\(_3\)); \(^{13}\)CNMR, 159 (ArC=N), 149 (CH\(_2\)C=N), 146 (C-3, C-5), 131 (C-4’), 128 (C-2’, C-6’), 120 (C-3’,C-5’), 118 (C-2), 112 ( C-6), 112 (C-1),109 (C-4), 73 (NCS), 39 (CCS), EIMS (70 eV): m/z (%): =354[M\(^{+}\)]\(^{-}\) (100), 191(21), 163(57).

v) 3-(3’,5’-Dimethoxy-4’-methylphenyl)-6-phenyl-1,2,4-triazolo[3,4-b][1,3,4-thiadiazine (8e)

Yield: 55%; m.p (°C): 215-216; Rf: (0.3); IR (KBr): 3312, 2990, 2981, 1633, 1598,
1424, 1335, 687, 622, cm⁻¹; ¹HNMR (CDCl₃): δ 9.12 (brs, 1H, NH); 7.11-6.8 (m, 5H_arom.), 6.72 (s, 1H_arom.), 3.9 (s, 9H, 3×OCH₃), 2.3 (s, 3H, CH₃); ¹³CNMR, 157 (ArC=N), 156.3 (CH₂C=N), 145 (C-3, C-5), 131 (C-4'), 128 (C-2', C-6'), 120 (C-3',C-5'), 118 (C-2), 117 (C-4), 112 ( C-6), 112 (C-1), 73 (NCS), 32 (CCS), EIMS (70 eV): m/z (%) =368 [M⁺] (100), 191(36), 177(72).

vi) 3-(3',4',5'-Trimethoxyphenyl)-6-phenyl-1,2,4-triazolo[3,4-b][1,3,4-thiadiazine (8f)

Yield : 55%); m.p.(°C ): 201-202; Rf: (0.2); IR (KBr): 3312, 2990, 2981, 1633, 1598, 1424, 1335, 687, 622, cm⁻¹; ¹HNMR (CDCl₃) : δ 9.12 (bs, 1H, NH); 7.11-6.8 (m, 5H_arom). 6.72 (s, 1H_arom), 3.9 (s, 6H, 3×OCH₃), 2.52 (s, 3H, CH₃), 2.3 (s, 3H, CH₃); ¹³CNMR, 157 (ArC=N), 156.3 (CH₂C=N), 145 (C-3, C-5), 131 (C-4'), 128 (C-2', C-6'), 120 (C-3',C-5'), 118 (C-2), 112 ( C-6), 112 (C-1), 73 (NCS), 32 (CCS), EIMS (70 eV): m/z (%) =368 [M⁺⁺] (100), 191 (26), 193 (66).

3.14.2 Synthesis of 1-Methyl-1-isochromanoyl acetic acids

i) 3,4,5-Trimethoxyphenylalchohol [125a]

Yield : 77%; m.p. (°C): oil; IR (NaCl Cell): 3012, 2910, 1611; ¹HNMR (CDCl₃-d) : 6.5 (s, 2H_arom), 4.2 (s, 2H, CH₂), 3.9 (s, 3H, OCH₃).

ii) 3,4,5-Trimethoxyphenylacetyl bromide [125b]

Yield : 83%; m.p. (°C): oil; IR (NaCl Cell): 2916, 1616; ¹HNMR (CDCl₃-d) : 6.6 ( s, 2H_arom), 4.2 (s, 2H, CH₂), 3.9 (s, 3H, OCH₃).
iii) 2-(3,4,5-Trimethoxyphenyl)acetonitrile

\[ \text{Yield: 78\%; m.p. (°C): oil; IR (NaCl Cell): 2910, 2243, 1611; }^{1}\text{HNMR (CDCl}_3\text{-d): 6.5 (s, 2H}_\text{arom}, 4.1 (s, 2H, CH}_2, 3.9 (s, 3H, OCH}_3)\]

iv) 3,4,5-Trimethoxyphenylacetic acid

\[ \text{Yield: 68\%; m.p. (°C): oil; IR (NaCl Cell): 3031, 2910, 1710, 1611; }^{1}\text{HNMR (CDCl}_3\text{-d): 10.1 (s, 1H, OH), 6.5 (s, 2H}_\text{arom}, 4.2 (s, 2H, CH}_2, 3.9 (s, 3H, OCH}_3)\]

v) 3,4,5-Trimethoxyphenylethyl alcohol \[^{[125]}\]

\[ \text{Yield: 62\%; m.p.: (Oil); Rf (Pet ether: ethyl acetate, 9:1): 0.3; IR(cm}^{-1}): 2919, 2910, 1732, 1461, 1235, 1012; }^{1}\text{HNMR (CDCl}_3\text{): 6.4 (s, 1H}_\text{arom}, 3.9 (s, 9H, 3×OCH}_3, 3.1(m, 2H, OCH}_2CH}_2, 2.9 (m, 2H, OCH}_2CH}_2, }^{13}\text{CNMR(CDCl}_3\text{): 169 (C=O), 151, 147, 146.1, 145, 129, 107, 65, 61, 59, 56.}\]

3.14.3 Synthesis of Methyl ester of 1-(1-methyl-isochromanyl)acetic acid \[^{[100]}\]

To a solution of aryl ethanol (0.001 mmol) in dry benzene (20 mL) methyl acetoacetate (0.013 mmol) was added. A catalytic amount of p-toluenesulfonic acid was added to the flask fitted with Dean-stark trap, reaction mixture was refluxed for 12 h. upon completion solvent was removed under reduced pressure affording a pale yellow oil which was dissolved in ethylactate and subjected to TLC.(Petroleum ether : Ethyl acetate, 9:1)
i) 1-(1-Methyl-5-chloroisochromanyl) methylacetate

\[
\text{Cl} \quad \text{H}_3\text{C} \quad \text{O} \quad \text{OMe} \\
\]

Yield: 86%; M.P(oil); Rf(Pet ether: ethyl acetate, 9:1): 0.9; \textbf{IR}(cm\(^{-1}\)): 2959, 2870, 1720, 1472, 1275, 1049, \textbf{\(^{1}\text{HNMR}\)(CDCl₃)}: 7.78 (d, \textit{J} = 5.1, 1H, H-6), 7.6 (d, \textit{J} = 4.2, 1H, H-8), 7.51 (d, \textit{J} = 4.6, 1H, H-7), 4.42 (m, 2H, H-3), 4.1 (q, 2H, OCH₂CH₃), 3.8 (s, 2H, H-11), 2.91 (m, 2H, H-4), 2.45 (s, 3H, H-13), 1.3 (t, 3H, OCH₂CH₃); \textbf{\(^{13}\text{CNMR}\)(CDCl₃)}: 165 (C=O), 142, 132, 131, 127, 126, 123, 75 (C-1), 59 (C-4), 56, 44 (C-11), 32, 25.

ii) 1-(1-Methyl-6,7-dimethoxy)-isochromanyl] methylacetate

\[
\text{MeO} \quad \text{O} \quad \text{OMe} \\
\]

Yield: 82%; M.P(oil); Rf(Pet ether: ethyl acetate, 9:1): 0.6; \textbf{IR}(cm\(^{-1}\)): 2933, 2870, 1724, 1458, 1261, 1049, \textbf{\(^{1}\text{HNMR}\)(CDCl₃)}: 6.98 (s, 2H\textit{arom}, H-5,8), 4.4 (q, 3H, OCH₂CH₃), 4.0 (m, 2H, H-3), 3.9 (s, 6H, 2\times OCH₃), 2.91 (s, 2H, H-11), 2.65 (m, 2H, H-4), 2.2 (s, 3H, H-13), 1.37 (t, 3H, OCH₂CH₃); \textbf{\(^{13}\text{CNMR}\)(CDCl₃)}: 166 (C=O), 146, 1.5, 146.3, 136, 127,112, 111, 75 (C-1), 59 (C-3), 56 (3\times OCH₃), 44(C-12), 32, 25.

iii) [1-(1-Methyl-6,7,8-trimethoxy)-isochromanyl] methylacetate

\[
\text{MeO} \quad \text{O} \quad \text{OMe} \\
\]

Yield:79%; m.p.: (oil); Rf (Pet ether: ethyl acetate, 9:1): 0.4; \textbf{IR}(cm\(^{-1}\)): 2930, 1731, 1467, 1235, 1025; \textbf{\(^{1}\text{HNMR}\)(CDCl₃)}: 6.51 (s, 1H\textit{aroms}, H-5), 4.1 (q, 3H, OCH₂CH₃), 3.95 (m, 2H, H-3), 3.9 (s, 9H, 3\times OCH₃), 2.93 (s, 2H, H-11), 2.65 (m, 2H, H-4), 2.2 (s, 3H, H-13), 1.37 (t, 3H, OCH₂CH₃); \textbf{\(^{13}\text{CNMR}\)(CDCl₃)}: 169 (C=O), 146, 148, 146.1, 136, 128, 124, 105, 75 (C-1), 65(C-3), 59 (C-4), 56(3\times OCH₃), 48, 32 (C-11), 25
3.15 Synthesis of 1-(1-Methyl-isochromanyl)acetyl hydrazides \[^{[100]}\]

To an ethanolic solution of isochromanyl acetic acid, 85 % hydrazine hydrate was added and refluxed for 72 h. At the end, the resulting mixture was concentrated and cold water was added in it. The solid product was separated, filtered, dried and subjected to recrystallization.

![Chemical reaction diagram]

3.15.1 1-(1-Methyl-5-chloroisochromanyl)acetyl hydrazide

Yield: 60%; m.p.: (°C): 210-211; Rf (Pet ether: ethyl acetate, 9:1): 0.1; \textbf{IR} (cm\(^{-1}\)): 3345, 3341, 2952, 1724, 1472, 1278, 1127; \textbf{\(^1\)HNMR} (CDCl\(_3\)): 8.2 (bs, 1H, NH), 7.78 (d, 1H\(_{arom}\), \(J = 4.1\)), 7.59 (d, 1H\(_{arom}\), \(J =3.2\)), 7.51 (d, 1H\(_{arom}\), \(J = 2.1\)), 7.24 (d, 1H\(_{arom}\), \(J = 3.3\)), 4.42 (m, 2H, H-3), 3.88 (s, 2H, H-11), 3.01 (m, 2H, H-4), 2.51 (s, 3H, H-13); \textbf{\(^{13}\)CNMR} (CDCl\(_3\)): 165 (CO), 142, 132, 131, 127, 126, 123, 75 (C-1), 59 (C-3), 56 (C-4), 44 (C-11).

3.15.2 1-(1-Methyl-6,7-dimethoxy)-isochromanyl]acetyl hydrazide

Yield: 78%; m.p.: (oil); Rf (Pet ether: ethyl acetate, 9:1): 0.1; \textbf{IR} (cm\(^{-1}\)): 3372, 3295, 3293, 1655, 1459, 1247, \textbf{\(^1\)HNMR} (CDCl\(_3\)): 7.71 (bs, 1H, NH), 6.55 (s, 2H\(_{arom}\), H-5,8), 4.0 (m, 2H, H-3 ), 3.9 (s, 6H, 2×OCH\(_3\)), 2.91 (s, 2H, H-11), 2.65 (m, 2H, H-4), 2.2 (s,3H,H-13); \textbf{\(^{13}\)CNMR} (CDCl\(_3\)): 166 (CO), 146, 1.5, 146.3, 136, 127,112, 111, 75 (C-1), 59, 56(2×OCH\(_3\)),

---

160
3.15.3 1-(1-Methyl-6,7,8-trimethoxy)-isochromanyl]acetyl hydrazide

Yield: 78%; m.p.: (°C): 164-165; Rf(Pet ether: ethyl acetate, 9:1): 0.1; IR (cm⁻¹): 3372, 3295, 1459, 1247; ¹HNMR (CDCl₃): 7.71 (bs, 1H, NH), 6.46 (s, 1H, H-5), 3.99 (m, 2H, H-3), 3.9 (s, 9H, 3×OCH₃), 3.07 (s, 2H, H-11), 2.6 (m, 2H, H-4), 1.98 (s, 3H, H-13); ¹³CNMR (CDCl₃): 169 (CO), 146, 148, 146.1, 136, 128, 124, 105, 75 (C-1), 65, 59, 56 (3×OCH₃), 48.

3.16 Synthesis of 1-(1-Methylisochromanyl)-3,5-dimethyl pyrazoles [¹²³] (9a-c)

A homogenized mixture of hydrazide and 2,4-pentanedione was irradiated for 30-70 s in an alumina bath inside a microwave oven. On completion of reaction, followed by TLC examination using hexane : ethyl acetate (8:2) the reaction mixture was diluted with ethyl acetate and subjected directly to thick layer chromatography on silica gel.

3.16.1 1-(1-Methyl-5’-chloro)isochromanyl]-3,5, dimethyl pyrazole (9a)

Yield: 67%; m.p.: (oil); Rf (Pet ether: ethyl acetate, 4:1): 0.8; IR (cm⁻¹): 2991, 2942, 1655, 1467, 1276, 1127; ¹HNMR (CDCl₃): 7.78 (d, 1H, H-7, J = 3.8), 7.36 (d, 1H, H-8, J = 4.1), 7.24 (d, 1H, H-7, J=3.3), 6.5 (s, 1H, H-4), 4.37 (m, 2H, H-3’), 3.8 (s, 2H, H-11’), 3.28 (m, 2H, H-4’), 2.4 (s, 3H, H-13’), 2.2 (s, 6H,2×CH₃); ¹³CNMR (CDCl₃):170 (CO), 145, 139, 133, 144.3, 143.1, 127, 126, 122, 105 (C-4), 74.1 (C-1’), 59, 29 (CH₃), 25, 17, 11; EIMS (70 eV): m/z (%), 318 [M⁺⁺] (100), 320 (4), 223 (42), 79 (1).
3.16.2 1-(1-Methyl-6’,7’,-dimethoxy)isochromanyl]-3,5 dimethyl pyrazole (9b)

Yield: 85%; m.p.: oil; Rf (Pet ether: ethyl acetate, 4:1): 0.6; IR (cm⁻¹): 2953, 2817, 1675, 1456, 1247; ¹HNMR (CDCl₃): 6.66 (s, 2H arom, H-5’,8’), 6.4 (s, 1H arom, H-4), 3.96 (m, 2H, H-3’), 3.9 (s, 6H, 2×OCH₃), 3.11 (s, 2H, H-11’), 2.47 (m, 2H, H-4’), 2.1(s, 6H, 2×CH₃), 1.5 (s, 3H, H-13’); ¹³CNMR (CDCl₃): 169 (CO), 147, 146, 144, 143, 136, 112, 111, 105 (C-4), 75 (C-1), 59, 43 (CH₃), 23, 17, 11; EIMS (70 eV): m/z (%), 344 [M⁺] (100), 249 (54), 79 (5).

3.16.3 [1-(1-Methyl-6’,7’,8’-dimethoxy)isochromanyl]-3,5 dimethyl pyrazole (9c)

Yield: 81%; m.p.: oil; Rf (Pet ether: ethyl acetate, 4:1): 0.5; IR (cm⁻¹): 2951, 1644, 1459, 1247; ¹HNMR (CDCl₃): 6.55 (s, 1H arom, H-5’), 6.4 (s, 1H arom, H-4), 3.96 (m, 2H, H-3’), 3.9 (s, 9H, 3×OCH₃), 3.07 (s, 2H, H-11’), 2.53 (m, 2H, H-4’), 1.81 (s, 6H, 2×CH₃), 1.5 (s, 3H, H-13’); ¹³CNMR (CDCl₃): 169 (CO), 149, 147, 144, 143, 136, 128, 121, 105 (C-4), 75(C-1), 58, 34, 17, 11, EIMS (70 eV): m/z (%), 374 [M⁺] (100), 279 (54), 79 (5).

3.17 Synthesis of Isochronanyl Substituted thia diazoles & triazoles

3.17.1 Synthesis of isothiocyanates[133a]

To a reaction mixture of substituted anilines (0.5 mol), carbon disulfide (0.8 mol) in methanol (10mL) at 0° ammonia (33%, 0.6 mol) was added and stirred for one hour. Crystal of dithiocabamate was separated and allowed to stand for overnight, filtered washed with ether and dissolved in water. Aqueous solution of lead nitrate (0.5 mol) was then added and subjected to steam distillation. Respected isocyanate was collected in a conical flask containing concentrated H₂SO₄ was extracted with ethyl acetate, organic layer was separated dried on anhydrous sodium sulfate, filtered and concentrated.
i) 2-Methoxyphenyl isothiocyanate

\[
\text{Yield: 54%; mp: oil; IR (KBr): 3010, 2966, 2932, 2901, 1587, 1326, 1496, 1459, cm}^{-1}.
\]

ii) 4-Methylphenyl isothiocyanate

\[
\text{Yield: 47%; mp: oil; IR (KBr): 3053, 2966, 2932, 28030, 1609, 1507, 1326, 1466, cm}^{-1}.
\]

iii) 4-Methoxylphenyl isothiocyanate:

\[
\text{Yield: 57%; mp: oil; IR (KBr): 3056, 2954, 2908, 28030, 2252, 1611, 1513, 1467, cm}^{-1}.
\]

iv) 4-Chlorophenyl isothiocyanate

\[
\text{Yield: 39%; mp: (°C): 43 (lit; 42-44). IR (KBr): 3053, 2966, 2932, 1622, 1512, 1466, cm}^{-1}.
\]

v) 3-Methoxylphenyl isothiocyanate

\[
\text{Yield: 35%; oil; IR (KBr): 3066, 2966, 2928, 2834, 1611, 1507, 1326, 1466, cm}^{-1}.
\]
3.18 Synthesis of 1-(1-Methyl)isochromanylphenyl semicarbazide [133] (10a-e)

To a solution of 1-(1-methyl-6,7,8-trimethoxy)-isochromanyl]-acetyl hydrazide in absolute ethanol, a solution of phenylisothiocyanate in ethanol was added portion wise and the reaction mixture was refluxed for 6 h. The solid product appeared was filtered, dried and subjected to recrystallization.

3.18.1 1-(1-Methyl-6,7,8-trimethoxy)isochromanyl-2′-methoxyphenyl semicarbazide (10a)

Yield: 73%; m.p.: (semisolid); R<sub>f</sub> (Pet ether: ethyl acetate, 1:9): 0.5; I.R (cm<sup>-1</sup>): 3272, 3261, 1634, 1451, 1232; <sup>1</sup>H NMR (CDCl<sub>3</sub>): 8.32 (s, 1H, NH), 7.93 (s, 1H, NH), 7.8 (d, 1H<sub>arom</sub>, J = 3.2), 7.61 (d, 1H<sub>arom</sub>, H-5′, J = 5.5), 7.43 (d, 1H<sub>arom</sub>, H-4′, J = 3.2), 7.1 (d, 1H<sub>arom</sub>, J = 6.1), 6.55 (s, 1H<sub>arom</sub>, H-5′), 6.4 (s, 1H<sub>arom</sub>, H-4), 3.96 (m, 2H, H-3′), 3.9 (s, 9H, 3×OCH<sub>3</sub>), 3.07 (s, 2H, H-11), 2.53 (m, 2H, H-4), 1.81 (s, 6H, 2×CH<sub>3</sub>), 1.5 (s, 3H, H-13); <sup>13</sup>C NMR (CDCl<sub>3</sub>): 181 (CS), 177 (CO), 158 (C-2′), 149 (C-8), 148 (C-6), 136 (C-7), 128 (C-10), 127 (C-6′), 121 (C-9, C-5′), 114 (C-3′), 75 (C-1), 65 (OCH<sub>3</sub>), 60 (C-3), 47 (CH<sub>2</sub>), 27 (CH<sub>3</sub>).

3.18.2 1-(1-Methyl-6,7,8-trimethoxy)isochromanyl-4′-methyl phenyl semicarbazide (10b)

Yield: 82%; m.p. (semisolid); R<sub>f</sub> (Pet ether: ethyl acetate, 1:9): 0.8; IR (cm<sup>-1</sup>): 3345, 3295, 1636, 1491, 1264; <sup>1</sup>H NMR (CDCl<sub>3</sub>): 8.3 (bs, NH), 7.40 (d, 2H<sub>arom</sub>, H-3′,5′, J = 5.3), 7.28 (d, 2H<sub>arom</sub>, H-2′,6′, J = 4.8), 7.1 (bs, NH), 6.5 (s, 1H, H-5), 3.9 (s, 9H,
3×OCH₃), 3.81 (m, 2H, H-3), 3.7 (s, 2H, H-11), 2.4 (m, 2H, H-4), 1.69 (s, 3H, CH₃), 1.5 (s, 3H, CH₃); ¹³CNMR (CDCl₃): 181 (CS), 177 (CO), 149 (C-8), 148 (C-6), 136 (C-7), 129 (C-3’, C-5’), 128 (C-10), 126 (C-2’, C-6’), 121 (C-9), 75 (C-1), 65 (3×OCH₃), 60 (C-3), 47 (CH₂), 27 (CH₃).

3.18.3 1-(1-Methyl-6,7,8-trimethoxy)isochromanyl]-4’-methoxy phenyl semicarbazide (10c)

![Chemical structure of 1-(1-Methyl-6,7,8-trimethoxy)isochromanyl]-4’-methoxy phenyl semicarbazide (10c)](image)

Yield: 77%; m.p. (semisolid): Rf (Pet ether: ethyl acetate, 1:9): 0.8; IR (cm⁻¹): 3314, 3288, 1651, 1467, 1246; ¹HNM(N(CDCl₃): 8.4 (bs, NH), 7.81 (s, NH), 7.3 (d, 2H arom, H-3’,5’, J = 5.1), 6.9 (d, 2H arom, H-2’,6’, J = 5.5), 6.5 (s, 1H arom, H-5), 4.02 (m, 2H, H-3), 3.84 (s, 12H, 4×OCH₃), 3.7 (s, 2H, H-11), 2.9 (m, 2H, H-4), 2.2 (s, 3H, H-13), 1.5 (s, 3H, CH₃); ¹³CNMR (CDCl₃): 181 (CS), 177 (CO), 149 (C-8), 148 (C-6), 136 (C-7), 129 (C-3’, C-5’), 128 (C-10), 126 (C-2’, C-6’), 121 (C-9), 75 (C-1), 65 (3OCH₃), 62 (OCH₃), 60 (C-3), 47 (CH₂), 27 (CH₃).

3.18.4 1-(1-Methyl-6,7,8-trimethoxy)isochromanyl]-4’-chlorophenyl thiosemicarbazide (10d)

![Chemical structure of 1-(1-Methyl-6,7,8-trimethoxy)isochromanyl]-4’-chlorophenyl thiosemicarbazide (10d)](image)

Yield: 80%; m.p. (semisolid): Rf (Pet ether: ethyl acetate, 1:9): 0.8; IR (cm⁻¹): 3326, 3281, 1634, 1461, 1223; ¹HNM(N(CDCl₃): 8.9 (bs, NH), 7.94 (s, NH), 7.5 (d, 2H arom, H-3’,5’, J = 5.3), 7.3 (d, 2H arom, H-2’,6’, J = 4.9), 6.3 (s, 1H arom, H-5), 3.9 (s, 9H, 3×OCH₃), 3.8 (m, 2H, H-3), 3.71 (s, 2H, H-11), 2.91 (m, 2H, H-4), 2.2 (s, 3H, H-13); ¹³CNMR(CDCl₃), 181 (CS), 177 (CO), 149 (C-8), 148 (C-6), 136 (C-7), 131 (C-4’), 130 (C-3’, C-5’), 129 (C-10), 126 (C-2’, C-6’), 121 (C-9), 75 (C-1), 65 (3×OCH₃), 60 (C-3), 47 (CH₂), 27 (CH₃).
3.18.5 1-(1-Methyl-6,7,8-trimethoxy)isochromanyl]-3'-methoxy phenyl thiosemicarbazide (10e)

Yield: 86%; m.p.: (semisolid); Rf (Pet ether: ethyl acetate, 1:9): 0.8; IR (cm⁻¹): 3372, 3295, 1663, 1462, 1242, ¹HNMR (CDCl₃): 8.45 (bs, NH), 7.67 (s, NH), 7.33 (d, 1Hₐrom, H-5', 4.3), 7.1 (d, 1Hₐrom, H-4', J = 4.2), 6.5 (d, 1Hₐrom, H-5, J = 3.3), 6.43 (d, 1Hₐrom, H-2', J = 3.9), 6.3 (s, 1Hₐrom, H-6'), 3.9 (s, 9H, 3×OCH₃), 3.8 (m, 2H, H-3), 3.71 (s, 2H, H-11), 2.91 (m, 2H, H-4), 2.2 (s, 3H, H-13); ¹³CNMR(CDCl₃): 181 (CS), 177 (CO), 162 (C-3'), 149 (C-8), 148 (C-6), 140 (C-1), 136 (C-7), 131 (C-4'), 129 (C-10), 126 (C-2', C-6'), 121 (C-9), 118 (C-5'), 104 (C-5), 75 (C-1), 65 (3×OCH₃), 64 (OCH₃), 60 (C-3), 47 (CH₂), 27 (CH₃).

3.19 Synthesis of N-(phenyl)-5-(6,7,8-trimethoxy-1-methyl-3,4-dihydro-1H-isochromen-1-yl)-1,3,4-thiadiazole-2-amines [¹³³] (11a-e)

To a cooled sulphuric acid at 0°C thiosemicarbazide, was added portion wise with constant stirring. After complete addition the reaction was stirred for 3 h, and then allowed to stand for overnight. The solution was then poured into ice cold water, filtered, washed thoroughly with cold water, dried and recrystallized from ethanol/water.

3.19.1 N-(2-methoxyphenyl)-5-(6,7,8-trimethoxy-1-methyl-3,4-dihydro-1H-isochromen-1-yl)-1,3,4-thiadiazole-2-amine (11a)

Yield: 80%; m.p.: (semisolid); Rf (Pet ether: ethyl acetate, 4:1): 0.6; IR (cm⁻¹): 3193, 1625, 1423, 1231; ¹HNMR (CDCl₃): 7.7 (bs, NH), 7.5 (d, 1Hₐrom, J = 3.2), 7.3(d, 1Hₐrom, J = 5.5), 7.1 (d, 1Hₐrom, J = 3.2), 6.5 (s, 1Hₐrom), 3.9 (s, 12H, 4×OCH₃), 3.82 (m, 2H,
3.19.2 N-(4-methylphenyl)-5-(6,7,8-trimethoxy-1-methyl-3,4-dihydro-1H-isochromen-1-yl)-1,3,4-thiadiazole-2-amine (11b)

Yield: 83%; m.p.: (semisolid); Rf (Pet ether: ethyl acetate, 4:1): (0.7); IR (cm$^{-1}$): 3305, 1617, 1367, 1271; $^{1}$HNMR (CDCl$_3$): 8.0 (bs, NH), 7.3 (d, 2H$_{arom}$, J = 5.6), 7.22 (d, 2H$_{arom}$, J = 4.3), 6.5 (s, 1H, H-5), 3.9 (s, 9H, 3×OCH$_3$), 3.84 (m, 2H, H-3), 3.7 (s, 2H, H-11), 2.5 (m, 2H, H-4), 2.3 (s, 3H, CH$_3$), 1.6 (s, 3H, CH$_3$); $^{13}$CNMR (CDCl$_3$): 168 (C$_5$N), 153 (C$_2$N), 148 (C-6’, C-8’), 141 (C-1”), 134 (C-7”), 130 (C-3”, C-5”), 129, (C-4”), 128 (C-10”), 124 (C-9”), 113 (C-2”, C-4”), 105 (C-5”), 70 (C-3’), 65 (3×OCH$_3$), 63 (OCH$_3$), 35 (C-4”), 26, 23, EIMS (70 eV): m/z (%): 442 [M$^{+}$] (100), 277 (45), 133 (52), 107 (32).

3.19.3 Synthesis of N-(4-methoxyphenyl)-5-(6,7,8-trimethoxy-1-methyl-3,4-dihydro-1H-isochromen-1-yl)-1,3,4-thiadiazole-2-amine (11c)

Yield: 77%; m.p.: (semisolid); Rf (Pet ether: ethyl acetate, 1:9): 0.8; IR (cm$^{-1}$): 3315, 1622, 1343, 1272; $^{1}$HNMR (CD$_3$OD): 8.1 (bs, NH), 7.7 (d, H$_{arom}$, J = 5.2), 7.4 (d, 2H$_{arom}$, J = 5.3), 6.5 (s, 1H, H-5), 3.92 (m, 2H, H-3), 3.84 (s, 12H, 4×OCH$_3$), 3.7 (s, 2H, H-11), 2.9 (m, 2H, H-4), 2.2 (s, 3H, H-13), 1.5 (s, 3H, CH$_3$); $^{13}$CNMR (CDCl$_3$): 169 (C$_5$N), 155 (C$_2$N), 148 (C-6’, C-8’), 141 (C-1”), 134 (C-7”), 130 (C-3”, C-5”), 129, (C-4”), 128 (C-10”), 124 (C-9”), 113 (C-2”, C-4”), 105 (C-5”), 70 (C-3’), 65 (3×OCH$_3$), 61 (OCH$_3$), 35 (C-4”), 26, 23, EIMS (70 eV): m/z (%): 457 [M$^{+}$] (100), 277 (45), 148 (52), 122 (32).
3.19.4  N-(4-chlorophenyl)-5-(6,7,8-trimethoxy-1-methyl-3,4-dihydro-
1H-isochromen-1-yl)-1,3,4-thiadiazole-2-amine (11d)

Yield: 81%; m.p.: (semisolid); R_f (Pet ether: ethyl acetate, 4:1): 0.8; IR (cm⁻¹): 3294, 1632, 1359, 1254, ¹HNMR (CD₃OD): 8.1 (bs, NH), 7.8 (d, 2H_arom, J= 5.0), 7.5 (d, 2H_arom, J = 5.0), 6.44 (s, 1H, H-5), 3.9 (s, 9H, 3×OCH₃), 3.85 (m, 2H, H-3), 3.71 (s, 2H, H-11), 2.93 (m, 2H, H-4), 2.2 (s, 3H, H-13); ¹³CNMR (CDCl₃), 171 (C₅N), 152 (C₂N), 148 (C-6’, C-8’), 141 (C-1”), 136 (C-3”, C-5”), 134 (C-7’), 129 (C-4”’), 128 (C-10’), 124 (C-9’), 121 (C-2”, C-4”), 105 (C-5’), 70 (C-3’), 65 (3×OCH₃), 61 (OCH₃), 35 (C-4’), 26, 23. EIMS (70 eV): m/z (%), 461 [M⁺] (100), 277 (45), 168 (52), 127 (32).

3.19.5  N-(3-methoxyphenyl)-5-(6,7,8-trimethoxy-1-methyl-3,4-dihydro-
1H-isochromen-1-yl)-1,3,4-thiadiazole-2-amine (11e)

Yield: 86%; m.p.: (semisolid); R_f (Pet ether: ethyl acetate, 4:1): 0.5; IR (cm⁻¹): 32785, 1589, 1346, 1256, ¹HNMR(CD₂OD): 8.15 (bs, NH), 7.7 (s, 1H), 7.66 (d, 1H_aroms, J = 4.5), 7.32 (d, 1H_aroms, J = 4.5), 6.6 (d, 1H_aroms, J = 3.2), 6.43 (s, 1H, H-5), 3.9 (s, 9H, 3×OCH₃), 3.87 (m, 2H, H-3), 3.75 (s, 2H, H-11), 2.91 (m, 2H, H-4), 2.25 (s, 3H, H-13); ¹³CNMR(CDCl₃): 169 (C₅N), 152 (C₂N), 148 (C-6’, C-8’), 145 (C-3”), 141 (C-1”), 134 (C-7’), 130 (C-5”), 128 (C-10’), 124 (C-9’), 121 (C-2”), 110 (C-6”), 105 (C-5’), 104 (C-4”), 70 (C-3’), 65 (3×OCH₃), 61 (OCH₃), 35 (C-4’), 26, 23, EIMS (70 eV): m/z (%), 442 [M⁺⁺] (100), 277 (45), 133 (49), 107 (36).
3.20 Synthesis of 5-(6,7,8-trimethoxy-1-methyl-3,4-dihydro-1H-isochromen-1-yl)-4H-1,2,4-triazole-3-thiones \cite{133} (12a-e)

To an aqueous solution of NaOH thiosemicarbazide was added portion wise. The reaction was refluxed for 2 h. On cooling solid appeared filtered, dried and subjected to analysis.

3.20.1 4-o-Methoxy-5-(6,7,8-trimethoxy-1-methyl-3,4-dihydro-1H-isochromen-1-yl)-4H-1,2,4-triazole-3-thione (12a)

Yield: 78%; m.p.: (semisolid), \( R_f \) (Petroleum ether: Ethyl acetate, 4:1): 0.6; \( \text{IR (cm}^{-1}) \): 3012, 1589, 1441, 1218, \( ^1\text{HNMR (DMSO)} \): 10.39 (bs, SH), 7.3 (d, 1H arom, \( J = 3.2 \)), 7.1 (d, 1H arom, \( J = 5.5 \)), 6.9 (d, 1H arom, \( J = 3.1 \)), 6.6(d, 1H arom, \( J = 4.1 \)), 6.5 (s, 1H, H-5), 3.9 (s, 12H, 4×OCH\(_3\)), 3.86 (m, 2H, H-3), 3.74 (s, 2H, H-11), 2.94 (m, 2H, H-4), 2.1 (s, 3H, H-13), 1.6 (s, 3H, CH\(_3\)); \( ^{13}\text{CNMR (CDCl}_3\) ): 160 (CS), 158 (C-2\(^\prime\)), 150 (CN), 149 (C-8), 148 (C-6), 136 (C-7), 128 (C-10), 127 (C-6\(^\prime\)), 121 (C-9, C-5\(^\prime\)), 114 (C-3\(^\prime\)), 75 (C-1), 65 (OCH\(_3\)), 60 (C-3), 47 (CH\(_2\)), 27 (CH\(_3\)), \( \text{EIMS (70 eV)} \): m/z (%), 457 [M\(^{+}\)] (100), 277(45), 148(52).

3.20.2 4-p-Methyl-5-(6,7,8-trimethoxy-1-methyl-3,4-dihydro-1H-isochromen-1-yl)-4H-1,2,4-triazole-3-thiol (12b)
Yield: 81%; m.p.: (semisolid); R_f (Pet ether: ethyl acetate, 4:1): 0.5; IR (cm⁻¹): 3122, 1598, 1423, 1247; HNMR (CDCl₃): 11.30 (bs, SH), 7.26 (d, 2H_arom, J = 5.1), 7.00 (d, 2H_arom, J = 4.6), 6.53 (s, 1H, H-5), 3.91 (s, 9H, 3×OCH₃), 3.85 (m, 2H, H-3), 3.69 (s, 2H, H-11), 2.5 (m, 2H, H-4), 2.3 (s, 3H, CH₃, H-11), 1.58 (s, 3H, CH₃); CNMR (CDCl₃): 161 (CS), 152 (CN), 149 (C-8), 148 (C-6), 136 (C-7), 129 (C-3', C-5'), 128 (C-10), 126 (C-2', C-6'), 121 (C-9), 75 (C-1), 65 (3×OCH₃), 60 (C-3), 47 (CH₂), 27 (CH₃), EIMS (70 eV): m/z (%), 442 [M+•] (100), 277 (45), 133 (52).

3.20.3 4-p-Methoxy-5-(6,7,8-trimethoxy-1-methyl-3,4-dihydro-1H-isochromen-1-yl)-4H-1,2,4-triazole-3-thiol (12c)

Yield: 66%; m.p.: (semisolid); R_f (Pet ether: ethyl acetate, 1:9): 0.8; IR (cm⁻¹): 3127, 1592, 1423, 1256; HNMR (CD₂OD): 9.8 (bs, SH), 7.4 (d, H_arom, J = 5.2), 7.33(d, 2H_arom, J = 5.3), 6.58 (s, 1H, H-5), 3.92 (m, 2H, H-3), 3.84 (s, 12H, 4×OCH₃), 3.72 (s, 2H, H-11), 2.91 (m, 2H, H-4), 2.24 (s, 3H, H-13), 1.58; CNMR (CDCl₃), 160 (CS), 149 (C-8), 148 (C-6), 143 (CN), 136 (C-7), 129 (C-3', C-5'), 128 (C-10), 126 (C-2', C-6'), 121 (C-9), 75 (C-1), 65 (3×OCH₃), 62 (OCH₃), 60 (C-3), 47 (CH₂), 27 (CH₃), EIMS (70 eV): m/z (%), 457 [M+•] (100), 277(45), 148(52).

3.20.4 4-p-Chloro-5-(6,7,8-trimethoxy-1-methyl-3,4-dihydro-1H-isochromen-1-yl)-4H-1,2,4-triazole-3-thiol (12d)

Yield: 77%; m.p.: (semisolid); R_f (Pet ether: ethyl acetate, 4:1): 0.7; IR (cm⁻¹): 3011, 1567, 1423, 1247, HNMR (CD₂OD): 9.1 (bs, SH), 7.65 (d, 2H_arom, J = 4.9), 7.51(d, 2H_arom, J = 5.1), 6.52 (s, 1H, H-5), 3.9 (s, 9H, 3×OCH₃), 3.85 (m, 2H, H-3), 3.71 (s, 2H, H-11), 2.93 (m, 2H, H-4), 1.90 (s, 3H, H-13); CNMR (CDCl₃): 158 (CS), 153 (CN),
3.20.5 4-m-Methoxy-5-(6,7,8-trimethoxy-1-methyl-3,4-dihydro-1H-isochromen-1-yl)-4H-1,2,4-triazole-3-thiol (12e)

Yield: 86%; m.p: (semi solid); Rf (Pet ether: ethyl acetate, 4:1): 0.6; IR (cm⁻¹): 3117, 1573, 1421, 1245; ^1HNMR (CD₃OD): 8.87 (bs, SH), 7.68 (s, 1H), 7.54 (d, 1H, H_arom, J = 4.1), 7.43 (d, 1H_arom, J = 4.6), 6.59 (d, 1H_arom, J = 5.1), 6.5 (s, 1H, H-5), 3.9 (s, 9H, 3×OCH₃), 3.87 (m, 2H, H-3), 3.75 (s, 2H, H-11), 2.92 (m, 2H, H-4), 1.98 (s, 3H, H-11), 1.65 (s, 3H, CH₃); ^13CNMR (CDCl₃), 160 (CS), 149.3 (CN), 162 (C-3’), 149 (C-8), 148 (C-6), 140 (C-1), 136 (C-7), 131 (C-4’), 129 (C-10), 126 (C-2’, C-6’), 121 (C-9), 118 (C-5’), 104 (C-5), 75 (C-1), 65 (3×OCH₃), 64 (OCH₃), 60 (C-3), 47 (CH₂), 27 (CH₃), EIMS (70 eV): m/z (%), 442 [M⁺] (100), 277 (45), 133 (49),

3.21 Biological Activities

All the synthesized compounds: oxadiazoles, mercaptoxadiazoles, triazoles, pyrazoles, pyrazolines, isochromans, isochromanyl pyrazoles, isochromanyl thiazadiazoles, isochromanyl thiadiazoles were tested for their biological activities: antibacterial, antifungal and phytotoxic activities.

3.21.1 Antibacterial Activities

In vitro antibacterial bioassay was carried out by using agar well diffusion method against gram positive strain of bacterium Bacillus subtilus and gram negative strain of bacterium Escherichia coli.

Ampicillin against negative strain of bacteria and Kanamycin against positive strain of bacteria were used as standard drugs. 3 mg/mL and 5 mg/mL of compound were dissolved in 1 mL of acetone.
Laboratory strain of gram positive bacterium, *Bacillus subtilis*, gram negative strain of bacterium, *Escherichia coli* were grown to log phase in LB (1% yeast extract, 1% peptone, and 1% dextrose) at 37°C (bacteria) overnight with constant shaking.

Log phase cultures were spread onto Muller-Hinton plates. After organisms were spread wells were introduced by using cork borer (4mm). These wells were loaded with 3 mg/mL and 5 mg/mL solution of compounds in acetone, negative control acetone and positive control Ampicillin and Kanamycin by using 5µL micropipette. These plates were incubated for 24 h on 37°C. The tests were repeated for three times and it was found that most significant results were obtained by using a concentration of 5mg/mL. After 24 h incubation time the zones of inhibition was measured in mm scale and was compared with standard drugs.\(^{[134]}\)

### 3.21.2 Antifungal Activities

Antifungal activities were carried out against yeast (*Saccharomyces cerevisiae*). Fluconazole was used as standard drug. 3 mg/mL and 5 mg/mL of compound were dissolved in 1 mL of acetone. Plates were loaded with solutions of samples, standard drug and negative control acetone by using 5µL micropipette. These plates were incubated for 24 h on 28°C.

The tests were repeated for three times and it was found that most significant results were obtained by using a concentration of 5mg/mL. After 24 h incubation time the zones of inhibition was measured and percentage of fungal inhibition was calculated and compared with standard drugs.\(^{[134]}\)

\[
\text{% age of fungal inhibition} = 100 - \frac{\text{fungal growth in test sample (cm)}}{\text{fungal growth in control (cm)}} \times 100
\]

### 3.21.3 Phytotoxic Activities

All the synthesized compounds were tested for their phytotoxic activities, effect of chemicals on the growth inhibition of plant. Leaves of *Physalis* plant, the fruit of this plant is called Cape gooseberry used as a decorative of cakes, were used for the above test. 3 mg/mL and 5 mg/mL of compound were dissolved in 1 mL of acetone. Solutions of compound were applied on the broad leaves of the *Physalis* plants. Inhibition was observed after 24 hours by blackening or pale yellowing of the leave.
REFERENCES


2007, 48, 129.


2006, 47, 6983.

4827.


2008, 43, 595.


Kalimuuthu, P.; John, S. A. \textit{Bioelectrochemistry}, \textbf{2009} article in press.


1,3,4-Oxadiazoles, Amino substituted 1,3,4-Oxadiazoles-2-thiones, 1,2,4-Triazoles, 3,5-Disubstituted pyrazoles, 3,5-Disubstituted pyrazolines, Isochromanyl thiadiazoles, Isochromanyl triazoles and Triazole thiadiazines were synthesised starting from hydrazides either by direct cyclization or through semicarbazides as intermediates. Some 1-Aryisochromans and Methyl1-methyl-1-isochromanyle acetates were synthesised using substituted phenyl ethanols as precursors. On the other hand some substituted morpholines were synthesised by protecting $\alpha$-amino alcohols with p-tolylmethylsulfinate to get sulfanilamides which were cyclized with bromoethylidiphenylsulphonium salt to get morpholines upon deprotection in the presence of concentrated hydrochloric acid, morpholines were obtained in good to excellent yields.

In case of microwave accelerated synthesis of 1,3,4-Oxadiazoles, 3,5-Dimethylpyrazoles and 1-Aryl-5-isochromans, time and solvent can be saved and crudes were directly used for purifications.

Structures were confirmed by using IR, NMR and Mass analysis. All of the Oxadiazoles, Triazoles, Pyrazoles, thia diazoles, and isochromans were subjected to biological assays: antibacterial, antifungal and phytotoxic studied. All showed excellent activities. Most significant results were found when F, Cl, and OCH$_3$ groups were present. Most significant inhibitions were observed by compounds: (1b), (2b), (3d), (3e), (4a), (4b), (4d), (5a), (5c), (6c), (6e), (8e), (9a), (9b), (9c), (11b), (11e) and (12d) during their antifungal, antibacterial and phytotoxic assays.
List of publications