GENERAL INTRODUCTION
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Pyrazines are a group of aromatic compounds with 1, 4-nitrogen substitutions in the benzene ring. They occur naturally and are also anthropogenic. They are widespread in nature. Pyrazines play an important role as intermediates for perfumes, pharmaceuticals, agricultural chemicals and food spices. Especially, amides and sulfonamides of pyrazines have been used on various topics as anti-tuberculosis, dyes and pigments, oral anti diabetics, nutrition supplement, insecticides and fungicides.

Pyrazine and their derivatives form an important class of compounds present in several natural flavors and complex organic molecules, it is also responsible for flavour and nice aroma in foodstuffs, like cheese, tea coffee, cooked meats etc.

SYNTHETIC ASPECT

Various methods for the preparation of pyrazine derivatives have been cited in literature, some of them are as under.

1. Joule and Mill reported that self condensation of 2-aminoketone or 2-aminoaldehyde followed oxidation results into symmetrical pyrazines.

2. A. Padwa et al. reported that diphenylazirine upon irradiation undergoes rearrangement and yields 2,3,5,6-tetraphenylpyrazine.
3. A. Shaabani\textsuperscript{8} et al. have synthesized pyrazine derivatives by direct conversion of $\alpha$-hydroxy ketones and $\alpha$-keto oximes in the presence of a catalytic amount of ceric ammonium nitrate.

\[
\begin{align*}
\text{NC} & \quad \text{NH}_2 \\
\text{NC} & \quad \text{NH}_2 \\
\text{O} & \quad \text{H}_2\text{O}, \text{rt}, 45\text{min} \\
\text{RC} & \quad \text{CN}, \text{Air} \\
\end{align*}
\]

4. B. M. Latha\textsuperscript{9} et al. have synthesized pyrazine from ethylenediamine followed by oxidation with copper oxide/copper chromite catalysts.

\[
\frac{2}{\text{NH}_2} \rightarrow \frac{\text{H}_2\text{N}}{\text{NH}_2} \rightarrow \frac{\text{N}}{-2\text{NH}_3} \rightarrow \frac{\text{N}}{-3\text{H}_2}
\]

5. T. Utsukihara\textsuperscript{10} et al. have reported Microwave-assisted synthesis of pyrazine derivatives from $\alpha$-halo ketone in 7% NH\textsubscript{3} solution.

\[
\begin{align*}
\text{R}_1 \quad \text{O} & \quad \text{7\% aq. NH}_3 \\
\text{R}_2 \quad \text{X} & \quad \text{Microwave} \\
& \quad \text{R}_1 \quad \text{N} \quad \text{R}_2 \\
& \quad \text{R}_1 \quad \text{N} \quad \text{R}_1 \\
\end{align*}
\]

6. R. Anand\textsuperscript{11} et al. have synthesized 2-methyl pyrazine from zinc-modified ferrierite (FER) catalysts.

\[
\begin{align*}
\text{NH}_2 & \quad \text{H}_2\text{N} \\
\text{NH}_2 & \quad \text{HO} \\
\text{HO} & \quad \text{Intra molecular cyclization} \\
\text{H} & \quad \text{dehydrogenation} \\
\text{ZnO-FER} & \quad \text{ZnO-FER}
\end{align*}
\]

7. W. T. Reichle\textsuperscript{12} et al. have given the synthesis which involve the reaction of diketones with appropriate diamines, which gave the diazine which readily oxidized to the pyrazines.

\[
\begin{align*}
\text{O} & \quad \text{H}_2\text{N} \\
\text{O} & \quad \text{H}_2\text{N} \\
\text{-2H}_2\text{O} & \quad \text{-H}_2 \\
\end{align*}
\]
THERAPEUTIC IMPORTANCE

Over the years there has been an increasing interest in the chemistry of pyrazines because of their biological significance. Pyrazines are known to show a wide range of therapeutic importance.

Table 1: List of marketed drugs having pyrazine nucleus along with its biological activity.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Structure and name</th>
<th>Therapeutic importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Aspergillic Acid</td>
<td>Bactericidal</td>
</tr>
<tr>
<td>2</td>
<td>Pyrazinamide</td>
<td>Antitubercular agent</td>
</tr>
<tr>
<td>3</td>
<td>Oltipraz</td>
<td>Anti-HIV agent</td>
</tr>
<tr>
<td>4</td>
<td>2-(allylthio) pyrazine</td>
<td>Chempreventive agent</td>
</tr>
<tr>
<td>5</td>
<td>Kefizine (2-p-aminobenzenesulfonamido-3-methoxypyrazine)</td>
<td>Antimalerial</td>
</tr>
</tbody>
</table>

Aspergillic Acid

Pyrazinamide

Oltipraz

2-(allylthio) pyrazine

Kefizine (2-p-aminobenzenesulfonamido-3-methoxypyrazine)
<table>
<thead>
<tr>
<th></th>
<th><img src="image" alt="Chemical Structure" /></th>
<th><strong>Description</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Amiloride hydrochloride</td>
<td>Potassium sparing diuretic</td>
</tr>
<tr>
<td>7</td>
<td>Thionazine</td>
<td>Nimaticide</td>
</tr>
<tr>
<td>8</td>
<td>Ligustrazine</td>
<td>Pulmonary heart disease</td>
</tr>
<tr>
<td>9</td>
<td>Emimycin (pyrine-2-4-oxide)</td>
<td>Growth Inhibitor</td>
</tr>
<tr>
<td>10</td>
<td>Glipizide(N(4[N(cyclohexylcarbamoyl)sulfooxyl]phenethyl)-5-methylpyrazine-2-carboxamide)\</td>
<td>Anti-diabetic drug</td>
</tr>
<tr>
<td>11</td>
<td>Bortezomib</td>
<td>Treating people with multiple myeloma</td>
</tr>
</tbody>
</table>
1. J. W. Corbett\textsuperscript{13} et al. have synthesized pyrazine derivatives and reported corticotrophin releasing factor type-1 receptor antagonists.

\begin{center}
\begin{tikzpicture}
  \node[draw, rectangle] (A) at (0,0) {\includegraphics[width=0.3\textwidth]{pyrazine.png}};
\end{tikzpicture}
\end{center}

2. N. Sinha\textsuperscript{14} et al. have synthesized and evaluated antimycobacterial activity of some pyrazine derivatives.

\begin{center}
\begin{tikzpicture}
  \node[draw, rectangle] (A) at (0,0) {\includegraphics[width=0.5\textwidth]{pyrazine2.png}};
\end{tikzpicture}
\end{center}

3. A. Olczak\textsuperscript{15} et al. have reported pyrazin-2-yl-formamide thiosemicarbazones as tuberculostatic agents.

\begin{center}
\begin{tikzpicture}
  \node[draw, rectangle] (A) at (0,0) {\includegraphics[width=0.3\textwidth]{pyrazine3.png}};
\end{tikzpicture}
\end{center}

4. G. G. Dubinina\textsuperscript{16} et al. have synthesized and reported new molecules 5,7-disubstituted 6-amino-5H-pyrrolo[3,2-b]pyrazine-2,3-dicarbonitriles as promising protein kinase inhibitors with antiproliferative activity.

\begin{center}
\begin{tikzpicture}
  \node[draw, rectangle] (A) at (0,0) {\includegraphics[width=0.3\textwidth]{pyrazine4.png}};
\end{tikzpicture}
\end{center}
5. H. Foksi\textsuperscript{17} et al. reported synthesis and tuberculostatic activity of pyrazinyl substituted derivatives.

\[
\begin{align*}
\text{R} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{S} & \quad \text{R'}
\end{align*}
\]

6. J. Bostrom\textsuperscript{18} et al. have designed, synthesized and studied structure activity relationships of 5,6-diaryl-pyrazine-2-amide derivatives and reported them as CB1 receptor antagonists.

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

7. C. G. Bonde and coworkers\textsuperscript{19} have synthesized and evaluated some pyrazine derivatives as antimicrobial agents.

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

Synthesis and biological evaluation of pyrido[2,3-\textit{b}]pyrazine-\textit{N}-oxide as selective glycine antagonists was reported by A. Cugola\textsuperscript{20} et al. J. E. Dowling\textsuperscript{21} et al. have synthesized of [1,2,4]triazolo[1,5-\textit{a}]pyrazines as adenosine A\textsubscript{2A} receptor antagonists. C. A. Hargreaves\textsuperscript{22} and coworkers have studied tetrahydropyrido[2,3-\textit{b}]pyrazine scaffolds. Synthesis and antimycobacterial activity of pyrazine derivatives documented by L. E. Seitz\textsuperscript{23} et al. Imidazo[1,2-\textit{a}]pyrazine shows the bronchodilatory and cyclic nucleotide phosphodiesterase inhibitory activities was given by T. O. Vitse\textsuperscript{24} et al.

Thus the important role displayed by pyrazine and its derivatives for various therapeutic and biological activities prompted us to synthesize some pyrazine derivatives in order to achieve compounds having better therapeutic activities, which summarized as under.

**PART-A:** STUDIES ON PYRAZINE 2-CARBOXYLIC ACID DERIVATIVES

**PART-B:** STUDIES ON IMIDAZO [1,2-a]PYRAZINES
REFERENCES


AIMS AND OBJECTIVES

Taking in view the applicability of heterocyclic compounds, we have undertaken the preparation of heterocycles bearing pyrazine nucleus.

During the course of our research work, looking to the application of heterocyclic compounds, several entities have been designed, generated and characterized using spectral studies. The details are as under.

- To do literature survey on the biological activities and synthesis of pyrazine based heterocyclic compounds.
- To study the pharmacological importance of pyrazine ring and previous synthetic approaches.
- To synthesize several bioactive derivatives of pyrazine 2-carboxydrazides, its derivatives and imidazo[1,2-a] derivatives
- To study importance of triazole, Schiff bases, triazolothiadiazoles, oxadiazole, thioacetamides and hydrazones in medicinal chemistry and report the synthesis, characterization and evaluation of biological activities
- To develop an efficient, simple, straight forward and green protocol for the synthesis of triazolo[3,4-b][1,3,4]thiadiazines and imidazo[1,2-a]pyrazines.
- To grow single crystal of the synthesized compounds and study there X-ray crystallography for establishment of the structure.
- To study Thermal parameters of some N-(substitutedphenyl)-2-((5-(pyrazin-2-yl)-1,3,4-oxadiazol-2-yl)thio) acetamides.
- To study UV-Vis/NIR analysis of some ((E)-4-substituted benzylideneamino)-5-(pyrazin-2-yl)-4h-1,2,4-triazole-3-thiols.
- To monitor the reaction and check purity of all synthesized compounds using thin layer chromatography. To characterize these synthesized products for structure elucidation using various spectroscopic techniques like IR, 'H and 'C NMR and mass spectral studies.
- To evaluate these new synthesized products for better drug potential against *Mycobacterium tuberculosis H_{37}Ra* and against different strains of bacteria and fungi.
Overview of synthesized compounds
MATERIALS AND METHODS

All chemicals and solvents were purchased of LR/AR grade and were used without further purification. Melting points were taken in open capillary method and are uncorrected. Thin-layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 F254 (Merck). Visualization was made with UV light (254 and 365nm) or with an iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS prob. $^1$H (400 MHz), $^{13}$C (100 MHz) NMR spectra were recorded on a Bruker AVANCE II spectrometer in CDCl$_3$ and DMSO-d$_6$. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). Solvents were evaporated with rotary evaporator.