Chapter 5

Synthesis of some new substituted azetidinones and thiazolidinones bearing benzofuran moiety
REVIEW OF LITERATURE
AZETIDINONES

INTRODUCTION

The four-membered heterocyclic ring compounds are heterocyclic analogues of cyclobutane and nitrogen containing heterocyclics are known as azetidine. Azetidine (266) is the name given to the completely saturated four-membered nitrogen containing compound, it is also designated as trimethyleneimine. The carbonyl derivative of azetidine is designated as 2-azetidinone (or) more commonly known as β-lactam. Azetidinone (267) derivatives occupy a central place among medicinally important compounds due to their diverse and interesting antibiotic properties. This ring system has been known since 1907 but the investigation of their chemistry laid dormant till 1943. In that year it was found that the important penicillin and cephalosporin series of antibiotics contain the β-lactam ring. Since then these compounds have been studied extensively and a variety of synthetic methods have been developed for their preparation.

![Structures](image)

Azetidin-2-one is an important moiety associated with the structure of penicillin molecule. The biological activity of the β-lactam antibiotic is generally believed to be associated with the chemical reactivity of its β-lactam ring, which in turn is thought to be dependent on the tail end (amide side chain) as well as on the head of the antibiotic molecule.
Initially, most of the research programs were concerned with the modification of the tail end, which led to the introduction of the large number of clinically useful penam and cephem derivatives. Subsequently, special attention was focused on the modification of the head of the antibiotic molecule. Replacements of sulphur atom of these bicyclic compounds by carbon, nitrogen or oxygen were carried out in order to enhance the reactivity of azetidinone carbonyl function and consequently enhancing the antibacterial, antitubercular and anti-inflammatory activity. Various ring homologues have also been synthesized with similar objective. Based on this moiety, molecular manipulations were attempted by various workers to find effective antibacterial, antifungal, anti tubercular and antiviral agents.

GENERAL METHODS OF SYNTHESIS OF AZETIDINES

1. Cyclization methods: Azetidine and its derivatives have been prepared by a number of methods which include intramolecular cyclization and cycloaddition. The heterocyclic rings are formed by intramolecular ring closure from their acyclic counterparts. The activation energy of ring closure depends largely on ring strain in
the cyclic product and the probability of the two ends coming into close proximity. These two factors make the three-membered rings relatively easy to form. Although three-membered rings possess a higher ring strain, the probability of the two ends of the chain to attain the right conformation is very high. This later factor makes the four-membered ring to form rather less easily.

γ-Haloalkylamines in the presence of a base have been employed to prepare azetidine and its derivatives by intramolecular cyclization. The parent compound azetidine is obtained from γ-haloalkylamines and base (Scheme 31).

\[
\begin{align*}
\text{Br-CH}_2\text{CH}_2\text{CH}_2\text{-NH}_2 + \text{OH}^- & \rightarrow \quad \text{HN}^+ + \text{Br}^- + \text{H}_2\text{O} \\
\text{Scheme 31}
\end{align*}
\]

Sulfate esters of γ-amino alcohol have also been used in place of γ-haloamines to affect the cyclization (Scheme 32).

\[
\begin{align*}
\text{OSO}_2\text{CH}_2\text{CH}_2\text{NH}_2^+ + \text{NaOH} & \rightarrow \quad \text{HN}^+ + \text{Na}_2\text{SO}_4 + \text{H}_2\text{O} \\
\text{Scheme 32}
\end{align*}
\]

2. From isoxazole derivatives: An alternative method for the preparation of azetidines involves the ring opening and closure of isoxazoles. Thus, the 3,5-dimethylisoxazole ring is first opened by treatment with sodium in n-pentanol and subsequently reacted with tosyl chloride and pyridine. Cyclization is then accomplished in the presence of a strong base to give intermediate. The final product
2,4-dimethylazetidine is obtained by reducing (Na/pentanol) this intermediate product (Scheme 33).

\[
\begin{align*}
\text{H}_3\text{C} & \xrightarrow{(i) \text{ Na, n-Pentanol}} \text{H}_3\text{C}-\text{CHCH}_2-\text{CH}_2\text{CH}_3 \\
\text{H}_3\text{C} & \xrightarrow{(ii) \text{ TsCl, Pyridine}} \text{H}_3\text{C}-\text{CHCH}_2-\text{CH}_2\text{CH}_3
\end{align*}
\]

\[
\begin{align*}
\text{NaOC}_2\text{H}_5 & \xrightarrow{-\text{OTs}} \text{H}_3\text{C}-\text{N}\text{Ts}-\text{CH}_3 \\
\text{Na} & \xrightarrow{\text{Na, n-Pentanol}} \text{H}_3\text{C}-\text{N}\text{Ts}-\text{CH}_3
\end{align*}
\]

2,4-dimethylazetidine

Scheme 33

3. From direct cyclization of amino acids: A commonly employed method is the cyclization of free amino acids using acyl chloride, phosphorus trichloride or thionyl chloride as illustrated below (Scheme 34).

\[
\begin{align*}
\text{H}_5\text{C}_6-\text{N}-\text{CH}_2-\text{CHCOOH} & \xrightarrow{\text{PCl}_3} \text{H}_5\text{C}_6-\text{N}-\text{C}_6\text{H}_5
\end{align*}
\]

1,4-diphenyl azetidin-2-one

Scheme 34

4. Direct Combination Methods: An older technique involves the direct combination of two appropriately substituted components. For instance, ketenes condense with imines to form \(\beta\)-lactams (Scheme 35).
5. Cyclization of β-amino acids: β-Amino acids cyclize cleanly in the presence of diphenylphosphorochloridite to β-lactams (Scheme 36).

Scheme 35

Scheme 36
THERAPEUTIC POTENTIAL OF AZETIDIN-2-ONES

It was reported in the literature that different substituted azetidin-2-ones possess anti-inflammatory, antitubercular, antibacterial and antifungal activities. Given below is a brief account of various modifications reported on azetidinone nucleus, which showed a variety of biological and pharmacological activities.

Desai et al.\(^3\) synthesized and reported the QSAR studies of 2-oxa-azetidines (268) exhibiting antibacterial activity.

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

(268)

Bhusari et al.\(^4\) reported the synthesis and QSAR studies on 2-azetidinones bearing benzothiophene nucleus (269), which exhibited antitubercular activity.

\[
\begin{align*}
\text{OCH}_3 & \\
\text{Cl} & \quad \text{NH} \quad \text{N} \\
\text{Cl} & \quad \text{Cl} \\
\end{align*}
\]

(269)
Srivastava et al.\textsuperscript{5} reported a conventional as well as microwave assisted synthesis of some new $N^9$-[hydrazinoacetyl-(2-oxa-3-chloro-4-substituted aryl azetidine)] -carbazoles (270) that showed significant antifungal and antibacterial activities.

\begin{center}
\textbf{(270)}
\end{center}

Sharma et al.\textsuperscript{6} reported a general and versatile synthesis of 3-phenylthio $\beta$-lactams as lead molecules for 3-methyl-2-azetidinones (271).

\begin{center}
\textbf{(271)}
\end{center}

Desai et al.\textsuperscript{7} synthesized azetidinones under microwave irradiation (272) and reported their antibacterial activity.

\begin{center}
\textbf{(272)}
\end{center}
Sharma et al.\textsuperscript{8} reported a general strategy for the stereospecific synthesis of 3-chloro-2-azetidinones (273).

\begin{center}
\begin{tikzpicture}
\begin{scope}
  \node[draw,shape=circle,inner sep=0pt,minimum size=0.5cm] (a) at (0,0) {Cl};
  \node[draw,shape=circle,inner sep=0pt,minimum size=0.5cm] (b) at (0.5,0) {CH\textsubscript{3}};
  \node[draw,shape=circle,inner sep=0pt,minimum size=0.5cm] (c) at (1.5,0) {CH\textsubscript{2}-C\textsubscript{6}H\textsubscript{5}};
  \node[draw,shape=circle,inner sep=0pt,minimum size=0.5cm] (d) at (1.5,1) {N};
  \node[draw,shape=circle,inner sep=0pt,minimum size=0.5cm] (e) at (2,1) {O};
  \node[draw,shape=circle,inner sep=0pt,minimum size=0.5cm] (f) at (2.5,1) {N};
  \node[draw,shape=circle,inner sep=0pt,minimum size=0.5cm] (g) at (2.5,0) {CH\textsubscript{3}};
\end{scope}
\end{tikzpicture}
\end{center}

(273)

Borosa et al.\textsuperscript{9} synthesized aminomethylazetidines by a regioselective reaction of mesyloxymethylazetidinones with various nucleophiles (274).

\begin{center}
\begin{tikzpicture}
\begin{scope}
  \node[draw,shape=circle,inner sep=0pt,minimum size=0.5cm] (a) at (0,0) {Cl};
  \node[draw,shape=circle,inner sep=0pt,minimum size=0.5cm] (b) at (1,0) {OCH\textsubscript{3}};
  \node[draw,shape=circle,inner sep=0pt,minimum size=0.5cm] (c) at (2,0) {N};
  \node[draw,shape=circle,inner sep=0pt,minimum size=0.5cm] (d) at (2,1) {NR\textsuperscript{2}R\textsuperscript{3}};
  \node[draw,shape=circle,inner sep=0pt,minimum size=0.5cm] (e) at (3,1) {NR\textsuperscript{2}R\textsuperscript{3}};
  \node[draw,shape=circle,inner sep=0pt,minimum size=0.5cm] (f) at (3,0) {NR\textsuperscript{2}R\textsuperscript{3}};
\end{scope}
\end{tikzpicture}
\end{center}

HNR\textsuperscript{2}R\textsuperscript{3} = \text{morpholino}

(274)

Verma et al.\textsuperscript{10} synthesized some substituted azetidinones (275) and screened them for their antibacterial and antifungal activities.
Girija et al. synthesized new 1,3,3-triaryl-1-methylspiro[azetidine-2,3-indoline]-21,4-diones (276).

\[
\text{Ar} \quad \text{Ar} \\
\begin{array}{c}
\text{N} \\
\text{CH}_3
\end{array} \\
\text{Ar} \quad \text{N} \quad \text{O}
\]

(276)

Ketan et al. synthesized azetidinone compounds using conventional and microwave technique (277) and studied for their antibacterial activity.

\[
\begin{array}{c}
\text{H}_3\text{CO} \\
\text{H}_2\text{C}
\end{array} \\
\text{N} \\
\text{O}
\]

(277)

Deshmukh et al. have reported the microwave assisted synthesis of azetidine-2-ones (278) possessing antibacterial activity.

\[
\begin{array}{c}
\text{NH}_2 \\
\text{OC}_6\text{H}_5
\end{array} \\
\text{H}_3\text{CO}
\]

(278)
Pravin et al.\textsuperscript{14} synthesized 5\textit{H}-dibenzo(\textit{b},\textit{f})azepine-5-carboxylic acid [3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl] amide (279).

![Chemical Structure Diagram](image)

Freddy et al.\textsuperscript{15} synthesized some azetidin-2-ones (280) as potential antimicrobial agents.

![Chemical Structure Diagram](image)

Noubade et al.\textsuperscript{16} prepared 2-[(2,3-dimethyl phenyl)amino] benzanamide azetidine-2-ones (281) and evaluated for antimicrobial activity.
Mulwad et al.\textsuperscript{11} synthesized N-[6'-coumarinylamino-3-chloro-4-aryl azetidine-2-ones] (282) that showed significant antimicrobial activity.

![Chemical structure](image1)

(282)

Srivastava et al.\textsuperscript{18} synthesized new 1,2,4-triazolo-2-oxoazetidines (283) possessing antimicrobial, anticonvulsant and anti-inflammatory activities.

![Chemical structure](image2)

(283)

Sharma et al.\textsuperscript{19} synthesized 2-azetidinones via ester enolate condensation reaction with imines and thioimidates (284).

![Chemical structure](image3)

(284)
Shah et al.\textsuperscript{20} synthesized 2-azetidinones having benzthiazole moiety (285) and screened them for their antimicrobial activity.

\begin{figure}
\centering
\includegraphics[width=0.4\textwidth]{285.png}
\caption{(285)}
\end{figure}

Girija et al.\textsuperscript{21} synthesized 1,3,3-triarylspiro[azetidine-2,3,1-indoline]-2,4-diones (286).

\begin{figure}
\centering
\includegraphics[width=0.4\textwidth]{286.png}
\caption{(286)}
\end{figure}

Desai et al.\textsuperscript{22} synthesized some new 2-oxo-azetidine derivatives (287) having antibacterial activity.

\begin{figure}
\centering
\includegraphics[width=0.4\textwidth]{287.png}
\caption{(287)}
\end{figure}
Girija et al.\textsuperscript{23} have reported the synthesis of novel spiroazetidinones (289).

Parekh et al.\textsuperscript{24} synthesized some 2-azetidinones (290) as potential antitubercular agents.

Srivastava et al.\textsuperscript{25} prepared some new pyrazolothiadiazoles and their azetidinones (291) and tested them for their antibacterial and antifungal activities.
Bansal et al.\textsuperscript{26} synthesized substituted azetidinylbenzidines (292) and evaluated them for anti-inflammatory activity.

\begin{center}
\includegraphics[width=0.5\textwidth]{292.png}
\end{center}

(292)

Shah et al.\textsuperscript{27} synthesized 2-azetidinones (293) and screened for their antimicrobial activity.

\begin{center}
\includegraphics[width=0.5\textwidth]{293.png}
\end{center}

(293)

Bari et al.\textsuperscript{28} reported the synthesis of azetidin-2-ones (294) possessing antimicrobial activity.

\begin{center}
\includegraphics[width=0.5\textwidth]{294.png}
\end{center}

(294)
Mogilaiah et al. synthesized 2-azetidinone derivatives (295) possessing antibacterial activity.

Srivastava et al. synthesized some new phenothiazinothiadiazoles and their azetidinones (296) exhibiting antifungal activity.

Hansa et al. synthesized azetidinones from hydrazine thieno[3,2-d]pyrimidines (297) and screened them for antimicrobial activity.
Sharma et al. synthesized 1-[4'-(5,6''-dimethoxypyrimidinosulphonamoyl)]phenylamino]-3-chloro-4,4-diphenylazetidin-2-one (298).

(298)

Sharma et al. synthesized N-sulphonamoylphenylamino-3-chloro-4-phenylazetidine-2-ones (299) exhibiting antibacterial activity.

(299)

Mazaahir et al. reported a microwave assisted synthesis of 2-azetidinones (300) possessing antifungal activity.

(300)
Shingare et al. synthesized some new azetidinones (301) having herbicidal activity.

\[
\text{(301)}
\]

Sandhu et al. reported an efficient one-pot synthesis of various 3-(N-aroylamino)-3-methyl-4-(4-oxobenzopyran-3-yl)-1-(N,N-dimethylamino)azetidin-2-ones (302).

\[
\text{(302)}
\]

Shah et al. prepared 2-azetidinone derivatives having thymol moiety (303) and evaluated them for antimicrobial and antitubercular activities.

\[
\text{(303)}
\]
Desai et al.\textsuperscript{38} synthesized 4-oxoazetidines (304) exhibiting antibacterial and tuberculostatic activities.

\begin{center}
\includegraphics[width=0.5\textwidth]{figure1.png}
\end{center}

(304)

Daniela et al.\textsuperscript{39} synthesized a new series of $N$-substituted -3-[1-alkyl (aryl)-4-piperidyl]azetidin-2-ones (305) as possible muscarinic agents.

\begin{center}
\includegraphics[width=0.2\textwidth]{figure2.png}
\end{center}

(305)

Hiskey et al.\textsuperscript{40} synthesized some new 3,3-dinitroazetidines (306) and screened them for antimicrobial activity.

\begin{center}
\includegraphics[width=0.25\textwidth]{figure3.png}
\end{center}

(306)
Nestor et al.\textsuperscript{41} synthesized and characterized a new 1-[1, 2, 3-triazol-1-yl]-4-aroylazetidin-2-one (307).

![Image of compound 307](image)

Hogale et al.\textsuperscript{42} synthesized azetidiones (308) and screened them for antibacterial and antifungal activities.

![Image of compound 308](image)

Shanker et al.\textsuperscript{43} prepared some new azetidinones (309) exhibiting antiparkinsonian activity.

![Image of compound 309](image)
**THIAZOLIDINONE**

Thiazolidinones are derivatives of thiazolidine with a carbonyl group at position 2, 4 and 5. The three possible combinations are as follows:

![Thiazolidinone structures](image)

4-Thiazolidinones were associated with wide range of industrial, pharmaceutical and biological applications\(^{44}\) and numerous reports have appeared in the literature, which highlighted their chemistry and use\(^{45-48}\).

**GENERAL METHODS OF SYNTHESIS**

Some 3-(quinazolin-4-one-3-yl acetamido)-2-aryl-1, 3-thiazolidin-4-ones were synthesized by cycloaddition of 3-benzylidine methyl hydrazidoquinazolin-4-ones with thioglycollic acid and these compounds exhibited promising antimicrobial activity\(^{49}\) (scheme 37).

![Scheme 37](image)

**SCHEME 37**

239
Gursoy et al.\textsuperscript{50} described the synthesis of 2-[4,5-bis(4-methoxyphenyl) imidazol-2-yl mercaptoacetyl]-hydrazone-3-alkyl/aryl-4-thiazolidinones by the cyclisation of thiosemicarbazides with ethyl \( \alpha \)-bromoacetate in the presence of anhydrous sodium acetate (Scheme 38).
Therapeutic Potential of Thiazolidinones

It was reported in the literature that different substituted thiazolidinones possess antimicrobial, anti-inflammatory, antitubecular, antihypertensive, hypnotic, and hypoglycemic activities.

Siddiqui et al. synthesized 2-(substituted phenyl)-3-[3(2-oxo-2H-chromen-3-yl)-5-thioxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]-1,3-thiazolidin-4-ones (310) and screened them for anticonvulsant activity.

\[
\begin{align*}
\text{(310)}
\end{align*}
\]

Desai et al. prepared 4-oxo-thiazolidines (311) having antibacterial activity.

\[
\begin{align*}
\text{(311)}
\end{align*}
\]
Rajanarendra et al.\textsuperscript{53} synthesized isoxazolylthiazolidinones (312).

\begin{center}
\includegraphics[width=0.3\textwidth]{312.png}
\end{center}

(312)

Bhusari et al.\textsuperscript{54} synthesized 4-thiazolidinones bearing benzothiophene nucleus (313) exhibiting antitubercular activity.

\begin{center}
\includegraphics[width=0.3\textwidth]{313.png}
\end{center}

(313)

Joshi et al.\textsuperscript{55} synthesized some new thiazolidinones (314) showing significant antimicrobial and antitubercular activities.

\begin{center}
\includegraphics[width=0.3\textwidth]{314.png}
\end{center}

(314)
Desai et al. synthesized 5-arylidene-4-oxothiazolidines (315) and evaluated them for antimicrobial activity.

![Chemical structure of 5-arylidene-4-oxothiazolidines (315)](image)

Vyas et al. synthesized quinoxaline based thiazolidinones (317) having antimicrobial activity.

![Chemical structure of quinoxaline based thiazolidinones (317)](image)

Pai et al. reported the synthesis of 2,4-thiazolidinediones (316) possessing antihyperglycemic activity.

![Chemical structure of 2,4-thiazolidinediones (316)](image)
Verma et al.\textsuperscript{59} synthesized some substituted thiazolidinonyl-1,3,4-thiadiazino $[6,5-b]$-indoles (318) that showed significant antimicrobial activity.

\begin{center}
\includegraphics[width=0.5\textwidth]{318.png}
\end{center}

Havaldar et al.\textsuperscript{60} prepared some thiazolidin-4-ones (319) exhibiting potential antimicrobial activity.

\begin{center}
\includegraphics[width=0.5\textwidth]{319.png}
\end{center}

Shah et al.\textsuperscript{61} synthesized some new 4-thiazolidinones having benzthiazole moiety (320) and screened them for antimicrobial activity.

\begin{center}
\includegraphics[width=0.5\textwidth]{320.png}
\end{center}
Desai et al.\textsuperscript{62} also synthesized some new 4-oxo-thiazolidines (321) and screened them for antibacterial activity.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {Ph\_245};
\end{tikzpicture}
\end{center}

(321)

Shah et al.\textsuperscript{63} synthesized 4-thiazolidinones (322) exhibiting their antimicrobial activity.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {OH};
\end{tikzpicture}
\end{center}

(322)

Parekh et al.\textsuperscript{64} synthesized thiazolidinones (323) that showed significant antimicrobial activity.
Therapeutically important drugs containing azetidinone moiety along with their structures are given below

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ACTIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin G (324)</td>
<td>Antibacterial agent</td>
</tr>
<tr>
<td>Oxacillin (325)</td>
<td>Antibacterial agent</td>
</tr>
<tr>
<td>Mecillinam (326)</td>
<td>Antibacterial agent</td>
</tr>
<tr>
<td>Theienamycin (327)</td>
<td>Antibacterial agent</td>
</tr>
</tbody>
</table>
Amoxcillin (328)  
Antibacterial agent

Cephalosporin (329)  
Antibacterial agent

Cefazoline (330)  
Antibacterial agent

Cephaloridine (331)  
Antibacterial agent
EXPERIMENTAL
PRESENT WORK

Aim and Objectives

✓ The foregoing discussion revealed the biological importance of various substituted azetidine-2-one and thiazolidinone derivatives. Recently various derivatives of azetidine-2-one and thiazolidinone synthesized have been shown to exhibit promising biological and pharmacological activities. Prompted by these observations, an attempt was made to synthesize compounds bearing benzofuranylazetidine-2-ones and benzofuranylthiazolidinones in a molecular framework and studied the effect of various substituents on biological activities.

✓ To synthesize and characterize some new hydrazines by the reaction 1-(5-bromo-1-benzofuran-2-yl)ethanonehydrazone with various aromatic aldehydes.

✓ To convert hydrazines into azetidinones and thiazolidinones by the reaction with chloroacetyl chloride and mercaptoacetic acid respectively.

✓ To characterize the synthesized compounds using spectral (IR, $^1$H NMR, Mass) methods and elemental analyses.

✓ To evaluate the newly synthesized compounds for anti-inflammatory, anti tubercular, antibacterial and antifungal activities.

✓ To identify the active compounds for further exploitation.
General Procedure

Synthesis of 2-substituted benzylidene-1-[1-(5-bromobenzofuran-2-yl)ethylidene] hydrazines (12a-g)

A solution of 1-(5-bromo-1-benzofuran-2-yl) ethanonehydrazone 3 (2.53 g, 0.01 mol) and substituted aromatic aldehydes (0.01 mol) in ethanol (30 mL) was refluxed for 30 min. The reaction mixture was cooled and the product separated was collected by filtration and crystallized from a suitable solvent. The purity of the compound was established by TLC using a mixture of hexane and ethyl acetate as a mobile phase.
Synthesis of 1-[(1-(5-bromo-1-benzofuran-2-yl) ethyldene) amino]-3-chloro-4-(substituted phenyl) azetidine-2-ones (13a-g)

A solution of Schiff's base 12a-g (0.01 mol), chloroacetyl chloride (0.01 mol) in dry benzene (30 mL) and a few drop of triethylamine was refluxed for 1 hr. The triethylamine hydrochloride obtained was filtered off, washed several times with benzene and the filtrate and washing were mixed and concentrated under reduced pressure. The residue obtained was filtered, dried and recrystallized from a suitable solvent. The purity of all compounds was established by TLC using a mixture of hexane and ethyl acetate as a mobile phase.

\[
\begin{align*}
\text{Br} & \quad \text{C} = \text{N} - \text{N} = \text{C} = \text{H} - \text{R} \\
\text{CH}_3 & \quad \text{ClCH}_2\text{COCl} / \text{Et}_3\text{N} \\
\text{dry benzene} & \\
\text{Br} & \quad \text{C} = \text{N} - \text{C} = \text{H} - \text{R} \\
\text{O} & \quad \text{Cl} \\
\text{N} & \\
\end{align*}
\]

\( R \)

a. \[ \text{C}_6\text{H}_5 \]

d. \[ \text{C}_6\text{H}_5\text{-Br} \]

g. \[ \text{C}_6\text{H}_5\text{-CHO} \]

b. \[ \text{C}_6\text{H}_5\text{-Cl} \]

e. \[ \text{C}_6\text{H}_5\text{-OCH}_3 \]

f. \[ \text{C}_6\text{H}_5\text{-N(CH}_3)_2 \]
Synthesis of 3-\{[1-(5-bromo-1-benzofuran-2-yl) ethylidine] amino\} 2-(substituted phenyl)-1, 3-thiazolidin-4-ones (14a-g)

A solution of Schiff’s base 12a-g (0.01mol), mercaptoaceticacid (0.01mol) in dimethylformamide (30mL) containing a pinch of anhydrous zinc chloride was refluxed for 8 hr. Then the reaction mixture was cooled and poured into ice cold water, the separated solid was filtered, washed with water and recrystallized with suitable solvent. The purity of all compounds was established by TLC using a mixture of hexane and ethyl acetate as a mobile phase.
EXPERIMENTAL

Synthesis of 4-methoxybenzaldehyde [1-(5-bromo-1-benzofuran-2-yl)ethylidene] hydrazone (12e).

A solution of 1-(5-bromo-1-benzofuran-2-yl) ethanone hydrazone 3 (2.53 g, 0.01 mol) and 4-methoxybenzaldehyde (1.36 g, 0.01 mol) in ethanol (30mL) was refluxed for 30 min and the product separated on cooling was collected by filtration and crystallized from ethanol. The purity of the compound was established by TLC using ethyl acetate and hexane mixture (20:80) as mobile phase.

Compound 12e analyzed for C\textsubscript{18}H\textsubscript{13}N\textsubscript{2}BrO\textsubscript{2}, m.p 269-271°C, well established by its molecular ion peak at m/z 371 and its isotopic peak at 373 in its mass spectrum (Fig 44).

The IR (cm\textsuperscript{-1}) spectrum (Fig 42) showed the characteristic absorption bands at 1575 (C=N), 1456 (C=C) and 752 (C-Br).

The \textsuperscript{1}H NMR (δ ppm) spectrum (Fig 43) of compound 12e exhibited a singlet at 2.4 and 3.9 due to three protons of methyl and methoxy groups respectively, a multiplet in the region between 7.1-7.8 for the eight protons of aromatic ring another singlet at 8.6 due to one proton of N=CH.

The results of elemental analysis were also in close agreement with those of the calculated values. Based on the above spectral data, the structure of the compound 12e was confirmed as 4-methoxybenzaldehyde [1-(5-bromo-1-benzofuran-2-yl) ethylidene] hydrazone.
Fig 42. IR Spectrum of 4-methoxybenzaldehyde [1-(5-bromo-1-benzofuran-2-yl)ethylidene]hydrazone (12e)
Fig 43. $^1$H NMR Spectrum of 4-methoxybenzaldehyde [1-(5-bromo-1-benzofuran-2-yl)ethylidene]hydrazone (12e)
Fig 44. Mass Spectrum of 4-methoxybenzaldehyde [1-(5-bromo-1-benzofuran-2-yl)ethylidene]hydrazone (12e)
Synthesis of 1-\{[1-(5-bromo-1-benzofuran-2-yl)ethyldene]amino\}-3-chloro-4-(4-methoxyphenyl)azetidin-2-one (13e).

A solution of 4-methoxybenzaldehyde[1-(5-bromo-1-benzofuran-2-yl)ethyldene] hydrazone 12e (3.71 g, 0.01 mol) and chloroacetyl chloride (1.12g, 0.01 mol) in dry benzene (30 ml), a few drop of triethylamine was refluxed for 1 hr. The triethylamine hydrochloride was filtered off, washed several times with benzene. The residue obtained was filtered, dried and recrystallized from ethanol. The purity of the compound was established by TLC using ethyl acetate and hexane mixture (30:70) as mobile phase.

Compound 13e analyzed for C_{20}H_{16}N_{2}C_{1}BrO_{3}, m.p 286-288°C, well established by its molecular ion peak at m/z 447 and its isotopic peak at 449 in its mass spectrum (Fig 47).

The IR (cm^{-1}) spectrum (Fig 45) exhibited characteristic intense bands at 1683 (C=O), 1612 (C=N), 1525, 1444 (C=C) and 800 (C-Br).

The ^1H NMR (δ ppm) spectrum (Fig 46) of compound 13e exhibited a singlet at δ 2.3 and 3.7 due to three protons of methyl and methoxy group respectively, a doublet at 6.1 due to one proton of CH-Cl of azetidinone and another doublet at 6.6 due to one proton of CH-R of azetidinone and a multiplet in between 7.2 –7.8 for the eight protons of aromatic ring.

The results of elemental analysis were also in close agreement with those of the calculated values. Based on the above spectral data, the structure of the compound 13e was confirmed as 1-\{[1-(5-bromo-1-benzofuran-2-yl) ethyldene] amino\}-3-chloro-4-(4-methoxyphenyl) azetidin-2-one.
Fig 45. IR Spectrum of 1-[[1-(5-bromo-1-benzofuran-2-yl)ethylidene]amino]-3-chloro-4-(4-methoxyphenyl)azetidin-2-one(13e)
Fig 46. $^1$H NMR Spectrum of 1-[[1-(5-bromo-1-benzofuran-2-yl)ethyldene]amino]-3-chloro-4-(4-methoxyphenyl)azetidin-2-one(13e)
The possible mass fragmentation pattern of 1-[[1-(5-bromo-1-benzofuran-2-yl) ethylidene] amino]-3-chloro-4-(4-methoxy phenyl) azetidin-2-one (13e)
Fig 47. Mass Spectrum of 1-[(5-bromo-1-benzofuran-2-yI)ethyIidene]amino}-3-chIoro-4-(4-methoxyphenyl)azetidin-2-one(13e)
Synthesis of 3-[[1-(5-bromo-1-benzofuran-2-yl)ethylidene]amino]-2-(4-methoxyphenyl)-1,3-thiazolidin-4-one (14e)

A solution of 4-methoxybenzaldehyde [1-(5-bromo-1-benzofuran-2-yl)ethylidene] hydrazone 12e (3.71 g, 0.01 mol), mercaptoacetic acid (0.92 g, 0.01 mol) in dimethylformamide (30 mL) containing a pinch of anhydrous zinc chloride was refluxed for 8 hr. Then the reaction mixture was cooled and poured into ice cold water the separated solid was filtered, washed with water and recrystallized from a suitable solvent. The purity of the compound was established by TLC using ethyl acetate and hexane mixture (30:70) as mobile phase.

Compound 14e analyzed for C_{20}H_{17}N_2BrO_3S, m.p 289-291°C, well established by its molecular ion peak at m/z 445 and its isotopic peak at 447 in its mass spectrum (Fig 50).

The IR (cm\(^{-1}\)) spectrum (Fig 48) showed the characteristic intense bands at 1643 (C=O), 1538, (C=N), 1438 (C=C) and 759 (C-Br).

The \(^1\)H NMR (\(\delta\) ppm) spectrum (Fig 49) of compound 14e exhibited a singlet at 2.3 due to three protons of methyl group, another singlet at 3.6 due to two protons of methylene of thiazolidinone, a singlet at 3.9 due to three protons of methoxy group and a multiplet in between 6.8-7.6 for the eight protons of aromatic ring.

The results of elemental analysis were also in close agreement with those of the calculated values. Based on the above spectral data, the structure of the compound 14e was confirmed as 3-[[1-(5-bromo-1-benzofuran-2-yl) ethylidene] amino]-2-(4-methoxyphenyl)-1, 3-thiazolidin-4-one.
Fig 49: 1H NMR Spectrum of 3-[(5-bromo-1-benzofuran-2-yl)ethylidene]amino]-2-(4-methoxyphenyl)-1,3-thiazolidin-4-one(14e)
The possible mass fragmentation pattern of 3-\{[1-(5-bromo-1-benzofuran-2-yl)ethylidene]amino\}-2-(4-methoxyphenyl)-1,3-thiazolidin-4-one (14e)
Fig 50. Mass Spectrum of 3-[(5-bromo-1-benzofuran-2-yl)ethylidene]amino]-2-(4-methoxyphenyl)-1,3-thiazolidin-4-one (14e)
By adopting the above synthetic procedures, compounds 12a, 12b, 12c, 12d, 
12f, 12g, 13a, 13b, 13c, 13d, 13f, 13g, 14a, 14b, 14c, 14d, 14f and 14g were also 
synthesized. All these compounds are new and the characteristic physical and spectral 
data were presented separately in the table form.

List of new synthesized compounds are

12a. 2-Benzylidene-[1-(5-bromo-1-benzofuran-2-yl)ethylidene]hydrazone
12b. 4-Chlorobenzaldehyde [1-(5-bromo-1-benzofuran-2-yl)ethylidene]hydrazone
12c. 4-Hydroxybenzaldehyde [1-(5-bromo-1-benzofuran-2-yl)ethylidene]hydrazone
12d. 4-Bromobenzaldehyde [1-(5-bromo-1-benzofuran-2-yl)ethylidene]hydrazone
12e. 4-Methoxybenzaldehyde [1-(5-bromo-1-benzofuran-2-yl)ethylidene]hydrazone
12f. 4-(Dimethylamino)benzaldehyde [1-(5-bromo-1-benzofuran-2-yl)ethylidene] 
        hydrazone
12g. 2-Furaldehyde [1-(5-bromo-1-benzofuran-2-yl)ethylidene]hydrazone
13a. 1-{{[1-(5-Bromo-1-benzofuran-2-yl)ethylidene]amino}-3-chloro-4- phenyl 
        azetidin-2-one
13b. 1-{{[1-(5-Bromo-1-benzofuran-2-yl)ethylidene]amino}-3-chloro-4-(4-chloro 
        phenyl)azetidin-2-one
13c. 1-{{[1-(5-Bromo-1-benzofuran-2-yl)ethylidene]amino}-3-chloro-4-(4-hydroxy 
        phenyl)azetidin-2-one
13d. 1-{{[1-(5-Bromo-1-benzofuran-2-yl)ethylidene]amino}-3-chloro-4-(4-bromo 
        phenyl)azetidin-2-one
13e. 1-{{[1-(5-Bromo-1-benzofuran-2-yl)ethylidene]amino}-3-chloro-4-(4-methoxy 
        phenyl)azetidin-2-one
13f. 1-{{[1-(5-Bromo-1-benzofuran-2-yl)ethylidene]amino}-3-chloro-4-[4-(dimethyl 
        amino)phenyl]azetidin-2-one
13g. 1-{{[1-(5-Bromo-1-benzofuran-2-yl)ethylidene]amino}-3-chloro-4-(2-furyl) 
        azetidin-2-one

255
14a. 3-\{[1-(5-Bromo-1-benzofuran-2-yl)ethylidene]amino\}-2-phenyl-1,3-thiazolidin-4-one
14b. 3-\{[1-(5-Bromo-1-benzofuran-2-yl)ethylidene]amino\}-2-(4-chlorophenyl)-1,3-thiazolidin-4-one
14c. 3-\{[1-(5-Bromo-1-benzofuran-2-yl)ethylidene]amino\}-2-(4-hydroxyphenyl)-1,3-thiazolidin-4-one
14d. 3-\{[1-(5-Bromo-1-benzofuran-2-yl)ethylidene]amino\}-2-(4-bromophenyl)-1,3-thiazolidin-4-one
14e. 3-\{[1-(5-Bromo-1-benzofuran-2-yl)ethylidene]amino\}-2-(4-methoxyphenyl)-1,3-thiazolidin-4-one
14f. 3-\{[1-(5-Bromo-1-benzofuran-2-yl)ethylidene]amino\}-2-[4-(dimethylamino)phenyl]-1,3-thiazolidin-4-one
14g. 3-\{[1-(5-Bromo-1-benzofuran-2-yl)ethylidene]amino\}-2-(2-furyl)-1,3-thiazolidin-4-one
<table>
<thead>
<tr>
<th>Comp. No</th>
<th>R</th>
<th>Molecular Formula</th>
<th>Relative Molecular Mass (RMM)</th>
<th>Melting Point (°C)</th>
<th>Yield (%)</th>
<th>Elemental Analysis Found (calculated) %</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>12a</td>
<td>-o</td>
<td>C_{17}H_{13}N_{2}BrO</td>
<td>341</td>
<td>258-260</td>
<td>70</td>
<td>59.85 (59.84) 3.83 (3.84) 8.20 (8.21)</td>
</tr>
<tr>
<td>12b</td>
<td>-Cl</td>
<td>C_{17}H_{12}N_{2}ClBrO</td>
<td>375</td>
<td>218-220</td>
<td>60</td>
<td>54.35 (54.32) 3.23 (3.22) 7.42 (7.46)</td>
</tr>
<tr>
<td>12c</td>
<td>-OH</td>
<td>C_{17}H_{13}N_{2}BrO$_2$</td>
<td>357</td>
<td>163-165</td>
<td>68</td>
<td>57.15 (57.16) 3.65 (3.67) 7.82 (7.84)</td>
</tr>
<tr>
<td>12d</td>
<td>-Br</td>
<td>C_{17}H_{12}N_{2}BrO$_2$</td>
<td>420</td>
<td>243-245</td>
<td>66</td>
<td>48.61 (48.60) 2.87 (2.88) 6.65 (6.67)</td>
</tr>
<tr>
<td>12e</td>
<td>-OCH$_3$</td>
<td>C_{18}H_{13}N_{2}BrO$_2$</td>
<td>371</td>
<td>269-271</td>
<td>56</td>
<td>58.23 (58.24) 4.05 (4.07) 7.53 (7.55)</td>
</tr>
<tr>
<td>12f</td>
<td>-N(CH$_3$_2)</td>
<td>C_{19}H_{18}N_{3}BrO</td>
<td>384</td>
<td>210-212</td>
<td>64</td>
<td>59.35 (59.39) 4.73 (4.72) 10.90 (10.94)</td>
</tr>
<tr>
<td>12g</td>
<td>-Q</td>
<td>C_{15}H_{11}N_{2}BrO$_2$</td>
<td>331</td>
<td>257-259</td>
<td>64</td>
<td>54.38 (54.40) 3.33 (3.35) 8.44 (8.46)</td>
</tr>
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Table 31

Physical and elemental analysis data of synthesized compounds (13a-g)

<table>
<thead>
<tr>
<th>Comp No</th>
<th>R</th>
<th>Molecular Formula</th>
<th>Relative Molecular Mass (RMM)</th>
<th>Melting Point (°C)</th>
<th>Yield (%)</th>
<th>Elemental Analysis Found (calculated) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>13a</td>
<td></td>
<td>C_{19}H_{14}N_{2}ClBrO_{2}</td>
<td>417</td>
<td>272-274</td>
<td>54</td>
<td>54.62 (54.64) 3.35 (3.38) 6.70 (6.71)</td>
</tr>
<tr>
<td>13b</td>
<td></td>
<td>C_{19}H_{13}N_{2}Cl_{2}BrO_{2}</td>
<td>452</td>
<td>252-254</td>
<td>58</td>
<td>50.46 (50.47) 2.90 (2.90) 6.22 (6.20)</td>
</tr>
<tr>
<td>13c</td>
<td></td>
<td>C_{19}H_{14}N_{2}ClBrO_{3}</td>
<td>433</td>
<td>142-144</td>
<td>64</td>
<td>54.61 (54.62) 3.35 (3.38) 6.70 (6.71)</td>
</tr>
<tr>
<td>13d</td>
<td></td>
<td>C_{19}H_{13}N_{2}ClBr_{2}O_{2}</td>
<td>496</td>
<td>267-269</td>
<td>54</td>
<td>45.95 (45.96) 2.65 (2.64) 5.63 (5.64)</td>
</tr>
<tr>
<td>13e</td>
<td></td>
<td>C_{20}H_{16}N_{2}ClBrO_{3}</td>
<td>447</td>
<td>286-288</td>
<td>69</td>
<td>53.64 (53.65) 3.60 (3.60) 6.25 (6.26)</td>
</tr>
<tr>
<td>13f</td>
<td></td>
<td>C_{21}H_{19}N_{3}ClBrO_{2}</td>
<td>460</td>
<td>180-182</td>
<td>68</td>
<td>54.73 (54.74) 4.15 (4.16) 9.10 (9.12)</td>
</tr>
<tr>
<td>13g</td>
<td></td>
<td>C_{17}H_{12}N_{2}ClBrO_{3}</td>
<td>407</td>
<td>243-245</td>
<td>74</td>
<td>50.07 (50.09) 2.96 (2.97) 6.86 (6.87)</td>
</tr>
</tbody>
</table>
Table 32

Physical and elemental analysis data of synthesized compounds (14a-g)

<table>
<thead>
<tr>
<th>Comp No</th>
<th>R</th>
<th>Molecular Formula</th>
<th>Relative Molecular Mass (RMM)</th>
<th>Melting Point (°C)</th>
<th>Yield (%)</th>
<th>Elemental Analysis Found (calculated) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>14a</td>
<td></td>
<td>C_{19}H_{15}N_{2}BrO_{2}S</td>
<td>415</td>
<td>274-276</td>
<td>70</td>
<td>C: 59.94 (59.95)  H: 3.64 (3.64)  N: 6.76 (6.75)</td>
</tr>
<tr>
<td>14b</td>
<td>-Cl</td>
<td>C_{19}H_{14}N_{2}ClBrO_{2}S</td>
<td>449</td>
<td>264-266</td>
<td>50</td>
<td>C: 50.74 (50.74)  H: 3.14 (3.14)  N: 6.22 (6.23)</td>
</tr>
<tr>
<td>14c</td>
<td>-OH</td>
<td>C_{19}H_{15}N_{2}BrO_{3}S</td>
<td>431</td>
<td>206-208</td>
<td>62</td>
<td>C: 52.90 (52.91)  H: 3.51 (3.51)  N: 6.50 (6.50)</td>
</tr>
<tr>
<td>14d</td>
<td>-Br</td>
<td>C_{19}H_{14}N_{2}Br_{2}O_{2}S</td>
<td>494</td>
<td>213-215</td>
<td>75</td>
<td>C: 46.17 (46.18)  H: 2.84 (2.86)  N: 5.66 (5.67)</td>
</tr>
<tr>
<td>14e</td>
<td>-OCH_{3}</td>
<td>C_{20}H_{17}N_{2}BrO_{3}S</td>
<td>445</td>
<td>289-291</td>
<td>67</td>
<td>C: 53.91 (53.90)  H: 3.84 (3.85)  N: 6.26 (6.29)</td>
</tr>
<tr>
<td>14f</td>
<td>-N(CH_{3})_{2}</td>
<td>C_{21}H_{20}N_{3}BrO_{2}S</td>
<td>458</td>
<td>243-245</td>
<td>63</td>
<td>C: 55.04 (55.03)  H: 4.40 (4.40)  N: 9.16 (9.17)</td>
</tr>
<tr>
<td>14g</td>
<td></td>
<td>C_{17}H_{13}N_{2}BrO_{3}S</td>
<td>405</td>
<td>208-210</td>
<td>59</td>
<td>C: 50.36 (50.38)  H: 3.24 (3.23)  N: 6.90 (6.91)</td>
</tr>
</tbody>
</table>
Table 33
IR, $^1$H NMR and Mass spectral data of 2-substituted benzylidene-1-[1-(5-bromo benzofuran-2-yl)ethylidene] hydrazines (12a-g)

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Comp No</th>
<th>R</th>
<th>IR (KBr disc) Position of absorption band (cm$^{-1}$)</th>
<th>$^1$H NMR Chemical shift $\delta$ (ppm)</th>
<th>Mass spectra (m/z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12a</td>
<td>[苯环]</td>
<td>1579 (C=N), 1460 (C=C), 754 (C-Br).</td>
<td>2.3 (3H, s, CH$_3$), 7.0 - 8.0 (9H, m, Ar-H), 8.6 (1H, s, N=CH).</td>
<td>341 [M]$^+$, 343 [M+2]$^+$</td>
</tr>
<tr>
<td>12b</td>
<td>-OCl</td>
<td>1569 (C=N), 1450 (C=C), 750 (C-Br).</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>12c</td>
<td>-OH</td>
<td>3665 (OH), 1569 (C=N), 1462 (C=C), 758 (C-Br).</td>
<td>2.3 (3H, s, CH$_3$), 7.0-8.0 (8H, m, Ar-H), 8.6 (1H, s, N=CH), 9.6 (1H, s, OH).</td>
<td>357 [M]$^+$, 359 [M+2]$^+$</td>
</tr>
<tr>
<td>12d</td>
<td>-Br</td>
<td>1559 (C=N), 1452 (C=C), 755 (C-Br).</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>12e</td>
<td>-OCH$_3$</td>
<td>1575 (C=N), 1456 (C=C), 752 (C-Br).</td>
<td>2.4 (3H, s, CH$_3$), 3.9 (3H, s, OCH$_3$), 7.0-8.0 (8H, m, Ar-H), 8.6 (1H, s, N=CH).</td>
<td>371 [M]$^+$, 373 [M+2]$^+$</td>
</tr>
<tr>
<td>12f</td>
<td>N(CH$_3$)$_2$</td>
<td>1570 (C=N), 1450 (C=C), 751 (C-Br).</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>12g</td>
<td>[furane]</td>
<td>1573 (C=N), 1455 (C=C), 752 (C-Br).</td>
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</tr>
</tbody>
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Table 34

IR, $^1$H NMR and Mass spectral data of 1-[(1-(5-bromo-1-benzofuran-2-yl) ethylidene) amino]-3-chloro-4-(substituted phenyl) azetidine-2-ones (13a-g)

<table>
<thead>
<tr>
<th>Comp No</th>
<th>R</th>
<th>IR (KBr disc) Position of absorption band (cm$^{-1}$)</th>
<th>$^1$H NMR Chemical shift $\delta$ (ppm)</th>
<th>Mass spectra (m/z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13a</td>
<td>- Ar</td>
<td>1652 (C=O), 1569 (C=N), 1438 (C=C), 790 (C-Br).</td>
<td>2.3 (3H, s, CH$_3$), 6.1 (1H, d, CH-Cl), 6.6 (1H, d, CH-R), 7.0 - 7.8 (9H, m, Ar-H).</td>
<td>417 [M]$^+$, 419 [M+2]$^+$</td>
</tr>
<tr>
<td>13b</td>
<td>- Ar-Cl</td>
<td>1650 (C=O), 1560 (C=N), 1440 (C=C), 780 (C-Br).</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>13c</td>
<td>- OH</td>
<td>3671 (OH), 1655 (C=O), 1570 (C=N), 1440 (C=C), 795 (C-Br).</td>
<td>2.3 (3H, s, CH$_3$), 6.1 (1H, d, CH-Cl), 6.6 (1H, d, CH-R), 7.0-8.0 (8H, m, Ar-H), 9.6 (1H, s, OH).</td>
<td>433 [M]$^+$, 435 [M+2]$^+$</td>
</tr>
<tr>
<td>13d</td>
<td>- Br</td>
<td>1653 (C=O), 1573 (C=N), 1443 (C=C), 793 (C-Br).</td>
<td>---</td>
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</tr>
<tr>
<td>13e</td>
<td>- OCH$_3$</td>
<td>1683 (C=O), 1612 (C=N), 1525 (C=C), 800 (C-Br).</td>
<td>2.3 (3H, s, CH$_3$), 3.7 (3H, s, OCH$_3$), 6.1 (1H, d, CH-Cl), 6.6 (1H, d, CH-R), 7.2-7.8 (8H, m, Ar-H).</td>
<td>447 [M]$^+$, 449 [M+2]$^+$</td>
</tr>
<tr>
<td>13f</td>
<td>- N(CH$_3$)$_2$</td>
<td>1620 (C=O), 1585 (C=N), 1460 (C=C), 800 (C-Br).</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>13g</td>
<td>- F</td>
<td>1635 (C=O), 1580 (C=N), 1450 (C=C), 800 (C-Br).</td>
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</tbody>
</table>
Table 35

IR, \(^1\)H NMR and Mass spectral data of 3-{[1-(5-bromo-1-benzofuran-2-yl) ethylidene] amino} 2-(substituted phenyl)-1, 3-thiazolidin-4-ones (14a-g)

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Comp No</th>
<th>R</th>
<th>IR (KBr disc) Position of absorption band (cm(^{-1}))</th>
<th>(^1)H NMR Chemical shift ((\delta) ppm)</th>
<th>Mass spectra (m/z)</th>
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<tbody>
<tr>
<td>14a</td>
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<td>1652 (C=O), 1568 (C=N), 1436 (C=C), 790 (C-Br)</td>
<td>2.3 (3H, s, CH(_3)), 3.7 (2H, s, CH(_2)), 6.8 - 7.5 (9H, m, Ar-H)</td>
<td>415 [M](^+), 417 [M+2](^+)</td>
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<td>14b</td>
<td>Cl</td>
<td>1658 (C=O), 1568 (C=N), 1448 (C=C), 790 (C-Br)</td>
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<tr>
<td>14c</td>
<td>OH</td>
<td>3700 (OH), 1659 (C=O), 1560 (C=N), 1448 (C=C), 800 (C-Br)</td>
<td>2.3 (3H, s, CH(_3)), 3.7 (2H, s, CH(_2)), 7.0-7.5 (8H, m, Ar-H), 9.7 (1H, s, OH)</td>
<td>431 [M](^+), 433 [M+2](^+)</td>
</tr>
<tr>
<td>14d</td>
<td>Br</td>
<td>1655 (C=O), 1555 (C=N), 1458 (C=C), 790 (C-Br)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>14e</td>
<td>OCH(_3)</td>
<td>1643 (C=O), 1538 (C=N), 1438 (C=C), 759 (C-Br)</td>
<td>2.3 (3H, s, CH(_3)), 3.6 (2H, s, CH(_2)), 3.9 (3H, s, OCH(_3)), 6.8-7.6 (8H, m, Ar-H)</td>
<td>445 [M](^+), 447 [M+2](^+)</td>
</tr>
<tr>
<td>14f</td>
<td>N(CH(_3))(_2)</td>
<td>1650 (C=O), 1570 (C=N), 1448 (C=C), 769 (C-Br)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>14g</td>
<td>F</td>
<td>1650 (C=O), 1556 (C=N), 1455 (C=C), 800 (C-Br)</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>
BIOLOGICAL EVALUATION
PRESENT WORK

A number of azetidinones and thiazolidinones were reported to possess diverse biological activities such as antimicrobial, anti-inflammatory, antituberculosis, anticonvulsant, muscarinic, herbicidal, antiparkinsonian, neurotoxicity and antihyperglycemic. In view of varied biological and pharmacological importance of different azetidinone and thiazolidinone derivatives, it was felt worthwhile to evaluate them for possible activities. These compounds therefore were screened for anti-inflammatory, antitubercular, antibacterial and antifungal activities.

EXPERIMENTAL METHODS

1. Acute toxicity: The same protocols and procedures that have been followed in Chapter-31 were used to study acute toxicity of azetidinones and thiazolidinones. All the azetidinones and thiazolidinones employed in the pharmacological screening have been found to be free from toxicity as well as toxic symptoms even at a high dose of 1000 mg/kg body weight and hence they were considered safe.

2. Anti-inflammatory activity: The same protocols and procedure that have been followed in Chapter-36 were used to study anti-inflammatory activity of synthesized compounds. The results are presented in Table 36 and Fig 51.

3. Antituberculosis activity: The same protocols and procedure that have been followed in Chapter-36 were used to study antituberculosis activity of synthesized compounds. The results are presented in Table 37.
4. **Antibacterial activity:** The same protocols and procedure that have been followed in Chapter-II were used to study antibacterial activity of synthesized compounds. The results are presented in **Table 38 and Fig 52.**

5. **Antifungal activity:** The same protocols and procedure that have been followed in Chapter-II were used to study antifungal activity of synthesized compounds. The results are presented in **Table 39 and Fig 53.**
Table 36

Anti-inflammatory activity of synthesized compounds (13a-g) and (14a-g)

<table>
<thead>
<tr>
<th>Comp No</th>
<th>R</th>
<th>Dose (mg/kg)</th>
<th>Mean value (±SE) of oedema volume at different intervals</th>
<th>Percentage of anti-inflammatory at different intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>2h</td>
<td>4h</td>
</tr>
<tr>
<td>Control (2% gum acacia)</td>
<td>--</td>
<td>--</td>
<td>0.254 (±0.009)</td>
<td>0.225 (±0.007)</td>
</tr>
<tr>
<td>Standard Aceclofenac</td>
<td>2</td>
<td>0.117 (±0.018)</td>
<td>0.032 (±0.003)</td>
<td>54.00</td>
</tr>
<tr>
<td>13a</td>
<td>C₆H₅</td>
<td>10</td>
<td>0.189 (±0.002)</td>
<td>0.135 (±0.003)</td>
</tr>
<tr>
<td>13b</td>
<td>C₆H₅Cl(p)</td>
<td>10</td>
<td>0.124 (±0.007)</td>
<td>0.047 (±0.006)</td>
</tr>
<tr>
<td>13c</td>
<td>C₆H₄OH(p)</td>
<td>10</td>
<td>0.157 (±0.003)</td>
<td>0.131 (±0.001)</td>
</tr>
<tr>
<td>13d</td>
<td>C₆H₄Br(p)</td>
<td>10</td>
<td>0.132 (±0.004)</td>
<td>0.053 (±0.004)</td>
</tr>
<tr>
<td>13e</td>
<td>C₆H₄OCH₃(p)</td>
<td>10</td>
<td>0.148 (±0.005)</td>
<td>0.088 (±0.001)</td>
</tr>
<tr>
<td>13f</td>
<td>C₆H₄N(CH₃)₂(p)</td>
<td>10</td>
<td>0.183 (±0.006)</td>
<td>0.147 (±0.005)</td>
</tr>
<tr>
<td>13g</td>
<td>C₄H₃O</td>
<td>10</td>
<td>0.197 (±0.001)</td>
<td>0.160 (±0.010)</td>
</tr>
<tr>
<td>14a</td>
<td>C₆H₅</td>
<td>10</td>
<td>0.191 (±0.003)</td>
<td>0.138 (±0.005)</td>
</tr>
<tr>
<td>14b</td>
<td>C₆H₄Cl(p)</td>
<td>10</td>
<td>0.127 (±0.010)</td>
<td>0.044 (±0.003)</td>
</tr>
<tr>
<td>14c</td>
<td>C₆H₄OH(p)</td>
<td>10</td>
<td>0.160 (±0.003)</td>
<td>0.139 (±0.002)</td>
</tr>
<tr>
<td>14d</td>
<td>C₆H₄Br(p)</td>
<td>10</td>
<td>0.136 (±0.011)</td>
<td>0.056 (±0.006)</td>
</tr>
<tr>
<td>14e</td>
<td>C₆H₄OCH₃(p)</td>
<td>10</td>
<td>0.145 (±0.007)</td>
<td>0.091 (±0.002)</td>
</tr>
<tr>
<td>14f</td>
<td>C₆H₄N(CH₃)₂(p)</td>
<td>10</td>
<td>0.179 (±0.005)</td>
<td>0.140 (±0.005)</td>
</tr>
<tr>
<td>14g</td>
<td>C₄H₃O</td>
<td>10</td>
<td>0.201 (±0.005)</td>
<td>0.169 (±0.005)</td>
</tr>
</tbody>
</table>
Fig 51. Anti-inflammatory activity of azetidinone and thiazolidinone derivatives (13a-g and 14a-g)
DISCUSSION ON THE RESULTS

The anti-inflammatory activity of azetidin-2-ones and thiazolidin-4-ones (13a-g and 14a-g) was evaluated by using carrageenan-induced rat paw edema method. Compounds (13a-g and 14a-g) showed significant activity when compared with standard drug aceclofenac. In particular, compounds 13b, 13d, 13e, 14b, 14d and 14e possessed maximum activity and this may be due to the presence of 4-chlorophenyl, 4-bromophenyl and 4-methoxyphenyl moieties at C-4 position of azetidinone and C-2 position of thiazolidinone respectively. All the other compounds also possessed moderate anti-inflammatory activity when compared with the standard drug.
Table 37
Antitubercular activity of synthesized compounds (13a-g) and (14a-g)

Minimum inhibitory concentration of H₃₇R₉

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Concentration (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25 µg/mL</td>
</tr>
<tr>
<td>Streptomycin (std)</td>
<td>S</td>
</tr>
<tr>
<td>13a</td>
<td>R</td>
</tr>
<tr>
<td>13b</td>
<td>S</td>
</tr>
<tr>
<td>13c</td>
<td>R</td>
</tr>
<tr>
<td>13d</td>
<td>S</td>
</tr>
<tr>
<td>13e</td>
<td>S</td>
</tr>
<tr>
<td>13f</td>
<td>R</td>
</tr>
<tr>
<td>13g</td>
<td>R</td>
</tr>
<tr>
<td>14a</td>
<td>R</td>
</tr>
<tr>
<td>14b</td>
<td>S</td>
</tr>
<tr>
<td>14c</td>
<td>R</td>
</tr>
<tr>
<td>14d</td>
<td>S</td>
</tr>
<tr>
<td>14e</td>
<td>R</td>
</tr>
<tr>
<td>14f</td>
<td>S</td>
</tr>
<tr>
<td>14g</td>
<td>R</td>
</tr>
</tbody>
</table>

R = Resistance     S = Sensitive
DISCUSSION ON THE RESULTS

The antitubercular activity of the azetidin-2-one and thiazolidin-4-one derivatives (13a-g and 14a-g) were determined against *Mycobacterium tuberculosis* H37Rv in the media middle brook 7H9 broth (MB 7H9 broth) by using streptomycin as standard drug.

The results of antitubercular activity revealed that the compounds 13b, 13d, 13e, 14b, 14d and 14e having 4-chlorophenyl, 4-bromophenyl and 4-methoxyphenyl moieties at C-4 position of azetidinone and C-2 position of thiazolidinone moiety respectively were found to possess high degree of activity at all the three dose levels tested, where as other compounds were active only at 50 µg/mL and 100 µg/mL dose level or only at 100 µg/mL dose levels.
<table>
<thead>
<tr>
<th>Comp No</th>
<th>R</th>
<th>Zone of inhibition (in mm)</th>
<th>Concentration of 100 μg/0.1mL.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>E.coli</td>
</tr>
<tr>
<td>13a</td>
<td>C₆H₅</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>13b</td>
<td>C₆H₄Cl(p)</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>13c</td>
<td>C₆H₄OH(p)</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>13d</td>
<td>C₆H₄Br(p)</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>13e</td>
<td>C₆H₄OCH₃(p)</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>13f</td>
<td>C₆H₄N(CH₃)₂(p)</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>13g</td>
<td>C₄H₃O</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>14a</td>
<td>C₆H₅</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>14b</td>
<td>C₆H₄Cl(p)</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>14c</td>
<td>C₆H₄OH(p)</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>14d</td>
<td>C₆H₄Br(p)</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>14e</td>
<td>C₆H₄OCH₃(p)</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>14f</td>
<td>C₆H₄N(CH₃)₂(p)</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>14g</td>
<td>C₄H₃O</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td><strong>Ciprofloxacin</strong> (Std)</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td></td>
<td><strong>Control (DMF)</strong></td>
<td></td>
<td>6</td>
</tr>
</tbody>
</table>
Fig 52. Antibacterial activity of azetidinone and thiazolidinone derivatives (13a-g and 14a-g)
DISCUSSION ON THE RESULTS

The entire azetidin-2-ones and thiazolidin-4-ones derivative (13a-g and 14a-g) have been evaluated for their antibacterial activity against *E.coli*, *P.aeruginosa* (Gram-negative) and *S.epidermatitis* and *B.subtilis* (Gram positive) using agar cup-plate method. The results of this evaluation were compared with ciprofloxacin as reference standard.

Compounds (13a-g and 14a-g) showed significant antibacterial activity at 100 µg concentration level when compared with standard drug. In particular, compounds 13b, 13d, 13e, 14b, 14d and 14e exhibited more antibacterial activity and this may be due to the presence of chlorophenyl, bromophenyl and methoxyphenyl moieties at C-4 position of azetidinone and C-2 position of thiazolidinone moiety respectively. All the other compounds also showed moderate to weak activity.
### Table 39
Antifungal activity of synthesized compounds (13a-g) and (14a-g)

<table>
<thead>
<tr>
<th>Comp No</th>
<th>R</th>
<th>Zone of inhibition (in mm)</th>
<th>Concentration of 100 μg/0.1mL.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aspergillus niger</td>
</tr>
<tr>
<td>13a</td>
<td>C₆H₅</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>13b</td>
<td>C₆H₅Cl(ₚ)</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>13c</td>
<td>C₆H₄OH(ₚ)</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>13d</td>
<td>C₆H₄Br(ₚ)</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>13e</td>
<td>C₆H₄OCH₃(ₚ)</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>13f</td>
<td>C₆H₄N(CH₃)₂(ₚ)</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>13g</td>
<td>C₄H₅O</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>14a</td>
<td>C₆H₅</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>14b</td>
<td>C₆H₄Cl(ₚ)</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>14c</td>
<td>C₆H₄OH(ₚ)</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>14d</td>
<td>C₆H₄Br(ₚ)</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>14e</td>
<td>C₆H₄OCH₃(ₚ)</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>14f</td>
<td>C₆H₄N(CH₃)₂(ₚ)</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>14g</td>
<td>C₄H₅O</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Fluconazole (Std)</td>
<td>22</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Control (DMF)</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>
Fig 53. Antifungal activity of azetidinone and thiazolidinone derivatives (13a-g and 14a-g)
DISCUSSION ON THE RESULTS

The antifungal activity of substituted azetidin-2-ones and thiazolidin-4-ones (13a-g and 14a-g) was evaluated against *A. niger* and *C. albicans* and fluconazole employed as reference standard to compare the results.

From the obtained results, it was clear that all the azetidin-2-ones and thiazolidin-4-ones derivatives tested showed considerable antifungal activity when compared with reference standard, fluconazole at 100 μg Concentration level. Compounds 13b, 13d, 13e, 14b, 14d and 14e exhibited well antifungal activity and this may be due to the presence of chlorophenyl, bromophenyl and methoxyphenyl moieties at C-4 position of azetidinone and C-2 position of thiazolidinone moiety respectively. All the other compounds also showed moderate to less activity.

FURTHER SCOPE

The results of biological activity studies on 5-bromo-2-acetylbenzofuran derivatives were promising and clearly indicated that the synthetic studies can be further extended by incorporating more number of such pharmacophores which displayed significant activities. Many more substituted pyrimidines and isoxazoles can be synthesized with a hope to get better analgesic and anti-inflammatory agents. Based on these studies, newer azetidinones and pyrazoles with different substituents can be synthesized to get potent antimicrobial agents. These studies also revealed that newer pyridines and thiazolidinones can be prepared with a hope to get promising antitubercular agents.
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