International Journal of Scientific Research in Engineering and Management (IJSREM)
Volume: 09 Issue: 06 | June - 2025 SJIF Rating: 8.586 ISSN: 2582-3930

Biological Activities of 1,3,4-Thiadiazole Derivatives: Review

Ram Dulare*
Department of Chemistry, Post Graduate College, Ghazipur, 233001 U.P.- India
*Corresponding Author: Ram Dulare Email Address: rdxpgcchem@gmail.com

Abstract
The molecules with 1,3,4-thiadiazole ring structures have potential biological relevance. These organic molecules have potentially reported for their medicinal importance. In this review, different biologically important molecules of 1,3,4-thiadiazole ring are briefly summarized and an attempt has been made with recent research findings on this nucleus. Anti-bacterial, anti-cancer, anti-inflammatory, anti-tubercular, anti-convulsant, anti-leishmanial, anti-viral, anti-fungal, anti-depressant, anti-anxiolytic, anti-diabetic, anti-oxidant, anti-diuretic, anti-neoplastic and analgesic activities of the title compounds are briefly reviewed. Its covers advances made in the last two decades.

Keywords: 1,3,4-Thiadiazole, anti-bacterial, anti-cancer, anti-inflammatory, anti-tubercular, anti-convulsant, anti-leishmanial, anti-viral

1. Introduction

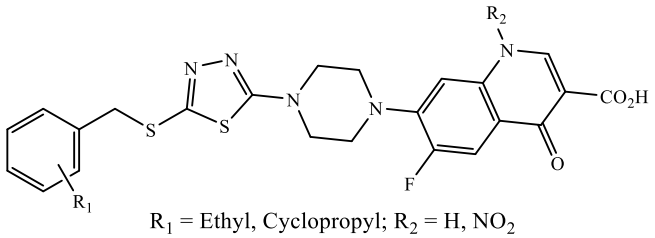
Thiadiazoles are azole family compound and the name originated from Hantzsch-Widman nomenclature. They are five-membered heterocyclic compounds having one sulfur and two nitrogen atoms with formula $C_2H_2N_2S$. It contains aromatic ring by virtue of their two double bonds and the sulfur lone pair. Basically, there are four isomeric forms of thiadiazole *viz*. 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole and 1,3,4-thiadiazole and exists only depending on relative positions of their heteroatoms. These forms do not interconvert and hence they are structural isomers and not tautomers [1]. In five-membered ring structures one or more heteroatoms are present, such as thiadiazole, oxadiazole, azole, thiazole, pyrrole and triazine. Amongst these, thiadiazole is considered as one of the most significant and well-known heterocyclic nuclei, as it is reported with various pharmacological performance [2]. 1,3,4-thiadiazole is the highly useful isomeric form because of its diverse biological actions in body. In particular, compounds bearing the 1,3,4-thiadiazole nucleus is known to have exclusive action as anti-bacterial, anti-cancer, anti-inflammatory, anti-tubercular, molluscicidal, anti-convulsant, anti-leishmanial, anti-viral, anti-fungal, anti-depressant, anti-anxiolytic, anti-diabetic, anti-oxidant, amoebicidal, anti-diuretic, anti-neoplastic and analgesic activities [3]. Drug resistibility is the major problem occurring worldwide and to deal with this, the need of synthesizing new compounds has been become one of the most interesting research areas. It is supposed that 1,3,4-thiadiazole derivatives exhibit various biological activities due to the presence of -N=C-S- moiety in ring of unsaturated structures. Most of the authors assume that the biological activities of 1,3,4-thiadiazole derivatives are due to the strong aromaticity of the ring, which also provides great *in vivo* stability to this five-membered ring system and low toxicity for higher vertebrates, including human beings [4]. The biological importance of 1,3,4-thiadiazole derivatives has been reported following the discovery of heterocyclic sulfonamides as reasonable antimicrobial agents (sulfathiazole). In analogy to sulfathiazole, other sulfonamides showing similar activity such as sulfamethizole, Rufol or sulfaethidole and Globucid. Except sulfathiazole that is still used in the treatment of *Haemophilus vaginalis* vaginitis, sulfamethizole and sulfaethidole currently possess only historical importance [5]. Moreover, the capability of the hydrogen binding domain allows the use of 1,3,4-thiadiazole as one of the potential agents in many drugs such as Desaglybuzole/Glybuzole/Gludiase (anti-diabetic), Litronesib (anti-cancer), Cefazedone/ Refosporin (anti-biotic), Sulfamethizole (anti-bacterial), Atibeprone (anti-depressant), Cefazoline/Cefazolin (anti-biotic), Sulfaethidole (anti-biotic), Methazolamide/Neptazane (anti-glucoma), Acetazolamide/Diacarb/Diamox (anti-

glucoma), Butazolamide (diuretic), Azetepa (anti-neoplastic), Megazol (anti-protozoa) and many more medicines are available in the market [6]. The review covers advances made in the last two decades and a brief account of various alterations done on the thiadiazoles nucleus.

2. Biological Activities

2.1. Anti-bacterial:

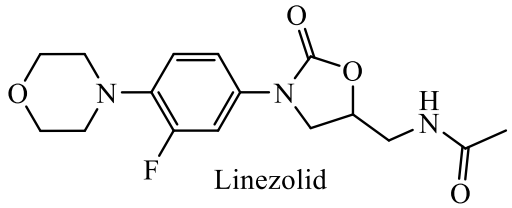
H. Muğlu *et al.*, have reported the synthesis of 1,3,4-thiadiazoles based on thiophene-2-carboxylic acid **1**. The antibacterial activities of these compounds were performed against Gram (-ve) bacteria (Salmonella enteritidis, Salmonella typhimurium, Enterobacter aerogenes, *Salmonella infantis*, *Salmonella kentucky* and *Escherichia coli*), Gram (+ve) bacteria (Staphylococcus aureus, Bacillus subtilis and Enterococcus durans) and the fungus Candida albicans using the disk diffusion method [7]. Antibacterial activity of *N*-(5-benzylthio-1,3,4-thiadiazol-2-yl) and *N*-(5-benzylsulfonyl-1,3,4-thiadiazol-2-yl)piperazinylquinolone derivatives have also been reported. Some of these derivatives exhibit high activity against Gram positive bacteria *Staphylococcus aureus* and *S. epidermidis*, compared to their parent *N*-piperazinyl quinolones norfloxacin and Ciprofloxacin as reference drugs [8].



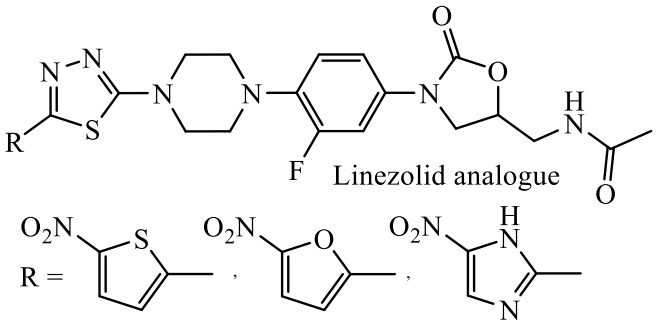
R_1 = Ethyl, Cyclopropyl; R_2 = H, NO_2

(1)

Khalaj *et al.*, evaluated thiadiazole derivatives with analogous structures of linezolid. The results obtained were compared with the activity of linezolid and ciprofloxacin, which were used as reference antibiotics [9]. S. Sahu *et al.*, have also synthesized a series of 1,3,4-thiadiazole derivatives and these derivatives were possessing prominent antibacterial activity [10].



Linezolid

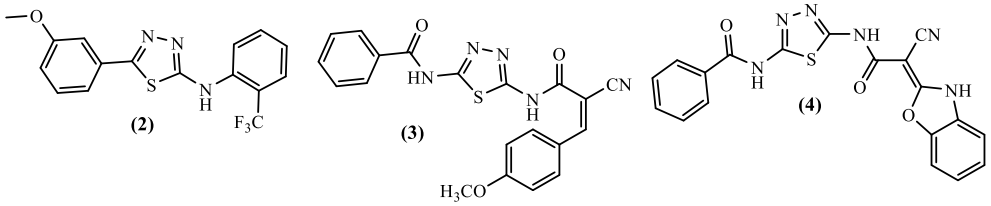


Linezolid analogue

2.2 Anti-cancer:

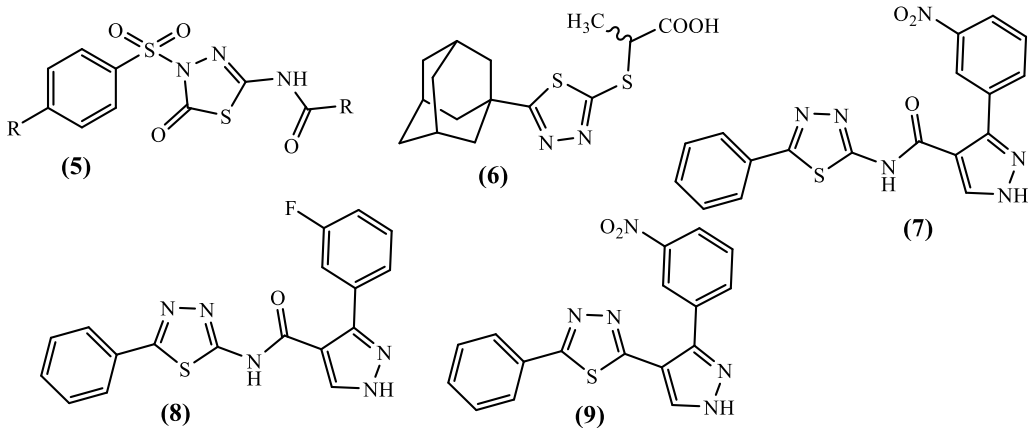
S. Janowska *et al.*, synthesized the 1,3,4-thiadiazole derivatives. The cytotoxic activity of the compounds was studies using MCF-7 and MDA-MB-231 breast cancer cells and normal cell line (fibroblasts). The results showed that in both breast cancer cell lines, the strongest anti-proliferative activity was exerted by 2-(2-trifluorometylophenylamino)-5-(3-methoxyphenyl)-1,3,4-thiadiazole **2**. The IC_{50} values of this compound against MCF-7 and MDA-MB-231 breast cancer cells were 49.6 µM and 53.4 µM, respectively. However, all new compounds have less cytotoxic activity on normal cell line than on breast cancer cell lines [11]. P. J. Chaudhari *et al.*, reported three crucial anticancer scaffolds indolin-2-one, 1,3,4-thiadiazole and aziridine synthesis based on the c-KIT kinase protein. The stem cell factor receptor c-KIT was selected as target because most U.S. FDA-approved receptor tyrosine kinase inhibitors bearing the indolin-2-one scaffold profoundly inhibit c-KIT. Among all three series of indolin-2-ones, the majority of compounds demonstrated broad-spectrum activity toward various

cancer cell lines. These compounds were further evaluated for a five-dose anticancer study. Machine learning algorithms were used to examine the metabolites and phase I and II regioselectivities and the results suggested that these compounds could be potential leads for the treatment of cancer [12]. A series of novel 1,3,4-thiadiazoles was synthesized by M. H. Hekal *et al.*, *via* the reaction of N-(5-(2-cyanoacetamido)-1,3,4-thiadiazol-2-yl)benzamide with different carbon electrophiles and evaluated as potential anticancer agents. In silico studies showed that these derivatives have a low blood-brain barrier penetration capability and high intestinal absorption. However, derivatives *N*-(5-(2-Cyano-3-(4-methoxyphenyl)acrylamido)-1,3,4-thiadiazol-2-yl)benzamide **3** and *N*-(5-(2-(Benzo[*d*]oxazol-2(3*H*)-ylidene)-2-cyanoacetamido)-1,3,4-thiadiazol-2-yl)benzamide **4** could serve as potential anticancer agents and merit further investigations [13]. R. M. El-Masry *et al.*, have synthesized a novel 1,3,4-thiadiazole derivatives and screened for cytotoxic activity. Substituted benzenesulfonamide scaffold exhibited remarkable potency against breast cancer (MCF-7), hepatoma ($HepG_2$), colon cancer (HCT116), and lung cancer (A549) cells and lower potency on the normal cells (WI-38), as well as, it possesses higher anticancer activity than starting 5-(4-chlorophenyl)-1,3,4-thiadiazole-2-amine and the positive control Staurosporine [14].

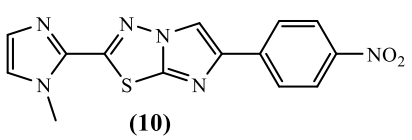


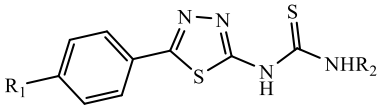
2.3 Anti-inflammatory:

Two series of *N*-[5-oxo-4-(arylsulfonyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl]-amides **5** were synthesized by S. Schenone *et al.*, and tested in *vivo* for their analgesic and anti-inflammatory activities. All the new compounds possess good antalgic action in the acetic acid writhing test and some terms of the series showed also fair anti-inflammatory activity in the carrageenan rat paw edema test. Ulcerogenic and irritative action on the gastrointestinal mucus, in comparison with indomethacin is low [15]. A. A. Kadi *et al.*, have reported the synthesis and in *vitro* activities against a panel of Gram-positive and Gram-negative bacteria and the yeast-like pathogenic fungus Candida albicans. Most of the synthesized compounds displayed marked activity against the Gram-positive bacteria, while few compounds were highly active against the Gram-negative bacteria. In addition, the in *vivo* anti-inflammatory activity of the synthesized compounds was determined using the carrageenan-induced paw oedema method in rats. The propionic acid derivative **6** shows good dose-dependent anti-inflammatory activity [16]. A new series of 1,3,4-thiadiazole with pyrazole-3-carboxamides and pyrrole-3-carboxamide moiety were prepared by S. Maddila *et al.*, using intermediate compounds 1,3,4-thiadiazolacrylamides. Among all the compounds, seven compounds were found to exhibit significant anti-inflammatory activity with 77.27, 75.89, 76.24, 68.55, 63.72, 57.41, 53.05% and 81.00, 80.55, 78.62, 71.45, 68.95, 61.89, 56.32% inhibition in paw edema at 3h and 5h respectively, compared to the standard drug indomethacin (74.82 and 80.32% at 3h and 5h) [17]. Compounds 4-(4-Nitrophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-1H-pyrazole-3-carboxamide **7**, 4-(4-Fluorophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-1H-pyrazole-3-carboxamide **8** and 4-(4-Nitrophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-1H-pyrrole-3-carboxamide **9** exhibited potent activity than standard drug.

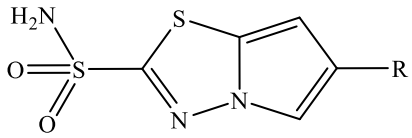


Anti-tubercular: H.M. Patel *et al*., have synthesized a series of imidazo[2,1-b][1,3,4]thiadiazoles and evaluated for their in *vitro* antitubercular activity against Mycobacterium tuberculosis $H_{37}R_v$ strain. Among these compounds, 2-(1-methyl-1H-imidazol-2-yl)-6-(4-nitrophenyl)imidazo[2,1-b][1,3,4]thiadiazole **10** has shown the highest inhibitory activity with MIC of 3.14µg/ml as compared to other tested compounds. Further, some potent compounds were also assessed for their cytotoxic activity against a mammalian Vero cell line using MTT assay. The results reveal that these compounds exhibit anti-tubercular activity [18]. D. Chandra Sekhar *et al*., reported a series of 5-phenyl-substituted 1,3,4-thiadiazole-2-amines and screened for their antitumor and antitubercular activities. Some of them showed significant *invitro* antitumor activities against breast cancer and normal human cell lines. Among them, *N*-benzyl-5-(4-fluorophenyl)-, *N*-benzyl-5-(4-nitrophenyl)-, and 5-phenyl-*N*-(*p*-tolyl)-1,3,4-thiadiazole-2-amines demonstrated higher inhibitory activities against the MDA-MB-231 cell line than the cisplatin. *N*-Benzyl-5-(4-methoxyphenyl)-, 5-phenyl-*N*-[4-(trifluoromethyl)phenyl]methyl-, *N*-benzyl-5-(4-fluorophenyl)- and *N*-benzyl-5-(4-nitrophenyl)-1,3,4-thiadiazole-2-amines exhibited high inhibitory activities against the HEK293T cell line as compared to the cisplatin. The antitubercular activity against *mycobacterium smegmatis* MC155 of 5-phenyl-*N*-[4-(trifluoromethyl)-phenyl]methyl-1,3,4-thiadiazole-2-amine compound shows more potency (MIC 26.46 ώg/mL) than Isoniazid (12 ώg/mL) [19]. A. Thomas *et al*., have described the synthesis of eight novel 1,3,4-thiadiazole derivatives and *in vitro* evaluation of their anti-tubercular activity against *Mycobacterium tuberculosis* H_{37} R_v strain. All the other derivatives tested exhibited negligible activity against the strain but only one derivative was found to be active. It can be concluded that 1, 3, 4-thiadiazole derivatives can be developed as agents in the fight against TB [20]. E. Tatar *et al*., synthesized prototypes that possess the advantage of the two pharmacophores of thiourea and 1,3,4-thiadiazole in a single molecular backbone as 5-(aryl)-N-phenyl-1,3,4-thiadiazole-2-amine **11**. Out of them only three compound show activity against *Mycobacterium tuberculosis* strain H_{37}Rv. Some compounds were the most active at minimum concentration values of 10.96 and 11.48 µM, respectively and also shown to inhibit *M. tuberculosis* strain H_{37}Rv with an MIC value of 17.81 µM [21].



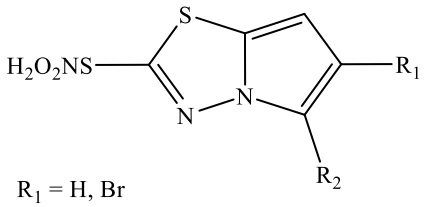


Anti-convulsant: Anticonvulsant activity of 6-alkyl/arylimidazo[2,1-b][1,3,4]thiadiazole-2-sulfonamides and their 2,5-alkyl derivatives has been studied by Barnish *et al.*, in male mice by the electroshock test method at a dose of 2.5, 6.25 and 16 mg/kg. Some of the compounds exhibits oral anticonvulsant ED_{50} values greater than 4-[(4-methoxypiperidino)sulfonyl]-2-chloro-benzenesulfonamide, acetazolamide and methazolamide standard drugs. The most active compound 6-tert-butylimidazo[2,1-b][1,3,4] thiadiazole-2-sulfonamide exhibited a oral ED_{50} value of 2.6 mg/kg.



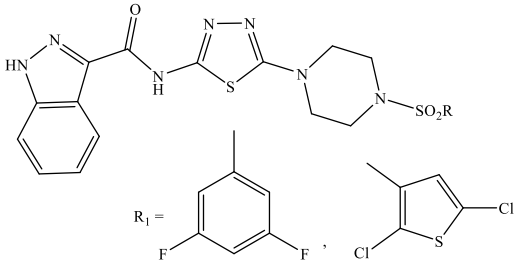
R = H, CH_3, C_2H_5, $(CH_3)_3C$, $C_{10}H_{15}$, C_6H_5,
2-OH-C_6H_4, 4-OH-C_6H_4, 4-CH_3-C_6H_4,
4-CH_3O-C_6H_4, 4-$NHCOCH_3$-C_6H_4, 2-C_6H_4S,
-$CH_2(CH_2)_2CH_2$-

Similarily, Khazi *et al.*, reported anticonvulsant activity of 6-arylimidazo[2,1-b][1,3,4]thiadiazole-2-sulfonamides using phenobarbitone sodium and phenytoin sodium as standard drugs. 6-Aryl derivatives were found to exhibit protection against pentylenetetrazole-induced convulsions and maximum electroshock-induced seizures in albino mice at the dose of 300 mg/kg b.w and the degree of protection ranged 67-83% and 33-83%, respectively. However, bromination at the C-5 position reduced activity.

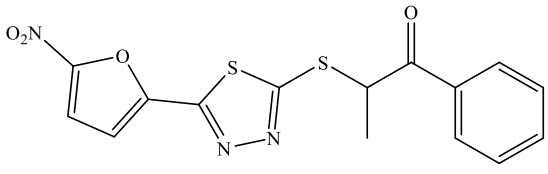


R_1 = H, Br
R_2 = 2-NO_2-C_6H_4, 4-C_6H_5-C_6H_4,
4-coumarinyl, 4-NO_2-2-thienyl,

Rajak *et al.*, synthesized some 2,5-disubstituted 1,3,4-thiadiazoles and evaluated their anticonvulsant activity. The results showed that compound with 4-nitrophenyl-substituted semicarbazone were the most active compound comparable with carbamazepine [22]. P. Harish *et al*., have synthesized a series of new indazole substituted 1,3,4-thiadiazole derivatives and their anticonvulsant activities were tested. Among the synthesized molecules some compounds show outstanding activity [23].

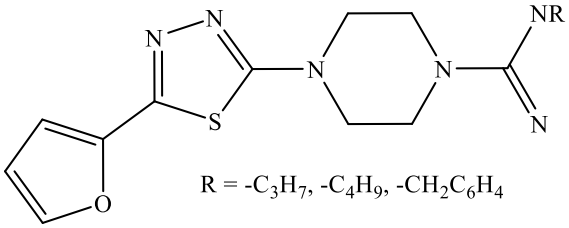


Anti-leishmanial: S.E. Sadat-Ebrahimi *et al*., have reported a series of compounds based on 5-(5-nitrothiophene2-yl)-1,3,4-thiadiazole possessing aryl thiopendant at C-2 position of thiadiazole ring is developed and evaluated as antileishmanial agents using MTT colorimetric assay. Through the methylimidazole containing derivative was recognized as the most active compound against *L. major* promastigotes exhibiting IC_{50} values of 11.2µg/mL and 7.1µg/mL after 24 and 48 h, respectively. This compound is > 4-fold more effective than Glucantime as a standard drug (IC_{50} = 50 µg/mL after 24 h and 25 µg/mL after 48 h) [24]. A large number of synthetic 1,3,4-thiadiazoles derivatives have been well documented and tested in the recent years as antileishmanial [25]. 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 IC_{50} values ranging from 1.11 to 3.16 lM. 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 showed IC_{50} of 1.11 lM against L. major promastigotes [26].



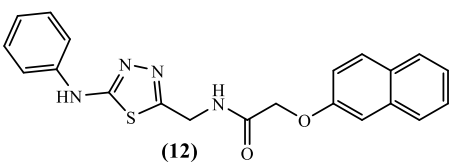
The 1-(5-(5-nitrofuran-2yl)-1,3,4-thiadiazole-2-yl)piperazines having n-propyl, n-butyl and benzyl side chain on benzamidine showed IC_{50} values of 0.08, 0.2 and 0.4 l M, respectively, against the promastigote form of L. major. SAR study revealed that substitution with benzamidine was favorable for activity and replacement by a five-

membered ring, namely the imidazoline and six-membered ring, namely tetrahydropyrimidine were devoid of activity [27].

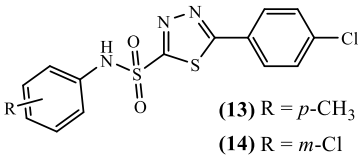


R = -C_3H_7, -C_4H_9, -$CH_2C_6H_4$

Anti-viral: Hamad *et al.,* synthesized 2-(naphthalen-2-yloxy)-N-((5-(phenylamino)-1,3,4-thiadiazol-2-yl)methyl) acetamide **12** 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 **12** which showed EC_{50} values of 0.96 lg/mL [28]. 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 **13** and **14** showed inhibitory activity of about 42% [29].



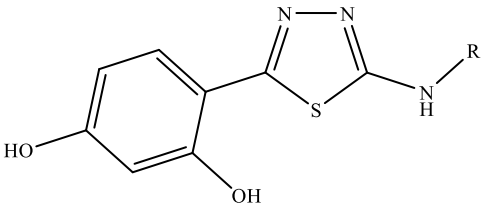
(12)



(13) R = *p*-CH_3
(14) R = *m*-Cl

Lu. Yu *et al.,* have synthesized 1,4-pentadien-3-one derivatives that have 1,3,4-thiadiazole moiety. The compounds were tested against tobacco mosaic virus as well as cucumber mosaic virus in *vivo*. The compounds show good protection activity against the tobacco mosaic virus (TMV). The EC_{50} values were 105.01, 254.77, 135.38, 297.40, 248.18 and 129.87 µg/mL respectively [30]. Chen *et. al.,* have synthesized 5-(4-chlorophenyl)-*N*-substituted-1,3,4-thiadiazole-2-sulfonamide derivatives from *p*-chlorobenzoic acid. The tested compounds showed promising antiviral activity against TMV [31].

Anti-fungal: A series of 5-substituted 2-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole derivatives have synthesized by Matysiak and Malinski and evaluated for antifungal activity against *C. albicans* and *Candida nonalbicans* species. Many derivatives exhibited higher activity against *C. nonalbicans* species compared to standard drugs, itraconazole (MIC =85.6 µg/mL) and fluconazole (MIC =120.8 µg/mL), 2,4-dichlorophenylamino derivative **18** (MIC =37.8 µg/mL) and morpholinoethylamino derivative **20** (MIC =34.4 µg/mL) being the most active compounds. The amino derivatives substituted with the methyl, phenyl, halogenophenyl, ethoxyphenyl and morpholinoalkyl groups showed higher antifungal activity against *C. albicans* strains. For some of them, such as phenylamino derivative **16** (MIC =36.3 µg/mL) and 2,4-dichlorophenylamino derivative **18** (MIC =32.6 µg/mL), an activity higher than that of itraconazole (MIC =47.5 µg/mL) was observed [32].

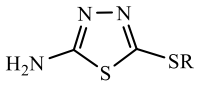


(15) R= CH_3
(16) R= C_6H_5
(17) R= 2-ClC_6H_4
(18) R= 2,4-$(Cl)_2C_6H_3$
(19) R= 4-$C_2H_5OC_6H_4$
(20) R= $O(CH_2CH_2)_2N(CH_2)_2$

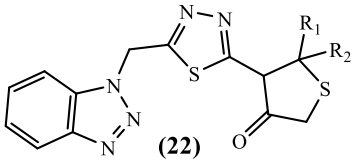
Recently, the antibacterial and antifungal activities of 1,3,4-thiadiazoles having imidazo [2,1-b]thiazole moiety against S. aureus ATCC 29213, P. aeruginosa ATCC 27853, E. coli ATCC 25922 and T. tonsurans NCPF245 with MIC of 64, 32, and 8 lg/mL, respectively [33]. Applying QSAR study, it has been observed that positions-2 or position-3 of benzene attached with thiadiazole ring whereas 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 [34].

Antidepressant & Anti-anxiolytic: F. Clerici *et al.*, have synthesized a series of 2-amino-5-sulfanyl-1,3,4-thiadiazole derivatives and evaluated for their central nervous system activity. Among them, the given compound **21** showed an outstanding psychopharmacological structure in animal activity with antidepressant and anxiolytic action [35]. 5-[(*N*-benzotriazolomethyl)-1,3,4-thiadiazolyl]-4-thiazolidinone derivatives **22** have also been synthesized and evaluated for their anxiolytic activity. The antianxiety activities of the synthesized derivatives were evaluated using Equine Protozoal Myeloencephalitis (EPM) test and Bright and dark box test experimental models of anxiety [36]. A series of 3-[5-substituted phenyl-1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3*H*)-ones were synthesized and evaluated for their anticonvulsant, sedative-hypnotic and CNS depressant activities. After i.p. injection to mice at doses of 30, 100, and 300 mg/kg body weight. 2-styrylquinazolin-4(3*H*)-one derivatives were examined in the maximal electroshock induced seizures (MES) and subcutaneous pentylenetetrazole (scPTZ) induced seizure models in mice. From the experimental observation it can be concluded that synthesized compound **23** exhibited relatively better sedative-hypnotic and CNS depressant activities [37].



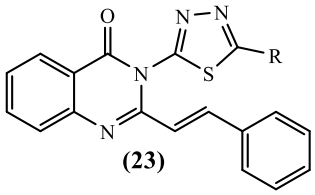
(21) R = 3-CH_3O-benzyl



(22)

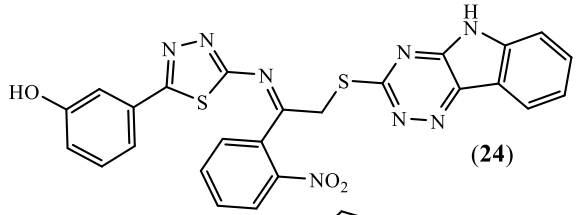
R_1 = H, CH_3, C_6H_5

R_2 = C_2H_5, C_6H_5, 4-Br-C_6H_5, 4-Cl-C_6H_5

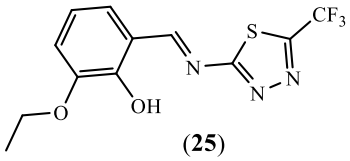


(23)

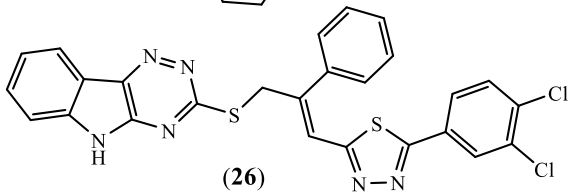
Anti-diabetic: Khan *et al.*, have reported twenty-five new derivatives of triazinoindole containing thiadiazole ring. The compounds were evaluated for in *vivo* anti-diabetic assay. It was observed that all the synthesized compounds were found to be potent, but compounds **24** and **25** showed high anti-diabetic activity by inhibiting α-glucosidase enzyme in comparison with the standard drugs. Further, they conducted a molecular docking study of all the compounds against α-glucosidase protein, finding that the synthesized compounds can be potent anti-diabetic agents in future use [38]. Y. Deswal *et al.*, have also synthesized some new Schiff base derivatives of thiadiazole and their metal complexes. Furthermore, they performed a comparative in *vitro* anti-diabetic activities and molecular docking study of all synthesized compounds and observed that the Schiff base metal complex derivatives **26** and **27** showed high inhibition against α-amylase and α-glucosidase enzymes in comparison to Schiff base derivative [39]. Similarily, P.V. Radha *et al.*, synthesized four Schiff base metal complex thiadiazole derivatives and evaluated them for in *vitro* anti-diabetic activities and found that compound **27** inhibited α-amylase enzyme more than standard and could be a potent anti-diabetic agent [40].



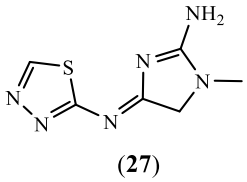
(24)



(25)



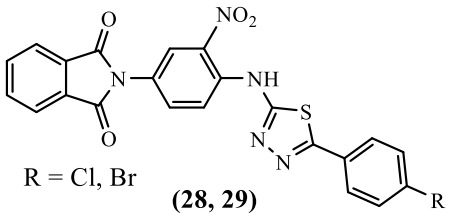
(26)



(27)

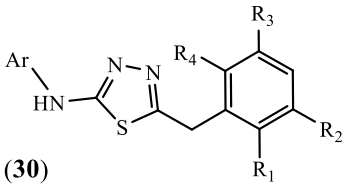
Anti-oxidant:

C. Kus *et al.,* have reported some new 1,3,4-thiadiazole derivatives *i.e., N*-phthalyl-(3-nitro anilino)-4" arylsubstituted-1,3,4-thiadiazoles. The synthesized compounds were evaluated for their in-*vitro* antioxidant activity by determining the reducing power and hydrogen peroxide scavenging potential. The results show that one derivative *N*-Phthalyl-(3'-nitroanilino)-5-(4"-chloro phenyl)-1, 3, 4-thiadiazole **28** had the best reducing ability while *N*-Phthalyl-(3'- nitroanilino)-5- (4"-bromo phenyl-1, 3, 4-thiadiazole **29** was the strongest oxidant [41]. D. Cressier *et al.,* have reported the synthesis and characterization of new compounds derived from benzothiazoles and thiadiazoles. They observed that structural modifications on these skeletons affected the antioxidant activity. Thiol and aminothiol compounds derived from thiadiazoles and benzothiazoles showed an interesting antioxidant property. The radioprotective activity has also been evaluated in mice. Some of these compounds could be good radioprotectors [42]. A.S. Mundey *et al.*, synthesized 5-(4-amino) substituted benzene sulphonamido-1,3,4-thiadiazol-2-sulphonamides **30** and screened their free radical scavenging activity by using 2,2-Diphenyl-1-Picrylhydrazyl (DPPH) method. They found that the unsubstituted derivative has shown moderate activity [43)].



R = Cl, Br

(28, 29)



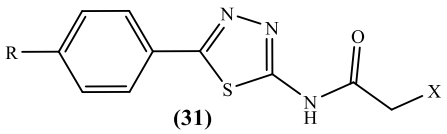
(30)

$R_1 = R_4 = H, F; R_2 = R_3 = Cl, F$

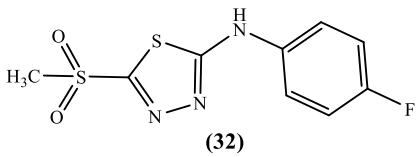
Ar = C_6H_5, 2-$CH_3C_6H_4$, 3-$CH_3C_6H_4$, 4-$CH_3C_6H_4$,3-$OCH_3C_6H_4$

A series of 1,3,4-thiadiazole derivatives including 2- and 3-methoxy cinnamic acids were synthesized, and their antioxidant activities of the compounds were practiced *via* different test methods such as 2,2-diphenyl-1-picryl-hydrazyl (DPPH), *N*,*N*-dimethyl-p-phenylenediamine (DMPD+), and 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS+) scavenging activity assays. When compared with standards (BHA-Butylated hydroxyanisole, RUT-Rutin, and TRO-Trolox), it was observed that especially methoxy groups at the o- and m-positions, respectively, show effective activities [44]. A series of semicarbazone, thiosemicarbazones, 1,3,4-oxadiazoles/thiadiazoles bearing pyrazole scaffold were designed and synthesized. The in *vitro* antioxidant activities of the 1,3,4-oxadiazoles/thiadiazoles were evaluated by DPPH, hydroxyl and nitric oxide radical scavenging assay. Among the tested compounds, compound with chloro substitution showed good antioxidant potential [45].

Anti-diuretic: 1,3,4-thiadiazoles derivatives **31** were synthesized by S. K Jaim *et al*., and studied their diuretic action. They found that the compound having R = H with X = di-n-propyl/di-isopropyl amino substituent and compound with R = CH_3 with X = pyrrolidinone substituent showed good activity. The compound having R = -CH_3O, -CH_3 and X = 2-pyrrolidinone substituent showed moderate activity. Resulting, di-iso propyl amino derivatives were more active than di-n-propyl amino derivatives [46].



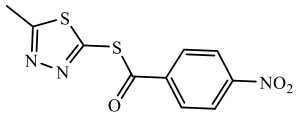
(31)

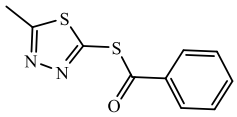


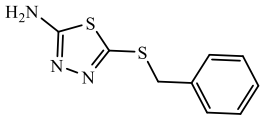
(32)

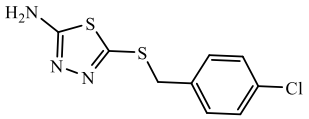
Varandas *et al.,* have reported the synthesis of 1,3,4-thiadiazole derivatives and evaluation of anti-inflammatory activity and exploring the molecular hybridization approach among diuretic drug acetazolamide and 1,3-

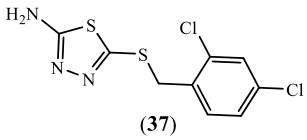
benzodioxole COX-2 inhibitor new lead compounds to classify the para-fluoro-substituted derivative **32** showed more active [47]. A. Ergena *et al.*, have reported synthesis of seven 2- and 5-thioate derivatives of 1,3,4-thiadiazoles and evaluated for in-*vivo* diuretic activity on mice. It was observed that compounds **33** and **34,** which were substituted with methyl group at 5th position, displayed high diuretic activity as compared to compounds substituted with amino group at 5th position [48]. V.I. Drapak *et al.*, have also synthesized sixteen 5-amino-1,3,4-thiadiazole-2-thiol derivatives and screened for their in-*vivo* diuretic activity in rats. It was observed that compounds having amine groups **35**, **36** and **37** are highly potent drug as diuretic [49].


(**33**)

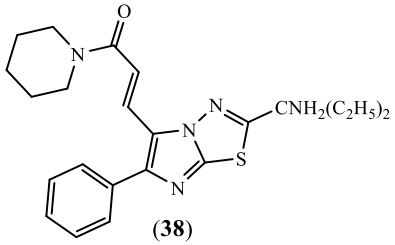

(**34**)

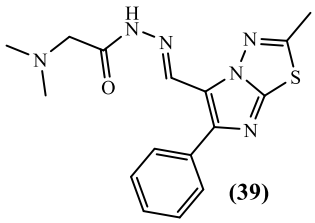

(**35**)


(**36**)


(**37**)

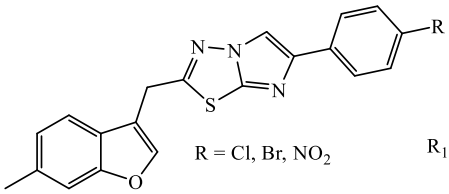
The effect of uricosuric drug candidate, 3-(2-diethylaminomethyl-6-phenylimidazo[2,1-b][1,3,4]thiadiazole-5-yl)-1-piperidin-1-yl-propenone **38** (BAY r4420) on kidney rat function demonstrated the increase in glomerular filtration rate as the major cause of diuretic action, while the uricosuric action was due to impairment of urate reabsorption in the later part of proximal tubule. These studies inspired for the development of new series of diuretic drug candidates [50]. Andreani *et al.*, have reported higher diuretic activity in rats for (E)-2-methyl-6-phenyl-imidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehyde dimethylamino-hydrazone **39** than standard drugs, hydrochlorothiazide and furosemide at the dose of 2.5, 10 and 40 mg/kg [51].


(**38**)

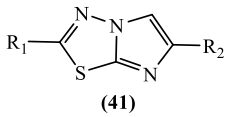

(**39**)

Anti-neoplastic: Acetazolamide is currently a good antiglaucoma agent. Its methylated derivative, "methazolamide" (Neptazane), is a more potent carbonic anhydrase inhibitor and displays diuretic, antiglaucoma and potential antineoplastic activity [52]. Some of the newly synthesized 1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazole derivatives showed substantial cytostatic and cytotoxic antineoplastic activity *in vitro* and they produced relatively low acute toxicities *in vivo*. Apoptotic protease-activating factor 1 (APAF1), tyrosine-protein kinase HCK, cell division protein kinase 2 (CDK2) and matrix metalloproteinase 3 (MMP3) may be involved in the biological activities of active analogues on ovarian and epithelial ovarian carcinoma and adenocarcinoma cell lines. Moreover, the lymphocyte-specific protein tyrosine kinase Lck may explain the activity on Acute T-lymphoblastic leukemia cell lines [53].

Analgesic: Jadhav *et al.*, evaluated anti-inflammatory and analgesic activities of 6-aryl-2-(6-methyl-benzofuran-3-ylmethyl)imidazo[2,1-b][1,3,4]thiadiazoles **40** and their 5-carbaldehyde/ (morpholin-4-yl)methyl derivatives. The 5-carbaldehyde substitution showed enhanced anti-inflammatory and analgesic activity [54]. Mazzone *et al.*, studied analgesic, antipyretic and antiphlogistic activities of 2,6-diaryl-imidazo[2,1-b][1,3,4]thiadiazoles **41** and reported to exhibit peripheral analgesic activity. Some of these compounds showed significant activity compared to indomethacin as standard drug ($p < 0.05$) [55].



(40)

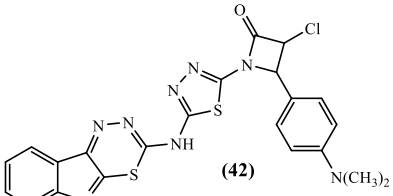


(41)

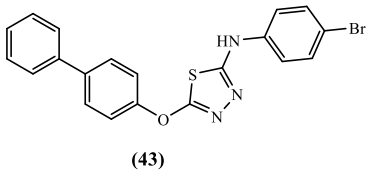
R_1 = 3,4,5-OMe_3-C_6H_2, 3,4(O-CH_2-O)-C_6H_3, 3,5-OMe_2,4-OEt-C_6H_2

R_2 = C_6H_5, 2-NO_2-C_6H_4, 4-NO_2-C_6H_4, 4-Br-C_6H_4, 3,5-OMe_2,4-OEt-C_6H_2, 4-Cl-C_6H_4

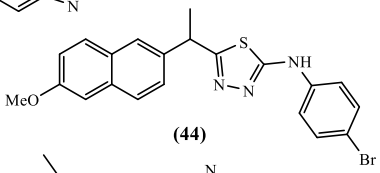
Bhati and Kumar reported that compound with 2-chlorophenyl group at C-4 of azetidin-2-one ring as substituent **42** exhibited the most potent anti-inflammatory (41.23%) and analgesic activity (38%) at a dose of 50 mg/kg than that of their corresponding thiazolidinone compounds [56]. Kumar *et al.*, [57] synthesized several 1,3,4-thiadiazole derivatives of biphenyl-4-yloxy acetic acid **43**. 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 **44** at second position of the thiadiazole ring showed 78.02% inhibition in rat paw edema [58]. 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 **45** with a *p*-fluoro phenyl substituent was the most active compound (51.4 of inhibition at 50 mg/kg) among the benzoyl sulfonamido derivatives [59]. Salgin-Goksen *et al.*, [60] synthesized 1,3,4-thiadiazoles containing 5-methyl-2-benzoxazolinone 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 **46** 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 **47** decreased anti-inflammatory as well as analgesic activity [61



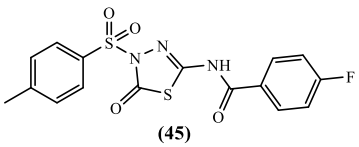
(42)



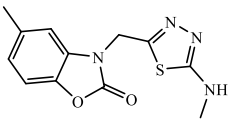
(43)



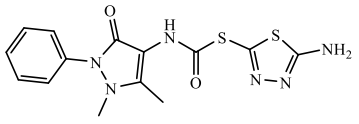
(44)



(45)



(46)



(47)

3. Conclusion

This review presents an overview of the 1,3,4-thiadiazoles and their derivatives. Its highlights the biological activities of the 1,3,4-thiadiazoles and the availability of varied drugs in the market containing the 1,3,4-thiadiazoles derivatives. Anti-bacterial, anti-cancer, anti-inflammatory, anti-tubercular, anti-convulsant, anti-leishmanial, anti-viral, anti-fungal, anti-depressant, anti-anxiolytic, anti-diabetic, anti-oxidant, anti-diuretic, anti-neoplastic and analgesic activities are also briefly reviewed.

References

1. Hu. Yang, Li. Cui-Yun, Wang. Xiao-Ming, Yang. Yong-Hua, Zhu. Hai-Liang, 1,3,4-Thiadiazole: Synthesis, Reactions, and Applications in Medicinal, Agricultural, and Materials Chemistry, *Chemical Reviews*, **2014**, *114*, 5572-5610. https://doi:10.1021/cr400131u .
2. Serban, G., Stanasel, O., Serban, E., Bota, S., 2-Amino-1,3,4-thiadiazole as a potential scaffold for promising antimicrobial agents, *Drug Des. Dev., Ther.* **2018**, *31*, 1545-1566. https://doi.org/10.1021/cr400131u.
3. Mohamed, A.E., Elgammal, W.E., Dawaba, A.M. *et al.* A novel 1,3,4-thiadiazole modified chitosan: synthesis, characterization, antimicrobial activity, and release study from film dressings. *Appl Biol Chem*, **2022**, *65*, 54. https://doi.org/10.1186/s13765-022-00725-7.
4. T. Anthwal, S. Nain, 1,3,4-Thiadiazole Scaffold: As Anti-Epileptic Agents, *Front. Chem*., **2022,** *9*, 2021. https://doi.org/10.3389/fchem.2021.671212.
5. A. A. Othman, M. Kihel, S. Amara, 1,3,4-Oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole derivatives as potential antibacterial agents, *Ar. J. of Chem.*, **2019**, *12*, 1660-1675. https://doi.org/10.1016/j.arabjc.2014.09.003.
6. M.M.S. Wassel, Y.A. Ammar, G. A.M. Elhag Ali, A. Belal, A. B.M. Mehany, A. Ragab, Development of adamantane scaffold containing 1,3,4-thiadiazole derivatives: Design, synthesis, anti-proliferative activity and molecular docking study targeting EGFR, *Bioorg. Chemistry*, **2021**, *110*, 104794. https://doi.org/10.1016/j.bioorg.2021.104794.
7. H. Muğlu, H. Yakan, H. A. Shouaib, New 1,3,4-thiadiazoles based on thiophene-2-carboxylic acid: Synthesis, characterization, and antimicrobial activities, *J. Mol. Struc.*, **2020**, *1203*, 127470 https://doi.org/10.1016/j.molstruc.2019.127470.
8. Foroumadi, A., Emami, S., Hassanzadeh, A., Rajaee, M., Sokhanvar, K., Moshafi, M. H., Shafiee, A. *Bioorg. Med. Chem. Lett.*, **2005**, *5*, 4488-4492. https://doi.org/10.1007/BF02977685.
9. Khalaj, A.; Nakhjiri, M.; Negahbani, A. S.; Samadizadeh, M.; Firoozpour, L.; Rajabalian, S. Samadi, N.; Faramarzi, M. A.; Adibpour, N.; Shafiee, A.; Foroumadi, A. Discovery of a novel nitroimidazolyleoxazolidinone hybrid with potent anti-Gram-positive activity: Synthesis and antibacterial evaluation. *Eur. J. Med. Chem.*, **2011**, *46*, 65. https://doi.org/10.1016/j.ejmech.2010.10.015.
10. Sagar Sahu, Tanesh Sahu, Gunjan Kalyani, Bina Gidwani, Synthesis and Evaluation of Antimicrobial Activity of 1,3,4-Thiadiazole Analogues for Potential Scaffold, *J. Pharmacopunture*, **2021**, *24*, 32-40. https://doi.org/10.3831/KPI.2021.24.1.32.
11. Janowska S, Khylyuk D, Bielawska A, Szymanowska A, Gornowicz A, Bielawski K, Noworól J, Mandziuk S, Wujec M. New 1,3,4-Thiadiazole Derivatives with Anticancer Activity. *Molecules*, **2022**, *27(6)*, 1814. https://doi.org/10.3390/molecules27061814.
12. P. J. Chaudhari, S. B. Bari, S. J. Surana, A. A. Shirkhedkar, C. G. Bonde, S. C. Khadse, V. G. Ugale, A. A. Nagar, R. S. Cheke, Discovery and Anticancer Activity of Novel 1,3,4-Thiadiazole and Aziridine-Based Indolin-2-ones *via* In Silico Design Followed by Supramolecular Green Synthesis, *ACS Omega*, **2022**, *7*, 17270-7294. https://doi.org/10.1021/acsomega.2c01198.
13. M. H. Hekal, P. S. Farag, M. M. Hemdan, A. A. El-Sayed, A. I. Hassaballah, W. M. El-Sayed, New 1,3,4-thiadiazoles as potential anticancer agents: pro-apoptotic, cell cycle arrest, molecular modelling, and ADMET profile, *RSC Advances*, **2023**, *13*, 15810-15825. http://dx.doi.org/10.1039/D3RA02716C.
14. R. M. El-Masry, M.A. Amin, M. Korani, S. Giovannuzzi, T. M. sakr, H. H. Kadry, C. T. Supuran, S. Shaarawy, A. T. Shalaby, Elaborating 5-(4-Chlorophenyl)-1,3,4-Thiadiazole Scaffold with A P-Tolyl Sulfonamide Moiety Enhances Cytotoxic Activity: Design, Synthesis, in Vitro Cytotoxicity Evaluation, Radio labelling and in *Vivo* Pharmacokinetic Study, *Egypt. J. Chem.*, **2023**, *66*, 19-30. doi-10.21608/ejchem.2022.162655.6977.

15.S. Schenone, C. Brullo, O. Bruno, F. Bondavalli, A. Ranise, W. Filippelli, B. Rinaldi, A. Capuano, G. Falcone, New 1,3,4-thiadiazole derivatives endowed with analgesic and anti-inflammatory activities, *Bioorg. & Med. Chem.*, **2006**, *14*, 1698-1705. https://doi.org/10.1016/j.bmc.2005.10.064.
16.A. A. Kadi, E. S. Al-Abdullah, I. A. Shehata, E. E. Habib, T. M. Ibrahim, A. A. El-Emam, Synthesis, antimicrobial and anti-inflammatory activities of novel 5-(1-adamantyl)-1,3,4-thiadiazole derivatives, *Eur. J. Med. Chem.*, **2010**, *45*, 5006-5011. https://doi.org/10.1016/j.ejmech.2010.08.007.
17.S. Maddila, S. Gorle, Ch. Sampath, P. Lavanya, Synthesis and anti-inflammatory activity of some new 1,3,4-thiadiazoles containing pyrazole and pyrrole nucleus, *J. Sau. Chem. Soc.*, **2016**, *20*, S306-S312. https://doi.org/10.1016/j.jscs.2012.11.007.
18.H.M. Patel, M.N. Noolvi, N. S. Sethi, A. K. Gadad, S. S. Cameotra, Synthesis and antitubercular evaluation of imidazo[2,1-b][1,3,4]thiadiazole derivatives, *Arab. J. Chem.*, **2017**, *10*, S996-S1002. https://doi.org/10.1016/j.arabjc.2013.01.001.
19.Chandra Sekhar, D., Venkata Rao, D.V., Tejeswara Rao, A. *et al.* Design and Synthesis of 1,3,4-Thiadiazole Derivatives as Novel Anticancer and Antitubercular Agents. *Russ. J. Gen. Chem.*, **2019**, *89*, 770-779. https://doi.org/10.1134/S1070363219040224.
20.Thomas, A., V. B., S. S. K. U., V. M. V., Development of novel 1,3,4-thiadiazoles as antitubercular agents-synthesis and in vitro screening, *Int. J.Current Pharm. Res.*, **2023**, *15*, 37-41. https://dx.doi.org/10.22159/ijcpr.2023v15i3.3009.
21.E. Tatar, S. Karakuş, S.G. Küçükgüzel, S. Ö. Okullu, N. Ünübol, T. Kocagöz, E. D. Clercq, G. Andrei, R. Snoeck, C. Pannecouque, S. Kalaycı, F. Şahin, D. Sriram, P. Yogeeswari, İ. Küçükgüzel, Design, Synthesis, and Molecular Docking Studies of a Conjugated Thiadiazole–Thiourea Scaffold as Antituberculosis Agents, *Bio. & Pharm. Bull.*, **2016**, *39*, 502-515. https://doi.org/10.1248/bpb.b15-00698.
22.Rajak H., Deshmukh R., Aggarwal N., Kashaw S., Kharya M.D., Mishra P., Synthesis of novel 2,5-disubstituted 1,3,4-thiadiazoles for their potential anticonvulsant activity: pharmacophoric model studies. *Arch. Pharm. Chem. Life Sci.*, **2009**, *342*, 453-461. https://doi.org/10.1002/ardp.200800213.
23.K.P. Harish, K.N. Mohana, L. Mallesha, *Drug Invent Today*, **2013**, *5(2)*, 92. https://doi.org/10.1016/j.dit.2013.06.002.
24.S. E. Sadat-Ebrahimi, M. Mirmohammadi, Z. M. Tabatabaei, M. A. Arani, S. Jafari-Ashtiani, M. Hashemian, P. Foroumadi, A. Yahya-Meymandi, S. Moghimi, M. H. Moshafi, P. Norouzi, S. K. Ardestani, A. Foroumadi, Novel 5-(nitrothiophene-2-yl)-1,3,4-Thiadiazole Derivatives: Synthesis and Antileishmanial Activity against promastigote stage of Leishmania major, *Iranian J. Pharm. Res.*, **2019**, *18*, 1816-1822. https://doi.org/10.22037/ijpr.2019.14547.12476.
25.Ibrar, A., Zaib, S., Jabeen, F., Iqbal, J., Saeed, A., Unraveling the Alkaline Phosphatase Inhibition, Anticancer, and Antileishmanial Potential of Coumarin-Triazolothiadiazine Hybrids: Design, Synthesis, and Molecular Docking Analysis. *Archiv Der Pharmazie*, **2016**, *349 (7)*, 553-565. doi: http://doi.org/10.1002/ardp.201500392.
26.Alipour E., Emami S., Meymand Yahya A., Nakhjiri M., Johari F., Ardestani S.K., Poorrajab F., Hosseini M., Shafiee A., Foroumadi A., Synthesis and antileishmanial activity of 5-(5-nitroaryl)-2-substituted-thio-1,3,4-thiadiazoles. *J. Enz. Inhib. Med. Chem.*, **2011**, *26*, 123-128. https://doi.org/10.3109/14756361003733654.
27.Tahghighi A., Marznaki F.R., Kobarfard F., Dastmalchi S., Mojarrad J.S., Razmi S., Ardestani S.K., Emami S., Shafiee S., Foroumadi A., Synthesis and antileishmanial activity of novel 5-(5-nitrofuran-2-y1)-1,3,4-thiadiazoles with piperazinyl-linked benzamidine substituents. *Eur. J. Med. Chem.*, **2011**, *46*, 2602-2608. https://doi.org/10.1016/j.ejmech.2011.03.053.
28.Hamad N.S., Al-Haidery N.H., Al-Masoudi I.A., Sabri M., Sabri L., Al-Masoudi N.A., Amino acid derivatives, part 4: synthesis and anti-HIV activity of new naphthalene derivatives. *Arch. Pharm. Chem. Life Sci.*, **2010**, *343*, 397-403. https://doi.org/10.1002/ardp.200900293.

29.Chen Z., Xu W., Liu K., Yang S., Fan H., Bhadury P.S., Hu D., Zhang Y., Synthesis and antiviral activity of 5-(4-chlorophenyl)-1,3,4-thiadiazole sulfonamides. *Molecules*, **2010**, *15*, 9046-9056. https://doi.org/10.3390%2Fmolecules15129046.

30.L. Yu, X. Gan, D. Zhou, F. He, S. Zeng, D. Hu, Synthesis and Antiviral Activity of Novel 1,4-Pentadien-3-one Derivatives Containing a 1,3,4-Thiadiazole Moiety, *Molecules*, 2017, *22(4)*, 1. https://doi.org/10.3390/molecules22040658.

31.Chen, Z. Xu, W.Liu, K. Yang, S. Fan, H. Bhadury, P.S. Huang, D.-Y. Zhang, Y., Synthesis and Antiviral Activity of 5-(4-Chlorophenyl)-1,3,4-Thiadiazole Sulfonamides, *Molecules*. **2010**, *15*, 9046-9056. https://doi.org/10.3390/molecules15129046.

32.Matysiak J, Malinski Z. 2-(2,4-Dihydroxyphenyl)-1,3,4-thiadiazole analogues: antifungal activity in vitro against *Candida* species. *Russ. J. Bioorg. Chem.*, **2007**, *33(6)*, 594-601. https://doi.org/10.1134/s1068162007060106.

33.Guzeldemirci N.U., Kucukbasmaci O., Synthesis and antimicrobial activity evaluation of new 1,2,4-triazoles and 1,3,4-thiadiazoles bearing imidazo[2,1-b]thiazole moiety. *Eur. J. Med. Chem.*, **2010**, *45*, 63-68. https://doi.org/10.1016/j.ejmech.2009.09.024.

34.Liu X., Shi Y., Maa Y., Zhang C., Dong W., Pan L., Wang B., Li B., Li Z., Synthesis, antifungal activities and 3D-QSAR study of N-(5-substituted-1,3,4-thiadiazol-2-yl)cyclopropanecarboxamides. *Eur. J. Med. Chem.*, **2009**, *44*, 2782-2786. https://doi.org/10.1016/j.ejmech.2009.01.012.

35.F. Clerici, D. Pocar, M. Guido, A. Loche, V. Perlini, and M. Brufani., *J. Med. Chem.*, **2001**, *44(6)*, 931. https://doi.org/10.1021/jm001027w.

36.Singh V. K., Bharadwaj P., Rishishwar P., Synthesis and Anxiolytic Activity of 2-(Substituted)-5-[(N-Benzotriazolomethyl)-1,3,4-Thiadiazolyl]-4-Thiazolidinone: *Drug Desig. & Intell. Prop. Int. Journal*, **2018**, *1*, 16-21 http://dx.doi.org/10.32474/DDIPIJ.2018.01.000104.

37.Jatav V., Mishra P., Kashaw S., Stables J. P., Synthesis and CNS depressant activity of some novel 3-[5-substituted 1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones, *Eur. J. Med. Chem.*, **2008,** *43*, 135-141. https://doi.org/10.1016/j.ejmech.2007.02.004.

38.Khan, A.A.; Rahim, F.; Taha, M.; Rehman, W.; Iqbal, N.; Wadood, A.; Ahmad, N.; Shah, A.A.S.; Ghoneim, M.M.; Alshehri, S.; et al. New biologically dynamic hybrid pharmacophore triazinoindole-based-thiadiazole as potent _-glucosidase inhibitors: In vitro and in silico study. *Int. J. Biol. Macromol.*, **2022**, *199*, 77-85. https://doi.org/10.1016/j.ijbiomac.2021.12.147.

39.Deswal, Y.; Asijaa, S.; Dubey, A.; Deswal, L.; Kumar, D.; Jindal, K.D.; Devi, J.J. Cobalt(II), nickel(II), copper(II) and zinc(II) complexes of thiadiazole based Schiff base ligands: Synthesis, structural characterization, DFT, antidiabetic and molecular docking studies. *J. Mol. Struct.*, **2022**, *1253*, 132266. https://doi.org/10.1016/j.saa.2010.08.004.

40.Radha, P.V.; Prabakaran, M. Novel thiadiazole-derived schiff base ligand and its transition metal complexes: Thermal behaviour, theoretical study, chemo-sensor, antimicrobial, antidiabetic and anticancer activity. *Appl. Org. Chem.*, **2022**, *36*, e6872. https://doi.org/10.1002/aoc.6872.

41.C. Kus, G. A. Kilcigil, S. Ozbey, Synthesis and antioxidant properties of novel *N*-methyl-1,3,4-thiadiazol-2-amine and 4-methyl-2*H*-1,2,4-triazole-3(4*H*)-thione derivatives of benzimidazole class, *Bioorg. and Med. Chem.*, **2008**, *16*, 4294-4303. https://ijcrr.com/uploads/665_pdf.pdf.

42.D. Cressier, C. Prouillac, P.Hernandez, C. Amourette, M. Diserbo, C. Lion, G. Rima, Synthesis, antioxidant properties and radioprotective effects of new benzothiazoles and thiadiazoles, *Bioorg. & Med. Chem.*, **2009**, *17*, 5275-5284. https://doi.org/10.1016/j.bmc.2009.05.039.

43.Chhajed MR, Khedekar PB, Mundhey AS, Synthesis and free radical scavenging activity of some 1,3,4-thiadiazole derivatives. *Indian J. Heterocycl. Chem.*, **2007,** *16*, 259-262. DOI: 10.29011/CRBOC -101.100003.

44.M. Gür, H. Muğlu, M. S. Çavuş, A. Güder, H. S. Sayıner, F. Kandemirli, Synthesis, characterization, quantum chemical calculations and evaluation of antioxidant properties of 1,3,4-thiadiazole derivatives including 2- and 3-methoxy cinnamic acids, *J. Mol. Struct.*, **2017,** *1134*, 40-50. https://doi.org/10.1016/j.molstruc.2016.12.041.
45.P. Gurunanjappa, Ajay Kumar Kariyappa, Design, synthesis and biological evaluation of 1,3,4-oxadiazoles/thiadiazoles bearing pyrazole scaffold as antimicrobial and antioxidant candidates, *Current Chemistry Letters*, **2016**, *5*, 109-122. Doi: 10.5267/j.ccl.2016.2.002.
46.Sanmati K Jaim, Mishra P, Preparation and evaluation of some 1,3,4-thiadiazoles as diuretic agents. *Indian J. Chem.*, **2004**, 43B, 184-188. http://nopr.niscair.res.in/handle/123456789/18720.
47.L. Varandas, C. Fraga, A. Miranda, and E. Barreiro, *Letters in Drug Design and Discovery*, **2005**, *2(1)*, 62. https://doi.org/10.2174/1570180053398235.
48.A. Ergena, Y. Rajeshwar, G. Solomon, Synthesis and diuretic activity of substituted 1,3,4-thiadiazoles. *Scientifica*, **2022**, *2022*, 3011531. https://doi.org/10.1155/2022/3011531.
49.I.V. Drapak, S.B. Zimenkovsky, V.M. Slabyy, M.S. Holota, O.L. Perekhoda, V.R. Yaremkevych, O.I. Nektegayev, Synthesis and diuretic activity of novel 5-amino-1,3,4-thiadiazole2-thiol derivatives. *Biopolym. Cell*, **2021**, *37*, 33-45. http://dx.doi.org/10.7124/bc.000A4A.
50.Sigrist, G., Greven, J., Fuchs, B., Effects of the New Uricosuric Diuretic Bay r 4420 on Rat Kidney Function. In: Andreucci, V.E., Dal Canton, A. (eds) Diuretics: Basic, *Pharmacological, and Clinical Aspects. Developments in Nephrology*, **1987**, *18*, 547-552. Springer, Boston, MA. https://doi.org/10.1007/978-1-4613-2067-8_140.
51.A. Andreani, M. Rambaldi, A. Locatelli, S. Malandrino, G. Pifferi, Synthesis and diuretic activity of (E)-2-methyl-6-phenylimidazo[2,1-b]-1,3,4-thiadiazole-5-carboxaldehyde dimethylaminoacetohydrazone. *Arzneim.-Forsch.*, **1994**, *44*, 618-619. https://pubmed.ncbi.nlm.nih.gov/8024634/.
52.Medindex [homepage on the Internet]. Available from: http://medindex.am/glossary/index.php/term/UMLS.+CSP-HL7-ICD9CM-NCI-NDFRT-RXNORM, METHAZOLAMIDE.xhtml. Accessed March 7, **2017**.
53.G. Charitos, D. T. Trafalis, P. Dalezis, C. Potamitis, V. Sarli, P.Zoumpoulakis, C. Camoutsis, Synthesis and anticancer activity of novel 3,6-disubstituted 1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazole derivatives, *Ar. J. Chem.*, **2019**, *12*, 4784-4794. https://doi.org/10.1016/j.arabjc.2016.09.015.
54.Jadhav, V.B., Kulkarni, M.V., Rasal, V.P., Biradar, S.S., Vinay, M.D., Synthesis and anti-inflammatory evaluation of methylene bridged benzofuranyl imidazo[2,1-b][1,3,4]thiadiazoles. *Eur. J. Med. Chem.*, **2008,** *43*, 1721-1729. https://doi.org/10.1016/j.ejmech.2007.06.023.
55.G. Mazzone, Bonina, F., Panico, A.M., Puglisi, G., Marchetta, G., Amico Roxas, M., Caruso, A., Blandino, G., Synthesis and biological evaluation of some 5-aryl-2-amino-1,3,4-oxa(thia)diazoles. *Farmaco Edizione Scientifica*, **1984**, *39*, 685-700. https://europepmc.org/article/med/6982830.
56.Bhati S.K., Kumar A., Synthesis of new substituted azetidinoyl and thiazolidinoyl-1,3,4-thiadiazino (6,5-b) indoles as promising anti-inflammatory agents. *Eur. J. Med. Chem.*, **2008,** *43*, 2323-2330. https://doi.org/10.1016/j.ejmech.2007.10.012.
57.Kumar H., Javed S.A., Khan S.A., Amir M., 1,3,4 Oxadiazole/thiadiazole and 1,2,4-triazole derivatives of biphenyl-4-yloxy acetic acid: synthesis and preliminary evaluation of biological properties. *Eur. J. Med. Chem.*, **2008**, *43*, 2688-2698. https://doi.org/10.1016/j.ejmech.2008.01.039.
58.Amir M., Kumar H., Javed S.A. Non-carboxylic analogues of naproxen: design, synthesis, and pharmacological evaluation of some 1,3,4-oxadiazole/thiadiazole and 1,2,4-triazole derivatives. *Arch. Pharm. Chem. Life Sci.*, **2007**, *340*, 577-585. https://doi.org/10.1002/ardp.200700065.
59.Schenone S., Brullo C., Bruno O., Bondavalli F., Ranise A., Filippelli W., Rinaldi B., Capuano A., Falcone G., New 1,3,4-thiadiazole derivatives endowed with analgesic and anti-inflammatory activities. *Bioorg. Med. Chem.*, **2006,** *14*, 1698-1705. https://doi.org/10.1016/j.bmc.2005.10.064.

60.Salgin-Goksen U., Gokhan-Kelekci N., Goktas O., Koysal Y., Kilic E., Isik S., Aktay G., Ozalp M., 1-Acylthiosemicarbazides, 1,2,4-triazole-5(4H)-thiones, 1,3,4-thiadiazoles and hydrazones containing 5-methyl-2-benzoxazolinones: synthesis, analgesic-antiinflammatory and antimicrobial activities. *Bioorg. Med. Chem.*, **2007,** *15*, 5738-5751. https://doi.org/10.1016/j.bmc.2007.06.006.

61.Rostom S.A.F., El-Ashmawy I.M., Abd El Razik H.A., Badr M.H., Ashour H.M.A., Design and synthesis of some thiazolyl and thiadiazolyl derivatives of antipyrine as potential non-acidic anti-inflammatory, analgesic and antimicrobial agents. *Bioorg. Med. Chem.*, **2009,** *17*, 882-895. https://doi.org/10.1016/j.bmc.2008.11.035.