PART-B

STUDIES ON 6-FLUOROCHROMAN-2-CARBOXYLIC ACID DERIVATIVES
INTRODUCTION

Although chroman was first prepared in 1905, little interest was shown in the compound until studies on the tocopherols (Vitamin-E) began to indicate that they were derivatives of chroman. Same as many derivatives of chroman were prepared like a nebivolol acid and nebivolol drug. The monoalkyl chromans can be divided into two groups-one with the alkyl substituted attacked to the benzene ring and the second with attacked to the heterocyclic ring. The former can be obtained from appropriate derivatives of benzene similar to those used for the preparation of chroman. Chroman is stable to acids and oxidizing agents. It is soluble in common organic solvents\(^1\).

Chroman is an aromatic heterocyclic organic compound. It is a bicyclic structure, consisting of a six-membered benzene ring fused to a six-membered oxygen hetero atom (benzopyrane).

\[
\text{6-Fluorochroman-2-carboxylic acid is a solid at room temperature. And it is a derivative of nebivolol drug. And it is also known as nebivolol acid. Nebivolol is an antihypertensive compound. Nebivolol has been studied in over 3000 patients with hypertension. The use of nebivolol is contraindicated in patients with, cardiogenic shock, uncontrolled heart failure, Sick sinus syndrome, Second and third degree heart block, Asthma, Hypotension, and Pregnancy. etc.}
\]

**6-FLUOROCHROMAN-2-CARBOXYLIC ACID (NEBIVOLOL ACID)**

**NEBIVOLOL [2,2’-azanediylbis(1-(6-fluorochroman-2-yl)ethanol)]**
Vitamin E refers to a family of eight molecules having a chromanol ring (chroman ring with an alcoholic hydroxyl group) and a 12-carbon aliphatic side chain containing two methyl groups in the middle and two more methyl groups at the end. Tocotrienols (found in high concentrations in palm oil) are many times more potent as anti-oxidants than are tocopherols, but they are poorly assimilated by digestion, are poorly distributed to tissues in blood and are rapidly metabolized and eliminated from the body. But tocotrienols are well-absorbed by the skin and thus are well suited for use as a Vitamin E cream.

SYNTHETIC ASPECT

1. K. J. Hodgetts² has developed a new method for 2-substituted chroman by intermolecular Mitsunobu reaction of a homochiral halopropanol and 2-bromophenol.

\[
\begin{align*}
\text{Ph} & \quad \text{OH} \\
\text{Br} & \quad \text{OH} \\
\text{THF} & \quad \\
\text{BuLi} & \quad \\
\rightarrow & \quad \\
\end{align*}
\]

2. C. Lherbet et al.³ have synthesized isochroman in the one pot-reaction by using different benzaldehydes and phenylethanethiol or phenyl ethanol in presence of bismuth triflate as a catalyst.

\[
\begin{align*}
\text{R-CHO, Bi(OTf)}_3 & \quad \text{Toluene} \\
\rightarrow & \quad \\
\end{align*}
\]

3. C. S. López et al.⁴ have developed a mild and convenient one-pot photochemical synthesis of chroman-4-one derivatives.

\[
\begin{align*}
\text{hv} & \quad \\
\rightarrow & \quad \\
\end{align*}
\]
4. H. Hamamoto et al.\textsuperscript{5} synthesized chroman by direct aromatic carbon–oxygen bond-formation reaction involving aromatic cation radical intermediates using the hypervalent iodine (III) reagent, phenyl iodine (III) bis(trifluoroacetate) (PIFA).

5. S. Emami et al.\textsuperscript{6} have synthesized azolyl chroman derivatives prepared as conformationally constrained analogs of (aryl alkyl) azoles.

6. M. Venkati et al.\textsuperscript{7} have synthesized chroman from substituted o-hydroxy acetophenone and substituted benzaldehyde in 60\% KOH.

7. R. R. Karimi et al.\textsuperscript{8} have developed simple, clean and benign route for synthesis of 2H-chromen-2-ones derivatives through one-pot condensation of β-ketoesters and substituted phenols in the presence of 1-chloromethyl-4-fluoro-1,4-diazaoniabicyclo[2.2.2]octane. Bistetrafluoroborate is (Selectfluor\textsuperscript{TM} - TEDABF\textsubscript{4}) was used as catalyst under solvent free reaction conditions.
8. S. R. Sarda et al.\textsuperscript{9} have synthesized 2,4-diphenyl-4\textit{H}-chromen-5-one from \(\alpha\), \(\beta\)-unsaturated carbonyl compounds and 1,3-cyclohexanedione under microwave irradiation in the presence ZnCl\textsubscript{2}/montmorillonite K-10.

![Chemical structure of S. R. Sarda et al.](image)

9. D. P. Kardile et al.\textsuperscript{10} have synthesized 7-hydroxy-4-methylcoumarin from various phenols like resorcinol, m-cresol etc. condensed with ethylacetoacetate (II) in presence of concentrated sulphuric acid by Pechmann reaction.

![Chemical structure of D. P. Kardile et al.](image)

10. R. Suthunuru et al.\textsuperscript{11} have developed highly effective, facile, one-pot regioselective synthesis of a series of 4,7-dihydroxy-4-phenyl-chroman-2-ones involves a die none-phenol rearrangement followed by a Michael type reaction.

![Chemical structure of R. Suthunuru et al.](image)

11. H. Lee et al.\textsuperscript{12} have synthesized 6-hydroxy-7-methoxy-4-chromanone using aluminum chloride as catalyst.

![Chemical structure of H. Lee et al.](image)
12. Q. Wang et al.\textsuperscript{13} have synthesized 6-hydroxy chroman from condensation of 2-methyl-3-butene-2-ol and substituted phenol in the presence of formic acid.

\begin{center}
\begin{tikzpicture}
\node[draw, rectangle] (a) at (0,0) {OH \hspace{1cm} OH \hspace{1cm} HCOOH} ;
\draw[->] (0.2,0.2) -- (3.8,0.2) ;
\node[draw, rectangle] (b) at (0.2,0.7) {OH} ;
\node[draw, rectangle] (c) at (0.7,0.7) {HO} ;
\node[draw, rectangle] (d) at (1.5,0.7) {\textsuperscript{2}C} ;
\node[draw, rectangle] (e) at (2.0,0.7) {\textsuperscript{3}B} ;
\node[draw, rectangle] (f) at (2.5,0.7) {OH} ;
\node[draw, rectangle] (g) at (3.8,0.7) {O} ;
\node[draw, rectangle] (h) at (4.3,0.7) {\textsuperscript{1}O} ;
\draw[->] (1.5,0.7) -- (3.8,0.7) ;
\end{tikzpicture}
\end{center}

13. X. Meng et al.\textsuperscript{14} have developed a novel domino reaction catalyzed by triphenylphosphine for synthesis of the highly functionalized chroman derivatives.

\begin{center}
\begin{tikzpicture}
\node[draw, rectangle] (a) at (0,0) {OH \hspace{1cm} NP(S)Ph\textsubscript{2}} ;
\draw[->] (0.2,0.2) -- (3.8,0.2) ;
\node[draw, rectangle] (b) at (0.2,0.7) {OH} ;
\node[draw, rectangle] (c) at (0.7,0.7) {NHP(S)Ph\textsubscript{2}} ;
\node[draw, rectangle] (d) at (1.5,0.7) {COOR} ;
\draw[->] (0.7,0.7) -- (1.8,0.7) ;
\node[draw, rectangle] (e) at (1.8,0.7) {PPh\textsubscript{3} (30 MOI %)} ;
\node[draw, rectangle] (f) at (2.2,0.7) {CH\textsubscript{2}Cl\textsubscript{2}} ;
\draw[->] (2.2,0.7) -- (3.8,0.7) ;
\node[draw, rectangle] (g) at (3.8,0.7) {OCOR} ;
\node[draw, rectangle] (h) at (4.3,0.7) {R = Et, Me} ;
\end{tikzpicture}
\end{center}

14. D.Lu et al.\textsuperscript{15} have developed symmetric tandem Michael addition hemiacetalization between aliphatic aldehydes and (E)-2-(2-nitrovinyl)phenols for constructing chroman backbones.

\begin{center}
\begin{tikzpicture}
\node[draw, rectangle] (a) at (0,0) {OH \hspace{1cm} OH \hspace{1cm} CHO} ;
\draw[->] (0.2,0.2) -- (3.8,0.2) ;
\node[draw, rectangle] (b) at (0.2,0.7) {OH} ;
\node[draw, rectangle] (c) at (0.7,0.7) {CHO} ;
\node[draw, rectangle] (d) at (1.5,0.7) {\textsuperscript{2}(E) - 2-(2-nitrovinyl)} ;
\node[draw, rectangle] (e) at (2.0,0.7) {phenols} ;
\node[draw, rectangle] (f) at (2.5,0.7) {R = Me, Et, Ph} ;
\draw[->] (2.0,0.7) -- (3.8,0.7) ;
\node[draw, rectangle] (g) at (3.8,0.7) {OH} ;
\node[draw, rectangle] (h) at (4.3,0.7) {NO\textsubscript{2}} ;
\node[draw, rectangle] (i) at (4.8,0.7) {R} ;
\end{tikzpicture}
\end{center}

15. M.Yoshida et al.\textsuperscript{16} have synthesized chroman in the presence of 5 mol % Pd\textsubscript{2}(dba)\textsubscript{3}·CHCl\textsubscript{3} and 20 mol % 1,1′-bis(diphenylphosphino)-ferrocene (DPPF) in dioxane at 120 °C for 5 min.

\begin{center}
\begin{tikzpicture}
\node[draw, rectangle] (a) at (0,0) {OH \hspace{1cm} OCO\textsubscript{2}Me} ;
\draw[->] (0.2,0.2) -- (3.8,0.2) ;
\node[draw, rectangle] (b) at (0.2,0.7) {OH} ;
\node[draw, rectangle] (c) at (0.7,0.7) {Ar} ;
\node[draw, rectangle] (d) at (1.5,0.7) {Ar} ;
\node[draw, rectangle] (e) at (2.0,0.7) {Ar} ;
\node[draw, rectangle] (f) at (2.5,0.7) {Ar} ;
\node[draw, rectangle] (g) at (3.8,0.7) {Ar} ;
\node[draw, rectangle] (h) at (4.3,0.7) {COOR} ;
\node[draw, rectangle] (i) at (4.8,0.7) {COOR} ;
\draw[->] (1.5,0.7) -- (3.8,0.7) ;
\node[draw, rectangle] (j) at (3.8,0.7) {Pd (O)} ;
\end{tikzpicture}
\end{center}
Studies on nitrogen containing heterocyclic...

16. C. Selenski et al.\textsuperscript{17} have synthesized chroman derivatives as like natural molecule of (+)-mimosifoliol.

\[
\begin{array}{c}
\text{OcoB} \\
\text{O} \\
\text{H}
\end{array}
\xrightarrow{\text{OR}}
\begin{array}{c}
\text{\textbullet} \\
\text{\textbullet} \\
\text{R}
\end{array}
\]

17. J. Barluenga et al.\textsuperscript{18} have synthesized chroman derivatives by the reaction of different ally phenyl ethers with Ipy\textsubscript{2}BF\textsubscript{4}.

\[
\begin{array}{c}
\text{Ph} \\
\text{O}
\end{array}
\xrightarrow{\text{Ipy}_2\text{BF}_4}
\begin{array}{c}
\text{Ph} \\
\text{I}
\end{array}
\]

18. M. M. Biddle et al.\textsuperscript{19} have synthesized flavanones and chromanone using bifunctional thiourea catalysts promote an asymmetric oxo-conjugate addition to a β-ketoester alkylidene.

\[
\begin{array}{c}
\text{OH} \\
\text{O}
\end{array}
\xrightarrow{\text{Chiral thiourea catalyst}}
\begin{array}{c}
\text{COOt-Bu} \\
\text{R}
\end{array}
\]

**REACTION MECHANISM**
THERAPEUTIC IMPORTANCE

The chroman ring system represents a privileged structure in drug discovery. The number of bioactive compounds containing this ring system is so vast that the complete range of their biological activities can be hardly classified. 

1. Antifungal
2. Antibacterial
3. Antioxidant
4. Anti HIV
5. Antiarrythmic
6. Antiepileptic agents
7. Antihypertensive
8. Antiviral
9. Antiallergic
10. Anti-inflammatory
11. Antitumor
12. Antitubercular
13. Antidiabetic
14. Hepatoprotective agents
15. Antiulcer activity

M.C.Patel et al. have synthesized some novel chroman derivative and studied their antibacterial and antifungal activities, using the E. coli, P.aeruginosa, S. aureus, and S.Pyogenus and Candida albicans.

G. Hua et al. have synthesized chroman- and 2,3-dihydrobenzofuran-based constraints as a potent and highly selective kappa opioid receptor agonists

B. S. Priya et al. have synthesized 6-fluoro-chroman-2-carboxamides by using nebulic acid chloride with different amines in presence of triethylamine as acid scavenger and dichloroethane as solvent. These molecules were evaluated for their efficacy as antimicrobials in vitro by disc diffusion and microdilution method against pathogenic strains such as Bacillus subtilis, Escherichia coli, Pseudomonas fluorescens.
Studies on nitrogen containing heterocyclic…


![Chemical Structure](image1)

P.V.Kumar et al.\textsuperscript{44} have synthesized 3-indolizin-2-yl-chromen-2-one as a antitubercular, antiviral and anticancer activities

![Chemical Structure](image2)

Z. Nazarian et al.\textsuperscript{45} have synthesized a chalconoids containing a 6-chloro-2\textit{H}-chromen-3-yl group and showed cytotoxicity assessment against mouse peritoneal macrophage cells. It showed that these compound display antileishmanial activity at non-cytotoxic concentrations.

![Chemical Structure](image3)

S. Gowrisankar et al.\textsuperscript{46} have synthesized 4-substituted 3-exo-methylenechroman derivatives and evaluated as a antimicrobial agents.

![Chemical Structure](image4)
Studies on nitrogen containing heterocyclic...

J. G. Kanga et al.\textsuperscript{47} have isolated 2-hydroxymethyl-chroman-4-one which exhibited good activities against phytopathogen such as \textit{Pythium ultimum}, \textit{Phytophthora capsici} and \textit{Sclerotinia sclerotiorum}

![Image of 2-hydroxymethyl-chroman-4-one](image)

K.Hatzade et al.\textsuperscript{48} have synthesized 7-hydroxy-3-pyrazolyl chromones and evaluated for their in vitro antimicrobial and anti-oxidant activity.

![Image of 7-hydroxy-3-pyrazolyl chromones](image)

M. Koufaki et al.\textsuperscript{49} have synthesized 5-substituted chroman and evaluated as a their activity against oxidative Stress Induced Cellular Damage.

![Image of 5-substituted chroman](image)

D. T. Witiak et al.\textsuperscript{50} have synthesized ethyl 6-substituted-chroman and evaluated as anti-hyperlipidemic agent.

![Image of ethyl 6-substituted-chroman](image)

K. A. Reddy et al.\textsuperscript{51} have synthesized benzyloxy containing chroman derivatives and evaluated for their euglycemic and hypolipidemic activities.
U. Gerlach et al.\textsuperscript{52} have synthesized various ethanesulfonamide containing chroman for development as an antiarrhythmic drug.

N. T. Hatzenbuhler et al.\textsuperscript{53} have worked on combining a 5-HT\textsubscript{1A} moiety (3-aminochroman scaffold) and a 5-HT transporter (indole analogues) linked through a common basic nitrogen via an alkyl chain attached at the 1- or 3-position of the indole evaluated for dual affinity at both the 5-HT reuptake site and the 5-HT\textsubscript{1A} receptor.

P. Holmberg et al.\textsuperscript{54} have synthesized novel 2-aminotetralin and 3-aminochroman derivatives as selective serotonin 5-HT\textsubscript{7} receptor agonists and antagonists.
Studies on nitrogen containing heterocyclic…

REFERENCES

Studies on nitrogen containing heterocyclic...

2745 (2005)


Studies on nitrogen containing heterocyclic...


PART-I

STUDIES ON 1,3,4- THIADIAZOLE DERIVATIVES.
INTRODUCTION

Thiadiazole derivatives have played an important role in pharmaceutical industries and exhibited various biological activities due to the presence of –N=C-S group. In thiadiazole ring system one sulphur and two nitrogen atoms are present in a five membered ring. According to their position, thiadiazole systems are classified as 1,2,3-thiadiazole (I), 1,2,4-thiadiazole (II), 1,3,4-thiadiazoles(III) and 1,2,5-thiadiazoles(IV).

Among these four types of thiadiazoles, 1,3,4-thiadiazole is well known. Fischer has described the first 1,3,4-thiadiazole in 1882 and further developed by Buch and co-workers.

SYNTHETIC ASPECT

Literature survey reveals that several publications and patents described the synthesis of 1,3,4-thiadiazole as under.

1. Li-xue Zhang et al. have synthesized 1,3,4-thiadiazoles by the cyclization of aromatic acid with triazole in presence of POCl₃.

2. J.Mohan et al. have prepared thiadiazole derivatives by the cyclization of amino mercapto triazole and aryl aldehyde in presence of p-Ts-OH
3. Microwave irradiation used for the preparation of thiadiazole using DMF as an energy transfer medium was reported by K. Mazaahir et al.\textsuperscript{5}

4. Zhong-Yi et al.\textsuperscript{6} have been prepared thiadiazole derivatives from amino mercapto triazole and aryl aldehyde in presence of L-(+)-tartaric acid.

5. Q.Bano and co-workers\textsuperscript{7} have been prepared 6-phenyl amino-1,3,4-thiadiazole by reacting triazole with amino acid.

6. A.A.Hassan et al.\textsuperscript{8} have prepared 1,3,4-thiadiazoles by the cyclization of tetracyanoethene and 4-phenyl thiosemicarbazides.
7. K. Zamani et al.\(^9\) have prepared thiadiazole from the thiosemicarbazide by the cyclization in sulphuric acid.

\[
\begin{align*}
\text{Con. H}_2\text{SO}_4 & \quad \text{H}_2\text{SO}_4 \\
\end{align*}
\]

8. J. Sun et al.\(^{10}\) have synthesized a series of 1,3,4-thiadiazole derivatives from 2,3-dihydro benzo[b][1,4] dioxine-6-carboxylic acid on treatment with thiosemicarbazide in presence of phosphoryl chloride.

\[
\begin{align*}
\text{POCl}_3 & \quad \text{POCl}_3 \\
\end{align*}
\]

9. F. Aryanasab et al.\(^{11}\) have synthesized a series of 2-amino-1,3,4-thiadiazoles in water.
REACTION MECHANISM

Studies on nitrogen containing heterocyclic...
Thiadiazole derivatives... 126

**THERAPEUTIC IMPORTANCE**

Literature survey revealed that various thiadiazoles have resulted in many potential drugs and are known to exhibit a broad spectrum of pharmacological properties. The specific pharmacological activities associated are as under.

1. Antitumor
2. Antiviral
3. Antibacterial
4. Amoebicidal
5. Antagonist agent
6. Antitubercular
7. Antipyretic
8. Antinelmimetic
9. CNS depressant
10. Antischistosomal
11. Herbicidal
12. Insecticidal
13. Pesticidal
14. Hypogemic

V. Fabrice et al. have synthesized 1,3,4-thiadiazole derivatives and screened for their antiinflammatory, anticancer and anti-HIV activity. U.V. Laddi et al. have discovered thiadiazoles possessing antimicrobial and antituberculosis activity. B.G. Ronald et al. have reported thiadiazoles as antiinflammatory agents. A.Mobinikhaledi et al. have investigated 1,3,4-thiadiazoles and tested for insecticidal activity. Che Chao et al. have prepared thiadiazole derivatives showed antifungal and plant growth regulating effect.

![Thiadiazole Chemical Structure](image)

C. Chazalete et al. have synthesized acetazolamide possessing diuretics and antiglaucoma activity. A. Varvaeso et al. suggested thiadiazoles and reported them as antidepressant. P. Mishra et al. have screened 1,3,4-thiadiazoles for their potent spasmylytic activity and anti-inflammatory activity. B. Masercel et al. have synthesized 1,3,4-thiadiazoles possessing potent...
Studies on nitrogen containing heterocyclic…

carbonic anhydrase inhibitor properties and also prepared 5-valproyl amino 1,3,4-thiadiazole-2-sulphonamide (XIII) as strong anticonvulsant.

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

C. T. Supuran and Andrea Scozzafava\textsuperscript{34} have reported 1,3,4-thiadiazole derivatives as carbonic anhydrase inhibitors and antitumor. E. Palaska et al.\textsuperscript{36} synthesized thiadiazoles containing anti-inflammatory activity. J. M. Colacino et al.\textsuperscript{37} have documented anti-influenza virus activity of thiadiazoles.

L.M. Thomasco et al.\textsuperscript{38} have prepared 1,3,4-thiadiazole possessing potent antibacterial activity against Gram positive and Gram negative organisms. S. A. Carvalho and co-workers\textsuperscript{39} have documented antitrypanosomal profile of 1,3,4-thiadiazole derivatives, Z. Kiani et al.\textsuperscript{40} have discovered thiadiazoles as antituberculosis agent

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

A. Faroumadi et al.\textsuperscript{41} have synthesized 1,3,4-thiadiazoles (XVI) and studied their leishmanicidal activity. H.N. Dogan et al.\textsuperscript{42} have prepared 2,5-disubstituted-1,3,4- thiazidazole derivatives as anticonvulsant and antimicrobial agent. N. Terzioglu

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{S} & \quad \text{N} \\
\text{NH} & \quad \text{OH}
\end{align*}
\]
Studies on nitrogen containing heterocyclic…

and A. Gursoy\textsuperscript{43} have discovered thia diazoles and studied their anticancer activity. A.
Foroumadi and co-workers\textsuperscript{44} have documented antituberculosis activity and
cytotoxicity of 1,3,4-thiadiazoles.

\[
\begin{array}{cc}
\text{O}^+ & \text{N} \\
\text{O} & \text{N} \\
\text{S} & \text{N} \\
\text{N} & \text{X= O,S} \\
\text{Y=CH}_2\text{O},\text{NR} & \\
\end{array}
\]

Recently S. Karakus and S. Rollas\textsuperscript{45} have screened thiadiazoles for
their antituberculosis activity. Jui-Yi Chou et al.\textsuperscript{46} have synthesized thiadiazoles and
reported them as anticancer agents.

A. R. Bhat et al.\textsuperscript{47} have synthesized new series of thiadiazoles evaluated on \textit{in vitro}
growth of microorganisms causing microbial infection.

\[
\begin{array}{cc}
\text{O} & \text{N} \\
\text{N} & \text{Cl} \\
\end{array}
\]

V. Jatav et al.\textsuperscript{48} have synthesized a series of 3-[5-substituted phenyl-1,3,4-
thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones and evaluated for anticonvulsant,
sedative-hypnotic and CNS depression activities.

\[
\begin{array}{cc}
\text{O} & \text{N} \\
\text{N} & \text{Cl} \\
\end{array}
\]

F. Poorrajab et al.\textsuperscript{49} have synthesized 1,3,4-thiadiazole derivatives and
evaluated \textit{in vitro} against \textit{Leishmania major}.
H. Rajak et al.\textsuperscript{50} have synthesised 2,5-disubstituted-1,3,4-thiadiazole and tested for antitumor activity against Ehrlich ascites carcinoma cells in Swiss albino mice.

Work done from our laboratory

K.M.Thaker\textsuperscript{51} have synthesized 2-(3′5′-dichlorobenzo[b]thiophen-2′-yl)-5-arylamino-1,3,4-thiadiazoles from triazole. S.L.Vasoya\textsuperscript{52} have synthesized some new thiosemicarbazide and 1,3,4-thiadiazole heterocycles bearing the benzo[b]thiophene nucleus as potent antituberculer and antimicrobial agents.

In light of wide varieties of therapeutic activities exhibited by thiadiazole, we have embarked upon the synthesis of some new thiadiazole derivatives which have been described in following sections.

SECTION-I: SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-(6-FLUOROCHROMAN-2-YL)-6-ARYL[1,2,4]TRIAZOLO[3,4-b] [1,3,4]THIADIAZOLE. 
Part – B

[Part – I (Section-i)]

Synthesis and biological evaluation of 3-(6-fluorochroman-2-yl)-6-aryl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles.
Thiadiazole derivatives are associated with broad spectrum of biological activities. In view of these finding it appeared of interest to synthesize some newer thiadiazole derivatives, with better potency. Thiadiazoles of type (I) have been prepared by cyclocondensation of 4-amino-5-(6-fluorochroman-2-yl)-4H-1,2,4-triazole-3-thiol with different aromatic acids in presence of phosphorous oxychloride, as shown in reaction scheme.

**REACTION SCHEME**
The constitution of all the synthesized compounds have been characterized by using elemental analysis, FT-IR, $^1$H NMR, $^{13}$C NMR spectroscopy and further supported by mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate.

All the synthesized compounds were tested for their antibacterial and antifungal activity (MIC) in vitro by broth dilution method with two Gram-positive bacteria, two Gram-negative bacteria and three fungal strains. The biological activities of the synthesized compounds have been compared with standard drugs.
EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV light. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using DRS (diffusive reflectance system) method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. $^1$H NMR and $^{13}$C NMR were determined in CDCl$_3$ and DMSO solution on a Bruker AC 300 MHz, 400 MHz and 100MHz spectrometer. Elemental analysis of the all the synthesized compounds were carried out on Euro EA 3000 elemental analyzer and the results are in agreements with the structures assigned.


6-Fluorochroman-2-carboxylic acid (2.0 gm, 0.01 mol) in methanol (10 ml) was stirred at room temperature for 5 minutes then add concentrated H$_2$SO$_4$ (0.5 ml, 0.01 mol) and stir the reaction mixture at room temperature for 10 hours. After the completion of the reaction checked by TLC, methanol was removed in vacuo and then add methelene dichloride (40 ml) and stir it further for 10 minutes. The resultant mixture was treated with saturated sodium bicarbonate until pH become neutral. The neutral solution was treated with sodium sulphate and then organic layer was removed in vacuo. Collect the crude product and there is no need to purification, the crude ester directly used for further reaction.


Methyl 6-fluorochroman-2-carboxylate (2.0 g, 0.01 mol) in absolute ethanol (25 ml) was cooled at 0-(-5)$^\circ$C. To the cooled solution add hydrazine hydrate (4.0 ml, 0.08 mol) and stir the reaction mixture at 0-(-5)$^\circ$C for 10 hours. After the completion of the reaction (monitored by TLC). The white color solid separated was filtered and washed with cold ethanol and crystallized from ethanol.

[C] Preparation of Potassium 2-[(6-fluorochroman-2-yl)carbonyl] hydrazine carbodithioate.

To a mixture of potassium hydroxide (8.40g, 0.15 mol) and 6-fluorochroman -2-carbohydrazide (17.0 g, 0.1 mol) in methanol (50 ml), carbon disulphide (11.4g, 0.15 mol) was added. This mixture was stirred for 22-24 hours at room temperature. Thus the
solid obtained was filtered and washed with diethyl ether and dried. There is no need to purify the salt for further reaction.

[D] **Preparation of 4-Amino-5-(6-fluorochroman-2-yl)-4H-1,2,4-triazole-3-thiol.**

A suspension of the potassium salt (2.45 g, 0.1 mol), hydrazine hydrate (15 ml, 0.3 mol) and water (5 ml) was refluxed with stirring for 30 hours. The color of the reaction mixture changed to green, hydrogen sulfide was evolved (lead acetate paper and odour) and a homogeneous solution was resulted. Dilute the solution with cold water (100 ml) and neutralized with glacial acetic acid. Thus the white solid precipitates were formed. The product was filtered, washed with cold water and crystallized from dioxane yield 50%, m.p. 173°C.

[E] **General procedure for the preparation of 3-(6-Fluorochroman-2-yl)-6-aryl-[1,2,4] triazolo [3,4-b][1,3,4]thiadiazoles.**

A mixture of 4-amino-5-(6-fluorochroman-2-yl)-4H-1,2,4-triazole-3-thiol (2.26 g, 0.01 mol) and different aryl acids (0.01 mol) in phosphorous oxychloride (15 ml) was refluxed with continuous stirring. After completion the reaction (15-16 hours monitoring by TLC), the content was cooled to room temperature then add ice cooled water and thus solid separated out was filtered, washed with water and neutralized with sodium bicarbonate solution. Crude product was purified by column chromatography to give the analytical pure compounds. The physical constants of the products are recorded in **Table-6a.**

[F] **Biological evaluation of 3-(6-Fluorochroman-2-yl)-6-aryl-[1,2,4] triazolo [3,4-b][1,3,4]thiadiazoles.**

Antimicrobial testing was carried out as described in Part-B, Part-I, Section-I, antimicrobial activity. The MIC values of the test compounds are recorded in **Table-6b.**
Studies on nitrogen containing heterocyclic...

Table-6a: Physical constant of 3-(6-Fluorochroman-2-yl)-6-aryl-[1,2,4] triazolo [3,4-b][1,3,4]thiadiazoles.

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Substitution R</th>
<th>M. F.</th>
<th>M. W.</th>
<th>Yield (%)</th>
<th>R_f value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>Cl</td>
<td>C_{18}H_{12}ClFN_{4}OS</td>
<td>386.83</td>
<td>95</td>
<td>0.49</td>
</tr>
<tr>
<td>6b</td>
<td></td>
<td>C_{20}H_{17}FN_{4}O_{3}S</td>
<td>412.43</td>
<td>79</td>
<td>0.31</td>
</tr>
<tr>
<td>6c</td>
<td>- NH_{2}</td>
<td>C_{18}H_{14}FN_{4}OS</td>
<td>367.40</td>
<td>87</td>
<td>0.59</td>
</tr>
<tr>
<td>6d</td>
<td></td>
<td>C_{18}H_{12}FN_{4}O_{3}S</td>
<td>397.38</td>
<td>94</td>
<td>0.38</td>
</tr>
<tr>
<td>6e</td>
<td>H_{2}N</td>
<td>C_{18}H_{14}FN_{4}OS</td>
<td>367.40</td>
<td>82</td>
<td>0.54</td>
</tr>
<tr>
<td>6f</td>
<td>Cl</td>
<td>C_{18}H_{12}ClFN_{4}OS</td>
<td>386.83</td>
<td>81</td>
<td>0.61</td>
</tr>
<tr>
<td>6g</td>
<td>Cl</td>
<td>C_{18}H_{12}ClFN_{4}OS</td>
<td>386.83</td>
<td>74</td>
<td>0.51</td>
</tr>
<tr>
<td>6h</td>
<td></td>
<td>C_{19}H_{15}FN_{4}OS</td>
<td>366.41</td>
<td>72</td>
<td>0.41</td>
</tr>
<tr>
<td>6i</td>
<td>- NH_{2}</td>
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<td>367.40</td>
<td>86</td>
<td>0.68</td>
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<tr>
<td>6j</td>
<td>O</td>
<td>C_{19}H_{13}FN_{4}O_{2}S</td>
<td>382.41</td>
<td>83</td>
<td>0.63</td>
</tr>
</tbody>
</table>

TLC solvent system:- E.A. : Hexane = 9 : 1
ANALYTICAL DATA

6-(3-Chlorophenyl)-3-(6-fluorochroman-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (6a). mp 150-154 °C; IR (DRS): 3073, 3031, 2957, 2847, 1625, 1462, 1442, 1325, 1258, 1140, 1065, 1018, 825, 748, 701, 685 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ ppm 2.44-2.48(m, 1H, 2CH), 2.74-2.76(m, 1H, 2CH), 3.04(m, 2H, 2CH), 5.66-5.68(m, 1H, CH), 6.82-6.84(m, 3H, ArH), 7.48-7.50(d, J = 5.79 Hz, 1H, ArH), 7.56(m, 1H, ArH), 7.73-7.75(d, J = 6.69 Hz, 1H, ArH), 7.90(s, 1H, ArH). ¹³C NMR (100 MHz, DMSO): δ ppm 23.47, 23.83, 38.97, 68.33, 102.68, 107.14, 113.57, 113.80, 115.01, 115.24, 117.38, 117.46, 122.81, 125.55, 126.44, 130.52, 130.92, 134.66, 146.13, 149.45, 161.22, 165.22, 175.36; MS: m/z = 386 [M⁺]; Anal. Calcd for C₁₈H₁₂ClFN₄OS: C, 55.89; H, 3.13; N, 14.48. Found: C, 55.83; H, 3.04; N, 14.08%.

6-(3,4-Dimethoxyphenyl)-3-(6-fluorochroman-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (6b). mp 119-121°C; IR (DRS): 3090(Ar, C-H str.), 3020(Ar, C-H str.), 2935(C-H str.), 2839(C-H str.), 1637(Ar, C=C str.), 1492(Ar, C=C str.), 1440(C-H ben), 1363(C-H ben), 1138(C-F str.), 1058(C-N str.), 1020(C-O-C str.), 810(C-H o,p, ben), 756(C-H o,p, ben), 705(C-C o,p, ben), 680(C-C o,p ben) cm⁻¹; ¹H NMR (400 MHz, DMSO): δ ppm 2.41-2.44(m, 1H, 2CH), 2.58-2.65(m, 1H, 2CH), 3.02-3.19(m, 2H, 2CH), 3.90(s, 6H, OCH₃, OCH₃), 5.70-5.73(d,d, J = 4.4 Hz, 3.4 Hz, 1H, CH), 6.78-6.93(m, 3H, ArH), 7.09-7.11(d, J = 8.44 Hz, 1H, ArH), 7.39(s, 1H, ArH), 7.49-7.51(d, J = 7.72 Hz, 1H, ArH). ¹³C NMR (100 MHz, DMSO): δ ppm 23.88, 38.92, 55.72, 68.23, 102.47, 108.96, 111.54, 113.59, 113.81, 115.04, 115.31, 117.47, 121.19, 122.98, 130.42, 130.80, 147.17, 149.14, 152.65, 161.11, 166.12, 166.55, 175.12; MS: m/z = 412 [M⁺]; Anal. Calcd for C₂₀H₁₇FN₄O₃S: C, 58.24; H, 4.15; N, 13.58. Found: C, 58.18; H, 3.99; N, 13.49%.

4-(3-(6-Fluorochroman-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)aniline (6c). mp 168-170 °C; IR (DRS): 3422, 3378, 3030, 2964, 2853, 1642, 1612, 1581, 1471, 1368, 1247, 1156, 1057, 1014, 819, 744, 710, 678 cm⁻¹; MS: m/z = 367 [M⁺]; Anal. Calcd for C₁₈H₁₄FN₅O₃S: C, 58.84; H, 3.84; N, 19.06. Found: C, 58.69; H, 3.78; N, 18.90%.

3-(6-Fluorochroman-2-yl)-6-(4-nitrophenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (6d). mp 158-160°C; IR (DRS): 3074, 2987, 2851, 1645, 1612, 1585, 1468, 1345, 1184, 1250, 1061, 1023, 820, 780, 744, 695, 566 cm⁻¹; MS: m/z = 397 [M⁺]; Anal. Calcd for C₁₈H₁₂FN₃O₃S: C, 54.40; H, 3.04; N, 17.62. Found: C, 54.28; H, 2.93; N, 17.44%.
Studies on nitrogen containing heterocyclic...

2-(3-(6-Fluorochroman-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)aniline (6e). mp 147-149 °C; IR (DRS): 3442, 3091, 2975, 2844, 1641, 1579, 1556, 1464, 1357, 1242, 1145, 1088, 1017, 832, 750, 687 cm\(^{-1}\); MS: \(m/z = 367\) [M]\(^+\); Anal. Calcd for C\(_{18}\)H\(_{14}\)FN\(_5\)OS: C, 58.84; H, 3.84; N, 19.06. Found: C, 58.41; H, 3.78; N, 18.99%.

6-(4-Chlorophenyl)-3-(6-fluorochroman-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (6f). mp 116-118°C; IR (DRS): 3080, 2983, 2867, 1629, 1572, 1525, 1462, 1381, 1245, 1196, 1046, 1011, 830, 778, 701, 665, 578 cm\(^{-1}\); MS: \(m/z = 386\) [M]\(^+\); Anal. Calcd for C\(_{18}\)H\(_{12}\)ClFN\(_4\)OS: C, 55.89; H, 3.13; N, 14.48. Found: C, 55.84; H, 2.97; N, 14.17%.

6-(2-Chlorophenyl)-3-(6-fluorochroman-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (6g). mp 183-185 °C; IR (DRS): 3077, 2978, 2863, 1625, 1609, 1563, 1464, 1331, 1238, 1142, 1038, 1014, 870, 832, 778, 668, 514 cm\(^{-1}\); MS: \(m/z = 386\) [M]\(^+\); Anal. Calcd C\(_{18}\)H\(_{12}\)ClFN\(_4\)OS: C, 55.89; H, 3.13; N, 14.48. Found: C, 55.67; H, 3.01; N, 14.21%.

3-(6-Fluorochroman-2-yl)-6-(o-tolyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (6h). mp 160-162°C; IR (DRS): 3063, 2962, 2854, 1603, 1545, 1542, 1452, 1325, 1260, 1146, 1060, 1023, 812, 754, 662, 518 cm\(^{-1}\); MS: \(m/z = 366\) [M]\(^+\); Anal. Calcd for C\(_{19}\)H\(_{15}\)FN\(_4\)OS: C, 62.28; H, 4.13; N, 15.29. Found: C, 62.19; H, 3.97; N, 15.24%.

3-(3-(6-Fluorochroman-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)aniline (6i). mp 109-111°C; IR (DRS): 3428, 3392, 3075, 2964, 2853, 1721, 1601, 1581, 1423, 1371, 1241, 1149, 1054, 1026, 888, 848, 766, 720, 665, 578 cm\(^{-1}\); MS: \(m/z = 367\) [M]\(^+\); Anal. Calcd for C\(_{18}\)H\(_{14}\)FN\(_5\)OS: C, 58.84; H, 3.84; N, 19.06. Found: C, 58.53; H, 3.71; N, 18.90%.

3-(6-Fluorochroman-2-yl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (6j). mp 224-226°C; IR (DRS): 3061, 2951, 2872, 1689, 1589, 1579, 1462, 1354, 1208, 1135, 1099, 1003, 819, 755, 688 cm\(^{-1}\); MS: \(m/z = 382\) [M]\(^+\); Anal. Calcd for C\(_{19}\)H\(_{15}\)FN\(_4\)O\(_2\)S: C, 59.67; H, 3.95; N, 14.65. Found: C, 59.08; H, 3.88; N, 14.62%.
SPECTRAL STUDY OF SYNTHESIZED COMPOUNDS

IR Spectrum of 6-(3,4-Dimethoxyphenyl)-3-(6-fluorochroman-2-yl)[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole(6b).

Mass spectrum of 6-(3-Chlorophenyl)-3-(6-fluorochroman-2-yl)[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole(6a).
Studies on nitrogen containing heterocyclic...

Mass spectrum of 6-(3,4-Dimethoxyphenyl)-3-(6-fluorochroman-2-yl)-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazole(6b).

$^1$H NMR spectrum of 6-(3-Chlorophenyl)-3-(6-fluorochroman-2-yl)-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazole(6a).
Studies on nitrogen containing heterocyclic...

Expanded spectrum of 6-(3-Chlorophenyl)-3-(6-fluorochroman-2-yl)-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazole (6a).

\[ \text{1H NMR spectrum of 6-(3,4-Dimethoxyphenyl)-3-(6-fluorochroman-2-yl)-} \]
\[ \text{[1,2,4]triazolo [3,4-b][1,3,4]thiadiazole (6b).} \]
Studies on nitrogen containing heterocyclic…

Expanded spectrum of 6-(3,4-Dimethoxyphenyl)-3-(6-fluorochroman-2-yl)-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazole(6b).

[Diagram]

Expanded spectrum of 6-(3,4-Dimethoxyphenyl)-3-(6-fluorochroman-2-yl)-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazole(6b).

[Diagram]

Thiadiazole derivatives…
Studies on nitrogen containing heterocyclic...

$^{13}$C NMR spectrum of 6-(3-Chlorophenyl)-3-(6-fluorochroman-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole(6a).

$^{13}$C NMR spectrum of 6-(3,4-Dimethoxyphenyl)-3-(6-fluorochroman-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole(6b).
Biological evaluation of 3-(6-fluorochroman-2-yl)-6-aryl-[1,2,4] triazolo [3,4-b][1,3,4]thiadiazoles.

All of the synthesized compounds (6a-j) were tested for their antibacterial and antifungal activity (MIC) \textit{in vitro} by broth dilution method with two Gram-positive bacteria \textit{Staphylococcus aureus} MTCC-96 and \textit{Streptococcus pyogenes} MTCC 442, two Gram-negative bacteria \textit{Escherichia coli} MTCC 443 and \textit{Pseudomonas aeruginosa} MTCC 441 and three fungal strains \textit{Candida albicans} MTCC 227, \textit{Aspergillus Niger} MTCC 282 and \textit{Aspergillus clavatus} MTCC 1323 taking gentamycin, ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin and greseofulvin as standard drugs. The standard strains were procured from the Microbial Type Culture Collection (MTCC), Institute of Microbial Technology, Chandigarh, India.

The minimal inhibitory concentration (MIC) values for all the newly synthesized compounds, defined as the lowest concentration of the compound preventing the visible growth, were determined by using micro dilution broth method according to NCCLS standards.\cite{38}

\textbf{Minimal Inhibition Concentration [MIC]}

The main advantage of the \textbf{Broth Dilution Method} for MIC determination lies in the fact that it can readily be converted to determine the MIC as well.

1. Serial dilutions were prepared in primary and secondary screening.
2. The control tube containing no antibiotic is immediately subcultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37 \textdegree C overnight.
3. The MIC of the control organism is read to check the accuracy of the drug concentrations.
4. The lowest concentration inhibiting growth of the organism is recorded as the MIC.
5. The amount of growth from the control tube before incubation (which represents the original inoculums) is compared.
Methods used for primary and secondary screening

Each synthesized compounds were diluted in DMSO to obtain 2000 μg mL\(^{-1}\) concentration, as a stock solution. Inoculum size for test strain was adjusted to 10\(^8\) cfu (colony forming unit) per milliliter by comparing the turbidity.

**Primary screen:** In primary screening 1000 μg mL\(^{-1}\), 500 μg mL\(^{-1}\) and 250 μg mL\(^{-1}\) concentrations of the synthesized compounds were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms.

**Secondary screen:** The compounds found active in primary screening were similarly diluted to obtain 200 μg mL\(^{-1}\), 100 μg mL\(^{-1}\), 50 μg mL\(^{-1}\), 25 μg mL\(^{-1}\), 12.5 μg mL\(^{-1}\), and 6.250 μg mL\(^{-1}\) concentrations.

**Reading Result:** The highest dilution showing at least 99 % inhibition zone is taken as MIC. The result of this is much affected by the size of the inoculums. The test mixture should contain 10\(^8\) organism/mL.

The results obtained from antimicrobial susceptibility testing are depicted in Table 6b.
### Table-6b: Antimicrobial activity of 3-(6-Fluorochroman-2-yl)-6-aryl-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazoles.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Antibacterial Activity</th>
<th>Antifungal activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimal bactericidal concentration µg/ml</td>
<td>Minimal fungicidal concentration µg/ml</td>
</tr>
<tr>
<td></td>
<td>Gram +ve Bacteria</td>
<td>Gram –ve Bacteria</td>
</tr>
<tr>
<td></td>
<td>S.aureus</td>
<td>S.pyogenus</td>
</tr>
<tr>
<td>6a</td>
<td>100</td>
<td>62.5</td>
</tr>
<tr>
<td>6b</td>
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<td>6c</td>
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<td>500</td>
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<tr>
<td>6h</td>
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<td>250</td>
</tr>
<tr>
<td>6i</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>6j</td>
<td>250</td>
<td>500</td>
</tr>
</tbody>
</table>

### MINIMAL INHIBITION CONCENTRATION

<table>
<thead>
<tr>
<th>Standard Drugs</th>
<th>S.aureus (microgramme/ml)</th>
<th>S.pyogenus</th>
<th>E.coli</th>
<th>P.aeruginosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamycin</td>
<td>0.25</td>
<td>0.5</td>
<td>0.05</td>
<td>1</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>250</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>50</td>
<td>50</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
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</tbody>
</table>

### MINIMAL FUNGICIDAL CONCENTRATION

<table>
<thead>
<tr>
<th>Standard Drugs</th>
<th>C.Albicans (microgramme/ml)</th>
<th>A.Niger</th>
<th>A.Clavatus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nystatin</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Greseofulvin</td>
<td>500</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
References

Studies on nitrogen containing heterocyclic...

38. L.M. Thomasco, R. C. Gadwood, E. A. Weaver, J. M. Ochoada, C. W. Ford. et al.,

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Studies on nitrogen containing heterocyclic…

44. A. Foroumadi, A. Asadipour, M. Mirzaci, J.Karimi, S. Emami., IL Farmaco, 57(9), 765-769 (2002).
PART-II

STUDIES ON 1,3,4-OXADIAZOLE DERIVATIVES.
INTRODUCTION

Oxadiazoles belong to an important group of heterocyclic compounds having $\text{N=O=C-N}$ linkage. It is well documented that oxadiazole system contains the following members which are numbered by designating the hetero atoms at particular position.

\[
\begin{align*}
(1) & \quad (2) & \quad (3) & \quad (4) \\
\end{align*}
\]

1,3,4-Oxadiazole is a heterocyclic molecule with oxygen atom at 1 and two nitrogen atoms at 3 and 4 position. 1,3,4-Oxadiazole is a thermally stable aromatic molecule.$^1$ They have been known for about 80 years it is only in the last decade that investigations in this field have been intensified. This is because of large number of applications of 1,3,4-oxadiazoles in the most diverse areas viz. drug synthesis, dye stuff industry, heat resistant materials, heat resistant polymers and scintillators. Reviews of the relevant literature prior to 1965 are available.$^2$

SYNTHETIC ASPECT

Most 1,3,4-oxadiazoles are best obtained by synthesis from acyclic precursors. Such reactions are ‘one bond’ or ‘two bond’ cyclization. Different methods for the synthesis have been cited in literature.$^3$-$^8$

1. B. Chandrakantha et al.$^9$ have synthesized oxadiazoles by the reaction of hydrazide and aromatic acid in presence of POCl$_3$.

2. D. Ramesh and B. Sreenivasan$^{10}$ have synthesized 1,3,4-oxadiazoles from semicarbazide in presence of POCl$_3$. 

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3. K. Mogilaiah and B. Sakram\textsuperscript{11} have prepared 1,3,4-oxadiazoles from acetophenone-2-trifluoromethyl-1,8-naphthyridine-3-carbonyl hydrazone in presence of acetic anhydride.

4. Yu Yuve have reported microwave-assisted synthesis protocol of oxadiazoles with 91 % of the yield.\textsuperscript{12}

5. L. Somogyi\textsuperscript{13} have been synthesized 1,3,4-oxadiazoles from several steps, from aryl hydrazides and aryl aldehydes.

6. Silica sulfuric acid catalyst used for the rapid and ecofriendly synthesis of 1,3,4-oxadiazoles at ambient temperature reported by M. Dabiri et al.\textsuperscript{14}
Studies on nitrogen containing heterocyclic…

7. Green chemistry and one-pot, solvent-free using microwave mediated synthesis of 1,3,4-oxadiazoles were reported by V. Polshettiwar.\(^\text{15}\)

\[
\begin{align*}
R-C(OEt)_3 + R^1 \text{NH-NH}_2 & \xrightarrow{\text{MW}} \text{MW} \quad 80^\circ\text{C}, 10 \text{ min} \\
& \quad \rightarrow R-N-N-R^1 \\
\end{align*}
\]

8. A mild, general, convenient, and efficient one-pot synthesis of 2-phenyl-5-substituted-1,3,4-oxadiazoles were reported by P. Stabile.\(^\text{16}\)

\[
\begin{align*}
\text{TsCl, TEA} & \rightarrow \text{acetone, 40}^\circ\text{C} \\
\end{align*}
\]

**REACTION MECHANISM**

\[
\begin{align*}
R=\text{Aryl} \\
\end{align*}
\]
**THERAPEUTIC IMPORTANCE**

2,5-Disubstituted-1,3,4-oxadiazole derivatives have been tested for various pharmacological activities, which have been summarized as under.

1. Antibacterial
2. Antinflammatory
3. Analgesic
4. Antiviral and anticancer
5. Antihypertensive
6. Anticonvulsant
7. Antiproliferative
8. Antifungal
9. Cardiovascular
10. Herbicidal
11. Hypoglycemic
12. Hypnotic and Sedative
13. MAO inhibitor
14. Insecticidal

S. R. Bishnoi et al. have screened oxadiazoles for their antimicrobial activity. A. El-Azzouny et al. have synthesized 1,3,4-oxadiazole derivatives and evaluated for their analgesic, anti-inflammatory, ulcerogenic effects and inhibitory activity on plasma prostaglandin E\(_2\) (PGE\(_2\)) Level.

S. V. Bhandari et al. have reported 1,3,4-oxadiazoles for their anti-inflammatory activity. Song Cao et al. have investigated some oxadiazoles possessing insecticidal activity. G. V. Suresh Kumar et al. have discovered oxadiazole derivatives and reported their antimycobacterial activity. Ali Almasired et al. have prepared 1,3,4-oxadiazoles of type as anticonvulsant agent. Meria Grazia Mamolo et al. have synthesized 3-substituted-5-(pyridine-4-yl)-3\(H\)-1,3,4-oxadiazole-2-ones of type and studied their antimycobacterial activity.

Krishna Kant Jha et al. have reported antimicrobial activity of oxadiazole derivatives. J. A. Christopher et al. have documented human immunodeficiency virus
Studies on nitrogen containing heterocyclic…

(HIV) infection of 1,3,4-oxadiazole derivatives. S. J. Gilani et al.\textsuperscript{40} have synthesized some oxadiazoles as anti-inflammatory and analgesic agents. K. Subrahmanya Bhat et al.\textsuperscript{41} have prepared new fluorine containing 1,3,4-oxadiazoles and reported them as potential antibacterial and anticancer agents. T. P. Mohan et al.\textsuperscript{42} have synthesized 2,5-disubstituted-1,3,4-oxadiazole derivatives and screened for their insecticidal activity.

Ronald Kim et al.\textsuperscript{43} have discovered oxadiazole derivatives useful as protease inhibitors. Mohd Amir and Kumar Shikha\textsuperscript{44} have documented anti-inflammatory, analgesic and ulcerogenic activity of some newly synthesized oxadiazoles. A. Ali et al.\textsuperscript{45} have investigated some oxadiazole derivatives possessing antimicrobial and anti-HIV-1 activity. A. Sherif et al.\textsuperscript{46} have reported oxadiazoles as potential antitumor and anti-HIV agents. A. Zarghi et al.\textsuperscript{47} have synthesized R-substituted-5-(2-benzyloxyphenyl)-1,3,4-oxadiazoles possessing anticonvulsant activity. M. Tareq et al.\textsuperscript{48} have synthesized 2,5-disubstituted-1,3,4-oxadiazoles useful as tyrosinase inhibitors.

Kiselyov et al.\textsuperscript{49} have synthesized novel derivatives of 1,3,4-oxadiazoles as potent mitostatic agents featuring strong microtubule depolymerizing activity in the sea urchin embryo and cell culture assays.
Work done from our laboratory

K. M. Thaker\textsuperscript{50} have synthesized 2-(3',5'-dichlorobenzo[\textit{b}]thiophen-2'-yl)-5-aryl-1,3,4-oxadiazoles in the presence of aromatic acid. S. L. Vasoya\textsuperscript{51} reported facile synthesis of some new acetyl oxadiazoles bearing benzo[\textit{b}]thiophene nucleus as a potent biological active agent. Preparation and antimicrobial activity of 2-aryl-5-(5',7'-diiodo-8'-quinolinoxy)-1,3,4-oxadiazoles have been reported by H. S. Joshi.\textsuperscript{52}

Thus with an effort to capitalize the biological potential of the heterocyclic system and to provide more interesting compounds for biological screening, we have undertaken the synthesis of several oxadiazoles which has been described as under.

SECTION-I: SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-(6-FLUOROCHROMAN-2-YL)-5-ARYL-1,3,4-OXADIAZOLES.
Synthesis and biological evaluation of 2-(6-fluorochroman-2-yl)-5-aryl-1,3,4-oxadiazoles.
SECTION-I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-(6-FLUOROCHROMAN-2-YL)-5-ARYL-1,3,4-OXADIAZoles.

Synthesis of 1,3,4-oxadiazole derivatives has attracted considerable attention in view of therapeutic applications. Looking to this, the synthesis of 1,3,4-oxadiazoles was undertaken by the condensation of different aromatic acid with 6-fluorochroman-2-carbohydrazide in presence of phosphorous oxychloride, as shown in reaction scheme.

REACTION SCHEME

The constitution of all the synthesized compounds have been characterized by using elemental analysis, FT-IR, $^1$H NMR, $^{13}$C NMR spectroscopy and further supported by mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate.

All the synthesized compounds were tested for their antibacterial and antifungal activity (MIC) in vitro by broth dilution method with two Gram-positive bacteria, two Gram-negative bacteria and three fungal strains. The biological activities of the synthesized compounds have been compared with standard drugs.
EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV light. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using DRS (diffusive reflectance system) method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. $^1$H NMR and $^{13}$C NMR were determined in CDCl$_3$ solution on a Bruker AC 400 MHz and 100 MHz spectrometer. Elemental analysis of the all the synthesized compounds were carried out on Euro EA 3000 elemental analyzer and the results are in agreements with the structures assigned.


See PART-B, part-I, section-I [B].

[B] General procedure for the preparation of 2-(6-Fluorochroman-2-yl)-5-aryl-1,3,4-oxadiazoles.

A mixture of 6-fluorochroman-2-carbohydrazide (2.0 g, 0.01mol) and different aryl acids (0.01mol) in phosphorous oxychloride (10 ml) was refluxed with continuous stirring. After completion of the reaction (13-15 hours monitoring by TLC), the content was cooled to room temperature then add ice cooled water and neutralized with sodium bicarbonate solution. Then the mixture was by extracted into ethyl acetate. The organic extracts was washed with water (2 x 10 ml), dried with Na$_2$SO$_4$, solvent was removed in vacuo and the resulting crude product was purified by column chromatography to give the analytical pure compound. The physical constants of the products are recorded in Table-7a.

[C] Biological evaluation of 2-(6-Fluorochroman-2-yl)-5-aryl-1,3,4-oxadiazoles.

Antimicrobial testing was carried out as described in Part-B, Part-II, Section-I, antimicrobial activity. The MIC values of the test compounds are recorded in Table-7b.
Table-7a: Physical constant of 2-(6-Fluorochroman-2-yl)-5-aryl-1,3,4-oxadiazoles.

![Oxadiazole derivative structure](image)

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Substitution R</th>
<th>M. F.</th>
<th>M. W.</th>
<th>Yield (%)</th>
<th>R&lt;sub&gt;f&lt;/sub&gt; value</th>
</tr>
</thead>
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<tr>
<td>7a</td>
<td>O</td>
<td>C&lt;sub&gt;18&lt;/sub&gt;H&lt;sub&gt;15&lt;/sub&gt;FN&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>326.32</td>
<td>94</td>
<td>0.47</td>
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<tr>
<td>7b</td>
<td></td>
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<td>88</td>
<td>0.39</td>
</tr>
<tr>
<td>7c</td>
<td>NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>C&lt;sub&gt;17&lt;/sub&gt;H&lt;sub&gt;14&lt;/sub&gt;FN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>77</td>
<td>0.52</td>
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<td>7d</td>
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<td>0.42</td>
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<td>7e</td>
<td>N</td>
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<td>0.50</td>
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<tr>
<td>7f</td>
<td>Cl</td>
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<tr>
<td>7g</td>
<td>N</td>
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<td>0.67</td>
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<tr>
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<td>330.74</td>
<td>79</td>
<td>0.62</td>
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</table>

TLC solvent system:- E.A.: Hexane = 7 : 3
ANALYTICAL DATA

2-(6-Fluorochroman-2-yl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (7a). mp 140-142 °C; IR (DRS): 3028, 2974, 2943, 2841, 1616, 1558, 1425, 1303, 1259, 1174,1080,1024, 873, 819, 798, 736, 636, 570 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) ppm 2.42-2.51(m, 2H, 2CH), 2.96-2.99(t, 2H, 2CH), 3.88(s, 3H, OCH\(_3\)), 5.39-5.42(d,d, \(J=3.76\) Hz, 3.68 Hz, 1H, CH), 6.79-6.87(m, 3H, ArH), 6.99-7.01(d, \(J=8.8\) Hz, 2H, ArH), 7.99-8.01(d, \(J=8.76\) Hz, 2H, ArH). \(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) ppm 23.59, 24.86, 44.20, 55.49, 68.80, 114.34, 114.50, 114.57, 115.36, 115.58, 116.06, 117.96, 118.04, 122.35, 122.43, 128.90, 149.31, 149.33,156.08, 158.46, 162.53, 164.06, 165.46; MS: \(m/z = 326\) [M]\(^+\); Anal. Calcd for C\(_{18}\)H\(_{15}\)FN\(_2\)O\(_3\): C, 66.10; H, 4.56; N, 8.30%.

2-(6-Fluorochroman-2-yl)-5-(p-tolyl)-1,3,4-oxadiazole (7b). mp 110-112°C; IR (DRS): 3036(Ar, C-H str.), 2955(C-H str.), 2922(C-H str.), 2852(C-H str.), 1616(Ar, C=C str.), 1570(Ar, C=C str.), 1496(Ar, C=C str.), 1390(C-H ben), 1263(C-H ben), 1178(C-F str.), 1139(C-F str.), 1080(C-N str.), 1016(C-O-C str.), 821(C-H o,p, ben), 767(C-H o,p, ben), 729(C-H o,p, ben), 700(C-C o,p, ben), 561(C-C o,p, ben) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) ppm 2.35-2.44(m, 5H, 2CH, 3CH), 2.88-2.91(t, 2H, 2CH), 5.32-5.35(d,d, \(J=3.76\) Hz, 3.72 Hz, 1H, CH), 6.72-6.80(m, 3H, ArH), 7.22-7.24(d, \(J=7.96\) Hz, 2H, ArH), 7.86-7.88(d, \(J= 8.08\) Hz, 2H, ArH). \(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) ppm 14.15, 21.68, 22.71, 23.58, 24.87, 29.38, 29.68, 29.72, 31.95, 44.20, 68.80, 114.34, 114.58, 115.36, 115.58, 117.97, 118.05, 120.80, 122.34, 122.42, 127.07, 129.79, 142.61, 149.29, 149.31, 156.09, 158.46, 164.30, 165.66; MS: \(m/z = 310\) [M]\(^+\); Anal. Calcd for C\(_{18}\)H\(_{13}\)FN\(_2\)O\(_2\): C, 69.67; H, 4.80; N, 8.93%.

4-(5-(6-Fluorochroman-2-yl)-1,3,4-oxadiazol-2-yl)aniline (7c). mp 138-140 °C; IR (DRS): 3452, 3403, 3030, 2964, 2853, 1642, 1612, 1581, 1471, 1378, 1245, 1156, 1077, 1025, 878, 819, 788, 721, 698, 558 cm\(^{-1}\); MS: \(m/z = 311\) [M]\(^+\); Anal. Calcd for C\(_{17}\)H\(_{14}\)FN\(_3\)O\(_2\): C, 65.59; H, 4.53; N, 13.50. Found: C, 65.57; H, 4.29; N, 13.44%.

2-(6-Fluorochroman-2-yl)-5-(O-tolyl)-1,3,4-oxadiazole (7d). mp 114-116 °C; IR (DRS): 3452, 3403, 3030, 2964, 2853, 1642, 1612, 1581, 1471, 1378, 1245, 1156, 1077, 1025, 878, 819, 788, 721, 698, 558 cm\(^{-1}\); MS: \(m/z = 310\) [M]\(^+\); Anal. Calcd for C\(_{18}\)H\(_{15}\)FN\(_2\)O\(_2\): C, 69.67; H, 4.87; N, 9.03. Found: C, 69.28; H, 4.83; N, 8.98%.
Studies on nitrogen containing heterocyclic…

2-(5-(6-Fluorochroman-2-yl)-1,3,4-oxadiazol-2-yl)aniline (7e). mp 161-163 °C; IR (DRS): 3419, 3371, 3081, 2975, 2844, 1641, 1579, 1556, 1464, 1362, 1232, 1176, 1060, 1004, 810, 756, 592 cm⁻¹; MS: m/z = 311 [M⁺]; Anal. Calcd for C_{17}H_{14}FN_{3}O_{2}: C, 65.59; H, 4.53; N, 13.50. Found: C, 65.41; H, 4.45; N, 13.39%.

2-(4-Chlorophenyl)-5-(6-fluorochroman-2-yl)-1,3,4-oxadiazole (7f). mp 105-107°C; IR (DRS): 3080, 2983, 2867, 1629, 1572, 1525, 1462, 1245, 1196, 1079, 1017, 830 cm⁻¹; MS: m/z = 330 [M⁺]; Anal. Calcd for C_{17}H_{12}ClFN_{2}O_{2}: C, 61.73; H, 3.66; N, 8.47. Found: C, 61.63; H, 3.58; N, 8.43%.

2-(6-Fluorochroman-2-yl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (7g). mp 133-135 °C; IR (DRS): 3077, 2978, 2863, 1625, 1609, 1563, 1464, 1384, 1238, 1142, 1058, 1022, 870, 798, 732, 687, 603 cm⁻¹; MS: m/z = 341 [M⁺]; Anal. Calcd C_{17}H_{12}FN_{3}O_{4}: C, 59.83; H, 3.54; N, 12.31. Found: C, 59.77; H, 3.40; N, 12.21%.

2-(2-Chlorophenyl)-5-(6-fluorochroman-2-yl)-1,3,4-oxadiazole (7h). mp 173-175°C; IR (DRS): 3012, 2962, 2854, 1603, 1545, 1542, 1452, 1345, 1260, 1146, 1082, 1010, 888, 825, 777, 731, 634, 512 cm⁻¹; MS: m/z = 330 [M⁺]; Anal. Calcd for C_{17}H_{12}ClFN_{2}O_{2}: C, 61.73; H, 3.66; N, 8.47. Found: C, 61.65; H, 3.57; N, 8.34%.

3-(5-(6-Fluorochroman-2-yl)-1,3,4-oxadiazol-2-yl)aniline (7i). mp 169-171°C; IR (DRS): 3443, 3401, 3075, 2964, 2853, 1721, 1601, 1581, 1423, 1392, 1228, 1149, 1054, 1013, 799, 720, 666 cm⁻¹; MS: m/z = 311 [M⁺]; Anal. Calcd for C_{17}H_{14}FN_{3}O_{2}: C, 65.59; H, 4.53; N, 13.50. Found: C, 65.25; H, 4.47; N, 13.37%.

2-(3-Chlorophenyl)-5-(6-fluorochroman-2-yl)-1,3,4-oxadiazole (7j). mp 181-183°C; IR (DRS): 3061, 2951, 2872, 1689, 1589, 1579, 1462, 1310, 1288, 1175, 1099, 1012, 798, 755, 678 cm⁻¹; MS: m/z = 330 [M⁺]; Anal. Calcd for C_{17}H_{12}ClFN_{2}O_{2}: C, 61.73; H, 3.66; N, 8.47. Found: C, 61.08; H, 3.61; N, 8.41%.

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SPECTRAL STUDY OF SYNTHESIZED COMPOUNDS

IR Spectrum of 2-(6-Fluorochroman-2-yl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (7a).

IR Spectrum of 2-(6-Fluorochroman-2-yl)-5-(p-tolyl)-1,3,4-oxadiazole (7b).
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Mass spectrum of 2-(6-Fluorochroman-2-yl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (7a).

Mass spectrum of 2-(6-Fluorochroman-2-yl)-5-(p-tolyl)-1,3,4-oxadiazole (7b).
Studies on nitrogen containing heterocyclic…

$^1$H NMR spectrum of 2-(6-Fluorochroman-2-yl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole(7a).

Expanded spectrum of 2-(6-Fluorochroman-2-yl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole(7a).
Studies on nitrogen containing heterocyclic...

Expanded spectrum of 2-(6-Fluorochroman-2-yl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (7a).

$^1$H NMR spectrum of 2-(6-Fluorochroman-2-yl)-5-(p-tolyl)-1,3,4-oxadiazole (7b).
Studies on nitrogen containing heterocyclic...

Expanded spectrum of 2-(6-Fluorochroman-2-yl)-5-(p-tolyl)-1,3,4-oxadiazole (7b).

Expanded spectrum of 2-(6-Fluorochroman-2-yl)-5-(p-tolyl)-1,3,4-oxadiazole (7b).
Studies on nitrogen containing heterocyclic...

\(^{13}\)C NMR spectrum of 2-(6-Fluorochroman-2-yl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole(7a).

\(^{13}\)C NMR spectrum of 2-(6-Fluorochroman-2-yl)-5-(p-tolyl)-1,3,4-oxadiazole (7b).
### Table-7b: Antimicrobial activity of 2-(6-Fluorochroman-2-yl)-5-aryl-1,3,4-oxadiazoles.

<table>
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<th>Sr. No.</th>
<th>Antibacterial Activity</th>
<th>Antifungal activity</th>
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<tr>
<td></td>
<td>Gram +ve Bacteria</td>
<td>Gram –ve Bacteria</td>
</tr>
<tr>
<td></td>
<td>Minimal bactericidal concentration μg/ml</td>
<td>Minimal fungicidal concentration μg/ml</td>
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<tr>
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<td>7b</td>
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**MINIMAL INHIBITION CONCENTRATION**

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**MINIMAL FUNGICIDAL CONCENTRATION**

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<th>A.Clavatus</th>
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<td>100</td>
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<tr>
<td>Greseofulvin</td>
<td>500</td>
<td>100</td>
<td>100</td>
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</tbody>
</table>
Oxadiazole derivatives...
Studies on nitrogen containing heterocyclic…


INTRODUCTION

1,2,4-Triazoles have proved to be most useful framework for biological activities among nitrogen containing five membered heterocycles. In five membered heterocyclic ring system 4-aryl triazole (I) have three nitrogen atoms at 1,2 and 4 positions, an aryl group at 4-position and free mercapto group at 3-position.

\[
\begin{aligned}
&N \quad N \\
&\text{X-} \quad \text{N-N} \quad \text{SH} \\
&R
\end{aligned}
\]

SYNTHETIC ASPECT

Several methods have been reported in the literature for the preparation of 4-aryl triazoles.

1. A.R.Katritzky et al.\(^1\) have synthesized 4-aryltriazoles by the cyclization of semicarbazide.

\[
\begin{aligned}
&\text{O} \\
&\text{N} \\
&\text{NHR} \\
&\text{N} \\
&\text{NNR} \\
&\text{N} \\
&\text{R_1}
\end{aligned}
\]

2. K. Zamani et al.\(^2\) synthesized 4-aryltriazole from thiosemicarbazide by ring closure reaction with 2N NaOH.

\[
\begin{aligned}
&\text{O} \\
&\text{N} \\
&\text{NHR} \\
&\text{N} \\
&\text{NH} \\
&\text{S} \\
&\text{NH} \\
&\text{N} \\
&\text{NN} \\
&\text{SH} \\
&\text{R}
\end{aligned}
\]

3. T. Plech et al.\(^3\) have synthesized s-triazoles by the reaction of 3- chlorobenzoic acid hydrazide, arylisothiocyanates and 1-[(3- chrophenyl) carbonyl]-4-sustituted thiosemicarbazides. The reaction was complete in short time. Which on alkaline
cyclization with 2% sodium hydroxide afforded the corresponding 5-(3-chromenyl)-4-substituted-2,4-dihydro-3H-1,2,4-triazole-3-thiones.

4. S.Shelke et al. have synthesized some novel azoles as antimicrobial agents. Thiosemicarbazides (2) have been prepared from acid hydrazide (1), and fluorinated aryl isothiocyanates. Thiosemicarbazides (2) in 1% NaOH gave compounds (3) with 72-88% yield under green technique.
5. R.J. Singh et al.\textsuperscript{5} have novel synthesized some 1,2,4-triazoles as potent bacteriocidal agents with the reaction of 4-methyl phenyl amine, carbon disulphide and ammonia in the methanol as a solvent and leadnitrate as a catalyst and compound (1) was obtained. Pyridine carboxylic acid hydrazides (a-c) were react with 4-methylphenylisothiocyanate in the presence of ethanol to give compound (2a-c) which on reaction with 2M sodium hydroxide solution to give final compounds (3a-c) with higher yield (75-85%).

\[
\begin{align*}
\text{NH}_2 \quad \text{CS}_2/\text{NH}_3/\text{Pb(NO}_3)_2 \\
\rightarrow \quad \text{NCS} \\
\rightarrow \quad \text{1} \\
\rightarrow \quad \text{2a-c} \\
\rightarrow \quad \text{3a-c}
\end{align*}
\]

6. G. Naganagowda et al.\textsuperscript{6} have been synthesized 5-substituted-4-aryl-3-mercapto-4h-1,2,4-triazoles. The compound (1) was treated with hydrazine hydrate to obtain 3-chloro-1-benzothiophene-2-carbohydrazide (2) in good yield. Then condensation of carbohydrazide (2) with aryl isothiocyanates separately afforded thiosemicarbazides (3) in good yields. Then the compounds 3a-b upon heating with 4N NaOH in ethanol underwent smooth cyclization through dehydration to form 5-substituted-4-aryl-3-mercapto-4H-1,2,4-triazoles (4).
I. Khan et al. have been synthesized some new 1,2,4-triazoles with antioxidant activities and urease inhibition. Substituted aromatic esters were synthesized by the reaction of corresponding acids with methanol in the presence of catalytic amount of sulfuric acid. Esters were converted to the corresponding acid hydrazides by refluxing with hydrazine (80%) and phenylisothiocyanates in methanol and obtained carbothioamides. Then compounds were synthesized by intramolecular dehydrative cyclization of carbothioamides when refluxed in 4N NaOH solution, followed by neutralization with concentrated HCl.
THERAPEUTIC IMPORTANCE

4-Aryltriazoles are reported to exhibit a wide variety of biological activities such as,

1. Antiinflammatory
2. Biocides
3. Cholesteryl ester transfer protein
4. Antidepressant

Chang et al. have synthesized aryltriazoles and reported them as antifungal drugs. O. Crisan et al. have screened antiinflammatory activity of triazoles. A.Varvaresou et al. have synthesized triazoles and reported their antimicrobial potency and antidepressant activities. Papakonstantinou et al. have investigated some triazole derivatives possessing significant antiviral activity. T. Konosu and co-workers have prepared aryltriazoles as fungicides.
N. Yasuda et al.\textsuperscript{17} have discovered aryltriazoles which have been extensively investigated for their antibacterial properties. S.C. Bahel et al.\textsuperscript{18} have documented antifungal activity of aryl triazoles. Athansia varvaresou et al.\textsuperscript{19} have synthesized aryltriazoles possessing antidepressant activity. Chu. Changhu et al.\textsuperscript{20} have screened 4-aryltriazoles for their antifungal activity.

Some aryltriazoles possessing analgesic and diuretic activities have been synthesized by Shrivastava S.K. et al.\textsuperscript{21} Wang Sheng et al.\textsuperscript{22} have reported triazoles as herbicidal agents.

R.F. Lowe and co-workers\textsuperscript{23} have reported aryltriazoles as useful antagonists. B.Holla et al.\textsuperscript{24} have documented anticancer activity of aryltriazoles. Welsh et al.\textsuperscript{25} have discovered aryltriazoles and reported them as analgesic agents.

R.J. Singh et al.\textsuperscript{5} synthesized some novel 1,2,4-Triazoles as potent bacteriocidal agents.
G. Naganagowda et al.\textsuperscript{6} have synthesized some new 3-chlorobenzothiophene-2-carbonylchloride derivatives which shown good activities like antimicrobial and anthelmintic.

![Chemical structure](image1)

G. Parameshwarappa et al.\textsuperscript{26} have been synthesized 5-bromo-3-amino benzofuran nucleus from 5-bromosalicylonitrile which was shown a good activities of anti-microbial.

![Chemical structure](image2)

A.A. Siddiqui et al.\textsuperscript{27} have designed, synthesized and screened \textit{in vivo} triazole incorporated with pyridazinones as a new class of antihypertensive agents.

![Chemical structure](image3)

S. Shelke et al.\textsuperscript{4} have discovered green synthesis of some novel azoles as antimicrobial agents.
M. D. Grandi et al.\textsuperscript{28} have synthesized 3,4,5- substituted triazoles derivatives as inhibitors of HIV RT Ribonuclease H

Work done from our laboratory

S.L.Vasoya\textsuperscript{29} have synthesized some new thiosemicarbazide and 1,2,4-triazoles heterocycles bearing the benzo[b]thiophene nucleus as potent antitubercular and antimicrobial agents.

In light of wide varieties of therapeutic activities exhibited by aryl triazole, we have embarked upon the synthesis of some new aryl triazole derivatives which have been described in following sections.

\textbf{SECTION-I: SYNTHESIS AND BIOLOGICAL SCREENING OF 5-(6-FLUOROCHROMAN-2-YL)-4-ARYL-4H-1,2,4 TRIAZOLE-3- THIOLS.}
Part – B

[Part – III (Section-i)]

Synthesis and biological evaluation of 5-(6-fluorochroman-2-yl)-4-aryl-4H-1,2,4-triazole-3-thiols
SYNTHESIS AND BIOLOGICAL EVALUATION OF 5-(6-FLUORO CHROMAN-2-YL)-4-ARYL-4H-1,2,4-TRIAZOLE-3- THIOLS.

4-Aryltriazole derivatives are associated with broad spectrum of pharmacological activity. In views of these findings, it appeared of interest to synthesize 5-(6-fluorochroman-2-yl)-4-aryl-4H-1,2,4-triazole-3-thiols. The synthesis of triazole derivatives of type (III) have been undertaken by heating dry potassium 2-[(6-fluorochroman-2-yl)carbonyl]hydrazine carbodithioate with different aromatic amines.

REACTION SCHEME

The constitution of all the synthesized compounds have been characterized by using elemental analysis, FT-IR, \(^1\)H NMR, \(^{13}\)C NMR spectroscopy and further supported by mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate.

All the synthesized compounds were tested for their antibacterial and antifungal activity (MIC) \textit{in vitro} by broth dilution method with two Gram-positive bacteria, two Gram-negative bacteria and three fungal strains. The biological activities of the synthesized compounds have been compared with standard drugs.
EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV light. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using DRS (diffusive reflectance system) method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. $^1$H NMR and $^{13}$C NMR were determined in CDCl$_3$ and DMSO solution on a Bruker AC 300 MHz, 400 MHz and 100MHz spectrometer. Elemental analysis of the all the synthesized compounds were carried out on Euro EA 3000 elemental analyzer and the results are in agreements with the structures assigned.

[A] Preparation of Potassium 2-[(6-fluorochroman-2-yl) carbonyl] Hydrazinecarbodithioate

See PART-B, part-I, section-I [C].

[B] General procedure for the preparation of 5-(6-Fluorochroman-2-yl)-4-aryl-4H-1,2,4-triazole-3-thiols.

A mixture of potassium 2-[(6-fluorochroman-2-yl) carbonyl] hydrazine carbodithioate (2.85g, 0.01M) and different aromatic amines (0.01M) was heated at 140-150$^\circ$C until the evolution of H$_2$S gas ceased (15 hours.). The product was dissolved in DMF (20ml), treated with dilute HCl and then poured in to crushed ice. The product was isolated and crystallized from ethanol. The physical constants of the products are recorded in Table-8a.

[C] Biological evaluation of 5-(6-Fluorochroman-2-yl)-4-aryl-4H-1,2,4-triazole-3-thiols.

Antimicrobial testing was carried out as described in Part-B, Part-III, Section-I, antimicrobial activity. The MIC values of the test compounds are recorded in Table-8b.
Table-8a: Physical constant of 5-(6-Fluorochroman-2-yl)-4-aryl-4H-1,2,4-triazole-3-thiols.

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Substitution R</th>
<th>M. F.</th>
<th>M. W.</th>
<th>Yield (%)</th>
<th>R_f value</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>-CH₃</td>
<td>C₁₉H₁₆FN₃OS</td>
<td>341.40</td>
<td>89</td>
<td>0.62</td>
</tr>
<tr>
<td>8b</td>
<td>-Cl</td>
<td>C₁₇H₁₃ClFN₃OS</td>
<td>361.82</td>
<td>86</td>
<td>0.42</td>
</tr>
<tr>
<td>8c</td>
<td>-F</td>
<td>C₁₇H₁₃F₂N₃OS</td>
<td>345.36</td>
<td>78</td>
<td>0.37</td>
</tr>
<tr>
<td>8d</td>
<td>-CH₃</td>
<td>C₁₉H₁₈FN₃OS</td>
<td>355.42</td>
<td>95</td>
<td>0.51</td>
</tr>
<tr>
<td>8e</td>
<td>-CH₃</td>
<td>C₁₉H₁₈FN₃OS</td>
<td>355.42</td>
<td>84</td>
<td>0.59</td>
</tr>
<tr>
<td>8f</td>
<td>-F</td>
<td>C₁₇H₁₃F₂N₃OS</td>
<td>345.36</td>
<td>79</td>
<td>0.69</td>
</tr>
<tr>
<td>8g</td>
<td>-Cl</td>
<td>C₁₇H₁₃ClFN₃OS</td>
<td>361.82</td>
<td>76</td>
<td>0.44</td>
</tr>
<tr>
<td>8h</td>
<td>-F</td>
<td>C₁₇H₁₂ClF₂N₃OS</td>
<td>379.81</td>
<td>87</td>
<td>0.31</td>
</tr>
<tr>
<td>8i</td>
<td>-OCH₃</td>
<td>C₁₈H₁₆FN₃O₂S</td>
<td>357.40</td>
<td>90</td>
<td>0.58</td>
</tr>
<tr>
<td>8j</td>
<td>-F</td>
<td>C₁₇H₁₂F₂N₃O₂S</td>
<td>363.35</td>
<td>75</td>
<td>0.70</td>
</tr>
</tbody>
</table>

TLC solvent system:- E.A. : Hexane = 5 : 5
Aryltriazole derivatives...

ANALYTICAL DATA

5-(6-Fluorochroman-2-yl)-4-(p-tolyl)-4H-1,2,4-triazole-3-thiol (8a). mp 170-172 °C; IR (DRS): 3076, 3039, 2924, 2862, 2773, 2731, 1735, 1699, 1637, 1514, 1429, 1319, 1138, 916,871, 815, 767, 694 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ ppm 2.02-2.44 (m, 5H, 2CH, 3CH), 2.65-2.96 (m, 2H, 2CH), 4.83-4.90 (d, d, J=12.6 Hz, 6 Hz, 1H, CH), 6.60-6.69 (m, 1H, ArH), 6.73-6.76 (m, 2H, ArH), 7.05-7.49 (m, 4H, ArH), 11.43 (s, 1H, SH). ¹³C NMR (100 MHz, DMSO): δ 22.87, 22.99, 38.96, 67.72, 113.50, 113.73, 114.98, 115.20, 117.18, 117.26, 122.83, 122.91, 127.92, 129.50, 130.83, 139.07, 148.95, 149.89, 161.80, 168.76; MS: m/z = 341 [M]+; Anal. Calcd for C₁₈H₁₆FN₃OS: C, 63.32; H, 4.72; N, 12.31. Found: C, 63.23; H, 4.41; N, 12.28%.

4-(3-Chlorophenyl)-5-(6-fluorochroman-2-yl)-4H-1,2,4-triazole-3-thiol (8b). mp 205-207°C; IR (DRS): 3066 (Ar, C-H str.), 2914 (C-H str.), 2850 (C-H str.), 2777 (-SH str.), 2533 (-SH str.), 1680 (Ar, C=C str.), 1647 (Ar, C=C str.), 1558 (Ar, C=C str.), 1494 (Ar, C=C str.), 1375 (C-Hben), 1203 (C-Cl str.), 1101 (C-F str.), 1087 (C-N str.), 1072 (C-N str.), 1041 (C-O-C str.), 815 (C-H o,p, ben), 769 (C-H o,p, ben), 707 (C-C o,p, ben), 663 (C-C o,p, ben), 511 (C-C o,p, ben) cm⁻¹; ¹H NMR (400 MHz, DMSO): δ ppm 2.27-2.30 (m, 2H, 2CH), 2.82-2.95 (m, 2H, 2CH), 4.92-4.95 (d, d, J=6.12 Hz, 12 Hz, 1H, CH), 6.50-6.54 (m, 1H, ArH), 6.75-6.79 (m, 2H, ArH), 7.41-7.43 (m, 1H, ArH), 7.53-7.55 (m, 3H, ArH), 14.0 (s, 1H, SH). ¹³C NMR (100 MHz, DMSO): δ ppm 22.69, 22.85, 38.95, 67.74, 102.75, 108.64, 113.53, 115.05, 117.14, 118.18, 122.91, 127.17, 128.52, 129.64, 130.44, 133.33, 134.77, 140.63, 143.11, 148.80, 149.67, 161.90, 168.71; MS: m/z = 361 [M]+; Anal. Calcd for C₁₇H₁₃ClFN₃OS: C, 56.43; H, 3.62; N, 11.61. Found: C, 56.18; H, 3.49; N, 11.59%.

5-(6-Fluorochroman-2-yl)-4-(4-fluorophenyl)-4H-1,2,4-triazole-3-thiol (8c). mp 188-190 °C; IR (DRS): 3030, 2964, 2853, 2658, 1642, 1612, 1581, 1471, 1378, 1225, 1156, 1045, 819, 777, 696, 513, cm⁻¹; MS: m/z = 345 [M]+; Anal. Calcd for C₁₇H₁₃F₂N₃OS: C, 59.12; H, 3.79; N, 12.17. Found: C, 59.02; H, 3.53; N, 12.01%.

4-(2,5-Dimethylphenyl)-5-(6-fluorochroman-2-yl)-4H-1,2,4-triazole-3-thiol (8d). mp 123-125°C; IR (DRS): 3074, 2987, 2851, 2710, 1645, 1612, 1585, 1468, 1330, 1281, 1184, 1074, 820, 766, 692, 587 cm⁻¹; MS: m/z = 355 [M]+; Anal. Calcd for C₁₉H₁₆FN₃OS: C, 64.21; H, 5.10; N, 11.82. Found: C, 64.16; H, 4.93; N, 11.78%.
4-(3,4-Dimethylphenyl)-5-(6-fluorochroman-2-yl)-4H-1,2,4-triazole-3-thiol (8e). mp 163-165 °C; IR (DRS): 3081, 2975, 2844, 2687, 1641, 1579, 1556, 1464, 1378, 1282, 1142, 1023, 887, 750, 687, 555 cm⁻¹; MS: \( m/z = 355 \) [M]+; Anal. Calcd for C₁₉H₁₈FN₃OS: C, 64.21; H, 5.10; N, 11.82. Found: C, 64.09; H, 5.03; N, 11.50%.

5-(6-Fluorochroman-2-yl)-4-(2-fluorophenyl)-4H-1,2,4-triazole-3-thiol (8f). mp 108-110°C; IR (DRS): 3080, 2983, 2867, 2661, 1629, 1572, 1525, 1462, 1341, 1245, 1196, 1094, 830, 774, 682, 575 cm⁻¹; MS: \( m/z = 345 \) [M]+; Anal. Calcd for C₁₇H₁₃F₂N₃OS: C, 59.12; H, 3.79; N, 12.17. Found: C, 58.96; H, 3.67; N, 12.06%.

4-(2-Chlorophenyl)-5-(6-fluorochroman-2-yl)-4H-1,2,4-triazole-3-thiol (8g). mp 192-194 °C; IR (DRS): 3077, 2978, 2863, 2712, 1625, 1609, 1563, 1464, 1310, 1238, 1142, 1044, 870, 798, 756, 656, 544 cm⁻¹; MS: \( m/z = 361 \) [M]+; Anal. Calcd C₁₇H₁₃ClFN₃OS: C, 56.43; H, 3.62; N, 11.61. Found: C, 55.97; H, 3.55; N, 11.59%.

4-(3-Chloro-4-fluorophenyl)-5-(6-fluorochroman-2-yl)-4H-1,2,4-triazole-3-thiol (8h). mp 139-141°C; IR (DRS): 3031, 2962, 2854, 2691, 1603, 1545, 1542, 1452, 1332, 1260, 1146, 1042, 878, 831, 778, 631, 542 cm⁻¹; MS: \( m/z = 379 \) [M]+; Anal. Calcd for C₁₇H₁₂ClFN₃OS: C, 53.76; H, 3.18; N, 11.06. Found: C, 53.69; H, 3.07; N, 10.90%.

5-(6-Fluorochroman-2-yl)-4-(2-methoxyphenyl)-4H-1,2,4-triazole-3-thiol (8i). mp 251-253°C; IR (DRS): 3075, 2964, 2853, 2711, 1721, 1601, 1581, 1423, 1355, 1281, 1149, 1075, 740, 602 cm⁻¹; MS: \( m/z = 357 \) [M]+; Anal. Calcd for C₁₈H₁₆FN₃O₂S: C, 60.49; H, 4.51; N, 11.76. Found: C, 60.39; H, 4.29; N, 11.37%.

4-(2,5-Difluorophenyl)-5-(6-Fluorochroman-2-yl)-4H-1,2,4-triazole-3-thiol (8j). mp 229-231°C; IR (DRS): 3061, 2951, 2872, 2635, 1689, 1589, 1579, 1462, 1352, 1099, 831, 755, 621, 510 cm⁻¹; MS: \( m/z = 363 \) [M]+; Anal. Calcd for C₁₇H₁₂F₂N₃O₂S: C, 56.19; H, 3.33; N, 11.56. Found: C, 56.06; H, 3.14; N, 11.32%.
SPECTRAL STUDY OF SYNTHESIZED COMPOUNDS

IR Spectrum of 5-(6-Fluorochroman-2-yl)-4-(p-tolyl)-4H-1,2,4-triazole-3-thiol (8a).

IR Spectrum of 4-(3-Chlorophenyl)-5-(6-fluorochroman-2-yl)-4H-1,2,4-triazole-3-thiol (8b).
Mass spectrum of 5-(6-Fluorochroman-2-yl)-4-(p-tolyl)-4H-1,2,4-triazole-3-thiol (8a).

Mass spectrum of 4-(3-Chlorophenyl)-5-(6-fluorochroman-2-yl)-4H-1,2,4-triazole-3-thiol (8b).
$^1$H NMR spectrum of 5-(6-Fluorochroman-2-yl)-4-(p-tolyl)-4H-1,2,4-triazole-3-thiol (8a).

Expanded spectrum of 5-(6-Fluorochroman-2-yl)-4-(p-tolyl)-4H-1,2,4-triazole-3-thiol (8a).
Studies on nitrogen containing heterocyclic...

\( ^1 \text{H NMR spectrum of } 4\text{-} \left(3\text{-Chlorophenyl}\right)\text{-}5\text{-} \left(6\text{-fluorochroman-2-yl}\right)\text{-}4H\text{-}1\text{,2,4-}
\text{triazole-3-thiol}(8b)\).
Expanded spectrum of 4-(3-Chlorophenyl)-5-(6-fluorochroman-2-yl)-4H-1,2,4-triazole-3-thiol (8b).

$^{13}$C NMR spectrum of 5-(6-Fluorochroman-2-yl)-4-(p-tolyl)-4H-1,2,4-triazole-3-thiol (8a).
$^{13}$C NMR spectrum of 4-(3-Chlorophenyl)-5-(6-fluorochroman-2-yl)-4$H$-1,2,4-triazole-3-thiol (8b).
Table-8b: Antimicrobial activity of 5-(6-Fluorochroman-2-yl)-4-aryl-4H-1,2,4-triazole-3-thiols.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Antibacterial Activity</th>
<th>Antifungal activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimal bactericidal concentration μg/ml</td>
<td>Minimal fungicidal concentration μg/ml</td>
</tr>
<tr>
<td></td>
<td>Gram +ve Bacteria</td>
<td>Gram –ve Bacteria</td>
</tr>
<tr>
<td>S.aureus</td>
<td>S.pyogenus</td>
<td>E.coli</td>
</tr>
<tr>
<td>8a</td>
<td>500</td>
<td>250</td>
</tr>
<tr>
<td>8b</td>
<td>62.5</td>
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<tr>
<td>8g</td>
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<tr>
<td>8h</td>
<td>62.5</td>
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</tr>
<tr>
<td>8i</td>
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<tr>
<td>8j</td>
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MINIMAL INHIBITION CONCENTRATION

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<th>S.pyogenus</th>
<th>E.coli</th>
<th>P.aeruginosa</th>
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<td>0.5</td>
<td>0.05</td>
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</tr>
<tr>
<td>Ciprofloxacin</td>
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<td>Norfloxacin</td>
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MINIMAL FUNGICIDAL CONCENTRATION

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<tbody>
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<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Greseofulvin</td>
<td>500</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
REFERENCES

10. A. Silkoski, James, *PCT Int. appl.wo* 99, 14,204 (Cl. Co7D249/12); *Chem. Abstr.*, 130, 237570b (1999).


PART-IV
STUDIES ON THIAZOLIDINONE DERIVATIVES
INTRODUCTION

Thiazolidinones, which belongs to an important group of heterocyclic compounds, have been widely explored for their applications in the field of medicine. Thiazolidinones, with a carbonyl group at position 2 in structure (1) and position 4 or 5 in structure (2, 3) have been subjected of widespread study in the recent past. Numerous gossips have appeared in the literatures which underscore their chemistry and use.

4-Thiazolidinones are derivatives of thiazolidinones with carbonyl group at 4-position (2). Substituent in the 2, 3 and 5 positions may be varied, but the greatest different in structure and properties is exerted by the groups attached to carbon atom at the 2-position and to nitrogen atom at the 3-position. The cyclic structure was assigned after recognition of mercaptoacetic acid as a primary product of hydrolysis of 3-phenyl-2-phenylimino-4-thiazolidinones.1 A well known antibiotic, actithiazic acid (4), isolated from a species of streptomyces shows specific in vitro activity against M. tuberculosis, but it is inactive in vivo probably due to antagonisation by biotin, bears the 4-thiazolidinone skeleton.

SYNTHETIC ASPECT

Several methods for the preparation of 4-thiazolidinones are narrated in literature.2-10

1. R.S. Harisha et al.11 have synthesized the one pot synthesis of thiazolidinone, by hydrolysis of 2- (trifluoromethyl)-1H-benzimidazole(1) in NaOH/ HCl gives the 1H- benzimidazole-2-carboxylic acid(2), which on treatment with thionyl chloride followed by hydrazine hydrate to gave the desired 1H-benzimidazole-2-carboxylic acid hydrazide (3) in 90% yield. Then the compound (3) on reaction
with benzaldehyde and mercapto acetic acid in ethanol as a solvent to give compound (4).

2. S.J. Gilani et al.\textsuperscript{12} have been synthesized main two types of derivatives of 4-thiazolidinones. To an equimolar methanolic solution of isonicotinic acid hydrazide (0.1 mol) and substituted benzaldehyde (0.1 mol), a few drops of glacial acetic acid were added. The mixture was refluxed on water bath for 5-6 hours, then allowed to cool and poured on to crushed ice. The product isolated and recrystallisation from methanol yielded compounds (1a-h). A mixture of (1) (0.01 mol) and thioglycolic acid (0.01 mol) was heated on oil-bath at 120-125\textdegree C for 12 hours, then treated with sodium bicarbonate to gave compounds (2a-h). Same as reaction carryout in thiomalic acid to gave compounds (3a-h).
3. D. Lingampalle et al.\textsuperscript{13} have synthesized a convenient one-pot, three-component cyclo condensation mediated by ionic liquid for obtaining 2,3-disstutated-4-thiazolidinones with excellent yields reported.

![Chemical Reaction Diagram]

4. A. Madhukar et al.\textsuperscript{14} have synthesized biphenyl-4-carboxylic acid 2-(aryl)-4-oxo-thiazolidin-3-yl-amide.
5. L.D.S. Yadav et al.\textsuperscript{15} reported a convenient CeCl$_3$·7H$_2$O/NaI- promoted structurally novel synthesis of thiazolidinones. Which is describe as under.
6. M.S. Mohamed et al.\textsuperscript{16} synthesized novel thiazolidinones bearing 6,8-dibromo-4(3H) quinazolinone, which shows a very good anti-bacterial and anti-fungal activity. The reaction scheme as under.

7. V.S. Palekar et al.\textsuperscript{17} have been synthesized some novel bis-4- thiazolidinone derivatives from terphthalic dihydrazide. Which shows good anti-bacterial activity. The reaction scheme are as under.
8. N. B. Patel et al. have synthesized some new 4-thiazolidinones of nicotinic acid with 2-amino-6-methyl benzothiazole. Which have been described as under.

\[
\begin{align*}
&\text{Nicotinic Acid} + \text{2-amino-6-methyl benzothiazole} \\
&\xrightarrow{\text{reaction}} \text{Product}
\end{align*}
\]

\[
\begin{array}{cccc}
1 & 2 & 3 & 4 \\
\text{Cl} & \text{NH}_2 & \text{S} & \text{NH}_2 \\
\text{Pyridine} & \text{Thiazole} & \text{Thiazole} & \text{Thiazole}
\end{array}
\]

- a; R = H
- b; R = 2-Cl
- c; R = 4-Cl
- d; R = 2-NO_2
- e; R = 3-NO_2
- f; R = 4-OH
- g; 4-OCH_3
- h; R = 3-OCH_3, 4-OH
- i; R = 3-OCH_3, 4-OH, 5-NO_2
- j; R = 2-Furyl

9. M. L. Berreca et al. have synthesized some novel 2,3-diaryl-1,3-thiazolidin-4-one derivatives from 2,3-dihalo substituted benzaldehyde, equivalent amount of aromatic amine and mercaptoacetic acid in refluxing with toluene.

\[
\begin{align*}
&\text{Aromatic Amine} + \text{Mercaptoacetic Acid} + \text{Benzaldehyde} \\
&\xrightarrow{\text{reaction}} \text{Product}
\end{align*}
\]

\[
\begin{array}{cccc}
& & & \\
\text{NH}_2 & \text{SH} & \text{R}
\end{array}
\]

R = Aryl
R' = Cl, F
10. Bioactive venlafaxine analogs such as 2,3-disubstituted-1,3-thiazolidinones have been synthesized and reported as antimicrobial agent by C. V. Kavitha and coworkers.\textsuperscript{20}

![Thiazolidinone derivative synthesis scheme](image1)

11. D. R. St. Laurent et al.\textsuperscript{21} have synthesized 4-thiazolidinone derivatives by the cyclization unsymmetrical thiourea. H. S. Joshi and co-workers\textsuperscript{22} have synthesized thiazolidinones bearing benzo[b]thiophene nucleus from N-arylaminothoxomethyl derivatives with chloroacetic acid in ethanol.

![Thiazolidinone derivative synthesis scheme](image2)

12. A. Dandia and co-workers\textsuperscript{23} have synthesized thiazolidinone derivatives and reported their antifungal activity.

![Thiazolidinone derivative synthesis scheme](image3)
REACTION MECHANISM

THERAPEUTIC IMPORTANCE

Much research has been accepted with intend to pronouncement therapeutic values of thiazolidinone moiety since their discovery. The thiazolidinones, substituted at 2 and 3 position are reported to demonstrate a wide variety of biological activities.

1. Antibacterial.\textsuperscript{24, 25} 7. Anti-HIV\textsuperscript{31, 32}
2. Anticancer.\textsuperscript{26} 8. Antimicrobial\textsuperscript{33, 34}
3. Antiinflammatory\textsuperscript{27} 9. Antifungal\textsuperscript{35}
4. Antitubercular.\textsuperscript{28} 10. Antioxidant\textsuperscript{36}
5. Antihistaminic.\textsuperscript{29} 11. Herbicidal\textsuperscript{37}
6. Antimalarial.\textsuperscript{30}

Goel et al.\textsuperscript{38} have synthesized thiazolidinone derivatives and compared their antiinflammatory activity, ulcerogenic liability, cardiovascular and CNS effects. M. Siddique et al.\textsuperscript{39} have prepared substituted thiazolidinones and reported their antibacterial, antifungal, antithyroid and amoebicidal properties. S. K. Srivastava et al.\textsuperscript{40} have prepared new thiazolidinones as antibacterial, antifungal, analgesic and diuretic agents. A. Rao et al.\textsuperscript{41} have been synthesized several 1,3-thiazolidin-4-ones bearing 2,6-dihalophenyl group at C-2 and a substituted pyrimidin-2-yl ring at the N-3 were synthesized and evaluated as anti-HIV agents.
R. Ottana et al.\textsuperscript{42} have designed and synthesised 5-arylidene-2-imino-4-thiazolidinone derivatives as novel antiinflammatory agent. A. Tsutoma et al.\textsuperscript{43} have synthesized thiazolidinones as a telomeres inhibitors. S. K. Chaudhary et al.\textsuperscript{44} have synthesized several 3-(3-(N-morpholin-4-yl-propyl)-2-(arylimino)-4-thiazolidinones and evaluated for their ability to potentiate pentobarbital-induced hypnosis in mice at a dose of 100 mg/kg.

Suzuki et al.\textsuperscript{45} have synthesized and examined the effects of CP-060S 3-{3-[(benzo[1,3]dioxol-4-yloxy)methyl]-methyl-amino}propyl]-2-(3,5-di-tert-butyl-4-hydroxy phenyl)-4-thiazolidinone on cardiac function and myocardial oxygen consumption (MVO2) in anesthetized dogs. V. K. Agraval et al.\textsuperscript{46} have investigated the antihistaminic (H1-antagonist) activity of 2,3-disubstituted thiazolidin-4-ones and concluded that the hydrophobic substitution at the 4-position of the phenyl ring. In another study, Diurno et al.\textsuperscript{47} have synthesized, characterized and evaluated a new series of 2-(substituted-phenyl)-3-[3-(N,N-dimethylamino)-propyl]-1,3-thiazolidin-4-ones for their capacity to inhibit contraction induced by histamine on guinea pig ileum. G. Kucukguzel et al.\textsuperscript{48} have been synthesized some thiazolididine derivatives and reported as anti-inflammatory agent.

N. Ulusoy et al.\textsuperscript{49} have prepared thiazolidinone derivatives as potent antimycobacterial agents. R. Govindarajan et al.\textsuperscript{50} have synthesized thiazolidinones as
antitubercular, antifungal and antibacterial agent. Hassan et al.\textsuperscript{51} have prepared 2-imino-4-thiazolidinones which have been found to possess antimicrobial activity. A. Dandia and co-workers\textsuperscript{52} have reported thiazolidinone derivatives as potential antifungal and antitubercular agents. C. Muanprasat et al.\textsuperscript{53} have prepared some new thiazolidinone derivatives as CFTR inhibitors. M. G. Vigorita et al.\textsuperscript{54} have prepared meso 3,3’-(1,2-ethanediyl)-bis[2-aryl-4-thiazolidinones] derivatives as antiinflammatory and analgesic agents. K. Babaoglu et al.\textsuperscript{55} have been prepared a virtual library of 2,3,5 trisubstituted-4-thiazolidinones (12,13) as inhibitors of dTDP-rhamnose synthesis.

C. J. Andres and co-workers\textsuperscript{56} have prepared some 4-thiazolidinone derivatives and reported as novel inhibitors of the bacterial enzyme Mur B which is a precursor acting during the biosynthesis of peptidoglycan. D. Maclean et al.\textsuperscript{57} reported the FSH agonist activity of an encoded 4-thiazolidinone library. M. M. Ramla et al.\textsuperscript{58} have been synthesized series of some new derivatives of 2-(1-benzyl-2-methyl-1H-benzimidazol-5-ylimino)-3-substituted-thiazolidin-4-ones and studied their inhibitory activity against the Epstein–Barr Virus-early antigen (EBV-EA) activation introduced by 12-Octadecanoylphorbol-13-acetate (TPA).
A. Kumar et al.\textsuperscript{59} have been synthesized 2-[(4'-oxo-3'-chloro-2'-phenylazetidin-1'-yl) aminomethyl]-3-[4''-(p-chlorophenyl) thiazol-2''-yl]-6-bromoquinazolin-4-ones and screened for their anti-inflammatory and analgesic activities at the dose of 50 mg/kg. R. P. Tenorio and co-workers\textsuperscript{60} have synthesized 4-thiazolidinones in one and two steps and synthesized compounds were submitted to evaluation against host cells infected with toxoplasma gondii. J. Wrobel et al.\textsuperscript{61} have been synthesized 5-alkylated thiazolidinones as follicle-stimulating hormone (FSH) receptor agonists.

R. Dayam et al.\textsuperscript{62} have reported some novel thiazolidinone derivatives as novel class of HIV- integrase inhibitors. N. D. Sonawane et al.\textsuperscript{63} have synthesized some new thiazolidinone derivatives as \textit{in vivo} pharmacology and antidiarrheal efficacy of a thiazolidinone CFTR inhibitor in rodents. Antimicrobial activity of some pyrazine containing thiazolidinones have been reported by C. G. Bonda.\textsuperscript{64} X. F. Wang et al.\textsuperscript{65} have synthesized some novel thiazolidinone derivatives described as new cystic fibrosis transmembrane conductance regulator inhibitor on Cl-conductance in human sweat ducts. F. Ur et al.\textsuperscript{66} have constructed some new 6-methylimidazo[2,1-b]thiazole-5- carboxyhydrazide derivatives and their antimicrobial activities. D. Reigada et al.\textsuperscript{67} have reported some new thiazolidinone derivatives as release of ATP from retinal pigment epithelial cells involves both CFTR and vesicular transport. Antiproliferative activities of 2-aryl-4-oxo-thiazolidin-3-yl-amides for prostate cancer have been reported by V. Gududuru et al.\textsuperscript{68} D. B. Salinas et al.\textsuperscript{69} documented thiazolidinone derivatives as CFTR inhibitor. H. S. Joshi et al.\textsuperscript{70} have been reported some thiazolidinones bearing benzo[b]thiophene moiety as antitubercular and antimicrobial agents. S. M. Rida and co-workers\textsuperscript{71} have been
prepared 2-[(1-benzofuran-2-yl-ethylidene)hydrazono]-5-(4-substitutedbenzylidene)-3-substituted-thiazolidin-4-ones as anticancer agents.

A series of novel 2-arylimino-3-aryl-thiazolidine-4-ones was designed, synthesized and tested for *in vitro* antibiofilm activity against *Staphylococcus epidermidis*. Among them tested, some compounds with carboxylic acid groups showed good antibiofilm activity. The antibiofilm concentration of 1x was 6.25 μM.

Liu et al. synthesized derivatives of 2-imino-3-(4-arylthiazol-2-yl)thiazolidin-4-ones and series of their 5-arylidene derivatives and tested for antifungal activity against seven agricultural fungi.
G.C. Sekhar et al.\textsuperscript{74} have synthesized compounds and most of them were found to possess moderate activity against fungi aspergillus flavus and candida albican respectively. The antifungal activities of test compounds were compared with standard salicylic acid (20 - 30 mm) and chlortrimazole (25 - 30 mm).

\begin{center}
\includegraphics[width=0.3\textwidth]{3-(3-methylquinoxalin-2-ylamino)-2-phenylthiazolidin-4-one.png}
\end{center}

V.V. Mulwad et al.\textsuperscript{75} have been screened compounds various thiazolidine derivetives for their antimicrobial activity by cup plate method and have found to exhibit significant activity against \textit{B.Subtilis, E.coli} at different concentration (50 and 100 μg/ml) using DMSO as solvent.

\begin{center}
\includegraphics[width=0.3\textwidth]{(E)-5-benzylidene-2-imino-3-(2-oxo-2\textsubscript{H}-chromen-6-yl)thiazolidin-4-one.png}
\end{center}

**Work done from our laboratory**

K.M.Thaker et al\textsuperscript{76} have synthesized 2-aryl-5H-(3’,5’-dichoro-2-benzo(b)thiophenoyl amino)-4-thiazolidinone bearing the benzo[b]thiophene nucleus as potent antimicrobial agents. S.L.Vasoya et al\textsuperscript{77} have synthesized some new2-aryl-5H-(3’-chloro-5’-phenoxybenzo(b)thiophenoyl-2-amino)-4-thiazolidinone nucleus as potent antimicrobial agents.

With an intention of preparing the compounds possessing better therapeutic activity, We have undertaken the synthesis of thiazolidinones bearing chroman nucleas which have been described as under.

**SECTION-I: SYNTHESIS AND BIOLOGICAL EVALUATION OF 6-FLUORO-N-(4-OXO-2-ARYLTHIAZOLIDIN-3-YL) CHROMAN-2-CARBOXAMIDES.**
Part – B

[Part – IV (Section-i)]

Synthesis and biological evaluation of 6-fluoro-N(4-oxo-2-arylthiazolidin-3-yl) chroman-2-carboxamides.
SECTION-I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 6-FLUORO-N-(4-OXO-2-ARYLTHIAZOLIDIN-3-YL)CHROMAN-2-CARBOXAMIDES.

With a view to getting better therapeutic agents and considering the association of various biological activities of thiazolidinonone heterocycles, the synthesis of thiazolidinones have been undertaken by the condensation of different aryl aldehydes with 6-fluorochroman-2-carbohydrazide and thioglycolic acid (mercapto acetic acid), as shown in reaction scheme.

REACTION SCHEME

The constitution of all the synthesized compounds have been characterized by using elemental analysis, FT-IR, $^1$H NMR, $^{13}$C NMR spectroscopy and further supported by mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate.

All the synthesized compounds were tested for their antibacterial and antifungal activity (MIC) \textit{in vitro} by broth dilution method with two Gram-positive bacteria, two Gram-negative bacteria and three fungal strains. The biological activities of the synthesized compounds have been compared with standard drugs.
EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV light. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using DRS (diffusive reflectance system) method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. \(^1\)H NMR and \(^{13}\)C NMR were determined in CDCl\(_3\) and DMSO solution on a Bruker AC 400 MHz and 100MHz spectrometer. Elemental analysis of the all the synthesized compounds were carried out on Euro EA 3000 elemental analyzer and the results are in agreements with the structures assigned


See PART-B, part-I, section-I [B].


A mixture of 6-fluorochroman-2-carbohydrazide (2.0 g,0.01mol), different aryl aldehydes (0.01 mol) and thioglycolic acid(mercapto acetic acid) (26.7 g=20.4 ml, 0.29 mol) in toluene (50 ml) was refluxed in a Dean-Stark assembly with continuous stirring. After completion of the reaction (48 hours monitoring by TLC), the content was cooled to room temperature then neutralized with sodium bicarbonate solution. The organic extracts was washed with water (2 x 10 ml), dried with Na\(_2\)SO\(_4\), solvent was removed in vacuo and the resulting crude product was purified by column chromatography to give the analytical pure compounds. The physical constants of the products are recorded in Table-9a.

[C] Biological evaluation of 6-Fluoro-N-(4-oxo-2-arylthiazolidin-3-yl)chroman-2-carboxamides.

Antimicrobial testing was carried out as described in Part-B, Part-IV, Section-I, antimicrobial activity. The MIC values of the test compounds are recorded in Table-9b.
### Table-9a: Physical constant of 6-Fluoro-N-(4-oxo-2-arylthiazolidin-3-yl)chroman-2-carboxamides.

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Substitution R</th>
<th>M. F.</th>
<th>M. W.</th>
<th>Yield (%)</th>
<th>R_f value</th>
</tr>
</thead>
<tbody>
<tr>
<td>9a</td>
<td></td>
<td>C_{20}H_{19}FN_{2}O_{4}S</td>
<td>402.43</td>
<td>85</td>
<td>0.55</td>
</tr>
<tr>
<td>9b</td>
<td></td>
<td>C_{19}H_{16}FN_{3}O_{5}S</td>
<td>417.41</td>
<td>95</td>
<td>0.62</td>
</tr>
<tr>
<td>9c</td>
<td></td>
<td>C_{19}H_{16}F_{2}N_{2}O_{3}S</td>
<td>390.40</td>
<td>89</td>
<td>0.57</td>
</tr>
<tr>
<td>9d</td>
<td></td>
<td>C_{19}H_{16}ClFN_{2}O_{3}S</td>
<td>406.85</td>
<td>77</td>
<td>0.44</td>
</tr>
<tr>
<td>9e</td>
<td></td>
<td>C_{19}H_{16}BrFN_{2}O_{3}S</td>
<td>451.30</td>
<td>90</td>
<td>0.38</td>
</tr>
<tr>
<td>9f</td>
<td></td>
<td>C_{19}H_{17}FN_{3}O_{4}S</td>
<td>388.41</td>
<td>73</td>
<td>0.58</td>
</tr>
<tr>
<td>9g</td>
<td></td>
<td>C_{20}H_{19}FN_{2}O_{3}S</td>
<td>386.43</td>
<td>84</td>
<td>0.49</td>
</tr>
<tr>
<td>9h</td>
<td></td>
<td>C_{19}H_{16}ClFN_{2}O_{3}S</td>
<td>406.85</td>
<td>71</td>
<td>0.33</td>
</tr>
<tr>
<td>9i</td>
<td></td>
<td>C_{19}H_{14}FN_{3}O_{2}</td>
<td>417.41</td>
<td>79</td>
<td>0.71</td>
</tr>
<tr>
<td>9j</td>
<td></td>
<td>C_{19}H_{16}FN_{3}O_{3}S</td>
<td>451.30</td>
<td>88</td>
<td>0.41</td>
</tr>
</tbody>
</table>

TLC solvent system: E.A. : Hexane = 5 : 5
ANALYTICAL DATA

6-Fluoro-N-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide (9a).
mp 98-100 °C; IR (DRS): 3383, 3081, 2858, 1714, 1688, 1542, 1465, 1356, 1278, 1152, 1077, 887, 712, 689, 584 cm⁻¹; MS: m/z = 402 [M]+; Anal. Calcd for C₂₀H₁₉FN₂O₄S: C, 59.69; H, 4.76; N, 6.96. Found: C, 59.23; H, 4.61; N, 6.88%.

6-Fluoro-N-(2-(2-nitrophenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide (9b).
mp 190-192°C; IR (DRS): 3392, 3205, 2918, 2850, 1712, 1678, 1523, 1485, 1390, 1259, 1190, 864, 702, 657, 561 cm⁻¹; ¹H NMR (400 MHz, DMSO): δ ppm 1.81-2.05(m, 2H, 2CH), 2.61-2.74(m, 2H, 2CH), 3.68-3.72(d, J=16.0 Hz, 1H, CH), 3.91-3.95(d, J=15.6 Hz, 1H, CH), 4.66-4.69(d, J=3.6 Hz, 3.2 Hz, 1H, CH), 6.12(s, 1H, CH), 6.12(s, 1H, CH), 6.72-6.79(m, 1H, ArH), 6.84-6.91(m, 2H, ArH), 7.60-7.63(t, 1H, ArH), 7.78-7.87(m, 2H, ArH), 8.04-8.06(d, J=8.0 Hz, 1H, ArH), 10.43-10.46(d, J=11.6 Hz, 1H, NH). ¹³C NMR (100 MHz, CDCl₃): δ ppm, 22.71, 23.56, 24.14, 29.29, 29.38, 29.71, 30.50, 50.43, 58.29, 75.20, 114.27, 114.51, 115.60, 115.83, 117.60, 123.26, 125.40, 127.95, 129.88, 134.07, 134.28, 148.30, 148.40, 156.16, 162.20, 169.32, 169.47. MS: m/z = 417 [M]+; Anal. Calcd for C₁₉H₁₆FN₃O₅S: C, 54.67; H, 3.86; N, 10.07. Found: C, 54.58; H, 3.49; N, 9.99%.

6-Fluoro-N-(2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide (9c).
mp 106-110 °C; IR (DRS): 3487(Ar, C-H str.), 3041(Ar, C-H str.), 2958(A-H str.), 2848(A-H str.), 1710(amide C=O str.), 1676(amide C=O str.), 1537(amide C=O str.), 1429(Ar, C=O str.), 1388(Ar, C=H ben), 1261(Ar, C=O str.), 1190(Ar, C=O str.), 1078(C-N str.), 891(C-H o,p, ben), 868(C-H o,p, ben), 813(C-H o,p, ben), 759(C-H o,p, ben), 709(C-H o,p, ben), 673(C-H o,p, ben), 650(C-Co,p, ben), 592(C-Co,p, ben) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ ppm 1.82-2.02(m, 2H, 2CH), 2.56-2.70(m, 2H, 2CH), 3.59-3.78(m, 2H, 2CH), 4.45-4.58(d, d, J=10.52 Hz, 11.52 Hz, 1H, CH), 5.79-5.83(d, J=17.32 Hz, 1H, CH), 6.54-6.72(m, 3H, ArH), 6.86-6.90(t, 1H, ArH), 6.99-7.03(t, 1H, ArH), 7.20-7.22(t, 1H, ArH), 7.33-7.36(t, 1H, ArH), 8.05-8.13(t, J=29.44 Hz, 1H, NH). ¹³C NMR (100 MHz, CDCl₃): δ ppm, 22.71, 23.07, 23.52, 23.87, 24.21, 29.37, 29.71, 30.06, 30.08, 31.94, 50.26, 62.05, 62.48, 74.81, 75.14, 114.23, 114.31, 114.46, 114.54, 115.44, 115.55, 115.67, 115.78, 115.89, 116.11, 117.54, 117.60, 117.68, 122.69, 122.77, 123.20, 123.27, 129.82, 129.90, 130.16, 130.25, 131.95, 131.98, 132.37, 132.40, 148.06, 148.24, 156.10, 158.49, 162.07, 162.17, 164.55, 164.65, 169.19, 169.33, 169.47. MS: m/z = 390 [M]+; Anal. Calcd for C₁₉H₁₆F₂N₂O₃S: C, 58.45; H, 4.13; N, 7.18. Found: C, 58.02; H, 4.03; N, 7.10%.
Studies on nitrogen containing heterocyclic...

$N$-(2-(3-chlorophenyl)-4-oxothiazolidin-3-yl)-6-fluorochroman-2-carboxamide (9d).
mp 151-153°C; IR (DRS): 3401, 3284, 3074, 2987, 2851, 1717, 1645, 1612, 1585, 1468, 1352, 1278, 1184, 1066, 820, 754, 710, 636, 541 cm$^{-1}$; MS: $m/z = 406$ [M]$^+$; Anal. Calcd for C$_{19}$H$_{16}$ClFN$_2$O$_3$S: C, 56.09; H, 3.96; N, 6.89. Found: C, 55.90; H, 3.83; N, 6.83%.

$N$-(2-(4-bromophenyl)-4-oxothiazolidin-3-yl)-6-fluorochroman-2-carboxamide (9e).
mp 118-120 °C; IR (DRS): 3412, 3081, 2975, 2844, 1706, 1641, 1579, 1556, 1464, 1332, 1272, 1045, 831, 750, 592, 545 cm$^{-1}$; MS: $m/z = 452$ [M+1]$^+$; Anal. Calcd for C$_{19}$H$_{16}$BrFN$_2$O$_3$S: C, 50.56; H, 3.57; N, 6.21. Found: C, 50.45; H, 3.28; N, 6.11%.

6-Fluoro-$N$-(2-(4-hydroxyphenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide (9f).
mp 132-134°C; IR (DRS): 3564, 3442, 3080, 2983, 2867, 1705, 1629, 1572, 1525, 1462, 1374, 1245, 1196, 1074, 830, 748, 676 cm$^{-1}$; MS: $m/z = 388$ [M]$^+$; Anal. Calcd for C$_{19}$H$_{17}$FN$_2$O$_4$S: C, 58.75; H, 4.41; N, 7.21. Found: C, 58.56; H, 4.34; N, 7.06%.

6-Fluoro-$N$-(4-oxo-2-(p-tolyl)thiazolidin-3-yl)chroman-2-carboxamide (9g).
mp 89-91°C; IR (DRS): 3410, 3077, 2978, 2863, 1714, 1625, 1609, 1563, 1464, 1322, 1238, 1142, 1054, 870, 798, 675, 542 cm$^{-1}$; MS: $m/z = 386$ [M]$^+$; Anal. Calcd C$_{20}$H$_{19}$FN$_2$O$_3$S: C, 62.16; H, 4.96; N, 7.25. Found: C, 62.07; H, 4.55; N, 7.09%.

$N$-(2-(2-chlorophenyl)-4-oxothiazolidin-3-yl)-6-fluorochroman-2-carboxamide (9h).
mp 158-160°C; IR (DRS): 3391, 3113, 3054, 2962, 2854, 1702, 1603, 1545, 1542, 1452, 1302, 1260, 1146, 1078, 1021, 841, 798, 756, 674, 651, 531 cm$^{-1}$; MS: $m/z = 406$ [M]$^+$; Anal. Calcd for C$_{19}$H$_{16}$ClFN$_2$O$_3$S: C, 56.09; H, 3.96; N, 6.89. Found: C, 55.93; H, 3.77; N, 6.84%.

6-Fluoro-$N$-(2-(4-nitrophenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide (9i).
mp 207-209°C; IR (DRS): 3405, 3075, 2964, 2853, 1721, 1601, 1581, 1423, 1385, 1254, 1149, 1021, 878, 754, 720, 678, 531 cm$^{-1}$; MS: $m/z = 417$ [M]$^+$; Anal. Calcd for C$_{17}$H$_{14}$FN$_3$O$_2$: C, 54.67; H, 3.86; N, 10.07. Found: C, 54.39; H, 3.79; N, 9.89%.

$N$-(2-(3-bromophenyl)-4-oxothiazolidin-3-yl)-6-fluorochroman-2-carboxamide (9j).

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IR Spectrum of 6-Fluoro-N-(2-(2-nitrophenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide(9b).

IR Spectrum of 6-Fluoro-N-(2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide(9c).
Studies on nitrogen containing heterocyclic...

Mass spectrum of 6-Fluoro-N-(2-(2-nitrophenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide(9b).

Mass spectrum of 6-Fluoro-N-(2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide(9c).
$^1$H NMR spectrum of 6-Fluoro-N-(2-(2-nitrophenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide (9b).

D$_2$O Exchange $^1$H NMR spectrum of 6-Fluoro-N-(2-(2-nitrophenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide (9b).
$^1$H NMR spectrum of 6-Fluoro-N-(2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide (9c).

Expanded spectrum of 6-Fluoro-N-(2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide (9c).
Studies on nitrogen containing heterocyclic...

Expanded spectrum of 6-Fluoro-N-(2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide(9c).

\[
\text{O} \quad \text{F} \quad \text{O} \quad \text{NHN S} \quad \text{N} \quad \text{+} \quad \text{O} \quad \text{O}
\]

\[ ^{13} \text{C NMR spectrum of 6-Fluoro-N-(2-(2-nitrophenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide(9b).} \]

Thiazolidinone derivatives...
$^{13}$C NMR spectrum of 6-Fluoro-N-(2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide(9c).
Table-9b: Antimicrobial activity of 6-Fluoro-N-(4-oxo-2-arylthiazolidin-3-yl) chroman-2-carboxamides.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Antibacterial Activity</th>
<th>Antifungal activity</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Gram +ve Bacteria</td>
<td>Gram -ve Bacteria</td>
</tr>
<tr>
<td></td>
<td>Minimal bactericidal concentration μg/ml</td>
<td>Minimal fungicidal concentration μg/ml</td>
</tr>
<tr>
<td></td>
<td>S.aureus</td>
<td>S.pyogenus</td>
</tr>
<tr>
<td>9a</td>
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</tr>
<tr>
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<td>9i</td>
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<td>250</td>
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<tr>
<td>9j</td>
<td>200</td>
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</table>

MINIMAL INHIBITION CONCENTRATION

<table>
<thead>
<tr>
<th>Standard Drugs</th>
<th>S.aureus (microgramme/ml)</th>
<th>S.pyogenus (microgramme/ml)</th>
<th>E.coli (microgramme/ml)</th>
<th>P.aeruginosa (microgramme/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamycin</td>
<td>0.25</td>
<td>0.5</td>
<td>0.05</td>
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<tr>
<td>Ampicillin</td>
<td>250</td>
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<td>100</td>
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<tr>
<td>Chloramphenicol</td>
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<td>50</td>
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<tr>
<td>Ciprofloxacin</td>
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<td>25</td>
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<tr>
<td>Norfloxacin</td>
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<td>10</td>
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</table>

MINIMAL FUNGICIDAL CONCENTRATION

<table>
<thead>
<tr>
<th>Standard Drugs</th>
<th>C.albicans (microgramme/ml)</th>
<th>A.niger (microgramme/ml)</th>
<th>A.clavatus (microgramme/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nystatin</td>
<td>100</td>
<td>100</td>
<td>100</td>
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<tr>
<td>Greseofulvin</td>
<td>500</td>
<td>100</td>
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</table>
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REFERENCES

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*Thiazolidinone derivatives...*


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