CHAPTER - 2

Section-2.1 : Literature survey and biological importance of phenothiazine and related compounds.

Section-2.2 : Literature survey and biological importance of carbazole and related compounds.

Section-2.3 : Literature survey and biological importance of thiazolidene and their 5-arylidene derivatives.

Section-2.4 : Aim and work plan of the research.
SECTION - 2.1: LITERATURE SURVEY AND BIOLOGICAL IMPORTANCE OF PHENOTHIAZINE AND RELATED COMPOUNDS

The first synthesis of phenothiazine was reported by Bernthsen\textsuperscript{19} about 80 years ago. Phenothiazine was of interest owing to its quinonoid derivatives an important aspect for sulphur dye chemistry. Research work in the field of phenothiazine was then stimulated by the discovery of the anthelmintic action of unsubstituted and C-substituted phenothiazines. During the last two decades, the exceptional pharmacological properties of some N-substituted phenothiazines for example the antihistaminic activity of promethazine [syn. 10-(2-dimethylamino-1-propyl)-phenothiazine] and particularly the psychotherapeutic action of chlorpromazine [syn. 2- Chloro-10-(3-dimethylamino-1-propyl)-phenothiazine], focused interest mainly on the synthesis and testing of a great number of compounds of this type. The phenothiazine drugs now play a very important part in chemotherapy.

It is more and more obvious that a deeper knowledge of the physical and chemical properties of the phenothiazine ring is necessary for the synthesis of new biologically active phenothiazine derivatives, and for the understanding of the mechanism of their interaction with the living organism. A small modification at the end of a side chain in phenothiazine, fundamental research in this field, has been carried out more intensively during the last two decades.
A large number of heterocyclic compounds are known today. Organic chemists have synthesised hundreds of new compounds every day. The description of all the heterocycles is not possible and is beyond the scope of the proposed work. However, a brief description of the presently selected heterocycle viz. phenothiazine has been given in this section.

Phenothiazines belong to a pharmaceutically important class of heterocycles\textsuperscript{20} and due to their pharmacological/biological efficacy, they are applied in a wide range such as tranquilizers\textsuperscript{21-26}, anthelmintics\textsuperscript{27-33}, antiinflammatory\textsuperscript{34-37}, antiemetics\textsuperscript{38-41}, neuroleptics\textsuperscript{42-46}, antihistamins\textsuperscript{47-57}, analgesics\textsuperscript{58-63}, sedatives\textsuperscript{64-65}, antipsychotics\textsuperscript{66-75}, antivirals\textsuperscript{76-77}, diuretics\textsuperscript{78-79}, fungicides\textsuperscript{80-82}, insecticides\textsuperscript{83-85}, anaesthetics\textsuperscript{86-87}, bactericides\textsuperscript{88-92}, antimalarials\textsuperscript{93-94}, tuberculostatics\textsuperscript{95-99} etc. Phenothiazines have also known significant effects against cancer\textsuperscript{100-118}. In addition to their pharmacological activities, they also find uses in industries as indicators\textsuperscript{119}, antioxidants\textsuperscript{120-122}, dyes\textsuperscript{123-124}, heatstabilizers\textsuperscript{125}, photosensitizers\textsuperscript{126} and lubricants\textsuperscript{127}. Saito has used phenothiazines in solid electrolytic batteries\textsuperscript{128}.

Most interestingly, phenothiazines are also able to cleave DNA upon photochemical induction\textsuperscript{129}. As a consequence of a low oxidation potential, phenothiazine (nitrogen-sulphur heterocycles) readily form stable radical cations and a key role of their physiological activities can be attributed to this circumstance\textsuperscript{130}.

Promethazine (67) (trade name Phenergan) are antihistaminic, antitiemetic, sedative, antimotion sickness and show powerful depressant effect on the central nervous system\textsuperscript{131}.
Phenothiazine is itself a veterinary anthelmintic agents as well as an insecticide. Methylene blue (68) has long been used as a biological strain\textsuperscript{131}.

1-(C-Aryl/trichloromethyl-C-aryl-amido/imido-methyl)-phenothiazines (69) are antiviral activity\textsuperscript{132}.

where \( R = \text{CCl}_3/H/C_6H_5; \quad R^1 = \text{benzamido/phthalamido} \)
Recent reported phenothiazine derivatives such as N-[2-substituted aryl-isoxazolin-4-yl]-phenothiazine (70), N[2-substituted aryl-3-substituted aryldiene-isoxazolin-4-yl]-phenothiazine (71) and N-[2-substituted aryl-3-substituted arylaminomethylene-isoxazolin-4-yl]-phenothiazines, (72) are reported as strong antipsychotic as well as anticonvulsant activities\textsuperscript{133}.

![Chemical Structures](image)

Where

\[ R = H /\text{OCH}_3/ N (\text{CH}_3)_2 \]
\[ R^1 = 4-\text{OH}, 3-\text{OCH}_3/4-N (\text{CH}_3)_2 \]
\[ R^2 = 2-\text{Cl}/3-\text{Cl}/2-\text{OCH}_3 \]
Promazine (73), chlorpromazine (74) and triflupromazine (75) are tranquilizer and antiemetic activity\textsuperscript{134}.

\begin{figure}
\begin{center}
\includegraphics[width=\textwidth]{figure1.png}
\end{center}
\caption{(73)}
\end{figure}

\begin{figure}
\begin{center}
\includegraphics[width=\textwidth]{figure2.png}
\end{center}
\caption{(74)}
\end{figure}

\begin{figure}
\begin{center}
\includegraphics[width=\textwidth]{figure3.png}
\end{center}
\caption{(75)}
\end{figure}

Pyrathiazine [trade name: Pyrrolazote] (76) showed antihistaminic and antiparkinsonian activity\textsuperscript{135}.

\begin{figure}
\begin{center}
\includegraphics[width=\textwidth]{figure4.png}
\end{center}
\caption{(76)}
\end{figure}
N\textsuperscript{10}- (N-Substituted piperazinoalkyl)-phenothiazines (77) are claimed as paranoid sedative and neuroleptic agents\textsuperscript{136,137}.

![Chemical structure of N\textsuperscript{10}- (N-Substituted piperazinoalkyl)-phenothiazines](image)

where \( R = \text{CH}_3/\text{C}_2\text{H}_5/\text{C}_3\text{H}_7 \) etc.

(77)

The following phenothiazine derivative (78) has reported as a good antidepressant agent\textsuperscript{138}.

![Chemical structure of a phenothiazine derivative](image)

(78)

\( \alpha\)-([Di-n-butylaminomethyl]-2-benzo[a]-phenothiazinyl)methanol hydrochloride (79) is a good antimalarial agent\textsuperscript{139}. 

![Chemical structure of \( \alpha\)-([Di-n-butylaminomethyl]-2-benzo[a]-phenothiazinyl)methanol hydrochloride](image)
10-[(2-(1-Methylpiperidin-2-one-6-yl)ethyl]-2-methylsulphinyl-10-H-phenothiazine-5-sulphoxide (80) and 10-[(2-(1-Methylpiperidin-2-one-6-yl)ethyl]-2-methylsulphonyl-10H-phenothiazine-5-sulphone (81) are reported as antipsychotic drugs\(^\text{140}\).
Arylated phenothiazines such as 5-aryl-2-(phenothiazine-10-yl-carbonyl methyl)-3-(substituted phenyl)-2H-tetrazolium chlorides (82) have been synthesised and displayed antiparkinsonian activity\textsuperscript{141}.

where $R = 2 - \text{CH}_3 / 3 - \text{CH}_3$
N-2-(Nitro substituted phenoxy)-acetyl-phenothiazine (83) has been synthesised and found to display anthelminitic activity\textsuperscript{142}.

![Chemical Structure](image)

Various N-substituted phenothiazines (84) have been synthesised which showed anthelmintic, antiinflammatory and antimicrobial activities\textsuperscript{142}.

![Chemical Structure](image)

where $R = H / CH_3$

![Chemical Structure](image)

A series of 2-arylideneamino-5-(N\textsuperscript{10}-phenothiazinomethyl)-1, 3,4-thiadiazoles (85) and 1-[N\textsuperscript{10}-phenothiazinomethyl]-1', 3', 4'-thiadiazol-2'-Y]-4-substituted aryl-2-azetidinones (86) have been synthesised which exhibited antifungal activity against some selected pathogens\textsuperscript{143}. 

![Chemical Structure](image)
where $R = H$ ; $R^1 = \text{substituted aromatic ring}$

(85)

where $R = H$ ; $R^1 = \text{substituted aromatic ring}$

(86)

4-Aryl-1-(Phenothiazinoamidyl)-2-azetidinones (87) are found to exhibit antiinflammatory activity$^{144}$.

where $\text{Ar} = \text{Phenyl} / \text{substituted phenyl}$

(87)
Thioproperazine (88) and its sulphonlic acid derivatives (89) have antimicrobial activity.\textsuperscript{145}

\begin{center}
\includegraphics[width=0.5\textwidth]{molecule88.png}
\end{center}

(88)

\begin{center}
\includegraphics[width=0.5\textwidth]{molecule89.png}
\end{center}

(89)

2-(4-Methylthiazol-2-yl)-10-(2-methyl-3,3-dimethylaminopropyl)-phenothiazine (90) and 2-thiocarboxamido-10-(2-methyl-3,3-dimethylaminopropyl)-phenothiazine (91) displayed antiinflammatory and antipsychotic activities.\textsuperscript{146}
2, 10-Disubstituted phenothiazines (92) are found to display antiinflammatory activity\textsuperscript{147}. 

(90) 

(91) 

(92)
Butaperazine (93) and acetophenazine (94) are good tranquilizer agents\textsuperscript{134}.

\begin{center}
\begin{align*}
\text{(93)} &= \\
\text{(94)} &= 
\end{align*}
\end{center}

1,3,7,9-Tetrabromo-10 \, [\alpha-(2-(4-substituted-phenyl)-3-chloro-2-oxo-1-azetidinylamino)-acetyl]-phenothiazines (95) are found to display tuberculostatic activity\textsuperscript{148}.

\begin{center}
\begin{align*}
\text{(95)} &= \\
\end{align*}
\end{center}

where \( X = \text{CH}_3 / \text{OCH}_3 / \text{OH} / \text{NO}_2 / \text{Cl} \)
8-Trifluoromethyl-phenothenazine-1-carboxylic acid (96) has interesting antiinflammatory activity. 8-chloro-3-hydroxy-phenothenazine-2-carboxylic acid (97) produced a significant inhibition of granuloma growth in carrageenan filter paper granuloma assay in adenal ectomized rats.

![Chemical Structures](image)

(96) ![Chemical Structures](image) (97)

10-Phenothenazinyl carbonyl-methyl β-10-phenothenazinyl propionate (98) has found to show anthelmintic property.

![Chemical Structures](image)

(98)

The phenothenazine derivatives (99) have been synthesised and found to possess antimicrobial activity against gram positive bacteria, Staphylococcus aureus and Escherichia coli.

![Chemical Structures](image)

where R=H/4-Cl/5-Cl/6-NO2/6-OCH3/6-COOC2H5/6-NHCOCH3

(99)
SECTION - 2.2: LITERATURE SURVEY AND BIOLOGICAL IMPORTANCE OF CARBAZOLE AND RELATED COMPOUNDS

The interest in the chemistry of carbazole is beginning to increase steadily since functionalized carbazoles are synthetically interesting building blocks for certain carbazole alkaloids and for pharmacologically attractive carbazole derivatives.

Carbazole, anthracene and phenanthrene occurs together in the same fraction of coal tar. The cost of isolation of any one of the three member depends on the utilization of all three. Phenathrene has never been in demand, and the potential supply of carbazole also has always been greater than sales. Thus anthracene remained the only member of major interest. As the European dyestuff industries until about 1920 depended almost entirely on coal-tar anthracene, as a source for anthraquinone, the utilization of carbazole became of vital interests to the dye and coal-tar industries alike.

The efficiency of carbazole derivatives as chemotherapeutic agents is well established and their chemistry has been extensively studied. Literature survey reveals that carbazole derivatives are associated with potent biological activities such as antiinflammatory, analgesic\textsuperscript{154}, antibiotic\textsuperscript{155}, insecticidal\textsuperscript{156}, fungicidal, bactericidal and trypanocidal\textsuperscript{157}, diuretic\textsuperscript{158}, anticonvulsant, antiallergic and neuroleptic\textsuperscript{159}.

2-Amino-5-(N\textsuperscript{0}-carbazolylmethyl -1,3,4-thiadiazole (100) is a good antifungal and antibacterial agents\textsuperscript{160}. 

2-substituted aryldenylamino-5-(N\textsuperscript{0}-carbazolylmethyl)-1,3,4-thiadiazoles (101) are found to exhibit antiinflammatory and analgesic activities\textsuperscript{154}.

\begin{equation}
\text{Ar} = \text{Substituted aryl}
\end{equation}

(101)

1-[5'-N\textsuperscript{0}-carbazolylmethyl]-1',3',4'-thiadiazol-2'-yl)-4-substituted aryl-3-chloro-2-oxo-azetidines (102) are reported to have an anticonvulsant activity\textsuperscript{159}.

\begin{equation}
\text{where } \text{Ar} = \text{Substituted aryl}
\end{equation}

(102)
Cis-9-[3-(3,5-Dimethyl-1-piperazinyl)-propyl]-carbazole (103) shows antipsychotic activity\textsuperscript{160}.

\begin{center}
\includegraphics[width=0.3\textwidth]{103}
\end{center}

(RR)-trans-9-[3-(3,5-Dimethyl-1-piperazinyl)propyl]-carbazole (104) is used as tranquilizer\textsuperscript{161}.

\begin{center}
\includegraphics[width=0.3\textwidth]{104}
\end{center}

$\beta$-1-(pyrrolidyl)-ethyl chloride of carbazole (105) is reported to have antihistamine activity\textsuperscript{162}.

\begin{center}
\includegraphics[width=0.3\textwidth]{105}
\end{center}
2-(3-Diethylamino-1-hydroxy-n-propyl)-9-methyl-carbazole (106) is an analgesic agent.

N-alkylamino carbazoles (107) and (108) were prepared and reported to have anticonvulsant and diuretic activities.\textsuperscript{163}
2-Chloro-9-(dimethylaminopropyl)-7-methoxy-carbazole (109) was found to show anticonvulsant and diuretic properties\textsuperscript{164}.

Oxacarbazole (110) showed antiallergic action\textsuperscript{165}. The analgesic and antiinflammatory properties of 2-carbazole propionic acid (Trade Name: Carpofen) (111) received widespread attention\textsuperscript{165} and its derivatives are comparable to those of indomethacin with a greater safety margin.
3-Nitro-9-0-Carboxyphenylcarbazole (112) is used as tranquilizer and antihistaminic agents\textsuperscript{166}.

![Chemical structure of 3-Nitro-9-0-Carboxyphenylcarbazole (112)]

9-(Diethoxymethyl)-carbazole (113) and 4-Methoxycarbazole-1-carboxaldehyde (114) are antiemetic, neuroleptic and antivomitic activities\textsuperscript{167}.

![Chemical structures of 9-(Diethoxymethyl)-carbazole (113) and 4-Methoxycarbazole-1-carboxaldehyde (114)]

A number of substituted 6H-pyridocarbazoles (115) and the corresponding octahydro compounds (116) were also synthesised and found to show anticancerous activity\textsuperscript{168}. 

![Chemical structures of A number of substituted 6H-pyridocarbazoles (115) and the corresponding octahydro compounds (116)]
Some new pyrido-carbazole derivatives were synthesised. The following compound (117) reported to exhibit neuroleptic and antiinflammatory activities\textsuperscript{169}.

![Chemical Structure](117)
SECTION - 2.3: LITERATURE SURVEY AND BIOLOGICAL IMPORTANCE OF THIAZOLIDINE AND THEIR 5-ARYLIDENE 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 structures]

Thiazolidine 4-oxo-thiazolidine

4-oxo-thiazolidines have been prepared by the reported methods as given in the literature starting with:

(i) N-aryl/aralkyl-α-aryl-sulphonyl-α-cyanothiactamides with chloroacetic acid\textsuperscript{170}.

(ii) 1-(4-substituted benzylidene)-2-substituted aryl-acetyl hydrazone treated with thioglycolic acid followed by substituted carbonyls in the presence of sodium ethoxide\textsuperscript{171} and

(iii) Substituted arylidene hydrazino heterocyclic compound on cyclocondensation with thioglycolic acid in the presence of anhydrous zinc chloride\textsuperscript{172}. 
4-oxo-thiazolidines and their 5-arylidene derivatives possess a variety of therapeutic activity such as antifungal\textsuperscript{173}, antibacterial\textsuperscript{175}, anticonvulsant\textsuperscript{176}, amoebicidal\textsuperscript{177}, hypnotic\textsuperscript{178}, antitubercular\textsuperscript{179}, nematocidal\textsuperscript{180}, mosquitorepellent\textsuperscript{181}, anti-HIV, anticancer and anaesthetic\textsuperscript{182} etc.

2-(phenylamino) imino-4-oxo-thiazolidine\textsuperscript{183} (118) act as a potent fungicides and bactericides.

\begin{center}
\begin{tikzpicture}
\node[draw] (1) at (0,0) {$\text{CH}_2$};
\node [draw] (2) at (0,-1) {$\text{NH}$};
\node [draw] (3) at (1,-1) {$\text{N}$};
\node [draw] (4) at (1,0) {$\text{C}$};
\node [draw] (5) at (1,1) {$\text{NH}$};
\node [draw] (6) at (1,2) {$\text{S}$};
\node [draw] (7) at (2,2) {$\text{CH}_2$};
\node [draw] (8) at (2,1) {$\text{NH}$};
\node [draw] (9) at (2,0) {$\text{CO}$};
\node [draw] (10) at (3,0) {$\text{R}$};
\node [draw] (11) at (3,-1) {$\text{O}$};
\node [draw] (12) at (3,-2) {$\text{CH}_3$};
\node [draw] (13) at (3,-3) {$\text{Br}$};
\node [draw] (14) at (4,0) {$\text{C}_6\text{H}_5$};
\node [draw] (15) at (4,-1) {$\text{N}$};
\node [draw] (16) at (5,-1) {$\text{S}$};
\end{tikzpicture}
\end{center}

\begin{center}(118)\end{center}

4-Thiazolidinone containing bromophenol residue (119) bears a versatile medicinal\textsuperscript{184} properties.

\begin{center}
\begin{tikzpicture}
\node [draw] (1) at (0,0) {$\text{CH}_3$};
\node [draw] (2) at (0,-1) {$\text{O}$};
\node [draw] (3) at (0,-2) {$\text{Br}$};
\node [draw] (4) at (1,0) {$\text{N}$};
\node [draw] (5) at (1,-1) {$\text{S}$};
\node [draw] (6) at (1,-2) {$\text{R}$};
\node [draw] (7) at (2,0) {$\text{C}_6\text{H}_5$};
\node [draw] (8) at (2,-1) {$\text{OH}$};
\node [draw] (9) at (2,-2) {$\text{R}$};
\end{tikzpicture}
\end{center}

\begin{center}(119)\end{center}

where $R = \text{H/CH}_3$

Thymol derivatives (120) of thiazolidinone are observed\textsuperscript{185} to possess antiseptics\textsuperscript{186} and antifungal properties\textsuperscript{187}.
where $R = \text{CH}_3/\text{C}_2\text{H}_5/\text{C}_3\text{H}_7$

\[(120)\]

The bacteriostatic, tuberculostatic, fungistatic and moluscicidal activities of benzamides\cite{188} when coupled with antibiotic and antimicrobial properties of thiazolidinone\cite{189} compounds with the structure (121) have been reported\cite{190} in literature.

\[(121)\]

Synthesis of spirothiazolidinones\cite{191, 192} (122 - 125) have been carried out and found to show fungicidal and bactericidal activities.

\[(122)\]  \[\text{NHCO} \quad \text{N} \quad \text{CO}\]
\[(123)\]  \[\text{N} \quad \text{CO}\]
Some new thienylthiazolidin-4-ones (126) are important to keep pace with the appearance of resistant bacterial strains.

where $X = H/Br$
Antimicrobial activity\textsuperscript{194,195} has been noted in 9-aminoacridine derivatives of 4-thiazolidinone (127).

\[
\begin{align*}
\text{NH} & \quad \text{N} \\
\text{R} & \quad \text{O} \quad \text{C} \quad \text{S} \\
\text{CH}_3 & \quad \text{C} \\
\end{align*}
\]

where $R = \text{C}_6\text{H}_5 / 2\text{Cl-} \text{C}_6\text{H}_4 / 2,6 \text{Cl}_2\text{C}_6\text{H}_3 / 3\text{-NH}_2\text{-} \text{C}_6\text{H}_4$

(127)

4-oxo-thiazolidines (128) 2-imino-4-oxo-thiazolidines (129) and their 5-arylidene derivatives (130,131) have been prepared and found to display anti-HIV, anticancer and antitubercular activities\textsuperscript{196}.

\[
\begin{align*}
\text{HC}_2&\quad \text{CONH-N-CH-CH-} \\
&\quad \text{O} \quad \text{C} \quad \text{S} \\
&\quad \text{OCH}_3
\end{align*}
\]

(128)

\[
\begin{align*}
\text{CH}_2 &\quad \text{CO-} \quad \text{NH-N-C=N-} \\
&\quad \text{C} \quad \text{S} \\
&\quad \text{OCH}_3
\end{align*}
\]

(129)
where \( R = \) Different aryl group

\[
(130)
\]

where \( R = \) Different aryl group

\[
(131)
\]

2-[3'-(4'-Acetyl aminophenyl)-2'-aryl-4'-thiazolidin-5-yl]-4, 5-dihydroimidazole (132) was found to be antitubercular activity against \( H_37Rv \) strain of \textit{Mycobacterium tuberculosis}. The substitution at 2-and 4-position of hydroxy group in phenyl ring are effective against \textit{Escherichia coli} \(^{197}\).

where \( R = 2\text{-OH/4-OH} \)

\[
(132)
\]
3-Arylamino-2-arylimino-4-thiazolidinones (133) have been synthesised through appropriate routes\textsuperscript{199} and evaluated for their cardiovascular activity in anaesthetized cats.

\[
\begin{align*}
\text{O} & \quad \text{N} \quad \text{N} \\
\text{C} & \quad \text{S} \\
\text{N} & \quad \text{N} \\
\text{R} & \quad \text{R}^1
\end{align*}
\]

where \( R = \text{H} / \text{Cl} \); \( R^1 = \text{H} / \text{CH}_3 / 2-\text{CH}_3 \)

\[(133)\]

Multiple biological\textsuperscript{199-201} activities have been associated with N-triazine substituted thiazolidinones (134 and 135).

\[
\begin{align*}
\text{NH} & \quad \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CH}_3 \\
\text{CH}_3 - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{HN} \\
\text{N} & \quad \text{C} \quad \text{S} \\
\text{N} & \quad \text{C} \quad \text{R}
\end{align*}
\]

where \( R = \text{C}_6\text{H}_6 / 4-\text{NH}_2\text{C}_6\text{H}_4 / 4-\text{NO}_2\text{C}_6\text{H}_4 \)

\[(134)\]
Where $R = \text{H/CH}_3$ ; $R^1 = \text{C}_6\text{H}_5 / 4\text{-OCH}_3 - \text{C}_6\text{H}_4 / 4\text{-CH}_3 - \text{C}_6\text{H}_4$

(135)

A possible structure activity relationship\(^{202}\) have been discussed for some 3-(1,3,4-thialiazol-2-yl)-4-thiazolidinones (136) with special studies on fungitoxicity\(^{203}\) caused by *Aspergillus niger* and *Helminthosporium oryzae*.

(136)

where $R = 4\text{-Cl} / 3\text{-CH}_3 / 2,4\text{-}(\text{CH}_3)_2$ ; $R^1 = \text{H/OH/Cl}$

Antibacterial and antituberculostatic activities have been noticed in heterocyclic derivatives of thiazolidinone\(^{204}\)(137).
where \( R = -C_6H_5/-ClC_6H_4/-NO_2-C_6H_4/-OH C_6H_4 \)

(137)

Antibacterial activities\(^{205}\) were observed in 5-carboxymethyl-4-thiazolidinones bearing bithiazole moiety\(^{206}\) (138).

where \( X = H/Cl/OCH_3/CH_3 \); \( Y = H/CH_3/OCH_3 \)

(138)

2-Aryl-3-[5'-0-hydroxyphenyl-1',3',4'-thiadiazol-2'-yl]-5H-methyl-4-thiazolidinones (139) have been synthesised and were screened for their antibacterial activity against *Streptococcus aureus* and *Escherichia coli*, and antifungal activity *Aspergillus niger* and *Candida albicans*\(^{207}\), which gave positive effect.
Some new 1,8-naphthyridinyl-4-thiazolidinones (140) have reported as antibacterial agents\(^{208}\).

4-oxo-thiazolidine (141) with the following structure has been reported as antibacterial activity\(^{209}\).
2-[(3'-methyl-7'-substituted-4H-1,4-benzothiazin-2'-yl)-methyl-ketoiminyl]-imino-3-(4''-substituted phenyl)-4-thiazolidinones (142) have been reported as antimicrobial agent\textsuperscript{210}.

where \( R = H/\text{CH}_3/\text{Cl} \); \( R^1 = H/\text{CH}_3/\text{OCH}_3/\text{Cl} \)  
(142)
SECTION - 2.4: AIM AND WORK PLAN OF THE RESEARCH

The literature survey on phenothiazines, carbazoles, 4-oxothiazolidines and their 5-arylidene derivatives has promoted the author to synthesise some new $\text{N}^{10}$- phenothiazine and $\text{N}^{9}$- carbazole derivatives of 4-oxo-thiazolidines and their 5-arylidene, 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: Characterisation of the compounds by chemical methods, micro analytical data and spectral techniques.


(a) *Antibacterial*,

(b) *Antifungal*,

(c) *Antiinflammatory and*

(d) *Diuretic*.

PART-I: SYNTHESIS OF NEW HETEROCYCLIC COMPOUNDS

Six series of the compounds have been synthesised by following the Schemes-1 (general), 2 and 3 respectively.
Scheme - 1

where

\[
\text{Het} \cong \text{NH} = \text{Phenothiazine} / \text{carbazole} \\
R = H/CH_3 \\
\text{Ar} = \text{C}_6\text{H}_5/\text{Cl}, \text{Br-Sub.C}_6\text{H}_4
\]
Scheme - 2

![Chemical reaction scheme](image)

VJ 1

VJ 2

VJ 3-9

VJ 10-16

VJ 17-23
SERIES-1:  \( N^{10\alpha}\text{-}(\text{SUBSTITUTED ARYLIDENEHYDRAZINO})\text{-ACETYL}\text{-}10\text{H-PHENOTHIAZINES} \)

The compounds of Series-1 (VJ 3-9) (Table-1) have been synthesised through the compounds 1 and 2 by the first two steps of the Scheme-2.

**TABLE 1: LIST OF THE COMPOUNDS SYNTHESISED UNDER SERIES-1**

<table>
<thead>
<tr>
<th>Compounds Code No.</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>VJ – 3</td>
<td>( N^{10\alpha}\text{-}(\text{Benzylidenehydrazino})\text{-acetyl}\text{-}10\text{H-phenothiazine} )</td>
</tr>
<tr>
<td>VJ – 4</td>
<td>( N^{10\alpha}\text{-}(\text{2-Chloroacetophenonlidinhydrazino})\text{-acetyl}\text{-}10\text{H-phenothiazine} )</td>
</tr>
<tr>
<td>VJ – 5</td>
<td>( N^{10\alpha}\text{-}(\text{3-Chloroacetophenonlidinhydrazino})\text{-acetyl}\text{-}10\text{H-phenothiazine} )</td>
</tr>
<tr>
<td>VJ – 6</td>
<td>( N^{10\alpha}\text{-}(\text{4-Chloroacetophenonlidinhydrazino})\text{-acetyl}\text{-}10\text{H-phenothiazine} )</td>
</tr>
<tr>
<td>VJ – 7</td>
<td>( N^{10\alpha}\text{-}(\text{2-Bromoacetophenonlidinhydrazino})\text{-acetyl}\text{-}10\text{H-phenothiazine} )</td>
</tr>
<tr>
<td>VJ – 8</td>
<td>( N^{10\alpha}\text{-}(\text{3-Bromoacetophenonlidinhydrazino})\text{-acetyl}\text{-}10\text{H-phenothiazine} )</td>
</tr>
<tr>
<td>VJ – 9</td>
<td>( N^{10\alpha}\text{-}(\text{4-Bromoacetophenonlidinhydrazino})\text{-acetyl}\text{-}10\text{H-phenothiazine} )</td>
</tr>
</tbody>
</table>
SERIES-2: 2-SUBSTITUTED ARYL-3-N\textsuperscript{10}-[(ACETYLAMINO)-1,3-
THIAZOLIDIN-4-ONES] -10H-PHENOTHIAZINES

The compounds of the Series-2 (VJ 10-16) (Table – 2) have
been synthesised by using the compounds of Series-1 (VJ 3-9) as
precursors by following the Scheme-2.

TABLE 2 : LIST OF THE COMPOUNDS SYNTHESISED UNDER SERIES-2

<table>
<thead>
<tr>
<th>Compounds Code No.</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>VJ – 10 : 2-[Benzylmethyl]-3-N\textsuperscript{10}-[(acetylamino)-1,3-thiazolidin-4-ones]-10H-pheno-thiazine.</td>
<td></td>
</tr>
<tr>
<td>VJ – 11 : 2-[(2-Chlorophenyl)-methyl]-3-N\textsuperscript{10}-[(acetylamino)-1,3-thiazolidin-4-ones]-10H-pheno-thiazine.</td>
<td></td>
</tr>
<tr>
<td>VJ – 12 : 2-[(3-Chlorophenyl)-methyl]-3-N\textsuperscript{10}-[(acetylamino)-1,3-thiazolidin-4-ones]-10H-pheno-thiazine.</td>
<td></td>
</tr>
<tr>
<td>VJ – 13 : 2-[(4-Chlorophenyl)-methyl]-3-N\textsuperscript{10}-[(acetylamino)-1,3-thiazolidin-4-ones]-10H-pheno-thiazine.</td>
<td></td>
</tr>
<tr>
<td>VJ – 14 : 2-[(2-Bromophenyl)-methyl]-3-N\textsuperscript{10}-[(acetylamino)-1,3-thiazolidin-4-ones]-10H-pheno-thiazine.</td>
<td></td>
</tr>
<tr>
<td>VJ – 15 : 2-[(3-Bromophenyl)-methyl]-3-N\textsuperscript{10}-[(acetylamino)-1,3-thiazolidin-4-ones]-10H-pheno-thiazine.</td>
<td></td>
</tr>
<tr>
<td>VJ – 16 : 2-[(4-Bromophenyl)-methyl]-3-N\textsuperscript{10}-[(acetylamino)-1,3-thiazolidin-4-ones]-10H-pheno-thiazine.</td>
<td></td>
</tr>
</tbody>
</table>
SERIES-3: 5-ARYLIDINE-2-SUBSTITUTED ARYL-3-N\textsuperscript{10}-(ACETYLAMINO) -1,3-THIAZOLIDIN-4-ONES]-10H-PHENOTHIAZINES

The compounds of Series-3 (VJ 17-23) (Table-3) have been synthesised by using the compounds of Series-2 (VJ 10-16) as precursors by following the Scheme-2.

TABLE 3: LIST OF THE COMPOUNDS SYNTHESISED UNDER SERIES-3

<table>
<thead>
<tr>
<th>Compounds Code No.</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>VJ - 17:</td>
<td>5-Benzylidene-2-phenyl-3-N\textsuperscript{10}[(acetylamino)-1,3-thiazolidin-4-ones]-10H-phenothiazine.</td>
</tr>
<tr>
<td>VJ - 18:</td>
<td>5-(2-Chloroacetophenonlidin)2-[(2-chlorophenyl)-methyl]-3-N\textsuperscript{10}[(acetylamino)-1,3-thiazolidin-4-ones]-10H-phenothiazine.</td>
</tr>
<tr>
<td>VJ - 19:</td>
<td>5-(3-Chloroacetophenonlidin)2-[(3-chlorophenyl)-methyl]-3-N\textsuperscript{10}[(acetylamino)-1,3-thiazolidin-4-ones]-10H-phenothiazine.</td>
</tr>
<tr>
<td>VJ - 20:</td>
<td>5-(4-Chloroacetophenonlidin)2-[(4-chlorophenyl)-methyl]-3-N\textsuperscript{10}[(acetylamino)-1,3-thiazolidin-4-ones]-10H-phenothiazine.</td>
</tr>
<tr>
<td>VJ - 21:</td>
<td>5-(2-Bromoacetophenonlidin)2-[(2-bromophenyl)-methyl]-3-N\textsuperscript{10}[(acetylamino)-1,3-thiazolidin-4-ones]-10H-phenothiazine.</td>
</tr>
<tr>
<td>VJ - 22:</td>
<td>5-(3-Bromoacetophenonlidin)2-[(3-bromophenyl)-methyl]-3-N\textsuperscript{10}[(acetylamino)-1,3-thiazolidin-4-ones]-10H-phenothiazine.</td>
</tr>
<tr>
<td>VJ - 23:</td>
<td>5-(4-Bromoacetophenonlidin)2-[(4-bromophenyl)-methyl]-3-N\textsuperscript{10}[(acetylamino)-1,3-thiazolidin-4-ones]-10H-phenothiazine.</td>
</tr>
</tbody>
</table>
Scheme - 3

CICOCH₂Cl

VJ - 1

COCH₂Cl

NH₂NH₂

VJ - 2

O =C<Ar

VJ 24-30

COCH₂NHN=C<Ar

HSCH₂COOH

VJ 31-37

C₂H₅ONa/O = C<Ar

VJ 38-44
SERIES - 4 : $N^9$-$[\alpha$-(SUBSTITUTED ARYLIDENEHYDRAZINO) ACETYL] - 9H - CARBAZOLE

The compounds of the Series-4 (VJ 24-30) (Table-4) have been synthesised through the compounds VJ-1 and VJ-2 by the first two steps of the Scheme-3.

**TABLE 4: LIST OF THE COMPOUNDS SYNTHESISED UNDER SERIES-4**

<table>
<thead>
<tr>
<th>Compounds Code No.</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>VJ – 24</td>
<td>$N^9$-[\alpha-(Benzylidenehydrazino) acetyl]-9H-carbazole.</td>
</tr>
<tr>
<td>VJ – 26</td>
<td>$N^9$-[\alpha-(3-Chloroacetophenonlidinhydrazino) acetyl]-9H-carbazole.</td>
</tr>
<tr>
<td>VJ – 27</td>
<td>$N^9$-[\alpha- (4-Chloroacetophenonlidinhydrazino) acetyl]-9H-carbazole.</td>
</tr>
<tr>
<td>VJ – 29</td>
<td>$N^9$-[\alpha- (3-Bromoacetophenonlidinhydrazino) acetyl]-9H-carbazole.</td>
</tr>
<tr>
<td>VJ – 30</td>
<td>$N^9$-[\alpha- (4-Bromoacetophenonlidinhydrazino) acetyl]-9H-carbazole.</td>
</tr>
</tbody>
</table>
SERIES - 5 : 2-SUBSTITUTED ARYL-3-N\(^9\)-[(ACETYLAMINO)-1,3-
THIAZOLIDIN- 4-ONES]-9H-CARBAZOLEs

The compounds of the Series- 5 (VJ 31-37) (Table-5) have
been synthesised by using the compounds of Series-4 (VJ 24-30) as
precursors by following the Scheme-3.

**TABLE 5: LIST OF THE COMPOUNDS SYNTHESISED UNDER SERIES-5**

<table>
<thead>
<tr>
<th>Compounds Code No.</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>VJ – 31: 2-(Benzylmethyl)-3-N(^9)-[(acetylamino)-1,3-thiazolidin-4-ones]-9H-carbazole.</td>
<td></td>
</tr>
<tr>
<td>VJ – 32: 2[(2-Chlorophenyl)-methyl]-3-N(^9)-[(acetylamino)-1,3-thiazolidin-4-ones]-9H-carbazole.</td>
<td></td>
</tr>
<tr>
<td>VJ – 33: 2[(3-Chlorophenyl)-methyl]-3-N(^9)-[(acetylamino)-1,3-thiazolidin-4-ones]-9H-carbazole.</td>
<td></td>
</tr>
<tr>
<td>VJ – 34: 2[(4-Chlorophenyl)-methyl]-3-N(^9)-[(acetylamino)-1,3-thiazolidin-4-ones]-9H-carbazole.</td>
<td></td>
</tr>
<tr>
<td>VJ – 35: 2[(2-Bromophenyl)-methyl]-3-N(^9)-[(acetylamino)-1,3-thiazolidin-4-ones]-9H-carbazole.</td>
<td></td>
</tr>
<tr>
<td>VJ – 36: 2[(3-Bromophenyl)-methyl]-3-N(^9)-[(acetylamino)-1,3-thiazolidin-4-ones]-9H-carbazole.</td>
<td></td>
</tr>
<tr>
<td>VJ – 37: 2[(4-Bromophenyl)-methyl]-3-N(^9)-[(acetylamino)-1,3-thiazolidin-4-ones]-9H-carbazole.</td>
<td></td>
</tr>
</tbody>
</table>
SERIES – 6 : 5-ARYLIDENE-2-SUBSTITUTED ARYL-3-N⁹-[ (ACETYL AMINO)-1,3-THIAZOLIDIN-4-ONES]-9H-CARBAZOLE

The compounds of the Series- 6 (VJ 38-44) (Table 6) have been synthesised by using the compounds of Series - 5 (VJ 31-37) as precursors by following the Scheme - 3.

TABLE 6 : LIST OF THE COMPOUNDS SYNTHESISED UNDER SERIES- 6

<table>
<thead>
<tr>
<th>Compounds Code No.</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>VJ – 38 :</td>
<td>5-Benzylidene-2-benzyl-3-N⁹-[ (acetylamino)-1,3-thiazolidin-4-ones]-9H-carbazole.</td>
</tr>
<tr>
<td>VJ – 39 :</td>
<td>5-(2-Chloroacetophenonlidin)-2-{[2-chlorophenyl]-methyl]-3-N⁹-[ (acetylamino)-1,3-thiazolidin-4-ones]-9H-carbazole.</td>
</tr>
<tr>
<td>VJ – 40 :</td>
<td>5-(3-Chloroacetophenonlidin)-2-{[3-chlorophenyl]-methyl]-3-N⁹-[ (acetylamino)-1,3-thiazolidin-4-ones]-9H-carbazole.</td>
</tr>
<tr>
<td>VJ – 41 :</td>
<td>5-(4-Chloroacetophenonlidin)-2-{[4-chlorophenyl]-methyl]-3-N⁹-[ (acetylamino)-1,3-thiazolidin-4-ones]-9H-carbazole.</td>
</tr>
<tr>
<td>VJ – 42 :</td>
<td>5-(2-Bromoacetophenonlidin)-2-{[2-bromophenyl]-methyl]-3-N⁹-[ (acetylamino)-1,3-thiazolidin-4-ones]-9H-carbazole.</td>
</tr>
<tr>
<td>VJ – 43 :</td>
<td>5-(3-Bromoacetophenonlidin)-2-{[3-bromophenyl]-methyl]-3-N⁹-[ (acetylamino)-1,3-thiazolidin-4-ones]-9H-carbazole.</td>
</tr>
<tr>
<td>VJ – 44 :</td>
<td>5-(4-Bromoacetophenonlidin)-2-{[4-bromophenyl]-methyl]-3-N⁹-[ (acetylamino)-1,3-thiazolidin-4-ones]-9H-carbazole.</td>
</tr>
</tbody>
</table>
PART-II: CHARACTERISATION OF THE SYNTHESISED COMPOUNDS

The melting points of the compounds were 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 infrared spectra of the representative compounds were recorded in KBr palletes on Acculab-10 spectrophotometer and $^1$HNMR spectra of the representative compounds were recorded on Brucker DRX 300 spectrometer 200 MHz using TMS as an internal standard.

PART-III: BIOLOGICAL ACTIVITY OF THE SYNTHESISED COMPOUNDS

The synthesised compounds were screened for their antibacterial, antifungal, antiinflammatory and diuretic activities by the reported methods. Some of the compounds were found to display remarkable biological activity.