Chapter - I

Introduction
Chapter I
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1.1 GENERAL INTRODUCTION OF 1,5-BENZOTHIAZEPINES

The heterocyclic systems with seven atoms, once considered chemical oddities, are today just as easily obtained as five and six membered analogues, and these compounds no longer remain the esoteric species, they were once considered to be. Quite to the contrary, the pace of research and development in this area is accelerating due to the substantial advances that have been made in the synthesis of these materials in the last few decades. As a result of this there seems to be virtually no limit to the number of interesting ring systems that can be created in the laboratory today by the combination of ingenuity and perseverance.

1,5-Benzothiazepines are bicyclic heterocyclic compounds with one nitrogen and one sulphur atom at 1 and 5 positions in a seven membered ring fused to a benzene ring. Basically 1,5-benzothiazepines are the 2,3 benzo-annelated derivatives of 1,4-thiazepines. Benzothiazepines are numbered as shown in (1.001) Fig.1.1. The numbering of these benzothiazepines proceeds in the opposite direction to that used for the unannulated thiazepines. The position of the odd hydrogen atom (even if occupied by another mono or divalent substituent) is indicated by the term 1H, 2H, 3H etc. In dihydro and tetrahydro benzothiazepines the odd hydrogen is given the lowest possible number. This is however, complicated by the fact that, first consideration is given to the position of a functional group which is expressed as a suffix to the name of the compound.

The development of privileged heterocyclic scaffolds is a rapidly emerging subject in medicinal chemistry. The chemical modification of privileged heterocyclic systems offers a continuous challenge to the medicinal chemists in search of compounds with bio-pharmacological activity\textsuperscript{1}. In view of the interesting biological properties shown by privileged heterocyclic compounds, the study of this system provides a very fascinating field for exploration in drug research. 1, 5-Benzothiazepine is an important privileged seven membered heterocyclic ring
system that features in a number of clinically used drugs due to their potential to provide an active pharmacophore for de novo exploration.

Incorporation of bioactive pharmacophores at position- 4 of the 1, 5-benzothiazepine nucleus has been shown to exert a profound influence in conferring the novel biological activity in these molecules. Based on these observations it could be anticipated that the incorporation of an active pharmacophore (like pyrazole, triazole, tetrazole, pyridine, pyrimidine, pyrrolidine, piperidine, morpholine, piperazine and sulphonamide group etc. which have the previous history of being biologically active), at 4-position of 1, 5-benzothiazepine nucleus could produce interesting series of compounds with enhanced biological properties.

1.1.1 Biological aspects of 1,5-benzothiazepines

The 1,5-benzothiazepine scaffold is extremely versatile and has featured in a number of clinically used drugs. 1,5-Benzotheiazepine and 1,5-benzodiazepine are the two main seven-membered heterocyclic ring systems reported for their cardiac and psychotherapeutic activities. Successful introduction of diltiazem and clentiazem for angina pectoris, hypertension, arrhythmias and other related cardiac disorders proved potential of 1,5-benzothiazepine moiety. The 1,5-benzothiazepine derivatives are of particular interest for lead discovery because they have been found active against different families of targets. The 1,5-benzothiazepine scaffold has been used as cardiovascular modulator such as vasodilator and antiarrhythmic, protease inhibitors, elastase/ACE inhibitors, antagonists of several G-protein coupled receptors such as cholecystokinin (CCK) receptor as interleukin-1b converting enzyme inhibitors / the angiotensin II receptor (ACE) inhibitors. Recently, anticancer activity, haemodynamic effects, antitumor activity and spasmyloytic activities have also been reported. First molecule used clinically was diltiazem, followed by clentiazem, for their cardiovascular action. Some of the 1,5-benzothiazepine derivatives were also used clinically for CNS disorders which includes thiazesim, and quetiapine fumarate.

A literature survey reveals the enhanced bioactivity of annulated 1,5-benzothiazepines. The recent demonstration that some of their derivatives can serve as potential agents in the control and treatment of AIDS has stimulated further interest in these compounds from yet another perspective.
Pharmacological properties of substituted derivatives of 1,5-benzothiazepines

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Structure of the compound</th>
<th>Trade name</th>
<th>Pharmacological Properties</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><img src="image1" alt="Structure 1" /></td>
<td>Diltiazem</td>
<td>Used in the treatment of hypertension, angina pectoris and some types of arrhythmia</td>
<td>33</td>
</tr>
<tr>
<td>2.</td>
<td><img src="image2" alt="Structure 2" /></td>
<td>Thiazesim</td>
<td>Acts as a heterocyclic antidepressant</td>
<td>35</td>
</tr>
<tr>
<td>3.</td>
<td><img src="image3" alt="Structure 3" /></td>
<td>GW-577</td>
<td>Treatment of lipoprotein disorders</td>
<td>3</td>
</tr>
<tr>
<td>4.</td>
<td><img src="image4" alt="Structure 4" /></td>
<td>KT-363</td>
<td>Shows antihypertensive, antiarrhythmic, Ca(^{2+}) channel antagonist activity</td>
<td>39</td>
</tr>
</tbody>
</table>

1.1.2 Synthetic aspects of 1,5-benzothiazepines

The broad spectrum of medicinal properties associated with these molecules has triggered the development of a variety of methods for the synthesis of these materials and has led to an impressive armoury of synthetic strategies to be devised in the literature for this class of compounds. In this context, it seems necessary to present in the discussion to follow a brief outline of some of the available literature methods, which have been employed to date for the synthesis of 1,5-benzothiazepines.
1.1.2.1 One pot synthesis of 1,5-benzothiazepines

1,5-Benzothiazepines are easily prepared by reacting the corresponding α,β-unsaturated ketones and o-aminothiophenol in the presence of a solvent and/or catalyst, in a one-pot reaction. Many experimental variations have been made in this broad procedural framework altering the substrate characteristics.

1. From α,β-unsaturated ketones or chalcones

Condensation reactions of o-aminothiophenol (1.003) and o-hydroxychalcones (1.002) under gallium(III) triflate catalysis produce functionalized 1,5-benzothiazepines (1.004) in good to excellent yields. The o-hydroxy group of chalcones is crucial for this unprecedented condensation process (Scheme 1.1).

![Scheme 1.1](image1)

When 2-aminobenzenethiol (1.003) were stirred with α,β-unsaturated ketones (1.005) at room temperature in the presence of LaY zeolite, the 2-carboxy-2,3-dihydro-1,5-benzothiazepine (1.006) were produced in 72-94% yield (Scheme 1.2).

![Scheme 1.2](image2)
Microwave enhanced solvent-free synthesis of 2-carboxy-2,3-dihydro-1,5-benzothiazepines \textbf{1.009} was carried out by reacting substituted o-aminothiophenols \textbf{1.007} with \(\alpha,\beta\)-unsaturated ketones \textbf{1.008} using montmorillonite clay\textsuperscript{42} (Scheme \textbf{1.3}).

\begin{center}
\begin{tikzpicture}
\node[above] at (0,0) {\textbf{1.007}};
\node[right] at (3,0) {\textbf{1.008}};
\node[above] at (6,0) {\textbf{1.009}};
\draw[-stealth] (0,0) -- (3,0);
\draw[-stealth] (3,0) -- (6,0);
\end{tikzpicture}
\end{center}

\textsuperscript{R}_1=H,CH_3,F,Cl,Br,OCH_3,OC_2H_5; R_2=H,CF_3; R_3=H,Cl,Br,CH_3,CF_3; R_4=H,CH_3; R_5=H,Cl,CF_3; R_6=H,F,OH

Scheme \textbf{1.3}

One of the most widely employed methods for the preparation of 1,5-benzothiazepines \textbf{1.011} involves the reaction of o-aminothiophenol \textbf{1.003} with \(\alpha,\beta\)-unsaturated ketones or chalcones \textbf{1.010} both under acidic and basic conditions\textsuperscript{43} (Scheme-\textbf{1.4})

\begin{center}
\begin{tikzpicture}
\node[above] at (0,0) {\textbf{1.003}};
\node[right] at (3,0) {\textbf{1.010}};
\node[above] at (6,0) {\textbf{1.011}};
\draw[-stealth] (0,0) -- (3,0);
\draw[-stealth] (3,0) -- (6,0);
\end{tikzpicture}
\end{center}

Scheme: \textbf{1.4}

2. From \(\beta\)-diketones

Oxidative cyclocondensation of phenolic \(\beta\)-diketones \textbf{1.012a-d} with o-aminothiophenol \textbf{1.003} in DMSO give benzofuro-annelated-2-phenyl-1,5-benzothiazepine derivatives \textbf{1.013a-d} in reasonable yields\textsuperscript{44} (Scheme \textbf{1.5}).

\begin{center}
\begin{tikzpicture}
\node[above] at (0,0) {\textbf{1.012a-d}};
\node[right] at (3,0) {\textbf{1.003}};
\node[above] at (6,0) {\textbf{1.013a-d}};
\draw[-stealth] (0,0) -- (3,0);
\draw[-stealth] (3,0) -- (6,0);
\end{tikzpicture}
\end{center}

Scheme: \textbf{1.5}
3. From β,β-dimethyl-acrylic acid and its ester

The reaction of β,β-dimethyl-acrylic acid and its ester 1.014a-d with o-aminothiophenol (1.003) give exclusively the benzothiazepines 45 1.015 (Scheme 1.6).

\[
\begin{align*}
\text{R}_1\text{H} & \quad \text{R}_2COOR_3 \\
\text{1.014a-d} & \\
a & \text{R}_1=\text{R}_3=\text{H}, \text{R}_2=\text{Me} \\
b & \text{R}_1=\text{R}_3=\text{H}, \text{R}_2=\text{Ph} \\
c & \text{R}_1=\text{R}_2=\text{Me}, \text{R}_3=\text{H} \\
d & \text{R}_1=\text{R}_2=\text{Me}, \text{R}_3=\text{Et}
\end{align*}
\]

1.003

1.015 (major)

1.016

Scheme: 1.6

1.2 PYRROLO-1,5-BENZOTHIAZEPINES

1.2.1 Biological aspects of pyrrolo-1,5-benzothiazepines

It has been recently reported that the synthesis of pyrrole and sulfur containing heterocycles are the precursors of compounds of potential pharmacological interest. Pyrrolo[2,1-c][1,4]benzothiazepines represent a class of compounds which are supposed to possess interesting biological properties, but are still largely unknown 46. Pyrrolo[2,1-c][1,4]benzothiazepine derivatives might show significant central nervous system (CNS) activity 47. A number of new pyrrolobenzothiazepine derivatives have been shown to possess affinity towards the ‘peripheral type’ benzodiazepine receptor 48 (PBR).

More recently, pyrrolo benzothiazepines and nevirapine related analogues have been studied as non-nucleoside inhibitors of HIV-1 virus. In particular, 3H-pyrrolo[2,3-b][1,5] benzothiazepine and 1H-pyrrolo [3,2-b][1,5] benzothiazepine derivatives inhibited HIV-1 replication in micromolecular levels 38. Moreover, 5H-pyrrolo [1,2-b ] [1,2,5] benzothiadiazepine (PBTD) 49 and pyrrolo [2,1-d][1,2,5] benzothiadiazepin-7(6H)-one-5,5 dioxide derivatives 50 have been reported to be potent RT inhibitors blocking viral cycle at submicromolecular concentrations. A number of 2H-pyrrolo[3,4-b][1,5]benzothiazepine derivatives 51 (PBTAs) have been shown to act as potential inhibitors of HIV-1 reverse transcriptase. 6-arylpyrrolo[2,1-d][1,5]benzothiazepine derivatives has been identified as a novel class of ligands that are specific for mitochondrial benzodiazepine (MBR) receptors 52. Novel
derivatives, having pyrrolo[1,5]benzoxa(thia)zepine nucleus have been evaluated as apoptotic agents\textsuperscript{53}.

### Pharmacological properties of some pyrrolo substituted derivatives of benzothiazepines

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Structure of the compound</th>
<th>Derivative name</th>
<th>Pharmacological Properties</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><img src="image1" alt="Structure 1" /></td>
<td>3H-pyrrolo[2,3-b][1,5] benzothiazepine derivative</td>
<td>Inhibited HIV-1 replication in the micromolar range</td>
<td>50</td>
</tr>
<tr>
<td>2.</td>
<td><img src="image2" alt="Structure 2" /></td>
<td>2H-pyrrolo [3,4-b][1,5]-benzothiazepine derivatives</td>
<td>Exhibits reverse transcriptase inhibitory activity</td>
<td>53</td>
</tr>
<tr>
<td>3.</td>
<td><img src="image3" alt="Structure 3" /></td>
<td>6-arylpyrrolo [2,1-d][1,5] benzothiazepine derivatives</td>
<td>Most potent ligands specific for mitochondrial benzodiazepine receptor (MBR)</td>
<td>52</td>
</tr>
<tr>
<td>4.</td>
<td><img src="image4" alt="Structure 4" /></td>
<td>6-arylpyrrolo [2,1-d][1,5] benzothiazepine derivatives</td>
<td>Most potent ligands specific for mitochondrial benzodiazepine receptor (MBR)</td>
<td>52</td>
</tr>
</tbody>
</table>

### 1.2.2 Synthetic aspects of pyrrolo-1,5-benzothiazepines

1. **From aldehydes**

   The synthetic pathway starts from the aldehyde 1.017 which was smoothly reduced to the corresponding alcohol 1.018 by using NaBH\textsubscript{4}. After demethylation, achieved by means of Na in N,N-dimethylacetamide and subsequent cyclisation using diisopropyl azodicarboxylate (DIAD) and triphenylphosphine (TPP) leads to 1.020. (Scheme-1.7)\textsuperscript{54}
2. From thiophenol

Thiophenol 1.021 after alkylation with α-bromophenyl acetic acid and intramolecular cyclisation was transformed to the ketone 1.023. Enolisation with potassium hydride and subsequent acylation with dimethylcarbamoyl chloride yielded the final pyrrolobenzothiazocine 1.024 (Scheme-1.8)55

3. From bis(2-N-pyrrolylphenyl)disulfides

From bis(2-N-pyrrolylphenyl)disulfides (1.025), acids 1.026 were obtained by a reductive alkylation by means of sodium borohydride and α-bromophenylacetic acid. Intramolecular cyclisation with phosphorous pentachloride gave the ketone 1.027 then their corresponding potassium enolates were treated with selected acyl chlorides to finally yield the pyrrolobenzothiazepines 1.028 (Scheme-1.9)52
1.3 AN OVERVIEW OF OXOKETENE DITHIOACETALS EMPLOYED AS INTERMEDIATE IN SYNTHESIS, IN PRESENT WORK

Heterocyclic ketene S,S-acetals 1.029, cyanoketene S,S-acetals (1.030), ketene N,S-acetals 1.031 or aminals 1.032 as well as ketoketene S,S-acetals 1.033 are important synthans for the synthesis of a wide variety of new heterocycles and fused heterocycles\(^{56}\). (Fig. 1.2)

![Fig. 1.2](image)

Oxoketene dithioacetals containing active functional groups have been exploited in a variety of synthetic applications. Conjugated olefin ketene dithioacetals have served as carbonyl Umpolung reagent and Diels-Alder dienes. \(\alpha\)-Oxoketene dithioacetals (1.034) have been extensively utilized for the synthesis of heterocyclic compounds\(^{57-58}\), Diels-Alder dienes\(^{59}\) and the synthesis of \(\beta\)-oxothiolcarboxylates\(^{60}\). (Fig. 1.3)

![Fig. 1.3](image)

The conjugated ketene dithioacetals contain masked ester functionality and hold considerable potential as substrates for functional group manipulation and sequential carbon-carbon bond forming transformations. \(\alpha\)-Oxoketene dithioacetals, especially the dimethyl thioacetal have recently received considerable attention due to their synthetic importance for the construction of a variety of alicyclic, aromatic and heterocyclic nucleus\(^{58}\). The direct displacement of the methylthio group of ketene dithioacetals by an addition-elimination mechanism\(^{61}\) has proved to be a convenient method for preparing the useful heterocyclic compounds\(^{62-63}\).
The polarized ketene dithioacetal$^{64}$ of the general formula \textbf{1.035}, which may carry either one or two electron withdrawing groups at the $\alpha$-carbon atom belong to a class of intermediates, generally known as either polarized, push-pull$^{65}$ or donor-acceptor ethylenes. (Fig. \textbf{1.4})

![FIG. 1.4](image)

The polarized ketone dithioacetals can be broadly classified in two categories:

1) The ketene dithioacetals, which include all variants of oxo groups, such as CHO, CO, COOR, CONH$_2$ and the CN (as latent oxo group) can be considered as oxoketene dithioacetals.

2) The other ketene dithioacetals that can be grouped separately include those which carry nitro, pyridinium and sulphonyl groups as $\alpha$-polar substituents.

3) The first category may further vary in its $\alpha$- substituents R$_1$ and R$_2$ of which R$_1$ has to be an oxo functionality, while R$_2$ could either be hydrogen or any other neutral group including polar variants of the other category.

The $\alpha$-oxoketene dithioacetals owe their potential synthetic applications to their varied intrinsic chemical properties like electrophilic properties and nucleophilic properties.

The presence of carbonyl functionality and its position in conjugation with double-bond carrying bis(alkyl thio) groups at the $\beta$-position places them among the versatile 1,3-electrophilic 3-carbon equivalents. The $\alpha$-oxoketene dithioacetals (\textbf{1.036}) and oxoketene N,S-acetals (\textbf{1.037}) can be considered as masked $\beta$-ketoesters that can be distinguished by having ambident electrophilicity at 1,3-carbon centres, due to presence of bisalkylthio groups, which can be converted into ester functionality when desired$^{66}$. (\textbf{Scheme 1.10})
The \( \alpha \)-oxoketene dithioacetals functionality can be viewed from several different perspectives. It is essentially a \( \beta \)-ketoester in which the ester functionality is protected as a ketene dithioacetal. Alternatively, it may be viewed as an \( \alpha,\beta \)-unsaturated ketone containing a highly functionalized \( \beta \)-carbon atom. These functionalities possess considerable potential for the regioselective construction of new bonds in compound 1.039 and 1.040 via 1,2-nucleophilic additions to the ketene carbonyl or 1,4 conjugate addition reaction to the \( \beta \)-carbon of enone system.

(Scheme 1.11)

The intermediate allylic alcohols and enones can, in turn, be exploited in additional bond forming transformations. Such reactivity patterns can also be
exploited in other conjugated ketene dithioacetals derived from esters, lactones and active methylene compounds. The \( \alpha \)-oxoketene dithioacetals functionality has received considerable attention as a versatile carbon fragment for heterocyclic synthesis. These heterocyclic synthesis generally exploit both the 1,2 and 1,4 nucleophilic addition reactions separately or sequentially in a cascade.

1.3.1 Synthesis and properties of oxoketene dithioacetals

\( \alpha \)-Oxoketene dithioacetals are easily prepared by reacting the corresponding active methylene compounds with carbon disulphide in the presence of a suitable base followed by alkylation, in a one pot reaction. Many experimental variations have been developed within this broad procedural framework from the substrate characteristics such as the acidities of active methylene hydrogens, specific base sensitive functional groups and the optimum yield of the corresponding dithioacetals. A large number of active methylene compounds can therefore be converted into the polarized ketene dithioacetals 1.041-1.047 with many permutations and combinations of substituents. (Fig. 1.5)

The first synthesis of an \( \alpha \)-oxoketene dithioacetals 1.050 was reported in 1910 by Kebler\(^{67}\) and co-workers and was obtained by alkylation of \( \beta \)-oxo dithioic acids 1.049 with alkyl halides under basic conditions. The \( \beta \)-oxo dithioic acids, however, were obtained in poor yield by reaction of an aryl ketone 1.048 with CS\(_2\) and KOH at 110\(^{\circ}\)C followed by neutralization with sulphuric acid. (Scheme 1.12)
The reaction of ketones and active methylene compounds with carbon disulphide in the presence of hydroxide and alkoxide bases has been known since 1891 when Meyer and Wege reported the preparation of the desaurins 1.052 by treatment of ketones 1.051 with carbon disulphide and powdered NaOH. (Scheme 1.13)

α-Oxoketene dithioacetals 1.054 have been prepared by reaction of α-diazoketones 1.053 with CS₂ (Scheme 1.14)

In 1960 Thuiller and Vialle investigated the chemistry of α-oxoketene dithioacetals 1.056 and found that they could be prepared directly from ketones 1.055 and CS₂ in good yields by using sodium t-amylate as the base and two equivalents of an alkyl halide. (Scheme 1.15)
Good yield of $\alpha$-oxoketene dithioacetals were obtained with NaOH and CS$_2$ from aromatic ketones (60-90%) and several workers have effectively employed this combination (in PhH, DMF, or DMSO) for the synthesis of conjugated ketene dithioacetals from aryl and heteroaryl ketones$^{71}$ and active methylene compounds$^{72-73}$. Potassium t-butoxide (in PhH, DMF or PhH/DMF) is also an effective base$^{74}$ and K$^+$t-BuO/THF/CS$_2$/RX combination has recently been developed as a particularly effective procedure for $\alpha$-oxoketene dithioacetals.

The use of strong amide bases have opened the way for the synthesis of conjugated ketene dithioacetals 1.058 and 1.060 from a variety of enolate anions such as $\alpha,\beta$-enones, esters 1.057, lactones 1.059, $\alpha,\beta$-unsaturated esters, nitriles and hydrazones. (Scheme 1.16, 1.17)

These procedures were also extended to the preparation of conjugated ketene dithioacetals from active methylene compounds such as malononitrile, cyanoketones, cyanoacetate, cyanoacetamides and heterocyclic acetonitriles, nitriles, nitromethane, aldehydes and phenol.

1.3.2 Importance of oxoketene dithioacetals in synthesis

$\alpha$-Oxoketene S,S-acetals have received considerable attention due to their synthetic importance in the construction of a variety of alicyclic, aromatic and heterocyclic nucleus$^{75}$. These compounds exhibit wide compatibility with olefin, ketone, ester and amide groups$^{76}$. 
The oxoketene dithioacetal 1.061 is a versatile starting material for the synthesis of wide variety of fused heterocycles. (Fig. 1.6)

\[
\text{O}
\begin{array}{c}
\text{C}_2\text{H}_5 \\
\text{H}_3\text{CS} \\
\text{SCH}_3
\end{array}
\]

1.061

Fig. 1.6

The presence of two $\beta$-alkylthio substituents affords a higher level of oxidation in functional group manipulation and in many instances generates a product containing a substituent or functional group that can be manipulated in additional synthetic transformations.

A variety of “one pot” transformations employing a cascade of 1,4-nucleophilic addition reactions to $\alpha$-oxoketene dithioacetals have been elegantly applied to a variety of heterocyclic synthesis. The presence of carbonyl functionality and its position in conjugation with double bond carrying bis(alkylthio) groups at the $\beta$-position places them among the versatile 1,3-electrophilic 3-carbon equivalents. The $\alpha$-oxoketene dithioacetals can be considered as masked $\beta$-ketoesters that can be distinguished by having ambident electrophilicity at 1,3-carbon centres, due to the presence of bis alkylthio groups, which can be converted into ester functionality when desired. $\alpha$-Oxoketene dithioacetal exhibits differential electrophilicity between $\beta$-carbon and carbonyl carbon atom.

$\alpha$-Oxoketene dithioacetal 1.061 can be further converted into enaminones 1.062 and $\beta$-alkoxy-$\alpha,\beta$-unsaturated ketones 1.063, making them highly functionalized master key intermediates, which could encompass the wide range of 1,3-electrophilic three-carbon fragment that are of great synthetic importance. (Scheme 1.18)
The carbonyl carbon and the β-carbon atom in the system such as 1.061 can also be regarded as hard and soft electrophilic centres, since the carbonyl is adjacent to the hard-base oxygen while the β-carbon is flanked by the soft-base thiomethyl groups 1.064 (Scheme 1.19)

α-Oxoketene dithioacetals 1.061 containing a highly functionalized β-C atom, possess considerable potential for the regioselective construction of new bonds via 1,2-nucleophilic additions to the ketone carbonyl of 1.065 or 1,4-conjugate addition reactions to the β-carbon of the enone system of 1.066 (Scheme 1.20)

The attacking carbon nucleophiles have accordingly displayed regioselectivity which can be broadly classified into hard and soft nucleophiles. Thus, organolithium\textsuperscript{77}, methyl Grignard\textsuperscript{78} and Reformatsky reagent\textsuperscript{79} have shown high 1,2-regioselectivity as hard nucleophiles. However, higher alkyl and polarized Grignard (C\textsubscript{6}H\textsubscript{5}MgBr and C\textsubscript{6}H\textsubscript{5}CH\textsubscript{2}MgBr) reagents lack this regioselectivity, and attack in sequential 1,4 followed by 1,2 fashion resulting, after hydrolysis, in the corresponding α,β-unsaturated ketones. The typical carbon, soft nucleophile such as organocuprates have shown distinct 1,4-regioselectivity and have been extensively investigated by Dieter and Coworkers\textsuperscript{80-81}. α-Oxoketene dithioacetals can be induced
to undergo a selective reaction with organocopper reagents to afford β-alkylthio-α,β-enones with some degree of stereoselectivity. The reaction of organocopper reagents with α,β-unsaturated carbonyl compounds containing a good leaving group at the β-carbon atom have been actively investigated. The substitution of the leaving group by the alkyl ligand of the cuprate generally afford β-alkyl-α,β-unsaturated carbonyl compounds in a chemoselective fashion, although bis-conjugated addition to afford β,β-dialkyl carbonyl compounds may be competitive with the more reactive cuprates and substrates.

Few studies, however, have examined α-oxoketene dithioacetal containing two good leaving groups at the β-carbon atom. Although the addition of organocuprates α-oxoketene dithioacetals 1.061 has been reported, the transformation has involved the addition of either two or three alkyl groups to afford α-alkylidine 1.067 or tertiary alkyl ketones 1.068 (Scheme 1.21)

![Scheme 1.21](image)

Many stabilized enolate anions have been similarly reacted with α-oxoketene dithioacetals which normally add in 1,4-fashion and these reactions were extensively investigated by Kobayashi and co-workers in the sixties and seventies. Depending on the functional group characteristics of the enolate anions and the structure of α-oxoketene dithioacetals, the 1,4-addition elimination combination may lead either to displacement of methylthio group or to subsequent cyclisation to give a diverse product range.
1.3.3 Application of $\alpha$-oxoketene dithioacetals in cyclisation reactions

The conjugate addition of enolate anions to $\alpha$-oxoketene dithioacetals may provide immense synthetic opportunities, provided the enolate anions are appropriately functionalized, so as to afford five- and six-membered carbo- and heterocycles.

Cyclization of phenylurea (1.069) with $\alpha$-oxoketene dithioacetals 1.061 afford the pyrimidines$^{85}$ 1.070 by the replacement of thiomethyl group of dithioacetals. (Scheme 1.22)

![Scheme 1.22](image)

$\alpha$-Pyridyl acetonitrile/acetate$^{86,87}$ (1.071) on heating with $\alpha$-oxoketene dithioacetal 1.061 derived from ethyl cyanoacetate, yield quinolizones 1.072 in which the thiomethyl group is easily replaced by $\beta$-aminopropionitrile to give, an intermediate in the synthesis of DL-allomedridine$^{88}$ 1.073 (Scheme 1.23)

![Scheme 1.23](image)

Tominaga and other coworkers$^{89}$ have extensively investigated the addition of enolate anions derived from ketone 1.074 to doubly activated ketene dithioacetals 1.061 to afford 4-methyl-2-pyrones (1.075) in low to moderate yield. (Scheme 1.24)

![Scheme 1.24](image)
1.3.4 Application of α-oxoketene dithioacetals in synthesis of heterocycles

The α-oxoketene dithioacetals have been recognized as useful 3-carbon 1,3-electrophilic fragments and have been exploited extensively for the construction of five- and six-membered heterocycles. Their reaction with hydrazine\(^9^0\), hydroxylamine\(^9^1\), guanidine\(^9^2\), amidine, enamine, cyanoacetamide anions, 1,2-diamine, 1,2-aminoalcohol and 1,2-aminothiols have been investigated. Subsequent developments involving their structural flexibility and reactivity with a variety of hetero nucleophiles to afford the novel class of heterocycles have also been reported.

1. Thiophenes

Two general strategies have been developed for the synthesis of thiophenes from conjugated ketene S,S- and N,S-acetals. The first involves the synthesis of conjugated ketene dithioacetal containing an S-alkyl group (e.g. CH\(_3\), CH\(_2\)CN, CH\(_2\)COR, CH\(_2\)COOR) that can undergo subsequent cyclisation onto the conjugated functionality (e.g. CN, COR, COOR).

The second strategy involves cyclization of the enamine moiety to N,S-acetals onto an S-alkyl unit (e.g. CH=C=CH\(_2\)). Thiophene formation was observed during studies on the alkylation of dithioic acid or the mono-anions derived from them. Gompper and Schafer\(^9^3\) have reported that alkylation of the dithioic acid \(1.076\) derived from ethylcyanoacetate with α-chloroacetamide \(1.077\) under acidic conditions yielded a thiophene \(1.078\) arising from initial S-alkylation followed by closure onto the nitrile. (Scheme 1.25)

![Scheme 1.25](image)

Under basic reaction conditions, cyclisation occurs onto the ester or ketone functionality in \(1.079\) and the thiophenes \(1.080\) are formed in low to moderate
yields. This procedure has been extended to ketene N,S-acetals 1.081 which afford 2-aminothiophenes 1.082 and to simple α-oxoketene dithioacetals employing α-chloroesters, nitriles and amides 91. (Scheme 1.26 and 1.27)

Scheme: 1.26

Scheme: 1.27

2. Isoxazoles

The reaction of symmetric bifunctional heteronucleophiles 1.083 with α-oxoketene dithioacetals 1.061 can yield two regioisomeric heterocycles 1.084 and 1.085 depending on the electrophilicity of 1,3-carbon centres of the dithioacetals, the nucleophilicity of the heteroatom in the bifunctional nucleophiles and the reaction conditions. (pH of the reaction medium, etc) (Scheme 1.28)

Scheme: 1.28

The doubly activated α-oxoketene dithioacetals 1.086 are known to react with hydroxylamine to give the corresponding 3-methyl thio-isoxazoles 94 1.087 (Scheme 1.29)
3. **Pyrazoles**

Chauhan and Junjappa\(^5\) examined the reaction of hydrazine with \(\alpha\)-oxoketene dithioacetal 1.061 to give 5(3)-alkylthiopyrazoles 1.088 (88-90\%). Treatment of the \(\alpha\)-oxoketene dithioacetal with sodium ethoxide prior to reaction with hydrazine afforded the 5(3)-alkoxy pyrazoles 1.089 (60-67\%) via the intermediate \(\alpha\)-oxoketene O,S-acetals. Rudorf and Augustein studied the reaction of \(\alpha\)-oxoketene dithioacetals with hydrazines. Several different pyrazoles were generated since unsymmetrical hydrazines can undergo the initial conjugate addition reaction with either N atom and subsequent cyclisation can occur on to either the nitrile or ketone to give 1.090, 1.091 and 1.092 (Scheme 1.30)

![Scheme 1.30](image-url)
4. **Pyridines**

\( \alpha \)-Oxoketene dithioacetals 1.093 have been used in the synthesis of 1,5-endiones 1.094 by reaction with ketone enolates. These 1,5-enediones can be converted into pyridines 1.095 (Scheme 1.31) and pyrilium salts 1.096 (Scheme 1.32)

![Scheme 1.31](image1.png)

![Scheme 1.32](image2.png)

5. **Imidazolidines, oxazolidines and thiazolidines**

These 5-membered ring heterocyclic compounds 1.099 containing two heteroatoms in the 1 and 3 position are readily synthesized by reaction of \( \alpha \)-oxoketene dithioacetals 1.097 with 1,2-diamines, 1,2-amino alcohols and 1,2-aminothiols 1.098 respectively 97. (Scheme-1.33) The aliphatic bifunctional nucleophiles lead to simple heterocyclic ring systems while the aromatic heteroatom nucleophiles afford annulated poly-aromatic heterocyclic ring system.

![Scheme 1.33](image3.png)
1.4 AIM AND PLAN OF RESEARCH WORK

Heterocyclic compounds are of immense physiological importance due to their wide spectrum of biological activity. It has been observed from the literature that nitrogen heterocycles such as tetrazole, triazole, quinazoline, sulphonamide, pyrrolidine, piperidine, morpholine, piperazine, oxadiazole and pyrazole are important constituents of wide variety of materials with pharmacodynamic applications.

Incorporation of bioactive pharmacophores at position-2 of the 1,5-benzothiazepine nucleus has been known to exert a profound influence in conferring the novel biological activity in these molecules. With this idea in mind, it was proposed in the present work to synthesize pyrrolo-1,5-benzothiazepines bearing the following bioactive pharmacophores in their molecules.

- Tetrazole ring
- Triazole ring
- Quinazoline ring
- Sulphonamide group
- Pyrrolidine ring
- Piperidine ring
- Morpholine ring
- Piperazine ring
- Oxadiazole ring
- Pyrazole ring

The synthesis of the above series of heterocycles was based on this assumption that incorporation of one or more than one bioactive heterocyclic moiety into a single molecular framework may result heterocycles with enhanced bioactivity.

Based on the precedence in literature on the medicinal activity of these compounds, it was proposed in the present work to synthesize a series of compounds 1.100-1.110 shown in Fig. 1.7. The strategy which was planned to be explored in the synthesis of compounds 1.100-1.110 have been outlined in Scheme 1.34-1.41. Scheme 1.35 envisages the preparation of compounds 1.100-1.103 which were formed from the reaction of key intermediate 1.115 with the indicated bidentate nucleophiles. The strategy which was utilized (as shown in Scheme-1.34 and 1.35)
in the preparation of face(a) annulated products, was based on the earlier precedence for such reactions in the literature\textsuperscript{98-99}.

In Scheme 1.36, the formation of compound 1.104(a-e) from 1.115 have been shown. The strategy depicted in Scheme 1.36 sought to incorporate sulphonamide scaffolds at 2-position. These were available on the reaction of 1.115 with the sulphadrugs such as sulphacetamide, sulphapyridine, sulphamerazine, sulphathiazole, sulphabenzothiazole etc. Sulphonamides have been known to exhibit a broad range of biological activities\textsuperscript{100-101}. In Scheme 1.37, the products 1.105(a-h) which were formed from 1.115 on its reaction with a variety of bioactive secondary amines have been shown. It has been previously mentioned that incorporation of the bioactive pharmacophores in the existing drug molecules, exerts a profound influence on the biological profile of the molecules, Greatly encouraged by this concept of drug design, the aim in the present work was to incorporate in 1.115, the structural features of pyrrolidine, piperidine, morpholine, N-methyl, N-ethyl, N-benzyl, N-ethoxy carbonyl and N-acetyl piperazines to afford the compounds 1.105(a-h), following the procedure described in the literature\textsuperscript{102}, for their incorporation in the related structures. The strategy outlined Scheme 1.38 shows the formation of 1.106(a-c) and 1.107(a-b) from the key intermediate 1.118, (which in turn was realized from 1.115 in two steps). Acid hydrazides have been known to provide a very convenient route to the synthesis of following heterocycles: (a)1,3,4-oxadiazole derivatives: which results from its reaction with CS\textsubscript{2} and KOH followed by treatment with acid\textsuperscript{103} or by the reaction with POCl\textsubscript{3} in presence of carboxylic acids\textsuperscript{104} (b) triazole derivatives: which results from its reaction with KSCN/HCl\textsuperscript{105(a-b)} followed by the treatment with alkali or by the reaction of hydrazine hydrate on the product formed from the reaction of the acid hydrazide with CS\textsubscript{2} and KOH (c) pyrazole derivatives: which are formed from its reaction with enolic ether of malononitrile\textsuperscript{106}. The strategies a, b and c described above were applied on 1.118 to give the compounds 1.106(a-c) and 1.107(a-b), respectively. (Scheme 1.38)

Scheme 1.39 and 1.40 envisaged the preparation of compounds 1.108a and 1.108b and 1.109 from the key intermediate 1.120. Path A of this strategy led to 1.108a, through the approach outlined in Scheme 1.39. This approach was based on
the formation of 1.120 from the reaction of acetophenone derivatives 1.119 with CS₂ and CH₃I in presence of a base¹⁰⁷, followed by the reaction of the obtained oxoketene dithioacetal derivatives 1.120 with aminoacetaldehyde dimethyl acetal and its instantaneous cyclocondensation reaction in situ afforded the pyrrole derivatives¹⁰⁸ 1.121. These transformations were demonstrated to proceed with great facility under milder conditions and give high yield of the products. The method was very flexible and gave the possibility to prepare a large number of the derivatives of 1.121 bearing various substituents in the benzene ring. The cyclocondensation of the key intermediate 1.121 with o-aminothiophenol in the subsequent step, allowed an straightforward access of 1.108a.

The Scheme 1.40 presented a very attractive approach to the synthesis of pyrrolo annulated 1,5-benzothiazepine derivatives bearing substituents in benzene as well as in the pyrrole ring. The strategy shown in Scheme 1.40, (path-B) was propelled forward through the reaction of 1.120 with the primary amines to give 1.122. The coupling of 1.122 with bromo acetaldehyde diethyl acetal in path B(i) and propargyl bromide in path B(ii), following the strategy reported for such reactions in the literature¹⁰⁹⁻¹¹⁰, and their cyclocondensations in situ generated the pyrrole derivatives, 1.123 and 1.124 respectively. The same strategy which operated upon 1.121 with o-aminothiophenol to produce 1.108a (in the previous Scheme 1.39) was applied on 1.123 and 1.124 in Scheme 1.40, to furnish the novel pyrrolo annulated 1,5-benzothiazepine derivatives 1.108b and 1.109 respectively.

In Scheme 1.41 the compounds 1.110a, 1.110b and 1.110c which were formed from the key intermediate 1.127 have been shown. Established trends available in the literature on the reactions of oxoketene dithioacetals was utilized in the subsequent reactions of 1.127 to obtain the products 1.110a, 1.110b and 1.110c as shown in Scheme 1.41. Use was made of the presence of the ester functionality on the adjacent carbon atom in 1.127 in conceiving the formation of pyrrolo annulated 1,5-benzothiazepine analogues from 1.127. The strategy depicted in Scheme 1.41 sought to incorporate the amine fragments in 1.127 through its reaction with ammonium acetate to furnish the pyrrolo annulated analogue 1.110a. In a likewise manner 1.127 was reacted with ethyl amine and propargyl amine to
form the intermediates 1.129 and 1.131 respectively. The cyclocondensation of the amine 111, with the ester functionality afforded 1.110b and 1.110c respectively.

The impressive biological properties exhibited by the pyrrolo condensed analogues of 1,5-benzothiazepines prompted us to devise, several novel synthetic routes to the synthesis of these materials in the present work. The aim of the present investigation was to examine the feasibility and versatility of the applications of the proposed Schemes 1.34-1.41 to the synthesis of these materials.

Fig. 1.7
Scheme 1.34

Scheme 1.35

Scheme 1.36
Introduction

Scheme 1.37

Selected heterocyclic secondary amines

(a) R =

(b) R =

(c) R =

(d) R =

(e) R =

(f) R =

(g) R =

Scheme 1.38

Scheme 1.39

R = 4-F, 4-Cl, 4-Br, 4-Me, 4-NO₂, 4-OMe