PART - III
Abstract

Part III presents the synthesis of new azetidin-2-ones and thiazolidin-4-ones, each possessing thiazolyl and chromonyl moieties and were synthesized using 2,4-disubstituted-5-carboethoxy thiazoles as a starting reactants. This part also narrates one pot environmental friendly synthetic method, developed to synthesise important fused heterocycles, 2,3-disubstituted-1,4-benzothiazines. The work presented in this part is described in four sections.

Section IIIA gives the details of one pot synthetic route, used to obtain excellent yields of 2-aryl-4-methyl-thiazol-5-yl-acid hydrazides (Fig. IIIA).

The condensation of the acid hydrazides and formyl chromones have been carried for getting $N^1-(4'\text{-methyl-2'-aryl-thiazolo-5'\text{-yl})-N^2-(6'\text{-substituted chromon-3'-ylidene})$ hydrazines (Schiffbases, Fig. IIIB) and the work is presented in the section IIIB.

The Schiffbases (IIIB) have been separately condensed with chloroacetyl chloride and thioglycollic acid to obtain the title compounds, 1-(2'-aryl-4'-methyl-thiazolo-5'-yl-amino)-3-chloro-4-(6'-substituted chromon-3'-yl)-azetidin-2-ones (Fig. IIIC1) and 2-(6'-substituted chromon-3'-yl)-3-(2'-aryl-4'-methyl thiazolo-5'-yl amino) thiazolidine-4-ones (Fig. IIIC2) and the work is incorporated in Section IIIC.

The Section IIID deals with the new one pot synthetic strategy developed to obtain 2,3-disubstituted-1,4-benzothiazines (Fig. IIID) by allowing the condensation of acetyl acetone/ethyl acetoacetate and 2-amino benzenethiols.
Synthesis of bridgehead or fused heterocycles

Fig. IIIA

Fig. IIIB

Fig. IIIC₁

Fig. IIIC₂

Fig. IIID
SECTION-III A

Synthesis of
2-aryl-4-methyl thiazol-5-yl acid
hydrazides
Thiazole derivatives exhibit a wide spectrum of biological activities. The utility of thiazoles as medicaments is firmly established. Some of the significant applications, displayed by thiazoles have been narrated in the introductory part. During past years considerable evidences have been accumulated to demonstrate the efficacy of the thiazoles bearing heteryl, amino, thiocarbamido and sulphonamido pharmacophores\(^1\).

2-Aminothiazoles constitute an important class of bioactive compounds. Their chemistry and biological potencies have widely investigated and extensively reviewed\(^2\textsuperscript{-5}\). The compounds bearing pharmacophoric group, hydrazino carbonyl (Fig. I) has been reported to be responsible for antibacterial\(^6\), antifungal\(^7\) and anticonvulsant\(^8\) activities.

![Fig. I](image_url)

On the other hand hydrazides/hydrazones\(^9,10\) are known to be responsible for wide variety of pharmacological effects. Isoniazid\(^11\) (INH), an nicotinyl acid hydrazide is clinically used as antitubercular drug.

![Isoniazid (INH)](image_url)

However a little work is reported on the synthesis of substituted thiazoles having ethoxy carbonyl and hydrazino carbonyl moieties at the five position of the thiazoles\(^12\). Compounds bearing functional groups like carboethoxy (ethoxy carbonyl), carbonyl, hydrazino carbonyl, hydrazido thiocarbamido and amino have significant synthetic importance as they are the potential precursors for the preparation of variety of biodynamic heterocyclic compounds.
As a part of the search in heterocycles that have been explored for developing pharmaceutically important molecules, fused heterocycles bearing thiazole have played an important role in medicinal chemistry\textsuperscript{13,14}.

In view of the high incidence of desirable pharmacological properties associated with thiazoles and considering the significance of reactive functional groups like hydrazide/hyrazino, it appeared of interest to design one pot synthetic strategy to obtain the thiazoles bearing hydrazide/hyrazino group so as to utilize them in getting the new fused heterocycles having thiazolyl moiety.

**Present work and method:**

In the present work attempts have been made to synthesise 2,4-disubstituted thiazol-5-yl-acid hydrazides.

The widely used methods for obtaining thiazoles are Hantzsch and Dodson-King.

1) **Hantzsch Method:**

In this method $\alpha$-haloketones and thioamides/thiocarbamides are condensed to obtain thiazoles\textsuperscript{15,16}. The drawback of Hantzsch synthesis is handling of lachrymatory haloketones. Recently several workers have modified the conventional Hantzsch method by performing condensation of ketones bearing $\alpha$-hydrogen with thioamides/thiocarbamides in the presence of safer halogenating agents like polymer supported pyridinium trihalide\textsuperscript{17}, NBS\textsuperscript{18}, HTID\textsuperscript{19}, IBD\textsuperscript{20} and polymer supported reagents\textsuperscript{20}.

2) **King and Dodson Method:**

King and Dodson have reported the condensation of ketones (bearing $\alpha$-hydrogen) and thioureas/thioamides, carried in presence of molecular iodine to obtain the cyclised products, thiazoles\textsuperscript{21,22}. The use of sulfuryl chloride\textsuperscript{23} in place of iodine for carrying the condensation has been reported. This cyclocondensation has several drawbacks, as this is time consuming and use to give comparatively poor yields of the thiazoles.
3) **Thiazoles from 2-thiocyanoketones:**

The rearrangement of 2-thiocyanoketones$^{24}$ is very rarely used method for the thiazole synthesis. This method has limited scope as it gives low yields.

In the present work the desired thiazole acid hydrazides have been synthesised using thioamides and ethyl-1-acyl-1-chloro-acetate$^{25}$. This condensation was attempted by following the conventional Hantzsch procedure and thus obtained 5-ethoxy carbonyl (carboethoxy) thiazoles, were then successfully condensed with hydrazine hydrate to get the required 2,4-disubstituted thiazol-5-yl-acid hydrazides. The Hantzsch procedure was employed as it gave unambiguous products, and the reaction conditions required for this method were found to be moderate. The condensation of ethoxy carbonyl thiazoles and hydrazine hydrate was carried out by using well-documented procedure to obtain the thiazolyl acid hydrazides.

Attempts were also made to obtain the desired thiazolyl acid hydrazides with quantitative yields by developing one pot synthetic strategy. In this strategy the ethyl-1-acyl-1-chloro acetate (3.01) and thioamides were condensed and without isolating the condensation products, (2-aryl-4-Me-5-ethoxy carbonyl thiazole hydrochlorides (3.02) the condensates were successively treated with stoichiometric excess of hydrazine hydrate, so as to get 2,4 disubstituted thiazolo-5-yl-acid hydrazides (3.03) with excellent yields (Scheme IIIA).

Where, $R =$ Phenyl, 4-methylphenyl, 4-methoxyphenyl, 4-chlorophenyl

**Scheme IIIA**
Experimental:

Synthesis of 4-methyl-2-methylphenyl thiazolo-5-yl acid hydrazide

A) Batch Procedure:

A mixture of ethyl-1-acyl-1-chloro acetate (0.01 mole) and 4-methyl thiobenzamide (0.01 mole) in ethanol (40ml) was refluxed for 4 hr. Ethanol was then removed under reduced pressure. The residue was diluted with cold water and neutralised with ammonia. Thus obtained 4-methyl-2-methylphenyl-5-carboxthio thiazole was extracted with chloroform, dried over calcium chloride and chloroform was distilled under reduced pressure. The residue was crystallised from ethanol, [3.02(A), b] mp =118°C, yield 71%.

Similarly other thiazoles were prepared, the physical data is as follows, [3.02(A), a] (R = phenyl), mp = 55°C, yield 78 %; [3.02(A), c] (R = 4-methoxy phenyl), mp = 80°C, yield 72 % and [3.02(A); d] (R = 4-chlorophenyl), mp = 72°C yield 70 %.

Then the thiazole (0.01 mole) and hydrazine hydrate (0.03 mole) were dissolved in ethanol (25 ml) and the reaction solution was refluxed for 6 hr. It was then cooled to room temperature, the solid appeared was filtered, washed with cold ethanol and crystallised from ethanol, 3.03 b, mp = 158°C, yield 65 %

b) One pot method:

The following one pot procedure was employed to obtain the acid hydrazides with better yields.

A mixture of ethyl-1-acyl-1-chloro acetate (0.01 mole) and 4-methyl thiobenzamide (0.01 mole) in ethanol (50 ml) was refluxed for 4 hr. Then the reaction mixture was cooled to room temperature and to this solution hydrazine hydrate (0.08 mole) was added and the reaction mixture was further heated under reflux for 6 hr. It was then cooled to room temperature, the solid appeared was filtered, washed with cold ethanol and crystallised from ethanol, mp = 158°C, yield 75 %. Similarly the other compounds of the series were prepared by following one pot method, 3.03 a (R = phenyl), mp = 167°C yield 80 %, 3.03 c (R = 4-methoxy phenyl), mp = 180°C, yield 78 % and 3.03 d, (R = 4-chlorophenyl), mp = 230°C yield 76 %.
Spectral discussion:

Following is a data of IR and $^1$HNMR spectra of a representative compound, 2-(4'-methyl phenyl)-4-methyl-5-carbethoxy thiazole of the series.

**IR (KBr cm$^{-1}$):** 3060 (CH, aromatic stretching), 2939-2909 (CH, aliphatic, asymmetric and symmetric stretchings, respectively), 1708 (C=O, ester carbonyl stretching) 1606 (C=C and C=N stretching), 1264 (COC stretching) and characteristics absorption of thiazole ring (Spectrum No. 3.01).

$^1$HNMR (CDCl$_3$): 1.35-1.40 (t, 3H, CH$_2$CH$_3$, methyl protons, J = 8 Hz), 2.38 (s, 3H, CH$_3$), 2.74 (s, 3H, CH$_3$), 4.28-4.35 (q, 2H, CH$_2$CH$_3$, methylene protons, J = 8Hz), 7.18-7.26 (d, 2H, J = 8 Hz, 1,4-disubstituted benzene splitting pattern), 7.80-7.83 (d, 2H, J = 8 Hz) (Spectrum No. 3.02).

The results of IR and $^1$HNMR scannings of 4-methyl-2-phenyl thiazolo-5-yl acid hydrazide (as a representative compound of the series) are presented below.

**IR (KBr cm$^{-1}$):** 3279 and 3204 (-NH asymmetric and symmetric stretchings, respectively), 3045 (CH, aromatic stretching), 2986 and 2916 (CH, aliphatic asymmetric and symmetric stretchings, respectively), 1695 (C=O stretching, CONHNH$_2$), 1625 (C=C aromatic and C=N stretchings) and characteristic absorptions of thiazole nucleus (Spectrum No. 3.03).

$^1$HNMR (CDCl$_3$ + DMSO$_d$_6): 2.63 (s, 3H, CH$_3$), 4.15 (s, 2H, NH$_2$, exchangeable with D$_2$O), 7.48-7.93 (m, 5H, Ar-H) and 8.89 (s, 1H, NH exchangeable with D$_2$O) (Spectrum No. 3.04).
SECTION-IIIIB

Synthesis of

$N^1$-(4′-methyl-2′-aryl thiazolo-5′-yl)$-N^2$-
(6′-substituted chromon-3′-ylidene)
hydrazines (Schiff bases)
The nitrogen analogues of ketones and aldehydes are called imines, azomethines or Schiff bases. Imine is the preferred name and imines are the condensation products of primary amines and carbonyl compounds. Imines are also called Schiff bases, especially when the amine is aniline derivative. The imine is much more basic than carbonyl compound, It is more extensively protonated at any given pH than is the aldehyde. The protonated imine is much more reactive as an electrophile than the neutral aldehyde. The protonated imine is the dominant reactive form and therefore is gaining synthetic importance and imines are therefore widely used as precursors for synthesizing bioactive heterocycles like thiazolidinones, azetidinones etc. Imines are often not very stable, yet they may be important intermediate in some reactions. A class of reactions of synthetic values are reductive amination of imines and conversion of primary to secondary or tertiary amines.

Literature reveals that considerable attention has been paid on the kinetics of oxidation, reduction and hydrolysis of imines. The use of imines as analytical reagents has been well explored. The Schiff bases are being important class of ligands, a large number of papers have appeared on the syntheses, characterisation and applications of metal complexes of the Schiff bases. Some of the metal complexes, of the Schiff bases have shown a remarkable pharmacological applications. Schiff base complexes have been suggested as models for enzymes such as galactose oxidase.

Schiff bases are well known for their pronounced biological activities. Their ready synthesis and myride properties have contributed greatly to their popularity to study various aspects of biological systems. A series of inert azo compounds containing nitrogen mustard moiety have been synthesised and are found to be active against Walker rat carcinoma 256. As isoster of the azo mustards a large number of Schiff bases have been prepared and tested against Dunning leukaemia in rats. Modi et al. have prepared some Schiff base mustards and screened them for antitumour activity. Many of the compounds have displayed significant activity against L1210 Lymphoid leukaemia, Walker 256 (intramuscular) and Dunning leukaemia. Schiff bases
without having alkylating nitrogen mustard moiety have been also synthesised and 4-hexyl-6-(2-hydroxy-phenyl-5-imino-methyl) resorcinol has shown activity against Ehrlich ascites carcinoma, Sarcoma 180 and Yashida sarcoma. From these and related observations it has been concluded that an azomethine linkage is perhaps an essential structural requirement for these activities.

An azomethine linkage has also played an important role in some biological reactions. Imines (Schiff bases) bearing heteryl moieties like thaidaizoly1, triazoly1, thiazoly1, thiaphenyl1, coumarinyl1, quinolinyl1 etc have displayed wide biological activities. Mazumdar et al.1 have recently reported some biologically active thiazoyl Schiff bases. Some phenothiazinyl Schiff bases are found to exhibit antimicrobial activities against Bacillus subtilis and Pseudomonas aeruginosa. Mahajan et al.13 have reported some Schiff bases from 2-amino thiazoles. Marvankar et al.14 have synthesised biologically active Schiff bases from 4-(4'-aminoophenyl)-thiazoles.

Oxygen containing fused heterocycles like chromones are found exclusively in the plant kingdom and have displayed a variety of biological activities. Khellin an important furochromone, isolated from fruits and seeds of ammivisnaga has been used for the treatment of bronchial asthma. The use of chromones as antiviral, analgesic, antiallergic, antiplatelet, antihypertensive and antispasmodic agents is well recognized.

The significant biological and synthetic importance associated with the imines, thiazoles (discussed in earlier sections) and chromones has aroused considerable interest to design the synthesis of azomethines bearing bioactive pharmacophores like thiazoles and fused moieties like chromones so as to get the molecules with intensified biological activities and to use them as synthetic precursors for getting new thiazolidinones and azetidinones.
Present work and method:

Literature reveals that primary, secondary and tertiary amines can add to aldehydes\textsuperscript{53} and ketones to give different kind of products. Primary amine gives imines\textsuperscript{54}. In contrast to imines in which the nitrogen is attached to hydrogen, these imines are stable enough for isolation. However in some cases especially with simple ‘R’ groups they rapidly decompose or polymerise unless there is at least one aryl group on the nitrogen or carbon. When there is an aryl group compounds are quite stable and the reaction is straightforward and proceeds in high yields. The initial N-substituted hemiaminals\textsuperscript{55} lose water to give the stable Schiff bases.

\[
\begin{align*}
\text{R} & \text{O} + \text{R'}\text{NH}_2 \rightarrow \text{R} \text{NH}_2 \text{R'} \quad \text{H}_2\text{O} \rightarrow \text{R} \text{NH}_2 \text{R'}
\end{align*}
\]

In general ketone reacts more slowly than aldehydes and higher temperatures and longer reaction time are often required\textsuperscript{56}. In addition the equilibrium must often be shifted usually by removal of water either azeotropically by distillation or with a drying agents such as TiCl\textsubscript{4}\textsuperscript{57}, or molecular sieves\textsuperscript{58}.

The preparation of imines in vitro becomes progressively more difficult as one passes from aldehydes to ketones and one employs aromatic, rather than aliphatic amines\textsuperscript{59}, Scientist Schiff showed that aldimine formation from aromatic amines is base catalysed\textsuperscript{60}. For the most difficult case, ketoimines bearing two or more aromatic groups, Reddelien found that a combination of proton and Lewis acid (ArNH\textsubscript{2}-HCl-ZnCl\textsubscript{2}) proved to be an effective iminating catalyst\textsuperscript{61}. The use of acidic or basic catalysts, coupled with the slower rates of ketoiminations, can lead to extensive side reactions. Therefore Eisch et al\textsuperscript{62} have synthesised bis dichloroaryl imides as potent iminating agents and are successfully used for the imination of carbonyl groups of aldehydes, ketones and \(\alpha, \beta\)-unsaturated carbonyls. Ketoimines have been prepared by the azeotrophic dehydration of aryl methyl ketones and anilines in toluene at reflux temperatures\textsuperscript{64}.
The use of alkyl amino-boranes has been explored to obtain ketoimines\textsuperscript{65}. Joshi \textit{et al}\textsuperscript{66} have reported the synthesis of ketomines by carrying condensation of aromatic primary amines and aromatic ketones in presence of anhydrous ZnCl\textsubscript{2} at 160\textdegree{}C.

Mazumdar \textit{et al}\textsuperscript{39} and Mahapatra\textsuperscript{67} and his co-workers have reported the synthesis of imines by performing the condensation of aryl aldehydes and amino thiazoles in refluxing alcohol in presence of catalytical amount of piperidine.

In the present work the imines have been synthesised by carrying the condensation of 3-formyl chromones and thiazole acid hydrazides in refluxing alcohol.

This method was employed because

i. It required moderate reaction conditions and was found to furnish the products in good yields.

ii. The starting amino compounds, thiazole acid hydrazides required were available (synthesis is given in the earlier section).

The formyl chromones required for the condensation were synthesised by following the literature procedure\textsuperscript{68,69}. The purity of the imines i.e. N\textsuperscript{1}-\textit{(4'-methyl-2'-aryl-thiazolo-5'-yl)}-N\textsuperscript{2}-\textit{(6'-substituted chromon-3'-ylidene)} hydrazines was checked by TLC and the structures were confirmed on the basis of their elemental and spectral analysis. The condensation course is depicted in Scheme IIIB and the characterisation data of the imines are presented in Table 3.1.

![Scheme IIIB](image)

Where, \( R = \) Phenyl, 4-methylphenyl, 4-methoxyphenyl, 4-chlorophenyl and \( R' = H, Me, Cl, Br \)

\[ \text{Scheme IIIB} \]
Synthesis of bridgehead or fused heterocycles

Experimental:

Synthesis of N¹-[4’-methyl-2’-(4”-methyl phenyl)-thiazolo-5’-yl]-N²-(6’-methyl chromon-3’-ylidene) hydrazine:

A mixture of 6-methyl-3-formyl chromone (0.01 mole) and 4-methyl-2-(4’-methylphenyl)-thiazol-5-yl-acid hydrazide (3.03 b), (0.01 mole) in dry ethanol (50 ml) was refluxed for 3 hr. Then the reaction mixture was cooled to room temperature. The solid obtained was filtered, washed with cold ethanol and crystallised from ethanol-dioxane mixture, mp = 240°C, yield= 82%. Similarly the other compounds of the series were obtained by following the above procedure.

Spectral discussion:

Following is a data of IR and ¹HNMR spectra of a representative compound, N¹-(4’-methyl-2’-(4’-methyl phenyl)-thiazolo-5’-yl)-N²-(6’-methyl chromon-3’-ylidene) hydrazine of the series.

IR (KBr, cm⁻¹): 3196 (-NH stretching), 3122 (CH, aromatic stretching), 2980 and 2916 (CH, aliphatic, asymmetric and symmetric stretchings, respectively), 1654 (C=O stretching), 1621 (C=N and/or C=C stretching), 1214 (C-O-C stretching) and characteristic absorptions of thiazole ring, (Spectrum No. 3.05).

¹HNMR (CDCl₃): 2.42 (s, 3H, CH₃ᵇ), 2.49 (s, 3H, CH₃ᵇ), 2.79 (s, 3H, CH₃ᵇ), 7.25-8.60 (m, 9H, eight aromatic protons and one -CH=N- proton) and 11.59 (s, 1H, NH, exchangeable with D₂O) (Spectrum No. 3.06).
Spectrum No. 3.06 (D<sub>2</sub>O exchange)
Table 3.1: $N^1$-(4'-methyl-2'-aryl thiazolo-5'-yl)-$N^2$-(6'-substituted chromon-3'-ylidene)-hydrazines (Schiff bases).

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SECTION-IIIC

Synthesis of

1-(2'-aryl-4'-methyl-thiazolo-5'-yl-yl-amino)-
3-chloro-4-(6'-substituted chromon-3'-yl)
azetidin-2-ones and 2-(6'-substituted
chromon-3'-yl)-3-(2'-aryl-4'-methyl-
thiazolo-5'-ylamino) thiazolidin-4-ones
The β-lactam drugs\textsuperscript{70} (azetidinone derivatives) are still the most prescribed antibiotics used in medicines. Penicillins and Cephalosporins represent two important classes of antibiotics having β-lactam ring fused to thiazolidine and to thiazine, respectively. The most of the clinically\textsuperscript{71} used β-lactam antibiotics appear to be side chain analogs of penicillin and Cephalosporin. A large number of such analogs have been in the use but in the recent years the bacterial resistance to the antibiotics is found to be increasing at an alarming rate due to their overuse. As a result successful treatment of bacterial infection is threatened. In order to overcome this problem there is an ever-growing need to synthesise a new series of antibiotics bearing β-lactam moiety.

Thienamycin, an early carbapenem reported by Merck Research group\textsuperscript{72} has exhibited an unusually broad spectrum of antibacterial activity\textsuperscript{73}.

\begin{center}
\includegraphics[scale=0.5]{thienamycin.png}
\end{center}

Thienamycin

Recently 2-azetidinones have been assessed for antiparkinson\textsuperscript{74}, anti-inflammatory\textsuperscript{75} and herbicidal\textsuperscript{76} activities. They also function as enzyme inhibitors and are effective on central nervous system\textsuperscript{77}.

4-Oxo-1,3-thiazolidine and 2-oxo-azetidines have been extensively investigated by medicinal chemists due to their close association with biological activities, such as analgesic\textsuperscript{78}, sedative\textsuperscript{79}, antifungal\textsuperscript{80}, anti-convulsant\textsuperscript{81}, CNS depressant\textsuperscript{82} and anti-inflammatory\textsuperscript{83}. In recent past these derivatives are also found to be active against several cellines of cancer and HIV\textsuperscript{84}.

2-Azetidinones are also associated with pharmacological activities viz hypnotic, antiviral, anti-convulsant and anaesthetic\textsuperscript{85,86}. Syntheses of 4-thiazolidinones and 2-azetidinones bearing naphthyridynyl moiety are gaining importance as these compounds are endowed with pharmacological activities\textsuperscript{87}.

55
Heteryl $\beta$-lactams have received considerable attention as a potent antibacterial, antiparkinson, diuretic, herbicidal, CNS active, anti-inflammatory and hypocholesterolmic agents\(^{48}\).

Azetidinones with biodynamic heteryl moieties like thiazolyl\(^{89}\), phenothiazinyl\(^{90}\), indolyl\(^{91}\) and thiadiazolyl\(^{92}\) have been synthesised and their pharmacological activities are investigated.

Stereo controlled synthesis of nonfused monocyclic $\beta$-lactams continues to be fascinating area of crucial importance in the field of $\beta$-lactam antibiotics. Chiral 3-hydroxy azetidin-2-ones are useful synths for different antibiotics\(^{93}\) as well as $\alpha$-hydroxy-$\beta$-amino acid\(^{94}\) derivatives, which occur in many biologically active compounds such as taxol\(^{95}\), the promising anticancer drug. Some monocyclic $\beta$-lactams, L-680, 833 and L-694, 458 having aryl-etheral moiety at C\(_4\) have proved to possess human leucocytes elastase (HLE) specificity\(^{96}\).

![Chemical structures](image)

Spiro azetidinones and spirothiazolidinones incorporated with quinazoline\(^{97}\) have recently synthesised.

It seems that considerable attention has been directed on the synthesis of azetidinones and thiazolidinones having bioactive heterocyclic moieties either in isolated or in fused form. There is scanty information on the synthesis of azetidinones and thiazolidinones each bearing thiazole and oxygen containing fused heterocyclic groups like chromone.

The biodynamic properties of these ring systems (The pharmacological significance of thiazoles, thiazolidinones and chromones has been already described in the earlier section of this work) have prompted to design new azetidinones and thiazolidinones bearing thiazolyl and chromonyl moieties with the hope to obtain biologically active derivatives.
Present work and method:

The present work deals with the synthesis of 1-(2'-aryl-4'-methyl-thiazolo-5'-yl-amino)-3-chloro-4-(6'-substituted chromon-3'-yl)-azetidin-2-ones and 2-(6'-substituted chromon-3'-yl)-3-(2'-aryl-4'-methyl-thiazolo-5'-yl-amino)-thiazolidin-4-ones.

These azetidinones and thiazolidinones were obtained using N1-(4'-methyl-2'-aryl-thiazolo-5'-yl)-N2-(6'-substituted chromon-3'-ylidene) hydrazines (Schiff bases, described in earlier section, IIIB) as the starting reactants.

a) Method for the synthesis of 4-thiazolidinones:

Various methods used for the synthesis of thiazolidinone derivatives are narrated in Section IIC of this work. In the present work the cyclocondensation of the Schiff bases and thioglycolic acid have been carried under microwave irradiation to obtain desired 4-thiazolidinones. This synthetic strategy has been used because of the following advantages.

1. The Schiff bases used in the work were newly synthesized and were readily available.
2. The time required for the condensation under microwave irradiation was so reduced that the condensation was found to complete within 5 minutes at 450W.
3. The products obtained by this strategy were pure and the products yields were better.

b) Methods for the synthesis of 2-azetidinones:

β-Lactams, 2-azetidinones have been prepared usually by following methods

1. The cyclocondensation of ketene azomethines and olefin isocyanates yields β-lactams.
2. Dehydrochlorinative cyclisation of n-substituted 3-halopropamide has been employed to obtain the β-lactams.
3. The discovery of non-classical β-lactams antibiotics has attracted considerable attention of synthetic chemists to explore and to develop new mild and better yielding synthetic route to obtain azetidinones. Recently
Reddy et al\textsuperscript{88} have reported synthesis of 4-quinozolinonyl \( \beta \)-lactams from easily accessible n-chloro acetyl acrylamino methyl quinazolinones.

4. In recent years various phosphorylating agents have been used to activate the carboxylic group of substituted acetic acids so as to have its cyclocondensation with imines to yield azetidin-2-ones. Handrikson et al\textsuperscript{98} have reported that diphosphonium trifluoromethane sulphonate is capable of activating oxygen of substituted acetic acid to effect its removal in an isohypric manner from activated organic molecule to have effective condensation with imines to obtain azetidinones. Using this strategy Bari\textsuperscript{99} et al have synthesised azetidinones in the presence of catalytic amount of triethyl amine.

5. The most widely used synthetic procedure to obtain 3-halo-2-azetidinone is by carrying condensation of imines and chloroacetyl chloride in the presence of tertiary amines\textsuperscript{100}. The use of microwave irradiation\textsuperscript{101} for the condensation of azomethines/hydrazone and chloroacetyl chloride to obtain 3-chloro azetidinones has been of recent origin.

The title azetidinones have been synthesised by allowing the condensation of \( N^1-(4^*\text{-methyl}-2^*\text{-aryl-thiazolo-5-yl})-N^2-(6^*\text{-substituted chromon-3^*-ylidene}) \) hydrazines (Schiff bases) and chloroacetyl chloride in presence of triethyl amine under microwave irradiation. This synthetic route was adopted because,
1. Ready availability of starting Schiff bases.
2. The route was relatively rapid, only five minutes are required for the condensation while conventional heating could partly perform the condensation even after 5-6 hours heating and the isolation of the products was nontedious and nonambiguous (Scheme IIIC).
Experimental:

1. Synthesis of 2-(6'-methyl-chromon-3'-yl)-3-[2'-(4''-methyl phenyl)-4'-methyl-thiazolo-5'-yl-amino]-thiazolidin-4-one:

A mixture N\(^1\)-[4''-methyl-2'-(4''-methyl phenyl) thiazolo-5'-yl]-N\(^2\)-(6'-methyl chromon-3'-ylidene) hydrazine (0.01 mole) and thioglycolic acid (0.015 mole) in dioxane was subjected to microwave irradiation at 450 W for 5 min. The reaction mass was then cooled and to this cold mass, water was added. Then thus obtained solid was filtered, washed with sodium bicarbonate solution and finally with water. The crude was crystallised from ethanol. The purity of the product was checked by TLC. The other compounds of the series were prepared by following the above procedure. The physical data of the compounds are recorded in Table 3.2.

Spectral Discussion:

The IR and \(^1\)HNMR spectra if a representative compound, 2-(6'-methyl-chromon-3'-yl)-3-[2'-(4''-methylphenyl)-4'-methyl-thiazolo-5'-yl-amino]-thiazolidin-4-one of the series is presented below.

**IR (KBr, cm\(^{-1}\))**: 3391 (-NH stretching), 3192 (CH, aromatic stretching), 2922 (CH, aliphatic stretching), 1691 (C=O stretching, tertiary amido), 1647 (C=O stretching of chromone ring), 1230 (C-O-C stretching), 669 (C-S-C stretching) and characteristic absorption of thiazole and benzenoid ring system (Spectrum No. 3.07).

**\(^1\)HNMR (CDCl\(_3\))**: 2.30 (s, 3H, CH\(_3^a\)), 2.43 (s, 3H, CH\(_3^b\)), 2.57 (s, 3H, CH\(_3^c\)), 3.73 (s, 2H, -S-CH\(_2\)-C=O), 5.93 (s, 1H, -S-CH\(_3\)), 7.26-8.14 (m, 9H, eight aromatic protons and one proton of CHCl\(_3\)) and no signal due to NH proton up to 8.55 (Spectrum No. 3.08).
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2. Synthesis of 1-(2'-(4''-methyl phenyl)-4'-methyl thiazolo-5'-yl-amino)-3-chloro-4-(6'-methyl chromon-3'-yl)-azetidin-2-one:

A mixture of N^1-[4'-methyl-2'-(4''-methylphenyl)-thiazolo-5'-yl]-N^2-(6'-methyl chromon-3'-ylidene) hydrazine (0.01 mole) and triethylamine (0.012 mole) in dioxane (10 ml) was stirred at room temperature. To this reaction mass chloroacetyl chloride (0.012 mole) was added. Then the reaction mixture was exposed at 150 W to microwave irradiation for about 5 min. The reaction mass was then cooled and poured on ice cold water. The solid obtained after filtration was washed with water and crystallised from ethanol. Similarly the other compounds of the series were prepared by following the above procedure. The physical data of the compounds are incorporated in Table 3.3.

Spectral discussion:

The results of IR, ^1HNMR and MASS scannings of 1-[2'-(4''-methyl phenyl)-4'-methyl thiazolo-5'-yl-amino]-3-chloro-4-(6'-methyl chromon-3'-yl)-azetidin-2-one as a representative compound of the series are presented below.

IR (KBr, cm^{-1}): 3424 (-NH stretching), 3123 (CH, aromatic stretching), 2924 (CH, aliphatic stretching), 1724 (C=O, β-lactam ring), 1628 C=N, C=C stretchings), 1331 (C-N stretching), 1205 (C-O-C stretching), 718 (-CH-Cl stretching) and 679 (-C-S-C stretching) (Spectrum No. 3.09).

^1HNMR (CDCl₃): 2.38 (s, 3H, CH₃a), 2.41 (s, 3H, CH₃b, the signal is merged in the earlier peak and difficult to diagnose), 2.49 (s, 3H, CH₃c), 4.15 (d, 1H, -N-CH, J=7.8Hz), 4.99 (d, 1H, CH-Cl, J=7.8 Hz), 6.83-8.12 (m, 8H, aromatic protons), 10.92 (bs, 1H, NH exchangeable with D₂O) (Spectrum No. 3.10).

MASS, m/z (% intensity): 445 (27.5), 368 (2.0), 286 (10.9), 259 (12.0), 233 (23.8), 216 (40.3), 202 (29.7), 186 (9.0), 156 (12.3), 134 (base peak, 100), 118 (17.9), 95 (24.4) and 83 (26.3). The expected molecular ion peak at m/z 493 was not observed as being unstable at the scanning conditions i.e at 70 ev (Spectrum No. 3.11).
Spectrum No. 3.11
Table 3.3: 1- (2'-Aryl-4'-methyl-thiazolo-5'-ylamino)-3-chloro-4-(6'-substituted chromon-3'-yl)-azetidin-2-ones

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<td>Bromo</td>
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<td>53</td>
<td>C₂₃H₁₄N₃O₄S₂Cl₂Br</td>
<td>579</td>
<td>7.09</td>
<td>7.25</td>
<td>5.12</td>
<td>5.22</td>
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</table>
SECTION-IIID

Synthesis of

2,3-disubstituted-1,4-benzothiazines
1,4-Benzothiazines resemble structurally with phenothiazines, well
established anti-psychotic drugs\textsuperscript{102,103}, in having a fold along the nitrogen sulfur
axis and can be anticipated to pass biological activities like phenothiazines.
The synthetic, chemical, physical, spectral and biological aspects of 1,4-
benzothiazines are well reviewed\textsuperscript{104}. The basic unit present in mammalian red
hair and feather is 1,4-benzothiazine nucleus\textsuperscript{105,106}. Luciferin and Rafamycin
vert are 1,4-benzothiazine derivatives, obtained by biosynthesis and are found
to possess immense pharmacological activities. 1,4-Benzothiazines are known
for their utility as dyestuff\textsuperscript{107}, photographic developers\textsuperscript{108}, ultraviolet light
absorber and antioxidant\textsuperscript{109}. Samotiadil, a derivative of 1,4-benzothiazines is
used as antihypertensive and antianginal drug\textsuperscript{110}. The efforts are directed now a
days to modify and to synthesise some new samotiadil derivatives to obtain the
products with enhanced antagonist activity. Pyrido and fluorinated 1,4-
benzothiazines are found to be inhibitors of mammalian topoisomerase-I and
malignant cell growth in mammals\textsuperscript{111}. The urea and nitrosourea derivatives of
1,4-benzothiazines are known to possess considerable antitumour activity\textsuperscript{112}.
Piperazinyl containing 1,4-benzothiazines have antihypertensive activity\textsuperscript{113}.
Some annulated 1,4-benzothiazines are found to be antimicrobial agents\textsuperscript{114}. The
1,1-dioxides of 1,4-benzothiazines with carbonyl function are antibacterial
agents\textsuperscript{115}. 1,4-Benzothiazines are found to possess antidiabetic\textsuperscript{116} antihypoxic\textsuperscript{117}
and diuretic properties\textsuperscript{118}. The use of 1,4-benzothiazines to reduce obesity\textsuperscript{119} has
been reported by Reddy’s group. There are reports on the 1,4-benzothiazines
possessing antiallergic\textsuperscript{120}, anti-inflammatory\textsuperscript{121}, potassium channel opener\textsuperscript{122},
anti HIV\textsuperscript{123}, dopamine receptor\textsuperscript{124}, antirheumatic\textsuperscript{125}, antiparkinson\textsuperscript{126}
and calcium antagonist activities\textsuperscript{127}. 

\begin{center}
\includegraphics[width=0.5\textwidth]{samotiadil.png}
\end{center}

Samotiadil
Synthesis of bridgehead or fused heterocycles

Recently more attention has been directed towards the syntheses and therapeutic applications of the fused 1,4-benzothiazines like naptho\textsuperscript{127}, triazino\textsuperscript{128}, indene\textsuperscript{129}, imidazolo\textsuperscript{130}, pyrrolo\textsuperscript{131}, pyrimidino\textsuperscript{132} and thieno\textsuperscript{133}, 1,4-benzothiazines. Also there is considerable work on the syntheses of 1,4-benzothiazines possessing halogeno\textsuperscript{135}, nitro\textsuperscript{136}, carboxy\textsuperscript{137}, carboethoxy\textsuperscript{138}, sulphonamido and acyl substituents in benzenoid ring. Attempts are directed towards the reactions of hydrazine hydrate, hydroxyl amine\textsuperscript{137} and aryl/alkyl isothiocyanate on 1,4-benzothiazines.

Keeping the above-referred significance of the nucleus in view, we have been working on the synthesis of new 1,4-benzothiazines\textsuperscript{138-140} and on the development of ecofriendly synthetic strategy for synthesizing the nucleus. Therefore here in we report environmentally benign one pot synthetic procedure to obtain 1,4-benzothiazines.

Present work and method:

In continuation of our interest on the synthesis of new sulfur and or nitrogen-fused heterocycles, it has been decided to develop new environmentally benign, one pot synthetic procedure to obtain bioactive fused heterocycles like 1,4-benzothiazines.

Literature reveals that there are various synthetic routes to obtain 1,4-benzothiazines. The synthetic methods used to obtain 1,4-benzothiazines are recently reviewed\textsuperscript{104} and following is a brief resume of the literature methods.

1. The cyclocondensation of 2-amino benzene thiols when carried separately with reactants like, acetylinic nitrile monoesters\textsuperscript{141}, \(\alpha,\beta\)-unsaturated acids\textsuperscript{142}, anhydrides\textsuperscript{143}, esters\textsuperscript{142}, epoxides\textsuperscript{144}, 1,2-dichloro/dibromo ethane\textsuperscript{145} and \(\alpha\)-chloro acid chlorides\textsuperscript{146} has been found to yield corresponding 1,4-benzothiazines.

2. Reductive cyclisation of 2-nitro benzene thiols with compounds like unsaturated dicarboxylic acids, esters, anhydrides\textsuperscript{104} and \(\alpha\)-halo acids\textsuperscript{147} is another method to obtain respective 1,4-benzothiazines.
3. 2,3-Disubstituted-4H-1,4-benzothiazines have been synthesised by condensing 2-amino benzene thiols with α-cyanomethyl thioacetophenones\textsuperscript{148} in dimethyl sulfoxide at 110\textdegree C.

4. 1,4-Benzothiazines have been synthesised by allowing the condensation of 2-amino benzene thiol and phenacyl bromide\textsuperscript{149}.

5. The oxidative cyclisation of 2-amino benzene thiols and β-diketones in dimethyl sulfoxide medium gives 4H-1,4-benzothiazines\textsuperscript{150}. It is considered that this condensation may proceed via an enaminoketone intermediate, which afterwards successively cyclises to 1,4-benzothiazine by scission of sulfur-sulfur bond due to intramolecular nucleophilic attack.
Mostly 1,4-benzothiazines are prepared by the reaction of 2-amino benzene thiols with α-haloketones or α-haloesters and by oxidative cyclocondensation of 2-amino benzene thiols with 1,3-dicarbonyl compounds using dimethyl sulphoxide (DMSO). The former method requires use of lachrymatory α-haloketones or α-haloesters as one of the reactants and the product obtained are in low yields and as isomeric mixtures\(^\text{104}\). In the later method, the yields and purities of products are better but dimethyl sulphoxide, a dipolar, aprotic solvent with several unfavourable properties is necessary to act as both solvent and oxidant. These methods do therefore need to be improved.

In DMSO a two-step mechanism has been suggested for the oxidative cyclocondensation\(^\text{151}\) of 2-amino benzene thiols and 1,3-dicarboxyls. In the first step, 2-amino benzene thiols are oxidised to the corresponding disulfides by dimethyl sulfoxide followed by the condensation with 1,3-dicarboxyls to yield 1,4-benzothiazines.

A literature search reveals that thiols are easily oxidised to disulfides by using hydrogen peroxide\(^\text{152}\), DMSO-iodine\(^\text{153}\), bromine under phase transfer conditions\(^\text{154}\), thallium (III) acetate\(^\text{155}\), methoxythributyltin-FeCl\(_3\)\(^\text{156}\), sodium perborate\(^\text{157}\), NO and NO\(_2\)\(^\text{158}\) as oxidising agents. Even the oxygen in the air oxidised thiols on standing particularly if a small amount of base in present\(^\text{159}\). The mechanism of the base catalysed air oxidation of thiols has been reported\(^\text{159}\). Recently Iyengar \textit{et al}\(^\text{160}\) have reported an efficient and mild procedure for the conversion of thiols to disulfides using catalytical amount of hydrazine hydrate.

In the present work an attempt has been made to confirm the role of hydrazine hydrate in the oxidation of thiols. Therefore the thiols in the
presence of stoichiometric amount of hydrazine hydrate under an inert medium, nitrogen/argon were allowed to react. It was found that thiols on their own were unreactive under inert medium. However a mixture of thiols and hydrazine hydrate in the presence of air was found to give quantitative yield of the disulphide at room temperature. This conclude that hydrazine hydrate is therefore acting as a base catalyst.

![Chemical structure](image)

Where, \( R = H, \text{Cl}, \text{CH}_3, \text{OCH}_3 \),
\( R_1 = \text{CH}_3, \text{C}_6\text{H}_5, 4\text{-Me-C}_6\text{H}_4 \),
\( R_2 = \text{CH}_3, \text{C}_6\text{H}_5, \text{OCH}_3, \text{OC}_2\text{H}_5, 4\text{-OH-C}_6\text{H}_4 \)

**Scheme III D**

Bearing in mind the mechanism of the formation of the disulfides from 2-amino benzene thiols using a catalytic amount of hydrazine hydrate in presence of air, progressed to condense equimolar quantities of 2-amino benzene thiols with 1,3-dicarbonyls using a catalytic amount of hydrazine hydrate at 100\(^\circ\)C and in the absence of solvent. The products of the condensation were found to be 2,3-disubstituted 1,4-benzothiazines and their melting points and spectral data are in good agreement with those reported in the literature\(^{161,162}\). The probable mechanism of the condensation is depicted in Scheme III D. Thus developed one pot synthetic route for 2,3-disubstituted 1,4-benzothiazines is convenient solvent free and environmentally benign. Melting points as well as the observed yields of the products are presented in Table 3.4.
Experimental:

Synthesis of 2-acyl-3-methyl-4H-1,4-benzothiazine (as a representative case):

A mixture of 2-amino benzene thiol (10 mmole) and hydrazine hydrate (1 mmole) was heated at 100°C for 3 minutes. To this mixture then acetyl acetone (2,4-pentadione, 10 mmole) was introduced and the reaction mixture was allowed to stand at 100°C for further 15 minutes. It was then cooled to room temperature. To this ethyl alcohol (5 ml) was added and the reaction mass was stirred. The separated solid was filtered and crystallised from ethyl alcohol, mp = 196°C, yield = 89%.

Similarly the other compounds of the series were prepared by using same procedure.

Spectral discussion:

The results of IR and $^1$HNMR scannings of the compound, 2-acyl-3-methyl-4H-1,4-benzothiazine as a representative compound of the series are presented below.

IR (Nujol cm$^{-1}$): 3310 (NH stretching), 1620 (C=O stretching), 1380 (C-CH$_3$ stretching) and 720 (C-S-C stretching).

$^1$HNMR (DMSO d$_6$) = 2.31 (s, 3H, CH$_3$), 2.4 (s, 3H, COCH$_3$), 6.5-7.5 (m, 4H, aromatic proton) and 8.8 (s, 1H, NH ,exchangeable with D$_2$O)(Spectrum No. 3.12).
Table 3.4: 2,3-Disubstituted-1,4-benzothiazines

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>R</th>
<th>R₁</th>
<th>R₂</th>
<th>M.P. in °C</th>
<th>Yield %</th>
</tr>
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<td>H</td>
<td>Methyl</td>
<td>Methyl</td>
<td>196&lt;sup&gt;a&lt;/sup&gt;</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
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<td>Methyl</td>
<td>Ethoxy</td>
<td>145&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>3</td>
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<td>189&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
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<tr>
<td>5</td>
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<td>Methyl</td>
<td>186&lt;sup&gt;b&lt;/sup&gt;</td>
<td>96</td>
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<tr>
<td>6</td>
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<td>137&lt;sup&gt;b&lt;/sup&gt;</td>
<td>91</td>
</tr>
<tr>
<td>7</td>
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<td>192&lt;sup&gt;b&lt;/sup&gt;</td>
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<sup>a</sup> = Reference Number 161
<sup>b</sup> = Reference Number 162
<sup>c</sup> = Reference Number 163
Synthesis of bridgehead or fused heterocycles

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