Mini Review
Volume 13:1, 2023

Medicinal Chemistry

ISSN: : 2161-0444 Open Access

1,3,4-Thiadiazole and its Derivatives: A Versatile Moiety

Tejashree Deokule*, Chaitrali Gosavi and Aditya Sarode

Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune-411044, Maharashtra, India

Abstract

The evaluation of thiazole's biological activity, such as antibacterial, antiprotozoal, antitubercular, antifungal and anthelmintic, with an emphasis on their potential medicinal applications, is desirable because the thiazole has an important component effect on the pharmacophores of a large number of medicinally significant molecules. We are particularly interested in investigating newly synthesized aminothiazoles, particularly 2-aminothiazole derivatives, a class of heterocyclic ring systems with antiviral, antimicrobial, anticancer and anti-inflammatory properties, respectively. Numerous human cancer cell lines, including breast, leukemia, lung, colon, CNS, melanoma, ovarian, renal and prostate cell lines, were the subjects of previous *in vitro* anticancer evaluation studies of a variety of 2-aminothiazole analogs. In its use as a core structure in a variety of therapeutic applications, substitutions at the 2-position of benzothiazole have emerged. Interesting results from studies on the structure-activity relationship show that changing the structure of a substituent group at its C-2 position frequently alters its bioactivity. Although 2-substituted benzothiazoles have numerous therapeutic applications, their anti-inflammatory activity has not been extensively studied. Additionally, the numerous pharmaceutical applications of thiazole derivatives have sparked a lot of interest. A wide range of biological properties can be found in thiazole derivatives, including cardiotonic, fungicidal, sedative, anesthetic, bactericidal and anti-inflammatory properties. Thiazole derivatives are also said to have a wide range of biological activities.

Keywords: Thiazole • Thiadiazole • Hetero cycles • Anti-diabetic • Antioxidant

Introduction

1,3,4-Thiadazoles 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 binding domain, sulphur 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 Many drugs containing 1,3,4-thiadiazole nucleus such as acetazolamide 1, methazolamide 2, megazol 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 ten 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 which can be classified into the following categories: (Figure 1).

Antibacterial and antifungal activity

1,3,4-Thiadiazole has shown a broad spectrum of activity against various pathogens and extensive research has been done 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 was evaluated *in vitro* antimicrobial activity against bacterial and fungal species. The results showed that the tested compounds possessed weak antibacterial and antifungal activity compared to 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 have been evaluated for antifungal activity against several clinical isolates of *C. albicans*. The compounds with methyl, phenyl, 4ethoxyphenyl and halogenophenyl groups at C-2 of thiadiazole ring showed higher antifungal activity [4]. Wahab A, et al. 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 hydrazonoyl chlorides [5]. Out of these synthesized compounds screened against bacterial strains, compound showed significant activity against *E. coli* and *C. albicans*. The tested compounds did not exhibit any activity against Gram-(+) strains up to the maximum concentration of 100 µg mL-1. Kadi, et al. reported the synthesis of a new series of 5-(1-adamantyl)-1,3,4-thiadiazole derivatives for their antimicrobial activity [6]. Upon evaluation of antibacterial activity, it was found that almost all the compounds, especially compound exhibited more activity than reference drugs (Gentamicin and Ampicillin) with respect to *E. coli* and *P. aeruginosa* and thus it could be a promising novel drug candidate. The findings revealed that antibacterial activity was greatly diminished on introduction of the benzylor 4-substituted benzyl moieties and antifungal activity increased on substitution with adamantly moiety on C-5 of thiadiazole

Figure 1. 1,3,4-thiadiazole.

***Address for Correspondence:** Tejashree Deokule, Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune-411044, Maharashtra, India, Tel- 9923101611; E-mail: tadeokule.tkcp@gmail.com*

Received: 28 December, 2022, Manuscript No. mccr-22-84904; **Editor Assigned:** 30 December, 2022, PreQC No. P-84904; **Reviewed:** 11 January, 2023, QC No. Q-84904; **Revised:** 16 January, 2023, Manuscript No. R-84904; **Published:** 23 January, 2023, DOI: 10.37421/2161-0444.2023.13.660

nucleus. The introduction of the 4- substituted-1 piperazinylmethyl 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-(sustitutedbenzyliden)-1,3-thiazolidin}-5-methyl-1,3,4-thiadiazol]-imino-4-phenyl-1,3-thiazole derivatives showed distinct antibacterial and antifungal activity [8] (Figure 2).

Antibacterial activity in a series of 3-(1,3,4-thiadiazole-2-yl)quinolines was found to be depended strongly on substitution at C_5 and C_2 of thiadiazole. From the findings Bhatt, et al. revealed that thiadiazole derivatives substituted with N-(o-toll)ace amide and N-(ptoll)ace amide groups at C_2 and 2,8- dichloroquinoline and 2-chloroquinoline at C_5 showed better activity against *S aureus* and *S.pyogenes* respectively [9]. He YW, et al. carried out synthesis of 5-(1-aryl-1H-tetrazol-5-ylsulfanylmethyl)-Nxylopyranosyl-1,3,4-thiadiazole-2-amine derivatives and investigated *in-vitro* anti-bacterial activity against *S. aureus* [10]. Among the synthesized compounds, only compound 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, B. subtilis, E. coli* and *K. pneumonia*. Among the synthesized compounds, 2-(bis((5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl)methylthio) methylene) malononitrile showed significant activity against *S. aureus* with zone of inhibition of 35 mm at a concentration of 200 µg/ml [11].

Linezolid is a well reported bacteriostatic agent and its analogues containing a nitroaryl 1,3,4-thiadiazole moiety inhibit protein synthesis by acting against the formation of the 70S initiation complex. These compounds were initially tested for antimicrobial activity by agardilution method and it was found that compound presented most pronounced activity. This compound was even found to be more potent than Ciprofloxacin against a panel of Grampositive and Gram-negative bacterias [12]. 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. pneumonia, P. aeruginosa, S. marscens* and *S. aureus* by Tomi IHR, et al. [13]. The findings suggested that the antibacterial activity was found to increase when the chain of the alkyl group (-CH_2)n in the central part of the molecules was increased. Compound showed good activity against *E. coli* and *S. aureus* and none of the compound showed activity against *P. aeruginosa* and *S. marscens* up to a concentration of 300 µg/µL. Various combines bio-labile molecules involving Schiff bases and 1,2,4-triazoles derivatised with the 1,3,4-thiadiazoles showed moderate to significant activity against bacteria at concentration of 100 µg/ml. Compounds with chloro group at the para position of the aryl ring were shown to increase antibacterial activity (15.6 µg/ml) where, the standard drug has shown MIC value at 12.5 µg/ml [14]. The antimicrobial activity of derivatives involving a seriesof 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 had more pronounced antibacterial activity and almost equipotent to Chloramphenicol [15].

Antibacterial activity of gatifloxacin derivatives incorporated with

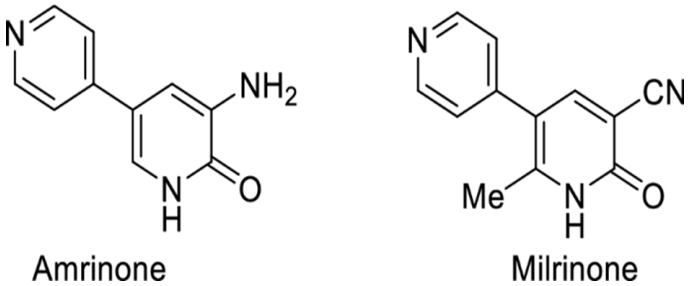

Figure 2. Thiazole derivatives with antibacterial activity.

5-(5-nitroheteroaryl)- 1,3,4-thiadiazol-2-yl groups at C-7 position had been studied by Jazayeri S, et al. [16]. The presence of nitrofuran 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 µg/ml), *B. subtilis* (MIC=0.0039 µg/ml), *E. faecalis* (MIC=0.125 µg/ml) and *M. luteus* (MIC=0.125 µg/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 have been synthesized and nearly all of the compounds exhibited moderate to good activity against some Gram-(+) bacteria i.e *S. aureus*, *E. faecelis*, *Bacillus sp* (MIC=1–5 µg ml–1) and showed poor activity against the Gram-negative bacteria. Substitution with methoxy group at C-8 and free – NH_2 group of 7-(4-aminophenyl-sulfonyl) piperazinyl fluorquinolonine was found to be the active compound in this series against all the tested Gram-positive strains of bacteria [17].

Foroumadi A, et al. reported the impact on actibacterial 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 µg/ml) against Gram-positive bacteria and moderate to poor activity (MIC=1–64 µg/ml) against Gram negative pathogens [18]. Compound 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 µg/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 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 µg/ml) with respect to the reference drugs (MIC=0.25–4 µg/ml) [19]. 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 exhibited more potent activity than chloramphenicol against *A. niger* and Nystatin against *P. aeruginosa* [20]. 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 showed moderate antibacterial activity against the Gram-positive bacteria]. Antifungal activity of 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-thiadiazoles was reported by Chen, et al. Thiadiazole ring instead of oxadiazole did not show significant activity, substitution with 2-methylsulphonyl-3-methoxyphenyl at C-5 of thiadiazole ring showed higher antifungal activities against *G. zeae*, *B. cinerea* and *S. sclerotiorum*.

Scozzafava and Supuran reported the synthesis of 5-mercapto-1,3,4-thiadiazole derivatives and tested their inhibitory activity against Matrix Metalloproteinase (MMP) and Bacterial Collagenase. MMPs 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. Amongst the synthesized compounds, compound 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 (k1=18 nm). Compounds with the sulfonylureido group were found to be selective and highly potent inhibitor of MMP-2,-8,-9 and ChC in a range of 0.1–8 µM.

Tomi, et al. 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* Demirbas, et al. prepared four different derivatives of 4-Amino-2-[(5-arylamino-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 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 resulted in improved antibacterial activity. An attempt to prepare active compounds in the series of thiadiazolyl derivatives of antipyrine turned up unsuccessful. All the synthesized derivatives bared weak growth inhibitory activity against the tested Gram positive bacteria (MIC 100 µg/ml). 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 comparable activity against *B. subtilis* and *E. coli* with reference to amphicillin (25 µg/ml). Compounds 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. A recently published paper reported the antibacterial and antifungal activity of 1,3,4- thiadiazoles bearing imidazo[2,1-b]thiazole moiety 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. 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. designed a compound 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. A novel series of 2,5-disubstituted-1,3,4- thiadiazoles derivatives 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 were found to be more active against *S. pyogenes, S. aureus, P. aeruginosa, K. pneumoniae* and *E. coli*.

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 showed 50% of inhibition against *B. subtilis* with respect to ampicillin. Compound having chloro group at para position of arylsulfonylmethane moiety attached with thiadiazole ring exhibited higher antimicrobial activity. 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 showed measurable activity against *T. mentagrophytes*. Ranjina, et al. synthesized a number of aminothiadiazole derivatives 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 Camoutsis, et al. synthesized a series of N-{5-[2-(N-substituted sulfamoyl)-4,5- dimethoxy benzyl]-1,3,4-thiadiazole-2-yl}-N-arylamines. All the newly Sulfonamide-1,2,4- thiadiazoles were assayed *in vitro* for their growth inhibitory activity against panel of selected Gram positive, 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 is an essential part for improving antibacterial activity.

Anticancer activity

Kumar, et al. 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 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 showed broad spectrum of growth inhibition activity against human tumor cells and remarkable cytotoxic activity on non-small 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 (PC3) having GI50 value -5.48. SAR study revealed that electron withdrawing group at position C-5 of thiadiazol was favorable for activity. 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 (PC_3, DU145 and LnCaP), breast (MCF7 and MDA-MB-231) and pancrease ($PaCa_2$). The SAR study showed that the 3,4,5-$(OCH_3)3C_6H_2$ at C-5 position was responsible for binding to the Colchicine siteon 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 displayed a greater potency towards pancreatic ($PaCa_2$) cancer cell lines (IC50=.3 µM). Marganakop, et al. 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 with methoxy at C- 6,7,8 of quinoline showed the potent anticancer activity and the cell lyses occurred only at 10 µg/ml Zheng, et al. 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 with electron with-drawing 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 was found to be the most potent one by the MTT assay against A549, PC-3 and HA22T]. A number of Nsubstituted 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 with ID50 two times lower (SW707, T47D) than that of cisplatin displayed the highest cytotoxicty. It was noticed that the compounds with electron donating groups at Cterminal of the phenyl ring did not increased its cytoselective toxicity and the compounds with electron withdrawing groups (Cl, F) resulted in an increased activity by inducing cell death. Compound 2-(4-fluorophenylamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole inhibited proliferation of tumor cells derived from cancers of nervous system

(medulloblastoma rhabdosarcoma, neuroblastoma and glioma) and peripheral cancers including colon adenocarcinoma and lung carcinoma.

Matysiak J, et al. examined the effect of various substitution at 5-position of 2-(2,4 dihydroxy-phenyl)-1,3,4-thiadiazoles on antiproliferative activity against different human tumour cell lines. 2-(2,4-Dihydroxyphenyl)-5-(4-methoxybenzyloxy)-1,3,4-thiadiazole showed ID50 of 1.1 μg ml–1 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 μM (Figure 3).

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 possessed high potency against FAK (EC50=10.79 μM). Compound showed EC50 values of 14.21– 32.45 μg/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 phenylpropinic acid >phenylacetic acid >benzoic acid. Compounds with substituted Cl group on benzene ring showed better antitumor activity than substitution with Br group Replacement of -Cl with $-CH_3$ group, however, led to decrease in cytotoxic activity against all cell lines.

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. Moshafi, et al. synthesized 5-(1-methyl-5- nitro-1H-imidazol-2-yl)-1,3,4-thiadiazoles and screened for bactericidal activity agains pylori. Compound, 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. pyroli activity at 0.5 μg/disc (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, Nbenzyl, 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. 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/disc). Compound 2-chloro-5-(5-nitrothiophene)-1,3,4- thiadiazole was found to be the most active with zone of inhibition >30 mm at 8 μg/disc 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. 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 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 (Figure 4).

4-[5-(5-Nitro-2-furyl)-1,3,4-thiadiazol-2-yl] thiomorpholine 1,1-dioxide containing thiomorpholine S,S-dioxide moiety showed the highest anti- H. pylori activity at a concentration of 8 μg/disc producing an average inhibition zone of more than 27 mm, which was Accepted Article © 2013 John Wiley & Sons A/S greater than that by metronidazole (16.3 mm). 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. Out of eight, four derivatives showed strong anti-H. pylori activity at concentration of 8–32 μg/disc and compound 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/disc.

Anticonvulsent 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 archieved 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. Recently Rajak, et al. 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-nitrophenylsubstituted semicarbazone were the most active compound comparable to carbamzepine. 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-NO_2 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 having nitro group attached to the phenyl ring adjacent to the thiazole moiety demonstrated more potent anticonvulsant activity and the removal or replacement of $–NO_2$ function by a -Cl, -Br moieties was responsible for loss of activity. In an attempt to improve the potency and selectivity of 2,5-Disubstituted-1,3,4-thiadiazoles. Dogan, et al. synthesized a series of 2-(N-alkyl/aryl-Nacetylamino)-5-(3- acetyloxy-2-naphthyl)-1,3,4-thiadiazole derivatives. Compound 2-ethylamino-5-(3-hydroxy-2- naphthyl)-1,3,4-thiadiazole 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-

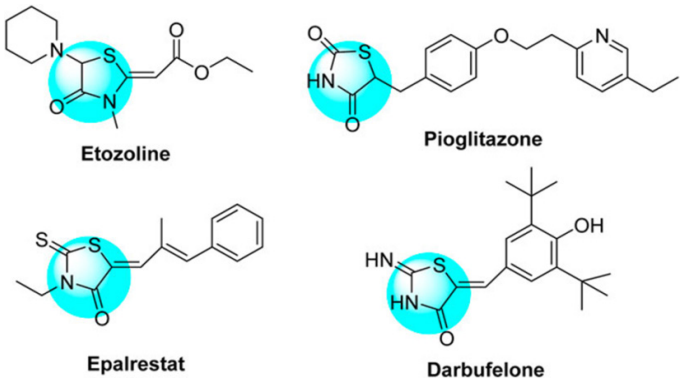

Figure 3. Thiadizoles with various substitutes.

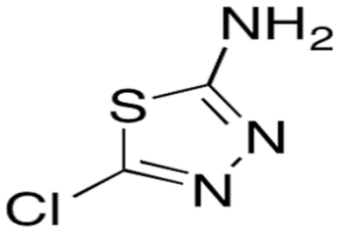

Figure 4. 2-chloro-5-(5-nitrothiophene)-1,3,4-+thiadiazole.

4''(3''H)-only]-1' ,3' ,4' -thiadiazol-2' -yl}-2-thiobarbituric acid showed high percentage protection 90% (50 mg/kg ip) in both MES and PTZ models (Figure 5).

A new series of sulfonamides incorporating valproyl and other lipophilic moieties has been synthesized by Masereel, et al. 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) was the best in the series since it exhibited very strong anticonvulsant activity in an MES test in mice.

Anti-inflammatory activity (COX-inhibitors)

Non-steroidal antiinflammatory drugs (NSAIDs) are important therapeutically active compounds used in the treatment of acute and chronic inflammation, pain and fever. Accepted Article © 2013 John Wiley & Sons A/S Thiadiazole, incorporated in different heterocyclic templates has been reported to possess potent anti-inflammatory activity. Most of the synthesized thiadiazole derivatives exert antiinflammatory 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. Interestingly compound 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. prepared several 2-amino-5-sulfanyl-1,3,4- thiadiazoles and concluded that the compounds were associated with lesser degree of antiinflammatory activity when compared to indomethacin. Only compound 4-[5-(4- Fluorophenylsulfanyl) –[1,3,4] thiadiazol-2-ylamino]benzenesulfonamide 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 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 antiinflammatory (41.23%) and analgesic activity (38%) at a dose of 50 mg/kg than that of their corresponding thiazolidinone compounds. Kumar, et al. synthesized several 1,3,4- thiadiazole derivatives of biphenyl-4-yloxy acetic acid. 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 analogues of naproxen carriying a 4-bromophenyl amino group at second position of the thiadiazole ring showed 78.02% inhibition in rat paw edema. 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 with a p-fluoro phenyl substituent was the most active compound (51.4 of inhibition at 50 mg/kg) amongst the benzoyl sulfonamido derivatives (Figure 6).

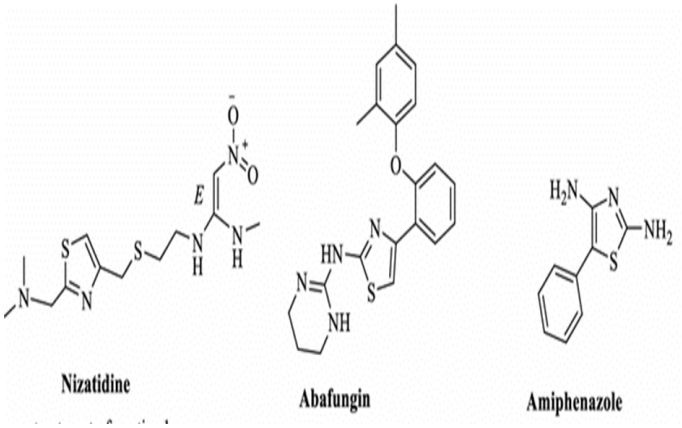

Figure 5. Thiadizoles with substitutes at various positions.

Goksen, et al. synthesized 1,3,4-thiadiazoles containing 5-methyl-2-benzoxazolinone derivatives and evaluated their anti-inflammatory activity. All the compounds exhibited antiinflammatory activity (at the dose 50 mg/kg p.o.) of varying degree from 53.2% to 85.3% in inhibition of oedema. Compound 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 decreased anti-inflammatory as well as analgesic activity.

2-(1-adamantylamino)-5-substituted-1,3,4-thiadiazole derivatives were found to be associated with lesser degree of anti-inflammatory activity compared to indomethacin, while 2- (1-adamantyl)-5-substituted-1,3,4-oxadiazoles appeared to exhibit good dose-dependent antiinflammatory activity. The spirothiadiazole derivative having 4-nitrophenyl group 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.

Antitubercular activity

The emergence of multi-drug 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. synthesized 2-(5-nitro-2-furyl)- and 2- (1- methyl-5-nitro-lH-imidazol-2-yl)-1,3,4-thiadiazole derivatives and screened their *in-vitro* antimycobacterial activity against *M. tuberculosis* H37Rv using alamar-blue susceptibility test. Compounds demonstrating atleast >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 and 4-nitrobenzyl substitution showed the highest activity against *M. tuberculosis* (MIC=3.13 µg/mL). Among nitrofuran derivatives, substitution of the thioester group at C-5 of 1,3,4-thiadiazole ring with a benzyl analogue 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. Moreover their nitrothienyl analogue was equally and highly active against *M. tuberculosis* H37Rv (Figure 7).

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

Chitra and co-workers synthesized 3-heteroarylthioquinoline derivatives of 1,3,4- thiadiazole and screened their *in-vitro* antimycobacterial activity against *M. tuberculosis* H37Rv Accepted Article © 2013 John Wiley & Sons

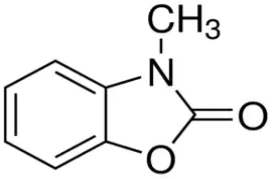

Figure 6. 3-Methyl-2-benzoxazolinone.

A/S 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 with chloro abd bromo substituted aromatic ring found to be more active (MIC=3.2-3.5 µg/ml). Analogues having methyl and methoxy groups at the C8 of quinoline nucleus showed inhibition (MIC) at 5 µg/ml.

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 Accepted Article © 2013 John Wiley & Sons A/S 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 microorganisms at concentrations of 6.25 µg/ml. Only compound 84 having cyclohexyl group showed the highest inhibition of 67%. None of the α-5-(5-Amino1,3,4-thiadiazol-2-yl)-2-imidazolylthio]acetic acid derivatives exhibited inhibitory activity against *M. tuberculosis* at single concentration of 6.25 µg/ml in BACTEC 12B Medium.

Antiviral activity

Human immunodeficiency virus type 1 (HIV-1) has been recognized as the contributing agent in the transmission and the development of acquired immuno deficiency 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 (Figure 8).

One of these, reverse transcriptase (RT) is a key enzyme which is packaged within the HIV virion capsid and plays an essential and multifunctional role in the replication of the virus. Hamad, et al. synthesized 2- (naphthalen-2-yloxy)-N-((5-(phenylamino)-1,3,4-thiadiazol-2-yl)methyl) acetamide and tested it's *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 which showed EC50 values of 0.96 µg/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 showed inhibitory activity of about 42%.

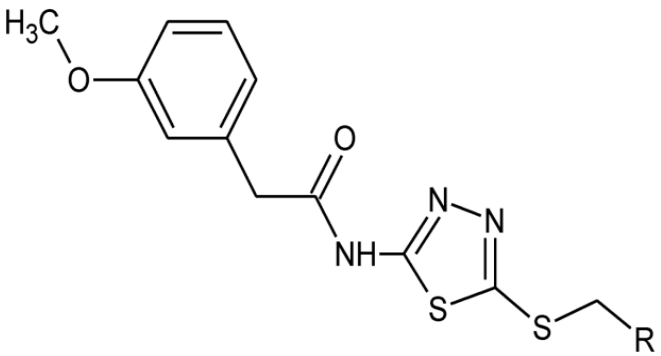

Figure 7. 2-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole.

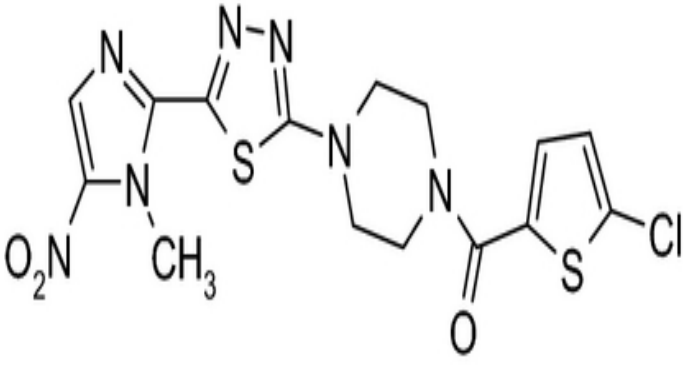

Figure 8. 2- (naphthalen-2-yloxy)-N-((5-(phenylamino)-1,3,4-thiadiazol-2-yl)methyl) acetamide.

Anti-leishmanial activity

Leishmaniasis is a disease caused by the Leishmania parasite and is transmitted to humans by sandflies. 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 antiLeishmania 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 showed IC50 of 1.11 µM against L. major promastigotes. A high activity level of IC50=0.1 µM against L. major promastigotes was observed for compound that contained a 4-phenyl-piperazine group at C-2 of 1,3,4-thiadiazole ring in a series of nitrofuran derivatives (Figure 9).

The 1-(5-(5-nitrofuran-2yl)-1,3,4-thiadiazole-2-yl)piperazines having n-propyl, nbutyl and benzyl side chain on benzamidine showed IC50 values of 0.08, 0.2 and 0.4 µM, respectively against the promastigote form of L. major. SAR study revealed that substitution with benzamidine was favourable for activity and replacement by a five-membered ring, namely the imidazoline and six-membered ring namely tetrahydropyrimidine were devoid of activity. Further substitution on phenyl group of piperazine with halogen did not increased antileishmanial activity against both promastigote and amastigote forms of L. major. Compound with 2-chlorobenzoyl on the piperazine ring showed anti-leishmania activity with IC50=10.73 µM. Poorrajab, et al. 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 (IC50 ≥ 80 µM) and high selectivity against intracellular amastigotes with selectivity index > 12. Compound 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

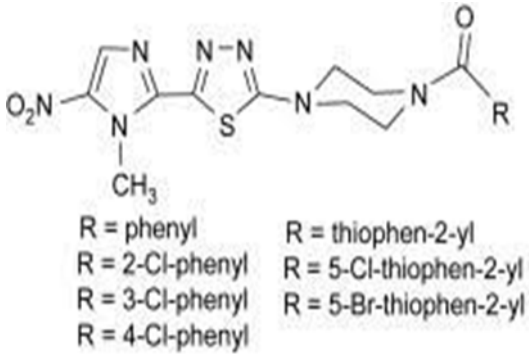

Figure 9. 1-[(5-chloro-2-thienyl)carbonyl]- 4-[5-(1-methyl-5-nitro-1H-imidazol-2-yl)-1,3,4-thiadiazol-2-yl]piperazine.

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 with an IC50 value of 9.35 μM against L. major promastigotes.

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. A number of new 1,3,4-thiadiazole-2-arylhydrazone derivatives of megazol were screened for trypanocidal (anti-epimastigote activity, %AE) using megazol-treated parasites as control. Some of the synthesized compounds showed IC50 value in the range of 5.3- 135.6 μM/ml. The compounds also showed nonspecific cytotoxicity to macrophages at this concentration. The most active hydrazone compound of series was 3,4- dihydroxyphenyl derivative which showed an IC50 of 5.3μM and was found to be superior in activity than the prototype megazol (IC50=9.9 μM). Salomao, et al. 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 Trypanosoma 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 Brazilizone. Trypanocidal activity of megazol [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 (megazol) with electron-donating or withdrawing substituents was found to reduce the trypnocidal activity. Removing the nitro group or changing the position made the compounds totally inactive. The activity of megazol was retained when N-acetylation was done. It was totally lost when substituted with trifluoromethyl analogue.

Carbonic anhydrase inhibitory activity

1,3,4-Thiadiazole-2-sulphonamides 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 CO_2/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 ureagenesis, bone resorption, calcification, tumourigenicity 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. Maresca, et al. have prepared several ®-/(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 towards to inhibition against mitochondrial isoform hCA VA. Generally the R-enantiomer was more active than the corresponding S-isomer. Nishimori, et al. 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 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 KI of 59 nM 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 isozymes 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 3.2–23nM against hCA IX, respectively. Out of the nine compounds, 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 (KI of 5.4 μM). Compound 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. Sulfanilamide derivatives were also synthesized by incorporating heterocyclic amines like morpholine, piperidines and piperazines using tail approach. Derivatives exhibited much better inhibition of carbonic anhydrase isoenzymes namely hCA I, hCA II and hCA IX than the parent compounds. Among sulfanilamide derivatives, the derivatives containing morpholine ring revealed best inhibitory activity. 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 showed most active inhibitory activity against hCA II and bCA IV with Ki value of 0.6 and 5 nM. Several pyrazole derivatives of 5-amino-1,3,4-thiadiazole-2-sulfonamide were synthesized and their inhibitory activity against hydratase and esterase property of carbonic anhydrase isoenzymes hCA I and hCA II were studied. Derivatives showed more inhibitory ac 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 isoenzymes hCA I, hCA II, hCA IV and hCA IX. Aminobenzyloamides 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-Flouro-5-chloro-4- aminobenzenesulfonamide derivative of sulphonylthiadiazole showed the best hCA IX inhibition with Ki of 12 nM which was two times more active than acetazolamide. Tivity than parent compounds, 5-amino-1,3,4-thiadiazole-2-sulfonamide and acetazolamide.

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 were 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-tertbutylphenylsulfonamido)-1,3,4-thiadiazole-2-sulfonamide and 5-(4-tertbutylphenylcarboxamido)-1,3,4-thiadiazole-2-sulfonamide were found to be very strong inhibitors of hpCA with KI of 12-13nM. Maseer, et al. synthesized a series of compounds first by reacting Valproic acid with aromatic and heterocyclic sulfonmaides in presence of carbodiimides and secondly reacting valproyl chloride with sulfonamide in 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's 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 was found to be more effective than acetazolamide and methazolamide against all three enzymes.

Thiadiazoles as miscellaneous agents

Vergne, et al. 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- $CONH_2$ on benzene ring 4-aminoquinazoline

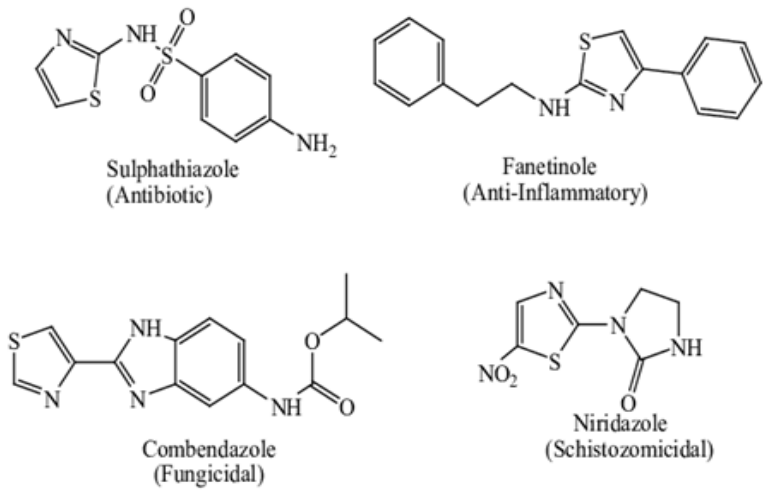

Figure 10. Thiadizoles with substitutes showing various activity.

and 2-methyl-4-aminoquinazoline 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 Introduction of an OH group on 3rd position of cyclohexyl group of represented IC50 of 0.088 nM towards PDE7. Modification of 4-$CONH_2$ group with sulfonamide significantly improved the pharmacokinetic profile and binding affinity for PDE7. De, et al. 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 (DELFIA) and the kinase activity (LANTHA) assays. Out of the synthesized compounds 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 the discovery of 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 (Figure 10).

Xiao, et al. discovered the 2-piperidinopiperidine-5-arylthiadiazoles as H_3 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 $COCH_3$ on phenyl ring increases the H_3 receptor antagonistic activity. Further replacement of phenyl ring with 2-pyridyl was found to be favorable while pyrimidine and pyrazole offered less activity. Compound with 3-methoxy group at 2-pyridyl ring substituted on C-5 of thiadiazole was found to be the most active.

Conclusion

The unusual heterocycle thiazole, which has atoms of nitrogen and sulphur, is significant in medicinal chemistry. It is a crucial core scaffold that is found in a variety of naturally occurring (like vitamin B1-thiamine) and synthesised compounds that are significant for medicine. The fact that the thiazole nucleus is a crucial component of the penicillin nucleus and some of its derivatives have demonstrated antimicrobial (sulfazole), antiretroviral (ritonavir), antifungal (abafungin), antihistaminic and antithyroid activities demonstrates the versatility of the thiazole nucleus. The recent use of thiazole derivatives as anticancer (tiazofurin), anthelmintic, vulcanizing accelerators (mercaptobenzothiazole) and photographic sensitizers has greatly boosted the synthetic value of thiazole derivatives, its reduced forms and condensed derivatives. Following the groundbreaking work of Hofmann and Hantsch, thiazole chemistry has gradually advanced. Significant advancements in this discipline were made by Bogert and his colleagues. The significance of the thiazole ring in cyanine dyes—used as a photographic sensitizer—was established by Mills. A fused derivative of thiazole called benzothiazole has also demonstrated its economic viability. The current paper describes the significance of thiazole and its condensed derivatives in terms of chemistry and biology, with a focus on recent advancements.

References

1. Supuran, Claudiu T. and Andrea Scozzafava. "Carbonic anhydrase inhibitors." *Curr Med Chem Immunol Endocr Metab Agents* 1 (2001): 61-97.
2. Iizawa, Y., K. Okonogi, R. Hayashi and T. Iwahi, et al. "Therapeutic effect of cefozopran (SCE-2787), a new parenteral cephalosporin, against experimental infections in mice." *Antimicrob Agents Chemother* 37 (1993): 100-105.
3. Önkol, Tijen, Deniz S. Doğruer, Leyla Uzun and Selcen Adak, et al. "Synthesis and antimicrobial activity of new 1, 2, 4-triazole and 1, 3, 4-thiadiazole derivatives." *J Enzyme Inhib Med Chem* 23 (2008): 277-284.
4. Matysiak, J. and Z. Malinski. "2-(2, 4-dihydroxyphenyl)-1, 3, 4-thiadiazole analogues: Antifungal activity *in vitro* against Candida species." *Russ J Bioorganic Chem* 33 (2007): 594-601.
5. Abdel-Wahab, Bakr F., Hatem A. Abdel-Aziz and Essam M. Ahmed. "Synthesis and antimicrobial evaluation of some 1, 3-thiazole, 1, 3, 4-thiadiazole, 1, 2, 4-triazole and 1, 2, 4-triazolo [3, 4-b][1, 3, 4]-thiadiazine derivatives including a 5-(benzofuran-2-yl)-1-phenylpyrazole moiety." *Monatsh Chem* 140 (2009): 601-605.
6. Kadi, Adnan A., Ebtehal S. Al-Abdullah, Ihsan A. Shehata and Elsayed E. Habib, et al. "Synthesis, antimicrobial and anti-inflammatory activities of novel 5-(1-adamantyl)-1, 3, 4-thiadiazole derivatives." *Eur J Med Chem* 45 (2010): 5006-5011.
7. Kadi, Adnan A., Nasser R. El-Brollosy, Omar A. Al-Deeb and Elsayed E. Habib, et al. "Synthesis, antimicrobial and anti-inflammatory activities of novel 2-(1-adamantyl)-5-substituted-1, 3, 4-oxadiazoles and 2-(1-adamantylamino)-5-substituted-1, 3, 4-thiadiazoles." *Eur J Med Chem* 42 (2007): 235-242.
8. Verma, S., S.K. Srivastava and P. Samadhiya. "Synthesis and antimicrobial activity of thiazolidine derivatives of thiazole." *Int J Pharm Res Dev* 11 (2011): 73-81.
9. Bhat, Abdul R., Amir Azam, Inho Choi and Fareeda Athar, et al. "3-(1, 3, 4-Thiadiazole-2-yl) quinoline derivatives: Synthesis, characterization and anti-microbial activity." *Eur J Med Chem* 46 (2011): 3158-3166.
10. He, Yao-Wu, Ling-Hua Cao, Jian-Bin Zhang and Duo-Zhi Wang, et al. "Synthesis and bioactivity of 5-(1-aryl-1H-tetrazol-5-ylsulfanylmethyl)-N-xylopyranosyl-1, 3, 4-oxa (thia) diazol-2-amines." *Carbohydr Res* 346 (2011): 551-559.
11. Padmavathi, V., G. Dinneswara Reddy, S. Nagi Reddy and K. Mahesh, et al.

"Synthesis and biological activity of 2-(bis ((1, 3, 4-oxadiazolyl/1, 3, 4-thiadiazolyl) methylthio) methylene) malononitriles." *Eur J Med Chem* 46 (2011): 1367-1373.

12. Khalaj, Ali, Maryam Nakhjiri, Amir Soheil Negahbani and Marjaneh Samadizadeh, et al. "Discovery of a novel nitroimidazolyl–oxazolidinone hybrid with potent anti Gram-positive activity: Synthesis and antibacterial evaluation." *Eur J Med Chem* 46 (2011): 65-70.
13. Tomi, Ivan Hameed R., Ali Hussein R. Al-Daraji, Raya Raad T. Al-Qaysi and Mohammed Mujbel Hasson, et al. "Synthesis, characterization and biological activities of some azo derivatives of aminothiadiazole derived from nicotinic and isonicotinic acids." *Arab J Chem* 7 (2014): 687-694.
14. Bansode, Soujanya and Ravindra Kamble. "Synthesis of novel 2-(3′-aryl-sydnon-4′-ylidene)-5′-substituted-[1, 3, 4]-thiadiazolylamines and [1, 3, 4]-thiadiazol-2′-yl-3-oxo-[1, 2, 4]-triazoles as antimicrobial agents." *Med Chem Res* 21 (2012): 867-873.
15. Padmavathi, V., G. Sudhakar Reddy, A. Padmaja and P. Kondaiah, et al. "Synthesis, antimicrobial and cytotoxic activities of 1, 3, 4-oxadiazoles, 1, 3, 4-thiadiazoles and 1, 2, 4-triazoles." *Eur J Med Chem* 44 (2009): 2106-2112.
16. Jazayeri, Seyyedehsamira, Mohammad Hassan Moshafi, Loghman Firoozpour and Saeed Emami, et al. "Synthesis and antibacterial activity of nitroaryl thiadiazole–gatifloxacin hybrids." *Eur J Med Chem* 44 (2009): 1205-1209.
17. Talath, S. and A. K. Gadad. "Synthesis, antibacterial and antitubercular activities of some 7-[4-(5-amino-[1, 3, 4] thiadiazole-2-sulfonyl)-piperazin-1-yl] fluoroquinolonic derivatives." *Eur J Med Chem* 41 (2006): 918-924.
18. Foroumadi, Alireza, Saeed Emami, Abdolreza Hassanzadeh and Majid Rajaee, et al. "Synthesis and antibacterial activity of N-(5-benzylthio-1, 3, 4-thiadiazol-2-yl) and N-(5-benzylsulfonyl-1, 3, 4-thiadiazol-2-yl) piperazinyl quinolone derivatives." *Bioorganic Med Chem Lett* 15 (2005): 4488-4492.
19. Foroumadi, Alireza, Shahla Mansouri, Saeed Emami and Javad Mirzaei, et al. "Synthesis and antibacterial activity of nitroaryl thiadiazole-Levofloxacin hybrids." *Arch Pharm Int J Pharm Med Chem* 339 (2006): 621-624.
20. Shelke, Sharad, Ganesh Mhaske, Sunil Gadakh and Charnsingh Gill, et al. "Green synthesis and biological evaluation of some novel azoles as antimicrobial agents." *Bioorganic Med Chem Lett* 20 (2010): 7200-7204.

How to cite this article: Deokule, Tejashree, Chaitrali Gosavi and Aditya Sarode. "1,3,4-Thiadiazole and its Derivatives: A Versatile Moiety." *J Med Chem* 13 (2023): 660.