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1,3,4-Thiadiazole and its Derivatives: A Review on Recent Progress in Biological Activities

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The 1,3,4-thiadiazole nucleus is one of the most important and well-known heterocyclic nuclei, which is a common and integral feature of a variety of natural products and medicinal agents. Thiadiazole nucleus is present as a core structural component in an array of drug categories such as antimicrobial, anti-inflammatory, analgesic, antiepileptic, antiviral, antineoplastic, and antitubercular agents. The broad and potent activity of thiadiazole and their derivatives has established them as pharmacologically significant scaffolds. In this study, an attempt has been made with recent research findings on this nucleus, to review the structural modifications on different thiadiazole derivatives for various pharmacological activities.

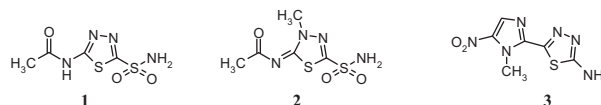
Key words: 1,3,4-thiadiazole, antimicrobial, thiadiazole

1,3,4-thiadiazoles have become an important class of heterocycles and a great interest of researches because of their broad types of biological activity. Thiadiazole is a 5-membered ring system containing hydrogen-bonding domain, sulfur atom, and two-electron donor nitrogen system that exhibit a wide variety of biological activity. They occur in four isomeric forms in the nature viz. 1,2,3-thiadiazole; 1,2,5-thiadiazole; 1,2,4-thiadiazole; and 1,3,4-thiadiazole (Scheme 1).



Scheme 1: Thiadiazole structures.

Many drugs containing 1,3,4-thiadiazole nucleus such as acetazolamide **1**, methazolamide **2**, megalol **3** are available in the market, although the only commercial 1,2,4-thiadiazole drug is the antibiotic cefozopram [1,2].



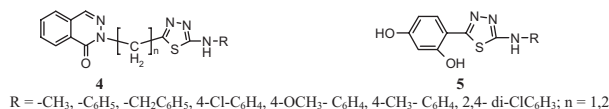
The present review, emphasizes on the biological activities revealed by substituted 1,3,4-thiadiazoles and structurally related thiadiazoles. The review covers advances made in the last 10 years and provides discussion on SAR.

Biological activity of 4-thiazolidinones

There are several reports in the literature describing the 1,3,4-thiadiazole derivatives for their various biological activities and the most relevant and recent studies have revealed that 1,3,4-thiadiazole derivatives have a broad spectrum of pharmacological activities that can be classified into the following categories.

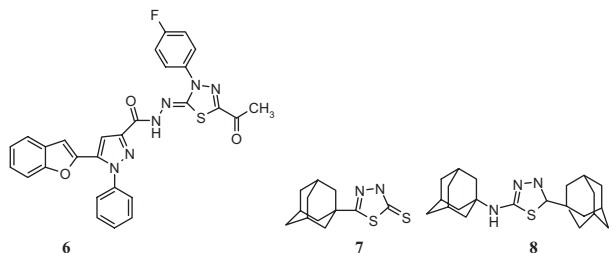
Antibacterial and Antifungal activity

1,3,4-Thiadiazole has shown a broad spectrum of activity against various pathogens, and extensive research has been performed on the synthesis of new potent antibacterial and antifungal agents. A new series of 2-[[1(2H)-phthalazinone-2-yl]methyl/ethyl]-5-arylamino-1,3,4-thiadiazole derivatives (**4**) was evaluated *in vitro* antimicrobial activity against bacteria and fungal species. The results showed that the tested compounds possessed weak antibacterial and antifungal activity compared with standard drugs chloramphenicol and rifampicin for antibacterial and ketoconazole for antifungal activity, respectively [3]. A number of 5-substituted 2-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole derivatives (**5**) have been evaluated for antifungal activity against several clinical isolates of *Candida albicans*. The compounds with methyl, phenyl, 4-ethoxyphenyl, and halogenophenyl groups at C-2 of thiadiazole ring showed higher antifungal activity [4].

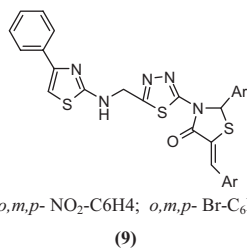


R = -CH₃, -C₆H₅, -CH₂C₆H₅, 4-Cl-C₆H₄, 4-OCH₃-C₆H₄, 4-CH₃-C₆H₄, 2,4-di-Cl-C₆H₃; n = 1,2

Abdel-Wahab *et al.* [5] described the synthesis of new 1,3,4-thiadiazole derivatives of 5-(benzofuran-2-yl)-1-phenylpyrazole moiety through the reactions of the potassium salt of hydrazinecarbodithioate with substituted hydrazonoil chlorides. Out of these synthesized compounds screened against bacterial strains, compound **6** showed significant activity against *Escherichia coli* and *C. albicans*. The tested compounds did not exhibit any activity against Gram-(+) strains up to the maximum concentration of 100 $\mu\text{g/mL}$. Kadi *et al.* [6] reported the synthesis of a new series of 5-(1-adamantyl)-1,3,4-thiadiazole derivatives for their antimicrobial activity. Upon evaluation of antibacterial activity, it was found that almost all the compounds, especially compound **7** exhibited more activity than reference drugs (gentamicin and ampicillin) with respect to *E. coli* and *Pseudomonas aeruginosa*, and thus, it could be a promising novel drug candidate. The findings revealed that antibacterial activity was greatly diminished on introduction of the benzyl- or 4-substituted benzyl moieties and antifungal activity increased on substitution with adamantyl moiety (**8**) on C-5 of thiadiazole nucleus. The introduction of the 4-substituted-1 piperazinyl-methyl moieties at N-3 position increased the activity of thiadiazole derivatives against Gram-(+) bacteria [7].



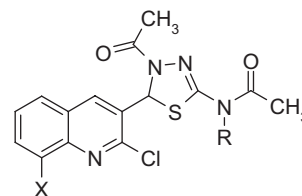
Some of the 2-[2-{2-(substitutedphenyl)-4-oxo-5-(substitutedbenzylidene)-1,3-thiazolidin}-5-methyl-1,3,4-thiadiazol]-imino-4-phenyl-1,3-thiazole derivatives (**9**) showed distinct antibacterial and antifungal activity [8].



Ar = *o,m,p*-Cl-C₆H₄; *o,m,p*-NO₂-C₆H₄; *o,m,p*-Br-C₆H₄; *o,m,p*-OCH₃-C₆H₄

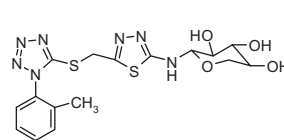
(9)

Antibacterial activity in a series of 3-(1,3,4-thiadiazole-2-yl)quinolines was found to be depended strongly on substitution at C5 and C2 of thiadiazole. From the findings, Bhat *et al.* [9] revealed that thiadiazole derivatives substituted with N-(*o*-tolyl)acetamide (**10**) and N-(*p*-tolyl)acetamide (**11**) groups at C2 and 2,8-dichloroquinoline and 2-chloroquinoline at C5 showed better activity against *S. aureus* and *S. pyogenes*, respectively.

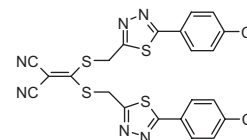


R = *o*-CH₃-C₆H₄, X = Cl (**10**); R = *p*-CH₃-C₆H₄; X = H (**11**)

He *et al.* [10] carried out synthesis of 5-(1-aryl-1H-tetrazol-5-ylsulfanylmethyl)-N-xylopyranosyl-1,3,4-thiadiazole-2-amine derivatives and investigated *in vitro* antibacterial activity against *S. aureus*. Among the synthesized compounds, only compound **12** was found to be the most active against tested strain and none of them showed activity against tested fungal strains. A series of 2-(bis(1,3,4-thiadiazolyl)methylthio)methylene)malononitriles were synthesized and evaluated *in vitro* against *S. aureus*, *Bacillus subtilis*, *E. coli* and *Klebsiella pneumoniae*. Among the synthesized compounds, 2-(bis((5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl)methylthio)methylene)malononitrile (**13**) showed significant activity against *S. aureus* with zone of inhibition of 35 mm at a concentration of 200 $\mu\text{g/mL}$ [11].

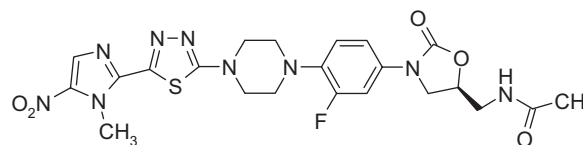


12



13

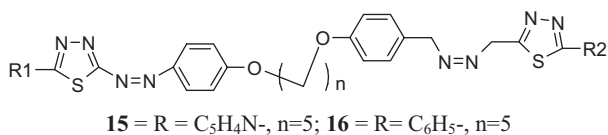
Linezolid is a well-reported bacteriostatic agent and its analogs containing a nitroaryl-1,3,4-thiadiazole moiety that inhibits protein synthesis by acting against the formation of the 70S initiation complex. These compounds were initially tested for antimicrobial activity by agar-dilution method, and it was found that compound **14** presented most pronounced activity. This compound was even found to be more potent than ciprofloxacin against a panel of Gram-positive and Gram-negative bacteria [12].



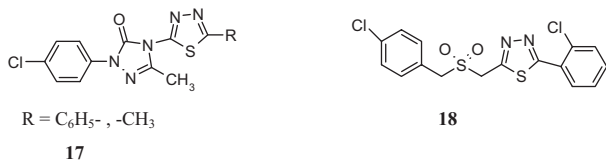
14

The *in vitro* antibacterial activity of azo derivatives of aminothiadiazole derived from nicotinic and isonicotinic acid have been evaluated against several microbes like *E. coli*, *K. pneumoniae*, *Pseudomonas aeruginosa*, *S. marcescens*, and *S. aureus* by Tomi *et al.* [13]. The findings suggested that the antibacterial activity was found to increase when the chain of the alkyl group (-CH₂)_n in the central part of the molecules was increased. Compound **15** and **16**

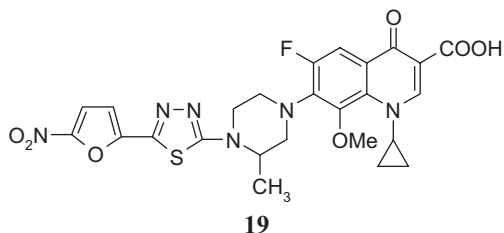
showed good activity against *E. coli* and *S. aureus*, and none of the compound showed activity against *P. aeruginosa* and *S. marcescens* up to a concentration of 300 $\mu\text{g}/\mu\text{L}$.



Various combines biolabile molecules involving Schiff bases and 1,2,4-triazoles derivatized with the 1,3,4-thiadiazoles showed moderate to significant activity against bacteria at concentration of 100 $\mu\text{g}/\text{mL}$. Compounds (**17**) with chloro group at the *para*-position of the aryl ring were shown to increase antibacterial activity (15.6 $\mu\text{g}/\text{mL}$) where the standard drug has shown MIC value at 12.5 $\mu\text{g}/\text{mL}$ [14]. The antimicrobial activity of derivatives involving a series of novel 2 (arylmethanesulfonyl-methyl)- 5-aryl-1,3,4-thiadiazoles was studied in experiments *in vitro* with respect to Gram-positive bacteria *S. aureus*, *B. subtilis* and Gram-negative bacteria *K. pneumonia*, *P. vulgaris*, and fungi *F. solani*, *C. lunata*, and *A. niger*. Most of the synthesized compounds showed moderate to comparable activity. Compounds with benzylsulfonyl group and chloro substituent were found to be the most active and only **18** had more pronounced antibacterial activity and almost equipotent to chloramphenicol [15].

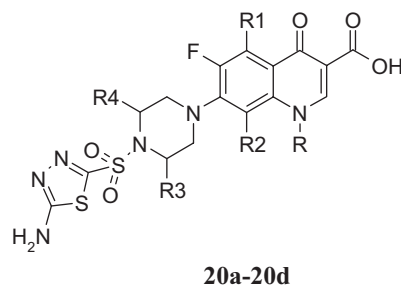


Antibacterial activity of gatifloxacin derivatives incorporated with 5-(5-nitroheteroaryl)-1,3,4-thiadiazol-2-yl groups at C-7 position had been studied by Jazayeri *et al.* [16]. The presence of nitrofuran (**19**) at C-2 of thiadiazole ring caused complete inhibition of DNA gyrase or DNA topoisomerase IV and exhibited more potent inhibitory activity against Gram-positive bacteria including *S. epidermidis* (MIC = 0.0078 $\mu\text{g}/\text{mL}$), *B. subtilis* (MIC = 0.0039 $\mu\text{g}/\text{mL}$), *E. faecalis* (MIC = 0.125 $\mu\text{g}/\text{mL}$), and *M. luteus* (MIC = 0.125 $\mu\text{g}/\text{mL}$).



In continuation of research on C-7 position of FQs, a novel series of 7-[4-(5-amino-1,3,4 thiadiazole-2-sulfonyl)]-1-piperazinyl fluoroquinolone derivatives **20a–20d** have been

synthesized, and nearly, all of the compounds exhibited moderate to good activity against some Gram-(+) bacteria, that is, *S. aureus*, *E. faecalis*, *Bacillus* sp (MIC = 1–5 $\mu\text{g}/\text{mL}$) and showed poor activity against the Gram-negative bacteria. Substitution with methoxy group at C-8 and free -NH₂ group of 7-(4-aminophenyl-sulfonyl) piperazinyl fluoroquinolone was found to be the active compound in this series against all the tested Gram-positive strains of bacteria [17] (Table 1).



Foroumadi *et al.* [18] reported the impact on antibacterial activity of N-substituted piperazinyl carrying benzylthio- and benzylsulfonyl-1,3,4-thiadiazole on C-7 position of quinolone. Most of the synthesized compounds exhibited a marked degree of activity (MIC = 0.03–4 $\mu\text{g}/\text{mL}$) against Gram-positive bacteria and moderate to poor activity (MIC = 1–64 $\mu\text{g}/\text{mL}$) against Gram-negative pathogens. Compound **21** was found to be the most potent and exhibited *in vitro* antibacterial activity against Gram-positive bacteria with an MIC of 0.5, 0.03, and 0.5 $\mu\text{g}/\text{mL}$ against *S. aureus*, *S. epidermidis*, and *B. subtilis*, respectively. SAR study of this series explained that S,S-dioxidation of thio compounds caused a diminution in antibacterial activity and nitro-substituent on benzyl moiety and cyclo-propyl instead of ethyl group at N-1 of quinolone enhanced the antibacterial activity. Similarly, levofloxacin-containing hybrids (**22**), carrying the 5-(nitroaryl)-1,3,4-thiadiazol-2-yl group have been tested against *Staphylococcus* strains, and the results revealed that these compounds expressed a comparable to better activity (MIC = 0.03–0.5 $\mu\text{g}/\text{mL}$) with respect to the reference drugs (MIC = 0.25–4 $\mu\text{g}/\text{mL}$) [19].

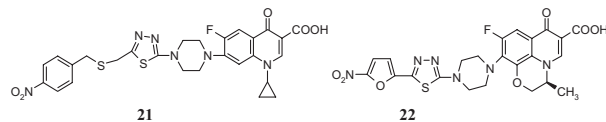
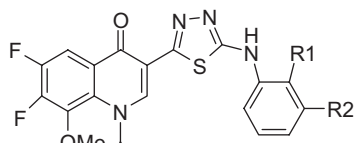


Table 1: Structural details of compounds **20a–20d**

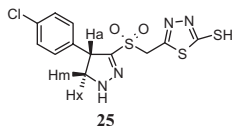
S.No.	R	R1	R2	R3	R4
a		H	H	H	H
b		H	H	H	H
c		-NH ₂	F	-CH ₃	-CH ₃
d		H	-OCH ₃	H	-CH ₃

Further substitution on C-3 position of quinolone significantly reduced its antibacterial as well as antifungal activity when compared to substitution on C-7. The thiadiazoles **23** and **24** exhibited more potent activity than chloramphenicol against *Aspergillus niger* and Nystatin against *P. aeruginosa* [20].

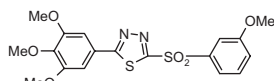


23 = R1 = H, R2 = H; **24** = R1 = CH₃, R2 = H

A series of pyrazole attached with 1,3,4-thiadiazoles hybrids were synthesized and the most promising compound 5'-[4-(4-chlorophenyl)-4,5-dihydro-1H-pyrazole-3-sulfonylmethyl]-[1',3',4']thiadiazole-2'-thiol (**25**) showed moderate antibacterial activity against the Gram-positive bacteria [21]. Antifungal activity of 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-thiadiazoles was reported by Chen *et al.* [22]. Thiadiazole ring instead of oxadiazole did not show significant activity, substitution with 2-methylsulphonyl-3-methoxyphenyl (**26**) at C-5 of thiadiazole ring showed higher antifungal activities against *G. zeae*, *B. cinerea*, and *S. sclerotiorum*.



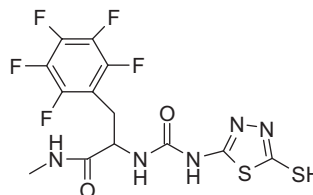
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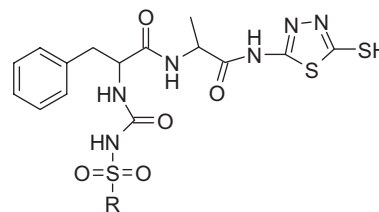
26

Scozzafava and Supuran [23] reported the synthesis of 5-mercapto-1,3,4-thiadiazole derivatives and tested their inhibitory activity against matrix metalloproteinase (MMP) and Bacterial Collagenase. Matrix metalloproteinases are zinc-dependent endopeptidases and involved in critical processes such as destruction of the extracellular matrix in a condition of chronic wounds, colonization and evasion of host immune defenses. Doxycycline and tetracyclines lowered the MMPs level by binding with the catalytic zinc atom at the MMP active site. Among the synthesized compounds, compound **27** was found to bind with zinc ion of the metalloprotease (MMP3) active site through the interaction of exocyclic sulfur atom of mercapto-thiadiazole ring and to S1 pocket of the protease by its urea-thiadiazole moiety, methylamide carbonyl moiety to S2 site of protease and the pentafluorophenyl moiety to S3 site of the protease ($k_1 = 18$ nm). Compounds (**28**) with the sulfonylureido group were found to be selective and highly potent inhibitor of MMP-2, MMP-8, MMP-9, and ChC in a range of 0.1–8 μ M (Table 2).

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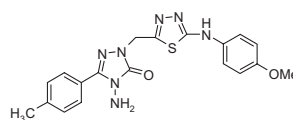
27



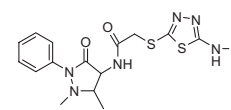
28a-28c

Tomi *et al.* [13] synthesized azo derivatives of aminothiadiazole derived from nicotinic and isonicotinic acid by cyclization, diazotization, and etherification steps, respectively, and tested them for *in vitro* antimicrobial activity against several microbes like: *E. coli*, *K. pneumonia*, *P. aeruginosa* and *S. aureus*. All the synthesized compounds showed good activity against *E. coli*. Compounds having 3-pyridyl group C-2 of thiadiazole were found to exhibit good activity against *K. pneumonia* (Scheme 2).

Demirbas *et al.* [24] prepared four different derivatives of 4-Amino-2-[(5-aryl-amino-4,5-dihydro-1,3,4-thiadiazol-2-yl)methyl]-5-(4-methylphenyl)-2,4-dihydro-3H-1,2,4-triazol-3-ones and investigated its antimicrobial activity. Thiadiazole (**29**) with 2-({5-[(4-methoxyphenyl) amino] group} was found to possess highest antibacterial activity, whereas N-alkylation at C-5 of thiadiazole ring did not result in improved antibacterial activity. An attempt to prepare active compounds in the series of thiadiazolyl derivatives (**30**) of antipyrine turned up unsuccessful. All the synthesized derivatives bared weak growth inhibitory activity against the tested Gram-positive bacteria (MIC 100 μ g/mL) [25].



29



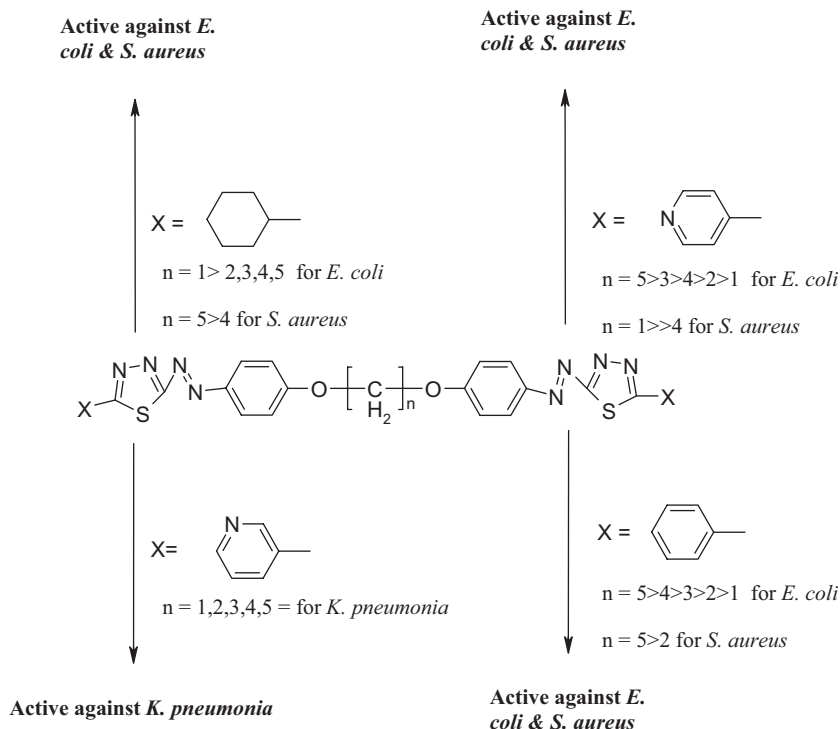
30

1,3,4-Thiadiazole and 2-azetidinones derivatives of 2-methyl-1H-benzimidazoles were tested for antibacterial, antifungal activity and some of the tested compounds had

Table 2: Structural details of compounds **28a–28c**

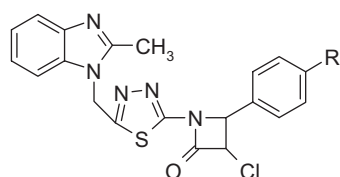
S. No.	R	K_i (μ M)				
		MMP-1	MMP-2	MMP-8	MMP-9	ChC
a	C ₆ H ₅ –	19	5	5	4	3
b	4-F–C ₆ H ₄ –	12	2	0.1	0.3	0.2
c	4-Cl–C ₆ H ₄ –	10	4	0.2	0.4	0.3

MMP, matrix metalloproteinase.



Scheme 2: Effect of various substituents on activity.

comparable activity against *B. subtilis* and *E. coli* with reference to ampicillin (25 µg/mL). Compounds (**31**) having *o*-chloro, *o*-methyl, *p*-methoxy, *o*-hydroxy, and *p*-amino group in phenyl ring showed good antibacterial activity. Antifungal activity data indicated that some of the derivatives revealed a broad spectrum of activity against tested fungi; however, none of the derivatives showed a better spectrum of activity when compared to the reference drug [26].

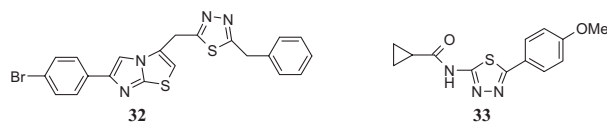


R = *o,p*-Cl; *o,p*-OCH₃; H; *o,m,p*-CH₃; *o,m,p*-OH; *p*-NH₂

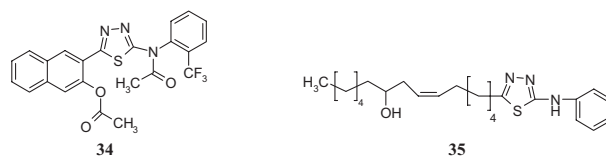
31

A recently published article reported the antibacterial and antifungal activity of 1,3,4-thiadiazoles bearing imidazo [2,1-b]thiazole moiety (**32**) against *S. aureus* ATCC 29213, *P. aeruginosa* ATCC 27853, *E. coli* ATCC 25922, and *T. tonsurans* NCPF245 with MIC of 64, 32, and 8 µg/mL, respectively [27]. Applying QSAR study, it has been observed that positions-2 or position-3 of benzene attached with thiadiazole ring where as electron-donating and bulky group would be favorable for higher antifungal activity. On the basis of CoMFA findings, Liu *et al.* [28]

designed a compound **33** which was found to display a good antifungal activity (79.38%).

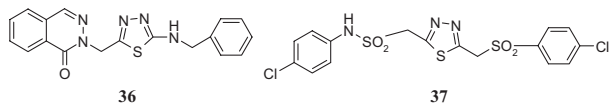


2-(*N*-acetyl-*N*-*m*-trifluoromethylphenylamino)-5-(3-acetyloxy-2-naphthyl)-1,3,4-thiadiazole was found to possess good activity against *P. aeruginosa* and equally active, comparable with the standard drug penicillin [29]. A novel series of 2,5-disubstituted-1,3,4-thiadiazoles derivatives (**34**) have been synthesized and showed good inhibition against both Gram-(+) and Gram-(−) bacterial strains at 6.25 µg/mL concentration. The hydroxyalkenyl chain at 5th position and internal double bond in the long alkenyl substituent of synthesized thiadiazoles (**35**) were found to be more active against *S. pyogenes*, *S. aureus*, *P. aeruginosa*, *K. pneumoniae*, and *E. coli* [30].

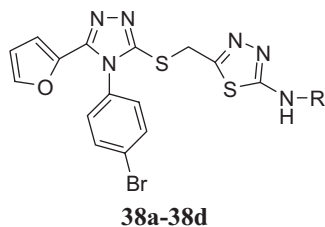


Antibacterial activity is strongly dependent on the nature of the substituents at 5-arylamino-1,3,4-thiadiazoles in a

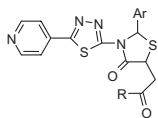
series of 2-[[1(2H)-phthalazinone-2-yl]methyl/ethyl]-5-arylamino-1,3,4-thiadiazole derivatives. Unsubstituted compound **36** showed 50% of inhibition against *B. subtilis* with respect to ampicillin [31]. Compound **37** having chloro group at para-position of arylsulfonylethane moiety attached with thiadiazole ring exhibited higher antimicrobial activity [32].



The antifungal activity of 1,2,4-triazolylmercaptomethyl-1,3,4-thiadiazoles has been tested against *M. gypseum* (NCPF-580), *M. canis*, *T. mentagrophytes*, *T. rubrum*, and *C. albicans* ATCC10231. Of the five synthesized compounds screened against fungal strains, four compounds (**38**) showed measurable activity against *T. mentagrophytes* [33] (Table 3).



Ranjina *et al.* [34] synthesized a number of aminothiadiazoles derivatives (**39**) containing 4-pyridyl and oxothiazolidin moieties in the same molecules. All the compounds had good antimicrobial activity but the compounds having a nitro group were present at the *-m* and *-p* position of the aryl ring, respectively, possessed stronger antibacterial activity than others.



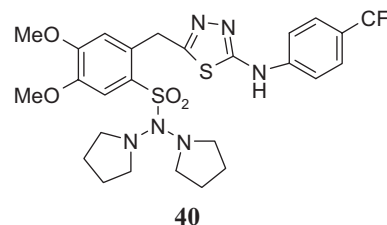
Ar = 4-OCH₃C₆H₄, 4-ClC₆H₄, 3,4,5-OCH₃C₆H₂, 3-NO₂C₆H₄, 4-NO₂C₆H₄, C₆H₅, 2-Furyl, 4-(CH₃)₂NHC₆H₄; R = phthalimidoxyl

Camoutsis *et al.* [35] synthesized a series of *N*-{5-[2-(*N*-substituted sulfamoyl)-4,5-dimethoxybenzyl]-1,3,4-thiadiazole-2-yl}-*N*-arylamines. All the newly sulfonamide-1,2,4-thiadiazoles were assayed *in vitro* for their growth

Table 3: Structural details of compounds **38a–38d**

S.No	R	<i>T. mentagrophytes</i> (MIC: μg/mL)
a	-C ₂ H ₅	4
b	-C ₄ H ₉	4
c	p-F-C ₆ H ₄	4
d	p-NO ₂ -C ₆ H ₄	4

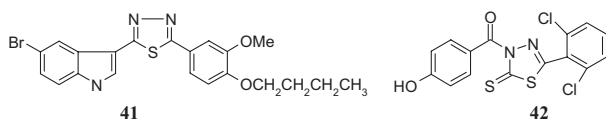
inhibitory activity against panel of selected Gram-positive bacteria, Gram-negative bacteria, and fungi and compared with reference drug ampicillin, streptomycin, bifonazole, and ketoconazole, respectively. The results of antimicrobial screening clearly indicated that the nature of substituents and their position on 1,3,4-thiadiazole nucleus affected the *in vitro* activity. SAR of the compounds revealed that pyrrolidine substituted compounds were found to be more potent than piperidine-, methylpiperazine-, and dimethylamino-containing compounds. Thus, it can be said that introduction of -CF₃ moiety and chloro atom in the *para*-position of the benzene ring of pyrrolidine substituted compound (**40**) is an essential part for improving antibacterial activity.



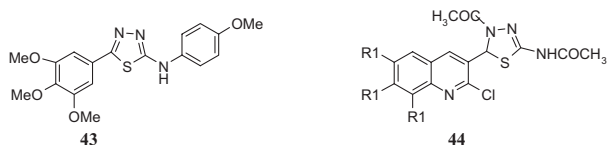
Anticancer activity

Kumar *et al.* [36] reported the synthesis of 5-(3-indolyl)-1,3,4-thiadiazoles and evaluated for anticancer activity. Primary screening was performed at a concentration ranging from 100 nM to 1 mM. Change in cell number and cell morphology in 96-well plates was observed at 24 and 48 h had been detected. Compounds that exhibited toxicity to cancer cell lines but not to normal cells were selected for the secondary confirmation assays. For secondary screening, the same concentration which was previously used in the primary screening was used and compounds were screened in triplicate. As a result, eight compounds were identified as potent agents for inducing cytoselective toxicity. It was found that substitution on C-2 position of the 1,3,4-thiadiazole ring plays an important role in imparting the cytotoxic activity to the compound. Replacement of phenyl ring at C-2 position with benzyl, 4-(dimethylamino)phenyl, 3,4-dimethoxyphenyl and 4-benzyloxy group enhanced the antiproliferative activity, while replacement of the phenyl group with p-chlorophenyl and introduction of third methoxy group reduced the biological activity. Compound 2-(4-(Benzyloxy)-5-(5-bromo-3-indolyl)-3-methoxyphenyl)-1,3,4-thiadiazole (**41**) with 4-benzyloxy-3-methoxyphenyl at C-2 position and 5-bromoindole at C-5 position was found to be the most potent compound of the series. Compound (4-hydroxyphenyl)[5-(2,6-dichloro)-2-thioxo-1,3,4-thiadiazol-3-yl]methanone (**42**) showed broad spectrum of growth inhibition activity against human tumor cells and remarkable cytotoxic activity on nonsmall lung cancer (HOP 92) having log GI₅₀ value at -6.49, colon cancer (HCC-2998) at GI₅₀ value -5.31 and significant cytotoxic activity on prostate cancer (PC-3) having GI₅₀

value -5.48 . SAR study revealed that electron withdrawing group at position C-5 of thiadiazole was favorable for activity [37].

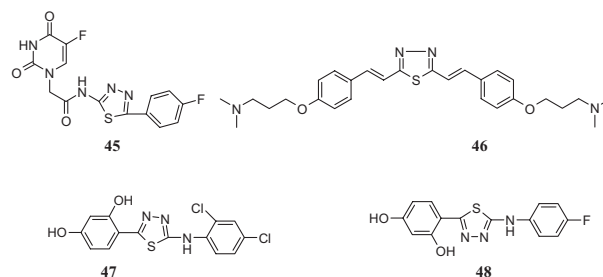


New derivatives of 2-arylamino-5-aryl-1,3,4-thiadiazoles were synthesized by refluxing aryl aldehydes, hydrazine hydrate, and aryl isothiocyanates in methanol followed by oxidative cyclization with ferric ammonium sulfate. Study of *in vitro* cytotoxic activity revealed a cytotoxic effect of individual compounds on cancer cells of prostate (PC3, DU145, and LnCaP), breast (MCF7 and MDA-MB-231), and pancreas (PaCa2). The SAR study showed that the 3,4,5-(OCH₃)₃C₆H₂ at C-5 position was responsible for binding to the Colchicine site on tubulin and found to be favorable for activity. Further variation of C-2 arylamino group was associated with lesser degree of effect on the activity of 1,3,4-thiadiazoles. Most of the synthesized compounds were moderate in activity and compound **43** displayed a greater potency toward pancreatic (PaCa2) cancer cell lines (IC₅₀ = 4.3 μ M) [38]. Marganakop *et al.* [39] synthesized quinolines derivatized with 1,3,4-thiadiazole via cyclization of quinoline thiosemicarbazones in a single step and investigated for their primary cytotoxic activity against cervical cancer cell lines (Hela). Compounds **44** with methoxy at C-6,7,8 of quinoline showed the potent anticancer activity and the cell lyses occurred only at 10 μ g/mL.

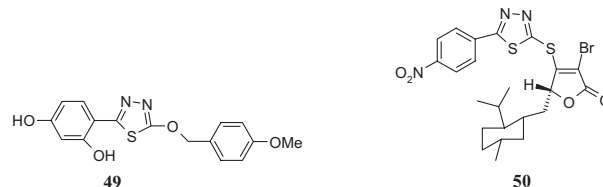


Zheng *et al.* [40] prepared several N¹-acetylamino-(5-alkyl/aryl-1,3,4-thiadiazole-2-yl)-5-fluorouracil derivatives. These compounds were evaluated for their anticancer activity on A-549 (human lung cancer cell), Bcap-37 (human breast cancer cell) by MTT assay. Compound **45** with electron withdrawing group attached to benzene ring was found to have activity against tested cell lines and possessed more potent antitumor inhibitory activity than 5-fluorouracil. Compound (E,E)-2,5-bis[4-(3-dimethyl-aminopropoxy)styryl]-1,3,4-thiadiazole (**46**) was found to be the most potent one by the MTT assay against A549, PC-3, and HA22T [41]. A number of N-substituted 2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole derivatives were investigated as antiproliferative agent, their *in vitro* cytotoxicity against the four human cell lines: SW707 (rectal), HCV29T (bladder), A549 (lung), and T47D (breast) suggested their potential as novel anticancer agents. Compound 2-(2,4-dichlorophenylamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole (**47**), with ID₅₀ two times lower (SW707, T47D) than that of cis-

platin displayed the highest cytotoxicity. It was noticed that the compounds with electron donating groups at C-terminal of the phenyl ring did not increase its cytoselective toxicity and the compounds with electron withdrawing groups (Cl, F) resulted in an increased activity by inducing cell death [42]. Compound 2-(4-fluorophenylamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole (**48**) inhibited proliferation of tumor cells derived from cancers of nervous system (medulloblastoma/rhabdomyosarcoma, neuroblastoma, and glioma) and peripheral cancers including colon adenocarcinoma and lung carcinoma [43].

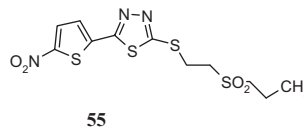
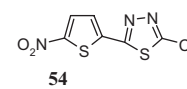
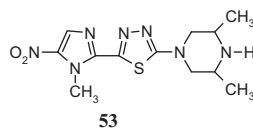
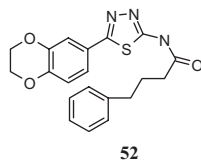
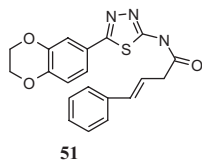


Matysiak *et al.* [44] examined the effect of various substitution at 5-position of 2-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles on antiproliferative activity against different human tumor cell lines. 2-(2,4-Dihydroxyphenyl)-5-(4-methoxybenzyloxy)-1,3,4-thiadiazole (**49**) showed ID₅₀ of 1.1 μ g/mL against HCV29T bladder cancer cell line and found to be significantly lower (T47D) than that of cisplatin, used as the reference compound. In a series of chiral 2,5-disubstituted 1,3,4-thiadiazoles possessing γ -butenolide moiety, compound **50** was screened against Hela cell lines by MTT assay and exhibited IC₅₀ of 0.9 μ M [45].



Focal adhesion kinase (FAK) is a 125 kDa protein that was involved in multiple cellular functions like cell proliferation, survival, motility, invasion, metastasis, and angiogenesis. The inhibition of FAK plays an important role in cancer therapy through decreased cellular viability, growth inhibition, or apoptosis. Recently, FAK was proposed to be a new potential therapeutic target in cancer. Sun *et al.* had designed a series of novel 1,3,4-thiadiazole derivatives containing 1,4-benzodioxan and evaluated their activity as FAK inhibitors. The results of the inhibitory activity of the designed compounds showed that compound **51** possessed high potency against FAK (EC₅₀ = 10.79 μ M). Compound **52** showed EC₅₀ values of 14.21–32.45 μ g/mL against HEPG2, HELA, SW1116 and BGC823 cell lines. The SAR study suggested that substitution with different acids led to different antitumor activity, and the

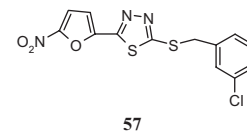
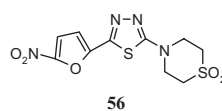
potency order was phenylpropionic acid >phenylacetic acid >benzoic acid. Compounds with substituted Cl group on benzene ring showed better antitumor activity than substitution with Br group (except compound **51** and **52**). Replacement of -Cl with -CH₃ group, however, led to decrease in cytotoxic activity against all cell lines [46].



Anti-*Helicobacter pylori*

Helicobacter pylori is a Gram-negative, microaerophilic bacterium found in the stomach. Acute infection of *H. pylori* may appear as an acute gastritis with abdominal pain (stomach ache) or nausea. The purpose of designing of agents for eradication of bacteria includes to overcome bacterial resistance and to inhibit proton pump. Moshaf *et al.* [47] synthesized 5-(1-methyl-5-nitro-1H-imidazol-2-yl)-1,3,4-thiadiazoles and screened for bactericidal activity against *H. pylori*. Compound **53**, substituted with 3,5-dimethylpiperazinyl moiety at the 2-position of the 5-(1-methyl-5-nitro-1H-imidazol-2-yl)-1,3,4-thiadiazole skeleton had strong anti-*H. pylori* activity at 0.5 μg/disk (average of inhibition zone >20 mm) which was superior to that of metronidazole. Attachment of pyrrolidine (instead of piperazine) to the 2-position of the thiadiazole and substitution with piperazine, methylpiperazine and 3,5-dimethyl substitution on the piperazine ring improved inhibitory activity. Further replacement of 3,5-dimethyl group with *N*-phenyl, *N*-benzyl, *N*-acetyl, and *N*-benzoyl on the piperazine ring diminishes the anti-*H. pylori* activity. 2-Substituted-5-nitroheterocycles were prepared by Foroumadi *et al.* [48] and evaluated for their anti-*H. pylori* activity. The authors further reported the SAR responsible for the activity. All the synthesized compounds exhibited high activity against clinical isolates of *H. pylori* with respect to standard drug, metronidazole (8 μg/disk). Compound 2-chloro-5-(5-nitrothiophene)-1,3,4-thiadiazole (**54**) was found to be the most active with zone of inhibition >30 mm at 8 μg/disk against metronidazole-sensitive *H. pylori* strain. Activity of this series was dependant on chloro amino, mercapto substituted 1,3,4-thiadiazole moiety attached to 5-nitroheteroaryl ring. In continuation of research, Foroumadi *et al.* [49] reported the effect of nitroaryl moiety and sulfur-containing alkyl side chain similar to tinidazole on 1,3,4-thiadiazole ring for their metronidazole-sensitive and metronidazole-resistant *H. pylori* strains. They suggested that among nitroheteroaryls, nitrothiophene analogs (**55**) showed more potent anti-*H. pylori* activity with respect to nitrofuran and nitroimidazole derivatives. Further, the S,S-dioxidation of ethylthio group attached to aryl-1,3,4-thiadiazoles improved its anti-*H. pylori* activity.

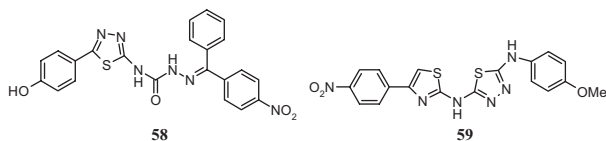
4-[5-(5-Nitro-2-furyl)-1,3,4-thiadiazol-2-yl] thiomorpholine 1,1-dioxide containing thiomorpholine S,S-dioxide moiety (**56**) showed the highest anti-*H. pylori* activity at a concentration of 8 μg/disk producing an average inhibition zone of more than 27 mm, which was greater than that by metronidazole (16.3 mm) [50]. Mohammadhosseini *et al.* tested eight compounds in a series of 2-[(chlorobenzyl)thio]-5-(5-nitro-2-furyl)-1,3,4-thiadiazoles for possible anti-*H. pylori* activity. Of eight, four derivatives showed strong anti-*H. pylori* activity at concentration of 8–32 μg/disk and compound **57** containing the 3-chlorobenzylthio moiety was found to exhibit the most potent and selective inhibitory activity against *H. pylori* with an inhibition zone of more than 20 mm at a concentration of 8 μg/disk [51].



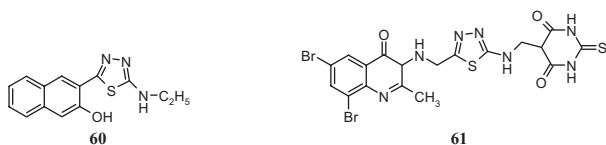
Anticonvulsant activity

Epilepsy is a brain disorder in which a person has repeated seizures (convulsions) over time and a collective term given to a group of syndromes that involve spontaneous, intermittent and abnormal electrical activity in the brain. The pharmacotherapy of epilepsy has been achieved during the last decade. Furthermore, although for the last twenty years new antiepileptic drugs have been introduced into clinical practice, the maximal electroshock (MES) test and the subcutaneous pentylenetetrazole (scPTZ) test are the most widely used animal models of epilepsy to characterize the anticonvulsant activity [52]. Recently, Rajak *et al.* [53] carried out the synthesis of some 2,5-Disubstituted 1,3,4-Thiadiazoles and evaluated their potential anticonvulsant activity. The results showed that compound with 4-nitrophenyl-substituted semicarbazone (**58**) were the most active compound comparable with carbamazepine. The SAR study suggested that [5-(4-substituted phenyl)-1,3,4-thiadiazol-2-yl] moiety as hydrophobic portion, two-electron donor atom and another hydrophobic distal aryl ring substituted with *p*-NO₂ group responsible for metabolism, played a crucial role for its anticonvulsant activity. Replacement of the proton on the carbimino carbon atom by phenyl ring increased its affinity for hydrophobic binding site. Siddiqui and Ahsan observed the effect of electron withdrawing and electron releasing groups on

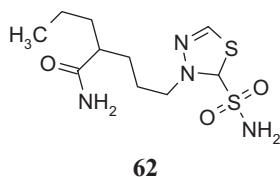
phenyl ring attached to thiazole and thiadiazole moiety on their anticonvulsant activity. Compound **59** having nitro group attached to the phenyl ring adjacent to the thiazole moiety demonstrated more potent anticonvulsant activity and the removal or replacement of $-\text{NO}_2$ function by a $-\text{Cl}$, $-\text{Br}$ moieties was responsible for loss of activity [54].



In an attempt to improve the potency and selectivity of 2,5-Disubstituted-1,3,4-thiadiazoles, Dogan *et al.* [55] synthesized a series of 2-(N-alkyl/aryl-Nacetylamino)-5-(3-acetoxy-2-naphthyl)-1,3,4-thiadiazole derivatives. Compound 2-ethylamino-5-(3-hydroxy-2-naphthyl)-1,3,4-thiadiazole (**60**) showed 90% protection against pentylenetetrazole-induced generalized convulsions. Further, substitution of ethyl and acetylation of thiadiazoles resulted in loss of activity. Compound 5-{2'-amino-5'-[3''-aminomethylene-2''-methyl-6'',8''-dibromoquinazolin-4'' (3''H)-onyl]-1',3',4'-thiadiazol-2'-yl}-2-thiobarbituric acid (**61**) showed high percentage protection 90% (50 mg/kg ip) in both MES and PTZ models [56].



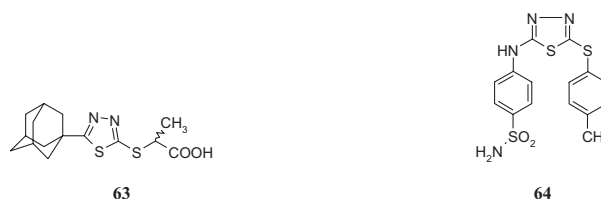
A new series of sulfonamides incorporating valproyl and other lipophilic moieties has been synthesized by Masereel *et al.* [57] to study the effect of different alkyl/arylcarboxamido/sulfonamido/ureido moieties on the 5th position of 1,3,4-thiadiazolesulfonamide on its anticonvulsant activity. Their findings revealed that the valproyl derivative of acetazolamide (5-valproylamido-1,3,4-thiadiazole-2-sulfonamide) **62** was the best in the series as it exhibited very strong anticonvulsant activity in an MES test in mice.



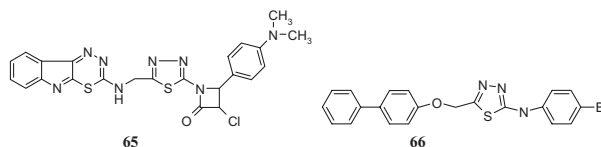
Anti-inflammatory activity (COX-inhibitors)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are important therapeutically active compounds used in the treatment of acute and chronic inflammation, pain, and fever. Thiadiazole incorporated in different heterocyclic templates has been reported to possess potent anti-inflammatory activity. Most of the synthesized thiadiazole derivatives exert anti-inflammatory activity by inhibition of the enzyme

involved in the first step of the conversion of arachidonic acid to prostaglandins (PGs). Anti-inflammatory activity of new series of 5-(1-adamantyl)-1,3,4-thiadiazole derivatives was reported by Kadi *et al.* [58]. Interestingly, compound **63**, substituted with propionic acid at 2nd position of 1,3,4-thiadiazoline-2-thiones, showed almost equal anti-inflammatory activity at 20 mg/kg to that of Indomethacin (5 mg/kg). Replacement of 2-propionic acid with acetic and 3-propionic acid was slightly detrimental to the anti-inflammatory activity. Sainy *et al.* [59] prepared several 2-amino-5-sulfanyl-1,3,4-thiadiazoles and concluded that the compounds were associated with lesser degree of anti-inflammatory activity when compared to indomethacin. Only compound 4-[5-(4-Fluorophenylsulfanyl)-[1,3,4]thiadiazol-2-ylamino]benzenesulfonamide **64** showed 65.90% inhibition of paw edema after 3 h at 56 mg/kg (body weight) dose and 66.40% protection in acetic acid induced inflammation in mice.

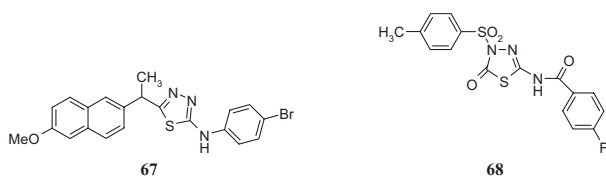


The anti-inflammatory activity of 2-aryl-3-{5-[[[1,3,4]thiadiazino[6,5-b]indol-3-ylamino) methyl]-1,3,4-thiadiazol-2-yl}-1,3-thiazolidin-4-one/azetidin-2-one (**65**) were studied using carrageenan induced rat's paw edema method. Bhati and Kumar noted that compound with 2-chlorophenyl group at C-4 of azetidin-2-one ring as substituent exhibited the most potent anti-inflammatory (41.23%) and analgesic activity (38%) at a dose of 50 mg/kg than that of their corresponding thiazolidinone compounds [60]. Kumar *et al.* [61] synthesized several 1,3,4-thiadiazole derivatives of biphenyl-4-yloxy acetic acid (**66**). All the compounds were screened for their anti-inflammatory and analgesic activity of varying degree from 27.27% to 63.63% at the dose of 10 mg/kg po.

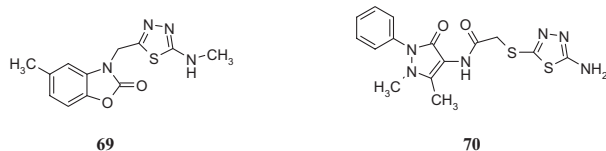


1,3,4-thiadiazole analogs of naproxen carrying a 4-bromophenyl amino group (**67**) at second position of the thiadiazole ring showed 78.02% inhibition in rat paw edema [62]. The presence of the tolyl substituent on the sulfonamide moiety on 4th position of 1,3,4-thiadiazole ring was found to be suitable for increasing the analgesic and anti-inflammatory activity. Substituent on the amide chain affected the activity which became more evident for example halogenated substituents on the para-position of the aromatic ring of the amide moiety improved the activity

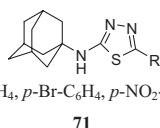
profile. Compound **68** with a *p*-fluoro phenyl substituent was the most active compound (51.4 of inhibition at 50 mg/kg) among the benzoyl sulfonamido derivatives [63].



Salgin-Goksen *et al.* [64] synthesized 1,3,4-thiadiazoles containing 5-methyl-2-benzoxazinone derivatives and evaluated their anti-inflammatory activity. All the compounds exhibited anti-inflammatory activity (at the dose 50 mg/kg p.o.) of varying degree from 53.2% to 85.3% in inhibition of edema. Compound **69** with methyl group showed analgesic activity similar to that of morphine and aspirin. Conversion of the amino group to the carbamate or phenylthioureido functionalities at 5th position of the 2-(5-amino-1,3,4-thiadiazol-2-ylthio)-*N*-(2,5-dihydro-2,3-dimethyl-5-oxo-1-phenyl-1H-pyrazol-4-yl)acetamide (**70**) decreased anti-inflammatory as well as analgesic activity [65].



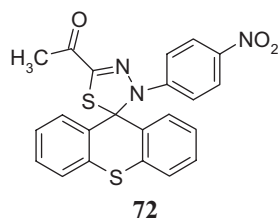
2-(1-adamantylamino)-5-substituted-1,3,4-thiadiazole derivatives (**71**) were found to be associated with lesser degree of anti-inflammatory activity compared with indomethacin, while 2-(1-adamantyl)-5-substituted-1,3,4-oxadiazoles appeared to exhibit good dose-dependent anti-inflammatory activity [7].



R = -C₆H₅, *p*-C₆H₄, *p*-Cl-C₆H₄, *p*-Br-C₆H₄, *p*-NO₂-C₆H₄, 2-thienyl, 1-adamantyl

71

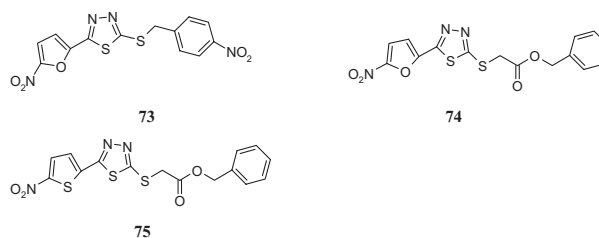
The spirothiadiazole derivative having 4-nitrophenyl group (**72**) exhibited promising maximum activity in induced paw inflammation model using mice and leukocyte accumulation in a carrageenan pleurisy model in the rat. Significant decrease in activity was found for the compounds with the replacement of 4-nitrophenyl group with the 4-bromophenyl and phenyl group [66].



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Antitubercular activity

The emergence of multidrug-resistant tuberculosis, coupled with the increasing overlap of the AIDS and tuberculosis pandemics has brought tuberculosis to the forefront as a major worldwide health concern. Foroumadi *et al.* [67] synthesized 2-(5-nitro-2-furyl)- and 2-(1-methyl-5-nitro-1H-imidazol-2-yl)-1,3,4-thiadiazole derivatives and screened their *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* H37_{Rv} using alamar-blue susceptibility test. Compounds demonstrating at least >90% inhibition in the primary screen were retested at lower concentration to determine the MIC in BACTEC 12B. The data compared with the standard drug rifampin at 0.031 μg/mL concentration which showed 97% inhibition. Compounds with 5-nitro-2-furyl (**73**) and 4-nitrobenzyl substitution showed the highest activity against *M. tuberculosis* (MIC = 3.13 μg/mL). Among nitrofurans derivatives, substitution of the thioester group at C-5 of 1,3,4-thiadiazole ring with a benzyl analog (**74**) was found to be the most active (MIC = 0.78 μg/mL). Substitution of the ester group with a propyl or butyl group resulted in compounds with significant loss of activity [68]. Moreover, their nitrothienyl analog (**75**) was equally and highly active against *M. tuberculosis* H37_{Rv} [69].



Similarly, 2-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole derivatives were investigated for antitubercular activity and it was found that compound **76** bearing a primary alkylthio substitution displayed good antitubercular activity (MIC = 3.13–6.25 μg/mL). Oxidation of thio group in ethylsulfonfyl analog increased its activity [70]. Oruc *et al.* [71] discussed the relationship between the structures of compounds and their antitubercular activity by electronic-topological method (ETM) and feed forward neural networks (FFNNs) trained with the back-propagation algorithm. They reported that 2-phenylamino-5-(4-fluorophenyl)-1,3,4-thiadiazole (**77**) showed highest% of inhibition.

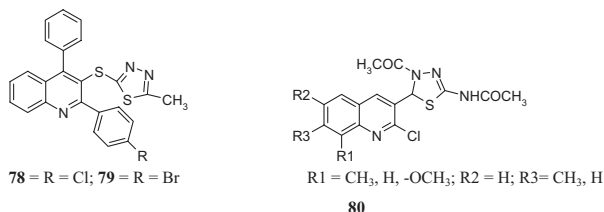


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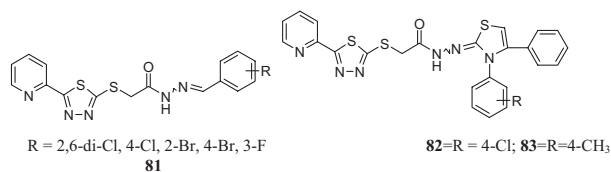
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Chitra *et al.* synthesized 3-heteroarylthioquinoline derivatives of 1,3,4-thiadiazole and screened their *in vitro* antimycobacterial activity against *M. tuberculosis* H₃₇R_v using Middle brook 7H11 agar medium supplemented with OADC by agar-dilution method. They found that the antitubercular activity was considerably affected by various

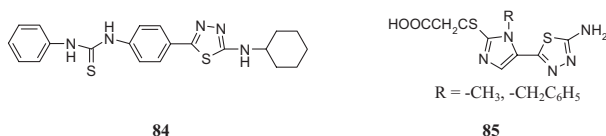
substituents like 2-methyl-1,3,4-thiadiazole, benzothiazole and 2-phenyl-2H-tetrazole on the 3-position of quinoline ring and it was further supported by the fact that compounds with no substitution did not show any considerable activity. Compounds **78** and **79** with chloro- and bromo-substituted aromatic ring found to be more active (MIC = 3.2–3.5 $\mu\text{g}/\text{mL}$) [72]. Analogs (**80**) having methyl and methoxy groups at the C8 of quinoline nucleus showed inhibition (MIC) at 5 $\mu\text{g}/\text{mL}$ [73].



Various [5-(pyridin-2-yl)-1,3,4-thiadiazol-2-ylthio]acetic acid arylidene-hydrazide derivatives (**81**) were examined as antitubercular agents against *M. tuberculosis* H37Rv. Some of them (when R = 2,6-di-Cl, 4-Cl, 2-Br, 4-Br, 3-F on the phenyl residue) showed activity with MIC = 20 $\mu\text{g}/\text{mL}$ against the tested strain. The activity of these compounds was due to partial resemblance to pyridine-2-carboxamidrazone [74]. Further replacement of arylidene moiety of the compounds by the 3,4-diaryl-3H-thiazol-2-ylidene did not significantly increase the antimycobacterial activity. Only compound **82** and **83** showed moderate activity toward all the clinical isolates of *M. tuberculosis* [75].

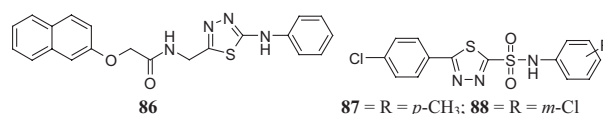


The activity of new *N*-phenyl-*N'*-[4-(5-alkyl/arylamino-1,3,4-thiadiazole-2-yl)phenyl]thiourea derivatives with various substituents in thiadiazole ring was studied for antitubercular activity against *M. tuberculosis* H37Rv by using BACTEC 460 radiometric system. Most of the investigated compounds were found to be virtually less active and did not suppress the growth of micro-organisms at concentrations of 6.25 $\mu\text{g}/\text{mL}$. Only compound **84** having cyclohexyl group showed the highest inhibition of 67% [76]. None of the α -5-(5-Amino-1,3,4-thiadiazol-2-yl)-2-imidazolylthio]acetic acid derivatives (**85**) exhibited inhibitory activity against *M. tuberculosis* at single concentration of 6.25 $\mu\text{g}/\text{mL}$ in BACTEC 12B Medium [77].



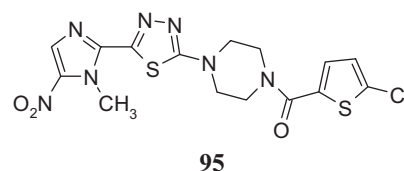
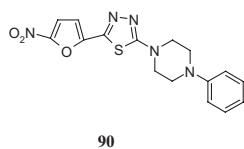
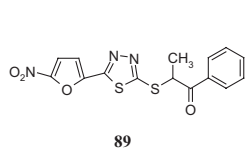
Antiviral activity

Human immunodeficiency virus type 1 (HIV-1) has been recognized as the contributing agent in the transmission and the development of acquired immunodeficiency syndrome (AIDS). With increasing resistance of the retrovirus HIV-1 to current drugs, there is a need for development of new compounds. The unique nature of the replicative cycle of HIV-1 provides many potential targets for therapeutic interventions. One of these, reverse transcriptase (RT) is a key enzyme that is packaged within the HIV virion capsid and plays an essential and multifunctional role in the replication of the virus [78]. Hamad *et al.* [79] synthesized 2-(naphthalen-2-yl)oxy)-*N*-((5-(phenylamino)-1,3,4-thiadiazol-2-yl)methyl)acetamide (**86**) and tested its *in vitro* anti-HIV-1 (strain IIIb) and anti-HIV-2 (strain ROD) activity by the inhibition of the virus induced cytopathic effect in the human T-lymphocyte (MT-4) cells, based on MTT assay. All the compounds were found to be inactive except for **86** which showed EC₅₀ values of 0.96 $\mu\text{g}/\text{mL}$. It should be noted that 5-(4-chlorophenyl)-1,3,4-thiadiazole sulfonamides were evaluated for antitobacco mosaic virus activity. It was found that some of the compounds with sulfonamide moiety were effective inhibitors of tobacco mosaic virus with less cytotoxicity. Compounds **87** and **88** showed inhibitory activity of about 42% [80].

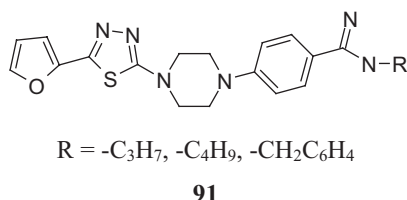


Anti-leishmanial activity

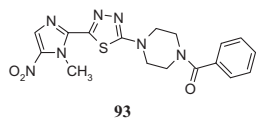
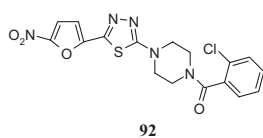
Leishmaniasis is a disease caused by the *Leishmania* parasite and is transmitted to humans by sandflies [81]. A large number of synthetic 1,3,4-thiadiazoles derivatives have been well documented and tested in the recent years in antileishmanial assays. Some of the new 5-(5-nitroaryl)-2-substituted-thio-1,3,4-thiadiazole derivatives were evaluated for their inhibitory activity against *Leishmania major* and all the tested compounds exhibited a high activity against *L. major* promastigotes with IC₅₀ values ranging from 1.11 to 3.16 μM . SAR study explained that different nitroaryl derivatives including furan, thiophene, and *N*-methylimidazole at C-5 and bulky residue attached to the 2-position of thiadiazole ring were responsible for the anti-*Leishmania* activity. Furthermore, these compounds were close in activity and the differences observed were not very significant. Compound 2-(5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-ylthio)-1-phenylpropan-1-one (**89**) showed IC₅₀ of 1.11 μM against *L. major* promastigotes [82]. A high activity level of IC₅₀ = 0.1 μM against *L. major* promastigotes was observed for compound that contained a 4-phenyl-piperazine (**90**) group at C-2 of 1,3,4-thiadiazole ring in a series of nitrofuran derivatives [83].



The 1-(5-(5-nitrofuran-2-yl)-1,3,4-thiadiazole-2-yl)piperazines (**91**) having *n*-propyl, *n*-butyl and benzyl side chain on benzamidine showed IC_{50} values of 0.08, 0.2, and $0.4 \mu M$, respectively, against the promastigote form of *L. major*. SAR study revealed that substitution with benzamidine was favorable for activity and replacement by a five-membered ring, namely the imidazoline and six-membered ring, namely tetrahydropyrimidine were devoid of activity [84].



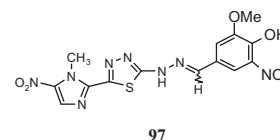
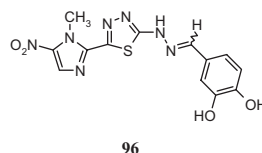
Further substitution on phenyl group of piperazine with halogen did not increase anti-leishmanial activity against both promastigote and amastigote forms of *L. major*. Compound with 2-chlorobenzoyl (**92**) on the piperazine ring showed anti-leishmania activity with $IC_{50} = 10.73 \mu M$ [85]. Poorrajab *et al.* [86] synthesized a series of 5-nitroimidazole, 5-nitrofuran, 5-nitrothiophene analogs of N-substituted-piperazinyl-1,3,4-thiadiazoles, and their anti-leishmania activity was evaluated against *Leishmania* wild-type species and intracellular parasite. Toxicity against host cells and inhibition of topoisomerases I and II was also determined. Most of the synthesized compounds exhibited low toxicity against the host cells ($IC_{50} \geq 80 \mu M$) and high selectivity against intracellular amastigotes with selectivity index >12 . Compound **93** containing a benzoyl group on the piperazine ring was found to be the most active derivative with varying degree of inhibition against *L. major* and inhibit the parasite protein Top I and II.



Some of the nitroimidazolyl-1,3,4-thiadiazoles were tested *in vitro* against *L. major*. Halogen substitution (chloro- or bromo-) on thiophen-2-carbonyl moiety seemed to be a beneficial structural feature for the most active compound was 1-[(5-chloro-2-thienyl)carbonyl]-4-[5-(1-methyl-5-nitro-1H-imidazol-2-yl)-1,3,4-thiadiazol-2-yl]piperazine (**94**) with an IC_{50} value of $9.35 \mu M$ against *L. major promastigotes* [87].

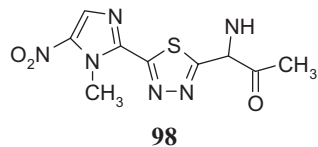
Trypanocidal (anti-epimastigote) activity

Trypanosomiasis is caused by the hemoflagellate protozoan *Trypanosoma cruzi*, which spread the infection in humans through the bite of a triatomine insect vector or blood transfusion. The infective trypomastigote form of the parasite penetrates into mammalian cells and convert into proliferative amastigotes. Rupture of these cells leads to liberation of the parasites and proliferation of the infection [88]. A number of new 1,3,4-thiadiazole-2-arylhydrazone derivatives of megaloz were screened for trypanocidal (anti-epimastigote activity, %AE) using megaloz-treated parasites as control. Some of the synthesized compounds showed IC_{50} value in the range of 5.3 – $135.6 \mu M/mL$. The compounds also showed non-specific cytotoxicity to macrophages at this concentration. The most active hydrazone compound of series was 3,4-dihydroxyphenyl derivative (**96**), which showed an IC_{50} of $5.3 \mu M$ and was found to be superior in activity than the prototype megaloz ($IC_{50} = 9.9 \mu M$) [89]. Salomao *et al.* [90] also reported that 3,4-dihydroxyphenyl derivatives showed a high *in vitro* potency while devoid of any *in vivo* effect on trypomastigotes. Replacement of 3-hydroxyphenyl and 3-bromophenyl groups instead of 3,4-dihydroxyphenyl group on 1,3,4-thiadiazole-2-arylhydrazones significantly decreased the level of *T. cruzi in vivo* as well as *in vitro*. In searching for better trypanocidal activity, Carvalho *et al.* reported the structurally related 1,3,4-thiadiazole-2-arylhydrazone derivatives. Replacement of 3,4-dihydroxyphenyl with 5-nitrovanillyl group was found to be less potent than the prototype Brazilozone (**97**) [91].



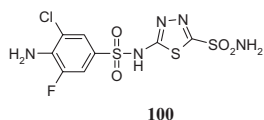
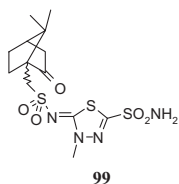
Trypanocidal activity of megaloz [2-amino-5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole] is associated with DNA damage of *T. cruzi*. Substitutions at 4th position of imidazole moiety of 5-(1-methyl-5-nitro-1H-2-imidazolyl)-1,3,4-thiadiazol-2-amine (megaloz) with electron-donating or withdrawing substituents was found to reduce the trypanocidal activity. Removing the nitro group or changing the position made the compounds totally inactive.

The activity of megaloz was retained when N-acetylation (**98**) was done. It was totally lost when substituted with trifluoromethyl analog [92].



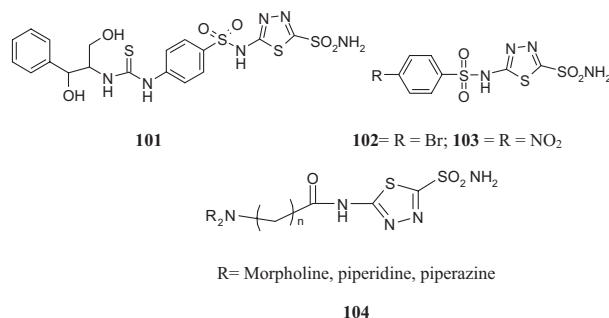
Carbonic anhydrase inhibitory activity

1,3,4-Thiadiazole-2-sulfonamides were earlier known as carbonic anhydrase inhibitors. Carbonic anhydrase enzymes (CAs) are ubiquitous zinc enzymes. These enzymes catalyze the interconversion between carbon dioxide and the bicarbonate ion and are involved in crucial physiological processes connected with respiration and transport of $\text{CO}_2/\text{HCO}_3^-$ between metabolizing tissues and the lungs, pH and CO_2 homeostasis, electrolyte secretion in a variety of tissues and organs, biosynthetic reactions such as gluconeogenesis, lipogenesis, and urea-genesis, bone resorption, calcification, tumorigenicity and several other physiological and pathological processes. Inhibition of CAs would be clinically useful in the treatment of various diseases such as glaucoma, epilepsy, congestive heart failure, mountain sickness, gastric and duodenal ulcers, and other neurological disorders [93,94]. Maresca *et al.* [95] have prepared several (R)-/(S)-10-camphorsulfonyl-substituted aromatic/heterocyclic sulfonamides and evaluated the inhibition of several mammalian isoforms of the zinc enzyme carbonic anhydrase (CA, EC 4.2.1.1). Compounds having R- and S-10-camphorsulfonyl moiety represented more susceptibility toward to inhibition against mitochondrial isoform hCA VA. Generally the R-enantiomer (**99**) was more active than the corresponding S-isomer. Nishimori *et al.* [96] investigated the inhibition of various sulfonamides and sulfamates on two β -carbonic anhydrases (CAs, EC 4.2.1.1) isolated from the bacterial pathogen *Salmonella enterica serovar Typhimurium*. Compound 3-Fluoro-5-chloro-4-aminobenzolamide (**100**) showed an inhibition constant of 51 nM against stCA 1 and of 38 nM against stCA 2, while acetazolamide inhibited stCA 1 and stCA2 with K_i of 59 and 84 nM, respectively.

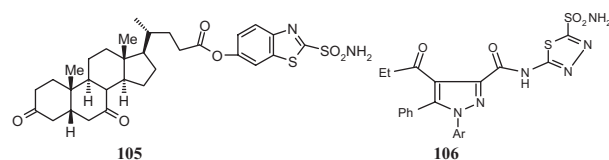


A small library of sulfonamides has been synthesized by Cecchi *et al.* using benzolamide as lead compound. The new derivatives were investigated as inhibitors of the cytosolic isoforms hCA I and II, as well as the tumor-associated isozyme hCA IX. New compounds showed excellent inhibitory activities against all three isozymes with inhibition constants in the range of 0.6–62 nM against hCA I,

0.5–1.7 nM against hCA II and 3.2–23 nM against hCA IX, respectively [97]. Out of the nine compounds, **101** showed maximum activity against the tested isoenzymes. The sulfanilamides acylated at the 4-amino group with short aliphatic/aromatic moieties incorporating 2–6 carbon atoms showed modest hCA XIV inhibitory activity which was found to be more potent than sulfanilamide (K_i of 5.4 μM). Compound **102** and **103** substituted with bromo and nitro group at 4th position of phenyl ring showed 3.15–4.10 times more effective than the lead compound acetazolamide [98]. Sulfanilamide derivatives were also synthesized by incorporating heterocyclic amines like morpholine, piperidines, and piperazines using tail approach. Derivatives (**104**) exhibited much better inhibition of carbonic anhydrase isoforms namely hCA I, hCA II and hCA IX than the parent compounds. Among sulfanilamide derivatives, the derivatives containing morpholine ring revealed best inhibitory activity [99].

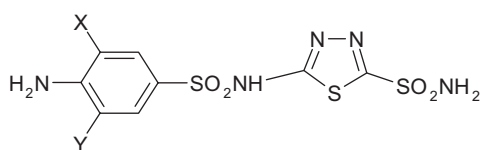


Scozzafava and Supuran synthesized a series of sulfonamides incorporating bile acid moiety. A large number of such derivatives showed strong inhibitory activity against three isozymes of carbonic anhydrase (CA, EC 4.2.1.1), that is CA I, II and IV. SAR study revealed that heterocyclic sulfonamide attached to acylating moiety dehydrocholic acid (**105**) showed most active inhibitory activity against hCA II and bCA IV with K_i value of 0.6 and 5 nM [100]. Several pyrazole derivatives of 5-amino-1,3,4-thiadiazole-2-sulfonamide (**106**) were synthesized and their inhibitory activity against hydratase and esterase property of carbonic anhydrase isoforms hCA I and hCA II were studied. Derivatives showed more inhibitory activity than parent compounds, 5-amino-1,3,4-thiadiazole-2-sulfonamide and acetazolamide [101].



Two series of halogenated sulfanilamide and aminobenzolamide containing one or two halogens (F, Cl, Br, I) were synthesized. Compounds were investigated for inhibitory activity against carbonic anhydrase isoforms hCA I, hCA II, hCA IV and hCA IX. Aminobenzolamides were

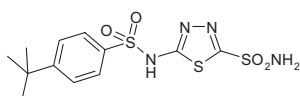
found to be more active than sulfonamides against hCA I, hCA II and hCA IV. SAR revealed that bromo derivatives were more active than fluoro derivatives which in turn were more active than iodo derivatives and least activity was observed in chloro derivatives. Different patterns were seen in activity against hCA IX. Both sulfanilamide and aminobenzolamide derivatives were found to be very potent inhibitors. 3-Fluoro-5-chloro-4-aminobenzenesulfonamide derivative of sulphonylthiadiazole (**107**) showed the best hCA IX inhibition with K_i of 12 nM which was two times more active than acetazolamide [102].



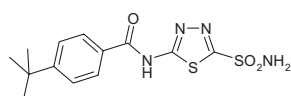
X= Cl, Br, I, F; Y=Cl, Br, I, F

107

Independent strains of *H. pylori* were obtained from different kinds of gastric mucosal lesions and from these hpCA (bacterial carbonic anhydrase) DNAs were cloned and sequenced. Library of sulfonamides was evaluated for inhibitory activity against hpCA. Among these sulfonamides, some compounds were commercially available, while some were synthesized. To benzenesulfonamide and 1,3,4-thiadiazole-2-sulfonamide, 4-tert-butylphenylcarboxamido or 4-tert-butylphenylsulfonamido tails were attached and 12 derivatives were prepared. Derivatives of 4-tert-butylphenylcarboxamido were found to be slightly less efficient in inhibiting hpCA than corresponding 4-tert-butylphenylsulfonamido derivatives. Compounds 5-(4-tert-butylphenylsulfonamido)-1,3,4-thiadiazole-2-sulfonamide (**108**) and 5-(4-tert-butylphenylcarboxamido)-1,3,4-thiadiazole-2-sulfonamide (**109**) were found to be very strong inhibitors of hpCA with K_i of 12–13 nM [103].

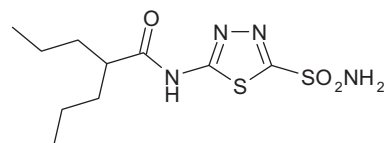


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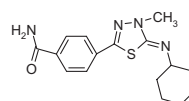
Maseerl *et al.* [104] synthesized a series of compounds first by reacting valproic acid with aromatic and heterocyclic sulfonamides in the presence of carbodiimides and secondly reacting valproyl chloride with sulfonamide in the presence of base. Derivatives were evaluated for inhibitory action against carbonic anhydrase enzymes, namely hCA I, hCA II (both of human origin), and bCA IV (bovine origin). Data revealed that inhibitory activity of compounds was greatly influenced by nature of sulfonamide attached to valproyl moiety. 5-Valproylamido-1,3,4-thiadiazole-2-sulfonamide (**110**) was found to be more effective than acetazolamide and methazolamide against all three enzymes.



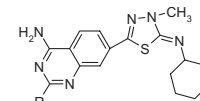
110

Thiadiazoles as miscellaneous agents

Vergne *et al.* [105] discussed the synthesis and SAR studies of a series of novel small thiadiazoles as inhibitors of PDE7. Out of the synthesized compounds, derivatives with 4-CONH₂ on benzene ring (**111**), 4-aminoquinazoline (**112**) and 2-methyl-4-aminoquinazoline (**113**) on C-5 of thiadiazole ring exhibited high PDE4 inhibitory activity with an IC₅₀ value of 0.061, 0.027, and 0.0039 μM, respectively. From SAR studies, they concluded that the 4-aminoquinazoline derivatives along with hydrophobic steric bulk attached with nitrogen of C-2 of thiadiazole showed an increase in activity because of its structural similarity with the adenine part of cAMP. Replacement of the cyclohexyl moiety with smaller ring was not as selective and found to be detrimental to the enzymatic activity.

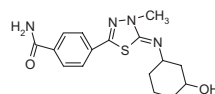


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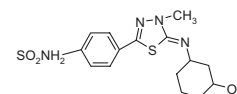


112 = R = H; **113** = R = -CH₃

Introduction of an OH group on 3rd position of cyclohexyl group of **114** represented IC₅₀ of 0.088 nM toward PDE7. Modification of 4-CONH₂ group with sulfonamide (**115**) significantly improved the pharmacokinetic profile and binding affinity for PDE7 [106].



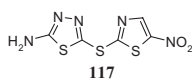
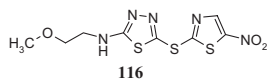
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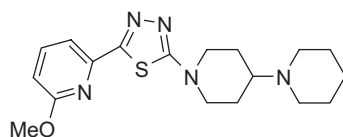
115

De *et al.* [107] reported novel small molecules thiadiazole derivatives as c-Jun N-terminal kinase inhibitors. On the basis of a lead structure from high throughput screening, they identified that substitution on 2nd-position with either 2-methoxyethyl group, sec-butyl group or n-propyl group improved the pepJIP1 displacement (DELFA) and the kinase activity (LANTHA) assays. Out of the synthesized compounds, **116** showed an IC₅₀ of 4.8 μM in the kinase assay substrate and it displaced pepJIP1 with an IC₅₀ of 158 nM. Modification on 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-5-(5-nitrothiazol-2-ylthio)-4H-1,2,4-triazol-3-ol which showed competitive inhibition of the interactions between JNK and pepJIP1 with an IC₅₀ of 280 nM resulted in the discovery of **117** which could bind at the JIP site with the nitrothiazol group crossing the ridge close to residues

Arg127 and Cys163 of enzyme side with an IC₅₀ of 239 nM [108].



Xiao *et al.* [109] discovered the 2-piperidinopiperidine-5-arylthiadiazoles as H₃ antagonists which lead to increase histamine levels by blocking the histaminergic neurons irreversibly and may be useful in treating obesity, diabetes as well as other CNS disorders such as cognitive disorders like Alzheimer's and Parkinson's disease. SAR investigations revealed that *o*, *m* and *p* substituent such as polar groups OMe, CN, and COCH₃ on phenyl ring increases the H₃ receptor antagonistic activity. Further replacement of phenyl ring with 2-pyridyl was found to be favorable, while pyrimidine and pyrazole offered less activity. Compound **118** with 3-methoxy group at 2-pyridyl ring substituted on C-5 of thiadiazole was found to be the most active.



118

Conclusions

1,3,4-Thiadiazole is an unique template that is associated with several biological activities. The potency of 4-thiazolidinone nucleus is clearly evident from the clinically used drugs such as acetazolamide, methazolamide, and megalol. Though the antibacterial, antitubercular, carbonic anhydrase inhibitors, and antiulcer are the four major areas of clinical use, other potential targets are still to be explored. Most of the positions were explored for improving the antibacterial and antitubercular profile of 1,3,4-thiadiazole, but still none of the derivatives showed promising antitubercular activity. The literature exhaustively analyzed to provide a meaningful overview of the structural requirements for activity, wherever possible.

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