INTRODUCTION
CHAPTER II

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Interest in the preparation of compounds containing thiazole moiety has been stimulated by successful application of highly active compounds such as Sulphathiazole, Promizole, Darvisul and some sulphanilamide analogues in the treatment of various bacterial infections. Preparation of 2-aminothiazole derivatives seems to be particularly encouraging since 2-aminothiazole itself possesses many chemotherapeutic properties amongst which its goitrogenic activity\(^1\) in young rats and antithyroid activity\(^2\) in rats are prominent. Further, the observation that various 2-aminothiazole derivatives possess antibacterial, antitubercular, antispasmodic as well as antihistaminic\(^3\) and fungicidal properties suggested a close investigation of effect of introducing suitable substituents at 4 or 5 and at both 4 and 5 positions of 2-aminothiazole molecule.

![2-Aminothiazole](image)

Therefore, it was contemplated to prepare 2-aminothiazole derivatives of the type :
1. Phenyl 2-amino-5-bromo-4-thiazolyl ketones and their 5-chloromercuri derivatives,
2. phenyl-2-amino-5-bromo-4-thiazolylmethanes and their 5-chloromercuri derivatives, and
3. phenyl 2-amino-5-thiazolyl sulphides and sulphones.

These compounds are expected to possess antimicrobial activity on account of the following reasons.

A. The ketones and methanes having 5-bromo and 5-chloromercuri substituents:

(1) Effect due to C<sub>2</sub>Br:

Hong-geon Salk during his extensive study on chemotherapy of tuberculosis reported that 2-amino-5-halo, 2-acetamido-5-halo, and 2-amino-5-nitrothiazoles inhibited the growth of tubercle bacilli considerably when tested against Mycobacterium tuberculosis var. hominis, strain H37 RV in Kirchner medium. The minimum concentration (\text{\gamma/ml}) to inhibit the growth in case of above thiazoles is given below:

<table>
<thead>
<tr>
<th>Compound</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Amino-5-bromothiazole</td>
<td>100</td>
</tr>
<tr>
<td>2-Amino-5-chlorothiazole</td>
<td>125</td>
</tr>
<tr>
<td>2-Amino-5-nitrothiazole</td>
<td>125</td>
</tr>
<tr>
<td>2-Acetamido-5-bromothiazole</td>
<td>250</td>
</tr>
<tr>
<td>2-Acetamido-5-chlorothiazole</td>
<td>250</td>
</tr>
</tbody>
</table>
Karizo Ishidate and al. tested a number of 2-aminothiazole derivatives against M. tuberculosis var. avian and concluded that 2-amino-5-bromo-thiazole and 2-amino-4-methyl-5-bromo-thiazole hydrochloride had promising activity.

Yuichi Yamamoto showed that bromination and nitration products of 2-aminothiazole exhibited enhanced activity when tested on E. coli, S. aureus and M. tuberculosis (avian). He also tested 2-hydroxy-4-methyl-5-thiazolyl alkyl ketones against human type of M. tuberculosis and observed maximum activity in case of n-amyl and isoamyl ketones.

G.N. Mahapatra in 1956 evaluated 2-amino-5-bromo-thiazole derivatives as non-metallic fungicides in addition to their antibacterial properties. He found that substituted 4-phenyl- and 6-naphthyl-5-bromo-thiazoles inhibited completely spore germination at 20-22 p.p.m. when Pricularia Oryzae was employed as a test fungus. He further showed that the same compounds were also active against Micrococcus pyogenes var. aureus at a dilution of 1:20,000 in Rideal-Walker serial drop dilution test. G.N. Mahapatra also tested 2-amino-4-phenethylthiazoles and their 5-bromo derivatives for fungistatic activity on Alternaria brassicace (Berk) employing the method of Montgomery and Moore and
for bactericidal activity on \text{E. coli} \text{ and S. aureus} employing Rideal-Walker serial drop dilution test method. Brominated thiazoles inhibited the spore germination at 50 p.p.m. while unbrominated thiazoles did so at 80 p.p.m. In bactericidal tests, some brominated thiazoles were effective on \text{E. coli} at 1:2,000 and on \text{S. aureus} at 1:20,000 while unbrominated thiazoles were effective at 1:1,000 on \text{E. coli} and 1:8,000 on \text{S. aureus}.

G.N. Mahapatra\textsuperscript{10}, during his study on bromothiazoles and their mercurated derivatives as fungicides and bactericides, showed that 2-anilino-4-phenylthiazoles having bromine substituents in one or both phenyl rings are less active than the corresponding 5-bromothiazoles. He has also shown that bromination at 5-position alone is responsible for the enhanced activity in the corresponding 5-bromothiazole compounds.

So it is evident from the brief survey of the foregoing description that introduction of halogen, especially bromine, at 5 position of 2-aminothiazole derivatives increases the antibacterial potency of the resulting compounds.

(ii) Effect due to \textsuperscript{C_5} chloromercuri group:

Rout, Padhi and Das\textsuperscript{11} initiated systematically the study on the use of mercurated thiazole derivatives as
fungistatic agents. They screened 26 compounds for fungicidal activity using *Altanaria polanduii* as the test fungus. They tested various mercurated 2-anilino-4,5-dimethylthiazoles having acetoxy-mercuri group in the phenyl ring and found them to completely inhibit the spore germination at 2 p.p.m. only; while the unmercurated thiazoles inhibited at 100 p.p.m. Further, Das, Mahapatra and Rout\(^1\) tested 2-anilino-4,5-dimethylthiazoles and their mercurated derivatives for bactericidal action against *E. coli* and *S. aureus* and observed that unmercurated thiazoles were active in maximum effective dilution (M.E.D.) of 1:1,000 while mercurated thiazoles were active in a dilution up to 1:75,000.

However, M.K.Rout\(^1\) showed that 2-anilino-4-styrylthiazoles were more powerful bacteriostatic and fungicidal compounds than 2-anilino-4-methyl and 2-anilino-4-phenylthiazoles. Some of the mercurated 2-anilino-4-styrylthiazoles were fungicidal at a dilution of 1:100,000 and bactericidal at a dilution of 1:95,000 on *E. coli* and 1:50,000 on *S. aureus*. But G.N.Mahapatra\(^1\) proved that mercurated 2-anilino-4-phenyl-5-bromothiazoles were more fungistatic and bacteriostatic than mercurated 2-anilino-4-styrylthiazoles because the former compounds were bactericidal at a dilution of 1:100,000 while the latter
were bactericidal at a dilution of 1:50,000 when tested against S. aureus.

So it can be inferred from the above discussion that mercuration of any thiazole derivative definitely augments the antibacterial as well as fungicidal activity and the activity is more pronounced in case of mercurated thiazole derivatives than respective 5-bromothiazoles. Hence, it was thought to introduce chloromercuri group at 5 position of 2-acetamido-4-benzoyl and 2-acetamido-4-benzylthiazoles and convert them to corresponding amino compounds.

(iii) Effect due to 4-benzoyl group:

An increase in the activity due to 4-benzoyl group in addition to the activity due to 5-chloromercuri or 5-bromo group in 2-amino-4-benzoyl-5-chloromercuri or 5-bromothiazole derivatives is expected on the following considerations.

Since thiazole nucleus is an isostere of benzene nucleus and, 2 and 5 positions of thiazole nucleus are para to each other, 5-benzylothiazoles are looked upon as corresponding benzophenones. On this analogy of isosterism, 4-benzylothiazoles may also be looked upon as virtual benzophenones. Faith, Bahler and Florestano have shown that substituted benzophenones are very good tuberculostatic, antibacterial, fungicidal and insecticidal compounds.
B.L. Freedlander tested a number of substituted benzophenones 'in vitro' for tuberculostatic action and concluded that most of the chloro, alkyl and alkoxy substituted benzophenones, except hydroxybenzophenones, were very effective. Therefore, 4-benzoylthiazoles are expected to possess such antimicrobial properties. For example, 2,4'-dichlorobenzophenone known to be efficient bacteriostat for tubercle bacilli 'in vitro' can be related to its isoster 4-p-chlorobenzoyl-5-bromo thiazole. Presence of 2-amino group in 2-amino-4-p-chlorobenzoyl-5-bromo thiazole may further enhance the activity.

(iv) **Effect due to 4-benzyl group:**

An increase in the activity due to benzyl group, in addition to the activity owing to the presence of 5-chloromercuri and 5-bromo group in 2-amino-4-benzyl-5-chloromercuri or 5-bromo thiazole derivatives, is expected on the following considerations.

(a) On the basis of theory of isosterism, 4-benzyl thiazoles may be looked upon as virtual diphenylmethanes which are known for their antibacterial and ochracidal properties, e.g., Kurt Kraft tested a number of diphenylmethanes on E.coli and S.aureus and found some of them to be strongly bacteriostatic.

(b) G.N. Mahapatra (loc.cit.) prepared a homologous
series of 2-amino-4-benzyl-5-bromothiazole i.e., 2-amino-
4-phenethyl-5-bromothiazoles as promising fungicides and
bacteriostats.

(c) A simple analogous compound 4-(2-hydroxy-5-chloro-
benzyl)-thiazole has been shown by Sugimoto and Shigematsu
18 to inhibit the growth of pathogenic filamentous fungus.

Both 2-amino-4-benzoyl-5-bromothiazole and 2-amino-
4-benzyl-5-bromothiazole derivatives seem to exert low
 toxicity, for Frear and Seiferle 19 have concluded, after
exhaustive study on chemical structure and insecticidal
efficiency, that

(a) toxicity will be reduced if a compound contains N in
form of azo, semicarbazone, diamine, urea or C2N2 (as
in heterocyclic systems),

(b) toxicity is minimum, if a compound contains only
one F, Br, or Cl in order of merit, and

(c) toxicity of a compound containing one primary,
secondary or tertiary amino group is often more than that
of a compound having such two groups.

Therefore, various (i) phenyl 2-amino-4-thiazoyl
ketones and their 2-acetamido-5-chloromercuri and 2-aceta-
mido-5-bromo derivatives and (ii) phenyl-2-amino-4-thia-
zolylmethanes and their 2-acetamido-5-chloromercuri and
2-acetamido-5-bromo derivatives, prepared during the present investigation, are expected to possess antibacterial activity. They are structurally represented as

(i) 
\[
\begin{align*}
R_1 & \quad \text{CO} \\
R_2 & \quad \text{NH}_2
\end{align*}
\]  
and 
\[
\begin{align*}
R_1 & \quad \text{CO} \\
R_2 & \quad \text{NH}_2 \\
\text{R} & \quad \text{HgCl}
\end{align*}
\]  
\(\text{(B1)}\)

where \(R = R_1 = \text{H, Cl and } R_2 = \text{H, Cl, CH}_3, \text{ OCH}_3, \text{ or NO}_2\).

(ii) 
\[
\begin{align*}
R_1 & \quad \text{CH}_2 \\
R_2 & \quad \text{NH}_2
\end{align*}
\]  
and 
\[
\begin{align*}
R_1 & \quad \text{CH}_2 \\
R_2 & \quad \text{NH}_2 \\
\text{R} & \quad \text{HgCl}
\end{align*}
\]  
\(\text{(B2)}\)

where \(R = R_1 = \text{H, Cl or OCH}_3 \text{ and } R_2 = \text{H, Cl, CH}_3, \text{ OCH}_3 \text{ or NO}_2\).

Most of the 2-amino-4-benzoylthiazole derivatives and 2-amino-4-benzyithiazole derivatives along with their respective 2-acetamido-5-bromo derivatives have been tested against \(E.\text{coli and Staph. aureus}\) using 0.5 per cent solution of a compound in acetone according to paper disc method described by Cold and Bowie. But 5-chloromercuri derivatives could not be tested by this method since they were insoluble in acetone or alcohol. The results of the testing of these compounds are described in Chapter No. VII.
However, it should be noted that the method of testing is purely qualitative.

B. Phenyl 2-amino-5-thiazolyl sulphides and sulphones:

(i) Phenyl 2-amino-5-thiazolyl sulphides can be looked upon as corresponding diphenyl sulphides as thiazole nucleus is an isoster of benzene nucleus. The various substituted diphenyl sulphides have been shown to be good antibacterials by following workers.

Freedlander and French tested a number of diphenyl sulphoxides, sulphides and sulphones 'in vitro' against avirulent strain no. 607 of the tubercle bacilli in synthetic media and found them to be bacteriostatic. The minimum concentration to inhibit the growth in case of a few compounds is given below.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-Aminophenyl p-chlorophenyl sulphide</td>
<td>1:800,000</td>
</tr>
<tr>
<td>p-Aminophenyl p-iodophenyl sulphide</td>
<td>1:800,000</td>
</tr>
<tr>
<td>p-acetamidophenyl p-chlorophenyl sulphide</td>
<td>1:400,000</td>
</tr>
<tr>
<td>4,4'-Diaminodiphenyl sulphone (DADS)</td>
<td>1:60,000</td>
</tr>
</tbody>
</table>

They found that sulphides were more powerful bacteriostats than sulphones 'in vitro' tests.
Pfleger et al. reported a systematic investigation of antimicrobial activity of various diphenyl sulphides having substituents like OH, Cl, Br, I and NO₂ groups. They concluded that chloro and hydroxy-chloro sulphides were most active.

So it can be concluded that introduction of Cl, NH₂ and OH groups in phenyl rings at para position to sulphur linkage increases the activity of diphenyl sulphide.

(ii) Phenyl 2-amino-5-thiazolyl sulphones may be looked upon as the corresponding diphenyl sulphones on the basis of theory of isosterism¹⁴. The diphenyl sulphones having various substituents are known for their superior antimicrobial properties. A few examples are given below.

Bis (4-aminophenyl)sulphone (DADS) which is a famous antitubercular and antileprotic drug was first evaluated by Buttle and his associates²³ as an antibacterial which was 100 times as active as sulphanilamide in Streptococcus infections.

Huisman²⁴ et al. in 1958 showed that introduction of chlorine in 4-aminodiphenyl sulphone resulted into compounds having acaricidal properties, e.g., 4-amino-2',4',5'-trichlorodiphenyl sulphone was found to have strong acaricidal activity with least phytocidal side-effects and toxicity for warm blooded animals.
Eaten and Davis tested a number of chloro substituted diphenyl sulphones like 4-chloro,4,4'-dichloro, 4-chloro-4'-methyldiphenyl sulphones against summer eggs and adult females of Metatetranyches ulmi and showed them to be highly active. The superior compounds amongst the diphenyl sulphones were diphenyl sulphone and 4-chlorodiphenyl sulphone.

Linnel and Stenlake found 4,4'-diamino-2,2'-dihydroxydiphenyl sulphone to possess pronounced antitubercular activity with fairly low toxicity as compared with DADS.

So it can be seen that introduction of NH₂, Cl and OH in one or both phenyl rings at para position to sulphur linkage increases the antibacterial potency of the resulting sulphones.

(iii) In order to increase the antibacterial activity and reduce the toxicity, usually one or both phenyl nuclei of diphenyl sulphides or sulphones are replaced by a heterocyclic nucleus such as thiazole, benzothiazole, pyridine, pyrimidine etc. The following few examples support the statement when thiazole is selected.

L.L. Bambas prepared p-aminophenyl 2-amino-5-thiazolyl sulphone (Promizole) which was found to be antitubercular as well as antithyroid and least toxic.
Richard Dahlboas et al. prepared hydroxypromizole which was found to be as active as sulphathiazole *in vitro* towards β-Hemolytic streptococci, type I pneumococci and E. coli, and 20-50 times as active as promizole.

Itai and Yamamoto prepared various substituted nitrophenyl 2-amino-6-benzothiazolyl sulphides and found them to be good chemotherapeutics for typhus.

Robinson and Gibbs showed that the introduction of 5-mercapto or 5-substituted mercapto group into thiazole ring imparts marked bacteriostatic properties to the resulting compound, e.g., bis(2-amino-4-methyl-5-thiazolyl) sulphide and 4-methyl-5-ethylmercaptothiazole were good bacteriostats.

French patent deals with preparation of bis (2-amino-4-methyl-5-thiazolyl) sulphide, bis (2-amino-4-n-propyl-5-thiazolyl) sulphide, and bis (2-amino-4-benzyl-5-thiazolyl) sulphides which were found to be good bacteriostats and insecticides.

Therefore, various phenyl 2-amino-5-thiazolyl sulphides and sulphones prepared during the present work are expected to possess antibacterial activity. They are structurally represented as,
where $R = R_1 = H, Cl, Br, CH_3$ or $OCH_3$ and

$R_2 = H, Cl, Br, CH_3, OCH_3, OC_2H_5, OC_3H_7$ and $OC_4H_9$.

Majority of the amino-sulphides and their hydrochlorides and corresponding amino-sulphones have been tested on E.coli and S.aureus employing paper disc method. The results of the testing are summarised in tables appearing in Chapter No.VII.
REFERENCES.