2.1 Mannich bases

From the early work of Carl Mannich, the synthesis of mannich bases mainly used in creating pharmacological active products like amino acids, phthalimides by direct amino methylation reaction. In the mid seventies, aryl amines were sporadically used and they are made to react with substrates containing an active hydrogen atom like heterocyclic compounds, phenols.

The researchers in China have produced a large number of arylamine mannich bases by employing arylaminomethylation of acetophenones through their addition to a Schiff’s bases formed in situ.

Mannich bases and their derivatives have many attractive applications, in paint and polymer chemistry as hardeners, cross linkers, reaction accelerations [157-158] etc. However, the most important applications are in the field of pharmaceutical products [159-160]. Studies on anti-neoplastic drugs, analgesic drug, antibiotic drugs etc [161-162], including labeled molecules [163-164] have received particular attention in the recent past. Mannich bases can either directly be employed or used as intermediates in chemicals synthesis. Literature survey reveals that mannich bases possess a broad spectrum of biological activities [165-166].

A review of recent literature concerning the synthesis and biological activity of various Mannich bases is furnished below.

Various 3-bromo-4-methyl-8-(substituted amino methyl) umbelliferone 2,3 and 4 have been synthesized by the Mannich reaction of 3-bromo-4-methylumbelliferone 1 with various primary/secondary amines. Thee compounds have been tested for their antibacterial-activity.
Mannich condensation on 3-sulfadiazinylisation 5 in the presence of formaldehyde and secondary amines furnished 3-aminomethyl analogs 6 which were evaluated as antimicrobial agents.
Pandeya et al [167] have reported the synthesis and anti-HIV activity of Mannich bases of isatin 8.
Lingaiah et al [168] have reported the synthesis and anti-inflammatory activity of some 1-aminomethyl-3-benzoylhydrazono-2-indolinones 10.

$$\begin{align*}
\text{Ethanol/CH}_3\text{COOH} \\
\text{HCHO, DMF, piperidine, morpholine, N-methylpiperazine}
\end{align*}$$
Gahane et al [169] have described the synthesis and anticonvulsant activity of Mannich reaction products of 3-aryldene-2-phenylimino-4-thiazolidinones 12.

![Mannich reaction](image)

Rajasekaran et al [170] have reported the synthesis and anti-inflammatory activity of 1,3-disubstituted indolinones 14.

![Indolinones](image)

The Mannich reaction of 3-(substituted)-4-(1-phenyl-3-methyl-5-chloro-4-pyrazolidine)amino-5-mercapto-1,2,4-triazoles 15 with formaldehyde and appropriate amines results in the formation of 1-aminomethyl-3-(substituted)-4-(1-phenyl-3-methyl-5-chloro-4-pyrazolidine)amino-1,2,4-triazole-5-thiones. These compounds have been tested for their antifungal and antibacterial activities [171].
Renukadevi and Biradar [172] have reported the synthesis and antimicrobial activity of 1-substituted aminomethyl-3-(5-substituted-3-phenylindol-2-yl-carbohydrazide)-2-indolinones 18.
Some important biologically active manich bases reported in the literature were shown in the following Table: 2.1.0.

Table: 2.1.0. Biologically potent Mannich base derivatives

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Compound</th>
<th>Activity</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image 1" /></td>
<td>Antitubercular</td>
<td>Dharmarajan et al [173]</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Image 2" /></td>
<td>Analgesic</td>
<td>R.Jayakumar et al [174]</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Image 3" /></td>
<td>Antifungal and anti-HIV</td>
<td>Sridharet al.[175]</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Image 4" /></td>
<td>Against like fungi</td>
<td>Erodonga et al [176]</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Image 5" /></td>
<td>Antimalarial</td>
<td>Shouhaiet al [177]</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6.png" alt="Image 6" /></td>
<td>Anti-inflammatory And Ucerogenic</td>
<td>Kumaret al [178]</td>
</tr>
</tbody>
</table>
Prompted by the above observations, a research project was undertaken to synthesize a series of Mannich derivatives carrying pyrazole-5-one with isatine derivatives. Mannich bases bearing organo phosphorous pyrazole 5-one moiety were found to possess antimicrobial, anti-inflammatory, antitubercular, cytotoxic, antibacterial, insecticidal, antifungal, analgesic activities.

2.2. 1,3,4-Oxadiazoles

1,3,4-Oxadiazole is a thermally stable and neutral hetero aromatic molecule. 1,3,4-Oxadiazoles have a wide variety of uses, particularly as biologically active compounds in medicine, agriculture, as dye stuffs, UV absorbing and fluorescent materials, heat resistant polymers and scintillators.

A review of literature concerning the synthesis and biological activity of 1,3,4-oxadiazoles is given below.

Substituted 1,3,4-oxadiazoles are of considerable pharmaceutical material interest, which is documented by a steadily increasing number of research publications and patents. For instance 2-amino-1,3,4-oxadiazole acts as muscle relaxant and shows antimitotic activity. Analgesic, anti inflammatory, anticonvulsive, diuretic and antiemetic properties are exhibited by 5-aryl-2-hydroxymethyl-1,3,4-oxadiazole derivatives. 2-hydroxyphenyl-1,3,4-oxadiazole acts as a hypnotic and sedative drug. Some material applications of 1,3,4-oxadiazoles are in the area of photosensitizers, liquid crystals and organic light emitting diodes.

Several derivatives of 5-substituted- 1,3,4-oxadiazoles 1 [X = SH, R = 2/3-CH₃C₆H₄] Synthesized by Kuharia and co workers were reported to posses hypoglycemic activity and found to be less toxic than the corresponding hydrazides.
Srivastava et al.[179], reported that 2-substituted-1,3,4-oxadiazoles and their derivatives 2 are active as antifungal and antiviral agents. All the tested compounds showed virucidal activity against plant virus SRV to the extent of 4.48% in vivo at 1 µg/mL.

Symmetrical 2,5-disubstituted-1,3,4-oxadiazoles 3 synthesized by Sharma and co-workers were screened for CNS depressant and anticonvulsant activities.

A German patent [180] described the synthesis of imino oxadiazole carboxylate 4 [R = C₆H₅, R₁ = C₂H₅] which acts as a drug and an agrochemical.

Nigam et al.,[181] reported the synthesis of some 3-(substituted aminomethyl)- 5-(3,5-dinitrophenyl)- 1,3,4-oxadiazol-2-thiones 5 [R₁ = CH₂NR₁R₂; NR₁R₂ = N-methylanilino, N-ethylanilino, morpholino, piperidino, N-phenylpiperazino]. These
compounds were screened for their cardiovascular and anti-inflammatory activity. The compounds were found to be non-toxic and psychotropic in nature.

Lee et al., [182] reported the synthesis of 1,3,4-oxadiazole derivatives 6 having phenol or thiophenol group. Treatment of a suspension of salicylic acid hydrazide in toluene with acetic anhydride or an acid chloride in the presence of an equimolar amount of methanesulphonic acid at room temperature, and then heating to reflux gave 1,3,4-oxadiazoles in 43-68% yield.

Yadav et al.,[183] synthesized a series of 2,7-diaryl-6-benzamido-6,7-dihydro-5H-1,3,4-oxadiazolo[3,2-a]-pyrimidin-5-ones 7 in an one pot reaction and compared their fungi toxicity with a commercial sample. Dithane M-45 against H. oryzae and C. Saccharii by agar plate method. Few of the tested compounds showed fungi toxic action almost equivalency to that of Dithane M-45 at 1000ppm concentration.
Yadava et al.,[184] reported the synthesis and biological activity of 2-aryl-5-(α-methyl-4-isobutylbenzyl)-1,3,4-oxadiazoles 8. These compounds exhibited significant antimicrobial and anti-inflammatory activities.

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{CH}_3 \\
\text{H} & \quad \text{N} \\
\text{C}_\text{H}_3 & \quad \text{H}_3\text{C} \\
\text{N} & \quad \text{O} \quad \text{R} \\
\text{CH}_3 & \quad \text{O} \\
\end{align*}
\]

2-5-disubstituted-1,3,4-oxadiazoles 9 prepared by Zhang and Qian [185] were tested for their fungicidal and insecticidal activities.

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

Synthesis, antimicrobial activity and heterocyclic ring transformation of 5-(pyrazol-5-yl)-1,3,4-oxadiazol-2(3H)-thiones 10 were reported by Shawali and co-workers [186].

\[
\begin{align*}
\text{N} & \quad \text{R}_1 \\
\text{N} & \quad \text{C} \quad \text{NH} \\
\text{O} & \quad \text{S} \\
\end{align*}
\]

Synthesis and antibacterial activities of 2-(1-aryl-5-methyl-1,2,3-triazol-4-yl)-1,3,4-oxadiazole derivatives 11 were reported by Zhang et al.,[187]. Most of the compounds were active against E.coli, P. aeruginosa, B. subtilis and S. aureus.
Dutta and Kataky [188] synthesized benzoic derivatives and diethylthiophosphonates of alkyl/aryl/aralkylaminomethyl-5-(2,4-dichlorophenyl)-1,3,4-oxadiazol-2-thiones 12 \( R = \text{CH}_2\text{NHR}_1, \text{CH}_2\text{N} (R_1^1) \text{COPh}, \text{CH}_2\text{N} (R_1^1) (\text{PS}) (\text{OEt})_2 \) with a view to get more potent insecticidal and bactericidal compounds.

![Image of molecule 12]

Synthesis and pharmacological properties of some new derivatives of 2-amino-5-(2-amino-3-pyridyl)-1,3,4-oxadiazole 13 were reported by Liszkiewicz and co-workers[189].

![Image of molecule 13]

3-Arylaminomethyl-5-(2,4-dichlorophenyl)-1,3,4-oxadiazole-2-thiones 14 \( R = \text{H}, \text{C}_6\text{H}_5, 2-\text{ClC}_6\text{H}_4, 3-\text{ClC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 2-\text{COOC}_6\text{H}_4, 2-\text{NO}_2\text{C}_6\text{H}_4, 3-\text{NO}_2\text{C}_6\text{H}_4, 4-\text{NO}_2\text{C}_6\text{H}_4, 2-\text{CH}_3\text{C}_6\text{H}_4, 4-\text{CH}_3\text{C}_6\text{H}_4, 4-\text{COOHC}_6\text{H}_4, 2-\text{OCH}_3\text{C}_6\text{H}_4, 4-\text{OCH}_3\text{C}_6\text{H}_4, -\text{CH}_2\text{C}_6\text{H}_5, N-(\text{CH}_2)_2\text{CH}_3 \) and 3-alkyl aryl alkyl-5-(2,4-dichlorophenyl)-1,3,4-oxadiazole-2-thiones 15 \( R_1^1 = -\text{CH}_3, -\text{CH}_2\text{CH}_3, n-(\text{CH}_2)_3\text{CH}_3, -\text{CH}_2\text{C}_6\text{H}_5, - \)
CH$_{2}$C$_{6}$H$_{5}$OCH$_{3}$(4), -CH$_{2}$COOEt] were synthesized by Goswami et al.[190]. These substituted oxadiazolethiones were screened for their fungitoxic properties. Most of the compounds showed toxicity against two test organisms, Curvularia verruciformis and Alternaria tenuis. The degree of inhibition ranged from 38-100% for a few compounds.

A novel series of 2-substituted amino-5-aryl-1,3,4-oxadiazole 16 [R = H, Br, R$_1$ =C$_6$H$_5$, m-CH$_3$C$_6$H$_4$, p-OCH$_3$C$_6$H$_4$, p-ClC$_6$H$_4$, p-BrC$_6$H$_4$, CH$_2$C$_6$H$_5$, CH$_2$CH$_2$-BrC$_6$H$_4$, CH$_2$C$_6$H$_5$, CH$_2$CH$_2$CH$_2$CH$_3$, C$_6$H$_{11}$] derivatives were synthesized for their potential anticonvulsant activity by Omar and Aboul Wafa[191].

Synthesis of 5-substituted-1,3,4-oxadiazole-2-(5-substituted-2-furfuraldehyde) hydrazones 17 [R = 2,4-dichlorophenyl, 4-chlorophenyl, 4-nitrophenyl, nitro; Ar = p-chlorophenoxyethyl, o-chlorophenoxyethyl β-napthyloxymethyl, p-cresyloxymethyl] was reported from our laboratory [192]. These compounds were screened for their biological activity against both Gram-positive and Gram-negative bacteria.
Synthesis of 2-arylsulfonamido-5-\(p\)-(3’,4’,5’-trimethoxy benzamido phenyl)-1,3,4-oxadiazoles 18 and 2-substituted benzamido-5-\(p\)-(3’,4’,5’-trimethoxy benzamido phenyl)-1,3,4-oxadiazoles 19 was reported by Joshi et al.,[193]. The compounds have been tested for their antimicrobial and antifungal activities.

Synthesis, anticonvulsant and antimicrobial activity of 2,5-disubstituted-1,3,4-oxadiazoles 20 and 2-amino-5-substituted-1,3,4-oxadiazoles 21, 22 and 23 was studied by Khan and co-workers [194].
Some important biologically potent 1,3,4-oxadiazole derivatives reported in the literature were shown in the following Table: 2.2.0.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Compound</th>
<th>Activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Compound 1" /></td>
<td>Antibacterial</td>
<td>Lokanatha Rai and Lingann [195]</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Compound 2" /></td>
<td>Antimicrobial</td>
<td>Gadaginamath and Pujar [196]</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Compound 3" /></td>
<td>Anti-inflammatory</td>
<td>Virginija Jakubkiene [197]</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Compound 4" /></td>
<td>Anti-inflammatory and antibacterial</td>
<td>Khan and co-worked [198]</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Compound 5" /></td>
<td>Anti-inflammatory</td>
<td>Milda Malvina Burbuliene et al [199]</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Compound 6" /></td>
<td>Antimicrobial and anti-inflammatory</td>
<td>Ravindra [200]</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7" alt="Compound 7" /></td>
<td>Anti mycobacterial</td>
<td>Mohamed Ashraf Ali et al [201]</td>
</tr>
</tbody>
</table>
2.3. 1,3,4–Thiadiazoles

1,3,4-Thiadiazole(1) was first described in 1882 by Fischer and further developed by Bush and his coworkers, but true nature of the ring system was demonstrated first in 1956 by Goerdler et al.

The chemistry of heterocyclic compounds has been an interesting field of study for a longtime. Heterocyclic nucleus 1, 3, 4-thiadiazole constitutes an important class of compounds for new drug development. The synthesis of novel thiadiazole derivatives and investigation of their chemical and biological behavior has gained more importance in recent decades.

1,3,4-Thiadiazoles represent one of the most biologically active classes of compounds, possessing a wide spectrum of activities. Thiadiazoles have become very important compounds in medicine, agriculture, and many fields of technology. A large number of 1,3,4-thiadiazoles have been patented in the agricultural field as herbicides and bactericides.
During the recent years, there has been intense investigation of different classes of thiadiazole compounds, many of which possess extensive pharmacological activities. Among of these compounds having 1,3,4-thiadiazole nucleus are known to exhibit unique antimicrobial activity. Antifungal, antidiabetic, anti-inflammatory, antileishmanial activity, antituberculosis activity, anticancer activity, anti-HIV activity, antioxidant /radio protective Activity, Carbonic anhydrase inhibitors. Anti-Helicobacter pylori activity. This paper focuses on the therapeutic importance of novel thiadiazole derivatives as anticonvulsant agents for future.

Some of the biological potent 1,3,4-thiadiazole derivatives reported in the literature were shown in the following Table: 2.3.0.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Compound</th>
<th>Activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td>Anticonvulsant</td>
<td>M.S.Yar, et al.,[206]</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Image" /></td>
<td>Anticonvulsan</td>
<td>B.Ahamad et al.,[207]</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Image" /></td>
<td>Antibacterial and Antifungal</td>
<td>Prasad DJ, et al.,[208]</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Image" /></td>
<td>Antibacterial</td>
<td>Pintilie O, et al.,[209]</td>
</tr>
<tr>
<td>No.</td>
<td>Chemical Structure</td>
<td>Activity</td>
<td>Reference</td>
</tr>
<tr>
<td>-----</td>
<td>-------------------</td>
<td>----------</td>
<td>-----------</td>
</tr>
<tr>
<td>5</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>Cytotoxic</td>
<td>Ahmedmal, et al., [210]</td>
</tr>
<tr>
<td>6</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>Anticonvulsant</td>
<td>V. Jatav, et al., [211]</td>
</tr>
<tr>
<td>7</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>Anticonvulsant</td>
<td>A. Varvaesou, et al., [212]</td>
</tr>
<tr>
<td>8</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>Antibacterial</td>
<td>Mirzaei J, et al., [213]</td>
</tr>
<tr>
<td>9</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>Anti-cancer agent</td>
<td>Angie R, et al., [214]</td>
</tr>
<tr>
<td>10</td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>Antibacterial and Antifungal</td>
<td>Karabasanag ouda T, A, et al., [215]</td>
</tr>
</tbody>
</table>
2.4. 1,2,4-Triazoles

Triazole is one of the classes of organic heterocyclic compounds containing a five member disubstituted ring structure composed of three nitrogen atoms at non adjacent positions. The synthesis of 1,2,4-triazole derivatives has attracted wide spread attention due to their diverse biological activities including antibacterial, anti-inflammatory, analgesic and antitumoral.

The Chemistry of heterocyclic compounds continues to be an explorable field in organic chemistry. The importance of [1, 2, 4] triazole derivatives lies in the field that these have occupied an unique position in heterocyclic chemistry due to their antimicrobial activit.

1,2,4-triazole can do exist in a tautomeric equilibrium between 1a and 1b.in which the hydrogen is transferred from the hydrazine to amine nitrogen.

\[ \begin{align*}
1a & \quad \overset{\text{HN}}{\text{N}} \quad \overset{\text{N}}{\text{N}} \quad \overset{\text{N}}{\text{N}} \\
1b & \quad \overset{\text{N}}{\text{N}} \quad \overset{\text{HN}}{\text{N}} \quad \overset{\text{N}}{\text{N}}
\end{align*} \]

1,2,4-triazole has also been called s-triazole to distinguish it from the isomeric 1,2,3-triazole termed √-triazole. Theoretical studies favor the 1H-structure 1a for triazole rather than the more symmetrical 4H-structure 1b. 1,2,4-triazole effectively contains two pyridine type atoms and one pyrrole type nitrogen atom. It is deactivated against electrophilic attack and thus resembles pyridine. Nitration, sulfonation and N-oxide do not occur with simple triazoles. Triazole anions however do react readily with electrophiles and the reactivity of the ring towards nucleophiles is increased in triazolium cations and mesomeric derivatives.

Triazoles are weakly basic like pyridine but more acidic than Imidazole

\[ \begin{align*}
1a & \quad \overset{\text{HN}}{\text{N}} \quad \overset{\text{N}}{\text{N}} \quad \overset{\text{N}}{\text{N}} \\
1b & \quad \overset{\text{N}}{\text{N}} \quad \overset{\text{HN}}{\text{N}} \quad \overset{\text{N}}{\text{N}}
\end{align*} \]

[1,2,4] Triazole

\[ \begin{align*}
2a & \quad \overset{\text{N}}{\text{N}} \quad \overset{\text{N}}{\text{N}} \\
2b & \quad \overset{\text{H}}{\text{N}} \quad \overset{\text{N}}{\text{N}}
\end{align*} \]

[1,2,3] Triazole
Triazoles are the most potent groups of growth retardants with multiple effects; these are commercially important for example (triadimefon) [1-(4-chloro phenoxy)-3,3-dimethyl-1-1-(1,2,4-triazol-1-yl)-2-butanol] is highly active systemic fungicide used against several economically important disease and named “bayleton”. Some triazoles like paclobutazole are active inhibiting extension growth.

The design and synthesis of fused 1,2,4-triazoles and their derivatives have attracted much attention due to their wide microbiological and pharmacological action, a brief account of the synthesis and biological significance of 1,2,4-triazoles and their derivatives reported in the literature presented below.


Mirjana Jankulovska, Ilinka Spirevska1, Katica _olan_eska-Rag_enovik reported [217] the behaviour of some newly synthesized substituted 1,2,4-triazoline-3-thiones in sulfuric acid media

The structure formulas of compounds are:

\[
\begin{align*}
&\text{CONNHNH}_{2} &\xrightarrow{\text{KOH,CS}_{2}} &\text{NH}_{3} &\xrightarrow{\text{ClCH}_{2}CONR}_{1}R_{2} &\xrightarrow{\text{SCH}_{2}CONR}_{1}R_{2} \\
&\text{CONH}& &\text{S} & &
\end{align*}
\]

(i) \( \text{C}_{6}\text{H}_{17} \)

(ii) \( \text{CH}_{2} \)

(iii) \( \text{C}_{6}\text{H}_{5} \)

Ali Almasirada, Nasim Vousooghib, Sayyed Abbas Tabatabaic, Abbas Kebriaeezadehd and Abbas Shafieee reported [218] the Synthesis, Anticonvulsant
and Muscle Relaxant Activities of Substituted 1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole

Soonsung Hong, Naotaka Yamada, Akiko Harada, Shinya Kawai and Eiichi Kuwano reported [219] the inhibition of trans-cinnamate-4-hydroxylase by 4-amino-5-aryl-2,3-dihydo-3H-1,2,4-triazole-3-thiones

Olga D. Cretu, Stefania F. Barbuceanu, Gabriel Saramet and Constantin Draghici reported [220] the Synthesis and characterization of some 1,2,4-triazole-3-thiones obtained from intramolecular cyclization of new 1-(4-(4-X-phenylsulfonyl) benzoyl)-4-(4-iodophenyl)-3-thiosemicarbazides
Jumat Salimon, Nadia Salih, Ayad Hameed, Hiba Ibraheem, Emad Yousif reported [221] the Synthesis of 1-acyl-2-alkylthio-1,2,4-triazolobenzimidazoles with antifungal, anti-inflammatory and analgesic effects

Monika Wujec, Monika Pitucha, Maria Dobosz1, Urszula Kosikowska, Anna Malm Reported [222] the Synthesis and potential antimycotic activity of 4-substituted-3-(thiophene-2-yl-methyl)-2--1,2,4-triazoline-5-thiones.
Xin Zhi Li, Zong Xing Si Reported [223] the Synthesis and Biological Activities of 3-(2-Furyl)-4-aryl-1,2,4-triazole-5-thiones.


Xiao-Xia Ye, Zhen-Fei Chen, An-Jiang Zhang and Li-Xue Zhang, reported [225] the Synthesis and Biological Evaluation of Some Novel Schiff’s Bases from 1,2,4-Triazole

P. Valentina, K. Ilango, M. Deepthi, P. Harusha, G. Pavani, K. Laxmi Sindhura and CH. Guru Keerthanan Reported [226] the Antioxidant Activity of Some Substituted 1,2,4 - Triazo-5-thione Schiff base.
S. Shawali, M. A. Abdallah, I. M. Abbas and G. M. Eid reported [227] the New Regioselective Synthesis and Biological Activity of Substituted 1H-\[1,2,4\]Triazolo[3,4-c][1,2,4]triazoles

Sevğ Karakuş1, Ufuk Çoruh, Bilgehan Barlas-Durgun, Ezequiel M. Vázquez-López,Suna Özbüş-Turan1, Jülide Akbuğa1, Sevim Rollas1 reported [228] the Synthesis and cytotoxic activity of some 1,2,4-triazoline-3-thione and 2,5-disubstituted- 1,3,4-thiadiazole derivatives.

Suvarna G. Kini, Anilchandra R. Bhat , Byron Bryant , John S. Williamson , Franck E. Dayan reported [229] the Synthesis, antitubercular activity and docking study of novel cyclic azole substituted diphenyl ether derivatives
2.5 Pirimidines

Pirimidines are one of two biologically important families of nitrogen-containing molecules called nitrogenous bases. (Purines are the other family of nitrogenous bases) Pirimidines can be identified by their structure: six atoms in the shape of a ring. This ring is known as a pyrimidine ring. The pyrimidine ring is a heterocyclic compound, which means it contains atoms from at least two different elements. A homocyclic compound, on the other hand, contains atoms from only one element.

Pyrimidine is the most important member of all the diazine (six-membered heterocyclics with two nitrogen atoms in the ring), it has the nitrogen atoms at positions 1 and 3 in the ring. Pyrimidine was first isolated by Gabriel and Colman in 1899. The chemistry of pyrimidine and its derivatives have been studied since the past century due to their diverse pharmacological properties. Pyrimidine (3) and Purine (4) are two nitrogens containing heterocyclic aromatic compounds are the parents of the “bases” that constitute a key structural unit of nucleic acids, even though pyrimidine itself does not exist in nature. Both pyrimidine and purine are planar and this flat shape is very important when we consider the structure of nucleic acids.

In terms of their chemistry, pyrimidine and purine resemble pyridine. They are weak bases and relatively unreactive towards electrophilic aromatic substitution. There is an important structural difference between pyrimidine derivatives that bear -OH groups and those with -NH₂ groups. The structure of a pyrimidine that bears an amino group follows directly from the structure of the parent ring system as seen in the case of cytosine. Equilibrium exists in the aminopyrimidines between the amino (5) and imino forms (6).
However, the corresponding pyrimidine having a hydroxyl group (7) resemble an enol, but exist instead in its keto form (8), contrary to the stable isomers with the hydroxyl groups on benzene like rings. This is because the keto form of the pyrimidine is also aromatic and stable owing to amide resonance as shown in below.

Resonance in keto form of 4-hydroxypyrimidine

Pyrimidine and its derivatives have gained importance because of their potential pharmaceutical values. Many pyrimidine derivatives play vital role in many physiological actions and biological actions.

Pyrimidines are present among the three isomeric diazines. Several (mainly uracil, thymine and cytosine) pyrimidines have been isolated from the nucleic acid hydrolys. The nucleic acids are essential constituents of all cells and thus, of all living matter cytosine is found in both types of nucleic acids i.e. ribonucleic acid (RNA) and deoxyribonucleic acid (DNA), while uracil present only in RNA and thymine only in DNA. The structure of cytosine (9), uracil (10) and thymine (11) are shown below.

In addition to this, pyrimidines are also found in vitamin B₁, barbituric acid (2,4,6-tri hydroxy pyrimidine) and their several derivatives e.g. (veranal), which is
used as hypnotics. The structure of barbituric acid (12) and veranal (13) are shown here.

![Structures of 12 and 13](image)

**Synthesis of Pyrimidines and its derivatives**

**Dialdehydes**

Sodium nitromalondialdehyde and 2, 4-diaminopyrimidin-6 (1H)-one yielded 2-amino-6-nitropyrido [2,3-d]pyrimidin-4 (3H)-one when heated under reflux with aqueous alkali. An interesting variation of this procedure relies upon the formation of malondialdehyde precursors in situ [230]. Vinylogs of Vilsmeier-Haack intermediates (15), formed from dimethylamino acroleins (14) and phosgene, undergo reaction with 2, 4, 6-triaminopyrimidine to yield 6-alkyl and 6-aryl substituted 2, 4-diaminopyrido [2, 3-d]pyrimidines (14). Dimethylaminoacroleins were found to be unsatisfactory [231].

![Reaction Scheme](image)

**Keto-aldehydes**

2, 4-diaminopyrimidine-6(1H)-one and 2-methyl-3-oxopentanal gave 2-amino-7-ethyl-6-methylpyrido[2, 3-d]pyrimidin-4-(3H)-one (15) as the only isolated product [213] which resulted from reaction of the aldehyde function with the 5-position of the pyrimidinering [232].

![Reaction Scheme](image)
**Ethoxymethylene compounds**

Ethoxymethyleneacetoacetates and ethoxymethyleneacetylacetones [233] have been used to prepare pyrido [2, 3-d] pyrimidines containing 6-ethoxycarbonyl or 6-acetyl substituents. For example, the substituted uracil and ethyl Ethoxymethyleneacetoacetate yielded the pyrido [2, 3-d] pyrimidine (16).

![Chemical structure of pyrimidine](image)

**Diketones**

4-Aminopyrimidines also react readily with 1, 3-diketones to yield various 5, 6, and 7 substituted pyrido [2, 3-d] pyrimidines. Acetyl acetone and 6-aminouracil, for example, yielded 5, 7-dimethylpyrido [2,3-d] pyrimidine-2, 4(1H, 3H)-dione (17) when heated together in phosphoric acid.

![Chemical structure of diketone reaction](image)

With unsymmetrical diketones the orientation of the reaction is again controlled by the reaction of the most reactive carbonyl group with the 5- position of the pyrimidine ring [234].

**β-Keto esters**

β-Keto esters have proved useful for the preparation of pyrido[2,3-d]pyrimidin-7(8H)-ones bearing alkyl and aryl substituents in the 5 and 6 positions. Again the reaction proceeds so that the most reactive carbonyl group (the ketone) attacks the 5- position of the pyrimidine ring. Thus, ethyl α-benzoylpropionate and 2,4, 6-triaminopyrimidine, in diphenyl ether, yield 2, 4-diamino-S-phenyl-6-methylpyrido [2,3-d]pyrimidin-7(8H)-one (18) [235]
Malonates

The reaction of malonic acid derivatives and 4-aminopyrimidines is useful for the synthesis of 6-substituted-5-hydroxypyrido [2, 3-d] pyrimidin-7(8H)-ones. Thus, methyl malonic acid and 6-amino-1,3-dimethyluracil, with acetic anhydride as catalyst, yielded the pyrido [2,3-d]pyrimidine (19)[236].

On perusal of literature survey, a comprised and a bridged list of potential biological active pirimidines and its derivatives were shown in the Table 2.5.0.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Compound</th>
<th>Activity</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td>Antibacterial and Anti fungal</td>
<td>Jayaveera et al., [237]</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Image" /></td>
<td>Antiproliferative activity</td>
<td>Rômulo F. et al., [238]</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Image" /></td>
<td>Antimicrotubular</td>
<td>Battastini O. et al., [239]</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Activity</td>
<td>Reference</td>
</tr>
<tr>
<td>-----</td>
<td>-----------</td>
<td>-------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>4</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>Cytotoxicity</td>
<td>Andressa Bernardi et al., [240]</td>
</tr>
<tr>
<td>5</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>Inhibition of KDR</td>
<td>Nikola Stiasni et al., [241]</td>
</tr>
<tr>
<td>6</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>Antifungal effect</td>
<td>Ignacio Regla et al., [242]</td>
</tr>
<tr>
<td>7</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>Antitumor potency</td>
<td>Mayur B. Buddh et al., [243]</td>
</tr>
</tbody>
</table>
2.6 Sulfonamides

Sulfonamides are organosulfur compounds and these are amide derivatives of sulfonic acid. These compounds contain RSO₂N< group. The general structures of sulfonamides are

![Sulfonamide structure]

Sulfonilamide was first identified by Domagk et al. in 1935 as the active metabolite of the red azo dye known as Prontosil 1. Prontosil does not possess any activity in vitro; however, it metabolizes in vivo to give the active agent sulfanilamide 2, which participates in the process of bacterial DNA synthesis and act as potent antibacterial agent. [244]

![Prontosil metabolism]

Thereafter, sulfonamides are used for efficient treatment of bacterial infections. They created a revolution in chemotherapy which helped to design rationally new therapeutic agents for over fifteen years. The sulfonamides were first used as antibacterial and antibiotic agents and now their applications have been extended to treat other diseases. Apart from the commercialized applications as antibacterial and antibiotic agents, various sulfonamides are known to inhibit several enzymes such as carbonic anhydrase, cysteine protease, HIV protease and cyclooxygenase [245]. Moreover, the potential value of sulfonamides led researchers
to the discovery of other drugs useful in the cure of impotence agent Viagra [246], hypoglyceamia[247], urinary diseases[248], and cancer[249]. These have been used against most gram-positive and many gram-negative organisms. Sulfonamides are drugs of choice in acute, uncomplicated urinary tract infections, especially in patients who are allergic to or cannot tolerate penicillin. Topical sulfonamides are employed in the cure of infections relating to eye, mucous membrane and skin. [250] In addition to these, a large number of structurally novel sulfonamide derivatives have been reported to function as anti-tumor agents and to possess remarkable antiviral activity such as anti-HIV.[251]

**Synthesis of sulfonamides:**

A wide variety of methods have been reported for the synthesis of sulfonamides.[252] The most common method involves the preparation of sulfonyl chloride which is usually obtained by sulfonation process.[253] The sulfonyl chloride thus obtained is made to react with amine to produce sulfonamides.

**Preparation of sulfonyl chloride:**

1. **Sulfonation using compounds of sulfur trioxide [254]**

   The addition of excess of chlorosulfonic acid to an organic compound at 0-30°C produces sulfonyl chloride.

   $\text{RH} + \text{CISO}_3\text{H} \rightarrow \text{RSO}_2\text{OH} + \text{HCl}$

   $\text{RSO}_2\text{OH} + \text{CISO}_3\text{H} \leftrightarrow \text{RSO}_2\text{Cl} + \text{H}_2\text{SO}_4$

2. **Sulfonation using compounds of sulfur dioxide [254]**

   (i) Alkenes form unsaturated sulfonic acids derivatives on reaction with sulfuryl chloride or chlorosulfate ester.
(ii) Conversion of alkylhalides to sulfonylhalides using Grignard reagent has been proved useful for synthesis of sulfonyl halides. Recent work, however, has shown that aromatic Grignard reagents in proper solvent mixture (THF + n-hexane) function satisfactorily in terms of yields.

\[
RMgCl + SO_2Cl_2 \rightarrow RSO_2Cl + MgCl_2
\]

3. Sulfonation by oxidative process [254]

In this method, sulfonyl chlorides, bromides or iodides are prepared from primary, secondary or tertiary alkylhalides. This method is best known for the preparation of tertiary alkane-sulfonyl halide.

\[
\begin{align*}
R-X & \xrightarrow{1. Mg} R-SO_2MgX \\
& \xrightarrow{2. SO_2} X_2 \rightarrow R-SO_2X
\end{align*}
\]

\(X = Cl, Br, I\)

Aluminium trialkyls on treatment with sulfur dioxide produces sulfinate salts which on further chlorination give alkyl-1-sulfonylchloride in excellent yield.

\[
R_3Al \xrightarrow{SO_2} (R-SO_2)_3Al \xrightarrow{Cl_2} 3R-SO_2Cl + AlCl_3
\]

4. Oxidative chlorination of thiols

Alkyl/aryl thiols on treatment with aq.chlorine in presence of hydrochloric acid or acetic acid produce aliphatic/aromatic sulfonyl chlorides.

\[
R-SH \xrightarrow{Cl_2 (aq)} R-SO_2Cl
\]
5. Direct Chlorosulfonation of 2-acyloothiophenes [255]

Thenoyl trifluoroacetone on reaction with chlorosulfonic acid produces 3- and 2- chlorosulfonated thenoyl trifluoroacetone isomers in 33% yield.

![Chemical Reaction]

Preparation of sulfonamides from sulfonylhalides

1. The sulfonyl halides have traditionally been converted to their corresponding sulfonamides by treatment with solid ammonium carbonate/conc. ammonia solution or with an appropriate amine. [256]

\[
\text{RSO}_2\text{Cl} + (\text{NH}_4)_2\text{CO}_3 \rightarrow \text{RSO}_2\text{NH}_2 + \text{HCl}
\]

\[
\text{RSO}_2\text{Cl} + \text{NH}_2\text{R} \rightarrow \text{RSO}_2\text{NHR} + \text{HCl}
\]

\[
\text{RSO}_2\text{Cl} + \text{NHRR}^* \rightarrow \text{RSO}_2\text{NR}^* + \text{HCl}
\]

2. Sulfonamides are synthesized from sulfonyl chloride on reaction with toluene in presence of AlCl₃. [257]

![Chemical Reaction]

3. Kataoka et al. [258] reported that arene and alkansulfonamides prepared by the treatment of the corresponding sodium sulfonates with triphenylphosphine dibromide followed by amines in presence of triethylamine and various sulfonylhalides by simple stirring.
4. C. Berthelette [259] developed a two step method for the synthesis of aliphatic and aromatic sulfonamides from the corresponding sulfinates using bis(2,2,2-trichloroethyl)-azodicarboxylate as the dichlorophilic nitrogen source. The intermediate hydrazides were cleaved under reductive conditions to the desired sulfonamides.

\[
\text{R}_1\text{SO}_3\text{Na} \xrightarrow{\text{CH}_3\text{CN}} \text{Ph}_3\text{PBr}_2 \xrightarrow{[\text{R}_1\text{SO}_2\text{Br}]} \xrightarrow{\text{HNR}_2\text{R}_3} \text{Et}_3\text{N}, 0^\circ\text{C, r.t., 30 Min-1h} \xrightarrow{\text{R}_{1}\text{SO}_2\text{NR}_2\text{R}_3}
\]

The solid sulfonamide moiety was introduced by reductive amination of a ketone in solid phase, followed by sulfonylation of the resulting amine.

5. Kunz et al. [260] described the copper catalyzed synthesis of aryl sulfonamides under microwave irradiation in very short time period (2-4h) using K₂CO₃ at 195°C.

6. El-Gaby et al. and Katritzky et al. [261] reported one step synthesis of sulfonamides bearing heterocyclic moiety from above two methods.
Sulfonamides from sulenanamides

Greenbaum et al. synthesized 6-uracilsulfonamide 3 (an antagonist of orotic acid) by effective oxidation of 6-uracil sulfenamide 4 using KMnO₄ with 64% yield. [262]

Schwam et al. [263] used similar methodology for the synthesis of 6-hydroxybenzothiazole-2-sulfonamide 5 from 2-(2-amino-6-(aminothio)-9H-purin-9-yl)-5-(hydroxymethyl) tetrahydrofuran-3,4-diol 6 as a potential carbonic anhydrase inhibitor in 80% yield.

In majority cases sulfonamide group has the same influence on the rest of the organic molecules, as an atom of oxygen in similar compounds. That means the chemical properties of non N-substituted sulfonamides similar to the properties of water; N-acylated sulfonamides derivatives have similar properties to the corresponding organic acids, N-alkilated to the properties of alcohols etc. Based on this idea Dr. Dubina V. discovered quite simple practical process of preparation of very active sulphonylimidoyl halides (sulfonamide derivatives) by interaction of sulfonamides with benzotrichloride. This reaction can be considered as analogous to reaction of partial hydrolysis of benzotrichloride to benzoyl chloride.
Sulfonamides represent an important class of medicinally important compounds which are extensively used as antitumor, hypoglycaemic, anti-thyroid, anti-carbonic anhydrase, anti-inflammatory, diuretic, COX-inhibitors, the enzyme dihydropteroate synthetase (DHPS) - the key enzyme involved in folate synthesis, anti-impotence drugs and also have been used as azo dyes for achieving improved light stability, water solubility and fixation to fiber. Sulfonamide-based compounds were extensively used for antibacterial agents and are the second antimicrobial agents. These derivatives still widely used today for the treatment of various bacterial, protozoal and fungal infections and the first effective chemotherapeutic agent used in safe therapeutic dosage ranges.

Literature survey revealed that sulphonamide shave many other activities like insulin releasing, carbonic anhydrase inhibitory, anti-inflammatory and anti-tumor activity Benzene sulfonamides have also been reported to use as aldose reductase inhibitors (ARIs), potent human pregnane X-receptor (Hpxr) agonists and anti-prostate cancer agents urinary tract infections.

Some important biologically active Sulfonamides reported in the literature were shown in the following Table: 2.6.0.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Compound</th>
<th>Activity</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Compound 1" /></td>
<td>Anti bacterial and Anti fungal</td>
<td>C. Naga Raju et al., [264]</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Compound 2" /></td>
<td>Anti malerial</td>
<td>Aastha Pareek et al.,[265]</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Compound 3" /></td>
<td>Anti bacterial</td>
<td>O’Shea, et al., [266]</td>
</tr>
<tr>
<td></td>
<td>Chemical Structure</td>
<td>Pharmacological Activity</td>
<td>Reference</td>
</tr>
<tr>
<td>---</td>
<td>--------------------</td>
<td>--------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>4</td>
<td><img src="image1" alt="Chemical Structure 1" /></td>
<td>Antimicrobial</td>
<td>Argyropoulou et al., [267]</td>
</tr>
<tr>
<td>5</td>
<td><img src="image2" alt="Chemical Structure 2" /></td>
<td>COX-2 inhibitor</td>
<td>de Leval et al., [268]</td>
</tr>
<tr>
<td>6</td>
<td><img src="image3" alt="Chemical Structure 3" /></td>
<td>Anti-inflammatory</td>
<td>Swingle, et al., [269]</td>
</tr>
<tr>
<td>7</td>
<td><img src="image4" alt="Chemical Structure 4" /></td>
<td>Pyrazole-based Inhibitor</td>
<td>Penning, T.D., et al., [270]</td>
</tr>
<tr>
<td>8</td>
<td><img src="image5" alt="Chemical Structure 5" /></td>
<td>Antimicrobial</td>
<td>Joshi, et al., [271]</td>
</tr>
<tr>
<td>9</td>
<td><img src="image6" alt="Chemical Structure 6" /></td>
<td>Anti-diabetic</td>
<td>Panchal, et al., [272]</td>
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<tr>
<td>10</td>
<td><img src="image7" alt="Chemical Structure 7" /></td>
<td>Antimicrobial</td>
<td>Argyropoulou, et al., [273]</td>
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</tbody>
</table>