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Review Article

1,3,4- Thiadiazole and Its Derivatives- A Review on Syntheic Account and Recent Progress on its Phermoacological Activities

Jadhav Kiran Mahadev*, Chitnis Akshata Nandkumar, Khandare Aishwarya Vishveswar, Salve P.L, Pise V.J

Arvind Gavali College of Pharmacy, Jaitapur, Satara 415004, India

A B S T R A C T

Many compounds containing a five-membered heterocyclic ring display exceptional chemical properties and versatile biological activities. The 1,3,4-thiadiazole nucleus is one of the most important and well-known heterocyclic nuclei, which is a common and integral feature of a variety of natural products and medicinal agents. Thiadiazole nucleus is present as a core structural component in an array of drug categories such as antimicrobial, anti-inflammatory, analgesic, antifungal, antiepileptic, antiviral, antineoplastic, and antitubercular agents. The broad and potent activity of thiadiazole and their derivatives has established them as pharmacologically significant scaffolds. The current review focused on the various biological performances exhibited by 1,3,4-thiadiazoles.

Keywords: 1, 3, 4-thiadiazole, antimicrobial, antifungal, scaffolds.

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*Address for Correspondence:
Jadhav Kiran Mahadev, Arvind Gavali College of Pharmacy, Jaitapur, Satara 415004, India

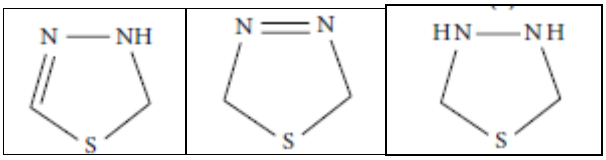
INTRODUCTION

Heterocyclic compounds are essential in medicinal chemistry because they have wide biological action. Furan, thiophene, and pyrrole are five-membered heterocyclic compounds, each with a heteroatom. In five-membered ring structures, one or more heteroatoms are present, such as thiadiazole, oxadiazole, azole, thiazole, pyrrole, and triazine, among others. As a result, heterocyclic chemistry continues to demonstrate synthetic organic chemists' knowledge and enormous scientific curiosity[1]. 1,3,4-Thiadiazoles 1,3,4-Thiadiazole was first described in 1882 by Fischer and further developed by Bush and his coworkers, but true nature of the ring system was demonstrated first in 1956 by Goerdler et al. The advent of sulphur drugs and the later discovery of mesoionic compound greatly accelerated the rate of progress in the field of thiadiazole. Thiadiazole carrying mercapto, hydroxyl, and amino substituents can exist in many tautomeric forms. The 1,3,4-thiadiazoles are conveniently divided into three subclasses:

(i) Aromatic systems which include the neutral thiadiazoles and constitute a major part of this paper;

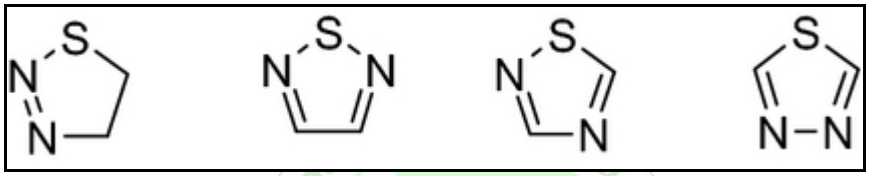
(ii) Mesoionic systems which are defined as fivemembered heterocycles which are not covalent or polar and possess a sextet of electrons in association with the five atoms comprising the ring;

(iii) Nonaromatic systems such as the 1,3,4-thiadiazoles and the tetrahydro 1,3,4-thiadiazoles. In the partially reduced systems, the position of the double bond is denoted by the prefix Δ, with being a Δ2 -1,3,4- thiadiazole (Structure 1, 2, and3)[2].



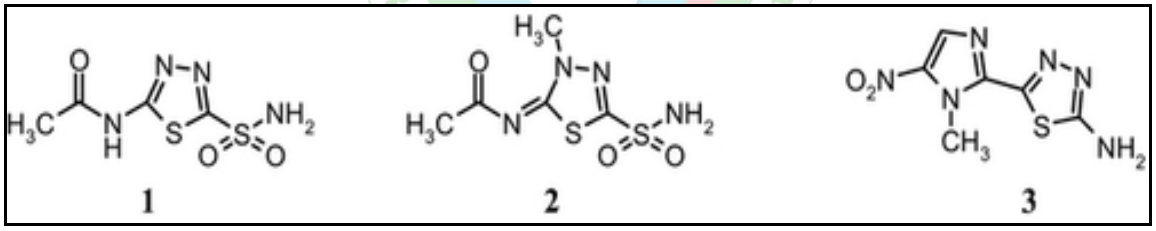
Structures no. 1, 2, and 3

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, sulfur atom, and two-electron donor nitrogen system that exhibit a wide variety of biological activity. They occur in four isomeric forms in the nature viz. 1,2,3-thiadiazole; 1,2,5-thiadiazole; 1,2,4-thiadiazole; and 1,3,4-thiadiazole (Thiadiazole structure 4, 5, 6, 7). Amongst which 1,3,4-thiadiazole to be considered as one of the most significant and well-known heterocyclic nuclei, as it is reported with various pharmacological performance such as anticancer, anticonvulsant, analgesic, anti-inflammatory, anti-tubercular, anti-leishmanial, antimicrobial, antihepatitis-B, antioxidant, diuretic, antihypertensive, central nervous system (CNS) depressant, antidiabetic, antiepileptic actions, and molluscicidal. In addition, thiadiazoles are also reported with this usage in agriculture, plastics, polymers, and dyes. It has been used in the different activities of molecules bearing the five-member heterocyclic ring.



Thiadiazole structure no. 4, 5, 6 and 7

Using the moiety 1,3,4- thiadiazole, the isomer of the thiadiazole progression number of studies have been carried out. Some of the drugs which contain 1,3,4-thiadiazole nucleus are acetazolamide 1, methazolamide 2, megazol 3 shown in structure 8, 9 and 10 respectively3.



Structure no. 8, 9 and 10 (1, 2, 3)

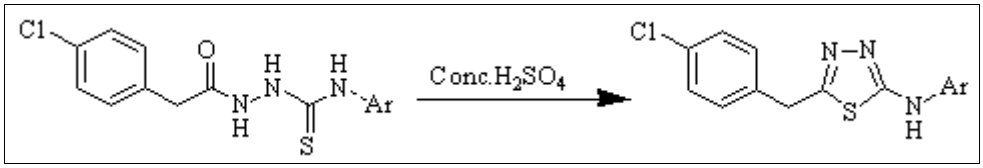
The present review, emphasizes on the biological activities revealed by substituted 1,3,4-thiadiazoles and structurally related thiadiazoles.

General methods of synthesisof Thiadiazoles

Thiadiazoles can be synthesized from mainlythiosemicarbazide or hydrazide by methods like conventional method, ultrasound or microwave using catalyst like H_2SO_4, $POCl_3$, CS_2, polyphosphoric acid and HCl[4].

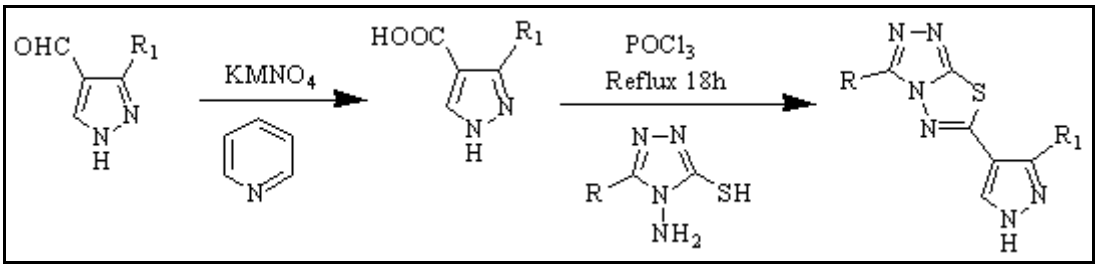
From Thiosemicarbazides

Thiadiazole are prepared by cyclization through sulphuric acid of thiosemicarbazide[5-6].



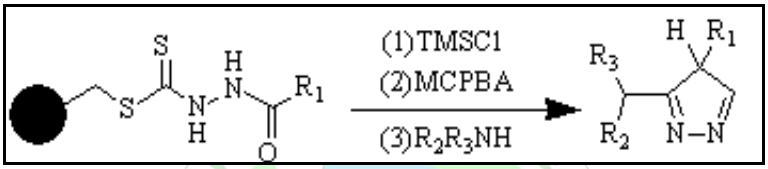
By using phosphorous oxychloride

Thiadiazole can be prepared by cyclization through $POCl_3$[7].



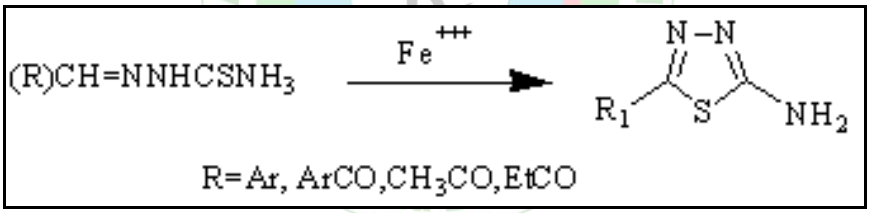
From Resin

Resin with TMSCl, MCPBA, and R_2R_3NH gave 1,3,4- thiadiazole[8].

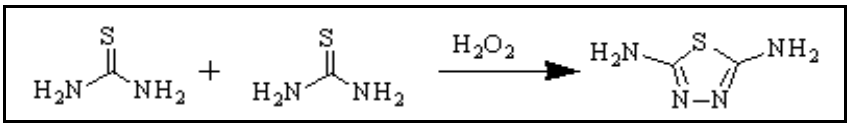


From Thiosemicarbazone

2-Amino-5-substituted thiadiazoles are prepared by oxidative cyclization of thiosemicarbazones with ferric chloride found 1,3,4-thiadiazole[9].



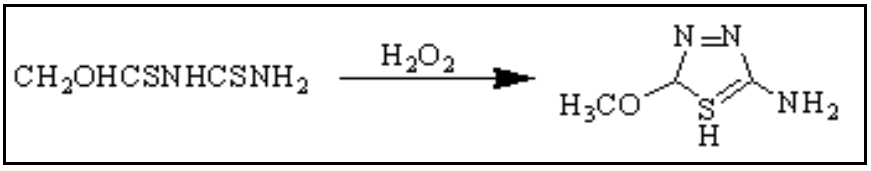
From Bithioureas



Bithiourea when treated with 3% hydrogen peroxide is cyclized to 2,5-diamino-1,3,4-thiadiazole[10].

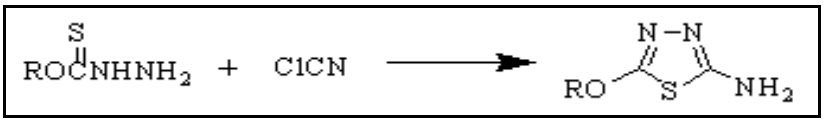
From Hydrazine

3-Thiocarbamoyl thione methyl carbonate on oxidation with H_2O_2 gave alkoxythiadiazole[11].



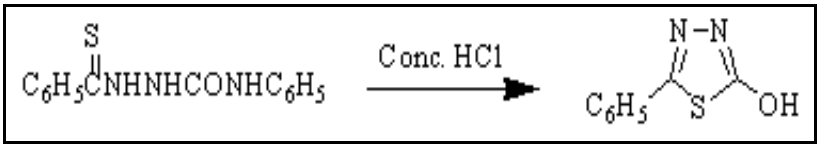
From Thionecarbazate

Thionecarbazate are cyclized by cyanogens chloride or bromide to give 1,3,4-thiadiazole[12].



From Semi carbazide

When 4-phenyl-1-(thiobenzole)semi carbazide reacts in the presence of concentrated HCl giving 2- hydroxyl-5-phenyl-1,3,4-thiadiazole[13].

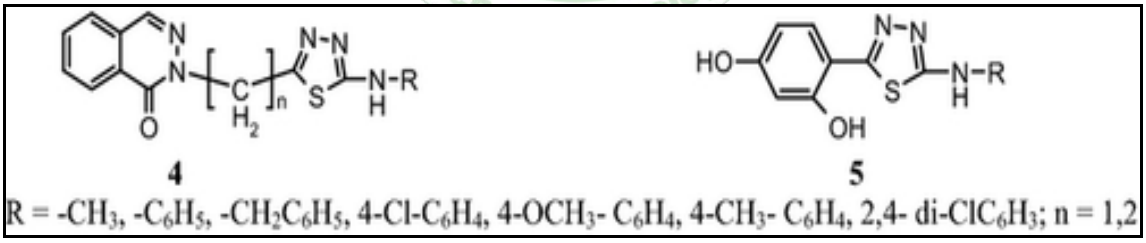


Biological activity of 4-thiazolidinones

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

Antibacterial and Antifungal activity

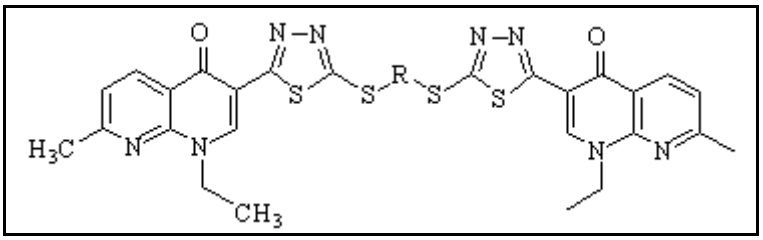
1,3,4-Thiadiazole has shown a broad spectrum of activity against various pathogens, and extensive research has been performed on the synthesis of new potent antibacterial and antifungal agents. A new series of 2-[[1(2H)-phthalazinone-2-yl] methyl/ethyl]-5-arylamino-1,3,4-thiadiazole derivatives (structure 4) 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 with standard drugs chloramphenicol and rifampicin for antibacterial and ketoconazole for antifungal activity, respectively [14]. A number of 5-substituted 2-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole derivatives (structure 5) have been evaluated for antifungal activity against several clinical isolates of *Candida albicans*. The compounds with methyl, phenyl, 4-ethoxyphenyl, and halogenophenyl groups at C-2 of thiadiazole ring showed higher antifungal activity [15].



Structure no. 11 and 12 (4,5)

Sagar Sahu et al synthesized and Evaluated of Antimicrobial Activity of 1, 3, 4-Thiadiazole Analogues for Potential Scaffold. A series of 1,3,4-Thiadiazole derivatives were synthesized by cyclization of a group of various benzaldehyde with thiosemicarbazide in the presence of various reagent like $FeCl_3$, HCHO by losing a molecule of water. These derivatives were found to possess prominent antimicrobial activity.The antibacterial activity of synthesized derivative of 1, 3, 4-Thiadiazole derivatives were carried out on Bacillus subtilis and Escherichia coli by using Agar diffusion method. Ciprofloxacin was used as a standard drug for evaluation.Thiadiazole ring has various biological activities. Amongst the isomers of thiadiazole, 1,3,4-thiadiazole derivatives are widely studied due to their broad scale of pharmacological activities. Though a few pharmacological effects are exhibited by 1,3,4-thiadiazole derivatives which are currently used clinically (e.g., antibacterial activity and carbonic anhydrase inhibiting activity), the substitution at Thiadiazole ring is an exigent approach to obtain agents with improved potency and lesser toxicity. Although the antibacterial activity, has been studied, other antimicrobial activities exhibited such as antifungal and antitubercular properties can also be explored[16].

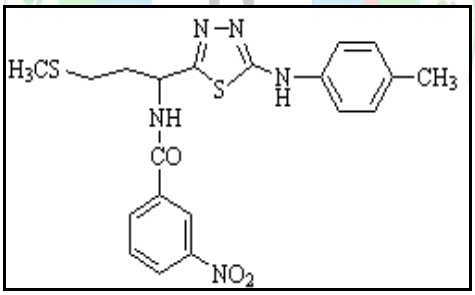
Aggarwal et al synthesized novel nalidixic acid-based1,3,4-thiadiazoles (structure 13)and demonstrated their antimicrobial activity. Disk diffusion was used for the demonstration of the antibacterial activity. The bacterial stain used included gram-positive bacteria, namely Staphylococcus aureus and Bacillus subtilis, and Gram-negative bacteria, namely Escherichia coli, Pseudomonas aeruginosa and Klebsiella pneumoniae. Streptomycin was used as standard drug. Some compounds depicted significant antimicrobial activities on comparison with standard drugs. Compound with 1,4-bis- (methylene)benzene group as a spacer between two 1,3,4-thiadiazoles showed remarkable antibacterial activity (MIC, 31.25–125 lμg/mL) against all the tested organisms[17].



R- -(CH2)0; -(CH2)4; -(CH2)6; -(CH2)8; -CH2C6H4CH2-

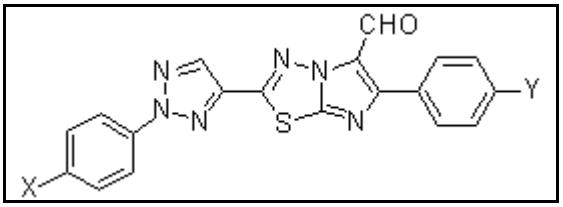
Structure no. 13

Pintilie et al synthesized some novel N-(5-(3-(methylthio)propyl)-1,3,4-thiadiazol-2yl)benzamide derivatives(structure 14) and investigated for their antimicrobial activities against five standard bacterial strains Staphylococcus aureus, Bacillus antracis, Bacillus cereus, Sarcinalutea and Escherichia coli by using double dilution method. Some of the investigated compounds exhibited excellent antimicrobial activities on comparison with their respective standard drugs. The most active compound against B.antracis and B. cereus was a compound with a 4-methylphenyl moiety on the heterocyclic ring[18].



Structure no. 14

Atta et al synthesized novel imidazo[2,1-b]-1,3,4-thiadiazoles (structure 15)and evaluated for their antimicrobial activity against Staphylococcus aureus, Candida albicans, Pseudomonas aeruginosa and Escherichia coli using agar diffusion method Ampicillin and Clotrimazole were used as reference drugs. Some of these compounds were found to possess slight to moderate activity against the microorganisms[19].

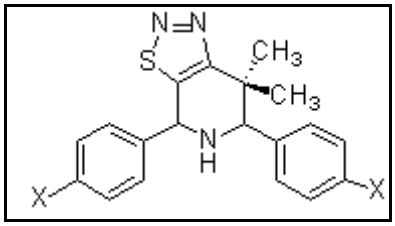


X- H; Br; Cl; I Y- H; Br; Cl

Structure no. 15

Gopalakrishnan et al synthesized 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridine [3,4-d]-1,2,3-thiadiazoles(structure 16). All of the newly synthesized novel target molecules were tested for their antibacterial activity in vitro against Staphylococcus aureus, β-Haemolytic streptococcus, Vibreocholerae, Salmonella

typhii, Shigella felxneri, Escherichia coli, Klebsiella pneumonia, and Pseudomonas by using Ciprofloxacin as standard drug for comparison. Synthesized compounds exerteda wide range of modest antibacterial activity and modest in vitro antifungal activity against Rhizopus and M. Gypsuem, compared to the standard drug Fluconazole[20].

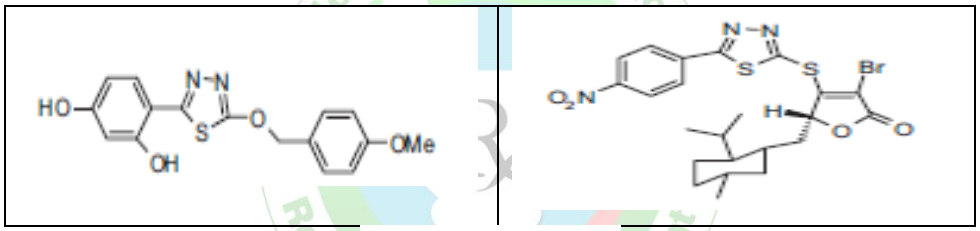


X- H; CH3; OCH3; Cl; F

Structure no. 16

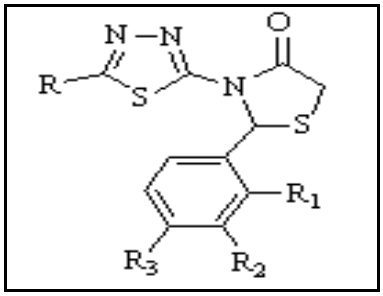
Anticancer activity

Matysiak 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 tumor cell lines. 2-(2,4-Dihydroxyphenyl)-5-(4-methoxybenzyloxy)-1,3,4-thiadiazole (structure 17) showed ID_{50} of 1.1 µg/mL against HCV29T bladder cancer cell line and found to be significantly lower (T47D) than that of cisplatin, used as the reference compound. In a series of chiral 2,5-disubstituted 1,3,4-thiadiazoles possessing c-butenolide moiety, structure18 was screened against Hela cell lines by MTT assay and exhibited IC_{50} of 0.9 µM [21-22].



Structure no.17 and 18

Joseph et al synthesized a series of novel 5-alkyl/aryl thiadiazole substituted thiazolidin-4-ones (structure 19) and screened for in vitro anti-proliferative activity on human breast adenocarcinoma cells (MCF-7) by MTT assay. Most of the derivatives showed an IC_{50} less than 150µmol L–1. Among the compounds tested, 2-(2-nitrophenyl)-3-(5-methyl-1,3,4-thiadiazol-2-yl)-thiazolidin-4-one, 2-(3-fluorophenyl)-3-(5-methyl-1,3,4-thiadiazol-2-yl)-thiazolidin-4-one, and 2-(4-chlorophenyl)-3--(5-methyl-1,3,4-thiadiazol-2-yl)-thiazolidin-4-one were found to be the most active derivatives with IC_{50} values of 46.34, 66.84 and 60.71 µmol L–1 , respectively[23].

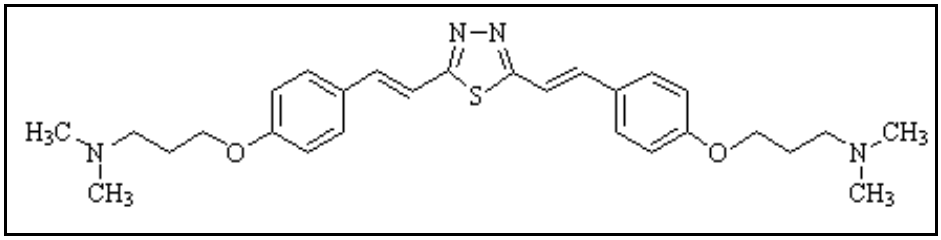


R- CH3; C2H5R1- H; Br, NO2

R2- H; Br; F R3- H; Cl; NO2

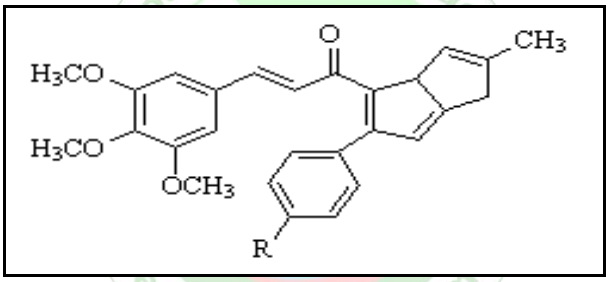
Structure no. 19

Chou et al this study synthesized several thiadiazole based compounds and examined their cytotoxic effects on human non-small cell lung cancer A549 cells. It was found that ((E, E)-2,5- bis[4-(3-dimethyl-aminopropoxy) styryl]-1,3,4-thiadiazole)(Structure 20) is the most effective one by the MTT assay. It induced the early-phase apoptosis in A549 cells via the Bcl-XL down-regulation, and that of the late-phase through up-regulation of Bax expression as well as inhibition of Akt/PKB activation. Besides the anticancer activity, it also showed equivalent anti-angiogenic activity in the nude mice angiogenesis model[24].



Structure no. 20

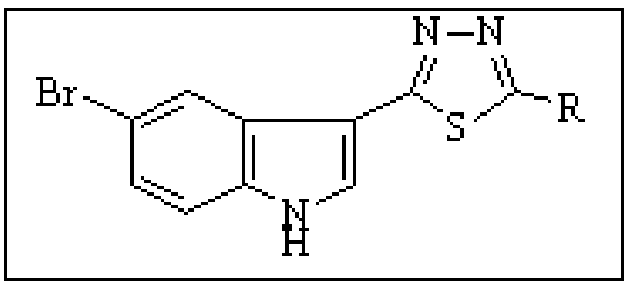
Kamal et al synthesized a series of new imidazo[2,1-b][1,3,4]thiadiazole-chalcones(Structure 21)by theClaisen-Schmidt condensation and evaluated for their cytotoxic activity against various human cancer cell lines taking Doxorubicin as standard drug. These compounds showed moderate to appreciable antiproliferative activities. Interestingly, two compounds exhibited significant cytotoxic activity with IC_{50} values ranging from 0.65 to 2.25 µM in certain cancer cell lines. The structure activity relationship (SAR) studies revealed that 3,4,5-trimethoxy group containing compounds showed superior cytotoxic activity against selected cancer cell lines compared to other chalcones[25].



R-F; OCH3

Structure no. 21

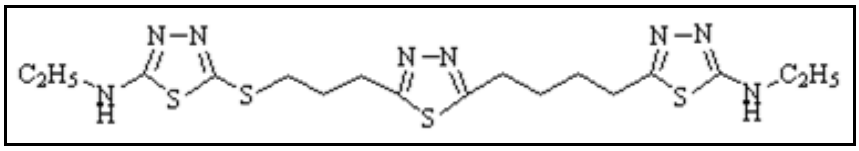
Kumar et al synthesized a series of 5-(3-indolyl)-2-substituted-1,3,4-thiadiazoles(Structure 22) and their cytotoxicityanalyzed against prostate (PC3,DU145and LnCaP), breast (MCF7 and MDA-MB-231) and pancreatic ($PaCa_2$) cancer cell lines with Doxorubicin as a reference drug. Indolyl-1,3,4- thiadiazole with 4-benzyloxy-3-methoxyphenyl and 5-bromoindolyl substituents is the most active insuppressing the growth of cancer cells (IC_{50} 1.5 µM, $PaCa_2$). The compounds bearing C2substituent as benzyl, 3,4-dimethoxyphenyl and 4-benzyloxy-3-methoxyphenyl, respectively, have shown significant cytotoxicity against multiple cancer cell lines. Introduction of 4-dimethylamino and 3,4,5-trimethoxy groups in the C-2 phenyl ring induced selectivity against MCF7 and MDAMB-231 cancer cell lines[26].



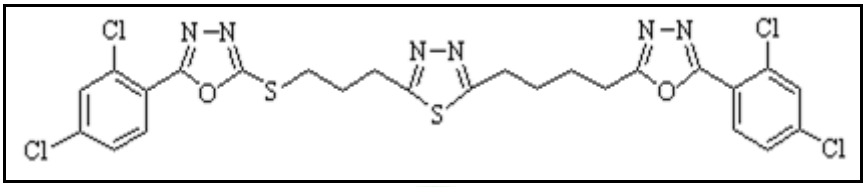
R- 4-BnO-3-OCH3C6H3

Structure no. 22

Rezki et al supported the synthesis of a new series of 2,5-disubstituted-1,3,4-thiadiazole tethered1,3,4-oxadiazole, 1,3,4-thiadiazole(Structure 23, 24)for the in vitro evaluation of their antiproliferative activities on four different human cancerous cell lines. Compounds substituted with ethyl group significantly potentiated the cytotoxic activities suggesting a steric factor mediating either transport or molecular interaction of these compounds with cellular targets. The addition of one Cl atoms into the structure of compound was successful in almost doubling its activity[27].

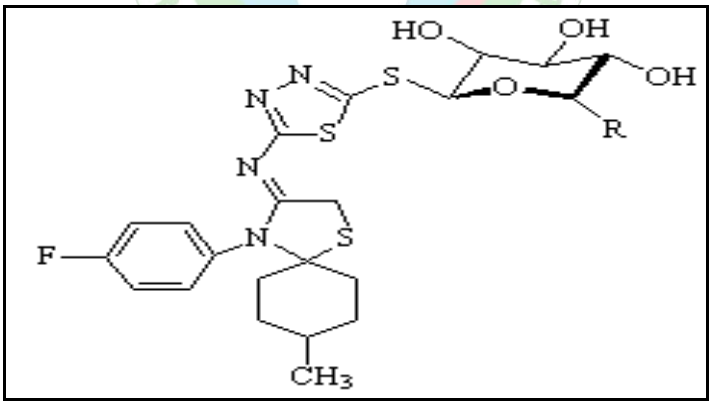


Structure no. 23



Structure no. 24

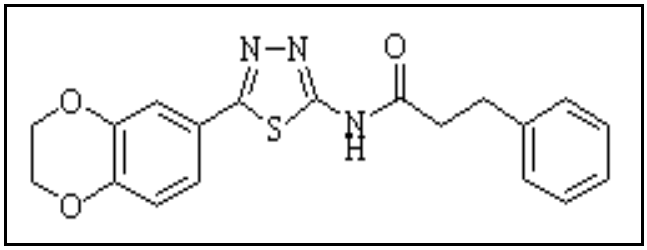
Flefel et al synthesized new series of 1-thia-4-azaspiro[4.5]decane, their derived and 1,3,4-thiadiazolethioglycosides(Structure 25)and examined in vitro for their anti-tumor activities against human liver hepatocellular carcinoma (HepG-2), human prostate adenocarcinoma (PC-3) and human colorectal carcinoma (HCT-116) cell lines using a MTT assay. Five compounds showed good anticancer activities against HCT-116 carcinoma cells with IC_{50} ranging from92.2 to 120.1 nM. The rest of the compounds showed moderate activities against HCT-116 cells. Two compounds showed good anticancer activities against PC-3 cancer cells[28].



R- H; CH2OH

Structure no. 25

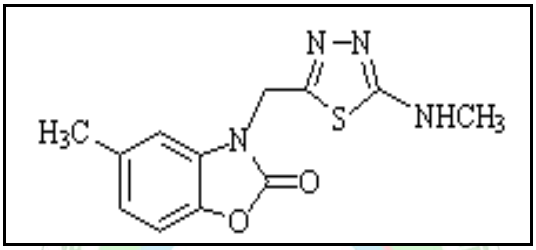
Sun et al synthesized a series of 1,3,4-thiadiazole derivatives containing 1,4-benzodioxan (Structure 26)and screened for FAK inhibitory activity. One compound showed the most potent biological activity against HEPG2 cancer cell line (EC50= 10.28µg/mL for HEPG2 and EC50= 10.79µM for FAK), which was comparable to the positive controls (5-Fluorouracil and Staurosporine). Docking simulation was performed to position this compound into the FAK structure active site to determine the probable binding model[29].



Structure no. 26

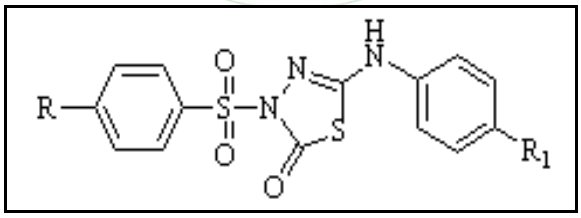
Analgesic and anti-inflammatory activity

Salgin-Goksen et al synthesized 2-Substituted amino-5-[(5-methyl-2-benzoxazolinone-3-yl)methyl]-1,3,4-thiadiazoles(Structure 27)and examined their analgesic and anti-inflammatory using acetic acid-induced writhing test, hot plate test in mice and carrageenan-induced hind paw oedema method respectively. Most of the compounds exhibited high analgesic-anti-inflammatory activity. One compound showed strong analgesia and the most prominent and consistent anti-inflammatory activity at 200 mg/kg dose when compared to the standards Aspirin and Morphine[30].



Structure no. 27

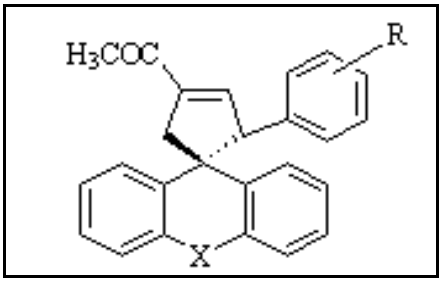
Schenone et al synthesized a series of 3-arylsulphonyl-5-arylamino-1,3,4-thiadiazol-2(3H)ones (Structure 28)and evaluated for their anti-inflammatory and analgesic activity using carrageenan rat paw edema and acetic acid induced writhing test. The compounds, endowed with an arylsulphonylside chain, possess good antalgic activity and fair anti-inflammatory properties. Three compounds were the most active (54.4, 53.8, and 51.3% of inhibition) showing an ED50of 37.33. It was evident that a good electron-donating group (OCH3) favours the antipain properties[31].



(31) R- H; CH3R1- H; CH3; F; Cl; OCH3

Structure no. 28

Hafez et al synthesized novel spiro-thioxanthene and spiro-xanthene-90,2-[1,3,4]thiadiazole derivatives (Structure 29) and were tested for anti-inflammatory and analgesic activities comparable to ibuprofen. The tested compounds showed anti-inflammatory activity ranging from 50% to 86% and the standard drug ibuprofen showed 92% inhibition after 4 h, both at 70mg/Kg dose. The derivatives having a 4-nitrophenyl group at position 3 and acetyl group at position 5 showed the maximum activity (84–86%). Also, the spiro compounds which having two phenyl groups at position 3 and 5, showed high activities (85% and 82%), respectively. The compounds showed analgesic activity ranging from 57% to 73%, whereas the standard drug ibuprofen showed 84% at a 70 mg/kg oral dose[32].

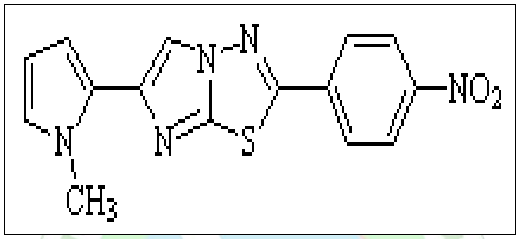


X- O; S

Structure no. 29

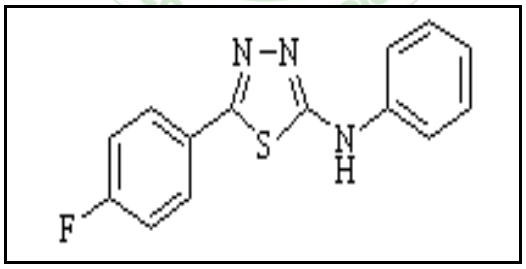
Antitubercular activity

Patel et al synthesized a series of imidazo[2,1-b][1,3,4]thiadiazole derivatives (Structure 30)and were evaluated for their in vitro antitubercular activity against Mycobacterium tuberculosisH37Rv strain by using Alamar Blue susceptibility test as part of the TAACF TB screening program. Among the tested compounds, 2-(1-methyl-1H-imidazol-2-yl)-6-(4-nitrophenyl)imidazo[2,1-b][1,3,4]thiadiazole has shown the highest (98%) inhibitory activity with MIC of 3.14 μg/ml as compared to another tested compound. Rifampicin was used as a standard drug[33].



Structure no. 30

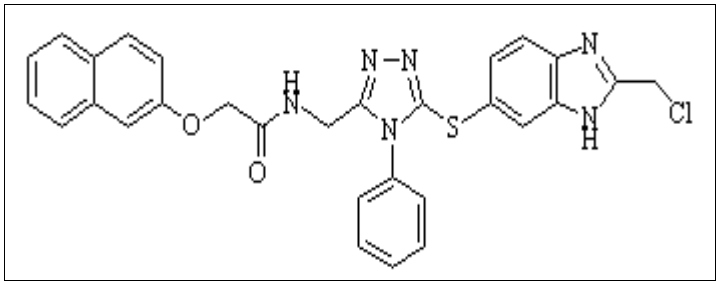
Oruc et al synthesized a series of 2,5-disubstituted-1,3,4-thiadiazoles (Structure 31) and screened for the antituberculosis activity against Mycobacterium tuberculosis H37Rv using the BACTEC 460 radiometric system. Among the tested compounds, 2-phenylamino-5-(4-fluorophenyl)-1,3,4- thiadiazole showed the highest inhibitory activity. The relationships between the structures of compounds and their antituberculosis activity were investigated by the Electronic-Topological Method (ETM)[34].



Structure no. 31

Antiviral activity

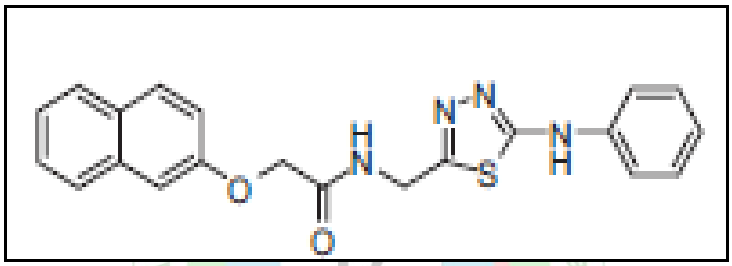
Hamad et al synthesized a new series of 2-(naphthalen-2-yloxy)-N-[(aryl-5-thioxo-4,5-dihydro1H-1,2,4-triazol-3-yl)methyl]acetamides (Structure 32)and screened for their inhibitory activity against HIV1 and HIV-2 in MT-4 cells using MTT assay. Efavirenz and Capravirine were included for comparison. One compound was found to be the potent inhibitor in vitro for the replication of HIV1 (EC50= 0.20μg/mL), suggesting a new lead in the development of an antiviral agent. Substitution of naphthalene bearing amino acid precursors carrying various potential thiadiazole blocking group showed higher activity than those of the corresponding substituted derivatives bearing 1,2,4-triazole derivatives[35].



Structure no. 32

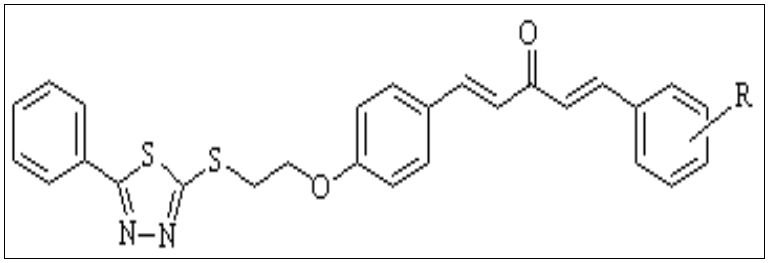
Hamad et al.synthesized 2-(naphthalen-2-yloxy)-N-((5-(phenylamino)-1,3,4-thiadiazol-2-yl)methyl) acetamide (Structure 33**)** and testedin vitro anti-HIV-1 (strain IIIB) and anti-HIV-2 (strain ROD) activity by the inhibition of the virus induced cytopathic effect in the human T-lymphocyte (MT-4) cells, based on MTT assay[36].

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. One of these, reverse transcriptase (RT) is a key enzyme that is packaged within the HIV virion capsid and plays an essential and multifunctional role in the replication of the virus [37].



Structure no. 33

Yu et al synthesized a series of novel 1,4-pentadien-3-one derivatives containing a 1,3,4-thiadiazole moiety (Structure 34)and evaluated for the antiviral activities against tobacco mosaic virus (TMV) and cucumber mosaic virus (CMV) in vivo. Most of compounds had remarkable antiviral activities against TMV and CMV, with EC_{50} values of 105.01-297.40 μg/mL which were superior to that of ribavirin (457.25 μg/mL). Small electron-withdrawing groups on the aromatic ring were favorable for anti-TMV activity. This finding suggests that 1,4-pentadien-3-one derivatives containing a 1,3,4-thiadiazole moiety may be considered as potential lead structures for discovering new antiviral agents[38].



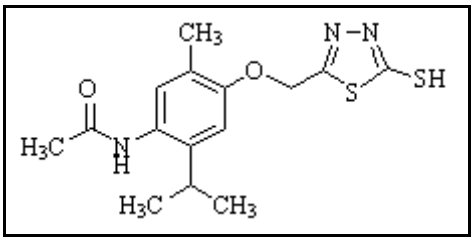
R- 2-F; 4-F; 4-Br; 4-Cl; 4-OCH3; 3-NO2

Structure no. 34

Antioxidant activity

Suresh et al synthesized carvacrol containing novel thiadiazole moieties(structure 35)and screened for their in-vitro antioxidant activity by using radical scavenger DPPH assay. All the compounds exhibited remarkable antioxidant activity, out of which some compounds showed better or similar antioxidant activity compared to standard compound ascorbic acid. Maximum DPPH radical scavenging activity observed was 89.98 and 94.52%, which is higher or comparable with standard antioxidant ascorbic acid (94.03%) at the same concentration. Compounds are also significant

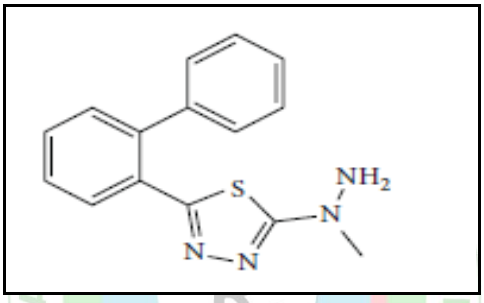
scavengers of the DPPH radical with % inhibition of 63.67%-67.21%[39].



Structure no. 35

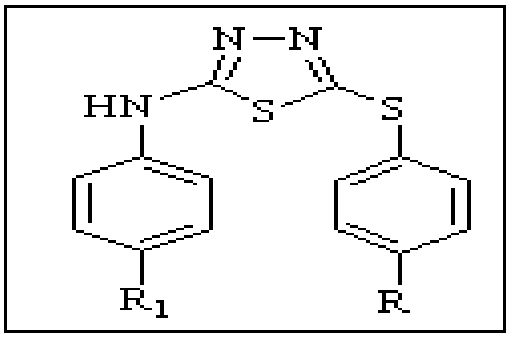
Anticonvulsant activity

Various N-(5-chloro-6-substituted-benzothiazol-2-yl)-N -(substituted phenyl)-[1, 3, 4]thiadiazole-2,5-diamines were designed and synthesized starting from substituted acetophenones. Structures of all the compounds were confirmed on the basis of spectral and elemental analyses. All the newly synthesized compounds were screened for their anticonvulsant activity and were compared with the standard drug phenytoin sodium. Interestingly, all the compounds showed protections against seizures in the range 50%–100% indicative of the promising nature of the compounds against seizure spread. Structure 36 showed complete protection against MES-induced seizures[40].



Structure no. 36

Sharma et al synthesized a new series of 2-amino-5-sulfanyl-1,3,4-thiadiazole derivatives (structure 37)and screened for anticonvulsant activity. Compound having sulphonamide group and chloride group having appreciable anticonvulsant activity. Among the halogen (electron-withdrawing group) substituted compounds only compound having fluoride or trifluoromethyl group and up to some extent chloride group on R1 position showed significant central nervous system activity, the possible reason could be a fluorine atom are small in size, lipophilic in nature and ability to form strong hydrogen bond. Compound having methyl (electron donating) group on R1 position showed broad window of CNS activity[41].

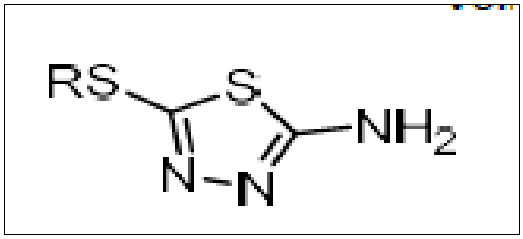


R- SO2NH2; SO2Cl2R1- F; Cl; Br; CF3; CH3; SO3Cl2; CCl3

Structure no. 37

Antidepressant and Anxiolytc Activity

F. Clerici et. al., have synthesized a series of 2-amino-5-sulfanyl-1,3,4-thiadiazole derivatives behaviorwith different substituents and to be monitored. They were evaluated for their central nervous systemactivity. Among them, Structure 38showed an outstanding psychopharmacological structure in animalactivity with antidepressant and anxiolytic action[42-43].

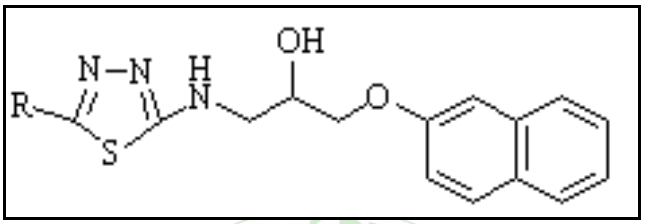


R-3-CH_3O-benzyl

Structure no. 38

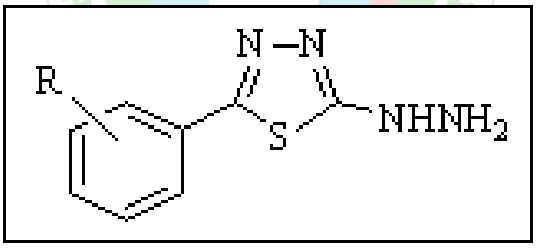
Antihypertensive activity

Samelet al synthesized 2-amino-5-aryl/alkyl-1,3,4-thiadiazoles (Structure 39)and screened for antihypertensive activity based on structure activity relationship with propanalol[44].



Structure no. 39

Turner et al afforded the synthesis of some 2-aryl-5-hydrazino-l,3,4-thiadiazole(Structure 40)and screened for antihypertensive activity. In general, compounds with a 2-substituted phenyl ring had higher activity than their 3- or 4-substituted counterparts or those containing heteroarylgroups. The 2- methylphenyl and 2-ethylphenyl derivatives were the most potent members of the series. Preliminary studies indicated that the hypotensive action of these compounds was due to a direct relaxant effect on vascular smooth muscle. Hydralazine and Minoxidil were used as standard drugs[45].



R- 2-CH3; 2-C2H5

Structure no. 40

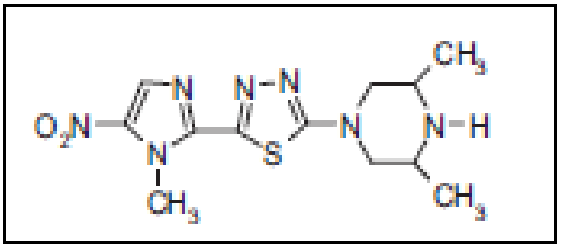
Diuretic Activity

Asrat Ergena et al synthesized seven 5- and 2-thioate derivatives of 1, 3, 4-thiadiazoles were by substitution reaction using acetone as solvent and K2CO3 as a base. &e compounds ware then characterized by using IR and NMR spectroscopy. &e diuretic activity of the compounds was evaluated on Swiss albino mice by measuring urine volume, urinary pH, and urinary Na+, K+, and Cl−. &e result showed increase in urinary excretion of both water and electrolytes. 5-Methyl-substituted derivatives of 1, 3, 4-thiadiazoles showed significant increase in excretion of both water and electrolytes when they are compared to both negative control and 5-amino-substituted derivatives. &e highest diuretic activity (0.82) was recorded for para-nitro-substituted benzene ring at 2-thioate group of 5- methyl-1, 3, 4-thiadiazole, while the least (0.56) was recorded for propanethioate group at 2nd position and amine group at 5th position of 1, 3, 4-thiadiazole. &e finding of the present study showed that all the compounds have diuretic activity and 5-methyl derivatives of 1, 3, 4-thiadiazoles exhibited significant diuretic activity[46].

Anti-Helicobacter pylori

Helicobacter pylori is a Gram-negative, microaerophilic bacterium found in the stomach. Acute infection of H. pylori may appear as an acute gastritis with abdominal pain (stomach ache) or nausea. The purpose of designing of agents for eradication of bacteria includes to overcome bacterial resistance and to inhibit proton pump.

Moshaf et al.synthesized 5-(1-methyl-5-nitro-1H-imidazol-2-yl)-1,3,4-thiadiazoles and screened for bactericidal activity against H. pylori. Structure 41**,** substituted with 3,5-dimethylpiperazinyl moiety at the 2-position of the 5-(1-methyl5-nitro-1H-imidazol-2-yl)-1,3,4-thiadiazole skeleton had strong anti-H. pyroli activity at 0.5 µg/disk (average of inhibition zone >20 mm) which was superior to that of metronidazole. Attachment of pyrrolidine (instead of piperazine) to the 2-position of the thiadiazole and substitution with piperazine, methylpiperazine and 3,5-dimethyl substitution on the piperazine ring improved inhibitory activity. Further replacement of 3,5-dimethyl group with N-phenyl, N-benzyl, N-acetyl, and N-benzoyl on the piperazine ring diminishes the anti-H. pylori activity[47].



Structure no. 41

CONCLUSION

1,3,4-Thiadiazole, a well-known heterocyclic, offers a wide range of biological activities. One of the most significant areas in medicinal chemistry is the development and discovery of new 1,3,4-thiadiazole moiety. As a result, researchers concentrated on and produced 1,3,4-thiadiazolebased biological agents. In this review, 1,3,4-thiadiazole compounds with high activity potency were examined. In conclusion, the discovery of molecules with a 1,3,4-thiadiazole nucleus is an appealing and promising field of medicinal chemistrywith this heterocyclic ring have the potential for dispersal. In general, 1,3,4-thiadiazole is a unique molecule with numerous biological functions. Anticancer, antimicrobial, antibacterial, and anti-inflammatory properties are all promising. Thisreview exhaustively analyzed to provide a meaningful overview of the structural requirements for the biological activity.

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