CHAPTER 2

LITERATURE REVIEW

2.1. Benzothiazoles
2.2. Benzamides
2.3. Triazines
2.4. Semicarbazones
2.5. Azetidinones
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2.1. BENZOTHIAZOLES
2.1.1: Introduction

The small and simple benzothiazole nucleus is present in compounds involved in research aimed at evaluating new products that possess interesting biological activities, such as antitumor, antimicrobial, anthelmintic, antileishmanial, anticonvulsant and antiinflammatory.

Benzene fused heterocyclic compounds containing one sulphur and one nitrogen atom separated by a carbon atom are called benzothiazole (1).

\[
\begin{align*}
\text{(1)} \\
\end{align*}
\]

The heterocyclic system exhibit aromatic characters and shares comparable chemical, physical and biological properties of quinoline isosteres. It is sparingly soluble in water but easily soluble in CS\(_2\).

Sulphur atom exhibit characteristics of both -S-, =S=, later sulphur atom has an expanded outer shell. Resonance of this type of the benzene ring of the benzothiazole implies electrophilic substitution at position 4 and 6.

\[
\begin{align*}
\text{2-amino derivative of benzothiazole has an interesting tautomerism.} \\
C_6H_4N=\text{C-NH}_2 \rightleftharpoons C_6H_4N(H)\rightleftharpoons \text{C-NH}
\end{align*}
\]
2.1.2: Synthesis

The development of new methods for the synthesis of heterocyclic compounds represents an expanding area of organic chemistry. The benzimidazole, benzoxazole and benzothiazole structural motifs are found in numerous pharmaceutical agents with wide range of biological properties. Although a wide range of methods are available for synthesis of the heterocyclic compounds, a real need exists for new simple procedures that support many kinds of structural diversity and various substitution patterns in the target. Benzothiazole is a privileged bicyclic ring system due to their potent antitumor activity and other important pharmaceutical utilities, the synthesis of these compounds is of considerable interests.

Saczewski et al. reported the reaction of o-amidinylhydroxylamine 1 with aryl isothiocyanates leading to the formation of benzothiazole derivatives 3a-c. (Fig 1)

Various methods of synthesis of benzothiazoles are known, among these is the Jacobson synthesis, oxidative cyclization of an arylthioamide on an unsubstituted ortho position, using potassium ferricyanide in a basic medium. This method has been well used for the preparation of substituted benzothiazoles.
Nadale et al. provided an efficient route to the synthesis of benzothiazoles 2a, 2b, 2e from ortho-methoxy thiobenzamides via the ispo substitution of an aromatic methoxy group. (Fig 2)

Dong et al. synthesized the new 7-methyl-3-substituted-1,2,4-triazolo[3,4-b]-benzothiazoles from p-methyl aniline 1 with various aromatic carboxylic acids in the presence of phosphorus oxychloride. The 2-hydrazino-6-methyl benzothiazole 3 (m.p. 225-226°C) was prepared from 1 to 2 (m.p. 195-196°C). Compound 4 was prepared on treatment with aromatic carboxylic acid in presence of phosphorous oxychloride to triazolo [3,4-b] benzothiazole. (Fig 3)
Further Costa et al.\textsuperscript{12} did condensation of aldehyde 2 with \textit{o}-aminobenzenethiol to give the desired compound 3 in good yield. (Fig 4)

1, 3-benzothiazoles are usually prepared from aldehydes or carboxylic acids by condensation with \textit{o}-aminobenzene thiol. Costa \textit{et al.}\textsuperscript{12} prepared a series of 2-(2-thienyl)-1, 3 benzothiazoles \textit{2a-f} in good yields (60-80\%) starting from formyl thiophenes \textit{1} which were heated with \textit{o}-amino benzene thiol in DMSO for 30-60 min. (Fig 5)

\begin{center}
\begin{tabular}{c}
\textbf{Fig 3} \\
\end{tabular}
\end{center}

\begin{center}
\begin{tabular}{c}
\textbf{Fig 4} \\
\end{tabular}
\end{center}

\begin{center}
\begin{tabular}{c}
\textbf{Fig 5} \\
\end{tabular}
\end{center}
Khalaf et al\textsuperscript{13} described mild reaction condition for the preparation of a number of 2-alkyl and 2-arylamino benzoxazoles and benzothiazole 3 from chlorobenzoxazole and 2-chlorobenzothiazole and \(N\)-methyl or other simple \(N\)-alkyl tertiary amines. The reaction proceeds neat or in THF solution and involves dealkylation of the amine reactant by nucleophilic substitution by chloride. (Fig 6)

\[
\begin{array}{c}
\text{1} \quad X = O, S; R_1 = \text{CH}_3, \text{CH}_2\text{CH}_3; R_2 = \text{CH}_2, \text{CH}_2\text{CH}_3, \text{Ph} \\
\end{array}
\]

\[
\begin{array}{c}
\text{2} \\
\end{array}
\]

\[
\begin{array}{c}
\text{3} \\
\end{array}
\]

**Proposed mechanism of dealklative substitution** (Fig 6)

Caleta et al\textsuperscript{14} described the multistep synthesis of a series of new substituted-benzothiazoles as hydrochloride or quaternary salts. 6-Amidino substituted-2-amino-benzothiazoles, \(N\)-methyl-2-(4-cyanostyryl)benzothiazolium iodide, cyano-substituted-2-styryl benzothiazoles and amidino and bis-amidino-substituted-2-styryl benzothiazoles were prepared. All amidino compounds were prepared in the several steps. The synthesis of the compound 5 started from 2-methyl benzothiazole 1 in which nitro was introduced. The nitro substituent in the position \(6\)\textsuperscript{15} 2, reduced into the amino derivative\textsuperscript{16,17} 3, which was converted into the cyano compound\textsuperscript{18} 4. Cyano compound 4 in the Pinner reaction\textsuperscript{19,20} was converted into the corresponding amidino compound 5. (Fig 7)
The compound 4 was prepared from 6-cyano-2-aminobenzothiazole and amidino compounds 5-7 were prepared according to the scheme shown in Fig 8.

**Reaction conditions**

(a) HNO$_3$, H$_2$SO$_4$; (b) SnCl$_2$, xH$_2$O, HCl, MeOH, reflux, 30 mins;  
(c) NaNO$_2$, HCl, H$_2$O, 0°C; (d) CuSO$_4$, xH$_2$O, KCN, H$_2$O, 80°C, 30 mins;  
(e) HCl (g), C$_2$H$_6$(abs.), 5°C; (f) (CH$_3$)$_2$CHNH$_2$, C$_2$H$_5$(abs.)

(Fig 7)

*N*-methyl iodide salt 4 of the 2-methylbenzothiazole 2 and of 2-(4-cyanostyryl) benzothiazole 3 was prepared by quaternization of the corresponding benzothiazole and subsequent condensation according to the Fig 9.
Amidino substituted styrylbenzothiazoles 4-9 were prepared from corresponding cyano substituted 2-methyl-benzothiazole by the condensation with corresponding benzaldehyde 1 and subsequent Pincher reaction. On this way Caleta and coworkers prepared first amidino substituted 2-styrylbenzothiazoles according to the scheme shown in Fig 10.

**Reaction Conditions**

(a) NaOMe/MeOH or t-BuOK/t-BuOH;
(b) HCl (g), EtOH (abs.);
(c) RNH₂, EtOH (abs.);
(d) HCl (g), EtOH (abs.)
Delmas et al. synthesized (1,3-benzothiazol-2-yl) amino-9-(10H)-acridinone derivatives via a procedure based on Ullman reaction. Compound 1 was prepared with amino aniline following a classical synthetic route (Fig 11) of amino acridone as described by Ullman and modified by Delmas nucleophilic substitution of 2-chlorobenzothiazole and the corresponding amino acridone were done in phenol, to give compounds 2 and 3. Further compound 4 was prepared in the presence of DMF.

The reported synthesis of 2-arylbenzothiazoles has commonly used one of two methods: (i) Condensation of ortho-amino thiophenols with substituted aldehydes, carboxylic acids, acyl chlorides, or nitriles. (ii) or Jackson's cyclization of thiobenzanilides mediated by potassium ferricyanide. Yields from these methods are relatively low and the condensation method also has the limitation of a readily oxidizable sulfur group.

Recently, Majo et al. reported Suzuki Cross-coupling reaction between 2-bromobenzothiazoles and boronic acids or esters however, the moderate to low yield and scarcity of commercially available boronic acids/esters limit the use of this reaction despite the remarkable advantage of a one-step synthesis.

\[
\begin{align*}
\text{Reagents & Conditions} \\
(\text{i}) \text{ DMF, Cu/Zn, ultrasound, 80°C, 2h; (ii) H}_2\text{SO}_4, 120°C, 2h} \\
(\text{iii}) 80°C (4 or 12h); (\text{iv}) \text{ DMF, H}_2, \text{Pd/C, 40 psi, 60°C, 5h}
\end{align*}
\]

(Fig 11)
Allagille et al.\textsuperscript{26} reported a simple and efficient synthesis of 2-arylbenzothiazoles 2 and 2-arylbenzoxazoles using a direct palladium catalyzed arylation of benzo[1,4]thiazines 1 with aryl bromides (Fig 12).

\[
\begin{align*}
\text{Y} \quad \text{X} & \quad \text{+ Ar-Br} \quad \xrightarrow{\text{Pd(OAc)}_2/\text{P(t-Bu)}_3 \text{, DMF, 150 °C, 1h}} \quad \text{Y} \quad \text{X} \quad \text{Ar} \\
\text{X = S, O} \quad \text{Ar} & \quad \text{Y = H, OCH}_3 \\
\end{align*}
\]

(Fig 12)

Charrier et al.\textsuperscript{27} suggested that oxidation of 2H-benzo[1,4]thiazines 1 with oxygen provides benzoylthiazolines, which then undergo a ring contraction with concomitant loss of benzaldehyde, giving rise to benzothiazoles 2. (Fig 13)

\[
\begin{align*}
\text{Ar-CHO} & \quad \xrightarrow{\text{O}_2} \quad \text{Ar} \\
\text{Ar = C}_6\text{H}_5, \text{p-CH}_3\text{OC}_6\text{H}_4; \text{R}_1 = \text{H}, \text{OCH}_3; \\
\text{R}_2 = \text{H}, \text{Cl}, \text{CH}_3, \text{OCH}_3, \text{SCH}_3 \\
\end{align*}
\]

(Fig 13)

Racane et al.\textsuperscript{28} gave the synthesis of the new compounds 2-[4-(6-cyanobenzothiazol-2-yl) phenyl]-5-(6-cyano-benzothiazol-2-yl) furan 6a and 2-[4-(6-cyanobenzothiazol-2-yl) phenyl]-5-(6-cyano-benzothiazol-2-yl) thiophene 6b by multi-step reactions from the corresponding 2-furan and 2-thiophene carboxaldehydes (route A), as well as from 2-furan and 2-thiophene carboxylic acids (route B). Route B involves one less step than route A, but the overall yields of the reactions are considerably lower. (Fig 14)
Starting from 2-aminothiophenol, a readily available starting material, Kundu et al. have developed a highly general method for the synthesis of (E)-2-(2-arylviny)-3-tosyl-2,3-dihydro-1,3-benzothiazoles 4. The method involves two metal-catalyzed
reactions, e.g., (i) a palladium-copper-catalyzed C-arylation of terminal alkynes giving rise to the disubstituted alkynes. (ii) a unique copper-catalysed cyclization which presumably involves a propargyl-allenic rearrangement and subsequently a nucleophilic attack by the tosylamide group on the terminal carbon of the allenic moiety. The process is highly regio and stero selective, only 5-membered ring formation took place leading to the benzothiazolines. (Fig 15)

![Chemical structure](image)

**Reaction Conditions**
(a) \((\text{Ph}_{3}P)_2\text{PdCl}_2\) (3 mol%), CuI (6 mol%), \(\text{Et}_3\text{N}, \text{CH}_2\text{CN, r.t., 24 h}\);
(b) \(p\)-TsCl, py, \(\text{CH}_2\text{Cl}_2, \text{r.t., 10 h}\);
(c) CuI (40 mol%), \(\text{Et}_3\text{N}, \text{THF, reflux, 36 h}\). \(\text{Ar} = \text{C}_6\text{H}_5, 1\)-naphthyl, 3-ClC\(_6\)H\(_4\), 2-thienyl

(Fig 15)

Novel benzothiazole derivatives were synthesized via the corresponding imino-1,2,3-dithiazoles (Fig 16) by Beneteau et al.

![Chemical structure](image)

**Reaction Conditions**
(a) pyridine, dichloromethane, \(-15^\circ\text{C}, 3 \text{ h (2a, 40%) or r.t., 3 h (2b, 84%)};
(b) toluene, sealed tube, reflux, 4 h (3a, 70%);
(c) PyHBr\(_3\), pyridine, reflux, 1.5 h (3b, 72%).

(Fig 16)
There are two major routes to benzothiazoles: (i) radical cyclization of potassium ferricyanide or bromine, (ii) Pd-catalysed cyclization of 2-bromophenylthioformamides (Fig 17). Mu et al. reported studies on using manganese (III) triacetate to replace potassium ferricyanide or bromine reagents for radical cyclization. 2-substituted benzothiazoles are generated in 6 min under microwave irradiation.

![Fig 17]

Matsushita et al. developed a simple and robust method for the conversion of polymer-bound esters into the corresponding benzimidazole and benzothiazole cleavage products by reaction with 1,2-phenylenediamines and 2-aminothiophenols in the presence of a Lewis’s acid. The reaction of 2-aminophenols with the polymer-bound esters failed to give the desired benzoxazole products using this procedure. (Fig 18)

![Fig 18]
The benzothiazole nucleus appears in many fluorescent compounds that have useful applications as a result of the ease of synthesis of this heterocycle and the high fluorescence quantum yields obtained when this small, rigid moiety is present in compounds. Batista et al\textsuperscript{17} reported the synthesis of the new fluorescent bithienyl-1,3-benzothiazole derivatives 3a-h from 5-formyl-5'-alkoxy- or 5-formyl-5'-N,N-dialkylamino-2,2'-bithiophenes 2 with o-aminobenzene thiol 1. Evaluation of the fluorescence properties of these compounds were carried out. They showed strong fluorescence in the 450-600 nm region, as well as high quantum yields and large stokes shifts. (Fig 19)

![Chemical Reaction Diagram](image)

(a) R = H; (b) R = OMe; (c) R = OEt; (d) R = NMe; (e) R = NEt;
(f) R = N(Pr-i); (g) R = piperidino; (h) R = morpholino

Fig 19
2.1.3: Biological Profile

Benzothiazoles are bicyclic ring systems with multiple applications. In the 1950s, a number of 2-aminobenzothiazoles were intensively studied as central muscle relaxants. Since then medicinal chemists have not taken active interest in this chemical family. Biologist's attention was drawn to this series when the pharmacological profile of Riluzole was discovered. Riluzole (6-trifluoromethoxy-2-benzothiazolamine, PK-26124, RP-25279, Rilutek) was found to interfere with glutamate neurotransmission in biochemical, electrophysiological and behavioral experiments. After that benzothiazole derivatives have been studied extensively, and found to have diverse chemical reactivity and broad spectrum of biological activity.

Although they have been known from long ago to be biologically active, their varied biological features are still of great scientific interest nowadays. Benzothiazoles show very intensive antitumor activity, especially the phenyl-substituted benzothiazoles, where as the condensed pyrimido benzothiazoles and benzothiazolo quinazolines exert antiviral activity. Recently, Racane et al. have described the synthesis of bis-substituted amidino benzothiazoles as potential anti-HIV agents. Substituted 6-nitro- and 6-aminobenzothiazoles show microbiological activity. Here is a brief account of various alterations conducted on benzothiazole ring and their associated biological activities.

Antitumor activity:

A series of potent and selective antitumor agents mostly from substituted 2-(4-aminophenyl) benzothiazoles were developed and examined for their in vitro, antitumor activity to ovarian, breast, lung, renal and colon carcinoma human cell lines. Pyrimido benzothiazole and benzothiazolo quinoline derivatives, imidazo benzothiazoles as well as, polymerized benzothiazoles also showed the antitumor activity.

2-(4-aminophenyl) benzothiazoles (1) comprise a novel mechanistic class of antitumor agents. Their unusual activity was first recognized from the distinctive biphasic dose response relationship shown in in vitro assays against sensitive breast tumor cell lines, e.g. MCF-7 and MDA-468. Potency against these breast lines and others was independent of the estrogen or growth factor receptor status of the cells. Introduction of methyl or halogen substituent into the 3'-position of the 2-phenyl group
enhances potency and extends the spectrum of action to certain colon, lung, melanoma, renal and ovarian cell lines.

\[
\text{R} = \text{CH}_3, \text{H, Cl, Br}
\]

(1)

6-amidino-substituted-2-aminobenzothiazoles (2), N-methyl-2-(4-cyanostyryl) benzothiazolium, cyano-substituted-2-styryl benzothiazoles (3) and amidino and bis-amidino-substituted 2-styryl benzothiazoles (4) were prepared by Caleta et al. All new compounds were tested on cytostatic activities against malignant cell lines.

(2)

(3)

(4)

Hutchinson et al. reported the synthesis of fluorinated analogues of 2-(4-aminophenyl) benzothiazoles which successfully block C-oxidation. 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazoles (5) is the favoured analogue for clinical consideration possessing enhanced efficacy \textit{in vitro} and superior potencies against human breast and ovarian tumor xenografts implanted in nude mice.
Quinol esters and ethers (6) derived from the oxidation of 2-(4-hydroxyphenyl) benzothiazoles and quinine monoketals (7) from the oxidation of 2-(3-hydroxyphenyl) benzothiazoles, respectively, have significantly improved and extended antitumor potency in vitro against pairs of breast and colon human tumor cell lines.

The oxidation reactions of 2-(4-hydroxy-3-methoxyphenyl) benzothiazole (8) were studied by Wells et al. In in vitro growth inhibition tests against the human breast cancer cell lines MCF-7 and MDA-468 (over 7 and 10 days respectively) determined by MTT assay, the phenolic benzothiazole gave IC₅₀ values (dose to inhibit cell growth by 50%) of 0.62 and 0.06 µM, respectively.

Beneteau et al. have described the synthesis of 2-cyano-4, 7-dimethoxybenzothiazoles (9). The 2-cyano derivatives exhibit interesting in vitro antitumor activity.
Benzothiazoles show a wide spectrum of chemotherapeutic activity and a considerable amount of work has been done on the synthesis of new potent antibacterial and antifungal benzothiazoles. Bhusari et al., prepared some new 2-(substituted phenylsulfonamido)-6-substituted benzothiazoles (10) and screened them for their antibacterial activity against *B. subtilis*, *S. typhi* and *S. dysentery*. Compounds with R = Br and R$_1$ = CH$_3$, NH$_2$ and I were found more active and others were less or moderately active.

Various benzothiazolo triazole derivatives (11) were prepared by Sreenivasa et al. and found to possess good activity against *S. aureus*, *E. coli* and *C. ablicans*. Some 6-fluoro-7-(substituted)-(2-N-phenylsulfonamido) benzothiazoles (12) [R = $o$-nitroanilino, $m$-nitroanilino, $p$-nitroanilino, $o$-chloroanilino, $m$-chloroanilino, $p$-chloroanilino, anilino, morpholino, piperazino, dimethylamino] were synthesized and studied for their antibacterial and antifungal activities. All compounds showed moderate activity against *S. aureus*, *S. albus* and *C. ablicans*. 

$$\text{Haplotcr.}$$

**Antimicrobial activity:**

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![Chemical structure](image)

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![Chemical structure](image)
Ojha et al\textsuperscript{72} reported the various benzothiazolyl carboxamido pyrazoline derivatives\textsuperscript{(13)} and studied their antimicrobial activity. Compounds having $R = \text{CH}_3$ and $R_1 = \text{o-OCH}_3\text{C}_6\text{H}_4$, showed no activity and when $R = \text{Cl}$ and $R_1 = \text{p-OCH}_3\text{C}_6\text{H}_4$, the was active against \textit{S. aureus}. The rest of the compounds showed the activity against, \textit{S. aureus}, \textit{E. coli}, \textit{P. aeruginosa}, \textit{K. pneumoniae} and \textit{P. mirabilis}.

\begin{align*}
\text{(13)}
\end{align*}

Some 8-[(6-substituted-1,3-benzothiazol-2-yl) aminomethyl] substituted hydroxy coumarins (14) were screened for their antibacterial activity against \textit{S. aureus} and \textit{E. coli}. The compounds were also screened for antifungal activity against \textit{A. brassicicola} and \textit{F. udum}. All the compounds showed moderate activity.\textsuperscript{73}

\begin{align*}
\text{(14)}
\end{align*}
Bareda et al\textsuperscript{74} worked on few 5,6-disubstituted-2-(substituted phenyl carboxamido) benzothiazoles (15) and found them active against \textit{M. tuberculosis}, \textit{S. typhi}, \textit{S. aureus}, \textit{C. albicans}, \textit{T. rubrum}, \textit{T. mentagrophytes} etc. The compounds were also active against some helminths like \textit{H. nana}. A few 2-(4-amino/2, 4-diaminophenyl) sulfonyl derivatives of benzothiazoles (16) were found to possess good activity against \textit{E. coli}.\textsuperscript{75}

\[
\text{X} = \text{S}, \text{SO}_2; \\
\text{Y} = \text{4-NH}_2, 2, \text{4-diNH}_2, 2, \text{4-diNHAc}
\]

\[(15)\]

\[
\text{R} = \text{5-Cl, 6-F, 5,6-diCl}; \\
\text{R}_1 = \text{H, 2-F, 4-F, 2,6-diF, 2-CF}_3, 3-\text{CF}_3
\]

\[(16)\]

Yildiz-Oren \textit{et al}\textsuperscript{76} has synthesized a series of multisubstituted benzoazoles, benzimidazoles and benzothiazoles (17) as non-nucleoside fused isosteric heterocyclic compounds and tested for their antibacterial activities against \textit{S. aureus}, \textit{S. faecalis}, \textit{B. subtilis} as gram positive and \textit{E. coli}, \textit{K. pneumoniae}, \textit{P. aeruginosa} as gram negative bacteria and yeast \textit{C. albicans} using twofold serial dilution technique. The synthesized compounds possessed a broad spectrum of activity against the tested microorganisms at MIC values between 100 and 3.12 \textmu g/ml. Benzothiazole ring system enhanced the antimicrobial activity against \textit{S. aureus}.

\[
\text{Y} = \text{O}; \text{Z} = \text{S}; \text{R} = \text{H}; \\
\text{R}_1 = \text{H, NO}_2, \text{Cl}; \text{R}_2 = \text{H, NO}_2
\]

\[(17)\]

Latrofa \textit{et al},\textsuperscript{77} prepared a series of \textit{N-cycloalkylidene-2,3-dihydro-1,3-benzothiazoles} (18), \textit{N-cycloalkyl-2-acylalkylidene-2,3-dihydro-1,3-benzothiazoles} (19), and \textit{N-alkyl-2-acylalkylidene-2,3-dihydro-1,3-benzothiazoles} (20) and tested for \textit{in vitro} antibacterial and antifungal activities against four gram positive and five gram negative bacteria. The findings obtained showed that some of the tested compounds
were effective against bacterial strains, whereas, only few compounds exhibited a 
moderate antifungal activity against the yeast strains evaluated.

\[
\text{X} = H, F, OCH_3, CH_3; n = 8, 3
\]
\[
R_1 = CH_3, C_2H_5, C_6H_5
\]
\[
C_6H_5, C_5H_11
\]

\[(18)\]

\[
\text{X} = H; n = 8, 3;
\]
\[
R_1 = CH_3, C_2H_5, C_6H_5(CH_2)_n;
\]
\[
R_2 = H, (CH_2)_n
\]

\[(19)\]

\[
\text{X} = H, Y = C_1H_2;
\]
\[
R_1 = C_6H_5-N(CH_2C_6H_5)(CH_2)_n;
\]
\[
R_2 = H, -CH_2-N(CH_2C_6H_5)-\text{CH}_3
\]

\[(20)\]

The series of 2-benzylsulfanyl derivatives of benzoxazole and benzothiazoles 
(21) were synthesized and evaluated for their in vitro antimycobacterial activity 
against \textit{M. tuberculosis} and non-tuberculous mycobacteria by Koci \textit{et al.}\textsuperscript{78} The 
substances bearing two nitro groups or a thioamide group exhibited appreciable 
activity particularly against non-tuberculous strains.

\[
\text{X} = O, S;
\]
\[
R = H, 4-NO_2, 3-NO_2, 2-NO_2, 3, 5-NO_2
\]
\[
2, 4-NO_2, 4-CN, 3-CN
\]

\[(21)\]

Various substituted 2-(4-acetamidophenylsulfonamido) benzothiazoles and 
2-(4-amino phenyl sulfonamido) benzothiazoles (22) having different functional 
groups were synthesized and screened for their in vitro antitubercular activity.
Compounds with \( R_1 = \text{CH}_3 \) and \( R_2 = \text{Br} \), were found to be most potent. Overall the compounds having electron withdrawing substituents (NO\(_2\), COOH and halogens) showed better activity than unsubstituted one.\(^9\)

\[
\text{NR}_1
\]

(22)

Antihelmintic activity:

Recent reports of resistance to benzimidazoles have now forced the researchers to urgently develop new drugs with anthelmintic activity, to fight helminthiasis, which is causing untold misery to the infected individuals. This prompted to synthesize benzothiazole derivatives, which were sulfur isostere of benzimidazole, in the hope of achieving better anthelmintic activity.

In the search of new anthelmintic agents of benzothiazole series, Nargund,\(^8\) synthesized few novel 8-fluoro/bromo-9-substituted (1,3) benzothiazolo (5,1-b)-1,3,4-triazoles (23). All these compounds were studied for their anthelmintic activity against earthworm, \( P. \text{posthuma} \). The compound with \( R_1 = \text{fluoro} \) and \( R = \text{o-nitroanilino} \) substituent was found to possess markedly higher anthelmintic activity, than other compounds compared with standard. Whereas compound with substituent \( R_1 = \text{bromo} \) and \( R = \text{4-carboxyanilino} \) and morpholino were found to be the most potent in the series.\(^9\)

Some substituted imidazobenzothiazoles (24) were tested for \( in \text{ viva} \) anthelmintic activity against \( H. \text{nana} \) infection and were found to show good to moderate activity.\(^9\)
Antileishmanial activity:

Delmas et al. synthesized (1,3-benzothiazol-2-yl) amino-9-(10H)-acridinone derivatives (25) and were assessed for their in vitro antileishmanial and anti-HIV activities. 1-(6-amino-benzothiazol-2-yl-amino)-10H-acridin-9-one, showed selective antileishmanial activity, mainly due to amastigote specific toxicity. Addition of a benzothiazoles group on a parent amino-9-(10H)-acridinone ring could enhance antileishmanial abilities. On position 4 amino chain was essential for specific anti-amastigote properties.

Delmas et al. has synthesized position 2 substitution bearing 6-nitro, 6-amino benzothiazoles and their corresponding anthranilic acids. The in vitro antiparasitic activity of each derivative against the parasites of the genus *L. infantum* and *T. vaginalis* compared to their toxicity towards human monocytes were assessed. The antiprotozoal properties depended greatly on the chemical structure of the position 2-substitution-bearing group. 2-[(2-Chloro-benzothiazol-6-yl) amino] benzoic acid, demonstrated an interesting antiproliferative activity towards parasites of the species *T. vaginalis*, while compound 2-[(2-hydroxyethyl) amino]-benzothiazol-6-yl amino) benzoic acid exhibited a promising activity against parasites of the species *L. infantum* in their intracellular amastigote form.
Anticonvulsant activity:

In the search of new anticonvulsant agents having benzothiazole nucleus, Jimonnet et al. synthesized a lot of substituted-2-benzothiazolamines (26). All the compounds were found to possess significant activity.

\[ R = \text{CH}_3, \text{C}_6\text{H}_5, \text{OCH}_3, \text{OCH}_2\text{C}_6\text{H}_5, \text{C}_6\text{H}_3\text{OC}, \text{OCH}_3, \text{OCH}_2\text{CF}_3, 4\text{-OCF}_3, 5\text{-OCF}_3, 7\text{-OCF}_3, \text{n-prop, i-prop, n-but, n-pen, t-pen} \]

(26)

A series of benzothiazolyl guanidines (27) were synthesized by Siddiqui et al. The compounds with \( R = 4\)-CH\(_3\) and 4-Cl were found to be equipotent (100%) in activity to phenobarbitone in maximal electroshock seizure test, blocked subcutaneous pentylentetrazole and strychnine seizures to some extent. All other compounds also had significant anticonvulsant activity.

\[ R = \text{H}, 2\text{-CH}_3, 3\text{-CH}_3, 4\text{-CH}_3, 2\text{-Cl, 3-Cl, 4-Cl, 2-OCH}_3, 4\text{-OCH}_3, 4\text{-Br} \]

(27)

Singh et al. synthesized some 2-(4-arylthiosemicarbazidocarbonylthio) benzothiazoles (28). The compounds were screened for their anticonvulsant activity against pentylentetrazole induced convulsions in mice and found that all the compounds possess measurable anticonvulsant activity. A large number of 2-(3H)-benzothiazolone derivatives (29) have been synthesized and evaluated for their anticonvulsant activity in mice and were found to be significantly active.

\[ Ar = \text{C}_6\text{H}_5, o\text{-CH}_3\text{C}_6\text{H}_4, m\text{-CH}_3\text{C}_6\text{H}_4, p\text{-CH}_3\text{C}_6\text{H}_4, o\text{-OCH}_3\text{C}_6\text{H}_4, p\text{-OCH}_3\text{C}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, \]

(28)
Antiinflammatory activity:

Pyrazolones and pyrazolinones rank among the more venerable non-steroidal antiinflammatory agents. In the recent years a number of benzothiazole derivatives have been synthesized and found to display antiinflammatory activity. Sawhney et al. have prepared some novel 2-(2-benzothiazolyl)-6-aryl-4,5-dihydro-3-(2H)-pyridazinone (30) and found that they possessed low to moderate antiinflammatory activity.

(Sawhney et al.)

Singh et al. prepared some new 2-(4-butyl-3,5-dimethylpyrazol-1-yl)-6-substituted benzothiazoles (31) and 4-butyl-1-(6-substituted-2-benzothiazolyl)-3-methylpyrazol-5-ones (32). The compounds were found to display significant antiinflammatory activity.
Paramshivappa et al.\(^1\) prepared a series of 2-[(2-alkoxy-6-pentadecylphenyl) methyl] thio]-1H-benzimidazoles/ benzothiazoles and benzoxazoles from an anacardic acid and investigated their ability to inhibit human cyclooxygenase-2-enzyme (COX-2). The active compounds were screened for cyclooxygenase-1 (COX-1) inhibition. Compound (33a) is 384 fold and (33b) is more than 470 fold selective towards COX-2 compared to COX-1. Dogruer et al.\(^2\) synthesized sixteen (2-benzothiazolone-3-yl and -2-benzoxazolone-3-yl) acetic acid derivatives (34). The compounds were tested for antinociceptive and antiinflammatory activity. 4-[2-(6-benzoyl-2-benzoxazolone-3-yl) acetyl] morpholino, 4-[2-[2-chloro-benzoyl]-2-benzoxazolone-3-yl] acetyl] morpholino, 4-[2-[2-chloro-benzoyl]-2-benzoxazolone-3yl] acetyl] morpholine, 1-[2-(5-chloro-2-benzoxazolone-3-yl) acetyl] pyrrolidine, methyl (6-methyl-2-benzoxazolone-3-yl) acetate and \(N, N\)-diethyl-2- (2-benzothiazolone-3-yl) acetamide have shown more potent antinociceptive activity than others.

\[
\text{X = O, S; } R_1 = \text{H, Cl; } R_2 = \text{H, CH}_3, \text{C}_6\text{H}_5\text{CO, o-Cl-C}_6\text{H}_4\text{CO} \\
A = 1\text{-morpholinyl, 1-pyrrolidinyl diethylamino, OCH}_3, \text{OC}_6\text{H}_5, \text{OH}
\]

\[(33a-b)\]

Miscellaneous:

Diouf et al.\(^3\) synthesized original derivatives of 2-piperazinyl benzothiazoles (35) and studied as mixed ligands for serotonergic 5-HT\(_{1A}\) and 5-HT\(_3\) receptors. The studied compounds exhibited significant affinities for these two serotonergic receptor subtypes. The pharmacological profile of these ligands was agonist for 5-HT\(_{1A}\) receptors and antagonist for 5-HT\(_3\) receptor sub sites. Compounds
with such a pharmacological profile are of clinical relevance in the treatment of psychotropic diseases, e.g. anxiety, depression and schizophrenia.

Brown et al\(^4\) reported a series of pyridazinylpiperidinyl capsid-binding compounds with novel bicyclic substituents and screened against human rhinovirus (HRV). HRV cause approximately one-half of all cases of respiratory tract infection (colds). Several 2-alkoxy, 2-akylthio-benzoxazole and benzothiazoles derivatives (36) showed excellent anti-HRV activity. When tested against a panel of 16 representatives HRV types, the 2-ethoxy-benzoxazole derivatives were found to have superior HRV activity (median EC\(_{50}\) 3.88 ng/mL) to known capsid-binders pleconaril and pirodavir.

Das et al\(^8\) prepared a series of structurally novel benzothiazoles based on small molecule inhibitors of p56\(^{ck}\) to elucitate structure activity relationships (SAR), respectively and cell activity in the T-cell proliferation assay. p56\(^{ck}\) (Lck), a member of the Src family of non-receptor protein tyrosine kinase is expressed primarily in T-lymphocytes and natural killer cells.

Selective inhibitors of Lck may have potential therapeutic utility in the treatment of T-cell mediated disorders such as autoimmune and inflammatory diseases and in the prevention of solid organ transplant rejection. BMS-243117 \(^9\) (37) is identified as a potent and selective Lck inhibitor with good cellular activity.
(IC$_{50}$ = 1.1 µM), whereas BMS-350751 (38) and BMS-358233 (39) were identified as potent Lck inhibitors with excellent cellular activities against T-cell proliferation.

(37)

(38)

(39)
References


80. Nargund, L. V. G. Anthelmintic Activity of 8-Fluoro-9-Substituted (1,3)-Benzothiazolo (5,1-b)-1,3,4-Triazoles on *Perinema posthuma*. *Ind. Drugs* 1999, 36, 137-139.


Chapter 2

Literature Review


2.2. BENZAMIDES
2.2.1: Introduction

Benzamides are a class of chemical compounds derived from Benzamid (R = H), the carbonic acid amide of benzoic acid.

Physical and Chemical properties:

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula</td>
<td>C₆H₅CONH₂</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>121.14</td>
</tr>
<tr>
<td>Synonyms</td>
<td>Benzoic acid amide; Phenylcarboxamide; Benzamid (German); Benzamida (Spanish); Benzamide (French); Benzoylamide.</td>
</tr>
<tr>
<td>Physical state</td>
<td>White Powder</td>
</tr>
<tr>
<td>Melting Point</td>
<td>132.5 - 133.5 °C</td>
</tr>
<tr>
<td>Boiling Point</td>
<td>290 °C</td>
</tr>
<tr>
<td>Specific Gravity</td>
<td>1.08</td>
</tr>
<tr>
<td>Solubility</td>
<td>Slightly soluble (soluble in ethanol, carbon tetrachloride)</td>
</tr>
</tbody>
</table>

General Description:

Amide is a group of organic chemicals with the general formula RCO-NH₂ in which a carbon atom is attached to oxygen in double bond and also attached to an hydroxyl group, where 'R' groups range from hydrogen to various linear and ring structures or a compound with a metal replacing hydrogen in ammonia such as sodium amide, NaNH₂. Amides are divided into subclasses according to the number of substituents on nitrogen. The primary amide is formed by replacement of the carboxylic hydroxyl group by the NH₂ amino group. An example is acetamide (acetic acid + amide). Amide is obtained by reaction of an acid chloride, acid anhydride, or ester with an amine. Amides are named with adding '-ic acid' or '-oic acid' from the name of the parent carboxylic acid and replacing it with the suffix 'amide'. Amide can be formed from ammonia (NH₃). The secondary and tertiary
amides are the compounds in which one or both hydrogens in primary amides are replaced by other groups. The names of secondary and tertiary amides are denoted by the replaced groups with the prefix capital \( N \) (meaning nitrogen) prior to the names of parent amides. Low molecular weight amides are soluble in water due to the formation of hydrogen bonds. Primary amides have higher melting and boiling points than secondary and tertiary amides.

**Medicine materials**

In psychiatry and related medical fields, two active substances from the group of Benzamides are in use:

- Sulpiride
- Amisulpiride

Another benzamide, Remoxipride was taken off the market in 1993 because of life threatening side effects.
2.2.2: Biological Profile

Anticonvulsant activity

A comparison of enaminones from various unsubstituted and p-substituted benzamides to the analogues benzyl amines has been undertaken with the aim of elucidating the essential structural parameters necessary for anticonvulsant activity by Foster et al.\textsuperscript{1} Initial studies on methyl 4-N-(benzylamino)-6-methyl-2-oxocyclohex-3-en-1-ate, (1), 3-N-(benzylamino)cyclohex-2-en-1-one (2) and 5, 5-dimethyl-3-N-(benzylamino)-cyclohex-2-en-1-one (3) indicated that benzylamines possessed significant anti-maximal electroshock seizure (MES) activity. Evaluation of the analogous benzamides revealed significant differences in their three dimensional structures.

\[
\begin{align*}
(1) & \quad \text{CH}_3 \quad \text{H} \quad \text{CO}_2\text{CH}_3 \quad \text{H} \\
(2) & \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \\
(3) & \quad \text{CH}_3 \quad \text{CH}_3 \quad \text{H} \quad \text{H}
\end{align*}
\]

Chan et al.\textsuperscript{2} identified a series of N-(tetrahydroisoxazolyl)-2-methoxybenzamides by high throughput screening at the novel SB-204269 binding site. SAR studies have provided compound (4) with high affinity and good anticonvulsant activity in animal models.

\[
\begin{align*}
\text{MeO} & \quad \text{NHCOR} \quad \text{R} = 4-\text{Butyl} \\
\text{Me} & \quad \text{N}
\end{align*}
\]

The new anticonvulsant N-(5-methylisoxazol-3-yl)-2,6-dimethylbenzamide (D2916), which presents two kinds of methyl groups which could be oxidized, was submitted to various chemical oxidizing agents by Adolphe-Pierre et al.\textsuperscript{3} Several sites and degrees of oxidization were observed. The main oxidized site was the aryl methyl
group without cleavage of the isoxazole ring, leading via carboxylic acid and primary alcohol intermediates to phthalimide and lactame derivatives. In no case was the methyl group of the isoxazole moiety hydroxylated.

A well documented study on the anticonvulsant properties of 4-amino-N-(2-ethylphenyl) benzamide (4-AEPB) (5) was provided by Diouf et al. In initial screening mice was dosed intraperitoneally, revealed that 4-amino-N-(2-ethylphenyl) benzamide (4-AEPB) was active in MES test at the dose of 10 and 100 mg/kg after 30 mins and 4 h, respectively against phenytoin.

\[
\text{(5)}
\]

A series of benzamides containing N, N, 2-trimethyl-1,2-propane diamine as the amide moiety was synthesized by Musso et al. The compounds were evaluated in the maximal electroshock (MES) and pentylenetetrazole (metrazole, MET) screens for anticonvulsant activity. The 3,5-trifluoromethyl, 3,5-dichloro, and 3-bromo analogues proved to be either equipotent with or more potent than phenytoin.

\[
\text{(6)}
\]

A short series of 4-nitro-N-phenylbenzamides (7) was synthesized and evaluated for anticonvulsant properties and neurotoxicity by Bailleux et al. In mice dosed intraperitoneally, three of the four 4-nitro-N-phenylbenzamides were efficient in the maximal electroshock-induced seizure (MES) test, especially \(N\)-(2,6-dimethylphenyl)-4-nitrobenzamide (ED\(_{50}\) value in the MES test = 31.8 μM/kg, TD\(_{50}\) = 166.9 μmol/kg, protective index PI = 5.2) and \(N\)-(2-chloro-6-methylphenyl)-4-nitrobenzamide (ED\(_{50}\) value in the MES test = 90.3 μmol/kg, TD\(_{50}\) = 1.068 μM/kg, PI = 11.8). The latter 4-nitro-N-phenylbenzamide was also found to be active against seizures induced by subcutaneous pentylenetetrazole (scPtz) and was selected for
further evaluation in rats dosed orally. In these conditions, \( N\)-(2-chloro-6-methylphenyl)-4-nitrobenzamide was found to be, three times more active than phenytoin and 4-amino-\( N\)-(2,6 dimethylphenyl) benzamide, two times more potent in the MES test.

\[
\begin{align*}
R_1 &= \text{F, CH}_3, \text{CH}_2, \text{C}_2\text{H}_5 \\
R_2 &= \text{F, CH}_3, \text{Cl, C}_2\text{H}_5
\end{align*}
\]

(7)

Antiinflammatory activity

Parsalmide (5-amino-\( N\)-butyl-2-(2-propyloxy)benzamide) (8), is a non-steroidal antiinflammatory drug (NSAID), commercialized in Italy until 1985 with the brand name of Synovial, that has been widely used to treat arthritic patient. In addition, it was shown to spare gastric mucosa. Here, Caliendo et al\(^7\) synthesized a series of novel substituted benzamides, related to Parsalmide, and have evaluated their activity \( \textit{in vitro} \) on COX-1 and COX-2 as well as \( \textit{in vivo} \) in the Carragenan-induced rat paw edema, a classical \( \textit{in vivo} \) antiinflammatory assay. Compounds (9) and (10), which showed a favourable profile \( \textit{in vitro} \) and \( \textit{in vivo} \), were screened in comparison with parsalmide for gastrointestinal (GI) tolerability \( \textit{in vivo} \) in the rats. Results obtained showed that Parsalmide and compound (10) inhibited both COX-1 and COX-2 \( \textit{in vitro} \) as well as they were active \( \textit{in vivo} \). Both compounds were devoid of gastric effect at the efficacious dose. In addition, both prevented indomethacin induced gastric damage.

\[
\begin{align*}
\text{HC} &\equiv \text{CCH}_2\equiv \text{O} \\
\text{CONH(CH}_3)\text{CH}_3
\end{align*}
\]

(8)
Two series of *N*-4-(alkyl)cyclohexyl]-substituted benzamides, i.e. a series of *N*-4-(tert-butyl) cyclohexyl]-substituted benzamides (11a-h) and a series of *N*-4-(ethyl) cyclohexyl]-substituted benzamides (12a-h) were synthesized and evaluated for their antiinflammatory and analgesic potencies, and gastro-intestinal irritation liability by Pau et al. As regards the antiinflammatory activity, best results were shown by (11f), followed by (11d) but many other compounds showed pharmacological potency. As regards the ulcerogenic action, the most potent compound was (12c), followed by (11c) and (11f), but in general all compounds showed a fairly high irritative capacity.

**Analgesic activity**

Two parallel synthetic methods were developed by Coats *et al.* to explore the structure activity relationship (SAR) of a series of potent opioid agonists. Series of tropanylidene benzamides synthesized by *N*-ethyl-4-[(8-phenethyl-8-aza-bicyclo [3.2.1] oct-3-ylidene)-phenyl]-methyl]-benzamide (13) proved extremely tolerant of structural variation while maintaining excellent opioid activity.

A subset was tested orally at 150 μmol/kg in the mouse, 48°C hot plate test. Some compounds provided robust antinociception and most induced Straub tail, a behavior often associated with μ opioid agonist activity. The 3 and 4-carboxy phenyl tropanyldenes provided little or no analgesic effects in the same testing paradigm.
most likely due to poor oral absorption or brain penetration. Authors observed no instances of convulsions or deaths with these compounds.

\[ \text{(13)} \]

Carrson et al.\(^6\) have prepared a series of \(N, N\)-dialkyl 4-[(8-azabicyclo [3.2.1]-oct-3-yldiene) phenyl methyl] benzamides. The lead compounds bind with exceptionally high affinity to the \(\delta\) opioid receptor and were also highly selective for \(\delta\) versus \(\mu\) opioid binding. They were full \(\delta\) agonists and were antinociceptive in the mouse abdominal irritant test. Importantly, they appear to have a lower convulsant liability than earlier \(\delta\) agonists. \(\delta\) opioid agonists have been seen as potentially safer alternatives to conventional \(\mu\) agonists as pain relieving agents. Alternative therapeutic roles for these agents, in neuropathic or inflammatory pain, depression, parkinson's disease and lung cancer have been suggested.

\(N\)-alkyl-4-[(8-azabicyclo[3.2.1]-oct-3-yldiene)phenylmethyl]-benzamides, were synthesized by Carson et al.\(^1\) The tertiary amide \(\delta\) opioid agonist (14) was a potent antinociceptive agent. Compound (14) was metabolized \textit{in vitro} and \textit{in vivo} to secondary amide, a potent and selective \(\mu\) opioid agonist. The SAR of a series of \(N\)-alkyl-4-[(8-azabicyclo [3.2.1]-oct-3-yldene) phenylmethyl] benzamides was also examined.

\[ \text{(14)} \]
Serotonin (5-HT) activity

Serotonin (5-HT) is a neurotransmitter responsible for a wide range of pharmacological reactions. Many gastrointestinal prokinetics such as benzamides (e.g., metoclopramide, cisapride) have binding affinity for 5-HT₄ receptors and the pharmacological effect of these compounds is thought to be based on 5-HT₄ receptor agonism.

Sonda et al\(^\text{12}\) prepared a set of benzamide derivatives and evaluated them as selective 5-HT₄ receptor agonists. They performed modification of the parent compound 4-amino-5-chloro-2-methoxy-\(N\)-[1-(6-oxo-6-phenylhexyl)piperidin-4-yl methyl] benzamide (15) which have the ability to enhance both upper and lower gastrointestinal motility without any significant adverse effects.

\[
\text{(15)}
\]

A Series of 4-amino-5-chloro-2-methoxy-\(N\)-(piperidin-4-yl-methyl) benzamides with a polar substituent group at the 1-position of the piperidine ring was synthesized and evaluated by Sonda et al\(^\text{13}\) for its effect on gastrointestinal motility. The benzoyl, phenylsulfonyl, and benzylsulfonyl derivatives accelerated gastric emptying and increased the frequency of defecation. One of them, 4-amino-\(N\)-[1-[3-benzylsulfonyl] propyl] piperidin -4-yl methyl]-5-chloro-2-methoxy benzamide (16), was a selective 5-HT₄ receptor agonist offering potential as a novel prokinetic with reduced side effects derived from 5-HT₃ and dopamine D₂ receptor binding affinity. In the oral route of administration, this compound enhanced gastric emptying and defecation in mice, and has a possibility as a prokinetic agent, which is effective on both the upper and lower gastrointestinal tract.
Azaadamantane was converted to a series of aminoazadamantane benzamides (17a-d) by Becker et al., which were profiled for serotonin receptor activity. Aminomethyl azadamantane SC-54750 is a potent 5-HT₄ agonist and 5-HT₃ antagonist with \textit{in vivo} efficacy in gastroparesis models and also inhibits cisplatin induced emesis.

Several fused bicyclic systems have been investigated by Zhang et al. to serve as the core structure of potent and selective 5-HT₁F receptor agonists. Replacement of the indole nucleus in (18) with indazole and inverted indazole provided more potent and selective 5-HT₁F receptor ligands (19). Indoline and 1,2-benzisoxazole systems also provided potent 5-HT₁F receptor agonists. The 5-HT₁A receptor selectivity of the indoline and 1,2-benzisoxazole-based 5HT₁F receptor agonists could be improved with modification of the benzoyl moiety of the benzamides.
The combination of D₄ and 5-HT₂A receptor blockade is attractive for a number of reasons. A favorable 5-HT₂/D₂ ratio may limit the propensity of a compound to induce extrapyramidal symptoms (EPS). 5-HT₂A antagonists are also known to be efficacious in the treatment of negative symptoms of schizophrenia. In addition, cortical dopaminergic systems are regulated by 5-HT indirectly via glutamatergic and GABAnergic systems, suggesting a synergistic relationship between the dopaminergic and serotonergic systems.

A series of N-[(3S)-1-benzylpyrrolidin-3-yl]-(2-thienyl) benzamides (21) has been prepared by Arora et al.¹⁶ and found to bind with high affinity to the human D₄(HD₄) and 5-HT₂A receptors. Several compounds displayed selectivity for these receptors versus HD₂ and α₁ adrenergic receptors of over 500-fold.

![Chemical structure of 21](image)

A series of novel N-[1-(1-substituted 4-piperidinyl]benzamides were prepared by Harda et al.¹⁷ and compounds were evaluated for their binding to 5-HT₄ receptors and effects on gastrointestinal motility in conscious dogs. 4-Amino-N-[1-(4-aminobutyl)-4-piperidinylmethyl]-4-piperidinyl]-5-chloro-2-methoxybenzamide (21) was found to have a potent binding affinity for 5-HT₄ receptor (IC₅₀: 6.47mM) and showed excellent prokinetic activity.

![Chemical structure of 21](image)

KDR-5169, 4-amino-5-chloro-N-[1-(3-fluoro-4-methoxybenzyl) piperidin-4-yl]-2-(2-hydroxyethoxy) benzamide hydrochloride dehydrate (22) is a new prokinetic with a dual action i.e., stimulation of the 5-HT₄ receptor and antagonism of the
dopamine D₂ receptor. In the study by Tazawa et al., they determined in vitro activities of KDR-5169 towards both receptors and demonstrated the effect of the compound on gastrointestinal motor activity in conscious dogs and rats.

![Chemical structure of the compound](image)

(22)

**Antitumor Activity**

Xu et al. synthesized a novel class of N-(4-([4-(1H-benzoimidazol-2-yl)aryl amino]methyl]-phenyl) benzamides and described them as inhibitors of the endo-β-glucuronidase that degrades heparanase. Heparanase, an endo-β-D-glucuronidase that degrades heparin sulfate glycosaminoglycans in the extra cellular matrix (ECM) and the basement membrane, is involved in tumor cell invasion, angiogenesis, and other physiological and pathological processes.

Among the synthesized compounds N-(4-([4-(1H-benzoimidazol-2-yl)phenylamino]methyl]-phenyl)-3-bromo-4-methoxybenzamide (23), and N-(4-([5-(1H-benzoimidazol-2-yl)]pyridin-2-yl-amino[methyl]-phenyl)-3-bromo-4-methoxybenzamide (24) displayed good heparanase inhibitory activity (IC₅₀ 0.23-0.29 μM), with the latter showing oral exposure in mice.

![Chemical structures of compounds 23 and 24](image)

(23)  (24)
Iodobenzamides are reported to possess some affinity for melanoma. In order to identify the compound having the most appropriate pharmacokinetic properties as a potential melanoma imaging agent, thirteen new \(^{125}\)I radioiodobenzamides with a butylenes amide-amine spacer and various substituents on the terminal amine group were investigated by Moins et al.\(^{20}\) Their synthesis, radioiodination and biodistribution in B16 melanoma bearing (57BL6 mice are described and compared to \(^{125}\)I labeled \(N\)-(2-diethylaminoethyl)-4-iodobenzamide (\(^{125}\)IBZA) (25), with reference compound changes in the terminal amino constituents induced modifications of lipophilicity, tumor uptake and organ distribution. The dimethylaminobutyl iodobenzamide appeared to be the most promising radiopharmaceutical imaging agent for the detection of melanoma and its metastases.

\[ \text{R}_1 = \text{H, CH}_3, \text{C}_2\text{H}_5, \text{n-C}_3\text{H}_7, \text{C}_6\text{H}_{13}, \text{n-C}_7\text{H}_{17}; \]
\[ \text{R}_2 = \text{H, CH}_3, \text{C}_2\text{H}_5, \text{n-C}_3\text{H}_7, \text{C}_6\text{H}_{13}, \text{n-C}_7\text{H}_{17}. \]

(25)

In the course of Moreau et al.\(^{21}\) investigations aimed at improving the biological characteristic of iodobenzamides for melanoma therapeutic applications, four new derivatives containing a spermidine chain have been prepared and radiolabeled with \(^{125}\)I. In vitro studies showed that all compounds displayed high affinity for melanin superior to the reference compound BZA. In vivo biodistribution was investigated in B16 melanoma-bearing mice. All four compounds, particularly benzamide (28), showed accumulation in the tumor, but lower, however than that of BZA. Moreover, high concentrations of radioactivity in the organs, namely, the liver and lungs, demonstrated nonspecific tumoral uptake. In view of these results, compounds (26), (27), (28), (29) donot appear to be suitable radiopharmaceuticals for melanoma radionuclide therapy.

\[ \text{R}_1, \text{R}_2 = (26) = \text{C}_2\text{H}_5, \text{H}; (27) = \text{C}_6\text{H}_{13}, \text{H}; \]
\[ (28) = \text{C}_6\text{H}_{13}, \text{CH}_2\text{Ph}; (29) = \text{C}_7\text{H}_{15}, \text{CH}_3. \]
Antimicrobial Activity

Narayana et al.\textsuperscript{22} prompted by the earlier investigations, contemplated to synthesize some new 5-(2-substituted-1,3-thiazol-5-yl)-2-hydroxybenzamides (30), 5-[(N-substituted aryl)aminol]-1,3-thiazol-5-yl]-2-hydroxybenzamides (31) and their 2-butoxy and 2-propyloxy derivatives (32) and their antifungal activity. Among the tested compounds, the compound 5-[(N-3-chlorophenyl)-1,3-thiazol-5-yl]-2-butoxybenzamide emerged as most active compound.

\begin{align*}
R_1 &= \text{H, NH}_2, \text{CH}_3\text{CH}(\text{CH}_3)_2 \\
R_1 &= \text{H, NH}_2, \text{CH}_3\text{CH}(\text{CH}_3)_2 \\
R_2 &= \text{CH}_3, \text{NH}_2, \text{NHCOCH}_3 \\
R_2 &= \text{CH}_3, \text{NH}_2, \text{NHCOCH}_3 \\
R_2 &= \text{Propyl, Butyl}
\end{align*}

The synthesis of some \(N\)-(2-hydroxy-4-substituted phenyl) benzamides, phenylacetamides and furamides as the possible metabolites of benzoxazoles was performed in order to determine their \textit{in vitro} antimicrobial activity against three gram positive bacteria, two gram negative bacteria and the fungus \textit{C. albicans} and their activities were compared with several control drugs by Senet et al.\textsuperscript{23} Some
compounds were found active at a MIC value of 12.5 μg/ml against the gram negative microorganism \( P. \) \textit{aeruginosa}. Most of the compounds showed antibacterial activity at MIC value 25 μg/ml against the gram positive bacteria \( S. \) \textit{aureus}. For the antifungal activity against \( C. \) \textit{albicans}, one of the compound was found to be more active than the other derivatives. One compound possessed two dilutions better antifungal activity than its cyclic analogue, benzoxazole IV, against \( C. \) \textit{albicans}.

Raffa \textit{et al.}\textsuperscript{24} given \( N\)-(1-Phenyl-4-carbetoxypyrazol-5-yl)-, \( N\)-(indazol-3-yl)- and \( N\)-(indazol-5-yl)-2-iodobenzamides (33), with benodanil-like structure, which were synthesized by refluxing in acetic acid the corresponding benzotriazinones with potassium iodide for 1 h in order to study the role on the antifungal activity of the \( N\)-substitution with an aromatic heterocyclic system on benzamide moiety. Among the tested iododerivatives, some of the compounds possessed interesting activities toward some phytopathogenic fungal strains.

\[ \text{Compound (33)} \]

The synthesis of some \( N\)-(o-hydroxyphenyl benzamides and benzacetamides (34a-p), was described by Sener \textit{et al.}\textsuperscript{25} in order to determine their \textit{in vitro} antimicrobial activity against two gram positive bacteria, three gram negative bacteria and the fungus \( C. \) \textit{albicans}. The new compounds were compared with several control drugs. The derivative (34g), 4-amino-\( N\)-(o-hydroxyphenyl) benzamide, was found active at an MIC value of 25 μg/ml against the gram negative microorganism \( K. \) \textit{pneumoniae}. Most of the compounds exhibited antibacterial activity at MIC value of 25 μg/ml against \( P. \) \textit{aureginosa}. For the antifungal activity against \( C. \) \textit{albicans}, compounds (34e), (34h) and (34m) were found more active than the other derivatives (MIC 12.5 μg/ml). The antimicrobial activity of some of these benzamides and phenylacetamide derivatives (34a, 34b, 34f, 34g, 34h and 34k), possible metabolites of benzoxazoles, was also compared with that of the cyclic analogues. Compound (34f) possessed two dilutions better antibacterial activity than its cyclic analogue the benzoxazole derivative against \( C. \) \textit{albicans}, where as it was possessing one dilution better antibacterial activity against \( S. \) \textit{faecalis} and \( K. \) \textit{pneumoniae}. 

---

\textit{Benzamides}
Antidepressant Activity

Although a wide assortment of agents is currently available for the treatment of depression, this disorder remains poorly managed in a large proportion of patients. Study by Dableh et al evaluated the effects of selective antagonists of the tachykinin NK1, NK2 and NK3 receptors in the forced swim test, a commonly used screen for antidepressants. Rats were given CP-96, 345 (2S,3S)-cis-2-(diphenylmethyl)-N-[2-methoxyphenyl]-methyl]-1-azabicyclo [2.2.2] octan-3-amine, SR 48968 (S)-N-methyl-N-[4-(4-acetylamino-4-phenylpiperidino)-2-(3,4-dichlorophenyl)-butyl]benzamide, or SR 142801 (S)-(N)-(1(3-(1-benzoyl-3-(3,4-dichlorophenyl) piperidin-3-yl) propyl-4-phenylpiperidin-4-yl)-N-methylacetamide antagonists of the NK1, NK2 and NK3 receptors, respectively at doses of 2.5, 5 and 10 mg/kg intraperitoneally. The time of immobility during the forced swim test was used as an indicator of antidepressant activity of the antagonists. All antagonists had decreased immobility times.

Miscellaneous

K<sub>ATP</sub> channels are found in different tissues, such as the heart vascular smooth muscle, central neurons and pancreatic beta cells. Activators of K<sub>ATP</sub> channels of smooth muscle (e.g., diazoxide and pinacidil) have been explored as drugs for treatment of cardiovascular diseases. Recently it has been suggested that activators of beta cell K<sub>ATP</sub> channels can be used in the treatment of metabolic diseases through an inhibition of insulin release to induce beta cell rest.

Nielsen et al has been identified 2-(4-methoxyphenoxy)-5-nitro-N-(4-sulfamoylphenyl) benzamides (35-43), its close analogues as a new activator of Kir6.2/SUR/K<sub>ATP</sub> channels of beta cells and inhibit glucose stimulated insulin release.
The NOP (ORL₁, OP₁) receptor is a G protein-coupled receptor closely related to the OP₁, OP₂ and OP₃ opioid receptors but having poor affinity with the opioid peptides. The NOP receptor is widely distributed in both central and peripheral nervous system and it is involved in many physiological effects including nociception, attenuation of anxiety, inhibition of learning and memory, stimulation of food intake, diuresis inhibition of reward pathways in drug addiction, inhibition of tachykinergic bronchoconstriction, hypotension, bradycardia, and inhibition of colonic motility.

A series of 4-amino-2-methylquinoline and 4-aminoquinazoline derivatives (44a-n), including the reference NOP antagonist JTC-801, were synthesized by an alternative pathway and their in vitro pharmacological properties were investigated by Sestili et al. 3-Substitution of the quinoline ring resulted very critical for affinity, so 3-methyl derivative (44c) showed a similar potency compared with reference (44a) while bulky lipophilic or electron withdrawing groups in the same position strongly decreased affinity.
The epidermal growth factor receptor (EGFR) protein tyrosine kinase (PTK) is one of the important kinases that play a fundamental role in signal transduction pathways. EGFR and its ligands (EGF, TGF-α) have been implicated in numerous tumors of epithelial origin and proliferative disorders of the epidermis such as psoriasis. Therefore, the design of inhibitors toward EGFR-PTK is an attractive approach for the development of new therapeutic agents.

The benzamides (45) and the benzamidines (46) as well as the cyclic benzamidines (47) were designed and synthesized by Asano et al. as the mimics of 4-anilino quinazolines for an inhibitor of EGFR tyrosine kinase. The specific inhibitions of v-Src kinase were observed in the benzamides, and the benzamidine, whereas the specific inhibitions of v-Src kinase were observed in the benzanamide and benzamidine at a 10 μg/1ml.

Vasudevan et al. in this report, described their continued quest for an orally active MCHr1 antagonist as an effective treatment for obesity, a series of potent benzamide containing MCHr1 antagonists have been identified. The compound with the best combination of MCHr1 binding affinity and functional activity had good oral...
bioavailability in dog and was evaluated in a DIO mouse model for efficacy. Compound (48) demonstrated sustained moderate efficacy when dosed at 30 mpk q.d in this chronic model of weight loss.

Several potent MCHr1 antagonists based on ortho-amino benzamide and nicotinamide scaffolds exemplified by (49) and (50) have been designed, synthesized, and evaluated for the treatment of obesity by Vasudevan et al. Compounds from both these series exhibit dose-dependent sustained efficacy in an obese murine weight loss model.

Screening efforts by Wrobel et al32 identified (bis) sulfonic acid, (bis) benzamides (51-54) as compounds that interact with the follicle stimulating hormone receptor (FSHR) and inhibit FSH-stimulated cAMP accumulation with IC50 values in the low micromolar range. Structure-activity relationship studies using novel analogues of (51-54) revealed that two phenylsulfonic acid moieties were necessary for activity and that the carbon-carbon double bond of the stilbene sub-series was the optimum spacer connecting these groups.

Selected analogues (52, 53 and 54) were also able to block FSHR-dependent estradiol production in rat primary ovarian granulose cells and progesterone secretion.
in a clonal mouse adrenal Y1 cell line. IC\textsubscript{50} values of these compounds in these assays were in the low micromolar range. Optimization of the benzoic acid side chains of (51-54) led to gains in selectivity versus activity at the thyroid stimulant hormone (TSH) and receptor (TSHR).

![Chemical Structures](image)
Two benzamide derivatives as dopamine D₄ receptor antagonists, YM-50001 (4) and N-[2-[4-(chlorophenyl)piperizin-1-yl]ethyl]-3-methoxybenzamide (55, 56), were labeled by positron-emitter (¹¹C), and their pharmacological specificities to dopamine D₄ receptors were examined by quantitative autoradiography and position emission tomography (PET) by Zhang et al.³³

A number of studies suggested that neurtokinin receptor antagonists especially dual NK₁/NK₂ antagonists, may represent a new treatment option for asthma and other airway diseases, particularly since lung tissue from asthma patients has been shown to over express NK₁ and NK₂ receptors. A study was given by Gerspacher et al³⁴ based on the structure of N-[R(R)-(E)-1-(4-Chlorobenzyl)-3-(2-oxoazepan-3-yl) carbonyl] allyl-N-methyl-3,5-bis (trifluoromethyl) benzamide (57, DNK 333) exhibiting a 5-fold improved affinity to the NK₂ receptor in comparison to (58). Simplification of the structure via elimination of a chiral centre led to 3-[N'-3,5-bis(trifluoromethyl)benzoyl-N-(3,4-dichlorobenzyl)-N'-methylhydrazino]-N-[R-2-oxo-azepan-3-yl]propionamide a potent and fairly balanced NK₁/NK₂ antagonist.
(±)-N-[5-(Diethylamino)-1-phenylpentyl]-4-nitrobenzamide hydrochloride (nibenton, 59) is known as the representative of new class III antiarrhythmic drugs which are highly effective and well tolerated in patients with atrial flutter and fibrillation or supraventricular tachycardia. A series of 1,5-diaminopentane derivatives, structurally related to nibenton, was synthesized and tested for antifibrillatory activity by Davydova et al. Some of the synthesized compounds were found to be more potent than nibenton and possessed a longer duration of action. The antifibrillatory activity of (±)-N-[5-(diethylamino)-1-(4-methoxyphenyl) pentyl]-4-nitrobenzamide hydrochloride was comparable to that of nibenton but exceeded the potency of D-sotalol and sematilide.
References


23. Sener, E. A.; Bingol, K. K.; Arpacl, O. T.; Yalcin, I.; Altanlar, N. Synthesis and Microbiological Activity of some N-(2-Hydroxy-4-Substituted


2.3. TRIAZINES
2.3.1: Introduction

The triazine structure is a heterocyclic ring, analogous to the six membered benzene ring but with three carbons replaced by nitrogens. The three isomers of triazine are distinguished from each other by the positions of their nitrogen atoms and are referred as 1,2,3-triazine, 1,2,4-triazine and 1,3,5-triazine. Other aromatic nitrogen heterocycles are pyridines with 1 ring nitrogen atom, diazines with 2 nitrogen atoms in the ring and tetrazines with 4 ring nitrogen atoms. Triazines are weaker bases than pyridine.

![Triazine structures](image)

The best known 1,3,5-triazine derivative is melamine with three amino substituents used in the manufacture of resins. Another triazine extensively used in resins is benzoguanamine. Triazine compounds are often used as the basis for various herbicides such as 2,4,6-trichloro-1,3,5-triazine or cyanuric chloride. Chlorine substituted triazines are also used as reactive dyes. These compounds react through a chlorine group with hydroxyl groups present in cellulose fibres in nucleophilic substitution, the other triazine positions contain chromophores.

A series of 1,2,4-triazine derivatives known as the BTPs have been considered in the liquid-liquid extraction community as possible extractants for use in the advanced nuclear reprocessing of used fuel. The BTPs are molecules containing a pyridine rings bonded to two 1,2,4-triazin-3-yl groups.

Synthesis

1,2,3-Triazines can be synthesized by thermal rearrangement of 2-azidocyclopropenes. 1,2,4-triazines are prepared from condensation of 1,2-dicarbonyl compounds with amidrazones. A classical triazine synthesis is the Bamberger triazine synthesis. Symmetrical 1,3,5-triazines are prepared by trimerization of cyanogen chloride or cyanamide. Benzoguanamine (with one phenyl and 2 amino substituents) is synthesised from benzonitrile and dicyandiamide in dimethoxyethane with potassium hydroxide.
Reactions

Although triazines are aromatic compounds the resonance energy is much lower than in benzene, and electrophilic aromatic substitution is difficult but nucleophilic aromatic substitution more frequent. 2,4,6-Trichloro-1,3,5-triazine is easily hydrolyzed to cyanuric acid by heating with water at elevated temperatures. 2,4,6-Tris(phenoxy)-1,3,5-triazine reacts with aliphatic amines in aminolysis, and this reaction can be used to give dendrimers. Pyrolysis of melamine under expulsion of ammonia gives the tri-s-triazine melem. Cyanuric chloride assists in the amidation of carboxylic acids.

The 1,2,4-triazines can react with electron rich dienophiles in an inverse electron demand Diels-Alder reaction. This forms a bicyclic intermediate which normally then extrudes out a molecule of nitrogen gas to form an aromatic ring again. In this way the 1,2,4-triazines can be reacted with alkynes or acetylenes to form pyridine rings. An alternative to using an acetylene is to use norbornadiene which can be thought of as a masked acetylene.
2.3.2.: Biological Profile

Substituted s-triazine derivatives are an important class of compounds having anticancer, antitumor, antiviral and antifungal activities. These compounds have been used in the treatment of depression and hence received a considerable therapeutic importance. These are valuable bases for estrogen receptor modulators and also used as bridging agents to synthesize herbicides. Further substituted s-triazines have been used as NLO materials, which have a wide range of applications in optoelectronics and telecommunications. Research on new substances possessing antibacterial activity has considerable attention owing to the continuous increase in bacterial resistance. It has been reported that substituted s-triazine derivatives possess antibacterial activity.

Antimicrobial activity

Srinivas et al. synthesized a series of 2,4,6-trisubstituted s-triazines and evaluated for antibacterial activity. Most of the compounds showed antibacterial activity. Among them (3) exhibited the most significant activity. Whereas (1), (2), (4) and (5) had displayed moderately large activity against both gram positive and gram negative microorganisms. Least activity was observed for triazine with benzylamine derivatives.

\[ R_1 \]
\[ R_2 \]

(1): \( R, R_1, R_2 = \text{Cl} \); (2): \( R, R_1, R_2 = \text{OCH}_3 \)

(3): \( R, R_1, R_2 = \text{H} \)
Dandia et al. synthesized pure fluorinated s-triazine in quantitative yield (96-99%) in 2-3 mins. in aqueous medium under microwaves. The antifungal activity of all synthesized compounds (6a-e) were tested against three pathogenic fungi namely R. solani, F. oxysporum and C. capsici by the position plate technique.

Deeb et al. reported a general method for the preparation of substituted pyridazo-pyrazolotriazines (7). The products were screened for their antimicrobial activity at different applied concentrations against E. coli, P. aeruginosa, S. aureus and also antifungal activity against C. albicans.
Jagmohan et al\(^7\) reported triazine derivatives (8-13) and evaluated for their antibacterial activity against *S. aureus*, *E. coli*, *P. aeruginosa* and the fungus *C. albicans*. All the compounds showed activity against *S. aureus* and may be used for local application in the form of powder or ointment. Further studies indicate the absence of toxicity following local application.

![Chemical structures](8-13)

A series of 3,7-dimethyl-pyrazolo[3,4-\(e\)][1,2,4] triazin-4-yl thiosemicarbazide derivatives were prepared by Singh *et al*\(^8\) and evaluated *in vitro* against HMI:1MSS strain of *E. histolytica* to identify the compounds for antiamoebic activity. They exhibited antiamoebic activity in the range \((\text{IC}_{50} = 0.81-7.31 \mu \text{M})\). The results were compared to the activity of known drug metronidazole. Some compounds were found to be significantly better inhibitors of *E. histolytica* since \(\text{IC}_{50}\) values in the \(\mu \text{M}\) range elicited by these compounds were much lower than metronidazole in *in vitro* studies. Compounds (14) and (15) had shown the most promising antiamoebic activity \((\text{IC}_{50} = 0.81\mu \text{M} \text{ of 11}, \text{IC}_{50} = 0.84 \mu \text{M}) \text{ versus (IC}_{50} = 1.81 \mu \text{M})\) metronidazole. The study
suggests the possibility of developed triazine analogues as potential drug candidates for antiamoebic activity.

![Chemical structures of compounds](image)

(Vzorov et al. screened over 70 related agents, including N-donor aromatic ligands and metal precursors, they had identified a novel class of platinum (II) formulations with 2-pyridyl-1,2,4-triazine (16) derivatives and Pt (II) formulations (17) with these derivatives (Pt. t compounds) as having the highest anti-HIV activity. The maximum activity was observed when the agents were added immediately post-infection. The PtI agents did not block cell fusion activity of HIV-1. The Ptt compounds exhibit low human epithelial cells, and are thus promising candidates for use as microbicides or antiviral agents against HIV.

Kidwai et al. reported the reaction of 2-hydrazino-4-methyl quinoline with diethylxalate and ethylbromoacetate in ethanol under MWI and the cyclized products were 6-methyl-3H-[1,2,4]triazino[4,3-a]quinolin 1,2-dione (18) and 6-methyl 3H-[1,2,4]triazino[4,3-a]quinolin-2-one (19) respectively. The newly synthesized compounds were screened for antifungal activity against fungi A. niger and A. flavous. It was found that compound (18) showed significant antifungal activity (20-22 mm) and compound (19) showed enhanced antifungal activity (22-25 mm) against A. flavous. Salicylic acid was used as standard antifungal agent (13-18 mm).
Tiwari et al.\textsuperscript{11} reported various 2-substituted-1,3,4-thiadiazolo [2,3-c]-1,2,4-triazino [5, 6-b]indoles (20-22) which were synthesized by cyclization of isatin-3-(5-substituted-1,3,4-thiadiazol-2-yl) hydrazones with conc. H$_2$SO$_4$. All the substituted thiadiazoles and triazines possessed antifungal activity against \textit{P. oryzae}, \textit{R. solani}, \textit{P. cubensis} and \textit{P. infestans}.

\begin{align*}
\text{(18,19)}
\end{align*}

\begin{align*}
\text{R} = & \text{H, 2-Cl, 4-Cl, 3-CH$_3$, 2-OH} \\
\text{R} = & \text{4-Cl, 4-CH$_3$, 3-Cl} \\
\text{R} = & \text{4-Cl, 4-CH$_3$, 4-OCH$_3$, 4-NO$_2$}
\end{align*}

\textbf{Antimalarial activity}

The nineteen 2,4,6-trisubstituted-1,3,5-triazines (23a-s) were synthesized as cycloguanil analogues by Agarwal \textit{et al.}\textsuperscript{12} Out of the synthesized compounds eight analogues have shown MIC in the range of 1-2 $\mu$g/mL, 32-64 times more potent than...
cycloguanil. These identified triazines can be new leads in antimalarial chemotherapy. These molecules are very useful for further optimization work in malarial chemotherapy.

\[
\begin{align*}
R & = -N - N - Me \\
& \quad - N - N - C - Ph \\
& \quad - N - N - C - Ph
\end{align*}
\]

(Katiyar et al.\cite{Katiyar})

Katiyar et al.\cite{Katiyar} prepared a series of 22 compounds and screened against \textit{P. falciparum} NF-54 strain. Compounds (24) showed MIC in the range between 1 and 2 \(\mu\)g/ml. These compounds were 32 times more potent than the cycloguanil which was used as the standard drug.

\[
\begin{align*}
R' & = -N - N - Me \\
& \quad - N - N - C - Ph \\
& \quad - N - N - C - Ph
\end{align*}
\]

(Sumaltec et al.\cite{Sumaltec})

Sumaltec et al.\cite{Sumaltec} reported novel analogues of pyrimethamine and cycloguanil (25) and tested as inhibitors of \textit{P. falciparum} dihydro folate reductase. Most of the compounds showed good antimalarial activities against \textit{P. falciparum}.

\[
\begin{align*}
R' & = -N - N - C - Ph \\
& \quad - N - N - C - Ph
\end{align*}
\]

(25)

**Antinociceptive activity**

Synthesis and pharmacological activity of 8-aryl-3,4-diaxo-2\(H\), 8\(H\)-6, 7-dihydroimidazo[2,1-c][1,2,4]triazines (28) was presented by Sztanke et al.\cite{Sztanke} with
relatively low acute toxicity (LD$_{50}$ in range from 1100 to over 2000 mg kg$^{-1}$, intraperitoneally, i.p.), some of them exhibited significant antinociceptive activity as the result of the writhing test indicated. Reversion of the antinociception for some compounds produced in the writhing test by 5 mg kg$^{-1}$ dose of naloxen can suggest an opioid like mechanism of their analgesic activity.

\[ \text{R} = \text{H}, 2-\text{CH}_3; 4-\text{CH}_3; 2, 3\text{-diCH}_3 \\
2-\text{CH}_2\text{O}; 4-\text{CH}_2\text{O}; 2-\text{Cl}, 3-\text{Cl} \\
4-\text{Cl}; 3, 4\text{-diCl} \]

Carboxylic anhydrase inhibitors

Garaj et al\textsuperscript{16} reported a series of benzenesulfonamide derivatives incorporating triazine moieties in their molecules obtained by reaction of cyanuric chloride with sulfonamide, homosulfanilamide, or 4-amino ethylbenzenesulfonamide. The library of sulfonamides incorporating triazinyl moieties was tested for the inhibition of three physiologically relevant carbonic anhydrase (CA, EC 4.2.1.1) isozymes, the cytosolic hCA I, II, the transmembrane and tumor associated hCA IX. These derivatives were interesting candidates for the development of novel unconventional anticancer strategies targeting the hypoxic areas of tumor clear renal cell carcinoma, which is the most lethal urologic malignancy.

Garaj et al\textsuperscript{17} reported a series of aromatic benzesulfonamide (29) derivatives incorporating triazine moieties in their molecules. The library of sulfonamides incorporating triazinyl moieties were tested for the inhibition of three physiologically relevant CA isozyme, the cytosolic hCA I, II, transmembrane and tumor associated hCA IX. The new compounds reported here inhibited hCA I with $K_i$ in the range of 31-8500 nM, hCA II with $K_i$ in the range of 14-765 nM and hCA IX with inhibition constants in the range of 1.0-640 nM. SAR was straightforward and rather simple in this class of CA inhibitors, with the derivatives incorporating compact moieties at the triazine ring (such as amino, hydrazine, ethylamino, dimethylamino or amino acyl) being the most active ones, and the derivatives incorporating such bulky moieties (n-propyl, n-butyl, diethylaminoethyl, piperazinylethyl, pyridoxal amine or phenoxy) being the most ineffective hCA, I, II and IX inhibitors.
Antiproliferative activity

A series of platinum (II) complexes with 6,8-dimethylimidazo [1,5-α]-1,3,5-triazin-4(3H)-one (6,8-diMe-4-0-IMT) (30) and 6,8-dimethyl-2-thioxo-2,3-dihydroimidazole [1,5-α]-1,3,5-triazin-4(1H)-one (6,8-diMe-4-0-2-S-IMT) (31) of formula trans-[PtCl₂(DMSO)] (6,8-diMe-4-O-IMT) and trans-[PtCl₂(dmso)] (6,8-diMe-4-O-2S-IMT) have been prepared and characterized with $^1$H, $^{13}$C, $^{15}$N, $^{195}$Pt NMR and IR by Lakomska et al. Significant $^{15}$NMR upfield coordination shifts (81-96 ppm) of N(7) atom indicate this nitrogen atom as a coordination site. The platinum (31) complexes were tested for their antiproliferative activity in vitro against the cells of four human cell lines: SW 707 rectal adenocarcinoma, A549 non-small cell lung carcinoma, T47D breast cancer and HCV 29 T bladder cancer.

Veronique et al. synthesized four pyrrolo[1,2-d][1,2,4]triazines and four thiazolo[3,4-d][1,2,4]triazines from trans-4-hydroxy-L-proline and L-thiaproline respectively. It was reported that the proliferative response to human lymphocyte mitogen (Phytohemagglutinin) revealed significant immunostimulating activity for all test drugs.

Brzozowski et al. synthesized various novel 2,4-diamino-1,3,5 triazine derivatives and screened for antitumor activities. 2-amino-6-bromomethyl-4-(3,5,5-trimethyl-2-pyrazoline)-1,3,5 triazine showed the most potent antitumor activity with the mean mid point value of log₁₀ GI₁₀, log₁₀ TGI₅₀ and log₁₀ LC₂₀ of all tests equal to -5.26, -4.81 and -4.37 respectively.
Again Brzozowski et al. synthesized and reported antitumor activities of novel 2-amino-4-(3,5,5-trimethyl-2-pyrazolino)-1,3,5-triazine (32) derivatives. All the compounds prepared were screened against tumor cell lines. Triazine exhibited modest or fairly high activity against one or more human tumor cell lines. Compound 2-[2-amino-4-(3,5,5-trimethyl-2-pyrazolino)-1,3,5-triazin-6-yl]-3-[5-nitro-2-thienyl] acrylonitrile was highly potent against some cell lines of leukemia, CNS cancer and breast cancer.

\[ \text{R} = \text{Ph-SO}_2\text{NH}_2 \]

(32)

Patrizia et al. reported pyrrolo [2,1-c][1,2,4] triazines (33a-g). These were directly obtained from the reaction of 2-diazopyrroles with the sodium salts of β dinitriles. Only when the 2-diazopyrroles were coupled with ethylcyanoacetate, it was possible to isolate together with the pyrrolotriazines, the intermediate hydrazones which in turn cyclized to title ring system. Pyrrolotriazines (33a-e) were evaluated for cytotoxic activity against a panel of 60 human cancer cell lines by the national cancer institute. Compounds showed inhibitory effect at $10^{-5}$ M level and in some cases at micromolar concentrations.

\[ \text{R} = \text{CH}_2, \text{C}_6\text{H}_5, \text{CN}, \text{CONH}_2, \text{COOC}_2\text{H}_5, \text{CH}_3, \text{NH}_2 \]

(33a-g)

Miscellaneous

Several efficient synthetic routes for 2-, 4- and 6-aryl-1,2,4-triazine-3, 5-diones were developed by Pontillo et al. Derivatives were synthesized and studied as gonadotropin-releasing hormone antagonist in an effort to understand structure-activity relationships of the monocyclic compounds. The results from these SAR
studies provide further evidence for the role of the 6-methyl group in the uracil, which is important for invoking a conformation that positions two key elements, the 5-phenyl and 1-benzyl groups, for favored interactions with the receptor. The improved potency of this compound (34) was possibly due to an increase in binding interactions of the 6-(2-chloro-3-methoxyphenyl) group with amino acid residue such as Asp-122 on the human GnRH receptor.

\[
\begin{align*}
\text{X} &= \text{CF}_3 \\
\text{Ar} &= 2\text{-Cl-3-MeOC}_6\text{H}_4
\end{align*}
\]

(Banavara et al\textsuperscript{24} reported two new templates, (R) 2-hydroxyethyl-pyridine and (R) 2-hydroxyethyl triazine. These were used to design novel sorbitol dehydrogenase inhibitors (SDIs). The design concept included spawning of these templates to function as effective ligands to the catalytic zinc within the enzyme through incorporation of optimally substituted piperazino-triazine side chains so as to accommodate the active site in the enzyme for efficient bonding. Orally active SDIs penetrate sciatic nerve of chronically diabetic rats. Compound 18 normalized the elevated sciatic nerve fructose by 96% at an oral dose of 10 mg/kg.

A convenient one-pot synthetic route was developed by Guo et al\textsuperscript{25} for the preparation of asymmetric 1,3-dialkyl-1,3,5-triazine-2,4,6-triones from readily available alkyl or aryl isocyanates, primary amines and N-chlorocarbonyl isocyanate in excellent yields. Subsequent alkylation with N-protected amino alcohols afforded the desired 1,3,5-triazine-2,4,6-triones in good yields. This methodology was applied to the synthesis of a chemical library acting as antagonists of the hGnRH receptor.

Leroux et al\textsuperscript{26} synthesized and reported various triazine derivatives. These derivatives showed tracheal smooth muscle relaxant and type 4-phosphodiesterase inhibitory activities. Highly significant correlation was reported between the two effects. Two compounds exhibited potent relaxant activity (EC\textsubscript{50} 17 and 24 mM) and might be useful for the treatment of asthma.
References


2.4. SEMICARBAZONES
2.4.1: Introduction

In organic chemistry, semicarbazone is a derivative of semicarbazide which contains an additional ketone functional group. Their structure is

\[ R_2C = \text{NNH}(=O)\text{NH}_2 \]

The semicarbazone is formed when ammonia related compounds (nucleophiles) such as semicarbazide is added to the carbonyl group, they form imine like derivatives. The conversion of aldehydes and ketones into imine like derivatives is an exothermic and pH dependent reaction (Fig. 1).

\[
\begin{align*}
R'\text{C}=\text{O} + \text{NH}_2\text{NHCONH}_2 & \xrightarrow{\text{H}^+} R'\text{C-NHNHCONH}_2 \\
& \xrightarrow{\text{OH}} \text{(Intermediate)} \\
& \text{R'-C-NHNHCONH}_2 + \text{H}_2\text{O} \\
\end{align*}
\]

(Fig. 1)

Recently semicarbazones have attracted attention as novel agents. From the study of structures of clinically established drugs, it can be concluded that the anticonvulsant properties have been displayed by various hydrazones (\(-\text{N-NH}\)-), amide (\(-\text{CONH}_2\)-) and carbamides (\(-\text{NHCONH}\)-). The prime need was to search for a molecule, which could complement in its structure. The events leading to the development of the semicarbazones as promising lead are indicated below.
2.4.2: Biological Profile

Anticonvulsant activity

A number of 4-bromophenyl semicabazones were synthesized and evaluated for anticonvulsant and sedative hypnentic activities by Pandeya et al.\textsuperscript{1} All the compounds showed anticonvulsant activity in one or more test models. Compounds (1, 2) showed greatest activity, being active in all the screens with very low neurotoxicity and no sedative hypnotic activity. Two compounds (3, 4) showed greater protection than sodium valporate. The essential structural features responsible for interaction with receptor site are established within a suggested pharmacophore.

\[
\begin{array}{c}
R = CH_3; R_1 = R_2 = R_3 = H \\
R = C_6H_5; R_1 = R_2 = R_3 = H \\
\end{array}
\]

(1, 2)

\[
\begin{array}{c}
R = R_1 = CH_3 \\
R = H; R_1 = piperanyl \\
\end{array}
\]

(3, 4)

Pandeya et al\textsuperscript{2} synthesized a series of thioureido derivatives of acetophenone semicarbazone and evaluated for anticonvulsant activity. The compound (5) was the most active compound in the series with a dose of 30 mg/kg\textsuperscript{-1} and ED\textsubscript{50} = 23.5 mg/kg\textsuperscript{-1} and equipotent to phenytoin ED\textsubscript{50} = 23.2 mg/kg\textsuperscript{-1}. The toxicity of the compounds was assessed by determination of their approximated TD\textsubscript{50} and LD\textsubscript{50} values in order to have a better assessment of their pharmacological profile and protective index.

\[
\begin{array}{c}
H_2C-N \sim N \sim S \\
H_2C-N \sim N \sim S \\
\end{array}
\]

(5)

Various 2,4-dimethoxyphenyl semicarbazones were synthesized by Thirumurugan et al\textsuperscript{3} starting from 2,4-dimethoxyaniline via a phenylcarbamate intermediate. The anticonvulsant activity of the synthesized compounds was
established after intraperitoneal administration in three seizure models in mice which include maximal electroshock seizure, subcutaneous pentylenetetrazole, and subcutaneous strychnine induced seizure screens. Nine compounds exhibited protection in all the three seizure models, and \( N'-(2,4\text{-dimethoxyphenyl})-N''-(\text{propan}-2\text{-one}) \) semicarbazone (6) emerged as the most active compound with no neurotoxicity.

\[
\text{MeO-} \quad \text{O} \quad \text{H} \quad \text{N} \quad \text{N} \quad \text{H} \quad \text{CH}_3
\]

\( (6) \)

A series of 4-sulphamoylphenyl semicarbazone derivatives were prepared by Yogeeswari et al\(^4\) starting from sulphanilamide and screened for anticonvulsant activity. Compounds with substituted acetophenone (7, 8) showed good activity in rat oral MES screen. Seven compounds exhibited anticonvulsant activity greater than sodium valproate. Among the new derivatives evaluated, one compound emerged as the most active compound as indicated by its protection in MES and scSTY screens and with low neurotoxicity. Seven compounds possessed sedative hypnotic activity.

\[
\begin{align*}
\text{R}_1 & \quad \text{R}_2 \\
\text{R} & = \text{H, CH}_3; \quad \text{R}_1 = \text{H, OCH}_3; \\
\text{R}_2 & = \text{H, OH, NO}_2; \\
\text{R}_3 & = \text{H, N(CH}_3)_2, \text{OCH}_3, \text{OH, CH}_3, \text{NO}_2, \text{NH}_2
\end{align*}
\]

(7)

Yogeeswari et al\(^5\) prepared the phenyl (thio) semicarbazide derivatives of phthalimido pharmacophore and evaluated for their anticonvulsant and neurotoxic properties. Compound (18c) afforded protection in MES, scPTZ and scSTY induced seizure threshold tests in mice. Except some compounds all compounds showed no neurotoxicity up to 300 mg/kg. Compound (9a), (9b), (10c), (10d), (10g) and (10i)
were found to show oral MES activity. The compound exhibited CNS depression and behavioral despair side effects, lesser than the conventional antiepileptic drugs.

\[
\begin{align*}
\text{X} &= \text{O, S;} \\
\text{R} &= 2-\text{Cl, 4-Cl, 4-NO}_2, 4-\text{OCH}_3, 4-\text{SO}_2\text{H, 4-NHCOCH}_3, \\
&\quad 4-\text{N=N-Ph, 4-OH, 4-COOH, 4-COOEt, 4-SO}_2\text{NH}_2
\end{align*}
\]

(9a-b) (10a-i)

A 1:1 inclusion compound of benzaldehyde semicarbazone (BS) (11) and hydroxypropyl-\(\beta\)-cyclodextrin (HP-\(\beta\)-CD) was prepared by Beraldo et al. The anticonvulsant activities of the free semicarbazone and of the inclusion compound were evaluated in rats using the MES and audiogenic screenings. In both tests the minimum dose of compound necessary to produce activity decreases from 100 mg/kg for the free semicarbazone to 35 mg/kg for the inclusion compound, indicating a significant increase in the bioavailability of the drug.

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

(11)

Yogeewari et al synthesized a series of 3-chloro-2-methylphenyl semicarbazones (12, 13, 14) and evaluated and CNS activities. The aryl urea and the semicarbazide showed anticonvulsant activity in the MES and scPTZ screens with acute neurotoxicity, whereas the semicarbazones derivatives showed good anticonvulsant potency in scPTZ screen with moderate activity against MES and scPTZ screens.

\[
\begin{align*}
\text{R} &= \text{H, Br, Cl, F, CH}_3
\end{align*}
\]

(12)
Various acetylhyclrazones, oxamoylhydrazones and semicarbazones were prepared as candidate anticonvulsants with a view to examining the viability of a putative binding site hypothesis by Dimmock et al. The biological results obtained revealed that in general the acetylhyclrazones and semicarbazones afforded good protection against convulsions while the oxamoylhydrazones were significantly less active. These data suggest that terminal electron donating groups enhanced the hydrogen bonding capabilities and anticonvulsant properties of these molecules.

A number of aryl, arylidene and aryloxyaryl semicarbazones were evaluated as candidate anticonvulsants by Puthucode et al. The greatest activity was displayed by a series of aryloxyaryl semicarbazones (15) which had oral activity in the MES screen substantially greater than phenytoin and with protection indices of over 100.

A series of 4-ethoxyphenyl semicarbazones (16-25) have been synthesized by Yogeeswari et al using an appropriate synthetic route and characterized by elemental analyses and spectral data. The anticonvulsant activity of all the synthesized compounds was evaluated against maximal electroshock induced seizures (MES) and subcutaneous pentylenetetrazole (scPTZ) induced seizure models in mice. The neurotoxicity was tested using the rotarod method. Among the tested compounds, except some compound all the compounds showed protection from seizures in both the...
animal models. Compounds (21) and (23) were found to increase γ-aminobutyric acid (GABA) levels in the medulla oblongata region of the rat brain.

\[
\begin{align*}
\text{R} & = \text{H, CH}_3, 4-\text{Cl} \\
\text{R}_1 & = 2-\text{Cl, 2-OH,4-CH}_3, 4-\text{OCH}_3
\end{align*}
\]

(16-22)

\[
\begin{align*}
\text{R} & = \text{CH}_3 \\
\text{R}_1 & = \text{CH}_2\text{COCH}_3, \text{CH}_2\text{CH(CH}_3)_2
\end{align*}
\]

(23-25)

Ten semicarbazone and nine thiosemicarbazone 1,3-dithiolanes (26) (α, β and γ) were prepared and tested as radioprotector agents by Taroua et al.\(^{11}\) The potential anticonvulsant activities of these compounds, since benzodiazepines have been observed to greatly decrease radioinduced convulsions. Among the tested compounds, the correlation between the anticonvulsant activity and radioprotective effect was not systematic.

\[
\begin{align*}
\text{X} & = \text{O, S} \\
\text{R} & = \text{CH}_3; \text{R}_1 = \text{CH}_3, \text{C}_2\text{H}_5, \text{i-Pr} \\
\text{R}_2 & = \text{H, C}_2\text{H}_5, \text{CH}_3
\end{align*}
\]

(26)

A number of aryl alicyclic ketones converted to their corresponding semicarbazones, thiosemicarbazones and bis-carbohydrazones by Dimmock et al.\(^{12}\) Anticonvulsant activity was displayed by most of the compounds in the maximal electroshock (MES) and subcutaneous pentylentetrazole (scPTZ) screens when given intraperitoneally to mice. However, on oral administration to rats, a marked selective activity in the MES screen only was noted. X-ray crystallography on five semicarbazones was undertaken in order to find correlations between the shapes of these molecules and anticonvulsant properties. The thiosemicarbazones displayed greater cytotoxicity to P388D1 and L1210 cells than the semicarbazones while a number of human tumors and different viruses were, in general, insensitive to representative compounds (27, 28).
Anticancer activity

Ni (II) complexes of ortho-napthaquinone thiosemicarbazone and semicarbazone were synthesized and spectroscopically characterized by Afrasai et al. The X-ray crystal structure of both the complexes describe a distorted octahedral coordination with two tridentate mono-deprotonated ligands. In vitro anticancer studies on MCF-7 human breast cancer cells reveal that the semicarbazone derivative along with its nickel complex is more active in the inhibition of cell proliferation than the thiosemicarbazone analogue (29).

A new semicarbazone derivative of curcumin (RSC) was synthesized and examined by Dutta et al for its antioxidant, antiproliferative, and antiradical activity and compared with those of curcumin (CR) (30). The antioxidant activity was tested by their ability to inhibit radiation induced lipid peroxidation in rat liver microsomes. The antiproliferative activity was tested by studying the in vitro activity of CRSC against estrogen dependent breast cancer cell lines MCF-7. Kinetics of reaction of (2,2'-diphenyl-1-picrylhydrazide) DPPH, a stable hydrogen abstracting free radical was studied to measure the antiradical activity using stopped flow spectrophotometer. Finally one electron oxidized radicals of CRSC were generated and characterized by pulse radiolysis. The results suggest that the probable site of attack for CRSC shows
efficient antioxidant and antiproliferative activity although its antiradical activity is less than that of CR.

As a contribution to the development of novel vanadium complexes with pharmacologically interesting moieties, new dioxovanadium (V) semicarbazone complexes with the formula cis-VO₂L, where L = 5-bromosalicylaldehyde semicarbazone and 2-hydroxy-naphthalen-1-carboxaldehyde semicarbazone have been synthesized by Noblia et al. Results were compared with those previously reported for other three analogues complexes of this series. The five complexes were tested in three different human tumor cell lines for bioactivity as potential antitumor agents, showing selective cytotoxicity on TK-10 cell line. Results showed that structural modifications on the semicarbazone moiety could have a significant effect on the antitumor activity of the vanadium complexes.

Antimicrobial activity

During the course of Sriram et al. work on the synthesis and screening of new drugs for tuberculosis, they have identified N1-(4-acetamido phenyl)-N4-(2-nitrobenzylidene) semicarbazone (32), which inhibited in vitro M. tuberculosis H₃₇ Rv; 100% inhibition at 1.56 μ/mL. This paper was first of its kind in which aryl semicarbazones are reported to possess antimycobacterials potency greater than p-aminosalicylic acid, ethionamide, ethambutol, ciprofloxacin and kanamycin.

\[ R = 4-\text{NHCOCH}_3; \]
\[ R_1 = 3-\text{NO}_2 \]
The thioureido derivative of 4-aminoacetophenone aryl semicarbazone have been prepared by Mishra et al.\(^7\) These derivatives have been characterized on the basis of different physicochemical evidences. The anti-HIV-1 (HTLV-III\(_B\)) and HIV-2 (ROD) activity and cytotoxicity of the compounds were tested. The compound (33) and (34) showed maximum protection among the series.

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{N} \quad \text{N} \\
\text{R} & = \text{R}_1 = p-\text{CH}_3 \\
\text{R} & = p-\text{CH}_3; \text{R}_1 = \text{OCH}_3
\end{align*}
\]

(33, 34)

Several novel semicarbazone derivatives were prepared by Cerecetto et al.\(^8\) from 5-nitro-2-furaldehyde or 5-nitrothiophene-2-carboxaldehyde, and tested \textit{in vitro} as potential antitrypanosomal agents. The compounds were prepared in good to excellent yields in 2-3 steps from readily available starting materials. Some derivatives (35) were found to be active against \textit{T. cruzi} with an activity similar to that of niturrimox.

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{N} \quad \text{N} \\
\text{R} & = \text{R}_1 = p-\text{CH}_3 \\
\text{R} & = p-\text{CH}_3; \text{R}_1 = \text{OCH}_3
\end{align*}
\]

(35)

Several novel semicarbazone derivatives were prepared from 5-nitro-2-furaldehyde or 5-nitrothiophene-2-carboxaldehyde and semicarbazides bearing a spermidine mimetic moiety by Cerecetto et al.\(^9\) These compounds were tested \textit{in vitro} as potential antitrypanosomal agents and some of them, together with the parent compounds, 5-nitro-2-furaldehyde and 5-nitrothiophene-2-carboxaldehyde semicarbazone derivatives, were also evaluated \textit{in vivo} using infected mice. Two of the compounds (36, 37) displayed the highest \textit{in vivo} activity. A correlation was found between lipophilic hydrophilic properties and trypanocidal activity, high \(R_m\) values being associated with low \textit{in vivo} effects.
To investigate the relationship between antimicrobial activities and the molecular structures of nickel (II) complexes with thiosemicarbazone and semicarbazone ligands, nickel (II) complexes with ligands Hmtsc (38), Htse (39), and H₂ dtmst (40), were prepared and characterized by Kasuaga et al. Their antimicrobial activities were evaluated by the MIC against four bacteria (B. subtilis, S. aureus, E. coli and P. aeruginosa), two yeasts (C. albicans and S. cerevisiae) and two molds (A. niger and P. citrimum). The 4-coordinate, diamagnetic nickel (II) complexes showed antimicrobial activities which were different from those of free ligands or the starting nickel (II) compounds. [Ni(mtsc)(Oac)] showed selective and effective antimicrobial activities against two gram positive bacteria (B. subtilis and S. aureus) and modest activities against a yeast (S. cerevisiae). [Ni(alsc)(Oac)] exhibited moderate activities against a gram positive bacterium (S. aureus) and [Ni(atsc)(Oac)] showed modest activities against gram positive bacteria (B. subtilis and S. aureus).

\[
\begin{align*}
\text{Y} &= \text{butylamino}, \ X = O \\
\text{Y} &= 2\text{-methoxycetylamino}
\end{align*}
\]

The structures of the ligands are shown below:

- **(36, 37)**

\[
\begin{align*}
\text{(38)} & \\
\text{(39)} & \\
\text{(40)}
\end{align*}
\]
Miscellaneous activities

The synthesis and the evaluation of the monoamine oxidase A and B inhibitory activities of 21 new substituted acyl hydrazones (41) of various aromatic aldehydes and 4-(benzyloxy)acetophenone, and four substituted semicarbazones of benzaldehyde and 4-(benzyloxy)benzaldehyde, are described by Bernard et al.\textsuperscript{21} The 4-(benzyloxy)phenyl group contributing to a high lipophilicity led to the most active compounds one of these, compound (IC\textsubscript{50} = 3 nM, MAO A/MAO B selectivity. 33000), found to act as a reversible and probably tight binding inhibitor. The studied acyclic hydrazones and semicarbazones are structurally related to other reversible and potent inhibitors e.g. heterocyclic compounds such as 1,3,4-oxadiazol-2 (3H)-one derivatives in which hydrazono group is intra cyclic. Some of the new inhibitors might find use in the symptomatic treatment of neurode generative processes.

\[
\text{Ar-CH=NN-N,}_{R_6}^{(CH_3)_2} \quad \text{Ar = C}_6\text{H}_5, \quad R_4 = \text{CN, OH}
\]
\[
\text{R}_6 = \text{COOEt, COMe, CONHMe}
\]

(41)

The physicochemical properties of some 5-nitro-2-furaldehyde semicarbazones (42) (nitrofurazones) and thiophene analogues were compared with their in vitro and in vivo trypanocidal activity against T. cruzi (Tulahuen strain) by Merino et al.\textsuperscript{22} T. cruzi is the etiologic agent of chagas disease.

\[
\text{X = O, S; R = H}
\]
\[
\text{R' = -CH}_3\text{CH}_2\text{OH, -CH}_3\text{CH}_2\text{OCH}_3, -\text{CH}_2\text{CH}_2\text{Ph}
\]

(42)
References


Chapter-2 Literature Review


2.5. AZETIDINONES
2.5.1: Introduction

The β-lactams are 4-membered cyclic amides derived from 3-aminopropanoic acids. Though the first member synthesized by Staudinger in 1907, the β-lactams as a class acquired importance since the discovery of penicillin which contains β-lactams unit as an essential structural feature of its molecule. In the late 1990s, several groups reported novel methodologies for the synthesis of azetidinones of potential biological activities by applying known methods. 1-13

In the literature, monocyclic β-lactams are usually referred to as azetidin-2-ones or 2-oxoazetidine, based on the nomenclature of the parent heterocycle, azetidine. However, the trivial names “penam” for the fused β-lactam (1a) and “cepham” for the bicyclic system (2a) are also used. Similarly, the term α-penam, α-cepham, azepenam and azacepham were coined for the bicyclic β-lactams (1b), (2b), (1c) and (2c) respectively. This trivial system of nomenclature is inadequate, especially in the case of fused β-lactams having no bridge head nitrogen atom, and in those having no heteroatom at position 1 or alterations in the positions of the hetero atom of the non-β-lactam ring. This discrepancy can be removed by adopting a new system in which fused β-lactams (3) and (4) may be called “Alkanam” and “isoalkanam” respectively. Thus, β-lactams containing 7, 8 and 9 atoms in the bicyclic system (3) may be given generic names, heptanam, octanam, nonanam and so on, using the corresponding latin roots. The numbering system in (1d) and (2d) is in conformity with the conventional penam will be termed as 1-thiaheptanam, and cepham as 1-thiaoctanam according to this system. Similarly, the fused β-lactams of the type (4) may be termed as isohextanam, isooctanam, isononanam and so on, depending on the number of atoms in the bicyclic system. The numbering of ring atoms in this case may be the one used for azetidin-2-ones, and is shown in (5).
A bicyclic β-lactam containing a double bond in the ring system may be given the corresponding generic name derived from the collective name "Alkenam" or "Isoalkenam" depending on the mode of fusion of the rings. For stereo description of the molecule, the terms "α" and "β" denoting the configuration of the substituents, which may be below or above the plane of the β-lactam ring, may be used as in case of steroids.

Reactions and Properties of β-lactams

Cleavage of the β-lactam bond:

The β-lactam bond undergoes rupture in the presence of an alkali, acid and β-lactamase, yielding 3-aminopropanoic acids. By selective degradation the natural β-lactams could afford useful amino acids.

In the presence of dry hydrogen chloride, a β-amino acid hydrochloride is generated. For example, the compound (6) gave (7) on treatment with hydrogen chloride in methylene chloride. Similarly, the β-lactam may be cleaved by imines.

Cleavage of the 2, 3-bond in azetidin-2-ones:

1-Haloazetidin-2-ones (8) undergo photolytic cleavage to give isocyanates (9) capable of undergoing secondary cyclisation under suitable conditions. Similarly, 3-azidoazetidin-2-one (10) on refluxing in diglyme, underwent ring expansion through 2, 3-bond cleavage.
Cleavage of 5,6-bond in penicillin:

Rearrangement of penicillin to penilloic acid (11) involves cleavage of 5,6-bond. Similar bond cleavage was observed in penicillin-1-oxide.\textsuperscript{16}

\[
\text{R,C()HN}
\]

Cleavage of the 1,4-bond in azetidin-2-ones and collapse of the bridge in bicyclic $\beta$-lactams:

$\beta$-lactams bearing a C-4 hetero atom are unstable and easily undergo 1,4-bond cleavage.\textsuperscript{17} For example, the 4-mercaptoazetidin-2-one (12) changes to isothiazolinone (13) in 40\% yield, on treatment with dimethylsulfoxide.

\[
\text{SH}_{\text{R},1}
\]

Fragmentation of $\beta$-lactams:

Monocyclic $\beta$-lactams on photolysis or thermolysis break up into ketenes and imines or alkenes and isocyanates, depending on the substituents present in the
molecule and which ever fragmentation is energetically profitable. This process is essentially a case of retrocycloaddition. Reagent induced fragmentation leads to diverse products, depending on the substituents and reagents used.

Fragmentation of penicillin and cephalosporin occurred on treatment with trifluoroacetic acid, the fragments being amido ketenes, and $\Delta^2$-thiazoline and $\Delta^2$-1,3-thiazine derivatives respectively. Sometimes the fragment formed as primary products may undergo secondary reactions. For example, $\beta$-lactam (14) on retro Michael reaction, gave (15) and subsequently (16) and (17).

\[
\text{H}_2\text{C}_6\text{O} \begin{array}{c} \text{S} \text{CH}_2\text{CH}_2\text{CO}_2\text{Me} \end{array} \xrightarrow{\text{Ph, C=C=O}} \text{H}_2\text{C}_6\text{O} \begin{array}{c} \text{S} \text{Ph} \end{array} \begin{array}{c} \text{CO}_2\text{Me} \end{array} + \begin{array}{c} \text{CH}_2=\text{C}\text{HCO}_2\text{Me} \end{array}
\]

(14) \hspace{1cm} (15)

\[
\begin{array}{c} \text{C}_6\text{H}_6\text{N} \end{array} \text{S} \begin{array}{c} \text{N} \end{array} \begin{array}{c} \text{O} \end{array} \begin{array}{c} \text{CO}_2\text{Me} \end{array} + \begin{array}{c} \text{C}_6\text{H}_5\text{N} \end{array} \text{S} \begin{array}{c} \text{N} \end{array} \begin{array}{c} \text{O} \end{array}
\]

(16) \hspace{1cm} (17)

Enzyme catalyzed fragmentation of benzylpenicillin was reported. It is noteworthy that the azido group in $\beta$-lactam (18a) on reduction with Adam's catalyst and subsequent acylation with phenoxyacetyl chloride and triethylamine afforded the 6-phenoxy compound (18c). Such an unusual result may be explained only on the assumption that the 6-amino compound (18b) undergoes fragmentation and generates a $\Delta^2$-thiazoline, which then reacts with phenoxyacetyl chloride and triethylamine in the usual way.

\[
\begin{array}{c} \text{R = H, Me; Z = N}_3, \text{NH}_2, \text{OC}_6\text{H}_3 \end{array}
\]

(18a-c)
2.5.1: Biological Profile

Antimicrobial activity

Azetidine and their derivatives have been extensively explored for their applications in the field of medicine. Likewise, azetidin-2-ones are of great importance because of β-lactam derivatives as an antibacterial agent. Recently, incorporation of these compounds have witnessed a great upsurge in the treatment of tuberculosis and other chemotherapeutic diseases. Sharma et al. reported synthesis and antibacterial activity of some N-sulphonamoylphenylamino-3-chloro-4-phenylazetidin-2-ones. Most of the compounds exhibited significant antibacterial activity. Compound 1-[4-(5,6-dimethoxypyrimidinosulphonamoyl)phenylamino]-3-chloro-4-phenylazetidin-2-one (19) has been found to be more potent than standard drug against E. coli.

\[
\text{RNHSO}_2\text{-N-N-Cl} \quad R = 4,5\text{-dimethoxypyrimidyl}
\]

(19)

A series of 1-[5-(N\text{\textsuperscript{10}}-phenothiazinomethyl)-1,3,4-thiadiazol-2-yl]-4-substituted-2-azetidinones as antifungal agents have been reported by Rawat et al. All the compounds were screened for their antifungal activity against the fungi C. albicans, R. oryzae and C. pannical. The fungicidal data indicated that all the compounds were moderately to highly toxic. The toxicity of compounds depends upon the nature and position of the substituents at the aryl moiety. Compound (20) displayed promising antifungal activity.

Shah et al. synthesized azetidinones (21) from hydrazine thieno [3,2-\text{\textit{d}}] pyrimidines as potential antimicrobial agents. All the products have been evaluated for
their \textit{in vitro} growth inhibitory activity against several microbes like \textit{B. megatilis}, \textit{B. subtilis}, \textit{E. coli}, \textit{A. aerogens} and \textit{A. awamori}. Most of the compounds exhibited maximum activity in the range of 21-27 mm against \textit{A. aerogens}. Other compounds showed either moderate or less activity against these organisms. None of the compounds synthesized was found to exhibit significant activity against \textit{B. subtilis}.

\begin{equation}
\text{R} = \text{H, CH}_3
\end{equation}

Parmar \textit{et al.}\textsuperscript{24} reported synthesis of azetidinones from hydrazinopyrimidine as potential antimicrobial agents. All the products were evaluated for their \textit{in vitro} growth inhibitory activity against several microbes like \textit{B. megaterium}, \textit{B. subtilis}, \textit{E. coli}, \textit{P. fluorescens} and \textit{A. awamori}. All the compounds exhibited mild to moderate antimicrobial activity against all microorganisms except (22) which exhibited promising activity with ampicillin and chloramphenicol against \textit{P. fluorescens}. Antimicrobial activity of azetidin-2-ones has also been reported by various authors.\textsuperscript{25-28}

\begin{equation}
\text{R} = \text{aryl/substitutedaryl group}
\end{equation}

\textbf{Antitubercular activity}

Synthesis and antitubercular activity of 1,3,4-trisubstituted-azetidin-2-ones (23) has been reported by Parikh \textit{et al.}\textsuperscript{29} The representative compounds were tested \textit{in vitro} for their antitubercular activity against \textit{M. tuberculosis} \textit{H37Rv}. The data were compared with standard drug rifampin. All the compounds showed moderate antitubercular activity against \textit{M. tuberculosis}. 

\textit{-110-}

\textit{Azetidinones}
Patel et al. have reported synthesis and antitubercular activity of 2-[4-(4-substitutedphenyl)-3-chloro-2-azetidinon-1-yl]-4-[2-(4-chlorobenzene sulphonamido)-phenyl] thiazoles (24). Primary screening of the compounds for antitubercular activity was conducted at 12.5 mcg/ml against M. tuberculosis H37Rv. Compounds demonstrating at least 99% inhibition in the primary screening were tested at lower concentrations against this microorganism to determine actual minimum inhibitory concentration. The antitubercular activity data showed that most of the azetidinone derivatives exhibited 100% inhibition in the primary screen at 12.5 mcg/ml concentration.

Vashi et al. have reported synthesis and antitubercular activity of 2-azetidinones bearing thymol moiety. The products displayed moderate to good tuberculostatic activity. Synthesis and antitubercular activity of 2-(4-aryl-3-chloro-2-azetidinon-1-yl-amino)-6-(4-chlorophenyl)-5-cyano-3-N-methyl-3,4-dihydropyrimidin-4-ones is reported by Modha et al. All the products displayed mild to moderate antitubercular activity against M. tuberculosis. Compound (25) was the most active member of this series.
Several 1-[5-(carbazolymethyl)-1,3,4-thiadiazol-2-yl]-4-(substitutedphenyl)-3-chloro-2-oxo-azetidines have been synthesized and evaluated for their antiinflammatory activity by Srivastava et al.\textsuperscript{32} All the compounds displayed mild to moderate antiinflammatory activity except compound (26) that showed antiinflammatory activity that was comparable to standard drug phenylbutazone.

Many 1-[5-(\textalpha\textsuperscript{10},2-chloro phenothiazino methyl)-1,3,4-thiadiazol-2-yl]-4-(substituted phenyl)-3-chloro-2-oxoazetidines have been synthesized and evaluated for their antiinflammatory activity by Srivastava et al.\textsuperscript{33} All the compounds tested for antiinflammatory activity exhibited mild to moderate activity. The compound (27) was the most potent and active member of this series. It displayed comparable antiinflammatory activity but lesser than the standard phenylbutazone.
Miscellaneous activities

Use of strain therapy is a key first line approach in preventing coronary heart disease events and stroke in people at increased risk of developing complications. Ezetimibe the first licensed azetidinone drug, is being promoted as an adjunct to strain therapy to achieve greater reduction in blood cholesterol concentrations than occur with a strain alone. Many workers have also reported azetidinones as cholesterol absorption inhibitors, antiviral agents, anticancer agents and human tryptase inhibitors.
References


Synthesis of Type II B-Turn Surrogate Dipeptides Based on Syn-α,β-Dialkyl-β-Lactams. *Org. Lett.* 2004, 6, 4443-4446.


42. Sun, L.; Vasilevich, N. I.; Fuselier, J. A.; Hocart, S. J.; Coy, D. H. Examination of the 1,4-Disubstituted Azetidinone Ring System as a Template for Azetidinones


2.6. THIADIAZOLES
Chapter-2

2.6.1: Introduction

The thiadiazole system contains the following members, the 1,2,3 thiadiazole (a) and then benzoderivatives (b), the 1,2,4 thiadiazoles (c), the 1,3,4-thiadiazoles (d), and the benzoderivatives (e), and then 1,2,5-thiadiazoles (f).

\[ \text{(a)} \]
\[ \text{(b)} \]
\[ \text{(c)} \]

1,3,4-thiadiazoles were first described in 1882 by Fischer and further developed by Bush and his co-workers. The advent of safer drugs and the discovery of mesoionic compounds greatly accelerated the rate of progress in the field of thiadiazoles.

Thiadiazoles carrying mercapto, hydroxyl, and amino substituents can exist in many tautomeric forms and this property is intensively studied using modern instrumental technique for example \(^1\)H NMR, combined spectroscopic methods, mass spectroscopy etc.

Possible structures of 1,3,4-thiadiazoles

The 1,3,4-thiadiazoles are conveniently divided into three subclasses.

1. Aromatic systems which include the neutral thiadiazoles (d) and constituted a major part of this research.

2. Mesoionic systems (j) which are defined as five membered heterocycles which are not covalent or polar and possess a sextet of electrons in association with the five atoms comprising the ring.

3. Non aromatic systems such as the 1,3,4-thiadiazolines (g),(h) and the tetrahydro 1,3,4-thiadiazolidines (i). In partially reduced systems, the position of the double bond is denoted by the prefix t, with (g) being as 1,3,4-thiadiazoles.
Thermodynamic aspects of 1,3,4-thiadiazoles

i) Melting and boiling points: 1,3,4-thiadiazole melt at 43°C while 2-methyl homologue melts with decomposition at 21°C. 2-Amino 1,3,4-thiadiazole has a melting point of 193°C and the 2-aminomethyl homologue melts at 165°C, 2-amino-5-methyl-1,3,4-thiadiazole melts at 224°C with decomposition.

ii) Solubility: 1,3,4-thiadiazole, as well as the following derivatives are soluble in water; 2-amino, 2,5-dimethyl, 2,5-diethyl, 2-methylamine and 2-aminomethyl -5-methyl, etc. Generally as the substituents in the 2- and 5-position increases the size, water solubility decreases, while solubility in organic solvent increases.

iii) Chromatography: 1,3,4-thiadiazole, like most other organic molecules have been extensively chromatographed on silica gel, using a variety of solvents.

iv) Thermochemistry: The combined transitional rotational and vibrational contribution to the molar heat capacity, heat content, free energy and entropy for 1,3,4-thiadiazoles are available between 50 and 2000 k. They are derived from the principal moments of inertia and the vapour phase, fundamental vibration frequency.

v) Aromaticity: The aromatic character of 1,3,4-thiadiazole can be demonstrated with the aid of microwave spectroscopy. Using the differences between the measured bond lengths and covalent radii, aromaticity as shown by π-electron delocalization, diminishes in the order 1,2,5-thiadiazole > thiophene > 1,3,4-thiadiazole > 1,2,5-oxadiazole.

vi) Tautomerism: 1,3,4-thiadiazole ring system with three heteroatoms does not exhibit tautomerism in its fully conjugated form. However certain substituents are present, tautomerism is possible.

vii) Reactivity: Some of the characteristic reactions of the 1,3,4-thiadiazole nucleus are ring opening by strong base, ease of nucleophilic attack and the formation of mesoionic compound by quaternization. The substituents in the 2- and 5-
positions have a large effect in determining the reactivity of the molecule as a whole. Thus the ambient nucleophilicity of 2-amino-thiadiazole gives rise to electrophilic attack on both the amino group and the nuclear nitrogen atom.

Ring formation of these two nitrogen atoms is also a common reaction. Nucleophiles easily displace nitrogen atoms from the thiadiazole nucleus. This is due to the electronegativity of the two nuclear nitrogen atoms which imparts a low electron density to the carbon atom of the nucleus.

Pharmacological aspect of 1,3,4-thiadiazoles

1,3,4-thiadiazol, the heterocyclic nucleus is a versatile pharmacophore which exhibits a wide variety of biological activities. A few of them, which are worth mentioning are diuretic, CNS depressants, hypoglycemic and antiinflammatory. The anticonvulsant activity has been reported frequently in the literature.
2.6.2: Biological Profile

A highly appreciable number of compounds obtained by laboratory synthesis have turned out to be potential chemotherapeutic and pharmacotherapeutic agents. Various useful synthetic analogues with improved therapeutic properties can be obtained from single lead compound by structural modification. The same applies to the group of 1,3,4-thiadiazoles which have broad spectrum of biological activity. A survey of literature revealed that 1,3,4-thiadiazole derivatives have been reported to have different types of biological activities.

Antibacterial activity

Decade of antibiotic use have resulted in the development of wide spread resistance to commonly prescribed antibacterial agents. Nosocomial infection by methicillin resistant *S. aureus* (MRSA) and vancomycin resistant enterococcus (VRE) are particularly serious problems. Recently a glycopeptides intermediate *S. aureus* (GISA) isolate with reduced susceptibility to vancomycin would be especially devastating. Within the community, penicillin and cephalosporin resistant *S. pneumonia* (PRSP) has become an increasing problem. In view of the increased resistance of gram positive bacteria to currently available antibacterial agents, there is an urgent need for new antibacterial agents.

1,3,4-thiadiazoles are the drugs of choice or alternates for a few other types of infections by virtue of toxophoric -N=C-S grouping. The advent of sulfur drugs and the later discovery of mesoionic compound and greatly accelerated the rate of progress in the fields of thiadiazoles.

Forumadi et al synthesized a series of *N-(5-aryoyl-1,3,4-thiadiazole-2-yl)* piprazinyl quinolone derivatives (I) and evaluated them for *in vitro* antibacterial activity against some Gram positive and Gram negative bacteria. The antibacterial data revealed that all nitroimidazole derivatives showed interesting activity against tested Gram positive bacteria (MIC= 0.008-0.03 mg/ml) while they did not show good activity against gram negative organisms. Despite the significant activity of nitroimidazole series all nitrophenyl analogues were inactive against both gram positive and gram negative bacteria. Among all of the tested compound, the compound having R = 1-methyl-5-nitro-2-imidazolyl substitution exhibited excellent activity against gram positive and gram negative.
Thomasco et al. synthesized a series of 1,3,4-thiadiazole phenyl oxazolidinone analogues (2) and evaluated them for in vitro antibacterial activity against a panel of gram positive and fastidious gram negative bacteria. All of these analogues exhibited good to excellent antibacterial activity including good activity against fastidious gram negative organisms. The in vitro activity of the 1,3,4-thiadiazolyl phenyloxazolidinone is relatively insensitive to the nature of the substituent at the 2 position. The thioacetamido analogues are extremely potent against gram positive and fastidious gram negative organisms.

\[
\text{R = H, OH, CH}_3, \text{C}_2\text{H}_5, \text{FCH}_3, \text{CH}_3\text{OCH}_3, \text{CH}_2\text{S(O)CH}_3, \text{CH}_3\text{SO}_2\text{CH}_2, \\
\text{X = O, S}
\]

(2)

Mohan et al. prepared new class of 6-amino-3-aryl-triazolo-[3,4-b]1,3,4-thiadiazoles (3) and evaluated for their in vitro antibacterial activity against gram positive S. aureus, the gram negative E. coli and P. aeruginosa by neat samples and serial plate dilution method. Among them compound having p-nitrosubstitution found to be active against P. aeruginosa.

\[
\text{R = p-NO}_2
\]

(3)
Patil et al. synthesized some new 2-mercapto-4-[6-’(2”-hydroxy-5’-methyl/chlorophenyl)-4’-heteropyridine-2’-yl amino]-1,3,4-thiadiazoles (4) and evaluated them for in vitro antimicrobial activity against E. coli and Rhizobium spp. using streptomycin sulphate as standard. It was observed that the compound having \( R = \text{methyl}, R_1 = \text{pyrid}-3’-\text{yl}, R = \text{m-chloro}, R_1 = \text{pyrid}-3’-\text{yl} \), showed excellent inhibition and compounds having \( R = \text{methyl}, R_1 = \text{fur}-2’-\text{yl}, R = \text{methyl}, R_1 = \text{thien}-2’-\text{yl} \) and \( R = \text{chloro}, R_1 = \text{fur}-2’-\text{yl} \) showed moderate inhibition against Rhizobium and E. coli at both the concentrations (250 ppm, 500 ppm).

\[
\begin{align*}
\text{OH} & \quad \text{N} \quad \text{N} \quad \text{R} \quad \text{CH}_2 \quad \text{Cl} \\
\text{HN} & \quad \text{N} \quad \text{SH} \\
\text{N} & \quad \text{N} \\
\end{align*}
\]

Wadokar et al. synthesized some new hetero acyl substituted 1,3,4-thiadiazoles (5) and evaluated them for in vitro antibacterial activity against gram negative and gram positive bacteria S. aureus, E. coli, S. dysenteriae, S. typhi and P. vulgaris following the cup plate method. Maximum activity was exhibited by the compound having \( R_1 = \text{OH}, R_2 = \text{H}, R_3 = \text{CH}_3 \), against S. dysenteriae and against P. mirabilis. Majority of compounds were highly active against E. vulgaris and all are moderately active against E. coli.

\[
\begin{align*}
\text{R}_1 & = \text{H, OH}, \\
\text{R}_2 & = \text{R}_3 = \text{H, CH}_3, \\
\end{align*}
\]

Zhang et al. synthesized several new 6-(1-aryl-5-methyl-1,2,3-triazole-4-yl)-3-(4-pyridyl)trizolo[3,4-p]-1,3,4-thiadiazole (6) and screened them for their antibacterial activity against B. subtilis and E. coli, employing cup plate method at the concentration 100 \( \mu \text{g/ml} \) in the nutrient agar medium. Compounds having
R = 3-chloro, 3-methyl were very sensitive to \textit{B. subtilis} comparable to chloromycin which was taken as standard drug at the concentration of 50 \textmu g/ml.

![Chemical structure](image)

Zhang \textit{et al} synthesized a series of 5-(5-methyl isoxazol-3-yl)-1,3,4-thiadiazoles (7) and evaluated them for \textit{in vitro} antibacterial activity against \textit{E. coli}, \textit{S. aureus} and \textit{P. aeruginosa} at 100 ppm concentrations using cup plate agar diffusion method. The compounds having R = 4-Cl and unsubstituted phenyl were found to be moderately active against \textit{S. aureus}.

![Chemical structure](image)

Kidwai \textit{et al} synthesized some new cephalosporin derivatives of 5-substitued-2-mercapto-1,3,4-thiadiazoles (8) and these derivatives are evaluated for their \textit{in vitro} antibacterial activity against \textit{P. vulgaris}, \textit{B. licheniformis}, \textit{E. berbicola}, \textit{E. coli}, \textit{R. japonicus} and \textit{C. rubrum} by cup plate diffusion method. Compounds having R = 1,3,4-thiadiazol-2-yl-thiomethyl, (2-aminothiazol-4-yl) showed very strong inhibition against almost all the bacterial strain, comparable to cefotoxime acid.

![Chemical structure](image)
Mogstaha et al. synthesized some new 6-aryl 3-(2'-methyl-1' 8'-naphthylidin-3'-yl)-1,2,4-triazol-1-yl)-1,3,4-thiadiazoles (9) and evaluated them for *in vitro* antibacterial activity against *E. coli* and *B. polymyxa* using Miller paper disc method at 400 and 600 μg/disc concentration. All the compounds were active against both the bacteria at the minimum inhibitory concentration (MIC) of 400 μg/disc.

Compounds having \( R = p \)-methoxyphenyl, \( p \)-chlorophenyl and \( p \)-hydroxyphenyl were most effective while compounds having \( R = \) phenyl, \( m \)-nitrophenyl, \( p \)-nitrophenyl and \( p \)-nitrobenzyl were found to have low toxicity. The most active compound of the series was \( R = p \)-methoxyphenyl showing activity against both the bacteria tested and most sensitive to *E. coli*.

\[
\text{Ar} = \text{C}_6\text{H}_4 \quad \text{p-OCH}_3 \quad \text{C}_6\text{H}_4 \quad \text{p-OH} \quad \text{C}_6\text{H}_4 \quad \text{m-NO}_2 \text{C}_6\text{H}_4
\]

(9)

Nargund et al. synthesized some new 2-arylamin-5-[4-(acetamido-phenoxo) methyl]-1,3,4-thiadiazoles (10) and evaluated them for *in vitro* antibacterial activity. The antibacterial activity of the target compounds and their relevant reference agents have been determined *in vitro* using serial 2-fold dilution technique on an assortment of gram negative and gram positive organisms. The compounds were found moderately effective against *B. subtilis*. It was noticed that introduction of \( R = 4\)-CH\(_3\)-C\(_6\)H\(_4\) group at position 2 of 1,3,4-thiadiazole moiety significantly increased the activity.

\[
\text{CH}_2\text{CONH} \quad \text{OCH}_3 \quad \text{N} \quad \text{NHR} \quad \text{R = C}_6\text{H}_4 \quad 4\text{-CH}_3\text{C}_6\text{H}_4 \quad 4\text{-OCH}_3\text{C}_6\text{H}_4
\]

(10)

Shah et al. synthesized a series of 2,5-disubstituted 1,3,4-thiadiazole derivatives (11) and evaluated them for *in vitro* antimicrobial activity. Compounds having \( R = 2, 6-\) (CH\(_3\))\(_2\)-C\(_6\)H\(_4\), 4-OCH\(_3\)-C\(_6\)H\(_4\) and 3-CH\(_3\)-C\(_6\)H\(_4\) exhibited comparable
activity with known standard drugs for example chloramphenicol and ampicillin against *S. aureus*. Compounds having \( R = 2\text{-CH}_3\text{C}_6\text{H}_4, \alpha\text{-C}_6\text{H}_5\text{-CH}_2 \) showed comparable activity with ampicillin against *S. citrtus*.

![Chemical structure](image)

\[
R = 2,6-(\text{Cl})_2\text{C}_6\text{H}_4, 4\text{-OCH}_3\text{C}_6\text{H}_4, \\
3\text{-CH}_3\text{C}_6\text{H}_4, 2\text{-CH}_3\text{C}_6\text{H}_4, \alpha\text{-C}_6\text{H}_5\text{-CH}_2
\]

(11)

Gadad *et al*\(^{12}\) prepared some 5-guanyl hydrazone thiocyanato-6-arylimidazo [2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide (12) derivatives. All the compounds were screened for antibacterial activity against *E. coli, S. aureus, S. typhi, P. aeruginosa* and *P. coccii*. The compounds were more active when \( R = p\)-chloro phenyl, \( p\)-bromophenyl, \( p\)-nitrophenyl, against both *E. coli* and *S. aureus*. They also concluded that presence of guanyl hydrazone and 5-thiocyanato group results in increased antibacterial activity.

![Chemical structure](image)

(12)

Zamani *et al*\(^{13}\) synthesized some of new 2,5-disubstituted-1,3,4-thiadiazoles containing isomeric pyridyl, (13) and screened them for their *in vitro* antibacterial activity against gram positive and gram negative strains. The result indicated that 2-benzylamino-5-(3-pyridyl)-1,3,4-thiadiazole was more active than other synthesized compounds against all the studied gram positive and gram negative bacteria, but it was less active than oxacillin, which was used as clinical antibiotic.

![Chemical structure](image)

(13)
Antiinflammatory activity

Paragludins (PGs) are well known to be mediators of inflammation, pain and swelling. They are produced by the action of cyclooxygenase (COX) enzyme on arachidonic acid. COX is known to be the principal target of non steroidal antiinflammatory drugs (NSAIDs). NSAIDs block the formation of PGs and have analgesic, antipyretic and antiinflammatory activity. However PGs are produced by mast cells and their presence in tissues elicits a broad array of biological response. Most notably, some PGs are cytoprotective in the gastrointestinal tract, responsible for normal renal function in the kidney and they allow platelet aggregation. In addition, PGs sensitive peripheral nerve endings to transmit pain signals to the brain and spinal cord. Recent studies have shown that COX exists in two iso forms, which differ in their basal expression, tissue localization and induction during inflammation.

A number of 1,3,4-thiadiazoles were identified as potent antiinflammatory compounds. Carrageenan induced foot paw edema (CPE) inhibitory activity of 1,3,4-thiadiazole derivatives were shown equipotent with naproxen, phenyl butazone, and hydrocortisone etc.

Udupi et al. synthesized several 3,5-disubstituted-6-thiono-5-triazolo [3,4-b] (1,3,4) thiadiazoles (14) and evaluated them for their in vitro antiinflammatory activity, using rat hind paw oedema method of Winter et al. Compounds having R = phenyl, 4-chlorophenyl and 4-amino phenyl possess significant activity compared with the standard drug Ibuprofen.

\[ R = \text{C}_6\text{H}_5, 4\text{-Cl-}, 4\text{-NH}_2\text{C}_6\text{H}_4 \]

(14)

Udupi et al. again synthesized appreciable number of compounds of 3-[(2'- (2",6"-dichlorophenyl) amino)-benzyl-6-substituted-1,2,4-triazolo[3,4-b] (1,3,4)-thiadiazoles (15) and assessed for antiinflammatory and analgesic activity by using formation induced hind paw oedema model.
Compounds having \( R = \) phenyl, 3,5-dinitrophenyl, 2-amino-phenyl and phenoxy methyl exhibit feeble to moderate activity when compared with standard drug diclofenac sodium.

Sharma et al.\(^{16}\) synthesized some new 1-acetyl-5-substituted aryl-3-[5'-(3''-indolylmethyl)-2'-amino-1,3,4-thiadiazol-2'-N-yl]-2-pyrazolines (16) and screened for their anti-inflammatory activity. Compounds having \( R = 4 \)-hydroxy, 3-methoxyphenyl substitution found to be most active compound of this series which showed 47.6\%, 49.0\% inflammation inhibitory activity at a dose of 50 mg/kg p.o. while standard drug phenylbutazone exhibit 45.6\% anti-inflammatory activity at the same dose.

Plaska et al.\(^{17}\) prepared some new compounds 2-(2-naphthoxy methyl)-5-substituted amino-1,3,4-thiadiazole (17) derivatives and evaluated them for \textit{in vitro} anti-inflammatory activity by using carrageenan induced foot paw edema array. All the compounds showed weak to moderate anti-inflammatory activity.
Srivastava et al. synthesized several 2-arylidene amino-5-(N\textsuperscript{10}-2-chlorophenothiazinomethyl)-1,3,4-thiadiazoles (18) and screened them for \textit{in vitro} antiinflammatory activity using carrageenan induced rat paw dema method and using phenyl butazone as a standard drug. Compounds having \( R = 2\)-nitrophenyl, and 2-bromophenyl showed maximum activity whereas compounds having \( R = 3\)-nitrophenyl, 3- bromophenyl and 4-bromophenyl showed moderate activity and rats are either inactive or weakly active.

\begin{equation}
\text{Ar} = 2\text{-NO}_2\text{-C}_6\text{H}_4, 3\text{-NO}_2\text{-C}_6\text{H}_3 \quad 4\text{-NO}_2\text{-C}_6\text{H}_3, 2\text{-Br-C}_6\text{H}_4 \quad 3\text{-Br-C}_6\text{H}_4, 4\text{-Br-C}_6\text{H}_3
\end{equation}

(18)

Amir et al. synthesized a number of 2-arylamino-5-substituted 1,3,4-thiadiazol (19) and evaluated for their antiinflammatory activity using rat paw edema method of Winter \textit{et al.} The compound having \( R = \text{methoxy naphthyl} \) substitution showed maximum activity.

\begin{equation}
\text{R} = \text{MeO-}
\end{equation}

(19)

\textbf{Antitubercular activity}

Tuberculosis is a chronic infection disease caused by several species of mycobacteria (Alireza Foroumadi). The incidence of tuberculosis is increasing world wide, partly due to poverty and inequity and partly to the HIV/AIDS pandemic, which greatly increase the risk of infection proceeding to the disease. The increase in drug resistant \textit{M. tuberculosis} isolates during recent years presents a therapeutic challenge to physicians selecting antimicrobial agents. Thus the development of new agents with potent antituberculosis activities and fewer adverse effects is urgently desired.

Several categories of synthetic compounds have been examined for antitubercular activity. Among the synthetic drugs which have come forth from
different programmes of study are aminosalicylic acid, thiacetazone, isoniazids, pyrazinamide, ethionamide, prothionamide, and ethambutol. For screening, the initial testing is carried out in mice infected with the human virulent strain of \textit{M. tuberculosis H}_{37}\textsubscript{Rv}, and active compounds are examined in the rhesus monkey \textit{M. mulatta} whose tuberculosis is akin to the human disease.

1,3,4-thiadiazole ring system is known to possess several biological activities and the antitubercular properties have been largely described.

Joshi \textit{et al} \textsuperscript{28} synthesized some 2-(3',5'-dichlorobenzof\[l\]thiophen-2-yl)-5-aryl amino-1,3,4-thiadiazoles (20) and evaluated them for \textit{in vitro} antituberculosis activity against \textit{M. tuberculosis H}_{37}\textsubscript{Rv} in BACTEC 12B medium using the BACTEC 460 radiometric system. Compounds having R = 2-nitrophenyl substitution was found highly active (98%).

\[
\text{R}=\text{2-NO}_2\text{C}_6\text{H}_4
\]

(20)

Foroumadi \textit{et al} \textsuperscript{21} synthesized a series of alkyl \(\alpha\)-(5-(5-nitro-2-thienyl)-1,3,4-thiadiazol-2-yl-thio) acetic acid esters (21) and screened them for \textit{in vitro} antituberculosis activity against \textit{M. tuberculosis} strain \textit{H}_{37}\textsubscript{Rv} using the BACTEC 460 radiometric system and BACTEC 12B medium. The antituberculosis data indicated that methyl, propyl, butyl and benzyl esters showed a significant \textit{in vitro} antimycobacterium tuberculosis activity (MIC = 0.39 - 0.78 μg/ml) and the ethyl analogue did not show a good activity (MIC = 6.25 μg/ml, % inhibition = 58). The most active compound of the series was \(n\)-propyl- \(\alpha\)-(5-(5-nitro-2-thienyl)-1,3,4-thiadiazole-2-yl-thio) acetate.

\[
\text{R} = \text{CH}_3, \text{C}_3\text{H}_7, \text{C}_4\text{H}_9, \text{C}_6\text{H}_5
\]

(21)

Foroumadi \textit{et al} \textsuperscript{22} synthesized a series of 2-(5-nitro-2-furyl)-1,3,4-thiadiazole-2-sulfide, sulfoxide and sulfones (22, 23) and evaluated for \textit{in vitro} antituberculosis
activity against \textit{M. tuberculosis} strain H\textsubscript{37}Rv using the radiometric BACTEC 460 - TB methodology. The results indicated that some compounds exhibited a good antituberculosis activity and the ethyl thio analogue was the most active compound (MIC = 0.78 \mu g/ml).

\begin{align}
O\text{N} & \text{N} \text{S} \text{C} \text{H} & \text{C} \text{H} _n & R = \text{C}_2 \text{H}_6, \text{CH}_3, \text{C}_6 \text{H}_1 \\
& O\text{N} \text{S} \text{C} \text{H} & \text{C} \text{H} & R = \text{C}_2 \text{H}_6, \text{CH}_3, \text{C}_6 \text{H}_1 \\
\end{align}

(22

(23

Mamolo \textit{et al}\textsuperscript{23} synthesized some \{5-(pyridine-2-yl)-1,3,4 thiadiazol-2-yl-thio\} acetic acid acylidene hydrazide derivatives (24) and tested them for their \textit{in vitro} antimycobacterial activity against \textit{M. tuberculosis} H\textsubscript{37}Rv and \textit{M. avium} strain 485. The compounds having 4-chloro, 2-bromo, 4-bromo, 3-fluoro and 2,6-dichloro substitution exhibited a moderate \textit{in vitro} antimycobacterial activity against \textit{M. tuberculosis} H\textsubscript{37}Rv.

(24

Fofoumadi \textit{et al}\textsuperscript{24} prepared a series of 2-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole-5-alkylsulfides, alkyl sulfoxide, and alkyl sulfones (25) and evaluated them for their \textit{in vitro} antimycobacterial activity against \textit{M. tuberculosis} M\textsubscript{37} RV. The compound having \textbf{R} = \text{CH}_3, \text{C}_2 \text{H}_5, \text{C}_4 \text{H}_7 showed good antituberculosis activity in the order \text{C}_4 \text{H}_7 > \text{C}_2 \text{H}_5 > \text{CH}_3. The oxidation of the thio group to sulfoxide in alkyl thio derivatives increased the antituberculosis activity in compounds having \textbf{R} = methyl, ethyl and propyl derivatives.
Anticancer activity

Until recently, the only approach for the treatment of cancer was surgery, localized and accessible tumors and radiotherapy. The era of chemotherapy of malignant diseases was born in 1941 when Higgins demonstrated that the administration of estrogen produced regression of elastatic prostate cancer. This was followed by the discovery of many alkylating agent, compounds and some natural products as anticancer. The search for anticancer drugs lead to the discovery of several 1,3,4-thiadiazol fused heterocycles having anticancer activity. An early report on 2-amino-1,3,4-thiadiazole derivatives deals with the activity of these compounds against several transplanted animal tumors.

Alargarsamy et al. synthesized a series of 2-substituted-1,3,4-thiadiazole (2,3-b) tetrahydrobenzo (b) thieno (3,2-e) pyrimidines (26) and evaluated them for anticancer activity. The compound having R = H showed 97, 102 and 95 percentage growth against lung, breast and CNS cancer respectively. Whereas compound having R = 3-methyl phenyl amino substitution showed 11, 16 and 40 percentage growth against lung, breast and CNS cancer respectively, hence this compound was further evaluated against a panel of 60 human cancer cell lines derived from nine different tissues and compound was at a minimum of five concentration at 10 fold dilution. A 48 h continuous drug exposure protocol was used and a SRB protein assay was used to estimate cell viability or growth. The GIso (concentration causing 50% h) growth inhibition was determined which corresponds to the IC50 value

The later compound showed weak cytotoxicity against both, ovarian cancer and prostate cancer but it showed good cytotoxicity against K562 lenkemia and CC-2 melanoma.
Iles et al. prepared 5-(4-amino-substituted-aryl-sulfonamide)-1,3,4-thiadiazole sulfonamides (27) and evaluated as inhibitors of the transmembrane, tumor associated isozyme carbonic anhydrase. Inhibition data against the classical, physiologically relevant isoforms I, II and IV were also obtained. Carbonic anhydrase IX showed an inhibition profile which in general, completely different from those of isoforms I, II, and IV, with potent inhibitors (inhibition constant in the range of 12-40 µm) among both simple aromatic (such as 3-fluoro, 5-chloro, 4-aminobenzene sulfonamide) as well as heterocyclic compounds (such as acetazolamide, methazolamide, 5-amino 1,3,4-thiadiazole-2-sulfonamide, aminobenzolamide and dihalogenated aminobenzolamides).

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{SO},\text{NH} \\
\text{X} \quad \text{Y} & \quad \text{N-N} \\
\text{N} \quad \text{X} = \text{F, Cl, Br, I} \\
\text{Y} = \text{Cl, Br, I}
\end{align*}
\]

(27)

Terzioglu et al. reported some novel 2,6-dimethyl-N'-substituted phenyl methylene-imidazo [2,1-b] [1,3,4] thiadiazole-5-carboxyhydrazide (28) and evaluated them in the national cancer institute's 3-Cell line by one dose in vitro primary cytotoxicity assay. Compound having R = 2-hydroxy phenyl and 4-nitrophenyl substitution which passed the criteria for activity in this assay (20-29% growth) were scheduled automatically for evaluation against the full panel of 60 human tumor cell lines at a minimum of five concentrations at 10 fold dilutions. Sulforhodamine B (SRB) protein assay was used to estimate cell stability or growth. Compound having R = 2-hydroxy phenyl substitution showed the most favourable cytotoxicity.

Alagarsamy et al. synthesized a series of novel 2-substituted (1,3,4) diazolothieno (3, 2-e) pyriaridin-5 (4H)-ones (29) and evaluated them for their in vitro anticancer activity. Out of these, two compounds having R = 3-amino propene and 4-methoxy amino phenyl selected for primary anticancer assay against a panel of 3 cell line i.e. lung, breast and CNS cancer. 3-amino propene substitution showed weak cytotoxicity against non-small cell lung cancer, colon cancer, melanoma ovarian cancer, prostate cancer, breast cancer but it showed good cytotoxic against SI leukemia and SF-268 CNS cancer.
Antifungal activity

There are several fungal species which are pathogenic for man. The fungal infections are superficial and systemic. The fungi causing infections, of the hair, mucous membranes, nails or skin include candida (candidiasis or candidosis) dermatophyte fungi as epidermophyton, microsporum and trichophyton and malassezia furfur ( pityriasis versicolor). The systemic infections include those due to Aspergillus, Bhartomyces, Candida, Coccidiodes, Cryptococcus, Histoplasma and Paracocidioides. Most of the antifungal agents used clinically are either natural antibiotics or synthetics related to imidazole and triazole heterocycles. Fungicidal activity in 1,3,4-thiadiazole derivative has been recognized since a long time. In this connection a number of compounds of some classes have shown appreciable activity against A. niger and P. oryzae.

Yadav et al synthesized a series of 2-amino-5-[substituted phenoxy methylene]-1,3,4-thiadiazoles (30) and screened them for their in vitro fungicidal activity by employing organ growth technique against two selected fungi viz. P. oryzae, and R. solani at 500 ppm. The compounds have R1 = H, chloro, and R2 = H, chloro and R3 = H and methyl substitution were found most active against P. oryzae and R. solani both. The rest were mild to moderately active.
Zhang et al. reported several \( \omega \)-((5-arylamino-1, 3, 4-thiadiazol-2-thiol)-\( \omega \)-(1H, 1,2,4-triazol-1-yl) acetophenones (31) and screened for \textit{in vitro} fungicidal activity employing the agar diffusion technique. The preliminary results indicated that they exhibited some inhibitory activity against plant pathogenic fungi at 50 ppm such as leaf rust of barley, leaf spot of beet, early blight of tomato, gray mold of cucumber and sclerotium blight of colza. The degree of inhibition ranged from 5.0% to 66.6% respectively.

![Chemical Structure](image)

\[ \text{Ar} = m \)-MeC\(_6\)H\(_4\), \ p \)-MeC\(_6\)H\(_4\), C\(_6\)H\(_4\) \]

(31)

Nismanuddin et al. synthesized 2-aryl/aryloxymethyl-1,3,4-thiadiazolo, [1,3-b][1,2,4]triazolo[5,4-c]thiazolo-spiro-7-cyclohexane (32) and assayed them for their fungicidal activity against \( P. oryzae \), \( P. cubensis \), \( S. fuliginea \), \( P. infestans \) and \( P. coronata \) at 500 ppm and 100 ppm concentrations respectively by agar growth technique. All the compounds showed moderate to strong activity, but their activity decreased upon dilution. Among these the most active compound having \( R = 4 \)-chloro substitution (92% at 500 ppm) nearly to that carbendazim (100% at 500 ppm).

![Chemical Structure](image)

(32)

Hazarika et al. synthesized a series of new 2-amino-4-[5-[(2-chloro phenyl)-1,3,4-thiadiazol-2-yl]-6-aryl/substituted-aryl-7-oxo-6,7-dihydrothiazolo[4,5-d] pyrimidine-5 \((H)\)-thiones-(33) and evaluated them for their \textit{in vitro} fungicidal activity employing agar plate diffusion technique. The compound having \( R = 2 \)-nitrophenyl, 3-nitrophenyl and naphthyl substitution were most effective while as rest were weak to moderately effective.
Padhy et al.\textsuperscript{33} reported several 2-aryl-3-(4-aryl-1,3,4-thiadiazolyl)-4-thiazolidinones (34) and screened for their fungicidal activity against \textit{A. clavatus}, and \textit{A. fumigatus} by dilution technique employing saboroids media selecting at random. Compounds having \( \text{Ar} = \text{phenyl} \) and \( \text{Ar} = \text{i-but phenyl} \), phenyl showed about 60\% retardation in growth at the concentration level of 100 mg/ml.

Khan et al.\textsuperscript{34} reported several 5-aryl-2-[spiro-(1,3-dithiolane)-2,4'-(3-chloro-2'-azetidinon)-1'-yl]-1,3,4-thiadiazoles (35) and assayed for their fungicidal activity against \textit{A. niger}, \textit{P. oryzae} and \textit{F. oxysporum} etc, by agar growth technique at 100 ppm concentration and results were compared with standard fungicide carbendazim. Compounds having \( \text{R} = \text{chloro} \) and 4-methoxy substitution showed activity 75-85\% at 100 ppm concentration against \textit{P. oryzae} and \textit{F. oxysporum}.

\begin{equation}
\text{R} = 4-\text{Cl, OCH}_3
\end{equation}

\textbf{Antiviral activity}

The diseases due to viral infections are more frequent. The well known diseases include common cold, influenza, bronchitis, hepatitis, herpes, poliomyelitis gastroenteritis, rabies, chicken pox, small pox, measles and mumps. The discovery of potent antiviral acyclic nucleosides like acyclovir and its analogues has led to significant progress in the development of useful antiviral agents. Similarly the
biological significance of naturally occurring acyclic C-nucleosides has promoted the synthesis of various compounds of this class. In the present study 1,3,4-thiadiazole has been used on nucleobases owing to their biological potential.

Kritsanida et al.\textsuperscript{35} reported some novel 3,6-disubstituted 1,2,4-thiazolo [3,4-b] [1,3,4] thiadiazol derivatives (36) and evaluated them for their \textit{in vitro} antiviral activity. No antiviral effects were noted with any of the compounds at subtoxic concentrations in accurately infected MT-4 cells where as most of the compounds were cytotoxic for the host cells.

\begin{center}
\begin{tabular}{c}
\includegraphics[width=0.5\textwidth]{image.png}
\end{tabular}
\end{center}

Yadav et al.\textsuperscript{36} synthesised some 2-arylamino-5-(D-glucopentyl)-5H-thiazolo [4,3-b]-1,3,4-thiadiazoles (37) and assayed them for their \textit{in vitro} antiviral activity against the viral species \textit{C. amaranticolor}. A standard antiviral agent, virazole was also tested under similar conditions for comparison. Compounds having Ar = p-methoxy phenyl and o-methyl phenyl and R = D-xylobutyl showed moderately active against \textit{C. amaranticolor} at 100 ppm concentration.

\begin{center}
\begin{tabular}{c}
\includegraphics[width=0.5\textwidth]{image.png}
\end{tabular}
\end{center}

Yadav et al.\textsuperscript{37} further synthesized two series of 1,3,4-thiadiazole derivatives as 2-arylamino-6-(5-aryl-1,3,4-thiadiazol-2-ythio)-5H-1,3,4-thiadiazine and 2-arylamino-6-(5)-dihydro-3,4-thiadiazol-2-ythio)-5-(D-glucopentyl)-6-methythio-4H, 5,6-1,3,4-thiadiazines (38), (39) and evaluated them for \textit{in vitro} oral activity against the viral species \textit{C. amaranticolor}. A standard antiviral agent virazol was tested under similar conditions for comparison. Both the compounds having R = Glucopentyl, Ar = 2-chlorophenyl and Ar' = 4-methoxy phenyl substitutions showed promising activity.
Several classes of ureas, thioureas, amides and heterocyclic bases have been screened for anticonvulsant activities. The first effective anticonvulsant drug sodium bromide was introduced by Charles Locoek (1857). Phenobarbitol one of the most important drug for treatment of epilepsy was introduced by Alfred Hamptman (1912). In the course of systematic pharmacological screening programme of potential anticonvulsant compounds, Merit and Putman discovered diphenyl hydantoin, the search for new anticonvulsant drug intensified. 1,3,4-thiadiazole, a heterocyclic compound of varied biological activities was found to be one of the new class of anticonvulsant agents revealed by literature survey.

Dogan et al. reported two new series of 2,5-disubstituted 1,3,4-thiadiazoles (40) for their possible anticonvulsant activity. The degree of protection afforded by these compounds at a dose of 100 mg/kg i.p. against pentylene terazole-induced convulsions in mice ranged from 0-90%. Among these compounds, the compounds having \( R = \text{ethyl} \) (90%) and \( R = \text{p-methoxy phenyl} \) (70%) showed maximum protection.

Kumar et al. synthesised a series of 3-((4-[2-alkylphenyl]-4-oxo-1,3,4-thiazolidin-3-yl]-1,3,4-thiadiazol-2-yl) methylamino)-2-methyl-6-mono substituted...
quazolin-4(3H)-one (41) and screened them for their anticonvulsant activity and were compared with the standard drugs, phenytoin sodium, lamotrigine, and sodium valproate. Out of the thirty compounds, the most active compound was 3-{4-(2-(4-methoxy-3-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl)-1,3,4-thiadiazol-2-yl}methylamino)-2-methyl-6-bromoquinazol in-4(3H)-one around 90%.

Lava et al. reported several 2-arylidendalamino-5 (N',1,2,4-thiadiazoles (42) and 1-[5-[N'-1,2,4-methyl)-1',3',4'-thiadiazol-2'-yl]-4' (substituted phenyl)-3-chloro-2-oxazetidines (43) and screened for their anticonvulsant activity against pentylene tetrazol induced convulsions in albino mice of either sex. Both compounds having Ar = 4-Br-C₆H₄ substitution showed maximum activity against seizures.

\[ \text{Ar} = 4-\text{Br}-\text{C}_6\text{H}_4 \]

Nasereel et al. synthesized a series of aromatic / heterocyclic sulfonamides incorporating valproyl moieties (44) to design antiepileptic compounds. The valproyl derivatives of acetazolamide (5-valproylamido-1,3,4-thiadiazole-2-sulfonamide) was one of the best anticonvulsant in an MES test. It was observed that some lipophilic derivatives such as 5-benzoylelamido, 5-toluenesulfonlamido, 5-adamantyl carboxamide, and 5-pivaloylamido-1,3,4-thiadiazole-2-sulfonamide show promising in vivo anticonvulsant properties and these compounds may be considered as interesting leads for developing anticonvulsant agents.
Siddiqui et al\textsuperscript{12} synthesized a series of 2-(alkyl carbamoylhydrazine-5-aryl-1,3,4-thiadiazoles (45) and screened for their anticonvulsant activity. Pharmacological screening of the compounds for anticonvulsant activity showed that the chlorophenyl substituted compound was most potent against maximal electroshock seizures. The other group substituted compounds showed either loss or no protection in MES test. In chemoshock seizure test the compounds showed protection to some extent.

Srivastava et al\textsuperscript{13} synthesized several 2-arylideneamino-5-carbazolylmethyl-1,3,4-thiadiazole (46) and 1[5\'-carbazolylmethyl]-1',3',4'-thiadiazol-2'-yl]-4-(substituted phenyl)-3-chloro-2-oxo-azetidines (47) and evaluated for their anticonvulsant activity against PTZ induced convulsion in albino mice. The compounds having Ar = 2-chlorophenyl substitution showed maximum protection.

\begin{align*}
\text{(44)}
\end{align*}

\begin{align*}
\text{(45)}
\end{align*}

\begin{align*}
\text{(46)}
\end{align*}

\begin{align*}
\text{(47)}
\end{align*}
Miscellaneous activities

In addition to the previously mentioned biological activities, 1,3,4-thiadiazoles are also reported to possess some other important activities such as leishmanicidal activity of 2-(5-nitro-2-furyl) and 2-(5-nitro-2-phenyl)-5-substituted-1,3,4-thiadiazoles (48) has been reported by Foroumadi et al.\textsuperscript{44} The compounds showed good activity against leishmania major promastigotes using 3H thymidine incorporation. Most of the compounds showed activity better than the reference drug sodium汐bogluconate (pentostatin). The most active compound having R = phenyl and X = oxy substitutions.

Similar activity has been reported by Ran et al\textsuperscript{45} in various 2-alkylthio-5-imino-7H-1,3,4-thiadiazolo[3,2-a] pyrimidin-7-ones (49). Some compounds were found very good leishmanicidal activity against \textit{L. donovani}.

Vergne et al\textsuperscript{45} reported some 1,3,4-thiadiazoles (50) as a novel structural class of potent and selective PDE7 (Phosphodiesterase) inhibitors.

![Diagram of molecule](source)

Recent findings on tissue distribution support the hypothesis that PDE7 could be good target for the treatment of airway diseases, T-cell related diseases, CNS disorders, leukemia, cardiovascular diseases and fertility disorders. Therefore the identification of selective inhibitors targeted against PDE7 enzyme has become an attractive area of research.

Chadha et al\textsuperscript{47} synthesised a lead compound megazol; 5-(1-methyl-5nitro-1H-2-imidazolyl)-1,3,4-thiadiazol-2-amine (51) and assayed for their trypanocidal activity against \textit{T. baucei}, \textit{T. cruzi}, and \textit{L. donovani}; as either extracellular cells or a infected macrophages. The result showed that is megazol was more active than its derivatives.
Saksena et al.\(^{38}\) reported a series of 2-(acetylxyloxyethyl)-5-(2'-mercapto-acetylaminobenzoxazol 2'-yl)-1,3,4-thiadiazoles (52) and screened for their cestocidal activity against *H. nana* infections in rats. The compounds having R = 4-nitrophenyl and 2-nitrophenyl showed maximum activity around 72.2 and 56.4%, other compounds exhibited appreciable activity at the same dose.

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

(51)

\[
\begin{align*}
&\text{O} \\
&\text{C} \\
&\text{N} \\
&\text{N} \\
&\text{S} \\
&\text{CH}_2\text{OR}
\end{align*}
\]

(52)

Li et al.\(^{39}\) reported some 2 (4-bromobenzoylamino)-5-aryloxy methyl-1,3,4-thiadiazoles (53). The preliminary tests of biological activities showed compounds having R = 2-chlorophenyl, 4-chlorophenyl showed promising effect on wheat growth at different concentration especially at low concentration and the promoting effect of new compounds were comparable with IAA, and 2,4-D in all of the cases studied.

\[
\begin{align*}
&\text{Br} \\
&\text{N} \\
&\text{S} \\
&\text{CH}_2\text{OAr}
\end{align*}
\]

(53)

Clerici et al.\(^{50}\) synthesised and reported 2-amino-5-sulfanyl-1,3,4-thiadiazole derivatives (54) bearing different substitutions and screened pharmacologically in order to evaluate their central nervous system activity by varying the substituent in the thiadiazone moiety. It was found that some of these compound possess marked antidepressant and anxiolytic properties comparable in efficiency to the reference drugs imipramine and diazepam. The most potent compound having R = 3-methoxy benzyl substituent, was further investigated to complete its pharmacological profile with respect to undesired side effects.
Scozzafava et al.\textsuperscript{51} reported perfluoralkyl/aryl-substituted derivatives of heterocyclic (1,3,4-thiadiazole) sulfonamides (55) as topical intraocular pressure lowering agent with prolonged duration of action. The compounds reported here were assayed for inhibition of three carbonic hydrase isozymes, two of them known to play a critical role in aqueous humor formation (CA II and CA IV) whereas the other one CAI is known to be important for the possible systemic side effects of such drugs. Some of the compounds were found to be active in vivo condition.

Further Scozzafava et al.\textsuperscript{52} reported some membrane impermeant low molecular weight sulfonamides possessing in vivo selectivity for the membrane bound versus cytosolic isozymes. Aromatic heterocyclic sulfonamides (56) act as strong inhibitors of the zinc enzyme CA. But the presently available compounds do not generally discriminate between the 14 isozyme isolated in higher vertebrates. This clinically used drugs from this class of pharmacological agents show many undesired side effects due to unselective inhibition of all CA isozyme present in tissue organs.

\textbf{56}

Jain et al.\textsuperscript{53} prepared some newer 2-(substituted acetamide)-5-aryl-1,3,4-thiadiazoles (57) and screened for diuretic activity. A few of the compounds having R = H, X = di-n-propylamino, R = H, X = diisopropylamino, R = CH\textsubscript{3}, X = pyrrolidine showed diuretic activity comparable with the standard drug acetazolamide at a dose level of 100 mg/kg, orally in male albino rats.

\textbf{57}
Turner et al.\textsuperscript{54} reported some 2-aryl-5-hydrazine-1,3,4-thiadiazoles (58) and screened for antihypertensive activity. In general, compounds with a 2-substituted phenyl ring had higher activity than their 3 or 4-substituted counterparts or those containing heteroaryl groups. The 2-methylphenyl and 2-ethyl phenyl derivatives were the most potent members of the series. The hypotensive action of these compounds was due to a direct relaxant effect on vascular smooth muscles.

$$\begin{array}{c}
\text{N} \\
\text{N} \\
\text{R} = 2-\text{C}_4\text{H}_8, 2-\text{C}_2\text{H}_4
\end{array}$$

(58)
References


7. Zhang, Y. Z.; Zhang, M. L.; Hui, P. X. Synthesis and Antibacterial Activities of 1,3,4-Thiadiazole, 1,3,4-Oxadiazole and 1,2,4-Triazole Derivatives of 5-Methylisoxazole. Ind. J. Chem. 1999, 38B, 1066-1069.


17. Plaska, E.; Shahin, G.; Kelicen, P.; Duslu, T. N.; Altinok, G.; Synthesis and Antiinflammatory Activity of 1-Acylthiosemicarbazides, 1,3,4-Oxadiazoles, 1,3,4-Thiadiazoles and 1,2,4-Thiazole-3-Thiones. *Il Farmaco* 2002, 57, 101-107.

Chapter 2

Literature Review


34. Khan, H. M.; Nizamuddin. Synthesis of 5-Aryl-2-[Spiro-(1,3-Dithiolane)-2,4-(3-Chloro-2-Azetidinon)-1’-yl]-1,3,4-Oxa (Thia)-Diazoles and 5-Aryl-2-[Spiro-(1,3-Dithiolane)-2,2’-(4-thiazolidinon)-3’-yl]-1,3,4-Oxa (Thia) Diazoles as Antimicrobial Agents. *Ind. J. Chem.* 1997, 36B, 625-629.


