CHAPTER II

2.1 - General Review of 2-Mercaptobenzothiazole and Related Compounds

2.2 - Aim and Work Plan of the Research Work
SECTION 2.1: APPLICATION OF THE SELECTED HETEROCYCLES

The authoress investigation is associated with the synthesis, characterization and therapeutical importance of some novel thia diazoles and their azetidinones; 4-oxo-thiazolidines and their 5-arylidene derivatives. These are combinational molecules composed of thiazole derivatives (having-SH group) fused to various compounds as mentioned above. A brief account of pharmacological and synthetic review are presented below:

The application of these compounds is really main fold and versatile. They are being used as CNS-active, antituberculous, antispasmodic, anthelminic, antihistamine, anaesthetic, analgesics, amoebicides, antithyroid, antineoplastic, anticonvulsant, antifungal and antibacterial activities.

Some of the derivatives are of interest such as fungicides, insecticides and rodenticides.

Some other important biological activities like antiviral, hypoglycemic and antirradiation have also been observed in some of the derivatives.

Apart from their pharmacological applications, many derivatives of these sulphur compounds have been found to be of interest as rubber vulcanization accelerators, in plastic adhesive, varnishes and in photography etc.

The medicinal important of such type of sulphur and nitrogen compounds and their derivatives is on record. Hence it was thought worthwhile to synthesize some novel sulphur and nitrogen compounds.
2-MERCAPTOBENZOTHIAZOLE

2-Mercaptobenzothiazole was firstly identified\textsuperscript{104} in 1887. 2-Mercaptobenzothiazole is also known as captax. These thiols are formally tautomeric with benzothiazolethions. 2-Mercaptobenzothiazole is one of the best known accelerator\textsuperscript{105,106} for rubber vulcanisation to which it presumable supplies free radical initiator.

\[
\begin{tikzpicture}
\node at (0,0) {\text{\textbf{2-Mercaptobenzothiazole}}};
\end{tikzpicture}
\]

Thiazole is the main function in the structure of mercaptobenzothiazole. Benzothiazole is a base which forms salt with strong acid and quaternary salt with alkyl halides. The methyl group at position 2 of 2,3-dimethyl benzothiazonium iodide is highly reactive and this compound has been converted to cyanine type dyes which are valuable photographic sensitizers.

\[
\begin{tikzpicture}
\node at (0,0) {\text{\textbf{2-Mercaptobenzothiazole is extremely good accelerator for rubber vulcanization which is prepared by the following reaction:}}};
\end{tikzpicture}
\]
Thiazole was first described by Hantzsch and Weber in 1887. Popp confirmed its structure in 1889. The thiazole ring has been extensively studied and it forms a part of vitamin B₁, penicillins and the antibacterial thiazoles. The most valuable thiazole synthesis is heating of an α-halogenated and aldehyde or ketone with a thioamide.

\[
\text{CHO-CH}_2\text{Cl} + \text{NH}_2\text{-CH}_2 \xrightarrow{-\text{H}_2\text{O}} \text{-HCl} \rightarrow \text{N} \begin{array}{c}
\text{S} \\
\text{S}
\end{array}
\]

Thiazole is a weak basic liquid and it forms a crystalline hydrochloride and aurichloride.

\[
\text{Thiazole} \quad \text{Vitamin-}B_1
\]
Thiazoles are structural components of a number of peptide derived natural products and antibiotics. Thiazole ring and its derivatives are well known pharmacophores\textsuperscript{107-110} Thiazole being an internal part of many chemotherapeutic agents display a wide range of biological activities such as bacteriostatic\textsuperscript{111-114}, fungistatic\textsuperscript{115,116}, antithrombic\textsuperscript{117}, anaesthetic\textsuperscript{118}, sedative\textsuperscript{119}, herbicidal\textsuperscript{120}, hypoglycemic\textsuperscript{121}, virucidal\textsuperscript{122}, molluscidal, insecticidal, antidepressant and several other biological properties like thyroid hypertrophy and cardiac activity.

Thiazoly guanidines\textsuperscript{123}(50) have shown marked antibacterial activity.

![Chemical structure](image)

(50): $R_1=$Aryl

2-Mercapto-4-chloro-6-nitrobenzothiazole (51) was shown as antitubercular activity\textsuperscript{124} in vivo and in vitro against *M. tuberculosis* H 37 RV and *M. smymaties* Atce 607.

![Chemical structure](image)

(51)
(2-Benzothiazolylthio)-phenothiazine (52) derivative was found to exhibit anthelmintic property.\textsuperscript{125-126}

\[
\text{\includegraphics[width=0.5\textwidth]{52.png}}
\]

The following compound (53) displayed antifungal activity.\textsuperscript{127}

\[
\text{\includegraphics[width=0.5\textwidth]{53.png}}
\]

The compound derived from 2-benzylbenzothiazole has (54) been synthesized and showed greater activity against certain bacteria, fungi and protozoa.\textsuperscript{128}

\[
\text{\includegraphics[width=0.5\textwidth]{54.png}}
\]

5-(Benzothiazol-2-yl-thiomethyl)-1,3,4-oxadiazoles, (55,56,57) 1,3,4-thiadiazole (58) and 1,2,4-triazole (59) have been synthesised and screened for their antibacterial and antiinflammatory activities.\textsuperscript{129}

\[
\text{\includegraphics[width=0.5\textwidth]{55.png}}
\]
Some new nitro phenoxy/halophenoxy acetyl/propionyl-2-mercaptobenzothiazole (60) have been prepared and found to be good antimicrobial activity.\textsuperscript{130}

(60): $R_1=\text{H/CH}_3$

$R_2=2,4,6-$Br/2,4-Br/2, 4,6-Cl/2,4,5-NO\textsubscript{2}$
2-Acetamido substituted benzothiazole hydrobromides (61) was found to display antibacterial and antifungal activity.\(^{131}\)

![Chemical Structure](image)

(61)

3-(5-substituted amino-1,3,4-thiadiazole-2-yl)-1,2 benzisothiadiazoles (62) and 3-(3-mercapto-4-alkyl/aryl-4H-1,2,4-triazol-5-yl)-1,2-benzisothiazoles (63) have been synthesized as potential non-acidic, non-steroidal antiinflammatory activity.\(^{132}\)

![Chemical Structures](image)

(62) and (63): Aryl/Sub.aryl

Some new 2-substituted 4,5,6,7-tetrahydrobenzothiazoles (64) and 5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzothiazoles (65) have been synthesized and tested for their antifungal and antibacterial activity against fungi \textit{C.albicans}, \textit{A. niger} and bacteria \textit{S.aureus} and \textit{E.coli}.\(^{133,134}\)

![Chemical Structures](image)

(64)  (65)

\[ R_1=\text{C}_6\text{H}_5\text{NH}/\text{C}_6\text{H}_5\text{CH}_2\text{NH}/2\text{-ClC}_6\text{H}_4\text{NH}/4\text{-BrC}_6\text{H}_4\text{NH} - \]
2-\((4'\text{-Butyl}-3',5'\text{-dimethylpyrazol}-1'\text{-yl})\)-6-substituted benzothiazole (66) and 4-butyl-1-(6'-substituted-2'-benzothiazolyl)-3-methylpyrazol-5-ol (67) have been synthesized and shown to exhibit antiinflammatory activity.$^{135,136}$

\[ \text{(66)} \quad \text{(67)} \]

Some new (2-benzothiazolythio)acetic acid [(3-pyridyl) (substituted phenyl)azo] methylene hydrazide (68) have been synthesised and tested for their anthelmintic activity against *H. nana* in mice.$^{137,138}$

\[ \text{(68): } R_1=4\text{-Br}/4\text{-NO}_2/4\text{-CH}_3/4\text{-OCH}_3 \]
Some new 4-alkyl/aryl-1-(benzothiazol-2'-yl)-1,2,4-triazolidin-3,5-diones (69) and 4-aryl/alkyl-1-(benzothiazol-2'-yl)-5-thio-1,2,4-triazolidin-3-ones (70) have showed anticancer activity.\textsuperscript{139}

(69): $R_1=\text{alkyl/aryl}$

(70): $R_1=\text{alkyl/aryl/subaryl}$

Some new ethyl-1,3-dioxobuturate-2-benzothiazolyl hydrazones (71) was found as possible potential antineoplastics.\textsuperscript{140}

(71): $R_1=\text{H/6-OC}_2\text{H}_5/6-\text{Br/5-NO}_2$

$R_2=R_3=\text{COCH}_3/-\text{CONHC}_6\text{H}_5/-\text{COOC}_2\text{H}_5$

2-(4-Aryl-2-thiazolylamino) benzothiazolyls (72) was found to exhibit antibacterial and antifungal activities.\textsuperscript{141,142}

(72): $R_1=\text{H/CH}_3/2-\text{Cl/4-Cl}$
A series of 3-[(2-benzothiazolylthio)-methyl]-1,2,4-triazolo-[3,4][1.3.4-thiadiazole-6-yl] substituted phenyl (73) have been synthesised and screened for their anthelmintic activity against H. nana in mice.\(^{143}\)

\[
\text{(73) } R_1=H/4-\text{NO}_2/3-\text{NO}_2/2-\text{Cl}/4-\text{Cl}/4-\text{OH}
\]

The compound 2-mercapto-5,6-dichlorobenzothiazole (74) was synthesized which showed bacteriostatic activity.\(^{144}\)
Compounds having a five membered ring containing one sulphur and two nitrogen atoms are called thiadiazoles or in the older literature it is also called as thiaiazoles. There are four classes of thiadiazoles.

\[
\begin{array}{c}
\text{HC} \quad \text{N} \\
\text{HC} \quad \text{S} \quad \text{N} \\
\text{CH} \quad \text{CH} \\
\text{N} \quad \text{S} \quad \text{N} \\
\text{HC} \quad \text{S} \quad \text{N} \\
\text{HC} \quad \text{S} \quad \text{CH}
\end{array}
\]

1:2:3 1:2:5 1:2:4 1:3:4 thiadiazole

Thiadiazoles shows versatile biological interest as pesticides and chemotherapeutic agents. Thiadiazoles are reported as antimicrobial,\textsuperscript{145-148} insecticide,\textsuperscript{149} pesticide,\textsuperscript{150} herbicide,\textsuperscript{151} CNS depressant, sedative, anticonvulsant, antiinflammatory and hypoglycemic agents.\textsuperscript{152}

Some new triazole-thiadiazoles,\textsuperscript{153} thiadiazolo-quinazolones,\textsuperscript{154-155} 1,3,4-thiadiazole pyrimidine ring system is associated with diverse biological activities like fungicide,\textsuperscript{156} algicide\textsuperscript{157} and as an antibiotics.\textsuperscript{158}

Among thiadiazoles,\textsuperscript{159} 5-sulpha-1,2,4-thiadiazole\textsuperscript{160} had no interesting level of activity \textit{in vitro} or \textit{in vivo} also characteristic of the 3-ethyl derivative.\textsuperscript{161} 3 or 4-sulpha-1,2,5-thiadiazoles are reportedly active.\textsuperscript{162} 4-sulpha-1,2,3-thiadiazole and its 5-methyl derivatives have good antibacterial properties.\textsuperscript{163}

Some new thiadiazole derivatives of pyrazolone (75) have found as effective bactericidal and fungicidal agents.\textsuperscript{164}
5-Arylamino-1,3,4-thiadiazole derivatives (76) have been reported as plant bactericides and fungicides.\textsuperscript{165,166}

Some workers have also reported 1,3,4-thiadiazole derivatives as antibacterial, antifungal, acetyl cholinesterase enzyme inhibitor and insecticides.

Derivatives of 1,2,4-thiadiazoles and 1,2,4-thiadiazolidines exhibit antifungal and antibacterial activities.

2-(2-Arylethyl)-5-phenyl amino-1,3,4-thiadiazole (77) are found to exhibit antimoeboic activity.\textsuperscript{167}
(77): $R_1=R_2=\text{H/OH/NO}_2/\text{CH}_3/\text{Cl/OCH}_3$

2-(Substituted acetyl)-amino-5-alkyl-1,3,4-thiadiazoles (78) are reported as CNS depressant.\textsuperscript{168}

\[ \text{R} \]

(78) $R_1=\text{acetyl/sub.acetyl}$

Various new pyrazole thiadiazoles have (79) been synthesized and are reported to antimicrobial activity against some selected pathogens.\textsuperscript{169}

\[ \text{R} \]

(79): $R_1=\text{Aryl}$

Some new N-methyl piperazinyl thiadiazoles (80) have been synthesised and exhibited antibacterial and antifungal activities.\textsuperscript{170}

\[ \text{R} \]

(80): $R_1=\text{C}_6\text{H}_5/\text{N(CH}_3)_2\text{C}_6\text{H}_4/2-\text{NO}_2\text{C}_6\text{H}_4/2-\text{ClC}_6\text{H}_4/4-\text{ClC}_6\text{H}_4/4-\text{OCH}_3\text{C}_6\text{H}_4/4-\text{CH=CHC}_6\text{H}_5$
5(1H-benzimidazol-2-yl)-thiomethyl]-N-[(phenyl)methylene]-1,3,4-thiadiazol-2-amine (81) and 5-[(substituted amino)-methyl-benzimidazol-2-yl]-thio]-methyl]-N-[(phenyl)-methylene]-1,3,4-thiadiazol-2-amine (82) have been synthesized and found to be anthelmintic activity\textsuperscript{171} against \textit{H. nana} in mice and \textit{N. brasiliensis} in rats.

![Chemical structure of 81](image)

(81)

![Chemical structure of 82](image)

(82): $R_1=R_2=$ Phenyl/sub. phenyl

2-2-Dialkylphosphate/thiophates of 2-amino-5-(2,4-dichlorophenyl)-1,3,4-thiadiazoles (83) are found to act as potential insecticides\textsuperscript{172}.

![Chemical structure of 83](image)

(83): $R_1=R_2=H/\text{CH}_3/\text{C}_2\text{H}_5$
2-Arylamino-5-[p-3-aryl-4-oxoquinoxolin-3-yl-methylamino) phenyl]-1,3,4-thiadiazoles (84) are found to display hypoglycemic activity.\textsuperscript{173}

\[
\text{(84): } R_1=R_2=H/OH/OCH_3/CH_3/Cl
\]

A series of 2-(N-substituted amino) aceta-amino-5-alkyl/aryl-1,3,4-thiadiazole (85) have been prepared and reported to show antimicrobial activity.\textsuperscript{174}

\[
\text{(85): } R_1=C_2H_6/n-C_4H_{10}/\text{iso-C}_4H_{10}/C_6H_5/\text{CH}_3\text{C}_6H_4 \\
R_2=R_3=C_6H_5/2-\text{ClC}_6H_4/2\text{NO}_2C_6H_4
\]

Substituted 1,3,4-thiadiazoles (86) was found to be potential antitubercular and antibacterial agents.\textsuperscript{175}

\[
\text{(86): } R_1=R_2/C_6H_5/2-\text{OHC}_6H_4/2-\text{ClC}_6H_4/C_4H_3O
\]
8-[(5-Aryl-1',3',4'-thiadiazol-2'-yl)aminomethyl]-7-hydroxylacetoxy-4-methyl coumarins (87) have been prepared and exhibited antifungal activity against *A. niger* and *H. oryzae*.

\[
\begin{align*}
R_1 & = H/4-Cl/2-Cl/4-OCH_3/2,4-Cl_2 \\
R_2 & = H/CH_3
\end{align*}
\]

(87)

2-Amino-2-[(2-thienyl)thiazol-4-yl]-1,3,4-thiadiazole (88) has been screened and found to be phototoxicity.

\[
\begin{align*}
\text{(88)}
\end{align*}
\]

Several 2-α-aryloxyethyl-6-phenyl-1,3,4-thiadiazole-[3,2-]
imidazoles (89) and 2-aryl-3-(5-α-aryloxyethyl-1,3,4-thiadiazol-2-yl)-4-thiazolidinones (90) have been prepared and showed fungicidal activity against the fungi *A. niger* and *H. oryzae*.

\[
\begin{align*}
(89): R_1 &= R_2 = 2-Cl/4-Cl/3-CH_3/4(CH_3)_3C
\end{align*}
\]
(90): $R_1=R_2=aryl/sub.aryl$

N-Acyl-N'-[5-(2,4-dichlorophenyl)-1,3,4-thiadiazol-2-yl]-thoureas (91) and 5-alkyl/aryl-2-(2,4-dichlorophenyl)-1,3,4-thiadiazolo-[3,2-j]-s-triazine-7-thiones (92) have been prepared and found to show antibacterial activity against gram negative *E.coli* and gram positive *B. cerus* and *B. megaterium* bacteria.

(91): $R_1=CH_3/C_6H_5/2,4-ClC_6H_3$

(92): $R_1=CH_3/C_6H_5/2,4-Cl_2C_6H_3/C_4H_3O$
Some new 4-(2-alkyl-1,3-quinoxolin-4-yl-oxymethyl)-2-(p-substituted phenylamino)-1,3,4-thiadiazoles (93) were synthesized and displayed antiinflammatory and anticonvulsant activity.\textsuperscript{180}

\[
\text{(93): } R_1=4/\text{CH}_3 \\
R_2=4-\text{CH}_3/4-\text{OCH}_3/4-\text{Cl}
\]

2-(4-Chlorophenoxy)methyl)-1,3,4-thiadiazolo [5,1]-imidazole-6-one (94) is reported as good pesticides.\textsuperscript{181}

\[
\text{(94)}
\]

2-Amino-5-(5\textsuperscript{1}-hydroxyalkoxyl-2',4-dialkoxyl-5'-nitroaryl)-1,3,4-thiadiazoles (95) and 2-anilino-5-[4'-((substituted anilino)-methyl]-1,3,4-thiadiazoles (96) are found to exhibit antimicrobial activity.\textsuperscript{182-183}

\[
\text{(95): } R_1=R_2=H/\text{CH}_3/\text{C}_2\text{H}_5
\]
(96): $R_1 = R_2 = H/OH/OCH_3/NO_2/Cl$
2-AZETIDINONE

The 2-carbonyl derivatives of the four-membered heterocyclic compounds containing one hetero atom in the ring are known as 2-azetidinone.

Staudinger,\textsuperscript{184} before 1912, initiated work on the chemistry of the azetidin-2-ones. The carbonyl derivative of azetidine is designated as 2-azetidinone or β-lactam. Azetidin-2-one was first obtained\textsuperscript{185} in 1949. It is a colourless solid, m.p. 73-74°, b.p. 106°. It is highly soluble in ethanol and chloroform. The physical state of other β-lactams varies widely with the degree and nature of the substituents. Since then these compounds have been studied extensively and a variety of synthetic methods have been developed for their preparation. The synthesis of β-lactams from direct cyclization of amino acids and ketones condense with imines to form β-lactams. Four-membered ring lactams are considerably more reactive than the larger ring lactams. The occurrence of the resonance form of β-lactam makes the carbonyl carbon of β-lactam more electrophilic after the addition of a nucleophile.
The most important antibiotic penicillins and cephalosporin containing fused 2-azetidinone ring. An antibiotic is a chemical substance that is produced by a micro-organism and that in a relatively high dilution, inhibits the growth or reproduction of some other micro-organism.

**Penicillin**

Penicillin is a generic term which refers to a class of compounds of the molecular formula C₉H₁₁N₂O₄SR, produced by various strains of *penicillium notatum*, *penicillium chrysogenum* and various other moulds. The basic structures commonly encountered in β-lactam antibiotics are the penam and cepham.

**Cephalosporin**

It is thought that the high reactivity of the 2-azetidinone is essential to the antibiotics activity of these compounds. There is a constant need for β-lactam antibiotics to combat bacteria which have built up resistance against the traditional penicillin resistance to penicillins and the related cephalosporin is mainly caused by the formation of enzymes
capable of opening the β-lactam ring common of these antibiotics. Some of the important penicillin and cephalosporin are containing 2-azetidinone moiety used in medicinal practice are the following.

**Penicillin – G**

**Amoxicillin**

**Cephalosporin**

**Cefoxitin**

A large number of antibiotics containing azetidinone moiety\(^{186-187}\) have been reported. The reactivity of azetidinones influences largely on substitution\(^{188-189}\). 2-Azetidinones and its derivatives possess variety of therapeutic activities\(^{190}\).

Several new synthesised 2-oxo-azetidinones (97) has reported and found as antibacterial activity\(^{191}\).
(97): $\text{Ar}=\text{Sub. benzene ring}$

Some new pyrazole (98) and N-methyl piperazinyl azetidinones (99) have been synthesised and reported to antimicrobial activity.\(^{192}\)

(98): $R_1=\text{C}_6\text{H}_5/2-\text{ClC}_6\text{H}_5/4-\text{ClC}_6\text{H}_4/2-\text{NO}_2\text{C}_6\text{H}_5/4-\text{OCH}_3\text{C}_6\text{H}_4$

(99): $R_1=\text{C}_6\text{H}_5/\text{N(CH}_3)_2\text{C}_6\text{H}_4/2-\text{NO}_2\text{C}_6\text{H}_4/2-\text{ClC}_6\text{H}_4/4-\text{ClC}_6\text{H}_4/4-\text{OCH}_3\text{C}_6\text{H}_4/-\text{CH}=\text{C}_6\text{H}_5$

Some new 1-[5'-(carbazolylmethyl)-1',3',4'-thiadiazolo -2'-yl]-4-(substituted phenyl)-3-chloro-2-oxo-azetidines (100) have been synthesised and evaluated for their antimicrobial anticonvulsant and antiinflammatory activities.\(^{193}\)
(100): R₁=Aryl/sub.4Aryl

Some new azetidinones (101) were prepared and showed herbicidal activity.¹⁹⁴

(101): R₁= Aromatic carbonyls

3-Chloro-2-oxo-4-(substituted phenyl)-azetidine-1-yl-thioureas are (102) found to exhibit antiparkinsonian activity.¹⁹⁵

(102): R₁=CH₃/OCH₃/OH/Cl
4-Aryl-3-chloro-1-(4-phenyl-2-oxazolyl)-azetidine-2-one (103)
and [1′-4′-aryl (2′,4′-bithiazol)-2′-yl]-4′-phenyl-2′-azetidinone (104) are found to display antibacterial activity.\(^{196}\)

![Chemical Structure 103](image)

![Chemical Structure 104](image)

Benzothiazolosulphonamidoazetidin-2-one (105) is prepared to exhibit antimicrobial activity\(^{197}\) against pathogen \textit{B-subtilis}, \textit{S. aureus}, \textit{E.coli} and \textit{P. aeruginosa}.

![Chemical Structure 105](image)
**Thiazolidinone and Their-5-Arylidene Derivatives**

Thiazolidinones (C$_3$H$_7$NS) 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.

![Thiazolidine and Derivatives Diagram]

**Thiazolidine**  4-oxo-thiazolidine  5-Arylidene-4-oxo-thiazolidine

R=R$_1$=R$_2$=alkyl/aryl/sub.aryl

Thiazolidines are synthesised by the condensation of β-aminomercaptans with aldehyde or ketones and may also be prepared by reducing 2-thiazolines with aluminium amalgam. The stability of thiazolidines depends greatly on the substituents present.

![Thiazolidine Derivatives Diagram]

Acylation increases the stability of the thiazolidine ring. This contrast in stability has significance for the structure of penicillin.
4-thiazolidinones and their 5-arylidene derivatives possess a variety of therapeutic activity such as antifungal,\textsuperscript{198} antibacterial\textsuperscript{199}, anticonvulsant\textsuperscript{200}, amoebicidal\textsuperscript{201}, hypnotic\textsuperscript{202}, antitubercular\textsuperscript{203}, nematocidal\textsuperscript{204}, mosquito repellent\textsuperscript{205}, antiHIV, anticancer\textsuperscript{206} and anaesthetic\textsuperscript{207} etc.

There are many articles on pharmacology and toxicology\textsuperscript{208} of thiazolidene carboxylic acid (106).

\begin{center}
\begin{tikzpicture}
\node [c] at (0,0) {\text{\text{HOOC}}} \node [c] at (0,-0.3) {\text{N}} \node [c] at (0,-0.7) {\text{S}};
\end{tikzpicture}
\end{center}

(106)

p-Bis-(2-imino-4-thiazolidinone, N\textsuperscript{2}-yl)biphenyl has (107 and 108) been synthesized\textsuperscript{209} and found to possess antifungal and antibacterial activities.

\begin{center}
\begin{tikzpicture}
\node [c] at (0,0) {\text{O}} \node [c] at (0.5,0) {\text{N}} \node [c] at (0.8,0) {\text{HN}} \node [c] at (1.1,0) {\text{CO}} \node [c] at (0.25,-0.5) {\text{S}} \node [c] at (0.55,-0.5) {\text{N}} \node [c] at (0.85,-0.5) {\text{N}} \node [c] at (1.15,-0.5) {\text{S}} \node [c] at (1.25,-0.5) {\text{N}} \node [c] at (1.55,-0.5) {\text{S}} \node [c] at (1.85,-0.5) {\text{N}} \node [c] at (2.15,-0.5) {\text{S}};
\end{tikzpicture}
\end{center}

(107)

\begin{center}
\begin{tikzpicture}
\node [c] at (0,0) {\text{O}} \node [c] at (0.5,0) {\text{N}} \node [c] at (0.8,0) {\text{HN}} \node [c] at (1.1,0) {\text{CO}} \node [c] at (0.25,-0.5) {\text{S}} \node [c] at (0.55,-0.5) {\text{N}} \node [c] at (0.85,-0.5) {\text{N}} \node [c] at (1.15,-0.5) {\text{S}} \node [c] at (1.25,-0.5) {\text{N}} \node [c] at (1.55,-0.5) {\text{S}} \node [c] at (1.85,-0.5) {\text{N}} \node [c] at (2.15,-0.5) {\text{S}};
\end{tikzpicture}
\end{center}

(108)

Mercurated derivatives of thiazolidinone as antitubercular\textsuperscript{210} and antifungal\textsuperscript{211} agents opened a new field in medicinal chemistry. Disubstituted thiazolidinone have been reported as local anaesthetic\textsuperscript{212},
anticonvulsant\textsuperscript{213}, fungicidal\textsuperscript{214}, antitubercular, amoebicidal, antibacterial\textsuperscript{215}, antiepileptic\textsuperscript{216}, antithyroid and other biological properties.

Incorporation of thiazolidinone moiety with hydrazido group, oxazine ring etc. enhances their biological activity\textsuperscript{217,218}.

A possible structure activity relationship\textsuperscript{219}(SAR) have been discussed for some 3-\((1,3,4\text{-thiadiazol\text{-2-yl}})\text{-}4\text{-thiazolidinones (109) with special studies on fungi toxicity}\textsuperscript{220} caused by \textit{Aspergillus niger} and \textit{Helminthosporium oryzae}.

\[\text{(109): } R=\text{4-Cl/ 3-CH}_3/ 2,4-(\text{CH}_3)_2 \]
\[R_1=\text{H/ OH/ Cl}\]

Quinazolinyl derivatives\textsuperscript{221}(110) of thiazolidinone were screened for their antibacterial activity against \textit{S. albus}, \textit{E. coli} and \textit{K. pneumoniae}.

\[\text{(110): } R_1=\text{H/ Cl/ OH} \]
\[R_2=\text{H/ -OH} \]
\[R_3=\text{OH/ -N (CH}_3)_2\text{Cl} \]
Antibacterial activity\textsuperscript{222}(111) were seen in 5-carboxymethyl-4-thiazolidinones bearing bithiazole moiety\textsuperscript{223}.

\[(111): \quad X=4/\text{Cl/OC}H\text{\textsubscript{3}/CH\textsubscript{3}} \quad Y=4/\text{CH\textsubscript{3}/OC}H\text{\textsubscript{3}/CH\textsubscript{3}}\]

Some new 1,8 naphthyridinyl-4-thiazolidinones\textsuperscript{224}(112) have been synthesized and reported as antibacterial agents.

\[(112): \quad \text{Ar=Aryl/sub.Aryl}\]

Some new 4-thiazolidinones with 1,4-benzothiaziny moiety (113) and imidazolyl moiety\textsuperscript{225}(114) has reported antimicrobial activity.
3-Arylamino-3-aryl-4-thiazolidinones (115) have been synthesized and possess considerable fungicidal activity.\textsuperscript{226}

(115): \( R = \text{CH}_3/\text{C}_2\text{H}_5/\text{C}_3\text{H}_7 \)

2-Aryl-3-aryl-4-thiazolidinones (116) were found to be active against psychomotor anticonvulsant and barbiturate potentiating activity in mice.\textsuperscript{227}

(116): \( R = \text{CH}_3/\text{C}_2\text{H}_5/\text{C}_3\text{H}_7 \)

Allyl side chain derivatives on \( N^3 \) of thiazolidinone(117) are found to be suitable for their herbicidal activity.\textsuperscript{228}
SECTION-2.2: AIM AND WORK PLAN OF THE RESEARCH

In view of many interesting pharmacological properties associated with 2-mercaptobenzothiazole and its derivatives it was thought worthwhile to synthesise series of compounds containing thiadiazole, azetidinone, 4-oxothiazolidine and their 5-arylidene moieties. This idea has promoted us to synthesize compounds RS 01-44 and their biological activities, particularly antifungal, antibacterial, anthelmintic and antiinflammatory have been studied.

Work Plan of Research

Present study have been divided into three parts-

Part - I : Synthesis of new heterocyclic compounds.
Part - II : Characterization of newly synthesized compounds.
Part - III : Pharmacological screening of the newly synthesized compounds.

PART-I: SYNTHESIS OF NEW HETEROCYCLIC COMPOUNDS

Four series of the compounds have been synthesized by Schemes-1 and 2 respectively.

SERIES-1: 2-ARYLIDENYLAMINO-5-(2-BENZOTHIAZOLYLTHIO)-METHYL-1,3,4 THIADIAZOLES:

The compounds of series-1 (RS 01-11) have been synthesized through the compounds 1-3 by the first four steps of the Scheme-1.
Scheme 1

\[
\begin{align*}
\text{RS-01-11} & \quad \text{ClCH$_2$COCl/Et$_3$N} \\
\text{RS-12-22} & \quad \text{Ar = Various aromatic aldehydes}
\end{align*}
\]
<table>
<thead>
<tr>
<th>Compound Code No.</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS-01</td>
<td>2-(3-Nitrobenzylidenylamino)-5-[2-benzothiazolylthio]-methyl -1,3,4-thiadiazole.</td>
</tr>
<tr>
<td>RS-02</td>
<td>2-(2,4-Dinitrobenzylidenylamino)-5-[2-benzothiazolylthio]-methyl -1,3,4-thiadiazole.</td>
</tr>
<tr>
<td>RS-03</td>
<td>2-(3-Chlorobenzylidenylamino)-5-[2-benzothiazolylthio]-methyl -1,3,4-thiadiazole.</td>
</tr>
<tr>
<td>RS-04</td>
<td>2-(2-Bromobenzylidenylamino)-5-[2-benzothiazolylthio]-methyl -1,3,4-thiadiazole.</td>
</tr>
<tr>
<td>RS-05</td>
<td>2-(3-Bromobenzylidenylamino)-5-[2-benzothiazolylthio]-methyl -1,3,4-thiadiazole.</td>
</tr>
<tr>
<td>RS-06</td>
<td>2-(4-Bromobenzylidenylamino)-5-[2-benzothiazolylthio]-methyl -1,3,4-thiadiazole.</td>
</tr>
<tr>
<td>RS-07</td>
<td>2-(3-Methoxybenzylidenylamino)-5-[2-benzothiazolylthio]-methyl -1,3,4-thiadiazole.</td>
</tr>
<tr>
<td>RS-08</td>
<td>2-(3,4,5-Trimethoxybenzylidenylamino)-5-[2-benzothiazolylthio]-methyl -1,3,4-thiadiazole.</td>
</tr>
<tr>
<td>RS-09</td>
<td>2-(2-Hydroxybenzylidenylamino)-5-[2-benzothiazolylthio]-methyl -1,3,4-thiadiazole.</td>
</tr>
<tr>
<td>RS-10</td>
<td>2-(3-Hydroxybenzylidenylamino)-5-[2-benzothiazolylthio]-methyl -1,3,4-thiadiazole.</td>
</tr>
<tr>
<td>RS-11</td>
<td>2-(4-Hydroxybenzylidenylamino)-5-[2-benzothiazolylthio]-methyl -1,3,4-thiadiazole.</td>
</tr>
</tbody>
</table>
SERIES-2: (2-BENZOTHIAZOLYLTHIO) METHYL-THIADIAZOLE-AZETIDINONES:

The compounds of series-2 (compounds RS 12-22) have been synthesized starting from the compounds of series-3 as precursor and by following the last step of the Scheme-1.

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

<table>
<thead>
<tr>
<th>Compound Code No.</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS-12</td>
<td>1-(5'{{(2-Benzothiazolylthio)methyl}-1',3',4'-thiadiazole-2'-yl}-4-(3-nitrophenyl)-3-chloro-2-oxo-azetidine</td>
</tr>
<tr>
<td>RS-13</td>
<td>1-(5'{{(2-Benzothiazolylthio)methyl}-1',3',4'-thiadiazole-2'-yl}-4-(2,4-dinitrophenyl)-3-chloro-2-oxo-azetidine</td>
</tr>
<tr>
<td>RS-14</td>
<td>1-(5'{{(2-Benzothiazolylthio)methyl}-1',3',4'-thiadiazole-2'-yl}-4-(3-chlorophenyl)-3-chloro-2-oxo-azetidine</td>
</tr>
<tr>
<td>RS-15</td>
<td>1-(5'{{(2-Benzothiazolylthio)methyl}-1',3',4'-thiadiazole-2'-yl}-4-(2-bromophenyl)-3-chloro-2-oxo-azetidine</td>
</tr>
<tr>
<td>RS-16</td>
<td>1-(5'{{(2-Benzothiazolylthio)methyl}-1',3',4'-thiadiazole-2'-yl}-4-(3-bromophenyl)-3-chloro-2-oxo-azetidine</td>
</tr>
<tr>
<td>RS-17</td>
<td>1-(5'{{(2-Benzothiazolylthio)methyl}-1',3',4'-thiadiazole-2'-yl}-4-(4-bromophenyl)-3-chloro-2-oxo-azetidine</td>
</tr>
<tr>
<td>RS-18</td>
<td>1-(5'{{(2-Benzothiazolylthio)methyl}-1',3',4'-thiadiazole-2'-yl}-4-(3-methoxyphenyl)-3-chloro-2-oxo-azetidine</td>
</tr>
<tr>
<td>RS-19</td>
<td>1-(5'{{(2-Benzothiazolylthio)methyl}-1',3',4'-thiadiazole-2'-yl}-4-(3,4,5-triethoxyphenyl)-3-chloro-2-oxo-azetidine</td>
</tr>
<tr>
<td>RS-20</td>
<td>1-(5'{{(2-Benzothiazolylthio)methyl}-1',3',4'-thiadiazole-2'-yl}-4-(2-hydroxyphenyl)-3-chloro-2-oxo-azetidine</td>
</tr>
<tr>
<td>RS-21</td>
<td>1-(5'{{(2-Benzothiazolylthio)methyl}-1',3',4'-thiadiazole-2'-yl}-4-(3-hydroxyphenyl)-3-chloro-2-oxo-azetidine</td>
</tr>
<tr>
<td>RS-22</td>
<td>1-(5'{{(2-Benzothiazolylthio)methyl}-1',3',4'-thiadiazole-2'-yl}-4-(4-hydroxyphenyl)-3-chloro-2-oxo-azetidine</td>
</tr>
</tbody>
</table>
Scheme 2

\[
\begin{align*}
&\text{ClCH₂COOC₂H₅} \\
&\text{H₂NNH₂} \\
&\text{H₂SCH₂COOH + anhydrous ZnCl₂} \\
&\text{Ar¹CHO} \\
&\text{Ar = Ar¹ = Various aromatic aldehydes}
\end{align*}
\]
SERIES-3: 2-{SUBSTITUTED ARYL}-3-[(2-BENZOTHIAZOLYLTHIO) ACETAMIDYL]-4-OXO-THIAZOLIDINES.

The compounds of Series-3 (RS 23-33) have been synthesized through the Compounds 1-3 by following the first four steps of the Scheme-2.

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

<table>
<thead>
<tr>
<th>Compound Code No.</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS-23</td>
<td>2-(3-Nitrophenyl)-3-[(2-benzothiazolylthio) acetamidyl]-4-oxo-thiazolidine</td>
</tr>
<tr>
<td>RS-24</td>
<td>2-(2,4-Dinitrophenyl)-3-[(2-benzothiazolylthio)acetamidyl]-4-oxo-thiazolidine</td>
</tr>
<tr>
<td>RS-25</td>
<td>2-(3-Chlorophenyl)-3-[(2-benzothiazolylthio)acetamidyl]-4-oxo-thiazolidine</td>
</tr>
<tr>
<td>RS-26</td>
<td>2-(3-Bromophenyl)-3-[(2-benzothiazolylthio)acetamidyl]-4-oxo-thiazolidine</td>
</tr>
<tr>
<td>RS-27</td>
<td>2-(3-Bromophenyl)-3-[(2-benzothiazolylthio)acetamidyl]-4-oxo-thiazolidine</td>
</tr>
<tr>
<td>RS-28</td>
<td>2-(4-Bromophenyl)-3-[(2-benzothiazolylthio)acetamidyl]-4-oxo-thiazolidine</td>
</tr>
<tr>
<td>RS-29</td>
<td>2-(3-Methoxyphenyl)-3-[(2-benzothiazolylthio)acetamidyl]-4-oxo-thiazolidine</td>
</tr>
<tr>
<td>RS-30</td>
<td>2-(3,4,5-Trimethoxyphenyl)-3-[(2-benzothiazolylthio)acetamidyl]-4-oxo-thiazolidine</td>
</tr>
<tr>
<td>RS-31</td>
<td>2-(2-Hydroxyphenyl)-3-[(2-benzothiazolylthio)acetamidyl]-4-oxo-thiazolidine</td>
</tr>
<tr>
<td>RS-32</td>
<td>2-(3-Hydroxyphenyl)-3-[(2-benzothiazolylthio)acetamidyl]-4-oxo-thiazolidine</td>
</tr>
<tr>
<td>RS-33</td>
<td>2-(4-Hydroxyphenyl)-3-[(2-benzothiazolylthio)acetamidyl]-4-oxo-thiazolidine</td>
</tr>
</tbody>
</table>
SERIES-4: 2-(SUBSTITUTED ARYL)-3-[(2-BENZOTHIAZOLYLTHIO) ACETAMIDYL]-5-(ARYLIDENE)-4-OXO-THIAZOLIDINES.

The compounds of Series-4 (RS 34-44) have been synthesized by the using the compounds of Series-3 as precursors and by following the last steps of the Scheme-2.

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

<table>
<thead>
<tr>
<th>Compound Code No.</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS-34</td>
<td>2-(3-Nitrophenyl)-3-[(2-benzothiazolylthio) acetamidyl]-5-(3-nitrobenzylidene)-4-oxo-thiazolidine</td>
</tr>
<tr>
<td>RS-35</td>
<td>2-(2,4-Dinitrophenyl)-3-[(2-benzothiazolylthio) acetamidyl]-5-(2,4-dinitrobenzylidene)-4-oxo-thiazolidine</td>
</tr>
<tr>
<td>RS-36</td>
<td>2-(3-Chlorophenyl)-3-[(2-benzothiazolylthio) acetamidyl]-5-(3-Chlorobenzylidene)-4-oxo-thiazolidine</td>
</tr>
<tr>
<td>RS-37</td>
<td>2-(2-Bromophenyl)-3-[(2-benzothiazolylthio) acetamidyl]-5-(2-bromobenzylidene)-4-oxo-thiazolidine</td>
</tr>
<tr>
<td>RS-38</td>
<td>2-(3-Bromophenyl)-3-[(2-benzothiazolylthio) acetamidyl]-5-(3-bromobenzylidene)-4-oxo-thiazolidine</td>
</tr>
<tr>
<td>RS-39</td>
<td>2-(4-Bromophenyl)-3-[(2-benzothiazolylthio) acetamidyl]-5-(4-bromobenzylidene)-4-oxo-thiazolidine</td>
</tr>
<tr>
<td>RS-40</td>
<td>2-(3-Methoxyphenyl)-3-[(2-benzothiazolylthio) acetamidyl]-5-(3-methoxybenzylidene)-4-oxo-thiazolidine</td>
</tr>
<tr>
<td>RS-41</td>
<td>2-(3,4,5-Trimethoxyphenyl)-3-[(2-benzothiazolylthio)acetamidyl]-5-(3,4,5-trimethoxybenzylidene)-4-oxo-thiazolidine</td>
</tr>
<tr>
<td>RS-42</td>
<td>2-(2-Hydroxyphenyl)-3-[(2-benzothiazolylthio) acetamidyl]-5-(2-hydroxybenzylidene)-4-oxo-thiazolidine</td>
</tr>
<tr>
<td>RS-43</td>
<td>2-(3-Hydroxyphenyl)-3-[(2-benzothiazolylthio) acetamidyl]-5-(3-hydroxybenzylidene)-4-oxo-thiazolidine</td>
</tr>
<tr>
<td>RS-44</td>
<td>2-(4-Hydroxyphenyl)-3-[(2-benzothiazolylthio) acetamidyl]-5-(4-hydroxybenzylidene)-4-oxo-thiazolidine</td>
</tr>
</tbody>
</table>
PART-II: CHARACTERISATION OF THE SYNTHESISED COMPOUNDS

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 infrared spectra of the representative compounds are recorded on Shimadzu 8201, PC FTIR spectrophotometer in cm⁻¹ (KBr) and ¹H-NMR spectra of the representative compounds were recorded on Brucker DRX-300 in CDCl₃ at 200 MHz on δ scale using TMS as an internal standard.

PART-III: PHARMACOLOGICAL ACTIVITY OF THE SYNTHESIZED COMPOUNDS

The synthesized compounds were screened for their antibacterial, antifungal, anthelmintic and anti-inflammatory activities. Some of the compounds were found to display remarkable biological activity.