CHAPTER 2

SECTION 2.1 Application of the Selected heterocycles (Phenothiazine, benotriazole, 4-oxo-thiazolidine and their 5-arylidines)

SECTION 2.2 Aim and work plan of the research work
SECTION-2.1. Applications of the selected heterocycles

The molecular modification of known pharmacodynamic compounds is a main kind of research in the field of chemotherapy. The structural modification can be carried out by substituting one group(s) by other group(s), adding new group(s), saturating the compound by adding hydrogens or by modifying the acidity or basicity. In each case a complex Structure Activity Relation is obtained. These relations are identical and serve as a guiding factors in mapping the structural features of the compounds with analogous activities.

A brief description regarding the applications of the heterocyclic moieties, (phenothiazine, benzotriazole, 4-oxo-thiazolidines and their-5-arylidine derivatives) present in the final compounds has been made herein to explain the suitability and importance of the proposed research work.

PHENOTHIAZINES

Phenothiazine derivatives exhibit significant antitumor\textsuperscript{23}, antiinflammatory\textsuperscript{24,25}, antimalarial\textsuperscript{26}, anthelmintic\textsuperscript{27}, tuberculostatic\textsuperscript{28}, antipsychotic\textsuperscript{29-31}, anaesthetic\textsuperscript{32}, analgesic\textsuperscript{33}, cardiovascular\textsuperscript{34} and antiparkinsonian\textsuperscript{35,36} activity. Methylene blue (1) is a good dye for cotton due to its fastness to washing, light and chlorine.
Thioridazine, Mesoridazine and Sulforidazine (2) are piperidine-type phenothiazine which have been found to display antipsychotic drugs\textsuperscript{37}.

\begin{center}
\textbf{2:} X=\text{S}/\text{SO}/\text{SO}_2
\end{center}

Chlorpromazine, (3) displays an amazing array of physiological actions including gangliolytic, adrenolytic, antifibrillatory, antioedema, antipyretic, anticonvulsant, antisock and antiemetic properties. The manyfold action of this drug has been discussed by Goodman\textsuperscript{38}.

\begin{center}
\textbf{(3)}
\end{center}
Phenothiazine derivatives (4-7) are reported as strong antimicrobial agents\(^{39-42}\).

\[
\begin{align*}
(4) & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \qu}
10-(Substituted phenyl hydrozonoacetyl) phenothiazines (8) are reported as good anticonvulsants\(^{43}\).

\[
\text{Ar} = \text{Phenyl, Sub. phenyl.}
\]

6-(4-phenoxy / 5-chloro-2-methoxy / 2,5-dimethyl anilino)-9-bromo/9-chloro/10-chloro-9-methoxyl / 10,11-dimethyl/8, 11-dichloro / 9-ethoxy-5H-benzo[a] phenothizine-5-ones (9), 12H-benzo[a] phenothiazine-5-ol derivatives (10), 5-acetoxy-12H-benzo[a] phenothiazines (11) and 5-methoxy-12H-benzo[a] phenothiazines (12) have been synthesised and displayed antimicrobial activity\(^{44}\).

\[
\text{(9); } R=\text{H/Br} \quad \text{(10); } R=\text{H/Br; } R^1=\text{H} \\
\text{(11); } R=\text{H/Br; } R^1=\text{Ac} \quad \text{(12); } R=\text{H/Br; } R^1=\text{CH}_3
\]
2,10-Disubstituted phenothiazines (13) and (14) are found to display antiinflammatory activity\(^\text{45}\).

\[
\begin{align*}
\text{(13)} & \quad \text{(14)} \\
\end{align*}
\]

\(\text{Ar}=\text{Phenyl, Sub. phenyl.}\)

1- (Di - n - butylaminomethyl) - 1/2 - phenothiazino - methanolhydrochlorides are reported as antimalarial agents\(^\text{46}\).

10-phenothiazenyl carbomylmethyl-\(\beta\)-10-phenothiaziny1propionate\(^\text{47}\), 2,4,6-trinitrophenoxyacetyl-N-10-phenothiazines\(^\text{48}\) are found to exhibit anthelmintic activity.

1-[2-(Chloroethyl)-3-(2-substituted-10H-phenothiazin-10-yl)alkyl]-1-ureas have been synthesised and reported as potent anticancer agents\(^\text{49}\).

Perazine, perphenazine and trifluoperazines are reported as neuroleptic and sedative agents\(^\text{50}\) while as 10-(substituted thiazolidinyl) phenothiazines are claimed as antiinflammatory agents.
Phenothiazine derivatives like promethazine (15), promazine (16), chlorpromazine, ethomethazine, and ethopromazine are used as tranquillizer and antihistaminic agents\textsuperscript{51}.

![Formula 15 and 16]

$N^{10}$-($N$-substituted piperazinoalkyl) phenothiazines (17) are claimed as paranoid, sedative and neuroleptic agents\textsuperscript{52,53}.

![Formula 17]

$R = \text{Alkyl}$

Mecazine pecatal (18) has found its application as psychiatric disorder removing agent and as a tranquillizer\textsuperscript{54,55}.
Some of the phenothiazine derivatives like ahiston and chlorproethazine are found to display antihistaminic, anticonvulsant, antiparkinsonian, antidepressant, antispasmodic, tranquilizer and muscle relaxant activity\textsuperscript{56,57}.

Phenothiazine (19) has reported as a good antidepressant agent\textsuperscript{58}.

2-(2-Amino-6-aryl-4-pyrimidinyl) phenothiazines (20) and 2-(5-aryl-4,5-dihydro-3-pyrazolyl)-phenothiazines (21) are reported as antiinflammatory agents\textsuperscript{59}.
\textbf{(20)} \hspace{1cm} \textbf{(21)}

\textit{Ar} = \text{Phenyl, Sub. phenyl.}

N-2- (nitro substituted phenoxy)-acetyl phenothiazines (22) have been synthesised which found to display anthelmintic activity\textsuperscript{48}.

\textbf{(22)}

Various N-substituted phenothiazine (23) have been prepared which showed anthelmintic, anti-inflammatory and antimicrobial activity\textsuperscript{60}. 
A series of 2-arylideneamino-5-(N<sup>10</sup>-phenothiazinomethyl)-1,3,4-thiadiazoles (24) and 1-[5’-(N<sup>10</sup>-phenothiazinomethyl)-1’, 3’, 4’-thiadiazol-2’-yl]-4-substituted-2-azetidinones (25) have been synthesised which exhibited antifungal activity against some selected pathogens.<sup>61</sup>
(25); $R^1=H$; $R^2=$Substituted aromatic ring
BENZOTRIAZOLES

Benzotriazole has its synthetic value for its numerous applications in industry and agriculture. It has an important place in dyestuffs\textsuperscript{62-64}, optical brighteners\textsuperscript{65-67}, fluorescents\textsuperscript{68-70}, corrosion inhibitors\textsuperscript{71}, agrochemicals\textsuperscript{72} and photostabilizers\textsuperscript{73-75}.

1-Ethoxy-4-nitrobenzotriazole (26) and 1-methoxy-4-nitrobenzotriazole (27) have been found to display strong herbicidal activity\textsuperscript{76}.

\[
\begin{align*}
\text{NO}_2 & \quad \text{NO}_2 \\
\text{N} & \quad \text{N} \\
oc_{2}h_{5} & \quad \text{OCH}_{3}
\end{align*}
\]

(26) (27)

Ethyl-2-(5-phenoxy-N\textsuperscript{1}-benzotriazolyl propionate (28) has also exhibited herbicidal activity\textsuperscript{77} whereas benzotriazolyl alkanoic acids (29) are reported as plant growth promoting agents\textsuperscript{78}.

\[
\begin{align*}
\text{H}_3\text{C}-\text{CH-COO}_{2}\text{H}_5 & \quad \text{R-CH-COOH} \\
\text{N} & \quad \text{N} \\
\end{align*}
\]

(28) (29); \quad R= \text{Alkyl}
A series of benzotriazole derivatives (30 and 31) structurally related to trazodone have been synthesised which showed antiserotonergic, antiadrenergic and antihistaminic in vitro activity\textsuperscript{79}.

![Chemical structure of 30 and 31](image)

(30); \(R\)=substituted aromatic/aliphatic nuclei

(31); \(R\)=substituted aromatic/aliphatic nuclei

Benzotriazole derivative (32) is used in whitening of fibres, cellulose acetate and plastics.

![Chemical structure of 32](image)

(32)
Benzotriazole derivatives are reported as corrosion inhibitors of many metals and alloys including copper, solder, brass, steel, cast iron and aluminium.

Chlorobenzotriazoles are excellent oxidants and chlorinating agents\textsuperscript{80}. On the other hand, 1-hydroxy benzotriazole (33) is used as a co-reagent in peptide-coupling\textsuperscript{81}.

\begin{equation}
\text{(33)}
\end{equation}

Benzotriazole derivatives have their important place in the therapeutics as a bactericide\textsuperscript{82}, antiinflammatory\textsuperscript{83}, antitumor\textsuperscript{84}, fungicide\textsuperscript{85,86}, antidepressant\textsuperscript{87}, muscle-relaxant\textsuperscript{88} and antineoplastic\textsuperscript{89} agent.

Benzotriazole [4,5-d] pyrimidine\textsuperscript{90}, 1,2,4-triazolo-1,3,4-thiadiazolobenzotriazoles\textsuperscript{91}, 1,2,4-triazolothiadiazanyl benzotriazoles\textsuperscript{91} and 1-H-benzotriazole derivatives of types (34) and (35) are reported as potential antimicrobials\textsuperscript{92}.

\begin{equation}
\text{(34)}
\end{equation}

\begin{equation}
\text{(35)}
\end{equation}
5-And-6-chloro-1-aryloyl benzotriazoles (36) and (37) are found to display antiinflammatory activity.

\[ \text{Cl} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{CO} \]
\[ \text{(36)} \]
\[ \text{Cl} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{CO} \]
\[ \text{(37)} \]

N-β-Ribofuranosyl benzotriazole, N-glycynyl benzotriazole, N-β-glucopyranosyl benzotriazole and 4-substituted benzotriazoles (38) are also found to display cytostatic activity\(^93\).

\[ \text{R} \]
\[ \text{N} \quad \text{N} \quad \text{H} \]
\[ \text{(38); } R = H/NH_2/NHCO_3/-CHCOOH \]
\[ \text{NH}_2 \]

Mannich bases of 5-nitrobenzotriazole (39) are reported as potential muscle-relaxant\(^94\).
2-Substituted benzotriazole derivatives of phenacetin and aspirin are found to exhibit analgesic activity\textsuperscript{95}. Benzotriazoles can be successfully applied as human skin protector from uv radiations. 2-(2-Methyl-2-hydroxyphenyl)-benzotriazole (40) is used as sun burn-protector.

2,4,6-Trichlorophenoxy acetyl benzotriazole (41) and naphthoxy-acetyl N\textsuperscript{1}-benzotriazole (42) found to display good antiinflammatory activity\textsuperscript{96,97}. 
4-Oxo-thiazolidines and their 5-arylidine derivatives

Thiazolidinones are five membered aliphatic heterocycles containing sulphur and nitrogen at positions 1 and 3 and carbonyl group at position-4 in the same ring. It is also known as 4-oxo-thiazolidine and numbered as shown below -

![Thiazolidine and 4-oxo-thiazolidine structure](image)

Thiazolidinones and their 5-arylidine derivatives can be prepared by the following methods for example : 2-methyl-2-(2-hydroxy-4, 5-dimethyl phenyl)- 3-phenyl-4-thiazolidinone (53) has been synthesised by dissolving optimum quantity of 2-hydroxy-4, 5-dimethyl acetophenone and thioglycolic acid in benzene under reflux condition with a pinch of ZnCl₂ as a catalyst.

![Synthesis of 4-Oxo-thiazolidine](image)

\[ \text{(53)} \]
A mixture of N¹, N⁵-dibenzyldine thiocarbohydrazide and thioglycolic acid in dry xylene on reflux yielded N¹, N⁵-di-(2-phenyl-4-oxo-thiazolidinyl)-thiourea (54) which on condensation with benzaldehyde in the presence of sodium ethoxide gave the product (55).

![Chemical Structure](image)

1-(4-Methoxy benzylidine)-2-phenyl acetyl hydrazone (56) on reaction with thioglycolic acid afforded 2-(4-methoxy phenyl)-3-phenylacetylamine-4-oxo-thiazolidine (57) which on reaction with benzaldehyde in the presence of sodium
ethoxide gave 2-(4-methoxy phenyl) 3-phenyl acetylamino-5-benzylidine-4-oxothiazolidine (58)\textsuperscript{100}.

\[
\begin{align*}
\text{CH}_2\text{-CO-NH-N}=\text{CH} & \quad \text{O-CH}_3 \\
\downarrow & \\
\text{SH-CH}_2\text{-COOH} & \text{(56)}
\end{align*}
\]

\[
\begin{align*}
\text{CH}_2\text{-CO-NH-N} & \quad \text{CH} & \quad \text{O}=\text{C} & \quad \text{S} \\
\text{O} & \quad \text{S} & \quad \text{(57)} & \downarrow \\
\text{C}_2\text{H}_5\text{ONa} & / & \text{R-CHO} & \\
\end{align*}
\]

\[
\begin{align*}
\text{CH}_2\text{-CO-NH-N} & \quad \text{CH} & \quad \text{O}=\text{C} & \quad \text{S} & \quad \text{CH-R} \\
\text{(58)} & & & & \\
\end{align*}
\]

\(R = \text{phenyl}\)

\(N^{10}\)-Arylidinehydrazidophenothiazones (59) on cyclocondensation with mercapto acetic acid in the presence of anhydrous zinc chloride in tetrahydrofuran afforded-4-thiazolidinones (60)\textsuperscript{101}. 
4-Thiazolidinones or 4-oxo-thiazolidines and their 5-arylidine derivatives possess a variety of therapeutic activity such as antifungal\textsuperscript{102, 103}, antibacterial\textsuperscript{104}, anticonvulsant\textsuperscript{105}, amoebicidal\textsuperscript{106}, hypnotic\textsuperscript{107}, antitubercular\textsuperscript{108}, nematocidal\textsuperscript{109}, mosquitorepellent\textsuperscript{110}, anti-HIV, anticancer\textsuperscript{100} and anaesthetic\textsuperscript{111} etc.

2-Arylimino-3-aryl-4-thiazolidinones (61) have been synthesised and possess considerable fungicidal activity\textsuperscript{112}. 2-Aryl-3-alkyl-4-thiazolidinones (62) were found to be active against psychomotor anticonvulsant and barbiturate potentiating activity in mice\textsuperscript{113}.
Thiazolidinones (63) and their 5-arylidine derivatives have been synthesised and found to be fungitoxicides\textsuperscript{99}. 2-Methyl-2-(2-hydroxy-4, 5-dimethyl phenyl (64) and aryl-4-thiazolidinone (65) have synthesised and found to exhibit potential fungicidal activity\textsuperscript{98}. 

\[ R = \text{CH}_3 / \text{C}_2\text{H}_5 / \text{C}_3\text{H}_7 \]
R = o-Cl/o-CH₃/o-OCH₃/o-NO₂
p-Cl/p-CH₃/p-OCH₃/p-NO₂ / m-Cl/m-CH₃/m-OCH₃/m-NO₂

N¹⁰-Arylidinehydrazidophenothiazine and their 4-thiazolidinones (66) and 2-azetidinones have been synthesised and shown antimicrobial activity¹⁰¹.

4-Oxo-thiazolidines (67), 2-imino-4-oxo-thiazolidines (68) and their 5-arylidine derivatives (69 and 70) have been prepared and found to display anti-HIV, anticancer and antitubercular activities¹⁰⁰.
4-Oxo-thiazolidines (71), 4-oxo-azetidines, malonanilic acid hydrazines and pyrazolins derivatives of phenothiazine have been synthesised and found to exhibit antibacterial and tuberculostatic activity\textsuperscript{114}. 

(71); R = H/2-OH/3-OH/4-OH/4-Cl/4-NO\textsubscript{2}/3-NO\textsubscript{2}/4-CH\textsubscript{3}
2-[3'-(4''-Acetyl aminophenyl) -2''-aryl- 4''- thiazolidinon -5-yl] 4, 5-dihydroimidazole (72) was found to antitubercular activity against H37Rv strain of *Mycobacterium tuberculosis*. The substitution at 2- and 4-position of hydroxy group in phenyl ring are effective against *Escherichia coli*\(^{115}\).

\[
\text{CH}_3\text{-CO-NH-} \quad \text{S} \quad \text{R}^1
\]

(72); \( R^1 = 2\text{-OH/4-OH} \)
SECTION-2.2 Aim and work plan of the research

The literature survey on structure-activity relationship of phenothiazines, benzotriazoles, 4-oxo-thiazolidines and their 5-arylidine derivatives has prompted the authors to synthesise some N\textsuperscript{10}-phenothiazinoacetamidyl-4-oxo-thioazolidines, and their 5-arylidine derivatives; N\textsuperscript{1}-benzotriazolylacetamidyl-4-oxo-thioazolidines and their 5-arylidine derivatives and to record their biological activity to get new compounds as a possible new age drugs.

Work plan of the research :

The work plan of the research has been divided into three parts:

Part-I: Synthesis of new heterocyclic compounds.

Part-II: Characterization of the compounds by microanalysis, physical data, chromatography and spectral techniques.


a. Antibacterial

b. Antifungal

c. Anti-inflammatory

d. Analgesic and

e. Anti-convulsant

PART-I: Synthesis of the new heterocyclic compounds:

Four series of compounds have been synthesised. The general scheme-1 (Page No.53) represents the common scheme of the synthesis of the compounds.
Scheme-1

\[
\begin{align*}
\text{Het } & \text{N-H} \\
\downarrow & \\
\text{Het } & \text{N-CH}_2\text{-COOC}_2\text{H}_5 \\
\downarrow & \\
\text{Het } & \text{N-CH}_2\text{-CO-NH-NH}_2 \\
\downarrow & \\
\text{Het } & \text{N-CH}_2\text{-CO-NH-N=CR}_1\text{R}_2 \\
\downarrow & \\
\text{Het } & \text{N-CH}_2\text{-CO-NH-N} \quad \text{S} \\
\downarrow & \\
\text{Het } & \text{N-CH}_2\text{-CO-NH-N} \quad \text{S} \\
\end{align*}
\]

Where: Het NH = Heterocycle (phenothiazine/benzotriazole); 
R_1=R_2=R_3=R_4=Selected carbonyl compounds.
Series-1: 2 - (Substituted aryl) - 3 - (N^{10} - phenothiazinoacetamidyl) - 4 - oxo - thiazolidines (Scheme-2)

1. \( \text{Cl-CH}_2\text{COOC}_2\text{H}_5 \)
2. \( \text{NH}_2\text{-NH}_2\cdot\text{H}_2\text{O} \)
3. \( \text{HS-CH}_2\text{-COOH} \)
Where,

SM-01 = \( R_1 = H; \quad R_2 = \text{furfuryl} \)

SM-02 = \( R_1 = H; \quad R_2 = \text{cinnamyl} \)

SM-03 = \( R_1 = H; \quad R_2 = \text{p-chlorophenyl} \)

SM-04 = \( R_1 = H; \quad R_2 = \text{o-chlorophenyl} \)

SM-05 = \( R_1 = R_2 = \text{C}_6\text{H}_5 \)

Table 2.1: List of the compounds synthesised under series-1

<table>
<thead>
<tr>
<th>Code No.</th>
<th>( R_1 )</th>
<th>( R_2 )</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>SM-01</td>
<td>H</td>
<td>Furfuryl</td>
<td>2-Furfuryl-3-((N^{10})-phenothiazinoacetamidyl)-4-oxo-thiazolidine.</td>
</tr>
<tr>
<td>SM-02</td>
<td>H</td>
<td>Cinnamyl</td>
<td>2-Cinnamyl-3-((N^{10})-phenothiazinoacetamidyl)-4-oxo-thiazolidine.</td>
</tr>
<tr>
<td>SM-03</td>
<td>H</td>
<td>p-Chlorophenyl</td>
<td>2-(p-Chlorophenyl)-3-((N^{10})-phenothiazinoacetamidyl)-4-oxo-thiazolidine.</td>
</tr>
<tr>
<td>SM-04</td>
<td>H</td>
<td>o-Chlorophenyl</td>
<td>2-(o-Chlorophenyl)-3-((N^{10})-phenothiazinoacetamidyl)-4-oxo-thiazolidine.</td>
</tr>
<tr>
<td>SM-05</td>
<td>\text{C}_6\text{H}_5</td>
<td>\text{C}_6\text{H}_5</td>
<td>2-(2,2-Diphenyl)-3-((N^{10})-phenothiazinoacetamidyl)-4-oxo-thiazolidine.</td>
</tr>
</tbody>
</table>
Series-2: 2-(Substituted aryl)-3-(N^{10}-phenothiazinoacetamidyl)-5-(arylidine)-4-oxo-thiazolidines:

The compounds of series-2 (compounds 06-20) have been synthesised through the compounds (SM 01-05). (Scheme-3)

Scheme-3

(SM-06-20)
Where,  

SM-06 : \( R_1 = R_3 = H; \ R_2 = \text{furfuryl}; \ R_4 = -\text{CH} = \text{CH-C}_6\text{H}_5 \)

SM-07 : \( R_1 = R_3 = H; \ R_2 = \text{furfuryl}; \ R_4 = -p-\text{Cl-C}_6\text{H}_4 \)

SM-08 : \( R_1 = R_3 = H; \ R_2 = \text{furfuryl}; \ R_4 = -o-\text{Cl-C}_6\text{H}_4 \)

SM-09 : \( R_1 = R_3 = H; \ R_2 = \text{furfuryl}; \ R_4 = -p-N(\text{CH}_3)_2 -\text{C}_6\text{H}_4 \)

SM-10 : \( R_1 = H; R_2 = \text{furfuryl}; \ R_3 = R_4 = \text{C}_6\text{H}_5 \)

SM-11 : \( R_1 = R_3 = H; \ R_2 = \text{cinnamyl}; \ R_4 = -p-\text{Cl-C}_6\text{H}_4 \)

SM-12 : \( R_1 = R_3 = H; \ R_2 = \text{cinnamyl}; \ R_4 = -o-\text{Cl-C}_6\text{H}_4 \)

SM-13 : \( R_1 = R_3 = H; \ R_2 = \text{cinnamyl}; \ R_4 = -p-N(\text{CH}_3)_2 -\text{C}_6\text{H}_4 \)

SM-14 : \( R_1 = H; \ R_2 = \text{cinnamyl}; \ R_3 = R_4 = \text{C}_6\text{H}_5 \)

SM-15 : \( R_1 = R_3 = H; \ R_2 = p-\text{chlorophenyl}; \ R_4 = o-\text{Cl-C}_6\text{H}_4 \)

SM-16 : \( R_1 = R_3 = H; \ R_2 = p-\text{chlorophenyl}; \ R_4 = -p-N(\text{CH}_3)_2 -\text{C}_6\text{H}_4 \)

SM-17 : \( R_1 = H; \ R_2 = p-\text{chlorophenyl}; \ R_3 = R_4 = \text{C}_6\text{H}_5 \)

SM-18 : \( R_1 = R_3 = H; \ R_2 = o-\text{chlorophenyl}; \ R_4 = -p-N(\text{CH}_3)_2 -\text{C}_6\text{H}_4 \)

SM-19 : \( R_1 = H; \ R_2 = o-\text{chlorophenyl}; \ R_3 = R_4 = \text{C}_6\text{H}_5 \)

SM-20 : \( R_1 = R_2 = \text{C}_6\text{H}_5; \ R_3 = H; \ R_4 = -p-N(\text{CH}_3)_2 -\text{C}_6\text{H}_4 \)
<table>
<thead>
<tr>
<th>Code No.</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>SM-06</td>
<td>H</td>
<td>Furfuryl</td>
<td>H</td>
<td>-CH=CH-C₆H₅</td>
<td>2-Furfuryl-3-(N₁⁰-phenothiazino-acetamidyl)-5-(cinnamylidine)-4-oxo-thiazolidine.</td>
</tr>
<tr>
<td>SM-07</td>
<td>H</td>
<td>Furfuryl</td>
<td>H</td>
<td>p-Cl-C₆H₄</td>
<td>2-Furfuryl-3-(N₁⁰-phenothiazino-acetamidyl)-5-(p-chlorobenzylidine)-4-oxo-thiazolidine.</td>
</tr>
<tr>
<td>SM-08</td>
<td>H</td>
<td>Furfuryl</td>
<td>H</td>
<td>o-Cl-C₆H₄</td>
<td>2-Furfuryl-3-(N₁⁰-phenothiazino-acetamidyl)-5-(o-chlorobenzylidine)-4-oxo-thiazolidine.</td>
</tr>
<tr>
<td>SM-09</td>
<td>H</td>
<td>Furfuryl</td>
<td>H</td>
<td>p-N(CH₃)₂-C₆H₄</td>
<td>2-Furfuryl-3-(N₁⁰-phenothiazino-acetamidyl)-5-(p-dimethylamino-benzylidine)-4-oxo-thiazolidine.</td>
</tr>
<tr>
<td>SM-10</td>
<td>H</td>
<td>Furfuryl</td>
<td>C₆H₅</td>
<td>C₆H₅</td>
<td>2-Furfuryl-3-(N₁⁰-phenothiazino-acetamidyl)-5-(benzophenylidine)-4-oxo-thiazolidine.</td>
</tr>
<tr>
<td>SM-11</td>
<td>H</td>
<td>Cinnamyl</td>
<td>H</td>
<td>p-Cl-C₆H₄</td>
<td>2-Cinnamyl-3-(N₁⁰-phenothiazino-acetamidyl)-5-(p-chlorobenzylidine)-4-oxo-thiazolidine.</td>
</tr>
<tr>
<td>SM-12</td>
<td>H</td>
<td>Cinnamyl</td>
<td>H</td>
<td>o-Cl-C₆H₄</td>
<td>2-Cinnamyl-3-(N₁⁰-phenothiazino-acetamidyl)-5-(o-chlorobenzylidine)-4-oxo-thiazolidine.</td>
</tr>
<tr>
<td>SM-13</td>
<td>H</td>
<td>Cinnamyl</td>
<td>H</td>
<td>p-N(CH₃)₂-C₆H₄</td>
<td>2-Cinnamyl-3-(N₁⁰-phenothiazino-acetamidyl)-5-(p-dimethylamino-benzylidine)-4-oxo-thiazolidine.</td>
</tr>
<tr>
<td>SM-14</td>
<td>H</td>
<td>Cinnamyl</td>
<td>C₆H₅</td>
<td>C₆H₅</td>
<td>2-Cinnamyl-3-(N₁⁰-phenothiazino-acetamidyl)-5-(benzophenylidine)-4-oxo-thiazolidine.</td>
</tr>
<tr>
<td>SM-15</td>
<td>H</td>
<td>p-Chlorophenyl</td>
<td>H</td>
<td>o-Cl-C₆H₄</td>
<td>2-(p-Chlorophenyl)-3-(N₁⁰-phenothiazinoacetamidyl)-5-(o-chlorobenzylidine)-4-oxo-thiazolidine.</td>
</tr>
</tbody>
</table>

Cont'd....
<table>
<thead>
<tr>
<th>Code No.</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>SM-16</td>
<td>H</td>
<td>p-Chlorophenyl</td>
<td>H</td>
<td>p-N(CH₃)₂-C₆H₄</td>
<td>2-(p-Chlorophenyl)-3-(N¹⁰-phenothiazinoacetamidyl)-5-(p-dimethylaminobenzylidene)-4-oxothiazolidine</td>
</tr>
<tr>
<td>SM-17</td>
<td>H</td>
<td>p-Chlorophenyl</td>
<td>C₆H₅</td>
<td>C₆H₅</td>
<td>2-(p-Chlorophenyl)-3-(N¹⁰-phenothiazinoacetamidyl)-5-(benzophenylidene)-4-oxothiazolidine</td>
</tr>
<tr>
<td>SM-18</td>
<td>H</td>
<td>o-Chlorophenyl</td>
<td>H</td>
<td>p-N(CH₃)₂-C₆H₄</td>
<td>2-(o-Chlorophenyl)-3-(N¹⁰-phenothiazinoacetamidyl)-5-(p-dimethylaminobenzylidene)-4-oxothiazolidine</td>
</tr>
<tr>
<td>SM-19</td>
<td>H</td>
<td>o-Chlorophenyl</td>
<td>C₆H₅</td>
<td>C₆H₅</td>
<td>2-(o-Chlorophenyl)-3-(N¹⁰-phenothiazinoacetamidyl)-5-(benzophenylidene)-4-oxothiazolidine</td>
</tr>
<tr>
<td>SM-20</td>
<td>C₆H₅</td>
<td>C₆H₅</td>
<td>H</td>
<td>p-N(CH₃)₂-C₆H₄</td>
<td>2-(2,2-Diphenyl)-3-(N¹⁰-phenothiazino-acetamidyl)-5-(p-dimethylamino-benzylidene)-4-oxothiazolidine</td>
</tr>
</tbody>
</table>
Series-3 : 2 - (Substituted aryl) - 3 - (N₁ - benzotriazolylacetamidyl) - 4 - oxo - thiazolidines (Scheme-4)
Where,

SM-21 = R_1 = H; R_2 = furfuryl

SM-22 = R_1 = H; R_2 = cinnamyl

SM-23 = R_1 = H; R_2 = p-chlorophenyl

SM-24 = R_1 = H; R_2 = o-chlorophenyl

SM-25 = R_1 = R_2 = C_6H_5

Table-2.3 : List of the compounds synthesised under series-3

<table>
<thead>
<tr>
<th>Code No.</th>
<th>R_1</th>
<th>R_2</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>SM-21</td>
<td>H</td>
<td>Furfuryl</td>
<td>2-Furfuryl-3-(N^1^-benzotriazolylacetamidyl)-4-oxo-thiazolidine.</td>
</tr>
<tr>
<td>SM-22</td>
<td>H</td>
<td>Cinnamyl</td>
<td>2-Cinnamyl-3-(N^1^-benzotriazolylacetamidyl)-4-oxo-thiazolidine.</td>
</tr>
<tr>
<td>SM-23</td>
<td>H</td>
<td>p-Chlorophenyl</td>
<td>2-(p-Chlorophenyl)-3-(N^1^-benzotriazolylacetamidyl)-4-oxo-thiazolidine.</td>
</tr>
<tr>
<td>SM-24</td>
<td>H</td>
<td>o-Chlorophenyl</td>
<td>2-(o-Chlorophenyl)-3-(N^1^-benzotriazolylacetamidyl)-4-oxo-thiazolidine.</td>
</tr>
<tr>
<td>SM-25</td>
<td>C_6H_5</td>
<td>C_6H_5</td>
<td>2-(2,2-Diphenyl)-3-(N^1^-benzotriazolylacetamidyl)-4-oxo-thiazolidine.</td>
</tr>
</tbody>
</table>
Series-4: 2-(Substituted aryl)-3-(N\textsuperscript{1}-benzotriazolylacetamidyl)-5-(arylidine)-4-oxo-thiazolidines:

The compounds of series-4 (compounds 26-40) have been synthesised through the compounds (SM 21-25). (Scheme-5)

Scheme-5

\[
\begin{align*}
\text{(4)} & \\
\text{(5)} & \\
\text{(SM-26-40)}
\end{align*}
\]
Where,

SM-26 : $R_1 = R_3 = H; \quad R_2 = \text{furfuryl}; \quad R_4 = -\text{CH}=\text{CH}-\text{C}_6\text{H}_5$

SM-27 : $R_1 = R_3 = H; \quad R_2 = \text{furfuryl}; \quad R_4 = -\text{p-Cl-C}_6\text{H}_4$

SM-28 : $R_1 = R_3 = H; \quad R_2 = \text{furfuryl}; \quad R_4 = -\text{o-Cl-C}_6\text{H}_4$

SM-29 : $R_1 = R_3 = H; \quad R_2 = \text{furfuryl}; \quad R_4 = -\text{p-N(CH}_3)_2\text{-C}_6\text{H}_4$

SM-30 : $R_1 = H; \quad R_2 = \text{furfuryl}; \quad R_3 = R_4 = \text{C}_6\text{H}_5$

SM-31 : $R_1 = R_3 = H; \quad R_2 = \text{cinnamyl}; \quad R_4 = -\text{p-Cl-C}_6\text{H}_4$

SM-32 : $R_1 = R_3 = H; \quad R_2 = \text{cinnamyl}; \quad R_4 = -\text{o-Cl-C}_6\text{H}_4$

SM-33 : $R_1 = R_3 = H; \quad R_2 = \text{cinnamyl}; \quad R_4 = -\text{p-N(CH}_3)_2\text{-C}_6\text{H}_4$

SM-34 : $R_1 = H; \quad R_2 = \text{cinnamyl}; \quad R_3 = R_4 = \text{C}_6\text{H}_5$

SM-35 : $R_1 = R_3 = H; \quad R_2 = \text{p-chlorophenyl}; \quad R_4 = -\text{o-Cl-C}_6\text{H}_4$

SM-36 : $R_1 = R_3 = H; \quad R_2 = \text{p-chlorophenyl}; \quad R_4 = -\text{p-N(CH}_3)_2\text{-C}_6\text{H}_4$

SM-37 : $R_1 = H; \quad R_2 = \text{p-chlorophenyl}; \quad R_3 = R_4 = \text{C}_6\text{H}_5$

SM-38 : $R_1 = R_3 = H; \quad R_2 = \text{o-chlorophenyl}; \quad R_4 = -\text{p-N(CH}_3)_2\text{-C}_6\text{H}_4$

SM-39 : $R_1 = H; \quad R_2 = \text{o-chlorophenyl}; \quad R_3 = R_4 = \text{C}_6\text{H}_5$

SM-40 : $R_1 = R_2 = \text{C}_6\text{H}_5; \quad R_3 = H; \quad R_4 = -\text{p-N(CH}_3)_2\text{-C}_6\text{H}_4$
<table>
<thead>
<tr>
<th>Code No.</th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>$R_3$</th>
<th>$R_4$</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>SM-26</td>
<td>H</td>
<td>Furfuryl</td>
<td>H</td>
<td>-CH=CH-C$_6$H$_5$</td>
<td>2-Furfuryl-3-(N$_{10}$-benzotriazolyl-acetamidyl)-5-(cinnamylidine)-4-oxothiazolidine.</td>
</tr>
<tr>
<td>SM-27</td>
<td>H</td>
<td>Furfuryl</td>
<td>H</td>
<td>p-Cl-C$_6$H$_4$</td>
<td>2-Furfuryl-3-(N$_{10}$-benzotriazolyl-acetamidyl)-5-(p-chlorobenzylidine)-4-oxo-thiazolidine.</td>
</tr>
<tr>
<td>SM-28</td>
<td>H</td>
<td>Furfuryl</td>
<td>H</td>
<td>o-Cl-C$_6$H$_4$</td>
<td>2-Furfuryl-3-(N$_{10}$-benzotriazolyl-acetamidyl)-5-(o-chlorobenzylidine)-4-oxo-thiazolidine.</td>
</tr>
<tr>
<td>SM-29</td>
<td>H</td>
<td>Furfuryl</td>
<td>H</td>
<td>p-N(CH$_3$)$_2$-C$_6$H$_4$</td>
<td>2-Furfuryl-3-(N$_{10}$-benzotriazolyl-acetamidyl)-5-(p-dimethylaminobenzylidine)-4-oxo-thiazolidine.</td>
</tr>
<tr>
<td>SM-30</td>
<td>H</td>
<td>Furfuryl</td>
<td>C$_6$H$_3$</td>
<td>C$_6$H$_5$</td>
<td>2-Furfuryl-3-(N$_{10}$-benzotriazolyl-acetamidyl)-5-(benzophenylidine)-4-oxo-thiazolidine.</td>
</tr>
<tr>
<td>SM-31</td>
<td>H</td>
<td>Cinnamyl</td>
<td>H</td>
<td>p-Cl-C$_6$H$_4$</td>
<td>2-Cinnamyl-3-(N$_{10}$-benzotriazolyl-acetamidyl)-5-(p-chlorobenzylidine)-4-oxo-thiazolidine.</td>
</tr>
<tr>
<td>SM-32</td>
<td>H</td>
<td>Cinnamyl</td>
<td>H</td>
<td>o-Cl-C$_6$H$_4$</td>
<td>2-Cinnamyl-3-(N$_{10}$-benzotriazolyl-acetamidyl)-5-(o-chlorobenzylidine)-4-oxo-thiazolidine.</td>
</tr>
<tr>
<td>SM-33</td>
<td>H</td>
<td>Cinnamyl</td>
<td>H</td>
<td>p-N(CH$_3$)$_2$-C$_6$H$_4$</td>
<td>2-Cinnamyl-3-(N$_{10}$-benzotriazolyl-acetamidyl)-5-(p-dimethylaminobenzylidine)-4-oxo-thiazolidine.</td>
</tr>
<tr>
<td>SM-34</td>
<td>H</td>
<td>Cinnamyl</td>
<td>C$_6$H$_3$</td>
<td>C$_6$H$_5$</td>
<td>2-Cinnamyl-3-(N$_{10}$-benzotriazolyl-acetamidyl)-5-(benzophenylidine)-4-oxo-thiazolidine.</td>
</tr>
<tr>
<td>SM-35</td>
<td>H</td>
<td>p-Chlorophenyl</td>
<td>H</td>
<td>o-Cl-C$_6$H$_4$</td>
<td>2-(p-Chlorophenyl)-3-(N$_{10}$-benzotriazolylacetamidyl)-5-(o-chlorobenzylidine)-4-oxo-thiazolidine.</td>
</tr>
</tbody>
</table>

Cont'd....
<table>
<thead>
<tr>
<th>Code No.</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>SM-36</td>
<td>H</td>
<td>p-Chlorophenyl</td>
<td>H</td>
<td>p-N(CH₃)₂-C₆H₄</td>
<td>2-(p-Chlorophenyl)-3-(N¹⁰-benzotriazolylacetamidyl)-5-(p-dimethylaminobenzylidene)-4-oxothiazolidine</td>
</tr>
<tr>
<td>SM-37</td>
<td>H</td>
<td>p-Chlorophenyl</td>
<td>C₆H₅</td>
<td>C₆H₅</td>
<td>2-(p-Chlorophenyl)-3-(N¹⁰-benzotriazolylacetamidyl)-5-(benzophenylidine)-4-oxothiazolidine</td>
</tr>
<tr>
<td>SM-38</td>
<td>H</td>
<td>o-Chlorophenyl</td>
<td>H</td>
<td>p-N(CH₃)₂-C₆H₄</td>
<td>2-(o-Chlorophenyl)-3-(N¹⁰-benzotriazolylacetamidyl)-5-(p-dimethylaminobenzylidene)-4-oxothiazolidine</td>
</tr>
<tr>
<td>SM-39</td>
<td>H</td>
<td>o-Chlorophenyl</td>
<td>C₆H₃</td>
<td>C₆H₅</td>
<td>2-(o-Chlorophenyl)-3-(N¹⁰-benzotriazolylacetamidyl)-5-(benzophenylidine)-4-oxothiazolidine</td>
</tr>
<tr>
<td>SM-40</td>
<td>C₆H₅</td>
<td>C₆H₅</td>
<td>H</td>
<td>p-N(CH₃)₂-C₆H₄</td>
<td>2-(2,2-Diphenyl)-3-(N¹⁰-benzotriazolyl-acetamidyl)-5-(p-dimethylamino-benzylidene)-4-oxothiazolidine</td>
</tr>
</tbody>
</table>
PART-II: Characterisation of the synthesised compounds by microanalysis, physical data, chromatography and spectral techniques

The melting points of the compounds have been determined in an open capillary and are uncorrected. Rf values were determined by TLC on silica gel coated plates using iodine as a developer. All the compounds were analysed for C, H and N percentage. The IR spectra of the representative compounds were recorded in KBr palletes on Acculab-10-spectrophotometer and $^1$H-NMR spectra of the representative compounds were recorded on Perking-Elmer R-32 spectrometer at 90 MHz using TMS as an internal standard.

PART-III: Evaluation of the biological activity of the synthesised products

The synthesised compounds were screened for their antibacterial, antifungal, antiinflammatory, analgesic and anticonvulsant activities. Some of the compounds were found to display remarkable pharmacological activity.