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REVIEW ARTICLE

Studies On Nitrogen And Sulphur Containing Heterocyclic Compound: 1,3,4 - thiadiazole.

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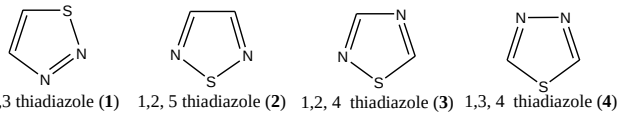
ABSTRACT

The chemistry of heterocyclic compounds has been an interesting field of study for a long time. Heterocyclic nucleus 1,3,4-thiadiazole constitutes an important class of compounds for new drug development. The synthesis of novel thiadiazole derivatives and investigation of their chemical and biological behaviour have gained more importance in recent decades. During the recent years there has been intense investigation of different classes of thiadiazole compounds, many of which possess extensive biological activities. Among of these compounds having 1,3,4 - thiadiazole nucleus are known to possess anti-inflammatory, analgesic, antimicrobial, antitumor, antifungal, antimycobacterial, anticonvulsant, antidiabetic, antiviral, activities. So far, modification of the thiadiazole ring have proven highly effective with improved potency and lesser toxicity. The present review highlights the recently synthesized thiadiazole possessing important biological activities.

Keywords: 1, 3, 4-Thiadiazole, antibacterial, antitubercular, vasodialatory, antifungal, cytotoxic, antiinflammatory, analgesic, hypolipidemic, anticancer and ulcerogenic activities.

INTRODUCTION

Thiadiazole is a 5-membered ring system containing hydrogen-binding domain, sulphur atom, and two-electron donor nitrogen system (–N=C–S) that exhibit a wide variety of biological activity. They occur in four isomeric forms in the nature viz. 1,2,3-thiadiazole (1); 1,2,5-thiadiazole (2); 1,2,4-thiadiazole (3); and 1,3,4-thiadiazole (4) five member ring. (Figure1). [Gupta et. al, 2005]



1,2,3 thiadiazole (**1**) 1,2, 5 thiadiazole (**2**) 1,2, 4 thiadiazole (**3**) 1,3, 4 thiadiazole (**4**)

Figure 1 Four Isomeric Form of Thiadiazole

Among these four types of thiadiazole, 1, 3, 4-thiadiazole is well known. 1,3,4-Thiadiazole and its derivatives continue to be of a great interest to a large number of researchers owing to their great pharmaceutical and industrial importance. [Holla et. al, 2002]

1,3,4-Thiadiazole was first described in 1882 by Fischer and further developed by Busch and his coworkers .The advent of sulfur drugs and the later discovery of mesoionic compounds greatly accelerated the rate of progress in this field. [Stellings et. al, 1986]

1,3,4-Thiadiazoles were conveniently divided into three subclasses:

a) Aromatic systems which include the neutral thiadiazole (4) and constitute a major part of this review.

b) Mesoionic systems (4a) which is defined as five-membered heterocycles which are not covalent or polar and possess a sextet of electrons in association with the five atoms comprising the ring.

c) Non aromatic systems such as the 1,3,4-thiadiazolines (4b, 4c) and the tetrahydo 1,3,4-thiadiazolidines (4d). [Grant et.al, 1972]

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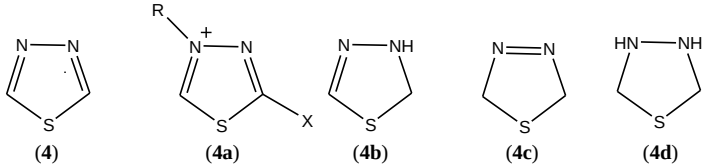
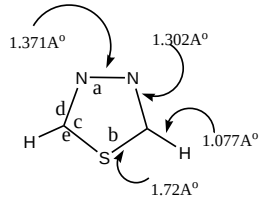


(4) (4a) (4b) (4c) (4d)

Literature survey revealed that various thiadiazoles have resulted in many potential drugs and are known to exhibit a broad spectrum of pharmacological properties. The specific pharmacological activities including Antitumor [Zhang et. al, 2009], Antiviral, Antibacterial, Amoebicidal, Antiinflammatory, Antitubercular, Antipyretic, Anticancer, CNS depressant, Antischistosomal, [Jain et. al, 2013] Herbicidal [Mahmoud et. al, 1997], Insecticidal, Pesticidal [Nidhi et. al, 2009], Hypoglycemic [Lei et. al, 2009].

PROPERTIES OF 1,3,4 THIADIAZOLE

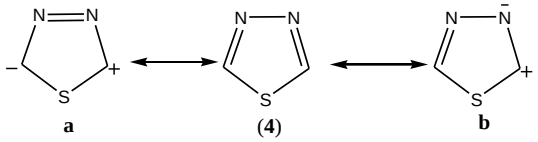
1,3,4-thiadiazole (4) can be looked upon as 4-azathiazole or 3,4- diazathiophene so far as they are electronically isosteric. However, the replacement of –CH= by electronegative –N= atom in the 5-membered thiophene ring changes the chemical/physical behavior considerably. The structure (4) represents π-excessive ring system as the two adjacent N atoms of the ring carry a lone pair of electrons each. Actually 1,3,4-thiadiazole molecule does not display a true aromatic behavior as do benzene, pyridine and thiophene. [Bak et. al, 1966] have made analysis of microwave spectra of this molecule and calculated bond lengths, bond angles and bond orders. They concluded that the aromatic character as measured by the π-electron delocalization decreases in the order of 1,2,5-thiadiazole > thiophene > thiazole > 1,3,4-thiadiazole. [Palmer et. al, 1977] made a series of M.O. calculations by HMO method using the Longuet Higgins model for the sulfur atom of thiadiazole isomers and showed that π- electron delocalisation is more in 1,2,5-isomer than in 1,3,4-thiadiazole and thiazole. [Bak et al.1962] have reported the dipole moment value of 3.25D for 1,3,4-thiadiazole and 1.61D for thiazole. These findings suggested that 1,3,4-thiadiazole is a polar symmetric molecule exhibiting pseudoaromatic character. The molecular geometry figure for 1,3,4-thiadiazole is given here which are calculated on the bases of M.O. method. [Sherman 1961; Sandstrom 1968; Paquette 1968]



a = 112.2°; b = 86.4°; c = 114.6°; d = 123.5°; e = 121.9°

(4)

Some important canonical forms of 1,3,4-thiadiazole (Figure 2) are written below, of which 4 with dienic behaviour is the maximum contributing structure. [Belenkaya et. al, 1982; Kurzer et. al, 1970,1989]



a (4) b

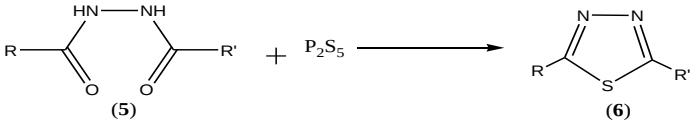
Figure 2 canonical forms of 1,3,4-thiadiazole

SYNTHETIC ASPECTS OF 1,3,4-THIADIAZOLES

The method commonly employed for the synthesis of 1,3,4-thiadiazole is the cyclization of thiosemicarbazide derivatives incorporating the basic structural unit. Other methods involve ring closure of dithiocarbazates, acylhydrazines, bisthioureas or interconversions of oxadiazoles in to 1,3,4-thiadiazoles have also been reported.

1. From 1,2-diacylhydrazines

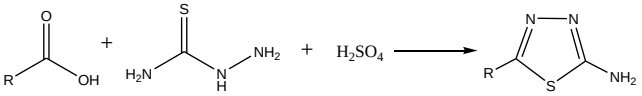
Stolle [1899], prepared a number of 2,5-dialkyl-1,3,4-thiadiazoles (6) from 1,2-diacylhydrazines (5) and P_2S_5. Instead of using P_2S_5, thioacylation of 1,2- diacylhydrazine is effected by carboxymethyldithioate which on heating gives 2,5- disubstituted thiadiazoles.



(5) (6)

2. From cyclisation of acylthiosemicarbazides

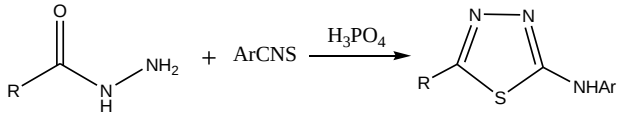
E. Hoggarth et. al, [1950] for the first time reported the synthesis of 2-amino-1,3,4- thiadiazoles, by cyclodehydration of acylthiosemicarbazides in presence of acid catalyst like H_2SO_4, H_3PO_4 etc. The required acylthiosemicarbazides were obtained by treating an acidhydrazide with an isothiocyanate. They were also prepared *in situ* by heating the carboxylic acid and thiosemicarbazide in the acid medium and were cyclised subsequently.



Turner et. al. [1988] have prepared 2-amino-5-aryl-1,3,4-thiadiazoles directly by heating a mixture of the carboxylic acid and thiosemicarbazide with PPA. Phosphorous oxychloride can also be used instead of PPA.

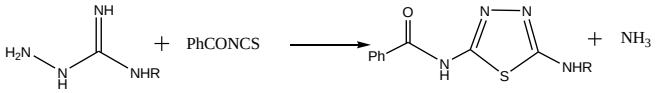
Fullop et. al. [1990] used ethanolic HCl for cyclodehydration of acylthiosemicarbazides.

Mahajanshetti et. al. [1984] synthesized thiadiazoles containing a long alkyl chain by using H_3PO_4 as dehydrating agent.



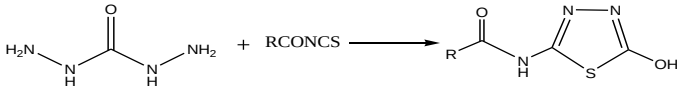
3. From cyclisation of aminoguinidines and diaminoguinidines

Kurzer [1970] prepared a number of 1,3,4-thiadiazoles by acid catalysed cyclisation of acylthiosemicarbazides obtained from the reaction of aminoguinidine salts and aroylisothiocyanates.



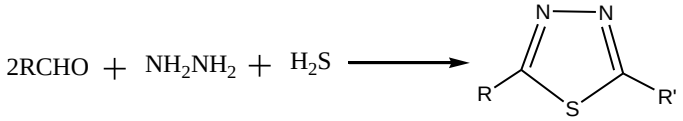
4. From carbohydrazide and acylisothiocyanate

Esmail et.al, [1977] prepared a number of 2-hydroxy-5-acylaminothiadiazoles by heating carbohydrazide with equimolar quantity of an acylisothiocyanate in DMF at 100˚C.



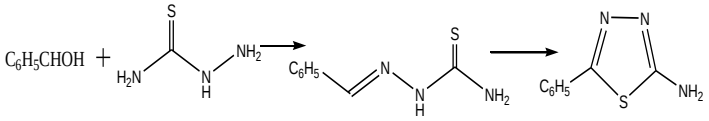
5. From hydrazine and hydrogen sulfide

K. Ruhlmall et. al [1959] obtained 2,5-dialkyl-1,3,4-thiadiazoles in high yields via thiadiazolidines prepared from the reaction of hydrazine, aliphatic aldehyde and hydrogen sulfide. The thiadiazolidinones thus prepared were further dehydrogenated by sulfur in boiling pyridine.



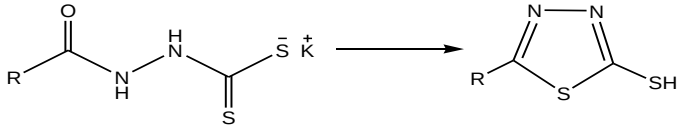
6. From the oxidation of thiosemicarbazones

Young et. al, [1901] prepared 2-amino-5-phenyl-1,3,4-thiadiazoles by oxidative cyclisation of corresponding aldehyde thiosemicarbazone by ferric chloride.

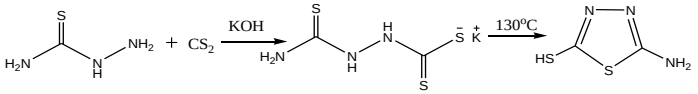


7. From dithiocarbazates

Various dithiocarbazates readily undergo the desired cyclisation to yield 2-substituted-5-mercapto-1,3,4-thiadiazoles [Neilson, 1970]

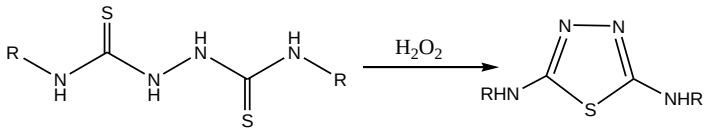


Guha 1922 synthesised 2-amino-5-mercapto-1,3,4-thiadiazoles by the reaction of thiosemicarbazide and carbondisulfide in presence of KOH, followed by heating the intermediate potassium dithiocarbazate.



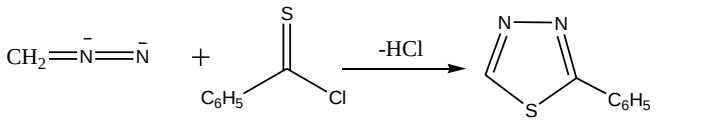
8. From bis thioureas

Bisthiourea and substituted bisthioureas when treated with 3% hydrogen peroxide are converted to 2,5-diamino-1,3,4-thiadiazole derivatives. [Fromm.et. al, 1923]



9. From 1,3-dipolar addition of diazomethane

An interesting method that involves the addition of diazomethane to an appropriate thiobenzoylchloride to yield 2-aryl-1,3,4-thiadiazole was reported by Sartorelli *et* al.



In the present investigation we have adopted the method of Hoggarth [1949] for the synthesis of 2-amino-5-alkyl-1,3,4-thiadiazoles using conc.H_2SO_4 as cyclodehydrating agent and $POCl_3$ for the synthesis of various 2-amino-5-aryl-1,3,4- thiadiazoles.

REACTIONS OF 1, 3, 4-THIADIAZOLE

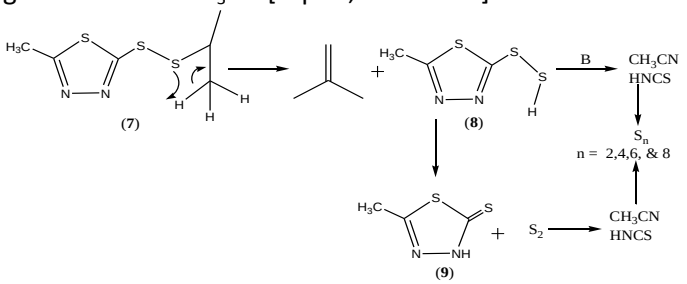
Some of the characteristic reactions of the 1,3,4-thiadiazole nucleus are ring opening by strong base, ease of nucleophilic attack and the formation of mesoionic compounds by quaternization. The substituents in the 2- and 5- positions have a large effect in determining the reactivity of the molecule as a whole. Thus, the ambident nucleophilicity of 2- aminothiadiazoles gives rise to electrophilic attack on both the amino group and the nuclear nitrogen atom. Ring formation between these two nitrogen atoms is also a common reaction. 2-Mercaptothiadiazoles reacts similarly to arenethiols while a methyl group on the thiadiazole ring has reactivity similar to that in picoline.

Nucleophiles easily displace halogen atoms from the thiadiazole nucleus. This is due to the electronegativity of the nuclear nitrogen atoms which impart a low electron density to the carbon atom of the nucleus. Selected examples in this part illustrate the general reactivity of 1,3,4-thiadiazole. [Sard et. al, 1985]

(i) Unimolecular thermal and photochemical reactions:

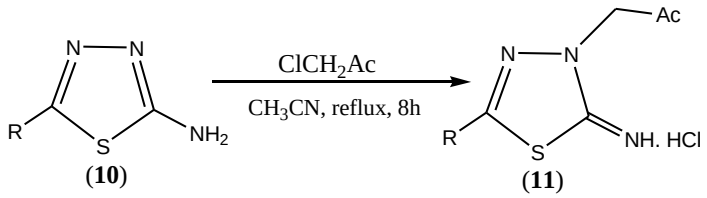
1,3,4-Thiadiazoles often undergo photochemical fragmentation similar to the fragmentation observed in the mass spectrometer [Kornis, 1996]. High-vacuum pyrolysis of 2-(*tert*-butyldithio)-5-methyl-1,3,4-thiadiazole 7 between ambient and 900 0C gave 2-methylpropene, HNCS, thiadiazole 9 ,CS_2, CH_3CN and sulfur species. The presence of 2-methylpropene might be caused by *β*-hydrogen elimination. This reaction would lead to the disulfanyl 8 which fragments further via two main paths (A and B). In reaction path A the bimolecular fragmentation of 8 gives S_2 and the thiadiazole 9, which above 500^0C decomposes to CH_3CN, HNCS, CS_2 and sulfur. Path B

results in direct elimination of S_2 from the disulfanyl 8 to give HNCS and CH_3CN [Hipler, et.al 2005]



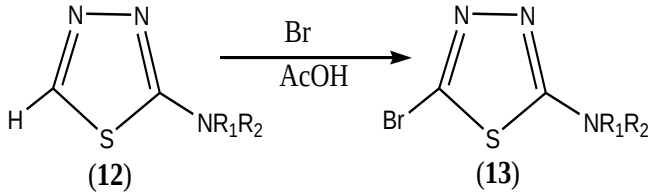
(ii) Electrophilic attack at nitrogen:

The ring nitrogens react with electrophiles to afford either 1,3,4-thiadiazolium salts or 1,3,4-thiadiazol-2(3*H*)-ones depending on the tautomerisability of the substituents at the C-2 or C-5 positions. While *N*-alkylation is the most common electrophilic reaction of 1,3,4-thiadiazole, reactions with acyl and cyanogen halides as well as Mannich salts have also been reported. 2-Amino-1,3,4-thiadiazole 10 reacts with chloroacetone to give the *N*-alkylated thiadiazolimine 11 [Morigi et. al, 2008]



(iii) Electrophilic attack at carbon:

Due to the low electron density at the carbon atoms in 1,3,4-thiadiazole, such reactions as nitration, sulphonation, acetylation, halogenations, etc. normally do not take place. However, 2-amino-substituted 1,3,4-thiadiazoles 12 react with bromine in acetic acid to give the 5-bromo derivatives 13 [Collier et. al, 2005]

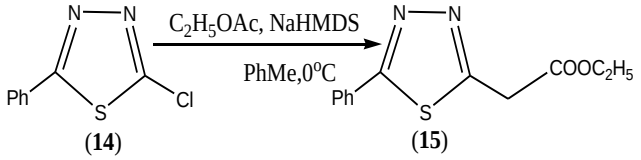


(iv) Electrophilic attack at sulfur:

The direct oxidation of thiadiazoles to form sulfoxides or sulfones has not been reported [Thiel et.al, 1990.]

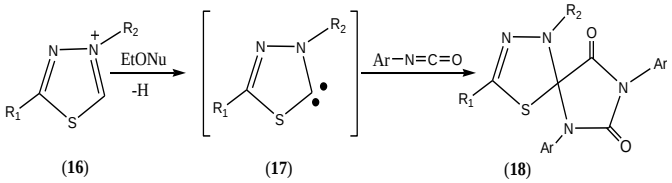
(v) Nucleophilic attack at carbon:

Nucleophilic reactions at the carbon atoms of 1,3,4-thiadiazoles occur readily owing to the electron-deficient nature of the ring. Halo-substituted thiadiazoles are, therefore, highly activated and react with a wide range of nucleophiles. Carbon-based nucleophiles such as malonate have been used in the synthesis of 2-substituted thiadiazoles. When 2-chlorothiadiazole 14 was treated with ethyl acetate in the presence of sodium hexamethyl disilazane (NaHMDS), the 5-phenyl-1,3,4-thiadiazol-2-ylacetic ester 15 was obtained [Shen et. al, 2006].



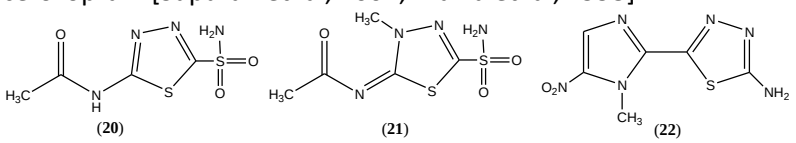
(vi) Nucleophilic attack at hydrogen attached to carbon:

Reaction of various alkylating agents with unsubstituted and 5-substituted thiadiazoles yielded 3-alkyl-1,3,4-thiadiazolium salts; these salts 15 were deprotonated with ethoxide to produce carbenes 17 which were trapped with aromatic isocyanates to yield spirocyclic compounds 18 [Haug et.al 1988].

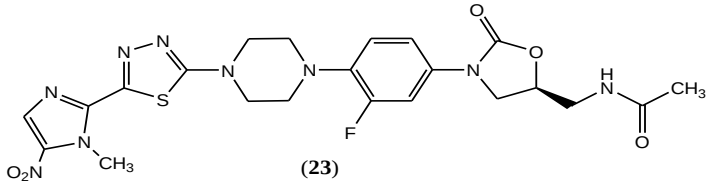


MODE OF ACTION OF 1,3,4-THIADIAZOLE

Many drugs containing 1,3,4-thiadiazole nucleus such as acetazolamide (19), methazolamide (20), megazol (21) are available in the market, although the only commercial 1,2,4-thiadiazole drug is the antibiotic cefozopram [Supuran et. al, 2001; lizawa et. al, 1993].



Linezolid is a well-reported bacteriostatic agent and its analogs containing a nitroaryl-1,3,4-thiadiazole moiety that inhibits protein synthesis by acting against the formation of the 70s initiation complex. These compounds were initially tested for antimicrobial activity by agar-dilution method, and it was found that compound 14 presented most pronounced activity. This compound was even found to be more potent than ciprofloxacin against a panel of Gram-positive and Gram-negative bacteria [Khalaj et.al 2011].



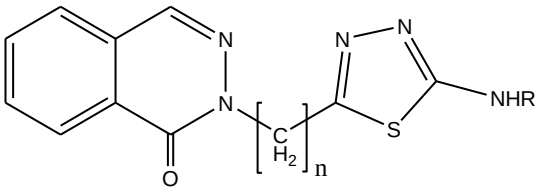
BIOLOGICAL ACTIVITY

1. 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

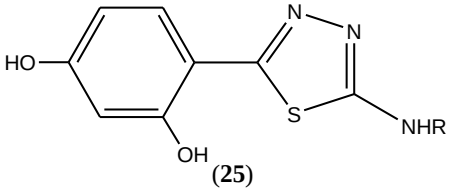
and antifungal agents. A new series of 2-[[1(2H)-phthalazinone-2-yl]methyl/ethyl]-5-arylamino-1,3,4-thiadiazole derivatives (24) was evaluated in vitro antimicrobial activity against bacterial and fungal species.

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 [Onkol T et.al, 2008].



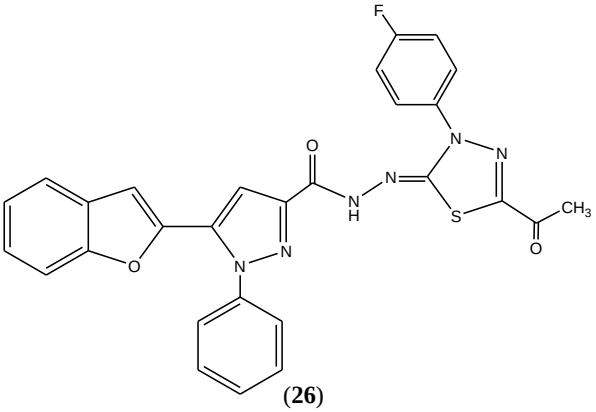
(**24**)

A number of 5-substituted 2-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole derivatives (25) have been evaluated for antifungal activity against several clinical isolates of *C. albicans*. The compounds with methyl, phenyl, 4-ethoxyphenyl, and halogenophenyl groups at C-2 of thiadiazole ring showed higher antifungal activity [Matysiak J et. al, 2007].



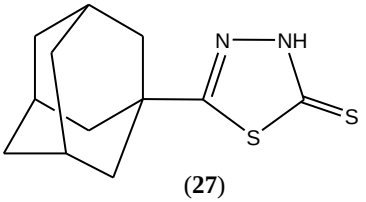
(**25**)

The synthesis of new 1,3,4-thiadiazole derivatives of 5-(benzofuran-2-yl)-1-phenylpyrazole moiety through the reactions of the potassium salt of hydrazine carbo-dithioate with substituted hydrazonoyl chlorides. Out of these synthesized compounds screened against bacterial strains, compound 26 showed significant activity against *E. coli* and *C. albicans.* The tested compounds did not exhibit any activity against Gram-(+) strains up to the maximum concentration of 100 µg/mL. [Abdel-Wahab et al., 2009]



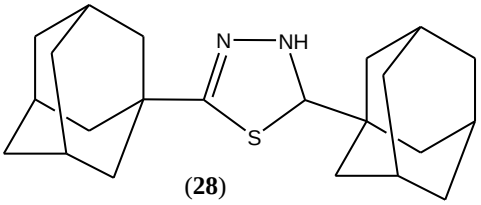
(**26**)

Synthesis of a new series of 5-(1-adamantyl)-1,3,4-thiadiazole derivatives for their antimicrobial activity. Upon evaluation of antibacterial activity, it was found that almost all the compounds, especially compound 27 exhibited more activity than reference drugs (gentamicin and ampicillin) with respect to *E. coli* and *P. aeuroginosa,* and thus, it could be a promising novel drug candidate. [Kadi et al., 2010]



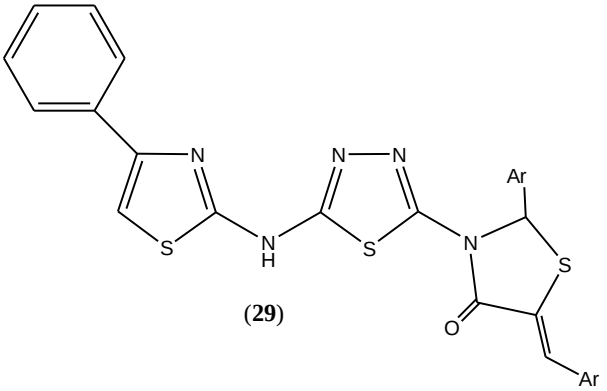
(**27**)

The findings revealed that antibacterial activity was greatly diminished on introduction of the benzyl- or 4-substituted benzyl moieties and antifungal activity increased on substitution with adamantly moiety (28) on C-5 of thiadiazole nucleus. The introduction of the 4-substituted-1 piperazinyl-methyl moieties at N-3 position increased the activity of thiadiazole derivatives against Gram-(+) bacteria [Kadi et al. 2007].



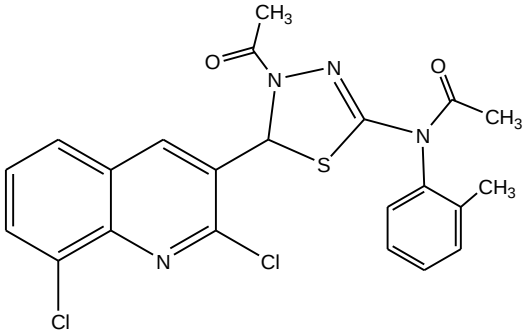
(**28**)

Some of the 2-[2-{2-(substitutedphenyl)-4-oxo-5-(sustitutedbenzyliden)-1,3-thiazolidin}-5-methyl-1,3,4-thiadiazol]-imino-4-phenyl-1,3-thiazole derivatives (29) showed distinct antibacterial and antifungal activity [Verma et.al, 2011].



(**29**)

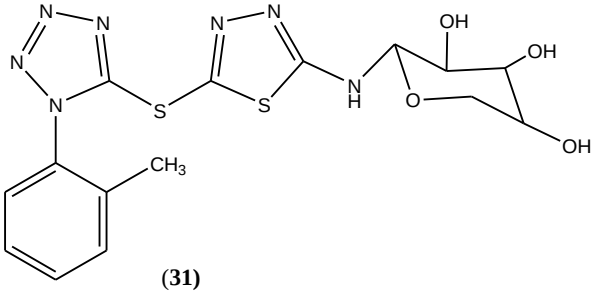
Thiadiazole derivatives substituted with N-(o-tolyl)acetamide (30) groups at C2 and 2,8-dichloroquinoline and 2-chloroquinoline at C5 showed better activity against *S. aureus* and *S. pyogenes*, respectively. [Bhat et. al, 2011]



(**30**)

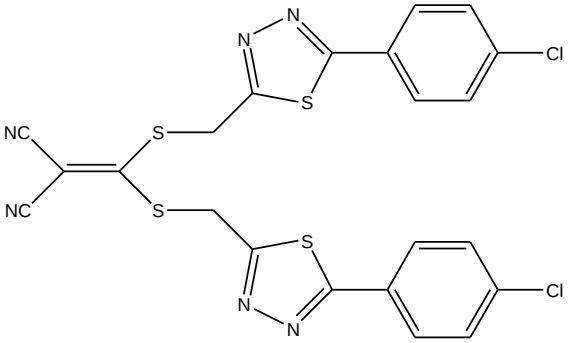
Synthesis of 5-(1-aryl-1H-tetrazol-5-ylsulfanylmethyl)-N-xylopyranosyl-1,3,4-thiadiazole-2-amine derivatives and

investigated in vitro antibacterial activity against *S. aureus.* Among the synthesized compounds, only compound 31 was found to be the most active against Bacterial strain and none of them showed activity against tested fungal strains. [He et. al. 2011]



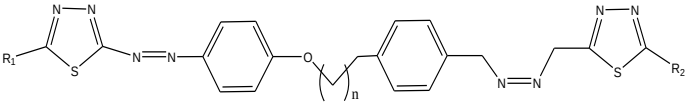
(**31**)

A series of 2-(bis(1,3,4-thiadiazolyl) methylthio)methylene)malononitriles were synthesized and evaluated in vitro against *S. aureus, B. subtilis, E. coli* and *K. pneumonia.* Among the synthesized compounds, 2-(bis((5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl)methylthio) methylene) malononitrile (32) showed significant activity against S. aureus with zone of inhibition of 35 mm at a concentration of 200 µg/mL. [Padhmavati et. al. 2011]



(**32**)

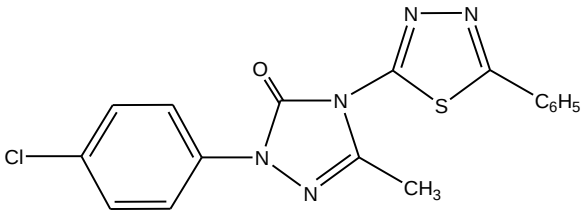
The in vitro antibacterial activity of Compound 33 of aminothiadiazole derived from nicotinic and isonicotinic acid have been evaluated against several microbes like *E. coli, K. pneumonia, P. aeruginosa, S. marscens,* and *S. aureus*. [Tomi et. al. 2010].



(**33**)

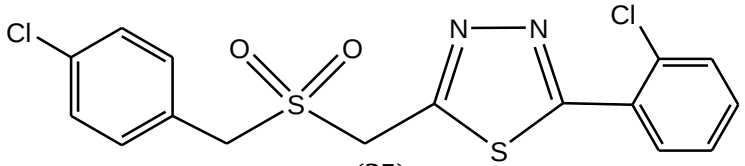
Various combines biolabile molecules involving Schiff bases and 1,2,4-triazoles derivatized with the 1, 3, 4-thiadiazoles showed moderate to significant activity against

bacteria at concentration of 100 µg/mL. Compounds (34) with chloro group at the para-position of the aryl ring were shown to increase antibacterial activity (15.6 µg/mL) where the standard drug has shown MIC value at 12.5 µg/mL [Bansode et.al, 2011].



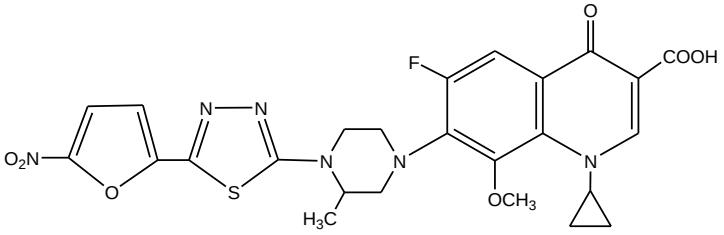
(**34**)

The antimicrobial activity of derivatives involving a series of novel 2 (arylmethanesulfonyl-methyl)- 5-aryl-1,3,4-thiadiazoles was studied in experiments in vitro with respect to Gram-positive bacteria S. aureus, B. subtilis and Gram-negative bacteria *K. pneumonia, P. vulgaris,* and fungi *F. solani, C. lunata, a*nd *A. niger*. Most of the synthesized compounds showed moderate to comparable activity. Compounds with benzylsulfonyl group and chloro substituent were found to be the most active and only compound 18 had more pronounced antibacterial activity and almost equipotent to chloramphenicol [Padhmavati et.al 2011].



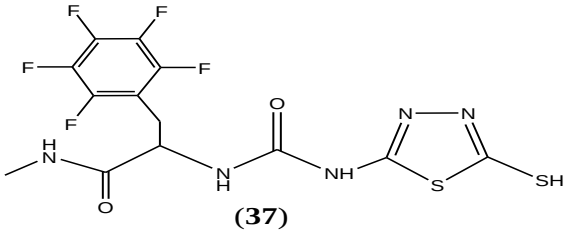
(**35**)

Antibacterial activity of gatifloxacin derivatives incorporated with 5-(5-nitroheteroaryl)-1,3,4-thiadiazol-2-yl groups at C-7 position had been studied. The presence of nitrofuran (36) at C-2 of thiadiazole ring caused complete inhibition of DNA gyrase or DNA topoisomerase IV and exhibited more potent inhibitory activity against Gram-positive bacteria [Jazayeri et al. 2008]



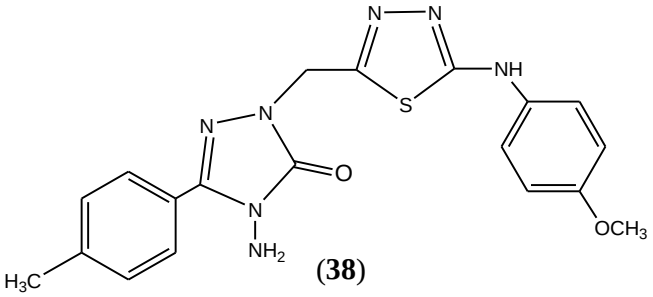
(**36**)

Synthesis of 5-mercapto-1,3,4-thiadiazole derivatives and tested their inhibitory activity against matrix metalloproteinase (MMP) and Bacterial Collagenase. Among the synthesized compounds, compound 37 was found to bind with zinc ion of the metalloprotease (MMP3) active site through the interaction of exocyclic sulfur atom of mercapto-thiadiazole ring and to S1 pocket of the protease by its urea-thiadiazole thiadiazole moiety, methylamide carbonyl moiety to S2 site of protease and the pentafluorophenyl moiety to S3 site of the protease (k1 = 18 nm). [Scozzafava et. al, 2002]



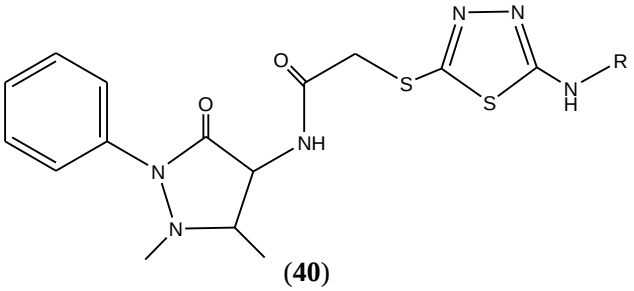
(37)

4-Amino-2-[(5-arylamino-4,5-dihydro-1,3,4-thiadiazol-2-yl)methyl]-5-(4-methylphenyl -2,4-dihydro-3H-1,2,4-triazol-3-ones (38) and investigated for antimicrobial activity. Thiadiazole (38) with 2-({5-[(4-methoxyphenyl) amino] group was found to possess highest antibacterial activity, whereas N-alkylation at C-5 of thiadiazole ring did not resulted in improved antibacterial activity. [Demirbas et al. 2009]



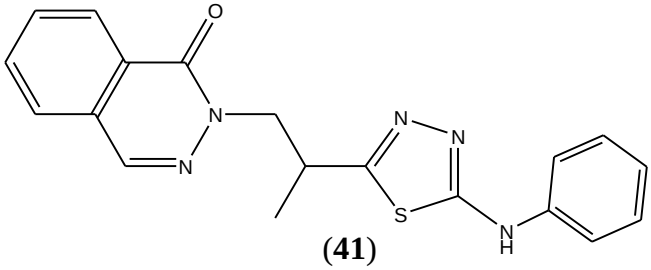
(38)

An attempt to prepare active compounds in the series of thiadiazolyl derivatives (39) of antipyrine turned up unsuccessful. All the synthesizedderivatives bared weak growth inhibitory activity against the tested Gram-positive bacteria (MIC 100 µg/mL) [Rostom S. A. et. al, 2009].



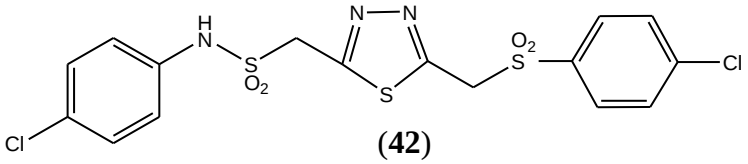
(40)

Antibacterial activity is strongly dependent on the nature of the substituents at 5-arylamino-1,3,4-thiadiazoles in a series of 2-[[1(2H)-phthalazinone-2-yl]methyl/ethyl]-5-arylamino-1,3,4-thiadiazole derivatives. Unsubstituted compound 41 showed 50% of inhibition against *B. subtilis* with respect to ampicillin [Onkol T. et. al, 2008].



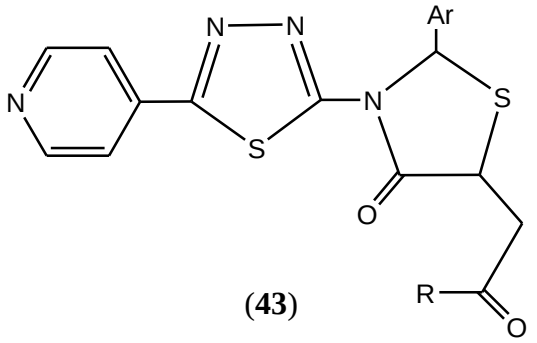
(41)

Compound 42 having chloro group at para-position of arylsulfonylmethane moiety attached with thiadiazole ring exhibited higher antimicrobial activity [Padmavathi et.al, 2010].



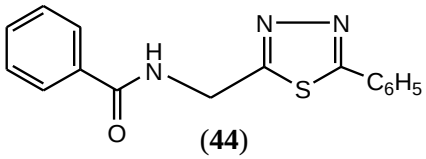
(42)

Aminothiadiazole derivatives (43) containing 4-pyridyl and oxothiazolidin moieties in the same molecules. All the compounds had good antimicrobial activity but the compounds having a nitro group were present at the -m and -p position of the aryl ring, respectively, possessed stronger antibacterial activity than others. [Ranjana et al. 2006]



(43)

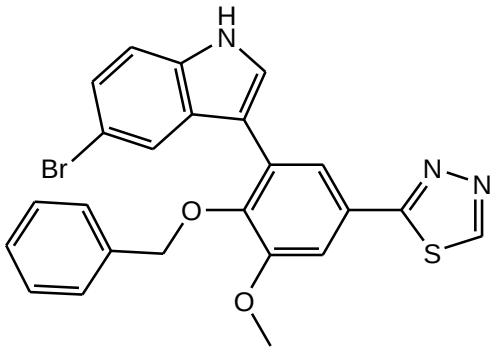
1,3,4-thiadiazole derivative of hippuric acid, *N*-((1,3,4-thiadiazol-2-yl)methyl) benzamide (44) was synthesized. The results showed that the tested compounds possessed weak antibacterial and antifungal activity compared with standard drugs Ciprofloxacin for antibacterial and ketoconazole for antifungal activity, respectively. [Shrivastava et. al, 2010]



(44)

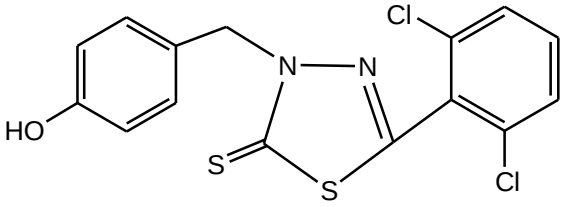
2. Anticancer activity

Synthesis of 5-(3-indolyl)-1,3,4-thiadiazoles and evaluated for anticancer activity. Primary screening was performed at a concentration ranging from 100 nM to 1 mM. Change in cell number and cell morphology in 96-well plates was observed at 24 and 48 h had been detected. Compounds that exhibited toxicity to cancer cell lines but not to normal cells were selected for the secondary confirmation assays. It was found that substitution on C-2 position of the 1,3,4-thiadiazole ring plays an important role in imparting the cytotoxic activity to the compound. Compound 2-(4-(Benzyloxy)-5-(5-bromo-3-indolyl)-3-methoxyphenyl)-1,3,4-thiadiazole (45) with 4-benzyloxy-3-methoxyphenyl at C-2 position and 5-bromoindole at C-5 position was found to be the most potent compound of the series. [Kumar et al. 2010]



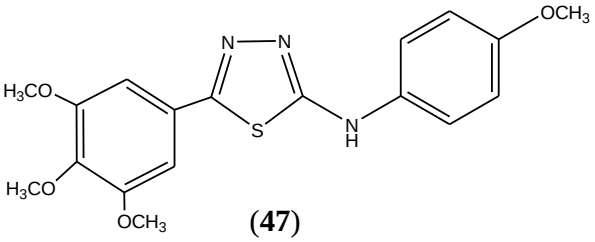
(**45**)

Compound (4-hydroxyphenyl)[5-(2,6-dichloro)-2-thioxo-1,3,4-thiadiazol-3-yl]methano-ne (46) showed broad spectrum of growth inhibition activity against human tumour cells and remarkable cytotoxic activity on non small lung cancer (HOP 92) having log GI_{50} value at -6.49, colon cancer (HCC-2998) at GI_{50} value -5.31 and significant cytotoxic activity on prostate cancer (PC-3) having GI_{50} value -5.48. SAR study revealed that electron withdrawing group at position C-5 of thiadiazole was favorable for activity [Bhole et.al, 2010].



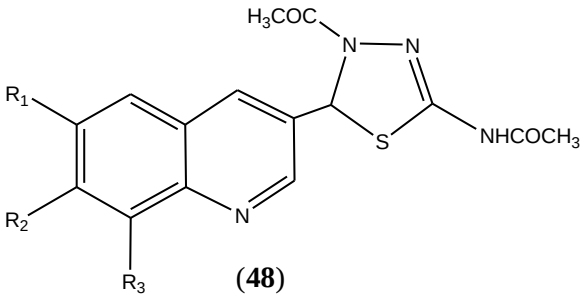
(**46**)

New derivatives of 2-arylamino-5-aryl-1,3,4-thiadiazoles were synthesized by refluxing aryl aldehydes, hydrazine hydrate, and aryl isothiocyanates in methanol followed by oxidative cyclization with ferric ammonium sulfate. Study of in vitro cytotoxic activity revealed a cytotoxic effect of individual compounds on cancer cells of prostate (PC3, DU145, and LnCaP), breast (MCF7 and MDA-MB-231), and pancrease (PaCa2). The SAR study showed that the 3,4,5-$(OCH_3)3C_6H_2$ at C-5 position was responsible for binding to the Colchicine siteon tubulin and found to be favorable for activity. Further variation of C-2 arylamino group was associated with lesser degree of effect on the activity of 1,3,4-thiadiazoles. Most of the synthesized compounds were moderate in activity and compound 47 displayed a greater potency toward pancreatic (PaCa2) cancer cell lines (IC50 = 4.3 lM) [Kumar D et.al, 2011].



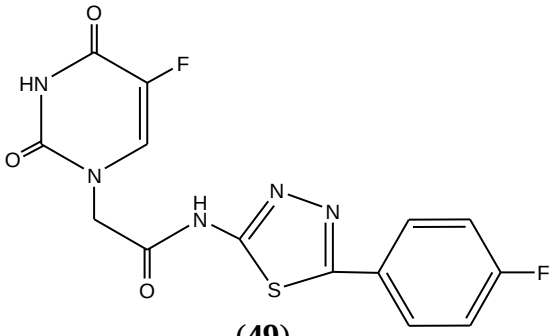
(**47**)

Quinolines derivatized with 1,3,4-thiadiazole by cyclization of quinoline thio-semicarbazones in a single step and investigated for their primary cytotoxic activity against cervical cancer cell line. Compounds 48 with methoxy at C-6,7,8 of quinoline showed the potent anticancer activity and the cell lyses occurred only at 10 µg/mL. [Marganakop et al. 2010]



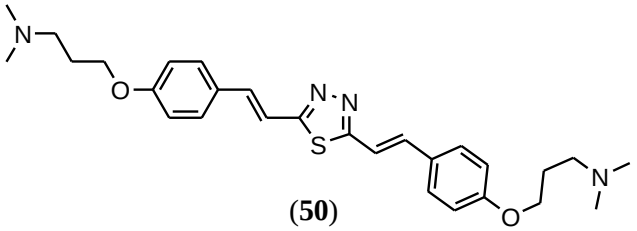
(**48**)

Several N1-acetylamino-(5-alkyl/ aryl-1,3,4-thiadiazole-2-yl)-5-fluorouracil derivatives. These compounds were evaluated for their anticancer activity on A-549 (human lung cancer cell), Bcap-37 (human breast cancer cell) by MTT assay. Compound 49 with electron with-drawing group attached to benzene ring was found to have activity against tested cell lines and possessed more potent antitumor inhibitory activity than 5-fluorouracil. [Zhang et al. 2008]



(**49**)

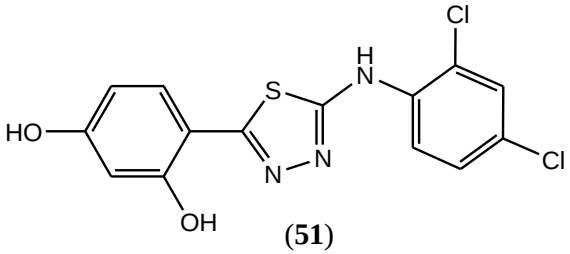
Compound (E,E)-2,5-bis[4-(3-dimethyl-aminopropoxy)styryl]-1,3,4-thiadiazole (50) was found to be the most potent one by the MTT assay against A549, PC-3, and HA22T [Chou et.al, 2003].



(**50**)

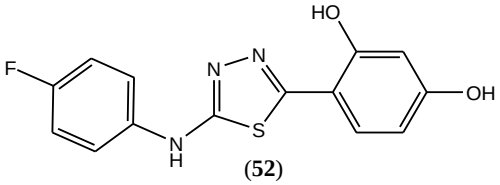
A number of N-substituted 2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole derivatives were investigated as antiproliferative agent, their in vitro cytotoxicity against the four human cell lines: SW707 (rectal), HCV29T (bladder), A549 (lung), and T47D (breast) suggested their potential as novel anticancer agents. Compound 2-(2,4-dichlorophenylamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole (51), with ID50 two

times lower (SW707, T47D) than that of cisplatin displayed the highest cytotoxicty. It was noticed that the compounds with electron donating groups at C-terminal of the phenyl ring did not increased its cytoselective toxicity and the compounds with electron withdrawing groups (Cl, F) resulted in an increased activity by inducing cell death [Matysiak et.al., 2006].



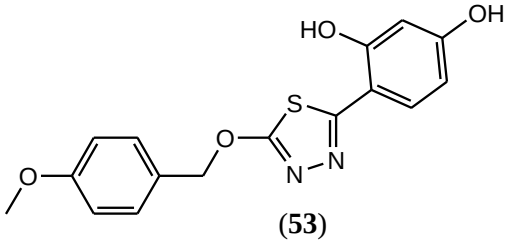
(**51**)

Compound 2-(4-fluorophenylamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole (52) inhibited proliferation of tumor cells derived from cancers of nervous system (medulloblastoma/rhabdosarcoma, neuroblastoma, and glioma) and peripheral cancers including colon adenocarcinoma and lung carcinoma [Rzeski et .al, 2007].



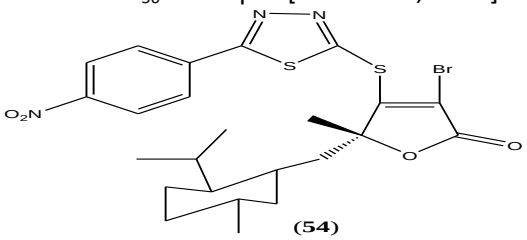
(**52**)

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 (53) 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. [Nasulewicz A. et al. 2006]



(**53**)

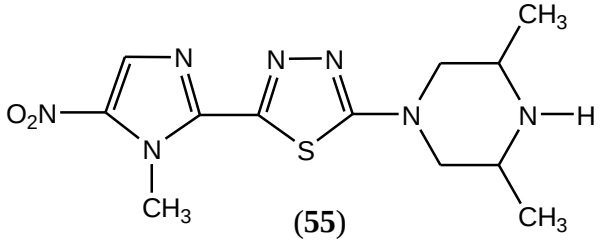
In a series of chiral 2,5-disubstituted 1,3,4-thiadiazoles possessing c-butenolide moiety, compound 50 was screened against Hela cell lines by MTT assay and exhibited IC_{50} of 0.9 µM [Wei et. al., 2009].



(**54**)

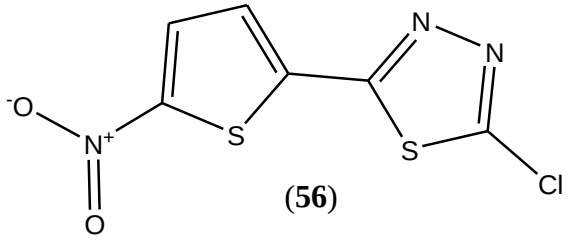
3. Anti-Helicobacter pylori

5-(1-methyl-5-nitro-1H-imidazol-2-yl)-1,3,4-thiadiazoles and screened for bactericidal activity against H. pylori. Compound 55, substituted with 3,5-dimethylpiperazinyl moiety at the 2-position of the 5-(1-methyl-5-nitro-1H-imidazol-2-yl)-1,3,4-thiadiazole skeleton had strong anti-H. pyroli activity at 0.5 µg/disk (average of inhibition zone >20 mm) which was superior to that of metronidazole. [Moshaf et al. 2011]



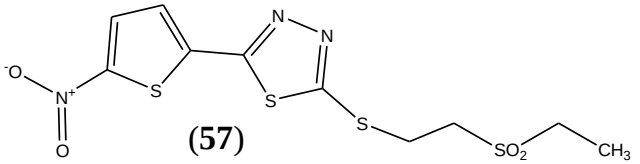
(**55**)

2-Substituted-5- nitroheterocycles were prepared and evaluated for their anti-H. pylori activity. The authors further reported the SAR responsible for the activity. All the synthesized compounds exhibited high activity against clinical isolates of H. pylori with respect to standard drug, metronidazole (8 µg/disk). Compound 2-chloro-5-(5-nitrothiophene)-1,3,4-thiadiazole (56) was found to be the most active with zone of inhibition >30 mm at 8 µg/disk against metronidazole sensitive H. pylori strain. Activity of this series was dependent on chloro amino, mercapto substituted 1,3,4-thiadiazole moiety attached to 5-nitroheteroaryl ring. [Foroumadi et al. 2009]



(**56**)

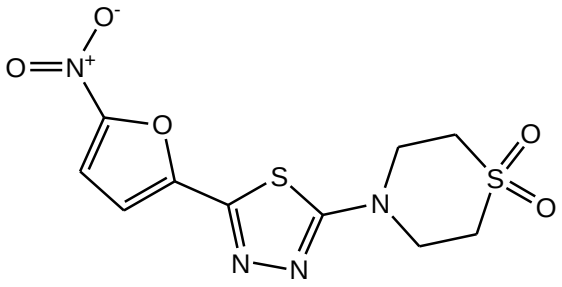
The effect of nitroaryl moiety and sulfur containing alkyl side chain similar to tinidazole on 1,3,4-thiadiazole ring for their metronidazole sensitive and metronidazole resistant H. pylori strains. Nitroheteroaryls, Nitrothiophene analogs (57) showed more potent anti-H. pylori activity with respect to nitrofuran and nitroimidazole derivatives. Further, the S, S-dioxidation of ethyl thio group attached to aryl-1,3,4-thiadiazoles improved its anti H. pylori activity. [Foroumadi et al. 2008]



(**57**)

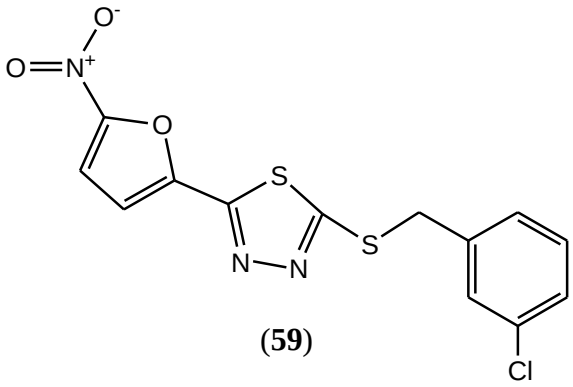
4-[5-(5-Nitro-2-furyl)-1,3,4-thiadiazol-2-yl] thiomorpholine 1,1-dioxide containing thiomorpholine S,S-dioxide moiety (58) showed the highest anti-H. pylori activity at a concentration of 8 µg/disk producing an average inhibition

zone of more than 27 mm, which was greater than that by metronidazole (16.3 mm) [Mirzaei et.al, 2008].



(**58**)

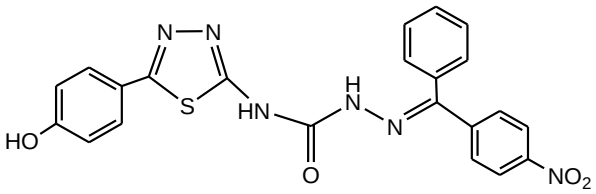
In a series of 2-[(chlorobenzyl) thio]-5-(5-nitro-2-furyl)-1,3,4-thiadiazoles for possible anti-H. pylori activity. Of eight, four derivatives showed strong anti-H. pylori activity at concentration of 8–32 µg/disk and compound 57 containing the 3-chlorobenzylthio moiety was found to exhibit the most potent and selective inhibitory activity against H. pylori with an inhibition zone of more than 20 mm at a concentration of 8 µg/disk [Mohammadhosseini et al. 2008].



(**59**)

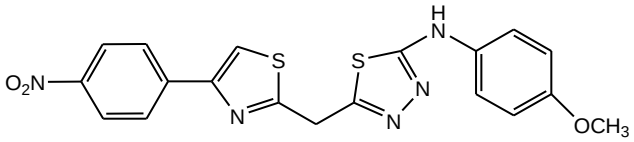
4. Anticonvulsant activity

Recently, synthesis of some 2,5-Disubstituted 1,3,4-Thiadiazoles and evaluated their potential anticonvulsant activity. The results showed that compound with 4-nitrophenyl-substituted semicarbazone (60) were the most active compound comparable with carbamzepine. The SAR study suggested that [5-(4-substituted phenyl)-1,3,4-thiadiazol-2-yl] moiety as hydrophobic portion, two-electron donor atom and another hydrophobic distal aryl ring substituted with *p*-NO_2 group responsible for metabolism, played a crucial role for its anticonvulsant activity. [Rajak et al., 2009]



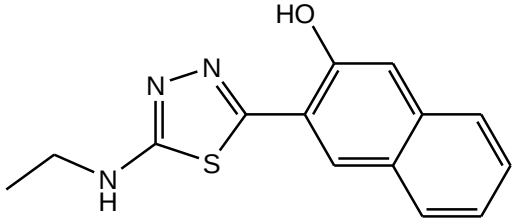
(**60**)

Compound 61 having nitro group attached to the phenyl ring adjacent to the thiazole moiety demonstrated more potent anticonvulsant activity and the removal or replacement of –NO_2 function by a -Cl, -Br moieties was responsible for loss of activity [Siddiqui et.al, 2011].



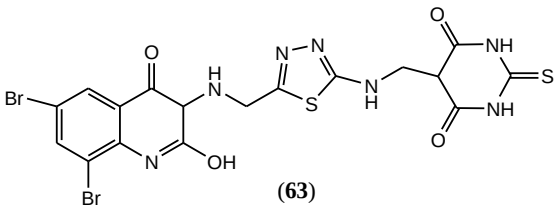
(**61**)

In an attempt to improve the potency and selectivity of 2,5-Disubstituted-1,3,4-thiadiazoles (62), synthesized a series of 2-(N-alkyl/aryl-Nacetylamino)-5-(3-acetyloxy-2-naphthyl)-1,3,4-thiadiazole derivatives. Compound 2-ethylamino-5-(3-hydroxy-2-naphthyl)-1,3,4-thiadiazole (62) showed 90% protection against pentylenetetrazole-induced generalized convulsions. Further, substitution of ethyl and acetylation of thiadiazoles resulted in loss of activity. [Dogan et al., 2002]



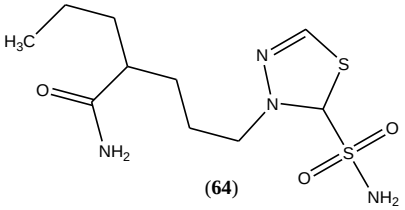
(**62**)

Compound 5-{2′-amino-5′-[3″-aminomethylene-2″-methyl-6″,8″-dibromoquinazolin-4″ (3″H)-onyl]-1′,3′,4′-thiadiazol-2′-yl}-2-thiobarbituric acid (63) showed high percentage protection 90% (50 mg/kg ip) in both MES and PTZ models [Srivastava et. al., 2004].



(**63**)

A new series of sulfonamides incorporating valproyl and other lipophilic moieties has been synthesized to study the effect of different alkyl/aryl carboxamido/ sulfonamido/ureido moieties on the 5th position of 1,3,4-thiadiazolesulfonamide on its anticonvulsant activity. Their findings revealed that the valproyl derivative of acetazolamide (5-valproylamido-1,3,4-thiadiazole-2-sulfonamide) 64 was the best in the series as it exhibited very strong anticonvulsant activity in an MES test in mice. [Masereel et al. 2002]

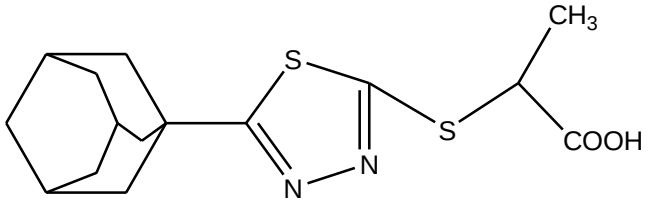


(**64**)

5. Anti-inflammatory activity (COX-inhibitors)

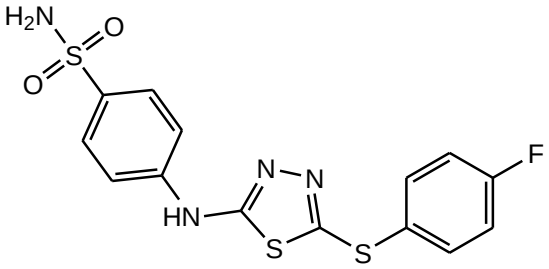
Thiadiazole incorporated in different heterocyclic moieties has been reported to possess potent anti-inflammatory activity. Most of the synthesized thiadiazole derivatives possess anti-inflammatory activity by inhibition of the enzyme involved in the first step of the conversion of arachidonic acid to prostaglandins (PGs). Anti-inflammatory activity of new series of 5-(1-adamantyl)-1,3,4-thiadiazole (27) derivatives. [Kadi et al. 2007].

Interestingly, compound 65, substituted with propionic acid at 2nd position of 1,3,4-thiadiazoline-2-thiones, showed almost equal anti-inflammatory activity at 20 mg/kg to that of Indomethacin (5 mg/kg). Replacement of 2-propionic acid with acetic and 3-propionic acid was slightly detrimental to the anti-inflammatory activity. [Kadi et al. 2007]



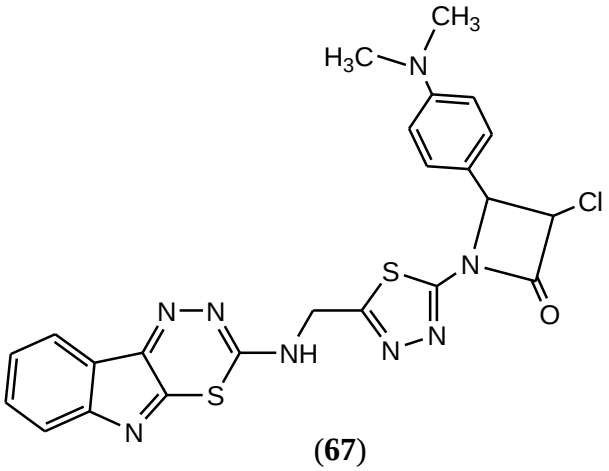
(**65**)

2-amino-5-sulfanyl-1,3,4-thiadiazoles and concluded that the compounds were associated with lesser degree of anti-inflammatory activity when compared to indomethacin. Only compound 4-[5-(4-Fluorophenylsulfanyl) -[1,3,4]thiadiazol-2-ylamino]benzene sulfonamide (66) showed 65.90% inhibition of paw edema after 3 h at 56 *mg/kg* (bodyweight) dose and 66.40% protection in acetic acid induced inflammation in mice. [Sainy et al. 2009]



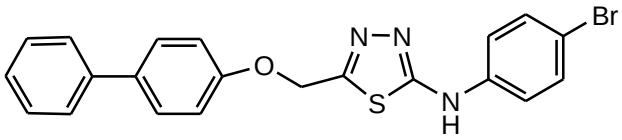
(**66**)

The anti-inflammatory activity of 2-aryl-3-{5-[([1,3,4] thiadiazino[6,5-b]indol-3-ylamino) methyl]- 1,3,4-thiadiazol-2-yl} -1,3-thiazolidin-4-one/azetidin-2-one (67) were studied using carrageenan induced rat's paw edema method. Compound with 2-chlorophenyl group at C-4 of azetidin-2-one ring as substituent exhibited the most potent anti-inflammatory (41.23%) and analgesic activity (38%) at a dose of 50 mg/kg than that of their corresponding thiazolidinone compounds [Bhati et. al, 2008].



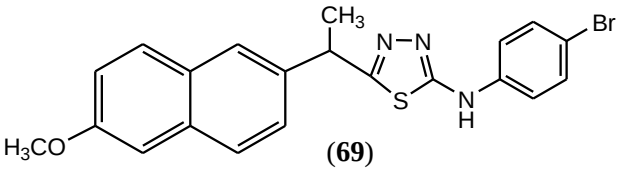
(**67**)

1,3,4- thiadiazole derivatives of biphenyl-4-yloxy acetic acid (68). 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. [Kumar et al. 2008]



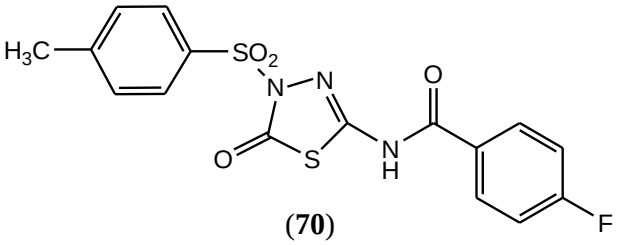
(**68**)

1,3,4-thiadiazole analogs of naproxen carrying a 4-bromophenyl amino group (69) at second position of the thiadiazole ring showed 78.02% inhibition in rat paw edema [Amir M et. al, 2007].



(**69**)

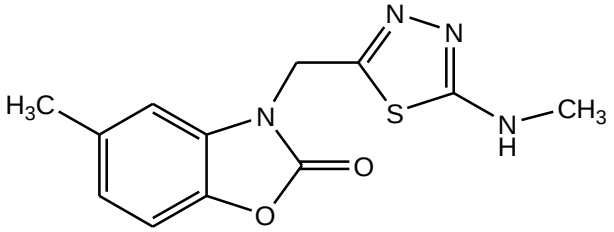
The presence of the tolyl substituent on the sulfonamide moiety on 4th position of 1,3,4-thiadiazole ring was found to be suitable for increasing the analgesic and anti-inflammatory activity. Compound 70 with a p-fluoro phenyl substituent was the most active compound (51.4% of inhibition at 50 mg/kg) among the benzoyl sulfonamido derivatives [Schenone S. et. al, 2006].



(**70**)

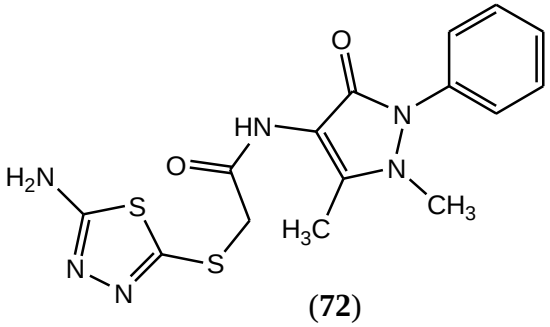
1,3,4-thiadiazoles containing 5-methyl-2-benzoxazolinone derivatives and evaluated their anti-inflammatory activity. All the compounds exhibited anti-inflammatory activity (at the dose 50 mg/kg p.o.) of varying degree from 53.2% to 85.3% in inhibition of edema. Compound 71 with methyl

group showed analgesic activity similar to that of morphine and aspirin. [Rostom S. A. et al., 2009]



(**71**)

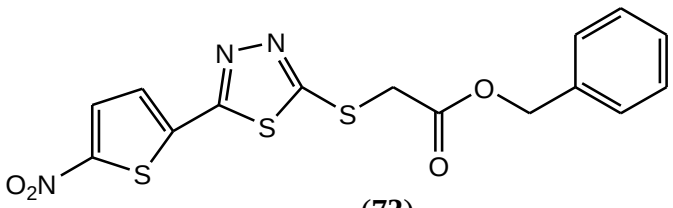
Conversion of the amino group to the carbamate or phenylthioureido functionalities at 5th position of the 2-(5-amino-1,3,4-thiadiazol-2-ylthio)-N-(2,5-dihydro-2,3-dimethyl-5-oxo-1-phenyl-1H-pyrazol-4-yl)acetamide (72) decreased anti-inflammatory as well as analgesic activity [Hafez H.N, 2008].



(**72**)

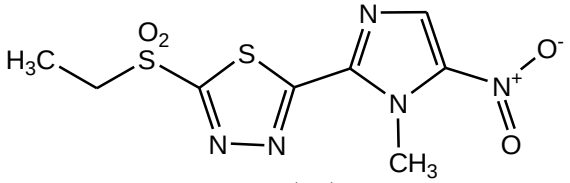
6. Antitubercular activity

The emergence of multidrug-resistant tuberculosis, coupled with the increasing overlap of the AIDS and tuberculosis pandemics has brought tuberculosis to the forefront as a major worldwide health concern. 2-(5-nitro-2-furyl)- and 2- (1-methyl-5-nitro-lH-imidazol-2-yl)-1,3,4-thiadiazole derivatives and screened for *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* $H37_{Rv}$ using alamar-blue susceptibility test. Compounds showing 90% inhibition in the primary screen were retested at lower concentration to determine the MIC. The data compared with the standard drug rifampicin at 0.031 µg/mL concentration which showed 97% inhibition. [Foroumadi et al., 2003] their nitrothienyl analog (73) was equally and highly active against M. tuberculosis $H37_{Rv}$ [69].



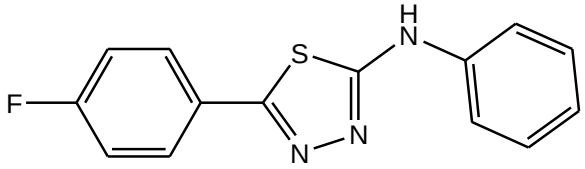
(**73**)

Similarly, 2-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole derivatives were investigated for antitubercular activity and it was found that compound 74 bearing a primary alkylthio substitution displayed good antitubercular activity (MIC = 3.13–6.25 µg/mL). Oxidation of thio group in ethyl sulfonyl analog increased its activity Foroumadi et al., 2001].



(**74**)

Antitubercular activity by electronic-topological method (ETM) and feed forward neural networks (FFNNs) trained with the back-propagation algorithm. They reported that 2-phenylamino-5-(4-fluorophenyl)-1,3,4-thiadiazole (75) showed highest% of inhibition. [Oruc et al. 2004]

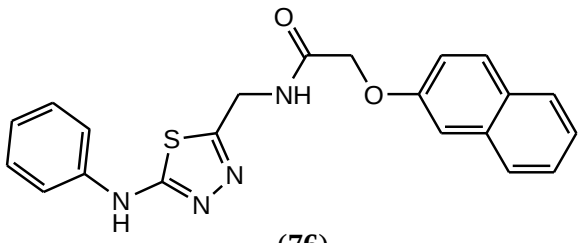


(**75**)

7. Antiviral activity & Anti HIV activity

Human immunodeficiency virus type 1 (HIV-1) has been recognized as the contributing agent in the transmission and the development of acquired immuno deficiency syndrome (AIDS). With increasing resistance of the retrovirus HIV-1 to current drugs, there is a need for development of new compounds. The unique nature of the replicative cycle of HIV-1 provides many potential targets for therapeutic interventions. 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 [Barreca M.L, et.al, 2001].

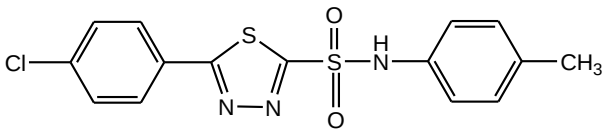
2-(naphthalen-2-yloxy)-N-((5-(phenylamino)-1,3,4-thiadiazol-2-yl)methyl) acetamide (76) and tested it's in vitro anti-HIV-1 (strain IIIB) and anti-HIV-2 (strain ROD) activity by the inhibition of the virus induced cytopathic effect in the human T-lymphocyte (MT-4) cells, based on MTT assay. All the compounds were found to be inactive except for 76 which showed EC_{50} values of 0.96 µg/mL. [Hamad et. al. 2010]



(**76**)

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. 5-

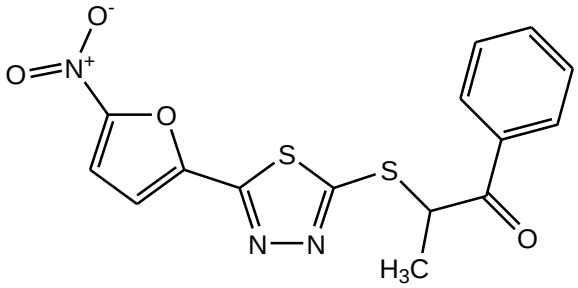
(4-chlorophenyl)-N-p-tolyl-1,3,4-thiadiazole-2-sulfinamide (77) showed inhibitory activity of about 42%. [Chen et. al, 2010]



(**77**)

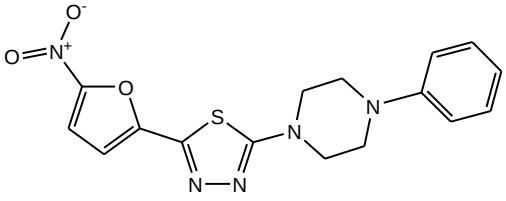
8. Anti-leishmanial activity

A large number of synthetic 1,3,4-thiadiazoles derivatives have been well documented and tested in the recent years in anti-leishmanial assays. Compound 2-(5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-ylthio)-1-phenylpropan-1-one (78) showed IC_{50} of 1.11 µM against L. major promastigotes. [Navarro M. et.al, 2000].



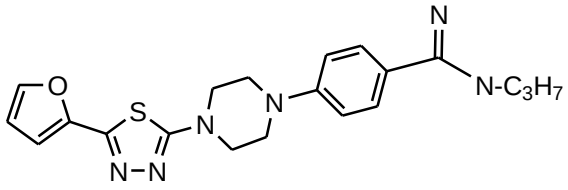
(**78**)

A high activity level of IC_{50} = 0.1 µM against L. major promastigotes was observed for compound that contained a 4-phenyl-piperazine (79) group at C-2 of 1,3,4-thiadiazole ring in a series of nitrofuran derivatives [Behrouzi et.al., 2008].



(**79**)

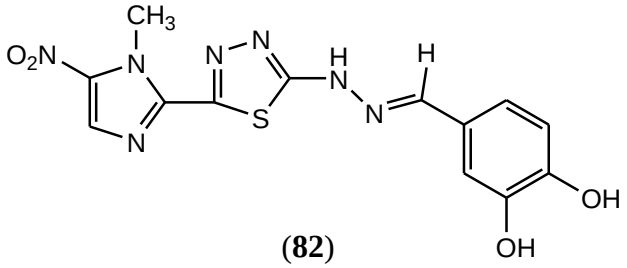
The 1-(5-(5-nitrofuran-2yl)-1,3,4-thiadiazole-2-yl)piperazines (80) having n-propyl, n-butyl and benzyl side chain on benzamidine showed IC_{50} values of 0.08, 0.2, and 0.4 µM, respectively, against the promastigote form of L. major. SAR study revealed that substitution with benzamidine was favorable for activity and replacement by a five-membered ring, namely the imidazoline and six-membered ring, namely tetrahydropyrimidine were devoid of activity. [Tahghighi A., 2011]



(**80**)

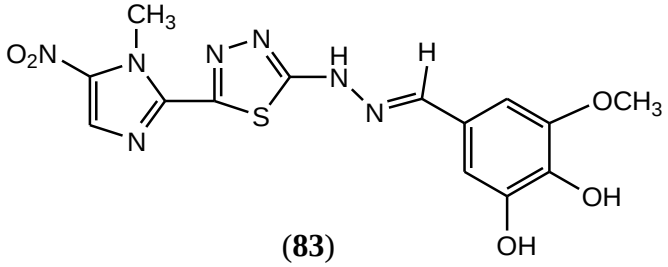
9. Trypanocidal (anti-epimastigote) activity

A number of new 1,3,4-thiadiazole-2-arylhydrazone derivatives of megazol were screened for trypanocidal (anti-epimastigote activity, %AE) using megazol-treated parasites as control. The most active hydrazone compound of series was 3,4-dihydroxyphenyl derivative (82), which showed an IC_{50} of 5.3 µM and was found to be superior in activity than the prototype megazol (IC_{50} = 9.9µM) [Carvalho S.A. et.al 2004].



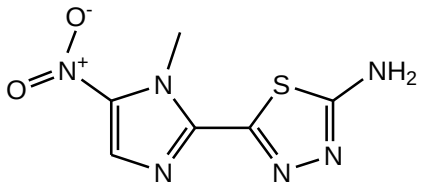
(**82**)

3,4-dihydroxyphenyl derivatives showed a high in vitro potency while devoid of any in vivo effect on trypomastigotes. Replacement of 3-hydroxyphenyl and 3-bromophenyl groups instead of 3,4-dihydroxyphenyl group on 1,3,4-thiadiazole-2-arylhydrazones (83) significantly decreased the level of T. cruzi in vivo as well as in vitro. [Salomao et al. 2010]



(**83**)

Trypanocidal activity of megazol [2-amino-5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole] is associated with DNA damage of T. cruzi. Substitutions at 4th position of imidazole moiety of 5-(1-methyl-5-nitro-1H-2-imidazolyl)-1,3,4-thiadiazol-2-amine (84) with electron-donating or withdrawing substituents was found to reduce the trypanocidal activity. [Chauviere G et. al, 2001]

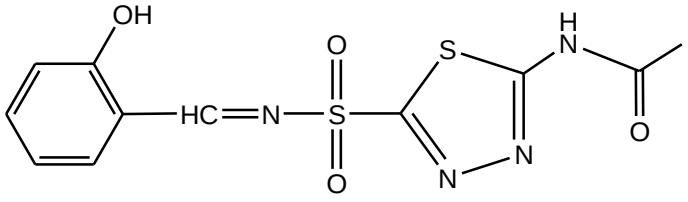


(**84**)

10. Carbonic anhydrase inhibitory activity

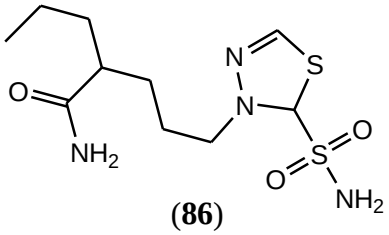
Reaction of 3- and 4-carboxybenzenesulfonyl chloride with 5-amino-1,3,4-thiadiazole-2-sulfonamide/5-imino-4-methyl-2-1,3,4-thiadiazoline-2-sulfonamide afforded two series of benzolamide analogues to which the carboxyl moiety has been derivatized as esters or amides, in order to reduce their very polar character. The new derivatives

showed low nanomolar affinity for three carbonic anhydrase (CA) isozymes. Schiff base metal chelates 85 are widely applicable because of their industrial and biological importance. [Suparna Ghosh et.al, 2009]



(**85**)

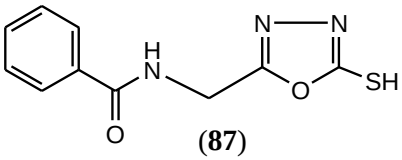
Data revealed that inhibitory activity of compounds was greatly influenced by nature of sulfonamide attached to valproyl moiety. 5-Valproylamido-1,3,4-thiadiazole-2-sulfonamide (86) was found to be more effective than acetazolamide and methazolamide against all three enzymes. [Masereel B. et. al, 2002]



(**86**)

11. Anthelmintic Activity

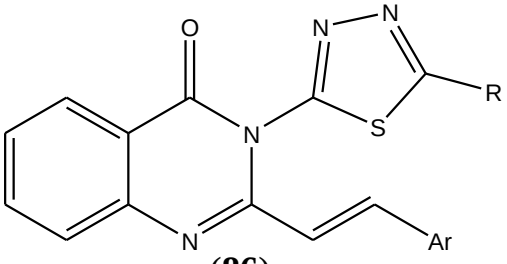
Shrivastava et. al, 1,3,4-oxadiazole derivative of hippuric acid, *N*-((5-mercapto-1,3,4-oxadiazol-2-yl) methyl) benzamide (87) synthesized and were found to possess potential antihelmentic activity against *Pheretima posthuma*.as compared to albedazole. [88]



(**87**)

12. Antidepressant agent:

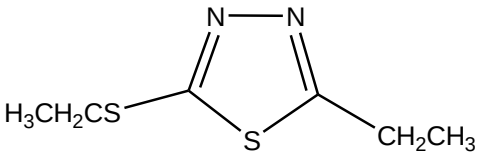
A series of novel 3-[5-substituted phenyl-1, 3, 4-thiadiazole-2-yl]-2-styryl quinazoline-4(3*H*)-ones were synthesized and evaluated for anticonvulsant, sedative-hypnotic and CNS depressant activities. [Jatav et.al, 2008]



(**86**)

13. Radioprotective agents:

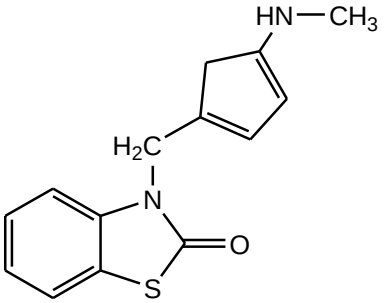
Thiol and aminothiol compounds are among the most efficient chemical radioprotectors. Synthesized thiol and aminothiol compounds derived from thiadiazole structures 87.They examined them for their ability to scavenge free radicals. [Prouillac et.al., 2009]



(**87**)

14. Antihistaminic agents:

2-Oxobenzothiazoline derivatives bearing substituents at position 3 with thiadiazole moiety have reported to exhibit antihistaminic activity. 3-((4-(methylamino)cyclopenta-1,3-dienyl)methyl)benzo[d]thiazol-2(3H)-one (88) were more potent than others and the standards in tail flick test. [Onkol Tijen et. al, 2004]



(**88**)

CONCLUSIONS

This review thus gives an overview of the various synthetic routes used to form a biologically rich thiadiazole moiety as well as the reactions the molecule undergoes to yield various other important molecules. It also highlights the therapeutic properties of the thiadiazole ring and the availability of varied drugs in the market containing the ring. Thus this paper proves to be significant for further research work on the bioactive thiadiazole ring.

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